

A Conjugate Addition—Radical Cyclisation Approach to Sesquiterpene Phenols

Barry S. Crombie,^a Alan D. Redhouse,^a Colin Smith^b and Timothy W. Wallace^{*a}

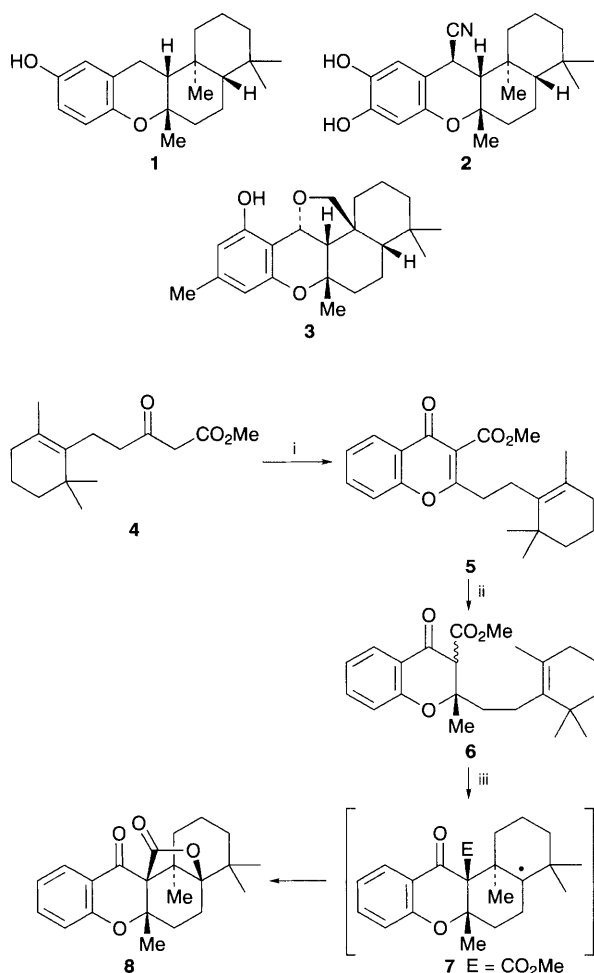
^a Department of Chemistry and Applied Chemistry, University of Salford, Salford, UK M5 4WT

^b Medicinal Chemistry II, Glaxo Research & Development Ltd., Greenford Road, Greenford, Middlesex, UK UB6 0HE

A polycyclic ring system consisting of fused sesquiterpene and phenolic units, whose structure was found by X-ray crystallography to coincide with that which forms the nucleus of a series of natural products, can be constructed from chromone and terpene precursors *via* sequential conjugate addition and manganese(III)-induced 6-*endo-trig* radical cyclisation reactions.

A series of natural products is based on a tetracyclic fusion of sesquiterpene and phenolic moieties. Examples include 8-epi-chromazonarol **1**¹ and the antiviral compound 15-cyanopuuphehenol **2**,² both sponge metabolites, and siccanin **3**, a fungal metabolite which has specific antifungal activity against human pathogenic dermatophytes such as *Trichophyton interdigitale*.³ We have been seeking a flexible synthetic route to compounds of this type, and herein describe the results of an investigation of potentially complementary conjugate addition–cyclisation approaches to their tetracyclic nucleus.

In the first approach to the desired ring system, the ketoester **4** was prepared⁴ in four steps from β -ionone,⁵ and condensed with 2-fluorobenzoyl chloride⁶ to obtain the chromone-3-carboxylate **5**[†] (Scheme 1). Treatment of the latter with lithium dimethylcuprate gave the corresponding chromanone **6** as the anticipated⁷ mixture of *cis*-keto, *trans*-keto and enol forms *via* conjugate addition. Cyclisation of **6** as an unresolved mixture



Scheme 1 Reagents and conditions: i, NaH, toluene, 40 min, then 2-FC₆H₄COCl, toluene, reflux, 72 h (72%); ii, Me₂CuLi, THF–Et₂O, –10 °C, 45 min (63%); iii, Mn(OAc)₃, Cu(OAc)₂, HOAc, 58 °C, 5 h (25%)

using manganese(III) acetate in the presence of copper(II) acetate⁸ gave several products (as judged by TLC and NMR spectroscopy), and a major component **8** was isolated in 25% yield by chromatography over silica gel. The constitution of **8** was established by spectroscopy, especially a ¹H–¹³C heteronuclear shift correlation NMR experiment, which suggested the presence of a new oxygenated quaternary carbon adjacent to the *gem*-dimethyl centre. The relative stereochemistry of **8** was confirmed by X-ray crystallography[‡] (Fig. 1) as that found in the natural products **1** and **2**, and is presumably the result of an initial 6-*endo-trig* cyclisation of the β -ketoester radical derived from **6**, leading to **7** which in the presence of copper(II) acetate undergoes further oxidation followed by lactonisation.⁸

A second approach to the desired ring system, potentially complementary to the first with respect to both the conjugate addition and the cyclisation steps, was also attempted (Scheme 2). Thus the iodide **9**¹⁰ was converted into a mixed cuprate reagent **10** using published techniques,¹¹ and the latter was treated with the chromone **11**⁶ to obtain the chromanone **12** as a mixture of diastereoisomers. Treatment of this mixture with

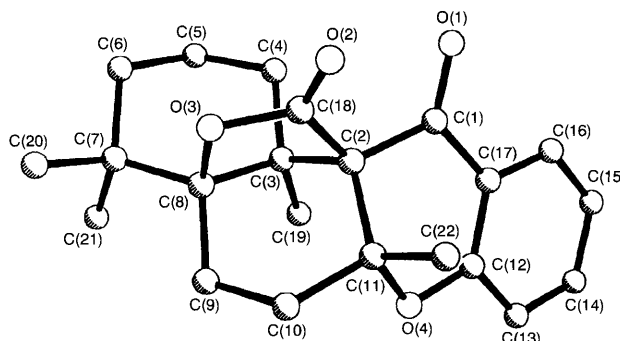
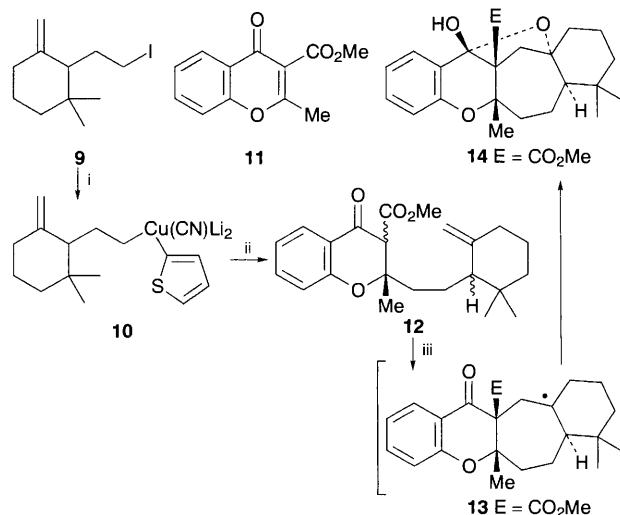


Fig. 1 X-Ray structure of **8**



Scheme 2 Reagents and conditions: i, Bu^tLi, Et₂O–pentane, –30 °C, 15 min, then 2-thienylCu(CN)Li, THF, –50 to –20 °C; ii, chromone **11**, Et₂O, –50 °C, 1 h (66% over 2 steps); iii, Mn(OAc)₃, HOAc, 65 °C, 3 h (30%)

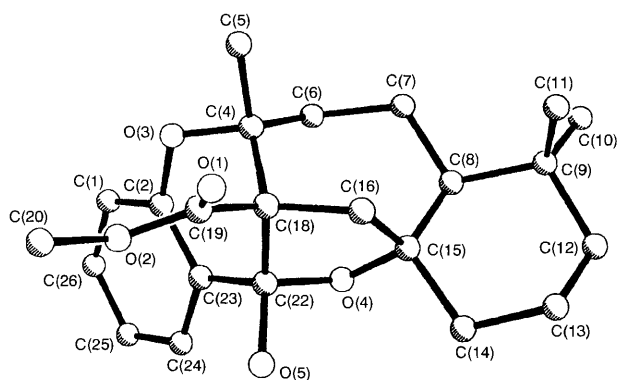


Fig. 2 X-Ray structure of **14**

manganese(III) acetate under anhydrous conditions⁹ gave a mixture which, after chromatography over silica gel, gave as a major product the crystalline hemiacetal **14**, whose structure was established by X-ray crystallography[‡] (Fig. 2) as that deriving from an initial *7-endo-trig* cyclisation to **13** of the presumed initially-formed β -ketoester radical.¹²

The transformation of the chromanone **6** into the lactone **8** is encouraging despite its low yield, since the overall sequence rapidly delivers the tetracyclic nucleus of **1** and **2**. Moreover, variation of the ester group in the intermediate **5** offers the opportunity to generate **6** diastereoselectively, and facilitate the lactonisation process which gives **8**. Experiments designed to explore these possibilities will be described in due course.

We are grateful to Robin Thompson (Salford) for helping with the X-ray diffraction studies, and Sean Lynn (Glaxo) for expert assistance with NMR spectra. We thank the SERC and Glaxo for funding under the CASE scheme.

Received, 29th November 1994; Com. 4/072971

Footnotes

[†] New compounds gave satisfactory spectroscopic and analytical data. Racemic materials were used for all synthetic work.

[‡] Crystal data for **8**: Colourless crystals from ethyl acetate: $C_{22}H_{26}O_4$, $M = 354.45$, monoclinic, $P2_1/c$, $a = 10.272(2)$, $b = 11.172(2)$, $c = 15.695(3)$ Å, $\beta = 95.23(2)^\circ$, $U = 1793.6(6)$ Å³, $Z = 4$, $D_c = 1.313$ g cm⁻³, λ (Mo-K α) = 0.71073 Å, $\mu = 0.83$ cm⁻¹, $F(000) = 760$, $T = 233$ K. Intensity data in the range $3 < 2\theta < 50^\circ$ were collected using a θ - 2θ scan technique on a Nicolet R3m/V diffractometer. The intensities of three reflections measured periodically showed no significant decrease over the data collection. A total of 3563 reflections were collected of which 3185 were independent, and 2118 for which $I > 2.0 \sigma(I)$ were used in the refinement. The structure was

solved by direct methods and refined using full-matrix least squares routines. Anisotropic thermal parameters were applied to all non-hydrogen atoms. The hydrogen atoms were placed in calculated positions and were refined isotropically using a riding model. At convergence $R = 5.20$ and $wR = 5.51\%$ ($R = 8.36\%$ and $wR = 5.99\%$ for all data), $w = [\sigma^2(F) + 0.0004F^2]^{-1}$, $S = 1.62$, $\Delta/\sigma < 0.001$. For **14**: Colourless crystals from petroleum ether (bp 60–80 °C): $C_{23}H_{30}O_5$, $M = 386.49$, orthorhombic, $P2_12_12_1$, $a = 8.130(3)$, $b = 13.108(3)$, $c = 18.407(6)$ Å, $U = 1961.6(11)$ Å³, $Z = 4$, $D_c = 1.309$ g cm⁻³, λ (Mo-K α) = 0.71073 Å, $\mu = 0.85$ cm⁻¹, $F(000) = 832$, $T = 233$ K. Intensity data in the range $3 < 2\theta < 50^\circ$ were collected using a θ - 2θ scan technique on a Nicolet R3m/V diffractometer. The intensities of three reflections measured periodically showed a decrease of less than 2% over the data collection. A total of 2027 reflections were collected of which 2005 were independent, and 1087 for which $I > 2.0 \sigma(I)$ were used in the refinement. The structure was solved by direct methods and refined using full-matrix least squares routines. Anisotropic thermal parameters were applied to all non-hydrogen atoms. The hydrogen atoms were placed in calculated positions and were refined isotropically using a riding model. At convergence $R = 5.84$ and $wR = 4.80\%$ ($R = 11.51\%$ and $wR = 5.89\%$ for all data), $w = [\sigma^2(F) + 0.0003F^2]^{-1}$, $S = 1.30$, $\Delta/\sigma < 0.001$. Calculations were performed using the SHELXTL-PLUS program package on a MICROVAX II. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Information for Authors, Issue No. 1.

References

- P. Djura, D. B. Stierle, B. Sullivan, D. J. Faulkner, E. Arnold and J. Clardy, *J. Org. Chem.*, 1980, **45**, 1435. See also J. Rodriguez, E. Quiñoa, R. Riguera, B. M. Peters, L. M. Abrell and P. Crews, *Tetrahedron*, 1992, **48**, 6667.
- M. T. Hamann and P. J. Scheuer, *Tetrahedron Lett.*, 1991, **32**, 5671.
- M. Kato, Y. Matsumura, K. Heima, N. Fukamiya, C. Kabuto and A. Yoshikoshi, *Tetrahedron*, 1987, **43**, 711, and references cited therein.
- J. D. White, R. W. Skeeane and G. L. Trammell, *J. Org. Chem.*, 1985, **50**, 1939.
- For the conversion of β -ionone into β -cyclocitral, see N. Müller and W. Hoffmann, *Synthesis*, 1975, 781.
- G. M. Coppola and R. W. Dodsworth, *Synthesis*, 1981, 523.
- S. T. Saengchantara and T. W. Wallace, *Tetrahedron*, 1990, **46**, 3029.
- For related reactions and mechanistic discussions, see S. A. Kates, M. A. Dombroski and B. B. Snider, *J. Org. Chem.*, 1990, **55**, 2427; D. P. Curran, T. M. Morgan, C. E. Schwartz, B. B. Snider and M. A. Dombroski, *J. Am. Chem. Soc.*, 1991, **113**, 6607; M. I. Colombo, S. Signorella, M. P. Mischne, M. Gonzalez-Sierra and E. A. Ruveda, *Tetrahedron*, 1990, **46**, 4149. For a pertinent review, see G. G. Melikyan, *Synthesis*, 1993, 833.
- P. Breuilles and D. Uguen, *Bull. Soc. Chim. Fr.*, 1988, 705, and references cited therein.
- M. J. Kurth and C. J. Soares, *Tetrahedron Lett.*, 1987, **28**, 1031; T. Eicher, K. Massonne and M. Herrmann, *Synthesis*, 1991, 1173.
- For a description and discussion of the methodology, see D. S. Dodd and A. C. Oehlschlager, *J. Org. Chem.*, 1992, **57**, 2794, and references cited therein.
- For a similar cyclisation, see A. K. Ghosh, K. Ghosh, S. Pal and U. R. Chatak, *J. Chem. Soc., Chem. Commun.*, 1993, 809; 1176.