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Synthesis of B-ring functionalised intermediates for the preparation of 1,9-dideoxy-forskolin derivatives

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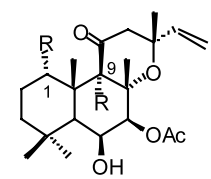
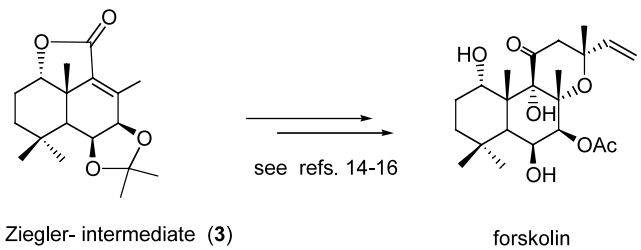
Abstract—Advanced intermediates towards the preparation of 1,9-dideoxy-forskolin derivatives have been synthesised from larixol; in such derivatives, the B-ring -6 and -7 hydroxyl groups are of the required beta configuration.

In contrast to forskolin, a natural product with a wide range of biological activities,[1,2] its 1,9-dideoxy analogue **1**, also isolated from *Coleus forskolii*, has been found to selectively inhibit glucose transport in rats adipocytes.[3] Our interest in such inhibitors[4] first led us to glucose-based probes; however, given their millimolar affinities,[5,6] 1,9-dideoxy-forskolin derivatives, whose affinities for the glucose transport protein are expected to be in the micromolar range,[1,3] have now become attractive targets.

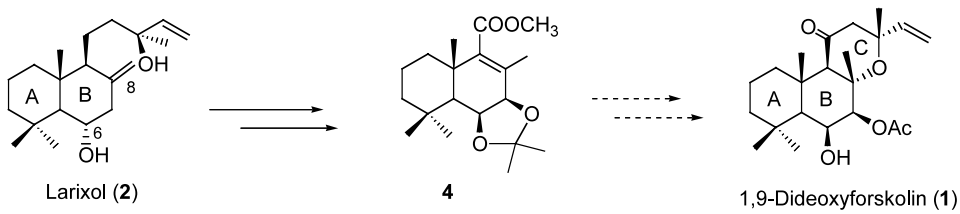


Forskolin: R = OH
1,9-Dideoxyforskolin (**1**): R = H



Ziegler- intermediate (**3**)

forskolin



Larixol (**2**)

4

1,9-Dideoxyforskolin (**1**)

Keywords: larixol; deoxy-forskolin; oxidation; labdane; terpenoids.

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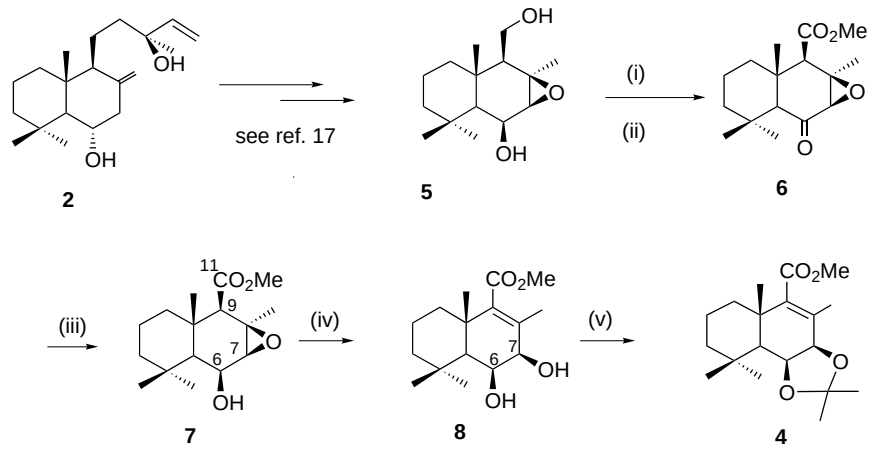


Scheme 1. (i) $RuCl_3 \cdot 3H_2O$, $NaIO_4$, $H_2O/CH_3CN/CCl_4$ (3/2/2), rt, 2 h, 75%; (ii) 0.3 M CH_2N_2, Et_2O, 0°C, 1 h, 92%; (iii) $NaBH_4$, MeOH, 0°C, 40 min, 63%; (iv) 30% NaOMe, dry MeOH, rt to 55°C, 1 h, Ar, 75%; (v) dimethoxypropane, H^+ cat., 1 day, Ar, 68%.

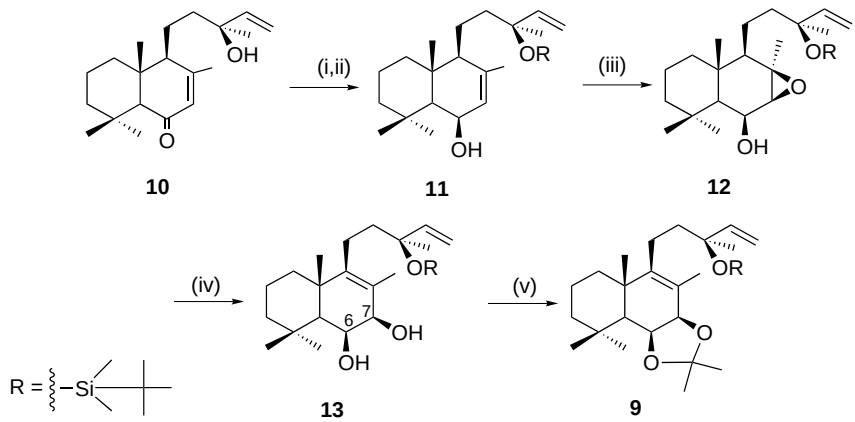
Previous synthetic approaches to (racemic) 1,9-dideoxy-forskolin derivatives started from *E*,*E*-farnesol,[7] which was followed by work focussing on construction of the C-ring.[8–10] Our own approach to **1** is based on the availability[11] and chemistry[12] of (+)-larixol (**2**), whose hydroxyl group at C-6 and double bond at C-8 could provide suitable synthetic handles for proper functionalisation of ring B.

For a preparation of 1-deoxy- or 1,9-dideoxy-forskolin, the preparation of a Ziegler-type intermediate such as **4** became our first target as the so-called Ziegler intermediate **3**[13] has been used for three total syntheses of forskolin;[14–16] such methodology could be similarly applied to **4**.

For the synthesis of **4**, we built on the recently described synthesis of uvidin-C (**5**), which has been obtained from larixol.[17] Thus, **5** was oxidised by RuO_4 (catalytically generated in situ from ruthenium trichloride and sodium periodate) and then esterified to give keto-ester **6**. Regeneration of the 6-hydroxyl group in the 6β configuration could be effected by sodium borohydride reduction, which yielded **7** ($J_{6,7}=6$ Hz). Opening of the epoxide ring to **8** occurred cleanly, provided that concentrated solutions of sodium methoxide were used. Also noteworthy is that when this reaction was carried out on uvidin C derivatives (i.e. with a CH_2OR group at C-11 instead of an electron-withdrawing group as in **7**), opening of the epoxide was troublesome; this suggests in the case of **7** participation of a carbanion at C-9 during opening of the epoxide. The vicinal hydroxyl groups in **8** were then protected as an acetal, which afforded the desired Ziegler-type intermediate **3** (see Scheme 1).

We also became interested in B-ring oxygenated labdanes, which would avoid a long sequence for shortening the larixol side-chain; compounds such as **9** could display interaction with the glucose transporter and also be amenable to further B-ring modifications (such as oxygenation at positions -8 and/or -9) to better mimic 1,9-dideoxy-forskolin.

Towards this goal, hydroxy-enone **10**,[18] which can be prepared in two steps from larixol,[19] was silylated and reduced to the 6-β alcohol **11**. Epoxidation of the intracyclic Δ^7 double bond provided the β-epoxide **12**



Scheme 2. (i) TBDMSiCl, imidazole, 5 days, 70°C, 96%; (ii) DIBAH, toluene, 1 h, −78°C to rt, 96%, (iii) TBHP, $VO(acac)_2$, 2 h, rt, 34%, (iv) H_2SO_4, 38%; (v) 2,2,-dimethoxypropane, H^+, 96%.

($J_{6,7}=6$ Hz). The stereochemical outcome of this epoxidation can be explained by assistance of the allylic hydroxyl group, similar results being observed in a related case.[20] Acidic opening of the epoxide ring afforded diol **13** ($J_{6,7}=4$ Hz) which was then converted to acetal **9**, in seven steps from larixol (Scheme 2).

Compounds **4** and **9** bear the 6β and 7β oxygens of the forskolin B-ring and, besides the synthesis of 1-deoxy or 1,9-dideoxy-forskolin derivatives in optically active form, they should be also useful by themselves to probe structure/affinity relationships for the proteins, which mediate transport of carbohydrates into the cells.[21–23]

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References

1. Laurenza, A.; McHugh Sutkowski, E.; Seamon, K. B. *Trends Pharm. Sci.* **1989**, *10*, 442–446.
2. Bath, S. V. *Progr. Chem. Natl. Compds.* **1992**, *62*, 1–73.
3. Joost, H. G.; Habberfield, A. D.; Simpson, I. A.; Laurenza, A.; Seamon, K. *Mol. Pharmacol.* **1988**, *33*, 449–453.
4. Brunet-Desruet, M.-D.; Morin, C.; Ghezzi, C.; Comet, M.; Fagret D. *Med. Nucl.* **1998**, *22*, 67–82; see also: Morin, C. In *Radiopharmaceutiques-Chimie des traceurs et applications biologiques*; Comet, M.; Vidal, M., Eds.; Presses Universitaires de Grenoble, 1998; pp. 295–305.
5. Abbadi, M.; Holman, G. D.; Morin, C.; Rees, W.; Yang, J. *Tetrahedron Lett.* **1999**, *40*, 5871–5864; see also Hashimoto, M.; Yang, J.; Holman, G. D. *ChemBiochem* **2001**, *2*, 52–59.
6. 2-*O*-Acetyl-D-glucose was prepared in order to mimic the B-ring functionalities of forskolin but its affinity for GLUT4 was found to be only of the millimolar range; see: Abbadi, M.; Morin, C. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1779–1782.
7. Zimmermann, S.; Bick, S.; Welzel, P.; Meuer, H.; Sheldrick, W. S. *Tetrahedron* **1995**, *51*, 2947–2952.
8. Behnke, D.; Hamm, S.; Hennig, L.; Welzel, P. *Tetrahedron Lett.* **1997**, *38*, 7059–7062.
9. Hamm, S.; Zimmermann, S.; Hennig, L.; Müller, D.; Welzel, P. *Tetrahedron Lett.* **1999**, *40*, 9225–9228.
10. Behnke, D.; Hennig, L.; Findeisen, M.; Welzel, P.; Müller, D.; Thormann, M.; Hofmann, H.-J. *Tetrahedron* **2000**, *56*, 1081–1095.
11. Larixol is readily extracted from the oleoresin of *Larix decidua*: (a) Sandermann, W.; Bruns, K. *Naturwissenschaften* **1965**, 560–561; (b) Mills, J. S. *Phytochemistry* **1973**, *12*, 2407–2412; (c) Bolster, M. G.; Jansen, B. J. M.; De Groot, A. E. *Tetrahedron* **2001**, *57*, 5663–5679.
12. (a) Morin, C.; Nedjar, N. *Tetrahedron Lett.* **1996**, *37*, 4705–4708; (b) Herlem, D.; Khuong-Huu, F. *Tetrahedron* **1997**, *53*, 673–680; (c) Bolster, M. G.; Lagnel, B. M. F.; Jansen, B. J. M.; Morin, C.; De Groot, A. E. *Tetrahedron*, in press.
13. Ziegler, F. E.; Jaynes, B. H.; Saindane, M. T. *Tetrahedron Lett.* **1985**, *26*, 3307–3310.
14. Ziegler, F. E.; Jaynes, B. H.; Saindane, M. T. *J. Am. Chem. Soc.* **1987**, *109*, 8115–8116.
15. Hashimoto, S.-I.; Sakata, S.; Sonegawa, M.; Ikegami, S. *J. Am. Chem. Soc.* **1988**, *110*, 3670–3672.
16. Corey, E. J.; Jardine, P. O. S.; Rohloff, J. C. *J. Am. Chem. Soc.* **1988**, *110*, 3672–3673.
17. Lagnel, B. M. F.; Morin, C.; De Groot, A. E. *Synthesis* **2000**, 1907–1916.
18. (a) Haeuser, J. *Bull. Soc. Chim. Fr.* **1965**, 2645–2647; (b) Norin, T.; Ohloff, G.; Willhalm, B. *Tetrahedron Lett.* **1965**, 3523–3528; (c) Chernenko, G. F.; Shmidt, E. N.; Radbil', B. A. *Khim. Prir. Soedin.* **1995**, *31*, 229–234 (Engl. Transl.: *Chem. Natl. Compds.* **1995**, *31*, 187–191).
19. Herlem, D.; Ouazzani, J.; Khuong-Huu, F. *Tetrahedron Lett.* **1996**, *37*, 1241–1244.
20. Ziegler, F. E.; Jaynes, B. H. *Tetrahedron Lett.* **1985**, *26*, 5875–5878.
21. Carruthers, A. *Physiol. Rev.* **1990**, *70*, 1135–1176.
22. Tatibouët, A.; Yang, Y.; Morin, C.; Holman, G. D. *Bioorg. Med. Chem.* **2000**, *8*, 1825–1833.
23. Woodrow, C. J.; Burchmore, R. J.; Krishna, S. *Proc. Natl. Acad. Sci. USA* **2000**, *97*, 9931–9936.
24. All compounds presented analytical data in accord with the proposed structures; selected data: **4**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.6 (dd, $J_{5-6}=2$ Hz, $J_{6-7}=7$ Hz, 1H, H-6), 4.3 (d, $J_{6-7}=7$ Hz, 1H, H-7), 3.7 (s, 3H, $OC\underline{H}_3$), 1.7 and 1.4 (s, 3H, $C\underline{H}_3$ of acetal); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.3 ($\underline{C}O_2Me$), 141.2 (C-8), 129.7 (C-9), 109.3 ($\underline{C}(CH_3)_2$), 77.3 (C-7), 72.5 (C-6). **7**: IR (film): $\nu=1740$ cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 4.5 (m, 1H, H-6), 3.7 (s, 3H, $OC\underline{H}_3$), 3.2 (d, $J_{6-7}=6$ Hz, 1H, H-7), 2.4 (s, 1H, H-9); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 171.7 ($\underline{C}O_2Me$), 65.2 (C-7), 60.9 (C-6), 60.5 (C-8), 54.2 (C-5), 51.4 (C-9). **9**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.9, 5.1, 5.0 (ABX system, H-14, H-15, -15′), 4.55 (dd, $J_{6-7}=6$ Hz, $J_{5-6}=2$ Hz, 1H, H-6), 4.3 (d, $J_{6-7}=6$ Hz, 1H, H-7). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 149.5 (C-14), 143.7 (C-8), 124.6 (C-9), 111.9 (C-15), 108.5 ($\underline{C}(CH_3)_2$), 78.9 (C-7), 75.8 (C-13), 72.5 (C-6), 51.75 (C-5), 26.1 and 23.8 ($\underline{C}H_3$ of acetal). **12**: ^{1}H NMR (C_6D_6, 200 MHz) δ 5.95, 5.2 and 5.1 (ABX system, H-14, -15, -15′), 4.4 (m, H-6), 2.9 (d, $J_{6-7b}=6$ Hz, 1H, H-7); ^{13}C NMR (C_6D_6, 50 MHz) δ 145.7 (C-14), 111.9 (C-15), 75.9 (C-13), 65.3, 63.5 (C-6, C-7), 63.9 (C-8).