Synthesis of *ent*-Herbasolide

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ent-Herbasolide is synthesised by elaboration of (+)-10-camphorsulfonyl chloride which involves homologation at C-10, cleavage of the C-2/C-3 bond, oxidation at C-5 and chain extension at C-3 of the camphor skeleton.

The structure of (+)-herbasolide 1,[1] a norsesquiterpene lactone of the marine sponge *Dysidea herbacea* which grows in the waters surrounding Papua-New Guinea has been determined by X-ray diffraction. Biosynthetically this compound is an oxidative catabolite of (−)-herbadysidolide 2 which must be also related to spirodysin 3, the progenitor of (+)-furodysin 4[2] and (+)-furodysinin 5.[2] Furodysin and furodysinin are most likely derived by elimination of acetic acid from spirodysin, involving a Wagner–Meerwein rearrangement to expand the cyclopentane ring. We have recently devised a concise synthesis of (−)-furodysin[3] and (−)-furodysinin[4] from (+)-limonene. We

also pursued a route towards herbasolide starting from the commercially available (+)-10-camphorsulfonyl chloride. Here we present our results.

Reaction of (+)-10-camphorsulfonyl chloride with diazomethane followed by treatment with triethylamine provided the vinyl derivative 6 *via* a Ramberg–Bäcklund reaction.[5] Hydroboration of 6 with 9-BBN led to 10-hydroxymethylcamphor 7 (70% yield) which was subjected to SeO2 oxidation in Ac2O–HOAc to furnish the camphorquinone derivative 8 (mp 84–86 °C, 94% yield) in which the primary alcohol had also been acetylated. Treatment of the α-diketone with alkaline hydrogen peroxide gave a cyclic anhydride which underwent lactonization involving the primary alcohol being released *in situ*. The lactonic acid 9 (mp 101–103 °C, 90% yield) contains the bicyclic framework of herbasolide but lacks the side chain and two ketone groups.

For the elaboration of the missing structural elements the acid was first reduced by borane–THF complex to give the alcohol 10 (mp 88–90 °C, 86% yield). The alcohol was transformed into the exocyclic methylene derivative in two steps *via* benzoylation (BzCl, DMAP → 11) (mp 86–87 °C, 92.5% yield) and pyrolysis (→ 12, mp 54–56 °C, 56% yield). Introduction of an allylic hydroxy group to give 13 (mp 116.5–118.5 °C, 79% for the major isomer; a combined yield of a 11:1 mixture was obtained in 85.5% yield) was performed by oxidation with SeO2–BuᵗO2H and the product was further oxidized with manganese dioxide to the conjugated ketone 14 (mp 83–85 °C, 82.5% yield). Whilst Michael addition to the enone using acetone enolate equivalents was not too successful, the final conversion of 14 to herbasolide {9,9-dimethyl-8-(3-oxobutyl)-2-oxaspiro[4.4]nonane-1,7-dione} (mp 97–98 °C, lit., 97–98 °C) was achieved by the two-step process of Sakurai–Hosomi reaction[6] with allyltrimethylsilane in the presence of TiCl4 (→ 15, 70% yield) and Wacker oxidation (O2, PdCl2, CuCl, DMF–H2O; 77% yield). The essentially neutral conditions of the oxidation preserved the product by preventing it from undergoing aldol cyclization. The generation of herbasolide in good yield suggests the Sakurai–Hosomi reaction was terminated by *C*-protonation from the side of the lactone carbonyl.

Using the more readily available (+)-10-camphorsulfonyl chloride in this synthesis resulted in *ent*-herbasolide. Thus the absolute configuration of (+)-herbasolide, indicated by 1 as arbitrarily assigned, is indeed correct. In view of the fact that (−)-furodysin was elaborated by a Fijian *Dysidea* sp.,[7] we strongly suspect that the (−)-isomer† synthesized by us will be found in this other source.
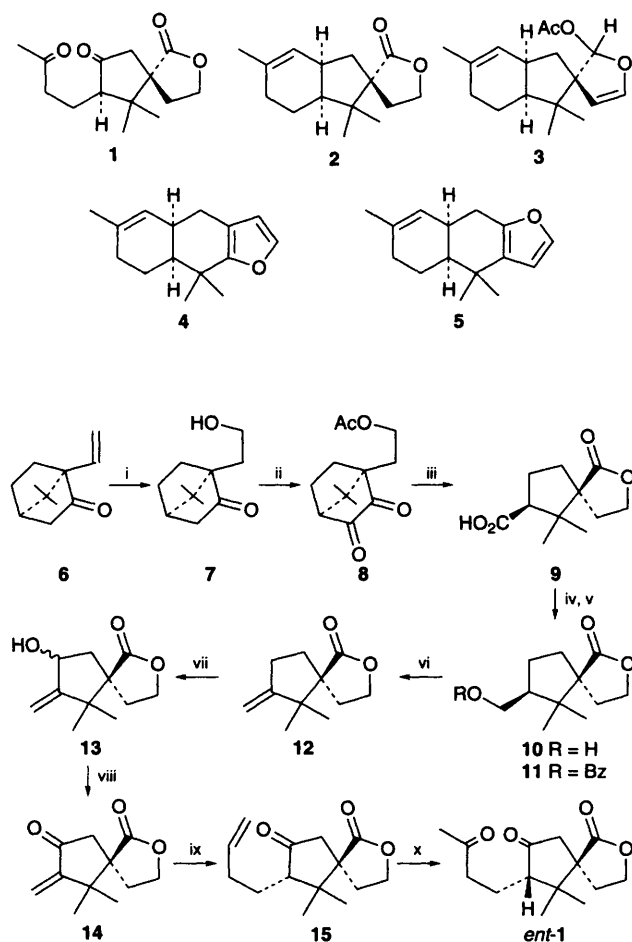
Scheme 1 *Reagents and conditions*: i, 9-BBN, THF, H2O2, NaOH; ii, SeO2, HOAc, Ac2O, heat; iii, 30% H2O2, NaOH; iv, BH3, THF; v, BzCl, DMAP, CH2Cl2; vi, 500 °C; vii, SeO2, BuᵗO2H, CH2Cl2; viii, MnO2, CH2Cl2; ix, CH2=CHCH2SiMe3, TiCl4, CH2Cl2; x, PdCl2, CuCl, O2, DMF, H2O

Footnote

† *Selected spectroscopic data* for *ent*-1. The mp and all spectral data of synthetic *ent*-1 are consistent with the assigned structure as well as the data reported in the literature [IR ν/cm⁻¹ 1757, 1740 and 1714. δH (300 MHz, CDCl3) 0.81 (3 H, s), 1.16 (3 H, s), 2.13 (3 H, s), 4.22 (1 H, m) and 4.30 (1 H, m). δC (75 MHz, CDCl3) 18.29 (t), 19.63 (q), 21.11 (q), 30.01 (q), 30.82 (t), 42.18 (t), 44.14 (s), 44.93 (t), 50.63 (s), 55.89 (d), 65.36 (t), 179.39 (s), 208.01 (s) and 215.19 (s). *M*+ 252.1359] except [α]D −5.86, [α]436 −134.1

(*c* 0.1 CHCl₃). The latter value is larger than the reported +95 which might indicate an optical inhomogeneity of the natural product.

References

1 C. Charles, J. C. Brackman, D. Daloze, B. Tursch, J. P. Declerq, G. Germani and M. Van Meerssche, *Bull. Soc. Chim. Belg.*, 1978, **87**, 481. Correlation of herbasolide with (−)-furodysin and (−)-furodysinin of the same natural source indicates its absolute configuration as shown by **1**.

2 R. Kazlauskas, P. T. Murphy and R. J. Wells, *Tetrahedron Lett.*, 1978, 4951.
3 T.-L. Ho and K.-Y. Lee, *Tetrahedron Lett.*, 1995, **36**, 947.
4 T.-L. Ho and R.-J. Chein, *Chem. Commun.*, 1996, 1147.
5 N. Fischer and G. Opitz, *Org. Synth.*, 1973, **5**, 877.
6 A. Hosomi and H. Sakurai, *J. Am. Chem. Soc.*, 1977, **99**, 1673.
7 P. Horton, W. D. Inman and P. Crews, *J. Nat. Prod.*, 1990, **53**, 143.