Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 6267–6270

Total synthesis of (+)-galanthamine starting from D-glucose

Hiroki Tanimoto, Tomoaki Kato and Noritaka Chida*

Department of Applied Chemistry, Faculty of Science and Technology, Keio University, 3-14-1 Hiyoshi, Kohoku-ku, Yokohama 223-8522, Japan

Received 20 June 2007; accepted 5 July 2007
Available online 30 July 2007

Abstract—The stereoselective total synthesis of (+)-galanthamine (+)-**1** starting from D-glucose is described. The cyclohexene ring in (+)-**1** was prepared in an optically active form from D-glucose using Ferrier's carbocyclization reaction, and the critical quaternary carbon was stereoselectively generated via chirality transfer based on the Claisen rearrangement of a cyclohexenol. The dibenzofuran skeleton was effectively constructed by the bromonium ion-mediated intramolecular cyclization of a cyclohexene possessing a phenolic ether function. After the introduction of a carbon–carbon double bond, the Pictet–Spengler type cyclization, followed by the reduction of the amide function completed the chiral synthesis of (+)-**1**.

(−)-Galanthamine (−)-**1**, an alkaloid isolated from some species of the *Amaryllidaceae* family,[1,2] has been reported to be a centrally acting acetylcholinesterase inhibitor[3] and an allosteric modulator of the neuronal nicotinic receptor for acetylcholine.[4] On the basis of these biological activities, (−)-galanthamine was developed as a medicine for Alzheimer's disease and has been clinically used in Europe and the USA.[2c] Its important and significant biological activity as well as its interesting structure have naturally received considerable attention from the synthetic community, and several synthetic approaches to **1** have been reported to date.[2,5,6] A number of successful total syntheses of galanthamine, employing the biomimetic oxidative bisphenol coupling,[2,5a,6a] intramolecular Heck reaction,[2,5b,6d,h,i] and semipinacol rearrangement[5c] for the construction of the characteristic tetracyclic skeleton possessing a spiro quaternary carbon, have appeared, however, reports of the chiral syntheses of **1** are rather limited.[6] Due to the scarce supplies of galanthamine from natural sources[7] and the necessity for preparing structural analogues for the development of more potent drugs, it is still important to establish a chiral and effective synthetic route to the alkaloid from readily available materials. In this Letter, we report a new and stereoselective total synthesis of (+)-galanthamine (+)-**1**, an enantiomer of the natural product, starting from D-glucose, which is readily utilized for the preparation of natural (−)-galanthamine and would be applicable for the synthesis of structural analogues that are not available through the biomimetic synthetic approach nor the chemical modification of the natural product.

Recently, we have reported the total synthesis of (+)-vittatine and (+)-haemanthamine, *Amaryllidaceae* alkaloids possessing the hexahydroindole skeleton with a 1,3-dioxolane ring at *m*- and *p*-positions in the phenyl group as the core structure, starting from D-glucose, and revealed that the methodology involving Claisen rearrangement on the chiral cyclohexenol derived from carbohydrates is effective for the stereoselective generation of quaternary carbons.[8] Our retrosynthetic analysis for (+)-galanthamine (+)-**1**, taking the successful synthesis of vittatine and haemanthamine into account, suggested that tetracyclic lactam **2**, which had been utilized in the synthesis of the racemic galanthamine by Guillou,[5b] would be a suitable intermediate for the total synthesis (Fig. 1). The dibenzofuran skeleton in **2** was expected to be constructed by the bromonium ion-mediated intramolecular dealkylating etherification of cyclohexene possessing a phenolic ether function[9] **3**, whose crucial quaternary carbon preparation was planned using the Claisen rearrangement[8,10] of cyclohexenol derivative **4**. Cyclohexenol **4**, in turn, was envisioned to be synthesized by the coupling reaction of an aryl metal species with cyclohexenone (+)-**5**, which is a known compound[11] and has been prepared in the optically pure form starting from D-glucose utilizing Ferrier's carbocyclization[12] as the key transformation.

Keywords: Galanthamine; Chiral synthesis; Claisen rearrangement.
* Corresponding author. Tel./fax: +81 455661573; e-mail: chida@applc.keio.ac.jp

0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.07.042

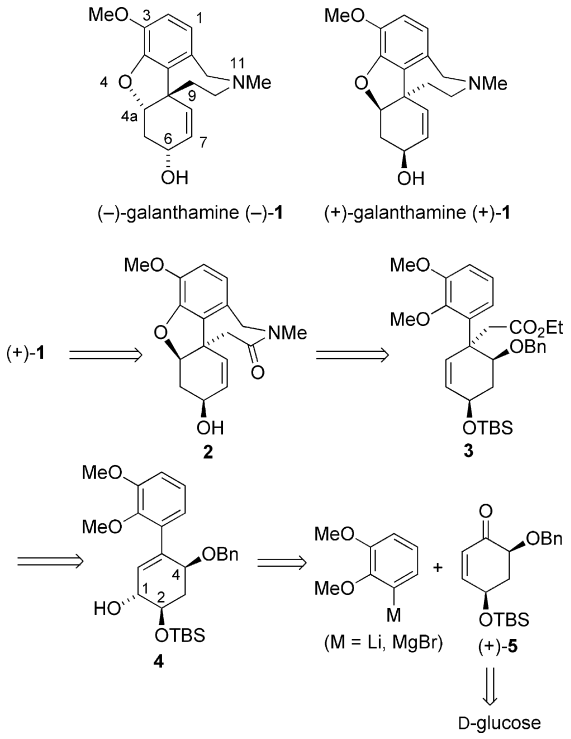
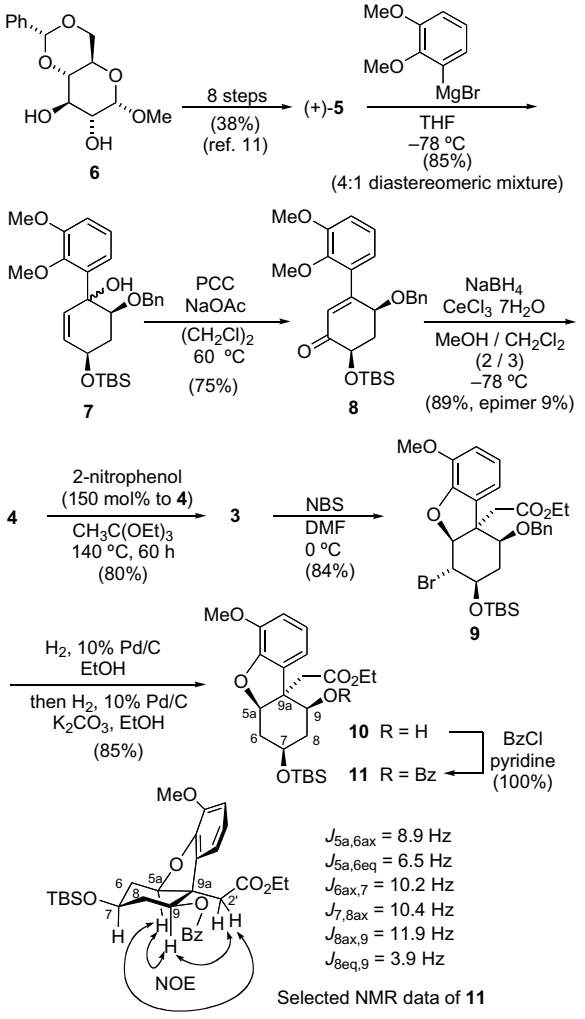


Figure 1. Structure of galanthamine and its retrosynthetic analysis. Bn = –CH_2Ph, TBS = –$SiMe_2(t\text{-Bu})$.

The treatment of (4*R*,6*S*)-6-benzyloxy-4-(*tert*-butyldimethylsilyloxy)-2-cyclohexenone[11] (+)-**5**, prepared from commercially available methyl 4,6-*O*-benzylidene-α-D-glucopyranoside **6** utilizing the catalytic Ferrier's carbocyclization[12c] as the key transformation in a total of eight steps with 38% overall yield, with 2,3-dimethoxyphenylmagnesium bromide at −78 °C gave 1,2-adducts **7** in 85% yield as a diastereomeric mixture (4:1) (Scheme 1).[13] The oxidation of **7** with pyridinium chlorochromate (PCC) afforded cyclohexenone **8** in 75% yield, which was reduced under the conditions of Luche[14] at −78 °C to give cyclohexenol **4** and its C-1 epimer in 89 and 9% isolated yields, respectively. The observed coupling constants in **4** ($J_{1,2} = 7.8$ Hz) and its C-1 epimer ($J_{1,2} = 4.1$ Hz) supported their assigned configurations. Johnson–Claisen rearrangement[15] of **4** in triethyl orthoacetate in the presence of 2-nitrophenol[8b,16] in a sealed tube at 140 °C for 60 h successfully afforded the rearranged product **3**[17] in 80% yield. It is important to note that the Johnson–Claisen rearrangement of **4**, possessing an *o*-methoxy substituent in the phenyl group, proceeded in a high yield when 2-nitrophenol was employed as the acid catalyst.[18] It has been reported that the conventional Johnson–Claisen rearrangement (using propionic acid as the catalyst) of the simple cyclohexenol systems similar to **4** resulted in the very poor yields of the rearranged products, probably due to the acid sensitivity of the substrates and the steric congestion at the reaction center caused by the presence of the *o*-methoxy substituent in the phenyl group.[9,10b,19] The acidity of 2-nitrophenol (pK_a 7.04) would be appropriate for the Johnson–Claisen rearrangement of **4**; its weaker acidity than that of propionic acid (pK_a 4.62) suppressed



Scheme 1. Bz = –C(O)Ph.

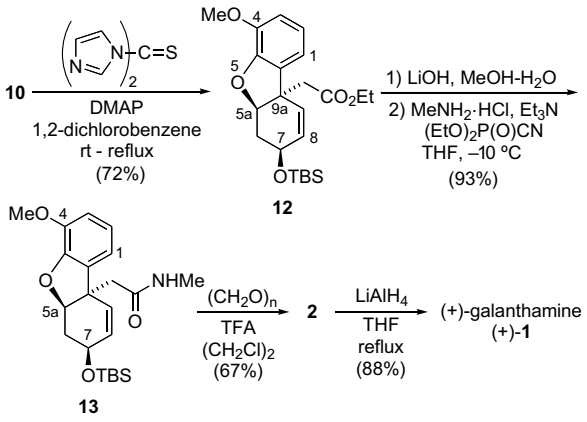
the decomposition of the substrate, but could catalyze the formation of a ketene acetal.

The treatment of **3** with *N*-bromosuccinimide (NBS) in DMF induced the intramolecular dealkylating etherification via a bromonium ion intermediate[9] to give bromo-dibenzofuran derivative **9**[17] in 84% yield. The formation of other possible products such as bromohydrins or lactones was not observed in the cyclization reaction. The hydrogenolysis of **9** in the presence of Pd on carbon and potassium carbonate in EtOH at room temperature under atmospheric pressure of H_2 caused the debromination as well as the deprotection of the *O*-benzyl group to provide **10**. However, under these basic conditions, the de-O-benzylation process was found to be very sluggish, and resulted in the low yield of **10** (less than 40%). In contrast, under similar hydrogenolytic conditions without potassium carbonate, deprotection of the *O*-benzyl group smoothly proceeded, but the debromination process became slow. After some attempts, it was found that the two-steps in a one-pot reaction gave satisfactory results. Thus, deprotection of the *O*-benzyl group in **9** under neutral conditions (Pd on carbon, atmospheric pressure of H_2 in EtOH) was first carried out. After completion of the de-*O*-ben-

zylation (TLC monitoring), potassium carbonate was added to the reaction mixture and the hydrogenolysis of the C–Br bond was further continued in the same reaction vessel to give **10** in 85% yield. The structure of compound **10** was confirmed by NMR analyses of the derived benzoate **11** (Scheme 1); the observed large coupling constants ($J_{5a,6ax}$, $J_{6ax,7}$, $J_{7,8ax}$ and $J_{8ax,9}$) revealed that the substituents at C-5a, C-7 and C-9 are all in the equatorial positions, and NOE experiments (correlations between H-5a and C-2′ methylene, and H-9 and C-2′ methylene) clearly assigned the stereochemistry of the quaternary carbon at C-9a as *R*.

To introduce the requisite carbon–carbon double bond, compound **10** was treated with (thiocarbonyl)diimidazole and DMAP in dichlorobenzene at 180 °C[20] to afford **12** in 72% yield from **10** (Scheme 2). Hydrolysis of the ethyl ester function in **12**, followed by condensation with methylamine under the conditions of Shioiri[21] successfully provided amide **13**[17] in 93% yield. The Pictet–Spengler type reaction of **13** with paraformaldehyde in the presence of TFA[5b,c] generated the ethano-bridge between the amide nitrogen and C-1, and induced the deprotection of the *O*-TBS group to give the tetracyclic lactam **2**, which is known as the intermediate for the synthesis of racemic galanthamine reported by the Guillou[5b] and the Tu[5c] groups in 67% yield. Finally, the reduction of **2** with $LiAlH_4$ cleanly afforded (+)-galanthamine (+)-**1**[17] in 88% yield. The ^1H and ^{13}C NMR data of the synthetic **1** were totally identical with those for natural (−)-galanthamine and the $[\alpha]_D$ value of the synthetic compound {$[\alpha]_D^{24}$ +111.5 (*c* 0.50, EtOH): lit.[1c] $[\alpha]_D^{20}$ −118.8 (*c* 1.378, EtOH)} confirmed its unnatural absolute configuration. Since we have already reported the preparation of the enantiomeric cyclohexenone (−)-**5** from the same starting material **6**,[11] the synthesis of (−)-galanthamine in the formal sense has also been achieved.

In summary, a new and non-biomimetic synthetic route to optically active galanthamine starting from D-glucose has been established. This synthesis, required 11 steps with a 12.8% overall yield from (+)-**5** (19 steps with a 4.9% overall yield from commercially available **6**), demonstrated that the methodology involving the Claisen rearrangement on chiral cyclohexenol derived from D-glucose is effective for the stereoselective generation of the quaternary carbon. The effectiveness of 2-nitrophenol as the acid catalyst for the Johnson–Claisen rearrangement is particularly noteworthy. It was also shown that the intramolecular dealkylating etherification using NBS is a useful procedure for the construction of benzofuran skeletons, which are commonly found in galanthanmine-type and morphine-type biologically significant alkaloids.



Scheme 2.

Acknowledgments

We thank the Ministry of Education, Culture, Sports, Science, and Technology, Japan (Grant-in-Aid for Scientific Research on Priority Area 'Creation of Biologically Functional Molecules' and Grant-in-Aid for the 21st Century COE program 'KEIO LCC') for financial assistance.

References and notes

1. (a) Proskurnina, N. F.; Yakovleva, A. P. *Zhur. Obschchei. Khim.* **1952**, *22*, 1899–1902; (b) Kobayashi, S.; Shingu, T.; Uyeo, S. *Chem. Ind.* **1956**, 177–178; (c)*The Merck Index*; Budavari, S., Ed., 12th ed.; Merck & CO.: Newyork, 1996; p 736, monograph number 4357.
2. For comprehensive reviews on biological activities and synthetic studies of galanthamine-type *Amaryllidaceae* alkaloids, see: (a) Martin, S. F. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, NY, 1987; Vol. 30, pp 251–376; (b) Hoshino, O. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: New York, NY, 1998; Vol. 51, pp 323–424; (c) Marco-Contelles, J.; Carreiras, M. D. C.; Rodriguez, C.; Villarroya, M.; Garcia, A. G. *Chem. Rev.* **2006**, *106*, 116–133.
3. (a) Rainer, M. *Drugs Today* **1997**, *33*, 273–279; Mucke, H. A. M. *Drugs Today* **1997**, *33*, 259–264; Giacobini, E. *Neurochem. Int.* **1998**, *32*, 413–419; Weinstock, M. *CNS Drugs* **1999**, *12*, 307–323; Sramek, J. J.; Frackiewicz, E. J.; Culter, N. R. *Expert Opin. Invest. Drugs* **2000**, *9*, 2393–2402.
4. Lilienfeld, S. *CNS Drug Rev.* **2002**, *8*, 159–176.
5. Recent reports on racemic syntheses of galanthamine, see: (a) Node, M.; Kodama, S.; Hamashima, Y.; Baba, T.; Hamamichi, N.; Nishide, K. *Angew. Chem., Int. Ed.* **2001**, *40*, 3060–3062; (b) Guillou, C.; Beunard, J.-L.; Gras, E.; Thal, C. *Angew. Chem., Int. Ed.* **2001**, *40*, 4745–4746; (c) Hu, X.-D.; Tu, Y. Q.; Zhang, E.; Gao, S.; Wang, S.; Wang, A.; Fan, C.-A.; Wang, M. *Org. Lett.* **2006**, *8*, 1823–1825.
6. For chiral total syntheses of (+)- and (−)-galanthamine, see: (a) Tomioka, K.; Shimizu, K.; Yamada, S.-i.; Koga, K. *Heterocycles* **1977**, *6*, 1752–1756; (b) Shimizu, K.; Tomioka, K.; Yamada, S.-i.; Koga, K. *Heterocycles* **1977**, *8*, 277–282; (c) Shimizu, K.; Tomioka, K.; Yamada, S.-i.; Koga, K. *Chem. Pharm. Bull.* **1978**, *26*, 3765–3771; (−)-Galanthamine, see: (d) Trost, B. M.; Tang, W. *Angew. Chem., Int. Ed.* **2002**, *41*, 2795–2797; (e) Trost, B. M.; Tang, W.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 14785–14803; (f) Kodama, S.; Hamashima, Y.; Nishide, K.; Node, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2659–2661; (g) Node, M.; Kodama, S.; Hamashima, Y.; Katoh, T.; Nishide, K.; Kajimoto, T. *Chem. Pharm. Bull.* **2006**, *54*, 1662–1679; (h) Satcharoen, V.; McLean, N. J.; Kemp, S.

C.; Camp, N. P.; Brown, R. C. D. *Org. Lett.* **2007**, *9*, 1867–1869; For preparation of (−)-galanthamine via spontaneous resolution of racemic narwedine, see: (i) Shieh, W.-C.; Carlson, J. A. *J. Org. Chem.* **1994**, *59*, 5463–5465; (j) Küenburg, B.; Czollner, L.; Fröhlich, J.; Jordis, U. *Org. Process Res. Dev.* **1999**, *3*, 425–431.

7. Bastida, J.; Viladomat, F.; Llabrés, J. M.; Quiroga, S.; Codina, C.; Rubiralta, M. *Planta Med.* **1990**, *56*, 123–124.
8. (a) Bohno, M.; Imase, H.; Chida, N. *Chem. Commun.* **2004**, 1086–1087; (b) Bohno, M.; Sugie, K.; Imase, H.; Yusof, Y. B.; Oishi, T.; Chida, N. *Tetrahedron* **2007**, *63*, 6977–6989.
9. Construction of benzofuran skeletons by way of the bromonium ion-mediated cyclization using Br_2, see: Mulzer, J.; Bats, J. W.; List, B.; Opatz, T.; Trauner, D. *Synlett* **1997**, 441–444.
10. For utilization of Claisen rearragement in the synthesis of related alkaloids, see: (a) Keck, G. E.; Webb, R. R., II. *J. Org. Chem.* **1982**, *47*, 1302–1309; (b) Labidalle, S.; Min, Z. Y.; Reynet, A.; Moskowitz, H.; Vierfond, J.-M.; Miocque, M. *Tetrahedron* **1988**, *44*, 1159–1169; (c) Parsons, P. J.; Penkett, C. S.; Shell, A. J. *Chem. Rev.* **1996**, *96*, 195–206; (d) Schkeryantz, J. M.; Pearson, W. H. *Tetrahedron* **1996**, *52*, 3107–3116; (e) Chida, N.; Sugihara, K.; Amano, S.; Ogawa, S. *J. Chem. Soc., Perkin Trans. 1* **1997**, 275–280; (f) Mulzer, J.; Trauner, D. *Chirality* **1999**, *11*, 475–482, see also Ref. 9; (g) Ng, F. W.; Lin, H.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2002**, *124*, 9812–9824.
11. Imuta, S.; Tanimoto, H.; Momose, K. M.; Chida, N. *Tetrahedron* **2006**, *62*, 6926–6944.
12. (a) Ferrier, R. J.; Middleton, S. *Chem. Rev.* **1993**, *93*, 2779–2831; (b) Ferrier, R. J.; Middleton, S. *Top. Curr. Chem.* **2001**, *215*, 277–291; (c) Chida, N.; Ohtsuka, M.; Ogura, K.; Ogawa, S. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 2118–2121.
13. All new compounds described in this Letter were characterized by 300 MHz ^{1}H NMR, 75 MHz ^{13}C NMR, IR, and mass spectrometric and/or elemental analyses.
14. Gemal, A. L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981**, *103*, 5454–5459.
15. Johnson, W. S.; Werthemann, L.; Bartlett, W. R.; Brocksom, T. J.; Li, T.-T.; Faulkner, D. J.; Petersen, M. R. *J. Am. Chem. Soc.* **1970**, *92*, 741–743; Castro, A. M. M. *Chem. Rev.* **2004**, *104*, 2939–3002.
16. Fukazawa, T.; Shimoji, Y.; Hashimoto, T. *Tetrahedron: Asymmetry* **1996**, *7*, 1649–1658.
17. *Data of* **3**: Colorless syrup; $[\alpha]_D^{26}$ −7.2 (*c* 0.38, $CHCl_3$); ν_{max} (neat) 1730 and 1470 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.35–7.21 (m, 6H), 6.95 (dd, 1H, $J = 8.0$ and 8.0 Hz), 6.83 (dd, 1H, $J = 1.4$ and 8.0 Hz), 6.03 (dd, 1H, $J = 1.7$ and 10.2 Hz), 5.66 (ddd, 1H, $J = 1.0$, 1.5 and 10.2 Hz), 4.66 and 4.53 (2d, each 1H, $J = 11.7$ Hz), 4.30 (dddd, 1H, $J = 1.5$, 1.7, 6.8 and 9.3 Hz), 4.00 (q, 2H, $J = 7.1$ Hz), 3.83 (dd, 1H, $J = 2.7$ and 12.2 Hz), 3.82 and 3.75 (2s, each 3H), 3.26 and 3.03 (2d, each 1H, $J = 14.9$ Hz), 2.06 (dddd, 1H, $J = 1.0$, 2.7, 12.2 and 12.2 Hz), 1.83 (ddd, 1H, $J = 9.3$, 12.2 and 12.2 Hz), 1.13 (t, 3H, $J = 7.1$ Hz), 0.87 (s, 9H), 0.05 and 0.03 (2s, each 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.9, 153.2, 149.5, 138.7, 134.2, 133.0, 130.4, 128.1, 127.9, 127.4, 124.01, 122.1, 111.5, 78.6, 71.7, 68.2, 60.3, 59.8, 55.8, 48.2, 42.4, 33.2, 25.9, 18.2, 14.1, −4.5, −4.6; LRMS (EI) *m*/*z* 540 (M^+, 4.7%), 483 (4.4), 406 (40.5), 175 (30.9), 91 (76.6), 75 (100); HRMS (EI) *m*/*z* 540.2908, Calcd for $C_{31}H_{44}O_6Si$, M^+, 540.2907. Anal. Calcd for $C_{31}H_{44}O_6Si$: C, 68.85; H, 8.20. Found: C, 68.74; H, 8.19. *Data of* **9**: Colorless syrup; $[\alpha]_D^{26}$ +26.1 (*c* 1.78, $CHCl_3$); ν_{max} (neat) 1730, 1640 and 1590 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.44–7.28 (m, 5H), 7.22 (dd, 1H, $J = 1.4$ and 6.8 Hz), 6.82–6.76 (m, 2H), 5.18 (br d, 1H, $J = 7.6$ Hz), 4.71 and 4.52 (2d, each 1H, $J = 11.6$ Hz), 4.19–4.00 (m, 3H), 3.87 (s, 3H), 3.76–3.62 (m, 2H), 2.89 and 2.48 (2d, each 1H, $J = 16.1$ Hz), 2.27 (ddd, 1H, $J = 3.4$, 3.4 and 12.7 Hz), 1.53 (m, 1H), 1.22 (t, 3H, $J = 7.2$ Hz), 0.86 (s, 9H), 0.13 and 0.07 (2s, each 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.0, 146.6, 145.9, 138.1, 132.0, 128.5, 127.81, 127.78, 122.3, 118.8, 113.2, 90.2, 75.4, 72.1, 69.8, 60.5, 60.1, 56.3, 54.5, 39.7, 36.3, 25.7, 18.0, 14.1, −4.4, −4.5; LRMS (EI) *m*/*z* 606 (M^+, 4.0%), 604 (M^+, 4.0), 549 (3.7), 547 (3.7), 531 (3.5), 529 (3.4), 337 (42.2), 247 (93.3), 91 (100), 73 (39.4); HRMS (EI) *m*/*z* 604.1857, Calcd for $C_{30}H_{41}{}^{79}BrO_6Si$, M^+ 604.1856. *Data of* **13**: Crystalline residue; mp 58–60 °C; $[\alpha]_D^{24}$ −3.5 (*c* 0.98, $CHCl_3$); ν_{max} (KBr disk) 3395, 3310, 1650 and 1645 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.83 (dd, 1H, $J = 7.3$ and 8.0 Hz), 6.74 (dd, 1H, $J = 1.5$ and 8.0 Hz, 1H, H-1), 6.71 (dd, 1H, $J = 1.5$ and 7.3 Hz), 5.99 (dd, 1H, $J = 2.0$ and 10.1 Hz), 5.82 (ddd, 1H, $J = 1.2$, 1.9 and 10.1 Hz), 5.18 (br s), 4.37 (dddd, 1H, $J = 1.9$, 2.0, 4.9 and 10.4 Hz), 3.86 (s, 3H), 2.69 (d, 3H, $J = 4.9$ Hz), 2.48 and 2.34 (2d, each 1H, $J = 13.8$ Hz), 2.31 (dddd, 1H, $J = 1.2$, 2.0, 4.9 and 11.7 Hz), 1.69 (ddd, 1H, $J = 10.4$, 11.6 and 11.7 Hz), 0.84 (s, 9H), 0.054 and 0.047 (2s, each 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.0, 145.9, 145.4, 134.2, 133.3, 127.1, 121.4, 115.4, 111.7, 84.9, 65.2, 56.0, 48.4, 47.0, 36.9, 26.2, 25.7, 18.0, −4.6, −4.8; LRMS (EI) *m*/*z* 403 (M^+, 9.0%), 346 (41.9), 328 (100), 254 (22.8), 181 (19.2), 158 (16.1), 75 (44.7), 73 (39.6); HRMS (EI) *m*/*z* 403.2165, Calcd for $C_{22}H_{33}NO_4Si$, M^+, 403.2179. *Data of* (+)-**1**: Crystalline residue; mp 124–125 °C (lit.[1c] mp 126–127 °C); $[\alpha]_D^{23}$ +111.5 (*c* 0.50, EtOH); ν_{max} (neat) 3360, 2920, 1505, 1440, 1280 and 1050 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.66 and 6.62 (2d, each 1H, $J = 8.3$ Hz), 6.06 (dd, 1H, $J = 1.2$ and 10.3 Hz), 6.00 (ddd, 1H, $J = 1.3$, 4.9 and 10.3 Hz), 4.61 (br s, 1H), 4.14 (br dd, 1H, $J = 4.9$ and 4.9 Hz), 3.83 (s, 3H), 4.08 and 3.68 (2d, each 1H, $J = 15.1$ Hz), 3.26 (ddd, 1H, $J = 1.7$, 13.0 and 14.6 Hz), 3.05 (ddd, 1H, $J = 3.2$, 3.9 and 14.6 Hz), 2.68 (dddd, 1H, $J = 1.3$, 1.5, 3.2 and 15.6 Hz), 2.40 (s, 3H), 2.08 (ddd, 1H, $J = 3.2$, 13.0 and 13.7 Hz), 2.00 (ddd, 1H, $J = 2.4$, 4.9 and 15.6 Hz), 1.85 (br s, 1H), 1.57 (ddd, 1H, $J = 1.7$, 3.9 and 13.7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 145.8, 144.2, 133.0, 128.5, 127.7, 126.7, 122.2, 111.2, 88.7, 62.0, 60.4, 55.9, 53.7, 48.1, 41.8, 33.6, 29.9; LRMS (EI) *m*/*z* 288 (18.1%), 287 (M^+, 100), 286 (84.1), 269 (14.1), 244 (14.0), 230 (19.6), 215 (11.3), 174 (18.8); HRMS (EI) *m*/*z* 287.1521; Calcd for $C_{17}H_{19}NO_4$, M^+, 287.1521.
18. When propionic acid was employed as the acid in the Johnson–Claisen rearrangement of **4**, the yield of **3** was found to be low (less than 25%) and the formation of significant amount of unidentified by-products was observed.
19. Trauner, D.; Bats, J. W.; Werner, A.; Mulzer, J. *J. Org. Chem.* **1998**, *63*, 5908–5918.
20. Williams, D. R.; Coleman, P. J.; Henry, S. S. *J. Am. Chem. Soc.* **1993**, *115*, 11654–11655.
21. Yamada, S.-i.; Kasai, Y.; Shioiri, T. *Tetrahedron Lett.* **1973**, *14*, 1595–1598; Shioiri, T.; Yokoyama, Y.; Kasai, Y.; Yamada, S.-i. *Tetrahedron* **1976**, *32*, 2211–2217.