Stereoelectronic Effects in the 6-Exo Free Radical Cyclization of Acyclic Sugar Derivatives: Synthesis of Branched Chain Cyclitols

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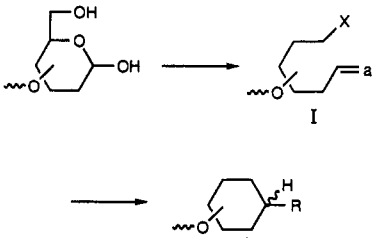
The synthesis and free radical carbocyclization (Bu_3SnH + AIBN) of acyclic sugar derivatives 1–12 is reported. The yields of these 6-exo cyclization processes are good and the diastereomeric excesses are from moderate to excellent. The resulting cyclohexanes are polyoxygenated, enantiomerically pure building blocks for the synthesis of complex branched chain cyclitols. The results obtained in the cyclization of radical precursors **1**, **4**, **6**, and **8** are in sharp contrast with the results observed in the ring closure of compounds **2**, **3**, **5**, and **7**. An electron-attracting group (acetate or mesylate), located in a vicinal position to the carbon-centered radical, modifies the conformation of the reacting species in the transition state and thus changes the stereochemical outcome of the cyclization. This allowed us to select the nature of the absolute configuration at the newly formed stereocenter by simply changing the type of the substituents at the vicinal carbon where the radical is generated.

Introduction

In the previous reports from this laboratory we have described a new free radical approach for the synthesis of enantiomerically pure polyhydroxylated cyclohexane rings.[1] We have shown for the first time that the 6-exo-trig[2] cyclization of acyclic sugar derivatives[3] **I** (X = leaving group, a = radical acceptor; Scheme I) is a reliable and efficient method for the preparation of aminocyclitols,[4] pseudo-sugars,[5] and branched chain cyclitols.[6] The success of our method is governed by the correct choice of radical acceptor. As expected, conformationally restricted precursors with α,β-unsaturated esters[7] as terminal acceptors have provided the best results. In our earlier work we have carefully analyzed the cyclization of fully oxygenated (C2–C5) 6-deoxy-6-halo sugar precursors with *gluco*, *manno*, or *gulo* absolute configurations.[1]

Scheme I



In order to evaluate, expand, and exploit the synthetic versatility and usefulness of this methodology,[1] a large number of differently substituted and functionalized substrates are needed. In addition, due to scarce examples of synthetically useful 6-exo free radical cyclizations,[8] the stereochemical outcome and stereoelectronic effects concerned with this process remain almost unknown in contrast with the rich literature about the 5-exo ring closure.[9] With these ideas in mind we have synthesized and cyclized compounds 1–12 (Scheme II). We have found that the absolute configuration at the new stereocenter formed during the carbocyclization of acyclic 6-heptenyl radicals depends upon the stereoelectronic effects of the vicinal substituent at the carbon where the radical is being generated. This is a novel and interesting result in the field of radical chemistry.[10]

Results and Discussion

Synthesis of Precursors (Schemes III, IV). The precursors were prepared from commercially available D-glucose diethyl dithioacetal **13**. The routine transfor-

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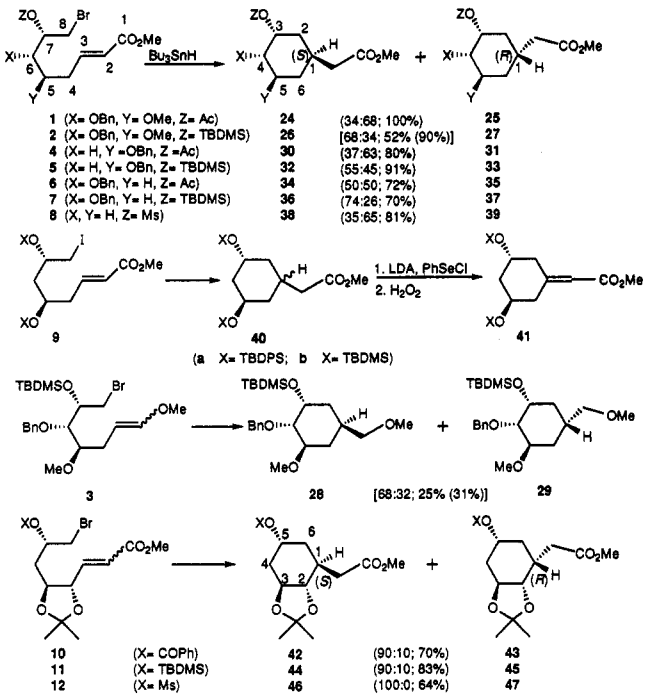
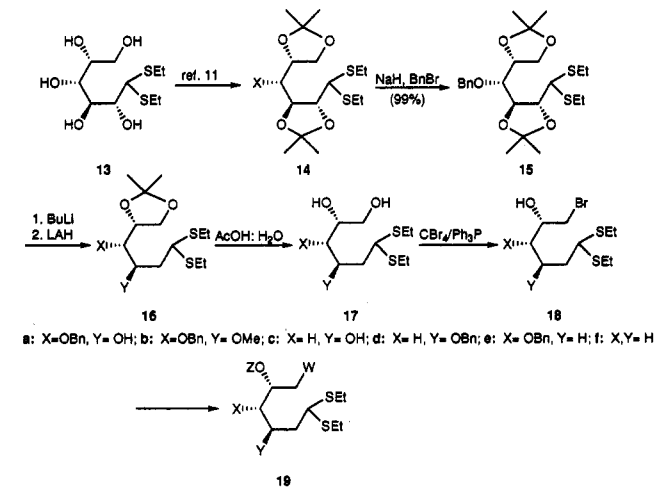
Scheme II



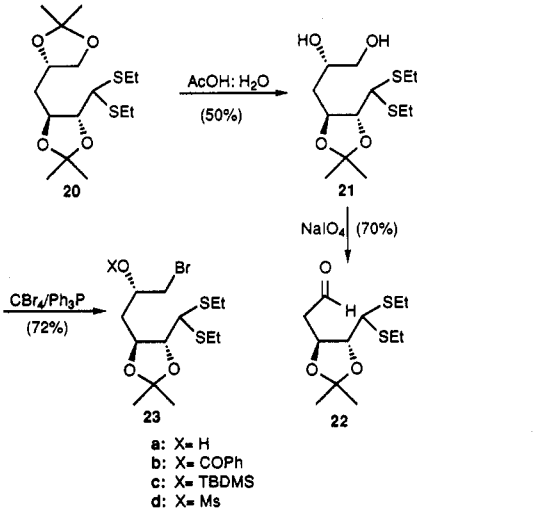
Scheme III



a: X= OBn, Y= OMe, Z= Ac, W= Br; b: X= OBn, Y= OMe, Z= TBDMS, W= Br; c: X= H, Y= OBn, Z= Ac, W= Br; d: X=H, Y= OBn, Z= TBDMS, W= Br; e: X= OBn, Y=H, Z= Ac, W= Br; f: X= OBn, Y=H, Z= TBDMS, W= Br; g: X, Y= H, Z= Ms, W= Br; h: X= H, Y= OTBDPS, Z= H, W= OH; i: X, Z= H, Y= OTBDPS, W= OTs; j: X=H Y=OTBDPS, Z= TBDPS, W= OTs; k: X= H, Y= OTBDPS, Z= TBDPS, W= I

mations are shown in Schemes III and IV, the details of which are given in the supplementary material. Simple acetonation of **13** as described[11] allowed us to obtain sugar **14**. Subsequent standard benzylation[12] or deoxygenation[13] afforded compounds **15** and **20**,[14] respectively. The required C2 deoxygenation was undertaken according to the methods described by Gray and Wong[15] modified by Redlich;[16] compounds **16a–f** were then obtained in multigram quantities in an overall good yield. Acid hydrolysis

Scheme IV



gave diols **17b,d–f**, which on selective bromination[17] at C6 provided bromohydrins **18b,d,e**. The selective mild acid hydrolysis of compound **20** gave 2,3-*O*-isopropylidene derivative **21**. The structure of this diol was demonstrated by its transformation into aldehyde **22** and compounds **23a–d**. Finally, the functionalization of the hydroxyl at C5 gave the dithioacetals **19a–k**. In the synthesis of compounds **19g**, **23g**, and **19k** we have used an alternative two-step method. Dimesylation of diols **17f** and **21** followed by reaction with lithium bromide in 2-butanone gave **19g** and **23g**, respectively. Monotosylation of diol **19h**, preparation of **19j**, and treatment with sodium iodide in dimethylformamide gave compound **19k**. Subsequent deprotection of the aldehyde and Wittig reaction gave the desired radical precursors. Compounds **1,2,4–9** were obtained by routine methods and cyclized as a mixture of *E*/*Z* isomers (97:3); enol ether **3** and radical precursors **1012** were synthesized as a mixture of *E*/*Z* isomers in 70:30 and 1:1 ratio, respectively. We were unable to separate these isomers and were cyclized together.

Free Radical Cyclizations. The free radical cyclizations were carried out by treatment of the precursors with tributyltin hydride and a catalytic amount of AIBN in refluxing toluene (see Experimental Section). The resulting carbocycles were obtained as a mixture of isomers (Scheme II). The *S*/*R* ratios have been determined in the crude reaction mixtures by ^{1}H NMR analysis. In some cases we could separate the isomeric carbocycles by flash chromatography.[18] The compounds **24–47** were characterized by the usual analytical and spectroscopic methods. Particularly, the assignment of absolute configuration at the new stereocenter C1 was possible by a detailed analysis of the ^{1}H NMR spectra. After extensive ^{1}H–^{1}H irradiation experiments we could locate the signals of the significant protons and measure the vicinal coupling constants. For a cyclohexane in a presumed chair-like conformation, these values easily allowed us to establish the stereochemical assignments.

The data reported in Scheme II deserve some comments: (1) In the 6-exo free radical cyclization of precursors **1–12** we have neither observed acetyl migration[7] nor 1,5-hydrogen shifts.[7] (2) As expected, the cyclization of the

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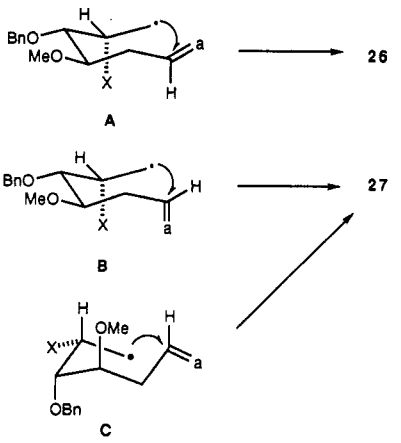
Scheme V



(X= OTBDMS, a= $CHCO_2Me$)

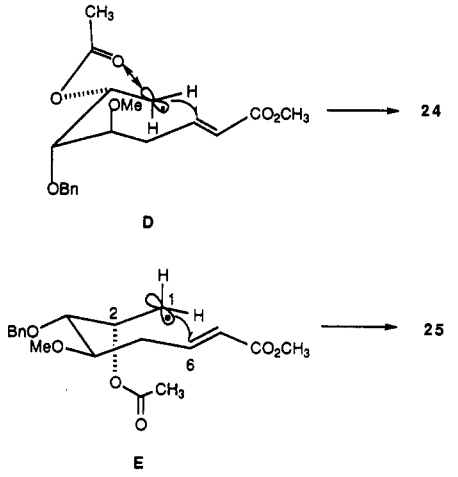
enol ether **3** gave a poor yield in comparison with the analogous precursor **2** with an α,β-unsaturated ester as radical acceptor. (3) The *S*/*R* ratios are dependent on the type of substituents in the acyclic precursor. The highest values have been observed for the conformationally restricted compounds **10–12** having an isopropylidenedioxy group at C4–C5. (4) In the cyclization of sugars **1–8** the absolute configuration at the new stereocenter depends on the nature of the substituent at C7: a *tert*-butyldimethylsilyl group (**2**, **3**, **5**, **7**) gives major C1 (*S*) branched chain cyclitols, while for an acetate or mesylate (**1**, **4**, **6**, **8**) a clear inversion of the stereogenic trend is observed and major C1 (*R*) isomers result. (5) Cyclization of precursor **9** (easily available from **19h**,[19] Scheme III) gave only one isomer (**40a**), a carbocycle with a *C2* symmetry axis. This compound was transformed into cyclohexane **41a** by standard α-selenation and elimination.[20] Compound **41a** is related to **41b**, a product that has been used in the preparation of cyclohexane ring analogues of 1α,-25-dihydroxyvitamin D_3.[21]

The different stereogenic results obtained in the cyclization of **1** (**4**, **6**, **8**) or **2** (**3**, **5**, **7**) which differ only by the nature of the substituent at C7 were totally unexpected, and to the best of our knowledge no similar stereodirecting properties have been reported in the literature.

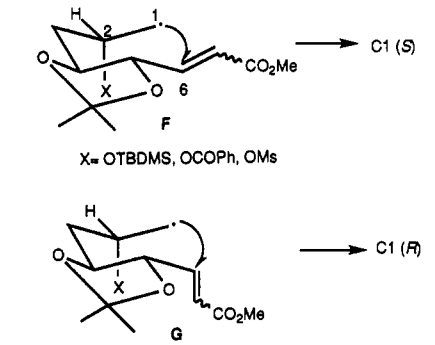
In Schemes V and VI we have given a possible explanation for these facts. As reported,[22] for these kinetically controlled processes, in the reactant-like transition state, the radical adopts a chair-like conformation with substituents in preferred pseudoequatorial positions. This suggests that, for instance in precursor **2**, the conformers **B** and **C** are clearly disfavored, as notorious 1,3-diaxial interactions develop in the transition state; in fact, low-energy conformer **A** gives **26** as major product (Scheme V).

Precursor **1**, with the less sterically hindered acetate group at C2 (hept-6-enyl radical numbering), should also follow the same trend, but in practice the opposite isomer **24** results. To explain this we propose that of the two transition states **D** and **E** (Scheme VI), that derived from

Scheme VI



Scheme VII



X= OTBDMS, OCOPh, OMs

D is of lower energy than the relatively less-stable conformer **E**. This is probably due to the superior stabilizing effect that the electron-attracting acetoxy group gives to the vicinal carbon-centered radical. We can interpret these effects in terms of a stabilizing interaction between the single occupied p-orbital (SOMO) of the radical and the σ^* LUMO of the vicinal bonded C–OR bond.[23] This powerful stereoelectronic effect overrides the steric repulsion due to the presence of substituents in a pseudoaxial position. In accordance with this, it is known that the stereoelectronic effects of the vicinal acetoxy groups in pyranoid cyclic radicals dramatically change the conformation of these species.[24] To the best of our knowledge similar effects as reported here for acyclic radicals have not been observed before.

We can conclude that the electronic nature of the substituent vicinal to the radical center has an important qualitative and quantitative effect in the formation of the new stereocenter in the 6-exo free radical cyclizations. The magnitude of this effect is related to the structure of the substrate.

Finally, the results obtained in the free radical cyclization of precursors **10–12** can also be rationalized in similar terms (Scheme VII). Major isomers have been obtained in the ring closure of carbon-centered radicals in chair-like conformations with the acceptors in preferred pseudoequatorial positions (conformer **F**, Scheme VII). The 4,5-*O*-isopropylidenedioxy group restricts here the conformational mobility, and the substituent X at C2 (hept-6-enyl radical numbering), in a pseudoaxial position,

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induces 1,3-steric repulsion with the acceptor at C6 (conformer G, Scheme VII).

Conclusion

In brief, the good yields obtained in the cyclization of the radical precursors synthesized here prove that this is a new convenient method for the synthesis of branched chain cyclitols from carbohydrates. In addition, we have observed an interesting stereoelectronic effect in the cyclization of these acyclic sugar derivatives: the stabilizing effect of electron-attracting groups vicinal to carbon-centered radicals determines the preferred conformation in the transition state and the stereochemical outcome of the process. A great deal of attention should be paid to these effects while using synthetic schemes based on these strategies.

Experimental Section

General Procedures. Melting points were determined in a Kofler apparatus and are uncorrected. The ^{1}H NMR coupling constants were verified by homonuclear decoupling experiments. The progress of all reactions was monitored by thin-layer chromatography (TLC), which was performed on aluminum plates precoated with silica gel HF-254 (0.2 mm layers) containing a fluorescent indicator (Merck, 5539). Detection was by UV (254 nm), followed by charring with sulfuric acid spray, or with a solution of ammonium molybdate (VI) tetrahydrate (12.5 g), and cerium sulfate hydrate (5.0 g) in 10% aqueous sulfuric acid (500 mL). Flash chromatography was performed by using Kiesegel 60 (230–400 mesh, Merck) silica gel and hexane ethyl/acetate mixtures as eluent.

Standard Procedure for Free Radical Cyclization. The bromide dissolved in dry toluene (0.015 M), at reflux, under argon was treated with tributyltin hydride (1.6 equiv) and AIBN (cat.) by dropwise addition (syringe pump) in 6 h. The reaction mixture was cooled and the solvent evaporated. The residue was dissolved in ether, 10% aqueous potassium fluoride solution was added, and the mixture was stirred for 18 h. The organic phase was separated, dried, and evaporated. Flash chromatography of the residue gave the product.

Free Radical Cyclization of Precursor 1. Following the standard procedure, from precursor **1** (500 mg, 1.1 mmol), after flash chromatography (hexane/EtOAc, 5%), we have obtained **24** (128 mg) and **25** (266 mg). Total: 394 mg (~100%). **24**: oil; $[\alpha]^{25}_D$ −50° (*c* 4.7, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (m, 5 H, aromatic), 5.45 (dt, $J_{3eq,4ax} = J_{3eq,2ax} = 3.2$ Hz, $J_{3eq,2eq} = 2.7$ Hz, 1 H, H3), 4.68 (d, $J = 11.7$ Hz, 1 H, $C_6H_5OCH_2$), 4.58 (d, 1 H, $C_6H_5OCH_2$), 3.67 (s, 3 H, CO_2CH_3), 3.53 (ddd, $J_{5ax,4ax} = 9.2$ Hz, $J_{5ax,6ax} = 11.2$ Hz, $J_{5ax,6eq} = 4.7$ Hz, 1 H, H5), 3.45 (s, 3 H, OCH_3), 3.29 (dd, 1 H, H4), 2.30–2.15 (m, 4 H, H1, $H6_{eq}$, $CH_2CO_2CH_3$), 2.09 (s, 3 H, $OCOCH_3$), 1.90 (m, 1 H, $H2_{ax}$), 1.64 (m, 1 H, $H2_{eq}$), 1.20 (m, 1 H, $H6_{ax}$). **25**: oil; $[\alpha]^{25}_D$ +12° (*c* 3.6, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 (m, 5 H, aromatic), 5.05 (ddd, $J_{3ax,2ax} = 11.8$ Hz, $J_{3ax,2eq} = 4.6$ Hz, $J_{3ax,4eq} = 3.1$ Hz, 1 H, H3), 4.67 (d, $J = 12.0$ Hz, 1 H, $C_6H_5OCH_2$), 4.58 (d, 1 H, $C_6H_5OCH_2$), 3.81 (t, $J_{4eq,5eq} = 3.1$ Hz, 1 H, H4), 3.66 (s, 3 H, CO_2CH_3), 3.54 (q, $J_{5eq,6ax} = J_{5eq,6eq} = 3.1$ Hz, 1 H, H5), 3.30 (s, 3 H, OCH_3), 2.30–2.20 (m, 2 H, $CH_2CO_2CH_3$), 2.20 (m, 1 H, H1), 2.02 (s, 3 H, $OCOCH_3$), 1.86–1.70 (m, 2 H, $H6_{eq}$, $H2_{ax}$), 1.62 (m, 1 H, $H2_{eq}$), 1.44 (m, 1 H, $H6_{ax}$).

Free Radical Cyclization of Precursor 2. Precursor **2** (929 mg, 1.7 mmol) in the usual conditions, after chromatography (hexane/EtAcO, 5%), gave **26** (253 mg), **2** (371 mg), and **27** (126 mg). Total: 379 mg [52% (90%) yield]. **26**: oil; $[\alpha]^{25}_D$ −34° (*c* 3.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (m, 5 H, aromatic), 4.65 (s, 2 H, $C_6H_5OCH_2$), 4.12 (td, $J_{3eq,2ax} = J_{3eq,4ax} = 2.6$ Hz, $J_{3eq,2eq} = 4.2$ Hz, 1 H, H3), 3.63 (s, 3 H, CO_2CH_3), 3.56 (ddd, $J_{5ax,4ax} = 9.2$ Hz, $J_{5ax,6ax} = 9.1$ Hz, $J_{5ax,6eq} = 4.7$ Hz, 1 H, H5), 3.42 (s, 3 H, OCH_3), 3.09 (dd, 1 H, H4), 2.25 (m, 1 H, H1), 2.24 (dd, $J_{gem} = 14.6$ Hz, $J = 6.4$ Hz, 1 H, $CH_2CO_2CH_3$), 2.16 (dd, $J = 7.8$ Hz, 1 H, $CH_2CO_2CH_3$), 2.11–2.02 (m, 1 H, $H6_{eq}$), 1.74 (ddd, $J_{2ax,2eq} = 13.3$ Hz, $J_{2ax,1ax} = 6.3$ Hz, 1 H, $H2_{eq}$), 1.06 (ddd, $J_{2ax,1ax} = 11.8$ Hz, 1 H, $H2_{ax}$), 0.95 (m, 1H, $H6_{ax}$), 0.86 [s, 9 H, $OSiC(CH_3)_3(CH_3)_2$], 0.02 [s, 6 H, $OSiC(CH_3)_3(CH_3)_2$]. **27**: oil; $[\alpha]^{25}_D$ −16° (*c* 3.6, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (m, 5 H, aromatic), 4.84 (d, $J = 11.9$ Hz, 1 H, $C_6H_5OCH_2$), 4.54 (d, 1 H, $C_6H_5OCH_2$), 3.90 (td, $J_{3ax,4eq} = 2.6$ Hz, $J_{3ax,2ax} = J_{3ax,3eq} = 7.4$ Hz, 1 H, H3), 3.59 (s, 3 H, CO_2CH_3), 3.55 (t, $J_{4eq,5eq} = 2.6$ Hz, 1 H, H4), 3.42 (m, $W_{h/2} = 5.2$ Hz, 1 H, H5), 3.20 (s, 3 H, OCH_3), 2.20–2.12 (m, 2 H, $CH_2CO_2CH_3$), 2.08–1.98 (m, 1 H, H1), 1.66 (dt, $J_{6eq,6ax} = 13.8$ Hz, $J_{6eq,5eq} = J_{6eq,1ax} = 2.8$ Hz, 1 H, $H6_{eq}$), 1.58–1.47 (m, 2 H, H2), 1.27 (dt, $J_{6ax,1ax} = 13.8$ Hz, $J_{6ax,5eq} = 2.8$ Hz, 1 H, $H6_{ax}$), 0.83 [s, 9 H, $OSiC(CH_3)_3(CH_3)_2$], 0.01 [s, 6 H, $OSiC(CH_3)_3(CH_3)_2$].

Free Radical Cyclization of Precursor 3. From precursor **3** (606 mg, 1.2 mmol) and following the general method, we have isolated, after chromatography (hexane/EtAcO, 5%) unreacted **3** (106 mg) and isomers **28** (84 mg) and **29** (41 mg) [25% (31%)]. **28**: oil; $[\alpha]^{25}_D$ −8° (*c* 0.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (m, 5 H, aromatic), 4.69 (s, 2 H, $C_6H_5OCH_2$), 4.17 (dt, $J_{3eq,2ax} = J_{3eq,2ax} = 2.1$ Hz, $J_{3eq,2eq} = 4.1$ Hz, 1 H, H3), 3.60 (ddd, $J_{5ax,4ax} = 9.2$ Hz, $J_{5ax,6ax} = 11.1$ Hz, $J_{5ax,6eq} = 4.5$ Hz, 1 H, H5), 3.45 (s, 3 H, OCH_3), 3.32 (s, 3 H, CH_2OCH_3), 3.30–3.10 (m, 3 H, H4, CH_2OCH_3), 2.25–2.10 (m, 2 H, H1, $H6_{eq}$), 1.71 (ddd, $J_{2eq,2ax} = 13.6$ Hz, $J_{2eq,1ax} = 5.4$ Hz, 1 H, $H2_{eq}$), 1.08 (ddd, $J_{2ax,1ax} = 11.7$ Hz, 1 H, $H2_{ax}$), 0.95 (m, 1 H, $H6_{ax}$), 0.88 [s, 9 H, $OSiC(CH_3)_3(CH_3)_2$], 0.02 [s, 6 H, $OSiC(CH_3)_3(CH_3)_2$]. **29**: oil; $[\alpha]^{25}_D$ −18° (*c* 2.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 (m, 5 H, aromatic), 4.90 (d, $J = 12.2$ Hz, 1 H, $C_6H_5OCH_2$), 4.62 (d, 1 H, $C_6H_5OCH_2$), 3.96 (ddd, $J_{3ax,2ax} = 9.9$ Hz, $J_{3ax,2eq} = 5.3$ Hz, $J_{3ax,4eq} = 2.6$ Hz, 1 H, H3), 3.63 (m, $W_{h/2} = 6.5$ Hz, 1 H, H4), 3.51 (q, $J_{5eq,4eq} = J_{5eq,6ax} = J_{5eq,6eq} = 3.1$ Hz, 1 H, H5), 3.24 (s, 3 H, CH_2OCH_3), 3.22, (s, 3 H, OCH_3), 3.22 (d, $J = 6.6$ Hz, 2 H, CH_2OCH_3), 2.00–1.30 (m, 5 H, H1, H6, H2), 0.90 [s, 9 H, $OSiC(CH_3)_3(CH_3)_2$], 0.08 [s, 6 H, $OSiC(CH_3)_3(CH_3)_2$].

Free Radical Cyclization of Precursor 4. Following the standard procedure, product **4** (460 mg, 1.2 mmol), after chromatography (hexane/EtAcO, 10%), gave **30** (65 mg), **30** + **31** (101 mg) and **31** (135 mg). Total: 301 mg; 80% yield. **30**: oil; $[\alpha]^{25}_D$ −12° (*c* 2.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 (m, 5 H, aromatic), 5.22 (p, $J_{3eq,4ax} = J_{3eq,4eq} = J_{3eq,2eq} = J_{3eq,2ax} = 3.2$ Hz, 1 H, H3), 4.55 (d, $J = 11.6$ Hz, 1 H, $C_6H_4OCH_2$), 4.53 (d, 1 H, $C_6H_5OCH_2$), 3.70 (m, 1 H, H5), 3.67 (s, 3 H, $CH_2CO_2CH_3$), 2.35–2.18 (m, 7 H, $CH_2CO_2CH_3$, H1, H2, H6), 2.03 (s, 3 H, $OCOCH_3$). **31**: oil; $[\alpha]^{25}_D$ −14° (*c* 2.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 (m, 5 H, aromatic), 5.11 (tt, $J_{3ax,2ax} = J_{3ax,4ax} = 11.2$ Hz, $J_{3ax,2eq} = J_{3ax,4eq} = 4.4$ Hz, 1 H, H3), 4.53 (d, $J = 12.0$ Hz, 1 H, $C_6H_5OCH_2$), 4.49 (d, 1 H, $C_6H_5OCH_2$), 3.87 (p, $J_{5eq,4eq} = J_{5eq,4ax} = J_{5eq,6eq} = J_{5eq,6ax} = 3.0$ Hz, 1 H, H5), 3.67 (s, 3 H, $CH_2CO_2CH_3$), 2.50–2.22 (m, 7 H, $CH_2CO_2CH_3$, H1, H2, H6), 2.02 (s, 3 H, $OCOCH_3$).

Free Radical Cyclization of Precursor 5. Following the general method from **5** (1.3 g, 2.7 mmol) and after chromatography (hexane/AcOEt, 5%), compounds **32** and **33** (1.0 g, 91%) were obtained. After careful chromatography, an aliquot of pure major **32** was isolated: oil; $[\alpha]^{25}_D$ −77° (*c* 0.81, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (m, 5 H, aromatic), 4.58 (d, $J = 11.9$ Hz, 1 H, $OCH_2C_6H_5$), 4.51 (d, 1 H, $OCH_2C_6H_5$), 4.20 (m, $W_{h/2} = 8.5$ Hz, 1 H, H5), 3.79 (tt, $J_{3ax,4ax} = J_{3ax,2ax} = 11$ Hz, $J_{3ax,4eq} = J_{3ax,2eq} = 4.2$ Hz, 1 H, H3), 3.67 (s, 3 H, CO_2CH_3), 2.40–2.05 (m, 5 H, $CH_2CO_2CH_3$, H1, H6eq, H4eq), 1.67 (broad d, 1 H, H2eq), 1.31 (td, $J = 12.0$ Hz, $J = 2.4$ Hz, 1 H, H6ax), 1.11 (td, $J = 12.3$ Hz, $J = 2.4$ Hz, 1 H, H4ax), 1.01 (q, $J_{2ax,1ax} = J_{2ax,2eq} = J_{2ax,3} = 11$ Hz, 1 H, H2ax), 0.87 [s, 9 H, $OSiC(CH_3)_3(CH_3)_2$], 0.03 [s, 6 H, $OSiC(CH_3)_3(CH_3)_2$].

Free Radical Cyclization of Precursor 6. In the typical free radical cyclization conditions compound **6** (188 mg, 0.47) gave (hexane/EtAcO, 5%) carbocycle **34** (48 mg), **34** + **35** (8 mg) and **35** (53 mg). Total yield: 72%. **34**: oil; $[\alpha]^{25}_D$ −55° (*c* 4.8, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (m, 5H, aromatic), 5.43 (m, $W_{h/2} = 8.5$ Hz, 1 H, H3), 4.63 (d, $J = 12.1$ Hz, 1 H, $OCH_2C_6H_5$), 4.46 (d, 1 H, $OCH_2C_6H_5$), 3.66 (s, 3 H, CO_2CH_3), 3.34 (td, $J_{4ax,5ax} = 13.1$ Hz, $J_{4ax,5eq}, J_{4ax,3eq} = 2.6$ Hz, 1 H, H4), 2.10–1.80 (m, H9, H2, H5, H6, H1, $CH_2CO_2CH_3$), 2.11 (s, 3 H, $OCOCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.78, 170.57 (CO_2CH_3, $OCOCH_3$), 138.19–127.40 (aromatic), 76.47, 67.84 (C3, C4), 70.06 ($OCH_2C_6H_5$), 51.38 (CO_2CH_3), 40.30, 30.00, 28.44, 26.42 (C2, 5, 6, $CH_2CO_2CH_3$), 34.97 (C1), 21.19 ($OCOCH_3$). **35**: oil; $[\alpha]^{25}_D$ −25° (*c* 2.1,

$CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.34 (m, 5 H, aromatic), 4.76 (ddd, $J_{3ax,2ax}$ = 10.6 Hz, $J_{3ax,2eq}$ = 2.8 Hz, $J_{3ax,4eq}$ = 5.8 Hz, 1 H, H3), 4.61 (d, J = 12.3 Hz, 1 H, $OCH_2C_6H_5$), 4.53 (d, 1 H, $OCH_2C_6H_5$) 3.79 (m, $W_{h/2}$ = 7.8 Hz, 1 H, H4), 3.66 (s, 3 H, CO_2CH_3), 2.03 (s, 3 H, $OCOCH_3$), 2.00–1.78 (m, 9 H, H5, H6, H2, H1, $CH_2CO_2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.78, 170.57 (CO_2CH_3, $OCOCH_3$), 138.19–127.40 (aromatic), 76.47, 67.84 (C3, C4), 70.06 ($OCH_2C_6H_5$), 51.38 (CO_2CH_3), 40.30, 30.00, 28.44, 26.42 (C2, 5, 6, $CH_2CO_2CH_3$), 34.97 (C1), 21.19 ($OCOCH_3$).

Free Radical Cyclization of Precursor 7. In the typical free radical cyclization conditions precursor **7** (451 mg, 0.96 mmol), after flash chromatography (hexane/EtOAc, 5%), gave a mixture of **36** + **37** (263 mg, 70%) that we could not separate: oil; ^1H NMR (300 MHz, $CDCl_3$) δ (major isomer **36**) 7.34 (m, 5 H, aromatic), 4.59 (d, J = 12.4 Hz, 1 H, $OCH_2C_6H_5$), 4.50 (d, 1 H, $OCH_2C_6H_5$), 4.16 (m, $W_{h/2}$ = 8.7 Hz, 1 H, H 3), 3.65 (s, 3 H, CO_2CH_3), 3.21 (ddd, $J_{4ax,5ax}$ = 11.7 Hz, $J_{4ax,5eq}$ = 4.1 Hz, $J_{4ax,3eq}$ = 2.3 Hz, 1 H, H4), 2.45–1.20 (m, 9 H, H2, H5, H6, H1, $CH_2CO_2CH_3$), 0.93 [s, 9 H, $OSi(CH_3)_3(CH_3)_2$], 0.17 [s, 6 H, $OSiC(CH_3)_3(CH_3)_2$].

Free Radical Cyclization of Precursor 8. Compound **8** (238 mg, 0.73 mmol) was transformed in the usual conditions into carbocycle **38** and **39** (147 mg, 81%). We have obtained them (hexane/EtOAc, 15%) as a mixture of isomers that we could not separate: oil; ^1H NMR (300 MHz, $CDCl_3$) δ (major isomer **39**) 4.62 (tt, $J_{3ax,2ax}$ = $J_{3ax,4ax}$ = 11.3 Hz, $J_{3ax,2eq}$ = $J_{3ax,4eq}$ = 4.6 Hz, 1 H, H3), 3.67 (s, 3 H, CO_2CH_3), 3.00 (s, H, OSO_2CH_3), 2.30–1.30 (m, 11 H, H2, H4, H5, H6, H1, $CH_2CO_2CH_3$).

Free Radical Cyclization of Precursor 9. Precursor **9** (251 mg, 0.32 mmol) was converted into **40** (163 mg, 77%; hexane/EtOAc, 5%) following the standard method: oil; $[\alpha]^{25}_D$ +2° (*c* 0.51, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.67–7.30 (m, 20 H, aromatic), 4.28 (tt, J = 10 Hz, J = 4.7 Hz, 1 H, Hax-OSi*t*BuPh$_2$), 4.06 (m, $W_{h/2}$ = 8.1 Hz, 1 H, Heq-OSi*t*BuPh$_2$), 3.59 (s, 3 H, CO_2CH_3), 2.28 (m, 1 H, H1), 2.18 (dd, J = 6 Hz, J = 14.7 Hz, 1 H, $CH_2CO_2CH_3$), 2.06 (dd, J = 8 Hz, 1 H, $CH_2CO_2CH_3$), 1.95 (m, 2 H), 1.50 (m, 2 H), 1.30 (m, 2 H), 1.04, 0.91 [s, s; 9 H, 9 H; $OC(CH_3)_3(C_6H_5)_2$].

Synthesis of Compound 41a. Lithium diisopropylamide (0.7 mmol, 5 equiv) in dry tetrahydrofuran (5 mL) was prepared as usual. To this solution product **40** (98 mg, 0.14 mmol), dissolved in dry tetrahydrofuran (1 mL), was added dropwise at −78 °C, under argon and stirring; after 1 h, diphenyl diselenide (43 mg, 0.14 mmol) in dry tetrahydrofuran (1 mL) was added. The reaction was continued for 2 h at this temperature; a saturated aqueous solution of ammonium chloride was added, the flask warmed at room temperature, the reaction diluted with ethyl acetate, washed with brine, dried, and evaporated. The residue was submitted to chromatography (hexane/EtOAc, 5%) giving an intermediate (83 mg) that without further analysis was dissolved in tetrahydrofuran (5 mL) and treated with hydrogen peroxide (30%) at 0 °C and at room temperature overnight. The solvent was evaporated and the residue diluted with ethyl acetate, washed with brine, dried, and evaporated. The residue was purified by chromatography (hexane/EtOAc, 5%) to give recovered **40** (13 mg) and **41a** (54 mg, 50%): oil; $[\alpha]^{25}_D$ −24° (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.70–7.27 (m, 20 H, aromatic), 5.54 (s, 1 H, = $CHCO_2CH_3$), 4.21 (m, 2 H, $HCOSi$*t*-BuPh$_2$), 3.62 (s, 3 H, CO_2CH_3), 3.01 (dd, J = 13.8 Hz, J = 6.4 Hz, 1 H), 2.85 (dd, J = 3.8 Hz, J = 13.8 Hz, 1 H), 2.25 (dd, J = 4 Hz, J = 13.1 Hz, 1 H), 2.05 (dd, = 7.6 Hz, J = 13.1 Hz, 1 H), 1.77 (m, 1 H), 1.70 (m, 1 H), 0.95 [s, 18 H, $OSiC(CH_3)_3(C_6H_5)$].

Free Radical Cyclization of Precursor 10. From ester **10** (2.1 g, 4.9 mmol) and following the standard protocol, after chromatography (hexane/EtOAc, 5%), compounds **42** and **43** (1.2 g, 70%) were isolated as a mixture of isomers that we could not separate: oil; ^1H NMR (300 MHz, $CDCl_3$) (major isomer **42**) δ 5.51 (m, $W_{h/2}$ = 6.5 Hz, 1 H, H5), 3.83 (ddd, $J_{3ax,4eq}$ = 4 Hz, $J_{3ax,4ax}$ = 12.5 Hz, $J_{3ax,2ax}$ = 8.6 Hz, 1 H, H3), 3.66 (s, 3 H, CO_2CH_3), 3.19 (dd, $J_{2ax,3ax}$ = 8.6 Hz, $J_{2ax,1ax}$ = 10.8 Hz, 1 H, H2), 2.73 (dd, $J_{7,1}$ = 4.4 Hz, $J_{7,7'}$ = 15.3 Hz, 1 H, $CH_2CO_2CH_3$), 1.75–1.49 (m, 6 H, H4, H6, H1, $CH_2CO_2CH_3$), 1.45 [s, 3 H, $OC(CH_3)_2O$], 1.40 [s, 3 H, $OC(CH_3)_2O$].

Free Radical Cyclization of Precursor 11. Starting with ester **11** (3.0 g, 6.8 mmol) and following the standard protocol, after flash chromatography (hexane/EtOAc, 5%), compound **44** (1.84 g) and **44** + 20% of **45** (192 mg) were obtained. Total: 2.03 g (83%). **44**: oil; $[\alpha]^{25}_D$ +4° (*c* 3.7, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 4.19 (m, $W_{h/2}$ = 7.1 Hz, 1 H, H5), 3.84 (ddd, $J_{3ax,4ax}$ = 12.0 Hz, $J_{3ax,2ax}$ = 8.5 Hz, $J_{3ax,4eq}$ = 3.9 Hz, 1 H, H3), 3.66 (s, 3 H, CO_2CH_3), 3.03 (dd, $J_{1,2}$ = 10.8 Hz, $J_{2,3}$ = 8.5 Hz, 1 H, H2), 2.72 (dd, $J_{7,7'}$ = 15.4 Hz, $J_{7,1}$ = 4.0 Hz, 1 H, $CH_2CO_2CH_3$), 2.44 (m, 1 H, H1), 2.16 (dd, $J_{7,7'}$ = 15.4 Hz, $J_{7',1}$ = 9.7 Hz, 1 H, $CH_2CO_2CH_3$), 2.14 (m, 1 H, H4 eq), 1.89 (ddd, $J_{5eq,6eq}$ = 2.7 Hz, $J_{6eq,1ax}$ = 5.3 Hz, $J_{6eq,6ax}$ = 13.7 Hz, 1 H, H6eq), 1.52 (td, $J_{4ax,4eq}$ = $J_{4ax,3ax}$ = 12 Hz, $J_{4ax,5eq}$ = 2.7 Hz, 1 H, H4ax), 1.43 [s, 3 H, $OC(CH_3)_2$], 1.41 [s, 3 H, $OC(CH_3)_2$], 1.17 (dd, $J_{6ax,5eq}$ = 2.7 Hz, $J_{6ax,6eq}$ = 12.8 Hz, $J_{6ax,1ax}$ = 11.7 Hz, 1 H, H6ax), 0.88 [s, 9 H, OSi $C(CH_3)_3(CH_3)_2$], 0.05 [s, 6 H, $OSiC(CH_3)_3(CH_3)_2$]; ^{13}C NMR δ 172.32 (CO_2CH_3), 108.81 (C8), 83.16, 75.43, 67.11 (C2, 3, 5), 51.24 (CO_2CH_3), 38.18, 37.01, 36.60 (C4, 6, $CH_2CO_2CH_3$), 32.74 (C1), 26.95, 26.81 (C9, 9'), 25.60, 17.8 [$OSiC(CH_3)_3(CH_3)_2$], −5.11 [$OSiC(CH_3)_3(CH_3)_2$].

Free Radical Cyclization of Precursor 12. From mesylate **12** (205 mg, 0.5 mmol) in the usual conditions, after flash chromatography (hexane/EtOAc, 30%), only compound **46** was formed and isolated (103 mg, 64%): mp 82–84 °C; $[\alpha]^{25}_D$ −8.1° (*c* 5.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 5.16 (p, J = 2.7 Hz, 1 H, H5), 3.74 (ddd, $J_{3ax,4eq}$ = 4.3 Hz, $J_{3ax,2ax}$ = 8.5 Hz, $J_{3ax,4ax}$ = 12.4 Hz, 1 H, H3), 3.68 (s, 3 H, CO_2CH_3), 3.10 (dd, $J_{1ax,2ax}$ = 10.7 Hz, $J_{2ax,3ax}$ = 8.5 Hz, 1 H, H2), 3.09 (s, 3H, OSO_2CH_3), 2.75 (dd, $J_{7,7'}$ = 15.9 Hz, $J_{7,1}$ = 4.0 Hz, 1 H, $CH_2CO_2CH_3$), 2.55 (m, 1 H, H4 eq), 2.45 (m, 1 H, H1), 2.37 (m, 1 H, H6eq), 2.22 (dd, $J_{7,7'}$ = 15.9 Hz, $J_{7',1}$ = 9.3 Hz, 1 H, $CH_2CO_2CH_3$), 1.76 (dt, $J_{4ax,5eq}$ = 2.7 Hz, $J_{4ax,3ax}$ = $J_{4ax,4eq}$ = 12.4 Hz, 1 H, H4ax), 1.43 [s, 3 H, $OC(CH_3)_2O$], 1.42 [s, 3H, $OC(CH_3)_2O$], 1.37 (m, 1 H, H6ax).

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Supplementary Material Available: Synthetic procedures and spectral data of the intermediates in the preparation of compounds 1–12; IR, MS, and analysis of products **24**–**47** (30 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from ACS; see any current masthead page for ordering information.