and chromatographed in methanol on Sephadex LH-20. Typically, a 20–30-g portion in methanol was subjected to steric exclusion chromatography on a 7.5 × 120 cm column prepared from Sephadex LH-20 (1 kg) and methanol. Progress of the chromatogram was followed by TLC using methylene chloride–methanol (95:5) as the mobile phase. The fraction (26.4 g) containing bryostatin 1 was chromatographed in 2–10-g amounts on columns of silica gel 60 in methylene chloride. Elution was conducted with methylene chloride followed by an increasing gradient of methanol. The bryostatin-containing fraction (2.2 g total) was rechromatographed at 5 psi by using a Lobar B silica gel 60 column with a hexane–acetone gradient to afford 630 mg of bryostatin 1 (**1a**). When bryostatin 2 containing fractions 13–15 (38 g) were subjected to the same chromatographic procedures used to isolated bryostatin 1 a total of 588 mg of pure bryostatin 2 (**1b**) was obtained.

Isolation of Bryostatins 12 and 13. Analytical TLC of adjacent fractions from the preceding purification of bryostatins 1 and 2, using 7:3 hexane–acetone and 3:2 ethyl acetate–hexane, revealed the possible presence of other bryostatin-type constituents in relatively minor amounts. Such fractions were individually chromatographed by employing RP-18 reversed-phase HPLC. In each case, elution was begun with methanol–water (1:1) at a flow rate of 2.0 mL/min with a gradient to methanol. By this means pure specimens of amorphous bryostatin 3 (1.6 mg), bryostatin 8 (13.2 mg),[2] bryostatin 9 (16.4 mg),[18] bryostatin 12 (3.7 mg), and bryostatin 13 (0.7 mg) were isolated. Known bryostatins 1, 2, 3, 8, and 9 were identified by direct comparison (principally by 400-MHz NMR and SP-SIMS molecular weight determinations) with authentic samples and by co-TLC in several solvent systems.

Bryostatin 12 (4): $C_{49}H_{72}O_{17}$; TLC R_f 0.56 (CH_2Cl_2–CH_3OH, 95:5); MS (SP-SIMS), m/z 971 ($[M + K]^+$), 957 ($[M + K - CH_3 + H]^+$), 897 ($[M + K - COCH_2CH_2CH_3 - 3H]^+$), and 883 ($[M + K - OCOCH_2CH_2CH_3 - H]^+$); $[\alpha]^{27}_D$ +39° (c 0.108, CH_3OH); UV (CH_3OH) λ_{max} 231 and 263 nm (log ϵ 4.46, 4.47); IR (thin film on NaCl) ν_{max} 3470, 3346, 2964–2949, 1734, 1717, 1660–1640, 1440, 1380, 1365, 1270, 1250, 1220, 1164, 1100, 1070, 1055, 1000, and 860 cm^{-1}. The ^1H NMR and ^{13}C NMR data have been entered in Table I and structure **4**, respectively.

Bryostatin 13 (5): $C_{41}H_{62}O_{15}$; TLC R_f 0.51 (CH_2Cl_2–CH_3OH, 95.5); MS (SP-SIMS), m/z 833 ($[M + K]^+$); low-resolution MS, m/z 817 ($[M + Na]^+$), 745 ($[M + Na - COCH_2CH_2CH_3 - H]^+$), and 727 ($[M + Na - OCOCH_2CH_2CH_3 - 3H]^+$); UV ($CH_3OH$) λ_{max} 228 nm (log ϵ 3.96); IR (thin film) ν_{max} 3475, 3359, 2926, 1734, 1717, 1685, 1653, 1606, 1436, 1380, 1153, 1096, and 1077 cm^{-1}. The ^1H NMR data has been recorded on structure **5**.

Conversion of Bryostatin 2 (1a) to Bryostatin 12 (4). A 20-mg sample of bryostatin 2 (**1a**) was treated with pyridine (0.25 mL and butyric acid anhydride (0.5 mL). The solution was allowed to stand for 44 h at room temperature (under nitrogen) and concentrated to dryness. Preparative TLC using 7:3 hexane–acetone led to 12 mg of bryostatin 2 dibutyrate (**1c**, $C_{53}H_{78}O_{18}$); TLC R_f 0.80 (CH_2Cl_2–MeOH, 95:5); MS (SP-SIMS), m/z 1041 ($[M + K]^+$).

To a solution of bryostatin 2 dibutyrate (**1c**, 12 mg) in ethanol (1 mL) was added 6.0 N hydrochloric acid (0.25 mL). After removal of the ethanol the residue was partitioned between methylene chloride and water. The chlorocarbon phase was dried over anhydrous sodium sulfate, the solvent evaporated and the residue purified by preparative TLC using 95:5 methylene chloride–methanol as the mobile phase to afford 2.5 mg of bryostatin 12 (**4**) identical (by comparison TLC and ^1H NMR, ^{13}C NMR, IR, UV, $[\alpha]_D$, and SP-SIMS spectral properties) and the natural product (**4**). Recovered starting material **1c** was resubmitted to the same hydrolysis procedure to improve the yield of bryostatin 12.

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Registry No. **1a**, 83314-01-6; **1b**, 87745-28-6; **1c**, 108268-91-3; **4**, 107021-10-3; **5**, 107021-11-4; bryostatin 3, 87370-86-3; bryostatin 8, 102580-64-3; bryostatin 9, 102604-78-4; butyric acid, 107-92-6.

Potent Prostacyclin Analogues Based on the Bicyclo[4.2.0]octane Ring System[1]

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The novel and biologically active prostacyclin mimetics **2** and **29** were prepared in a sequence based on the regioselective opening of epoxide **7** with a lithium acetylide in the presence of boron trifluoride etherate. The regioselectivity of epoxide opening was consistent with a mechanism involving coordination in the transition state of the epoxide and endo acetal oxygens with the Lewis acid boron. Diastereomers **10** and **11** were separated through formation of their dicobalt hexacarbonyl complexes **12** and **13**, followed by chromatography and oxidative cleavage. The individual racemic diastereomers **10** and **11** were then resolved into the four enantiomeric keto diols **23–26** through a four-step sequence. The side-chain alcohol (*S*)-**9a** was obtained through reduction of acetylenic ketone **27** with (*S*)-*B*-isopinocampheyl-9-borabicyclo[3.3.1]nonane, and its absolute stereochemistry was determined by its transformation to (*S*)-hexahydromandelic acid. The absolute stereochemical assignments for keto diols **23–26** were made on the basis of CD spectroscopy, single-crystal X-ray structural determination of **23**, and the transformation of (*S*)-**9a** into **23** and **26**. Prostacyclin mimetics **2** and **29**, which were obtained through Wittig olefination of **23** and **26**, had ca. 10 times the potency of PGE_1 in inhibiting the ADP-induced aggregation of human platelets.

Our previous research on prostacyclin mimetics resulted in the preparation of the bicyclo[3.2.0]heptane **1**, which was a potent inhibitor of ADP-induced aggregation of human platelets.[2] In seeking to extend this finding to the

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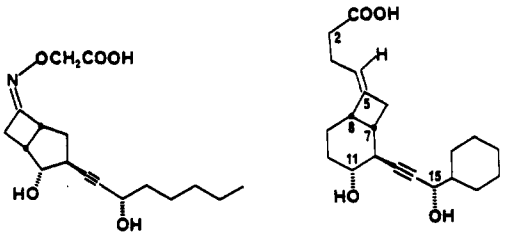
discovery of new systems possessing unique biological activity profiles, we chose to modify both the five-membered ring and the carboxyl-bearing side chain of **1** to give the bicyclo[4.2.0]octane system exemplified by **2**. We report herein the chemistry of this system and the remarkable biological activity of two isomeric final products.

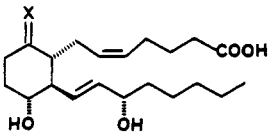
At the outset, results obtained from a related ring-expanded series did not augur well for finding significant biological activity in our target molecule. It was known that analogues **3a** and **3b**, which represented one-carbon expansions of the five-membered ring of PGE_2 (**4a**) and $PGF_{2\alpha}$ (**4b**), possessed less potency than their natural counterparts.[3] We reasoned, however, that the drop in potency observed with **3a** and **3b** could result from an intrinsic preference for a chair conformation in six-membered rings, which would lead to a decreased affinity of these analogues for prostaglandin receptors. Three principal determinants of receptor affinity for prostanoids were known to be the hydroxyls at C-11 and C-15 and the carboxylate at C-1,[4] and it was readily apparent upon attempted superimposition of Dreiding models of the all-equatorial substituted chair conformations of **3a** or **3b** with their natural five-membered ring counterparts that there was poor overlap of the corresponding C-11 and C-15 hydroxyl functions. However, conversion of models of either **3a** or **3b** into higher energy conformers, such as an all-axial substituted chair or a twist boat, permitted very good overlap to be achieved between the corresponding sets of hydroxyl groups. Since these higher energy conformers would be present to an extent of less than 1% at physiological temperature, the low biological activity of these ring-expanded analogues appeared to correlate with conformation.

Our proposed system **2**, on the other hand, seemed to have greater potential for bioisosterism with prostacyclin (**5**) than did either **3a** or **3b** with their natural counterparts. In essence, it was clear that the fusing of a four-membered ring to the cyclohexane ring, as in **2**, would distort the six-membered ring away from a pure chair conformation, and the resulting system could more readily adopt conformations that would present the key components for receptor affinity in an optimal fashion. Indeed, when we compared Dreiding and computer-generated models[5] of **2**[6] and **5**, we could achieve excellent superimposability of the two hydroxyl functions. Furthermore, when the sets of hydroxyls in **2** and **5** were superimposed in the models, it was clear that the carboxylic acid function should be connected to the ring system at position 5 by three carbon atoms in order to best share the locus of points defined by the carboxylic acid function of **5**. With these thoughts as our basis, we set out to prepare **2** for biological evaluation.

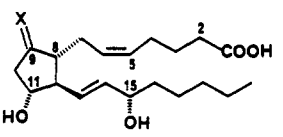


1

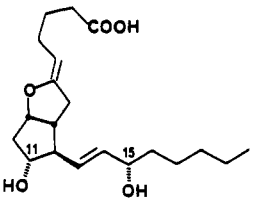
2



3a : X = O
3b : X = α-OH; β-H



4a : X = O
4b : X = α-OH; β-H



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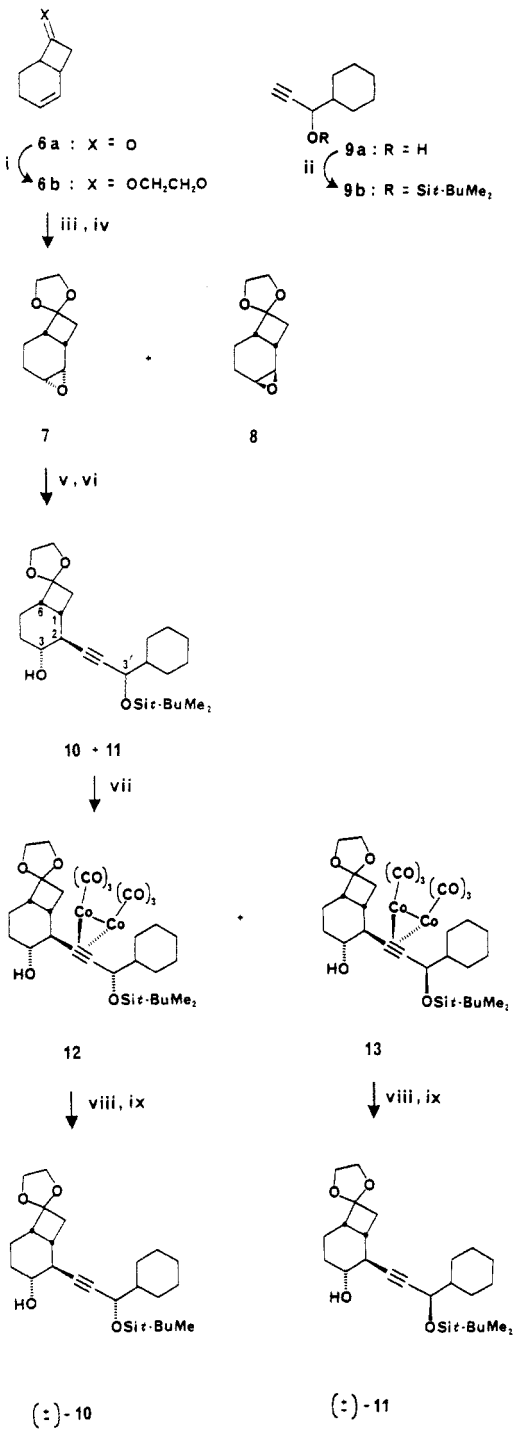
Results and Discussion

Preparation of Diastereomers 10 and 11. The synthesis of the racemic, diastereomeric intermediates **10** and **11** is outlined in Scheme I. The known racemic bicyclo[4.2.0]octenone (**6a**)[7] was transformed into acetal **6b**, which was then converted into a mixture of epoxides **7** and **8** (ca. 4:1) by reaction with *N*-bromoacetamide in aqueous acetone followed by reaction of the intermediate bromohydrin with potassium carbonate. The structural assignment for the major product **7** as the α-epoxide was based on the expectation that the major precursor bromohydrin would be formed through electrophilic attack by the bromonium ion from the less hindered β face of the alkene **6b**. The mixture of epoxides **7** and **8** was used without separation in a condensation with the lithium salt of acetylene **9b** in the presence of boron trifluoride etherate. Workup of this reaction afforded in 65% yield the diastereomers **10** and **11**, which appeared as a *single component* by TLC and GLPC analysis. The separation of **10** and **11** was achieved readily through the application of the elegant method of Fried,[8] wherein diastereomeric propargylic alcohols and their derivatives are rendered physically separable through the formation of their dicobalt hexacarbonyl complexes. Reaction of the mixture of **10** and **11** with dicobalt octacarbonyl produced a high yield of the red dicobalt hexacarbonyl complexes **12** and **13**, which were readily separable by chromatography. Ceric ion oxidation of each complex liberated the pure individual diastereomers **10** and **11**. In one experiment the ratio of **10** to **11** was 42:58. However, in subsequent runs of this sequence we observed ratios of nearly 1:1 for the isomers **10** and **11**, and therefore it appears that there was little diastereoselectivity in the epoxide opening.

The structural assignments for **10** and **11** were based initially on a combination of NMR and TLC evidence. The ^1H NMR spectra of **10** and **11** were in accord with the proposed gross structures, but these data alone were insufficient to allow the unambiguous assignment of either the regiochemistry of epoxide opening or the stereochem-

(1) Contribution No. 720 from the Institute of Organic Chemistry.
(2) O-Yang, C.; Kertesz, D. J.; Kluge, A. F.; Kuenzler, P.; Li, T.-t.; Marx, M.; Bruno, J. J.; Chang, L.-f. *Prostaglandins* **1984**, *27*, 851.
(3) Crossley, N. S. *Tetrahedron Lett.* **1971**, 3327.
(4) Andersen, N. H.; Ramwell, P. W. *Arch. Intern. Med.* **1974**, *133*, 30.
(5) Models were generated by using PRXBLD, Molecular Design, San Leandro, CA.
(6) A cyclohexyl substituent was used in lieu of the *n*-amyl substituent of the natural prostaglandin lower side chain because of the increased biological activity from this modification in the bicyclo[3.2.0]heptane series: O-Yang, C.; Wu, H. Y.; Kertesz, D. J.; Kluge, A. F., unpublished results.
(7) Ghosez, L.; Montaigne, R.; Roussel, A.; Vanlierde, H.; Mollet, P. *Tetrahedron* **1971**, *27*, 615.
(8) O-Yang, C.; Fried, J. *Tetrahedron Lett.* **1983**, *24*, 2533.

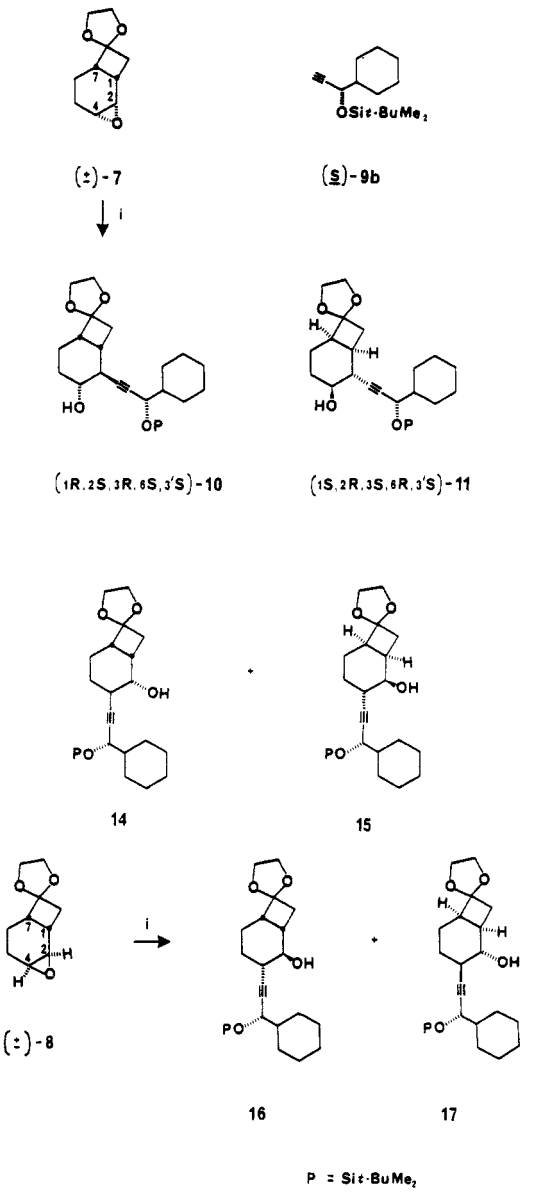
Scheme I. Preparation of Diastereomers 10 and 11[a]



[a] Reagents and conditions: (i) $HOCH_2CH_2OH$, *p*-TSA, C_6H_6, Δ; (ii) *t*-$BuMe_2SiCl$, Et_3N, CH_2Cl_2; (iii) *N*-bromoacetamide, H_2O, Me_2CO; (iv) K_2CO_3; (v) **9b** + *n*-BuLi, −78 °C; (vi) $BF_3{\cdot}Et_2O$; (vii) $Co_2(CO)_8$, Et_2O; (viii) flash chromatography; (ix) $Ce(NH_4)_2(NO_3)_4$.

istry at C-3′. The assignment of regiochemistry was made unequivocal by the isolation and characterization of both regioisomeric products from the opening of isolated epoxide **7** with the acetylide nucleophile derived from resolved silyl ether **9b** (vide infra). As shown in Scheme II, condensation of pure **7** with lithiated (*S*)-**9b** led to a highly regioselective ring opening and afforded two regioisomers (each a mixture of two optically pure diastereomers) in a ratio of 8.1:1. The structures for these products of the two different modes of epoxide opening were readily assigned on the basis of ^1H NMR decoupling experiments. In the spectrum of the minor product, diastereomers **14** and **15**,

Scheme II. Regiochemistry of Epoxide Opening[a]



[a] Reagents and conditions: (i) (*S*)-**9b** + *n*-BuLi; $BF_3{\cdot}Et_2O$, −78 °C.

irradiation of the proton on the ring carbon bearing the hydroxyl (H-2) produced a simplification in both the multiplet for the proton on the carbon bearing the acetylenic side chain (H-3) and also one of the bridgehead protons (H-1). The same decoupling experiment performed on the major product, diastereomers **10** and **11**, led to a simplification of the proton on the carbon bearing the side chain but did not produce any change in the signals of the bridgehead protons. The vicinal relationships indicated by these decoupling experiments established the correctness of the ring substitution indicated for **10** and **11**. The remaining issue of the relative stereochemistry at C-3′ as α-hydroxy in **10** and as β-hydroxy in **11** could not be resolved with NMR spectral information, and the initial and tentative structural assignments had to be made on the basis of the relative chromatographic mobilities of cobalt complexes **12** and **13** by analogy with their isomeric counterparts in the bicyclo[3.2.0]heptane series.[2] These assignments subsequently were made unequivocal by a combination of single-crystal X-ray analysis and conversion of a resolved intermediate to a compound of known absolute configuration.

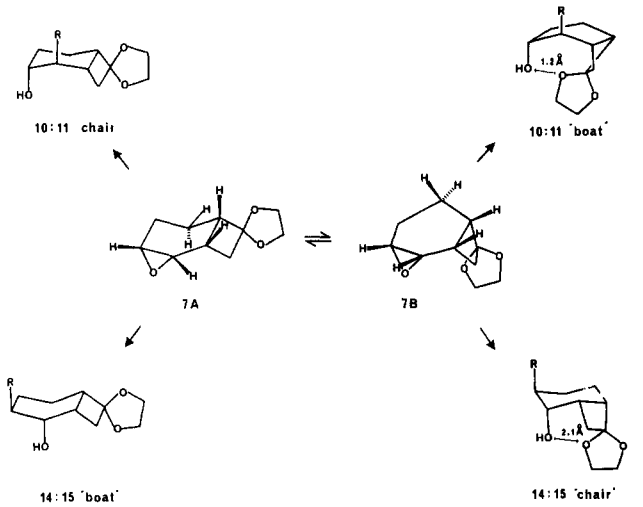


Figure 1.

We also examined the opening of the pure β-epoxide **8**. The reaction of the lithium acetylide prepared from (*S*)-**9b** with **8** in the presence of boron trifluoride etherate at −78 °C gave only a single regioisomer as the product. This proved to be the diastereomeric pair **16/17** in 62% yield. The structural assignment for **16/17** was straightforward since the ^{1}H NMR spectrum of **16/17** displayed well-resolved signals for H-1, H-2, H-6, H-8α, and H-8β, wherein the bridgehead proton H-1 was coupled to a proton on a hydroxyl-bearing carbon (H-2).

The reversal of regioselectivity seen in the openings of epoxide diastereomers **7** and **8** presents a noteworthy contrast. Nucleophilic attack occurred predominantly at position 4 in the β-epoxide **8**, whereas in the α-epoxide **7** the attach was predominantly at position 2. In the case of epoxide **8**, it is clear that the steric interaction between the acetylide nucleophile and the cyclobutane methylene would favor attack at position 4 over that at position 2. On the other hand, there are no such readily apparent steric factors governing the regiochemistry of opening of epoxide **7**. The normal stereochemical course of epoxide opening in a six-membered ring is a kinetically controlled, coplanar, trans-diaxial opening. This preference is seen in reactions with Grignard reagents,[9] cyanide–triethylaluminum,[10] organocopper species,[11] and lithium aluminum hydride.[12] As depicted in Figure 1, the epoxide **7** can exist as an equilibrium mixture of the two conformers **7A** and **7B**, and trans-diaxial openings of both could produce either the regioisomers **10/11** or **14/15** as "chair" or "boat" conformers. Examination of Dreiding models of conformers **7A** and **7B** did not reveal the operation of any steric factors that would bias the formation of one regioisomer over the other. However, examination of Dreiding models of the chair and boat conformers of both regioisomeric products did indicate the potential for interactions in the transition state that would direct the product mixture in the observed direction. In the models, the hydroxyl oxygen at C-3 and the "endo" oxygen of the acetal functionality are separated by ca. 1.2 Å in the major regioisomer (**10/11** boat) and by ca. 2.1 Å in the minor regioisomer (**14/15** chair). Therefore, the transition state leading to the major product presents a more favorable opportunity for coordination of those two oxygens with the Lewis acid boron, and it is this feature that appears to determine the observed regioselectivity of the epoxide opening.[13]

Table I. Ellipticities in CD Spectra[a]

keto diol	θ	keto diol	θ
23	+1478	**25**	+1357
24	−1342	**26**	−1324

[a] Solvent: CH_3OH.

Further insight into the dynamics of epoxide opening was gained through manipulation of the order of addition of reagents. No reaction occurred when epoxide **7** was mixed with the lithium acetylide in THF at −78 °C. Addition of boron trifluoride etherate to this mixture was followed by a rapid disappearance of starting material concomitant with the appearance of the product **10/11**. In contrast, no reaction was observed when epoxide **7** was added after 10 min to a reagent prepred by mixing the lithium acetylide with boron trifluoride etherate in THF at −78 °C. These observations were consistent with a mechanism wherein coordination of the epoxide oxygen with the boron trifluoride promoted the nucleophilic attack of the acetylide on the epoxide carbon. Ganem has shown that boron trifluoride etherate promotes the addition of alkyl-, alkenyl-, and aryllithiums to epoxides and oxetanes through such a complexation.[14] These studies by the Cornell group demonstrated that the coordination of the epoxide oxygen with boron trifluoride was rapid and that the reaction with the resulting complex was faster than reaction of the boron trifluoride with the alkynyllithium to give an alkynylborane.

Our failure to achieve a reaction with the epoxide after premixing of the lithium acetylide and boron trifluoride etherate is noteworthy in light of a report of successful alkynylations of epoxides using alkynylboranes. Yamaguchi has reported that a reagent prepared by mixing equivalent quantities of a lithium acetylide with boron trifluoride etherate in THF at −78 °C (presumably an alkynyldifluoroborane) gave high yields of addition products with a variety of epoxides.[15] The lack of a reaction in our case may point to the reduced reactivity of either our epoxide or our alkynyldifluoroborane reagent relative to the examples cited by Yamaguchi. Further controlled experiments will be necessary to clarify this matter.

Resolution of 10 and 11 and Proof of Absolute Stereochemistry. The racemic diastereomers **10** and **11** were resolved into their enantiomeric components as outlined in Scheme III. Condensation of both **10** and **11** with (*R*)-α-naphthylethyl isocyanate (**18**)[16] gave the pairs of diastereomeric carbamates **19–22**, which were then isolated by chromatography. Efficient formation of these carbamates from the hindered 3-endo alcohols required alteration of the literature recipe[16] to include the use of diisopropylethylamine as the solvent and (dimethylamino)pyridine (DMAP) as the catalyst. The preparation of the individual dihydroxy ketones **23–26** was achieved in a straightforward manner through reduction of the carbamate group with lithium aluminum hydride followed by acid hydrolysis of the silyl and acetal protective groups.

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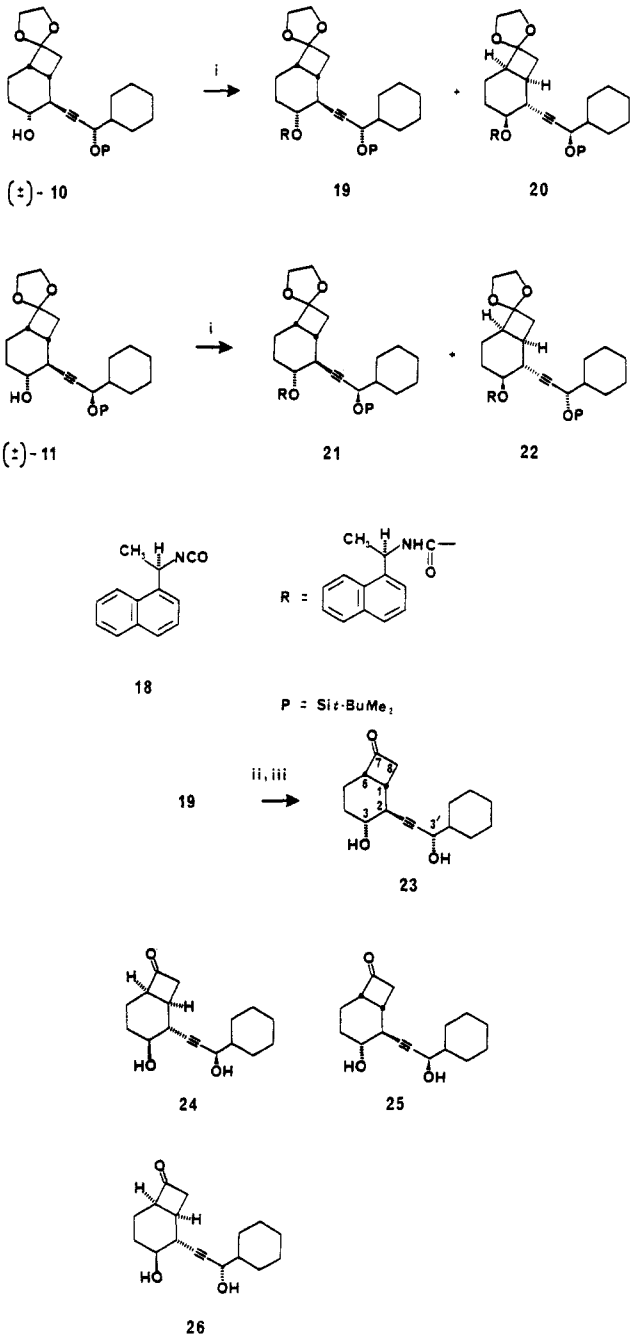
(12) Murphy, D. K.; Alumbaugh, R. L.; Rickborn, B. *J. Am. Chem. Soc.* **1969**, *91*, 2649.
(13) A similar argument has been proposed to explain the regioselectivity observed in the opening of a homologous epoxide in the bicyclo[3.2.0]heptane series: Cave, R. J.; Howard, C. C.; Klinkert, G.; Newton, R. F.; Reynolds, D. P.; Wadsworth, A. H.; Roberts, S. M. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2954.
(14) Eis, M. J.; Wrobel, J. E.; Ganem, B. *J. Am. Chem. Soc.* **1984**, *106*, 3639.
(15) Yamaguchi, M.; Hirao, I. *Tetrahedron Lett.* **1983**, *24*, 391.
(16) Pirkle, W. H.; Hoekstra, M. S. *J. Org. Chem.* **1974**, *39*, 3904.

Scheme III. Preparation of Enantiomers 22-26[a]



[a] Reagents: (i) 18, *i*-Pr_2NEt, DMAP; (ii) $LiAlH_4$; (iii) H_3O^+.

The assignment of absolute stereochemistry for four of the five asymmetric centers of **23–26** was then made through the use of circular dichroism spectroscopy. The signs of the Cotton curves measured for each isomer led to the assignment of stereochemistry at C-6. For example, the structure of ketone **23** was assigned on the basis of a positive Cotton effect (Table I). Examination of Dreiding models showed that **23** could exist in two conformations, as depicted in Figure 2. The six-membered ring portion of the bicyclo[4.2.0]octane skeleton was situated in a positive octant in either conformation **23A** or **23B**; however, the propargylic side chain was in a positive octant in **23A** and in a negative octant in **23B**. Our structural assignment was based on the assumption that the contributions to the Cotton effect made by the ring system and the propargylic side chain would roughly cancel each other in **23B** while they would reinforce each other in **23A** to give a positive sign to the ellipticity. Once having assigned the stereochemistry at C-6, the stereochemistry at C-1, C-2, and C-3 followed directly from the cis fusion of the ring juncture and the trans relationship of the C-2 side chain and the C-3 hydroxyl. At this point, there remained the matter of assigning the absolute configuration at C-3′ in keto diols **23–26**. The configuration of this stereocenter was assigned initially on the basis of the relative TLC mobilities of the dicobalt hexacarbonyl complexes **12** and **13** in analogy to the pattern previously observed in the bicyclo[3.2.0]heptane system.[2] Subsequent biological testing of prostacyclin analogues prepared from these keto diols strengthened our confidence in these assignments, since the biologically active compounds were those wherein the C-3′ center had been assigned the *S* absolute stereochemistry, which is the absolute stereochmistry normally associated with biological activity in prostaglandins and their analogues.

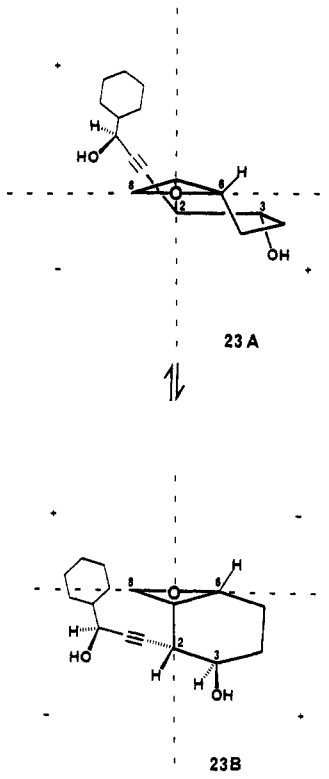


Figure 2. Octant projections of keto diol **23**.

A stronger link in the chain of proof was obtained from the single-crystal X-ray structure determination of **23**. As shown in Figure 3, the X-ray-derived structure was in complete accord with the assignment made on the basis of TLC mobility and biological activity correlations. However, since we lacked a heavy atom in **23**, the X-ray data were insufficient to make an assignment of absolute stereochemistry to the five stereocenters.

The final element of proof that established the stereochemistry at all five stereocenters of **23–26** was obtained through the correlation of the absolute stereochemistry of the proparglyic lower side chain of **23** with a compound of known absolute configuration. As shown in Scheme IV, the optically active lower side-chain component was prepared through reduction of the propargylic ketone **27** with (*S*)-*B*-isopinocampheyl-9-borabicyclo[3.3.1]nonane (*S*-Alpine Borane). On the basis of the transition state proposed by Midland,[17] this reagent would be expected to give (*S*)-**9a**. The crude product of this reduction was deter-

(17) Midland, M. M.; McDowell, D. C.; Hatch, R. L.; Tramontano, A. *J. Am. Chem. Soc.* **1980**, *102*, 867.

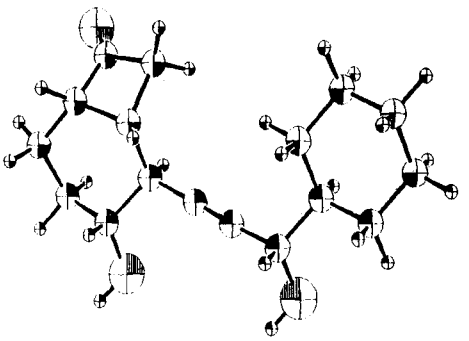
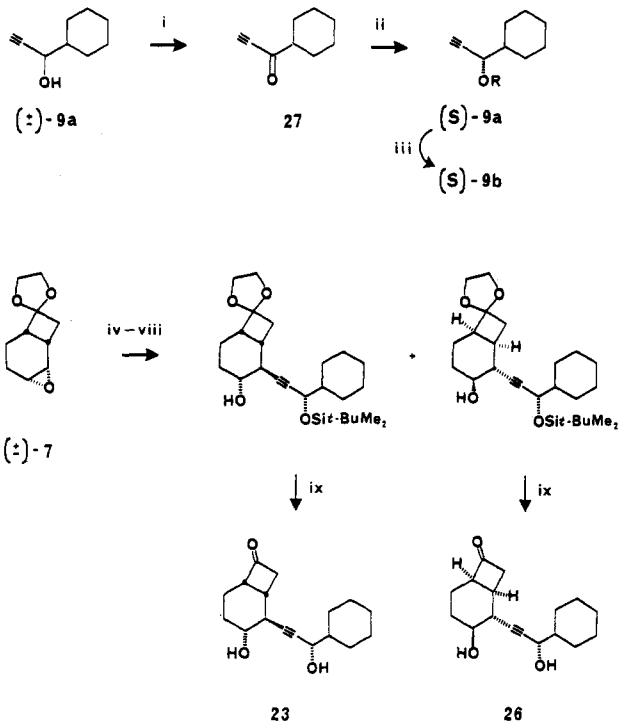


Figure 3. Stereoprojection of keto diol **23**.

Scheme IV. Preparation of Keto Diols 23 and 26[a]



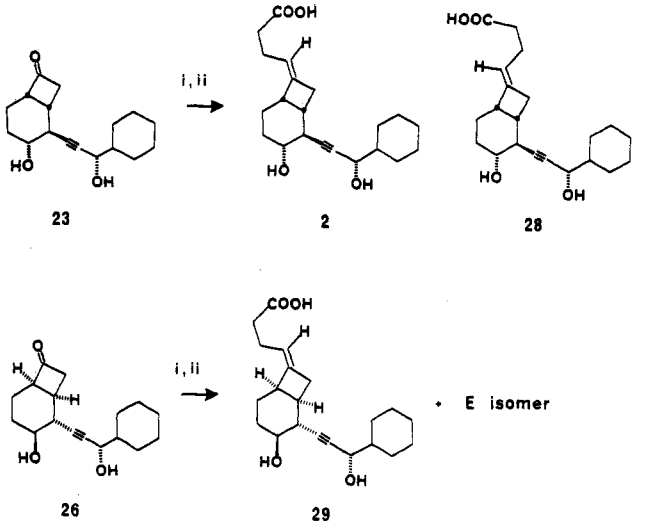
[a] Reagents and conditions: (i) H_2CrO_4; (ii) Alpine Borane; (iii) *t*-$BuMe_2SiCl$, Et_3N, CH_2Cl_2; (iv) (*S*)-**9b** + *n*-BuLi, −78 °C; (v) $BF_3{\cdot}Et_2O$, −78 °C; (vi) $Co_2(CO)_8$, Et_2O; (vii) flash chromatography; (viii) $Ce(NH_4)_2(NO_3)_4$; (ix) H_3O^+.

mined by ^1H NMR experiments utilizing a chiral shift reagent to be 92% ee, and recrystallization of this product gave material of greater than 99% ee. Transformation of (*S*)-**9a** to its *O*-*tert*-butyldimethylsilyl derivative (*S*)-**9b** followed by processing through the steps outlined in Scheme IV led to compounds **23** and **26**, which were in all respects identical with samples prepared via Scheme III. Finally, the conversion of (*S*)-**9a** into (*S*)-hexahydromandelic acid completed the proof of absolute stereochemistry for compound **23**. By deduction, this proof also permitted the unequivocal stereochemical assignment of the three other dihydroxy ketones **23–26**.

Prostanoids 2 and 29. As shown in Scheme V, a four-carbon carboxylic acid side chain was added to **23** by use of a Wittig reaction. This reaction gave approximately equal parts of *Z* isomer **2** and *E* isomer **28**. These isomers were readily distinguishable by the ^1H NMR signals for H-8, which were 0.15 ppm downfield in **2** relative to **28**. We also elaborated the four-carbon side chain on the remaining keto diols **24–26** to obtain the respective prostanoid products.

To our gratification, there was significant biological activity associated with several of these prostanoid products. When tested in an assay of ADP-induced aggregation of human platelets,[2] the naturally configured compound **2** displayed a potency of more than 10 times that of PGE_1.[18] Furthermore, compound **29** (derived from keto diol **26**), which is related to **2** by inversion of all stereocenters except C-3′, was equivalent to **2** in its antiaggregatory potency. While there were several precedents for biological activity in prostanoids with unnaturally configured stereocenters,[4] it was nonetheless very surprising to find parity between a compound with natural stereochemistry such as **2** and its "ent-15-epi" isomer **29**.[19]

Scheme V. Synthesis of Prostacyclin Analogues[a]



[a] Reagents: (i) $CH_3SOCH^-Na^+$, $Br^-Ph_3P^+CH_2CH_2CH_2CO_2H$, CH_3SOCH_3; (ii) H_3O^+.

In summary, results from platelet aggregation assays have clearly established the potential of the bicyclo[4.2.0]octane system as a useful scaffold for carrying the key determinants of prostacyclin-like biological activity.[20] A detailed description of the biological activity profiles of **2**, **29** and related analogues will be the subject of a subsequent publication of the medicinal chemistry of this series.

Experimental Section

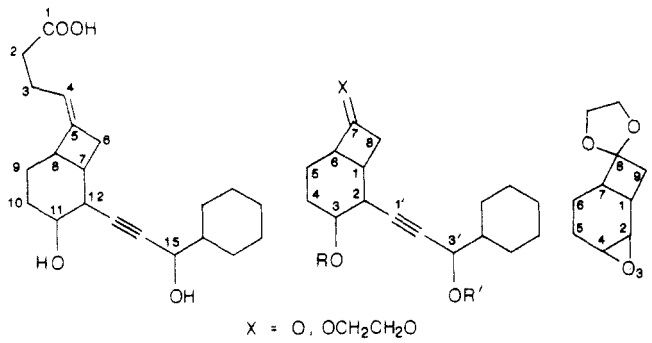
Measurements. ^1H NMR spectra were measured on a Bruker WM-300 spectrometer. ^{13}C NMR spectra were measured on either Bruker WH-90 or WM-300 instruments. Spectra were determined

(18) PGE_1 was used as a reference standard because of its relatively greater chemical stability over PGI_2. In the assay for ADP-induced platelet aggregation, PGI_2 has a potency of ca. 20 times that of PGE_1.

(19) For nomenclature, see: Cooper, E. L.; Yankee, E. W. *J. Am. Chem. Soc.* **1974**, *96*, 5876.

(20) For a recent review of prostacyclin analogues, see: Beck, G.; Bartmann, W.; Knolle, J.; Lau, H. H.; Rupp, H. R.; Wess, G.; Scholkens, B.; Weitmann, U. In *Innovative Approaches in Drug Design*; Harns, A. F., Ed.; Elsevier: New York, 1986; p 223.

in $CDCl_3$ solutions and were referenced to internal tetramethylsilane. Coupling constants are in hertz, and IR values are in reciprocal centimeters. Melting points were recorded on a Fisher-Johns apparatus and are uncorrected. Optical rotations were determined on a Perkin-Elmer 141 polarimeter. Elemental analyses were performed by the Syntex Analytical Research Services group. Mass spectra were obtained on a MAT CH-7 single-focusing instrument. The X-ray structural determination was done by Oneida Research Services, Inc., Whitesboro, NY. The following conventions are used for membering the compounds described in paper:



X = O, OCH_2CH_2O

(±)-Spiro(bicyclo[4.2.0]oct-2-ene-7,2′-[1,3]dioxolane) (6b). A mixture of 6.4 g (52.4 mmol) of bicyclo[4.2.0]oct-2-ene-7-one (**6a**), 16.7 mL of ethylene glycol, 100 mL of benzene, and 25 mg of *p*-toluenesulfonic acid was heated at reflux for 4 h with a Dean–Stark trap to effect continuous removal of water. The cooled reaction mixture was poured onto 100 mL of water, and the resulting mixture was extracted with three 75-mL portions of diethyl ether. The mixture was dried over sodium sulfate, the solvent was removed by evaporation, and the residue was isolated by Kugelrohr distillation [100 °C (0.1 mmHg)] to give 7.12 g (42.8 mmol, 83%) of **6b** as an oil: ^{1}H NMR δ 1.6–1.8 (m, 2), 1.83–1.95 (m, 1), 2.03–2.2 (m, 2), 2.42–5.59 (m, 2), 2.63–2.75 (m, 1), 3.8–3.95 (m, 4, CH_2O), 5.73–5.9 (m, 2, HC=). Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.49; H, 8.46.

(2*SR*,2*SR*,4*RS*,7*SR*)- and (1*SR*,2*RS*,4*SR*,7*SR*)-Spiro(3-oxatricyclo[5.2.0.0^{2,4}]nonane-8,2′-[1,3]dioxolanes) (7 and 8). A solution of 5 g (30.1 mmol) of **6b** in 40 mL of acetone and 20 mL of water was cooled to ca. 0 °C with an ice bath, and 4.76 g (38.4 mmol) of *N*-bromoacetamide was added over 1 h. This mixture was stirred at 23 °C for 20 h, and then 12.4 g of potassium carbonate was added in one portion. This mixture was stirred at 23 °C for 72 h. The mixture was saturated with sodium chloride and was extracted with four 150-mL portions of diethyl ether. The combined extract was washed with 100 mL of saturated sodium chloride solution and was dried over sodium sulfate. Removal of solvent by evaporation followed by chromatography over silica gel with 15% ethyl acetate–hexane gave 3.45 g (18.9 mmol, 63%) of a mixture of **7** and **8**: ^{1}H NMR δ 1.2–2.82 (m, 8), 3.095 (t, *J* = 4, H-2(3)), 3.23 (br t, *J* = 4, H-3(2)), 3.26–3.30 (m), 3.7–3.95 (m, 4, OCH_2). The integral for the absorptions from δ 3.05 to 3.3 was two protons. Comparison of the peak heights for corresponding carbons in the ^{13}C NMR of the mixture of **7** and **8** indicated an isomer ratio of 3.56–4.8:1. Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74. Found: C, 65.80, H, 7.66.

In another preparation, a mixture of 1.4 g (8.4 mmol) of **6b** and 2 g (9.9 mmol) of 3-chloroperoxybenzoic acid in 20 mL of dichloromethane was stirred at 23 °C for 16 h. The mixture was filtered, and the solids were washed with dichloromethane. The filtrate was washed with water, saturated sodium bicarbonate, and saturated sodium chloride. Evaporation of solvent and chromatography over silica gel using a mixture of hexane, dichloromethane, and acetone (14:14:1) led to the isolation of the epoxide isomers **7** and **8**. The less polar was **8** (420 mg, 2.3 mmol, 27%): ^{1}H NMR δ 3.072 (br d, 1, *J* = 4.1, H-2), 3.27 (m, 1, H-4), 3.82–3.97 (m, 4, CH_2O); ^{13}C NMR δ 16.29 (C-6), 20.84 (C-5), 22.26 (C-1), 36.96 (C-9), 41.89 (C-7), 52.98 (C-4), 54.03 (C-2), 63.51 and 64.73 (Ch_2O), 108.67 (C-8). The more polar isomer was **7** (300 mg, 1.8 mmol, 21%): ^{13}C NMR δ 15.46 (C-6), 20.46 (C-5), 22.82 (C-1), 36.59 (C-9), 43.16 (C-7), 51.70 (C-4), 52.77 (C-2), 63.30 and 64.51 (CH_2O), 108.52 (C-8).

Preparation of Diastereoisomers 10 and 11. To a 500-mL two-neck flask equipped with a septum, thermometer, and gas inlet tube was added a solution of 18.7 g (74.1 mmol) of acetylene (*RS*)-**9b** in 80 mL of THF. The contents of the flask were cooled to 0 °C and were maintained under a positive pressure of argon. A solution of 1.26 M *n*-butyllithium in hexane (60 mL, 75 mmol) was added over 15 min. This solution was cooled to −78 °C, and a solution of 9 g (49.4 mmol) of the epoxide mixture **7** + **8** in 20 mL of THF was added. Boron trifluoride etherate was added in two portions (4.2 and 1.8 mL, 48.8 mmol) at 10-min intervals. After the mixture was stirred at −78 °C, it was poured onto saturated sodium sulfate solution. The resulting mixture was extracted thoroughly with ethyl acetate. This procedure was repeated on the same scale and under the same conditions. The combined extract from these two experiments was evaporated and was purified by flash chromatography, eluting first with hexane to remove the excess **9** and then with 2% acetone–dichloromethane to give 14 g (32.2 mmol, 65%) of a mixture of **10** and **11**. Anal. Calcd for $C_{24}H_{42}SiO_4$: C, 69.08; H, 9.74. Found: C, 69.07; H, 9.53. To a solution of 14 g (34.1 mmol) of **10** + **11** in 500 mL of diethyl ether was added 13.2 g (38.6 mmol) of dicobalt octacarbonyl, and the resulting solution was stirred at 23 °C for 1 h. The solution was filtered through a short column of silica gel to remove polar impurities, and the column was washed with an additional ca. 200 mL of diethyl ether. The solvent was removed by evaporation, and the two components were separated by flash chromatography using 12% ethyl acetate–hexane: **12** (less polar) and **13** (more polar). Each of the individual cobalt hexacarbonyl complexes was dissolved in 400 mL of acetone–water (9:1), and 41.2 g (75 mmol) of ceric ammonium nitrate was added in portions to each solution over a ca. 15-min period. After the disappearance of the red color of the cobalt complex, the mixture was diluted with water (ca. 1 L), and the mixture was extracted thoroughly with diethyl ether. The combined ether extract was washed with saturated sodium chloride solution and was dried over sodium sulfate. Evaporation of solvent gave 4.7 g (10.8 mmol) of **10** and 6.56 g (15.1 mmol) of **11**. **10**: ^{1}H NMR δ 0.899 (s, 9, $(CH_3)_3C$), 0.95–1.9 (m, 15), 2.01 (dd, 1, *J* = 1.87, 12.4, H-8α), 2.1–2.2 (m, 1, H-1), 2.43 (ddd, 1, *J* = 1, 8, 12.4, H-8β), 2.58–2.72 (m, 2, H-2, H-6), 3.4 (m, 1, H-3), 3.8–4 (m, 4, CH_2O), 4.09 (dd, 1, *J* = 1.76, 6.41, H-3′). Anal. Calcd for $C_{25}H_{42}SiO_4$: C, 69.08; H, 9.74. Found: C, 69.11; H, 9.67. **11**: ^{1}H NMR δ 0.899 (s, 9, $(CH_3)_3C$), 0.95–1.9 (m, 15), 2.02 (dd, 1, *J* = 1.99, 12.4, H-8α), 2.07–2.22 (m, 1, H-1), 2.38–2.47 (ddd, 1, *J* = 1, 8, 12.4, H-8β), 2.58–2.72 (m, 2, H-2, H-6), 3.34–3.45 (m, 1, H-3), 3.8–4 (m, 4, CH_2O), 4.08 (dd, 1, *J* = 1.75, 6.35, H-3′). Anal. Calcd for $C_{24}H_{42}SiO_4$: C, 69.08; H, 9.74. Found: C, 69.22; H, 9.97.

Preparation of (*RS*)- and (*S*)-1-Cyclohexyl-2-propyn-1-ol (9a) and *tert*-Butyldimethylsilyl Ethers (*RS*)-9b and (*S*)-9b. (a) (*RS*)-1-Cyclohexyl-2-propyn-1-ol (9a). A solution of ethynylmagnesium bromide in THF was prepared by simultaneous addition over a 3-h period of dry acetylene and ethylmagnesium bromide (1.8 L of a 2 M solution in THF, 3.6 mol) to 800 mL of THF. After addition of the ethylmagnesium bromide, a slow stream of acetylene was passed into the solution for an additional 2 h. Cyclohexanecarboxaldehyde (300 g, 2.68 mol) was added dropwise to the stirred solution at 0 °C over a ca. 40-min period. The mixture was stirred at 23 °C for 16 h and was poured onto 3 L of saturated ammonium chloride solution. The layers were separated, and the aqueous layer was washed with a mixture of 300 mL of ethyl acetate plus 500 mL of hexane. The combined organic extract was dried over sodium sulfate. The solvent was removed by evaporation, and the residue was purified by Kugelrohr distillation [95 °C (ca. 5 mm)] followed by vacuum distillation [60–75 °C (1.5 mm)] to give 210 g (1.52 mol, 56.7%) of **9a**: ^{1}H NMR δ 0.8–2.1 (m, 11), 2.45 (d, 1, *J* = 1.8, HC=C), 2.67 (br s, 1, HO), 4.13 (m, 1, H-1). Anal. Calcd for $C_9H_{14}O$: C, 78.21; H 10.21. Found: C, 77.96; H, 10.36.

(b) Chromic Acid Oxidation of 9a. To a stirred solution of 295 g (2.14 mol) of **9a** in 430 mL of acetone at 0 °C was added 860 mL of Jones reagent (prepared from 150 g of chromium trioxide and 130 mL of concentrated sulfuric acid) over a 3-h period. The mixture was stirred at 0 °C for an additional 1 h and was diluted with ca. 1 L of water. The mixture was extracted thoroughly with diethyl ether. The combined extract was washed with saturated sodium sulfate and was dried over sodium sulfate.

Evaporation of solvent and purification by vacuum distillation gave 240 g (1.76 mol, 82%) of 1-cyclohexyl-2-propyn-1-one (**27**): ^{1}H NMR δ 1.15–2.1 (m, 10), 2.36–2.5 (m, 1, CHCO), 3.23 (s, 1, HC≡C).

(c) Reduction of 27 with (*S*)-Alpine Borane. (1*S*)-(−)-α-Pinene (126 g, 0.9 mol, $[\alpha]^{20}_D$ −45° (neat)) was added to a solution of 9-borabicyclo[3.3.1]nonane (1.6 L of a 0.5 M solution in THF). The mixture was heated at reflux under nitrogen for 4 h. The THF and excess α-pinene were removed by distillation, first at atmospheric pressure and then under vacuum, to leave (*S*)-*B*-isopinocampheyl-9-borabicyclo[3.3.1]nonane as a thick oil. This procedure was repeated twice, and the products were combined to give a total of 2.4 mol of (*S*)-*B*-isopinocampheyl-9-borabicyclo[3.3.1]nonane. This material was maintained under nitrogen and was cooled to 0 °C. The ketone **27** (240 g, 1.76 mol) was added with stirring, and the resulting mixture was stirred at 23 °C for 16 h. The excess Alpine Borane was destroyed by addition of 132 mL of propionaldehyde. After 1 h, the liberated α-pinene was removed by vacuum distillation. The residue was diluted with 1.2 L of THF followed by 900 mL of 3 N sodium hydroxide. A 30% solution of hydrogen peroxide (900 mL) was added dropwise at a rate sufficient to keep the temperature between 40 and 50 °C. The resulting mixture was heated at 40 °C for an additional 3 h. The mixture was cooled to 23 °C and was extracted thoroughly with diethyl ether. The combined extract was dried over magnesium sulfate, and the solvent was evaporated to give an oil that was purified by flash chromatography from 1.1 kg of silica gel to give 170 g of product. This material was crystallized from hexane to give 90 g of (*S*)-**9a**: mp 55–58 °C; $[\alpha]^{25}_D$ −11.2° (*c* 1, Et_2O); >99.5% ee by Eu(hfc)$_3$ NMR.

(d) Preparation of *tert*-Butyldimethylsilyl Ethers. A mixture of 18.3 g (132 mmol) of (*RS*)-**9a**, 21.95 g (145 mmol) of *tert*-butylchlorodimethylsilane, and 16 g (158 mmol) of triethylamine in 300 mL of dichloromethane was stirred at 23 °C for 15 h. The solution was washed successively with 500 mL of water, two 150-mL portions of 5% hydrochloric acid, 100 mL of water, and 100 mL of saturated sodium bicarbonate solution. The residue obtained after drying (sodium sulfate) and evaporation was filtered through 150 g of silica gel with 600 mL of hexane. Evaporation and Kugelrohr distillation [100 °C (1 mm)] gave 23.5 g (71%) of (*RS*)-**9b**.

Opening of Epoxide 7. The same procedure used to open the mixture of **7** and **8** was followed, and the quantities used were 522 mg (2.07 mmol) of (*S*)-**9b** in 2 mL of THF, 1.47 mL (1.94 mmol) of 1.32 M *n*-butyllithium in hexane, 215 mg (1.18 mmol) of **7** in 1.5 mL of THF, and 116 μL of boron trifluoride etherate. After workup and flash chromatography using 3% acetone–dichloromethane, two components were isolated. The first eluted fraction was a mixture of diastereoisomers **10** and **11** (242 mg, 47%): ^{13}C NMR δ 20.34 (C-5), 25.85 (CH_3), 29.64 (C-4), 31.12 (C-1), 40.28 (C-8), 41.38, 43.20, 26.03, 26.07, 26.59, 28.76, 45.04 (cyclohexyl C), 63.92 and 64.49 (CH_2O), 67.88 (C-3′), 71.52, 71.60 (C-3), 84.42 and 84.45 (C-1), 85.13 (C-2′), 110.61 (C-7).

The next eluted component was the diastereomeric mixture of **14** and **15** (30 mg, 6%): ^{1}H NMR δ 0.9 (s, 9, $(CH_3)_3C$), 0.95–2.8 (m, 19), 3.66–3.75 (m, 1, H-2), 3.78–4.0 (m, 4, CH_2O), 4.08 (dd, 1, *J* = 1.7, 6.3, H-3′); ^{13}C NMR δ 20.52 (C-5), 25.87 (CH_3), 27.56 (C-4), 28.43 (C-1), 33.80 (C-8), 34.18 (C-3), 45.13 (C-6), 26.05, 26.60, 28.76, and 45.10 (cyclohexyl C), 63.64 and 64.41 (CH_2O), 67.85 (C-3′), 71.77 (C-2), 83.55 (C-1′), 85.70 (C-2′), 108.15 (C-7).

Opening of Epoxide 8. The same procedure was used to open the mixture of **7** and **8**, and the following quantities were used: 460 mg (1.8 mmol) of (*S*)-**9b** in 1.5 mL of THF, 1.3 mL of 1.32 N *n*-butyllithium (1.72 mmol) in hexane, 190 mg of **8** in 1 mL of THF, and 140 μL of boron trifluoride etherate. Workup and flash chromatography using 3% acetone–dichloromethane gave 270 mg (62%) of the mixture of diastereomers **16** and **17** as an oil: ^{1}H NMR δ 0.91 (s, 9, $(CH_3)_3C$), 0.95–1.9 (m, 15), 1.98 (dddd, 1, *J* = 1.9, 8.2, 8.28, 9.2, H-1), 2.12 (dd, 1, *J* = 2.1, 12.4, H-8α), 2.09–2.19 (m, H-3), 2.34 (br s, 1, OH), 2.43 (ddd, 1, *J* = 0.95, 8.2, 12.4, H-8β), 2.86 (br t, 1, *J* = 8.28, H-6), 3.72 (t, *J* = 9.2, H-2), 3.8–4 (m, 4, CH_2O), 4.09 (m, 1, H-3′).

Preparation of (α-Naphthylethyl)carbamates 19–22. To a solution of racemic acetal silyl ether **10** (2.25 g, 5.18 mmol) and 4-(dimethylamino)pyridine (0.76 g, 6.2 mmol) in diisopropylethylamine (20 mL) was added (*R*)-(−)-1-(1-naphthyl)ethyl isocyanate (4.08 g, 20.7 mmol),[16] and the mixture was stirred under nitrogen at 45 °C for 8 h. The resulting slurry was cooled and was filtered, and the filtrate was evaporated to dryness under reduced pressure. This residue was dissolved in ethyl acetate, and the solution was washed three times with water, dried over sodium sulfate, and evaporated in vacuo to give a brown syrup. Silica gel flash chromatography of the residue using ethyl acetate–dichloromethane–hexane (7.5:22.5:70) and rechromatography of each major product in the same system then gave 1.31 g (40.1%) of the less polar carbamate **19** and 1.32 g (40.4%) of more the polar **20** as pure solids. The data for **20** (natural stereochemistry) were as follows: mp 57–59 °C; $[\alpha]^{25}_D$ −25.4° (*c* 0.2, $CHCl_3$); IR (KBr) 1710 (C=O); ^{1}H NMR δ 0.09 and 0.12 (2 s, 6, $SiCH_3$), 0.90 (s, 9, $(CH_3)_3C$), 1.64 (d, 3, *J* = 6.8, $CHCH_3$), 2.04–1.13 (m, 1, H-1), 2.13–2.26 (m, 1, H-8α), 2.35–2.48 (m, 1, H-8β), 2.59–2.79 (m, 2, H-2, H-6), 3.78–3.94 (m, 4, CH_2O), 4.08 (br d, 1, *J* = 5.4, H-3′), 4.56–4.66 (m, 1, H-3), 5.60–5.71 (m, 1, NCH), 7.42–8.17 (m, 7, naphthyl protons). Anal. Calcd for $C_{38}H_{53}O_5NSi$: C, 72.23; H, 8.45; N, 2.22. Found: C, 72.02; H, 8.42; N, 2.14.

The data for **20** (ent stereochemistry) were as follows: mp 107–109 °C; $[\alpha]^{25}_D$ +24.5° (*c* 0.05, $CHCl_3$); IR (KBr) 1720 (C=O); ^{1}H NMR δ −0.06–0.05 (2 s, 6, $SiCH_3$), 0.80 (s, 9, $(CH_3)_3C$), 1.64 (d, 3, *J* = 7.0, $CHCH_3$), 2.05–2.16 (m, 1, H-1), 2.16–2.25 (m, 1, H-8α), 2.32–2.43 (m, 1, H-8β), 2.57–2.80 (m, 2, H-2, H-6), 3.78–3.96 (m, 5, CH_2O, H-3′), 4.56–4.67 (m, 1, H-3), 5.59–5.73 (m, 1, NCH), 7.41–8.19 (m, 7, naphthyl protons). Anal. Calcd for $C_{38}H_{53}O_5NSi$: C, 72.23; H, 8.45; N, 2.22. Found: C, 72.10; H, 8.27; N, 2.20. The racemic acetal silyl ether **11** was similarly transformed into the less polar carbamate **21** (39.3%) and the more polar isomer **22** (35.1%). The data for **21** (15-epi stereochemistry) were as follows: mp 81–83 °C; $[\alpha]^{25}_D$ 25.0° (*c* 0.4, $CHCl_3$); IR (KBr) 1722 (C=O); ^{1}H NMR δ 0.09, 0.12 (2 s, 6, $SiCH_3$), 0.90 (s, 9, $(CH_3)_3C$), 1.64 (d, 3, *J* = 6.8, $CHCH_3$), 2.03–2.13 (m, 1, H-1), 2.13–2.26 (m, 1, H-8α), 2.35–2.48 (m, 1, H-8β), 2.58–2.80 (m, 2, H-2, H-6), 3.78–3.93 (m, 4, OCH_2), 4.07 (br d, *J* = 5.6, H-3′), 4.56–4.67 (m, 1, H-3), 5.60–5.71 (m, 1, NCH), 7.41–8.18 (m, 7, naphthyl H's). Anal. Calcd for $C_{38}H_{53}O_5NSi$: C, 72.23; H, 8.45; N, 2.22. Found: C, 72.22; H, 8.39; N, 2.16. The data for **22** (ent-15-epi stereochemistry) were as follows: mp 139–141 °C; $[\alpha]^{25}_D$ −28.9° (*c* 0.2, $CHCl_3$); IR (KBr) 1720 (C=O); ^{1}H NMR δ 0.00 (br s, 6, $SiCH_3$), 0.83 (s, 9, $(CH_3)_3C$), 1.64 (d, 1, *J* = 6.8, $CHCH_3$), 2.04–2.25 (m, 2, H-1, H-8α), 2.32–2.42 (m, 1, H-8β), 2.58–2.80 (m, 2, H-2, H-6), 3.78–3.96 (m, 5, CH_2O, H-3′), 4.55–4.65 (m, 1, H-3), 5.60–5.73 (m, 1, NCH_3), 7.40–8.19 (m, 7, naphthyl protons). Anal. Calcd for $C_{38}H_{53}O_5NSi$: C, 72.23; H, 8.45; N, 2.22. Found: C, 72.10; H, 8.22; N, 2.20.

Preparation of Keto Diols 23–26. To a stirred solution of lithium aluminum hydride (0.3 g, 8.0 mmol) in 50 mL of THF at 0 °C was added a solution of carbamate **19** (1.25 g, 1.98 mmol) in 1.0 mL of THF over a period of 15 min, and the mixture was then heated at reflux under nitrogen for 1 h. After cooling to 23 °C, the mixture was worked up by sequential dropwise addition of water (0.5 mL), 15% aqueous sodium hydroxide (0.5 mL), and water (0.5 mL).

Filtration and evaporation of the filtrate gave a residue that was redissolved in ethyl acetate, and the solution was then washed twice with water and dried over sodium sulfate. Evaporation gave a residue that was purified by silica gel flash chromatography using ethyl acetate–hexane (15.85), which gave 478 mg (55.6%) of the pure intermediate 3-hydroxy acetal silyl ether as an oil. A solution of this intermediate (465 mg, 1.07 mmol) in 16 mL of acetonitrile containing 0.5 N aqueous sulfuric acid (6 mL) was then stirred at 23 °C for 16 h, after which the mixture was diluted with ethyl acetate, was washed three times with water, and was dried over sodium sulfate. The solution was evaporated to dryness in vacuo, giving a white solid that was further purified by silica gel flash chromatography. Elution with ethyl acetate–hexane (6:4) gave 272 mg (92%) of pure ketone diol **23** (natural stereochemistry): mp 127–128 °C; $[\alpha]^{25}_D$ +4.15° (*c* 0.015, CH_3OH); θ +1478 (λ_{max} 297.8 nm); IR (KBr) 1778 (C=O); ^{1}H NMR δ 0.97–1.96 (m, 15), 2.06–2.19 (m, 1, H-2), 2.55–2.64 (m, 1, H-1), 2.66 (dd, 1, *J* = 2.0, 13.7, H-8α), 3.27–3.39 (m, 2, H-6, H-8β), 3.50 (dt, 1, *J* = 3.6, 10.4, H-3), 4.18 (dd, *J* = 1.7, 6.2, H-3′). Anal. Calcd for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75. Found: C, 73.86; H, 8.71. Carbamates **20**, **21**, and **22** were similarly converted into the crystalline ketone diol **24** (49.2%) and the amorphous glasses **25** (75.8%) and **26** (78.9%), respectively. The data for ketone **24** (ent stereochemistry) were

as follows: mp 125–126 °C; $[\alpha]^{25}_D$ 3.57° (*c* 0.15, CH_3OH); θ 1342 (λ_{max} 298.8 nm). Anal. Calcd for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75. Found: C, 73.79; H, 8.64. Data for ketone **25** were as follows: $[\alpha]^{25}_D$ +3.72° (*c* 0.15, CH_3OH); θ 1357 (λ_{max} 297.8 nm). Anal. Calcd for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75. Found: C, 73.94; H, 8.99. Data for **26** (ent-15-epi stereochemistry) were as follows: $[\alpha]^{25}_D$ −3.41° (*c* 0.017, CH_3OH); θ −1324 (λ_{max} 298.8 nm); IR (KBr) 1770 (C=O); ^1H NMR δ 2.66 (dd, 1, J = 2.0, 13.7, H-8α), 3.27–3.38 (m, 2, H-6, H-8β), 3.49 (dt, 1, J = 3.5, 10.4, H-3), 4.20 (dt, 1, J = 1.8, 6.0, H-3′). Anal. Calcd for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75. Found: C, 73.94; H, 8.70.

Preparation of 2, 28, and 29. A stock solution of dimsylsodium was prepared by mixing sodium hydride (21 g of a 50% oil dispersion, washed three times with hexane) in 350 mL of dimethyl sulfoxide for 1 h at 75 °C under nitrogen. To a solution of 81.6 g (190.0 mmol) of (3-carboxypropyl)triphenylphosphonium bromide in 250 mL of dimethyl sulfoxide under nitrogen was added 304 mL (380.0 mmol) of the stock solution of dimsylsodium. After 20 min at 23 °C, a solution of 13.0 g (47.5 mmol) of **23** in 100 mL of dimethyl sulfoxide was added in one portion. After 4 h at 23 °C, the mixture was poured onto 500 mL of 5% sodium carbonate solution. The mixture was washed with two 1-L portions of ethyl acetate and was then acidified with concentrated HCl. The aqueous layer was extracted three times with 1-L portions of diethyl ether. The combined ether extract was concentrated to 400 mL, and this was kept at 0 °C for 2 h. The resulting precipitate was filtered and was discarded. Evaporation of the filtrate gave a crude product with an approximate Z/E isomer ratio of 55:45 based on HPLC analysis (250 mm × 4.6 mm, Spherisorb, 5 μM ODS, methanol:H_2O:acetic acid = 70:29.94:0.06). The product was purified by silica gel flash chromatography using ethyl acetate containing 0.1% acetic acid. Further purification by silica gel flash chromatography using a solvent mixture of acetic acid–methanol–dichloromethane (0.1:5:94.9) separated the product mixture into the E and Z isomers.

The first eluted was **28** (6.5 g, 40%) as a colorless foam: mp 55–57 °C; ^1H NMR δ 0.9–2.5 (m, 22), 2.6–2.72 (m, 1, H-6α), 2.96 (m, 1, H-8), 3.3–3.4 (m, 1, H-11), 4.13 (dd, 1, J = 2, 6, H-15), 5.11 (m, 1, H-4); $[\alpha]^{25}_D$ +127° (*c* 0.44, $CHCl_3$). Anal. Calcd for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found: C, 72.58; H, 8.44.

The second eluted was **2** (7.5 g, 45%) as a colorless gum: ^1H NMR δ 0.95–2.45 (m, 22), 2.7–2.8 (br dd, 1, J = 14, 9, H-6α), 3.1 (m, 1, H-8), 3.46–3.55 (ddd, 1, J = 9.8, 10.0, 4.5, H-11), 4.15 (dd, 1, J = 1.7, 6, H-15), 5.15 (m, 1, H-4); $[\alpha]^{25}_D$ +117° (*c* 0.42, $CHCl_3$). Anal. Calcd for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found: C, 73.00; H, 8.51.

Starting with keto diol **26**, compound **29** was prepared similarly in 35% yield as a gum: ^1H NMR δ 0.95–2.4 (m, 22), 2.7–2.8 (br dd, 1, J = 14, 9, H-6α), 3.1 (m, 1, H-8), 3.44–3.55 (ddd, 1, J = 4.4, 8.7, 8.8, H-11), 4.17 (dd, 1, J = 2, 6, H-15), 5.15 (m, 1, H-4). Anal. Calcd for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found: C, 72.96; H, 8.82.

Conversion of (*S*)-9a to (*S*)-Hexahydromandelic Acid. To a solution of (*S*)-**9a** (2.0 g, 14.5 mmol) and pyridine (15 mL) was added acetic anhydride (6.8 mL), 72.5 mmol). After 48 h under nitrogen at 23 °C, the reaction mixture was poured into 50 mL of water and was extracted with three 50-mL portions of ethyl acetate. The combined extract was washed with brine and was dried over sodium sulfate. After removal of solvent and chromatographic purification (silica, 5% ethyl acetate–hexane), the acetate (2.5 g, 90%) was obtained: ^1H NMR δ 0.8–1.8 (m, 11), 2.21 (s, 3, CH_3CO), 2.4 (d, 1, J = 3, C-H), 5.2 (dd, 1, J = 3, 7, CHOAc).

A mixture of the acetate (1 g, 5.5 mmol) and 5% Pd on $BaSO_4$ (100 mg) in 5 mL of pyridine was stirred under hydrogen at atmosphere pressure for 6 h at 23 °C. The solution was filtered through Celite, was poured into 50 mL of water, and was extracted with three 50-mL portions of ethyl acetate. The combined extract was washed with brine and was dried over sodium sulfate. The solution was concentrated, and the residue was purified by chromatography (SiO_2, 5% ethyl acetate–hexane) to afford the olefin (0.96 g, 96%): ^1H NMR δ 0.9–1.9 (m, 11), 2.1 (s, 3, CH_3CO), 5.0–5.2 (m, 1, CHOAc), 5.2–5.6 (m, 3, vinyl protons).

Ozone was bubbled through a solution of the olefin (200 mg, 1.1 mmol) in 10 mL of dichloromethane at −78 °C for 3 h. Nitrogen was passed through the solution as the mixture was warmed to 23 °C. Removal of solvent followed by chromatographic purification (SiO_2, 5% ethyl acetate–hexane) gave an aldehyde (80 mg, 40%): ^1H NMR δ 0.8–1.9 (m, 11), 22 (s, 3, CH_3CO), 4.85 (d, 1, J = 5, 1 H, CHOAc), 9.55 (s, 1, CHO).

To a solution of the aldehyde (80 mg, 43 mmol) in acetone (3 mL) at 0 °C was added Jones reagent (0.3 mL of a 1.5 M solution, 0.43 mmol). After 15 min, the reaction mixture was poured into 30 mL of water and was extracted with three 25-mL portions of ethyl acetate. The combined extract was washed with brine, was dried over sodium sulfate, and was concentrated. This product was used directly in the next reaction by placement in 2 mL of methanol, followed by the addition of sodium hydroxide (36 mg, 9 mmol). After 1 h, the mixture was poured into 20 mL of water and was washed with 20 mL of ethyl acetate. The aqueous layer was acidified with 5% aqueous hydrochloric acid and was extracted with hree 25-mL portions of ethyl acetate. The combined extract was washed with brine and was dried over sodium sulfate. After solvent removal, (*S*)-hexahydromandelic acid was obtained (46 mg, 68%): mp 128–130 °C; $[\alpha]^{25}_D$ +23.03° (*c* 1, CH_3CO_2H) [lit.[21] mp 128–129 °C; $[\alpha]^{25}_D$ +23° (*c* 1.065, CH_3CO_2H)].

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Registry No. **2**, 105284-21-7; (±)-**6a**, 52466-03-2; (±)-**6b**, 108104-19-4; (±)-**7**, 108147-26-8; (±)-**8**, 108147-27-9; (±)-**9a**, 97563-45-6; (*S*)-**9a**, 105880-38-4; (*S*)-**9a** (R = Ac), 108104-21-8; (±)-**9b**, 108147-28-0; (*S*)-**9b**, 105803-39-2; (±)-**10**, 105880-44-2; (1*R*,2*S*,3*R*,6*S*,3′*S*)-**10**, 105803-40-5; (±)-**11**, 105880-45-3; (1*S*,2*R*,3*S*,6*R*,3′*S*)-**11**, 105880-43-1; **12**, 106208-08-6; **13**, 108210-90-8; **14**, 108104-20-7; **15**, 108147-29-1; **16**, 108147-30-4; **17**, 108147-31-5; **18**, 42340-98-7; **19**, 105881-33-2; **20**, 105803-41-6; **21**, 105880-47-5; **22**, 105880-46-4; **23**, 105803-42-7; **24**, 108147-32-6; **25**, 108147-33-7; **26**, 108147-34-8; **27**, 7560-69-2; **28**, 105880-50-0; **29**, 105880-66-8; HC≡CMgBr, 4301-14-8; HC≡CH, 74-86-2; $Br^-PH_3P^+(CH_2)_3CO_2H$, 17857-14-6; cyclohexanecarboxaldehyde, 2043-61-0; (*R*)-1-cyclohexyl-2-propen-1-ol acetate, 108104-22-9; (*S*)-hexahydromandelaldehyde acetate, 108104-23-0; (*S*)-hexahydromandelic acid acetate, 108104-24-1; (*S*)-hexahydromandelic acid, 61475-31-8.

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