Synthesis of Enantiomerically Pure, Highly Functionalized, Medium-Sized Carbocycles from Carbohydrates: Formal Total Synthesis of (+)-Calystegine B_2

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The free radical cyclization (FR) and the ring-closing metathesis (RCM) reaction have been analyzed in order to develop new and original synthetic protocols for the synthesis of enantiomerically pure, highly functionalized, medium-sized carbocycles from carbohydrates. As a result, we report here for the first time examples of the 7-exo FR cyclization of acyclic radical precursors derived from sugars. This process appears to be extremely sensitive to the conformational mobility of the radical species in the transition state. The use of two isopropylidene groups blocking four of the total present hydroxyl groups and a good radical acceptor (as an α,β-unsaturated ester) are mandatory conditions for a successful ring closure protocol. The RCM reaction by using Grubbs' catalyst on selected carbohydrate-derived precursors has afforded variable yields of the expected unsaturated cycloheptane or cyclooctane derivatives. The synthesis of the cycloheptitols has been carried out in good yields, regardless of the absolute configuration at the different stereocenters and the nature of the O-functional groups bound in allylic positions to one of the double bonds implicated in the metathesis reaction. Conversely, in the cyclooctane synthesis, we have observed that the success of the reaction depends not only on the absolute configuration at the different stereocenters close to the double bonds but also on the nature of the O-protecting groups on these stereocenters. Finally, the RCM strategy has been used in an attempt to prepare natural (+)-calystegine B_2 from D-glucose. The synthesis of compound **92** from D-glucose constitutes a formal total synthesis of (+)-calystegine B_2, showing the importance of the steric hindrance in allylic positions for a successful RCM reaction.

Introduction

The synthesis of medium-sized rings, notably seven- and eight-membered ring systems, has usually been hampered by entropic/enthalpic factors and transannular interactions between the methylene groups.[1] These are serious limitations, which have usually resulted in low chemical yields of the desired products.[2] Although some solutions to this formidable challenge have been advanced using cycloaddition or annulation strategies,[3] the cyclization approach for the synthesis of these structures still remains a partially unsolved problem.[4] In view of these difficulties, we reasoned that precursors derived from carbohydrates could probably be excellent substrates for testing the viability of these strategies for the preparation of chiral and densely functionalized, medium-sized carbocycles. An elegant example and precedent for this strategy was reported by Depezay and co-workers some years ago.[4k]

In this paper, we disclose full details of our recent efforts on the synthesis of polyhydroxylated, medium-sized ring systems in an enantiomerically pure form.[5] We have particularly directed our attention[6]to the free radical mediated (FR) cyclization[7] and the ring-closing metathesis (RCM)[8] reaction, two well-known strategies for ring closure protocols. We have applied the FR strategy to selected carbohydrate precursors **1**−**6** (Figure 1) and

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(3) See for example: (a) Rigby, J. H. *Acc. Chem. Res.* **1993**, *26*, 579. (b) Lautens, M. *Top. Curr. Chem.* **1997**, *190*, 1.

(4) For some selected references on the synthesis of seven-membered ring systems, see: (a) Barco, A.; Benetti, S.; De Risi, C.; Marchetti, P.; Pollini, G. P.; Zanirato, V. *Tetrahedron* **1999**, *55*, 5923. (b) Lautens, M.; Rovis, T. *J. Am. Chem. Soc.* **1997**, *119*, 11090. (c) Yoshizaki, H.; Yoshioka, K.; Sato, Y.; Mori, M. *Tetrahedron* **1997**, *53*, 5433. (d) Pearson, A.; Katiyar, S. *Tetrahedron* **2000**, *56*, 2297. (e) Pearson, A.; Srinivassan, K. *J. Org. Chem.* **1992**, *57*, 3965. (f) Falk-Heppner, M.; Hunger, U.; Keller, M.; Kaiser, C.; Krieger, R.; Friz, H.; Prinzbach, H. *Liebigs Ann./Recl* **1997**, 1481. (g) Trost, B. M.; Organ, M. G. *J. Am. Chem. Soc.* **1994**, *116*, 10320. (h) Johnson, C. R.; Bis, S. J. *J. Org. Chem.* **1995**, *60*, 615. (i) Johnson, C. R.; Golebioski, A.; Steensma, D. H. *J. Am. Chem. Soc.* **1992**, *114*, 9414. (j) Le Merrer, Y.; Gravier-Pelletier, C.; Maton, W.; Numa, M.; Depezay, J.-C. *Synlett* **1999**, 1322. (k) Duclos, O.; Duréault, A.; Depezay, J. C. *Tetrahedron Lett.* **1992**, *33*, 1059. (l) Wender, P. A.; Takahashi, H.; Witulski, B. *J. Am. Chem. Soc.* **1995**, *117*, 4720.

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(6) For a previous effort in this area using intramolecular 1,3-dipolar cycloaddition reaction on 7-alkenyl nitrones derived from D-mannose, see: Marco-Contelles, J.; de Opazo, E. *Tetrahedron Lett.* **1999**, *40*, 4445.

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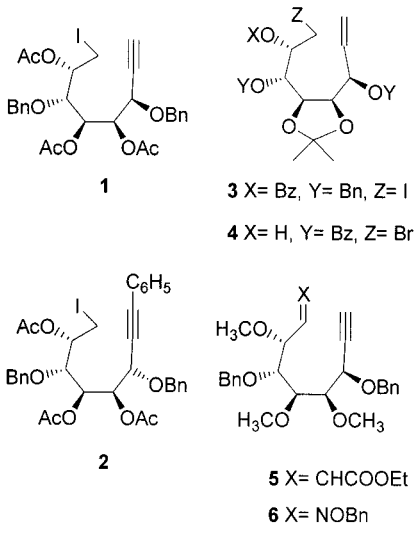

Figure 1. Radical precursors derived from D-mannose for the free radical strategy.

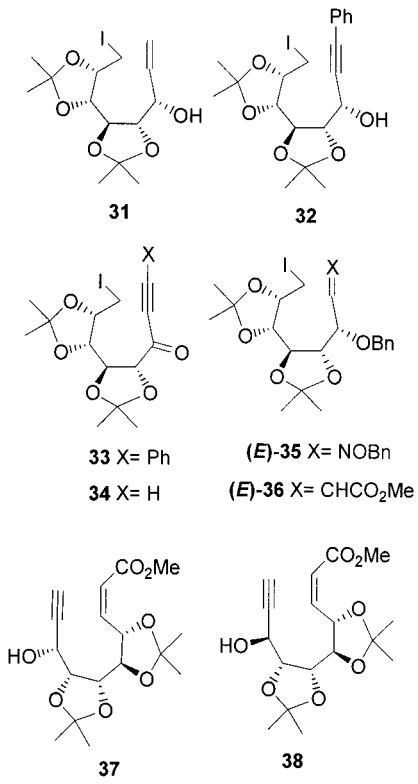

Figure 2. Radical precursors derived from D-glucose for the free radical strategy.

to compounds **31**−**38** (Figure 2), prepared from D-mannose and from D-glucose, respectively, to investigate the scope, synthetic potential, and limitations of this method for the synthesis of seven- or eight membered-ring systems. Using the RCM strategy, we have also explored the reactivity of intermediates (**60**−**66**) (Figure 3) obtained form D-glucose for the synthesis of unsaturated cyclohepta- or cycloctapolyol derivatives.

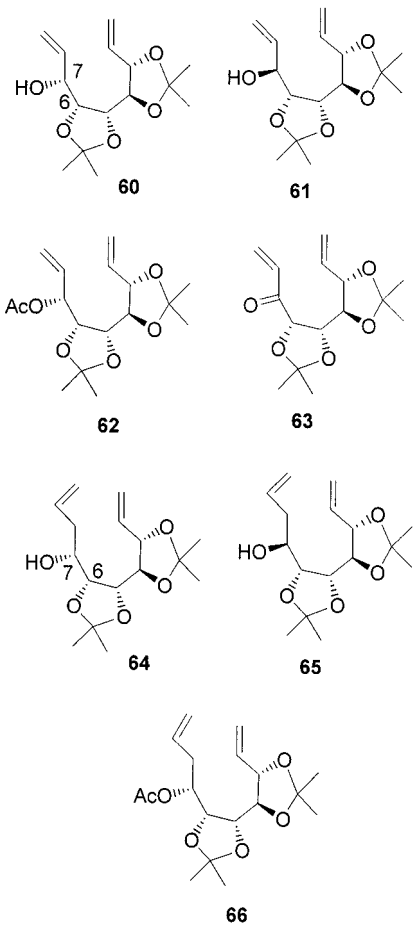

Figure 3. Radical precursors derived from D-glucose for the ring-closing metathesis strategy.

Due to the growing number of natural compounds containing medium-sized rings with attractive biological/pharmacological activity,[9,10] these synthetic efforts will presumably be useful for a rational design directed toward the synthesis of some members of this family of molecules. As a practical example, we describe here our work directed toward the synthesis of the glucosidase inhibitor (+)-calystegine B_2[11] from D-glucose (Figure 4).

Results and Discussion

A. Free Radical Cyclization Approach. In the last thirteen years, we have intensively and systematically analyzed the samarium diiodide and/or tributyltin hydride mediated free radical cyclizations of carbohydrate

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(9) (a) Banwell, M. G. *Aust. J. Chem.* **1991**, *44*, 1. (b) Fraga, B. M. *Nat. Prod. Rep.* **1992**, *9*, 217.

(10) Kupchan, S. M.; Eakin, A.; Thomas, A. M. *J. Med. Chem.* **1971**, *14*, 1147.

(11) (a) Goldmann, A.; Milat, M. L.; Ducrot, P. H.; Lallemand, J.-Y.; Maille, M.; Lepingle, A.; Charpin, I.; Tepfer, D. *Phytochemistry* **1990**, *29*, 2125. (b) Goldmann, A.; Message, B.; Tepfer, D.; Molyneux, R.; Duclos, O.; Boyer, F.-D.; Pan, Y. T.; Elbein, A. D. *J. Nat. Prod.* **1996**, *59*, 1137.

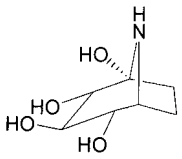


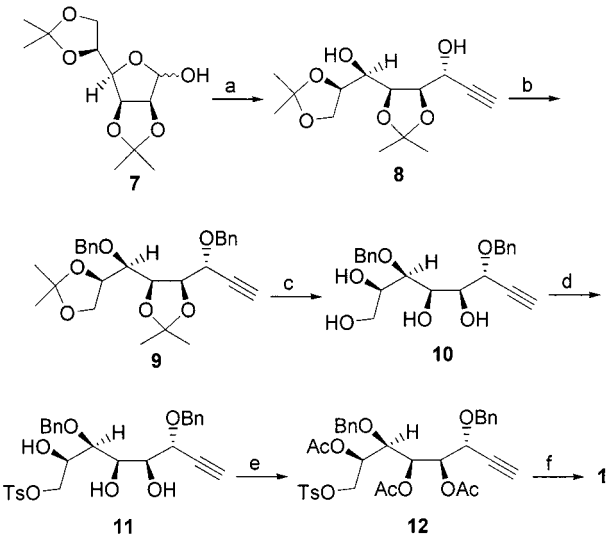
Figure 4. Calystegine B_2.

precursors for the synthesis of cyclitols.[12] Particular effort has been dedicated to exploring the synthetic scope of the 6-exo-trig free radical cyclization of acyclic intermediates[12a] and branched-chain sugars on furanose templates.[12b] Now we have focused our attention into the 7-exo-trig or 7-exo-dig free radical cyclization of open-chain, conveniently functionalized, radical precursors derived from sugars. In fact, the 7-exo mode of cyclization has been scarcely documented in literature,[1d,13,14] and to the best of our knowledge, in the sugar domain, only two examples have been recently described in furanose[15a] or pyranose[15b] templates.

For the first experiments,[16] we have synthesized the acyclic radical precursors **1**−**6** (Figure 1) from readily available and known 2,3:5,6-bis-*O*-isopropylidene-D-mannose (**7**).[17] Following well-known or standard protocols, we obtained the selected radical precursors according to the synthetic sequences shown in Schemes 1−5.[18a]

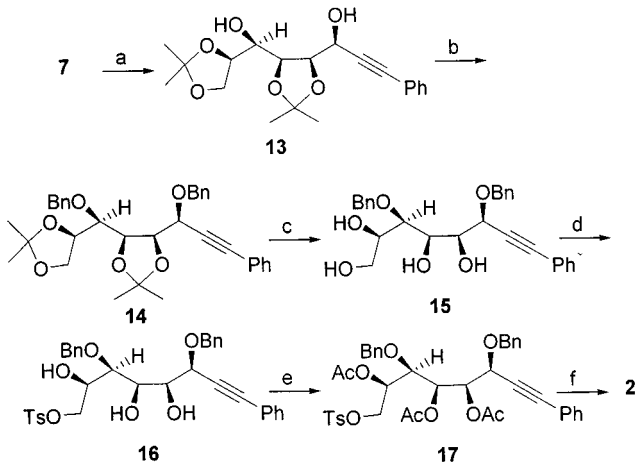
The addition of ethynylmagnesium bromide to lactol **7** is a known protocol that gives major anti product (**8**),[19]which could be easily manipulated (di-O-benzylation, acid hydrolysis, and selective tosylation of the primary hydroxyl group, followed by peracetylation and reaction with sodium iodide) via intermediates **9**−**12** for the synthesis of precursor **1** (Scheme 1). The addition of lithium phenylacetylide to the same lactol (**7**) gave major

Scheme 1. Synthesis of Precursor 1 for FR Cyclization[a]



[a] Reagents: (a) see ref 18; (b) NaH, BnBr, Bu_4NI, THF, 0 °C (92%); (c) 4/1 AcOH/H_2O, rt (82%); (d) ClTs, py, DMAP, 0 °C (85%); (e) Ac_2O, py, rt (85%); (f) NaI, acetone, reflux (78%).

Scheme 2. Synthesis of Precursor 2 for FR Cyclization[a]



[a] Reagents: (a) see ref 20a (lithium phenylacetylide, THF, 0 °C); (b) NaH, BnBr, Bu_4NI, THF, 0 °C (68%); (c) 4/1 AcOH/H_2O, rt (90%); (d) ClTs, py, DMAP, 0 °C (50%); (e) Ac_2O, py, rt (85%); (f) NaI, acetone, reflux (74%).

syn adduct **13** (Scheme 2);[20a] this is in agreement with the reported stereoselectivity for the reaction of lithium reagents with the same substrate.[20b] The same synthetic sequence as before for the synthesis of precursor **1** (see above) finally gave compound **2**. The addition of vinylmagnesium bromide to intermediate **7** gave major anti derivative **18** as described.[19d] This compound was also transformed into the known diol **19**,[17] which after selective tosylation at the primary hydroxyl group, followed by O-benzoylation and reaction with sodium iodide as usual, via compounds **20** and **21**, afforded precursor **3** (Scheme 3). Using also the alditol **18**,[19d] after perbenzoylation, partial acid hydrolysis, and bromination, we could

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(15) (a) Kim, G.; Kim, H. S. *Tetrahedron Lett.* **2000**, *41*, 225. (b) Leeuwenburgh, M. A.; Litjens, R. E. J. N.; Codée, J. D. C.; Overkleeft, H. S.; van der Marel, G. A.; van Boom, J. H. *Org. Lett.* **2000**, *2*, 1275.

(16) For a preliminary communication on this subject, see: Marco-Contelles, J.; de Opazo, E. *Tetrahedron Lett.* **2000**, *41*, 5341 (in this paper, the stereochemistry at carbons C-3 and C-4 in compounds **31** and **32** were drawn incorrectly).

(17) Van Boggelen, M. P.; van Dommelen, B. F. G. A.; Jiang, S.; Singh, G. *Tetrahedron* **1997**, *53*, 16897.

(18) (a) See Supporting Information. (b) See Experimental Section.

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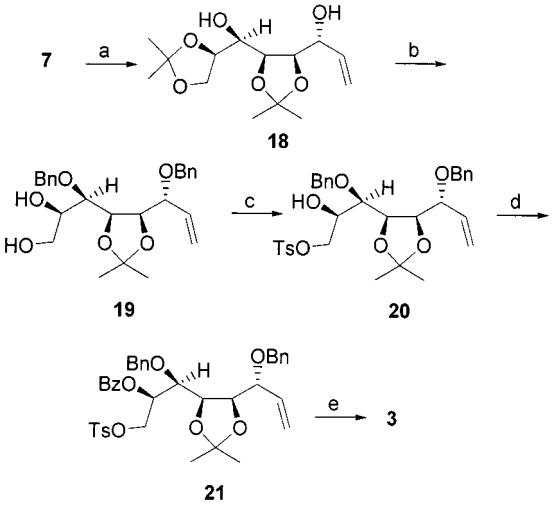
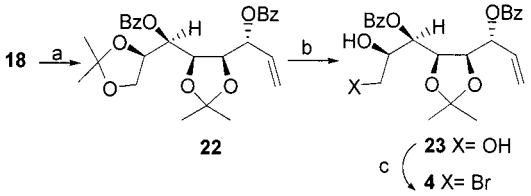
Scheme 3. Synthesis of Precursor 3 for FR Cyclization[a]



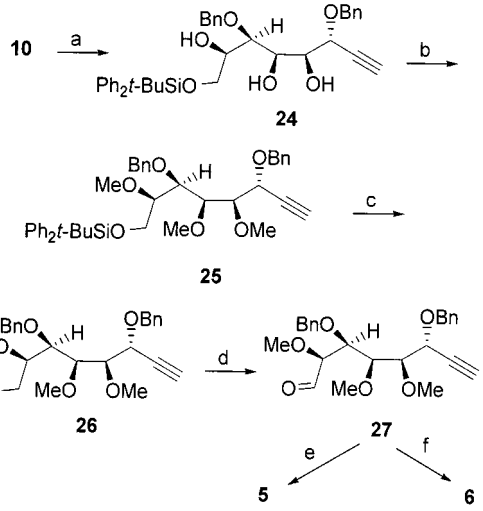
[a] Reagents: (a) see ref 19d; (b) see ref 17; (c) ClTs, py, 0°C (60%); (d) BzCl, py, DAMP, 0 °C (70%); (e) NaI, acetone, reflux [50% (80%)].

Scheme 4. Synthesis of Precursor 4 for FR Cyclization[a]



[a] Reagents: (a) ClBz, py, DMAP, 0 °C (65%); (b) 4/1 AcOH/H_2O, rt (60%); (c) CBr_4, Ph_3P, rt (60%).

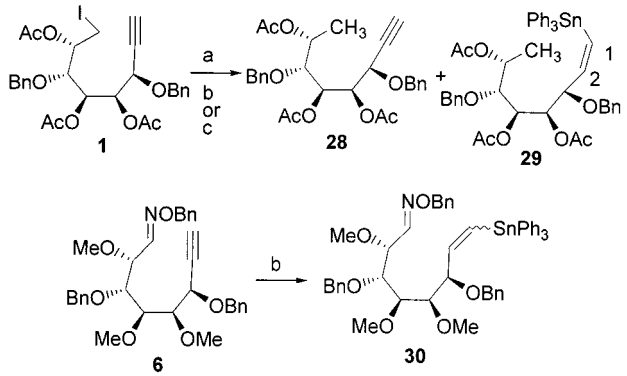
Scheme 5. Synthesis of Precursors 5 and 6 for FR Cyclization[a]



[a] Reagents: (a) *t*-$BuPh_2SiCl$, py, DMAP, 0 °C (88%); (b) IMe, NaH, BuNI, THF, 0 °C (60%); (c) Bu_4NF, THF, rt (75%); (d) PCC, CH_2Cl_2, NaOAc, molecular sieves, rt (65%); (e) $Ph_3P{=}CHCO_2Me$, CH_2Cl_2, rt [(*E*)-**5** (77%), (*Z*)-**5** (14%)]; (f) $BnONH_3Cl$, py, rt [9:1 (*E*)-**6**/(*Z*)-**6** (77%)].

prepare precursor **4** (Scheme 4). Finally, and from intermediate **10** (Scheme 1), after selective silylation at the primary hydroxyl group, permethylation, desilylation, and oxidation, via products **24**−**26**, the key and common aldehyde **27** was obtained in a very straightforward process. Subsequent Wittig reaction and standard oxime ether formation gave precursors **5** and **6**, respectively (Scheme 5). All these precursors showed excellent analytical and spectroscopic data.[18a]

Scheme 6. Free Radical Cyclization of Precursors 1 and 6[a]



[a] Reagents: (a) $[(CH_3)_3Si]_3SiH$, AIBN, toluene [**28**, 19% (48%); **29**, 0 %]; (b) Et_3B (2×), Ph_3SnH, −78 °C [**28**, 80%; **29**, 11 %; (*E*)-**30**, 40%; (*Z*)-**30**, 17%]; (c) Et_3B (2×), Ph_3SnH, rt (**28**, 47%; **29**, 16%).

From compound **1** and use of TTMS (tristrimethylsilylsilane) (or triphenyltin hydride) plus AIBN, with slow addition of reagents, an incomplete and complex reaction resulted, from which we could only isolate the reduced, uncyclized derivative **28** (Scheme 6). A more clear reaction was observed when AIBN was substituted by triethylborane. In this case, when the reaction was performed at −78 °C, in addition to product **28** (80%), we isolated the (*Z*)-stannylidene derivative **29** in 11% yield. When the reaction was carried out at room temperature, we obtained compounds **28** and **29** in 47 and 16% yields, respectively.[18a]

Radical precursor **2** afforded recovered starting material and a complex reaction mixture, which was not further elaborated. Very surprisingly, the same negative results were obtained with the isopropylidene-containing precursors **3** and **4**.

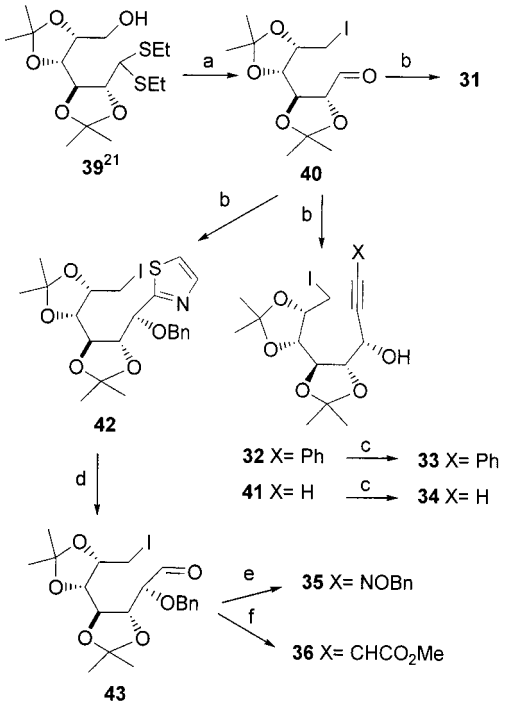
In view of these unsuccessful results, we turned our attention to precursors **5** and **6**, where more efficient radical traps were incorporated. Despite this, for compound **5**, a complex reaction occurred from which we could not reliably identify a reaction product. From oxime ether **6**, only the stannylated derivative **30** (isolated as a mixture of (*E*)- and (*Z*)-isomers) was obtained (Scheme 6).[18a] After these experiments, it was obvious that more conformationally restricted precursors were needed for a successful cyclization.

Then, we designed and prepared derivatives **31**−**38**[18a] (Figure 2). These products were obtained from D-glucose as a starting material via intermediates **39**[21] and **44**[22] (Schemes 7 and 8, respectively).

Iodination of compoud **39**[21] followed by desulfuration (HgO, $HgCl_2$, acetone, water) afforded aldehyde **40**[20] (Scheme 7). The preferential anti addition of vinylmagnesium bromide, phenylmagnesium bromide, or ethynylmagnesium bromide to this aldehyde gave major compounds **31**,[20a] **32**,[20a] and **41**,[20a] respectively. Oxidation of alcohols **32** and **41** with PCC and Dess−Martin's[23]

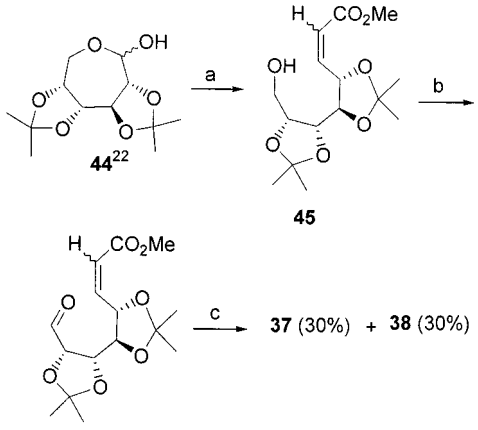
(21) Wong, M. Y. H.; Gray, G. R. *Carbohydr. Res.* **1980**, *80*, 87.
(22) Ng, C. J.; Stevens, J. D. *Methods Carbohydr. Chem.* **1968**, *7*, 7.
(23) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.

Scheme 7. Synthesis of the Radical Precursors 31−36[a]



[a] Reagents: (a) see ref 20a; (b) see ref 20a; (c) PCC, NaOAc, CH_2Cl_2, molecular sieves, rt [from **32** to **33**: 56% (63%)], Dess−Martin [from **41** to **34**: 60% (66%)]; (d) see ref 20c; (e) $BnONH_3Cl$, py, rt (*E*, 56%; *E* + *Z* (1:1), 33%; total, 89%); (f) $Ph_3P{=}CHCO_2Me$, CH_2Cl_2, rt (*E*, 73%; *Z*, 8%; total, 81%).

Scheme 8. Synthesis of the Radical Precursors 37 and 38[a]



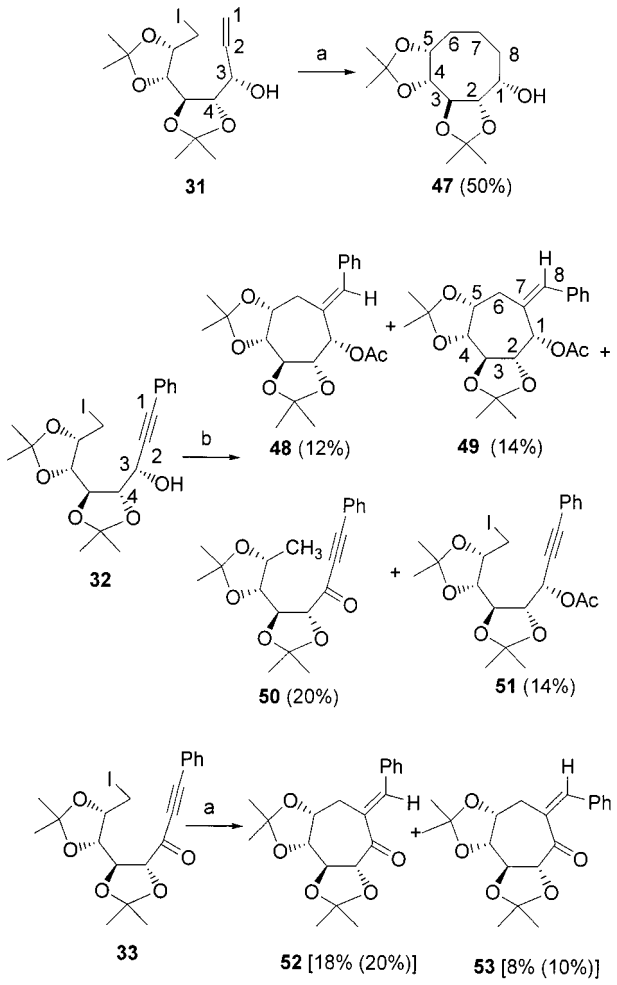
[a] Reagents: (a) $Ph_3P{=}CHCO_2Me$, CH_2Cl_2, rt (4/1 *Z*/*E*) (86%); (b) Dess−Martin [(*Z*)-**45** (56%); (*E*)-**45** + (*Z*)-**45** (6/4, 30%); (c) ethynylmagnesium bromide, THF, 0 °C [from (*Z*)-**45**].

method gave the ketones **33** and **34**, respectively. Dondoni's one-carbon homologation[24] on aldehyde **40**[20a] afforded the expected aldehyde **43**[20c] via intermediate **42**.[20a] Final oxime ether formation or Wittig reaction on anti aldehyde **43** gave precursor **35** and the α,β-unsaturated ester **36** (Scheme 7).

Compound **44**[22] afforded a mixture of (*E*)- and (*Z*)-isomers of the α,β-unsaturated esters **45**, which without separation, were submitted together to oxidation to give

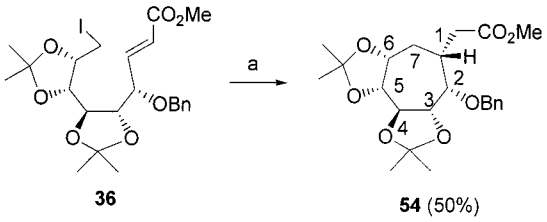
(24) Dondoni, A. *Synthesis* **1998**, 1681.

Scheme 9. Free Radical Cyclization of Precursors 36[a]



[a] Reagents: (a) AIBN, Bu_3SnH, toluene, 80 °C.

Scheme 10. Free Radical Cyclization of Precursors 37 and 38[a]

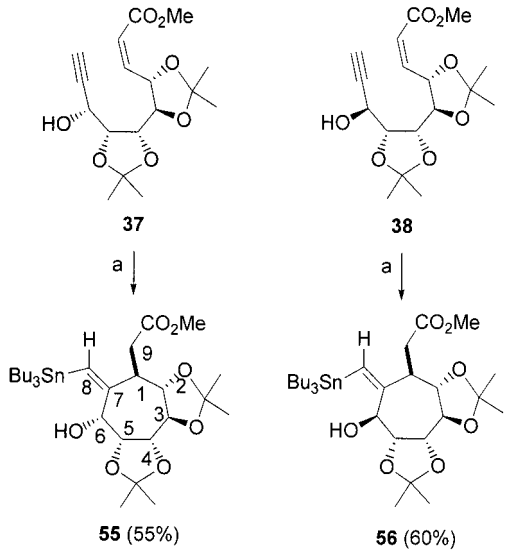


[a] Reagents: (a) AIBN, Bu_3SnH, toluene, 80 °C, slow addition, 5 h.

aldehyde **46**; then, the major (*Z*)-**46** isomer was reacted with ethynylmagnesium bromide to give an almost equimolecular mixture of the anti and syn isomers, **37** and **38**, respectively. The configuration at the newly formed stereocenter in these compounds could not be determined at this point, but it was finally established in the resulting carbocycles after free radical cyclization (see below). All these precursors showed excellent analytical and spectroscopic data.[18a]

The results of the cyclization of these substrates are shown in Schemes 9−11. In the usual free radical cyclization conditions mediated by tributyltin hydride, compound **31** afforded compound **47** in a reasonable

Scheme 11. Transition State for the Free Radical Cyclization of Precursor 36



chemical yield (50%) (Scheme 9),[25] whose NMR and analytical data clearly confirmed that this material was the cyclooctane derivative **47**[18b] and, consequently, the anti stereochemistry at carbons C-3 and C-4 in precursor **31**. Briefly, product **47** should be the result of the FR cyclization of a primary radical into the double bond in the endo mode. The formation of this 8-endo-trig[26] product was not unexpected in view of the theoretical and experimental results described by Beckwith and Schiesser.[27] This is indeed a rare example of a FR cyclization reaction leading to a cyclooctane derivative from carbohydrates[26b] and confirmed our expectations about the critical importance of the two isopropylidene groups for directing and promoting effective ring annulation.[28] However, the results were not satisfactory regarding our decided interest in the preparation of seven-membered ring systems.

Then, we reasoned that in order to prevent the 8-endo mode of cyclization, the incorporation of a substituent at the terminal position, by simple steric interactions, would prevent this chemical path, favoring the alternate 7-exo mode of cyclization. To implement this concept, we tested precursor **32**, with a phenyl group located at the terminal acetylene carbon. FR cyclization in the usual experimental conditions followed by chromatography and acetylation afforded four products (**48**−**51**) (Scheme 9). Compound **51** (14%) was the acetylated, unreacted starting material; product **50** (20%) was the reduced, uncyclized material oxidized at C-3,[29] and finally, compounds **48** (12%) and **49** (14%) were the expected 7-exo-dig resulting molecules. The structures of these carbocycles were clearly confirmed by their NMR and analytical data[18a] and consequently confirmed the anti stereochemistry at carbons C-3 and C-4 in precursor **32**.

Despite the complex cyclization reaction from precursor **32**, these results prove that the 7-exo-dig cyclization of an acyclic, polyfunctionalized precursor is possible, affording low yields of the desired products. To expand and improve these results, precursor **33** was submitted to cyclization, giving compounds **52** and **53**, albeit in low overall yield [26% (30%)] (Scheme 9).[18a]

Very interestingly, the FR cyclization of precursor **34** (Figure 2) afforded a complex reaction mixture. Unfortunately, we were unable to isolate and reliably identify a reaction product.

To control the regiochemistry and the efficiency of the carbocyclization reaction, more friendly radical acceptors such as the oxime ether (in precursor **35**) and the α,*β*-unsaturated ester (in precursor **36**) were tested next.

Very surprisingly, the cyclization of compound (*E*)-**35** (Figure 2) afforded a complex reaction mixture from which we could isolate some derivatives in a poor chemical balance whose structures could not be established. This is in sharp contrast to the reported moderate to good yields in our previously documented reaction of 6-exo-trig free radical of related precursors with oxime ethers as radical traps.[30]

Not unexpectedly the free radical cyclization compound (*E*)-**36** was more satisfactory, and again, only one isomer (**54**) (Scheme 10), in 50% chemical yield, was detected and isolated. The absolute configuration at the newly formed stereocenter at C-1 was assigned as *R* on the basis of the strong NOE effect between H-1 and H-2 and the full and detailed spectroscopic analysis.[18b]

The success of the α,*β*-unsaturated ester as a radical acceptor moved us to submit radical precursors **37** and **38** to cyclization (Scheme 11). FR cyclization of precursor **37** afforded carbocycle **55** in a reasonable yield (55%). The same synthetic protocol, from compound **38**, afforded carbocycle **56** in 60% yield. The analytical and spectroscopic data showed that, in both cases (**55** and **56**), only one stereoisomer at the newly formed stereocenter and at the exo double bond was present after FR cyclization. We could also demonstrate that the stereochemistry at the newly formed stereocenter (C-1) was *R* in both cases and the stereochemistry was *Z* at the exo double bond.[18b] In agreement with this, in the ^{1}H NMR spectra of compound **55**, we could detect NOE effects between H-8 and H-9 (securing the *Z* double-bond geometry), H-1 and H-9′, H-1 and H-3 (no significant NOE effect could be detected between protons H-1 and H-2 or H-9) (establishing *R* as the configuration at C-1), H-5 and H-6, and H-3 and O*H* (determining the anti stereochemistry in precursor **37**). As expected, in the ^{1}H NMR spectra of compound **56**, we could detect NOE effects between H-8 and H-9

(25) In this reaction, we also detected traces of a mixture of compounds (one of them possibly the reduced, uncyclized derivative of product **31**), which we were unable to separate, analyze, and characterize.

(26) For free radical 8-endo ring closures, see: (a) Manzoni, L.; Belvisi, L.; Scolastico, C. *Synlett* **2000**, 1287. (b) Chattopadhyay, P.; Mukherjee, M.; Ghosh, S. *Chem. Commun.* **1997**, 2139. (c) Gibson, S. E.; Guillo, N.; Tozer, M. J. *Chem. Commun.* **1997**, 637. (d) Hutchinson, J. H.; Dayhard, T. S.; Gillard, J. W. *Tetrahedron Lett.* **1991**, *32*, 573 (in this case, the ratio 7-exo ≪ 8-endo has been justified by the relatively long Si−O bond and the large O−Si−O bond angle). (e) Galatsis, O.; Millan, S. D.; Faber, T. *J. Org. Chem.* **1993**, *58*, 1215. (f) Ghosh, K.; Ghosh, A. K.; Ghatak, R. *J. Chem. Soc., Chem. Commun.* **1994**, 629.

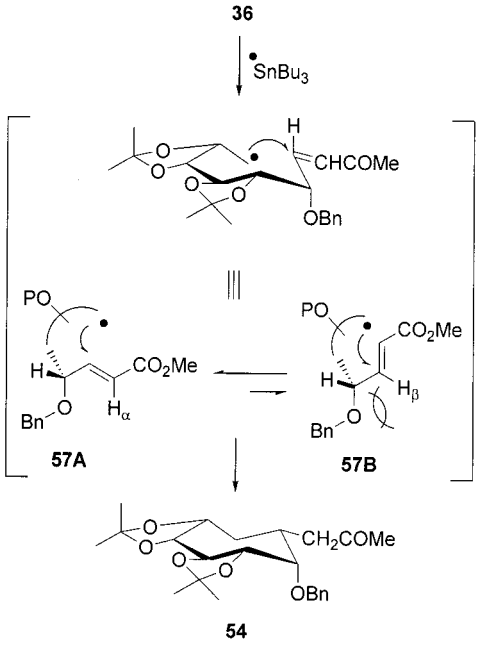
(27) Beckwith, A. L. J.; Schiesser, C. H. *Tetrahedron* **1985**, *41*, 3925.

(28) The importance of preexisting heterocycles in selected positions and orientations on acyclic precursors for successful carbocyclization processes has been previously demostrated in our laboratory: (a) Marco-Contelles, J.; Ruiz, P.; Martínez, L.; Martínez-Grau, A. *Tetrahedron* **1993**, *49*, 6669. (b) Marco-Contelles, J.; Bernabé, M.; Ayala, D.; Sánchez, B. *J. Org. Chem.* **1994**, *59*, 1234. For an application of the results reported in ref 28b, see: (c) Gómez, A. M.; Danelón, G. O.; Valverde, S.; López, J. C. *J. Org. Chem.* **1998**, *63*, 9626 (corrigendum: *J. Org. Chem.* **1999**, *64*, 7280).

(29) The formation of derivative **50** from compound **32** was unexpected and can be possibly attributed to the tin-mediated oxidation of the propargylic alcohol in the reaction conditions.

(30) Marco-Contelles, J.; Pozuelo, C.; Jimeno, M. L.; Martínez, L.; Martínez-Grau, A. *J. Org. Chem.* **1992**, *57*, 2625.

Scheme 12. Transition state for the free radical cyclization of precursor 36 Precursors 31−33[a]



(securing the *Z* double-bond geometry), H-1 and H-9′, and H-2 and H-4 or H-6, and no NOE effect was detected between H-1 and H-2 (establishing *R* as the configuration at C-1). A very significant vicinal coupling constant (J = 7.9 Hz between protons H-5 and H-6) was analyzed for a trans arrangement of these protons, in agreement with the syn stereochemistry at carbons C-7 and C-8 in precursor **38**.

Scheme 12 shows a possible rationale for the formation of the major isomer during the free radical cyclization of precursor (*E*)-**36**. According to Beckwith's model,[27] in the transition state leading to carbocycle **55**, the 7-exo-trig free cyclization of the radical species from precursor **36**, conformers **57A** and **57B** should be operative. In fact, the chairlike conformer **57A**, with most of the substituents in a preferred pseudoequatorial orientation, with the *O*-benzyloxy group at C-3 in an anti orientation regarding the *β*-vinyl proton in the double bond, and the radical trap in a pseudoequatorial orientation, should be more stable and afford the experimentally observed carbocycle with the substituent at the newly formed stereocenter located in the α-orientation. Conversely, conformer **57B** should be more disfavored in the equilibrium of conformers as the radical trap is in a pseudoaxial orientation in a more sterically demanding situation. For precursors (*Z*)-**37** and (*Z*)-**38**, tributyltin radical attack on the acetylene moiety gives a vinyl radical species **58A** with the radical acceptor in a pseudoequatorial orientation (compare with the less favored conformer **58B**) (Scheme 13), which should afford, after cyclization, carbocycles **55** and **56** with the same absolute configuration at the newly formed stereocenters (C-1), regardless of the absolute configuration at the propargylic carbon in the precursor. The formation of only one (*Z*)-stannylidene derivative has been documented in literature and is consistent with a reversible attack of the tributyltin radical to give major cis vinyl radical species **A**.[31]

(31) Nozaki, K.; Oshima, K.; Utimoto, K. *J. Am. Chem. Soc.* **1987**, *109*, 2547.

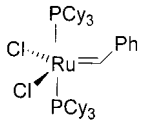
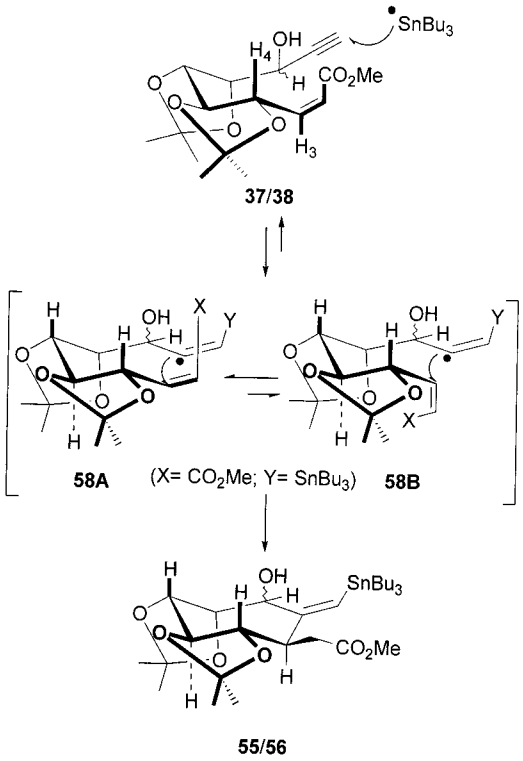


Figure 5. Grubbs' catalyst.

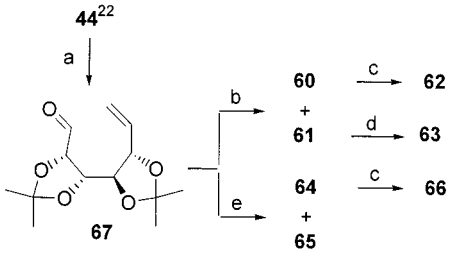
Scheme 13. Transition State for the Free Radical Cyclization of precursors 37 and 38



In summary, we have analyzed for the first time the 7-exo free radical cyclization of acyclic radical precursors derived from sugars for the synthesis of enantiomerically pure, highly functionalized, medium-sized rings. We conclude that the FR cyclization strategy is extremely sensitive to the conformational freedom of the radical species in the transition state. Apparently, the use of two isopropylidene groups blocking four of the total present hydroxyl groups and a good radical acceptor are mandatory conditions for a successful ring formation. In these conditions, we have obtained highly stereoselective reactions, with strong stereochemical control, leading to almost diastereomerically pure molecules at the newly formed stereocenters.

B. Ring-Closing Metathesis Approach. We have also investigated the synthetic possibilities of the intramolecular ring-closing metathesis reaction.[8] This is an increasingly popular method for the preparation of carbocycles that has been largely used in sugar templates for the synthesis of unsaturated cyclopentitols and conduritols.[32] Particularly attractive in this methodology are (a) the mild reaction conditions, (b) the cheap and easy manipulation of the Grubbs' catalyst (**59**, Figure 5), and (c) a simple experimental protocol that usually affords high chemical yields. Very recently, we reported the first synthesis of highly functionalized, medium-sized rings from sugar templates using this strategy.[33,b]

Scheme 14. Synthesis of Precursors 60−66[a]

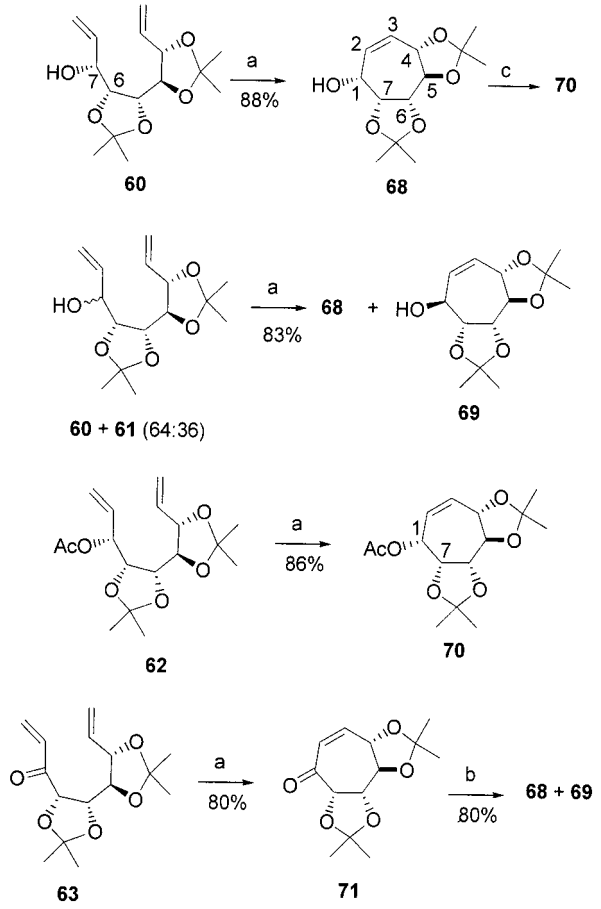


[a] Reagents: (a) (i) $Ph_3P{=}CH_2$, THF, −20 °C (84%), (ii) DMSO, DCC, CF_3CO_2H, rt, toluene (73%); (b) vinylmagnesium bromide, THF, 0 °C (**60**/**61**, 7/3, 73%); (c) Ac_2O, py, rt (from **60** to **62**, 90%); (from **64** to **66**, 80%); (d) Dess−Martin (60%); (e) allylmagnesium bromide, THF, 0 °C (**64**/**65**, 9/1, 80%).

In this context, we describe here the synthesis and RCM of the precursors **60**−**66** (Figure 3) for the preparation of unsaturated cyclohepta- and cyclooctapolyols, respectively. These cycloalkanols are ideal intermediates for the synthesis of enantiomerically pure polyhydroxylated heptanes (or octanes), very well-known precursors for the synthesis of glycosidase inhibitors,[34] antitumorals,[35] or *C*-glycosides.[36]

The synthesis of the precursors **60**−**66** has been achieved from compound **67** as shown in Scheme 14 from lactol **44**[22] (Scheme 8), after Wittig reaction and oxidation.[18a] Vinylmagnesium bromide addition to aldehyde **67** gave two products (**60** and **61**) in 73% yield, the major being the anti isomer **60**, which showed a lower vicinal coupling constant ($J_{6,7}$ = 0 Hz) compared to the value observed in product **61** ($J_{6,7}$ = 4.0 Hz). This tentative assignment was confirmed after their transformation into "cyclic" derivatives (see below). Intermediates **60** and **61** were used to prepare the *O*-acetyl (**62**) derivative and the olefin-tethered, α,*β*-unsaturated ketone (**63**). Precursors (**64**−**66**) have also been prepared from the same aldehyde (**67**) as shown in Scheme 14.[18a] In this case, we used the allylmagnesium bromide reagent for the chain sugar elongation and obtained compounds **64**/**65** in a better anti/syn ratio (8:1, respectively) and in good combined chemical yield (80%). As in the precedent case, the anti/syn assignment was confirmed after the carbocyclization step (see below).

Scheme 15. RCM Reaction of Precursors 60−63[a]



[a] Reagents: (a) Grubbs' reagent (10%), methylene chloride, rt; (b) DIBALH, toluene, −78 °C [**68** (70%) + **69** (10%)]; (c) Ac_2O, py, rt (96%).

With these products in hand, we tested the RCM reaction in the typical experimental conditions (rt, methylene chloride as the solvent, 0.02 M) using Grubbs' catalyst (10%). The RCM of the diastereomerically pure anti precursor **60** gave the expected cycloheptitol (**68**) in 88% yield (Scheme 15). The RCM of an inseparable mixture of the anti/syn precursors **60**/**61** afforded the mixture of cycloheptitols **68** and **69** in 83% total yield, which were easily separated by chromatography, allowing us to obtain pure carbocycle **69**. The new compounds showed good analytical and spectroscopic data.[18b] Particularly significant in compound **68** were the trans 1,2-diaxial (8.7 Hz) vicinal coupling constant for protons H-5/H-6 and H-5/H-4, which suggests a compound in a preferred chairlike conformation,[4d] and the vicinal coupling constant for H-1/H-7 (2.6 Hz), a value that places these protons in a cis arrangement, coherent with the assigned anti stereochemistry at carbons C-7/C-6 in precursor **60**. Regarding compound **69**, the epimer at C1, the observed, typical trans 1,2-diaxial vicinal coupling constants ($J_{4,5}$ = 9.6 Hz, $J_{5,6}$ = 8.3 Hz) indicate that hydroxyl groups at C1 and C5 are located in a pseudoequatorial orientation, suggesting a preferred boatlike conformation. In agreement with data obtained in com-

(32) For reviews on the metathesis reaction on sugar templates, see: (a) Roy, R.; Das, S. K. *Chem. Commun.* **2000**, 519. (b) Jorgensen, M.; Hadwiger, P.; Madsen, R.; Stütz, A.; Wrodnigg, T. M. *Curr. Org. Chem.* **2000**, *4*, 565. For selected papers on this subject, see: (c) Ovaa, H.; Codée, J. D. C.; Lastdrager, B.; Overkleeft, H. S.; van der Marel, G. A.; van Boom, J. H. *Tetrahedron Lett.* **1998**, *39*, 7987. (d) Ziegler, F. E.; Wang, Y. *J. Org. Chem.* **1998**, *63*, 7920. (e) Kornienko, A.; d'Alarca, M. *Tetrahedron: Asymmetry* **1999**, *10*, 827. (f) Sellier, O.; Van de Weghe, P.; Le Nouen, D.; Strehler, C.; Eustache, J. *Tetrahedron Lett.* **1999**, *40*, 853. (g) Kapferer, P.; Sarabia, F.; Vasella, A. *Helv. Chim. Acta* **1999**, *82*, 645. (h) Delgado, M.; Martín, J. D. *J. Org. Chem.* **1999**, *64*, 4798. (i) Hyldtoft, L.; Poulsen, C. S.; Madsen, R. *J. Am. Chem. Soc.* **2000**, *122*, 8444. (j) Dirat, O.; Vidal, T.; Langlois, Y. *Tetrahedron Lett.* **1999**, *40*, 4801. (k) Seepersaud, M.; Al-Abed, Y. *Org. Lett.* **1999**, *1*, 1463. (l) Lee, W.-W.; Chang, S. *Tetrahedron: Asymmetry* **1999**, *10*, 4473. (m) Gallos, J. K.; Koftis, T. V.; Sarli, V. C.; Litinas, K. E. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3075. (n) Callam, C. S.; Lowary, T. L. *Org. Lett.* **2000**, *2*, 167. (o) Ackermann, L.; El Tom, D.; Fürstner, A. *Tetrahedron* **2000**, *56*, 2195. (p) Holt, D. J.; Barker, W. D.; Jenkins, P. R.; Davies, D. L.; Garrat, S.; Fawcett, J.; Russell, D. R. Ghosh, S. *Angew. Chem., Int. Ed.* **1998**, *37*, 3298.

(33) (a) Marco-Contelles, J.; de Opazo, E. *J. Org. Chem.* **2000**, *65*, 5416. (b) Marco-Contelles, J.; de Opazo, E. *Tetrahedron Lett.* **2000**, *41*, 2439. For other recent papers on the synthesis of cyclohept- and cyclooctenols via ring-closing metathesis reactions on sugar precursors, see: (c) Hanna, I.; Ricard, L. *Org. Lett.* **2000**, *2*, 2651. (d) Boyer, F.-D.; Hanna, I.; Nolan, S. P. *J. Org. Chem.* **2001**, *66*, 4094. (e) McNulty, J.; Grunner, V.; Mao, J. *Tetrahedron Lett.* **2001**, *42*, 5609.

(34) Aoyagi, S.; Fujimaki, S.; Kibayashi, C. *J. Chem. Soc., Chem. Commun.* **1990**, 1457.

(35) Miller, S. A.; Chamberlain, A. R. *J. Am. Chem. Soc.* **1990**, *112*, 8100.

(36) Postema, M. H. D. *C-Glycoside Synthesis*; CRC Press: London, 1995.

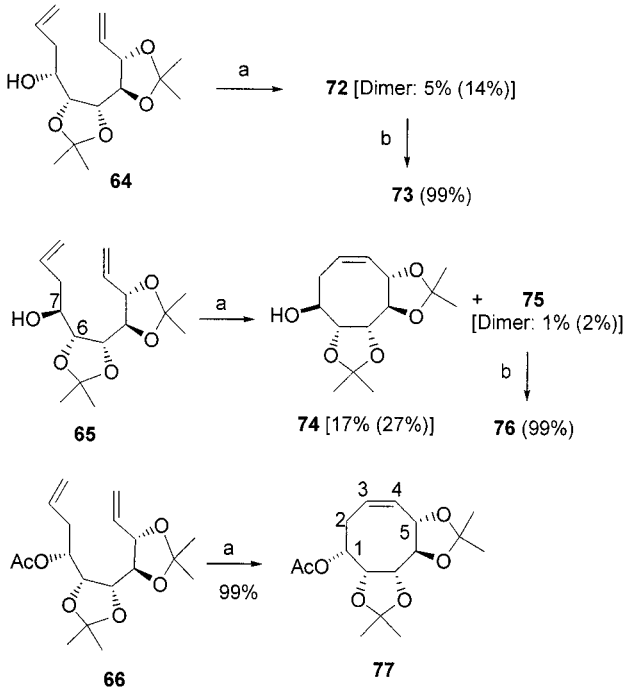
pound **68** for the vicinal coupling constant for protons H-1/H-7, here this value is higher ($J_{1,7}$ = 7.9 Hz), confirming the syn stereochemistry at carbons C-7 and C-6 in precursor **61**. Note also that both precursors **60** and **61** were transformed very efficiently and in a very quick reaction, regardless of the absolute configuration at C-7. As shown also by the reactivity of the acetyl derivative **62** (Scheme 15), the effect of the protecting group was also negligible, as a good chemical yield of product **70** (86%) was obtained.

The RCM of the α,β-unsaturated ketone **63** is noteworthy as the reaction proceeded without any additive (Lewis acid or titanium complex) to give cycloheptenone **71** in 80% yield. The spectroscopic analysis of this sample showed the typical pattern for a cyclohept-2-en-1-one.[18b] Although it is well-known that electron-deficient alkenes are poor precursors for RCM reactions,[37] some examples involving mainly acrylates have been described, these reactions requiring the presence of Lewis acids or titanium complexes.[38]In fact, olefin-tethered α,β-unsaturated ketones have been rarely tested in the RCM.[39] In a recent example described by Paquette,[39a] the use of Grubbs' catalyst in large amounts and for an extended period of time gave only a modest yield of the annulated product; to improve the chemical yield, the new *N*,*N*′-bis(mesityl)-imidazol-2-ylidene Ru−carbene complex had to be used.[40] The reduction of ketone **71** with DIBALH, at low temperatures, afforded a mixture of the 1,2-reduced derivatives **68** (major) and **69** (minor), identical in their spectroscopic and physical data to similar samples obtained in RCM processes (see above), in good yield with moderate diastereoselectivity (7:1). This result is coherent with similar observations reported previously.[4j,m]

To summarize, the RCM metathesis of the chiral, fully polyhydroxylated nonadienes (**69**−**72**) proceeds efficiently to give the desired and expected unsaturated cycloheptitols in a synthetic protocol that compares very well with other described approaches.[4]

As regards the RCM reaction of the analogous chiral, fully polyhydroxylated 1,9-decadienes for the synthesis of the unsaturated cyclooctanols, the first experiments were not very encouraging. Following the general method for the RCM reaction, precursor **64** afforded a dimer **72** (characterized as its peracetate **73**), as the only isolated compound, in very poor yield (5%) (Scheme 16).[18a] With the epimer at C7, precursor **65**, the reaction was not very successful again, as the desired cyclooctane **74** was obtained in 17% yield (27% taking into account the recovered starting material) along with dimer **75** [1% yield (2% taking into account the recovered starting material)], characterized as its peracetate **76**.[18a] As expected, in the ^{1}H NMR spectrum, we could analyze a vicinal coupling constant, $J_{1,8}$ = 9.5 Hz, a value that confirmed the syn stereochemistry at carbons C-7 and C-6 in precursor **74**. These results are coherent with known difficulties reported for the synthesis of this medium-sized ring.[2] However, and very interestingly, in the usual conditions, the major anti acetylated precursor **66** afforded the cyclooctane **77** in an almost quantitative yield.

Scheme 16. RCM Reaction of Precursors 64−66[a]



[a] Reagents: (a) Grubbs' reagent (10%), methylene chloride (0.02 M), 30 H, rt; (b) Ac_2O, py, rt.

These examples show the importance of the absolute configuration at the stereocenters at homoallylic positions and the type of functional or O-protecting groups at these positions for a successful RCM reaction. This is a very well-known fact described previously by us[33a,b] and others.[33c,d,41] In summary, the ring-closing metathesis reaction, using commercially available Grubbs' catalyst, on selected sugar-like precursors has afforded variable yields of the expected unsaturated cycloheptane or cyclocatane derivatives. Cycloheptitols have been obtained in good yields, regardless of the absolute configuration at the different stereocenters and the nature of the functional groups at allylic positions. Conversely, in the RCM for the cyclooctane synthesis, we have observed that these factors critically determine the chemical yield and the efficiency of the ring-closing reaction.

C. Formal Total Synthesis of (+)-Calystegine B_2. To investigate a practical synthetic application of the RCM reaction in the synthesis of natural products containing medium-sized rings, we considered the synthesis of (+)-calystegine B_2[11] (Figure 4), a very well-known glycosidase inhibitor[42] that selectively inhibits the rat liver β-glucosidase and the human lysosomal α-galactosidase A (α-Gal A) with an IC_{50} value of 30 μM. Several syntheses of this molecule have been reported.[43]

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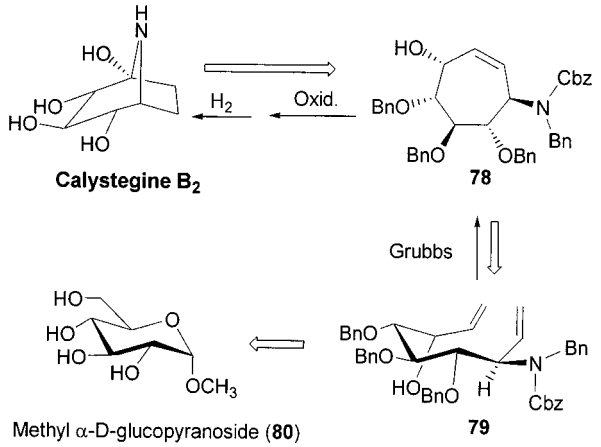
Scheme 17. Ring-Closing Metathesis Approach for Calystegine B_2

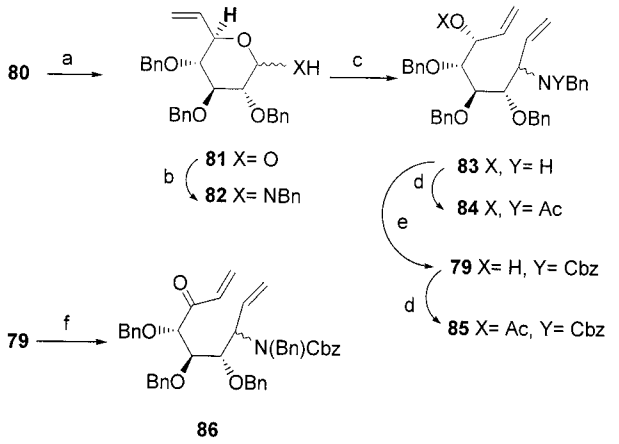


Our retrosynthetic analysis is shown in Scheme 17. The key compound **78**, with the correct absolute configuration at the different stereocenters, is conveniently functionalized for the synthesis of the target molecule after oxidation and hydrogenation. In turn, it is expected that this product should result after metathesis reaction of intermediate **79**. The choice of methyl-α-D-glucopyranoside **80** as a starting material was the obvious issue. Then, the synthetic strategy was relayed on by the two-carbon-chain elongation in a D-glucose derivative at C-1 (possibly via vinylmagnesium addition on a suitable glucosylamine intermediate) and the one-carbon homologation at C-6 (possibly via Wittig reaction), the key point being the control of the desired configuration at the carbon incorporating the nitrogen substituent.

To investigate the viability of this strategy, we prepared compound **81** (Scheme 18) as described.[2g,h] Reaction of this lactol with benzylamine in methylene chloride gave an inseparable mixture of anomers **82** in 70% yield. Vinylmagnesium addition to this mixture afforded the expected compound **83** as an inseparable mixture of isomers (1.5:1), the major isomer presumably being the syn adduct, according to the reported stereoselective syn addition of allylmagnesium bromide to related substrates described by Nicotra et al.[44] With this satisfactory result, which enabled us to attack the synthesis of natural (+)-calystegine B_2, we investigated the RCM on precursor **83** or on the differently functionalized compounds (**79**, **84**−**86**) prepared using standard methodology (Scheme 18).[18a]

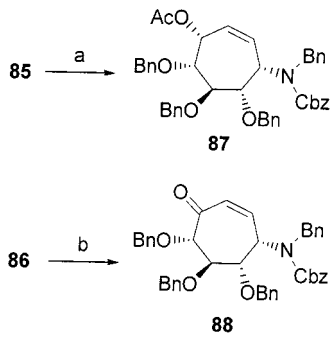
In our standard conditions (see above), using Grubbs' catalyst, unfortunately in no case was a clear and efficient carbocyclization observed. Only in the case of the 3-*O*-acetyl *N*-(benzyl)carbamate **85** and the olefin-tethered α,β-unsaturated ketone **86** did we detect metathesis products **87** and **88**, respectively, in low yields (Scheme 19). These molecules showed good analytical and spectroscopic data.[18a] Very interestingly, clear NOE effects between the corresponding protons, allowed us to assign the anti stereochemical arrangement at carbons C-6 and C-7 in product **87** and at carbons C-4 and C-5 in compound **88**.

Scheme 18. Synthesis of the RCM Precursors 79 and 83−86[a]



[a] Reagents: (a) see ref 2g,h; (b) $BnNH_2$, CH_2Cl_2, 5 days, rt (70%), (c) CH_2=$CHMgBr$, Et_2O, rt (65%); (d) Ac_2O, py (from **83** to **84**, 73%; from **79** to **85**, 93%); (e) ClCbz, $NaHCO_3$ (88%); (f) Dess−Martin (80%).

Scheme 19. RCM of Precursors 85 and 86[a]



[a] Reagents: (a) Grubbs' (10%), CH_2Cl_2, rt, 3 days [8% (40%)]; (b) Grubbs (10%), CH_2Cl_2, rt, $Ti(OPr)_4$, [4% (6%)].

At this point of the project, we reasoned that the steric hindrance at the allylic carbon containing the protected nitrogen atom in our precursors would probably prevent the carbocyclization reaction. To test this hypothesis we designed the new precursor **92** (Scheme 20) in which one of the terminal double bonds has a methylene group in the allylic position, free of steric constraints. It was expected that this 1,8-nonadiene should give a convenient carbocyclic derivative (**93**) for further transformation into the desired target molecule. The synthesis of compound **92** has been achieved as shown in Scheme 20, starting from compound **80** via the known intermediate **89**.[45] The reaction of this lactol with benzylamine followed by treatment with allylmagnesium bromide gave compound **91** in good yield as an inseparable mixture of syn/anti isomers in a 3:1 ratio, the syn derivative being tentatively assigned as the major isomer.[44] Several synthetic alternatives were possible in order to transform this 1,2-diol into the desired olefin; we chose the most simple protocol described by Garegg for this transformation.[46] Not un-

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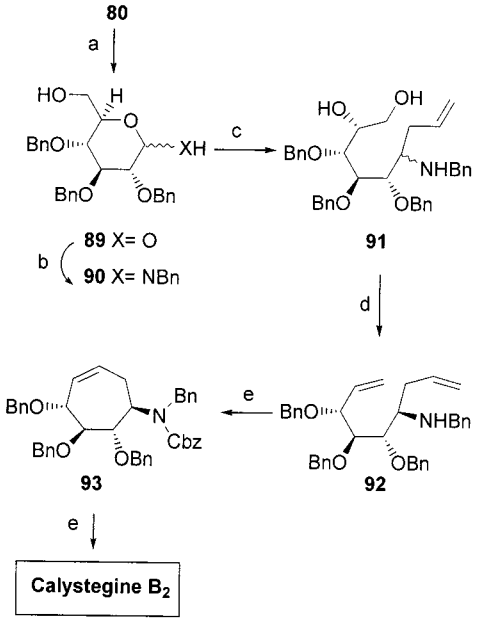
Scheme 20. Synthesis of Product 92 (Formal Total Synthesis of Calystegine B_2)[a]



[a] Reagents: (a) see ref 45; (b) $BnNH_2$, toluene, 80 °C, 2 h (85%); (c) $CH_2{=}CHCH_2MgBr$, Et_2O, rt, (88%); (d) I_2, Ph_3P, imidazole (15%); (e) see ref 43a,b.

expectedly, compound **92** was isolated in 15% yield. This compound showed excellent analytical and spectroscopic data.[18a] When we were trying other alternatives in order to improve this yield, we were aware of the synthesis of (+)-calystegine B_2 via intermediate **92**, which after carbamate protection and RCM efficiently gave product **93** (Scheme 20) using Grubbs' catalyst.[43a] This fact confirmed our hypothesis about the critical (and negative) influence of the steric effects on precursors **79** and **83**−**86**.

From a practical point of view, and according to the literature,[43a] the synthesis of compound **92** constitutes a formal total synthesis of (+)-calystegine B_2. We are now investigating other alternatives for the synthesis of this and other members of this family of compounds. These results will be reported in due course.

Experimental Section

General Methods. Reactions were monitored by TLC using precoated silica gel aluminum plates containing a fluorescent indicator. Detection was performed by UV (254 nm) followed by charring with sulfuric−acetic acid spray, 1% aqueous potassium permanganate solution, or 0.5% phosphomolybdic acid in 95% EtOH. Anhydrous Na_2SO_4 was used to dry organic solutions during workups, and the removal of solvents was carried out under vacuum with a rotary evaporator. Flash column chromatography was performed using silica gel 60 (230−400 mesh) and hexane/ethyl acetate mixtures as the eluent unless otherwise stated. ^{1}H NMR spectra were recorded using tetramethylsilane as the internal standard. Values with an asterisk can be interchanged.

General Method for Free Radical Cyclization. To a solution of the precursor in toluene (0.02 M) previously deoxygenated by bubbling argon into the solution was slowly added a solution of AIBN (0.5 equiv) and Bu_3SnH (2 equiv) via syringe pump in the indicated time under argon and at 80 °C (bath temperature). After complete reaction, the solvent was removed and the residue dissolved in a 1:1 mixture of ethyl ether/15% aqueous solution of KF and vigorously stirred overnight. Then, the organic layer was separated, dried, filtered, and evaporated, and the residue was submitted to chromatography (eluting with hexane/ethyl acetate mixtures) to give the product.

General Method for the Ring-Closing Metathesis Reaction. To a solution of the precursor in dry methylene chloride (0.02 M) was added the Grubbs' catalyst (10% mol). The mixture was stirred at room temperature for the indicated time in each case. When the reaction was complete, the solvent was removed and the residue was submitted to chromatography (eluting with hexane/ethyl acetate mixtures) to give the carbocyclic compound.

Free Radical Cyclization of Compound 31. Precursor **31** (85.3 mg, 0.21 mmol) was treated according to the General Method for FR Cyclization to give compound[25] **47** (30 mg, 50%) after chromatography (93/7 hexane/ethyl acetate). **47**: mp 65−67 °C; $[\alpha]_D^{25}$ +5 (*c* 0.13, $CHCl_3$); IR (film) ν 3600−3200 (OH), 3000, 2960, 1570, 1350, 1250, 1100 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.30 (t, $J_{2,3} = J_{3,4} = 8.4$ Hz, 1 H, H-3), 4.19−4.12 (m, 3 H, H-1, H-4, H-5), 3.71 (dd, $J_{2,3} = 8.4$ Hz, $J_{1,2} = 2.3$ Hz, 1 H, H-2), 2.32 (br t, $J = 7.4$ Hz, 1 H, OH), 2.03−1.82 (m, 4 H, 2 H-6, 2 H-8), 1.68−1.50 (m, 2 H, 2 H-7), 1.47, 1.46, 1.44, 1.36 [4 s, 2 × $OC(CH_3)_2O$]; ^{13}C NMR (75 MHz, $CDCl_3$) δ 108.4, 108.3 [2 × $OC(CH_3)_2O$], 81.4 (C-2), 79.8 (C-4)*, 76.1 (C-5)*, 73.9 (C-3), 70.0 (C-1), 28.9 (C-6)*, 28.5 (C-8)*, 28.0, 27.2, 26.9, 25.4 [4 C, 2 × $OC(CH_3)_2$], 17.7 (C-7); MS (70 eV) *m/z* 257 ($M^+ - 15$, 40), 157 (16), 139 (26), 115 (20), 93 (20), 43 (100). Anal. Calcd for $C_{14}H_{24}O_5$: C, 61.74; H, 8.88. Found: C, 62.01; H, 8.71.

Free Radical Cyclization of Compound 36. Precursor **36** (101 mg, 0.18 mmol) was treated according to the General Method for FR Cyclization ("one-pot" addition) to give compounds **54** [37.8 mg, 50%) after chromatography (87/13 hexane/ethyl acetate). **54**: oil; $[\alpha]_D^{25}$ −4 (*c* 0.68, $CHCl_3$); IR (film) ν 2987, 1737, 1455, 1371, 1167, 1047 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37−7.25 (m, 5 H, $OCH_2C_6H_5$), 4.74/4.66 (AB system: d, $J = 11.6$ Hz, 2 H, $OCH_2C_6H_5$), 4.44 (t, $J_{4,5} = J_{3,4} = 8.9$ Hz 1 H, H-4), 4.26 (ddd, $J_{5,6} = 7.6$ Hz, $J_{6,7} = 11.5$ Hz, $J_{6,7'} = 3.1$ Hz, 1 H, H-6), 4.17 (t, $J_{5,6} = J_{4,5} = 7.6$ Hz, 1 H, H-5), 3.78 (br s, 1 H, H-2), 3.68 (dd, $J_{2,3} = 2.0$ Hz, $J_{3,4} = 9.6$ Hz, 1 H, H-3), 3.66 (s, 3 H, $CH_2CO_2CH_3$), 2.62−2.60 (m, 1 H, H-1), 2.37 (dd, $J = 15.7$ Hz, $J = 7.2$ Hz, 1 H, $CH_2CO_2CH_3$), 2.30 (dd, $J = 15.7$ Hz, $J = 8.5$ Hz, 1 H, $CH_2CO_2CH_3$), 2.08 (ddd, $J_{6,7} = 11.5$ Hz, $J_{7,7'} = 14.7$ Hz, $J_{1,7} = 2.2$ Hz, 1 H, H-7), 1.70 (dd, $J_{1,7'} = 2.7$ Hz, $J_{7,7'} = 14.7$ Hz, $J_{6,7'} = 3.1$ Hz, 1 H, H-7′), 1.48, 1.45, 1.44, 1.34 [4 s, 2 × $OC(CH_3)_2O$]; ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.5 ($CH_2CO_2CH_3$), 138.5−127.5 ($OCH_2C_6H_5$), 110.0/109.2 [2 × $OC(CH_3)_2$], 78.8 (C-5), 78.3 (C-3)*, 76.9 (C-2)*, 74.8 (C-4), 73.3 ($OCH_2C_6H_5$), 72.8 (C-6), 51.9 ($CH_2CO_2CH_3$), 35.4 ($CH_2CO_2CH_3$), 33.9 (C-1), 28.8 (C-7), 29.7, 27.3 (2 C), 26.6, 24.4 [4 C, 2 × $OC(CH_3)_2O$]; MS (70 eV) *m/z* 420 (M^+, 1), 405 ($M^+ - 15$, 16), 304 (14), 231 (7), 198 (4), 91 (100). Anal. Calcd for $C_{23}H_{32}O_7$: C, 65.70; H, 7.67. Found: C, 65.57; H, 7.14.

Free Radical Cyclization of Compound 37. Precursor **37** (37 mg, 0.10 mmol) was treated according to the General Method for FR Cyclization (slow addition: 5 h) to give compounds **55** (37 mg, 55%) after chromatography (95/5 hexane/ethyl acetate). **55**: oil; $[\alpha]_D^{25}$ −19 (*c* 0.68, $CHCl_3$); IR (film) ν 3486, 2928, 1740, 1456, 1372, 1166, 1044 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.90 (s, 1 H, H-8), 4.55 (t, $J_{2,3} = J_{3,4} = 8.9$ Hz, 1 H, H-3), 4.43 (d, $J_{5,6} = 2.9$ Hz, 1 H, H-6), 4.20 (t, $J_{4,5} = J_{3,4} = 8.5$ Hz 1 H, H-4), 4.03 (dd, $J_{5,6} = 2.9$ Hz, $J_{4,5} = 8.2$ Hz, 1 H, H-5), 3.63 (s, 3 H, $CH_2CO_2CH_3$), 3.49 (dt, $J_{1,2} = J_{1,9} = 10.5$ Hz, $J_{1,9'} = 6.2$ Hz, 1 H, H-1), 3.17 (dd, $J_{1,2} = 10.5$ Hz, $J_{2,3} = 9.1$ Hz, 1 H, H-2), 2.85 (dd, $J_{9,9'} = 15.7$ Hz, $J_{1,9'} = 6.2$ Hz, 1 H, H-9′), 2.58 (dd, $J_{9,9'} = 15.7$ Hz, $J_{1,9} = 10.5$ Hz, 1 H, H-9), 2.57 (s, 1 H, OH), 1.57, 1.41, 1.38, 1.36 [4 s, 2 × $OC(CH_3)_2O$], 1.52−1.24 [m, 18 H, $(CH_3CH_2CH_2CH_2)_3Sn$], 0.96−0.85 [m, 9 H, $(CH_3CH_2CH_2CH_2)_3Sn$]; ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.8 (CO_2CH_3), 152.1 (C-7), 128.4 (C-8), 109.4/109.2 [2 × $OC(CH_3)_2$], 80.2 (C-2), 80.1 (C-5), 80.0 (C-3), 77.4 (C-4), 77.3 (C-6), 51.5 (CO_2CH_3), 40.2 (C-9), 29.0, 27.3, 13.6 [($CH_3CH_2CH_2CH_2)_3Sn$], 27.2, 27.0, 26.4, 23.2 [4 C, 2 × $OC(CH_3)_2O$], 10.3 [(CH_3CH_2-

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$CH_2CH_2)_3Sn$]; MS (70 eV) *m/z* 617 ($M^+ - 15$, 2), 575 (63), 517 (22), 459 (100), 375 (36), 291 (24), 251 (39), 177 (51), 59 (34). Anal. Calcd for $C_{29}H_{52}O_7Sn$: C, 55.16; H, 8.29. Found: C, 55.08; H, 8.15.

Free Radical Cyclization of Compound 38. Precursor **38** (36 mg, 0.10 mmol) was treated according to the General Method for FR Cyclization (slow addition: 5 h) to give compounds **56** (41 mg, 60%) after chromatography (95/5 hexane/ethyl acetate). **56**: oil; $[\alpha]_D^{25}$−20 (*c* 0.31, $CHCl_3$); IR (film) ν 3467, 2923, 1743, 1456, 1372, 1167, 1047 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.01 (s, 1 H, H-8), 4.21 (d, $J_{5,6} = 7.9$ Hz, 1 H, H-6), 4.20 (t, $J_{4,5} = J_{3,4} = 9.6$ Hz 1 H, H-4), 4.00 (t, $J_{2,3} = J_{3,4} = 9.4$ Hz, 1 H, H-3), 3.90 (dd, $J_{5,6} = 7.9$ Hz, $J_{4,5} = 9.2$ Hz, 1 H, H-5), 3.62 (s, 3 H, $CH_2CO_2CH_3$), 3.23 (t, $J_{1,2} = J_{2,3} = 10.3$ Hz, 1 H, H-2), 2.94−2.82 (m, 1 H, H-1), 2.83 (dd, $J_{9,9'} = 15.6$ Hz, $J_{1,9'} = 4.5$ Hz, 1 H, H-9′), 2.71 (s, 1 H, OH), 2.64 (dd, $J_{9,9'} = 15.6$ Hz, $J_{1,9} = 9.2$ Hz, 1 H, H-9), 1.52, 1.39, 1.37, 1.35 [4 s, 2 × $OC(CH_3)_2O$], 1.50−1.21 [m, 18 H, $(CH_3CH_2CH_2CH_2)_3Sn$], 0.94−0.75 [m, 9 H, $(CH_3CH_2CH_2CH_2)_3Sn$]; ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.8 (CO_2CH_3), 150.9 (C-7), 129.3 (C-8), 110.0/109.8 [2 × $OC(CH_3)_2$], 82.1 (C-5), 80.5 (C-3), 79.8 (C-2), 76.7 (C-4), 74.1 (C-6), 51.7 (CO_2CH_3), 46.7 (C-1), 35.1 (C-9), 29.2, 27.6, 13.8 [$(CH_3CH_2CH_2CH_2)_3Sn$], 27.2, 27.1 (2 C), 24.2 [4 C, 2 × $OC(CH_3)_2O$], 12.4 [$(CH_3CH_2CH_2CH_2)_3Sn$]; MS (70 eV) *m/z* 575 (100), 459 (27), 291 (18), 251 (36), 177 (39), 59 (64). Anal. Calcd for $C_{29}H_{52}O_7Sn$: C, 55.16; H, 8.29. Found: C, 55.23; H, 8.42.

(1*R*,4*S*,5*R*,6*R*,7*R*)-4,5:6,7-Bis(isopropylidenedioxy)-2-cyclohepten-1-ol (68). Following the General Method for the Ring-Closing Metathesis Reaction, diastereomerically pure precursor **60** (15 mg, 0.053 mmol) gave carbocycle **68** (12 mg, 88%) after chromatography (85/15 hexane/ethyl acetate). **68**: oil; $[\alpha]_D^{25}$ −3 (*c* 0.52, $CHCl_3$); IR (film) ν 3479 (OH), 2986, 1656, 1373, 1216, 1061 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.07 (dd, $J_{2,3} = 11.7$ Hz, $J_{3,4} = 1.7$ Hz, 1 H, H-3), 5.82 (ddd, $J_{2,3} = 11.7$ Hz, $J_{1,2} = 7.4$ Hz, $J_{2,4} = 2.6$ Hz, 1 H, H-2), 4.44 (t, $J_{4,5} = J_{5,6} = 8.7$ Hz, 1 H, H-5), 4.35 (dd, $J_{5,6} = 8.6$ Hz, $J_{6,7} = 7.3$ Hz, 1 H, H-6), 4.32 (dd, $J_{1,2} = 7.4$ Hz, $J_{1,7} = 2.6$ Hz, 1 H, H-1), 4.23 (dt, $J_{4,2} = J_{4,3} = 2.0$ Hz, $J_{4,5} = 8.7$ Hz, 1 H, H-4), 4.18 (dd, $J_{6,7} = 7.3$ Hz, $J_{1,7} = 2.6$ Hz, 1 H, H-7), 2.48 (br s, 1 H, OH), 1.57, 1.43 (2 s), 1.42 [4 s, 12 H, 2 × $OC(CH_3)_2O$]; ^{13}C NMR (75 MHz, $CDCl_3$) δ 131.8 (C-3)*, 125.8 (C-2)*, 110.7, 110.1 [2 C, $OC(CH_3)_2O$], 77.5 (C-7), 77.3 (C-5), 77.1 (C-7), 75.4 (C-4), 68.3 (C-1), 29.0, 27.0, 26.7, 24.3 [2 × $OC(CH_3)_2O$]; MS (70 eV) *m/z* 256 (M^+, 1), 241 ($M^+ - 15$, 48), 140 (50), 113 (51), 59 (68), 43 (100). Anal. Calcd for $C_{13}H_{20}O_5$: C, 60.92; H, 7.87. Found: C, 61.14; H, 7.64.

(1*S*,4*S*,5*R*,6*R*,7*R*)-4,5:6,7-Bis(isopropylidenedioxy)-2-cyclohepten-1-ol (69). Following the General Method for the Ring-Closing Metathesis Reaction, a mixture of precursors **60**/**61** (64:36) (49.4 mg, 0.17 mmol) gave carbocycle **68** (25.4 mg, 57%) and **69** (11.5 mg, 26%) after chromatography (9/1 hexane/ethyl acetate). **69**: oil; $[\alpha]_D^{25}$ +84 (*c* 0.77, $CHCl_3$); IR (film) ν 3447 (OH), 2989, 1622, 1374, 1222, 1062 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.84 (ddd, $J_{2,3} = 12.1$ Hz, $J_{3,4} = 2.6$ Hz, $J_{1,3} = 1.6$ Hz, 1 H, H-3)*, 5.66 (ddd, $J_{2,3} = 12.1$ Hz, $J_{1,2} = 2.2$ Hz, $J_{2,4} = 1.6$ Hz, 1 H, H-2)*, 4.37−4.33 (4.35: dd, $J_{1,7} = 8.0$ Hz, $J_{6,7} = 6.5$ Hz, 1 H, H-7; overlapping: m, 1 H, H-1), 4.28 (dm, $J_{4,5} = 8.3$ Hz, 1 H, H-4), 3.98 (dd, $J_{5,6} = 9.6$ Hz, $J_{6,7} = 6.5$ Hz, 1 H, H-6), 3.93 (dd, $J_{5,6} = 9.6$ Hz, $J_{4,5} = 8.3$ Hz, 1 H, H-5), 2.61 (br s, 1 H, OH), 1.52, 1.43 (2 s), 1.42 [4 s, 12 H, 2 × $OC(CH_3)_2O$]; ^{13}C NMR (75 MHz, $CDCl_3$) δ 131.9 (C-2)*, 125.9 (C-3)*, 110.8, 110.1 [2 C, $OC(CH_3)_2O$], 77.6 (C-6), 77.5 (C-5), 77.2 (C-7), 75.4 (C-4), 68.4 (C-1), 27.1 (2 C), 26.8, 24.4 [2 × $OC(CH_3)_2O$]; MS (70 eV) *m/z* 256 (M^+, 4), 241 ($M^+ - 15$, 15), 140 (36), 113 (87), 59 (69), 43 (100). Anal. Calcd for $C_{13}H_{20}O_5$: C, 60.92; H, 7.87. Found: C, 60.88; H, 7.75.

(1*S*,4*S*,5*R*,6*R*,7*R*)-1-*O*-Acetyl-4,5:6,7-bis(isopropylidenedioxy)-2-cycloheptен-1-ol (70). Following the General Method for the Ring-Closing Metathesis Reaction, precursor **62** (16.2 mg, 0.049 mmol) gave carbocycle **70** (12.6 mg, 86%) after chromatography (4/1 hexane/ethyl acetate). **70**: mp 137−140 °C; $[\alpha]_D^{25}$ −16 (*c* 0.85, $CHCl_3$); IR (KBr) ν 2926, 1730, 1374, 1243, 1059 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.07 (dd, $J_{2,3} = 11.5$ Hz, $J_{3,4} = 1.4$ Hz, 1 H, H-3), 5.81 (ddd, $J_{2,3} = 11.5$ Hz, $J_{1,2} = 7.5$ Hz, $J_{2,7} = 2.4$ Hz, 1 H, H-2), 5.36 (dd, $J_{1,2} = 7.5$ Hz, $J_{1,7} = 2.8$ Hz, 1 H, H-1), 4.38 (t, $J_{5,6} = J_{6,7} = 7.5$ Hz, 1 H, H-6), 4.29 (t, $J_{4,5} = J_{6,5} = 8.0$ Hz, 1 H, H-5), 4.26−4.22 (m, 2 H, H-7, H-4), 2.07 (s, 3 H, $OCOCH_3$), 1.45, 1.44, 1.42, 1.36 [4 s, 12 H, 2 × $OC(CH_3)_2O$]; ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.8 ($OCOCH_3$), 132.9 (C-3), 124.0 (C-2), 111.5, 110.4 [2 C, $OC(CH_3)_2O$], 77.4, 77.3, 76.1, 75.0 (C-7, C-6, C-5, C-4), 69.8 (C-1), 27.1, 27.0, 26.7, 25.3 [2 × $OC(CH_3)_2O$]; MS (70 eV) *m/z* 298 (M^+, 1), 283 ($M^+ - 15$, 27), 225 (4), 123 (30), 113 (11), 59 (16), 43 (100). Anal. Calcd for $C_{15}H_{22}O_6$: C, 60.39; H, 7.43. Found: C, 60.58; H, 7.65.

(4*S*,5*R*,6*S*,7*S*)-4,5:6,7-Bis(isopropylidenedioxy)-2-cyclohepten-1-one (71). Following the General Method for the Ring-Closing Metathesis Reaction, diastereomerically pure precursor **63** (59 mg, 0.20 mmol) gave carbocycle **71** (35.7 mg, 70%) after chromatography (4/1 hexane/ethyl acetate). **71**: oil; $[\alpha]_D^{25}$ +10 (*c* 0.8, $CHCl_3$); IR (film) ν 2991, 1693, 1374, 1227, 1078 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.75 (dd, $J_{2,3} = 12.2$ Hz, $J_{3,4} = 1.7$ Hz, 1 H, H-3), 6.08 (dd, $J_{2,3} = 12.2$ Hz, $J_{2,4} = 3.0$ Hz, 1 H, H-2), 4.68 (d, $J_{6,7} = 7.4$ Hz, 1 H, H-7), 4.57 (t, $J_{6,7} = J_{5,6} = 8.1$ Hz, 1 H, H-6), 4.53 (ddd, $J_{2,4} = 3.0$ Hz, $J_{4,5} = 8.4$ Hz, $J_{3,4} = 1.7$ Hz, 1 H, H-4), 3.81 (t, $J_{5,6} = J_{4,5} = 8.5$ Hz, 1 H, H-5), 1.60, 1.48, 1.45, 1.44 [4 s, 12 H, 2 × $OC(CH_3)_2O$]; ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.9 (C═O), 140.9 (C-3), 128.9 (C-2), 113.6, 111.6 [2 C, $OC(CH_3)_2O$], 82.5 (C-7), 80.9 (C-5), 77.3 (C-6), 76.9 (C-4), 27.1, 26.9, 26.8, 26.0 [2 × $OC(CH_3)_2O$]; MS (70 eV) *m/z* 255 ($M + 1^+$, 1), 239 ($M^+ - 15$, 88), 139 (58), 121 (20), 113 (77), 97 (39), 59 (64), 43 (100). Anal. Calcd for $C_{13}H_{18}O_5$: C, 61.41; H, 7.14. Found: C, 61.23; H, 7.34.

Reduction of (4*S*,5*R*,6*S*,7*S*)-4,5:6,7-Bis(isopropylidenedioxy)-2-cyclohepten-1-one (71). Ketone **71** (31.2 mg, 0.12 mmol) was dissolved in dry toluene (1.5 mL), cooled at −78 °C, and DIBALH (0.02 mL, 0.13 mmol, 1.1 equiv, 1.0 M in toluene) was added under argon and stirring. This operation was repeated twice after 2 h each. After 6 h total, the mixture was treated with MeOH at this temperature and the reaction was warmed to room temperature. The salts were filtered over Celite; the solvent was removed under vacuum, and the residue was submitted to chromatography (4/1 hexane/ethyl acetate) to give alcohols **68** (21.6 mg, 70%) and **69** (3.1 mg, 10%).

Ring-Closing Metathesis Reaction of Compound 66. Following the General Method for the Ring-Closing Metathesis Reaction, product **66** (131.4 mg, 0.09 mmol) afforded compound **77** (28.6 mg, 99%) after flash chromatography (eluting with 4/1 hexane/ethyl acetate). **(1*S*,5*S*,6*R*,S*R*,8*R*)-1-*O*-Acetyl-5,6:7,8-bis(isopropylidenedioxy)-3-cyclocten-1-ol (77)**: oil; $[\alpha]_D^{25}$ −35 (*c* 0.48, $CHCl_3$); IR (KBr) ν 2987, 1740, 1373, 1242, 1055 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.89 (dd, $J_{3,4} = 11.4$ Hz, $J_{4,5} = 3.9$ Hz, 1 H, H-4), 5.53 (ddt, $J_{3,4} = 11.4$ Hz, $J_{3,5} = 2.1$ Hz, $J_{2,3} = J_{2',3} = 7.2$ Hz, 1 H, H-3), 5.05 (d, $J_{1,2} = 9.5$ Hz, 1 H, H-1), 4.54 (ddd, $J_{4,5} = 3.8$ Hz, $J_{5,6} = 7.5$ Hz, $J_{5,3} = 2.0$ Hz, 1 H, H-5), 4.36 (t, $J_{7,8} = J_{6,7} = 7.7$ Hz, 1 H, H-7), 4.31 (dd, $J_{1,8} = 2.0$ Hz, $J_{7,8} = 7.7$ Hz, 1 H, H-8), 4.26 (t, $J_{6,7} = J_{5,6} = 7.9$ Hz, 1 H, H-6), 2.96 (dddm, $J_{2,2'} = 16.4$ Hz, $J_{2,3} = 7.3$ Hz, $J_{1,2} = 9.5$ Hz, 1 H, H-2), 2.07 (dd, $J_{2,2'} = 16.4$ Hz, $J_{2',3} = 7.2$ H z, 1 H, H-2′), 2.06 (s, 3 H, $OCOCH_3$), 1.49, 1.45, 1.41, 1.38 [4 s, 12 H, 2 × $OC(CH_3)_2O$]; ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.1 ($OCOCH_3$), 135.2 (C-3), 124.2 (C-4), 109.6, 109.2 [2 C, $OC(CH_3)_2O$], 81.4 (C-6), 80.8 (C-8), 79.6 (C-7), 74.8 (C-5), 72.9 (C-1), 27.2 (C-2), 27.3, 26.6, 25.9, 24.9 [2 × $OC(CH_3)_2O$], 21.0 ($OCOCH_3$); MS (70 eV) *m/z* 313 (M^+, 1), 297 ($M^+ - 15$, 16), 239 (5), 195 (12), 137 (25), 119 (11), 59 (15), 43 (100). Anal. Calcd for $C_{16}H_{24}O_6$: C, 61.52; H, 7.74. Found: C, 61.33; H, 7.65.

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Supporting Information Available: Experimental procedures for the synthesis and analytical and spectroscopic data of compounds **1**−**6**, **9**−**12**, **14**−**17**, **20**−**30**, **33**−**38**, **45**, **46**, **48**−**53**, **60**−**67**, **72**−**77**, **79**, **82**−**88**, and **90**−**92** and experimental procedures for the free radical cyclization of precursors **1**, **6**, and **32**−**33** and the ring-closing metathesis of compounds **64**, **65**, **85**, and **86**. This material is available free of charge via the Internet at http://pubs.acs.org.

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