SHORT PAPER

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Surface-mediated chemospecific hydrobromination of limonene: stereoselective transformation of the enantiomers of limonene into α-terpinyl bromide†

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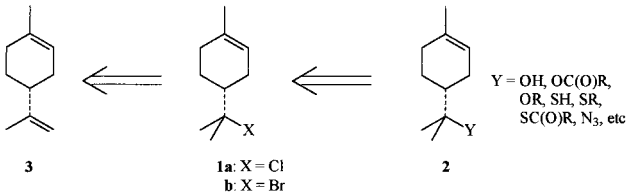
(*R*) and (*S*)-α–terpinyl bromide can easily be prepared in excellent yields by reaction of (*R*) and (*S*)-limonene, respectively, with PBr_3 / SiO_2 in dichloromethane.

HBr adds readily to most alkenes[1] predominantly with Markovnikoff regiochemistry. However, unless the substrate is rigorously purified (alkenes readily absorb oxygen from the air) and the reaction media is isolated from light and air to avoid formation of small amounts of peroxides, competing radical-chain addition to give the anti-Markovnikoff products occurs.[2] As the generation and transfer of the hygroscopic gas HBr is both inconvenient and difficult to perform stoichiometrically,[1] alternate methodologies for performing hydrobromination of alkenes are of great interest. Kropp and coworkers showed that oxalyl bromide or bromotrimethylsilane undergo hydrolysis in the surface of silica gel to generate HBr *in situ*, which produces alkyl bromides in high yields *via* highly Markovnikoff additions to olefins.[1]

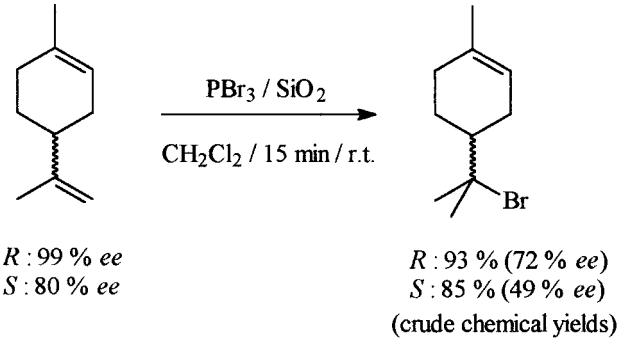
α-Terpinyl halides (**1**) [4-(1-halo-1-methylethyl)-1-methylcyclohexene], are precursors of diverse 8-substituted *p*-menthenes (**2**)[3] and in previous work we have studied the preparation of the chloride (**1a**) by hydrochlorination of limonene (**3**) using diverse methodologies[4] (Scheme 1) Curiously, α-terpinyl bromide (**1b**) is scarcely cited in the literature,[5] probably due to its difficult preparation. It can be prepared by hydrobromination of limonene by performing a laborious addition of dry HBr in light petroleum[6] (dihydrbromination is easy to perform producing both *cis*- and *transdibromides*[5]). Other methodologies are the low-yielding hydrobromination of 3-carene[7] and the $TiBr_4$-PhNHMe-complex-induced cyclization of nerol.[8]



Scheme 1

As part of our continuing interest in chemo- and regiospecific functionalization of 8,9-double bond limonene,[4,9] we now communicate our results for surface-mediated hydrobromination using the cheap and readily available PBr_3 as HBr donor.

The hydrobromination of (*R*)-(+)-limonene (99% *ee*) was carried out by stirring together a suspension of 10 mmol of limonene with 4 mmol PBr_3 and 5 g of silica gel in dichloromethane for only 15 min at room temperature which led to (*R*)-(+)-α-terpinyl bromide in 93% crude yield. The product was characterized by analytical methods and by comparison with the previously reported boiling point[6] and spectral data.[8] No significant amount of the regioisomer or diaddition products were detected in the crude reaction mixture by the analytical procedures employed (HRGC, high-resolution gas chromatography, ^1H and ^{13}C NMR). Chiral HRCG of the (*R*)–(+)–α-terpinyl bromide purified by reduced-pressure distillation showed > 72 % *ee*. The same reaction applied to (*S*)-(-)-limonene produced (*S*)-(-)-α-terpinyl bromide in nearly the same yield (85%). Chiral-HRGC of product indicated > 49% *ee*, but this low value is because the (*S*)-(-)-limonene employed was initially of low enantiomeric purity (> 80%). In fact the stereoselectivities (76% vs 61%) are similar (Scheme 2).



Scheme 2

Analysis of (*R*)-(+)–α–terpinyl bromide by chiral-HRGC showed partial (*ca* 27 %) racemization. This result could be explained by a competing reversible reversible hydride migration to give an achiral intermediate (**4**), an isomer of the initially formed[1] carbenium ion (Scheme 3). Similar results were observed for (*S*)-(-)-α-terpinyl bromide.

Several attempts to perform hydroiodination of limonene using PI_3 / SiO_2 or Me_3SiI / SiO_2[1] or P / I_2 / SiO_2 under different reaction conditions (temperatures, molar ratios) led to several products, some of them with incorporation of iodide in the substrate (determined by HRGC–MS). Attempts to perform hydrofluorination of limonene with CaF_2 / H_2SO_4[10] were disappointing as only oligomerization of limonene without incorporation of fluoride was detected by HRGC–and IR.

In conclusion, the preparation of both enantiomers of α-terpinyl bromides with reasonable enantiomeric excess is easily achieved by silica gel mediated reaction of PBr_3 with limonene. The yields are high, there is no need to generate anhydrous HBr, or use drying agents. Moreover, the utilization of PBr_3 as HBr donor is very convenient because it

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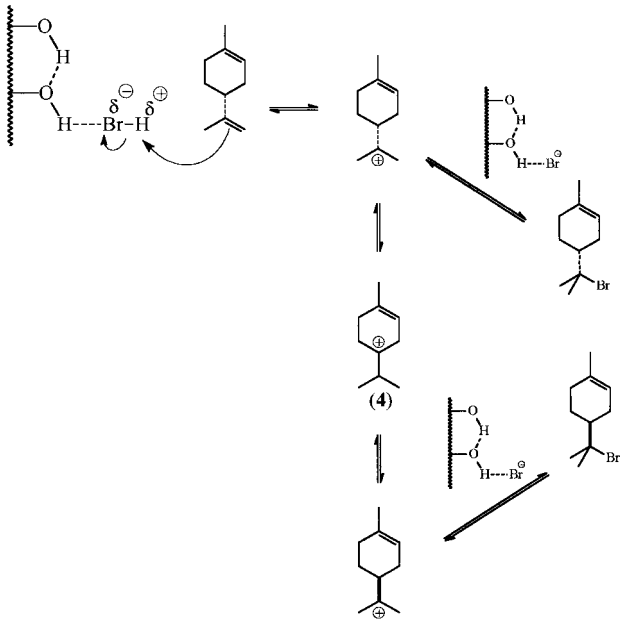

Scheme 3

is considerably cheaper than the alternative reagents, easily available, and more useful in atom economy.[11]

Experimental

(*R*)-(+)-Limonene {Dieberger, $[\alpha]_D^{28}$ + 118.7 (neat), lit.[12] $[\alpha]_D^{20}$ + 125.6 (neat)} [95 % (polarimetry), 99% *ee* (chiral-HRGC)] was distilled at 177°C (lit.[12] 178°C) and stored in a freezer. (*S*)-(-)Limonene {Aldrich, $[\alpha]_D^{28}$ – 103.4 (neat), lit.[12] $[\alpha]_D^{20}$ –122.1 (neat)}[85 % (polarimetry), 80% *ee* (chiral-HRGC)] was used without further purification. SiO_2 (Aldrich, 270-70 MESH, 60 Å), PBr_3 (Merck), and other chemicals were used as received. ^1H NMR and ^{13}C NMR were acquired on a Bruker AC-200 (200 MHz and 50 MHz, respectively) spectrometer in $CDCl_3$ solutions with TMS as internal standard. IR spectra were recorded on a Perkin-Elmer 1600 FT-IR spectrometer (KBr film). Polarimetric analyses were done on a Jasco DIP 370 polarimeter. MS were obtained on a Hewlett-Packard HP5896-A HRGC-MS using electron impact (70 eV). Chiral-HRGC analyses were performed on a CYCLODEXB column (resolution of both enantiomers of limonene) or on a DIMETBCD / SE-54 column (resolution of the enantiomers of α-terpinyl bromide).

(R)-(+)-α-terpinyl bromide: To a stirred suspension of (*R*)-(+)-limonene (1.36 g, 10 mmol) and SiO_2 (5 g) in CH_2Cl_2 (25 ml), a solution of PBr_3 (1.10 g, 4 mmol) in CH_2Cl_2 (10 ml) was added over 15 min at room temperature. After addition, the suspension was stirred for 2 min and then filtered. The SiO_2 was washed with CH_2Cl_2 (15 ml). The combined liquid was washed with 10 % $NaHCO_3$ (until no more gas was liberated) and brine (2x). The organic extract was then dried ($MgSO_4$). The solvent was evaporated in rotary evaporator at reduced pressure to give a light yellow residue (93% based on limonene) that showed good purity by HRGC. This residue was distilled over a short path at 86–87°C / 3 torr (lit.[6]: 108–112 / 12 Torr) with eicosane as chaser, obtaining 0.50 g of α-terpinyl bromide (23 % from limonene). $[\alpha]_D^{26}$ + 25.5 (c 1.00, CH_2Cl_2), 72% *ee* (by chiral-HRGC). δ_H 5.37 (broad s, 1H), 2.23–1.89 (m, 7H), 1.80 (s, 3H), 1.74 (s, 3H), 1.66 (s, 3H) ppm. δ_C 134.0, 120.1, 73.5, 47.4, 32.6, 31.6, 30.9, 28.2, 26.0, 23.2 ppm. ν_{max} / cm^{-1} (film) 2966, 2928, 2835, 1455, 1369, 1110, 916, 801, 784. m / *z* (%) 41 (31), 69 (40), 81 (100), 93 (43), 121 (35), 136 (35), 137 (56), 216 (M^+, 8), 218 (M^+ + 2,8).

(S)-(-)-α-Terpinyl bromide: Same as above, (*S*)-(-)-limonene used instead of (*R*)-(-)-limonene, 85% obtained. $[\alpha]_D^{26}$ – 18.6 (c 1.00, CH_2Cl_2), 49 % *ee* (by chiraL-HRGC).

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