mL of 4 M HCl was added, followed by 1.0 mL of 0.37 M $FeCl_3$ solution. The absorbance of the resulting solution was then measured.

(c) **Ester Assay.** A 1.0-mL volume of NaOH solution was placed in a 15-mL test tube to which 1.0 mL of 28% NH_2OH solution was also added. The absorbance of the resulting solution was then measured.

(d) **Amide Assay.** A 0.5-mL volume of NaOH solution was placed in a 15-mL test tube to which 1.0 mL of reaction mixture was added. After 20 min, 1.0 mL of 40% $NH_2OH \cdot HCl$ solution was added. This mixture was heated for 90 min at 90 °C and then allowed to cool to room temperature, after which 1.0 mL of 4 M HCl, 1.0 mL of 0.37 M $FeCl_3$, and 0.5 mL of water were added. The absorbance of the resulting solution was then measured.

Kinetic Measurements. Solutions for kinetic studies were prepared immediately before use. A 25-mL solution containing all the ingredients except acetyl phosphate was equilibrated at 40 °C in a water-jacketed beaker. The pH of the solution was monitored continuously with a pH meter standardized at 40 °C. The pH of the solution was adjusted to the desired level by adding a few drops of 1.0 N NaOH (for pH 9-11) or 0.1 N NaOH (for pH 7-9). An accurately weighed sample (ca. 2.3 mg) of dilithium acetyl phosphate was added to the solution, and aliquots were taken at 30-s to 3-min intervals, depending on the anticipated rate of the reaction. The course of the reaction was followed by means of the acetyl phosphate assay. Ester assays were performed whenever the possibility of ester formation existed, and amide assays were carried out when amines were present. The reactions were followed for a period of 10 min to 6 h. T_∞ aliquots were taken at 6-24 h, depending on the reaction rate. In all cases, the plot of the log values of the concentrations vs. time yielded a straight line. Rate constants were determined graphically and by a least-squares computer program. The rate constants for each reaction were determined 3 times from three separte runs, and a 5-7% range in the rate constant was generally observed.

Acknowledgment. This work was supported, in part, by a Biomedical Science Support Grant funded by the National Institutes of Health and administered by the Washington University Research Office.

Total Synthesis of a Novel Antiulcer Agent via a Modification of the Intramolecular Wadsworth-Emmons-Wittig Reaction†

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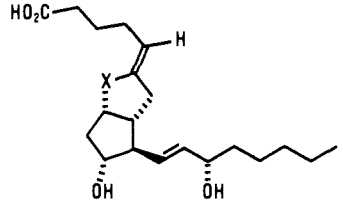
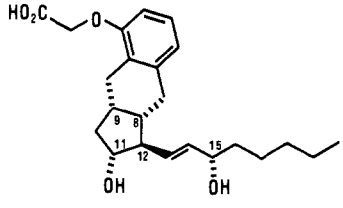
Contribution from The Upjohn Company, Kalamazoo, Michigan 49001. *Received May 8, 1985*

Abstract: A convergent synthesis of the novel, potent antiulcer agent U-68,215 (**3**), a benzindene prostacyclin analogue, is described. U-68,215 is prepared via a cyclopentane annulation sequence in optically pure form in 14 steps and 12% yield from 5-methoxy-2-tetralone (**8a**). The key step in the synthesis involves the coupling of the phosphonate reagent **6** (the chirality of which was derived from a Sharpless resolution of an allylic alcohol precursor) with the enol lactone **7a** (prepared in 50% overall yield from **8a**) to produce enone **5** via a modified intramolecular Wadsworth-Emmons-Wittig reaction. Hydrogenation of **5** followed by an unusual one-pot equilibration-reduction sequence generates the four centers around the cyclopentane ring with complete stereocontrol.

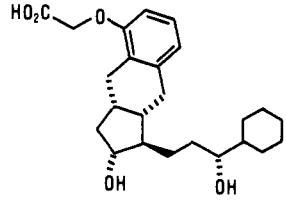
Several years ago, we first reported the synthesis and initial biological evaluation of the benzindene prostaglandins, chemically stable potent prostacyclin (PGI_2, **1a**) mimics.[1] The parent



1a X = O (PGI_2)
1b X = CH_2



2 (U-60,959)



3 (U-68,215)

compound U-60,959 (**2**), a carbacyclin (**1b**) type analogue containing a fused aromatic ring, was about one-fifth as active as PGI_2 at both inhibiting platelet aggregation and lowering blood pressure.[2] A less well-recognized property of prostacyclin is its ability to function as an antiulcer agent.[3] Further examination of U-60,959 indicated that it also was an effective gastric cytoprotective agent and weak inhibitor of gastric acid secretion.[4] More recent structural modification of the benzindene lower side chain has identified the cyclohexyl analogue **3** (U-68,215) as an exciting new antiulcer agent. While by the intravenous route of administration U-68,215 is equipotent with prostacyclin on platelets and blood pressure, given orally **3** is an extremely potent cytoprotective and gastric antisecretory agent.[5] Orally in rats, **3** is roughly 140 times as active as U-60,959 at inhibiting gastric acid secretion, being effective as an antiulcer agent at microgram/kilogram levels. Most importantly, U-68,215, which is a stable high melting crystalline solid, appears completely devoid of the typical side effects associated with prostaglandins of the E type; i.e., even at doses 100 times the antiulcer dose, it does not cause diarrhea, has no antifertility activity, and does not induce cellular proliferation of the gastrointestinal mucosa.[5]

† Dedicated to Prof. Albert Eschenmoser on the occasion of his 60th birthday.

(1) Aristoff, P. A.; Harrison, A. W. *Tetrahedron Lett.* **1982**, *23*, 2067.
(2) Aristoff, P. A.; Harrison, A. W.; Aiken, J. W.; Gorman, R. R.; Pike, J. E. In "Advances in Prostaglandin, Thromboxane, and Leukotriene Research"; Samuelsson, B., Paoletti, R., Ramwell, P. W., Eds.; Raven Press: New York, 1983; Vol. XI, p 267.
(3) Whittle, B. J. R.; Boughton-Smith, N. K.; Moncada, S.; Vane, J. R. *Prostaglandins* **1978**, *15*, 955.
(4) Aristoff, P. A.; Harrison, A. W.; Johnson, P. D.; Robert, A. In "Advances in Prostaglandin, Thromboxane, and Leukotriene Research"; Raven Press: New York, in press.
(5) Robert, A.; Aristoff, P. A.; Wendling, M. G.; Kimball, F. A.; Miller, W. L.; Gorman, R. R. *Prostaglandins*, in press.

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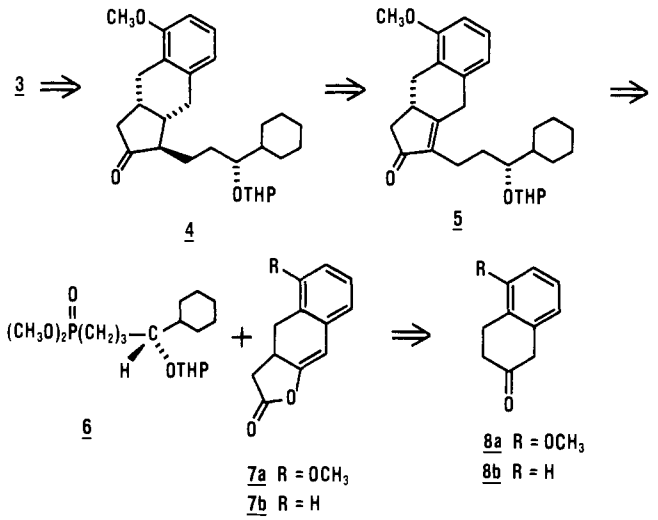
Scheme I



To prepare **3** by the original process used to make **2** required about 35 steps from commercially available starting material.[1,2] This was clearly too long a route to be feasible to prepare multigram quantities of U-68,215. Therefore, a much more efficient synthesis which incorporates several novel transformations and which is amenable to large-scale was developed. It was envisaged that a convergent sequence involving a cyclopentane annulation onto a naphthalene derivative would maximize the number of crystalline intermediates and minimize the number of steps (and chromatographic purifications).

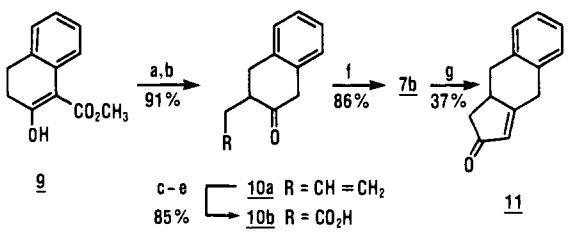
Our retrosynthetic analysis is shown in Scheme I. Reduction of ketone **4** from the least hindered face followed by protecting group removal and phenol alkylation should give **3**. Ketone **4** should be available from the reduction of enone **5** followed by equilibration of the lower side chain to the presumably thermodynamically favored 12-β isomer. The key step in the synthesis involves the direct coupling of the anion of phosphonate **6** with enol lactone **7a** in an intramolecular Wadsworth–Emmons–Wittig reaction.[6] The chirality of the final product is derived from **6** which hopefully should be optically pure at this stage. Finally **7a** should be obtainable from appropriate alkylation and dehydration of 5-methoxy-2-tetralone (**8a**).

Results and Discussion

At the outset, we were concerned with two problems with this approach: (1) the feasibility of the intramolecular Wittig reaction to give **5** and (2) the stereochemistry of the reduction of enone **5**.[7] Therefore, a simple model system starting from β-tetralone (**8b**) was first investigated. This choice of model system allowed us to readily assign the outcome of the enone reduction by ^{13}C NMR (vide infra).

Alkylation of β-tetralone typically occurs at the carbon between the ketone and the aromatic ring (C-1);[8] therefore, it is normally necessary to protect this position if alkylation at C-3 is desired.[9] We chose instead to investigate a dianion alkylation approach (Scheme II). While direct dianion formation and alkylation of β-tetralone was unsuccessful,[10] **8b** could be readily converted to the known β-keto ester **9** in 81% yield using sodium methoxide in warm dimethyl carbonate.[11] Although the dianion of **9** could

Scheme II

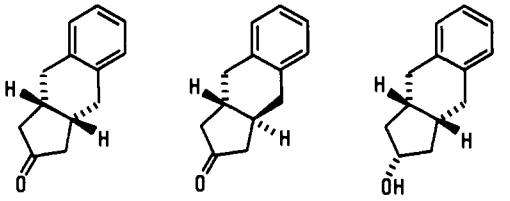


(a) LOA (2 equiv.), THF; $H_2C=CHCH_2Br$. (b) LiCl, H_2O, Me_2SO, 150°C. (c) $HOCH_2CH_2OH$, $HC(OEt)_3$, p-TsOH (cat.), CH_2Cl_2. (d) $NaIO_4$, $KMnO_4$ (cat.), t-BuOH, H_2O, K_2CO_3. (e) HCl, H_2O, CH_3COCH_3, 60°C. (f) $HClO_4$ (cat.), Ac_2O, EtOAc. (g) $(MeO)_2P(O)CH_2Li$, THF, -78°C→50°C.

be alkylated with a variety of agents,[12] overall the best results were obtained by using 2 equiv of lithium diisopropylamide (LDA) in tetrahydrofuran (THF) to generate the dianion[13] followed by alkylation with allyl bromide. Decarbomethoxylation of the crude product using the Krapcho procedure[14] afforded the desired C-3-alkylated product **10a** in overall 91% yield from **9**.

Attempted oxidation of olefin **10a** to acid **10b** directly gave only low yields of product due to competing oxidation of the tetralone system; therefore, it was necessary to protect ketone **10a** as its ethylene ketal. Following ketalization of **10a**, the crude product was oxidized with sodium metaperiodate and a catalytic amount of potassium permanganate and then treated with aqueous acid to give **10b** in overall 85% yield from **10a**. Dehydration of **10b** to give **7b** was effected by using acetic anhydride and a trace of perchloric acid in ethyl acetate.[15] Condensation of enol lactone **7b** with 1 equiv of lithium dimethyl methylphosphonate in THF at −78 °C followed by warming to 0 °C and then heating at 55 °C gave a 37% yield of enone **11**.

Now the reason for our choice of model system should become clear. Reduction of enone **11** can lead to either the desired cis-fused product **12** which contains a plane of symmetry or the trans-fused product **13** which contains an axis of symmetry. Each



of these compounds should exhibit a maximum of seven resonances in their ^{13}C NMR spectrum. However, whereas reduction of ketone **12** can give two alcohols (of which compound **14** would be expected to predominate because of attack from the less-hindered convex face of the molecule), both of these alcohols would still contain a plane of symmetry, and each should exhibit a total of seven ^{13}C NMR resonances. On the other hand, reduction of **13** can give only one product, an alcohol which no longer has any symmetry and which would be expected to show up to 13 reso-

(6) Henrick, C. A.; Böhme, E.; Edwards, J. A.; Fried, J. H. *J. Am. Chem. Soc.* **1968**, *90*, 5926. Review: Becker, K. B. *Tetrahedron* **1980**, *36*, 1717.

(7) Because of the additional phenyl ring, compound **5** is relatively flat, making it difficult to predict using simple molecular models the preferred direction of attack on the enone.

(8) An exception to this rule is the procedure of Pelletire (see: Beres, J. A.; Cannon, J. G. *Synth. Commun.* **1979**, *9*, 819 and references therein). However, this procedure is inconvenient and gave low yields on large scale.

(9) Nordmann, R.; Petcher, T. J. *J. Med. Chem.* **1985**, *28*, 367.

(10) Attempts to alkylate the dianion of 1-phenyl-2-propanone have likewise been reported to proceed poorly (Trimitsis, G. B.; Hinkley, J. M.; Ten-Brink, R.; Faburada, A. L.; Anderson, R.; Poli, M.; Christian, B.; Gustafson, G., Erdman, J.; Rop, D. *J. Org. Chem.* **1983**, *48*, 2957).

(11) We find the use of methanolic sodium methoxide more convenient and safer on large scale than the literature procedure (Oommen, P. K. *Aust. J. Chem.* **1976**, *29*, 1393) which uses sodium hydride to generate the ketone enolate.

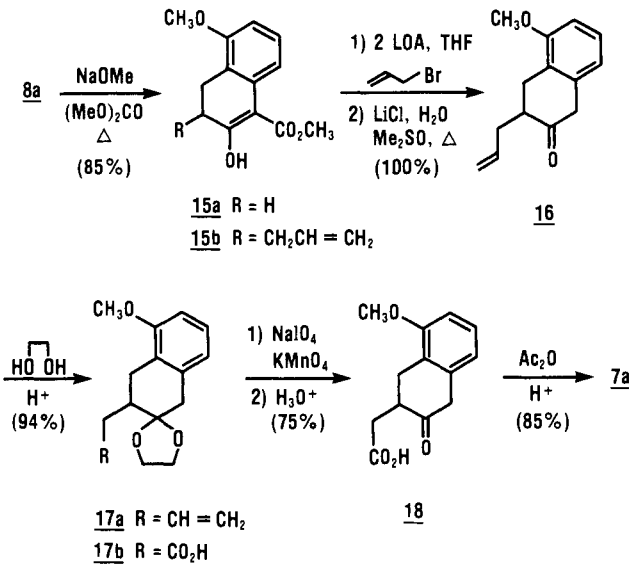
(12) While the reaction of the dianion of **9** with iodoacetonitrile, bromoacetaldehyde dimethyl acetal, or *tert*-butyl chloroacetate went poorly, alkylation with 3-chloro-2-methylpropene or *tert*-butyl bromoacetate gave acceptable yields of product. However, on large scale the best yield for the sequence **9** → **10b** involved using allyl bromide in the alkylation step.

(13) Huckin, S. N.; Weiler, L. *J. Am. Chem. Soc.* **1974**, *96*, 1082. The typical procedure using 1 equiv of sodium hydride followed by 1 equiv of *n*-butyllithium gave a slightly lower yield of product.

(14) Krapcho, A. P.; Weimaster, J. F.; Eldridge, J. M.; Jahngen, E. G. E.; Lovey, A. J.; Stephens, W. P. *J. Org. Chem.* **1978**, *43*, 138. Review: Krapcho, A. P. *Synthesis* **1982**, 893.

(15) Edwards, B. E.; Rao, P. N. *J. Org. Chem.* **1966**, *31*, 324.

Scheme III

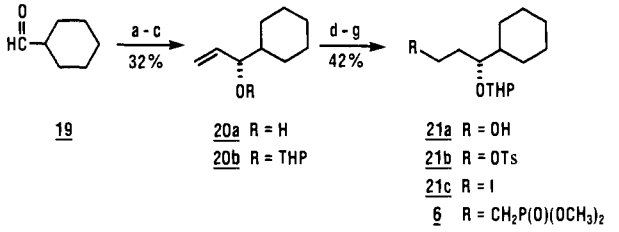


nances in its ^{13}C NMR spectrum. In the event, hydrogenation of enone **11** at atmospheric pressure in ethyl acetate using palladium on carbon catalyst afforded an 86% yield of a ketone (mp 97–99 °C) which did exhibit the expected seven resonances in the ^{13}C NMR.[16] Only a trace of a slightly less-polar byproduct was observed. Reduction of the hydrogenation product with sodium borohydride in methanol at −15 °C gave a single product (mp 109–111 °C) in essentially quantitative yield. The ^{13}C NMR spectrum of the resulting crude alcohol indicated exactly seven resonances, thus demonstrating that the desired cis-fused isomer **12** is stereospecifically formed in the hydrogenation of enone **11** and that the desired compound **14** is the exclusive product upon ketone reduction.

Although we were concerned about the low yield in the intramolecular Wittig step, otherwise the results of the model system looked very promising and encouraged us to try this approach in the real system. As shown in Scheme III, the reaction sequence used to prepare enol lactone **7a** is essentially the same as developed to prepare **7b**. Carbomethoxylation of 5-methoxy-2-tetralone (**8a**)[17] afforded β-keto ester **15a** in 85% yield following crystallization of the crude product. The allyl side chain was introduced in an overall contrathermodynamic sense (from **8a**) by dianion formation (2 equiv of LDA), alkylation with allyl bromide, and decarbomethoxylation of the resulting crude β-keto ester **15b**. The crude ketone product **16** was then ketalized to give compound **17a** in overall 94% yield from **15a**. Oxidative cleavage of olefin **17a** and ketal hydrolysis of the crude product **17b** afforded acid **18** in overall 75% yield from **17a** following crystallization of the crude product. Finally, dehydration of **18** gave the desired enol lactone **7a** in 85% yield. The overall yield of **7a** from 5-methoxy-2-tetralone (**8a**) is 50%. *All intermediates in this sequence are crystalline solids, and the only purification steps required are recrystallizations of compounds* ***15a***, ***18***, *and* ***7a***. Enol lactone **7a**, which is stable for greater than a year when stored at 0 °C, has proven to be a versatile intermediate in the synthesis of a variety of benzindene prostaglandin analogues.

The preparation of the optically active phosphonate **6**, which contains carbons C-12 through C-21 of the product, is outlined in Scheme IV. Treatment of cyclohexanecarboxaldehyde (**19**) with a slight excess of vinylmagnesium bromide afforded a quantitative yield of allyl alcohol (racemic **20a**). The crude product was subjected to a Sharpless kinetic resolution procedure[18]

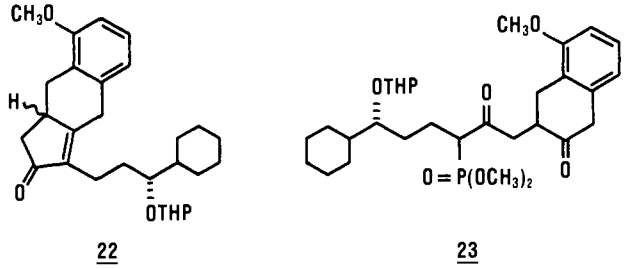
Scheme IV



(a) $H_2C{=}CHMgBr$, THF, 0°C.
(b) t-BuOOH, $Ti(O\text{-}i\text{-}Pr)_4$, (−)-diisopropyl-(D)-tartrate, CH_2Cl_2, −20°C.
(c) Dihydropyran, H^+, CH_2Cl_2. (d) 9-BBN, THF; H_2O_2, KOH.
(e) p-TsCl, pyridine, 0°C. (f) NaI, $EtN(i\text{-}Pr)_2$, CH_3COCH_3.
(g) $(MeO)_2P(O)CH_2Li$, THF, −78°C→10°C.

using *tert*-butyl hydroperoxide, (−)-diisopropyl D-tartrate, and titanium tetraisopropoxide to give optically pure **20a** in overall 32% yield from **19**.[19] The remainder of the synthesis of **6** is fairly straightforward. Following protection of **20a** as its tetrahydropyranyl (THP) ether, the crude product **20b** was subjected to a hydroboration–oxidation sequence using 9-BBN to give alcohol **21a** in overall 72% yield from **20a**. Tosylation of **21a** (85% yield) followed by treatment of the crude tosylate **21b** with sodium iodide in acetone containing some diisopropylethylamine (to inhibit THP hydrolysis) afforded iodide **21c** in 84% yield.[21,22] Finally, **21c** was converted to phosphonate **6** in 80% yield (overall about 40% yield from resolved alcohol **20a**) by reaction with 1 equiv of lithium dimethyl methylphosphonate in THF at −78 °C followed by slow warming to room temperature.[23]

The stage was now set to investigate the crucial coupling reaction of **6** with **7a**. Initially, similar results were obtained as had been observed in the model system to prepare **11**. Treatment of enol lactone **7a** with 1 equiv of the *n*-butyllithium-generated anion of phosphonate **6** in THF at −78 °C followed by slow warming to 60 °C typically gave only about a 25%–30% yield of the desired enone **22**. In addition, about 20–25% of the protonated presumed

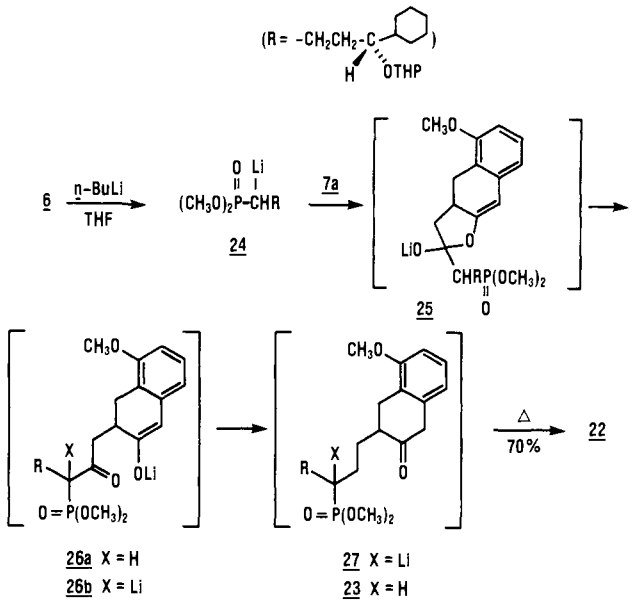


reaction intermediate **23** and about 50% of the starting phosphonate **6** were also isolated. Although **23** could be cyclized to **22** in about 60% yield using sodium hydride in glyme at 65 °C, we thought it should be possible to effect the transformation of **7a** → **22** in a more efficient manner.

Our initial results suggested a slightly different mechanism than that originally proposed for the conversion of enol lactones to cyclic α,β-unsaturated ketones.[6] As shown in Scheme V, reaction of phosphonate anion **24** with enol lactone **7a** should give initially the hemiketal intermediate **25**. It was originally presumed that

(16) Similar results were observed when using triethylammonium formate and palladium catalyst in toluene after the procedure of Heck: Cortese, N. A.; Heck, R. F. *J. Org. Chem.* **1978**, *43*, 3985.
(17) Cornforth, J. W.; Robinson, R. *J. Chem. Soc.* **1949**, 1855.
(18) Martin, V. S.; Woodard, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 6237.
(19) We deliberately epoxidized more than 50% of starting racemic alcohol **20a** in order to ensure high enantiomeric excess in the product. The resolved alcohol **20a** was shown to be of greater than 98% optical purity by HPLC and high-resolution NMR comparison of its Mosher ester[20] with that derived from the racemic alcohol.
(20) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.
(21) Alcohol **21a** could be directly converted to iodide **21c** by treatment with iodine, imidazole, and ethylenebis(diphenylphosphine) but the yield was low.
(22) To ensure that no racemization had taken place up to this point, the optical purity of iodide **21c** was confirmed as >98% by hydrolysis of its THP ether, Mosher ester formation,[20] and spectral comparison with the Mosher ester derived from racemic **21c** (prepared in an analogous manner from racemic **20a**).
(23) Direct conversion of tosylate **21b** to phosphonate **6** was unsuccessful.

Scheme V

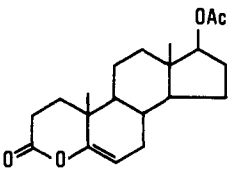


25 upon warming opens up to give the ketone enolate **26a** which undergoes proton transfer to generate the more stable β-ketophosphonate anion **27**. Upon further warming, **27** then undergoes an intramolecular Wadsworth–Emmons reaction to give **22**. We now believe that even at −78 °C, compound **25** rapidly opens up to give **26a** which immediately reacts with any phosphonate anion **24** present so as to generate the dianion **26b**. Dianion **26b** cannot cyclize unless it reacts with an external proton source (e.g., unreacted enol lactone **7a**) so as to generate the monoanion intermediate **27**. Starting with only 1 equiv of phosphonate anion **24** would lead to a theoretical maximum of only 50% yield of enone **22**. Thus, if this proposed mechanism is correct, one should use 2 equiv of phosphonate anion **24** and then add back 1 equiv of a proton source so as to produce the thermodynamically more stable monoanion **27**.

In the event, treatment of enol lactone **7a** with 2 equiv of **24**[24] at −78 °C in THF followed by warming to −10 °C, addition of 1 equiv of glacial acetic acid and then heating at 60 °C afforded a 70% yield of the desired enone **22**. The excess phosphonate reagent **6** can be readily removed chromatographically (as it is much more polar than the enone) and recycled if necessary. Only about 8% of the (easily separated) protonated reaction intermediate **23** was obtained by this procedure. On the other hand, treatment of **7a** with 2 equiv of phosphonate anion **24** but without any added proton source gave mainly **23** as expected, with only a minor amount of **22** being formed.

This modified cyclopentane annulation procedure has also proved applicable to the preparation of other lower side chain modified benzindene prostaglandins. In addition, this method works well for forming six-membered rings.[25] For example, treatment of enol lactone **28** with 2 equiv of lithium dimethyl methylphosphonate in THF at −78 °C followed by warming to −20 °C, addition of 1 equiv of acetic acid, and then stirring at 25 °C for 17 h afforded (after hydrolysis of the C-17 acetate with potassium carbonate in methanol) an 85% yield of testosterone (**29**).[25,26]

Because in the intramolecular Wittig reaction a racemic enol lactone (**7a**) is coupled with an optically active phosphonate (**6**), the resulting product (**22**) is a 1:1 mixture diastereomeric at C-9.



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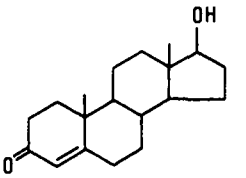
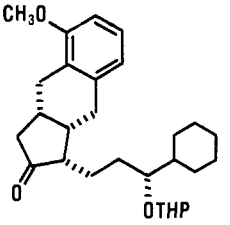


29

The desired isomer **5** could be isolated in pure form only with great difficulty. Therefore, we were forced to carry the mixture of diastereomers on through the synthesis and separate at a later stage.[27]

Hydrogenation of the more hindered tetrasubstituted enone **22** under the conditions developed in the model system for the reduction of enone **11** gave back mainly starting material. Dissolving metal reduction, the usual method for the reduction of tetrasubstituted enones, gave only the trans-ring-fused product.[28] A variety of conjugate metal hydride reduction methods gave back starting material or led to only reduction of the ketone. However, hydrogenation of enone **22** at slightly elevated pressure (3 atm) for several days using palladium on carbon catalyst in ethanol[29] effected the desired reaction to give the desired 1:1 mixture of cis-ring-fused ketones **30** and **31** in excellent yield. Only a trace of overreduction of the ketone to an alcohol was observed under these conditions.



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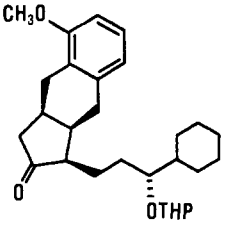
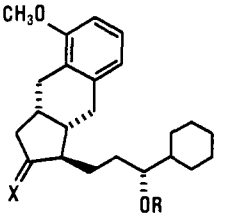
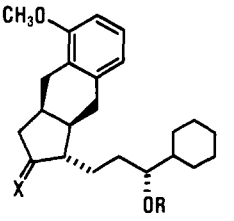


31

The mixture of **30** and **31** (which was only separable by HPLC) was equilibrated by treatment with aqueous sodium hydroxide in refluxing ethanol. Unfortunately, the equilibrium ratio of the resulting ketones **4** and **33a** to the starting ketones **30** and **31** was only 3:1, and separation of isomers was again difficult.[30] Reduction of the mixture of **4**, **33a**, **30**, and **31** using sodium borohydride in methanol at 25 °C followed by THP hydrolysis of the resulting alcohol mixture containing **32a** and **33b** gave a 75% overall yield of a slightly impure mixture of **32b** and **33c**.[31]



4 X = O; R = THP
32a X = α-OH, β-H; R = THP
32b X = α-OH, β-H; R = H



33a X = O; R = THP
33b X = β-OH, α-H; R = THP
33c X = β-OH, α-H; R = H

(24) Attempts to effect the reaction using 1 equiv of the phosphonate reagent **6** and 2 equiv of base (e.g., lithium diisopropylamide) followed by treatment with 1 equiv of **7a** at low temperature, warming to about 0 °C, addition of 1 equiv of glacial acetic acid, and heating at 60 °C gave only low yields of the desired product.

(25) Aristoff, P. A. *J. Org. Chem.* **1985**, *50*, 1765.

(26) Only about a 30% yield of testosterone was obtained when 1 equiv of lithium dimethyl methylphosphonate was used.[25]

(27) We had originally hoped to separate enone **5** from its C-9 diastereomer, and then subject its C-9 diastereomer to treatment with base under equilibrating conditions so as to regenerate the 1:1 mixture **22**.

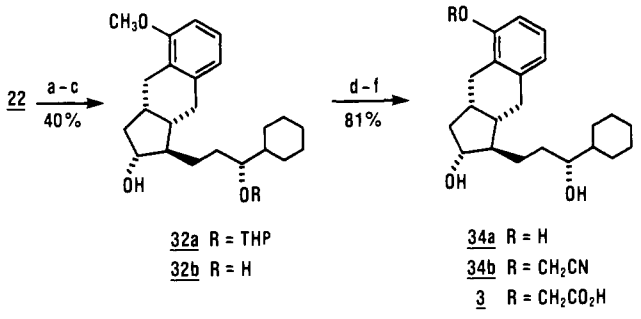
(28) Caine, D. In "Organic Reactions"; Dauben, W. G., Ed.; Wiley: New York, 1976; Vol. 23, Chapter 1, p 33.

(29) No reaction was observed when ethyl acetate was used as solvent.

(30) The mixture of **4** and **33a** was separated from **30** and **31** using medium-pressure liquid chromatography and subjected to the equilibration conditions (NaOH, H_2O, EtOH, 100 °C) to confirm the 3:1 equilibrium ratio.

(31) The alcohol byproducts resulting from the sodium borohydride reduction of **30** and **31** are very difficult to completely remove chromatographically.

Scheme VI



32a R = THP
32b R = H

34a R = H
34b R = CH_2CN
3 R = CH_2CO_2H

(a) H_2(3 atm), 10% Pd/C, EtOH. (b) $NaBH_4$, NaOH, H_2O, EtOH, -10°C. (c) H_2O, HOAc, THF, 45°C. (d) $LiPPh_2$, THF, 75°C. (e) K_2CO_3, $ClCH_2CN$, CH_3COCH_3, 60°C. (f) KOH, H_2O, CH_3OH, 90°C.

However, during the course of these experiments, we observed that the ketone of the desired isomer pair **4** and **33a** reduced at a somewhat faster rate than that of **30** and **31**.[32] *In fact, it was found that treatment of the 1:1 mixture of unequilibrated ketones **30** and **31** directly with sodium borohydride and sodium hydroxide in methanol at −10 °C led exclusively to the 1:1 mixture of equilibrated and reduced alcohols **32a** and **33b** in essentially quantitative yield.* Therefore, apparently in the presence of sodium borohydride and ethanolic sodium hydroxide, equilibration of **30** and **31** to the mixture with **4** and **33a** is fast, and while reduction of **30** and **31** is slow, reduction of **4** and **33a** is relatively fast. Thus, the net effect is that all of **30** and **31** is converted to **32a** and **33b**.

Following THP protecting group hydrolysis of the crude mixture of **32a** and **33b**, an overall 96% yield of the 1:1 mixture of **32b** and **33c** was obtained. HPLC analysis of the mixture indicated that <1% of any C-8 epi (i.e., trans-ring fused), C-11 epi (from ketone reduction from the concave face of the molecule), or C-12 epi (from incomplete equilibration) byproduct was present. Thus, starting from **22** in just two steps, the hydrogenation reaction and then the one-pot equilibration–reduction sequence, all four centers around the cyclopentane ring have been formed with >99:1 stereoselectivity. The methyl ether diols **32b** and **33c** turn out to be chromatographically separable at this point, and so, as shown in Scheme VI, enone mixture **22** can be converted to the desired optically pure diol **32b** in overall about 40% yield.

Completion of the synthesis involved attaching the upper side chain. This was accomplished without having to protect the alcohols at C-11 and C-15 (Scheme VI). Methyl ether cleavage of **32b** using an excess of lithium diphenylphosphide[33] in refluxing THF afforded a 96% yield of phenol **34a**.[34] Alkylation of phenol **34a** with potassium carbonate and chloroacetonitrile in refluxing acetone gave the nitrile **34b** in 91% yield. Finally, nitrile hydrolysis in hot ethanolic potassium hydroxide afforded the desired acid **3** (U-68,215) in overall 81% yield from **32b**. U-68,215 prepared by this route was identical in all respects including melting point and optical rotation with material prepared by the original benzindene synthesis.[1,2]

In conclusion, the synthesis of the novel antiulcer agent U-68,215 (**3**) has been achieved in just 14 steps and 12% overall yield from 5-methoxy-2-tetralone. U-68,415 is synthesized in optically pure form with the original chiral center arising via a Sharpless kinetic resolution and with complete stereocontrol of four of the five asymmetric centers. The benzindene nucleus has been formed via a convergent cyclopentane annulation route involving the conversion of an enol lactone to an enone in the key step. Using this approach, we have been able to prepare multigram quantities of U-68,215 and other benzindene prostaglandins for biological evaluation. Further exploration of the utility of the modified intramolecular Wadsworth–Emmons–Wittig reaction is in progress.

Experimental Section[35]

Methyl 3,4-Dihydroxy-2-hydroxy-5-methoxynaphthalenecarboxylate (15a). A solution of 20.6 g (117 mmol) of 5-methoxy-2-tetralone (**8a**)[17] in 350 mL of dimethyl carbonate at 0 °C was treated with 32 mL (140 mmol) of 25% methanolic sodium methoxide, heated at 70 °C for 18 h, cooled to 0 °C, quenched with 200 mL of 1 M aqueous hydrochloric acid, and extracted with ethyl acetate. The organic extract was washed with brine and dried ($MgSO_4$), and the solvents were removed under reduced pressure. The resulting crude product was crystallized from diethyl ether and hexane to give 23.2 g (85%) of **15a** as a white crystalline solid: mp 55–58 °C; R_f 0.47 (in 10% ethyl acetate in hexane); NMR δ 2.3–2.7 (m, 2 H), 2.8–3.0 (m, 2 H), 3.80 (s, 3 H), 3.90 (s, 3 H), 6.6–7.5 (m, 3 H), 13.35 (s, 1 H); ^{13}C NMR δ 19.37, 29.07, 51.54, 55.41, 99.81, 107.75, 118.94, 121.38, 126.56, 132.78, 155.75, 172.48, 178.80; IR (mull) 1640, 1600, 1585, 1565, 1420, 1380, 1310, 1275, 1220, 1205, 1085, 1050, 1030, 890, 785, 770, 720 cm^{-1}; mass spectrum, calcd for $C_{13}H_{14}O_4$ *m/e* 234.0892, found *m/e* 234.0902. Anal. Calcd for $C_{13}H_{14}O_4$: C, 66.65; H, 6.02. Found: C, 66.98; H, 6.13.

Methyl 3,4-Dihydro-2-hydroxy-5-methoxy-3-(2-propenyl)-naphthalenecarboxylate (15b). A solution of 39 mL (282 mmol) of diisopropylamine in 300 mL of THF at −50 °C was treated with 170 mL (272 mmol) of 1.6 M *n*-butyllithium (in hexane), stirred at −50 °C for 15 min and then at 0 °C for 15 min, and then treated dropwise with 30.0 g (128 mmol) of β-keto ester **15a** in 70 mL of THF. The resulting yellow suspension was stirred for 1 h at 0 °C and then treated with 13.5 mL (160 mmol) of allyl bromide in 50 mL of THF. The resulting orange solution was stirred for 1 h at 25 °C, cooled to 15 °C, quenched with 500 mL of 1 M aqueous hydrochloric acid, and extracted with ethyl acetate. The organic extract was washed with brine and dried ($MgSO_4$). the solvents were removed in vacuo to give 44.2 g of olefin **15b** as a tan solid which was used without further purification. An analytical sample was prepared by recrystallization from hexane and ether to give **15b** as a white crystalline solid: mp 70–71 °C; R_f 0.34 (in 10% ethyl acetate in hexane): NMR δ 1.8–3.2 (m, 5 H), 3.80 (s, 3 H), 3.90 (s, 3 H), 4.7–5.4 (m, 2 H), 5.5–6.1 (m, 1 H), 6.5–7.6 (m, 3 H), 13.4 (s, 1 H); ^{13}C NMR δ 24.00, 33.88, 38.75, 51.68, 55.62, 99.43, 107.97, 117.05, 118.75, 120.02, 126.54, 132.25, 135.74, 156.50, 172.79, 180.60; IR (mull) 1600, 1440, 1270, 1255, 1235, 1050, 1000, 885, 790, 770 cm^{-1};·mass spectrum, calcd for $C_{16}H_{18}O_4$ *m/e* 274.1205, found *m/e* 274.1201. Anal. Calcd for $C_{16}H_{18}O_4$: C, 70.05; H, 6.61. Found: C, 69.96; H, 6.62.

5-Methoxy-3-(2-propenyl)-2-tetralone (16). A solution of 44.1 g of β-keto ester **15b**, 6.0 g (142 mmol) of anhydrous lithium chloride, and 7.5 mL of water in 110 mL of Me_2SO was heated for 4 h at 150 °C, cooled, and partitioned between water and ethyl acetate. The organic extract was washed with brine and dried ($MgSO_4$). The solvents were removed to give 28 g (100% from **15a**) of ketone **16** as a yellow solid which was used without further purification. An analytical sample was prepared by recrystallization from ether and hexane to give **16** as a white crystalline solid: mp 39–40 °C; R_f 0.32 (in 10% ethyl acetate in hexane); NMR δ 1.8–2.8 (m, 4 H), 3.0–4.3 (m including 2 H broad singlet at δ

(32) Presumably while reduction from the concave face of the molecule is disfavored with all four isomers **30**, **31**, **4**, and **33a**, reduction of **30** and **31** from the convex face is somewhat inhibited by the strain in the product which has the C-11 alcohol syn to the C-12 side chain.

(33) Ireland, R. E.; Walba, D. M. *Tetrahedron Lett.* **1976**, 1071.

(34) Much lower yields in the demethylation step were observed when lithium *n*-butylmercaptide in hot hexamethylphosphoramide or sodium thioethoxide in dimethylformamide were used. For a review of ether cleavage see: Bhatt, M. V.; Kulkarni, S. U. *Synthesis* **1983**, 249.

(35) All melting points are uncorrected. Combustion analysis and IR, and mass spectra were obtained by the Physical and Analytical Chemistry Research Department of The Upjohn Co., with IR spectra being obtained either on neat samples (oils) or on Nujol mulls (solids). Mass spectra were recorded at high resolution for derivatized (Me_3Si) or underivatized compounds at 70 eV. 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. C-13 NMR spectra were obtained of chloroform-*d* solutions on a Varian CFT-20 spectrometer operating at 20 MHz. Chemical shifts are reported in δ (parts per million) relative to internal tetramethylsilane. Thin-layer chromatography (TLC) was conducted with Analtech (Uniplates) precoated with silica gel (E. Merck, 70–230 mesh). The TLC plates were visualized first by UV light (Mineralight UVS-11) and then by spraying with 50% aqueous sulfuric acid followed by heating. Unless otherwise noted, column chromatography utilized neutral silica gel (E. Merck, 70–230 mesh). Brine refers to a saturated aqueous solution of NaCl. THF was dried by distillation under nitrogen from sodium/benzophenone ketyl. All other solvents were reagent grade or reagent grade distilled from glass (Burdick & Jackson). Diisopropylamine and diethylamine were dried by distillation under nitrogen from calcium hydride. Allyl bromide was dried by distillation under nitrogen from anhydrous magnesium sulfate. All other reagents were used as purchased and were reagent grade where available. All reactions were degassed and were done under an inert atmosphere.

3.53 and 3 H singlet at δ 3.80, 6 H), 4.8–5.4 (m, 2 H), 5.5–6.1 (m, 1 H), 6.5–7.4 (m, 3 H); ^{13}C NMR δ 26.85, 34.06, 44.34, 46.76, 55.40, 108.38, 116.99, 120.30, 124.41, 127.53, 135.04, 135.73, 156.68, 211; IR (mull) 1715, 1640, 1600, 1590, 1470, 1440, 1435, 1260, 1080, 910, 770, 720, 610 cm^{-1}; mass spectrum, calcd for $C_{14}H_{16}O_2$ *m/e* 216.1150, found *m/e* 216.1145. Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 77.46; H, 7.81.

5-Methoxy-3-(2-propenyl)-2-tetralone Ethylene Ketal (17a). A solution of 27.8 g (128 mmol) of ketone **16**, 60 mL (450 mmol) of triethylorthoformate, 270 mg (1.41 mmol) of *p*-toluenesulfonic acid monohydrate, 150 mL (2.2 mol) of ethylene glycol, and 450 mL of methylene chloride was stirred at 25 °C for 22 h, treated with 7.5 mL of triethylamine and then 500 mL of half-sturated aqueous sodium bicarbonate solution, and extracted with methylene chloride. The organic extract was washed with water and brine and dried (Na_2SO_4). The solvents were concentrated under reduced pressure, and the residue was filtered through 100 g of silica gel with 800 mL of 10% ethyl acetate in hexane. The solvents were removed in vacuo to give 31.5 g (94%) of ketal **17a** as a white solid which was used without further purification: mp 34–35 °C; R_f 0.35 (in 10% ethyl acetate in hexane); NMR δ 1.7–3.3 (m including 2 H broad singlet at δ 2.90, 7 H), 3.4–4.4 (m including 3 H singlet at δ 3.77, 7 H), 4.8–5.3 (m, 2 H), 5.6–6.2 (m, 1 H), 6.5–7.4 (m, 3 H); ^{13}C NMR δ 27.51, 33.43, 38.46, 40.69, 55.27, 64.85, 65.19, 107.47, 108.9, 115.88, 121.22, 124.41, 126.53, 135.85, 137.45, 156.6; IR (mull) 1620, 1590, 1470, 1440, 1260, 1155, 1075, 950, 770 cm^{-1}; mass spectrum, calcd for $C_{16}H_{20}O_3$ *m/e* 260.1412, found *m/e* 260.1401. Anal. Calcd for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: C, 74.05; H, 7.72.

2-(5-Methoxy-2-oxo-1,2,3,4-tetrahydronaphthyl)acetic Acid (18). A solution of 66.5 g (310 mmol) of sodium metaperiodate in 1400 mL of water was treated with 1.0 g (6.4 mmol) of potassium permanganate, stirred 30 min at 25 °C, and treated with 5.0 g (36 mmol) of anhydrous potassium carbonate, 350 mL of alcohol, and then 8.9 g (34.2 mmol) of olefin **17a** in 350 mL of *tert*-butyl alcohol while maintaining the solution temperature at 20–30 °C. The resulting reddish-purple suspension was stirred for 2 h at 25 °C, treated with 10 mL (150 mmol) of ethylene glycol, stirred for 2 h, acidified to pH 4 with 1 M aqueous hydrochloric acid, and extracted with ethyl acetate. The combined organic extracts were washed with brine and dried (Na_2SO_4). The solvents were removed in vacuo to give 8.5 g (89%) of acid **17b** as a solid (mp 129–130 °C).

Withour further purification, a solution of 8.0 g (28.7 mmol) of **17b**, 80 mL of 3 M aqueous hydrochloric acid, and 80 mL of acetone was heated at 60 °C for 4 h and then cooled and partitioned between brine and ethyl acetate. The organic extracts were dried (Na_2SO_4) and the solvents removed in vacuo to give **18** as an orange solid. Recrystallization of the crude product from ether afforded 5.63 g (84%, 75% from **17a**) of **18** as a pale yellow solid: mp 129–131 °C; R_f 0.22 (in 35% ethyl acetate in hexane containing 1% acetic acid); NMR δ 2.2–3.2 (m, 4 H), 3.3–4.0 (m including 2 H broad singlet at δ 3.67 and 3 H singlet at δ 3.85, 6 H), 6.4–6.9 (m, 2 H), 7.1–7.3 (m, 1 H), 10.2 (br s, 1 H); ^{13}C NMR δ 27.74, 34.14, 43.66, 43.88, 55.47, 108.41, 120.46, 123.93, 127.79, 134.92, 156.56, 177.78, 211; IR (mull) 2910 (br), 1730, 1715, 1675, 1470, 1455, 1445, 1265, 1200, 1195, 1185, 1090, 775, 745, 725 cm^{-1}; mass spectrum, calcd for $C_{13}H_{14}O_4$ *m/e* 234.0892, found *m/e* 234.0889. Anal. Calcd for $C_{13}H_{14}O_4$: C, 66.65; H, 6.02. Found: C, 66.12; H, 6.01.

2,3,3a,4-Tetrahydro-5-methoxy-2-oxonaphtho[2,3-*b*]furan (7a). A solution of 1.75 g (7.47 mmol) of acid **18** in 88 mL of ethyl acetate was treated all at once with 88 mL of a freshly prepared reagent in ethyl acetate 2 M in Ac_2O and 10^{-2} M in $HClO_4$ (made by the addition of 20.0 mL of a solution of 0.40 mL of 70% perchloric acid in 100 mL of ethyl acetate to 50 mL of ethyl acetate and 19.2 mL of acetic anhydride and then diluted to 100 mL with ethyl acetate). The resulting solution was stirred for 5 min at 25 °C and treated with 100 mL of saturated aqueous sodium bicarbonate, and the layers were separated. The organic layer was washed with brine and dried (Na_2SO_4). The solvents were removed under reduced pressure, and the residue was filtered through 20 g of silica gel rapidly eluting with 15% ethyl acetate in hexane. The solvent was removed in vacuo and the resulting solid recrystallized from ethyl acetate and hexane to give 1.37 g (85%) of enol lactone **7a** as a white solid: mp 139–141 °C; R_f 0.32 (in 15% ethyl acetate in hexane); NMR δ 2.0–4.1 (m including 3 H singlet at δ 3.86, 8 H), 6.0–6.2 (d, J = 3 Hz, 1 H), 6.6–7.0 (m, 2 H), 7.0–7.4 (m, 1 H); ^{13}C NMR δ 27.29, 33.17, 34.76, 55.48, 101.09, 109.60, 119.48, 121.42, 127.79, 134.98, 154.89, 156.31, 173.94; IR (mull) 1800, 1685, 1570, 1470, 1445, 1265, 1075, 965, 865, 850, 780 cm^{-1}; mass spectrum, calcd for $C_{13}H_{12}O_3$ *m/e* 216.0786, found *m/e* 216.0783. Anal. Calcd for $C_{13}H_{12}O_3$: C, 72.21; H, 5.59. Found: C, 71.86; H, 5.53.

2,3,3a,4-Tetrahydro-2-oxonaphtho[2,3-*b*]furan (7b). In a similar manner to the conversion of β-keto ester **15a** to enol lactone **7a**, 39.0 g (191 mmol) of β-keto ester **9**[11] was first converted to 32.2 g (91%) of ketone **10a** and then ketone **10a** (29.0 g, 156 mmol) was converted to the corresponding ketal (34.9 g, 97%), a portion (15.0 g, 65 mmol) of which was oxidized to the ketal acid (14.5 g, 90%) of which 13.3 g (53.6 mmol) was converted to **10b** (10.6 g, 97%). Finally, acid **10b** (5.0 g, 24.5 mmol) was converted to **7b** (3.92 g, 86%).

10a: R_f 0.35 (in 10% ethyl acetate in hexane); NMR δ 1.9–3.2 (m, 5 H), 3.57 (s, 2 H), 4.9–5.2 (m, 2 H), 5.6–6.1 (m, 1 H), 7.2 (s, 4 H); IR (film) 3415, 1710, 1640, 1600, 1460, 1400, 995, 920, 750 cm^{-1}; mass spectrum, calcd for $C_{13}H_{14}O$ *m/e* 186.1045, found *m/e* 186.1050. Anal. Calcd for $C_{13}H_{14}O$: C, 83.82; H, 7.57. Found: C, 83.84; H, 7.77.

10b: mp 113–114 °C; R_f 0.22 (in 40:60:1 ethyl acetate–hexane–acetic acid); NMR δ 2.3–3.3 (m, 5 H), 3.67 (s, 2 H), 7.2 (s, 4 H), 10.0 (br s, 1 H); IR (mull) 3120, 1760, 1725, 1685, 1460, 1240, 1220, 1205, 1185, 865, 765 cm^{-1}; mass spectrum, calcd for $C_{12}H_{12}O_3$ *m/e* 204.0786, found *m/e* 204.0780. Anal. Calcd for $C_{12}H_{12}O_3$: C, 70.57; H, 5.92. Found: C, 70.24; H, 6.04.

7b: mp 105–106 °C; R_f 0.30 (in 15% ethyl acetate in hexane); NMR δ 2.3–3.6 (m, 5 H), 6.25 (d, J = 3 Hz, 1 H), 7.2 (s, 4 H); IR (mull) 1800, 1790, 1685, 1455, 1165, 1120, 1110, 990, 835, 760 cm^{-1}; mass spectrum, calcd for $C_{12}H_{10}O_2$, *m/e* 186.0681, found *m/e* 186–0686. Anal. Calcd for $C_{12}H_{10}C_2$: C, 77.33; H, 5.41. Found: C, 77.17; H, 5.45.

3,3a-Didehydro-2,3,3a,4,9,9a-hexahydro-2-oxo-1*H*-benz[*f*]indene (11). A solution of 0.12 mL (1.1 mmol) of dimethyl methylphosphonate in 5 mL of THF at −78 °C was treated dropwise with 0.88 mL (1.15 mmol) of 1.32 M *n*-butyllithium (in hexane), stirred at −78 °C for 30 min, treated with 0.19 mg (1.0 mmol) of enol lactone **7b** in 4 mL of THF, stirred at −70 °C for 30 min, then at 25 °C for 2 h, and then at 50 °C for 2 h, cooled, and quenched with 1 mL of 1 M aqueous hydrochloric acid, diluted with ethyl acetate, washed with brine, and dried ($MgSO_4$). The solvents were removed in vacuo, and the residue was chromatographed on silica gel eluted with 2:1 hexane/ethyl acetate to give 70 mg (37%) of enone **11** as a white solid: mp 69–71 °C; R_f 0.27 (in 2:1 hexane/ethyl acetate); NMR δ 2.0–3.4 (m, 5 H), 3.98 (s, 2 H), 6.10 (s, 1 H), 7.25 (s, 4 H); IR (mull) 1710, 1690, 1670, 1625, 1195, 755 cm^{-1}; mass spectrum, calcd for $C_{13}H_{12}O$ *m/e* 184.0888, found *m/e* 184.0882. Anal. Calcd for $C_{13}H_{12}O$: C, 84.75; H, 6.57. Found: C, 85.09; H, 6.74.

(3aα,9aα)-2,3,3a,4,9,9a-Hexahydro-2-oxobenz[*f*]indene (12). A suspension of 1.5 g (8.14 mmol) of enone **11** and 160 mg of 5% palladium on charcoal in 150 mL of ethyl acetate was hydrogenated at atmospheric pressure until the theoretical amount of hydrogen (178 mL) had been taken up (~7 h). The suspension was filtered through celite and the filtrate concentrated under reduced pressure. The resulting colorless oil was chromatographed on silica gel eluted with 15% ethyl acetate in hexane to give 1.30 g (86%) of **12** as a white solid: mp 98–99 °C; R_f 0.31 (in 20% ethyl acetate in hexane); NMR δ 1.7–3.3 (m, 10 H), 7.21 (s, 4 H); ^{13}C NMR δ 32.87, 33.33, 44.40, 126.26, 128.42, 136.12, 218.81; IR (mull) 1730, 1485, 1455, 1180, 755, 735 cm^{-1}; mass spectrum, calcd for $C_{13}H_{14}O$ *m/e* 186.1045, found *m/e* 186.1039. Anal. Calcd for $C_{13}H_{14}O$: C, 83.83; H, 7.58. Found: C, 83.88; H, 7.60.

(2α,3aα,9aα)-3a,4,9,9a-Tetrahydro-2-hydroxy-1*H*-benz[*f*]indene (14). A solution of 400 mg (10.5 mmol) of sodium borohydride in 50 mL of methanol at −30 °C was treated with 650 mg (3.5 mmol) of ketone **12** and 2.0 mL of methylene chloride in 40 mL of methanol, stirred at −30 °C for 30 min and allowed to warm to −15 °C over 1 h, quenched with 4.0 mL of acetic acid, and partitioned between brine and ethyl acetate. The combined organic layers were washed with saturated aqueous sodium bicarbonate and with brine and were dried ($MgSO_4$). The solvents were removed in vacuo to give 650 mg (99%) of **14** as a white solid: mp 110–111 °C; R_f 0.31 (in 2:1 hexane/ethyl acetate); NMR δ 0.84–1.4 (m, 2 H), 1.74 (s, 1 H), 1.89–2.98 (m, 8 H), 3.88–4.33 (m, 1 H), 7.20 (s, 4 H); ^{13}C NMR δ 34.51, 34.94, 41.81, 72.67, 126.00, 127.67, 139.08; IR (mull) 3250, 3205, 1455, 1355, 1095, 755, 745 cm^{-1}; mass spectrum, calcd for $C_{13}H_{16}O$ *m/e* 188.1201, found *m/e* 188.1179. Anal. Calcd for $C_{13}H_{16}O$: C, 82.94; H, 8.57. Found: C, 82.95; H, 8.60.

(3*R*)-3-Cyclohexylprop-1-en-3-ol (20a). A solution of 195 mL (254 mmol) of 1.3 M vinylmagnesium bromide (in THF) in 140 mL of THF at 0 °C was treated dropwise with 25.0 g (223 mmol) of cyclohexanecarboxaldehyde (**19**) in 40 mL of THF, stirred for 4 h at 0 °C, quenched with 1 L of aqueous ammonium chloride, and extracted with ethyl acetate. The organic extracts were washed with saturated aqueous sodium bicarbonate and with brine and were dried ($MgSO_4$). The solvents were concentrated under reduced pressure to give 35 g of racemic 3-cyclohexylprop-1-en-3-ol which was used without further purification.

A solution of 72.2 mL (243 mmol) of titanium(IV) isopropoxide and 62.2 mL (290 mmol) of (−)-diisopropyl D-tartrate in 2.2 L of methylene chloride at −25 °C was treated with 34 g of the above crude racemic 3-cyclohexylprop-1-en-3-ol in 80 mL of methylene chloride, stirred for 10 min at −25 °C, treated with 48.5 mL (146 mmol) of 3 M *tert*-butyl hydroperoxide in dichloroethane, stirred for 3 days at −20 °C, and then cannulated into a 0 °C solution of 200 g of tartaric acid and 400 g of ferrous sulfate in 2 L of water. The resulting suspension was stirred for

30 min at 0 °C and then filtered through Celite, rinsing with methylene chloride. The layers in the filtrate were separated, and the aqueous layer was extracted with methylene chloride. The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure to give a yellow residue which was dissolved in 650 mL of hexane and treated at 0 °C with 550 mL of 1 M aqueous sodium hydroxide. The resulting suspension was stirred for 40 min at 0 °C, and the layers were separated. The aqueous layer was extracted with hexane, and the combined organic layers were washed with brine and dried (Na_2SO_4). The solvents were removed under reduced pressure and the residue chromatographed on silica gel eluted with 12% ethyl acetate in hexane to give 9.59 g (32% from **19**) of alcohol **20a**[19] as a colorless oil: R_f 0.54 (in 25% ethyl acetate in hexane); NMR δ 0.73–2.67 (m, 12 H), 3.87 (t, 1 H), 5.07–5.43 (m, 2 H), 5.67–6.13 (m, 1 H); ^{13}C NMR δ 26.20, 26.60, 28.42, 28.85, 43.61, 115.35, 139.92; IR (film) 3370, 1450, 1020, 990, 975, 890 cm^{-1}; $[\alpha]_D$ +26° (*c* 1.142, 95% EtOH). Anal. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 77.48; H, 11.65.

(3*R*)-3-Cyclohexyl-3-(tetrahydropyran-2-yloxy)-1-propanol (21a). A solution of 22.07 g (157 mmol) of allyl alcohol **20a**, 0.145 g of pyridine hydrochloride, and 44.4 mL (466 mmol) of dihydropyran in 300 mL of methylene chloride was stirred for 18 h at 25 °C and diluted with 200 mL of saturated aqueous sodium bicarbonate. The layers were separated, and the organic layer was washed with brine and dried (Na_2SO_4). The solvents were removed in vacuo to give 37.3 g of compound **20b** as a yellow oil (R_f 0.62 in 25% ethyl acetate in hexane) which was used without further purification.

A solution of 37.3 g of **20b** in 800 mL of THF at 0 °C was treated dropwise with 800 mL (400 mmol) of 0.5 M 9-BBN in THF, stirred 1 h at 0 °C, and then treated with 230 mL of 30% aqueous hydrogen peroxide followed by 230 mL of 3 M aqueous potassium hydroxide. The resulting suspension was stirred for 35 min at 0 °C and then 1 h at 25 °C and then partitioned between brine and ethyl acetate. The organic extracts were washed with brine and dried (Na_2SO_4). The solvents were removed in vacuo, and the residue was chromatographed on silica gel eluted with ethyl acetate in hexane to give 27.29 g (72% from **20a**) of alcohol **21a** as a colorless oil: R_f 0.3 (in 30% ethyl acetate in hexane); NMR δ 0.63–2.90 (m, 20 H), 3.23–4.13 (m, 5 H), 4.03–4.87 (m, 1 H); IR (film) 3435, 1450, 1160, 1135, 1075, 1025, 990 cm^{-1}. Anal. Calcd for $C_{14}H_{26}O_3$: C, 69.38; H, 10.81. Found: C, 69.67; H, 11.29.

(3*R*)-3-Cyclohexyl-3-(tetrahydropyran-2-yloxy)-1-iodopropane (21c). A solution of 27.19 g (112 mmol) of alcohol **21a** and 25.7 g (135 mmol) of *p*-toluenesulfonyl chloride in 136 mL of pyridine was stirred for 20 h at 0 °C and then added to 350 g of ice, stirred for 75 min, diluted with water, and extracted with ethyl acetate. The combined ethyl acetate extracts were washed with saturated aqueous sodium bicarbonate and with brine and were dried (Na_2SO_4). The solvents were removed under reduced pressure to give 38.09 g (86%) of crude tosylate **21b** (R_f 0.48 in 20% ethyl acetate in hexane) which was used without further purification.

A solution of 36.74 g (92.65 mmol) of the above tosylate **21b**, 1.5 mL of diisopropylethylamine, and 83.3 g (550 mmol) of sodium iodide in 360 mL of acetone was stirred for 20 h at 25 °C. Most of the acetone was then removed under reduced pressure, and the residue was diluted with ethyl acetate, washed with 5% aqueous sodium thiosulfate and then with brine, and dried ($MgSO_4$). The solvents were removed in vacuo, and the residue was chromatographed on silica gel eluted with 3% ethyl acetate in hexane to give 27.47 g (84%, 72% from **21a**) of iodide **21c**[22] as a colorless oil: R_f 0.47 (in 10% ethyl acetate in hexane); NMR δ 0.63–2.53 (m, 19 H), 3.07–3.70 (m, 4 H), 3.77–4.01 (m, 1 H), 4.48–4.82 (m, 1 H); IR (film) 1450, 1200, 1130, 1115, 1075, 1065, 1035, 1025, 980 cm^{-1}. Anal. Calcd for $C_{24}H_{25}O_2$: C, 47.73; H, 7.15. Found: C, 48.05; H, 7.21.

Dimethyl [(4*R*)-4-Cyclohexyl-4-(tetrahydropyran-2-yloxy)butyl]-phosphonate (6). A solution of 4.24 mL (41.0 mmol) of diethylamine in 200 mL of THF at −35 °C was treated dropwise with 26 mL (40 mmol) of 1.55 M *n*-butyllithium (in hexane) and then stirred for 15 min at −35 °C, and treated with 4.51 g (36.3 mmol) of dimethyl methylphosphonate in 20 mL of THF at −78 °C. The resulting solution was stirred for 30 min at −78 °C and then treated dropwise with 11.6 g (32.9 mmol) of iodide **21c** in 40 mL of THF, stirred at −78 °C for 1 h, and allowed to slowly warm to −10 °C over 4 h. The reaction mixture was then partitioned between 1:1 brine–water and ethyl acetate. The organic extract was washed with brine and dried (Na_2SO_4). The solvents were removed under reduced pressure, and the residue was chromatographed on silica gel eluted with ethyl acetate to give 1.5 g (13%) of recovered iodide **21c** and 7.98 g (70%, 80% based on recovered starting material) of phosphonate **6** as a colorless oil: R_f 0.14 (in ethyl acetate); NMR δ 0.63–2.53 (m, 23 H), 3.23–4.20 (m, 3 H), 3.70 (s, 3 H), 3.83 (s, 3 H), 4.60 (br s, 1 H); IR (film) 1450, 1245, 1200, 1130, 1115, 1060, 1030, 990, 835, 815 cm^{-1}. Anal. Calcd for $C_{17}H_{33}O_5P$: C, 58.60; H, 9.55. Found: C, 58.63; H, 9.81.

15-Cyclohexyl-8,12-didehydro-9,11-dideoxy-13,14-dihydro-2′,9-methano-1,4,5,6,16,17,18,19,20-nonanor-3-oxa-11-oxo-3,7-(1′,3′-*inter*-phenylene)-PGF$_1$ 15-(Tetrahydropyranyl Ether) (22). A solution of 16.0 g (45.9 mmol) of phosphonate **6** in 450 mL of THF at −78 °C was treated dropwise with 30.9 mL (46.7 mmol) of 1.51 M *n*-butyllithium (in hexane), stirred for 1 h at −78 °C, and then treated dropwise at −78 °C with a solution of 4.78 g (22.1 mmol) of enol lactone **7a** in 100 mL of THF. The resulting solution was allowed to slowly warm to −10 °C over 4 h and then treated with a solution of 1.32 mL (23.0 mmol) of glacial acetic acid in 25 mL of THF and stirred at 25 °C for 30 min and then at 60 °C for 7 h. The reaction was then cooled to 0 °C, diluted with 500 mL of brine containing 23 mL of 1 M aqueous hydrochloric acid, and immediately extracted with ethyl acetate. The organic extracts were washed with brine and dried (Na_2SO_4). The solvents were concentrated in vacuo and the residue was chromatographed on silica gel eluted with 20% ethyl acetate in hexane and then with 100% ethyl acetate in hexane to give 8.9 g (56%) of recovered phosphonate **6** and 6.83 g (70%) of enone **22** as a colorless oil: R_f 0.21 (in 20% ethyl acetate in hexane); NMR δ 0.73–3.07 (m, 25 H), 3.20–3.43 (m, 3 H), 3.47–4.20 (m, 3 H), 3.83 (s, 3 H), 4.50–4.87 (m, 1 H), 6.80 (dd, $J_1 = J_2 = 7.5$ Hz, 2 H), 7.20 (dd, $J_1 = J_2 = 7.5$ Hz, 1 H); IR (film) 1690, 1645, 1585, 1470, 1450, 1365, 1270, 1250, 1200, 1160, 1135, 1115, 1090, 1075, 1050, 1030, 985 cm^{-1}. Anal. Calcd for $C_{28}H_{38}O_4$: C, 76.67; H, 8.73. Found: C, 76.89; H, 8.98.

15-Cyclohexyl-9-deoxy-13,14-dihydro-2′,9α-methano-3-oxa-1,4,5,6,16,17,18,19,20-nonanor-3,7-(1′,3′-*inter*-phenylene)-PGF$_1$ (32b). A suspension of 6.37 g (14.5 mmol) of enone **22**, 0.15 g of anhydrous potassium carbonate, and 2.15 g of 10% palladium on carbon in 300 mL of ethanol was hydrogenated at 50 psi for 43 h and then filtered through celite. The solvents were removed in vacuo to give 6.4 g of the mixture of **30** and **31** (R_f 0.34 in 20% ethyl acetate in hexane).

A solution of 6.0 g (13.6 mmol) of the ketone mixture **30** and **31** 120 mL of 10% aqueous sodium hydroxide, and 560 mL of 95% ethanol at −10 °C was treated with 0.49 g (13 mmol) of sodium borohydride, stirred 1 h at −10 °C, treated with another 0.51 g (13.5 mmol) of sodium borohydride, stirred 4 h at −10 °C, and quenched carefully with glacial acetic acid. The solution was concentrated under reduced pressure and then partitioned between ethyl acetate and brine. The organic extracts were washed with saturated aqueous sodium bicarbonate and with brine and were dried (Na_2SO_4). The solvents were removed in vacuo to give 6.2 g of a mixture of **32a** and **33b** as a yellow foam (R_f 0.18 in 25% ethyl acetate in hexane).

Without further purification, the 6.2-g alcohol mixture of **32a** and **33b** was dissolved in 40 mL of THF, 60 mL of water, and 12 mL of glacial acetic acid and then heated at 45 °C for 3 h, cooled, and partitioned between ethyl acetate and brine. The organic extracts were washed with saturated aqueous sodium bicarbonate and with brine and were dried (Na_2SO_4). The solvents were removed under reduced pressure, and the residue was filtered through silica gel rapidly eluted with 50% ethyl acetate in hexane to give 4.68 g (96%) of a 1:1 mixture of **32b** and **33c** as a colorless oil (>98% pure by HPLC). Further chromatography of the mixture of **32b** and **33c** on silica gel eluting with 4% isopropyl alcohol in isooctane afforded 1.06 g (22%) of the tetraepi isomer **33c** and 2.01 g (41%) of **32b** (with the remainder of the material being a mixture of **32b** and **33c**).

32b: R_f 0.33 (in 10% isopropyl alcohol in isooctane); NMR δ 0.73–3.10 (m, 26 H), 3.17–3.97 (m, 2 H), 3.80 (s, 3 H), 6.63–6.93 (m, 2 H), 7.00–7.23 (m, 1 H); IR (film): 3360, 1585, 1475, 1470, 1450, 1265, 1105, 1075, 1045, 1030, 770, 660 cm^{-1}; mass spectrum, calcd for $C_{29}H_{50}O_3Si_2$ [M + of bis(trimethylsilyl) derivative] *m/e* 502.3298, found *m/e* 502.3274. Anal. Calcd for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56. Found: C, 77.74; H, 9.51.

33c: R_f 0.35 (in 10% isopropyl alcohol in isooctane); NMR δ 0.77–3.07 (m, 26 H), 3.20–3.97 (m, 2 H), 3.82 (s, 3 H), 6.67–6.90 (m, 2 H), 7.03–7.23 (m, 1 H); IR (mull) 3450, 3395, 3325, 3235, 1585, 1480, 1460, 1455, 1445, 1380, 1310, 1265, 1245, 1235, 1120, 1105, 1100, 1080, 1050, 1020, 770, 735 cm^{-1}; mass spectrum, calcd for $C_{29}H_{50}O_3Si_2$ [M + of bis(trimethylsilyl) derivative] *m/e* 502.3298, found *m/e* 502.3299. Anal. Calcd for $C_{23}H_{3O3}$: C, 77.05; H, 9.56. Found: C, 76.74; H, 9.51.

15-Cyclohexyl-1,2,4,5,6,16,17,18,19,20-decanor-9-deoxy-13,14-dihydro-2′,9α-methano-3-oxa-3,7-(1′,3′-*inter*-phenylene)-PGF$_1$ (34a). A solution of 2.34 mL (13.1 mmol) of diphenylphosphine in 70 mL of THF at 0 °C was treated with 8.10 mL (12.7 mmol) of 1.57 M *n*-butyllithium (in hexane), stirred for 5 min at 0 °C and 30 min at 25 °C, and treated with 1.57 g (4.38 mmol) of alcohol **32b** in 20 mL of THF. The resulting red solution was stirred at reflux for 5.5 h, cooled to 0 °C, and treated with 3.25 mL (18.2 mmol) of diphenylphosphine followed by 11.3 mL (17.7 mmol) of 1.57 M *n*-butyllithium (in hexane). The resulting solution was refluxed for an additional 18 h, cooled, acidified with 45 mL of M aqueous hydrochloric acid, and partitioned between brine and ethyl acetate. The organic extract was dried (Na_2SO_4), and the solvents were

then removed under reduced pressure. The residue was chromatographed on silica gel eluted with 50% ethyl acetate in hexane to give 1.45 g (96%) of phenol **34a**: R_f 0.22 (in 25% acetone in methylene chloride); NMR 0.73-3.07 (m, 26 H), 3.23-3.97 (m, 2 H), 6.00-6.53 (m, 1 H), 6.63-6.90 (m, 2 H) 6.93-7.17 (m, 1 H); IR (film) 3285, 1590, 1465, 1375, 1340, 1285, 1265, 1240, 1215, 1085, 1065, 1045, 1025, 975, 890, 775, 745, 735, 720 cm^{-1}; mass spectrum, calcd for $C_{31}H_{56}O_3Si_3$ [M + of tris(trimethylsilyl) derivative] *m/e* 560.3537, found *m/e* 560.3524. Anal. Calcd for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 74.27; H, 9.29.

2-Cyano-15-cyclohexyl-2-decarboxy-9-deoxy-13,14-dihydro-2′,9α-methano-4,5,6,16,17,18,19,20-octanor-3-oxa-3,7-(1′,3′-*inter*-phenylene)-PGF$_1$ (34b). A solution of 1.31 g (3.80 mmol) of phenol **34a**, 11.3 g (81.5 mmol) of anhydrous potassium carbonate, and 8.79 mL (139 mmol) of chloroacetonitrile in 40 mL of acetone was refluxed for 48 h, cooled, and partitioned between 1:1 brine-water and ethyl acetate. The organic extract was washed with brine and dried (Na_2SO_4). The solvents were removed under reduced pressure, and the residue was chromatographed on silica gel eluted with 50% ethyl acetate in hexane to give 1.33 g (91%) of nitrile **34b**: R_f 0.40 (in 20% acetone in methylene chloride); NMR δ 0.73-3.00 (m, 26 H), 3.17-3.93 (m, 2 H), 4.77 (s, 2 H), 6.73-7.03 (m, 2 H), 7.17 (dd, $J_1 = J_2 = 7.5$ Hz, 1 H); IR (mull) 3330, 2240, 1725, 1685, 1605, 1585, 1445, 1275, 1235, 1175, 1110, 1080, 1025, 975, 890, 775 cm^{-1}; mass spectrum, calcd for $C_{24}H_3NO_3$ *m/e* 383.2475, found *m/e* 383.2460. Anal. Calcd for $C_{24}H_{33}NO_3$: C, 75.16; H, 8.67; N, 3.74. Found: C, 75.13; H, 8.59; N, 3.51.

15-Cyclohexyl-9-deoxy-13,14-dihydro-2′,9α-methano-4,5,6,16,17,18,19,20-octanor-3-oxa-3,7-(1′,3′-*inter*-phenylene)-PGF$_1$ (3). A solution of 0.97 g (2.53 mmol) of nitrile **34b** and 17 mL of 25% aqueous sodium hydroxide in 58 mL of methanol was stirred at reflux for 6 h, cooled to 0 °C, acidified to pH 5 with 1 M aqueous hydrochloric acid, and partitioned between ethyl acetate and brine. The organic extract was dried (Na_2SO_4), and the solvents were removed in vacuo to give **3** as a light-yellow solid. Recrystallization from ethyl acetate and hexane afforded 0.95 g (93%) of **3** (U-68,215) as a white solid (identical in all respects with authentic material prepared previously by an unambiguous route[2]): mp 119-120 °C; R_f 0.54 (in the organic phase of an equilibrated mixture of 9:2:5:10 ethyl acetate-acetic acid-cyclohexane-water); NMR (CD_3COCD_3) δ 0.70-4.00 (m, 29 H), 4.68 (s, 2 H), 6.60-6.90 (m, 2 H), 7.10 (dd, $J_1 = J_2 = 7.5$ Hz, 1 H); IR (mull) 3380, 1735, 1710, 1605, 1590, 1455, 1420, 1375, 1260, 1255, 1105, 1085, 1025, 1015, 910, 895, 775, 740 cm^{-1}; mass spectrum, calcd for $C_{33}H_{58}O_5Si_3$ [M + of tris(trimethylsilyl) derivative] *m/e* 618.3592, found *m/e* 618.3576; $[\alpha]_D$ +41° (*c* 0.864, 95% EtOH). Anal. Calcd for $C_{24}H_{34}O_5$: C, 71.61; H, 8.51. Found: C, 71.71; H, 8.63.

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Asymmetric Synthesis of 2-Alkylpyrrolidines and Piperidines. Synthesis of (+)-Metazocine

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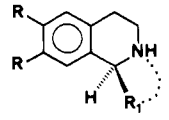
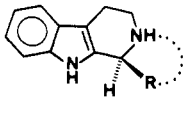
Abstract: Asymmetric alkylation of piperidines and pyrrolidines in the 2-position was efficiently accomplished by using a chiral formamidine derived from L-valinol. Since the saturated ring systems could not be metalated due to high pK_a's, the unsaturated systems were employed which possessed allylic protons. After asymmetric alkylation was complete (a mixture of 8-30% SN_2' alkylation was also observed), the formamidines were removed to give 2-alkylpyrrolines and 2-alkyltetrahydropyridines. Reduction of the unsaturation using Rh/C furnished the piperidine and pyrrolidine in 95-98% ee. Application of this method to the benzomorphan (+)-metazocine was also accomplished in 98% ee.

Our previous successes with asymmetric alkylation of tetrahydroisoquinolines **1**[1] and β-carbolines **2**[2] via chiral formamidines have led us to explore similar processes with simple saturated heterocycles such as pyrrolidine and piperidine. If this extension



1, R = H, R_1 = alkyl, cycloalkyl



2, R = alkyl, cycloalkyl

of the process was successful, a route to a variety of piperidine and pyrrolidine alkaloids and other important substances would be accessible.[3] However, the extension to simple saturated heterocycles was not routine and required major modification via an alternative approach. The successful implementation of this process forms the subject of this report.

As previously reported, the *tert*-butylformamidines of pyrrolidine and piperidine **3** are readily metalated with *tert*-butyllithium and, after conversion to the mixed cuprates, give high yields of alkylated products, **5**.[4] When these saturated heterocycles were transformed into formamidines **4** derived from L-valinol,[1,2] in an attempt to generate the α-lithioanions in a chiral environment, no metalation occurred at −78 °C, and as the temperature was allowed to warm to ~−45 °C, only addition of *t*-BuLi to the C=N link of the formamidine **6** took place. It was soon apparent that the oxygen ligand in the formamidine **4** was responsible for a complex with the lithium base **7**, which kept the latter at a distance such that the α-proton could not be satisfactorily removed. As the temperature was allowed to rise, the *t*-BuLi merely added to the formamidine π-system. Of further significance is the high pK_a for the α-protons in **3** and **4** relative to those in **1** and **2** which have been successfully deprotonated by using the chiral formamidines. The higher pK_a of **3** and **4** (no deprotonation at −78 °C) must, therefore, open up the alternative reaction path leading to **6**.

The failure to metalate **4** prompted us to incorporate an "activating element" such that the pK_a of the α-proton would be within the range of a common base. Toward this end, the 3-

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