Table II. Cycloadducts from Isobenzofuran Equivalents and DCB

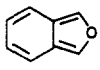
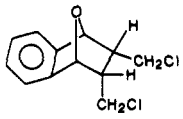
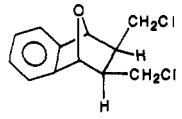
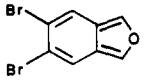
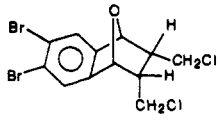
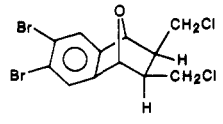
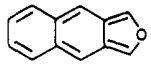
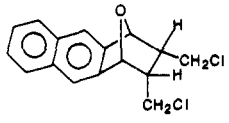
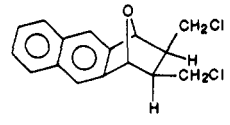
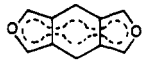
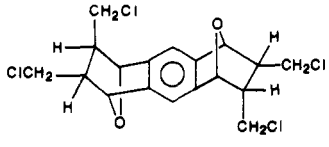
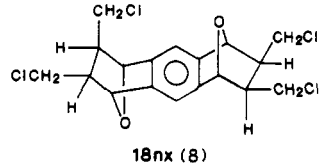
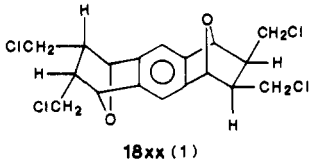
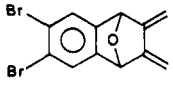
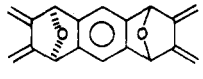
isobenzofuran equivalent	isobenzofuran	adducts (ratio)		% yield
7		 **15n** (89)	 **15x** (11)	69
10		 **16n** (87)	 **16x** (13)	63
12		 **17n** (90)	 **17x** (10)	78
14		 **18nn** (91)	 **18nx** (8)	54
		 **18xx** (1)		

Table III. Bis(methylene)oxabenzonorbornenes

bis(chloromethyl) substrate	product	% yield
15	**4**	96
16	 **19**	92
17	**5**	98
18nn	 **20**	90
18nx or 18xx	**20**	93

tracted with methylene chloride (3 × 80 mL). Combined organic layers were washed with water, dried, and concentrated to give, on recrystallization from 50–110 °C petroleum ether, 604 mg (92%) of **19** as a white solid, mp 149–151 °C; ^{1}H NMR δ 5.23 (s, 2 H), 5.34 (s, 2 H), 5.53 (s, 2 H), 7.57 (s, 2 H); ^{13}C NMR δ 83.07, 104.42, 123.17, 125.06, 143.04, 145.22; mass spectrum, *m/e* (relative intensity) 330 (16), 328 (29, M^+), 326 (15), 301 (10), 299 (21), 297 (12), 278 (11), 276 (23, M^+ for dibromoisobenzofuran), 274 (13), 249 (55), 247 (48), 221 (25), 219 (32), 167 (11), 140 (51), 139 (100), 113 (15), 87 (21), 69 (23). Anal. Calcd for $C_{12}H_8Br_2O$: C, 43.94; H, 2.46. Found: C, 44.11; H, 2.34.

Physical Data for Other Compounds in Table III. For 4: mp 73–74 °C (recrystallized from 35–60 °C petroleum ether); ^{1}H NMR δ 5.17 (s, 2 H), 5.28 (s, 2 H), 5.56 (s, 2 H), 7.15 (dd, 2 H), 7.28 (dd, 2 H); ^{13}C NMR δ 83.70, 103.27, 119.72 (overlapped peaks), 127.31, 144.33; mass spectrum, *m/e* (relative intensity) 170 (25, M^+), 169 (11), 141 (100), 118 (48, M^+ for isobenzofuran), 115 (44), 89 (21), 77 (12), 63 (24), 51 (19). Anal. Calcd for $C_{12}H_{10}O$: C, 84.68; H, 5.92. Found: C, 84.80; H, 5.88. **For 5**: mp 135–137 °C (lit.[5b] mp 136–138 °C); ^{1}H NMR δ 5.24 (s, 2 H), 5.33 (s, 2 H), 5.70 (s, 2 H), 7.44 (dd, 2 H), 7.70 (s, 2 H), identical with that reported.[5b] **For 20**: mp >255 °C dec; ^{1}H NMR δ 5.18 (s, 4 H), 5.28 (s, 4 H), 5.52 (s, 4 H), 7.25 (s, 2 H); ^{13}C NMR δ 83.50, 103.35, 112.08, 143.97, 144.10; mass spectrum, *m/e* (relative intensity) 262 (100, M^+), 233 (94), 205 (98), 204 (71), 189 (62), 181 (47), 165 (29), 153 (63), 152 (74), 139 (21), 127 (13), 115 (12), 102 (13), 89 (24), 76 (23), 63 (29), 51 (30). Anal. Calcd for $C_{18}H_{14}O_2$: C, 82.42; H, 5.38. Found: C, 82.30; H, 5.43.

Acknowledgment. We thank the National Science Foundation (Grant CHE-8712118) for financial support of this research.

Registry No. **4**, 119273-69-7; **5**, 73862-76-7; **6**, 573-57-9; **7**, 85798-64-7; **9**, 106750-88-3; **10**, 119273-70-0; **11**, 22187-13-9; **12**, 119273-71-1; **13**, 87207-46-3; **14**, 113451-37-9; **15n**, 119273-72-2; **15x**, 119363-66-5; **16n**, 119273-73-3; **16x**, 119363-67-6; **17n**, 119273-74-4; **17x**, 119363-68-7; **18nn**, 119363-69-8; **18nx**, 119363-70-1; **18xx**, 119363-71-2; **19**, 119273-75-5; **20**, 119363-72-3; DCB, 1476-11-5; tetraphenylcyclopentadienone, 479-33-4.

Hydroboration of Terpenes. 10. An Improved Procedure for the Conversion of α-Pinene into β-Pinene in High Chemical and Optical Yield Using a Combination of the Schlosser Allylic Metalation of α-Pinene and Allylborane Chemistry

Herbert C. Brown,* Marek Zaidlewicz,[1] and Krishna S. Bhat[2]

H. C. Brown and R. B. Wetherill Laboratories of Chemistry, Purdue University, West Lafayette, Indiana 47907

Received November 17, 1988

Pyrolysis of β-pinene gives myrcene, an important raw material in the perfume industry. Furthermore, β-pinene

(1) Visiting professor on a grant from the Dow Chemical Co.

0022-3263/89/1954-1764$01.50/0

Table I. Transformation of α-Pinene to β-Pinene[a]

molar ratio α-pinene/base	time of metalation, h	conversion β-pinene/α-pinene	total yield, % GC	total yield, % isolated	optical purity of β-pinene[b]
1:1	12	85:15			
	24	87:13			
	48	88:12		92	100
1:1.1	12	86:14			
	24	93:7			
	48	94:6	95	90	100
1:1.25	12	93:7			
	24	97:3			
	48	98:2	92	86	100
1:1.5	12	93.5:6.5			
	24	98.5:1.5			
	48	>99:<1	88	80	100

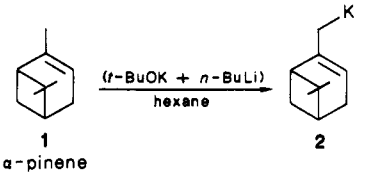
[a] Both (+)- and (−)-β-pinene were obtained starting from (+)- and (−)-α-pinene respectively. [b] Observed optical rotation for (+)-β-pinene is $[\alpha]^{23}_D$ +23.1° (neat), 99.7% GC pure.

is the starting material for the manufacture of various chemicals and polyterpene resins. Unfortunately, the content of the less valuable α-pinene in natural terpentine oil is much higher than that of the more valuable β-pinene.[3,4] This situation has led to many searches for simple methods of converting α-pinene into β-pinene.

There are many patents describing the conversion of α- to β-pinene. The most popular method, metal-catalyzed isomerization of α-pinene, gives a yield of only 3–7% of β-pinene.[5] More recently some new conversions of α- to β-pinene have been reported. Julia described a four-step process that involves a reductive fission of alkene phosphonates with lithium aluminium hydride, leading to β-pinene with an overall yield of 25%.[6] The conversion proposed by Cao yielded a mixture from which β-pinene could only be isolated only after a highly efficient distillation.[7] A two-step isomerization of α- to β-pinene in a 50% yield, via allylstannane, has been described.[8] (+)-β-Pinene has been obtained from (+)-α-pinene via hydroboration with diborane, thermal isomerization of the intermediate organoborane, and displacement either with a high-boiling olefin or benzaldehyde.[9,10] In another preparation based on hydroboration, the thermally isomerized organoborane derived from (+)-α-pinene and 9-BBN reacts with benzaldehyde to give (+)-β-pinene in 51% yield and 93.5% optical yield.[11] β-Pinene has also been prepared in low yield from (+)-10-camphenesulfonyl chloride.[12] Recently, the preparation of β-pinene by metalation of α-pinene, with KCH_2SiMe_3, conversion of the potassium salt to the Et_2B derivative, followed by protonolysis of the organoborane intermediate, provided β-pinene of low optical purity in yields of ~60%.[13] In this paper we report a considerably simplified procedure that provides optically pure β-pinene in isolated yields approaching 90%.

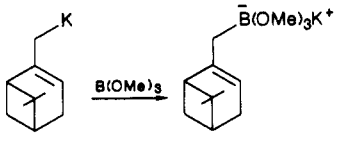
The preparation of β-pinene described here gives isomerically pure material in high optical yield. The intermediate is stable, and the chemicals used are commercially available at reasonable cost. The synthesis is a simple one-pot transformation. The procedure described here should be amenable to large-scale operations.

Recently, we had experienced considerable success in improving the Schlosser allylic metalation of (*Z*)- and (*E*)-2-butene with *n*-butyllithium and potassium *tert*-butoxide[14] to provide isomerically pure (*Z*)- and (*E*)-crotylpotassium.[15] Accordingly, we decided to examine the metalation of α-pinene by this reagent[16] to see if we could achieve a clean conversion into the potassium derivative **2** (eq 1). The metalation of the α-pinene by the Schlosser



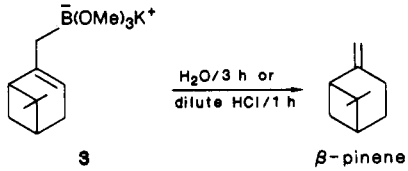
1 α-pinene **2** (1)

reagent was carried out in hexane solution, and consequently this procedure allows the functional use of allylic organopotassium intermediates without isolation. Accordingly the organopotassium formed was treated with trimethyl borate, providing the stable "ate" complex **3** (eq 2). The organoborane **3** can be hydrolyzed under very



2 **3** (2)

mild conditions (room temperature), either by stirring with water or with dilute hydrochloric acid. Separation of the organic phase and distillation provide β-pinene in high optical and chemical yield (eq 3). It was observed that



3 β-pinene (3)

the use of an equimolar ratio of α-pinene/base gave a

(2) Postdoctoral research associate on Grant GM 10937-24 from the National Institutes of Health.
(3) *Rodd's Chemistry of Carbon Compounds*, 2nd ed.; Coffey, S., Ed.; Elsevier Publishing Co.: Amsterdam, 1969; Vol. IIc, p 174.
(4) Banthorpe, D. V.; Whittaker, D. *Chem. Rev.* **1966**, *66*, 643.
(5) U. S. Patents 3359342 (1967), 3360581 (1967), 3225553 (1967); Neth. Appls. 6501986 (1965), 6610235 (1967).
(6) Harwood, L. M.; Julia, M. *Synthesis* **1980**, 456.
(7) Min, Y. F.; Zhang, B. W.; Cao, Y. *Synthesis* **1982**, 875.
(8) Andrianome, M.; Delmond, B. *J. Chem. Soc., Chem. Commun.* **1985**, 1203.
(9) Brown, H. C.; Bhatt, M. V. *J. Am. Chem. Soc.* **1960**, *82*, 2074.
(10) Brown, H. C.; Joshi, N. N. *J. Org. Chem.* **1988**, *53*, 4059.
(11) Midland, M. M.; Petre, J. E.; Zderic, S. A.; Kazubski, A. *J. Am. Chem. Soc.* **1982**, *104*, 528.
(12) Kirmse, W.; Gruber, W. *Chem. Ber.* **1972**, *105*, 2764.
(13) Zaidlewicz, M. *J. Organomet. Chem.* **1985**, *293*, 139.
(14) Schlosser, M.; Rauchschwalbe, A. *J. Am. Chem. Soc.* **1978**, *100*, 3258.
(15) Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 293.
(16) Schlosser, M.; Rauchschwalbe, A. *Helv. Chim. Acta* **1975**, *58*, 1095. The authors utilized *sec*-butyllithium and potassium *tert*-butoxide in this metalation but achieved only a 42% yield of product (+)-myrtenol.

product containing β-pinene/α-pinene, 87:13. Use of additional base led to a decrease in the α-pinene present in the product. Indeed, a reaction mixture from a 1:1.5 ratio of α-pinene to base gave a product with <1% α-pinene. Both (+)- and (−)-β-pinene were synthesized from the corresponding (+)- and (−)-α-pinene, respectively. Data on products obtained with their isomeric and optical purities are summarized in Table I.

Recommended Procedure for Conversion of (+)-α-Pinene to (+)-β-Pinene. All glassware was dried at 150 °C for at least 5 h, and reactions were carried under a static nitrogen atmosphere.[17] To a stirred suspension of *n*-BuLi (100 mL, 2.5 M, 250 mmol) in hexane and *t*-BuOK (28 g, 250 mmol) was added (+)-α-pinene (27.2 g, 200 mmol, 96.6% ee) slowly at −78 °C. After the addition was complete, the reaction mixture was warmed slowly to room temperature and stirred at that temperature for 48 h. The reaction mixture was then cooled to −78 °C, and trimethyl borate (67 g, 650 mmol) in 50 mL of dry ether was added slowly with efficient stirring[18] (^{11}B NMR indicated a peak at δ +3, confirming the formation of the "ate" complex). Then the mixture was slowly warmed to room temperature and stirred for 1 h. Hydrolysis was achieved by adding 100 mL, 10% hydrochloric acid and stirring for 1 h,[19] or 100 mL of water and stirring for 3 h. The organic layer was separated, and the aqueous layer was extracted with hexane (3 × 50 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. The residue was distilled (55 °C/12 mmHg) to furnish (+)-β-pinene, 23.3 g (86%), isomeric purity >98%. A careful distillation of a small prior fraction through an efficient column readily removes the minor amount of the α-pinene produced in the reaction (bp α-pinene, 156 °C; β-pinene, 165 °C). After preparative GC on a TPC column, 99.7% GC pure (+)-β-pinene was obtained: $[\alpha]^{23}_D$ +23.1° (neat).

By utilizing 1.5 equiv of metalating agent, β-pinene was obtained in ≥99% isomeric purity and 80% yield (Table I).

Rotation of 100% β-Pinene. As reported above, the rotation we achieved with β-pinene prepared from high optical purity α-pinene is $[\alpha]^{23}_D$ +23.1° (neat). This compares with the highest value previously reported for β-pinene made from (+)-10-camphenesulfonyl chloride,[12] $[\alpha]^{25}_D$ +22.8°. Both borane isomerization of α-pinene and recrystallization of tri-*cis*-myrtenylborane[10] gave products with $[\alpha]^{23}_D$ of +22.7° and −22.8°. Earlier, Lucas had reported a rotation of $[\alpha]^{25}_D$ −22.7°.[20] Even though our observed value is higher than those of all previous workers, it would be foolhardy to claim it must be optically purer. The presence of trace amounts of materials with high rotations can result in minor variations of the observed rotation, which confuse the situation.

Acknowledgment. We thank the National Institutes of Health (Grant GM 10937-24) and the Dow Chemical Co. for support of this research program.

(17) For handling air- and moisture-sensitive compounds, see: Brown, H. C.; Kramer, G. W.; Levy, A. B.; Midland, M. M. *Organic Synthesis via Boranes*; Wiley-Interscience: New York, 1975; p 191.

(18) The reaction of methyl borate with the potassium salt **2** is exothermic, and the reaction temperature must be kept at −78 °C. If the addition of methyl borate is too fast or the stirring is not efficient, local overheating occurs, leading to lower yields of β-pinene and increased amounts of a nonvolatile residue.

(19) Stirring the reaction mixture containing the dilute acid results in the formation of products exhibiting a longer retention time on GC analysis than that of β-pinene. Hence, a shorter stirring time is recommended during the hydrolysis by dilute hydrochloric acid.

(20) Comyns, A. E.; Lucas, H. J. *J. Am. Chem. Soc.* **1957**, *79*, 4339.

Mono-α-functionalization of 2,9-Dimethyl-1,10-phenanthroline[1a]

George R. Newkome,*[1b] Kevin J. Theriot,[1b] Vinod K. Gupta,[1c] Frank R. Fronczek,[1c] and Gregory R. Baker[1b]

Departments of Chemistry, University of South Florida, Tampa, Florida 33620, and Louisiana State University, Baton Rouge, Louisiana 70803-1804

Received August 10, 1988

There exists considerable interest in 1,10-phenanthroline and its derivatives (especially neocuproine) because of their biological activity,[2,3] complexation properties,[4-6] inclusion in novel macrocycles,[7] and other applications.[8] Moreover, there are very few literature reports of monofunctionalized derivatives of 2,9-dimethyl-1,10-phenanthroline (**1**), which may have important fungistatic properties[9,10] and offer a viable route to the inclusion of metal ions at selected sites on monoclonal antibodies.[11] This paper describes the monofunctionalization of **1** via mono-*N*-oxide formation (and subsequent Boekelheide rearrangement) and provides insight, via a single-crystal X-ray structure of **2**·2H_2O, into the existence of the proposed 1,10-phenanthroline bis(*N*-oxide).[12-14]

Direct alkyl functionalization of **1** by free-radical halogenation using either *N*-chloro-(NCS)[15,16] or *N*-bromosuccinimide(NBS)[17] under diverse reaction conditions[18] did not yield the monohalo product **6** in significant amounts (2%). Therefore, a more circuitous procedure using the intermediary *N*-oxide was employed, since the mono-*N*-oxide **2** can serve as an appropriate intermediate for the synthesis of unsymmetrical neocuproine derivatives. Mono-*N*-oxide **2** was readily obtained (68%) by oxidation of **1** with 30% hydrogen peroxide in glacial acetic acid[19-22]

(1) (a) Chemistry of Heterocyclic Compounds. Part 124. Previous paper in this series: Newkome, G. R.; Gupta, V. K. *Makromol. Chem., Rapid Commun.* **1988**, *9*, 609. (b) University of South Florida, Tampa, FL 33620. (c) Louisiana State University, Baton Rouge, LA 70803-1804.

(2) Shulman, A.; Dwyer, F. P. In *Chelating Agents and Metal Chelates*; Dwyer, F. P., Mellor, D. P., Eds.; Academic Press: New York, 1964; p 383.

(3) Mohindru, A.; Fisher, J. M.; Rabinovitz, M. *Biochem. Pharm.* **1983**, *32*, 3627.

(4) Gillard, R. D. *Coord. Chem. Rev.* **1975**, *16*, 67.

(5) Karayannis, N. M.; Speca, A. N.; Chasan, D. E.; Pytlewski, L. L. *Coord. Chem. Rev.* **1976**, *20*, 37.

(6) Engbersen, J. F. J.; Koudijs, A.; Joosten, M. H. A.; van der Plas, H. C. *J. Heterocycl. Chem.* **1986**, *23*, 989.

(7) Chandler, C. J.; Deady, L. W.; Reiss, J. A.; Tzimos, J. *J. Heterocycl. Chem.* **1982**, *19*, 1017. Dietrich-Buchecker, C. O.; Sauvage, J.-P. *Chem. Rev.* **1987**, *87*, 795. Albrecht-Gary, A.-M.; Dietrich-Buchecker, C.; Saad, Z.; Sauvage, J.-P. *J. Am. Chem. Soc.* **1988**, *110*, 1467.

(8) Sliwa, W. *Heterocycles* **1979**, *12*, 1207.

(9) (a) Blank, F. *Nature (London)* **1951**, *168*, 516. (b) Gysin, H.; Hodel, E. U.S. Patent 1952, 2,617,753; *Chem. Abstr.* **1953**, *47*, 2437.

(10) Rabinovitz, M. Unpublished results.

(11) Pollack, S. J.; Nakayama, G. R.; Schultz, P. G. *Science* **1988**, *242*, 1038.

(12) Gillard, R. D. *Inorg. Chim. Acta* **1981**, *53*, L173.

(13) Summers, L. *Adv. Heterocycl. Chem.* **1978**, *22*, 1.

(14) Linsker, F.; Evans, R. L. *J. Am. Chem. Soc.* **1946**, *68*, 403.

(15) Newkome, G. R.; Puckett, W. E.; Kiefer, G. E.; Gupta, V. K.; Xia, Y.-J.; Coreil, M.; Hackney, M. A. *J. Org. Chem.* **1982**, *47*, 4116.

(16) Newkome, G. R.; Kiefer, G. E.; Xia, Y.-J.; Gupta, V. K. *Synthesis* **1984**, 676.

(17) Newkome, G. R.; Gupta, V. K.; Fronczek, F. R. *Inorg. Chem.* **1983**, *22*, 171.

(18) Offermann, W.; Vogtle, F. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 464.

(19) Mlachowski, J.; Kloc, K. *Rocz. Chem.* **1973**, *47*, 727.

(20) Maerker, G.; Case, F. H. *J. Am. Chem. Soc.* **1958**, *80*, 2745.

(21) Corey, E. J.; Borror, A. L.; Foglia, T. *J. Org. Chem.* **1965**, *30*, 288.

(22) Reaction of **1** with *m*-chloroperbenzoic acid[10] gave low yields of **2**.

0022-3263/89/1954-1766$01.50/0