being stirred briefly, the mixture was allowed to stand until the sodium hydride had settled. The toluene layer was removed then with a syringe. Methyl iodide (5 g, 0.035 mol) followed by a solution of 0.43 g (0.003 mol) of 4-(hydroxymethyl)furan-3-carboxylic acid in 10 mL of THF was introduced into the flask, and the resulting mixture was stirred vigorously. After 42 h, the sodium salts were filtered, washed with 10 mL of ether, and then dissolved in 4 mL of water. The pH of this solution was brought to 3 by acidification with concentrated hydrochloric acid. The solid that separated from the aqueous phase was filtered, washed with 2 mL of water, dried, and recrystallized from ethyl acetate to yield 0.25 g (53%) of the methoxy acid **5b**; mp 132.5–133 °C.

Anal. Calcd for $C_7H_8O_4$: C, 53.85; H, 5.17. Found: C, 53.74; H, 5.12.

Similarly, **1b** had mp 95–96 °C (lit.[2] mp 94–95 °C), **2b** had mp 68–71 °C (lit.[4] mp 65–68 °C), and **6b** had mp 67–69 °C (petroleum ether).

Anal. (**6b**) Calcd for $C_7H_{10}O_3$: C, 59.14; H, 7.09. Found: C, 59.23; H, 7.13.

3-(Methoxymethyl)bicyclo[2.2.1]hepta-2,5-diene-2-carboxylic Acid (3b). A mixture of 5.94 g (0.09 mol) of freshly prepared cyclopentadiene and 5.7 g (0.05 mol) of 4-methoxytetrolic acid[7] in 3 mL of THF was stirred at room temperature for 3 days. After removal of the solvent, the residue was dissolved in 50 mL of ether and extracted with saturated aqueous sodium bicarbonate solution (4 × 20 mL). The combined bicarbonate layers were acidified at 0–5 °C with concentrated hydrochloric acid to pH 3.5 and then extracted with ether (4 × 50 mL). The ether solution was dried ($MgSO_4$) and then concentrated to a brown liquid (4.5 g). This residue was a mixture of methoxytetrolic acid (largely) and the bicyclic acid.

Separation was accomplished by fractional extraction of an ether solution of the mixture with aqueous sodium bicarbonate solution;[20] the bicyclic acid was observed in later fractions. Combination of the appropriate fractions and several recrystallizations of the bicyclic acid from petroleum ether gave **3b**; 0.17 g, mp 35–37 °C. On prolonged standing, this acid changes to a gummy material: IR (KBr pellet) cm^{-1} 3300–2300, 1670, 1620, 1430, 1500, 1270, 1200, 1110, 940, 730; NMR ($CDCl_3$) δ 10.94 (s, 1 H), 6.6–7.0 (m, 2 H), 4.61 ($^1/_2$ of AB quartet, 1 H, J = 14.0 Hz), 4.30 ($^1/_2$ of AB quartet, 1 H, J = 14.0 Hz), 3.7–4.05 (m, 2 H), 3.32 (S, 2 H), 1.9–2.25 (m, 2 H).

Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.53; H, 6.64.

3-(Acetoxymethyl)bicyclo[2.2.1]hepta-2,5-diene-2-carboxylic Acid. A solution of 3.0 g (0.021 mol) of 4-acetoxytetrolic acid[6] in 2 mL of ether was mixed with 3.0 g (0.045 mol) of freshly prepared cyclopentadiene and stirred at ambient temperature. After 68 h, the mixture was diluted with 20 mL of a 1:1 mixture of benzene and ether to decrease the viscosity. The solution was extracted with saturated aqueous sodium bicarbonate (3 × 10 mL). The combined aqueous solution on acidification at 0 °C with concentrated hydrochloric acid afforded a solid. Recrystallization from benzene gave 1.3 g (30%) of the bicyclic acetoxy acid, mp 91–93 °C. Further recrystallization gave an analytical sample: mp 93–94 °C; IR (KBr pellet) cm^{-1} 3500–2300, 1730, 1650, 1610, 1435, 1375, 1340, 1300, 1260, 1235, 1200, 1050, 940, 860, 715; NMR ($CDCl_3$) δ 8.6–9.5 (br, 1 H), 6.55–7.0 (m, 2 H), 5.31 ($^1/_2$ of AB quartet, 1 H, J = 14.5 Hz), 4.97 ($^1/_2$ of AB quartet, 1 H, J = 14.5 Hz), 3.8–4.0 (m, 1 H), 3.6–3.8 (m, 1 H), 2.0–2.3 (m, 5 H).

Anal. Calcd for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.84; H, 5.79.

3-(Acetoxymethyl)bicyclo[2.2.1]hept-2-ene-2-carboxylic Acid. A solution of 2.08 g (0.010 mol) of the diene acetate in 25 mL of ethyl acetate containing 0.2 g of 5% Pd/C was reduced in a Brown[2] hydrogenator. After consumption of 1 molar equiv of hydrogen, the reduction was stopped. Removal of the catalyst and evaporation of the solvent left a white solid. Two recrystalizations from benzene–petroleum ether gave the desired monoene acetate: mp 59–61 °C; IR (KBr pellet) cm^{-1} 3500–2200, 1725, 1660, 1610, 1415, 1295, 1235, 1045; NMR ($CDCl_3$) δ 11.2 (s, 1 H), 5.25 ($^1/_2$ of AB quartet, 1 H, J = 14.0 Hz), 4.92 ($^1/_2$ of AB quartet, 1 H, J = 14.0 Hz), 3.0–3.4 (m, 2 H), 2.10 (s, 3 H), 1.0–2.0 (m, 6 H).

Anal. Calcd for $C_{11}H_{14}O_4$: C, 62.84; H, 6.71. Found: C, 62.82; H, 6.70.

Titrations were carried out at 25.0 ± 0.1 °C by using the apparatus[12] and the procedure (pK_2)[1] described previously. All of the acid samples were of analytical purity. The scatter of pKa values during single titrations and between different titrations was ±0.01–0.02 for all acids except the methoxy cyclobutene compound where ±0.03 was observed. Zone-refined benzoic acid was used as a reference standard; frequent determinations of pKa gave 4.20 ± 0.01, in excellent agreement with the best available values for this acid.[21] Calculation of the pKa values was carried out as described by Albert and Serjeant with corrections for volume changes and activity coefficients.[22]

Registry No. **1a**, 612-20-4; **1b**, 88550-19-0; **2a**, 14668-74-7; **2b**, 32401-29-9; **3a** (acetate), 88550-20-3; **3b**, 88550-21-4; **4a** (acetate), 88550-22-5; **4b**, 88550-23-6; **5a**, 88550-24-7; **5b**, 88550-25-8; **6a**, 88550-26-9; **6b**, 88550-27-0; cyclopentadiene, 542-92-7; 4-methoxytetrolic acid, 24303-64-8; 4-acetoxytetralic acid, 88550-28-1.

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Revised Structure of Podolactone C, the Antileukemic Component of *Podocarpus milanjianus* Rendle

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Received March 29, 1983

The genus *Podocarpus* (Podocarpaceae) is distributed in tropical and subtropical areas of eastern Asia and the southern hemisphere.[1] Phytochemical studies of a number of species in this genus have led to elucidation of various terpenoids,[2] including the important nor- and dinorditerpenoid dilactone groups.[2,3] These compounds are of interest on the basis of their novel structures and biological activities including antitumor activity,[3-5] plant growth regulatory activity,[6,7] termiticidal activity,[8] and cytotoxicity toward insect larvae.[9,10] In a continuation of our studies involving the isolation of antineoplastic agents from higher plants, we have carried out an activity-directed fractionation of the stem bark of *Podocarpus milanjianus* Rendle, a conifer occurring in West Africa. We reported earlier that the stem bark, collected in Kenya, contained four norditerpenoid dilactones, nagilactones F and G and mi-

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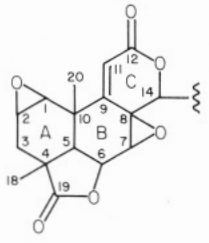
lanjilactones A and B,[11] which were cytotoxic toward KB nasopharynx carcinoma cells.[12] The fractions and compounds responsible for the in vivo activity against P388 lymphocytic leukemia do not contain the previously reported components, nagilactones F and G and milanjilactones A and B. In this paper, we report the isolation, structural revision, and antitumor activity of podolactone C (1).

Results and Discussion

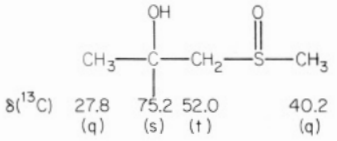
After several partitions of the 95% ethanol extract of coarsely ground plant material, the in vivo active (P388, 161% T/C at 200 mg/kg) fraction was identified and subjected to Florisil column chromatography, eluting with a gradient system containing toluene, ethyl acetate, and methanol. Of the eight fractions that resulted from combination based on thin-layer chromatography, the most polar residue was further purified by trituration, droplet countercurrent chromatography, and recrystallization to give a pure crystalline compound A.

Compound A, which crystallized from dichloromethane, gave UV absorption at 218 nm (ϵ 14 400), suggesting the existence of an α,β-unsaturated carbonyl group. The IR spectrum showed the characteristic absorptions for γ-lactone (1780 cm^{-1}) and α,β-unsaturated δ-lactone (1720 and 1640 cm^{-1}), which were verified by the observation of ^{13}C NMR signals at δ 180.3 (γ-lactone), 162.5, 159.3 (β), and 116.7 (α) (unsaturated δ-lactone). Low-resolution chemical ionization (CI) and electron impact (EI) mass spectra indicated the molecular weight 424. All these spectral data suggested the partial structure a for compound A. Exact mass measurement of the peak at m/z 304 (304.095) indicated a $C_{16}H_{16}O_6$ fragment. The ^{13}C NMR and ^1H NMR (Table I) analyses supported partial structure a. This analysis does not unequivocally locate the ring A epoxide which could be either 1,2 or 2,3.[2,13]



a

The ^1H NMR signals at δ 2.65 (s) and 1.84 (s) revealed the presence of methyl sulfoxide and methyl-substituted tertiary alcohol groups. ^{13}C NMR analysis supported the presence of moiety b incorporating these groups in compound A. It therefore became clear that this compound could be podolactone C, which was previously isolated from *Podocarpus neriifolius* D. Don ex Lamb. by Galbraith et al.[14] The structure of podolactone C (1) was determined



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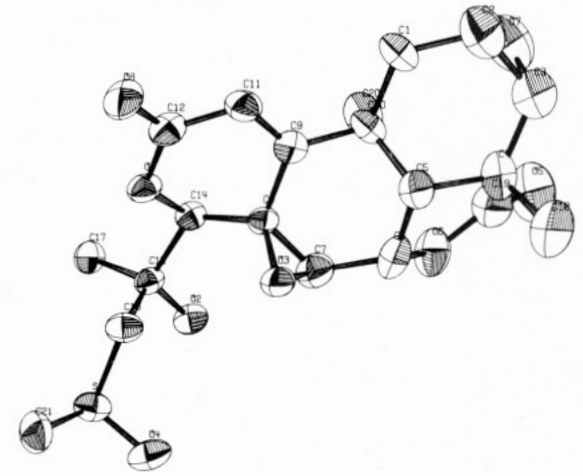
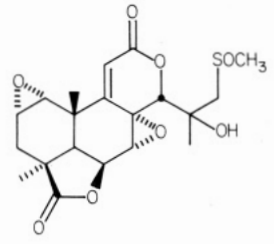


Figure 1.

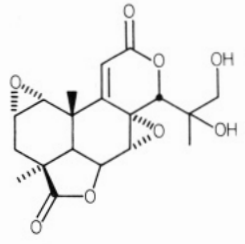
Table I. ^1H NMR Spectral Data of Norditerpenoid Dilactones

	podolactone C, δ	
	Me_2SO-d_6	pyridine-d_5
H_{1A}	2.23 (dd, 14.8, 2.0)	2.21 (dd, 15.0, 2.0)
H_{1B}	1.90 (bd, 14.8)	1.73 (dd, 15.0, 1.0)
H_2	3.39 (dt, 4.0, 2.0)	3.37 (m, 4.0, 2.0, 1.0)
H_3	3.16 (d, 4.0)	3.26 (d, 4.0)
H_5	1.81 (d, 4.6)	1.80 (d, 5.0)
H_6	5.11 (dd, 4.6, 0.1)	5.03 (dd, 5.0, 1.2)
H_7	4.67 (d, 1.1)	5.23 (d, 1.2)
H_{11}	5.99 (s)	6.19 (s)
H_{14}	4.57 (s)	4.83 (s)
H_{15}		
H_{16A}	3.08 (d, 13.8)	3.76 (d, 14.0)
H_{16B}	3.03 (d, 13.8)	3.39 (d, 14.0)
H_{17}	1.44 (s)	1.85 (s)
H_{18}	1.41 (s)	1.43 (s)
H_{20}	1.14 (s)	1.39 (s)
$SOCH_3$	2.56 (s)	2.66 (s)

primarily by analysis of ^1H NMR data and comparison to the ^1H NMR data reported for podolactone A (2).[14] The



1



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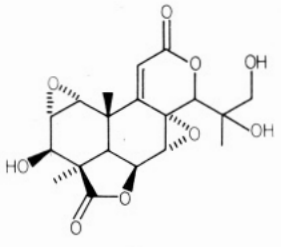

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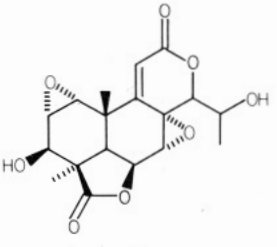

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structure of podolactone A has been elucidated by comparison with the ^1H NMR chemical shifts and coupling constants of podolactone B (3) and inumakilactone A (4).[15]

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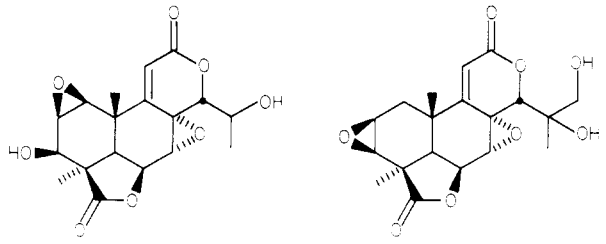
Inumakilactone A, proposed to be a 1,2-α-epoxide in ring A (**4**),[16] was later shown by X-ray analysis to be 1,2-β-epoxide **5** by Godfrey and Waters.[17] In this paper the authors also proposed that the structures of podolactone A (**2**) and podolactone B (**3**) should be modified in the same manner. However, X-ray analysis showed podolactone A to possess the 2,3-β-epoxide **6**[18]rather than the 1,2-α- or



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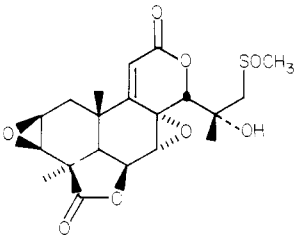

7

1,2-β-epoxide **2**. In order to unambiguously assign the structure of compound A and therefore podolactone C, we initiated a single-crystal X-ray analysis of this compound. The X-ray data clearly indicates that compound A possesses a 2,3-β-epoxide (**7**) as shown in the ORTEP projection (Figure 1). Since a comparison of physical and spectroscopic data indicated compound A to be identical with podolactone C, structure **7** can be assigned to this compound.

All norditerpenoid dilactones isolated from this plant showed cytotoxicity against either KB or P388 cells.[11] Podolactone C (151% T/C at 20 mg/kg) showed moderate antineoplastic activity against P388 in vivo. In view of the antineoplastic activity of compound **7**; further study of the importance of the methyl sulfoxide, α,β-unsaturated lactone, and epoxide functions to the anticancer activity of this compound are warranted and further evaluation of podolactone C in the NCI animal tumor panel is scheduled.

Experimental Section

Extraction and Fractionation. A sample of coarsely ground plant material (12.5 kg) was extracted with 100 L of 95% ethanol. The solvent was removed in vacuo at 40 °C, and the dried ethanol solubles (728 g) were partitioned between dichloromethane and water (1:1). The dried dichloromethane solubles (171 g) were then partitioned between petroleum ether and 10% aqueous methanol (1:1). The methanol solubles (132 g) were partitioned between dichloromethane and 40% aqueous methanol (1:1) to yield 100 g (dry weight) of 40% aqueous methanol solubles. This latter CH_2Cl_2 partition fraction showed significant P388 activity (161% T/C at 200 mg/kg). Based on this, 78 grams of this fraction (obtained by pooling two equivalent extracts) were subjected to column chromatography on 2.5 kg of Fisher F100 Florisil (60–100 mesh) in a 7 cm by 170 cm gravity flow column. The extract was adsorbed onto 200 g of Fisher Celite 545 for application to the column, which was developed by gradient elution with 12 L each of toluene, ethyl acetate, and methanol to a total of about 115 fractions. These were combined into 26 fractions and were tested and further combined into 8 fractions on the basis of thin-layer chromatography on EM silica gel 60 F_{254}. Three of these fractions yielded precipitates upon concentration. The least polar precipitate (fraction 2, eluted with ethyl acetate) showed significant cytotoxicity in P388 in vitro (ED_{50} 3×10^{-1} μg/mL), and it was noted that it contained nagilactones F and G and milanjilactones A and B, which were previously isolated.[11] The third residue precipitated from fraction 6, which was eluted with approximately 50% methanol in ethyl acetate. This precipitate, which also contained **7**, showed P388 in vitro activity (ED_{50} 2×10^{-2} μg/mL) and significant P388 activity in vivo (159% T/C at 125 mg/kg).

Isolation of Podolactone C (7). Fraction 6 was triturated with toluene and the toluene insoluble residue was dried and triturated with tetrahydrofuran (THF) to yield 1.45 g of a THF soluble fraction. A portion (420 mg) of this fraction was subjected to droplet countercurrent chromatography (DCCC) using $CHCl_3$/MeOH/H_2O (5:6:4) as the solvent system in the descending mode. Fractions (6 mL each) were collected and combined on the basis of TLC.

Fraction 10 (139 mg, 210 mL of eluant) contained compound A and was further separated by DCCC ($CHCl_3$/MeOH/H_2O, 5:6:4; ascending mode, 6-mL fractions). Fractions were collected and combined on the basis of TLC to give F12–F16. Volumes collected were F12 (540 mL), F13 (108 mL), F14 (54 mL), F15 (30 mL), F16 (198 mL). F15 gave compound A by crystallization from CH_2Cl_2.

Compound A (podolactone C, 7): mp 290–292 °C (dichloromethane) (lit.[14] 288–290 °C); UV (MeOH) λ_{max} 218 nm (ϵ 14 400; lit.[14] ϵ 12 500); IR (KBr) ν_{max} 3400, 1780 (γ-lactone), 1640 (olefin) cm^{-1}; chemical ionization MS, m/z 425 ($M^+ + 1$), 305; electron impact MS, m/z 424 (M^+) and 304.095 (304.095 calcd for $C_{16}H_{16}O_6$); ^1H NMR (dimethyl sulfoxide-d_6 and pyridine-d_5, see Table I); ^{13}C NMR (50 MHz, CD_2Cl_2)[13] δ 180.3 (C_{18}), 162.5 (C_{12}), 159.3 (C_9), 116.2 (C_{11}), 83.0 (C_{14}), 75.2 (C_{15}), 73.4 (C_6), 58.5 (C_8), 57.4 (C_7), 55.7 (C_3), 53.0 (C_2), 52.0 (C_{16}), 43.5 (C_5), 40.2 ($SOCH_3$), 36.1 (C_{10}), 31.1 (C_1), 27.9 (C_{17}), 26.1 (C_{19}), 21.7 (C_{20}).

The complete structure and stereochemistry of **7** were determined by single-crystal X-ray techniques using Cu Kα radiation. The structure was resolved by direct methods using MULTAN for 1588 reflections measured on a Syntex P3 automated diffractometer. The θ–2θ scan technique was used with variable scan speed ranging from 2.0 to 29.3 degrees per minute. Two standard reflections were measured every 50 reflections. The intensities were corrected for decay which was only 8%.

Oscillation and Weissenberg photographs showed the orthorhombic crystal of podolactone C ($C_{20}H_{22}O_8S$) to be in the $P2_12_12_1$ space group. Cell parameters were found to be a = 7.597 (3) Å, b = 11.794 (4) Å, and c = 22.330 (14) Å with four molecules per unit cell. Refinement of the structure resolved by direct methods was accomplished by using a block-diagonal least-squares method to yield an R factor of 0.1235. Further refinement using anisotropic temperature factors for the 29 non-hydrogen atoms and the inclusion of all hydrogen atoms with isotropic temperature factors yielded a final R factor of 0.0582. Interatomic distances, interatomic angles, and atomic positions are all presented in the supplementary material.

All melting points are uncorrected and were obtained on a Laboratory Devices MELTEMP apparatus. IR spectra were obtained in KBr on a Beckman Model IR-33 spectrophotometer. ^1H NMR spectra were obtained in the solvents indicated for the individual compounds on a Nicolet NTC-470, a Nicolet NTC-200, or a Varian FT-80 spectrometer.

^{13}C NMR spectra were measured on a Nicolet NTC-200 or a Varian XL-200 spectrometer. Low-resolution electron impact and chemical ionization mass spectra were done on a DuPont 21-492B mass spectrometer, and isobutane was used as the ionization source for chemical ionization. Field desorption mass spectra were obtained on a Varian MAT-731 spectrometer. Exact mass measurements were obtained from a CEC 21-110B mass spectrometer. UV absorption spectra were obtained on a Cary 17 spectrophotometer.

Acknowledgment. We acknowledge Mr. John Kozlowski for his assistance in obtaining the ^1H NMR spectra. High-resolution (470 MHz) NMR spectra were recorded at the Purdue University Biological Magnetic Resonance

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Laboratory (NIH Grant RR1077). Dr. John L. Occolowitz, Eli Lilly Laboratories, Indianapolis, IN provided FDMS. The cytotoxicity testing was provided by Dr. Linda Jacobsen, Purdue Cell Culture Laboratory, Purdue Cancer Center. This investigation was partially supported by contract NO1-CM-62091 and Grant No. CA-33326 awarded by the Division of Cancer Treatment of the National Cancer Institute, Public Health Service, Bethesda, MD, to Purdue University.

Registry No. 7, 35467-31-3.

Supplementary Material Available: Atomic positions and temperature factors (Table I), bond lengths (Table II), and bond angles (Table III) of podolactone C (3 pages). Ordering information is given on any current masthead page.

Improved Procedures for the Synthesis of Diisopinocampheylborane of High Optical Purity

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Received August 31, 1983

Diisopinocampheylborane (Ipc_2BH, **2**)[2] is one of the most versatile chiral reagents readily available for laboratory use. It has been applied to the synthesis of many chiral products, such as alcohols, halides, amines, ketones, hydrocarbons, and α-amino acids.[3] It has also been applied to the kinetic resolution of alkenes, dienes, and allenes.[3] Recently, Ipc_2BH has been converted to *B*-allyldiisopinocampheylborane, a new reagent for the synthesis of secondary homoallylic alcohols of high optical purity.[4]

A systematic study of the preparation of Ipc_2BH in THF was carried out recently.[5] The reaction of $THF{\cdot}BH_3$ with α-pinene proceeds rapidly to a mixture of Ipc_2BH and monoisopinocampheylborane ($IpcBH_2$).[2] $IpcBH_2$ reacts faster than Ipc_2BH with olefins. $IpcBH_2$ on hydroboration–oxidation gives an alcohol of configuration opposite to that produced by Ipc_2BH.[6,7] Therefore, a good asymmetric hydroboration cannot be achieved with such a mixture of reagents. In order to suppress the formation of $IpcBH_2$, a 15% excess of α-pinene **1** was used for the synthesis of Ipc_2BH. Equilibration of such a reaction mixture at 0 °C for 3 days resulted in the formation of Ipc_2BH, more optically pure than the initial α-pinene. Apparently the longer reaction time was accompanied by the selective incorporation of the major isomer of α-pinene into the crystalline Ipc_2BH, with concurrent accumulation of the minor isomer in the solution.

Table I. Synthesis of Ipc_2BH by Selective Crystallization[a]

solvent	molar ratio[b]	molarity, M	temp, °C	isolated yield, %	% ee[c]
EE	2.3:1	1.0	0	95	94
EE	2.3:1	0.5	0	80	94
THF	2.3:1	0.5	0	80	98
THF	2.3:1	0.5	−5	50	99
THF	2.3:1	1.0	−5	75	98
THF	2.3:1	0.5	−10	50	99
THF	2.3:1	0.5	−15	*d*	
THF	2.3:1	0.5	−25	*d*	
EE	2:1	1.0	0	82	94
THF	2:1	0.5	0	50	99
THF	2:1	1.0	0	70	98.8
THF	2:1	1.0	−5	70	98

[a] The reagent was prepared from (+)-α-pinene of 91.6% ee and BMS. [b] Molar ratio of α-pinene to BMS. [c] Based on measuring the rotation[13] of the α-pinene obtained from Ipc_2BH. [d] Reaction does not proceed to completion to give crystalline Ipc_2BH.

This procedure for the preparation of Ipc_2BH of high optical purity suffers from the limitation that it requires a concentrated solution of borane in THF (2.26 M) and α-pinene of relatively high optical purity (97.4% ee). Neither of these materials is currently available commercially.

More recently, a modified procedure utilizing the commercially available borane–methyl sulfide (BMS) and α-pinene (92% ee) was described.[8] This method, like the previous one, involves equilibration in THF with excess α-pinene at 0 °C for 3 days. Unfortunately, the methyl sulfide liberated in the hydroboration step interferes with the equilibration needed to improve the optical purity of the reagent. Consequently, it must be removed prior to the equilibration. Finally, the use of α-pinene of lower optical purity (84% ee) did not provide Ipc_2BH of the desired high optical purity.

In the course of our study of the preparation of Ipc_2BH, we always observed that a crystalline solid separated from the reaction mixture.[5,7,8] We speculated that the solid might be optically pure Ipc_2BH dimer, but never verified this experimentally. Accordingly, we explored the possibility that selective crystallization might provide an alternative, more rapid procedure for the preparation of Ipc_2BH of high optical purity (>99% ee). It is now well established that in the preparation of Ipc_2BH via hydroboration, $IpcBH_2$ is formed as an intermediate.[7] Surprisingly, there is no report available on the hydroboration of α-pinene with $IpcBH_2$. With the availability of a simple, convenient synthesis of optically pure $IpcBH_2$,[9] it became desirable to explore the usefulness of such $IpcBH_2$ for the synthesis of Ipc_2BH of very high optical purity. In this paper we report our results on two new, improved procedures for the preparation of essentially enantiomerically pure Ipc_2BH from the commercially available α-pinene of lower optical purity, 84% ee and 91.6% ee.

α-Pinene **1** readily undergoes hydroboration at 0 °C in tetrahydrofuran (THF) to form *sym*-tetraisopinocampheyldiborane **2**.[10,11] Even in the presence of excess α-pinene, the reaction does not proceed further. In the absence of excess α-pinene, there is evidence for a significant dissociation of **2** into α-pinene and triisopino-

(1) Postdoctoral research associate on Grant CHE 79-18881 from the National Science Foundation.
(2) These intermediates actually exist in the solution as the dimers, that is, as derivatives of the diborane molecule. However, it is convenient to refer to them as the simple borane derivatives.
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