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STEREOSELECTIVE SYNTHESIS OF (±)-BLASTMYCINONE AND FORMAL TOTAL SYNTHESIS OF ANTIMYCIN A_3

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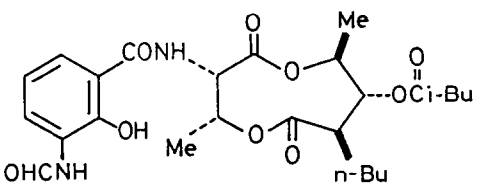
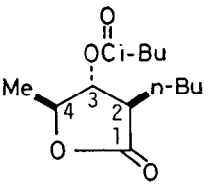
Summary: (±)-Blastmycinone (2) and the key intermediate 20 for the total synthesis of antimycin A_3 (1) have been synthesized based on the stereoselective reduction of β-keto ester and α-hydroxy ketone by means of $Zn(BH_4)_2$.

Antimycin A_3 (Blastmycin) (1),[1] produced by a number of Streptomyces species, is one of the major component of antifungal antibiotic antimycin A complex. The total synthesis of 1 has been accomplished in both racemic and optically active forms by M. Kinoshita et al.,[2] and blastmycinone (2),[1c,d] a degradation product of 1, has also been synthesized by several groups.[3] Antimycin A_3 (1) has a unique nine-membered dilactone ring involving 2,3-erythro-3,4-erythro-2-n-butyl-3,4-dihydroxy[4] and L-threonine moieties.

We previously reported an efficient method for the stereoselective syntheses of erythro-α-alkyl-β-hydroxy esters from β-keto esters by $Zn(BH_4)_2$ reduction,[5] and described the stereoselective syntheses of erythro-diols from α-hydroxy ketones by $Zn(BH_4)_2$ reduction[6] and threo-diols from its α-silyloxy derivatives by Vitride reduction.[6] Based on these stereoselective reductions, we succeeded in the stereoselective syntheses of (±)-blastmycinone (2) and the optically active key intermediate 20 for the total synthesis of antimycin A_3 (1) by M. Kinoshita et al..[7]



Antimycin A_3 (1)

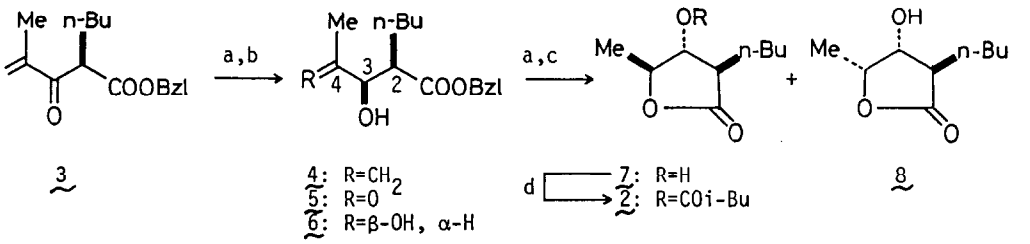


Blastmycinone (2)

Stereoselective Synthesis of (±)-Blastmycinone (2)

The β-keto ester 3[8,9] was reduced with $Zn(BH_4)_2$ in ether at 0°C to produce the desired erythro-2-n-butyl-3-hydroxy ester 4 [NMR ($CDCl_3$): δ 4.28 (dd, J=5.6, 3.4 Hz; C-3 H)] in 25 : 1 stereoselectivity (79% combined yield).[5] Ozonolysis of 4 followed by dimethyl sulfide workup afforded the α-hydroxy ketone 5 [NMR ($CDCl_3$): δ 2.23 (s; Ac), 4.47 (dd, J=4.6, 3.7 Hz; C-3 H)] in 84% yield. $Zn(BH_4)_2$ reduction[6] and the successive catalytic hydrogenolysis of 5 yielded two isomeric lactones 7 and 8 in a ratio of 7.5 : 1 (98% combined yield). The major lactone 7, mp

52.5-54.5°C, crystallized from n-hexane-ether, was assigned as 7 having 3,4-erythro structure.[6] The erythro-selectivity (7.5 : 1) in the reduction of 5 was much lower than that (96 : 4) observed in the reduction of the related compound.[10] The result may be attributable to the unfavourable coordination of the ester group to $Zn(BH_4)_2$, which should prevent the formation of the chelate involving the hydroxyl and keto groups necessary to yield the desired erythro-diol 6. Finally, treatment of 7 with isovaleryl chloride in pyridine afforded (±)-blastmycinone (2) in 97% yield. The NMR spectrum of the synthetic 2 was identical with that of (+)-blastmycinone.[3b]

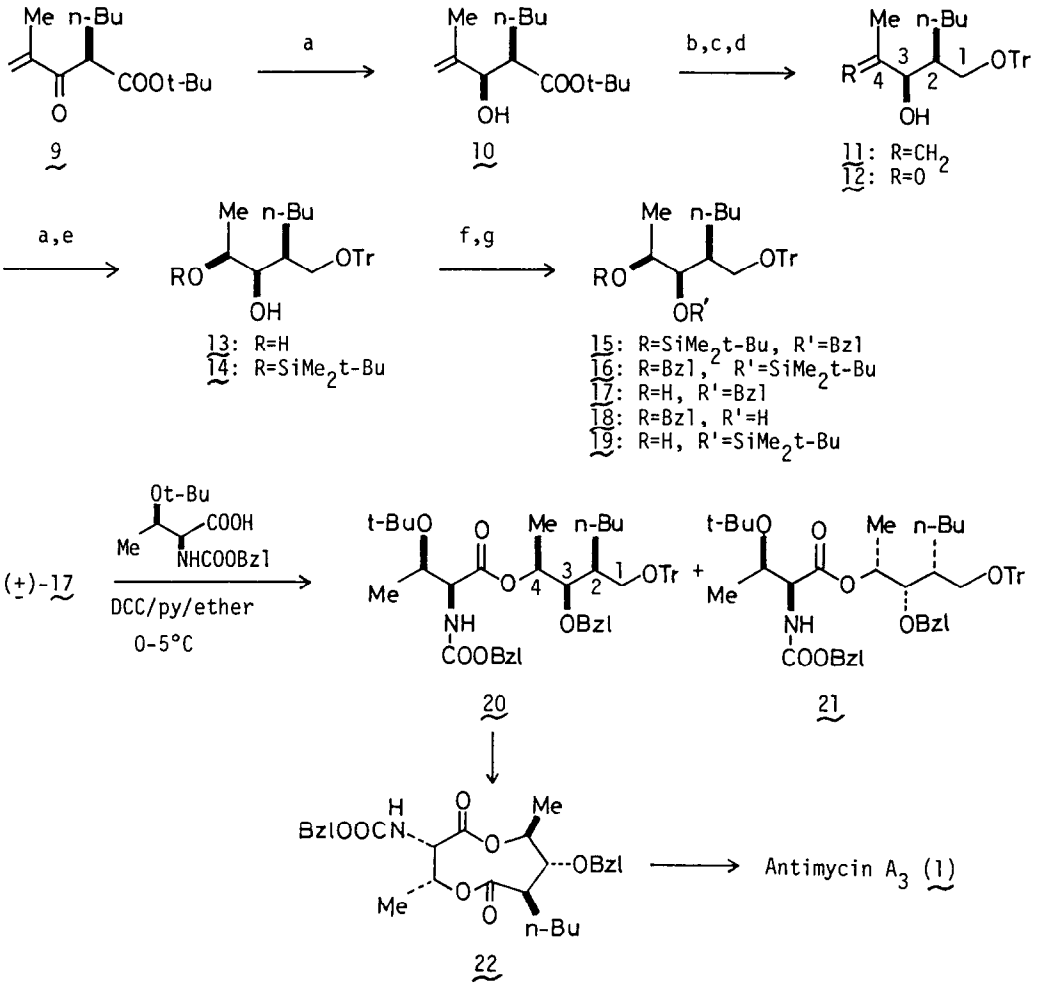


a: $Zn(BH_4)_2$/ether/0°C, b: O_3/MeOH/-78°C; Me_2S/-78°C→rt, c: H_2/10% Pd-C/c.H_2SO_4/MeOH/rt, d: i-BuCOCl/py/rt

Stereoselective Synthesis of the Key Intermediate 20

Reduction of the β-keto ester 9[8] with $Zn(BH_4)_2$ gave the erythro-hydroxy ester 10 [NMR ($CDCl_3$): δ 4.22 (dd, J=5.8, 3.2 Hz; C-3 H)] in 25 : 1 selectivity (70% combined yield).[5] At this stage, the ester group of 10 was converted to the trityloxymethyl group having almost no coordinating ability to $Zn(BH_4)_2$ by $LiAlH_4$ reduction followed by TrCl treatment (yield of 11, quantitative). The 1-trityloxy-3-ol 11 was then ozonolyzed to the α-hydroxy ketone 12 [IR (CCl_4): 3500, 1710 cm^{-1}; NMR ($CDCl_3$): δ 2.17 (s; Ac), 4.57 (dd, J=4.6, 2.0 Hz; C-3 H)] in 89% yield, which was subjected to $Zn(BH_4)_2$ reduction[6] to yield the erythro-diol 13 [mp 119-120°C; NMR ($CDCl_3$): δ 3.55 (m; C-3 H), 3.75 (m; C-4 H)] in 16 : 1 selectivity (96% combined yield). The erythro-selectivity (16 : 1) was much higher than the previous case (5→6; 7.5 : 1), as expected. Protection of 13 with t-butyldimethylsilyl chloride gave the 4-silyloxy-3-ol 14 [NMR ($CDCl_3$): δ 3.81 (quintet, J=5.9 Hz; C-4 H); 87% yield] regioselectively. Benzylation of 14 with KH and $PhCH_2Br$ in THF, followed by desilylation with n-Bu_4NF provided the 3-benzyloxy-4-ol 17[11] [mp 91-92°C; NMR ($CDCl_3$): δ 3.59 (dd, J=5.2, 4.5 Hz; C-3 H); 91% yield] along with the 4-benzyloxy-3-ol 18 (6% yield) via 15 and 16. Migration of the silyl group was found to take place at this benzylation stage. Interestingly, benzylation of the 3-silyloxy isomer 19 also produced a mixture of 15 and 16 in a ratio of 10 : 1. Finally, according to the procedure of M. Kinoshita,[2e] 17 was condensed with N-benzyloxycarbonyl-O-t-butyl-L-threonine in the presence of DCC in pyridine-ether to give a mixture of two optically active diastereomers 20[12] and 21[13], which was separated by Lobar column (ether : n-hexane = 1 : 3) in 41% and 37% yields, respectively. Less polar product 20 was identified as the compound 20 by comparison of the NMR spectrum and optical rotation with those of the authentic compound.[2e] Since 20 has been successfully converted to antimycin A_3 in nine steps via dilactone 22,[2e] the present synthesis of 20 represents a formal total synthesis of the optically active antibiotic (1).

In conclusion, (±)-blastmycinone (2) and the key intermediate 20 for the total synthesis of antimycin A_3 (1) were effectively synthesized starting from the β-keto esters based on the stereoselective ketone reduction by means of $Zn(BH_4)_2$ developed in this laboratory. The present method would be applicable to the synthesis of other family of antimycin antibiotics.



a: $Zn(BH_4)_2$/ether/0°C, b: $LiAlH_4$/ether/rt, c: TrCl/py/rt, d: O_3/MeOH/-78°C; Me_2S/-78°C→rt, e: t-BuMe_2SiCl/imidazole/DMF/rt, f: KH/$PhCH_2Br$/THF/0°C, g: n-$Bu_4NF \cdot 3H_2O$/THF/rt

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References and Notes

1. a) E. E. Van Tamelen, M. E. Dickie, M. E. Loomans, R. S. Dewey, and F. M. Strong, J. Am. Chem. Soc., 83, 1639 (1961); b) A. J. Birch, D. W. Cameron, Y. Harada, and R. W. Rickards, J. Chem. Soc., 889 (1961); c) H. Yonehara and S. Takeuchi, J. Antibiotics, Ser. A, 11, 254 (1958); d) M. Kinoshita, S. Aburaki, and S. Umezawa, J. Antibiotics, 25, 373 (1972).
2. For racemic form: a) M. Kinoshita, M. Wada, and S. Umezawa, J. Antibiotics, 22, 580 (1969). For optically active form: b) M. Kinoshita, M. Wada, S. Aburaki, and S. Umezawa, ibid., 24, 724 (1971); c) M. Kinoshita, S. Aburaki, M. Wada, and S. Umezawa, Bull. Chem. Soc. Japan, 46, 1279 (1973); d) S. Aburaki and M. Kinoshita, Chem. Lett., 701 (1976); e) S. Aburaki and M. Kinoshita, Bull. Chem. Soc. Japan, 52, 198 (1979).
3. a) H. Koyama, K. Kogure, K. Mori, and M. Matsui, Agr. Biol. Chem., 37, 915 (1973); b) S. Aburaki, N. Konishi, and M. Kinoshita, Bull. Chem. Soc. Japan, 48, 1254 (1975); c) C. H. Heathcock, M. C. Pirrung, J. Lampe, C. T. Buse, and S. D. Young, J. Org. Chem., 46, 2290 (1981); d) See also references 2a, 2b, and 2c.
4. The stereostructural nomenclature (erythro and threo) is based on Heathcock's convention; C. H. Heathcock, C. T. Buse, W. A. Kleschick, M. C. Pirrung, J. E. Sohn, and J. Lampe, J. Org. Chem., 45, 1066 (1980).
5. T. Nakata and T. Oishi, Tetrahedron Lett., 21, 1641 (1980).
6. T. Nakata, T. Tanaka, and T. Oishi, preceding paper.
7. This work was presented at the 102th Annual Meeting of the Pharmaceutical Society of Japan at Osaka, April, 1982. Abstracts of Papers, p. 405. This work was also presented at the 41th Symposium on the Synthetic Organic Chemistry at Tokyo, June, 1982. Proceeding, p. 29.
8. The β-keto ester 3 and 9 were easily prepared from methacrolein and α-bromo esters by the Reformatsky reaction followed by Swern's oxidation.[14]
9. Although the compounds 3~19 are racemic, only one of the enantiomers was depicted.
10. See entry 7 in the preceding paper.
11. The 3-benzyloxy-4-ol 17 can be synthesized in three steps from 11 [KH, $PhCH_2Br$ in THF, O_3 in MeOH, and $Zn(BH_4)_2$ in ether; ca. 56% overall yield]. However, the stereoselectivity in the $Zn(BH_4)_2$ reduction was 10 : 1, and acetylation and deacetylation of the crude 17 were needed for the purification.
12. NMR (400 MHz, $CDCl_3$): δ 0.81 (t, J=7.1 Hz; Me), 1.06 (s; t-Bu), 1.20 (d, J=6.1 Hz; Me of threonine), 1.27 (d, J=6.4 Hz; C-4 Me), 3.04 (dd, J=9.5, 7.3 Hz; C-1 Ha), 3.14 (dd, J=9.5, 3.9 Hz; C-1 Hb), 3.67 (dd, J=6.1, 2.9 Hz; C-3 H), 4.37, 4.68 (ABq, J=11.2 Hz; CH_2Ph), 4.92, 5.12 (ABq, J=12.2 Hz; $COOCH_2Ph$), 5.19 (dq, J=6.4, 2.9 Hz; C-4 H), 5.59 (d, J=9.3 Hz; NH); $[\alpha]_D^{22}$ +8.8°, $[\alpha]_{365}^{20}$ +24° (c 0.40, $CHCl_3$).
13. NMR (400 MHz, $CDCl_3$): δ 0.80 (t, J=7.1 Hz; Me), 1.09 (s; t-Bu), 1.21 (d, J=6.1 Hz; Me of threonine), 1.25 (d, J=6.4 Hz; C-4 Me), 3.06 (dd, J=9.8, 7.3 Hz; C-1 Ha), 3.15 (dd, J=9.8, 4.2 Hz; C-1 Hb), 3.69 (dd, J=6.1, 3.7 Hz; C-3 H), 4.40, 4.68 (ABq, J=11.2 Hz; CH_2Ph), 5.05, 5.14 (ABq, J=12.2 Hz; $COOCH_2Ph$), 5.21 (dq, J=6.4, 3.7 Hz; C-4 H), 5.56 (d, J=9.5 Hz; NH); $[\alpha]_D^{22}$ -15.7°, $[\alpha]_{365}^{20}$ -46° (c 0.40, $CHCl_3$).
14. A. J. Mancuso, S.-L. Huang, and D. Swern, J. Org. Chem., 43, 2480 (1978).

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