Synthesis of 1,6-Dioxadispiro[2.0.4.4]dodecan-7-one

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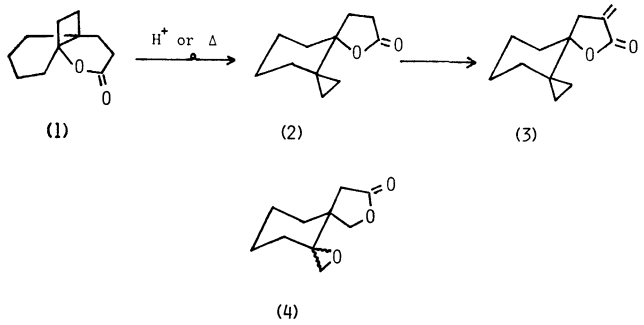
Synopsis. 1,6-Dioxadispiro[2.0.4.4]dodecan-7-one, a useful intermediate of dispiro-α-methylene-γ-butyrolactones, was synthesized in a good overall yield by the cycloaddition of dichloroketene to 1,2-dimethylenecyclohexane, and the zinc dust reduction of the chlorine atoms, followed by the Baeyer-Villiger oxidation with *m*-chloroperbenzoic acid.

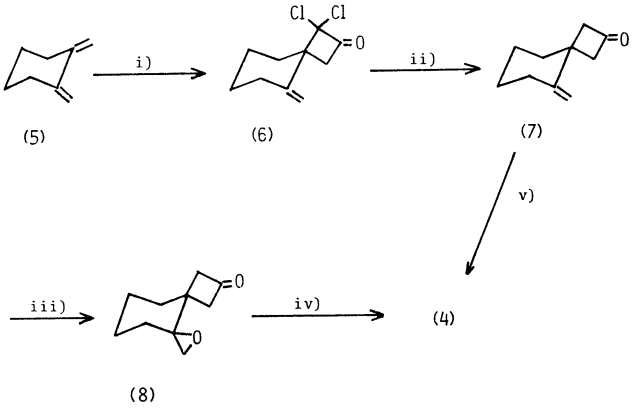
Recently, much attention has been paid on the chemistry of α-methylene-γ-butyrolactones, especially, concerning the structure-biochemical activity relationship, because a number of naturally occurring sesquiterpene lactones display antitumor and/or cytotoxic activity attributed to this moiety.[1] From the above point of view, we previously reported on the synthesis of the dispiro-γ-butyrolactone (**2**), being a useful intermediate of the dispiro-α-methylene-γ-butyrolactone (**3**) having a spiro cyclopropane ring,[2] by the acid catalyzed or thermally induced cyclobutyl-cyclopropylcarbinyl type rearrangement of the propellalactone (**1**).[5] As part of the study on the synthesis of various types of dispiro-γ-butyrolactones, we wish to report here a convenient synthesis of 1,6-dioxadispiro[2.0.4.4]-dodecan-7-one (**4**) having a spiro epoxide linkage which is expected to enhance the reactivity of the conjugated lactone toward biological nucleophiles.[1a]



The epoxy-γ-lactone **4** was prepared as outlined in Scheme 1; i) the cycloaddition of dichloroketene to 1,2-dimethylenecyclohexane employing the high-dilution method,[6] ii) the reductive removal of the chlorine atoms with zinc dust–acetic acid,[7] iii) the epoxidation with *m*-chloroperbenzoic acid (MCPBA), and iv) the Baeyer-Villiger oxidation.

A solution of equal amounts of trichloroacetyl chloride and phosphoryl chloride in ether was added dropwise over a period of 5 h to an ethereal solution of 1,2-dimethylenecyclohexane (**5**), which was readily available from *cis*-1,2-cyclohexanedicarboxylic anhydride, and excess of activated zinc, and the mixture was refluxed for 30 h. The 1 : 1 cycloadduct, that is the spiro dichlorocyclobutanone (**6**), was obtained in a 61% yield.[8] The reductive removal of the chlorine atoms from **6** with excess of zinc dust and acetic acid in ether at room temperature gave the spiro cyclobutanone (**7**) in a 71% yield. The epoxidation of **7** with 1.2 equivalent of MCPBA in chloroform at room temperature for 3 h afforded the epoxy cyclobutanone (**8**) in a 71% yield.[9] Finally, the Baeyer-Villiger oxidation of **8** with 1.2 equivalent of MCPBA in chloroform at room temperature for 6 d gave a 1 : 1 mixture of two epoxy-γ-lactones **4**[10] in a 70% yield. The γ-lactone **4** was also obtained directly from the cyclobutanone **7** by the oxidation with 3-fold excess of MCPBA for 6 d (77%).

In this way, 1,6-dioxadispiro[2.0.4.4]dodecan-7-one **4**, a key compound for the synthesis of dispiro-α-methylene-γ-butyrolactones having an epoxide linkage, was synthesized in a good yield by means of the efficient dichloroketene addition.



Scheme 1.

i) Cl_3CCOCl, Zn(Cu), $POCl_3$, Et_2O, 30 h; ii) Zn, AcOH, Et_2O, 30 h; iii) MCPBA (1.2 eq.), $CHCl_3$, 3 h; iv) MCPBA (1.2 eq.), $CHCl_3$, 6 d; v) MCPBA (3 eq.), $CHCl_3$, 6 d.

Experimental

IR spectra were recorded using a JASCO IR-G spectrometer. ^1H NMR spectra were obtained on a JEOL JNM-PS-100 spectrometer, using Me_4Si as an internal standard and CCl_4 as a solvent. MS spectra were measured with a Hitachi RMU-6E spectrometer.

1,2-Dimethylenecyclohexane (**5**)[11] was prepared in a similar method to that of Davalian *et al.*,[12] and purified by distillation using a spinning-band distillation column.

1,1-Dichloro-5-methylenespiro[3.5]nonan-2-one (6). A solution of 8.1 ml (0.078 mol) of freshly distilled trichloroacetyl chloride and 6.8 ml (0.078 mol) of phosphoryl chloride (distilled from K_2CO_3) in 440 ml of dry ether was added dropwise over 5 h to a mixture of 8.4 g (0.078 mol) of **5** and 7.6 g (0.114 mol) of activated zinc in 600 ml of dry ether under a nitrogen atmosphere. The reaction mixture was stirred at reflux for additional 30 h. The excess zinc was filtered and washed with ether. The filtrate was concentrated *in vacuo* to *ca.* 25% of its original volume, an equal volume of pentane added, and

the solution stirred for 1 h to precipitate zinc salts. The solution was decanted from the residue, washed successively with water, a cold saturated $NaHCO_3$ solution and brine, and dried (Na_2SO_4). The solvent was removed *in vacuo* and the residue was distilled under reduced pressure. After recovery of 2.6 g of **5** (bp 60 °C/90 Torr), 7.1 g of **6** was obtained as pale yellow oil (61%): bp 86—88 °C/0.8 Torr; IR 1800, 1635 cm^{-1}; NMR δ 1.16—2.50 (m, 8H), 2.66 (d, J= 17 Hz, 1H), 3.62 (d, J=17 Hz, 1H), 4.80 (s, 1H), 5.08 (s, 1H); MS *m/e* 222 (M^++4), 220 (M^++2), 218 (M^+). Found: C, 54.91; H, 5.56%. Calcd for $C_{10}H_{12}OCl_2$: C, 54.82; H, 5.52%.

5-Methylenespiro[3.5]nonan-2-one (7). A mixture of 7.0 g (0.032 mol) of **6**, 10 g of zinc, and 10 ml of acetic acid in 150 ml of dry ether was stirred at room temperature for 30 h.[13] The reaction mixture was filtered and the filtrate was washed with saturated $NaHCO_3$ solution, brine, and dried (Na_2SO_4). The solvent was removed *in vacuo* and the residue was distilled under reduced pressure to give 3.4 g of the cyclobutanone **7** (71%): bp 68—69 °C/3 Torr; IR 1775, 1635 cm^{-1}; NMR δ 1.45—1.82 (m, 6H), 2.02—2.28 (m, 2H), 2.45—2.80 (m, 2H), 2.88—3.24 (m, 2H), 4.68 (s, 1H), 4.78 (s, 1H); MS *m/e* 150 (M^+). Found: C, 79.84; H, 9.54%. Calcd for $C_{10}H_{14}O$: C, 79.95; H, 9.39%.

1-Oxadispiro[2.0.3.4]undecan-6-one (8). A solution of 250 mg (1.7 mmol) of **7** and 440 mg (2.0 mmol) of 80% MCPBA in 10 ml of chloroform was stirred at room temperature for 3 h. The solution was washed with saturated Na_2SO_3 solution, saturated $NaHCO_3$ solution, water, and dried (Na_2SO_4). The solvent was evaporated *in vacuo* to give 197 mg of **8** as colorless oil (71%). Analytical sample was obtained by preparative GLC: IR 1775 cm^{-1}; NMR δ 1.20—2.08 (m, 8H), 2.24—3.12 (m, 6H); MS *m/e* 166 (M^+). Found: C, 72.05; H, 8.70%. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49%.

1,6-Dioxadispiro[2.0.4.4]dodecan-7-one (5). A solution of 100 mg (0.65 mmol) of **8** and 170 mg (0.78 mmol) of 80% MCPBA in 10 ml of chloroform was stirred at room temperature and the progress of the reaction was monitored by GLC. After 6 d, the solution was treated as described above. Chromatography on silica gel (20% ether–petroleum ether) gave 87 mg of **4** as colorless oil (74%).[10] 471 mg of **4** was also obtained in 77% yield from the reaction of 500 mg (3.3 mmol) of **7** and 2.2 g (9.9 mmol) of 80% MCPBA in 27 ml of chloroform for 6 d: IR 1765 cm^{-1}; NMR δ 1.20—2.00 (m, 8H), 2.04—2.72 (m, 4H), 3.60—4.20 (m, 2H); MS *m/e* 182 (M^+). Found: C, 65.72; H, 7.75%. Calcd for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74%.

References

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2) α-Methylenation of **2** was readily conducted by the usual procedure[3] to afford **3** in a good yield.[4]

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4) Unpublished results.

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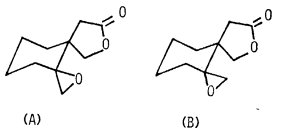
6) L. R. Krepski and A. Hassner, *J. Org. Chem.*, **43**, 2879 (1978).

7) D. A. Bak and W. T. Brady, *J. Org. Chem.*, **44**, 107 (1979).

8) The 1:2 cycloadduct was not obtained.

9) Trace of **4** was also obtained besides the epoxide **8**.

10) Though **4** consisted of two isomers (**A**) and (**B**) they could not be separated completely by GLC or column chromatography; therefore they were characterized as a mixture. Attempt on their separation and structure assignment is in progress.



(A) (B)

11) P. D. Bartlett, A. S. Wingrove, and R. Owyang, *J. Am. Chem. Soc.*, **90**, 6067 (1968).

12) D. Davalian and P. J. Garratt, *J. Am. Chem. Soc.*, **97**, 6883 (1975). **5** was prepared by esterification of *cis*-1,2-cyclohexanedicarboxylic anhydride, reduction with $LiAlH_4$, and treatment with methanesulfonyl chloride followed by reaction with $KOBu^t$.

13) After 2 h, the monochlorocyclobutanone was obtained as a main product which was purified by preparative GLC: bp 107—108 °C/5 Torr; IR 1785, 1635 cm^{-1}; NMR δ 1.16—2.20 (m, 8H), 2.85 (s, 2H), 4.82 (s, 1H), 4.86 (s, 1H), 4.95 (s, 1H); MS *m/e* 186 (M^++2), 184 (M^+). Found: C, 64.90; H, 7.13%. Calcd for $C_{10}H_{13}OCl$: C, 65.04; H, 7.10%.