Application of Newly Developed *Anti*-Selective Aldol Methodology: Synthesis of C6−C13 and C19−C28 Fragments of Miyakolide

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Stereospecific aldol reactions have been the subject of extensive investigation over the past two decades because of their wide applicability to the synthesis of stereochemically complex polyketide natural products exemplified by macrolides. While many excellent chiral *Z*(*O*) enolates have been employed for the construction of the *syn*-3-hydroxy-2-methyl carbonyl structural motif,[1] methods for the direct elaboration of the anti counterparts have met with limited success.[2] As a result, *anti*-selective aldol reactions are rarely utilized in natural product synthesis as strategic bond-forming reactions. To address this problem, we have recently developed a highly enantioselective *anti*-aldol reaction using the chiral *E*(*O*) enol borinate **1** generated from the chiral ester **2**.[3] Application of this *anti*-aldol methodology, along with the well-established *syn*-selective methods, allows greater flexibility in the synthetic design of polyketide-type compounds. We herein report that the chiral enol borinate **1** (Figure 1) has been successfully utilized in the synthesis of two key fragments of miyakolide via both single and double asymmetric aldol reactions.

Miyakolide, a bryostatin-like marine metabolite, was isolated from *Polyfibrospongia sp.* and shown to have the structure **3** in Scheme 1.[4] Our planned convergent synthesis of **3** involves the two major fragments **A** (C19−C28) and **C** (C6−C13), both of which contain the challenging *anti*-3-hydroxy-2-methyl carbonyl subunits. The efficient, stereoselective syntheses of these units through the *anti*-selective aldol methodology are shown below.

The synthesis of fragment **A** starts with the known chiral aldehyde **4** (Scheme 2)[5] and features a *double asymmetric anti-aldol reaction* that was fully evaluated with our newly devised methodology. Thus, aldehyde **4** was allowed to react with the enol borinate **1** (1*S*, 2*R*) to provide aldol **5** along with compound **6** as the minor isomer in a ratio of 15:1, whereas the reaction of **4** with *ent*-**1** (1*R*, 2*S*) resulted in the formation of aldol **7** as the only detectable isomer. This result is noteworthy because it implies that the directing effect of the chiral enol borinate **1** is high enough to overcome the intrinsic stereochemical bias of the chiral aldehyde, thereby dictating the stereochemical outcome in both matched and mismatched double asymmetric aldol reactions.[6]

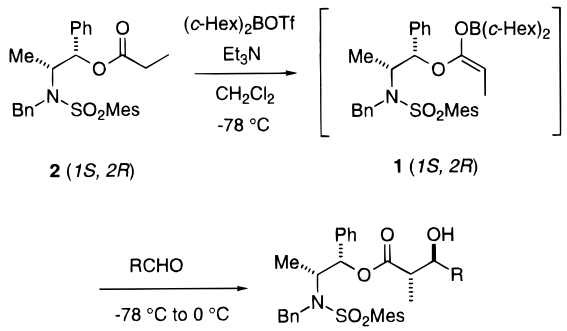
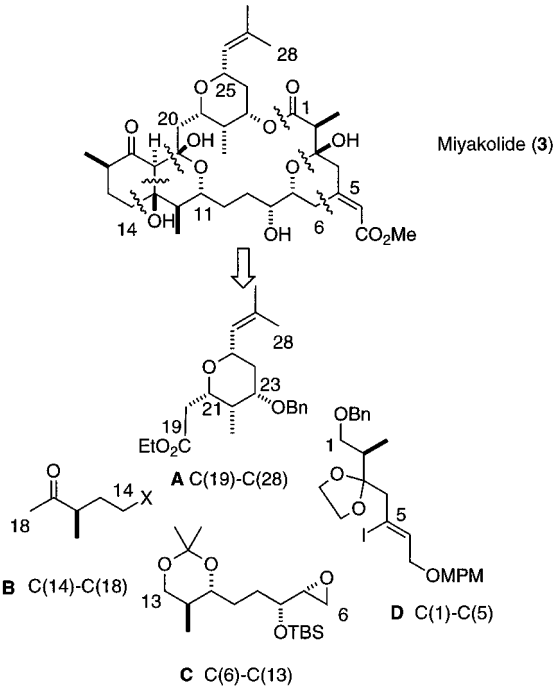
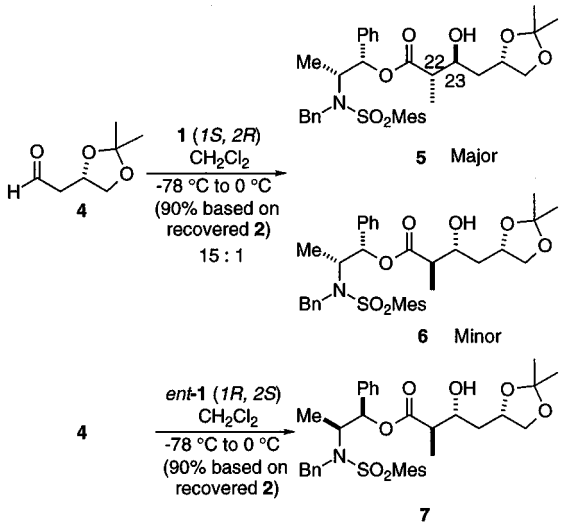


Figure 1.

Scheme 1



Scheme 2



(1) For a good review of asymmetric aldol reactions in natural product synthesis see: Kim, B.-M.; Williams, S. F.; Masamune, S. In *Comprehensive Organic Synthesis*; Heathcock, C. H., Ed.; Pergamon Press: New York, **1991**; Vol. 2, pp 239−275. For a recent review see: Norcross, R. D.; Paterson, I. *Chem. Rev.* **1995**, *95*, 2041.

(2) (a) See ref 3 and references therein. For indirect methods for this transformation, see: (b) Nagaoka, H.; Rutsch, W.; Schmid, G.; Iio, H.; Johnson, M. R.; Kishi, Y. *J. Am. Chem. Soc.* **1980**, *102*, 7962. (c) Schmid, G.; Fukuyama, T.; Akasaka, K.; Kishi, Y. *J. Am. Chem. Soc.* **1979**, *101*, 259. (d) Boschelli, D.; Ellingboe, J. W.; Masamune, S. *Tetrahedron Lett.* **1984**, *25*, 3395. (e) Evans, D. A. *Aldrichim. Acta* **1982**, *15*, 23.

(3) Abiko, A.; Liu, J.-F.; Masamune, S. *J. Am. Chem. Soc.* **1997**, *119*, 2586.

(4) Higa, T.; Tanaka, J.; Komesu, M.; Gravalos, D. G.; Puentes, J. L. F.; Bernardinelli, G.; Jefford, C. W. *J. Am. Chem. Soc.* **1992**, *114*, 7587.

(5) (a) Saito, S.; Ishikawa, T.; Kuroda, A.; Koga, K.; Moriwake, T. *Tetrahedron* **1992**, *48*, 4067. (b) Meyers, A. I.; Lawson, J. P. *Tetrahedron Lett.* **1982**, *23*, 4883.

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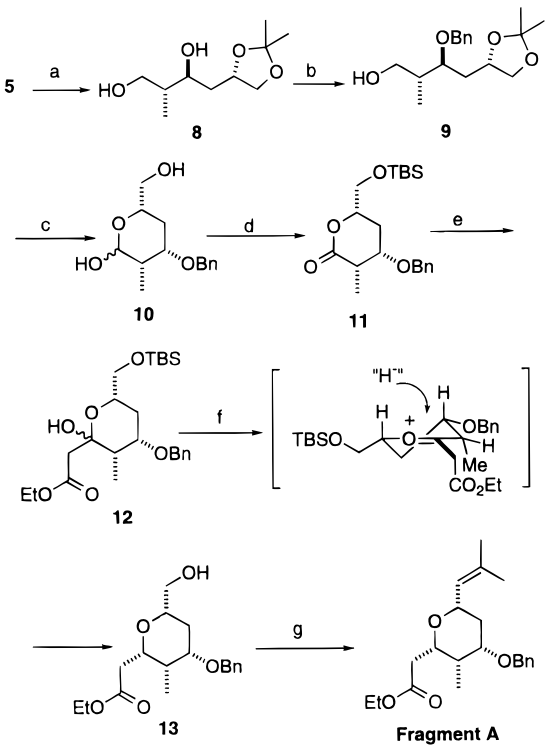
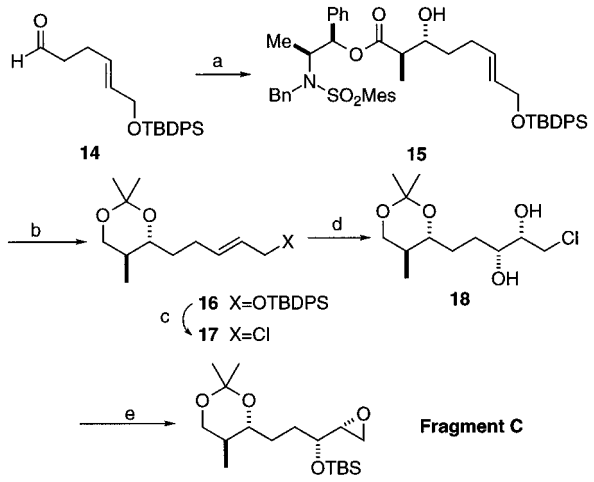
Scheme 3



[a] Key: (a) LAH, THF, 0 °C (60%); (b) (1) TBSCl, Et_3N, DMAP, CH_2Cl_2, 25 °C (83%); (2) BnBr, NaH, DMF, 25 °C (85%); (3) TBAF, THF, 25 °C (94%); (c) (1) Swern, −78 °C; (2) 1 N HCl, THF, 25 °C (98%;two steps); (d) (1) TBSCl, Et_3N, DMAP, CH_2Cl_2, 25 °C (95%); (2) PCC, CH_2Cl_2, 25 °C (93%); (e) LiHMDS, ethyl acetate, THF, −78 °C (92%); (f) Et_3SiH, $BF_3{\cdot}Et_2O$, CH_3CN, −10 °C to rt (90%); (g) (1) PDC, 4A MS, CH_2Cl_2, 25 °C; (2) isopropylphosphonium bromide, NaHMDS, toluene, −78 °C to rt (75%, two steps).

With the required configurations established at C22 and C23 in **5**, the chiral auxiliary was cleaved by LAH reduction to give diol **8** (Scheme 3). Standard protecting group manipulation afforded primary alcohol **9**, which was then oxidized to the aldehyde. Acid hydrolysis of the acetonide, followed by in situ cyclization, gave hemiacetal **10** in good yield. Selective silylation and PCC oxidation of the hemiacetal furnished lactone **11**. The last stereogenic center in fragment **A** was introduced by a stereoselective reduction. Thus, treatment of lactone **11** with lithium ethyl acetate in THF gave the expected aldol adduct **12**, which was then reduced with triethylsilane in the presence of boron trifluoride etherate, via an intermediate oxonium ion, to furnish compound **13** with excellent selectivity.[7] Under these conditions, the primary TBS group was cleanly removed. PDC oxidation of alcohol **13** and subsequent Wittig olefination with isopropylidene phosphorane completed the highly stereoselective construction of fragment **A**.[8]

Scheme 4



[a] Key: (a) *ent*-**2** (1*R*, 2*S*), (*c*-Hex)$_2$BOTf, Et_3N, CH_2Cl_2, −78 °C, then **14** −78 to 0 °C (85%); (b) (1) LAH, THF, 0 °C (85%); (2) 2,2-dimethoxypropane, PPTS, CH_2Cl_2, 25 °C (91%); (c) (1) TBAF, THF, 25 °C (95%); (2) PPh_3, CCl_4, THF, reflux (87%); (d) AD-mix-β, $CH_3SO_2NH_2$, *t*-BuOH, H_2O, 25 °C (65%); (e) (1) NaOH, THF, 0 °C (60%); (2) TBSCl, imidazole, CH_2Cl_2, 25 °C (95%).

The synthesis of fragment **C** involves another *anti*-selective aldol reaction and an asymmetric Sharpless dihydroxylation (Scheme 4). Thus, the readily synthesized aldehyde **14** was treated with chiral enol borinate *ent*-**1** (1*R*, 2*S*) to give aldol **15** in 85% yield with good selectivity (ca. 15:1).[9] After the removal of the auxiliary, the diol was protected as its acetonide **16**. Deprotection and halogenation delivered the allylic chloride **17**, which then underwent standard asymmetric Sharpless dihydroxylation[10] to give the chlorohydrin **18** smoothly. Brief treatment of **18** with freshly powdered sodium hydroxide led to the formation of the α-hydroxy epoxide,[10] which was subsequently silylated to furnish fragment **C** in good yield. The synthesis of fragment **D** (Scheme 1) was rather straightforward, and we are now in possession of sufficient quantities of fragments **A**, **C**, and **D** for further studies on the synthesis of miyakolide.

The successful construction of the two key fragments **A** and **C** has demonstrated that *anti*-selective aldol reactions with **1** are generally applicable and proceed smoothly. The reactions are indeed reliable enough to be incorporated in the synthetic schemes for complex polyketide natural products.

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Supporting Information Available: The detailed experimental procedures and characterization data for compounds **A**, **C**, and **5**−**18** in the synthesis of fragments **A** and **C**, including the determination of the stereochemistry of the aldol reaction in fragment **C** synthesis (13 pages).

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(6) For a review of double asymmetric synthesis, see: Masamune, S.; Choy, W.; Peterson, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.*, **1985**, *24*, 1.

(7) Lewis, M. D.; Cha, J. K.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4976.

(8) The absolute stereochemical assignments of fragment **A** have been achieved through NMR techniques. See the Supporting Information for details.

(9) For the confirmation of the absolute stereochemistry of this transformation, see the Supporting Information.

(10) Vanhessche, K. P. M.; Wang, Z.-M.; Sharpless, K. B. *Tetrahedron Lett.* **1994**, *33*, 3469. For a recent review, see: Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.