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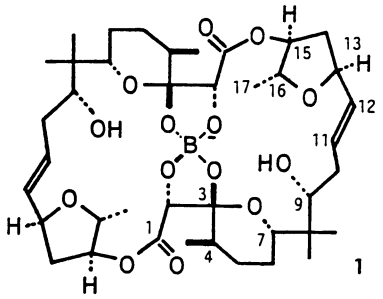
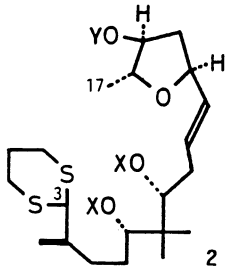
The C3-C17 segment of a boron containing ionophoric antibiotic aplasmomycin (**1**), the key intermediate in Corey's total synthesis of **1**, was stereoselectively synthesized in an optically active form through remote controlled asymmetric reductions.

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 reductions[4] 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]



1



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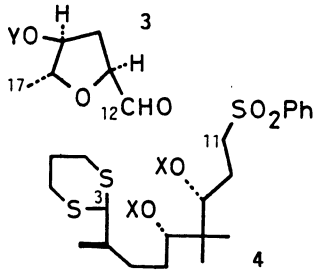

4

X = $SiMe_2{}^tBu$, Y = Si^iPr_3

(-)-(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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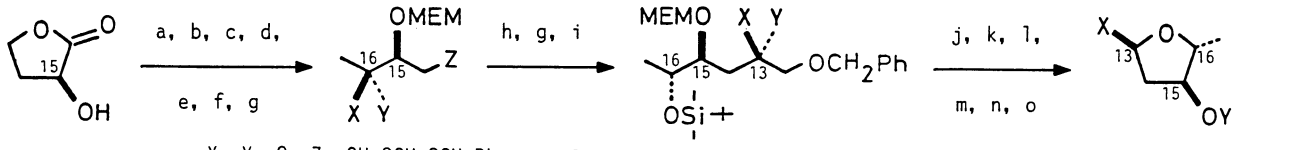


5

X = Y = O, Z = $CH_2OCH_2OCH_2Ph$ **6**
X = H, Y = OH, Z = $CH_2OCH_2OCH_2Ph$ **7**
X = H, Y = $OSiMe_2{}^tBu$, Z = CHO **8**

X = Y = O **9**
X = OH, Y = H **10**

X = CH_2OCH_2Ph, Y = H **11**
X = CH_2OH, Y = Si^iPr_3 **12**
X = CHO, Y = Si^iPr_3 **3**

a) MEMCl, $^iPr_2NEt$, rt b) MeLi, THF, -78 °C c) $PhCH_2OCH_2Cl$, $^iPr_2NEt$, rt d) $Zn(BH_4)_2$, ether, -78 °C e) TBDMSCl, ImH, DMF, 90 °C f) Li, liq NH_3, -78 °C g) CrO_3•2Py, CH_2Cl_2, rt h) $PhCH_2OCH_2Li$, THF, -78 °C i) $LiAlH(O^tBu)_3$, ether, -123 °C j) 1) MeLi, ether, rt 2) TsCl, rt k) $^nBu_4N$•F, THF, rt l) 3N-HCl, MeOH, reflux m) TIPSCl, DMAP, CH_2Cl_2, rt n) Na, liq NH_3, -78 °C o) 1) $(COCl)_2$, DMSO, CH_2Cl_2, -60 °C 2) Et_3N, 0 °C.

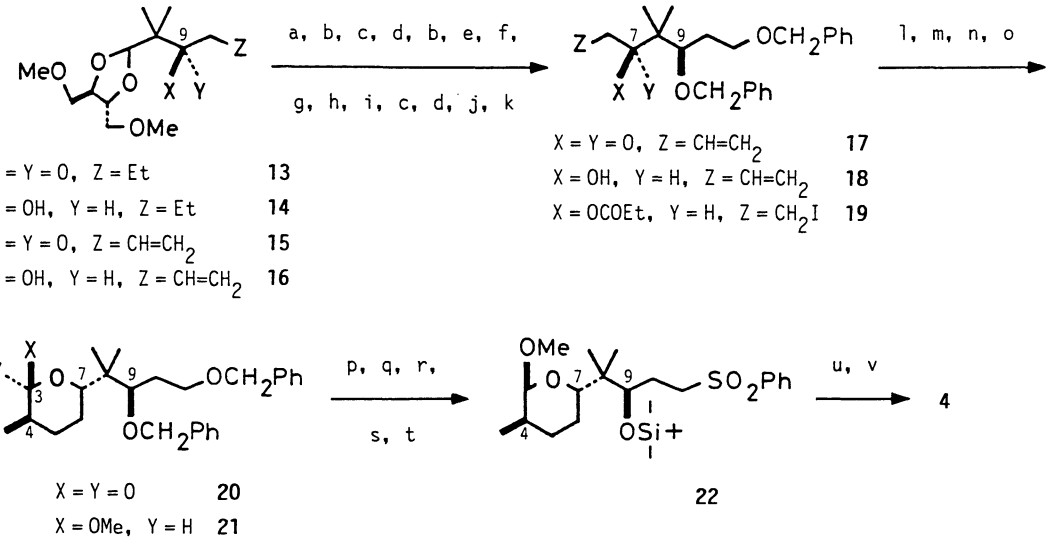
into the (-)-methylketone **6** in 77% overall yield. The desired (+)-*anti*-alcohol **7** was obtained selectively by $Zn(BH_4)_2$-reduction (**7**:16-*epi*-**7** = 16:1)[6] in 99% yield. After protection of the C-16 hydroxyl group as TBDMS ether, reductive cleavage of the benzyloxymethyl group followed by Collins oxidation gave the (-)-aldehyde **8** in 73% overall yield.[7] Treatment with $PhCH_2OCH_2Li$[8] 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 $^nBu_4N$•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 C_2-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 **15**[10] 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 (+)-β-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) $LiAlH_4$, LiBr, ether-PhMe (1:1), -78 °C b) $PhCH_2Cl$, ^tAmONa, DMSO, rt c) OsO_4, $NaIO_4$, ether-H_2O, rt d) $NaBH_4$, EtOH, 0 °C e) 3N-HCl, Me_2CO, reflux f) $CH_2=CHCH_2MgBr$, ether, rt g) Jones reagent, Me_2CO, 0 °C h) $LiAlH_4$, ether-THF (9:1), -123 °C i) $(EtCO)_2O$, DMAP, Py, rt j) TsCl, DMAP, Et_3N, rt k) KI, DMSO, rt l) LDA, THF, -78 °C m) MeOK, MeOH, rt n) DIBAL, PhMe, -78 °C o) CSA, MeOH, rt p) Na, liq NH_3, -78 °C q) TsCl, Et_3N, rt r) PhSLi, THF, rt s) TBDMSOTf, 2,6-Lu, CH_2Cl_2, rt t) mCPBA, CH_2Cl_2-sat $NaHCO_3$, rt, u) $HS(CH_2)_3SH$, $BF_3 \cdot OEt_2$, CH_2Cl_2, 0 °C, v) TBDMSOTf, 2,6-Lu, CH_2Cl_2, -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.

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] in 77% overall yield.

Coupling of (+)-**3** and (+)-**4** was carried out according to the Nakata-Oishi's procedure.[3b] Reaction of **4** with ^{n}BuLi (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 (Et_3N, 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, $CHCl_3$),[3b] in 41% overall yield from **4**. 400 MHz ^{1}H 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.*, 29, 1019 (1976).
2) H. Nakamura, Y. Iitaka, T. Kitahara, T. Okazaki, and Y. Okami, *J. Antibiot.*, 30, 714 (1977).
3) a) E.J. Corey, B.-C. Pan, D.H. Hus, and D.R. Deardroff, *J. Am. Chem. Soc.*, 104, 6816 (1982); E.J. Corey, D.H. Hus, B.-C. Pan, and S.P. Seiz, *ibid.*, 104, 6818 (1982); b) T. Nakata, K. Saito, and T. Oishi, *Tetrahedron Lett.*, 27, 6341, 6345 (1986); c) J.D. White, T.R. Vedananda, M.-C. Kang, and S.C. Choudhry, *J. Am. Chem. Soc.*, 108, 8105 (1986).
4) T. Matsumoto, F. Matsuda, K. Hasegawa, and M. Yanagiya, *Tetrahedron*, 40, 2337 (1984).
5) D.B. Collum, J.H. McDonald, II, and W.C. Still, *J. Am. Chem. Soc.*, 102, 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.*, 100, 1481 (1978).
9) Optical rotations and ^{1}H 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] (Me_2CO, 0 °C).
11) Racemic **22** was prepared from 2-(2-hydoxy-1,1-dimethyl-4-pentenyl)-1,3-dioxolane [T. Matsumoto *et al.*, *Tetrahedron Lett.*, 1978, 989] according to the same procedure as that of optically active **22**.

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