Benzindene Prostaglandins. Synthesis of Optically Pure 15-Deoxy-U-68,215 and Its Enantiomer via a Modified Intramolecular Wadsworth-Emmons-Wittig Reaction

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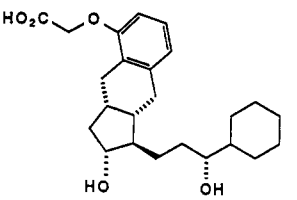
The optically pure [[1(*R*)-(3-cyclohexylpropyl)-2,3,3a,4,9,9a-hexahydro-2(*R*)-hydroxy-(3a*S*,9a*S*)-1*H*-benz[*f*]-inden-5-yl]oxy]acetic acid (**2a**) and its 1,2,3a,9a-tetraepi isomer (**2b**), 15-deoxy analogues (prostaglandin numbering) of the potent antiulcer agent 1 (U-68,215), have been synthesized. The resolution of the optical isomers was accomplished by LC (liquid chromatography) separation of the 2(*RS*)-(*S*)-α-methylbenzyl carbamates **8a,b**, which were obtained from the racemic alcohols **7a,b**. The racemic alcohols **7a,b** were initially synthesized via condensation of the enol lactone **4** with the phosphonate **3c** followed by the catalytic hydrogenation and sodium borohydride reduction of the adduct **5**. A second and improved route involved the coupling reaction of the anion of the phosphonate **3c** and the enolate of the γ-keto ester **12a**, both generated in situ in the presence of the excess lithium diisopropylamide, to give cyclopentenone **5** directly in 75% yield. The absolute configuration of the resolved isomers **7a** and **7b** was confirmed by comparison with authentic samples which were synthesized independently via selective deoxygenation of the side chain hydroxyl group from **16a** and **16b**, prepared with known absolute configuration. The racemic alcohols **7a,b** and the resolved optically pure isomers **7a** and **7b** were then converted separately in three steps to the racemic analogue **2a,b** and the optically pure isomers **2a** and **2b**, respectively. The absolute configuration of the optically pure isomers **2a** and **2b** was further established by comparing with the authentic samples synthesized independently from the authentic alcohols **7a** and **7b**, prepared from **16a** and **16b**, respectively. Interestingly, most of the biological activity seemed to reside with **2b**, the "unnatural" isomer in terms of prostaglandin analogues.

Introduction

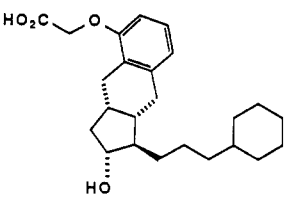
A benzindene prostaglandin analogue with a cyclohexyl side chain (**1**, U-68,215) was recently shown by us to be a potent antiulcer agent.[1,2] Moreover, unlike most prostaglandin analogues of interest in the gastrointestinal area, this compound is considerably more stable and exhibits no enteropooling, uterotonic, or gastrointestinal mucosa cellular proliferative activity.[1] However, it does have significant cardiovascular effects which could limit its therapeutic utility in antiulcer therapy. We were therefore interested in synthesizing some selected analogues of **1** in hopes of completely separating out the cardiovascular activity while maintaining the potent antiulcer behavior. The side chain deoxy analogue of **1** was chosen as one of the analogues to examine this possibility and was initially prepared in racemic form for the initial biological screening. Encouragingly, the racemate **2a,b** was found to demonstrate significant cytoprotective and gastric antisecretory activity while having only minor effects on blood pressure. However, unlike the corresponding dihydroxy analogue **1**, the racemic analogue **2a,b** exhibited enteropooling (the accumulation of fluid in the small intestine, an index of the diarrheogenic activity of prostaglandin) activity. We therefore set out to synthesize the optically pure isomer **2a** with natural configuration and its enantiomer (**2b**). The biological activity of each isomer, then, would enable us to determine which component of the racemate was responsible for the desirable cytoprotective/antisecretory activity and which one contributed to the undesirable enteropooling activity.

Results and Discussion

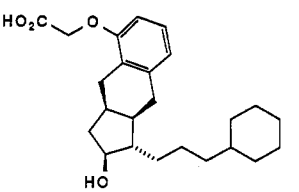
The synthesis of the racemic side chain deoxy analogue **2a,b** was accomplished in a straightforward manner as shown in Scheme I. Bromination of alcohol **3a** followed by displacement of the bromide **3b** with the anion of diethyl phosphite afforded the phosphonate reagent **3c** in 78% overall yield. The anion of this phosphonate, **3d**, generated in situ by reacting **3c** with 1 equiv of *n*-butyllithium at −78 °C, was coupled with 0.5 equiv of enol lactone **4**.[2] When the reaction mixture was warmed to room temperature, protonated with 0.5 equiv of acetic acid, and heated, the coupled product undergoes the intramolecular Wadsworth-Emmons-Wittig reaction to give cyclopentenone derivative **5** in 68% yield. A similar transformation has already been described in detail in the synthesis of the dihydroxy analogue **1**.[2] As shown in Scheme II, the mechanism of the coupling reaction of the enol lactone **4** with 2 equiv of the phosphonate anion **3d** proceeds via the initial adduct **13a**, a hemiketal intermediate which collapses to intermediate **13b**, which rapidly reacts with excess phosphonate anion **3d** to generate the dianion **13d**. Addition of 1 equiv of acetic acid (against 2 equiv of base used) as an external proton source upon warming to room temperature generates the monoanion **13e**. This monoanion undergoes an intramolecular Wadsworth-Emmons-Wittig reaction upon heating at 65



1 (U-68,215)



2a



2b

(1) Robert, A.; Aristoff, P. A.; Wendling, M. G.; Kimball, F. A.; Miller, W. L.; Gorman, R. R. *Prostaglandins* **1985**, *30*, 619.
(2) Aristoff, P. A.; Johnson, P. D.; Harrison, A. W. *J. Am. Chem. Soc.* **1985**, *107*, 7967.

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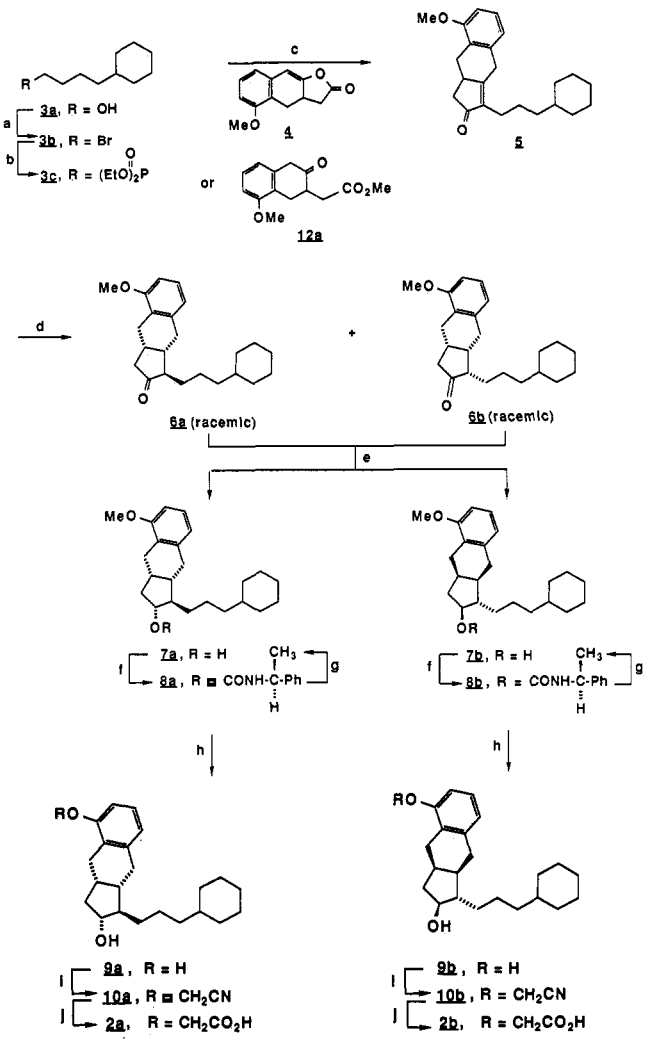
Scheme I[a]

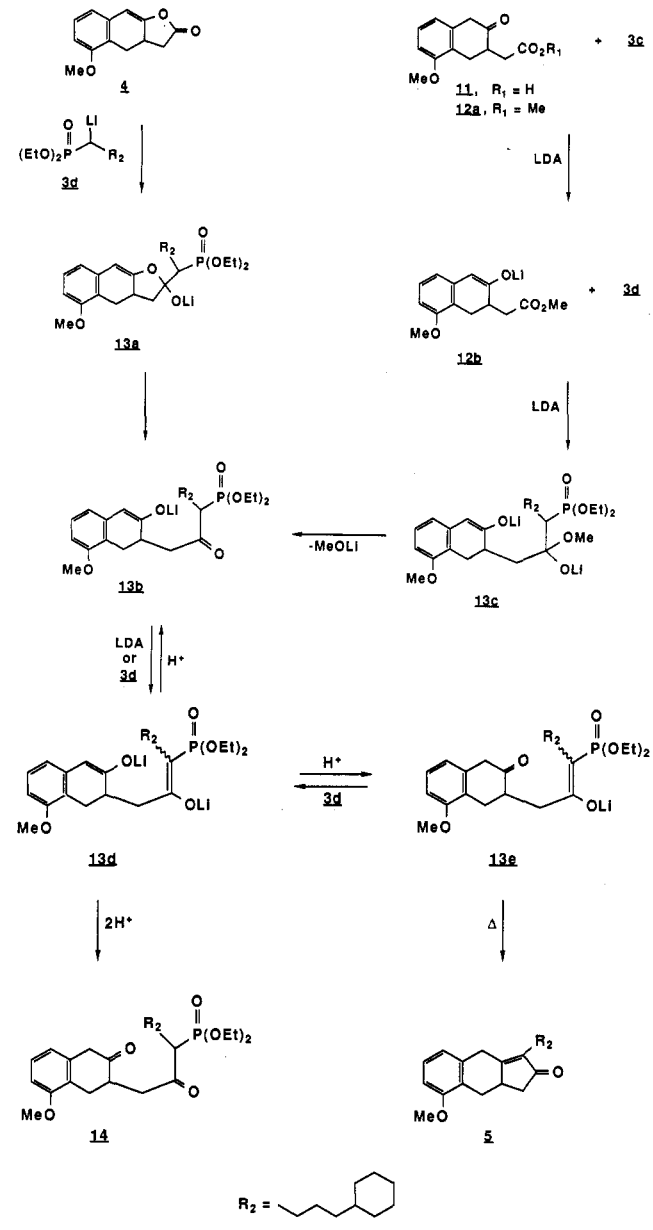


[a] (a) PBr_3, Δ; (b) $(EtO)_2P(O)Li$, THF, Δ; (c) 4 or **12a** (see Scheme II), base, THF; HOAc, Δ; (d) Pd/C, H_2, K_2CO_3, EtOH; (e) $NaOH/H_2O/EtOH/NaBH_4$, −10 °C; (f) phosgene, triethylamine, (*S*)-(−)-α-methylbenzylamine, toluene; (g) $LiAlH_4$/THF, Δ; (h) Ph_2PLi, THF, Δ; (i) K_2CO_3, $ClCH_2CN$, acetone, Δ; (j) KOH, EtOH, H_2O, Δ.

°C to give the desired cyclopentenone derivative **5**.

More recently, on the basis of this postulated mechanism, we have developed an improved process (Scheme II) which involves the direct coupling of the anion **3d** of the phosphonate **3c** and the lithium enolate **12b** of the γ-keto ester **12a**.[3] We rationalized that the enolate ester **12b** can also undergo a similar coupling reaction with the phosphonate anion **3d**. If the resulting coupled hemiketal intermediate, **13c**, suffers loss of lithium methoxide, intermediate **13b** would be obtained, which is then converted to **5** as described previously. This mechanistic consideration prompted us to try an in situ generation of both anions **3d** and **12b**. Since the enolate formation of the ketone is much faster than of the ester with a base such as lithium diisopropylamide, we decided to try this possibility. Thus, when 3 equiv of lithium diisopropylamide in tetrahydrofuran were added to a tetrahydrofuran solu-

Scheme II



tion containing 1 equiv of keto ester **12a**[3] and 1.5 equiv of phosphonate **3c** at −78 °C, followed by slow warming to room temperature, addition of 1.5–1.8 equiv of acetic acid, and heating at 65 °C, the desired cyclopentenone derivative **5** was isolated in 75% yield after chromatography. This result indicates that the deprotonation of **3c** and **12a** to form the phosphonate anion **3d** and the enolate anion **12b**, respectively, is much faster than the deprotonation to form the enolate of the ester in **12a**. Actually, when we monitored the reaction by quenching an aliquot with saturated aqueous ammonium chloride, 5–10 min after the addition of lithium diisopropylamide at −78 °C, the keto phosphonate **14** was isolated, indicating that the coupling reaction of **3d** and **12b** occurs rather rapidly. When the reaction was interrupted by quenching with excess acid before undergoing intramolecular Wadsworth–Emmons–Wittig reaction, i.e., before protonation with acetic acid and heating, the coupled product **14** was isolated in 75% yield after chromatography. This result shows that the intramolecular Wadsworth–Emmons–Wittig reaction (**13e** to **5**) is a high-yield process. Although the overall yield of this process, from the keto acid **11** to the enone **5** via the γ-keto ester **12a** (49%), is no better than the original

(3) The γ-keto ester **12a** used in the modified process was easily obtained in 66% yield from the keto acid **11**, which is the precursor to enol lactone **4** and an intermediate in the synthesis of 15-hydroxy analogue 1[2] (see Experimental Section). This successful conversion, in conjunction with the modified phosphonate chemistry described in this report, has provided the more viable and improved synthesis of the benzindene analogs.

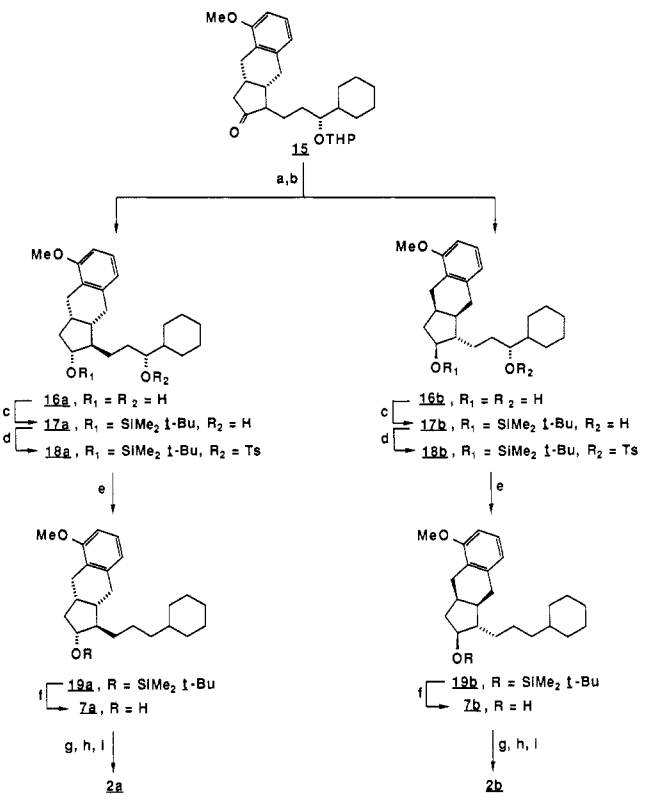
process via enol lactone (57%), in the large-scale preparation (>300 g), the process via the γ-keto ester has been found to have the following advantages: (1) the reproducibility of the conversion of the γ-keto ester **12a** to enone **5** was far better than the enol lactone **11**; (2) the conversion of the keto acid **11** to the γ-keto ester **12a** was much easier to accomplish on large scale than the conversion to the somewhat labile enol lactone, which required removal of large quantities of acetic anhydride in the workup; (3) when the resolved phosphonate is used for the condensation–cyclization, as in the case of synthesizing 15-hydroxy analogue **1**, there is a distinctive advantage in using less phosphonate for the reaction. Overall, this remarkable result indicates that this reaction is a potentially useful method for achieving the direct synthesis of cyclopentenone or cyclohexenone derivatives from γ- or δ-keto esters, respectively. We are currently examining the scope and limitations of this transformation.[4]

Hydrogenation of the enone **5** (Scheme I) using 10% palladium on carbon in ethanol with a catalytic amount of potassium carbonate present gave after 2 days at room temperature a difficultly separated mixture of the initial product **6b** (racemic) and its equilibrated isomer **6a** (racemic) in 80% yield (3:1 ratio of **6a** to **6b**). Apparently the long reaction time allowed significant equilibration of the initially formed product **6b** to **6a** in the presence of potassium carbonate. When the same hydrogenation was carried out with a different lot of 10% palladium on carbon, the hydrogenation was completed in 7 h, and the product ratio was reversed to 1:3 for **6a** to **6b**. Thus, the variations in activity of the catalyst play an important role in this hydrogenation reaction. The more active catalyst, however, also lowered the yield of **6a,b** to 73% and caused the formation of the side products such as overreduction to the alcohol (9%) and the deoxy compound (17%).

The mixture of racemic ketones **6a** and **6b** was converted directly in a one-pot operation to the racemic alcohol mixture **7a,b** in 84% yield by treatment with aqueous sodium hydroxide and sodium borohydride in ethanol. This reaction succeeds because whereas equilibration of **6b** to **6a** is fast, hydride reduction of **6b** is slow and that of **6a** is relatively fast.[2] The net effect is therefore that all of **6b** is converted to the racemic mixture of alcohols **7a,b**. Without resolution of the optical isomers **7a** and **7b**, initially the alcohol mixture **7a,b** was converted in three steps (90% overall yield) to the racemic 15-deoxy benzindene analogue **2a,b**, by using the same chemistry developed to prepare the parent 15-hydroxy compound **1**.[2] Thus, the alcohols **7a,b** were first demethylated with lithium diphenylphosphide in tetrahydrofuran (70 °C, 7 h) to give the diols **9a,b** in 95% yield.[5] The racemic diol mixture **9a,b** was then selectively alkylated with chloroacetonitrile in the presence of potassium carbonate in acetone (65 °C, 24 h) to afford the cyanomethyl ethers **10a,b** (99%). Finally, the hydrolysis of the cyano group was smoothly accomplished by heating **10a,b** in 25% aqueous potassium hydroxide in methanol or ethanol (90 °C, 5 h) in 97% yield. Thus, keto ester **12a** was converted in six steps and 46% overall yield to the racemic benzindene analogue **2a,b** (13 steps and 25% overall yield from 5-methoxy-2-tetralone).

For the synthesis of the optically active isomer **2a** with natural configuration and its enantiomer (**2b**), the resolution of the racemic mixtures at some stage of the synthesis was necessary. We decided to pursue the resolution of the racemic alcohols **7a,b** by reacting the alcohols with a chiral reagent and separating the diastereomers chromatographically. The absolute configuration of these two diastereomers was then determined by matching the HPLC peaks with the authentic diastereomer synthesized independently from the established route (vide infra). On an analytical scale, the carbamate formation from the racemic **7a,b**, and authentic **7a** and **7b** (vide infra), was initially carried out by using (*S*)-(−)-α-methylbenzyl isocyanate[6,7] in toluene at room temperature with dibutyltin acetate as the catalyst.[8] Apparently the catalyst was very effective for this transformation, and the reaction could be completed in 3–4 h at room temperature. Without this catalyst, however, refluxing in toluene for an extended period of time was required. From this analytical scale carbamate formation the absolute configuration of each carbamate was assigned by matching the HPLC peaks of the carbamates **8a** and **8b**, obtained from the authentic alcohols **7a** and **7b**, prepared from compounds of known configuration as shown in Scheme III. The less polar carbamate corresponded to the diastereomer **8a** and the more polar carbamate to the diastereomer **8b**. When the reaction was scaled-up for the synthesis, however, the reaction conditions to form carbamates **8a** and **8b** were altered to use the less expensive (*S*)-(−)-α-methylbenzylamine. Thus, the racemic alcohol mixture **7a,b** was reacted

Scheme III[a]



[a] (a) NaOH, H_2O, EtOH, $NaBH_4$, −10 °C; (b) HOAc–THF–H_2O (3:1.5:1), 45 °C, 3 h; (c) *t*-BDMSiCl, imidazole, THF; (d) TsCl, pyridine; (e) $LiAlH_4$, Et_2O; (f) HCl, 2-PrOH, H_2O; (g) Ph_2PLi, THF, Δ; (h) K_2CO_3, $ClCH_2CN$, acetone, Δ; (i) KOH, EtOH, H_2O, Δ.

(4) The direct conversion of a γ-keto ester with a hindered carbonyl group to a cyclopentenone derivative has also been reported, see: Haltman, R. L.; Vollhardt, K. P. C. *Tetrahedron Lett.* **1986**, 1461.

(5) Ireland, R. E.; Walba, D. M. *Tetrahedron Lett.* **1976**, 1071. See, for a useful review: Bhatt, M. V.; Kulkami, S. U. *Synthesis* **1983**, 249.

(6) Pirkle, W. H.; Hoekstra, M. S. *J. Org. Chem.* **1974**, *39*, 3904 and references cited therein.

(7) Morrison, J. D., Ed. In *Asymmetric Synthesis*; Academic: Orlando, 1983; Vol. 1, Chapter 6.

(8) Thomas, F.; Thorne, M. P. *Can. J. Chem.* **1976**, *54*, 24.

in toluene with phosgene, triethylamine, and the optically active amine, to form the mixture of carbamates **8a** and **8b**.[6] Preparative LC separation (liquid chromatography) afforded >99% pure **8a** and **8b** (see Experimental Section). Each of these carbamates **8a** and **8b**, was then converted back to the optically pure alcohols **7a** and **7b**, respectively, in 100% yield by treating the carbamates in tetrahydrofuran with lithium aluminum hydride. Each of these alcohols **7a** and **7b** was then converted in three steps, as described earlier for the synthesis of the racemic **2a,b**, to the optically pure **2a** and **2b**, respectively. These optically pure **2a** and **2b** showed physical properties identical with those of the racemic **2a,b** except for optical rotation and melting point (**2a,b**, mp 158–160 °C; **2a**, mp 133.5–135.5 °C; **2b**, mp 133.5–135.5 °C). The specific rotations of **2a** ($[\alpha]_D$ + 30.69°) and **2b** ($[\alpha]_D$ −28.16°) also showed **2a** and **2b** are enantiomers. The HPLC analyses also confirmed that **2a** and **2b** exhibited retention times identical with those of the authentic samples synthesized from the material with known absolute configuration.

The confirmation of the absolute configuration of **2a** and **2b** synthesized from the resolved alcohols **7a** and **7b** via chiral carbamates shown in Scheme I required the synthesis of authentic acids **2a** and **2b** for comparison. As shown in Scheme III, the 15-hydroxy intermediates **16a** and **16b** were synthesized from optically pure **15**[2] and separated during the course of the synthesis of **1**.[2] The diols **16a** (98.5% pure) and **16b** (>99% pure) were independently converted to alcohols **7a** and **7b**, respectively, via selective removal of the side chain hydroxyl group. These alcohols were then used as the reference for matching the peaks with the resolved alcohols **7a** and **7b**, thereby establishing the absolute configuration of each isomer. This selective removal was made possible based on the observation that the ring hydroxyl group was preferentially silylated over the side chain hydroxyl group. Thus, as shown in Scheme III, the diols **16a** and **16b** were therefore separately silylated using *tert*-butyldimethylsilyl chloride and imidazole in tetrahydrofuran.[9] The major products obtained were assigned as **17a** and **17b**, respectively. Each of these isomers was then subjected to tosylation (*p*-toluenesulfonyl chloride/pyridine) to give the tosylates **18a** and **18b** from **17a** and **17b**, respectively. The tosylates **18a** and **18b** were then treated with lithium aluminum hydride in ether to give the silyloxy products **19a** and **19b**, respectively. The removal of the silyl group from **19a** and **19b** in aqueous hydrochloric acid/2-propanol resulted in the formation of the authentic alcohols **7a** and **7b**, respectively. Alcohols **7a** and **7b** exhibited the opposite specific rotations but otherwise were spectroscopically and chromatographically identical. Finally, the alcohols **7a** and **7b** prepared from **16a** and **16b**, respectively, were converted to the authentic acids **2a** and **2b**, respectively, as previously described. The spectroscopic data, specific rotations, and retention times by HPLC of **2a** and **2b** obtained by the resolution process (Scheme I) matched the authentic acids **2a** and **2b** formed via the route shown in Scheme III.

The biological activities of the racemate **2a,b**, the "natural" isomer **2a**, and the "unnatural isomer" **2b** were tested orally in rats. The racemate **2a,b** was found to be cytoprotective (against ethanol-induced lesions, ED_{50} = 40 μg/kg), antiulcer (against aspirin-induced ulcers, ED_{50} = 35 μg/kg) and antisecretory (ED_{50} = 500 μg/kg). This racemate **2a,b** also did not lower blood pressure when given orally to anesthesized rats at 20 times the antisecretory ED_{50}. However, orally in rats, it was enteropooling (ED_{50} = 50 μg/kg) and diarrheogenic (ED_{50} < 150 μg/kg). When given subcutaneously, **2a,b** was not cytoprotective, enteropooling, nor antisecretory. Its two optical isomers, **2a** and **2b**, were also cytoprotective orally (ED_{50}'s = 65 and 15 μg/kg, respectively). Paradoxically, the isomer with an unnatural configuration, **2b**, was much more active than the isomer with a natural configuration, **2a** (antisecretory ED_{50}'s = 150 and 3000 μg/kg, respectively, for **2b** and **2a**). The unnatural isomer **2b** was also more enteropooling than the natural isomer **2a** when administered orally (ED_{50}'s = 50 and 2000 μg/kg, respectively). However, both were inactive at 5000 μg/kg when administered subcutaneously.

In conclusion, the synthesis of the racemic (**2a,b**) as well as the optically pure side chain deoxy analogue (**2a**) of a potent antiulcer agent **1** and its enantiomer (**2b**) has been achieved via the modification of the synthesis of **1** reported previously. The benzindene nucleus has been formed via a convergent cyclopentane annulation route, the key step either involving formation of **5** from enol lactone **4** or, via an improved process, from the keto ester **12a**. The synthesis of the optically pure isomers **2a** and **2b** has been achieved by resolving the intermediates **7a,b** via the preparative liquid chromatographic separation of their carbamates, **8a** and **8b**. The absolute configuration of each optically pure isomer has been established by comparing the physical and HPLC properties with the authentic samples, synthesized independently via deoxygenation from the side chain of the intermediates **16a** and **16b** with known configuration. It has also been found, for the first time, that the isomer with the "unnatural" configuration among the benzindene prostaglandin analogues has shown more potent biological activity than the isomer with the "natural" configuration.

Experimental Section[10]

1-Bromo-4-cyclohexylbutane (3b). To 8.1 mL (47 mmol) of 4-cyclohexyl-1-butanol (**3a**) was added dropwise 2.2 mL (23 mmol) of phosphorus tribromide. The mixture was stirred at 0 °C for 15 min, at room temperature for 2 h, and then at 100 °C for 1.5 h, cooled to 0 °C, quenched with 50 g of ice, diluted with 100 mL of brine, and extracted with ether. The organic layer was washed with brine, dried (Na_2SO_4), filtered, concentrated, and bulb-to-bulb distilled at 100 °C at 2 mmHg, to give 9.84 g (96%)

(9) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190. In this particular case, however, we found tetrahydrofuran to be a superior solvent to dimethylformamide for the selective silylation.

(10) All melting points were obtained with a Thomas-Hoover melting point apparatus and are uncorrected. The ^1H NMR spectra of chloroform-*d* solutions were obtained on a Varian EM-390 spectrometer operating at 90 MHz. Chemical shifts are reported in δ (parts per million) relative to internal tetramethylsilane. Combustion analyses, mass spectra (including high resolution), and infrared spectra (IR) were obtained by the Physical and Analytical Chemistry Unit of The Upjohn Company with IR spectra being obtained either on neat samples (oils) or on Nujol mulls (solids). GC/MS were obtained with a Hewlett-Packard 5992A GC/MS system. HPLC analyses were obtained with a Varian 5500 or 5560 HPLC chromatograph with appropriate columns and solvent systems. Optical rotations were measured by a Perkin-Elmer 241 polarimeter. Thin-layer chromatography (TLC) was conducted with silica gel GF plates (Analtech Uniplates). The TLC plates were visualized first by UV light (Mineralight UVS-11) and then sprayed with either 50% aqueous or methanolic sulfuric acid followed by heating. For the phosphonates, 0.5% zinc chloride/0.5% diphenylamine in acetone was used as the spraying agent. For flash chromatography and preparative liquid chromatography (LC), silica gel 60 (40–63 μm, E. Merck) was used. The liquid chromatography (LC) was performed either by various sizes of Michel-Miller columns (Ace Glass, Inc.) dry-packed with silica gel or by prepacked columns (E. Merck). The solvents were delivered by Milton-Ray pumps. For gravity column chromatography, silica gel 60 (63–200 μm, E. Merck) was used. The analyses of fractions were performed by TLC using an appropriate solvent or a mixture of solvents. All solvents were reagent grade or reagent grade distilled from glass (Burdick and Jackson). The dry solvents used in reactions, such as THF, DMF, and DMSO, were Burdick and Jackson brand high-purity solvents dried over 4-Å molecular sieves. All reactions were degassed and were conducted under an inert atmosphere.

of **3b** as a colorless liquid: ^{1}H NMR ($CDCl_3$, TMS) δ 3.43 (t, J = 7 Hz, 2 H), 2.3–0.6 (m, 17 H); IR (film) ν_{max} 732,648 cm^{-1}; high-resolution MS, m/z calcd for $C_{10}H_{19}{}^{79}Br$ (M^+) 218.0671, found 218.0664; R_f 0.54 (hexane).

Diethyl (4-Cyclohexylbutyl)phosphonate (3c). A solution of 6.7 mL (52 mmol) of diethyl phosphite in 400 mL of THF was cooled to −78 °C, and 36.4 mL (57 mmol) of *n*-butyllithium in hexane (1.57 M) was added dropwise. The resulting mixture was stirred at −78 °C for 30 min and at 0 °C for 30 min and then treated with 9.4 g (43 mmol) of 1-bromo-4-cyclohexylbutane (**3b**) in 50 mL of THF dropwise over 10 min. The resulting solution was stirred at room temperature for 1 h and at 60 °C for 4 h and then quenched with 500 mL of brine containing 40 mL of 1 N aqueous hydrochloric acid. The layers were separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated. The crude product was flash chromatographed on 200 g of silica gel 60, eluting with 1 L of 50%, 1 L of 60%, and 2 L of 70% ethyl acetate in hexane to give 9.6 g (81%) of **3c** as a colorless oil: ^{1}H NMR ($CDCl_3$, TMS) δ 4.13 (2 overlapping q, J = 7 Hz, J_{P-H} = 7 Hz, 4 H), 1.9–0.5 (m, including t at 1.33, 25 H); IR (film) ν_{max} 1392, 1244, 1229, 1164, 1098, 1059, 1032 cm^{-1}; high-resolution MS, m/z calcd for $C_{14}H_{29}O_3P$ (M^+) 276.1854, found 276.1852; R_f 0.14 (50% ethyl acetate/hexane). Anal. Calcd for $C_{14}H_{29}O_3P$: C, 60.84; H, 10.58. Found: C, 61.01; H, 10.96.

Methyl 5-Methoxy-2-oxo-1,2,3,4-tetrahydro-3-naphthaleneacetate (12a). The keto acid 11[2] (33.1 mmol) dissolved in 27 mL of acetonitrile was treated with a solution of anhydrous hydrochloric acid in methanol, prepared by adding 3.7 mL of acetyl chloride to 23 mL of methanol at 0 °C.[11] The mixture was stirred at room temperature for 3 h and then treated with 5.7 mL of water. The resulting mixture was stirred at room temperature overnight, quenched with saturated aqueous sodium bicarbonate to pH 5, and concentrated in vacuo. The residue was extracted with ethyl acetate, and the organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue (7.4 g) was purified by column chromatography on 200 g silica gel (63–200 μm), eluting with 15% ethyl acetate/hexane, and then recrystallized from *tert*-butyl methyl ether/hexane, to give in the first crop 4.93 g and in the second crop 0.5 g, with a total of 5.43 g (66%), of pure keto ester **12a** as a pale yellow solid: mp 71–72 °C; ^{1}H NMR ($CDCl_3$) δ 7.40–6.68 (m, 3 H), 3.84 (s, 3 H), 3.72 (s, 3 H), 3.72–2.32 (m, 7 H); IR (mull) 1731, 1709, 1588 cm^{-1}; high-resolution MS, m/z calcd for $C_{14}H_{16}O_4$ (M^+) 248.1049, found 248.1046, other ions at 217, 216, 188, 175, 174, 160, 146, 131, 115, 104, 91; R_f 0.35 (25% ethyl acetate/hexane). Anal. Calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50. Found: C, 67.50; H, 6.60.

(3a*RS*)-1-(3-Cyclohexylpropyl)-3,3a,4,9-tetrahydro-5-methoxy-2*H*-benz[*f*]inden-2-one (5). Method A. A solution of 496.5 mg (2.0 mmol) of keto ester **12a**, 829.1 mg (3.0 mmol) of phosphonate **3c**, and 10 mL of THF at −78 °C was treated dropwise over 1–2 h with 6.0 mmol of lithium diisopropylamide in 6 mL of 2:1 hexane/THF. The resulting light pink solution was stirred at −78 °C for 3 h and then at room temperature overnight, treated with 0.21 mL (3.6 mmol) of glacial acetic acid, and then heated to reflux (bath temperature, 70 °C). TLC analysis showed R_f 0.71, 0.66, and 0.21 for **12a**, **5**, and **14**, respectively, in 50% ethyl acetate/hexane. The phosphonate **3c** stayed at the origin in the same solvent system. After 7 h the mixture was cooled to 0–5 °C and quenched with 10% aqueous sodium bisulfate to pH 7–8. The THF was removed in vacuo, and the residue was extracted with ethyl acetate. The organic extract was washed with water, brine, and saturated aqueous sodium bicarbonate, dried (Na_2SO_4), filtered, and concentrated to give the crude product as a yellow oil. This oil was purified by liquid chromatography (LC), eluting with 2.8 L of 10% ethyl acetate/hexane and 3 L of ethyl acetate, to give 504.5 mg (74.5%) of pure cyclopentenone **5** as a near colorless oil and 220 mg (26.5%) of the recovered phosphonate **3c** as a light brown oil.

Method B. A solution of 2.17 g (7.85 mmol) of phosphonate **3c** and 150 mL of THF at −78 °C was treated with 5 mL (8.0 mmol) of 1.6 M *n*-butyllithium, in hexane, stirred at −78 °C for 1 h, and then treated dropwise with a solution of 0.80 g (3.7 mmol) of enol lactone **4**[2] in 20 mL of THF. The resulting mixture was stirred for 1 h at −78 °C and 2 h while warming to 0 °C, then treated with 0.21 mL (3.6 mmol) of glacial acetic acid, stirred at 0 °C for 15 min and at 55–60 °C for 6 h, cooled to 0 °C, and quenched with 250 mL of brine containing 6 mL of 1 N aqueous hydrochloric acid. The layers were separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine/saturated aqueous sodium bicarbonate (3:1) and brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude product was flash chromatographed on 200 g of silica gel 60, eluting with 1 L 10%, 1 L 15%, 1 L 20%, 2 L 50%, and 2 L 75% ethyl acetate in hexane to give 0.855 g (68%) of pure **5** as a near colorless oil.

The physical properties of compound **5** were as follows: ^{1}H NMR ($CDCl_3$, TMS) δ 7.30–6.60 (m, 3 H), 3.87 (s, 3 H), 4.10–3.40 (m, 3 H), 3.10–0.60 (m, 21 H); IR (film) ν_{max} 1700, 1655, 1595 cm^{-1}; high-resolution MS, m/z calcd for $C_{23}H_{30}O_2$ (M^+) 338.2246, found 338.2252; R_f 0.50 and 0.66 (25% and 50% ethyl acetate/hexane, respectively). Anal. Calcd for $C_{23}H_{30}O_2$: C, 81.61; H, 8.93. Found: C, 81.66; H, 9.42.

Diethyl [1-(3-Cyclohexylpropyl)-2-oxo-3-(2-oxo-5-methoxy-1,2,3,4-tetrahydro-3-naphthyl)propyl]phosphonate (14). The reaction was run in an identical manner as in the previous experiment (method A) for the preparation of cyclopentenone **5**. However, the reaction was interrupted by quenching with 10% aqueous sodium bisulfate (to pH 7) after the reaction mixture was stirred overnight at room temperature rather than treating with acetic acid and heating. The reaction mixture was then extracted with ethyl acetate, and the organic extract was washed with saturated sodium bicarbonate and brine, dried (Na_2SO_4), filtered, and concentrated in vacuo to give a brown oil. The oil was purified by LC on 200 g silica gel 60, eluting with 50% ethyl acetate/hexane to give 740.2 mg (75%) of **14** as a near colorless oil: ^{1}H NMR ($CDCl_3$, TMS) δ 7.34–6.65 (m, 3 H), 4.16 (quintet, J = 7 Hz, 4 H), 3.80 (s, 3 H), 3.78–0.78 (m, 25 H), 1.40 (t, J = 7 Hz, 6 H); IR (film) ν_{max} 1713, 1589, 1265, 1250 cm^{-1}; high-resolution MS, m/z calcd for $C_{27}H_{41}O_6P$ (M^+) 492.2641, found 492.2639; R_f 0.44 in 66% ethyl acetate/hexane. This material appeared to be unstable. The color of this oil turned to deep brown even though it was stored in the refrigerator at 0–5 °C.

1(*R*)-(3-Cyclohexylpropyl)-1,3,3a,4,9,9a-hexahydro-5-methoxy-(3a*S*,9a*S*)-2*H*-benz[*f*]inden-2-one and Its 1,3a,9a-Triepi Isomer (6a) and 1(*S*)-(3-Cyclohexylpropyl)-1,3,3a,4,9,9a-hexahydro-5-methoxy-(3a*S*,9a*S*)-2*H*-benz[*f*]inden-2-one and Its 1,3a,9a-Triepi Isomer (6b). A mixture of 1.37 g (4.05 mmol) of enone **5**, 490 mg of 10% palladium on carbon, and 50 mg (0.36 mmol) of anhydrous potassium carbonate in 75 mL of absolute ethanol was hydrogenated at 50 psi. After 46 h at room temperature, the mixture was filtered through a Celite pad, the pad being washed with ethyl acetate. The filtrate was concentrated in vacuo and then chromatographed on 100 g of silica gel 60, eluting with 10% ethyl acetate in hexane to give 1.10 g (80%) of 3:1 mixture of **6a** and **6b** as a colorless oil: ^{1}H NMR ($CDCl_3$, TMS) δ 7.30–6.60 (m, 3 H), 3.83 (s, 3 H), 3.30–0.60 (m, 26 H); IR (film) 1740, 1595 cm^{-1}; high-resolution MS, m/z calcd for $C_{23}H_{32}O_2$ (M^+) 340.2402, found 340.2427; R_f 0.55 (20% ethyl acetate/hexane). HPLC analyses were carried out by using a Varian 5560 with HP 3390A integrator, with Waters Resolve 3.9 × 150 mm column (5-μm SiO_2), eluting with 1% THF/hexane with 2 mL/min flow rate and detecting at 278 nm (0.05 AU/mV). Two peaks with retention times 5.80 and 6.60 min in a 3:1 ratio were assigned as **6a** and **6b**, respectively. Anal. Calcd for $C_{23}H_{34}O_2$: C, 81.15; H, 9.47; Found: C, 80.76; H, 9.55. When the hydrogenation was carried out by using a different lot of palladium on carbon, presumably more active, the reaction was completed in 7 h. The ratio was reversed to 1:3 for **6a** to **6b**, indicating the shorter reaction time gave nonequilibrated mixture in favor of the unnatural isomer **6b**.

1(*R*)-(3-Cyclohexylpropyl)-2,3,3a,4,9,9a-hexahydro-5-methoxy-(3a*S*,9a*S*)-1*H*-benz[*f*]inden-2(*R*)-ol and Its 1,2,3a,9a-Tetraepi Isomer (7a,b). A solution of 400 mg (1.17 mmol) of the mixture of **6a** and **6b**, 40 mL of absolute ethanol, and 4 mL of methylene chloride was cooled to −10 °C, treated with 8 mL of 10% aqueous sodium hydroxide, and stirred for 15 min, and 60 mg (1.59 mmol) of sodium borohydride was added.

(11) Fieser, L. F.; Fieser, M. In *Reagents for Organic Synthesis*; Vol. 1, p 11.

At 1, 3, and 6 h, an additional 60 mg (1.59 mmol) of sodium borohydride was added to the reaction mixture at −10 °C. After being stirred for an additional 2 h at −10 °C, the mixture was quenched with 2.9 mL of glacial acetic acid, diluted with 250 mL of brine, and extracted with ethyl acetate. The organic layers were combined, washed with saturated sodium bicarbonate and brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude product was purified by flash chromatography using 250 g of silica gel 60, eluting with 10% ethyl acetate/hexane, to give 373 mg (93%) of **7a,b** as a white oily solid: ^1H NMR ($CDCl_3$, TMS) δ 7.30–6.60 (m, 3 H), 3.83 (s, 3 H), 3.96–3.34 (m, 1 H), 2.90–0.60 (m, 27 H); IR (film) 3350, 1595 cm^{-1}; high-resolution MS, m/z calcd for $C_{23}H_{34}O_2$ (M^+) 342.2599, found 342.2547; R_f (20% ethyl acetate/hexane). Anal. Calcd for $C_{23}H_{34}O_2$: C, 80.65; H, 10.01; Found: C, 80.70; H, 10.23.

1(*R*)-(3-Cyclohexylpropyl)-2,3,3a,4,9,9a-hexahydro-(3a*S*,9a*S*)-1*H*-benz[*f*]indene-2(*R*),5-diol and Its 1,2,3a,9a-Tetraepi Isomer (9ab). A solution of 0.9 mL of diphenylphosphine and 30 mL of THF at 0 °C was treated with 3.2 mL (5.1 mmol) of *n*-butyllithium (1.6 M in hexane). After the mixture was stirred for 30 min, 557 mg (1.6 mmol) of **7a,b** in 10 mL of THF was added, and the resulting mixture was heated at 70 °C for 7 h, then cooled to 0 °C, treated with an additional 0.9 mL (5 mmol) of diphenylphosphine and 3.2 mL (5.2 mmol) of *n*-butyllithium in hexane, and stirred at room temperature for 30 min and then at 70 °C for 18 h. The mixture was then cooled to 0 °C, diluted with 100 mL of brine containing 10 mL of 1 N aqueous hydrochloric acid, and extracted with ethyl acetate. The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude product was purified by flash chromatography on 200 g of silica gel 60, eluting with 5% acetone/methylene chloride to give 509 mg (95%) of **9a,b** as a white foam: ^1H NMR ($CDCl_3$, TMS) δ 7.20–6.50 (m, 3 H), 3.90–3.40 (m, 1 H), 2.90–0.50 (m, 28 H); IR (mull) 3430, 3160, 1600 cm^{-1}; high-resolution MS, m/z calcd for $C_{22}H_{32}O_2$ (M^+) 328.2402, found 328.2409; R_f 0.24 (5% acetone/methylene chloride). Anal. Calcd for $C_{22}H_{32}O_5$: C, 80.44; H, 9.82; Found: C, 80.09; H, 10.14.

[[1(*R*)-(3-Cyclohexylpropyl)-2,3,3a,4,9,9a-hexahydro-2-(*R*)-hydroxy-(3a*S*,9a*S*)-1*H*-benz[*f*]inden-5-yl]oxy]acetonitrile and Its 1,2,3a,9a-Tetraepi Isomer (10a,b). A mixture of 450 mg (1.37 mmol) of **9a,b**, 1.8 mL (28 mmol) of chloroacetonitrile, 2.2 g (16 mmol) of anhydrous potassium carbonate, and 20 mL of acetone was heated at 65 °C for 24 h, then cooled, diluted with brine, and extracted with ethyl acetate. The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude product was purified by flash chromatography on 200 g of silica gel 60, eluting with 25% ethyl acetate/hexane, to give 498 mg (99%) of **10a,b** as a colorless oil, which solidified in the refrigerator: ^1H NMR ($CDCl_3$, TMS) δ 7.30–6.70 (m, 3 H), 4.74 (s, 2 H), 3.90–3.50 (m, 1 H), 3.0–0.6 (m, 27 H); IR (film) 3400, 1595 cm^{-1}; high-resolution MS, m/z calcd for $C_{24}H_{33}NO_2$ 367.2511, found 367.2500; R_f 0.33 (30% ethyl acetate/hexane). Anal. Calcd for $C_{24}H_{33}O_2N$: C, 78.43; H, 9.06; N, 3.81. Found: C, 78.18; H, 9.08; N, 3.97.

[[1(*R*)-(3-Cyclohexylpropyl)-2,3,3a,4,9,9a-hexahydro-2-(*R*)-hydroxy-(3a*S*,9a*S*)-1*H*-benz[*f*]inden-5-yl]oxy]acetic Acid and Its 1,2,3a,9a-Tetraepi Isomer (2a,b). A solution of 450 mg (1.22 mmol) of **10a,b**, 30 mL of methanol, and 10 mL of 25% aqueous potassium hydroxide was heated at 90 °C for 5 h, then cooled to 0 °C, acidified to pH 5–6 with 1 N aqueous hydrochloric acid, diluted with brine, and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude product was chromatographed on 90 g of CC-4 acid-washed silica gel, eluting with 250 mL of 20%, 30%, 40%, and 50% ethyl acetate/hexane, to give 461 mg (97%) of **2a,b**, which was crystallized from hot THF/hexane (1:2, 3 mL/100 mg) to give 305 mg of **2a,b** as a white solid (mp 158–160 °C), and 156 mg of a white solid (mp 150–155 °C) from the mother liquor: ^1H NMR ($CDCl_3$, TMS) δ 7.30–6.70 (m, 3 H), 4.73 (s, 2 H), 4.60–3.40 (m, 3 H), 3.0–0.6 (m, 26 H); IR (film) 3420, 1735, 1590 cm^{-1}; high-resolution MS, m/z calcd for $C_{30}H_{50}O_4Si_2$ (as $(TMS)_2$ derivative) 530.3247, found 530.3227; R_f 0.57 (ethyl acetate/acetic acid/cyclohexane/water (9:2:5:10)). HPLC analyses were carried out by using a Varian 5560 with an HP 3390A integrator equipped with an Altex Ultrasphere ODS C18 10 × 250 mm column, eluting with water/acetonitrile/methanol/85% phosphoric acid (500:350:150:1) with a 3-mL/min flow rate and detection at 217 nm (0.02 AU/mV). A single peak at retention time of 48.89 min was observed. Anal. Calcd for $C_{24}H_{34}O_4$: C, 74.57; H, 8.87. Found: C, 74.57; H, 9.12.

[[1(*R*)-(Cyclohexylpropyl)-2,3,3a,4,9,9a-hexahydro-5-methoxy-1*H*-(3a*S*,9a*S*)-benz[*f*]inden-2(*R*)-yl]oxy]-(*S*)-α-methylbenzyl Carbamate (8a) and Its 1,2,3a,9a-Tetraepi Isomer (8b). A solution of 572.4 mg (1.67 mmol) of **7a,b** and 75 mL of toluene was treated with 1.66 mL of 12.5% solution of phosgene in toluene and 0.59 mL of triethylamine. After 1.25 h, the resulting mixture was treated with 1.3 mL of 98% (*S*)-(−)-α-methylbenzylamine. The reaction was exothermic and the mixture became gelatinous within 1 min after the addition. After 25 min the mixture was diluted with 100 mL of Skellysolve B and filtered through a medium frittered disk Buchner funnel, washing with Skellysolve B. The filtrate was concentrated in vacuo at 35 °C to give 1.11 g of a yellow oil. This oil was chromatographed on 100 g of silica gel 60, which was slurry packed, and eluted with 5% acetone/Skellysolve B to give 785.1 mg of the mixture of **8a** and **8b**. This mixture was chromatographed on two Merck columns (size B) connected in series, conditioned, and eluted with 15% *tert*-butyl methyl ether/hexane. The mixture was applied to the column in toluene, eluting at 7 mL/min to give 328 mg (40%) of compound **8a** as a white solid (mp 108 °C, R_f 0.31 (15% *tert*-butyl methyl ether/Skellysolve B)), 117.3 mg of the mixture of **8a** and **8b**, and 273.8 mg (33.5%) of compound **8b** as a white solid (mp 115 °C, R_f 0.28 (the same solvent system as **8a**)). HPLC analyses were carried out by using a Varian 5560 with a Varian 4270 integrator equipped with an Altex Ultrasphere ODS C18, 10 × 250 mm column, eluting with acetonitrile/methanol/water (45:40:15), with a 3 mL/min flow rate and detection at 217 nm (0.05 AU/mV). The compound **8a** showed a single peak at 34.12 min whereas the compound **8b** showed a peak at 35.36 min with a minor contaminant at 34.08. The assignment of carbamates **8a** and **8b** was based on the comparison of the HPLC peaks with authentic carbamates **8a** and **8b**, prepared independently from authentic alcohols **7a** and **7b**, respectively. The carbamates were prepared in analytical scale by dissolving ca. 1 mg of these alcohols in 0.5 mL of toluene and adding 1 μL of dibutyltin diacetate and 5 μL of (*S*)-(−)-α-methylbenzyl isocyanate. After the mixture was stirred at room temperature for 4 h, the reaction was quenched with brine and extracted with ethyl acetate. The organic extract was dried (Na_2SO_4), filtered, and concentrated in vacuo.

1(*R*)-(3-Cyclohexylpropyl)-2,3,3a,4,9,9a-hexahydro-5-methoxy-(3a*S*,9a*S*)-1*H*-benz[*f*]inden-2(*R*)-ol (7a). A solution of 328 mg (0.67 mmol) of **8a** and 25 mL of THF was treated with lithium aluminum hydride (102.6 mg, 2.7 mmol), and the resulting mixture was heated at 60–65 °C for 4 h. The mixture was then cooled to room temperature and carefully quenched with 1 mL of water. Addition of brine was followed by aqueous sodium bisulfate until pH was 4. The mixture was then extracted three times with ethyl acetate, and the combined organic extracts were filtered through anhydrous sodium sulfate powder. The filtrate was concentrated in vacuo to give 285.9 mg of a yellow oil, which was chromatographed on 64 g of silica gel 60, eluting with 12% ethyl acetate/hexane to give 229.5 mg (100%) of pure **7a** as a colorless glass: ^1H NMR and IR spectra were identical with those of **7a,b**; $[\alpha]_D$ 30.6° (*c* 1.215, 95% ethanol); R_f 0.36 (15% ethyl acetate/Skellysolve B) and 0.20 (15% *tert*-butyl methyl ether/Skellysolve B); HPLC analysis (same condition as in the analyses of **8a** and **8b**) as in previous experiment, but eluting with acetonitrile/water/methanol (60:20:20), gave a single peak at 41.06 min.

1(*S*)-(3-Cyclohexylpropyl)-2,3,3a,4,9,9a-hexahydro-5-methoxy-(3a*R*,9a*R*)-1*H*-benz[*f*]inden-2(*S*)-ol (7b). A 273.8 mg (0.56 mmol) sample of **8b** was reacted and worked up in an identical manner as the reaction of **8a** to **7a** to obtain 267.2 mg of crude product as a yellow glass. This material was chromatographed on 65 g of silica gel 60, which was eluted with 10% ethyl acetate/hexane to give 191.8 mg (100%) of pure **7b** as a colorless glass: $[\alpha]_D$ −27.7° (*c* 1.139, 95% ethanol); HPLC analysis gave a single peak at 41.38 min.

1(*R*)-(3-Cyclohexylpropyl)-2,3,3a,4,9,9a-hexahydro-(3a*S*,9a*S*)-1*H*-benz[*f*]indene-2(*R*),5-diol (9a). A 233.9 mg (0.68 mmol) sample of **7a** was converted to **9a** in an identical manner as in the preparation of **9a,b** from **7a,b** to give 212.0 mg

(94.5%) of **9a** as a white foam: ^{1}H NMR and IR spectra were identical with those of **9a,b**; $[\alpha]_D$ 30.6° (*c* 1.09, 95% ethanol); R_f 0.25 (25% ethyl acetate/hexane).

1(*S*)-(3-Cyclohexylpropyl)-2,3,3a,4,9,9a-hexahydro-(3a*R*,9a*R*)-1*H*-benz[*f*]indene-2(*S*),5-diol (9b). A 194.6 mg (0.57 mmol) sample of **7b** was converted to **9b** in an identical manner as in the preparation of **9a,b** from **7a,b** to give 167.6 mg (90%) of **9b** as a white foam: ^{1}H NMR and IR spectra were identical with those of **9a,b**; $[\alpha]_D$ −29.2° (*c* 1.17, 95% ethanol); R_f 0.25 (25% ethyl acetate/hexane).

[[1(*R*)-(3-Cyclohexylpropyl)-2,3,3a,4,9,9a-hexahydro-2-(*R*)-hydroxy-(3a*S*,9a*S*)-1*H*-benz[*f*]inden-5-yl]oxy]acetonitrile (10a). A 212.0 mg (0.65 mmol) sample of **9a** was converted to **10a** in a similar manner as in the alkylation of **9a,b** to **10a,b** to give 211.6 mg (89%) of **10a**: mp 99–99.5 °C; ^{1}H NMR spectrum was identical with that of **10a,b**; $[\alpha]_D$ 30.5° (*c* 1.032, 95% ethanol); R_f 0.34 (25% ethyl acetate/Skellysolve B).

[[1(*S*)-(3-Cyclohexylpropyl)-2,3,3a,4,9,9a-hexahydro-2-(*S*)-hydroxy-(3a*R*,9a*R*)-1*H*-benz[*f*]inden-5-yl]oxy]acetonitrile (10b). A 167.6 mg (0.51 mmol) sample of **9b** was converted to **10b** in a similar manner as to conversion of **9a,b** to **10a,b** to give 164.9 mg (88%) of **10b**: mp 99.5–100 °C; ^{1}H NMR spectrum was identical with that of **10a,b**; $[\alpha]_D$ −28.4° (*c* 1.017, 95% ethanol); R_f 0.34 (25% ethyl acetate/Skellysolve B).

[[1(*R*)-(3-Cyclohexylpropyl)-2,3,3a,4,9,9a-hexahydro-2-(*R*)-hydroxy-(3a*S*,9a*S*)-1*H*-benz[*f*]inden-5-yl]oxy]acetic Acid (2a). A 211.6 mg (0.58 mmol) sample of **10a** was converted to **2a** in an identical manner as the conversion of **10a,b** to **2a,b** to give 203.3 mg of a pale yellow solid, which was recrystallized from ethyl acetate/hexane to give 156.1 mg (70%) of pure **2a** as a white solid: mp 133.5–135.5 °C, mixed mp with **2a** obtained from **16a** (Scheme III) was unchanged; ^{1}H NMR spectrum was identical with that of **2a,b**; MS, *m/z* calcd for $C_{24}H_{34}O_4$ (M^+) 386; other ions 368, 309, 243, 203, 157; $[\alpha]_D$ 30.69° (*c* 1.167, 95% ethanol), R_f 0.19 (acetone/methylene chloride/acetic acid (4:95:1)), 0.27 (the organic phase of ethyl acetate/acetic acid/2,2,4-trimethylpentane/water (9:2:5:10)), and 0.35 (ethyl acetate/Skellysolve B/acetic acid (35:64:1)).

[[1(*S*)-(3-Cyclohexylpropyl)-2,3,3a,4,9,9a-hexahydro-2-(*S*)-hydroxy-(3a*R*,9a*R*)-1*H*-benz[*f*]inden-5-yl]oxy]acetic Acid (2b). A 164.9 mg (0.45 mmol) sample of **10b** was converted to **2b** in an identical manner as the synthesis of **2a** from **10a** to give 139.7 mg (80%) of pure **2b** as a white solid: mp 133.5–135.5 °C, mixed mp with **2b** obtained from **16b** (Scheme III) was unchanged; ^{1}H NMR and MS spectra and R_f's in three-solvent system as described in the previous experiment were identical with those of **2a**; $[\alpha]_D$ −28.16 (*c* 1.079, 95% ethanol).

1(*R*)-(3-Cyclohexyl-3(*R*)-hydroxypropyl)-2,3,3a,4,9,9a-hexahydro-2(*R*)-[(*tert*-butyldimethylsilyl)oxy]-5-methoxy-(3a*S*,9a*S*)-1*H*-benz[*f*]indene (17a). A solution of 229.5 mg (0.64 mmol) of **16a** (98.5% pure, contaminated with 1.5% **16b**),[2] 87.1 mg (1.28 mmol) of imidazole, and 6.4 mL of THF at 0–5 °C was treated with 192.9 mg (1.28 mmol) of *tert*-butyldimethylsilyl chloride dissolved in 3.2 mL of THF. After the mixture was stirred 30 h at room temperature another portion of imidazole (17.4 mg, 0.256 mmol) and *tert*-butyldimethylsilyl chloride (38.6 mg, 0.256 mmol) was added, and the mixture was stirred for an additional 18 h, quenched at 0–5 °C with 5 mL of water, stirred for 30 min, and extracted with ethyl acetate. The organic extract was washed with water and brine, dried ($MgSO_4$), filtered, and concentrated in vacuo to give a near colorless oil. The oil was purified by LC on 215 g of silica gel 60, eluting with 2.4 L of 9% ethyl acetate/hexane and 600 mL ethyl acetate to give 21.2 mg (6.4%) of bis-silylated product, 197.9 mg (65.4%) of **17a**, and 46.2 mg (20%) of the recovered starting material **16a**. This material was resilylated by reacting with 122.5 mg (1.8 mmol) of imidazole and 271.3 mg (1.8 mmol) of *tert*-butyldimethylsilyl chloride in 5 mL of THF at room temperature for 48 h. Workup and LC purification using 52.5 g silica gel 60, as described above, gave an additional 56.5 mg of **17a**. The combined products yielded 254.2 mg (84%) of the desired monosilylated product **17a** as a colorless oil: ^{1}H NMR ($CDCl_3$, TMS) δ 7.30–6.68 (m, 3 H), 3.80 (s, 3 H), 3.86–3.12 (m, 2 H), 3.08–0.95 (m, 24 H), 0.88 (s, 9 H), 0.04 (s, 6 H); IR (film) 3430, 1580, 870, 840, 775, 730 cm^{-1}; R_f 0.48 (17% ethyl acetate/hexane).

1(*S*)-(3-Cyclohexyl-3(*R*)-hydroxypropyl)-2,3,3a,4,9,9a-hexahydro-2(*S*)-[(*tert*-butyldimethylsilyl)oxy]-5-methoxy-(3a*R*,9a*R*)-1*H*-benz[*f*]indene (17b). A 358.5 mg (1.0 mmol) sample of **16b** (>99% pure)[2] was converted to **17b** in an identical manner as the silylation of **16a** to **17a** to give 29.7 mg (5.1%) of bis-silylated product, 385.8 mg (81.6%) of **17b** as a colorless oil, and 40.7 mg (11.4%) of the recovered starting material **16b**. Spectral properties of **17b** were identical with those of **17a**.

1(*R*)-(3-Cyclohexylpropyl)-2,3,3a,4,9,9a-hexahydro-2-(*R*)-[(*tert*-butyldimethylsilyl)oxy]-5-methoxy-(3a*S*,9a*S*)-1*H*-benz[*f*]indene (19a). A solution of 245.9 mg (0.52 mmol) of **17a** and 5.2 mL of pyridine at 0–5 °C was treated with 594.8 mg (3.12 mmol) of *p*-toluenesulfonyl chloride. The resulting pink-colored solution was stirred at room temperature for 24 h, cooled to 0–5 °C again, treated with 0.52 mL of water, stirred for 30 min at room temperature, and extracted with ethyl acetate. The combined organic extracts were washed with water, 10% aqueous sodium bisulfate, saturated aqueous sodium bicarbonate, and brine, dried ($MgSO_4$), filtered, and concentrated in vacuo to give 0.33 g of tosylate **18a** as a light brown oil: ^{1}H NMR ($CDCl_3$, TMS) δ 7.94–6.68 (m, 7 H), 4.62–4.32 (m, 1 H), 3.80 (s, 3 H), 3.90–3.40 (m, 1 H), 3.04–0.95 (m, 24 H), 2.38 (s, 3 H), 0.88 (s, 9 H), 0.04 (s, 6 H); R_f 0.56 (17% ethyl acetate/hexane). Without further purification of the tosylate **18a**, this material was dissolved in 26.0 mL of anhydrous ether, cooled to 0–5 °C with an ice–water bath, and treated over 5 min with 197.3 mg (5.2 mmol) of lithium aluminum hydride. The cooling bath was then removed, and the gray suspension was stirred at room temperature for 24 h, cooled again to 0–5 °C, and treated carefully with 1 N hydrochloric acid until the pH of the mixture was about 7. The resulting mixture was extracted with ethyl acetate and the combined organic extracts were washed with water and brine, dried ($MgSO_4$), filtered, and concentrated in vacuo to give an oil. This oil was purified on 215 g of LC grade silica gel 60, eluting with 1.5 L of 5% and 1 L of 33% ethyl acetate/hexane to give 187.4 mg (78.9%) of pure **19a** as a colorless oil: ^{1}H NMR ($CDCl_3$, TMS) δ 7.24–6.66 (m, 3 H), 3.82 (s, 3 H), 3.92–3.50 (m, 1 H), 3.10–0.95 (m, 26 H), 0.88 (s, 9 H), 0.02 (s, 6 H); IR (film) 1600, 1580, 870, 835, 770 cm^{-1}; R_f 0.69 (17% ethyl acetate/hexane).

1(*S*)-(3-Cyclohexylpropyl)-2,3,3a,4,9,9a-hexahydro-2-(*S*)-[(*tert*-butyldimethylsilyl)oxy]-5-methoxy-(3a*R*,9a*R*)-1*H*-benz[*f*]indene (19b). A 378.2 mg (0.8 mmol) sample of **17b** was converted to **19b** in an identical manner as the conversion of **17a** to **19a**. However, the lithium aluminum hydride reduction was run in tetrahydrofuran instead of diethyl ether. This change of solvent resulted in isolation of 214.0 mg (58.6%) of the desired **19b** as a colorless oil: ^{1}H NMR and IR spectra and R_f were identical with those of **19a**.

1(*R*)-(3-Cyclohexylpropyl)-2,3,3a,4,9,9a-hexahydro-5-methoxy-(3a*S*,9a*S*)-1*H*-benz[*f*]inden-2(*R*)-ol (7a). A solution of 182.7 mg (0.40 mmol) of **19a**, 3.0 mL of 2-propanol, 2 mL of THF, and 1 mL of 3 N hydrochloric acid was stirred at room temperature for 24 h, treated with saturated aqueous sodium bicarbonate to pH 7–8, and extracted with ethyl acetate. The organic extract was washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo to give a colorless oil. This oil was chromatographed on 215 g of LC grade silica gel 60, eluting with 20% ethyl acetate/hexane to give 123.8 mg (90.4%) of **7a** as a colorless oil: ^{1}H NMR and IR spectra and R_f were identical with those of **7a,b**; $[\alpha]_D$ 31.8° (*c* 1.22, 95% ethanol). The carbamate **8a** of compound **7a** had an identical HPLC retention time as the carbamate **8a** resolved by liquid chromatography from the mixture **8a,b**.

1(*S*)-(3-Cyclohexylpropyl)-2,3,3a,4,9,9a-hexahydro-5-methoxy-(3a*R*,9a*R*)-1*H*-benz[*f*]inden-2(*S*)-ol (7b). A 205.6 mg (0.45 mmol) sample of **19b** was converted to **7b** in an identical manner as in the conversion of **19a** to **7a** to give 125.6 mg (81.5%) of **7b** as a colorless oil: ^{1}H NMR and IR spectra and R_f were identical with those of **7a,b**; $[\alpha]_D$ −31.5° (*c* 1.24, 95% ethanol). The carbamate **8b** of compound **7b** had an identical HPLC retention time as the carbamate **8b**, resolved by liquid chromatography from the mixture **8a,b**.

[[1(*R*)-(3-Cyclohexylpropyl)-2,3,3a,4,9,9a-hexahydro-2-(*R*)-hydroxy-(3a*S*,9a*S*)-1*H*-benz[*f*]inden-5-yl]oxy]acetic Acid (2a). Compound **7a** (obtained from **16a**) was converted to **2a** in an identical manner as previously described for the conversion of **7a** (obtained via resolution of **7a,b**) to **2a**. The specific

rotations of each intermediate were recorded: **9a**, $[\alpha]_D$ 31.4° (*c* 0.873, 95% ethanol); **10a**, $[\alpha]_D$ 29.5° (*c* 0.818, 95% ethanol). The HPLC analysis of the final product **2a** showed an identical retention time as that of **2a** obtained from the resolution of intermediate **7a,b** as shown on Scheme I. The spectral properties were also identical: $[\alpha]_D$ 31.3° (*c* 0.713, 95% ethanol); high-resolution MS (as TMS derivative), *m/z* calcd for $C_{30}H_{50}O_4Si_2$ 530.3247, found 530.3248.

[[1(*S*)-(3-Cyclohexylpropyl)-2,3,3a,4,9,9a-hexahydro-2-(*S*)-hydroxy-(3a*R*,9a*R*)-1*H*-benz[*f*]inden-5-yl]oxy]acetic Acid (2b). Compound **7b** (obtained from **16b**) was converted to **2b** in an identical manner as previously described for the conversion of **7b** (obtained via resolution of **7a,b**) to **2b**. The specific rotations of each intermediate were recorded: **9b**, $[\alpha]_D$ −31.8° (*c* 0.916, 95% ethanol); **10b**, $[\alpha]_D$ −30.0° (*c* 0.83, 95% ethanol). The HPLC analysis of the final product **2b** showed an identical retention time as that of **2b** obtained from the resolution of intermediate **7a,b** as shown in Scheme I. The spectral properties were also identical: $[\alpha]_D$ −31.4° (*c* 0.72, 95% ethanol); high-resolution MS (as TMS derivative), *m/z* calcd for $C_{30}H_{50}O_4Si_2$ 530.3247, found 530.3237.

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Novel Mitomycin C Amidines:[1] Synthesis and Their Reactions with Amines

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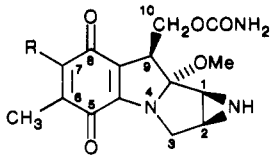
Reactions of formamide acetals (e.g., DMFDMA, **10**, **12**) with mitomycin C (**1**) has afforded novel amidine derivatives (e.g., **7–9**, **11**, **13**). Investigation of reactions of amines with bisamidine **8** in both polar and nonpolar solvents (e.g., MeOH vs $CHCl_3$) has led to the discovery that **8**, in its reactions with primary amines in methanol, behaves as a mitomycin A (**2**) equivalent to afford 7-N-substituted mitosanes (e.g., **16–19**). In contrast, bisamidine **8** undergoes a selective deamidination reaction with primary amines in chloroform to afford monoamidine **14**.

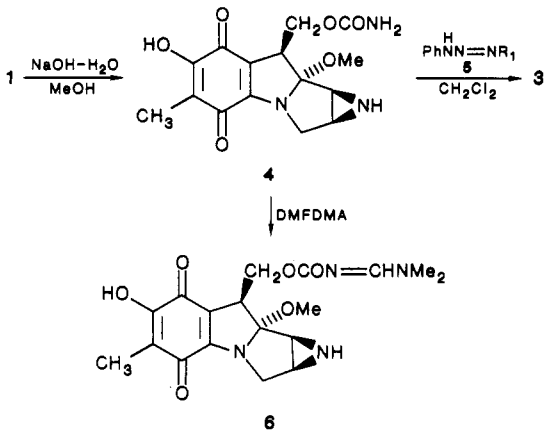
Fermentation-derived[3] antineoplastic antibiotics, mitomycin C (**1**) and mitomycin A (**2**),[4] are of great significance in cancer chemotherapy. While **1** is currently[5] in clincal use for the management of a variety of neoplasms, mitomycin A (**2**) is continuing to play a pivotal role in analogue research[6] which is directed toward discovery of new clinical agents endowed with less myelosuppressive properties and a broader spectrum of antitumor activity.



1: R = NH_2
2: R = OCH_3
3: R = OR_1

Recently,[7] we reported a practical approach to the synthesis of **2** and its analogues, namely 7-alkoxymitosanes **3**[8] from mitomycin C. The key reaction of this process

Scheme I



(Scheme I) involves O-alkylation of 7-hydroxymitosane (**4**) with an appropriate triazene (**5**) in a nonpolar solvent. During a similar attempt to methylate **4** with another well-established methylating agent, namely *N,N*-dimethylformamide dimethyl acetal (DMFDMA),[9] an amidine derivative, **6**, was obtained as the sole product in place of the desired product **2**. This finding was not surprising in light of the fact that DMFDMA is known to react with amines, amides, and urethanes to yield corresponding amidines. However, the observed functionalization[10] of the carbamoyl moiety of **4** is unprecedented. This encouraged us to investigate the reactions of formamide acetals with mitomycin C, which bears potentially three reactive amino

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(2) Present address: Hoechst-Roussel Pharmaceuticals, Inc. Somerville, NJ 08876.
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(4) According to the trivial system of nomenclature, which has found wide use in mitomycin literature, mitomycin C (**1**) is named as 7-amino-9a-methoxymitosane and mitomycin A (**2**) as 7,9a-dimethoxymitosane.
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(9) For a review on the chemistry of formamide acetals, see: Abdulla, R. F.; Brinkmeyer, R. S. *Tetrahedron* **1979**, *35*, 1675.
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