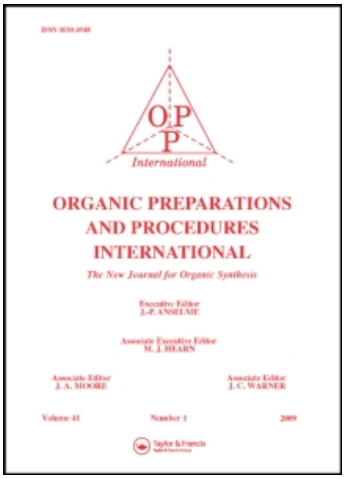


Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

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

Eckehard Volker Dehmlow[a]; Hans-Jorg Breyholz[a]; Beate Neumann[a]; Hans-Georg Stammler[a]
[a] Fakultät für Chemie, Universität Bielefeld, Bielefeld, GERMANY

To cite this Article Dehmlow, Eckehard Volker , Breyholz, Hans-Jorg , Neumann, Beate and Stammler, Hans-Georg(2001) 'TWO-FOLD CYCLOALKYLATIONS OF A BICYCLO[3.3.0]OCTANE-3,7-DIONE', Organic Preparations and Procedures International, 33: 4, 386 — 390
To link to this Article: DOI: 10.1080/00304940109356607
URL: http://dx.doi.org/10.1080/00304940109356607

13. W. M. Best, E. L. Ghisalberti and M. Powell, *J. Chem. Res.(s)*, 388 (**1998**).

14. Gavin M. Buchan and Alan B. Turner, *J. Chem. Soc. Perkin Trans. 1*, 2115 (**1975**).

15. H. W. Seely and P. J. V. Denmark, *Microbes in Action*, W. H. Freeman & Co., USA, 1972.

16. G. Bram, A. Loupy and M. Majdoub, *Tetrahedron*, **46**, 5167 (1990).

17. Heim, *Ber.*, **44**, 2016 (1911).

****

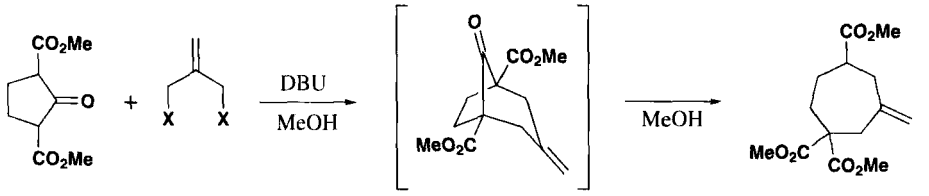
TWO-FOLD CYCLOALKYLATIONS OF A BICYCLO[3.3.0]OCTANE-3,7-DIONE

Submitted by (11/27/00)

Eckehard Volker Dehmlow*, Hans-Jörg Breyholz, Beate Neumann, and Hans-Georg Stammler

Fakultät für Chemie, Universität Bielefeld, Postfach 100 131, D-33501 Bielefeld, GERMANY
e-mail: dehmlow@post.uni-bielefeld.de; Fax:(xx49) 521-106-6146

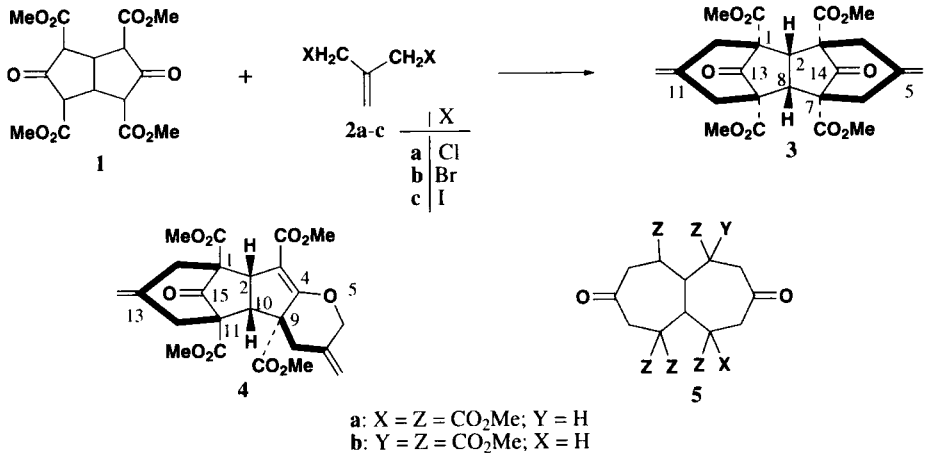
An elegant three-step one-pot ring enlargement of dimethyl cyclopentanone-2,5-dicarboxylate with 2-halomethylallyl halides to give cycloheptane derivatives was reported quite recently by Rodriguez *et al.* (Eq. 1)[1,2] Our interest in double ring enlargements of substituted bicyclo[3.3.0]octanes to bicyclo[5.5.0]dodecanes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



(1)

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 $C_{24}H_{26}O_{10}$ 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 ^{13}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).[6,7]



a: X = Z = CO_2Me; Y = H
b: Y = Z = CO_2Me; X = H

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_f values), by crystallization or by fractional sublimation, it was obvious from the ^{1}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,[8] 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

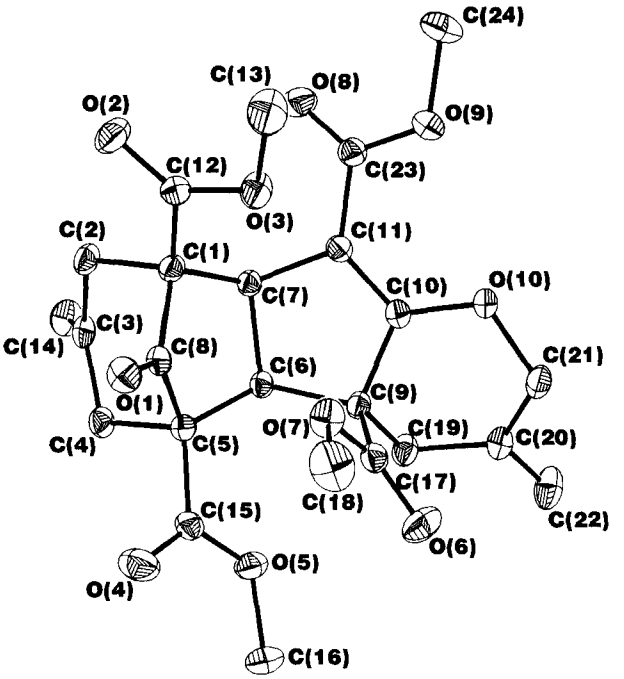


Fig 1. *ORTEP Drawing of Tetramethyl (1α,2β,9α,10β,11α)-7,13-dimethylene-5-oxa-15-oxotetracyclo[9.3.1.02,10.04,9]pentadec-3-ene-1,3,9,11-tetracarboxylate (4). Numbering not in accordance with chemical nomenclature.*

(**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.[2] 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.

Acknowledgements.- Partial support was given by "Fonds der Chemischen Industrie". Thanks are due to Prof. P. Jutzi of this faculty for making available his X-ray equipment.

EXPERIMENTAL SECTION

NMR spectra were recorded on Bruker instruments DRX 500 (^{1}H: 500 MHz, ^{13}C: 125.78 MHz) or AC-250P (^{1}H: 250 MHz, ^{13}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:[6,7] 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) Å, b = 10.5630(10) Å, c = 10.6000(10) Å, a = 97.750(10)°, b = 95.950(10)°, g = 104.510(10)°; volume: 1108.8(3) $Å^3$; Z : 2; D_{calc} 1.421 M g/m^3; F(000): 500; absorption coefficient 0.111 mm^{-1}; theta range for data collection: 1.96 to 30.00°; index ranges: 0 ≤ h ≤14, -14 ≤ k ≤ 14, -14 ≤ l ≤14; reflections collected/unique: 6785/6456 [R(int) 0 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 ≥ 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 e.$Å^{-3}$.

Tetramethyl (1α,2β,9α,10β,11α)-7,13-Dimethylene-5-oxa-15-oxotetracyclo[9.3.1.$0^{2,10}$.$0^{4,9}$]-pentadec-3-ene-1,3,9,11-tetracarboxylate (4).- To a solution of 2.22 g (6.0 mmol) of **1**[5] and 4.57 g (30.0 mmol) of DBU in 240 mL of dry methanol was added 1.50 g (12.0 mmol) of 2-chloromethylallyl chloride (**2a**[9]) or 2.6 g (12.0 mmol) of the bromide (**2b**), respectively, in 60 mL of dry methanol. The mixture was refluxed for 26 h. Thereafter the methanol was distilled off, and the residue was taken up in 120 mL of water, then extracted thrice with 200 mL of ether each time. The combined organic phases were washed twice with 50 mL of water, once with brine. The solution was dried over Na_2SO_4, then concentrated whereupon 85 mg (3%) [or 200 mg (7%), respectively] of a colorless crystalline solid separated from the solution, mp. 221-226°. The crystals were washed with cold petroleum ether.

IR (KBr): 1774, 1735, 1689, 1658 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 2.43 (d, J = 16.3 Hz, 1 H), 2.76 (dd, J = 14.2 + 2.6, 1 H), 2.86 (d, J = 9.7, 1 H), 2.97 (d, J = 14.6, 1 H), 3.00 (d, J = 14.2, 2 H), 3.48-3.71 (m, 14 H; including 4 s for CH_3), 4.48 (d, J = 13.2, 1 H), 4.61 (d, J = 13.2, 1 H), 5.07 (s, 2 H), 5.14 (s, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 39.1(CH), 47.7 (CH), 49.1 (CH), 51.2 (CH), 51.3 (CH_2), 51.6, 52.0, 52.1, 53.1 (4 x CH_3), 58.6, 59.3, 59.9 (3 x C_{quat}), 72.0 (CH_2), 106.6 (C_{quat}), 113.6 (CH_2), 118.2 (CH_2), 137.4 (C_{quat}), 138.0 (C_{quat}), 163.4, 164.2, 168.3, 169.2 (4 x CO_2Me), 170.5 (C_{quat}), 205.9 (CO). MS (EI, 70 eV, m/z (%): 474 (M^+, 15), 442 (27), 415 (35), 383 (100).

Anal. Calcd. for $C_{24}H_{26}O_{10}$: C, 60.76; H, 5.52; Found: C, 60.30; H, 5.55

Tetramethyl (1α,2β,3α,7α,8β,9α)-5,11-Dimethylene-13,14-dioxotetracyclo[7.3.1.1^{3,7}.$0^{2,8}$]-tetradecane-1,3,7,9-tetracarboxylate (3).- To a stirred solution of LDA (prepared at –78° from 2.67 g (26.4 mmol) of diisopropylamine and 17.0 mL (26.4 mmol) of a 1.55 M hexane solution of butyllithium in 30 mL of dry THF) was added 2.22 g (6.0 mmol) of **1** in 20 mL of THF over a period of 1/2 hr at –78°. The mixture was stirred for an additional hour and then treated dropwise with 4.06 g (13.2 mmol) of **2c** in 25 mL of THF within 30 min. at –78°. Stirring was continued for 90 min. in the cold, then for 15 h at RT. The solvents were removed and the residue was taken up in 100 mL of water. This solution was extracted four times with 30 mL of ether each time, and the combined organic phases were washed with water and brine, dried over Na_2SO_4 and concentrated. The orange colored semi-crystalline product which separated was crystallized from ethyl acetate to give 712 mg (25%) of **3** as a colorless solid, mp. 268-273° (dec.).

IR (KBr): 1781, 1739, 1654 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ 2.86 (d, J = 15.2 Hz, 4 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}C NMR (62 MHz, $CDCl_3$): δ 47.8 (CH_2), 50.0 (CH), 51.8 (CH_3), 60.1 (C-CO_2Me), 118.0 (C=CH_2), 138.0 (C=CH_2), 168.7 (CO_2Me), 205.1 (CO).

Anal. Calcd. for $C_{24}H_{26}O_{10}$: C, 60.76; H, 5.52; Found: C, 60.40; H, 5.56

REFERENCES

1. T. Lavoisier-Gallo, E. Charonet and J. Rodriguez, *J. Org. Chem.*, **63**, 900 (1998).

2. J. Rodriguez, *Synlett*, **5**, 505 (1999).

3. E. V. Dehmlow, Th. Heitkamp and D. Sielemann, *Eur. J. Org. Chem.*, 3135 (**1999**).

4. E. V. Dehmlow, H.-J. Breyholz, B. Neumann, A. Stammler and H.-G. Stammler, *Eur. J. Org. Chem.*, 1413 (**2001**).

5. S. H. Bertz, J. M. Cook, A. Gawish and U. Weiss, *Org. Synth.*, **64**, 27 (1986).

6. X-ray work was performed by B. Neumann, A. Stammler and H.-G. Stammler.

7. Other details of the crystal structure investigation have been deposited at the Cambridge Crystallographic Data Centre as supplementary publication no. 149052. Copies of the data are available free of charge on application to The Director, CCDC, 12 Union Road, Cambridge CB21EZ, UK (Fax: intern. (+) 441223336-033; e-mail: deposit@ccdc.cam.ac.uk.

8. E. V. Dehmlow and S. S. Dehmlow, *Phase-Transfer Catalysis*, 3rd Ed., VCH, Weinheim, (**1993**).

9. S. Latour and J.-D. Wuest, *Synthesis*, 742 (**1987**).

****