

# Asymmetric Glycine Enolate Aldol Reactions: Synthesis of Cyclosporine's Unusual Amino Acid, MeBmt<sup>1</sup>

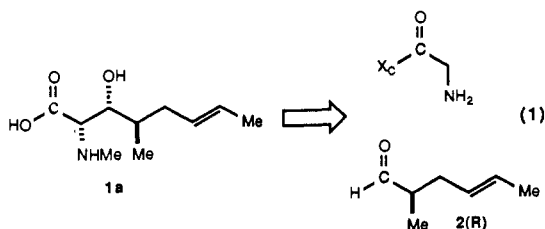
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**Abstract:** The chiral glycine synthon **3c**, as its derived stannous enolate, has been demonstrated to undergo a highly syn diastereoselective aldol addition reaction with representative aldehydes to give the adducts **5** (R = C<sub>6</sub>H<sub>5</sub>, Me, Me<sub>2</sub>CH) in yields ranging from 71 to 92%. The utility of these intermediates has been demonstrated via the subsequent three-step transformation of these adducts to the enantiomerically pure *N*-methyl  $\beta$ -hydroxy amino acids **1**. This reaction methodology has been applied to the asymmetric synthesis of (4*R*)-4-((*E*)-2-butenyl)-4,*N*-dimethyl-L-threonine (**1a**), an important constituent in the immunosuppressant peptide cyclosporine. Several additional structural analogues of **1a** were also prepared in conjunction with this study.

The unusual C<sub>9</sub> amino acid MeBmt (**1a**),<sup>1</sup> found in the immunosuppressive peptide cyclosporine,<sup>3</sup> appears to be critically involved in the observed biological activity of this chemotherapeutic agent. Limited structure-activity studies have demonstrated that modification of this amino acid moiety dramatically effects the immunosuppressive activity of the resultant cyclosporine analogue.<sup>4</sup> Although **1a** is not available via the degradation of cyclosporine, a 24-step synthesis of this amino acid from diethyl tartrate has recently been reported.<sup>5</sup> It is clear that an efficient synthesis of **1a** and related analogues would greatly facilitate the exploration of some of the important structure-activity relationships associated with this clinically important drug.

The successful approach to the synthesis of MeBmt (**1a**) and related compounds reported herein is predicated upon the development of a suitable chiral glycine enolate synthon and its participation in the desired aldol bond construction (eq 1).<sup>6</sup> In



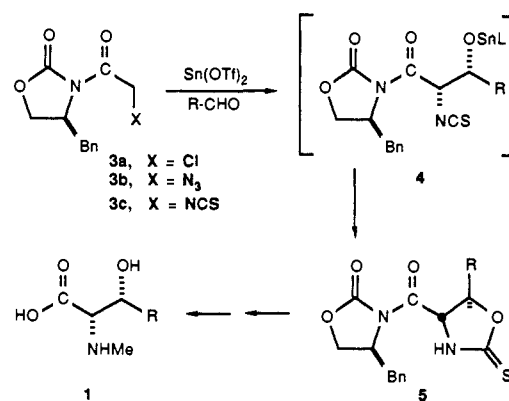
analogy with our earlier aldol studies,<sup>7</sup> we have relied upon oxazolidinone chiral auxiliaries for absolute stereochemical control. After exploring several other unsuccessful glycine enolate equivalents, we have found that the isothiocyanate **3c** performs admirably in the desired aldol process.<sup>8</sup> This compound was prepared in two steps from the chloroacetate precursor **3a**. Conversion of **3a** to **3b** with sodium azide (5 equiv, 1:1 CH<sub>2</sub>Cl<sub>2</sub>:H<sub>2</sub>O, 25 °C, 1.0 h) under phase transfer catalysis (0.1 equiv of *n*-Bu<sub>4</sub>NHSO<sub>4</sub>) afforded the desired azide in 99% yield. Azide **3b** was conveniently transformed into the desired isothio-

**Table I.** Diastereoselective Aldol Addition Reactions of **3c** with Representative Aldehydes (Scheme I)<sup>14</sup>

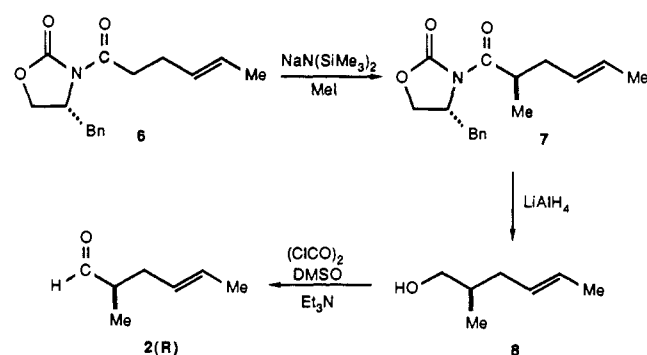
| R-CHO                  | ratio <sup>a</sup> | yield, % | adduct <sup>b</sup> |
|------------------------|--------------------|----------|---------------------|
|                        | 94:6               | 73       | <b>5a</b>           |
|                        | 97:3               | 71       | <b>5b</b>           |
|                        | 93:7               | 81       | <b>5c</b>           |
| Me <sub>2</sub> CH-CHO | 99:1               | 92       | <b>5d</b>           |
| Me-CHO                 | 91:9               | 75       | <b>5e</b>           |
| Ph-CHO                 | 99:1               | 91       | <b>5f</b>           |

<sup>a</sup>The ratio of product diastereomers defined as the fraction of desired isomer divided by the sum of all others. <sup>b</sup>Yields reported for the isolated major diastereomer in a diastereomeric purity >99% as determined by HPLC.

**Scheme I**



**Scheme II**



cyanate following literature precedent (PH<sub>3</sub>P, THF, CS<sub>2</sub>, 81% or H<sub>2</sub>, Pd-C, MeOH; Cl<sub>2</sub>CS, NaHCO<sub>3</sub>, CHCl<sub>3</sub>-H<sub>2</sub>O, 82%).<sup>9</sup>

(1) (4*R*)-4-((*E*)-2-Butenyl)-4,*N*-dimethyl-L-threonine (IUPAC/IUB three-letter amino acid notation).

(2) NSF predoctoral fellow, 1982-1985.

(3) *Cyclosporin A*; White, D. J. G., Ed.; Biomedical: Amsterdam, 1982.

(4) (a) Wenger, R. M. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 77. (b) Rich, D. H.; Dhaon, M. K.; Dunlap, B.; Miller, S. P. *J. Med. Chem.* **1986**, *29*, 978.

(5) Wenger, R. M. *Helv. Chim. Acta* **1983**, *66*, 2308.

(6) For other asymmetric glycine enolate aldol reactions see: (a) Schollkopf, U.; Nozulak, J.; Grauert, M. *Synthesis* **1985**, 55. (b) Belokon', Y. N.; Bulychev, A. G.; Vitt, S. V.; Struchkov, Y. T.; Batsanov, A. S.; Timofeeva, T. V.; Tsyryapkin, V. A.; Ryzhov, M. G.; Lysova, L. A.; Bakhtmutov, V. I.; Belikov, V. M. *J. Am. Chem. Soc.* **1985**, *107*, 4252. (c) Nakatsuka, T.; Miwa, T.; Mukaiyama, T. *Chem. Lett.* **1981**, 279.

(7) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127.

(8) For other examples of isothiocyanate aldol reactions see: (a) Volkmann, R. A.; Davis, J. T.; Meltz, C. N. *J. Am. Chem. Soc.* **1983**, *105*, 5946. (b) Hoppe, D.; Follmann, R. *Chem. Ber.* **1976**, *109*, 3047.

The requisite aldehyde **2(R)** can be synthesized, in principle, via crotyl bromide alkylation of the *N*-propionyl (*S*)-phenylalaninol-derived oxazolidinone or methylation of the *N*-hexenoyl (*R*)-phenylalaninol-derived oxazolidinone.<sup>10</sup> In practice, isomerically pure *trans*-crotyl bromide is not readily available, so the latter approach was chosen (Scheme II). Thus, the sodium enolate of *N*-hexenoyloxazolidinone **6** was treated with methyl iodide at  $-78\text{ }^{\circ}\text{C}$  to give a 10:1 ratio of diastereomers. The major diastereomer **7** was isolated chromatographically in 79% yield (>99% de). Reduction of **7** with lithium aluminum hydride afforded the corresponding alcohol **8** in 80% yield. Subsequent Swern oxidation provided a 93% yield of the desired aldehyde **2(R)**. The enantiomeric aldehyde **2(S)** was prepared in direct analogy with this route from the enantiomeric chiral oxazolidinone derived from (*S*)-phenylalaninol.

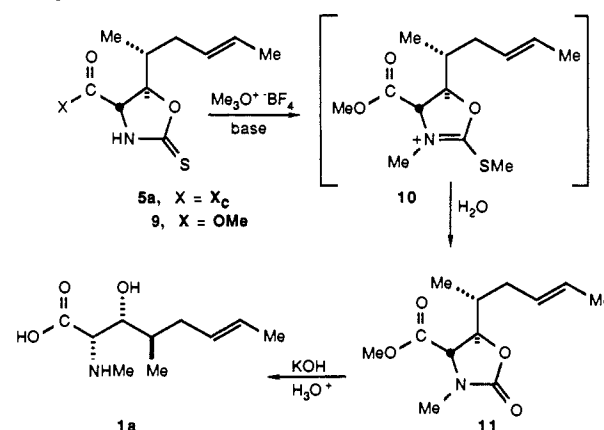
In the aldol reactions of isothiocyanate **3c** with representative aldehydes, disappointing levels of reaction diastereoselection were noted for both the lithium and dibutylboron enolates. In contrast, the stannous triflate mediated<sup>11</sup> aldol process of **3c** with a range of aldehydes afforded the desired syn aldol adducts **4**, which were isolated as the internally derivatized heterocycles **5** in good yield (Scheme I; Table I).

In a typical procedure, 1.2 equiv of stannous triflate in anhydrous tetrahydrofuran (THF) is cooled to  $-78\text{ }^{\circ}\text{C}$  and 1.5 equiv of *N*-ethylpiperidine is added, followed by a precooled solution of **3c** in THF. After the reaction mixture is stirred for 1.5 h, the aldehyde is added and stirring is continued at  $-78\text{ }^{\circ}\text{C}$  for 1.5–4 h. The reaction is quenched by the addition of pH 7 phosphate buffer, the resultant white slurry is filtered through Celite, and the product is isolated via an extractive workup. Purification by chromatography on silica gel or recrystallization gives **5** in diastereomerically pure ( $\geq 99\%$ ) form.

The sense of asymmetric induction in the aldol process was established in two of the reported cases. The relative and absolute stereochemistry of the acetaldehyde-derived aldol adduct **5e** ( $R = \text{Me}$ ) was established by its conversion (LiOH, THF– $\text{H}_2\text{O}$ ,  $0\text{ }^{\circ}\text{C}$ ; concentrated HCl, reflux) to L-threonine. The same stereochemical outcome was also observed in the synthesis of MeBmt (**1a**), vide infra. The sense of asymmetric induction in these reactions is directly analogous to the stereochemical outcome of the related boron enolate derived aldol reactions of our previously reported 3-acyl-2-oxazolidinones.<sup>7</sup> These results stand in contrast to the recent observations of Fujita and co-workers which suggest the opposite sense of asymmetric induction for similar stannous enolates.<sup>12</sup>

The general protocol for the conversion of the aldol adducts **5** into *N*-methyl amino acids is illustrated in the context of the synthesis of MeBmt (Scheme III; Table II). Transesterification of **5a** to the corresponding methyl ester **9** was accomplished with a solution of magnesium methoxide in methanol ( $0\text{ }^{\circ}\text{C}$ , 3 min, 91%). Bismethylation of **9** was achieved with freshly prepared trimethyloxonium tetrafluoroborate (2.1 equiv) and Proton Sponge (1.1 equiv,  $\text{CH}_2\text{Cl}_2$ ,  $0\text{ }^{\circ}\text{C}$ , 3 h) to give the salt **10**. Due to the pronounced tendency of this intermediate to undergo elimination, its hydrolysis was effected without isolation. The reaction from which **10** was derived was concentrated ( $0\text{ }^{\circ}\text{C}$ , in vacuo) and subsequently suspended in a 2:1 THF–aqueous pH 7 phosphate buffer ( $0\text{ }^{\circ}\text{C}$ , 1.5 h) to give the oxazolidone **11** in 74–86% yield. In the final step, **11** was hydrolyzed (2.0 N KOH,  $80\text{ }^{\circ}\text{C}$ , 12 h) and isolated according to the procedure of Wenger,<sup>5</sup> to afford the desired amino acid **1a** in 82–88% yield. This compound was found to be identical (NMR, mixture melting point) with a comparison sample of MeBmt.<sup>13</sup>

Scheme III

Table II. Physical Properties of the Amino Acids **1a–d**<sup>14</sup>

| amino acid <sup>a</sup>                   | mp ( $^{\circ}\text{C}$ ) | $[\alpha]_D^b$          | yield, <sup>c</sup> % |
|---|---------------------------|-------------------------|-----------------------|
| <b>1a</b> : $R = \text{C}_6\text{H}_{11}$ | 242–243                   | +17° ( <i>c</i> 0.51)   | 70                    |
| <b>1b</b> : $R = \text{C}_6\text{H}_{11}$ | 254–256                   | +0.85° ( <i>c</i> 0.59) | 67                    |
| <b>1c</b> : $R = \text{C}_3\text{H}_7$    | 248–249                   | +17° ( <i>c</i> 0.55)   | 70                    |
| <b>1d</b> : $R = \text{C}_3\text{H}_7$    | 261–262                   | –1.6° ( <i>c</i> 0.55)  | 69                    |

<sup>a</sup>The specific structures of the individual amino acids may be inferred from Table I. <sup>b</sup>Mesured in 0.4 N aqueous HCl (*c* in g/100 mL). <sup>c</sup>Values refer to the overall yield for the conversion of aldol adducts to the illustrated amino acids.

In addition to the synthesis of MeBmt, the  $\text{C}_4$  methyl diastereomer **1b** and the desmethyl analogue **1c** of this important amino acid were also prepared. The physical properties of these compounds are provided in Table II. Cyclosporine analogues derived from both **1b** and **1c** are currently being prepared. The biological properties of these new cyclosporine derivatives will be reported in due course. The full experimental details of the synthesis of MeBmt are included.

### Experimental Section

Tetrahydrofuran, diethyl ether, triethylamine, and *N*-ethylpiperidine were distilled from sodium metal/benzophenone ketyl. Methylene chloride and diisopropylamine were distilled from calcium hydride. Methanol was distilled from magnesium methoxide. Dimethyl sulfoxide was distilled from calcium hydride and stored over 4 Å sieves. Aldehydes were distilled and used immediately, or stored under nitrogen. Methyl iodide was passed through a column of activity 1 alumina immediately prior to use. All other reagents were used as received. Unless otherwise noted, all nonaqueous reactions were carried out under a dry nitrogen atmosphere with flame-dried glassware. Melting points are uncorrected.

**(2S)-2-Amino-3-phenylpropanol.**<sup>15</sup> A flame-dried, 3-L, 3-necked, round-bottomed flask equipped with a pressure-equalizing addition funnel, an 18-in. Vigreux column with a distillation head, and a mechanical stirring apparatus was charged with 200 g (1.21 mol) of (*S*)-phenylalanine and 600 mL of dry tetrahydrofuran (THF). Over a 30-min period, 172 g (149 mL, 1.21 mol) of boron trifluoride–etherate (Aldrich Chemical Co., purified, redistilled grade) was added. The pale yellow mixture was heated at reflux for 1 h after which the solid material had completely dissolved. The reaction temperature was adjusted to just below the reflux point, and 101 g (133 mL, 1.33 mol) of borane–methyl sulfide complex (Aldrich Chemical Co., 10 M) was added dropwise over 2 h. During the addition, hydrogen evolved, and methyl sulfide was allowed to distill as it was liberated. The clear, orange solution was heated at reflux for 6 h and cooled to ambient temperature. The remaining borane was quenched by careful addition of 150 mL of 1:1 THF/water. To the pale yellow solution was added 900 mL of 5 M aqueous sodium hydroxide solution. The reaction was heated at reflux for 12 h. The remaining THF was removed in vacuo, and the resulting slurry was extracted with five 200-mL portions of methylene chloride. The combined organic layers were dried over sodium sulfate, filtered, and concentrated in vacuo to give a colorless solid. Recrystallization from ethyl acetate (two crops) gave 156 g (85%) of the title compound as

(14) Satisfactory spectra data and elementary analyses were obtained for all compounds reported herein.

(15) Chapman, K. T.; Evans, D. A., unpublished results.

(9) (a) Staudinger, H.; Hauser, E. *Helv. Chim. Acta* **1921**, *4*, 861. (b) Floch, L.; Kovac, S. *Collect. Czech. Chem. Commun.* **1975**, *40*, 2845.

(10) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737.

(11) Mukaiyama, T.; Iwasawa, R. W.; Stevens, R. W.; Haga, T. *Tetrahedron* **1984**, *40*, 1381.

(12) Nagao, Y.; Yamada, S.; Kumagai, T.; Ochiai, M.; Fujita, E. *J. Chem. Soc., Chem. Commun.* **1985**, 1418.

(13) We thank Dr. R. M. Wenger, Sandoz Ltd., Basel, Switzerland, for kindly providing us with a sample of MeBmt.

colorless needles: mp 89.5–91.5 °C;  $[\alpha]_D -24.7^\circ$  (EtOH, *c* 1.03).

**(4S)-4-(Phenylmethyl)-2-oxazolidinone.**<sup>15</sup> A dry, 2-L, 3-necked, round-bottomed flask equipped with a thermometer, an 18-in. Vigreux column with a distillation head, and a mechanical stirring apparatus was charged with 203 g (1.35 mol) of (*S*)-phenylalaninol, 18.6 g (0.135 mol) of potassium carbonate, and 324 g (332 mL, 2.74 mol) of diethyl carbonate. The mixture was carefully heated to 135–140 °C, and ethanol was allowed to distill as it was formed. After 2 h, 180 mL of distillate had been collected. The light brown slurry was cooled to ambient temperature, diluted with 1 L of methylene chloride, and filtered to remove most of the remaining potassium carbonate. The solution was washed with 1 N aqueous sodium bicarbonate solution. The organic layer was dried over magnesium sulfate and concentrated in vacuo to give a pale yellow crystalline solid. Recrystallization from ethyl acetate/hexane (two crops) gave 201 g (84%) of the title compound as colorless needles: mp 87.0–88.5 °C; IR (CH<sub>2</sub>Cl<sub>2</sub>) 3460, 3020, 1760, 1480, 1405, 1220 cm<sup>-1</sup>; <sup>1</sup>H NMR (90 MHz, CDCl<sub>3</sub>) δ 7.30 (m, 5 H, aromatic H's), 6.25 (br s, 1 H, NH), 3.85–4.60 (m, 3 H, NCHCH<sub>2</sub>), 2.88 (m, 2 H, PhCH<sub>2</sub>); <sup>13</sup>C NMR (22.5 MHz, CDCl<sub>3</sub>) δ 159.9, 136.0, 129.1, 128.8, 127.0, 69.4, 53.6, 41;  $[\alpha]_D +4.9^\circ$  (EtOH, *c* 1.10).

**(4R)-4-(Phenylmethyl)-2-oxazolidinone.** This compound was synthesized from (2*R*)-2-amino-3-phenylpropanol in a manner analogous to that of its enantiomer.

**(4R)-3-((4'E)-4'-Hexenoyl)-4-(phenylmethyl)-2-oxazolidinone (6).** To a stirring, -78 °C solution of 6.76 g (59.3 mmol) of 4-hexenoic acid<sup>16</sup> and 6.85 g (9.40 mL, 67.7 mmol, 1.2 equiv) of triethylamine in 250 mL of anhydrous tetrahydrofuran (THF) was added 7.14 g (7.30 mL, 59.3 mmol, 1.05 equiv) of trimethylacetyl chloride. After the resultant white suspension was stirred for 10 min at -78 °C and 30 min at 0 °C, it was recooled to -78 °C and a -78 °C solution of metallated oxazolidinone (prepared by the addition of 35.3 mL (56.4 mmol, 1.6 M in hexane) of *n*-butyllithium to a -78 °C solution of 10.0 g (56.4 mmol) of (4*R*)-4-(phenylmethyl)-2-oxazolidinone in 250 mL of THF) was added via canula. The reaction mixture was stirred for an additional 30 min at 0 °C and then quenched by the addition of 150 mL of saturated aqueous ammonium chloride. Volatiles were removed in vacuo. The residue was extracted into three 200-mL portions of methylene chloride. The combined organic phases were washed with 300 mL of 1 N aqueous sodium hydroxide and 300 mL of 1 N aqueous sodium bisulfate, dried over sodium sulfate, and concentrated in vacuo to give 15.3 g (99% mass balance) of a pale yellow crystalline solid. Purification by flash chromatography (50 × 100 mm silica gel, 20% ethyl acetate/hexane) yielded 14.3 g (93%) of the title compound as a white, crystalline solid. An analytical sample was prepared by recrystallization from ether/hexane: *R*<sub>f</sub> 0.42 (25% ethyl acetate/hexane); mp 69–69.5 °C; IR (CH<sub>2</sub>Cl<sub>2</sub>) 3080–2850, 1784, 1704, 1455, 1386, 1353, 1215, 1200, 1100, 970 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.38–7.20 (m, 5 H, aromatic H's), 5.55–5.48 (m, 2 H, CH=CH), 4.70–4.64 (m, 1 H, C<sub>4</sub>-H), 4.23–4.15 (m, 2 H, C<sub>5</sub>-H<sub>2</sub>), 3.30 (dd, 1 H, *J* = 3.3, 13.4 Hz, CHHPh), 3.11–2.90 (m, 2 H, COCH<sub>2</sub>), 2.76 (dd, 1 H, *J* = 9.6, 13.4 Hz, CHHPh), 2.42–2.35 (m, 2 H, CH<sub>2</sub>CH=CH), 1.65 (m, 3 H, CH=CHCH<sub>3</sub>); <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>) δ 172.7, 153.3, 135.4, 129.3, 128.8, 127.2, 126.1, 66.1, 55.0, 38.0, 35.4, 27.2, 17.6;  $[\alpha]_D -80.6^\circ$  (CH<sub>2</sub>Cl<sub>2</sub>, *c* 1.04).

Anal. Calcd for C<sub>16</sub>H<sub>19</sub>NO<sub>3</sub>: C, 70.31; H, 7.01. Found: C, 70.47; H, 6.92.

**(4R)-3-((2'R,4'E)-2'-Methyl-4'-hexenoyl)-4-(phenylmethyl)-2-oxazolidinone (7).** To a -78 °C solution of 20.5 mL (20.5 mmol, 1.1 equiv, 1.0 M in tetrahydrofuran (THF)) of sodium hexamethyldisilylamide was added dropwise via canula a 0 °C solution of 5.10 g (18.7 mmol, 1.0 equiv) of (4*R*)-3-((4'E)-4'-hexenoyl)-4-(phenylmethyl)-2-oxazolidinone (6) in 20 mL of THF. After the reaction mixture was stirred at -78 °C for 30 min, 13.2 g (5.81 mL, 93.3 mmol, 5 equiv) of iodomethane in 2 mL of THF at -78 °C was added via canula. The solution was stirred for 4 h and then quenched by the addition of 20 mL of aqueous saturated ammonium chloride solution. Volatiles were removed by rotary evaporation, and the resultant slurry was extracted with three 100-mL portions of methylene chloride. The combined organic fractions were washed with a 200-mL portion of aqueous 1 M sodium bisulfate solution, dried over anhydrous sodium sulfate, and concentrated in vacuo to give 5.73 g (107% mass balance) of a pale yellow oil. GC analysis (DB-1, 175 °C, 15 psi) indicated a 10:1 ratio of the title compound (*t*<sub>r</sub> 6.80 min) to the minor isomer (*t*<sub>r</sub> 7.01 min). Purification by MPLC (Chromoflex 2 in. × 30 cm column, 5–15% ethyl acetate/hexane gradient) gave 4.22 g (79%, >99% diastereomeric purity by GC analysis) of the title compound as a clear oil: *R*<sub>f</sub> 0.48 (20% ethyl acetate/hexane); IR (CH<sub>2</sub>Cl<sub>2</sub>)

3050–2850, 1783, 1700, 1455, 1386, 1351, 1242, 1238, 1210, 1103, 971 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.37–7.20 (m, 5 H, aromatic H's), 5.53–5.34 (m, 2 H, HC=CH), 4.70–4.62 (m, 1 H, C<sub>4</sub>-H), 4.23–4.15 (m, 2 H, C<sub>5</sub>-H<sub>2</sub>), 3.76 (hex, 1 H, *J* = 6.9 Hz, COCH), 3.27 (dd, 1 H, *J* = 3.3, 13.3 Hz, CHHPh), 2.77 (dd, 1 H, *J* = 9.6, 13.3 Hz, CHHPh), 2.44–2.34 (m, 1 H, CHHCH=CH), 2.16–2.07 (m, 1 H, CHHCH=CH), 1.64 (dd, 3 H, *J* = 1.0, 5.9 Hz, CH=CHCH<sub>3</sub>), 1.21 (d, 3 H, *J* = 6.9 Hz, COCHCH<sub>3</sub>); <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>) δ 176.6, 153.0, 135.4, 129.4, 128.8, 127.9, 127.4, 127.2, 66.0, 55.3, 37.9, 37.8, 36.4, 17.7, 16.8;  $[\alpha]_D -104^\circ$  (CH<sub>2</sub>Cl<sub>2</sub>, *c* 1.07).

Anal. Calcd for C<sub>17</sub>H<sub>21</sub>NO<sub>3</sub>: C, 71.06; H, 7.37. Found: C, 71.22; H, 7.43.

**(2R,4E)-2-Methyl-4-hexen-1-ol (8).** To a 0 °C solution of 4.22 g (14.7 mmol) of (4*R*)-3-((2'R,4'E)-2'-methyl-4'-hexenoyl)-4-(phenylmethyl)-2-oxazolidinone (7) in 75 mL of diethyl ether was added 14.7 mL (0.56 g, 14.7 mmol, 1.0 equiv, 1.0 M in diethyl ether) of lithium aluminum hydride dropwise over 40 min, employing a syringe pump. The reaction mixture was stirred at 0 °C for an additional 15 min and then quenched by the addition of 0.56 mL of water, 0.56 mL of aqueous 15% sodium hydroxide, and then 1.68 mL of water. The resultant slurry was dried over anhydrous sodium sulfate, filtered through Celite, and concentrated in vacuo at 0 °C to give a clear oil and white solid. The product was isolated by Kugelrohr distillation (85 °C (20 mmHg)) to give a clear oil, 1.35 g (80%): *R*<sub>f</sub> 0.30 (20% ethyl acetate/hexane); IR (CH<sub>2</sub>Cl<sub>2</sub>) 3720–3200 (br), 3630, 3050–2700, 1455, 1440, 1378, 1025, 971 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 5.48–5.42 (m, 2 H, CH=CH), 3.52 (dd, 1 H, *J* = 6.1, 10.6 Hz, CHHOH), 3.44 (dd, 1 H, *J* = 6.1, 10.6 Hz, CHHOH), 2.11–2.04 (m, 1 H, CHHCH=CH), 1.93–1.84 (m, 1 H, CHHCH=CH), 1.74–1.63 (m, 4 H, CHCH<sub>3</sub>, CH=CHCH<sub>3</sub>), 1.60 (br s, 1 H, OH), 0.90 (d, 3 H, *J* = 6.8 Hz, CHCH<sub>3</sub>); <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>) δ 129.4, 126.5, 68.1, 36.6, 36.2, 17.7, 16.4;  $[\alpha]_D +2.5^\circ$  (CH<sub>2</sub>Cl<sub>2</sub>, *c* 1.08).

Anal. Calcd for C<sub>7</sub>H<sub>14</sub>O: C, 73.63; H, 12.36. Found: C, 73.52; H, 12.30.

**(2R,4E)-2-Methyl-4-hexenal (2(R)).** A solution of 1.85 g (1.27 mL, 14.6 mmol, 1.4 equiv) of oxalyl chloride in 30 mL of methylene chloride was cooled to -78 °C and 2.28 g (2.07 mL, 29.2 mmol, 2.8 equiv) of anhydrous dimethyl sulfoxide was added. After 5 min, a solution of 1.19 g (10.4 mmol) of (2*R,4E*)-2-methyl-4-hexen-1-ol (8) in 5 mL of methylene chloride was transferred via canula to the reaction mixture. The resultant white suspension was stirred at -78 °C for 30 min and then 4.64 g (6.39 mL, 45.9 mmol, 4.4 equiv) of triethylamine was added neat. The -78 °C cooling bath was replaced with a -30 °C bath, and the mixture was stirred for 1 h. It was then diluted with 150 mL of pentane, washed with two 100-mL portions of aqueous 1 M sodium bisulfate and two 100-mL portions of water, and dried over anhydrous sodium sulfate, and the pentane was removed by distillation at atmospheric pressure. The residue was purified by Kugelrohr distillation (65 °C (55 mmHg)) (to prevent racemization, it is important to keep the temperature below 70 °C during distillation) to give 1.08 g (93%) of the title compound as a clear oil, which was used immediately: *R*<sub>f</sub> 0.67 (20% ethyl acetate/hexane); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 9.64 (d, 1 H, *J* = 1.5 Hz, COH), 5.55–5.30 (m, 2 H, CH=CH), 2.43–2.34 (m, 2 H, CH(CH<sub>3</sub>)-CHH), 2.15–2.05 (m, 1 H, CH(CH<sub>3</sub>)-CHH), 1.66 (dd, 3 H, *J* = 0.9, 6.0 Hz, CH=CHCH<sub>3</sub>), 0.91 (d, 3 H, *J* = 6.7 Hz, CHCH<sub>3</sub>).

**(4S)-3-(Azidoacetyl)-4-(phenylmethyl)-2-oxazolidinone (3b).** To a -78 °C solution of 20.18 g (114 mmol) of (4*S*)-4-(phenylmethyl)-2-oxazolidinone in 250 mL of tetrahydrofuran was added 77 mL (114 mmol, 1.0 equiv, 1.47 M in hexane) of *n*-butyllithium. To the resultant yellow solution was added 14.15 g (10 mL, 125 mmol, 1.1 equiv) of chloroacetyl chloride. The reaction mixture was stirred for 15 min at -78 °C and 15 min at room temperature. It was then quenched by the addition of 50 mL of aqueous saturated ammonium chloride solution. Volatiles were removed by rotary evaporation. The residue was diluted with water and extracted with three 200-mL portions of methylene chloride, dried over anhydrous sodium sulfate, and concentrated to a volume of 100 mL. To this dark yellow solution was added a solution of 37.0 g (569 mmol, 5 equiv) of sodium azide in 100 mL of water, followed by 3.87 g (11.4 mmol, 0.1 equiv) of tetrabutylammonium hydrogen sulfate. The biphasic mixture was stirred vigorously at room temperature for 1 h. The layers were then separated. The organic phase was concentrated and the resultant brown oil was filtered through silica gel (40 × 50 mm, methylene chloride) to give 26.67 g (90%) of the title compound as a white crystalline solid. An analytical sample was prepared by recrystallization from ethyl acetate/hexane: *R*<sub>f</sub> 0.25 (methylene chloride); mp 69–70 °C; IR (CH<sub>2</sub>Cl<sub>2</sub>) 3110–2860, 2110, 1785, 1715, 1387, 1252, 1220, 1104, 702 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.40–7.20 (m, 5 H, aromatic H's), 4.76–4.68 (m, 1 H, C<sub>4</sub>-H), 4.51 (s, 2 H, CH<sub>2</sub>N<sub>3</sub>), 4.34–4.24 (m, 2 H, C<sub>5</sub>-H<sub>2</sub>), 3.36 (dd, 1 H, *J* = 3.3, 13.4 Hz, CHHPh), 2.83 (dd, 1 H, *J* = 9.6, 13.4 Hz, CHHPh); <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>) δ 167.8, 153.2,

(16) This compound was prepared from 1-buten-3-ol via the ortho ester Claisen rearrangement, followed by saponification. See: Johnson, W. S.; Werthemann, L.; Bartlett, W. R.; Brockman, T. J.; Li, Tsung-tu; Faulkner, D. J.; Petersen, M. R. *J. Am. Chem. Soc.* **1970**, *92*, 741.

134.8, 129.3, 129.0, 127.4, 67.2, 55.0, 52.6, 37.7;  $[\alpha]_D +95.7^\circ$  ( $\text{CH}_2\text{Cl}_2$ ,  $c$  1.79).

Anal. Calcd for  $\text{C}_{12}\text{H}_{15}\text{N}_4\text{O}_3$ : C, 55.38; H, 4.65. Found: C, 55.46; H, 4.81.

**(4S)-3-(Isothiocyanatoacetyl)-4-(phenylmethyl)-2-oxazolidinone (3c).**  
**Method A.** A solution of 3.39 g (13.0 mmol) of (4S)-3-(azidoacetyl)-4-(phenylmethyl)-2-oxazolidinone (**3b**) and 2.80 g (1.7 mL, 19.5 mmol, 1.5 equiv) of 70% aqueous perchloric acid in 28 mL of methanol was stirred over 10% palladium on carbon under an atmosphere of hydrogen overnight. After a stream of nitrogen was bubbled through the suspension for several minutes, the suspension was filtered through Celite. The filtrate was concentrated to give a white solid which was then dissolved in 130 mL of water. An equal portion of chloroform was added, and the resultant two-phase system was vigorously stirred as 1.64 g (1.1 mL, 14.3 mmol, 1.1 equiv) of thiophosgene was added, followed by 4.40 g (52.0 mmol, 4.0 equiv) of solid sodium bicarbonate. After the mixture was stirred at room temperature for 10 min, the phases were separated. The organic phase was washed with two portions of 0.1 N aqueous hydrochloric acid, dried over anhydrous sodium sulfate, and concentrated to give 3.5 g (92% mass balance) of a dark brown oil. Purification by flash chromatography ( $40 \times 150$  mm silica gel,  $800 \text{ mL} \times 20\%$ ,  $250 \text{ mL} \times 30\%$ , and  $250 \text{ mL} \times 50\%$  ethyl acetate/hexane) gave 2.94 g (82%) of an oil which crystallized upon standing. An analytical sample was prepared by recrystallization from ethyl acetate/hexane:  $R_f$  0.36 (methylene chloride); mp 101–102 °C; IR ( $\text{CH}_2\text{Cl}_2$ ) 3100–2900, 2034 (br), 1786, 1721, 1388, 1213, 1112  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.40–7.20 (m, 5 H, aromatic H's), 4.85 (s, 2 H,  $\text{CH}_2\text{NCS}$ ), 4.76–4.68 (m, 1 H,  $\text{C}_4\text{-H}$ ), 4.35–4.25 (m, 2 H,  $\text{C}_5\text{-H}_2$ ), 3.39 (dd, 1 H,  $J = 3.3, 13.4$  Hz,  $\text{CHHPh}$ ), 2.82 (dd, 1 H,  $J = 9.6, 13.4$  Hz,  $\text{CHHPh}$ );  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  165.4, 153.1, 139.4, 134.5, 129.2, 129.0, 127.5, 67.3, 55.2, 49.3, 37.5;  $[\alpha]_D +92.3^\circ$  ( $\text{CH}_2\text{Cl}_2$ ,  $c$  1.81).

Anal. Calcd for  $\text{C}_{13}\text{H}_{12}\text{N}_2\text{O}_3\text{S}$ : C, 56.51; H, 4.38. Found: C, 56.53; H, 4.49.

Note: In practice the reaction sequence converting the oxazolidinone to its *N*-isothiocyanatoacetyl derivative is carried out without purification of the intermediates. Thus, 20.2 g (0.11 mmol) of (4S)-4-(phenylmethyl)-2-oxazolidinone gave, after recrystallization, 18.8 g (60% overall yield) of (4S)-3-(isothiocyanatoacetyl)-4-(phenylmethyl)-2-oxazolidinone.

**Method B.** A 500-mL round-bottomed flask equipped with a reflux condenser was charged with 22.7 g (87.3 mmol) of (4S)-3-(azidoacetyl)-4-(phenylmethyl)-2-oxazolidinone (**3b**), 100 mL of tetrahydrofuran, and 100 mL of carbon disulfide. To the resultant solution at room temperature was added 34.3 g (1.31 mmol, 1.1 equiv) of triphenylphosphine in one portion. As the triphenylphosphine dissolved, the reaction mixture turned orange, gas evolved, and, after a short induction period, the temperature of the solution began to rise. Ice-bath cooling was used to maintain a gentle reflux. After the reaction mixture was stirred at room temperature for 1 h, it was concentrated in vacuo and purified by flash chromatography ( $80 \times 150$  mm silica gel, chloroform) to give, after rechromatography of mixed fractions ( $40 \times 150$  mm silica gel, 2.5:18 ether/chloroform/hexane), 19.5 g (81%) of the title compound as a white crystalline solid.

**Stannous Triflate.** This reagent was prepared according to the procedure of Batchelor and co-workers,<sup>17</sup> modified as follows. A 250-mL round-bottomed flask equipped with a stir bar, reflux condenser, nitrogen inlet, and nitrogen outlet connected to a gas scrubbing tower filled with 1 N aqueous sodium hydroxide was charged with 12.3 g of anhydrous stannous chloride and 100 mL of trifluoromethanesulfonic acid (triflic acid). The resultant white suspension was heated at 80–85 °C for 24 h. The heating bath was removed, and while the suspension was still hot, the reflux condenser was replaced by a schlenk filter stick. The apparatus was flipped over, allowing the suspension to cool on the filter. After the apparatus reached room temperature, vacuum (a water aspirator equipped with a drying tube was used) was applied for 5–10 min. The filter cake was washed thoroughly with ten 50-mL portions of anhydrous diethyl ether. (While covered with ether, the cake was broken up with a spatula.) The resultant white powder was transferred to a dry 50-mL flask. Residual solvent was removed by drying at room temperature under high (diffusion pump) vacuum overnight to give 19.5 g (76%) of a fine white powder.

The transfer of this compound to reaction flasks was done quickly, under a stream of nitrogen. If the diastereoselectivity of aldol reactions performed with this reagent is lower than reported, this problem can usually be remedied by rewashing the stannous triflate with diethyl ether.

**General Procedure for the Stannous Enolate Formation and Aldol Condensation of (S)-3-(Isothiocyanatoacetyl)-4-(phenylmethyl)-2-oxazolidinone (3c).** Stannous triflate (1.1–1.3 equiv) is quickly transferred to

a flame-dried flask purged with nitrogen. Tetrahydrofuran (THF) is added to form a 0.1–0.25 M solution, which is cooled to  $-78^\circ\text{C}$ . The stannous triflate precipitates at this temperature. To the resultant white suspension is added *N*-ethylpiperidine (1.5 equiv), followed after several minutes by a 0.5–1 M solution of (4S)-3-(isothiocyanatoacetyl)-4-(phenylmethyl)-2-oxazolidinone (**3c**) (1–1.2 equiv) in THF at  $-78^\circ\text{C}$  via canula. The precipitate dissolves, and after the pale yellow solution is stirred at  $-78^\circ\text{C}$  for 1.5 h, the aldehyde (0.85–1.3 equiv) is added neat or as a solution in THF. The reaction is stirred for 1.5–4 h at  $-78^\circ\text{C}$  (the longer reaction times are necessary for more hindered aldehydes) and then quenched by the addition of pH 7 phosphate buffer. The resultant white suspension is filtered through Celite. The filtrate is diluted with methylene chloride, washed with two portions of 1 N aqueous sodium bisulfate, dried over anhydrous sodium sulfate, and concentrated. The aldol adduct is isolated ( $\geq 99\%$  diastereomeric purity by HPLC analysis) by chromatography or recrystallization.

**(4S)-3-((4S,5R)-5-((1'R,3'E)-1'-Methyl-3'-pentenyl)-2'-thioxo-4'-oxazolidinylcarbonyl)-4-(phenylmethyl)-2-oxazolidinone (5a).** To the stannous enolate formed from 366 mg (1.32 mmol, 1.1 equiv) of (4S)-3-(isothiocyanatoacetyl)-4-(phenylmethyl)-2-oxazolidinone (**3c**), 502 g (1.20 mmol, 1.0 equiv) of stannous triflate, and 177 mg (0.22 mL, 1.56 mmol, 1.3 equiv) of *N*-ethylpiperidine in 2.5 mL of tetrahydrofuran (THF) was added 93 mg (0.82 mmol, 0.62 equiv) of freshly prepared (2*R*,3*E*)-2-methyl-4-hexenal (**2R**) in 2.5 mL of THF. After the reaction mixture was stirred at  $-78^\circ\text{C}$  for 4 h, the product was isolated according to the general procedure to give a yellow foam. HPLC analysis (Zorbax, 18% methylene chloride/40% *tert*-butyl methyl ether/42% isooctane, 2 mL/min, 244 nm) afforded a 0.90:93.7:0.89:4.51 mixture of diastereomers ( $t_r$  4.30, 5.38, 8.41, 11.51 min, respectively). Purification by flash chromatography ( $30 \times 150$  mm silica gel, 25% ethyl acetate/hexane) yielded, after rechromatography of mixed fractions, 235 mg (73%,  $>99\%$  diastereomeric purity) of the title compound as an oil:  $R_f$  0.44 (40% ethyl acetate/hexane); IR ( $\text{CH}_2\text{Cl}_2$ ) 3410, 3125–2815, 1780, 1713, 1473, 1395, 1182, 1116, 970  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.57 (br s, 1 H, *N-H*), 7.43–7.15 (m, 5 H, aromatic H's), 5.56–5.30 (m, 2 H,  $\text{CH}=\text{CH}$ ), 5.41, (dd, 1 H,  $J = 4.9, 5.9$  Hz,  $\text{C}(\text{S})\text{OCH}$ ), 4.84 (dd, 1 H,  $J = 1.9, 4.9$  Hz,  $\text{C}(\text{S})\text{NHCH}$ ), 4.78–4.71 (m, 1 H,  $\text{C}_4\text{-H}$ ), 4.42–4.34 (m, 2 H,  $\text{C}_5\text{-H}_2$ ), 3.20 (dd, 1 H,  $J = 3.5, 13.6$  Hz,  $\text{CHHPh}$ ), 2.93 (dd, 1 H,  $J = 8.5, 13.6$  Hz,  $\text{CHHPh}$ ), 2.26–2.19 (m, 1 H,  $\text{CHHCH}=\text{CH}$ ), 2.06–1.90 (m, 2 H,  $\text{CHCHHCH}=\text{CH}$ ), 1.66 (dd, 3 H,  $J = 0.7, 5.9$  Hz,  $\text{CH}=\text{CHCH}_3$ ), 0.95 (d, 3 H,  $J = 6.7$  Hz,  $\text{CHCH}_3$ );  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  188.5, 166.3, 153.7, 134.1, 129.3, 128.9, 128.0, 127.5, 127.1, 86.9, 67.5, 59.9, 55.1, 37.3, 36.8, 34.0, 17.7, 14.1;  $[\alpha]_D +214^\circ$  ( $\text{CH}_2\text{Cl}_2$ ,  $c$  1.06).

Anal. Calcd for  $\text{C}_{20}\text{H}_{24}\text{N}_2\text{O}_4\text{S}$ : C, 61.84; H, 6.23. Found: C, 61.78; H, 6.29.

**Methyl (4S,5R)-5-((1'R,3'E)-1'-Methyl-3'-pentenyl)-2-thioxo-oxazolidinone-4-carboxylate (9).** To a 0 °C solution of 160 mg (0.41 mmol) of aldol adduct **5a** in 2 mL of anhydrous methanol was added via canula a suspension formed by the addition of 0.14 mL (0.46 mmol, 1.1 equiv, 3.2 M in diethyl ether) of methylmagnesium bromide to 2 mL of anhydrous methanol. After the reaction mixture was stirred for 3 min, it was quenched by the addition of 2 mL of pH 7 phosphate buffer. Volatiles were removed in vacuo. The residue was dissolved in 1 N aqueous hydrochloric acid, extracted with three portions of methylene chloride, dried over anhydrous sodium sulfate, and concentrated to give 174 mg (100% mass balance) of a pale yellow oil. Purification by flash chromatography ( $15 \times 150$  mm silica gel, 250 mL of 30% and 200 mL of 50% ethyl acetate/hexane) afforded 67 mg (91%) of recovered oxazolidinone and 92 mg (91%) of the title compound as a clear oil:  $R_f$  0.38 (40% ethyl acetate/hexane); IR ( $\text{CH}_2\text{Cl}_2$ ) 3500–3360 (br), 3040–2840, 1756, 1488, 1246, 1222, 1183, 970  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.0 (br s, 1 H, *N-H*), 5.58–5.31 (m, 2 H,  $\text{CH}=\text{CH}$ ), 4.87 (br t, 1 H,  $J = 5.6$  Hz,  $\text{C}_5\text{-H}$ ), 4.32 (d, 1 H,  $J = 5.5$  Hz,  $\text{C}_4\text{-H}$ ), 3.83 (s, 3 H,  $\text{CO}_2\text{CH}_3$ ), 2.27–2.21 (m, 1 H,  $\text{CHHCH}=\text{CH}$ ), 2.06–1.92 (m, 2 H,  $\text{CHCHHCH}=\text{CH}$ ), 1.66 (dd, 3 H,  $J = 0.95, 6.1$  Hz,  $\text{CH}=\text{CHCH}_3$ ), 0.98 (d, 3 H,  $J = 6.6$  Hz,  $\text{CHCH}_3$ );  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  189.1, 169.2, 128.2, 127.0, 88.7, 59.2, 53.1, 37.3, 34.1, 17.7, 13.8;  $[\alpha]_D +80.6^\circ$  ( $\text{CH}_2\text{Cl}_2$ ,  $c$  1.02).

Anal. Calcd for  $\text{C}_{11}\text{H}_{17}\text{NO}_4\text{S}$ : C, 54.30; H, 7.04. Found: C, 54.30; H, 7.13.

**Methyl (4S,5R)-3-Methyl-5-((1'R,3'E)-1'-methyl-3'-pentenyl)-2-oxazolidinone-4-carboxylate (11).** To a 0 °C suspension of 735 mg (5.18 mmol, 2.1 equiv) of trimethyloxonium tetrafluoroborate<sup>18</sup> and 581 mg (2.71 mmol, 1.1 equiv) of 1,8-bis(dimethylamino)naphthalene in 10 mL of methylene chloride was added via canula a 0 °C solution of 600 mg (2.47 mmol) of methyl (4S,5R)-5-((1'R,3'E)-1'-methyl-3'-pentenyl)-2-

(17) Batchelor, R. J.; Ruddick, J. N. R.; Sams, J. R.; Aube, F. *Inorg. Chem.* **1977**, *16*, 1414.

(18) Curphey, T. J. *Org. Synth.* **1971**, *51*, 142. For best results, use newly prepared or freshly washed compound.

thioxazolidine-4-carboxylate (**9**) in 5 mL of methylene chloride. After the resultant white slurry was stirred for 3 h, it was concentrated in vacuo at 0 °C. The residue was suspended in 15 mL of tetrahydrofuran at 0 °C, and 7.5 mL of pH 7 phosphate buffer was added. The reaction mixture was stirred at 0 °C for 1.5 h, poured into 100 mL of 1 N aqueous sodium bisulfate, and extracted with three 75-mL portions of methylene chloride. The combined organic extracts were dried over anhydrous sodium sulfate and concentrated to give a white solid and a yellow oil. Purification by flash chromatography (20 × 100 mm silica gel, 30% ethyl acetate/hexane) afforded 455 mg (76%) of the title compound as a clear oil:  $R_f$  0.26 (30% ethyl acetate/hexane); IR (CH<sub>2</sub>Cl<sub>2</sub>) 3080–2860, 1754, 1438, 1400, 1216, 1048, 970 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 5.55–5.31 (m, 2 H, CH=CH), 4.28 (dd, 1 H,  $J = 4.8, 6.2$  Hz, C<sub>5</sub>-H), 3.97 (d, 1 H,  $J = 4.8$  Hz, C<sub>4</sub>-H), 3.82 (s, 3 H, CO<sub>2</sub>CH<sub>3</sub>), 2.91 (s, 3 H, NCH<sub>3</sub>), 2.25–2.17 (m, 1 H, CHHCH=CH), 2.00–1.83 (m, 2 H, CHCHHCH=CH), 1.66 (dd, 3 H,  $J = 1.1, 6.0$  Hz, CH=CHCH<sub>3</sub>), 0.95 (d, 3 H,  $J = 6.6$  Hz, CHCH<sub>3</sub>); <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>) δ 170.2, 157.2, 128.0, 127.3, 79.3, 61.8, 52.7, 37.6, 34.2, 30.0, 17.8, 13.8; [α]<sub>D</sub> +37.1° (CH<sub>2</sub>Cl<sub>2</sub>,  $c$  1.51).

Anal. Calcd for C<sub>12</sub>H<sub>19</sub>NO<sub>4</sub>: C, 59.73; H, 7.94. Found: C, 60.14; H, 8.19.

(2*S*,3*R*,6*E*)-3-Hydroxy-4-methyl-2-(methylamino)-6-octenoic Acid (**1a**). This reaction was carried out according to the procedure of Wenger.<sup>5</sup> A solution of 269 mg (1.11 mmol) of methyl (4*S*,5*R*)-3-methyl-5-((1'*R*,3'*E*)-1'-methyl-3'-pentenyl)-2-oxazolidinone-4-carboxylate (**11**) in 2.5 mL of 2 N aqueous potassium hydroxide solution was heated at 75–80 °C overnight. The solution was allowed to cool to room tem-

perature, and the pH was adjusted to 5 by the addition of 1 N aqueous hydrochloric acid. The solution was concentrated and chromatographed (40 g Sephadex LH-20, methanol) to give 183 mg (82%) of the title compound. An analytical sample was prepared by recrystallization from ethanol/water, which was identical (<sup>1</sup>H NMR (250 MHz), melting point, and mixture melting point) with a sample prepared by synthesis from diethyl tartrate:<sup>13</sup> mp 242–243 °C; IR (KBr pellet) 3210, 2960, 2930, 2890, 2700–2200 (broad), 1615, 1585, 1460, 1445, 1430, 1410, 1380, 1320, 1260, 1245, 1140, 1110, 1030, 990, 965, 930, 890, 850, 675 cm<sup>-1</sup>; <sup>1</sup>H NMR (250 MHz, D<sub>2</sub>O) δ 5.52–5.29 (m, 2 H, CH=CH), 3.65 (t, 1 H,  $J = 6.0$  Hz, C<sub>3</sub>-H), 3.50 (d, 1 H,  $J = 5.8$  Hz, C<sub>2</sub>-H), 2.61 (s, 3 H, N-CH<sub>3</sub>), 2.15 (br d, 1 H, 13.0 Hz, C<sub>5</sub>HH), 1.82–1.70 (m, 1 H, C<sub>5</sub>HH), 1.62–1.53 (m, 1 H, C<sub>4</sub>-H), 1.52 (d, 3 H,  $J = 5.4$  Hz, C<sub>8</sub>-H), 0.81 (d, 3 H,  $J = 6.7$  Hz, C<sub>4</sub>-CH<sub>3</sub>); <sup>13</sup>C NMR (75.5 MHz, MeOD-*d*<sub>3</sub>, amino acid hydrochloride salt) δ 170.1, 129.9, 128.3, 74.7, 64.9, 37.4, 35.6, 33.6, 18.1, 16.2; [α]<sub>D</sub> +11.4° (H<sub>2</sub>O at pH 7 (phosphate buffer Titrisol pH 7.00 from Merck),  $c$  0.50) [lit.<sup>5</sup> [α]<sub>D</sub> +13.5° (H<sub>2</sub>O at pH 7 (phosphate buffer Titrisol pH 7.00 from Merck),  $c$  0.50)].

Anal. Calcd for C<sub>10</sub>H<sub>19</sub>NO<sub>3</sub>: C, 59.68; H, 9.52. Found: C, 59.59; H, 9.44.

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## Chiral Synthesis via Organoboranes. 8. Synthetic Utility of Boronic Esters of Essentially 100% Optical Purity. Synthesis of Primary Amines of Very High Enantiomeric Purities

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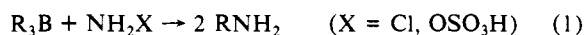
Contribution from the Richard B. Wetherill Laboratory, Purdue University, West Lafayette, Indiana 47907. Received May 22, 1986

**Abstract:** 2-Alkyl-1,3,2-dioxaborinanes, R\*BO<sub>2</sub>(CH<sub>2</sub>)<sub>3</sub>, of essentially 100% optical purity, prepared by the asymmetric hydroboration of readily available prochiral olefins with subsequent removal of the chiral auxiliary, can be converted into borinic ester derivatives, R\*MeBO(CH<sub>2</sub>)<sub>3</sub>OAc, of essentially 100% ee by reaction with MeLi. The intermediates, R\*MeBO(CH<sub>2</sub>)<sub>3</sub>OAc, react readily with hydroxylamine-*O*-sulfonic acid in tetrahydrofuran at 25 °C to provide the corresponding primary amines stereospecifically in very good yields and in very high optical purity. Consequently, it is now possible to convert prochiral olefins into either (+)- or (-)-primary amines of essentially 100% optical purity. The optical purities of the amines were determined by capillary GC analyses of their MTPA amides.

Optically active primary amines are of major biological and synthetic importance. For example, (*R*)-(-)-*sec*-butylamine is present in pharmacologically active species such as β-blockers<sup>2</sup> or central analgesics<sup>3</sup> and possess fungistatic activity.<sup>4</sup> Generally, optically active primary amines are either prepared by resolution of racemic amines<sup>5</sup> or synthesized from optically active precursors.<sup>6</sup> Asymmetric synthesis of primary amines using borane reagents has not yet achieved high enantioselectivity.<sup>7</sup>

Organoboranes are among the most versatile intermediates available to the organic chemist. Our studies have established

that organoboranes transfer the alkyl group to essentially most of the other elements of synthetic interest, including carbon, with complete maintenance of stereochemical integrity.<sup>8</sup> Several reactions are known where an alkyl group is transferred from organoborane to nitrogen leading to primary amine derivatives. We previously reported that trialkylboranes, on treatment with chloramine or hydroxylamine-*O*-sulfonic acid (HSA), give primary amines in 40–60% yield (eq 1).<sup>9</sup> Recently a new reagent, *O*-



mesitylenehydroxylamine, has been developed for the conversion of organoboranes into primary amines in 20–50% yield.<sup>10a</sup> Reaction of trialkylboranes with chloramine generated *in situ* has been reported to give primary amines in 25–60% yield.<sup>10b</sup> An alkyl

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(2) Casagrande, C.; Ferrari, G. *Farmaco, Ed. Sci.* **1966**, *21*, 229.

(3) Chiarino, D.; Della Bella, D.; Jommi, G.; Veneziani, C. *Arzneim.-Forsch.* **1978**, *28*, 1554.

(4) Eckert, J. W.; Rahm, M. L.; Kolbezen, M. J. *J. Agric. Food Chem.* **1972**, *20*, 104.

(5) (a) Thomé, L. G. *Chem. Ber.* **1903**, *36*, 582. (b) Holm, R. H.; Chakravorty, A.; Dudek, G. O. *J. Am. Chem. Soc.* **1964**, *86*, 379.

(6) (a) Santaniello, E.; Casati, R.; Milani, F. *J. Chem. Soc., Perkin Trans. I* **1985**, 919. (b) Ringdahl, B.; Smith, H. E.; Chen, F.-M. *J. Org. Chem.* **1977**, *42*, 4184.

(7) (a) Verbit, L.; Heftron, P. J. *J. Org. Chem.* **1967**, *32*, 3199. (b) Charles, J.-P.; Christol, H.; Solladié, G. *Bull. Soc. Chim. Fr.* **1970**, 4439.

(8) Brown, H. C.; Kramer, G. W.; Levy, A. B.; Midland, M. M. *Organic Synthesis via Boranes*; Wiley-Interscience: New York, 1975.

(9) (a) Brown, H. C.; Heydkamp, W. R.; Breuer, E.; Murphy, W. S. *J. Am. Chem. Soc.* **1964**, *86*, 3365. (b) Rathke, M. W.; Inoue, N.; Varma, K. R.; Brown, H. C. *Ibid.* **1966**, *88*, 2870.

(10) (a) Tamura, Y.; Minamikawa, J.; Fujii, S.; Ikeda, M. *Synthesis* **1973**, 196. (b) Kabalka, G. W.; Sastry, K. A. R.; McCollum, G. W.; Yoshioka, H. *J. Org. Chem.* **1981**, *46*, 4296. (c) Jigajinni, V. B.; Pelter, A.; Smith, K. *Tetrahedron Lett.* **1978**, 181.