Synthetic Studies on Quassimarin: Construction of the Pentacyclic Carbon Skeleton

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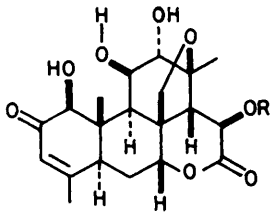
The synthesis of the pentacyclic ABCDE ring system (**3**), which constitutes the farthest advance toward the elaboration of quassimarin and related quassinoids, has been realized employing a metal–ammonia reduction of a dienone *cf.* (**11**) → (**12**).

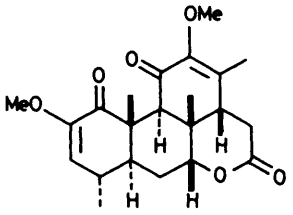
Quassinoids continue to occupy the attention of synthetic organic chemists.[1] However, despite the efforts of numerous synthetic groups worldwide, the total synthesis of these highly oxygenated, cytotoxic substances [*cf.* quassimarin (**1**)] has been recorded on only two previous occasions.[2] Seven years have now lapsed since the total synthesis of quassin (**2**) was communicated.[2a]

Our efforts in the quassinoid area have focused on the elaboration of a pentacyclic ring system suitable for transformation into quassimarin and related quassinoids.[3] In this communication we detail the synthesis of the pentacyclic lactone (**3**) possessing nine of the eleven stereocentres found on the carbocyclic framework of (**1**). The synthesis of (**3**) constitutes the farthest advance reported to date in the quassinoid area.

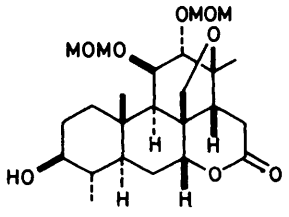
We have previously described the synthesis of the BCE tricyclic diester (**4**)[4] which constitutes a useful starting point for the preparation of (**3**). The two ester units in (**4**) can be readily differentiated (Scheme 1) by regiospecific lactone formation employing anhydrous toluene-*p*-sulphonic acid in refluxing benzene. Lactonization, which provided (**5**), m.p. 180.0—181.5 °C, proceeded smoothly in high yield with no trace of bislactone (**14**) being detected. Protection of the C-11 (steroid numbering) axial hydroxy group in (**5**) as a methoxy-



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

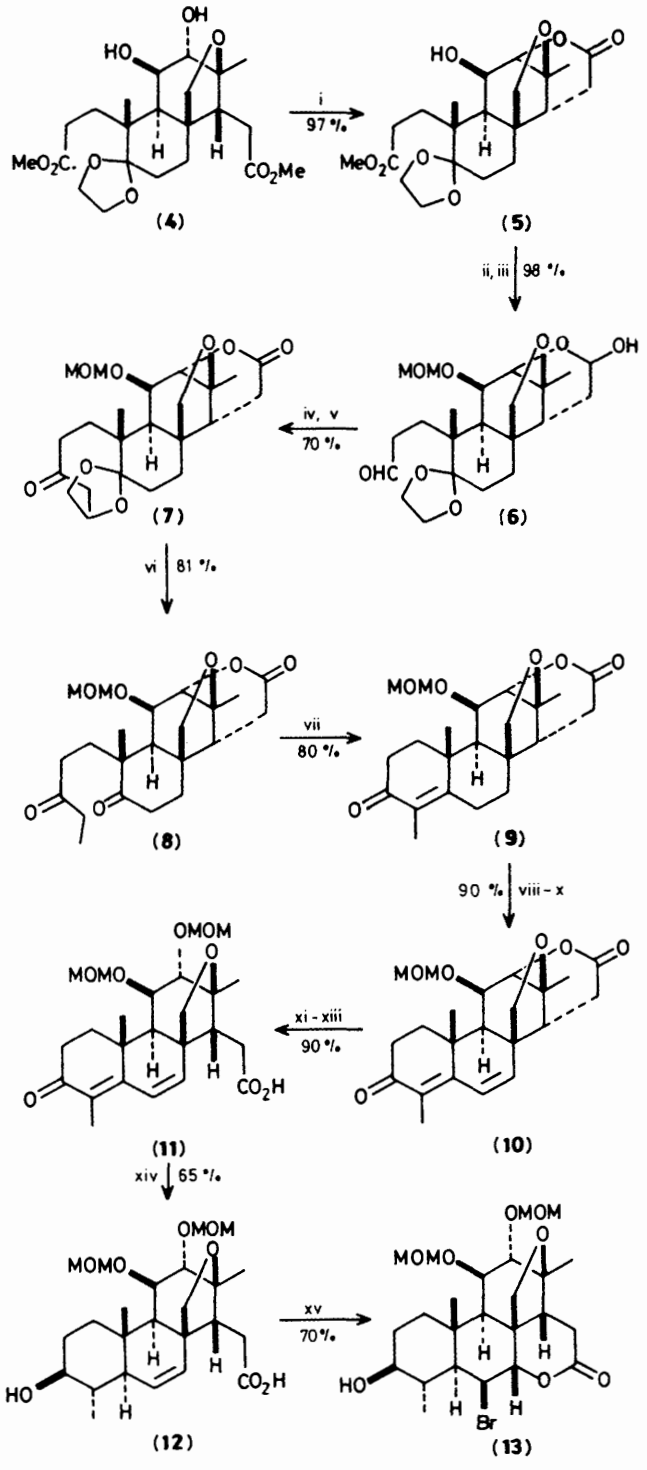


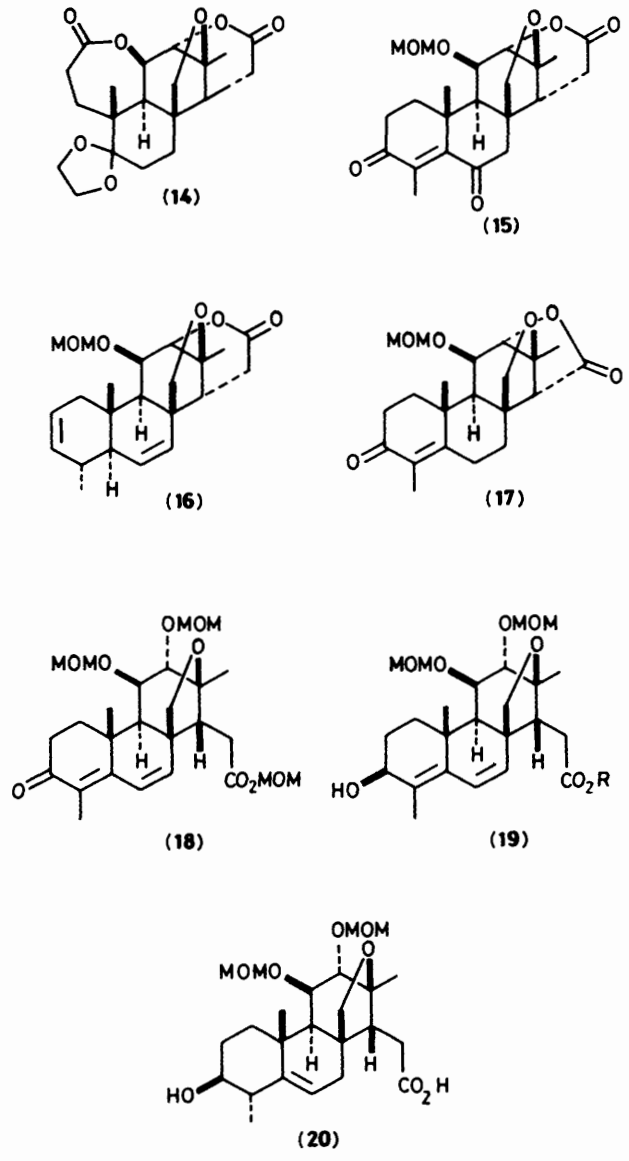
(**2**)



(**3**)

MOM = methoxymethyl





Scheme 1. Synthesis of the ABCDE ring system (**13**) of quassimarin. *Reagents and conditions:* i, *p*-TsOH (Ts = tosyl), C_6H_6, reflux, 1 h; ii, MOMCl, Pr^i_2NEt, CH_2Cl_2, 40—45 °C, 72 h; iii, Bu^i_2AlH, toluene, −78 °C, 1.5 h; iv, EtMeBr, tetrahydrofuran (THF), −78 °C (40 min) → 0 °C (40 min); v, CrO_3·2 pyridine, CH_2Cl_2, 1 h; vi, *p*-TsOH, acetone, $CaCl_2$, 72 h; vii, $KOBu^t$, toluene, 0 °C, 1 h; TsOH, acetone, $CaCl_2$, 5.5 h; viii, Me_3SiI, HMDS, C_5H_{12}, 0 °C, 1.5 h; ix, *N*-bromosuccinimide, THF, −78 °C (10 min) → 0 °C (20 min); x, DBU, THF, 30 min; xi, 1 M NaOH, MeOH, 16 h; xii, MOMCl, Pr^i_2NEt, CH_2Cl_2, 40 °C, 72 h; xiii, 1 M NaOH, MeOH, 16 h; xiv, NH_4Cl, NH_3, THF, Li; xv, Me_3CCO_2Tl, Br_2, CH_2Cl_2, 30 min.

methyl ether followed by reduction with di-isobutylaluminium hydride in toluene provided the sensitive aldehyde–lactol (**6**) in near quantitative yield. Addition of ethyl magnesium bromide to aldehyde (**6**) and subsequent Collins oxidation afforded keto lactone (**7**) in 70% overall yield. Deacetalization of (**7**), which was conducted in acetone containing a trace of toluene-*p*-sulphonic acid, generated crystalline dione (**8**), m.p. 138.5—139.0 °C, which set the stage for an aldol condensation with formation of an ABCDE pentacyclic intermediate. Exposure of dione (**8**) to potassium t-butoxide in toluene at 0 °C followed by dehydration of the resulting aldol with toluene-*p*-sulphonic acid in acetone containing calcium chloride provided the pentacyclic enone (**9**), m.p. 172—174 °C.

With enone (**9**) available, our studies focused on elaboration of the δ-lactone present in pentacyclic intermediate (**3**). Efforts to transform enone (**9**) into enedione (**15**) and eventually diene (**16**), which would set the stage for a halogenolactonization, met with no success despite ample precedent in the literature for the conversion of enones to enediones. For example, it is well known[5] that exposure of cholestenone to copper(II) salts in methanol containing pyridine and triethylamine under an atmosphere of oxygen

gives rise to a 75% yield of Δ^4-cholesta-3,6-diene. In our hands, treatment of (**9**) with 1.5 equiv. of copper(II) acetate monohydrate in methanol containing pyridine and Hunig's base under an atmosphere of oxygen for 40 h gave rise to the crystalline ring contracted γ-lactone (**17**), m.p. 194—195 °C, as the sole product in 85% yield.[6] The structure assigned to (**17**) was unambiguously established by single-crystal *X*-ray analysis.†

Once again our efforts were directed at elaboration of the ring D δ-lactone. Introduction of a double bond at C-6 and C-7 in (**9**) would provide dienone (**10**) which offers several avenues for the construction of the desired lactone unit. Toward this end, enone (**9**) was treated with trimethylsilyliodide and hexamethyldisilazane (HMDS) in pentane[7] giving rise to the thermodynamically stable silyl dienol ether. Bromination with *N*-bromosuccinimide in tetrahydrofuran followed by dehydrobromination with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) afforded (**10**) in 90% overall yield. Attempts to hydrolyse the lactone unit in (**10**) with protection of the resultant C-12 axial alcohol as its methoxymethyl ether gave rise to only traces of the desired carboxylic acid (**11**). The major product (*ca.* 50%) was the tetracyclic ester (**18**). The formation of (**18**) is difficult to avoid since alkylation of the carboxylate is faster than alkylation of the severely hindered C-12 axial hydroxy group. This problem was readily circumvented by treatment of the resultant hydroxy acid with excess of chloromethyl methyl ether (MOMCl) and Hunig's base in methylene chloride which provided (**18**) in 90% overall yield. Hydrolysis with 1 M sodium hydroxide in methanol afforded a near quantitative yield of (**11**).

Compound (**11**) offers numerous possibilities for construction of a δ-lactone at C-7. Several attempts were made to effect Michael addition of the carboxy to the dienone unit, however, these efforts were uniformly unsuccessful. Similarly disappointing were attempts to bring about a solvolytic-like ring closure employing aqueous and anhydrous acid on alcohol (**19**).

In order to overcome the difficulties encountered above, we turned our attention to the regioselective reduction of the $\Delta^{4,5}$ double bond in dienone (**11**).[8] Much to our surprise reduction of (**11**) in ammonia–THF (16:1) containing 110 equiv. of ammonium chloride with 100 equiv. of lithium (slow addition over 1 h) afforded tetracyclic alkene (**12**) in 65% yield contaminated with only a few percent of the undesired $\Delta^{5,6}$-isomer (**20**).

In practice one need not separate (**12**) and (**20**) since in the subsequent halogenolactonization step (**20**) is not expected to react. Indeed treatment of (**12**) with thallium pivalate[9] and bromine in methylene chloride provided in 70% yield bromolactone (**13**), m.p. 192—194 °C. The structure of (**13**) was unambiguously established by single-crystal *X*-ray analysis.† Debromination (Bu_3SnH, toluene, azoisobutyronitrile, 55 °C) of (**13**) gave rise to the pentacyclic compound (**3**) in 95% yield.

The ABCDE pentacyclic alcohol (**3**) represents a useful precursor to a number of naturally occurring quassinoids.

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† *Crystal data:* (**13**) $C_{24}H_{37}O_8Br$, M = 533.46, monoclinic, space group $P2_1/a$, a = 14.241(5), b = 24.648(13), c = 6.924(2) Å, β = 100.60(2)°, U = 2388.76 Å^3; D_c = 1.483 g cm^{-3}, Z = 4, Mo-K_α radiation, 3805 data collected, 3149 unique, $6° < 2\theta < 45°$, R = 0.0848, R_w = 0.0806. (**17**), $C_{21}H_{28}O_6$, M = 376.45, orthorhombic, space group $Pcab$, a = 32.301(21), b = 12.090(5), c = 9.448(4) Å, U = 3689.54 g cm^{-3}, D_c = 1.355, Z = 8, Mo-K_α radiation. 2910 data collected, 2431 unique, $6° < 2\theta < 45°$, R = 0.0646, R_w = 0.0619.

Atomic co-ordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

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