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Syntheses with organoboranes — VIII. Transformation of (1*S*,6*R*)-(+)-2-carene into (1*S*,6*R*)-(+)-3(10)-carene and (1*R*,5*R*)-(−)-α-thujene into (1*R*,5*R*)-(+)-sabinene †

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Abstract: The transformation of (1*S*,6*R*)-(+)-2-carene and (1*R*,5*R*)-(−)-α-thujene into (1*S*,6*R*)-(+)-3(10)-carene and (1*R*,5*R*)-(+)-sabinene, respectively, by metallation–transmetallation–hydrolysis via the corresponding allylic organoborane intermediates is described. © 1997 Published by Elsevier Science Ltd. All rights reserved.

Among bicyclic monoterpene olefins with an exocyclic double bond, 3(10)-carene is a rare compound reported only a few times in the long history of terpene chemistry.[1–7] Gollnick and Schade[4] prepared (+)-3(10)-carene by the Huang–Minlon reduction of (−)-3-carene-10-al synthesized from (+)-3-carene. Later, Paquette[7] obtained (+)-3(10)-carene of much higher rotation from the same aldehyde by the reduction of its tosylhydrazone with sodium borohydride or catecholborane. Consequently, the enantiomeric excess of (+)-3(10)-carene remains uncertain.

(+)-Sabinene occurs in a wide variety of essential oils and is isolated from oil of savin.[8] However, it is not a low cost material and no convenient synthesis of an optically active sabinene is known.

Several years ago we developed a contrathermodynamic isomerization of (+)-α-pinene into (+)-β-pinene via hydrolysis of diethylmyrtenylborane obtained by metallation–transmetallation.[9] The enantiomeric excess of the starting α-pinene is retained in the product. Later, (+)-β-pinene of >99% ee was prepared by this method.[10] Here, we wish to report an extention of this methodology to the isomerization of (+)-2-carene,[11a] (+)-3-carene[11b] and (−)-α-thujene.[11c]

Initially, the metallation of (+)-2-carene was carried out with *n*-butyllithium and potassium *tert*-butoxide in hexanes at room temperature for 48 h. The metallation product was treated with trimethyl borate and the intermediate complex was hydrolyzed with water or diluted hydrochloric acid. Although the procedure worked well for α-pinene it gave only a small amount of 3(10)-carene in a mixture with 2- and 3-carene (3:65:32).[12] Metallation with *n*-butyllithium and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) was earlier used for the transformation of (+)-2-carene into 3(10)-carene via allylstannanes.[6] However, the specific rotation of the product was not reported. We used this metallation procedure followed by transmetallation with trimethyl borate and hydrolysis. The product was also a mixture of 2- and 3-carene containing a small amount of 3(10)-carene (82:12:6). Finally, (+)-2-carene was metallated with trimethylsilylmethylpotassium[13] followed by transmetallation with chlorodiethylborane[14] and hydrolysis as shown in Eq. 1. (+)-3(10)-Carene containing (+)-2-carene (9%) and (+)-3-carene (9%) was isolated by simple distillation.[15] In the ^{1}H NMR spectrum,[16] signals corresponding to 2-, 3- and 3(10)-carene in the regions of vinylic protons and methyl groups are well separated, enabling identification. GC analyses on three different columns showed the same retention time for 2- and 3(10)-carene and a pure sample of 3(10)-carene could not be isolated by preparative GC. Correcting for the contamination with 2- and 3-carene, the specific rotation of (+)-3(10)-carene prepared was $[\alpha]_D^{20}$=+34.2 (neat).[17] Metallation of 2-carene with *n*-butyllithium and potassium *tert*-butoxide or TMEDA followed by transmetallation leads to organoborane intermediates which are hydrolyzed

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† Dedicated to Professor Herbert C. Brown on the occasion of his 85th birthday.

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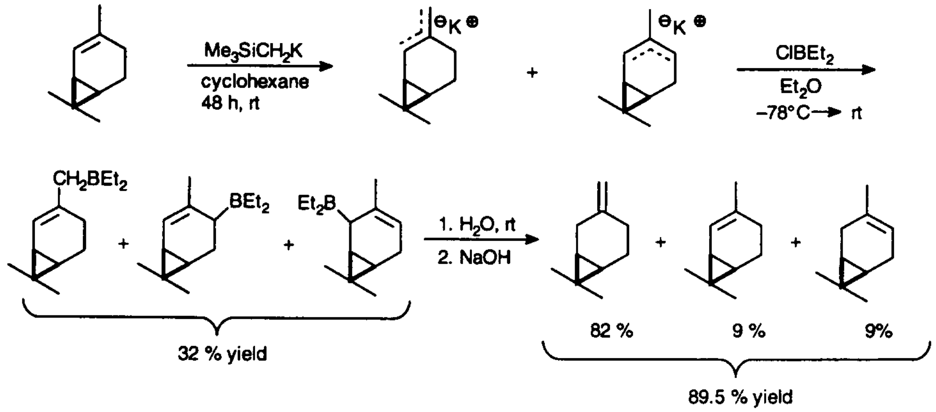
without isolation. Consequently, a substantial amount of unreacted 2-carene is isolated with the isomerization products, rendering separation difficult. Metallation with trimethylsilylmethylpotassium is free from this inconvenience. The unreacted 2-carene is readily separated from the solid metallation product, which is transformed into an allylic organoborane intermediate isolated by distillation.

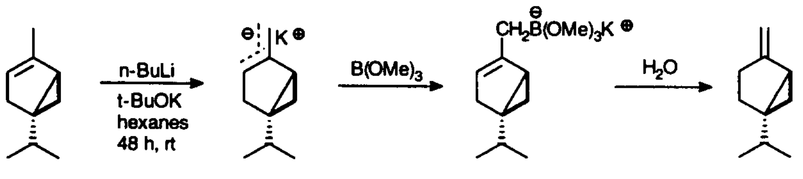


(1)

(+)-3-Carene gave a mixture of (+)-2- and (+)-3-carene by all three metallation–transmetallation–hydrolysis sequences described above. The ratio of 2- and 3-carene in the mixture was 2:3 for *n*-butyllithium–potassium *tert*-butoxide or TMEDA, and 3(10)-carene was not detected. The product obtained via metallation with trimethylsilylmethylpotassium contained 6% of 3(10)-carene in a mixture with 2- and 3-carene. The metallations were carried out for 48 h at room temperature using 20% excess of the metallation agent. Faster deprotonation of 3-carene at the C_2 methylene group, activated by the double bond and the cyclopropane ring, as compared to the C_{10} methyl group might be expected. Such double activation is not present in 2-carene and competitive metallation at the allylic C_{10} methyl group and the C_5 methylene group is possible.

Thermodynamically controlled isomerization of (+)-3-carene by strong bases at higher temperatures leads to an equilibrium mixture of 2- and 3-carene (2:3).[18] The equilibrium was approached from both sides.

(−)-α-Thujene was prepared in a mixture with (+)-β-thujene by the literature procedure.[19] It was isolated by fractional distillation on a Fischer Spaltrohr column. The amount of (−)-α-thujene in the mixture varies from 40 to 60% depending on the reaction temperature and the rate of addition of α-thujone tosylhydrazone. Metallation of (−)-α-thujene with a mixture of *n*-butyllithium and potassium *tert*-butoxide followed by transmetallation with trimethyl borate and hydrolysis according to Eq. 2 gave a mixture of (+)-sabinene and unreacted (−)-α-thujene.



(2)

(+)-Sabinene, 99% pure, $[\alpha]_D^{20}$=+107.4 (neat) was easily separated from (−)-α-thujene by preparative GC.[20] Alternatively, it was prepared in 47.9% overall yield by hydrolysis of the allylic organoborane derived from (−)-α-thujene by metallation with trimethylsilylmethylpotassium and transmetallation with chlorodiethylborane. Metallation of (−)-α-thujene proceeds relatively more easily than (+)-2-carene. It can be carried out with *n*-butyllithium–potassium *tert*-butoxide, the procedure being amenable to scale-up. The procedure provides simple access to (+)-sabinene from a readily available precursor.

In conclusion, (+)-3(10)-carene and (+)-sabinene can be prepared by hydrolysis of the corresponding allylic organoboranes derived from (+)-2-carene and (−)-α-thujene by metallation–transmetallation, respectively. The specific rotation of (+)-3(10)-carene prepared is in agreement with the value reported for the product prepared from (+)-3-carene.[4]

Acknowledgements

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11. (a) (+)-2-Carene, $[\alpha]_D^{20}$=+93.3 (neat), >98% pure by GC. (b) (+)-3-Carene, $[\alpha]_D^{20}$=+17.5 (neat), >98% pure by GC was isolated from *Pinus silvestris* turpentine by fractional distillation, stirred overnight at room temperature with 10 molar % of 9-borabicyclo[3.3.1]nonane and distilled at 10 mmHg. (c) (−)-α-Thujene, $[\alpha]_D^{20}$=−49.05 (neat), 97% pure by GC.
12. Identified by ^{1}H NMR and GC analysis on a 30 m×0.32 mm Supelcowax 10 capillary column by comparison with authentic samples of (+)-2- and (+)-3-carene. 2-Carene and 3(10)-carene showed the same retention time on the Supelcowax 10 column and also on 3 m×10 cm OV-17/Chromosorb W and Carbowax 20 M/Chromosorb P columns.
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15. Bis(trimethylsilylmethyl)mercury (18.72 g, 50 mmol) was added under argon atmosphere with mechanical stirring to a mixture of potassium sand (3.91 g, 0.1 mol) and cyclohexane (100 mL) keeping the temperature below 40°C. After 1 h, (+)-2-carene (27.24 g, 0.2 mol) was added and the mixture was stirred for 48 h at room temperature. It was centrifuged, the supernatant was decanted and the precipitate was kept under 0.1 mmHg for 5 h at room temperature. The pyrophoric powder was added with stirring under argon to a solution of chlorodiethylborane (10.44 g, 0.1 mol) in diethyl ether (100 mL) keeping the temperature below −50°C. The cooling bath was removed and the mixture was left at room temperature overnight. It was centrifuged, the supernatant was decanted and the insoluble solid was washed with diethyl ether (2×50 mL). The ethereal solutions were combined and the organoborane was isolated by distillation, 6.20 g, 32.2%, bp 78–80°C/0.3 mmHg, ^{11}B NMR ($CDCl_3$) δ, 80 ppm. The organoborane (5.13 g, 25 mmol) was added to water (10 mL) and the mixture was stirred vigorously for 5 h under argon at room temperature. The organic layer was separated and washed with 3 M aqueous sodium hydroxide (10 mL, 30 mmol), water (3 mL) and dried with magnesium sulfate. The product was isolated by distillation, 3.05 g, 89.5% yield, bp 50–52°C/10 mmHg, $[\alpha]_D^{20}$=+38.90 (neat). GC and ^{1}H NMR analysis[12] showed 3(10)-, 2- and 3-carene (82:9:9). ^{1}H NMR ($CDCl_3$) δ, ppm 0.65–0.75 (m, 2H, cyclopropyl H), 0.92 (s, 3H, CH_3), 0.98 (s, 3H, CH_3), 1.20–1.40 (m, 1H, CH_2), 1.80–2.15 (m, 3H, CH_2), 2.30 (d, J=16 Hz, 1H, CH_2), 2.50 (dd, J=16 Hz, J=7 Hz, 1H, CH_2), 4.60 (m, 1H, =CH_2), 4.63 (m, 1H, =CH_2); ^{13}C NMR ($CDCl_3$) δ, ppm 149.37 (C), 106.97 (CH_2), 32.20 (CH_2), 28.92 (CH_2), 28.75 (CH_3), 21.46 (CH), 21.39 (CH_2), 19.51 (CH), 18.27 (C), 14.72 (CH_3).

16. ^1H, ^{13}C and ^{11}B NMR spectra were recorded on a Varian Gemini 200 MHz instrument.
17. $[\alpha]_D^{20}$=+97.7 (neat)[18a] for (+)-2-carene and $[\alpha]_D^{20}$=+17.8 (neat) for (+)-3-carene were taken for the correction calculation. Brown, H. C.; Vara Prasad, J. V. N.; Zaidlewicz, M. *J. Org. Chem.* **1988**, *53*, 143–150.
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20. To a suspension of potassium *tert*-butoxide (1.44 g, 12.5 mmol) in hexenes (2.5 mL) 2.5 M *n*-butyllithium solution in hexanes (5 mL, 12.5 mmol) was added at −78°C under nitrogen. The mixture was allowed to warm to room temperature, (−)-α-thujene (1.36 g, 10 mmol) was added and the mixture was stirred for 48 h at room temperature. A solution of trimethyl borate (3.35 g, 32.5 mol) in diethyl ether (2.5 mL) was added at −78°C and the mixture was stirred for 2 h at room temperature. Water (5 mL) was added at 0°C at the mixture was stirred for 3 h at room temperature. The organic layer was separated, washed with 10% sodium bicarbonate solution (10 mL) and dried over magnesium sulfate. Distillation gave 1.25 g, bp 52–55°C/10 mmHg. GC analysis showed a mixture of (+)-sabinene and (−)-α-thujene (3:7). A sample, 99% pure, $[\alpha]_D^{20}$=+107.4 (neat) was isolated by preparative GC. Ohloff, G.; Uhde, G.; Thomas, A. F.; Kovats E. sz. *Tetrahedron* **1966**, *22*, 309–320, $[\alpha]_D^{20}$=+107.2. ^1H NMR ($CDCl_3$) δ ppm, 0.64 (s, 1H, CH_2 cyclopropyl), 0.66 (s, 1H, CH_2 cyclopropyl), 0.88 (d, J=7 Hz, 3H, CH_3), 0.95 (d, J=7 Hz, 3H, CH_3), 1.49 (septet, J=6 Hz, 1H, CH isopropyl), 1.55–1.65 (m, 1H), 1.65–1.84 (m, 2H), 1.90–2.24 (m, 2H), 4.60 (s, 1H, $=CH_2$), 4.80 (s, 1H, $=CH_2$); ^{13}C NMR ($CDCl_3$) δ ppm 154.22 (C), 101.56 (CH_2), 37.49 (C), 32.53(CH), 30.05 (CH), 28.87 (CH_2), 27.35 (CH_2), 19.67 (CH_3), 19.58 (CH_3), 15.90 (CH_2).

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