Table IV. Comparison of Activation Parameters and Specific Rate Constants for Some Methylenecyclopropane Rearrangements

entry	rearrangement	$\log_{10} A$, s^{-1}	$\Delta S^{\ddagger}_{180}$	$\Delta H^{\ddagger}_{180}$, kcal mol^{-1}	k_{180}, s^{-1}	relative rates	ref
1	**1c** → **2c**	13.73 ± 0.38	1.5 ± 2	40.5 ± 0.8	5.4×10^{-7} [a]	1	this work
2	**1a** → **2a**	10.47	−13.4	21.9	3.0×10^{-1}	5.5×10^{5}	2a
3	**1b** → **2b**	14.20 ± 0.22	3.6 ± 1.0	37.6 ± 0.5	4.46×10^{-5}	82	this work
4	**1d** → **2d**	11.5	−8.7	24.0	3.1×10^{-1}	5.7×10^{5}	2b
5	**3** → **4**	14.69 ± 0.21	5.9 ± 0.9	40.9 ± 0.3	3.36×10^{-6}	6.2	this work
6	**5** → **6**	13.88	2.2	39.2 ± 0.6	3.47×10^{-6}	6.4	5
7	**7** → **8**	14.0 ± 0.2	2.7 ± 0.5	35.5 ± 0.4	2.57×10^{-4} [a]	476	6
8	**9** → **10**	12.1	−6.0	23.8	1.57	2.9×10^{6}	7

[a] Corrected statistically for the number of equivalent cyclopropane positions.

mations **7** → **8** and **1b** → **2b** to be very similar, and indeed they differ in rate by only a factor of 5.8. The decrease in activation enthalpy on going to the tetramethyl compound **7** may well be due to an increased ground state energy for **7** due to the opposed methyl groups on the cyclopropane ring. This is supported by the observations[6] that $K_{180\,°C} = 653 \pm 33$ for the equilibrium **7** ⇄ **8** and $\Delta H = -5.2 \pm 0.2$ kcal mol^{-1} whereas $K_{180\,°C} = 4.12$ and $\Delta H = -1.17$ kcal mol^{-1} for **3** ⇄ **4**.

Experimental Section

Cyclopropylmethanol-α,α-d_2. Pulverized lithium aluminum deuteride (5.0 g, 0.12 mol) was refluxed in 300 mL of ether for 1 h under nitrogen. After the mixture was cooled to 0 °C methyl cyclopropane carboxylate (20 g, 0.2 mol) in 60 mL of ether was added dropwise and then refluxed for 10 h. Upon cooling the reaction mixture was treated with 5 mL of water, 5 mL of 15% sodium hydroxide, and 15 mL of water successively. Filtration, drying of the ether layer with magnesium sulfate, and distillation gave the product bp 120 °C (710 torr) [lit. value[12] bp 123 °C (1 atm)], 13 g: 90% yield; ^{1}H NMR ($CDCl_3$) δ 0.2 (m, 2 H), 0.5 (m, 2 H), 1.1 (m, 1 H), 1.9 (s, 1 H); ^{2}H NMR indicated >99% deuterium on the carbinyl carbon.

Cyclopropylmethyl Bromide-α,α-d_2. Cyclopropylmethanol-α,α-d_2 (6.4 g, 87 mmol) in 70 mL of dry DMF was mixed with freshly distilled tributylphosphine (22 mL, 89 mmol) under a nitrogen atmosphere.[13] Bromine (14.2 g, 88 mmol) was added slowly while the temperature was maintained below 50 °C. The volatile components were removed by distillation, up to 40 °C (14 torr), and trapped in a receiver cooled to −80 °C. Cold water was added to the distillate and the organic product extracted with pentane (4 × 25 mL) dried, concentrated, and distilled to give 8 g (69% yield): bp 100 °C (710 torr);[14] ^{1}H NMR ($CDCl_3$) δ 0.37 (m, 2 H), 0.75 (m, 2 H), 1.30 (m, 1 H) [indicated >98% isotopic purity]; ^{2}H NMR indicated deuterium at only one position.

Dideuteriomethylenecyclopropane (1c). The dehydrohalogenation was essentially that outlined by Dolbier.[15] Potassium *tert*-butoxide (8 g, 71 mmol) was added to 80 mL of dry Me_2SO under nitrogen. Cyclopropylmethyl bromide-α,α-d_2 (8 g, 59 mmol) was added over 0.5 h and the temperature was maintained at 35 °C. All volatile components were trapped in a receiver cooled to −80 °C. The product was purified by trap-to-trap distillation to give 2 g (61% yield): bp 10 °C (1 atm); ^{1}H NMR ($CDCl_3$) δ 1.06 (s, 4 H), 5.38 (s, 0.012 H) [and indicated 99 ± 1% deuterium at the exomethylene position].

2,2-Dimethylmethylenecyclopropane-3,3-d_2. The synthesis of the nondeuterated material by two successive reductions of 2,2-dibromo-3,3-dimethylmethylenecyclopropane using tri-*n*-butyltin hydride has been described earlier.[16] With freshly prepared tri-*n*-butyltin deuteride,[17] 2,2-dimethylmethylcyclopropane-3,3-d_2 was prepared in 24% yield: ^{1}H NMR ($CDCl_3$) δ 1.15 (s, 6 H), 5.26 (s, 1 H), 5.36 (s, 1 H); ^{2}H NMR indicated >99% of deuterium on the cyclopropyl ring.

Kinetic Measurements. Pyrex break-seals (18-mm diameter, 70 mm long) were evacuated and flamed before filling with 20 μL of sample transferred by trap-to-trap distillation. The tubes were immersed in a well stirred silicon oil bath for the appropriate length of time and then quenched in ice–water. The temperature was controlled by a Melabs Model CTC-1A proportional temperature controller and measured by an HP Model 2801A quartz thermometer calibrated by the National Bureau of Standards. The temperature stability of the oil bath was monitored by recording the analogue output of an HP Model 2802A platinum resistance thermometer with an HP Model 3420B digital voltmeter coupled to a strip chart recorder. The variation of temperature during any run was always less than 0.04 °C. The break-seals were reattached to the vacuum line and the contents transferred to an NMR tube containing $CDCl_3$. The tubes were then sealed and submitted to analysis using a 400-MHz ^{1}H NMR. The infinity tubes for the isomerization **1c** ⇄ **2c** gave $K = [\mathbf{2c}]/[\mathbf{1c}] = 0.50 \pm 0.02$ at 210 °C, and for **1b** ⇄ **2b**, $K = [\mathbf{2b}]/[\mathbf{1b}] = 1.00 \pm 0.04$. Each rate constant was calculated from 10 points by using duplicate tubes at each time. The least-squares analysis for all runs gave a correlation coefficient of 0.999 or better.

The samples for the isomerization **3** ⇄ **4** were analyzed by gas chromatography using toluene as a diluent and a 20-ft OV 101 on Chromosorb W column at 50 °C. Quintuple analysis on each of two samples were used to calculate each kinetic point. The equilibrium data for **3** ⇄ **4** were reported earlier.[6] The rates were calculated by using seven or more points, and each rate constant had a correlation coefficient of 0.999 or better.

Acknowledgment. We thank the NMR Spectral Services Laboratory at the University of Alberta for analysis, NSERC for funding, and Dr. H. Tokunaga for some preliminary work.

Registry No. **1b**, 99810-72-7; **1c**, 65264-10-0; **2b**, 99838-31-0; **3**, 4372-94-5; methyl cyclopropanecarboxylate, 2868-37-3; cyclopropylmethanol-α,α-d_2, 90568-07-3; cyclopropylmethyl bromide-α,α-d_2, 99838-30-9; 2,2-dibromo-3,3-dimethylmethylenecyclopropane, 5239-69-0.

(12) Smith, L. I.; McKenzie, S., Jr. *J. Org. Chem.* **1950**, *15*, 74–80.
(13) This is essentially the procedure of Wiley et al. (Wiley, G. A.; Hershkowitz, R. L.; Rein, R. M.; Chung, B. C. *J. Am. Chem. Soc.* **1964**, *86*, 964–965) and gave no evidence of rearranged bromide.
(14) Kirmse, W.; Kapps, M.; Hager, R. B. *Chem. Ber.* **1966**, *99*, 2855–2868.
(15) Dolbier, W. R., Jr.; Alonso, J. H. *J. Chem. Soc., Chem. Commun.* **1973**, 394–395.
(16) Dolbier, W. R., Jr.; Lomas, D.; Garza, T.; Harmon, C.; Tarrant, P. *Tetrahedron Lett.* **1972**, 3185–3189.
(17) Kuivila, H. G.; Beumel, O. F., Jr. *J. Am. Chem. Soc.* **1961**, *83*, 1246–1250.

A Mercury-Mediated Acyl Migration in a Pinacol-Type Rearrangement. Model Studies toward the Synthesis of Fredericamycin A

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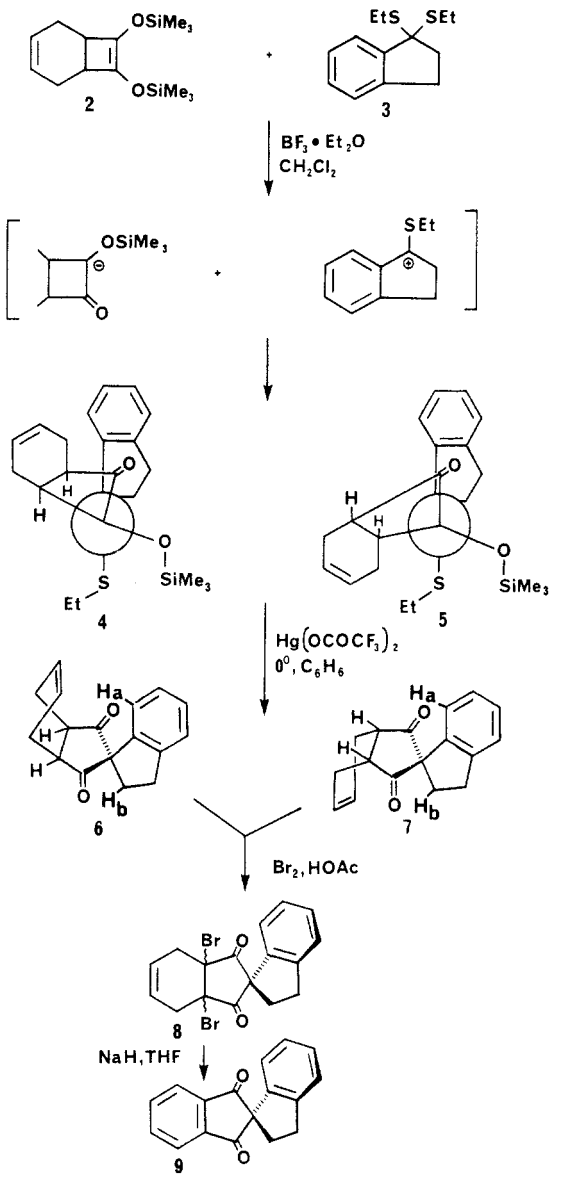
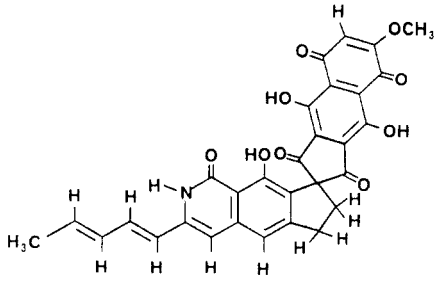
Fredericamycin A (**1**) contains a 1,4-diketospiro[4.4]-nonane structure and it exhibits both antibiotic and antitumor activity.[1] The novel spiro ring system possesses

0022-3263/86/1951-0749$01.50/0

Scheme I



a quinone moiety that is essentially at right angles to a substituted isoquinoline derivative. It is the first known antibiotic with this spatial orientation, and the spiro structure containing a unique 1,3-dione functionality poses an interesting synthetic challenge. Our objective is to develop a convergent approach to **1** that allows introduction of the spiro-1,4-diketo moiety late in the synthetic sequence. The one (spiro) quaternary center of asymmetry in the molecule can potentially be introduced by a spiroexpansion–spiroannulation reaction involving an acyl migration. We now report the synthesis of a model dibenzospiro[4.4]nonane under unusually mild reaction conditions that serves to exemplify this synthetic approach and to establish a skeletal rearrangement involving a mercury mediated 1,2-carbonyl shift (Scheme I) as a generally effective methodology for the introduction of spiro centers.



1

The acyloin condensation of *cis*-diethylcyclohexene-4,5-dicarboxylate in the presence of chlorotrimethylsilane afforded *cis*-7,8-bis[(trimethylsilyl)oxy]bicyclo[4.2.0]octa-3,7-diene (**2**).[2] Treatment of 1-indanone with ethanethiol in CH_2Cl_2 at −60 °C with stannic chloride (0.33 equiv) afforded 24.3 g (51%) of 1,1-(diethylthio)indane (**3**) after column chromatography on silica gel with hexane and ethyl acetate (19:1). α-Thioalkylation of **2** was readily achieved under the influence of the relatively mild Lewis acid, boron trifluoride etherate.[3]

In a typical reaction sequence, 11.9 g (0.05 mol) of dithioketal **3** in 50 mL of CH_2Cl_2 at −60 °C was treated with 18.5 mL (0.15 mol) of $BF_3{\cdot}Et_2O$. To this stirring solution was added dropwise 15.5 g (0.055 mol) of bis silyl ether **2** in 25 mL of CH_2Cl_2. The reaction mixture was stirred for 1.5 h at −40 °C. Chromatography on silica gel (3:1 hexane–ethyl acetate) afforded 16.3 g (84%) of 7-[1-(ethylthio)indanyl]-7-(trimethylsiloxy)bicyclo[4.2.0]oct-3-en-8-one as a mixture of diastereomers **4** and **5** in a 1:4 ratio.[4] The product ratio was determined by the 300-MHz ^1H NMR signals for the respective trimethylsilyl groups at δ 0.23 and 0.37. Stereospecific transformation of the mixture of **4** and **5** to **6** and **7** was effected smoothly by $Hg(OCOCF_3)_2$ in benzene at 0 °C for ~1 min (81%). Mercuric chloride, although less electrophilic, is also an effective thiophile in this reaction if higher temperatures are utilized. Thus, treatment of 9.65 g (0.025 mol) of **4** and **5** (1:4) with 1.1 equiv of $HgCl_2$ in refluxing benzene for 15 min afforded 5.6 g (88%) of **6** and **7** (1:4)[5] after distillation [144–160 °C (0.08 mm)]. Bromination of a mixture of **6** and **7** in acetic acid at room temperature afforded 1.2 g (98%) of dibromide **8** (mp 210–212 °C dec) after recrystallization from hexane–ethyl acetate.[6] The dibromide was refluxed in THF containing 2.2 equiv of NaH and elimination of HBr produced the desired 2-substituted indan-1,3-dione **9** (71%) that has mp 131–132 °C (hexane–ethyl acetate):[7] 300-MHz ^{13}C NMR ($CDCl_3$) 201.3, 145.6, 142.6, 141.8, 135.8, 128.3, 126.8, 125.2, 123.8, 122.7, 66.9, 32.6, 32.1 ppm; IR 1701 and 1743 cm^{-1}. Bromination of **6** at −78 °C in methylene chloride resulted in trans

(1) (a) Misra, R.; Pandey, R. D.; Silverton, J. V. *J. am. Chem. Soc.* **1982**, *104*, 4478; (b) *Chem. Eng. News*, **1982**, Aug 16, 27.

(2) (a) Bloomfield, J. J. *Tetrahedron Lett.* **1968**, 587. (b) Bloomfield, J. J.; Owsley, D. C., Nelke, J. M. *Org. React. (N.Y.)* **1976**, *23*, 259. (c) Bloomfield, J. J.; Nelke, J. M. *Org. Synth.* **1977**, *58*, 1.

(3) For earlier examples of α-thioalkylation of silyl enol ethers using $SnCl_4$ at low temperatures, see: Reetz, M. T.; Giannis, A. *Synth. Commun.* **1981**, *11*, 315. In the present case, the $SnCl_4$-mediated α-thioalkylation was accompanied by extensive cyclopentanedione ring cleavage of diastereomers **6** and **7**.

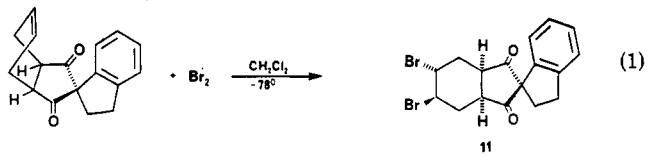
(4) The mixture of diastereomers could also be purified by short-path vacuum distillation [156–160 °C (0.05 mm)] in 52% isolated yield. Thermal rearrangement to **6** and **7** will accompany the distillation if caution is not exercised.

(5) The minor isomer **6** had mp 111–112 °C after separation by recrystallization from hexane–ethyl acetate. Epimerization of the activated hydrogens adjacent to the carbonyls also results upon heating and varying amounts of the trans-fused cyclohexyl compound **10** are produced. A mixture **7** and **10** had mp 77–78 °C, and a mixed melting point of 59–81 °C was observed for **6** and (**7** + **10**).

(6) Bromination of the double bond in **6** and **7** is readily achieved at 0 °C in CH_2Cl_2 solution in 30 min.

(7) Compound **9** has been prepared previously in 40% yield (mp 131–133 °C) by the thermal isomerization of a keto alcohol at 290–300 °C for 5 h. An X-ray crystallographic study confirmed the structure. Rama Rao, A. V.; Reddy, D. R.; Deshpande, V. H. *J. Chem. Soc., Chem. Commun.* **1984**, 1119.

addition of bromine to the double bond in the cyclohexyl ring affording **11** (eq 1). Dehydrohalogenation with NaH

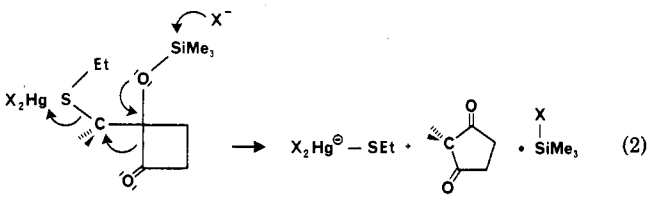


(1)

11

afforded the requisite diene as a relatively stable intermediate that was air oxidized to the dibenzo derivative **9**. The dibromides derived from **7** and the trans fused cyclohexyl derivative **10** have all been characterized.

Although it is not essential to our synthetic objective, we have tentatively assigned the relative stereochemistry of **6** and **7** on the basis of NMR spectral data. The aromatic proton H_a in **6**, that could potentially be shifted upfield by the anisotropy of the double bond, resonates at 6.80 ppm while the corresponding resonance in **7** is observed at 6.94 ppm. In addition, the ^{13}C signal for the carbon of the indane system bonded to H_b in **7** is observed at 33.26 ppm, while that in **6** is at 38.90 ppm. The upfield shift in **7** could be due to the bond compression resulting from the syn cyclohexyl ring in **7**. A rigorous assignment, however, must be tempered by the observation that the aromatic carbon bonded to H_a in **6** is at lower field (124.13 ppm) than that in **7** (122.21 ppm). The assigned stereochemistry of **4** and **5** is predicted on the assumption that the 1,2-acyl migration is a stereospecific reaction that proceeds with inversion of configuration at the migration terminus (eq 2). 1,2-Carbonyl migration in a chlorohydrin[8a] and in α,β-epoxy ketones[8b] and esters[8c] is a concerted reaction that involves neighboring group participation by the carbonyl carbon in solution[8d] and in the gas phase at high temperature.[8e] Carbenium ion intermediates in these reactions have been rigorously excluded. Steric considerations also suggest that the incipient "enolate anion" of **2** would approach the planar α-thio carbenium ion derived from **3** from the direction that will place the cyclohexenyl ring and the bulky trimethylsilyl ether trans to one another.[9] This orientation would afford a preponderance of **5** in support of the stereochemical assignment of **7** as the major product.



(2)

Our theoretical studies[8f] strongly suggest that the migrating σ-bond (C—C=O) must be antiperiplanar to the departing ethyl mercaptide group as depicted in diastereomers **4** and **5**. The increased rate of rearrangement with the more electrophilic mercury salt suggests that acyl migration is set into motion by a developing positive charge induced by C–S bond rupture. The low temperatures and essentially neutral reaction conditions utilized in this sequence should afford compatability with a wide range of functional groups. Elaboration of the cyclohexenyl moiety in **7** is now in progress.

In a comprehensive study, Kuwajima[10] has demonstrated the synthetic utility of a geminal acylation reaction involving acyl migration in a cyclobutanone, affording a variety of 1,3-cyclopentane diones.[10] He has also corroborated our earlier[8a] results on the stereochemistry of concerted 1,2-carbonyl migration. In this study we have shown that the overall aldol-type reaction in tandem with a pincol-type acyl migration is ideally suited to construct the molecular architecture that comprises fredericamycin A.[11]

Experimental Section

7-[1-(Ethylthio)indanyl]-7-[(trimethylsilyl)oxy]bicyclo-[4.2.0]-3-octen-8-one (4, 5). To a solution of 11.9 g (0.05 mol) of 1,1-(diethylthio)indan in 50 mL of methylene chloride at –60 °C was added 18.5 mL (0.15 mol) of boron trifluoride etherate. After addition of the Lewis acid 15.5 g (0.055 mol) of *cis*-7,8-bis[(trimethylsilyl)oxy]bicyclo[4.2.0]octa-3,7-diene in 25 mL of methylene chloride was added dropwise. The reaction mixture was allowed to warm to –40 °C and stirred for 1.5 h. The reaction mixture (–40 °C) was poured into 200 mL of saturated sodium bicarbonate. The organic layer was extracted and the aqueous layer was washed with 100 mL (3×) of methylene chloride. The combined organic layers were washed with water, brine, and dried ($MgSO_4$) and then concentrated, affording a mixture of 10.1 g (52%) of **4** (20%) and **5** (80%) after distillation: bp 156–160 °C (0.05 mm): ^{13}C NMR ($CDCl_3$) [**5**] 0.23 ($OSi(CH_3)_3$, s, 9 H), 1.22 (SCH_2CH_3, t, 3 H), [**4**] 213.9, 144.6, 142.7, 127.7, 127.2, 126.1, 125.3, 124.8, 97.4, 64.1, 51.2, 35.6, 32.5, 31.0, 23.9, 20.8, 19.8, 13.8, 2.3 ppm; ^1H NMR ($CDCl_3$) δ 0.37 ($OSi(CH_3)_3$, s, 9 H), 1.25 (SCH_2CH_3, t, 3 H); MS (70 eV), calcd for $C_{22}H_{30}O_2SiS$ 386.1735, found 386.1729.

Mercury-Meditated Acyl Migration. (a) Mercuric Chloride in Benzene. To a solution of 9.65 g (0.025 mol) of **4** and **5** in 50 mL of benzene was added 7.47 g (0.0275 mol) of mercuric chloride. The reaction mixture was allowed to reflux for 15 min and then cooled and filtered through Celite. The organic layer was washed with 10% hydrogen chloride, water, and saturated sodium chloride and dried ($MgSO_4$). The solvent was removed by rotary evaporator to give a mixture of **6** (20%) and **7** (80%). Distillation afforded 5.6 g (88%), bp 144–160 °C (0.075 mm), of a mixture of **6** (32%), **7** (48%), and **10** (20%). Recrystallization with hexane and ethyl acetate separated **6** and **7** from **10**. Attempts to separate **6** from **7** by recrystallization failed. Further purification was done by recrystallizing from hexane and ethyl acetate. **7**: ^{13}C NMR ($CDCl_3$) 214.5, 144.8, 141.4, 128.1, 125.8, 125.3, 122.2, 68.4, 45.1, 33.3, 31.9, 21.4 ppm; ^1H NMR ($CDCl_3$) δ 2.34–2.37 (t, 2 H), 2.23–2.24 (m, 4 H), 3.14–3.19 (t, 2 H), 3.3–3.4 (m, 2 H), 5.77–5.78 (t, 2 H), 6.92–6.95 (d, 1 H), 7.07–7.12 (t, 1 H), 7.16–7.20 (t, 1 H), 7.24–7.27 (d, 1 H); IR (KBr) 3027, 2938, 1763, 1721, 1660, 1479, 1225, 1206, 1187, 779, 780, 680, 659 cm^{-1}. **6**: mp 111–112 °C; ^{13}C NMR ($CDCl_3$) 215.2, 146.1, 140.0, 128.3, 127.0, 126.1, 124.7, 124.2, 68.7, 44.8, 39.0, 31.4, 21.2 ppm; ^1H NMR ($CDCl_3$) δ 2.31–2.33 (m, 2 H), 2.34–2.39 (t, 2 H), 2.49–2.56 (m, 2 H), 3.09–3.14 (t, 2 H), 3.30–3.35 (m, 2 H), 5.83–5.84 (t, 2 H), 6.78–6.81 (d, 1 H), 7.11–7.19 (t, 1 H), 7.20–7.24 (t, 1 H), 7.26–7.30 (d, 1 H); IR (KBr) 3034, 2943, 2901, 2826, 1766, 1726, 1662, 1482, 1283, 1199, 1185, 1146, 782, 761, 687, 699 cm^{-1}; MS (70 eV), calcd for $C_{17}H_{16}O_2$ 252.1150, found 252.1157.

(b) Mercuric Trifluoroacetate in Benzene. To a solution of 1.93 g (5 mmol) of **4** and **5** in 25 mL of benzene at 0 °C was added 2.4 g (5.5 mmol) of mercuric trifluoroacetate. The reaction was allowed to stir for 1 min at 0 °C and then allowed to warm

(8) (a) Domagala, J. M.; Bach, R. D. *J. Am. Chem. Soc.* **1979**, *101*, 3118. (b) Domagala, J. M.; Bach, R. D. *Ibid.* **1978**, *100*, 1605. (c) Domagala, J. M.; Bach, R. D.; Wemple, J. *Ibid.* **1976**, *98*, 1975. (d) Bach, R. D.; Domagala, J. M. *J. Org. Chem.* **1984**, *49*, 4181. (e) Bach, R. D.; Domagala, J. M. *J. Chem. Soc., Chem. Commun.* **1984**, 1472. (f) Bach, R. D.; Klix, R. C. *Tetrahedron Lett.* **1985**, 985.

(9) The mechanism inferred for the coupling of the two fragments in Scheme 1 should be taken as a working hypothesis. We do not advocate a fully developed anion and cation in this reaction. The increased rate of carbonyl migration with $Hg(OCOCF_3)_2$ suggests that this pinacol rearrangement is initiated by carbon–sulfur bond cleavage with eventual loss of the trimethylsilyl moiety after the rate-limiting step.

(10) Shimada, J. I.; Hashimoto, K.; Kim, B. H.; Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1984**, *106*, 1759 and references therein.

(11) For other approaches to the spirocyclic center in **1** that have appeared since our initial submission of this paper, see ref 12.

(12) (a) Parker, K. A.; Koziski, K. A.; Breault, G. *Tetrahedron Lett.* **1985**, *26*, 2181. (b) Kende, A. S.; Ebetino, F. H.; Ohta, T. *Tetrahedron Lett.* **1985**, 3063.

to room temperature before filtering through Celite. The reaction mixture was then washed with 10% hydrogen chloride, water, and saturated sodium chloride and dried ($MgSO_4$). The reaction mixture was concentrated to an oil, **6** (20%) and **7** (80%), which was chromatographed on silica gel with hexane and ethyl acetate (5:1) to afford 1.02 g (81%) of **6** (32%), **7** (48%), and **10** (20%).

Bromination at the α-Position. To solution of 756 mg (3 mmol) of the 1,3-diketone (**6**, **7**, **10**) in 10 mL of acetic acid at room temperature was added 338 μL of bromine. The reaction mixture was allowed to stir for 15 min, then washed with water, saturated sodium bicarbonate, and saturated sodium chloride, and dried ($MgSO_4$). The solvent was removed under reduced pressure to afford 1.2 g (98%) of a yellow solid: mp 210–212 °C dec (hexane–ethyl acetate); ^{13}C NMR ($CDCl_3$) 201.7, 153.9, 145.3, 140.7, 128.5, 127.9, 125.3, 122.4, 64.1, 45.2, 44.8, 31.9, 31.2, 27.6 ppm; ^1H NMR ($CDCl_3$) δ 2.43–2.48 (t, 2 H), 3.21–3.30 (m, 4 H), 3.56–3.64 (m, 2 H), 4.75–4.76 (m, 2 H), 6.78–6.81 (d, 1 H), 7.10–7.15 (t, 1 H), 7.20–7.26 (t, 1 H), 7.30–7.32 (s, 1 H); IR (KBr) 3009, 2946, 2931, 2848, 1695, 1639, 1404, 1292, 896 cm^{-1}; MS (70 eV), calcd for $C_{17}H_{14}O_2Br_2$ 409.9341, found 409.9346.

Bromination of the Double Bond. To a solution of 252 mg (1 mmol) of the 1,3-diketone (**6**, **7**, and **10**) in 10 mL of methylene chloride at −78 °C was added 56.4 μL (1.1 mmol) of bromine. The reaction was allowed to warm up to 0 °C, stirred for 30 min, then washed with saturated sodium bicarbonate, water, and saturated sodium chloride, and dried ($MgSO_4$). The solvent was removed under reduced pressure to yield 400 mg (97%) of a diastereomeric mixture of 1,2-dibromides as a white solid. The crude solid was recrystallized from pentane and ether to afford 306 mg (74%): mp 160 °C dec; ^{13}C NMR ($CDCl_3$) 212.2, 212.0, 211.0, 209.5, 145.6, 145.2, 141.6, 140.5, 128.5, 127.0, 125.5, 125.2, 123.1, 122.4, 68.9, 67.5, 51.1, 50.0, 49.5, 48.4, 47.2, 45.3, 44.4, 35.6, 35.0, 32.3, 31.9, 28.8, 28.6, 28.4 ppm; ^1H NMR ($CDCl_3$) δ 2.2–2.8 (m, 12 H), 3.05–3.65 (m, 8 H), 4.38–4.50 (m, 2 H), 4.78–4.84 (br s, 2 H), 6.82–6.84 (d, 1 H), 6.89–6.92 (d, 2 H), 7.13–7.32 (m, 6 H); IR (KBr) 2931, 2854, 1763, 1727, 1693, 1478, 1458, 1440, 1281, 1248, 1216, 1176, 748 cm^{-1}; MS (70 eV), calcd for $C_{17}H_{16}O_2Br_2$ 411.9498, found 411.9499.

Formation of Dibenzo 1,3-Diketone 9. To a mixture of 132 mg (5.5 mmol) of sodium hydride in 20 mL of dry THF was added 1.03 g (2.5 mmol) of the dibromide **8**. The reaction mixture was then refluxed for 75 min and quenched with water. The reaction mixture was extracted with methylene chloride, and the combined organic layers were washed with water and saturated sodium chloride and dried ($MgSO_4$). The methylene chloride was removed by rotary evaporator to yield a solid, which was recrystallized from hexane and ethyl acetate to afford 433 mg (71%): mp 131–132 °C; ^{13}C NMR ($CDCl_3$) 201.3, 145.6, 142.6, 141.8, 135.8, 128.3, 126.8, 125.2, 123.8, 122.7, 66.9, 32.6, 32.1 ppm; ^1H NMR ($CDCl_3$) 2.53–2.58 (t, 2 H), 3.28–3.33 (t, 2 H), 6.60–6.62 (d, 1 H), 7.01–7.06 (t, 1 H), 7.19–7.24 (t, 1 H), 7.31–7.34 (d, 1 H), 7.87–7.91 (m, 2 H), 8.04–8.10 (m, 2 H); IR (KBr) 3062, 2923, 2850, 1743, 1701, 1594, 1480, 1452, 1332, 1292, 1253, 858, 789, 757 cm^{-1}; MS (70eV), calcd for $C_{17}H_{12}O_2$ 248.0837, found 248.0843.

Bromination of Alkene 6. To a solution of 126 mg (0.5 mmol) of the 1,3-diketone **6** in 3 mL of methylene chloride at −78 °C was added 28.2 μL (0.5 mmol) of bromine. The reaction was allowed to stir at this temperature for 20 min and was allowed to warm up to −40 °C and then poured into water. The methylene chloride layer was then extracted and washed with brine and dried ($MgSO_4$) to afford 204 mg (99%) of **11**. The orange solid was recrystallized from ether and pentane to afford 157 mg (77%) of the 1,2-dibromide: mp 108–108.5 °C; ^{13}C NMR ($CDCl_3$) 212.2, 213.4, 146.2, 139.8, 128.6, 127.3, 124.9, 124.0, 68.0, 49.9, 49.1, 44.5, 43.9, 39.7, 31.5, 28.1, 27.3 ppm; ^1H NMR ($CDCl_3$) δ 2.2–2.5 (m, 3 H), 2.6–2.8 (m, 3 H), 3.1–3.3 (m, 3 H), 3.4–3.5 (m, 1 H), 4.4–4.6 (m, 2 H), 6.98–7.00 (d, 1 H), 7.18–7.33 (m, 3 H); IR (KBr) 2900, 2851, 1723, 1422, 1280, 1182, 1151, 989, 741 cm^{-1}.

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Registry No. 1, 80455-68-1; **2**, 18014-24-9; **3**, 100020-34-6; **4**, 100020-35-7; **6**, 100020-36-8; **6** (dibromide), 100101-38-0; **6** (diene), 100020-39-1; **7**, 100101-36-8; **8**, 100020-37-9; **9**, 95033-81-1; **10**, 100101-37-9; **11**, 100020-38-0; *cis*-diethyl cyclohexene-4,5-dicarboxylate, 4841-85-4; 1-indanone, 83-33-0; mercuric trifluoroacetate, 13257-51-7; mercuric chloride, 7487-94-7.

Synthesis of a Dithia-18-crown-6-tetracarboxylic Acid

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The synthesis, complexation properties and applications of macrocyclic polyethers of the crown ether and cryptand types continues to be a vigorous and growing area of chemistry.[1] It is widely recognized that variation in the nature of the donor sites (substitution of O by N or S, for example) leads to modified conformations of the ligands[2] and to control of complexation behavior.[3] Our interest in such heteroatom-substituted crown ethers is directed toward derivatives which would be capable of transporting group IIB (12)[19] and heavy metal cations across artificial membranes as an extension of our ongoing studies on group IA (1) and IIA (2) cations.[4-6] In addition, it is generally found that incorporation of tartrate-derived fragments into the 18-crown-6 framework results in a well-defined macrocycle conformation in which the carboxyl substituents are held pseudoaxially to the macrocycle plane.[7-10] Heteroatom substitution at the 7- and 16-positions would provide an additional NMR probe for the conformations of the ethylenedioxy fragments. Introduction of sulfur is also expected to provoke conformational changes due to the small C–S–C angle and the tendency for S binding sites to diverge from the macrocycle cavity.[2] From all these perspectives it was of interest to examine the synthesis of diheteroatom-substituted crown ethers incorporating tartrate-derived units. We report here the synthesis of the parent compound with sulfur donor sites namely **11** (Scheme I).

The first syntheses of sulfur-containing macrocycles currently recognized as crown ether derivatives substantially predate the syntheses of the "parent" oxa crown ethers and several different strategies have been reported.[12,13] In principle an efficient one-pot method like the

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