Aromatics to Diquinanes: An Expeditious Synthesis of Tetramethylbicyclo[3.3.0]octane Framework of Ptychanolide

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Abstract: An expeditious route to methyl-7-oxo-1,4,5,8-tetramethylbicyclo[3.3.0]octane-3-carboxylate from a simple aromatic precursor is described. Oxidative dearomatization of 2-hydroxymethyl-3,4,6-trimethylphenol into spiroepoxycyclohexa-2,4-dienone, its cycloaddition and triplet-sensitized 1,2-acyl shift, and stereochemical inversion are the key features of our methodology.

Key words: cycloaddition, oxa-di-π-methane rearrangement, diquinanes, Diels–Alder reaction

Efficient creation of structural, functional, and stereochemical complexity from simple precursor is one of the important aspect of development of synthetic methodology.[1] A cascade of reactions or domino reaction,[2] and multicomponent reactions[3] are often employed to achieve these goals. Reactive species from aromatics have also been employed for efficient synthesis of a wide variety of molecular architecture.[4] Recently, several terpenoids having embellished diquinane framework such as ptychanolide (**1**) and spirodensifolin A (**2**) were isolated from various sources.[5] The carbocyclic framework of these sesquiterpenes is formed by two cyclopentane rings fused in a *cis* manner which contains four contiguous methyl groups in *cis* fashion and a characteristic spiro-γ-lactone moiety (Figure 1).

While several routes to polyquinanes have been developed,[6,7] only two studies dealing with the synthesis of ptychanolide (**1**) and spirodensifolin A (**2**) have been reported.[8] It appears that synthesis of functionalized diquinanes with four contiguous methyl groups poses considerable synthetic challenge.

In view of the above and our continuing interest in creation of molecular complexity from aromatics,[9] we considered developing a route to diquinane framework of ptychanolide, especially the potential intermediate **3** which is endowed with four contiguous methyl groups and an ester function for further elaboration.

We envisaged that functionalized diquinane **3** might be accessible from the tricyclic precursor **4**, which is endowed with all the four methyl groups (out of which three are present in correct relative orientation) via a stereoselective reductive cleavage of cyclopropane ring (Scheme 1).

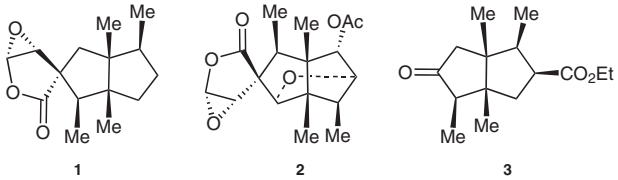
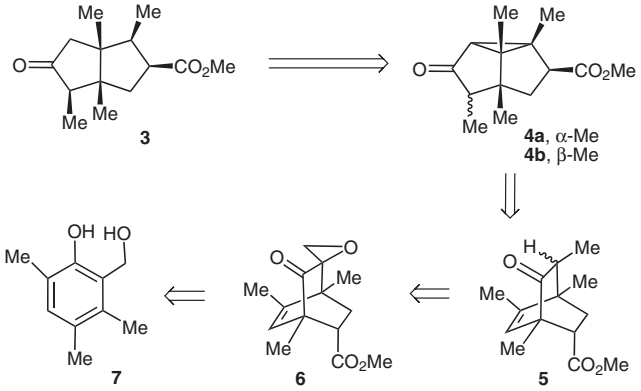


Figure 1



Scheme 1

It was further thought that it would be possible to place the methyl group α to carbonyl group in correct stereochemistry either via equilibration or other methods. The tricyclic compound **4** was thought to be obtainable by a triplet-sensitized 1,2-acyl shift or oxa-di-π-methane reaction of compound **5** endowed with a β,γ-enone chromophore. It was further contemplated that compound **5** might be obtained by manipulation of oxirane ring in compound **6** which in turn might be readily accessible via oxidation of compound **7** to cyclohexa-2,4-dienone and in situ cycloaddition with methyl acrylate (Scheme 1).

It may be interesting to note that all the four methyl groups required in the intermediates **3** and **4** are already present in the bicyclic precursor **5**. A photochemical rearrangement in **5** generates the diquinane framework having methyl groups at appropriate centers. Further, the intermediate **5** is generated from the aromatic precursor **7** (that contains three methyl groups) via the keto-epoxide **6**, which is readily assembled in a single step.

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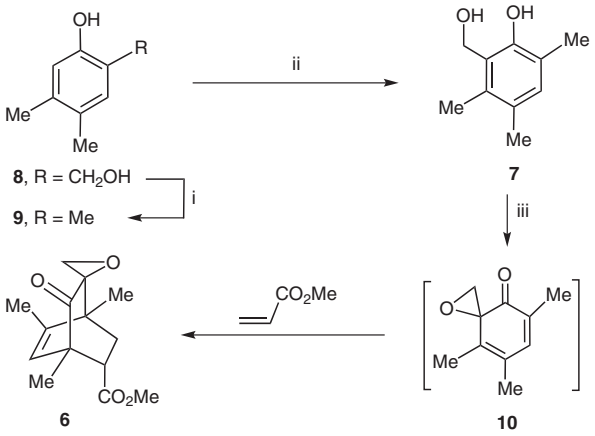
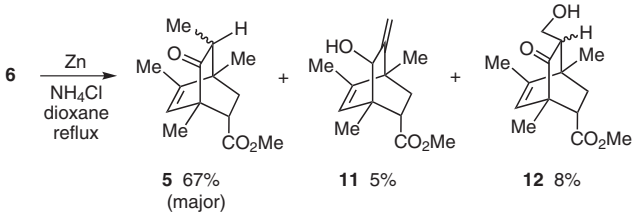
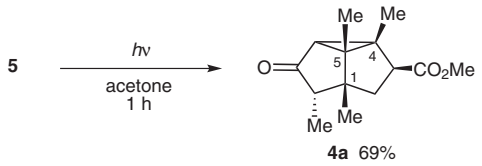


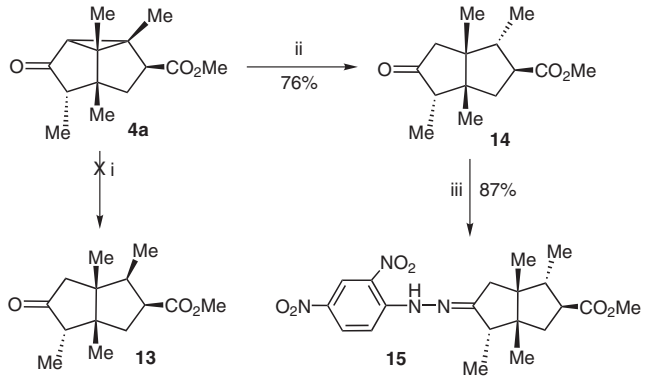
Scheme 2 *Reagents and conditions*: (i) H_2, Pd/C, MeOH, quant.; (ii) HCHO, NaOH, 59%; (iii) aq $NaIO_4$, aq MeCN, 0 °C to r.t., 67%.



Scheme 3



Scheme 4



Scheme 5 *Reagents and conditions*: (i) H_2 (14 atm), Pd/C (10%), MeOH, 15 h; (ii) Bu_3SnH–AIBN, anhyd benzene, reflux; (iii) 2,4-dinitrophenylhydrazine, MeOH, H_2SO_4.

The bicyclic chromophoric system **5** was efficiently prepared as described below. Thus, 2-hydroxymethyl-4,5-dimethyl phenol (**8**), readily prepared from 3,4-dimethyl phenol,[10] was reduced to give **9** which upon hydroxymethylation readily furnished desired aromatic precursor **7** (Scheme 2).

Oxidation of **7** with sodium metaperiodate[11a,b] in the presence of methyl acrylate, following a procedure developed in our laboratory,[11c] furnished the desired epoxy ketone **6** in good yield (67%, Scheme 2), as a result of in situ generation of cyclohexadienone **10**, and a tandem regio- and stereoselective cycloaddition. The structure of adduct **6** was deduced from its spectral features.[12] The *endo* stereochemistry of the ester group and stereochemical orientation of the oxirane group was suggested on the basis of general tendency of cyclohexa-2,4-dienones during their cycloaddition and comparison of the spectral features with analogous compounds.

Reduction of adduct **6** with activated Zn–NH_4Cl in anhydrous dioxane furnished the desired compound **5** as a major product (67%) [*syn*/*anti* mixture (1:9), ^{1}H NMR] and the keto alcohol **12** (8%) (*syn*/*anti* mixture) and enol **11** (5%) (*syn*/*anti* mixture) as minor products (Scheme 3).

The photochemical reactions of rigid β,γ-enones have stimulated considerable interest because of their synthetic potential.[13–15] In general, β,γ-enones undergo 1,2-acyl shift or oxa-di-π-methane rearrangement and a 1,3-acyl shift upon triplet-sensitized and direct excitation, respectively.[9,13–15] Demuth and co-workers have earlier examined 1,2-acyl shift in some bicyclo[2.2.2]octanes and demonstrated its synthetic potential.[13] The photoreaction of β,γ-enones, however, depends on the structure of the chromophoric system and functional groups in a subtle fashion.

Thus, a solution of the bicyclic compound **5** (*syn*/*anti* mixture containing *anti* as major isomer) in anhydrous acetone (both as sensitizer and solvent) was irradiated with a mercury vapor lamp (125 W, APP) in a Pyrex immersion well, whereupon a clean reaction occurred (TLC). Chromatography of the photolysate provided the compound **4a** as a single diastereomer (^{1}H NMR, ^{13}C NMR) in very good yield (69%) as a major product (Scheme 4).

The structure of the photoproduct was deduced from its spectral features and comparison with its precursor. The photoproduct **4a** contains three methyl groups (C-1, C-4, and C-5) in correct orientation as required, by virtue of the structure of the chromophore and mechanism of the oxa-di-π-methane reaction.

At this juncture, regioselective cleavage of cyclopropane ring in **4a** was required. There are several methods for cleavage of carbonyl conjugated cyclopropane ring. Initially, the compound **4a** was treated with Pd/C and H_2 in order to obtain compound **13**. However, no reduction was observed. Therefore, we attempted radical-induced cleavage. Thus, ketone **4a** was treated with $(Bu)_3SnH$–AIBN[16] in refluxing benzene which gave the diquinane **14** in very good yield (76%, Scheme 5).

The gross structure of compound **14** was deduced from the following spectral features.[17] Thus, IR spectrum showed the absorption band at 1735 cm^{-1} for carbonyl group, which suggested that peripheral cleavage of cyclopropane ring had occurred. ^{13}C NMR (100 MHz, $CDCl_3$)

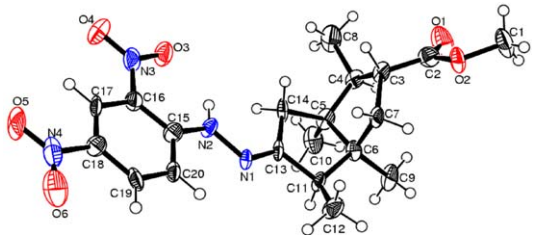
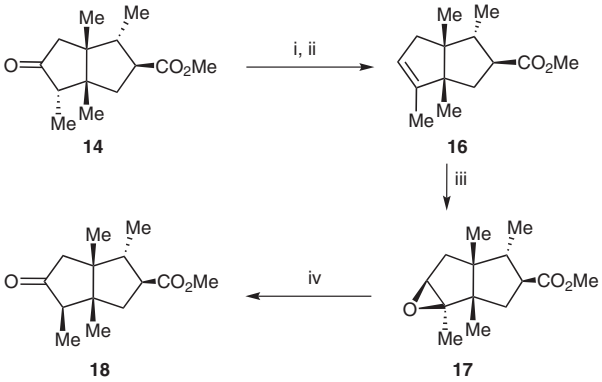


Figure 2 Crystal structure of compound **15**



Scheme 6 *Reagent and conditions*: (i) $NaBH_4$, MeOH, 0 °C to r.t., 98%; (ii) PTSA, anhyd benzene, reflux, 80%; (iii) MCPBA, anhyd CH_2Cl_2, 91%; (iv) $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0 °C to r.t., 68%.

spectrum displayed a characteristic down field signal at δ = 219.0 indicating the presence of CO group in a five-membered ring (and hence peripheral cleavage).

However, it was difficult to ascertain the stereochemical orientation of methyl group (present at the carbon β to carbomethoxy group) from the spectral data alone. Hence, the compound **14** was converted into hydrazone **15** (Scheme 5) and its single-crystal structure was determined which confirmed its structure (Figure 2).[18] This, in turn, also established the structure **14** for the product obtained after cleavage of the cyclopropane ring.

It was rather unfortunate that the radical induced cleavage of photoproduct **4a** did not give the desired stereoisomer, instead it gave **14** (Scheme 5). Nevertheless, it was thought to develop a method to change the stereochemical orientation of Me group α to carbonyl in diquinane **14**.

Thus, the compound **14** was converted into the olefinic compound **16** in excellent yield via reduction of the carbonyl group and acid-catalyzed elimination reaction (Scheme 6). The alkene **16** was treated with MCPBA to give the epoxide **17** in excellent yield, as a result of epoxidation from the convex face. Treatment of **17** with $BF_3{\cdot}OEt_2$ gave the diquinane **18** (Scheme 6) whose structure was suggested from its spectral features[19] and comparison with the spectral data of **14**.

The transformation of **17** to **18** apparently proceeds through the intermediate **I** (Figure 3). The oxirane ring undergoes Lewis acid mediated rearrangement that is followed by hydride transfer leading to **18**.

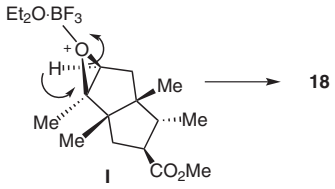


Figure 3

In summary, an efficient approach towards synthesis of bicyclo[3.3.0]octane ring system with four contiguous methyl groups from a simple aromatic precursor is presented. 2-Hydroxymethyl-3,4,6-trimethylphenol was oxidized to give 6,6-spiroepoxycyclohexa-2,4-dienone which upon cycloaddition with methyl acrylate gave the adduct **6** which was manipulated to give the bridged bicyclo[2.2.2]octane **5** endowed with all the methyl groups and a β,γ-enone chromophore. Sensitized irradiation of **5** furnished the compound **4a**, which was transformed into functionalized diquinane **18** related to ptychanolide.

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(12) All the compounds gave satisfactory spectral data.
Data of Compound 6
IR (neat): 1735 (br) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 5.55 (br s, 1 H), 3.68 (s, 3 H), 3.06 (part of an AB system, J = 5.86 Hz, 1 H), 2.92 (part of an AB system, J = 5.86 Hz, 1 H), 2.77 (dd, J_1 = 10.26 Hz, J_2 = 5.87 Hz, 1 H), 2.15 (dd, J_1 = 13.19 Hz, J_2 = 10.26 Hz, 1 H), 1.87 (d, J = 1.46 Hz, 3 H), 1.74 (dd, J_1 = 12.83 Hz, J_2 = 5.87 Hz, 1 H), 1.26 (s, 3 H), 1.04 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 204.3, 173.8, 146.2, 124.9, 59.1, 51.9, 50.6, 49.6, 45.2, 40.9, 36.7, 17.9, 15.7, 14.4. ESI-HRMS: *m/z* calcd for $C_{14}H_{19}O_4$: 251.1283 $[M + H]^+$; found: 251.1277 $[M + H]^+$.

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(17) **Data of Compound 14**
IR (neat): 1735 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.68 (s, 3 H), 2.44–2.36 (m, 1 H), 2.32–2.15 (m, 2 H), 2.01 (d of AB pattern, J = 19.42 Hz, 1 H), 1.92 (d of AB pattern, J = 19.42 Hz, 1 H), 1.76–1.62 (m, 2 H), 1.09 (s, 3 H), 1.04–0.98 (m, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 219.0, 176.6, 53.2, 52.0, 50.7, 48.1, 45.6, 45.1, 36.4, 23.5, 21.4, 20.7, 14.2, 8.8. ESI-HRMS: *m/z* calcd for $C_{14}H_{23}O_3$: 239.1647 $[M + H]^+$; found: 239.1655 $[M + H]^+$.

(18) **Data for Hydrazone Derivative 15**
IR (neat): 1731 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 10.82 (br s, 1 H), 9.13 (d, J = 2.44 Hz, 1 H), 8.30 (dd, J_1 = 8.85 Hz, J_2 = 1.83 Hz, 1 H), 7.97 (d, J = 9.47 Hz, 1 H), 3.69 (s, 3 H), 2.67–2.45 (m, 1 H), 2.41–2.31 (m, 1 H), 2.30–2.25 (m, 2 H), 2.10 (d, J = 18.32 Hz, 1 H), 1.74–1.62 (m, 2 H), 1.19 (d, J = 6.72 Hz, 3 H), 1.10–1.09 (m, 6 H), 1.03 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.6, 167.7, 145.2, 137.8, 130.1, 129.0, 123.7, 116.5, 53.4, 53.4, 52.0, 48.3, 47.9, 45.7, 35.8, 35.4, 20.9, 20.8, 14.3, 11.1. ESI-HRMS: *m/z* calcd for $C_{20}H_{27}O_6N_4$: 419.1931 $[M + H]^+$; found: 419.1939 $[M + H]^+$.
Crystal Data of Hydrazone Derivative 15
$C_{20}H_{26}N_4O_6$, M 418.45, space group, monoclinic, P 21/c, a = 20.475 (4), b = 14.245 (2), c = 7.3712 (12) Å, α = 90, β = 99.326 (19), γ = 90.0, U = 2121.5 (6)A^3, Z = 4, D_c = 1.310 g/m^3, T = 150 (2) K, F(000) = 888, size = 0.21 × 0.18 × 0.15 mm. Reflections/collected/unique 10087/3694 [R(int) = 0.1809], final R indices [$I > 2\sigma(I)$] = R_1 = = 0.0732, wR_2 = 0.1210 R indices (all data) R_1 = 0.2346, wR_2 = 0.1622. The complete crystal data can be obtained free of charge from The Cambridge Crystallographic data Centre via www.ccdc.cam.ac.uk/data_request/cif quoting the CCDC number 694681.

(19) **Data of Compound 18**
IR (neat): 1736 (br) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.70 (s, 3 H), 2.58–2.50 (dd with structure, J_1 = 18 Hz, J_2 = 9 Hz, 1 H), 2.41–2.34 (d with structure, J = 9 Hz, 1 H), 2.24–2.16 (m, 2 H), 2.00–1.86 (m, 3 H), 1.03 (d, partly merged with a s, J = 7.33 Hz, 3 H), 1.02 (s, 3 H), 1.00 (s, 3 H), 0.99 (d, partly merged with s, J = 6.72 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 220.3, 176.3, 53.2, 51.9, 50.9, 50.6, 49.0, 47.3, 46.1, 44.2, 23.7, 18.9, 15.2, 11.9. ESI-HRMS: *m/z* calcd for $C_{14}H_{23}O_3$: 239.1647 $[M + H]^+$; found: 239.1655 $[M + H]^+$.