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Lewis acid-induced rearrangment of α-[bis(methylthio)methylene]-ethyl-2-styrylcyclopropylcarbinols: unexpected formation of a novel bicyclo[3.2.1]octadiene framework

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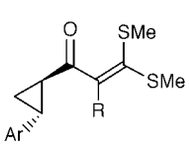
The α-[bis(methylthio)methylene]ethyl-2-styrylcyclopropylcarbinols **9a**–**c** undergo a simple but unexpected skeletal rearrangement in the presence of stannic chloride in nitromethane to afford bicyclo[3.2.1]octadiene derivatives **10a**–**c** exclusively in good yields. The structure of **10a** was conclusively elucidated by X-ray diffraction studies. A possible mechanism governing the formation of **10** is proposed.

In our earlier papers,[1–3] we have reported that the α-[bis(methylthio)methylene]alkyl 2-aryl/styrylcyclopropyl ketones of general formula **1** undergo simple acid-induced rearrangement to the corresponding cyclopentanones in moderate to excellent yields. The methodology was successfully extended for the synthesis of 11-oxosteroid precursors.[3] Also, the corresponding carbinols † obtained either by sodium borohydride reduction or by 1,2-addition of alkyl Grignard reagents to **1** underwent similar acid-assisted rearrangement to afford the corresponding cyclopentenes or the open-chain polyenes depending on the nature of the substituent or the reaction conditions.[4] In subsequent studies,[5] when a suitably oxygenated aryl ring was introduced in **1** [Ar = 3,4-$(MeO)_2C_6H_3$ or 3,4-$(OCH_2O)C_6H_3$, R = Me], the rearrangement followed an interesting tandem carbocationic cyclization to afford the corresponding cyclopent[*a*]indene framework involving intramolecular attack by the electron-rich aryl group on the intermediate cation. In continuation of these studies, we further noted that the styryl-substituted cyclopropyl ketones **2a**–**c** afforded bicyclo[3.3.0]-octenone derivatives **4a**–**c** under similar conditions *via* intramolecular trapping of initially formed (2-oxocyclopentyl)-(bismethylthio)methyl carbocation by the electron-rich styryl double bond in a cascade fashion.[6] On the other hand, the corresponding styrylcyclopropylcarbinols **5a**–**c** obtained by $NaBH_4$ reduction of the respective ketones **2a**–**c** followed a different course of rearrangement under identical conditions, yielding cyclopent[*a*]indenes **6b**,**c** (or the carbothioate **7a**) in highly stereocontrolled fashion instead of the expected bicyclo[3.3.0]octadienes **8**.[6]



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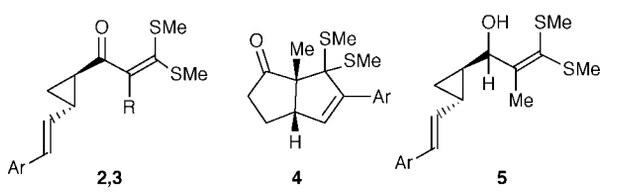
Intrigued by these studies, we further considered it of interest to examine tandem carbocationic rearrangements of the carbinols **9a**–**c** under similar conditions and, to our surprise, observed the formation of unexpected bicyclo[3.2.1]octadiene derivatives **10a**–**c** as the sole products. We herein describe this unusual rearrangement along with the probable mechanism and a few other studies in this paper.

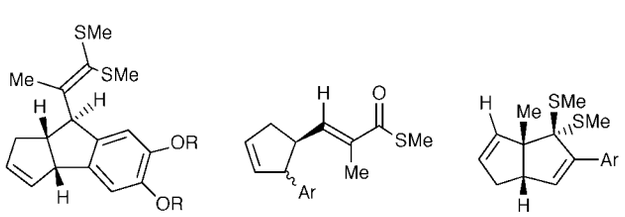
† The IUPAC name for carbinol is methanol.



2,3 **4** **5**

2-5a, Ar = 4-$MeOC_6H_4$, R = Me
b, Ar = 3,4-H_2C(O)$_2C_6H_3$, R = Me
c, Ar = 3,4-$(MeO)_2C_6H_3$, R = Me

2d, Ar = C_6H_5, R = Me
3a, Ar = 4-$MeOC_6H_4$, R = H
3b, Ar = 3,4-H_2C(O)$_2C_6H_3$, R = H



6b, R = -CH_2-
6c, R = CH_3

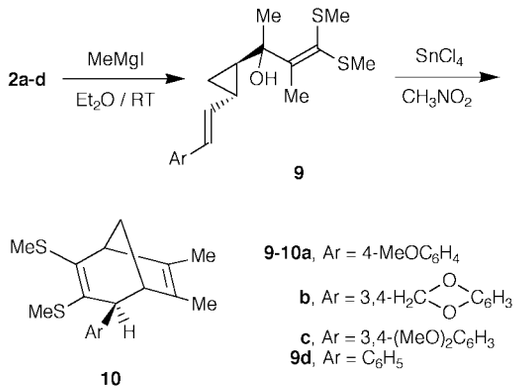
7a
Ar = 4-$MeOC_6H_4$

8

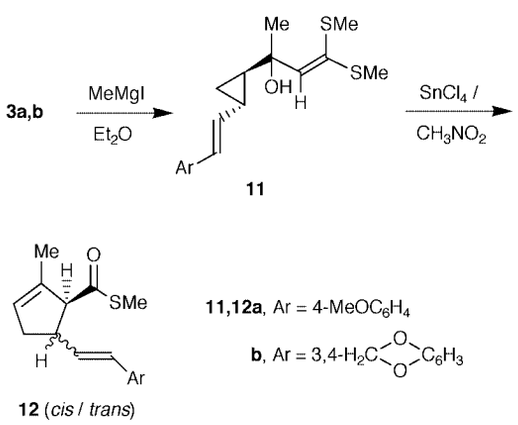
Results and discussion

The desired carbinoldithioketals **9a**–**d** were conveniently prepared by the addition of methylmagnesium iodide to the ketones **2a**–**d** in quantitative yields. Treatment of **9a** with stannic[tin(IV)]chloride in nitromethane at room temperature (7 h) followed by work-up afforded a single product which was characterized as the substituted bicyclo[3.2.1]octadiene **10a** obtained in 78% yield (Scheme 1). The structure of **10a** was established on the basis of its mass, ^1H and ^{13}C NMR spectral and X-ray crystallographic data.[7] The reaction was found to be general only for the carbinols bearing oxygenated aryl groups. Thus, the carbinols **9b** and **9c** also yielded the corresponding bicyclic dienes **10b**,**c** in comparable yields (Scheme 1) while the carbinoldithioketal **9d** (Ar = C_6H_5) failed to yield any well defined product when treated under identical conditions.

The carbinols **11a**,**b** derived from the respective ketones **3a**,**b** by addition of methyl magnesium iodide were also subjected to $SnCl_4$-induced rearrangement with a view to examining the



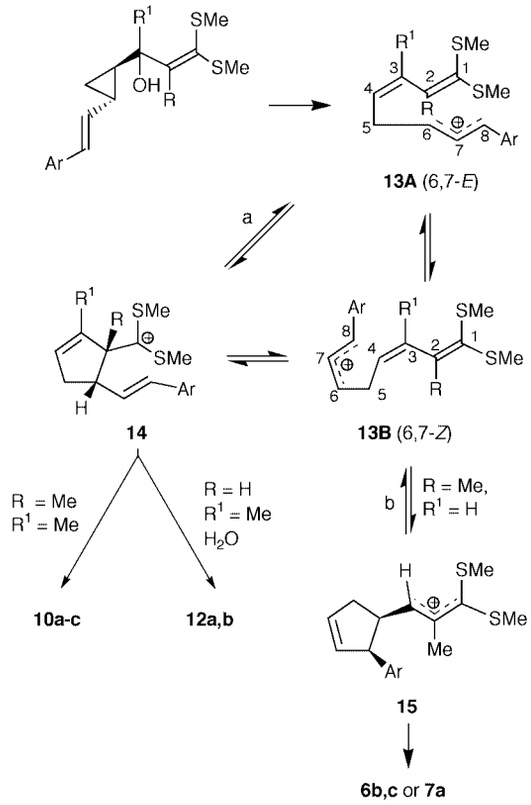
Scheme 1



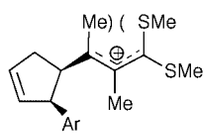
Scheme 2

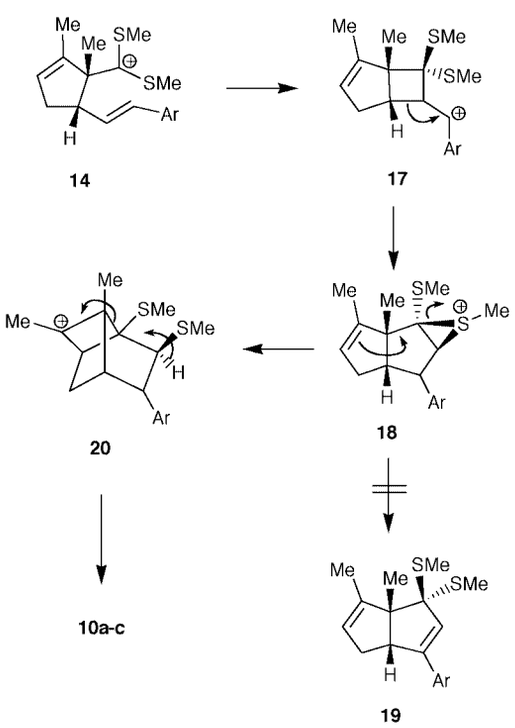
effect of the 2-methyl group on the course of reaction and product outcome (Scheme 2). Thus treatment of either **11a** or **11b** with $SnCl_4$ under the described conditions (in nitromethane or benzene) yielded only the corresponding 5-styrylcyclopent-2-enecarbothioates **12a** and **12b**, respectively, in good yields. Formation of any other rearrangement product, including the corresponding conjugated α,β-enecarbothioates by isomerization of the double bond, was not observed in these reactions.

The probable mechanistic pathways for the formation of bicyclic dienes **10a**–**c** from the carbinols **9a**–**c** and for the formation of different products from the various cyclopropyl carbinols (**5a**–**c** and **11a**,**b**) are depicted in Schemes 3 and 4. The dienylic allyl aryl carbocation **13A** (6,7-*E*) appears to be the initial intermediate formed *via* $SnCl_4$-assisted cleavage of the carbinols (**5**, **9** or **11**) and concomitant ring opening of the resulting cyclopropylalkyl carbocation (Scheme 3). The carbocation **13A** can undergo cyclization by intramolecular participation of the 1,2-double bond *via* a 5-*exo*-*trig* process to afford (cyclopent-2-enyl)(bismethylthio)methyl carbocation **14** (route *a*). The cation **13A** (6,7-*E*) exists in equilibrium with **13B** (6,7-*Z*) which can cyclize by an alternative 5-*exo*-*trig* pathway involving intramolecular participation of the 3,4-double bond, leading to the more stable 1,1-bis(methylthio)allylic carbocation **15** (route *b*). The latter pathway is followed for the carbinols **5a**–**c**, yielding the products **6b**,**c** or **7a** after subsequent rearrangement of the intermediate cation **15**. However, the corresponding carbocation **16** derived from the carbinol **9** *via* route *b* would be much less stable due to the steric interaction between bulkier methyl and methylthio groups.[8] Therefore the cation **13A** (R = R^1 = Me) from the carbinol **9** preferably cyclizes by route *a* to afford the carbocation **14** (R = R^1 = Me). The subsequent fate of **14** to give the bicyclo[3.2.1]octadienes **10** through a series of skeletal rearrangements is shown in Scheme 4. Thus the cation **14** undergoes intra-



Scheme 3





Scheme 4

molecular cyclization *via* a 4-*exo*-*trig* process followed by ring expansion to give intermediate bicyclic episulfonium ion **18** (**14** ⟶ **17** ⟶ **18**). The intermediate **18** could have reorgan-

ized itself by proton loss and episulfonium ring opening to yield the expected bicyclo[3.3.0]octadiene **19** which, however, was not detected in the reaction mixture.[9] On the other hand, **18** does undergo skeletal rearrangement by intramolecular double-bond participation and rapid ring cleavage along with proton loss *via* the tricyclic cation **20**, affording the bicyclic dienes **10** (Scheme 4). The driving force for the formation of diene **10** rather than **19** appears to be the stability of tertiary carbocation **20** and steric crowding in the bicyclic diene **19**. The absence of any bicyclic products from the carbinols **11a**,**b** under similar reaction conditions points to the importance of the 2-methyl group in these skeletal rearrangements for attaining favourable trajectory during intramolecular cyclization for the formation of the 3.2.1 bicyclic framework.

In summary we have observed an interesting carbocationic skeletal rearrangement through a series of novel, tandem termination events leading to the formation of unexpected bicyclo[3.2.1]octadienes during $SnCl_4$-induced rearrangement of the carbinols **9a**–**c**.

Experimental

Mps were determined on a Mel-Temp II (capillary method) apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 983 spectrophotometer. NMR spectra were recorded on Bruker ACF-300, JEOL 400 and Varian EM-390 spectrometers. Mass spectra were obtained on a JEOL JMS-D 300 mass spectrometer. Elemental analyses were carried out on a Heraeus CHN-O-Rapid analyzer. Single-crystal X-ray data for **10a** were collected at room temperature on an Enraf-Nonius CAD4-Mach diffractometer using graphite-monochromated Mo-Kα radiation ($\lambda = 0.71073$ Å) as described elsewhere.[10]

The cyclopropyl ketones **2a**–**d** and **3a**,**b** were prepared according to our earlier reported procedure[3,6] by cyclopropanation of the corresponding 1,1-bis(methylthio)-2-methyl/unsubstituted-7-arylhepta-1,4,6-trien-3-ones with dimethyl sulfoxonium methylide generated in the presence of phase-transfer catalyst. The spectral and analytical data for the cyclopropyl ketones **2a**–**d**[3,6] and **3a**[3] have been reported earlier whereas data for **3b** are given below. The addition of methylmagnesium iodide to ketones **2a**–**d** and **3a**,**b** to give the corresponding carbinols **9a**–**d** and **11a**,**b** were carried out according to the general procedure as described in our earlier paper.[4] The carbinols **9a**–**d** and **11a**,**b** were found to be unstable and used as such for rearrangements studies without further purification. The crude carbinols (**9a**–**d** and **11a**,**b**) were characterized by their IR and ^{1}H NMR spectra; the data for one of the carbinols, **11a** are given below.

2,2-Bis(methylthio)ethenyl 2-[2-(3,4-methylenedioxyphenyl)-ethenyl]cyclopropyl ketone 3b

Colorless crystals (81% yield); mp 114–115 °C (from chloroform–hexane); IR (KBr) ν_{max} 1645, 1495 cm^{-1}; ^{1}H NMR (90 MHz; $CDCl_3$) δ 0.76–1.06 (m, 1H, CH), 1.35–1.66 (m, 1H, CH), 1.77–2.20 (m, 2H, CH_2), 2.40 (s, 3H, SCH_3), 2.44 (s, 3H, SCH_3), 5.52 (dd, *J* 9, 16 Hz, 1H, =CH), 5.87 (s, 2H, methylenedioxy), 6.08 (s, 1H, =CH), 6.35 (d, *J* 16 Hz, 1H, =CH), 6.63 (m, 2H, ArH), 6.72 (m, 1H, ArH); MS (*m*/*z*, %) 334 (M$^+$, 16%), 319 (100), 219 (38) [Calc. for $C_{17}H_{18}O_3S_2$ (334.46): C, 61.05; H, 5.42. Found: C, 61.21; H, 5.49%].

1-{2-[2-(4-Methoxyphenyl)ethenyl]cyclopropyl}-1-methyl-3,3-bis(methylthio)prop-2-en-1-ol 11a

Viscous liquid (97% yield); IR (neat) ν_{max} 3419, 1608, 1510, 1247 cm^{-1}; ^{1}H NMR (300 MHz; $CDCl_3$) δ 0.62–0.65 (m, 1H, CH), 0.94–0.96 (m, 1H, CH), 1.10–1.20 (m, 2H, CH_2), 1.37 (s, 3H, CH_3), 2.28 (s, 3H, SCH_3), 2.37 (s, 3H, SCH_3), 3.78 (s, 3H, OCH_3), 4.44 (s, 1H, OH), 5.61–5.68 (m, 1H, =CH), 6.06 (s, 1H, =CH), 6.34 (d, *J* 16 Hz, 1H, =CH), 6.83 (d, *J* 9 Hz, 2H, ArH), 7.23 (d, *J* 9 Hz, 2H, ArH).

General procedure for $SnCl_4$-induced rearrangement of the carbinols 9a–c and 11a,b

To a solution of a carbinol **9** or **11** (30 mmol) in nitromethane (30 mL) was added $SnCl_4$ (1.5 mL, 0.1 mol) at 0 °C and the reaction mixture was stirred at room temperature for 3 h. It was then poured into aq. $NaHCO_3$ (100 mL) and extracted with chloroform (2 × 50 mL). The combined chloroform extracts were washed with water (2 × 50 mL), dried (Na_2SO_4) and evaporated to give a viscous residue which was purified by column chromatography on silica gel using hexane as eluent.

4-(4-Methoxyphenyl)-2,3-bis(methylthio)-6,7-dimethylbicyclo[3.2.1]octa-2,6-diene 10a. Colorless crystals (78% yield); mp 66–67 °C (from hexane); IR (KBr) ν_{max} 2919, 1606, 1503 cm^{-1}; ^{1}H NMR (200 MHz; $CDCl_3$) δ 1.68–1.96 (m, 2H, merged with CH_3 and SCH_3 signals), 1.76 (s, 3H, CH_3), 1.78 (s, 3H, CH_3), 1.92 (s, 3H, SCH_3), 2.38 (s, 3H, SCH_3), 2.47 (d, *J* 4 Hz, 1H, H-5), 2.98 (d, *J* 4 Hz, 1H, H-4), 3.44 (s, 1H, H-1), 3.79 (s, 3H, OCH_3), 6.86 (d, *J* 9 Hz, 2H, ArH), 7.17 (d, *J* 9 Hz, 2H, ArH); ^{13}C NMR (50 MHz; $CDCl_3$) δ_C 11.89, 13.64, 15.49, 15.73, 35.38, 47.54, 48.22, 54.34, 55.61, 114.47, 126.35, 129.85, 133.66, 136.94, 143.21, 143.57, 158.44; MS (*m*/*z*, %) 332 (M$^+$, 70.4%), 317 (13.2), 237 (100) [Calc. for $C_{19}H_{24}OS_2$ (332.51): C, 68.63; H, 7.27%. Found: C, 68.28; H, 6.89%].

6,7-Dimethyl-4-(3,4-methylenedioxyphenyl)-2,3-bis(methylthio)bicyclo[3.2.1]octa-2,6-diene 10b. Colorless crystals (72% yield); mp 102–103 °C (from hexane); IR (KBr) ν_{max} 2922, 1482, 1433 cm^{-1}; ^{1}H NMR (300 MHz; $CDCl_3$) δ 1.75–1.94 (m, 2H, merged with CH_3 and SCH_3 signals), 1.75 (s, 3H, CH_3), 1.78 (s, 3H, CH_3), 1.94 (s, 3H, SCH_3), 2.38 (s, 3H, SCH_3), 2.42 (d, *J* 4.8 Hz, 1H, H-5), 2.97 (d, *J* 4.8, 1H, H-4), 3.39 (s, 1H, H-1), 5.93 (s, 2H, OCH_2O), 6.69–6.77 (m, 3H, ArH); ^{13}C NMR (75 MHz; $CDCl_3$) δ_C 11.35, 13.12, 14.94, 15.09, 34.73, 47.39, 47.42, 53.71, 100.65, 107.96, 108.83, 121.24, 125.13, 132,98, 138.14, 142.67, 143.38, 145.70, 147.41; MS (*m*/*z*, %) 346 (M$^+$, 90%), 299 (10.3), 251 (100) [Calc. for $C_{19}H_{22}O_2S_2$ (346.50): C, 65.85; H, 6.40%. Found: C, 65.71; H, 6.44%].

4-(3,4-Dimethoxyphenyl)-6,7-dimethyl-2,3-bis(methylthio)-bicyclo[3.2.1]octa-2,6-diene 10c. Viscous liquid (68% yield); IR (CCl_4) ν_{max} 2916, 1610, 1501 cm^{-1}; ^{1}H NMR (200 MHz; $CDCl_3$) δ 1.68–1.94 (m, 2H, merged with CH_3 and SCH_3 signals), 1.73 (s, 3H, CH_3), 1.74 (s, 3H, CH_3), 1.90 (s, 3H, SCH_3), 2.39 (s, 3H, SCH_3), 2.46 (d, *J* 4 Hz, 1H, H-5), 2.98 (d, *J* 4, 1H, H-4), 3.42 (s, 1H, H-1), 3.86 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 6.76–6.90 (m, 3H, ArH); MS (*m*/*z*, %) 362 (M$^+$, 22.2%), 267 (27.9), 151 (100) [Calc. for $C_{20}H_{26}O_2S_2$ (362.54): C, 66.27; H, 7.20%. Found: C, 66.49; H, 7.36%].

***S*-Methyl 5-(4-methoxystyryl)-2-methylcyclopent-2-enecarbothioate 12a.** Viscous liquid consisting of a 1.5:1 mixture of diastereomers (60% yield); IR (CCl_4) ν_{max} 2920, 1668, 1595, 1498 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 2.24 (s, 3H, CH_3), 2.31 (s, 3H, SCH_3), 2.46–2.58 (m, 1H), 2.68–2.76 (m, 1H), 3.26–3.37 (m, 1H), 3.47–3.51 (m, 0.6H), 3.58–3.63 (m, 0.4H), 3.78 (s, 1.2H, OCH_3), 3.79 (s, 1.8H, OCH_3), 5.55–5.56 (m, 0.6H, olefinic H), 5.68 (br s, 0.4H, olefinic H), 6.05–6.13 (m, 1H, olefinic H), 6.33–6.40 (m, 1H, olefinic H), 6.80–6.85 (m, 2H, ArH), 7.22–7.30 (m, 2H, ArH); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 11.63, 11.71, 15.33, 15.85, 38.38, 38.75, 47.33, 47.68, 55.27, 67.39, 69.35, 113.93, 127.36, 127.64, 128.19, 129.18, 129.78, 130.03, 130.28, 130.44, 130.52, 130.59, 137.09, 138.18, 158.88, 158.94, 200.08, 201.55; MS (*m*/*z*, %) 288 (M$^+$, 20%), 213 (48.2),

134 (100) [Calc. for $C_{17}H_{20}O_2S$ (288.41): C, 70.80; H, 6.99%. Found: C, 70.97; H, 7.08%].

***S*-Methyl 2-methyl-5-(3,4-methylenedioxystyryl)cyclopent-2-enecarbothioate 12b.** Viscous liquid consisted of a 11 : 9 mixture of diastereomers (65% yield); IR (CCl_4) ν_{max} 2915, 1662, 1474, 1432 cm^{-1}; ^1H NMR (200 MHz; $CDCl_3$) δ 2.15 (s, 3H, CH_3), 2.22 (s, 3H, SCH_3), 2.39–2.44 (m, 1H), 2.56–2.68 (m, 1H), 3.17–3.26 (m, 1H), 3.37 (br s, 0.45H), 3.48–3.53 (m, 0.55H), 5.45 (br s, 0.55H), 5.58 (br s, 0.45H), 5.81 (s, 2H, OCH_2O), 5.90–6.02 (m, 1H, olefinic H), 6.19–6.21 (m, 0.55H), 6.27–6.28 (m, 0.45H), 6.62–6.64 (m, 2H, ArH), 6.76–6.80 (m, 1H, ArH); ^{13}C NMR (50 MHz; $CDCl_3$) δ_C 12.08, 15.74, 16.24, 38.74, 39.12, 47.60, 47.96, 67.76, 69.68, 101.35, 105.94, 106.06, 108.59, 121.08, 128.46, 129.84, 130.12, 131.06, 131.34, 132.10, 132.33, 137.50, 138.56, 147.32, 148.37, 200.20, 201.64; MS (*m*/*z*, %) 302 (M^+, 52.8%), 228 (72.4), 136 (100) [Calc. for $C_{17}H_{18}O_3S$ (302.39): C, 67.52; H, 6.00%. Found: C, 67.38; H, 6.09%].

Acknowledgements

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7 The X-ray crystallographic structure for **10a** was unfortunately not of sufficient quality to publish, but did confirm the general connectivity. We are attempting a low-temperature study which will be reported elsewhere.
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9 Our attempts to obtain bicyclo[3.3.0]octadiene derivatives **8** or **19** from the respective carbinols **5** or **9** under varying conditions using different Lewis/protic acids were not successful.
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