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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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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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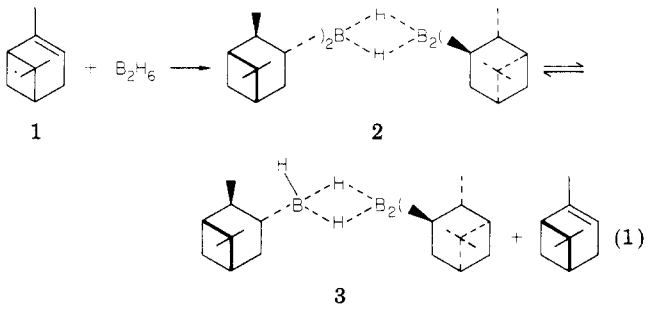
campheyldiborane[12] (3, eq 1). The dialkylborane 2 pre-



1 2 3 (1)

cipitates from the reaction mixture leaving 3, largely in solution. We observed that if the reaction mixutre was set aside without stirring, the dialkylborane 2 crystallized in fairly large crystals, which were easy to isolate and purify. In the course of our search for optimum conditions for preparation of highly optical purity Ipc_2BH by selective crystallization, we used commercially available BMS and (+)-α-pinene (91.6% ee). The reactants were mixed together, either in THF or in ethyl ether (EE), to make a solution of known molarity. The reaction mixture was then left at various temperatures without stirring for 12 h. The crystalline (−)-Ipc_2BH was then isolated, washed with EE, and dried at 25 °C, 12 mmHg. The enantiomeric purity of the crystalline (−)-Ipc_2BH was determined by measuring the rotation[13] of the α-pinene obtained in its reaction with half an equivalent of *N,N,N′,N′*-tetramethylethylenediamine (TMED).[9] The results are summarized in Table I.

It is evident that the major isomer becomes incorporated into the crystalline Ipc_2BH. The molar ratio of α-pinene to BMS has little or no influence on the optical purity of the crystalline Ipc_2BH. The selectivity in crystallization is better in THF than in EE. In EE the dialkylborane is highly insoluble and crystallizes without any significant selectivity. The reaction temperature has little effect on the optical purity of the crystalline Ipc_2BH. Selective crystallization from a 0.5 M THF solution gives an optically more pure Ipc_2BH, but in a lower yield, as compared to a 1.0 M THF solution. The dimethyl sulfide (DMS) generated in the hydroboration step does not interfere with the crystallization process. Consequently, it is not necessary to remove DMS from the reaction mixture prior to the crystallization of the Ipc_2BH.

Encouraged by these results, we then attempted to improve the yield of crystalline Ipc_2BH without compromising its optical purity. (+)-α-Pinene (91.6% ee, 50 mmol) and BMS (25 mmol) were mixed together in THF at 0 °C to give a 0.7 M solution. It was then left at 0 °C, without stirring, for 12 h. The crystalline (−)-Ipc_2BH was isolated in 75% yield and the optical purity was 99% ee. Following a similar procedure, (−)-α-pinene (92% ee) was converted to (+)-Ipc_2BH of 99% ee. After establishing conditions for the selective crystallization of Ipc_2BH, we examined the possible use of α-pinene of lower optical purity. Thus, hydroboration of (+)-α-pinene (84% ee) with BMS (2:1 ratio) produced (−)-Ipc_2BH of 98.3% ee after selective crystallization. When the reaction was scaled up (250 mmol), the yield of Ipc_2BH (99% ee) dropped to 55%.

This problem could be overcome by a slight modification of the procedure. Thus, α-pinene (250 mmol) was mixed with BMS (250 mmol) in THF at 0 °C and was left at 0 °C for 12 h. After 12 h, the seecond equivalent of α-pinene was added and left at 0 °C for crystallization (12 h). This modified method gave Ipc_2BH of 99% ee in 72% isolated yield. Fairly large crystals of Ipc_2BH of 99% ee, thus obtained, can be stored at 0 °C for at least 20 days without any appreciable loss of hydride activity or isomerization.

Finally, we turned our attention to examining the possible use of (−)-$IpcBH_2$ (100% ee)[9] for the synthesis of (−)-Ipc_2BH of very high optical purity. Thus, hydroboration of (+)-α-pinene (91.6% ee) with (−)-$IpcBH_2$ (1:1 ratio) afforded crystalline (−)-Ipc_2BH of ≥99.9% ee in 80% isolated yield. This is the first time that Ipc_2BH has been made in such high optical purity. Similarly, hydroboration of (+)-α-pinene (84% ee) with (−)-$IpcBH_2$ (1:1 ratio) gave (−)-Ipc_2BH of ≥99.9% ee after selective crystallization.

Experimental Section

All operations were carried out under a nitrogen atmosphere, with oven-dried glassware.[14] GC analyses were carred out on a Hewlett-Packard 5750 gas chromatograph with a 6 ft × 0.25 in. column packed with 10% Carbowax 20M on Chromosorb W. For preparative GC, a 6 ft × 0.5 in. column packed with 10% SE-30 on Chromosorb W was used. Optical rotations were measured on a Rudolph Autopol III polarimater.

Materials. Tetrahydrofuran (THF) was distilled from lithium aluminum hydride ($LiAlH_4$) and stored under nitrogen. *N,N,N′,N′*-Tetramethylethylenediamine (TMED) was distilled from calcium hydride. (−)-α-Pinene of 92% ee was prepared by isomerization of (−)-β-pinene.[15] (+)-α-Pinene of 84% ee was received as a gift from Dr. E. Klein of Dragoco Co., Holzminden, West Germany. $Me_2S{\cdot}BH_3$ (BMS) and (+)-α-pinene of 91.6% ee were purchased from Aldrich Chemical Co. All samples of α-pinene were distilled from $LiAlH_4$ and stored under nitrogen.

Preparation of Ipc_2BH. Reaction of BMS and (+)-α-Pinene of 91.6% ee in THF. A 50-mL centrifuge vial fitted with a rubber septum and magnetic stirring bar was charged with 2.58 mL of BMS (25 mmol) and 25 mL of THF. It was cooled to 0 °C, and 7.94 mL (50 mmol) of (+)-α-pinene ($[\alpha]^{23}_D$ +47.26° (neat), 91.6% ee) was added dropwise with stirring. After the addition of α-pinene, the stirring was stopped and the centrifuge vial was stored at 0 °C for 12 h. The supernatant solution was decanted by using a double-ended needle. The crystalline lumps of (−)-Ipc_2BH were broken, washed with EE (3 × 5 mL) and dried at 25 °C at 12 mmHg; 5.37 g (75% yield).

The crystalline Ipc_2BH (15 mmol) was suspended in EE (9.6 mL) and 1.13 mL of TMED (7.5 mmol) was added at 25 °C with stirring to form $TMED{\cdot}2BH_2Ipc$ within 1 h by displacement of (+)-α-pinene.[9] The solid $TMED{\cdot}2BH_2Ipc$ was filtered in air and the solvent was evaporated from the filtrate. The residue containing (+)-α-pinene and a trace of $TMED{\cdot}2BH_2Ipc$ was passed through a plug of SiO_2 gel (60–200 mesh, 4 in. × 2 in.) by using *n*-pentane (50 mL) as the eluent. The solvent was evaporated and the (+)-α-pinene was distilled from $LiAlH_4$ and purified by preparative GC: 0.82 g (80% yield); $[\alpha]^{23}_D$ +51.12° (neat), 99% ee.

Reaction of BMS and (−)-α-Pinene of 92% ee in THF. The experiment was carried out exactly as described above. (−)-α-Pinene ($[\alpha]^{23}_D$ −47.4° (neat), 92% ee) was used for the preparation of crystalline (+)-Ipc_2BH: 5.16 g (72% yield). The (−)-α-pinene isolated exhibited $[\alpha]^{23}_D$ −51.09° (neat), 99% ee.

Reaction of BMS and (+)-α-Pinene of 84% ee in THF. The experimental procedure described above was followed, using (+)-α-pinene ($[\alpha]^{23}_D$ +43.3° (neat), 84% ee) to afford (−)-Ipc_2BH: 4.3 g (60% yield). The (+)-α-pinene obtained by displacement exhibited $[\alpha]^{23}_D$ +50.72° (neat), 98.3% ee.

Preparation of (+)-Ipc_2BH on 250-mmol Scale. A solution of BMS (250 mmol) in 250 mL of THF was taken in a 500-mL round-bottomed flask and cooled to 0 °C. (−)-α-Pinene of 92% ee (39.7 mL, 250 mmol) was added with stirring. It was then left aside at 0 °C for 12 h. After 12 h, 39.7 mL of (−)-α-pinene was

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added and the reaction mixture was left at 0 °C for 12 h. The crystalline (+)-Ipc_2BH was isolated, washed with EE (3 × 30 mL), and dried at 25 °C at 12 mmHg: 51.5 g, 72% yield. The (−)-α-pinene obtained by displacement exhibited $[\alpha]^{23}_D$ −51.1° (neat), 99% ee.

Reaction of (−)-IpcBH$_2$ with (+)-α-Pinene of 91.6% ee in THF. A 50-mL centrifuge vial fitted with a rubber septum and a magnetic stirring bar was charged with 14.3 mL of (−)-$IpcBH_2$ (100% ee) in EE (10 mmol).[16] The solvent EE was evaporated at 25 °C under reduced pressure (12 mmHg). The neat (−)-$IpcBH_2$ was dissolved in 12.3 mL of THF to give a 0.7 M solution and cooled to 0 °C. (+)-α-Pinene of 91.6% ee (1.59 mL, 10 mmol) was added dropwise with stirring. After the addition of α-pinene was complete, the stirring was stopped and the centrifuge vial was stored at 0 °C for 12 h. The crystalline (−)-Ipc_2BH was collected as outlined previously: 2.3 g, 8.03 mmol, 80% yield. The (+)-α-pinene isolated exhibited $[\alpha]^{23}_D$ +51.55° (neat), ≥99.9% ee.

Reaction of (−)-IpcBH$_2$ with (+)-α-Pinene of 84% ee in THF. The experiment was carried out as described above. (+)-α-Pinene of 84% ee was used for the preparation of crystalline (−)-Ipc_2BH: 2.2 g, 7.7 mmol, 77% yield. The (+)-α-pinene isolated exhibited $[\alpha]^{23}_D$ +51.55° (neat), ≥99.9% ee.

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Registry No. (+)-1, 7785-70-8; (−)-1, 7785-26-4; (+)-2, 16997-72-1; (−)-2, 88764-06-1; BMS, 13292-87-0; TMED·$2BH_2$(Ipc), 67826-92-0; (−)-$IpcBH_2$, 74112-25-7.

(16) Brown, H. C.; Singaram, B., submitted for publication.

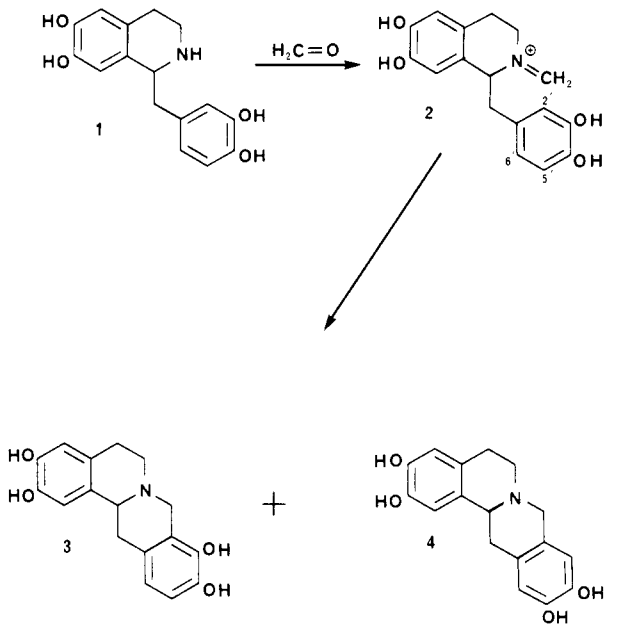
Communications

Kinetics and Product Distribution in Pictet–Spengler Cyclization of Tetrahydropapaveroline to Tetrahydroprotoberberine Alkaloids

Summary: The rate of Pictet–Spengler condensation of tetrahydropapaveroline (THP), a pharmacologically active 1-benzyltetrahydroisoquinoline alkaloid, with formaldehyde in aqueous buffer at 37.5 °C and pH 7.4 is very rapid (k_{obsd} = 30.1 M^{-1} s^{-1}), and this reaction appears to be a viable candidate for the nonenzymatic production of tetrahydroprotoberberine alkaloids in mammalian systems.

Sir: The chemistry of tetrahydropapaveroline (THP; norlaudanosoline; 1-(3,4-dihydroxybenzyl)-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline; **1**, Scheme I) is of interest for several reasons. The compound occupies the position of apparent central progenitor of many alkaloids found in plants.[1] Futhermore, it has been suggested that **1** may play a role in the development of some of the pharmacological manifestations of alcohol.[2] An integral part of this theory is the postulate that THP, once formed in mammals, may be converted to other pharmacologically active alkaloids, such as the tetrahydroprotoberberines. Publication of this hypothesis stimulated research focused on demonstrating the presence of THP or its metabolites in mammalian systems. THP was reported to be present in the brains of rats given L-dihydroxyphenylalanine (L-Dopa) orally.[3] The alkaloid has also been found in the urine of human patients receiving large amounts of L-Dopa during treatment for Parkinson's disease.[4] Additionally, several tetrahydroprotoberberine derivatives of **1** were demonstrated to be present in the urine of patients with Parkinson's disease receiving L-Dopa therapy and in the urine of rats receiving THP through intraperitoneal injection.[5] The first link between THP and alcohol-related

Scheme I



behavior was furnished by Myers and Melchior[6] who reported that chronic infusion of minute amounts of this compound into the cerebral ventricles of rats evoked marked and long-lasting increases in voluntary consumption of alcohol. This pharmacological action of THP was later confirmed by Duncan and Deitrich.[7]

Although the excessive voluntary selection of alcohol is reported to persist long after cessation of THP infusion,[6,7] it is also noted that brain levels of infused **1** are rapidly decreased.[8] THP, therefore, appears to be readily me-

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