Substrate-Controlled Aldol Reactions of Chiral Ethyl Ketones: Application to the Total Synthesis of Oleandomycin

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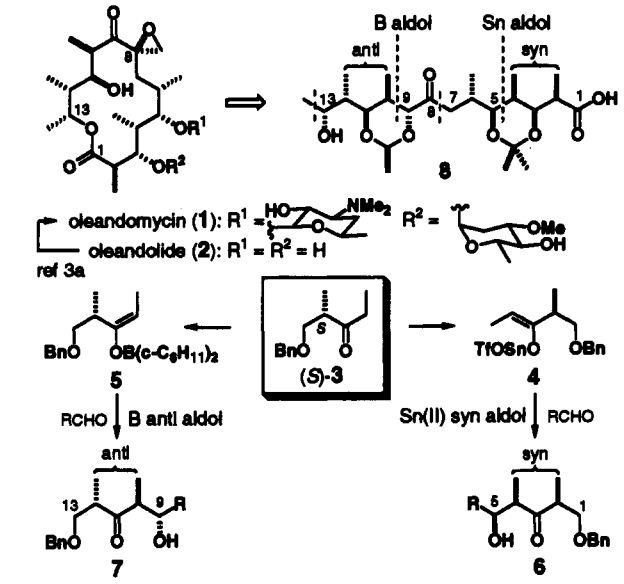
Oleandomycin (**1**), produced by the actinomycete *Streptomyces antibioticus*, is a 14-membered macrolide antibiotic[1] containing an unusual exocyclic epoxide at C_8 with β-D-desosamine and α-L-oleandrose sugars attached at C_5 and C_3.[2] It is widely used in both human and veterinary medicine as a treatment for bacterial infections by inhibiting bacterial RNA-dependent protein synthesis. A synthesis of oleandomycin has been recently completed by Tatsuta *et al.*[3] using a carbohydrate-based approach to construct the aglycone oleandolide (**2**). We now report a substantially shorter total synthesis[4-6] of oleandolide, achieving excellent stereochemical control (90% overall ds), based on recent aldol methodology developed in our laboratory.[7] This synthesis proceeds in 20 steps and 9% yield from the ethyl ketone (*S*)-**3**.

We have previously shown that efficient, substrate-based,[4] aldol stereocontrol from the tin(II)[7b] and boron[7c] enolates **4** and **5** facilitates the rapid assembly of complex polypropionate subunits, such as **6** and **7**, for a range of aldehydes (Scheme 1). For application to oleandolide, suitable elaboration and C_7–C_8 coupling to provide the seco acid derivative **8** was required. Achieving efficient macrolactonization[6c] of **8** and then correctly introducing the (8*R*)-epoxide were identified as critical issues for final completion of the synthesis.

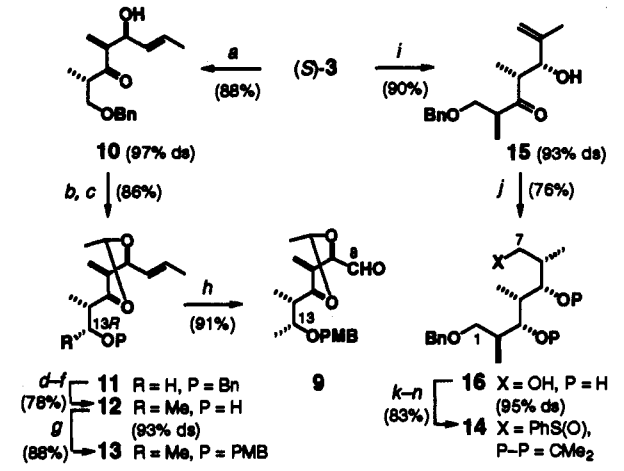
The synthesis of the C_8–C_{13} subunit **9** starts out (Scheme 2) with an anti–anti-selective boron aldol reaction of (*S*)-**3**[8] (*cf.* (*S*)-**3** → **7** in Scheme 1). Formation of the (*E*)-enol dicyclohexylborinate **5** and addition of crotonaldehyde gave **10** in 88% yield with 97% ds.[7c] Reduction[9] to the anti 1,3-diol with $Me_4NBH(OAc)_3$, followed by thermodynamically-controlled acetal formation[10] with $MeCH(OMe)_2$/TsOH (24 h), gave **11** as a single isomer (86%). A four-step sequence of (i) debenzylation to the primary alcohol, (ii) Swern oxidation to the aldehyde, (iii) addition of MeMgCl in CH_2Cl_2 to generate the (13*R*)-alcohol with 91% ds (Felkin–Anh control), and (iv) hydroxyl protection as the PMB ether gave **13** in 73% overall yield. Oxidative cleavage of the double bond then gave aldehyde **9** in 91% yield (50% yield over eight steps from (*S*)-**3**). The synthesis of the C_1–C_7 subunit **14** commenced with a syn–syn-selective tin(II) aldol reaction of (*S*)-**3** (*cf.* (*S*)-**3** → **6** in Scheme 1). Formation of the (*Z*)-tin(II) enolate **4** and addition of methacrolein provided **15** in 90% yield with 93% ds.[7b] Stereoselective alkene hydroboration and ketone reduction were accomplished in a single step, **15** → **16**, with 95% ds (76% yield) by employing the sterically demanding borane (+)-Ipc_2BH (5 equiv).[4a] A four-step sequence of (i) selective hydroxyl tosylation, (ii) acetonide formation, (iii) thiolate displacement of the tosylate, and (iv) sulfide oxidation gave the sulfoxides **14** in 81% yield (55% over six steps from (*S*)-**3**).

As shown in Scheme 3, fragment coupling was accomplished by α-lithiation of **14** (1.6 equiv), using $LiNEt_2$ in THF, and addition of the aldehyde **9**. Desulfoxidation of the resulting adduct mixture **17** using W-2 Raney nickel in ether, followed by selective[11]

Scheme 1



Scheme 2[a]



[a] (a) $(c\text{-}C_6H_{11})_2BCl$, Et_3N, Et_2O, 0 °C; (*E*)-MeCH=CHCHO, −78 °C; H_2O_2; (b) $Me_4NBH(OAc)_3$, AcOH, MeCN, −20 °C; (c) $MeCH(OMe)_2$, catalyst TsOH, CH_2Cl_2; (d) Li, 4,4′-di-*tert*-butylbiphenyl, THF, −78 °C; (e) $(COCl)_2$, DMSO; Et_3N, −78 °C → −20 °C; (f) MeMgCl, CH_2Cl_2, −100 °C; (g) KH, PMBCl, THF; (h) OsO_4, NMO, *t*-BuOH, THF, H_2O; $NaIO_4$; (i) $Sn(OTf)_2$, Et_3N, CH_2Cl_2, −78 °C; H_2C=C(Me)CHO; (j) (+)-Ipc_2BH, Et_2O; mCPBA; (k) TsCl, Et_3N, DMAP, CH_2Cl_2; (l) $Me_2C(OMe)_2$, PPTS, CH_2Cl_2; (m) LiSPh, THF, reflux; (n) $NaIO_4$, MeOH, H_2O.

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(8) Ketone (*S*)-**3** is readily prepared in three steps from (*S*)-methyl 3-hydroxy-2-methylpropionate (Aldrich); see ref 4a.

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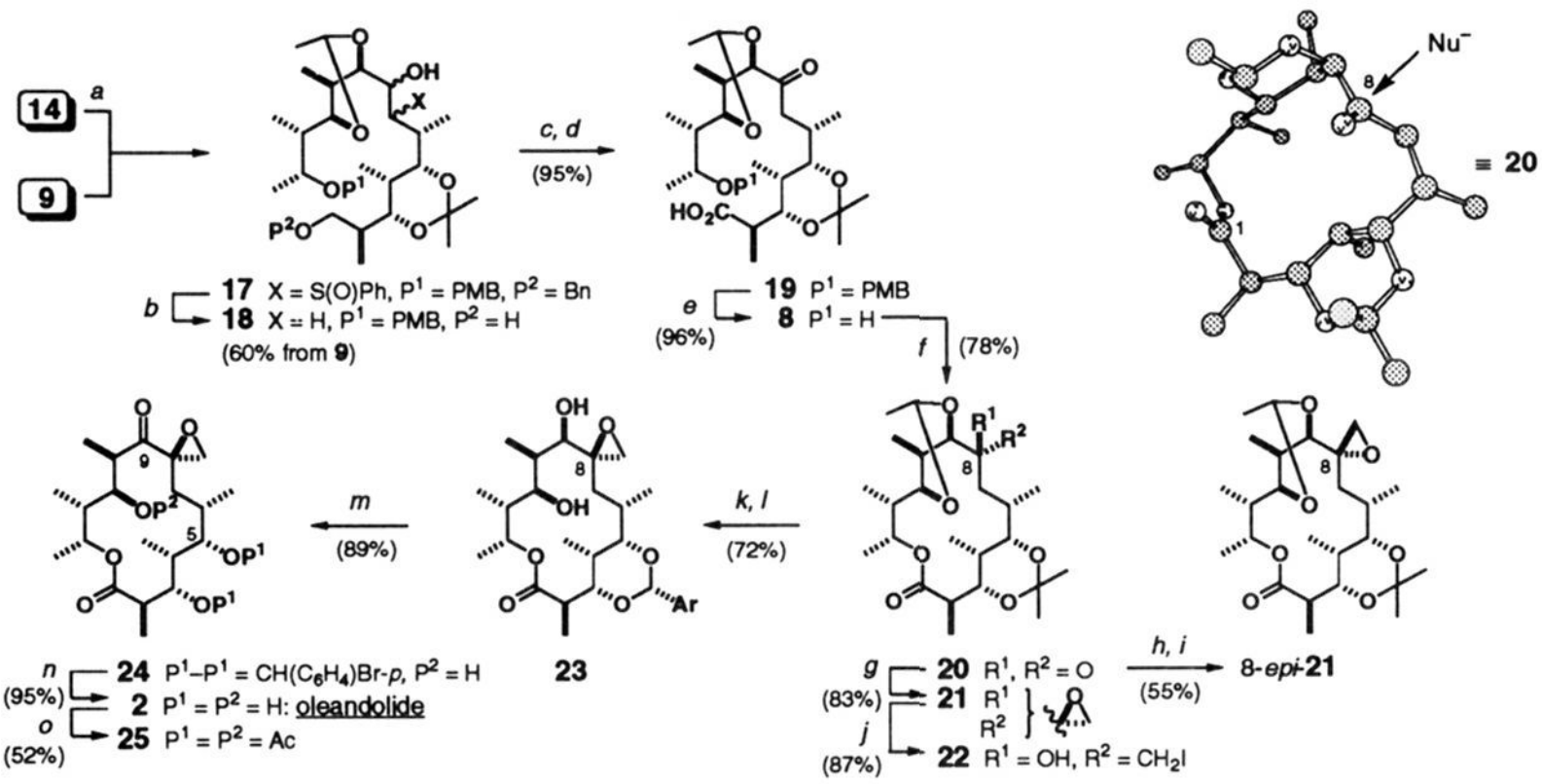
Scheme 3[a]



[a] (a) $LiNEt_2$, THF, –20 °C; **9**, –78 °C → –20 °C; (b) W-2 Raney Ni, Et_2O; H_2, EtOH; (c) $(COCl)_2$, DMSO; Et_3N, –78 °C → –20 °C; (d) $NaClO_2$, NaH_2PO_4, *t*-BuOH, H_2O; (e) H_2, 10% Pd/C, EtOH; (f) 2,4,6-$Cl_3(C_6H_2)COCl$, Et_3N, THF; add to DMAP, PhMe, 80 °C; (g) $Me_3S^+I^-$, NaH, DMSO, THF, 0 °C → 20 °C; (h) $Ph_3P^+Me\ Br^-$, KHMDS, PhMe, 70 °C; (i) mCPBA, CH_2Cl_2; (j) LiI, AcOH, THF; (k) 2 M HCl, THF, 50 °C; (l) *p*-$Br(C_6H_4)CH(OMe)_2$, CSA, CH_2Cl_2; aqueous $NaHCO_3$; (m) PCC/alumina, PhMe; (n) H_2, 10% Pd/C, $NaHCO_3$, EtOAc; (o) Ac_2O, py, DMAP.

hydrogenolysis of the benzyl group, then gave the diols **18** (60% from **9**). Swern oxidation of **18** to the keto aldehyde and further oxidation with $NaClO_2$ gave the acid **19** in 95% overall yield. Hydrogenolysis of the PMB ether then gave the protected seco acid **8** ready for macrolactonization. Cyclization to the 14-membered macrolide **20** was achieved in good yield (78%) using Yamaguchi's procedure (2,4,6-$Cl_3(C_6H_2)COCl$, DMAP).[12] The use of the ethylidene protecting group with the correct[10] acetal stereochemistry is crucial to the success of this reaction. The corresponding seco acid with acetonide protection at C_9–C_{11} could not be cyclized using these conditions,[13,14] presumably due to unfavorable steric interactions of the extra methyl group.

Molecular modeling[15] suggested that the *si* face of the ketone in **20** was blocked by the macrocyclic ring such that nucleophilic attack of a sulfur ylide should occur preferentially on the *re* face to give the desired (8*R*)-epoxide. In the event, reaction with dimethylsulfonium methylide[16] gave exclusively the desired epoxide **21** in 83% yield. Likewise, the (8*S*)-epoxide, 8-*epi*-**21**, was prepared with complete selectivity by mCPBA epoxidation of the corresponding alkene. Attempts to remove the acetonide and ethylidene protecting groups from **21** under acidic conditions proved difficult, necessitating temporary opening of the epoxide to the more robust iodohydrin **22** (87%). Treatment of **22** with HCl in THF gave the labile pentol, which was immediately protected as its C_3–C_5 *p*-bromobenzylidene derivative and worked up with aqueous $NaHCO_3$ to give **23** (72%). Selective oxidation at C_9 was best accomplished using PCC on alumina[17] to give the ketone **24** in 89% yield. Finally, hydrogenolysis of the acetal gave a 95% yield of oleandolide (**2**), $[\alpha]^{20}_D = -14.3°$ (*c* 1.05, $CHCl_3$) *vs* lit.[3] $[\alpha]^{20}_D = -13.0°$ (*c* 1.0, $CHCl_3$), obtained as a mixture of the keto and 5,9-hemiacetal forms. This had physical and spectroscopic data identical with those of material derived from oleandomycin. The 400-MHz ^1H NMR spectra of **2** ($CDCl_3$, C_6D_6) matched exactly spectra of oleandolide kindly provided by Professor Tatsuta. Peracetylation provided the known triacetate **25**, $[\alpha]^{20}_D = +39.7°$ (*c* 0.61, $CHCl_3$) *vs* lit.[3a] $[\alpha]^{20}_D = +43.0°$ (*c* 1.0, $CHCl_3$), which also had spectroscopic data in agreement with authentic spectra. Since the two sugar units have been previously introduced onto oleandolide by the Tatsuta group,[3a] the present synthesis also constitutes a formal total synthesis of oleandomycin itself.

In summary, we have completed an expedient synthesis of oleandolide (9% overall yield, 20 steps longest linear sequence with 90% overall ds, 26 steps in total). This is a paradigm of synthetic efficiency in the 14-membered macrolide field.[6] Key features include (i) short, highly stereocontrolled synthesis of coupling fragments **9** and **14** from the same starting ketone (*S*)-**3**, (ii) thermodynamic control on formation of the ethylidene acetal **11** enabling efficient macrocyclization, and (iii) introduction of the required (8*R*)-epoxide using macrocyclic stereocontrol. This work further demonstrates[18] the power of substrate-based aldol stereocontrol from our dipropionate reagent (*S*)-**3** and makes feasible the preparation of novel macrolides by total synthesis having modified antibiotic activity.

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Supplementary Material Available: Listing of spectroscopic and physical data, together with copies of ^1H and ^{13}C NMR spectra, for compounds **2**, **9**, **20**, **21** and **25** (16 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(10) Molecular modeling (MM2) suggested that acetal **11** should be thermodynamically preferred over its epimer by >99:1. Shorter reaction times (<24 h) or weaker acids (py·HOTs) led to a mixture.

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(13) A similar observation was made by Stork and Rychnovsky in their erythronolide synthesis. See: Stork, G.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **1987**, *109*, 1565.

(14) The 9,11-bis-TBS ether corresponding to **8** also failed to cyclize under the Yamaguchi conditions, while its 9-*epi*-derivative (ref 4a) was successfully cyclized in 60% yield.

(15) We used the MM2 force field in MacroModel, v 3.5: Mohamedi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440.

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