Tetrahedron Letters, Vol. 33, No. 13, pp. 1767-1770, 1992
Printed in Great Britain

0040-4039/92 $3.00 + .00
Pergamon Press Ltd

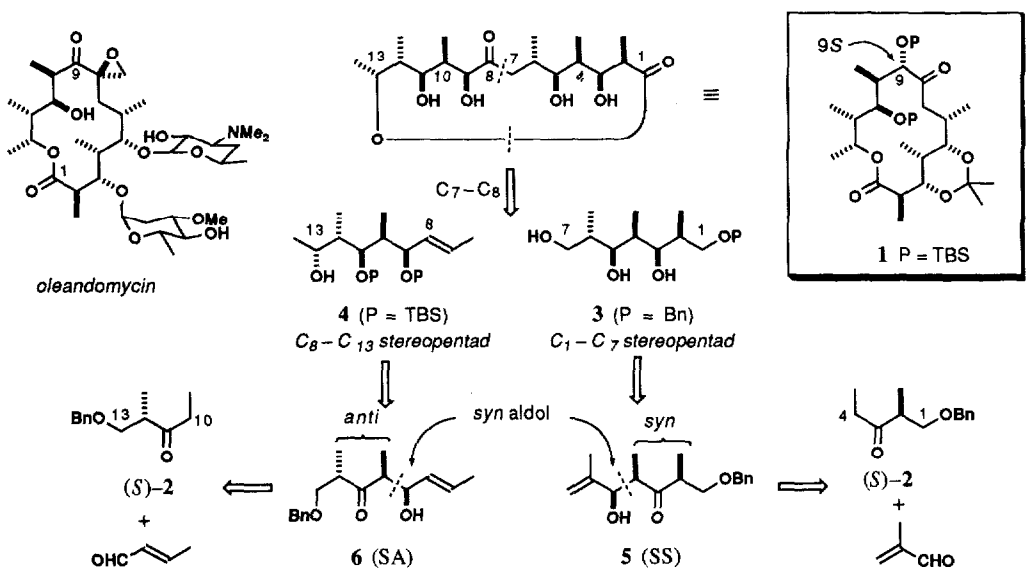
Studies in Macrolide Synthesis: A Stereocontrolled Synthesis of a (9*S*)–Macrolide Intermediate for Oleandomycin Using Chiral Boron Reagents.

Ian Paterson,* M. Anne Lister and Roger D. Norcross

University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, UK.

Abstract: The (9*S*)–macrolide **1** (P = TBS) was prepared in 14 steps (5% yield) with 63% overall ds starting from the ethyl ketone (*S*)-**2**. The C_1–C_7 and C_8–C_{13} segments, **3** and **4**, were obtained *via* boron enolate aldol reactions mediated by (+)- and (–)-$(Ipc)_2BOTf$, respectively.

Aldol reactions of chiral boron enolates are useful for the enantio- and diastereoselective synthesis of the characteristic polypropionate segments of macrolide antibiotics.[1] Until now, this approach has largely relied upon the use of a suitable chiral auxiliary attached to a propionate enolate or equivalent.[1,2] We have recently adopted an alternative strategy using the easily prepared chiral boron reagents, (+)- and (–)-disopinocampheylboron triflate, to control enolization stereoselectivity and the enolate π-face selectivity in aldol reactions of both achiral[3] and chiral[4] ethyl ketones with aldehydes. We now report an application of this methodology in the synthesis of the 14-membered macrolide **1** (P = TBS), an intermediate in a projected synthesis of the clinically-important antibiotic oleandomycin.[5,6] In this synthesis (**Scheme 1**), *six* of the ten stereogenic centres in **1** are controlled by two reagent-controlled aldol reactions of the *same* chiral ethyl ketone (*S*)-**2**.



Scheme 1

Scheme 1 outlines our retrosynthetic analysis of the (9*S*)–macrolide **1**, involving disconnection to the C_1–C_7 and C_8–C_{13} stereopentad segments **3** and **4**. These should be available in turn from the β-hydroxyketones **5** and **6**, both of which can be obtained[4b] by *syn*-selective aldol reactions of the ethyl ketone (*S*)-**2** using reagent control from (+)- and (–)-diisopinocampheylboron triflate ($(Ipc)_2BOTf$), respectively.

The synthesis of the (9*S*)-macrolide **1**, starting from the ethyl ketone (*S*)-**2** (97% ee),[7] is shown in **Scheme 2** and outlined below.

The *syn-syn* aldol isomer **5** (SS),[4b,8] required for the C_1–C_7 segment **3**, was prepared in enantiomerically pure form *via* (+)-$(Ipc)_2BOTf$ mediated enolisation of (*S*)-**2** giving the corresponding *Z* enol diisopinocampheylborinate **7**, followed by addition of methacrolein. Similarly, the *syn-anti* aldol isomer **6** (SA),[4b] required for the C_8–C_{13} segment **4**, was prepared *via* (–)-$(Ipc)_2BOTf$ mediated enolisation of (*S*)-**2** giving the *Z* enol diisopinocampheylborinate **8**, followed in this case by addition of crotonaldehyde. This led to 90% diastereoselectivity for **7** → **5**, $[\alpha]_D^{20}$ = +46.3° (*c* 4.0, $CHCl_3$), and 89% diastereoselectivity for **8** → **6**, $[\alpha]_D^{20}$ = +27.2° (*c* 6.3, $CHCl_3$), where chromatography on silica gel allowed separation from the minor *syn* isomers.

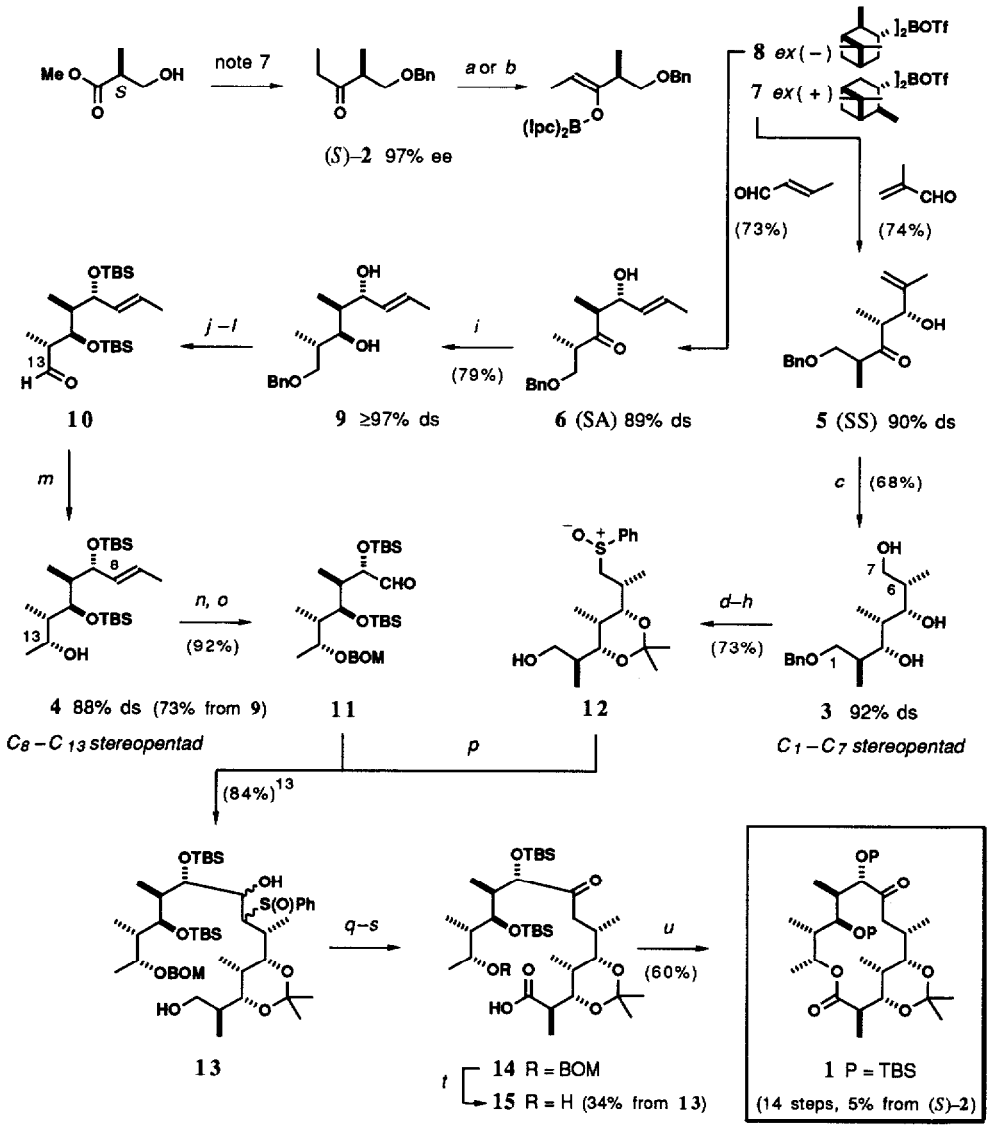
For a *rapid* synthesis of the C_1–C_7 segment **3** from the methacrolein aldol adduct **5**, we desired stereoselective alkene hydroboration and ketone reduction to set up the stereogenic centres at C_3 and C_6. We anticipated from related studies[9] that this should be possible in a one-pot reaction of **5** with the sterically demanding borane (+)-$(Ipc)_2BH$.[2b,10] Thus, treatment of **5** with (+)-$(Ipc)_2BH$ (3 equiv, Et_2O, 2 h), followed by oxidative workup (*m*CPBA), gave only *two* out of the four possible triols by HPLC analysis. These were the desired triol **3**[8], $[\alpha]_D^{20}$ = +9.3° (*c* 2.3, $CHCl_3$), and the epimeric triol at C_6, which were obtained in a ratio of 92:8 and in 68% yield. The five contiguous stereogenic centres spanning C_2–C_6 in oleandomycin were thus efficiently set up in only *two* steps from (*S*)-**2**.

The synthesis of the C_8–C_{13} segment **4** required a selective reduction of the ketone in the crotonaldehyde aldol adduct **6**, *i.e.* **6** → 9,11-*syn* diol **9**. This was accomplished with ≥97% ds (single isomer by 250 MHz ^1H NMR) and 79% yield by $LiBH_4$ reduction of the dibutylboron aldolate derived from reaction of **6** with $^nBu_2BOMe$.[11] Next, a three-step sequence of (*i*) bis-TBS protection with $^tBuMe_2SiOTf$, (*ii*) debenzylation using lithium di-*tert*-butylbiphenyl[12] in THF, and (*iii*) Swern oxidation (warming from –78 °C only as far as –23 °C after addition of Et_3N, to avoid β-elimination), provided the aldehyde **10** in readiness for stereoselective methyl addition at C_{13}. We required the Felkin-Cram adduct, and, of a number of reagents screened, MeMgCl gave both the highest yield and highest stereoselectivity. Thus, addition of MeMgCl to **9** at low temperature (–100 °C) gave the desired (13*R*) alcohol **4**[8], $[\alpha]_D^{20}$ = +5.3° (*c* 3.6, $CHCl_3$), with 88% diastereoselectivity and in 73% yield from **9**. This completed the construction of the five stereogenic centres spanning C_9–C_{13} in six steps from (*S*)-**2**.

Protection of the C_{13} hydroxyl in **4** as the BOM ether and subsequent ozonolysis gave the aldehyde **11** (92%), $[\alpha]_D^{20}$ = –1.9° (*c* 9.0, $CHCl_3$), in preparation for coupling with a nucleophilic C_1–C_7 fragment derived from **3**. Based on our previous studies,[5a] we chose to convert **3** into the known phenyl sulphoxides **12**. This was achieved by a straightforward five-step sequence in 73% overall yield: (*i*) selective tosylation of the primary hydroxyl; (*ii*) acetonide formation; (*iii*) hydrogenolysis of the benzyl ether; (*iv*) displacement of the tosylate by LiSPh; (*v*) $NaIO_4$ oxidation to the sulphoxides **12** (identical in all respects with that made previously[5a]).

Coupling of the C_1–C_7 and C_8–C_{13} segments was achieved by lithiation of **12** (LDA, 2.2 equiv, DME, –78 °C) followed by addition of the aldehyde **11**. This led to a complex mixture of adducts **13** in 84% yield, which were not separated.[13] Treatment of the adducts **13** with W–2 Raney nickel was followed by Swern oxidation and further oxidation of the C_1 aldehyde to the acid **14** using buffered $KMnO_4$.[14] Deprotection of the BOM ether at C_{13} was then achieved by hydrogenolysis to give the required seco-acid **15** (34% overall from **13**). This seco-acid was successfully macrolactonised in good yield (60%) under standard Yamaguchi conditions[15] to give the 14-membered macrolide, **15** → **1**[8], $[\alpha]_D^{20}$ = –3.8° (*c* 0.3, $CHCl_3$).

In summary, we have achieved a short and highly stereocontrolled synthesis of an advanced macrolide intermediate for oleandomycin (14 steps from (*S*)-**2** *via* **6** in 5% yield; 63% overall ds). This relies on two *syn*-selective aldol reactions under reagent control, **2** → **5** and **2** → **6**, and a novel one-pot reduction/hydroboration, **5** → **3**. This work demonstrates that efficient synthesis of macrolides can be achieved using aldol reactions controlled by chiral boron reagents. Studies towards the elaboration of **1** into oleandomycin are underway.



Scheme 2 (*a*) (+)-(Ipc)$_2$BOTf, ^{i}Pr$_2$NEt, CH_2Cl_2, 0 °C, 3 h; H_2C=C(Me)CHO, 16 h; H_2O_2, MeOH-pH7 buffer; (*b*) (-)-(Ipc)$_2$BOTf, ^{i}Pr$_2$NEt, CH_2Cl_2, 0 °C, 3 h; (*E*)-MeCH=CHCHO, 16 h; H_2O_2, MeOH-pH7 buffer; (*c*) (+)-(Ipc)$_2$BH, Et_2O, 0 → 20 °C, 2 h; *m*CPBA, 1 h; (*d*) TsCl, Et_3N, DMAP, CH_2Cl_2, 20 °C, 1 h; (*e*) $(MeO)_2CMe_2$, PPTS, CH_2Cl_2, 20 °C, 90 min; (*f*) H_2, 10% Pd/C, ^{i}Pr$_2$O, 2 h; (*g*) PhSLi, THF, 80 °C, 3 h; (*h*) $NaIO_4$, MeOH/H_2O, 20 °C, 21 h; (*i*) ^{n}Bu$_2$BOMe, THF/MeOH, –78 °C, 15 min; $LiBH_4$, –78 °C, 1 h; H_2O_2, 20 °C, 1 h; (*j*) ^{t}BuMe$_2$SiOTf, 2,6-lutidine, CH_2Cl_2, –78 °C, 1 h; (*k*) LiDBB, THF, –78 °C, 1 h; (*l*) $(COCl)_2$, DMSO, CH_2Cl_2, –78 °C, 1 h; Et_3N, -23 °C, 30 min; aq. NH_4Cl; (*m*) MeMgCl, THF, -100 °C, 1 h; (*n*) BOMCl, ^{i}Pr$_2$NEt, CH_2Cl_2, 20 °C, 48 h; (*o*) O_3, CH_2Cl_2/Et_2O, –78 °C, 5 min; Me_2S; (*p*) LDA, 2.2 equiv, DME, –78 °C, 15 min; **11**, –78 °C, 15 min; (*q*) W-2 Ra Ni, Et_2O, 20 °C, 1 h; (*r*) $(COCl)_2$, DMSO, CH_2Cl_2, –78 °C, 1 h; Et_3N, –23 °C, 30 min; (*s*) $KMnO_4$, ^{t}BuOH, pH7 buffer, 20 °C, 30 min; (*t*) H_2, 10% Pd/C, EtOH, 20 °C, 1 h; (*u*) 2,4,6-$Cl_3(C_6H_2)COCl$, Et_3N, THF, 20 °C, 2 h; DMAP, PhMe, 80 °C, 3 h.

Acknowledgement: We thank the SERC (GR/F73458; Quota studentship to MAL), Roussel Laboratories (CASE studentship to RDN), and Drs P. D. Kennewell and R. Westwood at Roussel for their support. RDN thanks Magdalene College for a Stothert Bye-Fellowship.

References and Notes

1. Reviews: (a) Paterson, I.; Mansuri, M. M. *Tetrahedron* **1985**, *41*, 3569; (b) Masamune, S.; McCarthy, P. A. in *Macrolide Antibiotics. Chemistry, Biology, and Practice*, Omura, S., Ed., Academic Press, Orlando (1984).

2. For some examples, see: (a) 6-deoxyerythronolide B: Masamune, S.; Hirama, M.; Mori, S.; Ali, Sk. A. A.; Garvey, D. S. *J. Am. Chem. Soc.* **1981**, *103*, 1568; (b) tylonolide: Masamune, S.; Lu, L. D.-L.; Jackson, W. P.; Kaiho, T.; Toyoda, T. *J. Am. Chem. Soc.* **1982**, *104*, 5523; (c) erythronolide A: Paterson, I.; Laffan, D. D. P.; Rawson, D. J. *Tetrahedron Lett.* **1988**, *29*, 1461; Paterson, I.; Rawson, D. J. *Tetrahedron Lett.* **1989**, *30*, 7463; (d) cytovaricin: Evans, D. A.; Kaldor, S. W.; Jones, T. K.; Clardy, J.A.; Stout, T. *J. Am. Chem. Soc.* **1990**, *112*, 7001.

3. (a) Paterson, I.; Lister, M. A.; McClure, C. K. *Tetrahedron Lett.* **1986**, *27*, 4787; (b) Paterson, I.; Goodman, J. M. *Tetrahedron Lett.* **1989**, *30*, 997; (c) Paterson, I.; Goodman, J. M.; Lister, M. A.; Schumann, R. C.; McClure, C. K.; Norcross, R. D. *Tetrahedron* **1990**, *46*, 4663.

4. (a) Paterson, I. *Chem. Ind. (London)*, **1988**, 390; (b) Paterson, I.; Lister, M. A. *Tetrahedron Lett.* **1988**, *29*, 585; (c) Paterson, I.; McClure, C. K. *Tetrahedron Lett.* **1987**, *28*, 1229; (d) Paterson, I.; McClure, C. K.; Schumann, R. C. *Tetrahedron Lett.* **1989**, *30*, 1293; (e) Paterson, I.; Lister, M. A.; Ryan, G. R. *Tetrahedron Lett.* **1991**, *32*, 1749.

5. For previous synthetic studies on oleandomycin, see: (a) Paterson, I. *Tetrahedron Lett.* **1983**, *24*, 1311 and ref 4c; (b) Costa, S. S.; Olesker, A.; Thang, T. T.; Lukacs, G. *J. Org. Chem.* **1984**, *49*, 2338; (c) Kobayashi, Y.; Uchiyama, H.; Kanbara, H.; Sato, F. *J. Am. Chem. Soc.* **1985**, *107*, 5541; (d) Paterson, I.; Arya, P *Tetrahedron* **1988**, *44*, 253; (e) Tatsuta, K.; Kobayashi, Y.; Gunji, H.; Masuda, H. *Tetrahedron Lett.* **1988**, *29*, 3975; (f) Sviridov, A. F.; Yashunsky, D. V.; Kuz'min, A. S.; Kochetkov, N. K. *Mendeleev Commun.* **1991**, 4.

6. For a recent total synthesis of oleandomycin using carbohydrate-based stereocontrol, see: Tatsuta, K.; Ishiyama, T.; Tajima, S.; Koguchi, Y.; Gunji, H. *Tetrahedron Lett.* **1990**, *31*, 709.

7. (*S*)-**2** was prepared from (*S*)-(+)-methyl 3-hydroxy-2-methylpropionate (Aldrich), in three steps and 62% yield (not from the (*R*)-(−)-propionate as we erroneously reported earlier), see ref 4b and 4e.

8. All new compounds gave spectroscopic data in agreement with the assigned structures. **3** had ^{1}H NMR δ ($CDCl_3$, 400 MHz) 7.37-7.26 (5H, m), 4.49 (2H, ABq, *J* = 12.0 Hz), 3.80 (1H, dd, *J* = 6.5, 3.1 Hz), 3.70 (1H, dd, *J* = 9.4, 1.8 Hz), 3.70 (1H, dd, *J* = 10.7, 3.9 Hz), 3.65 (1H, dd, *J* = 10.7, 8.3 Hz), 3.46 (1H, dd, *J* = 9.2, 4.7 Hz), 3.43 (1H, dd, *J* = 9.2, 5.0 Hz), 1.98 (1H, qddd, *J* = 6.9, 6.5, 5.0, 4.7 Hz), 1.88 (1H, ddqd, *J* = 9.4, 8.3, 6.9, 3.9 Hz), 1.80 (1H, qdd, *J* = 7.0, 3.1, 1.8 Hz), 1.07 (3H, d, *J* = 6.9 Hz), 0.96 (3H, d, *J* = 7.0 Hz), 0.72 (3H, d, *J* = 6.9 Hz); ^{13}C NMR δ ($CDCl_3$, 100 MHz) 138.1, 128.4, 127.6, 127.5, 82.6, 79.4, 74.1, 73.3, 69.1, 37.2, 36.8, 36.3, 13.4, 13.2, 5.5; HRMS (CI, NH_3) $[M+H]^+$ found 297.2071, $C_{17}H_{29}O_4$ requires 297.2066; **4** had ^{1}H NMR δ ($CDCl_3$, 400 MHz) 5.51 (1H, dq, *J* = 15.5, 6.0 Hz), 5.38 (1H, ddq, *J* = 15.5, 6.8, 1.5 Hz), 4.27 (1H, qd, *J* = 6.4, 1.8 Hz), 3.96 (1H, dd, *J* = 6.8, 5.0 Hz), 3.72 (1H, dd, *J* = 6.7, 2.0 Hz), 3.50 (1H, br s), 1.84 (1H, qdd, *J* = 7.1, 6.7, 5.0 Hz), 1.68 (3H, br d, *J* = 6.0 Hz), 1.59 (1H, qdd, *J* = 7.1, 2.0, 1.8 Hz), 1.11 (3H, d, *J* = 6.4 Hz), 0.99 (3H, d, *J* = 7.1 Hz), 0.95 (3H, d, *J* = 7.1 Hz), 0.90 (9H, s), 0.86 (9H, s), 0.09 (3H, s), 0.08 (3H, s), −0.01 (3H, s), −0.03 (3H, s); ^{13}C NMR δ ($CDCl_3$, 100 MHz) 133.2, 126.6, 79.3, 75.8, 66.6, 43.7, 41.2, 26.2, 25.9, 20.9, 18.4, 18.2, 17.6, 12.1, 11.4, −3.5, −3.6, −3.8, −4.9; HRMS (CI, NH_3) $[M+H]^+$ found 431.3375, $C_{23}H_{51}O_3Si_2$ requires 431.3377; **1** had ^{1}H NMR δ ($CDCl_3$, 400 MHz) 5.19 (1H, q, *J* = 6.4 Hz), 4.47 (1H, br d, *J* = 4.4 Hz), 3.82 (1H, d, *J* = 10.6 Hz), 3.56 (1H, br d, *J* = 10.8 Hz), 3.14 (1H, d, *J* = 8.7 Hz), 3.00 (1H, m), 2.65 (1H, dq, *J* = 10.8, 6.6 Hz), 2.54-2.40 (2H, m), 1.96 (1H, dq, *J* = 10.6, 6.6 Hz), 1.60-1.50 (2H, m), 1.41 (3H, s), 1.40 (3H, s), 1.22 (3H, d, *J* = 6.4 Hz), 1.08 (3H, d, *J* = 6.6 Hz), 1.02 (3H, d, *J* = 6.7 Hz), 0.97 (3H, d, *J* = 6.7 Hz), 0.94 (3H, d, *J* = 6.6 Hz), 0.91 (3H , d, *J* = 6.6 Hz), 0.90 (9H, s), 0.89 (9H, s), 0.10 (3H, s), 0.06 (3H, s), 0.01 (3H, s), −0.03 (3H, s); ^{13}C NMR δ ($CDCl_3$, 100 MHz) 212.5, 173.8, 99.7, 81.7, 75.6, 72.0, 71.4, 71.4, 43.7, 40.2, 40.1, 38.6, 32.8, 30.5, 29.7, 26.3, 25.7, 19.5, 18.8, 18.4, 18.0, 15.6, 12.4, 10.1, 8.7, 7.7, −2.8, -4.9, −5.0, −5.7; HRMS (CI, NH_3) $[M+NH_4]^+$ found 660.4692, $C_{34}H_{70}NO_7Si_2$ requires 660.4690.

9. (a) Paterson, I.; Channon, J. A. *Tetrahedron Lett.* **1992**, *33*, 0000; (b) Paterson, I.; Lister, M. A.; Channon, J. A. *unpublished results.*

10. (a) Brown, H. C.; Joshi, N. N. *J. Org. Chem.* **1988**, *53*, 4059; (b) For a recent review, see: Brown, H. C.; Jadhav, P. K.; Singaram, B. in *Modern Synthetic Methods*, Vol 4, Scheffold, R., Ed., Springer-Verlag, Berlin (1986).

11. (a) Narasaka, K.; Pai F.-C. *Tetrahedron* **1984**, *40*, 2233; (b) Chen, K.-M.; Hardtmann, G. E.; Prasad, K.; Repic, O *Tetrahedron Lett.* **1987**, *28*, 155.

12. Conventional reduction conditions using Li in NH_3/THF at −78 °C led to accompanying TBS migration to the C_{13} hydroxyl. This was avoided using LiDBB in THF at −78 °C: Ireland, R. E.; Smith, M. G. *J. Am. Chem. Soc.* **1988**, *110*, 854.

13. The coupling between **11** and **12** also produced some minor adducts (~20%) in which the TBS group at C_9 had migrated to the C_8 hydroxyl; these were separated chromatographically at the seco-acid stage.

14. Abiko, A.; Roberts, J. C.; Takemasa, T.; Masamune, S. *Tetrahedron Lett.* **1986**, *27*, 4537.

15. Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.*, **1979**, *52*, 1989.

(Received in UK 12 December 1991)