H, ArOCH_2[CH_2]$_9CH_3$), 7.03 (m, 6 H, Ar H), 8.18 (d, 2 H, J = 9.2 Hz, benzoate Ar H); ^{13}C NMR ($CDCl_3$) δ 13.9, 16.4, 22.5, 25.8, 28.9, 29.2, 29.4, 31.7, 56.6, 68.0, 17.5, 75.0, 114.0, 114.9, 115.2, 121.4, 122.2, 131.9, 144.4, 156.2, 163.2, 164.9; IR ($CHCl_3$) 2930, 2960, 1720, 1605, 1505 cm^{-1}; mass spectrum, m/z (rel intensity) 471 (P^+ +1, 17), 470 (P^+, 45), 291 (51), 290 (100). Anal. Calcd for $C_{29}H_{42}O_5$: C, 74.00; H, 9.00. Found: C, 74.22; H, 9.15.

4′-[(*S*)-2-Ethoxypropoxy]phenyl 4-(*n*-Dodecyloxy)benzoate (1, R^1 = *n*-Dodecyl, R^2 = Ethyl): ^{1}H NMR ($CDCl_3$) δ 0.89 (t, 3 H, J = 7.5 Hz, ArOCH$_2$CH$_2$[CH_2]$_9CH_3$), 1.24 (m, 24 H, ArOCH$_2$CH$_2$[CH_2]$_9CH_3$, ROCH$_2CH_3$, and ROCH$_2$CH[CH_3][OR]), 1.79 (m, 2 H, ArOCH$_2CH_2$-[CH_2]$_9CH_3$), 3.61 (m, 2 H, ROCH_2CH_3), 3.81 (m, 2 H, ArOCH_2CH_2-[CH_2]$_9CH_3$), 4.01 (m, 3 H, ROCH_2CH[CH_3][OR]), 6.92 (m, 4 H, hydroquinone Ar H), 7.08 (d, 2 H, J = 9.2 Hz, benzoate Ar H), 8.11 (d, 2 H, J = 9.2 Hz, benzoate Ar H); ^{13}C NMR ($CDCl_3$) δ 14.07, 15.66, 17.51, 22.70, 26.04, 29.18, 29.37, 29.39, 29.59, 29.61, 29.66, 31.95, 63.42, 64.75, 72.41, 73.63, 114.39, 115.40, 121.93, 122.52, 132.23, 144.89, 156.10, 163.58, 165.23; IR ($CHCl_3$) 2930, 2860, 1720, 1605, 1505 cm^{-1}. Anal. Calcd for $C_{30}H_{44}O_5$: C, 74.34; H, 9.15. Found: C, 74.26; H, 8.96.

4′-[(*S*)-2-Propoxypropoxy] 4-(*n*-Dodecyloxy)benzoate (1, R^1 = *n*-Dodecyl, R^2 = *n*-Propyl): ^{1}H NMR ($CDCl_3$) δ 0.89 (m, 6 H, ArOC-H_2[CH_2]$_9CH_3$, and ROCH$_2CH_2CH_3$), 1.25 (m, 21 H, ArOCH$_2$CH$_2$[C-H_2]$_9CH_3$ and ROCH$_2$CH[CH_3][OR]), 1.58 (m, 2 H, ROCH$_2CH_2CH_3$), 1.80 (m, 2 H, ArOCH$_2CH_2$[CH_2]$_9CH_3$), 3.50 (t, 2 H, J = 6.58 Hz, ROC$H_2CH_2CH_3$), 3.85 (m, 2 H, ArOCH_2CH_2[CH_2]$_9CH_3$), 4.01 (m, 3 H, ROCH_2CH[CH_3][OR]), 6.96 (m, 4 H, hydroquinone Ar H), 7.09 (d, 2 H, J = 9.2 Hz, benzoate Ar H), 8.11 (d, 2 H, J = 9.2 Hz, benzoate Ar H); IR ($CHCl_3$) 2930, 2860, 1720, 1605, 1505 cm^{-1}; mass spectrum m/z (rel intensity) 499 (P^+ + 1, 19), 498 (P^+, 38), 291 (47), 290 (100). Anal. Calcd for $C_{31}H_{46}O_5$: C, 74.66; H, 9.30. Found: C, 74.36; H, 9.20.

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Registry No. 1 (R^1 = *n*-decyl; R^2 = ethyl), 103239-85-6; **1** (R^1 = *n*-nonyl; R^2 = methyl), 103239-86-7; **1** (R^1 = *n*-nonyl; R^2 = ethyl), 103239-87-8; **1** (R^1 = *n*-nonyl; R^2 = *n*-propyl), 103239-88-9; **1** (R^1 = *n*-decyl; R^2 = methyl), 103239-89-0; **1** (R^1 = *n*-decyl; R^2 = *n*-propyl), 103239-90-3; **1** (R^1 = *n*-undecyl; R^2 = methyl), 103239-91-4; **1** (R^1 = *n*-undecyl; R^2 = ethyl), 103239-92-5; **1** (R^1 = *n*-undecyl; R^2 = *n*-propyl), 103239-93-6; **1** (R^1 = *n*-dodecyl; R^2 = methyl), 103239-94-7; **1** (R^1 = *n*-dodecyl; R^2 = ethyl), 103239-95-8; **1** (R^1 = *n*-dodecyl; R^2 = *n*-propyl), 103239-96-9; **12**, 103239-97-0; **13**, 103239-98-1; **14** (R^2 = ethyl), 103239-99-2; **14** (R^2 = methyl), 103240-00-2; **14** (R^2 = *n*-propyl), 103240-01-3; *p*-[(*S*)-2-ethoxypropoxy]phenol, 103240-02-4; *p*-[(*S*)-2-methoxypropoxy]phenol, 103240-03-5; *p*-[(*S*)-2-propoxypropoxy]phenol, 103240-04-6.

Stereocontrolled Asymmetric Total Synthesis of Protomycinolide IV

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Abstract: Stereocontrolled asymmetric total synthesis of protomycinolide IV (**1**) was achieved, based on the organoaluminum-promoted stereospecific pinacol-type 1,2-rearrangement. Two chiral fragments, C(1)–C(9) and C(11)–C(17) portions, were constructed from a common chiral starting material, (*S*)-ethyl lactate. High diastereoselectivity of the nucleophilic attack on the Me_3Si-bearing α-methyl-β,γ-unsaturated carbonyl compounds was fully utilized for establishing the chiral centers at C(5) and C(6) relative to C(4) and C(15) relative to C(14). For the stereocontrol of the Me substituent at C(8), two methods were newly devised: (i) thermodynamic equilibration of δ-lactone **16** and (ii) acid-catalyzed stereoselective cyclization of ketene dithioacetal possessing an internal hydroxyl group.

Recent interest in the total synthesis of macrolide or ionophore antibiotics invoked rapid progress of the stereoregulating method for the synthesis of acyclic molecules.[1] In this conjunction, a number of efficient methods have been recently devised,[2a] such as the stereoselective aldol condensation[2b] etc., which serve well for the control of the acyclic stereochemistry, both in enantio- and diastereomerical senses. However, there is room for further development, seeking generality and flexibility against structural diversity. Our recent investigation in this area revealed a viable approach based on 1,2-rearrangement in acyclic systems, which proved to be highly efficient in light of its excellent enantiospecificity.

Scheme I illustrates key features of our approach: Pinacol-type 1,2-rearrangement of the lactate-derived mesylate I proceeded with a full inversion of the C–OMs stereocenter to give *enantiomerically pure* α-chiral ketone II. The use of organoaluminums as the Lewis-acidic reaction promotor is essential for this success where Al-chelate VIII is postulated as an intermediate. A related chelate intermediate, reductively generated by reaction of DIBAL with IV, undergoes 1,2-rearrangement leading to the chiral aldehyde V. These 1,2-migration reactions effect net chirality transfer from the naturally abundant "C–O asymmetry" (e.g., carbohydrates, lactic or tartaric acid) into the chiral synthons possessing "C–C asymmetry", as can be seen in II or V.

These chiral synthons, α-methyl-β,γ-unsaturated carbonyls, are characterized by their high enantiomerical purity, but equally important is their inherent Cram selectivity observed when they are subjected to a nucleophilic attack upon the carbonyl carbon: Reduction of ketone II gives *threo*-alcohol III with high selectivity. *Erythro* isomer VI is also accessible by nucleophilic reaction with aldehyde V,[3] as anticipated by the Felkin–Anh model IX,[4] where

(1) Masamune, S.; Choy, W.; Peterson, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1–76. Paterson, I.; Mansuri, M. M. *Tetrahedron* **1985**, *41*, 3569–3624.

(2) (a) Review: Morrison, J. D. *Asymmetric Synthesis*; Academic: New York, 1984. (b) Reviews: Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1–115. Mukaiyama, T. *Org. React.* **1982**, *28*, 203–331. Heathcock, C. H. In ref 2a; Vol. 3, pp 111–212.

(3) For *threo*/*erythro* nomenclature, Heathcock's convention was used: Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. C.; Sohn, J. E.; Lampe, J. *J. Org. Chem.* **1980**, *45*, 1066–1081. The numbering system used for **1** is utilized in the discussion of all synthetic intermediates. The proper IUPAC numbering is found in the Experimental Section.

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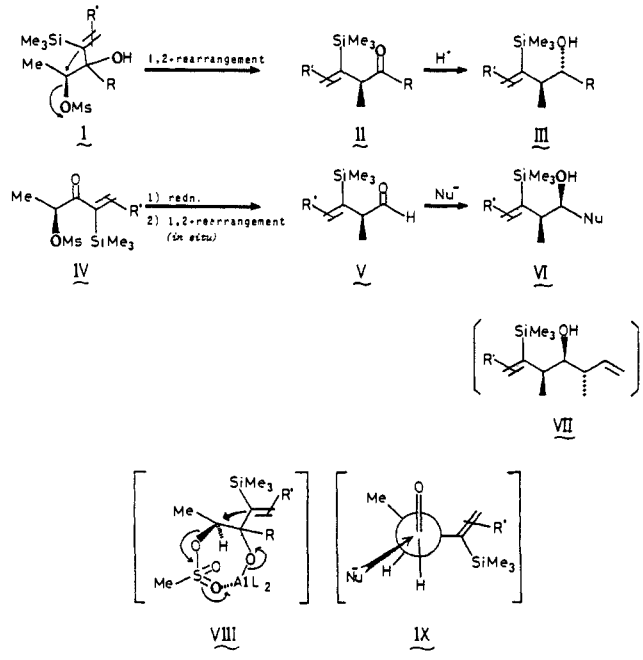
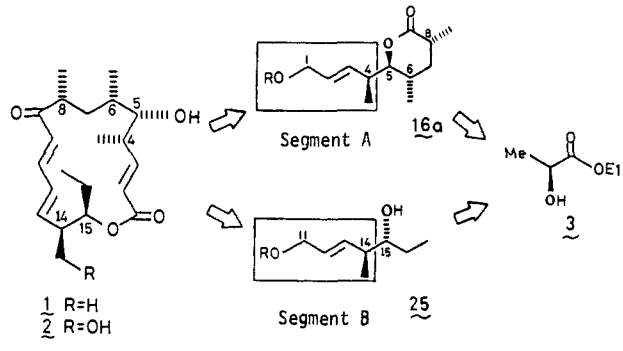
Scheme I



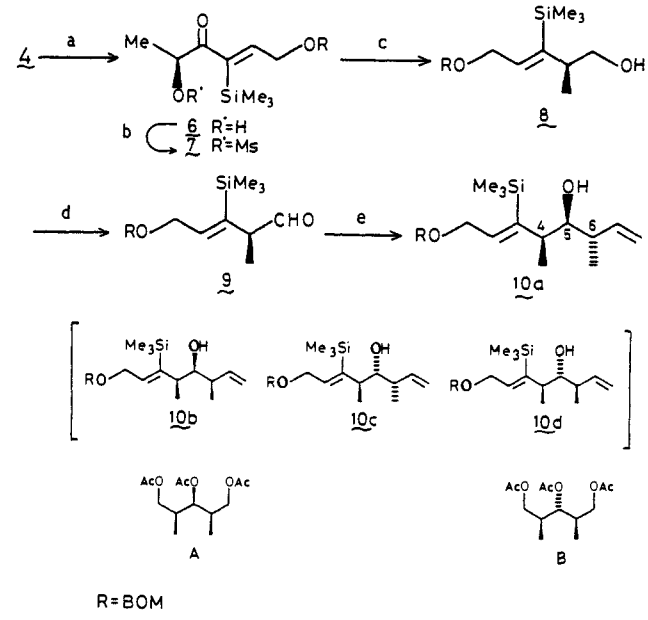
Scheme II



use of a diastereogenic nucleophile effects efficient control of the three contiguous chiral centers leading to functionalized synthons such as VII. The trimethylsilyl group, attached to the alkenyl moiety, gives two prominent benefits to the synthetic operations mentioned above: (1) rate-acceleration effect in the 1,2-migration step[5a] and (2) the enhancement of the Cram selectivity of II and V.[6,7] The overall process sets up novel and ready access to the macrolide skeletons in a highly enantio- and diastereocontrolled manner.

Protomycinolide IV (1) is a 16-membered macrolide isolated from the culture of *Micromonospora griseorubida* sp. nov. by Hayashi et al., which, as well as its oxygenated congener mycinolide IV (2), is of sizable biological interest as the putative biogenetic precursor of the macrolide antibiotics of the mycinamicin family.[8] Considering the pronounced activity of the mycinamicins against the Gram-positive bacteria, we undertook a study directed toward the total synthesis of this class of compounds by utilizing the novel arsenals stated above with a hope

Scheme III[a]



[a] (a) **5**, *n*-BuLi/Trapp solvent, −100 °C; H_2SO_4/dioxane (92%); (b) MsCl, Et_3N/CH_2Cl_2, −45 °C; (c) DIBAL then Et_3Al/CH_2Cl_2, −78 → −20 °C (**6** → **8**, 85%); (d) $(COCl)_2$, Me_2SO, Et_3N/CH_2Cl_2, −78 °C; (e) $MeCH{=}CHCH_2Br$, $CrCl_2$/THF, −20 → 0 °C (**8** → **10a**, 72%).

to exploit a general access to mycinamicin aglycons.[9] The successful outcome of such efforts, a stereocontrolled asymmetric total synthesis of **1**, is described herein.[10]

General synthetic plan is outlined in Scheme II.[3] Disconnections at C(9)–C(10) and C(10)–C(11) give rise to two chiral intermediates, the segments A (**16a**) and B (**25**). Recognition of a common structural feature in these segments (at C(1)–C(4) and C(11)–C(14)) immediately suggested a synthetic scheme in which *both of these are obtained by the pinacol-type rearrangement of a common C_3 migrating unit, starting from a common chiral starting material, (S)-ethyl lactate* (**3**) (Cf. Scheme I).[5] Subsequent stereochemical control relying on the Cram selectivity inherent to the α-methyl-β,γ-unsaturated carbonyls would effectively create the new stereocenters at C(5), C(6), and C(15).[6] The remaining stereochemical problem would be that of the Me substituent at C(8), for which we envisioned the control at the stage of lactone **16** relying on the two approaches of the different principles. Assembly of these two stereodefined fragments would accomplish the enantioconvergent total synthesis of **1**.[10]

Results and Discussion

The chiral starting material, (*S*)-ethyl lactate (**3**), was first converted to protected (*S*)-lactamide **4**. The common three-carbon unit **5**, the latent migrating group, was prepared from propargyl alcohol in three steps where hydroalumination–bromination[11] secured the requisite geometry of the alkenyl group. The trimethylsilyl group was introduced in prospect of doubled benefits as stated above.

Preparation of Segment A (16a). Synthesis of this portion started with the reductive 1,2-rearrangement as depicted in Scheme III. Halogen–lithium exchange of **5** was effected by reaction with *n*-BuLi at −100 °C.[11] Slow addition of amide **4** to this alkenyllithium species followed by acid quenching gave α-

(4) Chêrest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199–2204. Anh, N. T.; Eisenstein, O. *Nouv. J. Chim.* **1977**, *1*, 61–70.

(5) (a) Suzuki, K.; Katayama, E.; Tsuchihashi, G. *Tetrahedron Lett.* **1984**, *25*, 1817–1820. (b) Suzuki, K.; Katayama, E.; Matsumoto, T.; Tsuchihashi, G. *Ibid.* **1984**, *25*, 3715–3718.

(6) (a) Suzuki, K.; Katayama, E.; Tsuchihashi, G. *Tetrahedron Lett.* **1984**, *25*, 2479–2482. (b) Suzuki, K.; Katayama, E.; Tomooka, K.; Matsumoto, T.; Tsuchihashi, G. *Ibid.* **1985**, *26*, 3707–3710.

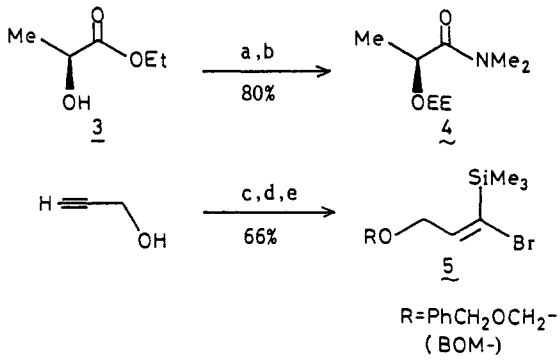
(7) Independent observation by Sato et al.; see: Kobayashi, Y.; Kitano, Y.; Sato, F. *J. Chem. Soc., Chem. Commun.* **1984**, 1329–1330.

(8) (a) Hayashi, M.; Ohno, M.; Satoi, S. *J. Chem. Soc., Chem. Commun.* **1980**, 119–121. (b) Hayashi, M.; Ohara, H.; Ohno, M.; Sakakibara, H.; Satoi, S.; Harada, K.; Suzuki, M. *J. Antibiot.* **1981**, *34*, 1075–1077.

(9) For the first total synthesis, see: Honda, M.; Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1984**, *25*, 3857–3860.

(10) A preliminary report of this synthesis has appeared: Suzuki, K.; Tomooka, K.; Matsumoto, T.; Katayama, E.; Tsuchihashi, G. *Tetrahedron Lett.* **1985**, *26*, 3711–3715.

(11) Eisch, J. J.; Damasevitz, G. A. *J. Org. Chem.* **1976**, *41*, 2214–2215. Uchida, K.; Utimoto, K.; Nozaki, H. *Ibid.* **1976**, *41*, 2215–2216. Zweifel, G.; Lewis, W. *Ibid.* **1978**, *43*, 2739–2744.

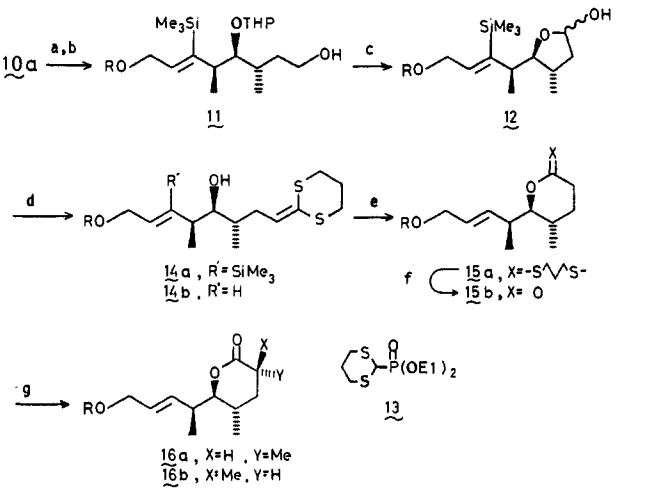


(a) Me_2NH, 70 °C; (b) $CH_2{=}CHOC_2H_5$, PPTS/CH_2Cl_2; (c) NaH, BOMCl; (d) EtMgBr, Me_3SiCl; (e) DIBAL, Br_2

hydroxy ketone **6** (92%) without concomitant *E*/*Z* isomerization of the alkenyl geometry. Mesylation of **6** with MsCl–Et_3N at −45 °C[12] followed by extractive workup gave unstable mesylate **7**, which was immediately used for the next rearrangement reaction. Dropwise addition of DIBAL (3.0 equiv) effected rapid reduction of α-mesyloxy ketone **7** (CH_2Cl_2, −78 °C, 5 min),[13] and the resultant aluminum alkoxide was treated in situ with 1 equiv of Et_3Al, which smoothly effected the 1,2-rearrangement of the alkenyl group and concomitant reduction to afford chiral alcohol **8** in 85% yield.[5b] During this 1,2-migration, no *E*/*Z* isomerization of the alkenyl geometry occurred, and more importantly, the reaction proceeded with complete enantiospecificity (by 400-MHz ^1H NMR analysis of the Mosher ester[14] of alcohol **8**).

Our next concern was the control of the three contiguous asymmetric centers, one of the typical problems in macrolide synthesis.[1] An aldolization approach in such situations had been hampered by the (generally low) Cram selectivity of chiral aldehydes, whereas employment of the inherent selectivity in β,γ-unsaturated carbonyls (especially Me_3Si-substituted ones)[6,7,15] offers a simpler solution using achiral nucleophiles. Thus, oxidation of chiral alcohol **8** by Swern procedure[16] cleanly furnished the β,γ-unsaturated aldehyde **9**,[17] which was then treated with Hiyama reagent ($MeCH{=}CHCH_2Br$–$CrCl_2$)[18] leading to the highly selective formation of alcohol **10a** possessing the required stereochemistry (4,5-erythro, 5,6-threo).[3] The ratio of four isomeric alcohols was **10a**/**b**/**c**/**d** = 60/1/2/6, which implies the Cram/anti-Cram ratio was **10a**,**b**/**10c**,**d** = 7/1. The desired alcohol **10a** was isolated by flash column chromatography.[45] The other isomers **10b–d** were also prepared stereoselectively, and their stereostructures were confirmed by correlation to meso triacetates A and B.[19d] Availability of these stereodefined alcohols would find sizable utility in macrolide synthesis.[20]

Scheme IV[a]



[a] R = BOM. (a) DHP, PPTS/CH_2Cl_2, room temperature (94%); (b) $(c\text{-}C_6H_{11})_2BH$/THF, 0 °C; H_2O_2 (97%); (c) $(COCl)_2$, Me_2SO, Et_3N/CH_2Cl_2, −78 °C; trace HCl/dioxane, room temperature (84%); (d) **12** → **14b**: KH, **13**/DME, 0 °C; NaOH/MeOH; (e) trace HCl/dioxane, room temperature (**12** → **15a**, 76%); (f) $HgCl_2/CH_3CN$–THF–pH 7 buffer, 0 °C (92%); (g) LDA, MeI/THF, HMPA, −78 °C (88%).

Having secured the C(4),C(5),C(6) chiral centers, we turned our attention to the conversion of **10a** to the segment A (**16a**). Of primary concern here was the control of the stereochemistry of the methyl group at C(8), which has been the subject of common interest in relation to the synthesis of the Prelog–Djerassi lactone and related compounds.[21] In this context, several attempts have been reported, including kinetic protonation of the lactone enolate by Grieco (α-Me/β-Me = 3.5/1)[21a] and Still (1.3/1)[21b] or stereoselective hydrogenation of suitable derivatives.[21c,d] For this, we examined *two approaches*: One approach is to equilibrate the epimeric lactones **16a**,**b**, which is doubtlessly in favor of the desired isomer **16a**. Another approach is based on the stereoselective cyclization of ketene dithioacetal, which turned out to possess considerable synthetic potential.

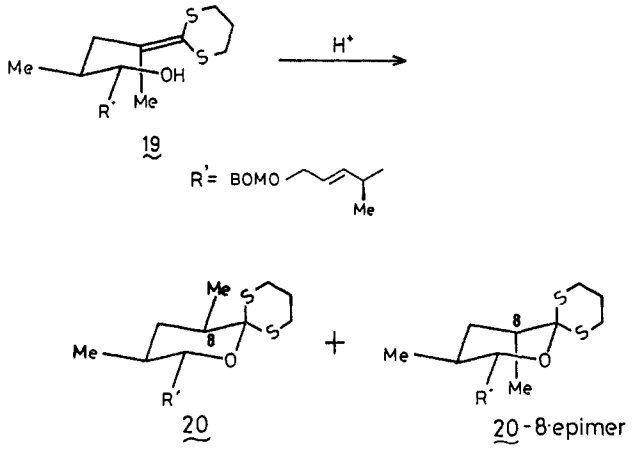
Equilibration Approach. Alcohol **10a** was converted to its THP ether, whose selective hydroboration using dicyclohexylborane[22] followed by oxidative workup gave alcohol **11**. Subsequent oxidation of alcohol **11** followed by acid treatment afforded lactol **12** in 77% yield from **10a**. One-carbon homologation of lactol **12** was cleanly effected via Horner–Emmons reaction using Mikołaiczyk reagent **13** (Na^+ salt, NaH/THF, 0 °C)[23,24] to afford ketene dithioacetal **14a** in 90% yield, which was then desilylated[25] to afford **14b**. Interestingly, reaction using the K^+ salt of **13** was accompanied by the in situ Brook-type rearrangement: After

(12) Crossland, R. K.; Servis, K. L. *J. Org. Chem.* **1970**, *35*, 3195–3196.
(13) Behavior of DIBAL as the 1,2-reducing agent of the α,β-unsaturated carbonyl compounds, see: Wilson, K. E.; Seidner, R. T.; Masamune, S. *J. Chem. Soc., Chem. Commun.* **1970**, 213–214.
(14) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543–2549.
(15) This behavior of β,γ-unsaturated carbonyl compounds was noted by Heathcock et al. in their synthetic endeavor toward erythronolide A; see: Heathcock, C. H.; Young, S. D.; Hagen, J. P.; Pilli, R.; Badertscher, U. *J. Org. Chem.* **1985**, *50*, 2095–2105.
(16) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *33*, 2480–2482.
(17) Without suitable respect, aldehyde **9** is prone to racemization: prolonged contact with $Et_3NH^+Cl^-$, formed by Swern oxidation, should be rigorously avoided (see Experimental Section).
(18) Hiyama, T.; Okude, Y.; Kimura, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 561–568. Of the two optional low-valent Cr reagents, (1) $CrCl_3$–$^1/_2LiAlH_4$ and (2) $CrCl_2$, the latter gave better results: The former, used in our preliminary study,[5b] was found to produce partially (ca. 15%) racemized alcohol **10a**, while the latter caused no loss of ee. This difference may be ascribable to the coexistence of Lewis-acidic aluminum salts in the former reagent system.
(19) Selective preparation of four possible isomers of related building blocks, RCHMeCHOHCHMeR′: (a) Johnson, M. R.; Nakata, T.; Kishi, Y. *Tetrahedron Lett.* **1979**, 4343–4346. (b) Nagaoka, H.; Kishi, Y. *Tetrahedron* **1981**, *37*, 3873–3888. (c) Nakata, T.; Fukui, M.; Ohtsuka, H.; Oishi, T. *Tetrahedron Lett.* **1983**, *24*, 2661–2664. (c) Oikawa, Y.; Nishi, T.; Itaya, H.; Yonemitsu, O. *Ibid.* **1983**, *24*, 1987–1990.
(20) Stereoselective access to other isomers has been described in ref 6b. Brief accounts of the methods follow: Isomer **10b** was obtained from **9** via syn-selective crotylation ($Bu_3SnCH_2CH{=}CHCH_3$–$BF_3{\cdot}OEt_2$, −78 °C: Yamamoto, Y.; Yatagai, H.; Naruta, Y.; Maruyama, K. *J. Am. Chem. Soc.* **1980**, *102*, 7107–7109). Oxidation–reduction sequence [(1) PDC/DMF; (2) $LiBEt_3H$, −78 °C] effected stereospecific conversion of **10a** to **10c** and **10b** to **10d**, respectively.
(21) (a) Grieco, P. A.; Ohfune, Y.; Yokoyama, Y.; Owens, W. *J. Am. Chem. Soc.* **1979**, *101*, 4749–4752. (b) Still, W. C.; Shaw, K. R. *Tetrahedron Lett.* **1981**, *22*, 3725–3728. (c) Ireland, R. E.; Daub, J. P. *J. Org. Chem.* **1981**, *46*, 479–485. (d) Schlessinger, R. H.; Poss, M. A. *J. Am. Chem. Soc.* **1982**, *104*, 357–358.
(22) Brown, H. C. *Organic Syntheses via Boranes*; Wiley: New York, 1975; pp 28–29.
(23) Use of Peterson-type reagents was totally ineffective in this transformation: Carey, F. A.; Court, A. S. *J. Org. Chem.* **1972**, *37*, 1926–1929. Seebach, D.; Kolb, M.; Gröbel, B. T. *Chem. Ber.* **1973**, *106*, 2277–2290; Hackett, S.; Livinghouse, T. *Tetrahedron Lett.* **1984**, *25*, 3539–3542.
(24) Mikołajczyk, M.; Grzejszczak, S.; Zatorski, A.; Mlotkowska, B.; Gross, H.; Costisella, B. *Tetrahedron* **1978**, *34*, 3081–3088.
(25) Sato, F.; Tanaka, Y.; Sato, M. *J. Chem. Soc., Chem. Commun.* **1983**, 165–166.

consumption of lactol **12** was ascertained by TLC monitoring (KH-**13**/DME, 0 °C, 10 min), the reaction was warmed up to room temperature causing C → O 1,4-silyl migration to give TMS ether of **14b**, which was hydrolyzed with base to afford alcohol **14b**. A trace of hydrochloric acid smoothly catalyzed the easy cyclization of alcohol **14b** to give spiro thioketal **15a**,[26] which was then hydrolyzed under mild conditions ($HgCl_2$, pH 7, 0 °C) to afford lactone **15b**. Methylation of **15b** with LDA–MeI furnished a 1/1 mixture of α-methyl lactones **16a** and **16b**, as expected[21,27] (Schene IV).

The epimers of lactones **16** in hand, conditions to improve the ratio were sought. After some experimentation, the following conditions were found to be optimal: Freshly sublimed *t*-BuOK in *t*-BuOH was added to a dilute solution of **16** in *t*-BuOH (10^{-2} M) and stirred overnight. HPLC analysis showed the equilibrated ratio **16a**/**16b** = 6/1.[28] This level of improvement of the isomeric ratio greatly facilitated the separation of these epimers by MPLC, and the desired lactone **16a** was isolated as a colorless liquid.[29]

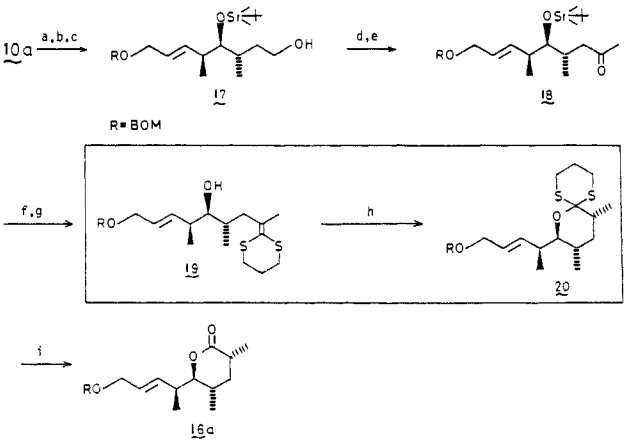
Stereoselective Cyclization Approach. The second route is a more direct one, which offered much higher selectivity. Ketene dithioacetal **19**, homologue of **14b**, is prochiral with respect to the *pro*-C(8) carbon, and its acid-catalyzed cyclization (vide supra)[26] provides a conceptually new opportunity for the stereocontrol of lactone **16** via bicyclic compound **20**. This scenario



attracted us from not only the synthetic but also the mechanistic standpoint, since no data have been available for this kind of cyclization.[30] Taking the possible reversibility of the protonation into account,[31] the thermodynamic stability of the bicyclic compounds might reflect on the stereochemical consequence.

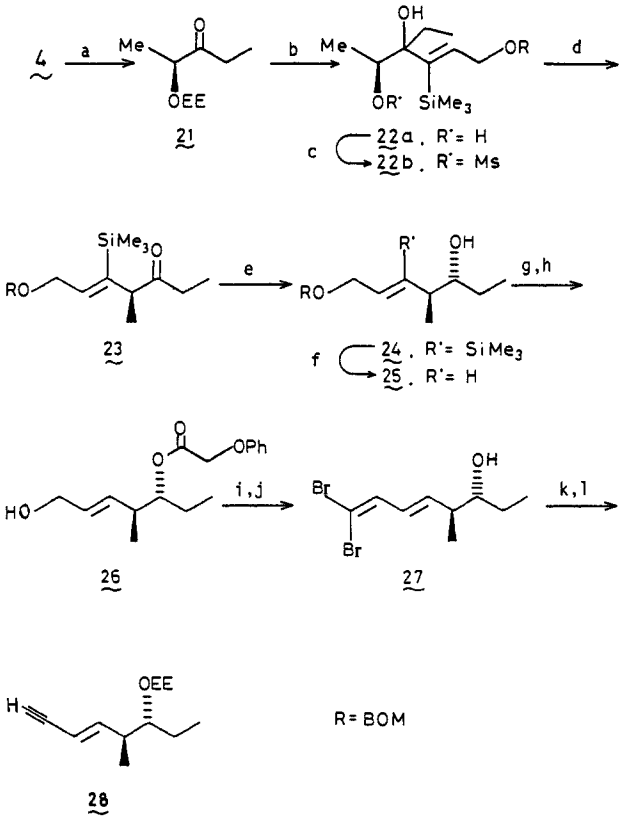
We were pleased to find that this question was answered in the affirmative: Treatment of ketene dithioacetal **19** (prepared from **10a**: Scheme V) in CH_2Cl_2 with 0.5 equiv of anhydrous HCl at 0 °C resulted in a 92% yield of the cyclized product. Subsequent hydrolysis of the thioacetal afforded the desired lactone **16a** in 15/1 preference over its epimer **16b**.

Scheme V[a]



[a] (a) NaH/HMPA, room temperature (92%); (b) *t*-$BuMe_2SiOTf$, 2,6-lutidine/CH_2Cl_2, room temperature (quantitative); (c) $(c\text{-}C_6H_{11})_2BH/Et_2O$, 0 °C; H_2O_2 (85%); (d) $(COCl)_2$, Me_2SO, Et_3N/CH_2Cl_2, −78 °C; MeMgBr, $CeCl_3$/THF, room temperature (96%; ref 33); (e) $(COCl)_2$, Me_2SO, Et_3N/CH_2Cl_2, −78 °C (85%); (f) KH, **13**/DME, room temperature (87%); (g) TBAF/THF, room temperature (93%); (h) dry HCl/CH_2Cl_2, 0 °C (92%); (i) $HgCl_2/CH_3CN$–THF–pH 7 buffer, room temperature (94%).

Scheme VI[a]



[a] (a) EtMgBr/THF, 0 °C (77%); (b) 5, *n*-BuLi/Trapp solvent, −100 °C; PPTS/MeOH, room temperature (quantitative); (c) MsCl, Et_3N/CH_2Cl_2, 0 °C; (d) Et_3Al/CH_2Cl_2, −78 °C (**22a** → **23**, 80%); (e) L-Selectride/THF, −78 °C (95%); (f) NaH/HMPA, room temperature (96%); (g) $PhOCH_2COCl$/pyridine, room temperature (quantitative); (h) PhSH, $BF_3{\cdot}OEt_2/CH_2Cl_2$, room temperature (95%); (i) $(COCl)_2$, Me_2SO, Et_3N/CH_2Cl_2, −78 °C (95%); (j) CBr_4, PPh_3, Zn/CH_2Cl_2, room temperature; NaOH/MeOH, room temperature (81%); (k) $CH_2{=}CHOC_2H_5$, PPTS/CH_2Cl_2, room temperature (quantitative); (l) LDA/THF, 0 °C (81%).

As for the mechanism, related model study revealed that the present cyclization is a rapidly reversible process wherein the favorable equilibration to the more stable isomer **20** is attained.[32]

(26) Corey, E. J.; Beames, D. J. *J. Am. Chem. Soc.* **1973**, *95*, 5829–5831.

(27) Evans, D. A. *Asymmetric Synthesis*; Academic: New York, 1983; Vol. 3, pp 1–110.

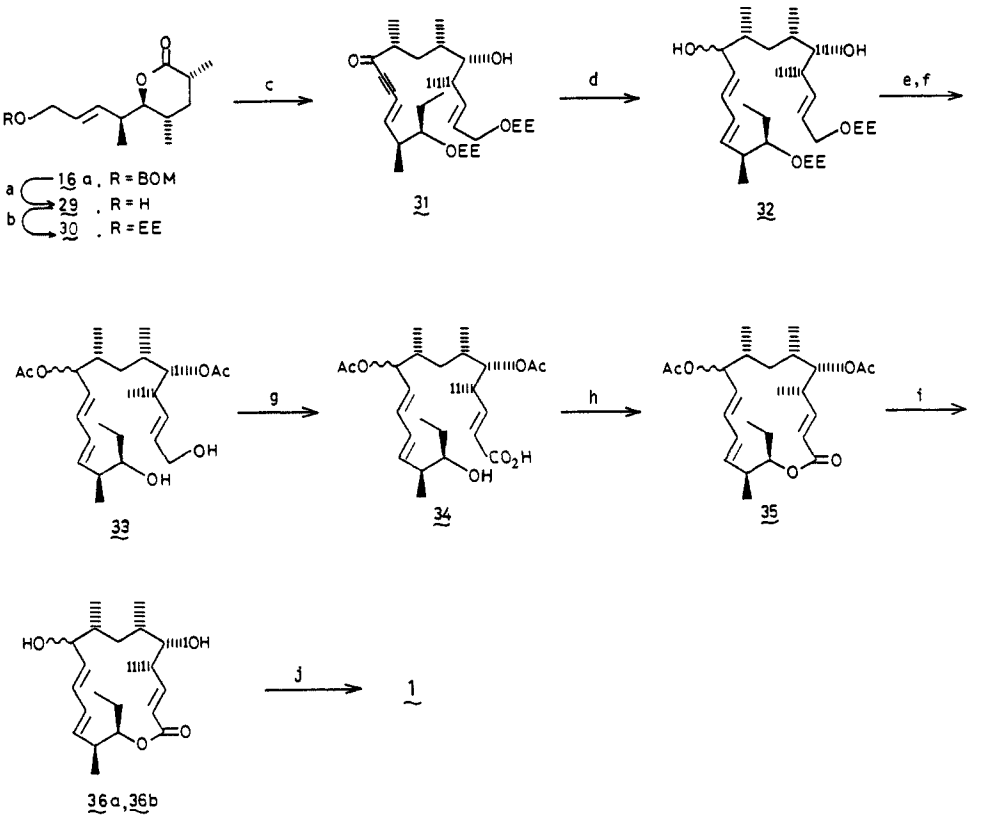
(28) Thermodynamic preference was calculated on the epimeric pair of the lactones possessing closely related structure to **16a**,**b** (MOM instead of BOM), which indicated an energy difference of 1.39 kcal/mol, predicting the 10/1 ratio at equilibrium. Calculation was done by Dr. Y. Fukazawa, on the basis of MM 2: Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 8127–8134.

(29) In early stage of this work,[10] the stereostructure of **16a** was determined by correlating it to Prelog–Djerassi lactone (O_3; H_2O_2) or to an intermediate in the Yamaguchi's synthesis[9] of **1**. We are indebted to Prof. Yamaguchi for the ^1H NMR spectrum.

(30) Bartlett, P. A. Asymmetric Synthesis; Morrison, J. D., Ed.; Academic: New York, 1984; Vol. 3, pp 411–454.

(31) Protonation of ketene dithioacetal is known to be a reversible process from the kinetic study of the acid-catalyzed hydrolysis; see: Okuyama, T.; Fueno, T. *J. Am. Chem. Soc.* **1980**, *102*, 6591–6592. Okuyama, T. *J. Am. Chem. Soc.* **1984**, *106*, 7134–7139. Okuyama, T.; Toyoda, M.; Fueno, T. *Can. J. Chem.*, in press.

Scheme VII[a]



[a] (a) PhSH, $BF_3 \cdot OEt_2/CH_2Cl_2$, room temperature (97%); (b) $CH_2{=}CHOC_2H_5$, PPTS, room temperature (95%); (c) **28**, *n*-BuLi/hexane, 0 °C (91%); (d) $LiAlH_4$/THF, room temperature (65%); (e) Ac_2O/pyridine, room temperature (98%); (f) PPTS/MeOH, room temperature (99%); (g) MnO_2/Et_2O, room temperature; $NaClO_2$, resorcinol/*t*-BuOH–pH 4 buffer, room temperature (79%); (h) 2,4,6-$Cl_3C_6H_2COCl$, Et_3N/THF, room temperature; 4-pyrrolidinopyridine/toluene, 110 °C (58%); (i) LiOH/MeOH–H_2O, room temperature (**36a**, 44%; **36b**, 46%); (j) MnO_2/Et_2O, room temperature (**36a** → **1**, 68%; **36b** → **1**, 59%).

In Figure 1 is depicted the lowest energy conformations of **20** and 8-*epi*-**20**.[34] The reversibility may well be understood on the analogy of the reversible mechanism in the acid-catalyzed hydration of ketene dithioacetals reported by Okuyama et al.[31]

Here, the preparation of the segment A (**16a**) was accomplished in a fully stereocontrolled manner. Of the two routes to this segment described above, the latter cyclization approach (Scheme V) showed a better overall efficacy, the yield and the selectivity.

Preparation of Segment B (25). The synthesis also started with (*S*)-lactamide **4**, as outlined in Scheme VI. Amide **4** was converted to diol **22a** as a mixture of diastereomers by three-step operations [(1) EtMgBr, (2) **5**–*n*-BuLi, −78 °C, (3) PPTS/MeOH[35]]. Mesylation of **22a** (MsCl–Et_3N, 0 °C)[12] proceeded regioselectively at the secondary hydroxyl to give β-mesyloxy alcohol **22b** in essentially quantitative yield. Mesylate **22b** underwent clean 1,2-rearrangement by reaction with Et_3Al (CH_2Cl_2, −78 °C) to afford chiral ketone **23** in 80% yield.[5a] Here again, the stereospecific feature of the 1,2-rearrangement was noticed: (1) no *E*/*Z* isomerization and (2) the complete enantiospecificity as described below.

Furthermore, reduction of **23** with L-Selectride (THF, −78 °C) proceeded with exceedingly high selectivity to give the *threo*-alcohol **24** as the sole isolable product.[36] Here again, the high Cram selectivity was effective for the control of the relative stereochemistry. Mosher analysis at this stage assured this intermediate to be enantiomerically pure,[14] and subsequent desilylation of **24**[25] afforded the desired alcohol **25**, that is, the segment B.

In order to complete the synthesis, C(10) was introduced to the segment B: After alcohol **25** was protected with phenoxyacetyl group, BOM protection was cleanly removed with $BF_3 \cdot OEt_2$–PhSH[37] to provide allylic alcohol **26**. Swern oxidation[16] of **26** followed by dibromomethylenation[38] and alkaline hydrolysis gave dibromide **27**. Alcohol **27** was then converted to the corresponding ethoxyethyl (EE) ether, whose treatment with LDA at 0 °C[39] in THF afforded enyne **28** as a distillable liquid, ready for the coupling with the segment A.

Coupling and Lactonization. After exchange of the protecting group of **16a** (BOM → EE)[37,40] to give lactone **30**, the coupling reaction was done with the lithio derivative of **28**: Lithiation of **28** with *n*-BuLi (0 °C, hexane) followed by the addition of lactone **30** in hexane at the same temperature afforded the adduct **31** in 91% yield.[41] Use of the other solvents (THF, Et_2O, toluene, etc.) caused substantial decrease of the yields. Reduction of the carbonyl group followed by trans-hydroalumination of **31** was cleanly effected by reaction with $LiAlH_4$ in THF[42] to give diol **32**, possessing the full carbon framework of the target with requisite stereochemistry. After diol **32** was converted to 1,15-diol

(32) Unpublished results of T. Masuda in this laboratory.
(33) Imamoto, T.; Takiyama, N.; Nakamura, K. *Tetrahedron Lett.* **1985**, *26*, 4763–4766.
(34) Calculations were kindly done by Dr. Y. Fukazawa.[28] The energy difference of the two epimers **20** and 8-*epi*-**20** was estimated to be 1.5 kcal/mol, corresponding to the 14/1 ratio.
(35) Miyashita, M.; Yoshikoshi, A.; Grieco, P. A. *J. Org. Chem.* **1977**, *42*, 3772–3774.
(36) For the purpose of comparison, the *erythro* isomer was prepared by Grignard addition to aldehyde **9** (EtMgBr/Et_2O, −78 °C; *erythro*/*threo* = 11/1).
(37) Deprotection proceeded cleanly without affecting the allylic moiety. This reagent system had been used for the removal of MOM protecting group: Kiezykowski, G. R.; Schlessinger, R. H. *J. Am. Chem. Soc.* **1978**, *100*, 1938–1940.
(38) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, 3769–3722.
(39) Dilute solution of LDA was the reagent of choice, since use of *n*-BuLi, the reagent used in the original report,[38] led to other undefined products in this instance.
(40) No epimerization of C(8) was detected under these conditions.
(41) Preliminary experiments using a model compound excluded the epimerization of C(8) at the ketone stage under the present reaction conditions, presumably by virtue of lactol formation.
(42) Grant, B.; Djerassi, C. *J. Org. Chem.* **1974**, *39*, 968–970.

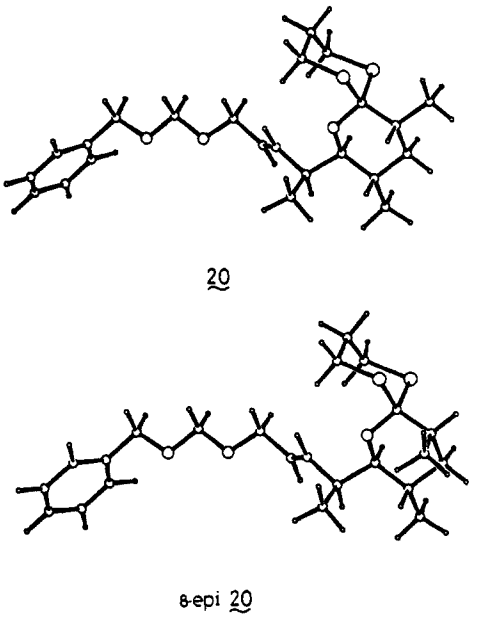


Figure 1.

33, selective oxidation of the allylic alcohol to aldehyde with MnO_2 followed by reaction with $NaClO_2$[43] provided the seco-acid **34**. Macrolactonization of **34** under Yamaguchi's conditions[44] afforded lactone **35** in 58% yield. Upon deacetylation (LiOH/MeOH–H_2O, room temperature), the C(9) epimers **36a** (44%) and **36b** (46%) were obtained, which were easily separable on TLC. Finally, oxidation of each component with activated MnO_2 provided protomycinolide IV (**1**) in 68% yield (from **36a**) and 59% yield (from **36b**), respectively. All the physical properties (TLC, ^1H NMR, IR, mp, $[\alpha]_D$, and MS) were in full accordance with those of the authentic specimen.

Here, the enantio-convergent total synthesis of protomycinolide IV (**1**) was accomplished based on the chirality transfer methodology by way of pinacol-type rearrangement utilizing readily available "C–O asymmetry" derived from (*S*)-ethyl lactate. The convergent sequence outlined here may offer a potentially more general and flexible approach to a number of related systems, including mycinamicin aglycons, and further investigation along these lines is now in progress.

Experimental Section

(*S*)-(*Z*)-6-[(Benzyloxy)methoxy]-2-hydroxy-4-(trimethylsilyl)-4-hexen-3-one (6). In order to strictly suppress the *E*/*Z* isomerization of the alkenyl group, especially in the large-scale run, the following procedure is recommended with respect to the solvent system and the rate of addition. To a solution of bromide **5** (5.02 g, 15.3 mmol) in the mixed solvent (THF/Et_2O/hexane = 4/1/1; 240 mL) was slowly added *n*-BuLi (1.62 M, hexane; 11.3 mL) during 20 min followed by amide **4** (3.46 g, 18.3 mmol) in the mixed solvent (30 mL) during 40 min. The mixture was stirred for 30 min and poured into ice-cold mixture of THF and 1 N H_2SO_4 (18.3 mL) with vigorous stirring. The crude oil, obtained by the extraction (Et_2O) and evaporation, was dissolved in 1,3-dioxane (80 mL) and treated with 1 N H_2SO_4 (10 mL) at room temperature for 20 min. Extractive workup followed by purification with flash column chromatography (hexane/AcOEt = 83/17) afforded ketone **6** as a colorless oil, 4.57 g, 92%. R_f 0.41 (hexane/AcOEt = 7/3); $[\alpha]^{30}_D$ +10° (*c* 1.2, $CHCl_3$); IR (neat) 3590, 2960, 2900, 1680, 1600, 1500, 1450, 1370, 1250, 1200, 1165, 1110, 1040, 840, 740, 700 cm^{-1}; ^1H NMR (CCl_4) δ 0.18 (s, 9 H), 1.20 (d, 3 H, J = 7.5 Hz), 3.2 (br, 1 H), 4.22 (d, 2 H, J = 6 Hz), 4.3–4.8 (m, 1 H), 4.54 (s, 2 H), 4.67 (s, 2 H), 6.53 (t, 1 H, J = 6 Hz), 7.25 (s, 5 H); HRMS, m/z 305.1559 (305.1571 calcd for $C_{17}H_{25}O_3Si$, $M^+ - OH$).

(*R*)-(*Z*)-5-[(Benzyloxy)methoxy]-2-methyl-3-(trimethylsilyl)-3-penten-1-ol (8): To a solution of alcohol **6** (1.90 g, 5.91 mmol) and Et_3N (1.19 g, 11.8 mmol) in CH_2Cl_2 (40 mL) was slowly added MsCl (1.02 g, 8.86 mmol) in CH_2Cl_2 (13 mL) at −45 °C, and the mixture was stirred for 20 min and quenched with pH 7 phosphate buffer. The products were extracted with CH_2Cl_2 and washed successively with saturated $(COOH)_2$ aqueous solution, brine, 4% $NaHCO_3$ aqueous solution, and brine and dried over Na_2SO_4. Since the mesylate **7** was highly unstable as a neat liquid, the complete evaporation should be avoided.

To the solution of the mesylate **7** in CH_2Cl_2, partially evaporated to ca. 80 mL, was slowly added DIBAL (3.3 mL, 17.7 mmol) at −78 °C, followed by Et_3Al (0.81 mL, 5.91 mmol). After the temperature was gradually raised to −20 °C during 2 h, the mixture was poured into ice-cold saturated NH_4Cl solution. After decomposition of the remaining organoaluminums with 2 N HCl, the products were extracted with Et_2O and dried over Na_2SO_4 and evaporated. Purification by flash column chromatography (hexane/Et_2O = 6/4) afforded **8** as an oil, 1.54 g, 85%. R_f 0.44 ($CHCl_3$/acetone = 19/1); $[\alpha]^{28}_D$ −7.3° (*c* 2.2, $CHCl_3$); IR (neat) 3450, 2950, 2875, 1610, 1500, 1450, 1380, 1250, 1165, 1100, 1040, 840 cm^{-1}; ^1H NMR (CCl_4) δ 0.16 (s, 9 H), 1.02 (d, 3 H, J = 7 Hz), 2.2–2.6 (m, 1 H), 2.66 (br s, 1 H), 3.25 (dd, 1 H, J_1 = 6, J_2 = 10.5 Hz), 3.48 (dd, 1 H, J_1 = 7.5, J_2 = 10.5 Hz), 4.12 (d, 2 H, J = 7 Hz), 4.55 (s, 2 H), 4.66 (s, 2 H), 6.05 (t, 1 H, J = 7 Hz), 7.26 (s, 5 H); HRMS, m/z 306.1623 (306.1649 calcd for $C_{19}H_{26}O_3Si$, $M^+ - 2$).

The (*R*)-MTPA ester of racemic alcohol **8** showed diagnostic signals in the 400-MHz ^1H NMR spectrum (C_6D_6): that is, two sets of doublet at δ 0.94 and 0.97 ($CHCH_3$, J = 6.8 Hz for each). The Mosher ester prepared from the chiral alcohol **8** showed only one doublet at δ 0.94 indicating >95% ee of the parent alcohol.

(*R*)-(*Z*)-5-[(Benzyloxy)methoxy]-2-methyl-3-(trimethylsilyl)-3-pentenal (9).[16] To a solution of $(COCl)_2$ (1.07 g, 8.44 mmol) in CH_2Cl_2 (10 mL) was added Me_2SO (1.32 g, 16.9 mmol) in CH_2Cl_2 (10 mL) at −78 °C, and the resulting solution was stirred for 2 min. To this was added alcohol **8** (1.30 g, 4.22 mmol) in CH_2Cl_2 (15 mL) and the mixture was stirred for 10 min, followed by addition of Et_3N (2.56 g, 25.3 mmol) in CH_2Cl_2 (10 mL). The temperature was gradually raised to 0 °C during 30 min and the reaction was stopped with a few drops of phosphate buffer (pH 7) and diluted with hexane, and the resulting precipitates, $Et_3NH^+Cl^-$, were removed by filtration. The mixture was further diluted with hexane and washed with water (×3) and brine and dried. This workup procedure using hexane is effective for the removal of Et_3NH^+-Cl^-, which could cause racemization of aldehyde **9**. After evaporation, the aldehyde was used for the next step. R_f 0.65 (hexane/AcOEt = 7/3); IR (neat) 2950, 2700, 1720, 1605, 1495, 1450, 1375, 1250, 1165, 1100, 1040, 840 cm^{-1}; ^1H NMR (CCl_4) δ 0.17 (s, 9 H), 1.16 (d, 3 H, J = 7 Hz), 3.04 (q, 1 H, J = 7 Hz), 4.13 (d, 2 H, J = 6.5 Hz), 4.53 (s, 2 H), 4.63 (s, 2 H), 5.97 (t, 1 H, J = 6.5 Hz), 7.25 (s, 5 H), 9.38 (d, 1 H, J = 2 Hz); HRMS, m/z 306.1652 (306.1650 calcd for $C_{17}H_{26}O_3Si$, M^+).

(3*S*,4*S*,5*R*)-(*Z*)-8-[(Benzyloxy)methoxy]-3,5-dimethyl-3-(trimethylsilyl)-1,6-octadien-4-ol (10a). To a suspension of anhydrous $CrCl_2$ (2.08 g, 16.9 mmol) in THF (15 mL) at −20 °C was added a THF (15 mL) solution of **9** (1.29 g, 4.22 mmol), followed by crotyl bromide (1.14 g, 8.44 mmol) in THF (10 mL), and the mixture was stirred overnight at 0 °C. The reaction was stopped with water, filtered through a Celite pad, extracted, and dried over Na_2SO_4. TLC analysis (hexane/Et_2O = 7/3) indicated two spots, A (R_f 0.43) and B (R_f 0.29), which were separated with flash column chromatography (hexane/AcOEt = 92/8). The fraction A was the minor one (157 mg, 10%), which was composed of anti-Cram isomers **10c** and **10d** in a ratio of 1/3. The major fraction B (1.10 g, 72%) was the essentially pure desired isomer **10a**, containing ca. 1.5% of **10b**.

10a: $[\alpha]^{30}_D$ −3.2° (*c* 1.9, $CHCl_3$); IR (neat) 3500, 2950, 1635, 1605, 1500, 1450, 1380, 1250, 1165, 1100, 1040, 910, 840, 760, 740, 700 cm^{-1}; ^1H NMR (CCl_4) δ 0.13 (s, 9 H), 1.02 (d, 6 H, J = 7 Hz), 1.30 (br s, 1 H), 2.1–2.6 (m, 2 H), 3.20 (dd, 1 H, J_1 = J_2 = 6 Hz), 4.12 (d, 2 H, J = 7 Hz), 4.53 (s, 2 H), 4.63 (s, 2 H), 4.8–5.1 (m, 2 H), 5.6–6.0 (m, 1 H), 6.07 (t, 1 H, J = 7 Hz), 7.23 (s, 5 H); HRMS, m/z 362.2278 (362.2275 calcd for $C_{21}H_{34}O_3Si$, M^+).

Ratios of **10a**/**10b** and **10c**/**10d** were determined by HPLC analyses of the separated fractions A and B [**10a**/**10b** = 60/1, Develosil ODS-5 (4.6 × 250, Nomural), MeOH/H_2O = 4/1; **10c**/**10d** = 1/3, ZORBZX SIL 4.6 × 250, Du Pont), hexane/AcOEt = 30/1]. Comparison samples of other isomers **10b–d** were prepared by suitable methods,[6b] whose ^1H NMR and IR data are listed as supplementary material.

The (*R*)-MTPA ester of racemic alcohol **10a** showed diagnostic signals in the 400-MHz ^1H NMR spectrum ($CDCl_3$) for the two diastereomers, that is, four singlets at δ 4.61, 4.62, 4.75, 4.77. The (*R*)-MTPA ester prepared from chiral alcohol **10a** showed only two singlets at δ 4.61 and 4.75 (2 H + 2 H, $PhCH_2CH_2O$), indicating the ee of **10a** to be >95%.

(2*S*,3*S*)-2-[(*S*)-(*E*)-4-[(Benzyloxy)methoxy]-1-methyl-2-buten-1-yl]-1-oxa-7,11-dithiaspiro[5.5]undecane (15a). To a suspension of KH (34% in oil, 272 mg, 2.3 mmol) in 1,2-dimethoxyethane (DME; 4 mL) was added a mixture of lactol **12** (208 mg, 0.55 mmol) and phosphonate

(43) Lindgren, B. O.; Nilsson, T. *Acta Chim. Scand.* **1973**, *27*, 888–890.
(44) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989–1993.

13[24] (422 mg, 1.65 mmol) in DME (10 mL) at 0 °C; the mixture was stirred for 10 min and then at room temperature for 30 min and quenched with H_2O. After extraction and drying, the products were passed through a short plug of silica gel (hexane/AcOEt = 85/15) to give the TMS ether of alcohol **14b**, which was hydrolyzed by stirring in 0.5 N NaOH/MeOH at room temperature for 3 h. After evaporation of MeOH and usual extractive workup, **14b** was obtained by passing through a short column of silica gel (hexane/AcOEt = 75/25). To this alcohol **14b** in 1,3-dioxane (6 mL) was added 3 drops of 0.02 N HCl: the mixture was stirred for 1 h at room temperature and quenched by addition of solid $NaHCO_3$. After filtration and evaporation, the residue was purified on PTLC (hexane/AcOEt = 87/13) to give **15a** as a colorless oil (171 mg, 76%). R_f 0.52 (hexane/Et_2O = 2.5/1); $[\alpha]^{34}_D$ +106° (*c* 1.3, $CHCl_3$); IR (neat) 2930, 1450, 1380, 1270, 1230, 1160, 1100, 1040, 1000, 980, 900, 880, 800, 730, 700 cm^{-1}; ^1H NMR (CCl_4) δ 0.86 (d, 3 H, J = 5 Hz), 1.07 (d, 3 H, J = 7 Hz), 1.2–2.1 (m, 7 H), 2.2–3.6 (m, 6 H), 3.99 (d, 2 H, J = 6 Hz), 4.50 (s, 2 H), 4.63 (s, 2 H), 5.47 (dt, 1 H, J_1 = 15, J_2 = 6 Hz), 5.88 (dd, 1 H, J_1 = 15, J_2 = 7.5 Hz), 7.23 (s, 5 H); HRMS, *m/z* 408.1783 (408.1790 calcd for $C_{22}H_{32}O_3S_2$, M^+).

(4*S*,5*S*,6*S*)-(*E*)-9-[(Benzyloxy)methoxy]-4,6-dimethyl-7-nonen-5-olide (15b). $HgCl_2$ (1.06 g, 3.89 mmol) was added portionwise to a solution of thioacetal **15a** (636 mg, 1.56 mmol) in 80% CH_3CN–THF–pH 7 phosphate buffer (v/v/v = 10/2/1; 39 mL) and the resulting mixture was stirred for 1 h at room temperature, quenched with H_2S, and filtered. Usual extractive workup and purification with flash column chromatography (hexane/AcOEt = 75/25) gave lactone **15b** as a colorless oil, 454 mg, 92%. R_f 0.20 (hexane/AcOEt = 2.5/1); $[\alpha]^{31}_D$ +43° (*c* 1.8, $CHCl_3$); IR (neat) 2930, 2870, 1730, 1450, 1380, 1240, 1210, 1100, 1040, 1000, 740, 700 cm^{-1}; ^1H NMR (CCl_4) δ 0.97 (d, 3 H, J = 6 Hz), 1.03 (d, 3 H, J = 6 Hz), 1.2–2.1 (m, 3 H), 2.2–2.7 (m, 3 H), 3.80 (dd, 1 H, J_1 = 9, J_2 = 3 Hz), 4.02 (d, 2 H, J = 6 Hz), 4.53 (s, 2 H), 4.66 (s, 2 H), 5.50 (dt, 1 H, J_1 = 15, J_2 = 6 Hz), 5.78 (dd, 1 H, J_1 = 15, J_2 = 7.5 Hz), 7.27 (s, 5 H); HRMS, *m/z* 319.1925 (319.1908 calcd for $C_{19}H_{27}O_4$, M^+ + 1).

Equilibration of 16. To a mixture of lactones **16a,b** (81 mg, 0.24 mmol) in *t*-BuOH (21.4 mL) was added freshly sublimed *t*-BuOK (27.3 mg, 0.24 mmol) in *t*-BuOH (3 mL) at room temperature, and the mixture was left standing overnight at room temperature. After the reaction was stopped by saturated NH_4Cl solution, extractive workup and purification on PTLC afforded an equilibrated mixture of **16** (73 mg, 90%). The ratio was **16a**/**16b** = 6/1 by HPLC analysis (Develosil ODS-5, 4.6×250, Nomura; MeOH/H_2O = 6/4). Lactone **16a** was isolated by medium-pressure chromatography (benzene/Et_2O 19/1). **16a**: R_f 0.51 (benzene/Et_2O = 9/1, three developments; cf. **16b** R_f 0.55); $[\alpha]^{23}_D$ +38° (*c* 1.2, $CHCl_3$); IR (neat) 2980, 2950, 2880, 1730, 1500, 1450, 1380, 1330, 1190, 1160, 1110, 1040, 990, 970, 740, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.96 (d, 3 H, J = 6 Hz), 1.06 (d, 3 H, J = 6 Hz), 1.26 (d, 3 H, J = 7 Hz), 1.4–2.1 (m, 3 H), 2.1–2.7 (m, 2 H), 3.93 (dd, 1 H, J_1 = 9, J_2 = 3 Hz), 4.10 (d, 2 H, J = 6 Hz), 4.60 (s, 2 H), 4.80 (s, 2 H), 5.4–6.0 (m, 2 H), 7.30 (s, 5 H); HRMS, *m/z* 333.2048 (333.2063 calcd for $C_{20}H_{29}O_4$, M^+ + 1).

Stereoselective Cyclization. To a solution of alcohol **19** (32.7 mg, 0.078 mmol) at 0 °C was added freshly prepared anhydrous HCl/CH_2Cl_2 (0.12 M, 0.32 mL), and the mixture was stirred for 30 min at 0 °C. The reaction was stopped by 3 drops of Et_3N and evaporated at reduced pressure, and the residue was chromatographed on PTLC (hexane/Et_2O = 3/1) to give **20** as a colorless oil (30.1 mg, 92%). According to the similar procedure described in the conversion of **15a** to **15b**, thioacetal **20** was converted to lactone **16** which was purified on PTLC (hexane/AcOEt = 2.5/1); 19.8 mg, 94%. HPLC analysis of the material showed the ratio **16a**/**16b** = 15/1. **20**: R_f 0.70 (hexane/Et_2O = 1/1); $[\alpha]^{28.5}_D$ +86° (*c* 1.1, $CHCl_3$); IR (neat) 2960, 2920, 1495, 1450, 1380, 1270, 1165, 1105, 1025, 1000, 975, 800, 735, 695 cm^{-1}; ^1H NMR (CCl_4) δ 0.83 (d, 3 H, J = 6.5 Hz), 1.02 (d, 3 H, J = 7 Hz), 1.06 (d, 3 H, J = 7 Hz), 1.0–2.2 (m, 6 H), 2.2–3.7 (m, 6 H), 4.01 (d, 2 H, J = 5.5 Hz), 4.50 (s, 2 H), 4.63 (s, 2 H), 5.52 (dt, 1 H, J_1 = 16, J_2 = 5.5 Hz), 5.86 (dd, 1 H, J_1 = 16, J_2 = 7 Hz), 7.25 (s, 5 H); HRMS, *m/z* 422.1934 (422.1947 calcd for $C_{23}H_{34}O_3S_2$, M^+).

(*S*)-2-(1-Ethoxyethoxy)pentan-3-one (21). EtMgBr (2.05 M/THF, 25 mL) was added to **4** (9.45 g, 50.0 mmol) in THF (50 mL) at 0 °C during 15 min, the mixture was stirred for 20 min at 0 °C, and the temperature was gradually raised to room temperature during 2 h. The reaction was stopped with pH 7 phosphate buffer, and the products were extracted with Et_2O and dried over Na_2SO_4. After careful evaporation of the solvents, the residue was distilled at reduced pressure to give ketone **21** as a colorless liquid (6.76 g, 77%). Bp 86–88 °C (20 mmHg); R_f 0.51 (hexane/AcOEt = 8/2); IR (neat) 3550, 2990, 2950, 2880, 1720, 1440, 1380, 1345, 1320, 1080, 950, 850, 800, 750 cm^{-1}; ^1H NMR (CCl_4) δ 0.85–1.5 (m, 12 H), 2.15–2.8 (m, 2 H), 3.2–3.7 (m, 2 H), 3.85 (q, J = 7 Hz) and 4.02 (q, J = 7 Hz) (1 H), 4.60 (q, 1 H, J = 5.5 Hz); HRMS, *m/z* 173.1196 (173.1177 calcd for $C_9H_{17}O_3$, M^+ – 1).

(2*S*,3*RS*)-(*Z*)-6-[(Benzyloxy)methoxy]-3-ethyl-4-(trimethylsilyl)-4-hexene-2,3-diol (22a). To a solution of **5** (5.59 g, 17.0 mmol) in THF (120 mL), Et_2O (30 mL), and hexane (18 mL) at −100 °C was slowly added *n*-BuLi (1.5 M, hexane; 12.5 mL), followed by the addition of **21** (3.29 g, 18.7 mmol) in the mixed solvent (THF/Et_2O/hexane = 4/1/1; 60 mL), and the mixture was stirred for 30 min and poured into an ice-cold pH 7 phosphate buffer–THF mixture. The crude oil, obtained by extractive workup and evaporation, was dissolved in MeOH and treated with a catalytic amount of PPTS[35] at room temperature for 1 h. After neutralization with solid $NaHCO_3$, filtration, and evaporation, the products were extracted and purified with flash column chromatography (hexane/AcOEt = 4/1) to give **22a** as a diastereomeric mixture (5.98 g, quantitative). R_f 0.27 (CH_2Cl_2/AcOEt = 9/1); IR (neat) 3480, 2950, 1950, 1730, 1605, 1450, 1370, 1245, 1160, 1100, 840, 740, 700, 630 cm^{-1}; ^1H NMR (CCl_4) δ 0.20 (s, 9 H), 0.79 (t, 3 H, J = 7 Hz), 1.07 (t, 3 H, J = 6.5 Hz), 1.54 (q, J = 7 Hz) and 1.77 (q, J = 7 Hz) (2 H), 2.05–2.75 (br, 2 H), 3.45–4.0 (m, 1 H), 4.22 (d, J = 6.5 Hz) and 4.25 (d, J = 6.5 Hz) (2 H), 4.56 (s, 2 H), 4.68 (s, 2 H), 6.22 (t, 1 H, J = 6.5 Hz), 7.29 (s, 5 H); HRMS, *m/z* 335.2055 (335.2041 calcd for $C_{19}H_{31}O_3Si$, M^+ – H_2O).

(*R*)-(*Z*)-7-[(Benzyloxy)methoxy]-4-methyl-5-(trimethylsilyl)-5-hepten-3-one (23). MsCl (48.3 mg, 0.42 mmol) in CH_2Cl_2 (3 mL) was added to a mixture of **22a** (99.0 mg, 0.28 mmol) and Et_3N (85.2 mg, 0.84 mmol) in CH_2Cl_2 (5 mL) at 0 °C; the mixture was stirred for 30 min and quenched with pH 7 phosphate buffer. After extraction with CH_2Cl_2, the combined extracts were successively washed with saturated $(COOH)_2$ aqueous solution, brine, 4% $NaHCO_3$ aqueous solution, and brine. Crude **22b**, obtained after drying over Na_2SO_4 and evaporation, was used without further purification for the next step.

To a solution of the mesylate **22b**, thus obtained, in CH_2Cl_2 (5 mL) at −78 °C was slowly added Et_3Al (0.90 M, hexane; 0.64 mL), and the mixture was stirred for 1 h and carefully poured into ice-cold dilute NH_4Cl solution. After remaining organoaluminums were destroyed by 2 N HCl, the products were extracted with Et_2O, and the combined extracts were washed with brine and dried. Purification with flash chromatography (hexane/AcOEt = 93/7) afforded **23** as a colorless oil (73.7 mg, 80%). R_f 0.66 (hexane/AcOEt = 7/3); $[\alpha]^{27}_D$ +107° (*c* 2.3, $CHCl_3$); IR (neat) 2950, 1710, 1605, 1500, 1450, 1410, 1375, 1340, 1250, 1170, 1105, 1045, 840, 740, 695 cm^{-1}; ^1H NMR (CCl_4) δ 0.18 (s, 9 H) 0.98 (t, 3 H, J = 7 Hz), 1.10 (d, 3 H, J = 7 Hz), 1.95–2.65 (m, 2 H), 3.16 (q, 1 H, J = 7 Hz), 4.15 (d, 2 H, J = 6.5 Hz), 4.54 (s, 2 H), 4.64 (s, 2 H), 5.96 (t, 1 H, J = 6.5 Hz), 7.27 (s, 5 H); HRMS, *m/z* 334.1957 (334.1961 calcd for $C_{19}H_{30}O_3Si$, M^+).

(3*R*,4*R*)-(*Z*)-7-[(Benzyloxy)methoxy]-4-methyl-5-(trimethylsilyl)-5-hepten-3-ol (24). To a solution of **23** (73 mg, 0.22 mmol) in THF (4 mL) was added L-Selectride (1 M, THF, 0.44 mL) at −78 °C, and the mixture was stirred for 30 min. The reaction was stopped with pH 7 buffer and to this was added 35% H_2O_2 (1.5 mL) and the solution was stirred for 15 min at 0 °C. Extractive workup and purification with PTLC (hexane/AcOEt = 7/3) afforded *threo*-alcohol **24** (70 mg, 95%) as the sole isolable product. R_f 0.60 (hexane/AcOEt = 7/3); $[\alpha]^{25}_D$ −19° (*c* 1.7, $CHCl_3$); IR (neat) 3530, 3000, 1510, 1460, 1390, 1255, 1170, 1115, 1050, 980, 850, 745, 705 cm^{-1}; ^1H NMR (CCl_4) δ 0.17 (s, 9 H), 0.92 (t, 3 H, J = 7 Hz), 0.92 (d, 3 H, J = 7 Hz), 1.05–1.8 (m, 2 H), 1.58 (s, 1 H), 2.32 (dq, 1 H, J_1 = J_2 = 7 Hz), 3.35 (dt, 1 H, J_1 = 7, J_2 = 3 Hz), 4.14 (d, 2 H, J = 6.5 Hz), 4.55 (s, 2 H), 4.66 (s, 2 H), 6.17 (t, 1 H, J = 6.5 Hz), 7.3 (s, 5 H); HRMS, *m/z* 336.2092 (336.2066 calcd for $C_{19}H_{32}O_3Si$, M^+).

Erythro isomer, prepared by addition of EtMgBr to aldehyde **9** in Et_2O at −78 °C (*erythro*/*threo* = 11/1), exhibited the following physical properties: R_f 0.56 (hexane/AcOEt = 7/3); IR (neat) 3470, 2950, 1495, 1450, 1375, 1245, 1160, 1100, 1035, 960, 900, 830, 730, 695 cm^{-1}; ^1H NMR (CCl_4) δ 0.15 (s, 9 H), 0.8–1.1 (m, 6 H), 1.2–1.7 (m, 3 H), 2.2–2.6 (m, 1 H), 3.1–3.5 (m, 1 H), 4.15 (d, 2 H, J = 7.5 Hz), 4.55 (s, 2 H), 4.65 (s, 2 H), 6.1 (t, 1 H, J = 7.5 Hz), 7.25 (s, 5 H).

The (*R*)-MTPA ester of racemic alcohol **24** showed diagnostic signals in the 400-MHz ^1H NMR spectrum ($CDCl_3$), that is, the two sets of triplets centered at δ 6.16 (J = 6.6 Hz) and 6.20 (J = 6.3 Hz). The MTPA ester of chiral alcohol **24** showed only one triplet at δ 6.20 (1 H, CH_2CH=C) indicating >95% ee of **24**.

(3*R*,4*S*)-(*E*)-7-[(Benzyloxy)methoxy]-4-methyl-5-hepten-3-ol (25). To a solution of **24** (84.7 mg, 0.25 mmol) in HMPA (4 mL) was added a catalytic amount of NaH (60% in oil), and the mixture was stirred for 30 min at room temperature.[25] The reaction was stopped by H_2O and extracted with Et_2O, and the combined extracts were washed with H_2O followed by brine and dried. Purification with PTLC (hexane/AcOEt = 7/3) afforded **25** as an oil (63.7 mg, 96%). R_f 0.46 (hexane/AcOEt = 7/3); $[\alpha]^{21}_D$ −9.6° (*c* 1.3, $CHCl_3$); IR (neat) 3470, 2940, 1495, 1450, 1375, 1160, 1100, 1040, 970, 735, 700 cm^{-1}; ^1H NMR (CCl_4) δ 0.91 (t,

3 H, J = 7 Hz), 0.99 (d, 3 H, J = 7 Hz), 1.1–1.8 (m, 2 H), 1.61 (s, 1 H), 1.9–2.4 (m, 1 H), 3.21 (dt, 1 H, J_1 = 7, J_2 = 4.5 Hz), 3.95–4.1 (m, 2 H), 4.54 (s, 2 H), 4.65 (s, 2 H), 5.25–5.8 (m, 2 H), 7.28 (s, 5 H); HRMS, m/z 265.1780 (265.1801 calcd for $C_{16}H_{25}O_3$, $M^+ + 1$).

(5*S*,6*R*)-(*E*)-6-(1-Ethoxyethoxy)-5-methyl-3-octen-1-yne (28). Alcohol **27** was converted quantitatively to the corresponding ethoxyethyl (EE) ether by standard procedure (CH_2=$CHOEt/CH_2Cl_2$, catalytic PPTS[35]). After passing through a silica gel short column (hexane/Et_2O = 20/1 containing 0.5% Et_3N), this labile EE ether was immediately subjected to the next reaction. LDA (0.2 M, THF, 25.8 mL) was slowly added to a solution of the EE ether (478 mg, 1.29 mmol) in THF (10 mL) at 0 °C, and the mixture was stirred for 5 min and quenched with 4% $NaHCO_3$ solution. After extraction (Et_2O), drying (K_2CO_3), and careful evaporation of the solvents, the residue was passed through a silica-gel short column (hexane/Et_2O = 9/1 containing 0.5% of Et_3N). After the mixture was dried over K_2CO_3, bulb-to-bulb distillation gave enyne **28** as a colorless liquid (220 mg, 81%). Bp 90–110 °C (20 mmHg); R_f 0.46 (hexane/Et_2O = 9/1 containing 0.5% of Et_3N); IR (neat) 3320, 2980, 2945, 2880, 2105, 1450, 1380, 1340, 1125, 1080, 1055, 990 cm^{-1}; ^1H NMR (CCl_4) δ 0.75–1.7 (m, 14 H), 2.2–2.65 (m, 1 H), 2.6–2.65 (m, 1 H), 3.2–3.65 (m, 3 H), 4.59 (q, J = 5 Hz) and 4.62 (q, J = 5 Hz) (1 H), 5.35 (d, 1 H, J = 16.5 Hz), 6.07 (dd, J_1 = 16.5, J_2 = 3 Hz) and 6.18 (dd, J_1 = 16.5, J_2 = 3 Hz) (1 H); HRMS, m/z 181.1228 (181.1228 calcd for $C_{11}H_{17}O_2$, $M^+ - C_2H_5$).

(2*R*,4*S*,5*S*,6*S*)-(*E*)-2,4,6-Trimethyl-9-hydroxy-7-nonen-5-olide (29). To a mixture of lactone **16a** (169 mg, 0.51 mmol) and PhSH (115 mg, 1.05 mmol) in CH_2Cl_2 (4.5 mL) was slowly added BF_3-OEt_2 (299 mg, 2.11 mmol) in CH_2Cl_2 (1.5 mL) at 0 °C; the solution was further stirred for 12 h at 0 °C and quenched with pH 7 phosphate buffer. After usual extractive workup and evaporation, purification with flash column chromatography (hexane/AcOEt = 4/6) gave lactone **29** as a colorless oil (105 mg, 97%). R_f 0.48 (hexane/AcOEt = 1/2.5); $[\alpha]^{23}_D$ +57° (c 1.4, $CHCl_3$); IR (neat) 3425, 2970, 2940, 2880, 1725, 1450, 1380, 1330, 1200, 1110, 1040, 990, 660, 630 cm^{-1}; ^1H NMR (CCl_4) δ 0.98 (d, 3 H, J = 6 Hz), 1.00 (d, 3 H, J = 7 Hz), 1.18 (d, 3 H, J = 7.5 Hz), 1.0–2.1 (m, 3 H), 2.1–2.7 (m, 2 H), 2.88 (br s, 1 H), 3.8–4.2 (m, 3 H), 5.4–5.9 (m, 2 H); HRMS, m/z 195.1368 (195.1383 calcd for $C_{12}H_{19}O_2$, M^+ – OH).

(4*S*,5*S*,6*S*,8*R*,9*RS*,14*S*,15*R*)-(2*E*,10*E*,12*E*)-1,15-Bis(1-ethoxyethoxy)-4,6,8,14-tetramethyl-2,10,12-heptadecatrien-5,9-diol (32). To a solution of enyne **28** (183 mg, 0.87 mmol) in hexane (6.5 mL) was added n-BuLi (1.63 M, hexane, 0.83 mmol) at 0 °C, and the mixture was stirred for 30 min at 0 °C. To the mixture was added lactone **30** (118 mg, 0.415 mmol) in hexane (4 mL); the solution was stirred for 30 min, quenched with pH 7 phosphate buffer, and extracted. TLC inspection (hexane/AcOEt = 75/25) revealed roughly two new products (R_f 0.50 and 0.63), which were separated from the starting material(s) on PTLC (hexane/AcOEt = 6/4 containing 0.5% of Et_3N); 187 mg, 91%. This material was used for the next step.

To a suspension of $LiAlH_4$ (72 mg, 1.90 mmol) in THF (2 mL) at 0 °C was added **31** (187 mg, 0.379 mmol), described above, in THF (8 mL), and the mixture was stirred at room temperature overnight. The reaction was stopped with pH 7 phosphate buffer and extracted. Purification on silica gel TLC (hexane/Et_2O = 1/3) afforded diol **32** as an oil (122 mg, 65%). R_f 0.29 (hexane/Et_2O = 1/1); IR (neat) 3450, 2980, 2950, 1665, 1450, 1380, 1335, 1125, 1085, 1050, 990 cm^{-1}; ^1H NMR (CCl_4) δ 0.8–2.15 (m, 33 H), 2.1–3.0 (m, 4 H), 3.0–3.65 (m, 6 H), 3.7–4.2 (m, 3 H), 4.63 (q, 2 H, J = 5.5 Hz), 5.35–6.35 (m, 6 H); HRMS, m/z 435.3470 (435.3471 calcd for $C_{27}H_{47}O_4$, $M^+ - C_2H_5O - H_2O$).

(4*S*,5*S*,6*S*,8*R*,9*RS*,14*S*,15*R*)-(2*E*,10*E*,12*E*)-5,9-Diacetoxy-15-hydroxy-4,6,8,14-tetramethyl-2,10,12-heptadecatrienoic Acid (34). A mixture of diol **33** (58.0 mg, 0.132 mmol) and activated MnO_2 (800 mg, 9.20 mmol) in Et_2O (14 mL) was stirred at room temperature for 2.5 h. After filtration through a Celite pad and evaporation, the obtained crude aldehyde was dissolved in t-BuOH (8.5 mL), to which was added resorcinol (26.5 mg, 0.240 mmol) in pH 4 acetate buffer (3.4 mL) followed by $NaClO_2$ (20.8 mg, 0.230 mmol) in H_2O (5.0 mL).[43] The mixture was stirred at room temperature overnight and evaporated at reduced pressure. After extractive workup (Et_2O), purification on PTLC (AcOEt/hexane = 3/1) followed by another PTLC ($CHCl_3$/acetone/AcOH = 4/1/0.005) gave seco-acid **34** as an oil (47.2 mg, 79%). R_f 0.18 ($CHCl_3$/acetone/AcOH = 4/1/0.005); IR (neat) 3600–2500 (br), 2990, 1730, 1660, 1605, 1460, 1375, 1240, 1020, 990, 970, 790, 765 cm^{-1}; ^1H NMR (CCl_4) δ 0.8–1.1 (m, 15 H), 1.1–2.8 (m, 8 H), 2.00 (s, 6 H), 3.15–3.45 (m, 1 H), 4.65–4.9 (m, 1 H), 4.9–5.2 (m, 1 H), 5.2–6.5 (m, 7 H), 6.86 (dd, 1 H, J_1 = 15.5, J_2 = 8 Hz).

For an analytical purpose, seco-acid **34** was converted to the corresponding methyl ester with CH_2N_2: R_f 0.56 (hexane/AcOEt = 1/1); IR (neat) 3520, 2960, 1725, 1655, 1455, 1430, 1370, 1230, 1190, 1170, 1015, 985, 960 cm^{-1}; ^1H NMR (CCl_4) δ 0.8–1.1 (m, 15 H), 1.1–2.9 (m, 9 H), 2.00 (s, 6 H), 3.1–3.5 (m, 1 H), 3.68 (s, 3 H), 4.65–4.85 (m, 1 H), 5.0–5.2 (m, 1 H), 5.2–6.4 (m, 5 H), 6.77 (dd, 1 H, J_1 = 15, J_2 = 8.5 Hz); HRMS, m/z 406.2708 (406.2716 calcd for $C_{24}H_{38}O_5$, M^+ – CH_3COOH).

(4*S*,5*S*,6*S*,8*R*,9*RS*,14*S*,15*R*)-(2*E*,10*E*,12*E*)-5,9-Diacetoxy-4,6,8,14-tetramethyl-2,10,12-heptadecatrien-15-olide (35) (Macrolactonization).[44] To a solution of **34** (71.1 mg, 0.157 mmol) in THF (7 mL) were successively added Et_3N (99 μL, 0.710 mmol) and 2,4,6-$Cl_3C_6H_2COCl$ (90 μL, 0.562 mmol); the mixture was stirred for 3 h at room temperature.

After evaporation of THF at reduced pressure, toluene (10 mL) was added, and the resulting precipitate was removed by filtration through a plug of glass wool. After the filtrate was further diluted to 82 mL with toluene, the mixed anhydride was slowly added by means of a motor-driven syringe to refluxing solution of 4-pyrrolidinopyridine (140 mg, 0.945 mmol) in toluene (15.7 mL) during 14 h, and this was stirred for a further 30 min. After it was cooled down and diluted with Et_2O, the solution was washed successively with saturated aqueous $(COOH)_2$ solution, H_2O, 4% $NaHCO_3$ solution, and H_2O and dried. Purification with flash column chromatography (hexane/Et_2O = 3/1) gave lactone **35** as a colorless oil (39.3 mg, 58%). R_f 0.48 (hexane/AcOEt = 3/1); IR (neat) 2970, 2935, 1735, 1650, 1635, 1460, 1370, 1320, 1230, 1180, 985 cm^{-1}; ^1H NMR (CCl_4) δ 0.7–1.1 (m, 15 H), 1.1–2.8 (m, 14 H), 4.58 (dt, 1 H, J_1 = 9, J_2 = 2.5 Hz), 4.7–4.95 (m, 1 H), 5.0–6.4 (m, 6 H), 6.64 (dd, J_1 = 15, J_2 = 10 Hz) and 6.68 (dd, J_1 = 16, J_2 = 10 Hz) (1 H); HRMS, m/z 434.2652 (434.2665 calcd for $C_{25}H_{38}O_6$, M^+).

(4*S*,5*S*,6*S*,8*R*,9*RS*,14*S*,15*R*)-(2*E*,10*E*,12*E*)-5,9-Dihydroxy-4,6,8,14-tetramethyl-2,10,12-heptadecatrien-15-olide [C(9) Epimers 36a and 36b]. To a solution of **35** (38.1 mg, 0.088 mmol) in MeOH (6 mL) was added 1 N LiOH aqueous solution (1.8 mL), and the mixture was stirred at 30 °C for 6 h. Brine was added to the mixture, which was extracted with Et_2O, and the combined extracts were washed with brine and dried. TLC inspection revealed two new spots, both of which were isolated with purification on PTLC (hexane/Et_2O = 1/4), gave **36a** (13.4 mg, 44%) and **36b** (14.1 mg, 46%) as white needles, respectively. **36a**: mp 54.5–59.0 °C; R_f 0.23 (hexane/Et_2O = 1/2); IR (KBr) 3450, 2960, 1700, 1650, 1455, 1225, 1175, 1140, 1075, 985 cm^{-1}; ^1H NMR (CCl_4) δ 0.8–1.2 (m, 15 H), 1.2–2.5 (m, 10 H), 3.1–3.4 (m, 1 H), 4.0–4.2 (m, 1 H), 4.4–4.7 (m, 1 H), 5.17 (dd, 1 H, J_1 = 14.5, J_2 = 9 Hz), 5.5–6.4 (m, 4 H), 6.59 (dd, 1 H, J_1 = 15, J_2 = 10 Hz); HRMS, m/z 350.2448 (350.2454 (calcd for $C_{21}H_{34}O_4$, M^+). **36b**: mp 79.0–82.0 °C; R_f 0.17 (hexane/Et_2O = 1/2); IR (KBr) 3450, 2960, 1700, 1650, 1455, 1225, 1175, 1140, 1075, 985 cm^{-1}; ^1H NMR (CCl_4) δ 0.8–1.1 (m, 15 H), 1.1–2.6 (m, 10 H), 3.1–3.4 (m, 1 H), 3.96 (dd, 1 H, J_1 = 9, J_2 = 4 Hz), 4.4–4.7 (m, 1 H), 5.05–6.2 (m, 5 H), 6.53 (dd, 1 H, J_1 = 15, J_2 = 10 Hz); HRMS, m/z 350.2438 (350.2454 calcd for $C_{21}H_{34}O_4$, M^+).

Preparation of Protomycinolide IV (1).[46] To a suspension of activated MnO_2 (120 mg, 1.38 mmol) in Et_2O (4.4 mL) was added lactone **36a** (11.9 mg, 0.034 mmol) in Et_2O (3 mL), and the mixture was stirred at room temperature for 2.5 h. TLC showed a new product which was coincidental with authentic protomycinolide IV (R_f 0.29; benzene/Et_2O = 2/3). After filtration through a Celite pad and evaporation, the product was purified on PTLC (benzene/Et_2O = 1/1) to give pure prorotomycinolide IV (**1**) as white solids, 8.0 mg, 68%). Recrystallization from hexane–acetone gave white needles: mp 158.5–159.5 °C; $[\alpha]^{27.5}_D$ +18.3° (c 0.60, MeOH) [lit.[8a] mp 159–160.5 °C; $[\alpha]^{26}_D$ +18.9° (c 1.0, MeOH)].

Structure of **1** was confirmed by direct spectroscopic comparison with the authentic sample. The ^1H NMR spectra (400 MHz) taken for synthetic and natural materials showed complete identity in the entire range: ^1H NMR ($CDCl_3$) δ 0.94 (t, 3 H, J = 7.3 Hz), 1.00 (d, 3 H, J = 6.7 Hz), 1.09 (d, 3 H, J = 6.7 Hz), 1.12 (d, 3 H, J = 6.7 Hz), 1.18 (d, 3 H, J = 7.0 Hz), 1.4–1.8 (m, 5 H), 1.75–1.9 (m, 1 H), 2.25–2.35 (m, 1 H), 2.45–2.6 (m, 2 H), 3.25–3.35 (m, 1 H), 4.65 (dt, 1 H, J_1 = 2.8, J_2 = 9.2 Hz), 5.71 (dd, 1 H, J_1 = 9.5, J_2 = 15.0 Hz), 5.77 (d, 1 H, J = 15.6 Hz), 6.08 (dd, 1 H, J_1 = 11.0, J_2 = 15.0 Hz), 6.23 (d, 1 H, J = 15.0 Hz), 6.59 (dd, 1 H, J_1 = 10.1, J_2 = 15.6 Hz), 7.10 (dd, 1 H, J_1 = 11.0, J_2 = 15.0 Hz). Comparative data for IR and mass spectra were fully identical in all respects: IR (KBr) 3530, 3410, 2970, 1705, 1670, 1650, 1625, 1585, 1455, 1350, 1275, 1230, 1175, 1145, 1080, 990 cm^{-1}; HRMS, m/z 348.2300 (348.2299 calcd for $C_{21}H_{32}O_4$, M^+).

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(46) Oxidation of the epimeric lactone **36b** by the same procedure led to 59% yield of **1**, which was also indistinguishable from the authentic material in all respects.

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Supplementary Material Available: General experimental procedure and a listing of the physical properties for compounds **4**, **5**, **10b–d**, **11**, **12**, **17**, **18**, **19**, **26**, **30**, **31**, and **33** (5 pages). Ordering information is given on any current masthead page.

1,3-Dipolar Cycloaddition Reactions of Transition-Metal Carbene Complexes and the Formal [3 + 2 + 1] Pyridinannulation of the Cycloadducts

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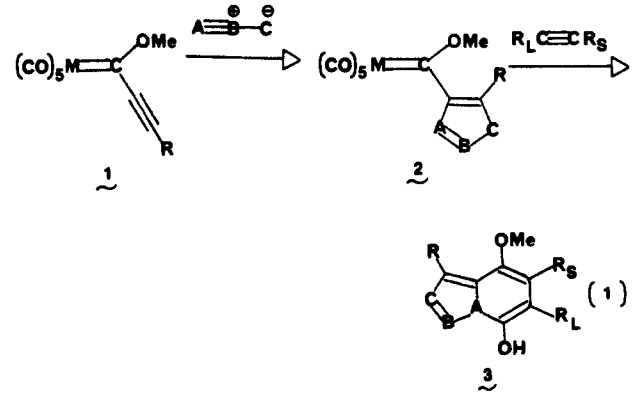
Abstract: The first examples of 1,3-dipolar cycloadditions of α,β-unsaturated carbene complexes are described. The reaction of alkynylcarbene complexes with diazomethane gives a mixture of two products. The first arises from a [3 + 2] cycloaddition on the carbon–carbon triple bond of the alkynyl complex to give a pyrazole carbene complex and the second is most likely a secondary product which arises from attack of diazomethane on the metal–carbon double bond of the pyrazole complex. Substitution of trimethylsilyldiazomethane for diazomethane suppresses the second reaction and provides good yields of pyrazole carbene complexes for a variety of alkynylcarbene complexes. The regioselectivity of these reactions was established in two cases to be greater than 300:1, whereas in the corresponding carbon analogues (tetrolate esters) the selectivity is 35:65. The chromium or tungsten pentacarbonyl groups also has a large influence on the rates as well as on the regioselectivity and thus can be considered as reactivity auxiliaries. The regioselectivity was shown to correlate with the ^{13}C NMR chemical shifts of the α- and β-acetylene carbons of these complexes which were assigned on the basis of carbon–carbon coupling constants. Other substituted diazoalkanes such as 3-diazopropene also give selective formation of the pyrazole [3 + 2] cycloadducts. The alkynylcarbene complexes can serve as synthons for acetylenic esters in the 1,3-dipolar cycloaddition reactions with diazoalkanes since the pyrazole carbene complexes can be efficiently converted to pyrazole esters. The pyrazole carbene complexes are demonstrated to have synthetic value that transcends their ability to be converted to pyrazole esters since their reactions with alkynes produces pyrazolo[1,5-*a*]pyridines.

The [3 + 2]-cycloaddition reactions of 1,3-dipoles have been intensely investigated in the last 20 years[1] and their importance in natural product synthesis has been thoroughly established.[2] Transition-metal carbene complexes bearing an alkenyl[3] or alkynyl[4] group on the carbene carbon have recently been found to be potent dienophiles. These complexes undergo rapid and highly stereo- and regioselective [4 + 2] cycloaddition reactions with a variety of dienes and can serve as synthons for a number of dienophiles in the Diels–Alder reaction.[3] This report describes for the first time the isolation of cycloadducts from the [3 + 2] cycloadditions of α,β-unsaturated carbene complexes with 1,3-dipoles and discusses an initial examination of the synthetic potential of the annulation reactions of the cycloadducts of the type **2** with alkynes (eq 1).

The clearest cut example of a 1,3-dipolar cycloaddition to a transition-metal–carbon double bond is the [3 + 2] cycloaddition of a nitrile oxide to the metal–carbon double bond of a carbon monoxide ligand that produces a stable cycloadduct.[5] Casey was the first to report that the metal–carbon double bond of a carbene complex could be cleaved with diazoalkanes to give enol ethers of the type **6**.[3,6,7] It is possible that these enol ethers result from



the fragmentation of an initially formed [3 + 2] cycloadduct. α,β-Unsaturated carbene complexes such as the alkynyltungsten complex **9** have two possible sites for 1,3-dipolar cycloadditions: the tungsten–carbon double bond and the carbon–carbon triple bond. Thirteen years ago Fischer observed that in the presence of 4 equiv of diazomethane complex **9** is converted to the tungsten pentacarbonyl coordinated pyrazole **10** which has incorporated 2 of the 4 equiv of diazomethane.[8a] One explanation for the formation of **10** is that diazomethane reacts with the carbon–carbon triple bond to give the pyrazole carbene complex **7** which

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