Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 45 (2004) 9299–9301
Tetrahedron Letters

The first stereoselective total synthesis of (6*S*)-5,6-dihydro-6-[(2*R*)-2-hydroxy-6-phenylhexyl]-2*H*-pyran-2-one☆

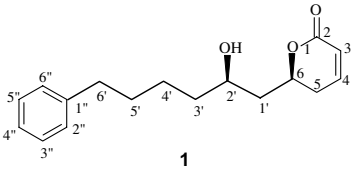
S. Chandrasekhar,* Ch. Narsihmulu, S. Shameem Sultana and M. Srinivasa Reddy

Indian Institute of Chemical Technology, Hyderabad 500 007, India

Received 27 August 2004; revised 30 September 2004; accepted 8 October 2004

Abstract—Iterative asymmetric allylations and ring-closing metathesis have been effectively performed for the first stereoselective total synthesis of (6*S*)-5,6-dihydro-6-[(2*R*)-2-hydroxy-6-phenylhexyl]-2*H*-pyran-2-one, a novel α,β-unsaturated-δ-lactone having antifungal activity, isolated from *Ravensara crassifolia*.

The 6-substituted 5,6-dihydro-2*H*-pyran-2-ones (α,β-unsaturated-δ-lactones) are important structural subunits in many biologically active natural products. These structural units are important for a wide variety of biological activities such as plant growth inhibition as well as antifungal, antifeedent, antibacterial, and antitumour properties.[1] Biological activity, structural uniqueness and the challenge to synthesize them in optically pure form have made them attractive targets for many total syntheses. Due to the significant biological activity of this class of natural products, several research groups have reported the synthesis of cryptocaryalactone,[2] kurizilactone,[3] tetrachloranthuslactone,[4] strictifoline,[5] boronolide,[6] and many others.[7] (6*S*)-5,6-Dihydro-6-[(2*R*)-2-hydroxy-6-phenylhexyl]-2*H*-pyran-2-one **1** is an example of this class of natural product, and was isolated by Hostettmann and co-workers,[8] from *Ravensara crassifolia*. They showed that **1** exhibited antifungal activity against the phytopathogenic fungus *Cladosporium cucumarinum* in a bioautographic TLC assay.

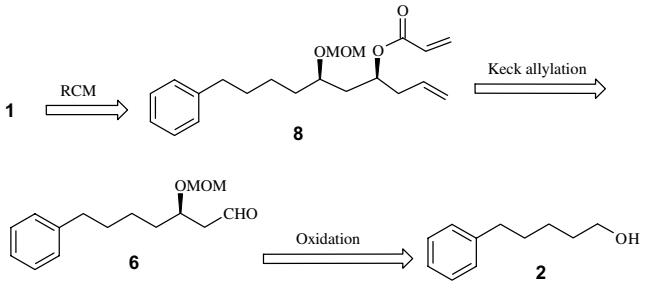


1

The relatively accessible skeleton, strategically fixed *syn* 1,3-diol system and our interest in the synthesis of bioactive molecules[9] prompted us to investigate and develop a strategy for the synthesis of **1** and also to develop a general method for installing the 1,3-diol system.

Accordingly, the enantioselective synthesis of compound **1** has been achieved in just eight steps starting from commercially available 5-phenyl-1-pentanol **2** as retrosynthetically delineated in (Scheme 1). The asymmetric Keck allylation[10] and analogous Maruoka allylation[11] in highly enantioselective fashion have been employed including RCM to achieve the target molecule in 28% overall yield.

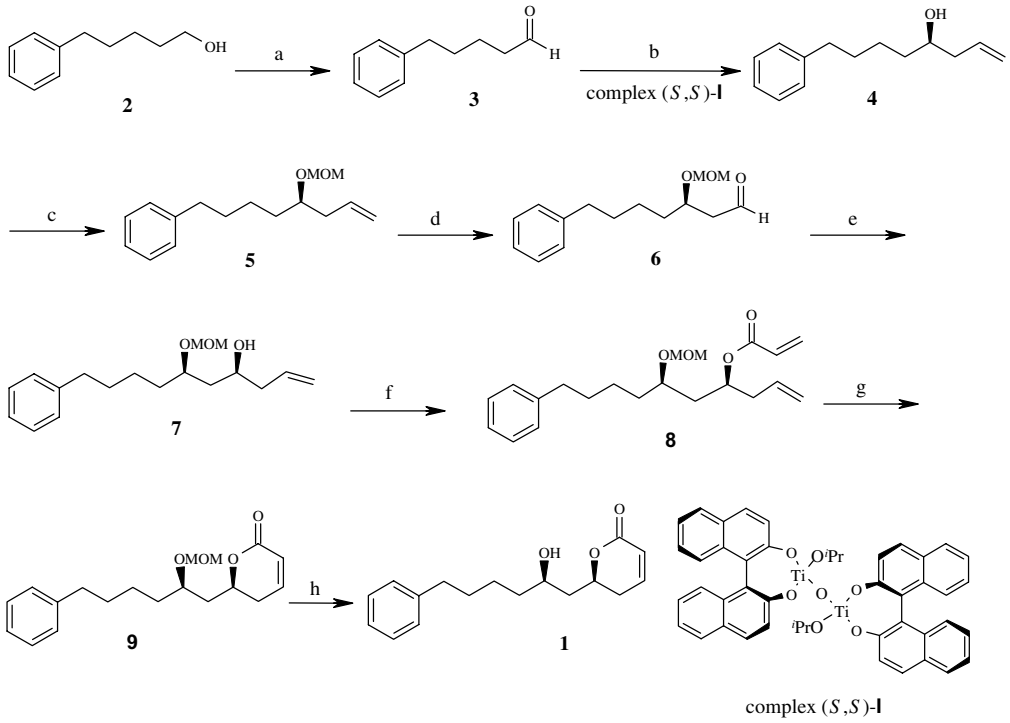
The synthesis began with the oxidation of 5-phenyl-1-pentanol **2** using 2-iodoxybenzoic acid (IBX) to give 5-phenyl-1-pentanal **3**. The Maruoka asymmetric allylation of **3** with titanium complex (*S*,*S*)-**I** gave homoallyl alcohol **4** in 82% yield and 97% enantiomeric exess.



Scheme 1.

Keywords: Maruoka asymmetric allylation; Keck asymmetric allylation; Ring-closing metathesis.
☆ IICT Communication No. 040816.
* Corresponding author. Tel.: +91 40 27193434; fax: +91 40 27160512; e-mail: srivaric@iict.res.in

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.10.059



Scheme 2. Reagents, conditions, and yields: (a) IBX, DMSO–THF, rt, 4 h, 88%; (b) $TiCl_4$ (5 mol%), $Ti(O^iPr)_4$ (15 mol%), rt, 1 h, Ag_2O (10 mol%), rt, 5 h, *S*-BINNOL (20 mol%), rt, 2 h, allyltri^{n}butyltin, 0 °C, 12 h, 82%; (c) MOMCl, DIPEA, CH_2Cl_2, 3 h, 0 °C, 90%; (d) (i) OsO_4 (0.5 mol%), NMO, acetone–H_2O, rt, 4 h, (ii) $NaIO_4$, rt, 2 h; (e) $Ti(O^iPr)$ (10 mol%) *S*-BINOL (20 mol%) *S*-BINOL (20 mol%), rt, 1 h, allyltri^{n}butyltin, CH_2Cl_2, rt, 12 h, 72%; (f) acryolyl chloride, DIPEA, CH_2Cl_2, rt, 3 h, 85%; (g) Grubbs' catalyst, (5 mol%), DCM, rt, 18 h, 80%; (h) 6 N HCl–THF–H (1:2:1), rt, 24 h, 90%.

The hydroxy functionality of **4** was protected as its methoxymethyl (MOM) ether **5**. The MOM protection played a crucial role in further transformation as other protecting groups viz., TBDMS and MPM ethers gave unsatisfactory results.[12] The MOM protecting group also turned out to be a superior group for the later Keck allylation. After the dihydroxylation–oxidative cleavage of MOM ether **5** with OsO_4/NMO and $NaIO_4$, the resulting aldehyde **6** was subjected to asymmetric Keck allylation to furnish the homoallyl alcohol **7** in an overall yield of 72% with a 9:1 *syn*:*anti* diastereomeric ratio resulting over the two steps. The relative stereochemistries of the stereogenic centers at C(2′) and C(6) were deduced from ^{13}C NMR analysis of the corresponding acetonide derivative.[13] The *syn* relative configuration of the hydroxy groups was confirmed by analysis of the ^{13}C NMR spectra which showed signals at 30.2 and 19.7 ppm for the two-methyl groups and 98.5 ppm for the quaternary center of the acetonide. The MOM protected homoallyl alcohol **7** was converted to its acryolyl ester **8** and subsequent ring closing metathesis (RCM) using the first-generation Grubbs' catalyst[14] yielded lactone **9**. Finally, deprotection with 1:2:1 (6 N HCl–THF–H_2O) gave the target molecule **1**. The spectroscopic data (IR, MS, ^1H, and ^{13}C NMR) and $[\alpha]_D$ were identical to those reported.

In conclusion, we have completed the first total synthesis of the biologically active natural product (6*S*)-5,6-dihydro-6-[(2*R*)-2-hydroxy-6-phenylhexyl]-2*H*-pyran-2-one **1** in eight steps with an overall yield of (28%) (Scheme 2).

Spectral data for selected compounds: compound **4**: $[\alpha]_D^{25}$ +9.42 (*c* 0.9, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 7.28–7.06 (m, 5H), 5.90–5.66 (m, 1H), 5.11 (d, 2H, J = 11.8 Hz), 3.66–3.52 (m, 1H), 2.61 (t, 2H, J = 7.4 Hz), 2.34–2.00 (m, 2H), 1.72–1.34 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.2, 134.5, 128.0, 127.9, 125.3, 117.6, 70.2, 41.6, 36.2, 35.5, 31.1, 24.9. MS (EI): *m*/*z* M^+ 204, 145, 117, 104, 91, 65, 55, and 41.

Compound **7**: $[\alpha]_D^{25}$ −26.54 (*c* 1.2, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 7.27–7.08 (m, 5H), 5.88–5.72 (m, 1H), 5.08 (d, 2H,J = 15.1 Hz), 4.72–4.56 (m, 2H), 3.86–3.70 (m, 2H), 3.37 (d, 3H, J = 14.2 Hz), 2.70–2.55 (m, 2H), 2.24-2.16 (m, 2H), 1.91–1.82 (m, 2H), 1.72–1.50 (m, 5H), 1.41–1.22 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.3, 134.7, 128.1, 125.8, 117.4, 95.1, 96.9, 70.0, 55.7, 42.0, 40.8, 35.7, 34.1, 30.7, 31.4, and 24.4. MS (FAB): *m*/*z* M^+ 292, 261 (M^+-OCH_3), 233, 189, 171, 155, 137, 109, 95, 81, 69, and 55.

Compound **1**: $[\alpha]_D^{25}$ −58.85 (*c* 0.65, $CHCl_3$), (lit. $[\alpha]_D^{25}$ −66); ^1H NMR (200 MHz, $CDCl_3$): δ 7.24–7.10 (m, 5H), 6.85–6.83 (m, 1H), 5.98 (d, 1H, J = 9.7 Hz), 4.73–4.69 (m, 1H), 4.00–3.96 (m, 1H), 2.62 (t, 2H, J = 7.5 Hz), 2.34–2.30 (m, 2H), 1.88–1.71 (m, 2H), 1.65–1.56 (m, 2H), 1.48–1.36 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.3, 145.3, 142.3, 128.3, 128.2,

125.6, 121.2, 75.0, 66.7, 42.2, 37.8, 35.8, 31.2, 29.8, and 25.0. MS (FAB): *m*/*z* M^+ 275 (M^++1), 274 (M^+), 256, 171, 154, 143, 117, 104, 91, 77, 55, and 43.

Acknowledgements

We C.N., S.S.S., and M.S.R. thank CSIR New Delhi for financial support and S.C. thanks DST, New Delhi for a grant.

References and notes

1. (a) Jodynis-Liebert, J.; Murias, M.; Bloszyk, E. *Planta Med.* **2000**, *66*, 199–205; (b) Drewes, S. E.; Schlapelo, B. M.; Horn, M. M.; Scott-Shaw, R.; Sandor, O. *Phytochemistry* **1995**, *38*, 1427–1430.
2. (a) Meyer, H. H. *Liebigs Ann. Chem.* **1978**, 327–344; (b) Meyer, H. H. *Liebigs Ann. Chem.* **1984**, 977–981; (c) Nakata, T.; Hata, N.; Nakashima, K.; Oishi, T. *Chem. Pharm. Bull.* **1987**, *35*, 4355–4358; (d) Mori, Y.; Furukawa, H. *Chem. Pharm. Bull.* **1994**, *42*, 2161–2163.
3. Jiang, B.; Chen, Z. *Tetrahedron: Asymmetry* **2001**, *12*, 2834–2843.
4. Garaas, S. D.; Hunter, T. J.; O'Doherty, G. A. *J. Org. Chem.* **2002**, *67*, 2682–2685.
5. Juliawaty, L. D.; Watanabe, Y.; Kitajima, M.; Achmad, S. A.; Takayama, H.; Aimi, N. *Tetrahedron Lett.* **2002**, *43*, 8657–8660.
6. Chandrasekhar, M.; Chandra, K. L.; Singh, V. K. *J. Org. Chem.* **2003**, *68*, 4039–4045.
7. (a) Bhatt, U.; Christmann, M.; Quitschalle, M.; Claus, E.; Kalesse, M. *J. Org. Chem.* **2001**, *66*, 1885–1893; (b) Kalesse, M.; Christmann, M. *Synthesis* **2002**, 981–1003, and references cited therein.
8. Raoelison, G. E.; Terreaux, C.; Queiroz, E. F.; Zsila, F.; Simonyi, M.; Antus, S.; Randriantsoa, A.; Hostettmann, K. *Helv. Chim. Acta* **2001**, *84*, 3470–3476.
9. (a) Reviews: Rychnovsky, S. D. *Chem. Rev.* **1995**, *95*, 2021–2040; (b) Schneider, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 1375–1378; Synthesis strategies: (c) Paterson, I.; Collett, I. A. *Tetrahedron Lett.* **2001**, *42*, 1187–1191; (d) Sinz, C. J.; Rychnovsky, S. D. *Angew. Chem., Int. Ed.* **2001**, *40*, 3224–3227.
10. Keck, G. E.; Geraci, L. S. *Tetrahedron Lett.* **1993**, *34*, 7827–7828.
11. Hanawa, H.; Hashimoto, T.; Maruoka, K. *J. Am. Chem. Soc.* **2003**, *125*, 1708–1709.
12. Kurosu, M.; Lorca, M. *Tetrahedron Lett.* **2002**, *43*, 1765–1769.
13. (a) Rychnovsky, S. D.; Skalitzky, D. J. *Tetrahedron Lett.* **1990**, *31*, 945–948; (b) Evans, D. A.; Rieger, D. L.; Gage, J. R. *Tetrahedron Lett.* **1990**, *31*, 7099–7100.
14. Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413–4450.