^{1}H NMR ($CDCl_3$) δ 0.006, 0.017, and 0.021 (s, 6 H), 0.836 and 0.845 (s, 9 H), 1.44–1.57 (m, 1 H), 1.91 (m, 1 H), 2.27–2.45 (m, 3 H), 2.76 (overlapping dd, 1 H), J = 5.1, 13.7), 3.63–3.67 (m and two methyl s, 4 H), 4.12 (m, 1 H), 4.95 and 4.96 (dd, 2 H), 7.39 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ −4.72, −4.80, −4.93, −4.96, 17.70, 17.67, 25.56, 38.30, 39.18, 39.81, 42.11, 51.45, 54.63, 54.96, 66.54, 66.97, 78.07, 78.18, 128.46, 128.49, 128.81, 128.86, 129.21, 129.24, 135.13, 135.20, 163.91, 164.12, 171.05, 171.10; high-resolution MS calcd for $C_{21}H_{33}NO_5Si$ 407.2128, found 407.2127.

Methyl 4-[1-(Benzyloxy)-2-oxo-4-azetidinyl]-β-hydroxybutyrate (15). To a stirred solution of **14** as a mixture of diastereomers (339 mg, 0.80 mmol) in THF (2 mL) was added acetic acid (46 μL, 0.80 mmol) followed by tetrabutylammonium fluoride (2.4 mL of a 1 M solution in THF, 2.4 mmol). The resulting orange solution was stirred for 18 h, concentrated to one-half volume, and partitioned between ethyl acetate (15 mL) and brine (15 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (2 × 15 mL). The organic layers were combined, dried ($MgSO_4$), and filtered, and the solvents were evaporated to give an oil which was passed through a short column of silica gel, eluting with ethyl acetate. Concentration and flash chromatography on silica gel (3:1 hexanes/ethyl acetate) of the residue provided the diastereomeric alcohols **15** (202 mg, 86%) as a pale yellow oil: IR ($CHCl_3$) 3530 (br), 3020, 2960, 1765, 1725 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.39–1.89 (series of m, 2 H), 2.35–2.46 (m, 3 H), 2.80 (overlapping dd, 1 H, J = 5.2, 13.8), 3.05 and 3.13 (br d, 1 H), 3.71 and 3.79 (m overlapping with s, 4 H), 3.95–4.15 (m, 1 H), 4.95 and 4.96 (dd, 2 H), 7.37 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 37.78, 38.50, 38.56, 39.27, 41.09, 41.27, 51.66, 55.02, 55.20, 64.97, 65.42, 77.95, 78.03, 128.47, 128.85, 129.19, 129.33, 135.09, 164.13, 164.16, 172.47, 172.56; high-resolution MS calcd for $C_{15}H_{19}NO_5$ 293.1263, found 293.1263.

Methyl 4-[1-(Benzyloxy)-2-oxo-4-azetidinyl]-β-ketobutyrate (3). A solution of pyridine (0.679 mL, 8.4 mmol) in CH_2Cl_2 (10 mL) was cooled to 0 °C (external temperature), and to this was added finely powdered CrO_3 (423 mg, 4.23 mmol) against a positive flow of argon. The heterogeneous dark burgundy mixture was allowed to warm to room temperature (23 °C), stirred for 15 min, and cooled to 0 °C at which time the alcohol **15** (205 mg, 0.7 mmol) in CH_2Cl_2 (1 mL) was added via cannula, along with a 0.5 mL of CH_2Cl_2 rinse of the flask. The resulting dark solution was stirred at 0 °C for 15 min and then at room temperature for 1 h. The reaction was concentrated to approximately half the volume under reduced pressure, diluted with Et_2O (20 mL), and filtered through Celite. The remaining black residue was rinsed with several portions of ether and filtered through Celite. Removal of the solvent by rotary evaporation and removal of pyridine under high vacuum (0.05 Torr, 1 h) gave a brown oil which was filtered through a plug of silica gel eluting with ethyl acetate. Concentration of this solution gave the β-keto ester **3** (147 mg, 72%) as a pale yellow oil: IR ($CHCl_3$) 3010, 2960, 1770 (br), 1720 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.33 (dd, 1 H, J = 2.4, 13.9), 2.65 (dd, 1 H, J = 6.8, 18.0), 2.81 (dd, 1 H, J = 6.3, 18.0), 2.84 (dd, 1 H, J = 5.3, 13.9), 3.40 and 3.41 (center lines of AB q, 2 H), 3.69 (s, 3 H), 4.02 (m, 1 H), 4.85 (d, 1 H, J = 10.9), 4.91 (d, 1 H, J = 10.9), 7.38 (m, 5 H); ^{13}C NMR ($CDCl_3$/TMS) δ 38.11, 45.05, 49.06, 52.37, 52.49, 77.86, 128.61, 128.97, 129.41, 135.16, 164.07, 167.07, 199.86; high-resolution MS calcd for $C_{15}H_{17}NO_5$ 291.1107, found 291.1110.

Rearrangement Product (5). Compound **3** (100 mg, 0.34 mmol) was dissolved in ethyl acetate (5 mL), and to this was added 10% Pd-C (8 mg). The stirred solution was placed under an atmosphere of H_2 (balloon). After 70 min, the reaction was filtered through Celite and the solvent was removed under reduced pressure. The residue was flash chromatographed on silica (100% ethyl acetate) to give 45 mg of a colorless oil. After allowing the oil to stand under vacuum (4 h, 1–2 Torr), NMR showed approximately a 1:1 mixture of products. The progress of the rearrangement was monitored by NMR. After the mixture was allowed to remain in an NMR tube in $CDCl_3$ for a total of 42 h at −5 °C and 3 h at room temperature (time accumulated while sample was analyzed by NMR), ^{1}H and ^{13}C analysis indicated >98% coversion to **5**: R_f = 0.21 (100%, ethyl acetate); IR (CCl_4) 1770, 1750 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.60 (ddd, 1 H, J = 1.9, 4.9, 12.4), 2.71 (d, 1 H, J = 12.4), 2.81 (dd, 1 H, J = 4.4, 18.5), 2.95 (d, 1 H, J = 16.3), 2.97 (apparent dt, collapses to a dd upon irradiation at δ 4.05, 1 H, J = 18.6, 1.9), 3.19 (d, 1 H, J = 16.3), 3.72 (s, 3 H), 6.62 (br s, 1 H); ^{13}C NMR ($CDCl_3$/TMS ref) δ 38.22, 38.48, 41.45, 52.02, 53.03, 106.70, 168.17, 168.39; high-resolution MS calcd for $C_8H_{11}NO_5$ 201.0637, found 201.0639.

Phenyl Isocyanate Adduct (18). A solution of **5** (11 mg, 0.054 mmol) in THF (1 mL) was cooled to 0 °C (ice bath, external temperature), and phenyl isocyanate (6 μL, 0.055 mmol) was added dropwise via a microsyringe. The mixture was stirred at 0 °C for 1 h at which time an additional 1 μL of phenyl isocyanate was added and the reaction was allowed to warm to room temperature. After 1 h, 1 μL more of phenyl isocyanate was added, and the mixture was stirred an additional hour. The solvent was then removed under reduced pressure, and the thick oil obtained was purified by flash chromatography (1.5:1 ethyl acetate/hexanes) to yield 12 mg (70%) of **18** as a colorless semisolid. Recrystallization provided colorless prisms: mp = 128–130 °C (CH_2Cl_2/hexanes); R_f = 0.28 (1.5:1 ethyl acetate/hexanes); IR (KBr) 3380, 1755, 1740, 1700, 1600, 1580, 1535 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.45 (d, 1 H, J = 12.5), 2.51 (ddd, 1 H, J = 1.8, 4.7, 12.5), 2.91 (dd, 1 H, J = 4.2, 18.9), 3.16 (m, 1 H), 3.17 (d, J = 16), 3.25 (d, J = 16), 3.37 (s, 3 H), 5.04 (m, 1 H), 7.14–7.51 (m, 5 H), 7.92 (br s, 1 H); high-resolution MS calcd $C_{15}H_{16}N_2O_6$ 320.1008, found 320.1005.

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Supplementary Material Available: NMR spectra copies for **3**, **5**, **11**, **12**, **13**, **14**, **15**, and **18** and X-ray data for **18** (24 pages). Ordering information is given on any current masthead page.

A New Aspect of the High-Field NMR Application of Mosher's Method. The Absolute Configuration of Marine Triterpene Sipholenol-A

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We have reported on the use of high-field NMR to elucidate the absolute configurations of organic compounds possessing a secondary alcohol moiety by measuring the ^{1}H NMR spectra of their methoxy(trifluoromethyl)-phenylacetic (MTPA) esters on a superconductive NMR spectrometer.[1] This method (as well as an analogue using MTPA esters[2] and another using *O*-methylmandelates[3]) is based on Mosher's concept[4] that MTPA ester groups exist in a conformation in which the carbinyl proton, the C–O carbonyl bond, and the trifluoromethyl group (or the α-proton of a mandelate) are located in the same plane (Figure 1A). In an MTPA ester with the absolute configuration shown in Figure 1B, protons ($H_{A,B,C}$) on the right side of the MTPA plane should have positive Δδ ($\Delta\delta = \delta_S - \delta_R$) values, and protons ($H_{X,Y,Z}$) on the left side of the plane should have negative Δδ values because of the anisotropic effects of the phenyl groups of the (*R*)- and (*S*)-MTPA esters. However, if steric compression around the ester moiety is serious, the conformation of the ester may deviate significantly from the one assumed, which would cause irregular anisotropic shifts of the protons.

Sipholenol-A (**1**), a marine triterpene from the Red Sea sponge *Siphonochalina siphonella*, is an example. The

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Table I. ^{1}H NMR Spectral Data for the MTPA Esters (δ, $CDCl_3$)[a]

compd	no.	(S)-MTPA	(R)-MTPA	Δδ (Hz) (500 MHz)	compd	no.	(S)-MTPA	(R)-MTPA	Δδ (Hz) (500 MHz)
1a	2a	1.410	1.441	−15.5	2a	2a	1.79	1.77	+10
	2b	1.221	1.304	−41.5		2b	1.27	1.27	0
	3a	2.033	2.080	−23.5		3a	2.159	2.074	+42.5
	3b	1.949	1.849	+50		3b	1.52	1.43	+45
	4	5.044	5.190	−73		4	4.964	4.960	+2
	7	3.150	3.139	+5.5		7	3.207	3.210	−1.5
	8a	1.696	1.696	0		8a	1.79	1.79	0
	8b	1.288	1.279	+4.5		8b	1.37	1.38	−5
	9	1.56	1.54	+10		9a	1.62	1.62	0
	11	0.610	0.560	+25		9b	1.43	1.43	0
	12	1.485	1.475	+5		11	0.77	0.77	0
	24	0.957	0.964	−3.5		12	1.51	1.51	0
	25	1.190	1.202	−6		12	1.15	1.15	0
	26	1.086	1.087	−0.5		24	0.972	0.956	+8
	27	1.075	1.057	+9		25	1.09	1.187	−48.5
						26	1.033	1.066	−16.5
						27	1.09	1.09	0

[a] The protons on the A and B rings of **1a** and **2a** are listed.

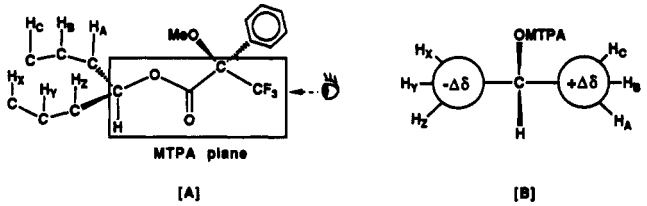


Figure 1. [A] The MTPA plane of the (*R*)-MTPA ester of a secondary alcohol. [B] The rule for determining the absolute configurations of secondary alcohols ($\Delta\delta = \delta_S - \delta_R$).

structure of **1** has been established by X-ray[5] and NMR[6] analyses, but its absolute configuration has remained unknown. In order to determine it, (+)-(*R*)- ($\mathbf{1}_R$) and (−)-(*S*)-MTPA ($\mathbf{1}_S$) esters of **1** were prepared, and the $\Delta\delta$ values[1] (500 MHz) of all assignable protons (H, H-COSY, HOHAHA, phase-sensitive NOESY) on rings A and B were determined (Table I, Figure 2). It can be seen that the positive and negative $\Delta\delta$ values are irregularly dispersed on the left and right sides of the MTPA plane. Molecular models of $\mathbf{1}_R$ and $\mathbf{1}_S$ revealed that, in each compound, the ester group is axial and is sterically hindered by the axial 2-H and 7-H as well as by the adjacent *gem*-dimethyl groups. If this steric crowding around the ester moiety is the principal reason for the irregularity, conversion of the hydroxy group into a less hindered one should solve the problem.

Episipholenol-A (**2**) was prepared by $NaBH_4$ reduction[6a] of sipholenone-A (**3**) (obtained by treatment of **1** with PDC). The protons of its MTPA esters $\mathbf{2}_R$ and $\mathbf{2}_S$, in which the hydroxy group is equatorial, have $\Delta\delta$ values that are perfectly consistent with the rule for determining absolute configurations (Figure 1B). This result gave us the absolute configurations of both **2** and **1**, shown in the respective structures.

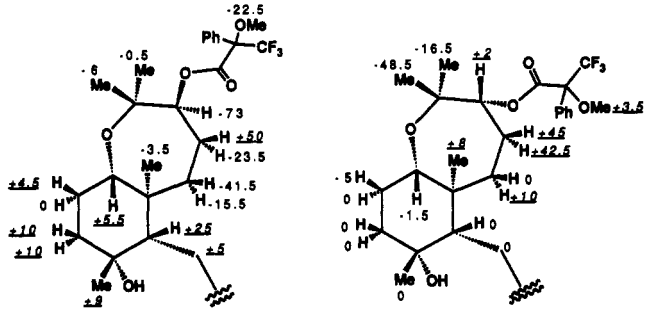
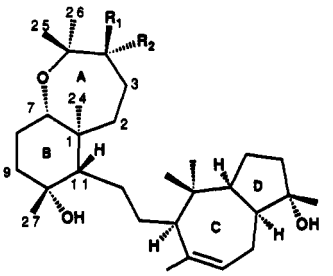


Figure 2. $\Delta\delta$ values ($\Delta\delta = \delta_S - \delta_R$ in hertz at 500 MHz) obtained for MTPA esters $\mathbf{1}_R/\mathbf{1}_S$ (**1a**) and $\mathbf{2}_R/\mathbf{2}_S$ (**2a**).



1; R_1 = OH, R_2 = H

2; R_1 = H, R_2 = OH

3; R_1, R_2 = O

These results indicate that the high-field NMR application of Mosher's method may not work for a compound that possesses a sterically hindered secondary hydroxy group and that the problem can be overcome by inverting the hydroxy group.

Experimental Section

Materials. Commercially available (+)- and (−)-MTPA acids were used without purification. The (+)- and (−)-MTPA chlorides were prepared according to ref 7.

NMR Measurement. A Bruker AM-500 spectrometer was used. All 1D ^{1}H NMR spectra were recorded in $CDCl_3$ with the data size of 32K and spectral width of 15 ppm (digital resolution

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per point: 0.46 Hz). For determination of chemical shifts, a Gaussian window function (LB = -2, GB = 0.2) was manipulated on FID. The ^{1}H NMR spectral data for **1a** and **2a** are listed in Table I.

Preparation of (*R*)- and (*S*)-MTPA Esters of Sipholenol-A (1). To a solution of sipholenol-A (5.2 mg, 11 μmol) and (dimethylamino)pyridine (5.4 mg, 44 μmol) in 0.3 mL of dichloromethane (distilled from P_2O_5) were added triethylamine (2.3 μL, 16 μmol) and (-)-MTPA chloride (4.1 μL, 22 μmol), and the solution was allowed to stand at room temperature for 3.5 h. 3-(Dimethylamino)propylamine (2.7 μL, 21 μmol) was added, and after 10 min, the solvent was evaporated. The residue was subjected to prep TLC [Merck, Kieselgel 60, F_{254}, hexane-EtOAc, 1:1 (v/v)], affording the pure (^{1}H NMR) (*S*)-MTPA ester (1_S) (5.9 mg, 78%): HREIMS *m/z* calcd for $C_{40}H_{59}O_6F_3$ 692.4263, found 692.4263. (*R*)-MTPA ester (1_R): HREIMS *m/z* calcd for $C_{40}H_{59}O_6F_3$ 692.4263, found 692.4278.

Preparation of Episipholenol-A (2). A solution of sipholenol-A (20.8 mg, 44 μmol) in 1.0 mL of dichloromethane (distilled from P_2O_5) was treated with pyridinium dichromate (27.5 mg, 73 μmol), and the mixture was stirred at room temperature for 7 h. After removal of the solvent, the residue was filtered through a silica gel column by using ethyl acetate to yield **3** (18.8 mg, 91% yield). The ketone **3** was dissolved in 1.5 mL of methanol, $NaBH_4$ (30.8 mg) was added, and the mixture was allowed to stand at room temperature for 1.5 h. The solvent was evaporated, and the residue was separated by prep TLC [CH_2Cl_2-EtOAc, 7:6 (v/v), 6 times development] to afford **1** (13.5 mg, 72%) and **2** (3.5 mg, 19%).

Preparation of (*R*)- and (*S*)-MTPA Esters of Episipholenol-A (2). A solution of episipholenol-A (1.6 mg, 3.4 μmol), (dimethylamino)pyridine (1.6 mg, 13 μmol), and triethylamine (0.7 μL, 5 μmol) in 0.3 mL of dichloromethane (distilled from P_2O_5) was treated with (-)-MTPA chloride (1.3 μL, 7 μmol), and the mixture was allowed to stand at room temperature for 3.5 h. 3-(Dimethylamino)propylamine (0.8 μL, 7 μmol) was added, and the residue obtained after evaporation of the solvent was applied to prep TLC [hexane-EtOAc, 2:3 (v/v)] to give pure (^{1}H NMR) (*S*)-MTPA ester (2_S) (2.5 mg, quant): HREIMS *m/z* calcd for $C_{40}H_{59}O_6F_3$ 692.4263, found 692.4267. (*R*)-MTPA ester (2_R): HREIMS *m/z* calcd for $C_{40}H_{59}O_6F_3$ 692.4263, found 692.4269.

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Registry No. 1, 78518-73-7; 2, 86783-85-9; 3, 78518-74-8.

Observation of a Transannular Cannizzaro Reaction in a Caged [7]Prismane Related System

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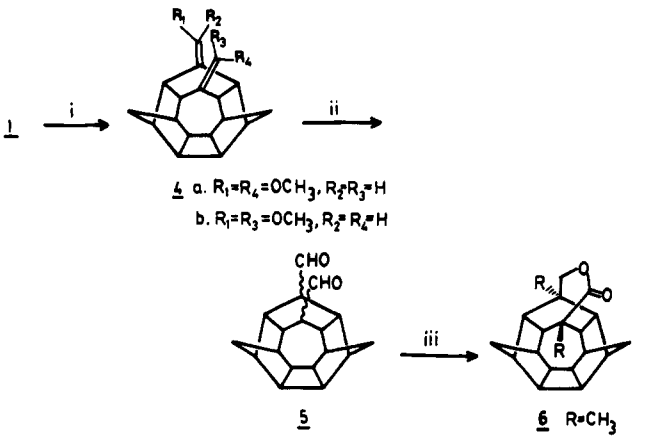
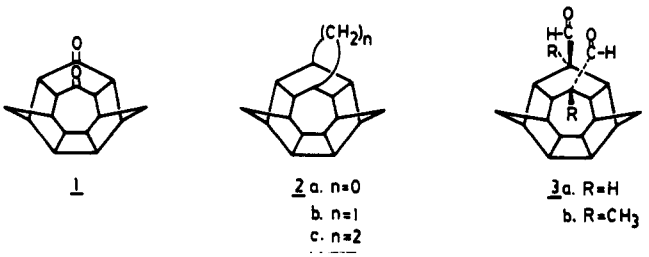
Recently, we reported a short and convenient synthesis of the caged heptacyclic dione **1** from the readily available norborneno-*p*-benzoquinone.[1] The dione **1** is formally a 1,4-bishomo-6-seco[7]prismane derivative, which we reckoned was well suited for further manipulation to [7]prismane analogues, e.g., **2**. Such an elaboration of **1** to **2** required establishment of a carbon bridge between the two transannularly located carbonyl groups. When several of our efforts to prepare **2a** and **2b** from **1**, employing a variety of tactics, failed,[2] we aimed at the synthesis of **2c** via the *endo,endo*-dialdehyde **3** in which the key step was to be a pinacolic coupling employing the methodology pioneered by McMurry.[3] However, during a base-promoted reaction proceeding via **3b**, we unexpectedly encountered a novel transannular Cannizzaro reaction, and this observation is the subject of this paper.

Scheme I[a]



[a] Reagents and yield: (i) $CH_3OCH_2PPh_3Cl$, $C_5H_{11}O^-Na^+$, ether-THF, room temperature, 10 min; (ii) 35% $HClO_4$, ether, ~5 °C, 3 h, 40% (2 steps); (iii) KH, THF, -10 °C, MeI, 10 min, 40%.



Bis-homologation of the dione **1** with excess of (methoxymethyl)triphenylphosphonium chloride in the presence of a base furnished a mixture of bis-enol ethers **4a,b** (δ 5.84, s, and 3.52, s, 1:3) which was directly hydrolyzed with aqueous perchloric acid to furnish a diastereomeric mixture of *exo,exo*-, *exo,endo*-, and *endo,endo*-dialdehydes **5** (δ 9.76, 9.67, 9.40, 9.38). In order to project and lock the two aldehyde groups in the *endo,endo*-position as in **3a,b** and to obtain a single dialdehyde **3b**, **5** was treated with excess of KH and the resulting enolate anion quenched with methyl iodide. However, instead of the expected **3b**, a novel octacyclic lactone **6** was isolated in 40% yield as a very nice crystalline compound. The structure of **6** flowed mainly from the presence of mirror plane symmetry (14 ^{13}C lines) and the ^{13}C resonances due to a lactone carbonyl (δ 178.1) and oxygen attached carbon (δ 87.6). In addition, the ^{1}H NMR spectrum shows a 2 H singlet at δ 3.92 ($CH_2OC(O)$) and two 3 H singlets at δ 1.32 (CH_3C-C(O)) and 1.04 (CH_3C) in full conformity with the structure. The direct formation of a lactone moiety and the presence of two quaternary methyl groups in **6** revealed that a facile transannular Cannizzaro-type reaction[4] had taken place in the intermediate **3b** to furnish the observed product (Scheme I). The Cannizzaro reaction is perhaps occurring in the basic medium generated during the workup. It is quite apparent that this transannular Cannizzaro reaction in **5** is an outcome of the proximity of the two reacting aldehyde groups induced by the rigid caged structure.[5,6]

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