

# Highly Diastereoselective *anti*-Aldol Reactions Utilizing the Titanium Enolate of *cis*-2-Arylsulfonamido-1-acenaphthenyl Propionate

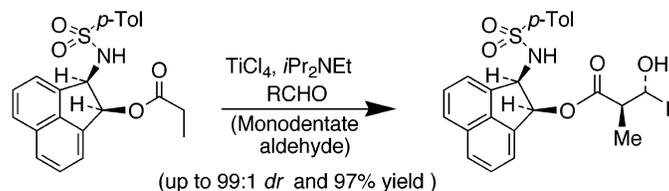
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## ABSTRACT



*anti*-Aldol reaction of Ti-enolate derived from *cis*-2-arylsulfonamido-1-acenaphthenyl propionate with representative aldehydes proceeded in excellent yield with high diastereoselectivity. Both enantiomers of *cis*-2-amino-1-acenaphthenol were synthesized employing lipase-catalyzed kinetic resolution as the key step.

Enantioselective synthesis of *anti*- $\alpha$ -alkyl- $\beta$ -hydroxycarbonyl units are of major interest in organic synthesis as these structural features are inherent to numerous bioactive natural products.<sup>1</sup> However, there exist few processes that are convenient and operationally simple and offer a high level of diastereoselectivity and generality. Development of effective *anti*-aldol methodologies constitutes a very important area in organic synthesis. A number of methodologies leading to diastereoselective *anti*-aldol reactions have been reported over the years.<sup>2</sup> We recently reported<sup>3</sup> *cis*-1-arylsulfonamido-2-indanyl ester-derived titanium enolate aldol reactions with high *anti*-diastereofacial selectivity. Subsequently, we have established that the choice of the *p*-toluenesulfonamido group and the presence of the indanyl ring are critical to the observed *anti*-aldol diastereoselectivity. The stereochemical outcome was rationalized based upon a Zimmerman–Traxler<sup>4</sup> transition state model in which a  $\pi$ -stacking interaction between the aromatic rings was postulated. We have

subsequently speculated that planarity in conjunction with aromaticity of the acenaphthene moiety may further enhance  $\pi$ – $\pi$  stacking interactions with the arylsulfonamide functionality. This may lead to further improvement of *anti*-diastereoselectivity. Herein, we report that aldol reactions of optically active *cis*-2-arylsulfonamido-1-acenaphthenyl

(2) (a) Meyers, A. I.; Yamamoto, Y. *Tetrahedron* **1984**, *40*, 2309. (b) Helmchen, G.; Leikauf, U.; Taufer-Knopfel, I. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 874. (c) Gennari, C.; Bernardi, A.; Colombo, L.; Scolastico, C. *J. Am. Chem. Soc.* **1985**, *107*, 5812. (d) Masamune, S.; Sato, T.; Kim, B. M.; Wollman, T. A. *J. Am. Chem. Soc.* **1986**, *108*, 8279. (e) Corey, E. J.; Kim, S. S. *J. Am. Chem. Soc.* **1990**, *112*, 4976. (f) Meyers, A. G.; Widdowson, K. L. *J. Am. Chem. Soc.* **1990**, *112*, 9672. (g) Walker, M. A.; Heathcock, C. H. *J. Org. Chem.* **1991**, *56*, 5747. (h) Braun, M.; Sacha, H. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1318. (i) Oppolzer, W.; Lienard, P. *Tetrahedron Lett.* **1993**, *34*, 4321. (j) Paterson, I.; Wren, S. P. *J. Chem. Soc., Chem. Commun.* **1993**, 1790. (k) Abiko, A.; Liu, J.-F.; Masamune, S. *J. Am. Chem. Soc.* **1997**, *119*, 2586. (l) Kurosu, M.; Lorca, M. *J. Org. Chem.* **2001**, *66*, 1209. (m) Evans, D. A.; Tedrow, J. S.; Shaw, J. T.; Downey, C. W. *J. Am. Chem. Soc.* **2002**, *124*, 392. (n) Denmark, S. E.; Wynn, T.; Beutner, G. L. *J. Am. Chem. Soc.* **2002**, *124*, 13405 and references therein.

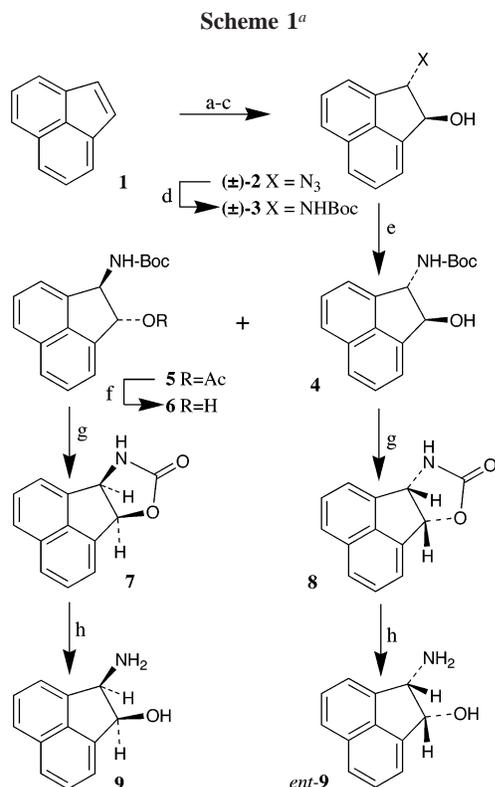
(3) (a) Ghosh, A. K.; Onishi, M. *J. Am. Chem. Soc.* **1996**, *118*, 2527. (b) Ghosh, A. K.; Fidanze, S.; Onishi, M.; Hussain, K. A. *Tetrahedron Lett.* **1997**, *38*, 7171.

(4) Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920.

(1) (a) Heathcock, C. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, p 111. (b) Masamune, S.; Choy, W.; Peterson, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1. (c) Franklin, A. S.; Paterson, I. *Contemp. Org. Synth.* **1994**, 317.

propionate-derived titanium enolate with a variety of aldehydes provided *anti*-aldols in excellent diastereoselectivity and isolated yields. Both enantiomers of *cis*-2-amino-1-acenaphthenol were prepared in high enantiomeric excess (>98%) with use of an enzymatic acylation of racemic *trans*-2-*N*-Boc-amino-1-acenaphthenol as the key step.

To access multigram quantities of both enantiomers of *cis*-2-amino-1-acenaphthenol, our plan was to carry out an enzymatic resolution of the racemic alcohol.<sup>5</sup> The synthesis of enantiomerically pure *cis*-2-amino-1-acenaphthenol is shown in Scheme 1. Commercially available acenaphthylene



<sup>a</sup> Reagents and conditions: (a) NBS, DMSO, 23 °C, 0.5 h; (b) NaOH, Et<sub>2</sub>O, 23 °C, 3 h; (c) NaN<sub>3</sub>, NH<sub>4</sub>Cl 80%–EtOH, 80 °C, 3 h; (d) 10% Pd–C, H<sub>2</sub>, (Boc)<sub>2</sub>O, EtOAc, 23 °C, 40 h; (e) PS 30 lipase, vinyl acetate/DME (1:1), 37 °C, 40 h; (f) Et<sub>3</sub>N, MeOH/H<sub>2</sub>O (2:1), 23 °C, 27 h; (g) MsCl, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, 23 °C, 4 h; (h) NaOH, MeOH/H<sub>2</sub>O (1:1), 80 °C, 18 h.

**1** was exposed to *N*-bromosuccinimide in DMSO in the presence of water to provide the corresponding *trans*-bromohydrin, which was reacted with NaOH in ether to furnish the epoxide. The resulting epoxide was treated with NaN<sub>3</sub> and NH<sub>4</sub>Cl in 80% aqueous EtOH to give *trans*-azido alcohol **2** in 78% yield for three steps.<sup>6</sup> Racemic azido

alcohol **2** was hydrogenated over 10% Pd–C in the presence of (Boc)<sub>2</sub>O in ethyl acetate to afford racemic *N*-Boc-amino alcohol **3** in one pot in 80% yield. The racemic alcohol (**3**) was exposed to lipase-catalyzed enantioselective transesterification with immobilized Amano PS 30 lipase on Celite (20 wt % with respect to PS 30)<sup>5</sup> in a mixture of dimethoxyethane and vinyl acetate at 37 °C for 40 h. These reaction conditions resulted in unreacted (1*S*,2*S*)-*N*-Boc-2-amino-1-acenaphthenol **4** (48%, >99% ee) and acylated (1*R*,2*R*)-*N*-Boc-2-amino-1-acetoxy acenaphthene **5** (49%, 99% ee) after silica gel chromatography. Enantiomerically pure acetate **5** was hydrolyzed by triethylamine in aqueous methanol to provide the corresponding alcohol (**6**) in 99% yield. Enantiomeric excess of **4** and **6** was determined by chiral HPLC (Daicel Chiral OD column, 10% 2-propanol/hexane; exhibiting retention time 9.6 and 10.9 min, respectively).

It should be noted that our initial attempt to resolve racemic *cis*-2-azido-1-acenaphthenol<sup>7</sup> with PS 30 Amano lipase-catalyzed resolution under a variety of conditions resulted in enantiopure *cis*-1-azido-2-acenaphthenol in up to 72% ee.<sup>8</sup> However, attempts to further improve the enantioselectivity of lipase-catalyzed resolution of both *cis*- and *trans*-1-azido-2-acenaphthenol were unsuccessful because of very little steric differentiation between the azide and alcohol groups. Subsequently, we have converted the azide functionality to a *tert*-butyloxycarbonyl group to establish steric discrimination between the substituents. This led to excellent optical resolution and isolated yield. Optically pure *N*-Boc protected amino alcohols **4** and **6** were treated with methanesulfonyl chloride and triethylamine at 23 °C to afford the corresponding *cis*-oxazolidinones **8** (86% yield) and **7** (92% yield), respectively.<sup>9</sup> Hydrolysis of oxazolidinones **7** and **8** with aqueous sodium hydroxide in methanol furnished optically pure chiral amino alcohol **9** in 85% yield and its enantiomer (*ent*-**9**) in 87% yield. The overall route is very efficient and both enantiomers of *cis*-2-amino-1-acenaphthenol were obtained in multigram quantities. Other access to enantiomerically pure 2-amino-1-acenaphthenol is thus far limited.<sup>10</sup>

The utility of the *cis*-2-amino-1-acenaphthenol template in diastereoselective *anti*-aldol reactions has been demonstrated. As shown in Scheme 2, optically active amino alcohol **9** was treated with *p*-toluenesulfonyl chloride and triethylamine in the presence of DMAP in CH<sub>2</sub>Cl<sub>2</sub> to afford *N*-tosylated alcohol **10** in 77% yield. *N*-Tosylated amino alcohol also can be prepared from oxazolidinone **7** in two steps by treatment with NaH and *p*-toluenesulfonyl chloride in THF followed by mild hydrolysis of the resulting *N*-tosylated oxazolidinone with cesium carbonate in aqueous MeOH to provide **10** in 81% yield. Reaction of **10** with

(7) Sudo, A.; Hashimoto, Y.; Kimoto, H.; Hayashi, K.; Saigo, K. *Tetrahedron: Asymmetry* **1994**, *5*, 1333.

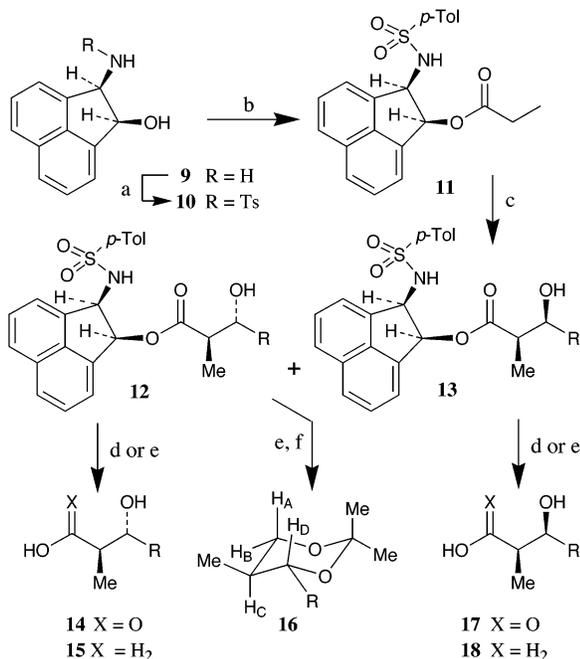
(8) Lipase-catalyzed reactions in the presence of vinyl acetate in DME at 37 °C for 24 h provided (*R,R*)-*cis*-1-azido-2-acenaphthenol in 42% yield and 72% ee and (*S,S*)-*cis*-1-azido-2-acenaphthenyl acetate in 50% yield and 58% ee by chiral HPLC.

(9) (a) Ghosh, A. K.; Shin, D.; Mathivanan, P. *Chem. Commun.* **1999**, 1025. (b) Beneditti, F.; Norbedo, S. *Tetrahedron Lett.* **2000**, *41*, 10071.

(10) Saigo, K.; Hashimoto, Y.; Sudo, A. *Russ. J. Org. Chem.* **1996**, *32*, 230 and references therein.

(5) (a) Ghosh, A. K.; Kincaid, J. K.; Haske, M. G. *Synthesis* **1997**, 541. (b) Wong, C.-H.; Whitesides, G. M. In *Enzymes in Synthetic Organic Chemistry*; Pregamon Press: London, UK, 1993; Chapter 2. (c) Faber, K. *Biotransformations in Organic Chemistry*; Springer-Verlag: Berlin, Germany, 1992; pp 248–301.

(6) Pöchlauer, P.; Müller, E. P.; Peringer, P. *Helv. Chim. Acta* **1984**, *67*, 1238.

Scheme 2<sup>a</sup>

<sup>a</sup> Reaction conditions: (a) TsCl, Et<sub>3</sub>N, DMAP, CH<sub>2</sub>Cl<sub>2</sub>, 23 °C, 2 h. (b) EtCOCl, Py, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, 2 h (c) TiCl<sub>4</sub>, *i*Pr<sub>2</sub>NEt, 0 °C, 1 h, then RCHO, TiCl<sub>4</sub>, CH<sub>3</sub>CN, CH<sub>2</sub>Cl<sub>2</sub>, -78 °C, 1.5 h. (d) LiOH, THF/H<sub>2</sub>O, 23 °C, 15 h. (e) LiBH<sub>4</sub>, THF/MeOH, 23 °C, 10 h. (f) Me<sub>2</sub>C(OMe)<sub>2</sub>, PPTS, CH<sub>2</sub>Cl<sub>2</sub>, 23 °C.

propionyl chloride and pyridine in CH<sub>2</sub>Cl<sub>2</sub> furnished propionate ester **11** in 95% yield after chromatography followed by trituration in cold hexane. Treatment of **11** with TiCl<sub>4</sub> (1.1 equiv, 1 M solution in CH<sub>2</sub>Cl<sub>2</sub>) in CH<sub>2</sub>Cl<sub>2</sub> at 0 °C followed by addition of *N,N'*-diisopropylethylamine (3 equiv) after 10 min and stirring of the resulting mixture at 0 °C for 1 h generated the corresponding titanium enolate. This enolate was reacted with isobutyraldehyde precomplexed with TiCl<sub>4</sub> (2.2 equiv) at -78 °C for 2 h. This afforded a mixture of aldol products in 75% yield with the *anti*-isomer as the major product (*anti*:*syn* ratio 78:22). Out of four possible diastereomers, formation of *anti*-diastereomer **12** and *syn*-diastereomer **13** was observed by <sup>1</sup>H NMR and <sup>13</sup>C NMR analysis. However, the extent of *anti*-diastereoselectivity is significantly lower compared to the aminoindanol-derived chiral template that provided a single *anti*-diastereomer.<sup>3a</sup> The reaction with benzaldehyde proceeded with moderate *syn*-selectivity (*anti*:*syn* ratio 38:62, 77% yield), which is consistent with previous results.<sup>3a</sup>

In an effort to improve *anti*-diastereoselectivity of the reaction between **11** and isobutyraldehyde, we investigated the effect of additives and ligands on titanium.<sup>11</sup> Among additives used, acetonitrile resulted in significant improve-

(11) For previous investigations with PPh<sub>3</sub>, NMP, and THF as additives, see: (a) Gennari, C.; Colombo, L.; Bertolini, G.; Schimperna, G. *J. Org. Chem.* **1987**, *52*, 2754. (b) Palazzi, C.; Colombo, L.; Gennari, C. *Tetrahedron Lett.* **1986**, *27*, 1735. (c) Crimmins, M. T.; King, B. W.; Tabet, E. A.; Chaudhary, K. *J. Org. Chem.* **2001**, *66*, 894. (d) Nerz-Stormes, M.; Thornton, E. R. *J. Org. Chem.* **1991**, *56*, 2489.

ment with respect to selectivity and yield. Full investigation with other additives and chiral auxiliaries will be reported in due course. Representative reactions in Table 1 with

Table 1. Aldol Reaction with Representative Aldehydes

entry	aldehyde	major ptd	yield <sup>a</sup>	<i>anti</i> ( <b>12</b> ): <i>syn</i> ( <b>13</b> ) <sup>b</sup>
1	<i>i</i> BuCHO	<b>12a</b>	95	97:3
2	MeCHO	<b>12b</b>	71	80:20
3	EtCHO	<b>12c</b>	92	92:8
4	PrCHO	<b>12d</b>	85	91:9
5	<i>i</i> PrCHO	<b>12e</b>	95	96:4
6	Cy-hexCHO	<b>12f</b>	84	99:1
7	PhCHO	<b>12g</b>	93	93:7 <sup>c</sup>
8	BnCH <sub>2</sub> CHO	<b>12h</b>	97	95:5
9	BnOCH <sub>2</sub> CHO	<b>13i</b>	91	1:99

<sup>a</sup> Isolated yield of diastereomeric mixtures. <sup>b</sup> Ratio determined by <sup>1</sup>H NMR before chromatography.<sup>12</sup> <sup>c</sup> A mixture of three diastereomers (*anti*:*syn* 80:13:7).

various aldehydes and CH<sub>3</sub>CN were carried out as follows: the Ti-enolate of **11**, prepared as described above, was added to isovaleraldehyde precomplexed with 1 M TiCl<sub>4</sub> in CH<sub>2</sub>-Cl<sub>2</sub> (2.2 equiv) in the presence of CH<sub>3</sub>CN (2.2 equiv) at -78 °C to afford aldolate **12a** in excellent *anti*-diastereoselectivity (97:3 dr, entry 1) and isolated yield (95%). As can be seen in Table 1, the reaction of propionate ester **11** with other aldehydes also proceeded with excellent *anti*-diastereoselectivity and the yields are particularly improved compared to the aminoindanol-derived system.<sup>13</sup> Reaction with isobutyraldehyde also afforded the aldol product with excellent *anti*-diastereoselectivity and isolated yields (entry 5). The reaction with cyclohexanecarboxaldehyde proceeded with nearly complete *anti*-diastereoselectivity (entry 6). Even reaction with benzaldehyde provided the *anti*-aldol product selectively (entry 7). In the case of a bidentate aldehyde (entry 9), the aldol reaction furnished only a single *syn*-diastereomer as in the case of previously documented aminoindanol-based aldol reactions.<sup>3b</sup>

The relative stereochemistry of aldol products was assigned based upon comparison of observed vicinal coupling constants ( $J_{2,3} = 6.8\text{--}7.6$  Hz for *anti*-aldols and  $J_{2,3} = 2.1$  Hz for *syn*-aldol) with the literature.<sup>14</sup> Further confirmation of the relative stereochemistry of *anti*-aldols **12f–h** and *syn*-aldol **13i** was established by their conversion to the corresponding isopropylidene derivatives **16f–i** and comparison of coupling constants with the literature values.<sup>15,16</sup> The absolute configuration of the aldolates was established after

(12) Diastereomeric ratio was determined by an integration ratio of CHOH proton or acenaphthenyl ring protons.

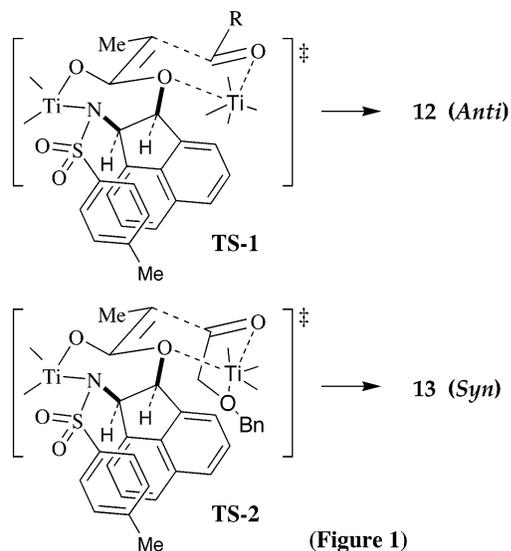
(13) Aldol reactions of (1*S*,2*R*)-*cis*-1-arylsulfonamido-2-indanyl propionate provided *anti*-aldol diastereoselectivity of 90:10 dr and 95% yield for isobutyraldehyde and 96:4 dr and 73% yield for benzaldehyde.

(14) (a) Yan, T.-H.; Tan, C.-W.; Lee, H.-C.; Lo, H.-C.; Huang, T.-Y. *J. Am. Chem. Soc.* **1993**, *115*, 2613. (b) Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. C.; John, J. E.; Lampe, J. *J. Org. Chem.* **1980**, *45*, 1066.

(15) Barret, A. G. M.; Rys, D. J. *J. Chem. Soc., Perkin Trans. 1* **1995**, *8*, 1009.

(16) Marshall, J. A.; Wang, X.-J. *J. Org. Chem.* **1992**, *57*, 1242.

removal of the chiral auxiliary by either mild saponification with LiOH in aqueous THF at 23 °C or LiBH<sub>4</sub> reduction in THF–MeOH at 23 °C. Optical rotations and spectroscopic data of the resulting acids and alcohols were compared with literature values.<sup>17</sup> The observed *anti*-aldol diastereoselectivities with monodentate aldehydes and *syn*-selectivity with bidentate aldehyde can be rationalized on the basis of Zimmerman–Traxler<sup>4</sup> transition state models **TS-1** and **TS-2**, respectively (Figure 1).<sup>3</sup> The reason for enhancement of



**Figure 1.**

*anti*-selectivity associated with added acetonitrile is presumably due to its coordination to titanium, which resulted in better steric bias on the metal center. Gennari also reported additive effects of triphenylphosphine which resulted in an

enhanced *anti*-selectivity in Mukaiyama aldol reactions.<sup>11a,b</sup> Also, oxygen bearing heterocyclic compounds such as THF and *N*-methyl pyrrolidinone were reported to alternate the stereochemical outcome in titanium-mediated aldol reactions.<sup>11c,d</sup>

In summary, the current methodology represents a practical and enantioselective entry to a range of *anti*-aldols in optically pure form. The generality has been demonstrated with a number of different aldehydes. Also, synthesis of both enantiomers of *cis*-2-amino-1-acenaphthenol provides convenient access to either *anti*-aldol enantiomer with high optical purity. Further investigations including mechanistic studies are underway.

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**Supporting Information Available:** Experimental procedures, spectral data for compounds **3–13**, and <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra for compounds **12–18**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(17) Chloroform was used in all cases. **14a** (R = *i*Bu): [ $\alpha$ ]<sub>D</sub><sup>23</sup> +17.4 (*c* 0.72) (lit.<sup>3b</sup> [ $\alpha$ ]<sub>D</sub><sup>23</sup> –18.2 (ent)). **14e** (R = *i*Pr): [ $\alpha$ ]<sub>D</sub><sup>23</sup> –11.7 (*c* 0.69) (lit.<sup>18</sup> [ $\alpha$ ]<sub>D</sub><sup>23</sup> –14.3). **14g** (R = Ph): [ $\alpha$ ]<sub>D</sub><sup>23</sup> –40.7 (*c* 0.93) (lit.<sup>19</sup> [ $\alpha$ ]<sub>D</sub><sup>23</sup> –53.4). **15c** (R = Et): [ $\alpha$ ]<sub>D</sub><sup>23</sup> 21.6 (*c* 0.55) (lit.<sup>20</sup> [ $\alpha$ ]<sub>D</sub><sup>23</sup> –22.6 (ent)). **15d** (R = Pr): [ $\alpha$ ]<sub>D</sub><sup>23</sup> 32.5 (*c* 0.58) (lit.<sup>21</sup> [ $\alpha$ ]<sub>D</sub><sup>23</sup> 33.6). **15f** (R = Cy-Hex): [ $\alpha$ ]<sub>D</sub><sup>23</sup> 24.1 (*c* 0.83) (lit.<sup>22</sup> [ $\alpha$ ]<sub>D</sub><sup>23</sup> 24.3). **15h** (R = CH<sub>2</sub>Bn): [ $\alpha$ ]<sub>D</sub><sup>23</sup> 45.3 (*c* 0.95). **17i** (R = CH<sub>2</sub>OBn) [ $\alpha$ ]<sub>D</sub><sup>23</sup> –12.78 (*c* 1.2) (lit.<sup>3b</sup> [ $\alpha$ ]<sub>D</sub><sup>23</sup> 12.97 (ent)). **18i** (R = CH<sub>2</sub>OBn): [ $\alpha$ ]<sub>D</sub><sup>23</sup> –2.8 (*c* 0.85).

(18) Draanen, N. A. V.; Arseniyadis, S.; Crimmins, M. T.; Heathcock, C. H. *J. Org. Chem.* **1991**, *56*, 2499.

(19) Yang, Y.-C.; Hung, A.-W.; Chang, C.-S.; Yan, T.-H. *J. Org. Chem.* **1996**, *61*, 2038.

(20) Mori, K.; Sano, S.; Yokoyama, Y.; Bando, M.; Kido, M. *Eur. J. Org. Chem.* **1998**, *6*, 1135.

(21) Masamune, S.; Sato, T.; Kim, B.-M.; Wollmann, T. S. *J. Am. Chem. Soc.* **1986**, *108*, 8279.

(22) Harada, T.; Kurokawa, H.; Kagamihara, Y.; Tanaka, S.; Inoue, A.; Oku, A. *J. Org. Chem.* **1992**, *57*, 1412.