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Favorskii Reactions of a Bromoquadricyclanone

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The [*n*]-prismanes are an interesting class of highly symmetrical $(CH)_n$ polyhedranes whose novel structure and reactivity has stimulated significant synthetic[1] and theoretical[2] attention. Prismane ([3]-prismane) (**1**),[3] cubane ([4]-prismane) (**2**),[4] and pentaprismane ([5]-prismane) (**3**)[5] have been synthesized and are known to have D_{3h}, O_h, and D_{5h} symmetry, respectively. Whereas prismane (**1**) was prepared via photochemical denitrogenation, both the cubane and pentaprismane skeletons were constructed using the Favorskii ring-contraction. Moreover, most of the synthetic approaches toward the unknown higher order prismanes (**4**−**6**)[6] have also utilized the Favorskii ring-contraction and with good reason. This reaction has proven to be a very reliable method for the synthesis of not only prismatic ring systems, but also of a variety of other strained ring compounds. As yet, however, there have been no reports of the use of this reaction for the synthesis of the [3]-prismane skeleton. This is likely a result of the fact that Favorskii ring-contractions are typically run at elevated temperatures and that [3]-prismanes are thermally labile. Indeed, the parent hydrocarbon **1** has a half life of 11 h at 90 °C. Nonetheless, we were intrigued by this approach, particularly because the immediate product of Favorskii ring-contraction, [3]-prismane carboxylic acid (**11**), could then be metalated using the protocol of Eaton.[7] It would then be possible to synthesize a host of new substituted [3]-prismanes. Finally, the fact that a readily available Favorskii precursor quickly unveiled itself further enhanced the appeal of this approach.


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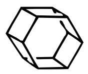
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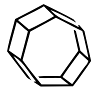
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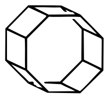
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In order to evaluate the feasibility of this approach, the increase in strain energy for the conversion of quadricyclane to [3]-prismane was computed using geometry optimized ab initio calculations at the HF/6-31G* level, and this value was compared to the strain energy increase for the transformation of homocubane to cubane and homopentaprismane to pentaprismane. The results of these calculations are shown in Table 1. It is noteworthy that the increase in strain energy of 50.4 kcal/mol for the proposed quadricyclane to prismane transformation is not significantly different than that for the homocubane to cubane (47.6 kcal/mol) and homopentaprismane to pentaprismane (44.5 kcal/mol) transformations. Indeed this value appears to fall below the threshold proposed by Mehta and Osawa,[8] further bolstering our hope that the Favorskii ring-contraction to the [3]-prismane skeleton would be successful.

Table 1. Geometry Optimized HF/6-31G* Total Energies, Heats of Formation (ΔH_f), and Strain Energies (SE) for Quadricyclane, Prismane, Homocubane, Cubane, Homopentaprismane, and Pentaprismane

compound	*E* (HF) au	ΔH_f (kcal/mol)[a]	SE (kcal/mol)[b]
quadricyclane	−269.61822	80.9[d]	97.2
prismane	−230.5032877	136.2	147.6
homocubane	−346.5044871	93.7	113.9
cubane	−307.3939067	146.3[c]	161.5
homopentaprismane	−423.4474219	71.0	95.0
pentaprismane	−384.3418194	120.5	139.5

[a] Calculated using the group equivalent method of Ibrahim and Schleyer (Ibrahim, M. R.; Schleyer, P. *J. Comput. Chem.* **1985**, *6*, 157. [b] Calculated from Benson group equivalents (Benson, S. W.; Cruickshank, F. R.; Golden, D. M.; Haugen, G. R.; O'Neal, H. E.; Rodgers, A. S.; Shaw, R.; Walsh, R. *Chem. Rev.* **1969**, *69*, 279.). [c] The experimental heat of formation is 148.7 kcal/mol (Wiberg, K. B. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 312.). [d] The experimental heat of formation is 79.5 kcal/mol (Rodgers, D. W.; Ling, S. C.; Girellini, R. S.; Holmes, T. J.; Allinger, N. L. *J. Phys. Chem.* **1980**, *84*, 1810.).

Our synthesis of an appropriate [3]-prismane Favorskii precursor relied on the work of Klumpp and co-workers who have shown that a variety of cyclopropyl carbinols, including quadricyclanol (**7**), may be readily lithiated via treatment with an alkyllithium.[9] Expanding on this work of Klumpp, Szeimies reported that lithiation of quadricyclanol (**7**) with 2 equiv of *n*-butyllithium, followed by addition of dibromoethane, afforded an unseparated 85:15 mixture of brominated alcohols **8** and **9**.[10] We found that **8** and **9** could be separated via careful silica gel chromatography, provided that the eluent contains 2% triethylamine to prevent isomerization of the quadricyclanol to the norbornadiene. Oxidation of *pure* bromohydrin **8** was then carried out with tetrapropylammonium perruthenate(VII) (TPAP)/*N*-methylmorpho-

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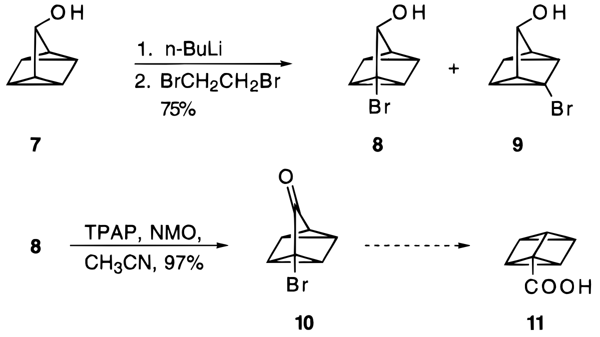
Scheme 1



Scheme 2

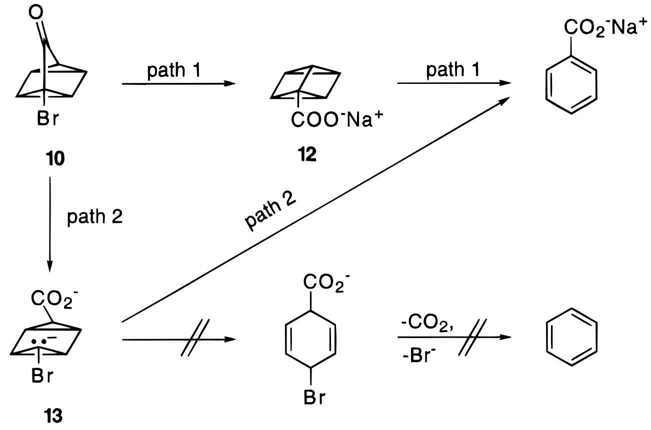


Table 2. Summary of Attempted Favorskii Ring-Contractions of Bromo Ketone 10

reaction conditions	product	yield
NaOH, THF, reflux, 4 d	benzoic acid	96%
NaOH, toluene, reflux, 12 h	benzoic acid	98%
LiOH, H_2O, 80 °C, 8 h	decomposition	–
KOH, H_2O, reflux, 26 h	decomposition	–

line *N*-oxide (NMO) in 97% yield to afford bromo ketone **10**, ideally functionalized for Favorskii ring-contraction (Scheme 1).

Because Favorskii ring-contractions are often sensitive to reaction conditions, ring-contractions of **10** were carried out under several different conditions as shown in Table 2. Reaction with sodium hydroxide in refluxing THF and reaction with sodium hydroxide in refluxing toluene both furnished excellent yields of benzoic acid as the sole product (entries 1 and 2). The benzoic acid may be derived from the thermal isomerization of the putative prismane carboxylate salt **12**, or alternatively, from an intermediate anion (**13**) resulting from Haller–Bauer type cleavage of bromo ketone **10** (Scheme 2). However, attempts at running these reactions at lower temperatures in order to limit this potential isomerization were met with failure, for only unreacted bromo ketone **10** was recovered.

In contrast to the results found in nonaqueous solvents, Favorskii ring-contractions carried out in aqueous base (entries 3 and 4) took a very different course. In these instances, only trace amounts of organic solvent soluble material could be recovered. To eliminate the possibility that the Haller–Bauer intermediate **13** had fragmented to benzene as shown in Scheme 2, the reactions in aqueous media were conducted in sealed tubes. However, upon completion of these reactions, no benzene was detected. Given these results, we attribute this difference in reactivity in aqueous solvents to C–Br bond ionization which, in water, takes place in preference to hydroxide attack at the carbonyl. This ionization is further promoted when lithium hydroxide is used as the base, for **10** reacts faster and at lower temperature in aqueous LiOH (entry 3) than in aqueous KOH (entry 4). Indeed, it is well-known that lithium ion can act as a Lewis acid,[11] and here it appears to enhance C–Br ionization and subsequent decomposition of **10**. In further support of this theory, stirring an aqueous solution of **10** in $LiClO_4$ at 80 °C for 4 h leads to complete destruction of the starting bromo ketone **10** and recovery of little organic solvent soluble material. In addition, refluxing an aqueous solution of **10** for 17 h leads to complete destruction of this bromo ketone. Furthermore, heating **10** in acid-free deuterochloroform for 17 h leads to little loss of starting material. No bromobenzene was detected in either experiment. Finally, attempts at running these reactions for shorter time periods led only to partial recovery of starting bromo ketone **10**; the amount of **10** recovered was inversely proportional to reaction time.

In summary, attempts to prepare the [3]-prismane skeleton via Favorskii ring-contraction under a variety of conditions have not been successful. In nonaqueous solvents, only benzoic acid is obtained. Given the thermal instability of [3]-prismanes, this result is not surprising, though we cannot eliminate the possibility that a Haller–Bauer cleavage pathway to the benzoic acid is operative. Reactions run in aqueous base led to preferential C–Br bond ionization and ultimate destruction of the starting bromo ketone **10** prior to hydroxide attack at the ketone. Alternative approaches to [3]-prismane carboxylic acid, and ultimately the parent hydrocarbon, are underway in these laboratories.

Experimental Section

General Methods. All solvents and reagents were reagent grade or better and were used without purification unless otherwise indicated. Prior to drying at 125 °C for 5–6 h, all glassware was washed sequentially with concentrated NH_4OH, 5% aqueous EDTA, and distilled water to prevent isomerization of the quadricyclane ring system. ^1H NMR spectra were obtained in $CDCl_3$ at 500 MHz with $CHCl_3$ (δ 7.24) as an internal standard. ^{13}C NMR spectra were obtained at 125 MHz with $CDCl_3$ (δ 77.0) as an internal standard. Reactions were monitored by thin-layer chromatography and were carried out on silica gel plates using anisaldehyde as a developing stain. Flash chromatography was carried out using the method of Still.[12] Melting points are reported uncorrected.

2-Bromotetracyclo[3.2.0.0^{2,7}.0^{4,6}]heptan-3-ol (8). A crude mixture of 2-bromotetracyclo[3.2.0.0^{2,7}.0^{4,6}]heptan-3-ol (**8**) and 1-bromotetracyclo[3.2.0.0^{2,7}.0^{4,6}]heptan-syn-3-ol (**9**) was prepared as described by Szeimies and Heywang.[10] The crude product mixture was distilled at 51–55 °C/0.2 mm and the distillate subjected to flash chromatography using 65% diethyl ether/33% petroleum ether/ 2% triethylamine to afford pure **8** ($R_f = 0.5$) as a colorless oil whose spectral properties were identical to those reported.

2-Bromotetracyclo[3.2.0.0^{2,7}.0^{4,6}]heptan-3-one (10). To a stirred mixture of 514 mg (2.75 mmol) of **8**, 2.49 g of crushed 4A molecular sieves, 850 mg (7.38 mmol) of 4-methylmorpholine *N*-oxide in 10 mL of acetonitrile under nitrogen was added 90 mg (9 mol %) of TPAP all at once. After 17 min, TLC (65% diethyl ether/35% petroleum ether, alcohol $R_f = 0.5$; ketone $R_f = 0.7$) indicated that the reaction was finished. The greenish mixture was then placed on the rotovap to remove the acetonitrile, and the resultant green-black solid was filtered through a small pad of silica gel using 96% ethyl acetate/4% triethyl-

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amine. The silica gel had previously been deactivated by washing with the aforementioned solvent. Concentration of the filtrate yielded 491 mg (97%) of slightly off-white crystalline **10** that was >95% pure by NMR. An analytical sample was obtained by slow evaporation from hexane/ethyl acetate to yield colorless crystals: mp 45−47 °C; IR ($CDCl_3$, cm^{-1}) 3060, 1760, 1270; ^1H NMR δ 2.47−2.49 (m, 2H), 2.36−2.38 (m, 2H), 1.24−1.28 (m, 1H); ^{13}C NMR δ 209.1, 30.7, 28.1, 22.3, 17.9; HRMS (M^+) calcd 184.9602, obsd 184.9600. Anal. Calcd for C_7H_5BrO: C, 45.44; H, 2.72. Found C, 45.36; H, 2.74

Favorskii Ring-Contractions. 1. NaOH/Toluene. A suspension of 1.5 g of powdered NaOH in toluene (10 mL) was refluxed for 45 min to azeotropically remove traces of water via a Dean−Stark trap. The mixture was cooled to ambient temperature and bromo ketone **10** (366 mg, 1.98 mmol) in toluene (4 mL) was added and the mixture then refluxed for 12 h. After 12 h, TLC indicated that **10** had undergone reaction, and the mixture was diluted with water (10 mL), cooled in an ice bath, and acidified with 10% HCl to ca. pH 3. The viscous brown aqueous solution was extracted with 3:1 CH_2Cl_2/*t*-BuOH (5 × 30 mL) and the combined organic extracts were brine washed (1 × 25 mL) and dried over $MgSO_4$. Filtration and concentration yielded a white solid (238 mg, 98%) identified as benzoic acid via comparison to an authentic sample.

2. NaOH/THF. To a magnetically stirred solution of bromo ketone **10** (148 mg, 0.800 mmol) in THF (2 mL) at 0 °C was added powdered NaOH (130 mg) all at once. The mixture was allowed to warm to ambient temperature for several hours, fitted with a refux condenser, and refluxed for 4 days. The THF was evaporated and the residue diluted with 15 mL of water and 15 mL of 3:1 CH_2Cl_2/*t*-BuOH. After cooling in a ice bath, the mixture was acidified to ca. pH 3−4 with 10% HCl. The layers were separated, and the organic layer was extracted with 3:1 CH_2Cl_2/*t*-BuOH (3 × 10 mL). Combined organics were brine washed (1 × 20 mL), dried over $MgSO_4$, and concentrated to give 94.1 mg (96%) of a white solid identified as benzoic acid via comparison to an authentic sample.

3. KOH/H_2O. A magnetically stirred mixture of bromo ketone **10** (340 mg, 1.84 mmol) in 20% KOH (10 mL) was refluxed for 26 h at which time TLC indicated complete loss of **10**. The dark viscous mixture was cooled in an ice bath and acidified with 10% HCl to ca. pH 3−4. The mixture was then extracted with 3:1 CH_2Cl_2/*t*-BuOH (4 × 35 mL). Combined organics were brine washed (1 × 30 mL), dried over $MgSO_4$, and concentrated to a black oil. NMR revealed only two, broad unresolved peaks at δ 0.8−1.1.

4. LiOH/H_2O. A magnetically stirred mixture of bromo ketone **10** (198 mg, 1.07) in 1M LiOH (5.6 mL) was heated to 80 °C for 8 h at which time tlc indicated complete loss of **10**. The dark viscous mixture was cooled in an ice bath and acidified with 10% HCl to ca. pH 3−4. The mixture was then extracted with CH_2Cl_2 (4 × 25 mL). Combined organics were brine washed (1 × 30 mL), dried over $MgSO_4$, and concentrated to a small amount (<20 mg) of yellowish oil. NMR revealed a broadened baseline and two, larger, broad unresolved peaks at δ 0.8−1.1.

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