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SYNTHETIC STUDIES ON (+)-APLASMOMYCIN. 2. STEREOSELECTIVE SYNTHESIS OF COREY'S KEY INTERMEDIATE, A FORMAL TOTAL SYNTHESIS

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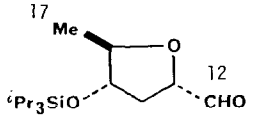
Abstract: The C-3 ~ C-11 segment 2 of (+)-aplasmomycin was synthesized stereoselectively starting from (+)-pantolactone (4) and the C-3 ~ C-17 segment 3 was synthesized via coupling of 1 and 2.

Having achieved the stereoselective synthesis of the C-12 ~ C-17 segment 1 of (+)-aplasmomycin,[1] we then focused our attention on the synthesis of the C-3 ~ C-11 segment 2, a counterpart leading to a key intermediate 3 in Corey's total synthesis of (+)-aplasmomycin.[2] The present paper deals with the stereoselective synthesis of 2 based on the synthetic method for 1,3-syn-polyol[3] and coupling of 2 and the previously synthesized 1[1] producing 3.



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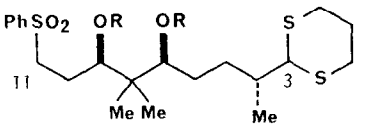
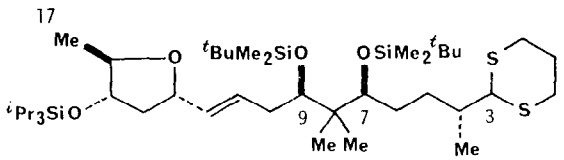


2: R=$SiMe_2{}^{t}Bu$



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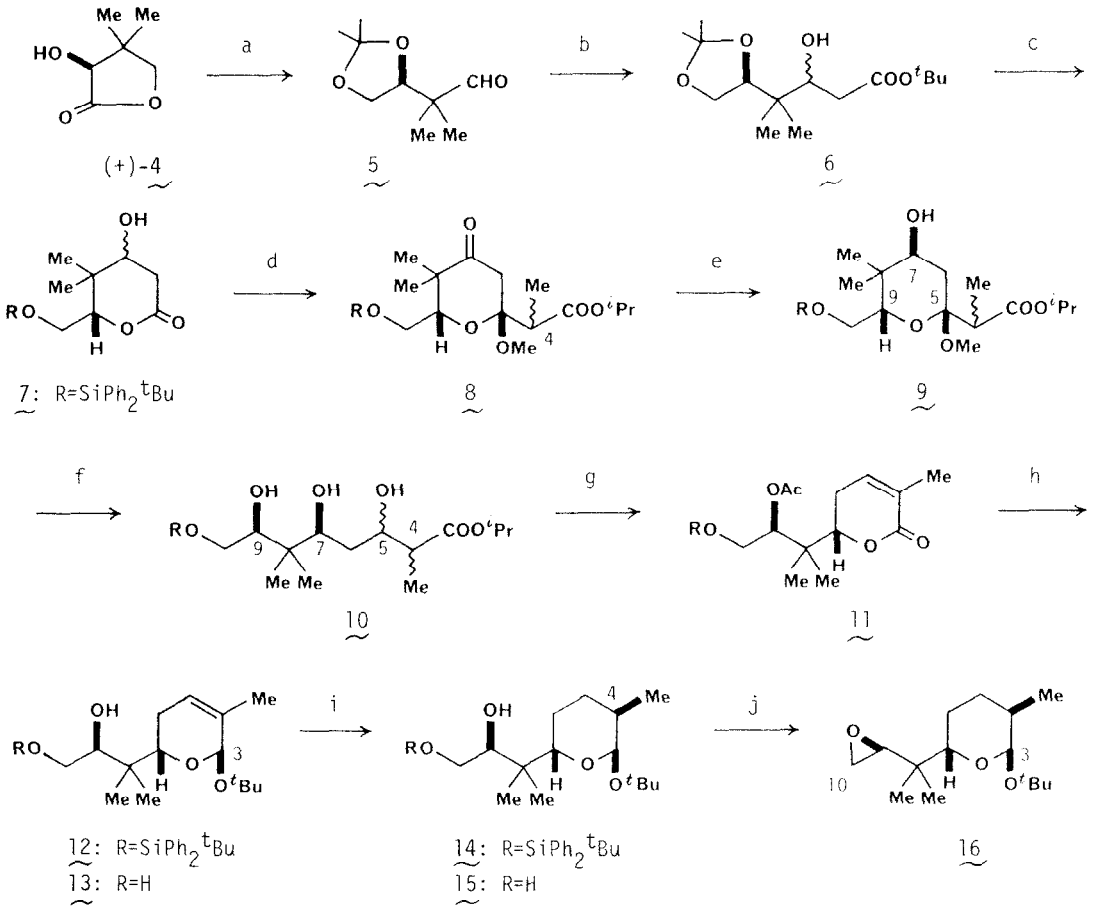
Commercially available (S)-(+)-pantolactone[4] (4) was chosen as a suitable starting material, since it contains requisite functionalities at the desired positions. Lactone 4 was converted into aldehyde 5 (78% overall yield) following essentially the known procedures ($LiAlH_4$ reduction, acetonization, and PCC oxidation).[5] Aldol condensation of 5 with lithium enolate of t-butyl acetate gave a mixture of β-hydroxy ester 6 which was subjected to deacetonization-lactonization (c. HCl/aq. MeOH) and silylation (t-$BuPh_2SiCl$/imidazole/DMF) providing lactone 7 in 75% yield (from 5). After protection of the hydroxyl group as the ethoxyethyl(EE) ether, 7 was converted into ketone 8

(an epimeric mixture at the C-4 position) in 3 steps: 1) introduction of i-propyl propionate (LDA/EtCOO-i-Pr), 2) methoxylation of the resulting hemiacetal and simultaneous deprotection of EE group (CSA/MeOH/CH_2Cl_2), 3) oxidation (PCC/3A-molecular sieves/CH_2Cl_2). Reduction of 8 with L-Selectride in THF[3] at -78° exclusively gave 7S(axial)-alcohol 9[6] corresponding to 7,9-syn-diol in 87% yield (60% from 7). The configuration of the C-7 hydroxyl group of 9 was assigned as axial based on small coupling constants (J=2.7, 3.7 Hz) between C-6α,β H and C-7 H. Hydrolysis of 9 with 1N HCl and successive $NaBH_4$ reduction afforded acyclic triol 10 (66%). Lactonization of 10 with CSA in benzene, acetylation of the remaining alcohols with Ac_2O followed by DBU

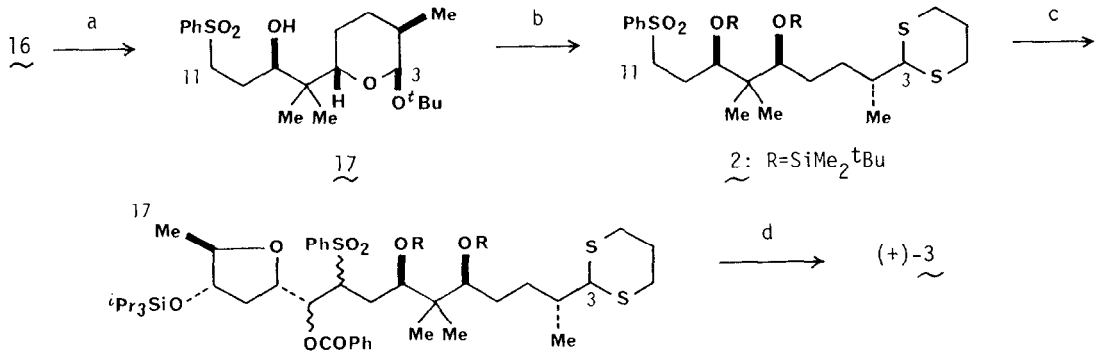


a) $LiAlH_4$/THF; acetone/p-TsOH; PCC/3A-MS/CH_2Cl_2, b) LDA/MeCOO-t-Bu/THF/-78°, c) c. HCl/aq. MeOH; t-$BuPh_2SiCl$/imidazole/DMF, d) CH_2=CHOEt/PPTS/CH_2Cl_2; LDA/EtCOO-i-Pr/THF/-78°; CSA/MeOH/CH_2Cl_2; PCC/3A-MS/CH_2Cl_2, e) L-Selectride/THF/-78°, f) 1N-HCl/THF; $NaBH_4$/MeOH, g) CSA/PhH/30°; Ac_2O/DMAP/pyridine; DBU/PhH, h) DIBAH/PhMe/-78°; PPTS/t-BuOH/CH_2Cl_2; n-Bu_4NF/THF, i) H_2 (1 atm)/5% Rh-Al_2O_3/THF; t-$BuPh_2SiCl$/imidazole/DMF; n-Bu_4NF/THF, j) KH or NaH/TsCl/DMF/THF

treatment afforded α,β-unsaturated lactone 11 (72%). Reduction of 11 with DIBAH and successive treatment with PPTS in t-BuOH-CH_2Cl_2 gave 3β-t-butoxy acetal 12 (75%) which was desilylated with n-Bu_4NF giving diol 13 (94%). Catalytic hydrogenation of 13 over 5% Rh-Al_2O_3 in THF proceeded stereoselectively from the less hindered α-side.[7] In order to facilitate the removal of the contaminated C-4α epimer, the reduction product was again silylated with t-$BuPh_2SiCl$ and subjected to column chromatography on silica gel giving 14[8] (84% from 13) along with the C-4α epimer (6.6%). Desilylation of 14 with n-Bu_4NF gave diol 15[6] (97%) which on treatment with KH (2.5 equiv) or NaH and TsCl was converted effectively into epoxide 16 in 91 % yield.

The additional carbon one-unit corresponding to C-11 position should be introduced to 16. The use of $PhSO_2Me$ for this purpose was presumed to be advantageous since the reaction product possessing active methylene group would be used directly to the condensation with aldehyde 1. However, attack of $PhSO_2CH_2Li$ (2 equiv, n-BuLi/HMPA/THF) to the hindered model epoxide[9] did not proceed smoothly. After several attempts, addition of $BF_3 \cdot Et_2O$[10] (2 equiv) to the reaction mixture was found to increase the yield dramatically. Thus, using this procedure, 17[6] was obtained from 16 in excellent yield. Treatment of 17 with 1,3-propanedithiol and $BF_3 \cdot Et_2O$ and successive disilylation with t-$BuMe_2SiOTf$ gave thioacetal 2[6] (82% from 16). Addition of 1.4 equiv of aldehyde 1 to 2 (n-BuLi/HMPA/THF) followed by benzoylation afforded 18. Conversion of β-benzoyloxy sulfone moiety in 18 into the required E-olefin was successfully achieved by 6% Na-Hg treatment (46% yield from 2) producing (+)-3, the C-3 ~ C-17 segment. 400 MHz ^1H NMR spectral data of (+)-3 were in good accord with those reported by Corey.[2]

As 3 has already been converted into (+)-aplasmomycin,[2] the present synthesis of (+)-3 represents a formal total synthesis.



a) $PhSO_2Me$/n-BuLi/HMPA/$BF_3 \cdot Et_2O$/THF/-78°, b) $HS(CH_2)_3SH/BF_3 \cdot Et_2O/CH_2Cl_2$/0°; TBDMSOTf/2,6-lutidine/CH_2Cl_2, c) n-BuLi/HMPA/THF/-78°; addition of 1 in THF/-78°; PhCOCl/DMAP/pyridine/ 50-60°, d) 6% Na-Hg/THF/MeOH/-20°

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References and Notes

1) T. Nakata, K. Saito, and T. Oishi, Tetrahedron Lett., preceding paper.

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

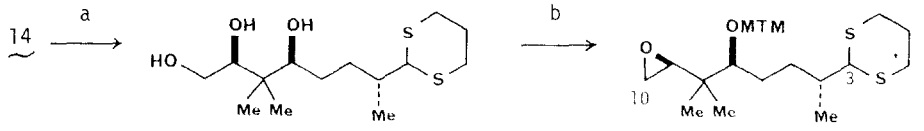
4) Purchased from Tokyo Kasei Kogyo Co., Ltd.

5) T. Matsuo, K. Mori, and M. Matsui, Tetrahedron Lett., 1979 (1976); R. E. Dolle and K. C. Nicolaou, J. Am. Chem. Soc., 107, 1691 (1935).

6) ^{1}H NMR spectra were taken on a JEOL JNM GX-400 instrument in $CDCl_3$. 9: NMR δ 2.99 (q, J=7.3 Hz; 4-H), 3.06 (q, J=7.1 Hz; 4-H), 3.30, 3.34 (each s; 5-OMe), 3.32 (m; 7-H). 15: mp 82-84°, NMR δ 0.79 (d, J=6.6 Hz; 4-Me), 4.91 (d, J=3.2 Hz; 3-H), $[\alpha]_D^{20}$ +99.2° (c=2.0, $CHCl_3$). 17: mp 94-95°, NMR δ 0.77 (d, J=6.6 Hz; 4-Me), 3.75 (dd, J=11.0, 2.4 Hz; 7-H), 4.86 (d, J=2.9 Hz; 3-H), 2: NMR δ 3.36 (dd, J=5.9, 3.9 Hz; 7-H), 3.71 (dd, J=6.6, 3.9 Hz; 9-H), 4.10 (d, J=4.2 Hz; 3-H). 3: NMR δ 3.53 (dd, J=6.6, 3.2 Hz; 7-H), 3.68 (dd, J=6.4, 3.9 Hz; 9-H), 3.89 (m; 16-H), 4.03 (m; 15-H), 4.11 (d, J=4.2 Hz; 3-H), 4.42 (q, J=7.1 Hz; 13-H), 5.63 (dd, J=15.4, 7.1 Hz; 12-H), 5.67 (ddd, J=15.4, 7.6, 4.9 Hz; 11-H), $[\alpha]_D^{20}$ +7.1 (c=0.96, $CHCl_3$). 20: NMR δ 1.10 (d, J=6.8 Hz; Me), 2.99 (dd, J=4.2, 2.9 Hz; 9-H), 3.28 (dd, J=7.3, 3.4 Hz; 7-H), 4.15 (d, J=3.9 Hz; 3-H), $[\alpha]_D^{25}$ +30.0° (c=0.5, $CHCl_3$).

7) cf. R. H. Schlessinger and M. A. Poss, J. Am. Chem. Soc., 104, 357 (1982).

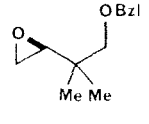
8) The stereostructure of 14 was further confirmed by the conversion into Corey's intermediate 20[2] in 5 steps as shown below. ^{1}H NMR data of the synthetic 20[6] were identical with those of the authentic 20.



a) $HS(CH_2)_3SH/BF_3 \cdot Et_2O$, b) p-TsOH/acetone; $DMSO/Ac_2O/AcOH$; aq. AcOH; NaH/TsCl/DMF

9) The epoxide i was used in the model experiment.

10) cf. M. Yamaguchi and I. Hirao, Tetrahedron Lett., 24, 391 (1983); M. J. Eis, J. E. Wrobel, and B. Ganem, J. Am. Chem. Soc., 106, 3693 (1984); B. Achmatowicz, E. Baranowska, A. R. Daniewski, J. Pankowski, and J. Wicha, Tetrahedron Lett., 26, 5597 (1985).



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