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TOTAL SYNTHESIS OF NEOMETHYNOLIDE

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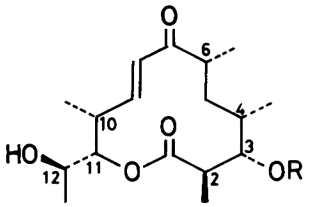
(+)-Neomethynolide, the aglycone of a twelve-membered ring macrolide, neomethymycin, was totally synthesized via its 8,9-didehydro derivative. The synthesis also established the stereochemistry of neomethynolide at C-10, C-11, C-12, and 8,9-double bond which had remained unproved.

Neomethynolide (1) was obtained by Djerassi et al.[1a,c] as the authentic aglycone by the controlled acid hydrolysis of a macrolide antibiotic, neomethymycin (2), which had been isolated besides its isomer, methymycin, from the culture filtrate of *Streptomyces* M-2140.[1a,c] Maezawa et al.[1d] later isolated the aglycone (1) directly from the culture filtrate of a mutant strain, *S. venezuelae* MCRL-0376. The chemical structure and 2R, 3S, 4S, and 6R configuration of 1 were established by Djerassi et al.[1b,c] and Rickards et al.[2] From the analogy with methynolide,[3] 1 was also considered to have 10R, 11S, and 8,9-*trans* configuration though no experimental evidence was available. The present authors further postulated the 12R stereochemistry on the basis of biogenetic consideration and carried out the synthesis of the compound having a structure represented by 1 in its optically active form. The comparison of 1 thus obtained with the specimen of natural origin proved that they were identical and hence the complete stereochemistry of neomethynolide was established beyond doubt by the present total synthesis.

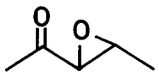


1 Neomethynolide
R = H

2 Neomethymycin
R = Desosamyl

The skeleton of the hydroxy acid to be cyclized to the twelve-membered lactone, was constructed by the condensation of two fragments, an acetylenic intermediate (7) which was synthesized in stereoselective manner, and Prelog-Djerassi lactonic acid methyl ester (8).

3,4-Epoxy-2-pentanone (3)[4] was reduced to the epoxy alcohol (4, 77%) with high stereoselectivity by stirring it with a mixture of sodium borohydride and zinc perchlorate in ether at -78°C for 1 h and then by warming



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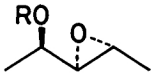
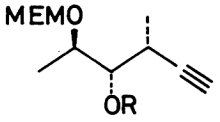
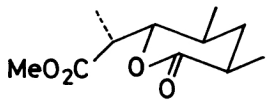


4 R = H
5 R = MEM



6 R = H
7 R = Si(*t*-Bu)Me$_2$ (TBDMS)



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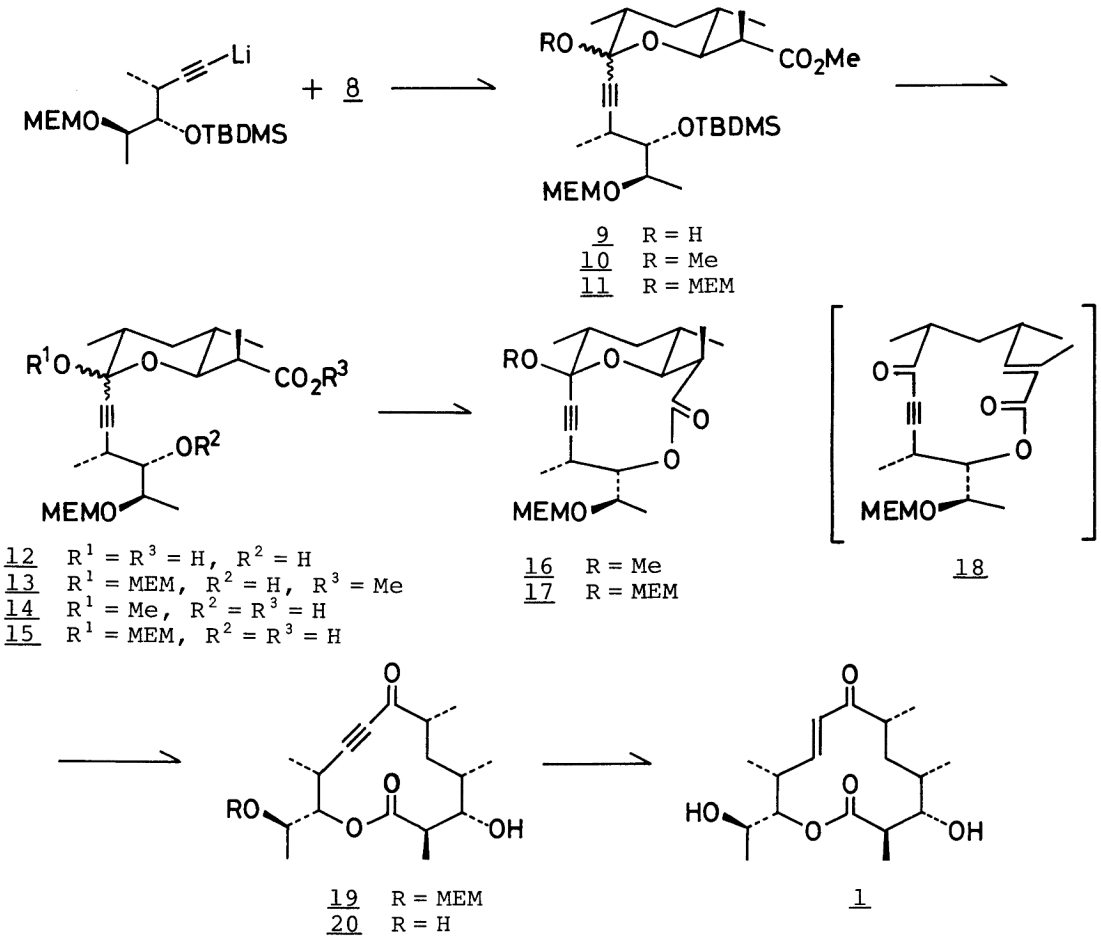
the mixture to 0°C over a period of 1 h. ^{13}C-NMR analysis of 4 and gas chromatographic analysis of its acetate revealed that the ratio of 4 to its 2-epimer was >99 : 1.[5] Treatment of 4 with methoxyethoxymethyl chloride (MEM chloride) and diisopropylethylamine afforded the MEM ether (5) in 80% yield. 5 reacted with 2 eq. of lithium acetylide-ethylenediamine complex in a mixture of dimethyl sulfoxide and hexamethylphosphoric triamide (1 : 1) at room temperature for 60 h giving the acetylenic alcohol (6) in 65% yield after purification by chromatography on silica gel. 6 was then treated with (S)-(+)-O-methylmandelic acid chloride[6] in dichloromethane at 40°C in the presence of 4-dimethylaminopyridine to give a mixture of diastereomeric esters, which could be easily separated by column chromatography on silica gel. The early fraction gave, upon hydrolysis with aqueous methanolic potassium hydroxide, the (-)-alcohol in 90% yield. $[\alpha]_D^{23}$ -24.4° (c=1.064, $CHCl_3$). On correlation[7] to (R)-(-)-2-methylbutyric acid, the (-)-alcohol proved to have a (2R, 3S, 4R)-configuration required for the synthesis of 1. Reaction of (-)-6 with *tert*-butyldimethylsilyl chloride and imidazole in dimethylformamide produced the desired silylated acetylene (7), $[\alpha]_D^{23}$ -2.0° (c=1.01, $CHCl_3$).

The other intermediate, (+)-Prelog-Djerassi lactonic acid methyl ester (8) was prepared by the method described in the total synthesis of methynolide.[8] The acetylene (7) was lithiated by treatment with butyllithium at 0°C for 1 h and then condensed[9] with 8 in tetrahydrofuran (THF) at -20°C for 1 h to afford a mixture of the hemiacetals (9, 90%).[10] 9 was treated with a catalytic amount of p-toluenesulfonic acid in methanol to give a mixture of the methyl acetals (10) which were difficult to separate. The relative intensity of the protons of anomeric methoxy groups at C-7 in NMR was 3.5 (axial) : 1 (equatorial). Desilylation of the mixture (Bu_4NF, THF) and subsequent hydrolysis of the resulting alcohols (12) (1N NaOH-MeOH, rt, 12 h) gave a mixture of the seco-acids (14). Alternatively, the treatment of 9 with MEM chloride and diisopropylethylamine afforded a mixture of MEM ethers (11, 90.4%; axial OMEM : equatorial OMEM was ca. 1 : 4) which could be separated by preparative TLC on silica gel. The major, less polar isomer (equatorial OMEM) was converted into the single seco-acid (15) by the same procedure as above in 87.6% yield.

Lactonization of the seco-acid mixture (14) and that of 15 were carried out by mixed anhydride method using 2,4,6-trichlorobenzoyl chloride.[11] The highly strained lactones (16) and (17) were obtained in 12.0% and 33.2% yield, respectively. 16: $[\alpha]_D^{25}$ +5.64° (c=1.24, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 3.39(6H, s), 4.24(1H, dd), 4.83 (1H, dd), 4.71 and 4.84(1H each, ABq, J=7.22 Hz). 17: $[\alpha]_D^{25}$ +17.2° (c=0.29, $CHCl_3$); ^{1}H-NMR δ 3.40(3H, s), 4.82(1H, dd), 4.69 and 4.82(1H each, ABq, J=6.56 Hz), 4.93 and 5.05(1H each, ABq, J=5.91 Hz). In both cases, an elimination product, 2-unsaturated compound [18: $[\alpha]_D^{25}$ +97.3° (c=1.13, $CHCl_3$); ^{1}H-NMR δ 1.87(3H, d), 3.39(3H, s), 4.83 (1H, dd), 4.72 and 4.84(1H each, ABq, J=7.22 Hz), 6.94(1H, dq)], was isolated as a by-product in 9-13% yield.

Deprotection of 17 with trifluoroacetic acid (TFA) in dichloromethane at room temperature for 14 h gave the mono-MEM ether (19, 61%) and the diol (20, 16%). 19: $[\alpha]_D^{24}$ +15.5° (c=0.517, MeOH); ^{1}H-NMR δ 3.18(1H, dq), 3.39(1H, s), 4.70 and 4.82(1H each, ABq, J=7.22 Hz), 5.11(1H, dd). 20: Colorless needles, mp 74-76°C (monohydrate); $[\alpha]_D^{24}$ +27.0° (c=0.223, MeOH); UV (EtOH) 220 nm (ε=4.27); IR ($CHCl_3$)



2200, 1725, 1660 cm^{-1}; ^{1}H-NMR δ 3.24(1H, dq), 3.65(1H, dd), 3.86(1H, dq), 5.03(1H, dd). Prolonged reaction or high concentrations of TFA gave a complicated mixture. 19 was treated with zinc bromide in a mixture of dichloromethane and nitromethane to afford 20, in 58% yield (totally 51% from 17). Treatment of 16 with zinc bromide also gave 19 and 20 in 38 and 44% yield, respectively.

Reduction of 20 by chromous sulfate in aqueous dimethylformamide[12] at room temperature for 10 h gave neomethynolide (1) in 65% yield. 1: Colorless needles, mp 92-93°C (monohydrate);[13] $[\alpha]_D^{24}$ +112.5° (c=0.160, MeOH), UV (EtOH) 227 nm (ε= 4.08); IR ($CHCl_3$) 1725, 1685, 1625 cm^{-1}; ^{1}H-NMR δ 3.57(1H, m), 3.89(1H, m), 4.83(1H, dd, J=2.41, 9.19 Hz), 6.42(1H, dd, J=0.87, 15.75 Hz), 6.79(1H, dd, J=5.03, 15.75 Hz). Lit.[1c] mp 90-120°C (monohydrate); $[\alpha]_D$ +108° ($CHCl_3$); UV (EtOH) 227.5 nm (ε= 4.10); IR ($CHCl_3$) 2.93, 5.75, 5.90, 6.10 μ. Diacetate: mp 198-199°C; $[\alpha]_D^{25}$ +82°C (c=0.1225, MeOH) [lit.[1c] mp 199-201°C; $[\alpha]_D$ +84° ($CHCl_3$)].

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5) 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, Y. Tani, M. Hatozaki, and T. Oishi, The 101 Annual Meeting of Japan Pharmaceutical Society (Kumamoto, 1981), Abstract Paper, p. 451].

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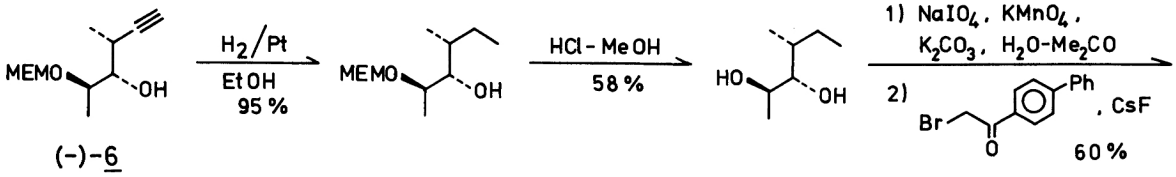
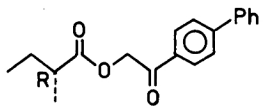
7) The (-)-alcohol (6) was transformed into (-)-4-phenylphenacyl 2-methylbutyrate (i) [$[\alpha]_D^{23}$ -7.6° (c=1.055, C_6H_6)] by the following sequence. (R)-(-)-2-methylbutyric acid is known to give the (-)-4-phenylphenacyl ester: $[\alpha]_D^{23}$ -4° [D. H. Calam and D. A. H. Taylor, *J. Chem. Soc.* (C), 1966, 949].



(-)-6



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The corresponding ester derived from (+)-6 gave $[\alpha]_D^{23}$ +11.0° (c=1.730, C_6H_6), which on hydrolysis gave (S)-(+)-2-methylbutyric acid, $[\alpha]_D^{23}$ +25.2° (c=0.595, H_2O). Lit. $[\alpha]_D^{21.2}$ +19.30 (neat) [G. Odham, *Arkiv för Kemi*, 20, 507 (1963)].

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10) Most reaction products were purified by TLC on silica gel with appropriate solvents unless otherwise specified.

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13) A sample recrystallized from ether-hexane gave satisfactory CH analysis for a monohydrate. Important intermediates, 5, 6, 7, 9, 10, 11, 12, 13, 17, and 20, also gave correct CH analyses.

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