

# A Stereodivergent Approach to Amino Acids, Amino Alcohols, or Oxazolidinones of High Enantiomeric Purity

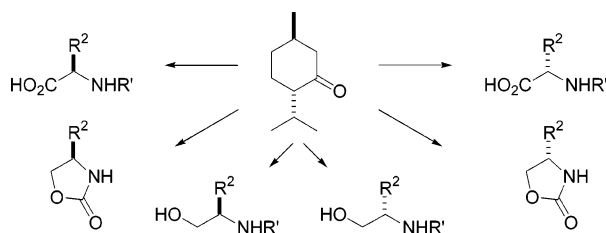
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Received June 7, 2004

## ABSTRACT

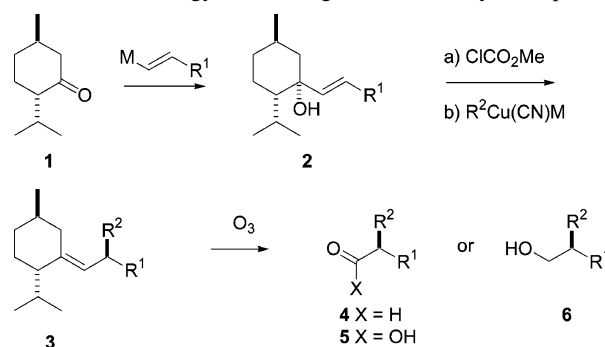


(-)-Menthone, an inexpensive chiral auxiliary, was used to prepare both enantiomers of  $\alpha$ -amino acids, amino alcohols, or oxazolidinones. The sequence includes the  $S_N2'$  displacement by a cuprate reagent and a Curtius rearrangement as key steps.

Amino acids<sup>1</sup> and amino alcohols<sup>2,3</sup> are compounds of immense interest and importance for the pharmaceutical industry. In addition to their medicinal importance, they are widely being used as chiral ligands for many organic transformations.<sup>2,3</sup> Herein, we report a stereodivergent and efficient route to prepare amino alcohols of high enantiomeric purity.<sup>4</sup> The latter can be converted to amino acids or oxazolidinones, of course, but our strategy also allows for the direct preparation of amino acids or oxazolidinones without the intermediacy of amino alcohols. In addition, amino aldehydes can be prepared.

We have reported earlier the sequence shown in Scheme 1 to create chiral centers  $\alpha$  to a carbonyl with optical purities >99%.<sup>5</sup> In this strategy, menthone serves as a readily

**Scheme 1.** Strategy for Making Chiral Carbonyl Compounds



(1) (a) For a review on synthetic methods of  $\alpha$ -amino acids, see: Duthaler, R. O. *Tetrahedron* **1994**, *50*, 1539–1650. (b) Williams, R. H. *Synthesis of Optically Active  $\alpha$ -Amino Acids*; Pergamon Press: New York, 1989. (c) Schollkopf, U. *Top. Curr. Chem.* **1983**, *109*, 65–84.

(2) Bergmeier, S. C. *Tetrahedron* **2000**, *56*, 2561–2576.

(3) Ager, D. J.; Prakash, I.; Schaad, D. R. *Aldrichimica Acta* **1997**, *30*, 3–12.

(4)  $\alpha,\alpha$ -Dialkylated amino acids can be made from a related system. See: Spino, C.; Gobdout, C. *J. Am. Chem. Soc.* **2003**, *125*, 12106–12107.

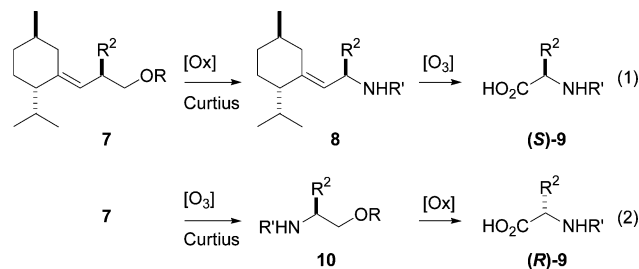
available and recyclable chiral auxiliary for a short sequence of reactions that includes as one of the key steps the highly

(5) (a) Spino, C.; Beaulieu, C.; Lafrenière, J. *J. Org. Chem.* **2000**, *65*, 7091–7097. (b) Spino, C.; Beaulieu, C. *J. Am. Chem. Soc.* **1998**, *120*, 11832–11833. (c) Spino, C.; Beaulieu, C. *Tetrahedron Lett.* **1999**, *40*, 1637–1640.

regioselective and stereospecific  $S_N2'$  displacement of an allylic carbonate by a cuprate reagent.<sup>6,7</sup> This alternative to chiral enolate alkylation is very broad in scope and allows the synthesis of hindered chiral carbons next to a carbonyl.<sup>8</sup>

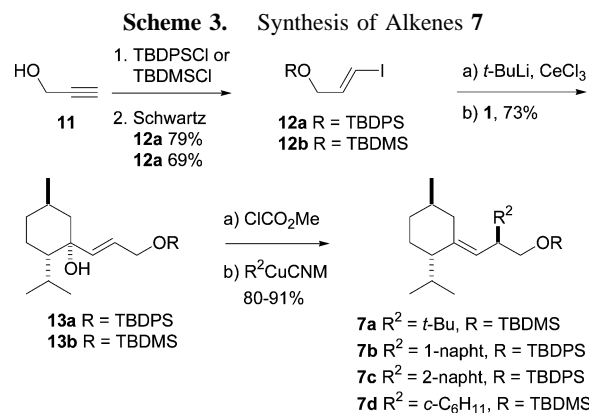
We envisaged that if compound **2** contained a hydroxy-methyl substituent ( $R^1 = \text{CH}_2\text{OH}$ ), we could access very easily chiral amines **8** using the Curtius rearrangement or its analogues (Scheme 2, eq 1).<sup>9</sup> Compound **8** would be easily

**Scheme 2.** Stereodivergent Synthetic Design of Amino Acids



converted to the amino acid **9** by ozonolysis under oxidative workup. Likewise, amino alcohols would be accessible by a simple change in the treatment of the ozonide, whereas oxazolidinones would be obtained by heating the intermediate hydroxy-carbamate or isocyanate with base. Importantly, we realized that this system could be used to make both enantiomers of an amino acid from a single precursor **7** simply by inverting the sequence of reactions (Scheme 2, eq 2). Thus, oxidative cleavage of the auxiliary would permit the Curtius rearrangement, and oxidation of the primary alcohol would complete the desired synthesis. Added to the fact that menthone is available in both enantiomeric series and that  $R^1$  and  $R^2$  are interchangeable (vide infra), this method looked very flexible indeed.

This prediction was born out. We prepared vinyl iodides **12a** and **12b** from the cheaply available propargyl alcohol using standard *O*-silylation techniques and Schwartz's hy-



drozirconation protocol<sup>10</sup> (Scheme 3). Iodine–lithium exchange and addition of the resulting vinyl lithium to menthone in the presence of dry  $\text{CeCl}_3$  afforded high yields of alcohols **13a,b**, each as a single diastereomer. Conversion of each alcohol to the carbonate followed by addition of a dialkyl or cyanoalkyl cuprate gave a series of diastereomerically pure alkenes **7a–c** (GC analysis). For unknown reasons, compound **7d** was only 88% de, even though we have added cyclohexylcuprates to a similar system before and obtained the usual >99% de.<sup>11</sup>

The sequence shown above is efficient because a single alcohol **13** may serve to prepare a whole series of alkenes **7** via the carbonate–cuprate sequence. This would be particularly advantageous in the context of making combinatorial libraries of amino acids or derivatives.<sup>12</sup> However, some cuprate reagents are difficult to prepare, are unreactive, or may add with a lower stereospecificity. For example, the cuprate reagents derived from cyclohexylmagnesium bromide added with only 88% de to **13b**. In such cases, the desired compound can still be accessed as shown below. We prepared alcohol **16** from the addition of lithium cyclohexylacetylide (derived from cyclohexylcarboxaldehyde **14** via the Corey–Fuchs procedure) to menthone **1** (Scheme 4).<sup>13</sup> Compound **15** was isolated as a 7:1 mixture of two alcohols easily separable by silica gel column chromatography. The alkyne in **15** was then reduced to the *E*-alkene **16** with Red-Al. Alternatively, the cyclohexylacetylene could be isolated, converted to the corresponding vinyl iodide and then to the vinyl lithium, and added to **1** with complete stereoselectivity, thus alleviating the need for diastereomer separation. Adding the cuprate derived from the lithium anion of *tert*-butylmethyl ether to the carbonate made from **16** furnished adduct **7e** with complete transfer of chirality.

There is no particular advantage to using the sequence depicted in Scheme 4, because a different alcohol (**16**) must

(6) (a) Harrington-Frost, N.; Leuser, H.; Calaza, M. I.; Kneisel, F. F.; Knochel, P. *Org. Lett.* **2003**, *5*, 2111–2114. (b) Belelie, J. L.; Chong, J. M. *J. Org. Chem.* **2001**, *66*, 5552–5555. (c) Belelie, J. L.; Chong, J. M. *J. Org. Chem.* **2002**, *67*, 3000–3006. (d) Denmark, S. E.; Marble, L. K. *J. Org. Chem.* **1990**, *55*, 1984–1986.

(7) For other related approaches, see: (a) Kakinuma, K.; Li, H.-Y. *Tetrahedron Lett.* **1989**, *30*, 4157–4160. (b) Kakinuma, K.; Koudate, T.; Li, H.-Y.; Eguchi, T. *Tetrahedron Lett.* **1991**, *32*, 5801–5804. (c) Eguchi, T.; Koudate, T.; Kakinuma, K. *Tetrahedron* **1993**, *49*, 4527–4540. (d) Clayden, J.; McCarthy, C.; Cumming, J. G. *Tetrahedron Lett.* **2000**, *41*, 3279–3283. (e) Savage, I.; Thomas, E. J.; Wilson, P. D. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3291–3303. (f) Clayden, J.; McCarthy, C.; Cumming, J. G. *Tetrahedron: Asymmetry* **1998**, *9*, 1427–1440. (g) Hung, S.-C.; Wen, Y. F.; Chang, J.-W.; Liao, C.-C.; Uang, B. J. *J. Org. Chem.* **2002**, *67*, 1308–1313.

(8) For a review on chiral enolate equivalent, see: Spino, C. *Org. Prep. Proced. Int.* **2003**, *35*, 1–140.

(9) For selected examples of the use of Curtius or similar rearrangements in making amino acids, see: (a) Evans, D. A.; Wu, L. D.; Wiener, J. J. M.; Johnson, J. S.; Ripin, D. H. B.; Tedrow, J. S. *J. Org. Chem.* **1999**, *64*, 6411–6417. (b) Braibante, M. E. F.; Braibante, H. S.; Costenaro, E. R. *Synthesis* **1999**, 943–947. (c) Ghosh, A. K.; Fidanze, S. *J. Org. Chem.* **1998**, *63*, 6146–6152. (d) Sibi, M. P.; Lu, J.; Edwards, J. J. *J. Org. Chem.* **1997**, *62*, 5864–5872. (e) Charette, A. B.; Côté, B. *J. Am. Chem. Soc.* **1995**, *117*, 12721–12732. (f) Tanaka, M.; Oba, M.; Tamai, K.; Suemune, H. *J. Org. Chem.* **2001**, *66*, 2667–2673.

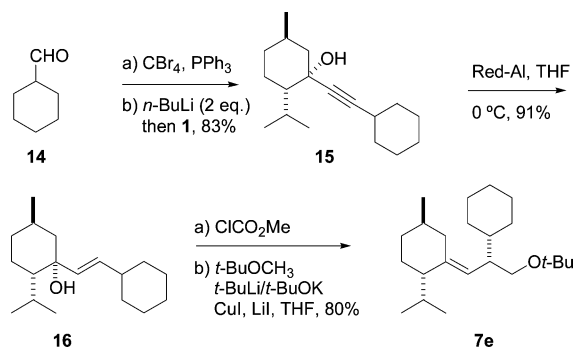
(10) (a) Lipshutz, B. H.; Keil, R.; Ellsworth, E. L. *Tetrahedron Lett.* **1990**, *31*, 7257–7260. (b) Schwartz, J.; Labinger, J. A. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 333–340.

(11) See ref 5. The source of the cyclohexylmagnesium bromide or chloride was varied without success in this particular case.

(12) We have developed a resin-bound version of this chiral auxiliary. Patent 2,413,713 filed for Canada-U.S. in December 2003. Manuscript for publication in preparation.

(13) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *13*, 3769–3772.

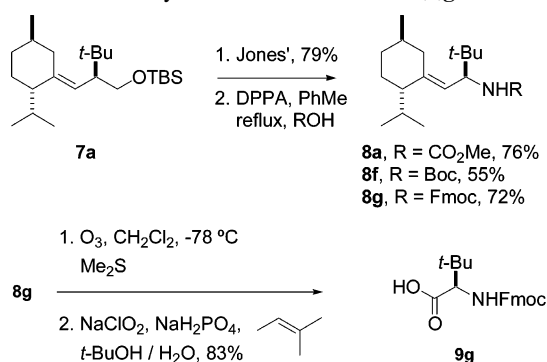
**Scheme 4.** Synthesis of Alkene **7e**



be prepared for each desired amino acid. However, it is stereochemically complementary to the sequence depicted in Scheme 3, and in addition, it may provide alkene **7** with increased enantiomeric excess, as was the case for **7e** vs **7d**.

We first tested the Curtius rearrangement on **7a**. The primary alcohol was deprotected and oxidized in the same step while the resulting carboxylic acid was treated with diphenylphosphoryl azide in toluene at reflux to give, after heating the intermediate isocyanate at reflux in methanol, carbamate **8a** (Scheme 5). Carbamates **8f** and **8g** were

**Scheme 5.** Synthesis of Carbamates **8a,f,g** from **7a**

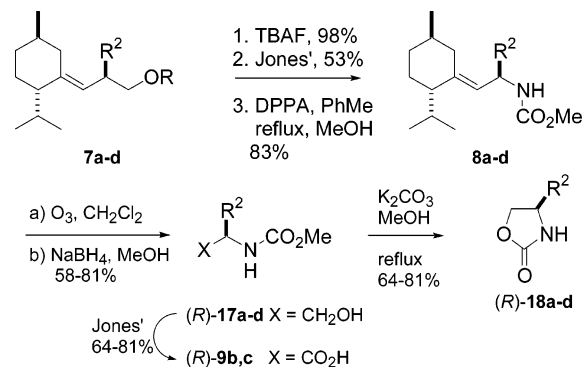


prepared by trapping the isocyanate intermediate with *tert*-butyl alcohol or 9-fluorenylmethanol, respectively. Note that we chose to make the methyl carbamate in all of the other cases because it facilitates the cyclization to the oxazolidinone subsequently. Compound **8g** was amenable to single-crystal X-ray diffraction analysis, which confirmed the stereochemistry of **7a** and, by inference, of all other cuprate adducts. The carbamate **8g** was then transformed to *N*-protected *tert*-leucine **9g** by ozonolysis to the aldehyde and subsequent oxidation with NaClO<sub>2</sub>. The mildness of these conditions to generate the highly sensitive amido aldehydes is noteworthy. Such molecules are sensitive but useful intermediates for the synthesis of complex amino alcohols and alkaloids.<sup>14</sup>

(14) See, for example: Gryko, D.; Chalko, J.; Jurczak, J. *Chirality* **2003**, *15*, 514–541.

Then, we converted adducts **7a–d** to the corresponding amido alcohols **17a–d** via the carbamate **8** (Scheme 6, Table

**Scheme 6.** Synthesis of Amino Alcohols (*R*)-**17a–d**, Amino Acids (*R*)-**9b,c**, and Oxazolidinones (*R*)-**18b,c**



1, entries 5–8). The cyclization to the oxazolidinone **18a–d**<sup>15</sup> was performed with potassium carbonate in reflux-

**Table 1.** Preparation of Amino-acids **9**, Alcohols **17**, and Oxazolidinones **18**

entry	product	R <sup>2</sup>	yield (%)	% ee
1	( <i>R</i> )- <b>9b</b>	1-naphth	64	>99
2	( <i>R</i> )- <b>9c</b>	2-naphth	81	>99
3	( <i>S</i> )- <b>9b</b>	1-naphth	72	>99
4	( <i>S</i> )- <b>9d</b>	<i>c</i> -C <sub>6</sub> H <sub>11</sub>	84	>99
5	( <i>R</i> )- <b>17a</b>	<i>t</i> -Bu	81	>99 <sup>a</sup>
6	( <i>R</i> )- <b>17b</b>	1-naphth	76	>99 <sup>b</sup>
7	( <i>R</i> )- <b>17c</b>	2-naphth	58	>99 <sup>b</sup>
8	( <i>R</i> )- <b>17d</b>	<i>c</i> -C <sub>6</sub> H <sub>11</sub>	65	90 <sup>a,c</sup>
9	( <i>S</i> )- <b>17b</b>	1-naphth	93	>99 <sup>b</sup>
10	( <i>S</i> )- <b>17d</b>	<i>c</i> -C <sub>6</sub> H <sub>11</sub>	81	>99 <sup>a</sup>
11	( <i>R</i> )- <b>18a</b>	<i>t</i> -Bu	73	>99
12	( <i>R</i> )- <b>18b</b>	1-naphth	82	>99 <sup>d</sup>
13	( <i>R</i> )- <b>18c</b>	2-naphth	80	>99 <sup>d</sup>
14	( <i>R</i> )- <b>18d</b>	<i>c</i> -C <sub>6</sub> H <sub>11</sub>	96	90 <sup>c</sup>
15	( <i>S</i> )- <b>18b</b>	1-naphth	82	>99
16	( <i>S</i> )- <b>18d</b>	<i>c</i> -C <sub>6</sub> H <sub>11</sub>	78	>99 <sup>e</sup>

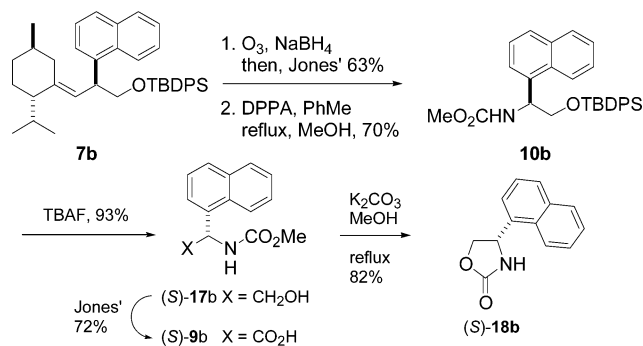
<sup>a</sup> Determined by <sup>19</sup>F NMR of the corresponding Mosher esters. <sup>b</sup> Determined by HPLC of the corresponding oxazolidinone. <sup>c</sup> Prepared from **7d**, which was 90% de. <sup>d</sup> Determined by HPLC. <sup>e</sup> Prepared from **7e**.

ing methanol (entries 11–14). The amino acids **9b,c** were made by Jones oxidation of the alcohols **7b,c** (entries 1 and 2).<sup>16</sup> The % ee of each amino alcohol **17** was determined by fluorine NMR of the corresponding Mosher ester or by chiral HPLC on the corresponding oxazolidinone.

(15) **18a**: Dauz, K.; Jahn, W.; Schwarm, M. *Chem. Eur. J.* **1995**, *1*, 538–540. **18b**: Pirkle, W. H.; Simmons, K. A. *J. Org. Chem.* **1983**, *48*, 2520–2527. **18c**: Takacs, J. M.; Jaber, M. R.; Vellekoop, A. S. *J. Org. Chem.* **1998**, *63*, 2742–2748. **18d**: Evans, D. A.; Chapman, K. T.; Bisaha J. *J. Am. Chem. Soc.* **1988**, *110*, 1238–1256.

(16) This method of oxidation has been shown to proceed without racemization of the amino acid. See: (a) Kashima, C.; Harada, K.; Fujioka, Y.; Maruyama, T.; Omote, Y. *J. Chem. Soc., Perkin Trans. 1* **1988**, 535–539. (b) Dondoni, A.; Mariotti, G.; Marra, A. *J. Org. Chem.* **2002**, *67*, 4475–4486.

**Scheme 7.** Synthesis of Amino Acid (*S*)-**9b**, Amino Alcohol (*S*)-**17b**, and Oxazolidinone (*S*)-**18b** via a Stereodivergent Approach



In the case of **7e**, the *t*-Bu protecting group was removed using  $\text{FeCl}_3$ /acetic acid followed by hydrolysis to give the free primary alcohol in 96% yield.<sup>17</sup> This alcohol led to (*S*)-**17d** and thus to (*S*)-**18d** (entries 10 and 16) using the same reaction sequence as per (*R*)-**17d**, except the enantiomeric excess was now >99%.

We then tackled the question of stereodivergence in the strategy. We succeeded in making both enantiomers of each of the amino acid **9b**, amino alcohol **17b**, and oxazolidinone **18b** starting from a single intermediate **7b** (Scheme 6,  $R^2 = 1$ -naphthyl). The *S* isomer of these compounds was prepared by reversing the order of reactions used for the *R* isomer. Ozonolysis of **7b** to the carboxylic acid followed by a Curtius rearrangement yielded carbamate **10b** (Scheme 7). Deprotection of the primary alcohol afforded (*S*)-**17b** (entry 9), which was converted to the amino acid (*S*)-**9b** (entry 3) and oxazolidinone (*S*)-**18b** (entry 15).

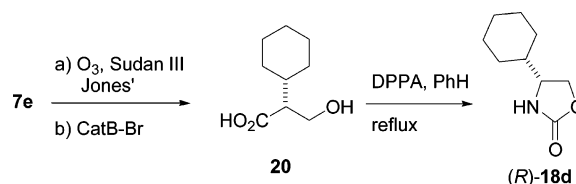
The *tert*-butyldimethylsilyl protecting group in **7** is more appropriate than its *tert*-butyldiphenyl analogue if the

(17) Alexakis, A.; Gardette, M.; Colin, S. *Tetrahedron Lett.* **1988**, *29*, 2951–2954.

divergence strategy is not needed, the reason being that it can be cleaved in the oxidation step with the Jones reagent (i.e., the TBAF step becomes unnecessary).

A shorter route to oxazolidinone is also possible. When **7e** was ozonolyzed to the acid and the alcohol deprotected, this free alcohol cyclized the moment the intermediate isocyanate was formed after the Curtius rearrangement (Scheme 8). This is actually the method of choice to make oxazoli-

**Scheme 8.** Cyclization to Oxazolidinone **18e** Immediately after Curtius Rearrangement



dinones if the corresponding amino acids or amino alcohols are not needed.

In conclusion, we have developed an efficient methodology to prepare amino acids and related molecules in high optical purity. Extensions of this strategy to other chiral compounds are underway in our laboratory.

**Acknowledgment.** We thank the Natural Sciences and Engineering Council of Canada, Boehringer-Ingelheim (Canada) Ltd., The ACS Petroleum Research Fund (Grant No. 36256-AC1), and the Université de Sherbrooke for financial support.

**Supporting Information Available:** Experimental and NMR spectra for all new compounds and ORTEP drawing of **8g**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL048936Q