

## Application of the Asymmetric Chelate-Enolate Claisen Rearrangement to the Synthesis of 5-*epi*-Isifagomine

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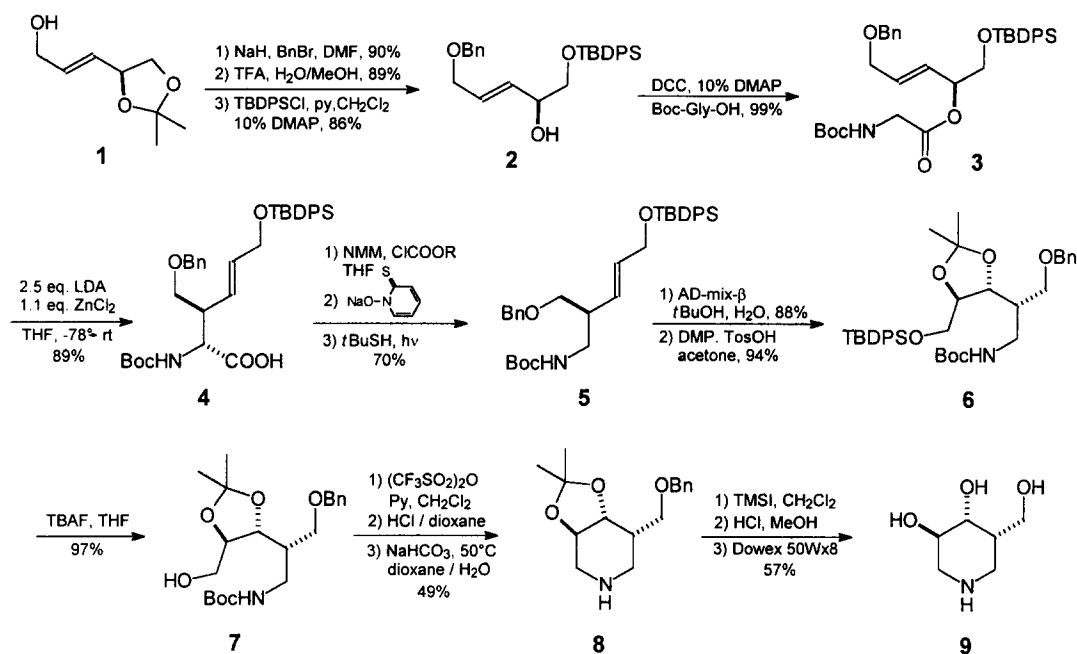
Received 11 November 1997; revised 8 December 1997; accepted 12 December 1997

**Abstract:** Chelate-enolate Claisen rearrangement of a *N*-protected chiral amino acid ester gave rise to a  $\gamma,\delta$ -unsaturated amino acid, which could be converted to the potential glycosidase inhibitor 5-*epi*-isifagomine (**9**) in a straightforward and a highly stereoselective fashion. © 1998 Elsevier Science Ltd. All rights reserved.

Based on their structural relationship to sugars, polyhydroxylated piperidines (azasugars) and pipercolinic acid derivatives are interesting candidates for the inhibition of various glycosidases. Protonated azasugars act as transition state analogues of these enzymes.<sup>1</sup> These naturally occurring alkaloids are closely related to sugars, only the ring oxygen is replaced by nitrogen. Recently, Bols et al. reported the synthesis of isifagomine,<sup>2</sup> a new type of glycosidase inhibitor. In this structure the nitrogen replaces the anomeric carbon atom instead of the oxygen. Isifagomine in the *N*-protonated form is especially suitable to mimic a carbenium ion, which is a reasonable intermediate in the enzymatic glycosyl cleavage. Therefore isifagomine is the strongest inhibitor of  $\beta$ -glycosidases so far.<sup>2</sup>

Recently, we developed a new variation of the Claisen rearrangement of amino acid esters, proceeding *via* chelated allylic ester enolates.<sup>3</sup> If esters of chiral alcohols are employed, the corresponding chiral amino acids are obtained in a highly stereoselective fashion.<sup>4</sup> Because of our interest into the synthesis of polyhydroxylated piperidine alkaloids,<sup>5</sup> we investigated an approach to this class of compounds, based on this chelate enolate Claisen rearrangement. As a target an isomer of isifagomine, 5-*epi*-isifagomine (**9**) was chosen.

The required, suitable protected chiral allylic ester **3** was easily obtained from the protected unsaturated alcohol **1**.<sup>6</sup> Chelate-enolate Claisen rearrangement,<sup>4</sup> using LDA as a base and zinc chloride as chelating agent, gave rise to the  $\gamma,\delta$ -unsaturated amino acid **4**. Because of their low polarity, the *N*-protected amino acid could be purified directly by flash chromatography. For the following decarboxylation step, the Barton procedure, developed for amino acids, was used.<sup>7</sup> Subsequent Sharpless dihydroxylation<sup>8</sup> of the protected unsaturated amine **5** using AD-mix- $\beta^{\circ}$  provided the corresponding diol, which was converted to the isopropylidene derivative **6**. The diastereoselectivity in the hydroxylation step was excellent (> 97% ds, *matched case*). Removal of the silyl protecting group gave the alcohol **7**, which was converted to the triflate. Without further purification the triflate was used directly in the cyclization step giving rise to **8**.<sup>9</sup> To finish the synthesis, only the protecting groups had to be removed. Catalytic hydrogenation of the benzyl ether was unsuccessful, therefore the benzyl group was removed with trimethylsilyl iodide. Cleavage of the ketal and subsequent ion exchange chromatography provided 5-*epi* isifagomine (**9**).<sup>10</sup>



In conclusion we have shown that the chelate-enolate Claisen rearrangement is not only a suitable method for the construction of unsaturated amino acids, but can also be applied to other classes of natural products such as alkaloids.

**Acknowledgments.** We thank Prof. Dr. G. Helmchen for his generous support. Financial support by the Deutsche Forschungsgemeinschaft as well as the Fonds der Chemischen Industrie is gratefully acknowledged.

## REFERENCES AND NOTES

- Sinnott, M. L. *Chem. Rev.* **1990**, *90*, 1171, and references cited therein.
- a) Jespersen, T. M.; Dong, W.; Soerks, M. R.; Skrydstrup, T.; Lundt, I.; Bols, M. *Angew. Chem.* **1994**, *106*, 1858; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1778. b) Bols, M.; Hazell, R. G.; Thomsen, I. B. *Chem. Eur. J.* **1997**, *3*, 940. b) Thomsen, I.; Ernholz, B. V.; Bols, M. *Tetrahedron* **1997**, *53*, 9357.
- Kazmaier, U. *Angew. Chem.* **1994**, *106*, 1096; *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 998. Review: Kazmaier, U. *Liebigs Ann. Chem. / Recueil* **1997**, 285.
- Kazmaier, U.; Schneider, C. *Synlett*, **1996**, 975.
- Grandel, R.; Kazmaier, U. *Tetrahedron Lett.* **1997**, *38*, 8009.
- Kametani, T.; Suzuki, T.; Nishimura, M.; Sato, E.; Unno, K. *Heterocycles*, **1981**, *19*, 205.
- Barton, D. H. R.; Crich, D.; Motherwell, W. B. *Tetrahedron* **1995**, *41*, 3901.
- Kolb, H. C.; vanNieuwenzhe, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.
- 8**: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ = 1.36 (s, 3H), 1.41 (s, 3H), 1.87 (m, 1H), 2.49 (m, 1H), 2.63 (m, 2H), 3.32 (m, 2H), 3.35 - 3.77 (m, 4H), 4.47 (d, *J* = 11.9 Hz, 1H), 4.55 (d, *J* = 11.9 Hz, 1H), 7.30 (m, 5H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ = 26.63, 26.73, 39.58, 46.25, 48.25, 48.92, 66.29, 72.77, 73.34, 80.37, 108.33, 127.56, 127.62, 128.34, 128.41, 138.32; [α]<sub>D</sub><sup>20</sup> = -82.2° (c 0.2, CHCl<sub>3</sub>).
- 9**: <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ = 2.10 (m, 1H), 2.75 (m, 3H), 3.07 (dd, *J* = 13.4, 2.4 Hz, 1H), 3.60 (m, 3H), 3.80 (m, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ = 39.76, 43.75, 47.61, 62.69, 68.88, 69.95; [α]<sub>D</sub><sup>20</sup> = -10.3° (c 0.5, MeOH).