Formation of (1S,2S,5R,6S)-(+)-6-Carbanilino-1,5-dimethyltricyclo[3.2.0.0^{2,6}]heptane from (1R,4S)-(+)-3,8,8-Tribromocamphor via a Facile Intramolecular Cyclization–Favorskii Rearrangement Process

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The Favorskii rearrangement is the base-catalyzed skeletal rearrangement of α-halo ketones[1] and is known to occur *via* two pathways.[2] For ketones which cannot undergo enolization toward the α-carbon, the rearrangement is most probably taking place by a semibenzilic rearrangement process (quasi-Favorskii reaction).[3] Favorskii rearrangement has become a reliable method for the preparation of highly branched acyclic carboxylic acid derivatives.

During the course of our studies directed toward the development of a camphor-based chiral auxiliary[4] for the asymmetric synthesis of α-amino acids, we have observed an interesting transformation of (1R)-(+)-3,3,8-tribromocamphor (3) to a novel tricyclic compound. Here we wish to report our findings.

As depicted in Scheme I, tribromocamphor 3 was prepared from (1R)-(+)-camphor (1) in two steps. Compound 1 was first converted to (1R)-(+)-3,3-dibromocamphor (2) using a literature procedure[5] with modification. Under the modified reaction conditions described in the Experimental Section, an improvement of the yield of ca. 25% (71% vs 95%) has been achieved. Further bromination of compound 2 using procedures reported by Money *et al.*[6] gave the tribromocamphor 3.

Attempted hydrolysis of tribromocamphor 3 with aqueous potassium hydroxide in refluxing DMF failed to provide the desired 8-bromocamphorquinone. Instead it gave 7-bromo-1,5-dimethyltricyclo[3.3.0.0^{2,7}]octane (4) in 82% yield (Scheme II). Likewise, compound 4 could be obtained in 88% yield when 3,3,8-tribromocamphor was reacted with potassium hydride in THF at room temperature. When compound 4 was subsequently treated with potassium anilide (generated *in situ* from potassium hydride and aniline) in either THF or DMF at room temperature for approximately 6 h, an interesting tricyclic compound, 6-carbanilino-1,5-dimethyltricyclo[3.2.0.0^{2,6}]-heptane (5), was formed in 85% yield. The structure of this compound was confirmed by a single crystal X-ray crystallographic analysis.[7] Compound 5 could also be prepared directly from 3,3,8-tribromocamphor by treatment with potassium anilide in THF at room temperature for 7 h in high yield (85%). When the reaction was monitored by NMR, compound 4 was found to be the predominant product after 30 min. This intermediate was eventually converted to compound 5 under the reaction condition.

The formation of compound 5 from tribromide 3 could be rationalized by invoking the intermediacy of compound 4, resulting from the intramolecular alkylation of enolate 6, generated by nucleophilic attack of a base at the bromine atom α to the carbonyl as delineated in Scheme III. Anilide-initiated Favorskii rearrangement of compound 4 then afforded the title compound. The ease of the rearrangement reaction is apparently facilitated by the fact that the C5–C6 bond of compound 4 is situated antiperiplanar to the C–Br bond which should be able to migrate easily to form the Favorskii rearrangement product.[8]

In agreement with the proposed mechanistic rationale, dibromide 2 was found to undergo debromination upon treatment with potassium anilide in THF at room temperature to give a mixture of *endo*- and *exo*-3-bromocamphor.[9] Furthermore, similar results were observed when compound 2 was reacted with potassium hydride in THF at room temperature. When 3,3-dibromocamphor was subjected to treatment with aniline or potassium iodide in THF, however, starting material was recovered intact even after prolonged reaction at elevated temperatures.

The above results indicate that the initial formation of enolate ion 6 requires a strong base such as sodium hydroxide, potassium hydride, or potassium anilide. The facile rearrangement to compound 5 renders further evidence for the stereochemical requirement for quasi-Favorskii rearrangement. Moreover, this reaction provides a convenient method for preparing strained tricyclic systems involving small bridges.[10]

Experimental Section

Melting points are uncorrected. Infrared spectra were recorded in chloroform solutions. ^{1}H NMR (Me_4Si as internal standard) and ^{13}C NMR ($CDCl_3$ at 77.0 ppm as internal standard) spectra were measured in deuteriochloroform solutions. Optical rotations were measured at the sodium D line. Solvents and reagents were dried prior to use as required. KH was washed with dry *n*-hexane

(1) (a) Favorskii, A. E. *J. Russ. Phys. Chem. Soc.* **1894**, *26*, 559. (b) Kende, A. S. *Org. React.* **1960**, *11*, 261. (c) Rappe, C.; Knutsson, L. *Acta Chem. Scand.* **1967**, *21*, 163. (d) Waring, A. J. In *Comprehensive Organic Chemistry*; Stoddart, J. F., Ed.; Pergamon Press: Oxford, 1979; Vol. 1, p 1091.

(2) (a) McPhee, W. D.; Klingsberg, E. *J. Am. Chem. Soc.* **1944**, *66*, 1132. (b) Loftfield, R. B. *J. Am. Chem. Soc.* **1951**, *73*, 4707. (c) Warnhoff, E. W.; Wong, C. M.; Tai, W. T. *J. Am. Chem. Soc.* **1968**, *90*, 514. (d) Akhrem, A. A.; Ustynyuk, T. K.; Titov, Y. A. *Russ. Chem. Rev.* **1970**, *39*, 732. (e) Rappe, C. In *The Chemistry of the Carbon-Halogen Bond, Part 2*; Patai, S., Ed.; John Wiley: New York, 1973; Chapter 17. (f) Chenier, P. J. *J. Chem. Ed.* **1978**, *55*, 286. (g) Hunter, D. H.; Stothers, J. B.; Warnhoff, E. W. In *Rearrangements in Ground and Excited States*; de Mayo, P., Ed.; Academic: New York, 1980; Vol. 1, Chapter 6. (h) Baretta, A.; Waegell, B. In *Reactive Intermediates*; Abramowitch, A. E., Ed.; Plenum Press: New York, 1982; Vol. 2, p 527.

(3) (a) Tchoubar, T.; Sackur, O. *Compt. Rend.* **1939**, *208*, 1020. (b) Stevens, C. L.; Farkkas, E. *J. Am. Chem. Soc.* **1952**, *74*, 5352. (c) Smissman, E.; Hite, G. *J. Am. Chem. Soc.* **1959**, *81*, 1201.

(4) (a) Money, T. *Nat. Prod. Rep.* **1985**, *2*, 253. (b) Oppolzer, W. *Tetrahedron* **1987**, *43*, 1969. (c) Hutchinson, J. H.; Money, T.; Piper, S. E. *Can. J. Chem.* **1986**, *64*, 854.

(5) Shive, B.; Crouch, W. W.; Lochte, H. L. *J. Am. Chem. Soc.* **1941**, *63*, 2979.

(6) (a) Money, T.; Eck, C. R.; Mills, R. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 251. (b) Money, T.; Eck, C. R.; Cachia, P.; Darby, N. *J. Chem. Soc., Perkin Trans. 1* **1976**, 359.

(7) Jong, T.-T.; Jean, M.-Y.; Lu, T.-J. *Acta Crystallogr. Sect. C*, in press.

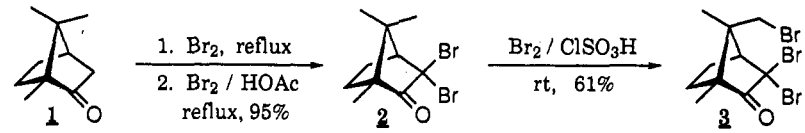
(8) The quasi-Favorskii rearrangement is known to be stereospecific: (a) Warnhoff, E. W.; Wong, C. M.; Tai, W. T. *J. Am. Chem. Soc.* **1968**, *90*, 514. (b) Baudry, D.; Begue, J.-P.; Charpentier-Morize, M. *Tetrahedron Lett.* **1970**, 2147. (c) Martin, P. *Helv. Chim. Acta* **1983**, *66*, 1189.

(9) A ketocarbenoid was generated when 3,3-dibromocamphor was treated with Et_2Zn, see: Scott, L. T.; Cotton, W. D. *J. Am. Chem. Soc.* **1973**, *95*, 2708.

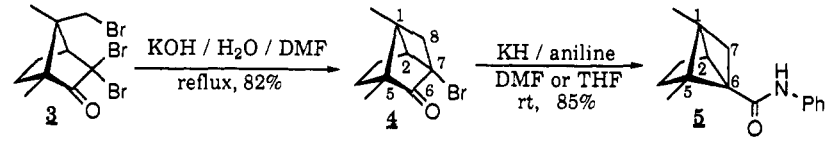
(10) (a) Wiberg, K. B.; Lowry, B. R. *J. Am. Chem. Soc.* **1963**, *85*, 3188. (b) Larson, H. O.; Ooi, T.-C.; Luke, W. K. H.; Ebisu, K. *J. Org. Chem.* **1969**, *34*, 525. (c) For a review of bicyclic [*n*.1.1]alkane derivatives, see: Meinwald, J.; Meinwald, Y. C. *Adv. Alicycl. Chem.* **1966**, *1*, 1–51.

0022-3263/93/1958-7945$04.00/0

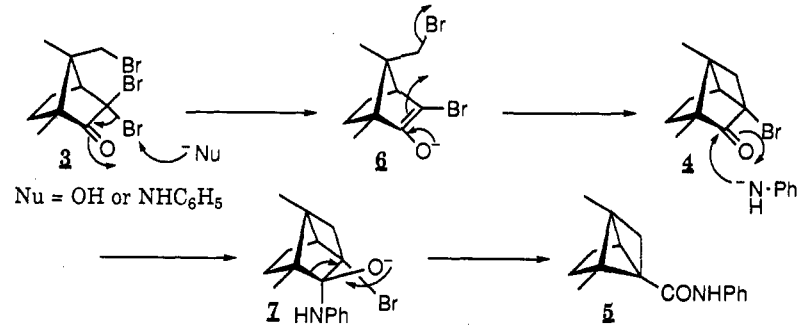
Scheme I



Scheme II



Scheme III



before use. Reactions were monitored by analytical thin-layer chromatography using silica gel 60 F-254, layer thickness 0.2 mm. Flash chromatography was carried out utilizing silica gel 60, 70–230 mesh ASTM. Medium-pressure liquid chromatography was carried out using Merck Lobar prepacked silica gel columns and a Fluid Metering, Inc. pump. (1*R*)-(+)-camphor was kindly provided by China Camphor Co. Ltd., Taipei, Taiwan.

(1*R*)-(+)-3,3-Dibromocamphor (2). To (1*R*)-(+)-camphor (15.732 g, 0.103 mol) was added bromine (37.985 g, 12.17 mL, 0.238 mol) dropwise over a period of 30 min. The reaction mixture was heated in an oil bath (130–135 °C) until the evolution of HBr ceased (*ca.* 7 h). Water (5 mL) and glacial acetic acid (*ca.* 120 mL) were added to form a homogeneous solution. The solution was heated for 6 h. The excess bromine was removed under reduced pressure (aspirator) at *ca.* 110 °C for 4 h. The resulting mixture was poured into ice (*ca.* 100 g), and the off-white dibromocamphor precipitate was collected by filtration to give 35.140 g of the crude product. Recrystallization from petroleum ether gave 30.437 g (95%) of the pure product as colorless crystals (mp 62.0–62.5 °C; lit.[11] 61 °C). $[\alpha]^{25}_D$ = +37.0° (*c* = 1.6, EtOH, lit.[11] $[\alpha]$ = 37.1°); ^{1}H NMR δ 2.82 (d, *J* = 4.2 Hz, 2H), 2.37–2.29 (m, 1H), 2.14–2.02 (m, 1H), 1.67–1.62 (m, 2H), 1.24 (s, 3H), 1.11 (s, 3H), 1.02 (s, 3H); ^{13}C NMR δ 206.7, 63.4, 59.4, 57.7, 46.0, 29.0, 24.0, 22.4, 10.1.

(1*S*,2*S*,5*R*,7*S*)-7-Bromo-1,5-dimethyl-6-oxotricyclo[3.3.0.0^{2,7}]-octane (4). Method A: A solution of 3,3,8-tribromocamphor (1.142 g, 2.94 mmol), H_2O (2 mL), and KOH (150.0 mg, 2.67 mmol) in DMF (20 mL) was heated at 110 °C (bath temp) for 10 h. After cooling to rt, ethyl acetate (40 mL) was added and the resulting mixture washed successively with water (6 × 20 mL), 5% aqueous HCl (10 mL), saturated aqueous $NaHCO_3$ (10 mL), and brine (20 mL). Drying ($MgSO_4$) and concentration of the organic layer gave 0.841 g of the crude product. Purification by flash chromatography (EtOAc/hexane = 1/50) provided 670.0 mg (82%) of compound 4 as a colorless solid (mp 57.2–57.8 °C): $[\alpha]^{25}_D$ = −31.2 (*c* = 1.03, CH_3OH); ^{1}H NMR δ 2.76 (d, *J* = 4.8 Hz, 1H), 2.28 (d, *J* = 8.0 Hz, 1H), 2.17 (d, *J* = 8.0 Hz, 1H), 1.98–1.80 (m, 2H), 1.70–1.52 (m, 1H), 1.49 (dt, *J* = 14.4, 8.3 Hz, 1H), 1.13 (s, 3H), 1.12 (s, 3H); ^{13}C NMR δ 209.4, 67.4, 65.7, 56.0, 49.5, 44.6, 37.3, 21.2, 13.7, 10.4; exact mass, *m/z* calcd for $C_{10}H_{13}BrO$ 228.0149, found 228.0144. Anal. Calcd for $C_{10}H_{13}BrO$: C, 52.42; H, 5.72; Br, 34.88; O, 6.98. Found: C, 52.25; H, 5.76; Br, 34.88; O, 7.11.

Method B: To a suspension of KH (110.0 mg, 2.74 mmol) in THF (10 mL), cooled at 0 °C (ice bath), was added a solution of 3,3,8-tribromocamphor (709.3 mg, 1.83 mmol) in THF (5 mL). The mixture was stirred at rt until TLC analysis indicated that the reaction was complete (12 h). The reaction was quenched by addition of a 50% aqueous THF solution (20 mL). Most of the organic solvent was removed under reduced pressure and the remaining aqueous solution was extracted with Et_2O (3 × 10 mL) and EtOAc (10 mL). The combined organic layers were washed with saturated aqueous NaCl (20 mL), dried ($MgSO_4$), and concentrated to give the crude product. Flash chromatography (EtOAc/hexane = 1/50) furnished 366.8 mg (88%) of the desired product as a colorless solid.

(1*S*,2*S*,5*R*,6*S*)-6-Carbanilino-1,5-dimethyltricyclo-[3.2.0.0^{2,6}]heptane (5). Method A: At 0 °C, to a suspension of KH (230.0 mg, 5.73 mmol) in THF (10 mL), was slowly added to a solution of aniline (0.52 mL, 5.73 mmol) in THF (5 mL). The resulting mixture was stirred at rt for 30 min. A solution of compound 4 (436.0 mg, 1.91 mmol) in THF (5 mL) was added dropwise. The reaction mixture was stirred at rt and the progress of the reaction monitored by TLC. No more starting material was detected after 24 h. At this time, a 50% aqueous THF solution (20 mL) was added. The resulting solution was concentrated and the residue extracted with ether (3 × 20 mL) and EtOAc (20 mL). The combined organic layers were washed with saturated aqueous NaCl (20 mL), dried ($MgSO_4$), and concentrated to give the crude product. Purification by flash chromatography (EtOAc/hexane = 1/50 → 1/20) yielded 377.3 mg (82%) of the title compound as a yellow solid: mp 68–70 °C; $[\alpha]^{25}_D$ = +11.0 (*c* = 0.5, $CHCl_3$); ^{1}H NMR δ 7.50 (d, *J* = 7.5 Hz, 2H), 7.29 (t, *J* = 7.5 Hz, 2H), 7.07 (t, *J* = 7.5 Hz, 1H), 6.89 (br, s, 1H), 2.68 (s, 1H), 2.30 (d, *J* = 3.0 Hz, 1H), 2.06 (d, *J* = 3.0 Hz, 1H), 1.97 (ddd, *J* = 12.0, 9.3, 2.7 Hz, 1H), 1.83 (ddd, *J* = 12.0, 9.3, 1.6 Hz, 1H), 1.71–1.53 (m, 2H), 1.23 (s, 3H), 0.84 (s, 3H); ^{13}C NMR δ 167.6, 137.7, 128.9, 124.1, 119.5, 68.9, 65.3, 47.1, 41.9, 41.4, 32.8, 22.2, 10.2, 9.3; IR ($CHCl_3$) 3448, 3050, 1674 (C=O), 1440 cm^{-1}; exact mass, *m/z* calcd for $C_{16}H_{19}NO$ 241.1466, found 241.1466. Anal. Calcd for $C_{16}H_{19}NO$: C, 79.63; H, 7.94; N, 5.80. Found: C, 79.66; H, 7.92; N, 5.81.

Method B: To a suspension of KH (210.0 mg, 5.24 mmol) in THF (10 mL) was slowly added a solution of aniline (0.50 mL, 5.24 mmol) in THF (5 mL). The reaction mixture was stirred

(11) Eck, C. R.; Mills, R. W.; Money, T. *J. Chem. Soc., Perkin Trans. 1* 1975, 251.

at rt for 30 min. A solution of 3,3,8-tribromocamphor (677.1 mg,1.75 mmol) in THF (5 mL) was added over a 10-min period. The reaction mixture was stirred for 24 h at rt. A 50% aqueous THF solution (20 mL) was added. The reaction was worked up as above and the product was purified by flash chromatography (EtOAc/hexane = 1/50 → 1/20) to give 357.5 mg (85%) of the desired product.

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