reached at the agreement factors listed in Table 4 (supplementary material). No unusually high correlations were noted between any of the variables in the last cycle of least-squares refinement, and the final difference density map showed no peaks greater than 0.20 e/Å^3. All calculations were made using Molecular Structure Corporation's TEXRAY 230 modifications of the SDP-PLUS series of programs.

Acknowledgment. Financial support from the Robert A. Welch Foundation and the National Science Foundation (Grant CHE-8607935) is gratefully acknowledged. The NMR spectrometer was partially funded by the NSF (Grant CHE-866352). We thank Dr. James Korp for assistance with the X-ray crystal analysis and J.-L.L. would like to thank Prof. A. Emran for his generous assistance.

Registry No. **3a**, 25282-60-4; **4a**, 529-23-7; **4b**, 7521-41-7; **4c**, 70127-96-7; **4d**, 126522-16-5; **5a**, 113258-54-1; **5b**, 131251-68-8; **5c**, 131251-69-9; **5d**, 131251-70-2; **7**, 131251-63-3; **8**, 58228-96-9; **9a**, 131251-64-4; **9b**, 131251-71-3; **10a**, 113258-55-2; **10b**, 131251-74-6; **10c**, 131251-75-7; **10d**, 131251-76-8; **10e**, 131251-77-9; **10f**, 131251-78-0; **11**, 131251-65-5; **12**, 131251-72-4; **13**, 131251-66-6; **14a**, 113258-57-4; **14b**, 131251-79-1; **14c**, 113258-56-3; **15a**, 5661-06-3; **15c**, 131251-73-5; **16**, 131251-67-7; **17**, 35005-74-4; cyclopentanone, 120-92-3.

Supplementary Material Available: Four tables of data collection and processing parameters, positional parameters and ESD's, bond distances, and bond angles and the ^{1}H and ^{13}C NMR spectra of compounds **5a-d**, **9a,b**, **10b,f**, **11-13**, **14a-c**, **15c**, **16**, and **17** (22 pages). Ordering information is given on any current masthead page.

Chiral Synthesis via Organoboranes. 29. A General Synthesis of α-Chiral Monosubstituted Acetylenes and Their Trimethylsilyl Derivatives from Enantiomerically Pure Boronic Esters

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Received August 23, 1990

The procedure for the synthesis of RC≡CH by the iodination of $[R_3BC{\equiv}CH]^-Li^+$ is impractical for the synthesis of the corresponding chiral derivatives, R*C≡CH, due to the unavailability of the required R^*_3B compounds. RThxBOMe and $R^*ThxBOCH_3$, now readily available by established procedures, serve handily for the syntheses of RC≡CR′ and R*C≡CR respectively from LiC≡CR, but fail for the syntheses of either RC≡CH or R*C≡CH, in reasonable yield, from LiC≡CH. Fortunately, this difficulty can be circumvented by utilizing $LiC{\equiv}CSiMe_3$. Indeed, treatment of enantiomerically pure monoalkylthexylborinates, $R^*ThxBOCH_3$, readily prepared from enantiomerically pure boronic esters, with $LiC{\equiv}CSiMe_3$ forms an ate complex which readily undergoes the desired iodine-induced rearrangement, forming α-chiral (trimethylsilyl)acetylenes, $R^*C{\equiv}CSiMe_3$. The (trimethylsilyl)acetylenes are easily desilylated to afford the corresponding α-chiral terminal acetylenes, R*C≡CH, in yields of ~70% and essentially 100% enantiomeric excess (≥99%). These intermediates, $R^*C{\equiv}CSiMe_3$ and R*C≡CH, can be readily converted by simple procedures into a wide variety of pure enantiomers: $R^*CH{=}CH_2$, R^*CH_2CHO, R^*CO_2H, $R^*CH_2CO_2H$, R^*COCO_2R, etc. Since both (+)- and (-)-alkylboronic esters are now readily available in essentially 100% enantiomeric purity, it is now possible to synthesize (+)- and (-)-α-chiral monosubstituted acetylenes and their trimethylsilyl derivatives in very high enantiomeric purities. This provides the first general, efficient synthesis of these valuable synthons in such high enantiomeric purities.

In 1961, asymmetric hydroboration marked a milestone in achieving chiral synthesis approaching 100% ee by a nonenzymatic process.[2] Since then, we[3] and others[4] have refined this method to the point where many functional groups of interest to the organic chemist are now readily accessible in essentially enantiomerically pure form. Among the chiral organoboranes attainable via this process, enantiomerically pure boronic esters,[5] $R^*B(OR)_2$, have emerged as particularly versatile reagents. They have been converted into enantiomerically pure alcohols,[6] aldehydes,[7] acids,[7] and homologated alcohols,[7] as well as borohydrides,[8] diols,[9] and amines.[10] As part of our continuing research efforts to develop simple, practical methods for enantioselective synthesis via optically pure boronic esters, we undertook to find an efficient, general synthesis of α-chiral monosubstituted acetylenes, R*C≡CH. Previous syntheses of such acetylenes have utilized optically active precursors. α-Chiral 1-alkynes have been also prepared earlier, in moderate optical purities, by applying Wittig-type reaction of the reagent, (dichloromethylene)tris(dimethylamino)phosphorane, $(Me_2N)_3P{=}CCl_2$, to α-chiral aldehydes, followed by elimination of the intermediate with *n*-butyllithium.[11] A conventional method for preparing these compounds is the bromination-dehydrobromination of α-chiral olefins.[12] The former approach suffers from substantial racemization of the product, while the latter

(1) (a) Postdoctoral research associate on Grant GM 10937-26 from the National Institute of Health. (b) Postdoctoral research associate on Grant CHE 87-06102 from the National Science Foundation.
(2) Brown, H. C., Zweifel, G. *J. Am. Chem. Soc.* **1961**, *83*, 486.
(3) For a detailed review of asymmetric hydroboration, see: Brown, H. C.; Jadhav, P. K. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1983; Vol. 2, Chapter 1.
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(6) For leading references, see: Srebnik, M.; Ramachandran, P. V. *Aldrichimica Acta* **1987**, *20*, 9.
(7) Brown, H. C.; Imai, T.; Desai, M. C.; Singaram, B. *J. Am. Chem. Soc.* **1985**, *107*, 4980.
(8) Brown, H. C.; Singaram, B.; Cole, T. E. *J. Am. Chem. Soc.* **1985**, *107*, 460.
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(10) Brown, H. C.; Kim, K. W.; Singaram, B.; Cole, T. E. *J. Am. Chem. Soc.* **1986**, *108*, 6761.
(11) Marcassi, F.; Giacomelli, G.; Menicagli, R. *Gazz. Chim. Ital.* **1980**, *110*, 195.
(12) Lardicci, C.; Botteghi, C.; Benedetti, E. *J. Org. Chem.* **1966**, *31*, 1534.

0022-3263/91/1956-1500$02.50/0

method is tedious and not of synthetic importance. The fact that the literature does not record any efficient method for the synthesis of α-chiral monosubstituted acetylenes of high enantiomeric purity, approaching 100% ee, implies the difficulties involved in the synthesis of R*C≡CH by currently available methods.

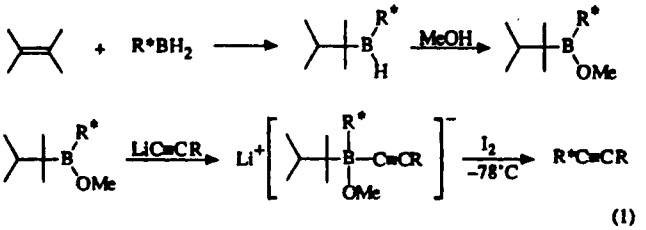
Results and Discussion

The synthesis of achiral disubstituted acetylenes has been achieved by adding the appropriate lithium acetylide to the appropriate trialkylborane.[13] Addition of iodine to the ate complex at −78 °C provided the desired disubstituted acetylene. However, this procedure would not work for the synthesis of monosubstituted acetylenes.[14] Fortunately, use of the commercially available ethylenediamine adduct of LiC≡CH solved the problem,[13] and excellent yields of the desired products were realized.

In applying these procedures for the synthesis of optically active acetylenes, we faced a major hurdle. The necessary optically active derivatives, R^*_3B, are currently not available. Even if they were available, only one R group is utilized in these reactions. This would mean a yield of the optically active groups of only 33%, as a maximum.

We had previously solved that problem for the synthesis of achiral disubstituted acetylenes by utilizing the thexylmonomethoxyboron moiety as a blocking group to provide a more satisfactory yield based on the R groups utilized.[15] This procedure provides satisfactory yields and adequate utilization of the R groups.

However, this procedure cannot be utilized for the synthesis of the corresponding R* derivatives. We previously overcame this problem by converting the optically active boronic esters, $R^*BO_2(CH_2)_3$, into the corresponding boranes, R^*BH_2.[8] Hydroboration of 2,3-dimethyl-2-butene with the chiral monoalkylborane provides the desired intermediate (eq 1).[16] This procedure made possible the

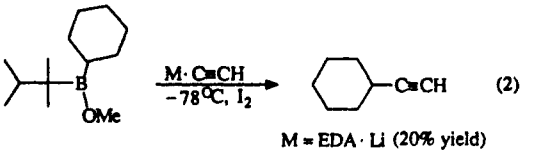


(1)

synthesis of chiral disubstituted acetylenes in very high % ee.[16] In this paper, we report on the utilization of the enantiomerically pure monoalkylthexylborinates, R*ThxBOMe, for an enantioselective synthesis of α-chiral monosubstituted acetylenes, R*C≡CH, and their trimethylsilyl derivatives, $R^*C{\equiv}CSiMe_3$. Here, it may be pointed out that though the synthesis of RC≡CR′ and R*C≡CR from monoalkylthexylborinates is known, the successful syntheses of either RC≡CH or R*C≡CH have never been achieved from the monoalkylthexylborinates.

In order to establish appropriate conditions for the conversion of enantiomerically pure monoalkylthexylborinates into chiral acetylenes of high enantiomeric excess and facilitate their isolation, we initially decided to test the experimental protocol on achiral monoalkylthexylborinates. The achiral methyl monoalkylthexylborinates, RThxBOMe, required for investigating the methodology, can be prepared either by the direct hydroboration of a hindered olefin with thexylborane[17] followed by methanolysis or by hydroboration of an olefin with thexylchloroborane[18] followed by methanolysis. In the present study, we employed the latter procedure due to ready availability of thexylchloroborane. Previously, we have shown that lithium ethynyltrialkylborates react with iodine to form terminal acetylenes stereospecifically.[13]

Treatment of cyclohexylthexylborinate with lithium acetylide–ethylenediamine (HC≡CLi·EDA), followed by iodination, produced the corresponding terminal acetylene, but in very poor yield (20%) (eq 2, M = EDA Li). The

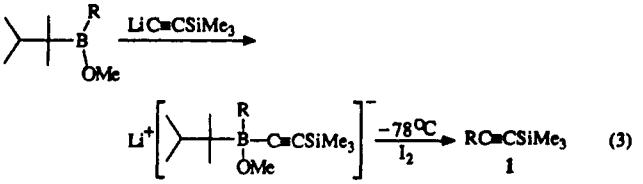


(2)

M = EDA·Li (20% yield)
M = Li (40% yield)

reaction of the borinate with lithium acetylide, prepared from acetylene and *n*-butyllithium, followed by iodination gave the 1-alkyne in somewhat better yield (40%), but still not in a satisfactory range (eq 2, M = Li).

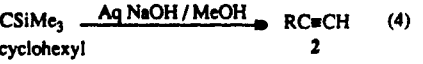
Various modifications of the experimental conditions did not help. Finally, we explored the possibility of using lithium (trimethylsilyl)acetylide for achieving this transformation. When the ate complex, derived from methyl cyclohexylthexylborinate and lithium (trimethylsilyl)-acetylide, was treated with iodine at −78 °C, the trimethylsilyl derivative of the desired monosubstituted acetylene, $RC{\equiv}CSiMe_3$, was obtained in excellent yield (78%) (eq 3). The (trimethylsilyl)acetylenes undergo a



(3)

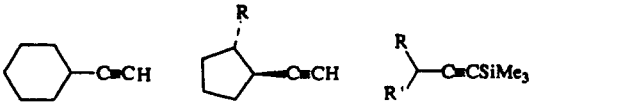
R = cyclohexyl

facile desilylation[19] on treatment with aqueous sodium hydroxide to afford the desired 1-alkynes in essentially quantitative yield (eq 4).



(4)

By use of the general procedure described above, the following terminal acetylenes and (trimethylsilyl)acetylenes were prepared in excellent yields (62–78%).



2: (78%)
3: R = Me (67%)
4: R = Ph (62%)
5: R = Me, R′ = Et (72%)
6: R = Me, R′ = *i*-Pr (64%)
7: R = Et, R′ = Pr (75%)

Having demonstrated the feasibility of effectively using lithium (trimethylsilyl)acetylide in the iodine-induced rearrangement of ate complex, we turned our attention to

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(14) Midland, M. M.; Sinclair, J. A.; Brown, H. C. *J. Org. Chem.* **1974**, *39*, 732.
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(16) Brown, H. C.; Bakshi, R. K.; Singaram, B. *J. Am. Chem. Soc.* **1988**, *110*, 1529.
(17) Brown, H. C.; Negishi, E.; Katz, J. J. *J. Am. Chem. Soc.* **1975**, *97*, 2791.
(18) Brown, H. C.; Sikorski, J. A.; Kulkarni, S. U.; Lee, H. D. *J. Org. Chem.* **1982**, *47*, 863.
(19) Harris, S. J.; Walton, D. R. M. *Tetrahedron* **1978**, *34*, 1037.

Table I. α-Chiral Terminal Acetylenes and (Trimethylsilyl)acetylenes Obtained from Enantiomerically Pure Boronic and Borinic Esters

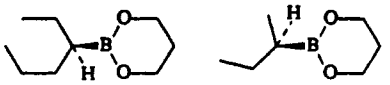
boronic/borinic esters $R^*BO_2(CH_3)_2/R_2^*BOCH_3$, R* =	acetylenes $R^*C{\equiv}CSiMe_3/R^*C{\equiv}CH$	config of acetylenes	α^{23}_D, deg[d]	% ee	yield, % (isolated)[f]
(*R*)-2-butyl[a]	1-(trimethylsilyl)-3-methyl-1-pentyne (13)	*R*	−26.2	≥99	70
(*S*)-3-methyl-2-butyl[a]	1-(trimethylsilyl)-3,4-dimethyl-1-pentyne (14)	*S*	+16.7	≥99	64
(*R*)-3-hexyl[a]	1-(trimethylsilyl)-3-ethyl-1-hexyne (15)	*R*	−4.3	≥99	73
(1*S*,2*S*)-*trans*-2-methylcyclopentyl[a]	*trans*-(2-methylcyclopentyl)ethyne (18)	1*S*,2*S*	+111.7[e]	≥99	62
(1*S*,2*S*)-*trans*-2-phenylcyclopentyl[a]	*trans*-(2-phenylcyclopentyl)ethyne (19)	1*S*,2*S*	−170.2	≥99	59
(2*S*,3*R*)-isopinocampheyl[b]	*trans*-isopinocampheylethyne (20)	1*R*,2*R*,3*R*,5*S*	−43.2	≥99	75[g]
(2*R*,3*S*)-isopinocampheyl[c]	*trans*-isopinocampheylethyne	1*S*,2*S*,3*S*,5*R*	+43.1	≥99	74[g]

[a] Boronic esters prepared by using chiral auxillary obtained from (+)-α-pinene. [b] Borinic ester obtained from (+)-α-pinene. [c] Borinic ester obtained from (−)-α-pinene. [d] Observed rotation (neat, *l* 1.0). [e] Specific rotation, recorded in solution (*c* 2.31, CCl_4). [f] Based on the corresponding methyl monoalkylthexylborinate. [g] Based on the corresponding methyl diisopinocampheylborinate.

the synthesis of representative α-chiral monosubstituted acetylenes, R*C≡CH, and (trimethylsilyl)acetylenes, R*C≡CSiMe$_3$.

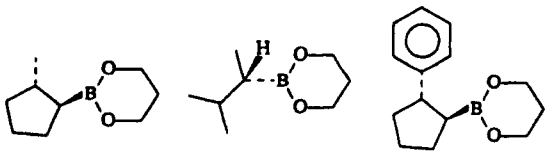
The optically active organoborane intermediates required for the synthesis of monoalkylthexylborinates, R*ThxBOMe, were prepared by the asymmetric hydroboration of prochiral olefins either with diisopinocampheylborane, Ipc_2BH (≥99% ee),[20] or with monoisopinocamphenylborane, $IpcBH_2$ (≥99% ee),[21,22] both readily prepared form (+)-α-pinene. Thus, asymmetric hydroboration of *cis*-3-hexene with (−)-Ipc_2BH forms trialkylborane,[23] which, upon treatment with 1.8 equiv of benzaldehyde, results in the selective, facile elimination of the chiral auxiliary, providing the corresponding boronic ester. The boronic ester was extracted from the reaction mixture with 3 N sodium hydroxide. Acidification with 3 N hydrochloric acid provided 3-hexylboronic acid of high enantiomeric purity. The optically active 2-alkyl-1,3,2-dioxaborinanes were then prepared by esterification[24] of the corresponding boronic acids with 1,3-propanediol.

By use of the general procedure described above, the following two boronic esters of high enantiomeric purity (≥99% ee) were prepared.



Similarly, the asymmetric hydroboration of methylcyclopentene with isopinocampheylborane ($IpcBH_2$),[25] followed by crystallization, privides ≥99% optically pure dialkylborane,[22] which, upon treatment with acetaldehyde under mild conditions, eliminates the chiral auxiliary and provides the corresponding boronic ester of high enantiomeric purity. The optically active 2-alkyl-1,3,2-dioxaborinanes were then prepared by esterification[24] of the corresponding boronic acids with 1,3-propanediol.

By use of the general procedure described above, the following three boronic esters of high enantiomeric purity (≥99% ee) were prepared.



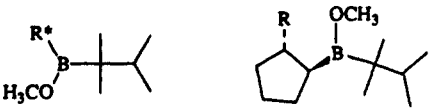
The relatively inert chiral alkylboronic esters, upon treatment with lithium aluminum hydride ($LiAlH_4$), give quantitatively the more reactive monoalkylborohydrides, R^*BH_3Li, of very high enantiomeric purity (eq 5).[8]

$$R^*BO_2(CH_2)_3 \xrightarrow[0\,^\circ C,\ 0.5h]{LiAlH_4} R^*BH_3Li + \tfrac{1}{4}\,HAlO_2(CH_2)_3 \qquad (5)$$

The monoalkylboranes (R^*BH_2)[22] are generated from the R^*BH_3Li by conveniently simple reaction with trimethylsilyl chloride. Reaction of optically active monoalkylboranes, R^*BH_2, with 10% excess of 2,3-dimethyl-2-butene at 0 °C affords the desired monoalkylthexylboranes.[16,26] The chiral monoalkylthexylboranes, R*ThxBH, were converted into the enantiomerically pure methyl monoalkylthexylborinates, R*ThxBOMe, by methanolysis at 0 °C (eq 6).

$$R^*BH_3Li \xrightarrow[2)\ Me_3SiCl]{1)} R^*ThxBH \xrightarrow[0\,^\circ C]{MeOH} R^*ThxBOMe \qquad (6)$$

By use of the general procedure described above, the following representative methyl monoalkylthexylborinates were prepared in enantiomeric purities approaching 100% ee.



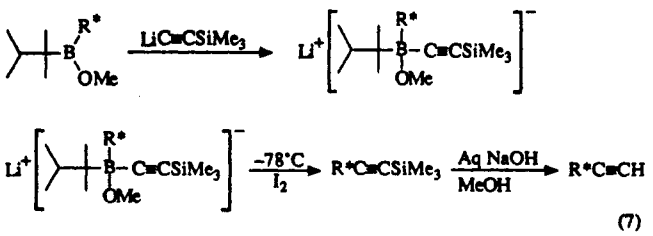
8: R* = (*R*)-2-butyl
9: R* = (*S*)-2-methyl-3-butyl
10: R* = (*R*)-3-hexyl
11: R = Ph
12: R = Me

The enantiomeric excess of all these organoborane intermediates was determined by capillary GC analysis of the appropriate derivatives of the alcohols obtained following alkaline hydrogen peroxide oxidation.[7]

Treatment of the enantiomerically pure methyl monoalkylthexylborinates with (trimethylsilyl)acetylide followed by iodination forms the corresponding α-chiral monosubstituted (trimethylsilyl)acetylenes. The trimethylsilyl group was readily cleaved by treatment with alkali in aqueous methanol, in a manner analogous to the achiral derivatives, to furnish the desired α-chiral monosubstituted acetylenes without observable racemization (eq 7).[19]

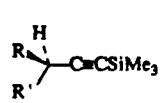
By use of the general procedure described above, the following α-chiral terminal acetylenes and (trimethylsilyl)acetylenes were prepared in optical purities ap-

(20) Brown, H. C.; Singaram, B. *J. Org. Chem.* **1984**, *49*, 945.
(21) Brown, H. C.; Schwier, J. R.; Singaram, B. *J. Org. Chem.* **1978**, *43*, 4395.
(22) These organoboranes actually exist in solution as dimers, that is, as derivatives of diborane molecules. However, it is convenient to refer to them as simple borane derivatives.
(23) Brown, H. C.; Desai, M. C.; Jadhav, P. K. *J. Org. Chem.* **1982**, *47*, 5065.
(24) Brown, H. C.; Bhat, N. G.; Somayaji, V. *Organometallics* **1984**, *2*, 1311.
(25) Brown, H. C.; Singaram, B. *J. Am. Chem. Soc.* **1984**, *106*, 1797.
(26) Actually these monoalkylthexylboranes generally exist as the monomer–dimer equilibria.

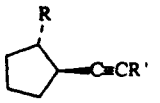


(7)

proaching 100% ee (Table I).



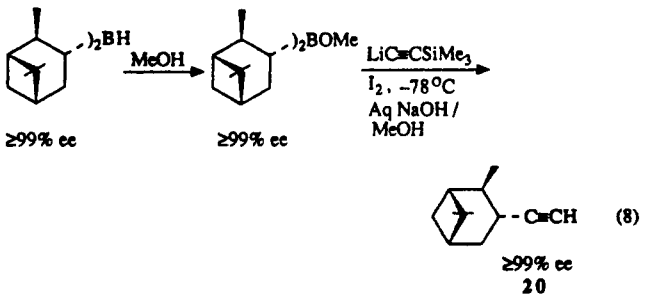
13: R = Me, R' = Et
14: R = *i*-Pr, R' = Me
15: R = Et, R' = Pr



16: R = Me, R' = $SiMe_3$
17: R = Ph, R' = $SiMe_3$
18: R = Me, R' = H
19: R = Ph, R' = H

Acetylenes 13, 14, and 15 were characterized as their trimethylsilyl derivatives because of the high volatilities of their parent acetylenes. The less volatile derivatives, compounds 16 and 17, were converted into their corresponding parent acetylenes 18 and 19, respectively, and characterized. Theoretically, starting from α-pinene, there are ~10 steps involved in this enantiomerically pure terminal acetylene synthesis, but many intermediates need not be isolated, and thus the synthesis does not involve more than five steps.

This method appears to be quite general, working well for hindered as well as unhindered derivatives. However, we encountered problems with one highly hindered derivative. Fortunately, it proved possible to circumvent this problem. Hydroboration of 2,3-dimethyl-2-butene with monoisopinocamphenylborane ($IpcBH_2$) did not proceed to completion, but to an equilibrium mixture containing ~70% of the desired thexylmonoisopinocampheylborane.[27] The following modified approach circumvented the difficulty. Diisopinocampheylborane (Ipc_2BH) was methanolyzed to give the corresponding methyl borinate. This, upon treatment with lithium (trimethylsilyl)acetylide, followed by iodination, furnished isopinocamphenyl(trimethylsilyl)acetylene in good yield. The acetylene was desilylated, as described earlier, to afford isopinocampheylacetylene (eq 8). By using diisopinocampheylborane, prepared from (−)-α-pinene, the other optical isomer of the acetylene was also prepared.

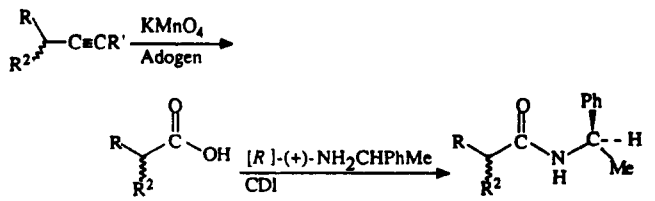


(8)

All the α-chiral monosubstituted acetylenes and their (trimethylsilyl)acetylene derivatives synthesized are new compounds. No method was found in the literature to establish their enantiomeric purities. The following procedure proved satisfactory and was adopted to establish the enantiomeric purities of these acetylenes. The acetylenes were oxidized to carboxylic acids with potassium permangnate, under phase-transfer catalytic conditions.[28]

(27) Brown, H. C.; Negishi, E. *Synthesis* **1974**, 77.
(28) Lee, D. G.; Chang, V. S. *Synthesis* **1978**, 462.

Scheme I



[a] R' = $SiMe_3$, H

The acids were coupled to (*R*)-(+)-α-methylbenzylamine in the presence of 1,1'-carbonyldiimidazole (CDI) to yield the diastereomeric amides (Scheme I).[29] Each pair of diastereomeric amides was readily resolvable by capillary GC (SPB-5, 30 m). Racemic acids gave two peaks for the amides in 1:1 ratio, thus assuring that no kinetic resolution had taken place.

In this study the chiral monoalkylthexylborinates are prepared from enantiomerically pure boronic esters. Since chiral boronic esters of either the (+) or (−) series are readily available in essentially pure enantiomeric form,[9] we can now synthesize both (+)- and (−)-α-chiral monosubstituted acetylenes and their trimethylsilyl derivatives of known absolute configuration and of consistently high enantiomeric excess.

Experimental Section

All operations were carried out under a nitrogen atmosphere with oven-dried glassware.[30] The ^{11}B NMR spectra were recorded on a Varian FT-80A instrument. The ^1H NMR (60 MHz) spectra were scanned on a Varian T-60 spectrometer, and the ^{13}C spectra were obtained on a Varian FT-80 instrument. The chemical shifts are in δ relative to Me_4Si for ^1H and ^{13}C NMR spectra. IR and mass spectra were recorded on Perkin-Elmer 137 and Finnegan GC/mass spectrometers, respectively. Gas chromatographic analyses were carried out with a Hewlett-Packard 5750 chromatograph with a TC-detector. Optical rotations were measured on a Rudolph Polarimeter Autopol III to ±0.01°, but rounded off to 0.1°. Capillary gas chromatographic analyses were carried out with a Hewlett-Packard 5890 chromatograph fitted with 50-m methylsilicone, 15-m Supelcowax, or 30-m SPB-5 columns.

Materials. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl. Anhydrous diethyl ether (EE) was purchased from Mallinckrodt, Inc., and used directly. Lithium aluminum hydride (1.0 M) in EE and (−)-menthyl chloroformate were purchased from the Aldrich Chemical Co. The boronic esters used in this study were prepared by procedures described previously[11] starting from (+)-α-pinene. (*R*)-MTPA was purchased from Aldrich, converted to the acid chloride,[31] and distilled.

General Procedure for the Synthesis of Achiral/Racemic (Trimethylsilyl)acetylenes and Monosubstituted Acetylenes. The following procedure for the synthesis of (trimethylsilyl)-cyclohexylethyne 1 and cyclohexylethyne 2 is representative. Methyl cyclohexylthexylborinate was prepared according to the literature procedure.[18] A solution of (trimethylsilyl)acetylene (1.43 mL, 10 mmol) was taken in THF (10 mL) and cooled to −78 °C. To it *n*-butyllithium in *n*-hexane (5 mL, 10 mmol) was added dropwise, and the mixture was stirred for 0.5 h. A 1 M solution of methyl cyclohexylthexylborinate (10 mmol) was added to it, and the mixture was stirred at −78 °C for another 0.5 h when the ^{11}B NMR indicated the formation of an ate complex (δ−0.9). Iodine (2.54 g, 10 mmol) in THF (15 mL) was added slowly and the mixture was stirred at −78 °C for 3 h and at 25 °C for 2 h. Methanol (10 mL) and 3 M NaOH (3.3 mL) were added successively, and the mixture was stirred for 15 min. The reaction mixture was diluted with *n*-pentane (35 mL), washed with 3 M NaOH (3 × 5 mL), aqueous saturated $Na_2S_2O_3$ (5 mL), water (3

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× 5 mL), and brine (5 mL), and dried over $MgSO_4$. The solvent was evaporated (12 Torr), and the residue was distilled to give (trimethylsilyl)cyclohexylethyne (1): 1.40 g (78%); bp 72–73 °C (2.5 Torr). The acetylene was further purified by preparative GC: IR (neat) cm^{-1}; ^1H NMR (CCl_4) 0.12 (s, 9 H), 1.0–2.48 (m, 9 H). Anal. Calcd for $C_{11}H_{20}Si$: C, 73.33; H, 11.11. Found: C, 73.07; H, 11.20.

To a solution of (trimethylsilyl)cyclohexylethyne (1) (7.8 mmol, 1.40 g) in methanol (15 mL) was added 3 M NaOH (1.4 mL). The mixture was stirred at room temperature for 24 h. The reaction mixture was diluted with ether (50 mL), washed with water (15 mL), 3 M HCl (15 mL), water (2 × 15 mL), and brine (15 mL), and dried over $MgSO_4$. The solvent was removed by using a Vigreux column, and the residue was distilled to give cyclohexylethyne (2): 0.77 g (94%); bp 130–132 °C (lit.[32] bp 130–132 °C). The spectral data of the acetylene was found to be consistent with that of the literature.[33]

Synthesis of Methyl Monoalkylthexylborinates of Very High Enantiomeric Purity. The following procedure for the synthesis of methyl ((1*S*,2*S*)-*trans*-2-methylcyclopentyl)thexylborinate (12) is typical. To an ice-cooled solution of ((1*S*,2*S*)-*trans*-2-methylcyclopentyl)borohydride (89 mL, 0.45 M, 40.1 mmol) in a 100-mL flask fitted with a rubber septum and a magnetic stirrer were added 2,3-dimethyl-2 butene (5.69 mL, 48.2 mmol) and trimethylsilyl chloride (5.6 mL, 44.1 mmol) successively with stirring. The reaction mixture was stirred for 1 h at 0 °C, and the LiCl precipitate was allowed to settle. The clear supernatant solution containing the ((1*S*,2*S*)-*trans*-2-methylcyclopentyl)thexylborane was withdrawn and estimated by hydride analysis:[30] 0.42 M, 94% yield; ^{11}B NMR δ +80 (unresolved d, J_{BH} = 95 Hz), +33 (broad s); IR 2439, 1542 cm^{-1}.

Methanol (66 mmol) was added to the above 0.42 M solution of ((1*S*,2*S*)-*trans*-2-methylcyclopentyl)thexylborane (33.2 mmol) at 0 °C, and the mixture was stirred at 0 °C for 1 h. ^{11}B NMR spectroscopy of the reaction mixture indicated the formation of the corresponding borinate (δ +54). The solvent was evaporated under reduced pressure (12 Torr) at 25 °C, and *n*-pentane (40 mL) was added. The LiCl precipitated was removed by centrifugation. The solvent was removed under reduced pressure (12 Torr) to get methyl ((1*S*,2*S*)-*trans*-2-methylcyclopentyl)thexylborinate 12 (6.64 g, 96% yield). A small portion of the borinate was oxidized (H_2O_2/NaOH). The product alcohol, (1*S*,2*S*)-(+)-*trans*-2-methylcyclopentanol exhibited $[\alpha]^{23}_D$ +46.8° ± 0.01 (neat), suggesting ≥99% ee for the borinate.

General Procedure for the Preparation of α-Chiral (Trimethylsilyl)acetylenes of Very High Enantiomeric Purity. The following procedure for the synthesis of ((1*S*,2*S*)-*trans*-2-methylcyclopentyl)(trimethylsilyl)ethyne (16) is representative. To a solution of (trimethylsilyl)acetylene (33.2 mmol, 4.75 mL) in THF (30 mL), cooled to −78 °C, was added *n*-butyllithium in *n*-hexane (33.2 mmol, 15.2 mL). The mixture was stirred for 0.5 h at −78 °C. The above methyl ((1*S*,2*S*)-*trans*-2-methylcyclopentyl)thexylborinate (12) (6.64 g, 31.8 mmol) was dissolved in THF (33 mL) and transferred to the reaction mixture by using a double-ended needle. The mixture was stirred for another 0.5 h, when a clean formation of an ate complex was indicated by the ^{11}B NMR (δ +0.26). Iodine (33.2 mmol, 8.5 g) in THF (30 mL) was added slowly (15 min), and the mixture was stirred at −78 °C for 3 h and at 25 °C for 2 h. Methanol (33 mmol) and 3 M NaOH (11 mL) were added successively. After 15 min the reaction mixture was diluted with *n*-pentane (100 mL), washed with 3 M NaOH (2 × 20 mL), saturated aqueous $Na_2S_2O_3$ (20 mL), water (3 × 20 mL), and brine (20 mL), and dried over $MgSO_4$. The solvent was evaporated (25 °C, 12 Torr), and the residue was distilled to give ((1*S*,2*S*)-*trans*-2-methylcyclopentyl)(trimethylsilylethyne (16): 3.70 g (62%); bp 60–62 °C (2 Torr); IR (neat) 2170 cm^{-1}; ^1H NMR (CCl_4) 0.15 (s, 9 H), 1.05 (m, 3 H), 1.42–2.30 (m, 8 H).

General Procedure for Desilylation of α-Chiral Organyl(trimethylsilyl)acetylenes To Afford α-Chiral Monosubstituted Acetylenes of Very High Enantiomeric Purity. The following procedure for the preparation of ((1*S*,2*S*)-*trans*-2-methylcyclopentyl)ethyne (18) is representative. To a solution of ((1*S*,2*S*)-*trans*-2-methylcyclopentyl)(trimethylsilyl)ethyne (16) (7.7 mmol, 1.4 g) in methanol (15 mL) was added 3 M NaOH (1.4 mL). The mixture was stirred at room temperature (~24 °C) for 24 h, diluted with ether (50 mL), washed with water (15 mL), 3 M HCl (15 mL), water (2 × 15 mL), and brine (15 mL), and dried over $MgSO_4$. The solvent was removed by using a Vigreux column, and the residue was distilled to give ((1*S*,2*S*)-*trans*-2-methylcyclopentyl)ethyne (18): 0.78 g (93%); bp 115–117 °C (750 Torr). The acetylene was further purified by preparative GC: IR (neat) 2110, 3299 cm^{-1}; ^1H NMR ($CDCl_3$) 1.05 (m, 3 H), 1.37–2.20 (m, 9 H); ^{13}C NMR ($CDCl_3$) 18.7, 23.5, 33.2, 33.8, 38.3, 42.5, 68.0, 88.0; *m/e* 93 ($M^+ - CH_3$); $[\alpha]^{23}_D$ +111.68° ± 0.01 (*c* 2.31, CCl_4). Anal. Calcd for C_8H_{12}: C, 88.88; H, 11.11. Found: C, 88.52; H, 11.25.

Synthesis of (1*R*,2*R*,3*R*,5*S*)-(−)-*trans*-Isopinocampheylethyne (20). To a stirring suspenion of Ipc_2BH,[20] prepared from (+)-α-pinene (100% ee) (22.3 mmol, 6.37 g) in ether (25 mL) was added methanol (22.3 mmol, 0.90 mL) slowly at −5 °C. The reaction mixture was stirred at −5 °C for 1 h when the ^{11}B NMR indicated the formation of the corresponding borinate (δ +54). The solvent was evaporated under high vacuum (2.0 Torr, 25 °C), and the residue (7.04 g) was dissolved in THF (25 mL). To a solution of (trimethylsilyl)acetylene (22.3 mmol, 3.18 mL) in THF (25 mL), cooled to −78 °C, was added *n*-butyllithium in *n*-hexane (22.3 mmol, 10.15 mL). The mixture was stirred for 0.5 h at −78 °C, and then the above borinate was added using a double-ended needle. The mixture was stirred for another 0.5 h, when a clean formation of an ate complex was indicated by ^{11}B NMR (δ +0.23). Iodine (22.3 mmol, 5.66 g) in THF (20 mL) was added slowly (15 min), and the mixture was stirred at −78 °C for 3 h and at 25 °C for 2 h. Methanol (22 mmol) and 3 M NaOH (7 mL) were added successively. After 15 min the mixture was diluted with *n*-pentane (60 mL), washed with 3 M NaOH (2 × 15 mL), saturated $Na_2S_2O_3$ (15 mL), water (3 × 15 mL), and brine (15 mL), and then dried over $MgSO_4$. The solvent was evaporated (25 °C, 12 Torr), and the residue was distilled to give (trimethylsilyl)((1*R*,2*R*,3*R*,5*S*)-*trans*-isopinocamphenyl)ethyne: 3.82 g (75%); bp 80–82 °C (1.0 Torr).

To a solution of (trimethylsilyl)((1*R*,2*R*,3*R*,5*S*)-*trans*-isopinocamphenyl)ethyne (8.5 mmol, 2.0 g) in methanol (20 mL) was added 3 M NaOH (2.0 mL). After 24 h at room temperature, the mixture was diluted with *n*-pentane (50 mL), washed with water (15 mL), 3 M HCl (15 mL), water (2 × 15 mL), and brine (15 mL), and dried over $MgSO_4$. The solvent was evaporated at 25 °C (12 Torr), and the residue was distilled to give (1*R*,2*R*,3*R*,5*S*)-(−)-*trans*-isopinocampheylethyne (20): 1.32 g (96%); bp 108–110 °C (70 Torr). The acetylene was further purified by preparative GC: IR (neat) 2104, 3305 cm^{-1}; ^1H NMR ($CDCl_3$) 1.02 (d, 3 H), 1.22 (s, 6 H), 1.62–2.6 (m, 9 H); ^{13}C NMR ($CDCl_3$) 21.6, 23.0, 28.1, 28.4, 34.5, 35.4, 38.3, 41.4, 45.0, 47.7, 67.2, 91.51; *m/e* 147 ($M^+ - CH_3$); α^{23}_D −43.16° ± 0.01 (neat, *l* 1.0). Anal. Calcd for $C_{12}H_{18}$: C, 88.88; H, 11.11. Found: C, 89.00; H, 11.22.

1-(Trimethylsilyl)-(*R*)-(−)-3-methyl-1-pentyne (13): yield 70%; bp 68–70 °C (50 Torr); IR (neat) 2170 cm^{-1}; ^1H NMR (CCl_4) 0.12 (s, 9 H), 0.8–1.65 (m, 8 H), 2.3 (m, 1 H); ^{13}C NMR ($CDCl_3$) 0.42, 11.7, 20.6, 28.5, 29.8, 84.2, 111.57; *m/e* 154 (M^+); α^{23}_D −26.18° ± 0.01 (neat, *l*, 1.0). Anal. Calcd for $C_9H_{18}Si$: C, 70.12; H, 11.68. Found: C, 69.85; H, 11.37.

1-(Trimethylsilyl)-(*S*)-(+)-3,4-dimethyl-1-pentyne (14): yield 64%; bp 78–80 °C (20 Torr); IR (neat) 2170 cm^{-1}; ^1H NMR (CCl_4) 0.12 (s, 9 H), 1.8–1.2 (m, 9 H), 1.6 (m, 1 H), 2.3 (m, 1 H); ^{13}C NMR ($CDCl_3$) 0.34, 18.3, 18.6, 20.6, 32.8, 33.6, 84.0, 109.6; *m/e* 168 (M^+); α^{23}_D +16.72° ± 0.01 (neat, *l* 1.0). Anal. Calcd for $C_{10}H_{20}Si$: C, 71.42; H, 11.90. Found: C, 71.60; H, 12.08.

1-(Trimethylsilyl)-(*R*)-(−)-3-ethyl-1-hexyne (15): yield 73%; bp 92–94 °C (20 Torr); IR (neat) 2180 cm^{-1}; ^1H NMR (CCl_4) 0.12 (s, 9 H), 0.9–1.8 (m, 12 H), 2.0–2.4 (m, 1 H); ^{13}C NMR ($CDCl_3$) 0.29, 11.6, 13.9, 20.3, 27.9, 34.0, 36.8, 85.0, 110.4; *m/e* 182 (M^+); α^{23}_D −4.28° ± 0.01 (neat, *l* 1.0). Anal. Calcd for $C_{11}H_{22}Si$: C, 72.52; H, 12.08. Found: C, 72.75; H, 12.46.

(1*S*,2*S*)-(−)-*trans*-(2-Phenylcyclopentyl)ethyne (19): yield 59%; bp 90–92 °C (0.1 Torr); IR (neat) 3292 cm^{-1}; ^1H NMR (CCl_4) 1.5–2.25 (s, 7 H), 2.45–3.2 (m, 2 H), 7.28 (s, 5 H); ^{13}C NMR ($CDCl_3$) 24.3, 33.9, 34.1, 38.5, 53.2, 69.3, 87.5, 126.6, 127.3, 128.5, 143.6; *m/e* 170 (M^+); α^{23}_D −170.16° ± 0.01 (neat, *l* 1.0). Anal. Calcd

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for $C_{13}H_{14}$: C, 91.76; H, 8.23. Found: C, 91.49; H, 8.46.

(1*S*,2*S*,3*S*,5*R*)-(+)-*trans*-Isopinocampheylethyne: yield 74%; bp 108–110 °C (70 Torr); IR (neat) 2104, 3305 cm^{-1}; ^1H NMR (CCl_4) 1.02 (d, 3 H), 1.22 (s, 6 H), 1.62–2.6 (m, 9 H); ^{13}C NMR ($CDCl_3$) 21.6, 23.0, 28.1, 28.4, 34.5, 35.4, 38.3, 41.4, 45.0, 47.7, 67.2, 91.5; α^{23}_D +43.10° ±0.01 (neat, *l* 1.0).

General Procedure for the Determination of Optical Purity of Acetylenes. The acetylene (7.8 mmol, 1.2 g) was dissolved in CH_2Cl_2 (25 mL) and a solution of methyltrialkylammonium chloride (Adogen 464) (0.8 g) in CH_2Cl_2 (25 mL) was added. To the mixture was added AcOH (5 mL) followed by a solution of $KMnO_4$ (17.7 mmol, 2.8 g) in water (50 mL). The mixture was refluxed with stirring for 6 h and then allowed to come to room temperature. Sodium bisulfite (solid) was added, in portions, until the mixture became colorless. The organic and aqueous layers were separated, and the aqueous layer was cooled to 0 °C and acidified with concentrated HCl. It was saturated with NaCl and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic portion was washed with brine (20 mL) and dried over $MgSO_4$. The solvent was removed to obtain the residue, which was dissolved in ether (15 mL) and extracted with 3 M NaOH (saturated aqueous $NaHCO_3$ in the case of chiral compounds). The aqueous portion was cooled to 0 °C, acidified with 3 M HCl, saturated with NaCl, and extracted with ether (3 × 20 mL). The combined ether portion was washed with brine (15 mL) and dried over $MgSO_4$. The solvent was evaporated under reduced pressure (25 °C, 12 Torr), and the residue was distilled to afford the α-chiral carboxylic acid. The carboxylic acids were obtained in yields of 65–70%. The acid (0.02 mmol) was coupled (16 h) to (*R*)-(+)-methylbenzylamine (0.02 mmol) in the presence of 1,1′-carbonyldiimidazole (0.02 mmol) in ether to give the desired amide. The crude amide was taken up in EE and analyzed on capillary GC.

Acknowledgment. We thank the National Institutes of Health (Grant 10937-27) and the National Science Foundation (Grant CHE 87-06102) for their generous support of this work.

Supplementary Material Available: ^1H NMR, ^{13}C NMR, and IR spectra for **13**, **14**, **15**, **18**, **19**, and **20** (18 pages). Ordering information is given on any current masthead pages.

Boronic Acid Catalyzed Hydrolyses of Salicylaldehyde Imines

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Received May 14, 1990

The hydrolysis of salicylaldehyde imines is catalyzed by boric acid, substituted arylboronic acids, and diphenylborinic acid. These reactions show saturation kinetics, allowing the determination of first-order catalytic constants and dissociation constants. Dissociation constants reflect single-ionization p*K* values similar to the p*K* values of the boronic acids. Binding is best on the acid side of the p*K*. Use of the Brønsted and the Hammett relationships shows that the binding constants are improved by electron-withdrawing substituents on the catalysts. Catalytic constants are nearly independent of pH, of Hammett σ, and of the p*K* of the catalyst. The reactions display no solvent deuterium isotope effect.

Introduction

Enzyme models that show binding prior to chemical reaction steps are studied for various reasons; one of these is an effort to understand the mechanisms of enzyme-catalyzed reactions. Most of these systems have used oligomeric or polymeric substances[1] such as synthetic polymers,[2,3] micelles,[4] cyclodextrins,[5] macrocyclic ethers,[6,7] substituted oligonucleotides,[8] and antibodies.[9-11] Small molecules that exhibit reversible binding prior to the catalytic steps are less common. One such example is the boron family of acids, comprising boric, boronic, and borinic acids.

The chemistry of these compounds has long been of interest due to their Lewis acid character. Boron in trivalent compounds has one vacant orbital which is available for the formation of a fourth covalent bond with electron donor. Boric and boronic acids are trigonal about the boron atom. They ionize to become tetrahedral boronate anions by accepting an electron pair from OH^- as shown in eq 1.[12]

$$RB(OH)_2 + {}^-OH \rightleftharpoons RB(OH)^-_3 \qquad (1)$$

The ability of boronates to bind to polyols and various hydrolytic enzymes is well known. This binding depends on the ability of boronates to rapidly and reversibly esterify to alcohols.[13-19]

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