

## A Stereodivergent Approach to Chiral Nonracemic N-Protected $\alpha,\alpha$ -Dialkylated Amino Acids

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$\alpha,\alpha$ -Dialkylated amino acids are attractive molecular building blocks for the synthesis of peptides with specific properties.<sup>1</sup> The inclusion of such a unit in a peptide may affect its secondary or tertiary structure by inducing particular conformations.<sup>2</sup> In addition, some  $\alpha,\alpha$ -dialkylated amino acids are powerful enzyme inhibitors.<sup>3</sup> Making them optically pure is a challenging task, and few methods are general.<sup>4</sup> Recently, we have reported a new methodology to create quaternary carbon centers of high optical purity using an  $S_N2'$  displacement on pivalate esters.<sup>5</sup> We now report a useful extension of this methodology to make chiral nonracemic  $\alpha,\alpha$ -dialkylated amino acids.

The stereoselective preparation of pivalate esters **4**, **7**, and **8** is one of the pivotal steps in the strategy. Their synthesis could be achieved in one of several ways. Propargyl alcohol underwent a zirconium-catalyzed methylalumination,<sup>6</sup> and the intermediate vinylsilane added stereoselectively to menthyl aldehyde **1a** to give two easily separable diols in a 10:1 ratio (Scheme 1).<sup>5</sup> Protection of the primary alcohol in the major isomer **2** and esterification of its secondary alcohol gave **4a** in high overall yield. This is the most direct route to pivalate **4a**, but it is limited by the fact that carboalumination is essentially restricted to methylation.<sup>7</sup>

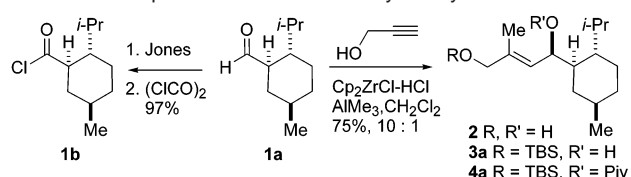
By contrast, the copper-catalyzed carbomagnesiation of propargyl alcohol allows the introduction of a wide variety of alkyl, aryl, and vinyl groups.<sup>8</sup> The cyclic magnesium intermediate adds efficiently to menthyl aldehyde **1a** to give, after protection of the primary alcohol as its silyl ether, **5a** ( $\beta$ -OH) and **5b** ( $\alpha$ -OH) in a 2:1 ratio (Scheme 2). Separation of **5a** and **5b** was possible but not necessary.

Gratifyingly, oxidation of the 2° alcohol and reduction of the resulting ketone with lithium triethylborohydride gave alcohol **5b** with complete stereoselectivity! The same was true for **6b**. This reaction appears general as several other ketones (not shown) were reduced in >99% de. The origin of the selectivity is not understood at the moment. Surprisingly, Dibal-H and Luche's reagent (NaBH<sub>4</sub>/CeCl<sub>3</sub>) gave predominantly alcohol **5a** (4:1 and 2:1). Alcohols **5b** and **6b** were then converted to the corresponding pivalate esters **7b** and **8b**.

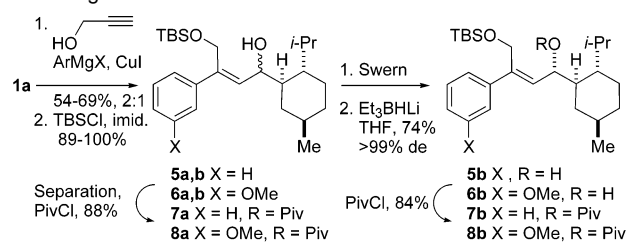
The above sequence could be made more convergent by starting with acyl chloride **1b** (Scheme 1). Vinyl silane **10** was prepared by the copper-catalyzed carbomagnesiation of **9** and protection of the alcohol (Scheme 3). Compound **10** underwent an electrophilic addition to **1b** catalyzed by tin tetrachloride to give ketone (*E*)-**11** directly and exclusively. Other Lewis acids catalyzed this transformation less efficiently. Ketone **11** was reduced with complete stereoselectivity to alcohol **3b** which was esterified to **4b**. Admittedly, large-scale operations are more cumbersome and lower yielding than those with the methodology depicted in Scheme 2.

Pivalate esters **4b**, **7b**, and **8b** were then subjected to an  $S_N2'$  displacement with a monoalkylcyanocuprate after deprotection of the TBS ether (Scheme 4). Prior deprotection of the primary alcohol was necessary to obtain better yields of adducts. The transfer of

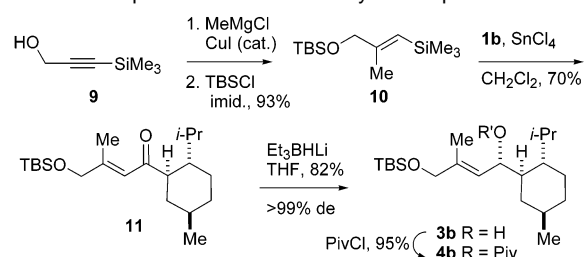
### Scheme 1. Preparation of Pivalate **4a** by Methylalumination



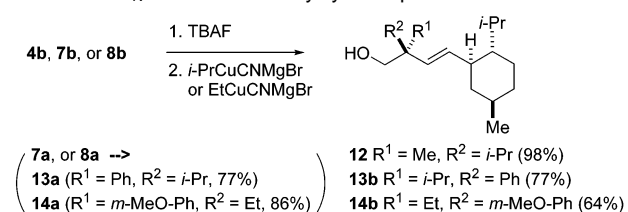
### Scheme 2. Preparation of Pivalates **7** and **8** by Carbomagnesiation



### Scheme 3. Preparation of Ketone **12** by Electrophilic Addition



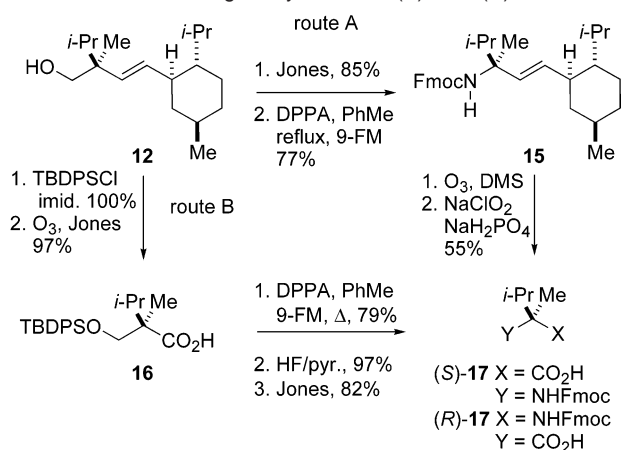
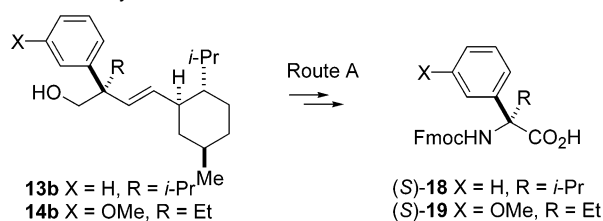
### Scheme 4. $S_N2'$ Addition of Alkylcyanocuprates to Pivalate Esters



chirality was >98% in the case of **12** and **13b**, while **14b** contained 3% of **14a** (HPLC analysis).

The cuprate displacement reactions were also performed on the diastereomeric pivalate esters **7a** and **8a** (obtained from **5a** and **6a**, respectively, cf. Scheme 2). The displacements occurred with complete stereoselectivity to give **13a** and **14a**, respectively, demonstrating that the configuration at the carbinol carbon has little or no effect on the transfer of chirality.

(*S*)-Methyl valine was obtained from alcohol **12** by first oxidizing it to the acid with Jones' reagent (Scheme 5, route A). A Curtius rearrangement<sup>9</sup> using diphenylphosphoryl azide (DPPA) was then performed on the resulting acid followed by a 9-fluorenylmethanol quench to give carbamate **15** in 77% yield. The final amino acid

**Scheme 5.** Stereodivergent Synthesis of (*S*)- and (*R*)-**17****Scheme 6.** Synthesis of **17b** and **17c**

(*S*)-**17**, in its *N*-protected form, was obtained by treating **15** with ozone followed by workup with dimethyl sulfide. The *N*-protected amino aldehyde was isolated as a 95:5 mixture of enantiomers (chiral HPLC). Oxidation to the acid occurred in 55% yield for the two steps. This two-stage oxidation is not necessary, but the aldehydes were easier to separate than the acids on chiral HPLC, allowing us to determine their enantiomeric purity.

The enantiomer (*R*)-methyl valine was prepared from the same alcohol **12** by first protecting it as its *tert*-butyldiphenylsilyl ether followed by oxidative cleavage of the auxiliary, providing acid **16** in 97% yield (Scheme 5, route B). The chiral auxiliary was also recovered in 86% yield. The Curtius protocol gave the carbamate, and deprotection and oxidation of the primary alcohol furnished (*R*)-**17** in 63% for three steps. The corresponding aldehyde was prepared and shown to be a 97:3 mixture of *R* and *S* (chiral HPLC).

Two more  $\alpha,\alpha$ -dialkylated amino acids, (*S*)-**18** and (*S*)-**19**, were prepared by route A and were obtained in 10% and 8% overall yield, respectively (Scheme 6). Analysis by chiral HPLC of the protected amino aldehydes revealed enantiomeric excesses of 98% and 96%, respectively. Each of the diastereomers **13a** and **14a** were also converted to the corresponding *N*-protected amino acids (*R*)-**18** and (*R*)-**19**. Both were produced in >98% ee (analysis of the aldehydes). The small discrepancies in optical purity in going from the cuprate adducts to the amino acids may be due to an inadvertent separation of isomers during purification steps.

This strategy has a high degree of flexibility because, in addition to the possibility of stereodivergence, it is possible to access either enantiomer from (+)- or (–)-menthyl carboxaldehyde or by interchanging R<sup>1</sup> and R<sup>2</sup>. Other  $\alpha,\alpha$ -dialkylated amino acids, as well as other nitrogen-containing products, are currently being prepared, and their synthesis will be reported in due course.

**Acknowledgment.** We thank the Natural Sciences and Engineering Council of Canada, Boehringer-Ingelheim (Canada) Ltd., The ACS Petroleum Research Fund, and the Université de Sherbrooke for financial support.

**Supporting Information Available:** Experimental and NMR spectra of all new compounds (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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JA037078A