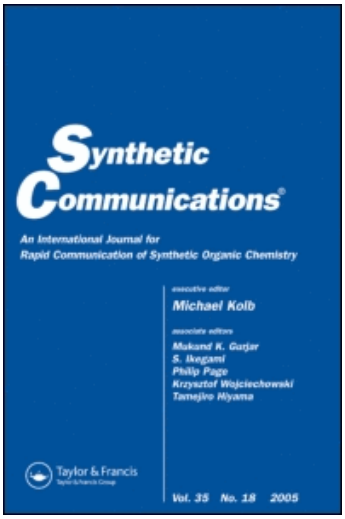


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# A New Route to the Synthesis of 7-Functionalised Bicyclo[2.2.1]Heptane Derivatives

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# A NEW ROUTE TO THE SYNTHESIS OF 7-FUNCTIONALISED BICYCLO[2.2.1]HEPTANE DERIVATIVES

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**Abstract:** A new route to the synthesis of 7-functionalised bicyclo[2.2.1]heptane derivatives having a bridgehead alkoxy group is described involving Wolff rearrangement of α-diazo ketone in a bicyclo[2.2.2]octane derivative.



Bicyclo[2.2.1]heptane derivatives are attractive intermediates to condensed[1], spiro[2] and bridged[3] ring systems present in many natural products. In connection to our synthetic programme[4] toward antitumor and antileukemic diterpene taxol[5] through these derivatives, we required the synthesis of a functionalised bicyclo[2.2.1]heptane derivative **2** the preparation of which requires a cycloaddition between anhydride **1** and an appropriately functionalised cyclopentadiene derivative (Route A, Scheme-1). The inertness of the anhydride **1** to undergo cycloaddition[6] with 5,5-disubstituted cyclopentadiene derivatives made difficult the synthesis of functionalised derivatives e.g. **2**. Alternatively, we envisioned that a bicyclo[2.2.2]octane derivative **3** (Route B, Scheme-1), available in principle by cycloaddition between **1** and an alkoxy cyclohexadiene, may be induced to undergo a skeletal rearrangement. The resulting bicyclo[2.2.1]heptane derivative **2** will then have the functional groups at C-1 and C-10 for elaboration in the desired direction. Realisation of this concept

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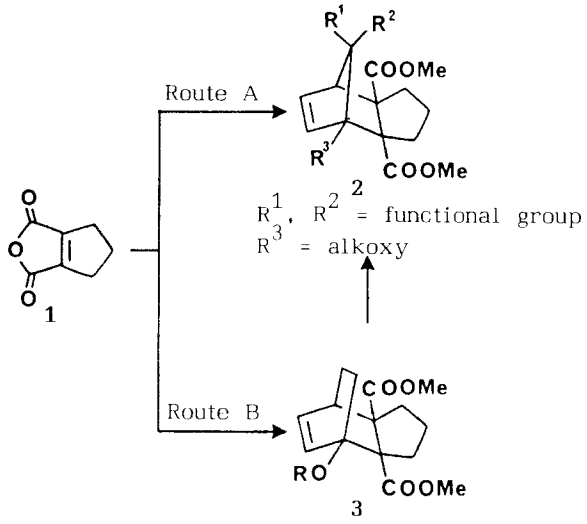
Scheme-1



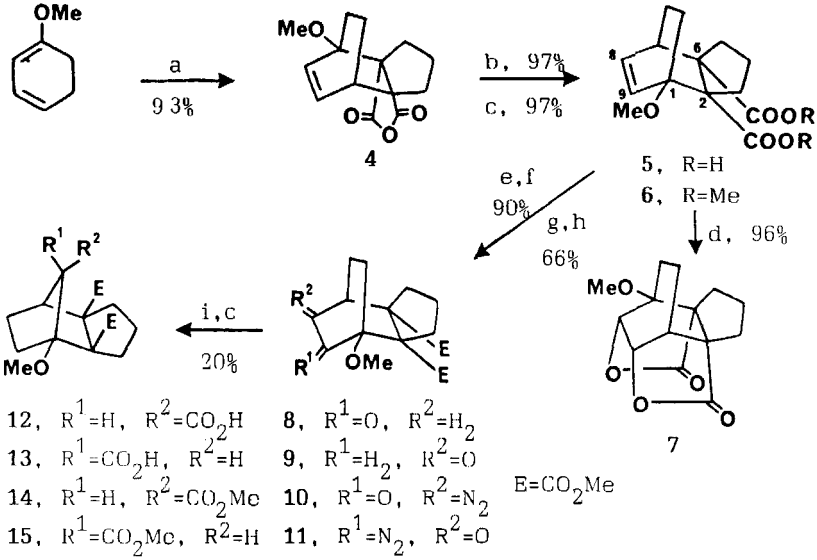



leading to a new route[7] to the synthesis of functionalised bicyclo-[2.2.1]heptane derivatives **14** and **15** is described bere.

Refluxing a toluene solution of the anhydride **1**[8] with an excess of 1-methoxy-1,3-cyclohexadiene[9] afforded the adduct **4** (Scheme-2) as a crystalline solid in 93% yield. While the structure of the adduct **4** became apparent from the spectral data of **4** and the corresponding dimethyl ester **6**, the endo-assignment to **4** could be made unambiguously by its quantitative transformation to the crystalline dilactone **7**. Of the several ways available for effecting skeletal rearrangement, we became interested in the photolytic Wolff rearrangement of $\alpha$-diazo ketone which has been reported to proceed efficiently in several bridged ring systems[10]. Toward this end, it was necessary to transform the diester **6** to a ketone derivative and was accomplished as follows.

Hydroboration of the diester **6** in THF solution with $BH_3$-THF followed by alkaline hydrogen peroxide oxidation of the intermediate organoborane gave a mixture of diols which were

Scheme-2




12, $R^1$=H, $R^2$=$CO_2H$ 8, $R^1$=O, $R^2$=$H_2$

13, $R^1$=$CO_2H$, $R^2$=H 9, $R^1$=$H_2$, $R^2$=O

14, $R^1$=H, $R^2$=$CO_2Me$ 10, $R^1$=O, $R^2$=$N_2$

15, $R^1$=$CO_2Me$, $R^2$=H 11, $R^1$=$N_2$, $R^2$=O

E=$CO_2Me$

**Reagents**: a, 2, toluene, reflux. b, $NaHCO_3$-EtOH-$H_2O$, reflux. c, $CH_2N_2$-$Et_2O$. d, $NaHCO_3$-$H_2O$-$I_2$-KI, r.t. e, $BH_3$-THF, NaOH-30% $H_2O_2$. f, Jones reagent, acetone, 5°C. g, NaH-$HCO_2Et$-$Et_2O$. h, 4-carboxy benzene sulfonylazide-$K_2CO_3$-acetonitrile. i, $h\nu$, dioxane-$H_2O$

directly transformed to a mixture of the diketones **8** and **9**. Silica gel chromatography of this mixture afforded the pure ketones **8** (82%) and **9** (8%). The structural assignment to these ketones were made by comparison of the observed chemical shifts of $C_1$-OMe and $C_7$-H in $^1H$ NMR. The $C_1$-OMe protons in the major ketone were found to be deshielded by 0.22 ppm over the minor ketone suggesting the proximity of the methoxy and the carbonyl group in the major ketone. The major ketone was thus assigned the structure **8**. This assignment was further supported by the appearence of $C_7$-H of the major ketone **8** at a higher field ( $\delta$ 3.02-3.26) than the minor ketone **9** in which $C_7$-H appears at $\delta$ 3.3-3.5. Although, such regioselectivity in

hydroboration has been reported[11] previously in very few acyclic and flexible cyclic olefines having allylic methoxy group, the observation of high degree of regioselectivity in hydroboration of this multifunctionalised olefine **6** having a rigidly held methoxy group at the allylic position deserves special mention. The methoxy group at C-1 and the carbomethoxy group at C-2 are expected to offer substantial steric hindrance to attack at C-9 favouring attack by boron at C-8. The observed regioselectivity in hydroboration of **6** is thus the result of the electronic effect transmitted by the methoxy group which overrides the steric effect and is fully in accord with Hehr's reactivity model[12].

The mixture of ketones **8** and **9** was transformed to the α-diazoketones **10** and **11** through reaction of their formyl derivatives with 4-carboxybenzene sulfonyl azide using potassium carbonate either in solution[13] or in the solid phase[14] in nearly the same yield. Irradiation of the diazoketone mixture in dioxane-water (2:1) afforded a mixture of syn and anti-carboxylic acids **12** and **13** which were then characterised as their methyl esters **14** and **15**. Thus, the present investigation offers a simple new route for the synthesis of C-1 and C-10 functionalised bicyclo[2.2.1]heptane derivatives **14** and **15** which are not available by direct Diels-Alder reaction of the corresponding cyclopentadiene derivatives with the anhydride **1**.

## Experimental Section

Melting points were taken in open capillary in a sulphuric acid bath. IR spectra were recorded on a Perkin-Elmer 298 spectrometer in $CHCl_3$ solution. $^1H$ NMR were recorded in $CDCl_3$ solution at 200 MHz on Varian XL-200 spectrometer using TMS as internal standard. Organic extracts were dried over anhydrous sodium sulphate. Column chromatography was performed in silica gel column. Petroleum refers to fractions of petroleum ether boiling in the ranges 60-80°C.

**endo-1-Methoxy bicyclo[2.2.2]oct-8-ene-2,6-dicarboxylic anhydride (4).** A solution of the anhydride **1** (600 mg, 4.35 mmol) in toluene (20 ml) was refluxed with 1-methoxy cyclohexa-1,3-diene (1 g, 9.1 mmol) for 18 h.Solvent and volatile materials were removed in vacuum and the residual mass was chromatographed [petroleum-ethylacetate (19:1)] to afford the anhydride **4** (1.0 g, 93%), m.p. 93°C; IR 1835, 1775 $cm^{-1}$; $^1H$ NMR $\delta$ 1.40-2.30 (10H), 2.92 (H, m), 3.44 (3H, m), 6.41 (H, dd, J = 8 and 4 Hz) and 6.54 (H, d, J = 8 Hz). Anal. calcd. for $C_{14}H_{16}O_4$ : C, 67.72; H, 6.49. Found: C, 67.57; H, 6.46.

**endo-1-Methoxy bicyclo[2.2.2]oct-8-ene-2,6-dicarboxylic acid (5).** A solution of the anhydride **4** (500 mg, 2.02 mmol) in ethanol (3 ml) and water (10 ml) was refluxed with sodium bicarbonate (400 mg, 4.8 mmol) for 4 h. The reaction mixture was cooled to r.t. and extracted with ether to remove unhydrolysed material. The aqueous part was acidified with 6N HCl and extracted with ether (3 x 25 ml). The ether extract was washed with brine, dried and evaporated to dryness to afford the acid **5** (500 mg, 97%). It was crystallised from ether-petroleum to afford an analytical sample, m.p. 163°C; IR 1730, 1690 $cm^{-1}$. Anal. calcd. for $C_{14}H_{18}O_5$ : C, 63.14; H, 6.81. Found : C, 62.97; H, 6.93.

**endo-Dimethyl-1-methoxy bicyclo[2.2.2]oct-8-ene-2,6-dicarboxylate (6).** A solution of the diacid 5 (130 mg, 0.48 mmol) was treated with excess of ethereal diazomethane. After removal of ether, the residual mass was filtered through a short column of neutral alumina to afford the dimethyl ester **6** (140 mg, 97%); $^1H$ NMR : $\delta$ 1.16-2.22 (10H), 2.56-2.82 (H), 3.34 (3H, s), 3.56 (3H, s), 3.6 (3H, s), 6.32-6.56 (2H). Anal. calcd. for $C_{16}H_{22}O_5$ : C, 65.29; H, 7.53. Found : C, 65.36; H, 7.61.

**Transformation of the diacid 5 to the dilactone 7.** The dicarboxylic acid **5** (400 mg, 1.5 mmol) was dissolved in an

aqueous (10 ml) sodium bicarbonate (400 mg, 4.76 mmol) solution. To it was added an iodine solution [prepared by adding iodine (500 mg, 1.97 mmol) and potassium iodide (1 g, 6.66 mmol) to water (3 ml)] and the resulting mixture was stirred at r.t. for 36 h. The clear solution was extracted with ether (3 x 30 ml). The ether extract was washed with aqueous sodium thiosulfate (5%) and dried. Removal of ether afforded the dilactone **7** (380 mg, 96%). An analytical sample was prepared by crystallisation from ether-methylene chloride, m.p. 184°C; IR 1790 $cm^{-1}$; $^1H$ NMR : $\delta$ 1.6-2.44 (11H), 3.28 (3H, s), 4.88 (2H, d, J = 2 Hz). Anal. calcd. for $C_{14}H_{16}O_5$ : C, 63.62; H, 6.10. Found : C, 63.38; H, 6.39.

**1-Methoxy bicyclo[2.2.2]octan-9-one (8) and 1-methoxy bicyclo[2.2.2]octan-8-one (9).** A solution of the diester **6** (450 mg, 1.53 mmol) in THF (18 ml) was treated with a solution of borane (1.6 ml, 17 mmol, 30%) in THF at 0°C for 24 h.A few drops of water was then added followed by addition of aqueous sodium hydroxide (7.5 ml, 3M) and hydrogen peroxide (7.5 ml, 30%). The reaction mixture was stirred at r.t. for 1 h and then extracted with ether (3 x 40 ml). The ether extract was washed with brine, dried and concentrated. The residual mass was dissolved in acetone (10 ml) and Jones reagent (1.3 ml, 0.7M) was added to the ice-cold solution with stirring. Stirring was continued for additional 30 min. After dilution with water, the reaction mixture was extracted with ether (3 x 50 ml). The ether extract was washed with aqueous saturated sodium bicarbonate, brine and dried. The solvent was removed and the residual viscous mass was chromatographed [petroleum-ethyl acetate (3:1)] to afford **8** (390mg, 82%), m.p. 86°C; IR 1725 $cm^{-1}$; $^1H$ NMR : $\delta$ 1.68-2.8 (12H), 3.02-3.26 (H), 3.46 (3H, s), 3.62 (3H, s), and 3.64 (3H, s). Anal. calcd. for $C_{16}H_{22}O_6$ : C, 61.92; H, 7.15. Found : C, 62.17; H, 7.19; and **9** (40 mg, 8%), m.p. 98°C; IR 1735 $cm^{-1}$; $^1H$ NMR : $\delta$ 1.56-2.82 (12H), 3.24 (3H, s), 3.3-3.5 (H), 3.62 (3H, s), and 3.68 (3H, s).

Anal. calcd. for $C_{16}H_{22}O_6$ : C, 61.92; H, 7.15. Found : C, 61.75; H, 7.07.

**Trimethyl-1-methoxy bicyclo[2.2.1]heptane-2,6,10-tricarboxylates 14 and 15.** To a magnetically stirred suspension of sodium hydride (200 mg, 4.1 mmol, 50%) in dry ether (4 ml) cooled to 0°C was added ethyl formate (70 mg, 0.94 mmol) and a solution of the ketone mixture **8** and **9** (150 mg, 0.48 mmol) in ether (1 ml) followed by a drop of methanol. The reaction mixture was stirred at 0°C for 3 h and left overnight. It was poured onto ice and extracted with ether to remove unreacted ketone. The basic aqueous part was acidified with cold 6N HCl and extracted with ether (3 x 10 ml). The ether extract was washed with brine, dried and concentrated to leave a brown mass (150 mg).A solution of this crude formyl derivative in acetonitrile was stirred with potassium carbonate (160 mg, 1.1 mmol) and 4-carboxybenzene sulfonyl azide (120 mg, 0.6 mmol) for 24 h. Acetonitrile was removed in vacuum and the residue was dissolved in ether-petroleum (1:1) and filtered through neutral alumina to afford the diazoketones **10** and **11** (100 mg, 66%), IR 2100 $cm^{-1}$ which without further purification was irradiated in aqueous dioxane [90 ml, dioxane-water (2:1)] through a pyrex immersion well using Hanovia 450 W medium pressure mercury vapor lamp for 10 h. Dioxane and water were removed under vacuum. The residual mass was dissolved in ether and the solution was washed with saturated aqueous sodium bicarbonate. Removal of ether afforded a viscous liquid (70 mg) which was not characterised. The basic aqueous washing on acidification with cold 6N HCl was extracted with ether to afford the acids **12** and **13** (20 mg, 20%). Treatment of the acids with excess of ethereal diazomethane afforded the triesters **14** and **15**; $^1H$ NMR : $\delta$ 1.46-3.08 (12H), 3.38, 3.46 (both s, 3H), 3.64, 3.66, 3.68, 3.73 (all s, 9H).

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