A New Chiral Auxiliary Derived from (2*S*)-Phenylglycinol: an Access to Enantiomerically Pure β-Amino Acids

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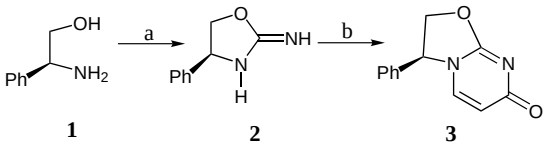
Abstract: A new bicyclic heterocycle **3**, which is potentially useful for the synthesis of β-amino acids, has been obtained from a reaction between *(S)*-phenylglycinol and cyanogen bromide followed by a condensation with methyl propiolate. Conjugate additions of different organocuprate reagents to this chiral Michael acceptor occurred with complete diastereoselectivity. An optically pure β amino acid was obtained in excellent yield from the masked chiral derivative **4a**.

Key words: β-amino acids, chiral auxiliary, asymmetric synthesis, organocuprates.

The asymmetric synthesis of β-amino acids has attracted much attention in recent years.[1] Actually, although less abundant than their α-analogs, β-amino acids are crucial structural features of numerous biologically active natural products[2] and were often used as building blocks for the synthesis of β-lactam antibiotics.[3] Racemic β-amino acids have been prepared by using several methods but their enantioselective syntheses have been described only recently.[4] In this paper, we report a highly diastereoselective conjugate addition of organocuprate reagents to a new bicyclic chiral building block **3**. Chiral auxiliaries have already been used in the synthesis of substituted β-amino acids. Some of them are especially noteworthy: (i) 6-substituted perhydropyrimidin-4-one and dihydropyrimidinones, respectively used by Cardillo et al[5] and by Chu and Konopelski,[6] (ii) chiral derivatives of 3-aminopropionic acid which allowed Seebach and Juaristi[7] to develop many syntheses, (iii) lithiated hydropyrimidines used by Seebach et al[8] to synthesize α-branched β-amino acids.

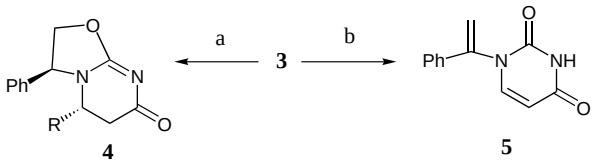
Compound **3** was obtained by the following two-step sequence: (i) a reaction between (2*S*)-phenylglycinol **1** and cyanogen bromide[9] affording compound **2**[10] (ii) a condensation of this product with methyl propiolate[11] which afforded bicyclic heterocycle **3**[12] (Scheme 1).



1 **2** **3**

Scheme 1 a) BrCN, EtOH, reflux, 98%; b) methyl propiolate, EtOH, reflux, 67%.

The bicyclic compound **3** was used in Michael reactions with three different organocuprate reagents.[13] In all cases, this reaction afforded compounds **4a-c** as pure diastereomers in high yields (Scheme 2).



4 **5**

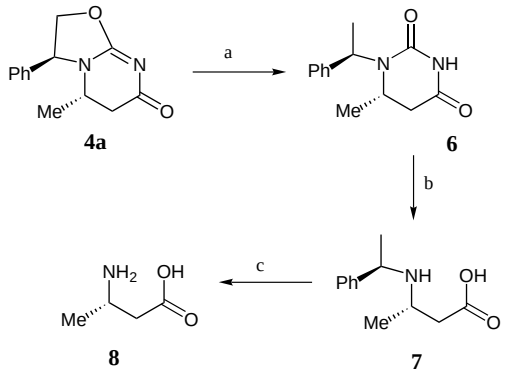
4a R=Me 86% (de>95%)
4b R=*n*-Bu 93% (de>95%)
4c R=Ph 81% (de>95%)

Scheme 2 a) R_2CuLi, TMSCl, Et_2O/THF, -78 °C to rt. b) Me_2CuLi, THF, 91%.

The observed stereoselectivity corresponds to an attack of the nucleophile in an *anti* orientation with respect to the phenyl group. It is interesting to note that the efficiency of the reaction was highly improved when it was performed in the presence of TMSCl, whose utility, in similar cases, is well-established.[14] Thus, in the absence of TMSCl, product **5** was formed via a β-elimination process involving the abstraction of the benzylic hydrogen (Scheme 2).

In order to liberate the corresponding β-amino acid and to determine the absolute configuration of the new chiral center, we synthesized β-amino acid **8** derived from compound **4a**. Some difficulties were encountered when it came to hydrogenolyze the benzylic C-N bond. Surprisingly, it appears that the reacting bond was the C-O one. Reaction with hydrogen in presence of palladium on carbon, platinum oxide or palladium hydroxide in acidic, basic or neutral medium gave the reduced product **6**. Nevertheless, dihydrouracil **6** was hydrolyzed by the action of sodium hydroxide.[15] Finally, after purification on an acidic cation exchanger, the amino acid **7** was submitted to the action of hydrogen in the presence of palladium hydroxide to afford optically pure *(S)*-3-aminobutanoic acid **8**.[16]

In conclusion, we have developed a novel and diastereoselective method for the asymmetric synthesis of β-substituted β-amino acids. Asymmetric syntheses which make further use of chiral derivative **3** are currently in progress.



Scheme 3 a) H_2, Pd/C, EtOH, 100%; b) NaOH 1M, then Dowex (50W x 8), 88%; c) H_2, $Pd(OH)_2$, EtOH, 100%

References and Notes

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(9) Compound **2** was already described in racemic form: Kampe, K.D. *Liebigs Ann. Chem.*, **1974**, 593-607.

(10) Data for compound **2**: ^{1}H NMR (250 MHz, $CDCl_3$): 4.17 (dd, J = 8 and 7.3 Hz, 1H), 4.74 (dd, J = 8 and 9 Hz, 1H), 4.95 (ls, 2H), 5.13 (dd, J = 7.3 and 9 Hz, 1H), 7.14-7.30 (m, 5H). ^{13}C NMR (63 MHz, $CDCl_3$): 65.7, 75.6, 126.7, 127.7, 128.8, 142.2, 162.1. mp 114 °C. $[\alpha]^{20}_D$:+11 (*c* 1, $CHCl_3$).

(11) Lin, T.S.; Luo, M.Z.; Liu, M.C. *Tetrahedron Lett.*, **1994**, *35*, 3477-3480.

(12) Selected data for compound **3**: ^{1}H NMR (250 MHz, $CDCl_3$): 4.49 (dd, J = 7.8 and 9.2 Hz, 1H), 5.01 (t, J = 9.2 Hz, 1H), 5.23 (dd, J = 7.8 and 9.2 Hz, 1H), 5.95 (d, J = 7.5 Hz, 1H), 6.90 (d, J = 7.5 Hz, 1H), 7.23-7.31 (m, 5H). ^{13}C NMR (63 MHz, $CDCl_3$):61.9, 73.9, 109.8, 127.1, 129.7, 130.1, 135.1, 135.8, 160.9, 172.0. mp 186 °C. $[\alpha]^{20}_D$: -18 (*c* 0.4, MeOH).

(13) General procedure for Michael addition. To a solution of compound **3** (0.93 mmol) in THF (10 ml) were successively added, at –78 °C, trimethylsilylchloride (0.93 mmol) and a solution of alkyl organocuprate (1.4 mmol, 0.15 M in diethyl ether, prepared by addition, at –10 °C, of a solution of commercially organolithium (2.8 mmol) to a suspension of CuI (1.4 mmol) in diethyl ether). The reaction was allowed to reach room temperature within 1 hour and the mixture was stirred at rt for 2 hours. An aqueous solution saturated with ammonium chloride (15 ml) was added and the reaction mixture was extracted with CH_2Cl_2 (2 x 20 ml). After evaporation the residue was chromatographed (EtOAc / MeOH). Selected data for **4a**: ^{1}H NMR (250 MHz, $CDCl_3$): 1.20 (d, J = 6.4 Hz, 3H), 2.35 (dd, J = 15.9 and 6.6 Hz, 1H), 2.59 (dd, J = 15.9 and 6.9 Hz, 1H), 3.39-3.44 (m, 1H), 4.32 (dd, J = 8.9 and 6.3 Hz, 1H), 4.81 (t, J = 8.9 Hz, 1H), 5.03 (dd, J = 8.6 and 6.2 Hz, 1H), 7.22-7.39 (m, 5H). ^{13}C NMR (63 MHz, $CDCl_3$):17.2, 37.1, 45.5, 60.3, 73.2, 126.9, 128.6, 129.7, 135.5, 167.2, 178.1. $[\alpha]^{20}_D$:+119 (*c* 1, $CHCl_3$).

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(16) Selected data for the *(S)*-3-aminobutanoic acid **8**: $[\alpha]^{20}_D$:+34 (*c* 0.6, H_2O); [lit.[7a]: $[\alpha]^{28}_D$:+32.2 (*c* 0.9, H_2O); lit.[17]:$[\alpha]^{23}_D$:+37.2 (*c* 0.3, H_2O)].

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