High π-Face Selectivity in Anti Aldol Reactions of *E*-Enol Borinates from Chiral Alkoxymethyl Ketones: Stereocontrolled Synthesis of a C_{24}–C_{32} Polyol Subunit of Rapamycin

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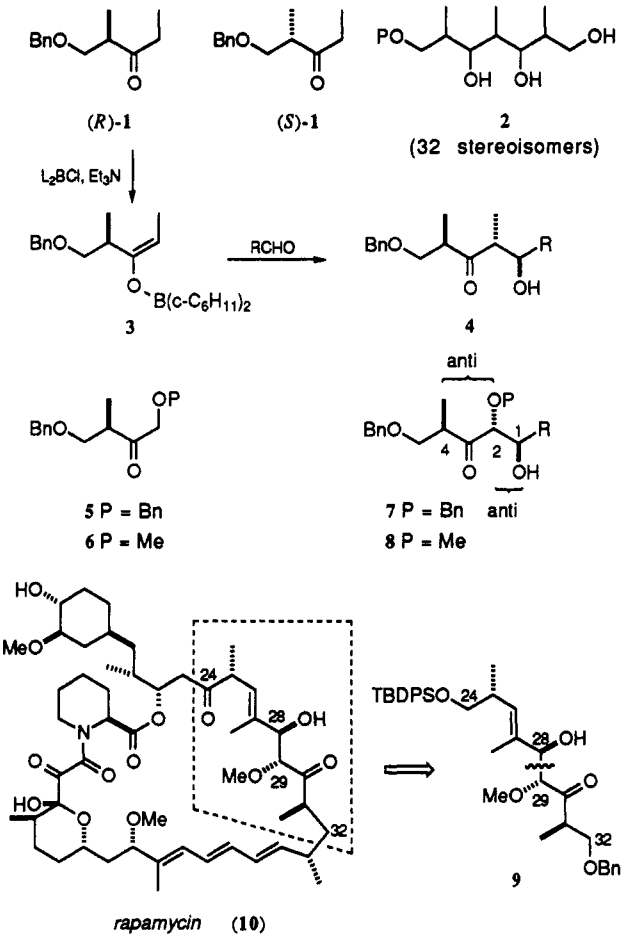
Summary: Using $(c\text{-}C_6H_{11})_2BCl/Et_3N$, the aldol reactions of the α-chiral alkoxymethyl ketones **5** and **6** with achiral aldehydes gives the 1,2-anti-2,4-anti adducts **7** and **8** in 83–95% yield with ≥95% diastereoselectivity. This novel aldol reaction was applied to a concise and highly stereocontrolled synthesis of the C_{24}–C_{32} subunit **9** of rapamycin (**10**).

We have introduced the α-chiral ethyl ketones (*R*)- and (*S*)-**1** (Scheme I) to serve as versatile dipropionate reagents for the construction of polyketide-derived natural products (macrolides, polyethers, *etc.*).[1,2] Using the derived boron[2a,b] and tin(II)[2c] enolates, their aldol addition reactions with aldehydes allow the expedient synthesis of complex polypropionate subunits,[3] *e.g.*, enabling selective access to all possible stereoisomers of the common stereopentad unit **2** from methacrolein.[4] This powerful methodology relies upon efficient regio- and stereocontrol during the enolization of ketone **1**, together with high levels of π-face selectivity in the aldehyde addition step through *substrate*- or, in some cases, *reagent*-control. For example, the boron-mediated anti aldol reaction, **1** → **3** → **4**, proceeds with ≥95% diastereoselectivity (ds) for all aldehydes examined to date.[2b,3b-d]

To allow access to more highly oxygenated structures, an extension to the synthesis of contiguous polyols was of interest. By starting from the analogous α-chiral alkoxymethyl ketones **5** and **6**, we now report the aldol construction of the anti keto glycol derivatives **7** and **8** with high diastereoselectivity. This novel aldol reaction was applied to a short synthesis of the C_{24}–C_{32} subunit **9** of rapamycin (**10**).

The starting ketones **5** and **6** are readily available with ≥97% ee by adaptation of our existing synthesis[2a,4e] of the ethyl ketone (*R*)-**1** from (*R*)-(−)-methyl 3-hydroxy-2-methylpropionate (**10**) *via* **11** and **12** (Scheme II). Addition of the appropriate (benzyloxymethyl)- or (methoxymethyl)lithium reagent to the Weinreb amide[5] **12** ($POCH_2Sn^nBu_3$, ^{n}BuLi, THF, −78 → 0 °C) gave the ketones **5** (78%), $[\alpha]^{20}_D$ = −17.1° (c 0.16, $CHCl_3$), and **6** (80%), $[\alpha]^{20}_D$ = −32.5° (c 0.16, $CHCl_3$), respectively. The enantiomeric ketones should be available in a similar fashion starting from (*S*)-**10**.[2a,4a] The reaction conditions for

Scheme I



E-selective[6] enolization of these ketones with dicyclohexyl boron chloride are based on that of Brown *et al.*[7] and our protocol[2b] for the related process **1** → **3**. Thus, enolization of **5** or **6** was performed[8] in Et_2O (−78 → 0 °C, 45 min) using $(c\text{-}C_6H_{11})_2BCl$ (1.5 equiv) and Et_3N (1.7 equiv), followed by cooling to −78 °C, and addition of the appropriate aldehyde.

As shown in Scheme II, this gave high yields (83–95%) of the aldol adducts **13**–**16** for a range of achiral aldehydes. In each case, HPLC and 400-MHz ^{1}H NMR analysis of the crude product mixture indicated the formation of a major aldol isomer with ≥95 ds,[8] which was shown to be the 1,2-anti-2,4-anti adduct. The chiral aldehydes[2c,9] (*R*)- and (*S*)-**17** gave the respective adducts **18** and **19** with 80% (mismatched) and 95% (matched) ds. In these double stereodifferentiation experiments,[10] the high level of π-face

(1) Paterson, I. *Pure Appl. Chem.* **1992**, *64*, 1821.
(2) Paterson, I.; Lister, M. A. *Tetrahedron Lett.* **1988**, *29*, 585. (b) Paterson, I.; Goodman, J. M; Isaka, M. *Tetrahedron Lett.* **1989**, *30*, 7121. (c) Paterson, I.; Tillyer, R. D. *Tetrahedron Lett.* **1992**, *33*, 4233.
(3) Oleandomycin: Paterson, I.; Lister, M. A.; Norcross, R. D. *Tetrahedron Lett.* **1992**, *33*, 1767. (b) Denticulatin A and B: Paterson, I.; Perkins, M. V. *Tetrahedron Lett.* **1992**, *33*, 801. (c) Muamvatin: Paterson, I.; Perkins, M. V. *J. Am. Chem. Soc.* **1993**, *115*, 1608. (d) Swinholide A and misakinolide A: Paterson, I.; Cumming, J. G. *Tetrahedron Lett.* **1992**, *33*, 2847. (e) Tirandamycin A: Paterson, I.; Lister, M. A.; Ryan, G. R. *Tetrahedron Lett.* **1991**, *32*, 1749.
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(6) For a rationalization for this enolization selectivity, see: Goodman, J. M.; Paterson, I. *Tetrahedron Lett.* **1992**, *33*, 7223.
(7) Brown, H. C.; Dhar, R. K.; Bakshi, R. K.; Pandiarajan, P. K.; Singaram, B. *J. Am. Chem. Soc.* **1989**, *111*, 3441. (b) Brown, H. C.; Dhar, R. K.; Ganesan, K.; Singaram, B. *J. Org. Chem.* **1992**, *57*, 499. (c) Brown, H. C.; Dhar, R. K.; Ganesan, K.; Singaram, B. *J. Org. Chem.* **1992**, *57*, 2716.

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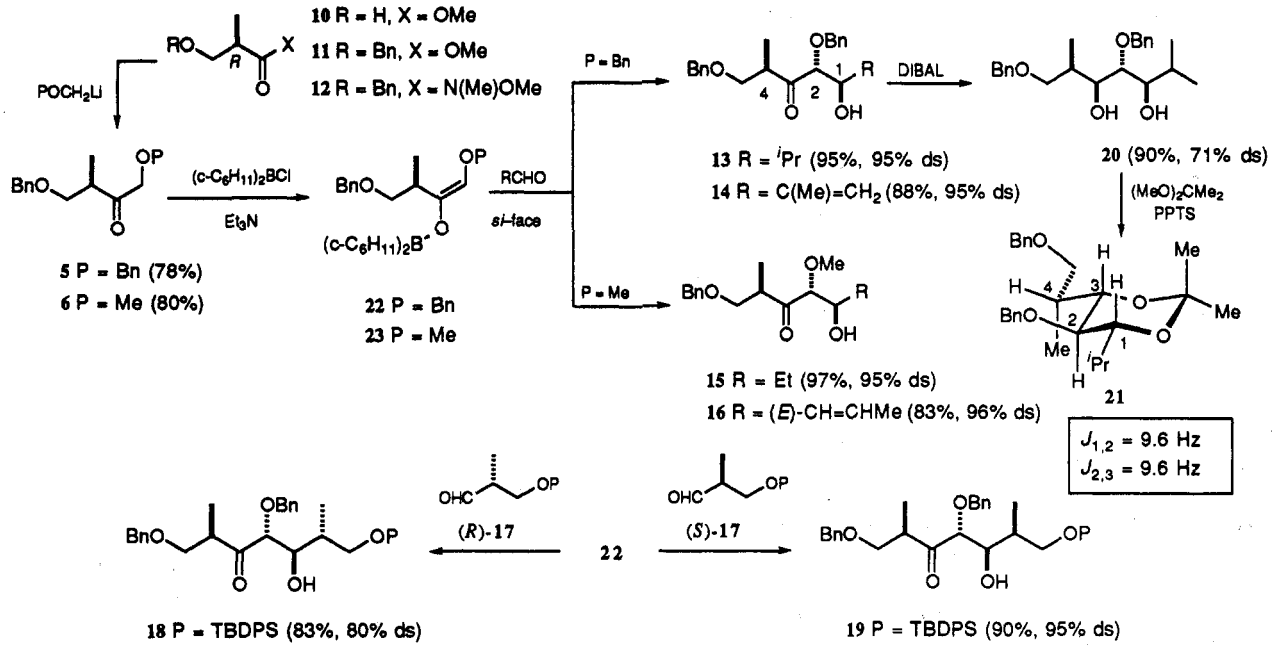
Scheme II



selectivity from the *E*-enolate partner overrides any Felkin–Anh-type influence[11] from the aldehyde stereocenter. The 1,2-anti relationship was suggested by the large vicinal coupling constant ($J_{1,2}$ = 5.7–8.7 Hz)[2b,12] observed in all cases and established for **13** by DIBAL reduction to the syn 1,3-diol **20** and ^{1}H NMR analysis of the derived acetonide **21**. Furthermore, the absolute configuration at the hydroxyl-bearing center was established as (*R*) by ^{1}H NMR analysis[13] of the derived (*R*)- and (*S*)-MTPA esters of **13**. Taken together with the (*R*)-configuration in the starting ketone **7**, this requires a 2,4-anti relationship of the methyl- and oxygen-bearing stereocenters (also *cf.* 1 → 4 in Scheme I).

The high level of stereodifferentiation operating in these anti aldol reactions[14] is remarkable and can be traced to the relative steric and electronic properties of the three substituents—H, Me, and CH_2OBn—at the adjacent stereocenter. For the enolates **22** and **23**, we propose that the preferred chairlike transition structure TS-I is responsible[8,15] for the high level of aldehyde π-face selectivity (*si*:*re* > 20:1). This minimizes A(1,3) allylic strain[16] with the *E*-enol alkoxy group and has the methyl group pointing outwards and the benzyloxymethyl directed in toward the aldehyde. This apparent contrasteric preference for TS-I (*si*-face attack) over TS-II (*re*-face attack) is considered

(8) The optimum reaction conditions required the use of 1.5 equiv of boron chloride. Changing the stoichiometry in the range 0.8–2.5 equiv only affected the yield and not the overall diastereoselectivity. Hence, we believe that acyclic aldol transition states are not involved in this reaction. **Representative experimental procedure:** To a stirred solution of dicyclohexylboron chloride (1.5 equiv) and Et_3N (1.7 equiv) in dry Et_2O (3 mL/mmol of boron reagent) at −78 °C was added a solution of the ketone **5** or **6** in Et_2O. After 15 min, the reaction mixture was warmed to 0 °C for 45 min and then recooled to −78 °C. A solution of the aldehyde (3–5 equiv for simple aldehydes, 0.9–1.5 equiv for more precious aldehydes) in Et_2O (1 mL/mmol) was added. After 30 min, the reaction mixture was kept at −20 °C for 14 h (freezer) and then partitioned between pH 7 buffer and Et_2O. The aqueous layer was extracted with Et_2O, and the organic extracts were combined and concentrated *in vacuo*. The residual oil was dissolved in MeOH (6 mL/mmol of ketone) and pH 7 buffer (6 mL/mmol), and aqueous H_2O_2 (30%, 3 mL/mmol) was added. After being stirred for 1 h, the mixture was then partitioned between pH 7 buffer and CH_2Cl_2 and worked up. The crude product was purified by flash chromatography and/or HPLC to give the major 1,2-anti-2,4-anti aldol adduct **7** or **8**. The reaction diastereoselectivity was generally determined by weighing the chromatographically separated aldol adducts, which agreed with the isomer ratios obtained from analytical HPLC and 400-MHz ^{1}H NMR spectroscopy performed on the crude reaction mixture.

(9) (*R*)- and (*S*)-**17** were prepared from (*R*)- and (*S*)-(+)-methyl 3-hydroxy-2-methylpropionate (Aldrich), respectively.

(10) For a review of double stereodifferentiation in boron aldol reactions, see: Kim, M.; Williams, S. F.; Masamune, S. In *Comprehensive Organic Synthesis*, Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 2, p 239.

(11) For the origins of diastereofacial selectivity in the aldol reactions of chiral α-methyl aldehydes, see: (a) Roush, W. R. *J. Org. Chem.* **1991**, *56*, 4151. (b) Gennari, C.; Vieth, S.; Comotti, A.; Vulpetti, A.; Goodman, J. M.; Paterson, I. *Tetrahedron* **1992**, *48*, 4439.

(12) Heathcock, C. H. In *Asymmetric Synthesis*; Morrison J. D., Ed.; Academic Press: New York, 1984; Vol. 3, p 111. (b) Evans, D. A.; Nelson, J. V.; Taber, T. R. In *Topics in Stereochemistry*: Wiley-Interscience: New York , 1982; Vol. 13, p 1.

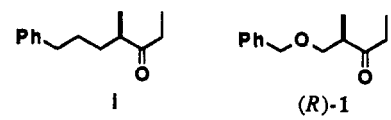
(13) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092. (b) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512. (c) Sullivan, G. R.; Dale, J. A.; Mosher, H. S. *J. Org. Chem.* **1973**, *38*, 2143.

(14) Note that the corresponding *Z*-enol borinate derivative of the ethyl ketone **1** provides negligible substrate-induced stereoselectivity in syn aldol reactions (ref 2a).

(15) For transition-state modeling of the anti aldol addition **3** → **4**, see: Vulpetti, A.; Bernardi, A.; Gennari, C.; Goodman, J. M.; Paterson, I. *Tetrahedron* **1993**, *49*, 685.

(16) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841.

(17) This is supported by the results for the corresponding anti aldol reaction of the ketone **i**, where a CH_2 group replaces the benzyl ether oxygen in **1**. A dramatic erosion of π-face selectivity with methacrolein is now observed → 72:28 (*si*:*re* or *re*:*si*) for **i** *vs* 98:2 (*si*:*re*) for (*R*)-**1** itself.



i (*R*)-**1**

(18) For *contrasting* stereoselectivities in the anti aldol reactions of some other chiral ethyl ketones, see ref 15 and: (a) Paterson, I.; Hulme, A. N.; Wallace, D. J. *Tetrahedron Lett.* **1991**, *32*, 7601. (b) Evans, D. A.; Ng, H. P.; Clark, J. S.; Rieger, D. L. *Tetrahedron* **1992**, *48*, 2127.

(19) Lone-pair repulsion has been used by Roush to rationalize the asymmetric induction occurring in tartrate-mediated allylboration reactions. Roush, W. R.; Banfi, L. *J. Am. Chem. Soc.* **1988**, *110*, 3979.

(20) Hale, M. R.; Hoveyda, A. H. *J. Org. Chem.* **1992**, *57*, 1643. (b) Meyer, S. D.; Miwa, T.; Nakatsuka, M.; Schreiber, S. L. *J. Org. Chem.* **1992**, *57*, 5058. (c) Romo, D.; Johnson, D. D.; Plamondon, L.; Miwa, T.; Schreiber, S. L. *J. Org. Chem.* **1992**, *57*, 5060. (d) Fisher, M. J.; Myers, C. D.; Joglar, J.; Chen, S.-H.; Danishefsky, S. J. *J. Org. Chem.* **1991**, *56*, 5826. (e) Chen, S.-H.; Horvath, R. F.; Joglar, J.; Fisher, M. J.; Danishefsky, S. J. *J. Org. Chem.* **1991**, *56*, 5834. (f) Sin, N.; Kallmerten, J. *Tetrahedron Lett.* **1993**, *34*, 753.

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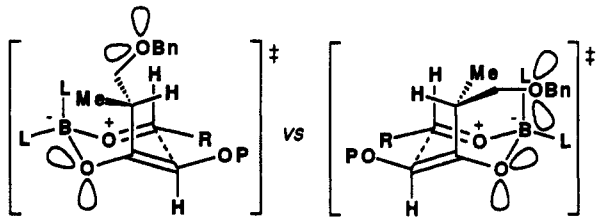
(22) (a) Schreiber, S. L. *Science* **1991**, *251*, 283. (b) Rosen, M. K.; Schreiber, S. L. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 384.

to have an electronic origin,[1,15,17,18] possibly with TS-II destabilized by lone-pair repulsion[19] between the oxygen atoms.



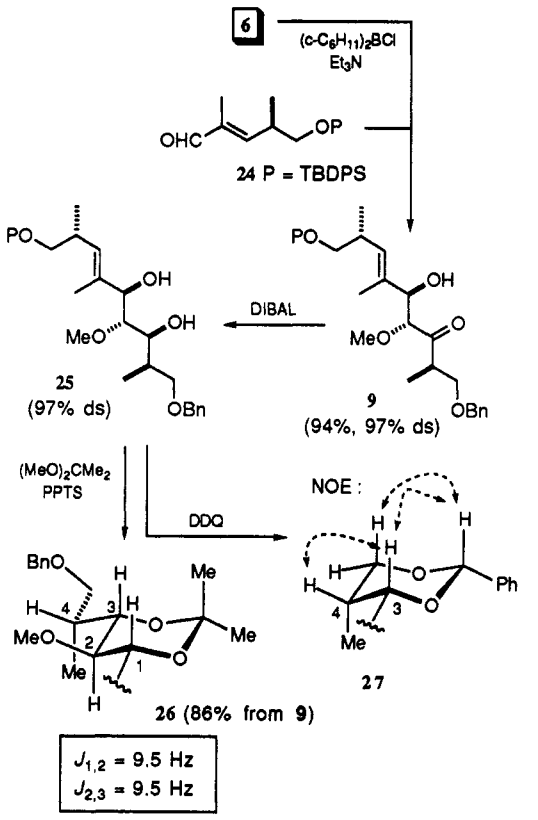
TS-I
si-face attack
FAVOURED

TS-II
re-face attack

The macrolide antibiotic rapamycin (**10** in Scheme I) has recently attracted considerable synthetic[20] attention due to its challenging structure[21] and potent immunosuppressant activity.[22] We envisaged that the C_{28}–C_{29} bond might be constructed with a high level of stereocontrol using a boron-mediated anti aldol reaction.[23] For the present study (Scheme III), our target was the C_{24}–C_{32} subunit **9**. The aldehyde **24** was prepared by straightforward chemistry[24] via (*S*)-**17**.[9] Under our standard conditions,[8] the aldol addition of the ketone **6** with **24** proceeded smoothly, via the *E*-enol dicyclohexyl borinate **23**, to give a 94% yield of **9**, $[\alpha]^{20}_D = -5.1°$ (c 0.24, $CHCl_3$), with 97% ds. The 1,2-anti-2,4-anti relative stereochemistry was established as shown by selective reduction of **9** (DIBAL, CH_2Cl_2, −78 °C; 97% ds) to the corresponding syn 1,3-diol **25**. This was then converted into the acetonide **26**, $[\alpha]^{20}_D = -8.2°$ (c 0.1, $CHCl_3$), as well as the benzylidene acetal **27** (DDQ, CH_2Cl_2)—permitting a secure stereochemical assignment by ^1H NMR spectroscopy.

In summary, we have achieved a short and highly diastereoselective synthesis of the C_{24}–C_{32} subunit **9** of rapamycin. The key step, forming the C_{28}–C_{29} bond, is based upon the anti-anti aldol reaction of the chiral ketone **6**. This process should be useful for coupling with more complex aldehydes, available either by synthesis or from the controlled retro-aldol cleavage[23] of rapamycin. More generally, the aldol reactions of the readily available alkoxymethyl ketones **5** and **6** (and their enantiomeric forms) should prove to be useful in the synthesis of other highly oxygenated natural products of polyketide origin.

Scheme III



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Supplementary Material Available: Experimental procedures and characterization data for all new compounds (7 pages). This material is contained in 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.

(23) For retro-aldol cleavage of the C_{28}–C_{29} bond in the degradation of rapamycin, see: (a) Yohannes, D.; Danishefsky, S. J. *Tetrahedron Lett.* **1992**, *33*, 7469. (b) Luengo, J. I.; Konialian, A. L.; Holt, D. A. *Tetrahedron Lett.* **1993**, *34*, 991.

(24) The enal **24** (*E*:*Z* = 95:5) was prepared by Wittig reaction of (*S*)-**17** with $MeO_2CC(Me)=PPh_3$, followed by DIBAL reduction and Dess–Martin oxidation. (a) Diez-Martin, D.; Kotecha, N. R.; Ley, S. V.; Menendez, J. C. *Synlett* **1992**, 399. (b) Nagaoka, H.; Kishi, Y. *Tetrahedron* **1981**, *37*, 3873.