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TOTAL SYNTHESIS OF PROTOMYCINOLIDE IV

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Summary: A 16-membered macrolide antibiotic, protomycinolide IV, was synthesized from two fragments to which the chirality was introduced by asymmetric epoxidation of the appropriately chosen allylic alcohols. A new synthesis of the Prelog-Djerassi lactonic acid from one of the intermediates of the synthesis was also carried out.

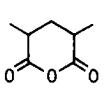
Mycinamicin I~V and protomycinolide IV (34), a group of 16-membered antibiotics isolated[1] from Micromonospora griseorubida sp. nov. and structurally elucidated,[1b,2] have the same partial structure [C(1)~C(11)]. An intermediate (15), an equivalent of C(1)~C(9) part of these antibiotics, is, therefore, considered to be a useful common building block for the construction of this class of compounds. In the present communication are described a chiral synthesis of 15 via a hydroxy lactone (9), and the total synthesis of protomycinolide IV,[1b] by combining a fragment (16) which was obtained from 15 by conventional transformations, with another chiral fragment (27). Asymmetric epoxidation[3] has been used for the introduction of chirality to both 15 and 27. The oxidation of an intermediary hydroxy lactone (9) provided a new chiral synthesis of the Prelog-Djerassi lactonic acid (11).[4]

The fragment (16). The synthesis started with meso-2,4-dimethylglutaric anhydride (1).[5] Reduction of 1 (LAH, ether, refl.) followed by partial benzyloxymethylation [ϕCH_2OCH_2Cl(BOMCl), NaH, THF] gave the mono-BOM ether (2, 56%).[6] 2 was then subjected to Swern oxidation[7] and the resulting crude aldehyde [PMR, δ 0.97 (d, J=6.7 Hz, 3H), 1.11 (d, J=7.0 Hz, 3H), 3.41 (d, J=5.6 Hz, 2H), 4.59 (s, 2H), 4.74 (s, 2H), 9.58 (d, J=2.4 Hz, 1H)] was treated with 1-ethoxycarbonylethylidenetriphenylphosphorane (CH_2Cl_2, refl.). Column separation[8] gave the (E)-unsaturated ester [3, 90%; PMR, δ 0.93 (d, J=8.5 Hz, 3H), 1.00 (d, J=8.8 Hz, 3H), 1.29 (t, J=7.1 Hz, 3H), 1.85 (d, J=1.3 Hz, 3H), 2.40-2.85 (br. m, 1H), 3.39 (d, J=5.9 Hz, 2H), 4.18 (q, J=7.0 Hz, 2H), 4.59 (s, 2H), 4.74 (s, 2H), 6.51 (dd, J=10.2 and 1.4 Hz, 1H), 7.34 (s, 5H)] and the corresponding (Z)-isomer [5%; PMR, δ 0.90 (d, J=6.6 Hz, 3H), 0.99 (d, J=6.6 Hz, 3H), 1.29 (t, J=7.0 Hz, 3H), 1.88 (d, J=1.3 Hz, 3H), 3.10-3.50 (br. m, 1H), 3.38 (d, J=6.4 Hz, 2H), 4.19 (q, J=7.0 Hz, 2H), 4.60 (s, 2H), 4.75 (s, 2H), 5.60 (dd, J=10.2 and 1.4 Hz, 1H), 7.34 (s, 5H)]. 3 was reduced (LAH, ether, -10°C, 5 min; column purification) to the allyl alcohol (4, 96%) which was then epoxidized[3] under the presence of (+)-diisopropyl tartrate to give a mixture of diastereomeric epoxides [5 and 5a (1:1), 96%] after column purification. Each isomer could be separated,[9] but as the separation could be most easily effected at the stage of the unsaturated lactone esters (13 and 13a), subsequent several steps were carried out as diastereomeric mixtures. Regioselective reduction of the epoxides (5 and 5a) was achieved by Red-al[10] (THF, 45°C, 2 days), favoring the formation of the 1,3-diols (6 and its diastereomer) over the 1,2-diols with a ratio of >9:1 [PMR, 1,3-diol, δ ca.0.98 (d, 3H); 1,2-diol, δ 1.18 (s, 3H)]. The crude diol mixture was acetylated and the minor 1,2-diol diacetates were

eliminated by column chromatography to give a mixture of 1,3-diol diacetates [7 and its diastereomer (1:1), 89%]. Removal of BOM protection (H_2, 5% Pd-C, THF, 5 days) and subsequent oxidation ($RuCl_3$, H_2O-CH_3CN-CCl_4)[11] gave a carboxylic acid mixture (8 and its diastereomer, 97%) which was then saponified (LiOH, H_2O-THF) and acidified to give diastereomeric hydroxy lactones [9 and its diastereomer (55:45)[12]]. The hydroxy lactone mixture was subjected to Swern oxidation and the resulting aldehydes (12 and its diastereomer) were immediately condensed with trimethyl phosphonoacetate (NaH, THF). A Lobar column separation gave the desired lactone ester [13, mp 78-79°C (hexane), 41%; PMR, δ 1.01 (d, J=6.4 Hz, 3H), 1.11 (d, J=7.0 Hz, 3H), 1.27 (d, J=7.0 Hz, 3H), 2.57 (m, 2H), 3.73 (s, 3H), 4.04 (dd, J=10.0 and 2.3 Hz, 1H), 5.88 (dd, J=15.8 and 1.3 Hz, 1H), 7.08 (dd, J=15.8 and 7.2 Hz); $[\alpha]_D^{25}$+72.4°(c=2.0, MeOH)] and its diastereomer [13a, 32%; PMR, δ 0.91 (d, J=7.0 Hz, 3H), 1.19 (d, J=6.4 Hz, 3H), 1.23 (d, J=6.6 Hz, 3H), 3.75 (s, 3H), 4.04 (dd, J=9.9 and 2.5 Hz, 1H), 5.94 (dd, J=15.6 and 0.8 Hz, 1H), 6.78 (dd, J=15.6 and 9.0 Hz, 1H)]. Partial saponification [KOH (1 equiv.), H_2O-MeOH] and subsequent silylation (TBDMSCl, imidazole, DMF, 50°C) gave the disilyl compound, of which the TBDMS ester was selectively cleaved ($KF\cdot 2H_2O$, DMF, rt, 30 min) to the carboxylic acid [15, 98%; PMR, δ 0.44 (s, 6H), 0.90 (s, 9H), 1.04 (d, J=6.8 Hz, 3H), 1.19 (d, J=6.8 Hz, 3H), 3.40 (dd, J=6.4 and 3.1 Hz, 1H), 3.73 (s, 3H), 5.79 (dd, J=15.8 and 1.1 Hz, 1H), 6.92 (dd, J=15.8 and 8.3 Hz, 1H); $[\alpha]_D^{23}$-23.2° (c=0.69, EtOH)]. After converting [$(COCl)_2$, benzene] 15 into the corresponding acid chloride, the latter reacted (ether, -100°C) with the lithium salt of dimethyl methylphosphonate to afford the desired fragment as a phosphonate [16, 56%; PMR, δ 3.10 (double AB q, J=22.8 and 16.1 Hz, 2H), 3.42 (dd, J=5.4 and 3.5 Hz, 1H), 3.71 (d, J=1.3 Hz, 3H), 3.73 (s, 3H), 3.83 (d, J=1.3 Hz, 3H) 5.82 (dd, J=15.7 and 1.1 Hz, 1H), 6.95 (dd, J=15.7 and 8.3 Hz, 1H)].

The fragment (27). (E)-2-penten-1-ol, prepared from propargyl alcohol[13], was epoxidized[3] [(-)-diisopropyl tartrate] to 17 [80%, bp 77-78°C/2266 Pa; $[\alpha]_D^{21}$+32.1° (c=0.56, EtOH); >95% ee (PMR of its MTPA ester); PMR, δ 1.01 (t, J=7.3 Hz, 3H), 1.60 (m, 2H), 2.95 (m, 2H), 3.75 (m, 2H)]. Methylation of 17 ($LiMe_2Cu$, ether, -20°C) did not show any regioselectivity, affording a mixture of isomeric diols [18 and 22 (1:1), 88%]. Controled monobenzoylation (φCOCl, Py, CH_2Cl_2, 0°C, 1 h) and column separation gave a single monobenzoate [19, 44%; PMR, δ 1.00 (t, J=6.8 Hz, 3H), 1.06 (d, J=3.4 Hz, 3H), 3.50 (m, 1H), 4.42 (m, 2H), 7.5 (m, 3H), 8.05 (m, 2H)]. Successive protection (DHP, PPTS, CH_2Cl_2), saponification (KOH, MeOH), and Swern oxidation gave a crude aldehyde (24, 95% from 19) which was immediately condensed with trimethyl phosphonoacetate (NaH, benzene) to give the (E)-ester [25, 82%; PMR, δ 2.65 (m, 1H), 3.73 (s, 3H), 4.65 (m, 1H), 5.83 (d, J=17.5 Hz, 1H)] after column separation from the minor (Z)-isomer. 25 was reduced [$(i\text{-}Bu)_2AlH$, ether, 0°C] to the allyl alcohol (26, 91%), Swern oxidation of which gave the aldehyde [27, 99%; PMR, δ 2.75 (m, 1H), 4.65 (m, 1H), 9.52 (d, J=7.6 Hz, 1H)] as the desired C(11)~C(17) fragment.

Synthesis of protomycinolide IV (34). The phosphonate (16) was deprotonated (t-BuOK, THF, ether, -78°C~rt) and condensed (rt~80°C) with the aldehyde (27) to give the dienone (28), which was deprotected (PPTS, MeOH, 50°C) and reduced ($NaBH_4$-$CeCl_3$, MeOH, 0°C) to a mixture of the diols epimeric at C(9) [30, 74% from 16; PMR, δ 3.2-3.5 (m, 2H), 3.73 (s, 3H), 3.85-4.05 (m, 1H), 6.97 (dd, J=15.7 and 8.1 Hz, 1H)]. Hydrolysis (KOH, MeOH-H_2O, 50°C) of 30 gave the epimeric seco-acids (31, 95%). Cyclization of 31 by using TCBA procedure[14] afforded the two epimeric lactones (32, 52:48, 53%), which were separated on a Lobar column. The more polar 32;



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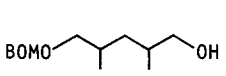

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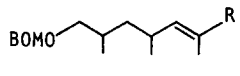
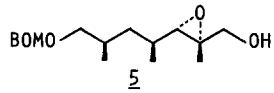


3 R=COOEt

4 R=CH_2OH



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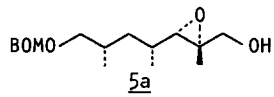
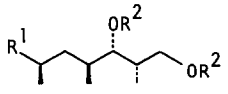


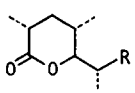
5a



6 R^1=CH_2OBOM, R^2=H

7 R^1=CH_2OBOM, R^2=Ac

8 R^1=COOH, R^2=Ac

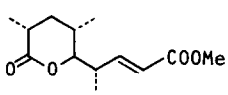


9 R=CH_2OH

10 R=COOMe

11 R=COOH

12 R=CHO



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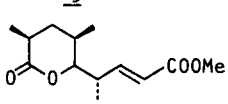
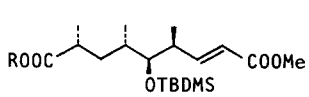
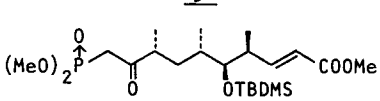


13a



14 R=TBDMS

15 R=H



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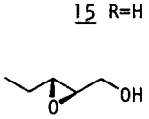

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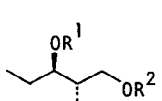
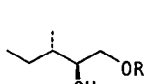


18 R^1=R^2=H

19 R^1=COØ, R^2=H

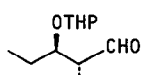
20 R^1=COØ, R^2=THP

21 R^1=H, R^2=THP

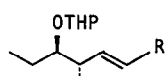


22 R=H

23 R=COØ



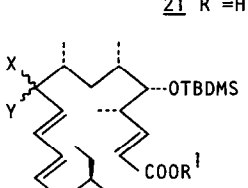
24



25 R=COOMe

26 R=CH_2OH

27 R=CHO

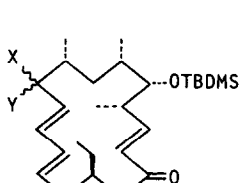


28 X,Y=O, R^1=Me, R^2=THP

29 X=H, Y=OH, R^1=Me, R^2=THP

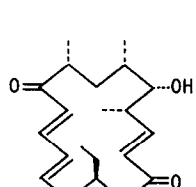
30 X=H, Y=OH, R^1=Me, R^2=H

31 X=H, Y=OH, R^1=R^2=H



32 X=H, Y=OH

33 X,Y=O



34

PMR, δ 0.04 (s, 6H), 0.91 (s, 9H), 3.37 (dd, J=8.3 and 0.9 Hz, 1H), 4.06 (dd, J=9.0 and 4.1 Hz, 1H), 4.64 (ddd, J=10.3, 9.8 and 2.8 Hz, 1H), 6.67 (dd, J=15.5 and 9.9 Hz, 1H). The less polar 32; PMR, δ 0.06 (s, 6H), 0.88 (s, 9H), 3.34 (dd, J=6.6 and 3.6 Hz, 1H), 4.65 (ddd, J=9.4, 7.9, and 3.1 Hz, 1H), 6.80 (dd, J=15.8 and 9.2 Hz, 1H). The more polar 32 was submitted to Swern oxidation and the dienone [33; PMR, δ 0.06 (s, 6H), 0.92 (s, 9H), 3.31 (dd, J=9.41 and 1.1 Hz, 1H), 4.64 (ddd, J=ca.11, ca.10 and 3.7 Hz, 1H)] obtained was desilylated (HF, CH_3CN) to give protomycinolide IV (34, mp 158.5~160°C, 16% from the more polar 32), which was identical with natural specimen[1b] in every respect examined. Oxidation of the less polar 32 with PCC also gave 33 (35%).

Prelog-Djerassi lactonic acid (11). The diastereomeric mixture of the hydroxy lactones [9 and its diastereomer (65:35)[12]] was smoothly oxidized ($RuCl_3$, H_2O-CH_3CN-CCl_4, 30 min) to the

corresponding acid mixture. Esterification (CH_2N_2, ether) followed by silica gel TLC gave Prelog-Djerassi lactonic acid methyl ester (10, 57% from the hydroxy lactone mixture) and its diastereomer [12.5%; PMR, δ 0.92 (d, J=7.0 Hz, 3H), 1.19 (d, J=6.4 Hz, 3H), 1.36 (d, J=6.8 Hz, 3H), 3.71 (s, 3H), 4.34 (dd, J=10.3 and 2.8 Hz, 1H)]. The methyl ester (10) was saponified to the lactonic acid (11) by known procedure. Both 10 and 11 were perfectly identical with the authentic specimens[4] in every respect. The overall yield from meso-dimethylglutaric anhydride (1) was 18%.

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References and Notes

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