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### TWO-FOLD CYCLOALKYLATIONS OF A BICYCLO[3.3.0]OCTANE-3,7-DIONE

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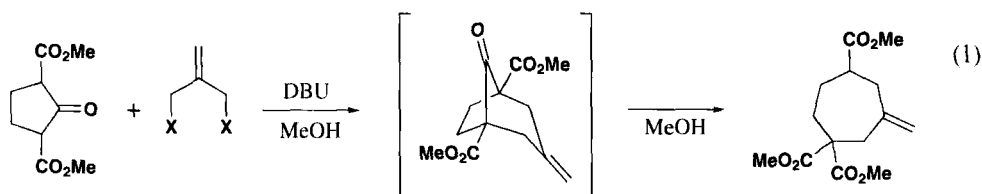
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## TWO-FOLD CYCLOALKYLATIONS OF A BICYCLO[3.3.0]OCTANE-3,7-DIONE

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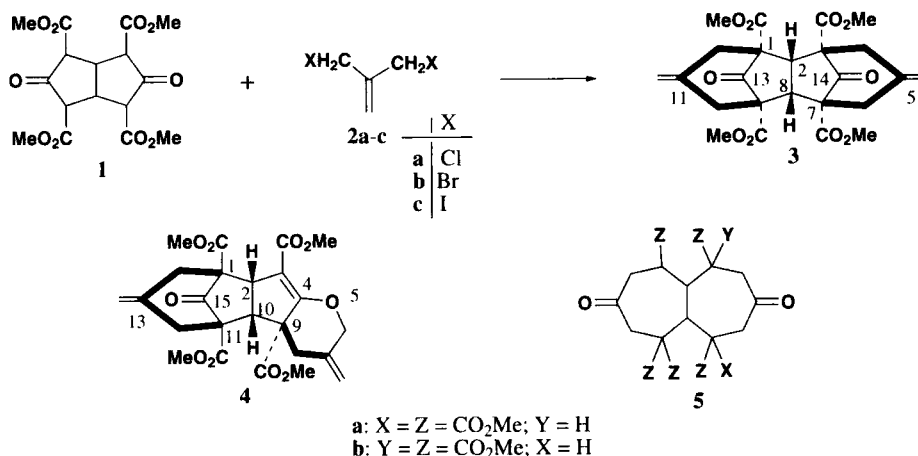
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An elegant three-step one-pot ring enlargement of dimethyl cyclopentanone-2,5-dicarboxylate with 2-halomethylallyl halides to give cycloheptane derivatives was reported quite recently by Rodriguez *et al.* (Eq. 1)<sup>1,2</sup> Our interest in double ring enlargements of substituted bicyclo[3.3.0]octanes to bicyclo[5.5.0]dodecanes as possible intermediates for certain polycycles,<sup>3,4</sup> prompted us to apply this new reaction to compound **1**.<sup>5</sup>



When **1** was treated with two equivalents of dichloro compound **2a** and five eq. of DBU, a tarry mixture was formed from which a low yield (3%) of crystals could be obtained. The product had the composition of C<sub>24</sub>H<sub>26</sub>O<sub>10</sub> and thus could not be the desired mixture of compounds **5a** and **5b** (*Scheme 1*). On the other hand, two molecules of **2** had been incorporated. The <sup>13</sup>C NMR spectrum included twenty four signals. There were indications for the presence of four methyl esters, one keto group, and three double bonds, and consequently the new compound could not be the precursor **3** either. The

most likely structure was **4**, the product of one "normal" C,C *bis*-alkylation and a second O,C *bis*-alkylation of the intermediate ambident ions. This was verified by an X-ray structure determination (Fig. 1).<sup>6,7</sup>

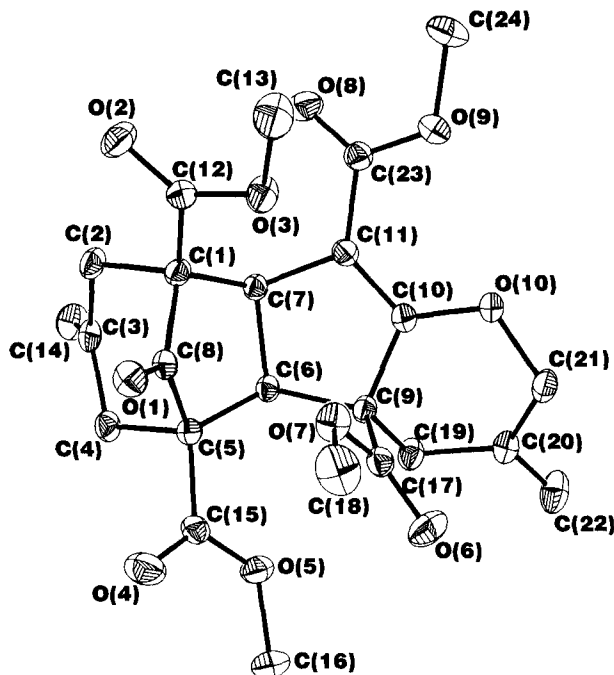


**Scheme 1**

As softer leaving groups favor C alkylations generally, the experiment was repeated with the bromo (**2b**) and the iodo (**2c**) compounds, instead of **2a**. With **2b**, the yield of **4** rose to 7%, but again **4** was the only definite product which could be isolated. When **2c** was used under the same reaction conditions, however, a second compound was formed and the total yield increased to 23%. Although it was not practical to separate the two compounds by chromatography (identical *R<sub>f</sub>* values), by crystallization or by fractional sublimation, it was obvious from the <sup>1</sup>NMR spectra that compound **3** was present. The ratio of **3**:**4** was about 1:2. To test which *bis*-alkylation was the primary path, an equivalent mixture of **1** and **2c** was reacted as before. Here again only **4** was observed. Since often C alkylations of ambident molecules are improved by phase-transfer catalysis,<sup>8</sup> the reaction was also performed in toluene with NaH as a base and tetrabutylammonium bromide as a catalyst. In this case, a very unpleasant mixture was obtained that could not be purified. The alkylation was also performed with potassium carbonate as a base in acetone. Then a 1:2 mixture of the isomers **3** and **4** was formed in a yield of 20%.

In all the cases considered up to this point, relatively weak bases were used which would generate only a small equilibrium concentration of the anions. With lithium diisopropylamide (LDA), it was hoped that *bis*-anions might be formed and trapped immediately. This procedure did indeed prove to be effective for when the conversion was carried out at low temperature, **3** was obtained as the sole product in 25% yield. Thus, pure **3** finally became available. A base-catalyzed isomerization **4** to **3** could not be effected with either DBU or very dilute NaOMe in methanol.

Compound **3** represents an interesting starting material for other polycycles. Unfortunately however, the originally planned retro-Claisen ring opening of **3** to a bicyclo[5.5.0]dodecane system



**Fig 1.** ORTEP Drawing of Tetramethyl ( $1\alpha,2\beta,9\alpha,10\beta,11\alpha$ )-7,13-dimethylene-5-oxa-15-oxotetracyclo[9.3.1.0<sub>2,10</sub>.0<sub>4,9</sub>]pentadec-3-ene-1,3,9,11-tetracarboxylate (**4**). Numbering not in accordance with chemical nomenclature.

(**5a** or **5b**) could not be made to occur although the more simple case of reaction (Eq. 1) could be reproduced easily. The failure of this conversion is in agreement with a report in the literature on a related system; the product from **1** and 2,3-(diiodomethyl)-butadiene could not be opened up by a retro-Claisen reaction either.<sup>2</sup> Furthermore, we were unable to extend the reaction of **1** with 1,3-diiodoacetone or 1,3-dibromoacetone dimethylketals to give compounds related to **3**. No conversions were observed under conditions similar to the ones used before.

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## EXPERIMENTAL SECTION

NMR spectra were recorded on Bruker instruments DRX 500 ( $^1\text{H}$ : 500 MHz,  $^{13}\text{C}$ : 125.78 MHz) or AC-250P ( $^1\text{H}$ : 250 MHz,  $^{13}\text{C}$ : 62.89 MHz) with TMS as internal standard. Mass spectra: Varian MAT-311 A (70 eV). IR spectra: Mattson Genesis FT-IR with Win-First software. Melting points are uncorrected.

**X-ray Structure Determination.**<sup>6,7</sup> Instrument Siemens P2(1); programs used: Siemens SHELXTL plus/SHELXL-97. Data for **4**: FW 474.45; crystal size: 1.0 x 0.5 x 0.3 mm; crystal system, space

group: triclinic P-1; unit cell dimensions:  $a = 10.431(2) \text{ \AA}$ ,  $b = 10.5630(10) \text{ \AA}$ ,  $c = 10.6000(10) \text{ \AA}$ ,  $\alpha = 97.750(10)^\circ$ ,  $\beta = 95.950(10)^\circ$ ,  $\gamma = 104.510(10)^\circ$ ; volume:  $1108.8(3) \text{ \AA}^3$ ;  $Z : 2$ ;  $D_{\text{calc}} 1.421 \text{ M g/m}^3$ ;  $F(000): 500$ ; absorption coefficient  $0.111 \text{ mm}^{-1}$ ; theta range for data collection:  $1.96$  to  $30.00^\circ$ ; index ranges:  $0 \leq h \leq 14$ ,  $-14 \leq k \leq 14$ ,  $-14 \leq l \leq 14$ ; reflections collected/unique:  $6785/6456$  [ $R(\text{int}) 0.0210$ ]; absorption correction: none; refinement method: full matrix least squares on  $F^2$ ; data/restraints/parameters:  $6456/0/412$ ; goodness-of-fit on  $F^2$ :  $1.020$ ; final  $R$  indices [ $I \geq 2s(1)$ ]:  $R1 = 0.0453$ ,  $wR2 = 0.1111[5150]$ ;  $R$  indices (all data):  $R1 = 0.0603$ ,  $wR2 = 0.1208$ ; extinction coefficient:  $0.067(4)$ ; largest diff. peak and hole:  $0.387$  and  $-0.248 \text{ e.\AA}^{-3}$ .

**Tetramethyl (1 $\alpha$ ,2 $\beta$ ,9 $\alpha$ ,10 $\beta$ ,11 $\alpha$ )-7,13-Dimethylene-5-oxa-15-oxotetracyclo[9.3.1.0<sup>2,10</sup>.0<sup>4,9</sup>]-pentadec-3-ene-1,3,9,11-tetracarboxylate (4).**- To a solution of  $2.22 \text{ g}$  ( $6.0 \text{ mmol}$ ) of **1**<sup>5</sup> and  $4.57 \text{ g}$  ( $30.0 \text{ mmol}$ ) of DBU in  $240 \text{ mL}$  of dry methanol was added  $1.50 \text{ g}$  ( $12.0 \text{ mmol}$ ) of 2-chloromethylallyl chloride (**2a**<sup>9</sup>) or  $2.6 \text{ g}$  ( $12.0 \text{ mmol}$ ) of the bromide (**2b**), respectively, in  $60 \text{ mL}$  of dry methanol. The mixture was refluxed for  $26 \text{ h}$ . Thereafter the methanol was distilled off, and the residue was taken up in  $120 \text{ mL}$  of water, then extracted thrice with  $200 \text{ mL}$  of ether each time. The combined organic phases were washed twice with  $50 \text{ mL}$  of water, once with brine. The solution was dried over  $\text{Na}_2\text{SO}_4$ , then concentrated whereupon  $85 \text{ mg}$  ( $3\%$ ) [or  $200 \text{ mg}$  ( $7\%$ ), respectively] of a colorless crystalline solid separated from the solution, mp.  $221\text{--}226^\circ$ . The crystals were washed with cold petroleum ether.

IR (KBr):  $1774, 1735, 1689, 1658 \text{ cm}^{-1}$ .  $^1\text{H}$  NMR ( $500 \text{ MHz}$ ,  $\text{CDCl}_3$ ):  $\delta$   $2.43$  (d,  $J = 16.3 \text{ Hz}$ ,  $1 \text{ H}$ ),  $2.76$  (dd,  $J = 14.2 + 2.6$ ,  $1 \text{ H}$ ),  $2.86$  (d,  $J = 9.7$ ,  $1 \text{ H}$ ),  $2.97$  (d,  $J = 14.6$ ,  $1 \text{ H}$ ),  $3.00$  (d,  $J = 14.2$ ,  $2 \text{ H}$ ),  $3.48\text{--}3.71$  (m,  $14 \text{ H}$ ; including  $4 \text{ s}$  for  $\text{CH}_3$ ),  $4.48$  (d,  $J = 13.2$ ,  $1 \text{ H}$ ),  $4.61$  (d,  $J = 13.2$ ,  $1 \text{ H}$ ),  $5.07$  (s,  $2 \text{ H}$ ),  $5.14$  (s,  $2 \text{ H}$ ).  $^{13}\text{C}$  NMR ( $125 \text{ MHz}$ ,  $\text{CDCl}_3$ ):  $\delta$   $39.1(\text{CH})$ ,  $47.7(\text{CH})$ ,  $49.1(\text{CH})$ ,  $51.2(\text{CH})$ ,  $51.3(\text{CH}_2)$ ,  $51.6$ ,  $52.0$ ,  $52.1$ ,  $53.1$  ( $4 \times \text{CH}_3$ ),  $58.6$ ,  $59.3$ ,  $59.9$  ( $3 \times \text{C}_{\text{quat}}$ ),  $72.0(\text{CH}_2)$ ,  $106.6(\text{C}_{\text{quat}})$ ,  $113.6(\text{CH}_2)$ ,  $118.2(\text{CH}_2)$ ,  $137.4(\text{C}_{\text{quat}})$ ,  $138.0(\text{C}_{\text{quat}})$ ,  $163.4$ ,  $164.2$ ,  $168.3$ ,  $169.2$  ( $4 \times \text{CO}_2\text{Me}$ ),  $170.5(\text{C}_{\text{quat}})$ ,  $205.9(\text{CO})$ . MS (EI,  $70 \text{ eV}$ ,  $m/z$  (%):  $474$  ( $\text{M}^+$ ,  $15$ ),  $442$  ( $27$ ),  $415$  ( $35$ ),  $383$  ( $100$ ).

Anal. Calcd. for  $\text{C}_{24}\text{H}_{26}\text{O}_{10}$ : C,  $60.76$ ; H,  $5.52$ ; Found: C,  $60.30$ ; H,  $5.55$

**Tetramethyl (1 $\alpha$ ,2 $\beta$ ,3 $\alpha$ ,7 $\alpha$ ,8 $\beta$ ,9 $\alpha$ )-5,11-Dimethylene-13,14-dioxotetracyclo[7.3.1.1<sup>3,7</sup>.0<sup>2,8</sup>]-tetradecane-1,3,7,9-tetracarboxylate (3).**- To a stirred solution of LDA (prepared at  $-78^\circ$  from  $2.67 \text{ g}$  ( $26.4 \text{ mmol}$ ) of diisopropylamine and  $17.0 \text{ mL}$  ( $26.4 \text{ mmol}$ ) of a  $1.55 \text{ M}$  hexane solution of butyllithium in  $30 \text{ mL}$  of dry THF) was added  $2.22 \text{ g}$  ( $6.0 \text{ mmol}$ ) of **1** in  $20 \text{ mL}$  of THF over a period of  $1/2 \text{ hr}$  at  $-78^\circ$ . The mixture was stirred for an additional hour and then treated dropwise with  $4.06 \text{ g}$  ( $13.2 \text{ mmol}$ ) of **2c** in  $25 \text{ mL}$  of THF within  $30 \text{ min.}$  at  $-78^\circ$ . Stirring was continued for  $90 \text{ min.}$  in the cold, then for  $15 \text{ h}$  at RT. The solvents were removed and the residue was taken up in  $100 \text{ mL}$  of water. This solution was extracted four times with  $30 \text{ mL}$  of ether each time, and the combined organic phases were washed with water and brine, dried over  $\text{Na}_2\text{SO}_4$  and concentrated. The orange colored semi-crystalline product which separated was crystallized from ethyl acetate to give  $712 \text{ mg}$  ( $25\%$ ) of **3** as a colorless solid, mp.  $268\text{--}273^\circ$  (dec.).

IR (KBr):  $1781, 1739, 1654 \text{ cm}^{-1}$ .  $^1\text{H}$  NMR ( $250 \text{ MHz}$ ,  $\text{CDCl}_3$ ):  $\delta$   $2.86$  (d,  $J = 15.2 \text{ Hz}$ ,  $4 \text{ H}$ ),  $3.09$  (d,  $J$

= 15.2, 4 H), 3.23 (s, 2 H), 3.62 (s, 12 H), 5.17 (s, 4 H).  $^{13}\text{C}$  NMR (62 MHz,  $\text{CDCl}_3$ ):  $\delta$  47.8 ( $\text{CH}_2$ ), 50.0 (CH), 51.8 ( $\text{CH}_3$ ), 60.1 (C-CO<sub>2</sub>Me), 118.0 (C=CH<sub>2</sub>), 138.0 (C=CH<sub>2</sub>), 168.7 (CO<sub>2</sub>Me), 205.1 (CO).

Anal. Calcd. for  $\text{C}_{24}\text{H}_{26}\text{O}_{10}$ : C, 60.76; H, 5.52; Found: C, 60.40; H, 5.56

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