Synthetic Studies on Quassinoids: Construction of the BCE Ring System of Quassimarin and Related Natural Products

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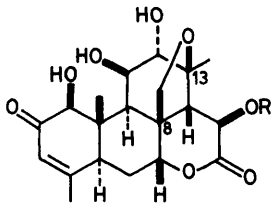
The synthesis of the tricyclic BCE ring system (**3**) of quassimarin possessing seven contiguous stereocentres has been realized *via* a novel epoxymethano bridging reaction.

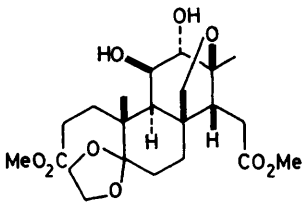
Quassimarin (**1**)[1] and related quassinoids [*cf.* simalikalactone D (**2**)[2]] continue to attract considerable attention[3] among synthetic organic chemists due to their intriguing, highly oxygenated pentacyclic ring system and, to a lesser extent, their potent cytotoxic properties. Our efforts in this area have focussed on construction of a suitable BCE ring system possessing all of the necessary functionality and stereochemistry for elaboration into quassimarin. In this regard we detail below the synthesis of diol (**3**).

Our approach (Scheme 1) commences with the known octalone (**4**) which represents rings B and C of quassimarin. Alkylation of (**4**) with allyl bromide gave rise to ketone (**5**)



(1) R = COC(OAc)(Me)Et

(2) R = COCH(Me)Et



(3)

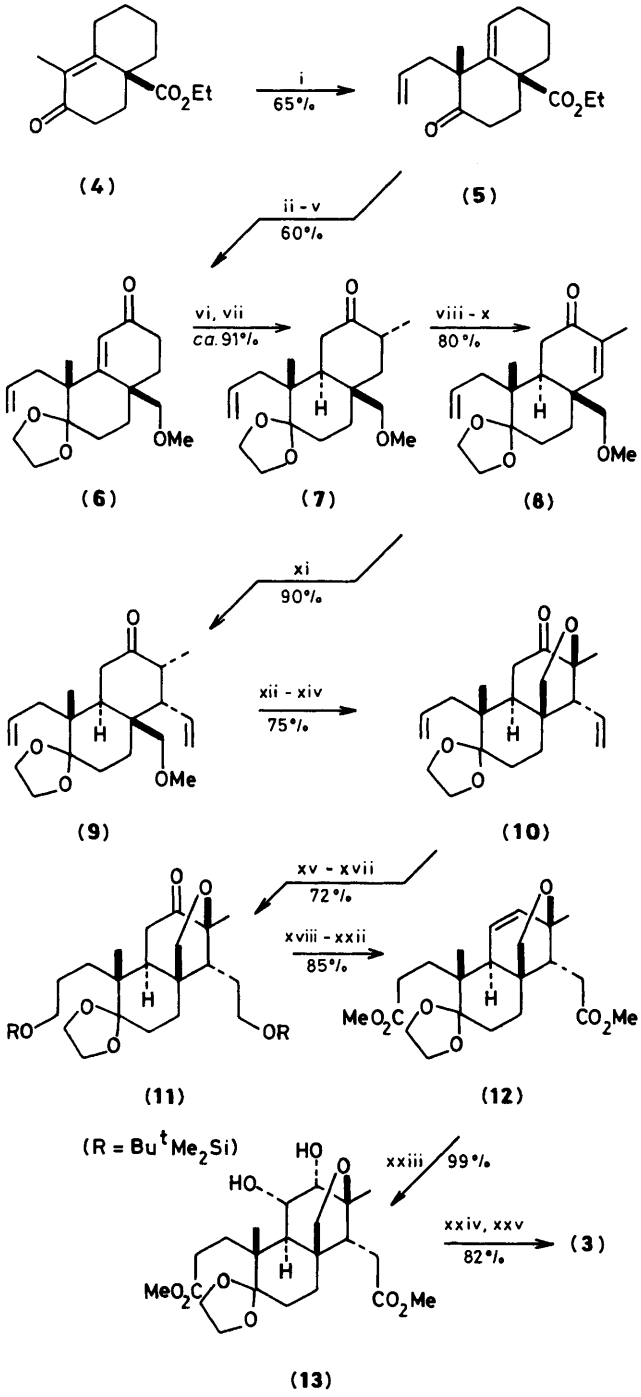
possessing the proper configuration at the newly created stereocentre (*vide infra*). This result stands in contrast to work by McQuillin[4] who previously demonstrated that alkylation of (**4**) and related systems possessing polar axial substituents at the angular position (*e.g.* methoxycarbonyl, cyano) results in β-alkylation. For example, alkylation of the sodium enolate of (**4**) with chloromethyl benzyl ether in dioxane affords an 8:1 mixture of α-benzyloxymethyl derivatives (A) and (B).[4]

Acetalization of (**5**) and subsequent reduction of the ethoxycarbonyl group followed by protection of the resultant alcohol as its methyl ether provided the corresponding octalin which upon subjection to allylic oxidation gave way to octalone (**6**), m.p. 68.0—69.5 °C, in 60% overall yield. The transformation of (**6**) into decalone (**7**) m.p. 78—79 °C, which establishes the *trans* relationship between rings B and C, was readily accomplished in *ca.* 91% yield by alkylation and subsequent Birch reduction. Introduction of a double bond into decalone (**7**) [*cf.* octalone (**8**), m.p. 47.5—49.0 °C] was achieved *via* selenenylation of the thermodynamic trimethylsilylenol ether followed by oxidation and loss of benzeneselenenic acid.

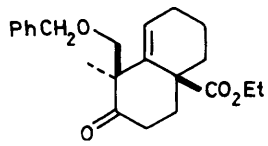
Octalone (**8**) represents a viable intermediate for incorporation of the axial acetic acid unit located at C(14) of quassimarin *via* Michael addition. It was anticipated that addition of a nucleophile to enone (**8**) would take place from the alpha face of the molecule. Treatment of (**8**) with equimolar amounts of copper(I) iodide and vinyl-lithium, and 2.5 equiv. of tri-n-butylphosphine[5] in diethyl ether provided decalone (**9**) in 90% yield. Elaboration of the C(8), C(13) epoxymethano bridge of quassimarin was achieved employing a novel reaction. Heating of the bromide (C) derived from decalone (**9**) (Scheme 1) at 140 °C for 20 min in dimethylformamide (DMF) provided crystalline tricyclic ketone (**10**), m.p. 176—178 °C, in 90% yield. The structure of (**10**) was unambiguously established by a single crystal *X*-ray analysis.

With the availability of tricyclic ketone (**10**), we focussed our efforts on incorporating the C(11), C(12) *trans* diaxial vicinal diol unit into ring C. Toward this end, decalone (**10**) was smoothly transformed (72%) into crystalline ketone (**11**) m.p. 69.5—70.0 °C. The tosylhydrazone derived from ketone (**11**) upon treatment with an excess of methyl-lithium and subsequent desilylation provided the corresponding diol, m.p. 123.5—124.5 °C, which was oxidized to diester (**12**), m.p. 92.5—94.0 °C, in 85% overall yield. Exposure of olefin (**12**) to osmium tetroxide in pyridine generated after work-up with sodium hydrogen sulphite a near quantitative yield of *cis*-diol (**13**), m.p. 138.5—139.0 °C. Selective oxidation[6] of the equatorial hydroxy group gave rise to the corresponding ketone which upon reduction afforded exclusively the bicyclic BCE ring system (**3**), m.p. 171.5—173.0 °C, of quassimarin in 82% overall yield.

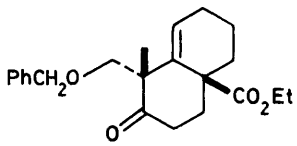
The BCE tricyclic diol (**3**) possesses seven of the twelve stereocentres present in quassimarin. Studies to transform (**3**) into (**1**) and/or (**2**) are currently in progress.



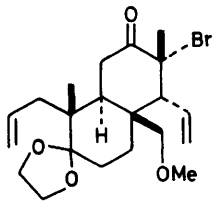
Scheme 1. Synthesis of the BCE ring system (**3**) of quassimarin. *Reagents:* i, NaH, Me_2SO, $CH_2{=}CHCH_2Br$; ii, diethylene glycol, *p*-TsOH (Ts = tosyl), C_6H_6, reflux; iii, $LiAlH_4$, Et_2O; iv, NaH, tetrahydrofuran (THF), MeI; v, $CrO_3{\cdot}2$pyridine (py), CH_2Cl_2, 24 h; vi, Lithium di-isopropylamide, THF, hexamethylphosphoramide, MeI, −78 → 0 °C; vii, Li, NH_3, Bu^tOH, −78 °C; viii, Me_3SiI, hexamethyldisilazane (HMDS), C_5H_{12}; ix, PhSeCl, C_6H_6, 0 °C; x, 30% H_2O_2, py, CH_2Cl_2; xi, CuI, $CH_2{=}CHLi$, Bu^n_3P, Et_2O, −78 °C→ 25 °C; xii, Me_3SiI, HMDS, C_5H_{12}; xiii, *N*-bromosuccinimide, THF, −23 °C; xiv, DMF, reflux, 20 min; xv, B_2H_6, THF; 30% H_2O_2; xvi, Bu^tMe_2SiCl, 4-*N*,*N*-dimethylaminopyridine, Et_3N, CH_2Cl_2; xvii, $CrO_3{\cdot}2$py, CH_2Cl_2; xviii, $TsNHNH_2$, HCl, THF; MeLi (excess), THF; xix, Bu^n_4NF, THF; xx, $(COCl)_2$, Me_2SO, Pr^i_2NEt, CH_2Cl_2; xxi, Ag_2O, 1 M NaOH, EtOH; xxii, CH_2N_2, EtOAc; xxiii, OsO_4, py; xxiv, $(COCl)_2$, Me_2SO, Pr^i_2NEt, CH_2Cl_2, −78 °C; xxv, $NaBH_4$, MeOH.



(A)



(B)



(C)

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