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Diastereoselective synthesis of 2,4,5-trisubstituted piperidines from enantiopure β-amino esters

Dawei Ma* and Haiying Sun

State Key Laboratory of Bioorganic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, China

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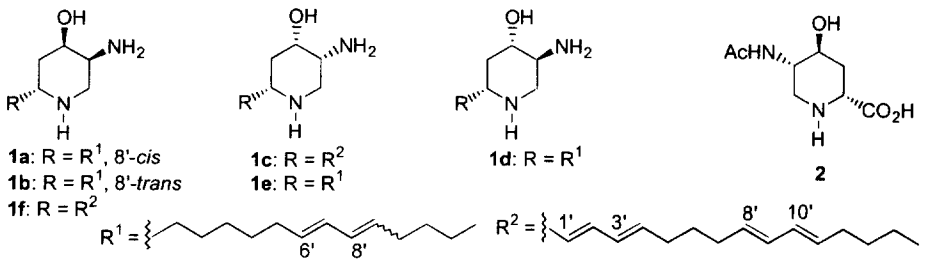
Abstract: Reaction of (*R*)-β-amino esters with methyl acrylate followed by Dieckmann condensation and enol silylation afforded the enol ethers **5**, which were hydrogenated with catalysis by Raney-Ni to provide 2,4,5-trisubstituted piperidines with high diastereoselectivity.

2,4,5-Trisubstituted piperidines are common structures in natural products and synthetic compounds with biological activity.[1-5] For example, pseudodistomins A (**1a**) and B (**1b**) are potent antineoplastic piperidine alkaloids with calmodulin antagonist activity,[2] while four other pseudodistomins, C (**1c**), D (**1d**), E (**1e**), and F (**1f**) were found to be active in a cell-based assay for DNA damage induction.[3,4] In addition, (2*R*,4*S*,5*S*)-5-acetamido-4-hydroxy-pipecolinic acid (**2**) was found to be an inhibitor of sialidases.[5] Therefore the stereoselective construction of these piperidines has been an important goal during the past two decades.[4-7] As part of our program on the synthesis from enantiopure β-amino acid derivatives,[8] we developed a general method for the diastereoselective synthesis of 2,4,5-trisubstituted piperidines. Herein we wish to detail our results.

Scheme 1



Our strategy for synthesizing 2,4,5-trisubstituted piperidines is outlined in Scheme 2. *N,N*-Disubstituted β-amino esters **3** could be obtained in high diastereoselectivity according to Davies's procedure[9]. Deprotection of **3** by Pd/C catalyzed hydrogenation followed by Michael addition of the amine to methyl acrylate afforded an amino diester, which was protected with a Boc group to yield **4**.

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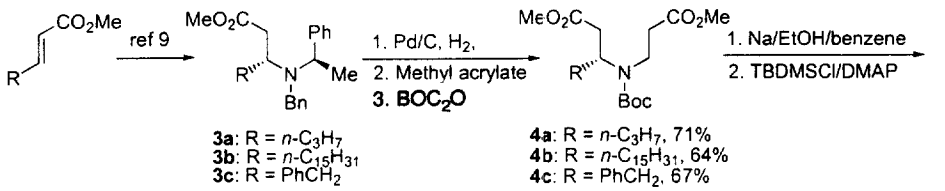
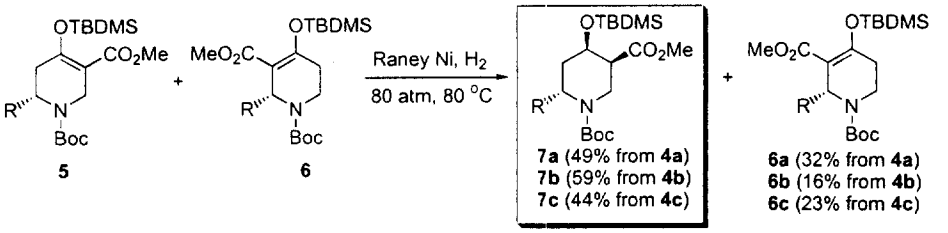
Dieckmann condensation of **4** using sodium/methanol provided the cyclization products, which were treated with *tert*-butyldimethylsilyl chloride to give a mixture of **5** and **6**. These two isomers could not be separated by column chromatography but their ratio could be determined by ^{1}H NMR. Thus, we could establish that the regioselectivity was about 1.5, 3.8, 1.7 for **4a**, **4b**, **4c**, respectively. The key problem was how to reduce the C-C double bond of **5** or **6** diastereoselectively to create two stereogenic centers. After some experimentation, it was found that hydrogenation of the mixture of **5** and **6** at 80 atm and 80 °C under the action of Raney-Ni gave **7** as a single isomer together with unreacted **6**. Under these conditions, 100% conversion of **5** could be achieved while no hydrogenation of **6** was detected. However, it was found that part of **6** could be reduced by prolonging the reaction time and increasing the reaction temperature to 100 °C. The difference in reactivity of **5** and **6** might result from steric hindrance. It is notable that if the *tert*-butyl carbamate of **4** was changed to a methyl carbamate, much lower diastereoselectivity was observed. These results indicated that the Boc protecting group plays a crucial role in the diastereoselective hydrogenation.

Scheme 2





After the success in obtaining the reduced products **7** diastereoselectively, the next problem was assignment of the stereochemistry of two new stereogenic centers. We planned to solve this problem by further conversion of these products. As shown in Scheme 3, treatment of **7** with *tert*-*n*-butylammonium fluoride followed by hydrolysis with aqueous sodium hydroxide provided the corresponding β-hydroxy acids **8a** and **8b**.[10] The compound **8a** gave fine crystals which allowed us to determine its structure by X-ray analysis. As outlined in Figure 1, the X-ray studies of **8a** clearly indicated that the 4-hydroxy and 5-carboxylate groups are *cis* to each other and both *trans* to the *n*-

propyl group. Thus, we concluded that **8a** has the (2*R*,4*R*,5*S*)-configuration. To demonstrate the usage of the present methodology, we converted **8b** to octahydropseudodistomin F acetate **10**. Accordingly, treatment of **8b** with DPPA gave the corresponding azide, which was transformed into the cyclic carbamate **9b** by means of a Curtius rearrangement. After deprotection and protection, the carbamate **9b** was transformed into **10**[11] in 84% yield.

Scheme 3

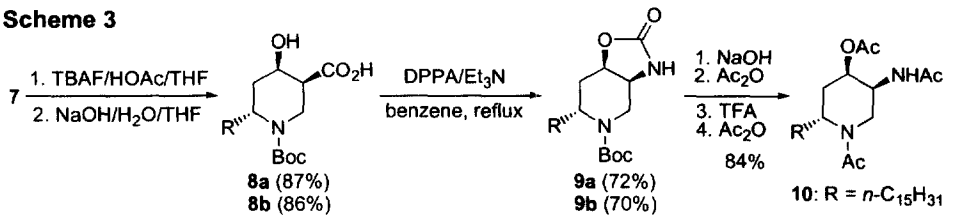


Figure 1: X-ray structure of **8a**

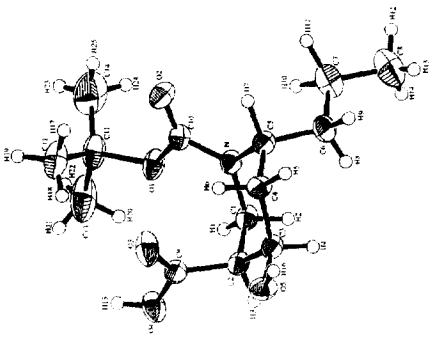
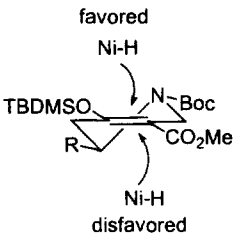


Figure 2



The diastereoselectivity in the Raney-Ni catalyzed hydrogenation may be due to attack on the less hindered face (see Figure 2). This hypothesis is supported by the X-ray structure of **8a** in which the Boc group and *n*-propyl are *trans* to each other.

In conclusion, we have developed a new methodology for the synthesis of 2,4,5-trisubstituted piperidines from β-amino ester which involves a Raney-Ni catalyzed hydrogenation as a key step. Using this method, octahydropseudodistomin F acetate **10** was synthesized in 12 steps and 19% overall yield. Further applications of this method to the syntheses of the pseudodistomin family, as well as other related natural products, are underway.

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10. Selected data for **8a**: $[\alpha]^{25}_{D}$ = -10.9 (*c* 0.59 $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 6.50 (br s, 2H), 4.57 (d, *J* = 14.1 Hz, 1H), 4.35 (m, 1H), 4.05 (m, 1H), 2.97 (dd, *J* = 14.1, 3.1 Hz, 1H), 2.88 (m, 1H), 1.98 (m, 1H), 1.80 (m, 1H), 1.70-1.20 (m, 13H), 0.93 (t, *J* = 7.2 Hz, 3H).
11. Selected data for **10**: $[\alpha]^{28}_{D}$ = +29.2 (*c* 0.37 $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 6.00 (d, *J* = 7.2 Hz, 2/3H), 5.67 (m, 1/3H), 5.14 (m, 1H), 4.90 (m, 2/3H), 4.60 (d, *J* = 14.2 Hz, 1/3H), 4.51 (m, 1/3H), 4.35 (m, 2/3H), 3.97 (m, 1/3H), 3.92 (d, *J* = 14.3 Hz, 2/3H), 3.30 (d, *J* = 14.2 Hz, 2/3H), 2.91 (d, *J* = 14.3 Hz, 1/3H), 2.25-2.00 (m, 6H), 1.72-1.61 (m, 4H), 1.25-1.12 (m, 26H), 0.87 (t, *J* = 7.2 Hz, 3H). ^1H NMR analysis of **10** indicates that two amide rotamers exist in solution, which is similar with those of other related compounds.[7]