776 *J. Org. Chem.* **1993,** *58,* 776–778

Multiple Functionalization of Medium-Sized Carbocyclic Rings. From Cyclooctanone to a 1,5-Dialkoxycyclooctatetraene

Leo A. Paquette,* Timothy J. Watson, and Dirk Friedrich

Evans Chemical Laboratories, The Ohio State University, Columbus, Ohio 43210

Received August 25, 1992

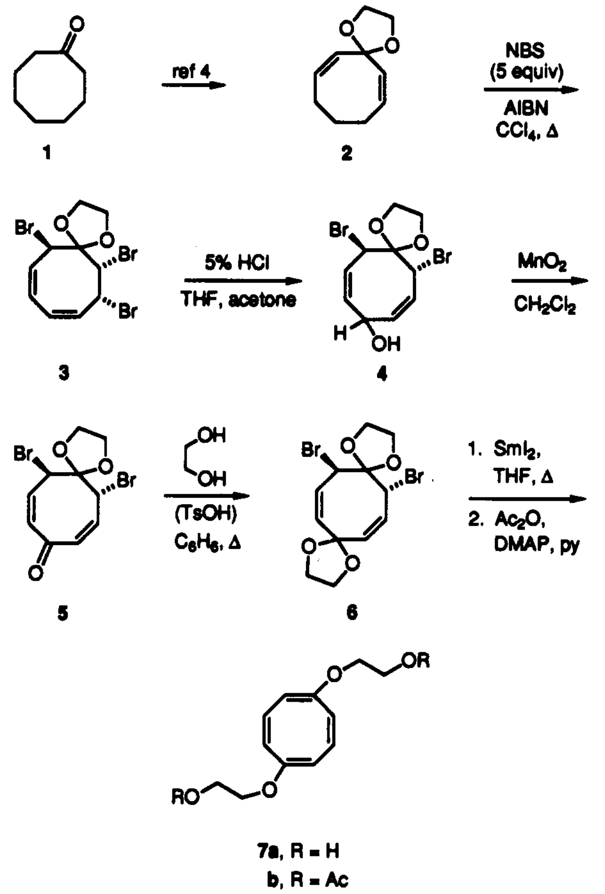
The intense scrutiny given by the Cope school to medium-sized carbocycles successfully established that transannular reactions occur with particular facility in 8-, 9-, and 10-membered rings.[1] This predilection stems from the existence of ring strain brought on by transannular interactions and the close spatial proximity attained by atoms in these sterically congested environments. In recent years, interest has grown considerably in the synthesis and properties of cyclooctatetraenes.[2] Also, the discovery of more than 100 cyclooctanoid-based sesqui-, di-, and sesterterpenes has spurred extensive activity in the total synthesis of this class of natural products.[3]

However, neither of these endeavors has provided the occasion for scrutinizing the degree to which an eight-membered ring can be functionalized *without* fostering one or another unwanted transannular process. We detail here a series of transformations that leads from cyclooctanone to a 1,5-dialkoxycyclooctatetraene. Although formed via rather unusual mechanisms, the several richly functionalized intermediates in the scheme are seen to maintain cyclooctanoid integrity throughout.

Results and Discussion

The conversion of cyclooctanone (1) to diene ketal 2 was accomplished straightforwardly by means of the Garbisch procedure (Scheme I).[4,5] Heating 2 with 5 equiv of *N*-bromosuccinimide (NBS) and a catalytic quantity of AIBN in CCl_4 for 5 days gave tribromide 3, a highly crystalline solid isolated in 25% yield. 2-D NMR analysis of this product in tandem with NOE studies (Table I) indicated 3 to have the stereochemistry shown. This conclusion was further substantiated by X-ray crystallographic analysis (Figure 1).[6] The predominant conformer of 3 in solution exhibits chemical exchange with a minor constituent (~10%), as seen from the effects of cosaturation in NOED and negative cross-peaks in phase-sensitive 2D-NOESY.

Scheme I



The formation of 3 can be rationalized in the context of only two reasonable working assumptions: (a) bromine is incorporated uniquely via allylic substitution, and (b) allylic rearrangement, when operative, occurs suprafacially. Consideration of the several possible pathways involving these two processes in random order results in eventual merging into the syn,anti-tribromo substitution plan. The latter is considered to be the thermodynamically most stable arrangement from among the possible isomers related by suprafacial 1,3-shifting. Simplification arises if only those hydrogen atoms positioned perpendicular to the allylic plane engage in reaction. Additionally, pathways that minimize steric interactions involving those bromide atoms already incorporated should be kinetically favored. Considerable restriction of the available options materializes if all 1,4-bromination steps are regarded as electronically disfavored because of the electron-withdrawing influence of the neighboring bromine substituent.[7]

Reliance on the preceding considerations leads us to advance Scheme II as the probable course of events leading to the production of 3. For steric reasons, **A** and **B** are further functionalized only by 1,3-anti and 1,5-anti bromination, respectively. Intermediate **C** presumably engages in third-stage allylic substitution because C-5 is doubly activated. Symmetry considerations in **C** discount the need for concern about π-facial stereoselectivity.

Stirring 3 with 5% HCl in a 1:1 mixture of acetone and THF for 2 days at rt resulted not in ketal hydrolysis but in solvolysis to give alcohol 4. The S_N' nature of this reaction was strongly supported by 2D-COSY studies performed at 300 MHz (Table I). Near-quantitative conversion of 4 to 5 resulted upon exposure of the former to activated manganese dioxide in CH_2Cl_2 solution. That

---

(1) Cope, A. C.; Martin, M. M.; McKervey, M. A. *Quart. Rev.* **1966,** *20,* 119.

(2) (a) Paquette, L. A. *Tetrahedron* **1975,** *31,* 2855. (b) Fray, G. I.; Saxton, R. G. *The Chemistry of Cyclooctatetraene Derivatives*; Cambridge University Press: Cambridge, 1978. (c) Paquette, L. A. In *Advances in Theoretically Interesting Molecules*; Thummel, R. P., Ed.; JAI Press: Greenwich, 1992; Vol. 2, pp 1–77. (d) Paquette, L. A. *Acc. Chem. Res.*, submitted for publication.

(3) Petasis, N. A.; Patane, M. A. *Tetrahedron* **1992,** *48,* 5757.

(4) Garbisch, E. *J. Org. Chem.* **1965,** *30,* 2109.

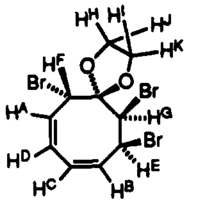
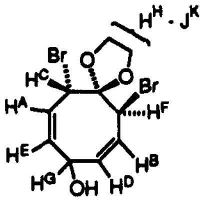
(5) For a recent application of this tactic in a different setting, see: Paquette, L. A.; Bacqué, E.; Bishop, R.; Watson, T. J. *Tetrahedron Lett.* **1992,** *33,* 6559.

(6) The authors have deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK.

(7) Pizey, J. S. *Synthetic Reagents*; Ellis Horwood: Chichester, 1974; Vol. II, Chapter 1.

0022-3263/93/1958-0776$04.00/0

Table I. 300-MHz ^{1}H NMR Spectral Data, Coupling Constants, and NOE Studies Involving 3 and 4 (9:1 $CDCl_3/C_6D_6$ Solution)[a]

 **3**		 **4**	
A, 5.93 dd	^2J: HJ = IK = 7.5	A, 5.72 ddd	^3J: AC = 8.5
B, 5.84 dd	^3J: AD = BC = 10.5	B, 5.60 ddd	AE = 12.0
C, 5.75 dd (br)	HK = 8.5	C, 5.49 ddd	BD = 11.5
D, 5.70 dd (br)	AF = 8.0	D, 5.39 dddd	BF = 9.5
E, 4.95 d (br)	BE = 7.0	E, 5.30 dddd	DG = 3.0
F, 4.89 d (br)	HI = JK = 6.5	F, 5.06 d (br)	EG = 5.5
G, 4.08 s (br)	IJ = 4.0	G, 4.40 m (br)	^4J: AG = 1
H, 4.03 ddd	CD = 3.5	H–K, 4.15–4.02 m	BG = 3.0
I, 3.92 ddd	EG = <1		CE = 1.5
J, 3.81 ddd	^4J: CE ≈ DF <1		DE = 1
K, 3.61 ddd			DF = 1
			^5J: CG = 1
			FG < 1

NOE

↯H^G → H^E, H^K

↯H^E → H^G

↯H^K → H^G

[a] The chemical shift values are in δ; the *J* values are in Hz.

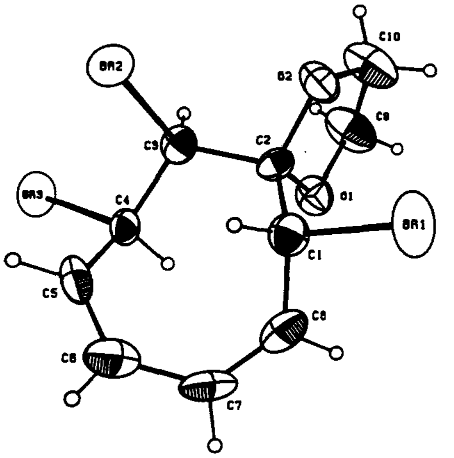
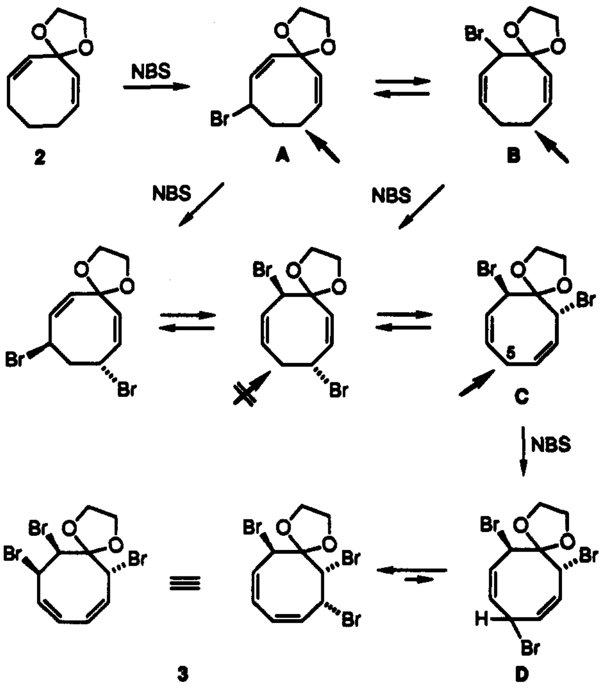


Figure 1.

a C_2-symmetric intermediate had been formed was clearly evident from the simplified ^{1}H and six-line ^{13}C NMR spectra.

Ketalization of **5** set the stage for assessing the ease of reductive debromination of **6** and the particular direction that would be followed when such a process was triggered. Remarkably, **6** proved unreactive toward nickel carbonyl in DMF[8,9] over the temperature range 0–25 °C. At ca. 50 °C, rapid decomposition set in. In contrast, admixture of **6** with samarium iodide in THF[10] at the reflux temperature led cleanly to the formation of **7a**, a labile diol, in modest yield. The sensitivity of this cyclooctatetraene must surely be related to the confluence of the monosubstituted ethylene glycol residues and the central polyolefinic ring. Direct acetylation provided the more stable **7b**. At both stages, it was clear that no significant amounts of bicyclo[3.3.0]octadiene end-products had been formed by

Scheme II



---

[8] Semmelhack, M. *Org. React.* **1972**, *19*, 115.

[9] (a) Paquette, L. A.; Trova, M. P.; Luo, J.; Clough, A. E.; Anderson, L. B. *J. Am. Chem. Soc.* **1990**, *112*, 228. (b) Paquette, L. A.; Kesselmayer, M. A.; Underiner, G. E.; House, S. D.; Rogers, R. D.; Meerholz, K.; Heinze, J. *J. Am. Chem. Soc.* **1992**, *114*, 2644.

[10] Girard, P.; Namy, J. L.; Kagan, H. B. *J. Am. Chem. Soc.* **1980**, *102*, 2693.

transannular ring closure. The structural features of **7b** followed convincingly from its spectral features. The six olefinic protons appear as three sets of signals, each of area 2, consisting of a doublet of doublets (J = 11 and 4 Hz) at δ 5,80 and two doublets. Of the latter, the downfield one at δ 5.74 has the larger coupling constant (11 Hz), while that at the higher field (δ 4.70) is attributable to the vinyl ether protons which are less spin interactive (4 Hz). The simplified ^{13}C NMR spectrum (eight lines) conforms to the molecular symmetry, and the UV maximum at 226 nm in CH_3CN agrees with the anticipated tub-shaped conformation of the [8]annulene core.[2]

In conclusion, we have achieved a short synthesis of a 1,5-difunctionalized cyclooctatetraene from cyclooctanone. In doing so, a number of heavily functionalized intermediates were traversed, none of which showed a propensity for transannular ring closure. A general preparative route to structurally related compounds has likely been opened.

Experimental Section

General Experimental Data. See ref 11 for details.

(6*R,11*R**,12*S**)-6,11,12-Tribromo-1,4-dioxaspiro[4.7]dodeca-7,9-diene (3).** A mixture of **2** (1.0 g, 8.2 mmol), *N*-bromosuccinimide (7.4 g, 41 mmol), AIBN (5 mg), and CCl_4 (30 mL) was heated at reflux for 5 days, cooled, and filtered to remove succinimide. The filtrate was concentrated, dissolved in ethyl acetate–petroleum ether, and stored in a freezer for 4 weeks to give 0.83 g (25%) of **3** as a colorless crystalline solid, mp 120 °C (from ethyl acetate–petroleum ether). When the product mixture was directly subjected to preparative HPLC (silica gel, elution with 5% ethyl acetate in petroleum ether), **3** could be isolated using peak-shaving technqiues in 12% yield: ^{1}H NMR (see Table I); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 136.8, 135.7, 126.9, 125.9, 106.2, 67.2, 65.7, 60.8, 52.1, 47.4; MS m/z ($M^+ + 1$) calcd 402.8366, obsd 402.8307.

Anal. Calcd for $C_{10}H_{11}Br_3O_2$: C, 29.81; H, 2.75. Found: C, 30.02; H, 2.83.

***trans*-6,12-Dibromo-1,4-dioxaspiro[4.7]dodeca-7,10-dien-9-ol (4).** To a solution of **3** (47.2 mg, 0.117 mmol) in acetone (1 mL) and THF (1 mL) was added 5% HCl (1 mL). This mixture was stirred at rt for 2 days, concentrated in vacuo, and partitioned between water and ether. The product was extracted into ether (3 × 10 mL), and the combined organic phases were dried and evaporated to give **4** (31 mg, 80%) as a white solid, mp 113–114 °C (from ethyl acetate-petroleum ether): IR (KBr, cm^{-1}) 3220, 1185; ^{1}H NMR (see Table I); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 134.6, 133.4, 132.6, 129.7, 110.0, 68.6 68.5, 67.0, 53.1, 52.7; MS m/z ($M^+ - 1$) calcd 336.9075, obsd 336.9035.

Anal. Calcd for $C_{10}H_{12}Br_2O_3$: C, 35.33; H, 3.56. Found: C, 35.30; H, 3.62.

***trans*-6,12-Dibromo-1,4-dioxaspiro[4.7]dodeca-7,10-dien-9-one (5).** A solution of **4** (27.7 mg, 0.082 mmol) in CH_2Cl_2 (5 mL) was treated with activated MnO_2 (35.6 mg, 0.41 mmol). This mixture was stirred at rt for 24 h, filtered through Celite, and concentrated to furnish pure **5** (27.2 mg, 98%) as a white solid, mp 147 °C (from ethyl acetate–petroleum ether): IR (KBr, cm^{-1}) 1635, 1610, 1185; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.65 (dd, J = 12.3, 8.8 Hz, 2 H), 6.24 (dd, J = 12.3, 1 Hz, 2 H), 5.51 (dd, J = 8.8, 1.3 Hz, 2 H), 4.45 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 189.2, 143.1, 133.9, 113.3, 68.8, 52.1; MS m/z (M^+) calcd 337.8987, obsd 337.8969.

Anal. Calcd for $C_{10}H_{10}Br_2O_3$: C, 35.54; H, 2.98. Found: C, 35.89; H, 3.29.

***trans*-8,14-Dibromo-1,4,10,13-tetraoxadispiro[4.3.4.3]hexadeca-6,15-diene (6).** A solution of **5** (20 mg, 0.060 mmol), ethylene glycol (0.5 mL), and *p*-toluenesulfonic acid (1 mg) in benzene (2 mL) was heated to reflux under a Dean-Stark trap for 48 h, cooled, treated with anhydrous Na_2CO_3 (4 mg), and freed of solvent in vacuo. The residue was treated with water (5 mL) and extracted with ether (3 × 10 mL). The combined organic layers were dried and evaporated to leave a solid that was purified by column chromatography (silica gel, elution with 10% ethyl acetate in petroleum ether). There was isolated 22 mg (82%) of **6** as a white solid, mp 118–121 °C (from ethyl acetate–petroleum ether): IR (KBr, cm^{-1}) 1185; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.99 (dd, J = 11.9, 8.9 Hz, 2 H), 5.69 (d, J = 12.2 Hz, 2 H), 5.54 (dd, J = 8.9, 1.1 Hz, 2 H), 4.38 (m, 4 H), 3.99 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 133.3, 133.1, 112.1, 103.5, 68.5, 65.1, 52.5; MS m/z (M^+) calcd 379.9259, obsd 379.9214.

Anal. Calcd for $C_{12}H_{14}Br_2O_4$: C, 37.73; H, 3.69. Found: C, 37.72; H, 3.82.

2,2′-(1,3,5,7-Cyclooctatetraene-1,5-diyldioxy)diethanol Diacetate (7b). To **6** (98 mg, 0.257 mmol) in a dry, N_2-purged apparatus was added a freshly prepared solution of SmI_2 [ca. 10 equiv, from CH_2I_2 (0.20 mL, 2.48 mmol) and excess Sm powder] in THF (20 mL) at rt, and the reaction mixture was heated at reflux for 1 h, cooled to rt, and exposed to air to destroy the excess Sm(II). The product was directly acetylated after dilution with benzene (1.5 mL) by the addition of pyridine (1.0 mL), DMAP (50 mg), and acetic anhydride (0.4 mL). After 2 h at rt, this mixture was diluted with ether, filtered through a pad of Celite, and evaporated. The soluble portion of the residue was purified by flash chromatography on silica gel (elution with 33% petroleum ether in ether) to give **7b** (12.6 mg, 19%) as a light yellowish oil: IR (CCl_4, cm^{-1}) 1745, 1640, 1230, 1170; $\lambda_{max}^{CH_3CN}$ 226 nm with shoulders at 245 and 300 nm; ^{1}H NMR (300 MHz, C_6D_6) δ 5.80 (dd, J = 11, 4 Hz, 2 H), 5.74 (d, J = 11 Hz, 2 H), 4.70 (d, J = 4 Hz, 2 H), 4.02 and 3.42 (pair of m, AA′XX′, 4 H),1.59 (s, 6 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 170.0, 155.7, 132.7, 127.2, 101.4, 65.6, 62.5, 20.2; FAB MS m/z ($M^+ - 1$) calcd 307.1, obsd 307.1.

Acknowledgment. We gratefully acknowledge the National Science Foundation for their support of this research effort and Professor Robin Rogers for his assistance in obtaining the X-ray crystallographic data.

Supplementary Material Available: ORTEP, data collection, and structure refinement details of **3** (2 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

---

(11) Paquette, L. A.; Negri, J. T.; Rogers, R. D. *J. Org. Chem.* **1992**, *57*, 3947.