Tetrahedron Letters,Vol.27,No,52,pp 6341-6344,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

SYNTHETIC STUDIES ON (+)-APLASMOMYCIN. 1. STEREOSELECTIVE SYNTHESIS OF THE C-12∼C-17 SEGMENT

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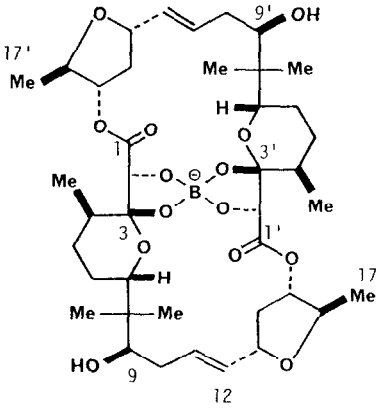
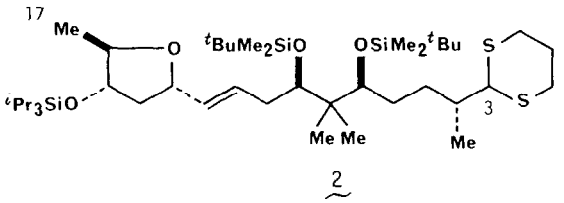
Abstract: The C-12∼C-17 segment 3 of (+)-aplasmomycin (1) was synthesized stereoselectively starting from (-)-malic acid based on the stereoselective ketone reduction.

(+)-Aplasmomycin (1), isolated from a cultured marine-derived strain of Streptomyces griseus, is a novel boron-containing antibiotic having a symmetrical C_2 structure and exhibits activities against Gram-positive bacteria and Plasmodia.[1] Recently, the first total synthesis of (+)-1 has been achieved by Corey and co-workers.[2] We also accomplished the synthesis of 2 corresponding to the C-3∼C-17 segment of 1 based on the stereoselective ketone reduction[3] and the strategy used for 1,3-syn-polyol synthesis.[4] Since 2 has been used as a key intermediate in Corey's synthesis, the present synthesis corresponds to the formal total synthesis of (+)-1. In this paper, synthesis of the C-12∼C-17 segment 3 is described.



Aplasmomycin (1)



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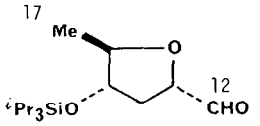
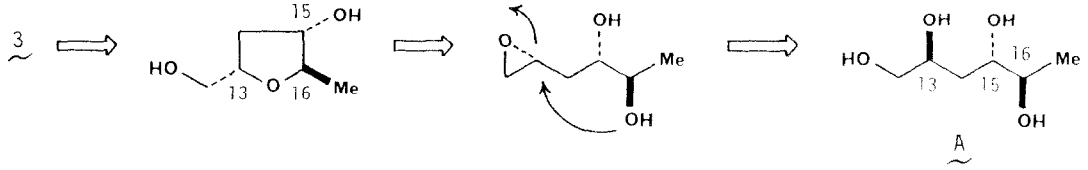
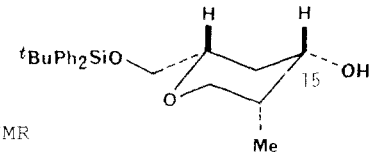


3

Retrosynthetic analysis reveals that tetrol A could be a precursor of 3. (13S)-Hydroxyl group of A can be derived from (S)-(-)-malic acid and 13,15-anti and 15,16-anti stereoselections are expected to be attained by the stereoselective ketone reduction.



Aldehyde 4,[5] prepared from (S)-(-)-malic acid, was subjected to aldol condensation (LDA/EtCOO-i-Pr/THF/-78°) to give a mixture of β-hydroxy ester 5 in 64% yield, which was converted into lactone 6 in 3 steps: 1) deacetonization (c. HCl/aq. MeOH), 2) selective silylation of the primary alcohol (t-$BuPh_2SiCl$/imidazole/DMF), 3) lactonization (CSA/PhH); 62% overall yield. DIBAH reduction of 6 and successive treatment with CSA, $CH(OMe)_3$ in MeOH-CH_2Cl_2 afforded acetal 7. PCC oxidation of 7 followed by NaOMe treatment in THF gave enone 8 in 56% yield (from 6). $Zn(BH_4)_2$ reduction of 8 afforded the desired α-alcohol 9 stereoselectively but the yield was unsatisfactory (65% based on the consumed 8). Alternatively, reduction of 8 with $NaBH_4$-$CeCl_3$[6] in MeOH gave 94% yield of a single α-alcohol 9[7] corresponding to 13,15-anti-diol.[8] The configuration of the C-15 hydroxyl group of 9 was confirmed as follows. Catalytic hydrogenation of 9 over 10% Pd-C in MeOH gave stereoselectively 16α-Me alcohol 10 whose ^1H NMR analysis showed that the C-15 hydroxyl group is in equatorial position ($W_{1/2}$=21.4 Hz; thus, C-15 H, axial).



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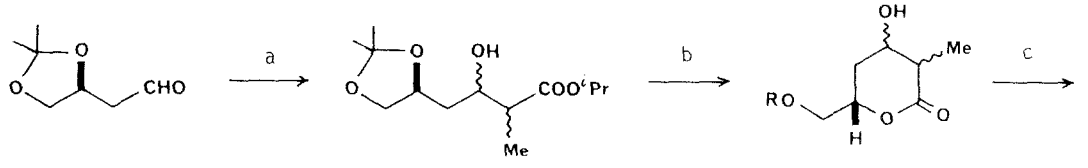
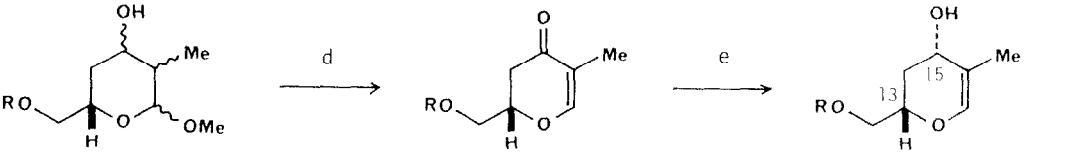


4 5 6: R=$SiPh_2{}^tBu$

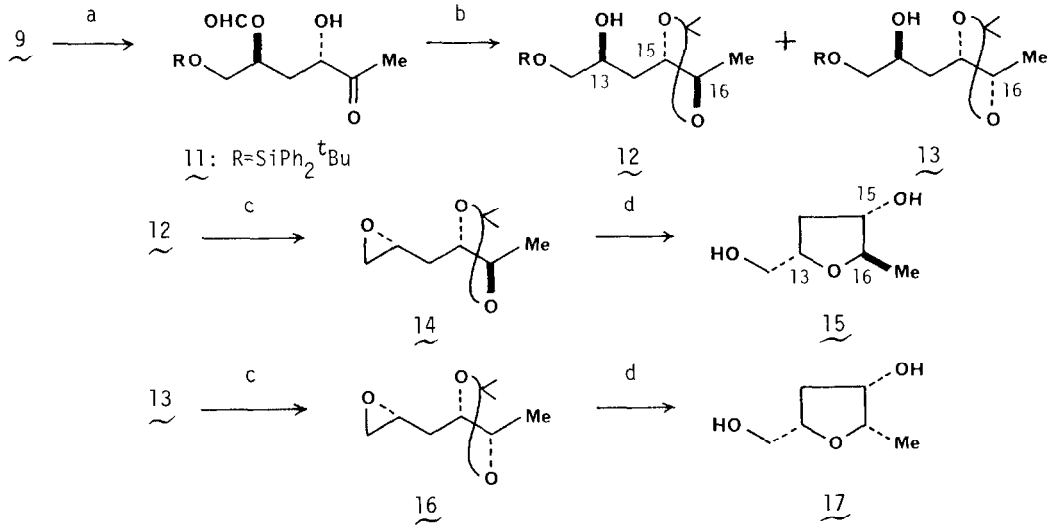


7 8 9

a) LDA/EtCOO-i-Pr/THF/-78°, b) c. HCl/aq. MeOH; t-$BuPh_2SiCl$/imidazole/DMF; CSA/PhH, c) DIBAH/PhMe/-78°; CSA/$CH(OMe)_3$/MeOH/CH_2Cl_2, d) PCC/3A-MS/CH_2Cl_2; NaOMe/THF, e) $NaBH_4$/$CeCl_3 \cdot 7H_2O$/MeOH

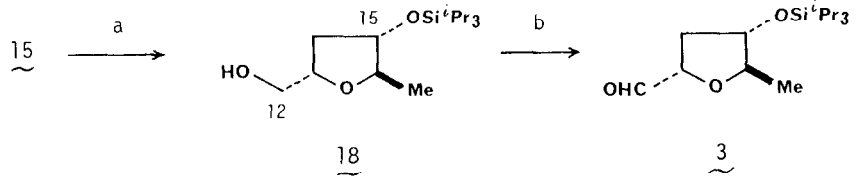
Ozonolysis of 9 afforded acyclic α-hydroxy ketone 11[7] in 98% yield. Reduction of 11 with $Zn(BH_4)_2$ in ether[3] at -78° followed by deformylation

(K_2CO_3/MeOH) and acetonization (acetone/p-TsOH) produced acetonide 12[7] (66% yield from 11) and C-16α epimer 13[7] (18%), which could be separated easily by column chromatography on silica gel. Major isomer 12 was assigned to have the desired 15,16-anti configuration based on the previoulsy reported anti-selective reduction of α-hydroxy ketone with $Zn(BH_4)_2$.[3] Mesylation of 12 with MsCl followed by successive treatment with n-Bu_4NF and NaOMe gave epoxide 14 with inversion of configuration at the C-13 position. On treatment with aq. AcOH, 14 was deprotected and cyclized smoothly to tetrahydrofuran 15[7] in 70% yield (from 12). C-16 epimer 13 was also converted into tetrahydrofuran 17[7]



a) O_3/MeOH/-78°; Me_2S, b) $Zn(BH_4)_2/Et_2O$/-78°; K_2CO_3/MeOH; acetone/p-TsOH, c) MsCl/pyridine; n-Bu_4NF/THF; NaOMe/MeOH, d) 80% aq. AcOH

via epoxide 16 (61% overall yield) in the same manner. C-16 Methyl signal of 15 appeared slightly in higher field [δ 1.12 (d)] than that of 17 [δ 1.29 (d)] which clearly shows that C-15 OH and C-16 Me groups are in trans arrangement. 15,16-anti-Configuration of 12 was thus confirmed. 15 was converted into silyloxy alcohol 18 in 3 steps: 1) benzoylation of the C-12 alcohol (PhCOCl, pyridine), 2) silylation of the C-15 alcohol (i-Pr_3SiCl), 3) cleavage of benzoate (K_2CO_3, MeOH); 73% overall yield. PCC oxidation of 18 afforded the required (+)-aldehyde 3[7] in 92% yield.[9]



a) PhCOCl/pyridine; i-Pr_3SiCl/imidazole/DMF/50-60°; K_2CO_3/MeOH, b) PCC/3A-MS/CH_2Cl_2

Acknowledgement: The authors are grateful to Professor E. J. Corey (Harvard University) for providing the authentic sample of 20 and its ^{1}H NMR data.

References and Notes

1) T. Okazaki, T. Kitahara, and Y. Okami, J. Antibiotics, 28, 176 (1975); H. Nakamura, Y. Iitaka, T. Kitahara, T. Okazaki, and Y. Okami, ibid., 30, 714 (1977).

2) E. J. Corey, B.-C. Pan, D. H. Hua, and D. R. Deardorff, J. Am. Chem. Soc., 104, 6816 (1982); E. J. Corey, D. H. Hua, B.-C. Pan, and S. P. Seitz, ibid., 104, 6818 (1982).

3) T. Nakata, T. Tanaka, and T. Oishi, Tetrahedron Lett., 24, 2653 (1983).

4) T. Nakata, S. Takao, M. Fukui, T. Tanaka, and T. Oishi, Tetrahedron Lett., 24, 3873 (1983).

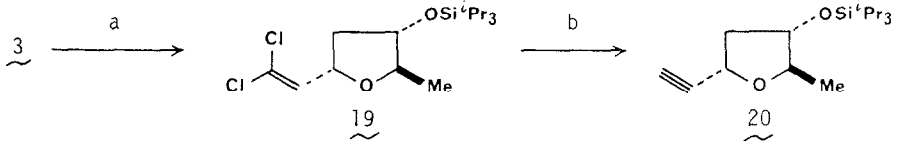
5) S. Hanessian, A. Ugolini, D. Dubé, and A. Glamyan, Can. J. Chem., 62, 2146 (1984).

6) J.-L. Luche, J. Am. Chem. Soc., 100, 2226 (1978).

7) ^{1}H NMR spectra were taken on a JEOL JNM GX-400 instrument in $CDCl_3$. 9: NMR δ 1.63 (t like; Me), 4.21 (br; 15-H), 6.17 (br s; C=CH), $[\alpha]_D^{24}$ +22.3° (c=1.06, $CHCl_3$). 11: mp 60-62°, NMR δ 2.22 (s; COMe), 4.16 (ddd, J=10.7, 4.9, 2.4 Hz; 15-H), 8.09 (s; OCHO). 12: NMR δ 1.12 (d; J=6.4 Hz; Me), 4.27 (m; 16-H), 4.34 (ddd, J=9.8, 5.9, 3.7 Hz; 15-H). 13: NMR δ 1.25 (d; J=5.9 Hz; Me), 3.71 (dq, J=8.5, 5.9 Hz; 16-H), 3.76 (td, J=8.5, 2.9 Hz; 15-H). 15: NMR δ 3.99 (m; 15-H), 4.14 (qd, J=6.6, 1.0 Hz; 16-H), 4.29 (m; 13-H), $[\alpha]_D^{26}$ +45.7° (c=0.84, $CHCl_3$). 17: mp 61-63°, NMR δ 3.85 (qd, J=6.1, 2.7 Hz; 16-H), 3.99 (m; 15-H), 4.18 (dq like; 13-H). 3: NMR δ 1.16 (d, J=6.4 Hz; Me), 4.11 (m; 15-H), 4.22 (q like; 16-H), 4.37 (m, 13-H), 9.75 (br; CHO), $[\alpha]_D^{20}$ +17.0° (c=1.0, $CHCl_3$). 20: NMR δ 1.25 (d, J=5.9 Hz; Me), 2.47 (d, J=2.2 HZ; 11-H), 4.71 (ddd, J=7.8, 5.6, 2.2 Hz; 13-H), $[\alpha]_D^{26}$ +44.0° (c=1.87, $CHCl_3$).

8) cf. S. J. Danishefsky and C. J. Maring, J. Am. Chem. Soc., 107, 1269 (1985); T. Nakata, S. Nagao, and T. Oishi, Tetrahedron Lett., 26, 75 (1985).

9) The stereostructure of 3 was further confirmed by the conversion into Corey's intermediate 20[2] as shown below. ^{1}H NMR data of the synthetic 20[7] were identical with those of authentic 20.



a) $BrCCl_3/P(NMe_2)_3/CH_2Cl_2$, b) n-BuLi/THF

(Received in Japan 31 July 1986)