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A Formal Synthesis of Aplasmomycin. Assembly of the C3-C17 Segment Based on Remote Controlled Asymmetric Reductions

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The C3-C17 segment of a boron containing ionophoric antibiotic aplasmomycin (1), the key intermediate in Corey's total synthesis of 1, was stereoselectively synthesized in an optically active form through remote controlled asymmetric reductions.

Aplasmomycin (1), a boron containing ionophoric antibiotic from Streptomyces griseus, inhibits Gram-positive bacteria in virto and also Plasmodium berghei in vivo.¹⁾ Its structure had been determined by an X-ray crystallographic study as a C_2 -symmetric diolide composed of two identical subunits with a borate bridge spanning the macrocycle.²⁾ The unique structure and biological activity of 1 distinguish this molecule as a very interesting target for synthesis and three independent total syntheses of 1 have been reported.³⁾ In this communication we would like to report a formal synthesis of 1. This synthesis involved stereoselective construction of the two segments, (+)-aldehyde 3 (C12-C17) and (+)-dithiane 4 (C3-C11), based on remote controlled asymmetric reductions⁴⁾ as key steps and connection of them through the trans-double bond to elaborate the (+)-dithiane 2 (C3-C17), the key intermediate in Corey's total synthesis of 1.^{3a)}



 $(-)-(S)-2-Hydroxy-4-butanolide (5)^{5}$ was selected as the starting material for the synthesis of the C12-C17 segment. According to the Still's procedure,⁵ sequential protection of the C-15 hydroxyl group as MEM ether, reaction with MeLi, and protection of the primary hydroxyl group as benzyloxymethyl ether converted 5

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a) MEMC1, ⁱPr₂NEt, rt b) MeLi, THF, -78 °C c) PhCH₂OCH₂Cl, ⁱPr₂NEt, rt d) Zn(BH₄)₂, ether, -78 °C e) TBDMSC1, ImH, DMF, 90 °C f) Li, liq NH₃, -78 °C g) CrO₃ · 2Py, CH₂Cl₂, rt h) PhCH₂OCH₂Li, THF, -78 °C i) LiAlH(O^tBu)₃, ether, -123 °C j) 1) MeLi, ether, rt 2) TsCl, rt k) ⁿBu₄N · F, THF, rt 1) 3N-HCl, MeOH, reflux m) TIPSC1, DMAP, CH₂Cl₂, rt n) Na, liq NH₃, -78 °C o) 1) (COCl)₂, DMSO, CH₂Cl₂, -60 °C 2) Et₃N, 0 °C.

into the (-)-methylketone 6 in 77% overall yield. The desired (+)-anti-alcohol 7 was obtained selectively by $\text{Zn}(\text{BH}_4)_2$ -reduction (7:16-epi-7 = 16:1)⁶) in 99% yield. After protection of the C-16 hydroxyl group as TBDMS ether, reductive cleavage of the benzyloxymethyl group followed by Collins oxidation gave the (-)-aldehyde 8 in 73% overall yield.⁷) Treatment with PhCH₂OCH₂Li⁸) and successive Collins oxidation converted 8 into the (-)- β -benzyloxyketone 9 in 71% overall yield.

As described previously,⁴⁾ 1,3-asymmetric induction was anticipated to occur selectively in hydride reduction of the β -alkoxyketones to afford the corresponding *syn*-alcohols as the major epimers. As expected, in LiAlH(O^tBu)₃-reduction (ether, -78 °C) of 9 the desired (-)-*syn*-alcohol 10 was obtained predominantly (10:13-*epi*-10 = 5:1). Lowering the reaction temperature rose selectivity remarkably. Ultimately, at -123 °C, the highest degree of 1,3-asymmetric induction was obtained affording 10 and 13-*epi*-10 in a ratio of 10:1 and in 98% yield.

After tosylation of the C-13 hydroxyl group of 10, desilylation with ${}^{n}\text{Bu}_{4}\text{N}\cdot\text{F}$ resulted in simultaneous tetrahydrofuran ring formation. Subsequent cleavage of the MEM ether gave the (+)-tetrahydrofuran 11 in 64% overall yield.⁷⁾ Successive protection of the C-15 hydroxyl group as TIPS ether, cleavage of the benzyl ether, and Swern oxidation of the alcohol 12 produced 3,⁹⁾ in 68% overall yield.

It had been found previously that high 1,5-asymmetric induction took place in $LiAlH_4$ -reduction of the C₂-symmetric (+)-acetalketone 13 in the presence of LiBr [ether-PhMe (1:1), -123 °C], giving the (+)-(R)-alcohol 14 in 98% e.e. (in 100 mg scale with vigorous stirring).⁴⁾ Thus, for the synthesis of the C3-C11 segment, the (+)- β , γ -unsaturated ketone 15¹⁰) was employed. Reduction of 15 in 100 mg scale gave almost the same results as 13. However, in multigram scale, e.e. value fell by lowering the reaction temperature below -100 °C, because effective vigorous stirring was difficult at this temperature. Carrying out the reduction at -78 °C with vigorous stirring, 1,5-asymmetric induction occurred in 86% e.e. even in multigram scale to yield the (+)-(R)-alcohol 16 in 97% yield.

The $(+)-\beta$ -benzyloxyketone **17** was derived from **16** (86% e.e.) in 43% overall yield by (1) protection of the C-9 hydroxyl group as benzyl ether, (2) Lemieux-Johnson oxidation of the double bond, (3) reduction of the product aldehyde, (4)



a) LiAlH₄, LiBr, ether-PhMe (1:1), -78 °C b) PhCH₂Cl, ^tAmONa, DMSO, rt c) $0sO_4$, $NaIO_4$, ether-H₂O, rt d) NaBH₄, EtOH, O °C e) 3N-HCl, Me₂CO, reflux f) CH_2 =CHCH₂MgBr, ether, rt g) Jones reagent, Me₂CO, O °C h) LiAlH₄, ether-THF (9:1), -123 °C i) (EtCO)₂O, DMAP, Py, rt j) TsCl, DMAP, Et₃N, rt k) KI, DMSO, rt 1) LDA, THF, -78 °C m) MeOK, MeOH, rt n) DIBAL, PhMe, -78 °C o) CSA, MeOH, rt p) Na, liq NH₃, -78 °C q) TsCl, Et₃N, rt r) PhSLi, THF, rt s) TBDMSOTf, 2,6-Lu, CH₂Cl₂, rt t) mCPBA, CH₂Cl₂-sat NaHCO₃, rt, u) HS(CH₂)₃SH, BF₃·OEt₂, CH₂Cl₂, 0 °C, v) TBDMSOTf, 2,6-Lu, CH₂Cl₂, -20 °C.

protection of the primary hydroxyl group as benzyl ether, (5) removal of the chiral source, (6) Grignard reaction with $CH_2=CHCH_2MgBr$, and (7) Jones oxidation.

As expected,⁴⁾ 1,3-asymmetric induction took place in $LiAlH_4$ -reduction of 17 (ether, -123 °C) to afford the desired (+)-*syn*-alcohol 18 predominantly (18:7-*epi*-18 = 5:1). Employing ether-THF solvent system selectivity rose remarkably and the highest degree of 1,3-asymmetric induction was obtained in 9:1 ether-THF mixture to give 18 and 7-*epi*-18 in a ratio of 16:1 (-123 °C) and in 97% yield.⁷⁾

The alcohol 18 was converted into the (+)-iodide 19 in 71% overall yield by (1) protection of the C-7 hydroxyl group in a form of propionate, (2) Lemieux-Johnson oxidation of the double bond, (3) reduction of the product aldehyde, (4) tosylation of the primary hydroxyl group, and (5) displacement of the tosylate by iodide. Treatment of 19 with LDA (2 equiv.) effected intramolecular alkylation giving an almost 1:1 mixture of the lactones, 20 and 4-epi-20, in 88% yield. Equilibration of the epimeric mixture with MeOK in MeOH yielded 20 in high selectivity (20:4-epi-20 = 17:1) and in 93% yield.

Reduction of 20 using DIBAL followed by CSA-treatment in MeOH afforded a 2:1 mixture of the readily separable C-3 anomers, (+)-21 and (-)-3-epi-21, in 57 and 30% yield, respectively. Mainly from practical reasons, only 21 was converted into the (+)-sulfone 22 according to the following synthetic scheme. The other anomer was treated with CSA in MeOH (rt) to give an equilibrium mixture (21:3-epi-21 = 1:1). Separation of the anomers by silica gel chromatography gave a 45% yield of 21 and a 46% yield of 3-epi-21, which was recycled.

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Conversion of 21 into 22 was performed in 61% overall yield by the sequence of (1) removal of the benzyl group, (2) selective tosylation of the primary hydroxyl group, (3) treatment with PhSLi, (4) protection of the C-9 hydroxyl group as TBDMS ether, and (5) mCPBA-oxidation. The hexane solution of 22 was seeded by the addition of a few crystals of racemic 22^{11} and the separated racemic crystals were removed. Optically pure 22 was obtained in 65% yield by further recrystallization of enriched 22 from ether-hexane solvent system. After removal of the TBDMS group, dithian formation followed by protection of the two hydroxyl groups as TBDMS ether gave rise to $4, 9^{9}$ in 77% overall yield.

Coupling of (+)-3 and (+)-4 was carried out according to the Nakata-Oishi's procedure.^{3b)} Reaction of 4 with ⁿBuLi (THF, -78 °C) produced the lithiated sulfone, which was coupled with 3 (1.5 equiv., HMPA-THF, -50 °C). Treatment of the adduct with BzCl (Et₃N, rt) and reductive elimination of a isomeric mixture of the β -benzoyloxysulfones by Na-Hg (AcOEt-MeOH, -20 °C) afforded 2, $[\alpha]_D^{20}$ +6.92° (c 1.00, CHCl₃),^{3b)} in 41% overall yield from 4. 400 MHz ¹H NMR spectral data of synthetic 2 were identical with those reported by Nakata and Oishi.^{3b)} Thus, our synthesis of (+)-2 represents a formal synthesis of 1.

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References

- 1) Y. Okami, T. Okazaki, T. Kitahara, and H. Umezawa, J. Antibiot., <u>29</u>, 1019 (1976).
- 2) H. Nakamura, Y. Iitaka, T. Kitahara, T. Okazaki, and Y. Okami, J. Antibiot., <u>30</u>, 714 (1977).
- 3) a) E.J. Corey, B.-C. Pan, D.H. Hus, and D.R. Deardroff, J. Am. Chem. Soc., <u>104</u>, 6816 (1982); E.J. Corey, D.H. Hus, B.-C. Pan, and S.P. Seiz, *ibid.*, <u>104</u>, 6818 (1982); b) T. Nakata, K. Saito, and T. Oishi, *Tetrahedron Lett.*, <u>27</u>, 6341, 6345 (1986); c) J.D. White, T.R. Vedananda, M.-C. Kang, and S.C. Choudhry, J. Am. Chem. Soc., <u>108</u>, 8105 (1986).
- 4) T. Matsumoto, F. Matsuda, K. Hasegawa, and M. Yanagiya, *Tetrahedron*, <u>40</u>, 2337 (1984).
- 5) D.B. Collum, J.H. McDonald, II, and W.C. Still, J. Am. Chem. Soc., <u>102</u>, 2118 (1980).
- 6) T. Nakata, T. Tanaka, and T. Oishi, Tetrahedron Lett., 24, 2653 (1983).
- 7) The minor epimer was separated by silica gel chromatography at this stage.
- 8) W.C. Still, J. Am. Chem. Soc., <u>100</u>, 1481 (1978).
- 9) Optical rotations and ¹H NMR spectral data of synthetic **3** and **4** were identical with those reported by Nakata and Oishi.^{3b)}
- 10) The β_{γ} -unsaturated ketone 15 was prepared in 99% yield by Jones oxidation of a 1:1 mixture of 16 and $epi-16^{4}$ (Me₂CO, 0 °C).
- 11) Racemic 22 was prepared from 2-(2-hydoxy-1,1-dimethyl-4-pentenyl)-1,3dioxolane [T. Matsumoto et al., Tetrahedron Lett., <u>1978</u>, 989] according to the same procedure as that of optically active 22.