Studies in the Synthesis of the Thromboxane Receptor Antagonist EP 092 and Its Enantiomers

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An improved synthesis of EP 092 was developed. Resolution of an early intermediate was achieved by using butane-2(*R*),3(*R*)-diol ketals. Both enantiomers of EP 092 were found to possess platelet aggregation inhibition activity, but the *l* enantiomer was much more potent. A new synthesis was devised for the enantiomers starting from known enantiomerically pure chiral intermediates. It was found that the symmetry of these starting materials permitted the facile inversion of one enantiomer into the other via the Wharton reaction. Molecular mechanics studies provided a basis for explaining partial kinetic resolution during ketal formation as well as differences in the ease of Baeyer-Villiger oxidation of epimeric α-methyl ketones.

Jones and Wilson described the synthesis[1] and potent thromboxane receptor antagonist activity[2,3] of EP 092, (±)-**15**. In order to prepare larger quantities of this material for further study, we desired a shorter, more efficient process. Since EP 092 was a racemate, we were uncertain whether the biological activity might reside in one enantiomer. Harris et al.[4] have described interesting variations in the activity of isomers and enantiomers of their family of thromboxane antagonists. Thus, there was good reason to seek the individual enantiomers of EP 092.

Results

Brown, Rothberg, and Vander Jagt[5] described the facile synthesis of **1** from cyclopentadiene dimer. Methylation of the lithium enolate of **1** (Scheme I) with methyl iodide produced (±)-**2** in 62% yield along with 9% of a symmetrical dimethyl compound, **3**, and a trace of (±)-**4**. Prolonged exposure to base permitted some isomerization of (±)-**2** to (±)-**5** and **3** to (±)-**6**. Baeyer-Villiger oxidation of (±)-**2** with *m*-chloroperoxybenzoic acid (MCPBA) produced a lactone, (±)-**7**, in 96% yield. Diisobutylaluminum hydride (DIBAL) reduction led to (±)-**8** in 88% yield. Reaction with the ylide derived from (4-carboxybutyl)-triphenylphosphonium bromide produced a 9:1 mixture of (±)-**9** and (±)-**10** in virtually quantitative yield. Jones oxidation to (±)-**11** and (±)-**12** followed by facile base isomerization produced a 9:1 mixture of (±)-**13** and (±)-**14** in 90% yield. Reaction with 4-phenyl-3-thiosemicarbazide produced EP 092, (±)-**15**, in 73% yield. Since (±)-**15** is readily crystallized, it is easily separated from the *E* isomer, (±)-**16**. Thus the synthesis of the racemate had been reaily accomplished.

The ease of this synthesis prompted us to seek a resolution of (±)-**2** in order to prepare the individual enantiomers. Butane-2(*R*),3(*R*)-diol ketals have been used for ketone resolutions.[6,7] Reaction of this diol with (±)-**2** in the presence of camphorsulfonic acid (CSA) produced a partial kinetic resolution (Scheme II) with further enrichment by chromatography producing *ent*-**17** (enantiomer of **17**) in 84% de. This reaction also produced some epimer **5**. The recovered ketone fraction was similarly reacted with butane-2(*S*),3(*S*)-diol to provide **17** in 90% de. Aqueous oxalic acid hydrolysis of *ent*-**17** produced *ent*-**2** (84% ee) while hydrolysis of **17** produced **2** (90% ee). These enantiomers were carried through the same sequence of reactions as used for the racemate to produce *ent*-**15** and **15**.

We had hoped that we could find an intermediate which would crystallize in a manner permitting the isolation of the pure enantiomers. However, while (±)-**7** had a mp of 51-52 °C, **7** or *ent*-**7** only provided crystals melting at about 42-43 °C with no improvement in rotation. Likewise, while (±)-**8** melts at 93-94 °C, **8** or *ent*-**8** did not crystallize. Indeed attempts at crystallization of *ent*-**8** (84% ee) produced enough crystalline (±)-**8** to increase the purity of the residual *ent*-**8** to ca. 90% ee. Our problems were further compounded when the final products **15** and *ent*-**15** could not be crystallized even though (±)-**15** had a 130-132 °C melting point. This meant that we were unable to readily separate the *Z* and *E* isomers. Thus the samples we produced were a 9:1 mixture of **15** and **16** (90% ee) and a 9:1 mixture of *ent*-**15** and *ent*-**16** (90% ee). Preliminary biological testing of these crude samples showed the first to possess about 10 times the potency of the second in inhibition of U-46619 stimulated platelet aggregation.

Since it was apparent that there was a marked difference in the activity of the enantiomers, we decided to undertake a new synthesis based on enantiomerically pure starting materials. A suitable starting material was provided by the work of Zwanenburg et al.,[8] who showed that porcine liver esterase hydrolysis of (±)-**19** produced pure **20** and the residual ester could provide *ent*-**20** (Scheme III). They also demonstrated that decarboxylation of **20** provided **21** for which the absolute configuration could be proven. Thus, we prepared **21** and *ent*-**21** by their method and hydrogenated them to **22** and *ent*-**22**, which proved to be suitable enantiomerically pure starting materials.

Mc Murry and Scott[9,10] developed a method for the preparation of alkyl-substituted olefins from ketones via the enol triflates and cuprate reagents. Thus **22** when treated with lithium isopropylcyclohexylamide (LiIPCHA) and *N*-phenyltrifluoromethanesulfonimide produced the enol triflate, **23**, which reacted with lithium dimethyl-

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(6) Casanova, J.; Corey, E. J. *Chem. Ind. (London)* **1961**, 1664-1665.
(7) Plattner, J. J.; Rapoport, H. *J. Am. Chem. Soc.* **1971**, *93*, 1758-1761.
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(9) Mc Murry, J. E.; Scott, W. J. *Tetrahedron Lett.* **1983**, *24*, 979-982.
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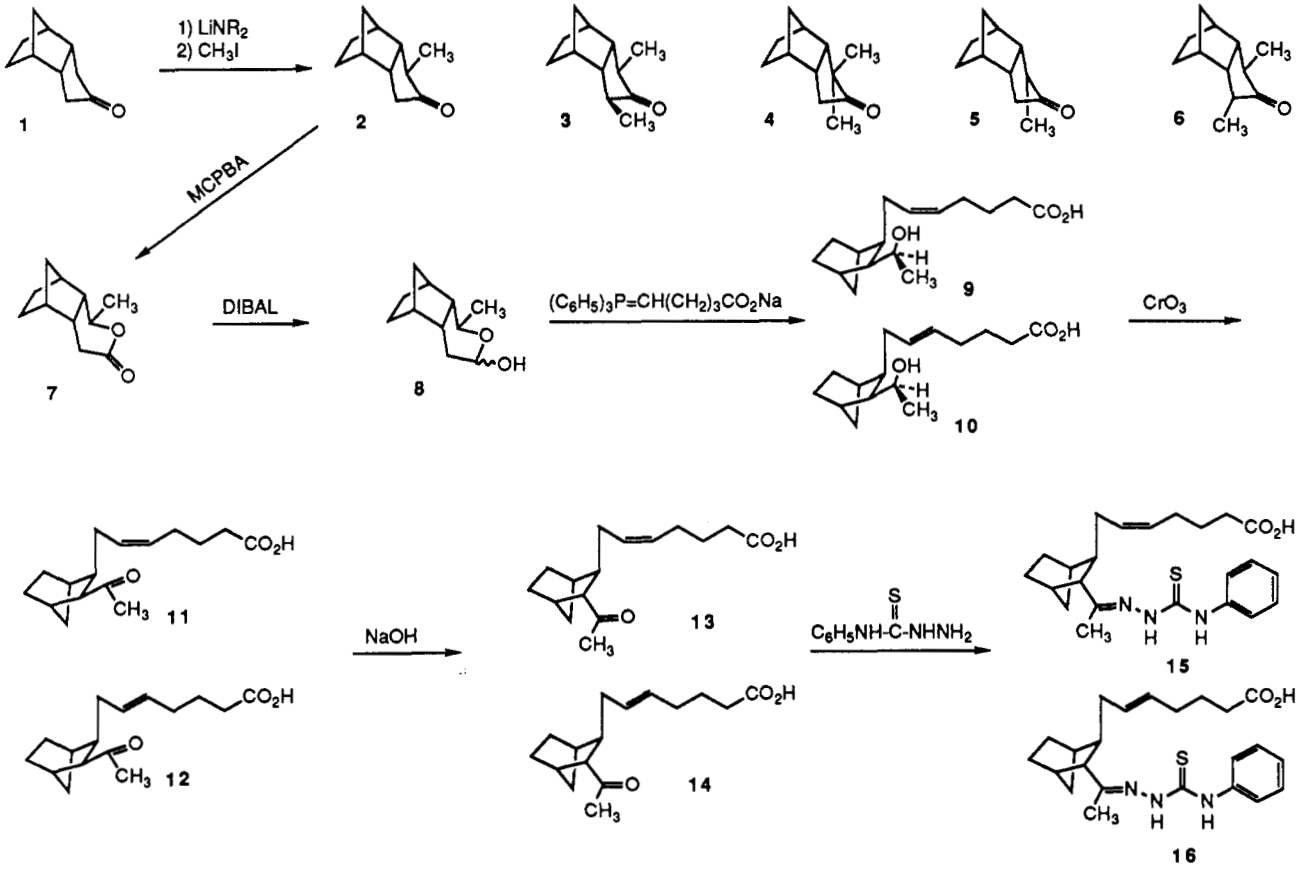
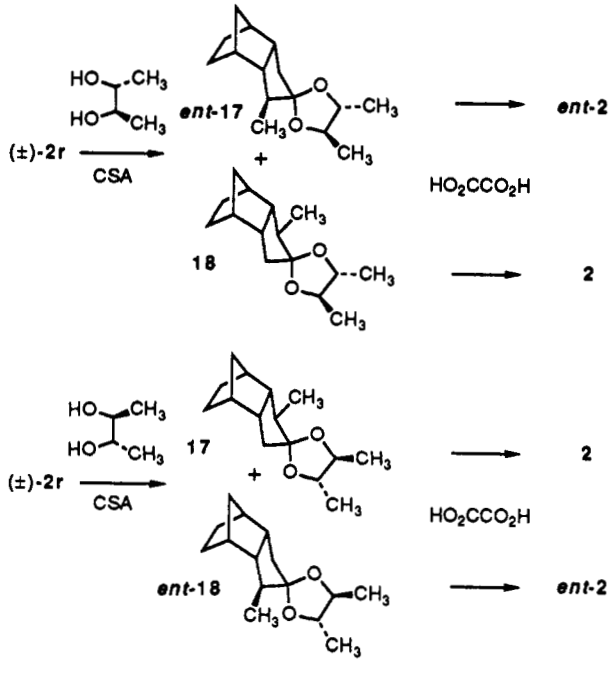
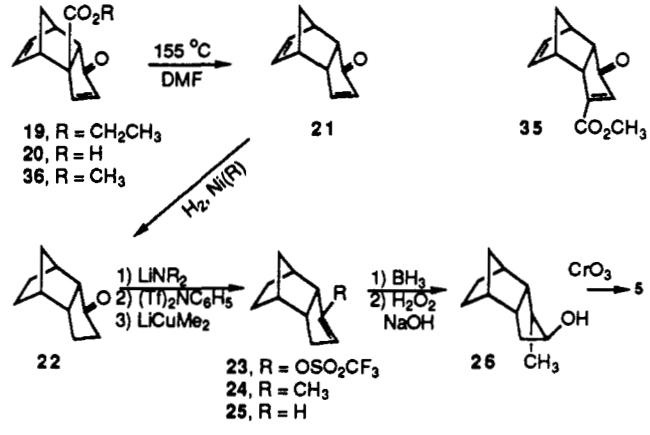
Scheme I



Scheme II



Scheme III

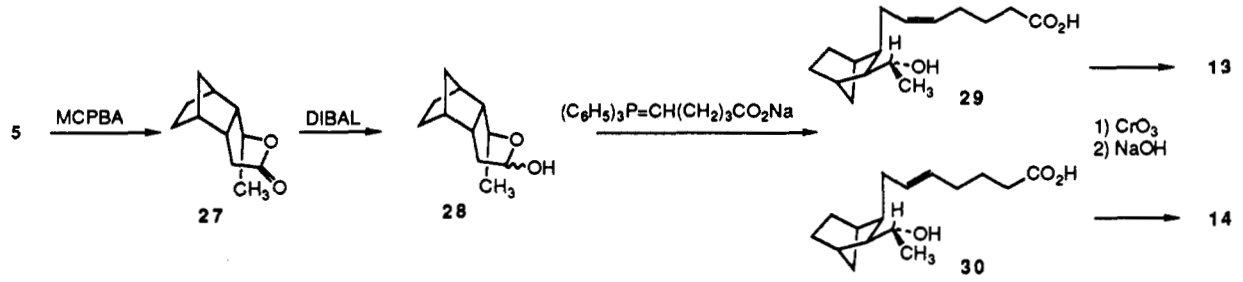


cuprate to form a mixture (4:1) of **24** and a reduction product, **25**. Hydroboration and oxidation produced the alcohol **26**, which was oxidized to **5** in 26% yield from **22**. This material was shown to be 100% ee by preparation of a ketal with butane-2(*R*),3(*R*)-diol. With use of a reaction sequence similar to that employed with (±)-**2**, **5** was oxidized to **27** (Scheme IV) slowly and in poor yield (44% after 5 days). Reduction to **28** went well but the Wittig reaction to produce **29** and **30** was less efficient than had been observed with the isomeric compound **8**. However, it was possible to separate **29** (44%) and **30** (8%) by chromatography. Jones oxidation and base epimerization led to pure isomers **13** and **14**, which led to pure **15** and **16**. Even though no impurities were detectable, neither of these compounds could be obtained in crystalline form.

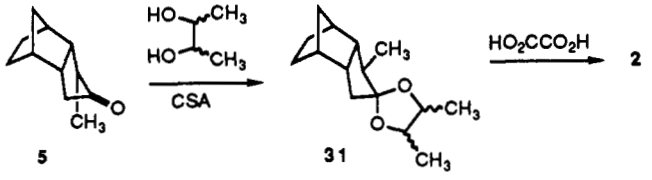
Because of poorer yields from the endo methyl compound **5**, the route for the synthesis of the less active enantiomer *ent*-**15** was modified. Thus, *ent*-**5** was ketalized with a butane-2,3-diol mixture (Scheme V) to provide the exo methyl ketals *ent*-**31**.[11] Aqueous oxalic acid hydrolysis leads to *ent*-**2**, which by the route of Scheme I leads to *ent*-**15**. In this case the *Z* isomer was obtained pure by

(11) No ketal of any endo methyl compound was ever observed. Under the acidic conditions for ketalization, equilibration occurs and the exo methyl ketone forms the ketal.

Scheme IV



Scheme V



chromatography of the methyl esters of *ent*-**13** and *ent*-**14**. Only the faster moving isomer leading to *ent*-**13** was obtained pure.

Discussion

Stereochemistry. The absolute configuration of the methyl ketones **2** and *ent*-**2** obtained via resolution could be assigned on the basis of the ORD and CD data. Application of the ketone–aldehyde octant rule[12] to **2** and *ent*-**2** clearly shows that the methyl group of **2** lies in a negative octant and the methyl group of *ent*-**2** lies in a positive octant. The symmetry of **2** and *ent*-**2** is such that the signs of the Cotton effects are determined by contributions from the methyl groups. Similarly, the methyl group of **5** lies in a positive octant while the methyl group of *ent*-**5** lies in a negative octant. When (±)-**2** was reacted with butane-2(*R*),3(*R*)-diol, the recovered ketone fraction was enriched in the slower reacting enantiomer. With careful chromatography the ketones could be separated into a fraction enriched in **2** and exhibiting a negative Cotton effect and a fraction enriched in **5** and having a positive Cotton effect. Likewise, after hydrolysis of the purified major ketal product, the ketone obtained, *ent*-**2**, exhibited a positive Cotton effect. There is some vibrational fine structure in these curves, as is often observed for ketones in hexane,[13] but the CD curves are distinctly positive or negative.

While the conditions of ketal formation were capable of epimerizing the methyl configuration as shown by the recovery of endo methyl compound **5**, we were not able to detect any endo methyl ketal product. In fact, the endo methyl ketone **5** derived from enantiomerically pure **21** was converted to the exo configuration under ketalization conditions. These compounds also corresponded to the identical products obtained from the chiral templates, **21** and *ent*-**21**, of known absolute configuration.[8]

Molecular Mechanics Studies. In order to study the nature of the enantioselective ketal formation, an exhaustive molecular mechanics and conformational analysis of the starting material, the reaction products, and possible reaction intermediates was undertaken, using the MacroModel[14] MM2 force field. Models related to purported transition states in proposed mechanisms for cyclic ketal formation[15] were also included in this analysis.

In the exo methyl ketone **2**, there are two conformational minima, 0.8 kcal apart, in which the cyclopentanone ring has a roughly equal and opposite pucker about the carbonyl group, with the exo methyl in an equatorial disposition in one and pseudo-axial in the other. In the endo methyl ketone **5**, there is only one minimum, 0.4 kcal above the exo case, close in geometry to the unsubstituted parent but with the methyl substituent pseudo-equatorial. In both the exo and endo cases the trajectory of incoming nucleophiles toward the carbonyl must be from the relatively unhindered exo face of the ketone. The loss of an α-proton from the protonated exo methyl ketone[16] to give the most stable enol, followed by facile reprotonation from the least hindered face, leads to inversion of the methyl substituent, as has been observed as a minor side reaction.

Calculations on model hydrates suggest that the transformation of the ketone sp^2 center to sp^3 is intrinsically less favorable for the endo methyl case by 2.2 kcal compared to the exo methyl case, which may reflect its inability to assume the puckered conformation, which is the global minimum in the exo methyl hydrate.

This same flexibility persists in the spiroketal products, where the residual mobility of the dioxolane ring leads to further multiplicity of the accessible manifold. In the exo methyl products the global minima of *ent*-**17** and **18** are almost identical in energy, so that their relative thermodynamic stabilities cannot account for preferential formation of *ent*-**17**. The corresponding endo methyl products are calculated to be 2–3 kcal less stable, which explains their absence under ketalization conditions that are capable of epimerization via the enol.

Among the accessible hemi-ketal intermediates there is a spread in the relative energies of the global minima, which favors that derived from **2** by ca. 2.5 kcal, but this difference is reversed when one considers their full conformational trajectories en route to the corresponding 5-*exo-tet* transition states (Figure 1) suggested by Reddy and Rao.[15] In order to reach a flattened five-coordinate transition state, the hemi-ketal from *ent*-**2** (**33**) follows a trajectory ca. 5 kcal lower in energy than that from **2** (**32**), due to the buttressing effects of methyl substituents in the latter, early along the reaction coordinate where the parameterization of the MM2 force field still holds true. This net difference of 2.5 kcal in the activation energy translates into a kinetic preference for the formation of *ent*-**17** over **18**, in reasonable agreement with the experimentally observed 62:38 product ratio at the 80 °C reaction temper-

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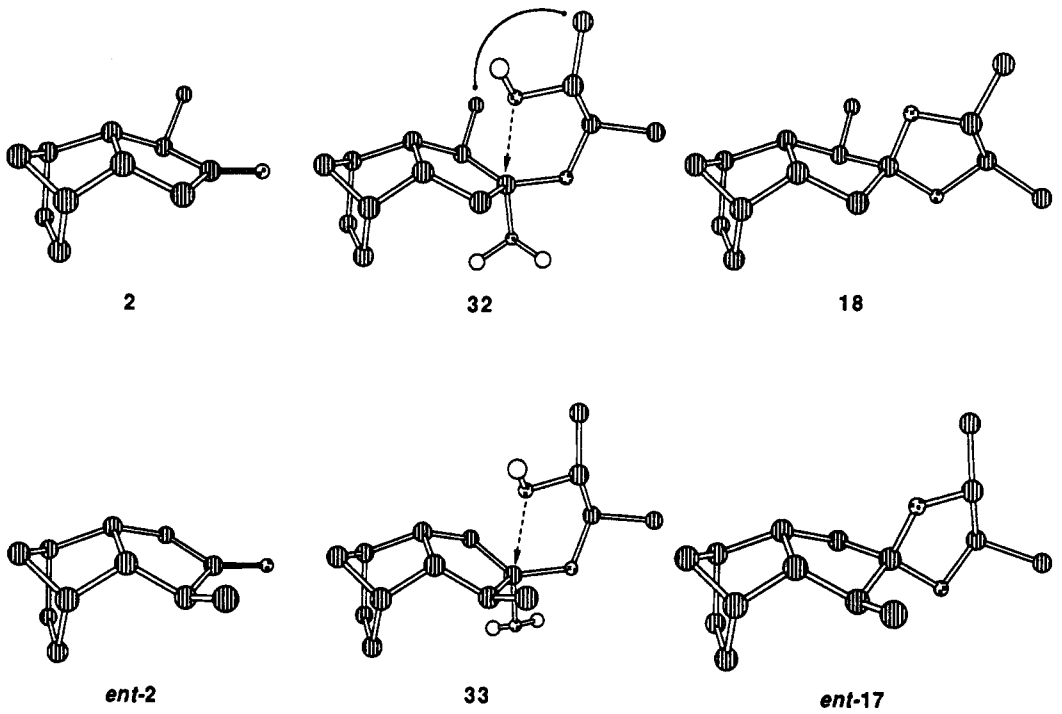

Figure 1. Minimum energy conformations for **2** and *ent*-**2** and their butane-2(*R*),3(*R*)-diol ketals **18** and *ent*-**17** with hemiketal conformations approaching a possible transition state to ketal.

ature of refluxingg benzene.

The calculated relative stabilities of the exo and endo hydrates might also explain the observed difference in reactivities of the ketone epimers toward Baeyer–Villiger oxidation. The relative energies of the peroxy hemi-ester intermediates[17] should parallel those of the corresponding hydrates so that the exo methyl peroxy hemi-ester is likely to form more readily. The exo and endo lactone products **7** and **27** are calculated to be equal in energy and geometry, save for the disposition of the methyl group.

NMR. The diastereomeric purity of the ketal fractions were determined by using ^{13}C NMR spectroscopy. The use of ^{13}C NMR analysis of butane-2(*R*),3(*R*)-diol ketals for determining chiral purity has been recommended by Hiemstra and Wynberg.[18] Our observation of kinetic resolution suggests that for this method to be accurate, ketalization must be complete. In order to avoid a mistaken interpretation of purity, we checked the purity of **5** and *ent*-**5** by reaction with the diol having the configuration that would react more slowly with the product we were checking. Even under these conditions, which would favor reaction of any minor isomer present, no such product was detected. Therefore, we confirm that **21** and *ent*-**21** can indeed be obtained in 100% ee.

Lemiêre et al.[19] have suggested an empirical model for ^{13}C NMR relative chemical shifts for butane-2(*R*),3(*R*)-diol ketals of cyclohexanones. We observed similar shifts for ketals *ent*-**17**, **18**, and **34** (prepared from **1**). The ^{13}C shift assignments along with Lemiêre's model are given in Figure 2. This effect is not normally observed in five-membered-ring ketone derivatives and may be due to the puckered conformations of the ketals.

Enantiomerically Pure 21 and *ent*-21. While our experience confirms the results of Zwanenburg et al.[8] for

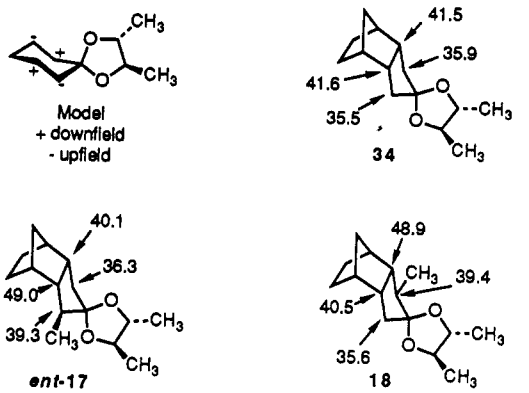

Figure 2. Lemiêre[17] Model for ^{13}C NMR chemical shifts in cyclohexanone butane-2(*R*),3(*R*)-diol ketals and shifts for *ent*-**17**, **18**, and **34**. For **34**, application of Model is assumed.

the preparaton of enantiomerically pure **21** and *ent*-**21**, we feel some comment may be helpful. We found that crystallization of the acid **20** provides enantiomeric purification such that the second crop may be lower melting and lower in rotation. In order to obtain pure *ent*-**20** we repeated the esterase treatment of the recovered ester fraction as recommended before hydrolysis to the acid, which likewise was purified by crystallization. The pyrolytic decarboxylation that worked very well on a small scale showed evidence of some racemization when done on a larger quantity. We examined the recovered acid fraction from this run and discovered there was some racemization and also some byproduct formation. One of the byproducts, isolated as the methyl ester (±)-**35**, appears to be a product of retro-Diels–Alder reaction and recombination. This process may be responsible for the racemization observed. Even though the large scale reaction was run a much shorter time, more racemization was observed. Thus, it seems unlikely that **21** undergoes the racemization after it has formed. The fortuitous purification by crystallization (second crop having lower melting point and rotation) permits absolute enantiomeric purity in **21** as indicated by ketal analysis of **5** and *ent*-**5** products.

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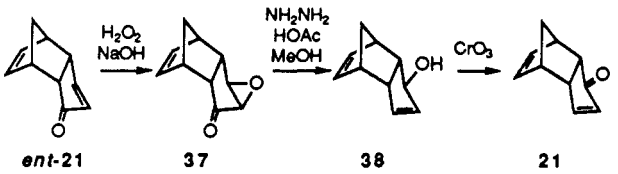
(18) Hiemstra, H.; Wynberg, H. *Tetrahedron Lett.* **1977**, *18*, 2183–2186.
(19) Lemiêre, G. L.; Dommisse, R. A.; Lepoivre, J. A.; Alderweireldt, F. C.; Hiemstra, H.; Wynberg, H.; Jones, J. B.; Toone, E. J. *J. Am. Chem. Soc.* **1987**, *109*, 1363–1370.

Scheme VI



ent-21 37 38 21

Wharton Reaction. The symmetry of **21** and *ent*-**21** suggested a possible inversion via the Wharton reaction.[20,21] Thus, *ent*-**21** was epoxidized to **37** (Scheme VI), which reacted with hydrazine in the presence of acetic acid to produce **38**. Jones oxidation provided **21** in high optical purity. Since our work was completed, an alternate synthesis of **38** and *ent*-**38** and interconversion via the Wharton reaction has been reported by Takano, Inomata, and Ogasawara.[22]

Biology. Pure samples of **15**, (±)-**15**, and *ent*-**15** were administered iv to rats, blood samples were drawn, and ex vivo U-46619 induced platelet aggregation was measured. The doses required for a 50% reduction in aggregation were 8.7, 31, and 45 μg/kg, respectively.[23]

Experimental Section

The identity and purity of all products were determined on the basis of ^{13}C NMR spectroscopy. Compositions of mixtures of isomers were determined from peak heights for comparable carbons. ^1H and ^{13}C NMR spectra were determined in $CDCl_3$ using a Varian VXR-200, Varian VXR-400, Varian VXR 500, or GE QE-300 spectrometer. CD data were obtained on a Jasco J-20 ORD/CD spectropolarimeter using hexane solutions. CD data for curves with vibrational fine structure were calculated without smoothing.[24] Flash chromatography was carried out on Merck 60 silica gel. Acidic silica chromatography was carried out in a similar manner, using Mallinckrodt SilicAR CC-4. Low pressure liquid chromatography (LPLC) was run on Woelm pH Controlled Scientific silica gel columns (three 1 m × 15 mm in series). Burdick and Jackson high purity solvents were used. A number of compounds, notably **1**–**6** and **21**–**26**, are volatile and must be handled carefully. Solutions were concentrated on a rotating evaporator with a water aspirator using bath temperatures of 25 °C or lower, followed by drying under high vacuum. Ether and hexane could be removed with minimal losses but some of the yields may reflect volatility losses. Combustion analyses were determined by E. Zielinski and associates of these laboratories. Noncrystalline products were dissolved in a small amount of pentane or ether, filtered, and dried before analysis.

(±)-(3aα,7aα)-Octahydro-1α-methyl-4α,7α-methano-2*H*-inden-2-one ((±)-2). To a solution of 6.9 mL (5.93 g, 41.9 mmol) of *N*-isopropylcyclohexylamine in 20 mL of dry tetrahydrofuran (THF) cooled in a −78 °C bath was added 25 mL of 1.58 M *n*-butyllithium in hexane. After 15 min a solution of 5.62 g (37.5 mmol) of (3aα,7aα)-octahydro-4α,7α-methano-2*H*-inden-2-one (**1**)[5] in 20 mL of THF was added over 20 min. This mixture was stirred for 15 min and 5 mL (11.4 g, 80 mmol) of methyl iodide was added. After 30 min more, the mixture was allowed to warm to room temperature and 50 mL water was added. The mixture was extracted twice with ether, washed with water and brine, and then dried (Na_2SO_4). The solvents were evaporated and the residue was chromatographed (Flash, hexane–EtOAc 99:1) to provide first 596 mg (9%) of (3aα,7aα)-octahydro-1α,3α-dimethyl-4α,7α-methano-2*H*-inden-2-one (**3**). Anal. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.57; H, 10.23. This was followed by 3.81 g (62%) of (±)-**2**. Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.29; H, 9.76. Finally a small amount of crude **1** was recovered. In some runs the early part of the (±)-**2** fraction contained traces of (±)-(3aα,7aα)-octahydro-1,1-dimethyl-4α,7α-methano-2*H*-inden-2-one ((±)-**4**) as evidenced by NMR. In a run that was allowed to stand at room temperature overnight before workup, a small amount of (±)-(3aα,7aα)-octahydro-1α,3β-dimethyl-4α,7α-methano-2*H*-inden-2-one ((±)-**6**) followed **3** closely. Anal. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.69; H, 10.28. In this same run traces of the isomeric (±)-(3aβ,7aβ)-octahydro-1α-methyl-4β,7β-methano-2*H*-inden-2-one ((±)-**5**) followed the main product closely. This isomer also forms under acidic equilibration.

(±)-(4aα,8aα)-Octahydro-1α-methyl-5α,8α-methano-3*H*-2-benzopyran-3-one ((±)-7). To a solution of 3.81 g (23.2 mmol) of (±)-**2** in 50 mL of dry methylene chloride was added 5.5 g (4.67 g, 27 mmol) of 85% MCPBA. After 3 days the solids were removed by filtration and rinsed with hexane. The filtrate was washed with 5% $NaHCO_3$, water, and brine. After evaporation of solvents, chromatography (Flash, hexane–EtOAc 4:1) provided 47 mg of crude (±)-**2**. This was followed by 4.02 g (96%) of (±)-**7**. Crystallization from a small amount of hexane provided a solid melting at 51–52.5 °C. Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.29; H, 8.89.

(±)-(4aα,8aα)-Octahydro-1α-methyl-5α,8α-methano-1*H*-2-benzopyran-3-ol ((±)-8). A solution of 4.02 g (22.3 mmol) of (±)-**7** in 5 mL of toluene was chilled in a −78 °C bath and 30 mL of 1 M DIBAL in toluene was added and stirred at −78 °C for 2 h. The mixture was quenched cautiously with 5 mL of MeOH. After warming to room temperature, 50 mL more MeOH was added. The solid was removed by filtration, rinsing thoroughly with MeOH. The filtrate was evaporated, and the residue was crystallized from hexane to provide 3.23 g of (±)-**8**, mp 93–94 °C. Chromatography of the mother liquors (Flash, hexane–EtOAc, 4:1–1:1) provided a small amount of crude (±)-**7** followed by a product fraction that was crystallized from hexane to provide an additional 0.33 g of (±)-**8**. Total yield: 3.56 g (88%). Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.34; H, 9.91.

(±)-7-[3β-(1(*S)-Hydroxyethyl)-(1α,4α)-bicyclo[2.2.1]-hept-2β-yl]-5(*Z*)-heptenoic Acid ((±)-9).** To a suspension of 13.5 g (30.6 mmol) freshly crushed and dried (60 °C, high vacuum) (4-carboxybutyl)triphenylphosphonium bromide in 75 mL of dry THF was added 60 mL of 1 M sodium bis(trimethylsilyl)amide in THF. The mixture was stirred at room temperature for 18 h under nitrogen, and then a solution of 3.38 g (18.5 mmol) of (±)-**8** in 50 mL of THF was added over 10 min. The temperature rose from 27 to 35 °C during the addition. During 1 h the color faded quickly and more white solids formed. After the addition of 100 mL of water, the mixture was extracted with ether. The aqueous layer was acidified with 10% HCl and extracted twice with ether, which was washed with water and brine. After being dried (Na_2SO_4) the solvents were evaporated, and the residue was chromatographed on acidic silica (hexane–EtOAc, 4:1) to provide 4.90 g (99%) of a crude product fraction consisting of about 90% (±)-**9** and 10% of the 5*E* isomer, (±)-**10**. Anal. Calcd for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84. Found: C, 72.28; H, 9.92.

(±)-7-(3α-Acetyl-(1α,4α)-bicyclo[2.2.1]hept-2β-yl)-5(*Z*)-heptenoic Acid ((±)-13). A solution of 4.90 g (18.4 mmol) of crude (±)-**9** in 150 mL of acetone was chilled in an ice bath and titrated with Jones reagent (5.5 mL). The supernatant was decanted and concentrated to ca. 20 mL, which was recombined with the solids and 100 mL of water. The mixture was extracted with ether. After washing with water and brine, followed by drying (Na_2SO_4), the solvents were evaporated to leave 4.60 g of crude (±)-7-(3β-acetyl-1α,4α-bicyclo[2.2.1]hept-2β-yl)-5(*Z*)-heptenoic acid ((±)-**11**) with 10% of the 5*E* isomer, (±)-**12**, which had partially isomerized to (±)-**13** and its 5*E* isomer (±)-**14**. This material was dissolved in 50 mL of 1 N NaOH and stirred at room temperature for 1 h. After acidification with 10% HCl, the product was extracted with ether, which was washed with water and brine and dried (Na_2SO_4). After evaporation of the solvents, chromatography on acidic silica (hexane–EtOAc, 4:1) provided 4.38 g (90%) of a mixture containing ca. 90% (±)-**13** and 10% (±)-**14**. Anal. Calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.48; H, 9.28.

(±)-7-[3α-[1-[[(Phenylamino)thioxomethyl]hydrazono]-ethyl]-(1α,4α)-bicyclo[2.2.1]hept-2β-yl]-5(*Z*)-heptenoic Acid

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(23) The biological evaluations were carried out by L. Feigen, N. Nicholson, and B. Taite of these laboratories. The details of these and other tests will be published elsehwere.
(24) Djerassi, C. *Optical Rotatory Dispersion*; McGraw-Hill: New York, 1960; p 162.

((±)-15) (EP 092). A solution of 1.20 g (4.5 mmol) of the mixture of (±)-13 and (±)-14 and 0.85 g (5.08 mmol) of 4-phenyl-3-thiosemicarbazide in 5 mL of pyridine was stirred at room temperature for 22 h. A solution of the mixture in 100 mL of methylene chloride was washed twice with 100 mL of 5% HCl, water, and brine. After drying (Na_2SO_4) and evaporation of solvent, the residue was crystallized from 10 mL of ether to provide 1.364 g (73%) of (±)-15, mp 129–132 °C. Anal. Calcd for $C_{23}H_{31}N_3O_2S$: C, 66.80; H, 7.55; N, 10.16; S, 7.75. Found: C, 66.78; H, 7.57; N, 10.10; S, 7.78.

Resolution of (±)-2. A solution of 2.26 g (13.8 mmol) of (±)-2, 1.07 g (11.9 mmol) of butane-2(*R*),3(*R*)-diol, and 10 mg of CSA in 40 mL of benzene was refluxed under a Dean–Stark trap for 12 h and then distilled to a volume of ca. 10 mL. After the addition of a few drops of Et_3N and concentration in vacuo, the residue was chromatographed (flash, hexane–hexane–EtOAc, 49:1) to provide 1.95 g of a product fraction (*ent*-17 and 18 in a 62:38 ratio) followed by 430 mg of (±)-2 enriched in the *l* enantiomer (– Cotton effect) and then by 66 mg of (±)-5 enriched in the *d* enantiomer (+ Cotton effect). The product fraction was repeatedly chromatographed (LPLC Woelm, hexane–Et_2O 49:1), cutting small fractions arbitrarily and combining those with >90% diastereomeric purity.[25] The major isomer was (3′aα,7′aα)-octahydro-(1′α)-1′(*S*),4(*S**),5(*S**)-trimethylspiro[1,3-dioxolane-2,2′-[4′α,7′α]methano[2*H*]indene] (*ent*-17), which was also the faster moving isomer. Eventually, a combined fraction of 851 mg of 92% *ent*-17 and 8% (3′aα,7′aα)-octahydro-(1′α)-1′(*R*),4(*R**),5(*R**)-trimethylspiro[1,3-dioxolane-2,2′-[4′α,7′α]methano[2*H*]indene] (18) (based on ^{13}C NMR) was obtained. The 430 mg of recovered (±)-2, 300 mg of butane-2(*S*),3(*S*)-diol, and 5 mg of CSA in 35 mL of benzene were refluxed under a Dean–Stark trap for 16 h. After cooling, adding Et_3N, and evaporating in vacuo, flash chromatography as above provided 636 mg of a product fraction allowed by a miture of 48 mg of (±)-2 and (±)-5 isomers. LPLC of the product fractions as above provided 271 mg of the faster moving fractions consisting of 95% (3′aα,7′aα)-octahydro-(1′α)-1′(*R*),4(*S**),5(*S**)-trimethylspiro[1,3-dioxolane-2,2′-[4′α,7′α]methano[2*H*]indene] (17) and 5% (3′aα,7′aα)-octahydro-(1′α)-1′(*S*),4(*R**),5(*R**)-trimethylspiro[1,3-dioxolane-2,2′-[4′α,7′α]methano[2*H*]indene] (*ent*-18).

(3aα,7aα)-Octahydro-(1*S*)-1α-methyl-4α,7α-methano-2*H*-inden-2-one (*ent*-2). The 851-mg fraction (92% *ent*-17) was dissolved in 15 mL of MeOH. A solution of 800 mg of oxalic acid dihydrate in 2 mL of water was added. From time to time, as the cloudiness cleared, water was added until a total of 5 mL had been added. The mixture was stirred for 18 h more, diluted with water, an extracted 3× with hexane. The extracts were washed with 5% $NaHCO_3$, water, and brine. After drying (Na_2SO_4) and evaporation, flash chromatography (hexane–EtOAc, 19:1) provided 460 mg (78%, 84% ee) of *ent*-2, $[\alpha]_D$ +21.2° (1.118% hexane), CD $[\Theta]_{298}$ +2260.

(3aα,7aα)-Octahydro-(1*R*)-1α-methyl-4α,7α-methano-2*H*-inden-2-one (2). The 271 mg fraction (95% 17) was dissolved in 15 mL of MeOH and a solution of 400 mg of oxalic acid dihydrate in 5 mL of water was added. After being stirred at room temperature for 18 h, the mixture was diluted with water and extracted 3× with hexane. The extracts were washed with 5% $NaHCO_3$, water, and brine. After drying (Na_2SO_4) and evaporation, the residue was chromatographed (flash, hexane–EtOAc, 19:1) to provide 154 mg (82%, 90% ee) of 2, $[\alpha]_D$ –21.2° (0.998, hexane), CD $[\Theta]_{296}$ –2600.

7-[3α-[1-[[(Phenylamino)thioxomethyl]hydrazono]-ethyl]-(1*S*,1α,4α)-bicyclo[2.2.1]hept-2β-yl]-5(*Z*)-heptenoic Acid (*ent*-15). Using conditions similar to those for the preparation of (±)-15, 84% ee *ent*-2 was converted to *ent*-15. Some enantiomeric enrichment of intermediate *ent*-8 was achieved by removing crystals of a small amount of (±)-8, which raised the ee to about 90%. Since *ent*-15 did not crystallize the product contained about 10% of its 5*E* isomer, *ent*-16.

7-[3α-[1-[[(Phenylamino)thioxomethyl]hydrazono]-ethyl]-(1*R*,1α,4α)-bicyclo[2.2.1]hept-2β-yl]-5(*Z*)-heptenoic Acid (15). Using conditions similar to those for the preparation of (±)-15, 90% ee 2 was converted to 15 (90% ee) containing about 10% of its 5*E* isomer, 16.

1,4,7,7aα-Tetrahydro-1-oxo-4α,7α-methano-3a*H*-indene-(3a*S*)-3aα-carboxylic Acid (20).[8] A solution of 46.2 g of KH_2PO_4 in 3.4 L of water was adjusted to pH 7.8 with 1 N NaOH, and 42.4 g of ethyl 1,4,7,7aα-tetrahydro-1-oxo-4α,7α-methano-3a*H*-indene-3aα-carboxylate ((±)-19) and 35 mL (27.5 g, 0.67 M) of acetonitrile were added. After the addition of 7580 units of porcine liver esterase (Sigma), the mixture was stirred at 27 °C for 22 h, maintaining the pH at 7.8 with 1 N NaOH (96.2 mL, 49%). After chilling in an ice bath, the pH was adjusted to 9.8, and the mixture extracted with 3 × 500 mL of ether. After washing with water and brine and drying (Na_2SO_4), evaporation of solvents left 22.91 g of crude *ent*-19, $[\alpha]_D$ +91.3° (1.177% MeOH); lit.[8] for *ent*-19 is +106.3°. The alkaline layer was acidified to pH 2.0 with 10% HCl and extracted with 3 × 400 mL of EtOAc, and the extracts were washed with water and brine. After drying (Na_2SO_4) and evaporation of solvents the residue (17.8 g) was crystallized from ether–hexane (1:1) to yield 14.48 g (39%) of 20, mp 136–137 °C, $[\alpha]_D$ –85.3° (0.907% MeOH) (lit.[8] mp 125–130 °C, $[\alpha]_D$ –83°). Anal. Calcd for $C_{11}H_{10}O_3$: C, 69.47; H, 5.30. Found: C, 69.23; H, 5.35. A second crop of 2.73 g, mp 128–130 °C, $[\alpha]_D$ –51.5° (0.964% MeOH), was obtained after boiling off half of the solvents. The recovered ester fraction was exposed to similar conditions in 2 L of 0.1 M KH_2PO_4 and 20 mL of acetonitrile with 18.8 mL of 1 N NaOH consumed over 43 h. The acid fraction from ether–hexane gave 0.91 g of (±)-20, mp 137–138 °C, $[\alpha]_D$ +0.7° (0.98% MeOH) and a second crop of 0.79 g, mp 127–137 °C, $[\alpha]_D$ –31.4°. The ester fraction provided 20.27 g of crude *ent*-19, $[\alpha]_D$ +101.2°.

1,4,7,7aα-Tetrahydro-1-oxo-4α,7α-methano-3a*H*-indene-(3a*R*)-3aα-carboxylic Acid (*ent*-20). A solution of 20.1 g of crude *ent*-19 in 50 mL of MeOH was chilled in an ice bath while five 20-mL portions of 1 N NaOH were added with vigorous stirring at ca. 1-h intervals (permitting cloudiness to clear each time). After 1 h more, the mixture was concentrated to ca. half volume, diluted with 200 mL of water, treated with activated charcoal, and filtered. The filtrate was acidified with 10% HCl and extracted with EtOAc, and the extract was washed with water and brine. After drying (Na_2SO_4) and evaporation of solvents, crystallization from ether–hexane provided 14.7 g (84%) of *ent*-20, mp 137.5–138.5 °C, $[\alpha]_D$ +87.8° (0.856% MeOH). Anal. Calcd for $C_{11}H_{10}O_3$: C, 69.46; H, 5.30. Found: C, 69.38; H, 5.27.

(3a*S*)-3aα,4,7,7aα-Tetrahydro-4α,7α-methano-1*H*-inden-1-one (*ent*-21).[8] Using a 170 °C bath, a solution of 14.29 g of *ent*-20 in 10 mL of DMF was refluxed 10 min from the time gas evolution started. After cooling, the mixture was diluted with water and extracted with hexane. The extract was washed with 5% $NaHCO_3$, water, and brine. After drying (Na_2SO_4), solvents were removed and the residue was chromatographed (flash, hexane–ether, 9:1). Crystallization from hexane gave 6.35 g (58%) of *ent*-21, mp 76–77 °C, $[\alpha]_D$ –150.0° (0.954% CH_2Cl_2), lit.[22] mp 59–60 °C, $[\alpha]_D$ –152°. Anal. Calcd for $C_{10}H_{10}O$: C, 82.16; H, 6.90. Found: C, 82.30; H, 7.04. A second crop of 1.12 g had mp 60–61 °C and $[\alpha]_D$ –95.1° (0.983% CH_2Cl_2). The combined aqueous layers were acidified with 10% HCl and extracted with EtOAc. The extract was washed with water and brine. After drying (Na_2SO_4) and evaporation of solvents, flash chromatography (hexane–EtOAc, 1:1) gave a crude fraction, which was crystallized from ether–hexane to give 1.28 g, mp 124–137 °C. After esterification with diazomethane, LPLC (hexane–EtOAc, 85:15) gave partial separation of two minor impurities. The impurity preceding the main fraction (*ent*-36) was crystallized from ether–hexane to give 80 mg of methyl (3aα,4,7,7aα)-tetrahydro-1-oxo-4α,7α-methano-1*H*-indene-3-carboxylate ((±)-35), mp 102–103 °C. Anal. Calcd for $C_{12}H_{12}O_3$: C, 70.58; H, 5.92. Found: C, 70.42; H, 6.01. Closely following the main fraction was a minor product, which crystallized from ether to give 9 mg of methyl 2,3-dihydro-1-oxo-1*H*-indene-5-carboxylate,[26] mp 114–115 °C, lit.[27] mp 115–117 °C: ^{13}C NMR 25.5, 36.3, 52.3, 123.4, 127.9, 128.3, 135.2, 140.0, 154.5, ~167, 206.0; ^1H NMR 2.76 (m, 2 H), 3.21 (m, 2 H),

(25) The NMR analysis was based on the relative peak heights for a methylene carbon at ca. 36.3 ppm in isomers 17 and *ent*-17 vs 35.6 ppm in isomers 18 and *ent*-18, and a methine carbon at ca. 40.1 ppm in isomers 17 and *ent*-17 vs 40.5 ppm in isomers 18 and *ent*-18.

(26) We cannot be certain that this small quantity of material did not arise from a trace impurity in the starting material.

(27) Aono, T.; Imanishi, M.; Kawano, Y.; Kishimoto, S.; Noguchi, S., *Chem. Pharm. Bull.* **1978**, *26*, 2475–2482.

3.97 (s, 3 H), 7.81 (d, J = 8 Hz, 1 H), 8.04 (dd, J = 8, 1 Hz, 1 H), 8.17 (d, J = 1 Hz, 1 H). Anal. Calcd for $C_{11}H_{10}O_3$: C, 68.46; H, 5.30. Found: C, 68.49; H, 5.43.

(3a*R*,3aα,7aα)-Octahydro-4α,7α-methano-1*H*-inden-1-one (22). A solution of 5.65 g of **21**[8] in 50 mL of THF was hydrogenated over a small amount of W-2 Raney nickel at atmospheric pressure and 25 °C over 2 h. After removing the catalyst and distillation of the solvent, flash chromatography (hexane–ether, 4:1) provided 5.21 g (90%) of **22**, a waxy solid, $[\alpha]_D$ +260.5° (0.925% hexane). Anal. Calcd for $C_{10}H_{14}O$: C, 79.96; H, 9.39. Found: C, 79.76; H, 9.44.

(3a*S*)-3aα,4,5,6,7,7aα-Hexahydro-3-methyl-4α,7α-methano-1*H*-indene (24). To a solution of 9.8 mL (8.38 g, 59.4 mmol) of *N*-isopropylcyclohexylamine in 45 mL of THF at −78 °C was added 41.7 mL (59.6 mmol) of 1.43 M *n*-butyllithium in hexane. After stirring for 45 min, a solution of 8.05 g (53.7 mmol) of **22** in 35 mL THF was added. After 2 h at −78 °C, a solution of 21.29 g (59.6 mmol) of *N*-phenyltrifluoromethanesulfonimide in 60 mL of THF was added, and the mixture was stirred at 0 °C for 16 h. After the addition of 100 mL of water, the product was extracted with hexane, and the extracts washed with water and brine. After evaporation of solvents the residue was chromatographed (Flash, hexane) to provide 9.0 g of crude (3a*S*)-3aα,4,5,6,7,7aα-hexahydro-4α,7α-methano-1*H*-inden-3-yl trifluoromethanesulfonate (**23**), $[\alpha]_D$ −14.6° (1.012% hexane). A solution of this material in 5 mL of ether was added to a −30 °C solution of lithium dimethylcuprate prepared from a slurry of 7.26 g (38.1 mmol) of copper iodide in 25 mL ether at −78 °C and 64.6 mL (76.2 mmol) of 1.18 M methyllithium–lithium bromide complex in ether. The mixture was maintained at −20 °C for 20 h and then 5 mL of methyl iodide was added. After being warmed to 20 °C, 100 mL of saturated NH_4Cl and a small amount of NH_4OH were added. After being stirred at room temperature for 20 h, the mixture was extracted with hexane, and the extracts were washed with water and brine and dried (Na_2SO_4). After concentrating the solution, chromatography (flash, hexane) provided 4.17 g of a mixture of **24** and (3a*R*)-3aα,4,5,6,7,7a-hexahydro-4α,7α-methano-1*H*-indene[5] (**25**) (4:1).

(3aβ,7aβ)-Octahydro-(1*S*)-1α-methyl-4β,7β-methano-2*H*-inden-2-one (5). To a solution of 4.17 g of crude **24** (above) in 34 mL of THF at 0 °C was added 20 mL of 2 M borane–methyl sulfide complex in THF. The mixture was allowed to warm to room temperature and stirred for 3 h. After again cooling to 0 °C, 10 mL of water and 40 mL of 1 N NaOH were added, followed by 20 mL of 30% hydrogen peroxide. The mixture was allowed to warm to room temperature and stirred for 45 min more. After the addition of 50 mL of 20% Na_2CO_3, the products were extracted with ether, and the extracts were washed with water and brine. After drying (Na_2SO_4), solvents were evaporated and the residue amounted to 5.16 g of crude (3aβ,7aβ)-octahydro-(1*R*)-1α-methyl-2β-hydroxy-4β,7β-methano-2*H*-indene (**26**). A solution of this material in 50 mL of acetone was chilled in an ice bath. Jones reagent was added until a slight excess persisted (ca. 10 mL). After dilution with 200 mL of water, the mixture was extracted with ether, and the extracts were washed with water, 5% $NaHCO_3$, and brine. After removal of solvents, chromatography (flash, hexane–ether, 98:1) provided 2.35 g of **5**, $[\alpha]_D$ +20.2° (1.107% hexane), CD $[\Theta]_{302}$ +2670. Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.23; H, 9.79. This was followed by a mixture of (3aα,7aα)-octahydro-4α,7α-methano-1*H*-inden-1-one (**22**) and (3aα,7aα)-octahydro-4α,7α-methano-2*H*-inden-2-one (**1**).[5]

Optical Purity Test of 5. A solution of 240 mg of **5**, 300 mg of butane-2(*R*),3(*R*)-diol, and 5 mg of CSA in 20 mL of benzene was refluxed under a 20-cm Vigreaux column for 6 h, distilling out about half the volume at the end. After cooling, a few drops of Et_3N were added and the mixture was concentrated to a small residue. Flash chromatography (hexane–Et_2O, 49:1) provided 150 mg of a ketal fraction, which contained only **18** by ^{13}C NMR analysis.[25] Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.23; H, 10.24. Found: C, 76.15; H, 10.31. This was followed by 27 mg of **2** and then 103 mg of recovered **5**. Hydrolysis of **18** with oxalic acid as described above provided 93 mg of **2**, $[\alpha]_D$ −21.4° (0.823% hexane), CD $[\Theta]_{296}$ −2600. Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.17; H, 9.69.

(4aβ,8aβ)-Octahydro-(1*S*)-1α-methyl-5β,8β-methano-3*H*-2-benzopyran-3-one (27). A solution of 1.53 g (9.4 mmol) of **5** and 2.47 g (12 mmol) of 85% MCPBA in 20 mL of methylene chloride was stirred at room temperature for 5 days. The solid was removed by filtration, rinsing well with hexane. The filtrate was evaporated and the residue chromatographed (flash, hexane–EtOAc, 9:1 to 4:1) to provide 0.38 g (25%) of recovered **5**, followed by 0.74 g (44%) of **27**, $[\alpha]_D$ −73.9° (1.088% hexane). Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.31; H, 9.08.

(4aβ,8aβ)-Octahydro-(1*S*)-1α-methyl-5β,8β-methano-1*H*-2-benzopyran-3-ol (28). To a solution of 740 mg (4.11 mmol) of **27** in 5 mL of toluene at −78 °c was added 10.3 mL of 1 M DIBAL in toluene. After 4 h at −78 °C, 30 mL of MeOH was added and the mixture was allowed to warm to room temperature. After 2 h the solids were removed by filtration, rinsing thoroughly with MeOH. The filtrate was evaporated and the residue chromatographed (flash, hexane–EtOAc, 7:3) to provide 620 mg (83%) of **28**, $[\alpha]_D$ −21.3° (0.588% hexane). Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.26; H, 10.07.

7-[3β-(1(*R)-Hydroxyethyl)-(1*R*,1α,4α)-bicyclo[2.2.1]-hept-2β-yl]-5(*Z*)-heptenoic Acid (29) and 7-[3β-(1(*R**)-hydroxyethyl)-(1*R*,1α,4α)-bicyclo[2.2.1]hept-2β-yl]-5(*E*)-heptenoic Acid (30).** To a suspension of 3.02 g (6.8 mmol) of (4-carboxybutyl)triphenylphosphonium bromide in 20 mL of THF was added 13.6 mL of 1 M sodium bis(trimethylsilyl)amide in THF. After 18 h of stirring at room temperature, the mixture was cooled in an ice bath and a solution of 0.62 g (3.4 mmol) of **28** in 20 mL of THF was added. After 4 h the mixture was allowed to warm to room temperature for 20 h more and then 20 mL of water was added. The aqueous layer was separated and acidified with 10% HCl. The products were extracted with ether, and the extract was washed with water and brine. After drying (Na_2SO_4) and evaporation of solvent, repeated LPLC (hexane–EtOAc, 3:2) provided first 70 mg (8%) of **30**. Anal. Calcd for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84. Found: C, 72.03; H, 9.76. After an overlap fraction of 20 mg, 400 mg (44%) of **29** was obtained. Anal. Calcd for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84. Found: C, 71.93; H, 9.64.

7-(3α-Acetyl-(1*R*,1α,4α)-bicyclo[2.2.1]hept-2β-yl)-5(*Z*)-heptenoic Acid (13). A solution of 360 mg (1.35 mmol) of **29** in 12 mL of acetone was chilled in an ice bath and about 1 mL of Jones reagent was added until a slight excess persisted. After dilution with 20 mL of water, extraction with ether, washing with water and brine, and drying (Na_2SO_4), evaporation of solvents left a residue of 340 mg. This material was dissolved in 15 mL of 1 N NaOH. After 1 h at room temperature the solution was acidified with 10% HCl and extracted with ether. The extract was washed with water and brine, dried (Na_2SO_4), and evaporated to dryness. Chromatography on acidic silica (hexane–EtOAc, 4:1) provided 160 mg (45%) of **13**, $[\alpha]_D$ −21.1° (0.989% CH_2Cl_2). Anal. Calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.53; H, 9.07.

7-(3α-Acetyl-(1*R*,1α,4α)-bicyclo[2.2.1]hept-2β-yl)-5(*E*)-heptenoic Acid (14). A solution of 62 mg (0.26 mmol) of **30** in 3 mL of acetone was chilled in an ice bath and titrated with Jones reagent (ca. 0.08 mL). After dilution with water, the mixture was extracted with ether, which was washed with water and brine and dried (Na_2SO_4). Evaporation of solvent left a residue of 80 mg. This material was dissolved in 1.5 mL of 1 N NaOH. After 1 h at room temperature the solution was acidified with 5% HCl, the product was extracted with ether, and the extract was washed with water and brine. After drying (Na_2SO_4) and evaporation of solvents, chromatography on acidic silica gave 40 mg (65%) of **14**, $[\alpha]_D$ −17.2°. Anal. Calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.43; H, 8.98.

7-[3α-[1-[[(Phenylamino)thioxomethyl]hydrazono]-ethyl]-(1*R*,1α,4α)-bicyclo[2.2.1]hept-2β-yl]-5(*Z*)-heptenoic Acid (15). A solution of 140 mg (0.53 mmol) of **13** and 106 mg (0.64 mmol) of 4-phenyl-3-thiosemicarbazide in 0.6 mL of pyridine was stirred at room temperature for 20 h. A solution of the mixture in 20 mL of methylene chloride was washed twice with 20 mL of 5% HCl, water, and brine. After drying (Na_2SO_4) and evaporation of solvent, the residue was chromatographed on acidic silica (hexane–EtOAc, 4:1) to provide 160 mg (73%) of **15**, $[\alpha]_D$ −113.1° (0.946% CH_2Cl_2). Anal. Calcd for $C_{23}H_{31}N_3O_2S$: C, 66.80; H, 7.55; N, 10.16; S, 7.75. Found: C, 66.69; H, 7.64; N, 10.10; S, 7.63.

7-[3α-[1-[[(Phenylamino)thioxomethyl]hydrazono]-ethyl]-(1*R*,1α,4α)-bicyclo[2.2.1]hept-2β-yl]-5(*E*)-heptenoic Acid (16). A solution of 38 mg (0.15 mmol) of **14** and 30 mg (0.18

mmol) of 4-phenyl-3-thiosemicarbazide in 0.4 mL of pyridine was stirred at room temperature for 20 h. A solution of the mixture in 20 mL of methylene chloride was washed twice with 20 mL of 5% HCl, water, and brine. After drying (Na_2SO_4) and evaporation of solvent, the residue was chromatographed on acidic silica (hexane–EtOAc, 4:1) to provide 40 mg (67%) of **16**, $[\alpha]_D$ −75.0° (1.002% CH_2Cl_2). Anal. Calcd for $C_{23}H_{31}N_3O_2S$: C, 66.80; H, 7.55; N, 10.16; S, 7.75. Found: C, 66.50; H, 7.55; N, 10.09; S, 7.68.

(3aβ,7aβ)-Octahydro-(1*R*)-1α-methyl-4β,7β-methano-2*H*-inden-2-one (*ent*-5). In a manner similar to that for the preparation of **5**, *ent*-**21** was converted via *ent*-**22**, *ent*-**23**, *ent*-**24**, and *ent*-**26** to *ent*-**5**. Preparation of a ketal with butane-2(*S*),3(*S*)-diol as above provided a sample containing only ketal *ent*-**18** by ^{13}C NMR analysis.[25]

(3aα,7aα)-Octahydro-(1*S*)-1α-methyl-4α,7α-methano-2*H*-inden-2-one (*ent*-2). A solution of 278 mg of *ent*-**5**, 1 mL of butane-2,3-diol (mixture of isomers) and 5 mg of CSA in 25 mL of benzene was refluxed under a Dean–Stark trap for 40 h. After adding 0.5 mL of Et_3N and concentration of the resulting solution, the residue was passed through a short flash column with hexane to provide a total ketal fraction, **31**, of 387 mg. This material and 400 mg of oxalic acid dihydrate were stirred in 10 mL of MeOH and 2 mL of water for 20 h. After dilution with 20 mL of 5% $NaHCO_3$, the mixture was extracted with hexane, and the extract was washed with 5% $NaHCO_3$, water, and brine. After removal of solvents, the residue consisted of 240 mg of *ent*-**2**, $[\alpha]_D$ +21.3°. Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.33; H, 9.68.

7-[3α-[1-[[(Phenylamino)thioxomethyl]hydrazono]-ethyl]-(1*S*,1α,4α)-bicyclo[2.2.1]hept-2β-yl]-5(*Z*)-heptenoic Acid (*ent*-15). In a manner similar to that for the preparation of (±)-**13**, 240 mg of *ent*-**2** was converted to 250 mg of a mixture of *ent*-**13** and *ent*-**14** (9:1). After esterification with diazomethane, chromatography (LPLC, Woelm CH_2Cl_2–acetone, 199:1) provided 27 mg of the pure methyl 7-(3α-acetyl-(1*S*,1α,4α)-bicyclo-[2.2.1]hept-2β-yl)-5(*Z*)-heptenoate, followed by a mixture of this and the 5*E* isomer. Saponification of the pure material provided 20 mg of 7-(3α-acetyl-(1*S*,1α,4α)-bicyclo[2.2.1]hept-2β-yl)-5-(*Z*)-heptenoic acid (*ent*-**13**). In the same manner as in the preparation of **15**, this material provided 22 mg of *ent*-**15**.

Inversion of *ent*-21 to 21. To a solution of 2.76 g (18.9 mmol) of *ent*-**21** in 20 mL of acetone at 0 °C was added 3 mL of 20% Na_2CO_3, followed by 6 mL of 30% hydrogen peroxide. The mixture was allowed to warm to room temperature over 1 h. After dilution with water, the product was extracted with ether, washed with water and brine, and dried (Na_2SO_4). Evaporation of solvents left 2.72 g (89%) of (1a*R*)-1aα,1bβ,2,5,5aβ,6aα-hexahydro-2β,5β-methano-6*H*-indeno[1,2-*b*]oxiren-6-one (**37**) as a soft solid, $[\alpha]_D$ −180.9° (1.000% CH_2Cl_2), CD $[\theta]_{321}$ +2070, $[\theta]_{287}$ −406. Anal. Calcd for $C_{10}H_{12}O_2$: C, 74.06; H, 6.21. Found: C, 74.07; H, 6.20. A solution of this material in 10 mL of MeOH was chilled in an ice bath while 2 mL of hydrazine hydrate and then 0.15 mL of acetic acid were added. The bath was removed and the temperature rose slowly to 20 °C and then quickly (5 min) with gas evolution to 60 °C. After 30 min more, the mixture, which had cooled, was diluted with 50 mL of water and extracted with ether, washing with 5% HCl, 5% $NaHCO_3$, and brine. After drying (Na_2SO_4) and removal of solvents, the residue was chromatographed (flash, hexane–ether, 1:1) and the product fraction crystallized from hexane to provide 1.27 g (51%) of (3a*R*)-3aα,4,7,7aα-tetrahydro-4α,7α-methano-1(*H*)-inden-1α-ol (**38**), mp 72–73 °C, $[\alpha]_D$ +97.3° (1.059% CH_2Cl_2), lit.[22] mp 72.5–73 °C, $[\alpha]_D$ +99.1°. Anal. Calcd for $C_{10}H_{12}O$: C, 81.04; H, 8.16. Found: C, 80.93; H, 8.23. A solution of this material in 40 mL of acetone at −10 °C was treated with a slight excess of Jones reagent. The mixture was diluted with water and extracted into ether. After being washed with 5% HCl, 5% $NaHCO_3$, and brine, the solution was dried (Na_2SO_4) and evaporated. After flash chromatography (hexane–ether, 4:1), the product was crystallized from hexane to provide 0.94 g (75%) of **21**, mp 76–77 °C, $[\alpha]_D$ +148.7° (1.010% CH_2Cl_2).

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Registry No. **1**, 19138-60-4; (±)-**2**, 129521-18-2; *ent*-**2**, 129569-35-3; **2**, 129569-36-4; (±)-**4**, 129521-19-3; (±)-**5**, 129521-20-6; **5**, 129569-37-5; *ent*-**5**, 129569-38-6; (±)-**6**, 129521-21-7; (±)-**7**, 129521-22-8; **7**, 129569-39-7; *ent*-**7**, 129569-40-0; (±)-**8**, 129521-23-9; (±)-**9**, 129569-41-1; (±)-**10**, 129569-42-2; (±)-**11**, 129569-43-3; (±)-**12**, 129569-44-4; (±)-**13**, 76945-61-4; **13**, 129569-45-5; *ent*-**13**, 129569-46-6; (±)-**14**, 129569-47-7; **14**, 129569-48-8; (±)-**15**, 96384-09-7; **15**, 129569-49-9; *ent*-**15**, 129569-50-2; **16**, 129569-51-3; **17**, 129521-24-0; *ent*-**17**, 129569-52-4; **18**, 129569-53-5; *ent*-**18**, 129569-54-6; (±)-**19**, 121312-57-0; *ent*-**19**, 129569-55-7; **20**, 105469-25-8; *ent*-**20**, 105500-36-5; (±)-**20**, 129645-61-0; **21**, 105500-35-4; *ent*-**21**, 111136-75-5; **22**, 129569-56-8; *ent*-**22**, 129569-57-9; **23**, 129521-25-1; *ent*-**23**, 129521-26-2; **24**, 129521-27-3; *ent*-**24**, 129521-28-4; **25**, 129569-58-0; *ent*-**25**, 129569-59-1; **26**, 129521-29-5; *ent*-**26**, 129521-30-8; **27**, 129569-60-4; **29**, 129569-61-5; **30**, 129569-62-6; **31**, 129521-31-9; **34**, 129521-32-0; (±)-**35**, 129539-54-4; *ent*-**36**, 111057-56-8; **37**, 129569-63-7; **38**, 105367-92-8; (4-carboxybutyl)triphenylphosphonium bromide, 17814-85-6; 4-phenyl-3-thiosemicarbazide, 5351-69-9; methyl 2,3-dihydro-1-oxo-1*H*-indene-5-carboxylate, 68634-02-6.

Supplementary Material Available: Full details of experiments leading to 90% ee **15** and *ent*-**15** as well as those leading to pure *ent*-**15** and the preparation of **21** by the method of Zwanenburg,[8] additional conformation depictions of ketones, ketone hydrates, Baeyer–Villager intermediates, and lactones, and carbon and proton NMR data and assignments of all compounds (30 pages). Ordering information is given on any current masthead page.