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Stereospecific Retro-Diels–Alder Fragmentation of Stereoisomeric 3-Methoxy- and 3,6-Dialkoxytricyclo[6.2.2.0^{2,7}]dodeca-9-enes upon Electron Ionization

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The stereoisomeric 2,3-*cis*- and 2,3-*trans*-3-methoxytricyclo[6.2.2.0^{2,7}]dodeca-9-enes *endo*-1 and *exo*-1 (*endo* and *exo* refer to the methoxy group) exhibit different behavior under electron ionization (EI): the *m*/*z* 80 cyclohexa-1,3-diene radical cation formed by retro-Diels–Alder (RDA) fragmentation is the most abundant ion in the 70 eV mass spectrum of *endo*-1, whereas *exo*-1 exhibits preferential formation of an *m*/*z* 111 ion corresponding to the *O*-methylcyclohex-2-en-1-one structure (ion a), which may be obtained by an RDA fragmentation accompanied by a hydrogen migration (RDA − H), with the charge retained in the dienophile moiety. A similar effect has been observed in the EI mass spectra of the four stereoisomeric 3-ethoxy-6-methoxytricyclo[6.2.2.0^{2,7}]dodeca-9-enes 2; *endo*-2, with both *endo*-alkoxy groups, gives rise to the most abundant *m*/*z* 80 ion via the regular RDA process, whereas the other three stereoisomers, with at least one *exo*-alkoxy group, afford the most abundant *m*/*z* 155 ions via the RDA − H process, which correspond to the 4-alkoxy-substituted analogues of the *m*/*z* 111 ion a obtained from *exo*-1. Collision-induced dissociation measurements and a deuterium labeling study showed that the *m*/*z* 155 ions obtained from the two *trans*-diethers (*trans*-2a and *trans*-2b) have isomeric structures b and c (a mixture of b and c is formed in the case of *exo*-2), and that the highly stereospecific RDA − H process involves a double hydrogen transfer, one from position 4 to the diene moiety and the other from position 3 to 4. The above stereospecific behavior shows that the thermodynamically favored RDA − H process has a higher activation energy than the regular RDA fragmentation in the case of *endo*-1 and *endo*-2. In all other isomers, which have at least one *exo*-alkoxyl, the activation energy of the RDA − H process is lower than that of RDA. The latter effect is ascribed to anchimeric assistance of the alkoxyl in the initial C—C bond cleavage in the stepwise RDA − H process, which is possible only when at least one alkoxyl has the *exo* configuration. © **1998 John Wiley & Sons, Ltd.**

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KEYWORDS: retro-Diels–Alder fragmentation; hydrogen transfer; stereospecific fragmentation; electron ionization; anchimeric assistance; collision-induced dissociation; deuterium labeling; ethers

INTRODUCTION

Retro-Diels–Alder (RDA) fragmentation is one of the most important processes used in mass spectrometric structural analysis of systems containing a double bond in a six-membered ring. The mechanism of the RDA fragmentation of organic gas-phase ions has been explored since the early days of organic mass spectrometry. The question that has been posed was whether this fragmentation takes place by a single-step concerted mechanism, analogous to the ground-state thermal process occurring in neutral molecules in the condensed phase, or whether it is a stepwise dissociation.[1–3] Stereochemistry has been used by numerous groups as a probe in this problem under electron ionization (EI) and chemical ionization (CI) conditions.[1–4]

Processes related to the RDA dissociation involving hydrogen transfers between the diene and dienophile moieties have been also reported in systems containing one or two carbonyl groups.[2] Three groups of such processes, which involve migration of one or two hydrogen atom from the diene to the dienophile upon EI, are (i) RDA − 2H giving rise to $[\text{diene} - 2\text{H}]^{+\bullet}$; (ii) RDA + H giving rise to $[\text{dienophile} + \text{H}]^{+}$, and (iii) RDA + 2H affording $[\text{dienophile} + 2\text{H}]^{+\bullet}$. We are not aware of a report of an RDA − H process involving migration of a hydrogen atom from the dienophile to the diene moiety, which would give rise to a $[\text{dienophile} - \text{H}]^{+}$ cation.

In the course of our investigation of the CI mass spectrometry of some bi- and tricyclic ethers[4,5] we observed an unexpected highly stereospecific RDA and RDA − H fragmentation behavior under EI conditions (the latter affording a $[\text{dienophile} - \text{H}]^{+}$ cation), that

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sheds some light on the problem of the concertedness of these processes. The results of this investigation are the subject of the present paper.

RESULTS AND DISCUSSION

The stereoisomeric 2,3-*cis*- and 2,3-*trans*-3-methoxytricyclo[6.2.2.0^{2,7}]dodeca-9-enes *endo*-**1** and *exo*-**1** (*endo* and *exo* refer to the methoxy group) exhibit different behavior under electron ionization (see Fig. 1). The expected *m/z* 80 cyclohexa-1,3-diene radical cation formed by RDA fragmentation is the most abundant ion in the 70 eV mass spectrum of *endo*-**1**. This ion is much less important in the mass spectrum of *exo*-**1** (relative abundance 44%), which affords the *m/z* 111 ion as the most abundant species. The latter ion corresponds to the *O*-methylcyclohex-2-en-1-one structure (ion **a**), which may be obtained by an RDA fragmentation accompanied by a hydrogen migration (RDA − H), with the charge retained in the dienophile moiety (Scheme 1).

The effect of the configuration of the alkoxy group on the nature of the RDA fragmentation under EI is further demonstrated in the mass spectra of the four stereoisomeric 3-ethoxy-6-methoxytricyclo[6.2.2.0^{2,7}]dodeca-9-enes **2** (Fig. 2). The 2,3-*cis*-6,7-*cis*-isomer *endo*-**2**, with both alkoxy groups attaining the *endo* configuration, is the only one that gives rise to the *m/z* 80 cyclohexadiene radical cation via the regular RDA process. The other three stereoisomeric diethers *trans*-**2a**, *trans*-**2b** and *exo*-**2**, with at least one *exo*-alkoxy group, afford most abundant *m/z* 155 [dienophile − H]$^+$ ions, which correspond to the 4-alkoxy-substituted analogues of the *m/z* 111 ion **a** obtained from *exo*-**1** (Scheme 2).

The stereospecific nature of formation of the *m/z* 111 ion from *exo*-**1**, which requires an *exo* configuration of

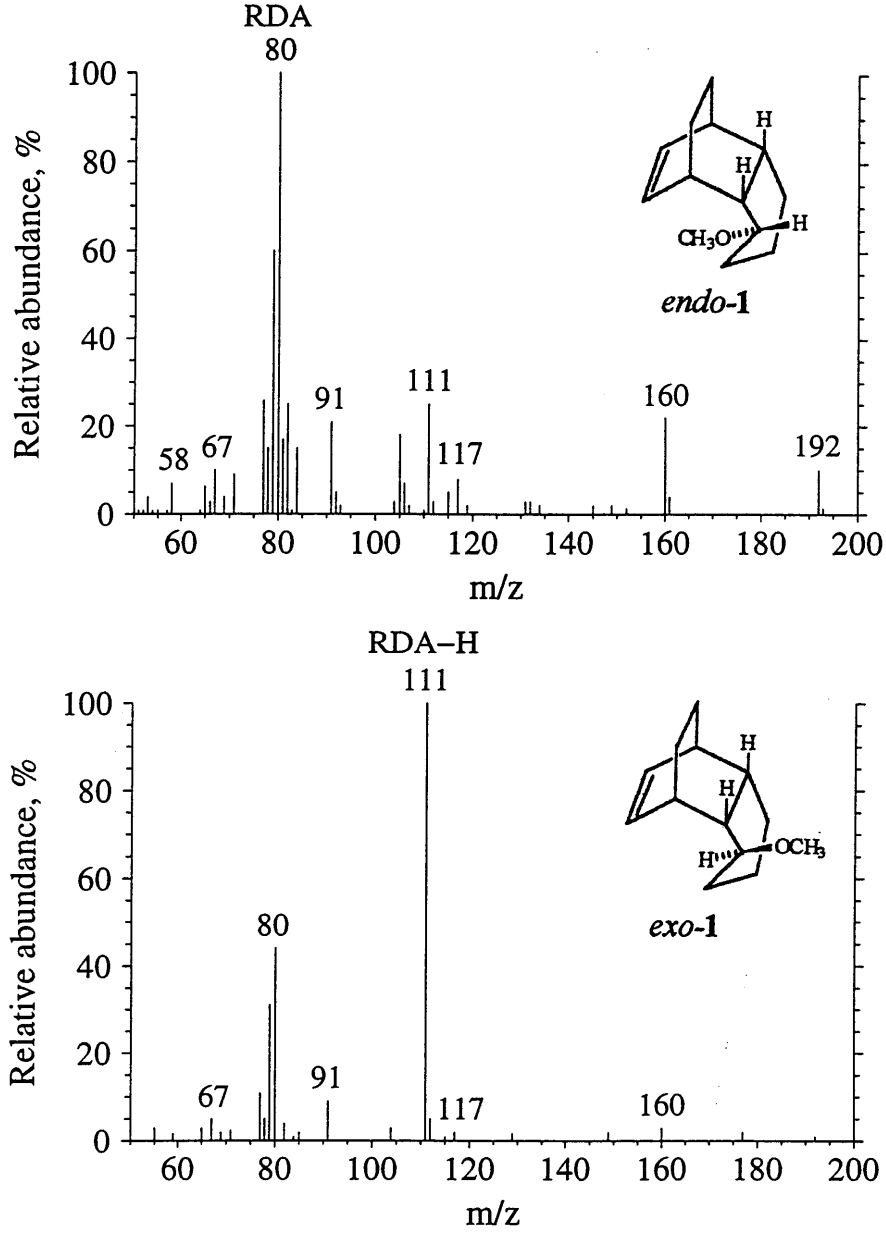
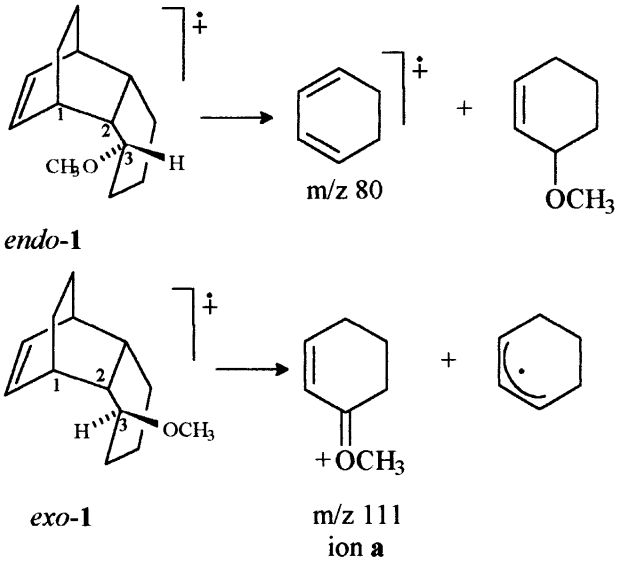


Figure 1. 70 eV EI mass spectra of *endo*-**1** and *exo*-**1**.



Scheme 1

the methoxy group (Scheme 1), suggests isomeric structures for the *m/z* 155 ions obtained from *trans*-**2a** and *trans*-**2b**, with the *exo*-ethoxy and *exo*-methoxy groups, respectively. This assumption was verified by low-energy CID measurements (see Scheme 2 and Fig. 3): the *m/z* 155 ion **b** obtained from *trans*-**2a** gave rise to an *m/z* 123 product ion by elimination of methanol, whereas that (ion **c**) formed from *trans*-**2b** gave an *m/z* 109 ion by elimination of ethanol. It is noteworthy that the products of elimination of both methanol and ethanol were observed in the CID spectrum of the *m/z* 155 ion obtained from *exo*-**2** (*m/z* 123 and 109 ions; see Scheme 2 and Fig. 4), indicating EI-induced formation of a mixture of the two *m/z* 155 isomeric fragment ions **b** and **c** from this particular stereoisomer, with both the methoxy and the ethoxy groups in an *exo* configuration.

CID measurements

The analogy found in the behavior of the stereoisomeric mono- and diethers **1** and **2** suggests structures **b** and **c** shown in Scheme 3 for the two isomeric *m/z* 155 ions obtained from *trans*-**2a** and *trans*-**2b**, respectively (and as a mixture from *exo*-**2**). The distinctive elimination of methanol from ion **b** (singly bound methoxyl) and of ethanol from **c** (singly bound ethoxyl) under CID conditions is consistent with the proposed structures. A comparative CID study was undertaken in order to find additional support for these structural assignments.

3-Butyl-3-ethoxy-6-methoxy- and 3-butyl-3-methoxy-6-ethoxycyclohexene (**3** and **4**) were prepared for this purpose. The EI-induced loss of the butyl radical from the $M^{+\cdot}$ ions of **3** and **4** resulted in the formation of ions **b** and **c**, respectively (Scheme 4). The CID spectra of these two ions and of those obtained from the *m/z* 155 ions of *trans*-**2a** and *trans*-**2b** are shown in Fig. 3. The remarkable similarity of the respective pairs of CID spectra provides strong support for the proposed structural assignments shown in Schemes 3 and 4. It is noteworthy that the isomeric *m/z* 155 *O*-ethyl-5-

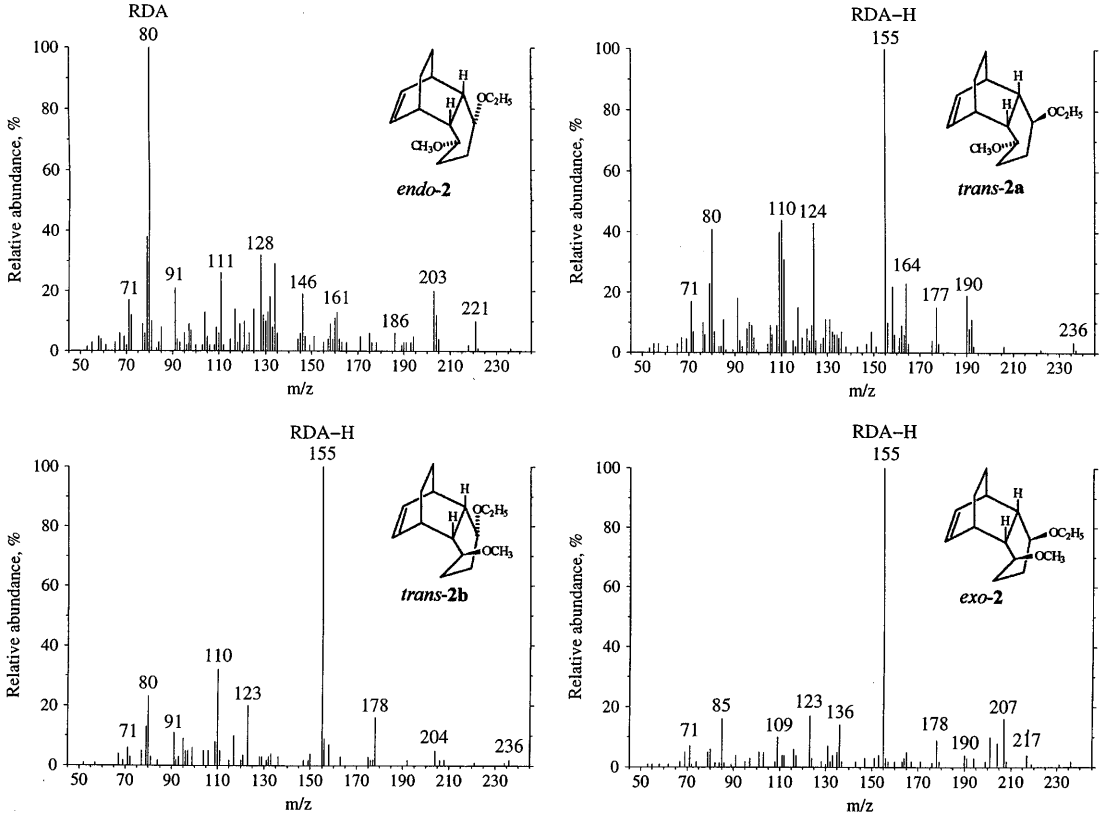
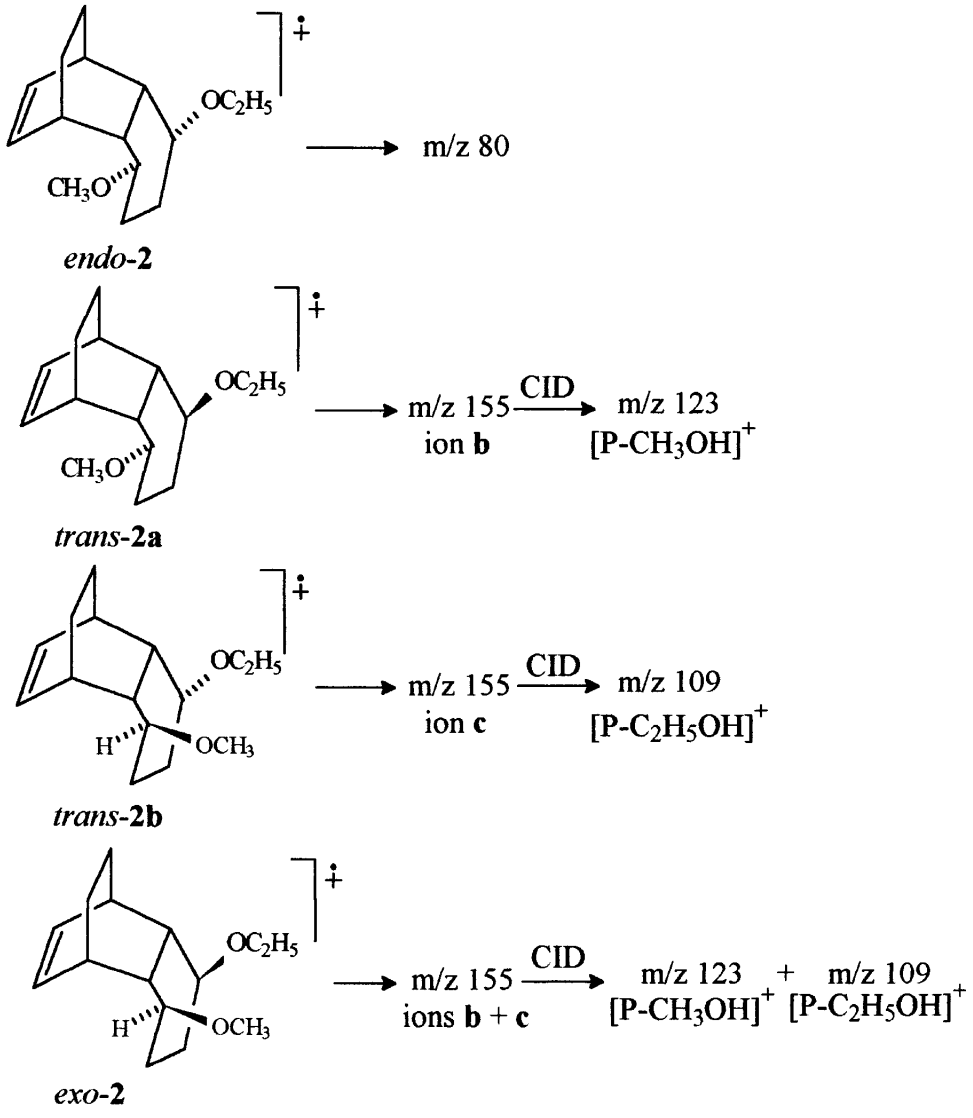


Figure 2. 70 eV EI mass spectra of *endo*-**2**, *trans*-**2a**, *trans*-**2b** and *exo*-**2**.



Scheme 2

methoxycyclohex-3-en-1-one ion **d** (obtained upon EI from 3-methoxy-5-butyl-5-ethoxycyclohexene (**5**); see Scheme 5) gives rise to a different CID spectrum (the *m/z* 85 ion appears only in this isomer, and other ions differ in their abundances; see Fig. 5), which indicates the reliability of the low-energy CID technique in the structural assignment of ions **b**, **c** and **d**.

Deuterium labeling

A deuterium labeling study was undertaken in order to identify the hydrogen atom migrating from the dienophile to the diene part of the tricyclo[6.2.2.0^{2,7}]dodeca-9-ene system in the course of the RDA − H process leading to the formation of ions **a**, **b** and **c**. The *m/z* 111 ion **a** of *exo*-**1** was shifted quantitatively to *m/z* 112 in the monodeuterated analogue d_1-*exo*-**1** (Scheme 6), indicating retention of the hydrogen atom of position 3 in the charged dienophile moiety. On the other hand, this ion was shifted to *m/z* 113 in the mass spectrum of the 2,4,4-trideutero analogue d_3-*exo*-**1**, indicating transfer of a hydrogen atom from one of the two positions 2 or 4 (presumably position 4, see Scheme 6) to the diene moiety in the course of the RDA − H process leading to ion **a**. These results indicate a complicated sequence of events in the formation of ion **a**. The hydrogen atom of position 3 in *exo*-**1** has to leave that position, but it migrates within the dienophile ring and is retained in ion **a**, whereas another H-atom from position 4 is transferred to the neutral moiety in the course of formation of ion **a**.

Similar results were obtained in the isotope labeling study of system **2**. The dideutero-diethers d_2-*trans*-**2a**, d_2-*trans*-**2b** and d_2-*exo*-**2**, specifically labeled at positions 3 and 6, gave rise to the *m/z* 157 ions d_2-**b**, d_2-**c** and their mixture, respectively, which retained the two deuterium atoms (Scheme 7). On the other hand, the trideutero analogue d_3-*trans*-**2a**, labeled at positions 2 and 4, afforded the *m/z* 157 d_2-**b**′ ion, indicating migration of one of the two deuterium atoms from position 4 to the neutral C_6-moiety (Scheme 8). Similarly, the isomeric trideutero analogue d_3-*trans*-**2b**′, labeled at positions 5 and 7, afforded the *m/z* 157 d_2-**c** ion, indicating migration of one of the two deuterium atoms from position 5 (Scheme 8). The other isomeric *trans*-diethers d_3-*trans*-**2b** and d_3-*trans*-**2a**′, specifically labeled at posi-

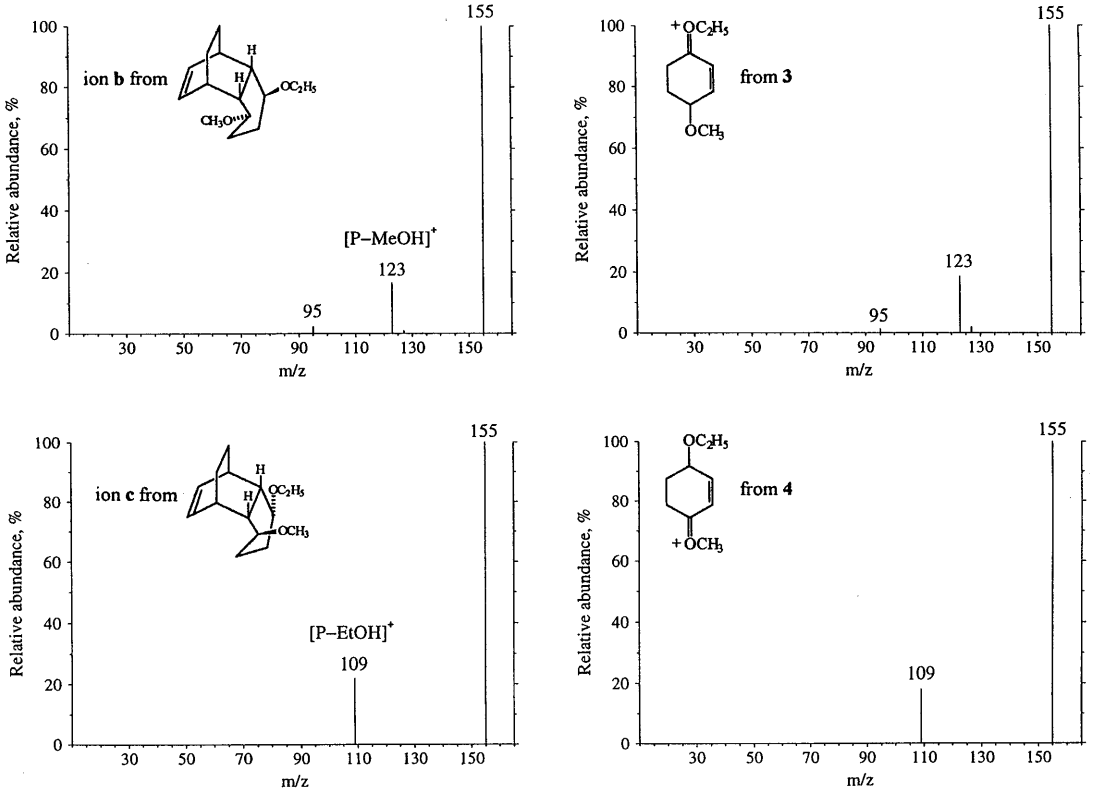


Figure 3. CID spectra (10 eV collision energy) of the *m/z* 155 ions **b** and **c**: (a) obtained from *trans*-**2a**; (b) obtained from **3**; (c) obtained from *trans*-**2b**; (d) obtained from **4**.

tions adjacent to the *endo*-alkoxyl, exhibit no migration of deuterium (*m/z* 158 ions d_3-**c** and d_3-**b**′, respectively; see Scheme 8). Consistent results were also obtained with the hexadeutero analogues d_6-*trans*-**2a** and d_6-*trans*-**2b**, labeled at positions 2, 4, 5 and 7, which gave rise to the *m/z* 160 ions d_5-**b** and d_5-**c**, respectively (Scheme 9). All these results indicate the occurrence of a double hydrogen transfer in the course of formation of ions **b** and **c**, one from position 4 or 5 (adjacent to the *exo*-alkoxyl) to the original diene moiety and the other from position 3 to 4 or 6 to 5 in *trans*-**2a** and *trans*-**2b**, respectively. The preferential elimination of unlabeled ROH apparently results from a considerable deuterium isotope effect. The different abundance ratios of the $[P - ROH]^+$ and $[P - ROD]^+$ ions (P = parent), observed in the CID spectra of ions d_2-**b** and d_2-**c** obtained from d_2-*trans*-**2a**, d_2-*trans*-**2b** and d_2-*exo*-**2** (see Scheme 7), suggest different stereoisotopomer composition of ions d_2-**b** and d_2-**c** obtained from the stereoisomeric diethers.

CID measurements of the deuterium-labeled ions **b** and **c** (ratios of ROH and ROD elimination shown in Schemes 7, 8 and 9) provide an additional insight into their structures and the pathways of their formation. The exclusive elimination of C_2H_5OH from ion d_3-**c** obtained from d_3-*trans*-**2b** and of CH_3OH from ion d_3-**b**′ obtained from d_3-*trans*-**2a**′ (see Scheme 8) indicates exclusive involvement of hydrogen from position 6 in this process (1,3-elimination). The observation of both $[P - ROH]^+$ and $[P - ROD]^+$ ions in each of the CID spectra of ions d_2-**b**, d_2-**c** (Scheme 7), d_2-**b**′, d_2-**c**′ (Scheme 8), d_5-**b** and d_5-**c** (Scheme 9) is consistent with this conclusion, and all the results of the CID measurements of the variety of the deuterium-labeled diethers support the proposed structures of the isomeric ions **b** and **c**.

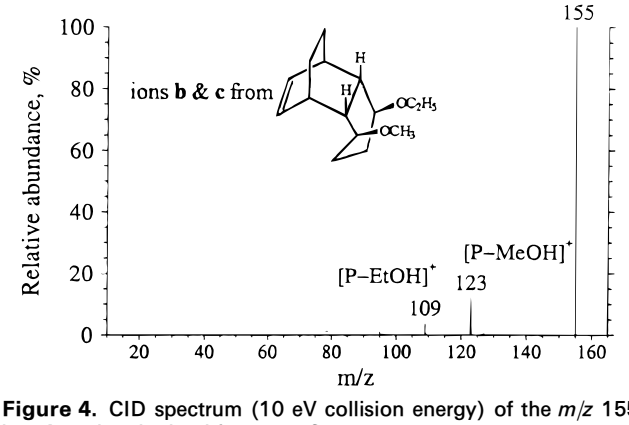
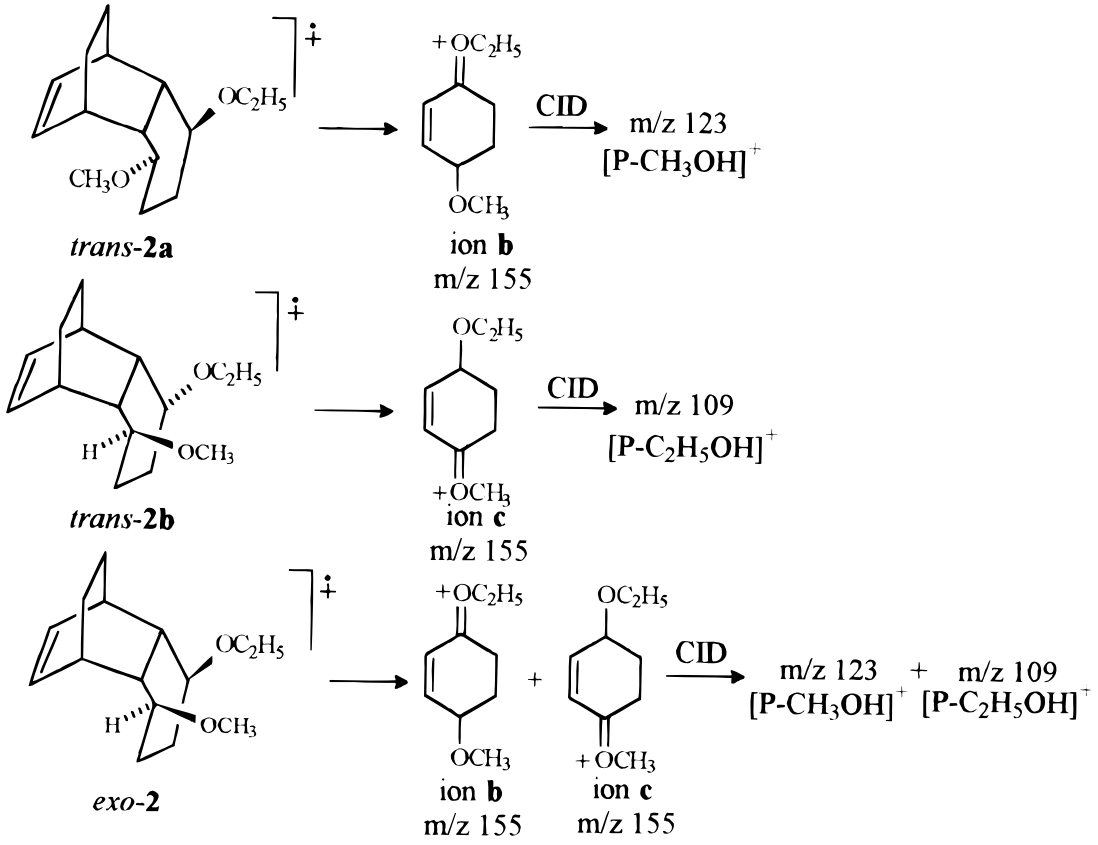


Figure 4. CID spectrum (10 eV collision energy) of the *m/z* 155 ions **b** and **c** obtained from *exo*-**2**.

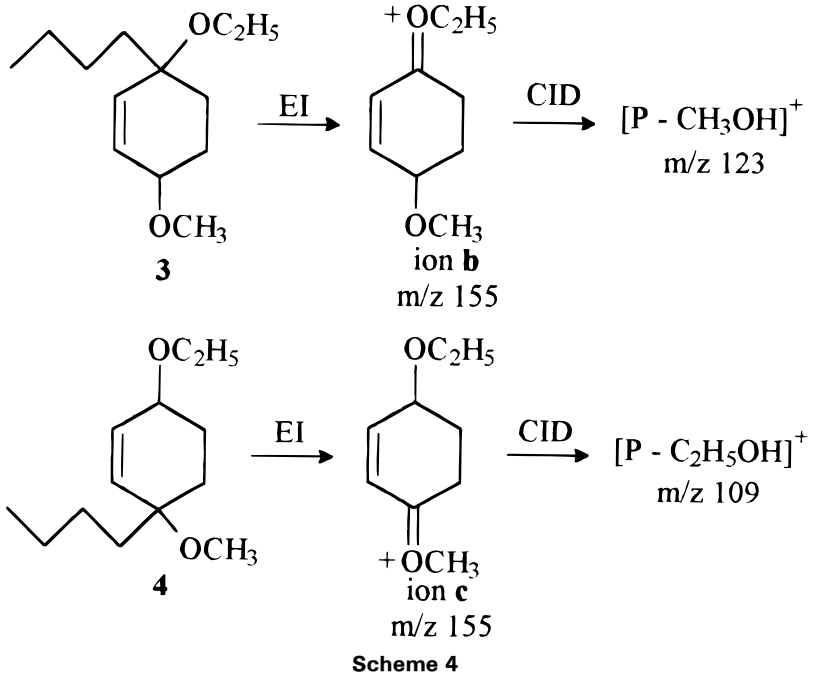
Thermochemistry of the RDA and RDA — H processes

The estimated enthalpies of formation of ions and neutral species, formed from the molecular ions of **1** by the RDA and RDA — H processes, are given in Scheme 10.

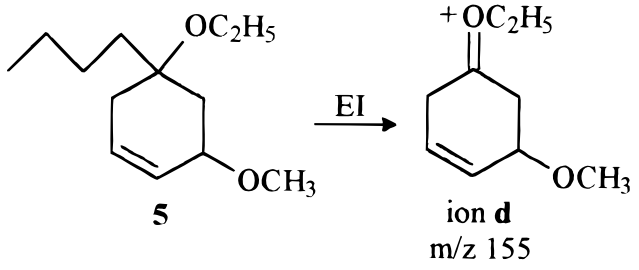


Scheme 3

The ΔH_f of **1** was estimated as -41 kcal mol^{-1} (1 kcal = 4.184 kJ) using the macroincrementation approach.[7–9] The following heats of formation were used: 4.9 kcal mol^{-1} for bicyclo[2.2.2]octene,[7] -69.3 kcal mol^{-1} for cyclohexanol,[7] -20.1 kcal mol^{-1} for ethane[7] and 3.6 kcal mol^{-1} for the difference between alcohol and methyl ether. Semi-empirical calculations (AM1 and PM3) suggest a small energy difference ($\sim$0.5 kcal mol^{-1}) between the two stereoisomers *endo*-**1** and *exo*-**1**. The ionization energy (*IE*) of **1** was estimated as 8.7 eV based on the *IE* of bicyclo[2.2.2]octene (8.92 eV[7]) and on the shift of ~ -0.2 eV in the *IE* values of similarly substituted *vs.* unsubstituted analogues.[7] The above data lead to $\Delta H_f = 160$ kcal mol^{-1} for the $M^{+\cdot}$ ion of **1**. The reported enthalpy of formation of the cyclohexa-1,3-diene radical cation is 215.6 kcal mol^{-1},[7] and that of 3-methoxycyclohexene, -36 kcal mol^{-1}, was estimated using the macroincrementation method. These values lead to the conclusion that the RDA gas-phase ion reaction of the molecular ion of **1** affording



Scheme 4



Scheme 5

the *m/z* 80 cyclohexa-1,3-diene radical cation is endothermic, and the estimated enthalpy of this reaction is 20 kcal mol^{-1}. It should be noted that the non-observed RDA fragmentation leading to the charged dienophile (3-methoxycyclohexene radical cation) is considerably more endothermic (the estimated enthalpy is 35 kcal mol^{-1}).

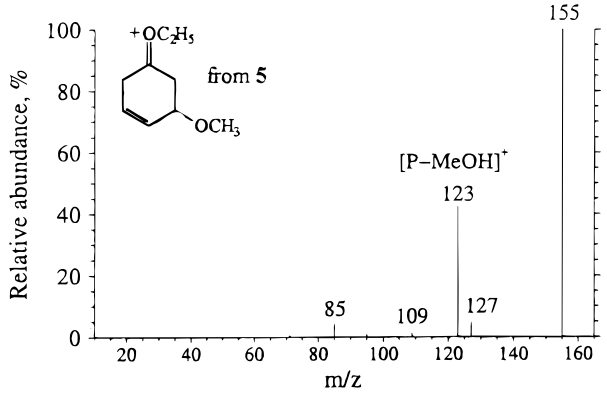
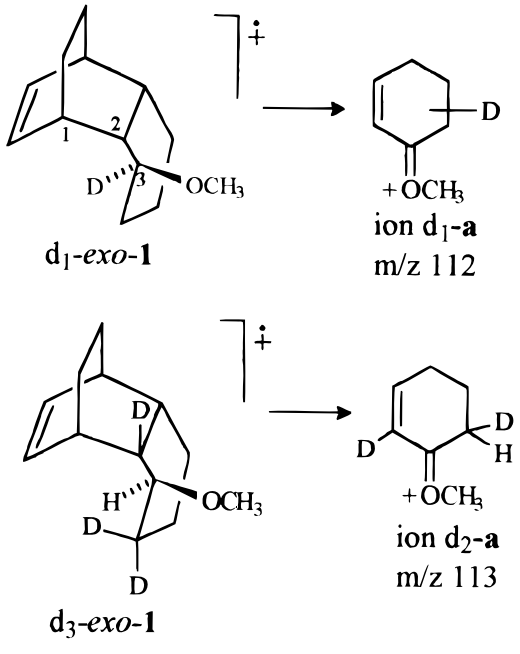


Figure 5. CID spectrum (10 eV collision energy) of the *m/z* 155 ion **d** obtained from **5**.



Scheme 6

The reported enthalpy of formation of cyclohex-3-enyl radical is 30 kcal mol^{-1}.[10] The ΔH_f of ion **a**, 125 kcal mol^{-1}, was estimated as follows: the reported ΔH_f of cyclohex-2-en-1-one is -28 kcal mol^{-1}.[7] The proton affinity of cyclohex-2-en-1-one was estimated as 208 kcal mol^{-1}.[11] The difference between the enthalpies of formation of methylated and protonated cyclohexenone was estimated as -5 kcal mol^{-1}, based on the ΔH_f values of *O*-protonated and *O*-methylated acrolein (153 and 148 kcal mol^{-1}, respectively[7]). These results indicate that the RDA – H process is exothermic, and the estimated reaction enthalpy is -5 kcal mol^{-1}.

In summary, the above thermochemical data (shown in Scheme 10) lead to the conclusion that the enthalpy of the RDA fragmentation affording the *m/z* 80 cyclohexadiene radical cation (20 kcal mol^{-1}) is considerably higher than that of the RDA – H process leading to ion **a** (-5 kcal mol^{-1}). It is reasonable to assume that this relationship is also true for the diethers **2**.

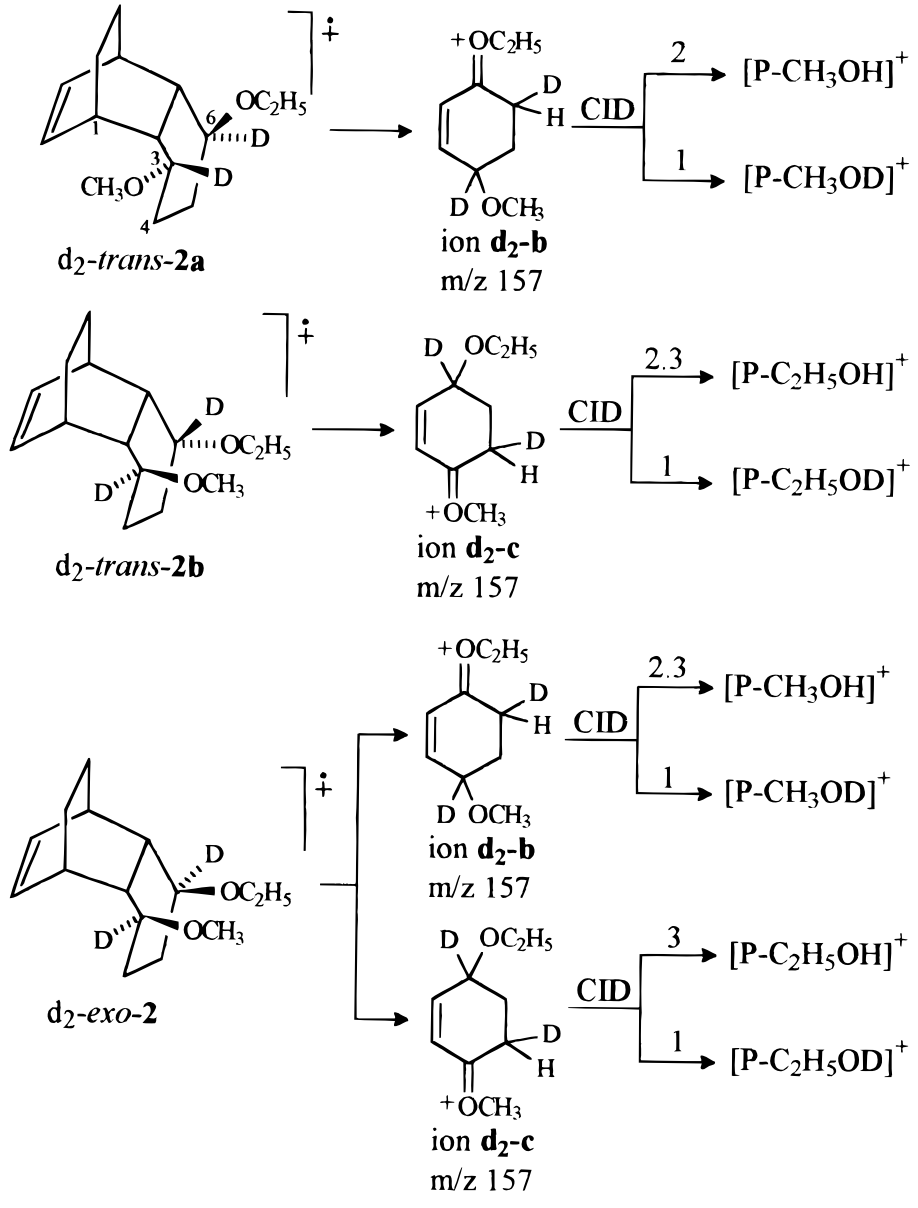
Stereospecificity of the RDA and RDA – H processes

The results discussed above indicate a high activation energy for the thermodynamically favoured RDA – H process in the case of *endo*-**1**, which exhibits predominant formation of the *m/z* 80 ion by the competing regular RDA fragmentation, despite its higher reaction enthalpy. The high abundance of the *m/z* 111 ion **a** in the mass spectrum of *exo*-**1** indicates a considerably lower activation energy of the RDA – H process in this particular stereoisomer, which is now below that of the regular RDA dissociation.

It is reasonable to assume that the activation energy of the regular RDA fragmentation should not be significantly affected by the configuration at position 3. Examination of the structures of the two epimers *endo*-**1** and *exo*-**1** suggests possible involvement of anchimeric assistance of the methoxy group in the cleavage of the anti-periplanar C-1—C-2 bond in the $M^{+\cdot}$ ion of *exo*-**1**, which is the initial step in the RDA – H fragmentation. The proposed mechanism of this multi-step fragmentation of *exo*-**1**, which is consistent with the results of the CID and deuterium labeling studies, is shown in Scheme 11.

The involvement of anchimeric assistance in the rate-determining step may result in a significant decrease of the activation energy of the RDA – H process, which is lower in *exo*-**1** than that of the regular RDA fragmentation. A proposed simplified (not including all the proposed steps of the RDA – H process) energy profile of the fragmentation behavior of *endo*-**1** and *exo*-**1** is shown in Fig. 6.

The configuration of one of the two alkoxyls at positions 3 and/or 6, or of both, may have a similar effect on the relative activation energies of the two processes RDA and RDA – H in the stereoisomeric diethers **2**. Only the *exo*-alkoxyl is capable of anchimeric assistance in the molecular ions of *trans*-**2a** and *trans*-**2b**, resulting in the formation of ion **b** and ion **c**, respectively, by the RDA – H process. In *exo*-**2**, each of the two alkoxy groups may assist in the C—C bond cleavage, and consequently both ions **b** and **c** are formed in this stereoisomer (see Scheme 2). On the other hand, anchimeric



Scheme 7

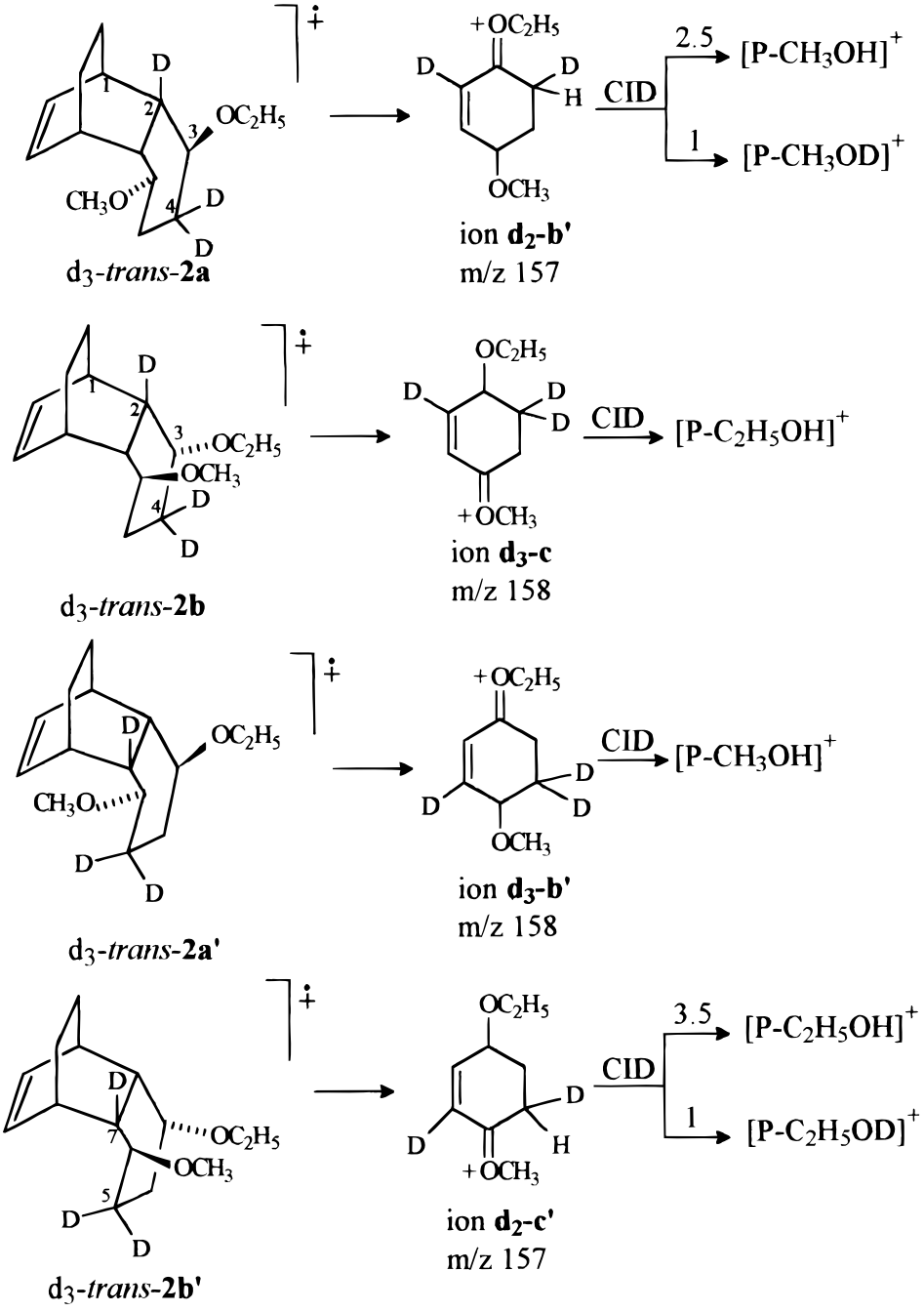
assistance is not possible in *endo*-**2** with both *endo*-alkoxyls, which consequently exhibits predominant formation of the *m/z* 80 cyclohexadiene radical cation via the regular RDA dissociation.

CONCLUSION

We have shown that an apparently small stereoelectronic interaction, allowed in a particular configuration of an appropriately situated substituent remote from the reaction center, may strongly affect the nature of EI-induced dissociation of stereoisomers. The frequently observed RDA fragmentation, which is the major fragmentation pathway occurring in *endo*-**1** and *endo*-**2**, is suppressed in the stereoisomeric ethers *exo*-**1**, *exo*-**2**, *trans*-**2a** and *trans*-**2b**, whereby the *exo*-alkoxyl(s) facilitate the competing multi-step RDA − H process via an anchimerically assisted mechanism.

Ab initio calculations could provide a quantitative insight into the anchimerically assisted and non-assisted mechanisms of the RDA − H process of the stereoisomeric ethers *endo*-**1** and *exo*-**1**. An effort in this direction will be made in the future. Such calculations at the MP3/6–31G*//6–31G* level, recently reported from this laboratory, have shown that the energy difference between the anchimerically assisted and non-assisted mechanisms of elimination of H_2O from the MH^+ ion of *trans*-cyclohexane-1,4-diol is 2–3 kcal mol^{-1}.[1,12]

Stereospecific EI-induced RDA fragmentation has been reported previously in numerous systems differing in the geometry of the junction between the dissociating cyclohexane and an adjacent ring joined to it at the two homoallylic positions.[1,2] To the best of our knowledge, the present work is the first case of a stereospecific EI-induced RDA fragmentation of stereoisomers with identical configuration at the ring fusion, differing only in the configuration of a substituent remote from the reaction center.



Scheme 8

EXPERIMENTAL

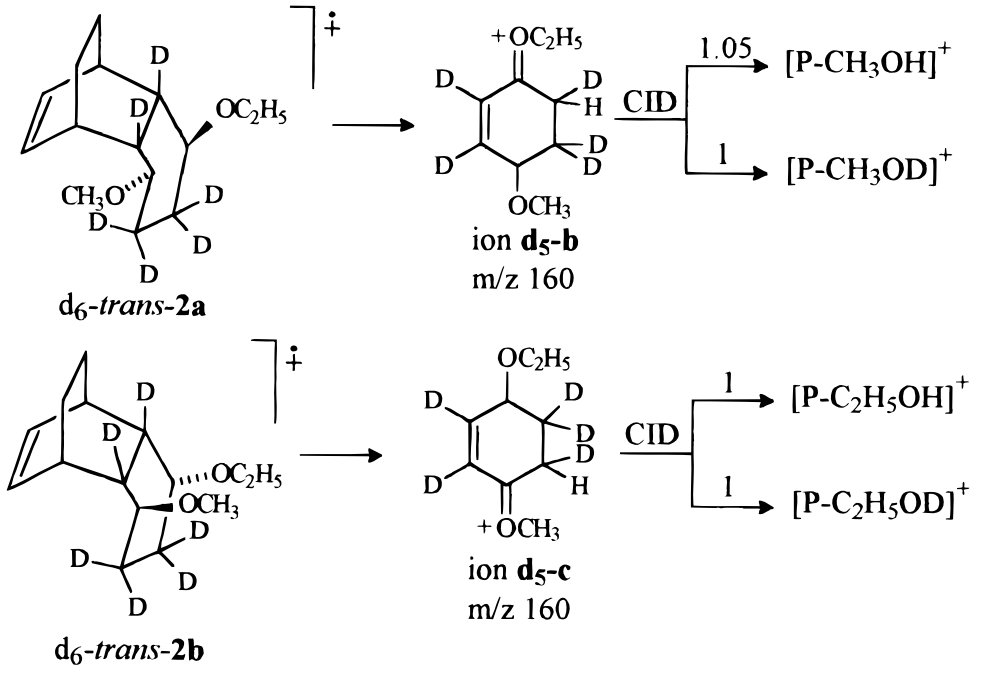
Mass spectrometry

Gas chromatographic/electron ionization mass spectrometric analyses and CID measurements were carried out on a Finnigan TSQ-70B triple-stage quadrupole spectrometer. The stereoisomers were introduced as mixtures, and the separations were performed on a DB-5 (0.25 μm film thickness) capillary column (30 m × 0.25 mm i.d.). The temperature was programmed from 60 to 230 °C at 10 °C min^{-1}. The scan rate was 1 scan s^{-1}. The elution sequence of the monoethers was *endo*-**1**, *exo*-**1** and that of the diethers was *trans*-**2b**, *trans*-**2a**, *exo*-**2**, *endo*-**2**.

EI measurements were performed at a 150 °C ion source temperature and 70 eV electron energy. CID measurements were performed with argon as the target gas [0.3 mTorr, (1 Torr = 133.3 Pa)] at 10 eV collision energy (indicated).

Materials

The stereoisomeric ethers *endo*-**1** and *exo*-**1** and *trans*-**2a**, *trans*-**2b**, *exo*-**2** and *endo*-**2** were prepared by previously reported procedures.[5]



Scheme 9

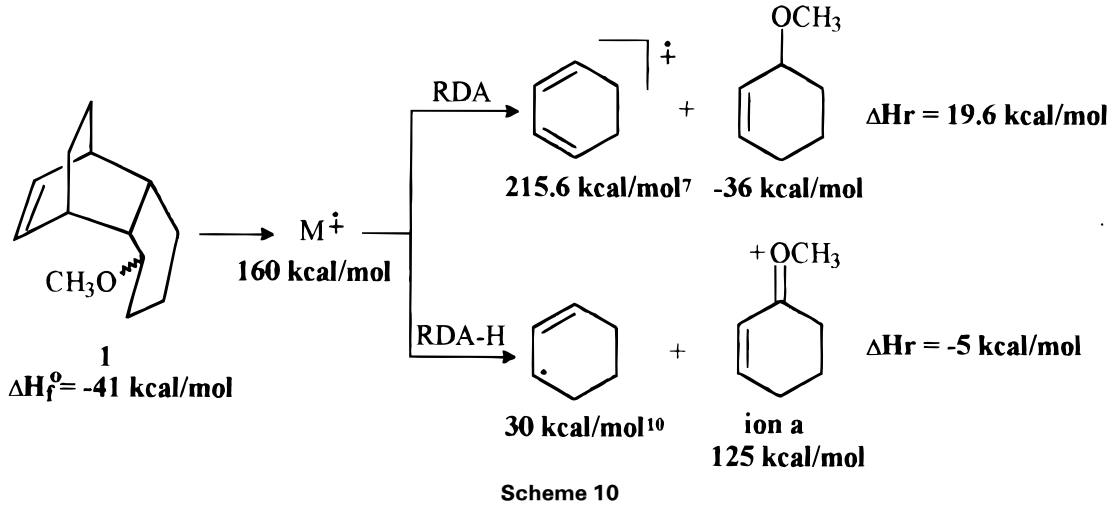
Deuterium-labeled analogues d_1-**1** (two stereoisomers) and d_2-**2** (four stereoisomers) were obtained by $LiAlD_4$ reduction of the corresponding ketones and subsequent etherification of the resulting alcohols and diols. Deuterium-labeled compounds d_3-**1** (two stereoisomers), d_3-**2** (eight isomers) and d_6-**2** (four stereoisomers) were prepared from the corresponding d_3- and d_6-labeled ketones. The deuterated ketones were prepared by the following typical procedure: a suspension of the ketone in D_2O and Et_3N (10 wt%) was stirred for 24 h at room temperature. The reaction mixture was extracted with diethyl ether and the solvent was evaporated under reduced pressure.

The model compounds **3** (R = Me, R′ = Et) and **4** (R = Et, R′ = Me) were prepared by the route outlined in Scheme 12.

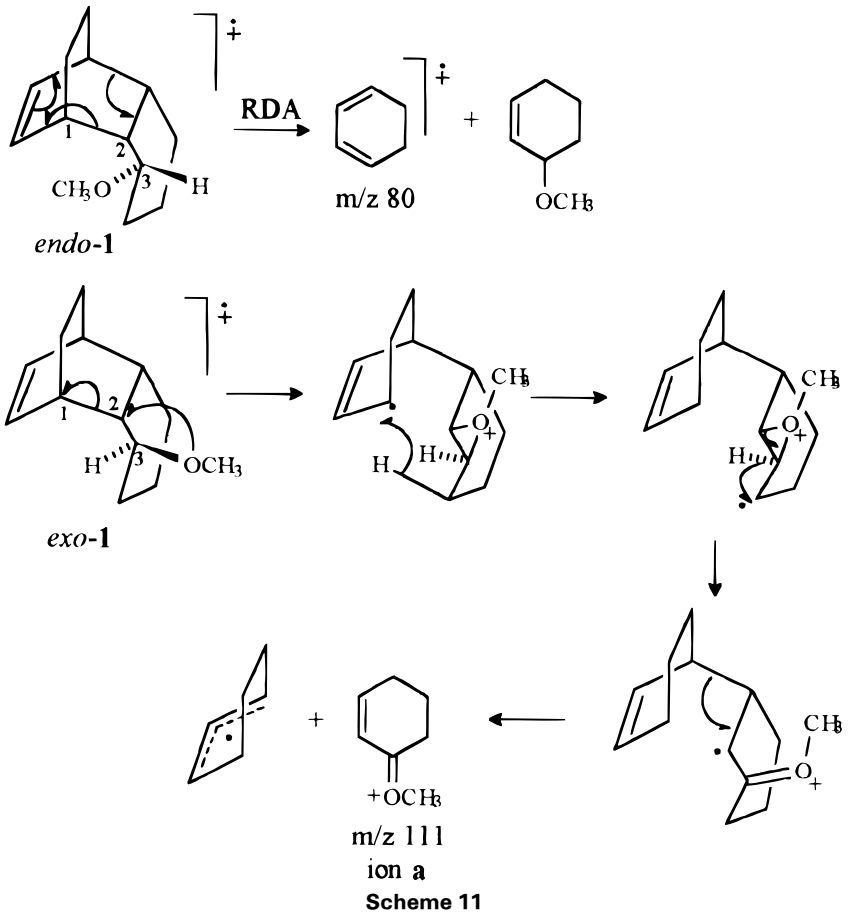
4-Methoxy-2-cyclohexen-1-one, 8(Me). 2-Bromo-4-methoxycyclohexanone ethylene ketal was obtained from **7(Me)**[12] by route *c*:[13] pyridinium bromide perbromide (PBB) (3.35 g, 10.04 mmol) was added to **7(Me)** (1.2 g, 7 mmol) dissolved in dry THF (50 ml). The reaction mixture was refluxed for 2 h and 50 ml of water were added. The organic phase was separated and the aqueous layer was extracted with diethyl ether. Evaporation of the ether followed by chromatographic purification on a Florisil column [hexane–ethyl acetate (40:1)] yielded 75% of the product.

4-Methoxycyclohex-2-en-1-one ethylene ketal was prepared by route *d*: potassium *tert*-butoxide (0.45 g, 4 mmol) was added to a stirred solution of 2-bromo-4-methoxycyclohexanone ethylene ketal (0.5 g, 2 mmol) in dry DMSO (25 ml). After stirring for 0.5 h at room temperature, water was added and the solution was extracted with hexane. Evaporation of the solvent afforded 95% the product.

4-Methoxycyclohex-2-en-1-one, **8(Me)**, was prepared by route *e*:[14] an aqueous solution of 15% oxalic acid (0.1 g, four drops) was added to a stirred suspension of silica gel (1 g, silica gel 60, (Merck), 70–230 mesh) in dichloromethane (3 ml). After 5 min, the aqueous phase disappeared and 4-methoxycyclohex-2-en-1-one ethyl-



Scheme 10



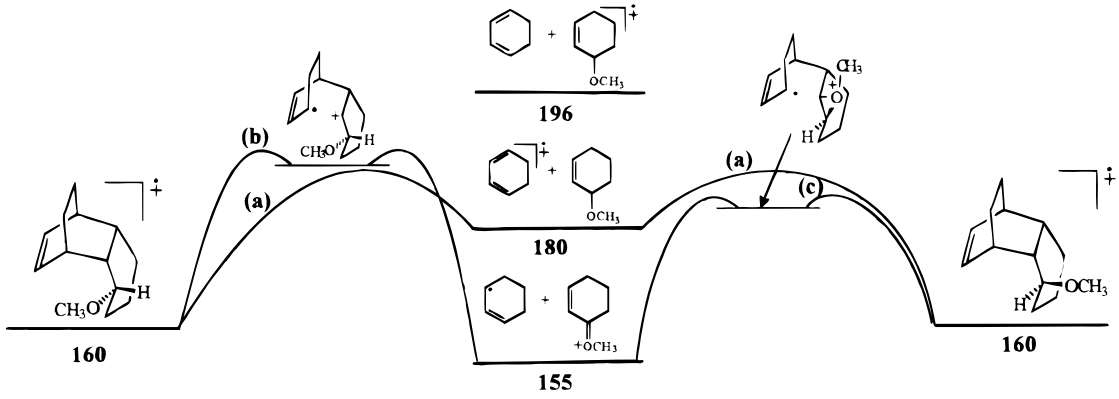
Scheme 11

ene ketal (0.3 g, 1.8 mmol) dissolved in 0.5 ml of dichloromethane was added. The reaction mixture was stirred for 2 h at room temperature, saturated $NaHCO_3$ aqueous solution was added and the resulting mixture was filtered through Celite. The aqueous phase was extracted with diethyl ether. Solvent evaporation followed by chromatographic purification [silica gel, hexane–ethyl acetate (20:1)] yielded 90% of **8**.

4-Ethoxy-2-cyclohexen-1-one, 8(Et). This was prepared from **7(Et)** by the procedure described above for **8(Me)**.

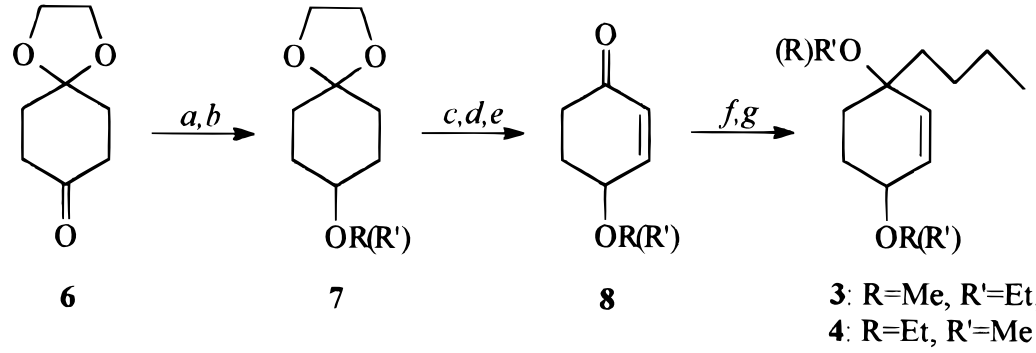
3-Butyl-3-ethoxy-6-methoxycyclohexene, 3. 1-Butyl-4-methoxycyclohexen-1-ol was synthesized by route *f*: *n*-BuLi (1.04 ml, 2 M solution in hexane) was added dropwise to an ice-cooled solution of **8(Me)** (0.2 g, 1.6 mmol) in dry Et_2O (10 ml). The cooling bath was removed and the reaction mixture was stirred for 2.5 h at room temperature, carefully quenched with saturated aqueous NH_4Cl and extracted with diethyl ether. Solvent evaporation afforded 85% of the product.

The model compound **3** was prepared by route *g*; 1-butyl-4-methoxycyclohexen-1-ol (0.1 g, 0.54 mmol in 2



(a) Regular RDA dissociation.
(b) Initial step of the RDA-H process.
(c) Anchimerically assisted RDA-H process.

Figure 6. The proposed energy profile of the RDA and RDA − H processes of *endo*-**1** and *exo*-**1** upon EI.



(*a*) $LiAlH_4$; (*b*) NaH, RI (R'I); (*c*) Pyridinium bromide perbromide; (*d*) *t*-BuOK, DMSO; (*e*) SiO_2-H_2O/CH_2Cl_2, $(HOOC)_2$; (*f*) n-BuLi, Et_2O; (*g*) NaH, R'I (RI).

Scheme 12

ml of dry THF) was added to stirred NaH (52 mg, 1.1 mmol 50% in oil, washed with hexane) in THF (2 ml). The reaction mixture was maintained at 40 °C for 0.5 h and EtI (0.17 g, 1.1 mmol) was added, followed by further heating overnight. The cooled reaction mixture was hydrolyzed by dropwise addition of water. Extraction with diethyl ether and evaporation followed by chromatographic purification on a silica gel column [hexane-ethyl acetate (30:1)] yielded 85% of the product.

3-Butyl-3-methoxy-6-ethoxycyclohexene, 4. This was prepared from **8(Et)** by the procedure described above for **3**, but using MeI instead of EtI.

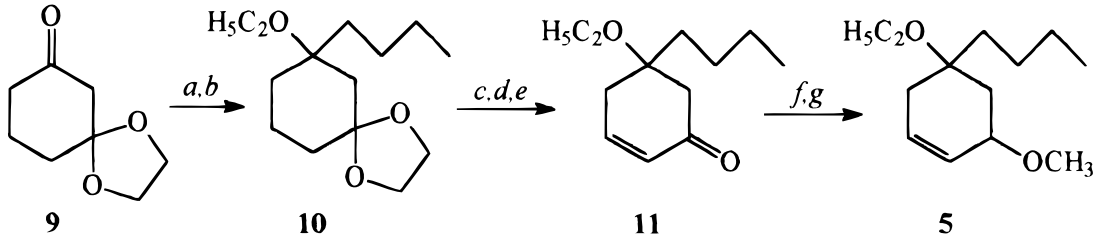
Model diether 5. Compound **5** was prepared by the route outlined in Scheme 13.

Cyclohexane-1,3-dione monoethylene ketal, 9. A benzene solution of cyclohexane-1,3-dione (5 g, 44.6 mmol), ethylene glycol (2.12 ml, 37.9 mmol) and a catalytic amount of TsOH was refluxed in a Dean–Stark apparatus for 1.5 h. The mixture was washed with aqueous $NaHCO_3$ and brine, evaporated and separated by column chromatography on silica gel [hexane–ethyl acetate (3:1)] to give 80% of **9**.

3-Butyl-3-ethoxycyclohexanone ethylene ketal, 10. 3-Butyl-3-hydroxycyclohexanone ethylene ketal was prepared from **9** by route *a*: *n*-BuLi (4.7 ml, 2 M solution in hexane) was added dropwise to an ice-cooled solution of **9** (1.22 g, 7.8 mmol) in dry Et_2O (10 ml). The cooling bath was removed and the reaction mixture was stirred for 2.5 h at room temperature, carefully quenched with saturated aqueous NH_4Cl and extracted with diethyl ether. Solvent evaporation afforded 85% of the product. 3-Butyl-3-ethoxycyclohexanone ethylene ketal, **10**, was obtained from 3-hydroxy-3-butylcyclohexanone ethylene ketal in 87% yield by the procedure described above for **3** (route *b*).

5-Butyl-5-ethoxy-2-cyclohexen-1-one, 11. 3-Butyl-3-ethoxycyclohexanone ethylene ketal was added to a THF–H_2O (4:1) solution with a catalytic amount of TsOH. The reaction mixture was stirred overnight at 65 °C, 10% aqueous $NaHCO_3$ solution was added and the product was extracted with diethyl ether. Evaporation yielded 95% of 3-butyl-3-ethoxycyclohexanone. Pyridinium bromide perbromide (PBB) (0.73 g, 2.3 mmol) was added in portions to 3-butyl-3-ethoxycyclohexanone (0.45 g, 2.3 mmol) dissolved in dry THF (50 ml) at −20 °C. The reaction mixture was allowed to warm up to −5 °C and stirred for 0.5 h at this temperature. Water were added, the organic phase was separated and the aqueous layer was extracted with diethyl ether. Evaporation of the ether followed by chromatographic purification on a Florisil column [hexane–ethyl acetate (30:1)] yielded 70% of 2-bromo-5-butyl-5-ethoxycyclohexanone.

5-Butyl-5-ethoxy-2-cyclohexen-1-one, **11**, was obtained by route *e*:[15] a mixture of 2-bromo-5-butyl-5-ethoxycyclohexanone (0.18 g, 0.65 mmol), Li_2CO_3 (0.125 g, 1.7 mmol) and LiBr (0.01 g, 1.1 mmol) in anhydrous DMF (8 ml) was stirred at 130 °C for 2 h and cooled to room temperature. Saturated aqueous NH_4Cl



(*a*) n-BuLi, Et_2O; (*b*) NaH, EtI; (*c*) THF-H_2O, TsOH, (*d*) PBB; (*e*) LiBr, Li_2CO_3, DMF; (*f*) $LiAlH_4$; (*g*) NaH, MeI

Scheme 13

was added and the mixture was extracted with diethyl ether. The organic layer was washed with brine and evaporated. Chromatographic purification on a silica gel column [hexane–ethyl acetate (30:1)] afforded 85% of **11**.

2-Methoxy-4-butyl-4-ethoxycyclohexene, 5. 2-Hydroxy-4-butyl-4-ethoxycyclohexene was obtained in 95% yield by $LiAlH_4$ reduction of **11** (route *f*). Compound **5** was prepared from this material by the procedure described above for **8** (90% yield).

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