N-Acetyl-[(S)-4-amino-6-methyl-2-(dimethylsulfonio)-3-oxoheptanoyl]-L-alanine Isoamylamide (12). The title compound was prepared from the hydrochloride salt of deprotected **10** prepared by general procedure B. The hydrochloride was acylated by acetic anhydride as described in general procedure C: R_f 0.38; NMR ($CDCl_3$) δ 0.80–1.05 (m, 12 H), 1.24–1.70 (m, 9 H, includes 1.44 (d)), 2.00 (s, 3 H), 3.06 (s, 6 H), 3.25 (m, 2 H), 4.38 (t, 1 H, $J \simeq 7$ Hz), 5.29 (q, 1 H, $J \simeq 8$ Hz), 6.54 (s, 1 H), 9.90 (d, 1 H, $J \simeq 7$ Hz). Anal. Calcd for $C_{20}H_{37}N_3O_4S$: C, 57.80; H, 8.97; N, 10.11. Found: C, 57.67; H, 9.09; N, 9.91.

N-Isovaleryl-L-valyl-[(S)-4-amino-6-methyl-2-(dimethylsulfonio)-3-oxoheptanoyl]-L-alanine Isoamylamide (5). The title compound was prepared from the hydrochloride salt of deprotected **4**, prepared by general procedure B. The hydrochloride was acylated by isovaleric anhydride as described in general procedure C: R_f 0.44; NMR ($CDCl_3$) δ 0.82–1.04 (m, 24 H), 1.25–1.90 (m, 10 H, includes 1.42 (d, 3 H, $J \simeq 7$ Hz)), 2.00–2.20 (m, 3 H), 3.06 (s, 6 H), 3.18–3.30 (m, 2 H), 4.22–4.32 (m, 1 H), 4.41 (q, 1 H, $J \simeq 7$ Hz), 5.25 (q, 1 H, $J \simeq 7$ Hz), 5.96 d, 1 H, $J \simeq 8$ Hz), 6.56 (br, 1 H), 9.86 (d, 1 H, $J \simeq 7$ H). Anal. Calcd for $C_{28}H_{52}N_4O_5S$: C, 60.40; H, 9.41; N, 10.06. Found: C, 60.57; H, 9.21; N, 9.90.

N-Isovaleryl-L-valyl-L-valyl-[(S)-4-amino-6-methyl-2-(dimethylsulfonio)-3-oxoheptanoyl]-L-alanine Isoamylamide (13). The title compound was prepared from the hydrochloride salt of deprotected **11**, prepared by general procedure B. The hydrochloride was acylated by isovaleric anhydride as described in general procedure C: R_f 0.39; NMR ($CDCl_3$) δ 0.82–1.00 (m, 30 H), 1.22–1.62 (m, 10 H, includes 1.42 (d, 3 H, J $\simeq$ 7 Hz)), 2.02–2.19 (m, 4 H), 3.05 (s, 6 H), 3.25 (m, 2 H), 4.20 (m, 2 H), 4.40 (quintet, 1 H, $J \simeq 7$ Hz), 5.27 (m, 1 H), 6.14 (d, 1 H, $J \simeq 8$ Hz), 6.46–6.63 (m, 3 H), 9.88 (d, 1 H, $J \simeq 7$ Hz). Anal. Calcd for $C_{33}H_{61}N_5O_6S$: C, 60.43; H, 9.37; N, 10.68. Found: C, 60.19; H, 9.47; N, 10.52.

N-Acetyl-[(S)-4-amino-6-methyl-3-oxoheptanoyl]-L-alanine Isoamylamide (14). The title compound was prepared from **12** by general procedure D: R_f 0.29; NMR ($CDCl_3$) δ 0.84–0.99 (m, 12 H), 1.34–1.50 (m, 7 H, includes 1.40 (d, 3 H, $J \simeq 7$ Hz)), 1.52–1.74 (m, 2 H), 2.05 (s, 3 H), 3.20–3.32 (m, 2 H), 3.50 (dd, 2 H, $J_{AB} \simeq 15$ Hz), 4.41 (quintet, 1 H, $J \simeq 7$ Hz), 4.52 (m, 1 H), 6.07 (d, 1 H, $J \simeq 7$ Hz), 6.42 (s, 1 H), 6.90 (d, 1 H, $J \simeq 7$ Hz). Anal. Calcd for $C_{18}H_{33}N_3O_4$: C, 60.82; H, 9.36; N, 11.82. Found: C, 60.96; H, 9.45; N, 11.68.

N-Isovaleryl-L-valyl-[(S)-4-amino-6-methyl-3-oxoheptanoyl]-L-alanine Isoamylamide (3). The title compound was prepared from **5** by general procedure D. This material was identical by NMR, TLC, and melting point with the material prepared previously[1] by a different route.

N-Isovaleryl-L-valyl-L-valyl-[(S)-4-amino-6-methyl-3-oxoheptanoyl]-L-alanine Isoamylamide (15). The title compound was prepared from **13** by general procedure D. The product was isolated as a white crystalline solid: mp 213–214 °C (uncorrected); R_f 0.49; NMR (MeOH-d_4) δ 0.80–1.04 (m, 30 H), 1.27–1.46 (m, 9 H, includes 1.34 (d, 3 H, $J \simeq 8$ Hz), 1.52–1.73 (m, 3 H), 1.97–2.16 (m, 4 H), 3.23 (m, 2 H, partially obscured by solvent), 4.17 (d, 2 H, $J \simeq 7$ Hz), 4.31 (q, 1 H, $J \simeq 7$ Hz), 4.41 (m, 1 H). Anal. Calcd for $C_{31}H_{57}N_5O_6$: C, 62.49; H, 9.64; N, 11.75. Found: C, 62.17; H, 9.74; N, 11.56.

Acknowledgment. We are grateful to P. G. Schmidt (Oklahoma Medical Research Foundation) for running the 270-MHz ^1H NMR spectra of reported peptides. This work was supported by a grant from the National Institutes of Health (No. AM 20100).

Registry No. 1, 72155-63-6; 3, 81485-13-4; 4, 85702-25-6; 4 deprotected hydrochloride, 85702-33-6; 5, 81875-70-9; 6, 77658-87-8; 7, 77699-22-0; 8, 85719-05-7; 9, 81921-68-8; 10, 85702-27-8; 10 deprotected hydrochloride, 85702-34-7; 11, 85702-28-9; 11 deprotected hydrochloride, 85702-35-8; 12, 85702-29-0; 13, 85702-30-3; 14, 85702-31-4; 15, 85702-32-5; isovaleric anhydride, 1468-39-9; sulfur trioxide–pyridine complex, 26412-87-3.

Total Synthesis of Dioxane Analogues Related to Zoapatanol

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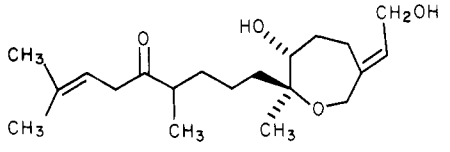
Received November 15, 1982

The zoapatanol-related dioxane analogues [(2*RS*,5*SR*)-5-(5-hydroxy-4,8-dimethyl-7-nonen-1-yl)-5-methyl-1,4-dioxan-2-yl]acetic acid (**3a**) and the corresponding 8-nonen-1-yl isomer (**3b**) have been synthesized. The dioxane ring is formed by a regioselective transacetalization and subsequent ring closure under basic conditions. The configurational assignments to the dioxane reaction products have been established by the separation and spectral investigation of a single epimer, **16a**.

The isolation and structural elucidation of a novel oxepane diterpenoid, zoapatanol (**1**), from the Mexican plant



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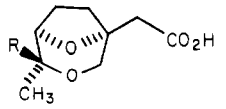
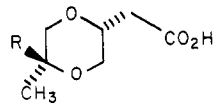
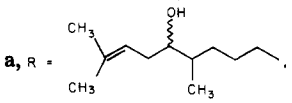
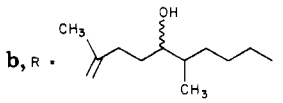


2a,b



3a,b





zoapatle has been reported.[1] During the course of a structure–activity relationship study, bicyclic compounds **2a** and **2b**[2] with similar pharmacological profiles[1-4] were obtained. As a continuation of our interest in this series, the structurally simplified 1,4-dioxane analogues **3a** and **3b** were synthesized. A recent publication by Wani et al.[3] describing the preparation of compounds within this series by a totally different synthetic route prompts this report of our results.

In light of the total synthesis of **2a** and **2b**,[4] a synthetic

(1) (a) Levine, S. D.; Adams, R. E.; Chen, R.; Cotter, M. L.; Hirsch, A. F.; Kane, V. V.; Kanojia, R. M.; Shaw, C.; Wachter, M. P.; Chin, E.; Huettemann, R.; Ostrowski, P.; Mateos, J. L.; Noriega, L.; Guzman, A.; Mijarez, A.; Tovar, L. *J. Am. Chem. Soc.* **1979**, *101*, 3404. (b) Kanojia, R. M.; Wachter, M. P.; Levine, S. D.; Adams, R. E.; Chen, R.; Chin, E.; Cotter, M. L.; Hirsch, A. F.; Huettemann, R.; Kane, V. V.; Ostrowski, P.; Shaw, C. J.; Mateos, J. L.; Noriega, L; Guzman, A.; Mijarez, A.; Tovar, L.; Shefter. E. *J. Org. Chem.* **1982**, *47*, 1310.

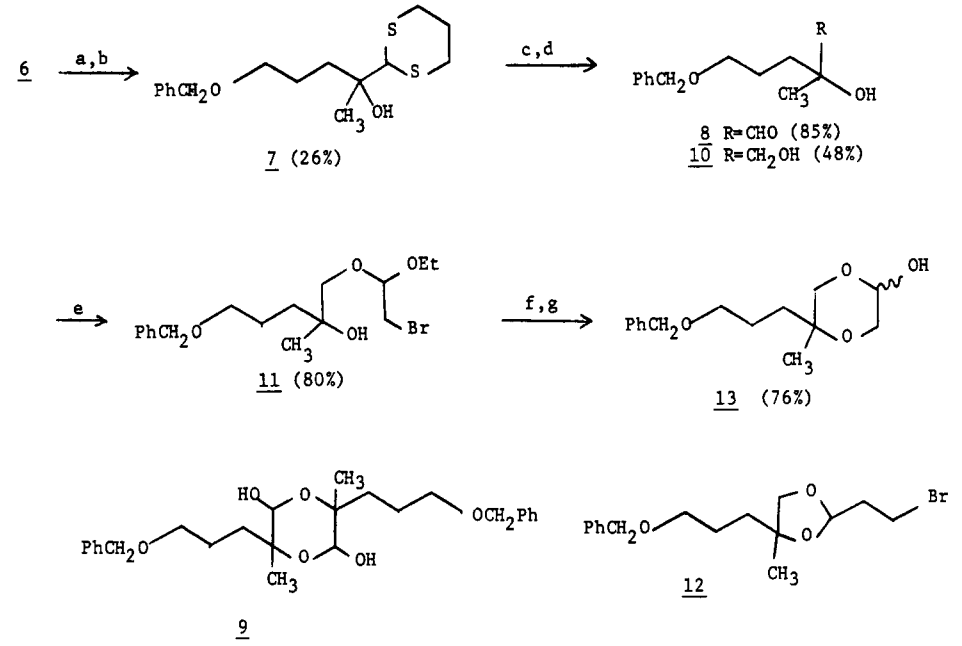
(2) Kanojia, R. M.; Wachter, M. P.; Chen, R. H. K. U.S. Patent 4 102 895, 1978.

(3) Wani, M. C.; Vishnuvajjala, B. R.; Swain, W. E.; Rector, D. H.; Cook, C. E.; Petrow, V.; Reel, J. R.; Allen, K. M.; Levine, S. G. *J. Med. Chem.* **1983**, *26*, 426.

(4) Hajos, Z. G. U.S. Patent 4 284 565, 1981.

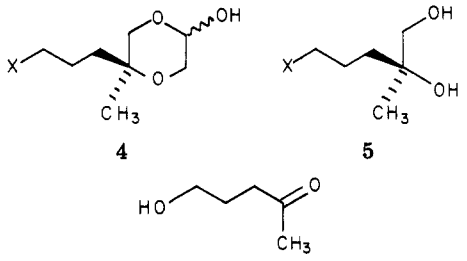
0022-3263/83/1948-2001$01.50/0

Scheme I[a]



[a] (a) $PhCH_2Cl$, $PhCH_2N(n\text{-}Bu)_3Cl$, K_2CO_3, H_2O; (b) $SCH_2SCH_2CH_2CH_2$, *n*-BuLi, THF; (c) HgO, $HgCl_2$, CH_3CN, H_2O; (d) $NaBH_4$, EtOH; (e) $BrCH_2CH(OEt)_2$, HCl; (f) KOH, MeOH; (g) HCl, acetone.

strategy involving the dioxane intermediate **4**, in which the hemiacetal moiety and the functional group X could be employed for introducing the respective C-2 and C-5 side chains, was investigated.



4 **5**

6

One obvious route to **4** would be to establish the dioxane ring by forming two C–O–C bonds from the diol **5**. Since the dioxane ring in **4** is nonsymmetrical, it would be preferable to form the ether linkages sequentially. The elaboration of diol **5** (X = $PhCH_2O$, **10**) from keto alcohol **6** and its subsequent conversion to dioxane **13** is depicted in Scheme I. The hydroxy group of **6** was converted to a benzyl ether (51%) under basic conditions by using a phase-transfer catalyst,[5] and the resulting benzyloxy ketone was allowed to react with the anion generated from 1,3-dithiane and *n*-BuLi in THF[6] to provide the tertiary alcohol **7** (50%). After numerous unsuccessful attempts[7] to establish the initial C–O–C linkage at C-2 from **7**, we sought to remove the bulky cyclic thioacetal group. A variety of methods for thioacetal hydrolysis were investigated[8] and resulted in our use of a mixture of $HgCl_2$ and HgO in a molar ratio of 1:2 in aqueous acetonitrile. Rapid dimerization of the resulting hydroxy aldehyde **8** to **9** (85%) at 20 °C necessitated the immediate reduction ($NaBH_4$/EtOH) of **8** to **10** (48%). Fortunately, any dimer isolated could be reduced under these same conditions to furnish **10** as the sole product.

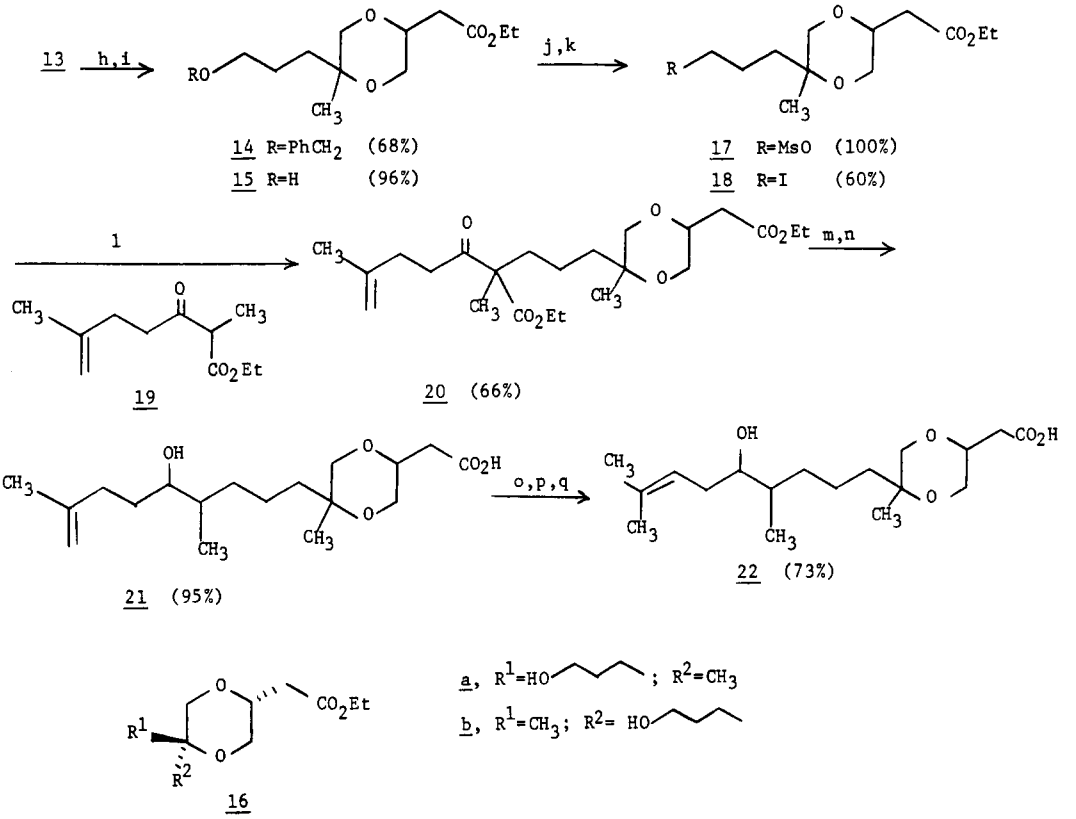
The upper C–O–C linkage of the dioxane ring was formed by a regioselective transacetalization between the primary OH of **10** and the diethyl acetal of bromoacetaldehyde under carefully controlled conditions to give **11** (80%). Under these conditions, we also isolated a small quantity (15%) of the 1,3-dioxolane product **12** from the same reaction.[9] Ring closure of **11** with 5% KOH in MeOH at reflux and hydrolysis of the resultant cyclic acetal with 2 N aqueous HCl in acetone at reflux furnished the hemiacetal **13** (76%).

The subsequent elaboration of the C-2 and C-5 side chains is depicted in Scheme II. Wittig reaction of **13** in the presence of crown ether[10] afforded **14** (68%) as an epimeric mixture (1:1 by NMR). Attempts to separate the epimers at this stage by chromatography were unsuccessful. However, fractional crystallization after hydrogenolysis of the benzyl protecting group resulted in the isolation of the pure epimer **16a** (mp 61–62 °C).[11] The stereochemistry was based on the distinct NMR signals for the epimeric C-5 methyl groups. Epimer **16a** most likely exists in a chair conformation, in which the two side chains are both equatorial and the C-5 methyl group is axial, and displays an NMR signal at δ 1.07. The other CH_3 singlet at δ 1.30 in the NMR spectrum of the hydrogenolysis mixture **15** belongs to **16b** which probably exists in a skew-boat conformation, allowing the bulky C-5 propanol group to assume a quasi-equatorial orientation. These methyl group assignments are consistent with those of bicyclic compounds **2a** and **2b**[4] which in turn are in accord with that of the natural product, zoapatanol.[1]

The synthesis was continued by conversion of the mixture of alcohols **15** to the mesylate **17** (100%) which in turn

(5) Golding, B. T.; Ioannou, P. V. *Synthesis* **1977**, 423.
(6) Seebach, D.; Corey, E. J. *J. Org. Chem.* **1975**, *40*, 231.
(7) For example, **7** did not react with epichlorohydrin under ordinary nucleophilic substitution conditions.
(8) For a review of the hydrolysis of cyclic dithioacetals and -ketals, see: Green, T. W. "Protective Groups in Organic Synthesis"; Wiley: New York, 1981; pp 133–138 and references cited therein.
(9) Dioxolane **12** became either the major or sole product under more vigorous conditions.
(10) Boden, R. M. *Synthesis* **1975**, 784.
(11) The epimeric purity of **16a** was confirmed by NMR and GC/MS; the average yield of **16a** from **15** was 43%.

Scheme II[a]



[a] (h) $Ph_3P{=}CHCO_2Et$, K_2CO_3, CH_2Cl_2, 18-crown-6; (i) H_2, Pd/C, EtOH; (j) MsCl, pyridine, CH_2Cl_2; (k) NaI, acetone; (l) NaH, DMF; (m) NaOH, MeOH; (n) $NaBH_4$, EtOH; (o) Ac_2O, pyridine; (p) *p*-TSA, benzene; (q) NaOH, MeOH.

was transformed into iodide **18** (60%). Nucleophilic displacement of the iodide of **18** by the anion of keto ester **19**[12] in dry DMF gave rise to the keto diester **20** (66%). One-pot hydrolysis and decarboxylation in a refluxing mixture of 1 N aqueous NaOH and MeOH followed by reduction with $NaBH_4$ in EtOH at 20 °C yielded **21** (95%).[13]

Double bond isomerization (*p*-TSA in refluxing benzene, 87%) was carried out after protection of the hydroxyl group in **21** as an acetate (Ac_2O/pyr, 79%).[14] The isomerized acetate could only be obtained under anhydrous conditions. However, complete isomerization was not achieved even upon prolonged refluxing. Hydrolysis of the acetate in aqueous NaOH and MeOH at 20 °C furnished alcohol **22** (98%) as an epimeric mixture at C-5 of the dioxane ring containing approximately 7% of its regioisomer **21**.

The same sequence was applied to the conversion of epimer **16a** to regioisomers **3a** (7.2% overall, eight steps) and **3b** (21.3% overall, five steps), having the stereochemistries corresponding to those of **2a** and **2b**. While the separation of the epimeric mixture **22** from **21** was unsatisfactory, the pure epimer **3a** was separated cleanly from its regioisomer **3b** by flash column chromatography.[15]

Experimental Section

Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. The IR spectra were recorded on a Beckman IR-8 infrared spectrophotometer, while the NMR spectra were measured in the indicated solvent with tetramethylsilane as an internal standard by using a Varian T-60A spectrometer. EI/CI mass spectra were obtained on a Finnigan 1015D quadrupole mass spectrometer coupled to a Finnigan 9500 gas chromatograph. Symbols of elements refer to microanalyses with results within 0.4% of calculated values. Flash column chromatography was performed on silica gel (silica gel 60, E. Merck).

2-[2-Hydroxy-5-(benzyloxy)pent-2-yl]-1,3-dithiane (7). A mixture of **6** (1 g, 10 mM), benzyl chloride (3.1 mL, 26 mM), K_2CO_3 (12 g, 86.2 mM in 12 mL of H_2O), and $PhCH_2N(n\text{-}Bu)_3Cl$ (80 mg, 0.26 mM) was vigorously stirred at 65 °C for 12 h, cooled to 20 °C, and extracted with Et_2O. The combined Et_2O extracts were washed with H_2O, dried ($MgSO_4$), filtered, evaporated in vacuo, and distilled (105–110 °C, 0.5 torr) to give the benzyl ether: 0.98 g (51%); NMR ($CDCl_3$) δ 7.27 (s, 5 H, Ph), 4.40 (s, 2 H, $PhCH_2O$), 3.40 (t, J = 6 Hz, 2 H, OCH_2), 2.47 (t, J = 6 Hz, 2 H, CH_2CO), 2.07 (s, 3 H, $COCH_3$), 1.8 (m, 2 H, CH_2CH_2CO).

To a solution of 1,3-dithiane (2.5 g, 20 mM) in dry THF (40 mL) was added dropwise under N_2 at −40 °C *n*-BuLi (22 mM). Following 3 h of stirring at −40 °C, the benzyl ether (3.9 g, 20 mM) was added dropwise over a 30-min period at −30 to −40 °C. The resultant solution was stirred for 16 h at 5 °C, evaporated in vacuo, treated with H_2O, and extracted with Et_2O. The combined Et_2O extracts were washed with brine, dried ($MgSO_4$), filtered, evaporated in vacuo, and chromatographed (CH_2Cl_2) to give **7**: 3.1 g (50%); IR (neat) 3450 cm^{-1}; NMR ($CDCl_3$) δ 7.23 (s, 5 H, Ph), 4.43 (s, 2 H, $PHCH_2O$), 4.12 (s, 1 H, SCHS), 3.47 (m, 2 H, OCH_2), 2.83 (q, J = 3 Hz, 4 H, 2 SCH_2), 2.63 (s, 1 H, OH, D_2O exchangeable), 1.70 (m, 6 H, aliphatic H), 1.27 (s, 3 H, CH_3). Anal ($C_{16}H_{24}O_2S_2$): C, H.

5-(Benzyloxy)-1,2-dihydroxy-2-methylpentane (10). A mixture of $HgCl_2$ (21 g, 79.2 mM), HgO (8.7 g, 39.6 mM), and **7** (11.2 g, 36 mM) in 75% aqueous CH_3CN (600 mL) was stirred at reflux under N_2 for 20 h, cooled to 20 °C, and filtered through Celite, and the solid was washed with hexane/CH_2Cl_2 (1:1). The filtrate was then evaporated in vacuo, dissolved in CH_2Cl_2, washed with 5 M NH_4OAc and H_2O, dried ($MgSO_4$), filtered, and evap-

(12) The keto ester **19** was prepared according to a procedure described by: Pinnick, H. W.; Chang, Y. H. *Tetrahedron Lett.* **1979**, 837.

(13) The free carboxyl group resulting from the hydrolysis of the keto diester **20** did not interfere with our synthesis, and therefore **21** was not converted to its ester.

(14) Naegeli, P.; Weber, G. *Tetrahedron Lett. 1970*, 959.

(15) These compounds were highly viscous oils and very hygroscopic. Attempts to prepare anhydrous samples for microanalysis were unsuccessful. This point has been noted by Wani et al.[3] as well.

orated in vacuo to give 8: 6.4 g (85%); IR (neat) 3420, 1730 cm^{-1}. To a solution of 8 (6.4 g, 30 mM) in EtOH (60 mL) was added $NaBH_4$ (0.56 g, 15 mM). The resultant solution was stirred at 20 °C for 20 h, treated with H_2O, neutralized with concentrated HCl, and extracted with Et_2O. The extracts were washed with H_2O, dried ($MgSO_4$), filtered, evaporated in vacuo, and chromatographed (Et_2O) to give 10: 3g (48%); IR (neat) 3400 cm^{-1}; NMR ($CDCl_3$) δ 7.30 (s, 5 H, Ph), 4.52 (s, 2 H, $PhCH_2O$), 3.42 (m, 4 H, OCH_2 and CH_2OH), 3.01 (s, 2 H, OH, D_2O exchangeable), 1.67 (m, 4 H, aliphatic H), 1.17 (s, 3 H, CH_3). Anal. ($C_{13}H_{20}O_3$): C, H.

2,5-Bis[3-(benzyloxy)propyl]-3,6-dihydroxy-2,5-dimethyl-1,4-dioxane (9). Compound 9 was isolated by chromatography either from a neat sample of 8 (standing at 20 °C for 24 h) or from a solution of 8 in CH_2Cl_2 with a catalytic amount of *p*-TSA stirred at reflux for 48 h and was purified by chromatography (10% Et_2O in CH_2Cl_2): IR (neat) 3390, 1730 cm^{-1}; NMR ($CDCl_3$) δ 7.27 (s, 10 H, 2 Ph), 4.83 (d, J = 2 Hz, 2 H, 2 OCHO), 4.47 (s, 4 H, 2 $PhCH_2O$), 3.40 (m, 4 H, 2 CH_2O), 1.77 (m, 8 H, 2 CH_2CH_2), 1.23 (m, 6 H, 2 CH_3). Anal. ($C_{26}H_{36}O_6$): C, H.

5-[3-(Benzyloxy)propyl]-2-hydroxy-5-methyl-1,4-dioxane (13). Concentrated HCl (0.06 mL) was added to a solution of 10 (9.6 g, 43 mM) in α-bromoacetaldehyde diethyl acetal (65 mL, 430 mM) with stirring at 0–5 °C. After 72 h at 20 °C, CH_2Cl_2 (50 mL) was added, and the resultant solution was washed with saturated K_2CO_3, dried ($MgSO_4$), filtered, and evaporated in vacuo (30–35 °C, 0.5 torr). The residual oil was chromatographed (CH_2Cl_2) to give first 12: 2.14 g (15.1%); IR (neat) 1100 cm^{-1}; NMR ($CDCl_3$) δ 7.3 (s, 5 H, Ph), 5.2 (2 t, J = 3 Hz, 1 H, OCHO), 4.48 (s, 2 H, $PhCH_2O$), 3.5 (m, 6 H, 2 CH_2O and CH_2Br), 1.7 (m, 4 H, CH_2CH_2), 1.3 (2 s, 3 H, 2 epimeric C-4 CH_3). Anal. ($C_{15}H_{21}O_3Br$): C, H. The more polar product 11 was obtained as an oil: 12.86 g (79.7%); IR (neat) 3440 cm^{-1}; NMR ($CDCl_3$) δ 7.32 (s, 5 H, Ph), 4.67 (t, J = 4 Hz, 1 H, OCHO), 4.50 (s, 2 H, $PhCH_2O$), 3.40 (m, 8 H, OCH_2, 2 OCH_2, and CH_2Br), 2.60 (s, 1 H, OH), 1.23 (t, J = 6 Hz, 3 H, ethoxy CH_3), 1.2 (s, 3 H, CH_3). A solution of 11 (12.86 g, 34 mM) in 5% methanolic KOH (193 mL) was stirred at reflux for 6 h, evaporated in vacuo, dissolved in Et_2O, washed with brine, dried ($MgSO_4$), evaporated in vacuo, and chromatographed (CH_2Cl_2) to give the cyclized acetal as an oil (5.5 g, 55%). The oil (4.2 g, 14.27 mM) was dissolved in acetone (55 mL) and 2 N aqueous HCl (13.5 mL), stirred at reflux for 8 h, cooled to 20 °C, and evaporated in vacuo. The oily residue was dissolved in Et_2O, washed with saturated $NaHCO_3$, dried (Na_2SO_4), filtered, evaporated in vacuo, and chromatographed (10% Et_2O in CH_2Cl_2) to give the cyclic hemiacetal 13: 2.87 g (76%); IR (neat) 3380 cm^{-1}; NMR ($CDCl_3$) δ 7.33 (s, 5 H, Ph), 4.83 (m, 1 H, OCHOH), 4.5 (s, 2 H, $PhCH_2O$), 3.50 (m, 7 H, 3 OCH_2, and OH), 1.67 (m, 4 H, CH_2CH_2), 1.17 (2 s, 3 H, 2 epimeric CH_3). Anal. ($C_{15}H_{22}O_4$): C, H.

Ethyl 5-[3-(Benzyloxy)propyl]-5-methyl-1,4-dioxane-2-acetate (14). A mixture of 13 (15.5 g, 68.5 mM), $Ph_3P{=}CHCO_2Et$ (48 g, 137 mM), 18-crown-6(200 mg), and K_2CO_3 (9.5 g. 68.5 mM) in CH_2Cl_2 (300 mL) was stirred at reflux under N_2 for 13 h, cooled to 20 °C, filtered through a silica gel pad, and evaporated in vacuo. The oily residue was then dissolved in hexane (200 mL), stirred for 16 h, filtered through Celite, evaporated in vacuo, and chromatographed (CH_2Cl_2) to give ester 14: 15.6 g (68%); IR (neat) 1740 cm^{-1}; NMR ($CDCl_3$) δ 7.23 (s, 5 H, Ph), 4.40 (s, 2 H, $PhCH_2O$), 4.1 (q, J = 7 Hz, 2 H, CO_2CH_2), 3.37 (m, 7 H, 3 OCH_2 and OCH), 2.33 (dd, J_1 = 5 Hz, J_2 = 1 Hz, 2 H, CH_2CO_2), 1.43 (m, 4 H, CH_2CH_2), 1.17 (t, J = 7 Hz, 3 H, ethyl ester CH_3), 1.20 and 0.97 (2 s, 3 H, 2 epimeric CH_3). Anal. ($C_{19}H_{28}O_5$): C, H.

[5-(5-Hydroxy-4,8-dimethyl-8-nonenyl)-5-methyl-1,4-dioxan-2-yl]acetic Acid (21). Dioxane 14 (7.5 g, 22.3 mM) was hydrogenated in a Parr shaker over 10% Pd/C (2.5 g) at 40 lb of H_2 in absolute EtOH (30 mL) for 48 h. The mixture was filtered, and the catalyst was rinsed with EtOH. The filtrate was evaporated in vacuo and then chromatographed (Et_2O) to give first 14 (0.3 g) followed by 15: 5.3 g (96%); NMR ($CDCl_3$) δ 4.13 (q, J = 7 Hz, 2 H, CO_2CH_2), 3.47–4.0 (m, 7 H, 3 CH_2O and OCH), 2.43 (dd, J_1 = 6 Hz, J_2 = 1.5 Hz, 2 H, CH_2CO), 2.30–1.50 (m, 4 H, CH_2CH_2), 1.30 and 1.07 (2 s, 3 H, 2 epimeric CH_3), 1.25 (t, J = 7 Hz, 3 H, ethyl ester CH_3). Mesyl chloride (3.8 mL, 50 mM) was added under N_2 to a solution of 15 (5.3 g, 21.6 mM) in CH_2Cl_2 (200 mL) and pyridine (3.9 g, 50 mM) at 20 °C. The resultant solution was stirred at reflux for 8 h, cooled, filtered through a short silica gel column which was further washed with Et_2O, evaporated in vacuo, and chromatographed (Et_2O) to give mesylate 17 (5.4 g, 76.9%). To an acetone solution (200 mL) of 17 was added NaI (3.7 g, 24.7 mM), and the resultant yellow mixture was stirred under N_2 at reflux for 7 h, cooled to 20 °C, filtered through a Celite pad, evaporated in vacuo, dissolved in Et_2O (100 mL), washed with saturated aqueous Na_2SO_3, dried ($MgSO_4$), and filtered. After evaporation of the solvent, the light yellowish oil was chromatographed (Et_2O) to give the iodide 18: 4.5 g (75.3%); IR (neat) 1740 cm^{-1}; NMR ($CDCl_3$) δ 4.15 (q, J = 7 Hz, 2 H, CO_2CH_2), 4.0–3.47 (m, 5 H, CH_2OCHCH_2O), 3.33–3.07 (m, 2 H, ICH_2), 2.45 (dd, J_1 = 6 Hz, J_2 = 1.5 Hz, 2 H, CH_2CO_2), 2.20–1.40 (m, 4 H, CH_2CH_2), 1.28 and 1.07 (2 s, 3 H, 2 epimeric CH_3), 1.27 (t, J = 7 Hz, 3 H, ethyl ester CH_3).

A solution of 19 (1.38 g, 6.95 mM) in DMF (2 mL) was added dropwise over a 10-min period under N_2 to an ice-cooled mixture of NaH (6.9 mM, washed free of oil with pentane) and DMF (12 mL). The mixture was then stirred for 30 min before a solution of 18 (2.4 g, 6.9 mM) in DMF (2 mL) was slowly added. The resultant greenish mixture was stirred at 20 °C for 3 h and kept at 5 °C overnight. The semisolid was then allowed to warm to 20 °C, diluted with CH_2Cl_2 (20 mL), and poured into a mixture of ice–water (50 mL), CH_2Cl_2 (20 mL), and 2 N aqueous HCl (10 mL). After separation of the organic layer and evaporation of the solvent, the residual oil was dissolved in Et_2O (100 mL), washed with H_2O followed by brine, dried ($MgSO_4$), filtered, and evaporated in vacuo. Column chromatography (50% Et_2O in hexane) gave 20: 1.92 g (65.8%); mass spectrum, m/e 426 (M^+).

A mixture of the keto diester 20 (1.92 g, 4.5 mM), MeOH (10 mL), and 1 N aqueous NaOH (10 mL) was stirred at reflux for 3.5 h, cooled to 20 °C, diluted with H_2O (50 mL), and extracted with Et_2O. The aqueous layer was carefully acidified with 2 N HCl and extracted with Et_2O. The Et_2O extracts were dried ($MgSO_4$), filtered, and evaporated in vacuo to give an oil which was dissolved in EtOH (30 mL). The ethanolic solution was stirred at 20 °C under N_2 and treated portionwise with $NaBH_4$ (340 mg, 9 mM). After 6 h at 20 °C, H_2O (100 mL) was added, and the mixture was extracted with Et_2O. The combined Et_2O extracts were dried ($MgSO_4$), filtered, and evaporated in vacuo to give an oily residue which was then chromatographed (Et_2O/petroleum ether/AcOH, 20:20:1) to give the hydroxy acid 21: 1.2 g (79%); IR ($CHCl_3$) 3500, 1720, 1670, 1100 cm^{-1}; NMR ($CDCl_3$) δ 5.63 (br, 2 H, OH and COOH), 4.73 (s, 2 H, $CH_2{=}$), 4.33–3.33 (m, 6 H, CHO and CH_2OCHCH_2O), 2.48 (d, J = 6 Hz, 2 H, CH_2CO_2), 2.33–2.00 (m, 2 H, vinyl CH_2), 1.75 (s, 3 H, vinyl CH_3), 1.67–0.87 (m, 15 H, allylic CH_2 and $-CH(CH_3)CH_2CH_2CH_2(CH_3)C(O-)-$). Anal. ($C_{18}H_{32}O_5{\cdot}0.25H_2O$): C, H.

5-(5-Hydroxy-4,8-dimethyl-7-nonenyl)-5-methyl-1,4-dioxan-2-yl]acetic Acid (22). A solution of 21 (6.75 g, 20.6 mM) in pyridine (10 mL) was treated under N_2 with Ac_2O (20 mL). The resultant solution was stirred at 20 °C under N_2 for 18 h, diluted with Et_2O (1 L), filtered through a short silica gel column which was further eluted with Et_2O (500 mL), and evaporated in vacuo. The residual oil was then dissolved in Et_2O, washed with H_2O and brine, dried ($MgSO_4$), filtered, evaporated in vacuo, and chromatographed (Et_2O/petroleum ether/HOAc, 20:20:1) to give the acetate as an oil which was dissolved in benzene (50 mL). The benzene solution was then added into a prerefluxed (2 h, H_2O removed by Dean–Stark trap) solution of *p*-TSA (0.6 g) in benzene (500 mL). The resultant solution was stirred at reflux for 24 h, cooled to 20 °C, evaporated in vacuo, and chromatographed (Et_2O/petroleum ether/AcOH, 20:20:1) to give an oil which was dissolved in MeOH (60 mL). The methanolic solution was treated with 2 N aqueous NaOH (60 mL), and the resultant mixture stirred at 20 °C for 24 h, evaporated in vacuo, dissolved in Et_2O (250 mL), and extracted with H_2O.

The aqueous layers were acidified with 2 N aqueous HCl, saturated with NaCl, and extracted with Et_2O. The combined extracts were dried ($MgSO_4$), filtered, evaporated in vacuo, and chromatographed (Et_2O/petroleum ether/AcOH, 20:20:1) to give the isomerized hydroxy acid 22: 2.63 g (73%); IR (neat) 3400, 2940, 1720 cm^{-1}; NMR ($CDCl_3$) δ 6.25 (br, 2 H, OH, and COOH), 5.13 (t, J = 7 Hz, 1 H, CH=), 3.43 (m, 6 H, C-2, C-3, C-6 H, and CHO), 2.43 (d, J = 6 Hz, 2 H, CH_2CO_2), 2.1 (m, 2 H, vinyl CH_2), 1.58 and 1.68 (2 s, 6 H, 2 vinyl CH_3), 1.20 and 1.0 (2 s, 3 H, 2

epimeric CH_3), 1.30–0.80 (m, 10 H, $CH(CH_3)CH_2CH_2CH_2$). Anal. ($C_{18}H_{32}O_5 \cdot 0.25H_2O$): C, H.

[(2*RS*,5*SR*)-5-(5-Hydroxy-4,8-dimethyl-8-nonenyl)-5-methyl-1,4-dioxan-2-yl]acetic Acid (3b). Fractional crystallization of **15** from Et_2O/hexanes gave **16a** (43% from **15**; mp 61–62 °C) which was converted to **3b** (21.2%) according to the same procedure described for compound **21**: IR (neat) 3420, 1730, 1105 cm^{-1}; NMR ($CDCl_3$) δ 6.27 (br, 2 H, OH and COOH), 4.73 (br, 2 H, CH_2=), 3.83–3.27 (m, 6 H, C-2, C-3, C-6 H, and CHO),2.48 (d, J = 6 Hz, 2 H, CH_2CO_2), 2.20–1.97 (m, 2 H, vinyl CH_2), 1.77 (s, 3 H, vinyl CH_3), 1.65–1.23 (m, 9 H, allylic CH_2 and $CHCH_2CH_2CH_2$), 1.07 (s, 3 H, C-5 CH_3), 0.60 (d, J = 6 Hz, 3 H, side-chain CH_3). Anal. ($C_{18}H_{32}O_5 \cdot 0.25H_2O$): C, H.

[(2*RS*,5*SR*)-5-(5-Hydroxy-4,8-dimethyl-7-nonenyl)-5-methyl-1,4-dioxan-2-yl]acetic Acid (3a). The double bond isomerization of **3b** was carried out as described for **21**. The crude reaction product was purified free of residual **3b** by chromatography (silica gel impregnated with 20% $AgNO_3$; Et_2O/petroleum ether/AcOH, 20:20:1), giving **3a** as a colorless oil: 34%; IR (neat) 3400, 2950, 1730 cm^{-1}; NMR ($CDCl_3$) δ 6.30 (br, 2 H, OH and COOH), 5.18 (m, 1 H, CH=), 3.77–3.28 (m, 6 H, C-2, C-3, C-6 H, and CHO), 2.48 (d, J = 6 Hz, 2 H, CH_2CO_2), 2.17 (m, 2 H, vinyl CH_2), 1.77 and 1.68 (2 s, 3 H each, 2 vinyl CH_3), 1.38 (m, 7 H, $CHCH_2CH_2CH_2$), 1.08 (s, 3 H, C-5 CH_3), 0.93 (d, J = 6 Hz, 3 H, side-chain CH_3). Anal. ($C_{18}H_{32}O_5 \cdot 0.25H_2O$): C, H.

Acknowledgment. We thank E. Deegan for the preparation of some of the intermediates, Dr. M. L. Cotter for spectroscopic results, and C. Shaw for GC/MS data. We are also in debt to Dr. S. D. Levine for constant encouragement and interest in this work and to Professor J. A. Marshall for helpful discussions.

Registry No. 3a, 84143-14-6; **3b**, 85665-05-0; **6**, 1071-73-4; **6** benzyl ether, 13329-18-5; (±)-**7**, 85665-06-1; (±)-**8**, 85665-07-2; **9**, 85665-08-3; (±)-**10**, 85665-09-4; **11**, 85665-10-7; **12**, 85665-11-8; **13**, 85665-12-9; **14**, 85665-13-0; **15**, 85665-14-1; (±)-**16a**, 85665-15-2; **17**, 85665-16-3; **18**, 85665-17-4; (±)-**19**, 85665-18-5; **20**, 85665-19-6; **22**, 84143-14-6; $BrCH_2CH_2(OEt)_2$, 2032-35-1; Ph_3P=$CHCO_2Et$, 1099-45-2.

Photochemical Transformations. 34. Some Studies on the Di-π-methane Rearrangement of 7-(Ethoxycarbonyl)dibenzobarrelene[1]

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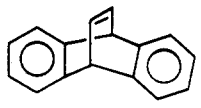
A detailed study of the rearrangement of 7-(ethoxycarbonyl)dibenzobarrelene to 1-(ethoxycarbonyl)dibenzosemibullvalene has been carried out. Lifetimes of the triplet intermediate(s) were measured by three quenching techniques and were in the 0.2–0.9-ns range in both direct and benzophenone-sensitized photoreactions. Difficulties in discussion of mechanism in systems that have a number of excited-state intermediates on the path from reactant to product are discussed.

Our group has been interested for some time in the measurements of rate constants for excitation transfer between triplet sensitizers and acceptor molecules and of lifetimes of triplets produced by sensitization.[2] It is necessary, in order to test various quenching techniques[1,3] for such measurements, to have a system where intersystem crossing from the directly excited singlet state of a substrate occurs to give a triplet species identical with that formed by sensitization.

Among the most studied reactions[4-6] in photochemistry is the di-π-methane rearrangement. The rearrangements of dibenzobarrelene (**1**) and its derivatives to corresponding dibenzosemibullvalenes **2** represents some of the early examples[7] of this reaction. A detailed study of the conversion of **1** to **2**, which is a triplet reaction, has recently been carried out in our laboratory.[1] Ciganek[7] reported that the methoxycarbonyl derivative (**3**-CH_3) rearranged to the semibullvalene derivative (**4**-CH_3) upon direct irradiation in hydrocarbon solvents or upon acetone sensitization,



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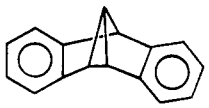

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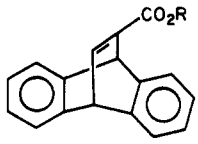

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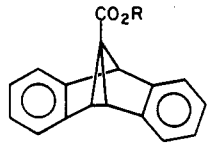

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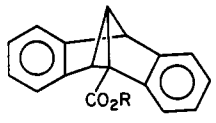
without the formation of the other isomeric semibullvalene **5**-CH_3 or of the dibenzocyclooctatetraenecarboxylic ester



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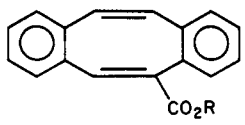

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6-CH_3, and this was confirmed by Friedman and coworkers.[8] Thus, unlike the parent dibenzobarrelene (whose excited singlet leads irreversibly to the intermediate

(1) Paper 33: Cristol, S. J.; Kaufman, R. L.; Opitz, S. M.; Szalecki, W.; Bindel, T. H. *J. Am. Chem. Soc.*, in press.
(2) Ilenda, C. S.; Daughenbaugh, R. J.; Cristol, S. J. *Mol. Photochem.* **1976**, *7*, 287.
(3) Cristol, S. J.; Bindel, T. H. *J. Am. Chem. Soc.* **1981**, *103*, 7287.
(4) (a) Zimmerman, H. E.; Grunewald, G. L. *J. Am. Chem. Soc.* **1966**, *88*, 183. (b) Zimmerman, H. E.; Binkley, R. W.; Givens, R. S.; Sherwin, M. A. *Ibid.* **1967**, *89*, 3932. (c) Zimmerman, H. E., Bender, C. O. *Ibid.* **1970**, *92*, 4366.
(5) Hixson, S. S.; Mariano, P. S.; Zimmerman, H. E.; *Chem. Rev.* **1975**, *73*, 531.
(6) Zimmerman, H. E. In "Rearrangements in Ground and Excited States"; de Mayo, P., Ed.; Academic Press: New York, 1980; Vol. III, pp 131–166.
(7) Ciganek, E. *J. Am. Chem. Soc.* **1966**, *88*, 2882.
(8) Rabideau, P. W.; Hamilton, J. B.; Friedman, L. *J. Am. Chem. Soc.* **1968**, *90*, 4466.

0022-3263/83/1948-2005$01.50/0