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Studies on the reactivity of a tertiary allylic alcohol in an acetophenonic series, a model for natural products synthesis

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Abstract

The synthesis of benzopyranic simplified analogues of dibenzopyranic natural compounds is described, together with the access to a precursor of a new furobenzopyranic natural product. These natural products have anti-cancer activity. The 1,3-diacetoxy-2-acetyl-4-(3-hydroxy-3-methylbut-1-enyl)benzene synthone is used as a common precursor to these structures.

Introduction

As part of our work on natural product isolation, diverse coumarinic coumpounds were isolated from *Calophyllum dispar*. Among these structures, a known dipyranobenzenic (**1**) and a new furobenzopyranic (**2**) molecule were characterized (Figure 1) and demonstrated weak activity against N6 non small-cell lung cancer strain (Guilet 2000). Coumarins are widely spread in nature and are known to be responsible for a variety of biological and clinical actions (O'Kennedy & Thornes 1997).

We recently described photo-oxygenation as a straighforward access to *ortho*-(2-hydroxy-3-methylbut-3-enyl)phenols without the need of any phenolic protecting group by using the diphenolic compound **3** (Helesbeux et al 2000). The reduction of the Schenk-ene reaction products, **4** and **5**, conducted at low temperature, yields secondary (**6**) and tertiary (**7**) alcohols (Figure 2). Attempt to separate this ultimate mixture, over silica gel, leads to the isolation of **6** and a very small amount of **7**, along with the benzopyranic compound **8**.

A 2-(3-hydroxy-3-methylbut-1-enyl)phenol pattern could represent a key intermediate for the synthesis of both pyrano (**1**) and furano (**2**) derivatives. Therefore, we first decided to focus our work on improving the pathway leading to this type of compound.

Materials and Methods

NMR spectra were recorded on Jeol GSX WB 270 MHz and Bruker Avance DRX 500 MHz instruments using tetramethylsilane as the internal standard.

1,3-Diacetoxy-2-acetyl-4-(3-hydroxy-3-methylbut-1-enyl)benzene (13)

Dried air was bubbled through a solution of diacetate **9** (764 mg, 2.51 mmol) in acetone (150 mL) containing haematoporphyrin (10 mg, 0.017 mmol). The reaction

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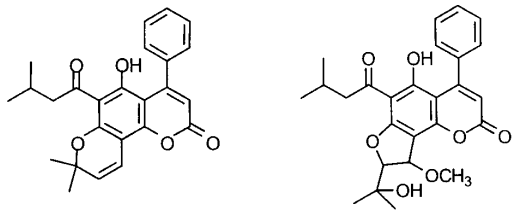

Figure 1 Dipyranobenzenic (**1**) and furobenzopyranic (**2**) coumarins isolated from *Calophyllum dispar*.

mixture was water-cooled at 15°C and irradiated with a halogen lamp (500 W) for 3 h. After evaporation, the residue was chromatographed over silica gel, eluted with a cyclohexane–ethyl acetate mixture (70:30), to give **10** and **11** (Figure 3). The mixture was introduced into a 100-mL flask containing a solution of dichloromethane (30 mL) and 292 mg of triphenylphosphine (1.1 mmol). The solution was stirred overnight. The residue after evaporation was chromatographed over silica gel (dichloromethane–acetone, 90:10) to yield 260 mg of the amorphous mass **13**. The overall yield was 32%. ^{1}H NMR ($CDCl_3$) δ 1.41 (6H, 2s, 2 CCH_3), 2.29, 2.30 (6H, 2s, 2 OCOCH_3), 2.46 (3H, s, COCH_3), 6.33 (1H, d, C*H*=CH, J = 16.2 Hz), 6.56 (1H, d, CH=C*H*, J = 16.2 Hz), 7.07 (1H, d, CH=C*H*, J = 8.6 Hz), 7.57 (1H, d, CH=C*H*, J = 8.6 Hz).

8-Acetyl-7-hydroxy-2,2-dimethyl-2*H*[1]benzopyran (14)

To a solution of 20 mg of **13** in 1.5 mL methanol and 0.75 mL water was added 0.75 mL of saturated sodium hydrogen carbonate solution. After one hour stirring, the solution was neutralized with 1N hydrochloride solution, extracted with ethyl acetate, dried and evapo-

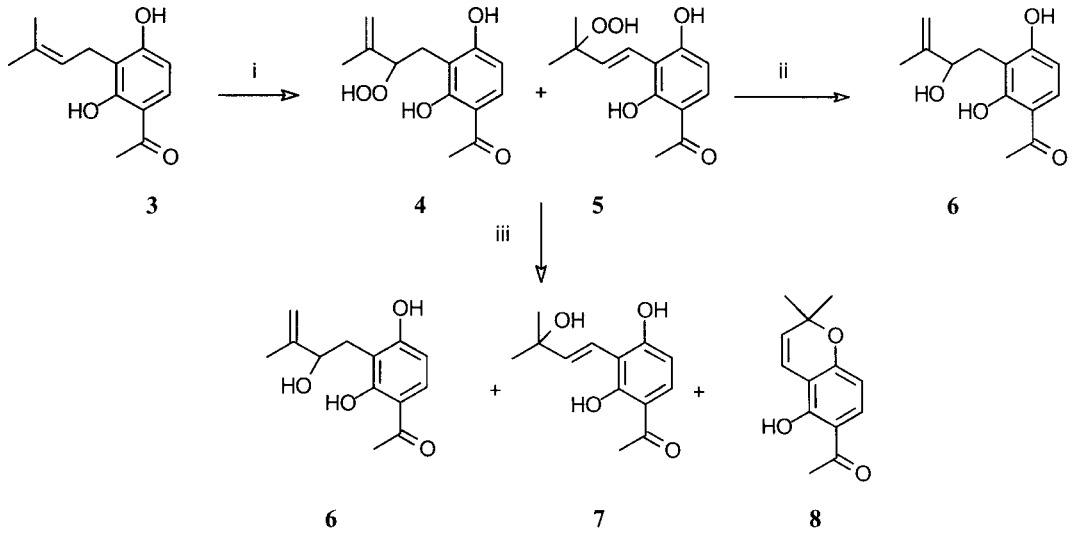

Figure 2 Synthesis of secondary (**6**) and tertiary (**7**) alcohols and benzopyranic compound (**8**). Reagents: i, TPP, CH_2Cl_2, O_2, −30°C, hν; ii, PPh_3, CH_2Cl_2, RT; iii, PPh_3, CH_2Cl_2, −30°C, liquid chromatography.

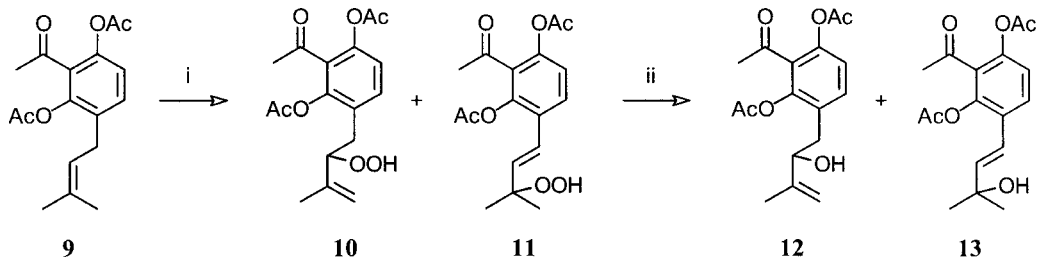

Figure 3 Synthesis of diphenolic secondary (**12**) and tertiary (**13**) allylic alcohol diacetate derivatives. Reagents: i, TPP, CH_2Cl_2, O_2, 15°C, hν; ii, PPh_3, CH_2Cl_2, liquid chromatography.

rated. The residue was subjected to TLC (cyclohexane–ethyl acetate, 80:20) to yield 8 mg of the amorphous mass **14**. ^{1}H NMR ($CDCl_3$) δ 1.52 (6H, s, 2 CCH_3), 2.73 (3H, s, COCH_3), 5.48 (1H, d, CH=CH, J = 9.9 Hz), 6.25 (1H, d, CH=CH, J = 9.9 Hz), 6.46 (1H, d, CH=CH, J = 8.0 Hz), 7.06 (1H, d, CH=CH, J = 8.0 Hz), 13.05 (1H, OH).

1,3-Diacetoxy-2-acetyl-4-(1,2-epoxy-3-hydroxy-3-methylbutyl)-benzene (15)

Compound **13** (29 mg; 0.09 mmol) and *meta*-chloroperbenzoic acid (5 mol equiv) were stirred at room temperature for 2 h, in dry dichloromethane (8 mL). The solution was then washed successively with 10% aqueous sodium sulphite (2 × 10 mL) and 5% aqueous sodium hydrogen carbonate solution (2 × 10 mL). After evaporation, the residue was chromatographed on a silica column (chloroform–ethyl acetate, 70:30) to yield 23 mg of the amorphous mass **15** (76% yield). ^{1}H NMR ($CDCl_3$) δ 1.36, 1.49 (6H, 2s, 2 CCH_3), 2.30, 2.31 (6H, 2s, 2 OCOCH_3), 2.47 (3H, s, COCH_3), 2.87 (1H, d, CH-CH, J = 2.2 Hz), 3.97 (1H, d, CH-CH, J = 2.2 Hz), 7.09 (1H, d, CH=CH, J = 8.6 Hz), 7.37 (1H, d, CH=CH, J = 8.6 Hz).

1,3-Dihydroxy-2-acetyl-4-(2-acetoxy-3-hydroxy-1-methoxy-3-methyl-but-1-enyl)-benzene (17)

Activated zinc (5 mg) was added to 30 mg of **15** in 4 mL dry methanol and 4 mL dichloromethane. The suspension was stirred for 72 h. The zinc was filtered through celite and washed with methanol. The solvents were then evaporated under reduced pressure. The residue was subjected to TLC (dichloromethane–ethyl acetate, 65:35) to yield 9 mg of **17** (32% yield), mp 160–162°C. ^{1}H NMR ($CDCl_3$) δ 1.20, 1.41 (6H, 2s, 2 CCH_3), 1.98 (3H, s, OCOCH_3), 2.70 (3H, s, COCH_3), 3.38 (3H, s, OCH_3), 5.00 (1H, broad s, H_3COCH), 4.98 (1H, d, CH-OCOCH$_3$, J = 2.9 Hz), 6.47 (1H, d, CH=CH, J = 8.5 Hz), 7.13 (1H, d, CH=CH, J = 8.5 Hz), 11.2 (1H, OH) ; ^{13}C NMR δ 20.5 (OCOCH$_3$), 26.8 (CH$_3$), 27.7 (CH$_3$), 33.5 (COCH$_3$), 57.1 (OCH$_3$), 72.7 (CHOH), 78.3 (CHOCOCH$_3$), 80.7 (CHOCH$_3$), 108.0 (CH=C), 110.9 (CH=C), 111.2 (C=C), 134.9 (CH=C), 160.2 (HO-C=C), 162.3 (HO-C=C), 170.1 (C=O), 205.5 (C=O).

Results and Discussion

Different works on coumarins have shown that the protection of the phenolic groups could greatly improve the yield of tertiary allylic alcohol (Fourrey et al 1970; Murray & Forbes 1978; Ito & Furukawa 1989; Murray & Zeghdi 1989; Ito et al 1991). The diphenolic secondary (**12**) and tertiary (**13**) allylic alcohol diacetate derivatives are obtained from **9** (Jain et al 1970) in an overall good yield and in a ratio of 1:2 (Figure 3).

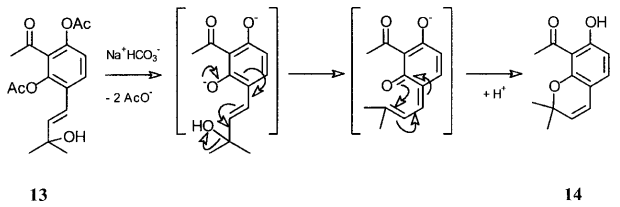

Figure 4 Synthesis of the 8-acetyl-7-hydroxy-2,2-dimethyl-2*H*[1]-benzopyran **14**.

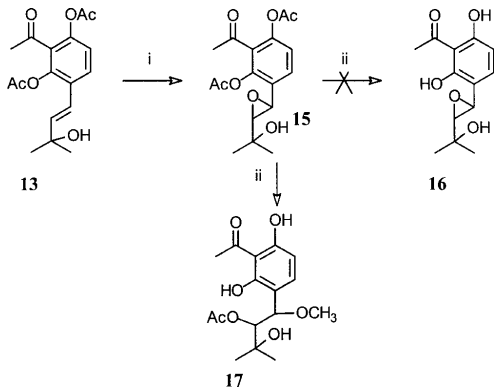

Figure 5 Oxidation of compound **13** followed by deacylation, to produce the diphenol **17** instead of the expected epoxyphenol **16**. Reagents: i, mCPBA, CH_2Cl_2, RT; ii, Zn, MeOH–CH_2Cl_2.

Before embarking on the functionalization of the exocyclic double bond, the hydrolysis of the diacetate **13** was attempted under alkaline conditions. A single product was identified as the benzopyranic phenol **14**. This compound was presumably obtained through a [4+2] cycloaddition of a methylenequinone formed after rearrangement of the phenate along with loss of the tertiary hydroxy group (Figure 4).

Taking into account these results and with the aim of synthesizing furobenzenic structures, we considered the funtionalization of the aliphatic side chain prior to the phenolic deprotection. Hence, oxidation of **13** using *meta*-chloroperbenzoic acid led to the corresponding epoxide **15** in a good yield (Figure 5). Then we used deacetylating conditions, via a catalytic-type reaction, by treatment with activated zinc in methanol (Gonzales et al 1981). This method, which was carried out in neutral medium, was expected to give the epoxyphenol **16**, but instead we isolated the unexpected diphenol **17**.

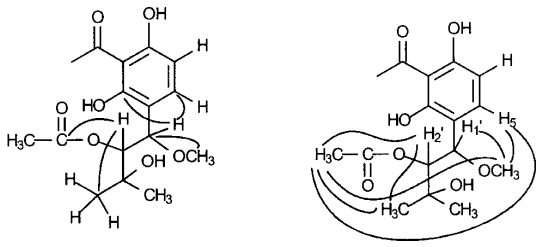

Figure 6 A. Selected HMBC correlations. B. Selected significant nuclear Overhauser enhancement results.

The structure of this compound was elucidated using extensive NMR spectroscopy. Analyses of the ^{1}H and ^{13}C NMR spectra, including correlation spectroscopy and heteronuclear multiple-quantum correlation, suggested the presence of an aliphatic chain consisting of an acetoxyl group (δ_C 20.5; δ_H 1.98), a methine group linked to another one (δ_C 80.6, δ_C 78.2; δ_H 5.00, δ_H 4.98) and two methyl groups adjacent to a quaternary carbon bearing a hydroxyl group (δ_C 27.7, δ_C 26.7; δ_H 1.20, δ_H 1.41). The linked arrangement of these partial structural units was elucidated by heteronuclear multiple-bond coherence spectroscopy. Significant C-H long-range correlations useful in the structure determination are shown as lines in Figure 6A. Long-range correlations of a methyl carbon signal at δ_C 27.0 (C-4′) with proton signals at δ_H 4.98 (H-2′), correlations of the carbonyl (δ_C 170.1) with H-2′ (δ_H 4.98) and correlations of the benzylic H-1′ proton (δ_H 5.00) with C-3 and C-4 (δ_C 160.2, δ_C 134.9) allowed linkage of structural units as shown in structure **17**. The salient proton enhancements from nuclear Overhauser and exchange spectroscopy experiments are summarized in Figure 6B. Among the most prominent were those recorded following pre-saturation of the methoxy, acetoxy, H-1′ and H-2′ protons. Pre-saturation of the methoxy protons caused enhancements of H-5, H-1′ and acetoxy protons. Moreover, irradiation of the acetoxy group led to H-2′ and 4-methyl proton enhancements (a weak enhancement was recorded on H-5 proton).

During this synthesis, the oxirane ring opening, involving a nucleophilic methanolic attack concomitantly with the deprotection of the phenols and transacetylation reaction involving the generated secondary alcohol and the nearest acetylated phenol, is observed.

In summary, we have shown that benzopyranic cyclization is easily obtained when basic conditions are used on allylic tertiary alcohol. These results could explain the presence of this sort of derivative in plant extracts. Our preliminary syntheses have led to a polyfunctionalized acetophenonic precursor (**17**), which could yield, by further cyclization, to a model of the new coumarin **2**. Further studies toward synthesis of the benzodihydrofuranic structure using direct nucleophilic substitution of the acetate, or involving Mitsunobu reaction, are currently under investigation in our laboratory. Anti-cancer pharmacological studies on these simplified structures are in progress.

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