Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 47 (2006) 1433–1435
Tetrahedron Letters

# An enantiospecific synthesis of (+)-hydroxy-*exo*-brevicomin

Kavirayani R. Prasad* and Pazhamalai Anbarasan

*Department of Organic Chemistry, Indian Institute of Science, Bangalore 560 012, India*

Received 3 November 2005; revised 9 December 2005; accepted 15 December 2005

**Abstract**—A concise enantiospecific synthesis of the pine beetle pheromone (+)-hydroxy-*exo*-brevicomin was achieved from L-(+)-tartaric acid in high yield. The key step involves the reduction of a keto-Weinreb amide derived from tartaric acid.


Several species of the Western pine beetle produce alkylated 6,8-dioxabicyclo[3.2.1]octanes, which play a major role in their communication systems. Extensive outbreaks of bark beetles may result in the destruction of millions of trees per year causing great ecological and economic damage. Brevicomin **1**, 7-ethyl-5-methyl-6,8-dioxabicyclo[3.2.1]octane was the first pheromone of this kind that was identified from the frass of the females of the Western pine beetle, *Dendroctonus brevivomis*.[1] Similar structures having varied bicyclooctane structures such as frontalin **2** and multistriatin **3** were isolated in addition to a number of other compounds from different *Dendroctonus* species. Interestingly, marine tunicates belonging to the genus *Dedemnum* produce serinolipids such as didemniserinolipid **5** which possess the same bicyclic core[2] (Fig. 1). Francke et al. reported the isolation and synthesis of hydroxy-*exo*-brevicomin **4**, 1-(5-methyl-6,8-dioxabicyclo[3.2.1]oct-7-yl)ethanol from the head-space extracts from *Dendroctonus ponderosae*.[3]

There are only a few approaches for the enantioselective synthesis of hydroxy-*exo*-brevicomin reported in the literature employing either a chiron approach or other asymmetric methodologies.[4,5] In continuation of our efforts on the utility of chiral pool L-(+)-tartaric acid in natural product synthesis,[6] herein, we report an efficient enantiospecific synthesis of (+)-hydroxy-*exo*-brevicomin starting from chiral pool L-(+)-tartaric acid.

We reasoned that the keto-amide **7**, which is produced by controlled addition of the appropriate Grignard reagent to the bis-Weinreb amide **6** derived from tartaric acid, could be elaborated to the title compound (Scheme 1).

Thus, controlled addition of 4-pentenylmagnesium bromide (1.5 equiv) to the bis-Weinreb amide[7] **6** produced the mono keto-amide **7** in 92% yield. A highly diastereoselective reduction of the ketone group in **7** was achieved

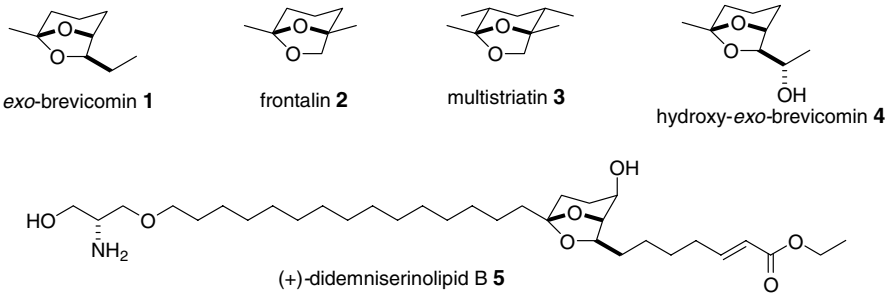
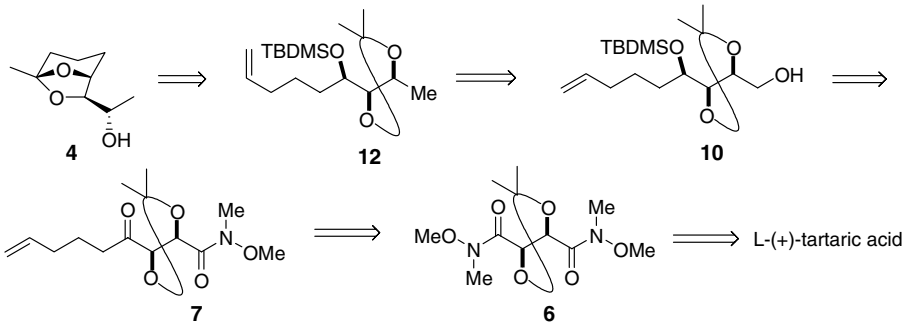


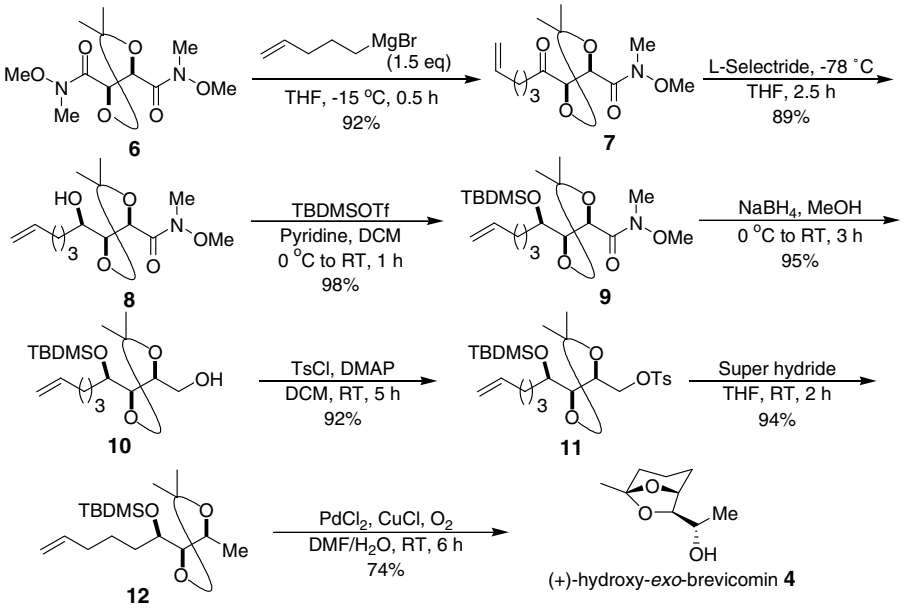

**Figure 1.** Bio-active bicyclic acetals possessing the 6,8-dioxabicyclo[3.2.1]octane skeleton.

*Keywords*: Stereoselective reduction; L-(+)-Tartaric acid; Hydroxy-*exo*-brevicomin.
* Corresponding author. Fax: +91 80 23600529; e-mail: prasad@orgchem.iisc.ernet.in

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2005.12.094




**Scheme 1.** Retrosynthesis of (+)-hydroxy-*exo*-brevicomin.




**Scheme 2.** Synthesis of (+)-hydroxy-*exo*-brevicomin.

with L-selectride furnishing a single diastereomer of the corresponding alcohol **8** with the requisite stereochemistry. Protection of the hydroxy group in **8** as its silyl ether **9** ($[\alpha]_D^{25}$ −6.2 (*c* 1.3, $CHCl_3$)) was effected with TBDMSOTf in almost quantitative yield. The high reactivity of the Weinreb amide was then exploited by reduction to the corresponding alcohol with sodium borohydride to give **10** in 95% yield. The primary alcohol group in **10** was converted to the corresponding tosylate **11**, which on reduction with super hydride[8] gave **12** in excellent yield. The trihydroxy-protected alkene **12** under Wacker oxidation[9] conditions, produced (+)-hydroxy-*exo*-brevicomin ($[\alpha]_D^{25}$ +61.2 (*c* 2.4, $CHCl_3$); lit[5a] $[\alpha]_D^{25}$ +61.3 (*c* 1.18, $CHCl_3$)), via the formation of the ketone and simultaneous deprotection of the silyl and acetonide group followed by intramolecular ketalization (Scheme 2). The synthetic sample exhibited spectral data identical to that of an authentic sample.[10]

In conclusion, we have achieved an efficient enantiospecific synthesis of (+)-hydroxy-*exo*-brevicomin in an overall yield of 48% in seven steps starting from the bis-Weinreb amide **6** derived from L-(+)-tartaric acid. Further application of the strategy for the synthesis of a number of other similar bicyclic systems is currently underway.

## Acknowledgements

We thank DST, New Delhi, for funding this project. P.A. thanks IISc, Bangalore, for financial support.

## References and notes

1. Silverstein, R. M.; Brownlee, R. G.; Bellas, T. E.; Wood, D. L.; Browne, L. E. *Science* **1968**, *159*, 889–891.
2. Gonzalez, N.; Rodriguez, J.; Jiminez, C. *J. Org. Chem.* **1999**, *64*, 5705–5707.
3. Francke, W.; Schroder, F.; Philipp, P.; Meyer, H.; Sinnwell, V.; Gries, G. *Bioorg. Med. Chem.* **1996**, *4*, 363–374.
4. Kumar, D. N.; Rao, B. V. *Tetrahedron Lett.* **2004**, *45*, 2227–2229.
5. (a) Yokoyama, Y.; Mori, K. *Liebigs Ann. Chem.* **1997**, 845–849; (b) Kumar, D. N.; Rao, B. V. *Tetrahedron Lett.*

**2004**, *45*, 7713–7714; (c) Kumar, D. N.; Rao, B. V.; Ramanjaneyulu, G. S. *Tetrahedron: Asymmetry* **2005**, *16*, 1611–1614; (d) List, B.; Shabat, D.; Barbas, C. F., III; Lerner, R. A. *Chem. Eur. J.* **1998**, *4*, 881–885.

6. (a) Prasad, K. R.; Chandrakumar, A. *Tetrahedron: Asymmetry* **2005**, *16*, 1897–1900; (b) Prasad, K. R.; Gholap, S. L. *Synlett* **2005**, 2260–2262; (c) Prasad, K. R.; Anbarasan, P. *Tetrahedron: Asymmetry* **2005**, *16*, 3951–3953.
7. Nugiel, D. A.; Jakobs, K.; Worley, T.; Patel, M.; Kaltenbach, R. F., III; Meyer, D. T.; Jadhav, P. K.; De Lucca, G. V.; Smyser, T. E.; Klabe, R. M.; Bacheler, L. T.; Rayner, M. M.; Seitz, S. P. *J. Med. Chem.* **1996**, *39*, 2156–2169.
8. (a) Krishnamurthy, S.; Brown, H. C. *J. Org. Chem.* **1976**, *41*, 3064–3066; (b) Krishnamurthy, S. *J. Organomet. Chem.* **1978**, *156*, 171–181.
9. Tsuji, J. *Synthesis* **1984**, 369–384.
10. All the compounds exhibited spectral data consistent with their structures. Spectral data for selected compounds: compound **7**, $[\alpha]_D^{25}$ +6.6 (*c* 1.8, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 5.77 (ddt, $J = 17.1$,10.2, 6.6 Hz, 1H), 5.06–4.97 (m, 3H), 4.82 (d, $J = 5.4$ Hz, 1H), 3.71 (s, 3H), 3.23 (s, 3H), 2.77–2.55 (m, 2H), 2.11–2.04 (m, 2H), 1.76–1.66 (m, 2H), 1.49 (s, 3H), 1.44 (s, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 208.1, 169.7, 137.7, 115.3, 112.7, 82.2, 73.9, 61.6, 38.4, 32.9, 32.5, 26.6, 26.2, 22.1. HRMS for $C_{14}H_{23}NO_5$+Na calcd 308.1474; found 308.1480. Compound **8** $[\alpha]_D^{25}$ −5.5 (*c* 1.8, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 5.79 (ddt, $J = 17$, 10.2, 6.6 Hz, 1H), 5.03–4.93 (m, 2H), 4.75 (br s, 1H), 4.36 (br s, 1H), 3.74 (s, 3H), 3.62–3.60 (m, 1H), 3.23 (s, 3H), 2.08–2.04 (m, 2H), 1.68–1.42 (m, 4H), 1.48 (s, 3H), 1.45 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 170.6, 138.5, 114.7, 111.1, 80.7, 73.8, 70.2, 61.6, 38.4, 34.0, 33.5, 27.0, 26.1, 25.1. Compound **10**, $[\alpha]_D^{25}$ +12.1 (*c* 2.4, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 5.70 (ddt, $J = 16.8$, 10.2, 6.6 Hz, 1H), 4.96–4.82 (m, 2H), 3.93 (dt, $J = 8.1$, 4.8 Hz, 1H), 3.80–3.45 (m, 4H), 2.37 (br s, 1H), 1.98–1.94 (m, 2H), 1.60–1.24 (m, 4H), 1.31 (s, 3H), 1.30 (s, 3H), 0.81 (s, 9H), 0.01 (s, 6H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 138.5, 114.7, 108.6, 80.5, 77.0, 71.9, 62.9, 33.7, 31.9, 27.0, 26.9, 25.8, 25.3, 18.1, −4.2, −4.7. HRMS for $C_{18}H_{36}O_4Si$+Na calcd 367.2281; found 367.2281. Compound **12**, $[\alpha]_D^{25}$ +16.0 (*c* 1.5, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 5.80 (ddt, $J = 17.1$, 10.5, 6.6 Hz, 1H), 5.05–4.9 (m, 2H), 3.99 (dq, $J = 8.4$, 6.3 Hz, 1H), 3.80–3.69 (m, 1H), 3.53 (dd, $J = 8.4$, 4.2 Hz, 1H), 2.06 (m, 2H), 1.59–1.38 (m, 4H), 1.39 (s, 3H), 1.37 (s, 3H), 1.29 (d, $J = 6.3$ Hz, 3H), 0.89 (s, 9H), 0.07 (s, 6H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 138.6, 114.5, 107.7, 84.6, 72.7, 71.9, 33.7, 32.4, 27.3, 26.9, 25.9, 25.1, 18.8, 18.2, −4.1, −4.6. (+)-Hydroxy-*exo*-brevicomin **4**: $[\alpha]_D^{25}$ +61.2 (*c* 2.4, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 4.23 (s, br, 1H), 3.77 (d, $J = 7.2$ Hz, 1H), 3.63 (dq, $J = 7.2$, 6.3 Hz, 1H), 2.58 (s, br, 1H), 1.76–1.94 (m, 2H), 1.62–1.71 (m, 3H),1.47–1.51 (m, 1H), 1.45 (s, 3H), 1.14 (d, $J = 6.3$ Hz, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 108.4, 83.8, 76.5, 69.2, 34.6, 27.6, 24.8, 18.4, 17.1.