Synthesis of (±)-Smenochromene D (Likonide B) Using a Regioselective Claisen Rearrangement

Marjorie Bruder, Christopher J. Moody*

School of Chemistry, University of Nottingham, University Park, Nottingham, NG7 2RD, UK
Fax +44(115)9513564; E-mail: c.j.moody@nottingham.ac.uk

Received 3 December 2007

Abstract: A synthesis of the unusual ansa farnesyl hydroquinone smenochromene D (likonide B) is described, in which the key steps are a regioselective microwave-mediated Claisen rearrangement of an aryl propargyl ether to deliver the chromene ring, and macrocyclisation via an intramolecular Mitsunobu reaction.

Key words: natural products, *ansa*-macrocycles, rearrangements, chromenes, Mitsunobu reaction

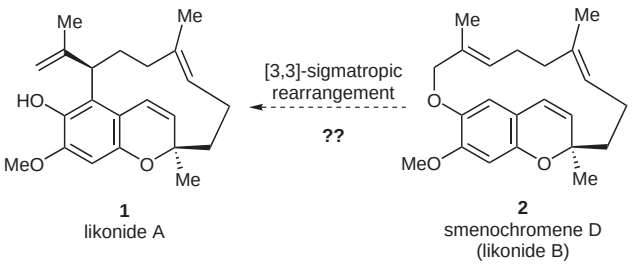


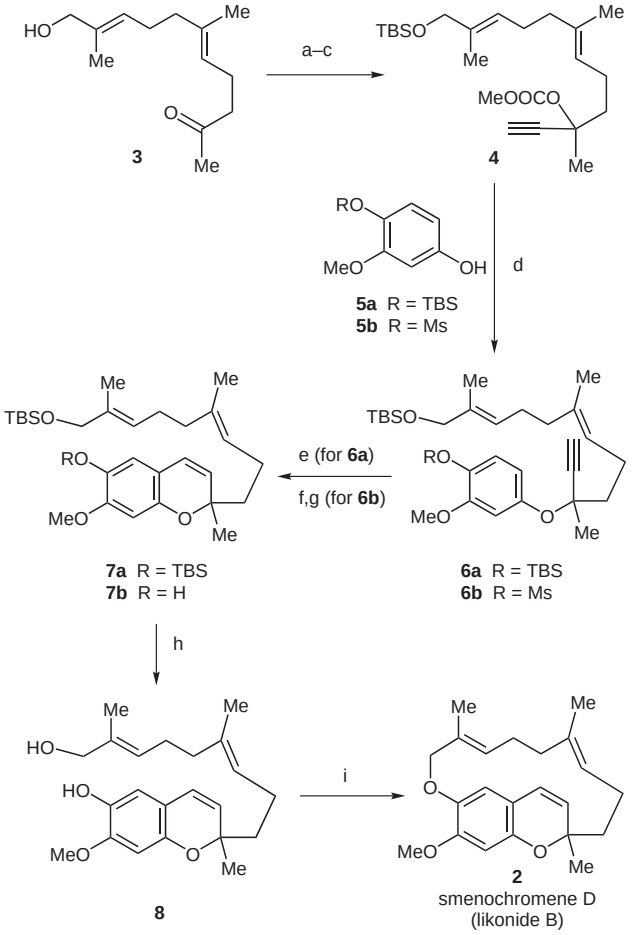
Figure 1

Sesquiterpenoid quinone and hydroquinone derivatives occur widely in nature.[1–3] In 2004 Kashman and co-workers reported two new examples with an unusual ansa farnesyl structure.[4] The compounds, named likonide A and B (**1** and **2**), were isolated from a marine sponge *Hyatella* sp. found off the coast of Likoni, Kenya, and their structures and absolute configurations were determined by detailed spectroscopic studies. Although the likonides were described as new ansa compounds,[4] Faulkner and Clardy and colleagues had reported a series of very similar ansa farnesyl hydroquinones, the smenochromenes isolated from a Seychelles sponge *Smenospongia* sp., in 1991.[5] The structure and spectroscopic data for one of these compounds, smenochromene D, appeared to be identical to those of likonide B in all respects except optical rotation: smenochromene D, $[\alpha]_D$ –68.5 (*c* = 0.35, CH_2Cl_2);[5] likonide B, $[\alpha]_D$ +27 (*c* = 0.08, MeOH).[4] The confusion has recently been resolved by the synthesis of (±)-smenochromene D by Olson and Trauner,[6] which clearly established that smenochromene D and likonide B are identical in terms of relative stereochemistry. Hence the natural products appear to be enantiomers, or possibly, given the large discrepancy in optical rotation, to have an enantiomeric excess in the opposite sense. Intriguingly, it is also noted that likonides A and B are formally related by a [3,3]-sigmatropic process, since Claisen rearrangement of likonide B should give likonide A (Figure 1). However, Trauner and co-workers have recently shown that heating of likonide B (smenochromene D) does not result in such a Claisen rearrangement, but rather in an alternative rearrangement to give the ring skeleton of smenochromene B.[7] In view of the continuing interest in these and other sesquiterpene quinones and hydroquinones,[8–10] we report a new synthesis of (±)-smenochromene D using a regioselective Claisen rearrangement to form the chromene and an intramolecular Mitsunobu reaction as key steps.

The synthesis started with the known allylic alcohol **3**, readily available by allylic oxidation of commercial geranylacetone with selenium dioxide and *tert*-butyl hydroperoxide.[11,12] Protection as the *tert*-butyldimethylsilyl (TBS) ether was followed by addition of ethynylmagnesium bromide and acylation with methyl chloroformate to give the tertiary propargylic alcohol carbonate **4** in preparation for coupling to a phenol. The first phenol investigated was 3-methoxy-4-*tert*-butyldimethylsiloxyphenol (**5a**).[13] However, attempts to couple phenol **5a** with the propargylic carbonate **4** (or the corresponding trifluoroacetate) in the presence of DBU and copper(II) chloride[14,15] gave only poor yields (12–26%) of the desired propargylic ether **6a**. Nevertheless, sufficient material was obtained to establish that the planned Claisen rearrangement exhibited the required regioselectivity.[15–17] Thus microwave heating[18] of **6a** in DMF at 200 °C for 30 minutes gave the chromene **7a** in a 4:1 mixture with the regioisomeric product.

In order to improve the yield in the key copper-catalysed coupling step, a number of simple model studies were performed (data not shown) which established that the reaction proceeded better if an electron-withdrawing protecting group was installed on the *para*-hydroxyl group. Thus the coupling reaction of propargylic carbonate **4** was repeated using the mesyl-protected phenol **5b** resulting in an acceptable yield (68%) of the propargylic ether **6b**. However, the Claisen rearrangement of the mesylate derivative **6b** exhibited poor regioselectivity (ratio 2:1), and therefore the mesylate group was cleaved using LDA in THF at low temperature.[19] Gratifyingly, the resulting phenolic propargylic ether underwent a highly selective Claisen rearrangement upon microwave heating in *N*,*N*-diethylaniline at 140 °C for 40 minutes to give the desired chromene **7b** in 87% yield with no evidence for the

SYNLETT 2008, No. 4, pp 0575–0577
Advanced online publication: 12.02.2008
DOI: 10.1055/s-2008-1032090; Art ID: D40107ST



Scheme 1 *Reagents and conditions*: (a) *t*-BuMe$_2$SiOTf, 2,6-lutidine, CH_2Cl_2 (89%); (b) ethynylmagnesium bromide, THF, diethylether (85%); (c) *n*-BuLi, THF, then MeO_2CCl (86%); (d) **5a**, DBU, $CuCl_2$, MeCN (26%) or **5b**, DBU, $CuCl_2$, MeCN (68%); (e) DMF, microwave (300 W), 200 °C, 30 min (52% as 4:1 mixture of regioisomers); (f) LDA, THF, –78 °C (71%); (g) $PhNEt_2$, microwave (300 W), 140 °C, 40 min (87%); (h) H_2SiF_6, MeCN, 0 °C (83%); (i) 1,1′-(azodicarbonyl)dipiperidine, *n*-Bu_3P, toluene (27% + 13% dimer **9**).

formation of the alternative regioisomer.[20] Thereafter the silyl protecting group was removed from the side chain to give the precursor **8** for the macrocyclisation reaction. The cyclisation was effected using an intramolecular Mitsunobu reaction [tri-*n*-butylphosphine, 1,1′-(azodicarbonyl)dipiperidine] and gave smenochromene D (likonide B) in 27% yield (Scheme 1),[21] the poor yield probably reflecting the strained nature of the ansa ring.[22] A small amount of a dimer assigned as structure **9** (Figure 2; mixture of diastereomers) was also isolated. The NMR spectroscopic data for synthetic smenochromene D were identical to those described for the natural product[4,5] and the aforementioned synthetic racemic material.[6]

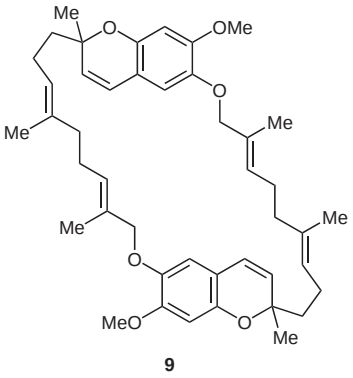


Figure 2

Acknowledgment

We thank Professor Dirk Trauner for copies of the NMR spectra of synthetic (±)-likonide B.

References and Notes

(1) Thomson, R. H. *Naturally Occurring Quinones*, 2nd ed.; Academic Press: London, **1971**.
(2) Thomson, R. H. *Naturally Occurring Quinones III: Recent Advances*, 3rd ed.; Chapman and Hall: London, **1987**.
(3) Thomson, R. H. *Naturally Occurring Quinones IV: Recent Advances*, 4th ed.; Blackie: London, **1997**.
(4) Rudi, A.; Benayahu, Y.; Kashman, Y. *Org. Lett.* **2004**, *6*, 4013.
(5) Venkateswarlu, Y.; Faulkner, D. J.; Steiner, J. L. R.; Corcoran, E.; Clardy, J. *J. Org. Chem.* **1991**, *56*, 6271.
(6) Olson, B. S.; Trauner, D. *Synlett* **2005**, 700.
(7) Rosa, C. P.; Kienzler, M. A.; Olson, B. S.; Liang, G.; Trauner, D. *Tetrahedron* **2007**, *63*, 6529.
(8) Stahl, P.; Waldmann, H. *Angew. Chem. Int. Ed.* **1999**, *38*, 3710.
(9) Aoki, S.; Kong, D.; Matsui, K.; Rachmat, R.; Kobayashi, M. *Chem. Pharm. Bull.* **2004**, *52*, 935.
(10) Takahashi, Y.; Kubota, T.; Fromont, J.; Kobayashi, J. *Tetrahedron* **2007**, *63*, 8770.
(11) McMurry, J. E.; Dushin, R. G. *J. Am. Chem. Soc.* **1989**, *111*, 8928.
(12) Umbreit, M. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1977**, *99*, 5526.
(13) Fischer, J.; Reynolds, A. J.; Sharp, L. A.; Sherburn, M. S. *Org. Lett.* **2004**, *6*, 1345.
(14) Godfrey, J. D.; Mueller, R. H.; Sedergran, T. C.; Soundararajan, N.; Colandrea, V. J. *Tetrahedron Lett.* **1994**, *35*, 6405.
(15) For related Claisen rearrangements, see ref. 16 and the following: Kahn, P. H.; Cossy, J. *Tetrahedron Lett.* **1999**, *40*, 8113.
(16) Yamaguchi, S.; Maekawa, M.; Murayama, Y.; Miyazawa, M.; Hirai, Y. *Tetrahedron Lett.* **2004**, *45*, 6971.
(17) For a discussion of regioselectivity in rearrangements of aryl propargyl ethers, see: Yamaguchi, S.; Ishibashi, M.; Akasaka, K.; Yokoyama, H.; Miyazawa, M.; Hirai, Y. *Tetrahedron Lett.* **2001**, *42*, 1091.
(18) For an earlier example of a microwave-assisted Claisen rearrangement of an aryl propargyl ether, see: Moghaddam, F. M.; Sharifi, A.; Saidi, M. R. *J. Chem. Res., Synop.* **1996**, 338.
(19) Ritter, T.; Stanek, K.; Larrosa, I.; Carreira, E. M. *Org. Lett.* **2004**, *6*, 1513.
(20) **6-Hydroxy-2-[(3*E*,7*E*)-9-*tert*-butyldimethylsilyloxy-4,8-dimethylnona-3,7-dienyl]-7-methoxy-2-methyl-2*H*-chromene (7b)**: A solution of the propargyl aryl ether (98 mg, 0.21 mmol) in *N*,*N*-diethylaniline (3.5 mL) in a sealed tube was heated at 140 °C for 40 min at 300 W in a CEM

Discover™ microwave reactor. The reaction mixture was evaporated and the resulting oil was purified by flash chromatography on silica gel, eluting with light PE–Et_2O (8:2), to give the title compound (85 mg, 87%) as a orange-yellow oil. IR ($CHCl_3$): 3630, 3553, 2929, 2856, 1628, 1583, 1501, 1458, 1360, 1290, 1124 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.56 (s, 1 H, H-5), 6.41 (s, 1 H, H-8), 6.27 (d, *J* = 9.8 Hz, 1 H, H-4), 5.47 (d, *J* = 9.8 Hz, 1 H, H-3), 5.38 (m, 1 H, CH=CMe), 5.19 (s, 1 H, OH), 5.13–5.16 (m, 1 H, CH=CMe), 4.02 (s, 2 H, OCH_2), 3.86 (s, 3 H, OMe), 2.10–2.14 [m, 4 H, OC(Me)CHHCH_2, =CHCH_2CH_2], 2.00–2.03 (m, 2 H, =CHCH_2CH_2), 1.66–1.75 [m, 2 H, OC(Me)CHHCH_2], 1.61 (s, 6 H, 2 × CMe=CH), 1.39 (s, 3 H, Me), 0.93 (s, 9 H, CMe_3), 0.08 (s, 6 H, $SiMe_2$). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.7 (C), 146.6 (C), 139.2 (C), 135.0 (C), 134.3 (C), 127.6 (CH), 124.3 (CH), 122.4 (CH), 121.5 (CH), 113.9 (CH), 111.7 (C), 100.0 (CH), 78.1 (C), 68.6 (CH_2), 55.9 (Me), 40.9 (CH_2), 39.3 (CH_2), 26.0 (CH_2), 25.9 (Me), 25.8 (Me), 22.6 (CH_2), 18.4 (C), 15.9 (Me), 13.4 (Me), –5.3 (Me). HRMS (EI): *m*/z $[M + Na]^+$ calcd for $C_{28}H_{44}O_4Si$: 495.2901; found: 495.2918.

(21) **(±)-Smenochromene D [(±)-Likonide B](2)**: Into a stirring 8 mM solution of 6-hydroxy-2-[(3*E*,7*E*)-9-hydroxy-4,8-dimethylnona-3,7-dienyl]-7-methoxy-2-methyl-2*H*-chromene (**8**; 50 mg, 0.14 mmol) and dipiperidinyl azodicarboxylate (105 mg, 0.42 mmol) in anhyd toluene (17.4 mL) was bubbled argon for 10 min, while cooling the solution to 0 °C. A first batch (40 μL) of tributylphosphine (140 μL, 0.55 mmol) was added dropwise and the reaction mixture was stirred for 20 min at 0 °C followed by the addition of a second batch of tributylphosphine (100 μL). The reaction mixture was then allowed to reach r.t. and was stirred for 24 h. A second batch of dipiperidinyl azodicarboxylate was added at 0 °C, tributylphosphine was added over 1 h and the whole was stirred for 8 h at r.t. H_2O was added to the mixture and the aqueous phase was extracted into EtOAc (2 ×). The organic layer was reduced in vacuo, the crude product was taken up in light PE and filtered. The resulting solution was dried over $MgSO_4$, filtered and evaporated in vacuo. The crude oil was purified by flash chromatography on silica gel, eluting with hexane–EtOAc (9:1), to give the title compound (13 mg, 27%). IR ($CHCl_3$): 3630, 2930, 1618, 1503, 1450, 1365, 1289, 1124 cm^{-1}. ^1H NMR (400 MHz, DMSO): δ = 6.61 (s, 1 H, H-16), 6.38 (d, *J* = 9.9 Hz, 1 H, H-1), 6.34 (s, 1 H, H-19), 5.41 (d, *J* = 9.8 Hz, 1 H, H-2), 4.85–4.87 (m, 1 H, H-6), 4.74–4.78 (m, 1 H, H-10), 4.38 (d, *J* = 11.4 Hz, 1 H, H-12), 4.07 (d, *J* = 11.4 Hz, 1 H, H-12′), 3.66 (s, 3 H, H-22), 1.96–2.12 (m, 4 H, H-9, H-5, H-8), 1.83–1.92 (m, 1 H, H-5′), 1.64–1.68 (m, 1 H, H-4), 1.53–1.62 (m, 5 H, H-8, H-15, H-4′), 1.41 (s, 3 H, H-13), 1.32 (s, 3 H, H-14). ^{13}C NMR (100 MHz, DMSO): δ = 153.0 (C), 149.8 (C), 138.9 (C), 131.2 (CH), 131.0 (C), 129.6 (C), 126.3 (CH), 125.6 (CH), 123.2 (CH), 118.9 (CH), 112.9 (C), 99.9 (CH), 78.9 (CH), 78.6 (C), 55.3 (OMe), 40.7 (CH_2), 38.5 (CH_2), 29.7 (Me), 24.0 (CH_2), 22.5 (CH_2), 14.2 (Me), 13.9 (Me). HRMS (ES): *m*/*z* $[M + Na]^+$ calcd for $C_{22}H_{28}O_3$: 363.1931; found: 363.1919. The cyclic dimer **9** (13 mg, 13%) was also isolated.

(22) A similarly modest yield in the macrocyclisation step was also observed in the previous synthesis of smenochromene D (ref. 6).