Synthesis of functionalized cis-syn-cis triquinanes

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Functionalized cis-syn-cis triquinane ring systems are identified as useful precursors to higher polyquinanes. In this regard, two strategies to prepare these triquinane ring systems from caged compounds are described.

Polyquinanes are an important class of compounds whose members include a variety of natural products (e.g., corilolin) and non-natural products such as dodecahedrane. The past two decades have witnessed an explosive growth of research in this area. Useful biological properties, combined with the structural complexity of these molecular entities isolated from various natural resources, has attracted the attention of synthetic chemists for their preparation. The main reason is that these molecules have inherent interest because their chemical and physical properties merit study. These studies have advanced our knowledge in understanding structure, bonding and chemical reactivity principles.

As a part of our program directed towards the synthesis of [6]-peristylylene 1, we needed an effective and general methodology for the synthesis of functionalized polyquinane frames with all cis-syn-cis geometry. In this regard, the retrosynthetic pathway identifies 2 and 3 as possible intermediates (Figure 1).

Results and Discussion

In order to prepare the pentaquinane system 2, we needed an efficient method to synthesize a triquinane framework with suitable functionality. In this regard, the dione 4, reported by Mehta and co-workers was allylated using the Claisen rearrangement (CR) as a key step. Thus, the reaction mixture consisting of the dione 4, 2,2’-dimethoxy propane and allyl alcohol was heated in toluene in the presence of p-toluene-sulphonic acid (p-TSA), yielding the tetracyclic ether 5 (33%, mp 66-67°C) and the monoallyl diketone 6 (39%, Scheme I).

The structure of 5 was assigned by considering 13C NMR spectral data and particularly the peak 123.1 and 65.2 which are typical values for (O O) and (O-C-CH3) carbon resonances, respectively. The structure of the monoallyl compound 6 deduced to be a mixture of epimers on the basis of 13C NMR spectrum and further established by
and mass spectral data (M* 218). Attempts to prepare the diallyl compound 3 were not successful even under forcing CR conditions.

In view of the literature report for the synthesis of cis-syn-cis triquinane starting from a Cookson’s caged diione,5 our strategy begins with the known caged diione 11 prepared from 10.5 Selective C-C bond cleavage reaction of 13 was expected to deliver interesting triquinanes for further synthetic manipulation. The required compound 11 was prepared from p-benzoquinone and 2,3-dimethyl-1,3-butadiene via 9. During the preparation of the required compound 11, we also obtained 12 as a minor product (11%, Scheme II). Product 12 arises due to the over-oxidation during MnO2 oxidation reaction. Since quinone 9 is sensitive to light, purification was not attempted.

In view of the literature reports, it was thought that under flash vacuum pyrolysis (FVP) conditions hexacyclic system 11 would generate the functionalized triquinane derivative such as 14 via the pentacyclic derivative 13. In this regard, compound 11 was subjected to C-C bond cleavage with ruthenium(III) chloride and sodium metaperiodate according to the Sharpless conditions to give 13 in 53% isolated yield after column chromatography. The symmetrical nature of 13 was revealed by 9-line 13C NMR spectrum. The bis-enone 14 was obtained by uncaging of the pentacyclic compound 13 under FVP conditions. The 9-line 13C NMR spectrum indicated the symmetrical nature of 14 (Scheme III).

Hydrogenation of 14 gave the saturated dione 15 as a mixture of isomers as supported by 13C NMR spectral data.

Conclusions

We have prepared highly functionalized triquinane system 14 using the FVP reaction as a key step. Some of the polycyclic compounds reported here may be useful precursors to higher polyquinanes.

Experimental Section

General. Tetrahydrofuran (THF) was distilled from sodium benzoephene immediately prior to use. Melting points are uncorrected. Analytical thin layer chromatography (TLC) was performed on glass plates coated with Acme’s silica gel G or GF 254 containing 13% calcium sulfate as a binder. Visualization of the spots on TLC plates was achieved either by exposure to iodine vapor or UV light. Flash chromatography was performed using Acme’s silica gel (100-200 mesh). Pet. ether refers to fraction having boiling point 60-80°C. Yields refer to the chromatographically isolated yield. All the commercial grade reagents were used without further purification. Infra red spectra were recorded on a Nicolet 400 FT IR spectrometer in KBr/CHCl3/CCl4 and the absorptions are reported in cm⁻¹. 1H NMR spectra were determined on a Brucker 300 MHz spectrometer as CDCl3 solutions (J values are in hertz) and chemical shifts are expressed in ppm downfield from internal tetramethylsilane. Mass spectra were recorded on a GCD 1800A Hewlett-Packard GC-MS spectrometer. Microanalyses were carried out on a Carlo-Erba Struentazione MOD 1106 instrument.

Attempted diallylation of dione 4. To a solution of dione 4 (267 mg, 1.5 mmoles) in dry toluene (8 mL) in a three-necked flask fitted with vigurex condenser, allyl alcohol (1 mL), p-TSA (20 mg, 0.1 mmoles) and 2,2'-dimethoxy propane (0.75 mL) were added and the reaction mixture was heated at 110°C over a period of 2 hr. The vigurex condenser was then replaced by a reflux condenser and the
reaction mixture was heated at 135°C for 6 hr. The reaction mixture was cooled, washed with sodium bicarbonate, brine and dried over magnesium sulfate. The solvent was removed under reduced pressure and the resulting residue was purified by column chromatography using silica gel to give the diallyl ether 5 (137 mg, 33%) as a colourless solid. mp 66-67°C; IR (KBr): ν 2943 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 1.44-1.98 (m, 8H), 2.20-2.30 (m, 2H), 2.75 (q, J = 6.0 Hz, 2H), 3.11 (dd, J = 2.9, 7.3 Hz, 2H), 4.02 (dd, J = 5.5, 9.0 Hz, 2H), 4.20 (dd, J = 5.5, 9.0 Hz, 2H), 5.10-5.18 (m, 2H), 5.22-5.34 (m, 2H), 5.88-6.02 (m, 2H); ¹³C NMR (75.5 MHz, CDCl₃): δ 32.1, 36.7, 37.8, 45.4, 60.3, 65.3, 116.3, 123.2, 135.4; Mass: m/z 276 (M⁺), Anal. Found: C, 75.3, 76.4, 76.5; H, 6.0, 6.6, 7.2; CH₃O requires C, 75.1, 75.4, 75.5; H, 5.8, 6.1, 6.5.

The solvent was removed under reduced pressure and the resulting residue was purified by column chromatography using silica gel to give the diallyl ether 5 (137 mg, 33%) as a colourless solid. mp 66-67°C; IR (KBr): ν 2943 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 1.44-1.98 (m, 8H), 2.20-2.30 (m, 2H), 2.75 (q, J = 6.0 Hz, 2H), 3.11 (dd, J = 2.9, 7.3 Hz, 2H), 4.02 (dd, J = 5.5, 9.0 Hz, 2H), 4.20 (dd, J = 5.5, 9.0 Hz, 2H), 5.10-5.18 (m, 2H), 5.22-5.34 (m, 2H), 5.88-6.02 (m, 2H); ¹³C NMR (75.5 MHz, CDCl₃): δ 32.1, 36.7, 37.8, 45.4, 60.3, 65.3, 116.3, 123.2, 135.4; Mass: m/z 276 (M⁺), Anal. Found: C, 75.3, 76.4, 76.5; H, 6.0, 6.6, 7.2; CH₃O requires C, 75.1, 75.4, 75.5; H, 5.8, 6.1, 6.5.

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stirred for 5 min. To this biphasic solution, RuCl₃ (15 mg, 0.07 mmole) was added and the entire mixture was stirred vigorously for 3 hr at room temperature. Then, CH₂Cl₂ (10 mL) was added and the layers were separated. The aqueous phase was extracted with CH₂Cl₂ (2 × 25 mL). The combined organic layer was filtered through celite pad and the filtrate was concentrated and dried over MgSO₄. The crude product was purified by a short silica gel column.

Elution of the column with ether mixture = 18.1 Hz, 1H) , 2.87 (d, J = 18.1 Hz, 1H), 2.87 (d, J = 18.1 Hz, 1H), 2.82 (d, J = 1.6 Hz, 2H), 2.97-2.98 (m, 2H), 3.05-3.09 (m, 2H); \( \text{\text{C}} \) NMR (75.5 MHz, CDCl₃): \( \delta \) 30.3, 40.1, 40.7, 43.8, 44.2, 51.8, 55.3, 204.7, 212.2; Mass: m/z 286 (M⁺). Anal. Found: C, 71.63; H, 6.47. C₁₇H₁₈O₂ requires C, 71.31; H, 6.34%.

Flash vacuum pyrolysis of caged dione 13. The caged dione 13 (300 mg, 1.04 mmole) was slowly sublimed through a quartz tube connected through a vacuum pump and provided with a collection flask and solvent trap. The quartz tube was heated with nichrome wire wound around it and was insulated with asbestos padding. The temperature of the pyrolysis tube was controlled by variac and was measured by digital thermometer. The quartz tube was pre-heated and equilibrated at 620°C. The solid condensate in the receiver was collected and chromatographed using a small silica gel column to give the product 14 (170 mg, 56 %) as a colourless liquid: IR (CCl₄): 1710 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): \( \delta \) 1.25 (s, 2H), 2.17 (s, 6H), 3.20 (s, 4H), 3.28 (dd, J = 1.3, 2.2 Hz, 2H), 3.45-3.54 (m, 4H), 7.32 (t, \( J = 1.3 \) Hz, 2H); \( \text{\text{C}} \) NMR (75.5 MHz, CDCl₃): \( \delta \) 30.4, 31.5, 38.6, 48.7, 53.0, 138.0, 162.8, 204.4, 206.2; Mass: m/z 286 (M⁺). HRMS: Found: 286.121. C₁₇H₁₈O₄ requires 286.120.

Hydrogenation of compound 14. The compound 14 (170 mg, 0.59 mmole) was dissolved in ethyl acetate (5 mL) and was added 10% Pd-C (28 mg) and the mixture was stirred under H₂ atmosphere (1 atm pressure) for 18 hr. The reaction mixture was filtered off with a aid of celite pad and the filtrate was concentrated under reduced pressure to give crude product which was purified by a short silica gel column to deliver compound 15 (110 mg, 64%) as a colourless liquid (mixture of isomers). IR (CCl₄): 1743, 1712 cm⁻¹; UV (CH₃CN): \( \lambda_{\text{max}} \) (M⁻¹ cm⁻¹) 211 (17.655 x 10⁴); \( \text{\text{H}} \) NMR (300 MHz, CDCl₃): \( \delta \) 1.22 (s, 2H), 2.20 (s, 6H), 2.32-2.60 (m, 6H), 2.70-2.94 (m, 4H), 3.04-3.10 (m, 4H); Mass: m/z 290 (M⁺). HRMS: Found: MH⁺ 291.161 C₁₇H₁₉O₄+H requires 291.152.

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References

7 Although compounds 7 to 11 are reported, the detailed experimental procedures and IR NMR spectral data are not available in the literature.