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Cyclization Reactions Induced by Samarium(II) Iodide

Zhihong Zhou

A Thesis

in

The Department

of

Chemistry and Biochemistry

Presented in Partial Fulfilment of the Requirements
for the Degree of Master of Science at
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Montreal, Quebec, Canada

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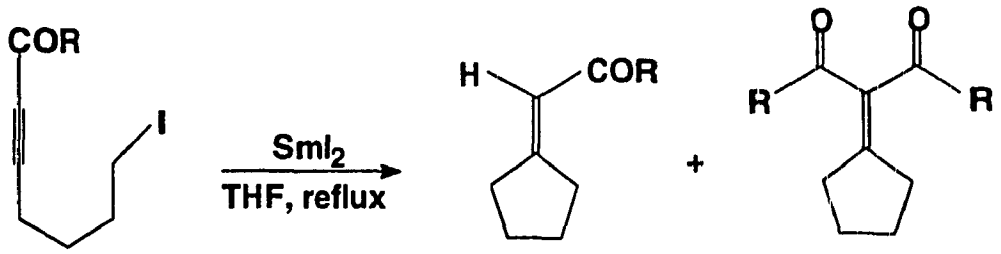
ABSTRACT

Cyclization Reactions Induced by Samarium(II) Iodide

Zhihong Zhou

This thesis describes studies on SmI_2 mediated cyclizations to prepare cyclopentane analogs (schemes A and B). The alkynyl iodide **30** was prepared and its reactions with SmI_2 were studied (scheme A). An organosamarium species is involved as an intermediate in this reductive cyclization. The reaction of SmI_2 with **23** is also presented.

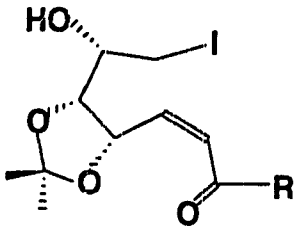
Scheme A

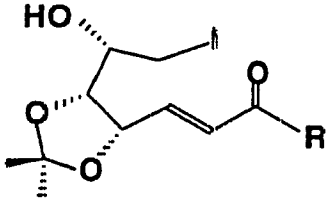


R = NEt_2, 30, **31,** **35**

R = OMe, 23

The carbohydrate derived substrates **44-46a**, **44-46b**, **48** and **49** were prepared. The reactions of SmI_2 with **48** and **49** to give highly functionalized cyclopentane derivatives are reported (scheme B). The cyclizations proceed in good yield and with good diastereoselectivity. The reactions of SmI_2 with **45a,46a** and **45b** are also presented.

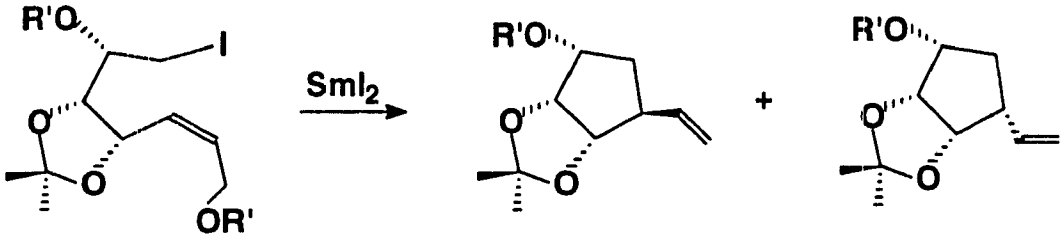




R = O*t*-Bu,	44a
R = NMe_2,	45a
R = NEt_2,	46a

R = O*t*-Bu,	44b
R = NMe_2,	45b
R = NEt_2,	46b

Scheme B



R' = H,	48,	55,	56
R' = Ac,	49,	58,	59

To my Parents

To my husband and son

ACKNOWLEGEMENTS

I wish to express my sincere gratitude to my research supervisor, Dr. Sharon M. Bennett, for her precious guidance and encouragement throughout the course of this research and in the preparation of this thesis. This has been a valuable and memorable experience for me.

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CHAPTER 3

LIST OF ABBREVIATIONS

Groups, reagents and solvents

Ac	Acetyl
Ac_2O	Anhydrous acetic anhydride
AIBN	*azo-bis*-Isobutyronitrile
Bu	Butyl
CH_2Cl_2	Dichloromethane
DHP	Dihydropyran
DIBAL-H	Diisobutylaluminum hydride
DMAP	4-Dimethylaminopyridine
DMPU	1,3-Dimethyl-3,4,5,6,-tetrahydro-2(*1H*)-pyrimidinone
Et_3N	Triethylamine
Et_2O	Diethyl ether
EtOD	Ethyl alcohol-*d*
HMPA	Hexamethylphosphoric triamide
LDA	Lithium diisopropylamine
Ms	Methanesulfonyl
NIS	*N*-Iodosuccinimide
Ph_3P	Triphenylphosphine
Ph_3PO	Triphenylphosphine oxide
Ph	Phenyl
PTSA	*p*-Toluenesulfonic acid
TBS	*tert*-butyldimethylsilyl
THF	Tetrahydrofuran
THP	Tetrahydropyran-2-yl
TMS	Trimethylsilyl

Techniques

APT	Attached proton test
COSY	Homonuclear correlated spectroscopy
^{13}C NMR	Carbon 13 nuclear magnetic resonances
DEPT	Distortionless enhancement by polarization transfer
FTIR	Fourier transfer infared resonances
GC	Gas chromatography
HMBC	Heteronuclear multiple bond connectivity
HMQC	Heteronuclear multiple-quantum coherence
^{1}H NMR	Proton nuclear magnetic resonances
HOM2DJ	Homo *J*-resolved ^{1}H-^{1}H spectroscopy
MS	Mass spectroscopy
nOe	Nuclear Overhauser enhancement
TLC	Thin layer chromatography

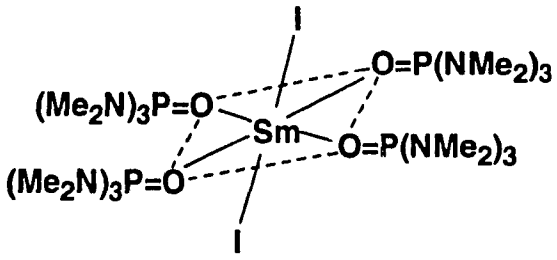
Chapter 1. General Introduction

Samarium is a member of the lanthanide (Ln) elements which were discovered between 1850 (Ce) and 1945 (Pm).[1] The main uses of lanthanides are in ceramics and glasses (additives and dyes), metallurgy, electronics (magnetic or luminescence materials) and in the petrochemical industry (catalytic cracking or oxidation catalyzed by lanthanide oxides).[1] The electron configuration of lanthanides are [Xe] $4f^n\ 5d^{n'}6s^2$ (n = 1,2,3,...14; n' = 0,1) and their main oxidation state is +3.[1] Lanthanide compounds having a +4 oxidation state (*i.e.* CeO_2), are powerful oxidants. The Ln(II) compounds are powerful one-electron reducing reagents; these include samarium(II) ($Sm^{2+} = 4f^6$), europium(II) ($Eu^{2+} = 4f^7$) and ytterbium(II) ($Yb^{2+} = 4f^{14}$) compounds which have the 4f electron configuration of near half shell, half shell and near full shell.[1]

Like other lanthanide ions, samarium ions are flexible in their coordination number.[1] This is especially true with oxygen containing ligands. The studies of the complex of SmI_3 with HMPA indicate that two types of the crystals (cubes and irregular prisms) can exist.[2] The analysis of the cubes by X-ray diffraction indicated that the central samarium ion is hepta-coordinated by two HMPA ligands and five H_2O molecules to form a pentagonal bipyramid stucture. The three iodide anions are not directly bonded to Sm(III). The analysis of the irregular prismatic crystal showed that the central Sm(III) ion is also hepta-coordinated by three HMPA ligands and four H_2O molecules to form a distorted pentagonal bipyramid stucture. The three iodide anions are also not directly bonded to Sm(III).

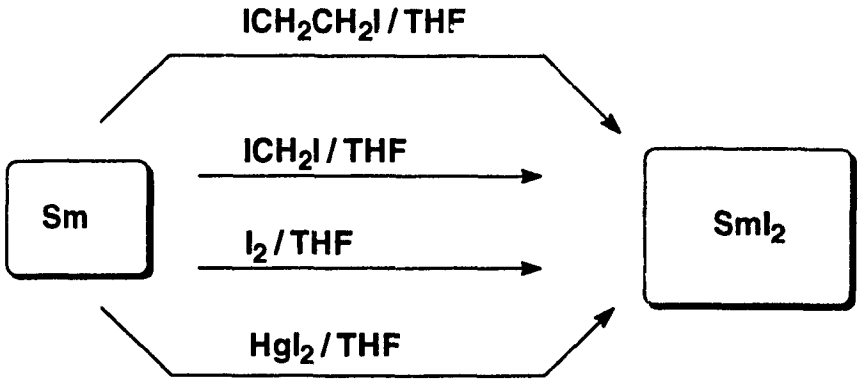
The complex of samarium (II) iodide with hexamethylphosphoramide (HMPA) was isolated as black-purple crystals $[SmI_2(HMPA)_4]$.[3] The stuctural characterization was carried out by X-ray analysis . The Sm(II) ion sits in the centre and is bonded by two iodide anions and four HMPA ligands in a distorted octahedron. The central Sm(II) ion and the oxygen atoms of the four HMPA ligands are exactly coplanar and the iodide anions are mutually trans (Scheme 1.1).

Scheme 1.1 The structure of the $[SmI_2(HMPA)_4]$ complex[3]



Samarium(II) iodide can be prepared in tetrahydrofuran (THF) as an approximately 0.1 M solution from samarium metal through its oxidation with 1,2-diiodoethane[4a], diiodomethane,[11] molecular iodine[4b] or mercuric iodide[4c] (Scheme 1.2).

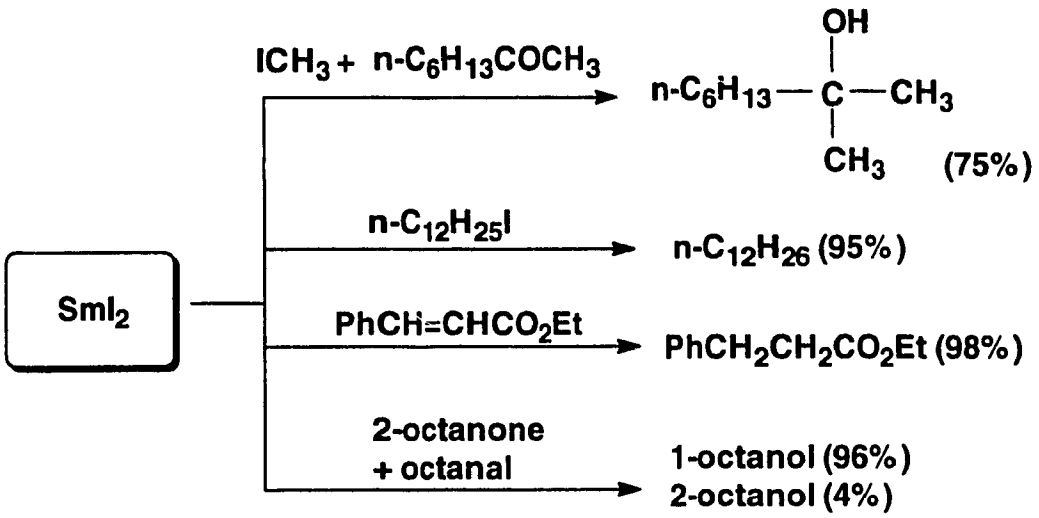
Scheme 1. 2. The preparations of SmI_2



Commercial solutions of samarium(II) iodide are also available from some chemical companies; Aldrich sells a 0.1 M solution of SmI_2 in THF. Solutions of samarium(II) iodide in THF are stable for extended periods (under air and moisture exclusion conditions). Solutions of samarium(II) iodide in THF are dark blue and addition of HMPA results in a colour change to dark purple. Mixtures of SmI_2 in THF-DMPU are also purple but are heterogeneous. Once the Sm(II) has been oxidized, a colour change from dark blue or purple to yellow, is observed and Sm(III) salts may precipitate out of solution. Therefore the progress of the reduction of an organic substrate by SmI_2 can be monitored by color change. The reduction potential of Sm^{+2}/Sm^{+3} is -1.55 V in water but is higher in THF[5]. The addition of certain co-solvents (such as HMPA, DMPU, H_2O or MeOH) is known to change the reactivity of the Sm(II) species. These molecules may themselves complex with the samarium ion and this results in a change of the reduction potential of Sm^{+2}/Sm^{+3} in these solvent systems. Additionally H_2O and MeOH also play a role as proton sources in the reaction mixture.[5]

H. B. Kagan and co-workers introduced SmI_2 as a synthetic reagent in 1977.[6] A more detailed follow up study was published in 1980.[4a] The reactivity of this powerful one-electron reducing agent towards a variety of functional groups was tested in their research and some of the results are depicted in Scheme 1.3.[4a] Some examples included: (1) Grignard-type reactions between ketones and saturated organic halides; (2) The reduction of aliphatic halides and tosylates to the corresponding alkanes; (3) The reduction of highly conjugated α,β-unsaturated esters to the corresponding saturated esters; (4) The selective reduction of aliphatic aldehydes to primary alcohols even in the presence of aliphatic ketones.

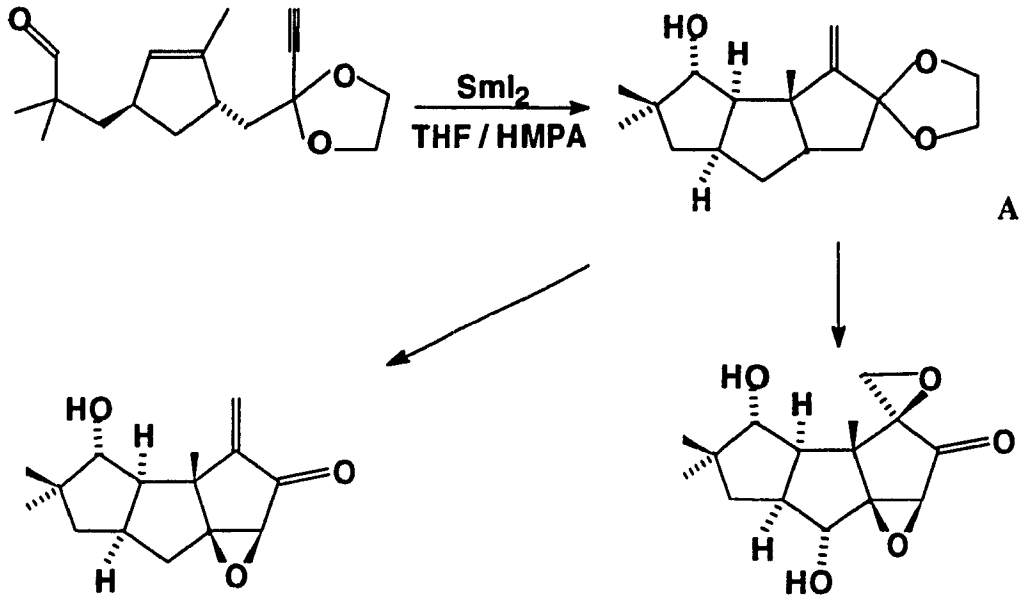
Scheme 1. 3. Some examples of SmI_2 mediated reacitons reported by Girard, Namy and Kagan in 1980[4a]



Since Kagan's first reports, interest in the synthetic applications of samarium(II) iodide has grown exponentially. Several review papers have been published.[1,5,7] Some examples will be discussed in the following paragraphs.

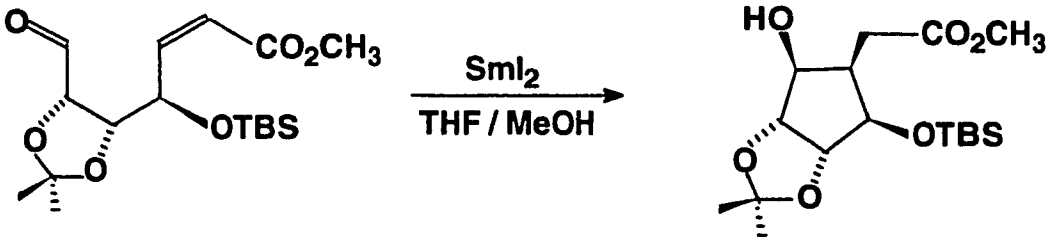
SmI_2 has been used to carry out synthetic transformations involving radical and/or organosamarium intermediates.[1,5,7] It had been used to carry out fairly simple transformnations and to prepared cyclic stuctures. An elegant example, which involved carbocyclization reactions was reported by D. P. Curran and co-workers.[8] They used SmI_2 to quickly construct a tricyclic system by tandem radical cyclizations. They successfully obtained the oxygenated triquinane ring system with a high degree of stereoselectivity (Scheme 1.4). Compound A (Scheme 1. 4) is an important precursor to the natural polycyclic compounds hypnophilin and coriolin.

Scheme 1. 4. The SmI_2 tandem cyclization reported by Curran's group[8]



E. J. Enholm's group has used SmI_2 in reactions involving carbohydrate derivatives and have obtained highly functionalized and densely oxygenated cyclic compounds (see Scheme 1.5).[9]

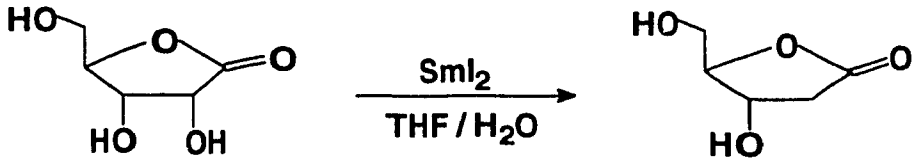
Scheme 1. 5. The reaction of SmI_2 with a carbohydrate derivative reported by Enholm's group[9]



The reactions described by Scheme 1.4 and 1.5 involve reduction of an aldehyde to a ketyl radical which can then add onto a double bouble in a radical fashion.

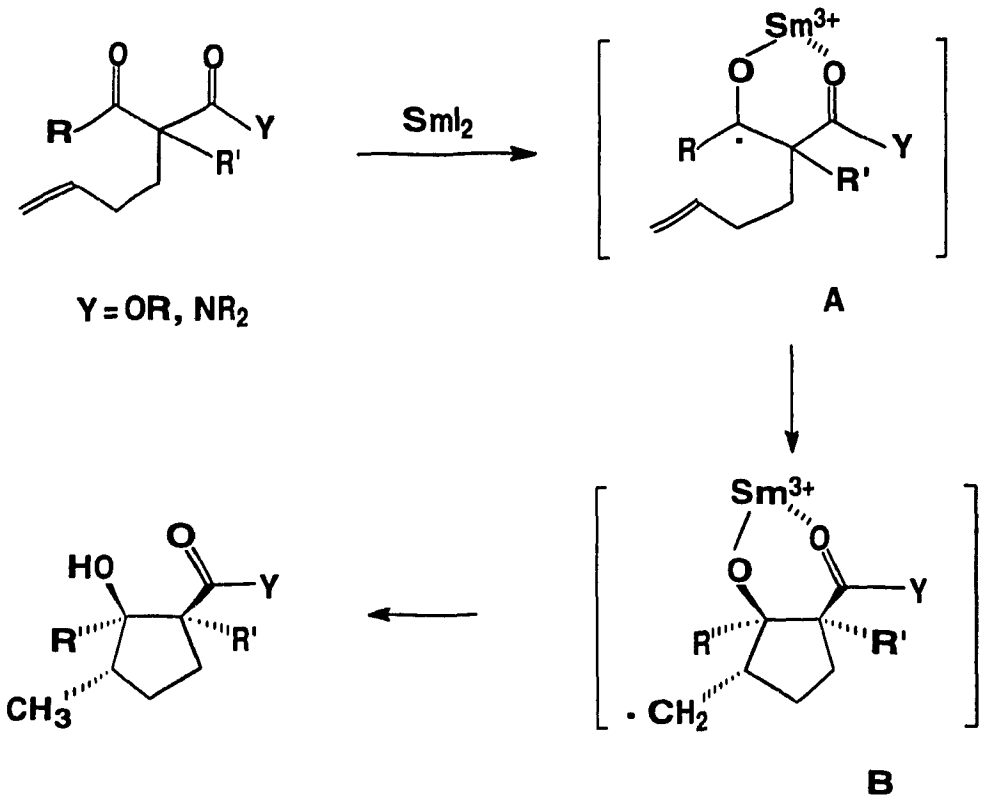
Among the numerous transformations mediated by SmI_2, deoxygenation α to carbonyl is particularly interesting. One example is the synthesis of 2-deoxy-D-ribonolactones and their derivatives from the corresponding lactones. This work was reported by S. Hanessian and C. Girard (see Scheme 1.6).[10]

Scheme 1. 6. The deoxygenation of a ribonolactone by SmI_2 reported by Hanessian's group[10]



Samarium (II) and samarium (III) are oxophilic and are Lewis acids. These properties are very interesting to organic chemists. They allow us to essentially complex the metal ion with certain functional groups and lock a molecule or a reaction intermediate in a particular conformation (see Scheme 1.7 for an example). G. A. Molander and his co-workers successfully use this strategy to carry out a number of synthetic transformations with a high degree of stereoselectivity (for an example see Scheme 1.7).[11]

Scheme 1.7. The reaction of SmI_2 with alkenyl β-keto esters or amides reported by Molander'group[11]



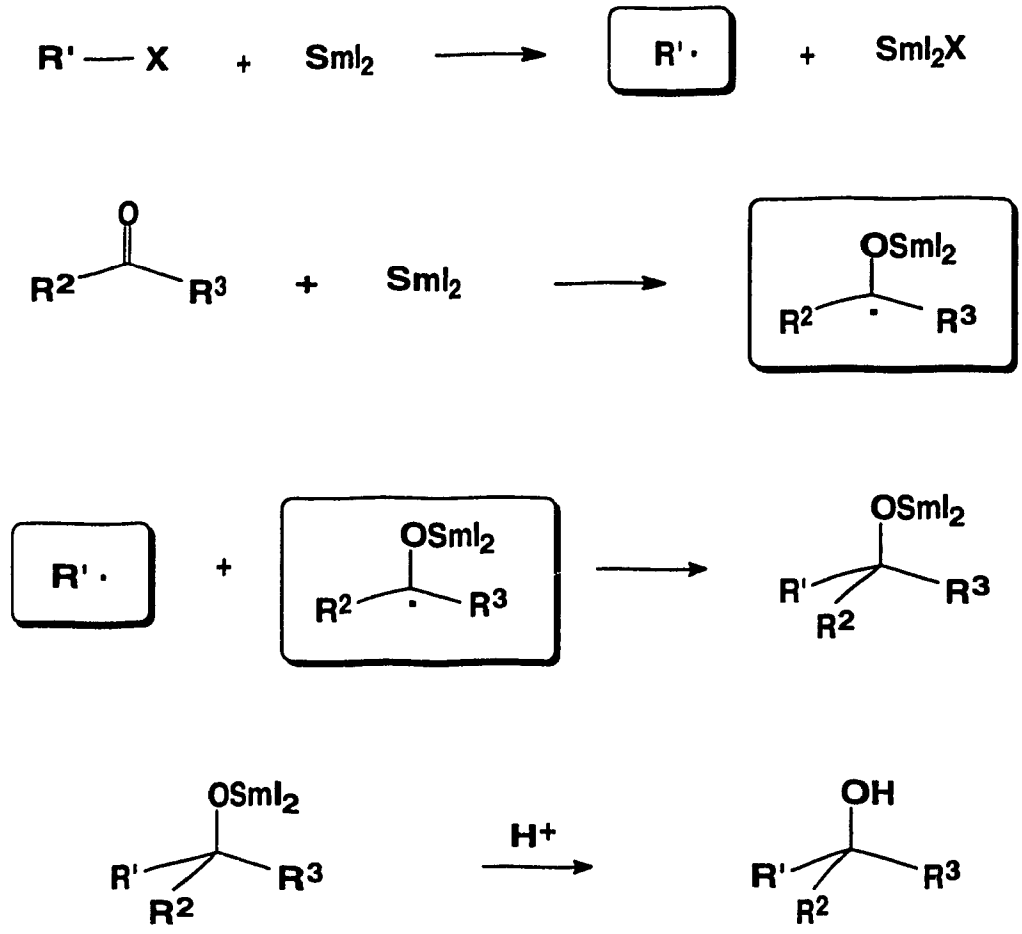
The mechanism of the intramolecular ketone-olefin reductive coupling reaction, shown in Scheme 1.7, involves formation of chelated ketyl radical intermediate **A** which undergoes 5-exo cyclization to form radical **B**. The species **B** is reduced by a second equivalent of SmI_2 and then transformed to the final product. The chelation of the samarium ion (+2 / +3) explains the formation of a cyclopentane product in which the hydroxyl and the ester or amide functional groups are *cis* to one another.

It has been found that SmI_2 mediated reactions may proceed through either radical or anionic chemistry.[5] The reaction pathways depend on several conditions such as: substrate identity, reaction conditions, and even on the order of addition of chemicals.

Kagan and co-workers divided the reactions of organic substrates with SmI_2 into three major categories:[5] (a) *Functional group reduction*. These reactions include reductions of halides, sulfoxides, epoxides and carbonyl compounds etc. (Scheme 1.3); (b) *Reductive coupling of two bonds*. These reactions include several types of coupling reactions (for an example see Scheme 1.5); (c) *Reductive coupling of halides with a π- bond.* The π-bond here refered to by Kagan is a carbonyl bond (for an example see Scheme 1.3). We are particularly interested in this third class of reaction but in a broader sense. The samarium Barbier reactions and the samarium Grignard reactions fall into this third class.[12] In both cases an aldehyde or a ketone reacts with an alkyl halide in the presence of SmI_2 to give the corresponding alcohol.

Some earlier work from Kagan's group suggested that the samarium Barbier reactions proceed via a ketyl radical and alkyl radical coupling pathway.[11] The reaction mechanism is outlined in Scheme 1.8 and involved: (1) simultaneous reduction of alkyl halides and ketones to the corresponding alkyl radicals and ketyl radicals; (2) coupling of alkyl radicals and ketyl radicals to give the samarium alkoxide and protonation to give the alcohol.

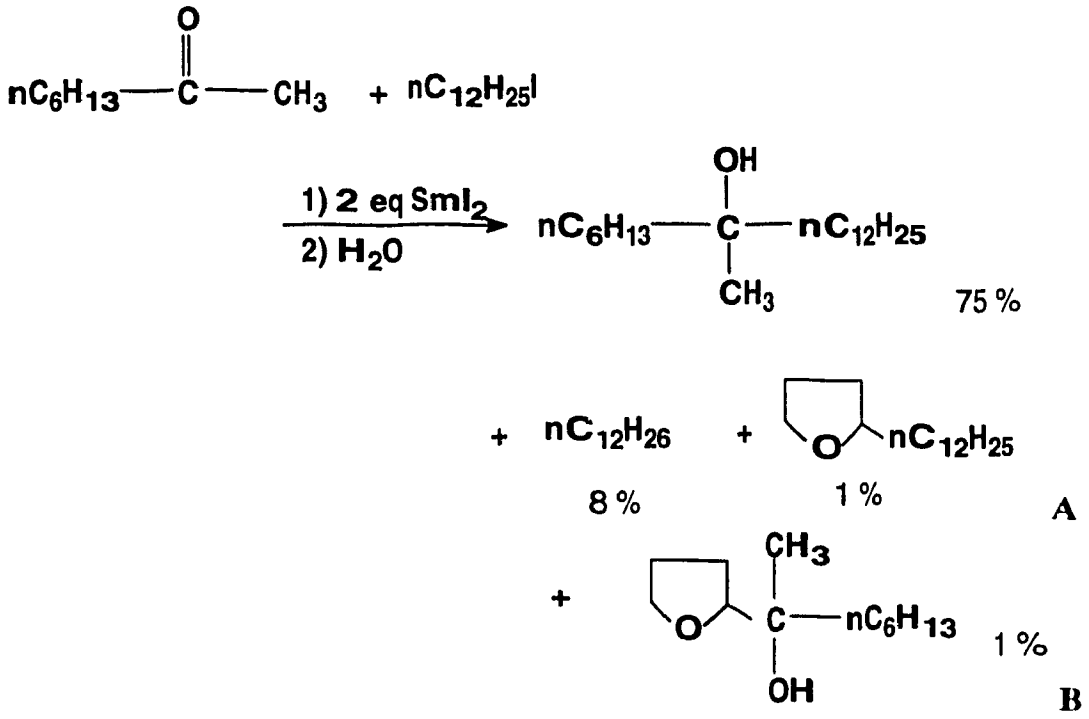
Scheme 1. 8. The mechanism of ketyl-radical coupling[5]



X = halides

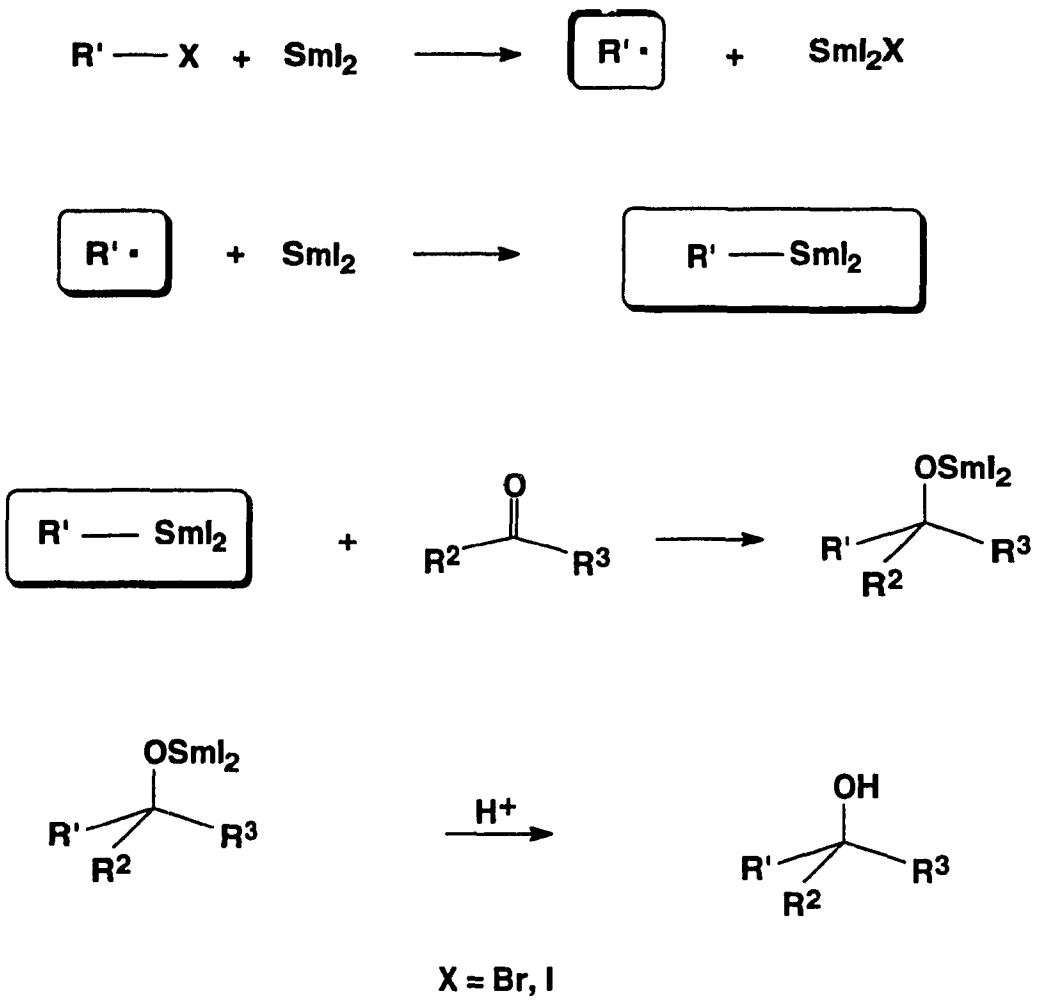
The evidence for alkyl radical intermediates in this coupling reaction comes from the studies carried out in Kagan's group describing the isolation of THF substituted compounds **A** and **B** (see Scheme 1.9).[13] Some of the alkyl radicals or the ketyl radicals abstract hydrogen atoms from the solvent (THF) to give THF radicals. These THF radicals then coupled with other alkyl or ketyl radicals to form compounds **A** and **B** (in Scheme 1.9).

Scheme 1. 9. The reaction of SmI_2 with 2-octanone and 1-iodododecane reported by Kagan's group[13]



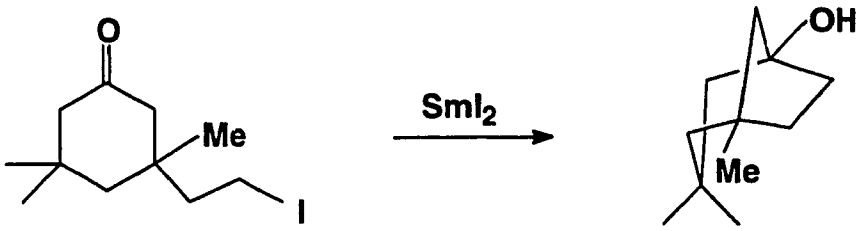
Several years later, Curran's group further studied the reaction mechanism of these reactions. They carried out several types of samarium Barbier reactions in THF or THF / HMPA and used *deuterium trapping experiments* to trap organosamarium intermediates with MeOD *in situ*.[14] They concluded that samarium Barbier reactions of primary or secondary halides (RI, RBr) with carbonyl compounds in THF or THF / HMPA proceed by an organometallic coupling mechanism. The general mechanism is outlined in Scheme 1.10.[5] These involved: (1) SmI_2 reduction of alkyl halides to alkyl radicals; (2) reduction of alkyl radicals by a second equivalent of SmI_2 to give alkyl organosamarium reagents; (3) reactions of alkyl samarium species with aldehydes or ketones in a standard anionic fashion and (4) protonation to give the corresponding alcohols.

Scheme 1. 10. The mechanism of organometallic coupling[5]



Molander's group carried out a number of intramolecular reductive coupling reactions. One example of the SmI_2 promoted intramolecular samarium Barbier reaction is shown in Scheme 1.11.[15] An organosamarium intermediate is involved in this reaction.

Scheme 1. 11. Intramolecular samarium Barbier reaction involving a substituted cycloalkanonyl iodide reported by Molander's group[15]



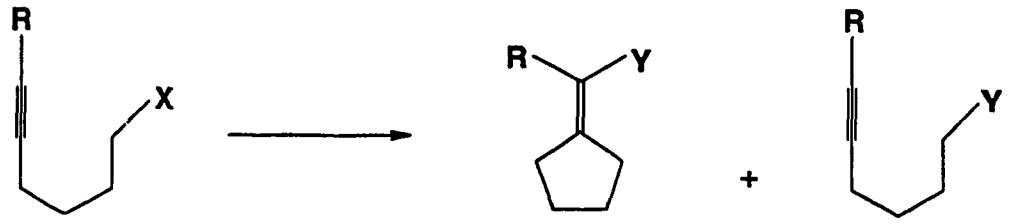
In the following sections our work involving reactions of samarium(II) iodide with some alkynyl halides (chapter 2) and with some carbohydrate derived halides (chapter 3) is described. In both cases the reactions with SmI_2 involve the *intramolecular* reactions of alkyl halides with *carbon-carbon* (and *not* carbon-oxygen) π-bonds.

Chapter 2. Reactions of Alkynyl Halides with Samarium(II) Iodide

Introduction

As discussed in chapter 1, samarium(II) iodide (SmI_2) can reduce an alkyl halide to the corresponding alkyl radical species. This intermediate may then react in a typical radical fashion. Alternatively, the radical may be reduced by a second equivalent of SmI_2 to give an organosamarium reagent which can then undergo anionic chemistry.

Scheme 2. 1. SmI_2 induced cyclizations of some alkynyl halides



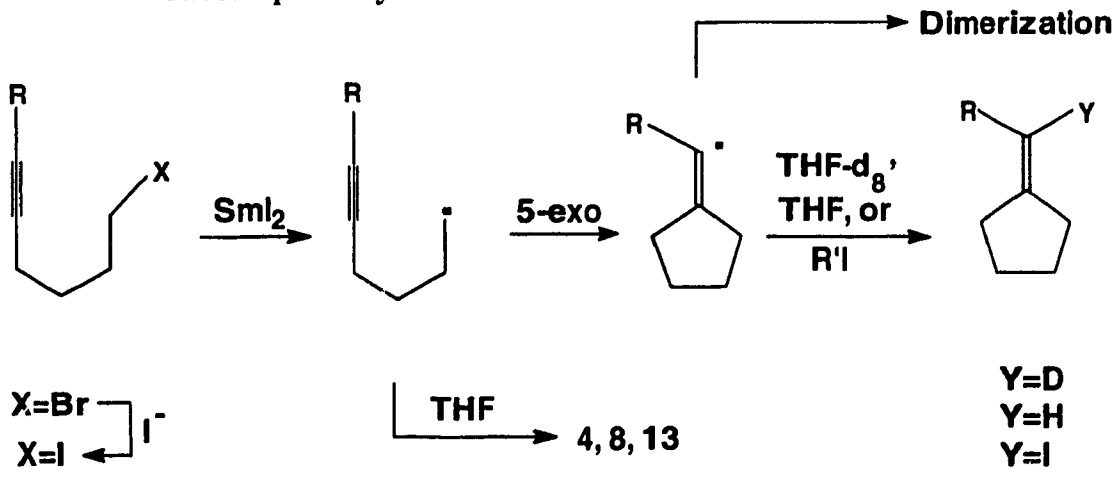
1	**R = Ph**	**X = Br**	**3**	**R = Ph**	**Y = H**	**4**	**R = Ph**	**Y = H**
2	**R = Ph**	**X = I**						
5	**R = nBu**	**X = Br**	**6**	**R = nBu**	**Y = H**	**8**	**R = nBu**	**Y = H**
			7	**R = nBu**	**Y = I**	**9**	**R = nBu**	**Y = I**
10	**R = TMS**	**X = Br**	**11**	**R = TMS**	**Y = H**	**13**	**R = TMS**	**Y = H**
			12	**R = TMS**	**Y = I**	**14**	**R = TMS**	**Y = I**

Mr. Denis Larouche, a fomer student in our laboratory, and Dr. Sharon Bennett[1] reported that alkynyl halides **1**, **2**, **5** and **10** react with SmI_2 in refluxing tetrahydrofuran (THF) to give cyclized products **3**, **6** and **11** in good yield (*i.e.* from 67% to 83%, see Scheme

2.1)[16]. Under these conditions, the simple reduction products **4**, **8** and **13** account for only a minor portion of the reaction products. In general, the use of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)pyrimidinone (DMPU) as a cosolvent in refluxing THF improved the efficiency of the cyclization reactions. It also catalyzed the transformation of the unsaturated bromide substrates **1**, **5** and **10** to the corresponding iodides **2**, **9** and **14**.[16]

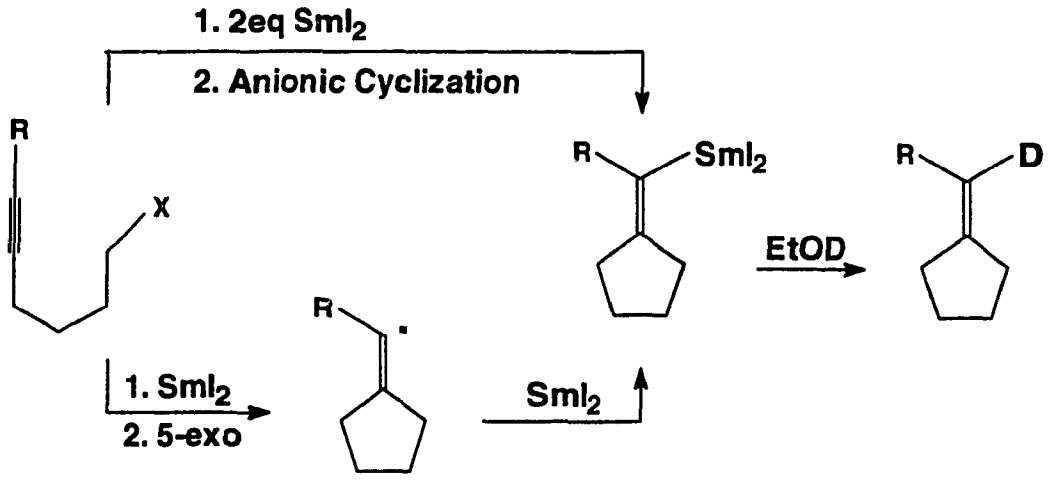
Later Larouche carried out a study with substrate **9** and found that *significant* amounts of iodine-atom tranfer cyclization product **7** were present in some reaction mixtures.[18] The iodine-atom transfer cyclization product **12** was also isolated from a room temperature reaction mixture with substrate **10**.[16] Compounds **7** and **12** can be transformed to **6** and **11** by reduction with SmI_2 under reflux conditions. The formation of such iodine-atom transfer cyclizaiton products indicates that vinyl radicals are involved as intermediates in the reductive cyclization process (see Scheme 2.2).[17] Dr. Bennett and Mr. Larouche did not have any such evidence for the presence of vinyl radical intermediates in those reaction involving substracts **1** and **2** however and so mechanistic studies were carried out in an attempt to trap the reactive intermediates.

Scheme 2. 2. Reactions of some alkynyl halides with SmI_2 in THF/DMPU via a radical pathway



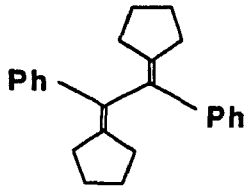
By using *in situ* quenching experiments with EtOD as a cosolvent or THF-d_8 as a solvent they elucidated the reaction mechanism for these reductive cyclizations.[17] They found that when compound **2** was allowed to react with SmI_2 in a THF/EtOD a 9% deuterium incorporation at the vinylic position of **3** was observed. When they carried out the SmI_2 reaction in THF/DMPU/EtOD with compound **2**, a 18% deuterium incorporation into **3** was observed. Deuterium incorporation at the vinylic position of **3**, under these conditions, would be consistent with an organosamarium reaction intermediate (see Scheme 2.3).

Scheme 2. 3. Reactions of some alkynyl halides with SmI_2 via an anionic pathway



Compound **2** was also allowed to react with an excess of SmI_2 in THF-d_8 under reflux conditions.[17] Four compounds were isolated from the reaction mixture: starting material **2** (21%), the expected cyclization product **3** (40 %; 32 % deuterium incorporation), a small amount of the simple reduction product **4** (5 %), and the product of vinyl radical dimerization (**26**, 14%). The formation of **26** (14 %), together with a 32 % level of

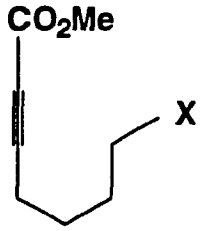
deuterium incorporation in **3**, is indicative of the presence of cyclized vinyl radicals as reaction intermediates (Scheme 2.2).



26

The results of the deuterium incorporation experiments, together with the observation of the formation of iodine atom transfer cyclization products, in some cases, suggest that the reductive cyclization reactions, with **1**, **2**, **5**, **9** and **10**, proceed primarily via a radical pathway (Scheme 2.2). An alternative minor anionic pathway may also operating (Scheme 3.3).

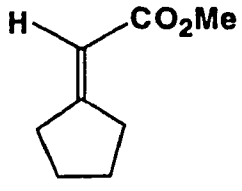
The study involving alkynyl halides was expanded to include methyl 7-bromohept-2-enoate (**19**), methyl 7-iodohept-2-enoate (**23**) and *N,N*-diethyl-7-iodohept-2-enamide; the reactions of these compounds with SmI_2 *differ* from the pattern seen with compounds **1**, **2**, **5**, **9** and **10**. [17]



X = Br **19**

X = H **21**

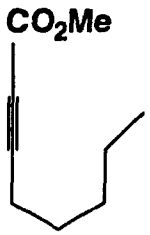
X = I **23**



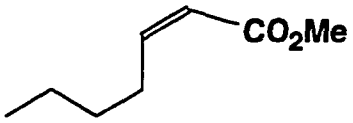
20

Mr. Larouche had found that treatment of methyl 7-bromohept-2-ynoate (**19**) with SmI_2 led to degradation of the starting material.[18] In fact, Dr. Bennett found that exposure of

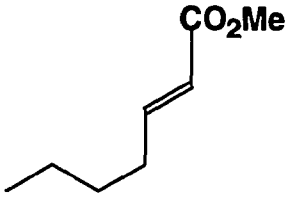
21 with 3 eq of SmI_2 in THF at room temperature for 24 h leads to degradation of the starting material.[17] This degradation is minimized if milder conditions are used (i. e. -78 C, 4 h; 0°C, 2 h) and if a proton source (MeOH) is added to the mixture. NMR, GC, and GC-MS analysis of the reaction products indicated the presence of three compounds: recovered starting material **21** (66%), and (*Z*)- and (*E*)- α,β-unsaturated ester **22a** (11%) and **22b** (12%).



21



22a



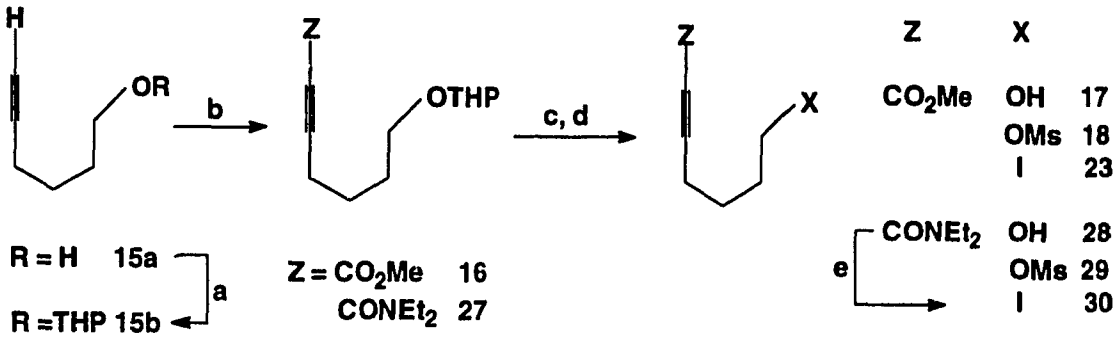
22b

The details of the reactions of methyl 7-iodohept-2-ynoate (**23**) and *N*, *N*-diethyl-7-iodohept-2-ynamide with SmI_2 will be described in the following paragraphs.

2. 2. Synthesis of Starting Material: Methyl 7-iodohept-2-ynoate (23) and *N*, *N*-diethyl 7-iodohept-2-ynamide (30)

Compound **23** is a known compound and was prepared by Dr. Bennett following a literature procedure.[17,19] We found no reports in the literature of compound **30**. We prepared this compound from commercially available hex-5-yn-1-ol by a modified literature procedure (Scheme 2.4).[17]

Scheme 2. 4. Synthesis of substrates 23 and 30



a) DHP, pTSA·H_2O, CH_2Cl_2, rt; b) (1) nBuLi,THF and (2) $ClCO_2Me$ to give **16** (83% overall from **15a**) or (3) LDA, THF and (4) $ClCONEt_2$ to give **27** (63% overall from **15a**); c) MeOH, pTSA·H_2O to give **17** (90%) and **28** (97%); (d) (1) MsCl, Et_3N, CH_2Cl_2 to give **18** (97%) and **29** [95%] and (2) NaI, acetone to give **23** [69% (89%)] and **30** [95% (97%)]; e) Ph_3P, imidazole, I_2, CH_2Cl_2, 94%.[20]

The hydroxyl group of commercially available hex-5-yn-1-ol (**15a**) was protected as a THP ether. Compound **15b** was transformed to *N*, *N*-diethyl-7-(tetrahydro-pyranyloxy)hept-2-ynamide (**27**) by treatment with LDA and *N*, *N*-diethyl carbamyl chloride (overall 63% yield from **15a**). Deprotection of compound **27** with MeOH and a catalytic amount of *p*-toluenesulphonic acid monohydrate gave *N*, *N*-diethyl-7-hydroxyhept-2-ynamide (**28**) in excellent yield (97%). The compound **28** was mesylated

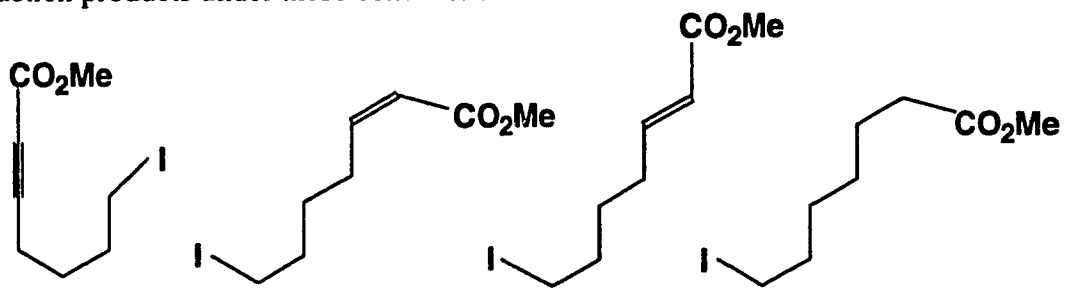
to give **29** (95%) which reacts with sodium iodide to give *N*, *N*-diethyl-7-iodohept-2-ynamide (**30**) [95% (97% when corrected for the recovered unreacted starting material)]. Alternatively, compound **30** can be prepared directly from **28** by the action of triphenylphosphine, imidazole and iodine (94%).

2. 3. Reactions of Alkynyl Halides with Samarium (II) Iodide

2. 3. 1. Reaction of Methyl 7-iodohept-2-enoate (23) with Samarium(II) Iodide

As we discussed in the introduction of this chapter, Mr. Larouche had found that treatment of methyl 7-bromohept-2-ynoate **19** with SmI_2 led to degradation of the starting material and Dr. Bennett found that the degradation of simple alkynyl ester **21** is minimized if milder reaction conditions are used (1.5 eq of SmI_2/THF/MeOH, -78° C, 4 h; 0°C, 2 h).

We wondered if the use of the *more reactive* iodide substrate **23** would allow formation of the cyclized reduction product. In fact, the reaction of **23** with SmI_2 under our mild reaction conditions did not result in the formation of a cyclizaton product. We isolated, instead, compounds **24a**, **24b**, and **25** [21] together with some recovered starting material from our reaction mixture. We were unable to find any evidence for carbon-iodine bond reduction products under these conditions.

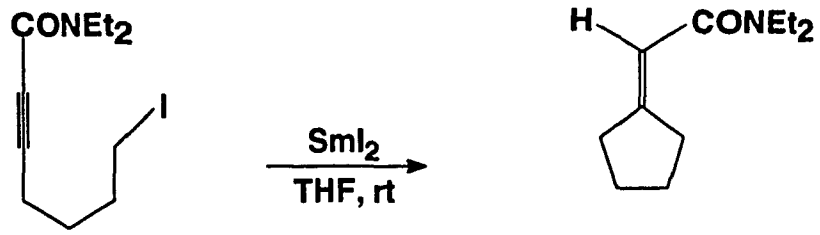


23 **24a** **24b** **25**

2. 3. 2. Reactions of *N*, *N*-diethyl-7-iodohept-2-ynamide (30) with Samarium (II) Iodide

Our attempts to convert iodo-amide **30** to compound **31** led to some interesting results (see Scheme 2.5). Reaction mixtures were often complex and the separation and purification of the various components was sometimes difficult to achieve. We have, however, been able to define conditions under which **30** can be efficiently and cleanly converted to **31**.

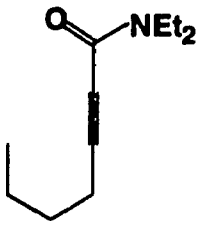
Scheme 2. 5. Reductive cyclization of 30 under SmI_2/THF/rt conditions



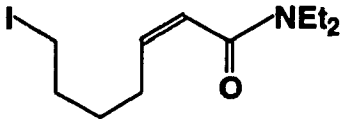
30 **31**

Reduction of **30** with SmI_2 (5 eq, THF, 44h; [RI] = 0.015M) at room temperature gave the cyclized product **31** in 41% yield after purification; unreacted starting material was also recovered (44%). We saw no evidence of the simple reduction product **32**[22] (as determined by GC, TLC and ^1H NMR) under these conditions. We hoped to improve the yield of **31** and considered a number of possible modifications to our reaction conditions. Some of our early attempts to improve the efficiency of this transformation only served to complicate our reaction mixtures. For example, when SmI_2 was added to a THF/MeOH solution of **30** at room temperature minor reaction products **32**, **37a**, **37b** and **38**[21], in addition to compound **31**, were isolated from our reaction mixtures (similar results were obtained when EtOD was used as a co-solvent under the same reaction conditions).

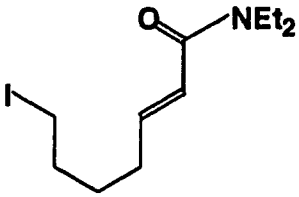
Before implementing other changes, we first needed to ensure that these modifications did not also result in the undesired reduction of the triple bond or amide functional groups.



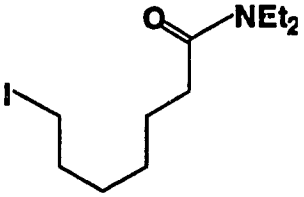
32



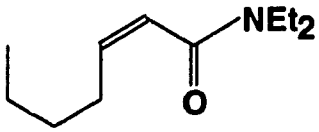
37a



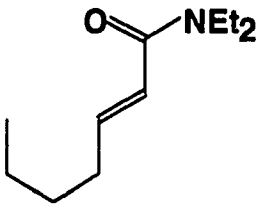
37b



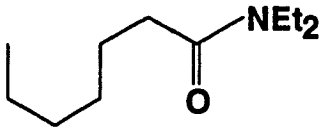
38



33a



33b

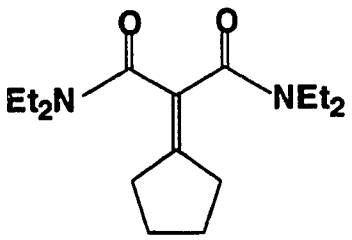


34

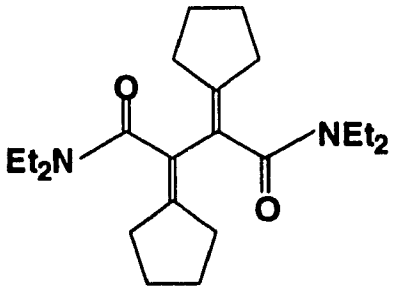
We investigated the reaction of **32** itself with SmI_2 so to define "non-destructive conditions" which could then be applied to our actual substrate **30**. The crude reaction mixtures were analyzed by TLC, GC and / or GC-MS and by ^1H NMR so as to determine the extent of any reaction. Compound **32** is less reactive than propargyl ester **21** toward SmI_2 reduction but much more reactive than either **4**, **8**, or **13**.[23] Propargyl amide **32** is inert to the usual room temperature conditions (3eq SmI_2/THF/48h) and is recovered in good yield (87%) from the reaction mixture. It is degraded when larger quantities of SmI_2 (8.5 eq, THF, 48h) are used or when HMPA is added as a cosolvent (5%) to the THF solution at either room temperature or 0° C. The material balance under these conditions was poor and we have not been able to isolate analytically pure samples of the reduction products; NMR and GC-MS analysis of the crude and partially purified reaction

mixtures indicate the presence of the *Z* and *E* α, β-unsaturated amides **33a** and **33b**, and of alkyl amide **34**.[21] Reduction of the triple bond of amide **32** under the SmI_2/THF/HMPA conditions is minimized or eliminated however if the quantity of SmI_2 used is lowered to 1.3 eq and if the reaction mixture is cooled to -78°C.

The addition of either DMPU or HMPA to the reaction mixtures of **30** and SmI_2 did not result in an increase in the yield of **31**. The yields of cyclized product were typically less than 30% and purification was complicated by the presence of a number of different side products in the reaction mixture. One of the side products was determined to be the bis amide **35**. GC-MS and high resolution MS analysis of a second side product was consistent with a dimeric species having a molecular formula of $C_{22}H_{36}O_2N_2$. ^1H and ^{13}C NMR data were consistent with the structure **36** but our assignment remains tentative due to our failure to obtain an analytically pure sample. In addition, analysis of the ^1H and ^{13}C spectra is complicated by the possibility of conformational isomers of **36**.



35



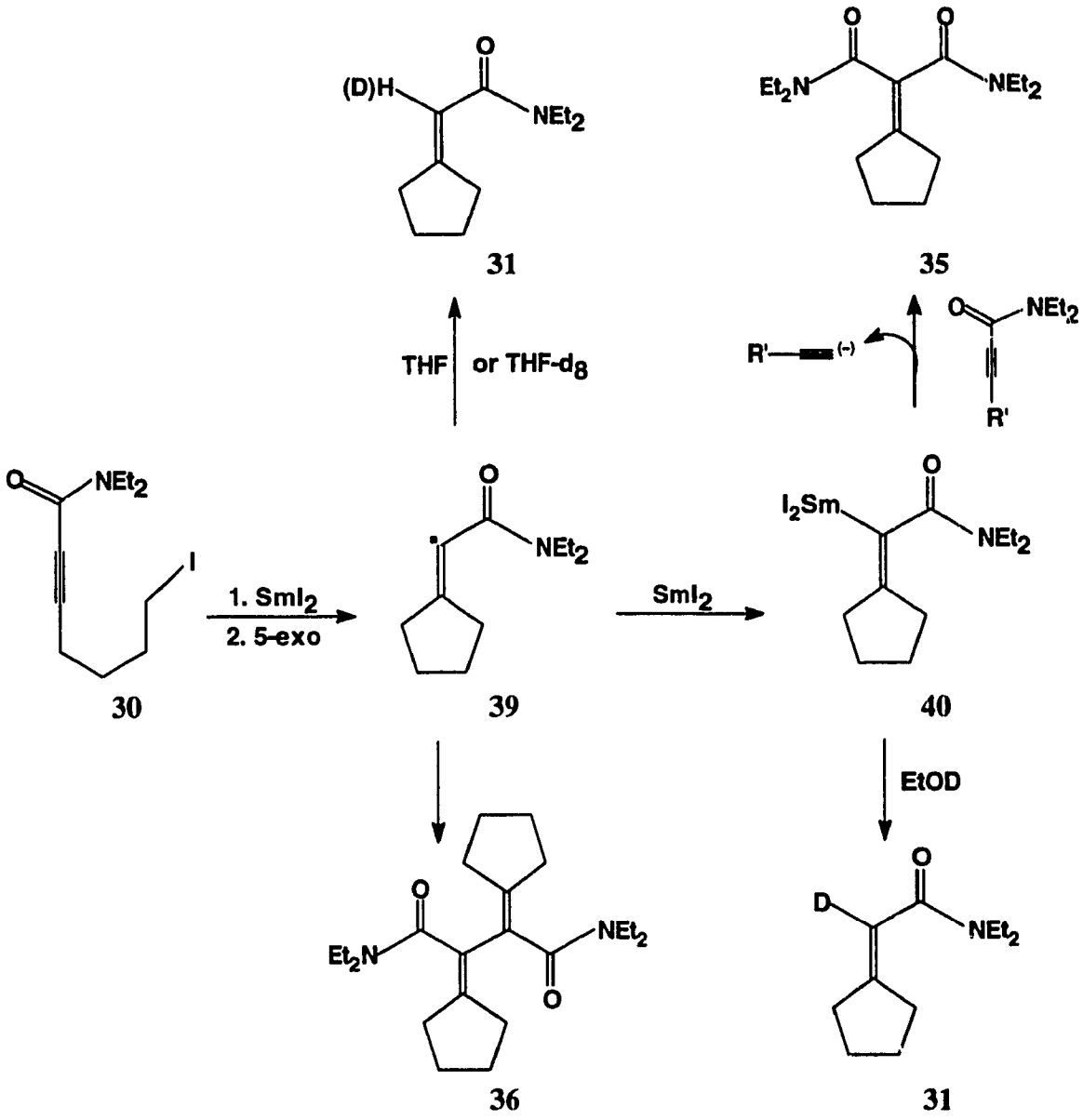
36

Our attempts to increase the yield of **31** by increasing the reaction temperature led to some interesting results. Under overnight reflux reaction conditions in THF all of our starting material reacts and we obtain a 25% yield of the cyclized mono-amide **31**. The reaction was quenched by addition of D_2O but we were unable to detect any deuterium incorporation at the vinylic position of **31**. In addition to **31**, we also isolated 19 % of

compound **35** from our reaction mixture. If the reaction is carried out in the presence of EtOD (under the same overnight reflux reaction conditions in THF) we are able to increase the yield of **31** to 88 % and avoid formation of **35**. This time we observe a *significant* amount of deuterium incorporation at the vinylic position i.e. 68% as determined by MS analysis. The complementary experiment was carried out with **30** and SmI_2 in THF-d_8 under reflux conditions. In this instance the level of deuterium incorporation in **31** is only 7%.

We have rationalized these results as follows (see Scheme 2.6): **30** is reduced by SmI_2 to give the corresponding alkyl radical which cyclizes in a 5-exo fashion to give the vinylic radical **39**. Radical **39** may then (1) abstract a hydrogen atom from THF to give non-deuterated **31** (or abstract a deuterium atom from THF-d_8 to give deuterated **31**); (2) couple with another molecule of **39** to form dimer **36**, or (3) be reduced by a second equivalent of SmI_2 to give vinyl organosamarium species **40**.[24] The organosamarium intermediate **40** reacts with EtOD to give deuterated **31** or may (under overnight reflux conditions), in the absence of EtOD, react with a molecule of propargyl amide to give **35** and an acetylide anion.

Scheme 2. 6. SmI_2 induced reductive cyclization of iodo-alkynyl amide 30



2. 4. Conclusions

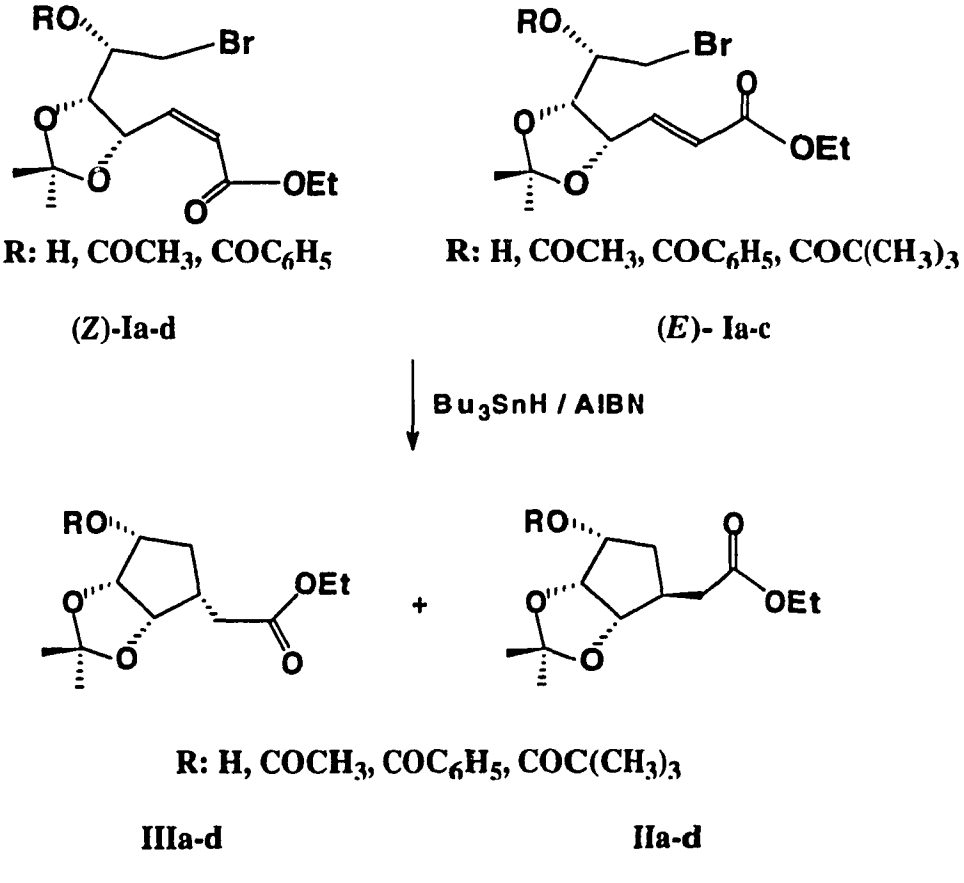
The choice of reaction conditions is essential for the clean and efficient conversion of iodo-amide substrate **30** to the corresponding cyclization product **31**. The transformation of **30** to **31** in refluxing THF appears to involve an unstable organosamarium species as a key intermediate; this conclusion is based on the isolation of bis amide **35** from certain reaction mixtures and on *in situ* trapping experiments with EtOD and THF-d_8. Methyl 7-iodohept-2-ynoate (**23**) is not an appropriate substrate for this cyclization methodology as it undergoes triple bond reduction faster than carbon-iodine bond reduction under our reaction conditions.

Chapter 3. Reactions of SmI_2 with Various Carbohydrate Derived Alkenyl Iodides

3. 1. Introduction

The use of carbohydrates as a starting material in organic synthesis can lead to the formation of highly oxygenated and optically active compounds. These type of products can be useful in the synthesis of complex natural products.[25]

Scheme 3.1. Reactions of carbohydrate derived compounds with Bu_3SnH/AIBN reported by Wilcox and Thomasco[26b]



Wilcox and Thomasco used carbohydrate derived compounds as starting materials to make carbocylic compounds.[26a-c] They used radical cyclization chemistry to transform compounds (*Z*)- **Ia-d** and (*E*)- **Ia-c** to compounds **IIa-d** and **IIIa-d** (Scheme 3.1).[26b] When they used the compound (*Z*)-**Ia** as a starting material they obtained two isomeric products **IIa** and **IIIa** (80% yield; ratio of **IIa** to **IIIa** is 6:1). If compound (*E*)-**Ia** was used as the starting material they isolated these same two diastereoisomers, **IIa** and **IIIa**, in a 2:1 ratio and in 80%. The ratio of **II** to **III** depended on the olefin geometry and on the nature of the protecting group on the C-1 hydroxyl. The (*Z*)- olefins consistently afforded greater stereocontrol when compared with the corresponding (*E*)- isomers (see Table 3.1).

Table 3.1. Results reported by Wilcox and Thomasco for the Reactions of (*Z*)- Ia d and (*E*)- Ia-c with Bu_3SnH/AIBN[26b]

entry	starting material	R	yield %	ratio (**II** / **III**)
1	(*Z*)-**Ia**	H	80	6 / 1
2	(*E*)-**Ia**	H	80	2 / 1
3	(*Z*)-**Ib**	$COCH_3$	80	5 / 1
4	(*E*)-**Ib**	$COCH_3$	82	1 / 1
5	(*Z*)-**Ic**	COC_6H_5	89	10 / 1
6	(*E*)-**Ic**	COC_6H_5	87	1 / 1.2
7	(*Z*)-**Id**	$COC(CH_3)_3$	87	11 / 1

We wondered if a similar type of carbocyclization could be mediated by SmI_2 and whether or not such a cyclization would be stereoselectively different from the Bu_3SnH/AIBN reactions.

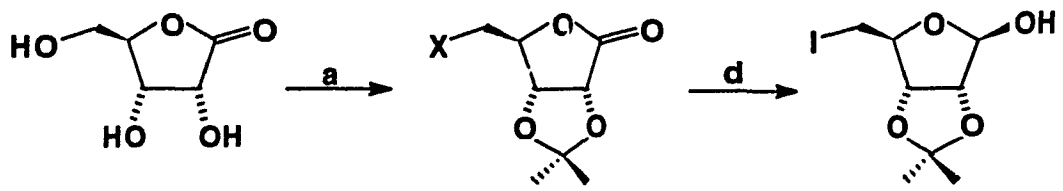
Only a few groups have extensively studied the synthetic reactions of carbohydrates, and their derivatives, with SmI_2. Several examples of such methodologies were described in chapter 1.[3a, b, c] These include, for example, deoxygenation of D-ribonolactone by Hanessian's group (see Scheme 1.6.)[10] and the cyclization of carbohydrate derivatives by Enholm's group (see Scheme 1.5.). [9]

3. 2. Synthesis of Carbohydrate Derived Starting Materials

3. 2. 1. Synthesis of 5-deoxy-5-iodo-2,3-*O*-(1-methylethylidene)-β-D-ribose (43)

5-Deoxy-5-iodo-2,3-*O*-(1-methylethylidene)-β-D-ribose (**43**) was made from commercially available D-ribonolactone **41a** in three steps (Scheme 3.2). D-Ribonolactone **41a** was protected by treatment with acetone and hydrochloric acid[27] at room temperature to afford the isopropylidene protected lactone **41b** in 82% yield. Alternatively, the protected lactone **41b** could be purchased from Pfanstiehl. Iodonation of **41b** was prepared using a modified literature procedure and was best accomplished by the action of imidazole, triphenylphosphine and iodine[20] to give **42**[29] in 74%. This same transformation could also be carried out using *N*-iodosuccinimide and triphenylphosphine[28] to give **42**[29] in 70% yield, however the purification step was more difficult. Iodo lactone **42** was then reduced by diisobutylalumimum hydride (DIBAL-H) to give **43** in 86%. Two possible ribose derivatives may be formed by the reduction of the lactone **42**. Under the conditions described in the experimental section, we obtained only one isomer from the reduction with DIBAL-H. The stereochemistry of D-iodo-ribose **43** was determined by ^1H NMR, COSY and 1 D ^1H-^1H decouping experiments (the ^1H NMR data are given in Table 3.2).

Scheme 3. 2. Synthesis of 5-deoxy-5-iodo-2,3-*O*-(1-methylethylidene)-β-D-ribose (43)



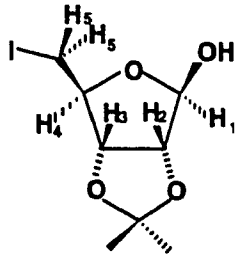
41a **b or c** → **X = OH 41b**, **X = I 42** **43**

(a) HCl, acetone to give **41b** (84%); (b) NIS, Ph_3P, CH_2Cl_2 to give **42** (69.9%); (c) I_2, Ph_3P, imidazole, CH_2Cl_2 to give (74%); (d) DIBAL-H, CH_2Cl_2 to give **43** (86%).

Table 3. 2. ^1H NMR data of 5-deoxy-5-iodo-2,3-*O*-(1-methylethylidene)-β-D-ribose (43)

δ	Multiplicity and J (Hz)		Integration	Assignment
5.57	d	$J_{1.OH}$ = 2.9, collapses to a s upon D_2O exchange	1 H	H-1
4.83	dd	$J_{3.4}$ = 0.9, $J_{3.2}$ = 5.8	1 H	H-3
4.68	d	$J_{2.3}$ = 5.8	1 H	H-2
4.46	ddd	$J_{4.3}$ = 1.0 $J_{4.5}$ = 6.2 $J_{4.5}$ = 9.7	1 H	H-4
3.24-3.38	m	overlapping multiplets[a]	2 H	H-5a and H-5b
2.91	d	$J_{OH.1}$ = 2.9, D_2O exchange-able	1 H	O-H
1.49	s		3 H	CH_3
1.35	s		3 H	CH_3

[a]The signal is very complex. A more detailed description of this signal is given in the experimental section.



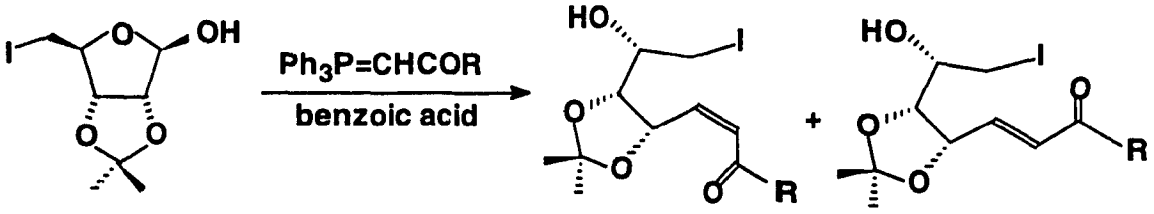
43

The signal of *H-1* (at 5.57 ppm) appears as a doublet ($J_{OH,1}$ = 2.9 Hz) which collapses to a singlet upon D_2O exchange. The COSY and 1 D ^1H-^1H decoupling experiments show no other couplings. The fact that we observe no coupling of *H-1* and *H-2* suggests that the dihedral angle[30] between *H-1* and *H-2* is about 90° i.e. *H-1* and *H-2* are trans to each other. The hydroxy group at *C-1* is in the β- position.[45]

3. 2. 2. Synthesis of *tert*-Butyl (*2Z*)- and (*2E*)-2,3,7-trideoxy-7-iodo-4,5-*O*-(1-methylethylidene)-D-*ribo*-hept-2-enoate (44a and 44b), (*2Z*)- and (*2E*)-*N*, *N*-Dimethyl-2,3,7-trideoxy-7-iodo-4,5-*O*-(1-methylethylidene)-D-*ribo*-hept-2-enamide (45a and 45b) and (*2Z*)- and (*2E*)-*N*, *N*-Diethyl-2,3,7-trideoxy-7-iodo-4,5-*O*-(1-methylethylidene)-D-*ribo*-hept-2-enamide (46a and 46b)

The use of a Wittig reaction is a conventional method to convert carbonyl functions to olefins. Reactions may be carried out selectively to give either predominantly the (*Z*)- or the (*E*)- olefins.[31a] Wilcox and coworkers had already shown that ribofuranose compounds react with the ylide [(carbethoxymethylene)triphenylphosphorane in the presence of a catalytic amount of benzoic acid to give the corresponding α,β-unsaturated esters.[31b] The (*Z*)- isomer was predominant under their conditions. We applied their methods to the synthesis of compounds **44-46a** and **44-46b** (Scheme 3.3).

Scheme 3. 3 Reactions of iodo ribose 43 with Wittig reagents



R	(*Z*)-	(*E*)-
O*t*-Bu	44a	44b
NMe_2	45a	45b
NEt_2	46a	46b

The *t*-butyl esters **44a** and **44b** were carefully prepared from **43** by reaction with commercially available [(*t*-butyloxycarbonyl)methylene]triphenylphosphorane and a catalytic amount of benzoic acid in CH_2Cl_2 (97% yield; the ratio of **44a** to **44b** is 7.8:1).

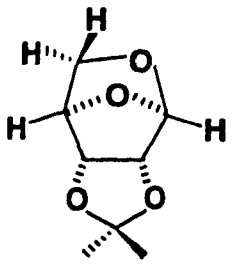
Ylides **62**[32,33] and **64**[34] were prepared from Ph_3P and $ClCH_2CONR_2$ (R: Me or Et; Scheme 3.4) using literature procedures. Both ylides are soluble in anhydrous organic solvents such as ethyl acetate, dichloromethane, ethyl ether or tetrahydrofuran (THF). These compounds are degraded in the presence of water however.[35]

Scheme 3. 4. Synthesis of Wittig reagents 62 and 64

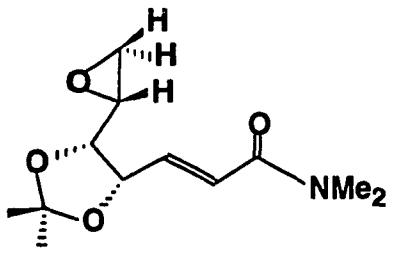
$$Ph_3P + ClCH_2CONR_2 \longrightarrow Ph_3P^+CH_2CONR_2Cl^- \qquad \textbf{Me (61), Et (63)}$$

$$\textbf{61, 63} \longrightarrow Ph_3P{=}CHCONR_2 \qquad \textbf{Me (62), Et (64)}$$

Compounds **45a** and **45b** were prepared by careful treatment of ylide **62** with compound **43** and a catalytic amount of benzoic acid under an argon atmosphere in tetrahydrofuran (THF). The reaction mixtures were usually very complex. Purification of the crude product by flash column chromatography gave four major compounds: **45a** (25%), **45b** (27%), **60** (8.5%)[36] and **47** (0.4%). The use of a different solvent, such as dichloromethane, increased the yield of the (*Z*)- isomer **45a** to 41 % but decreased the yield of (*E*)- isomer **45b** to 2.5% yield. Side products **60** (15%) and **47** (17%) were also isolated after purification by chromatography.



60



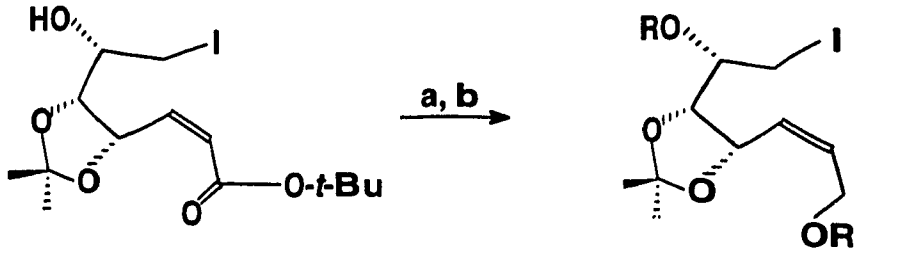
47

Both compounds **60** and **47** involve displacement of the iodine atom by a hydroxy group in a S_N2 fashion. Compound **60** is formed directly from the starting material **43** and compound **47** is formed by a unwanted reaction of the Wittig product **45b**. Compound **60** is a known compound and our spectral data matched those reported in the literature.[36] Compound **47** is a new compound and it's structure was determined by analysis of the ^1H NMR, ^{13}CNMR, COSY, DEPT, HMQC and FTIR spectra. The details of our spectral analysis are described in the experiment section. The reaction of **43** with ylid **64** was similar to that one involving ylid **62**. The crude product was even more complex as indicated by TLC. Three major products [**46a** (41%), **46b** (8.7%) and **60** (16%)] were isolated from the reaction mixture.

3. 2. 3. Synthesis of (2*Z*)-2,3,7-Trideoxy-7-iodo-4,5-*O*-(1-methylethylidene)-D-*ribo*-hept-2-enitol (48) and (2*Z*)-1,6-Di-*O*-acetyl-2,3,7-trideoxy-7-iodo-4,5-*O*-(1-methylethylidene)-D-*ribo*-hept-2-enitol (49)

Care must be taken in choosing a reagent to reduce an iodo ester **44a** to the corresponding iodo alcohol **48**. A common reagent such as $LiAlH_4$ may not be appropriate as it can also transform alkyl iodides to the corresponding alkanes[37]. We decided to try sodium diethyldihydroaluminate $[(C_2H_5)_2AlH_2]Na$[37] and diisobutylaluminum hydride (DIBAL-H)[38a-c] as our reducing reagents. Treatment of sodium diethyldihydroaluminate with **44a** didn't result in the formation of alcohol **48**. TLC analysis indicated that the reaction mixture was very complex.

Scheme 3. 5. Synthesis of substrates 48 and 49

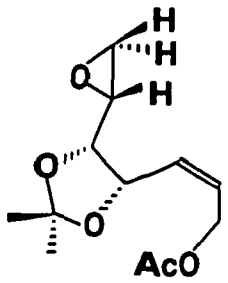


44a **R: H (48); R: Ac (49)**

(a) DIBAL-H, CH_2Cl_2, -25°C to -35°C to give **48** [73.5% (85.9%)]; (b) Ac_2O, DMAP, NEt_3, CH_2Cl_2, -78° C to give **49** (95%).

Reduction of **44a** by use of DIBAL-H gave us some interesting results (Scheme 3.5). Use of two equivalents of DIBAL-H at 0°C in dichloromethane under a nitrogen atmosphere resulted in a low yield (36%) of reduction product **48**. No starting material was recovered under these reaction conditions. When the reaction was carried out at -78°C we obtained only partially pure products. The presence of down field signals[30], at 9.82 ppm (s) on ^1H

NMR and at 199.7 ppm on ^{13}C NMR spectra, indicated that the mixture contained an aldehyde. We found that use of six equivalents of DIBAL-H in anhydrous dichloromethane at -25°C to -35°C under a nitrogen atmosphere gave the best results: 68.7% yield of pure product **48** and 4.8% yield of impure product **48** were isolated together with a 12.4% recovery of starting material after purification by chromatography.



50

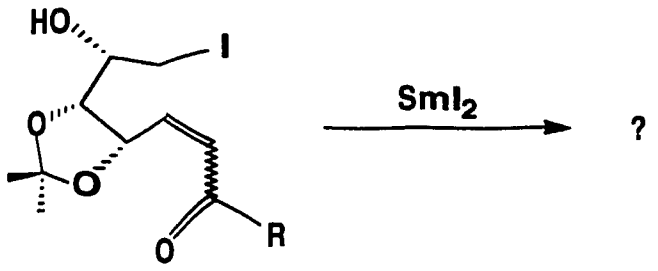
An attempt at monoacetylation[39a-c] of **48** by use of acetic anhydride (1.5 eq), triethylamine (1.5eq) and DMAP (0.08 eq) in anhydrous dichloromethane at -78°C was not successful. Diacetate **49** (77.5%) and epoxide **50** (12.1%) were isolated instead. Diacetylation of **48** was effectively accomplished by treatment with DMAP (0.096 eq), triethylamine (4.2 eq) and acetic anhydride (4.2 eq) at -78°C under anhydrous conditions. The reaction mixture was clean and **49** was isolated in 95% yield (Scheme 3.5).

3. 3. Reactions of SmI_2 with Various Carbohydrate Derived Alkenyl Iodides

3. 3. 1. Reactions of SmI_2 with (*2Z*)- and (*2E*)-*N*, *N*-Dimethyl-2,3,7-trideoxy-7-iodo-4,5-*O*-(1-methylethylidene)-D-*ribo*-hept-2-enamide (45a and 45b) and (*2Z*)-*N*, *N*-Diethyl-2,3,7-trideoxy-7-iodo-4,5-*O*-(1-methylethylidene)-D-*ribo*-hept-2-enamide (46a)

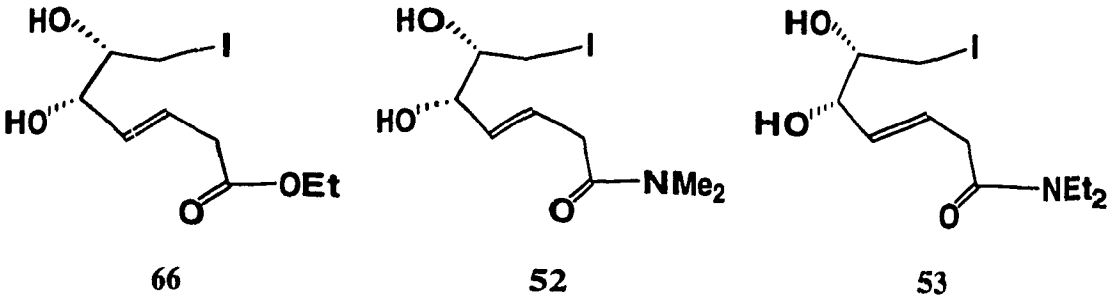
We studied the reactions of SmI_2 with **65**, **45a**, **45b** and **46a**. We hoped that these compounds would undergo reductive cyclizations and we wanted to study the diastereoselectivity of such a reaction (Scheme 3.6).

Scheme 3. 6. Reactions of SmI_2 with (*Z*)- and (*E*)- iodo alkenyl amides



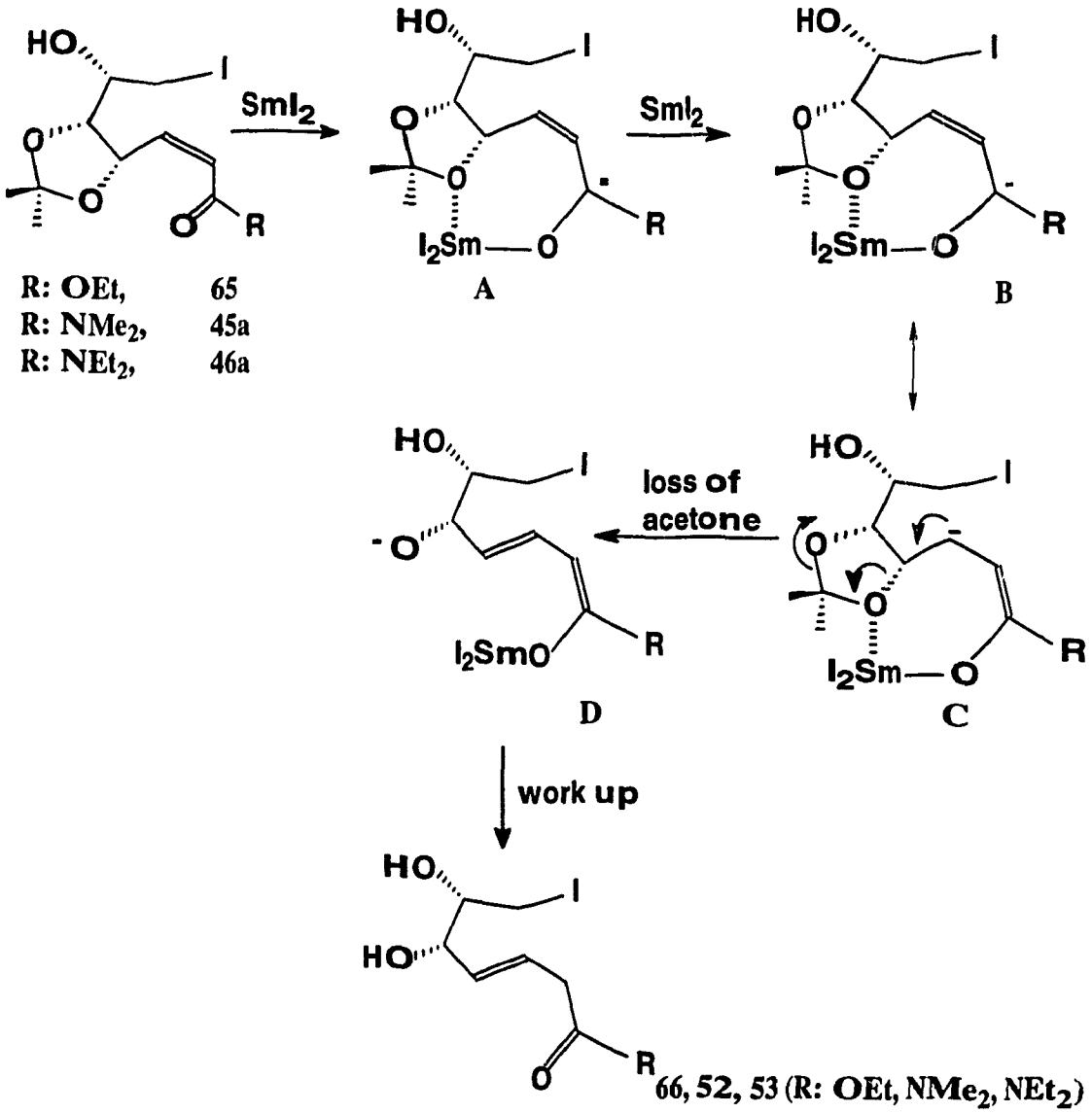
R: OEt [(*Z*)- 65], NMe_2 [(*Z*)- 45a; (*E*)- 45b], NEt_2 [(*Z*)- 46a].

Dr. Sharon Bennett had found that ethyl ester **65** failed to cyclized after exposure of **65** to 3 equivalents of SmI_2 in THF at room temperature. Instead of having reduction of the carbon-iodine bond of 65, she observed instead reduction of this α, β-unsaturated ester to give compound **66** (see Scheme 3.7).[40,41] We wondered if an α, β-unsaturated amide might be less susceptible to reduction by SmI_2. Our studies with *alkynyl halides* (chapter 2) prompted us to consider compounds **45a**, **45b** and **46a** as alternate candidates for our studies.



66 52 53

Scheme 3. 7. Reactions of SmI_2 with (Z)- iodo alkenyl amides and esters



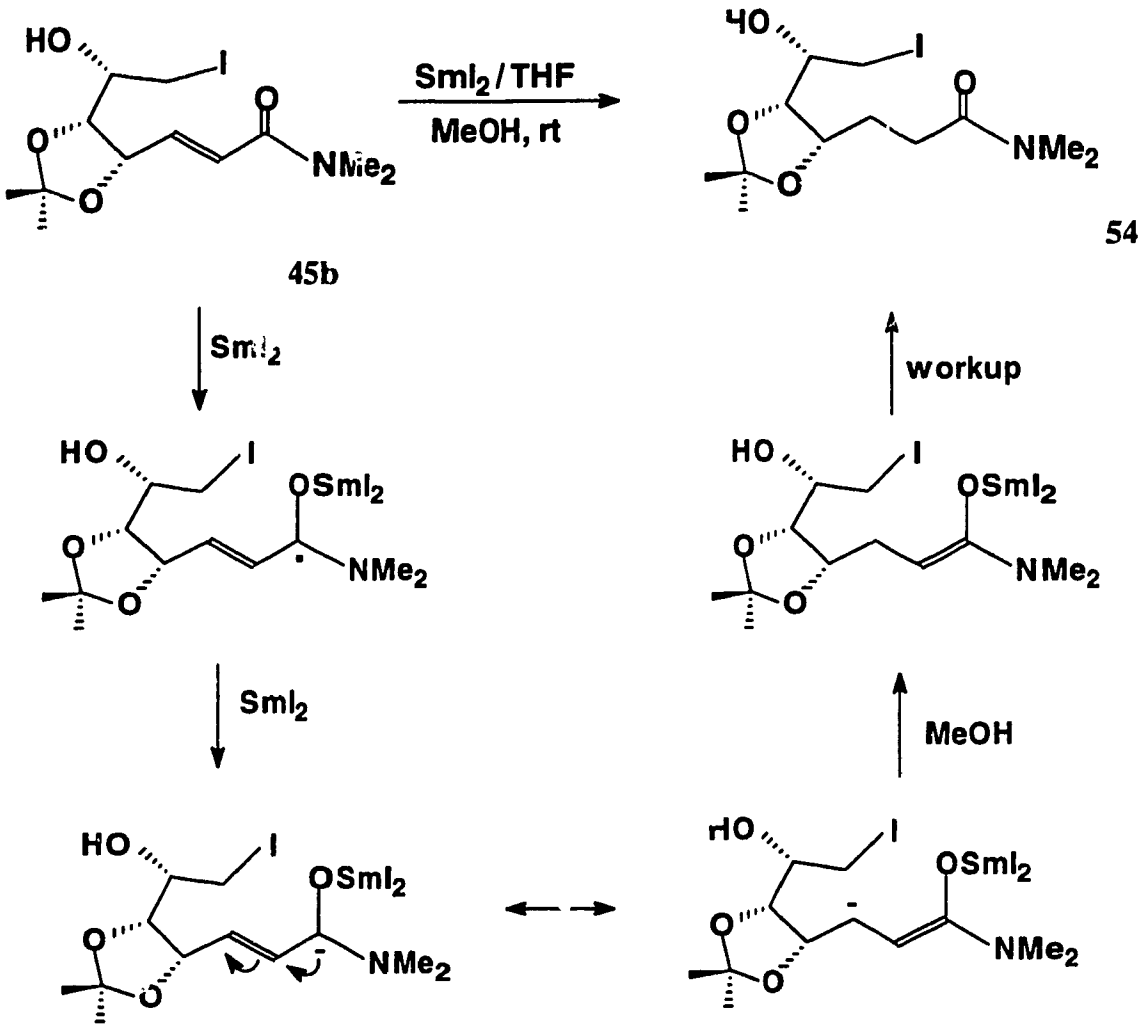
R: OEt, 65
R: NMe_2, 45a
R: NEt_2, 46a

Treatment of **45a** with 3 eq of SmI_2 in THF at either room temperature or at -78°C resulted in a rapid degradation of the starting material. We found no evidence for cyclization products and only a small portion of the starting material was recovered (30 % recovery of **45a** after chromatography of room temperature mixture; 34% recovery of **45a** after chromatography of -78°C mixture). The addition of MeOH as a co-solvent and a proton source was not helpful in this case. We isolated the reductive elimination product **52** (9.5% yield) and recovered only 1.4% of **45a**. Similarly, reaction of **46a** with SmI_2 (3 eq) in THF/MeOH at room temperature also resulted in a reductive elimination reaction We isolated 30% yield of **53** and recovered 34% of the unreacted starting material **46a**.

Normal α, β-unsaturated esters and amides are not usually reduced by SmI_2 under our reaction conditions.[42] Complexation of the ester/amide carbonyl with a samarium ion may however make it more susceptible to reduction. The mechanism we propose to explain our observations is outlined in Scheme 3.7 and is consistent with studies described by Enholm[41]. This involves: (1) Complexation and one-electron transfer to form the radical **A**; (2) Reduction of **A** by a second equivalent of SmI_2 to give **B**; (3) Fragmentation resulting in cleavage of the carbon-oxygen bond and formation of a molecule of acetone; (4) Protonation and tautomerizaton upon workup to give compounds **66**, **52** and **53**.

The (*E*)-diastereoisomer **45b** was also allowed to react with SmI_2. We thought that a trans derivative might be less likely to undergo the reductive elimination process. Complexation of the carbonyl oxygen and the C-4 oxygen seemed less likely in the basis of geometry constraints. In practice we found that reduction of the carbon-iodine bond was still a problem. Although we did not have a reductive elimination reaction occuring in the case of **45b**, the only product we were able to isolate was the simple saturated iodo-amide **54** (see Scheme 3.8).[43]

Scheme 3. 8. Reaction of SmI_2 with (*E*)- iodo alkenyl amide 45b.

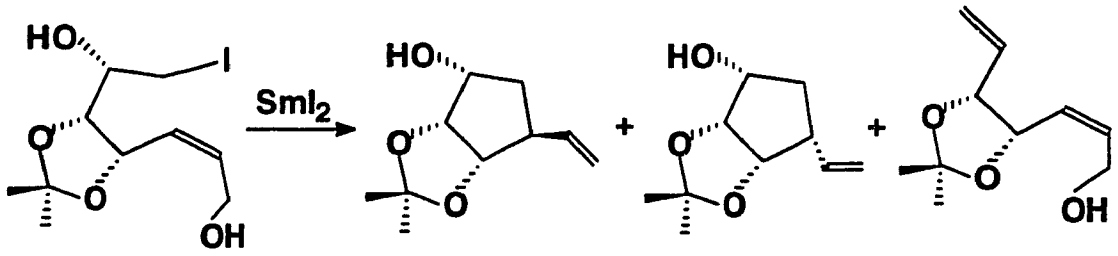


3. 3. 2. Reactions of SmI_2 with (*2Z*)-2,3,7-Trideoxy-7-iodo-4,5-*O*-(1-methyl-ethylidene)-D-*ribo*-hept-2-enitol (48)

Treatment of **48** with SmI_2 gave us some interesting results (Scheme 3.9). The reaction conditions and results are shown in Table 3.3. Reaction of **48** with SmI_2 using our standard reaction conditions (3 equivalent of SmI_2, THF, room temperature) led to the formation of the cyclization *and* reductive elimination products **55** and **56**. Our first attempt however resulted in poor diastereoselectivity (Table 3.3, entry 1). When the reaction was carried out in the presence of MeOH, as a co-solvent, the efficiency of cyclization was increased but the reaction mixture was even more complex. A fair amount of slightly impure non-cyclized reductive elimination product **57** (19% yield) was isolated after purification of the crude product by chromatography (Table 3.3, entry 2).

Addition of HMPA as a co-solvent effectively increased the yield and the diastereoselectivity of the cyclization reaction (see Table 3.3, entries 3-5). Compound **55** was the major product and we found no evidence of compound **56** (as determined by TLC and ^1H NMR analysis of both the crude and purified products). The addition of MeOH as a proton source was beneficial. This is evident when we compare the results described in entries 3 and 4 of Table 3.3. The yield of **55** is higher (51% versus 38%) under the conditions described in entry 3 and our mass balance is better (81% versus 51%). Our best results were obtained using those conditions described in entry 3. The reaction is not complete however and we recovered the unreacted starting material. Attempts to push the reaction to completion by using a larger quantity of SmI_2 were unsuccessful however (Table 3.3, entry 5). Although all of the stating material **48** had reacted, the yield of **55** was lower and we also observed formation of the non-cyclized reductive elimination product **57**.

Scheme 3. 9. Reaction of SmI_2 with iodo alcohol 48



48 55 56 57

Table 3. 3. Reactions of dialcohol 48 with SmI_2

		yields (%)			
entry	reaction conditions	**55**	**56**	**57**	recovery of st. material[a]
1	3 eq SmI_2/THF rt, 3 h	10.9	3.2	3.5	50.2 (67.8)
2	3 eq SmI_2/THF/MeOH rt, 4 h	35	13	19[b]	36[b]
3	5 eq SmI_2/THF/MeOH/HMPA -78°C, 2 h; 0°C, 2 h	51.0	0	0	30.1 (81.1)
4	5 eq SmI_2/THF/HMPA -78°C, 2 h; 0°C, 2 h	38	0		13 (51)
5	7 eq SmI_2/THF/MeOH/HMPA -78°C, 2 h; 0°C, 5h 20 min	46.6	0	8.7	0 (55.3)

[a] The value in parentheses indicates the total mass balance. [b] This compound was isolated as slightly impure sample as determined by ^1H NMR.

The compounds **55**, **56** and **57** were characterized by ^{1}H NMR, ^{13}C NMR, IR and MS and our ^{1}H NMR data for **55** and **56** are summarized in Tables 4-6. The stereochemistry of compounds **55** and **56** were determined with the help of nOe, 1 D ^{1}H-^{1}H decoupling and COSY experiments.

Table 3. 4. ^{1}H NMR ($CDCl_3$) of compound 55

δ (ppm)	Multiplicity	J (Hz)	Integration	Assignment
5.75	ddd,	$J_{1',4} = 6.5$, $J_{cis} = 10.5$, $J_{trans} = 17.2$	1 H	H-1'
5.09	overlapping signal[a]		2 H	H-2' and H-3'
4.49	apparent d[a]	J = 3.3	2 H	H-2 and H-3
4.08	broad signal	$W_{1/2}$ = 15 Hz	1 H	H-1
2.75	m		1 H	H-4
2.40	broad signal	D_2O exchangeable	1 H	O-H
1.90	m		2 H	H-5a and H-5b
1.52	s		3 H	CH_3
1.36	s		3 H	CH_3

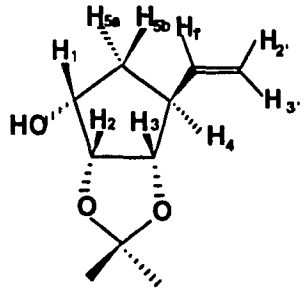
[a]The signal is more complex. The detailed description is given in the experimental section.

Table 3. 5. ^{1}H NMR (acetone-d_6) data of compound 55

δ (ppm)	Multiplicity	J (Hz)	Integration	Assignment
5.80	ddd,	$J_{1',4} = 6.8$, $J_{cis} = 10.5$, $J_{trans} = 17.3$	1 H	H-1'
5.07	ddd	$J_{allylic} = 1.6$, $J_{gem} = 1.6$, $J_{trans} = 17.4$	1 H	H-3'
5.00	ddd	J = 1.6, J = 1.5, $J_{cis} = 10.5$		H-2'
4.45	apparent d[a]		2 H	H-2 and H-3
3.97	broad signal	$W_{1/2} = 15$ Hz	1 H	H-1
3.10	d	$J_{OH,H-1}$ = 8.1, D_2O exchangeable	1 H	O-H
2.60	m[a]		1 H	H-4
1.87	ddd	$J_{5a,4} = 6.9$, $J_{5a,1} = 9.0$, $J_{5a,5b} = 12.4$	1 H	H-5a
1.73	poorly resolved ddd	$J_{5b,4} = 3.6$, $J_{5b,1} = 5.7$, $J_{5a,5b} = 12.4$	1 H	H-5b
1.41	s		3 H	CH_3
1.28	s		3 H	CH_3

[a]The signal is more complex. The detailed description is given in the experimental section.

The dihedral angle associated with two vicinal protons (H_x and H_y) in a cyclopentane system directly affects the corresponding coupling constant (J).[30] If H_x and H_y are trans with respect to one another then the dihedral angle will be close to 90°; in this case we expect the associated coupling constants to close to, or equal to zero.



55

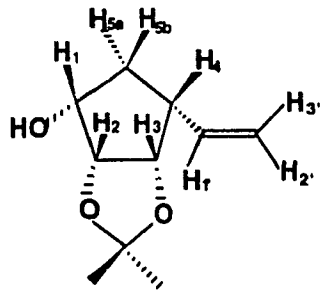
A detailed representation of **55** is given above. Analysis of the coupling constants associated with the *H-3* and *H-4* protons is complicated by the fact that *H-4* appears as a complex multiplet and that the *H-3* and *H-2* signals overlap and appear as a doublet ^1H NMR spectra of **55** were recorded in both $CDCl_3$ and acetone-d_6. We did observe better resolution of some signals when we used actone-d_6 (*i.e. H-2'*, *H-3'*, *H-5a* and *H-5b*) but still observed overlap of the *H-2* and *H-3* signals in both solvents. The COSY and 1 D decoupling experiments were useful but were not conclusive (see experimental section). For example, irradiation of the *H-4* proton showed no obviously effect on the appearence of the *H2+H3* signal. Although the COSY spectrum run in $CDCl_3$ indicates a coupling, the one run in acetone-d_6 shows no coupling. In order to be sure above our structural assignment we carefully studied the other diastereoisomer **56** by NMR and then finally carried out nOe experiments with both compounds.

Table 3. 6. ^{1}H NMR of compound 56

δ (ppm)	Multiplicity	J (Hz)	Integration	Assignment
5.91	m, contains ddd	$J_{cis} = 9.9$, $J_{trans} = 17.5$ $J_{1'.4} = 7.4$	1 H	H-1'
5.08 - 5.16	m		2 H	H2' + H3'
4.54	apparent t[a]	$J_{3.2} = 5.5$, $J_{3.4} = 4.6$	1 H	H-3
4.47	apparent t [a]	$J_{2.1} = 5.7$, $J_{2.3} = 5.4$	1 H	H-2
3.91	broad m[a]	$W_{1/2} = 21$ Hz	1 H	H-1
2.41	d	$J_{OH.H-1} = 10.7$, D_2O exchangeable	1 H	O-H
2.28	m[a]		1 H	H-4
1.94	ddd[a]	$J_{5a.4} = 5.6$, $J_{5a.1} = 6.1$ $J_{5a.5b} = 12$	1 H	H-5a
1.63	m		1 H	H-5b
1.50	s		3 H	CH_3
1.35	s		3 H	CH_3

[a]The signals are more complex. The detailed descriptions are given in the experimental section.

As previously mentioned, the dihedral angle associated with two vicinal protons (H_x and H_y) in a cyclopentane system directly affects the corresponding coupling constant (J).[30] If Hx and Hy are cis with respect to one another then the dihedral angle will be close to zero and we would expect that the associated coupling constant will be ~8 Hz.



56

A detailed representation of **56** is given above. Contrary to compound **55**, the analysis of the NMR data of compound **56** was easier due the fact that the *H-2* and *H-3* signals are not overlapped. The *H-4* signal appears as a multiplet (Table 3.6). By using 1 D decoupling we could indirectly measure $J_{4,3}$ value. The *H-3* signal appears as a t but is actually an overlapping dd ($J_{3,2}$ = 5.5 Hz, $J_{3,4}$ = 4.6 Hz). Irradiation of the *H-1* signal (δ 3.91) resulted in collapse of the *H-2* signal to a poorly resolved d ($J_{2,3}$ = 5.2 Hz). Irradiation of the *H-4* signal (δ 2.28) simplified the *H-3* signal to a poorly resolved d ($J_{2,3}$ = 5.3 Hz). Our conclusions are that the $J_{4,3}$ value is *ca.* 5 Hz and that the *H-3* and *H-4* protons are cis to one another. We therefore assigned structure **56** to the minor diastereoisomer that we isolated from the reaction of **48** with SmI_2 in THF/MeOH (Table 3.3, entry 2).

We carried out nOe experiments which supported our structural assignments for compounds **55** and **56**. We saw a smaller nOe between the signals of *H-4* and of *H2+H3* in the case of anomer **55** (where *H-4* and *H-3* are trans; and the *H-2* and *H-3* signals are overlapped) than what we saw in the case of anomer **56** (where *H-4* and *H-3* are cis).

Irradiation of **55** (acetone-d_6) at δ 2.60 (*H-4*) resulted in a total nOe of 1.3% for the overlapping *H2+H3* signals. Irradiation of **56** at δ 2.28 (*H*-4) resulted in a total nOe of 4.6% for the combined *H2+H3* signals. A detailed description is given in experimental section.

Advanced NMR techniques such as APT, DEPT, HMBC and HMQC are helpful tools to analysize ^{13}C NMR spectra. Using these techniques we were able to assign, with confidence, the ^{13}C NMR data for both compounds **55** and **56** (see Tables 3.7 and 3.8).

Table 3. 7. ^{13}C NMR of compound 55

δ (ppm)	Assignment	δ (ppm)	Assignment
138.0	*C*H=CH_2	71.1	C-1
115.3	CH=*C*H_2	44.3	C-4
111.6	$O_2C(CH_3)_2$	36.0	C-5
84.3	C-2 or C-3	26.1	CH_3
79.0	C-2 or C-3	24.3	CH_3

Table 3. 8. ^{13}C NMR of compound 56

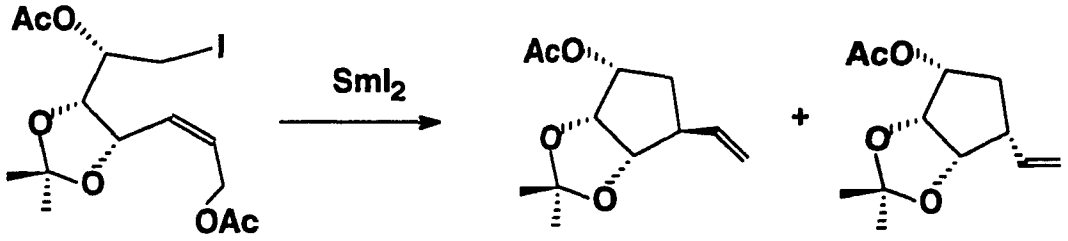
δ (ppm)	Assignment	δ (ppm)	Assignment
135.8	*C*H=CH_2	72.2	C-1
116.2	CH=*C*H_2	42.8	C-4
110.6	$O_2C(CH_3)_2$	35.5	C-5
81.6	C-3	25.6	CH_3
78.8	C-2	24.1	CH_3

High resolution mass spectrum* of **55** indicated that the molecular formula is $C_{10}H_{16}O_3$. The low resolution mass spectrum showed typical fragmentation at m/z, 169 (100%, loss of CH_3), 126 (10.6%, loss of CH_3COCH_3) and 59 [54.4%, $(CH_3)_2COH^+$] associated with isopropylidene protected carbohydrate analogs.[46] The fourier transform infrared spectra* of **55** showed characteristic bands at 3457 cm^{-1} (O-H), at 1638 cm^{-1} (C=C) and at 1163, 1087, 1052 and 1210 cm^{-1} (C-O).

3. 3. 3. Reactions of SmI_2 with (*2Z*)-1,6-Di-*O*-acetyl-2,3,7-trideoxy-7-iodo-4,5-*O*-(1-methylethylidene)-D-*ribo*-hept-2-enitol (49)

The diacetate **49** also reacted with SmI_2 to give carbocyclic compounds (see Scheme 3.10). The efficiency and the diastereoselectivity of the reaction vary with the reaction conditions (Table 3.9).

Scheme 3. 10. Reaction of SmI_2 with iodo allylic acetate 49



49 **58** **59**

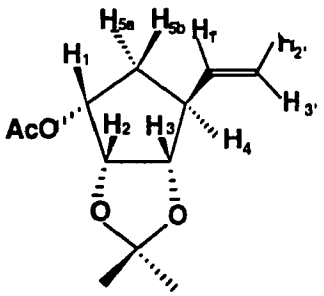
*Due to the limited quantity of **56** that we isolated, we were unable to obtain its mass spectrum and FTIR spectrum.

Table 3. 9. Reactions of diacetate 49 with SmI_2

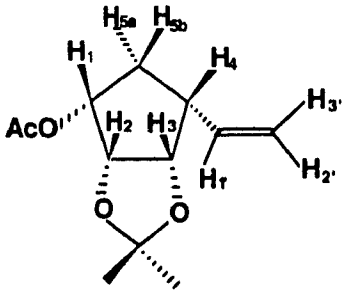
entry	reaction condition	yield (%)		
		58	**59**	recovery of st. material[a]
1	3 eq SmI_2/THF rt, 7 h	23	trace	71 (94)
2	3 eq SmI_2/THF/HMPA -78°C, 4 h	24	8	56 (88)
3	5 eq SmI_2/THF rt, overnight	34.4	17.6	39 (91)
4	5 eq SmI_2/THF reflux, overnight	50	16.8	0 (66.8)
5	5 eq SmI_2/THF/HMPA -78°C, 2 h; 0°C, 5 h	54	0.7	0 (54.7)
6	5 eq SmI_2/THF/DMPU -78°C, 2 h; 0°C, 5 h	28[b]	0.7	22 (50.7)[b]
7	5 eq SmI_2/THF/MeOH/HMPA -78°C, 2 h; 0°C, 1.3 h	76	5.6	0 (81.6)

[a] The value in parentheses indicates the total mass balance. [b] Compounds were isolated as slightly impure samples as determined by ^1H NMR.

The use of 3 equivalents of SmI_2 resulted in only partial transformation. The yield of the cyclization products was less than 30% even though the material mass balance was high (94% and 88% respectively, entries 1 and 2 of Table 3.9). If we increase the amount of SmI_2 to 5 equivalents, we also improved the cyclization efficiency. The results with regard to the diastereoselectivity varied greatly, however, depending on the other reaction conditions used. The mass balance also varied. We found that HMPA was more effective as a cosolvent than DMPU (see entries 5 and 6, Table 3.9). Under the conditions of entry 5 we obtained the products **58** in 54% yield and **59** in 0.7% yield. The diastereoselectivity here was high (ratio of **58** / **59** is about 77/1) and the reaction mixture was very clean (as determined by analysis of the crude product by TLC and ^1H NMR). The addition of MeOH as a proton source accelerated the reaction. Our best result was obtained using entry 7 (Table 3.9) conditions (5 eq of SmI_2, THF/MeOH/HMPA, -78°C to 0°C). The diastereoselectivity was high and all our starting material reacted under these conditions. Our cyclization/reductive elimination yield was 81.2% yield and ratio of **58** / **59** is 13.6/1.



58



59

Compounds **58** and **59** were fully characterized by ^1H NMR, ^{13}C NMR, FTIR and MS. The data and assignments for ^1H NMR are summarized in Table 10 and Table 11. The *H-4* signal of **58** is broad ($W_{1/2}$ = 18 Hz) and the *H-3* signal appears as an apparent d ($J_{3,2}$ = 5.7 Hz). The COSY and the 1 D decouping experiments showed that there was no coupling between *H-4* and *H-3*. On the contrary, coupling between the signals of *H-4* and

H-3 for **59** was indicated by COSY, HOM2DJ and 1 D decoupling experiments. The $J_{3,4}$ coupling constants (4.8 Hz) of **59** was measured by use of 1 D decoupling and HOM2DJ experiments. Therefore, the relative configurations of compounds **58** (β anomer) and **59** (α anomer) are as shown.[45]

Table 3. 10. ^{1}H NMR of compound 58

δ (ppm)	Multiplicity	J(Hz)	Integration	Assignment
5.77	ddd	J_{cis} = 10.6, J_{trans} = 17.2 $J_{1'.4}$ = 6.4	1 H	H-1'
5.07 - 5.16	overlapping signals[a]		2 H	H-2' + H-3'
4.91	m[a]		1 H	H-1
4.67	apparent t [a]	$J_{2.1}$ = 5.5, $J_{2.3}$ = 5.5	1 H	H-2
4.48	apparent d [a]	$J_{3.2}$ = 5.7	1 H	H-3
2.77	broad signal[a]	$W_{1/2}$ = 18 Hz	1 H	H-4
2.09-2.22	m[a]		4 H	OCOC*H*$_3$ + H-5a
1.95	ddd	$J_{5b.4}$ = 2.8, $J_{5b.1}$ = 6.2 $J_{5b.5a}$ = 12.5	1 H	H-5b
1.50	s		3 H	CH_3
1.33	s		3 H	CH_3

[a] The signals are more complex. See experimental section for more details.

Table 3. 11. ^{1}H NMR of compound 59

δ (ppm)	Multiplicity	J (Hz)	Integration	Assignment
5.93	m[a], 1 D decoupling at δ 2.35 (*H-4*) found some J values.	J_{cis} = 9.8, J_{trans} = 17.6	1 H	H-1'
5.10-5.17	overlapping m[a]		2 H	H-2' + H-3'
4.70	m[a]		2 H	H-1 + H-2
4.53	apparent t [a]	$J_{3,2}$ = 5.1, $J_{3,4}$ = 4.8	1 H	H-3
2.35	m[a]		1 H	H-4
2.13	s		3 H	C*H*$_3$CO
1.95	m[a]		2 H	H-5a + H-5b
1.49	s		3 H	CH_3
1.32	s		3 H	CH_3

[a] The signals are more complex. See experimental section for more details.

Our nOe experiments supported the stereochemical assignment. Upon irradiation of the *H*-3 signal (δ 4.48) of anomer **58** we observed a smaller nOe effect for *H-4* (2.0 %) than what we did in the corresponding case of anomer **59** (4.3 % for the same proton). Upon irradiation of *H-4* (δ 2.77) of anomer **58**, we saw a smaller nOe effect for proton *H-3* (1.6%) than what we did in the case of anomer **59** (5.7%). A detailed description is given in the experimental section.

Using APT, DEPT, and HMQC we were able to assign, with confidence, the ^{13}C NMR data for both **58** and **59** (see Table 3.12 and Table 3.13).

Table 3. 12. ^{13}C NMR of compound 58

δ (ppm)	Assignment	δ (ppm)	Assignment
170.7	C=O	73.3	C-1
137.7	*C*H=CH_2	43.8	C-4
115.5	CH=*C*H_2	31.7	C-5
111.4	$O_2C(CH_3)_2$	26.1	CH_3
84.1	C-3	24.5	CH_3
77.9	C-2	20.9	*C*H_3CO

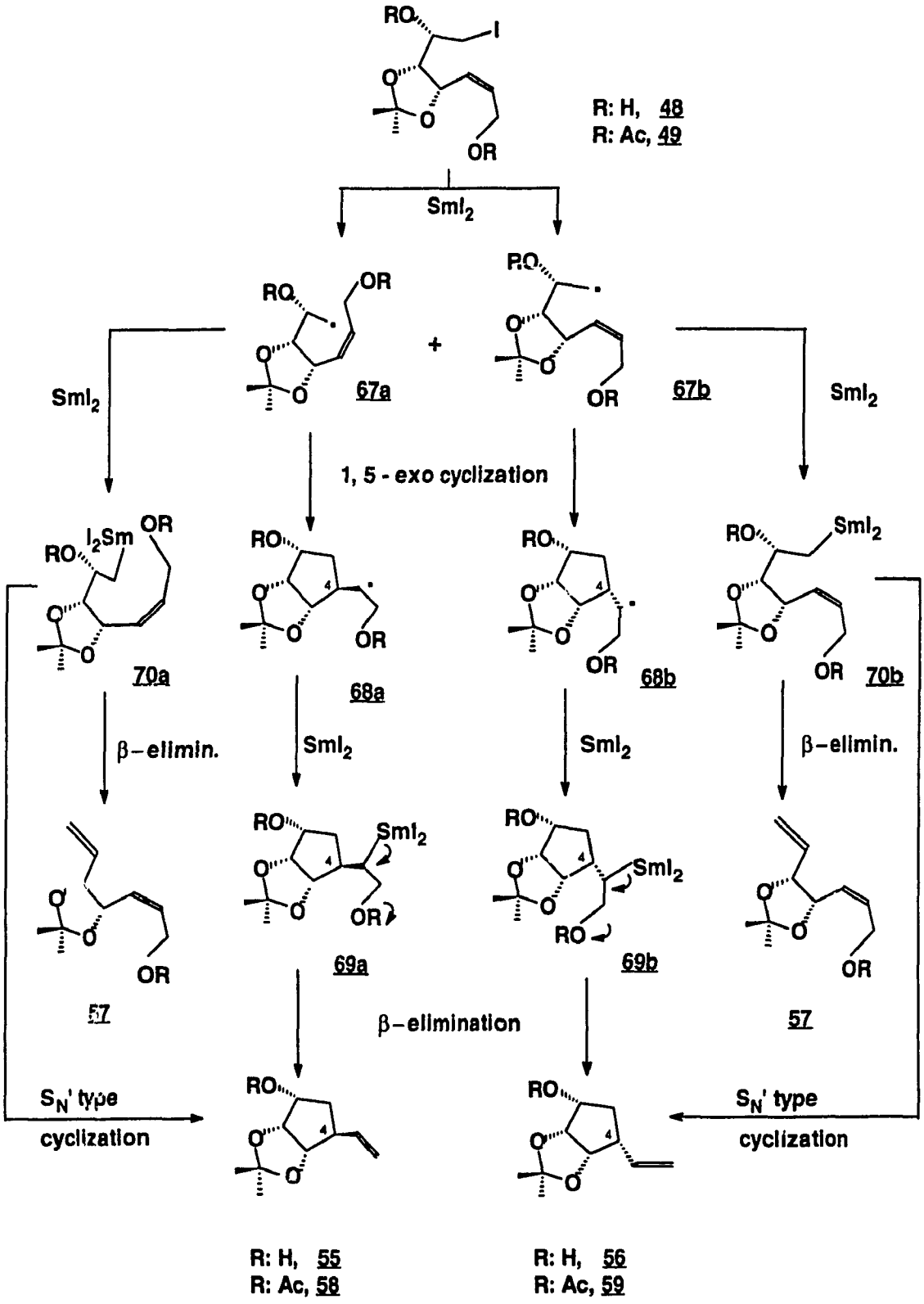
Table 3. 13. ^{13}C NMR of compound 59

δ (ppm)	Assignment	δ (ppm)	Assignment
170.9	C=O	73.7	C-1 or C-2
135.7	*C*H=CH_2	42.5	C-4
116.4	CH=*C*H_2	31.5	C-5
110.8	$O_2C(CH_3)_2$	25.7	CH_3
81.3	C-3	24.2	CH_3
77.8	C-1 or C-2	20.9	*C*H_3CO

The high resolution mass spectra of **58** and **59** indicated that they both have the same molecular formula, $C_{12}H_{18}O_4$. The low resolution mass spectra of **58** and **59** were quite similar. We observed a low intensity peak at m/z = 226 for the molecular ion [**58** (0.6%), **59** (1.1%)]. In both compounds we see an intensity signal at m/z = 211 [**58** (72.3%), **59** (100%)]. The 211 signal corresponds to loss of CH_3 from the molecular ion. McLafferty fragmentation is evident from the signal at m/z = 166 for both **58** (5.0%) and **59** (8.5%). This corresponds to loss of CH_3COOH from the molecular ion. [46]

The FTIR spectrum of **58** showed characteristic bands at 1739 cm^{-1} (C=O) and at 1243, 1210, 1165, 1072 and 1044 cm^{-1} (C-O). A weak band was also observed at 1637 cm^{-1} (C=C). The FTIR spectrum of **59** showed charateristic bands at 1738 cm^{-1} (C=O) and at 1243, 1212, 1093 cm^{-1} (C-O). A weak band was also observed at 1644 cm^{-1} (C=C).

Scheme 3. 11. The reactions of 48 and 49 with SmI_2



The mechanisms we propose to explain our observations are outlined in Scheme 3.11. They involve either a radical or an anionic cyclization.[47,48] Organosamarium intermediates *are* involved at some stage, however, and result in the formation of β-elimination products. Scheme 3.11 presents both possible pathways. SmI_2 reduction of compounds **48** or **49** give radicals **67**. Radical **67** may adopt either conformation **67a** or **67b**. Cyclization of **67a** would eventually give a compound in which the *C-4* substituent will be on the opposite side as all the other ring substituents. Cyclization of **67b** would eventually give a compound in which the *C-4* substituent will be on the same side as all the other ring substituents. Radical **67a** and **67b** may then either (1) cyclize in a 5-exo fashion to give the cyclic radical **68a** and **68b**; or (2) be reduced by a second equivalent of SmI_2 to give non-cyclic organosamarium species **70a** and **70b**. These two intermediates **70a** and **70b** may then either (1) undergo β-elimination[44] to give non-cyclized reductive elimination product **57**; or (2) undergo intramolecular nucleophilic substitution in a S_N' type fashion to give final cyclization *and* reductive elimination products **55**, **56**, **58** and **59**. The cyclic radicals **68a** and **68b** further be reduced by a second equivalent of SmI_2 to give cyclic organosamarium intermediates **69a** and **69b**. The organosamarium species **69a** and **69b** undergo β-elimination to form final products **55**, **56** **58** and **59**.[44]

3. 4. Conclusions

Compounds **48** and **49** are good substrates for our cyclization methodology. We obtained carbocyclic compounds in good yield and with good diastereoselectivity. Compounds **45a** and **46a** are not appropriate substrates as they undergo γ-deoxygenation faster than carbon-iodine bond reduction under our reaction conditions. Compound **45b** is transformed to the corresponding saturated iodo amide by SmI_2.

Chapter 4. Experimental

4. 1. General

Unless otherwise noted, ^{1}H NMR, ^{13}C NMR, nOe (nuclear Overhauser enhancement difference), ^{1}H-^{1}H decoupling, COSY (Homonuclear Correlated Spectroscopy), HOM2DJ (Homo *J*-resolved ^{1}H-^{1}H Spectroscopy), APT (Attached Proton Test) and DEPT (Distortionless Enhancement by Polarization Transfer) spectra were recorded in $CDCl_3$ on a Varian Gemini 300 BB (at 300 MHz or 75 MHz) instrument. HMBC (Heteronuclear Multiple Bond Connectivity) and HMQC (Heteronuclear Multiple-Quantum Coherence) spectra were recorded in $CDCl_3$ on a Bruker AMX2-500 (at 500 MHz or 125 MHz) instrument. The following descriptions are used regarding the NMR spectra: br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. FTIR spectra were recorded on a Perkin Elmer Series 1600 instrument. Liquid samples were run as neat films by placing one drop of the liquid between two sodium chloride plates. In general, IR spectra of solids were run on the corresponding KBr pellets. In those cases where the quantity of material was limited, the following procedure was followed (for both liquids or solids): A film was prepared by placing one or two drops of a CCl_4 solution of the compound on a sodium chloride plate. The solvent was evaporated and a spectrum was then run of the finally dispersed material. Mass Spectra were recorded on a Kratos 25 RFA instrument at McGill University by Mr. Nadim Saade. GC spectra were recorded on a Varian 3300 instrument (SPB-5 column, 15 meters length, 0.25μm internal diameter, 2 cm / min flow rate). GC-MS spectra were recorded on a Varian 3500 instrument (DB-5 column, 30 meters length and 0.25

μm internal diameter, 2 cm / min flow rate) with a Finnigan 700 Ion Trap Detector at McGill University by Mr. Nadim Saade. Optical rotations were measured at 25°C at 589 nm in ethanol (100%, A. C. S.) with a JASCO DIP-370 Digital Polarimeter at the Institute Armand - Frappier. The reported concentrations (c) are in g / 100 mL.

All glassware, needles and cannulas were oven-dried overnight (160°C) and cooled in a desiccator over Drierite. Solvents for reactions were dried by distillation from a suitable drying agent under an argon or a nitrogen atmosphere and then transferred by oven-dried glass syringes or by using disposable polypropylene / polyethylene syringes (Aldrich). Liquid chemicals and dry solvents were delivered to reaction flasks by disposable polypropylene / polyethylene syringes (Aldrich) with or without a syringe pump. Reaction mixtures were stirred by use of Teflon coated magnetic stirring bars. Commercial solvents (reagent A. C. S.) for chromatography and extraction were used. Crude products were purified by either flash column chromatography (silica gel 60, 230-400 mesh ASTM, EM Science), or radial chromatography [Chromatotron; plates were made by either use of silica gel (Merck, TLC grade 7749 with gypsum binder and fluoresent indicator) or use of Adsorbosil-plus P combined with calcium sulfate hemihydrate as described in the instruction manual for Harrison Research Chromatotron Model 7924T]. Products were further purified by distillation in a Kugelrohr apparatus when necessary. The crystalline solid products may be recrystallized directly from crude products for certain compounds. During product isolation, solutions were evaporated under water aspirator vacuum at 30°C using a rotoevaporator and the residues were dried under oil-pump vacuum. The purity of products were checked by ^{1}H NMR. Melting points (mp) were determined on a Fisher-Johns Melting

Point Apparatus. Boiling point (bp) measured for products distilled in a Kugelrohr apparatus refer to oven temperature. Commercial thin layer chromatography (TLC) plates (aluminum sheets, silica gel 60 F_{254}, 0.2 mm, EM separations) were used. TLC plates were examined under uv radiation (short wave uv, 254 nm). The plates were then developed by dipping them into an oxidizing solution (prepared from ceric sulfate [1 g, $Ce(HSO_4)_4$] and ammonium molybdate(IV) tetrahydrate [1.25 g, $(NH_4)_6Mo_7O_{24}\ 4H_2O$] in 100 mL of 10% sulfuric acid) and drying them with a heat gun.

4. 2. Material

Anhydrous triethylamine (Et_3N), diisopropylamine, toluene, dihydropyran (DHP) and dichloromethane (CH_2Cl_2) were purified by distillation from calcium hydride. Those solvents / reagents were then stored over molecular sieves (3A°). Tetrahydrofuran (THF) and ethyl ether (Et_2O) were distilled immediately before use from sodium and benzophenone ketyl. Dry hexamethylphosphoric triamide (HMPA) and 1,3-dimethyl-3,4,5,6,-tetrahydro-2(*1H*)-pyrimidinone (DMPU) were distilled from calcium hydride under reduced pressure and stored over molecular sieves (3A°) under an argon atmosphere. Anhydrous methanol was distilled from magnesium. Acetone was dried over potassium carbonate before use. Acetic anhydride (Ac_2O) was distilled before use. Tetrahydrofuran-d_8 (THF-d_8, CDN Isotopes) was dried as follows: A new ampoule was opened under an argon atmosphere. Calcium hydride was added and the resulting suspension was centrifuged.

The following reagents were purchased from Aldrich and were used, as received, without further purification: solutions of SmI_2 in THF (0.1 M), *n*-butyllithium in hexanes (1.4 M), diisobutylaluminum hydride (DIBAL-H, 1.0 M) in hexanes, sodium diethyldihydroaluminate, mesyl chloride (methanesulfonyl chloride), 4-dimethylaminopyridine (DMAP), *N*-iodosuccinimide (NIS), *N*, *N*-diethyl carbamyl chloride, imidazole, D-ribonic γ-lactone, sodium diethyldihydroaluminate, and [(t-butyloxycarbonyl)-methylene]triphenylphosphorane. The following commercially available reagents were also use as received: benzoic acid (Fisher Scientific), triphenylphosphine (Ph_3P, BDH), 2,3-*O*-isopropylidene-D-*ribonic* γ-lactone (Pfanstiehl), iodine (Anachemia), sodium iodide (NaI, Anachemia), sodium fluoride (NaF, Fisher Scientific), *p*-toluenesulfonic acid monohydrate (pTSA·H_2O, Fisher Scientific), *N*, *N*-diethyl 2-chloroacetamide ($ClCH_2CONEt_2$, Fluka), *N*, *N*-dimethyl 2-chloroacetamide ($ClCH_2CONMe_2$, Fluka), and Sm metal powder (40 mesh, Cerac).

4. 3. General procedure for reactions of alkynyl amide with SmI_2

A solution of SmI_2 in THF (available from Aldrich; 30 mL of a 0.1 M solution) was transferred via cannula to a solution of the starting material (1 mmol in 20 mL THF) under an argon atmosphere. Where appropriate, DMPU (7.0 mL), HMPA (6.5 mL), EtOD (0.355 mL) or MeOH (0.240 mL) was then added.[1] The reactions were quenched by addition of 0.1 M HCl unless otherwise specified and worked up as follows: the mixture was diluted with H_2O (50 mL) and extracted with ether (3 x 50 mL). The combined extracts were washed with H_2O (50 mL or 3 x 50 mL when DMPU or HMPA was used), saturated aqueous

$Na_2S_2O_3$ (50 mL) and brine (50 mL). The organic layer was dried over $MgSO_4$, and concentrated (where appropriate, GC analysis was carried out at this stage). The crude products were purified by flash chromatography on silica gel using a mixture of EtOAc and hexanes or CH_2Cl_2 as the eluant.

4. 4. General procedure for the reaction of carbohydrate derived substrates with commercial solutions of SmI_2

A solution of the starting material (0.15 mmol) in THF (volume = 2.5 - 5.5 mL depending on the number of equivalents of SmI_2 to be added) was prepared under an argon atmosphere. Where appropriate, HMPA (5% v/v) and/or MeOH (1.5 mmol) was added. SmI_2 in THF [0.1 M (Aldrich), 4.5 mL to 7.5 mL, 0.45 - 0.75 mmol] was transferred via cannula to the reaction mixture. The final concentration of starting material was *ca.* 0.015 M. The reactions were quenched by addition of a saturated aqueous solution of NH_4Cl (5 mL) unless otherwise specified and worked up as follows: the mixture was diluted with H_2O (5 mL) and extracted with EtOAc (3 x 10 mL). The combined extracts were washed with H_2O (20 mL or 3 x 20 mL when HMPA or DMPU was used), saturated aqueous $Na_2S_2O_3$ (20 mL) and brine (20 mL). The organic layer was dried over $MgSO_4$, and concentrated. The crude products were purified by chromatography using a chromatotron (Harrison Research) [2 mm plate (silica gel) or 1mm plate (adsobosil)] using a mixture of EtOAc and hexanes as the eluant.

4. 5. Synthesis and Charaterization of Substrates

4. 5. 1. Alkynyl Halides

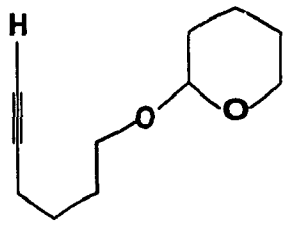
1-(tetrahydropyranyloxy)hex-5-yne (15b)

$C_{11}H_{18}O_2$

MW = 182 g · mol $^{-1}$

bp: 127° - 130°C (oven) at 4.8 mmHg

R_f = 0.16 (5% EtOAc:hexanes)



15b

^{1}H NMR ($CDCl_3$, 300 MHz) δ: **4.59** (m, 1H, OCHO), **3.73-3.90** (m, 2H, OC*H*H, O*CH*H, includes a dt, J=6.4, 9.8 Hz), **3.38-3.54** (m, 2H, OCH*H*, OCH*H*, includes a dt, J=6.2 Hz, 9.6Hz), **2.25** (dt, 2H, J=2.7, 6.9 Hz, C≡CCH_2), **1.95** (t, J=2.7 Hz, 1H, C≡CH, 1.46-1.91 (m, 10H, CH_2 x 3; CH_2 x 2),

^{13}C NMR ($CDCl_3$, 75 MHz) δ: 98.8, 84.4, 68.3, 66.9, 62.3, 30.7, 28.8, 25.5, 25.3, 19.6, 18.2.

FTIR (neat): 3295 (m, C≡CH), 2120 (m, C≡C) cm^{-1}.

MS (low resolution EI, 70ev) m/z: 182 (0.1%, $M^{+\cdot}$), 85 (100%, M-C_6H_9O).

Paration of compound 15b

To a 25ml oven dried round bottom flask containing stir bar, septum and pTSA·H_2O (0.1865g, 9.80 mmol), was added CH_2Cl_2 (20 mL) and DHP (2.00mL, 0.02358 mmol). To this mixture was added a solution of hex-5-yn-1-ol (1.2354g, 0.0126 mmol) in

CH_2Cl_2 (10 mL). The reaction solution was allowed to stir at room temperature overnight, then diluted with CH_2Cl_2 (35 mL) and washed with a saturated aqueous solution of $NaHCO_3$ (50 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL) and the combined organic layers were washed with a saturated aqueous $NaHCO_3$ solution (50 mL) and brine (50 mL), dried over $MgSO_4$, filtered and concentrated. Purification of the residue by flash chromatography (5% EtOAc, hexanes, 22 x 5 cm silica gel) followed by Kugelrohr oven distillation (bp: 127° - 130°C (oven) at 4.8 mmHg) gave the THP ether **15b** (1.4516g, 63% yield).

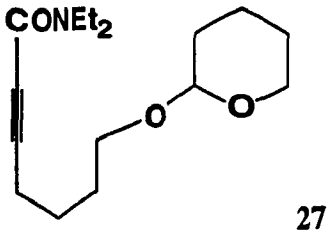
***N,N*-diethyl 7-(tetrahydropyranyloxy)hept-2-ynamide (27)**

$C_{16}H_{27}O_3N$

MW = 281.199 g · mol $^{-1}$

pale yellow oil

R_f = 0.18 (30% EtOAc : hexanes)



27

^{1}H NMR ($CDCl_3$, 300 MHz) δ: **4.58** (m, 1H, OCHO), **3.36-3.92** [m, 8H, OCH_2 x 2; NCH_2 x 2; includes 2 quartets at 3.41 (J=7.16 Hz), and 3.57(J=7.13 Hz)], **1.46-1.89** (m, 10H, CH_2 x 5), 2.40(m, 2H, $C{\equiv}CCH_2$), **1.21** (t, J=7.1 Hz, 3H, CH_3), **1.13** (t, J=7.2 Hz, 3H, CH_3),

^{13}C NMR ($CDCl_3$, 75 MHz) δ: 154.1, 98.9, 91.5, 74.5, 66.8, 62.4, 43.5, 39.1, 30.7, 29.0, 25.5, 24.9, 19.6, 18.8, 14.3, 12.8.

FTIR (neat): 2247 and 2221 (m, C≡C), 1623 (s, C=O) cm^{-1}.

LRMS (low resolution, 70ev) m/z: 281 (0.9%, $M^{+\cdot}$), 85 (100%, M-$C_{11}H_{18}NO_2$).

HRMS calculated for $C_{16}H_{27}O_3N$: 281.1991, found : 281.1995.

Preparation of compound 27

A freshly prepared solution of LDA (18.5 mL, 1M in THF, 0.0185 mol) was added dropwise over 40 min to a solution of THP ether **15b**[7a] (2.7921g, 0.01532 mol) in THF (38.5 mL) at -78°C under an argon atmosphere. The mixture was stirred at -78°C for 60 min before addition of N,N-diethylcarbamyl chloride (2.6 mL, 0.0199 mol). The reaction solution was then stirred at -78°C for another 75 min, warmed to 0°C over 60 min and then warmed up to room temperature overnight. The reaction mixture was quenched with brine (50 mL), diluted with H_2O (40 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. Purification of the residue by flash chromatography (30% EtOAc:hexanes, 22 x 5 cm silica gel) allowed for the separation of recovered starting material **15b** (0.7220g, slightly impure sample by ^1H NMR) from the desired product **27** (3.2275g, yield 75%).

***N*, *N*-diethyl 7-hydroxyhept-2-ynamide (28)**

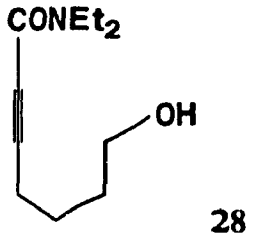
$C_{11}H_{19}O_3N$

MW = 197.14 g · mol $^{-1}$

pale yellow oil

bp: 188°-193°C (oven), 2.7 mmHg

R_f = 0.34 (75% EtOAc:hexanes)



28

^{1}H NMR ($CDCl_3$, 300 MHz) δ: **3.69** (m, 2H, CH_2OH), **3.57** (q, J=7.1 Hz, 2H, NCH_2), **3.41** (q, J=7.1 Hz, 2H, NCH_2), **2.41**(m, 2H, $C{\equiv}CCH_2$), **1.70** (m, 4H, CH_2CH_2), **1.48** (br, 1H, OH, exchanges with D_2O), **1.21** (t, J=7.2 Hz, 3H, CH_3), **1.13** (t, J=7.2 Hz, 3H, CH_3).

^{13}C NMR ($CDCl_3$, 75 MHz) δ: 154.0, 91.5, 74.7, 62.1, 43.5, 39.1, 31.8, 24.2, 18.7, 14.3, 12.8.

FTIR (neat): 3417 (s, OH), 2248 and 2223 (m, C≡C), 1610 (s, broad, C=O) cm^{-1}.

LRMS (low resolution, EI, 70 ev) m/z: 197 (16.6%, $M^{+\cdot}$), 138 (59.6%, M-C_3H_7O), 125 (100%, M-$C_4H_{10}N$).

HRMS calculated for $C_{11}H_{19}O_3N$ · 197.1416; found : 197.1408.

Preparation of compound 28

To a 50 mL oven dried round bottom flask containing THP ether amide **27** (1.0572g, 3.78 mmol), pTSA·H_2O (0.0715g, 0.376 mmol), was added MeOH (19 mL). The reaction solution was stirred under an argon atmosphere for 22 h. The mixture was quenched with brine (30 mL), diluted with H_2O (20 mL), and the aqueous layer was extracted with EtOAc (3 x 70 mL). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated. Purification of the residue by flash chromatography (75% EtOAc:hexanes, 3 x 15 cm silica gel) followed by Kugelrohr oven distillation gave the desired product **28** (0.7176g, 97% yield).

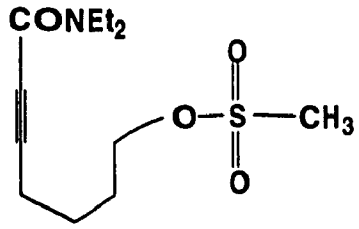
***N*, *N*-diethyl 7-mesyloxyhept-2-ynamide (29)**

$C_{12}H_{21}NO_4S$

MW = 275.12 g · mol $^{-1}$

pale yellow oil

R_f = 0.66 (EtOAc)]



29

^{1}H NMR ($CDCl_3$, 300 MHz) δ: **4.28** (t, J = 6.2 Hz, 2H, CH_2OMs), **3.57** (q, J = 7.1 Hz, 2H, NCH_2CH_3), **3.42** (q, J = 7.2 Hz, 2H, NCH_2CH_3), **3.03** (s, 3H, OSO_2CH_3), **2.44** (t, J = 6.9 Hz, 2H, $CH_2C{\equiv}C$), **1.91** (m, 2H, CH_2-CH_2OMs), **1.75** (m, 2H, $CH_2CH_2C{\equiv}C$), **1.22** (t, J=7.1 Hz, 3H, NCH_2CH_3), **1.14** (t, J=7.2 Hz, 3H, NCH_2CH_3).

^{13}C NMR ($CDCl_3$, 75 MHz) δ: 153.8, 90.3, 75.1, 69.1, 43.5, 39.1, 37.4, 28.2, 23.9, 18.4, 14.3, 12.8.

FTIR (neat): 2248 and 2222 (m, C≡C), 1620 (s, broad, C=O) cm^{-1}.

LRMS (low resolution, EI, 70 ev) m/z: 275 (1.7%, $M^{+\cdot}$), 196 (70.8%, M-CH_3SO_2), 79 (100%, M-$C_{11}H_{18}NO$).

HRMS calculated for : $C_{12}H_{21}NO_4S$: 275.1191, found : 275.1201.

Preparation of compound 29

To a 50 mL round bottom flask containing hydroxy amide **28** (0.2992g, 1.52 mmol) was added CH_2Cl_2 (9.0 mL) and Et_3N (0.375 mL, 2.69 mmol) under an argon atmosphere. The mixture was cooled to 0°C and CH_3SO_2Cl (0.1775 mL, 2.29 mmol) was added dropwise over 3 min; the mixture was then warmed up to room temperature overnight.

The reaction was quenched with MeOH (4 mL), and the mixture diluted with H_2O (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL) and the combined organic layers washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated. Purification of the residue by flash chromatography (EtOAc, 3 x 24 cm silica gel) gave the product **29** (0.3954g, 95%, yield).

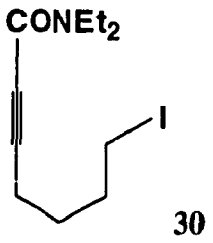
***N*, *N*-diethyl-7-iodohept-2-ynamide (30)**

$C_{11}H_{18}INO$

MW = 307.04 g · mol $^{-1}$

pale yellow oil

R_f = 0.57 (50% EtOAc : hexanes)



30

^{1}H NMR ($CDCl_3$, 300 MHz) δ: **3.57** (q, J=7.14 Hz, 2H, NCH_2), **3.42** (q, J=7.14 Hz, 2H, NCH_2), **3.22** (t, J=6.7, 2H, ICH_2), **2.42** (t, J=7.0 Hz, 2H, $CH_2C{\equiv}C$), **1.97** (m, 2H, CH_2CH_2I), **1.71** (m, 2H, $CH_2CH_2C{\equiv}C$), **1.22** (t, J=7.15 Hz, 3H, NCH_2CH_3), **1.14** (t, J=7.15 Hz, 3H, NCH_2CH_3).

^{13}C NMR ($CDCl_3$, 75 MHz) δ: 153.9 (C=O); 90.6($C{\equiv}CCONEt_2$); 75.0($C{\equiv}CCONEt_2$); 43.5, 39.0 (2 x NCH_2); 32.3, 28.5, 17.9 (3 x CH_2); 14.3, 12.8 (2 x NCH_2CH_3), 5.6 (ICH_2).

FTIR (neat): 2247, 2220 (m, C≡C), 1622 (s, broad, C=O) cm^{-1}.

LRMS (low resolution EI, 70ev) m/z: 307 (0.5%, $M^{+\cdot}$), 235 (100%, M-$C_4H_{10}N$).

HRMS calculated for $C_{11}H_{18}INO$: 307.0435, found : 307.0434.

Preparation of compound 30

To a 50 mL round bottom flask containing mesyl amide **29** (0.8248g, 3.0 mmol) was added a solution of NaI (2.0407g, 0.0136 mol) in acetone (21.1 mL). The reaction soln was allowed to stir at room temperature overnight under anhydrous conditions. The solvent was evaporated and the residue was diluted with a saturated aqueous solution of $Na_2S_2O_3$ (50 mL). The mixture was extracted with CH_2Cl_2 (3 x 100 mL) and the combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated. Purification of the residue by flash chromatography (50% EtOAc : hexanes, 3 x 20 cm silica gel) allowed for the separation of recovered starting material **29** (0.0105g, 2% yield of recovered starting material) from the desired product **30** (0.8705g, yield 95%). Attempts to distill this compound led to decomposition of the material.

Alternate synthesis of 30[10]

To a solution of **28** (0.5693g, 2.886 mmol) in CH_2Cl_2 (21.0 mL) at room temperature was added sequentially, and in small portions, Ph_3P (1.1082g, 4.25 mmol), imidazole (0.5744g, 8.437 mmol) and I_2 (1.10176g, 4.009 mmol). The reaction mixture was stirred at room temperature for 2 h and filtered over silica gel to remove the white precipitate that had formed during the reaction. The filter cake was washed with EtOAc and the filtrate was concentrated. The residue was dissolved in a minimum of EtOAc. Hexanes were added in order to precipitate the $Ph_3P=O$ and the solution was cooled to 0°C, filtered and concentrated. Purification of the residue was accomplished by use of a chromatotron (30% EtOAc : hexanes, 4 mm plate, silica gel) to give product **30** (0.8347g, 94% yield). This sample was identical to those samples prepared using the mesylation and halogenation sequence.

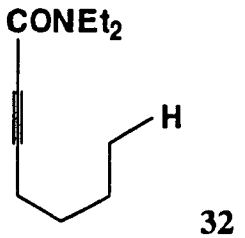
***N*, *N*-diethyl-hept-2-ynamide (32)**

$C_7H_{19}NO$

MW = 181.27 g · mol $^{-1}$

pale yellow oil

R_f = 0.33 (30% EtOAc : hexanes)]



32

^{1}H NMR δ: **0.93** (t, J=7.2 Hz, 3H, CH_3), **1.13** (t, J=7.1 Hz, 3H, NCH_2CH_3), **1.21** (t, J=7.1 Hz, 3H, NCH_2CH_3), **1.38-1.63** (m, 4H, CH_2CH_2), **2.36** (t, J = 7.0 Hz, 2H, $C{\equiv}CCH_2$), **3.42** (q, J = 7.1 Hz, 2H, NCH_2), **3.57** (q, J=7.1 Hz, 2H, NCH_2).

^{13}C NMR ($CDCl_3$, 75 MHz) δ: 154.2 (C=O); 91.8 ($C{\equiv}CC{=}O$); 74.4 ($C{\equiv}CC{=}O$); 43.4, 39.1 (2 x NCH_2); 29.9 ($C{\equiv}CCH_2$); 22.0, 18.6 (2 x CH_2); 14.3, 13.5 (2 x NCH_2CH_3); 12.8 (CH_3).

MS (low resolution, EI, 70ev) m/z: 181 (17.7%, $M^{+\cdot}$), 166 (14.3%, M-CH_3), 152 (14.0%, M-C_2H_5), 138 (36.3%, M-C_3H_7), 109 (100%, M-$C_4H_{10}N$).

Preparation of compound 32

A freshly prepared solution of LDA (16.5 mL, 1M in THF, 0.0165 mol) was added dropwise over 20 min to a cooled (-78°C) solution of hex-1-yne (1.233 g, 0.0150 mol) in THF (37.5 mL) under an argon atmosphere. The mixture was stirred at -78°C for 60 min before addition of *N*,*N*-diethylcarbamyl chloride (2.9 mL, 0.0222 mol). The reaction solution was then stirred at -78°C for another 75 min, warmed up to room temperature overnight, and quenched with brine (50 mL). The mixture was diluted with H_2O (40 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 x 100 mL). The combined organic

layers were dried over $MgSO_4$, filtered and concentrated. Purification of the residue by flash chromatography (30% EtOAc, hexanes, 22 x 5 cm silica gel) gave the desired product **32** (1.7109g, 63% yield). These data were in agreement with those reported by Fananas and Hoberg for an alternate synthesis of this compound.[11]

4. 5. 2. Reactions of SmI_2 with Alkynyl Halides

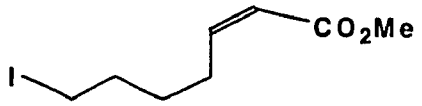
(Z)-Methyl 7-iodohept-2-enoate (24a)

$C_8H_{13}IO_2$

MW = 267.996 g · mol $^{-1}$

colourless liquid

R_f = 0.23 (3% EtOAc:Hexanes)



24a

^{1}H NMR ($CDCl_3$, 300 MHz) δ: **6.22** (dt, J = 11 4, 7.6 Hz, 1H, *H*C=CHCO$_2$Et), **5.81** (d, J = 11.5 Hz, 1H, HC=C*H*CO$_2$Et), **3.72** (s, 3H, OC*H*$_3$), **3.22** (t, J = 6.9 Hz, 2H, C*H*$_2$I), **2.70** (m, 2H, C*H*$_2$CH=CH), **1.89** (m, 2H, C*H*$_2$), **1.58** (m, 2H, C*H*$_2$).

^{13}C NMR ($CDCl_3$, 75 MHz) δ: 166.7 (C=O); 149.6 (*C*H=CHCO$_2$Et); 119.9 (CH=*C*HCO$_2$Et); 51.1 (OCH$_3$); 33.0, 29.8, 27.8 (3 x CH$_2$); 6.5 (ICH$_2$).

FTIR (neat): 1719 (s, C=O), 1647 (m, C=C) cm^{-1}.

LRMS (low resolution, EI, 70 eV) m/z: 268 (29.5%, M$^{+\cdot}$) 237 (24.2%, M-OCH$_3$), 141 (100%, M-I), 81 (87.7%).

HRMS calculated for $C_8H_{13}IO_2$: 267.9962; found: 267.9965.

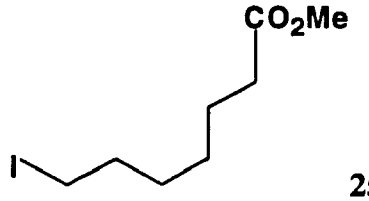
Methyl 7-iodoheptanoate (25)

$C_8H_{15}IO_2$

MW = 270 g · mol $^{-1}$

pale yellow oil

R_f = 0.24 (5% EtOAc: Hexanes)



25

^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.70 (s, 3H, OCH_3), **3.19** (t, 2H, J=7.0 Hz, ICH_2), **2.32** (t, 2H, J=7.5 Hz, CH_2CO_2Me) **1.83** (m, 2H, CH_2CH_2I), **1.65** (m, 2H, $CH_2CH_2CO_2Et$), **1.28-1.45** (m, 4H, CH_2CH_2).

^{13}C NMR ($CDCl_3$, 75 MHz) δ: 174.1 (C=O); 51.6 (OCH_3); 34.0, 33.3, 30.2, 28.1, 24.8 (5 x CH_2); 6.92 (ICH_2).

MS (low resolution EI, 70ev) m/z: 270 (0.8%, $M^{+\cdot}$), 239 (28.8%, M-OCH_3), 143 (100%, M-I).

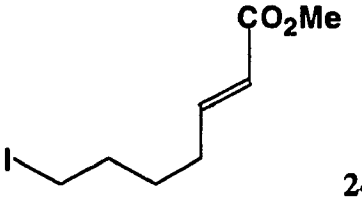
(*E*)-Methyl 7-iodohept-2-enoate (24b)

$C_8H_{13}IO_2$

MW = 267.996 g · mol $^{-1}$

pale yellow oil

R_f = 0.19 (10%, CH_2Cl_2:CCl_4)



24b

^{1}H NMR ($CDCl_3$, 300 MHz) δ: **6.96** (dt, J=15.7, 6.9 Hz, 1H, C*H*=CHCO$_2$Me), **5.85** (dt, J=15.7, 1.5 Hz, 1H, CH=C*H*CO$_2$Me), **3.74** (s, 3H, OC*H*$_3$), **3.20** (t, J = 6.9 Hz, 2H, IC*H*$_2$), **2.20** (m, 2H, C*H*$_2$CH=CH), **1.87** (m, 2H, C*H*$_2$CH$_2$I), **1.60** (m, 4H, 2 x CH$_2$).

^{13}C NMR ($CDCl_3$, 75 MHz) δ: 166.9 (C=O); 148.4 (*C*H=CHCOOMe); 121.5 (CH=*C*HCOOMe); 51.4 (OCH_3); 32.7, 31.0, 28.9 (3 x CH_2); 6.0 (CH_2I).

FTIR (CCl_4): 1728 (s, C=O), 1660 (m, C=C) cm^{-1}.

LRMS (low resolution, 70ev) m/z: 268 (26.4%, $M^{+\cdot}$), 237 (27.2%, M-OCH_3), 141 (93.2%, M-I), 81 (100%).

HRMS calculated for $C_8H_{13}IO_2$: 267.9962, found: 267.9966.

Preparation of (*Z*)- Ester 24a, (*E*)- Ester 24b and Saturated Ester 25 *Reaction of SmI_2 with iodo-ester (23)*

A solution of **23** (0.2640 g, 0.992 mmol), MeOH (0.240 mL, 5.93 mmol) and SmI_2 (29.70mL, 0.1M, 2.97 mmol) in THF (20 mL) was stirred at -78 ^{o}C for 4 h and then warmed up to 0°C over 2 h. The reaction mixture was worked up and the crude residue was purified by flash column chromatography (5% EtOAc: hexanes, 3 x 22 cm silica gel) to allow for the separation of fractions **A, B** and **C** [R_f = 0.31, 0.23, and 0.20 respectively, (TLC, silica, 5% EtOAc: hexanes)]. Further purification of fraction **A** by flash chromatography (3% EtOAc: hexanes, 2x17 cm silica gel) gave the *Z* ester **24a** (0.039g, 15% yield) as a colourless liquid. Further purification of fraction **B** by flash chromatography (5% EtOAc; hexanes, 2 x 16 cm, silica) gave the saturated ester **25** (0.00173g, 7% yield). Purification of fraction **C** by flash chromatography (10%

CH_2Cl_2:CCl_4, 2.5x22 cm silica gel) allowed the separation of recovered starting material **23** [0.0527g, 20% yield) and the *E* ester **24b** [0.05673g, 21% yield).

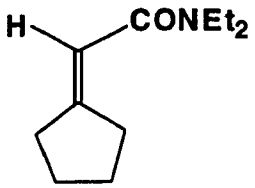
***N*, *N*-diethyl-methylenecyclopentanecarboxamide (31)**

$C_{11}H_{19}NO$

MW = 181.14 g · mol $^{-1}$

pale yellow oil

R_f = 0.35 (5% EtoAc:CH_2Cl_2)



31

^{1}H NMR ($CDCl_3$, 300 MHz) δ: **6.06** (m, 0.24 H, C*H*=C, deuterium incorporation = 76% as determined by ^{1}H NMR), **3.38** [(2 overlapping quartets at δ 3.41 (J = 7.1 Hz) and δ 3.35 (J = 7.1 Hz)), 4H, NCH_2 x 2], **2.74** (m, 2H, CH_2C=C), **2.42** (m, 2H, CH_2C=C), **1.50 -1.81** (m, 4H, CH_2CH_2), **1.16** [(2 overlapping triplets at δ 1.18 (J = 7.1 Hz) and δ 1.14 (J = 7.1 Hz)), 6H, NCH$_2$CH_3 x 2].

^{13}C NMR ($CDCl_3$, 75 MHz) δ: 167.0 (C=O); 162.6 (*C*=CHCO); 111.4 (C=*C*HCO); 42.4, 40.0 (2 x NCH_2); 35.7, 32.0 (2 x allylic CH_2); 26.6, 25.5 (2 x homoallylic CH_2); 14.6 , 13.3 (2 x CH_3).

FTIR (Neat): 1656 (s, C=O), 1621 (s, C=C) cm^{-1}.

LRMS (low resolution EI, 70ev) m/z: 182 [68.3%, M$^{\cdot+}$ for $C_{11}H_{18}DNO$ and (M+1) for $C_{11}H_{19}NO$; deuterium incorporation = 68%], 181 (30.3%, M$^{+\cdot}$ for $C_{11}H_{19}NO$), 167 (7.3%, $C_{11}H_{18}DNO$ - CH_3), 166 (3.1%, $C_{11}H_{19}NO$ - CH_3), 153 (19.8%,

$C_{11}H_{18}DNO - C_2H_5$), 152 (8.4%, $C_{11}H_{19}NO - C_2H_5$), 110 (100%, $C_{11}H_{18}DNO - C_4H_{10}N$), 109 (47.7%, $C_{11}H_{19}NO - C_4H_{10}N$).

MS (for a non-deuterated sample, low resolution EI, 70ev) m/z: 181 (55.7%, $M^{+\cdot}$), 166 (6.4%, M-CH_3), 152 (17.9%, M-C_2H_5), 109 (100%, M-$C_4H_{10}N$).

HRMS calculated for $C_{11}H_{19}NO$: 181.1467, found: 181.1465.

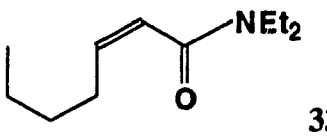
Preparation of compound 31 *Reaction of SmI_2 with iodo alkynyl amide* **30**

A solution of compound **30** (0.2807g, 0.9138 mmol), SmI_2 (27.6 mL, 0.1 M solution in THF, 2.76 mmol) and EtOD (0.320 mL, 5.44 mmol) in THF (18.5 mL) was refluxed for 10 h. The reaction mixture was worked up and the crude residue was purified by flash chromatography (5% EtoAc : CH_2Cl_2, 2.5 x 23 cm column of silica gel) to give compound **31** (0.1457 g, 88% yield) as a colourless oil (bp: 96.5 ^oC, Kugelrohr, 4.0 mmHg).

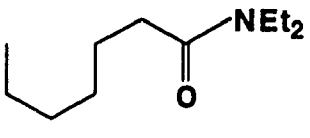
Alternate preparation of compound 31 *Reaction of SmI_2 with iodo alkynyl amide* **30** *in THF-d_8*

A freshly prepared solution of SmI_2 (2.9 Ml, ca. 0.1 M) was transferred via cannula to a THF-d_8 solution of **30** (0.0307 g, 0.100 mmol, in 2.0 Ml) and the solution was stirred at reflux until all of SmI_2 was consumed (35 min). The reaction mixture was worked up and the reaction products separated using a Chromatotron (1 mm silica plate, 1:3 EtOAc:hexanes). We isolated some starting material (0.0155 g, 37.5 % recovery) along with the expected compound **31** [0.0058 g, 32 % yield, 7 % incorporation as determined by MS analysis (average M/M+1 ratio = 50.2/10.2). ^1H NMR analysis is consistent with this level of deuterium incorporation at vinylic position of **31**.

Mixture of (*Z*)-*N*, *N*-diethyl-hept-2-enamide (33a) and *N*, *N*-diethyl-heptamide (34) *



33a



34

$C_{11}H_{21}NO$ $C_{11}H_{23}NO$

MW = 183 g · mol $^{-1}$ MW = 185 g · mol $^{-1}$

pale yellow oil

R_f = 0.56 (47% EtOAc : hexanes)

^{1}H NMR ($CDCl_3$, 300 MHz) δ: **5.98** (dt, J = 1.3, 11.6 Hz, C*H*=CHCONEt$_2$ of **33a**); **5.87** (dt, J = 7.1, 11.6 Hz, CH=C*H*CONEt$_2$ of **33a**); **3.34** (m, NCH_2 of both **33a** and **34**); **2.36** (m, C*H*$_2$CH=CH of **33a**); **2.27** (t, J = 7.7 Hz, C*H*$_2$CONEt$_2$ of **34**); **1.63** and **1.30** (2m, CH_2 of both **33a** and **34**), **1.14** (m, NCH_2CH_3 of both **33a** and **34**); **0.88** (m, C*H*$_3$ of both **33a** and **34**).

^{13}C NMR ($CDCl_3$, 75 MHz) δ: 172.3 (C=O of **34**); 167.1 (C=O of **33a**); 141.4 (*C*H=CHCONEt$_2$ of **33a**); 122.1 (CH=*C*HCONEt$_2$ of **33a**); 42.4 (NCH_2 of **33a**); 42.0, 40.0 (2 x NCH_2 of **34**); 39.4 (NCH_2 of **33a**); 33.2 (*C*H$_2$CONEt$_2$ of **34**); 31.7 (*C*H$_2$CH$_2$CONEt$_2$ of **34**); 31.3 (*C*H$_2$CH=CH of **33a**); 29.7 (homoallylic CH_2 of **33a**); 29.2, 25.5, 22.5 (3 x CH_2 of **34**); 22.4 (CH_2 of **33a**); 14.4 (NCH_2CH_3 of **34**); 14.3 (NCH_2CH_3 of **33a**); 14.0 (NCH_2CH_3 of **34**); 13.9 (NCH_2CH_3 of **33a**); 13.1 (CH_3 of both **33a** and **34**).

GC – MS (GC: T_{int} = 100 °C for 1 min followed by gradient of 4 °C / min to a T_{fin} = 125 °C which was held for 2 min; MS: low resolution, EI, 70 eV) m/z (for **33a** t_R = 4.4 min): 184 (55.53%, $M^{+\cdot}$ + 1), 183 (21.05%, $M^{+\cdot}$), 154 (57.25%, M-C_2H_5), 126 (25.80%,

M-C_4H_9), 55 (100%); m/z (for **34**, t_R = 5.07 min): 186 (66.85%, $M^{+\cdot}$ + 1), 185 (8.04%, $M^{+\cdot}$), 115 (38.67%), 100 (68.38%, M-C_6H_{13}), 72 (31.78%, M-$C_6H_{13}CO$), 58 (100%).

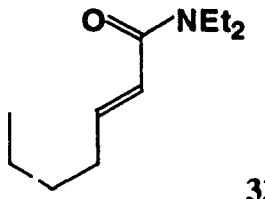
(*E*)-*N*, *N*-diethyl-hept-2-enamide (33b)**

$C_{11}H_{21}NO$

MW = 183 g · mol $^{-1}$

pale yellow oil

R_f = 0.50 (47% EtOAc : hexanes)



33b

^{1}H NMR ($CDCl_3$, 300 MHz) δ: **6.91** (dt, J = 7.1, 15.1 Hz, C*H*=CHCONEt$_2$), **6.18** (dt, J = 1.5, 15.0 Hz, CH=C*H*CONEt$_2$), **3.40** (m, 2 x NCH_2), **2.21** (m, CH_2CH=CH), **1.06-1.50** (m, 2 x CH_2 and 2 x NCH_2CH_3), **0.90** (m, CH_3).

^{13}C NMR ($CDCl_3$, 75 MHz) δ: 166.0 (C=O); 146.2 (*C*H=CHCONEt$_2$); 120.3 (CH=*C*HCONEt$_2$); 42.1, 40.7 (NCH_2); 32.2 (*C*H_2CH=CH); 30.5, 22.3 (2 x CH_2); 14.8, 13.8 (2 x NCH_2CH_3).

GC – MS (GC: T_{int} = 100 °C for 1 min followed by gradient of 4 °C / min to a T_{fin} = 125 °C which was held for 2 min; MS: low resolution, EI, 70 eV) m/z (t_R = 6.02 min): 184 (29.43%, $M^{+\cdot}$ + 1), 183 (3.60%, $M^{+\cdot}$), 126 (35.0%, M-C_4H_9), 111 (25.44%, M-$C_4H_{10}N$), 55 (100%)

Preparation of compounds 33a, 33b and 34 *Reaction of amide 32 with SmI_2*

A solution of compound **32** (0.0935g, 0.5161 mmol) and SmI_2 (43.9 mL, 0.1 M in THF, 4.39 mmol) in THF (10 mL) was stirred for 51 h at room temperature. The crude product

was purified by chromatography (47% EtOAc : hexanes) to allow for the partial separation of recovered **32** [0.0025g, 2.7% yield, R_f = 0.64 (TLC, silica, 47% EtOAc : hexanes)] from a mixture of **33a, 33b** and **34**. Two additional fractions were obtained; the first one was a mixture of **33a, 34** and recovered **32** [0.0250 g, R_f = 0.56 (TLC, silica, 47% EtOAc : hexanes) which contained 0.0052g of **33a** (5.5% yield), 0.0185g of **34** (19.6% yield) and 0.0013g of recovered **32** (1.4% yield) as determined by ^{1}H NMR and confirmed by GC-MS]. We were not able to obtain pure samples of compounds **33a** and **34** due to separation problems. The other fraction was a mixture of 4 compounds: **33a, 33b, 34** and recovered **32** [0.0152g, R_f = 0.50 (TLC, silica, 47% EtOAc : hexanes), which contained 0.0023g of **33a** (2.4% yield), 0.0018g of **33b** (1.9% yield), 0.0062g of **34** (6.5% yield) and recovered **32** 0.0049g (5.2% yield) as determined by ^{1}H NMR and confirmed by GC-MS].

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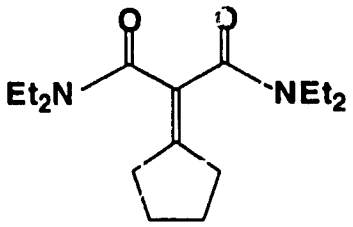
*Compounds **33a** and **34** were isolated as an unseparated mixture with **32**. The NMR spectra of the mixture was analyzed and the NMR signals which correspond to compounds **33a** and **34** are reported.

Compounds **33b was isolated as an unseparated mixture with **32, 33a** and **34**. It is important to mention that the ^{1}H and ^{13}C spectra were not obtained for a pure sample of **33b** due to separation problems. The NMR spectra of the mixture was analyzed and the NMR signals which were attributed to compound **33b** are reported.

Bis amide 35



$C_{16}H_{28}N_2O_2$

MW = 280.2 g · mol $^{-1}$

pale yellow oil

R_f = 0.11 (25% EtOAc:hexanes)

^{1}H NMR ($CDCl_3$, 300 MHz) δ: **3.60** (q, J=7.1 Hz, 4H, NC*H*$_2$ x 2), **3.41** (q, J=7.1 Hz, 4H, NC*H*$_2$ x 2), **2.30** (m, 4H, allylic CH_2 x 2), **1.69** (m, 4H, homoallylic C*H*$_2$ x 2), **1.14** (multiplet, 12H, C*H*$_3$ x 4).

^{13}C NMR ($CDCl_3$, 75 MHz) δ: 167.0(C=O), 148.0 (*C*=CCONEt$_2$), 126.8 (C=*C*CONEt$_2$), 42.5, 38.7 (2 x NCH_2), 30.8 (allylic CH_2), 26.0 (homoallylic CH_2), 14.1, 12.6 (2 x CH_3).

FTIR (CCl_4): 1624 (s, broad, C=O, C=C) cm^{-1}.

LRMS (low resolution EI, 70ev) m/z: 280 (18.8%, $M^{+\cdot}$), 208 (15.1%, M-$C_4H_{10}N$), 180(10.4%, M-$C_5H_{10}NO$), 100 (25.4%, M-$C_{11}H_{18}NO$, 72 (100%, M-$C_{12}H_{18}NO_2$).

HRMS calculated for $C_{16}H_{28}N_2O_2$: 280.2151, found: 280.2145.

Preparation of compound 35 *Reaction of SmI_2 with iodo alkynyl amide* **30**

A solution of **30** (0.3070g, 0.9994 mmol) and SmI_2 (29.45 mL, 0.1 M solution in THF, 2.945 mmol) in THF (20 mL) was refluxed overnight and then quenched with D_2O. The reaction mixture was worked up and the crude residue was purified by flash chromatography (25% EtOAc : hexanes, 2.5 x 20 cm, silica gel) to allow for the separation of product **31** (0.0444g, 25% yield) and **35** (0.0260g, 19% yield, slightly

impure by ^1H NMR) as a colourless oil . Attempts to further purify **35** by Kugelrohr distillation led to decomposition of the material.

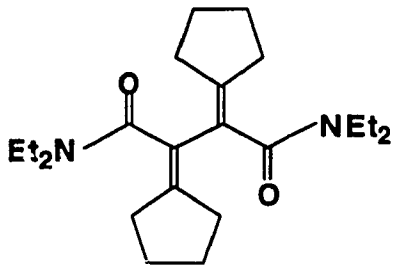
Dimer 36

$C_{22}H_{36}N_2O_2$

Mw = 360.27 g · mol $^{-1}$

pale yellow oil

R_f = 0.20 (60% EtOAc : hexanes)



^1H NMR ($CDCl_3$) δ: **3.10 – 3.50** (broad poorly defined signal, $W_{1/2}$ = 88.5Hz, 8H, NCH_2 x 4), **2.00 – 2.70** (broad poorly defined multiplet containing signals at δ: 2.60, $W_{1/2}$ = 37.5 Hz, 1H; δ: 2.34, $W_{1/2}$ = 38.4 Hz, 2H; δ: 2.15, $W_{1/2}$ = 15.3 Hz, 5H; totally allylic CH_2 x 4) **1.65** (broad signal, $W_{1/2}$ = 24.0 Hz, 8H, homoallylic CH_2 x 4), **1.00 – 1.20** (m, 12H, CH_3 x 4).

^1H NMR (DMSO – d_6, 300 MHz, T = ambient) δ: **3.10 – 3.30** (broad m, 8H, NCH_2 x 4), **1.93 – 2.29** (broad signal, $W_{1/2}$= 27 Hz, 8H, allylic CH_2 x 4), **1.45 – 1.52** (broad signal, $W_{1/2}$ = 21.9 Hz, 8H, homoallylic CH_2 x 4), **0.91 – 1.12** (m, 12H, CH_3 x 4).

^1H NMR (DMSO – d_6, 300 MHz T = 128°C) δ: **3.20 – 3.40** (multiplet, sharper than the corresponding signal at room temperature), **1.95 – 2.35** (broad multiplet containing signals at δ: 2.30, $W_{1/2}$ = 13.2 Hz, 2H; δ: 2.18, $W_{1/2}$ = 42 Hz, 2H, δ: 2.10, $W_{1/2}$ = 13.8 Hz, 4H, totally allylic 4 x CH_2), **1.50 – 1.68** (broad signal, $W_{1/2}$ = 19.8 Hz, 8H, homoallylic 4 x CH_2), **0.9 – 1.12** (m, 12H, 4 x CH_3).

^{13}C NMR ($CDCl_3$, room temperature, 75 MHz) δ: 171.7, 169.8 (2 x C=O); 146.7 (*C*=CCONEt$_2$); 132.4(*C*=CCONEt$_2$ and C=*C*CONEt$_2$); 128.0 (C=*C*CONEt$_2$); 43.1 (NCH_2); 41.9 (a small broad signal, NCH_2); 38.5 (NCH_2); 37.8 (a small broad signal, NCH_2); 31.7, 31.6, 29.4, 28.2 (4 x allylic CH_2); 29.7 (low broad signal, impurity); 26.1, 26.0, 22.7, 22.0 (4 x homoallylic CH_2); 14.4, 14.0 (a small broad signal), 12.9, 12.8 (a small broad signal) (4 x CH_3).

LRMS (low resolution, EI, 70 ev) m/z: 360 (14.7%, $M^{+\cdot}$), 287 (32.7%, M - 73). 260 (100%, M-CONEt$_2$).

HRMS: calculated for $C_{22}H_{36}N_2O_2$: 360.2777; found: 360.2763.

Preparation of compound 36 *Reaction of SmI_2 with iodo alkynyl amide* **30**

HMPA (3.25 mL, 18.7 mmol) was added dropwise over 12 min to a solution of **30** (0.1558g, 0.5072 mmol) and SmI_2 (15.2 mL, 1.52 mmol) in THF (10 mL) at 0°C. Stirring was continued for another 3 min before the reaction was worked up. The crude product was purified by flash chromatography [once using 60% EtOAc : hexanes and another time using 30% EtOAc : hexanes] to allow the separation of very slightly impure samples (as determined by ^1H NMR) of the desired product **31** [0.0257g, 28% yield, R_f = 0.59 (TLC, silica, 60% EtOAc · hexanes)], the bis amide **35** [0.0029g, 4% yield, R_f = 0.48 (TLC, silica, 60% EtOAc : hexanes)] and the dimer **36** [0.0389g, 42.6% yield, R_f = 0.20 (TLC, silica, 60% EtOAc : hexanes).

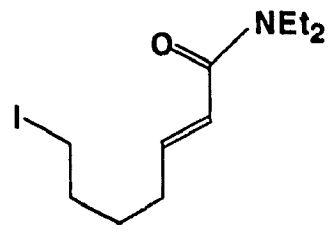
(*E*)-*N*, *N*-diethyl-7-iodohept-2-enamide (37b)

$C_{11}H_{20}INO$

MW = 309.05 g · mol $^{-1}$

pale yellow oil

R_f = 0.13 (25% EtOAc : hexanes)



37b

^{1}H NMR ($CDCl_3$, 300 MHz) δ: **6.88** (dt, J = 15.0, 7.0 Hz, 1H, C*H*=CHCONEt$_2$), **6.21** (dt, J = 15.0, 1.5 Hz, 1H, CH=C*H*CONEt$_2$), **3.40** (m, 4H, NCH_2 x 2), **3.20** (t, J = 7.0 Hz, ICH_2), **2.26** (m, 2H, C*H*$_2$CH=CH), 1.87 (m, 2H, CH_2), **1.59** (m, 2H, CH_2), **1.17** (m, 6H, CH_3 x 2).

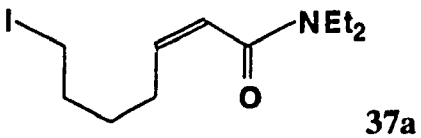
^{13}C NMR ($CDCl_3$, 75 MHz) δ: 165.8 (C=O); 144.9 (*C*H=CHCONEt$_2$); 121.1 CH=*C*HCONEt$_2$); 42.1, 40.8 (2 x NCH_2); 32.8, 31.2, 29.2 (3 x CH_2); 14.9, 13.2 (2 x NCH_2CH_3); 6.2 (ICH_2).

FTIR (neat): 1660 (s, C=O), 1614 (s, C=C), 1379 (m).

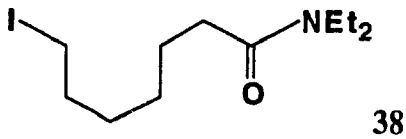
MS (low resolution, EI, 70 eV) m/z: 309 (21.5%, $M^{+\cdot}$), 237 (67.0%, M-$C_4H_{10}N$), 182(100%, M − I), 154 (22.7%, M-C_2H_4I), 126 (81.5%, M-C_4H_8I).

HRMS: calculated for $C_{11}H_{20}INO$: 309.0591; found : 309.0589.

Mixture of (*Z*)-*N*, *N*-diethyl-7-iodohept-2-enamide (37a) and *N*, *N*-diethyl-7-iodoheptamide (38)*



37a



38

$C_{11}H_{20}INO$ $C_{11}H_{22}INO$

MW = 309.05 g · mol $^{-1}$ MW = 311.1 g · mol $^{-1}$

pale yellow oil

R_f = 0.32 (TLC, silica, 10% ether : CH_2Cl_2)

^{1}H NMR ($CDCl_3$) δ: **6.03** (dt, J = 1.4, 11.5 Hz, C*H*=CHCONEt$_2$ of **37a**); **5.87** (dt, J = 7.3, 11.5 Hz, CH=C*H*CONEt$_2$ of **37a**); **3.34** (m, NCH_2 of both **37a** and **38**); **3.19** (m, ICH_2 of both **37a** and **38**); **2.41** (m, C*H*$_2$CH=CH of **37a**); **2.35** (t, J = 7.5 Hz, C*H*$_2$CONEt$_2$ of **38**); **1.84** (m), **1.65** (m), **1.54** (m), **1.39** (m) (CH_2 of both **37a** and **38**); **1.17** (m, CH_3 of both **37a** and **38**).

^{13}C NMR ($CDCl_3$, room temperature, 75 MHz) δ: 172.0(C=O of **38**); 166.8 (CH=CH*C*=O of **37a**); 140.7 (*C*H=CHCONEt$_2$ of **37a**); 122.7 (CH=*C*HCONEt$_2$ of **37a**); 42.4, 41.9, 40.0, 39.5 (NCH_2 of both **37a** and **38**); 33.3; 33.0; 32.7; 30.3; 29.9; 28.3; 28.0, 25.1 (4 x CH_2 for each of compounds **37a** and **38**); 14.4, 14.3, 13.1 (NCH$_2$*C*H$_3$ of both **37a** and **38**, 13.1 is a broad singlet); 6.8, 7.1 (ICH_2 of both **37a** and **38**).

GC – MS (GC: T_{int} = 100 °C for 1 min followed by gradient of 8 °C / min to a T_{fin} = 180 °C which was held for 4 min; MS: low resolution, EI, 70 eV) m/z (for **37a**, t_R = 9.8 min): 310 (51.15%, $M^{+\cdot}$ + 1), 309 (15.24%, $M^{+\cdot}$), 237 (2.9%, M-$C_4H_{10}N$), 182 (100%, M – I), 154 (53.69%, M-C_2H_4I); m/z (for **38**, t_R = 10.4 min): 313 (13.53%, $M^{+\cdot}$ + 2), 312

(4.26%, $M^{+\cdot}$ + 1), 184 (50.31%, M − I), 115 (40.70%, M-C_5H_9I), 100 (100%, M-$C_6H_{12}I$).

LRMS (low resolution, CI, NH_3 carrier gas) m/z (for a mixture of **37a** and **38**): 312 [20.8%, ($M^{+\cdot}$ + 1) of **38**], 311 (4.6%, 310 [30.6%, ($M^{+\cdot}$ + 1) of **37a**], 309 (21.8%, $M^{+\cdot}$ of **37a**); **MS** (low resolution, EI, 70ev) m/z (for a mixture of **37a** and **38**): 311 (2.5%, $M^{+\cdot}$ of **38**); 310 [2.1%, (M^{+} + 1) of **37a**], 309 (12.3%, $M^{+\cdot}$ of **37a**).

Preparation of compounds 37a, 37b and 38 *Reaction of iodo-amide* **30** *with* SmI_2 *in the presence of MeOH*

A solution of compound **30** (0.1841g, 0.5993 mmol), SmI_2 (18.0 mL, 0.1 M THF, 1.8 mmol) and MeOH (0.150 mL, 3.69 mmol) in THF (11.8 mL) was stirred for 9.5 h at room temperature. The crude product was purified by chromatotron (once using 25% EtOAc : hexanes and another time using 10% ether : CH_2Cl_2) to allow for the separation of four fractions. The first fraction contained an inseparable mixture of compound **31** [0.0211g, 19.5% yield, R_f = 0.28 (TLC, silica, 25% EtOAc : hexanes)] and **32** (1% yield as determined by ^1H NMR and GC). The second fraction contained recovered starting material **30** [0.0404g, 21.9% yield, R_f = 0.43 (TLC, silica, 10% ether : CH_2Cl_2)] and the third fraction was compound **37b** [0.0103g, 5.6% yield, R_f = 0.13 (TLC, silica, 25% EtOAc : hexanes); The fourth fraction contained 15.8 mg of a mixture of **37a** and **38** [R_f = 0.32 (TLC, silica, 10% ether : CH_2Cl_2)] as a slightly impure sample. The yield of each compound was determined by ^1H NMR (**37a:** 0.0088g, 4.7%; **38:** 0.0070g 3.8%).

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* compounds **37a** and **38** were isolated as an unseparated mixture due to separation problems. The NMR spectra of the mixture were analyzed and the signals which correspond to compound **37a** and **38** are reported.

4. 5. 3. Carbohydrate derived Alkenyl Iodides

2, 3-*O*-(1-methylethylidene)-D-ribonic acid-γ-lactone (41b)

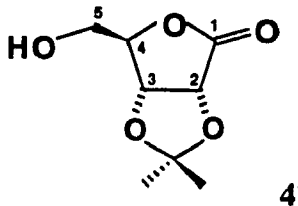
$C_8H_{12}O_5$

MW = 188.18g / mol

R_f = 0.19 (hexanes: EtOAc: MeOH = 7.5 : 1.5 : 1)

mp = 126° -128°C (cf. 133° - 138 °C[27])

$[\alpha]_D$ = -72.1° *c* 1.19



41b

^{1}H NMR ($CDCl_3$, 300 MHz) δ: **4.85** (d, $J_{2,3}$ = 5.6 Hz, 1H, *H-2*), **4.79** (d, $J_{3,2}$ = 5.6 Hz, 1H, *H-3*), **4.64** [apparent t (dd, $J_{4,5b}$ = 1.8 Hz, $J_{4,5a}$ = 2.1 Hz), 1H, *H-4*], **3.98 - 4.04** (ddd, $J_{5a,5b}$ = 12.1 Hz, $J_{5a,OH}$ = 5.2 Hz, $J_{5a,4}$ = 2.3; 1H, *H-5a*), **3.79 - 3.86** (ddd, $J_{5b,5a}$ = 12.1 Hz, $J_{5b,OH}$ = 5.4 Hz, $J_{5b,4}$ = 1.8 Hz, 1H, *H-5b*), **1.93** [apparent t which is actually a dd, $J_{OH,5a}$ = 5.2 Hz, $J_{OH,5b}$ = 5.2 Hz, 1 H, *-OH*); **1.49, 1.39** (2 s, 6H, CH_3 x 2).

^{13}C NMR (acetone-d_6, 50 MHz) δ: 174.6 (C=O); 112.8 (quaternary carbon of isopropylidene protecting group), 83.1, 79.2, 76.2 (C-2, C-3, C-4); 62.0 (C-5); 26.9, 25.4 (2 x CH_3).

IR (nujol): 3463 (s, br, -OH), 1766 (s, br, C=O), 1073 (m, br, C-O) cm^{-1}.

Preparation of Compound 41b

Compound **41b** can be purchased from Pfanstiehl Laboratories or can be prepared from D-ribonolactone using a literature procedure.[27] i.e.: Hydrochloric acid (0.82 mL, 12 M, 9.8 mmol) was added dropwise to a solution of D-ribonolactone (2.3270 g, 0.01571mol) in

acetone (85 mL) and the reaction mixture was stirred at rt for 48 h. The mixture was neutralised by the addition of an excess of $PbCO_3$ and the resulting white suspension was filtered with the aid of Celite. The filtrate was concentrated and the crude product was purified by flash chromatography [5 x 30 cm, silica, R_f = 0.19 (TLC, silica, hexanes: EtOAc: MeOH = 7.5 : 1.5 : 1)] using the following series of eluants: 15 % EtOAc: hexanes (1.7 litres), 5 % MeOH;CH_2Cl_2 (1 litre), and 10 % MeOH:CH_2Cl_2 (0.5 litres). Concentration of the front and tail fractions gave 0.6536 g (22.1%) of a slightly impure sample of **41b** and evaporation of the middle fractions gave 1.8424 g of (62.3 %) of a pure sample. Compound **41b** was isolated as a white crystalline solid. Our spectral data matched those obtained for an authentic sample of **41b** and are in agreement with the data previously reported in the literature.[27]

5-Deoxy-5-iodo-2,3-*O*-(1-methylethylidene)-D-ribonic acid-γ-lactone (42)

$C_8H_{11}O_4I$

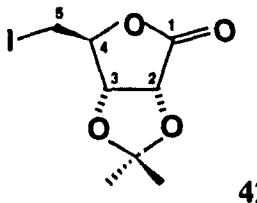
MW = 298.07g / mol

mp = 90 - 93 °C (cf. 92 °C[29])

R_f = 0.23 (20 % hexanes : EtOAc)

$[\alpha]_D$ = -28.0° *c* 1.85;

$[\alpha]_D$ = -24.3° *c* 1.92 (acetone, cf. -31° *c* 1.33[29])



42

^{1}H NMR ($CDCl_3$,300 MHz) δ: **5.00** (d, $J_{2,3}$ = 6.0 Hz, 1H, *H-2*), **4.60 - 4.70** [overlapping signals at 4.65 (dd, $J_{4,5a}$ = 3.6 Hz, $J_{4,5b}$ = 5.6 Hz, *H-4*) and 4.62 (d, $J_{3,2}$ = 6.2 Hz, *H-3*) which together integrate to 2 H], **3.36-3.50** [overlapping signals at 3.45 (dd, $J_{5a,4}$ = 3.2 Hz, $J_{5a,5b}$ = 11.1 Hz, *H-5a*) and 3.40 (dd, $J_{5b,4}$ = 5.2 Hz, $J_{5b,5a}$ = 11.3 Hz, *H-5b*) which together integrate to 2H], **1.49** (s, 3H, CH_3), **1.41** (s, 3H, CH_3).

^{13}C NMR ($CDCl_3$, 50 MHz) δ: 172.9 (C=O), 114.0 (quaternary carbon of isopropylidene protecting group), 80.8, 80.3, 75.2 (C-2, C-3, C-4), 26.5, 26.4 (CH_3 x 2); 5.5 (CH_2I).

IR (nujol): 1774 (s, C=O) cm^{-1}.

MS (low resolution EI) m/z: 283 (100 %, M-CH_3).

Preparation of compound 42 *Procedure (1)*

Compound **42** may be prepared using the general method of Hanessian et al.[28] A solution of N-iodosuccinimide (NIS, 5.4468 g, 0.0242 mol) and 2,3-O-isopropylidene-D-ribonic γ-lactone **41b** (2.0721g, 0.01102 mol) in CH_2Cl_2 (56 mL) was cooled to 0 °C under a nitrogen atmosphere. To this mixture was added, dropwise over 2 h, a solution of triphenylphosphine (Ph_3P, 6.3417 g, 0.02418 mol) in CH_2Cl_2 (28 mL). The flask containing the Ph_3P was rinsed with additional solvent (2 x 5 mL) and the washing were added to the reaction mixture. The reaction mixture was warmed up to rt overnight and then quenched by addition of MeOH (10 mL). The mixture was then diluted with H_2O (50 mL) and the aqueous layer extracted with CH_2Cl_2 (25 mL x 2). The combined organic layers were washed with a saturated aqueous solution of $Na_2S_2O_3$ (50 mL), H_2O (50 mL) and brine (50 mL). The organic layer was then dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography (5 x 20 cm, silica, 20 % hexanes : EtOAc). The front and tail fractions were combined and concentrated to give 0.9016 g (27.4 % yield) of a very slightly impure product. Upon evaporation of the middle fractions, we isolated 1.3970 g (42.5 % yield) of pure **42** as a white crystalline solid. Our spectral data matched those previously reported for an alternate synthesis of this compound.[29]

Preparation of compound 42 *Procedure (2)*

Alternatively, **42** may be prepared according to the general procedure of Wu and Ahlberg.[20] A solution of 2,3-O-isopropylidene-D-ribonic γ-lactone **41b** (3.5495 g, 0.01890 mol) in CH_2Cl_2 (113 mL) was prepared. To this solution was added sequentially, and in small portions, Ph_3P (7.1729 g, 0.02735 mol), imidazole (3.7348 g, 0.05486 mol) and I_2 (6.6132 g, 0.02610 mol). The reaction mixture was stirred at room temperature for 1.5 h and then filtered over silica gel to remove the white precipitate that had formed during the reaction. The filtrate was concentrated and the residue purified by flash chromatography (7 x 22 cm, silica, 20% EtOAc : hexanes) to give the 4.1806 g (74 % yield) of pure **42**. This sample had the same spectral characteristics as those samples prepared using the procedure (1).

5-Deoxy-5-iodo-2,3-*O*-(1-methylethylidene)-β-D-ribose (43)

$C_8H_{13}IO_4$

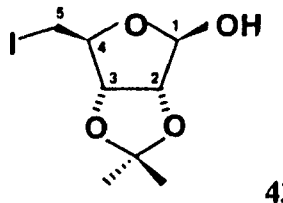
MW = 300.08 g · mol $^{-1}$

pale yellow crystalline solid

mp: 88-90°C

R_f = 0.28 (20% EtOAc:hexanes)

$[\alpha]_D$ = -39.7 ° *c* 1.33



43

^{1}H NMR ($CDCl_3$, 300 MHz) δ: **5.57** [d, $J_{1,OH}$ = 2.9 Hz, 1 H, collapses to a singlet upon D_2O exchange, *H-1*], **4.83** [dd, $J_{3,4}$ = 0.9 Hz, $J_{3,2}$ = 5.8 Hz, 1 H, *H-3*. The COSY experiment shows that this signal is coupled with the signals at δ 4.68 (*H-2*) and δ 4.46 (*H-4*). 1 D decoupling experiments shows that upon irradiation of the signal at δ 4.46 (*H-4*), the signal at δ 4.83 (*H-3*) collapsed to a d ($J_{3,2}$ = 5.5 Hz).], **4.68** [d, $J_{2,3}$ = 5.8 Hz, 1 H, *H-2*. The COSY experiment shows that this signal is coupled with the signal at δ 4.83 (*H-3*).], **4.46** [ddd, $J_{4,3}$ =1.0 Hz, $J_{4,5a}$ =6.2 Hz, $J_{4,5b}$ = 9.7 Hz, 1 H, *H-4*. The COSY experiment and the 1 D

decoupling experiments indicate coupling with the signals at δ 4.83 (*H-3*) an δ 3.24-3.38 (*H-5a+H-5b*). Upon irradiation at δ 4.46 (*H-4*) the signals for the *H-5a+H-5b* protons were simplified and the signal for *H-3* collapsed to a d ($J_{3,2}$ = 5.5 Hz). Likewise, irradiation at each of the *H-3*, *H-5a+H-5b* signals resulted in a change in the appearence of the *H-4* signal at δ 4.46 *ie.* (1) Irradiation at *H-3* resulted in a change of the *H-4* signal to a dd ($J_{4,5a}$ = 6.2 Hz, $J_{4,5b}$ = 9.6 Hz); (2) Irradiation at *H-5a+H-5b* signals resulted in a change of the *H-4* signal to a singlet.], **3.24-3.38** [2 H, overlapping multiplets at 3.35 ppm (dd, $J_{5a,4}$ = 6.2 Hz, $J_{5a,5b}$ = 10.0 Hz, *H-5a*) and at 3.28 ppm (apparent t which is actually an overlapping dd, $J_{5b,4}$ = 9.8 Hz, $J_{5b,5a}$ = 9.9 Hz, *H-5b*). The COSY experiment shows that these signals are coupled with the signal at δ 4.46 (*H-4*).], **2.91** [d, J = 2.9 Hz, 1 H, D_2O exchangeable, *O-H*], **1.49** [s, 3 H, CH_3], **1.35** [s, 3 H, CH_3].

^{13}C NMR ($CDCl_3$, 50 MHz) δ: 112.7 (quaternary carbon of isopropylidene protecting group), 103.3 (C-1), 87.5, 85.9, 83.5 (C-2, C-3, C-4), 26.4, 24.9 (2 x CH_3), 7.5 (ICH_2).

FTIR (nujol): 3380 (s, br, O-H), 1248 (w, C-O), 1063 (m, C-O), 1012 (w, C-O) cm^{-1}.

LRMS: 285 (58.3%, M-CH_3), 196 (14.0%), 127 (22.7%, I^+), 115 (17.3%, loss of CH_3 and ICH_2CHO), 98 (17.0%), 71 (14.1%), 69 (81.6%), 59 [100%, $(CH_3)_2COH^+$].

HRMS: found 284.96220; calculated for M-CH_3 = $C_7H_{10}IO_4$: 284.96256

Preparation of Compound 43

Compound **43** was made by a modified literature procedure.[26b] A solution of iodo-lactone **42** (1.0944g, 3.672 mmol) in CH_2Cl_2 (40.0 mL) was cooled at -78°C under an argon atmosphere. A solution of DIBAL-H (5.50 mL, 20% in hexanes, 7.734 mmol) was added dropwise (over 5 min) to this mixture . The reaction mixture was stirred for 3 h and then

quenched with a saturated aqueous solution of NH_4Cl (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL) and the combined organic layers were washed with a saturated solution of $NaHCO_3$ (40 mL), H_2O (50 mL) and brine (50 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (5 cm x 20 cm, 20% EtOAc:hexanes) to give product **43** (0.9499g, 86% yield).

tert-Butyl (2*Z*)-2,3,7-trideoxy-7-iodo-4,5-*O*-(1-methylethylidene)-D-*ribo*-hept-2-enoate (44a)

$C_{14}H_{23}IO_5$

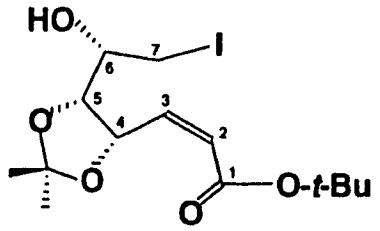
MW = 398.22 g · mol^{-1}

pale yellow crystalline solid

mp: 44-46 °C

R_f = 0.32 (acetone:EtOAc:hexanes = 2:8:90)

$[\alpha]_D$ = +115.8° *c* 1.18



44a

^{1}H NMR ($CDCl_3$, 300 MHz) δ: **6.14** [dd, $J_{3,4}$ = 8.5 Hz, J_{cis} = 11.6 Hz, 1 H, *H-3*. The COSY spectrum shows that this is coupled with the signals at δ 5.97 (*H-2*) and δ 5.48 (*H-4*)], **5.97** [dd, $J_{2,4}$ = 1.2 Hz, J_{cis} =11.6 Hz, 1 H, *H-2*. The COSY spectrum shows that this signal is coupled with the signal at δ 6.14 (*H-3*).], **5.48** [ddd, $J_{4,2}$ = 1.1 Hz, $J_{4,5}$ = 6.2 Hz, $J_{4,3}$ = 8.4 Hz, 1 H, *H-4*. The COSY spectrum indicates coupling with the signals at δ 6.14 (*H-3*) and δ 4.21 (*H-5*)], **4.21** [The signal appears to be a poorly resolved dd ($J_{4,5}$ = 6.2 Hz, $J_{5,6}$ = 8.2 Hz), 1 H, *H-5*. The COSY spectrum indicates coupling with the signals at δ 5.48 (*H-4*) and δ 3.35 (*H-6*).], **3.91** [m, 1 H, *O-H*, D_2O exchangeable. The COSY spectrum shows that this signal is coupled with the signal at δ 3.35 (*H-6*).], **3.51** [1 H, *H-7a*, m. The COSY spectrum shows that this signal is coupled with the signals at δ 3.35 (*H-6+H-7b*)], **3.35** [overlapping

multiplets, 2 H, *H-7b+H-6*. The COSY spectrum shows that this signal is coupled with the signals at δ 3.51 (*H-7a*), δ 4.21 (*H-5*) and δ 3.91 (*O-H*). The signal is sharpened upon D_2O exchange but is still very complex.], **1.51** [s, 3 H, CH_3], **1.48** [s, 9 H, 3 x CH_3], **1.40** [s, 3 H, CH_3].

^{13}C NMR ($CDCl_3$, 75 MHz) δ: 167.0 (C=O), 144.6 (C-3), 124.5 (C-2); 109.7 (quaternary carbon of isopropylidene protecting group); 82.5 [O*C*$(CH_3)_3$], 81.4, 74.6, 69.0 (C-4, C-5, C-6), 28.04 [OC(*C*$H_3)_3$], 27.99, 25.5 (2 x OCH_3); 11.9 (ICH_2).

FTIR: 3434 (s, O-H), 1680 (s, C=O), 1636 (m, C=C), 1461 (w, C-H), 1410 (s, C-H), 1370 (m, CH_3), 1259 (s, C-O), 1215 (m, C-O), 1159 (s, C-O), 1136 (m, C-O), 1067 (m, C-O), 1039 (s, C-O) cm^{-1}.

CIMS: 399 (20.8%, M+1), 360 (27.8%), 343 [100%, (M+1)-C_4H_8], 171 (90.9%, ICH_2CHOH^+).

LRMS: 383 (0.5%, M-CH_3), 342 (5.4%, loss of C_4H_8), 327 (8.5%, loss of C_4H_8 and CH_3), 267 (15.5%), 171 (53.6%, ICH_2CHOH^+), 157 (16.2%, loss of ICH_2CHOH, CH_3 and C_4H_7), 142 (22.9%), 113 (33.2%), 97 (27.1%), 85 (13.0%), 84 (26.8%), 59 (82.2%, $(CH_3)_2OH^+$), 57 (100%, $C_4H_9^+$).

HRMS: found 383.03650; calculated for M-CH_3 = $C_{13}H_{20}IO_5$: 383.03572

***tert*-Butyl (*2E*)-2,3,7-trideoxy-7-iodo-4,5-*O*-(1-methylethylidene)-D-*ribo*-hept-2-enoate (44b)**

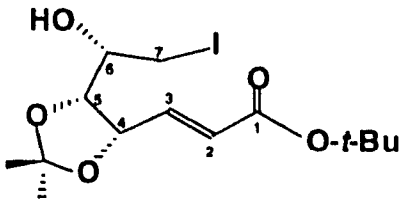
$C_{14}H_{23}IO_5$

MW = 398.22 g · mol^{-1}

pale yellow oil

R_f = 0.19 (acetone : EtOAc : hexanes = 2:8:90)

$[\alpha]_D$ = -10.9 ° *c* 1.63



44b

^{1}H NMR ($CDCl_3$, 300 MHz) δ: **6.96** [dd, $J_{3,4}$ = 5.1 Hz, J_{trans} = 15.6 Hz, 1 H, *H-3*. The COSY spectrum shows that this signal is coupled with the signals at δ 6.08 (*H-2*) and δ 4.85 (*H-4*)], **6.08** [dd, $J_{2,4}$ = 1.7 Hz, J_{trans} = 15.6 Hz, 1 H, *H-2*. The COSY spectrum indicates coupling with the signal at δ 6.96 (*H-3*) and weak coupling with the signal at δ 4.85 (*H-4*)], **4.85** [ddd, $J_{4,2}$ = 1.7 Hz, $J_{4,3}$ = 5.1 Hz, $J_{4,5}$ = 8.3 Hz, 1 H, *H-4*. The COSY spectrum indicates coupling with the signals at δ 6.96 (*H-3*) and δ 4.05 (*H-5*) and weak coupling with the signal at δ 6.08 (*H-2*)], **4.05** [appears to be a dd ($J_{5,6}$ = 6.6 Hz, $J_{5,4}$ = 8.6 Hz) but is actually more complex, 1 H, *H-5*. The COSY spectrum indicates coupling with the signals at δ 4.85 (*H-4*) and δ 3.36 (*H-6*) and weak coupling with the signal at δ 3.55 (*H-7a*).], **3.55** [appears to be a dd ($J_{7a,6}$ = 6.0 Hz, $J_{7a,7b}$ = 13.6 Hz) but is actually more complex , 1 H, *H-7a*. The COSY spectrum shows that this signal is coupled with the signals at δ 3.36 (*H-6+H-7b*) and weakly coupled with the signals at δ 4.05 (*H-5*) and δ 2.61 (*O-H*)], **3.36** [overlapping multiplets, 2 H, *H-7b* + *H-6*. The COSY spectrum shows that this signal is coupled with the signals at δ 3.55 (*H-7a*), δ 4.05 (*H-5*) and δ 2.61 (*O-H*)], **2.61** [d, J = 5.2 Hz, D_2O exchangeable, 1 H, *O-H*. The COSY spectrum shows that this signal is coupled with the signals at δ 3.36 (*H-6*) and weakly coupled with the signals at δ 3.55 (*H-7a*)], **1.49** [s, 12 H, 4 x CH_3], **1.37** [s, 3 H, CH_3].

^{13}C NMR ($CDCl_3$, 75 MHz) δ: 165.6 (C=O), 141.8 (C-3), 124.3 (C-2); 109.5 (quaternary carbon of isopropylidene protecting group); 80.7 [$OC(CH_3)_3$], 79.9, 76.5, 69.0 (C-4, C-5, C-6), 28.1 [$OC(CH_3)_3$], 27.6, 25.1 (2 x OCH_3); 14.5 (ICH_2).

FTIR: 3444 (strong broad signal, O-H), 2981 (s, C-H), 2933 (m, C-H), 1714 (s, C=O), 1695 (s, C=O), 1657 (m,C=C), 1456 (w, C-H), 1381 (m, CH_3), 1369 (s, CH_3), 1318 (s, CH_3), 1258 (m, C-O), 1217 (m, C-O), 1153 (s, C-O), 1057 (s, C-O).

LRMS: 383 (10.6%, M-CH_3), 342 (8.8%, M-C_4H_8), 327 (2.9%, loss of CH3 and C_4H_8), 325 (5.1%), 227 (18.7%, loss of ICH_2CHOH), 171 (31.2%, ICH_2CHOH^+), 157 (20.7%, loss of ICH_2CHOH, CH_3 and C_4H_7), 142 (48.1%), 114 (36.3%), 97 (32.7%), 84 (38.8%), 59 [65.4%, $(CH_3)_2OH^+$], 57 (100%, $C_4H_9^+$).

HRMS: found 383.03600; calculated for M-CH_3 = $C_{13}H_{20}IO_5$: 383.03572

Preparation of Compounds 44a and 44b

A solution of (t-Butyloxycarbonyl)methylenetriphenylphosphorane (0.2924 g, 0.7767 mmol) in CH_2Cl_2 (8.0 mL) was prepared at 0°C under an argon atmosphere. To this solution was added, dropwise over 10 min, a solution of iodo-lactol **43** (0.1503 g, 0.5008 mmol) and benzoic acid (0.9 mg, 0.008 mmol) in CH_2Cl_2 (2 mL plus 2 x 1 mL). The reaction flask was covered with aluminum foil and the solution was stirred at 0°C for 10 min and then at rt for 4.5 h. Saturated aqueous NH_4Cl (10 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers were washed with a saturated solution of $NaHCO_3$ (25 mL), H_2O (25 mL) and brine (25 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated and the residue was dissolved in EtOAc (1.5 mL). Hexanes (25 mL) were added and the resulting cloudy solution was cooled at 0°C overnight. The white crystalline triphenylphosphine oxide was removed by filtration and the filtrate was

concentrated. Purification of the residue by flash chromatography (2.5 cm x 26 cm, silica gel, acetone:EtOAc:hexanes = 2:8:90) allowed the separation of *cis* ester **44a** (0.1713g, 86 % yield) and *trans* ester **44b** (0.0222g, 11 %, yield).

(2*Z*)-*N*, *N*-Dimethyl-2,3,7-trideoxy-7-iodo-4,5-*O*-(1-methylethylidene)-D-*ribo*-hept-2-enamide (45a)

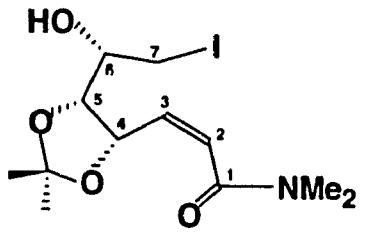
$C_{12}H_{20}INO_4$

MW = 369.187 g · mol^{-1}

pale yellow oil

R_f = 0.43 (70% EtOAc:hexanes)

$[\alpha]_D$ = +122.5 ° *c* 1.84



45a

^{1}H NMR ($CDCl_3$, 300 MHz) δ: **6.32** [d, J_{cis} = 11.5 Hz, 1 H, *H-2*. The COSY spectrum shows that this signal is coupled with the signals at δ 6.01 (*H-3*) and weakly coupled with the signal at δ 5.18 (*H-4*)], **6.15** (poorly resolved s, 1 H, *O-H*, D_2O exchangeable. The COSY spectrum shows that this signal is coupled with the signals at δ 3.33 (*H-7b*+*H-6*) and δ 3.52 (*H-7a*)], **6.01** [dd, $J_{3,4}$ = 9.1, J_{cis} = 11.5 Hz, 1 H, *H-3*. The COSY spectrum shows that this signal is coupled with the signals at δ 6.32 (*H-2*) and δ 5.18 (*H-4*)], **5.18** [m, 1 H, *H-4*. The COSY spectrum indicates coupling with the signals at δ 6.01 (*H-3*) and δ 4.14 (*H-5*) and a weak coupling with the signal at δ 6.32 (*H-2*).], **4.14** [m, 1 H, *H-5*. The COSY spectrum indicates coupling with the signals at δ 5.18 (*H-4*) and δ 3.33 (*H-7b*+*H-6*) and a weaker coupling with the signal at δ 3.52 (*H-7a*).], **3.52** [m, 1 H, *H-7a*. The COSY spectrum show that this signal is coupled with the signals at δ 6.15 (*O-H*) and δ 3.33 (*H-7b*) and weakly coupled with the signal at δ 4.14 (*H-5*). The signal is somewhat sharpened upon D_2O exchange but is still very complex.], **3.33** [m, 2 H, (*H-6*+*H-7b*). The COSY spectrum shows that this signal is coupled with the signals at δ 4.14 (*H-5*), δ 6.15 (*O-H*) and δ 3.52 (*H-7a*).

The signal is sharpened upon D_2O exchange but is still very complex.], **3.04** [s, 3 H, NCH_3], **2.97** [s, 3 H, NCH_3], **1.50** [s, 3 H, CH_3], **1.37** [s, 3 H, CH_3].

^{13}C NMR ($CDCl_3$, 75 MHz) δ: 167.1 (C=O), 141.5 (C-3), 124.2 (C-2); 109.6 (quaternary carbon of isopropylidene protecting group), 81.9, 75.3, 68.3 (C-4, C-5, C-6), 37.9, 35 2 (2 x NCH_3), 28.0, 25.4 (2 x CH_3); 12.0 (ICH_2).

FTIR (film): 3249 (br, O-H), 1649 (w, C=C), 1607 (s, C=O), 1381 (w, CH_3), 1217 (w, C-O), 1065 (w, C-O), 1048 (m, C-O), 871 (m, vinylic C-H bending) cm^{-1}.

LRMS: 369 (0.3%, $M^{+\bullet}$), 354 (3.4%, M-CH_3), 184 (15.5%, loss of ICH_2 and NMe_2), 170 (24.3%, loss of I and $CONMe_2$), 141 (100%, ICH_2^+), 111 (45.0%, loss of ICH_2CHOH, CH_3 and $CONMe_2$), 97 (26.0%), 72 (45.2%, $CONMe_2^+$).

HRMS: found 354.02080; calculated for M-CH_3 = $C_{11}H_{17}INO_4$: 354.02041

(*2E*)-*N*, *N*-Dimethyl-2,3,7-trideoxy-7-iodo-4,5-*O*-(1-methylethylidene)-D-*ribo*-hept-2-enamide (45b)

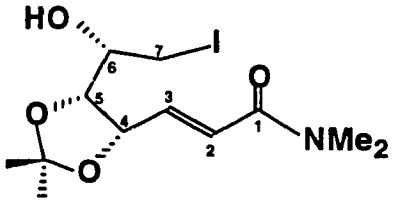
$C_{12}H_{20}INO_4$

MW = 369.187 g · mol^{-1}

pale yellow oil

R_f = 0.16 (70% EtOAc:hexanes)

$[\alpha]_D$ = -18.9 ° *c* 1.50



45b

^{1}H NMR ($CDCl_3$, 300 MHz) δ: **6.98** [apparent dd, $J_{3,4}$ = 4.8 Hz, J_{trans} = 15.1 Hz, 1 H, *H-3*. The COSY spectrum shows that this signal is coupled with the signals at δ 6.60 (*H-2*) and δ

4.91 (*H-4*)], **6.60** [apparent dd, $J_{2,4}$ = 1.6 Hz, J_{trans} = 15.1 Hz, 1 H, *H-2*. The COSY spectrum shows that this signal is coupled with the signals at δ 6.98 (*H-3*) and δ 4.91 (*H-4*)], **4.91** [m, 1 H, *H-4*. The COSY spectrum indicates coupling with the signals at δ 6.98 (*H-3*), δ 4.09 (*H-5*) and δ 6.60 (*H-2*).], **4.36** [broad s, 1 H, *-OH*, D_2O exchangeable. The COSY spectrum indicates coupling with the signal at δ 3.30-3.44 (*H-6*). The chemical shift for the *O-H* proton is variable.], **4.09** [dd, J = 6.9, 8.3 Hz, 1 H, *H-5*. The COSY spectrum indicates coupling with the signals at δ 4.91 (*H-4*) and δ 3.30-3.44 (*H-6*).], **3.53** [the signal appears to be a distorted d, 1 H, *H-7a*. The COSY spectrum shows that this signal is coupled with the signal at δ 3.30-3.44 (*H-6+H-7b*). Upon D_2O exchange this signal sharpens to a dd ($J_{7a,6}$ = 2.2 Hz, $J_{7a,7b}$ = 9.9 Hz).], **3.30-3.44** [m, 2 H, *H-6+H-7b*. The COSY spectrum shows that this signal is coupled with the signals at δ 3.53 (*H-7a*), δ 4.36 (*O-H*) and δ 4.09 (*H-5*). After D_2O exchange the signal attributed to *H-7b* is clearly visible as a dd centered at 3.31 ppm ($J_{7b,6}$ = 6.8 Hz, $J_{7a,7b}$ = 9.8 Hz) and the signal attributed to *H-6* is somewhat simplified. The *H-6* signal appears as an apparent dt centered at 3.39 ppm but is actually a distorted ddd. We were only able to determine, with confidence, two of the coupling conctants (J = 2.2, 6.8 Hz).], **3.11** [s, 3 H, NCH_3], **3.03** [s, 3 H, NCH_3], **1.50** [s, 3 H, CH_3], **1.40** [s, 3 H, CH_3].

^{13}C NMR ($CDCl_3$, 75 MHz) δ: 166.5 (C=O), 140.5 (C-3), 121.3 (C-2), 109.2 (quaternary carbon of isopropylidene protecting group), 80.1, 76.8, 68.7 (C-4, C-5, C-6); 37.5, 35.8 (2 x NCH_3); 27.6, 25.1 (2 x CH_3); 14.5 (ICH_2).

FTIR (film): 3354 (br, O-H), 1662 (m, C=C), 1608 (s, C=O), 1401 (m), 1381 (m, CH_3), 1216 (m, C-O), 1150 (w, C-O), 1056 (m, C-O) cm^{-1}.

CIMS: 370 (40.7%, $M^{+\bullet}$+1), 354 (4.4%, M-CH_3), 242 (18.9%, loss of I), 184 (24.5%, loss of ICH_2 and NMe_2), 141 (100%, ICH_2^+), 111 (81.2%, loss of ICH_2CHOH, CH_3 and $CONMe_2$).

LRMS: 369 (0.8%, $M^{+\bullet}$), 354 (3.0%, M-CH_3), 205 (26.0%), 184 (26.5%, loss of ICH_2 and NMe_2), 141 (60.7%, ICH_2^+), 111 (58.9%, loss of ICH_2CHOH, CH_3 and $CONMe_2$), 97 (28.7%), 84 (40.4%), 72 (100%, $CONMe_2^+$).

HRMS: found: 369.04340; calculated for $C_{12}H_{20}INO_4$: 369.04388

(*2E*)-*N*, *N*-Dimethyl-6,7-anhydro-2,3-dideoxy-4,5-*O*-(1-methylethylidene)-D-*ribo*-hept-2-enamide (47)

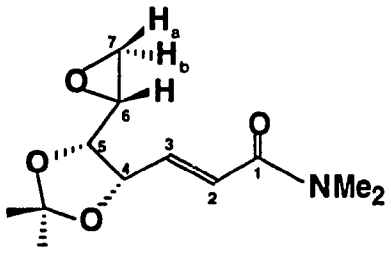
$C_{12}H_{19}NO_4$

MW = 241.277 g · mol^{-1}

pale yellow oil

R_f = 0.13 (70% EtOAc:hexanes)

$[\alpha]_D$ = -7.7 ° *c* 1.43



47

^{1}H NMR ($CDCl_3$, 300 MHz) δ: **6.94** [dd, $J_{3,4}$ = 5.4 Hz, J_{trans} = 15.1 Hz, 1 H, *H-3*. The COSY experiment shows that this signal is coupled with the signals at δ 6.64 (*H-2*) and δ 4.93 (*H-4*).], **6.64** (dd, $J_{2,4}$ = 1.5 Hz, J_{trans} = 15.1 Hz, 1 H, *H-2*. The COSY experiment only showed coupling with the signal at δ 6.94 (*H-3*).], **4.93** [m, 1 H, *H-4*. The COSY experiment indicates coupling with the signal at δ 6.94 (*H-3*) and δ 3.90 (*H-5*).], **3.90** [apparent t which is actually a dd, $J_{5,6}$ = 6.9 Hz, $J_{5,4}$ = 6.9 Hz, 1 H, *H-5*. The COSY experiment shows that this signal is coupled with the signal at δ 4.93 (*H-4*) and δ 2.93 (*H-6*).], **3.11** [s, 3 H, NCH_3], **3.02** [s, 3 H, NCH_3], **2.93** [m, 1 H, *H-6*. The COSY experiment shows that this signal is coupled with the signals at δ 3.90 (*H-5*), δ 2.83 (*H-7a*) and δ 2.72 (*H-7b*).], **2.83** [m, 1 H, *H-7a*. The COSY experiment shows that this signal is coupled with the signals at δ 2.93 (*H-6*) and δ 2.72 (*H-7b*).], **2.72** [dd, J = 2.6, 5.1 Hz, 1 H, *H-7b*. The COSY experiment shows that

this signal is coupled with the signals at δ 2.93 (*H-6*) and δ 2.83 (*H-7a*).], **1.55** [s, 3 H, CH_3], **1.40** [s, 3 H, CH_3].

^{13}C NMR ($CDCl_3$, 75 MHz) δ: 165.7 (C=O), 138.8 (C-3), 122.4 (C-2); 109.8 (quaternary carbon of isopropylidene protecting group), 78.8, 77.2 (C-4, C-5), 49.9 (C-6), 45.8 (C-7), 37.4, 35.7 (2 x NCH_3), 27.6, 25.1 (2 x CH_3).

FTIR (film): 1666 (m, C=C), 1622 (s, C=O), 1398 (w, CH_3), 1215 (w, C-O), 1052 (w, C-O).

CIMS: 242 (90.5%, M+1), 226 (3.9%, M-CH_3), 184 (11.8%), 169 (8.3%, loss of $CONMe_2$), 111 (100%, loss of CH_2CHO, CH_3 and $CONMe_2$).

LRMS: 241 (0.8%, $M^{+\cdot}$), 226 (5.7%, M-CH_3), 169 (12.7%, loss of $CONMe_2$), 149 (23.7%), 111 (100%, loss of epoxide ring CH_2CHO, CH_3 and $CONMe_2$), 97 (22.5%), 82 (17.6%), 72 (32.6%, $CONMe_2^+$).

HRMS: found 226.10770; calculated for M-CH_3 = $C_{11}H_{16}NO_4$: 226.10792

Preparation of Compounds 45a, 45b and 47

A solution of Ph_3P=$CHCONMe_2$ **62** (0.2055g, 0.5915 mmol) in THF (8.0 mL) was prepared at O° C under an argon atmosphere. To this solution was added, dropwise over 10 min, a solution of iodo lactol **43** (0.1173g, 0.3908 mmol) and benzoic acid (0.6 mg, 0.0053 mmol) in THF (1.5 mL plus 0.25 mL x 2). The reaction flask was covered with aluminum foil and the solution was stirred at O°C for 10 min and at rt overnight. A saturated aqueous solution of NH_4Cl (6 mL) was added and the mixture was diluted with H_2O (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 15 mL) and the combined organic layers were washed with saturated aqueous solution of $NaHCO_3$ (20 mL), H_2O (20 mL) and brine (30 mL). The

organic phase was dried over $MgSO_4$, filtered and concentrated and the residue was dissolved in a minimum amount of CH_2Cl_2. Hexanes were added and the resulting cloudy solution was cooled at 0^0C overnight. The white crystalline solid triphenylphosphine oxide was removed by filtration and the filterate was then concentrated. Purification of the residue by flash chromatography (2 cm x 19 cm silica gel, 70% EtOAc:hexanes) allowed for the separation of four major fractions. The first fraction contained starting material **43** (0.0304g, 26 % yield) and diacetal **60** (0.0087g, 8.5% yield). The second fraction contained the desired *cis* α, β-unsaturated amide **45a** (0.0350g, 25% yield) and the third fraction contained the *trans* isomer **45b** (0.0382g, 27 % yield). The fourth fraction contained a trace amount of the epoxide **47** (0.0005g, 0.4 % yield).

(*2Z*)-*N*, *N*-Diethyl-2,3,7-trideoxy-7-iodo-4,5-*O*-(1-methylethylidene)-D-*ribo*-hept-2-enamide (46a)

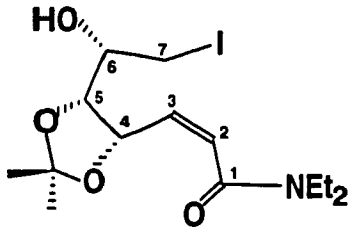
$C_{14}H_{24}INO_4$

$MW = 397.237\ g \cdot mol^{-1}$

pale yellow oil

$R_f = 0.83$ (70% EtOAc:hexanes)

$[\alpha]_D = +131.1^{\circ}\ c\ 2.02$



46a

^{1}H NMR ($CDCl_3$, 300 MHz) δ: **6.31** [apparent d, J_{cis} = 11.7 Hz, 2 H, *H-2+O-H*. The COSY spectrum shows that this signal is coupled with the signals at δ 6.01 (*H-3*) and δ 3.21-3.59 (*H-6*). Upon D_2O exchange, the signal appears as a dd ($J_{2,4}$ = 1.0 Hz, J_{cis} = 11.5 Hz) which integrates to 1 H. The D_2O exchange COSY experiment shows that the signal is now only coupled with the signal at δ 6.01 (*H-3*).], **6.01** [dd, $J_{3,4}$ = 9.1 Hz, J_{cis} = 11.5 Hz, 1 H, *H-3*. The COSY spectrum shows that this signal is coupled with the signals at δ 6.31 (*H-2*) and δ 5.20 (*H-4*)], **5.20** [dd, $J_{4,5}$ = 6.2 Hz, $J_{4,3}$ =9.0 Hz, 1 H, *H-4*. The COSY spectrum indicates

coupling with the signals at δ 6.01 (*H-3*) and δ 4.17 (*H-5*)], **4.17** [m, 1 H, *H-5*. The COSY spectrum indicates coupling with the signal at δ 5.20 (*H-4*) and 2 couplings with the m between δ 3.21-3.59], **3.21-3.59** [7 H, overlapping signals, *H-6*, *H-7a*, *H-7b* and 2 x NCH_2. The COSY spectrum shows that the signals are coupled with those at δ 4.17 (*H-5*), δ 6.31 (*O-H*), δ 1.20 (NCH_2CH_3) and δ 1.14 (NCH_2CH_3). Furthermore, the COSY experiment shows that there are additional couplings between protons within the δ 3.21-3.59 region. The coupling between the δ 6.31 and δ 3.21-3.59 signals disappars upon D_2O exchange.], **1.51** [s, 3 H, CH_3], **1.39** [s, 3 H, CH_3], **1.20** [t, J = 7.2 Hz, 3 H, NCH_2CH_3. The COSY experiment shows that this signal is coupled with the signal at δ 3.21-3.59 (NCH_2).], **1.14** [t, J = 7.1 Hz, 3 H, NCH_2CH_3. The COSY experiment shows coupling with the signal at δ 3.21-3.59 (NCH_2).].

^{13}C NMR ($CDCl_3$, 75 MHz) δ: 166.4 (C=O), 141.5 (C-3), 124.4 (C-2); 109.6 (quaternary carbon of isopropylidene protecting group), 82.0, 75.4, 68.3 (C-4, C-5, C-6), 43.0, 40.4 (2 x NCH_2), 28.0, 25.5 (2 x CH_3); 14.1, 12.9 (2 x NCH_2CH_3), 12.1 (ICH_2).

FTIR (film): 3252 (br, O-H), 1644 (w, C=C), 1602 (s, C=O), 1486 (w), 1381 (w, CH_3), 1270 (w, C-O), 1217 (m, C-O), 1048 (m, C-O) cm^{-1}.

LRMS: 397 (0.6%, $M^{+\bullet}$), 382 (4.2%, M-CH_3), 322 (7.7%), 212 (34.1%), 198 (32.4%), 169 (100%, loss of ICH_2, CH_3 and NEt_2), 139 (51.9%, loss of ICH_2CHOH, CH_3 and NEt_2), 124 (18.7%), 100 (36.0%, $CONEt_2^+$), 74 (36.6%), 72 (36.0%, NEt_2^+).

HRMS: found: 397.07500; calculated for $C_{14}H_{24}INO_4$: 397.07518

(2*E*)-*N*, *N*-Diethyl-2,3,7-trideoxy-7-iodo-4,5-*O*-(1-methylethylidene)-D-*ribo*-hept-2-enamide (46b)

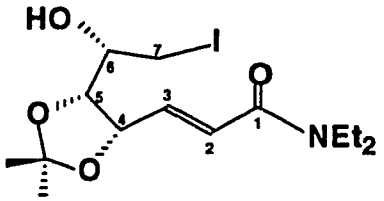
$C_{14}H_{24}INO_4$

MW = 397.237 g · mol^{-1}

pale yellow oil

R_f = 0.35 (70% EtOAc:hexanes)

$[\alpha]_D$ = -4.5 ° *c* 0.4



46b

^{1}H NMR ($CDCl_3$, 300 MHz) δ: **6.99** [apparent dd, $J_{3,4}$ = 5.0 Hz, J_{trans} =15.1 Hz, 1 H, *H-3*. The COSY spectrum shows that this signal is coupled with the signals at δ 6.54 (*H-2*) and δ 4.90 (*H-4*)], **6.54** (dd, $J_{2,4}$ = 1.7 Hz, J_{trans} =15.1 Hz, 1 H, *H-2*. The COSY spectrum indicated coupling with the signals at δ 6.99 (*H-3*) and a weak coupling with the signal at δ 4.90 (*H-4*)], **4.90** [ddd, $J_{4,2}$ = 1.7 Hz, $J_{4,3}$ =5.0 Hz, $J_{4,5}$ = 6.6 Hz, 1 H, *H-4*. The COSY spectrum indicates coupling with the signals at δ 6.99 (*H-3*) and δ 4.10 (*H-5*) and a weak coupling with the signal at δ 6.54 (*H-2*)], **4.10** [m, 1 H, *H-5*. The COSY spectrum indicates coupling with the signals at δ 4.90 (*H-4*) and δ 3.41 (*H-6*). The signal is simplified to a dd ($J_{5,6}$ = 8.8 Hz, $J_{5,4}$ = 6.9 Hz) upon D_2O exchange.], **3.56** [The signal appears as a poorly resolved dd, 1 H, *H-7a*. The COSY spectrum only showed coupling with the signal at δ 3.41 (*H-6, H-7b*). The signal is simplified to a well resolved dd ($J_{7a,6}$ = 2.2 Hz, $J_{7a,7b}$ = 9.9 Hz) upon D_2O exchange.], **3.41** [6 H, overlapping signals of *H-6*, *H-7b* and 2 x CH_2. The COSY spectrum shows that this signal is coupled with the signals at δ 3.56 (*H-7a*), δ 4.10 (*H-5*), 1.21 (NCH_2CH_3) and 1.16 (NCH_2CH_3). The signal is sharpened upon D_2O exchange but is still very complex.], **2.25** [s, 1 H, *O-H*, D_2O exchangeable], **1.50** [s, 3 H, CH_3], **1.40** [s, 3 H, CH_3], **1.21** [t, J = 7.1 Hz, 3 H, NCH_2CH_3. The COSY experiment shows that this signal is

coupled with the signal at δ 3.41 (NCH_2).], **1.16** [t, J = 7.1 Hz, 3 H, NCH_2CH_3. The COSY experiment shows that this signal is coupled with the signal at δ 3.41 (NCH_2).]

^{13}C NMR ($CDCl_3$, 75 MHz) δ: 165.4 (C=O), 140.2 (C-3), 122.1 (C-2); 109.4 (quaternary carbon of isopropylidene protecting group), 80.1, 76.9, 68.9 (C-4, C-5, C-6), 42.3, 40.8 (2 x NCH_2), 27.7, 25.2 (2 x CH_3); 14.8 (NCH_2CH_3), 14.5 (ICH_2), 13.1 (NCH_2CH_3).

FTIR (film): 3353 (br, O-H), 1661 (m, C=C), 1604 (s, C=O), 1461 (m, C-H), 1381 (m, CH_3), 1217 (m, C-O), 1057 (m, C-O) cm^{-1}.

LRMS: 397 (1.2%, $M^{+\bullet}$), 382 (3.2%, M-CH_3), 212 (38.0%), 198 (43.5%), 169 (45.9%, loss of ICH_2, CH_3 and NEt_2), 139 (72.9%, loss of ICH_2CHOH, CH_3 and NEt_2), 126 (51.5%, loss of ICH_2CHOH and $CONEt_2$), 100 (100%, $CONEt_2^+$), 72 (94.5%, NEt_2^+).

HRMS: found: 397.07540; calculated for $C_{14}H_{24}INO_4$: 397.07518

1,5-Anhydro-2,3-*O*-(1-methylethylidene)-β-D-ribose (60)

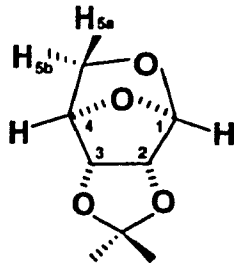
$C_8H_{12}O_4$

MW = 172.2 g · mol^{-1}

white crystalilne solid

mp: 63-64 °C (cf.[36] 64-66 °C)

R_f = 0.23 (acetone:EtOAc:hexanes = 5:2:43)



60

^{1}H NMR ($CDCl_3$, 300 MHz) δ: **5.46** [s, 1 H, *H-1*], **4.72** (d, $J_{4,5b}$ = 3.8 Hz, 1 H, *H-4*. The COSY experiment shows that this signal is only coupled with the signal at δ 3.45 (*H-5b*).],

4.35 [d, J = 5.5 Hz, 1 H, *H-2* or *H-3*. The COSY experiment indicates coupling with the signal at δ 4.30.], **4.30** [d, J = 5.5 Hz, 1 H, *H-2* or *H-3*. The COSY experiment indicates coupling with the signal at δ 4.35.], **3.45** (dd, $J_{5b,4}$ = 3.8 Hz, $J_{5b,5a}$ = 7.2 Hz,1 H, *H-5b*. The COSY experiment indicates coupling with the signal at δ 4.72 (*H-4*) and δ 3.32 (*H-5a*)], **3.32** [d, $J_{5a,5b}$ = 7.3 Hz, 1 H, *H-5a*. The COSY experiment shows that this signal is only coupled with the signal at δ 3.45 (*H-5b*).], **1.47** [s, 3 H, CH_3], **1.30** [s, 3 H, CH_3]

^{1}H NMR (C_6D_6, 300 MHz) δ: **5.38** [s, 1 H, *H-1*], **4.14** (d, J = 3.9 Hz, 1 H, *H-4*], **3.96** [d, J = 5.4 Hz, 1 H, *H-2* or *H-3*], **3.66** [d, J = 5.5 Hz, 1 H, *H-2* or *H-3*], **2.91** [dd, J = 3.7, 7.2 Hz, 1 H, *H-5b*], **2.55** [d, J = 7.1 Hz, 1 H, *H-5a*], **1.47** [s, 3 H, CH_3], **1.10** [s, 3 H, CH_3].

^{13}C NMR ($CDCl_3$, 75 MHz) δ: 112.2 (quaternary carbon of isopropylidene protecting group), 99.8 (C-1), 81.3, 79.3, 77.7 (C-2, C-3 and C-4), 63.0 (C-5), 25.9, 25.3 [$(CH_3)_2C$].

FTIR (KBr): 2971 (w, C-H), 1388 (m, CH_3), 1279 (w, C-O), 1216 (m, C-O), 1163 (w, C-O), 1092 (s, C-O), 1055 (s, C-O) cm^{-1}.

LRMS: 157 (45.1%, M-CH_3), 114 (43.5%), 85 (45.4%), 68 (100%), 59 [69.9%, $(CH_3)_2COH^+$], 43 (71.4%, CH_3CO^+).

These spectral data are in agreement with those in the literature report[36]

Preparation of Compounds 46a, 46b and 60

A solution of Ph_3P=CHCONEt_2 **64** (0.2926g, 0.7889 mmol) in CH_2Cl_2 (8.0 mL) was prepared at 0°C under an argon atmosphere. To this solution was added, dropwise over 10 min, a solution of iodo-lactol **43** (0.1527g, 0.5085 mmol) and benzoic acid (0.0011g, 0.0098 mmol) in CH_2Cl_2 (2.0 mL plus 1 mL x 2). The reaction flask was covered with aluminum foil and the solution was stirred at 0°C for 10 min and then at rt overnight. A saturated

aqueous solution of NH_4Cl (6 mL) was added and the mixture was diluted with H_2O (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$ (25 mL), H_2O (25 mL) and brine (25 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated and the residue was dissolved in a minimum amount of CH_2Cl_2. Hexanes were added and the resulting cloudy solution was cooled at 0°C overnight. The precipitated white crystalline triphenylphosphine oxide was removed by filtration and the filtrate was then concentrated. Purification of the residue by flash chromatography (3 cm x 20 cm, silica gel, using a series of eluants [(1). acetone:EtOAc:hexanes = 5:2:43; (2) 70% EtOAc:hexanes] allowed us to separate three major fractions. The first fraction contained the side product **60** (0.0144g, 16% yield). The second fraction contained the desired *cis* N,N-diethyl amide **46a** (0.0818g, 41% yield). The third fraction contained *trans* N,N-diethyl amide **46b** (0.0161g, 8.7% yield).

(2*Z*)-2,3,7-Trideoxy-7-iodo-4,5-*O*-(1-methylethylidene)-D-*ribo*-hept-2-enitol (48)

$C_{10}H_{17}IO_4$

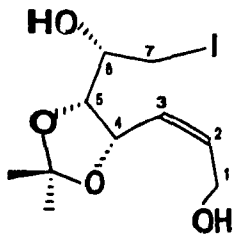
MW = 328.41 $g \cdot mol^{-1}$

pale yellow crystalline solid

mp: 88-90 °C

R_f = +0.27 (50% EtOAc :hexanes)

$[\alpha]_D = 30.4^\circ$ *c* 16.5



48

^{1}H NMR ($CDCl_3$, 300 MHz) δ: **5.97** [1H, *H-2*, the signal has appearance of a m but is actually a dddd in which there is some overlap of the spectral lines. We were able to determine the following associated J values: J_{cis} = 11.2 Hz; $J_{2,4}$ = 1.1 Hz. The $J_{2,1a}$ (7.4 Hz) and $J_{2,1b}$ (6.4 Hz) values were determined by analysis of the δ 4.29 and δ 4.13 signals. The COSY spectrum indicates coupling with the signals at δ 5.67 (*H-3*), δ 4.29 (*H-1a*) and δ 4.13

(*H-1b*).], **5.67** [1H, *H-3*, the signal has appearance of a m but is actually a ddd ($J_{3,1a}$ = 1.3 Hz, $J_{3,4}$ = 9.5 Hz, J_{cis} = 11.1 Hz). The COSY spectrum indicates coupling with the signals at δ 5.15 (*H-4*) and δ 5.97 (*H-2*).], **5.15** [ddd, $J_{4,2}$ = 1.0 Hz, $J_{4,5}$ = 6.1 Hz, $J_{4,3}$ = 9.4 Hz, 1 H, *H-4*. The COSY spectrum indicates coupling with the signals at δ 5.67 (*H-3*) and δ 4.04 (*H-5*).], **4.29** [ddd, $J_{1a,3}$ = 1.5 Hz, $J_{1a,2}$ = 7.4 Hz, $J_{1a,1b}$ = 12.4 Hz, 1 H, *H-1a*. The COSY spectrum shows that this signal is coupled with the signals at δ 5.97 (*H-2*) and δ 4.13 (*H-1b*).], **4.13** [dd, $J_{1b,2}$ = 6.4 Hz, $J_{1b,1a}$ = 12.3 Hz, 1 H, *H-1b*. The COSY spectrum indicates coupling with the signals at δ 5.97 (*H-2*) and δ 4.29 (*H-1a*).], **4.04** [dd, $J_{5,4}$ = 6.2 Hz, $J_{5,6}$ = 8.7 Hz, 1 H, *H-5*. The COSY spectrum indicates coupling with the signals at δ 5.15 (*H-4*) and δ 3.42 (*H-6*).], **3.58** [1H, *H-7a*, m. The COSY spectrum shows that this signal is only coupled with the signal at δ 3.42 (*H-6* + *H-7b*).], **3.42** [overlapping multiplets which together integrate to 3 H, *H-6*, *H-7b* and *O-H*. Upon D_2O exchange the integration of the signal changes to 2 H. The COSY spectrum indicates coupling with the signals at δ 4.04 (*H-5*) and δ 3.58 (*H-7a*).], **2.71** [broad signal, 1 H, *O-H*, D_2O exchangeable], **1.49** [s, 3 H, CH_3], **1.38** [s, 3 H, CH_3].

^{13}C NMR ($CDCl_3$, 75 MHz) δ: 131.4, 130.8 (C-2, C-3); 109.5 (quaternary carbon of isopropylidene protecting group); 80.4, 73.5, 68.3 (C-4, C-5, C-6); 57.9 (C-1); 28.1, 25.5 (2 x CH_3); 13.7 (ICH_2).

FTIR: 3357 (strong broad signal, O-H), 1412 (w, C-H), 1377 (m, CH_3), 1217 (s, C-O), 1163 (m, C-O), 1129 (s, C-O), 1044(s, C-O), 1018 (s, C-O), 870 (m, Out-of-plane C-H bending) cm^{-1}.

CIMS: 346 (1.0%, M+NH_4), 329 (2.3%, M+1), 313 (4.3%, M-CH_3), 311 [7.6%, (M+1)-H_2O], 295 (11.2%, loss of H_2O and CH_3), 253 (100%, loss of H_2O and $CH{=}CHCH_2OH$),

235 (13.4%), 157 (10.7%, loss of ICH_2CHOH), 141 (11.2%, ICH_2^+), 125 (24.0%, loss of CH_3, OH and ICH_2CHOH).

LRMS: 313 (4.7%, M-CH_3), 171 (12.4%, ICH_2CHOH^+), 157 (13.2%, loss of ICH_2CHOH), 128 (12.6%, $HI^{+\cdot}$), 125 (8.1%, loss of CH_3, OH and ICH_2CHOH), 99 (81.0%), 59 [100%, $(CH_3)_2COH^+$].

HRMS: found 312.99340; calculated for M-CH_3 = $C_9H_{14}IO_4$: 312.99386

Preparation of Compound 48

A solution of the *cis* ester **44a** (0.4097g, 1.0288 mmol) in THF (23.3 mL) was cooled to -25° C – -35°C under a nitrogen atmosphere. To this solution was added, dropwise over 10 min, a solution of DIBAL-H [6.20 mL, 1.0 M solution in hexanes (Aldrich), 6.20 mmol]. The reaction mixture was stirred under these condition for 55 min and then quenched with MeOH (8.5 mL). Ether (6.5 mL), NaF (0.18g, 4.29 mmol) and H_2O (0.99 mL)[38c] were added and the resulting cloudy solution was filtered. The filter cake was washed by EtOAc (5 mL x 3) and the combined filtrates were concentrated. The residue was purified by radial chromatography [Chromatotron, 50% EtOAc:hexanes on a 4 mm silica gel plate] to allow the separation of starting material **44a** (0.0509g, 12.4% recovery) from the product **48** (0.2319g, 68.7% yield of pure sample and 0.0162g, 4.8% yield of a slightly impure sample as determined by ^1H NMR).

(2*Z*)-1,6-Di-*O*-acetyl-2,3,7-trideoxy-7-iodo-4,5-*O*-(1-methylethylidene)-D-*ribo*-hept-2-enitol (49)

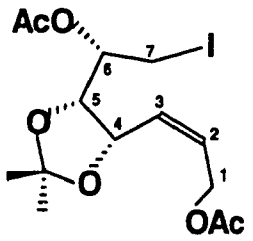
$C_{14}H_{21}IO_6$

MW = 412.21 g · mol^{-1}

pale yellow oil

R_f = 0.34 (20% EtOAc : hexanes)

$[\alpha]_D$ = +15.0° *c* 1.69



49

^{1}H NMR ($CDCl_3$, 300 MHz) δ: **5.75** [m, 1 H, *H-2*. The COSY spectrum indicates coupling with the signals at δ 5.57 (*H-3*), δ 4.71 (*H-1a*) and δ 4.58 (*H-1b*).], **5.57** [m, 1 H, *H-3*. The COSY spectrum indicates coupling with the signals at δ 4.99 (*H-4*) and δ 5.75 (*H-2*).], **4.99** [ddd, J = 1.1, 6.2, 8.6 Hz, 1 H, *H-4*. The COSY spectrum indicates coupling with the signals at δ 5.57 (*H-3*) and δ 4.22 (*H-5*)], **4.71** [ddd, $J_{1a,3}$ = 1.1 Hz, $J_{1a,2}$ = 7.1 Hz, $J_{1a,1b}$ = 13.3 Hz, 1 H, *H-1a*. The COSY spectrum shows that this signal is coupled with the signals at δ 5.75 (*H-2*) and δ 4.58 (*H-1b*)], **4.58** [ddd, $J_{1b,3}$ = 1.6 Hz, $J_{1b,2}$ = 6.2 Hz, $J_{1b,1a}$ = 13.3 Hz, 1 H, *H-1b*. The COSY spectrum indicates coupling with the signals at δ 5.57 (*H-2*) and δ 4.71 (*H-1a*).], **4.40** [m, 1 H, H-6. The COSY spectrum indicates coupling with the signals at δ 4.22 (*H-5*) and δ 3.42-3.53 (*H-7a* + *H-7b*).], **4.22** [dd, J = 6.2, 8.3 Hz, 1 H, *H-5*. The COSY spectrum shows that this signal is coupled with the signals at δ 4.99 (*H-4*) and δ 4.40 (*H-6*).], **3.42-3.53** [overlapping signals at δ 3.53 (dd, $J_{7a,6}$ = 3.4 Hz, $J_{7a,7b}$ = 11.1 Hz) and δ 3.49 (dd, $J_{7b,6}$ = 3.9 Hz, $J_{7a,7b}$ = 11.1 Hz) which together integrate to 2 H and which correspond to *H-7a* and *H-7b*. The COSY spectrum indicates that this signal is only coupled with signal at δ 4.40 (*H-6*).], **2.06** [s, 3 H, CH_3CO], **2.02** [s, 3 H, CH_3CO], **1.45** [s, 3 H, CH_3], **1.37** [s, 3 H, CH_3].

^{13}C NMR ($CDCl_3$, 75 MHz) δ: 170.5 (C=O), 169.4 (C=O), 128.6 (C-3), 128.1 (C-2); 109.4 (quaternary carbon of isopropylidene protecting group); 77.8 (C-5), 73.0 (C-4), 68.8 (C-6), 59.8 (C-1), 27.6, 25.1 (2 x OCH_3); 20.91, 20.86 (2 x $COCH_3$), 7.3 (ICH_2).

FTIR (film): 1741 (s, C=O), 1373 (m, CH_3), 1232 (s, C-O), 1164 (w, C-O), 1107 (w, C-O), 1068 (m, C-O), 1044 (m, C-O) cm^{-1}.

LRMS: 397 (6.6%, M-CH_3), 235 (12.6%), 170 (21.2%, ICH_2CHO^+), 141 (28.9%, ICH_2^+), 112 (37.3%, loss of the I, CH_3, $OCOCH_3$ and $CH{=}CHCH_2OCOCH_3$), 43 (100%, CH_3CO^+).

HRMS: found 397.01530; calculated for M-CH_3 = $C_{13}H_{18}IO_6$: 397.01499

Preparation of Compound 49

A solution of dialcohol sugar **48** (0.1697g, 0.5173 mmol) and DMAP (0.0061g, 0.0499 mmol) in CH_2Cl_2 (2.7 mL) was prepared at -78 °C under anhydrous conditions. Ac_2O (0.21 mL, 2.226mmol) and NEt_3 (0.30 mL, 2.15 mmol) were then simultaneously added dropwise (over 3 min) to this mixture. The reaction mixture was stirred for 1.5 h, quenched with a mixture of H_2O/ether (5 mL, 1:1 v/v) and then warmed up to rt. The aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organic layers were washed with aqueous citric acid (20 mL, 10%), saturated aqueous $NaHCO_3$ (20 ml) and brine (20 mL). The organic phase was then dried over $MgSO_4$, filtered and concentrated. Purification of the residue by radial chromatography (Chromatotron, 20% EtOAc : hexanes on a 2 mm silica gel plate) gave pure diacetate **49** (0.2017g, 95% yield).

(2*Z*)-6,7-Anhydro-2,3-dideoxy-4,5-*O*-(1-methylethylidene)-D-*ribo*-hept-2-enitol (50)

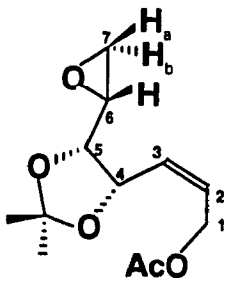
$C_{12}H_{18}O_5$

MW = 242.26 g · mol^{-1}

pale yellow oil

R_f = 0.25 (20% EtOAc:hexanes)

$[\alpha]_D$ = +4.4 ° *c* 0.13



50

^{1}H NMR ($CDCl_3$, 300 MHz) δ: **5.84** [m, 2 H, *H-2* + *H-3*. The COSY spectrum indicates coupling with the signals at δ 5.09 (*H-4*) and δ 4.73 (*H-1a* + *H-1b*).], **5.09** [apparent t which is actually an overlapping dd with J = 7.0, 6.6 Hz, 1 H, *H-4*. The COSY spectrum shows that this signal is coupled with the signals at δ 5.84 (*H-3*) and δ 3.76 (*H-5*).], **4.73** [overlapping multiplets, 2 H, *H-1a* + *H-1b*. The COSY spectrum shows that this signal is only coupled with the signals at δ 5.84.], **3.76** [apparent t which is actually an overlapping dd with $J_{5,6}$ = 7.3 Hz, $J_{5,4}$ = 6.6 Hz, 1 H, *H-5*. The COSY spectrum shows that this signal is coupled with the signals at δ 5.09 (*H-4*) and δ 2.95 (*H-6*).], **2.95** [ddd, $J_{6,7b}$ = 2.6 Hz, $J_{6,7a}$ = 3.9 Hz, $J_{6,5}$ = 7.4 Hz, 1 H, *H-6*. The COSY spectrum indicates coupling with the signals at δ 3.76 (*H-5*), δ 2.83 (*H-7a*) and δ 2.67 (*H-7b*).], **2.83** [dd, $J_{7a,6}$ = 3.9 Hz, $J_{7a,7b}$ = 5.0 Hz, 1 H, *H-7a*. The COSY spectrum indicates coupling with the signals at δ 2.95 (*H-6*) and δ 2.67 (*H-7b*).], **2.67** [dd, $J_{7b,6}$ = 2.5 Hz, $J_{7b,7a}$ = 5.1 Hz, 1 H, *H-7b*. The COSY spectrum shows that this signal is coupled with the signals at δ 2.95 (*H-6*) and δ 2.83 (*H-7a*).], **2.08** [s, 3 H, CH_3CO], **1.53** [s, 3 H, CH_3], **1.39** [s, 3 H, CH_3].

^{13}C NMR ($CDCl_3$, 75 MHz) δ: 170.7 (C=O), 128.7, 128.4 (C-2 and C-3), 109.5 (quaternary carbon of isopropylidene protecting group); 79.3, 73.9 (C-4 and C-5), 60.3 (C-1), 49.7 (C-6), 45.5 (C-7), 27.7, 25.1 (2 x OCH_3); 20.9 ($COCH_3$).

FTIR (film): 1739 (s, C=O), 1375 (m, CH_3), 1234 (s, C-O), 1163 (w, C-O), 1045 (m, C-O) cm^{-1}.

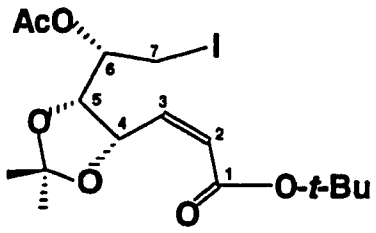
LRMS: 227 (6.2%, M-CH_3), 170 (8.4%), 125 (14.2%, loss of CH_2OCH, CH_3 and $OCOCH_3$), 112 (42.4%), 110 (37.5%), 107 (20.9%), 101 (10.9%), 97 (20.5%), 95 (25.8%), 82 (21.5%), 69 (18.7%), 59 [39.6%, $(CH_3)_2OH^+$], 43 (100%, $COCH_3^+$).

HRMS: found: 227.09270; calculated for M-CH_3 = $C_{11}H_{15}O_5$: 227.0919

Preparation of Compound 50

Occasionally compound **50** was isolated as a side product in the bis acetylation of dialcohol **48**. A solution of **48** (0.0820g, 0.2499 mmol) and DMAP (0.0024g, 0.0196 mmol) in CH_2Cl_2 (1.0 mL) was prepared at -78 ^oC under anhydrous conditions. To this mixture was added, dropwise over 3 min, Ac_2O (0.035 mL, 0.3709 mmol) and NEt_3 (0.05 mL, 0.3587 mmol) simultaneously. The reaction mixture was stirred for 2.7 h, quenched with a mixture of H_2O/ether (2 mL, 1:1 v/v) and then warmed up to rt. The aqueous layer was extracted with EtOAc (3 x 10mL) and the combined organic layers were washed with aqueous citric acid (20 mL, 10%), saturated aqueous $NaHCO_3$ (20 ml) and brine (20 mL). The organic phase was then dried over $MgSO_4$, filtered and concentrated. Purification of the residue by radial chromatography (Chromatotron, 20% EtOAc : hexanes on a 2 mm silica gel plate) allowed us to separate diacetate **49** [0.0798 g, 78% yield, R_f = 0.31 (TLC, 20% EtOAc : hexanes, silica gel)] from a slight impure sample (by ^1H NMR) of the epoxide **50** [0.0073g, 12% yield, R_f = 0.25 (TLC, 20% EtOAc:hexanes, silica gel)].

***Tert*-Butyl (2*Z*)-6-*O*-acetyl-2,3,7-trideoxy-7-iodo-4,5-*O*-(1-methylethylidene)-D-*ribo*-hept-2-enoate (51)**



51

$C_{16}H_{25}IO_6$

MW = 440.26 g · mol^{-1}

pale yellow oil

R_f = 0.54 (20% EtOAc : hexanes)

$[\alpha]_D$ = +109 ° *c* 3.12

^{1}H NMR ($CDCl_3$, 300 MHz) δ: **6.12** [dd, $J_{3,4}$ = 7.5 Hz, J_{cis} = 11.6 Hz, 1 H, *H-3*. The COSY spectrum shows that this signal is coupled with the signals at δ 5.85 (*H-2*) and δ 5.73 (*H-4*).], **5.85** [dd, $J_{2,4}$ = 1.6 Hz, J_{cis} = 11.6 Hz, 1 H, *H-2*. The COSY spectrum only showed that this signal is coupled with the signal at δ 6.12 (*H-3*).], **5.73** [overlapping ddd, $J_{4,5}$ = 5.9 Hz, $J_{4,3}$ = 7.5 Hz, $J_{4,2}$ = 1.6 Hz, 1 H, *H-4*. The COSY spectrum only showed coupling with the signals at δ 6.12 (*H-3*) and δ 4.46-4.56 (*H-5*).], **4.46-4.56** [m, 2 H, *H-5* + *H-6*. The COSY spectrum indicates that this signal is coupled with those at δ 5.73 (*H-4*) and δ 3.39-3.48 (*H-7a* + *H-7b*).], **3.39-3.48** [m consisting of 2 overlapping and distorted dd, 2 H, *H-7a* + *H-7b*. The COSY spectrum only indicated that this signal is coupled with the signal at δ 4.46-4.56.], **2.01** [s, 3 H, CH_3CO], **1.51** [s, 9 H, $C(CH_3)_3$], **1.49** [s, 3 H, CH_3], **1.40** [s, 3 H, CH_3].

^{13}C NMR ($CDCl_3$, 75 MHz) δ: 169.5 (CH_3C=O), 164.6 [$COO(CH_3)_3$], 142.2 (C-3), 124.4 (C-2), 109.3 (quaternary carbon of isopropylidene protecting group), 81.2 [$C(CH_3)_3$], 77.8 (C-5 or C-6), 73.8 (C-4), 69.5 (C-5 or C-6), 28.1 [$C(CH_3)_3$], 27.6, 25.1 (2 x OCH_3), 21.0 ($COCH_3$), 6.6 (ICH_2).

FTIR (film): 1749 (s, C=O), 1713 (s, C=O), 1647 (w, C=C), 1414 (w, C-H), 1370 (m, CH_3), 1236 (s, C-O), 1157 (s, C-O), 1056 (m, C-O) cm^{-1}.

LRMS: 425 (0.4%, M-CH_3), 384 [5.0%, loss of C_4H_8 (McLaffery)], 309 [40.0%, loss of $OC(CH_3)_3$, CH_3, and CH_3CO], 267 (13.6%), 249 (13.3%), 243 (21.2%), 227 (8.9%, loss of $ICH_2CHOCOCH_3$), 197 [28.5%, loss of I, $COCH_3$ and $OC(CH_3)_3$], 171 [69.7%, loss of CH_3, I and $CH=CHCOOC(CH_3)_3$], 165 (11.4%), 142 (40.0%), 139 [75.0%, loss of $ICH_2CHOCOCH_3$, CH_3 and $OC(CH_3)_3$], 121 (24.0%), 113 (42.5%), 97 (24.1%), 84 (41.6%), 59 [68.8%, $(CH_3)_2COH^+$], 57 [100%, $C(CH_3)_3^+$], 43 (97.1%, CH_3CO^+).

HRMS: found 425.04610; calculated for M-CH_3 = $C_{15}H_{22}IO_6$: 425.04629

Preparation of Compound 51

In certain instances compound **51** was isolated as the major component in the preparation of compound **49** from compound **44a**. A solution of *cis t*-butyl ester **44a** (0.1094 g, 0.2747 mmol) in THF (6.2 mL) was prepared at -25 °C – -35 °C under a nitrogen atmosphere. To this solution was added, dropwise over 10 min, a solution of DIBAL-H (1.65 mL, 1.0 M solution in hexanes from Aldrich, 1.65 mmol). The reaction mixture was stirred under these conditions for 55 min and then quenched with MeOH (3.0 mL). To this mixture was then added ether (30 mL), NaF (0.05 g, 4.29 mmol) and H_2O (0.3 mL). The resulting cloudy solution was filtered and the filter cake was washed by EtOAc (5 mL x 3). The filtrate was concentrated to give 0.10 g of crude material. The partially reduced crude material was used as is. A solution in CH_2Cl_2 (1.5 mL) was prepared and cooled to -78 °C under anhydrous solution. To the CH_2Cl_2 solution was added DMAP (0.1874 g, 1.534 mmol) and Ac_2O (0.120 mL, 1.27 mmol, over 10 min.). The reaction mixture was stirred for 20 min, quenched with a mixture of H_2O (1.5 mL)/ether (2.0 mL) and then warmed up to rt. The aqueous layer was extracted with ether (2 x 10mL) and the combined organic layers were washed with

aqueous citric acid (20 mL, 10%), saturated aqueous $NaHCO_3$ (20 ml) and brine (20 mL). The organic phase was then dried over $MgSO_4$, filtered and concentrated. The residue was purified by radial chromatography [Chromatotron, 10% EtOAc : hexanes and 20 % EtOAc : hexanes on a 2 mm silica gel plate] to allow the separation of diacetate **49** (0.0336 g, 30% yield) from the acetylated *t*-butyl ester **51** 90.0414g, 35% yield).

4. 5. 4. Reactions of SmI_2 with Carbohydrate Derived Alkenyl Iodides

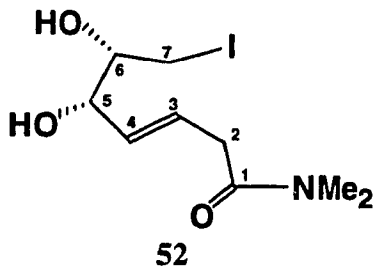
(*3E*)-*N*, *N*-Dimethyl-2,3,4,7-tetradeoxy-7-iodo-D-*ribo*-hept-3-enamide (52)

$C_9H_{16}INO_3$

MW = 313.27 g · mol^{-1}

pale yellow oil

R_f = 0.13 (4% MeOH : EtOAc)



52

^{1}H NMR ($CDCl_3$, 300 MHz) δ: **5.94** [appears to be a ddt (J_{trans} = 15.6 Hz, $J_{3,2}$ = 6.8 Hz, J = 1 Hz), 1 H, *H-3*. The COSY spectrum indicated that this signal is coupled with the signals at δ 5.66 (*H-4*) and 3.16 (*H-2*).], **5.66** [appears to be a poorly resolved dd (J_{trans} = 15.6 Hz, $J_{4,5}$ = 6.9 Hz) but is actually more complex, 1 H, *H-4*. The COSY spectrum shows that this signal is coupled with the signals at δ 5.94 (*H-3*), 4.24 (*H-5*) and 3.16 (*H-2*).], **4.24** [appears as an apparent t (J = 6 Hz), 1 H, *H-5*. The COSY spectrum indicates coupling with the signals at δ 5.66 (*H-4*) and 3.66 (*H-6*).], **3.66** [appears as a poorly resolved dt (J= 4.9, 6.8 Hz), 1 H, *H-6*. The COSY spectrum indicated that this signal is coupled with the signals at δ 4.24 (*H-5*) and 3.27-3.39 (*H-7*).], **3.27-3.39** [m, consists of overlapping signals at δ 3.33 (dd, J = 7.0, 10.4 Hz) and 3.34 (dd, J ≈ 10, 10 Hz) which together integrate to 2 H, *H-7a* + *H-7b*. The COSY spectrum shows that this signal is coupled with the signal at δ 3.66 (*H-6*).], **3.16**

[d, J = 6.6 Hz, 2 H, *H-2*. The COSY spectrum indicates coupling with the signal at δ 5.94 (*H-3*) and a weak coupling with the signals at δ 5.66 (*H-4*) and 2.96 (NCH_3).], **2.92-3.06** [8 H; consists of a low broad signal (2 x *O-H*) and 2 singlets at δ 3.02 (NCH_3) and δ 2.96 (NCH_3). Upon exchange with D_2O this signal simplifies to 2 singlets integrating to 6 H.].

^{13}C NMR ($CDCl_3$, 75 MHz) δ: 171.0 (C=O), 131.5 (C-4), 127.5 (C-3), 74.4, 73.9 (C-5 and C-6), 37.4, 35.6 (2 x NCH_3), 36.8 (C-2), 9.8 (ICH_2).

FTIR (neat): 3353 (strong broad signal, O-H), 1618 (s, C=O, C=C) cm^{-1}.

CIMS (low resolution, NCH_3) m/z: 314 (76.2%, $M^{+\cdot}$+1), 296 [39.6%, (M+1)-H_2O], 186 (57.0%, M-I), 168 (35.1%, loss of H_2O and I), 142 (100%, loss of ICH_2CHOH).

Unidentified THF Derivative B:

R_f = 0.18 (4% MeOH : EtOAc)
yellow oil

^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.42, 1.63 (1:1 ratio of 2 broad signals which appear to be narrow, poorly resolved multiplets). The COSY spectrum indicates that these two signals are coupled to each other.

^{13}C NMR ($CDCl_3$, 75 MHz) δ: 70.6, 26.5 (The APT spectrum shows that these two signals are both CH_2).

Preparation of Compound 52 *Reaction of SmI_2 with cis N,N-dimethyl iodo-amide 45a in THF / MeOH*

A solution of iodo-amide **45a** (0.1074g, 0.2909 mmol), MeOH (0.090 mL, 2.21mmol) and THF (11 mL) was prepared at rt under an argon atmosphere. SmI_2 (8.70 mL, 0.1 M solution in THF, 0.870 mmol) was then added dropwise to this solution by using a cannula. After 15 min at rt the reaction mixture changed colour from blue to yellow. A solution of 0.1 M HCl (15 mL) was added and the mixture was worked up as usual. The crude residue was purified by radial chromatography [4% MeOH:EtOAc, 1 mm adsorbosil plus p plate] to allow the separation of starting material **45a** (0.0015g, 1.4% yield of recovered starting material) from compound **52** (0.0087g, 9.5% yield) and from an unidentified THF derivative **B** (0.0047g).

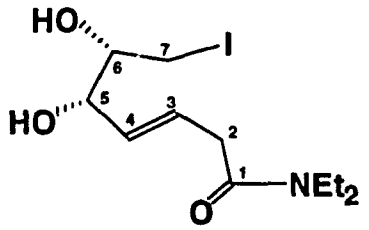
(*3E*)-*N*, *N*-Diethyl-2,3,4,7-tetradeoxy-7-iodo-D-*ribo*-hept-3-enamide (53)

$C_{11}H_{20}INO_3$,

MW = 341.18 g · mol^{-1}

pale yellow oil

R_f = 0.33 (pure EtOAc)



53

^{1}H NMR ($CDCl_3$, 300 MHz) δ: **5.93** [ddt, $J_{3,5}$ = 1.0 Hz, $J_{2,3}$ = 6.8 Hz, J_{trans} = 15.6 Hz, 1H, *H-3*. The COSY spectrum indicates coupling with the signals at δ 5.67 (*H-4*) and 3.14 (*H-2*).], **5.67** (appears to be a ddt, $J_{2,4}$ = 1.0 Hz, $J_{4,5}$ = 6.8 Hz, J_{trans} = 15.6 Hz, 1H, *H-4*. The COSY spectrum shows that this signal is coupled with the signals at δ 5.93 (*H-3*), δ 4.23 (*H-5*) and δ 3.14 (*H-2*).], **4.23** [appears as a poorly resolved t, J = 6 Hz, 1H, *H-5*. The COSY spectrum indicates coupling with the signals at δ 5.67 (*H-4*) and δ 3.66 (*H-6*).], **3.62-3.75** [m, 1 H, *H-6*. Upon D_2O exchange this multiplet sharpens and is centered at 3.66 ppm. The COSY spectrum indicates coupling with the signals at δ 4.23 (*H-5*) and δ 3.26-3.42 (*H-7*).],

3.26-3.42 [overlapping 2 x NCH_2 and ICH_2 signals which together integrate to 6 H. The COSY spectrum shows that this signal is coupled with the signals at δ 3.62-3.75 (*H-6*), δ 1.20 (NCH_2CH_3) and δ 1.12 (NCH_2CH_3)], **3.14** [apparent d, J = 6.6 Hz, 2 H, *H-2*. The COSY spectrum indicates coupling with the signal at δ 5.93 (*H-3*) and a weaker coupling with the signal at δ 5.67 (*H-4*).], **2.12** [broad signal, 2 H, 2 x *O-H*, exchange with D_2O], **1.20** [t, J = 7.2 Hz, 3H, NCH_2CH3. The COSY spectrum indicates that this signal is coupled with the signals at δ 3.26-3.42 (NCH_2).], **1.12** [t, J = 7.1 Hz, 3H, NCH_2CH_3. The COSY spectrum shows that this signal is coupled with the signals at δ 3.26-3.42 (NCH_2).].

^{13}C NMR ($CDCl_3$, 75 MHz) δ: 170.3 (C=O), 131.6 (C-4), 127.6 (C-3), 74.4 (C-5), 73.9 (C-6), 42.2, 40.5 (2 x NCH_2), 36.6 (C-2), 14.3, 13.0 (2 x NCH_2CH_3), 9.7 (ICH_2).

FTIR: 3360 (br, O-H), 2921 (s, C-H), 1612 (s, C=O, C=C) cm^{-1}

LRMS: 341 (0.7%, $M^{+\cdot}$), 214 (17.5%, loss of I), 171 (48.9%, ICH_2CHOH^+), 170 (60.6%, loss of ICH_2CHOH), 140 [15.7%, C_4-C_5 bond cleavage, loss of $ICH_2CH(OH)CH(OH)$], 115 (25.8%), 100 (100%, Et_2NCO^+), 72 (57.1%, NEt_2^+).

HRMS: found 214.14440; calculated for M-I = $C_{11}H_{20}NO_3$: 214.14431.

Preparation of Compound 53 *Reaction of SmI_2 with cis N,N-diethyl iodo-amide **47a** in THF / MeOH*

A solution of iodo-amide **47a** (0.0555g, 0.1397 mmol), MeOH (0.070 mL, 1.72 mmol) and THF (5.1 mL) was prepared at rt under an argon atmosphere. SmI_2 (4.20 mL, 0.1 M solution in THF, 0.420 mmol) was then added dropwise to this solution by using a cannula. After 15 min at rt, the reaction mixture changed colour from blue to light green. The reaction mixture was quenched with 0.1 M HCl solution (5 mL) and then worked up as usual. The crude

residue was purified by radial chromatography [using a Chromatotron and the following series of eluants: (1) 30% of EtOAc:hexanes (80 mL), (2) 58% of EtOAc:hexanes (100 mL), (3) EtOAc (50 mL), and (4) MeOH (80 mL) on a 1 mm adsorbosil plus p plate] to allow the separation of starting material **47a** (0.0190g, 34%) from the partially purified product **53**. The compound **53** was further purified by radial chromatography (EtOAc on a 1mm adsorbosil plus p plate) to give pure product (0.0143g, 30%).

***N*, *N*-Dimethyl-2,3,7-trideoxy-7-iodo-4,5-*O*-(1-methylethylidene)-D-*ribo*-heptanamide (54)**

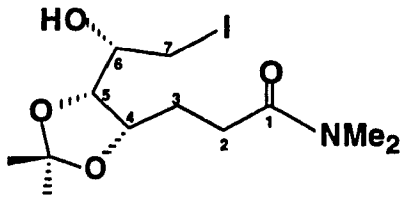
$C_{12}H_{22}INO_4$

MW= 371.23 g · mol^{-1}

pale yellow oil

R_f = 0.31 (75% EtOAc : CH_2Cl_2)

$[\alpha]_D$ = +14.9 ° *c* 0.56



54

^{1}H NMR ($CDCl_3$, 300 MHz) δ: **4.20** [ddd, $J_{4,5}$ = 5.6 Hz, J = 3.3, 9.3 Hz, 1 H, *H-4*. The COSY spectrum indicates coupling with the signals at δ 3.92 (*H-5*), δ 2.17 (H-3a) and δ 1.81 (*H-3b*).], **3.92** [dd, $J_{5,4}$ = 5.7 Hz, $J_{5,6}$ = 8.6 Hz, 1 H, *H-5*. The COSY spectrum indicates coupling with the signals at δ 4.20 (*H-4*) and δ 3.50-3.65 (*H-6*)], **3.50-3.65** [2 H, overlapping signals due to *H-6* and *H-7a*. The signal attributed to *H-7a* has the appearance of dd ($J_{7a,6}$ = 2.4 Hz, $J_{7a,7b}$ = 9.8 Hz) and is centered at 3.61 ppm. The signal attributed to *H-6* is centered at 3.55 ppm and has the appearance of a broad doublet (J = 7 Hz) which sharpens to a poorly resolved dd: $J_{6,7a}$ = 2.4 Hz, $J_{6,5}$ = 8.9 Hz upon D_2O exchange). The COSY spectrum shows that these overlapping signals are coupled with the signals at 3.92 (*H-5*) and 3.38 (*H-7b*).], **3.38** [dd, $J_{7b,6}$ = 6.6 Hz, $J_{7b,7a}$ = 9.9 Hz, 1 H, *H-7b*. The COSY spectrum shows that this signal is only coupled with the signal at δ 3.50-3.65.], **3.25** [small broad signal, 1 H, *O-H*,

D_2O exchangeable], **3.03** [s, 3 H, NCH_3], **3.00** [s, 3 H, NCH_3], **2.57** [ddd, J = 5.3, 9.1, 16.1 Hz, 1 H, *H-2a.* The COSY spectrum shows that this signal is coupled with the signals at δ 2.44 (*H-2b*), δ 2.17 (*H-3a*) and 1.81 (*H-3b*).], **2.44** [ddd, J = 6.9, 8.7, 15.9 Hz, 1 H, *H-2b.* The COSY spectrum indicates coupling with the signals at δ 2.57 (*H-2a*), δ 2.17 (*H-3a*) and δ 1.81 (*H-3b*).], **2.17** [m, 1 H, *H-3a.* The COSY spectrum shows that this signal is coupled with the signals at δ 4.20 (*H-4*), δ 2.57 (*H-2a*), 2.44 (*H-2b*) and 1.81 (*H-3b*)], **1.81** [m, 1 H, *H-3b.* The COSY spectrum shows that this signal is coupled with the signals at δ 4.20 (*H-4*), δ 2.17 (*H-3a*), 2.57 (*H-2a*) and 2.44 (*H-2b*).], **1.41** [s, 3H, CH_3], **1.34** [s, 3H, CH_3].

^{13}C NMR ($CDCl_3$, 75 MHz) δ: 172.8 (C=O), 108.3 (quaternary carbon of isopropylidene protecting group), 79.5, 77.2, 68.4 (3 x CH; C-4, C-5, C-6), 37.2, 35.5 (2 x NCH_3), 30.1 (CH_2), 28.2, 25.7 (2 x OCH_3), 25.6 (CH_2), 15.3 (ICH_2).

FTIR: 3363 (br, O-H), 1625 (s, C=O), 1219 (m, C-O), 1062 (m, C-O) cm^{-1}.

CIMS: 372 (23.8%, $M^{+\cdot}$+1), 356 (6.7%, M-CH_3), 244 (25.3%, M-I), 226 (16.2%, loss of H_2O and I), 186 (35.0%, loss of $ICH_2$and NMe_2), 168 (34.3%, loss of H_2O, $ICH_2$and NMe_2), 142 [100%, loss of CH_3, I and CH_2=C(OH)NMe_2 (McLafferty)].

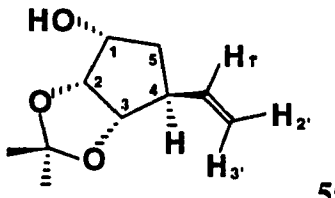
LRMS: 356 (10.8%, M-CH_3), 200 (9.3%, loss of ICH_2CHOH), 186 (17.1%, loss of $ICH_2$and NMe_2), 172 (13.3%, loss of I and $CONMe_2$), 168 (15.9%, loss of H_2O, $ICH_2$and NMe_2), 142 [100%, loss of CH_3, I and CH_2=C(OH)NMe_2 (McLafferty)], 87 [10.6%, $C_4H_9NO^+$ (McLafferty)].

HRMS: found: 356.03650; calculated for M-CH_3 = $C_{11}H_{19}INO_4$: 356.03606.

Preparation of Compound 54 *Reaction of SmI_2 with trans N,N-dimethyl iodo-amide **45b** in THF / MeOH*

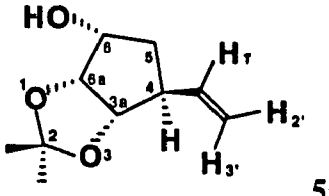
A solution of *trans* iodo-amide **45b** (0.0616 g, 0.1668 mmol), MeOH (0.055 mL, 1.35 mmol) and THF (6.5 mL) was prepared at rt under an argon atmosphere. SmI_2 (5.0 mL, 0.1 M solution in THF, 0.50 mmol) was then added dropwise to this solution by using a cannula. After 1 h and 20 min the reaction mixture changed colour from blue to yellow. A 0.1 M HCl solution (5 mL) was then added and the mixture was worked up as usual. The crude residue was purified by radial chromatography [Chromatotron, 38% Et_2O: CH_2Cl_2 on a 1 mm "adsorbosil plus p" plate] to allow the separation of starting material (0.0135g, 22% recovery) from the partially purified product **54**. Compound **54** was further purified by radial chromatography (75% EtOAc:CH_2Cl_2 on a 1 mm plate) to give 0.0093 g (15% yield) of a pure sample and 0.0073g (12 % yield) of a slightly impure sample of **54**.

(*1R, 2R, 3S, 4S*)-2,3-(Dimethylmethylenedioxy)-4-ethenylcyclopentanol (*IUPAC name for characterization*) **(55)**



55

(*3aS, 4S, 6R, 6aR*)-4-Ethenyl-tetrahydro-6-hydroxy-2,2-dimethyl-4*H*-cyclopenta-1,3-dioxole (*CA name*) **(55)**



55

$C_{10}H_{16}O_3$

MW = 184.23g · mol^{-1}

pale yellow oil

R_f = 0.26 (20% EtOAc:hexanes)

$[\alpha]_D$ = +16.6 ° *c* 1.22

^{1}H NMR ($CDCl_3$, 300 MHz) δ: **5.75** [ddd, J = 6.5, 10.5, 17.2 Hz, 1 H, *H-1'*], **5.09** [2 H, overlapping signals, *H-2'* and *H-3'*. The signal attributed to *H-3'* consists of a ddd (J = 17.3, 1.4, 1.6 Hz) but has the appearence of a dt and is centered at δ 5.09. The signal attributed to *H-2'* also consists of a ddd (J= 10.6, 1.4, 1.5 Hz) but has the appearence of a dt and is centered at δ 5.07 ppm], **4.49** [2 H, apparent doublet, *H-2* and H-*3* ; this signal has the appearence of a d (J=3.3 Hz). The COSY spectrum showed that this signal is coupled to those at δ 4.08 (*H-1*), and 2.75 (*H-4*) and weakly coupled to the signal at 1.90 (*H-5a* and *H-5b, long range coupling*). In addition 1 D decoupling experiments showed that upon irradiation at δ 4.08 (*H-1*), the signal at δ 4.49 (*H2+H3*) collapses to a singlet at δ 4.50. Irradiation at δ 2.75 (*H-4*) or at 1.90 (*H-5a* and *H-5b*) had no obvious effect on the appearence of the *H-2* + *H-3* signal.], **4.08** [broad signal, $W_{1/2}$ = 15 Hz, 1 H, *H-1*. The COSY spectrum indicates a coupling with the signals at δ 4.49 (*H2+H3*) and 1.90 (*H5a+H5b*). 1 D decoupling experiments showed that upon irradiation at δ 4.49 (*H2+H3*) or

1.90 (*H5a+H5b*) there is a sharpening of the *H-1* signal at δ 4.08. We could not extract out any of the coupling constants though.], **2.75** [m, 1 H, *H-4*. The COSY spectrum indicated a coupling between *H-4* and (*H2+H3*), *H-1'*, *H2'+H3'* and *H5a+H5b*. 1 D decoupling experiments showed that upon irradiation at δ 2.75 the signals for some of these protons were simplified *ie*. *H-1'* (dd, $J_{1',3'}$ = 17.5, $J_{1',2'}$ = 10.5 Hz), *H-2'* (dd, $J_{2',1'}$ = 10.6, $J_{2',3'}$ = 1.2 Hz), *H-3'* (dd, $J_{3',1'}$ = 17.4, $J_{3',2'}$ = 1.2 Hz), The *H5a+H5b* signal was somewhat simplified but we are not able to extract out any of the J values. Likewise, irradiation at each of the *H-1'*, *H-2'*, *H-3'* and *H5a+H5b* signals resulted in a change in the appearence of the δ 2.75 signal. The simplified signals at δ 2.75 (*H-4*) are still very complex however and we can not extract out any of the coupling constants.], **2.40** [broad signal, 1H, *OH*, D_2O exchangeable], **1.90** [m, 2 H, *H5a+H5b*. The COSY spectrum indicates that this signal is coupled with the signals at δ 4.08 (*H-1*), 2.74 (*H-4*) and 4.49 (*H2+H3*, long range coupling). 1 D decoupling experiments showed that upon irradiation of the *H-1* or *H-4* signal , the signal at δ 1.90 (*H5a+H5b*) is somewhat simplified.], **1.52** (s, 3H, CH_3), **1.36** (s, 3H, CH_3).

^{1}H NMR (acetone-d_6, 300 MHz) δ: **5.80** [ddd, J = 6.8, 10.5, 17.3 Hz, 1 H, *H-1'*. The COSY spectrum indicated coupling with the signal at δ 5.80 and the signals at δ 5.07 (*H-3'*), 5.00 (*H-2'*) and 2.60 (*H-4*). Irradiation (1 D decoupling) at δ 2.60 (*H-4*) resulted in the collapse of the signal to a dd (J = 10.5, 17.3 Hz)], **5.07** [appears as a dt but is actually a ddd, J= 17.4, 1.6, 1.6 Hz, 1 H, *H-3'*. The COSY spectrum indicated coupling with *H-2'*, *H-1'* and *H-4* (long range coupling). Upon irradiation (1 D decoupling) at δ 5.80 (*H-1'*), the signal at 5.07 (*H-3'*) is simplified but is poorly resolved. Upon irradiation at δ 2.60 (*H-4*), the signal at δ 5.07 (*H-3'*) is simplified to dd ($J_{3',1'}$ = 17.4, $J_{3',2'}$ = 1.5 Hz)], **5.00** [appears as a dt but is actually a ddd, J= 10.5, 1.6, 1.5 Hz, 1 H, *H-2'*. The COSY spectrum indicates coupling with *H-3'*, *H-1'* and *H-4* (long range coupling). Irradiation (1 D decoupling) of signal at δ 2.60 (*H-4*) results in a collapse of the *H-2'* signal at δ 5.00 to a dd ($J_{2',1'}$ = 10.4, $J_{2',3'}$ = 1.6 Hz)], **4.45** [2 H, *H2+H3*, this signal has the appearence of a d. The COSY spectrum shows that this

signal is coupled with the signals at δ 3.97 (*H-1*), 1.87 (*H-5a*) and 1.73 (*H-5b*). Irradiation (1 D decoupling) of signal at δ 3.97 (*H-1*) resulted in a collapse to a singlet at δ 4.46.], **3.97** [broad signal, $W_{1/2}$ = 15 Hz, 1 H, *H-1*. The COSY spectrum shows that this signal is coupled with the signal at δ 4.45 (*H2+H3*), 3.10 (*OH*), 1.87 (*H-5a*) and 1.73 (*H-5b*). Upon decoupling (1 D) of the signal at δ 3.97 (*H-1*), the signal for all of the above signals were simplified *i.e. H2+H3* (s), *OH* (broad s), *H-5a* (poorly resolved dd, $J_{5a,4} \cong 7$ Hz, $J_{5a,5b} \cong 12$ Hz) and *H-5b* (poorly resolved dd, $J_{5b,5a} \cong 13$ Hz, $J_{5b,4} \cong 4$ Hz). Likewise, irradiation at each of the *H-1, H2+H3, OH, H-5a* and *H-5b* signals resulted in a change of the appearence of the δ 3.97 signal but in each case the 3.97 signal remained complex.], **3.10** [d, $J_{OH,H-1}$ = 8.1 Hz, 1 H, *-OH*, D_2O exchangeable], **2.60** [m, 1 H, *H-4*. The COSY spectrum indicated coupling with *H-4* and *H-1'*, *H-2'*, *H-3'*, *H-5a* and *H-5b*. Upon irradiation at δ 2.60 the signals for all of these protons were simplified *ie. H-1'* (poorly resolved dd, $J_{1',2'}$ = 10.5, $J_{1',3'}$ = 17.3 Hz), *H-2'* (dd, $J_{2',1'}$ = 10.4, $J_{2',3'}$ = 1.6 Hz), *H-3'* (dd, $J_{3',1'}$ = 17.4, $J_{3',2'}$ = 1.5 Hz), *H-5a* (poorly resolved dd, $J_{5a,1} \cong 9$ Hz, $J_{5a,5b} \cong 12$ Hz) and *H-5b* (poorly resolved dd, $J_{5b,5a} \cong 12$ Hz, $J_{5b,1} \cong$ 5.5 Hz). Likewise, irradiation at each of the *H-1'*, *H-2'*, *H-3'*, *H-5a* and *H-5b* signals resulted in a change in the appearence of the δ 2.60 signals. However the δ 2.60 signals are all still complex.], **1.87** [ddd, 1 H, *H-5a*, $J_{5a,H-4}$ = 6.93, $J_{5a,H-1}$ = 9.0, $J_{5a,5b}$ = 12.4 Hz, The COSY spectrum shows that this signal is coupled with the signals at δ 3.97 (*H-1*), 2.60 (*H-4*), 1.73 (*H-5b*) and 4.45 (*H1+H2*, long range coupling). However only irradiation of the signal at δ 2.60 let us extract out of the J values ($J_{5a,5b}$ = 12.3, $J_{5a,1}$ = 9.0 Hz)], **1.73** [poorly resolved ddd, $J_{5b,H-4}$ = 3 6, $J_{5b,H-1}$ = 5.7, $J_{5b,5a}$ = 12.4 Hz, 1 H, *H-5b*. The COSY spectrum shows that this signal is coupled with the signal at δ 3.97 (*H-1*), 2.60 (*H-4*), 1.87 (*H-5a*) and 4.45 (*H2+H3*, long range coupling). However only decoupling of the signal at δ 2.60 allowed us to determine the $J_{5a,5b}$ (12.1 Hz) and the $J_{5b,1}$ (5.5 Hz) values.], **1.41** [s, 3H, CH_3], **1.28** [s, 3H, CH_3].

nOe (acetone-d_6): We see a smaller nOe between the signals at δ 2.60 (*H-4*) and 4.45 (*H2+H3*) in the case of anomer **55** than we do in the case of anomer **56**. Irradiation at δ 2.60 (*H-4*) results in a total nOe of 1.3% for the overlapping *H2+H3* signals. Effects are also observed for *H-1'* (0.8%), *H2'+H3'* (1.0%) and *H5a+H5b* (1.7%).

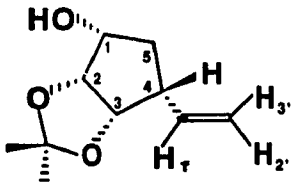
^{13}C NMR ($CDCl_3$, 75 MHz) δ: 138.0 (*C*H=CH_2), 115.3 (CH=*C*H_2), 111.6 (quaternary carbon of isopropylidene protecting group), 84.3, 79.0 (C-2, C-3), 71.1 (C-1), 44.3 (C-4), 36.0 (C-5), 26.1 (CH_3), 24.3 (CH_3).

FTIR (Neat, cm^{-1}): 3457 (br, -OH), 2926(s,C-H), 1734 (w), 1638 (w, C=C), 1457 (w, C-H), 1381 (CH_3); 1163 (w), 1087(w), 1052 (w) and 1210 (m) are attributed to C-O.

LRMS: 184 (0.5%, $M^{+\cdot}$), 169 (100%, M-CH_3), 126 (10.6%, loss of CH_3COCH_3), 109 (37.2%), 83 (31.9%), 81 (22.2%), 71 (12.0%), 67 (11.1%), 59 [54.5 %, $(CH_3)_2COH^+$], 54 (42.4%), 43 (21.7%, CH_3CO^+).

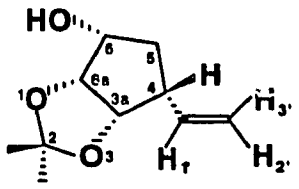
HRMS: found: 169.08620; calculated for M-CH_3 = $C_9H_{13}O_3$: 169.08646.

(*1R, 2R, 3S, 4R*)-2,3-(Dimethylmethylenedioxy)-4-ethenylcyclopentanol (*IUPAC name for characterization*) **(56)**



56

(*3aS, 4R, 6R, 6aR*)-4-Ethenyl-tetrahydro-6-hydroxy-2,2-dimethyl-4*H*-cyclopenta-1,3-dioxole (*CA name*) **(56)**



56

$C_{10}H_{16}O_3$

MW = 184.23g · mol^{-1}

pale yellow oil

R_f = 0.18 (20% EtOAc:hexanes)

^{1}H NMR ($CDCl_3$, 300 MHz) δ: **5.91** [m, 1 H, *H-1'*, contains ddd, $J_{1',2'}$ = 9.9, $J_{1',3'}$ = 17.5, $J_{1',4}$ = 7.4 Hz. The COSY spectrum indicated coupling between the signal at δ 5.91 and the signals at δ 5.12 (*H2'*+H3') and 2.28 (*H-4*). Irradiation (1 D decoupling) at δ 2.28 (*H-4*) resulted in the collapse of the signal to a poorly resolved dd (J = 10, 18Hz).], **5.08 - 5.16** [m, 2 H, *H2'+H3'*. The COSY spectrum shows that the signal is only coupled with *H-1'*. Irradiation (1 D decoupling) of the signal at δ 5.91 (*H-1'*) resulted in a change of the appearence of the signal (δ 5.11, m); irradiation of the signal at δ 2.28 (*H-4*) also resulted in a simplification of the *H2'+H3'* signal.], **4.54** [apparent t, which is actually an overlapping dd, J= 5.5, 4.6 Hz, 1 H, *H-3*. The COSY spectrum indicates coupling between the signal at δ 4.54 (*H-3*) and the signals at δ 4.47 (*H-2*) and 2.28 (*H-4*). Irradiation (1 D decoupling) of signal at δ 2.28 (*H-4*) results in a collapse of the *H-3* signal at δ 4.54 to a poorly resolved d ($J_{2,3}$ = 5.3 Hz).], **4.47** [apparent t, which is actually an overlapping dd, J= 5.7, 5.4 Hz, 1 H, *H-2*. The COSY spectrum shows that this signal is coupled with the signal at δ 4.54 (*H-3*)

and 3.91 (*H-1*). Irradiation (1 D decoupling) of signal at δ 3.91 (*H-1*) resulted in a collapse of the signal to a poorly resolved d ($J_{2,3}$ = 5.2 Hz).], **3.91** [broad m, $W_{1/2}$ = 21 Hz, 1 H, *H-1*. This multiplet is sharpened upon D_2O exchange. The COSY spectrum shows that this signal is coupled with the signals at δ 4.47 (*H-2*), 2.41 (O*H*), and 1.63 (*H-5b*). Upon decoupling (1 D) of the signal at δ 3.91 (*H-1*), the signal for all of the above protons were simplified *i.e. H-2* (poorly resolved d, $J_{2,3}$ = 5.2 Hz,), O*H* (broad s), *H-5a* (poorly resolved dd, $J_{5a,4} \cong$ 5.6 Hz, $J_{5a,5b} \cong$ 12 Hz) and *H-5b* (m, contains poorly resolved d, $J_{5b,5a} \cong$ 12 Hz,). Likewise, irradiation at each of the *H-2, H-5a* and *H-5b* signals resulted in a change of the appearence of the δ 3.91 signal but in each case the δ 3.91 signal remained complex. Irradiation at δ 2.41 (*O-H*) resulted in a collapse of the δ 3.91 signal (*H-1*) to a 5 line multiplet. This was analysed as an overlapping ddd (J = 5.6, 5.6, 11 Hz).], **2.41** [d, $J_{OH,H-1}$ = 10.7 Hz, 1 H, *-OH*, D_2O exchangeable], **2.28** [m, 1 H, *H-4*. The COSY spectrum indicated coupling with *H-4* and *H-1'*, *H-3*. *H-5a* and *H-5b*. Upon irradiation at δ 2.28 the signals for some of these protons were simplified *ie*. *H-3* (poorly resolved d, $J_{2,3}$ = 5.3), *H-1'* (poorly resolved dd, $J_{1',2'}$ = 10, $J_{1',3'}$ = 18 Hz). Likewise, irradiation at each of the *H-1'*, *H-3, H-5a* and *H-5b* signals resulted in a change of the appearence of the δ 2.28 signals but in each case the δ 2.28 (*H-4*) signals are all still complex.], **1.94** [1 H, *H-5a*. This signal is a 5 line multiplet and was analyzed as an overlapping ddd ($J_{5a,H-4}$ = 5.6, $J_{5a,H-1}$ = 6.1, $J_{5a,5b}$ = 12 Hz). The COSY spectrum only showed that this signal is coupled with the signal at δ 2.28 (*H-4*) and 1.63 (*H-5b*). The 1 D decoupling experiment, however, indicated that there is a coupling between the *H-5a* signal and the *H-1*, *H-4* and *H-5b* signals. Irradiation of the signal at δ 1.94 (*H-5a*) resulted in a change of the appearence of the signals *H-1*, *H-4*, and *H-5b*. Likewise, irradiation of the signal at δ 3.91 (*H-1*) resulted in a collapse of the signal at δ 1.94 (*H-5a*) to a poorly resolved dd ($J_{5a,5b}$ = 12, $J_{5a,4}$ = 5.6 Hz). Irradiation of the *H-4* signal or the *H-5b* signal simplified the *H-5a* signal but in each case we could not extract out any of the J values], **1.63** [m, 1 H, *H-5b*. The COSY spectrum shows that this signal is coupled with the signals at δ 3.91 (*H-1*),

2.28 (*H-4*) and 1.94 (*H-5a*). 1 D decoupling experiments were not useful, in this particular case, for J value determinations.], **1.50** [s, 3H, CH_3], **1.35** [s, 3H, CH_3].

nOe Irradiation at δ 2.28 (*H*-4) results in a total nOe of 4.6% for the combined *H2+H3* signals. Effects are also observed for *H-1'*(1.1 %), *H2'+H3'* (1.7% in total) and *H-5a* (1.2%).

^{13}C NMR ($CDCl_3$, 75 MHz) δ: 135.8 (*C*H=CH_2), 116.2 (CH=*C*H_2), 110.6 (quaternary carbon of isopropylidene protecting group), 81.6 (C-3), 78.8 (C-2), 72.2 (C-1), 42.8 (C-4), 35.5 (C-5), 25.6 (CH_3), 24.1 (CH_3).

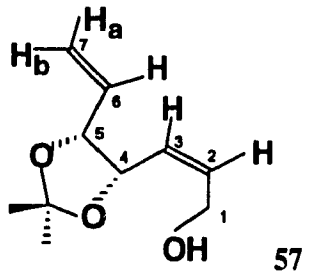
(*2Z*)-2,3,6,7-Tetradeoxy-4,5-*O*-(1-methylethylidene)-D-*ribo*-heptadi-2,6-enitol (57)

$C_{10}H_{16}O_3$

MW = 184.23 $g \cdot mol^{-1}$

pale yellow oil

R_f = 0.39 (26% EtOAc:CH_2Cl_2)



57

^{1}H NMR ($CDCl_3$, 300 MHz) δ: **5.71-5.89** [2 H, overlapping multiplets, *H-2* and *H-6*. The COSY spectrum shows that this signal is coupled with the signals at δ 4.60 (*H-5*), δ 5.32 (*H-7b*) and δ 5.25 (*H-7a*). The COSY spectrum also indicates that this signal is coupled with the signals at δ 5.55 (*H-3*), δ 4.29 (*H-1a*) and δ 4.15 (*H-1b*).], **5.55** [m, 1 H, *H-3*. The COSY spectrum indicates coupling with the signal at δ 5.71-5.89 (*H-2*) and the signals at δ 5.00 (*H-4*), δ 4.29 (*H-1a*) and δ 4.09-4.20 (*H-1b*)], **5.32** [ddd, J= 1.1, 1.7, 17.2 Hz, 1 H, *H-7b*. The COSY spectrum shows that this signal is coupled with the signals at δ 5.25 (*H-7a*), δ 4.60 (*H-5*) and δ 5.71-5.89 (*H-6*).], **5.25** [ddd, J = 1.0, 1.7, 10.3 Hz, 1 H, *H-7a*. The COSY spectrum shows that this signal is coupled with the signals at δ 5.71-5.89 (*H-6*) and 5.32 (*H-7a*).], **5.00** [m, 1 H, *H-4*. The COSY spectrum shows that this signal is coupled with the

signals at δ 4.60 (*H-5*) and 5.55 (*H-3*).], **4.60** [m, 1 H, *H-5*. The COSY spectrum shows that this signal is coupled with the signals at δ 5.00 (*H-4*) and ö 5.71-5.89 (*H-6*).], **4.29** [ddd, J = 1.3, 7.0, 13.3 Hz, 1 **H**, *H-1a*. The COSY spectrum shows that this signal is coupled with the signals at δ 4.15 (*H-1b*), δ 5.55 (*H-3*) and 5.71-5.89 (*H-2*).], **4.09-4.20** [m contains the *H-1b* signal and an unidentified signal from an impurity; the *H-1b* signal is centred at δ 4.15 (ddd, J = 1.4, 6.0, 13.3 Hz), 1 H. The COSY spectrum shows that this signal is coupled with the signals at δ 4.29 (*H-1a*) and 5.71-5.89 (*H-2*).], **1.53** [s, 3H, CH_3], **1.41** [s, 3H, CH_3].

^{13}C NMR ($CDCl_3$, 75 MHz) δ: 134.2, 132.4, 128.3 (C-2, C-3, C-6), 118.4 (C-7), 109.0 (quaternary carbon of isopropylidene protecting group), 80.0, 74.4 (C-4, C-5), 58.8 (C-1), 28.0 (CH_3), 25.5 (CH_3).

FTIR (neat): 3421 (strong broad signal, -OH), 1645 (w, C=C), 1457 (w, C-H), 1429 (w, C-H), 1376 (m, CH_3), 1246 (m, C-O), 1216 (m, C-O), 1163 (m, C-O), 1035 (s, C-OH).

Preparation of Compounds 55, 56 and 57 *Reaction of SmI_2 with **48** in THF / MeOH*

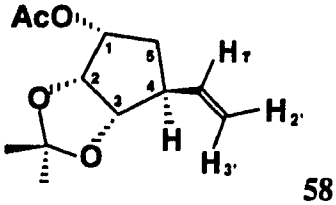
A solution of **48** (0.0743g, 0.2264 mmol), MeOH (0.085 mL, 2.09 mmol) and THF (8.5 mL) was prepared at rt under argon atmosphere. A solution of SmI_2 (6.80 mL, 0.1 M solution in THF, 0.68 mmol) was then transferred by cannula to our reaction mixture and the solution was stirred at rt for 4h, quenched with 0.1 M HCl solution (5 mL) and then worked up as usual. The crude residue was purified by chromatography [using a Chromatron and the following series of eluants: 6% EtOAc:CH_2Cl_2 (80 mL), 26% EtOAc:CH_2Cl_2, (100 mL), 50% EtOAc:CH_2Cl_2 (50 mL); 2 mm silica gel plate] to allow the separation of starting material (0.0268g, 36%, slightly impure by ^{1}H NMR) from two other fractions (**A** and **B**). Further purification of fraction **A** (20% EtOAc:hexenes, 1 mm plate) allowed for the separation of the cyclopentanol derivatives **55** (0.0144g, 34.5%) and **56** (0.0055g, 13.2%). We attempted to further purify fraction **B** (26% EtOAc:CH_2Cl_2, 1 mm plate) but were only

able to obtain a slightly impure sample of the non-cyclized elimination product **57** (0.0078g, 18.7 % yield).

Selective Preparation of Compound 55 *Reaction of SmI_2 with 48 in THF / MeOH / HMPA*

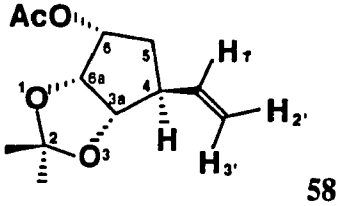
A solution of **48** (0.0614g, 0.1871 mmol), MeOH (0.080 mL, 1.97 mmol), HMPA (0.66 mL, 0.3793 mmol) and THF (3.1 mL) was prepared at -78°C under an argon atmosphere. A solution of SmI_2 (9.40 mL, 0.1 M solution in THF, 0.94 mmol) was then transferred by cannula to the reaction mixture. The solution was stirred at -78°C for 2 h and then warmed up to 0°C for 2 h. The reaction mixture was quenched with 0.1 M HCl solution (5 mL) and then worked up as usual. The crude residue was purified by radial chromatography [using a Chromatotron and the following series of eluants: 20% EtOAc:hexanes (220 mL); 60% EtOAc:hexanes (60 mL) on a 2 mm silica gel plate] to allow the separation of starting material **48** (0.0185g, 30%, slightly impure by ^1H NMR) from the cyclized product **55** (0.0176g, 51% yield).

(*1R, 2S, 3S, 4S*)-2,3-(Dimethylmethylenedioxy)-4-ethenylcyclopentyl acetate (*IUPAC name for characterization*) **(58)**



58

(*3aS, 4S, 6R, 6aS*)-Tetrahydro-6-acetoxy-4-ethenyl-2,2-dimethyl-4*H*-cyclopenta-1,3-dioxole (*CA name*) **(58)**



58

$C_{12}H_{18}O_4$

MW = 226.26g · mol^{-1}

pale yellow oil

R_f = 0.29 (12% EtOAc:hexanes)

$[\alpha]_D$ = +95.4 ° *c* 1.49

^{1}H NMR ($CDCl_3$, 300 MHz) δ: **5.77** [ddd, J = 6.4, 10.6, 17.2 Hz, 1 H, *H-1'*], **5.07 - 5.16** [2 H, overlapping signals, *H-2'* and *H-3'*. The signal attributed to *H-3'* consists of a ddd (J = 17.4, 1.2, 1.7 Hz) but has the appearence of a dt and is centered at δ 5.12. The signal attributed to *H-2'* also consists of a ddd (J= 10.6, 1.4, 1.3 Hz) but has the appearence of a dt and is centered at δ 5.10 ppm], **4.91** [m, 1 H, , *H-1*; this signal is complex but has the appearence of a poorly resolved dt. COSY and 1 D decoupling experiments show that this signal is coupled to those at δ 4.67 (*H-2*) and 2.09-2.22 (*H-5a*) and 1.95 (*H-5b*). The HOM2DJ and 1 D decoupling experiments allowed us to determine only two of the J values (10, 5.5 Hz)], **4.67** [apparent t which is actually an overlapping dd (J = 5.5, 5.5 Hz), 1H, *H-2*], **4.48** [apparent d, $J_{2,3}$ = 5.7 Hz, 1 H, *H-3*; 1 D decoupling experiments also indicate weak long range coupling with *H-5b* and *H-1*. Upon decoupling of the signal at δ 4.67 (*H-2*) the signal at δ 4.48 now appears as a sharp multiplet. Decoupling at δ 1.95 (*H-5b*) results in a change of the signal to a dd ($J_{2,3}$ = 5.7, $J_{1,3}$ = 1.3 Hz). Decoupling at 4.91 (*H-1*) results a

change of the signal to a poorly resolved dd ($J_{2,3}$ = 5.8, $J_{3,5b}$ = 0.8 Hz)], **2.77** [broad signal, $W_{1/2}$ = 18 Hz, 1 H, *H-4*. The COSY and the 1 D decoupling experiments indicated a coupling between *H-4* and *H-1'*, *H-2'*, *H-3'*, *H-5a* and *H-5b*. Upon irradiation at δ 2.77 the signals for all of these protons were simplified *ie. H-1'* (dd, $J_{1',2'}$ = 10.6, $J_{1',3'}$ = 17.4 Hz), *H-2'* (dd, $J_{2',1'}$ = 10.5, $J_{2',3'}$ = 1.1 Hz), *H-3'* (dd, $J_{3',1'}$ = 17.4, $J_{3',2'}$ = 1.1 Hz), *H-5a* (poorly resolved dd, $J_{5a,1} \cong 10$ Hz, $J_{5a,5b} \cong 13$ Hz) and *H-5b* (poorly resolved dd; $J_{5b,5a} \cong 12$ Hz, $J_{5b,1} \cong$ 6 Hz). Likewise, irradiation at each of the *H-1'*, *H-2'*, *H-3'*, *H-5a* and *H-5b* signals resulted in a change in the appearence of the δ 2.77 signal *ie.* (1) Irradiation at the *H2'* + *H3'* signals resulted in a slight sharpening of the *H-4* signal; (2) Irradiation at the *H-1'* signal results in a change of the *H-4* signal to a poorly resolved dd (J = 2, 6 Hz); (3) Irradiation at the *H-5a* signal resulted in a change of the *H-4* signal to poorly resolved d (J = 5.6 Hz); (4) Irradiation at the *H-5b* signal resulted in a change of the *H-4* signal to a poorly resolved dt (J ≅ 1, 6 Hz)], **2.09-2.22** [m, 4 H, contains a singlet at δ 2.12 ($OCOCH_3$) and multiplet attributed to *H-5a*. Analysis of data from HOM2DJ experiment allowed us to determine the following coupling constants: $J_{5a,5b}$ = 12.6, $J_{5a,1}$ = 9.8, $J_{5a,4}$ = 7 Hz. Upon irradiation at δ 4.91 (*H-1*) the multiplet at δ 2.09-2.22 is simplified to what appears to be a dd (J = 7.2, 11.8 Hz). Upon irradition at δ 2.77 (*H-2*) the *H-5a* signal is simplified to what appears to be a dd (J = 9.9, 13.2 Hz)], **1.95** [ddd, 1 H, *H-5b*, $J_{4,5b}$ = 2.8, $J_{1,5b}$ = 6.2, $J_{5a,5b}$ = 12.5 Hz. The COSY spectrum indicates coupling of the signal at δ 1.95 (*H-5b*) with those at δ 4.91 (*H-1*), δ 2.77 (*H-4*) and δ 2.09-2.22 (*H-5a*). 1 D decoupling at δ 4.91 (*H-1*) resulted in a collapse of the signal at δ 1.95 to a dd (J = 13, 2.5 Hz), 1 D decoupling at δ 2.77 (*H-4*) resulted in a collapse of the signal at δ 1.95 to a dd (J = 6.1, 12.3 Hz)], 1.50 (s, 3H, CH_3), 1.33 (s, 3H, CH_3).

nOe: Upon irradiation of the *H*-3 signal (δ 4.48) of anomer **58** we observed a smaller nOe effect for *H-4* (2.0 %) than we did in the corresponding case of anomer **59** (4.3 % for the same proton). We also saw an effect for *H-2* (3.7 %) and smaller effects for *H-1* (1.0 %), *H-1'*(2.6 %) and *H-2'*+ *H-3'* (1.4 % in total for the sum of both protons). Upon irradiation of

H-4 (δ 2.77) of anomer **58**, we see a smaller nOe effect for proton *H-3* (1.6%) than we do in the case of anomer **59** (5.7%). Very small nOe effects are also seen for *H-1* (0.2%) and *H-2* (0.13%).

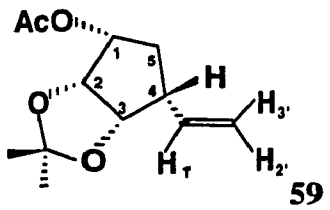
^{13}C NMR ($CDCl_3$, 75 MHz) δ: 170.7 (C=O); 137.7 (*C*H=CH_2), 115.5 (CH=*C*H_2), 111.4 (quaternary carbon of isopropylidene protecting group), 84.1 (C-3), 77.9 (C-2), 73.3 (C-1), 43.8 (C-4), 31.7 (C-5), 26.1 (CH_3), 24.5 (CH_3), 20.9 (*C*H_3CO).

FTIR (Neat, cm^{-1}): 1739 (s, C=O), 1637 (w, C=C), 1456 and 1428 (w, C-H), 1376 (m, CH_3), signals at 1243 (s), 1210 (m), 1165 (w), 1072 (m) and 1044 (m) are all attributable to C-O.

LRMS: 226 (0.6%, $M^{+\cdot}$), 211 (72.3%, M-CH_3), 168 (12.6%, loss of CH_3 and CH_3CO), 166 [5.0%, loss of CH_3COOH (McLacfferty)], 109 (35.9%, loss of CH_3COO and CH_3COCH_3), 108 (38.4%), 91 (44.7%), 79 (23.0%), 59 [15.8 %,$(CH_3)_2COH^+$], 43 (100%, CH_3CO^+).

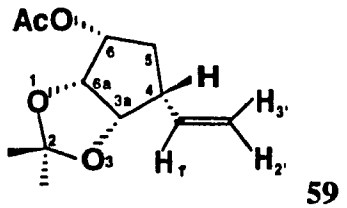
HRMS: found 211.09730; calculated for M-CH_3 = $C_{11}H_{15}O_4$: 211.09703.

(*1R, 2S, 3S, 4R*)-2,3-(Dimethylmethylenedioxy)-4-ethenylcyclopentyl acetate (*IUPAC name for characterization*)



59

(*3aS, 4R, 6R, 6aS*)-Tetrahydro-6-acetoxy-4-ethenyl-2,2-dimethyl-4*H*-cyclopenta-1,3-dioxole (*CA name*)



59

$C_{12}H_{18}O_4$

MW = 226.26g · mol^{-1}

pale yellow oil

R_f = 0.21 (12% EtOAc:hexanes)

^{1}H NMR ($CDCl_3$, 300 MHz) δ: **5.93** [m, 1 H, *H-1'*. The COSY spectrum indicates coupling with the signal at δ 5.14 (*H-2' + H-3'*) and a weak coupling with the signal at δ 2.35 (*H-4*). 1 D decoupling allowed us to only find two of the coupling constants associated with this signal. Irradiation at δ 2.35 (*H-4*) simplified the δ 5.93 signal and we are able to determine that $J_{1',2'}$ = 9.8 Hz and that $J_{1',3'}$ = 17.6 Hz. Irradiation of the *H-3* or the *H-5a + H-5b* signals had no obvious effect on the appearance of the *H-1'* signal], **5.10-5.17** [m, 2 H, overlapping *H-2'* and *H-3'* signals. The COSY spectrum indicates coupling with the signal at δ 5.93 (*H-1'*). Irradiation at δ 5.93 (*H-1*) or at δ 2.35 (*H-4*) resulted in a change in the appearance of the δ 5.10-5.17 signal but we were unable to extract out any of the coupling constants for *H-2'* or *H-3'*], **4.70** [m, 2 H, overlapping *H-1* and *H-2* signals. The COSY spectrum indicates coupling with the signals δ 4.53 (*H-3*) and δ 1.95 (*H-5a + H-5b*).], **4.53** [apparent t, appears to be an overlapping dd ($J_{3,2}$ = 5.1, $J_{3,4}$ = 4.8 Hz) but is actually more complex, 1 H, *H-3*. The COSY spectrum indicates a coupling with this signal and those at δ 2.35 (*H-4*) and δ 4.70 (*H-1 + H-2*). Irradiation at δ 2.35 (*H-4*) results in a collapse of the

signal to a d, $J_{3,2}$ = 5.2 Hz. Irradiation at δ 4.70 (*H-1* + *H-2*) however results in a change of the δ 4.70 signal to a m.], **2.35** [m, 1 H, *H-4*. The COSY spectrum indicates coupling with the signals at δ 5.93 (*H-1'*), δ 4.53 (*H-3*) and δ 1.95 (*H-5a* and *H-5b*). 1 D decoupling experiment did not allow us to extract the associated coupling constants for this signal. Irradiation at δ 4.53 (*H-3*) or at δ 1.95 (*H5a* + *H5b*) resulted in a pronounced simplification of the δ 2.35 signal.], **2.13** (s, 3H, CH_3CO), **1.95** (m, 2H, *H-5a and H-5b*. The COSY experiment indicates coupling with the signals at δ 2.35 (*H-4*) and δ 4.70 (*H-1* + *H-2*). Irradiation at δ 2.35 (*H-4*) and 4.70 (*H-1* +*H-2*) affected the appearance of the (*H5a* + *H5b*) signals; the signal is somewhat simplified but we are not able to identify a simple spin pattern.], **1.49** (s, 3H, CH_3), **1.32** (s, 3H, CH_3).

nOe: Upon irradiation of *H*-4 (δ 2.35) of anomer **59**, we see a nOe effect for *H-3* (5.7%) and one for the overlapping *H-1* and *H-2* signals (4.70 ppm, 2.8% in total). Upon irradiation at *H*-3 (δ 4.53) of **59** we see a nOe effect of 4.3 % for *H-4* (c.f. 2.0 % in the case of anomer **58**). We also see an effect on the overlapping *H-2* + *H-1* signals at 4.70 ppm (in total 3.4 %) and we see smaller effects on the *H-1'* (0.8%) and on the overlapping *H-2'*+ *H-3'* (0.30 %) signals.

^{13}C NMR ($CDCl_3$, 75 MHz) δ: 170.9 (C=O); 135.7 ($CH=CH_2$), 116.4 ($CH=CH_2$), 110.8 (quaternary carbon of isopropylidene protecting group), 81.3 (C-3), 77.8, 73.7 (C-1 and C-2), 42.5 (C-4), 31.5 (C-5), 25.7 (CH_3), 24.2 (CH_3), 20.9 (CH_3CO).

FTIR (Neat): 1738 (s, C=O), 1644 (w, C=C), 1450 (w, C-H), 1377 (m, CH_3), 1243 (s, C-O), 1210 (m, C-O), 1093 (m, C-O).

LRMS: 226 (1.1%, $M^{+\cdot}$), 211 (100%, M-CH_3), 168 (18.2%, loss of CH_3 and CH_3CO), 166 [8.5%, loss of CH_3COOH (McLacfferty)], 109 (28.9%, loss of CH_3COO and CH_3COCH_3),

108 (47.4%), 97 (11.4%), 91 (56.8%), 79 (23.1%), 59 [11.5 %, $(CH_3)_2COH^+$], 43 (54.5%, CH_3CO^+).

HRMS: found 211.09680; calculated for M-CH_3 = $C_{11}H_{15}O_4$: 211.09703.

Preparation of Compounds 58 and 59 *Reaction of SmI_2 with 49 in THF / MeOH / HMPA*

A solution of SmI_2 (7.90 mL, 0.1 M in THF, 0.79 mmol) was added dropwise to a cooled (-78 °C) solution of diacetate **49** (0.0648 g, 0.1572 mmol), MeOH (0.090 mL, 2.2 mmol), and HMPA (0.55 mL, 3.2 mmol, 5% v/v) in THF (2.6 mL). The reaction mixture was stirred at -78 °C for 2 h, warmed up to O °C for 1h 20 min, quenched with saturated aqueous NH_4Cl solution (5 mL) and then worked up as usual. The crude residue was chromatographed [12% EtOAc:hexanes, 1 mm adsorbosil plate] to allow for the separation of cyclized compounds **58** (0.0269 g, 75.6 %) and **59** (0.0020 g, 5.6 %).

4. 6. Synthesis of Wittig Reagents

[(*N*,*N*-Dimethylcarbamoyl)methylene]triphenylphosphonium chloride (61)

$C_{22}H_{23}ClNOP$

MW = 383.834 g · mol^{-1}

$Ph_3P^+CH_2CONMe_2Cl^-$ **(61)**

white crystalline solid

mp: 214-216 °C (cf.[32] 222 °C)

^{1}H NMR ($CDCl_3$, 300 MHz) δ: **7.83** [m, 6 H, CH-aromatic], **7.62** [m, 3 H, CH-aromatic (para)], **7.52** [m, 6 H, CH-aromatic], **5.65** [d, $J_{P,H}$ = 12.9 Hz, 2 H, CH_2], **3.33** [s, 3 H, NCH_3], **2.75** [s, 3 H, NCH_3].

^{13}C NMR ($CDCl_3$, 75 MHz) δ: 163.8 (C=O), 134.1 (d, $J_{P,C}$ = 3.1 Hz, C-4 of the phenyl group), 133.8 (d, $J_{P,C}$ = 10.5 Hz, C-3 of the phenyl group), 129.6 (d, $J_{P,C}$ = 13.6 Hz, C-2 of the phenyl group), 119.4 (d, $J_{P,C}$ = 90.3 Hz, C-1 of the phenyl group), 39.0, 35.5 (2 x NCH_3); 33.7 (d, $J_{P,C}$ = 67.7 Hz, CH_2).

FTIR (KBr): 1632 (s, C=O); 1435 (m, aromatic ring stretch); 1110 (m, in-plane aromatic C-H bending); 879, 749, 715 and 688 (m, out-of plane aromatic C-H bending) cm^{-1}.

LRMS: 348 (2.4%, M-Cl), 347 (10.0%, M-HCl), 305 (2.4%), 304 (22.0%), 303 (100%, loss of NMe_2 and HCl), 302 (31.8%), 301 (71.6%), 300 (4.5%), 277 (17.3%), 262 (13.6%, Ph_3P^+), 183 (26%), 165 (15.8%).

Preparation of Compound 61

The compound **61** was made by a literature procedure.[32,33] i.e: A solution of $ClCH_2CONMe_2$ (5.0508g, 0.04155 mol) and Ph_3P (10.9005g, 0.04156 mol) in dry ether (75 mL) was refluxed overnight under an argon atmosphere. The reaction mixtuire was cooled down in an ice bath and then filtered by suction. The filter cake was washed with ether in order to remove the excess $ClCH_2CONMe_2$ and Ph_3P. The solid material was then recrystallized from $CHCl_3$-ether to give a white crystalline solid **61** (4.1834g, 26 % yield).

[(*N*,*N*-Dimethylcarbamoyl)methylene]triphenylphosphorane (62) *IUPAC name*

***N*, *N*-Dimethyl-2-(triphenylphosphoranylidene)-acetamide** *CA name*

$C_{22}H_{22}NOP$

MW = 347.373 g · mol^{-1} **Ph_3P=CHCONMe$_2$ (62)**

white crystalline solid

mp: 151-152 °C (cf.[33] 152 °C)

^{1}H NMR ($CDCl_3$, 300 MHz) δ: **7.69** [m, 6 H, CH-aromatic], **7.40-7.59** [m, 9 H, CH-aromatic], **2.96** [s, 6 H, 2 x NCH_3], **2.86** [small broad signal, 1 H, P=CH].

^{13}C NMR ($CDCl_3$, 75 MHz) δ: 173.0 (d, $J_{P,C}$ = 9.8 Hz, C=O), 133.0 (d, $J_{P,C}$ = 9.6 Hz, C-3 of the phenyl group), 131.3 (d, $J_{P,C}$ = 3.2 Hz, C-4 of the phenyl group), 129.4 (low broad signal of a d, $J_{P,C}$ = 76.7 Hz, C-1 of the phenyl group), 128.5 (d, $J_{P,C}$ = 12.4 Hz, C-2 of the phenyl group), 36.7 (s, NCH_3), 30.7 (d, $J_{P,C}$ = 130.3 Hz, P=CH) (Note: The ^{13}C NMR of our synthetic sample indicate the presence of a minor impurity whose chemical shifts matched those of Ph_3PO).

FTIR (KBr): 1539 (s, C=O and aromatic ring stretch); 1481, 1438 (m, aromatic ring stretch), 1383 (s); 1129, 1104 (m, in-plane aromatic C-H bending); 906, 751, 694 (m, out-of plane aromatic C-H bending) cm^{-1}.

LRMS: 347 (12.9%, $M^{+\bullet}$), 305 (2.9%), 304 (25.8%), 303 (100%, loss of NMe_2), 302 (12.3%), 301 (26.1%), 183 (20.4%).

HRMS: found: 347.14250; calculated for $C_{22}H_{22}NOP$: 347.14389.

Preparation of Compound 62

The compound **62** was prepared according to a literature procedure.[32,33] A clear solution of $Ph_3P^+CH_2CONMe_2Cl^-$ **61** (0.5736g, 1.4943 mmol) in filtered distilled deionized water (4.00 mL) was cooled to 0^oC. To this solution was added, dropwise over 10 min, a solution of NaOH (aqueous 2.000 N solution, 0.750 mL, 1.500 mmol). The reaction mixture was stirred for 4 h at rt and changed it's appearance with time from a suspension of a sticky white gum to a powder-like precipitate. The suspension was filtered by suction. The precipitate was washed with filtered distilled deionized water (3 x 5 mL) and then dried by use of a rotoevaporator connected to a vacuum pump to give 0.3620 g (70 % yield) of product **62**. This compound was used immediately in the subsequent Wittig reaction.

[(*N*,*N*-Diethylcarbamoyl)methylene]triphenylphosphonium chloride (63)

$C_{24}H_{27}ClNOP$

MW = 411.894 g · mol^{-1}

$Ph_3P^+CH_2CONEt_2Cl^-$ (63)

white crystalline solid

mp: 194-196 °C

^1H NMR ($CDCl_3$, 300 MHz) δ: **7.91** [m, 6 H, CH-aromatic], **7.70** [m, 3 H, CH-aromatic (para)], **7.61** [m, 6 H, CH-aromatic], **5.71** [d, $J_{P,H}$ = 12.9 Hz, 2 H, CH_2], **3.88** [q, J = 7.1 Hz, 2 H, NCH_2], **3.25** [q, J = 7.1 Hz, 2 H, NCH_2], **1.24** [t, J = 7.1 Hz, 3 H, CH_3], **1.00** [t, J = 7.1 Hz, 3 H, CH_3].

^{13}C NMR ($CDCl_3$, 75 MHz) δ: 163.26 (d, $J_{P,C}$ = 3.6 Hz, C=O), 134.23 (d, $J_{P,C}$ = 2.8 Hz, C-4 of the phenyl group), 134.04 (d, $J_{P,C}$ = 10.3 Hz, C-3 of the phenyl group), 129.85 (d, $J_{P,C}$ = 12.7 Hz, C-2 of the phenyl group), 119.99 (d, $J_{P,C}$ = 90.3 Hz, C-1 of the phenyl group), 44.0, 40.9 (2 x NCH_2), 34.19 (d, $J_{P,C}$ = 67.0 Hz, CH_2), 14.5, 12.8 (2 x CH_3).

FTIR: 1632 (s, C=O); 1435 (m, aromatic ring stretch); 1111 (m, in-plane aromatic C-H bending); 879 (m), 746 (m), 717 (w) and 687 (m), out-of plane aromatic C-H bending. cm^{-1}.

LRMS: 375 (6.5%, M-HCl), 304 (13.6%), 303 (66.5%, loss of NEt_2 and HCl), 302 (45.0%), 301 (100%), 300 (3.9%), 277 (21.9%), 262 (17.7%, Ph_3P^+), 196 (11.9%), 183 (30.0%), 165 (20.3%).

Preparation of Compound 63

Compound **63** was prepared by a modified literature procedure:[33] A solution of $ClCH_2CONEt_2$ (5.0116 g, 33.50 mmol) and Ph_3P (8.7877 g, 33.50 mol) in toluene (40 mL)

was heated at 76-78°C overnight under a nitrogen atmosphere. The reaction mixture was cooled down to rt and diluted with ether (200 mL). The mixture was filtered and the filter cake was washed with ether (3 x 20 mL) to remove the excess $ClCH_2CONEt_2$ and Ph_3P. The solid material was then recrystallized from $CHCl_3$-ether (90 mL:200 mL) to give a white crystalline solid **63** (7.0055 g, 51% yield).

[(*N*, *N*-Diethylcarbamoyl)methylene]triphenylphosphorane (64) (*IUPAC name*)

***N*, *N*-Diethyl-2-(triphenylphosphoranylidene)-acetamide (64)** (*CA name*)

$C_{24}H_{26}NOP$

MW = 375.433 mol^{-1} **$Ph_3P=CHCONEt_2$ (64)**

white crystalline solid

mp: 149-151 °C (cf.[34] 151-152 °C)

^1H NMR ($CDCl_3$, 300 MHz) δ: **7.68** [m, 6 H, CH-aromatic], **7.39-7.55** [m, 9 H, CH-aromatic], **3.36** [q, J = 7 Hz, 4 H, 2 x NCH_2], **2.83** [small broad signal, 1 H, P=CH], **1.15** [t, J = 7.1 Hz, 6 H, 2 x CH_3].

^{13}C NMR ($CDCl_3$, 75 MHz) δ: 171.45 (d, $J_{P,C}$ = 9.1 Hz, C=O), 133.05 (d, $J_{P,C}$ = 9.9 Hz, C-3 of the phenyl group), 131.05 (d,, $J_{P,C}$ < 3 Hz, C-4 of the phenyl group), 129.70 (low broad signals of a d, $J_{P,C}$ = 91.9 Hz, C-1 of the phenyl group), 128.41 (d, $J_{P,C}$ = 11.8 Hz, C-2 of the phenyl group), 40.9 (2 x NCH_2), 30.49 (d, $J_{P,C}$ = 129.6 Hz, P=CH), 14.2 (2 x CH_3).

FTIR (KBr): 1537 (s, C=O and aromatic ring stretch); 1480, 1438 (m, aromatic ring stretch); 1382 (s); 1187, 1122, 1104 (m, in-plane aromatic C-H bending); 910, 755, 718 , 695 (m, out-of-plane aromatic C-H bending) cm^{-1}.

LRMS: 375 (12.6%, $M^{+\bullet}$), 346 (2.9%, loss of CH_2CH_3), 305 (2.9%), 304 (22.6%), 303 (100%, loss of NEt_2), 302 (20.9%), 301 (45.2%), 277 (13.8%), 276 (24.2%), 275 (29.7%, loss of $CONEt_2$), 262 (18.3%, Ph_3P^+), 183 (26.0%).

HRMS: found: 375.1754; calculated for $C_{24}H_{26}NOP$: 375.17519

Preparation of Compound 64

The preparation of **64** was similar to that of compound **62**. A clear solution of $Ph_3P^+CH_2CONEt_2Cl^-$ **63** (0.5156g, 1.2517 mmol) in filtered distilled deionized water (2.6 mL) was cooled to 0°C. To this solution was added, dropwise over 10 min, a solution of NaOH (aqueous 2N solution, 0.635 mL, 1.27 mmol). The reaction mixture was stirred for 4 h at rt. The reaction mixture changed its appearance with time from a suspension of a sticky gum to a powder-like precipitate. The suspension was filtered by suction. The precipitate was washed with filtered distilled deionized water (3 x 5 mL) and dried using a rotoevaporator connected to a vacuum pump to give 0.3774 g (80% yield) of product **64**. This compound was used immediately in the subsequent Wittig reaction.

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