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The Oxidative Ring Expansion of Spiro-annulated Chroman-4-ones: Syntheses of the Rotenoid Core and Related Benzoxanthones

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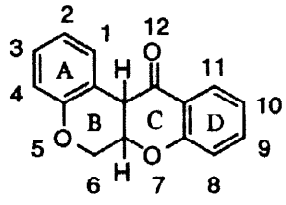
Abstract: Syntheses of dehydrorotenoid and benzoxanthone units from 2'-hydroxyacetophenone are described which feature a novel migration of spiro-substituted chroman-4-ones during their oxidative ring expansion. Conjugate reduction affords a *trans* B/C fused rotenoid and the related *cis* and *trans* fused tetrahydrobenzoxanthones.

INTRODUCTION

The tetracyclic unit, *cis*-6a,12a-dihydro-6*H*,12*H*-[1]benzopyrano[3,4-*b*][1]benzopyran-12-one **1**, is the key structural feature of the class of tropical plant products known as the rotenoids.[1] The principal active component of this class, rotenone **2**, contains an additional furan ring.[2] The rotenoids possess a wealth of pharmacological properties including insecticidal,[3] antifeedant,[4] piscicidal[5] and antiviral activity.[6]



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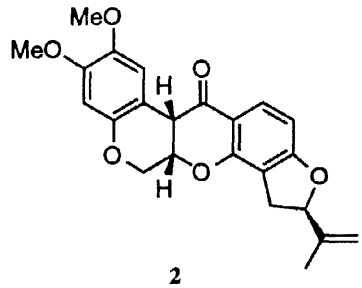

2

A number of synthetic strategies have been used to construct the rotenoid system including the use of Hoesch condensations,[7] thermal condensation of 4-ethoxycarbonylchroman-3-ones with activated phenols,[8] reaction of isoflavones with dimethylsulfoxonium methylide,[9] Claisen rearrangment of prop-2-ynyl ethers,[10] aroylation of 4-lithiochromenes,[11] enamines[12] and 4-phenylsulfonylchromans,[13] intramolecular radical cyclisations[14a,b] and combined Wadsworth-Emmons - Mukaiyama aldol methodologies.[15] We now describe syntheses of the tetracyclic rotenoid core and some carbon isosteres. The key step of this route bears a close relationship to the biosynthesis of the rotenoid system, which has been shown to proceed by a 1,2-aryl migration of the A ring from C-6a to C-12a of the final product.[16]

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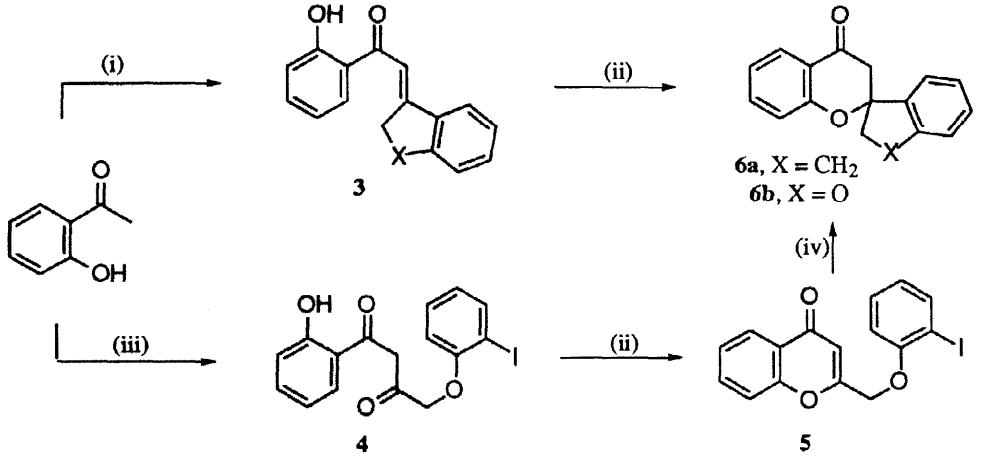
DISCUSSION

Condensation of 2'-hydroxyacetophenone with 1-indanone according to the general procedure described by Kabbe[17] unexpectedly gave the chalcone **3** (X = CH_2) in moderate yield. Ring closure to the spirocycle **6a** was accomplished by refluxing **3** (X = CH_2) in acetic acid containing HCl (Scheme 1). The heterocycle was characterised by its ^1H NMR spectrum which exhibited an AB system for H-3 (δ 2.9, 3.2; *J* 16.5 Hz) and a chemical shift of δ 8.0 for H-5, typical of chroman-4-ones. The presence of a low field signal at δ 192.5 for C-4 in the ^{13}C NMR is another feature associated with chroman-4-ones.[18]



Reagents and conditions: (i) cyclic ketone, pyrrolidine, PhMe, Δ; (ii) c.HCl, AcOH, Δ; (iii) 2-$IC_6H_4OCH_2CO_2Et$, NaH, THF, Δ; (iv) AIBN, nBu_3SnH, PhH, N_2, Δ.

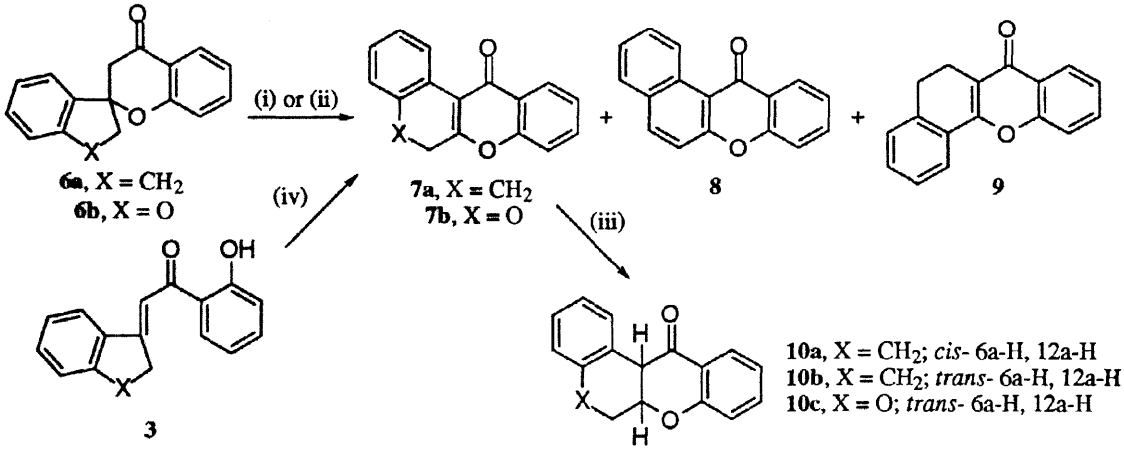
Scheme 1

In our hands, the Kabbe reaction of 2'-hydroxyacetophenone with 2,3-dihydrobenzofuran-3-one failed to give any of the desired spirocycle **6b** despite the reported success of this reaction[19] and instead the starting materials were recovered. Our alternative approach to **6b** relied upon the Claisen condensation of 2'-hydroxyacetophenone with ethyl (2-iodophenoxy)acetate to afford the β-diketone **4**. Acid-catalysed cyclisation of **4** proceeded smoothly to the 2-(2-iodophenoxymethyl)chromone **5** in an overall yield of 60%. This new route represents a significant improvement over the current literature protocol.[14a] The ^1H NMR spectrum of the chromone displayed the typical low field signal for H-5 at δ 8.1 and a singlet at δ 6.6 (H-3). Intramolecular radical cyclisation of **5**[20] proceeded by a kinetically favoured 5-*exo-trig* closure to afford the spirocycle **6b** in 72% yield (Scheme 1). The ^1H NMR spectrum of this compound exhibited similarities to the carbon isostere **6a**, showing an AB system for H-3 (δ 3.1, 3.4; *J* 16.6 Hz) and also for H-2' (δ 4.4, 4.8; *J* 10.8 Hz), whilst H-5 again resonates at δ 8.0.

The key step of this rotenoid synthesis is the hypervalent iodine-promoted[21] oxidative ring expansion of the spirocycles **6a** and **6b** to the benzoxanthones **7a**, **8** and **9** and the dehydrorotenoid **7b**, respectively. The conversion of 2-phenylchromanones (flavanones) to 3-phenylchromones (isoflavones) by an oxidative 1,2-phenyl migration promoted by [hydroxy(tosyloxy)-iodo]benzene (HTIB) has been reported,[22] as has the ring expansion of the cyclopentane unit of spiro[chroman-2,1'-cyclopentan]-4-one to afford a tetrahydroxanthone using HTIB and ultrasound.[23] Heating a solution of **6a** in acetonitrile containing HTIB and 4-TsOH under sonication gave a three component mixture[24] comprising **7a** (14%), resulting from an aryl migration, the benzo[*a*]xanthone **8** (20%)[25] from an aryl migration and subsequent aromatisation and **9** (24%) resulting from an

alkyl migration (Scheme 2). When the procedure was applied to the oxygen analogue **6b** but without sonication, the dehydrorotenoid **7b** was obtained *via* a regiospecific phenyl migration and was accompanied by the chalcone **3** (X = O). This rearrangement constitutes the first example of aryl migration involving a spiro-linked benzo-fused heterocyclic system. The *E*-geometry of **3** (X = O) was determined by NOESY experiments which showed a significant interaction between H-6' and the methylene protons. The ^{1}H NMR spectrum of **7b** shows distinct low field double doublets at δ 8.36 (H-11) and δ 8.82 (H-1) in accord with a planar array.

A two step sequence utilising a thallium (III) nitrate (TTN)-promoted rearrangement and subsequent acid catalysed ring closure has been advocated for the conversion of 2'-hydroxychalcones to isoflavones.[26] Whilst treatment of a methanolic solution of **3** (X = O) with TTN failed to give any of **7b** even after prolonged heating, application of this methodology to chalcone **3** (X = CH_2) afforded the dihydroxanthone **7a** exclusively in a single step in 62% yield. Thus, the oxidative aryl migration is now completely regiospecific.



Reagents and conditions: (i) HTIB, 4-TsOH, MeCN, ultrasound, Δ; (ii) HTIB, 4-TsOH, MeCN, Δ; (iii) DIBAL, THF, -70°C - RT, N_2; (iv) $Tl(NO_3)_3.3H_2O$, MeOH, RT.

Scheme 2

The conjugate reduction of the dehydrorotenoid **7b** was accomplished using diisobutylaluminium hydride (DIBAL) and gave exclusively the unnatural *trans B/C* fused rotenoid **10c**.[27] The spectroscopic data for this compound are in full agreement with those reported by Crombie *et al.*[28] Application of an identical reductive protocol to the carbon analogue **7a** gave the *trans*- (54%) and *cis*- (20%) fused tetrahydrobenzo[*a*]xanthones **10b** and **10a**, respectively, after separation by flash chromatography. The geometry of the ring fusion is clearly evident from ^{1}H NMR spectroscopy, which reveals that H-12a resonates as a doublet at δ 4.09 (J = 12.5 Hz) for **10b** and at δ 3.91 (J = 3.5 Hz) for **10a**.

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