Journal of the Chinese Chemical Society, **1998**, *45*, 381-385

The Synthesis and Chemistry of 8-Substituted Bicyclo[5.1.0]oct-1(8)-ene

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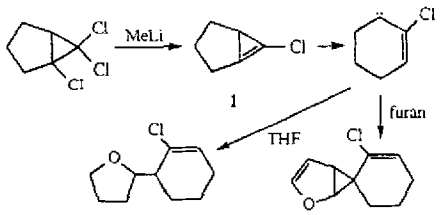
8-Bromobicyclo[5.1.0]oct-1(8)-ene (**7**), an intermediate for the preparation of 8-substituted bicyclo[5.1.0]oct-1(8)-enes, was synthesized by debromination of 1,8,8-tribromobicyclo[5.1.0]octane (**6**). Compound **7** underwent bromo-lithium exchange followed by nucleophilic substitution reactions to generate bicyclo[5.1.0]oct-1(8)-ene (**5**), 8-methylbicyclo[5.1.0]oct-1(8)-ene (**10**), and 8-trimethylsilylbicyclo[5.1.0]oct-1(8)-ene (**11**). The bicyclic cyclopropenes **7**, **5**, **10**, and **11** reacted with cyclopentadiene to form adducts **12**, **13**, **14**, and **15**, respectively. All of these Diels-Alder adducts are endo-exo isomers (endo-addition from the view of the cyclopropene and exo-addition from the view of the cyclooctene).

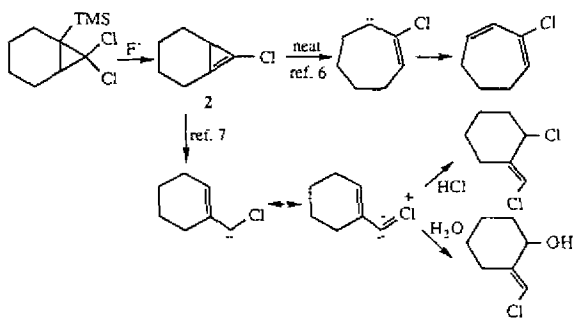
INTRODUCTION

Although the first derivative of cyclopropene was obtained as early as 1881,[1] it was not until 1974 that the 1,3-fused bicyclic cyclopropene was synthesized.[2,3] The chemistry of cyclopropene is unusual because of its high strain (27.7 kcal/mol of olefinic strain energy and 55.2 kcal/mol of total strain energy).[4] The strain energy of 1,3-fused bicyclic cyclopropene is higher than cyclopropene itself, therefore, 1,3-fused bicyclic cyclopropene is more reactive and difficult to synthesize than cyclopropene. The synthetic routes to 1,3-fused bicyclic cyclopropenes with various substituents at C2 are quite different. By dechlorination of 1,6,6-trichlorobicyclo[3.1.0]hexane, Baird and co-workers generated 6-chlorobicyclo[3.1.0]hex-1(6)-ene (**1**) which reacted with solvent (THF) or furan (Scheme I).[5] Billups reported that 7-chlorobicyclo[4.1.0]hept-1(7)-ene (**2**) which was formed via dehalotrimethylsilylation of 1-trimethylsilyl-7,7-dichlorobicyclo[4.1.0]heptane, rearranged to 2-chlorocycloheptа-1,3-diene in neat condition,[6] and Banwell's group claimed that compound **2** reacted with water and hydrochloride to form (*E*)-2-(chloromethylene)cyclohexanol and (*E*)-1-chloro-2-(chloromethylene)cyclohexane (Scheme II).[7] Billups also reported that bicyclo[4.1.0]hept-1(7)-ene (**3**) underwent ene reaction to generate ene dimer, which reacted with oxygen to give carbonyl compounds and formed tricyclo[3.1.0.0^{2,4}]hexanes via [2+2] cycloadditions (Scheme III).[6] Banwell's group also claimed 8-chlorobicyclo-[5.1.0]oct-1(8)-ene (**4**) reacted with hydrochloride to form (*E*)-1-chloro-2-(chloromethylene)cycloheptane.[7] All cyclopropenes **2**, **3** and **4** were prepared by the fluoride-induced elimination of β-chlorocyclopropyltrimethylsilane. Recently we reported that compound **4**, which was formed by debromochlorination of 1-bromo-8,8-dichlorobicyclo-[5.1.0]octane, under vacuum and neat condition, underwent ene dimerizations to give 8-chloro-7-(8-chlorobicyclo[5.1.0]oct-8-yl)bicyclo[5.1.0]oct-1(8)-ene and 8-chloro-7-(8-chlorobicyclo[5.1.0]oct-1-yl)bicyclo[5.1.0]oct-1(8)-ene (Scheme IV).[8] The parent compound of **4**, bicyclo-[5.1.0]oct-1(8)-ene (**5**), which was synthesized by dechlorotrimethylsilylation underwent ene dimerization in neat condition but the stereochemistry of this reaction was not determined.[6] Moreover, the Diels-Alder reactions of cyclopropenes with furans generated two stereoisomers (exo- and endo-adducts),[9] and with cyclopentadiene formed only one stereoisomer (endo-adducts).[10] The reactions of 1,3-fused bicyclic cyclopropenes with furans also gave two stereoisomers,[7] but those with cyclopentadiene have not been studied yet.

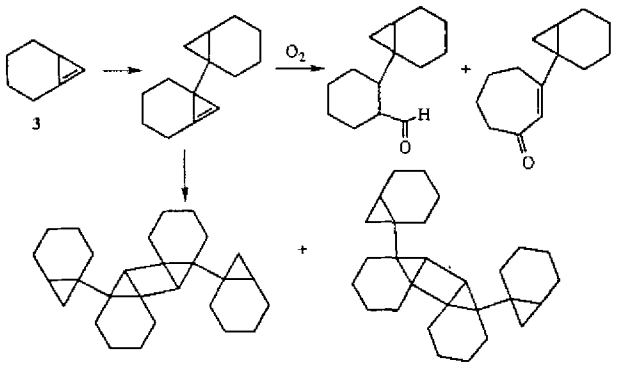
Scheme I



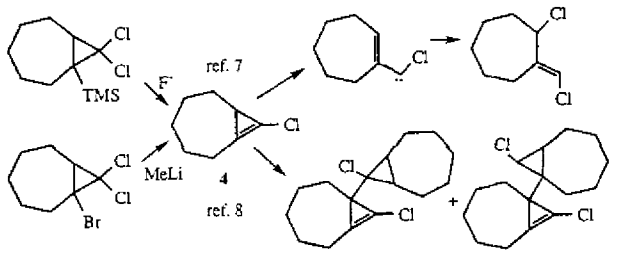
Scheme II



Scheme III



Scheme IV



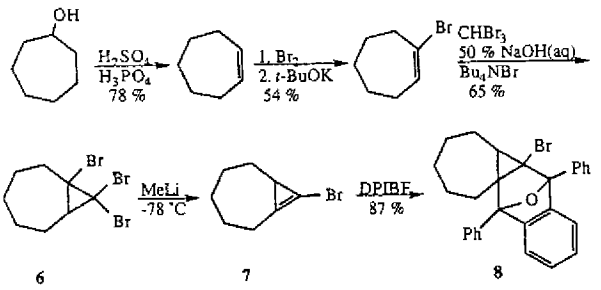
In order to study the chemistry of the various C2-substituents bicyclic cyclopropenes, finding an easy route for the synthesis of these bicyclic cyclopropenes becomes important. To the best of our knowledge, none of the 8-alkylbicyclo[5.1.0]oct-1(8)-enes has ever been reported in the literature. In this paper, we wish to report the synthesis of 8-substituted bicyclo[5.1.0]oct-1(8)-enes by using halo-lithium exchange followed by nucleophilic substitution reactions, and the stereochemistry of Diels-Alder reactions of these compounds with cyclopentadiene.

RESULTS AND DISCUSSION

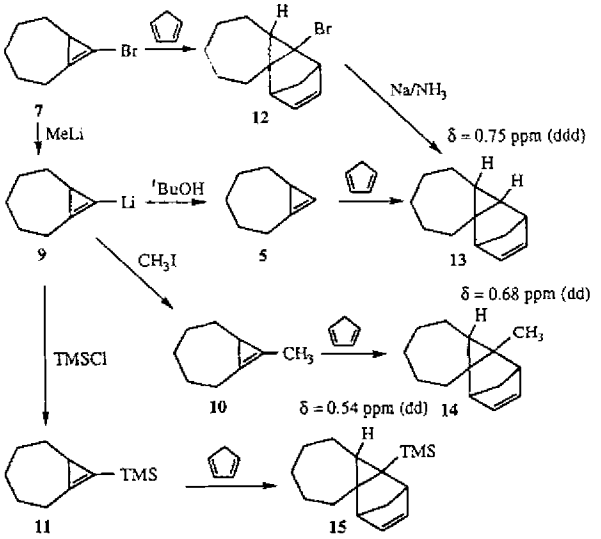
1,8,8-Tribromobicyclo[5.1.0]octane (**6**), the immediate precursor of 8-bromobicyclo[5.1.0]oct-1(8)-ene (**7**) via dehalogenation, was prepared from cycloheptanol by sequential dehydration, bromination, dehydrobromination,[10] and dibromocarbene addition. Tribromocyclopropane **6** reacted with methyllithium in ether at -78 °C to give **7** which further formed an adduct **8** with diphenylisobenzofuran in 87% isolated yield (Scheme V).

Treatment of compound **6** with 2 equiv methyl lithium generated cyclopropenyl anion **9**, which further reacted with *tert*-butyl alcohol, methyliodide, and trimethylsilylchloride to produce bicyclo[5.1.0]oct-1(8)-ene (**5**), 8-methylbicyclo[5.1.0]oct-1(8)-ene (**10**), and 8-trimethylsilylbicyclo-[5.1.0]oct-1(8)-ene (**11**), respectively. Cyclopropenes **7**, **5**, **10**, and **11** were trapped with cyclopentadiene to give the corresponding [4+2] cycloadducts (Scheme VI).

Scheme V



Scheme VI



In principle, four isomers (two *trans*-fused and two *cis*-fused) can be formed in the Diels-Alder reactions of these 1,3-fused bicyclic cyclopropenes with cyclopentadiene (Fig. 1), but only one of them was formed in each of these reactions and identified to be **12**, **13**, **14**, and **15**, respectively. Because the *trans*-fused bicyclo[n.1.0]alkanes are unstable when $n \leq 5$, these Diels-Alder reactions can not generate *trans*-fused adducts (exo-endo and endo-endo, endo-addition from the view of the cyclooctene). In order to understand the stereochemistry of these compounds, we compared the ^{1}H NMR spectra of these adducts with *endo*- and *exo*-tricyclo[3.2.1.$0^{2,4}$]oct-6-enes (Fig. 2).[11] The chemical shifts of the proton at cyclopropane (the highest field exclusive of TMS group) of **13**, **14**, and **15** were 0.75 (ddd, 1H, J = 12, 6, 2 Hz), 0.68 (dd, 1H, J = 12, 6 Hz), and 0.54 ppm (dd, 1H, J = 14, 2 Hz), respectively. When compared with

endo- and *exo*-tricyclo[3.2.1.$0^{2,4}$]oct-6-enes, these three adducts were endo-exo isomers (endo-addition from the view of the cyclopropene and exo-addition from the view of the cyclooctene).

Because compound **12** contains the electron-withdrawing atom (Br) at cyclopropane, it is difficult to distinguish between the exo-exo and endo-exo isomers using the chemical shifts of the proton at cyclopropane. In order to assign the stereochemistry of **12**, this adduct was reduced by using sodium in liquid ammonia and compound **13** was obtained. According to this result, we can prove that the stereochemistry of the compound **12** is also an endo-exo configuration. Because the C-C bond of cyclopropene is intermediate in character between σ and π,[12,13] the stereoselectivity of these Diels-Alders reactions follows the endo rule.

We have demonstrated an easy way to prepare a series of 8-substituted bicyclo[5.1.0]oct-1(8)-enes. The stereoselectivity of the Diels-Alder reactions of these 1,3-fused bicyclic cyclopropenes with cyclopentadiene is similar to cyclopropene itself, and these reactions only generate endo-exo products. It has been shown that the Diels-Alder reactions of cycloprepenes with furans produce two stereoisomers and with cyclopentadiene only one stereoisomeric product.

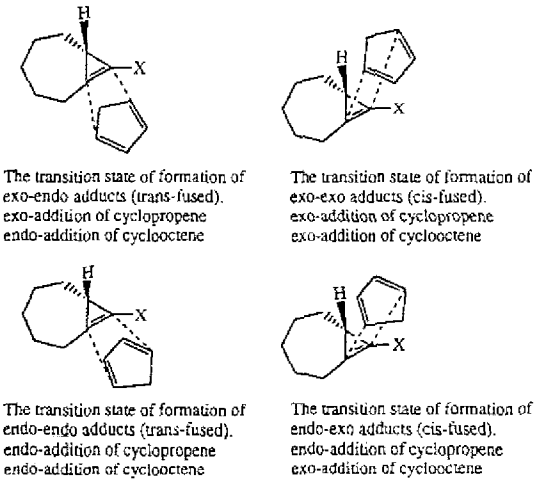


Fig. 1. The transition states of the Diels-Alder reactions of bicyclo[5.1.0]oct-1(8)-enes with cyclopentadiene.

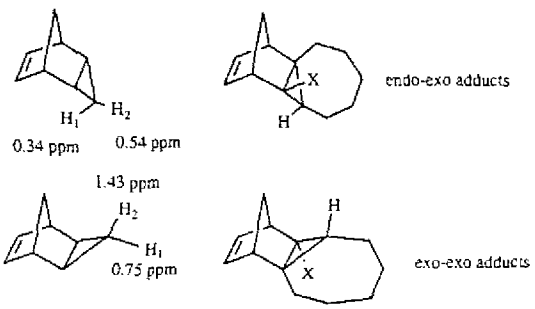


Fig. 2. The chemical shifts of the proton at cyclopropanes.

EXPERIMENTAL SECTION

Melting points were determined on a Fargo MP-1D and are uncorrected. Proton and carbon-13 NMR spectra were measured with a Bruker AC-300 NMR spectrometer in $CDCl_3$ solution, with $CHCl_3$ as the internal standard. Chemical shifts (δ) are expressed in ppm downfield from tetramethylsilane. Coupling constants are expressed in hertz. Infrared spectra were recorded on a Beckman Acculab TM1 spectrophotometer. Mass spectra and high resolution mass spectra were recorded on a JOEL-JMS-SX/SX 102A. HPLC was carried out with a Lichrosorb (Merck) column. Silica gel (70-230 mesh) for column chromatography and silica gel (230 mesh) for flash chromatography are from E. Merck. Solvents are of reagent grade.

Synthesis of 1,8,8-Tribromobicyclo[5.1.0]octane (6)

A modification of the previously reported procedure is used.[9] A suspension of 1-bromocyclooctene (10.0 g, 52.9 mmol) and 30 mL bromoform, 30 mL of 50% of sodium hydroxide, and 0.1 g of *n*-tetrabutylammonium bromide were placed in a 100 mL flask. The mixture was stirred for 24 h at room temperature, and then 25 mL of methylene chloride and 30 mL of water were added. The water layer was extracted with methylene chloride (3 × 25 mL). The combined organic solution was washed with water and brine and dried over anhydrous magnesium sulfate. Filtration and distillation gave **6** (80-84 °C, 1.5 torr, 13.9 g, 76%). Compound **6**: IR (neat, cm^{-1}) 2924, 2852, 1455, 1441, 1168, 1104, 975, 775, 735, 705; ^1H NMR ($CDCl_3$): δ 2.56-2.48 (m, 1H), 2.32-2.22 (m, 1H), 2.05-1.88 (m, 6H), 1.64-1.45 (m, 1H), 1.35-1.17 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 50.5 (C), 44.8 (C), 44.5 (CH), 39.7 (CH_2), 31.4 (CH_2), 30.0 (CH_2), 227.7 (CH_2), 26.9 (CH_2); MS *m/z* (%): 350 (M^+ + 6, 0.37), 270 (M^+, 5.96), 191 (100); HRMS calcd. for $C_8H_{11}Br_3$ *m/z* 343.8410, found 343.8410.

Synthesis and Trapping of 8-Bromobicyclo[5.1.0]oct-1(8)-ene (7) with Diphenylisobenzofuran

To a solution of compound **6** (1.10 g, 3.17 mmol) and diphenylisobenzofuran (1.35 g, 5.0 mmol) in 5 mL dry ether at -78 °C was added methyl lithium (10 mL, 1.5 M) in ether over 10 min. The mixture was stirred for 20 min, allowed to warm to room temperature, and stirred 6 h. Water was

added, and the mixture was extracted with ether (3 × 25 mL). The ethereal solution was dried, concentrated, and chromatographed to give **8** (1.28 g, 87%, mp 155.8-156.0 °C). Compound **8**: IR (neat, cm^{-1}): 2937, 2914, 2855, 1636, 1604, 1459, 1300, 986, 970, 912, 765, 750, 689; ^1H NMR ($CDCl_3$): δ 7.82-7.77 (m, 4H), 7.67-7.64 (m, 1H), 7.50-7.39 (m, 6H), 7.31-7.25 (m, 2H), 2.84-2.78 (m, 1H), 2.29-2.23 (m, 1H), 1.96-1.89 (m, 1H), 1.79-1.76 (m, 2H), 1.65-1.59 (m, 1H), 1.51-1.15 (m, 6H); ^{13}C NMR ($CDCl_3$): δ 149 (C), 147.1 (C), 136.3 (C), 134.2 (C), 129.6 (CH), 128.5 (CH), 128.4 (CH), 128.2 (CH), 126.9 (CH), 126.4 (CH), 126.2 (CH), 122.9 (CH), 121.4 (CH), 90.6 (C), 89.5 (C), 62.0 (C), 42.2 (CH_2), 34.8 (CH), 32.9 (CH_2), 29.9 (CH_2), 28.2 (CH_2), 27.5 (CH_2), 27.3 (C); MS *m/z* (%): 458 (M^+ + 2, 0.39), 456 (M^+, 0.40), 377 (100), 270 (18), 105 (30); HRMS calcd. for $C_{28}H_{25}BrO$ *m/z* 456.1090, found 456.1098.

Synthesis and Trapping of 8-Bromobicyclo[5.1.0]oct-1(8)-ene (7) with Cyclopentadiene

To a solution of compound **6** (1.07 g, 3.08 mmol) in 5 mL dry ether at -78 °C was added methyl lithium (2.5 mL, 1.5 M) in ether over 5 min. The mixture was stirred for 20 min and allowed to warm to -40 °C and stirred 6 h. Cyclopentadiene (10 mL) was added and the mixture was stirred 4 hr. Water was added, and the mixture was extracted with ether (3 × 25 mL). The ethereal solution was dried, concentrated, and chromatographed to give **12** (0.64 g, 82%). Compound **12**: IR (neat, cm^{-1}): 2917, 2848, 1640, 1450, 960, 823, 790, 736; ^1H NMR ($CDCl_3$): δ 5.97-5.89 (m, 2H), 3.13-3.10 (m, 1H), 2.65-2.63 (m, 1H), 2.02 (d, 1H, *J* = 7 Hz) 1.89-1.61 (m, 6H), 1.39-1.19 (m, 6H); ^{13}C NMR ($CDCl_3$): δ 135.1 (CH), 132.0 (CH), 59.3 (CH_2), 57 (C), 56 (CH), 51.0 (CH), 39.6 (CH), 32.2 (CH_2), 32.1 (C), 31.9 (CH_2), 29.4 (CH_2), 28.3 (CH_2), 28.0 (CH_2); MS *m/z* (%): 254 (M^+ + 2, 11), 252 (M^+, 11), 173 (81), 131 (56), 117 (77), 91 (100); HRMS calcd. for $C_{13}H_{17}Br$ *m/z* 252.0514, found 252.0515.

Synthesis and Trapping of Bicyclo[5.1.0]oct-1(8)-ene (5) with Cyclopentadiene

To a solution of compound **6** (1.12 g, 3.23 mmol) in 5 mL dry ether at -78 °C was added methyl lithium (6.5 mL, 1.5 M) in ether over 30 min and then 1.0 mL *tert*-butyl alcohol was added. The mixture was stirred for 20 min, cyclopentadiene (10 mL) was added, and the mixture was allowed to warm to -40 °C and stirred 6 h. Water was added, and the mixture was extracted with ether (3 × 25 mL). The ethereal solution was dried, concentrated, and chromatographed to give **13** (0.44 g, 78%). Compound **13**: IR (neat, cm^{-1}): 2917, 2848, 1466, 1321, 900, 824, 747, 651; ^1H NMR ($CDCl_3$): δ 5.82-5.80 (m, 1H), 5.75-5.72 (m, 1H), 2.80-2.75 (m, 1H), 2.53-2.48 (m, 1H), 2.30-0.85 (m, 13H), 0.75 (ddd, 1H, *J* = 12, 6, 2 Hz); ^{13}C NMR ($CDCl_3$): δ 132.4 (CH), 131.1 (CH), 61.4 (CH_2), 49.6 (CH), 44.1 (CH), 34.9 (CH), 34.0 (CH_2), 32.5 (CH_2), 30.0 (CH_2), 29.6 (C), 29.2 (CH_2), 29.0 (CH_2), 28.3 (CH); MS *m/z* (%): 174 (M^+, 29), 131 (43), 115 (33), 91 (100); HRMS calcd. for $C_{13}H_{18}$ *m/z* 174.1409, found 174.1415.

Synthesis and Trapping of 8-Methylbicyclo[5.1.0]oct-1(8)-ene (10) with Cyclopentadiene

To a solution of compound **6** (1.11 g, 3.20 mmol) in 5 mL dry ether at -78 °C was added methyl lithium (6.5 mL, 1.5 M) in ether over 30 min and then 0.2 mL methyl iodide (3.20 mmol) was added. The mixture was stirred for 1 hr and cyclopentadiene (10 mL) was added. The mixture was then allowed to warm to -40 °C and stirred 6 h. Water was added, and the mixture was extracted with ether (3 × 25 mL). The ethereal solution was dried, concentrated, and chromatographed to give **14** (0.51 g, 85%). Compound **14**: IR (neat, cm^{-1}): 2914, 1652, 1567, 1449, 933, 854, 733; ^1H NMR ($CDCl_3$): δ 5.84-5.81 (m, 2H), 2.49-2.48 (m, 2H), 1.75-1.11 (m, 15H), 0.68 (dd, 1H, *J* = 12, 6 Hz); ^{13}C NMR ($CDCl_3$): δ 132.8 (CH), 131.6 (CH), 58.8 (CH_2), 52.2 (CH), 51.0 (CH), 36.7 (CH), 32.8 (CH_2), 30.3 (C), 29.8 (CH_2), 29.6 (CH_2), 29.0 (CH_2), 26.9 (C), 26.7 (CH_2), 13.7 (CH_3); MS *m/z* (%): 188 (M^+, 20), 174 (23), 145 (28), 131 (51), 117 (65), 105 (45), 91 (100); HRMS calcd. for $C_{14}H_{20}$ *m/z* 188.1365, found 188.1366.

Synthesis and Trapping of 8-Trimethylsilylbicyclo-[5.1.0]oct-1(8)-ene (11) with Cyclopentadiene

To a solution of compound **6** (1.06 g, 3.05 mmol) in 5 mL dry ether at -78 °C was added methyl lithium (6.5 mL, 1.5 M) in ether over 30 min and then trimethylsilyl chloride (0.45 mL, 3.54 mmol) was added. The mixture was stirred for 1 hr and cyclopentadiene (10 mL) was added. The mixture was then allowed to warm to -40 °C and stirred 6 h. Water was added, and the mixture was extracted with ether (3 × 25 mL). The ethereal solution was dried, concentrated, and chromatographed to give **15** (0.51 g, 85%). Compound **15**: IR (neat, cm^{-1}): 2955, 2916, 2848, 1566, 1448, 875, 737; ^1H NMR ($CDCl_3$): δ 5.86-5.84 (m, 1H), 5.61-5.58 (m, 1H), 2.71-2.69 (m, 1H), 2.43-2.42 (m, 1H), 1.84-1.09 (m, 12H), 0.52 (dd, 1H, *J* = 14, 2 Hz), 0.13 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 139.1 (CH), 129.9 (CH), 60.0 (CH_2), 49.8 (CH), 48.7 (CH), 38.9 (CH), 36.8 (C), 32.3 (CH_2), 32.0 (CH_2), 30.2 (CH_2), 29.0 (CH_2), 28.3 (CH_2), 18.8 (C), 1.1 (CH_3); MS *m/z* (%): 246 (M^+, 44), 231 (10), 172 (68), 129 (31), 117 (26), 91 (47), 73 (100); HRMS calcd. for $C_{14}H_{26}Si$ *m/z* 246.1804,

found 246.1810.

Reduction of Compound 12

Sodium (0.52 g, 22.7 mmol), 20 mL of ether, and 10 mL of ammonia were placed into a 3-neck 100 mL flask which was fitted with an equilibrating addition funnel, a 50 mL flask containing 1.00 g of ammonium chloride connected by a rubber tube, a nitrogen inlet, and a magnetic stirrer. The mixture was cooled to -78 °C for 0.5 hr and then the addition funnel was charged with **12** (0.52 g, 2.05 mmol) in 5 mL of ether. Compound **12** was added dropwise. After the addition was completed, the mixture was refluxed for 4 hr. Solid ammonium chloride was added until the blue color was discharged. Hexanes (30 mL) were added, and the ammonia was allowed to evaporate. The organic solution was dried, concentrated, and chromatographed to give compound **13** (0.35 g, 98%).

ACKNOWLEDGMENT

Financial support from the National Science Council of the Republic of China (NSC 86-2113-M-030-009) is gratefully acknowledged.

Received November 26, 1997.

Key Words

Cyclopropene; 8-Substituted bicyclo[5.1.0]oct-1(8)-ene; Bicyclo[5.1.0]oct-1(8)-ene; 8-Bromobicyclo[5.1.0]oct-1(8)-ene; 8-Methylbicyclo[5.1.0]oct-1(8)-ene; 8-Trimethylsilylbicyclo[5.1.0]oct-1(8)-ene.

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