products are slightly lower. Ratios of stereoisomers 11 and 12, 72:28.

15a and 15b (R = CH_3) were obtained from complex 14, the alkylating agent being CH_3I, and separated on TLC (eluent ether–petroleum ether 1:7). The higher band gave pure 15a (63%). The lower band gave both 15b (14%) and 14 (23%). The best way to get 15b was found to epimerize pure 15a (NaH/DMF and further hydrolysis). Alkylation of 14 with benzyl bromide only gave one isomer 15a (R = CH_2Ph). 15b (R = CH_2Ph) was produced by epimerization of 15a as described above, and then was separated from 15a by TLC (eluent ether–petroleum ether 1:4). Ratio 15a/15b, 72:28.

Complex 16 was prepared starting from 15 (R = CH_3; benzyl bromide) or 15 (R = CH_2Ph; CH_3I) and then purified from ether, yield 70%.

Analytical and physical data are given in Tables IX and X.

Competitive Methylation of Enolates Shown in Table IV. Equivalent amounts of methyl diphenylacetate enolate and mono- (or di-) complexed enolate (from 5 or 6) were prepared in the usual way with equivalent amounts of NaH (completion of the reaction after 10 min can be checked in a side experiment by methylation with excess CH_3I). About 30–40% of the equivalent quantity of CH_3I vs. one enolate is injected with a syringe. After stirring for 10 min and usual workup, the crude mixture was separated on a thick-layer plate of silica gel (eluent: ether–petroleum ether 20:80). Two bands were observed: one contained a mixture of noncomplexed alkylated and nonalkylated products, while the other contained the same for complexed products. The later mixture was decomplexed according to literature methods.[7d] Every fraction was analyzed by GC after adding the same quantity of internal standard (diphenylacetonitrile) as described above.

Acknowledgment. We are indebted to Professor Alper, University of Ottawa, Canada, who kindly reviewed this manuscript.

Registry No.—4, 3469-00-9; NaH, 7646-69-7; $Cr(CO)_6$, 13007-92-6; CH_3I, 74-88-4; $PhCH_2Br$, 100-39-0; $CH_2{=}CHCH_2Br$, 106-95-6; $HC{\equiv}CCH_2Br$, 106-96-7; $BrCH_2COOCH_3$, 96-32-2; $PhMeACCO_2Me$, 31508-44-8; $PhCH_2COOC(Me)_3$, 16537-09-0; $MeOC_6H_4$-o-CH_2COOMe, 27798-60-3; $MeOC_6H_4$-o-$CH_2COOC(Me)_3$, 63730-75-6; methyl 1-indancarboxylate, 26452-96-0; 3-phenyldihydro-3H-furan-2-one, 6836-98-2.

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Stereochemistry and Absolute Configuration in Homoadamantane and Protoadamantane Derivatives[1]

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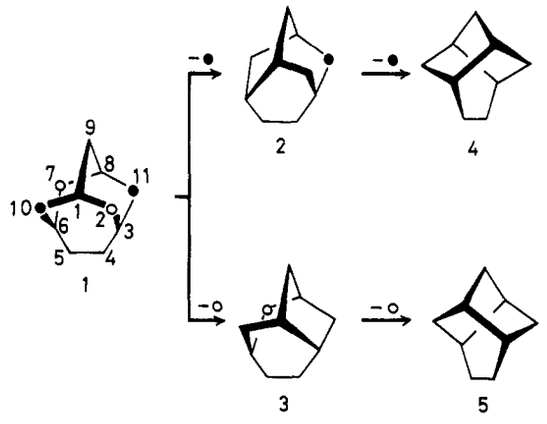
Double Favorskii rearrangement of (+)-3,6-dibromohomoadamantane-2,7-dione (6) eventually led to (+)-(1*S*,3*R*,6*R*,8*S*)-twist-brendane (4), assigning the (1*R*,3*S*,6*S*,8*R*) configuration to the (+)-dibromodione 6. (−)-Protoadamantane (tricyclo[4.3.1.$0^{3,8}$]decane) 3 was obtained by the sequence of reactions involving single Favorskii rearrangement of the (−)-dibromodione 6, and this correlation gave the (1*R*,3*S*,6*R*,8*R*) configuration to (−)-protoadamantane. Temperature-dependent circular dichroism spectrum analyses of (+)-homoadamantane-2,7-dione (15) and (+)-homoadamantan-2-one (23) suggested the C_{2v} untwisted conformation to the homoadamantane (tricyclo[4.3.1.$1^{3,8}$]undecane) (1) molecule.

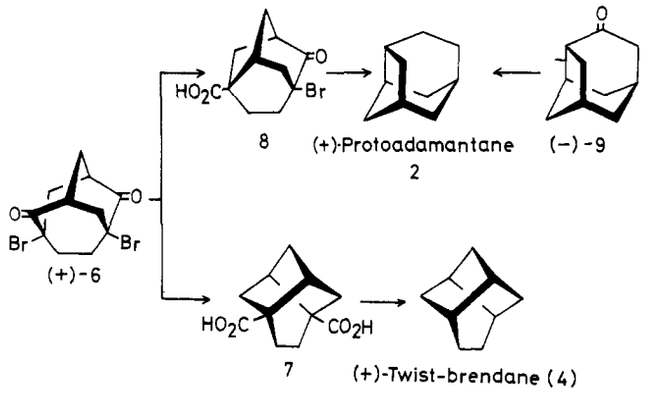
On ring expansion of adamantane by one carbon atom, the high-symmetry T_d inherent to this molecule permits homoadamantane (1)[2] to emerge as a sole product. Although an inspection of the molecular model indicates a flexible structure, for convenience of discussion homoadamantane (1) will be regarded as a rigid molecule with C_{2v} symmetry until we shortly return to discuss this conformational complexity (vide infra) (Chart I).

In the C_{2v} molecular model 1, we can discern two sets of homotopic methylene groups: $C_2{=}C_7$ and $C_{10}{=}C_{11}$. Since the molecule possesses two planes of symmetry which contain the C_2 axis and are mutually perpendicular, these four methylene

Chart I



Scheme I



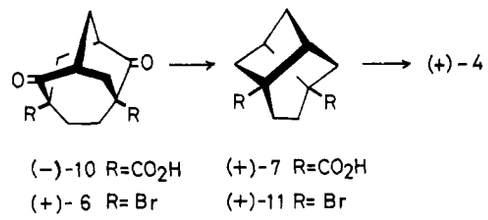
groups also form four sets of enantiotopic methylene groups: C_2/C_{11}, C_7/C_{10}, C_2/C_{10}, and C_7/C_{11}. Removal of one of these methylene groups destroys the C_{2v} symmetry, furnishing asymmetric (C_1 symmetry) protoadamantane[3] **2** or **3**, and which methylene group in each of these sets of enantiotopic groups is removed determines the chiralities of the enantiomeric protoadamantane molecules. Removal of two homotopic methylene groups, on the other hand, conserves the original C_2 axis of homoadamantane (**1**) to give twist-brendane[4] **4** or **5** with C_2 symmetry.

This time again, the chiralities of the enantiomeric twist-brendane molecules are determined by the choice of the set of homotopic methylene groups to be removed, C_2=C_7 or C_{10}=C_{11}.

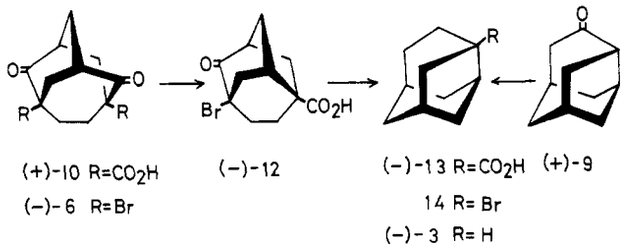
Consideration on these molecular geometries permitted us to choose optically active 3,6-dibromohomoadamantane-2,7-dione (**6**) as a go-between whose single and double Favorskii rearrangements[5] should correlate the absolute configurations of optically active protoadamantane **2** and twist-brendane **4**, via the carboxylic acids **7** and **8**, respectively (Scheme I).

Our continuing interests[4,6] on the syntheses and chiroptical properties of high-symmetry chiral (gyrochiral[6b]) cage-shaped molecules currently center on the microbiological reduction of carbonyl groups constrained in various chiral cage-shaped molecular frameworks, and during these experiments[7] (+)-protoadamantan-4-one (**9**) [the enantiomer of (−)-**9** in Scheme I] was isolated from a culture solution containing (±)-protoadamantan-4-one[8] as the substrate. Information about the absolute configuration of this optically active protoadamantan-4-one (**9**) was required to formulate a rule which specifies stereoselectivity in phytochemical reduction, and in this paper we report the configurational relationship between optically active twist-brendane **4** and protoadamantane **2** following the sequence outlined in Scheme I, which eventually leads to the absolute configuration of protoadamantan-4-one (**9**); also reported is an examination of the conformational mobility of

Scheme II



Scheme III



the homoadamantane framework by means of temperature-dependent circular dichroism (CD) measurements on (+)-homoadamantane-2,7-dione (**15**) and (+)-homoadamantan-2-one (**23**).

Results and Discussion

Configurational Correlation between (−)-Homoadamantane-2,7-dione-3,6-dicarboxylic Acid (10) and (+)-Twist-brendane 4. Optical resolution of (±)-homoadamantane-2,7-dione-3,6-dicarboxylic acid (**10**)[5b] was accomplished by working with cinchonidine as the resolving agent. Crystallization of the salt from ethanol followed by recrystallization of the separated dicarboxylic acids from acetone–ether resulted in fairly good resolution, as evidence by optical rotations of the resolved dicarboxylic acids, $[\alpha]_D$ +41.1° and $[\alpha]_D$ −43.7°, obtained respectively from the sparingly soluble and the soluble cinchonidine salts.

The silver salt, prepared from the (−)-dicarboxylic acid **10**, $[\alpha]_D$ −43.7°, was treated with bromine in carbon tetrachloride to afford the (+)-dibromide **6**, $[\alpha]_D$ +34.0°, whose double Favorskii type ring contraction[5b] with ethanolic potassium hydroxide gave an 82% yield of (+)-twist-brendane-3,6-dicarboxylic acid (**7**). The second Hunsdiecker reaction carried out on the silver salt of (+)-twist-brendane-3,6-dicarboxylic acid (**7**) provided (+)-3,6-dibromo-twist-brendane (**11**) which was refluxed with sodium in *tert*-butyl alcohol to give (+)-twist-brendane **4**: mp 163.5–164.5 °C; $[\alpha]_D$ +280° (98% optical purity[4a]) (Scheme II).

Since our unambiguous synthesis starting from the precursor with known absolute configuration has assigned the (1*S*,3*R*,6*R*,8*S*) configuration to (+)-twist-brendane **4**, the configurational correlation in Scheme II indicates the (1*R*,3*S*,6*S*,8*R*) configuration to (−)-homoadamantane-2,7-dione-3,6-dicarboxylic acid (**10**).

Configurational Correlation between (+)-Homoadamantane-2,7-dione-3,6-dicarboxylic Acid (10) and (−)-Protoadamantane (3). In operating a one carbon atom ring contraction on the homoadamantane framework, we started again from the optically active 2,7-dione-3,6-dicarboxylic acid **10**. In contrast to Scheme II, however, the dextrorotatory dicarboxylic acid **10** was our starting material in this correlation experiment (Scheme III).

The Hunsdiecker reaction converted (+)-homoadamantane-2,7-dione-3,6-dicarboxylic acid (**10**), $[\alpha]_D$ +30.0°, into the (−)-dibromide **6** which was, following Vogt's procedure,[5a] refluxed with 10% sodium bicarbonate solution in ethanol to give a 71% yield of the (−)-monobromoketocarboxylic acid **12**. Clemmensen reduction of (−)-**12** furnished (−)-protoadamantan-3-carboxylic acid (**13**) whose carboxyl group was re-

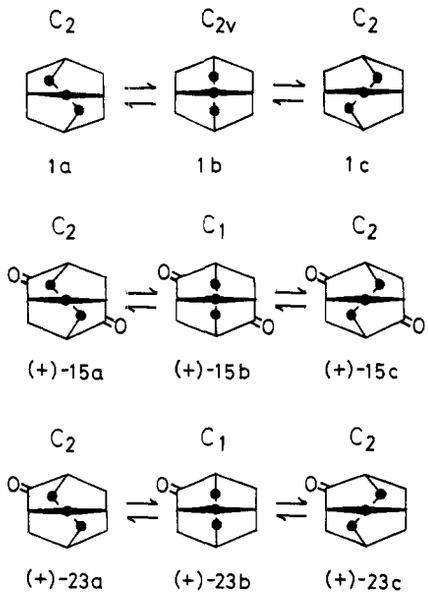
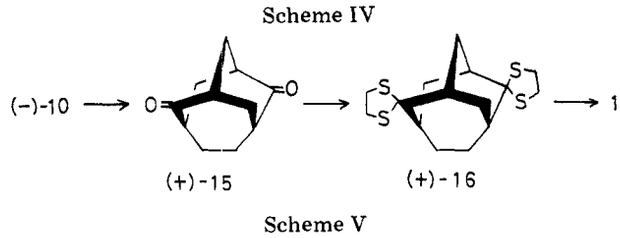
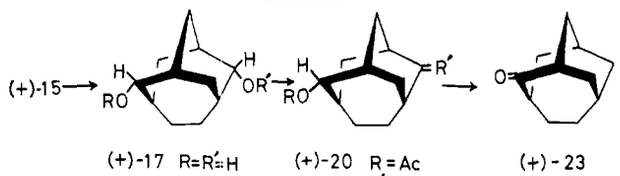


Figure 1. Conformational equilibria in homoadamantane derivatives. (The moleculars are viewed from the C_9 carbon atom in the direction of the C_2 axis of homoadamantane.)

Scheme IV



Scheme V



moved by the Hunsdiecker reaction of the silver salt of the carboxylic acid **13** followed by reduction of the resulting monobromide **14** with sodium in *tert*-butyl alcohol. Optically active protoadamantane **3** obtained by this sequence of reactions was levorotatory, $[\alpha]_D$ −118°, and melted at 174–177 °C.

These configurational correlations clearly indicate the (1*R*,3*S*,6*R*,8*R*) configuration to (−)-protoadamantane (tricyclo[4.3.1.0^{3,8}]decane) **3**, and the Wolff–Kishner reduction of (+)-protoadamantan-4-one (**9**) to (−)-protoadamantane **3** assigns the (1*S*,3*S*,6*R*,8*S*) configuration to this ketone **9** isolated from a culture solution containing the racemic ketone **9** as the substrate.[9]

Preparation of (+)-Homoadamantane-2,7-dione (15) and (+)-Homoadamantan-2-one (23). Successful bisdecarboxylation of the racemic dionedicarboxylic acid **10** demonstrated by Vogt[5b] provided (+)-(1*S*,3*R*,6*R*,8*S*)-homoadamantane-2,7-dione (**15**), mp 285–288 °C; $[\alpha]_D$ +49.4°, from the (−)-dionedicarboxylic acid **10**, $[\alpha]_D$ −35.7° (Scheme IV).

One of two homotopic carbonyl groups of (+)-dione **15** was removed via the (+)-diol **17**, prepared from the (+)-dione **15** by lithium aluminum hydride reduction. A sharp single acetyl peak (δ 2.08) observed in the NMR spectrum of the acetate **18** indicated stereochemical equivalence of the two hydroxyl groups, suggesting C_2 symmetry for the diol **17**. This, together with a plausible assumption of hydride attack from the less hindered methano bridge sides, suggested endo–cis configuration to the diol **17**, which was supported by the preparation of the endo alcohol **21** from the diol **17** (vide infra) (Scheme V).

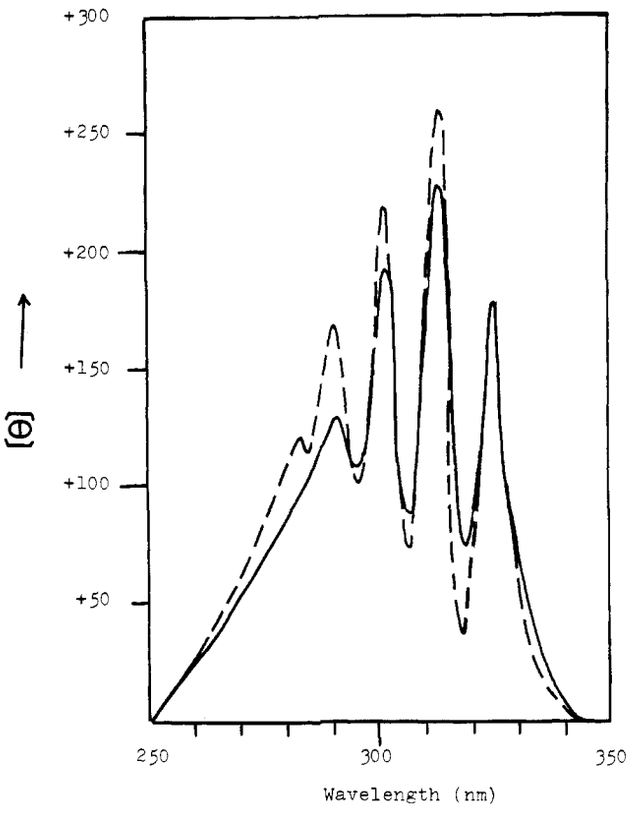


Figure 2. Temperature-dependent CD spectra of (+)-homoadamantan-2-one (**23**) (in methylcyclohexane–isopentane 75:15): (—) at 25 °C; (---) at − 68 °C.

Acetylation of the (+)-diol **17** with an equimolar amount of acetic anhydride in pyridine furnished the (+)-monoacetate **19** whose Jones' oxidation afforded the (+)-keto acetate **20**. The (+)-monoalcohol **21** obtained by the Wolff–Kishner reduction of the (+)-keto acetate **20** exhibited a double doublet for the methine proton at δ 3.88 in the NMR spectrum, and was found identical with the endo alcohol reported by Murray, Jr.,[10] supporting the endo–cis configuration previously assigned to the diol **17**.

Final oxidation with Jones' reagent completed the preparation of (+)-homoadamantan-2-one (**23**), $[\alpha]_D$ +32.8°, to which the configurational correlations illustrated in Schemes II, IV, and V assigned the (1*S*,3*R*,6*S*,8*S*) configuration.

Conformational Mobility in the Homoadamantane Framework. In the introductory part, a brief mention was made on the drastic change of conformational mobility brought by the mere one carbon atom ring expansion from rigid adamantane to flexible homoadamantane. Although Dreiding models, which are apt to mislead by overemphasizing angle strain, give a pair of enantiomeric conformational isomers **1a** and **1c** (C_2 symmetry) (Figure 1), Schleyer has favored the conformer **1b** with C_{2v} symmetry by his computor conformational analysis calculations[11] and temperature-dependent NMR study of homoadamantane.[12]

Desymmetrization of the homoadamantane framework by introducing carbonyl groups in the 2 or 2,7 positions changes the original pair of enantiomeric conformers **1a** ⇌ **1c** to the

pair of diastereomeric conformers (+)-**15a** ⇌ (+)**15c** and (+)-**23a** ⇌ (+)-**23c**, respectively (Figure 1).

Numerous examples[13] have confirmed the utility of the Cotton effect in detecting these subtle conformational changes, and we expected the temperature-dependent CD spectrum analysis of (+)-homoadamantan-2-one (**23**) and (+)-homoadamantane-2,7-dione (**15**) should furnish information on this homoadamantane conformational complexity.

If the molecules are twisted and the barriers between these diastereomeric conformers are large enough, the CD spectra should be temperature dependent. No such temperature dependence for (+)-**23** was observed in the range of +25 to −68 °C (Figure 2).

Although the CD spectrum of (+)-**15** (in EPA) showed a small bathochromic shift (5 mm) on going from −190 to 25 °C, almost no change of pattern and intensities was observed in this temperature range. These, together with the optical inactivity observed in a specimen of homoadamatane prepared from (+)-homoadamantane-2,7-dione via the (+)-bis(ethylene) ketal **16** (Scheme IV), appear to support Schleyer's view that the preferred conformation in homoadamantane (**1**) is essentially untwisted (**1b** in Figure 1) with C_{2v} symmetry.

Experimental Section

IR data were obtained from a Hitachi EPI-S2 spectrophotometer. NMR spectra were obtained from a JNM-MH-100 spectrometer. UV spectra were recorded on a Beckman DB spectrometer. Optical rotations were measured with a JASCO DIP-SL automatic polarimeter. Circular dichroism data were measured on a JASCO J-40 spectropolarimeter. Elemental analyses were determined on a Yanagimoto CHN-Corder Type II. All melting and boiling points are uncorrected.

(±)-Homoadamantane-2,7-dione-3,6-dicarboxylic Acid (10). Dimethyl bicyclo[3.3.1]nonane-2,6-dione-3,7-dicarboxylate[14] (32.4 g, 0.120 mol) was added slowly to a suspension of NaH (7.50 g, 0.312 mol) in dry 1,2-dimethoxyethane (120 mL). The mixture was stirred for 15 min at room temperature and then the solvent was distilled away. Ethylene bromide (204 g, 1.09 mol) was added and the mixture was stirred for 20 h at 118–120 °C. The cooled reaction mixture was poured onto ice, acidified with HCl, and extracted with $CHCl_3$, and the extract was washed with water and dried over $MgSO_4$. The solvent was removed, and the residue was dissolved in 80 mL of ether–benzene (9:1, v/v). Chilling overnight deposited 14.7 g of dimethyl homoadamantane-2,7-dione-3,6-dicarboxylate (41% yield). Recrystallization from benzene afforded an analytical sample, mp 196–197 °C (lit.[5b] mp 197–198 °C).

Anal. Calcd for $C_{15}H_{18}O_6$: C, 61.21; H, 6.17. Found: C, 61.05; H, 6.09.

A solution of this ester (14.0 g, 47.3 mmol) in acetic acid (210 mL) and 12 N HCl (150 mL) was refluxed for 3 h, poured into water (600 mL), and extracted for 3 days with ether. The extract was dried over $MgSO_4$ and the solvent was evaporated to give 8.40 g of **10** (66% yield), which was recrystallized from acetone–ether to give a pure sample: mp 287 °C (with gas evolution) (lit.[5b] mp 288–290 °C); IR (KBr) 1710, 1295, 1275, 1250, 1225, 945, and 720 cm^{-1}.

Anal. Calcd for $C_{13}H_{14}O_6$: C, 58.64; H, 5.30. Found: C, 58.58; H, 5.33.

Optical Resolution of Homoadamantane-2,7-dione-3,6-dicarboxylic Acid (10). To a solution of **10** (43.8 g, 0.165 mol) in 1 L of EtOH was added cinchonidine (95.0 g, 0.323 mol), and the mixture was refluxed for 5 h. After standing overnight at room temperature, the solution deposited 96.0 g of the cinchonidine salt: $[\alpha]^{15}_D$ −77.0° (*c* 0.374, EtOH). The filtrate was reserved for isolation of the enantiomer (−)-**10** (vide infra). Several times fractional recrystallization from EtOH afforded 56.5 g of the levorotatory salt: $[\alpha]^{14}_D$ −74.5° (*c* 0.430, EtOH), which was stirred for 6 h with 10% HCl (700 mL). The acidic solution was extracted for 7 days with ether. The extract was dried over $MgSO_4$ and the solvent was evaporated to give 14.7 g of (+)-**10**, $[\alpha]^{15}_D$ +30.0° (*c* 1.20, acetone), a part of which was recrystallized several times from acetone–ether (3:1, v/v) to give an analytical sample of (+)-**10**: $[\alpha]^{18}_D$ +41.1° (*c* 0.538, acetone); mp 266 °C (with gas evolution); IR (KBr) 1710, 1292 (sh), 1275, 1225 (sh), 945, and 710 cm^{-1}.

Anal. Calcd for $C_{13}H_{14}O_6$: C, 58.64; H, 5.30. Found: C, 58.43; H, 5.33.

The filtrate was concentrated to give 30.5 g of a viscous oily salt, which was treated with 10% HCl. The same workup described above afforded 6.40 g of (−)-**10**, $[\alpha]^{18}_D$ −36.2° (*c* 0.414, acetone), which was recrystallized several times from acetone–ether to yield 2.90 g of (−)-**10**, $[\alpha]^{18}_D$ −43.7° (*c* 0.529, acetone), mp 267 °C (with gas evolution).

Anal. Calcd for $C_{13}H_{14}O_6$: C, 58.64; H, 5.30. Found: C, 58.50; H, 5.32.

(+)-Twist-brendane-3,6-dicarboxylic Acid (7). A solution of (−)-**10** (2.66 g, 0.0100 mol), $[\alpha]^{18}_D$ −43.7°, in MeOH (20 mL) was neutralized with 1 N aqueous KOH and then made slightly acidic with diluted nitric acid. A solution of silver nitrate (3.40 g, 0.0200 mol) in MeOH (12 mL) and H_2O (6 mL) was added dropwise. After stirring for 30 min, disilver dicarboxylate was collected on a filter, washed with water and MeOH, and dried over phosphorus pentoxide at 70 °C (5 mm) for 5 days. When the disilver dicarboxylate (4.39 g, 9.14 mmol) was added to a solution of bromine (3.40 g, 21.5 mmol) in dry CCl_4 (10 mL), carbon dioxide evolved immediately. The mixture was stirred for 30 min at room temperature and then refluxed for 3 h. A solid was separated from the cooled reaction mixture and extracted with hot $CHCl_3$ for 6 days. The extract was concentrated and the residue was stirred with 5% $NaHCO_3$ solution for 2 h at room temperature to remove unreacted carboxylic acids. The insoluble dibromide **6** was collected to yield 1.70 g of **6** (50% yield), $[\alpha]^{17}_D$ +34.0° (*c* 0.356, $CHCl_3$), mp 288–290 °C, which was used for the following reaction without further purification.

A mixture of (+)-**6** (1.58 g, 4.70 mmol), KOH (3.53 g), EtOH (7 mL), and water (7 mL) was refluxed for 4 h. The chilled reaction mixture was made acidic with HCl and then concentrated under reduced pressure. To the residual solid was added acetone and the mixture was refluxed for 5 h. The insoluble solid was filtered off and the filtrate was treated with Norit. After filtration, the solvent was evaporated to yield 686 mg of (+)-**7** (82% yield): $[\alpha]^{20}_D$ +166° (*c* 0.634, MeOH); mp >300 °C; IR (KBr) 1690, 1415, 1305, and 1120 cm^{-1}.

Anal. Calcd for $C_{11}H_{14}O_4$: C, 62.84; H, 6.71. Found: C, 62.56; H, 6.62.

(+)-Twist-brendane 4. A solution of (+)-**7** (630 mg, 3.00 mmol) in MeOH (6 mL) was neutralized with 1 N aqueous KOH solution and then made slightly acidic with diluted nitric acid. A solution of silver nitrate (1.02 g, 6.00 mmol) in MeOH (4 mL) and water (2 mL) was added, and the mixture was stirred for 30 min. Disilver dicarboxylate was collected on a filter, washed with MeOH–H_2O, and dried over phosphorus pentoxide at 70 °C (5 mm) for 3 days. To a solution of bromine (1.60 g, 6.65 mmol) in dry CCl_4 (4 mL) was added the disilver dicarboxylate (1.20 g, 2.84 mmol). The mixture was stirred for 3 h at room temperature and then refluxed for additional 3 h. The cooled reaction mixture was filtered and the filtrate was washed with sodium thiosulfate solution, saturated $NaHCO_3$ solution, and water, and dried over $MgSO_4$. The solvent was removed to give 620 mg of **11**, $[\alpha]^{20}_D$ +163° (*c* 0.393, EtOH). The bromide **11** (570 mg) and dry *tert*-butyl alcohol (850 mg) were dissolved in dry THF (8.5 mL), and sodium (424 mg) was added. After the mixture was stirred for 30 min at room temperature, additional *tert*-butyl alcohol (1.5 g) was added. The mixture was refluxed for a further 3 h. To the chilled reaction mixture was added few milliliters of MeOH to destroy the excess sodium. The mixture was poured onto ice and extracted with pentane. The extract was washed with water and dried over $MgSO_4$. Evaporation of the solvent gave 110 mg of twist-brendane (30% yield), which was sublimed at 40 °C (20 mm) to afford a pure sample: $[\alpha]^{20}_D$ +280° (*c* 0.393, EtOH) (98% optical purity[4a]); mp 163.5–164.5 °C (in a sealed tube). This was identified as twist-brendane **4** by comparison with an authentic sample[4a] (IR spectrum and VPC, TLC behaviors).

(−)-Protoadamantane-3-carboxylic Acid (13). The same procedure described for the (−)-enantiomer converted (+)-**10** (3.99 g, 15.0 mmol), $[\alpha]^{25}_D$ +30.0°, into (−)-**6** (1.81 g, 36% yield), $[\alpha]^{24}_D$ −24.0°. A mixture of (−)-**6** (1.76 g, 5.24 mmol), 10% $NaHCO_3$ solution (16 mL), and EtOH (16 mL) was refluxed for 1 h. The reaction mixture was extracted with $CHCl_3$ to remove neutral substances and then made acidic with HCl. The acidic solution was extracted with $CHCl_3$, and the extract was washed with water and dried over $MgSO_4$. Evaporation of the solvent gave 1.01 g of **12** (71% yield), $[\alpha]^{25}_D$ −85.8° (*c* 0.410, $CHCl_3$). A mixture of (−)-**12** (930 mg, 3.41 mmol), zinc amalgam (4.0 g), and 12 N HCl (6 mL) was refluxed for 5 h and extracted with ether. The extract was washed with water and dried over $MgSO_4$. Evaporation of the solvent gave a semisolid, which was triturated with pentane to afford 150 mg of **13** (24% yield): $[\alpha]^{22}_D$ −119° (*c* 0.299, acetone); mp 85–88 °C; IR (KBr) 3400, 2600, 1690, and 1290 cm^{-1}.

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.18; H, 8.88.

(−)-Protoadamantane 3. (−)-Protoadamantane-3-carboxylic acid

(13) (540 mg, 3.00 mmol) was converted into its silver carboxylate (715 mg, 83% yield) by the same procedure described above. When the silver carboxylate (715 mg, 2.49 mmol) was added to a solution of bromine (520 mg, 3.24 mmol) in dry CCl_4 (4 mL), carbon dioxide evolved immediately. The mixture was stirred for 3 h at room temperature and then refluxed for 3 h. After cooling, an inorganic solid was filtered off, and the filtrate was washed with sodium thiosulfate solution, $NaHCO_3$ solution, and water, and dried over $MgSO_4$. Evaporation of the solvent gave 290 mg of bromide **14.** Because of contamination with the corresponding chloride, a correct elemental analysis was not obtained.

To a mixture of the halide **14,** *tert*-butyl alcohol (280 mg), and dry THF (3 mL) was added sodium (140 mg). After the mixture was stirred for 3 h at room temperature, an additional amount of *tert*-butyl alcohol (0.55 g) was added, and the mixture was refluxed for a further 3 h. After the addition of a few drops of MeOH to the chilled reaction mixture, the mixture was poured onto ice and extracted with pentane. The extract was washed with water and dried over $MgSO_4$. Evaporation of the solvent gave a solid, which was sublimed at 50 °C (20 mm) to yield 102 mg of **3** (25% yield based on **13**): $[\alpha]^{26}_D$ −118° (*c* 0.177, EtOH); mp 212.5–214 °C (in a sealed tube) (lit.[5a] racemate, mp 215–216 °C); IR (KBr) 2850, 2790, 1460, 1350, 1335, 1320, 1305, 1100, 1070, 1008, 985, and 812 cm^{-1}.

Anal. Calcd for $C_{10}H_{16}$: C, 88.16; H, 11.84. Found: C, 87.85; H, 11.70.

(+)-Homoadamantane-2,7-dione (15). (−)-Dicarboxylic acid **10** (6.18 g, 23.2 mmol), $[\alpha]^{15}_D$ −35.7°, was heated at 270–290 °C under reduced pressure (30 mm). A white solid was observed to condense on an inner wall of the condenser. After cooling, the solid was dissolved in ether, and the ethereal solution was washed with saturated $NaHCO_3$ solution and water and dried over $MgSO_4$. Evaporation of the solvent gave a solid, which was sublimed at 130–140 °C (5 mm) to yield 2.82 g of **15** (68% yield): $[\alpha]^{20}_D$ +49.4° (*c* 1.22, $CHCl_3$); mp 285–288 °C (in a sealed tube); IR (KBr) 1698, 1460, 1360, 1120, 1070, 1008, and 950 cm^{-1}; NMR ($CDCl_3$) δ 1.78–1.95 (m, 6 H), 2.08–2.35 (m, 4 H), 2.60–3.10 (m, 4 H); CD *c* 1.95×10^{-2} (isooctane, at 25 °C) [θ] (nm) 0 (244), $+8.72 \times 10^2$ (sh, 285), $+1.09 \times 10^3$ (292.7), $+1.33 \times 10^3$ (302.2), $+1.21 \times 10^3$ (312.7), $+6.21 \times 10^2$ (324.8), 0 (345); *c* 1.53×10^{-3} (EPA, at 25 °C) 0 (245), $+8.52 \times 10^2$ (294), $+1.04 \times 10^3$ (302), $+9.67 \times 10^2$ (311.5), $+4.97 \times 10^2$ (320), 0 (340); *c* 1.53×10^{-3} (EPA, at −68 °C) 0 (240), $+9.31 \times 10^2$ (292), $+1.12 \times 10^3$ (300.5), $+1.06 \times 10^3$ (310.5), $+5.23 \times 10^2$ (322), 0 (340); *c* 1.53×10^{-3} (EPA, at −190 °C) +89 (250), $+1.14 \times 10^3$ (288.5), $+1.28 \times 10^3$ (297), $+1.15 \times 10^3$ (308), $+5.50 \times 10^2$ (319), 0 (335).

Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.02; H, 7.89.

(+)- and (±)-Homoadamantane-2,7-diol (17). A solution of (+)-**15** (2.31 g, 13.0 mmol), $[\alpha]^{20}_D$ +49.4°, in dry ether (150 mL) was added to a suspension of $LiAlH_4$ (494 mg, 13.0 mmol) in dry ether (50 mL), and the mixture was refluxed for 4 h. Saturated NH_4Cl solution was added to the chilled reaction mixture and an inorganic solid was filtered off. The filtrate was dried over $MgSO_4$ and the solvent was evaporated to yield 2.07 g of **17** (88% yield): $[\alpha]^{20}_D$ +18.8° (*c* 0.680, $CHCl_3$); mp 326–328 °C (in a sealed tube); IR (KBr) 3350, 1080, 1048, 1022, 930, and 875 cm^{-1}.

Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.96. Found: C, 72.20; H, 9.97.

(±)-Homoadamantane-2,7-diol (**17**) was prepared from (±)-**15** by the same procedure described above; mp >330 °C.

Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.96. Found: C, 72.31; H, 9.99.

(±)-2,7-Diacetoxyhomoadamantane (18). Acetic anhydride (1 mL) was added to a cooled (0 °C) solution of (±)-**17** (153 mg, 0.841 mmol) in pyridine (5 mL). After standing overnight at room temperature, the reaction mixture was poured onto ice. A deposited solid was collected and washed with water and dried to give 181 mg of **18** (81% yield): mp 99.5–100 °C; NMR ($CDCl_3$) δ 1.2–2.1 (m, 12 H), 2.08 (s, 6 H), 2.2–2.5 (m, 2 H), 4.99 (dd, *J* = 6.6 and 6.3 Hz, 2 H); IR (KBr) 1735, 1365, 1255, and 1030 cm^{-1}.

Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33. Found: C, 67.65; H, 8.32.

(+)-2-Acetoxyhomoadamantan-7-ol (19). Acetic anhydride (1.11 g, 10.9 mmol) was added to a cooled (0 °C) solution of (+)-**17** (1.98 g, 10.9 mmol) in dry pyridine (5 mL). The mixture was stirred for 4 h with ice cooling and then kept overnight at room temperature. It was poured onto ice and extracted with ether. The extract was washed with 10% HCl, saturated $NaHCO_3$ solution, and water, and dried over $MgSO_4$. After evaporation of the solvent, the residue (1.94 g) was chromatographed on silica gel. Fractions eluted with $CHCl_3$ gave 720 mg of impure (+)-**18** (25% yield), whose structure was confirmed by comparison with the racemic modification **18.** Fractions eluted with ether afforded 995 mg of **19** (41% yield): $[\alpha]^{27}_D$ +12.8° (*c* 0.665, $CHCl_3$); mp 108–111 °C; IR (KBr) 3480, 1710, 1270, and 1030 cm^{-1}.

Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.90; H, 8.96.

Final fractions with ether–MeOH (9:1, v/v) gave 150 mg of the starting material (**17**).

(+)-2-Acetoxyhomoadamantan-7-one (20). To a cooled (0 °C) solution of (+)-**19** (840 mg, 3.75 mmol) in acetone (5 mL) was added excess of Jones' reagent. After stirring for 1 h at this temperature, the reaction mixture was poured into ice water and extracted with ether. The extract was washed with saturated $NaHCO_3$ solution and water, dried ($MgSO_4$), and concentrated. The concentrated product on distillation gave 660 mg of **20** (79% yield), bp 130–140 °C (bath temperature) (5 mm), which solidified in the receiver: mp 69–72 °C; $[\alpha]^{27}_D$ +24.5° (*c* 0.868, $CHCl_3$); IR (KBr) 1725, 1700, 1370, 1245, and 1035 cm^{-1}; NMR ($CDCl_3$) δ 1.55–2.05 (m, 11 H), 2.09 (s, 3 H), 2.4–2.8 (m, 3 H), 5.09 (dd, *J* = 6.6 and 6.2 Hz, 1 H).

Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 69.97; H, 8.11.

(+)-Homoadamantan-2-ol (21). To a mixture of KOH (0.39 g), 100% hydrazine hydrate (0.4 mL), and triethylene glycol (4 mL) was added (+)-**20** (610 mg, 2.75 mmol). The mixture was heated for 1.5 h at 160 °C and then for additional 3 h at 190–200 °C. After cooling, a white solid condensed on an inner wall of the condenser was dissolved in ether. The chilled reaction mixture was diluted with water and extracted with ether. Combined ether solutions were washed with water and dried over $MgSO_4$. The solvent was evaporated to give a solid, which was sublimed at 100 °C (5 mm) to afford 380 mg of **21** (83% yield): $[\alpha]^{25}_D$ +7.4° (*c* 0.653, $CHCl_3$); mp 276–278 °C (in a sealed tube) (lit.[10] racemate, mp 283.5–285.5 °C); IR (KBr) 3300, 1450, 1065, and 1025 cm^{-1}; NMR ($CDCl_3$) δ 1.1–2.4 (m, 17 H), 3.88 (dd, *J* = 5.5 and 5.0 Hz, 1 H).

Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.92. Found: C, 79.63; H, 10.77.

(+)-2-Acetoxyhomoadamantane (22). To a solution of (+)-**21** (75 mg, 0.452 mmol) in dry pyridine (5 mL) was added acetic anhydride (200 mg, 1.96 mmol), and the mixture was stirred for 5 h at 0–5 °C. After standing overnight at room temperature, the mixture was poured onto ice and extracted with ether. The extract was washed with 10% HCl, saturated $NaHCO_3$ solution, and water, and dried (MSO_4). After removal of the solvent, the residue was chromatographed on silica gel. Fractions eluted with pentane–ether (1:1, v/v) gave an oily product, which was distilled to give 64 mg of (+)-**22** (68% yield): bp 110–120 °C (bath temperature) (5 mm); $[\alpha]^{21}_D$ +0.73° (*c* 0.480, $CHCl_3$); IR (neat film) 1735, 1250, 1240, 1040, and 1020 cm^{-1}; NMR ($CDCl_3$) δ 1.1–2.1 (m, 15 H), 2.08 (s, 3 H), 2.2–2.5 (br s, 1 H), 5.02 (dd, *J* = 6.4 and 6.1 Hz, 1 H).

Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.70; H, 9.59.

(+)-Homoadamantan-2-one (23). To a solution of (+)-**21** (300 mg, 1.81 mmol) in acetone (3 mL) was added excess of Jones' reagent with ice cooling, and the mixture was stirred for 1 h at this temperature. The reaction mixture was diluted with water and extracted with ether. The extract was washed with saturated $NaHCO_3$ solution and water and dried ($MgSO_4$). After removal of the solvent, a solid was sublimed at 100 °C (5 mm) to give 240 mg of **23** (80% yield): $[\alpha]^{25}_D$ +32.8° (*c* 0.629, $CHCl_3$); mp 262–263 °C (in a sealed tube); IR (KBr) 1698, 1450, 1113, 1068, 1000, and 960 cm^{-1}; CD *c* 2.61×10^{-2} (isooctane, at 25 °C) [θ] (nm) 0 (238), +84.3 (sh, 275), $+1.09 \times 10^2$ (282.5), $+1.34 \times 10^2$ (291.3), $+1.78 \times 10^2$ (301.2), $+2.32 \times 10^2$ (312.2), $+1.76 \times 10^2$ (324.5), 0 (340); *c* 4.81×10^{-3} [methylcyclohexane–isopentane (75:15), at 25 °C] 0 (250), $+1.30 \times 10^2$ (292), $+1.90 \times 10^2$ (302), $+2.30 \times 10^2$ (312.5), $+1.80 \times 10^2$ (325), 0 (340); *c* 4.81×10^{-3} [methylcyclohexane–isopentane (75:15), at −68 °C] 0 (250), $+1.20 \times 10^2$ (284), $+1.70 \times 10^2$ (291.5), $+2.20 \times 10^2$ (301.5), $+2.60 \times 10^2$ (312.5), $+1.80 \times 10^2$ (325), 0 (340).

Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.83. Found: C, 80.23; H, 9.73.

Homoadamantane (1). A mixture of (+)-**15** (400 mg, 2.25 mmol, $[\alpha]^{20}_D$ +49.4°), ethanedithiol (2.00 g, 21.2 mmol), and borontrifluoride etherate (2 mL) was stirred for 60 h at room temperature. The reaction mixture was poured onto ice and neturalized with Na_2CO_3. After extraction with $CHCl_3$, the extract was washed with water and dried ($MgSO_4$). The solvent was evaporated and the residue was triturated with pentane to give 500 mg of **16** (67% yield), $[\alpha]^{22}_D$ +25.7° (*c* 0.503, $CHCl_3$). To a solution of (+)-**16** (450 mg, 1.36 mmol) in EtOH (10 mL) was added Raney nickel (5 g), and the mixture was refluxed for 8 h. After Raney nickel was removed, the filtrate was concentrated to give

a solid, which was sublimed at 90 °C (30 mm) to yield 120 mg of 1 (58% yield): $[\alpha]^{24}_D$ 0° (c 2.81, $CHCl_3$); mp 256–258 °C (in a sealed tube) (lit.[2] mp 258–259 °C).

Anal. Calcd for $C_{11}H_{18}$: C, 87.92; H, 12.08. Found: C, 87.67; H, 12.04.

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Registry No.—**1**, 281-46-0; (−)-**3**, 63902-00-1; (+)-**4**, 57287-49-7; (+)-**6**, 63903-40-2; (−)-**6**, 63902-01-2; (+)-**7**, 63902-02-3; (+)-**7** 2Ag, 63949-41-7; (±)-**10**, 63833-52-3; (+)-**10**, 63903-41-3; (+)-**10**, 63902-03-4; (−)-**10** cinchonidine salt, 63949-43-9; (−)-**10** 2Ag, 63949-44-0; (+)-**11**, 63833-53-4; (−)-**12**, 63902-04-5; (−)-**13**, 63902-05-6; (−)-**13** Ag salt, 63949-45-1; **14**, 63833-54-5; (±)-**15**, 63833-55-6; (+)-**15**, 63902-06-7; (+)-**16**, 63833-56-7; (±)-**17**, 63833-57-8; (+)-**17**, 63902-07-8; (±)-**18**, 63833-58-9; (+)-**19**, 63833-59-0; (+)-**20**, 63833-60-3; (+)-**21**, 63902-08-9; (+)-**22**, 63902-09-0; (+)-**23**, 63902-10-3; (±)-dimethyl bicyclo[3.3.1]nonane-2,6-dione-3,7-dicarboxylate, 54696-28-5; ethylene bromide, 106-93-4; (±)-dimethyl homoadamantanedione-3,6-dicarboxylate, 63833-61-4; cinchonidine, 485-71-2.

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Stereochemistry and Total Synthesis of (±)-Ivangulin

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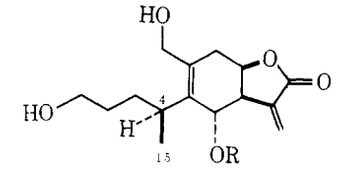
The stereochemistry and total synthesis of the novel secoeudesmanolide ivangulin (**3**) is reported. The introduction of the β-oriented C-15 methyl group involves acid-catalyzed opening of cyclopropyl ketal **4** and equilibration to the more stable β position (**4** → **5**). The establishment of the β-oriented γ-lactone functionality is facilitated by the presence of the angular α-methyl group in diene **6**. Cleavage of ring A in compound **10** via a Baeyer–Villiger oxidation completes the construction of the side chain.

The isolation and structure eluciation of two novel highly oxygenated secoeudesmanolides, eriolangin (**1**) and eriolanin (**2**), from the chloroform extracts of *Eriophyllum lanatum*



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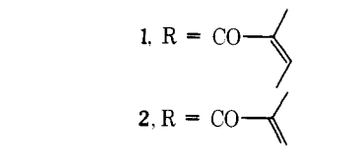

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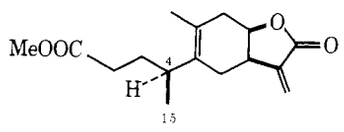
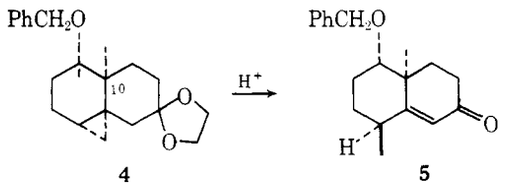


3

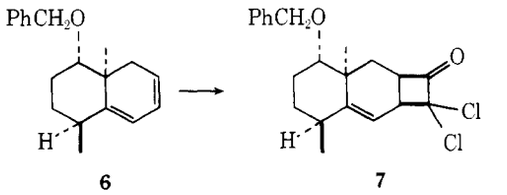
Forbes (Compositae) has been reported by Kupchan.[1] The significant in vivo tumor-inhibitory activity associated with both **1** and **2** can be attributed to the presence within each molecule of two α,β-unsaturated carbonyl functions.[2] In 1967, Herz and co-workers isolated, as a result of examining several collections of *Iva angustifolia* Natl. (section *Linearbractea*) found in Texas and Oklahoma, the only other 1,10-seconeudesmanolide, ivangulin (**3**), whose structure was based on IR, NMR, and chemical degradative data.[3] However, no information regarding the stereochemistry at C-4 was provided.

In conjunction with our efforts to synthesize eriolangin and eriolanin, we have examined several model systems and report herein our preliminary findings which have resulted in the successful synthesis of **3** whose NMR and IR were identical with the spectra of natural ivangulin, thus establishing the stereochemistry at C-4.[4]

Of prime importance to any synthesis of ivangulin and its



4 **5** (1)



6 **7** (2)