

## Stereoselective Aldol Condensation. Use of Chiral Boron Enolates

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The structures of numerous macrolide and ionophore antibiotics<sup>1</sup> readily reveal the potential application of aldol-type reactions in the syntheses of these natural products. An illustrative example is 6-deoxyerythronolide B (**1**) (Chart 1).<sup>2</sup> The construction of the carbon framework of this compound, in principle, can be achieved in a straightforward manner through a sequence of four aldol condensations, as indicated by the dotted lines in **1**. Each condensation creates two new chiral centers. Thus, the success of this synthetic strategy relies heavily upon our abilities to execute the stereoselective synthesis of two aldol products, **2** and **3**, with the absolute configurations indicated. This crucial transformation has now been achieved with notable success. We wish to demonstrate herein the remarkably high stereoselectivity exhibited by several boron enolates derived from chiral ethyl ketones **4** and **5**,<sup>3,4</sup> in the aldol reaction and then describe in the accompanying communication<sup>5</sup> the synthesis of 6-deoxyerythronolide B (**1**) through the extensive use of these new reagents.

The preparation of **4**<sup>6</sup> and **5**<sup>6</sup> is straightforward and starts with optically pure (*S*)- and (*R*)-mandelic acids (**6** and **7**), both of which are commercially available. A tedious process of resolution encountered in our earlier, similar work<sup>3d</sup> is thus avoided. Catalytic hydrogenation (Rh/Al<sub>2</sub>O<sub>3</sub>) of **6** and **7** proceeded smoothly.<sup>7</sup> Treatment of the resulting hexahydro derivatives **8**<sup>6</sup> and **9**<sup>6</sup> with 3.5 equiv of ethyllithium (ether, -78 °C → 0 °C) provided a 75% yield of the corresponding ethyl ketones **10**<sup>6</sup> and **11**<sup>6</sup> which were in turn silylated to afford **4** and **5**, respectively. Generation of boron enolates **12a-c** (or **13a-c**) from **4** (or **5**) and subsequent aldol condensation with a variety of aldehydes **14** are standardized and were performed as follows: To a CH<sub>2</sub>Cl<sub>2</sub> (5 mL) solution of **4** (1.0 mmol) was added at -78 °C, under nitrogen, diisopropylethylamine (1.0 mmol) and then a dialkylboron trifluoromethanesulfonate (**15**) (0.9 mmol) (Scheme I). After stirring the mixture for 1 h and 45 min at 0 °C, an aldehyde (**14**) (0.5 mmol) was added dropwise (Scheme II), and the resulting mixture was stirred an additional 45 min. The usual workup, including preparative TLC, provided a mixture of diastereomeric isomers,

Chart I

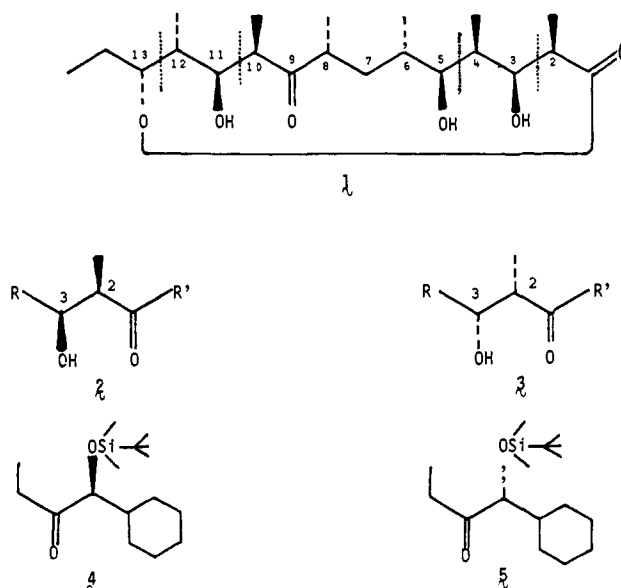


Table I. Results of the Aldol Condensations of Achiral Aldehydes (**14**) with Dialkylboron Enolates (**12a-c**)

aldehyde ( <b>14</b> )	boron enolate	ratio of <sup>a</sup> 16 to 17	major $\beta$ -hydroxy acid ( <b>18</b> )
C <sub>6</sub> H <sub>5</sub> -CHO <b>14a</b>	<b>12a</b>	14:1	
	<b>12b</b>	40:1	
	<b>12c</b>	75:1	
CH <sub>3</sub> CH <sub>2</sub> -CHO <b>14b</b>	<b>12a</b>	17:1	
	<b>12b</b>	50:1	
	<b>12c</b>	>100:1	
C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> CH <sub>2</sub> CHO <b>14c</b>	<b>12a</b>	16:1	
	<b>12b</b>	28:1	
	<b>12c</b>	100:1	
CH <sub>3</sub> CHO <b>14d</b>	<b>12a</b>	>100:1	
	<b>12b</b>	>100:1	
	<b>12c</b>	no reaction	

<sup>a</sup> The product ratios are based mainly on the relative intensities of several sets of the corresponding signals observed in the 250-MHz <sup>1</sup>H NMR spectrum of each diastereomeric mixture.

\* The authors wish to dedicate this communication to Professor George Hermann Büchi on the occasion of his 60th birthday.

(1) (a) For a recent review on macrolide antibiotics, see: Masamune, S.; Bates, G. S.; Corcoran, J. W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 585. (b) For ionophore antibiotics, see: Westley, J. W. *Adv. Appl. Microbiol.* **1977**, *22*, 177.

(2) Martin, J. R.; Rosenbrook, W. *Biochemistry* **1967**, *6*, 435.

(3) Use of chiral enolates in the aldol reaction has been reported recently: (a) Heathcock, C. H.; White, C. T. *J. Am. Chem. Soc.* **1979**, *101*, 7076. (b) Heathcock, C. H.; Pirrung, M. C.; Buse, C. T.; Hagen, J. P.; Young, S. D.; Sohn, J. E. *Ibid.* **1979**, *101*, 7077. (c) Hoffmann, R. W.; Zeiss, H.-J. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 218. (d) Masamune, S.; Ali, S. K. A.; Snitman, D. L.; Garvey, D. S. *Ibid.* **1980**, *19*, 557.

(4) For a recent review on the subject of acyclic stereoselection, see: Bartlett, P. A. *Tetrahedron* **1980**, *36*, 3.

(5) Masamune, S.; Hiram, M.; Mori, S.; Ali, S. K. A.; Garvey, D. S. *J. Am. Chem. Soc.* **1981**, *103*, following paper in this issue.

(6) The specific rotations [ $\alpha$ ]<sub>D</sub> (°C, concentration, solvent) of compounds used in this work are **4** (25, 1.15, CHCl<sub>3</sub>) -60.30; **5** (25, 1.19, CHCl<sub>3</sub>) +59.83; **8** (24, 1.07, CH<sub>3</sub>CO<sub>2</sub>H) +23.02; **9** (25, 1.01, CH<sub>3</sub>CO<sub>2</sub>H) -22.82; **10** (24.5, 1.22, CHCl<sub>3</sub>) +128.5; **11** (25, 1.00, CHCl<sub>3</sub>) -128.03; **18a** (25, 1.07, CHCl<sub>3</sub>) +31.03; **18b** (25.5, 1.72, CHCl<sub>3</sub>) -4.10 (concentration dependent); **18c** (28, 0.9, C<sub>2</sub>H<sub>5</sub>OH) -16.07; **18d** (25, 1.40, CHCl<sub>3</sub>) +10.54°. These compounds, except for the carboxylic acids, have been shown to be enantiomerically pure to the limit of detection by NMR using Eu(hfc)<sub>3</sub>. Additional physical data of these and other compounds are described in the supplementary material.

(7) Hirano, T.; Inoue, S.; Tsuruta, T. *Makromol. Chem.* **1976**, *177*, 3237.

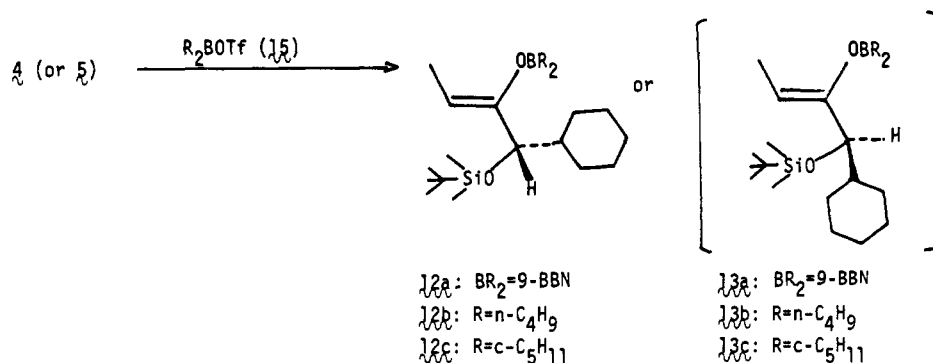
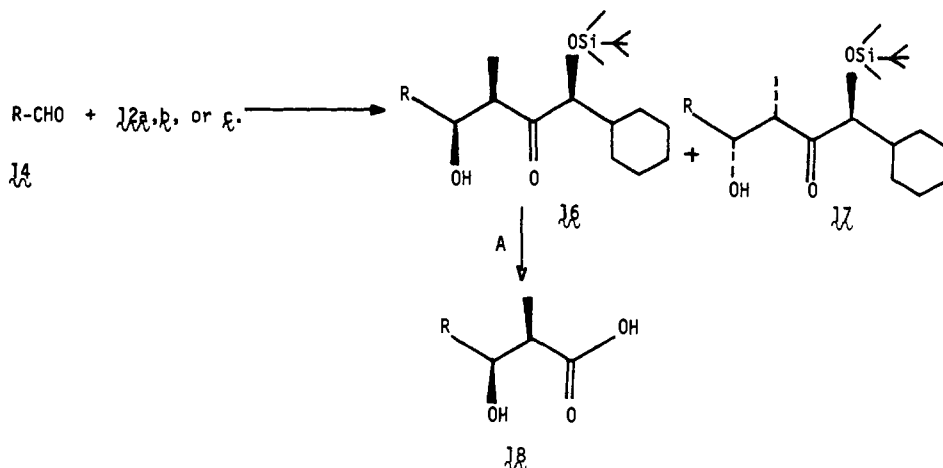
**16** and **17**, uniformly in 70-85% isolated yield based on **14**.<sup>8,9</sup> The major isomer **16**, which constituted at minimum 93% of the product mixture, was further converted quantitatively into the corresponding 3-hydroxy-2-methylcarboxylic acid (**18**)<sup>6</sup> via two steps: desilylation<sup>10</sup> and sodium metaperiodate oxidation. The structure and absolute configuration of **18** was established by comparison with that derived from a compound of known stereochemistry in each case.<sup>11</sup>

(8) The conditions of this reaction are patterned after the Mukaiyama procedure: (a) Mukaiyama, T.; Inoue, T. *Chem. Lett.* **1976**, 559. Inoue, T.; Uchimara, T.; Mukaiyama, T. *Ibid.* **1977**, 153. For the stereoselective aldol condensation using boron enolates, see: (b) Masamune, S.; Mori, S.; Van Horn, D. E.; Brooks, D. W. *Tetrahedron Lett.* **1979**, 1665. (c) Hiram, M.; Masamune, S. *Ibid.* **1979**, 2225. (d) Van Horn, D. E.; Masamune, S. *Ibid.* **1979**, 2229. (e) Hiram, M.; Garvey, D. S.; Lu, L. D.-L.; Masamune, S. *Ibid.* **1979**, 3937. (f) Evans, D. A.; Vogel, E.; Nelson, J. V. *J. Am. Chem. Soc.* **1979**, *101*, 6120.

(9) The high ratio of the reagent to an aldehyde is deliberately chosen in order to illustrate the case where the aldehyde is valuable. The use of excess aldehydes (which are inexpensive) leads to equally good yields based on the reagent.

(10) Newton, R. F.; Reynolds, D. P.; Finch, M. A. W.; Kelly, D. R.; Roberts, S. M. *Tetrahedron Lett.* **1979**, 3981.

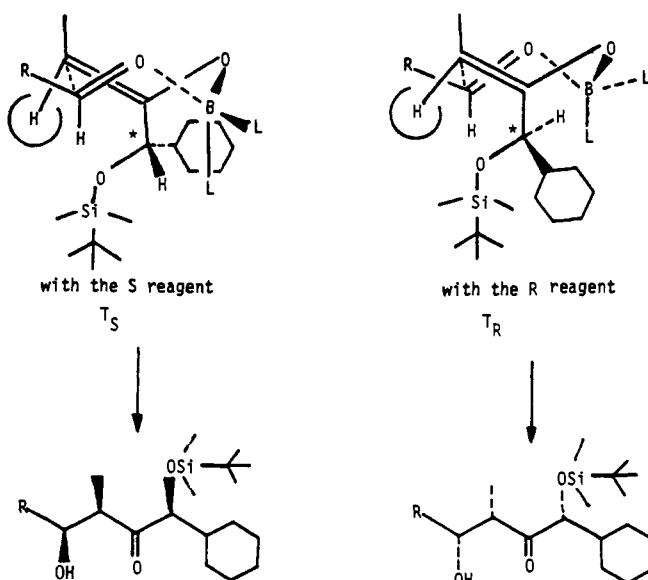
Scheme I

Scheme II<sup>a</sup>

<sup>a</sup> (A) (1) Concentrated  $HF-CH_3CN$  (1:20 v/v), room temperature, 3.5h. (2)  $NaIO_4$  ( $CH_3OH/H_2O$ ), room temperature, 3 h.

Table I summarizes the results of the aldol condensations with three different boron enolates **12a–c**, carrying the 9-borabicyclo[3.3.1]non-9-yl (9-BBN), di-*n*-butyl, and dicyclopentyl ligands, respectively. Several notable features are evident. (1) In all cases the aldol products consist of 2,3-*syn*<sup>12,13</sup> products **16** and **17**, and no trace of the corresponding 2,3-*anti* isomers is found to the limit of our analytical methods. In view of the earlier findings,<sup>8b–f,14</sup> this indicates the exclusive formation of (*Z*)-enolates from **4** as shown in **12a–c**. (2) The ratios of **16** and **17** are impressively high and increase with the size of the ligands attached to the boron. With the dicyclopentylboron enolate **12c**, both benzaldehyde and the two other aldehydes with no substituents at the  $\alpha$  position provide a single aldol product, virtually free from its diastereoisomer. In the case of the  $\alpha$ -branched aldehyde **14d**, excellent stereoselection is already achieved with the less bulky reagents **12a** and **12b**, but the fact that the reaction does not proceed with **12c** is very likely due to steric congestion in the transition state. (3) The absolute configurations of the two chiral centers present in each of **18a–d** are determined as shown in Table I and are experimentally correlated with the stereochemistry of the ethyl ketone **4**. The use of **5** instead of **4** obviously leads to the formation

Chart II



(11) While **18b** was found to be the enantiomer of the corresponding degradation product ( $C_{11}-C_{13}$  fragment) obtained from **1** (see ref 5), **18a**, **18c**, and **18d** were reduced to the diols which were correlated from those prepared from (*S*)-(+)-3-hydroxy-2-methylpropanoic acid (Cohen, N.; Eichel, W. F.; Lopresti, R. J.; Newkom, C.; Saucy, G. *J. Org. Chem.* **1976**, *41*, 3505). The conversions are somewhat elaborate and described in the supplementary material.

(12) For the definition of "syn" and "anti", see footnote 7 of ref 3d.

(13) The relative stereochemistry of the two substrates at the 2 and 3 positions of **16** and **17** is mainly based on the size of pertinent coupling constants measured in their NMR spectra (see, e.g., ref 8b–f). The stereochemical assignments to **16** have also been confirmed through conversion of **16** to **18**.

(14) (a) Buse, C. T.; Heathcock, C. H. *J. Am. Chem. Soc.* **1977**, *99*, 8109. (b) Pirrung, M. C.; Heathcock, C. H. *J. Org. Chem.* **1980**, *45*, 1727. (c) Heathcock, J.-H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. C.; Sohn, J. E.; Lampe, J. *Ibid.* **1980**, *45*, 1066.

of the enantiomers of **18a–d**, and thus the diastereoselective synthesis of **16** followed by oxidative cleavage of the  $\alpha$ -hydroxy-keto group constitutes an enantioselective synthesis of  $\beta$ -hydroxy- $\alpha$ -methylcarboxylic acids. Many natural product syntheses potentially utilize these compounds as starting materials, which are now available in optically active form with ease and in quantity. We recommend the use of **12a** for aldehydes with an  $\alpha$  substituent and that of **12c** for aldehydes carrying no  $\alpha$  substituent.

Although the stereochemical course of the aldol reaction is extremely complicated, the commonly accepted  $6\pi$ -electron chair-type transition state may serve to rationalize, at least ten-

tatively, the high selectivity described above. In the transition states  $T_S$  and  $T_R$  proposed for the reaction of **12a-c** and **13a-c** with an aldehyde, the substituents attached to the chiral center(\*) of the enolate reagent are so oriented as to minimize the steric congestion (Chart II). The interactions of cyclohexyl moiety with the (circled) vinylic hydrogen and the ligands attached to boron are avoided as shown in  $T_S$  and  $T_R$ . Thus, the stereochemistry of the chiral center dictates the approach of the enolate with respect to the aldehyde [approach from the  $\alpha$  face of the aldehyde as depicted in  $T_S$ , from the  $\beta$  face as shown in  $T_R$ ] which is translated into the absolute configuration of the final aldol product.

Reaction of **12a-c** or **13a-c** with a chiral aldehyde is of great interest. We have already demonstrated recently that the high diastereoselectivity of a chiral enolate can outweigh many other factors<sup>15</sup> (such as the Cram/anti-Cram selectivity of the aldehyde<sup>16</sup>) which influence the enolate approach to the aldehyde. As a consequence, the stereochemistry at both 2 and 3 positions of compounds **2** and **3**, relative to those existing in (chiral) *R*, can be controlled.<sup>3d</sup> The diastereoselectivity of our new reagents **12** and **13** is far superior to that of our earlier reagents<sup>3d</sup> and exhibits the remarkable stereochemical control in many complex cases as exemplified in the following paper.<sup>5</sup>

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**Supplementary Material Available:** A listing of spectral data (4 pages). Ordering information is given on any current masthead page.

(15) Masamune, S. Lecture presented at the Third IUPAC Symposium on Organic Synthesis, held at Madison, WI, June 15-20; *Pure Appl. Chem.*, in press.

(16) For recent reviews, see: (a) Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* 1978, 10, 175-285. (b) Morrison, J. D.; Mosher, H. S. In "Asymmetric Organic Reactions"; American Chemical Society: Washington, DC, 1976.

## Total Synthesis of 6-Deoxyerythronolide B

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6-Deoxyerythronolide B (**1**), produced by blocked mutants of *Streptomyces erythreus*, is a common biosynthetic precursor leading to all the erythromycins presently known.<sup>1-3</sup> The structure of **1** is rich in chirality: ten asymmetric centers are embedded in the monocyclic, 14-membered lactone system. With the de-

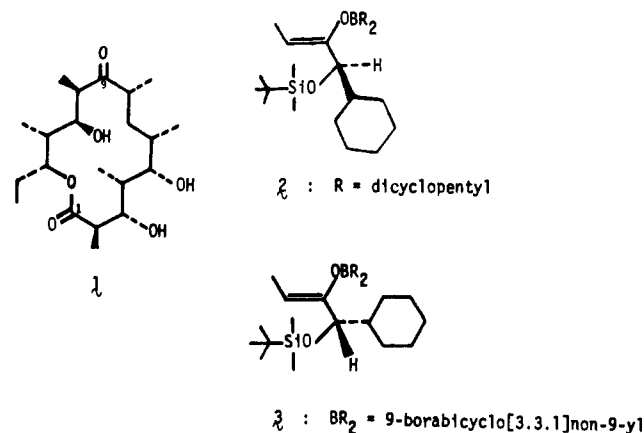
\* The authors wish to dedicate this article to Professor George Hermann Büchi on the occasion of his 60th birthday.

(1) (a) Martin, J. R.; Rosenbrook, W. *Biochemistry* 1967, 6, 435. (b) Perun, T. J.; Egan, R. S. *Tetrahedron Lett.* 1969, 387. (c) Egan, R. S.; Perun, T. J.; Martin, J. R.; Mitscher, L. A. *Tetrahedron* 1973, 29, 2525.

(2) For a recent review on the chemistry and biochemistry of macrolide antibiotics, see: Masamune, S.; Bates, G. S.; Corcoran, J. W. *Angew. Chem., Int. Ed. Engl.* 1977, 16, 585.

(3) Erythronolide A and B recently yielded to syntheses. (a) Corey, E. J.; Hopkins, P. B.; Kim, S.; Yoo, S.-E.; Nambiar, K. P.; Falck, J. R. *J. Am. Chem. Soc.* 1979, 101, 7131. (b) Corey, E. J.; Trybulski, E. J.; Melvin, L. S.; Nicolaou, K. C.; Secrist, J. A.; Lett, R.; Sheldrake, P. W.; Falck, J. R.; Brunelle, D. J.; Haslanger, M. F.; Kim, S.; Yoo, S.-E. *Ibid.* 1978, 100, 4618. (c) Corey, E. J.; Kim, S.; Yoo, S.; Nicolaou, K. C.; Melvin, L. S.; Brunelle, D. J.; Falck, J. R.; Trybulski, E. J.; Lett, R.; Sheldrake, P. W. *Ibid.* 1978, 100, 4620.

Chart I



velopment of new synthetic methodology utilizing the chiral boron enolates **2** and **3** outlined in the preceding paper,<sup>4</sup> the aldol strategy has now been utilized successfully in the synthesis of **1** (Chart I). All of the crucial carbon-carbon bond forming reactions involved in the construction of the carbon framework are exclusively aldol condensations, and more importantly, the overall stereoselection of these *four* reactions now reaches 85%. This achievement fulfills an objective originally set for this synthetic project and demonstrates the state of the art in the stereochemical control of this complex reaction. A summary of the synthesis of **1** follows.

The seco-acid derivative **4** formally derived from **1** is divided into two portions [the left-hand fragment (C<sub>11</sub>-C<sub>13</sub>) (**5**) and the right-hand one (C<sub>1</sub>-C<sub>10</sub>) (**6**)] (Scheme I), each of which has been synthesized.

**Left-Hand Fragment 5.** The enantioselective synthesis (selectivity 100:1, 85% yield) of the corresponding hydroxy acid **7**, using propionaldehyde and the *R*-chiral reagent (**2**), is already described.<sup>4</sup> A sequence of routine operations consisting of methylation (CH<sub>2</sub>N<sub>2</sub>), triethylsilylation, reduction [(*i*-C<sub>4</sub>H<sub>9</sub>)<sub>2</sub>AlH], and Collins' oxidation convert **7** into **5**<sup>5</sup> in 75% overall yield.

**Right-Hand Fragment 6.** The construction of **6** starts with the C<sub>5</sub>-C<sub>9</sub> fragment (see **6**). The condensation of (-)-aldehyde **8**<sup>6</sup> with the *S*-chiral reagent (**3**) proceeds smoothly (85% yield, stereoselection 40:1) to provide an aldol product (**9**)<sup>5</sup> which, after successive treatments with hydrogen fluoride and sodium metaperiodate, is converted quantitatively into the Pregel-Djerassi lactonic acid (**10**)<sup>6-8</sup> [ $\alpha$ ]<sub>D</sub><sup>25</sup> +47.5° (*c* 1.10, CHCl<sub>3</sub>) (Scheme II). Thus, this compound **10**, a key intermediate in the syntheses of several natural products, is most readily available in multigram quantities and in optically pure form. Not surprisingly, when (-)-**8** is reacted with the corresponding *R* reagent, compound **9'** becomes the predominant product (stereoselection of 15:1 in favor of **9'**). This aldol product **9'** is converted to **10'** with the structure indicated.<sup>6a</sup> Thus, this set of aldol reactions clearly demonstrates that with both reagents one can indeed create the *syn*-3-

(4) Masamune, S.; Choy, W.; Kerdesky, F. A. J.; Imperiali, B. *J. Am. Chem. Soc.* 1981, 103, preceding paper in this issue.

(5) The specific rotations [ $\alpha$ ]<sub>D</sub><sup>25</sup> (°C, concentration) in CHCl<sub>3</sub> of compounds prepared in this work are **4** (24, 0.61) -26.2; **5** (27, 2.50) +49.8; **6** (25, 1.86) -37.0; **7** (25.5, 1.72) +4.1; **8** (25, 0.785) -18.7; **9** (24.5, 2.17) -17.2; **11** (26, 3.62) +27.0 (crude); **12** (24.5, 3.90) +37.3; **13** (26, 1.74) +22.3; **14** (25, 0.41) -33.5; **20** (26, 0.14) -51.0.

(6) (a) Masamune, S.; Ali, S. K. A.; Snitman, D. L.; Garvey, D. S. *Angew. Chem., Int. Ed. Engl.* 1980, 19, 557. (b) Bartlett, P. A.; Adams, J. L. *J. Am. Chem. Soc.* 1980, 102, 337.

(7) (a) Anliker, R.; Dvornik, D.; Gubler, K.; Heusser, H.; Prelog, V. *Helv. Chim. Acta* 1956, 39, 1785. (b) Djerassi, C.; Zderic, J. A. *J. Am. Chem. Soc.* 1956, 78, 6390.

(8) The compound has recently been synthesized via several different routes. (a) Masamune, S.; Kim, C. U.; Wilson, K. E.; Spessard, G. O.; Georgiou, P. E.; Bates, G. S. *J. Am. Chem. Soc.* 1975, 97, 3512. (b) White, J. D.; Fukuyama, Y. *Ibid.* 1979, 101, 226. (c) Stork, G.; Nair, V. *Ibid.* 1979, 101, 1315. (d) Grieco, P. A.; Ohfun, Y.; Yokoyama, Y.; Owens, W. *Ibid.* 1979, 101, 4749. (e) Hirama, M.; Garvey, D. S.; Lu, L. D.-L.; Masamune, S. *Tetrahedron Lett.* 1979, 3937. Also see ref 6.