Pergamon

Tetrahedron Letters 41 (2000) 8293–8296

TETRAHEDRON LETTERS

Asymmetric synthesis of C-6 substituted pipecolic acid derivatives

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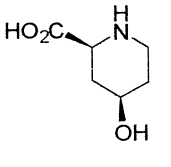
Received 12 July 2000; accepted 1 September 2000

Abstract

The synthesis of C-6 substituted pipecolic acid derivatives using an intramolecular Mannich-type reaction is described. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: asymmetric synthesis; piperidines; pipecolic acid.

Pipecolic acid and especially the C-4 oxygenated derivatives are natural non-proteinogenic α-amino acids, and, by this way, often display interesting and potent biological activities. For example (2*S*,4*R*)-4-hydroxypipecolic acid **1** (Fig. 1), which has been isolated from the leaves of *Calliandra pittieri* and *Strophantus scandeus*,[1] has been used in the elaboration of rigid analogues of NMDA receptors antagonists.[2] Compound **1** is also used for the synthesis of palinavir **2** which is a potent HIV protease inhibitor.[3] Moreover, substituted pipecolic acid derivatives are used as conformationally constrained amino acids and, for this reason, could serve as building blocks for the synthesis of peptidomimetics.[4] For all these goals, easy and chiral routes to these substances, differently substituted on the piperidine ring, have yet to be proposed. A lot of



(2*S*,4*R*)-**1**

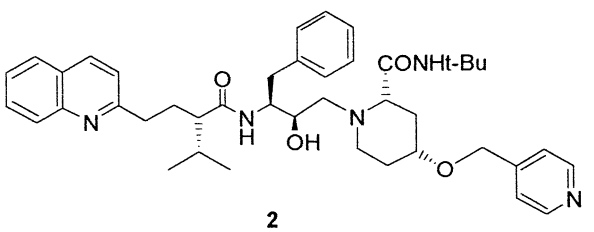


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Figure 1.

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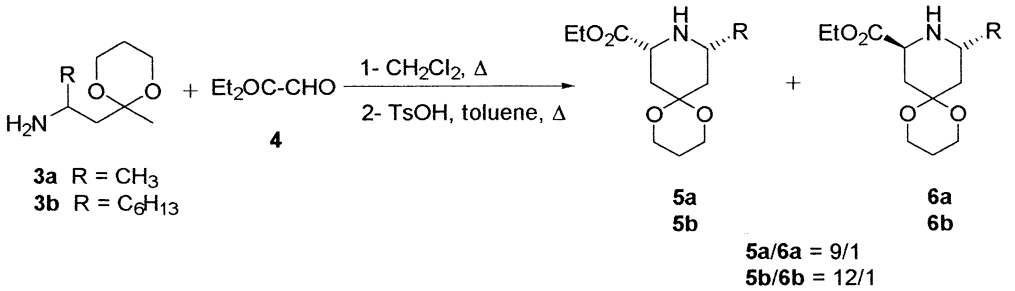
PII: S0040-4039(00)01463-5

pathways for the synthesis of **1** have been developed,[5] together with the preparation of substituted compounds.[6] In this letter, we wish to describe our approach to the synthesis of C-6 substituted pipecolic acid derivatives.

In continuation of our studies on the asymmetric elaboration of polysubstituted piperidines by intramolecular Mannich type cyclization reactions[7], we used ethyl glyoxylate **4** as an aldehyde. Thus, reaction of amine **3a**[7] with ethyl glyoxylate **4** in refluxing dichloromethane, in the presence of magnesium sulphate as a drying agent, led quantitatively to the transient imine which was directly treated with *para*-toluenesulfonic acid at 70°C in toluene. After cooling to room temperature, the mixture was washed with saturated aqueous $NaHCO_3$ and extracted with ethyl acetate. The combined extracts were dried and evaporated. Chromatography of the oily residue afforded the two diastereoisomeric piperidines **5a** and **6a** in an 83% overall yield (Scheme 1).



Scheme 1.

As expected, the 2,6-*cis* diastereoisomer **5a** was formed predominantly[7] (*cis*/*trans* ratio = 9/1), and the relative configuration of compounds **5a** and **6a** was deduced from their analytical data.[8] For compound **6a** two conformations may exist: a significant difference in energy (1.6 kcal mol^{-1}) in favour of conformer **B** was found,[9] as observed for the cyclohexane analogues[10] (Fig. 2).

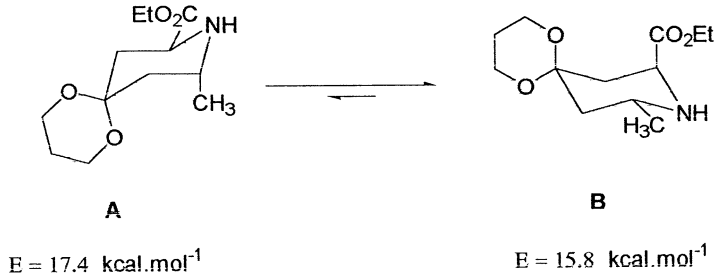
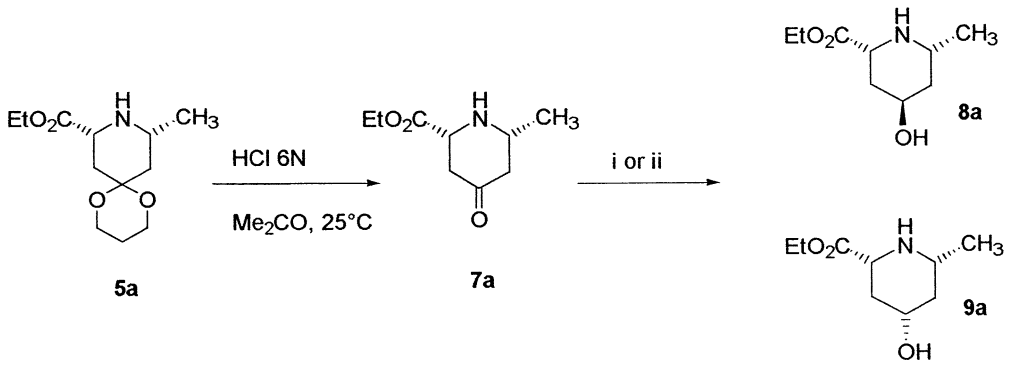


Figure 2. Conformational analysis for compound **6a**

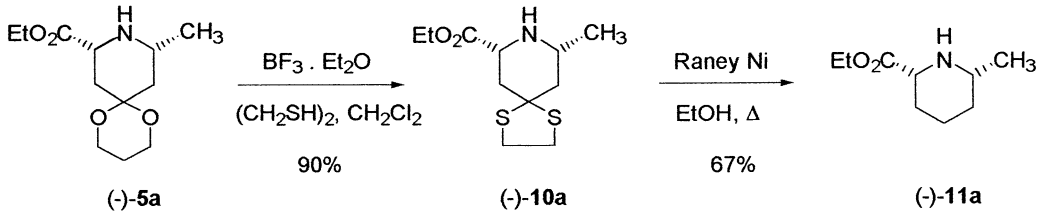
An analogous reaction conducted with amine **3b**[11] in the same conditions also led to a mixture of piperidines **5b** and **6b** (overall yield 60%), but in a 12/1 ratio.

The use of homochiral amine (−)-**3a**[12] for the same reaction furnished (−)-**5a**[8] and (+)-**6a**,[8] showing that by this way we could have an entry to the asymmetric synthesis of C-6 substituted pipecolic acid derivatives. Cleavage of the dioxane appendage on (−)-**5a** (HCl/acetone) gave the piperidone (+)-**7a** whose selective reduction, with either L-Selectride® or sodium borohydride, afforded the axial **8a** and the equatorial **9a** piperidinol[13] as the major products, respectively (Scheme 2).



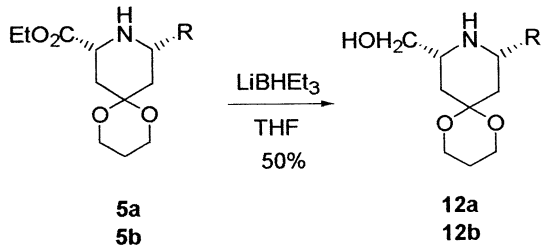
Scheme 2. (i) L-Selectride®, −78°C, THF, 95%; (ii) $NaBH_4$, MeOH, 25°C, 70%

Treatment of (−)-**5a** with ethane dithiol in the presence of $BF_3{\cdot}OEt_2$ furnished the dithiolane derivative (−)-**10a** (90% yield) which was converted by desulfurization with Raney nickel W2 in 6-methyl pipecolic acid ethyl ester (−)-**11a** (Scheme 3).



Scheme 3.

On the other hand, reduction of piperidines **5a** and **5b** with Super Hydride® in THF at 0°C led to the alcohols **12a** and **12b** in 50% yield (Scheme 4).



Scheme 4.

In conclusion, we have described an efficient preparation of C-6 substituted pipecolic acid derivatives, through an intramolecular Mannich-type reaction starting from homochiral amine (−)-**3a** or amine **3b**. Extension of this reaction to the synthesis of alkaloids is currently in progress.

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8. **5a**: $[\alpha]_D^{20}$ −12 (*c* 0.95, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 4.09 (q, 2H, $J=7.1$ Hz), 3.83 (m, 4H), 3.45 (dd, 1H, $J=2.8$, 12.2 Hz, H-2), 2.80 (m, 1H, H-6), 2.55 (dt, 1H, $J=2.7$, 13.3 Hz, H-3e), 2.27 (s br, 1H, NH), 2.07 (dt, 1H, $J=2.7$, 13.1 Hz, H-5e), 1.64 (m, 2H), 1.26 (t, 1H, $J=12.5$ Hz, H-3a), 1.16 (t, 3H, $J=7.1$ Hz), 1.05 (d, 3H, $J=6.4$ Hz), 1.04 (t, 1H, $J=12.6$ Hz, H-5a); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 96.8, 60.8, 59.1, 59.0, 55.3, 47.3, 41.5, 35.3, 25.4, 21.9, 14.0.
   6a: $[\alpha]_D^{20}$ +26 (*c* 0.95, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 4.16 (q, 2H, $J=7.1$ Hz), 3.90 (m, 3H), 3.72 (dd, 1H, $J=2.4$, 6.0 Hz, H-2), 3.69 (m, 1H), 3.23 (m, 1H, H-6), 2.99 (dt, 1H, $J=2.6$, 13.7 Hz, H-3e), 2.70 (s br, 1H, NH), 1.94 (dt, 1H, $J=2.8$, 13.0 Hz, H-5e), 1.79, 1.71 (dd, 1H, $J=6.4$, 13.7 Hz, H-3a), 1.53 (m, 1H), 1.27 (t, 3H, $J=7.1$ Hz), 1.24 (t, 1H, $J=13.0$.Hz, H-5a), 1.07 (d, 3H, $J=6.3$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9, 96.4, 60.8, 59.6, 59.4, 54.4, 44.0, 42.8, 31.2, 25.4, 22.4, 14.2.
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