Highly Enantioselective Aldol Reaction: Development of a New Chiral Auxiliary from *cis*-1-Amino-2-hydroxyindan

Arun K. Ghosh,* Tien T. Duong and Sean P. McKee

Department of Medicinal Chemistry, Merck Research Laboratories, West Point, Pennsylvania 19486, USA

Boron enolates obtained from optically active oxazolidinone derivative of *cis*-1-amino-2-hydroxyindan are reacted with various aldehydes to provide highly enantioselective aldol products in good yields.

Reaction of chiral enolates derived from a chiral auxiliary with aldehydes has emerged as an extremely useful method for enantiocontrolled generation of aldol products with high optical purity.[1] In this context, a large number of suitable chiral auxiliaries have been developed and utilized efficiently in the enantioselective synthesis of various natural products and biologically active molecules.[2] Nonetheless, readily accessible and versatile chiral auxiliaries are still in demand. Although optically active cyclic *cis*-1,2-aminoalcohols were employed as amino acid surrogates for HIV-1 protease inhibitors,[3] their utility as chiral auxiliaries in the aldol reaction has not been reported. The synthesis[4] and resolution of *cis*-1-amino-2-hydroxyindan has been described previously by our laboratories[3a] and its use in amide enolate alkylation has been recently reported.[5] Here, we describe our results on enantioselective aldol reactions with a new chiral auxiliary which contains a conformationally rigid oxazolidinone derivative of the aminoalcohol **1**.

Both enantiomers of *cis*-1-amino-2-hydroxyindan were obtained in multigram quantities as described previously. Chiral oxazolidinone **2**, m.p. 205 °C, $[\alpha]_D$ −79.4 (*c* 1.4, $CHCl_3$) was readily prepared by reaction of aminoalcohol **1** with disuccinimidyl carbonate (1.5 equiv.) in acetonitrile in the presence of triethylamine (3 equiv.) at 23 °C for 12 h (88% yield).† Compound **2** was then lithiated with Bu^nLi (1.0 equiv.) in dry tetrahydrofuran (THF) and reacted with propionyl chloride (1.1 equiv., −78 °C) to furnish the acylated oxazolidinone **3** (85% yield), m.p. 130 °C, $[\alpha]_D$ + 268 (*c* 2.4, $CHCl_3$).

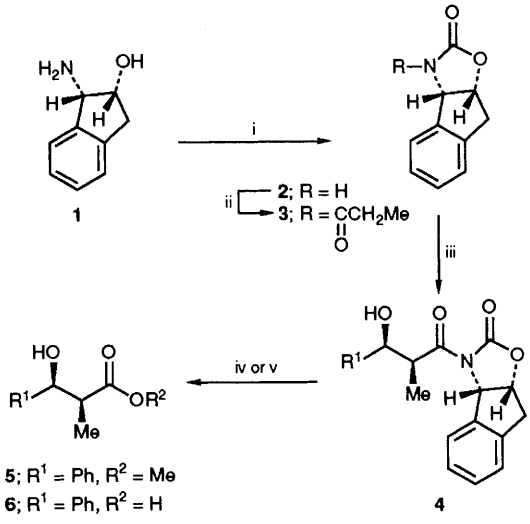
Reaction of **3** with di-n-butylboryl trifluoromethanesulfonate (1.1 equiv.) and triethylamine (1.2 equiv.) at −78 °C for 30 min and then at −78 to 0 °C for 1 h afforded the boron enolate.[6] Condensation of this resulting enolate with various aldehydes at −78 to 0 °C for several hours as monitored by TLC (2–5 h), resulted in only the diastereoisomer **4** after workup. No other diastereoisomers were detected by

† Reaction of aminoalcohol **1** with di(2-pyridyl) carbonate (1.5 equiv.) and triethylamine (3 equiv.) in CH_2Cl_2 also provided a good yield (81%) of oxazolidinone **2**.

Table 1 Aldol reaction of **3** with aldehydes

Entry	Aldehyde	Yields (%)[a]	$[\alpha]_D$ (**4**)	(%) d.e. (**4**)[b]
1	PhCHO	64	+166	>99
2	PhCH=CHCHO	62	+181	>99
3	MeCHO	71	+191	>99
4	Me_2CHCHO	73	+184	>99

[a] Yield of pure products after silica gel chromatography. [b] Determined by HPLC and 400 MHz ^1H NMR spectroscopy.

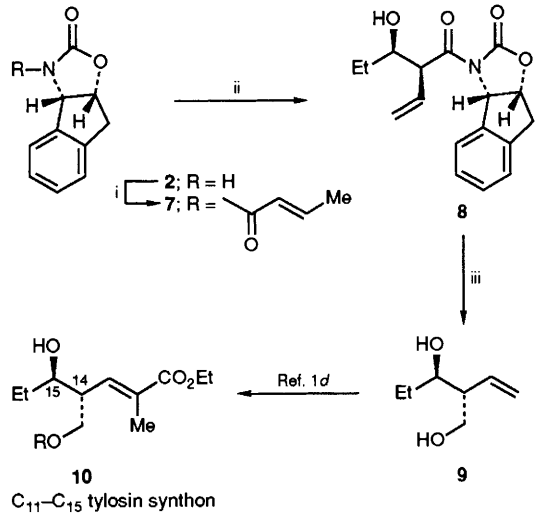


Scheme 1 *Reagents and conditions*: i, Disuccinimidyl carbonate, Et_3N, MeCN, 23 °C; ii, Bu^nLi, THF, 0 °C then $MeCH_2COCl$, THF, −78 °C; iii, Bu^n_2BOTf, Et_3N, CH_2CL_2, −78 to 0 °C then R^1CHO, −78 to 0 °C; iv, NaOMe, MeOH, 0 °C; v, LiOH, THF–H_2O (1 : 1), 0 °C; (Tf = trifluoromethylsulfonyl)

400 MHz ^1H NMR spectroscopy or by HPLC analysis. The absolute configurations of the aldol products were firmly established by comparison of the optical rotation of the corresponding methyl ester with the literature values.[2a] *E.g.*, exposure of the aldol product **4** (R^1 = Ph) with sodium methoxide (2 equiv.) in methanol at 0 °C for 1 h resulted in the corresponding methyl ester **5** ($[\alpha]_D$ −23.2 *c* 2.5; $CHCl_3$) in 89% isolated yield. The results of the aldol reaction of the oxazolidinone **3** with four different aldehydes are summarized in Table 1. As evidenced, the corresponding aldol products were obtained in good yields. Furthermore, owing to the configurational rigidity of the tricyclic ring system of chiral auxiliary **2**, almost complete diastereofacial selectivity (>99% d.e.) was observed in the aldol condensation with various aldehydes.

The removal of the chiral auxiliary was effectively carried out under exceptionally mild hydrolysis conditions. Thus, treatment of the aldol adduct **4** (R^1 = Ph) with 1 mol dm^{-3} lithium hydroxide solution in THF at 0 °C for 2 h afforded the acid **6** (89% yield) and good recovery (77–85%) of the chiral auxiliary **2**. To further demonstrate the applicability of this new chiral auxiliary, the synthesis of the C_{11}–C_{15} segment of the macrolide antibiotic tylosin[7] was undertaken. Deprotonation of the oxazolidinone **2** with Bu^nLi followed by acylation with the mixed anhydride resulting from the reaction of crotonic acid and pivaloyl chloride in the presence of triethylamine provided *N*-crotonylimide **7** in 82% yield after silica gel chromatography.

Formation of boron enolate with boron trifluoromethanesulfonate and subsequent condensation with propionaldehyde afforded only isomer **8** in 51% isolated yield. Aldol adduct **8** was then reduced smoothly with lithium aluminium hydride



Scheme 2 *Reagents and conditions*: i, Bu^nLi, THF, 0 °C then crotonic acid, Bu^tCOCl, Et_3N, −78 °C; ii, Bu^n_2BOTf, Et_3N, CH_2Cl_2, −78 to 0 °C then EtCHO, −78 to 0 °C; iii, LAH, THF, 0 °C

(LAH) in THF at 0 °C to furnish the alcohol **9** (81% yield)‡ which was previously converted to C_{11}–C_{15} tylosin segment.[1d]

In conclusion, this new chiral auxiliary complements the monocyclic chiral oxazolidinones derived from amino acids.[2] Further application of this methodology in the synthesis of biologically important molecules is in progress.

The authors thank Dr Wayne J. Thompson for helpful discussions and acknowledge the encouragement and support of Drs Joel R. Huff and Paul S. Anderson.

Received, 5th August 1992; Com. 2/04225H

References

1 (*a*) C. H. Heathcock, in *Asymmetric Synthesis*, ed. J. D. Morrison Academic Press: New York, 1984, vol. 3, p. 111; (*b*) D. A. Evans, in *Asymmetric Synthesis*, ed. J. D. Morrison, Academic Press. New York, 1984, vol. 3, p. 1; (*c*) D. A. Evans, J. V. Nelson and T. R. Taber, *Top. Stereochem.*, 1983, **13**, 1; (*d*) D. A. Evans, *Aldrichimica Acta*, 1982, **15**, 23.

2 (*a*) D. A. Evans, J. Bartroli and T. L. Shih, *J. Am. Chem. Soc.*, 1981, **103**, 2127; (*b*) W. Oppolzer, J. Blagg, I. Rodriguez and E. Walther, *J. Am. Chem. Soc.*, 1990, **112**, 2767; (*c*) H. Roder, G. Helmchen, E.-M. Peters and H.-G. von Schmering, *Angew. Chem., Int. Ed. Engl.*, 1984, **23**, 898; (*d*) G. Gardillo, M. Orena, M. Romero and S. Sandri, *Tetrahedron*, 1989, **45**, 1501; (*e*) W. Sankhavasi, M. Yamamoto, S. Kohmoto and K. Yamada, *Bull. Chem. Soc. Jpn.*, 1991, **64**, 1425; (*f*) S. E. Drewes, D. S. Malissar and G. P. Roos, *Chem. Ber.*, 1991, **124**, 2913; (g) D. A. Evans, J. R. Gage and J. L. Leighton, *J. Org. Chem.*, 1992, **57**, 1964 and references cited therein.

3 (*a*) W. J. Thompson, P. M. D. Fitzgerald, M. K. Holloway, E. A. Emini, P. L. Darke, B. M. McKeever, W. A. Schleif, J. C. Quintero, J. A. Zugay, T. J. Tucker, J. E. Schwering, C. F. Homnick, J. Nunberg, J. P. Springer and J. R. Huff, *J. Med. Chem.*, 1992, **35**, 1685; (*b*) T. A. Lyle, C. M. Wiscount, J. P. Guare, W. J. Thompson, P. S. Anderson, P. L. Darke, J. A. Zugay, E. A. Emini, W. A. Schleif, J. C. Quintero, R. A. F. Dixon, I. S. Sigal and J. R. Huff, *J. Med. Chem.*, 1991, **34**, 1228.

4 A. K. Ghosh, S. P. McKee and W. M. Sanders, *Tetrahedron Lett.*, 1991, **32**, 711.

5 D. Askin, M. A. Wallace, J. P. Vacca, R. A. Reamer, R. P. Volante, I. Shinkai, *J. Org. Chem.*, 1992, **57**, 2771.

6 D. A. Evans, R. L. Dow, T. L. Shih, J. M. Takacs and R. Zahler, *J. Am. Chem. Soc.*, 1990, **112**, 5290.

7 K. C. Nicolaou, M. R. Pavia and S. P. Seitz, *J. Am. Chem. Soc.*, 1982, **104**, 2027; 2030.

‡ All new compounds gave satisfactory spectroscopic and analytical results.