

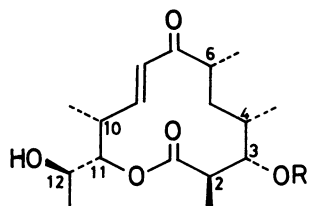
TOTAL SYNTHESIS OF NEOMETHYNOLIDE

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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.

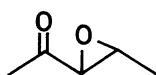
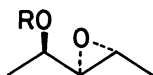
Neomethynolide (1) was obtained by Djerassi et al.^{1a,c)} as the authentic aglycone by the controlled acid hydrolysis of a macrolide antibiotic, neomethymycin (2), which had been isolated besides its isomer, methymycin, from the culture filtrate of *Streptomyces* M-2140.^{1a,c)} Maezawa et al.^{1d)} 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.



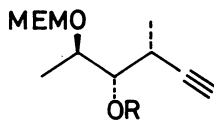
- 1 Neomethynolide
R = H
2 Neomethymycin
R = Desosamyl

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).

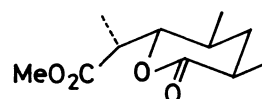
3,4-Epoxy-2-pentanone (3)⁴⁾ was reduced to the epoxy alcohol (4, 77%) with high stereoselectivity by stirring it with a mixture of sodium borohydride and zinc perchlorate in ether at -78°C for 1 h and then by warming

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4 R = H
5 R = MEM



6 R = H
7 R = Si(t-Bu)Me₂
(TBDMS)

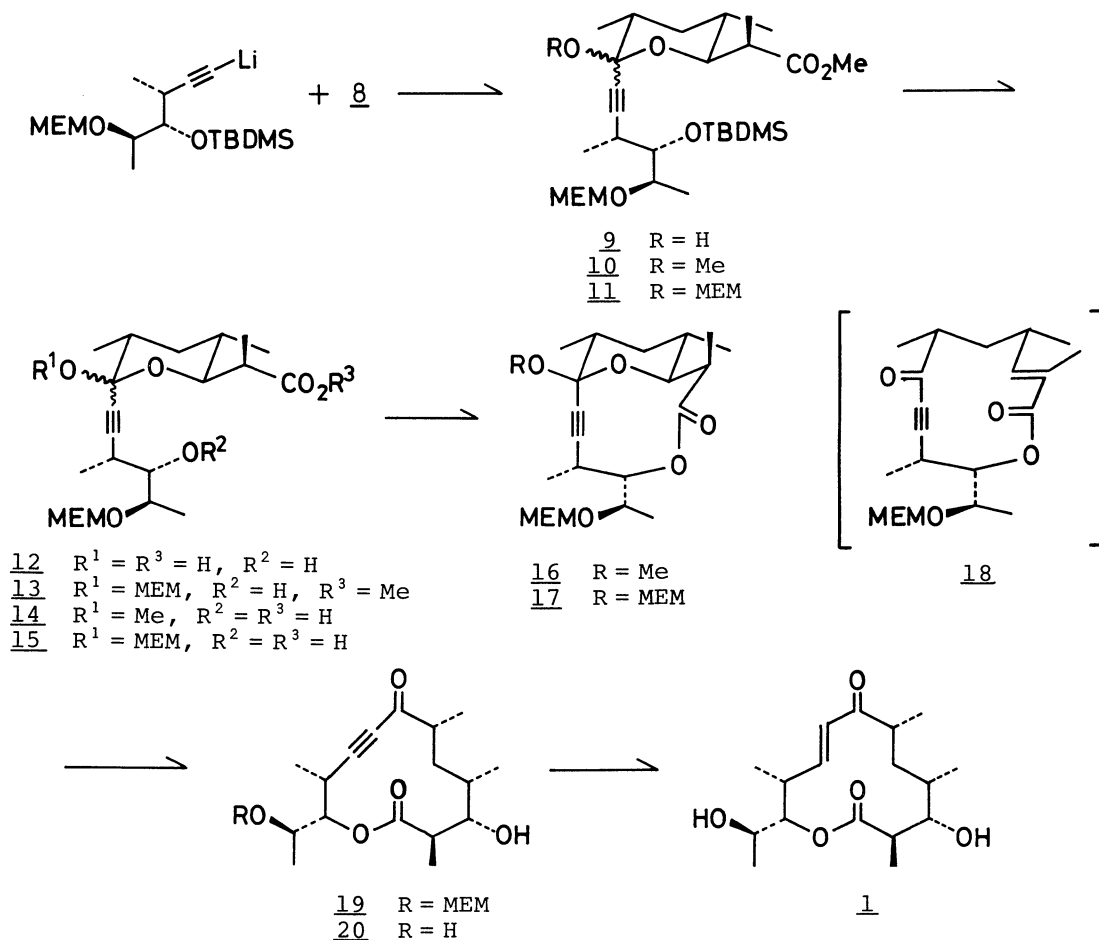
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the mixture to 0°C over a period of 1 h. ^{13}C -NMR analysis of 4 and gas chromatographic analysis of its acetate revealed that the ratio of 4 to its 2-epimer was >99 : 1.⁵⁾ Treatment of 4 with methoxyethoxymethyl chloride (MEM chloride) and diisopropylethylamine 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 chloride⁶⁾ 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. $[\alpha]_{\text{D}}^{23}$ -24.4° (c=1.064, CHCl_3). On correlation⁷⁾ 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), $[\alpha]_{\text{D}}^{23}$ -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 condensed⁹⁾ 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: $[\alpha]_{\text{D}}^{25}$ +5.64° (c=1.24, CHCl_3); ^1H -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: $[\alpha]_{\text{D}}^{25}$ +17.2° (c=0.29, CHCl_3); ^1H -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: $[\alpha]_{\text{D}}^{25}$ +97.3° (c=1.13, CHCl_3); ^1H -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: $[\alpha]_{\text{D}}^{24}$ +15.5° (c=0.517, MeOH); ^1H -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); $[\alpha]_{\text{D}}^{24}$ +27.0° (c=0.223, MeOH); UV (EtOH) 220 nm (ϵ =4.27); IR (CHCl_3)



2200, 1725, 1660 cm^{-1} ; $^1\text{H-NMR}$ 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 dimethylformamide¹²⁾ at room temperature for 10 h gave neomethynolide (**1**) in 65% yield. **1**: Colorless needles, mp 92-93°C (monohydrate);¹³⁾ $[\alpha]_{\text{D}}^{24} +112.5^\circ$ ($c=0.160$, MeOH), UV (EtOH) 227 nm ($\epsilon=4.08$); IR (CHCl_3) 1725, 1685, 1625 cm^{-1} ; $^1\text{H-NMR}$ 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); $[\alpha]_{\text{D}} +108^\circ$ (CHCl_3); UV (EtOH) 227.5 nm ($\epsilon=4.10$); IR (CHCl_3) 2.93, 5.75, 5.90, 6.10 μ . Diacetate: mp 198-199°C; $[\alpha]_{\text{D}}^{25} +82^\circ$ ($c=0.1225$, MeOH) [lit.^{1c)} mp 199-201°C; $[\alpha]_{\text{D}} +84^\circ$ (CHCl_3)].

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- $(-)\text{-}\underline{6} \xrightarrow[\text{EtOH, 95\%}]{\text{H}_2/\text{Pt}} \text{MEMO-CH(CH}_3\text{)-CH}_2\text{-CH}_2\text{-OH} \xrightarrow[58\%]{\text{HCl-MeOH}} \text{HO-CH(CH}_3\text{)-CH}_2\text{-CH}_2\text{-OH} \xrightarrow[60\%]{\begin{array}{l} 1) \text{ NaIO}_4, \text{ KMnO}_4, \\ \text{K}_2\text{CO}_3, \text{ H}_2\text{O-Me}_2\text{CO} \\ 2) \text{ Br-CH}_2\text{-C(=O)-Ph, CsF} \end{array}} \text{Ph-CH}_2\text{-C(=O)-O-CH(CH}_3\text{)-CH}_2\text{-CH}_2\text{-C(=O)-Ph}$
- $\text{Ph-CH}_2\text{-C(=O)-O-CH(CH}_3\text{)-CH}_2\text{-CH}_2\text{-C(=O)-Ph}$
i
- The corresponding ester derived from (+)-6 gave $[\alpha]_D^{23} +11.0^\circ$ ($c=1.730$, C_6H_6), which on hydrolysis gave (S)-(+)-2-methylbutyric acid, $[\alpha]_D^{23} +25.2^\circ$ ($c=0.595$, H_2O). Lit. $[\alpha]_D^{21.2} +19.30$ (neat) [G. Odham, *Arkiv för Kemi*, **20**, 507 (1963)].
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 - 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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