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A New Approach to the Ring Opening Reactions of 2,7,7-Trimethyl-3,3-dibromotricyclo[4.1.1.$0^{2,4}$]octane

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The reaction of $\alpha-$pinene and dibromocarbene produced a fairly unstable product, 2,7,7-trimethyl-3,3-dibromotricyclo[4.1.1.$0^{2,4}$]octane, from which 3-bromo-7,7-dimethyl-2-methylenebicyclo[4,1,1]oct-3-ene and 3-bromo-2,7,7-trimethylbicyclo [4,1,1]octa-2,4-diene were obtained in chloroform at room temperature and in various other media and conditions. Two new compounds, 3-bromo-2,7,7-trimethylbicyclo [4.1.1]oct-3-en-2-ol and 2-(4-bromo-5-methylcyclohepta-3,5-dien-1-yl) propan-2-ol, were observed in aqueous acetone in addition to the previous two. The stability and formation mechanism of the formed products are discussed.

Introduction

It is well known that *gem*-dibromocyclopropanes are important compounds in organic synthesis and can be easily synthesized by the addition of dibromocarbene generated from bromoform in an α-elimination process to alkenes. The product of these reactions are useful intermediates in making larger rings because of the tendencies of the strained cyclopropane rings with 2 geminal halogens to the ring-opening reactions. There are numerous reviews covering the synthesis of dihalocyclopropanes and their chemistry[1−5].

The introduction of 2 geminal halogen substituents to a cyclopropane ring results in the shortening of the adjacent bonds and a lengthening of the opposite bond[6,7]. As a consequence, most often the C_2-C_3 bond is broken during the ring-opening reactions. In spite of that fact, the products formed by the addition of dibromocarbene to 5- and 6-membered rings are stable under normal conditions. For example, dibromoadducts **1**[8,9] and **3**[10] undergo ring opening reactions at higher temperatures (160-190 °C) (Scheme 1). The first step in the thermal rearrangement of *gem*-dibromocyclopropanes is a concerted, disrotatory, electrocyclic ring opening at the C_2-C_3 bond, followed by the ionization of a carbon-halogen bond (*endo*-bromide undergoes ionization in bicyclic systems). The allylic cation formed is then captured by the halide counter ion. The allylic cation can also undergo proton elimination to form 1,3-dienes. The latter process is especially favored in the presence of a base.

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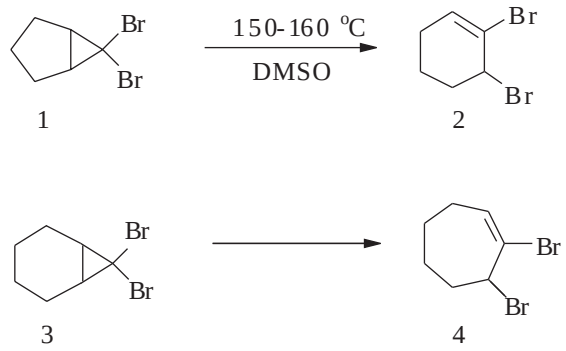
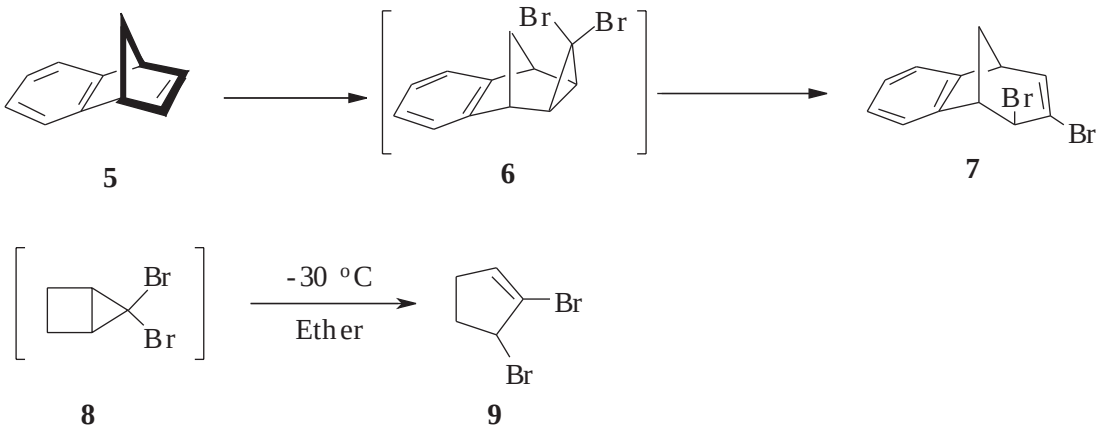


Scheme 1

If the ring strain in the alkene is increased, the dibromocarbene products added become unstable. For example, the 5-membered ring in benzonorbornadiene **5** is incorporated in a bicyclic system. 1,3-Bridging in **5** causes an additional strain in the 5-membered ring. Therefore, the dibromocarbene adduct **6**[11−13] undergoes a ring-opening reaction at room temperature to give **7** (Scheme 2).



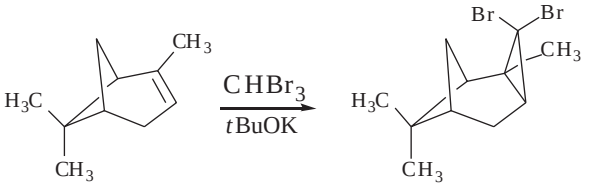
Scheme 2

If the dibromocarbene is added to smaller rings, such as a 4-membered ring, the formed dibromocarbene adduct **8**[14] becomes unstable and it undergoes a ring-opening reaction even at temperatures below room temperature. Recently, we reported that the addition of dibromocarbene products to cyclobutene rearranges the ring-opening product **9** at -30 °C[14].

In this paper, we report the dibromocarbene addition to the natural product α-pinene, which contains a highly strained skeleton, and the ring-opening reaction of the formed dibromocarbene adduct under different conditions.

Results and Discussion

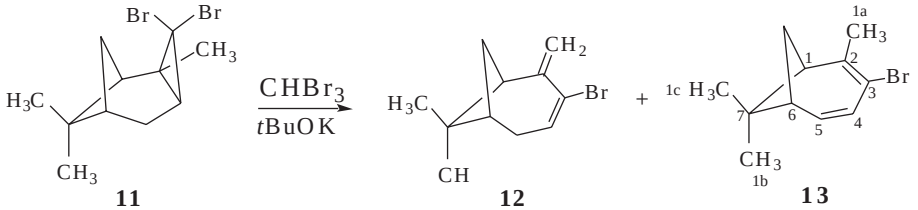
Dibromocarbene addition to α-pinene **10** was carried out by Hatem and Waegell[15−18], in which they reported that the formed cycloaddition product **11** is unstable when left at room temperature due to the strain arising from the 3-membered ring, as well as from the α–pinene skeleton (Scheme 3)[19,20].



10 **11**

Scheme 3

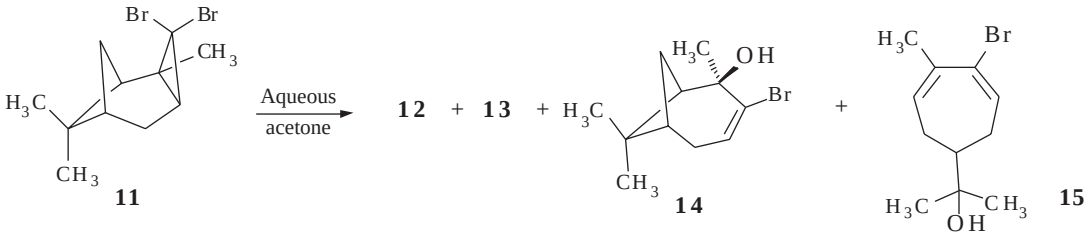
Furthermore, they reported the conversion of the non-isolable adduct **11** to the products **12** and **13** derived from the ring-opening reaction of **11** (Scheme 4)[15−18].



11 **12** **13**

Scheme 4

Compound **11,** as an example for this discussion, was synthesized from α-pinene and dibromocarbene at temperatures between -10 and -5 °C in 59% yield. The adduct **11** is a white needles crystalline compound that is stable in hexane but rearranges in polar solvents such as chloroform and acetone to give ring-opening products immediately. It was purified by crystallization in hexane, which additionally demonstrated that it is not as unstable as is mentioned in the literature[15−18].



11 **14** **15**

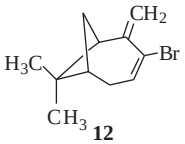
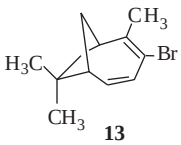
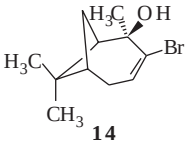
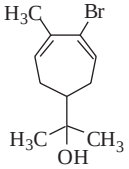
Scheme 5

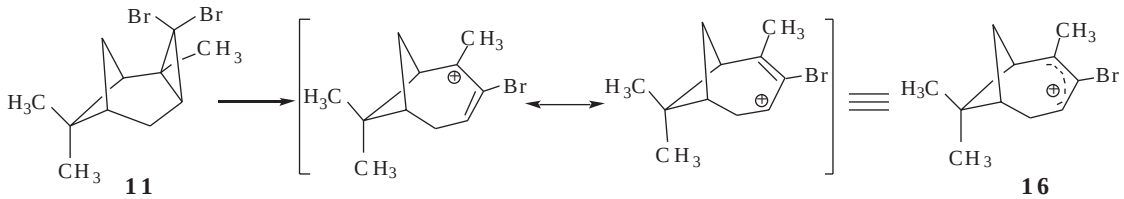
Ring-opening reactions of **11** were examined in different media and conditions. Two new products, **14** and **15,** were also isolated from the reported compounds, **12** and **13,** when the reaction was carried out in aqueous acetone. Compounds **12** and **13** were observed with results consistent with the literature in terms of ratio and yield[15−18]. The products were purified by column chromatography and identified by IR and NMR spectroscopy.

A ring-opening reaction possibly proceeds through an allylic intermediate **16** after the departure of the *endo*-geminal bromide (Scheme 6). For further stabilization, the formed allylic cation undergoes proton elimination either from the adjacent methyl group or from the methylene group to give the conjugated dienes **12** and **13,** respectively (Scheme 4). It is noteworthy that the formed allylic carbocation **16** does not undergo Wagner-Meerwein rearrangement, which would result in the further release of the strain that exists in the 4-membered ring. We assume that solvents such as chloroform and methylene chloride will not stabilize the formed tertiary carbocation **17**. The ratio of the ring-opening products **12** and **13** was always about 5:1 in the chlorinated solvents. In order to understand this ratio we performed some AM1 calculations

which showed that the *endo*-cyclic diene **13** has heat of formation 2.63 kcal/mol lower than that of the *exo*-cyclic diene **12**. The preferential formation of the kinetically less-favored isomer **12** can be attributed to activation energy lower than that necessary for the formation of the *endo*-isomer **13**. Furthermore, MM+ calculations indicate that the total strain energy of **13** is about 1.24 kcal/mol higher than that of **12.** The thermodynamic stability of **13** can be attributed to a better conjugation of the diene unit.

Table 1. Ratios and total yields of the products of the ring opening reactions of **11.**

Ring-Opening Reactions		 **12**	 **13**	 **14**	 **15**	Total yield
in $CHCl_3$	at room temp.	5 (83%)	1 (17%)	—	—	100
	at 60-70 °C	5 (83%)	1 (17%)	—	—	100
	with acid	4 (76%)	1 (19%)	—	—	95
in CH_2Cl_2	with triethylamine	10 (78%)	1 (8%)	—	—	86
	with pyridine	5 (20%)	1 (4%)	—	—	24
in aqueous acetone		1 (12%)	trace	2 (25%)	4 (49%)	86
in hexane		No reaction observed after 7 days of stirring				0



11 **16**

Scheme 6

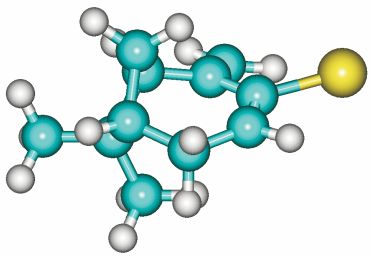
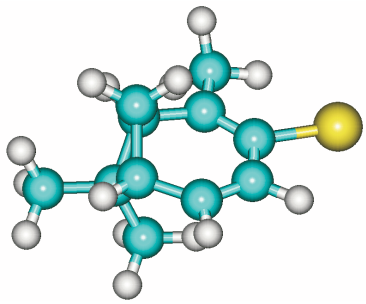
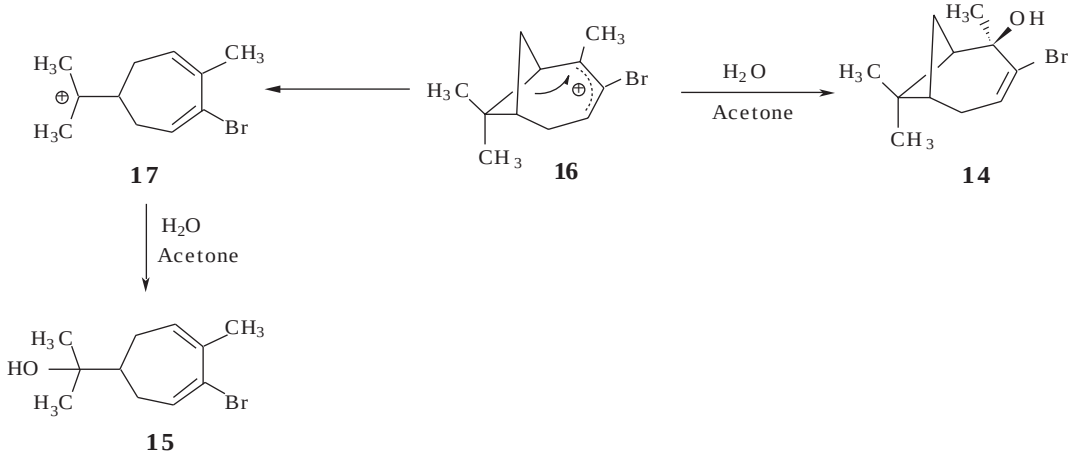
Compounds	 **12**	 **13**
Relative energies In kcal/mol	2.63	0.0

Figure 1. AM-1 optimized geometries and relative energies of the bromodienes **12** and **13**.

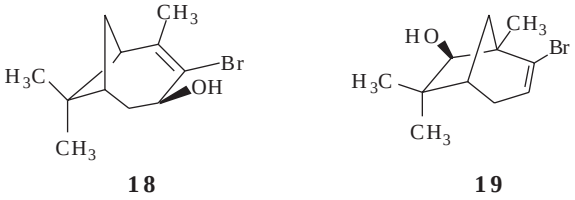
When the reaction was run in the presence of bases such as NEt_3 and pyridine, the distribution of the isomeric bromodienes **12** and **13** was unaffected. However, the yield in pyridine was reduced from 86-100%

to 24%.



Scheme 7

In aqueous acetone, however, allylic carbocation **16** either directly reacts with water to give the allylic alcohol **14** or undergoes a Wagner-Meerwein-type rearrangement to produce a 7-membered ring having a tertiary carbocation **17** that can be easily captured by water molecules to form **15** (Scheme 7).



Careful examination of the reaction mixture did not reveal any trace of the isomeric alcohol **18** or Wagner-Meerwein product **19,** which would arise from a 1,2-alkyl shift.

In summary, the title compound **11** was prepared, and its stability in different solvents was tested. It was stable in non-polar solvents. However, it underwent a ring-opening reaction in chlorinated solvents and the kinetically controlled product was formed as the major product. In polar solvents such as acetone and water, it forms additional products such as **14** and **15** were given.

Experimental

General: Melting points were determined with a Gallenkamp melting point apparatus in open capillaries and were uncorrected. The IR spectra were recorded on a Shimadzu I.R. 470 infrared spectrophotometer on NaCl disks. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker Avance 400 megahertz instrument. NMR studies included the analyses of HH-COSY, DEPT, HMQC and HMBC spectra. All of the solvents and reagents were purchased from Aldrich, Merck and Fluka, and were used without additional purification.

2,7,7-trimethyl-3,3-dibromotricyclo[4.1.1.0^{2,4}]octane 11:[15−18]6.812 g (50 mmol) of $\alpha-$pinene and 16.83 g (150 mmol) of potassium t-butoxide were mixed in 60 mL of dry hexane and placed in a 250-mL round-bottom flask. A pressure equalized dropping funnel containing 9 mL (100 mmol) of bromoform in 30 mL of dry hexane was fitted onto one of the necks of the flask. The other neck was connected to the N_2

source. The flask was placed in a salted ice bath and kept between -5 °C and -10 °C while the bromoform solution was added dropwise to a magnetically stirred mixture. After the addition was completed, the cooling bath was removed and the mixture was stirred at room temperature for 2 h. Then a small amount of water was added and the mixture was poured into brine. The organic phase was separated, and the aqueous phase was washed several times with hexane. Combined organic phases were dried over $CaCl_2$ and filtered and the hexane was evaporated. The remaining solid material was recrystallized from hexane in a deep freeze giving 9.089 g (59%) **11**: mp. 68-69.5 °C (dec).

^{1}H NMR (400 MHz, CCl_4-$CDCl_3$) δ 0.93 (s, CH_3), 1.25 (s, CH_3), 1.38 (s, CH_3), 1.59-1.63 (m, H-6), 1.64 (bd, J = 9.5 Hz, H-4), 1.8 (d, J = 14.7 Hz, H-5b), 1.84-1.89 (ddd, J = 11.5, 6.4 and 2.3 Hz, H-8g), 2.06 (t, J = 6.4 Hz, H-1), 2.15 - 2.23 (dddd, J = 2.3, 3.7, 9.5, 14.7, Hz, H-5a), 2.51 (d, J = 11.5 Hz, H-8f); ^{13}C NMR (100 MHz, CCl_4-$CDCl_3$) δ 22.4(Cb), 26.3 (C-8), 26.6 (C-5), 26.7 (Cc), 27.1 (Ca), 35.0 (C-4), 32.7 (C-7), 36.9 (C-6), 43.4 (C-2), 48.6 (C-1), 51.2 (C-3).

Opening reactions of the geminal dibromocyclopropane ring 11: The ring opening reactions of the synthesized dibromo compound **11** in different media and conditions were examined and 4 products were observed. The residue was chromatographed on silica gel (85 g), eluting first with n-hexane and then with $CHCl_3$-CH_3OH, to give the 4 products in the order **12, 13, 14** and **15.**

3-bromo-7,7-dimethyl-2-methylenebicyclo[4,1,1]oct-3-en (12): IR (KBr) ν_{max} 2944, 1673, 1587, 1456, 1366, 1228, 1075, 979, 902, 854, 809 cm^{-1}; ^{1}H NMR (400 MHz, CCl_4-$CDCl_3$) δ 0.74 (s, CH_3), 1.23 (s, CH_3), 1.51 (dt, J = 10.5 and 1.2 Hz, H-8endo), 2.0 (m, H-6), 2.34 (m, H-5), 2.40 (dt, J = 10.5 and 7.7 Hz, H-8exo), 2.73 (dd, J = 4.0 and 7.7 Hz, H-1), 5.07 (s, C=CH), 5.49 (s, C=CH), 6.26 (1H, t, J = 4.6 Hz, H-4); ^{13}C NMR (100 MHz, CCl_4-$CDCl_3$) δ 20.7 (Cb), 26.6 (C-8), 30.2 (Cc), 35.5 (C-5), 39.6 (C-7), 40.5 (C-6), 51.7 (C-1),121.9 (Ca), 123.3 (C-3), 133.4 (C-4), 145.9 (C-2);

3-Bromo-2,7,7-trimethylbicyclo[4,1,1]octa-2,4-diene (13): IR (KBr) ν_{max} 2944, 1609, 1456, 1374, 1244, 966, 928, 867, 812, 732 cm^{-1}; ^{1}H NMR (400 MHz, CCl_4-$CDCl_3$) δ 0.74 (s, CH_3), 1.15 (dd, H-8endo), 1.21 (s, CH_3), 1.96 (s, CH_3), 2.35 (dt, J = 8.3 and 4.8 Hz, H-6), 2.5 (m, H-1 and H-8exo), 5.82 (dd, J = 8.3 Hz, H-5), 6.09 (d, J =11.7 Hz, H-4); ^{13}C NMR (100 MHz, CCl_4-$CDCl_3$) δ 19.8 (C-8), 20.9 (Cb), 24.4 (C-7), 27.3 (Cc), 28.2 (Ca), 42.3 (C-6), 50.42 (C-1), 114.6 (C-3), 129.9 (C-4), 134.3 (C-5), 142.1 (C-2).

3-Bromo-2,7,7-trimethylbicyclo[4.1.1]oct-3-en-2-ol (14): IR (KBr) ν_{max} 3456, 2944, 1657, 1449, 1417, 1366, 1283, 1228, 1155, 1084, 1017, 960, 889, 838, 812 cm^{-1}; ^{1}H NMR (400 MHz, CCl_4-$CDCl_3$) δ0.91 (s, CH_3), 1.23 (s, CH_3), 1.36 (s, CH_3), 1.57 (d, J = 10.4 Hz, H-8endo), 1.9—2.0 (m, H-6), 2.20—2.31 (m, H-1, H-5 and H-8exo), 6.01 (t, J = 4.3 Hz, H-4); ^{13}C NMR (100 MHz, CCl_4-$CDCl_3$) δ 22.2 (Cb), 24.2 (C-8), 29.0 (Cc), 31.5 (Ca), 33.9 (C-5), 37.0 (C-7), 40.7 (C-6), 53.1 (C-1), 77.1 (C-2), 133.1 (C-3), 130.5 (C-4).

2-(4-Bromo-5-methylcyclohepta-3,5-dien-1-yl) propan-2-ol (15): IR (KBr) ν_{max} 3408, 2976, 1670, 1622, 1440, 1372, 1139, 937, 889, 860, 825 cm^{-1}; ^{1}H NMR (400 MHz, CCl_4-$CDCl_3$) δ 1.09 (s, 2xCH_3), 1.81 (s, CH_3), 1.91–2.03 (m, H-2 and H-7), 2.28 (qui, J = 7.2 Hz, H-1), 5.89 (dt, J = 7.4 and 1.32 Hz, H-6), 6.36 (t, J = 7.4 Hz, H-3); ^{13}C NMR (100 MHz, CCl_4-$CDCl_3$) δ 22.0 (Ca), 28.3 (Cb), 28.4 (C-7), 28.4 (Cc), 29.7 (C-2), 62.8 (C-1), 73.5 (Cd), 124.2 (C-4), 131.2 (C-6), 134.2 (C-3), 137.2 (C-5).

Ring-opening reaction of 11 in chloroform at room temperature: A solution of 110 mg (0.357 mmol) of **11** in 15 mL of $CHCl_3$ was stirred magnetically in a 25-mL flask equipped with a $CaCl_2$ tube for

keeping humidity out. After 2 h of stirring, chloroform was evaporated, obtaining a mixture of 81 mg (100 %) of **12** and **13** in a ratio of 5:1.

Ring-opening reaction of 11 in chloroform at high temperature: A solution of 200 mg (0.650 mmol) of **2** in 25 mL of $CHCl_3$ was placed in a 50-mL flask equipped with a condenser. The mixture was stirred magnetically in a water bath at 60-70 °C for 2 h. Then $CHCl_3$ was evaporated, yielding 147.6 mg (100%) of **12** and **13** in a ratio of 5:1.

Ring-opening reaction of 11 in acidic chloroform solution: A small amount of gas HBr was passed from chloroform in a 2-neck flask chilled at 0 °C in an ice bath on the plate of a magnetic stirrer. Then 185 mg (0.60 mmol) **11** was added to this medium and stirring was started immediately. Some additional HBr was passed from the reaction mixture and was allowed to warm up to room temperature. After 2 h of stirring, chloroform was evaporated and a 129 mg (95%) mixture of **12** and **13** was obtained in a ratio of 4:1.

Ring-opening reaction of 11 dichloromethane with triethylamine: To a solution of 145 mg (0.37 mmol) of **11** in 20 mL of CH_2Cl_2 in a 50 mL flask was added 2 mL of triethylamine dropwise and the mixture was stirred magnetically. CH_2Cl_2 was evaporated after 2 h of stirring and 15 mL of hexane was added to the remaining residue. The final solution was washed with a 2 M aq. HCl solution. The organic phase dried over $CaCl_2$ and hexane was evaporated after filtration, giving a 91 mg (86%) mixture of **12** and **13** in a ratio of 10:1.

Ring-opening reaction of 11 in dichloromethane in the presence of pyridine: The same procedure in the previous opening was followed, giving (24%) **12** and **13** in a ratio of 5:1.

Ring-opening reaction of 11 in aqueous acetone: 862 mg (2.8 mmol) of **11** was dissolved in a mixture of 20 mL of acetone and 10 mL of water in a 50-mL flask and stirred magnetically at room temperature. Monitoring by TLC showed that the reaction was complete in 45 min. Then acetone was evaporated and the remaining aqueous mixture was extracted with hexane (3 x 15 mL). The organic phase was dried over $MgSO_4$ and filtered and hexane was evaporated, giving a 581 mg (86%) mixture of **3**, **4**, **5** and **6** (1:trace:2:4).

Ring-opening reaction of 11 in hexane at room temperature: The opening reaction of **11** in hexane at room temperature produced no reaction in 7 days.

Acknowledgments

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