Synthesis of (−)-furodysinin from (+)-limonene

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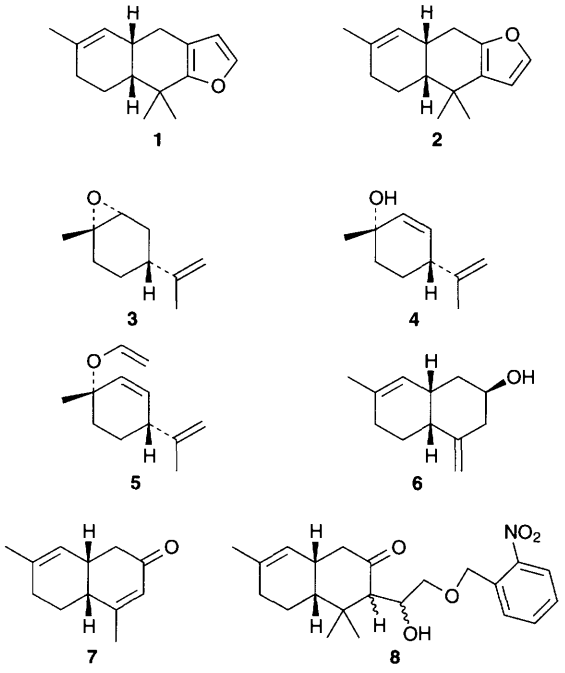
Furodysinin is synthesised by elaboration of (1*R*, 2*R*)-(+)-limonene oxide; key reactions include a tandem Claisen rearrangement–ene reaction and trapping of a conjugate adduct of an enone providing a bicyclic precursor of the sesquiterpene.

(+)-Furodysin and (+)-furodysinin are two sesquiterpenes isolated from pantropical marine sponges of the genus *Dysidea*.[1] Their absolute configurations were subsequently established by the synthesis of their (−)-isomers from (+)-9-bromocamphor.[2] Interestingly, (−)-furodysinin was found in the Mediterranean *D. tupha*[3] and both (−)-furodysin **1** and (−)-furodysinin **2** were shown to occur in *D. herbacea* from Fiji.[4] In 1987 the total synthesis of the racemic substances was reported.[5]

In connection with our interests in using readily available chiral terpenes to synthesize other natural products[6] we launched a synthetic study of these compounds and reported a route to (−)-furodysin.[7] We have now completed an approach to (−)-furodysinin by a different method which is described here. (1*S*, 2*R*, 4*R*)-1,2-Epoxymenth-8-ene **3** was transformed into the tertiary allylic alcohol **4**[7] and then *O*-vinylated (→**5**, 69%) and thermolysed at 200 °C to afford the bicyclic alcohol **6** (73.7%).† In the thermal reaction the allyl vinyl ether underwent a tandem Claisen rearrangement and an intramolecular ene reaction.[8] The route was actually designed to take advantage of the stereoselectivity of the Claisen rearrangement to establish the aldehyde sidechain and thence the stereochemistry of the bicyclic system. At lower temperatures and shorter reaction times the aldehyde intermediate could be isolated. Swern oxidation of **6** led to the conjugated ketone **7**† directly (92%). Our plan for the introduction of the remaining structural unit of furodysinin was by a conjugate addition to the enone and trapping the resulting enolate with an electrophile suitable for elaboration of the furan ring. The best result among the many trials ensued when MeMgI–CuI was used as the nucleophile and α-(*o*-nitrobenzyloxy)acetaldehyde was used as the trapping agent. The parent α-benzyloxyacetaldehyde was found to be unsuitable because of the difficulty we encountered in debenzylation of the aldols. The diastereoisomeric aldols **8** thus obtained (56.7%) were photolysed to dislodge the substituted benzyl group,[9] and the keto diols were exposed to acid to generate (−)-furodysinin **2**† (77% in two steps) whose spectral data are consistent with those reported in the literature.



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Footnote

† *Selected physical data* for **6** $[\alpha]_D$ −10.39 (*c* 1, $CHCl_3$,); IR ν_{max}/cm^{-1} 3230 and 1645; δ_H(300 MHz, $CDCl_3$) 1.41–1.51 (3 H, m), 1.63 (3 H, s), 1.73–2.04 (4 H, m), 2.16 (1 H, m), 2.37–2.46 (3 H, m), 4.00 (1 H, m), 4.75 (1 H, s), 4.29 (1 H, s) and 5.29 (1 H, br.s); δ_C(75 MHz, $CDCl_3$) 23.56, 23.65, 30.15, 32.27, 35.97, 39.00, 42.18, 67.00, 111.67, 125.28, 133.58 and 148.30. *m/z* (M^+) 178.1361. For **7** $[\alpha]_D$ +3.23 (*c* 1, $CHCl_3$); IR ν_{max}/cm^{-1} 1668 and 1627; δ_H(300 MHz, $CDCl_3$) 1.63 (3 H, s), 2.02 (3 H, s), 5.33 (1 H, m) and 5.85 (1 H, s); δ_C(75 MHz, $CDCl_3$) 22.54, 22.63, 23.40, 30.56, 34.70, 39.56, 40.11, 123.85, 126.42, 134.37, 164.41 and 198.64; *m/z* (M^+) 176.1205. For **2** mp 51–53 °C; $[\alpha]_D$ −60.39 (*c* 0.48, $CHCl_3$); IR ν_{max}/cm^{-1} 1632; δ_H(300 MHz, $CDCl_3$) 1.16 (3 H, s), 1.18 (3 H, s), 1.23–1.29 (2 H, m), 1.53 (1 H, m), 1.67 (3 H, s), 2.01 (2 H, m), 2.27 (1 H, m), 2.63–2.74 (2 H, m), 5.60 (1 H, br), 6.18 (1 H, d) and 7.17 (1 H, s); δ_C(75 MHz, $CDCl_3$) 19.25, 23.21, 26.24, 27.56, 31.20, 31.69, 32.86, 33.12, 44.51, 108.18, 124.64, 126.10, 133.61, 140.43 and 147.39.

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