Stereoselective Allyl Amine Synthesis via Enantioselective Addition of Diethylzinc and Sigmatropic Rearrangement; Synthesis of Lentiginosine

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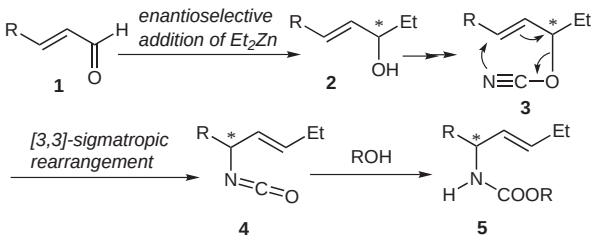
Abstract: A new synthetic method for the preparation of allyl amine derivatives has been developed. The key steps of this method are enantioselective addition of diethylzinc (Soai protocol) and allyl cyanate-to-isocyanate rearrangement. Successful application of this procedure realized the synthesis of lentiginosine (**6**).

Key words: stereoselective, asymmetric synthesis, amines, rearrangements, natural products

In connection with ongoing efforts to explore [3,3]-sigmatropic rearrangement of allyl cyanate for the synthesis of natural products,[1] we recently developed a stereoselective allyl amine synthesis as shown in Scheme 1.



Scheme 1

The reaction sequence starts with the preparation of stereochemically defined allyl alcohol **2** employing an enantioselective addition of diethylzinc to α,β-unsaturated aldehyde **1**.[2] The resulting allyl alcohol **2** is then transformed into allyl cyanate **3** which rearranges into allyl isocyanate **4** with high degree of 1,3-chirality transfer.[3] Finally, treatment of **4** with alcohols furnish a variety of carbamates **5**. This method will offer a useful entry to the stereoselective synthesis of the protected allyl amine derivatives. In this manuscript, we described successful application of this procedure to the synthesis of the most potent inhibitor of amyloglucosidase, lentiginosine (**6**),[4] from L-tartaric acid (Figure 1).

Synthesis of lentiginosine (**6**) began with the *o*-iodoxybenzoic acid (IBX) oxidation of allyl alcohol **7**,[5] which was prepared from L-tartaric acid employing known procedure[6] (Scheme 2). Enantioselective addition of diethylzinc to the resulting α,β-unsaturated aldehyde **8** catalyzed by 7 mol% of (*S*)-diphenyl(1-methylpyrrolidin-2-yl)methanol (DPMPM) smoothly afforded **9** and its epimer as an inseparable 93:7 mixture.[7] Treatment of **9** with trichloroacetyl isocyanate followed by hydrolysis with potassium carbonate in aqueous methanol gave the carbamate **10**. Dehydration of **10** with triphenylphosphine, carbon tetrabromide and triethylamine at –20 °C gave the allyl cyanate **11**, which underwent [3,3]-sigmatropic rearrangement to afford the allyl isocyanate **12**. Since isolation of **12** using an aqueous work-up would result in a decrease of yield due to the hydrolysis of the isocyanate group, isocyanate **12** was treated in situ with 2,2,2-trichloroethanol to afford trichloroethoxy (Troc) carbamate **13** in 86% yield from **10**.

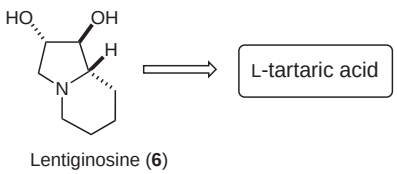
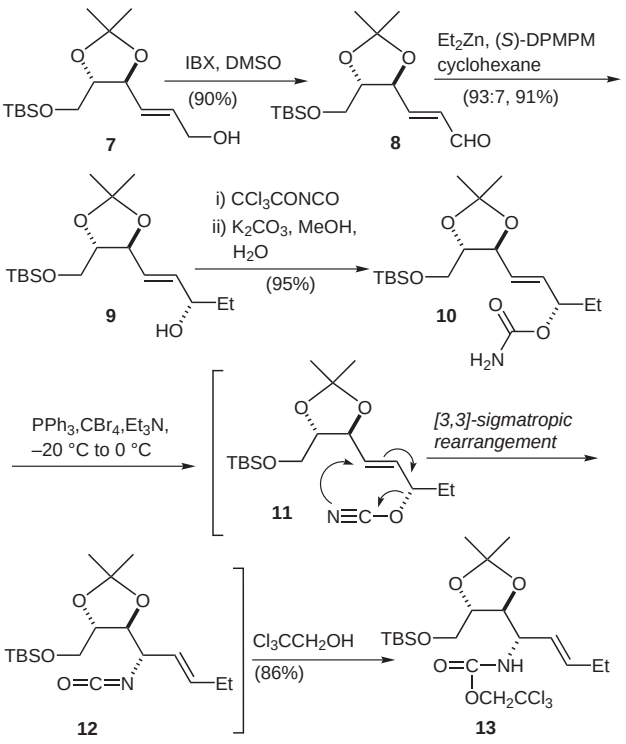


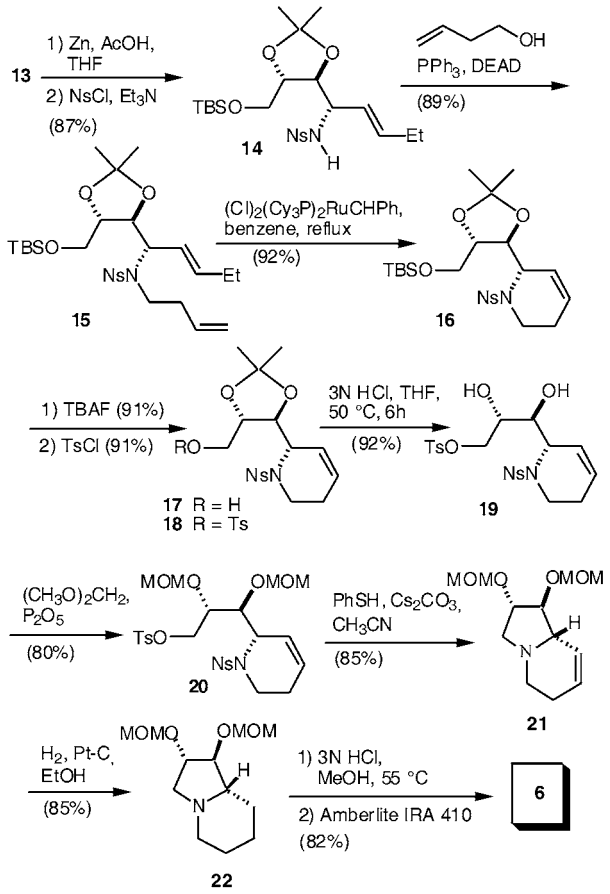
Figure 1



Scheme 2

Synlett 2003, No. 7, Print: 02 06 2003.
Art Id.1437-2096,E;2003,0,07,1034,1036,ftx,en;U04303ST.pdf.

Since allyl carbamate **13** has three stererogenic centers necessary for lentiginosine synthesis, we next turned to the construction of indolizidine ring system using ring-closing metathesis (RCM) (Scheme 3).



Scheme 3

Thus, deprotection of **13** with zinc and acetic acid in THF followed by treatment of the resulting amine with 2-nitrobenzenesulfonyl chloride and Et_3N furnished the nosyl amide **15** as crystals.[8] Alkylation of **14** with 3-buten-1-ol under Mitsunobu condition (PPh_3, DEAD, benzene) afforded 1,7-diene **15**.[9] A ruthenium-catalyzed RCM using Grubbs catalysis (6 mol%) in refluxing benzene gave the cyclized product **16**.[10] Removal of the silyl protecting group in **16** with tetra-*n*-butylammonium fluoride followed by tosylation of the resulting primary alcohol **17** furnished the tosylate **18**. Two-step protective group manipulation involving acetonide hydrolysis (3 N HCl, aq THF, 50 °C) and MOM protection (dimethoxymethane, P_2O_5) gave **20**. Deprotection of the nosyl group with concomitant cyclisation was achieved by the reaction of **20** with thiophenol and cesium carbonate to afford the cyclized product **21**. Catalytic hydrogenation of **21** (H_2, Pt-C, EtOH) gave **22**, and acid-catalyzed hydrolysis of the two MOM protecting groups in **22** (3 N HCl, aq MeOH, 55 °C) followed by treatment with ion exchange resin (Amberlite IRA 410) furnished lentiginosine **6,** whose spectroscopic properties were identical with those previously reported.[11]

In summary, a combination of Soai protocol and sigmatropic rearrangement for the stereoselective allyl amine synthesis has been realized in the context of the synthesis of lentiginosine (**6**). Further examination to test the generality of this stereocontrolled ally amine synthesis is now under way.

Acknowledgment

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References

(1) (a) Ichikawa, Y. *Synlett* **1991**, 238. (b) Ichikawa, Y.; Osada, M.; Ohtani, I.; Isobe, M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1449.

(2) Soai, K.; Ookawa, A.; Kaba, T.; Ogawa, K. *J. Am. Chem. Soc.* **1987**, *109*, 7111.

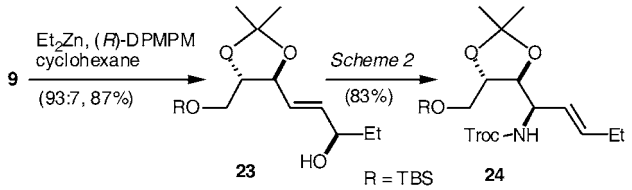
(3) Ichikawa, Y.; Tsuboi, K.; Isobe, M. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2791.

(4) (a) Isolation: Pastuszak, I.; Molyneux, R. J.; James, L. F.; Elbein, A. D. *Biochemistry* **1990**, *29*, 188. (b) For the synthetic works, see: Yoda, H.; Kitayama, H.; Katagiri, T.; Takabe, K. *Tetrahedron: Asymmetry* **1993**, *4*, 1455. (c) Gurjar, M. K.; Ghosh, L.; Syamala, M.; Jayasree, V. *Tetrahedron Lett.* **1994**, *35*, 8871. (d) Nukui, S.; Sodeoka, M.; Sasai, H.; Shibasaki, M. *J. Org. Chem.* **1995**, *60*, 398. (e) Giovannini, R.; Marcantoni, E.; Petrini, M. *J. Org. Chem.* **1995**, *60*, 5706. (f) Goti, A.; Cardona, F.; Brandi, A. *Synlett* **1996**, 761. (g) Yoda, H.; Kawauchi, M.; Takabe, K. *Synlett* **1998**, 137. (h) McCaig, A. E.; Meldrum, K. P.; Wightman, R. H. *Tetrahedron* **1998**, *54*, 9429. (i) Ha, D.-C.; Yun, C.-S.; Lee, Y. *J. Org. Chem.* **2000**, *65*, 621. (j) Yoda, H.; Katoh, H.; Ujihara, Y.; Takabe, K. *Tetrahedron Lett.* **2001**, *42*, 2509. (k) Rasmussen, M. O.; Delair, P.; Greene, A. E. *J. Org. Chem.* **2001**, *66*, 5438. (l) Lim, S. H.; Ma, S.; Beak, P. *J. Org. Chem.* **2001**, *66*, 9056. (m) Rabiczko, J.; Urbanczyk-Lipkowska, Z.; Chmielewski, M. *Tetrahedron* **2002**, *58*, 1433. (n) Chandra, K. L.; Chandrasekhar, M.; Singh, V. K. *J. Org. Chem.* **2002**, *67*, 4630. (o) Feng, Z.-X.; Zhou, W.-S. *Tetrahedron Lett.* **2003**, *44*, 497. (p) Ayad, T.; Genisson, Y.; Baltas, M.; Gorrichon, L. *Chem. Commun.* **2003**, 582.

(5) (a) Corey, E. J.; Palani, A. *Tetrahedron Lett.* **1995**, *36*, 3485. (b) Frigerio, M.; Santagostino, M.; Sputore, S.; Palmisano, G. *J. Org. Chem.* **1995**, *60*, 7272.

(6) Iida, H.; Yamazaki, N.; Kibayashi, C. *J. Org. Chem.* **1987**, *52*, 3337.

(7) In this reaction, it should be noted that we can avoid matched-mismatched problems when R has stererogenic centers (Scheme 1), because asymmetric induction is carried out at the remote position where the effect of R group becomes negligible. In fact, synthesis of the diastereomer **23** was also achieved with Soai protocol simply employing (*R*)-DPMPM to furnish **23** with 93:7 diastereoselecctivity. Further transformation of **23** using similar procedures in Scheme 2 afforded the allyl carbamate **24** in good yield (Scheme 4). For the matched-mismatched problems, see the reference: Masamune, S.; Choy, W.; Peterson, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1984**, *24*, 1.



Scheme 4

(8) The minor isomer produced in the step (**8** → **9**) was removed at this stage by recrystallisation of **14**.

(9) Fukuyama, T.; Jow, C.-K.; Cheung, M. *Tetrahedron Lett.* **1995**, *36*, 6373.

(10) (a) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl.* **1995**, 2039. (b) Grubbs, R. H.; Chang, S. *Tetrahedron* **1988**, 4413.

(11) Spectroscopic data of our synthetic lentiginosine(**6**): $[\alpha]_D^{27}$ +1.06 (*c* 0.47, MeOH). ^{1}H NMR (300MHz, $CDCl_3$): δ = 1.14–1.34 (2 H, m, H-8), 1.38–1.69 (2 H, m, H-6), 1.74–1.97 (2 H, m, H-7), 1.88–1.97 (1 H, m, H-8a), 2.04 (1 H, td, *J* = 11, 3 Hz, H-5), 2.61 (1 H, dd, *J* = 11, 7.5 Hz, H-3α), 2.82 (1 H, dd, *J* = 11, 2 Hz, H-3β), 2.93 (1 H, br d, *J* = 11 Hz, H-5), 3.64 (1 H, dd, *J* = 9, 4 Hz, H-1), 4.06 (1 H, ddd, *J* = 8, 4, 2 Hz, H-2). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.8, 23.8, 27.4, 52.4, 60.1, 68.3, 75.5, 82.8.