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Influence of Various Promoters on the Diastereoselectivity of Samarium(II) Iodide Mediated Reductive Carbocyclizations of ω-Iodo-α,β-unsaturated Esters Prepared from 2-Deoxy-D-ribose

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Abstract—ω-Iodo-α,β-unsaturated esters were reduced with SmI_2 or Bu_3SnH under different conditions to give carbocyclic compounds in good yield. The stereoselectivity of the SmI_2 cyclizations varies with the choice of promoter, the reaction temperature, the identity of the hydroxyl protecting groups and the geometry of the double bond.

Introduction

Samarium(II) iodide is a versatile reducing reagent that has been the subject of a large number of scientific papers over the past 20 years.[1] The reduction of organic halides by SmI_2 in THF was first described by Kagan's group[2] and several years later Inanaga and coworkers reported that these reactions are faster when hexamethylphosphoramide (HMPA) is added to the reaction mixtures.[3a] Electrochemical studies on SmI_2/THF/HMPA solutions[3b] and X-ray structures of $SmI_2(hmpa)_4$[3c] and $[Sm(hmpa)_6]I_2$[3d] have since been published. Kinetic studies comparing SmI_2 in THF with SmI_2 in THF/HMPA,[3e] and studies on the mechanism of electron transfer (*inner-* versus *outer-sphere*) between Sm(II) and organic substrates,[3f,g] have been reported. An article describing the structure and energetics of the SmI_2-HMPA complex in THF has also appeared in the literature.[3h] Together these papers have given us an appreciation of the role HMPA plays in changing the redox properties of divalent samarium. While the addition of HMPA to SmI_2 reaction mixtures is now fairly common, significant efforts have been directed towards finding safer promoters of SmI_2 reductions. Alternate promoters include *N*,*N*′-dimethylpropyleneurea (DMPU),[4] transition metal salts such as NiI_2[5,6] and visible light.[7,8]

The SmI_2 reduction of organic halides has been used to initiate carbon–carbon bond formation by radical or carbanionic processes. These reductions involve the formation of an intermediate radical species that either reacts in a typical radical fashion or else is reduced by a second equivalent of SmI_2 to give the corresponding organosamarium species.[9] SmI_2 reductions are often run in the presence of a proton source so as to allow for the in situ protonation of reactive organosamarium species: methanol or *tert*-butyl alcohol are common choices.

The chemoselective reduction of the carbon–halogen bond of *multifunctional* organic halides by divalent samarium reagents can be challenging.[1] We recently reported that SmI_2 reductions of *ribonolactone* derived ω-halo-γ-oxygenated-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 cyclopentane products is favored when HMPA is used as a cosolvent, the halogen is an iodine atom and when *tert*-butyl esters are used.[10] A number of examples of Bu_3SnH mediated radical cyclizations of carbohydrate derived ω-halo-α,β-unsaturated esters have appeared in the literature.[11] The high levels of stereoselectivity achieved for *Z* substrates, having an oxygen substituent at the γ-position, have been rationalized in terms of allylic strain effects.[11,12] The level of stereoselectivity obtained for the Bu_3SnH reduction of the corresponding *E* substrates is often much lower however.

In a recent letter[13] we described the reactions of some 2-deoxyribose derived unsaturated *tert*-butyl esters with Bu_3SnH and SmI_2/HMPA. These previously reported results are summarized in Table 1. These substrates lack an oxygen substituent at the γ-position and so allylic strain effects are not expected to play a prominent role in determining the stereochemical outcome of the reductive carbocyclizations. We observed high levels of diastereoselectivity, in favor of *cis* cyclization products, for some of the SmI_2 reactions of the *E* substrates **1**, **7** and **9**.

Keywords: alkenyl halides; carbohydrates; cyclization; samarium and compounds.

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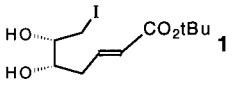
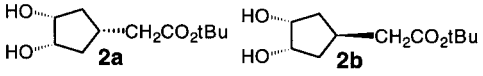
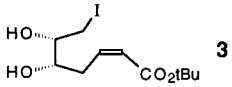
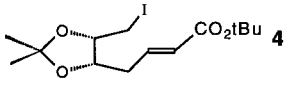
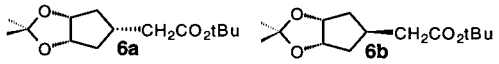
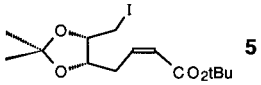
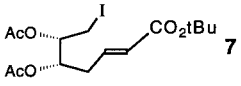
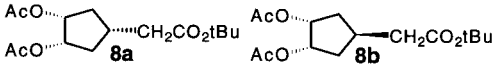
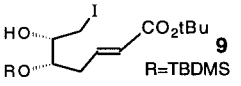
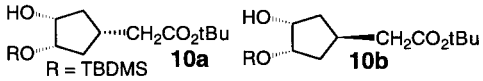
Table 1. Comparison of the stereoselectivity of Bu_3SnH and SmI_2/HMPA mediated reactions

Entry	Substrate and Conditions	Products: % yield (*cis*/*trans*)[d,e]
	 **1**	 **2a** **2b**
a	SmI_2 (4 eq)[a], -78 °C 4.5 h.	91 (7.2/1.0)[f]
b	SmI_2 (4 eq)[b], -78 °C 4.3 h.	83 (20.7/1.0)[g]
c	Bu_3SnH (1.4 eq), AIBN, Benzene, 80 °C 3 h.	79 (2.3/1.0)[f]
	 **3**	**2a** (*cis*) and **2b** (*trans*)
d	SmI_2 (4 eq)[a], -78 °C 4.2 h.	49 (1.0/2.0)[g]
e	SmI_2 (4 eq)[b], -78 °C 3 h, 0 °C 0.4h.	71 (1.0/2.1)[f]
	 **4**	 **6a** **6b**
f	SmI_2 (4 eq)[a], -78°C 3.5 h, 0 °C 0.8 h.	89 (1.0/1.2)[g]
g	SmI_2 (4 eq)[b], -78 °C 3.5 h, 0 °C 0.7h.	83 (1.0/1.3)[f]
h	Bu_3SnH (1.4 eq), AIBN, Benzene, 80 °C 3 h.	71 (1.0/1.6)[f]
	 **5**	**6a** (*cis*) and **6b** (*trans*)
i	SmI_2 (4 eq)[a], -78 °C 4 h, 0 °C 0.5 h.	51 (1.0/1.9)[f]
j	Bu_3SnH (1.4 eq), AIBN, Benzene, 80 °C 3 h.	68 (1.0/3.0)[f]
	 **7**	 **8a** **8b**
k	SmI_2 (5 eq)[a], -78 °C 1 h.	92 (16.1/1.0)[g]
l	SmI_2 (4 eq)[b], -78 °C 1 h.	85 (14.9/1.0)[g]
m	Bu_3SnH (1.5 eq), AIBN, Benzene, 80 °C 3.5 h.	88 (1.7/1.0)[g]
	 **9** R=TBDMS	 R = TBDMS **10a** **10b**
n	SmI_2 (4 eq)[a,c], -78 °C 4.5 h.	75 (3.4/1.0)[f]
o	SmI_2 (4 eq)[b], -78 °C 3h, 0 °C 0.5 h.	92 (13.1/1.0)[f]

[a] SmI_2 in THF/MeOH/HMPA under the *precomplexation conditions*.
[b] SmI_2 in THF/MeOH/HMPA *without precomplexation*.
[c] For this reaction only we used 2% v/v of HMPA.
[d] Isolated yield of purified compounds.
[e] Isomers were not separable by radial chromatography.
[f] GC–MS ratio.
[g] ^1H NMR ratio.

There has been an effort by researchers to identify environmentally friendly compounds or reaction conditions that enhance the reactivity of SmI_2 towards organic substrates. *We were interested in examining the effectiveness and the stereochemical consequences of replacing HMPA with either visible light, DMPU or NiI_2 in our SmI_2 reactions.* There is literature precedence for using each of these promoters. Some recent papers from the groups of Ogawa,[7a] Scaiano[7b] and Molander[8] report that irradiation of SmI_2 reaction mixtures of organic halides with visible light results in a significant enhancement of reactivity. We, and others, have used DMPU as a promoter of SmI_2 mediated reductive carbocyclizations of unsaturated alkyl halides.[4] Molander and Harris have published an account describing the use of SmI_2 in THF in the presence of excess samarium, a proton source and a catalytic amount of NiI_2, to promote the conjugate addition reaction of alkyl halides onto α,β-unsaturated esters.[6]

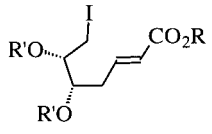
We ran some new reactions with the *E* substrates **1**, **4** and **7** and expanded our study to include the new ethyl ester substrates **11** and **13**. Our results with the four different promoters (HMPA, visible light, DMPU and NiI_2) are discussed in the following section. Reduction of the carbon–iodine bond is clearly preferred over reduction of the unsaturated ester and variations in the reaction conditions, or in the promoter used, did not result in a loss of chemoselectivity.[10a] New comparative studies were done

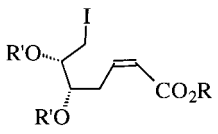
with Bu_3SnH at −78°C for several of our substrates in order to better evaluate the influence of the reducing reagent and the effect of temperature on the stereoselectivity of the radical cyclization reactions. We have also studied the consequences of reducing the concentration of HMPA in our reaction mixtures and of using *tert*-butyl alcohol rather than methanol as the proton source. The full details of these new studies, together with the details of the synthesis and the spectral characterization of all new compounds, are included in this article.

Results and Discussion

Preparation of starting materials from carbohydrate precursors

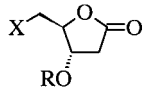
Substrates **1**, **3** and **11**[15] were prepared from 2-deoxy-D-ribose in a two steps using a Wittig reaction[16] and iodination sequence;[17] protection of the hydroxyl groups under standard conditions, then gave substrates **4**, **5**, **7** and **13**.

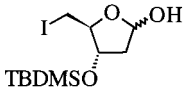




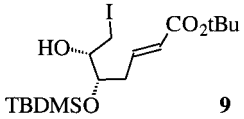
1 R = *t*-Bu, R′ = H, **3** R = *t*-Bu, R′ = H
4 R = *t*-Bu, R′= CMe_2, **5** R = *t*-Bu, R′ = CMe_2
7 R = *t*-Bu, R′= Ac
11 R = Et, R′= H
13 R = Et, R′ = Ac

The strategy used to prepare our ω-iodo-α,β-unsaturated ester **9** was based on a literature report from Thomasco and Wilcox.[11] The key steps involved: transformation of the 1° hydroxyl group of **15** to the corresponding iodide, protection of the 2° hydroxyl group of **16** as a silyl ether, reduction of lactone **17** with DIBAL-H and finally reaction of **18** with a stabilized Wittig reagent to give **9** as the major product.





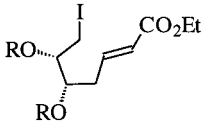
15: R = H, X = OH **18**
16: R = H, X = I
17: R = TBDMS, X = I



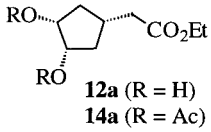
9

Bu_3SnH versus SmI_2-HMPA

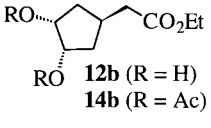
We previously reported that, for the *E tert*-butyl esters **1** and **7**, the diastereoselectivity of the SmI_2-HMPA cyclization reactions run in THF/MeOH at −78°C is higher than that of the corresponding Bu_3SnH/AIBN reactions run at 80°C in benzene (see Table 1). We have since observed the same tendency with the bis acetylated ethyl ester **13**: reaction with SmI_2 in THF/MeOH/HMPA at −78°C under our *non precomplexation* conditions gave us 89% yield of **14a**:**14b** in a 13.3:1.0 ratio in favor of the *cis* product.[†] The yield and the diastereoselectivity of the Bu_3SnH reaction with **13** in benzene were lower: we isolated impure **14a**:**14b** (ratio=1.6:1.0) in 50% yield after chromatography. The reduction of **11** with SmI_2-HMPA also gave us a higher level of *cis* stereoselectivity (**12a**:**12b**=17.0:1.0 crude) than was observed for the corresponding Bu_3SnH reaction (**12a**:**12b**=1.9:1.0, yield=59%) but the mass balance was modest for both reactions. The crude yield from the SmI_2 reaction was 62% and after chromatography we recovered only the *cis* isomer **12a** in 35% yield. Our method was not very stereoselective for the less accessible *Z* substrates **3** and **5**; low levels of selectivity were obtained with both Bu_3SnH and SmI_2-HMPA. For the *E* substrate **4**, there was no stereochemical advantage in using SmI_2-HMPA to mediate these reactions.



11 (R = H)
13 (R = Ac)



12a (R = H)
14a (R = Ac)



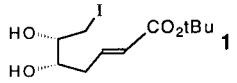
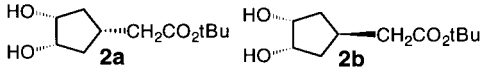
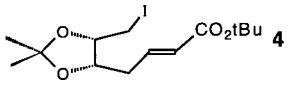
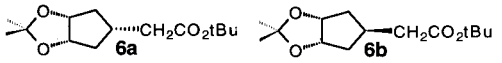
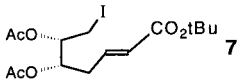
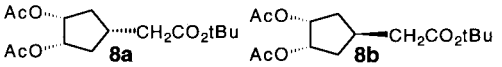
12b (R = H)
14b (R = Ac)

We wondered if the diastereoselectivity of the Bu_3SnH reactions would be improved by lowering the reaction temperature and decided to run some Bu_3SnH reactions with Et_3B in CH_2Cl_2 at −78°C[18] (see Table 2). The diastereomeric ratios for the reactions with **4** and **7**, run in benzene at 80°C, were not notably different from those run in CH_2Cl_2 at −78°C. We also ran several experiments with **1** under the Bu_3SnH/Et_3B conditions however analysis of the crude product by GC–MS and ^1H NMR showed a mixture of compounds that did not include the expected products **2a** and **2b** and we decided not to pursue this any further. As shown in Table 2, the levels of stereoselectivity for the Bu_3SnH reactions were low at both temperatures. The selectivity enhancement seen with SmI_2-HMPA at −78°C is not due simply to the reaction temperature. We have found that the reaction temperature *can* affect the stereoselectivity of some of the SmI_2 mediated reactions that we studied though (vide infra).

The Bu_3SnH mediated reactions involve a radical cyclization via a boat or a chair transition state. Each of the four conformations depicted in Fig. 1 have an oxygen substituent in an axial and an equatorial position. The unsaturated iodoester substrates discussed in this paper lack a substituent at the γ-position and so allylic strain effects are not expected to be a dominant factor in these reactions; the diastereomeric ratios of the *cis–trans* cyclization

[†] The term *non precomplexation* is used to describe reactions in which a THF solution of SmI_2 is added dropwise to a solution of the iodoester in THF/MeOH/HMPA. The term *precomplexation* is used to describe those reactions in which a solution of HMPA and SmI_2 in THF is prepared and stirred at rt for 10 min prior to being added dropwise to a solution of the iodoester in THF/MeOH. See Experimental for more details.

Table 2. Influence of temperature on the stereoselectivity of Bu_3SnH reductive carbocyclizations

Entry	Substrate and Conditions	Products: % yield (*cis/trans*)[a,b]
	 **1**	 **2a** **2b**
a	Bu_3SnH (2 eq), Et_3B (0.6 eq), CH_2Cl_2, -78 °C 2 h.	--[c]
b	Bu_3SnH (1.4 eq), AIBN, Benzene, 80 °C 3 h.	79 (2.3/1.0)[d]
	 **4**	 **6a** **6b**
c	Bu_3SnH (2 eq), Et_3B (0.6 eq), CH_2Cl_2, -78 °C 2 h.	88 (1.3/1.0)[d]
d	Bu_3SnH (1.4 eq), AIBN, Benzene, 80 °C 3 h.	71 (1.0/1.6)[d]
	 **7**	 **8a** **8b**
e	Bu_3SnH (2 eq), Et_3B (0.6 eq), CH_2Cl_2, -78 °C 2 h.	84 (1.9/1.0)[e]
f	Bu_3SnH (1.5 eq), AIBN, Benzene, 80 °C 3.5 h.	88 (1.7/1.0)[e]

[a] Isolated yield of purified compounds.
[b] Isomers were not separable by radial chromatography.
[c] GC–MS and ^1H NMR analysis of the crude product indicated a complex mixture of compounds that does not include compounds **2a/2b** or **1**.
[d] GC–MS ratio.
[e] ^1H NMR ratio.

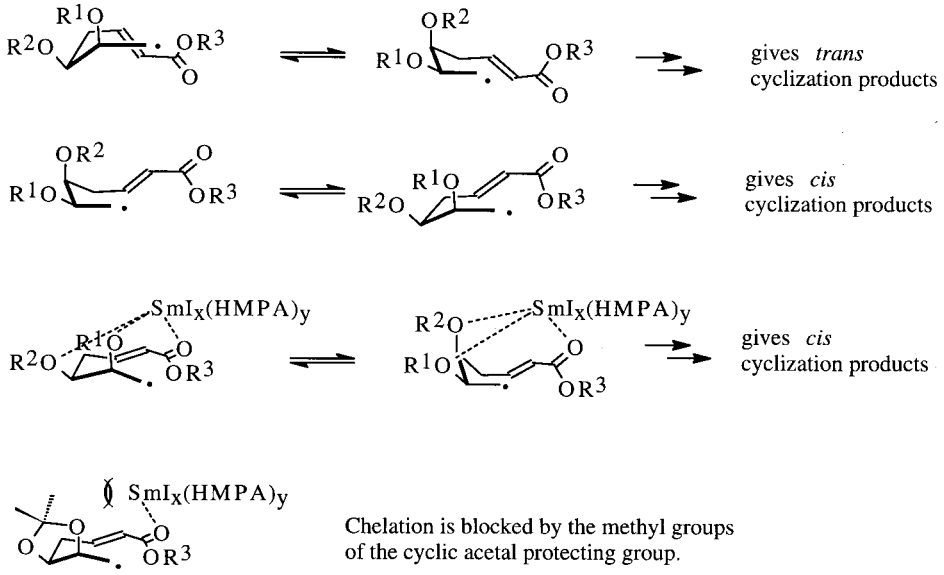


Figure 1. Rationalization of the diastereoselectivity observed with SmI_2-HMPA and Bu_3SnH.

products are low. As previously mentioned, we can in some cases obtain higher diastereomeric ratios using SmI_2-HMPA. Although the SmI_2-HMPA mediated cyclizations may conceivably involve either radical or anionic intermediates, we believe that our reaction conditions and our results are most consistent with a radical cyclization pathway.[‡]

The reactions of **1**, **7**, **9**, **11** and **13** with SmI_2-HMPA gave the more sterically hindered *cis* compounds as the major products. The hydroxylated compounds **1** and **9** were particularly sensitive to the order of addition of SmI_2 and HMPA and the most interesting results were obtained when an excess of SmI_2 in THF was added dropwise to a cooled solution of the substrate in THF/MeOH/HMPA (i.e. *without* precomplexation of SmI_2 and HMPA).

We rationalized our results in terms of a chelation-

[‡] The question of a radical versus an anionic cyclization pathway has been discussed in detail in a previous paper.[10a]

controlled radical cyclization.[13] Complexation of a samarium ion with the carbonyl oxygen and one or more of the hydroxyl groups, or acetyl groups, is one possible explanation for the difference in the levels of diastereoselectivity observed in the Bu_3SnH and the SmI_2-HMPA reactions (see Fig. 1).[14] We tested this hypothesis by carrying out experiments with substrate **4**: the methyl groups of the isopropylidene protecting group block such a chelation (see Fig. 1) and there was no advantage in using SmI_2-HMPA over Bu_3SnH. One of the referees of this paper questioned our rationalization and found it unlikely that samarium ions would prefer relatively weak Lewis bases, like alcohols and esters, in preference to HMPA. We have attempted to address this point in more detail in the following paragraphs.

Researchers have begun to study the details of the mechanism of electron transfer between SmI_2 and some very simple organic substrates and have found evidence to support both inner- and outer-sphere electron transfer processes. Enemaerke et al.[3f] have reported studies supporting the conclusion that electron transfer from $SmI_2(THF)_x$ to benzyl bromide involves an outer-sphere electron transfer whereas the reduction of acetophenone appears to be an inner-sphere electron transfer process. Immediate extrapolation to our multifunctional substrates and our reaction conditions is not obvious.

A recent paper from Shotwell et al.[3h] describes studies on the stoichiometry of the complex formed between SmI_2 and HMPA in THF. The authors concluded that, under conditions commonly used by synthetic chemists, there are up to four HMPA ligands coordinated to Sm(II) and that the reductant in solution is $SmI_2(HMPA)_4$. These HMPA ligands are tightly bound but the equilibrium constant for the fourth HMPA ligand is 2 orders of magnitude lower than for the first three. The researchers found that the interaction of the first HMPA ligand with $SmI_2(THF)_x$ is endothermic (ΔH=0.39 kcal/mol) despite HMPA being a better ligand for Sm(II) than THF.[3h] The authors suggest that the first HMPA is displacing multiple THF ligands and that the driving force, for the coordination of the first HMPA molecule, is a favorable entropy of binding (ΔS=22.3 cal/mol K). The binding of the second and third HMPA molecules is exothermic (ΔH=−2.46 and −0.87 kcal/mol respectively) with a favorable entropy factor (ΔS=13 and 19.8 cal/mol K respectively); binding of the fourth HMPA molecule is favored with respect to the entropy term (ΔH=−9.0 kcal/mol) but disfavored with respect to enthalpy (ΔS=−22 cal/mol K). Their paper also includes an analysis of crystallographic data of some samarium complexes reported by other groups: the data shows that upon coordination of HMPA the Sm–I bond distance increases. The inference is that the iodide ligands are perhaps more easily displaced from the inner coordination sphere of Sm(II) once HMPA ligands have displaced THF ligands.

We found that the order of addition of HMPA and samarium diiodide influences the diastereoselectivity of the cyclization reactions. Under our *precomplexation* conditions we are presumably generating a solution of $SmI_2(HMPA)_4$ and then transferring it dropwise to a cooled solution of our iodoesters in THF/MeOH. Higher *cis–trans* ratios are observed for the hydroxy compounds **1** and **9** when the order of addition is changed i.e. when a solution of SmI_2 in THF is added dropwise to a cooled solution of these iodoesters in THF/MeOH/HMPA. The acetylated substrate **7** gives good results under both sets of conditions. In all of these SmI_2-HMPA reactions (i.e. with or without *precomplexation*) we note an immediate consumption of samarium(II) as determined by the dissipation of colour. We detect no reaction between our substrates and SmI_2 at −78°C in the absence of HMPA and so we know that the coordination of HMPA to SmI_2 is required if reductive cyclization is to occur at low temperature. The number of HMPA ligands bound to SmI_2 affects the reduction potential of the divalent samarium species, the steric environment around the Lewis acidic samarium ion, and presumably the lability of the other ligands. We do not know how many HMPA ligands are bound to the divalent samarium species that interacts with our substrates under our *non precomplexation* reaction conditions. On the basis of the results, from the *precomplexation* versus *non precomplexation* studies (Table 1) and from the studies on HMPA concentration versus diastereoselectivity (Table 6, vide infra), we suggest that the number of HMPA ligands bound to samarium(II) is not necessarily four.

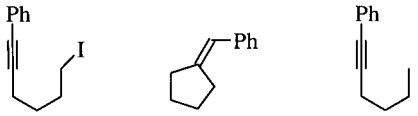
The cartoons shown in Fig. 1 depict coordination between a samarium ion and all three oxygen functional groups and show both a chair and a boat conformation; the oxidation state of the samarium ion (II/III) is not stated nor are the numbers of iodide (possibly 0–3) and HMPA ligands (up to but not more than 4). Although Fig. 1 shows a cartoon in which there is coordination with three oxygen substituents, our results can also be rationalized in terms of coordination with the ester carbonyl and only one of the two other oxygen substituents. We do not know if the proposed radical intermediate is generated through an inner-sphere or an outer-sphere electron transfer process but, in the event of an outer sphere process, coordination with oxygen substituents may occur after electron transfer. Our hypothesis of a chelation-controlled radical cyclization does not require that coordination of oxygen substituents of our substrates occurs in preference to coordination with HMPA but rather in addition to coordination with HMPA.

Visible light versus HMPA as a promoter for SmI_2 mediated conjugate addition reactions

The first SmI_2 promoter that we considered as an alternative to HMPA was visible light. Literature reports describe the efficient reduction of organic chlorides by the photoirradiation of SmI_2 reaction mixtures;[7,8] the absorbance of visible light by SmI_2 in the 560–700 nm range has been attributed to a $4f^6$ to $4f^5 5d^1$ electronic transition. The observed reactivity enhancement has been associated with an efficient electron transfer between photoexcited SmI_2 and the organic halides.[7a]

A preliminary study with substrate **19** in THF at rt gave encouraging results: GC–MS and NMR analysis of the crude residue indicated that **20** and **21** represented 95 and 3% respectively of the total reaction products. These results are comparable to those obtained previously in our laboratory using either SmI_2 in refluxing THF or using

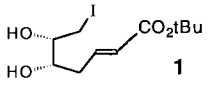
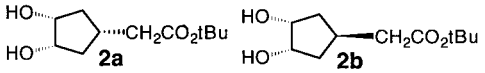
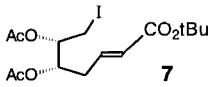
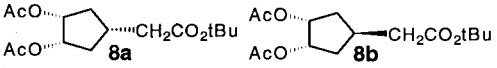
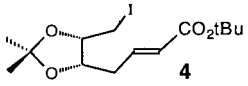
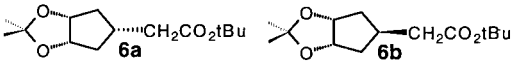
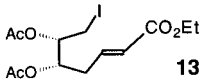
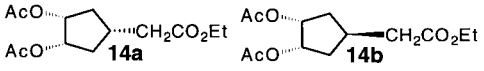
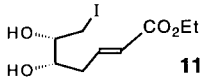
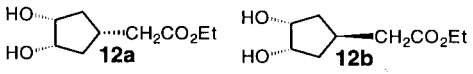
SmI_2-DMPU/THF at rt.[4d,e] Chromatography allowed for a partial separation of **20** (73% isolated yield) from **21**.



19 **20** **21**

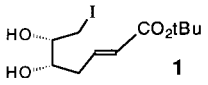
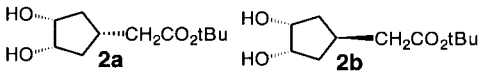
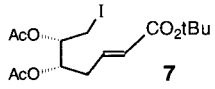
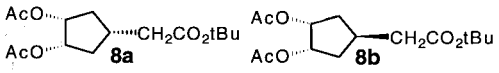
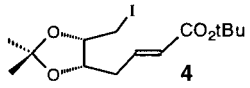
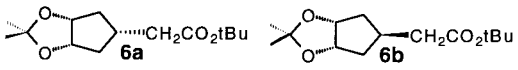
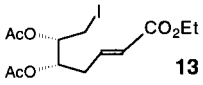
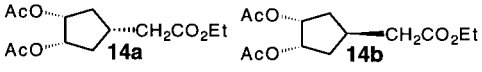
The results of our studies with the multifunctional substrates **1**, **4**, **7**, **11** and **13** are summarized in Table 3. Entries a, d and g were reported in Table 1 and are repeated here for the sake of comparison. Reactions run with HMPA at −78°C were carried out by adding an excess of a commercial solution of SmI_2 in THF dropwise to a cooled solution of the substrate in THF/MeOH/HMPA, i.e. without *precomplexation* of SmI_2 and HMPA. For the SmI_2-hν conditions, irradiation of reaction mixtures with visible light was done using Pyrex reaction flasks and a 150 W xenon lamp with appropriate filters.[19] The reaction times indicated in Tables 1, 3–6 refer either to the time at which all of the SmI_2 had been consumed or to the time at which the reaction was stopped. The actual time required for complete conversion of starting materials into products may be shorter. Due to the air sensitivity of SmI_2 we did not generally follow the progress of these reactions by TLC as we did not want to inadvertantly introduce air into our reaction vessels. Crude and purified products were analyzed by GC–MS and by NMR and, with the exception of compound **11**, we saw no significant change in the diastereomeric ratios of the cyclized products

Table 3. Visible light versus HMPA as a promoter of stereoselective SmI_2 reductive carbocyclizations

Entry	Substrate and Conditions	Products % yield (*cis*/*trans*)[a,b]
	 **1**	 **2a** **2b**
a	SmI_2 (4 eq), MeOH/THF/HMPA, -78 °C 4.3 h.	83 (20.7/1.0)[c]
b	SmI_2 (4 eq), MeOH/THF/visible light, -78 °C 0.6 h.	65 (4.8/1.0)[c,d,f]
c	SmI_2 (4 eq), MeOH/THF/visible light, rt 2 h.	59 (2.0/1.0)[c, d]
	 **7**	 **8a** **8b**
d	SmI_2 (4 eq), MeOH/THF/HMPA, -78 °C 1 h.	85 (14.9/1.0)[c]
e	SmI_2 (6 eq), MeOH/THF/visible light, -78 °C 1.8 h.	74 (4.0/1.0)[c]
f	SmI_2 (4 eq), MeOH/THF/visible light, rt 1.5 h.	58 (2.3/1.0)[c]
	 **4**	 **6a** **6b**
g	SmI_2 (4 eq), MeOH/THF/HMPA, -78°C 3.5 h ; 0°C 0.7 h	83 (1.0/1.3)[e]
h	SmI_2 (4 eq), MeOH/THF/visible light, -78 °C 0.8 h.	82 (1.3/1.0)[e]
i	SmI_2 (4 eq), MeOH/THF/visible light, rt 0.9 h.	ratios of **6a**:**6b** varied from 1/2 to 1/24[e]
	 **13**	 **14a** **14b**
j	SmI_2 (4 eq), MeOH/THF/HMPA, -78 °C 0.8 h.	89 (13.3/1.0)[c,g]
k	SmI_2 (4 eq), MeOH/THF/visible light, -78 °C 0.8 h.	77 (4.5/1.0)[c,g]
l	SmI_2 (4 eq), MeOH/THF/visible light, rt 0.8 h.	78 (1.9/1.0)[c,g]
	 **11**	 **12a** **12b**
m	SmI_2 (4 eq), MeOH/THF/HMPA, -78 °C 0.8 h.	64% crude: (**12a**:**12b** = 17/1)[c,e] after chromat.: 35% (**12a** only)[c,d,e]
n	SmI_2 (5 eq), MeOH/THF/visible light, -78 °C 1.5 h.	83% crude: (**12a**:**12b** = 6.0/1.0)[c,e] after chromat.: 58% (12.5/1)[d,e]
o	SmI_2 (4 eq), MeOH/THF/visible light, rt 0.4 h.	49% (2.4/1.0)[c,e,h]

[a] Isolated yield of purified compounds.
[b] Isomers were not separable by chromatography.
[c] ^{1}H NMR ratio.
[d] Isolated as a slightly impure sample.
[e] GC–MS ratio.
[f] Recovered 8.5% of **1**.
[g] Purified by Kugelrohr distillation.
[h] Recovered 11% of **11** as an impure sample.

Table 4. Results of SmI_2 reactions run in THF/MeOH in the presence of either DMPU or HMPA

Entry	Substrate and Conditions	Products % yield (*cis*/*trans*)[a,b]
		
a	SmI_2 (4 eq), HMPA, -78 °C 4.3 h.	83 (20.7/1.0)[c]
b	SmI_2 (4 eq), DMPU, -78 °C 1.5 h.	72 (5.8/1.0)[c]
		
c	SmI_2 (4 eq), HMPA, -78 °C 1 h.	85 (14.9/1.0)[c]
d	SmI_2 (4 eq), DMPU, -78 °C 1.3 h.	74 (9.8/1.0)[c]
		
e	SmI_2 (4 eq), HMPA, -78 °C 3.5 h ; 0°C 0.7 h.	83 (1.0/1.3)[d]
f	SmI_2 (4 eq), DMPU, -78 °C 1 h.	60 (1.0/1.4)[d]
		
g	SmI_2 (4 eq), HMPA, -78 °C 0.8 h.	89 (13.3/1.0)[c,e]
h	SmI_2 (4 eq), DMPU, -78 °C 0.9 h.	78 (8.7/1.0)[c,e]

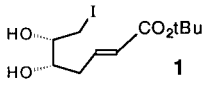
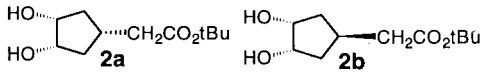
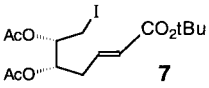
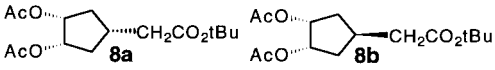
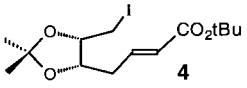
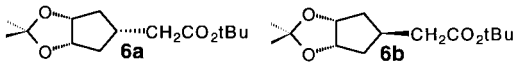
[a] Isolated yield of purified compounds.
[b] Isomers were not separable by chromatography.
[c] ^1H NMR ratio.
[d] GC–MS ratio.
[e] Purified by distillation (Kugelrohr).

following purification by chromatography and/or Kugelrohr distillation.

We were surprised to find that the SmI_2-hν experiments run at room temperature gave stereochemical results that were similar to those for our Bu_3SnH reactions (Table 2) and much lower than we had observed for our SmI_2-HMPA reactions. This suggests that the stereochemical outcome of the rt photoinitiated SmI_2 cyclization reactions is *not* chelation controlled. Why do the SmI_2-HMPA and the SmI_2-visible light reaction conditions give such different levels of diastereoselectivity? As previously mentioned, Shotwell et al. found that coordination of the first HMPA molecule to $SmI_2(THF)_x$ is an endothermic process despite HMPA being a better ligand for Sm(II) than THF; several of the THF molecules are displaced from the inner coordination sphere of Sm(II) upon binding of the first HMPA molecule.[3h] In view of this, it is perhaps not unreasonable to suggest that with photo-excited $SmI_2(THF)_x$ electron transfer and cyclization, without prior chelation of a samarium ion to the functional groups of our substrate, are faster than electron transfer and cyclization via a chelated radical intermediate. A modest increase in the *cis–trans* ratios was noted for compounds **1**, **7**, **13** and **11** at −78°C but we did not attain the same levels of *cis* stereoselectivity observed with SmI_2-HMPA.

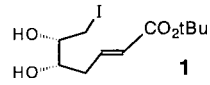
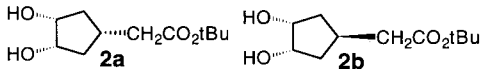
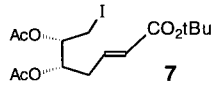
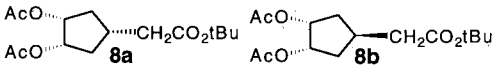
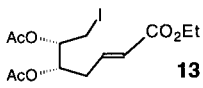
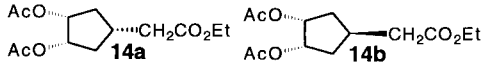
The results for substrate **4**, under the SmI_2-hν conditions at room temperature, are puzzling. The diastereomeric ratios that we observed varied anywhere from 1:2 to 1:24 in favor of the *trans* cyclization product **6b**. Despite our efforts to carefully control the reaction conditions we were unable to find the cause for the variability of our results. This was only observed for reactions carried out under rt conditions and was not an issue for the reactions run at −78°C. We observed the same phenomenon when experiments were run with **4** and SmI_2/HMPA at room temperature with the ratios of **6a**:**6b** varying from 1:2 to 1:24. One possible explanation, for those reactions where a high *trans* diastereoselectivity was noted, is that unfavorable steric interactions between the isopropylidene group and a samarium complexed carbonyl oxygen disfavors formation of the *cis* product. If cyclization occurs without prior coordination of a samarium ion, to either the acetal oxygens or the carbonyl oxygen, then the ratios of *trans–cis* products are expected to be much lower (as in the case of the reactions run at −78°C). We have not been able to identity the factors that would allow us to favor one pathway over the other when the reaction is run at room temperature. We thought that *precomplexation* of SmI_2 and HMPA prior to addition of the divalent samarium solution to our substrate might help us resolve this issue but this was not the case.[10a] The diastereomeric ratios of **6a**:**6b** were similar for experiments run with or without precomplexation of SmI_2 and HMPA.

Table 5. Results of SmI_2-HMPA reactions run in the presence of either MeOH or *t*-BuOH

Entry	Substrate, Proton Source and Conditions	Products % yield (*cis/trans*)[a,b]
	 **1**	 **2a** **2b**
a	SmI_2 (4 eq), MeOH/THF/HMPA, -78 °C 4.3 h.	83 (20.7/1.0)[c]
b	SmI_2 (4 eq), *t*-BuOH/THF/HMPA, -78 °C 1.2 h.	66 (6.4/1.0)[c]
	 **7**	 **8a** **8b**
c	SmI_2 (4 eq), MeOH/THF/HMPA, -78 °C 1 h.	85 (14.9/1.0)[c]
d	SmI_2 (4 eq), *t*-BuOH/THF/HMPA, -78 °C 1.1 h.	89 (16.6/1.0)[c]
	 **4**	 **6a** **6b**
e	SmI_2 (4 eq), MeOH/THF/HMPA, -78°C 3.5 h ; 0°C 0.7 h.	83 (1.0/1.3)[d]
f	SmI_2 (4 eq), *t*-BuOH/THF/HMPA, -78 °C 1.7 h.	63 (1.0/2.1)[d,e]

[a] Isolated yield of purified compounds.
[b] Isomers were not separable by chromatography.
[c] ^1H NMR ratio.
[d] GC–MS ratio.
[e] Ratio of **6a/6b**=1.0:2.1 for the crude products; after chromatography we isolated 63% of **6a/6b** in a ratio of 1.0:2.9.

Table 6. Reactions of **1**, **7** and **13** with SmI_2 in THF/MeOH at various HMPA concentrations

Entry	Substrate, Promoter and Conditions	Products % yield (*cis/trans*)[a,b]
	 **1**	 **2a** **2b**
a	SmI_2 (4 eq), HMPA (5 %), -78°C 4.3 h.	83 (20.7/1.0)[c]
b	SmI_2 (4 eq), HMPA (2 %), -78°C 1 h.	64 (6.3/1.0)[c,d]
c	SmI_2 (4 eq), HMPA (0.5 %), -78°C 3 h.	40 (4.9/1.0)[c,e]
	 **7**	 **8a** **8b**
d	SmI_2 (4 eq), HMPA (5 %), -78°C 1 h.	85 (14.9/1.0)[c]
e	SmI_2 (4 eq), HMPA (2 %), -78°C 1.5 h.	97 (13.3/1.0)[c,f]
f	SmI_2 (4 eq), HMPA (0.5 %), -78°C 3.5 h.	63 (7.1/1.0)[c, g]
	 **13**	 **14a** **14b**
g	SmI_2 (4 eq), HMPA (5%), -78°C 0.8 h.	89 (13.3/1.0)[c,h]
h	SmI_2 (4 eq), HMPA (2 %), -78°C 1 h.	81 (12.7/1.0)[c,h]
i	SmI_2 (4 eq), HMPA (0.5 %), -78°C 2.8 h.	83 (5.6/1.0)[c, h,i]

[a] Isolated yield of purified compounds.
[b] Isomers were not separable by chromatography.
[c] ^1H NMR ratio.
[d] Impure; purity by GC=91%.
[e] 35% of impure **1** was also recovered from the reaction mixture.
[f] Purity by GC=96%.
[g] The reaction is incomplete after 3.5 h and we recovered 24% of unreacted **7**.
[h] Purified by distillation (Kugelrohr).
[i] Kugelrohr distillation gave a mixture of **13** (6.8% recovery) and **14a/14b** (83% yield).

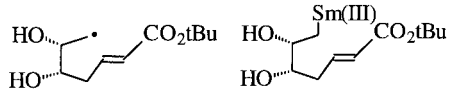
DMPU versus HMPA as a promoter for SmI_2 mediated conjugate addition reactions

DMPU has often been employed in reaction mixtures as a safe alternative to HMPA. It shares many of the characteristics of HMPA and is also a promoter of SmI_2 reactions. Our interest in SmI_2-DMPU dates back to our initial investigations involving cyclization reactions of alkynyl halides.[4d] The results of the SmI_2 reactions run at low temperature using DMPU as the promoter are summarized in Table 4. These reactions were run as follows: SmI_2 in THF was added dropwise to a cooled solution of the substrate in THF/MeOH/DMPU. The final concentration of the substrate, after addition of the SmI_2, was ca. 0.015 M and the quantity of DMPU used corresponded to 5% v/v. The reaction mixtures were clean and the stereoselectivity trends observed with DMPU are qualitatively similar to those noted for the HMPA reactions.

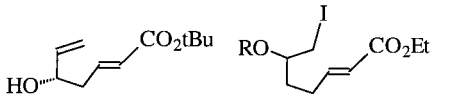
The ratios of *cis–trans* cyclization products for the acetylated substrates **7** and **13** with SmI_2-DMPU are not quite as high as those obtained using SmI_2-HMPA, but they are higher than those obtained in the SmI_2-hν reactions (Table 3). For some applications, however, the drop in stereoselectivity may be an acceptable price to pay for substituting HMPA with a safer SmI_2 promoter. Once again the more sterically hindered *cis* compounds (**8a** and **14a**) were the major products. Compound **1** behaved similarly under the SmI_2-hν conditions (Table 3, entry b), the SmI_2-DMPU conditions and the SmI_2-HMPA precomplexation conditions (Table 1, entry a). Better results were obtained when the reaction was run without precomplexation of SmI_2 and HMPA (vide supra). Compound **4** reacts similarly with SmI_2-DMPU and SmI_2-HMPA at −78°C; neither reaction gives synthetically useful *cis–trans* ratios.

NiI_2 versus HMPA as a promoter for SmI_2 mediated conjugate addition reactions and *tert*-butyl alcohol versus methanol as a proton source

We first ran SmI_2–NiI_2–*t*BuOH reactions with **1** using a modification of the protocol described by Molander and Harris.[6,20] A flask containing a catalytic amount of NiI_2 was charged with a solution of SmI_2 in THF and cooled to −78°C. A solution of **1** and *t*-BuOH in THF was then quickly added in one shot. The reaction mixture was stirred at −78°C for 1 h (after which time we detected only a trace of **2a/2b** by TLC analysis of the reaction mixture) and then allowed to warm to room temperature over 2.5 h. The reaction mixture was complex and purification was difficult. We isolated the cyclized compounds **2a** and **2b** in 32% yield (ratio of **2a**:**2b**=7.8:1.0) and recovered 20% of unreacted **1** as a slightly impure sample. We also isolated an appreciable amount (26%) of the β-elimination product **24**.[20] Carrying out the SmI_2–NiI_2 reduction of **1** in the presence of excess Sm metal also gave a mixture of **2a**, **2b** and **24**.[20] We were surprised by this result as Molander and Harris had studied the reductive cyclization of the structurally similar compounds **25** and **26**[6] but they found no evidence of the corresponding β-elimination products in their reaction mixtures. Compound **24** is presumably formed because reduction of the acylic radical intermediate (**22**), to the corresponding organosamarium species (**23**), competes with radical cyclization under the conditions that we used; β-elimination of a samarium-complexed hydroxyl would then explain formation of compound **24**. We thought that we could avoid the formation of **24** by reversing the order of addition of reagents but this was not the case. A solution of SmI_2 in THF was added dropwise to a suspension of **1**, *t*-BuOH and NiI_2 in THF at 0°C. The mixture was stirred for 1.2 h and worked up: NMR and GC–MS analysis of the crude products showed that **2a**, **2b** and **24** represented 44,14 and 33% respectively of the total reaction products.



22 **23**



24 **25** (R = H), **26** (R = Ac)

We used *tert*-butyl alcohol as the proton source in these initial NiI_2 reactions and wondered if the observed drop in stereoselectivity (i.e. as compared to the HMPA/MeOH reactions) was due to the use of the bulkier alcohol.[21] The alcohol is added to our reaction mixtures as a proton source but it is also a potential ligand for samarium; complexation of either the neutral alcohol or of the corresponding alkoxide may change both the redox properties and the steric bulk of the samarium reagent.[21] We ran some new experiments with **1**, **4** and **7** and SmI_2/HMPA/THF using *t*-BuOH rather than MeOH as the proton source (see Table 5). Inferior results were obtained for **1** when *t*-BuOH was used instead of MeOH but **7** behaved similarly with the two alcohols; we observed a slight increase in the *trans–cis* ratio when *t*-BuOH was used with substrate **4**.

We also ran parallel reactions with SmI_2–NiI_2 using 10 equiv. of either MeOH or *t*-BuOH as the proton source. The reactions run with **1**, **4** and **7** in the presence of either *t*-BuOH or MeOH (method A[20]) were incomplete. NiI_2 offered no stereochemical advantage over the other promoters studied and the *cis–trans* ratios of the cyclized products for the reactions run with either *t*-BuOH or MeOH were similar. For the acetylated substrate **7**, for example, the *cis–trans* ratio of the cyclized products **8a** and **8b** was 3.6:1.0 with MeOH and 3.0:1.0 with *t*-BuOH.

Can we reduce the concentration of HMPA in our reaction mixtures?

The best levels of *cis* diastereoselectivity, for hydroxy or acetoxy ω-iodo *E* conjugate esters, were found when HMPA was used as the promoter for the SmI_2 mediated reductive cyclizations. Substituting HMPA by either visible light, DMPU or NiI_2 gave inferior results. We wondered if we could decrease the concentration of HMPA in our reaction mixtures and still maintain an appreciable level of stereo-

selectivity. We tested the effect of HMPA concentration on the diastereoselectivity of the SmI_2 reductive cyclization of three of our substrates (see Table 6). As previously stated (vide supra), our *non precomplexation* SmI_2-HMPA reaction conditions involve adding an excess of a commercial solution of SmI_2 in THF dropwise to a cooled solution of our substrate in THF/MeOH/HMPA. We typically observe an immediate consumption of the SmI_2 (as evidenced by the rapid color change) and the purple colour begins to persist after ca. 2 equiv. of SmI_2 have been added. The concentration of HMPA after addition of the SmI_2 solution was 5% v/v and this corresponds to a SmI_2:HMPA ratio of 1.0:4.8. For the acetylated substrates **7** and **13** the concentration of HMPA can be lowered to 2% without a dramatic loss in stereoselectivity; compound **1** however was more sensitive to the change in conditions. When the concentration of HMPA is lowered to 0.5% (SmI_2-HMPA=1.0:0.5) the reactions are incomplete and we see a further drop in the diastereoselectivity.

Conclusions

The stereoselectivity of the reductive carbocyclizations of a series of ω-iodo-α,β-unsaturated esters, prepared from 2-deoxy-D-ribose, was investigated. The Bu_3SnH mediated cyclizations, at either −78°C or at 80°C, gave low to modest levels of diastereoselectivity with all of the substrates studied. Some of these substrates however react with SmI_2 to give much higher diastereomeric ratios in favor of the *cis* cyclization products. The SmI_2 methodology is particularly useful for *E* esters having hydroxy or acetoxy substituents. The SmI_2 reactions require the use of a promoter as these ω-iodo-α,β-unsaturated esters do not react with SmI_2/THF alone at −78°C in the dark. The identity of the promoter used, the geometry of the double bond and the nature of the hydroxyl protecting groups all have an impact on the diastereoselectivity of these reactions. The bis acetoxy substrates are the most tolerant to changes in the reaction parameters. Of the different promoters that we studied with our substrates, NiI_2 was the least appropriate; HMPA gave the best levels of *cis* diastereoselectivity and the SmI_2/HMPA reactions appear to be chelation controlled. Either visible light or DMPU can be used as safer alternatives to HMPA for these SmI_2 reductive carbocyclizations but one pays a price in terms of loss of stereoselectivity. The diastereomeric ratios for reactions run with the bis hydroxy and bis acetoxy substrates at room temperature with SmI_2/visible light are as low as those obtained with Bu_3SnH suggesting that the cyclizations are not chelation controlled under these conditions.

Experimental

General experimental

Unless otherwise noted, ^1H (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded in $CDCl_3$ on a Varian Gemini 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; electron ionization detector) GC–MS methods: (A) Oven ramp: initial temp=50°C, final temp=275°C, rate=22°C/min; (B) Oven ramp: initial temp=50°C, final temp=275°C, rates=25°C/min (50–165°C), 3°C/min (165–180°C) and 25°C/min (180–275°C); (C) Oven ramp: initial temp=50°C, final temp=275°C, rates=20°C/min (50–160°C), 0.5°C/min (160–168°C) and 40°C/min (168–275°C); (D) Oven ramp: initial temp=50°C, final temp=275°C, rates=25°C/min (50–135°C), 2°C/min (135–180°C) and 25°C/min (180–275°C). Optical rotations were measured at 589 nm in ethanol (100%) with a JASCO DIP-370 Digital Polarimeter or with a JASCO P-1010 Digital Polarimeter. The reported concentrations (*c*) are in g/100 mL.

***tert*-Butyl (2*E*)-2,3,4,7-tetradeoxy-7-iodo-D-*ribo*-hept-2-enoate (1) and *tert*-butyl (2*Z*)-2,3,4,7-tetradeoxy-7-iodo-D-*ribo*-hept-2-enoate (3).** The preparation and characterization of compound **1** was described previously;[10a] the same method was used to prepare compound **3**. The (*E*) and (*Z*) isomers **1** and **3** are separable by chromatography. *Compound **3**:* oil, R_f=0.59 (TLC, silica, 2:2:3 EtOAc–hexanes–CH_2Cl_2). ^1H NMR δ: 6.31 (ddd, *J*=7.9, 9.1, 11.5 Hz, 1H, *H-3*), 5.95 (d, *J*=11.5 Hz, 1H, *H-2*), 3.71 (m, 1H, *H-5*), 3.64–3.38 [region integrates for 4H; O*H* (low broad signal), *H-7a* at 3.58 ppm (dd, *J*=3.0, 10.2 Hz), *H-7b* at 3.47 ppm (dd, *J*=6.8, 10.2 Hz), *H-6* at 3.38 ppm (m)], 2.94 (partially resolved dddd, *H-4a*, *J*=0.8, 7.5, 9.2, 13.7 Hz), 2.81 (partially resolved dddd, *H-4b*, *J*=1.1, 3.5, 7.9, 13.8 Hz), 2.73 (br, 1H, O*H*), 1.49 (s, 9H, $OC(CH_3)_3$). ^{13}C NMR δ: 167.4 (s′, C=O), 143.3 (d′, C-3), 125.0 (d′, C-2), 81.6 (s′, $C(Me)_3$), 73.45 and 73.37 (d′, C-5, C-6), 32.1 (t′, C-4), 28.1 (q′, $C(CH_3)_3$), 13.3 (t′, C-7). FTIR (film): 3416 (s), 1711 (s), 1685 (s), 1640 (w) cm^{-1}. MS [EI] *m/z*: 286 [2.2%, M−C_4H_8 (McLafferty)], 269 [7.6%, M−$OC(CH_3)_3$], 251 [8.9%, M−($OC(CH_3)_3$ and H_2O)], 115 [87.6%, M−(ICH_2CHOH and C_4H_8)], 97 (73.8%), 86 (39.7%), 57 (100%, C_4H_9). HRMS [EI] found: 285.97020; calcd for M−C_4H_8=$C_7H_{11}IO_4$: 285.97039.

***tert*-Butyl (2*E*)-2,3,4,7-tetradeoxy-7-iodo-5,6-*O*-(1-methylethylidene)-D-*ribo*-hept-2-enoate (4) and *tert*-butyl (2*Z*)-2,3,4,7-tetradeoxy-7-iodo-5,6-*O*-(1-methylethylidene)-D-*ribo*-hept-2-enoate (5).** A mixture of **1** and **3** (0.9413 g, 2.75 mmol) was treated with 2,2-dimethoxypropane (5 mL) and *p*TSA–H_2O (15 mg) at rt for 1.5 h. The soln was diluted with a 5% aq soln of $NaHCO_3$ (20 mL) and CH_2Cl_2 (40 mL). The organic layer was separated, dried and concentrated. Purification of the residue by flash chromatography (5×17 cm, silica gel, 1:1:8 Et_2O–CH_2Cl_2–hexanes) allowed for the separation of the *E* and *Z* isomers **4** and **5** (combined yield of diastereoisomers=78.4%.)

*Compound **4** (E isomer):* solid, mp=42–43.5°C. $[\alpha]_D$=−23.5 (*c* 1.14, 24°C, EtOH 100%). R_f=0.32 (TLC, silica, 1:1:8 Et_2O–CH_2Cl_2–hexanes). ^1H NMR δ: 6.87 (dt, 1H, *H-3*, *J*=15.7, 6.9 Hz), 5.86 (dt, 1H, *H-2*, *J*=15.7, 1.5 Hz), 4.40 (m, 1H, *H-6*), 4.26 (dt, 1H, *H-5*, *J*=5.5,

8.0 Hz), 3.20 (dd, 1H, *H-7a*, *J*=10.1, 7.6 Hz), 3.12 (dd, 1H, *H-7b*, *J*=10.2, 6.5 Hz), 2.46 (m, 2H, *H-4a*, *H-4b*), 1.49 (s, 9H, $C(CH_3)_3$), 1.48 (s, 3H, CH_3), 1.37 (s, 3H, CH_3). ^{13}C NMR δ: 165.4 (s′, C=O), 142.6 (d′, C-3), 125.0 (d′, C-2), 109.0 (s′, $C(CH_3)_2$), 80.4 (s′, $C(Me)_3$), 78.0 (d′, C-5/C-6), 76.3 (d′, C-5/C-6), 32.2 (t′, C-4), 28.4 (q′, CH_3), 28.1 (q′, $OC(CH_3)_3$), 25.7 (q′, CH_3), 2.6 (t′, C-7). FTIR (cast) 1713 (s), 1654 (m) cm^{-1}. GC–MS (method A): t_R=9.09 min, *m/z*: 367 (18.2%, M−CH_3), 311 [7.5%, M−(CH_3 and C_4H_8)], 251 (19.5%), 241 (100%, M−ICH_2), 185 [24.2%, M−(ICH_2 and C_4H_8)], 183 (32.5%). HRMS [EI] found: 367.04060; calcd for M−CH_3=$C_{13}H_{20}IO_4$: 367.04081. MS [CI, NH_3] *m/z*: 400 (9.6%, M+18), 383 (5.6%, M+1), 367 (51.5%, M−CH_3), 344 (25.2%), 327 (81.8%), 251 (48.5%), 241 (100%, M−ICH_2).

Compound ***5*** *(Z isomer):* solid, mp=28–29°C. $[\alpha]_D$=−20.4 (*c* 0.73, 24°C, EtOH 100%). R_f=0.36 (TLC, silica, 1:1:8 Et_2O–CH_2Cl_2–hexanes). ^{1}H NMR δ: 6.24 [apparent dt (ddd with some overlap of lines, *J*=7.4, 6.6, 11.5 Hz), 1H, *H-3*], 5.83 [apparent dt (ddd with some overlap of lines, *J*=1.8, 1.7, 11.5 Hz), 1H, *H-2*], 4.40 (m, 1H, *H-6*), 4.24 (partially resolved ddd, *J*=4.1, 5.5, 9.7 Hz, 1H, *H-5*), 3.21 (d, *J*=6.7 Hz, 2H, *H-7a,7b*), 3.05 (dddd, *J*=1.8, 4.2, 7.4, 15.6 Hz, 1H, *H-4a*), 2.81 (partially resolved dddd, *J*=1.8, 6.6, 9.7, 15.6 Hz, 1H, *H-4b*), 1.49 (s, 9H, $C(CH_3)_3$), 1.48 (s, 3H, CH_3), 1.37 (s, 3H, CH_3). ^{13}C NMR δ: 165.6 (s′, C=O), 143.3 (d′, C-3), 123.6 (d′, C-2), 108.8 (s′, $C(CH_3)_2$), 80.4 (s′, $C(Me)_3$), 78.5 (d′, C-5/C-6), 77.13 (d′, C-5/C-6), 29.0 (t′, C-4), 28.27 (q′, CH_3), 28.21 (q′, $OC(CH_3)_3$), 25.7 (q′, CH_3), 3.1 (t′, C-7). MS [EI] *m/z*: 367 (0.8%, M−CH_3), 326 (6.6%, M−C_4H_8), 311 [49.0%, M−(CH_3 and C_4H_8)], 251 (91.5%), 241 (100%, M−ICH_2), 185 (25.8%, M−(ICH_2 and C_4H_8)], 183 (53.5%). HRMS [EI] found: 326.00140; calcd for M−C_4H_8=$C_{10}H_{15}IO_4$=326.00169. FTIR (cast) 1712 (s), 1642 (m) cm^{-1}.

***tert*-Butyl (2*E*)-2,3,4,7-tetradeoxy-5,6-di-*O*-acetyl-7-iodo-D-*ribo*-hept-2-enoate (7).** To a 0°C soln of **1** (0.4578 g, 1.338 mmol) in CH_2Cl_2 (15 mL) was added pyridine (0.70 mL) and Ac_2O (1.3 mL). The reaction mixture was stirred at 0°C for 45 min, warmed to rt overnight and then diluted with H_2O and CH_2Cl_2. The organic layer was separated, washed with a dil soln of HCl (0.1 M, 15 mL) and with saturated solns of $NaHCO_3$ and NaCl, dried over $MgSO_4$, filtered and concentrated. The residue was purified by radial chromatography (Chromatotron, 4 mm plate, 1:2 Et_2O–hexanes) to give 0.544 g (95.4% yield) of pure **7**: oil, R_f=0.29, silica, 1:2 Et_2O–hexanes. $[\alpha]_D$=3.6 (*c* 1.04, 24°C, EtOH 100%). ^{1}H NMR δ: 6.74 (dt, *J*=7.2, 15.6 Hz, 1H, *H-3*), 5.80 (dt, *J*=1.4, 15.6 Hz, 1H, *H-2*), 5.15 (partially resolved dt, *J*=5.3, 7.0 Hz, 1H, *H-5*), 4.99 (ddd, *J*=4.1, 5.5, 7.3 Hz, 1H, *H-6*), 3.35 (dd, *J*=4.1, 11.0 Hz, 1H, *H-7a*), 3.25 (dd, *J*=7.4, 11.0 Hz, 1H, *H-7b*), 2.52 (m, 2H, *H-4a*, *H-4b*), 2.12 (s, 3H, CH_3), 2.08 (s, 3H, CH_3), 1.48 (s, 9H, $C(CH_3)_3$). ^{13}C NMR δ: 169.73 (s′, C=O, Ac), 169.69 (s′, C=O, Ac), 165.2 (s′, C=O, C-1), 140.8 (d′, C-3), 126.3 (d′, C-2), 80.5 (s′, $OC(Me)_3$), 72.5 (d′, C-5/C-6), 71.9 (d′, C-5/C-6), 32.6 (t′, C-4), 28.1 (q′, $OC(CH_3)_3$), 20.8 (q′, 2×CH_3), 2.1 (t′, C-7). GC–MS (method A) t_R=9.72 min, *m/z*: 370 (2.3%, M−C_4H_8), 353 (3.6%, M−OC_4H_9), 311 [40.5%, M−(C_4H_8 and OAc)], 310 [20.5%, M−(C_4H_8 and CH_3CO_2H)], 299 (17.7%, M−I), 251 (25.4%), 243 (28.7%, loss of I and C_4H_8), 141 (15.8%, ICH_2), 123 (51.6%), 97 (62.9%), 57 (71.7%, C_4H_9), 43 (100%, CH_3CO). MS [CI] *m/z*: 444 (2.7%, M+18), 427 (5.2%, M+1), 311 (100%). HRMS [EI] found: 369.99180; calcd for M−C_4H_8=$C_{11}H_{15}IO_6$=369.99151. FTIR (cast): 1749 (s), 1711 (m), 1655 (w) cm^{-1}.

Ethyl (2*E*)-2,3,4,7-tetradeoxy-7-iodo-D-*ribo*-hept-2-enoate (11). A mixture of 2-deoxy-D-ribose (1.0828 g, 8.073 mmol) and Ph_3PCHCO_2Et (3.2714 g, 9.390 mmol) in THF (15 mL) was stirred at rt under a nitrogen atmosphere for 24 h. Silica gel and THF (30 mL) were then added to the yellow soln; the solvent was evaporated and the dry silica gel, impregnated with the crude product, was loaded onto a column of silica gel (5×20 cm). Flash chromatography allowed for the separation of Ph_3PO from the unsaturated esters (1.5119 g, 91%). Carbon tetraiodide (0.521 g, 1.00 mmol), imidazole (0.0862 g, 1.27 mmol), and a portion of the inseparable mixture of (*E*) and (*Z*) ethyl 2,3,4-trideoxy-D-*ribo*-hept-2-enoates (0.204 g, 1.00 mmol) were transferred to a reaction flask. The flask was purged with argon and charged with CH_2Cl_2 (3 mL). To the resulting mixture was added dropwise a soln of Ph_3P (0.404 g, 1.54 mmol) in CH_2Cl_2 (2 mL). The mixture was stirred at rt for 12 h and filtered. The filtrate was diluted with CH_2Cl_2 and aqueous $Na_2S_2O_3$. The aqueous phase was extracted with CH_2Cl_2 (3×10 mL) and the combined organic layers washed with saturated solns of $NaHCO_3$ and NaCl, dried over $MgSO_4$, filtered and concentrated. Purification by radial chromatography allowed for the separation of the major component **11** (0.169 g, 53.7%) from the minor reaction products. *Compound* ***11:*** white solid, mp=68–69°C. $[\alpha]_D$=−2.05 (*c* 1.07, 26.4°C, EtOH 100%). R_f=0.33 (TLC, silica, 2:2:3 EtOAc–CH_2Cl_2–hexanes). ^{1}H NMR ($CDCl_3$/D_2O) δ: 7.00 (partially resolved ddd, *J*=7.0, 7.9, 15.6 Hz, 1H, *H-3*), 5.97 (apparent dt, *J*=15.7, 1.4 Hz, 1H, *H-2*), 4.21 (q, 2H, OCH_2 CH_3, *J*=7.1 Hz), 3.78 (partially resolved ddd, 1H, *H-5*, *J*=3.4, 5.2, 8.7 Hz), 3.53–3.39 (m, 3H, *H-7a*, *H-7b*, *H-6*), 2.61 (dddd, *H-4a*, *J*=1.6, 3.5, 6.9, 14.6 Hz), 2.43 (m, 1H, *H-4b*), 1.30 (t, 3H, OCH_2CH_3, *J*=7.1 Hz). ^{13}C NMR δ: 166.6 (s′, C=O), 145.1 (d′, C-3), 124.0 (d′, C-2), 73.5 and 72.4 (d′, C-5, C-6), 60.5 (t′, OCH_2CH_3), 35.4 (t′, C-4), 14.1 (q′, OCH_2CH_3), 11.7 (t′, C-7). FTIR (cast): 3285 (s), 3200 (s), 1718 (s), 1653 (m), 1058 (s) cm^{-1}. GC–MS (method A): t_R=8.90 min; *m/z*: 269 (0.7%, M−OC_2H_5), 251 (7.1%, loss of OC_2H_5 and H_2O), 143 (56.6%, M−ICH_2CHOH), 114 [36.0%, M−(ICH_2CHOH and C_2H_5)], 97 [100%, M−(ICH_2CHOH, C_2H_4, and H_2O)], 86 (33.2%). MS [CI, NH_3] *m/z*: 332 (18.2%, M+18), 315 (69.9%, M+1). HRMS [EI] found: 250.95730; calcd for M−(OEt and H_2O)=$C_7H_8IO_2$: 250.95709.

Ethyl (2*E*)-2,3,4,7-tetradeoxy-5,6-di-*O*-acetyl-7-iodo-D-*ribo*-hept-2-enoate (13). To a 0°C soln of **11** (0.3000 g, 0.9555 mmol) in pyridine (2.0 mL) was added Ac_2O (5 mL). The reaction mixture was stirred at rt overnight and then concentrated. The crude residue was diluted with H_2O (20 mL) and ether (20 mL). The aqueous phase was extracted with ether (3×20 mL) and the combined organic layers washed with a saturated soln of NaCl, dried over $MgSO_4$, filtered and concentrated to give pure **13**

(0.3683 g, 96.9% yield): oil, R_f=0.35 (TLC, silica, 1:1 Et_2O–hexanes). $[\alpha]_D$=2.77 (*c* 1.04, 26.7°C, EtOH 100%). ^1H NMR δ: 6.84 (dt, *J*=7.4, 15.7 Hz, 1H, *H-3*), 5.87 (dt, *J*=1.4, 15.7 Hz, 1H, *H-2*), 5.16 (dt, *J*=5.2, 7.1 Hz, 1H, *H-5*), 4.98 (ddd, *J*=4.1, 5.5, 7.1 Hz, 1H, *H-6*), 4.18 (q, 2H, *J*=7.1 Hz, OCH_2CH_3), 3.35 (dd, *J*=4.1, 11.0 Hz, 1H, *H-7a*), 3.24 (dd, *J*=7.4, 11.0 Hz, 1H, *H-7b*), 2.54 (m, 2H, *H-4a*, *H-4b*), 2.12 (s, 3H, CH_3), 2.07 (s, 3H, CH_3), 1.28 (t, 3H, *J*=7.1 Hz, OCH_2CH_3). ^{13}C NMR δ: 169.74 (s′, C=O, Ac), 169.69 (s′, C=O, Ac), 165.8 (s′, C=O, C-1), 142.1 (d′, C-3), 124.6 (d′, C-2), 72.3 (d′, C-5/C-6), 71.8 (d′, C-5/C-6), 60.4 (t′, OCH_2CH_3), 32.7 (t′, C-4), 20.8 (q′, 2×CH_3), 14.2 (q′, OCH_2CH_3), 2.1 (t′, C-7). GC–MS t_R=9.416 min (method A) *m/z*: 339 (2.2%, M−OAc); 311 (13.1%, M−OAc and C_2H_4), 271 (31.8%, M−I), 251 (7.7%, M−(OAc, C_2H_4 and CH_3CO_2H)], 185 (3.0%, M−OAc, C_2H_4 and I), 143 (23.1%), 125 (27.4%, M−OAc, C_2H_4, I and CH_3CO_2H), 97 (24.6%), 43 (100%, CH_3CO). HRMS [EI] found: 339.00889; calcd for M−OAc=$C_{11}H_{16}IO_4$=339.00934. FTIR (film): 1743 (s), 1716 (s), 1654 (w), 1370 (m), 1221 (s), 1042 (m) cm^{-1}.

2,5-Dideoxy-5-iodo-D-ribonic acid-γ-lactone (16). A soln of **15**[23] (0.3948 g, 2.99 mmol) in THF (2 mL) was added to a soln of Ph_3P (1.1733 g, 4.47 mmol), imidazole (0.2471 g, 3.63 mmol) and CI_4 (1.5526 g, 2.99 mmol) in CH_2Cl_2 (10 mL). The reaction mixture was stirred at rt for 12 h, filtered, and the filtrate diluted with an aqueous soln of $Na_2S_2O_3$ and extracted with EtOAc (3×30 mL). The combined organic layers were washed with satd solns of $NaHCO_3$ and NaCl, dried over $MgSO_4$, filtered and concentrated; the crude product was purified by radial chromatography (silica, 1:1 EtOAc–hexanes) to give 0.4858 g (67% yield) of slightly impure **16** as a yellow oil. A portion of the slightly impure material was rechromatographed in order to obtain an analytical sample and the remainder was transformed into **17**. Compound **16** was also prepared using NIS/Ph_3P. R_f=0.30 (TLC, silica, 1:1 EtOAc–hexanes). $[\alpha]_D$=−75.92 (*c* 1.084, 25°C, EtOH 100%). ^1H NMR δ: 4.47 (m, 2H, *H-3* and *H-4*), 3.42 (dd, 1H, *H-5a*, *J*=4.3, 10.8 Hz), 3.29 (dd, 1H, *H-5b*, *J*=7.2, 10.8 Hz), 3.00 (dd, 1H, *H-2a*, *J*=7.2, 18.3 Hz), 2.60 (dd, 1H, *H-2b*, *J*=4.2, 18.3 Hz), 2.31 (s, 1H, *OH*). ^{13}C NMR δ: 174.2 (s′, C-1), 85.4 (d′, *C-3* or *C-4*), 71.8 (d′, *C-3* or *C-4*), 37.8 (t′, *C-2*), 3.8 (t′, *C-5*). FTIR (film) 3426 (s), 1770 (s) cm^{-1}. MS (EI) *m/z*: 242 (83.5%, $M^{\cdot+}$), 214 (89.2%, M−CO), 171 (65.3%), 97 [100%, M−(I et H_2O)]. HRMS [EI] found: 241,94440; calcd for M=$C_5H_7IO_3$: 241.94417.

2,5-Dideoxy-5-iodo-3-*O*-(*tert*-butyldimethylsilyl)-D-ribonic acid-γ-lactone (17). A flask containing compound **16** (0.2026 g, 0.8372 mmol), imidazole (0.0635 g, 0.9327 mmol) and TBDMSCl (0.3291 g, 2.183 mmol) was purged with argon and charged with CH_2Cl_2 (5 mL). The mixture was stirred at rt overnight, filtered and concentrated. The crude residue was purified by radial chromatography (15% EtOAc–hexanes) to give recovered starting material (0.0165 g, 8.1%) and compound **17** as a colorless oil (0.2289 g, 76.7%): R_f=0.41 (15% EtOAc–hexanes). $[\alpha]_D$=−7.7 (*c* 1.62, 24°C, EtOH 100%). ^1H NMR δ: 4.41 (partially resolved ddd, 1H, *H-3*, *J*=3.3, 4.3, 7.0 Hz), 4.29 (partially resolved ddd, 1H, *H-4*, *J*=3.3, 4.3, 6.6 Hz), 3.35 (dd, 1H, *H-5a*, *J*=4.3, 11.0 Hz), 3.29 (dd, 1H, *H-5b*, *J*=6.6, 11.0 Hz), 2.88 (dd, 1H, *H-2a*, *J*=6.9, 17.8 Hz), 2.49 (dd, 1H, *H-2b*, *J*=4.3, 17.8 Hz), 0.90 (s, 9H, $SiC(CH_3)_3$), 0.14 (s, 3H, $SiCH_3$), 0.12 (s, 3H, $SiCH_3$). ^{13}C NMR δ: 173.7 (s′, C-1), 85.4 (d′, *C-4*), 72.2 (d′, *C-3*), 38.3 (t′, *C-2*), 25.6 (q′, $SiC(CH_3)_3$), 17.8 (s′, $SiC(CH_3)_3$), 3.6 (t′, *C-5*), −4.6 (q′, $SiCH_3$×2). FTIR (film) 1790 (s) cm^{-1}. HRMS [EI] found: 298.96000; calcd for M−C_4H_9=$C_7H_{12}IO_3Si$: 298.96023.

2,5-Dideoxy-5-iodo-3-*O*-(*tert*-butyldimethylsilyl)-D-ribose (18). A flask containing compound **17** (0.167 g, 0.469 mmol) was purged with argon, charged with CH_2Cl_2 (2 mL) and cooled to −78°C. A soln of DIBAL-H (0.60 mL, 1.0 M in hexanes, 0.60 mmol) was added dropwise to this soln and the progress of the reaction was followed by TLC. After 2 h the reaction was quenched by the addition of a saturated aqueous soln of NH_4Cl (2 mL). The mixture was diluted with EtOAc and filtered through a short pad of silica gel and celite; the pad was washed with EtOAc several times (total volume=100 mL) and the combined filtrates were dried and concentrated to give 0.156 g of **18** as a mixture of isomers. The crude residue was characterized by ^1H NMR and FTIR spectroscopy and then used directly in the subsequent step. ^1H NMR signals assigned to the major isomer δ: 5.50 (dd, 1H, *H-1*, *J*=4.5, 11.1 Hz), 4.38 (m, 1H, *H-3*), 4.30 (ddd, 1H, *H-4*, *J*=1.4, 4.5, 8.9 Hz), 3.89 (d, 1H, *OH*, *J*=11.1 Hz; D_2O exchangeable), 3.18 (dd, 1H, *H-5a*, *J*=4.5, 10.3 Hz), 2.92 (dd, 1H, *H-5b*, *J*=8.9, 10.3 Hz), 2.25–2.05 (m, 2H, *H-2a*, *H-2b*), 0.91 (s, 9H, $SiC(CH_3)_3$), 0.18 (s, 3H, $SiCH_3$), 0.16 (s, 3H, $SiCH_3$). FTIR (film) 3424 (s) cm^{-1}.

***tert*-Butyl (2*E*)-2,3,4,7-tetradeoxy-7-iodo-4-*O*-(*tert*-butyldimethylsilyl)-D-*ribo*-hept-2-enoate (9).** A soln of Ph_3PCHCO_2tBu (0.1765 g, 0.469 mmol) and **18** (0.1626 g, 0.454 mmol) in dry CH_2Cl_2 (2.5 mL) was stirred at rt overnight and then concentrated. The crude residue was dissolved in a minimum of Et_2O and hexanes were added in order to precipitate the Ph_3PO; the mixture was filtered and concentrated and the residue was purified by radial chromatography (2:3:6 Et_2O–CH_2Cl_2–hexanes) in order to separate the minor *Z* isomer (0.049 g, 23.5% yield) from the major *E* isomer **9** (0.1397 g, 67.1%). *Compound **9** (E isomer):* colorless oil. R_f=0.14 (TLC, silica, $CHCl_3$). $[\alpha]_D$=12.0 (*c* 2.83, EtOH, 24°C). ^1H NMR δ: 6.87 (partially resolved ddd, *J*=6.6, 8.3, 15.7 Hz, 1H, *H-3*), 5.82 (apparent dt, *J*=1.3, 15.7Hz, 1H, *H-2*), 3.82 (m, 1H, *H-5*), 3.49 (m, 1H, *H-6*), 3.38 (dd, 1H, *H-7a*, *J*=4.1, 10.2 Hz), 3.30 (dd, 1H, *H-7b*, *J*=7.1, 10.2 Hz), 2.52 (partially resolved dddd, *J*=1.3, 5.9, 8.3, 14.5 Hz, 1H, *H-4a*), 2.40 (partially resolved dddd, *J*=1.6, 4.6, 6.6, 14.5 Hz, 1H, *H-4b*), 2.22 (d, 1H, *J*=4.9 Hz, *OH*), 1.48 (s, 9H, $OC(CH_3)_3$)), 0.90 (s, 9H, $SiC(CH_3)_3$)), 0.12 (s, 3H, $SiCH_3$), 0.11 (s, 3H, $SiCH_3$). ^{13}C NMR δ: 165.5 (s′, C-1), 143.2 (d′, C-3), 126.0 (d′, C-2), 80.2 (s′, $OC(CH_3)_3$), 73.5 (d′, C-5), 73.4 (d′, C-6), 35.1(t′, C-4), 28.1 (q′, $OC(CH_3)_3$), 25.8 (q′, $SiC(CH_3)_3$), 18.0 (s′, $SiC(CH_3)_3$), 11.5 (t′, C-7), −4.3 (q′, $SiCH_3$), −4.5 (q′, $SiCH_3$). FTIR (film): 3465 (m), 1715 (s), 1696 (s), 1653 (m) cm^{-1}. MS [CI, NH_3] *m/z*: 475 (29.7%, 457+18), 474 (31.6%, M+18), 457 (32.1%, M+1), 325 (100%). HRMS [EI] found: 383.05430; calcd for M−OC_4H_9=$C_{13}H_{24}IO_3Si$: 383.05412.

Typical procedure for reactions with SmI_2 under precomplexation conditions (method A). A soln of the substrate (0.35 mmol) in THF (9.2 mL) and MeOH (0.14 mL) was prepared under an argon atmosphere under anhyd conditions 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 under a positive pressure of argon. 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 Et_2O (3×ca. 20 mL). The combined extracts were washed with H_2O (3×ca. 30 mL), saturated aq $Na_2S_2O_3$ (ca. 30 mL) and brine (ca. 30 mL). The organic layer was dried over $MgSO_4$, filtered, and concd. The crude residue was analyzed by ^1H NMR and/or by GC–MS and then purified by radial chromatography [Harrison Research Chromatotron, silica gel plates].

Typical procedure for reactions with SmI_2 without precomplexation of SmI_2 and HMPA (method B): As per Method A vide supra with the following exception: A soln of the substrate (0.35 mmol) in THF (9.2 mL), MeOH (0.14 mL) and HMPA (1.2 mL) was prepared under an argon atmosphere under anhyd conditions and cooled down to −78°C. SmI_2 [0.1 M THF solution (Aldrich), 14.0 mL, 1.4 mmol] was then transferred dropwise, over ca. 10 min, to the cooled reaction mixture via cannula under a positive pressure of argon.

Typical procedure for reactions with Bu_3SnH/AIBN. A soln of the substrate (0.3285 mmol, 1.0 equiv.), AIBN (5.4 mg, 0.1 equiv.) and Bu_3SnH (0.13 mL, 0.48 mmol, 1.46 equiv., Aldrich) in benzene (21.9 mL) was prepared under an argon atmosphere under anhyd conditions at rt. The final concn of substrate was 0.015 M. The reaction mixture was heated to 80°C for 3.5 h, cooled down to rt and concd. The residue was diluted with ether (20 mL) and the soln was stirred with an aq soln of KF (4.5 g in 15 mL water).[22] The organic layer was separated, dried over $MgSO_4$, filtered and concd. The residue was analyzed by ^1H NMR and/or by GC–MS and then purified by radial chromatography [Chromatotron, 2 mm plate] using a mixture of EtOAc, or Et_2O, and hexanes as the eluant.

Typical procedure for reactions with $Bu_3SnH/Et_3B/CH_2Cl_2$.[18] A soln of the substrate (0.1376 mmol) and Bu_3SnH (0.2752 mmol) in CH_2Cl_2 (1.37 mL) was prepared under an argon atmosphere under anhyd conditions and cooled to −78°C. The final concn of substrate was 0.1 M. Three portions of Et_3B (3×0.0275 mmol) were sequentially added in 5 min intervals and the mixture stirred for 2 h at −78°C and then warmed to rt and diluted with hexanes (5 mL); the soln was stirred with a soln of TBAF (0.35 mL, 1 M soln in THF) for 0.5 h and then filtered through a short pad of silica gel. The silica was washed with ether and the combined filtrates were concd. The residue was analyzed by ^1H NMR and GC–MS and then purified by radial chromatography or Kugelrohr distillation.

Products from SmI_2 or Bu_3SnH reactions. Crude and purified products were analyzed by GC–MS and by NMR and, unless otherwise reported, we saw no significant change in the diastereomeric ratios of the cyclized products following purification by chromatography and/or Kugelrohr distillation. The stereochemistry of the cyclized products was determined from NOE experiments and from the known configuration of carbons 1 and 2 or via chemical derivation. The characterization of compounds **2a/2b** and **6a/6b** were described in a previous report.[10a]

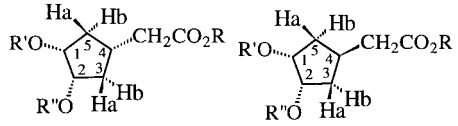


Figure 2. Stereochemistry of cyclized products.

NMR analysis of mixtures of 8a (*cis*) and 8b (*trans*) isolated from reactions with 7. ^{13}C NMR [125 MHz, $CDCl_3$] chemical shifts assigned to the *cis* isomer **8a**: δ 171.6 (s′, C═O), 170.2 (s′, C═O), 80.5 (s′, O*C*$(CH_3)_3$), 73.4 (d′, C-1+C-2), 42.8 (t′, *C*H_2CO_2tBu), 34.79 (t′, C-3+C-5), 29.8 (d′, C-4), 28.1 (q′, OC(*C*$H_3)_3$), 20.9 (q′, 2×*C*H_3); chemical shifts assigned to the *trans* isomer **8b**: δ 171.6 (s′, C═O), 170.3 (s′, C═O), 80.5 (s′, O*C*$(CH_3)_3$), 73.9 (d′, C-1+C-2), 42.0 (t′, *C*H_2CO_2tBu), 34.76 (t′, C-3+C-5), 30.8 (d′, C-4), 28.1 (q′, OC(*C*$H_3)_3$), 20.9 (q′, 2×*C*H_3). ^1H NMR (500 MHz, $CDCl_3$) chemical shifts assigned to the *cis* isomer **8a**: δ 5.13 (m, *H-1+H-2*), 2.38–2.30 (m, *H-4+CH*$_2$), 2.30–2.20 [m, *H-3a+H-5a*(overlaps with CH_2 signal for *trans* isomer)], 2.04 (s, 2×CH_3), 1.52 (m, *H-3b+H-5b*), 1.45 (s, 9H, OC(*C*$H_3)_3$); chemical shifts assigned to the *trans* isomer **8b**: δ 5.23 (m, *H-1+H-2*), 2.71 (m, *H-4*), 2.30–2.20 (m, CH_2 of *trans* isomer; overlaps with signal for *H-3a+H-5a* protons of the *cis* isomer), 2.08–2.00 [m, *H-3b+H-5b* of *trans* overlaps with CH_3 singlet at 2.04 ppm (2×CH_3, *cis* and *trans*)], 1.65 (m, *H-3a+H-5a*), 1.45 (s, 9H, OC(*C*$H_3)_3$). Compounds **8a** and **8b** were not separable by GC–MS using our conditions.

Assignment of relative configuration. A mixture of **2a/2b** (ratio of *cis*–*trans*=2:1) was acetylated with acetic anhydride and pyridine to give a mixture of **8a** and **8b**. The reaction was clean and complete and the crude products were analyzed by ^1H NMR and GC–MS. The signals of the major diastereoisomer were attributed to compound **8a**.

NMR and GC–MS analysis of mixtures of 10a (*cis*) and 10b (*trans*) isolated from reactions with 9. GC–MS (method D): t_R=18.95 min, *cis* compd **10a** *m/z*: 257 (11.2%, M−O*t*Bu), 217 [31.9%, M−(*t*Bu and C_4H_8)], 199 (100%, M−OTBDMS), 157 (65.0%), 125 [42.5%, M−(OTBDMS, C_4H_8 and H_2O)], 75 (62.7%), 57 (53.6%, C_4H_9). t_R=18.70, *trans* compound **10b** *m/z*: 257 (1.5%, M−O*t*Bu), 217 [15.5%, M−(*t*Bu and C_4H_8)], 199 (28.9%, M−OTBDMS), 157 (37.0%), 125 [100%, M−(OTBDMS, C_4H_8 and H_2O)], 75 (88.0%), 57 (67.7%, C_4H_9). ^{13}C NMR

[75 MHz, $CDCl_3$] chemical shifts assigned to the *cis* isomer **10a**: δ 172.3 (s′, C=O), 80.07 (s′, $OC(CH_3)_3$), 74.6 (d′, C-2), 73.2 (d′, C-1), 42.9 (t′, CH_2CO_2tBu), 38.0 (t′, C-3 or C-5), 37.5 (t′, C-3 or C-5), 30.6 (d′, C-4, 28.1 (q′, $OC(CH_3)_3$, 25.8 (q′, $SiC(CH_3)_3$), 18.0 (s′, $SiC(CH_3)_3$), −4.56 (q′, $SiCH_3$), −5.0 (q′, $SiCH_3$); chemical shifts assigned to the *trans* isomer **10b**: δ 172.0 (s′, C=O), 80.14 (s′, $OC(CH_3)_3$), 74.6 (d′, C-2 or C-1), 73.6 (d′, C-2 or C-1), 42.4 (t′, CH_2CO_2tBu), 38.2 (t′, C-3 or C-5), 37.9 (t′, C-3 or C-5), 31.7 (d′, C-4), 28.1 (q′, $OC(CH_3)_3$, 25.8 (q′, $SiC(CH_3)_3$), 18.0 (s′, $SiC(CH_3)_3$), −4.61 (q′, $SiCH_3$), −5.0 (q′, $SiCH_3$). ^{1}H NMR (300 MHz, $CDCl_3$) chemical shifts assigned to the *cis* isomer **10a**: δ 3.98 (ddd, 1H, *H-2*, *J*=4.9, 6.2, 7.4 Hz), 3.87 (m, 1H, *H-1*), 2.55 [s, *OH*; in some spectra the OH signal appeared as a doublet at 2.58 ppm (*J*=4.2 Hz)], 2.30 (d, 2H, *J*=6.8 Hz, CH_2CO_2tBu), 2.17 (m, 1H, *H-4*), 2.12 (m, 2H, *H-3a* and *H-5a*), 1.43 (s, 9H, $OC(CH_3)_3$), 1.39–1.29 (m, 2H, *H-3b* and *H-5b*), 0.90 (s, 9H, $SiC(CH_3)_3$), 0.09 (s, 6H, 2×$SiCH_3$); chemical shifts assigned to the *trans* isomer **10b**: δ 4.15 (apparent dt, 1H, *H-2*, *J*=6.8, 4.7 Hz), 3.98 (m, 1H, *H-1*; the *H-1* signal of the *trans* isomer overlaps with the *H-2* signal of the *cis* isomer), 2.74–2.63 [*OH* signal (d at 2.66 ppm; *J*=4.1 Hz) overlaps with the *H-4* multiplet], 2.2 (the CH_2CO_2tBu doublet of the *trans* isomer overlaps with the *H-4* multiplet of the *cis* isomer), 1.94 (m, 1H, *H-3b* or *H-5b*), 1.87 (m, 1H, *H-3b* or *H-5b*), 1.52–1.32 (m, *H-3a*, *H-5a*; partially overlaps with the O*t*Bu signal at 1.43 ppm of both isomers and the *H-5b*+*H-3b* signals of the *cis* isomer), 1.43 (s, 9H, $OC(CH_3)_3$), 0.90 (s, 9H, $SiC(CH_3)_3$), 0.09 (s, 6H, 2×$SiCH_3$).

NOE experiments. The stereochemistry of the cyclized products (Fig. 2) was determined from NOE experiments on $CDCl_3$ solutions of the mixture of isomers and from the known configuration of carbons 1 and 2. In compound **10a** the CH_2CO_2tBu group and the H-3b, H-5b and OH protons are on the same side of the ring; the H-1, H-2, H-3a, H-5a and H-4 protons are likewise on the same side of the ring. Upon irradiation at the H-1 signal (3.87 ppm) we observed NOE effects for H-2 (4.5%), OH (3.9%), H-5a+H-3a (4.3%); smaller effects were seen for H-3b+H-5b (1.98%) and a long distance effect was seen for H-4 (1.1%). Upon irradiation at the H-3a+H-5a multiplet we observed NOE effects for the H-1 (3.05%), H-2 (3.10%), H-4 (1.4%) and the H-5b+H-3b (23.5%) protons. Upon irradiation of the H-3b+H-5b multiplet we observed NOE effects for the H-3a+H-5a (18.7%), the OH (1.8%) and the CH_2CO_2tBu (3.7%) protons. We concluded that the major isomer was the *cis* diastereoisomer.

NMR and GC–MS analysis of mixtures of 12a (*cis*) and 12b (*trans*) isolated from reactions with 11. GC–MS (method B): t_R=7.12 min, *cis* compd **12a** *m/z*: 170 (3.0%, M−H_2O), 143 (7.9%, M−OCH_2CH_3), 142 [7.9%, M−(C_2H_4 and H_2O)], 125 [33.3%, M−(OCH_2CH_3 and H_2O)], 124 (20.6%), 114 (11.5%), 98 (48.0%), 97 [41.1%, M−($CO_2CH_2CH_3$ and H_2O)], 96 (41.1%), 88 (25.3%, M−$C_5H_8O_2$), 83 [100%, M−(CH_2CO_2Et and H_2O)]. t_R= 7.22 min, *trans* compound **12b** *m/z*: 170 (3.7%, M−H_2O), 143 (10.5%), 142 (11.3%), 125 (46.9%), 124 (34.2%), 114 (18.7%), 98 (75.8%), 97 (59.9%), 96 (64.1%), 88 (39.9%), 83 [100%, M−(CH_2CO_2Et and H_2O)]. ^{13}C NMR [75 MHz, $CDCl_3$] chemical shifts assigned to the *cis* isomer **12a**: δ 173.2 (s′, C=O), 73.4 (d′, C-1, C-2), 60.3 (t′, OCH_2CH_3), 40.68 (t′, CH_2CO_2Et), 37.3 (t′, C-3, C-5) 30.0 (d′, C-4), 14.1 (q′, OCH_2CH_3); chemical shifts assigned to the *trans* isomer **12b**: δ 172.8 (s′, C=O), 73.4 (d′, C-1, C-2), 60.3 (t′, OCH_2CH_3), 40.82 (t′, CH_2CO_2Et), 37.8 (t′, C-3, C-5), 31.2 (d′, C-4), 14.1 (q′, OCH_2CH_3). ^{1}H NMR (500 MHz, $CDCl_3$) chemical shifts assigned to the *cis* isomer **12a**: δ 4.11 (q, 2H, OCH_2 CH_3, *J*=7.4 Hz), 3.99 (m, 2H, *H-1* and *H-2*), 3.00 (s, 2×*OH*),[§] 2.44 (d, *J*=6.9 Hz, CH_2CO_2Et), 2.23 (m, 1H, *H-4*), 2.13 (m, 2H, *H-3a* and H-5a), 1.43 (partially resolved ddd, 2H, *H-3b* and *H-5b*, *J*=13.0, 5.8, 8.5 Hz), 1.24 (t, 3H, OCH_2CH_3, *J*=7.3 Hz); chemical shifts assigned to the *trans* isomer **12b**: δ 4.11 (q, 2H, OCH_2CH_3, *J*=7.4 Hz), 3.99 (m, 2H, *H-1* and *H-2*), 2.93 (s, l, 2×*OH*),[§] 2.71 (m, 1H, *H-4*), 2.29 (d, *J*=7.7 Hz, CH_2CO_2Et), 1.94 (m, 2H, *H-3b* and *H-5b*), 1.52 (m, 2H, *H-3a* and *H-5a*), 1.24 (t, 3H, OCH_2CH_3, *J*=7.3 Hz).

NOE experiments. The stereochemistry of the cyclized products was determined from NOE experiments on $CDCl_3$ solutions of the mixture of isomers and from the known configuration of carbons 1 and 2. In compound **12a** the CH_2CO_2Et group and the H-3b, H-5b protons are on the same side of the ring: upon irradiation at the H-3b/H-5b signal at 1.43 ppm we observed NOE effects for the geminal protons H-3a/H-5a at 2.13 ppm (13.9%) and for the CH_2CO_2Et signal at 2.44 ppm (2.5%). As expected much smaller effects were observed for the H-4 signal at 2.23 ppm (0.6%) and for the H-1/H-2 signals at 3.99 ppm (1.5%). Upon irradiation of the H-3a/H-5a signal at 2.13 ppm we observed NOE effects for the geminal protons H-3b/H-5b (15.1%), for the H-1/H-2 protons at 3.99 ppm (4.2%) and for the H-4 proton at 2.23 ppm (1.1%). Irradiation of the H-4 signal at 2.23 ppm resulted in NOE effects for H-1/H-2 (2.6%), H-3a/H-5a (2.17%), H-3b/H-5b (1.47%) and CH_2CO_2Et (4.3%). We concluded that the major isomer was the *cis* diastereoisomer. In the case of the minor *trans* isomer **12b**, the CH_2CO_2Et group is on the same side of the ring as the H-3a/H-5a and the H-1/H-2 protons. Upon irradiation of the H-3a/H-5a signal at 1.52 ppm we observed NOE effects for the geminal protons H-3b/H-5b at 1.94 ppm (14.9%), the CH_2CO_2Et signal at 2.29 ppm (2.8%) and the OCH_2CH_3 signal at 4.11 ppm (5.0%). As expected the NOE effect for the H-4 signal at 2.71 ppm was small (0.6%). Additional experiments were run with $CDCl_3/D_2O$ solutions of **12a/12b**: Upon irradiation of the H-3b/H-5b signal at 1.94 ppm we observed NOE effects for the geminal protons H-3a/H-5a (15.1%) and the H-4 signal at 2.71 (4.4%) but saw no effect for the H-1/H-2 signal.

NMR and GC–MS analysis of mixtures of 14a (*cis*) and 14b (*trans*) isolated from reactions with 13. GC–MS (method C): t_R=14.20 min, *cis* compd **14a** *m/z*: 212 (1.8%, M−CH_3CO_2H), 185 (28.2%, M−$CH_2CO_2CH_2CH_3$), 170 (62.0%), 169 (35.8%), 152 (23.8%, M−2×CH_3CO_2H), 143 (16.4%), 141 (13.3%), 125 [13.1%, M−(C_2H_5 and 2×OAc)], 124 (11.4%), 97 (25.1%), 83 (37.7%), 82 (20.9%), 81 [100%, M−($CO_2CH_2CH_3$ et 2×OAc)].

[§] Note in some spectra the OH signals for the major and minor isomers were unresolved and appeared as a wide signal at 2.9 ppm.

t_R=14.28, *trans* compound **12b** *m/z*: 227 (2.4%, M−OCH_2CH_3), 185 (8.0%, M−$CH_2CO_2CH_2CH_3$), 170 (71.6%), 169 (32.0%), 152 (20.8%, M−2×CH_3CO_2H), 141 (12.7%), 125 [18.1%, M−(C_2H_5 and 2×OAc)], 124 (11.9%), 97 (30.2%), 96 (12.4%), 83 (41.0%), 82 (22.2%), 81 [100%, M−($CO_2CH_2CH_3$ et 2×OAc)]. ^{13}C NMR [125 MHz, $CDCl_3$] chemical shifts assigned to the *cis* isomer **14a**: δ 172.2 (s′, C=O), 170.2 (s′, C=O), 73.4 (d′, C-1, C-2), 60.4 (t′, O*C*H_2CH_3), 41.4 (t′, *C*H_2CO_2Et), 34.8 (t′, C-3, C-5) 29.6 (d′, C-4), 20.9 (q′, 2×CH_3), 14.2 (q′, OCH_2CH_3); chemical shifts assigned to the *trans* isomer **14b**: δ 172.2 (s′, C=O), 170.2 (s′, C=O), 73.8 (d′, C-1, C-2), 60.4 (t′, O*C*H_2CH_3), 40.6 (t′, *C*H_2CO_2Et), 34.8 (t′, C-3, C-5), 30.7 (d′, C-4), 20.9 (q′, 2×CH_3), 14.2 (q′, OCH_2CH_3). ^{1}H NMR (500 MHz, $CDCl_3$) chemical shifts assigned to the *cis* isomer **14a**: δ 5.13 (m, 2H, *H-1* and *H-2*), 4.13 (q, 2H, O*CH*$_2$CH$_3$, *J*=7.3 Hz), 2.45 (d, 2H, *J*=7.1 Hz, *CH*$_2$CO$_2$Et), 2.38 (m, 1H, *H-4*), 2.27 (m, 2H, *H-3a* and H-5a), 2.04 (s, 6H, 2×CH_3), 1.52 (m, 2H, *H-3b* and *H-5b*), 1.26 (t, 3H, OCH_2CH_3, *J*=7.3 Hz); chemical shifts assigned to the *trans* isomer **14b**: δ 5.23 (m, 2H, *H-1* and *H-2*), 4.13 (q, 2H, O*CH*$_2$CH$_3$, *J*=7.3 Hz), 2.75 (m, 1H, *H-4*), 2.38 (m, 2H, *H-3b* and *H-5b*), 2.35 (d, 2H, *J*=7.5 Hz, *CH*$_2$CO$_2$Et), 2.04 (s, 6H, 2×CH_3), 1.65 (m, 2H, *H-3a* and *H-5a*), 1.26 (t, 3H, OCH_2CH_3, *J*=7.3 Hz).

Assignment of relative configuration. A mixture of **12a/12b** (ratio of *cis*–*trans*=2.4:1.0) was acetylated with acetic anhydride and pyridine to give a mixture of **14a** and **14b**. The reaction was clean and complete and the crude products were analyzed by ^{1}H NMR and GC–MS. The signals of the major diastereoisomer were attributed to compound **14a**.

***tert*-Butyl (2*E*, 5*S*)-5-hydroxyhepta-2,6-dienoate (24).** This was isolated as a slightly impure sample (purity by GC=94%, t_R=6.17 min, method A): ^{1}H NMR δ 6.85 (dt, 1H, *J*=7.4, 15.7 Hz, H-3), 5.89 (ddd, 1H, *J*=17.0, 10.4, 6.0 Hz, H-6), 5.85 (dt, 1H, *J*=15.5, 1.5 Hz, H-2), 5.29 (apparent dt, 1H, H-7a; $J_{7a,7b}$ and $J_{7a,5}$=1.4 Hz, J_{trans}=17.0 Hz), 5.17 (apparent dt, 1H, H-7b, $J_{7a,7b}$ and $J_{7b,5}$=1.4 Hz, J_{cis}=10.4 Hz), 4.28 (m, 1H, H-5), 2.43 (m, 2H, H-4a and H-4b), 1.69 (large s, 1H, OH), 1.48 (s, 9H, O(CH_3)$_3$). ^{13}C NMR**:** δ 165.6 (s′, C-1), 142.9 (d′, C-3), 139.8 (d′, C-6), 125.9 (d′, C-2), 115.5 (t′, C-7), 80.3 (s′, O*C*(CH_3)$_3$), 71.6 (d′, C-5), 39.7 (t′, C-4), 28.1 (q′, OC(*C*H_3)$_3$. FTIR (film): 3431 (s), 1714 (s), 1699 (s), 1654 (m) cm^{-1}. MS [EI] *m/z*: 142 [5.0%, M−C_4H_8 (McLafferty)], 125 [11.3%, M−OC(CH_3)$_3$], 124 [2.8%, M−(C_4H_8 and H_2O)], 97 [2.6%, M−$CO_2C(CH_3)_3$], 86 (100%), 69 (22.9%), 68 [15.0%, M−OC(CH_3)$_3$ and CH_2=CHCHOH)], 57 (79.5%, C_4H_9). HRMS [EI] found: 142.06380; calcd for M−C_4H_8=$C_7H_{10}O_3$: 142.06299.

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20. *Method A:* A flask containing a catalytic amount of NiI_2 (0.037 mmol) was charged with a soln of SmI_2 in THF (0.1 M, 8.9 mL, 0.89 mmol) and cooled to −78°C. A soln of **1** (0.30 mmol) and *t*-BuOH (0.60 mmol) in THF (2.3 mL) was then quickly added in one shot. The reaction mixture was stirred at −78°C for 1 h (after which time we detected only a trace of **2a/2b** by TLC analysis of the reaction mixture) and then allowed to warm to rt over 2.5 h. *Method B:* SmI_2 in THF was added dropwise to a suspension of **1a**, *t*-BuOH and NiI_2 in THF at 0°C; reaction time=1.2 h. NMR and GC–MS analysis of the crude products showed that **2a**, **2b** and **24** represented 44, 14 and 33% respectively of the total reaction products. *Method C:* As per method A except that the flask containing NiI_2 (0.0178 mmol) also contained Sm metal (0.047 mmol); quantity of other reagents: **1** (0.15 mmol), SmI_2 (0.45 mmol), *t*-BuOH (0.30 mmol). NMR and GC–MS analysis of the crude products showed that **2a**, **2b** and **24** represented 50, 9 and 25% respectively of the total reaction products.
21. Keck et al. have reported that the stereoselectivity of SmI_2 reductions of β-hydroxy ketones is affected by the identity of the proton source used. See: Keck, G. E.; Wager, C. A.; Sell, T.; Wager, T. T. *J. Org. Chem.* **1999**, *64*, 2172–2173.
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