

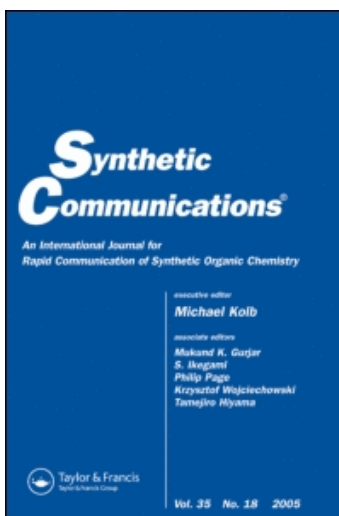
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REACTION OF BIS-LACTONE IN RIGID POLYCYCLES WITH
ALKYL LITHIUMS. SYNTHESIS OF NOVEL
OXA-CAGE COMPOUNDS

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Abstract : Reaction of bis-lactone embodied in the rigid tircyclo[5.2.1.0^{2,6}]decane **5** with MeLi and t-BuLi produced the novel oxa-cage compounds **9** and **11** instead of the expected ketones **6**.

Rigid polycyclic systems, because of the inherent ring strain, offer attractive opportunities for facile construction of a variety of interesting structural patterns. The thermal conversion¹ of pentacycloundecane to linear triquinane and our recent work² involving transformation of the tricyclo[5.2.1.0^{2,6}]decene **1** to bicyclo[5.2.1]decene **2** towards the synthesis of taxane diterpenes³ are two representative examples where inherent ring strain has been put to use. Another important characteristic feature of the rigid systems is the proximity of the nonbonded atoms that may interact resulting in unexpected reaction course. This is demonstrated by extremely fast and high yielding ring closure⁴ of the C₂, C₃-substituents of the diketone **4** to form the propellane **3**. In connection to an approach towards the synthesis of the novel

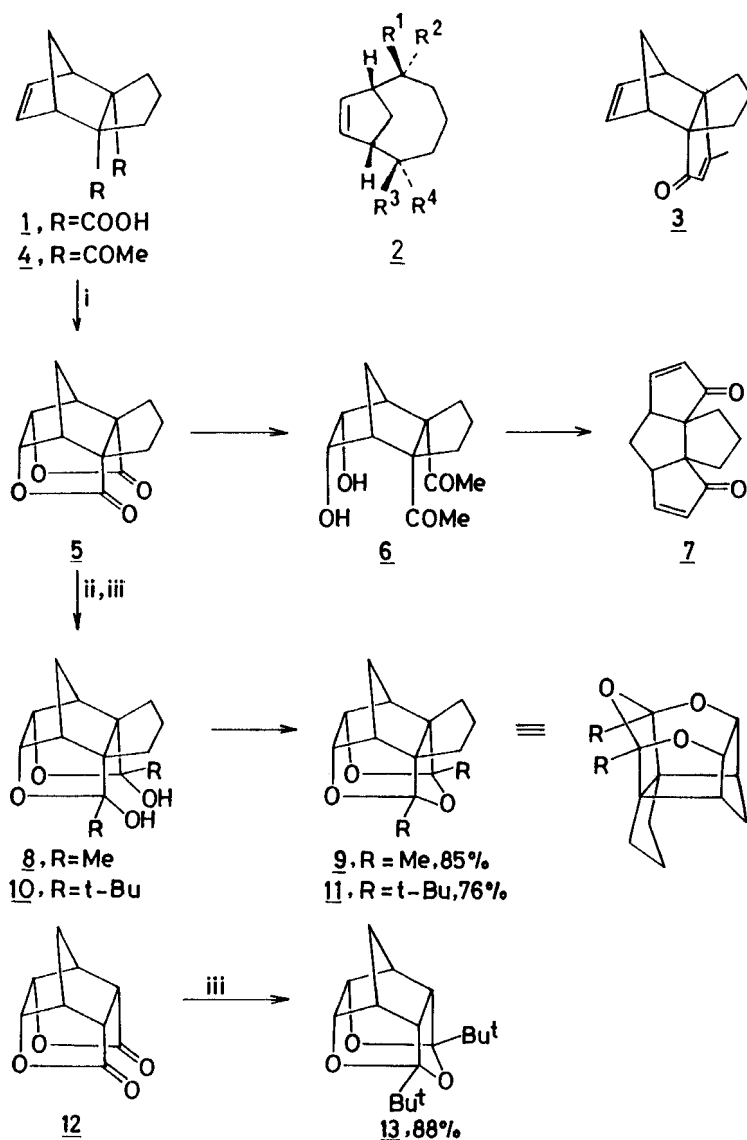
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tetraquinane **7**⁵ from **1**, we have encountered such an unusual reactivity mode that has led to facile synthesis of novel oxa-cage compounds. The results of this investigation is reported here.

The bis-lactone **5** was chosen as an intermediate for the projected synthesis of the tetraquinane **7**. The bis-lactone **5**, mp 188°C was prepared from the dicarboxylic acid **1** in 84% yield following the conventional procedure of iodo-lactonisation (Scheme-1). It was anticipated that reaction of the bis-lactone **5** with two equivalents of MeLi would produce the hydroxy-ketone **6** which after periodate cleavage of the diol and subsequent aldol ring closure would provide the tetraquinane **7**. When the bis-lactone **5** was allowed to react with 2.5 equivalent of MeLi in ether, the desired diketone **6** was not at all produced. The only compound, mp 98°C, isolated from this reaction in 85% yield was found to be the pentacyclo oxa-cage compound **9**. The highly symmetrical structure of this compound could easily be deduced from its ¹H NMR spectrum. A singlet at δ 1.28 for the methyl protons, a broad singlet at δ 2.38 for the bridge-head protons and a narrow triplet at δ 4.05 for the methine protons attached to oxygen are the characteristic spectral features of the structure **9**. The formation of this compound could be rationalised through the intermediate **8** which is initially formed on addition of MeLi to the lactone carbonyls. Because of the proximity of the rigidly held OH groups, the intermediate **8** undergoes spontaneous ring closure on elimination of a mole of water to produce the cage compound **9**. Similarly, when the bis-lactone **5** was allowed to react with *t*-BuLi, the oxa-cage compound **11** was formed in 76% yield. The simple bis-lactone **12** was also found to produce the pentacyclo oxa-cage **13** in excellent yield on reaction with *t*-BuLi.

Surprisingly, the oxa-cage compounds thus obtained, inspite of the presence of hydrolysis prone acetal units, were found to be totally resistant to hydrolytic conditions. The extreme stability of these compounds is possibly due to the

Scheme - 1



Reagents: i) I_2 - $NaHCO_3$ -KI, water, room temperature, 84%; ii) MeLi Ether, $0^\circ C$, 6-7h; iii) t-BuLi, Ether, $0^\circ C$ 6-7h.

existence of the acetal units being locked in a chair conformation as shown in Scheme-1.

In the context of the current interest associated with the synthesis and properties of cage compounds,⁶ in particular oxa-cage compounds,⁷ the present work describing the synthesis of a few novel oxa-cage compounds is significant. It will be of interest if the cavity enclosed by the three tetrahydrofuran rings of these compounds can be employed for cation-binding.

Experimental Section

endo-8,9-Dihydroxy tricyclo[5.2.1.0^{2,6}]decane-2,6-dicarboxylic acid Lactone (5). The diacid **1** (1.2 g, 5 mmol) was dissolved in a solution of NaHCO₃ (1.25 g, 15 mmol) in water (20ml). To it was added an iodine solution prepared by adding iodine (1.9 g, 7.5 mmol) and KI (3.45 g, 22.2 mmol) in water (10ml). The resulting homogeneous mixture was kept at room temperature for 3 days. It was then extracted with ethyl acetate (3x30ml). The organic extract was washed with aqueous Na₂S₂O₃ (5%), brine and dried (Na₂SO₄). Removal of solvent in vacuum afforded the dilactone **5** (1.1 g, 84%). Crystallisation from Et₂O-CH₂Cl₂ gave an analytically pure sample, mp 188 °C; IR 1780 cm⁻¹; ¹H NMR (60 MHz) : δ (CDCl₃) 1.26-2.80 (8H, m), 3.16 (2H, m) and 4.63 (2H, m). Anal. Calcd for C₁₂H₁₂O₄ : C, 65.44; H, 5.49. Found : C, 65.05; H, 5.41.

General procedure for reaction of the bis-lactones with alkyl lithiums. Synthesis of the oxa-cage compounds. To a well stirred ice-cold solution of the bis-lactone (2 mmol) in ether (10ml) was added the alkyl lithium (2.5 equivalent) under N₂ atmosphere. Stirring was continued for 6-7h at this temperature when a white precipitate appeared. The reaction mixture was then quenched with dropwise addition of saturated NH₄Cl solution. The organic layer was separated and dried (Na₂SO₄). Removal of solvent followed by column chromatography through silica gel (60-120 mesh) afforded the oxa-cage compounds.

Compound 9 : Yield 85%; mp 98 °C; ^1H NMR (60 MHz): δ (CCl_4) 1.21–2.18 (8H, m), 1.28 (6H, s), 2.38 (2H, br s) and 4.05 (2H, t, $J=3$ Hz). Anal. Calcd for $\text{C}_{14}\text{H}_{18}\text{O}_3$: C, 71.77; H, 7.74; Found : C, 71.46; H, 7.82.

Compound 11 : Yield 76%; mp 109 °C; ^1H NMR (60 MHz): δ (CCl_4) 1.03 (18H, s), 1.13–1.76 (8H, m), 2.36 (2H, br s) and 4.15 (2H, t, $J=3$ Hz). Anal. Calcd for $\text{C}_{20}\text{H}_{30}\text{O}_3$: C, 75.43; H, 9.49. Found : C, 75.1; H, 9.25.

Compound 13 : Yield 88%; mp 121 °C; ^1H NMR (60 MHz): δ (CCl_4) 0.96 (18H, s), 1.25 (2H, m), 1.71 (2H, br s), 2.55 (2H, br s) and 4.15 (2H, t, $J=3$ Hz). Anal. Calcd for $\text{C}_{17}\text{H}_{26}\text{O}_3$: C, 73.34; H, 9.41. Found : C, 72.78; H, 9.09.

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