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Stereoselective Synthesis of Cyclic Ethers by Intramolecular Trapping of Dicobalt Hexacarbonyl-Stabilized Propargylic Cations†

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The intramolecular attack of a hydroxy group on an *exo*-biscobalthexacarbonyl propargylic cation provides cyclic ethers with six- to nine-membered rings. The scope and limitations of the methodology are described. The reaction is stereoselective when additional stereocenters are present, providing iterative methodology to access ladder-like cyclic ethers.

Introduction

Maitotoxin (MTX) was first discovered as one of the toxins responsible for ciguatera seafood poisoning and was afterward found to be produced by the dinoflagellate *Gambierdiscus toxicus*.[1] MTX is the largest nonpolymer known to date and its lethality against mammalians is only exceeded by a few proteinous toxins.[2] Many other marine ladder biotoxins, which show strong biological activities by interacting with cation channels of cellular membranes,[3] have been isolated from marine dinoflagellates.[4] The high complexity of these compounds is reflected in the presence of a large number of oxygens located in a long carbon chain that are woven into a polyoxacyclic macromolecule that includes trans-fused rings ranging in size from five to nine members. The synthetically challenging structures and potent biological activities have attracted the attention of numerous synthetic chemists and a variety of approaches have been explored.[5] As a result of our studies directed to the synthesis of such molecules we have first developed a general methodology to synthesize fused tetrahydropyrans based on an intramolecular hetero-Michael addition in alkoxy γ-benzoyloxy-α,β-unsaturated esters.[6] This methodology can be extended to the synthesis of substituted oxepenes, albeit for limited cases.[7] Here we describe our results relative to the use of an intramolecular Nicholas reaction as an alternative and general key step to synthesize isolated and fused oxacycles in a stereocontrolled manner.

Results and Discussion

Synthesis of Isolated Oxanes, Oxepanes, Oxocanes, and Oxonanes. Our strategy for the synthesis of cyclic ethers is based on the possibility of using an intramolecular Nicholas reaction[8] to form the saturated oxacycle.[9] Additional methods using acetylenic cobalt complexes have also been reported. Isobe et al. reported methods based on the use of *endo*-cobalt complexes derived from sugar derivatives.[10] Hanaoka et al. used the intramolecular opening of *exo*-epoxy-alkyne complexes to

† In memory of Professor Antonio González.

(1) Yasumoto, T.; Bagnis, R.; Venoux, J. P. *Bull. Jpn. Soc. Sci. Fish.* **1976**, *42*, 359−365.

(2) (a) Murata, M.; Naoki, H.; Iwashita, T.; Matsunaga, S.; Sasaki, M.; Yokohama, A.; Yasumoto, T. *J. Am. Chem. Soc.* **1993**, *115*, 2060−2062. (b) Murata, M.; Naoki, H.; Matsunaga, S.; Satake, M.; Yasumoto, T. *J. Am. Chem. Soc.* **1994**, *116*, 7098−7107. (c) Sataki, M.; Matsumori, N.; Maruyama, T.; Nonomura, T.; Murata, M.; Tachibana, K.; Yasumoto, T. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1672−1675. (d) Nonomura, T.; Sasaki, M.; Matsumori, N.; Murata, M., Tachibana, K.; Yasumoto, T. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1675−1678.

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(4) Representative examples of marine ladder toxins. (a) *Brevetoxin-B*: Lin, Y.-Y.; Risk, M.; Ray, S. M.; Van Engen, D.; Clardy, J.; Golik, J.; James, J. C.; Nakanishi, K. *J. Am. Chem. Soc.* **1981**, *103*, 6773−6775. (b) *Brevetoxin-A*: Shimizu, Y.; Chou, H.-N.; Bando, H.; VanDuyne, G.; Clardy J. C. *J. Am. Chem. Soc.* **1986**, *108*, 514−515. (c) *Hemibrevetoxin-B*: Krishna Prasad, A. V.; Shimizu, Y. K. *J. Am. Chem. Soc.* **1989**, *111*, 6476−6477. (d) *Ciguatoxin*: Murata, M.; Legrand, A. M.; Ishibashi, Y.; Fukui, M.; Yasumoto, T. *J. Am. Chem. Soc.* **1990**, *112*, 4380−4386. (e) *Gambieric acids*: Nagai, H.; Murata, M.; Torigoe, K.; Satake, M.; Yasumoto, T. *J. Org. Chem.* **1992**, *57*, 5448−5453. (f) *Gambierol*: Satake, M.; Murata, M.; Yasumoto, T. *J. Am. Chem. Soc.* **1993**, *115*, 361−362. (g) *Prymnesin-2*: Igarashi, T.; Satake, M.; Yasumoto, T. *J. Am. Chem. Soc.* **1996**, *118*, 479−480. (h) *Scaritoxin*: Satake, M.; Ishibashi, Y.; Legrand, A.-M.; Yasumoto, T. *Biosci. Biotech. Biochem.* **1996**, *60*, 2103−2105 (i) *Yessotoxin*: Satake, M.; Terasawa, K.; Kadowaki, Y.; Yasumoto, T. *Tetrahedron Lett.* **1996**, *37*, 5955−5958. (j) *Adriatoxin*: Ciminello, P.; Fattorusso, E.; Forino, M.; Magno, S.; Poletti, R.; Viviani, R. *Tetrahedron Lett.* **1998**, *39*, 8897−8900.

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(7) Palazón, J. M.; Soler, M. A.; Martín, V. S. *Tetrahedron Lett.* **1993**, *34*, 5471−5474.

(8) (a) Caffyn, A. J. M.; Nicholas, K. M. In *Comprehensive Organometallic Chemistry-II*; Hegedus, L. S., Ed.; Pergamon: Oxford, UK, 1995; Vol. 12, Chapter 7.1, pp 685−702. (b) Nicholas, K. M. *Acc. Chem. Res.* **1987**, *20*, 207−214. (c) Teobald, B. J. *Tetrahedron* **2002**, *58*, 4133−4170.

(9) For a preliminary communication, see: Palazón, J. M.; Martín, V. S. *Tetrahedron Lett.* **1995**, *36*, 3549−3552.

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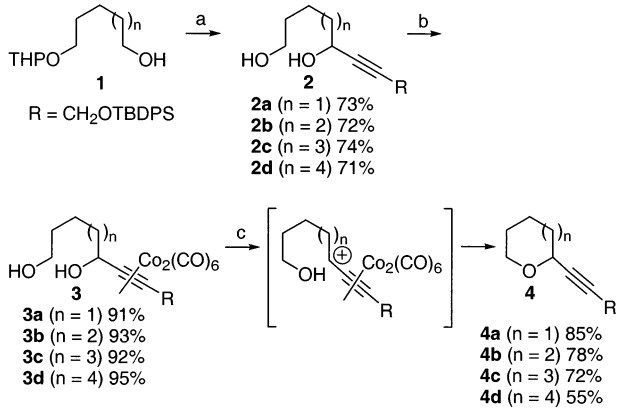
SCHEME 1[a]



[a] Reagents and conditions: (a) (i) SO_3·Py, DMSO, Et_3N, CH_2Cl_2, rt; (ii) LiC≡$CCH_2OTBDPS$, THF, −78 °C to rt; (iii) Dowex 50Wx8, MeOH, rt. (b) $Co_2(CO)_8$, CH_2Cl_2, rt. (c) (i) BF_3·OEt_2, CH_2Cl_2, −30 °C; (ii) CAN, acetone, 0 °C.

synthesize 3-hydroxytetrahydropyrans and oxepanes.[11] We report here on our results based on the intramolecular attack of a hydroxy group located in a suitable chain on a carbocation generated by acid treatment of *exo*-$Co_2(CO)_6$-propargyl alcohols as a method for cyclic ether formation (Scheme 1). The starting propargylic alcohols **2** were obtained by direct addition of lithium acetylide to the suitable aldehyde. Further complexation of the acetylene moiety by direct reaction with $Co_2(CO)_8$ in CH_2Cl_2 afforded the complexed diol **3**. Satisfactorily, the cyclization step proceeded smoothly with different acids (BF_3·OEt_2, HBF_4) providing the corresponding complexed oxacycles. Interestingly the maximum rate of cyclization was achieved for the oxepane formation with a rough order of formation of 7- > 6- > 8- > 9-membered rings. From the synthetic point of view, the demetalation step, using standard conditions [$Ce(NH_4)_2(NO_3)_6$, acetone], proceeded cleanly to yield the corresponding acetylenic compound **4** in good yields.

Diastereoselective Synthesis of 2,3-Substituted Oxanes, Oxepanes, and Oxocanes. In light of our results relative to the ring formation we explored the application of such methodology to the stereocontrolled synthesis of more substituted heterocycles considering further application to the synthesis of fragments of the above-mentioned toxins. Two basic considerations were explored: (a) the influence of a stereocenter located at an *endo*-homopropargylic position and (b) a double asymmetric induction by an additional chiral group located at an *exo*-distal position of the acetylene (Scheme 2).[12,13]

The required propargylic alcohols with a different length in the carbon chain **7** were prepared by conventional methods by using the Katsuki-Sharpless asymmetric epoxidation to induce chirality at the homopropargylic position.[14] Thus, the benzyl diols **6**, prepared from the corresponding monoprotected diols **5** in accordance with methods previously reported from our laboratory,[6a] were consecutively cleaved ($NaIO_4$) to the corresponding aldehydes, treated with the suitable acetylides, and deprotected (*n*-Bu_4NF) to yield **7** (Scheme 3). To probe the ideas outlined above, three kinds of derivatives depending on the degree of the substitution on **7** were prepared: (a) with no additional stereocenter (**7a**→**7c**), (b) with a stereochemically defined fragment geminal to the triple bond (**7d**→**7e**), and (c) with an additional C−O bond that potentially may be broken under the reaction conditions (**7f**→**7g**). The necessary $Co_2(CO)_6$-acetylene complexes **8** were prepared from **7** in good yields (>90%) under the usual conditions.

The diols **8** were treated under acidic conditions (BF_3·OEt_2) at different temperatures (Table 1) and cyclization was successfully achieved to the six- and seven-membered ring, but any attempt to obtain the 3-substituted oxocane ring (Entry 20) was fruitless. We found the reaction to be stereoselective and the selectivity temperature dependent not only on the products but also on the remaining starting material. Thus, when the

SCHEME 2

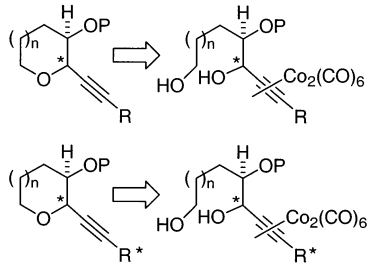
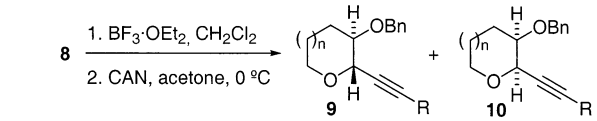


TABLE 1. Acid-Catalyzed Cyclization of Hydroxyl $Co_2(CO)_6$-Propargylic Alcohols with a Benzyloxy Substituent at the Homopropargylic Position



entry	product	temp (°C)	reaction time	**9**:**10**	yield (%)
1	**8a** (*n* =1)	20	20 min	10:1	94
2		0	24 min	9.8:1	88
3		−20	2.5 h	1.2:1	70
4		−20	18 h	9.9:1	87
5	**8d** (*n* =1)	20	30 min	8:1	80
6		0	5 h	3:1	69
7		−20	25 h	6:1	76
8	**8f** (*n* =1)	20	5 min	1:1.7	53
9		0	20 min	1:2	44
10		−20	1 h	1:2.7	10
11	**8b** (*n* = 2)	20	15 min	4:1	75
12		0	2 h	4:1	92
13		−20	18 h	1:1.4	52
14	**8e** (*n* = 2)	20	45 min	21:1	63
15		0	4 h	4.5:1	78
16		−20	21 h	1:1	24
17	**8 g** (*n* = 2)	20	15 min	1:2.5	43
18		0	30 min	3:1	32
19		−20	1 h	4:1	5
20	**8c** (*n* = 3)	20	24 h		

(10) Kira, K.; Tanda, H.; Hamajima, A.; Baba, T.; Takai, S.; Isobe, M. *Tetrahedron* **2002**, *58*, 6485−6492 and references therein.

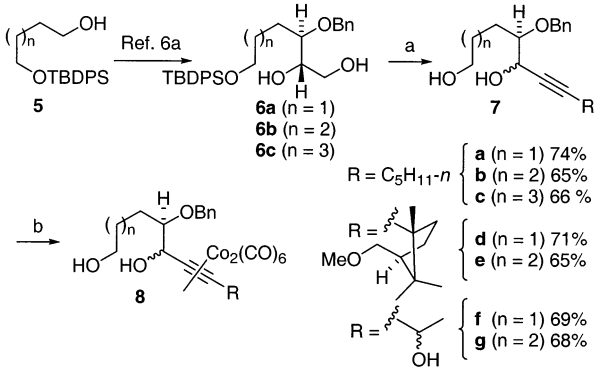
(11) Mukai, C.; Yamaguchi, S.; Sugimoto, Y.; Miyakoshi, N.; Kasamatsu, E.; Hanaoka, M *J. Org. Chem.* **2000**, *65*, 6761−6765 and references therein.

(12) Betancort, J. M.; Rodríguez, C. M.; Martín, V. S. *Tetrahedron Lett.* **1998**, *39*, 9773−9776.

(13) For the influence of a secondary carbinol to control the cyclization stereochemistry in isolated rings, see: Díaz, D. D.; Betancort, J. M.; Crisóstomo, F. R. P.; Martín, T.; Martín, V. S. *Tetrahedron* **2002**, *58*, 1913−1919.

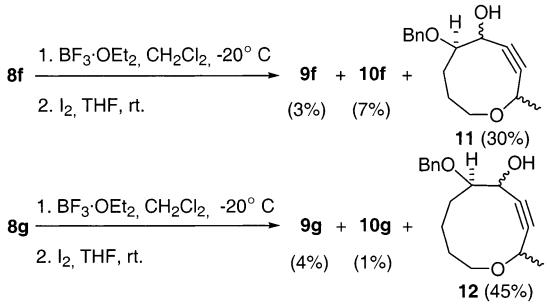
(14) Katsuki, T.; Martín, V. S. *Organic Reactions*; Paquette, L. A., et al., Eds.; Wiley: New York, 1996; Vol. 48, pp 1−299.

SCHEME 3[a]



[a] Reagents and conditions: (a) (i) $NaIO_4$, THF:H_2O (5:1), rt; (ii) LiC≡CR, THF, −78 °C to rt; (iii) *n*-Bu_4NF, THF, rt. (b) $Co_2(CO)_8$, CH_2Cl_2, rt.

SCHEME 4

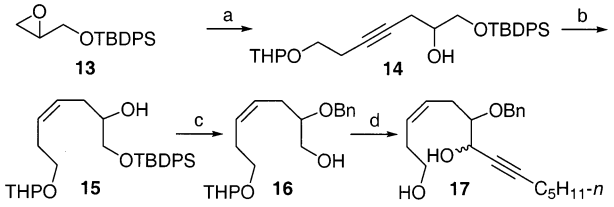


unreacted **8a** in Entry 3 was recovered the starting 1:1 mixture had evolved to a diastereomeric ratio of 10:1. In general terms, the reaction yielded the thermodynamically more stable trans-derivative **9** when long periods or high temperatures were used. In the tetrahydropyran formation no influence was observed relative to the nature of the distal group R. Interestingly, when a seven-membered ring was formed, the presence of an additional chiral center at such substituent was essential to achieve a large diastereomeric ratio in the ring formation (Entries 14 and 17). In general, the better yields were obtained when an additional propargylic C−O was not present. In all cases the stereochemistry was determined by NOE experiments and by study of the coupling constants.

Although cyclization with the functionalized **3c** proceeded smoothly to the corresponding oxocane (**4c**), all attempts to perform a similar reaction on the substituted precursor **8c** were fruitless. In the cases of double propargylic diols, **8f** and **8g**, we were able to isolate and characterize the *endo*-cyclization products, **11** and **12**, respectively (Scheme 4), these being the major products obtained when the cyclization reaction was performed at −20 °C. In such cases, the use of a different oxidation procedure of the $Co_2(CO)_6$ complexes with I_2 was necessary.[15]

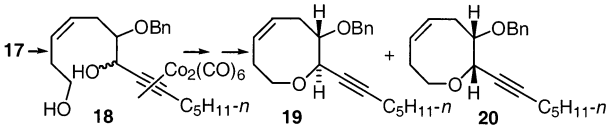
Considering previous experience related to C−O cyclization[16] we envisaged that the introduction of a cis double bond in the linear chain might introduce an entropic activation to succeed in the ring formation

SCHEME 5[a]



[a] Reagents and conditions: $THPO(CH_2)_2C{\equiv}CH$, *n*-BuLi, $BF_3{\cdot}OEt_2$, THF, −78 °C then **13**, 75%. (b) H_2, Lindlar catalyst, EtOAc, rt, 91%. (c) (i) BnBr, NaH, *n*-Bu_4NI, THF; (ii) TBAF, THF, rt, 81% overall yield. (d) (i) $SO_3{\cdot}$Py, DMSO, Et_3N, CH_2Cl_2, rt; (ii) LiC≡CC_5H_{11}-*n*, THF, −78 °C to rt; (iii) Dowex 50W×8, MeOH, rt, 57% overall yield.

TABLE 2. Acid-Catalyzed Cyclization of (*Z*)-Unsaturated Hydroxyl $Co_2(CO)_6$-Propargylic Alcohols to Oxocenes



entry	temp (°C)	reaction time	**19**:**20**	yield (%)
1	20	40 min	10:1	61
2	0	5.5 h	9.8:1	50
3	−20	72 h	1.2:1	32

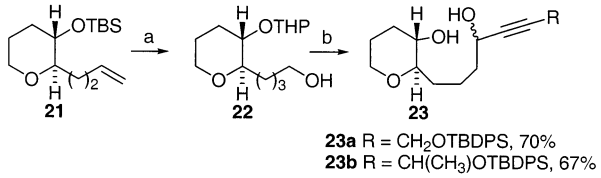
reaction. To probe our idea the benzyl-diol **17** was prepared from commercially available racemic glycidol according to Scheme 5. The silyl-protected glycidol **13** was reacted with the lithium salt of THP-protected 3-butyn-1-ol to afford **14** that was selectively hydrogenated with Lindlar's catalyst to afford the *Z*-olefin **15**. Benzylation of the secondary alcohol and cleaving silyl ether yielded the corresponding primary alcohol **16**. The oxidation of **16** with the $SO_3{\cdot}$Py complex, further treatment of the crude aldehyde with the 1-heptyne lithium acetylide, and ulterior THP cleavage under acidic conditions provided **17**.

To perform the cyclization studies, **17** was treated with $Co_2(CO)_8$ to afford complex **18**. When submitted to the usual acidic and demetalation conditions (Table 2), in all the temperatures assayed, cyclization occurred yielding the cis-diastereoisomer **20** as the major isolated isomer.

Diastereoselective Synthesis of Ladder Cyclic Ethers. To apply the methodology to the synthesis of the marine ladder toxins and considering our preceding works in the field[6] we directed our attention to fused rings to a tetrahydropyran unit. We omitted the 6+6 combination since it was previously solved via our reported methodology using hetero-Michael cyclization of the suitable ϵ-hydroxy-γ-benzoyl-α,β-unsaturated ester.[6] To study the scope and limitations of our method we considered for these studies the synthesis of different combinations ranging in ring size and functionalities. Following a similar sequence to that of the preceding session we focused our studies first on the stereochemistry of the ring formation and later on the synthesis of the more complicated α,β,α′,β′-tetrasubstituted systems. The necessary tetrahydropyran precursors were obtained either via the already mentioned intramolecular hetero-

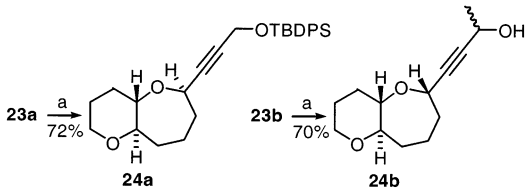
(15) Yenjai, C.; Isobe, M. *Tetrahedron* **1998**, *54*, 2509−2520.
(16) Palazón, J. M.; Soler, M. A.; Martín, V. S. *Tetrahedron Lett.* **1993**, *34*, 5471−5474.

SCHEME 6[a]



[a] Reagents and conditions: (a) (i) *n*-Bu_4NF, THF, rt; (ii) DHP, O=PCl_3, CH_2Cl_2, 0 °C to rt; (iii) BH_3·$S(CH_3)_2$, THF, 0 °C to rt, then 30% H_2O_2, 3 N NaOH, 0 °C to rt, 67% overall yield. (b) (i) SO_3·Py, DMSO, Et_3N, CH_2Cl_2, rt; (ii) LiC≡CR (R = CH_2OTBDPS and CH(CH_3)OTBDPS), THF, −78 °C to rt; (iii) CSA (cat.), MeOH, rt.

SCHEME 7[a]



[a] Reagents and conditions: (a) (i) $Co_2(CO)_8$, CH_2Cl_2, rt; (ii) BF_3·OEt_2, CH_2Cl_2, −30 °C; (iii) CAN, acetone, 0 °C.

Michael cyclization[6] or with tri-*O*-acetyl-*D*-glucal as precursor.[17]

To access the simplest oxane−oxepane system the required propargylic diols **23** were prepared in accordance with Scheme 6. The starting alkene **21**[18] was converted, after changing the protecting group, to the primary alcohol **22** via oxidative hydroboration. As before, the propargylic diols **23** were obtained by direct addition of the suitable lithium acetylide to the aldehyde obtained via oxidation of **22**, and ulterior THP cleavage under acidic conditions.

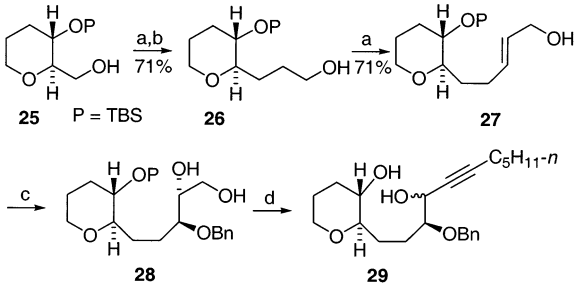
When the $Co_2(CO)_6$ complex of diol **23a** was treated under the usual acidic conditions (BF_3·OEt_2) and further demetalized, the *anti*-oxepane ring **24a** was formed as the only stereoisomer (Scheme 7). Gratifyingly, when the same sequence of reactions was applied to **23b** the complementary syn-isomer **24b** was obtained albeit with cleavage of the silyl protecting group.[19]

In light of these results we focused our attention on a more substituted case with a greater resemblance to those present in the marine toxins. Thus, we directed our attention to the propargylic diol **29** for whose synthesis a similar scheme to those previously discussed was envisioned. In this case the starting material was the tetrahydropyran **25**[17] and the carbon chain was enlarged by a sequence based on the suitable Wittig−Horner elongation (Scheme 8), further reduction and hydrogenation affording **26**. The iterative sequence of reactions was applied to **26** to obtain the allylic alcohol **27**. The new stereocenters were introduced by a Katsuki−Sharpless catalytic asymmetric epoxidation followed by an "in situ" Ti(OPr-*i*)$_4$ assisted opening of the formed 2,3-epoxyalcohol with benzoic acid. After exchange of the benzoate group for a benzyl group, the propargylic diol **29** was obtained by oxidative cleavage of diol **28**, ulterior treatment with the suitable acetylide, and deprotection of the silyl ether.

With the propargylic alcohol **29** in our hands, and after complexation with $Co_2(CO)_8$, the cyclization reaction was attempted over **30** under similar acidic conditions to those previously discussed. Once again, we found the cyclization reaction to be temperature dependent. Thus, when the reaction was performed at −20 °C, and after demetalation, a 1:2 mixture of **31**:**32** was obtained in 65% yield, but when the ring formation was performed at room temperature only the trans-syn-trans-isomer **31** was isolated in 81% yield. As above, the stereochemistry was stablized by NOE experiments in accordance with the arrows outlined in Scheme 9.

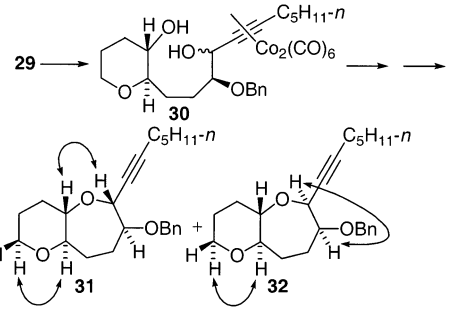
With this satisfactory result in our hands we contemplated the possibility of obtaining the 6+8 system using

SCHEME 8[a]



[a] Reagents and conditions: (a) (i) SO_3·Py, DMSO, Et_3N, CH_2Cl_2, rt; (ii) $(MeO)_2P(O)CH_2CO_2Me$, NaH, benzene, 0 °C; (iii) DIBAL, ether, 0 °C. (b) H_2, PtO_2, MeOH, rt, 100%. (c) (i) (*S*,*S*)-(−)-DET, Ti(OPr-*i*)$_4$, TBHP, CH_2Cl_2, −20 °C; (ii) PhCOOH, Ti(OPr-*i*)$_4$, CH_2Cl_2, rt, 71% overall yield; (iii) $PhCH(OMe)_2$, CH_2Cl_2, CSA (cat.), rt; (iv) NaH, MeOH, CH_2Cl_2, 0 °C, 85% overall yield; (v) BnBr, NaH, *n*-Bu_4NI, rt; (vi) CAS (cat.), MeOH, rt, 80% overall yield. (d) (i) $NaIO_4$, THF:H_2O (5:1), rt; (ii) LiC≡CC_5H_{11}-*n*, THF, −78 °C; (iii) *n*-Bu_4NF, THF, rt, 73% overall yield.

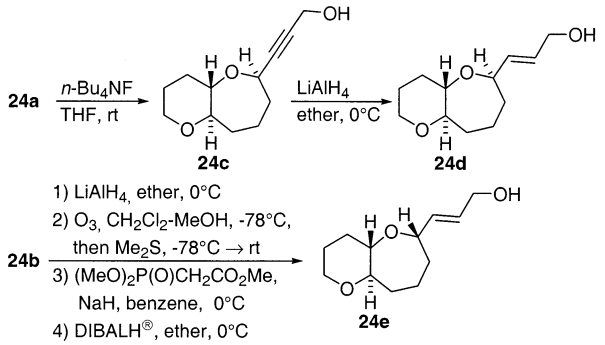
SCHEME 9



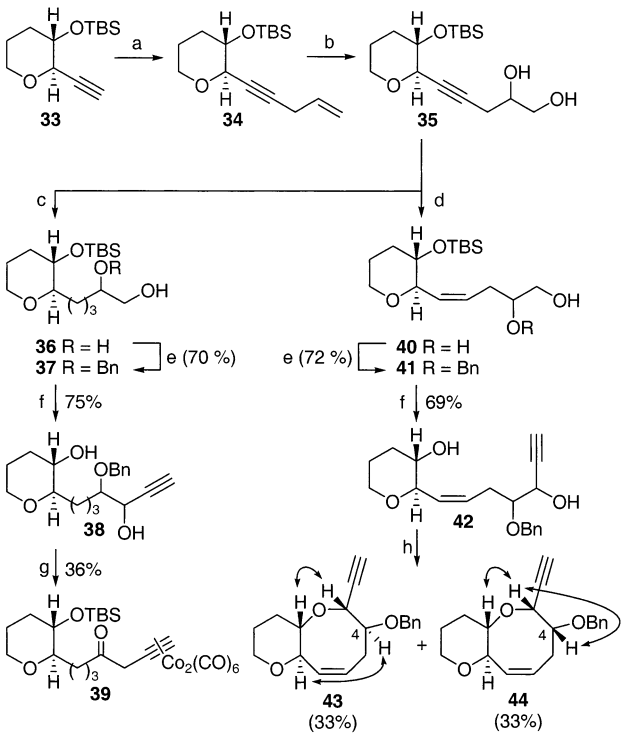
(17) Nicolaou, K. C.; Hwang, C.-K.; Marron, B. E.; DeFress, S. A.; Couladourus, E. A.; Abe, Y.; Carroll, P. J.; Snyder, J. P. *J. Am. Chem. Soc.* **1990**, *112*, 3040−3054.

(18) Hori, N.; Matsukura, H.; Matsuo, G.; Nakata, T. *Tetrahedron*, **2002**, *58*, 1853−1864.

(19) The stereochemistry was clarified by NOE studies over **24c** and **24b** and by chemical transformation to the diastereoisomers **24d** and **24e** (see Supporting Information).



SCHEME 10[a]



[a] Reagents and conditions: (a) K_2CO_3, TBAB (cat.), CuI (cat.), allyl bromide, DMF, 60 h, 93%. (b) NMO, OsO_4 (cat.), THF:acetone: H_2O, 96%. (c) H_2, Pd(C), AcOEt, rt, quantitative. (d) H_2, Lindlar catalyst, AcOEt, rt, 95%. (e) (i) $PhCH(OMe)_2$, CH_2Cl_2, CSA (cat.), rt; (ii) DIBAL-H, CH_2Cl_2, 0 °C. (f) (i) Oxalyl chloride, DMSO, Et_3N, CH_2Cl_2, −78 to rt; (ii) LiC≡CTMS, THF, −78 °C to rt; (iii) *n*-Bu_4NF, THF, rt. (g) (i) $Co_2(CO)_8$, CH_2Cl_2, rt; (ii) $BF_3{\cdot}OEt_2$, CH_2Cl_2, rt, 36% overall yield. (h) (i) $Co_2(CO)_8$, CH_2Cl_2, rt; (ii) $BF_3{\cdot}OEt_2$, CH_2Cl_2, rt; (iii) CAN, acetone, 0 °C, 65% overall yield.

a similar strategy. We pondered two possibilities: (a) considering that the presence of a ring could introduce enough entropic activation to succeed in the cyclization reaction and (b) the cyclization using a linear chain with a *Z* double bond in the linear chain, in a manner similar to that discussed above for the synthesis of an isolated ring. Thus, we prepared compounds **38** and **42** in a divergent manner from the common precursor **35**, which was obtained in accordance with Scheme 10. The starting alkyne **33**[20] was alkylated with allyl bromide to afford the skipped enine **34**, in which dihydroxylation of the terminal alkene generated the diol **35**. Unfortunately any attempt to perform Sharpless asymmetric dihydroxylation in the enyne **34** did not show any diastereomeric excess.

To prepare compound **38,** total hydrogenation of **35** provided the diol **36** that after protection of the diol as the benzylidene acetal and subsequent reductive cleavage afforded the benzyl ether **37** in good yield (Scheme 10). Swern reaction of **37** and further treatment of the crude aldehyde with the lithium acetylide of (trimethylsilyl)-acetylene and ulterior silyl-cleavage under standard conditions provided the diol **38**.

Alternatively, **35** was submitted to partial hydrogenation to the *Z*-olefin **40**, and to the same sequence as above to afford **42**.

When the acetylenic cobalt complex of the diol **38** was treated under the standard acidic conditions ($BF_3{\cdot}OEt_2$) we observed reaction only at room temperature, yielding the homopropargylic ketone complex **39** as the main product. Although we did not obtain any cyclic product, this result is in agreement with previously reported results by our group,[21] since when β-hydroxy or β-benzyloxy groups are present in the hexacarbonyl dicobalt propargylic alcohols complex, an elimination can yield such ketones. In this case the elimination was faster than the cyclization reaction.

On the other hand, the acidic treatment of the cobalt complex of the diol **42** ($BF_3{\cdot}OEt_2$, room temperature) generated after demetalation the *syn*-oxocenes **43** and **44**, in a 1:1 ratio. Considering that both products are epimers at C4 and that this stereocenter has its origin in the mixture of diols **35**, we can conclude that the reaction is highly stereoselective to obtain the desired syn-stereochemistry. Thus, the presence of both a fused ring and a *Z*-double bond in the linear chain overcomes the unfavorable entropic effect to obtain the eight-membered rings.

Conclusions

We have described a very reliable approach to cyclic ethers based on the intramolecular attack of a suitable hydroxy group to a propargylic cation generated from $Co_2(CO)_6$-complexed propargylic alcohols. When the attacking alcohol is primary the method yields ethers with sizes ranging from 6- to 9-member. The reaction is stereoselective when additional stereocenters are present. In addition, the method is useful for the synthesis of fused systems usually found in marine ladder toxins. The potential of the method was demonstrated by the stereoselective synthesis of fused 6,7- and 6,8-membered bicyclic ethers.

Experimental Section

Materials and Methods. ^1H NMR spectra were recorded at 400 and 300 MHz, ^{13}C NMR spectra were recorded at 75 MHz, and chemical shifts are reported relative to internal Me_4Si. Optical rotations were determined for solutions in chloroform. Column chromatography was performed on silica gel, 60 Å and 0.2−0.5 mm. Compounds were visualized by use of UV light and/or 2.5% phosphomolybdic acid in ethanol with heating. All solvents were purified by standard techniques.[22] Reactions requiring anhydrous conditions were performed under argon or nitrogen. Anhydrous magnesium sulfate was used for drying solutions.

General Preparation of Propargylic diols. Preparation of 8-(*tert*-Butyldiphenylsilanyloxy)-6-octyne-1,5-diol (2a). To a solution of 5-(tetrahydropyran-2-yloxy)pentan-1-ol (1 g, 5.3 mmol) in dry CH_2Cl_2 (26 mL) under argon were added Et_3N (5.2 mL, 37 mmol) and DMSO (3.5 mL) at 0 °C. After 15 min of stirring, $SO_3{\cdot}Py$ (2.53 g, 15.9 mmol) was added. The reaction was allowed to warm to room temperature and monitored for TLC until complete conversion (2 h). The reaction was diluted with CH_2Cl_2 and washed with HCl aqueous solution (5% w/v), a saturated aqueous solution of $NaHCO_3$, and brine, dried over $MgSO_4$, and concentrated. The

(20) Candenas, M. L.; Pinto, F. M.; Cintado C. G.; Morales E. Q.; Brouard, I.; Díaz, M. T.; Rico, M.; Rodríguez, E.; Rodríguez, R. M.; Pérez, R.; Pérez, R. L.; Martín, J. D. *Tetrahedron* **2002**, *58*, 1921−1942.

(21) Soler, M. A.; Martín, V. S. *Tetrahedron Lett.* **1999**, *40*, 2815−2816.

(22) Armarego, W. L. F.; Perrin, D. D. *Purification of Laboratory Chemicals*, 4th ed.; Butterworth-Heinemann: Oxford, UK, 1996.

crude obtained was filtered through a pad of silica gel and the aldehyde was used in the next reaction.

n-BuLi (5 mL of a 1.5 M solution in hexane, 7.44 mmol) was added dropwise via syringe to a cooled (−78 °C) solution of *tert*-butyldiphenyl-2-propynyloxysilane (2.35 g, 8 mmol) in anhydrous THF (45 mL) under argon. After 15 min, the crude aldehyde dissolved in THF (5 mL) was added. The resulting mixture was stirred for 2 h and then quenched with saturated aqueous NH_4Cl and diluted with Et_2O. The aqueous layer was extracted with Et_2O and the combined organic layers were dried, filtered, and concentrated to yield the crude propargylic alcohol as an oil, which was used without further purification.

To a stirred solution of the crude propargylic alcohol in MeOH (30 mL) was added Dowex 50W×8 (500 mg, 30% (w)) at room temperature. The reaction mixture was vigorously stirred for 15 h, until TLC showed complete conversion. After filtration, the solution was concentrated and purified by silica gel flash chromatography, yielding **2a** (1.53 g, 73% overall yield).^{1}H NMR ($CDCl_3$) 1.05 (s, 9H), 1.40−1.63 (m, 6H), 3.32 (s, 1H), 3.62 (t, J = 5.9 Hz, 2H), 4.30 (t, J = 6.3 Hz, 1H), 4.36 (s, 2H), 7.41 (m, 6H), 7.71 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 19.1 (s), 21.2 (t), 26.7 (q), 32.2 (t), 37.1 (t), 52.7 (t), 62.1 (d), 62.6 (t), 83.2 (s), 86.2 (s), 127.7 (d), 129.8 (d), 133.2 (s), 135.6 (d); IR (film) (cm^{-1}) 3370, 2933, 2860, 1425, 1051; MS *m*/*z* (rel intensity) 378 $(M - H_2O)^+$ (0.2), 321 $(M - H_2O -$ Bu-*t*) (44), 243 (27), 199 (100). HRMS calcd for $C_{24}H_{30}O_2Si$ $[M - H_2O]^+$ 378.20151, found 378.20161.

General Procedure for the Preparation of Cobalt-Complexed Propargyl Alcohols. Solid $Co_2(CO)_8$ (376 mg, 1.1 mmol) was added to a solution of the corresponding alkyne (1 mmol) in anhydrous CH_2Cl_2 (5 mL) under argon atmosphere. The dark solution was stirred at room temperature until TLC showed the formation of the complex to be completed (ca. 4 h). The solvent of the resulting reaction mixture was then removed under vacuum, and the residue was purified by silica gel column chromatography to yield the $Co_2(CO)_8$−alkyne complex as a dark red oil (ca. 90% yield) that was used in all cases without further characterization.

General Procedure of Cyclization and Demetalation. Preparation of *tert*-Butyl(3-tetrahydropyran-2-yl-2-propynyloxy)diphenylsilane (4a). The general procedure for the preparation of the dicobalt hexacarbonyl complexes described above was applied to **2a** on a 200-mg (0.5 mmol) scale, yielding **3a** (310 mg, 91% yield) as a dark red oil.

To a solution of cobalt complex **3a** (200 mg, 0.29 mmol) in CH_2Cl_2 (3 mL) under argon atmosphere was added dropwise $BF_3{\cdot}Et_2O$ (45 μL, 0.35 mmol) at −30 °C. After 50 min, TLC showed complete conversion to a less polar complex. The mixture was poured into saturated aqueous $NaHCO_3$ (5 mL) with vigorous stirring. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated to yield the crude cobalt complex as an oil, which was used without further purification.

The cobalt complex previously obtained was dissolved under argon atmosphere in 3 mL of reagent grade acetone at 0 °C. Ceric ammonium nitrate (643 mg, 1.17 mmol) was added in portions with stirring until evolution of CO ceased and the CAN color persisted (10 min). The solvent was removed under vacuum and the pink solid residue was then partitioned between Et_2O and distilled H_2O. The aqueous phase was extracted additionally twice with Et_2O. The combined organic extracts were dried, filtered, concentrated, and subjected to silica gel flash chromatography yielding **4a** (94 mg, 85% yield) as an oil. ^{1}H NMR ($CDCl_3$) 1.06 (s, 9H), 1.50−1.82 (m, 6H), 3.51 (m, 1H), 3.93 (m, 1H), 4.30 (m, 1H), 4.38 (s, 2H), 7.41 (m, 6H), 7.71 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 19.2 (s), 21.5 (t), 25.7 (t), 26.7 (q), 31.9 (t), 52.7 (t), 66.1 (t), 66.8 (d), 83.7 (s), 84.0 (s), 127.7 (d), 129.8 (d), 133.2 (s), 135.7 (d); IR (film) (cm^{-1}) 2935, 2857, 1425, 1110; MS *m*/*z* (rel intensity) 321 $(M -$ Bu-*t*$)^+$ (47), 243 (30), 199 (100), 139 (23); HRMS calcd for $C_{20}H_{21}O_2Si$ $[M -$ Bu-*t*$]^+$ 321.13108, found 321.13090. Anal. Calcd for $C_{24}H_{30}O_2Si$: C, 76.14; H, 7.99. Found: C, 76.16; H, 8.37.

Preparation of (4*R*,5*R*)- and (4*R*,5*S*)-4-Benzyloxy-6-dodecyne-1,5-diol (7a). To a stirred solution of **6a** (300 mg, 0.63 mmol) in THF:H_2O (5:1, 6 mL) was added $NaIO_4$ (536 mg, 2.5 mmol) at room temperature. After 30 min, the mixture was diluted with ether and the organic layer separated. The organic phase was washed with water and brine, dried, filtered, and concentrated, yielding the crude aldehyde as an oil, which was used without further purification.

n-BuLi (0.8 mL of a 1.5 M solution in hexane, 1.1 mmol) was added dropwise via syringe to a cooled (−78 °C) solution of 1-heptyne (0.16 mL, 1.25 mmol) in anhydrous THF (10 mL) under argon. After 15 min, the crude aldehyde dissolved in THF (5 mL) was added. The resulting mixture was stirred for 2 h and then quenched with saturated aqueous NH_4Cl and diluted with Et_2O. The aqueous layer was extracted with Et_2O and the combined organic layers were dried, filtered, and concentrated to yield the crude propargylic alcohol as an oil, which was used without further purification.

To a stirred solution of the crude propargylic alcohol in dry THF (7 mL) under argon was added TBAF (0.9 mL of a 1 M solution in THF, 0.8 mmol) at room temperature. After 12 h, water and Et_2O were added. The separated aqueous layer was extracted with Et_2O, and the combined organic layers were dried, filtered, and concentrated. Silica gel column chromatography of the residue gave **7a** (142 mg, 74% overall yield) as an oil: ^{1}H NMR ($CDCl_3$) 0.89 (dd, J = 6.9, 6.9 Hz, 6H), 1.32 (m, 8H), 1.51 (m, 4H), 1.71 (m, 8H), 2.21 (dd, J = 7.1, 7.1 Hz, 4H), 3.52 (m, 2H), 3.61 (dd, J = 6.1, 6.1 Hz, 4H), 4.36 (ddd, J = 5.6, 2.2, 2.2 Hz, 1H), 4.54 (ddd, J = 3.4, 1.7, 1.7 Hz, 1H), 4.60 (d, J = 11.5 Hz, 1H), 4.67 (d, J = 11.2 Hz, 1H), 4.69 (d, J = 11.5 Hz, 1H), 4.75 (d, J = 11.2 Hz, 1H), 7.30 (m, 2H), 7.35 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 13.9 (q), 18.7 (t), 22.1 (t), 26.2 (t), 27.3 (t), 28.2 (t), 28.3 (t), 28.8 (t), 31.0 (t), 62.8 (t), 63.8 (d), 64.7 (d), 72.3 (t), 73.2 (t), 78.0 (s), 78.7 (s), 81.7 (d), 82.1 (d), 86.9 (s), 87.2 (s), 127.8 (d), 127.9 (d), 128.0 (d), 128.4 (d), 128.5 (d), 138.0 (s); IR ($CHCl_3$) (cm^{-1}) 3410, 3014, 2934, 2863, 1455, 1210; MS *m*/*z* (rel intensity) 246 $(M - 58)^+$ (3), 179 (6), 135 (3), 105 (82), 91 (100). Anal. Calcd for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27. Found: C, 74.76; H, 9.43.

Preparation of *tert*-Butyloxiranylmethoxydiphenylsilane (13). To a solution of glycidol (5 g, 67.5 mmol) in dry CH_2Cl_2 (500 mL) under argon atmosphere were sequentially added imidazole (14 g, 203 mmol) and *tert*-butylchlorodiphenylsilane (18.4 mL, 70.9 mmol) at 0 °C. After 3 h, H_2O (500 mL) was added to the reaction mixture. The aqueous phase was separated and extracted with CH_2Cl_2. The combined organic layers were dried, filtered and concentrated in vacuo. The residue was purified by flash silica gel chromatography to give **13** (15.8 g, 75% yield) as an oil: ^{1}H NMR ($CDCl_3$) δ 1.07 (s, 9H), 2.62 (dd, J = 4.9, 2.6 Hz, 1H), 2.75 (dd, J = 4.9, 4.9 Hz, 1H), 3.13 (m, 1H), 3.72 (dd, J = 11.8, 4.7 Hz, 1H), 3.86 (dd, J = 11.8, 3.2 Hz, 1H), 7.42 (m, 6H), 7.69 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 19.2 (s), 26.7 (q), 44.4 (t), 52.2 (d), 64.3 (t), 127.7 (d), 129.7 (d), 133.3 (s), 135.5 (d), 135.6 (d); IR ($CHCl_3$) (cm^{-1}) 3012, 2932, 2859, 1427, 1112; MS *m*/*z* (rel intensity) 256 $(M - 57)^+$ (11), 255 (54), 183 (73), 117 (100). Anal. Calcd for $C_{19}H_{24}O_2Si$: C, 73.03; H, 7.74. Found: C, 73.07; H, 7.76.

Preparation of 1-(*tert*-Butyldiphenylsilanyloxy)-7-(tetrahydropyran-2-yloxy)-4-heptyn-2-ol (14). *n*-BuLi (27 mL of a 1.4 M solution in hexane, 37.7 mmol) was added dropwise via syringe to a cooled (−78 °C) solution of 2-but-3-ynyloxytetrahydropyran (6.5 g, 42.2 mmol) in anhydrous THF (400 mL) under argon. After 5 min, $BF_3{\cdot}OEt_2$ (5.2 mL, 42.2 mmol) was added and in another 5 min, a solution of **13** (6.9 g, 22 mmol) in THF (50 mL) was added dropwise. The resulting mixture was stirred for 30 min and then quenched with saturated aqueous $NaHCO_3$ (300 mL) and diluted with Et_2O (100 mL). The aqueous layer was extracted with Et_2O (3 × 200 mL) and the combined organic layers were dried ($MgSO_4$), filtered, concentrated, and purified by silica gel column chromatography to yield **14** (7.7 g, 75% yield based on the epoxide) as an oil: ^{1}H NMR ($CDCl_3$) δ 1.07 (s, 18H), 1.53 (m, 8H), 1.68

(m, 2H), 1.80 (m, 2H), 2.43 (m, 8H), 3.49 (m, 4H), 3.72 (m, 8H), 3.84 (m, 2H), 4.60 (dd, J = 3.3, 3.3 Hz, 2H), 7.41 (m, 12 H), 7.67 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 19.2 (s), 19.4 (t), 20.2 (t), 23.6 (t), 25.4 (t), 26.8 (q), 30.5 (t), 62.3 (t), 65.9 (t), 66.3 (t), 70.4 (d), 76.8 (s), 79.4 (s), 98.7 (d), 127.7 (d), 127.8 (d), 129.8 (d), 133.1 (s), 135.5 (d), 135.6 (d); IR ($CHCl_3$) (cm^{-1}) 3565, 3012, 2932, 2859, 1113; MS m/z (rel intensity) 409 $(M - 57)^+$ (1), 325 (10), 247 (26), 199 (62), 135 (9), 85 (100). Anal. Calcd for $C_{28}H_{38}O_4Si$: C, 72.06; H, 8.21. Found: C, 72.08; H, 8.33.

Preparation of (4*Z*)-1-(*tert*-Butyldiphenylsilanyloxy)-7-(tetrahydropyran-2-yloxy)-4-hepten-2-ol (15). A mixture of alkyne **14** (5 g, 10.7 mmol), Lindlar's catalyst (50 mg), and quinoleine (1 drop) in 75 mL of EtOAc was placed under a H_2 atmosphere. The reaction mixture was vigorously stirred for 2 h and then filtered through Celite. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel to afford **15** (4.5 g, 91% yield) as an oil: ^{1}H NMR ($CDCl_3$) δ 1.09 (s, 18H), 1.54 (m, 8H), 1.68 (m, 2H), 1.81 (m, 2H), 2.31 (dd, J = 6.3, 6.3 Hz, 4H), 2.37 (m, 4H), 3.4 (dddd, J = 9.7, 6.5, 6.5, 3.1 Hz, 2H), 3.49 (m, 2H), 3.61 (dd, J = 10.1, 6.7 Hz, 2H), 3.68 (dd, J = 10.1, 4.3 Hz, 2H), 3.77 (m, 4H), 3.85 (m, 2H), 4.58 (dd, J = 3.5, 3.5, 2H), 5.54 (m, 4H), 7.42 (m, 12 H), 7.68 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 19.2 (s). 19.5 (t), 25.4 (t), 26.9 (q), 28.0 (t), 30.6 (t), 31.2 (t), 62.2 (t), 66.7 (t), 66.8 (t), 67.5 (t), 71.6 (d), 98.7 (d), 98.8 (d), 126.9 (d), 127.7 (d), 127.8 (d), 128.9 (d), 129.8 (d), 133.3 (s), 135.5 (d), 135.6 (d); IR ($CHCl_3$) (cm^{-1}) 3576, 3493, 2932, 2860, 1115; MS m/z (rel intensity) 433 $(M - 35)^+$, 327 (3), 249 (11), 199 (100). Anal. Calcd for $C_{28}H_{40}O_4Si$: C, 71.75; H, 8.60. Found: C, 71.73; H, 8.89.

Preparation of (4*Z*)-2-Benzyloxy-7-(tetrahydropyran-2-yloxy)-4-hepten-1-ol. (16). To a stirred suspension of NaH (60% in mineral oil, 150 mg, 3.76 mmol) in dry THF (30 mL) at 0 °C were sequentially and slowly added a solution of **15** (1.6 g, 3.4 mmol) in THF (8 mL), a catalytic amount of Bu_4NI, and benzyl bromide (0.57 mL, 4.8 mmol). The reaction mixture was stirred at room temperature for 24 h. Then, the mixture was diluted with Et_2O, washed with brine, dried, concentrated, and used without further purification. To a stirred solution of the crude benzyl ether in dry THF (17 mL) under argon was added TBAF (5.1 mL of a 1 M solution in THF, 5.1 mmol) at room temperature. After 12 h, water and Et_2O were added. The separated aqueous layer was extracted with Et_2O, and the combined organic layers were dried, filtered, and concentrated. Silica gel column chromatography of the residue gave **16** (885 mg, 81% overall yield) as an oil: ^{1}H NMR ($CDCl_3$) δ 1.53 (m, 8H), 1.58 (m, 2H), 1,71 (m, 2H), 1.82 (m, 2H), 2.10 (m, 2H), 2.38 (m, 8H), 3.42 (ddd, J = 9.0, 6.9, 6.9 Hz, 2H), 3.5 (m, 2H), 3.56 (m, 4H), 3.67 (m, 2H), 3.77 (ddd, J = 9.2, 7.0, 7.0 Hz, 2H), 3.86 (ddd, J = 10.9, 7.8, 3.1, 2H), 4.56 (d, J = 11.8, 2H), 5.52 (m, 4H), 7.28 (m, 2H), 7.35 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 19.5 (t), 19.6 (t), 25.4 (t), 28.1 (t), 28.7 (t), 30.6 (t), 62.3 (t), 62.4 (t), 63.7 (t), 66.8 (t), 66.9 (t), 71.4 (t), 79.2 (d), 98.9 (d), 126.4 (d), 127.7 (d), 128.4 (d), 128.7 (d), 138.2 (s); IR ($CHCl_3$) (cm^{-1}) 3475, 2947, 2358, 1351, 1074; MS m/z (rel intensity) 249 $(M - 71)^+$ (3), 220 (3), 123 (5), 105 (42), 91 (45), 85 (100). Anal. Calcd for $C_{19}H_{28}O_4$: C, 71.22; H, 8.81. Found: C, 71.25; H, 8.91.

Preparation of 4-[(2*R*,3*S*)-3-(Tetrahydropyran-2-yloxy)tetrahydropyran-2-yl]butan-1-ol (22). To a stirred solution of the silyl ether **21**[17] (1.5 g, 5.55 mmol) in dry THF (28 mL) under argon was added TBAF (8.4 mL of a 1 M solution in THF, 8.4 mmol) at room temperature. After 12 h, water and Et_2O were added. The separated aqueous layer was extracted with Et_2O, and the combined organic layers were dried, filtered, and concentrated, yielding the crude alcohol, which was used without further purification. To a stirred solution of the crude alcohol in dry CH_2Cl_2 (14 mL) under argon were added dihydropyran (1.01 mL, 11.1 mmol) and a catalytic amount of phosphorus oxychloride at 0 °C. The reaction was allowed to warm to room temperature and stirred for 6 h. The reaction mixture was poured into ice and extracted with CH_2Cl_2 (2 × 30 mL). The combined organic phases were washed with brine (70 mL), dried, and concentrated. The crude tetrahydropyranyl ether obtained was purified by flash chromatography. To a stirred solution of this ether in dry THF (55 mL, 0.1 M) under argon was added dropwise the complex BH_3·SMe_2 2 M in THF (3.9 mL, 7.8 mmol) at 0 °C. The reaction was allowed to warm slowly to room temperature and stirred additionally for 12 h until TLC showed the end of the reaction. The reaction mixture was cooled to 0 °C and H_2O_2 (30% w/v, 2.7 mL), NaOH (3 M, 1.2 mL), and H_2O (1.2 mL) were added sequentially with stirring. The mixture was allowed to warm to room temperature and stirred. After 0.5 h the mixture was extracted with ether and the combined organic solutions were washed with brine (100 mL), dried, evaporated in vacuo, and purified by silica gel column chromatography, giving the alcohol **22** (960 mg, 67% overall yield) as an oil. ^{1}H NMR ($CDCl_3$) δ 1.23−1.78 (m, 30H), 2.21 (m, 2H), 3.08−3.51 (m, 8H), 3.63 (m, 4H), 3.89 (m, 4H), 4.61 (m, 1H), 4.76 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 19.6 (t), 19.9 (t), 21.1 (t), 21.6 (t), 25.3 (t), 25.4 (t), 25.7 (t), 28.6 (t), 31.0 (t), 31.6 (t), 31.9 (t), 32.6 (t), 32.7 (t), 60.4 (t), 62.6 (t), 62.8 (t), 62.9 (t), 67.7 (t), 72.2 (d), 78.3 (d), 80.7 (d), 81.1 (d), 94.2 (d), 101.0 (d); IR ($CHCl_3$) (cm^{-1}) 3426, 2940, 2861, 1441, 1201; MS m/z (rel intensity) 259 $(M + 1)^+$ (5), 258 $(M)^+$ (1), 175 (20), 85 (100). Anal. Calcd for $C_{14}H_{26}O_4$: C, 65.09; H, 10.14. Found: C, 65.09; H, 10.46.

Preparation of 3-[(2*R*,3*S*)-3-(*tert*-Butyldimethylsilanyloxy)tetrahydropyran-2-yl]propan-1-ol (26). To a solution of **25**[17] (8.5 g, 34.6 mmol) in dry CH_2Cl_2 (173 mL) under argon were added Et_3N (33.7 mL, 242 mmol) and DMSO (22.8 mL) at 0 °C. After 15 min of stirring, SO_3·Py (22.1 g, 138 mmol) was added. The reaction was allowed to warm to room temperature and monitored for TLC until complete conversion (2 h). The reaction was diluted with CH_2Cl_2 and washed with HCl aqueous solution (5% w/v), a saturated aqueous solution of $NaHCO_3$, and brine, dried over $MgSO_4$, and concentrated. The crude obtained was filtered through a pad of silica gel and the aldehyde was used in the next reaction.

To a suspension of sodium hydride (1.35 g, 80% in mineral oil, 45 mmol) in dry benzene (250 mL) at 0 °C was slowly added a solution of (trimethylphosphono)acetate (7.9 mL, 48.5 mmol) in dry benzene (50 mL). After complete addition the mixture was stirred for 30 min and the crude aldehyde dissolved in benzene (50 mL) was added dropwise. The reaction mixture was stirred for 30 min, after which time TLC showed complete conversion to the unsaturated ester. The reaction was quenched with saturated aqueous NaCl solution and diluted with ether. The aqueous layer was separated and extracted with Et_2O. The combined organic layers were dried, filtered, and concentrated. Silica gel flash chromatography provided α,β-unsaturated ester (8.5 g, 82% overall yield, E:Z > 20:1) as an oil. To a stirred solution of the α,β-unsaturated ester (7.6 g, 25.3 mmol) in dry Et_2O (250 mL) in an ice-cold bath was added slowly dropwise DIBAL (56 mL, 1.0 M in hexane, 55.7 mmol) with additional stirring for 30 min. To the reaction mixture were sequentially added with stirring H_2O (7.9 mL), NaOH aqueous solution (15% w/v, 7.9 mL), and H_2O (23 mL). The mixture was allowed to reach room temperature, dried, filtered through a thick pad of Celite, concentrated, and purified by silica gel column chromatography to yield the allylic alcohol (5.9 g, 86% yield) as a colorless oil: $[\alpha]^{25}_D$ + 37.1 (c 3.91, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.01 (s, 3H), 0.03 (s, 3H), 0.85 (s, 9H), 1.47 (m, 1H), 1.64 (m, 2H), 2.01 (m, 1H), 3.30 (ddd, J = 10.5, 8.9, 4.5 Hz, 1H), 3.36 (m, 1H), 3.52 (dd, J = 8.4, 6.4 Hz, 1H), 3.91 (m, 1H), 4.13 (br s, 2H), 5.76 (dddd, J = 15.6, 6.0, 1.4, 1.4 Hz, 1H), 5.90 (dddd, J = 15.6, 5.3, 5.3, 0.9 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ −4.6 (q), −4.2 (q), 18.0 (s), 25.5 (t), 25.7 (q), 33.6 (t), 63.2 (t), 67.5 (t), 71.3 (d), 82.5 (d), 130.1 (d), 131.7 (d); IR ($CHCl_3$) (cm^{-1}) 3456, 2951, 2858, 2361, 1253; MS m/z (rel intensity) 254 $(M - 17)^+$ (1), 215 (15), 197 (13), 161 (17), 145 (83), 75 (100). Anal. Calcd for $C_{14}H_{28}O_3Si$: C, 61.72; H, 10.36. Found: C, 61.77; H, 10.25.

A mixture of the allylic alcohol (5.5 g, 20.2 mmol) and PtO_2 (20 mg) in MeOH (125 mL) was placed under a H_2 atmosphere. The reaction mixture was vigorously stirred until TLC showed complete conversion. The mixture was filtered through Whatman paper no. 4. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography to afford quantitatively **26** (5.53 g) as an oil: $[\alpha]^{25}_D$ + 51.0 (*c* 3.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.42 (s, 6H), 0.86 (s, 9H), 1.39 (m, 2H), 1.65 (m, 4H), 2.00 (m, 2H), 2.83 (br s, 2H), 3.01 (ddd, J = 8.7, 8.7, 2.2 Hz, 1H), 3.30 (m, 2H), 3.59 (m, 2H), 3.87 (m, 1H); ^{13}C NMR ($CDCl_3$) δ −4.8 (q), −4.1 (q), 17.8 (s), 25.5 (t), 25.7 (q), 29.0 (t), 29.1 (t), 33.5 (t), 62.9 (t), 67.7 (t), 70.9 (d), 82.8 (d); IR ($CHCl_3$) (cm^{-1}) 3398, 3006, 2955, 2858, 1463, 1257; MS *m*/*z* (rel intensity) 217 $(M - 57)^+$ (3), 205 (10), 199 (100). Anal. Calcd for $C_{14}H_{30}O_3Si$: C, 61.26; H, 11.02. Found: C, 61.27; H, 11.12.

Preparation of Benzoic Acid (1*S*,2*R*)-1-{2-[(2*R*,3*S*)-3-(*tert*-Butyldimethylsilanyloxy)tetrahydropyran-2-yl]ethyl}-2,3-dihydroxypropyl Ester (28). Crushed, activated 4 Å molecular sieves (20% w) were added to stirred CH_2Cl_2 (125 mL) under argon. The flask was cooled to −20 °C and Ti(OPr-*i*)$_4$ (0.4 mL, 1.3 mmol), (*S*,*S*)-(−)-diethyl tartrate (0.27 mL, 1.6 mmol), and the allylic alcohol **27** (4 g, 13.3 mmol) in CH_2Cl_2 (8 mL) were added sequentially with stirring. The mixture was stirred for 15 min, and *tert*-butyl hydroperoxide (5.3 mL, 4.5 M in isooctane, 23.9 mmol) was added slowly. After the addition, the reaction was maintained with stirring overnight. The reaction was allowed to reach room temperature, and benzoic acid (2.92 g, 23.9 mmol) was added. The mixture was additionally stirred for 15 min, and Ti(OPr-*i*)$_4$ (4.75 mL, 16 mmol) was added. Then, the mixture was allowed to warm to room temperature and the solution was stirred for 2 h. Tartaric acid aqueous solution (15% w/v, 125 mL) was added, and stirring was continued until clear phases were reached (30 min). The layers were separated, and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were washed with a saturated aqueous solution of $NaHCO_3$ and brine, dried, concentrated, and purified by silica gel column chromatography, to yield the diol benzoate (4.1 g, 71% overall yield) as an oil: $[\alpha]^{25}_D$ +21.6 (*c* 2.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ −0.1 (s, 3H), −0.01 (3H), 0.73 (s, 9H), 1.37 (m, 2H), 1.62 (m, 2H), 1.79 (m, 1H), 1.96 (m, 1H), 2.04 (m, 1H), 2.16 (m, 1H), 2.6 (br s, 1H), 2.94 (br s, 1H), 2.91 (ddd, J = 9.0, 9.0, 2.4 Hz, 1H), 3.26 (m, 1H), 3.62 (dd, J = 11.8, 5.4 Hz, 1H), 3.72 (m, 1H), 3.86 (m, 1H), 5.1 (m, 1H), 7.43 (dd, J = 8.0, 8.0 Hz, 2H), 7.56 (dd, J = 7.6, 7.6 Hz, 1H), 8.03 (d, J = 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ −4.9 (q), −4.0 (q), 17.8 (s), 25.6 (q), 25.8 (t), 27.0 (t), 28.3 (t), 33.6 (t), 62.6 (t), 67.8 (t), 71.2 (d), 73.3 (d), 75.4 (d), 82.7 (d), 128.4 (d), 129.7 (s), 129.8 (d), 133.3 (d), 167.1 (s); IR ($CHCl_3$) (cm^{-1}) 3459, 2930, 2857, 1713, 1211; MS *m*/*z* (rel intensity) 381 (M − 57) (11), 259 (15), 199 (6), 122 (24), 105 (100). Anal. Calcd for $C_{23}H_{38}O_6Si$: C, 62.98; H, 8.73. Found: C, 62.66; H, 8.99.

To a stirred solution of diol benzoate (4 g, 9.1 mmol) in dry CH_2Cl_2 (91 mL) were sequentially added a catalytic amount of CSA (100 mg, 0.46 mmol) and benzaldehydedimethyl acetal (2.05 mL, 13.7 mmol) at room temperature. The reaction mixture was stirred for 2 h, after which time TLC showed complete conversion to the benzylidene derivative. Then, Et_3N was added until pH ∼7, and the mixture was stirred for 5 min and evaporated under reduced pressure.

To a suspension of NaH (546 mg, 60% in mineral oil, 13.7 mmol) in dry CH_2Cl_2 (80 mL) was slowly added dry MeOH (0.74 mL, 20 mmol) at 0 °C. The mixture was stirred for 10 min, and a solution of the crude benzylidene derivative dissolved in CH_2Cl_2 (10 mL) was added dropwise. The mixture was allowed to warm to room temperature and stirred for 1 h. A saturated NH_4Cl solution was added at 0 °C, and the mixture was extracted with CH_2Cl_2. The combined extracts were washed with brine, dried, filtered, concentrated, and purified by silica gel column chromatography to yield alcohol benzylidene (3.3 g, 85% overall yield) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 0.06 (s, 12H), 0.88 (s, 18H), 1.43 (m, 2H), 1.61 (m, 8H), 1.82 (m, 2H), 2.02 (m, 4H), 3.08 (m, 2H), 3.34 (m, 4H), 3.74 (m, 1H), 3.79 (m, 1H), 3.89 (d, J = 11.1 Hz, 2H), 4.05 (m, 1H), 4.09 (m, 3H), 4.17 (m, 1H), 4.24 (dd, J = 6.0, 6.0 Hz, 1H), 5.80 (s, 1H), 5.94 (s, 1H), 7.37 (m, 6H), 7.48 (m, 4H); ^{13}C NMR ($CDCl_3$) δ −4.7 (q), −3.9 (q), 17.9 (s), 25.5 (t), 25.7 (q), 27.6 (t), 27.6 (t), 29.4 (t), 29.5 (t), 33.5 (t), 67.3 (t), 67.6 (t), 67.8 (t), 70.4 (d), 70.5 (d), 71.8 (d), 71.9 (d), 78.7 (d), 79.2 (d), 82.8 (d), 82.9 (d), 103.9 (d), 104.1 (d), 126.4 (d), 126.6 (d), 128.3 (d), 128.4 (d), 129.1 (d), 129.3 (d), 137.4 (s), 138.2 (s); IR ($CHCl_3$) (cm^{-1}) 3364, 2930, 1461, 1255, 1094; MS *m*/*z* (rel intensity) 422 $(M)^+$ (4), 273 (28), 259 (17), 167 (40), 149 (21), 141 (55), 105 (77), 97 (100). Anal. Calcd for $C_{23}H_{38}O_5Si$: C, 65.36; H, 9.06. Found: C, 65.34; H, 9.18.

To a stirred suspension of NaH (60% in mineral oil, 63 mg, 1.56 mmol) in dry THF (10 mL) at 0 °C were sequentially and slowly added a solution of the alcohol benzylidene (550 mg, 1.3 mmol) in THF (3 mL), a catalytic amount of Bu_4NI, and benzyl bromide (0.22 mL, 1.82 mmol). The reaction mixture was stirred at room temperature for 24 h. Then, the mixture was diluted with Et_2O, washed with brine, dried, and concentrated.

To a stirred mixture of the crude product in MeOH (13 mL) was added concentrated HCl until pH ∼1 at room temperature. The reaction mixture was stirred at room temperature until TLC showed completion of the reaction (ca. 5 min), whereupon it was quenched with Et_3N until pH ∼7. The reaction mixture was stirred for 5 min and concentrated under reduced pressure, and the crude residue obtained was purified by silica gel column chromatography to yield **28** (442 mg, 80% overall yield) as a colorless oil: $[\alpha]^{25}_D$ +53.9 (*c* 0.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.05 (s, 3H), 0.06 (s, 3H), 0.87 (s, 9H), 1.37 (m, 1H), 1.45 (m, 1H), 1.64 (m, 2H), 1.69 (m, 1H), 1.76 (m,1H), 1.99 (dd, J = 12.2, 2.5 Hz, 1H), 2.07 (m, 1H), 2.46 (br s, 1H), 2.88 (br s, 1H), 3.01 (ddd, J = 8.8, 8.8, 1.7 Hz, 1H), 3.28 (m, 2H), 3.56 (m, 1H), 3.73 (m, 3H), 3.87 (dd, J = 10.1, 1.6 Hz, 1H), 4.54 (d, J = 11.4 Hz, 1H), 4.64 (d, J = 11.4 Hz, 1H), 7.29 (m, 1H), 7.32 (m, 4H); ^{13}C NMR ($CDCl_3$) δ −4.6 (q), −4.0 (q), 17.9 (s), 25.7 (t), 25.8 (q), 26.1 (t), 27.9 (t), 33.6 (t), 63.4 (t), 67.8 (t), 71.4 (d), 72.5 (d), 81.5 (d), 82.8 (d), 127.7 (d), 127.8 (d), 128.4 (d), 138.2 (s); IR ($CHCl_3$) (cm^{-1}) 3565, 3470, 2931, 2858, 1211, 1092; MS *m*/*z* (rel intensity) 367 $(M - 57)^+$ (1), 363 (3), 259 (4), 171 (3), 101 (10), 91 (100). Anal. Calcd for $C_{23}H_{40}O_5Si$: C, 65.05; H, 9.49. Found: C, 65.05; H, 9.79.

Preparation of *tert*-Butyl(dimethyl){[(2*R*,3*S*)-2-(4-penten-1-ynyl)tetrahydro-2*H*-pyran-3-yl]oxy}silane (34). To a stirred solution of the alkyne **33**[18] (1.3 g, 5.4 mmol) in dry DMF (18 mL) under argon were sequentially added K_2CO_3 (1.06 g, 7.6 mmol), tetrabutylammonium bromide (227 mg, 0.7 mmol), and copper(I) iodine (52 mg, 0.27 mmol) at room temperature. After 10 min, allyl bromide (0.61 mL, 7.04 mmol) was added. The reaction mixture was stirred for 60 h. Then it was poured into H_2O and extracted with ether. The combined organic phases were washed with brine, dried, and concentrated. The crude obtained was purified by silica gel flash chromatography, yielding **34** (1.4 g, 93% yield) as a colorless oil: $[\alpha]^{25}_D$ + 37.0 (*c* 2.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.07 (s, 3H), 0.08 (s, 3H), 0.88 (s, 9H), 1.35−1.75 (m, 3H), 2.02 (m, 1H), 2.99 (dd, J = 5.5, 1.7 Hz, 2H), 3.37 (m, 1H), 3.56 (m, 1H), 3.87 (m, 2H), 5.08 (dd, J = 10.1, 1.4 Hz, 1H), 5.27 (dd, J = 16.9, 1.4 Hz, 1H), 5.79 (m, 1H); ^{13}C NMR ($CDCl_3$) δ −4.7 (q), −4.5 (q), 18.0 (s), 23.2 (t), 24.2 (t), 25.7 (q), 32.3 (t), 66.8 (t), 70.7 (d), 73.7 (d), 80.5 (s), 82.8 (s), 116.3 (t), 132.2 (d); IR (film) (cm^{-1}) 2931, 2872, 2858, 1463, 1252, 1101. Anal. Calcd for $C_{16}H_{28}O_2Si$: C, 68.52; H, 10.06. Found: C, 68.54; H, 10.53.

Preparation of (2*R* and 2*S*)-5-[(2*R*,3*S*)-3-(*tert*-Butyldimethylsilyloxy)tetrahydro-2*H*-pyran-2-yl]-4-pentyne-1,2-diol (35). To a stirred solution of 4-methylmorpholine *N*-oxide (0.85 g, 7.3 mmol) in H_2O (14 mL) were added OsO_4 (10 mg, 0.04 mmol) and the alkene **34** (1.2 g, 4.3 mmol) in THF/acetone (1:1) (28 mL) at room temperature. The mixture was vigorously stirred overnight. Then it was diluted with EtOAc and washed

with a saturated solution of $NaHSO_3$. The aqueous phase was extracted with EtOAc and the combined organic phases were washed with H_2O, dried, filtered, and concentrated. Silica gel flash column chromatography yielded the diol **35** (1.21 g, 90% yield) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 0.07 (s, 3H), 0.08 (s, 3H), 0.87 (s, 9H), 1.35−1.75 (m, 3H), 1.99 (m, 1H), 2.42 (m, 2H), 3.35 (ddd, J = 10.9, 10.9, 2.7 Hz, 1H), 3.54 (m, 2H), 3.70 (dd, J = 11.3, 3.2 Hz, 1H), 3.84 (m, 2H); ^{13}C NMR ($CDCl_3$) δ −4.7 (q), −4.6 (q), 17.9 (s), 23.7 (t), 24.1 (t), 25.6 (q), 32.3 (t), 65.4 (t), 66.9 (t), 70.2 (d), 70.5 (d), 73.2 (d), 80.6 (s), 82.1 (s); IR (film) (cm^{-1}) 3401, 2925, 2883, 2858, 1462, 1252, 1100. Anal. Calcd for $C_{16}H_{30}O_4Si$: C, 61.11; H, 9.61. Found: C, 61.17; H, 9.70.

Preparation of (2*R* and 2*S*)-5-[(2*R*,3*S*)-3-(*tert*-Butyldimethylsilanyloxy)tetrahydropyran-2-yl]pentane-1,2-diol (36). A mixture of diol **35** (0.6 g, 1.9 mmol) and 5% Pd(C) (5 mg) in EtOAc (19 mL) was placed under a H_2 atmosphere. The reaction mixture was vigorously stirred until TLC showed complete conversion. The mixture was filtered through a pad of Celite. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography to afford quantitatively **36** (0.6 g) as an oil: ^{1}H NMR ($CDCl_3$) δ 0.05 (s, 6H), 0.87 (s, 9H), 1.25−1.53 (m, 6H), 1.60 (m, 2H), 1.83 (m, 1H), 1.97 (m, 1H), 2.18 (br s, 2H), 2.98 (m, 1H), 3.28 (m, 2H), 3.44 (m, 1H), 3.64 (d, J = 10.9 Hz, 1H), 3.70 (m, 1H), 3.85 (m, J = 11.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ −4.7 (q), −4.0 (q), 17.9 (s), 21.2 (t), 21.5 (t), 25.7 (q), 25.8 (t), 31.8 (t), 31.9 (t), 33.1 (t), 33.2 (t), 33.6 (t), 66.7 (t), 67.7 (t), 71.2 (d), 71.3 (d), 71.4 (d), 72.1 (d), 72.2 (d), 82.6 (d), 82.7 (d); IR (film) (cm^{-1}) 3384, 2934, 2857, 1462, 1253, 1099. Anal. Calcd for $C_{16}H_{34}O_4Si$: C, 60.33; H, 10.76. Found: C, 60.32; H, 11.02.

Preparation of (2*R* and 2*S*)-2-Benzyloxy-5-[(2*R*,3*S*)-3-(*tert*-butyldimethylsilanyloxy)tetrahydropyran-2-yl]pentan-1-ol (37). To a stirred solution of diol **36** (0.5 g, 1.57 mmol) in dry CH_2Cl_2 (15 mL) were sequentially added a catalytic amount of CSA (17 mg, 0.08 mmol) and benzaldehydedimethyl acetal (0.35 mL, 2.35 mmol) at room temperature. The reaction mixture was stirred for 2 h, after which time TLC showed complete conversion to the benzylidene derivative. Then Et_3N was added until pH ∼7, and the mixture was stirred for 5 min, evaporated under reduced pressure, and used in the next step without further purification.

To a stirred solution of the benzylidene derivative in dry CH_2Cl_2 (15 mL) at 0 °C was added dropwise DIBAL-H (7.85 mL, 1 M in hexane, 7.85 mmol). The reaction mixture was stirred for 30 min and then quenched with water (500 μL) and allowed to warm to room temperature. The mixture was stirred for 30 min, dried over $MgSO_4$, and filtered through a pad of Celite. The solvent was evaporated and the residue was purified by silica gel flash chromatography, yielding **37** (0.45 g, 70% overall yield) as an oil: ^{1}H NMR ($CDCl_3$) δ 0.06 (s, 6H), 0.89 (s, 9H), 1.30−1.66 (m, 8H), 1.82 (m, 1H), 1.98 (m, 1H), 2.37 (br s, 1H), 2.98 (ddd, J = 8.7, 8.7, 2.1 Hz, 1H), 3.27 (m, 2H), 3.52 (m, 2H), 3.67 (d, J = 10.5 Hz, 1H), 3.86 (d, J = 10.3 Hz, 1H), 4.52 (dd, J = 11.5, 3.6 Hz, 1H), 4.61 (dd, J = 10.9, 3.4 Hz, 1H), 7.26−7.34 (m, 5H); ^{13}C NMR ($CDCl_3$) δ −4.8 (q), −4.0 (q), 17.9 (s), 21.1 (t), 21.3 (t), 25.7 (q), 25.7 (t), 30.7 (t), 30.9 (t), 32.3 (t), 33.6 (t), 64.2 (t), 67.6 (t), 71.3 (d), 71.4 (d), 71.4 (t), 79.8 (d), 79.9 (d), 82.3 (d), 82.4 (d), 127.6 (d), 127.7 (d), 128.3 (d), 138.5 (s); IR (film) (cm^{-1}) 3445, 2932, 2857, 1462, 1252, 1099. Anal. Calcd for $C_{23}H_{40}O_4Si$: C, 67.60; H, 9.87. Found: C, 67.54; H, 9.97.

Preparation of (3*R* and 3*S*,4*R* and 4*S*)-4-Benzyloxy-7-[(2*R*,3*S*)-3-(*tert*-butyldimethylsilanyloxy)tetrahydropyran-2-yl]-1-heptyn-3-ol (38). To a solution of the oxalyl chloride (56 μL, 0.65 mmol) in dry CH_2Cl_2 (3.3 mL) under argon was added DMSO (61 μL, 0.86 mmol) at −78 °C. After 15 min of stirring, a solution of **37** (175 mg, 0.43 mmol) in dry CH_2Cl_2 (1 mL) was added. After 1 h, Et_3N (0.24 mL, 1.72 mmol) was added and the reaction was allowed to warm to room temperature. The reaction was diluted with CH_2Cl_2 (5 mL) and washed with HCl aqueous solution (5% w/v, 5 mL), a saturated aqueous solution of $NaHCO_3$ (5 mL), and brine (5 mL), dried over $MgSO_4$, and concentrated. The crude obtained was filtered through a pad of silica gel and the aldehyde was used in the next reaction.

n-BuLi (0.52 mL of a 1.5 M solution in hexane, 0.77 mmol) was added dropwise via syringe to a cooled (−78 °C) solution of ethynyl(trimethyl)silane (114 μL, 0.86 mmol) in anhydrous THF (4 mL) under argon. After 15 min, the crude aldehyde dissolved in THF (0.5 mL) was added. The resulting mixture was stirred for 2 h and then quenched with saturated aqueous NH_4Cl (5 mL) and diluted with Et_2O (3 mL). The aqueous layer was extracted with Et_2O (3 × 3 mL) and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated to yield the crude propargylic alcohol as an oil that was used without further purification.

To a stirred solution of the crude propargylic alcohol in dry THF (5 mL) under argon was added TBAF (1.3 mL of a 1 M solution in THF, 1.3 mmol) at room temperature. After 12 h, water (5 mL) and Et_2O (5 mL) were added. The separated aqueous layer was extracted with Et_2O (3 × 5 mL), and the combined organic layers were dried ($MgSO_4$), filtere, and concentrated. Silica gel column chromatography of the residue gave **38** (102 mg, 75% overall yield) as an oil: ^{1}H NMR ($CDCl_3$) δ 1.25−1.82 (m, 16H), 2.02 (m, 2H), 2.47 (s, 2H), 2.64 (br s, 2H), 2.95 (m, 2H), 3.24 (m, 4H), 3.52 (m, 2H), 3.85 (d, J = 11.1 Hz, 2H), 4.33 (m, 1H), 4.45 (m, 1H), 4.67 (m, 4H), 7.26−7.37 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 21.0 (t), 21.0 (t), 21.1 (t), 21.5 (t), 25.5 (q), 30.0 (t), 30.7 (t), 30.7 (t), 31.8 (t), 32.8 (t), 63.8 (d), 64.1 (d), 64.1 (d), 67.4 (t), 70.2 (d), 70.2 (d), 72.4 (t), 72.5 (t), 73.1 (t), 73.2 (t), 73.9 (d), 74.2 (d), 81.3 (d), 81.5 (d), 81.7 (d), 81.8 (d), 82.1 (d), 82.9 (s), 127.7 (d), 127.9 (d), 128.0 (d), 128.4 (d), 138.1 (s); IR (film) (cm^{-1}) 3393, 3294, 2940, 2859, 1455, 1095; Anal. Calcd for $C_{19}H_{26}O_4$: C, 71.67; H, 8.23. Found: C, 71.63; H, 8.22.

Preparation of (4*Z*,2*R* and 2*S*)-5-[(2*R*,3*S*)-3-(*tert*-Butyldimethylsilyloxy)tetrahydro-2*H*-pyran-2-yl]-4-pentene-1,2-diol (40). A mixture of alkyne **35** (0.6 g, 1.9 mmol), Lindlar's catalyst (10 mg), and quinoleine (one drop) in EtOAc (19 mL) was placed under a H_2 atmosphere. The reaction mixture was vigorously stirred for 2 h and then filtered through Celite. The solvent was removed under reduced pressure and the residue purified by column chromatography on silica gel to afford **40** (574 mg, 95% yield) as an oil: ^{1}H NMR ($CDCl_3$) δ 0.02 (s, 3H), 0.04 (s, 3H), 0.05 (s, 3H), 0.06 (s, 3H), 0.84 (s, 9H), 0.85 (s, 9H), 1.24 (m, 2H), 1.66 (m, 4H), 2.03 (m, 2H), 2.21−2.45 (m, 4H), 3.40 (m, 4H), 3.51 (m, 2H), 3.58−3.90 (m, 8H), 5.59 (m, 2H), 5.72 (m, 2H); ^{13}C NMR ($CDCl_3$) δ −4.7 (q), −4.6 (q), 17.9 (s), 18.0 (s), 25.3 (t), 25.4 (t), 25.6 (t), 25.7 (q), 25.8 (t), 31.9 (t), 32.1 (t), 32.5 (t), 32.8 (t), 33.3 (t), 33.4 (t), 65.8 (t), 66.3 (t), 67.4 (t), 67.5 (t), 69.9 (d), 70.6 (d), 70.9 (d), 71.2 (d), 71.6 (d), 77.7 (d), 78.0 (d), 78.1 (d), 130.5 (d), 130.9 (d), 131.7 (d), 132.0 (d); IR (film) (cm^{-1}) 3405, 2935, 2882, 2854, 1253, 1101. Anal. Calcd for $C_{16}H_{32}O_4Si$: C, 60.72; H, 10.19. Found: C, 60.71; H, 10.26.

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Supporting Information Available: Experimental details for the preparation of compounds **2b**, **2c**, **2d**, **4b**, **4c**, **4d**, **7d**, **7f**, **7b**, **7e**, **7g**, **9a**, **10a**, **9b**, **10b**, **9d**, **10d**, **9e**, **10e**, **9f**, **10f**, **11**, **10g**, **12**, 2-but-3-ynyloxytetrahydropyran, **17**, **19**, **20**, **23a**, **23b**, **24a**, **24b**, **27**, **29**, **31**, **32**, **39**, **41**, **42**, **43**, and **44**; ^{1}H and ^{13}C NMR spectra for compounds **4a**, **4b**, **4c**, **4d**, **9a**, **10a**, **9b**, **10b**, **11**, **12**, **19**, **20**, **24a**, **24b**, **24c**, **24d**, **24e**, **31**, **32**, **39**, **43**, and **44**; COSY and NOE experiments for compounds **24c**, **24b**, **31**, **32**, **39**, **43**, and **44**. This material is available free of charge via the Internet at http://pubs.acs.org.

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