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Total Synthesis of Neomethynolide

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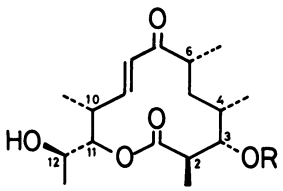
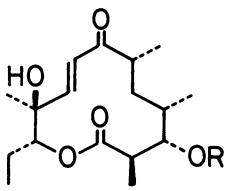
Neomethynolide (**1**), the aglycone of a twelve-membered ring macrolide, neomethymycin, was totally synthesized in its optically active form via 8,9-didehydro-**1**. The construction of the skeleton was carried out by condensing a stereoselectively synthesized fragment, 4-*t*-butyldimethylsiloxy-5-(2-methoxyethoxymethoxy)-3-methyl-1-hexyne, with Prelog-Djerassi lactonic ester, and mixed anhydride method was used for the lactonization of an intermediary hydroxy acid. The full stereochemistry of **1** was established by this synthesis.

A total synthesis and consequent establishment of whole stereochemistry of neomethynolide (**1**), the aglycone of a macrolide antibiotic, neomethymycin (**2**), have recently been communicated.[1] The full details of the work will be disclosed here.



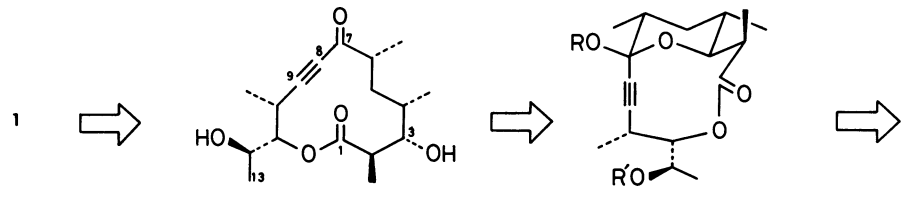
1 Neomethynolide (R=H)
2 Neomethymycin (R=Desosaminyl)



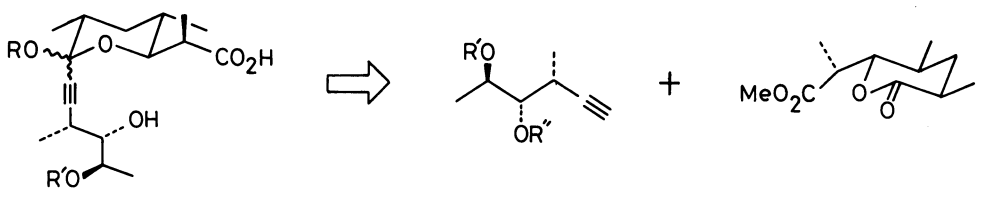
Methynolide (R=H)
Methymycin (R=Desosaminyl)

Neomethymycin belongs besides methymycin and YC-17,[2] to a twelve-membered ring family of typical macrolides and has been isolated from the culture filtrate of *Streptomyces* M-2140.[3a,c] Neomethynolide (**1**) was first obtained by the mild acid-hydrolysis of **2** as the authentic aglycone by Djerassi et al.,[3a,c] and Maezawa et al.[4] later reported that a mutant strain, *Streptomyces venezuelae* MCRL-0376 produced the aglcone **1** itself. Its chemical structure as 10-deoxy-12-hydroxymethynolide was given by Djerassi et al.[3b,c] and the partial stereochemistry, 2*R*, 3*S*, 4*S*, and 6*R*, was later established when Rickards et al.[5] carried out the precise ^{1}H NMR examination of a degradation product (Prelog–Djerassi lactonic acid) and its derivatives. From the analogy with methynolide[6] and on the basis of biogenetic consideration, **1** was also considered to have 10*R*, 11*S*, and 8,9-*trans* configuration though no experimental evidence was available. The present authors further postulated the 12*R* stereochemistry and carried out the synthesis of the compound having a structure represented by **1** in its optically active form.

The basic strategy in the present synthesis is similar in principle to that we previously adopted in the synthesis of methynolide.[7] The 8,9-double bond of the target molecule was introduced as triple bond and the latter was reserved until the later stage of the synthesis. This not only circumvented the instability of δ-hydroxy-α,β-enone structure in the molecule



1 **20** **16** or **17**



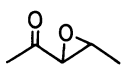
14 or **15** **7** **8**

which tended to undergo vinylogous retro-aldol type cleavage of 10,11-bond[8] but also enabled the choice of well-documented acetylenic ketone synthesis for the construction of basic skeleton by combining C(8)–C(13) (**7**) and C(1)–C(7) (**8**, Prelog–Djerassi lactonic ester) fragments. Instead of our previous procedure with silver acetylide and acid chloride,[7] the direct condensation[9] of lithiated **7** and **8** was adopted this time, which unnecessitated the tedious manipulation of **8** via several steps, and consequently much simplified the synthesis.

The next point is the use of hemi- or mixed acetal intermediates such as **9**—**17**. The 3-hydroxyl group and the conjugated 7-oxo group were thus intramolecularly protected at the same time minimizing protection-deprotection procedures and preventing the facile cleavage between triple bond and carbonyl group under alkaline hydrolytic conditions.

Lactonization to a highly strained bicyclic compound (**16** or **17**) by virtue of the very efficient mixed anhydride method[10] and the removal of 7-*O*-protection with the concomitant generation of 3-hydroxyl, 7-carbonyl, and monocyclic lactone structure should also be noted.

The stereoselective synthesis of the C(8)–C(13) fraction was started with 3,4-epoxy-2-pentanone (**3**).[11] We first examined the reduction of **3** to an *erythro*-epoxy alcohol (**4**) according to the method of Chautemps and Pierre[12] where the reduction with sodium borohydride in methanol at 0 °C was reported to give the *erythro*-isomer predominantly with over 95:5 ratio. However, we could not reproduce the result only obtaining a selectivity of about 72:28, and a number of other reducing agents were then examined under a variety of conditions to obtain higher selectivity. Some results are listed in the Table.



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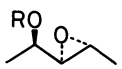
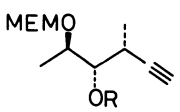


4 R=H
5 R=MEM



6 R=H
7 R=TBDMS

Although a sterically-crowded reagent prepared from sodium borohydride and 1-naphthol afforded fairly good *erythro*-selectivity (94:6), it was disadvantageous that excess reagent was required to complete the reaction and that the yield of the product was low (≈36%) mainly because of the difficulty of isolation from a large amount of naphthol which was liberated after aqueous workup (Entry 2). Reduction with sodium hydridobis(2-methoxyethoxy)aluminate (Red-Al), diisobutylaluminum hydride (DIBAL-H), or lithium tri-*t*-butoxyhydridoaluminate did not give satisfactory selectivity. Chelation controlled hydride reduction was then examined with a combination of sodium borohydride and appropriate metal salts. When zinc bromide or chloride was used, a highly stereoselective reduction took place accompanied with concomitant formation of 3-halo-1,2-diols as a result of nucleophilic attack of halogenide ions on epoxide ring (Entries 9 and 10). In order to prevent such ring openings, low nucleophilic counter anions such as fluoride or perchlorate were examined. Thus, by using a mixture of sodium borohydride and zinc perchlorate[13] in ether, the desired *erythro*-epoxy alcohol (**4**) was obtained exclusively in good yield (Entry 12).

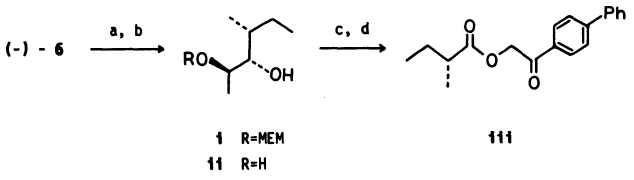
Table 1. Reduction of Epoxy Ketone (**3**) with Various Reducing Agents[a]

Entry	Reducing agent	Solv.	Temp	Time	Ratio[b] (E:T)[c]
1	$NaBH_4$	MeOH	0 °C	30 min	72:28
2	$NaBH_4+3C_{10}H_7OH$[d]	THF	RT	13 h	94: 6
3	Red-Al	THF	−78~0 °C	6 h	81:19
4	DIBAL-H	Toluene	RT	10 min	58:42
5	$LiAlH(OBu^t)_3$	THF	0 °C	10 h	60:40
6	$Zn(BH_4)_2$	DME	0 °C	30 min	60:40
7	$NaBH_4+LiCl$	Et_2O	RT	12 h	76:24[e]
8	$NaBH_4+CaCl_2$	THF	−100 °C	20 min	87:13
9	$NaBH_4+ZnBr_2$	Et_2O	−78~−20 °C	3 h	>95: 5[f]
10	$NaBH_4+ZnCl_2$	THF	−78 °C	6 h	96: 4[g]
11	$NaBH_4+ZnF_2$	Et_2O	RT	10 min	83:17
12	$NaBH_4+Zn(ClO_4)_2$[h]	Et_2O	−78~0 °C	2 h	>95: 5

a) The reaction was carried out in 1 mmol scale with 1.0—1.1 equiv of reducing agent. b) Ratio was determined by ^{13}C NMR analysis of a mixture of epoxy alcohols and/or GLC analysis (Silicone GE, SE-30) of its acetates. c) E=% *erythro*; T=% *threo*. d) $NaBH_4$ (1 equiv) and 1-naphthol (3 equiv) was stirred in THF for several hours until no more hydrogen gas was evolved. e) 4-Chloro-2,3-pentanediol (ca. 20%) was produced as a by-product. f) 4-Bromo-2,3-pentanediol (ca. 8%) was also produced. g) 4-Chloro-2,3-pentanediol (ca. 10%) was also formed. h) Zinc perchlorate hexahydrate was used.

Hydroxyl group of **4** was protected with 2-methoxyethoxymethyl (MEM) chloride and *N,N*-diisopropylethylamine to afford the corresponding MEM ether (**5**) in 80% yield. Reaction of **5** with lithium acetylide–ethylenediamine complex was best performed in dimethyl sulfoxide (DMSO)–hexamethylphosphoric triamide (HMPA) at room temperature to give 65% yield of the desired acetylenic alcohol (**6**).

Resolution of **6** was carried out via its optically active *O*-methylmandelates. Treatment of **6** with (*S*)-(+)-*O*-methylmandelic acid chloride in the presence of 4-dimethylaminopyridine gave a mixture of diastereomeric esters which could be easily separated by column chromatography on silica gel. The early fraction gave, upon hydrolysis, the (−)-alcohol (**6**) in 95% yield. According to the following scheme (−)-**6** was degraded to 2-methylbutyric acid and, on correlation to (*R*)-(−)-*p*-phenylphenacyl 2-methylbutyrate (**iii**),[14] it proved to have a (2*R*,3*S*,4*R*)-configuration required for the synthesis of **1**.

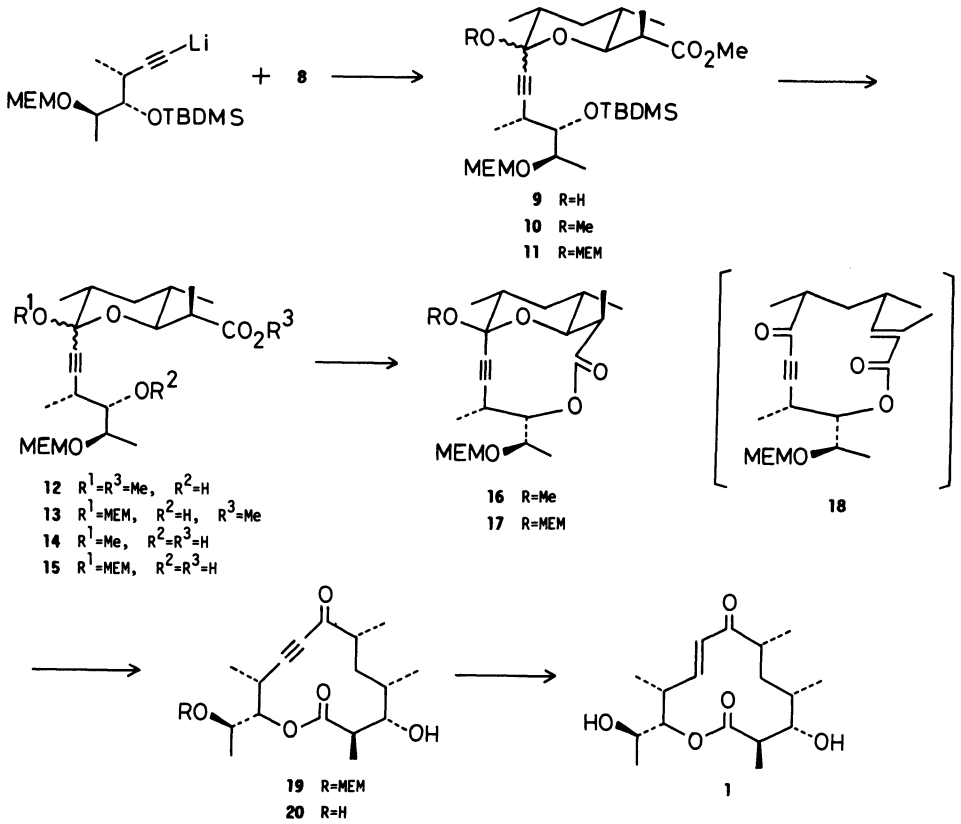


a: H_2/Pt, EtOH. b: HCl-MeOH. c: $NaIO_4$, $KMnO_4$, K_2CO_3, H_2O-Me_2CO. d: p-phenylphenacyl bromide, CsF.

The (−)-alcohol (**6**), thus obtained, was protected with *t*-butyldimethlysilyl (TBDMS) chloride and imidazole in *N,N*-dimethylformamide (DMF) to give the acetylenic silyl ether (**7**) in 98% yield as a key intermediate.

Another key intermediate, (+)-Prelog–Djerassi lactonic ester (**8**) was prepared in an non-stereoselective way according to the method used in the synthesis of methynolide.[15]

Condensation of the two fragments, lithium acetylide of (−)-**7** and (+)-**8**, was carried out in THF at −20 °C affording a mixture of hemiacetals (**9**, ca. 1:3.5 by ^{1}H NMR) in 90% yield. The major isomer was later found to have an equatorial hydroxyl group by converting the above mixture to the corresponding MEM ethers under nonequilibrium conditions followed by the examination of their ^{1}H NMR spectra as will be discussed later. The mixture **9** was treated with a catalytic amount of *p*-toluenesulfonic acid in methanol for 2 h to give an equilibrium mixture of the methyl acetals (**10**) which were difficult to separate. Since it is well-known that the anomeric methoxyl group of six-membered acetals preferentially occupies an axial position under equilibrium conditions,[16] the major isomer of the above methyl acetals (**10**) must have an axial methoxyl group. The relative intensity of the protons of anomeric methoxyl groups at C-7 in ^{1}H NMR spectrum was 3.5 (axial, δ=3.25):1 (equatorial, δ=3.35). On the other hand,



treatment of **9** with MEM chloride and *N,N*-diisopropylethylamine afforded a mixture of MEM ethers (**11**) in 90.4% yield which could be separated by preparative TLC on silica gel. Judging from ^{1}H NMR spectra of the above MEM ethers, the isomeric ratio of axial OMEM (δ=4.71 or 4.73)[17] to equatorial OMEM (δ=4.94)[17] was ca. 1:4, reflecting the original ratio of hemiacetals (**9**). The mixture of methyl acetals (**10**) was desilylated with tetrabutylammonium fluoride and the resulting alcohols (**12**) were hydrolyzed with aqueous methanolic sodium hydroxide to give a ca. 3 (axial OMe):1 (equatorial OMe) mixture of the hydroxy acids (**14**) in 83.3% overall yield. Alternatively, the major, less polar isomer with equatorial OMEM group **11** was converted into a single seco-acid (**15**) by the same procedures as above in 87.6% yield.

Lactonization of the seco-acid mixture **14** and that of **15** were carried out in refluxing benzene by mixed anhydride method using 2,4,6-trichlorobenzoyl chloride.[10] From the examination of molecular models it became apparent that the seco-acid having an axial methoxyl group (or OMEM group) has almost no chance of intramolecular cyclization, however it seems possible to lactonize the seco-acid having equatorial methoxyl group (or OMEM group) at C-7 position though they seem to still suffer from considerable strain in cyclization. In fact, the highly-strained bicyclic lactones (**16**) and (**17**) were obtained in 12.0% and 33.2% yield, respectively. The low yield of **16** compared with that of **17** seems to be due to the low content of the seco-acid with an equatorial methoxyl group in the mixture **14**. In both cases, the 2-unsaturated compound **18** was isolated as a by-product in 9—13% yield.

Deprotection of **16** with 1% trifluoroacetic acid (TFA) in dichloromethane for 14 h gave the mono-MEM ether (**19**) and the diol (**20**) in 61% and 16% yield, respectively. Prolonged reaction or high concentrations of TFA produced a complicated mixture. Pyridinium *p*-toluenesulfonate (PPTS) in refluxing ethanol did not give good result for the generation of the diol (**20**). Treatment of **17** with zinc bromide in dichloromethane also gave **19** and **20** in 38% and 44% yield, respectively. Since **19** could be further converted to **20** in 60% yield with zinc bromide, totally 67% yield of **20** was attained from **17**.

Reduction of 8,9-didehydroneomethynolide (**20**) by chromium(II) sulfate in aqueous DMF[18] at room temperature smoothly gave 65% yield of neomethynolide (**1**) as colorless needles. Melting point and combustion analysis of synthetic **1** revealed that it existed as monohydrate. All spectral data (NMR, IR, UV, Mass) of synthetic **1** as well as melting point of its diacetate were identical with those of the specimens of natural origin and hence the complete stereochemistry of neomethynolide (**1**) was established by the present total synthesis.

Experimental

Melting points and boiling points are uncorrected. IR spectra were determined on a Hitachi R-215, UV spectra on a Hitachi 200-10, and mass spectra on a Hitachi RML-6MG or JEOL JMS-OISG-2 spectrometer. ^{1}H NMR spectra were recorded at either 60 (Hitachi R-20B) or 90 MHz (JEOL JNM-FX90Q) as indicated and ^{13}C NMR spectra at 25 MHz (JEOL JNM-FX90Q) instrument. All NMR spectra were taken in deuteriochloroform solutions with tetramethylsilane as an internal standard. Optical rotations were determined on a Yanagimoto OR-50 Polarimeter.

Reactions were run under an atmosphere of nitrogen unless otherwise stated. Dry solvents were prepared according to the standard procedures. Anhydrous magnesium sulfate was used for drying solutions. Thin-layer chromatography (TLC) was carried out on Merck glass plates precoated with silica gel 60F-254 (0.25 mm).

3,4-Epoxy-2-pentanol (4). 3,4-Epoxy-2-pentanone[11] (**3**, 5.6 g, 56 mmol) was added to a cold (−78 °C) suspension of zinc perchlorate hexahydrate (23.5 g, 63 mmol) in dry ether (50 ml) and stirred for 10 min. Sodium borohydride (2.2 g, 58 mmol) was added all at once and the mixture was stirred vigorously at −78 °C for 1 h and at −78—0 °C for 1 h. The reaction was quenched carefully by the dropwise addition of saturated aqueous $NaHCO_3$ at 0 °C. The precipitate was filtered and washed well with ether. The combined ether solution was washed with saturated aqueous $NaHCO_3$, dried, and concentrated. The crude product was distilled to give **4** (4.4 g, 77%) as an oil: Bp 66—69 °C/2666 Pa; ^{1}H NMR (90 MHz) δ=1.25 (3H, d, J=6.4 Hz), 1.34 (3H, d, J=5.1 Hz), 2.73 (1H, dd, J=3.9 and 2.6 Hz), 3.07 (1H, dq, J=2.6 and 5.4 Hz), 3.18 (1H, broad s), and 3.86 (1H, dq, J=3.9 and 6.4 Hz); ^{13}C NMR δ=17.04, 18.69, 51.28, 62.55, and 65.07. This alcohol proved to be >95% pure *erythro*-**4** by the comparison of its ^{13}C NMR spectrum with that of an authentic mixture of the *erythro*- and the *threo*-epoxy alcohol which was obtained by sodium borohydride reduction of epoxy ketone (**3**) in methanol according to the literature.[12] *threo*-**4**: ^{13}C NMR δ=18.69, 19.42, 52.50, 63.50, and 67.36.

Gas chromatographic analysis (SE-30) of the acetate of **4** also showed the same purity of *erythro*-isomer. Retention time at 75 °C (column temp): *erythro*-**4**, 2.8 min; *threo*-**4**, 3.6 min.

2-(2-Methoxyethoxymethoxy)-3,4-epoxypentane (5). MEM chloride (2.22 ml, 19.4 mmol) was added dropwise to a cold (0 °C) solution of **4** (1.8 g, 17.6 mmol) and *N,N*-diisopropylethylamine (3.69 ml, 21.2 mmol) in methanol-free dichloromethane (18 ml) and the mixture was stirred at room temperature for 20 h. The solvent was evaporated in vacuo and the crude product was extracted with ether, washed successively with saturated aqueous NaCl, 3% aqueous phosphoric acid, and saturated aqueous $NaHCO_3$, dried, concentrated, and distilled to give **5** (2.69 g, 80%): A colorless oil; Bp 65 °C/400 Pa; ^{1}H NMR (60 MHz) δ=1.26 (3H, d, J=6.4 Hz), 1.33 (3H, d, J=5.2 Hz), 2.63 (1H, dd, J=4.8 and 2.4 Hz), 2.98 (1H, dq, J=2.4 and 5.4 Hz), 3.38 (3H, s) 3.3—3.9 (5H, m), and 4.73 (2H, s). Found: C, 56.62; H, 9.56%. Calcd for $C_9H_{18}O_4$: C, 56.82; H, 9.54%.

2-(2-Methoxyethoxymethoxy)-4-methyl-5-hexyn-3-ol (6). A mixture of **5** (190 mg, 1.0 mmol) and lithium acetylide-ethylenediamine complex (184 mg, 2.0 mmol) was stirred in a mixture of DMSO-HMPA (1:1, 2 ml) at room temperature for 60 h. After the addition of water (3 ml), the reaction mixture was saturated with NH_4Cl and extracted with diisopropyl ether. The extract was washed with aqueous NH_4Cl and brine, dried, and concentrated. The crude product was purified by preparative TLC (benzene-ethyl acetate, 8:2) to give the *dl*-acetylenic alcohol (**6**, 139 mg, 64%) as a colorless oil: R_f=0.4; ^{1}H NMR (60 MHz) δ=1.20 (3H, d, J=6.6 Hz), 1.32 (3H, d, J=6.6 Hz), 2.10 (1H, d, J=2.7 Hz), 3.40 (3H, s), 3.4—4.3 (6H, m), and 4.80 (2H, s). Found: C, 60.89; H, 9.42%. Calcd for $C_{11}H_{20}O_4$: C, 61.09; H, 9.32%.

Resolution of the *dl*-Alcohol (6). A mixture of the above *dl*-**6**, (2.40 g, 11.1 mmol), (*S*)-(+)-*O*-methylmandelic acid chloride[19] (2.46 g, 13.3 mmol), and 4-dimethylaminopyridine (1.76 g, 14.4 mmol) in dry dichloromethane was stirred at 40 °C for 65 h. The reaction mixture was diluted with ether and the resulting precipitate was filtered. The filtrate was washed successively with 2% aqueous phosphoric acid, saturated aqueous NaCl, and saturated aqueous $NaHCO_3$, dried, and concentrated. The crude mixture of diastereomeric esters was separated by column chromatography on silica gel (Merck) (petroleum ether-ethyl acetate, 9:1).

The less polar ester (1.83 g, 45.2%): A colorless oil; R_f=0.64 (benzene-ethyl acetate, 4:1); $[\alpha]_D^{23}$ +35.6° (*c* 1.41, $CHCl_3$); IR (neat) 3270 and 1750 cm^{-1}; ^{1}H NMR (90 MHz) δ=0.95 (3H, d, J=6.3 Hz), 1.11 (3H, d, J=6.8 Hz), 2.08 (1H, d, J=2.6 Hz), 2.67 (1H, m), 3.37 (3H, s), 3.44 (3H, s), 3.54 (4H, m), 4.02 (1H, m), 4.57 (2H, s), 4.80 (1H, s) 5.07 (1H, dd, J=8.1 and 4.2 Hz), and 7.2—7.6 (5H, m). Found: C, 65.57; H, 7.65%. Calcd for $C_{20}H_{28}O_6$: C, 65.91; H, 7.74%.

The more polar ester (1.69 g, 41.8%): A colorless oil; R_f=0.56 (benzene-ethyl acetate, 4:1); $[\alpha]_D^{23}$ +51.0° (*c* 1.35, $CHCl_3$); ^{1}H NMR (90 MHz) δ=0.79 (3H, d, J=6.0 Hz), 1.18 (3H, d, J=6.3 Hz), 2.00 (1H, d, J=2.6 Hz), 2.48 (1H, m), 3.39 (3H, s), 3.42 (3H, s), 3.63 (4H, m), 4.16 (1H, m), 4.67 (1H, d, J=7.2 Hz), 4.77 (1H, d, J=7.2 Hz), 4.79 (1H, s), 5.08 (1H, dd, J=8.8 and 3.7 Hz), and 7.2—7.6 (5H, m).

The less polar ester (1.839 g, 5.05 mmol) was stirred with NaOH (440 mg, 11 mmol) in methanol-water (1:1, 8.8 ml) at room temperature for 12 h. After the removal of methanol in vacuo and saturation of the solution with NaCl, the crude product was extracted with ethyl acetate, washed with saturated aqueous NaCl, dried, and concentrated to give (−)-**6** (1.036 g, 95%) as a colorless oil: $[\alpha]_D^{23}$ −24.4° (*c* 1.06, $CHCl_3$).

Similarly, the more polar ester was hydrolyzed to give (+)-**6**: $[\alpha]_D^{23}$ +23.1° (*c* 1.34, $CHCl_3$).

Determination of the Absolute Configuration of (+)-and (−)-Alcohol (6). A solution of (+)-**6** (197.4 mg, 0.913 mmol) in ethanol (2 ml) was shaken with platinum oxide (5 mg) at room temperature for 1 h under an atmosphere of hydrogen. After filtration of the catalyst, the filtrate was concentrated in vacuo to give a saturated alcohol (**i**, 191.6 mg, 95.3%) as a colorless oil: $[\alpha]_D^{23}$ +19.0° (*c* 1.16, $CHCl_3$); ^{1}NMR (60 MHz) δ=0.7—1.8 (12H, m), 2.3 (1H, broad s), 3.3—4.1 (6H, m) 3.40 (3H, s), and 4.77 (2H, s).

The alcohol (**i**, 218.1 mg, 0.99 mmol) was heated with 10% hydrochloric acid at 60 °C for 3 h. The reaction mixture was neutralized at 0 °C and then saturated at room temperature with anhydrous K_2CO_3. The crude product was extracted with ether, dried, concentrated, and subjected to preparative TLC (benzene-ethyl acetate, 1:1) to give the diol (**ii**, 75.3 mg, 58%) as a colorless oil: R_f=0.23; $[\alpha]_D^{23}$ −3.9° (*c* 1.28, $CHCl_3$); ^{1}H NMR (60 MHz) δ=0.7—2.0 (12H, m), 2.6 (2H, broad s), 3.40 (1H, dd, J=6.0 and 4.6 Hz), and 3.6—4.1 (1H, m).

A solution of the diol (**ii**, 25.5 mg, 0.19 mmol) in acetone (0.5 ml) was added to a stirred solution of $NaIO_4$ (123.8 mg, 0.58 mmol) in water (0.5 ml). To this mixture was added a solution of $KMnO_4$ (9.1 mg, 0.058 mmol) and K_2CO_3 (16.0 mg, 0.12 mmol) in acetone-water (1:1, 0.8 ml) and the whole mixture was stirred at 12 °C for 12 h. Insoluble material was filtered and washed with acetone. After evaporation of acetone, Na_2SO_3 (200 mg) was added and the mixture was acidified with 10% aqueous sulfuric acid to give a colorless solution, which was saturated with NaCl. The mixture was extracted with dichloromethane, dried, and concentrated to give crude 2-methylbutyric acid (13.8 mg) as a colorless oil. The acid thus obtained was mixed with CsF (44 mg) in acetonitrile (0.5 ml) and refluxed for 10 min. *p*-Phenylphenacyl bromide (58.4 mg) was added to this and the mixture was refluxed for 3 h. The precipitate was filtered and washed with acetone. After removal of solvents, the residue was subjected to preparative TLC (benzene) to give the pure ester (**iii**, 34.6 mg, 60% from the diol, **ii**) as a crystalline solid: R_f=0.30; $[\alpha]_D^{23}$ + 11.0° (*c* 1.73, C_6H_6); ^{1}H NMR (60 MHz) δ=1.01 (3H, t, J=6.9 Hz), 1.27 (3H, d, J=7.1 Hz), 1.4—2.0 (2H, m), 2.3—2.9 (1H, m), 5.37 (2H, s), and 7.3—8.2 (9H, m).

This ester (**iii**), upon hydrolysis, gave (*S*)-(+)-2-methylbutyric acid: $[\alpha]_D^{23}$ +25.2° (*c* 0.60, H_2O). Lit,[20] $[\alpha]_D^{21.2}$ +19.3° (neat).

(−)-**6** was also converted into the corresponding *p*-phenylphenacyl 2-methylbutyrate in the same manner: $[\alpha]_D^{23}$ −7.6° (*c* 1.06, C_6H_6). Lit,[14] $[\alpha]_D^{23}$ −4°.

4-*t*-Butyldimethylsiloxy-5-(2-methoxyethoxymethoxy)-3-methyl-1-hexyne (7). A mixture of (−)-**6** (1.03 g, 4.77 mmol), TBDMS chloride (1.44 g, 9.55 mmol), imidazole (1.30 g, 19.1 mmol), and dry DMF (5 ml) was stirred at room temperature for 65 h. After removal of solvent under reduced pressure the crude product was extracted with ethyl acetate, washed successively with 3% aqueous hydrochloric acid, saturated aqueous NaCl, and saturated aqueous $NaHCO_3$. Organic layer was dried and concentrated in vacuo to give the practically pure silyl ether (**7**, 1.55 g, 98.4%). Analytical sample was prepared by preparative TLC. A colorless oil; R_f=0.65 (benzene-ethyl acetate, 9:1); $[\alpha]_D^{23}$ −2.0° (*c* 1.01, $CHCl_3$); ^{1}H NMR (90 MHz) δ=0.09 (6H, s), 0.90 (9H, s), 1.14 (3H, d, J=6.3 Hz), 1.21 (3H, d, J=7.2 Hz), 2.07 (1H, d, J=2.6 Hz), 2.48 (1H, m), 3.39 (3H, s), 3.4—3.9 (5H, m), 4.06 (1H, dq, J=6.3 and 3.1 Hz), and 4.74 (2H, s). Found: C, 61.79; H, 10.34%. Calcd for $C_{17}H_{34}O_4Si$: 61.77; H, 10.37%.

Methyl (2*R*,3*S*,4*S*,6*R*,7*S*,10*R*,11*S*,12*R*)-11-*t*-Butyldimethylsiloxy-3,7-epoxy-7-hydroxy-12-(2-methoxyethoxymethoxy)-2,4,6,10-tetramethyl-8-tridecynoate and Its C-7 Epimer (9). A lithium acetylide solution was prepared from (−)-**7** (258 mg, 0.78 mmol) and butyllithium in hexane (1.6 mol

dm^{-3}, 819 μl) by stirring in dry THF (0.8 ml) at room temperature for 1 h. This solution was added dropwise to a cold (−20 °C) solution of (+)-Prelog-Djerassi lactonic acid methyl ester (**8**, 152 mg, 0.709 mmol) in THF (1.4 ml) and the reaction temperature was raised gradually to 0 °C over a period of 1 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl. After evaporation of THF, the crude product was extracted with ethyl acetate, washed with saturated aqueous $NaHCO_3$, dried, and concentrated. The concentrate was subjected to preparative TLC (benzene–ethyl acetate, 3:1) to give a ca. 3.5:1 mixture of hemiacetals (**9**, 348 mg, 90%) as a colorless oil: IR (neat) 3350, 2200, and 1720 cm^{-1}; ^1H NMR[21] (90 MHz) δ=0.09 (3H, s), 0.10 (3H, s), 0.91 (9H, s), 3.38 (3H, s), 3.69 (3H, s), 4.68 (1H, d, J=7.2 Hz), and 4.78 (1H, d, J=7.2 Hz). Found: C, 61.68; H, 9.75%. Calcd for $C_{28}H_{52}O_8Si$: C, 61.73; H, 9.62%. The mixture was used for the next step without separation.

Methyl (2*R*,3*S*,4*S*,6*R*,7*R*,10*R*,11*S*,12*R*)-11-*t*-Butyldimethylsiloxy-3,7-epoxy-7-methoxy-12-(2-methoxyethoxymethoxy)-2,4,6,10-tetramethyl-8-tridecynoate and Its C-7 Epimer (10). A mixture of hemiacetals (**9**, 544 mg, 1.0 mmol) and *p*-toluenesulfonic acid monohydrate (9.7 mg, 0.05 mmol) in methanol (2.4 ml) was stirred at room temperature for 2 h. Saturated aqueous $NaHCO_3$ was added and methanol was removed in vacuo. The crude product was extracted with ethyl acetate, washed with saturated aqueous $NaHCO_3$, dried, and concentrated to give a practically pure mixture of C-7 epimeric methyl acetals (**10**, 550 mg, 98%), which were difficult to separate. The relative intensity of the protons of anomeric methoxyl groups at C-7 in NMR (90 MHz) spectrum was 3.5 (axial, δ=3.25):1 (equatorial, δ=3.35). Analytical sample was prepared by preparative TLC. A colorless oil: R_f=0.71 (benzene–ethyl acetate, 3:1). Found: C, 62.18; H, 9.67%. Calcd for $C_{29}H_{54}O_8Si$: C, 62.33; H, 9.74%.

Methyl (2*R*,3*S*,4*S*,6*R*,7*S*,10*R*,11*S*,12*R*)-11-*t*-Butyldimethylsiloxy-7,12-bis(2-methoxyethoxymethoxy)-3,7-epoxy-2,4,6,10-tetramethyl-8-tridecynoate and Its C-7 Epimer (11). A solution of **9** (458 mg, 0.84 mmol), MEM chloride (384 μl, 3.36 mmol), and *N*,*N*-diisopropylethylamine (644 μl, 3.70 mmol) in methanol-free dry dichloromethane (3.5 ml) was stirred at room temperature for 60 h. After removal of solvent, the crude product was extracted with ethyl acetate, washed with water, 3% aqueous phosphoric acid, brine, and saturated aqueous $NaHCO_3$. Organic layer was dried and concentrated to give a crude C-7 epimeric mixture of the MEM hemiacetals (**11**). The mixture was separated by preparative TLC (benzene–ethyl acetate, 3:1). The less polar zone gave the C-7 equatorial OMEM hemiacetal (384 mg, 72%) as a colorless oil: R_f=0.55; ^1H NMR (90 MHz) δ=0.08, 0.09, and 0.10 (6H, each s), 0.61 (3H, d, J=6.3 Hz), 0.91 (9H, s), 0.94 (3H, d, J=6.4 Hz), 1.11 (3H, d, J=6.1 Hz), 1.18 (3H, d, J=6.4 Hz), 1.26 (3H, d, J=7.0 Hz), 3.37 (3H, s), 3.38 (3H, s), 3.68 (3H, s), 4.73 (2H, s), and 4.94 (2H, s). Found: C, 60.97; H, 9.43%. Calcd for $C_{32}H_{60}O_{10}Si$: C, 60.73; H, 9.56%. The more polar zone gave C-7 axial OMEM hemiacetal (96 mg, 18%) as a colorless oil: R_f=0.41; ^1H NMR (90 MHz) δ=0.10 (6H, s), 0.90 (9H, s), 2.4—3.0 (2H, m), 3.3—4.1 (11H, m), 3.38 (6H, s), 3.68 (3H, s), 4.71 (2H, s), and 4.73 (2H, s).

Methyl (2*R*,3*S*,4*S*,6*R*,7*S*,10*R*,11*S*,12*R*)-3,7-Epoxy-11-hydroxy-7-methoxy-12-(2-methoxyethoxymethoxy)-2,4,6,10-tetramethyl-8-tridecynoate and Its C-7 Epimer (12). A solution of **10** (an epimeric mixture, 217 mg, 0.389 mmol) in dry THF (0.5 ml) was stirred with a THF solution of tetrabutylammonium fluoride (1 mol dm^{-3}, 1.93 ml, 0.82 mmol) at room temperature for 1.5 h. The reaction mixture was neutralized by the addition of saturated aqueous NH_4Cl. After removal of THF under reduced pressure, the crude product was extracted with ethyl acetate, washed with saturated aqueous $NaHCO_3$, dried, and concentrated. Purification by preparative TLC (benzene–ethyl acetate, 1:1) gave the alcohol (**12**, 147 mg, 85%, R_f=0.50) as a ca. 3.3 (axial OMe) : 1 (equatorial OMe) mixture of hemiacetals which were difficult to separate.

Methyl (2*R*,3*S*,4*S*,6*R*,7*S*,10*R*,11*S*,12*R*)-3,7-Epoxy-11-hydroxy-7,12-bis(2-methoxyethoxymethoxy)-2,4,6,10-tetramethyl-8-tridecynoate (13). To a stirred solution of **11** (the equatorial C-7 OMEM epimer, 344 mg, 0.544 mmol) in dry THF (1 ml) was added a tetrabutylammonium fluoride solution in THF (1 mol dm^{-3}, 2.14 ml) and the mixture was stirred at room temperature for 7 h. Similar workup as described above for desilylation of silyl ether (**10**) followed by preparative TLC (benzene–ethyl acetate, 1:1) of the crude product gave **13** (261 mg, 93%) as a colorless oil: R_f=0.43; ^1H NMR (90 MHz) δ=0.82 (3H, d, J=6.1 Hz), 0.94 (3H, d, J=6.6 Hz), 1.12 (3H, d, J=7.2 Hz), 1.26 (3H, d. J=6.1 Hz), 1.30 (3H, d, J=7.0 Hz), 2.46—2.94 (2H, m), 3.38 (3H, s), 3.40 (3H, s), 3.68 (3H, s), 4.78 (2H, m), 4.85 (1H, d, J=6.3 Hz), and 5.05 (1H, d, J=6.3 Hz). Found: C, 59.84; H, 8.85%. Calcd for $C_{26}H_{46}O_{10}$: C, 60.21, H, 8.94%.

(2*R*,3*S*,4*S*,6*R*,7*S*,10*R*,11*S*,12*R*)-3,7-Epoxy-11-hydroxy-7-methoxy-12-(2-methoxyethoxymethoxy)-2,4,6,10-tetramethyl-8-tridecynoic Acid and Its C-7 Epimer (14). An epimeric mixture of **12** (277 mg, 0.624 mmol), aqueous NaOH (1 mol dm^{-3}, 940 μl) and methanol (940 μl) was stirred at room temperature for 12 h. After removal of methanol under reduced pressure the crude product was diluted with a small amount of water and washed with ether. The aqueous alkaline layer was acidified (pH≈4) with 3% aqueous phosphoric acid. The organic acid was extracted with ethyl acetate, washed with saturated aqueous NaCl, dried, and concentrated to give **14** (263 mg, 98%) as a viscous oil. Anomeric isomers ratio was ca. 3 (axial OMe, δ=3.30) : 1 (equatorial OMe, δ=3.37).

(2*R*,3*S*,4*S*,6*R*,7*S*,10*R*,11*S*,12*R*)-3,7-Epoxy-11-hydroxy-7,12-bis(2-methoxyethoxymethoxy)-2,4,6,10-tetramethyl-8-tridecynoic Acid (15). A mixture of **13** (166.5 mg, 0.32 mmol), aqueous NaOH (1 mol dm^{-3}, 482 μl), and methanol (482 μl) was stirred at room temperature for 12 h. Usual workup as described above for saponification of **12** gave the hydroxy acid (**15**, 157 mg, 97%) as a viscous oil, which was dried over P_2O_5 under vacuum at 50 °C for 40 h. ^1H NMR (90 MHz) δ=0.84 (3H, d, J=6.1 Hz), 0.94 (3H, d, J=6.3 Hz), 1.12 (3H, d, J=6.8 Hz), 1.19 (3H, d, J=6.1 Hz), 1.35 (3H, d, J=6.8 Hz), 3.37 (3H, s), 3.40 (3H, s), 4.84 (2H, s), and 4.99 (2H, s).

(1*S*,2*R*,5*S*,6*R*,9*S*,10*R*,12*S*,1′*R*)-4,13-Dioxa-9-methoxy-5-[1-(2-methoxyethoxymethoxy)ethyl]-2,6,10,12-tetramethylbicyclo[7.3.1]tridec-7-yn-3-one (16). 2,4,6-Trichlorobenzoyl chloride[22] (90.9 μl, 0.566 mmol) was added to a solution of **14** (243.4 mg, 0.566 mmol) and triethylamine (85.8 μl, 0.679 mmol) in dry THF (1.5 ml). The mixture was stirred at room temperature for 4 h and then filtered through a Celite column. The filtrate was diluted with dry benzene (420 ml)

and added to a refluxing solution of 4-dimethylaminopyridine (414 mg, 340 mmol) in benzene (150 ml) over 24 h. After additional refluxing for 1 h the reaction mixture was washed successively with water, 3% aqueous phosphoric acid, saturated aqueous NaCl, and saturated aqueous $NaHCO_3$. Organic layer was dried and concentrated to give the crude product (219 mg), which was subjected to preparative TLC (benzene–ethyl acetate, 3:1). The bicyclic lactone (**16**, 28 mg, 12%): A coloress oil: R_f=0.60; $[\alpha]_D^{25}$ +5.64° (*c* 1.24, $CHCl_3$); ^1H NMR (90 MHz) δ=0.86 (3H, d, *J*=6.4 Hz), 0.89 (3H, d, *J*=6.3 Hz), 1.11 (3H, d, *J*=7.0 Hz), 1.24 (3H, d, *J*=5.1 Hz), 1.31 (3H, d, *J*=6.6 Hz), 2.6—3.2 (2H, m), 3.39 (6H, s), 3.4—4.0 (5H, m), 4.34 (1H, dd, *J*=10.3 and 2.2 Hz), 4.69 (1H, d, *J*=7.2 Hz), 4.83 (1H, dd, *J*=9.2 and 2.6 Hz), and 4.85 (1H, d, *J*=7.2 Hz). An elimination product (**18**, 26 mg, 12%): A colorless oil: R_f=0.53; $[\alpha]_D^{25}$ +97.3° (*c* 1.13, $CHCl_3$): IR ($CHCl_3$) 2200, 1700, and 1670 cm^{-1}; ^1H NMR (90 MHz) δ=1.07 (3H, d, *J*=6.8 Hz), 1.10 (3H, d, *J*=6.6 Hz), 1.33 (3H, d, *J*=6.1 Hz), 1.40 (3H, d, *J*=7.0 Hz), 1.87 (3H, d, *J*=1.3 Hz), 3.39 (3H, s), 4.72 (1H, d, *J*=7.2 Hz), 4.83 (1H, dd, *J*=3.5 and 7.4 Hz), 4.84 (1H, d, *J*=7.2 Hz), and 6.94 (1H, dq, *J*=10.9 and 1.3 Hz).

(1*S*,2*R*,5*S*,6*R*,9*S*,10*R*,12*S*,1′*R*)-4,13-Dioxa-9-(2-methoxyethoxymethoxy)-5-[1-(2-methoxyethoxymethoxy)ethyl]-2,6,10,12-tetramethylbicyclo[7.3.1]tridec-7-yn-3-one (17). 2,4,6-Trichlorobenzoyl chloride (50.0 µl, 0.311 mmol) was added to a solution of **15** (156.9 mg, 0.311 mmol) and triethylamine (47.1 µl, 0.342 mmol) in anhydrous THF (1 ml). After stirring at room temperature for 3 h, the resulting precipitate was filtered though a Celite column. The filtrate was diluted with dry benzene (150 ml) and added to a refluxing solution of 4-dimethylaminopyridine (227.6 mg, 1.87 mmol) in benzene (50 ml) over 20 h. Similar workup as described above for the lactonization of **14** gave the crude product (160.4 mg), which was subjected to preparative TLC (benzene–ethyl acetate, 3:1). The bicyclic lactone (**17**, 50.2 mg, 33.2%): A colorless oil: R_f=0.25; $[\alpha]_D^{25}$ +17.2° (*c* 0.29, $CHCl_3$): ^1H NMR (90 MHz) δ=0.85 (3H, d, *J*=5.6 Hz), 0.92 (3H, d, *J*=5.9 Hz), 1.08 (3H, d, *J*=7.0 Hz), 1.23 (3H, d, *J*=5.9 Hz), 1.30 (3H, d, *J*=6.3 Hz), 2.5—3.2 (2H, m), 3.39 (6H, s), 3.4—4.0 (8H, m), 4.36 (1H, dd, *J*=10.1 and 2.3 Hz), 4.68 (1H, d, *J*=7.2 Hz), 4.82 (1H, dd, *J*=9.0 and 2.6 Hz), 4.84 (1H, d, *J*=7.2 Hz), 4.93 (1H, d, *J*=5.9 Hz), and 5.06 (1H, d, *J*=5.9 Hz). Found: C, 61.65; H, 8.68%. Calcd for $C_{25}H_{42}O_9$: C, 61.70; H, 8.70%. The elimination product (**18**, 10.0 mg, 8.5%) was also isolated.

7,8-Didehydro-12-*O*-(2-methoxyethoxymethyl)neomethynolide (19) and 7,8-Didehydroneomethynolide (20). $ZnBr_2$ (42.8 mg, 0.19 mmol) was added to a solution of **17** (18.4 mg, 0.038 mmol) in dry dichloromethane (5 ml) and the mixture was subjected to ultrasonication at room temperature for 1 h. Another portion of $ZnBr_2$ (42.8 mg) was added and treated in a ultrasonic bath for 1 h. This procedure was repeated twice and then the mixture was further stirred at room temperature for 12 h. Saturated aqueous $NaHCO_3$ was added and the crude product was extracted with ethyl acetate, washed with saturated aqueous NaCl, dried, and concentrated. The concentrate was subjected to preparative TLC (benzene–ethyl acetate, 1:1) to give 8,9-didehydroneomethynolide (**20**) and its 12-*O*-MEM ether (**19**). **20**: colorless needles (5.5 mg, 44%): R_f=0.45; Mp 74—76 °C (monohydrate); $[\alpha]_D^{24}$ +27.0° (*c* 0.223, MeOH); IR ($CHCl_3$) 2200, 1725, 1660, and 1210 cm^{-1}; UV (EtOH) 220 nm (log ε=4.27); ^1H NMR (90 MHz) δ=0.97 (3H, d, *J*=6.3 Hz), 1.17 (3H, d, *J*=6.8 Hz), 1.22 (3H, d, *J*=6.1 Hz), 1.36 (6H, d, *J*=7.0 Hz), 3.24 (1H, m), 3.65 (1H, broad d, *J*=9.6 Hz), 3.86 (1H, m), and 5.03 (1H, dd, *J*=9.0 and 3.1 Hz); MS *m/z* 310 (M-18). Found: C, 62.21; H, 8.46%. Calcd for $C_{17}H_{26}O_5 \cdot H_2O$: C, 62.17; H, 8.59%.

19: A colorless oil (5.8 mg, 38%): R_f=0.59; $[\alpha]_D^{24}$ +15.5° (*c* 0.517, MeOH); ^1H NMR (90 MHz) δ=0.97 (3H, d, *J*=6.6 Hz), 1.16 (6H, d, *J*=6.3 Hz), 1.33 (3H, d, *J*=7.0 Hz), 1.35 (3H, d, *J*=6.6 Hz), 3.18 (1H, m), 3.39 (3H, s), 4.69 (1H, d, *J*=7.2 Hz), 4.83 (1H, d, *J*=7.2 Hz), and 5.11 (1H, dd, *J*=9.0 and 2.6 Hz).

19 (9 mg, 0.0226 mmol) and $ZnBr_2$ (127 mg, 0.564 mmol) were stirred in dichloromethane–nitromethane (10:1, 2.2 ml) at room temperature for 8 h. Similar workup as above followed by preparative TLC gave **20** (4.5 mg, 60%) and the starting **19** (1.5 mg, 17%).

8,9-Didehydroneomethynolide (20) from 16. A solution of **16** (8.8 mg, 0.0213 mmol) and trifluoroacetic acid (88 µl) in dry dichloromethane (8.8 ml) was stirred at room temperature for 14 h. Saturated aqueous $NaHCO_3$ was added and the crude product was extracted with ethyl acetate, washed with water, dried, and concentrated. The concentrate was subjected to preparative TLC (benzene–ethyl acetate, 1:1) to give **20** (1.1 mg, 16%) and **19** (5.2 mg, 61%).

Neomethynolide (1) Monohydrate. To a stirred solution of **20** (7.0 mg, 0.022 mmol) in absolute DMF (700 µl) was added an aqueous solution of chromium(II) sulfate[18] (1 mol dm^{-3}, 700 µl) and the mixture was stirred at room temperature for 10 h. The resulting deep green solution was saturated with ammonium sulfate, extracted with ethyl acetate, washed with saturated aqueous NaCl, dried, and concentrated in vacuo. The crude product was subjected to preparative TLC (benzene–ethyl acetate, 1:1) to give neomethynolide (**1**, 4.6 mg, 65%, R_f=0.28). Crystallization from acetone–hexane mixture gave colorless needles: Mp 92—93 °C (monohydrate) $[\alpha]_D^{24}$ +112.5° (*c* 0.160, MeOH); IR ($CHCl_3$) 1725, 1685, 1625, and 1215 cm^{-1}; UV (EtOH) 227 nm (log ε=4.08); ^1H NMR (90 MHz) δ=0.9—1.4 (15H, m), 3.57 (1H, broad d, *J*=10.7 Hz), 3.89 (1H, m), 4.83 (1H, dd, *J*=9.2 and 2.4 Hz), 6.42 (1H, dd, *J*=15.8 and 0.9 Hz), and 6.79 (1H, dd, *J*=15.8 and 5.0 Hz). Found: C, 61.54; H, 9.17%. Calcd for $C_{17}H_{28}O_5 \cdot H_2O$: C, 61.79; H, 9.15%. Found: *m/z* 312.1931. Calcd for $C_{17}H_{28}O_5$: M, 312.1935. Lit,[3c] Mp 90—120 °C (monohydrate); $[\alpha]_D$ +108° ($CHCl_3$); IR($CHCl_3$) 2.93, 5.75, 5.90, and 6.10 µ; UV (EtOH) 227.5 nm (log ε=4.10).

Neomethynolide Diacetate. This was prepared from **1** (monohydrate) and acetic anhydride in the presence of 4-dimethylaminopyridine. Colorless needles (acetone–hexane): Mp 198—199 °C; $[\alpha]_D^{25}$ +82° (*c* 0.123, MeOH); IR ($CHCl_3$) 1740, 1690, 1630, and 1240 cm^{-1}; ^1H NMR (90 MHz) δ=0.8—1.4 (15H, m), 2.08 (3H, s), 2.09 (3H, s), 4.9—5.3 (3H, m), 6.4 (1H, dd, *J*=5.5 and 0.9 Hz), and 6.76 (1H, dd, *J*=5.5 and 4.8 Hz); MS *m/z* 396 (M^+). Found: C, 63.53; H, 8.17%. Calcd for $C_{21}H_{32}O_7$: C, 63.61; H, 8.14%. Lit,[3c] Mp 199—201 °C; $[\alpha]_D$ +84° ($CHCl_3$); IR ($CHCl_3$) 5.71, 5.88, and 6.08 µ.

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References

1) J. Inanaga, Y. Kawanami, and M. Yamaguchi, *Chem. Lett.*, **1981**, 1415.

2) A. Kinumaki and M. Suzuki, *J. Chem. Soc., Chem. Commun.*, **1972**, 744.

3) a) C. Djerassi and O. Halpern, *J. Am. Chem. Soc.*, **79**, 2022 (1957); b) C. Djerassi and O. Halpern, *J. Am. Chem. Soc.*, **79**, 3926 (1957); c) C. Djerassi and O. Halpern, *Tetrahedron*, **3**, 255 (1958).

4) I. Maezawa, A. Kinumaki, and M. Suzuki, *J. Antibiot.*, **27**, 84 (1974).

5) R. W. Rickards and R. M. Smith, *Tetrahedron Lett.*, **1970**, 1025.

6) Total absolute configuration: Reference 3, 4, and D. G. Manwaring, R. W. Rickards, and R. M. Smith, *Tetrahedron Lett.*, **1970**, 1029.

7) J. Inanaga, T. Katsuki, S. Takimoto, S. Ouchida, K. Inoue, A. Nakano, N. Okukado, and M. Yamaguchi, *Chem. Lett.*, **1979**, 1021.

8) J. Inanaga, A. Takeda, N. Okukado, and M. Yamaguchi, *Mem. Fac. Sci., Kyushu Univ., Ser. C, Chem.*, **9**, 293 (1975).

9) For condensations of lithium acetylides and lactones: see J. C. Chabala and J. E. Vincent, *Tetrahedron Lett.*, **1978**, 937.

10) J. Inanaga, K. Hirata, H. Saeki, T. Katsuki, and M. Yamaguchi, *Bull. Chem. Soc. Jpn.*, **52**, 1989 (1979).

11) I. G. Tishchenco, A. A. Akhrem, and I. N. Nazarov, *Zh. Obschei Khim.*, **29**, 809 (1959).

12) J. L. Pierre and P. Chautemps, *Tetrahedron Lett.*, **1972**, 4371; P. Chautemps and J. L. Pierre, *Tetrahedron*, **32**, 549 (1976).

13) While the present study was in progress, a general, highly stereoselective reduction of α,β-epoxy ketones to *erythro*-epoxy alcohols by using $Zn(BH_4)_2$ in ether was reported: T. Nakata, T. Tanaka, and T. Oishi, *Tetrahedron Lett.*, **22**, 4723 (1981). We are gratefull to Dr. Oishi for his kind information on their results prior to publication.

14) D. H. Calam and D. A. H. Taylor, *J. Chem. Soc. (C)*, **1966**, 949.

15) A. Nakano, S. Takimoto, J. Inanaga, T. Katsuki, S. Ouchida, K. Inoue, M. Aiga, N. Okukado and M. Yamaguchi, *Chem. Lett.*, **1979**, 1019. See also Ref. 7.

16) For example: R. U. Lemieux, A. A. Pavia, J. C. Martin, and K. A. Watanabe, *Can. J. Chem.*, **47**, 4427 (1969).

17) Indicated chemical shifts were assigned to methylene protons between two oxygens of anomeric OMEM groups.

18) C. E. Castro, *J. Am. Chem. Soc.*, **83**, 3262 (1961); C. E. Castro and R. D. Stephens, *ibid.*, **86**, 4358 (1964).

19) E. J. Corey, P. B. Hopkins, S. Kim, S. Yoo, K. P. Nambiar, and J. R. Falck, *J. Am. Chem. Soc.*, **101**, 7131 (1979).

20) G. Odham, *Arkiv för Kemi*, **20**, 507 (1963).

21) Some characteristic peaks of major isomer were indicated.

22) R. C. Fuson, J. W. Bertetti, and Wm. E. Ross, *J. Am. Chem. Soc.*, **54**, 4380 (1932). Recently a very facile preparation of 2,4,6-trichlorobenzoic acid has been reported: M. A. Sutter and D. Seebach, *Liebigs Ann. Chem.*, **1983**, 939. We further modified the latter method as follows giving a higher yield: To a cold solution of 1,3,5-trichlorobenzene (290 mg, 1.6 mmol) in dry THF (10 ml) at −78 °C was added slowly a hexane solution of *n*-BuLi (1.63 mol dm^{-3}, 1.0 ml) and the mixture was stirred for 2 h at the same temperature. Dry carbon dioxide was bubbled in over 15 min at −78 °C and then the cooling bath was removed. Gas evolution started around 0 °C. After stirring for 30 min at room temperature, solvent was evaporated. The resulting solid was dissolved in water and washed with ether. The aqueous layer was saturated with NaCl and acidified by the addition of aqueous HCl (5 mol dm^{-3}). The product was extracted with ether, dried over anhydrous Na_2SO_4, and concentrated to give the acid as white crystalline solid (343 mg, 95%). The sample had an enough purity (^1H NMR) for the conversion to the corresponding acid chloride.