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TOTAL SYNTHESIS OF METHYNOLIDE

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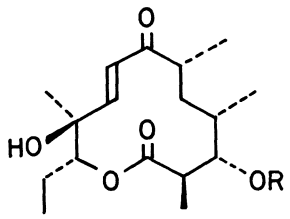
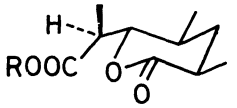
(+)-Methynolide, the aglycon of a macrolide antibiotic, methymycin, was synthesized via its acetylenic analogue, 8,9-didehydromethynolide. The lactonization of the seco-acids was carried out by the newly developed mixed anhydride method using 2,4,6-trichlorobenzoyl chloride.

Methynolide (1) is the aglycon of a twelve-membered ring macrolide, methymycin (2), which was first isolated from the culture of Streptomyces M-2140.[1] Its chemical structure was elucidated by Djerassi et al.[2] and the complete stereochemistry was given by Rickards et al.[3] The first total synthesis of methynolide and methymycin has been published by Masamune et al. in the form of communications.[4]

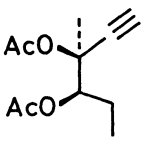


Methynolide 1
R=H

Methymycin 2



3 R=H
4 R=CH_3



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Here we wish to describe another total synthesis of methynolide, which proceeds through the acetylenic intermediates. The synthesis of the two starting materials, the (+)-Prelog-Djerassi lactonic acid (3)[2,5] and (+)-3,4-diacetoxy-3-methyl-1-hexyne (5), has been reported in the preceding paper.[6]

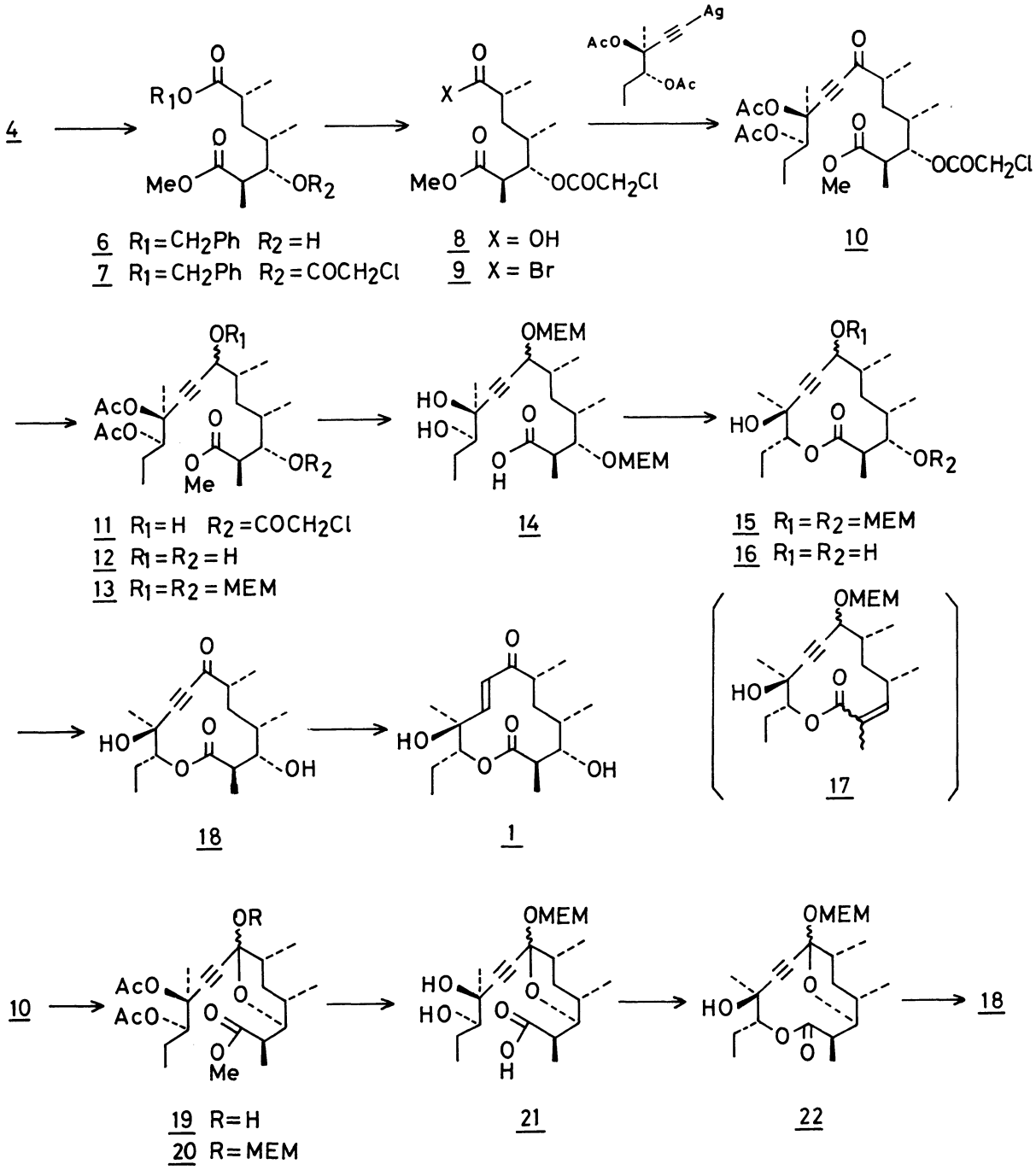
The preliminary studies carried out with the racemic materials or with the appropriate model compounds, disclosed the following facts which were taken into account in the selection of the synthetic route. 1) Acetylenic ketones such as 10 were not so stable to strong bases, and especially when the 3-hydroxyl group was free, they were easily cleaved hydrolytically between the 7-keto group and the triple bond. 2) Acetylenic ketone like 10 could be catalytically hydrogenated with palladium-barium sulfate giving a cis-enone, which could be smoothly converted into a trans-enone by addition and elimination of 1-propanethiol in a Michael fashion, but the corresponding γ,δ-dihydroxy enone was very vulnerable to acids.[7] 3) In the lactonization of the seco-acids like 14, in which the 3-hydroxyl group was protected by chloroacetyl or even by acetyl group, the mixed anhydride method employed in the present study resulted in the formation of 2-unsaturated product like 17 to a large extent. Therefore it was desirable to use an ethereal protective group. 4) Protection of the two hydroxyl groups of the diol

(12) with dimethyl-t-butylsilyl group could be achieved in ca. 50% yield but the selective saponification of the methoxycarbonyl group gave the product only in poor yield (ca. 20%).

Thus the synthesis was finally carried out as described below.

The (+)-methyl ester (4)[6] was converted into the mono-sodium salt and then treated with benzyl bromide in HMPA to give the benzyl methyl ester (6). Protection of 3-hydroxyl group with chloroacetic anhydride in the presence of 4-dimethylaminopyridine gave 7, $[\alpha]_D^{20}$-4.2°(c 0.92, $CHCl_3$), PMR($CDCl_3$) δ 4.00(2H, s), 5.10(2H, s), in 87% yield from 4. The benzyl ester (7) was hydrogenolized to the acid (8, 95%), PMR($CDCl_3$) δ 3.68(3H, s), 4.10(2H, s), 5.18(1H, dd), which was then converted into the acid bromide (9) with oxalyl bromide in benzene. The acid bromide was condensed[8] with the silver salt of the acetylenic diacetate (5, 1.5 eq.) in refluxing carbon tetrachloride under an atmosphere of nitrogen to give the acetylenic ketone (10, 85% from 8), $[\alpha]_D^{20}$+45.2°(c 0.69, $CHCl_3$), IR (liquid film) 2210, 1746, 1676 cm^{-1}, PMR($CDCl_3$) δ 3.64(3H, s), 4.08(2H, s), 5.14(2H, m). This ketone (10) possesses all the carbon atoms and the functionalities with proper stereochemistry necessary for the further transformation to methynolide. As the direct deprotection of chloroacetyl group of 10 with sodium carbonate in aqueous methanol under controlled conditions gave the cyclic hemiacetal(19, 67%), PMR($CDCl_3$) δ 1.70(3H, s), 2.05(3H, s), 2.14(3H, s), 3.70(3H, s), 5.13(1H, dd), the 7-keto group was reduced by sodium borohydride in THF at 0°C to a mixture of the alcohol (11, 55%) and the diol (12, 29%).[9] Removal of the chloroacetyl group of 11 gave 12 (the combined yield from 10, 82%). PMR of 12 showed that it was the mixture of the two diastereomeric alcohols and the relative intensity of the epimeric protons at C-7, δ($CDCl_3$) 4.14(m) : 4.36(m) was ca. 1 : 1.7. Reprotection of the two hydroxyl groups to 13 (98%) by means of methoxyethoxymethyl chloride and dicyclohexylethylamine in methylene chloride, followed by saponification with aqueous methanolic potassium hydroxide gave the seco-acid (14, 92%), PMR($CDCl_3$) δ 1.45(3H, s), 3.41(6H, s). For the lactonization, a newly developed procedure was employed in which the mixed anhydride of a hydroxy acid with 2,4,6-trichlorobenzoic acid was added to 4-dimethylaminopyridine in refluxing benzene. This method has been proved to be very effective for the rapid and mild esterifications as well as for the large-ring lactonizations.[10] Thus the lactone (15), IR (liquid film) 1730 cm^{-1}, PMR($CDCl_3$) δ 1.42(3H, s), 3.37(6H, s), 3.2-4.0(9H, m), 4.05 and 4.34(1H, each d, C-7 epimeric protons), 4.5-5.1(5H, m), was obtained under high-dilution conditions in 42% yield after the TLC separation. The isomeric ratio due to the configurations at C-7 was ca. 2:1. A small amount (ca. 8%) of the elimination product, the 2-unsaturated compound (17), PMR($CDCl_3$) δ 1.87(3H, s), 6.72(1H, d), was isolated as one of the byproducts. It has been known that the above mixed anhydride method causes some racemization at the α-carbon atom of the carboxyl function when conducted at an elevated temperature.[10] Therefore the reason for the formation of the lactone with the proper stereochemistry at the 2-C atom in fairly good yield, is not clear at present as to whether the extent of isomerization is not so serious or the R-configuration of the 2-C atom is thermodynamically preferred one. Deprotection with a mixture of trifluoroacetic acid, 2-propanol and water gave the two triols (16 a and b, 67%), one of which was obtained in crystalline state [16a, colorless needles,

mp 155-157°, PMR(CD_3OD) δ 4.23(1H, d); 16b(crude), an oil, PMR(CD_3OD) δ 4.44(1H, dq)]. Both the triols gave the same 8,9-didehydromethynolide (18, 87%) on treatment with γ-manganese dioxide[11] in dichloromethane at room temperature. 18: Colorless needles; mp 185.5-186.5°C; $[\alpha]_D^{25}$+48°(c 0.25, MeOH); IR(KBr) 2220, 1730, 1680 cm^{-1}; PMR(CD_3COCD_3) δ 0.90(3H, t), 0.94(3H, d), 1.14(3H, d), 1.34(3H, d), 1.53(3H, s), 3.55(1H, m), 5.09(1H, dd); MS m/e 252 (M-58). Reduction of 18 by chromous sulfate in aqueous DMF at room temperature gave methynolide (1, 53%), though the open chain analogue could not be reduced. The strain in the twelve-membered acetylenic lactone seems to be responsible to this disparity. 1: Colorless needles; mp 162-163°C; $[\alpha]_D^{25}$+64°(c 0.25, MeOH); UV(EtOH) 225 nm (logε=3.92); IR($CHCl_3$) 1730, 1695, 1635 cm^{-1};



PMR($CDCl_3$) δ 0.92(3H, t), 1.22(3H, d), 1.34(3H, d), 1.39(3H, s), 3.60(1H), 4.80(1H, dd), 6.48(2H, ABq, J=16.5 Hz); MS m/e 254 (M-58) [lit.[2] mp 163-165°C; $[\alpha]_D^{25}$+63° (MeOH); UV(EtOH) 225 nm (logε=4.03); IR($CHCl_3$) 5.76, 5.91, 6.08 μ]. Monoacetate, mp 198-199°C (lit.[2] 198-200°C).

The hemiacetal(19) could also be transformed to didehydromethynolide (18) as follows. 7-Hydroxyl group was protected by methoxyethoxymethyl group to give 20 (83%)[12] which was then saponified to the seco-acid (21, 99%), PMR($CDCl_3$) δ 1.44(3H, s), 3.36(3H, s). Lactonization of 21 by the same method as described above and the subsequent TLC separation afforded a small amount of the highly strained bicyclic monomer (22, 17.6%), MS m/e 340 (M-58), 295, 281, 265, besides a large amount of polymers. The bicyclic lactone (22) expectedly gave 18 (29%) by deprotection with trifluoroacetic acid.

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References and Notes

1) M. N. Donin, J. Pagano, J. D. Dutcher, and C. M. McKee, "Antibiotics Annual 1953-1954", Medical Encyclopedia, Inc., New York, p.179. Reviews for macrolides: W. Keller-Schierlein, Fortschr. Chem. Org. Naturst., 30, 313 (1973); W. D. Celmer, Pure Appl. Chem., 28, 413 (1971).
2) C. Djerassi and J. A. Zderic, J. Am. Chem. Soc., 78, 2907, 6390 (1956).
3) R. W. Rickards and R. M. Smith, Tetrahedron Lett., 1025 (1970); D. G. Manwaring, R. W. Rickards, and R. M. Smith, ibid., 1029 (1970).
4) S. Masamune, C. U. Kim, K. E. Wilson, G. O. Spessard, P. E. Georghiou, and G. S. Bates, J. Am. Chem. Soc., 97, 3512 (1975); S. Masamune, H. Yamamoto, S. Kamata, and A. Fukuzawa, ibid., 97, 3513 (1975).
5) R. Anliker, D. Dvornik, K. Gubler, H. Heusser, and V. Prelog, Helv. Chim. Acta, 39, 1785 (1956).
6) A. Nakano, S. Takimoto, J. Inanaga, T. Katsuki, S. Ouchida, K. Inoue, M. Aiga, N. Okukado, and M. Yamaguchi, Chem. Lett., 1979, in press.
7) J. Inanaga, A. Takeda, N. Okukado, and M. Yamaguchi, Mem. Fac. Sci., Kyushu Univ., Ser. C, Chem., 9, 293 (1975).
8) R. B. Davis and D. H. Scheiber, J. Am. Chem. Soc., 78, 1675 (1956).
9) Reduction in ethanol resulted in the complete removal of chloroacetyl group and at the same time the methoxycarbonyl group was partly reduced.
10) J. Inanaga, K. Hirata, H. Saeki, T. Katsuki, and M. Yamaguchi, Bull. Chem. Soc. Jpn., 52, 1989 (1979).
11) L. I. Vereshchagin, S. R. Gainulina, S. A. Podskrebysheva, L. A. Gaivoronskii, L. L. Okhapkina, V. G. Vorob'eva, and V. P. Latyshev, J. Org. Chem. of USSR, 8, 1143 (1972).
12) The isomeric ratio due to the configurations at 7-C was ca. 2.9:1. From the PMR data, the major isomer is considered to have the acetylenic residue at the axial position (7R) in regard to the oxane ring [($CDCl_3$) δ 4.97, $-OCH_2O-$] and the minor isomer at the equatorial position (7S) [($CDCl_3$) δ 4.74, $-OCH_2O-$].

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