Anal. Calcd for $C_7H_{14}OS$: C, 57.49; H, 9.72; S, 21.92. Found: C, 57.24; H, 9.53; S, 22.20.

Stirring **42** in methanol with Raney nickel afforded *trans*-2-methylcyclohexanol whose infrared spectrum was identical with that of an authentic sample.[20]

Reduction of Cis Sultone 19. Reduction of 2.167 g (12.29 mmol) of cis sultone **19**, contaminated with some trans sultone **20**, gave, after chromatography on silica gel, 1.06 g (56%) of *cis*-2-(mercaptomethyl)cyclohexanol (**43**): IR 2.92, 3.89, 8.54, 10.34 μm; NMR 1.04–1.95 (m, 9), 2.25–2.9 (m, 4), 4.1 ppm (br s, 1); mass spectrum, *m/e* (relative intensity) 146 (15), 128 (42), 95 (81), 94 (53), 81 (100), 79 (45), 69 (21), 68 (35), 67 (52), 57 (45), 55 (39), 41 (83).

Column fractions which eluted later contained 0.21 g (12%) of trans mercapto alcohol **42**.

Stirring cis mercapto alcohol **43** with Raney nickel afforded *cis*-2-methylcyclohexanol whose infrared spectrum was identical with that of an authentic sample.[20]

Reduction of Propane Sultone 1. Reduction of 1.71 g (14 mmol) of propane sultone **1** in refluxing ether for 22 h was carried out and the reaction mixture worked up in the usual manner. The aluminum salts were removed by filtration, and examination of the filtrate indicated the absence of organic products. The aluminum salts were dissolved in 200 mL of 25% sulfuric acid, and KOH was added to bring the pH to 10–12, resulting in a thick white precipitate. The solid was removed by filtration, and the filtrate was neutralized to a light phenolthalein pink. The resulting solution was evaporated to dryness, and the solid was dried at 100 °C for 12 h. The solid was treated with 25 g of PCl_5 at ambient temperature for 5 h and at 150 °C for 30 min. The mixture was stirred with hot benzene for 15 min and filtered, and the salts were washed with benzene. The benzene solution was cautiously washed with water, dried ($MgSO_4$), and concentrated to about 50 mL. The solution was cooled to 0 °C and added to 200 mL of concentrated ammonium hydroxide. After being allowed to stand at ambient temperature for 30 min, the aqueous phase was extracted with benzene and methylene chloride. The combined organic phases were dried ($MgSO_4$) and evaporated to leave a yellow oil. Recrystallization from ether–pentane gave 0.1 g (6%) of 1-propanesulfonamide (**44**) as white needles: mp 46.8–47.5 °C (lit.[21] mp 52 °C); NMR 1.1 (t, 3, J = 7.9 Hz), 1.68–2.14 (m, 2), 3.12 (t, 2), 5.07 ppm (br s, 2).

Registry No. **1**, 1120-71-4; **2**, 1121-03-5; **3**, 69873-07-0; **4**, 75732-42-2; **5**, 75732-43-3; **6**, 5981-19-1; **7**, 75732-44-4; **8**, 75732-45-5; **9**, 75732-46-6; **10**, 75732-47-7; **11**, 75732-48-8; **12**, 75732-49-9; **13**, 75732-50-2; **14**, 4362-71-4; **15**, 75732-51-3; **16**, 75732-52-4; **17**, 75732-53-5; **18**, 75732-54-6; **19**, 27304-60-5; **20**, 75732-55-7; **21**, 38932-04-6; **22**, 27304-57-0; **23**, 75732-56-8; **24**, 1653-32-3; **25**, 75732-57-9; **26**, 5921-92-6; **27**, 38146-95-1; **28**, 75751-06-3; **29**, 75732-58-0; **30**, 3465-14-3; **31**, 75732-59-1; **32**, 75732-60-4; **33**, 75732-61-5; **34**, 75732-62-6; **35**, 75732-63-7; **36**, 887-15-0; **37**, 1726-14-3; **38**, 13023-60-4; **39**, 14202-62-1; **40**, 75732-64-8; **41**, 75732-65-9; **42**, 75732-66-0; **43**, 75732-67-1; **44**, 24243-71-8; 2,3-dimethyl-3-phenyl-2-butanol, 2371-91-7; 5-methyl-1,4-hexanediol, 38624-36-1; 1,1-diphenyl-1,4-butanediol, 1023-94-5; SO_3, 7446-11-9; 1-tetradecene, 1120-36-1; 3,3-dimethyl-2-phenyl-1-butene, 5676-29-9; 3,3-diethyl-1,3-propandiol dimesylate, 75732-68-2; 1-(3-hydroxy-1-mercaptopropan-1-yl)cyclohexanol, 75732-69-3.

(20) "Sadtler Infrared Prism Spectra", Spectra No. 13370 and 13371.

(21) F. Asinger, W. Schmidt, and F. Ebeneder, *Chem. Ber.*, **75**, 34 (1942).

Synthesis and Absolute Configuration of the First Optically Active Organic Molecule with *T* Symmetry: (-)-1,3,5,7-Tetrakis[[(2-(1*S*,3*S*,5*R*,6*S*,8*R*,10*R*)-D_3-trishomocubanyl)acetoxy]methyl]adamantane

Masao Nakazaki* and Koichiro Naemura

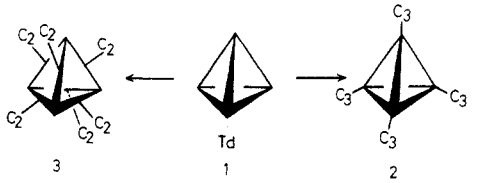
Department of Chemistry, Faculty of Engineering Science, Osaka University, Toyonaka, Osaka 560, Japan

Received June 15, 1980

By starting from the Diels–Alder adduct **12** between 2-(methoxycarbonyl)-1,4-benzoquinone (**11**) and cyclopentadiene, the modified Barborak synthesis of D_3-trishomocubane afforded (-)-2-(1*S*,3*S*,5*R*,6*S*,8*R*,10*R*)-D_3-trishomocubaneacetic acid (**19**) whose esterification with 1,3,5,7-tetrakis(hydroxymethyl)adamantane (**27**) gave (-)-**28**, the first *T* symmetric organic molecule with known absolute configuration.

Among the gyrochiral[1] organic molecules so far synthesized, ones with the highest symmetry have been D_3 molecules with symmetry number 6. In a preceding paper,[2] we have reported the preparation and absolute configuration determination of (+)-D_3-trishomocubane (**7**), a typical cage-shaped molecule with this symmetry, and this prompted us to explore possible synthetic routes to organic molecules of polyhedral *T* symmetry. The inherent symmetry number 12 for the *T* point group demands 12 asymmetric units with same chirality to be arranged around the axes of rotation of a regular tetrahedron.[3]

Scheme I



One way to achieve this is that first we prepare a chiral molecular component with C_3 symmetry by arranging these

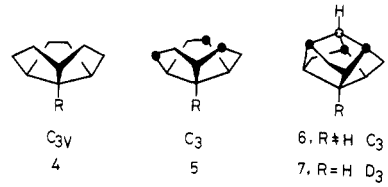
(1) This name has been given to describe the symmetry of a shape which is chiral but not asymmetric. Nakazaki, M.; Naemura, K.; Yoshihara, H. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 3278.

(2) Nakazaki, M.; Naemura, K.; Arashiba, N. *J. Org. Chem.* **1978**, *43*, 689. For other syntheses of optically active D_3-trishomocubane see: Helmchen, G.; Staiger, G. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 116; Eaton, P. E.; Leipzig, B. *J. Org. Chem.* **1978**, *43*, 2483.

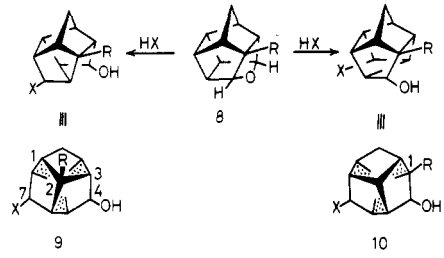
(3) Farina, M.; Morandi, C. *Tetrahedron* **1974**, *30*, 1819.

0022-3263/81/1946-0106$01.00/0

Chart I



Scheme II



three asymmetric units and then put four of them on the four apexes of a regular tetrahedron (T_d symmetry, 1) to obtain 2 (Scheme I). As an alternative, we may put six prefabricated chiral C_2 components on the both ends of three twofold axes of rotation of the regular tetrahedron to obtain 3.

The first was our choice, mainly because we have a stock of candidates with a T_d basic molecular framework possessing four functional groups at their apexes, e.g., pentaerythritol and 1,3,5,7-tetrasubstituted adamantanes.

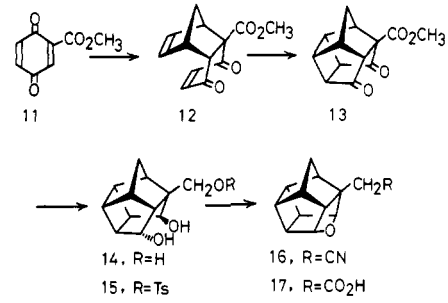
This strategy led us to secure ways to prepare a suitable C_3 component which, beside obvious symmetric and synthetic restrictions, hopefully fulfills the following requirements: (a) feasible preparation in an optically active modification with high optical purity, (b) high optical stability, and (c) compact size which is essential to overcome the expected congestion around the T_d basic framework. We reasoned that dessymmetrization of a 10-substituted hexahydrotriquinacene (4)[4] of C_{3v} symmetry should provide a smallest possible C_3 unit, 5, from which the D_3-trishomocubane structure 7 can be conceptually constructed by combining the three dessymmetrizing centers (the closed circles) to a central atom (the open circle) (Chart I).

In our projected preparation of the T symmetric molecule, preparation of an appropriate D_3-trishomocubane derivative 6 in an optically active form had become the initial task. Guided by our previous experiences in a D_3-trishomocubane (7) study,[2] we initiated a laboratory approach to 6, which involved the preparation of optically active 8 and its acidic rearrangement to 9 and/or 10 (Scheme II). And this paper describes a successful synthesis of (−)-2-D_3-trishomocubaneacetic acid (19) in an optically active modification (Scheme IV), whose eventual esterification with 1,3,5,7-tetrakis(hydroxymethyl)-adamantane (27) furnished (−)-1,3,5,7-tetrakis[[(2-D_3-trishomocubanyl)acetoxy]methyl]adamantane (28) (Scheme VI), the first T symmetric organic molecule with known absolute configuration.

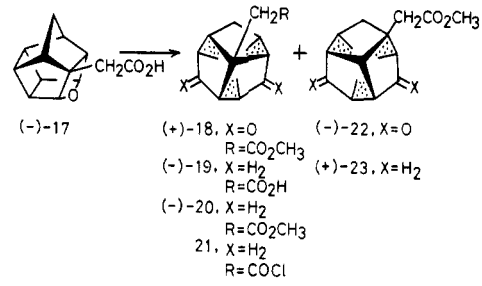
Results and Discussion

Synthesis of 4-(Carboxymethyl)-5-oxahexacyclo-[7.2.1.$0^{2,8}$.$0^{3,7}$.$0^{4,11}$.$0^{6,10}$]dodecane (17) and Its Optical Resolution (Scheme III). Careful examination of the Diels–Alder product between 2-(methoxycarbonyl)-1,4-benzoquinone (11) and cyclopentadiene revealed that the adduct 12 (mp 69–71 °C) was the sole isolable product (45% yield) whose structure was supported by two olefinic proton signals (δ 6.05–6.17, 2 H; 6.60, 2 H) observed in the ^{1}H NMR spectrum as well as its eventual conversion into the 2-substituted D_3-trishomocubane 19.

Scheme III



Scheme IV



Irradiation with a medium-pressure mercury lamp converted 12 into the pentacyclic diketone 13 whose lithium aluminum hydride reduction yielded the triol 14.[5]

Homologation of the side chain was carried out via the tosylate 15 which was treated with sodium cyanide in *N,N*-dimethylformamide to give the nitrile 16. The oxolane structure was supported by the IR spectrum and the characteristic ^{1}H NMR signals at δ 4.58 and 4.80, corresponding to the two hydrogen atoms flanking the oxolane oxygen atom.

Alkaline hydrolysis afforded the carboxylic acid 17 (mp 110–111 °C) whose optical resolution was accomplished by working with cinchonidine as the resolving agent. Fractional recrystallization from water–ethanol yielded a sparingly soluble salt ($[\alpha]_D$ −77.9°[6] from which (−)-17[7] (mp 109–110 °C; $[\alpha]_D$ −39.3°) was obtained. From the combined mother liquors, there was isolated a salt ($[\alpha]_D$ −49.0°) which provided a specimen of (+)-17: mp 107–110 °C; $[\alpha]_D$ +29.2°.

Acidic Rearrangement of (−)-17 to D_3-Trishomocubane Derivatives (Scheme IV). Heating (−)-17 ($[\alpha]_D$ −39.3°) in a sealed tube with concentrated sulfuric acid and acetic acid for 42 h at 150–160 °C gave a dark-colored reaction mixture whose saponification, successively followed by diazomethane esterification and Corey oxidation, afforded a 1:1 mixture (GLC analysis) of the diketo ester 18 and 22.

The product was chromatographed over silica gel, and concentration of the pentane–ether (3:1) eluates left an oily residue which deposited the (+) diketo ester 18: 15% yield (from 17); mp 112–113 °C; $[\alpha]_D$ +233° ($CHCl_3$). The

(4) Woodward, R. B.; Fukunaga, T.; Kelly, R. C. *J. Am. Chem. Soc.* **1964**, *86*, 3162.

(5) The endo stereochemistry of the two secondary hydroxyl groups was assigned from analogy with preceding examples.[8]

(6) Unless noted otherwise, all optical rotations reported in this paper refer to ethanolic solution.

(7) In this paper, all structural formulas with (+) or (−) rotational specifications are illustrated in their absolute configurations.

Table I. ^{1}H NMR Spectra[a] (δ) of (+)-23, (−)-20 and *T* Symmetric (−)-28

(+)-23	(−)-20	(−)-28	assignment
1.37 (br s, 4 H)	1.32 (s, 6 H)	1.33 (s, 24 H)	CH_2 (T)[b]
1.47 (s, 2 H)			CH_2 (T)
		1.36 (s, 12 H)	CH_2 (A)[c]
1.92 (br s, 7 H)	1.96 (br s, 7 H)	1.89 (br s, 12 H)	CH (T)
		2.00 (br s, 16 H)	CH (T)
2.40 (s, 2 H)	2.32 (s, 2 H)	2.26 (s, 8 H)	CH_2CO
3.78 (s, 3 H)	3.60 (s, 3 H)	3.73 (s, 8 H)	CO_2CH_2 (or CH_3)

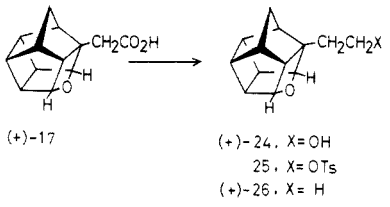
[a] In $CDCl_3$ at 100 MHz. [b] (T) = protons of D_3-trishomocubane moiety. [c] (A) = protons of adamantane moiety.

Table II. ^{13}C NMR Spectra[a] (δ) of (−)-20 and *T* Symmetric (−)-28

(−)-20	(−)-28	assignment
31.88 (T)[b]	32.08 (T, A)[c]	CH_2
	34.37 (T)	>C<
40.10	40.35	$COCH_2$
41.31 (T)	41.37 (T)	CH
47.61 (T)	47.74 (T)	CH
50.76 (T)	50.96 (T)	>C<
51.02		OCH_3
52.37 (T)	52.51 (T)	CH
	72.50 (A)	OCH_2
172.61	172.10	CO

[a] In $CDCl_3$ at 100 MHz. [b] (T) = carbons of D_3-trishomocubane moiety. [c] (A) = carbons of adamantane moiety.

Scheme V



Wolff–Kishner reduction removed the carbonyl groups to give the (−)-carboxylic acid **19** (mp 108–110 °C; $[\alpha]_D$ −68.9°) which was then converted into the (−) methyl ester **20** ($[\alpha]_D$ −68.5°) with diazomethane.

The oily mother liquor of (+)-18, after the Wolff–Kishner reduction followed by esterification, gave a 1:4 mixture (GLC analysis) of the two methyl esters, **20** and **23**, whose chromatography over alumina afforded a specimen of (+)-**23** ($[\alpha]_D$ +77.8°) contaminated with 5% of (−)-**20**.

Inspection of the ^{1}H NMR data summarized in Table I should suffice to assign the unsymmetrical structure **23** to the (+) isomer which exhibits two kinds of methylene proton signals at δ 1.37 (4 H) and 1.47 (2 H), corresponding to the presence of two and one methylene groups, respectively, close to and remote from the methoxycarbonyl group.

This automatically led us to assign the C_3 symmetric structure **20** to the (−) isomer, and further support of this conclusion was provided by the ^{13}C NMR spectrum (Table II) which, reflecting its high symmetry, exhibits the five discret groups of carbon atoms of the D_3-trishomocubane moiety.

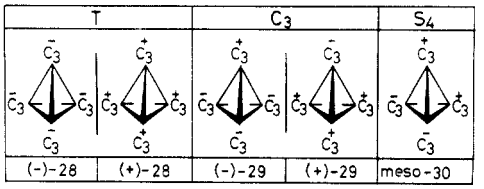


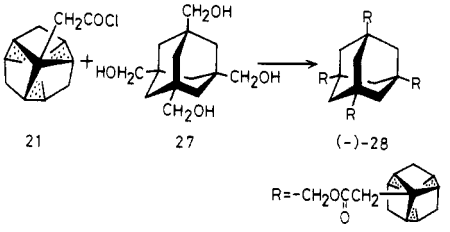
Figure 1. Possible arrangements of the C_3 components around a regular tetrahedron.

Table III. Absolute Rotations $[\alpha]_{D(abs)}$, deg

(+)-26	(−)-17	(−)-19	(−)-20	(+)-23	(−)-28
+30.0[a]	−40.6[a]	−71.0[a]	−70.6[a]	+88.1[a]	−54.0[b]

[a] In ethanol. [b] In chloroform.

Scheme VI



Absolute Configuration and Optical Purity (Scheme V). An interesting feature in the Barborak rearrangement[8] (Scheme II) starting from an optically active precursor **8** is that we can expect to have two positionally isomeric products, **9** and **10**, with enantiomeric D_3-trishomocubane frameworks. Our accumulated data on the chiroptical properties of various cage-shaped hydrocarbons including (+)-D_3-trishomocubane (**7**)[2] indicated that C_3 symmetric (−)-**19** must have the (−)-D_3-trishomocubane framework, with the bicyclo[2.2.2]octane moiety of *M* helicity assigning the 1*S*,3*S*,5*R*,6*S*,8*R*,10*R* configuration to (−)-**19**. The opposite is true for the (+) position isomer **23**, confirming the predicted pathways in the Barborak rearrangement.

We now divert our attention to evaluation of their optical purity which should prove to be of prime importance in preparing *T* symmetry molecules from any C_3 component because of the expected contamination from possible diastereoisomers (Figure 1).

Our experience[2] told us that the two protons flanking the oxolane oxygen atom in **8** can be expected to exhibit a clear enantiomer differential shift in its NMR spectra with addition of a chiral shift reagent.

To be freed of the interference from the carbonyl group, (+)-**17** ($[\alpha]_D$ +29.2°) was converted into the (+) ethyl derivative **26** ($[\alpha]_D$ +21.6°) via the alcohol **24** and the tosylate **25** (Scheme V).

With addition of tris[3-(2,2,2-trifluoro-1-hydroxy-ethylidene)-*d*-camphorato]europium (Eu(TFC)$_3$; substrate to chiral shift reagent molar ratio of 1:0.3), the original broad singlets centered at δ 4.30 and 4.54 shifted to low field with splitting into δ 10.68 and 11.28 and δ 11.88 and 14.70, respectively. Integrated signal areas of both split peaks were found to be 14:86, corresponding to 72% optical purity of (+)-**26**, and this permitted us to calculate absolute rotations of the various compounds reported in Table III.

Synthesis of (−)-1,3,5,7-Tetrakis[[(2-(1*S*,3*S*,5*R*,6*S*,8*R*,10*R*)-D_3-trishomocubanyl)acetoxy]methyl]adamantane (28; Scheme VI). Preparation of the *T* symmetric compound **28** was rather straightforward and involved conversion of (−)-**19** ($[\alpha]_D$ −68.9°, 97%

(8) Smith, E. C.; Barborak, J. C. *J. Org. Chem.* **1976**, *41*, 1433.

optical purity) into the acyl chloride **21** followed by esterification with 1,3,5,7-tetrakis(hydroxymethyl)adamantane (**27**) in pyridine. The product, purified through chromatography over alumina, was a highly viscous oil, which, although distillable under high vacuum [bath temperature 210 °C (10^{-3} mm)], gradually crystallized on being allowed to stand at room temperature for 2 weeks. The tetrakis ester **28**, after recrystallization from ethanol, melted at 197–198 °C and was found to be levorotatory with $[\alpha]_D$ −54.0° ($CHCl_3$).

While the elemental analysis, IR spectrum, saponification back to **19** and **27**, and mass spectrum (obsd M^+ at m/e 1000, $C_{66}H_{80}O_8$) supported the structure **28**, convincing evidence was obtained from its ^1H and ^{13}C NMR spectra.

The apparently simple pattern observed in the ^1H NMR spectrum of (−)-**28** (Table I) undoubtedly reflects its highly symmetrical structure, and this is buttressed by the ^{13}C NMR spectrum (Table II) which reveals that the 66 carbon atoms are distinctly classified into 10 groups[9] as the symmetry requires. Furthermore, almost no discernible change of signals observed in the temperature-dependent ^1H NMR experiment at +60 to −60 °C confirms the dynamic T symmetry inherent to (−)-**28** in this temperature range. Finally, it seems pertinent here to discuss the absolute rotation of our final product **28**. Neglecting any kinetic discrimination, simple statistical calculation permits us to predict that the (−) C_3 components **19** with 97% optical purity should afford a mixture of five possible stereoisomers (Figure 1) containing (−)-**28**, (+)-**28**, (−)-**29**, (+)-**29**, and *meso*-**30** in a ratio of $1:5.4 \times 10^{-8}:6.0 \times 10^{-2}:1.6 \times 10^{-5}:1.4 \times 10^{-3}$.

This indicates that the only serious contamination (ca. 6%) worth taking into account will be that from the (−) diastereoisomer **29**, and it seems fairly safe to say that our recrystallized final product **28** with $[\alpha]_D$ −54.0° ($CHCl_3$) is almost optically pure. And this permits us to calculate its absolute molecular rotation $[M]_{D(abs)}$ as −540°, approximately four times the $[M]_{D(abs)}$ −150° value calculated for the (−) C_3 component ester **20**.

Experimental Section

Infrared spectral data were obtained from a Hitachi 260-10 spectrophotometer. ^1H NMR and ^{13}C NMR spectra were obtained from a JNM-C-60 and a JNM-FX-100. Chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane. Optical rotations were measured with a JASCO DIP-SL automatic polarimeter. Mass spectra were taken with a Matsuda-type double-focusing spectrometer equipped with a silicon emitter.[10] GLC analyses were performed on a JGC-20K equipped with a FID and using a 2 m × 3 mm i.d. column of 10% PEG 20M on UniportHP. Elemental analyses were determined on a Yanagimoto CHN-Corder, Type II. All melting and boiling points are uncorrected.

2-(Methoxycarbonyl)-1,4-benzoquinone (11). To a mixture of methyl 2,5-dihydroxybenzoate (25.0 g, 0.149 mol), anhydrous magnesium sulfate (52 g), and ether (500 mL) was added silver oxide prepared from silver nitrate (85.0 g, 0.500 mol), and the mixture was stirred for 3 h at room temperature. After filtration of the inorganic substances, the solvent was evaporated under reduced pressure to give 22.5 g (91% yield) of **11** as an orange solid, which was used for the Diels–Alder reaction without further purification.

Diels-Alder Reaction of 11 with Cyclopentadiene. To a chilled (0–5 °C) suspension of **11** (16.5 g, 89.9 mmol) in ether (150 mL) was added freshly distilled cyclopentadiene (15.0 g, 0.227 mol) dropwise, and then the mixture was stirred for 30 min at room temperature. After evaporation of the solvent, the residue was trituated with ether–hexane (2/1 v/v), and the deposit was collected. Recrystallization from ether afforded 9.82 g (45% yield based on **11**) of **12**: mp 69–71 °C; ^1H NMR ($CDCl_3$) δ 1.58–1.70 (m, 2 H), 3.35–3.50 (m, 2 H), 3.69 (s, 3 H), 3.75 (br s, 1 H), 6.05–6.17 (m, 2 H), 6.60 (br s, 2 H); IR (KBr) 1738, 1670, 1605, 1240 cm^{-1}.

Anal. Calcd for $C_{13}H_{12}O_4$: C, 67.23; H, 5.21. Found: C, 67.30; H, 5.25.

Photocyclization of 12. A solution of **12** (4.00 g, 16.4 mmol) in ether (300 mL) was irradiated in a photolysis tube placed in an ice–water bath with a medium-pressure mercury lamp (SHL-100 UV, Toshiba) for 3 h. The solvent was removed to give a solid which was recrystallized from benzene–hexane (5/1 v/v) to afford 2.18 g (55% yield) of **13**: mp 99–101 °C; IR (KBr) 1758, 1730 cm^{-1}.

Anal. Calcd for $C_{13}H_{12}O_4$: C, 67.23; H, 5.21. Found: C, 67.11; H, 5.18.

9-(Hydroxymethyl)pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-8,11-diol (14). A solution of **13** (1.09 g, 4.70 mmol) in dry THF (40 mL) was added slowly to a suspension of $LiAlH_4$ (360 mg, 9.47 mmol) in dry THF (20 mL), and the mixture was refluxed for 6 h. After the mixture was cooled, diluted sulfuric acid was carefully added to the chilled reaction mixture. An inorganic solid was filtered off, the filtrate was dried ($MgSO_4$), and the solvent was evaporated to give a solid. Recrystallization of the solid from methanol yielded 610 mg (62% yield) of **14**: mp 303 °C; IR (KBr) 3200, 1105, 1070, 1038 cm^{-1}.

Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 68.97; H, 7.86.

4-(Cyanomethyl)-5-oxahexacyclo[7.2.1.0^{2,8}.0^{3,7}.0^{4,11}.0^{6,10}]dodecane (16). To a chilled solution of **14** (7.50 g, 36.1 mmol) in dry pyridine (90 mL) was added *p*-toluenesulfonyl chloride (16.5 g, 0.866 mol). The mixture was stirred for 3 h with ice cooling and then allowed to stand overnight at room temperature. After being poured into ice–water, the mixture was made acidic with aqueous HCl and extracted with $CHCl_3$. The extract was washed with aqueous $NaHCO_3$ solution and water, dried ($MgSO_4$), and concentrated under reduced pressure. To a solution of the residue in *N,N*-dimethylformamide (60 mL) was added sodium cyanide (3.75 g, 75.0 mmol), and the mixture was heated for 12 h at 110–120 °C. After the mixture cooled an inorganic solid was filtered off, and the filtrate was concentrated under reduced pressure. The residue was diluted with water and extracted with ether. The extract was washed with diluted aqueous HCl, aqueous $NaHCO_3$ solution, and water and dried ($MgSO_4$). The solvent was evaporated, and the residue was chromatographed on neutral alumina (Woelm, activity III). Fractions eluted with benzene were combined and distilled to give 2.00 g (28% yield based on **14**) of **16**: bp 170 °C (5 mm); ^1H NMR ($CDCl_3$) δ 1.4–2.0 (m, 2 H), 2.1–2.5 (m, 5 H), 2.6–2.8 (m, 4 H), 4.58 (br s, 1 H), 4.80 (br s, 1 H); IR (neat film) 2250, 1020, 1005, 940, 920 cm^{-1}.

Anal. Calcd for $C_{13}H_{13}ON$: C, 78.36; H, 6.58; N, 7.03. Found: C, 78.11; H, 6.57; N, 7.02.

4-(Carboxymethyl)-5-oxahexacyclo[7.2.1.0^{2,8}.0^{3,7}.0^{4,11}.0^{6,10}]dodecane (17). A mixture of **16** (3.55 g, 17.8 mmol), KOH (4.00 g), and ethylene glycol (60 mL) was heated at 150–160 °C for 12 h with stirring. After cooling, the reaction mixture was poured into water, and the mixture was made acidic with aqueous HCl and extracted with ether. The extract was washed with water, dried ($MgSO_4$), and concentrated. The residue was kept in a refrigerator to precipitate a solid. Recrystallization from ether gave 3.30 g (86% yield) of **17**: mp 110–111 °C; IR (KBr) 1722, 1210, 1190, 1160, 915, 895 cm^{-1}.

Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.49; H, 6.63.

Optical Resolution of 17. A mixture of **17** (19.4 g, 89.0 mmol), cinchonidine (24.0 g, 81.6 mmol), and 95% ethanol (100 mL) was refluxed for 4 h. Allowing the mixture to stand overnight at room temperature resulted in a solid precipitate which was collected to yield 41.3 g of the salt, $[\alpha]^{22}_D$ −61.3° (*c* 0.552, EtOH). Fractional recrystallization of the salt from ethanol–water (1/4 v/v, six times) gave 24.2 g of the salt, $[\alpha]^{22}_D$ −77.9° (*c* 0.907, EtOH). A mixture of the salt (24.0 g) and 10% aqueous HCl (750 mL) was stirred for 10 h at room temperature and extracted with ether. The

(9) Although ^{13}C NMR was found to be unable to distinguish two kinds of methylene groups separately belonging to adamantane and D_3-trishomocubane moieties, ^1H NMR clearly discriminated between these two (δ 1.33 and 1.36; see Table I).

(10) Matsuo, T.; Matsuda, H.; Katakuse, I. *Anal. Chem.* **1979**, *51*, 69.

extract was washed with aqueous HCl and water and dried ($MgSO_4$). Evaporation of the solvent gave 8.96 g of (−)-**17** ($[\alpha]^{22}_D$ −32.6° (*c* 0.690, EtOH)) which was recrystallized from ether to afford 6.15 g of (−)-**17**: $[\alpha]^{22}_D$ -39.3° (*c* 0.613, EtOH); mp 109–110 °C.

Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.31; H, 6.38.

Concentration of the combined mother liquors precipitated 10.0 g of the salt, $[\alpha]^{22}_D$ −49.0° (*c* 0.469, EtOH). The same treatment of this salt as described above for the diastereomeric salt afforded (+)-**17** (3.10 g; $[\alpha]^{22}_D$ +20.6° (*c* 0.564, EtOH)) which was recrystallized from ether to give 1.21 g of (+)-**17**: $[\alpha]^{22}_D$ +29.2° (*c* 0.499, EtOH); mp 107–110 °C.

Acidic Rearrangement of (−)-17. A mixture of (−)-**17** (6.10 g, 27.9 mmol; $[\alpha]_D$ −39.3°), acetic acid (92 mL), and concentrated sulfuric acid (760 mg) was divided in 30 reaction tubes which after being sealed were heated for 42 h at 150–160 °C. After the tubes cooled, sodium acetate (5.0 g) and activated charcoal were added to each reaction mixture, and the mixture was stirred for 1 h at room temperature. After filtration, the filtrate was concentrated under reduced pressure, and the residue was dissolved in 50% aqueous methanol (200 mL). To the solution was added KOH (11.0 g), and the mixture was refluxed for 4 h. The methanol was removed on a rotary evaporator, and the residue was diluted with water, made acidic with aqueous HCl, and extracted with ether. The extract was washed with water and dried ($MgSO_4$). The ether solution was treated with ethereal diazomethane with ice cooling. The routine procedure afforded an oily product, which was dissolved in CH_2Cl_2 (60 mL). The solution was added to a suspension of pyridinium chlorochromate[11] (19.0 g) in CH_2Cl_2 (190 mL), and the mixture was stirred for 6 h at room temperature. An organic layer was separated by decantation, washed with 5% aqueous NaOH solution and water, and dried ($MgSO_4$). The solvent was evaporated, and the residue was chromatographed on silica gel. Fractions eluted with CH_2Cl_2–ether (3/1 v/v) were concentrated to give **18**: 1.06 g (15% yield based on **17**); mp 112–113 °C; $[\alpha]^{20}_D$ +232° (*c* 0.401, $CHCl_3$); optical purity 97%; IR (KBr) 1760, 1725, 1200 cm^{-1}.

Anal. Calcd for $C_{14}H_{14}O_4$: C, 68.28; H, 5.73. Found: C. 68.47; H, 5.72.

After evaporation of the solvent, the mother liquor gave 2.36 g of an oily product containing (+)-**18** and (−)-**22**, which was reserved for the subsequent Wolff–Kishner reduction.

(−)-2-D_3-Trishomocubaneacetic Acid (19). The mixture of **18** (1.03 g, 4.19 mmol; $[\alpha]_D$ +232°), KOH (1.72 g), 80% hydrazine hydrate (2.52 g), and triethylene glycol (12 mL) was heated in an oil bath whose temperature was gradually raised to 200 °C over a 2-h period. After being kept at this temperature for 3 h, the reaction mixture was diluted with water and made acidic with aqueous HCl to deposit crystals. The colorless crystals were filtered, washed with water, and dried to afford **19**: 780 mg (91% yield); mp 108–110 °C; $[\alpha]^{20}_D$ −68.9° (*c* 0.258, EtOH); optical purity 97%; IR (KBr) 1690, 1320, 1298 cm^{-1}.

Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.25; H, 7.85.

(−)-Methyl 2-D_3-Trishomocubaneacetate (20). (−)-Carboxylic acid **19** (200 mg, 0.980 mmol; $[\alpha]_D$ −68.9°) was esterified with ethereal diazomethane to give **20**: 170 mg (79% yield); bp 122 °C (bath temperature; 5 mm); $[\alpha]^{24}_D$ −68.5° (*c* 0.471, EtOH); optical purity 97%; IR (neat film) 1735, 1105 cm^{-1}.

Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 76.81; H, 8.20.

(−)-Methyl 2-D_3-Trishomocubaneacetate (20) and (+)-Methyl 1-D_3-Trishomocubaneacetate (23). The mother liquor (2.36 g, 9.59 mmol) of (+)-**18**, containing **18** and **22**, was mixed with KOH (3.66 g), 80% hydrazine hydrate (5.36 g), and triethylene glycol (25 mL). A procedure similar to that described for the reduction of **18** yielded a crude mixture which was treated with an excess of ethereal diazomethane. The mixture of methyl esters weighing 1.88 g was analyzed by GLC which indicated a 2:8 ratio of **20** and **23**. The product was chromatographed on neutral alumina (Woelm, activity III). Early pentane eluates gave 120 mg of **20**. These fractions were followed by intermediate fractions which afforded a mixture of **20** and **23** (650 mg). The subsequent pentane eluates were combined to give 240 mg of **23** as an oil ($[\alpha]^{24}_D$ +77.8° (*c* 0.465, EtOH)) whose GLC analysis showed a 5:95 ratio of **20** and **23**.

Preparation of (−)-28. A mixture of (−)-**19** (490 mg, 2.70 mmol; $[\alpha]_D$ −68.9°; optical purity 97%) and thionyl chloride (2.00 g, 16.8 mmol) was stirred for 48 h at room temperature and then heated for 1 h at 70–80 °C. After the excess thionyl chloride was removed under reduced pressure, the residue was dissolved in dry pyridine (4 mL) with ice cooling. To the chilled mixture was added 1,3,5,7-tetrakis(hydroxymethyl)adamantane[12] (**27**; 77 mg, 0.30 mmol). The mixture was stirred for 6 h with ice cooling and for 36 h at room temperature. The reaction mixture was poured into ice–water, made acidic with aqueous HCl, and extracted with $CHCl_3$. The extract was washed successively with aqueous $NaHCO_3$ solution and water and dried ($MgSO_4$). (The alkaline solution was reserved for recovery of the carboxylic acid **19**, vide infra.) The solvent was removed, and the residue was chromatographed on neutral alumina (Woelm, activity III). Benzene eluates were combined to give 195 mg of **28** (65% yield based on **27**) as an oil [bp 120 °C (bath temperature; 10^{-3} mm)] which was crystallized from ethanol: mp 197–198 °C; $[\alpha]^{20}_D$ −54.0° (*c* 0.343, $CHCl_3$); IR (KBr) 2950, 2880, 1735, 1180, 1140 cm^{-1}; mass spectrum, *m/e* 1000 (M^+).

Anal. Calcd for $C_{66}H_{80}C_8$: C, 79.16; H, 8.05. Found: C, 79.11; H, 7.84.

The alkaline washing was made acidic with diluted sulfuric acid and extracted continuously for 5 days with ether. Evaporation of the ether furnished 80 mg of **19**.

Hydrolysis of (−)-28. A mixture of (−)-**28** (80 mg, 0.080 mmol), KOH (72 mg), and 50% aqueous methanol (4 mL) was gently refluxed for 4 h. After cooling, the reaction mixture was neutralized with aqueous HCl, and then methanol was removed under reduced pressure. The residue was made acidic with aqueous HCl and extracted continuously for 2 days with ether. The ethereal extract was esterified with diazomethane. Evaporation of the solvent with excess of diazomethane afforded 75 mg of a mixture of **20** and **27**, which was identified by GLC analysis.

(+)-4-(2-Hydroxyethyl)-5-oxahexacyclo[7.2.1.0^{2,8}.0^{3,7}.0^{4,11}.0^{6,10}]dodecane (24). A solution of (+)-**17** (1.00 g, 4.59 mmol; $[\alpha]_D$ +29.2°) in dry THF (30 mL) was added to a suspension of $LiAlH_4$ (260 mg, 6.89 mmol) in dry THF (20 mL). After being refluxed for 4 h, the reaction mixture was worked up as described for the preparation of **14**. The crude product was distilled to afford 810 mg (86% yield) of **24**: bp 105–110 °C (0.1 mm); $[\alpha]^{25}_D$ +23.6° (*c* 0.820, EtOH); IR (neat film) 3370, 1045, 1015 cm^{-1}.

Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.20; H, 7.85.

(+)-4-Ethyl-5-oxahexacyclo[7.2.1.0^{2,8}.0^{3,7}.0^{4,11}.0^{6,10}]dodecane (26). To a solution of (+)-**24** (800 mg, 3.97 mmol; $[\alpha]_D$ +23.6°) in dry pyridine (10 mL) was added *p*-toluenesulfonyl chloride (1.70 g, 8.92 mmol), and the mixture was stirred for 4 h with ice cooling. After being allowed to stand overnight at room temperature, the reaction mixture was poured into ice–water, made acidic with aqueous HCl, and extracted with ether. The extract was washed with water, dried ($MgSO_4$), and concentrated to give the tosylate **25** as a viscous oil. An ethereal solution (50 mL) of **25** was added to a suspension of $LiAlH_4$ (730 mg, 19.1 mmol) in dry ether (20 mL). After being refluxed for 12 h, the reaction mixture was worked up by the routine procedure to afford 540 mg (72% yield based on **24**) of **26**: bp 65–70 °C (0.05 mm); $[\alpha]^{22}_D$ +21.6° (*c* 1.06, EtOH); ^1H NMR ($CDCl_3$) δ 0.8–1.6 (m, 6 H), 1.8–2.3 (m, 4 H), 2.4–2.7 (m, 4 H), 4.30 (br s, 1 H), 4.54 (br s, 1 H); IR (neat film) 2960, 1460, 1020, 925 cm^{-1}.

Anal. Calcd for $C_{13}H_{16}O$: C, 82.93; H, 8.57. Found: C, 82.86; H, 8.59.

Acknowledgment. This research was partially supported by grants from the Ministry of Education, Japan (434025), and the Yamada Science Foundation. The authors are indebted to Professor Hisashi Matsuda and Dr. Takekiyo Matsuo (Department of Physics, Faculty of

(11) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647.

(12) Landa, S.; Kamycek, Z. *Collect. Czech. Chem. Commun.* **1959**, *24*, 4004.

Liberal Arts, Osaka University), who kindly made the mass spectral data of our final product available.

Registry No. 11, 3958-79-0; (±)-12, 75534-45-1; (±)-13, 75534-46-2; (±)-14, 75534-47-3; (±)-16, 75534-48-4; (±)-17, 75534-49-5; (-)-17, 75597-71-6; (-)-17 cinchonidine salt, 75657-47-5; (+)-17, 75597-72-7; (+)-18, 75534-50-8; (-)-19, 75534-51-9; (-)-20, 75534-52-0; (-)-22, 75534-53-1; (+)-23, 75534-54-2; (+)-24, 75534-55-3; 25, 75534-56-4; (+)-26, 75534-57-5; 27, 75534-58-6; (-)-28, 75548-49-1; methyl 2,5-dihydroxybenzoate, 2150-46-1; cyclopentadiene, 542-92-7.

Intramolecular α-Amidoalkylation of an Olefin for the Synthesis of a Useful Prostaglandin Intermediate†

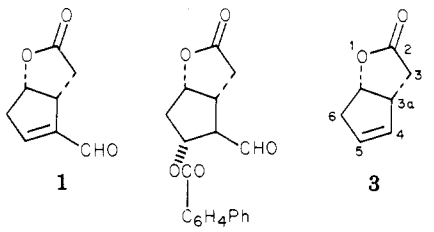
Tsung-Tee Li,* Particia Lesko, Robert H. Ellison, N. Subramanian, and John H. Fried

Institute of Organic Chemistry, Syntex Research, Palo Alto, California 94304

Received May 7, 1980

The α,β-unsaturated aldehyde 1 is an important intermediate in the preparation of a number of prostaglandins such as prostaglandin C_2 and thromboxane B_2. A method was developed by starting with the ene lactone 3 and using an intramolecular α-amidoalkylation reaction as the key step that made available this useful molecule in six operations. Formation of the lactam 15, as well as its final conversion to the target aldehyde 1, will be discussed.

The α,β-unsaturated aldehyde 1 is a tantalizing target for synthesis. To date, it has served as the key intermediate in the preparation of three different prostaglandin derivatives, namely, the 11,12-difluoromethano-prostaglandins,[1] prostaglandin C_2[2] and thromboxane B_2.[3] Substance 1 is available via the Corey intermediate 2 by



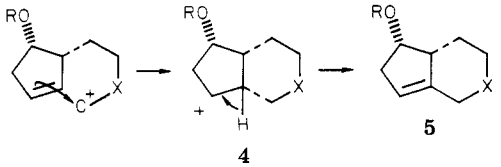
1 2 3

the base-promoted elimination of the C_{11} substituent, thus destroying two of the four meticulously constructed asymmetric centers. A search for an alternative and possibly more straightforward approach to 1 was therefore undertaken.

Discussion

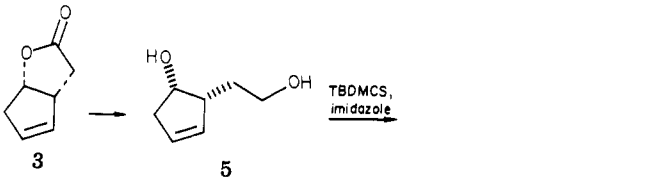
The commercially available ene lactone 3 has been prepared in optically active form.[4] It already possesses both the asymmetric centers of 1 and is obviously an attractive starting material. The problem at hand is therefore the regiospecific introduction of a carbon atom at one end of the double bond, namely, C_4. We considered a strategy involving the delivery of a carbonium ion by the two-carbon side chain on the cyclopentene ring to effect an electrophilic attack on the unsaturated center.

Loss of a proton from the more substituted carbon in the initial intermediate 4 (eq 1) would lead to the bicyclic olefin 5, where X = O or N, and conversion of the latter into the desired aldehyde 1 should be achievable by standard synthetic methodology.



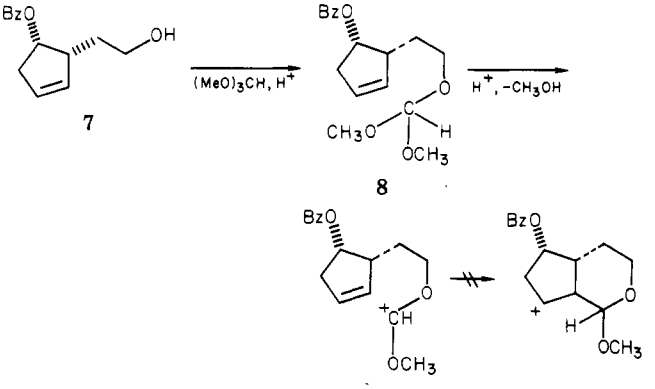
4 5 (1)

Scheme I



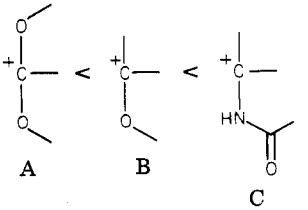
3 5 6 7

Scheme II



7 8 8a

Three types of carbonium ions with increasing reactivity were studied: the doubly stabilized A, the singly stabilized B, and the α-amido carbonium ion C.



A B C

† Contribution No. 570.

(1) P. Crabbe and A. Cervantes, *Tetrahedron Lett.*, 1319 (1973).
(2) R. C. Kelly, I. Schletter, and R. L. Jones, *Prostaglandins*, 4(5), 653 (1973).
(3) N. A. Nelson and R. W. Jackson, *Tetrahedron Lett.*, 3275 (1976).
(4) J. J. Partridge, N. K. Chadha, and M. R. Uskokovic, *J. Am. Chem. Soc.*, 98, 7171 (1973).

0022-3263/81/1946-0111$01.00/0