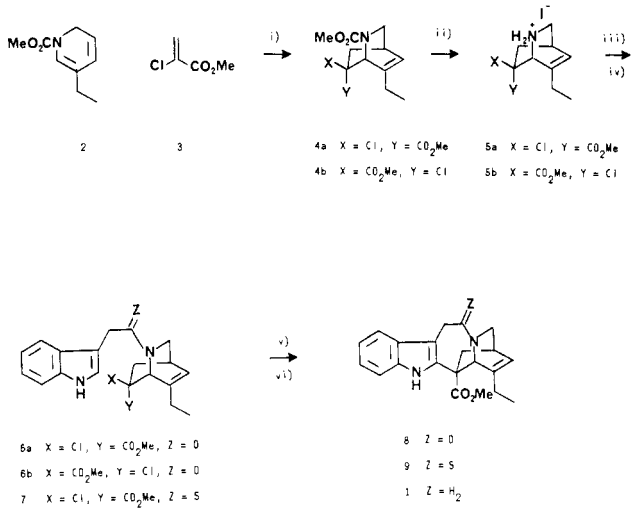
Scheme I[a]



[a] (i) 2 equiv of **3**, 5 mol % hydroquinone, 90 °C, 22 h, 2.5 M in toluene; (ii) 2.2 equiv of $Me_3SiSiMe_3$, 1.1 equiv of I_2 120 °C, 15 min; **4**, 25 °C, 20 h; excess MeOH; (iii) 2.2 equiv of *O,N*-bis(trimethylsilyl)acetamide, 0 °C, 30 min, CH_2Cl_2; 1.2 equiv of indole-3-acetyl chloride, 25 °C, 2.5 h; (iv) 0.8 equiv of Lawesson's reagent, 65 °C, 1 h, 0.1 equiv of HCl, 65 °C, 3 h; (v) irradiation of 8×10^{-4} M solution of **7** in CH_3CN/H_2O (30:70) containing $NaHCO_3$ (20 equiv) with a 450-W Hanovia mercury lamp/Pyrex filter, 6 h; (vi) 1.3 equiv of Et_3OBF_4, CH_2Cl_2, 0 to 25 °C, 45 min; 5 equiv of $NaBH_3CN$, 5 equiv of HOAc, MeOH, 0 to 25 °C, 5 h.

9 (Scheme I).

Diels–Alder reaction of **2**, available in five steps and 63% overall yield from 3-ethylpyridine,[4] and methyl α-chloroacrylate (**3**) gave a 1:1.4 mixture of the isomers **4a** and **4b** in 96% yield.[6] Although it is possible to separate **4a** and **4b** by careful flash chromatography,[7] and thus assign stereochemistry,[8] this separation is unnecessary for the synthesis of **1**. Treatment of the mixture of **4a** and **4b** with excess freshly prepared trimethylsilyl iodide[9] gave a mixture of **5a** and **5b** which was reacted without purification first with *O,N*-bis(trimethylsilyl)acetamide[10] and then with indole-3-acetyl chloride[11] to provide the indoles **6a** and **6b** as a 1:1.4 mixture of isomers in 97% overall yield from **4**. The above transformations were also carried out on pure samples of **4a** and **4b** in order to obtain pure samples of **6a** and **6b**. Solutions of pure **6a** or **6b** in $CDCl_3$ were found to equilibrate to a 1:1 mixture of **6a** and **6b** when exposed to catalytic amounts of anhydrous HCl.

Numerous attempts to effect photochemical cyclization[5] by irradiation of dilute solutions of **6a** or **6b** (or mixtures of **6a** and **6b**) in $MeOH/H_2O$ or CH_3CN/H_2O containing $NaHCO_3$ under argon with a 450-W Hanovia mercury lamp, with or without Pyrex or Vycor filters, afforded only trace amounts of **8**, despite the fact that the corresponding 20-deethyl compound (mixture of endo/exo isomers) provides 5-oxo-20-deethylcatharanthine in moderate yield under these reaction conditions.[12]

The isomer **6a** could be readily converted to the thioamide **7** in 85% yield by treatment with Lawesson's reagent;[13] in contrast, **6b** could not be converted to a thioamide with either Lawesson's reagent or P_2S_5. However, when a 1:1.4 mixture of the isomers **6a** and **6b** was reacted with Lawesson's reagent in dimethoxyethane containing a catalytic amount of anhydrous HCl, the thioamide **7** was obtained in 70% yield, presumably via isomerization of **6b** to **6a** and subsequent thionation.

Irradiation of an 8×10^{-4} M solution of the thioamide **7** in CH_3CN/H_2O (30:70) containing $NaHCO_3$ under argon with a 450-W Hanovia mercury lamp with a Pyrex filter for 6 h provided **9** in 30% crude yield. The thiolactam **9** was reduced[14] without further purification by treatment with Et_3OBF_4 followed by $NaBH_3CN$ to provide (±)-catharanthine (**1**) in 21% overall yield from **7**.

This synthesis of (±)-catharanthine requires a total of 11 steps and proceeds in an overall yield of 9% from commercially available 3-ethylpyridine. We are currently pursuing an enantioselective synthesis of (+)-catharanthine through the use of chiral auxiliaries in the Diels–Alder reaction.

Acknowledgment. We thank Professor J. P. Kutney (University of British Columbia) for providing us with an authentic sample of (+)-catharanthine and Professor R. J. Sundberg (University of Virginia) for providing us with a sample of 5-oxo-20-deethylcatharanthine. This investigation was supported by PHS Grant Number CA-32976, awarded by the National Cancer Institute, DHHS. MS data were obtained on a VG 7070 GC/MS and associated VG 2035F/B data system funded by NIH Biomedical Research Development Grant 1 508 RR 09082.

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Efficient Asymmetric Reduction of Acyl Cyanides with *B*-3-Pinanyl-9-BBN (Alpine-Borane)

Summary: Acyl cyanides are effectively reduced to optically active β-amino alcohols by using Alpine-Borane followed by sodium borohydride/cobaltous chloride.

Sir: The trialkylborane *B*-3-pinanyl-9-borabicyclo[3.3.1]nonane (Alpine-Borane[1]) is an effective asymmetric

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Table I. Yields and Enantiomeric Efficiencies in the Formation of Substituted 2-Ethanolamines from Acyl Cyanides

$RCHOHCH_2NH_2$	% yield[a]	% ee[b]
C_6H_5	77[c]	90 (98)
o-ClC_6H_4	74	86 (94)
p-$CH_3C_6H_4$	78	87 (95)
m-$CH_3C_6H_4$	84	85 (92)
n-C_6H_{13}	86[c]	77 (84)

[a] Isolated yield based on one-pot conversion from the acyl chloride except as noted. [b] By NMR, values given in parentheses are corrected for the optical purity of the α-pinene (92% ee). High optical purity α-pinene is available. [c] Isolated yield based on starting acyl cyanide.

reducing agent.[2] The course of the reduction appears to be governed largely by steric considerations. Aldehydes and acetylenic ketones are reduced much faster than other ketones. In addition, electron-withdrawing groups enhance the rate of reduction. The strong electron-withdrawing nature of a nitrile coupled with its steric resemblance to an acetylene made it appear that acyl cyanides would be ideal substrates for reduction. The resulting cyanohydrin would be a useful precursor to further products.[3] However, the reduction of the acyl cyanides and subsequent workup did not prove to be as straightforward as expected. Herein we report on our findings.

Benzoyl cyanide[1] was added to neat Alpine-borane (1.5 equiv). The mixture immediately became orange.[4] After 2 h, the benzoyl cyanide had completely reacted as indicated by ^1H NMR. However, the expected cyanohydrin-/9-BBN product built up to a maximum and then slowly decreased with the subsequent appearance of a 9-BBN/benzyl alcohol adduct. After 15 h of stirring, the cyanohydrin product had completely disappeared. At this point the major products were benzaldehyde and the benzyl alcohol/9-BBN adduct. Apparently the 9-BBN/cyanohydrin adduct undergoes an elimination reaction to provide benzaldehyde which then may undergo further reduction. The use of 1 equiv of Alpine-borane also led to considerable amounts of the undesired products. In this case the desired bimolecular reduction process cannot compete with the elimination reaction during the later stages of the reaction. It is thus important to use excess reducing agent.

Reduction of the cyanohydrin/9-BBN adduct to an amino alcohol was then investigated.[5] Several standard methods for achieving this transformation provided only benzyl alcohol. However, clean reduction was achieved by using sodium borohydride and methanolic cobaltous chloride.[6] The product, (−)-(*R*)-2-amino-1-phenylethanol was isolated in 77% yield and 90% ee. The asymmetric reduction thus proceeds by the stereochemical model proposed for acetylenes. Since the starting α-pinene was 92% ee, the reduction occurs in greater than 98% efficiency.[7]

With an effective procedure in hand, the reduction of a variety of substituted benzoyl cyanides was investigated. The substrates were prepared by treating the benzoyl chlorides with trimethylsilyl cyanide and tin tetrachloride.[8] The tin tetrachloride was removed by washing the mixture with ice water and the crude acyl cyanide used directly.[9] Reduction with neat Alpine-borane proceeded rapidly (0.5–1.5 h) at room temperature. The progress of the reaction was followed closely by NMR and the sodium borohydride/cobaltous chloride reduction was carried out as soon as reduction of the carbonyl was complete. Warming the reaction mixture or letting it stand for longer times lead to considerable aldehyde and alcohol formation. Isolated yields and enantiomeric purities were uniformly high (Table I). In addition to the aromatic compounds, an aliphatic substrate, 2-oxooctanenitrile,[1] also gave good results. The opposite enantiomer could be obtained by using (−)-α-pinene.

The following procedure is representative. A neat solution of 15 mmol of (*R*)-Alpine-Borane (from (+)-α-pinene and 9-BBN) was prepared in a 100-mL flask under nitrogen.[10] The flask was briefly opened to the atmosphere while being flushed with nitrogen and the acyl cyanide (10 mmol) was added in one portion. The progress of the reaction was monitored by NMR, with samples removed periodically by syringe and injected into an NMR tube containing deuteriochloroform. When reduction was complete (determined by the collapse of the aromatic region from approximately 8.1 ppm to a multiplet at approximately 7.4 ppm, the appearance of a cyanohydrin/9-BBN adduct resonance at approximately 6.0 ppm, and the appearance of α-pinene at 5.2 ppm) the solution was treated with 75 mL of methanol containing 9.52 g of cobaltous chloride. Sodium borohydride (7.56 g) was added in small portions, and the resulting black solution was stirred for 1–3 h. Acid (3 M hydrochloric acid, 100 mL) was added and the solution was stirred until all the precipitate dissolved. The organic byproducts were removed by washing the aqueous solution 3 times with 75 mL of chloroform and 3 times with 75 mL of ether. The aqueous layer was then made basic by the addition of concentrated ammonium hydroxide. Extraction with chloroform (3 × 75 mL) gave, after drying and concentrating, the product. Enantiomeric purities were determined by NMR shift studies using $Eu(hfc)_3$. The *S* enantiomer (minor product) shifted downfield faster than the *R* enantiomer. Assignment of configuration was made by the mode of reduction and comparison of the sign of rotation to literature values.

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performing preliminary experiments.

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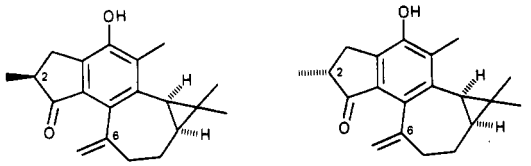
Total Synthesis of (+)-Jatropholone A and B

Summary: The first total synthesis of jatropholones A and B in homochiral form is disclosed; the absolute stereochemistry is thereby established.

Sir: High-pressure techniques (3–15 kbar) have become increasingly evident in organic synthesis. Benefits include mild reaction conditions and greatly enhanced yields for those reactions that involve a negative change in the activation volume ($\Delta V^{\ddagger}$); documented examples include the Diels–Alder reaction,[2] 1,3-dipolar cycloadditions,[3] the aldol[4] and Michael[5] reactions, introduction of protecting groups,[6] and preparation of Wittig reagents.[7] Thus the availability of the high-pressure technique permits the design of synthetic strategies not previously feasible.

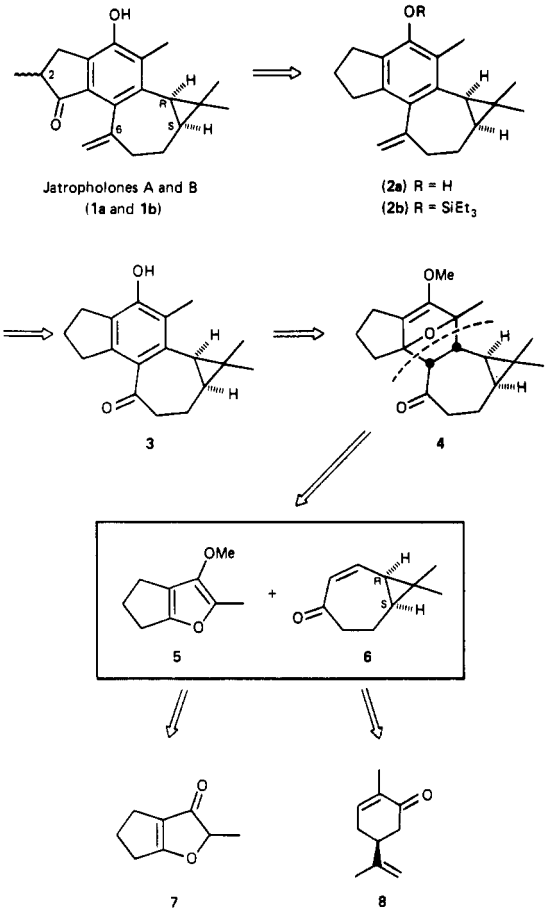
In this communication we wish to record the *first* total synthesis of jatropholone A and B (**1a** and **1b**), two novel diterpenes isolated from the roots of *Jatropha gossypiifolia L.* (Euphorbiaceae),[8] the plant that also yields jatrophone[9,10] and the hydroxyjatrophones A–C.[11] The



Jatropholones A and B

synthetic scheme, which proved viable *only* through aegis of a high-pressure Diels–Alder reaction, is short (i.e., 12 steps), reasonably efficient (ca. 6%), and establishes for the first time the absolute stereochemistry of the jatropholones.[12]

Scheme I



From the retrosynthetic perspective, assembly of the fully-substituted aromatic ring was viewed as the central synthetic challenge. Toward this end, we envisioned a Diels–Alder reaction of furan **5** with homochiral enone **6** (Scheme I). The former was anticipated to be available through O-methylation of bicyclic 3(2*H*)-furanone **7**,[14] while the latter, prepared from (*S*)-carvone (**8**), was recently exploited in our laboratory for the synthesis of (+)-hanegokedial.[15] Subsequent aromatization of the 7-oxabicyclo[2.2.1]heptene system **4**, introduction of the exo methylene, regioselective oxidation at C(3), and methylation at C(2) would then complete the synthetic venture.

We initiated synthesis of furan **5** with commercially available 1-pyrrolidinocyclopentene.[16] Acylation with acid chloride **9**[17] followed by hydrolysis [AcOH, H_2O, THF (1:1:2)] afforded **10**[18] in 68% yield. Subsequent removal of the acetate group [H_2SO_4, H_2O, THF (1:9:5)] and cy-

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