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 4² 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 (-)-furodysin³ and (-)-furodysinin⁴ from (+)-limonene. We



Scheme 1 Reagents and conditions: i, 9-BBN, THF, H_2O_2 , NaOH; ii, SeO₂, HOAc, Ac₂O, heat; iii, 30% H_2O_2 , NaOH; iv, BH₃, THF; v, BzCl, DMAP, CH₂Cl₂; vi, 500 °C; vii, SeO₂, BuⁱO₂H, CH₂Cl₂; viii, MnO₂, CH₂Cl₂; ix, CH₂=CHCH₂SiMe₃, TiCl₄, CH₂Cl₂; x, PdCl₂, CuCl, O₂, DMF, H₂O

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 \rightarrow 11) (mp 86–87 °C, 92.5% yield) and pyrolysis (\rightarrow 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-Bu^tO₂H 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)-°C, 2-oxaspiro[4.4]nonane-1,7-dione} (mp 97-98 lit., 97-98 °C) was achieved by the two-step process of Sakurai-Hosomi reaction⁶ with allyltrimethylsilane in the presence of TiCl₄ (\rightarrow 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.

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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 v/cm⁻¹ 1757, 1740 and 1714. δ_H (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). δ_C (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.

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