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Rearrangement of methylenecamphor during electrophilic bromination: remarkably clean access to the unnatural fenchyl (1,3,3-trimethylbicyclo[2.2.1]heptane) system

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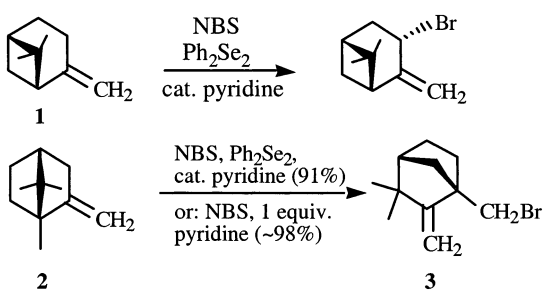
Abstract—Treatment of (+)-methylenecamphor (**2**) with NBS in the presence of pyridine resulted in a rapid and remarkably clean rearrangement to yield a brominated (+)-methylenefenchone (**3**) in high yield and purity (>96%). The structure of the product was established by X-ray crystallography and the stereochemistry confirmed by both polarimetric and chiral GC analyses. Two transformations of the product were also performed to elucidate the structure.

In the course of preparing terpene-derived asymmetric catalysts and reagents,[1] we desired to brominate methylenecamphor[2] (**2**) in the allylic position as had been reported[3] for β-pinene (**1**), shown below. The reaction proceeded cleanly (~90%), and was improved to ~98% yield of a single product by use of stoichiometric pyridine; the presence of diphenyldiselenide was found to be of no consequence. *N*-Chlorosuccinimide gave the same reaction, but less cleanly (~80%). However, these reactions had clearly followed an unexpected course, evidenced, for example, by the presence of only two methyl singlets, rather than the expected three, in the ^{1}H NMR spectrum. We were able to prove the structure to be that of a previously unreported compound (**3**, see Scheme 1).

The structure proof of compound **3** was done primarily by X-ray analysis of ammonium carboxylate salt **7** and



Scheme 1.

9-fluorenyl derivative **8**, made via the organolithium **5** as shown in Scheme 2. The organolithium was prepared by either of two ways, via metal–halogen exchange of the iodide,[4] or direct reaction of the bromide with the radical anion of 4,4′-di-*tert*-butylbiphenyl.[5] While both crystal structures confirmed the basic structure of **3**, the absolute configuration could not be assigned with certainty because of disorder and/or the lack of heavy atoms. Many other derivatives failed to provide suitable crystals for X-ray analysis.[6]

Fortunately, the absolute configuration and enantiopurity of compound **3** could be established by chiral gas chromatography. Reaction of racemic methylenecamphor with NBS/pyridine produced racemic **3**, the enantiomers of which were adequately separated[7] on a Cyclosil-B[8] capillary column (30 m×0.25 mm). Similar analysis of **3** from (+)-methylenecamphor showed only one peak. To establish the absolute configuration, we prepared methylenefenchone (**10**) by debromination of **3** that had been prepared from both (+)-camphor and racemic camphor, and (in low yield) by Wittig methylenation of natural (−)-fenchone (**9**). Again, the enantiomers were adequately separated,[9] and each of the optically active samples exhibited single peaks at different retention times (Scheme 3).

The formation of **3** can be understood in terms of an initial attack by electrophilic bromine, followed by rearrangement and elimination of the resulting cation, as shown in Scheme 4. This rearrangement is remarkable in that cation **I** does not rearrange further, possi-

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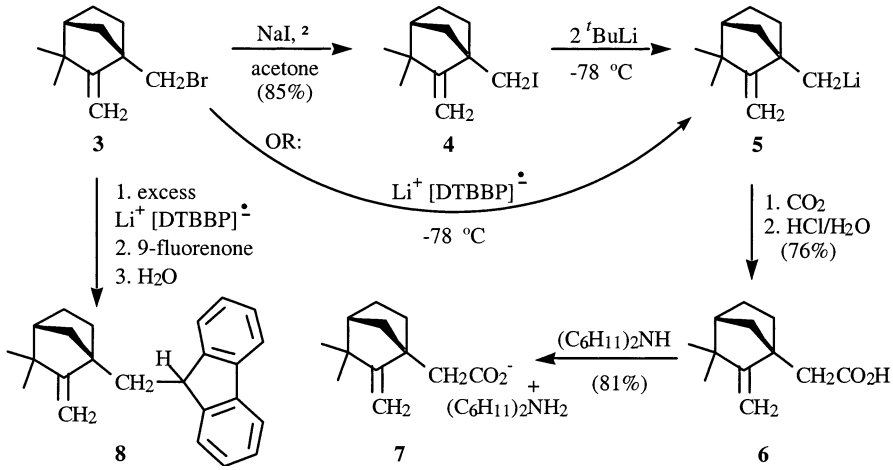
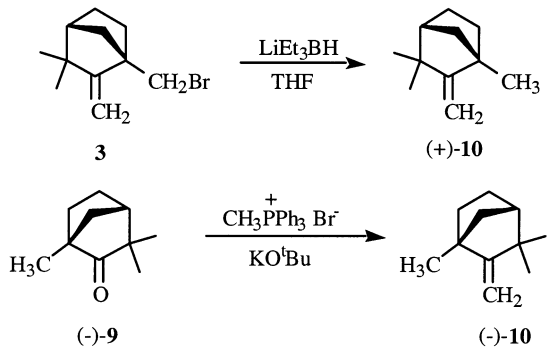


Scheme 2.



Scheme 3.

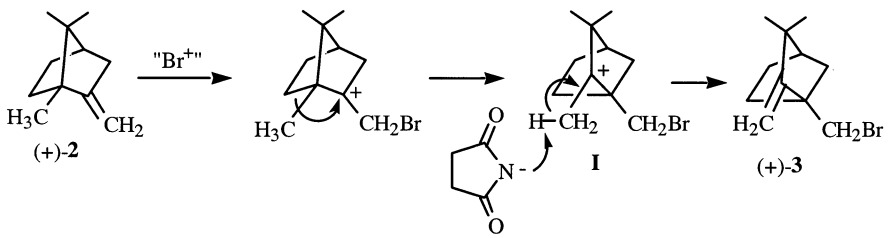
bly because the reaction is occurring under basic conditions which quickly deprotonate **I**. In contrast, treatment of methylenecamphor with H_2SO_4/HOAc[10] or HBr[11] proceeds through a cation corresponding to **I** but rearranges further (two additional alkyl shifts) and, in the former case, partially racemizes. Indeed, to our knowledge there has been only one efficient rearrangement-based synthesis of a fenchyl system reported,[12] and none based on methylenecamphor. A bicyclo[3.1.1]heptane derivative has been reported[12] to give a doubly oxygenated fenchyl product in 80% yield. Although cationic intermediates corresponding to **I** have been postulated,[10,11,13] these reactions generally produce a wide variety of products and are not synthetically useful.

The ready availability of (+)-**3** now provides access to an enantiomerically pure derivative of the unnatural enantiomer of the fenchone system, functionalized for transformations into synthetically useful non-racemic materials.

Experimental

*(1*R*,4*R*)-(+)-1-Bromomethyl-3,3-dimethyl-2-methylene-bicyclo[2.2.1]heptane* ***(3)***: A solution of methylenecamphor (2.03 g, 13.5 mmol; prepared[2] from (+)-camphor) and pyridine (1.1 mL, 13.6 mmol) in dry dichloromethane (50 mL) was cooled to 0°C under an inert atmosphere, and, with good stirring, recrystallized[14] *N*-bromosuccinimide (2.99 g, 16.8 mmol) was added in one portion. The heterogeneous mixture was allowed to warm to room temperature and was stirred overnight. Hexanes (25 mL) were added to precipitate succinimide. The mixture was filtered through a 2 cm layer of silica gel in a fritted funnel and the filtrate was concentrated by rotary evaporation to give 2.98 g (13 mmol, 96%) of **3** as a colorless oil that was >98% pure by GC. Density = 1.28 g/mL. ^{1}H NMR ($CDCl_3$, 360 MHz): 1.04 (s, 3H), 1.09 (s, 3H), 1.14–1.25 (m, 1H), 1.40 (dd, 1H, J = 9.7, 1.4), 1.55–1.65 (m, 1H), 1.68–1.84 (m, 3H), 1.86–1.92 (m, 1H), 3.66 (d, 1H, J = 10.4), 3.70 (d, 1H, J = 10.4), 4.65 (s, 1H), 4.66 (s, 1H); ^{13}C NMR ($CDCl_3$, 90 MHz): 25.5, 26.0, 29.3, 32.5, 36.7, 41.9, 43.7, 46.7, 54.3, 99.2, 164.8. IR: 1651 cm^{-1}. MS: 230/228 (M+), 149 (M−Br, base peak).

*(1*S*,4*R*)-(+)-3,3-Dimethyl-2-methylene-bicyclo[2.2.1]-heptane-1-acetic acid* ***(6)***: Bromide **3** was first converted to the iodide (NaI, acetone, reflux, 30 h). A solution of the purified iodide (3.37 g, 12.2 mmol) in ether (40 mL) and hexanes (60 mL), cooled to −78°C and treated with



Scheme 4.

tert-butyllithium (1.77 M in pentane, 15.0 mL, 26.6 mmol). The cloudy orange suspension was allowed to warm to room temperature and was stirred for 1 hour. The mixture was then transferred by cannula to a 1 L flask containing solid CO_2 (20 g) [**Caution**: extensive gas evolution, vent adequately!]. After warming to room temperature, the organic phase was extracted with 5% aqueous Na_2CO_3 solution (3×30 mL). The combined aqueous extracts were washed with hexanes (2×15 mL), then acidified with 6 M HCl to pH 2–3. Extraction of the aqueous with ethyl acetate (3×30 mL), drying with $MgSO_4$, and concentration gave a colorless oil (1.81 g, 76%) which was 99% pure by capillary GC. Alternatively, 4,4′-di-*tert*-butylbiphenyl in dry THF under argon at 0°C was treated with lithium metal (4 h), and the resulting dark green solution was cooled to −78°C and treated dropwise with bromide **3** just until the dark color faded (at least 2 equiv. of radical anion are required per bromide). The resulting organolithium reagent was added to carbon dioxide and worked up as described above. The product occasionally crystallized on standing to give a low-melting solid (mp ~34°C). $[\alpha]_D = +49$ (66 mg/mL, ethyl acetate). ^{1}H NMR ($CDCl_3$, 360 MHz): 1.03 (s, 3H), 1.08 (s, 3H), 1.2–1.31 (m, 1H), 1.45 (dd, 1H, $J = 9.8$, 1.2), 1.52–1.65 (m, 1H), 1.68–1.79 (m, 2H), 1.83–1.92 (m, 2H), 2.65 (s, 2H), 4.60 (s, 1H), 4.64 (s, 1H), 11.2 (br s, 1H); ^{13}C NMR ($CDCl_3$, 90 MHz): 24.8, 26.0, 29.4, 33.6, 38.3, 41.6, 43.0, 47.0, 50.9, 98.2, 166.9, 179.2; IR: 1654, 2500–3500 cm^{-1}. MS: 194 (M+), 179, 149, 105 (base peak).

*(1*S*,4*R*) - (+) - 1 - Methyl - 3,3 - dimethyl - 2 - methylene-bicyclo[2.2.1]heptane (**10**)*: (+)-Bromide **3** (1.53 mL, 8.6 mmol) was added slowly to a solution of lithium triethylborohydride (1.0 M in THF, 17 mL, 17 mmol) in 20 mL of additional THF under an inert atmosphere and refluxed for 6 hours. The crude mixture was quenched with water (5 mL), and the product was extracted with hexanes and, after drying and evaporation to constant weight, 746 mg (58%) gave **10** that was found to be greater than 95% pure by capillary GC. $[\alpha]_D = +68.3$ ($c = 37$ mg/mL, methanol); the same compound prepared[2] from (−)-fenchone exhibited $[\alpha]_D = -69.4$ ($c = 50$ mg/mL, methanol). ^{1}H NMR ($CDCl_3$, 360 MHz): 1.02 (s, 3H), 1.07 (s, 3H), 1.18 (s, 3H), 1.25 (dd, 1H, $J = 14.4$, 1.3), 1.41–1.57 (m, 4H), 1.69–1.74 (m, 1H), 1.81 (br s, 1H), 4.53 (s, 1H), 4.60 (s, 1H); ^{13}C NMR ($CDCl_3$, 90 MHz): 18.3, 25.4, 26.1, 29.5, 35.6, 42.8, 44.3, 47.3 49.9, 96.9, 169.4; IR: 1651 cm^{-1}. MS: 150 (M+), 107 (base peak).

Acknowledgements

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References

1. Thomas, A. A. *M.S. Thesis*; Baylor University: Waco, TX, 1994.
2. Fitjer, L.; Quabeck, U. *Synth. Commun.* **1985**, *15*, 855–864.
3. Sharpless, K. B.; Hori, T. H. *J. Org. Chem.* **1979**, *44*, 4204.
4. Bailey, W. F.; Punzalan, E. R. *J. Org. Chem.* **1990**, *55*, 5404.
5. Freeman, P. K.; Hutchinson, L. L. *J. Org. Chem.* **1980**, *45*, 1924.
6. Other derivatives studied include ammonium salts using DABCO, DMAP, TMEDA, 1,8-bis-dimethylaminonaphthalene, and ammonia; the (+)-methylmandelate ester (no evidence of diastereomers by proton NMR); and the alcohols from the reaction of organolithium **5** with (+)-camphor. In all these cases, either liquids or needles too fine for X-ray analysis resulted.
7. The observed resolution, defined as (1.18×difference in retention times)/(sum of peak widths at half-height), was 0.78.
8. J&W Scientific, 91 Blue Ravine Road, Folsom, CA 95630, USA.
9. The observed resolution was 0.67.
10. Clase, J. A.; Li, D. L. F.; Lo, L.; Money, T. *Can. J. Chem.* **1990**, *68*, 1829.
11. Money, T.; Palme, M. H. *Tetrahedron: Asymmetry* **1993**, *4*, 2363.
12. (a) Bosworth, N.; Magnus, P. D. *Chem. Commun.* **1971**, 618–619; (b) Bosworth, N.; Magnus, P. D. *J. Chem. Soc., Perkin Trans. 1* **1972**, 943–948.
13. (a) Giddings, R. A.; Jones-Parry, R.; Salmon, J. R.; Whittaker, D. *J. Chem. Soc., Perkin Trans. 2* **1982**, 725–728; (b) Paruch, E.; Ciunik, Z.; Wawrzenczyk, C. *Liegibs Ann.* **1997**, 2341–2345; (c) Rodig, O. R.; Sysko, R. J. *J. Am. Chem. Soc.* **1972**, *94*, 6475–6479.
14. The use of recrystallized (colorless) NBS is important. Samples of NBS that were orange caused significant gas evolution (HBr?) and other mono- and di-brominated products were formed. Impure material was recrystallized from hot water (10 mL/g) followed by filtration and cooling in a refrigerator.