Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 46 (2005) 6567–6570
Tetrahedron Letters

Chelation-controlled reduction: an enantioselective synthesis of (−)-tarchonanthuslactone☆

Gowravaram Sabitha,* K. Sudhakar, N. Mallikarjuna Reddy, M. Rajkumar and J. S. Yadav

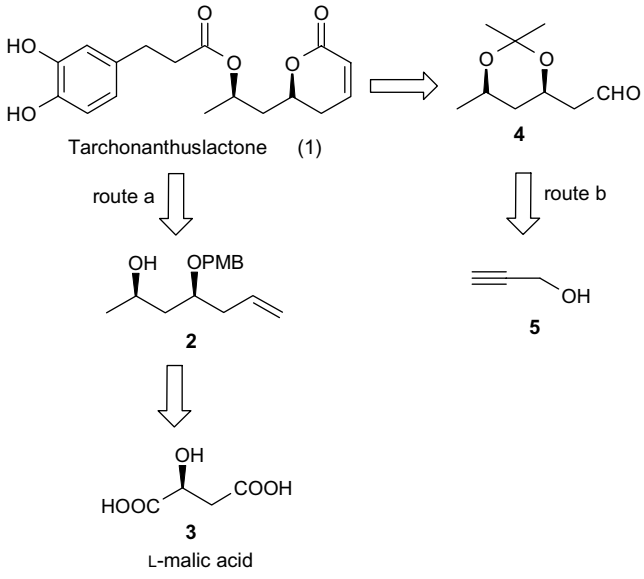
Organic Division I, Indian Institute of Chemical Technology, Hyderabad 500 007, India

Received 19 May 2005; revised 23 June 2005; accepted 15 July 2005

Abstract—The total synthesis of tarchonanthuslactone (**1**) has been achieved by two different routes. In the first approach, $LiAlH_4$–LiI reduction and RCM protocols, and in the second approach, Wacker oxidation and $LiAlH_4$–LiI reduction were used as key steps.

Many natural products possessing the α,β-unsaturated δ-lactone moiety exhibit biological activities such as antitumor, antibacterial, antifungal, and immunosuppressive properties. Tarchonanthuslactone (**1**), an α,β-unsaturated δ-lactone was isolated in 1979 by Bohlmann from the leaves of a tree called *Tarchonanthus trilobus*.[1] Later, its absolute configuration was established by Nakata et al.[2] by asymmetric synthesis. The basic structure of tarchonanthuslactone (a dihydrocaffeic acid ester) consists of a *syn*-1,3-diol unit with one hydroxyl group involved in an unsaturated lactone and the other esterified with 3,4-dihydroxyhydrocinnamic acid. Caffeic acid has been established as an active principle that lowers the plasma glucose levels in diabetic rats[3a] and several lactones from the Compositae family show significant medicinal properties.[3b] Consequently, several approaches have been reported for the synthesis of this molecule. Mori and co-workers[4] synthesized from a chiral dithiane using a 16 step sequence. Solladie and Gressot-Kempt[5] utilized a chiral sulfoxide in their synthesis of **1**. Apart from these above asymmetric substrate-controlled synthetic methodologies there have been reagent-controlled[6] and other syntheses[7] reported. Herein, we report two different protocols for the synthesis of tarchonanthuslactone (**1**) based on reagent controlled synthesis. Our retrosynthetic pathway is outlined in Scheme 1.

In route a, the known alcohol **6**[8] derived from L-malic acid, was treated with IBX in DMSO to give aldehyde **7**, which on further treatment with allyl bromide and activated zinc in THF–aq NH_4Cl at 0 °C, under Barbier reaction conditions, gave carbinol **8** as a diastereomeric mixture. Oxidation of carbinol **8** with IBX in DMSO



Scheme 1.

Keywords: Chelation-controlled reduction; Tarchonanthuslactone; RCM; Wacker oxidation.

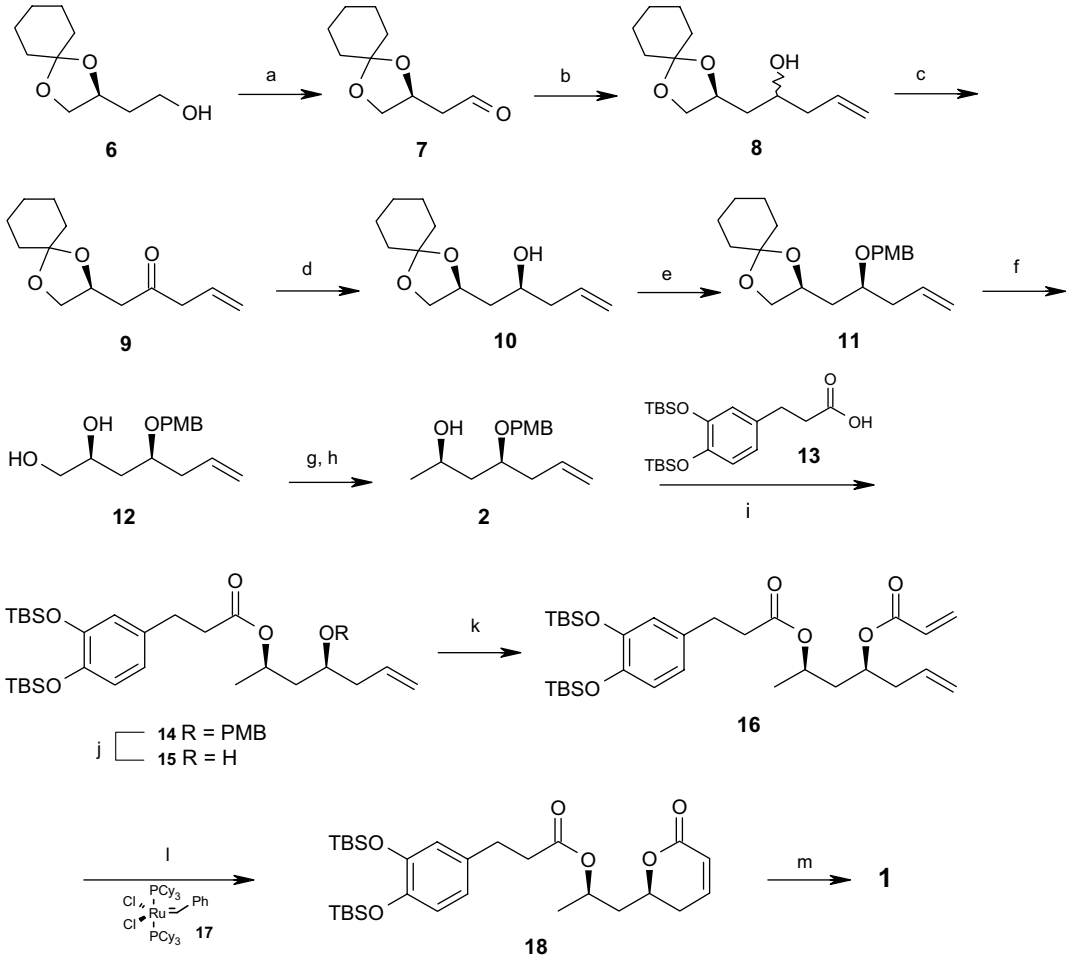
☆ IICT Communication No. 050505.

* Corresponding author. Tel./fax: +91 40 27160512; e-mail: sabitha@iictnet.org

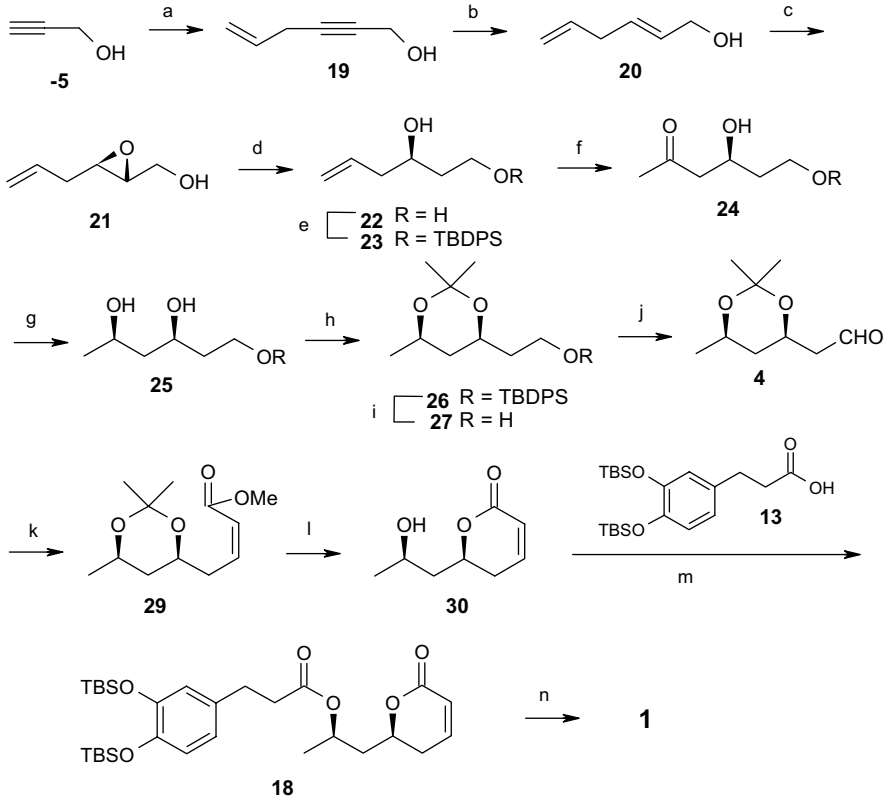
0040-4039/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2005.07.075

gave ketone **9**. A highly *syn*-stereoselective 1,3-asymmetric reduction was carried out using $LiAlH_4$–LiI[9] in ether at −100 °C to provide the desired *syn*-diol **10**[10] in 94% yield (*syn*:*anti* = 95:5). The hydroxy group was protected as the PMB ether **11** with PMBBr and subjected to acid catalyzed hydrolysis in aq MeOH to give diol **12**. Selective tosylation of the primary hydroxy group and further reduction with LAH in THF afforded monohydroxy compound **2**. Treatment of **2** with TBDMS-protected dihydrocaffeic acid **13** using DCC, DMAP provided the corresponding ester **14** in 86% yield. PMB deprotection using DDQ furnished homoallylic alcohol **15** in 81% yield, which was esterified with acryloyl chloride to provide the diester **16**. The RCM reaction in refluxing DCM using Grubbs' bis(tricyclohexylphosphine)benzylidene ruthenium(IV) dichloride catalyst (**17**)[11] furnished TBDMS-protected ester **18**[12] in 76% yield (Scheme 2). Finally, TBDMS deprotection was carried out using oxone in aq MeOH[13] to furnish the target molecule, tarchonanthuslactone **1**[14] in 80% yield, $[\alpha]_D^{25} = -80$ (*c* 0.4, $CHCl_3$). The ^1H NMR and ^{13}C NMR spectral data and optical rotation value of synthetic sample **1** were in good accord with those of the natural product.[5]

An alternative strategy has also been devised for the synthesis of tarchonanthuslactone **1** (route b). Propargyl alcohol **5** on alkylation with allyl bromide in the presence of Na_2CO_3/TBAI, CuI afforded the alkylated product **19** in 82% yield, which was reduced to *trans* allylic alcohol **20** under LAH/THF conditions. Allylic alcohol **20** was subjected to Sharpless asymmetric epoxidation with (−)-DET, Ti(isopropoxide)$_4$ and TBHP to afford the epoxide **21** in 82% yield, which on reduction with Red-Al yielded diol **22**. The primary hydroxy group was protected as the TBDPS ether **23** and this compound, when subjected to Wacker oxidation, gave ketone **24** in 65% yield. The key intermediate, *syn*-1,3-diol **25** was prepared conveniently by reduction of β-hydroxy ketone using a LiI/$LiAlH_4$ protocol.[9] This reaction has been shown to proceed with high diastereoselectively (*syn*:*anti* selectivity up to >99:1). Compound **25** was subsequently transformed into the isopropylidene derivative **26**[15] with 2,2-dimethoxy propane and catalytic PPTS in CH_2Cl_2. In the ^{13}C NMR of **26**, the acetonide methyl groups resonated at 19.8 and 30.3 ppm and the quaternary carbon resonated at 98.4 ppm thereby confirming the 1,3-*syn* relationship.[16] Removal of the TBDPS group by treatment with TBAF



Scheme 2. Reagents and conditions: (a) IBX, DMSO, DCM, 3 h, 90%; (b) allyl bromide, Zn, THF, NH_4Cl, 4 h, 92%; (c) IBX, DMSO, DCM, 3 h, 85%; (d) $LiAlH_4$–LiI (3 equiv, 1:1), THF, −100 °C, ether, 94%; (e) NaH, PMBBr, THF, 87%; (f) PTSA, MeOH, 30 min, 0 °C, 90%; (g) TsCl, Et_3N, cat. DMAP, 3 h, DCM, 75%; (h) $LiAlH_4$, THF, rt, 3 h, 72%; (i) DCC, DMAP, DCM, 0 °C to rt, 2 h, 86%; (j) DCM–H_2O (9:1), DDQ, 2 equiv, rt, 2 h, 81%; (k) acryloyl chloride, Et_3N, DMAP, 0 °C to rt, 2 h, 70%; (l) 10 mol % **17**, DCM, rt, 3 h, 76%; (m) oxone, aq MeOH, rt, 24 h, 80%.



Scheme 3. Reagents and conditions: (a) (1) allyl bromide, Na_2CO_3/TBAI; (2) CuI, DMF, rt, 82%; (b) $LiAlH_4$, THF, rt, 75%; (c) (1) (−)-DET, Ti(O-*i*-Pr)$_4$; (2) TBHP, 4 Å MS; (3) DCM, −20 °C, 82%; (d) Red-Al, THF, −15 °C to rt, 90%; (e) imidazole, TBDPS–Cl, DCM 0 °C to rt, 1 h, 95%; (f) $PdCl_2$, CuCl, O_2, THF–H_2O (10:1) rt, 3–4 h, 65%; (g) $LiAlH_4$, LiI (1:1), Et_2O, −78 °C to rt, 1 h, 84%; (h) 2,2-DMP, PPTS, 12 h, 94%; (i) TBAF, THF, 1 h, 90%; (j) (1) Dess–Martin periodinane; (2) DCM, rt, 1 h, 88%; (k) $(CF_3CH_2O)_2$ P(O)CH_2COOCH_3, NaH, THF, −80 °C, 0.5 h, 78%; (l) (1) 0.1 N HCl, MeOH, 86%; (2) $ZnCl_2$, THF, Δ, 80%; (m) DCC, DMAP, 82%; (n) oxone, aq MeOH, rt, 24 h, 80%.

in THF provided the alcohol **27**, which was oxidized to aldehyde **4**. A modified Wadsworth–Emmons reaction of **4** using methyl(bistrifluoroethyl)phosphonoacetate in the presence of NaH in THF gave *Z*-unsaturated ester **29**, exclusively. After hydrolyzing the acetonide with dilute acid, lactonization of the hydroxy ester was achieved by treatment with $ZnCl_2$ in THF at reflux to give hydroxylactone **30**,[17] which was identical to that of the material prepared by Solladie and Gressot-Kempt.[5] Next, this was acylated with **13** following the O'Doherty procedure[7a] to provide protected tarchonanthuslactone **18** in 80% yield. The spectral data of **18** was identical to those of the material prepared by us. Deprotection of TBS groups as before completed the total synthesis of tarchonanthuslactone **1** (Scheme 3).[14] The spectral data and optical rotation were again in agreement with those of the natural product.[5]

In summary, the total synthesis of (−)-tarchonanthuslactone has been accomplished using chelation-controlled reduction reaction as a key step via two different approaches.

Acknowledgements

K.S. thanks UGC, and N.M.R. and M.R. thank CSIR, New Delhi, for the awards of fellowships.

References and notes

1. Bohlmann, F.; Suwita, A. *Phytochemistry* **1979**, *18*, 677.
2. Nakata, T.; Hata, N.; Iida, K.; Qishi, T. *Tetrahedron Lett.* **1987**, *46*, 5661.
3. (a) Hsu, F.; Chem, Y. C.; Cheng, J. T. *Planta Med.* **2000**, *66*, 228; (b) Jodynis-Liebert, J.; Murias, M.; Bloszyk, E. *Planta Med.* **2000**, *66*, 199.
4. (a) Mori, Y.; Suzuki, M. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1809; (b) Mori, Y.; Kageyama, H.; Suzuki, M. *Chem. Pharm. Bull.* **1990**, *38*, 2574.
5. Solladie, G.; Gressot-Kempt, L. *Tetrahedron: Asymmetry* **1996**, *7*, 2371.
6. Reddy, M. V. R.; Yucel, A. J.; Ramachandran, P. V. *J. Org. Chem.* **2001**, *66*, 2512.
7. (a) Garaas, S.-D.; Hunter, T. J.; O'Doherty, G. A. *J. Org. Chem.* **2002**, *67*, 2682; (b) Enders, D.; Steinbusch, D. *Eur. J. Org. Chem.* **2003**, 4550.
8. Hanessian, S.; Ugolini, A.; Dube, D.; Glamyan, A. *Can. J. Chem.* **1984**, *62*, 2146.
9. Ghosh, A. K.; Lei, H. *J. Org. Chem.* **2002**, *67*, 8783.
10. *Spectral data of compound* **10**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.30–1.60 (m, 10H), 1.60–1.70 (m, 2H), 2.20 (m, 2H), 3.54 (t, 1H, $J = 7.3$ Hz), 3.80–3.90 (m, 1H), 4.00 (dd, 1H, $J = 8.1$, 5.6 Hz), 4.20–4.30 (m, 1H), 5.00 (s, 1H), 5.12 (d, 1H, $J = 3.2$ Hz), 5.70–5.90 (m, 1H). EI Mass: *m/z* 226 (M^+), $[\alpha]_D^{25}$ +1.54 (*c* 1.5, $CHCl_3$).
11. For a review, see: Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413.

12. *Spectral data of compound* **18**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.18 (s, 6H), 0.19 (s, 6H), 0.97 (s, 9H), 0.98 (s, 9H), 1.26 (d, $J = 6.5$ Hz, 3H), 1.80 (m, 1H), 2.15 (m, 1H), 2.26 (m, 1H), 2.35 (m, 1H), 2.55 (t, $J = 8$ Hz, 2H), 2.80 (t, $J = 8$ Hz, 2H), 4.40 (m, 1H), 5.10 (m, 1H, 6.01 (d, $J = 9.6$ Hz, 1H), 6.60–6.76 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): −4.1, 18.4, 20.2, 25.9, 29.1, 30.2, 36.11, 40.8, 67.1, 74.8, 120.8, 121.1, 121.4, 133.4, 144.5, 145.2, 146.6, 163.9, 172.4. $[\alpha]_D^{25}$ −43.8 (*c* 1.2, $CHCl_3$).
13. Sabitha, G.; Syamala, M.; Yadav, J. S. *Org. Lett.* **1999**, *11*, 1701.
14. *Spectral data of compound* **1**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.21 (d, $J = 6.0$ Hz, 3H) 1.78 (m, 1H) 2.10 (m, 1H) 2.15–2.35 (m, 2H) 2.62 (t, $J = 6.9$ Hz, 2H) 2.82 (t, $J = 6.9$ Hz, 2H) 4.25 (m, 1H) 5.08 (m, 1H) 6.03 (d, $J = 10.3$ Hz, 1H) 6.59 (m, 1H) 6.70–6.86 (m, 3H). EI Mass: *m*/*z* 320 (M^+), $[\alpha]_D^{25}$ −80 (*c* 0.4, $CHCl_3$).
15. *Spectral data of compound* **26**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.04 (s, 9H), 1.12 (d, 3H, $J = 6.0$ Hz), 1.20–1.46 (m, 2H), 1.34 (s, 3H), 1.41 (s, 3H), 1.64 (m, 2H), 3.60–3.70 (m, 1H), 3.80–3.96 (m, 2H), 4.07 (m, 1H), 7.25–7.39 (6H, ArH), 7.60–7.65 (4H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): 19.2, 19.8, 22.2, 27.1, 30.3, 39.3, 40.1, 60.1, 65.1, 65.6, 98.4, 127.62, 127.65, 129.50, 135.5; IR 3071, 2933, 1428, 1109 cm^{-1}. FAB Mass: 412 (M^+); $[\alpha]_D^{25}$ −2.5 (*c* 0.2, $CHCl_3$).
16. (a) Rychnovsky, S. D.; Skalitzky, D. J. *Tetrahedron Lett.* **1990**, *31*, 945; (b) Evans, D. A.; Rieger, D. L.; Gage, J. R. *Tetrahedron Lett.* **1990**, *31*, 7099.
17. *Spectral data of compound* **30**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.24 (d, 3H, $J = 6$ Hz), 1.80–1.88 (m, 2H), 2.30–2.50 (m, 2H), 4.07 (m, 1H), 4.60 (m, 1H), 6.10 (dt, 1H, $J = 10, 2$ Hz), 6.90 (ddd, 1H, $J = 10, 4.4, 3.8$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): 23.6, 30.2, 43.5, 65.0, 76.8, 121.1, 145.4, 164.2; EI Mass: *m*/*z* 156 (M^+); IR: 3422, 2925, 1712, 1253, 1117 cm^{-1}. $[\alpha]_D^{25}$ −110 (*c* 1, $CHCl_3$), lit.[5] −111 (*c* 1, $CHCl_3$).