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Studies on the Chemoselectivity and Diastereoselectivity of Samarium(II) Iodide Mediated Transformations of Carbohydrate Derived ω-Halo-α,β-Unsaturated Esters

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Abstract: Some carbohydrate derived ω-bromo- and ω-iodo- α,β- unsaturated esters were reduced with SmI_2 under a variety of conditions. The chemoselectivity varies dramatically with the choice of solvent system, the identity of halogen atom, the type of ester used, the geometry of the double bond, and the oxygenation pattern of the substrate. The stereoselectivity of the SmI_2 mediated reactions is also influenced by the reaction parameters. © 1998 Elsevier Science Ltd. All rights reserved.

INTRODUCTION

Samarium(II) iodide is a versatile reducing reagent that has been studied by many research groups over the past two decades.[1] Exposure of carbohydrate derived multifunctional ω-halo-α,β–unsaturated esters (**A**) to SmI_2 may conceivably give rise to a number of different products. Some of these are represented in figure 1.

In the event that carbon-halogen bond reduction is favored,[2] then one may obtain: the simple reduction product **B**,[3] the *cis* or *trans* reductive cyclization compounds **C**[4-6] or the β-elimination product **D**.[5,7] If, however, reduction of the conjugated ester is preferred, then reaction with SmI_2 may lead to: 1,4-reduction of the conjugated ester (**E**),[8] reductive elimination of the γ-alkoxy substituent to afford the corresponding β, γ - unsaturated ester (**F**)[9] or hydrodimerization to give either *anti* or *syn* 1,6 diesters (**G**).[10] Because of the number of possible reaction pathways open to type **A** compounds, it is useful to have an appreciation of the factors that have a direct impact on the chemoselectivity and diastereoselectivity of SmI_2 mediated reactions of these multifunctional substrates.[11] Such an appreciation will allow one to make a judicious selection of both reaction conditions and substrate characteristics so as to permit the efficient synthesis of highly functionalized reaction products.

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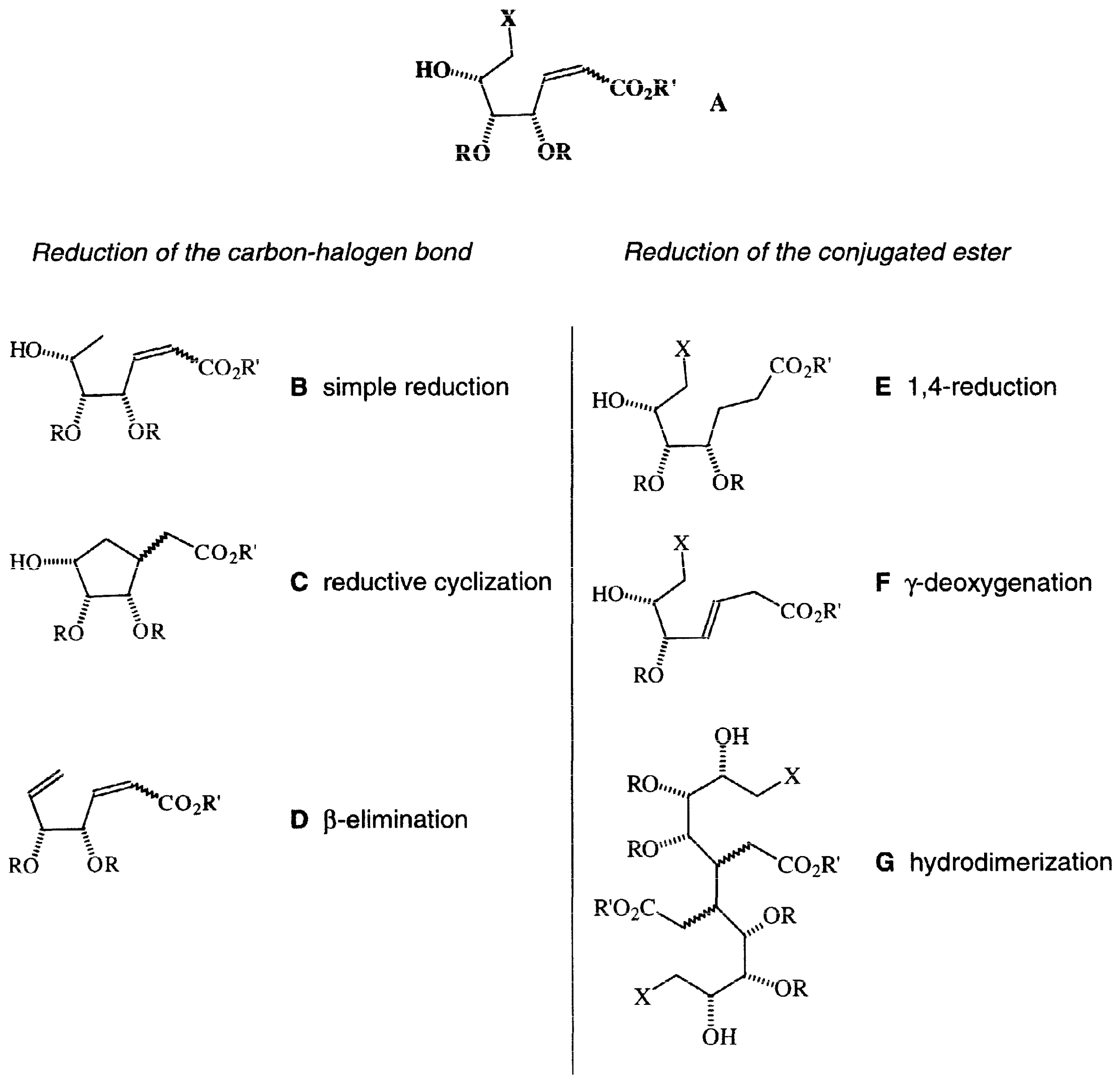
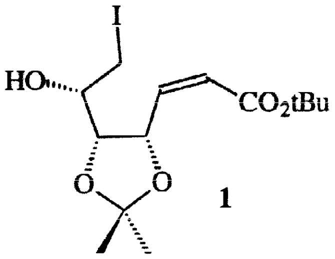


Figure 1: Some possible products from SmI_2 reactions with ω-halo-α,β-unsaturated esters.

We recently reported[5] that **1** reacts efficiently with SmI_2 in THF/HMPA/MeOH to give **2a** and noted that the choice of reaction conditions is critical to the chemoselectivity of the SmI_2 reduction.[4,6,12,13] We have expanded our study in order to better understand the factors that control the selectivity of SmI_2 reactions with type **A** compounds. In this report we describe some studies with ω-halo-α,β-unsaturated esters which vary with respect to: the double bond geometry, the identity of the halide, the oxygen substitution pattern and the type of ester. Reactions were run under a variety of reaction conditions and comparative studies were done with Bu_3SnH for some of the substrates.



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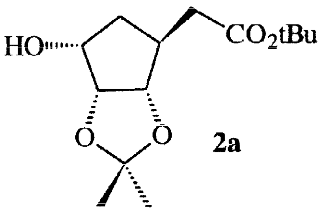
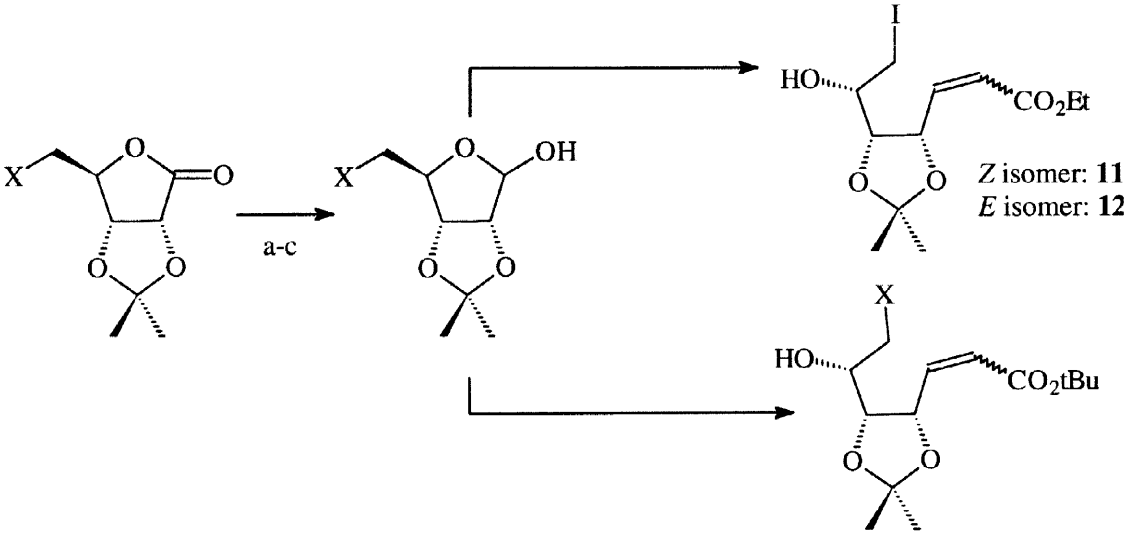


2a

RESULTS AND DISCUSSION

Preparation of starting materials

The strategy used to prepare our ω-halo-α,β-unsaturated esters **1** and **8-12** was based on a literature report from Thomasco and Wilcox.[4] Compounds **4** and **5** were prepared[4,14] from the commercially available γ- lactone **3**, and reduction of these lactones with DIBAL-H gave lactols **6** and **7**.



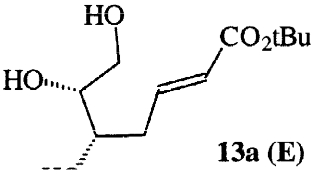
3: X = OH
4: X = I
5: X = Br

6: X = I
7: X = Br

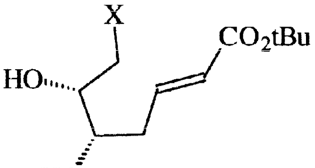
X = I, *Z* isomer: 1
X = I, *E* isomer: 8
X = Br, *Z* isomer: 9
X = Br, *E* isomer: 10

Scheme 1: (a) Ph_3P, imidazole, I_2, CH_2Cl_2 or (b) NBS, Ph_3P, CH_2Cl_2. (c) DIBAL-H, CH_2Cl_2, -78°C.

Reaction of **6** and **7** with the stabilized Wittig reagent Ph_3PCHCO_2tBu[15] gave the conjugated esters **1**, **8**, **9** and **10**. The reaction of the bromo-lactol **7** with Ph_3PCHCO_2Et was described by Thomasco and Wilcox[4] and we had expected that the corresponding reaction of the iodo-lactol **6** would allow us easy access to the unsaturated ethyl esters **11** and **12**. In our hands, this stabilized Wittig reaction was problematic and the purification of **11** and **12** was complicated by the presence of tetrahydrofuran side products.[11] We were only able to obtain a pure sample of **11**.



13a (E)
13b (Z)



14a (X = Br)
14b (X = I)

Substrates **14a** and **14b**, in contrast to the previously described substrates, lack an oxygen substituent at the γ-position. They were prepared in a two step sequence: Wittig reaction between 2-deoxy-D-ribose and Ph_3PCHCO_2tBu[16] gave **13a** and **13b** in good yield and monohalogenation of **13a** then afforded either **14a** or **14b** in a modest yield.

*Reduction reactions with the trans iodo-ester **8***

The reactions of the *E* iodo-substrate **8** with SmI_2 were generally very chemoselective. Carbon-iodine bond reduction is preferred to reduction of the conjugated ester: we isolated only carbocyclic compounds **2a** and **2b**. Treatment of **8** with an excess of SmI_2 in THF/MeOH/HMPA (table 1, entry 1) at low temperature gave the *trans* reductive cyclization compound **2a** in excellent yield (91 %). GC-MS analysis of the chromatographed product indicated the presence of only a trace amount of the *cis* compound **2b**. The diastereoselectivity of this reaction is lowered slightly when the reaction was carried out at room temperature (table 1, entry 2).

The SmI_2/THF/HMPA/MeOH conditions compare well with, and are *complementary* to, the corresponding Bu_3SnH/AIBN reaction. The *cis* compound **2b** was the major isomer formed in the Bu_3SnH reaction with **8** (table 1, entry 4).

The stereochemistry of the cyclization products was determined from nOe experiments, from the $J_{3a,4}$ coupling constants and from the known configuration of carbons 6a, 3a and 6. In the case of compund **2a**, the H-3a and H-4 protons have a *trans* relationship and a small coupling constant (< 2 Hz). In contrast, the H-6a and H-3a protons of **2a** have a *cis* relationship and the $J_{3a,6a}$ coupling constant is 6 Hz. Upon irradiation at the H-3a signal of **2a** we observed nOe effects for the H-6a signal (5.9 %) and for the CH_2CO_2tBu signals (total combined effect = 4.2 %); smaller nOe effects are seen for the H-4 signal (2.9 %) and the *exo* methyl group of the isopropylidene protecting group (2.1%). For compound **2b**, the H-3a proton is *cis* to both the H-4 and the H-6a protons; both $J_{3a,4}$ and $J_{3a,6a}$ have a value of 5 Hz.

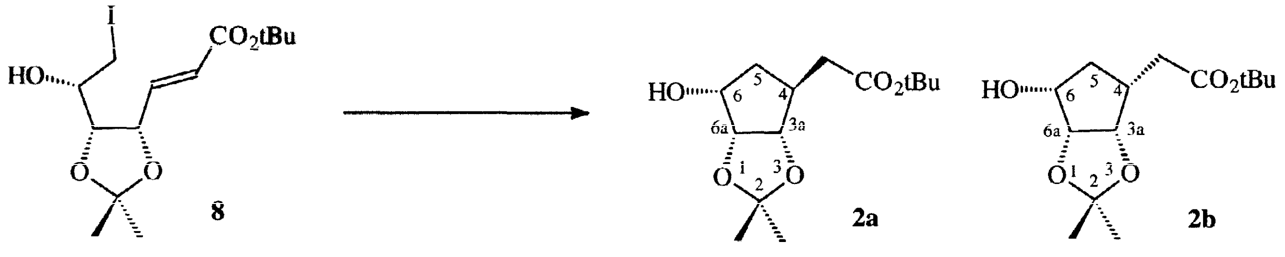


Table 1: Summary of reactions run with *E* iodide 8

Entry	Reagents and reaction conditions[a, b, c]	% Yield of cyclized product[d] (ratio of **2a** /**2b**)[e]	% recovery of **8**[d]
1	SmI_2 (4 eq), MeOH/THF/HMPA, -78°C 4h, 0°C 2h.	91.3 (78.4/1)	--
2	SmI_2 (3 eq), MeOH/THF/HMPA, rt, 2h.	66.8 (27.1/1)	18.2[f]
3	SmI_2 (3 eq), MeOH/THF, rt, 7h.	18.0 (1/2.4)	55.8
4	Bu_3SnH (1.4 eq), AIBN (0.1 eq)/Benzene[g], 80°C, 3 h.	78.6[f] (1/2.6)	--

a) All SmI_2 and Bu_3SnH reactions were run under anhyd conditions under an argon atmosphere. b) Final concn of **8** = 0.015 M. Co-solvents used: HMPA - 5% v/v of the final reaction soln; Final concn of MeOH = 0.15 M. c) The dark blue soln of SmI_2 (0.1 M in THF, Aldrich) was transferred, via cannula under a positive pressure of argon, to a flask containing HMPA. The resulting dark purple soln was stirred for 10 min at rt and then transfered via cannula, to the reaction mixture. d) Isolated yield of pure compd. e) As determined by GC-MS analysis. f) Isolated as a slightly impure sample. g) A benzene soln of the substrate, AIBN and Bu_3SnH was prepared at rt and then heated to 80 °C.

The influence that HMPA has on the efficiency of SmI_2 reductions is well known[12a] and it is not surprising that, in the absence of HMPA, the reductive cyclization of **8** is sluggish (table 1, entry 3). The publication of the X-ray structure of $SmI_2(HMPA)_4$[12b]and the recent report of electrochemical studies on SmI_2/THF/HMPA solutions[12c] give us a better understanding of the role HMPA plays in changing the redox properties of divalent samarium. It is interesting to note that the addition of HMPA *increases the efficiency and reverses the diastereoselectivity* of the carbocyclization reaction of **8**. Our interpretation of this result is that the addition of HMPA increases the steric bulk around the samarium atom. This, in turn, results in an increase in the steric interactions between a samarium-complexed carbonyl oxygen and the methyl groups of the isopropylidene protecting group (see figure 2). Bulky Lewis acids are known to promote highly stereoselective radical cyclizations onto α,β-unsaturated esters.[17] Such interactions might explain the observed change in diastereoselectivity in favor of the *trans* product **2a** (table 1, entries 2 and 3).

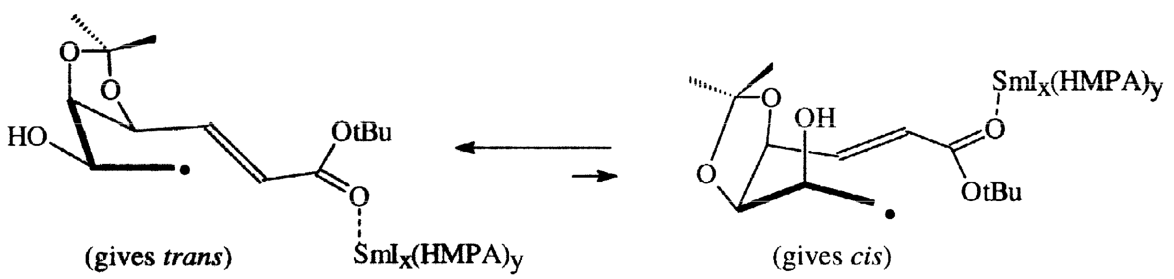


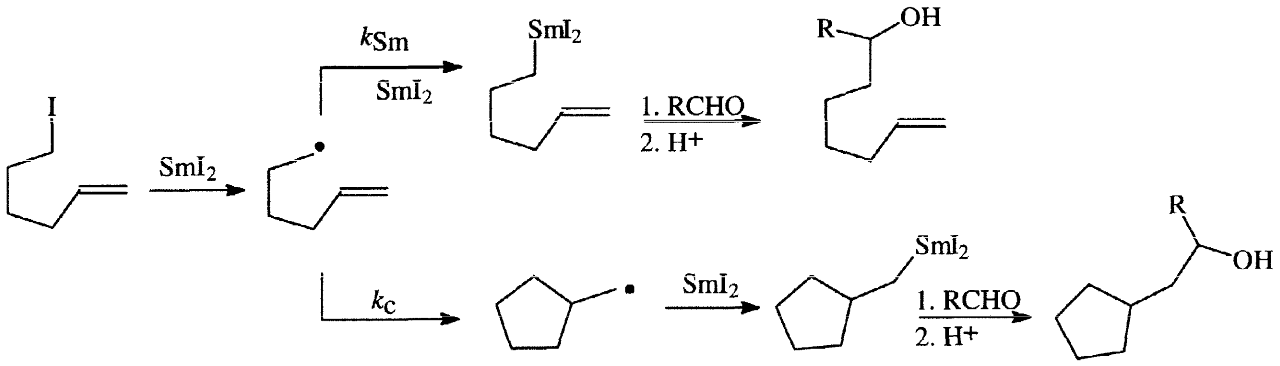
Figure 2: Rationalization for the observed diastereoselectivity reported in entries 1 and 2 of table 1.[18]

A referee has proposed that the change in diastereoselectivity observed upon addition of HMPA may be an indication of a change in mechanism. It was suggested that, under the SmI_2/HMPA/MeOH conditions, the transformation involves an anionic rather than a radical cyclization. This would require that: (a) reduction of the initially formed 1° radical (shown in figure 2) to give the corresponding carbanion is faster than radical cyclization onto the activated double bond, and (b) that cyclization of the resulting 1° organosamarium species is much faster than either protonation or β-elimination (*vide infra*, scheme 3). We have considered this possibility but, for the reasons discussed in the following section, we believe that our results are more consistent with a radical cyclization pathway.[19]

Radical versus anionic cyclization

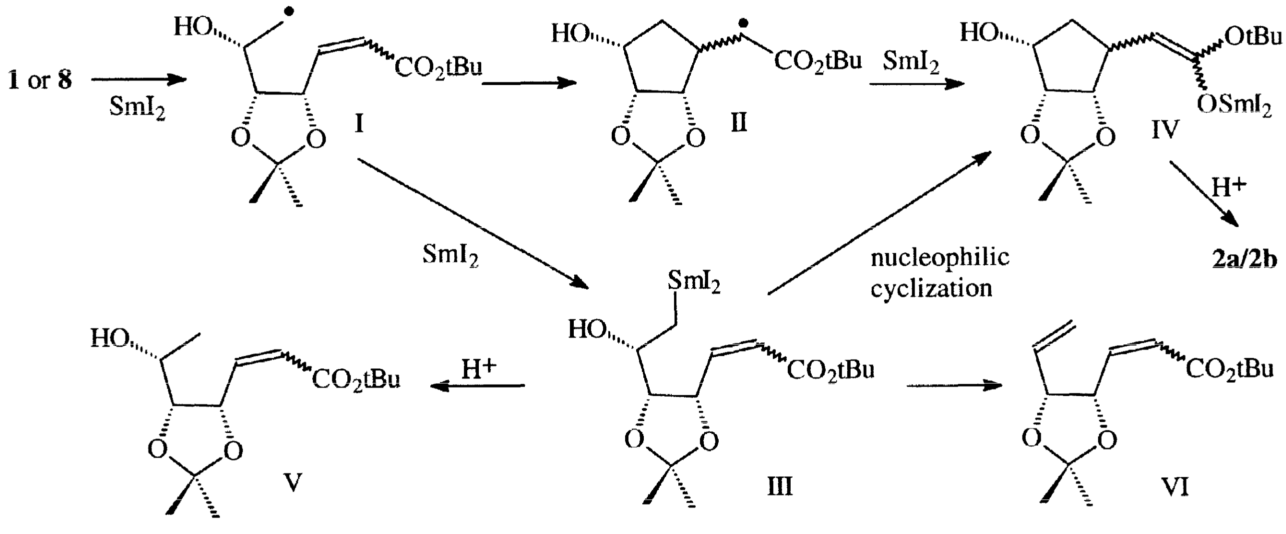
The SmI_2 mediated reduction of a 1° alkyl iodide substrate tethered to an olefin may lead to the formation of reductive cyclization compounds or simple reduction products.[3] The reaction involves the initial formation of a 1° alkyl radical as a reaction intermediate. This radical may either cyclize onto the olefin or be reduced by SmI_2 to give an acyclic alkylsamarium species.[3] Hasegawa and Curran have determined rate constants for the reduction of 1° alkyl radicals by SmI_2 in THF/HMPA at room temperature by using a competitive hexenyl radical clock (see scheme 2).[20] A solution of 6-iodohex-1-ene was added to a solution of SmI_2 (2 equiv of SmI_2 per equiv of alkenyl iodide) in THF/HMPA. After consumption of the SmI_2, *p*-anisaldehyde was added as a trap. The ratio of cyclized to noncyclized product was measured and the bimolecular rate constant k_{Sm} was determined. A series of experiments was run at different concentrations of HMPA.

The ratio of cyclized : noncyclized product (see scheme 2) is influenced by the value of k_{Sm} and by the concentration of SmI_2. The value of k_{Sm} varies with the amount of HMPA used. An increase in the amount of HMPA resulted in an increase in the proportion of the initially formed 1° radicals that were reduced to the corresponding 1° organosamarium species before they could cyclize onto the terminal unactivated olefin.[20] When *ca.* 2 equivalents of HMPA were used per equivalent of SmI_2 ($[SmI_2] = 0.095$ M) the ratio of cyclized to noncyclized product was 9:1 or better ($k_c = 2.4 \times 10^5\ s^{-1}$ at 25°C; $k_{Sm} = 5 \times 10^5\ M^{-1}s^{-1}$).[20] When *ca.* 4-13 equivalents of HMPA were used, however, the ratio of cyclized to noncyclized product was close to 1:1. For example, at 5 equivalents of HMPA and for a SmI_2 concentration of 0.097 M, the ratio of cyclized to noncyclized product was 45:55 ($k_{Sm} = 6.5 \times 10^6$ $M^{-1}s^{-1}$). For reactions run at lower concentrations of SmI_2 ($[SmI_2] = 0.021$ M), but with the same ratio of HMPA to SmI_2 (5:1), the ratio of cyclized to noncyclized product shifted in favor of cyclization (4:1 to 3:1 ratios).[20]



Scheme 2: Determination of rate constants by Hasegawa and Curran[20]

An alkyl iodide tethered to an α,β-unsaturated ester can be reduced by a variety of reagents to give reductive cyclization compounds; such a transformation may proceed via a radical or an anionic cyclization pathway. Radical cyclizations mediated by Bu_3SnH work well for both simple and complex substrates.[4] An anionic or nucleophilic cyclization, mediated by BuLi, works well for *simple* ω-iodo-α,β-unsaturated *t*-butyl esters.[21] It is conceivable that the SmI_2 mediated reductive cyclization may involve a radical and/or an anionic cyclization step (see scheme 3). The mechanistic issue of this type of transformation has been discussed in some detail in a recent paper by Molander and Harris.[6] Our own results are most consistent with a radical cyclization pathway (*vide infra*) but they are not a rigorous proof of the mechanistic details of this reaction.[19]



Scheme 3: Possible cyclization pathways

If compounds **2a** and **2b** are formed by a radical cyclization pathway then cyclization of the 1° radical (I to II) must be faster than reduction to the 1° organosamarium species (I to III).[22] The rate constant for the addition of an alkyl radical onto a carbon-carbon double bond is significantly increased by the presence of an electron withdrawing group on the olefin.[22] For example, the rate constant for the addition of a methyl radical onto methyl acrylate is 97 x larger than that for addition onto ethylene.[23] It is reasonable to assume that the rate of cyclization of I to II (see scheme 3) would be significantly faster than the rate of cyclization of the 5-hexenyl radical (see scheme 2).

As previously discussed, the addition of HMPA to SmI_2 reaction mixtures increases the rate constant for the SmI_2 reduction of a 1° alkyl radical to the corresponding organosamarium species. The rate of this bimolecular reduction however decreases with a decrease in the concentration of SmI_2 used. The concentration of SmI_2 will be very low, at least initially, if SmI_2 is added slowly to a solution of the substrate. This is likely to be successful tactic for favoring radical cyclization (I to II) over reduction (I to III) in those cases where SmI_2 reacts very rapidly with the iodide substrate.

Our reactions are carried out as follows: A solution of SmI_2 in THF and HMPA (*ca.* 8:1 HMPA: SmI_2), was added dropwise, over an approximately 10 min period, to a solution of our substrate in THF/MeOH. We typically see an immediate dissipation of the purple color of the SmI_2/THF/HMPA solution upon addition to our reaction mixtures; the purple color begins to persist after the addition of *ca.* 2 equivalents of the reagent. An excess of SmI_2 was used and reaction mixtures were usually allowed to stir under an argon atmosphere for several hours.

Our reaction conditions and our results are inconsistent with an anionic cyclization pathway. All of our substrates contain at least one free hydroxyl group and our SmI_2 reductions were routinely run in the presence of 10-13 equivalents of MeOH per equivalent of substrate. While the cyclization of an anion onto a conjugated ester is expected to be fast,[21] it seems unlikely that cyclization of III to IV would occur at the total exclusion of either protonation to give V or β-elimination to give VI. We found no evidence of either V or VI in our reaction mixtures. Previous work from our laboratory has shown that organosamarium species similar to III are prone to β-elimination reactions.[5] It is interesting to note that Molander and Harris[6] report that exposure of ω-iodo-α,β-unsaturated esters to SmI_2 in the presence of HMPA gives products resulting from simple reduction of the carbon-halogen bond and from 1,4-reduction of the conjugated ester; reductive cyclization products were not formed under their conditions.[24]

Reduction reactions with the cis iodo-ester 1

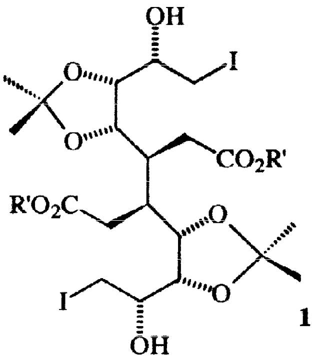
The chemoselectivity of the SmI_2 reduction of the *cis* iodide **1** , in contrast to the *trans* iodide **8**, varies significantly with the choice of reaction conditions (see Table 2). Compound **2a** is diastereoselectively obtained in good yield when the reaction is run under the SmI_2/THF/HMPA/MeOH reaction conditions at room temperature. In this instance there is no advantage in running the reaction at -78°C. The removal of HMPA or the substitution of HMPA by DMPU[25] altered the chemoselectivity of the SmI_2 reduction. We were surprised to discover that the use of DMPU as a co-solvent resulted in the formation of a new compound whose spectral data are consistent with the $C_{28}H_{48}I_2O_{10}$ dimer **15**.

Table 2: Summary of reactions run with *Z* iodide 1

Entry	Reagents and conditions[a,b,c]	% Yield of cyclized product[d] (ratio of **2a/2b**)[e]	% recovery of **1**[d]	Other products
1	SmI_2 (3 eq), MeOH/THF/HMPA,[c] rt, 30 min.	85.6 (>99.9/0.1)	--	--
2	SmI_2 (4 eq), MeOH/THF/HMPA,[g] -78°C 4h, 0°C 2h.	70.0 (>99.9/0.1)	6.1	--[f]
3	SmI_2 (4 eq), MeOH/THF/DMPU,[g] -78°C 4.5h, 0°C 1h.	59.6 (>99.9/0.1)	--	$C_{28}H_{48}I_2O_{10}$ Dimer **15** 20.2% yield
4	SmI_2 (3 eq), MeOH/THF, rt, 10 min.	--	13.6	compound **16** [f] 44.3%
5	Bu_3SnH (1.2 eq), AIBN/Benzene[h] 80°C, 3.5h.	36.5[i]	--	cyclic ether **18**, 18.2% yield
6	Bu_3SnH (1.2 eq), AIBN/Benzene[j] 80°C, 3.5h.	56.6 (99.8/0.2)	--	--[f]

a - e) As per Table 1. f) We detected *trace* amounts of some other compds by TLC and ^{1}H NMR analysis of the crude product but these compds were not pursued. g) SmI_2 in THF was added to a chilled soln of **1** in THF/MeOH/HMPA or THF/MeOH/DMPU. h) A soln of Bu_3SnH and AIBN was slowly added to a refluxing soln of **1** over 3.5 h. i) Isolated as a slightly impure sample; this sample was not analyzed by GC-MS j) A benzene soln of the substrate, AIBN and Bu_3SnH was prepared at rt and then heated to 80 °C.

The dimer **15** is formed despite the fact that the reaction was run under fairly dilute reaction conditions. The initial concentration of **1**, prior to transfer of the SmI_2 solution, was 0.033 M; the final concentration (after all of the SmI_2 solution had been transferred) was 0.014 M. Hydrodimerization may give either *syn* or *anti* 1,6-diesters. The configuration of the two new stereocenters were determined indirectly by chemical conversion from compound **22**. We were able to obtain an X-ray crystal structure for the $C_{28}H_{48}Br_2O_{10}$ dibromide **22** (*vide infra*). Treatment of **22** with an excess of NaI in acetone overnight gave a compound whose ^{1}H and ^{13}C NMR spectra were identical to those obtained for **15**.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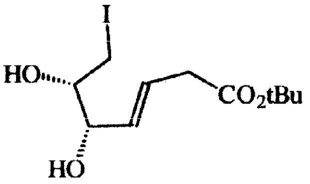
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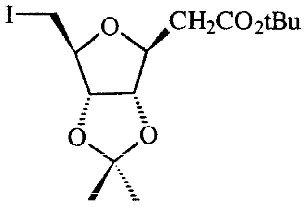
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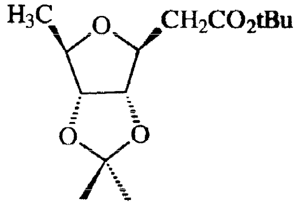
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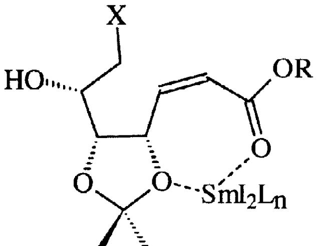
The chemoselectivity of the SmI_2 reduction of **1** changes when the reaction is run at rt in THF/MeOH: the mass balance is poor and the γ-deoxygenation compound **16** is the major product formed under these conditions. This was not observed with the *trans* iodide substrate **8**. It seems reasonable to suggest that, in the case of the *cis* iodo-ester, complexation of the carbonyl oxygen *and* the *syn* γ-oxygen substituent with samarium (see **19**) renders reduction of the conjugated ester competitive with carbon-iodine bond reduction.

The formation of both compounds **15** and **16** presumably involves the transfer of an electron from SmI_2 to the conjugated ester and in the formation of a radical-anion (see **20**). If **20** is further reduced then the carbanion species **21** that is formed can undergo reductive cleavage of the carbon-oxygen bond at the γ -position to give the β,γ -unsaturated ester **16**.[9] Hydrodimerization of **1** to give **15** may occur by a number of different reaction pathways. These may involve (a) dimerization of a radical intermediate (the radical-anion **20** or the corresponding neutral radical that is formed by protonation of **20**) or (b) the 1,4-addition of a reactive intermediate (radical-anion, neutral radical, or carbanion) onto a molecule of starting material.[10,26]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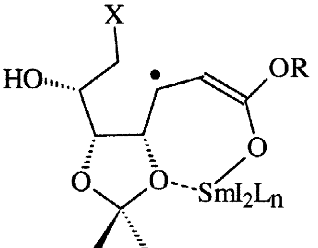
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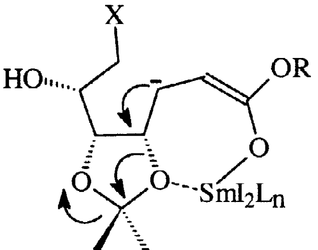
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The SmI_2 mediated cyclization of **1** compares well with the corresponding Bu_3SnH mediated radical cyclization (see Table 2, entries 5 and 6).[4] Slow simultaneous addition of 1.2 equiv of Bu_3SnH and 0.12 equiv of AIBN over 3.5 h to a refluxing solution of **1** in benzene gave compound **18** in addition to compound **2a**.[27] The cyclic ether **18** is presumably formed via a 1,4-addition of the hydroxyl group onto the double bond to form intermediate **17**. Compound **17** is then reduced *in situ* by Bu_3SnH to give **18**. The formation of **18** is avoided if one first prepares a solution of **1**, Bu_3SnH and AIBN at room temperature under an argon atmosphere and then heats the solution at 80°C for 3.5 h. The concentration of Bu_3SnH in the reaction mixture is initially higher under these conditions and therefore Michael addition is no longer competitive with the carbon-iodine bond reduction. The isolated yield of the reductive cyclization product under these conditions was 57%[27] and the diastereomeric ratio of *trans* **2a** to *cis* **2b** cyclization compounds was 99.8:0.2. When these same conditions were applied to the *E* isomer **8**, we isolated the reductive cyclization compounds in 78.6 % yield. GC-MS analysis of the purified products indicated a *trans:cis* ratio of 1.0/2.6. The diastereoselectivity of the Bu_3SnH reductive cyclization is dependent on the double bond geometry. These results are consistent with the report by Wilcox and Thomasco describing the Bu_3SnH mediated radical cyclizations of ω-bromo-α,β-unsaturated *ethyl* esters, derived from D-ribonolactone.[4]

Bromides versus iodides as substrates

A change in the identity of the halogen atom, from iodine to bromine, resulted in a marked change in the chemoselectivity of the reduction. Although the use of SmI_2/THF/HMPA to reduce both alkyl iodides and bromides is well known,[12a] carbon-halogen bond reduction is no longer the *preferred* pathway (see figure 1) for the ω-bromo-α, β unsaturated ester substrates *with a γ -oxygen substituent.*

Table 3: Summary of reactions run in MeOH/THF/HMPA with *Z and E* ω-Bromides 9 and 10

Entry	Substrates, reagents and conditions[a, b,c]	% Yield of cyclized product[d] (ratio of *2a/2b*)[e]	% recovery of s. mat.	Other products (% yield)
1	Substrate **9**: SmI_2 (4 eq), -78°C 4 h, 0°C 1h.	13.0 (>99.9/0.1)	--	**22** ($C_{28}H_{48}Br_2O_{10}$,40.0), **23** ($C_{28}H_{49}BrO_{10}$, 11.9), **24** ($C_{28}H_{47}BrO_9$,16.4)[f]
2	Substrate **9**: SmI_2 (1.3 eq), -78°C 20 min.	4.2[f] (>99.9/0.1)	22.2[f]	$C_{28}H_{48}Br_2O_{10}$ dimer **22** (51.8)[d], γ-deoxygenation compd[d] **26** (6.8)
3	Substrate **10**: SmI_2 (4 eq), -78°C 4h, 0°C 1h.	20.1 (78.4/1)	--	saturated ester[d] **27** (18.3)[g], new $C_{28}H_{48}Br_2O_{10}$ dimer **25**[d] (23.4)

a) SmI_2 reactions were run under anhyd conditions under an argon atmosphere. b) Final concn of substrate = 0.015 M. Co-solvents used: HMPA - 5% v/v of the final reaction soln; Final concn of MeOH = 0.15 M. c) The dark blue soln of SmI_2 (0.1 M in THF, Aldrich) was transferred, via cannula under a positive pressure of argon, to a flask containing HMPA. The resulting dark purple soln was stirred for 10 min at rt and then transferred via cannula, to the cooled reaction mixture. d) Isolated yield of pure compd. e) As determined by GC-MS analysis. f) Isolated as a slightly impure sample. g) TLC, GC-MS and NMR analysis of the crude and partially purified product indicated that small amounts of other compds were also present in the reaction mixture.

We ran reactions with the *cis* and *trans* bromides **9** and **10** in the presence of 4 equivalents of SmI_2 under the THF/HMPA/MeOH conditions (entries 1 and 3, Table 3). The bromide reaction mixtures are complex with the reductive cyclization products **2a** and **2b** accounting for only a small portion of the reaction mixture. When the reaction was run with **9** and 1.3 equivalents of SmI_2 the reaction mixture was somewhat simpler (See entry 2, Table 3). Compound **22** is by far the major component; **26** and **2a** are the minor reaction products. The predominant pathway in the case of the *cis* substrate **9**, under both sets of conditions, involves a diastereoselective reductive hydrodimerization to give the dimer **22**.[28] The absolute stereochemistry of the two new stereocenters was determined from an X-ray crystal structure (see figure 3). As shown in figure 3, the hydrogen atoms of C(22) and C(15) of **22** are *anti* to one another, as are those of C(7) and C(8). Most of the other hydrogen atoms have been omitted from the diagram for the sake of clarity.

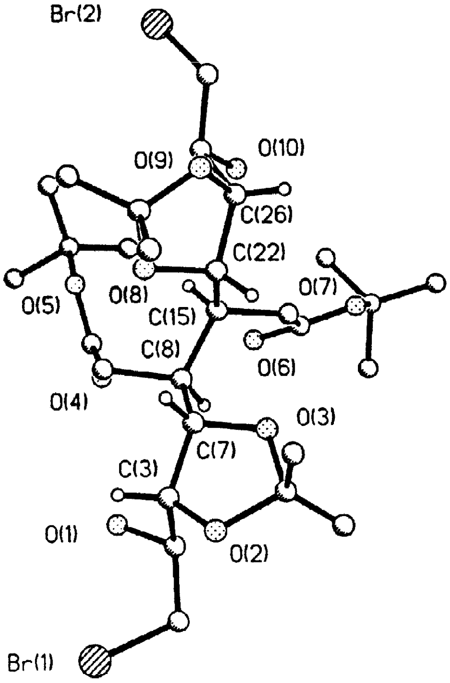
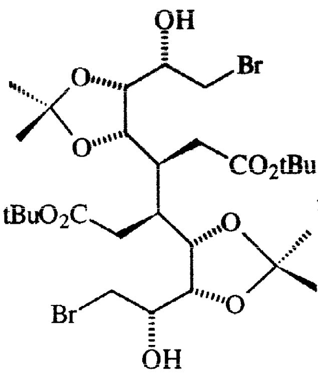
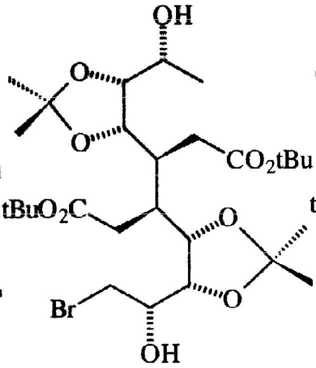


Figure 3: X-ray crystal structure of compound **22**.

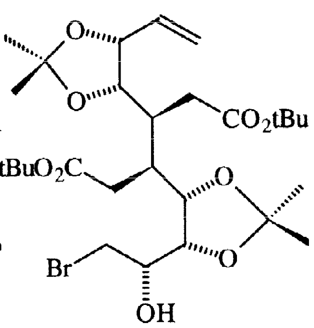
Compounds **23** and **24**, formed when 4 equivalents of SmI_2 was used, are the result of the reaction of **22** with the excess of SmI_2 present in the reaction mixture. We presume that the absolute configuration of the two new stereocenters of **23** and **24** match those of **22**.



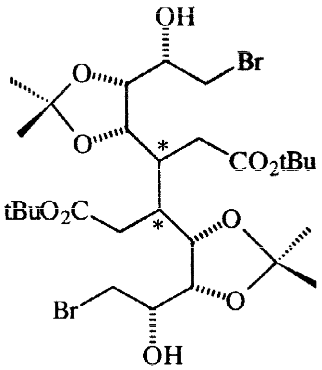
$C_{28}H_{48}Br_2O_{10}$ **22**



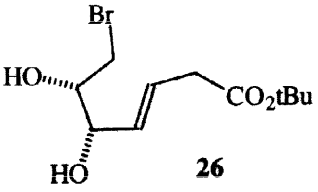
$C_{28}H_{49}BrO_{10}$ **23**



$C_{28}H_{47}BrO_9$ **24**



$C_{28}H_{48}Br_2O_{10}$ **25**



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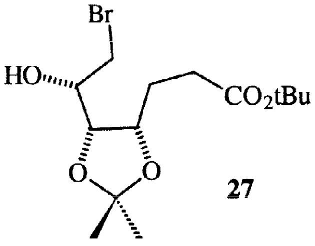
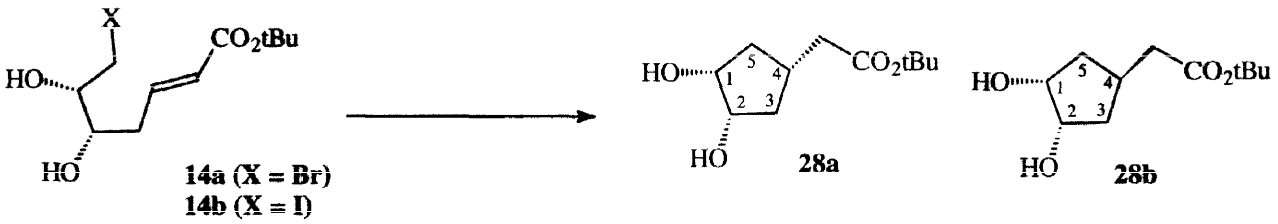


27

Reaction of the *trans* bromide **10** with an *excess* of SmI_2 resulted in the formation of a new $C_{28}H_{48}Br_2O_{10}$ diastereoisomer **(25)** whose NMR spectrum are different from those of **22**. Compound **25** was isolated as an oil and the configuration of the two new stereocenters was not determined. We also isolated the saturated ester **27** and the reductive carbocyclization compounds **2a** and **2b**. This is not a synthetically useful reaction, because of the product distribution, but it is interesting from a mechanistic point of view. The double bond geometry affects the chemoselectivity of the conjugated ester reduction: the *cis* ω-bromo unsaturated ester **9** gave rise to γ-deoxygenation product **26** whereas the saturated ester **27** was formed from the corresponding *trans* ester **10**. The diastereoselectivity of the hydrodimerization is also a consequence of double bond geometry with **9** giving **22** and **10** giving **25**.

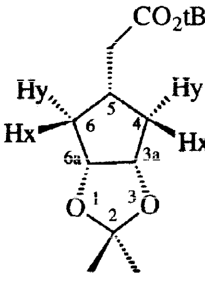
Unlike bromides **9** and **10**, compound **14a** lacks a γ-oxygen substituent. We wondered if this modification of the substrate would allow us to preferentially reduce the carbon-halogen bond. Exposure of **14a** to an excess of SmI_2 (4 equivalents) under the low temperature HMPA/MeOH/THF reaction conditions resulted in the formation of several compounds. The major products were compounds **28a** and **28b** (3.8/1.0 ratio) isolated in 40% yield as a slightly impure sample. We were unsuccessful in our attempts to obtain pure material from this reaction mixture. The reaction of **14b** with SmI_2, under the same conditions, was much cleaner and gave only **28a** and **28b** (91% yield) in a 7.2:1.0 ratio. These results compare well with the corresponding Bu_3SnH/AIBN reduction of **14b** in refluxing benzene: under these conditions we isolated **28a** and **28b** in 78.7 % yield in a 2.3:1.0 ratio.



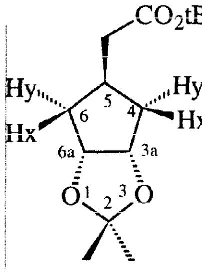
14a (X = Br)
14b (X = I)

28a

28b



29a



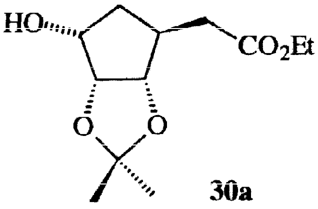
29b

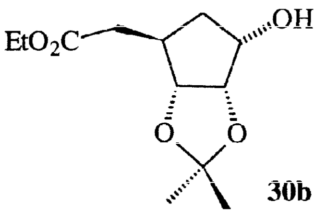
The stereochemistry of the cyclized products was determined from nOe experiments on the acetal derivatives **29a** and **29b** and from the known configuration of carbons 6a and 3a. In compound **29a** the CH_2CO_2tBu group and the Hy protons are on the same side of the ring: upon irradiation at the Hy signal of **29a** we observed nOe effects for the geminal Hx protons (19.25%), and for the CH_2CO_2tBu signal (2.95%). As expected, much smaller effects are seen for the H-5 signal (1.53%) and the H-3a/H-6a signal (0.99%). The H-5 proton, the Hx protons and the H-3a/H-6a protons are all on the same side of the ring in **29a**. Upon irradiation at H-5 of **29a**, we observed a strong nOe for Hx (7.41%) and a moderate one for H-3a/H-6a (2.3%); we saw only a weak effect for Hy (1.04%). In the case of the *trans* diastereoisomer **29b**, the Hx protons are on the same side of the ring as the H-3a/H-6a protons and the CH_2CO_2tBu group. Irradiation of the Hx signal of **29b** resulted in a strong geminal effect for Hy (19.94%) and in moderate effects for the H-3a/H-6a signal (6.39%) and the CH_2CO_2tBu signal (2.74%).

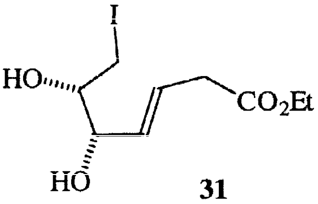
Ethyl esters versus t-butyl esters

When the reduction of the ω-iodo *cis* ethyl ester **11** was run with SmI_2 (3 eq) in THF alone at room temperature we isolated the γ -deoxygenation compound **31** as the major reaction product in modest yield. We found, however, that reduction of **11** in THF/MeOH/HMPA (-78°C) with SmI_2 (4 eq) led to a complex mixture of compounds. TLC and NMR analysis of the crude reaction product indicated the presence of at least six compounds. The reduction was not selective and there was no clear preference for either carbon-halogen bond reduction or conjugate ester reduction these conditions. We also ran the reduction using two equivalents of SmI_2: the reaction was incomplete and the reaction mixture was still very complex. We isolated the reductive cyclization product **30a**[4] in only 17% yield (purity by GC >99%). Our ^{1}H and ^{13}C NMR data are in agreement with those previously reported in the literature for **30a**[4] and for its enantiomer **30b**.[29]

The chemoselectivity of the SmI_2 reduction is sensitive to the nature of the ester used - at least for *cis* substrates having γ-oxygen substituents. Replacing the *t*-butyl ester with an ethyl ester (**1** versus **11**), resulted in a marked deterioration of the chemoselectivity of the SmI_2 reduction: there is no longer a clear preference for the carbon-iodine bond reduction/ carbocyclization sequence under our HMPA/MeOH conditions. We propose that the loss of chemoselectivity with the ethyl ester substrate is due to a decrease in the steric bulk of the ester. The use of a smaller OR group (see **19**) would facilitate the formation of the chelate and, consequently, make the reduction of the conjugated ester portion of the molecule competitive with carbon-iodine bond reduction.[19]


30a


30b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Conclusions

The chemoselectivity and the diastereoselectivity of SmI_2 reductions of D-ribonolactone derived ω-halo-α,β -unsaturated esters is affected by: the solvent system used, the identity of the halide, the double bond geometry, and the type of ester used. The reaction of SmI_2 with ω-halo-α,β–unsaturated esters gave compounds resulting from reduction of the carbon-halogen bond and/or reduction of the conjugated ester.

Reductive carbocyclization to give highly functionalized products is favored when HMPA is used as a co-solvent, the halogen is an iodine atom and when *t*-butyl esters are used. The diastereoselectivity of these SmI_2 cyclization reactions compares favorably with that of the corresponding Bu_3SnH reactions.

Reduction of the conjugated ester was the preferred pathway when the halogen atom was bromine and when the conjugated ester had a γ-oxygen substituent. We isolated products arising from: hydrodimerization, simple reduction of the carbon-carbon double bond, and from the reductive elimination of the γ-oxygen substituent. In the absence of a γ-oxygen substituent reductive carbocyclization products were obtained in moderate yield from a 2-deoxy-D-ribose derived ω-bromo- α,β-unsaturated ester. The yields are much better, however for the corresponding iodide substrate.

The effects of various parameters on the *diastereoselectivity* of reductive carbocyclizations of a series of ω-halo-α, β–unsaturated esters is currently being investigated in our laboratory and will be reported in due course.[19]

Acknowledgements: We are grateful to the Natural Sciences and Engineering Research Council of Canada (NSERC), Bio-Méga/Boehringer Ingelheim Canada Ltd. and to the Université du Québec à Montréal (UQAM) for funding our research. We thank Mr. N. Saade (McGill University) for mass spectra results, Dr. H. Le Thanh (UQAM) for help with the nOe and HMQC NMR experiments, Dr. G. Sauvé (Institut Armand Frappier) and Professor R. Kazlauskas (McGill University) for providing access to polarimeters, Professor F.D. Rochon (UQAM) for X-ray analysis and Ms. N. Yee for assistance with the preparation of some starting materials.

Experimental

General experimental: Unless otherwise noted, ^{1}H (300 MHz) and ^{13}C NMR (75 Mz) spectra were recorded in $CDCl_3$ on a Varian 300 BB instrument. HMQC and nOe NMR experiments were run on a Brüker AMX2 500 instrument. The symbols s', d', t', and q', used for ^{13}C NMR data, represent carbons having zero, one, two or three attached hydrogens, respectively. FTIR spectra were recorded on a Perkin Elmer Series 1600 instrument and mass spectra were run on a Kratos 25 RFA instrument. Melting points were recorded on a Fisher-Johns apparatus and are uncorrected. GC-MS analysis were run on a Hewlett Packard GCD Plus instrument (HP-5 column, 30 m length, 0.25 mm diameter, 1 mL/min flow rate, Oven ramp: initial temp = 50°C, final temp = 275°C, rate = 22 °C /min.) with an electron ionization detector. Optical rotations were measured at 25°C at 589 nm in ethanol (100%) with a JASCO DIP-370 Digital Polarimeter (system A) or at 22° in either EtOH or $CHCl_3$ with a JASCO DIP-140 Digital Polarimeter (System B). The reported concentrations (*c*) are in g / 100 mL.

5-Deoxy-5-iodo-2,3-*O*-(1-methylethylidene)-D-ribonic acid-γ-lactone (4): To a soln of **3** (3.5495 g, 0.01890 mol) in CH_2Cl_2 (113 mL) 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).[14b] The reaction mixture was stirred at rt for 1.5 h and then filtered over silica gel to remove the white precipitate that had formed during the reaction. The filtrate was concd 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 **4**. Our spectral data matched those reported for an alternate synthesis of this compd.[30]

5-Deoxy-5-iodo-2,3-*O*-(1-methylethylidene)-β-D-ribofuranse (6): A soln of DIBAL-H (5.50 mL, 20% in hexanes, 7.7 mmol) was added dropwise (over 5 min) to a cooled (-78°C) soln of **4** (1.0944g, 3.672 mmol) in CH_2Cl_2 (40 mL) under an argon atmosphere. The reaction mixture was stirred for 3 h and then quenched with a saturated aq soln of NH_4Cl (10 mL). The aq layer was extracted with CH_2Cl_2 (3 x 50 mL) and the combined organic layers were washed with a saturated soln of $NaHCO_3$ (40 mL), H_2O (50 mL) and brine (50 mL). The organic phase was dried, filtered and concd. Purification by flash chromatography (5 x 20 cm silica, 20% EtOAc: hexanes) gave **6** (0.9499g, 86% yield): mp = 88-90°C. R_f= 0.28 (TLC, 20% EtOAc: hexanes). $[\alpha]_D$ = -39.7 [*c* 1.33, system A]. **^{1}H NMR** δ: **5.57** (d, J = 2.9 Hz, 1 H, *H-1*, collapses to a s upon D_2O exchange), **4.83** (dd, J= 0.9, 5.8 Hz, 1 H, *H-3*), **4.68** (d, J = 5.8 Hz, 1 H, *H-2*), **4.46** (ddd, J =1.0, 6.2, 9.7 Hz, 1 H, *H-4*), **3.24-3.38** (2 H, m, *H-5a* and *H-5b*), **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** (50 MHz) δ: 112.7 (s'), 103.3 (d'), 87.5 (d'), 85.9 (d'), 83.5 (d'), 26.4 (q'), 24.9 (q'), 7.5 (t'). **FTIR** (nujol): 3380 cm^{-1}. **HRMS** [EI]: found 284.96220; calcd for M-CH_3 = $C_7H_{10}IO_4$: 284.96256. **MS** [CI, NH_3] m/z: 318 (17.2%, M + 18), 301 (33.4%, M + 1), 300 (100%, M), 285 (94.9%, M-15).

***tert*-Butyl (2*Z*)-2,3,7-trideoxy-7-iodo-4,5-*O*-(1-methylethylidene)-D-*ribo*-hept-2-enoate (1) and *tert*-Butyl (2*E*)-2,3,7-trideoxy-7-iodo-4,5-*O*-(1-methylethylidene)-D-*ribo*-hept-2-enoate (8):** A soln of iodolactol **6** (1.0617 g, 3.538 mmol) and benzoic acid (29 mg, 0.24 mmol) in CH_2Cl_2 (10 mL plus 2 x 3 mL rinse) was added, dropwise over 10 min, to a 0°C soln of Ph_3PCHCO_2tBu (1.7239 g, 4.580 mmol; Aldrich) in CH_2Cl_2 (45 mL) under an argon atmosphere. The soln was stirred at 0°C for 10 min and then at rt for 4 h. Saturated aq NH_4Cl (50 mL) was added and the mixture was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with saturated aq $NaHCO_3$ (40 mL), H_2O (40 mL) and brine (40 mL). The organic phase was dried, filtered and concd. The residue was dissolved in a minimum of EtOAc (~6 mL); hexanes (~40 mL) were added and the resulting cloudy soln was cooled at 0°C overnight. The precipitated Ph_3PO was removed by filtration and the filtrate was concd. Purification of the residue by flash chromatography (5x17 cm, silica, 1:4 EtOAc: hexanes) and radial chromatography (Chromatrotron, 4 mm silica gel plate, 1:5 EtOAc:hexanes) allowed for separation of the *Z* and *E* diastereoisomers **1** (1.1073 g, 78.6 % yield) and **8** (0.1606 g, 11.4%).

1: white solid, mp = 46-49°C. $R_f = 0.43$ (TLC, silica, 1:5 EtOAc: hexanes). $[\alpha]_D = +116.0$ (*c* 1.18, system A). ^{1}**H NMR** δ: **6.14** [dd, J= 8.5, 11.6 Hz, 1 H, *H-3*], **5.97** [dd, J = 1.2, 11.6 Hz, 1 H, *H-2*], **5.48** [ddd, J = 1.1, 6.2, 8.4 Hz, 1 H, *H-4*], **4.21** [apparent dd, 1 H, *H-5*], **3.91**[m, 1 H,*OH*, D_2O exchangeable], **3.51** [m, 1 H, *H-7a*], **3.35** [m, 2 H, *H-7b+H-6*], **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** δ: 167.0 (s'), 144.6 (d'), 124.5 (d'), 109.7 (s'), 82.5 (s'), 81.4 (d'), 74.6 (d'), 69.0 (d'), 28.04 (q'), 27.99 (q'), 25.5 (q'), 11.9 (t'). **FTIR** (cast): 3434, 1680, 1636 cm^{-1}. **MS** [EI] m/z: 383 (0.5%, M-CH_3), 171 (53.6%, ICH_2CHOH^+), 59 (82.2%), 57 (100%, $C(CH_3)_3$). **HRMS** [EI]: found 383.03650; calcd for M-CH_3 = $C_{13}H_{20}IO_5$: 383.03572. **MS** [CI, NH_3] m/z: 399 (20.8%, M+1), 343 [100%, 399 - C_4H_8], 171 (90.9%, ICH_2CHOH^+).

8: oil. $R_f = 0.29$ (TLC, silica, 1:5 EtOAc : hexanes). $[\alpha]_D = -11.0$ (*c* 1.63, system A). ^{1}**H NMR** δ: **6.96** [dd, J = 5.1, 15.6 Hz, 1 H, *H-3*], **6.08** [dd, J = 1.7, 15.6 Hz, 1 H, *H-2*], **4.85** [ddd, J = 1.7, 5.1, 8.3 Hz, 1 H, *H-4*], **4.05** [apparent dd, 1 H, *H-5*], **3.55** [apparent dd, 1 H, *H-7a*], **3.36** [m, 2 H, *H-7b* + *H-6*], **2.61** [d, J = 5.2 Hz, D_2O exchangeable, 1 H, *OH*], **1.49** [s, 12 H, 4 x CH_3], **1.37** [s, 3 H, CH_3]. ^{13}**C NMR** δ: 165.6 (s'), 141.8 (d'), 124.3 (d'), 109.5 (s'), 80.7 (s'), 79.9 (d'), 76.5 (d'), 69.0 (d'), 28.1 (q'), 27.6 (q'), 25.1 (q'), 14.5 (t'). **FTIR** (cast): 3444, 1714, 1695, 1657 cm^{-1}. **MS** [EI] m/z: 383 (10.6%, M- CH_3), 342 (8.8%, M - C_4H_8), 227 (18.7%, M - ICH_2CHOH), 171 (31.2%, ICH_2CHOH^+), 59 [65.4%, $(CH_3)_2COH^+$], 57 (100%, $C_4H_9^+$). **HRMS** [EI]: found 383.03600; calcd for M-CH_3 = $C_{13}H_{20}IO_5$: 383.03572.

***tert*-Butyl (2*Z*)-2,3,7-trideoxy-7-bromo-4,5-*O*-(1-methylethylidene)-D-*ribo*-hept-2-enoate (9) and *tert*-Butyl (2*E*)-2,3,7-trideoxy-7-bromo-4,5-*O*-(1-methylethylidene)-D-*ribo*-hept-2-enoate (10):** A soln of bromolactol **7**[4] (0.5806 g, 2.294 mmol) and benzoic acid (10 mg) in CH_2Cl_2 (6 mL plus 2 x 2 mL rinse) was added, dropwise over 10 min, to a 0°C soln of Ph_3PCHCO_2tBu (1.456 g, 3.868 mmol; Aldrich) in CH_2Cl_2 (30 mL) under an argon atmosphere. The soln was stirred at 0°C for 40 min, at rt for 4 h and then worked up as previously described for **1** and **8**. Purification of the residue by flash and radial chromatography allowed for the separation of the *Z* and *E* diastereoisomers **9** (59.5% yield pure sample; 9.5% yield impure sample) and **10** (7.6 % yield) from a little unreacted starting material (1.2%).

9: white solid. mp = 39.5-41.5 °C. $R_f = 0.42$ (TLC, silica, 1:5 EtOAc: hexanes). $[\alpha]_D = +100$ (*c* 1.02, EtOH, System B). ^{1}**H NMR** δ: **6.16** [dd, J = 8.4, 11.6 Hz, 1 H, *H-3*], **5.98** [dd, J= 1.3, 11.6 Hz, 1 H, *H-2*], **5.52** [ddd, J= 1.3, 6.2, 8.4 Hz, 1 H, *H-4*], **4.30** [dd , J= 6.2, 8.1Hz, 1 H, *H-5*], **3.66 - 3.78**[m, 3 H, *OH*, *H-6*, *H-7a*], **3.56** [m, 1 H, *H-7b*], **1.51** [s, 3 H, CH_3], **1.48** [s, 9 H,$C(CH_3)_3$], **1.40** [s, 3 H, CH_3]. ^{13}**C NMR** δ: 166.8, 144.3, 124.5, 109.7, 82.4, 79.9, 74.6, 69.5, 37.0, 28.06, 27.95, 25.5. **FTIR** (cast): 3435, 1711, 1686 cm^{-1}. **MS** [CI, NH_3] m/z: 353 (16.0%, M+1 for M = $C_{14}H_{23}{}^{81}BrO_5$), 351 (17.1% , M + 1 for M = $C_{14}H_{23}{}^{79}BrO_5$), 297 (98.5%, 353 - C_4H_8), 295 (100%, 351 - C_4H_8). **MS** [EI] m/z: 296 (0.9%, M = $C_{14}H_{23}{}^{81}BrO_5$ - C_4H_8), 294 (1.0%, M = $C_{14}H_{23}{}^{79}BrO_5$ - C_4H_8), 221 (18.6%), 219 (19.5%), 171 (55.4%) 59 (100%), 57 (97.1 %, $C(CH_3)_3$). **HRMS** [EI]: found 294.01070; calcd for M = $C_{14}H_{23}{}^{79}BrO_5$ - C_4H_8: 294.01033.

10: oil. $R_f = 0.33$ (TLC, silica, 1:5 EtOAc : hexanes). ^{1}**H NMR** δ: **6.98** [dd, J= 5.0, 15.6 Hz, 1 H, *H-3*], **6.10** [dd, J = 1.7, 15.6 Hz, 1 H, *H-2*], **4.87** [partially resolved ddd, J = 1.7, 5.1, 6.6 Hz, 1 H, *H-4*], **4.12** [dd, J = 6.6, 8.9 Hz, 1 H, *H-5*], **3.75** [dd, J = 2.4, 10.1 Hz, 1 H, *H-7a*], **3.68** [m, 1 H, *H-6*], **3.55** (dd, J=6.6, 10.1 Hz, 1H, *H-7b*), **2.26** (d, J = 5.4 Hz, 1H, OH), **1.50** (s, 12H, CH_3 and $C(CH_3)_3$), **1.38** (s, 3H, CH_3). ^{13}**C NMR** δ: 165.4 (s'), 144.4 (d'), 124.4 (d'), 109.5 (s'), 80.6 (s'), 78.7 (d'), 76.6 (d'), 69.2 (d'), 38.9 (t'), 28.1 (q'), 27.6 (q'), 25.2 (q'). **FTIR** (cast): 3444, 1714, 1695, 1657 cm^{-1}. **MS** [CI, NH_3] m/z: 370 (4.2%, M = $C_{14}H_{23}{}^{81}BrO_5$ + 18), 368 (4.1%, M = $C_{14}H_{23}{}^{79}BrO_5$ + 18), 351 (13.4%, M = $C_{14}H_{23}{}^{81}BrO_5$ - 1), 349 (12.5%, M = $C_{14}H_{23}{}^{79}BrO_5$ -1), 195 (83.6%), 193 (81.2%), 155 (100%).

Ethyl (2*Z*)-2,3,7-trideoxy-7-iodo-4,5-*O*-(1-methylethylidene)-D-*ribo*-hept-2-enoate (11): A soln of iodolactol **6** (0.3383 g, 1.127 mmol) and benzoic acid (2.7 mg) in CH_2Cl_2 (3 mL plus 2 x 2 mL rinse) was added, dropwise over 10 min, to a 0°C soln of Ph_3PCHCO_2Et (0.6389 g, 1.834 mmol; Aldrich) in CH_2Cl_2 (15 mL) under an argon atmosphere. The soln was stirred at 0°C for 10 min, at rt for 4.5 h and then worked up as previously described for compds **1** and **8**. The crude residue was purified by flash column and then by radial chromatography several times to give the *cis* alkene **11** (25.4% yield of pure compd and 46.5% yield of a slightly impure sample) but we were unable to separate the *trans* alkene (10% yield) from unreacted starting material (3%).

11: oil. R_f = 0.31 (TLC, silica, 15% EtOAc in hexanes). $[\alpha]_D$ = +102 (*c* 2.08, $CHCl_3$, System B). **^{1}H NMR** (200 MHz) δ: **6.24** (dd, J = 8.3, 11.6 Hz, 1H, *H-3*), **6.02** (dd, *J* = 11.6, 1.2 Hz, 1H, *H-2*), **5.54** (m, 1H), **4.05-4.35** [3H, overlapping m (1H) and q (**4.20**, 2H, J = 7.1 Hz, OCH_2CH_3)], **3.26-3.55** (m, 4H, upon D_2O exchange this signal integrates for 3H), **1.49** (s, 3H, CH_3), **1.38** (s, 3H, CH_3), **1.29** (t, 3H, J = 7.1 Hz, OCH_2CH_3). **^{13}C NMR** [50.3 MHz] δ: 167.1, 145.8, 122.6, 109.7, 81.2, 74.5, 69.2, 61.3, 27.9, 25.4, 14.1, 12.0. **FTIR** (film): 3448, 1716 (shoulder at 1695), 1652 cm^{-1}. **MS** [EI, 70eV] m/z: 355 (8.6% , M-15), 199 (46.9%, loss of ICH_2CHOH), 141 (93.6%), 113 (56.9%), 97 (56.6%), 85 (74.0%), 43 (100%). **HRMS** [EI] found: 355.00470; calcd for $M-CH_3 = C_{11}H_{16}IO_5$: 355.00442.

***tert*-Butyl (2*E*)-2,3,4-trideoxy-D-*ribo*-hept-2-enoate (13a):** A soln of Ph_3PCHCO_2tBu (24.7 mmol, see reference 16) and 2-deoxy-D-ribose[15] (3.00 g, 22.4 mmol) in THF (50 mL) was stirred at 60°C for 6 h under an argon atmosphere and then cooled to rt. Silica gel (*ca* 100 mL) and CH_2Cl_2 (*ca* 50 mL) were added and the solvent evaporated. The impregnated silica was then loaded onto a column of silica gel and elution with 12% MeOH in CH_2Cl_2 allowed for a partial separation of the *E* and *Z* isomers: Mixed isomers (1.22 g, 23% yield, 1.3/1.0 mixture of **13a**/**13b**) and pure **13a** (3.03 g, 58% yield).

13a: oil. R_f = 0.43 (TLC, silica, 12% MeOH in CH_2Cl_2). $[\alpha]_D$ = -16 (*c* 0.91, system A). **^{1}H NMR** ($CDCl_3/D_2O$) δ: **6.88** [m, 1 H, *H-3*], **5.84** [d, *J* = 15.7 Hz, 1 H, *H-2*], **3.50-3.90** [m, 4H, *H-5, H-6, H-7a, H-7b*], **2.52-2.25** (m, 2H, *H-4a, H-4b*), **1.46** (s, 9H, $C(CH_3)_3$). **^{13}C NMR** ($CDCl_3/D_2O$) δ: 166.4 (s′), 144.5 (d′), 125.3 (d′), 80.6 (s′), 73.9 (d′), 71.4 (d′), 62.9 (t′), 35.6 (t′), 28.1 (q′). **MS** [CI, NH_3] m/z: 250 (22.8%, M = $C_{11}H_{20}O_5$ + 18), 233 (7.5%, M+1), 194 (100%). **MS** [EI] m/z: 176 (2.7%, M = $C_{11}H_{20}O_5$ - C_4H_8), 115 (24.8%), 86 (60.7%), 57 (100%, $C(CH_3)_3$). **HRMS** [EI] found: 176.06860; calcd for M = $C_{11}H_{20}O_5$ - C_4H_8 : 176.06847.

***tert*-Butyl (2*E*)-2,3,4,7-tetradeoxy-7-bromo-D-*ribo*-hept-2-enoate (14a):** A soln of PPh_3 (0.450 g, 1.70 mmol) in CH_2Cl_2 (3.4 mL) was added dropwise, over 45 min, to a cooled soln (0°C) of N-bromosuccinamide (0.3072 g, 1.726 mmol) and **13a** (0.3618 g, 1.558 mmol) in CH_2Cl_2 (15 mL) under an argon atmosphere. The mixture was stirred at 0°C for a total of 2 h and then warmed to rt overnight. Silica gel (*ca* 40 mL) was added to the reaction mixture and the solvent evaporated. The impregnated silica was loaded onto a column of silica gel and elution with 2:3 EtOAc - hexanes gave compd **14a** (0.1821 g, 39.6% yield): mp = 61-62 °C. R_f = 0.33 (TLC, silica, 2:3 EtOAc-hexanes). $[\alpha]_D$ = -3.2 (*c* 0.79, system A). **^{1}H NMR** δ: **6.88** [ddd, *J* = 6.9, 8.0, 15.6 Hz, 1 H, *H-3*], **5.88** [apparent dt, *J* = 1.4, 15.6 Hz, 1 H, *H-2*], **3.81** [m, 1 H, *H-5*], **3.66** [m, 3 H, *H-6, H-7a,7b*], **2.61** [dddd, J = 1.5, 3.4, 6.7, 14.6 Hz, 1 H, *H-4a*], **2.41** [m, 3 H, *H-4b*, 2 x OH], **1.48** (s, 9H, $C(CH_3)_3$). **^{13}C NMR** δ: 165.6 (s'), 143.0 (d'), 126.3 (d'), 80.6 (s'), 73.3 (d'), 71.6(d'), 37.1 (t'), 35.7 (t′), 28.1 (q'). **FTIR** (cast): 3420, 1691, 1653 cm^{-1}. **MS** [CI, NH_3] m/z: 314 (18.1%, M = $C_{11}H_{19}{}^{81}BrO_4$ + 18), 312 (18.6%, M = $C_{11}H_{19}{}^{79}BrO_4$+ 18), 297 (15.2%, M = $C_{11}H_{19}{}^{81}BrO_4$ + 1), 295 (15.6%, M = $C_{11}H_{19}{}^{79}BrO_4$+1), 258 (100%), 256 (94.5%). **MS** [EI] m/z: 240 (14.7%, M = $C_{11}H_{19}{}^{81}BrO_4$ - C_4H_8), 238 (14.5%, $C_{11}H_{19}{}^{79}BrO_4$ - C_4H_8), 223 (14.2%, $C_{11}H_{19}{}^{81}BrO_4$ - $OC(CH_3)_3$), 221 (15.0%, $C_{11}H_{19}{}^{79}BrO_4$ - $OC(CH_3)_3$), 115 (69.4%), 97 (31.4%), 86 (70.2%), 57 (100%, $C(CH_3)_3$). **HRMS** [EI] found: 237.98430; calcd for M = $C_{11}H_{19}{}^{79}BrO_4$-C_4H_8: 237.98412.

***tert*-Butyl (2*E*)-2,3,4,7-tetradeoxy-7-iodo-D-*ribo*-hept-2-enoate (14b):** A soln of PPh_3 (1.73 g, 6.60 mmol) in CH_2Cl_2 (13.0 mL) was added dropwise, over 70 min, to a cooled soln (0°C) of N-iodosuccinamide (1.604 g, 7.13 mmol) and **13a** (1.41 g, 6.07 mmol) in CH_2Cl_2 (40 mL) under an argon atmosphere. The mixture was stirred at 0°C for a total of 2 h and then warmed to rt overnight. Silica gel (*ca* 100 mL) was added to the reaction mixture and the solvent evaporated. The impregnated silica was loaded onto a column of silica gel and elution with 2:3 EtOAc - hexanes gave compd **14b** (0.9097 g, 43.8% yield): R_f = 0.39 (TLC, silica, 2:3 EtOAc-hexanes). **^{1}H NMR δ: 6.87** [ddd, *J* = 6.9, 8.0, 15.6 Hz, 1 H, *H-3*], **5.88** [apparent dt, *J* = 1.4, 15.6 Hz, 1 H, *H-2*], **3.76** [m, 1 H, *H-5*], **3.46** [m, 3 H, *H-6, H-7a,7b*], **2.59** [dddd, *J* = 1.6, 3.6, 6.9, 14.6 Hz, 1 H, *H-4a*], **2.38** (m, 1H, *H-4b*), **1.99** [broad s, 2 H, 2 x OH], **1.48** (s, 9H, $C(CH_3)_3$). **^{13}C NMR δ:** 165.4 (C=O), 142.8 (C-3), 126.4 (C-2), 80.5 (*C*(Me)$_3$), 73.3 and 72.4 (C-5, C-6), 35.5 (C-4), 28.1 ($C(CH_3)_3$), 12.4 (C-7). **MS** [EI] m/z: 286 [3.85%, M-C_4H_8 (McLafferty)], 115 (46.5%), 57 [100%, $C(CH_3)_3$]. **HRMS** [EI] found: 285.97020; calcd for M = $C_{11}H_{19}IO_4$-C_4H_8: 285.97039. **MS** [CI, NH_3] m/z: 360 (16.9%, M + 18), 343 (10.7%, M + 1), 304 (100%).

Typical procedure for reactions with SmI_2: A soln of the substrate (0.35 mmol) in THF (9.2 mL) and MeOH (0.14 mL) was prepared under an argon atmosphere and cooled to -78°C. In a second flask a mixture of HMPA (1.2 mL) and SmI_2 [0.1 M THF solution (Aldrich), 14.0 mL, 1.4 mmol] was stirred for 10 min at rt under an argon atmosphere. The resulting deep purple soln was then transferred dropwise, over *ca.* 10 min, to the cooled soln of the substrate via cannula. The final concn of substrate was 0.014 - 0.015 M. The mixture was stirred at -78°C and then warmed to 0 °C. The reactions were quenched by the addition of a saturated aq soln of NH_4Cl or 0.1 M HCl (*ca.* 20 mL) and then worked up as follows: the mixture was diluted with H_2O (*ca.* 10 mL) and extracted with EtOAc (3 x *ca.* 20 mL). The combined extracts were washed with H_2O (3 x *ca.* 30 mL), saturated aq $Na_2S_2O_3$ (*ca.* 30 mL) and brine (*ca.* 30 mL). The organic layer was dried over $MgSO_4$ and concd. The crude products were purified by flash column chromatography or by radial chromatography [Harrison Research Chromatotron, silica gel or adsorbosil plates] using a mixture of EtOAc and hexanes as the eluant.

Reaction of 1 with Bu_3SnH/AIBN under slow addition conditions in benzene: Solutions of AIBN (0.0041g, 0.029 mmol; 1 mL benzene) and Bu_3SnH (0.08 mL, 0.29 mmol; 1 mL benzene) were simultaneously added dropwise (over 3.5 h) to a refluxing soln of **1** (0.0994g, 0.2496 mmol; 14.6 mL benzene). The reaction mixture was stirred for another 0.5 h, then cooled down to rt and concd. The residue was diluted with ether (10 mL) and and the soln was stirred with an aq soln of KF (3g in 10 mL water) for 3 h.[27] The organic layer was filtered twice through a short pad of silica gel and the filtrate was concd. The residue was diluted with ether (10 mL) and then DBU (0.060 mL, 0.40 mmol) was added. The mixture was titrated with a 1 M soln of iodine in ether (1.5 mL, *ca* 1.5 mmol).[27] A yellow precipitate was formed and the mixture was filtered through a short column of silica gel (2 x 3 cm). The column was washed with ether (3 x 10 mL). The combined filtrates were concd and the residue was loaded on a short column of silica gel (2 x 3 cm). The column was washed with hexanes (15 mL) and then ether (25 mL). The ether fraction was concd and the residue was purified by radial chromatography [1 mm plate, 10% EtOAc:hexanes (50 mL) followed by 25% EtOAc:hexanes (70 mL)]. We isolated **2a** (0.0248g, 36.5 % yield) as a slightly impure sample (as determined by ^{1}H NMR) and compd **18** [0.0124 g, 18.2% yield].

3,6-Anhydro-2,7-dideoxy-4,5-O-(1-methylethylidene)-D-allo-Heptonic acid *tert*-butyl ester (18): pale yellow oil. R_f = 0.71 (30% EtOAc:hexanes). $[\alpha]_D$ = -3.9 (*c* 0.62, System A). **^{1}H NMR δ: 4.54** [dd, *J* = 4.6, 7.1 Hz, 1 H, *H-4*], **4.28** [dd, J = 5, 7 Hz, 1H, *H-5*], **4.16** [m, 1 H, *H*-3], **3.95** [m, 2H, H-6], **2.56** [d, J = 6.5 Hz, 2H, CH_2CO_2tBu], **1.54** [s, 3H, CH_3], **1.46** [s, 9H, $C(CH_3)_3$], **1.34** [s, 3 H, CH_3], **1.30** [d, J = 6.4 Hz, 3H, C-7 CH_3]. **nOe**: Upon irradiation of the H-4 signal (4.54 ppm) we observed large nOe effects for the H-5 (7.54%) and the H-2 protons (5.22%) and smaller nOe effects for the H-3 proton (2.67%) and the *exo* CH_3 signal of the isopropylidene group (1.34 ppm, 2.25%). Upon irradiation of the H-6 signal (3.95 ppm) we observed large nOe effects for the H-7 protons (4.47%) and the H-3 proton (5.60%) and a smaller nOe for the H-5 proton (2.24%). Upon irradiation of the H-5 signal (4.28 ppm) we observed large nOe effects for the H-4 protons (8.49%) and with the C-7 CH_3 protons (3.28%) and a smaller nOe for the H-6 proton (1.84%) and for the *exo*-CH_3 of the isopropylidene protecting group (1.34 ppm, 2.34%). **^{13}C NMR** δ: 169.7 (s′, C=O), 114.8 (s′, $C(CH_3)_2$), 86.1 (d′ , C-5), 84.7 (d′, C-4), 80.9 (s′, $C(CH_3)_3$), 80.4 (d′, C-3), 80.3 (d′, C-6), 39.7 (t′, C-2), 28.1 (q′, $C(CH_3)_3$), 27.4 (q′, CH_3), 25.5 (q′, CH_3), 19.0 (q′, C-7). **FTIR** (cast): 1732 (s, C=O) cm^{-1}. **MS** [CI, NH_3] m/z: 290 (1.2 %, M + 18), 273 (4.8%, M + 1), 217 (92.6%), 201 (100%). **HRMS** [EI] found: 257.13930; calculated for M - 15 = $C_{13}H_{21}O_5$: 257.13889.

***tert*-Butyl (3a*S*, 4*S*, 6*R*, 6a*R*) tetrahydro-6-hydroxy-2,2-dimethyl-4H-cyclopenta-1,3-dioxole-4-acetate (2a)**: mp: 69 - 70°C. R_f = 0.24 (30% EtOAc in hexanes). $[\alpha]_D$ = +11 (*c* 1.25, EtOH, System B). **^{1}H NMR δ:**

4.50 [1 H, *H-6a*, apparent t (dd, J = 5.8 and 5.7 Hz)], **4.39** [partially resolved dd, $J_{3a,6a}$ = 6.2 Hz, $J_{3a,4}$ = 1.6 Hz, 1H, *H-3a*], **4.07** [m, 1 H, *H-6*], **2.47** [m, 1H, *H-4*.], **2.41** [d, J = 8.0Hz,1H, *OH*, D_2O exchangeable], **2.21** [dd, J = 7.8, 15.2 Hz, 1H, C*H*CO_2tBu], **2.13** [dd, J = 8.1, 15.2 Hz, 1H, C*H*CO_2tBu], **1.93** [m, 1H, *H-5a*], **1.71** [m, 1H, *H-5b*], **1.50** [s, 3 H, CH_3], **1.44** [s, 9 H, $C(CH_3)_3$], **1.33** [s, 3H, CH_3]. **nOe**: Upon irradiation of the *H*-3a signal (4.39 ppm) we observed nOe effects for the H-6a signal (4.50 ppm, 5.89%), and for the CH_2CO_2tBu signals (2.21 and 2.13 ppm, total combined effect = 4.19%); smaller nOe effects are seen for the H-4 signal at 2.47 ppm (2.87%) and the *exo* methyl group of the isopropylidene protecting group (1.33 ppm, 2.06%). **^{13}C NMR** δ: 171.2 (C=O), 111.8 (s′, *C*$(CH_3)_2$), 84.3 (d′ , C-3a), 80.7 (s′, *C*$(CH_3)_3$), 79.1 (d′, C-6a), 71.1 (d′, C-6), 38.2 (d′, C-4), 38.1 (t′, CH_2CO_2tBu), 36.6 (t′, C-5), 28.07 (q′, $C(CH_3)_3$), 26.1 (q′, CH_3), 24.3 (q′, CH_3). **FTIR** (cast): 3493, 1720 cm^{-1}. **MS** (EI) m/z: 257 (3.1%. M-15), 201 (100%, loss of CH_3 and C_4H_8 (McLafferty)]. **HRMS** (EI): found: 257.13860; calculated for M-15 = $C_{13}H_{21}O_5$: 257.13889.

NMR and GC-MS analysis of mixture of 2b and 2a isolated from Bu_3SnH reaction with 8: GC-MS: t_R = 7.80 min, *cis* compd **2b** [m/z: 257 (2.6 %, M-CH_3), 201 (25.5%, M - [CH_3 and C_4H_8 (McLafferty)], 141 (43.9%), 57 (100%)]; t_R = 7.84 min, *trans* compd **2a** [m/z: 257 (0.6%, M - CH_3), 201 (69.4%, M - [CH_3 and C_4H_8 (McLafferty)], 141 (56.6%), 57 (100%, $C(CH_3)_3$)]. **^{1}H NMR** (500 MHz, $CDCl_3$): *region A*, integrates for a total of 2 H [**4.56** (**2b**, H-3a, apparent t, coupled to H-6a and H-4, $J_{3a,6a}$ and $J_{3a,4}$ = 5 Hz.), **4.50** (**2a**, H-6a, apparent t, coupled to H-3a and H-6, J = 5.7, 5.6 Hz), **4.41** (**2b**, H-6a, apparent t, coupled to H-6 and H-3a, J = 5.5, 5.5 Hz), **4.39** (**2a**, H-3a, apparent d, J = 6 Hz. Note that in a well resolved 300 MHz spectrum this signal appeared as a dd, $J_{3a,6a}$ = 5.9 Hz, $J_{3a,4}$ = 1 Hz.)]; *region B*, integrates for 1 H [**4.07** (**2a**, m, H-6), **3.87** (**2b**, m, H-6)]; *region C*, integrates for 5 H in $CDCl_3$ and for 4 H in $CDCl_3/D_2O$ [**2.50** (dd (J = 6.9, 16.0 Hz, C*H*CO_2tBu, cis isomer **2b**) superimposed on the C-4 multiplet of the trans isomer **2a**.), **2.41** (**2a**, d, J = 7.9 Hz, OH), **2.36** (**2b**, d, J = 10.4 Hz), **2.31**(**2b**, dd , J = 6.9, 16.0 Hz, C*H*CO_2tBu), **2.17** (**2a**, m, *CH*$_2CO_2$tBu), **1.95** (m, H-5a of **2a** and **2b** and H-4 of **2b**)]; *region D*, integrates for 16 H [**1.71** (**2a**, H-5b, m), **1.51** (**2a**, CH_3), **1.47** (**2b**, CH_3), **1.45** (**2a** and **2b**, $C(CH_3)_3$), **1.34** (**2a**, CH_3), **1.33** (**2b**, CH_3), **1.40** - **1.20** (**2b**, m, H-5b, partially masked by CH_3 signals). Compound **2b**:**^{13}C NMR** [125 MHz, $CDCl_3$] chemical shifts assigned to the *cis* isomer **2b**: δ [172.1 (s′, C=O), 110.5 (s′, *C*$(CH_3)_2$), 80.32 (s′, *C*$(CH_3)_3$), 80.27 (d′, C-3a), 78.7 (d′, C-6a), 72.1 (d′, C-6), 35.6 (t′, C-5), 34.9 (d′, C-4), 34.4 (t′, *CH*$_2CO_2$tBu), 28.09 (q′, C(*CH*$_3)_3$, 25.7 (q′, CH_3), 24.2 (q′, CH_3).]. Signals for the *trans* isomer **2a** are listed in the preceeding paragraph.

$C_{28}H_{48}I_2O_{10}$ Dimer 15: White solid. Recristallized from MeOH-H_2O. mp = 144.5-146°C. $[\alpha]_D$ = +31 (*c* 1.22, EtOH, System B). R_f = 0.52 (1:3 EtOAc:hexanes). **^{1}H NMR** (500 MHz, $CDCl_3/D_2O$) δ: **4.40** [dd, J = 4.7, 11.1 Hz, 2 H, *H-4, H-4′*] , **3.92** [dd, J = 4.8, 8.3 Hz, 2H, *H-5, H-5′*], **3.65** [m, 2 H, *H*-6, H-6′], **3.60** [dd, J = 1.9, 9.6 Hz, 2H, *H-7a, H-7′a*], **3.38**[dd, J = 7.3, 10.3 Hz 2H, *H-7b, H-7′b*], **2.76** [dd, J =10.4, 14.4 Hz, 2H, *H-2a, H-2′a*], **2.49** [apparent t, 2H, *H-3, H-3′*], **2.38** [partially resolved, dd, J = 1.7, 14.7 Hz, 2H, *H-2b, H-2′b*], **1.49** [s, 18 H, 2 x $C(CH_3)_3$], **1.43** (s, 6H, 2 x CH_3), **1.33** (s, 6H, 2 x CH_3). **^{13}C NMR** (125 MHz) δ: 173.2 (s′, 2 x C=O), 108.0 (s′, 2 x *C*$(CH_3)_2$), 81.3 (s′, 2 x *C*$(CH_3)_3$), 80.0 (d′, C-5, C-5′), 78.6 (d′, C-4, C-4′), 68.5 (d′, C-6, C-6′), 37.8 (t′, C-2, C-2′), 36.7 (d′, C-3, C-3′), 28.19 (q′, 2 x C(*CH*$_3)_3$), 28.17 (q′, 2 x CH_3), 25.5 (q′, 2 x CH_3), 14.1 (t′, C-7, C-7′). **FTIR** (cast) 3489, 3321, 1732, 1698 cm^{-1}. **MS** [FAB, m-nitrobenzylalcohol/KCl matrix, 7 kV Xe] m/z: 837 (67.3 %, M = $C_{28}H_{48}I_2O_{10}$ + K), 799 (24.4%, M = $C_{28}H_{48}I_2O_{10}$ +1).

***tert*-Butyl (*E*) (5*S*, 6*S*) 5,6-dihydroxy-7-iodohept-3-enoate (16):** oil. R_f = 0.13 (30% EtOAc:hexanes). $[\alpha]_D$ = -8.1 (*c* 0.58, System A). **^{1}H NMR** δ: **5.87** [m, 1 H, *H-3*], **5.64** [ddt, J = 15.7, 6.9, 1 Hz, 1H, *H-4*], **4.23** [apparent t, 1 H, *H*-5. This signal is coupled with those at 5.64 and 3.68 ppm.], **3.68** [m, 1H, *H-6*], **3.29** [m, 2H, CH_2I], **3.02** [dd, J = 7, 1 Hz, 2H, *CH*$_2CO_2$tBu], **2.92** [broad s, 1H, C-6 *OH*, D_2O exchangeable], **2.87**[broad s, 1H, C-5 *OH*, D_2O exchangeable], **1.45** [s, 9 H, $OC(CH_3)_3$]. **^{13}C NMR** δ: 171.0 (s′, C=O), 131.5 (d′, C-4), 126.9 (d′ , C-3), 81.2 (s′, *C*$(CH_3)_3$), 74.2 (d′, C-5), 73.7 (d′, C-6), 38.8 (t′, C-2), 28.0 (q′, C(*CH*$_3)_3$), 9.4 (t′, C-7). **FTIR** (cast) 3405, 1727, 1712 cm^{-1}. **MS** (EI) m/z: 171 (15.8%, M-ICH_2CHOH), 115 (67.3%), 58 (100%). **MS** (CI, NH_3) m/z: 343 (5.2%, M+1), 303 (100%). **HRMS** [EI] found: 171.10200; calcd for M=$C_{11}H_{19}IO_4$ - ICH_2CHOH: 171.10211.

$C_{28}H_{48}Br_2O_{10}$ Dimer 22: white solid. Recristallized from MeOH-H_2O. mp = 128-129.5 °C. $[\alpha]_D$ = + 36 (*c* 1.05, EtOH, System B). R_f = 0.60 (1:2 EtOAc:hexanes). **^{1}H NMR** δ: **4.43** [dd, J = 4.4, 11.0 Hz, 2 H, *H-4, H-4′*] , **3.89 - 4.05** [m 4H, *H-5, H-5′,H-6*, H-6′], **3.78** [dd, J = 2.1, 10.4 Hz, 2H, *H-7a,H-7′a*], **3.59**[dd, J = 6.5, 10.4 Hz, 2H, *H-7b, H-7′b*], **3.35** [d, J = 4.9 Hz, 2H, OH x 2, D_2O exchangeable], **2.75** [dd, J = 10.3, 14.3 Hz, 2H,*H-2a, H-2′a*], **2.51** [apparent t, coupled with signals at 4.43, 2.75 and 2.35 ppm, 2H, *H-3, H-3′*], **2.35** [dd, J = 2.2, 14.5 Hz, 2H, *H-2b, H-2′b*], **1.48** [s, 18 H, 2 x $C(CH_3)_3$], **1.44** (s, 6H, 2 x CH_3), **1.33** (s, 6H, 2 x CH_3). **^{13}C NMR** (125 MHz, $CDCl_3/D_2O$) δ: 173.0 (s′, 2 x C=O), 108.1 (s′, 2 x $\mathit{C}(CH_3)_2$), 81.2 (s′, 2 x $\mathit{C}(CH_3)_3$), 79.0 (d′, C-5, C-5′), 78.7 (d′, C-4, C-4′), 68.6 (d′, C-6, C-6′) 38.7 (t′, C-7, C-7′), 37.8 (t′, C-2, C-2′), 36.5 (d′, C-3, C-3′), 28.15 (q′, 2 x $C(\mathit{CH_3})_3$), 28.11 (q′, 2 x CH_3), 25.5 (q′, 2 x CH_3). **FTIR** (cast) 3473, 3312, 1732, 1703 cm^{-1}. **MS** [CI, NH_3] m/z: 724 (2.4%, M = $C_{28}H_{48}{}^{81}Br_2O_{10}$ + 18), 722 (5.9%, M = $C_{28}H_{48}{}^{81}Br^{79}BrO_{10}$ + 18), 720 (2.3%, M = $C_{28}H_{48}{}^{79}Br_2O_{10}$ + 18), 707 (16.3%, M = $C_{28}H_{48}{}^{81}Br_2O_{10}$ + 1), 705 (29.0%, M = $C_{28}H_{48}{}^{81}Br^{79}BrO_{10}$ + 1), 703 (15.0%, M = $C_{28}H_{48}{}^{79}Br_2O_{10}$ + 1).

Crystallographic Measurements and Structure Resolution of **22**:

The crystals were recrystallized in a MeOH-H_2O mixture. All of the crystals were quite small and not of perfect quality. The best one was selected after examination under a polarizing microscope for homogeneity. The unit cell parameters and the reflection data were measured at room temperature, on a Siemens P4 diffractometer using graphite-monochromatized MoKα radiation. Two independent molecules were found in the unit cell. The coordinates of the Br atoms were determined from direct methods and the positions of all the other non-hydrogen atoms were found by the usual Fourier methods. The refinement was done by full-matrix least-squares calculations. An absorption correction was made based on the equations of the crystal faces. The H atoms were fixed at their calculated positions (riding model) with U = 0.08 A^{o2}. The scattering curves from the International Tables[31] were used. The calculations were done on a SHELXTL PLUS.[32] The crystal data are listed in reference 33. The two independent molecules were found to be very similar.

$C_{28}H_{49}BrO_{10}$ Compound 23: white foam. mp = 42 - 43 °C. R_f = 0.3 (1:3 EtOAc:hexanes). **^{1}H NMR** (500 MHz, $CDCl_3/D_2O$) δ: **4.45** (dd, J = 5.1 11.1 Hz, 1H), **4.39** (dd, J = 5.3, 11.1 Hz, 1H), **3.98** (m, 3H), **3.88** (apparent t, 1H), **3.77** (d, J = 11.3 Hz), **3.59** (dd, J = 7.2, 10.7 Hz, 1H),**2.78** (m, 2H), **2.48** (m, 2H), **2.37** (d, J = 14.7 Hz, 1H), **2.29** (d, J = 14.1 Hz, 1H), **1.50 - 1.20** [CH_3 signals, this region integrates for 33 H: **1.479** (s), **1.468** (s), **1.438** (s), **1.33** (s), **1.32** (s), **1.28** (d, J = 5.6 Hz)]. **^{13}C NMR** (125 MHz, $CDCl_3/D_2O$) δ: 173.07 (s′), 173.02 (s′), 108.1 (s′), 107.7 (s′), 81.8 (d′), 81.3 (s′), 81.1 (s′), 79.0 (d′), 78.6 (d′), 78.3 (d′), 68.6 (d′), 65.5 (d′), 38.7 (t′), 38.0 (t′), 37.7 (t′), 36.7 (d′), 36.6 (d′), 28.1 (q′), 27.7 (q′), 25.6 (q′), 25.5 (q′), 20.1 (q′). **FTIR** (cast) 3453, 1728 (shoulder at 1706) cm^{-1}. **MS** [CI, NH_3] m/z: 644 (6.2%, M = $C_{28}H_{49}{}^{81}BrO_{10}$ + 18), 642 (6.3%, M = $C_{28}H_{49}{}^{79}BrO_{10}$ + 18), 627 (58.9%, M = $C_{28}H_{49}{}^{81}BrO_{10}$ + 1), 625 (58.2%, M = $C_{28}H_{49}{}^{79}BrO_{10}$ + 1).

$C_{28}H_{47}BrO_9$ Compound 24: oil. R_f = 0.62 (1:3 EtOAc:hexanes). **^{1}H NMR** (500 MHz, $CDCl_3/D_2O$) δ: **5.90** (m, 1H), **5.29** (m, 2H), **4.46 - 4.35** (m, 3H), **3.98** (m, 2H), **3.76** (apparent d, J = 10.3 Hz), **3.58** (m 1H), **2.77** (dd, J = 14.6, 10.7 Hz, 1H), **2.62** (m, 2H), **2.41** (apparent d, J = 14.7 Hz, 1H), **2.27** (m, 1H), **1.97** (poorly resolved dd, 1H), **1.52** (s, 3H), **1.46** (s, 18H), **1.43** (s, 3H), **1.345** (s, 3H), **1.338** (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3/D_2O$) δ: 173.1, 171.6, 134.3, 118.9, 108.5, 107.9, 80.8, 80.5, 80.3, 78.9, 78.8, 78.4, 68.4, 38.8, 37.5, 37.03, 36.97, 35.6, 28.3, 28.1, 25.7, 25.4. **FTIR** (cast) 3452, 3078(weak), 2982, 2934, 1732 cm^{-1}. **MS** [CI, NH_3] m/z: 626 (5.1%, M = $C_{28}H_{47}{}^{81}BrO_9$ + 18), 624 (5.5%, M = $C_{28}H_{47}{}^{79}BrO_9$ + 18), 609 (38.1%, M = $C_{28}H_{47}{}^{81}BrO_9$ + 1), 607 (36.7%, M = $C_{28}H_{47}{}^{79}BrO_9$ + 1).

$C_{28}H_{48}Br_2O_{10}$ Dimer 25: oil. R_f = 0.23 (1:4 EtOAc:hexanes). $[\alpha]_D$ = +10.5 (*c* 0.84, System A). **^{1}H NMR** δ: **4.14** [apparent t, 2 H, *H-4, H-4′*] , **4.05** [dd, J = 5.8, 9.0 Hz, 2H, *H-5, H-5′*], **3.93** [m, 2 H, simplified upon D_2O exchange, *H-6*, H-6′], **3.78** [dd, J = 2.3, 10.3 Hz, 2H, *H-7a, H-7′a*], **3.60**[dd, J = 6.2, 10.6 Hz 2H, *H-7b, H-7′b*], **3.15** [dd, J = 1.1, 6.3 Hz, 2H, OH x 2, D_2O exchangeable],**2.85** [m, 2H, *H-3, H-3′*], **2.41** [dd, J = 5.6, 16.3 Hz, 2H, *H-2a, H-2′a*], **2.32** [dd, J = 5.7, 16.4 Hz, 2H, *H-2b, H-2′b*],**1.46** [s, 18 H, 2 x $C(CH_3)_3$], **1.37** (s, 6H, 2 x CH_3), **1.29** (s, 6H, 2 x CH_3). **^{13}C NMR** (125 MHz) δ: 173.0 (s′, 2 x C=O), 108.1 (s′, 2 x $\mathit{C}(CH_3)_2$), 80.6 (s′, 2 x $\mathit{C}(CH_3)_3$), 80.1

(d′, C-4, C-4′), 78.0 (d′, C-5, C-5′), 68.4 (d′, C-6, C-6′), 39.4 (t′, C-7, C-7′), 36.8 (d′, C-3, C-3′), 34.0 (t′, C-2, C-2′), 28.1 (q′, 2 x C(CH_3)$_3$), 27.3 (q′, 2 x CH_3), 25.0 (q′, 2 x CH_3). **MS:** [FAB, m-nitrobenzylalcohol/NaCl matrix, 7 kV Xe] m/z: 729 (2.9%, M = $C_{28}H_{48}{}^{81}Br_2O_{10}$ + Na), 727 (5.8%, M = $C_{28}H_{48}{}^{81}Br^{79}BrO_{10}$ + Na), 725 (2.5%, M = $C_{28}H_{48}{}^{79}Br_2O_{10}$ + Na), 707 (3.6%, M = $C_{28}H_{48}{}^{81}Br_2O_{10}$ + 1), 705 (9.5 %, M = $C_{28}H_{48}{}^{81}Br^{79}BrO_{10}$ + 1), 703 (5.0 %, M = $C_{28}H_{48}{}^{79}Br_2O_{10}$ + 1).

***tert*-Butyl (*E*) (5*S*, 6*S*) 7-bromo-5,6-dihydroxyhept-3-enoate (26):** oil. R_f = 0.18 (1:2 EtOAc:hexanes). **^{1}H NMR** δ: **5.91** [partially resolved ddt, J = 1.0, 15.6, 7.0 Hz, 1 H, *H-3*], **5.66** [ddt, J = 15.6, 6.9, 1.3 Hz, 1H, *H-4*], **4.28** [m, 1 H, *H*-5], **3.84** [m, 1H, *H*-6], **3.54** [m, 2H, CH_2Br], **3.04** [d, J = 7.0 Hz, 2H, $\underline{CH_2}CO_2tBu$], **2.58** [d, J = 4.4 Hz, C-6 *OH*], **2.27** [d, 1H, C-5 *OH*], **1.46** [s, 9 H, $C(CH_3)_3$]. **^{13}C NMR** ($CDCl_3$, 125 MHz) δ: 171.7 (C=O), 131.3 (C-4), 127.1 (C-3), 81.1 ($C(CH_3)_3$), 73.57 and 73.54 (C-5, C-6), 38.8 (C-2), 35.5 (CH_2Br), 28.1 ($C(CH_3)_3$). **FTIR** (cast) 3407, 1726, 1711 cm^{-1}. **MS** (CI, NH_3) m/z: 314 (27.1%, M = $C_{11}H_{19}O_4{}^{81}Br$ +18), 312 (27.2%, M = $C_{11}H_{19}O_4{}^{79}Br$ +18), 297 (4.2%, M = $C_{11}H_{19}O_4{}^{81}Br$ +1), 295 (4.2%, M = $C_{11}H_{19}O_4{}^{79}Br$ +1), 258 (98.1%), 256 (100%). **MS** [EI] m/z: 223 (0.68 %, $C_{11}H_{19}{}^{81}BrO_4$ - $OC(CH_3)_3$), 221 (0.76 %, $C_{11}H_{19}{}^{79}BrO_4$ - $OC(CH_3)_3$), 171 (2.3%, M - $BrCH_2CHOH$), 125 (7.5%, $^{81}BrCH_2CHOH$), 123 (9.0%, $^{79}BrCH_2CHOH$), 115 (72.0%), 57 (100%, $C(CH_3)_3$). **HRMS** [EI] found: 171.10230; calcd for M - $BrCH_2CHOH$ = $C_9H_{15}O_3$: 171.10211.

***tert*-Butyl 7-bromo-2,3,7-trideoxy-4,5-*O*-(1-methylethylidene)-D-*ribo*-heptanoate (27):** oil. R_f = 0.34 (1:4 EtOAc:hexanes). **^{1}H NMR δ:** **4.19** [ddd, J = 3.6, 5.7, 10.2 Hz, 1 H, *H-4*], **3.93** [dd, J = 8.9, 5.6 Hz, 1H, *H-5*], **3.75 - 3.86** [m, 2 H, *H*-6 and H-7a], **3.59** [dd, J = 7.3, 10.8 Hz, 1H, *H-7b*], **2.54 - 2.29** [m, 3H, OH and CH_2CO_2tBu], **2.07** [m, 1H, *H-3a*], **1.81** [m, 1H, *H-3b*], **1.45** [s, 9 H, $C(CH_3)_3$], **1.40** (s, CH_3), **1.32** (s, 3H, CH_3). **^{13}C NMR** ($D_2O/CDCl_3$) δ:172.8 (C=O), 108.4 ($C(CH_3)_2$), 80.3 ($C(CH_3)_3$), 78.1 (C-5), 77.04 (C-4), 68.9 (C-6), 39.8 (CH_2Br), 32.4 (C-2), 28.1 (CH_3 and $C(CH_3)_3$), 25.6 (CH_3), 25.1 (C-3). **FTIR** (cast): 3433, 1726, 1707 cm^{-1}. **MS** [CI, NH_3] m/z: 355 (2.8%, M = $C_{14}H_{25}{}^{81}BrO_5$ +1), 353 (2.8%, M = $C_{14}H_{25}{}^{79}BrO_5$ +1), 299 (32.0%), 297 (34%), 173 (100%).

NMR and GC-MS analysis of mixture of 28a (*cis*) and 28b (*trans*) isolated from SmI_2 reaction with 14:

GC-MS: t_R = 8.607 min, *cis* compd **28a** [m/z: 216 (0.1 %, $M^{\cdot+}$), 215 (0.34%, M-1), 201 (0.69%, M-CH_3), 160 [3.5%, M- C_4H_8 (McLafferty)], 142 (29.1%, M- C_4H_8 and H_2O), 125 (29.4%), 97 (34.5%), 83 (100%), 57 (91.4%, $C(CH_3)_3$)]. t_R = 8.661, *trans* compound **28b** [m/z: 215 (0.6%, M-1), 201 (1.3%, M-CH_3), 160 (2.6%, M- C_4H_8 (McLafferty)], 142 (27.6.1%, M- C_4H_8 and H_2O), 125 (31.9%), 97 (33.7%), 83 (76.0%), 57 (100%, $C(CH_3)_3$)]. **^{13}C NMR** [75 MHz, $CDCl_3$] chemical shifts assigned to the *cis* isomer **28a**: δ [172.6 (s′, C=O), 80.5 (s′, $C(CH_3)_3$), 73.5 (d′, C-1, C-2), 41.8 (t′, CH_2CO_2tBu), 37.2 (t′, C-3, C-5) 30.1 (d′, C-4), 28.1 (q′, $(CH_3)_3$). **^{13}C NMR** [75 MHz, $CDCl_3$] chemical shifts assigned to the *trans* isomer **28ba**: δ [172.2 (s′, C=O), 80.4 (s′, $C(CH_3)_3$), 73.5 (d′, C-1, C-2), 42.3 (t′, CH_2CO_2tBu), 37.8 (t′, C-3, C-5), 31.4 (d′, C-4), 28.1 (q′, $(CH_3)_3$). **^{1}H NMR** (300 MHz, $CDCl_3$): *region A* integrates for a total of 2 H [**4.15** (**28b**, *H-1*, *H-2*, m), **4.10** (**28a**, m, *H-1*, *H-2*)] ; *region B* integrates for 7 H [**2.69** (**28b**, m, *H-4*), **2.43** (broad s, 2 x *OH*), **2.37** (d, J = 6.6 Hz, CH_2COtBu **28a**), **2.30-2.07** (m; overlaps with doublet at **2.21** ppm (*J* = 7.5 Hz, CH_2CO_2tBu, **28b**), **1.94** (m, **28b**)]; *region C* integrates for 11 H [**1.60-1.40** (m; overlaps with $(CH_3)_3$ singlets at 1.44 and 1.43 ppm).

Compounds 29a and 29b: A soln of the diols **28a and 28b** (36.5 mg) and p-toluenesulfonic acid (8 mg) in 2,2-dimethoxypropane (3 mL) was stirred at rt for 15 min. The solution was diluted with ether (ca 20 mL), washed with $NaHCO_3$ (5%, *ca* 10 mL) and brine (*ca* 10 mL), dried over Na_2SO_4 and concentrated. The mixture of diastereoisomers was analyzed by GC-MS and NMR.

NMR and GC-MS analysis of mixture of acetal derivatives 29a (*cis*) and 29b (*trans*):

GC-MS: t_R = 8.304 min, *cis* compd **29a** [m/z: 241 (18.9 %, M-CH_3), 183 [16.2%, M- $OC(CH_3)_3$)], 125 (100%). t_R = 8.161, *trans* compound **29b** [m/z: 241 (3.3 %, M-CH_3), 185 (100%, M- CH_3 and C_4H_8 (MacLafferty)], 125 (95.2%). **^{13}C NMR** [75 MHz, $CDCl_3$] chemical shifts assigned to the *cis* isomer **29a**: δ [172.4 (s′, C=O), 110.7 (s′, C-2), 81.1(d′, C-3a, C-6a), 80.1 (s′, $C(CH_3)_3$), 41.0 (t′, CH_2CO_2tBu), 37.9 (t′, C-4, C-6), 35.4 (d′, C-5), 28.0 (q′, $(CH_3)_3$), 26.8 (q′, CH_3), 24.0 (q′, CH_3). **^{13}C NMR** [75 MHz, $CDCl_3$] chemical shifts assigned to the *trans* isomer **29ba**: [171.9 (s′, C=O), 108.8 (s′, C-2), 80.3 (d′, C-3a, C-6a), 80.0 (s′, $C(CH_3)_3$), 39.9 (t′, CH_2CO_2tBu), 39.4 (t′, C-4, C-6) 32.9 (d′, C-5), 28.0 (q′, $(CH_3)_3$), 26.0 (q′, CH_3), 23.7 (q′, CH_3). **^{1}H NMR** (500 MHz, $CDCl_3$): *region A* integrates for a total of 2 H [**4.62** (m, *H-3a/H-6a*, **29a** and **29b**)], *region B* [**2.53** (m, *H-5*, **29b**), **2.45** (d, J = 7.3 Hz, CH_2COtBu, **29a**), **2.38** (m, *H-5*, **29a**), **2.22** (d, *J* = 7.5 Hz, CH_2CO_2tBu, **29b**), **2.00** [m, H_x (C-4/C-6), **29a** and H_y (C-4/C-6) of **29b**], **1.65** (m, H_y (C-4/C-6) **29a**)]; *region C* integrates for 15H [CH_3 singlets at 1.50, 1.443, 1.439, 1.29, 1.28)]; *region D*, **1.18** (m, H_x (C-4/C-6), **29b**).

Ethyl (*E*) (5*S*, 6*S*) 5,6-dihydroxy-7-iodohept-3-enoate (31): white solid. mp = 64 - 65 °C. R_f = 0.3 (TLC, silica, 1:1 EtOAc-hexanes). $[\alpha]_D = -13$ (*c* 2.12, EtOH, System B) **^{1}H NMR δ**: **5.98 - 5.86** (ddt, $J_{3,5}$ = 1.0 Hz, $J_{2,3}$ = 7.0 Hz and $J_{3,4}$ = 15.5 Hz, 1H, *H*-3.), **5.74 - 5.64** (ddt, $J_{2,4}$= 1.2 Hz, $J_{4,5}$ = 6.9 Hz and $J_{3,4}$ = 15.6 Hz, 1H, *H*-4), **4.25** (broad m, 1H, *H*-5, simplifies upon D_2O exchange.), **4.15** (q, J = 7.1 Hz, 2H OCH_2CH_3), **3.68** (broad m, 1H, *H*-6, simplifies upon D_2O exchange.), **3.35 - 3.26** (m, 2H, ICH_2), **3.12** [apparent d, J = 7 Hz, 2H, CH_2CO_2Et. In some well spectra resolved this signal appears as a dd ($J_{2,3}$ = 7.0, $J_{2,4}$ = 0.7 Hz.)], **2.81** (broad poorly resolved d, 1H, OH, D_2O exchangeable.), **2.71** (broad signal, 1H, OH, D_2O exchangeable), **1.27** (t, J = 7.1 Hz, 3H, OCH_2CH_3). **^{13}C NMR δ**: 171.4 (s'), 131.6 (d', $CH=CHCH_2CO_2Et$), 126.6 (d', $CH=CHCH_2CO_2Et$), 74.1 (d', *C-5*), 73.7 (d', *C-6*), 60.9 (t', $CO_2CH_2CH_3$), 37.6 (t', $CH=CHCH_2CO_2Et$), 14.2 (q', $CO_2CH_2CH_3$), 9.7 (t', CH_2I). **FTIR** (cast) 3242, 1728, 1672 cm^{-1}. **MS** [CI, NH_3] m/z: 332 (12.9%, M + 18), 315 (6.7%, M + 1), 297 (100 %, 315 - H_2O). **HRMS** [CI, NH_3] m/z: 332.03730 [calcd for M + 18 (i.e. $C_9H_{15}IO_4 + NH_4$): 332.03606.

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