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An Investigation of the Formation Mechanism of Allene or Alkyne in the 6,7-Benzobicyclo[3.2.1]octane System by Deuterium Labeling Experiments

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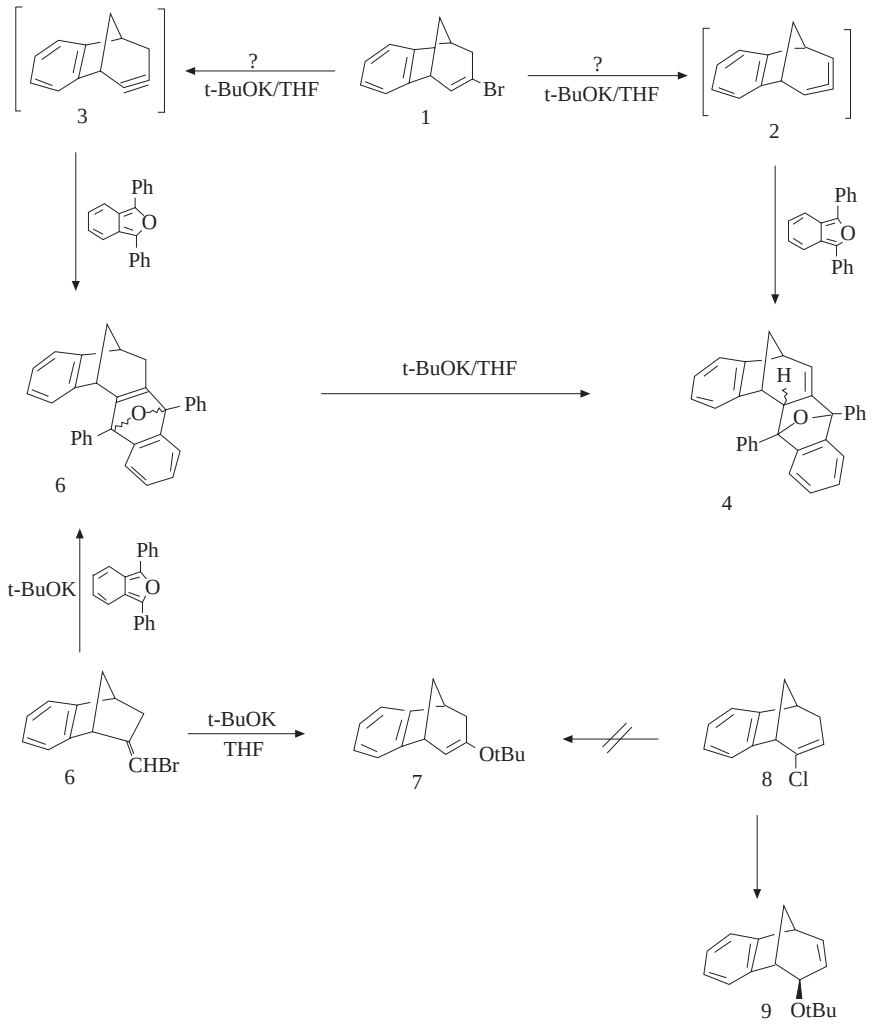
In order to reveal the real intermediate in the base-promoted reaction of **1**, 3-bromo-4,4-dideuterio-6,7-benzobicyclo[3.2.1]octa-2,6-diene **10** was synthesized and its HBr elimination reaction studied. Reaction of **10** with potassium *tert*-butoxide yielded butoxyl ether **18** in which proton-deuterium exchange has occured.

Key words: Cyclic allene, Cyclic alkynes, Deuterium Labeling

Introduction

Allenes are an important class of unsaturated hydrocarbons which contain two cumulated double bonds in an orthogonal geometry. In cyclic allenes, ring constraints bend and twist the normally linear, perpendicular allene and will engender substantial strain and resultant kinetic reactivity. [2]

Recently, we reported the possible formation of the highly strained allene **2**.[3] For the generation of the allene intermediate, we applied base-promoted elimination of HBr from bromocyclo alkene **1** and trapped the formed allene **2** with 1,3-diphenylbenzoisofuran (DPI) as [2+4] cycloadducts **4** (Scheme 1). However, as an alternative mechanism for the formation of **4**, we suggested the dehydrobromination of **1** to yield the bicyclic alkyne **3**, which undergoes cycloaddition with DBI to give adducts **5**. The base-catalyzed isomerization of the double bond in **5** would give the observed products **(4)** (Scheme 1).



Scheme 1

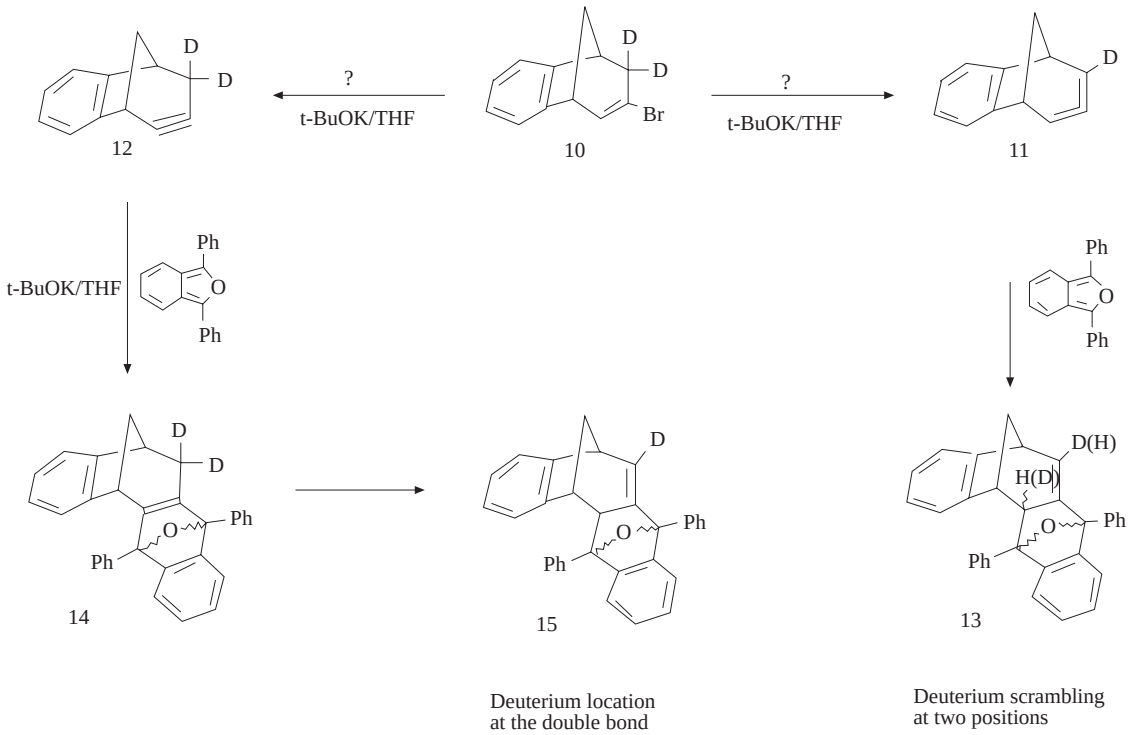
In order to distinguish between the two possible mechanisms, we investigated generation of the alkyne **3** by two alternate procedures.[4,5] Exocyclic bromomethylene compound **6** and vinylic chloride **8** were synthesized for this purpose and subjected to base-promoted elimination reaction in the presence of a trapping agent. The same allenic adducts **(4)** were obtained from the reaction of methylene compound **6** with **2** mol of potassium tertrbutoxide in the presence of DBI as obtained from the reaction of **1** using potassium *tert*-butoxide (Scheme 1).[4] These experiments indicate clearly that the ring-expanded alkyne **(3)** formed initially reacts with DBI to yield alkyne-like adducts **(5)** which rearrange completely to allene-like adducts **(4)** in the presence of excess base. In contrast to our expectations, the reaction of vinylic chloride **8** with potassium *tert*-butoxide resulted in the formation of allyl ether **9**[5] (Scheme 1).

The identical product distribution from the two different reactions, 1) base-promoted reaction of **1** in the presence of DBI and 2) base-promoted reaction of **6** in the presence of DBI, implies that the intermediates must have the same structure. Since the allene intermediate **(2)** can not be generated from the base-promoted reaction of **6**, we have concluded that the real intermediate is alkyne **3**.

All these observations indicate that alkyne **3** was probably generated when **1** was reacted with potassium tert-butoxide. Even at this stage, however, we can not exclude the allene formation in the

base-promoted reaction of **1**. It is not unlikely if we propose that the base-promoted reaction of **1** in the presence of DBI forms the allene **2** as the intermediate, and the base-promoted reaction of **6** in the presence of DBI forms the alkyne **3** as the intermediate.

In order to solve the problem of what the real intermediate is in the base-promoted reaction of **1**, we decided to label the allylic position of bromocyclo alkene **1** with two deuterium atoms and submit this compound, **10**, to a dehydrobromination reaction. Formation of an allene intermeditae would result in the scrambling of deuterium atoms, as shown in scheme 2. However, alkyne formation will give product **15** where deuterium is located at the double bond. We describe the synthesis and dehydrobromination reaction of **10**.



Scheme 2

Experimental Section

General. Melting points were determined on a Thomas-Hoover capillary melting point apparatus. Solvents were concentrated at reduced pressure. Infrared spectra were obtained from films on NaCl plates for liquids or from solution in 0.1 mm cells or KBr pellets for solids on a regular instrument. The ^{1}H and ^{13}C NMR spectra were recorded on 60, and 200 MHz spectrometers. Preparative thin-layer chromatography (TLC) was performed on silica gel 60_{254} plates. Column chromatography was done on silica gel (60-200 mesh) and alumina (Grade IV, neutral). Exo-dibromide **16**[6], and *exo*-tribromide **23**[10] were prepared as reported.

2-exo-Hydroxy-3-bromo-6,7-benzobicyclo[3.2.1]octa-2,6-diene 17. A solution of *exo*-dibromide **16** (13.26 g, 42.2 mmol) in 30 mL of acetone was added dropwise to a stirred solution of $AgClO_4$ (8.74 g, 42 mmol) in 40/30 mL of acetone/water mixture over 20 min at room temperature. The mixture was stirred at room temperature for 2h and AgBr removed by filtration. The aqueous solution was extracted with ether (2×150 mL). The combined ether extracts were washed with water and dried over $MgSO_4$. After removal

of the solvent, the residue was crystallized from n-hexane. The formed crystals were identified as *exo*-bromo alcohol **17**[6] (7.25 g, 68%). mp 118-119°C (Lit[6]. 121.5-122.5°C), white crystals.

After filtration of *exo*-bromo alcohol **17**, the solvent was evaporated and the oily viscous residue (2.9 g) was subjected to preparative thin-layer chromatography (silica gel/petroleum ether-ether 9:1) to give 200 mg (1.8%) of *endo*-bromo **18:** colorless crystals, mp 115°C from ether; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.41 (m, 1H, ArH), 7.15 (m, 3H ArH), 6.68 (d, J=7.1 Hz, 1H, H_4), 4.49 (d, J=5.5 Hz, 1H, H_2), 3.65 (t=5.1 Hz, 1H, H_1), 3.35 (dd, J=7.1, 4.2 Hz, 1H, H_5), 2.42 (dt, J=10.6, 4.6 Hz, 1H, H_{8syn}, 2.27 (d, J=10.6 Hz, 1H, H_{8anti}), 1.72 (br s, 1H, -OH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 153.63, 142.26, 140.21, 129.19, 128.68, 128.63, 126.06, 123.68, 73.94, 50.62, 46.35, 45.25. IR (KBr, cm^{-1}) 3300, 3040, 2960-2920, 2860, 1620, 1465, 1450, 1320, 1300, 1170, 1070, 1060, 900, 845.

3-Bromo-6,7-benzobicyclo[3.2.1]octa-3,6-diene-2-one 19. To a solution of *exo*-bromo alcohol **17** (5 g, 19.9 mmol) in CH_2Cl_2 (100 mL) was added 3.46 g (39.8 mmol) of activated MnO_2. The resulting reaction mixture was stirred at room temperature for 4 days, filtered, and the filtercake washed thoroughly with methanol. After the solvent was removed, the residue was crystallized from ether/pentane to give **19**[8] (2.08 g, 42%) as a colorless crystals, mp 104-105°C (Lit[8]. 109-110°C). The ^{1}H NMR spectrum was identical to that reported[8].

Reaction of 3-bromo-6,7-benzobicyclo[3.2.1]octa-3,6-diene-2-one 19 with $LiAlH_4$ or $LiAlD_4$. To a suspension of 0.16 g (4.21 mmol) of $LiAlH_4$ in 60 mL of dry and freshly distilled ether was added dropwise a solution of 1.0 g (2.86 mmol) of 3-bromo ketone **19** in 10 mL of dry ether over 5 min. The resulting reaction mixture was stirred magnetically at room temperature for 1.5 h. Wet ether was added to the resulting reaction mixture (while cooling with ice bath) as long as no reaction was observed. The formed precipitate was dissolved by adding dilute HCI solution. The organic layer was washed 3-4 times with water and dried over $MgSO_4$. After removal of the solvent, the residue was crystallized from ether to yield 830 mg (83%) of *endo*-bromo alcohol **18**.

The same reaction was carried out with $LiAlD_4$ and obtained 2-*endo*-hydroxy-2-deuterio-3-bromo-6,7-benzobicyclo[3.2.1]octa-3,6-diene **20** in the same yield (83%). ^{1} H NMR (200 MHz, $CDCI_3$) δ 7.42 (m, 1H, ArH), 7.27-7.12 (m, 3H, ArH), 6.70 (d, J=7.0 Hz, 1H, olefinic H), 3.66 (d, J=4.5 Hz, 1H, H_1), 3.36 (dd, J=7.0, 4.7 Hz, 1H, H_5), 2.45 (dt, J=10.8, 4.7 Hz, 1H, H_{8syn}), 2.28 (d, J=10.8 Hz, 1H, H_{8anti}), 1.72 (br s, 1H, -OH); ^{13}C NMR (50 MHz, $CDCI_3$) δ 152.11, 140.77, 138.77, 127.69, 127.20, 127.14, 124.51, 122.19, 72.46, 72.01, 71.55, 49.01, 44.87, 43.74.

Reaction of 2-endo-hydroxy-3-bromo-6,7-benzobicyclo[3.2.1]octa-2,6-diene 18 (or deuterioted derivative 20) with p-toluenesulfonyl chloride. To a solution of 0.33 g (1.31 mmol) of *endo*-bromo alcohol **18** in 15 mL of CH_2Cl_2 was added 0.27 g (1.44 mmol) of p-toluenesulfonyl chloride and 0.2 g (2.62 mmol) of anhydrous pyridine. The reaction mixture was stirred overnight at room temperature and then the mixture was poured onto ice and treated with dilute HCI solution. The aqueous solution was extracted with CH_2Cl_2, washed thoroughly with water, and dried over $MgSO_4$. After removal of the solvent, the oily residue was chromatographed over silica gel with petroleum ether-ether (9:1) yielding 0.49 g (92%) of tosillated compound **21** as a colorless liquid: ^{1}H NMR (60 MHz, $CDCl_3$) δ 7.90 (d, J=9.0 Hz, 2H, ArH), 7.10-7.60 (m, 6H, ArH), 6.80 (d, J=7.0 Hz, 1H, olefinic H), 5.45 (d, J=5.6 Hz, 1H, H_2), 3.95 (t, J=4.0 Hz, 1H, H_1), 3.40 (dd, J=7.0, 4.0 Hz, 1H, H_5), 2.45 (s, 3H, methyl protons), 2.35 (m, 2H, H_8); IR (film) 3060-2860, 1600, 1470, 1365, 1185, 1175, 1095, 965 cm^{-1}.

The same reaction was also done with **20** and obtained deuterated derivative **22** in the same yield (92%). ^{1} H NMR (200 MHz, $CDCI_3$) d 7.87 (d, J=8.3 Hz, 2H, ARH), 7.43 (m, 1H, ArH), 7.33 (d, J=8.1, Hz, 2H, ArH), 7.14 (m, 3H, ArH), 6.78 (d, J=7.3 Hz, 1H, olefinic H), 3.91 (d, J=4.8 Hz, 1H, H_1), 3.36 (dd,

J=7.3, 4.1 Hz, 1H, H_5), 2.44 (s, 3H, methyl protons), 2.42 (dt, J=11.1, 4.1 Hz, 7H, H_{8syn}), 2.29 (d, J=11.1 Hz, 1H, H_{8anti}); ^{13} C NMR (50 MHz, $CDCI_3$) δ 152.18, 146.76, 144.11, 142.07, 135.91, 131.57, 130.21, 129.58, 129.08, 128.78, 123.24, 79.88, 79.15, 78.56, 49.64, 46.82, 44.88, 23.60

3-Bromo-4,4-dideuterio-6,7-benzobicyclo[3.2.1]octa-2,6-diene 10. To a stirred solution of 400 mg (1.02 mmol) of tribromide **23** in 30 mL of dry and freshly distilled ether was added 94 mg (2.24 mmol) of $LiAID_4$. The resulting reaction mixture was stirred at room temperature for 5 days. Wet ether was added to the resulting reaction mixture (while cooling with an ice bath) as long as no reaction was observed. The formed precipitate was dissolved by adding dilute HCI solution. The organic layer was washed with water, dried over $CaCl_2$, filtered, and concentrated to yield an oil. The residue was filtered over 30 g of silica gel, eluting with hexane to yield 132 mg (41%) of dideuterated compound **10.** ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.28 (m, 1H, ArH), 7.16 (m, 3H, ArH), 6.47 (d, J=7.0 Hz, 1H, H_2), 3.36 (m, 2H, H_1 and H_5), 2.28 (dt, J=10.3, 4.5 Hz, 1H, H_{8syn}), 2.05 (d, J=10.3 Hz, 1H, H_{8anti}); ^{13}C NMR (50 MHz, $CDCI_3$) δ (152.27, 147.35, 136.99, 128.48, 128.41, 125.55, 122.81, 121.78, 44.63, 43.92, 43.76, 43.52, 43.12, 42.99.

Reaction of Dideuterated Compound 10 with Potassium tert-Butoxide. To a stirred solution of **10** (200 mg, 0.84 mmol) in 10 ml of dry and freshly distilled THF was added 113 mg (1.0 mmol) of potassium *tert*-butoxide. The reaction was refluxed for 6 h and then cooled to room temperature. The mixture was diluted with water and the aqueous solution was extracted with ether, washed with water, and dried over $CaCl_2$. After removal of the solvent, the residue was chromatographed over alumina (50 g, grade IV, neutral). Elution with hexane yielded 125 mg (65%) of the butoxy ether **25** as a colorless liquid. The NMR spectrum indicated the scrambling of deuterium in the molecula.

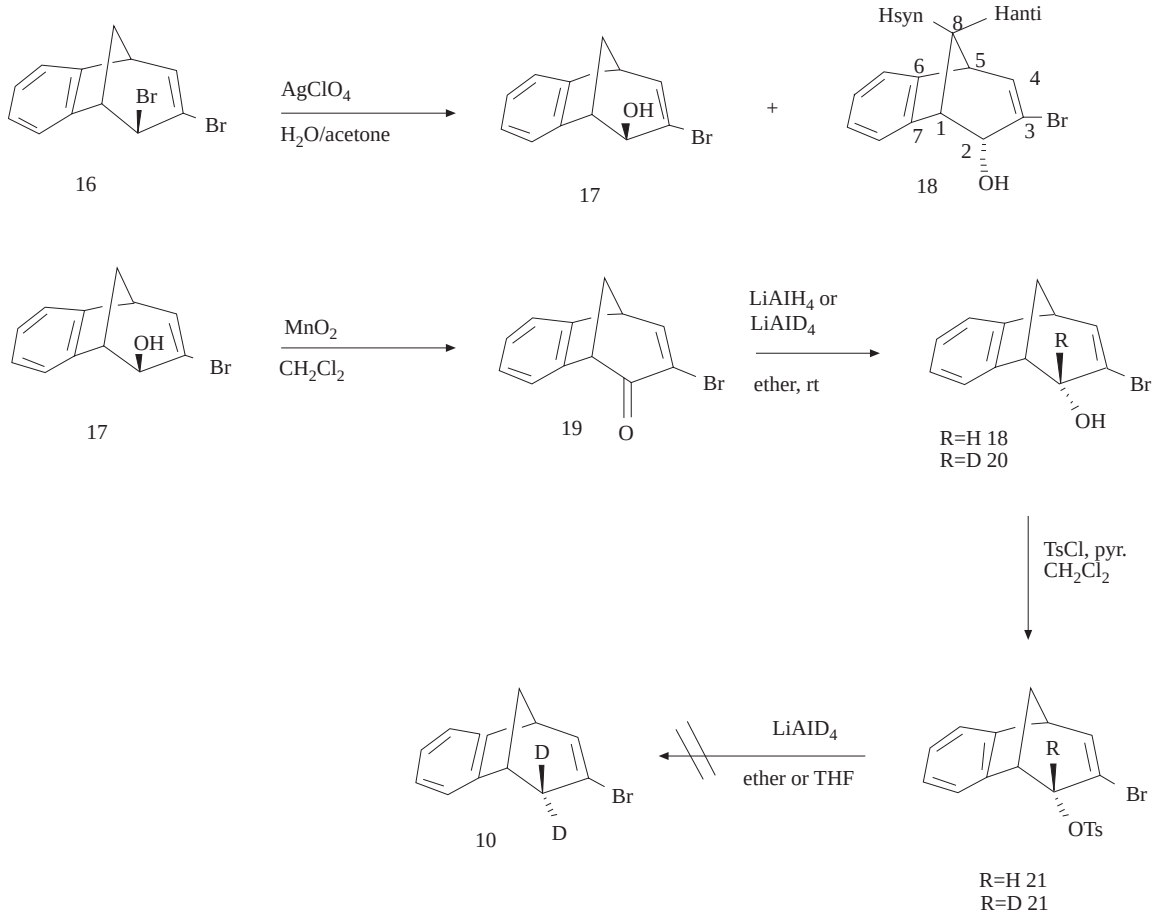
Results and Discussion

The starting material for the synthesis of **10**, the *exo*-dibromide **16**[6] was prepared by addition of dibromocarbene to the readily available benzonorbornadiene[7] as reported in the literature. Silver ion catalysed hydrolysis of **16** in aqueous acetone gave the known *exo*-bromoalcohol **17**[6] (68%) (Scheme 3). *Endo*-bromoalcohol **18** was also isolated from this reaction in a yield of 1.8%, which has not been reported previously[6]. The structure of **17** was determined on the basis of spectral data. The position and *endo* configuration of the -OH group was established by measuring of the coupling constants between the H_1 and H_2 protons in the ^{1}H NMR spectrum. ^{13}C NMR data of **17** was also consistent with the proposed structure showing 4 sp^3 and 8 sp^2 carbons.

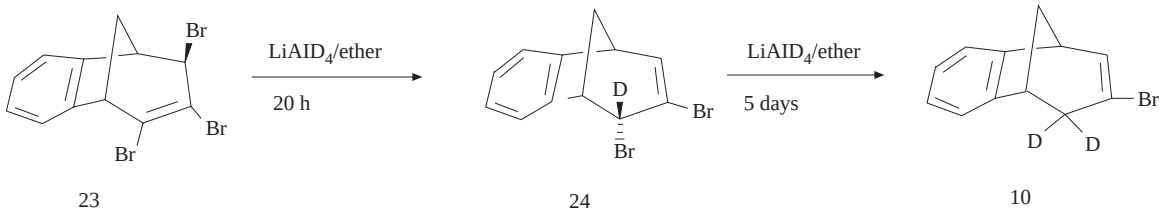
Active MnO_2 oxidation of *exo*-bromoalcohol **17** smoothly afforded bromo ketone **19**[8] (Scheme 3). Bromoketon **19** was identified by comparison of the spectral data with those of reported in the literature. $LiAIH_4$ or $LiAID_4$ reduction of **19** furnished the *endo*-bromoalcohol **18** or **20**, respectively in high yield[9] (Scheme 3). The attack of the hydride ion on carbonyl carbon occurs stereospecifically from the *exo* face of the molecule to give *endo*-alcohol **20** as the sole product. Subsequent reaction of **18** or **20** with p-toluenesulfonyl chloride in pyridine afforded the corresponding tosylate **21** or **22** in high yield (92%). The structures of **20** and **22** were determined on the basis of spectral data, and especially by comparison of their ^{1} H NMR data with those of undeuterated derivatives **18** and **21**. All attemps to reduce **22** to the corresponding dideuterated compound **10** failed.

Preparation of **10** via the reduction route of **22** was unsuccessful. Therefore, another approach leading to **10** was attempted starting from the *exo*-tribromide **23** (Scheme 4). The tribromide **23** was prepared starting from *exo*-dibromide **16** by our published method[10]. Treatment of tribromide **23** with $LiAID_4$ in ether at room temperature for 5 days gave **10** in a yield of 41% (Scheme 4). Furthermore, we

have shown that the partial reduction of **23** with $LiAlD_4$ at room temperature for 20 hours results in the formation of monodeuterated compound **24** by a stereospecific cis process involving a $S_{N^2\prime}$ mechanism[10]. This experiment clearly indicates that **24** is formed as the intermediate during this reduction experiment.



Scheme 3



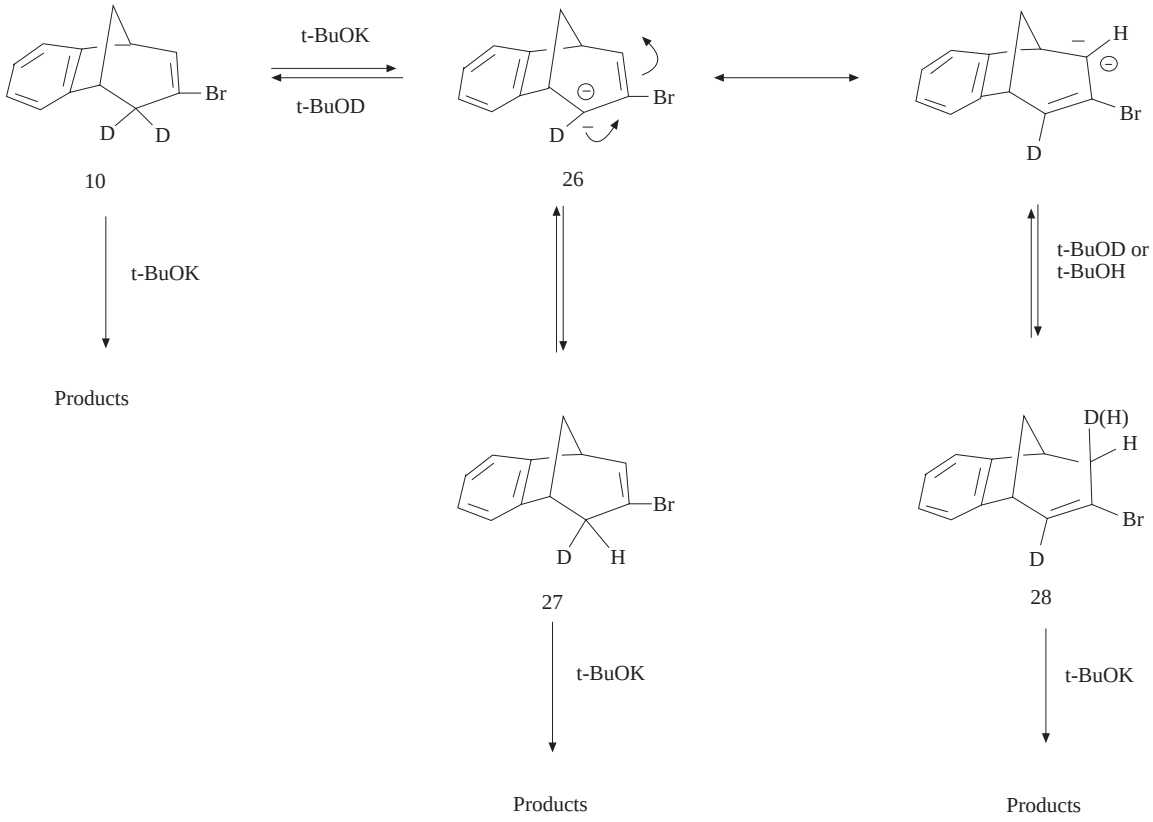
Scheme 4

After successful synthesis of the target compound **10**, we submitted it to the base-promoted HBr-elimination reaction with potassium *tert*-butoxide in refluxing THF. The isolated product, enolether, indicated the scrambling of the deuterium atom in molecule which indicated the allene formation (Scheme 5).

10 25

Scheme 5

In order to establish whether the starting material **10** undergoes any H/D exchange reaction before HBr-elimination, we have stopped the HBr-elimination reaction after 50% consumption of the starting material and analyzed the unreacted starting material **10** by NMR spectroscopy. To our surprise we noticed a remarkable amount of the H-incorporation in the starting material and scrambling of the deuterium atom through the following reversible reaction mechanism (Scheme 6).



Scheme 6

29 30

Scheme 7

However, we were not able to determine the origin of the H-incorporation. We believe that tert-butanol, which is found in potassium *tert*-butoxide, can serve as a source for proton. This observation, of course, prevents us from drawing any conclusion in view of the reaction mechanism.

After the failure of this attempted route to determine the real structure of the intermediate, we have extended our work on the synthesis of the following compounds 29 and 30 whose elimination reactions might give some idea about the mechanism of the reaction and the structure of the formed intermediate. We are expecting to force the system to undego allene formation by blocking the double bond protons by any alkyl groups.

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