Intramolecular reactions of dialkoxycarbenes with a carbonyl group

Małgorzata Dawid and John Warkentin

Abstract: Thermolysis of 5,5-dimethyl-2-methoxy-2-(2-oxocyclohexylmethoxy)-Δ^3–1,3,4-oxadiazoline (**3a**) in benzene at 110°C generated a carbonyl ylide intermediate that gave, in a minor side reaction, a product of 1,3-dipolar cycloaddition to the carbonyl group. The major fate of the ylide was fragmentation to acetone and a dialkoxycarbene, MeO-(RCH_2O)C:, where R = 2-oxocyclohexyl. The carbene, in turn, underwent overall [2 + 1] cycloaddition to the carbonyl group, presumably to afford diastereomeric dialkoxyoxiranes that could not be isolated. A product of methanolysis of the presumed oxiranes was isolated by GC and its structure was determined by means of X-ray diffraction. Methanol is believed to result from reaction of an intermediate or product with adventitious water. Deliberate hydrolysis of the product of methanolysis gave a hydroxy lactone, the structure of which was also secured by means of single crystal X-ray diffraction. Those structures indicated the likely structures of the oxirane precursors. A second, and major, product from the carbene was a bicyclic ketone. Similar products were obtained from intramolecular reactions of a carbene tethered to cyclopentanone through a two-carbon or a one-carbon tether. Some compounds that are apparently "dimers" of the oxiranes were also isolated and identified by means of X-ray diffraction. These dimers are thought to originate from the reaction of a ring-opened oxirane (a dipole or a cation from electrophilic opening of the oxirane) with a molecule of the oxirane rather than from bimolecular reaction between two oxirane molecules. The oxiranes open by cleavage of the $(RO)_2C$—O bond rather than the oxirane C—C bond, the normally observed sense of thermal ring opening. The properties of the carbenes and the presumed oxiranes serve to point out the options available to such intermediates and suggest that some new, synthetically useful reactions may become possible.

Key words: bicyclic ketone, dialkoxycarbene, dialkoxyoxirane, hydroxylactone, "oxirane dimers".

Résumé : La thermolyse de la 5,5-diméthyl-2-méthoxy-2-(2-oxocyclohexylméthoxy)-Δ^3-1,3,4-oxadiazoline (**3a**), dans le benzène, à 110 °C, génère la formation d'un ylure de carbonyle comme intermédiaire qui réagit, dans une réaction latérale mineure, pour former un produit de cycloaddition 1,3-dipolaire sur le groupe carbonyle. La réaction principale de l'ylure est une fragmentation en acétone et en dialkoxycarbène, MeO(RCH_2O)C:, dans lequel R = 2-oxocyclohexyle. Par la suite, le carbène subit une réaction globale de cycloaddition [2 + 1] sur le groupe carbonyle qui fournit probablement les dialkoxyoxiranes diastéréomères qui n'ont pas été isolés. Faisant appel à la CG, on a toutefois pu en isoler un produit de méthanolyse et on a déterminé sa structure par diffraction des rayons X. On croit que le méthanol est issu de la réaction d'un intermédiaire ou d'un produit avec de l'eau présente de façon fortuite. L'hydrolyse délibérée du produit de méthanolyse conduit à une hydroxylactone dont la structure a été déterminée par diffraction des rayons X sur un cristal unique. Ces structures suggèrent celles des oxiranes qui leur ont donné naissance. Un deuxième et le plus important produit provenant du carbène est une cétone bicyclique. Des produits semblables ont été obtenus par le biais de réactions intramoléculaires d'un carbène auquel on a attaché une cyclopentanone par le biais de rallonges à un ou deux atomes de carbones. On a aussi isolé des composés qui sont apparemment des dimères d'oxiranes et on les a identifiés par le biais de la diffraction des rayons X. On croit que ces dimères trouvent leur origine dans la réaction d'un oxirane à cycle ouvert (un dipôle ou un cation résultant de l'ouverture électrophile de l'oxirane) avec une molécule d'oxirane plutôt par une réaction bimoléculaire entre deux molécules d'oxirane. Les oxiranes s'ouvrent par rupture de la liaison $(RO)_2C$—O plutôt que par ouverture de la liaison C—C de l'oxirane, le sens d'ouverture normalement observé dans l'ouverture thermale du cycle. Les propriétés des carbènes et des oxiranes suggérés permettent de préciser les diverses options ouvertes à ces intermédiaires et de suggérer que de nouvelles réactions utiles en synthèse puissent se développer.

Mots clés : cétone bicyclique, dialkoxycarbène, dialkoxyoxirane, hydroxylactone, dimères d'oxirane.

[Traduit par la Rédaction]

Received 8 August 2002. Published on the NRC Research Press Web site at http://canjchem.nrc.ca on 22 May 2003.

Dedicated to Professor Don Arnold, for his exemplary devotion to excellence in chemistry.

M. Dawid and J. Warkentin.[1] Department of Chemistry, McMaster University, 1280 Main St. West, Hamilton, ON L8S 4M1, Canada.

[1]Corresponding author (e-mail: warkent@mcmaster.ca).

 doi: 10.1139/V02-200

Introduction

The nucleophilicity of dialkoxycarbenes was first reported by Hoffmann's group, and other examples followed (1). Relative nucleophilicities of various carbenes have been quantified by Moss et al. (2). The nucleophilic characteristics of dialkoxycarbenes are evident from their sluggish reactions with simple alkenes, such as cyclohexene (1*b*, 3) and their greater reactivity toward Michael acceptors such as isocyanates and diphenylketene (1*d*), for example. Donor-atom-substituted carbenes are also capable of bimolecular nucleophilic displacements. Nucleophilic substitution at unsaturated carbon occurs between an imidazolylidene and 2,3,4,5,6-pentafluoropyridine (4) and in reactions of dimethoxycarbene (DMC) with hexachlorocyclopentadiene (5), 1-fluoro-2,4-dinitrobenzene, and hexafluorobenzene (6), for example, although the yields can be very low (6).

A common reaction of nucleophiles with carbonyl compounds is addition, to change the geometry at the carbonyl carbon from planar to tetrahedral. Diaminocarbenes were known to attack at the carbonyl carbon atom of aldehydes (7), and DMC appears to add to the carbonyl group of hexafluoroacetone (Scheme 1) (8), fluorenone (9), and cyclohexanone (10). Recently it was shown that DMC reacts to effect insertion into the bond between the carbonyl carbon and the α-oxygen atom of anhydrides (11) and a lactone (12). Similar apparent insertion into the bond between a carbonyl carbon and the α-carbon of strained cyclic ketones was reported (12) (Scheme 2). Such reactions could be concerted or they could involve tetrahedral intermediates with dipolar or diradical characteristics. Either of those intermediates could rearrange by ring enlargement or cyclize to isolable dialkoxyoxiranes, as in the case of addition of dimethoxycarbene to cyclohexanone (Scheme 3) (10). Dimethoxycarbene also reacts with thiocarbonyl compounds to form dimethoxythiiranes (13). Although imidazolylidenes are known to form stable dipolar intermediates by forming a single bond to carbon disulfide (14), carbon dioxide (15), or sulfur trioxide (16), attack of a less-nucleophilic dialkoxycarbene at a carbonyl or thiocarbonyl group could be concerted, leading directly to a dialkoxyoxirane or a dialkoxythiirane.

The nucleophilic reactivity of dialkoxycarbenes was suggested by the previously demonstrated reactions of vinylogous dialkoxycarbenes with ketones (17–19). It is not surprising that vinylogous dialkoxycarbenes are better nucleophiles than saturated analogues because the former carbenes are presumably more polarizable and can disperse positive charge better in a stepwise or nonsynchronous concerted reaction. The stepwise pathway for vinylogous dialkoxycarbenes is illustrated in Scheme 4.

It was of interest to us to explore further the possible intramolecular reactions of non-vinylogous dialkoxycarbenes with a tethered carbonyl group. Previously only one case of such a process had been reported and that was for reaction with the carbonyl group of a tethered cyclobutanone (12). We now report reactions of a dialkoxycarbene with the carbonyl group of a cyclohexanone tethered at the α-position with a one-carbon tether to the carbene, as well as reactions of dialkoxycarbenes tethered analogously to cyclopentanone with a one- or two-carbon tether.

Methods, results, and discussion

The oxadiazoline precursors (**3**) of dialkoxycarbenes were prepared from 2-hydroxyalkyl cyclanones (**2**) and 2-acetoxy-2-methoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (**1**) by the exchange method (19), as illustrated in Scheme 5. The exchange had to be done carefully to minimize dehydration of **2a** or destruction of **3** subsequent to their formation. Protection of the carbonyl group of **2a** with 1,2-ethane dithiol and subsequent exchange followed by deprotection was achieved but that route did not offer any improvement of the yield of **3a**. Compounds **3** were isolated by chromatography on silica.

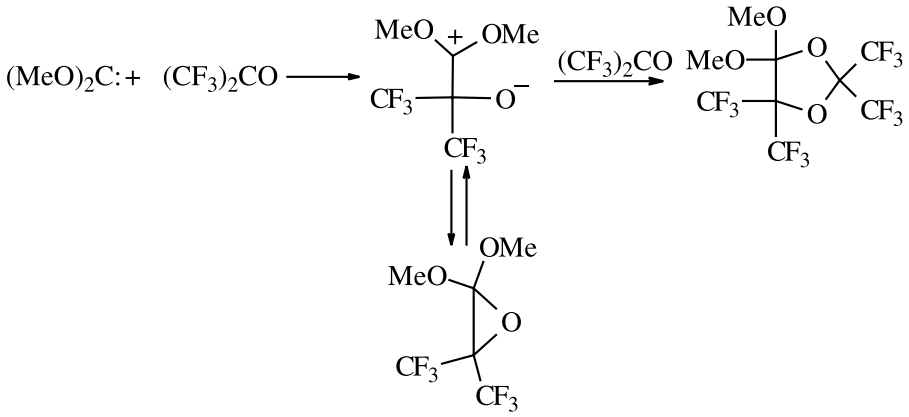
After purification of **3a** by chromatography, a benzene solution was heated for 24 h at 110°C in a sealed glass tube. Products isolated by chromatography on silica included **4** (7%) and 1-methoxy-8-oxa-9-oxobicyclo[4.2.1]nonane (**5**, 31%), as shown in Scheme 6. Acetal **6** (16%), which had two methoxy signals in the ^{1}H NMR spectrum and the correct mass for **6**–OMe, was isolated by means of GC. Despite many attempts the material could not be crystallized. Structure **6** was inferred from the structure of the single product of hydrolysis of the material (below). In addition, diastereomers **7a** and **7b**, both crystalline solids, were isolated by means of radial chromatography on silica. Compound **7a** was identified completely by means of single crystal X-ray diffraction and **7b** was assigned on the basis of its NMR spectra, which closely resembled those of **7a**.

The products can be accounted for as follows. Oxadiazoline **3a** loses N_2 in the first step to generate carbonyl ylide **8** (Scheme 7). Intramolecular cycloaddition of the ylide to the carbonyl group leads to **4**, the stereochemistry of which was assigned on the basis of the structure of the product of acid-catalyzed hydrolysis of **4**, hydroxy lactone **9**. The structure of **9** was secured by means of single crystal X-ray diffraction.

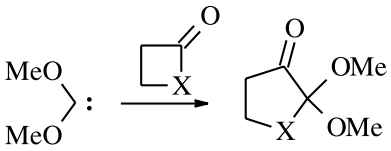
A major fate of the carbonyl ylide must be the well-precedented loss of acetone (1*k*) to afford carbene intermediate **10**, which attacks the carbonyl group of the cyclohexanone to generate intermediate **11** or, possibly, the oxiranes **12** (Scheme 7). The intermediacy of diasteromers **12** is speculative because many attempts to isolate a sample by gas chromatography gave material that contained **6** and, possibly, the diastereomers **12**. Deliberate hydrolysis of such samples led to hydroxy lactone **9** only. The structure of **9** means that both the ylide **8** (precursor of **4**) and the carbene **10** (precursor of **11**) react from that conformation in which the side chain is axial, as shown in Scheme 7.

Although the rearrangement of **10** to **5** amounts to an insertion (overall) of the carbene into a C—CO bond of the carbonyl group, the reaction is not necessarily concerted. Reactions of cyclic ketones with diazomethane, leading to products of ring expansion, are believed to be stepwise (20). Those reactions are reasonable models for ring expansion of cyclic ketones by reaction with dialkoxycarbenes. It was shown previously that migration of the more-substituted carbon is preferred when α-alkylcyclobutanones react with dimethoxycarbene to afford corresponding dimethoxycyclopentanones (12). In the case of postulated intermediate **11**, in which migration of the more-substituted carbon would lead to a four-membered ring (Scheme 7), the less-substituted α-carbon migrated to expand the ring from six-

Scheme 1.

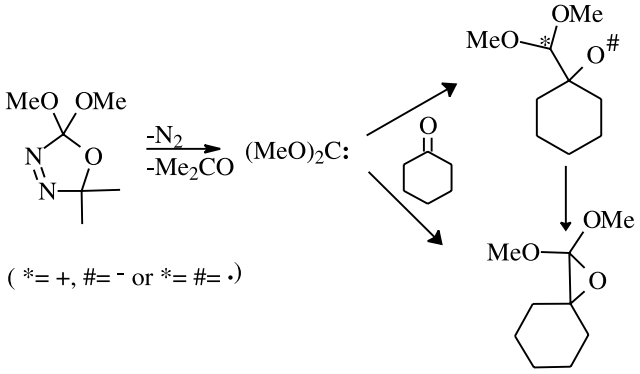


Scheme 2.



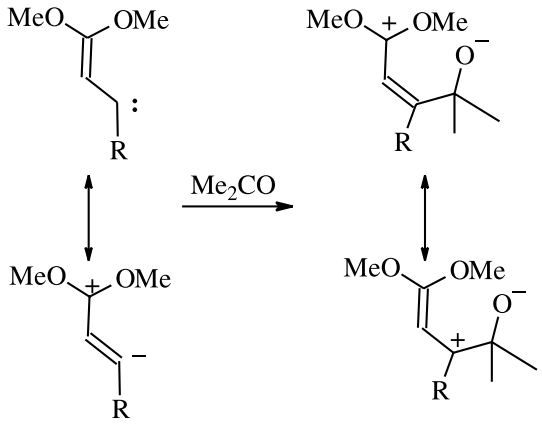
(X= O or C; 3-membered rings were included for X= C)

Scheme 3.



(*= +, #= - or *= #= •)

Scheme 4.



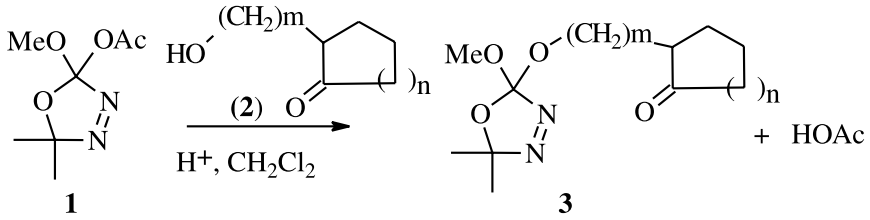
to seven-membered. A simple model that aids in visualization of the transition state charge separation is the enolate alkylation model (12) shown in Scheme 8. It should perhaps be emphasized that such structures, with enolate and cation character, are simply models for actual transition states or intermediates.

An additional product from thermolysis of **3a** was the complex compound **13**, consisting essentially of 3 equiv of the proposed oxirane intermediate. Its structure was determined by means of single crystal X-ray diffraction. Scheme 9 is a rationalization for its formation from reaction of the ring-opened oxirane with the oxirane. It should be emphasized that the mechanism, involving intermediates **11** and **13**, is speculative. Instead of the dipolar species **11**, one could invoke a cationic intermediate formed by protonation (by adventitious water) and subsequent ring-opening of an oxirane **12**. That cation could then act as an electrophile to open a second molecule of oxirane. The connectivity of **14** does require that the oxirane intermediates *do not open to carbonyl ylides*; the usual sense of thermal ring opening of oxiranes. Presumably there were other compounds, analogous to **14**, that we were unable to isolate.

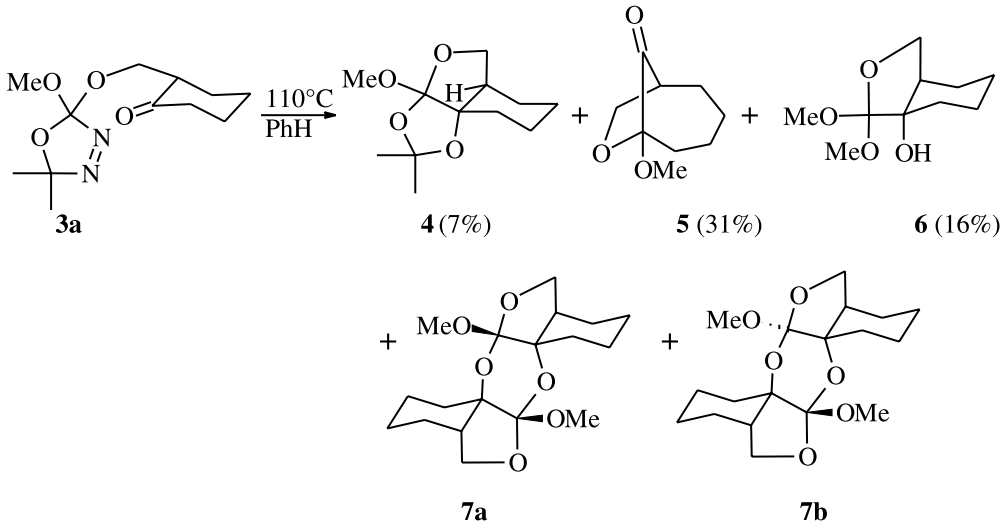
Heating of a solution of **3b** in benzene afforded similar products. A major product (33%) was 1-methoxy-2-oxa-8-oxobicyclo[3.3.1]nonane (**17**). Again there was indirect evidence for isomeric oxirane intermediates, probably **15** and **16** (Scheme 10), although they were too unstable to be isolated. Preparative gas chromatography gave fractions that changed during the collection process, probably because of hydrolysis. Two stable compounds (**18** and **19**) were also isolated by means of GC and identified by means of single crystal X-ray diffraction. Compound **18** is probably formed by the methanolysis of **15** and **16**. The source of methanol is again assumed to be hydrolysis of an intermediate by adventitious water.

The hexahydropyranyl ring of **19** is fused *trans* to the 1,4-dioxanyl ring and the ring juncture of the hexahydropyranyl and cyclopentyl rings is *cis*. It is analogous to compound **11** that was obtained from **3a**, and it appears, at first sight, to be a head-to-tail dimer of the dipolar intermediate that would result from stepwise addition of the nucleophilic carbene center to the carbonyl group (Scheme 10). Such a dimerization is unlikely, of course, because reactive intermediates are not expected to accumulate to concentrations that

Scheme 5.



Scheme 6.



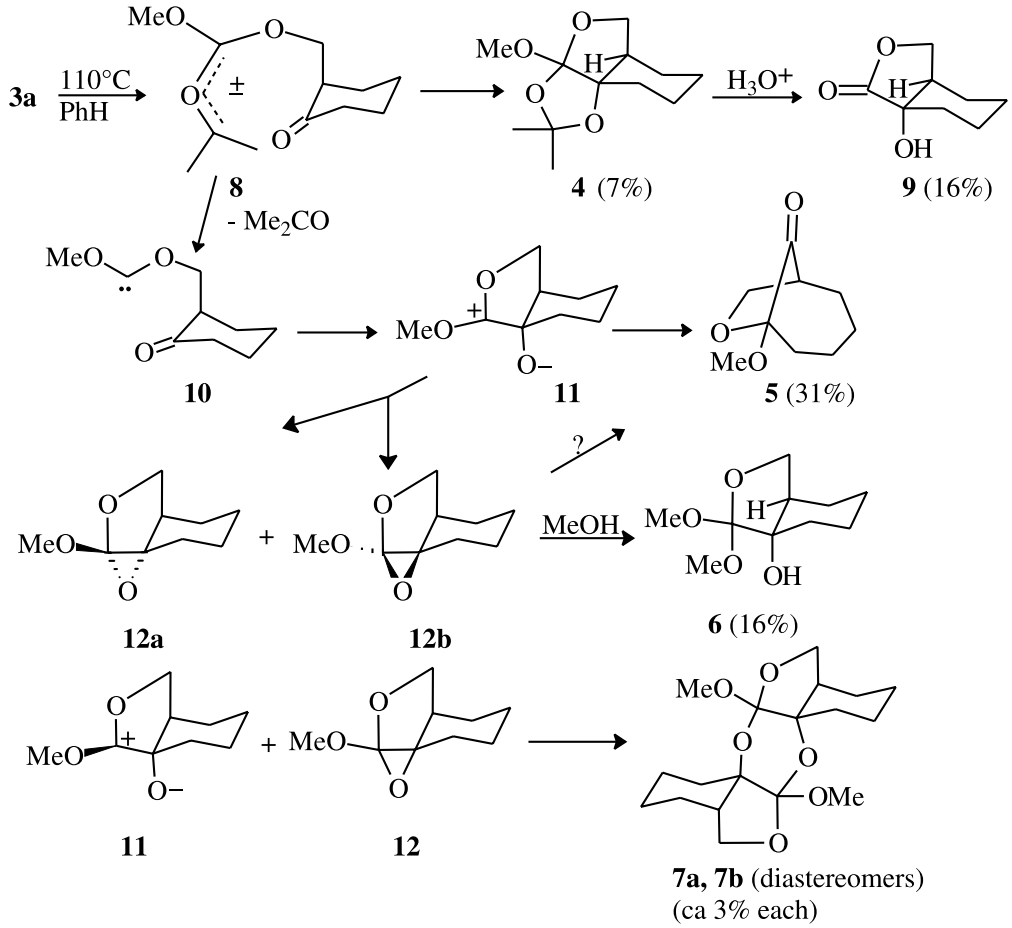
could lead to bimolecular reactions between them. We are therefore led to propose, again, that there is a bimolecular reaction between a dipolar species, in equilibrium with the oxirane precursor and the oxirane. Alternatively, a cationic species, from electrophile-catalyzed ring opening of the oxirane, reacts with the oxirane to generate **19**. Isomers of **19** might be expected, given that isomeric oxiranes such as **15** and **16** could result from the carbene. The GC trace showed compounds with retention times similar to that of **19**, and we assume that isomers of **19** were generated and that they account for some of material imbalance.

Thermolysis of **3c** gave products analogous to those from **3a** and **3b** (Scheme 11). Compound **22** (2%) can be attributed to dipolar cycloaddition of the ylide from **3c** to the carbonyl group, and the carbene from **3c** afforded **23** and **24**, because we were able to isolate a product (**25**) of apparent methanolysis of **24**. Lactone **26** was also obtained as was bicyclic ketone **28** (28%), possibly from rearrangement of a dipolar intermediate **23**. In the case of **3c**, two dimers (**29** and **30**) of the putative oxirane intermediate could be obtained in crystalline form suitable for single crystal X-ray diffraction. Compound **27** is apparently the product of hydrolysis of a product like **29**. In diastereomer **29** the 1,4-dioxanyl ring is in the chair conformation, and it is fused *cis* to the tetrahydrofuranyl rings. In diastereomer **30** the 1,4-dioxanyl ring is in a boat conformation, and both tetrahydrofuranyl rings are again fused *cis* to it. As in cases of **3a** and **3b**, there were other products with GC retention times similar to those of **29** and **30**. Those products were probably also dimers, isomers of **29** and **30**.

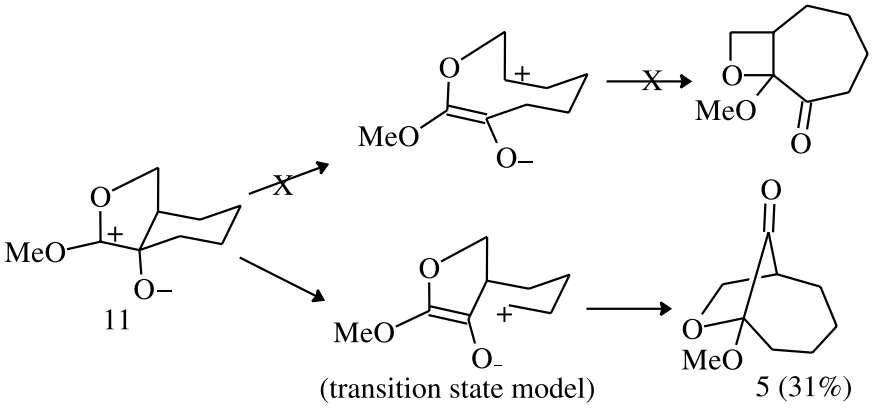
In order to trap a possible intermediate, thermolysis of **3a** was carried out in the presence of dimethyl acetylenedicarboxylate (DMAD). The yield of **5** was reduced by a factor greater than two, and there were formed, instead, two products isolated in essentially equal amounts, ca. 3% each, with greater GC retention times. It was possible to isolate those compounds, by means of semipreparative GC followed by MPLC, and to determine that they were diastereomers **32** and **33** (Scheme 12). Structure **32** was secured by means of single crystal X-ray diffraction while **33** was inferred from its NMR spectrum, which was very similar to that of **32**. It is clear from the connectivity that DMAD *had not intercepted a carbonyl ylide* such as **30**, which is the intermediate that is normally obtained from thermal, conrotatory ring opening of an oxirane, but something like dipole **31** or the cation from protonation of **31**. The cation mechanism appears to fit best because a cationic intermediate would not be likely to attack the triple bond but it could coordinate instead to carbonyl oxygen.

In summary dialkoxycarbenes, tethered *alpha* to the carbonyl group of cyclohexanone or cyclopentanone, react intramolecularly with the carbonyl group to generate an intermediate with a new five- or six-membered ring. Dialkoxyoxirane intermediates could not be isolated but they were

Scheme 7.



Scheme 8.



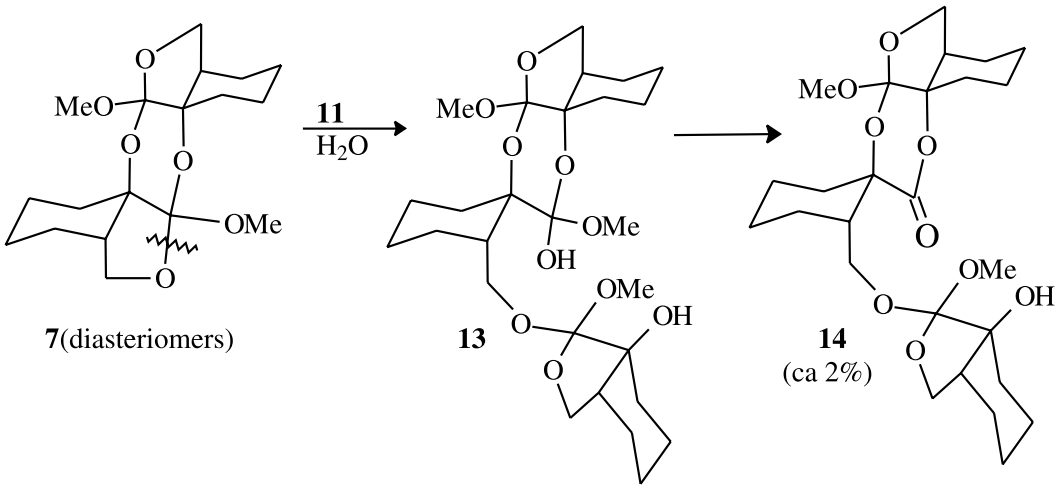
inferred from products of their ring opening by methanol or water. Some novel oxirane dimers were isolated, as well as, in each case, a bicyclic ketone.

Experimental

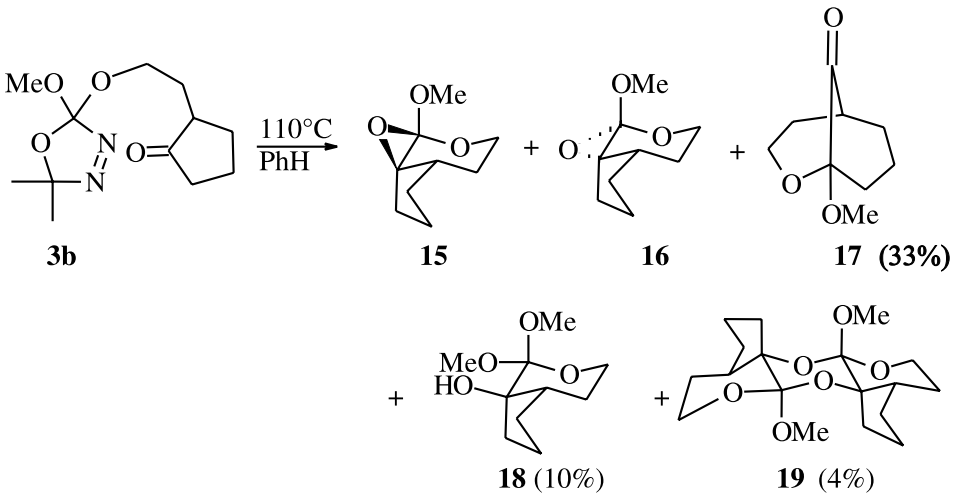
Preparation of oxadiazoline 3a

A solution of 2-acetoxy-2-methoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (**1**) in CH_2Cl_2, containing about 30% of an acyclic isomer (19), was treated with hydroxy ketone **2a** (21) and trifluoroacetic acid in dichloromethane. After washing with dilute base, the organic layer was dried and the solvent was evaporated. Chromatography of the residue (silica gel, hexane:ethyl acetate:Et_3N (85:15:0.5)) gave oxadiazoline **3a** (67% of pure product) as a colourless oil. IR (neat, KBr) (cm^{-1}): 2989, 2944, 2865, 1711, 1452, 1211, 1167, 1136, 914. ^1H NMR (300 MHz, $CDCl_3$, 1:1 mixture of two diastereoisomers) δ: 4.14 (dd, J = 9.9, 5.1 Hz, 1H, OCH_a),

Scheme 9.



Scheme 10.



4.04 (dd, J = 9.9, 5.1 Hz, 1H, OCH_a), 3.71 (dd, J = 9.9, 7.7 Hz, 1H, OCH_b), 3.59 (dd, J = 9.9, 7.7 Hz, 1H, OCH_b), 3.45 (s, 6H), 2.65 (m, 2H), 2.34 (m, 6H), 2.03 (m, 2H), 1.90 (m, 2H), 1.67 (m, 4H), 1.54 (s, 12H), 1.44 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 210.7, 137.1, 119.3, 63.9, 52.0, 50.4, 42.2, 31.4, 24.7, 24.2, 24.1. EI-MS *m*/*z* (%): molecular ion not observed, 225 ([M – OMe^+], 3), 170 (7), 129 (15), 111 (59), 94 (47), 73 (60), 55 (100). CI-MS (NH_3) *m*/*z*: 274 ([M + NH_4^+], 28).

Thermolysis of 3a in benzene

A solution of **3a** (0.51 g, 2 mmol) in benzene (20 mL) in a sealed tube was heated at 110°C for 18 h. Evaporation of the solvent left a residue that was chromatographed on silica (hexane:ethyl acetate, 90:10) to afford bicyclic ketone **5** (31%), hydroxy orthoester **6** (16%), **4** (7%), and compounds **7** (<5%).

Semipreparative gas chromatography (OV-17, 5%, helium at 50 mL min^{-1}; temperature program, 80°C for 5 min, increased at 4°C min^{-1} to 250°C; retention time 26–29 min) gave **6**, which is probably a product of oxirane methanolysis, as a semicrystalline material. A crystal suitable for X-ray crystallography could not be obtained. Exposure of the sample to the atmosphere led to its slow hydrolysis to **9**.

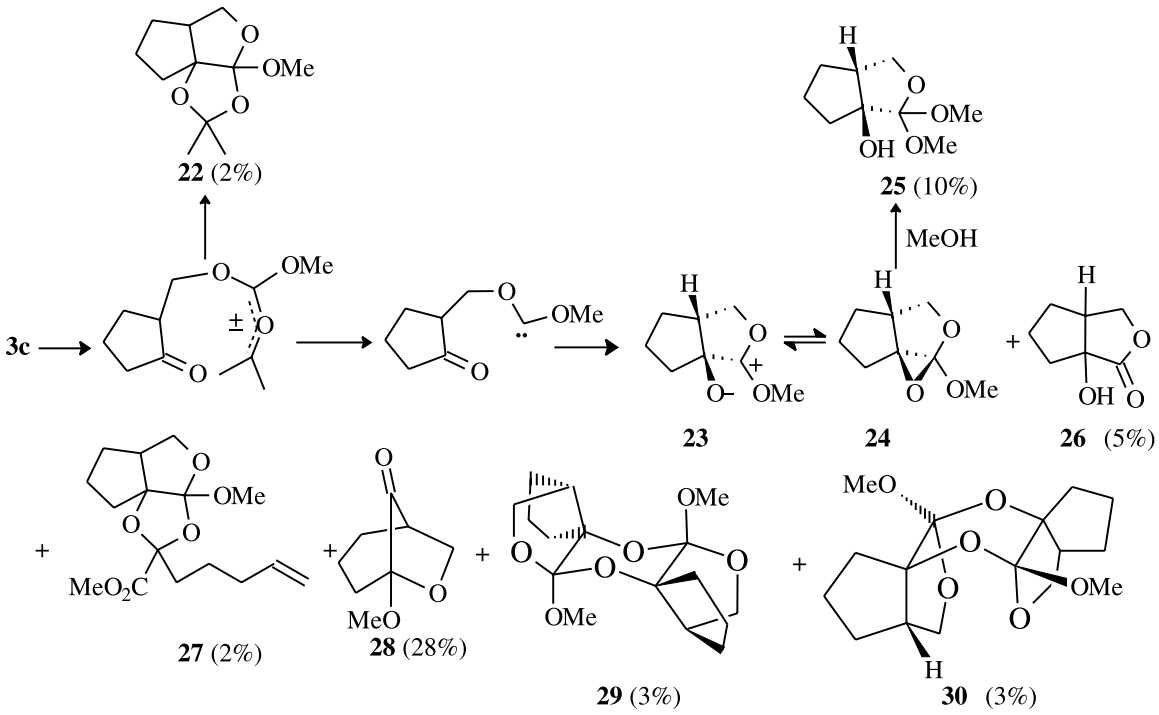
Product 4

Yield: 7%, colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.12 (dd, J = 8.3, 4.7 Hz, 1H), 3.57 (d, J = 8.3 Hz, 1H), 3.35 (s 3H), 2.20 (m, 1H), 2.03 (m, 1H), 1.44 (s, 6H), 1.4–1.85 (m, 7H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 126.5, 108.8, 87.6, 71.0, 51.4, 44.6, 32.1, 29.3, 28.1, 28.0, 23.5, 23.0. EI-MS *m*/*z* (%): 229 ([M + 1]$^+$, 4), 213 (55), 154 (45), 153 (48), 111 (41), 93 (100), 81 (66), 55 (84), 43(80). Compound **4** in $CDCl_3$ was converted rapidly to lactone **9** during storage.

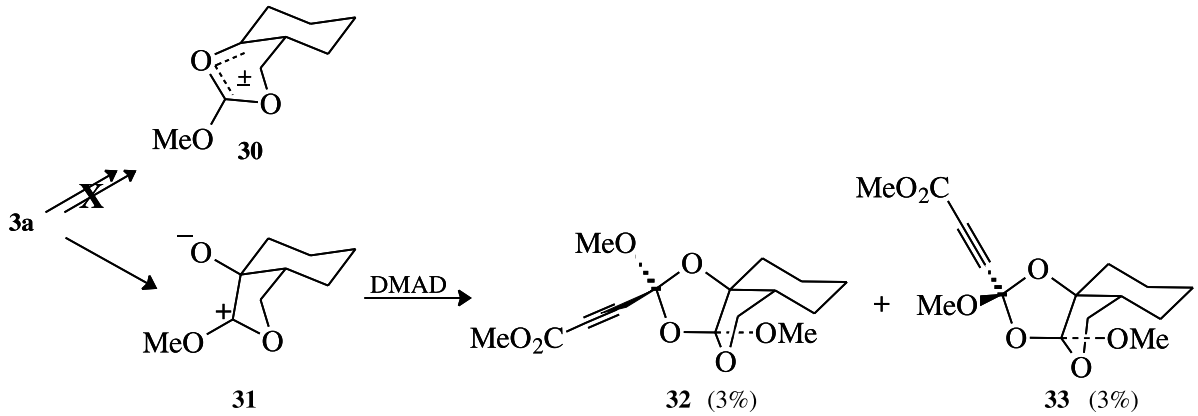
1-Methoxy-8-oxa-9-oxobicyclo[4.2.1]nonane (5)

Yield: 31%, colourless oil. IR (neat) (cm^{-1}): 2938, 2866, 1767, 1456, 1189, 1158, 1075, 998. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 4.34 (dd, J = 8.8, 5.2 Hz, 1H), 4.07 (d, J = 8.8 Hz, 1H), 3.28 (s, 3H), 2.67 (m, 1H), 1.15–1.90 (m, 8H). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 216.0, 104.9, 70.3, 51.1, 45.6, 33.0, 31.2, 23.7, 22.6. EI-MS *m*/*z* (%): 171 ([M + 1]$^+$, 15),

Scheme 11.



Scheme 12.



142 (42), 110 (68), 83 (55), 74 (100), 53 (92), 41 (100). CI-MS (NH_3) *m/z*: 188 ($[M + NH_4]^+$, 100).

Product 6

Semicrystalline. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.80 (dd, *J* = 14.4, *J* = 2.5 Hz, 2H), 3.39 (s, 3H), 3.35 (s, 3H), 2.43 (d, *J* = 1.4, 1H), 2.37 (m, 1H), 1.44–1.90 (m, 6H). EI-MS *m/z* (%): 171 ($[M – OMe]^+$, 100), 147 (18), 112 (73), 97 (56), 83 (23), 69 (14). Compound **6** was rapidly converted to lactone **9** during storage.

Product 7a

Colourless crystals, mp 118°C. ^{1}H NMR (200 MHz, C_6D_6) δ: 4.02 (t, *J* = 7.8 Hz, 2H), 3.50 (dd, *J* = 7.8, 4.1 Hz, 2H), 3.45 (s, 6H), 2.68 (m, 2H), 2.13 (m, 2H), 1.94 (m, 2H), 1.69–1.55 (m, 6H) 1.40–1.26 (m, 6H). ^{13}C NMR (50 MHz, C_6D_6) δ: 116.7, 79.6, 68.9, 48.7, 42.5, 29.9, 25.2, 22.3, 22.2. EI-MS *m/z* (%): 341 ($[M + 1]^+$, 100), 340 ($[M]^+$, 78), 339 (46), 154 (100), 153 (22), 139 (19), 109 (21), 95 (29), 79 (30). The connectivity and stereochemistry of **7a** were established by means of single crystal X-ray diffraction.

Product 7b

Colourless crystals, mp 148°C. ^{1}H NMR (200 MHz, C_6D_6) δ: 4.21 (t, *J* = 7.7 Hz, 2H), 3.45 (s, 6H), 3.21 (dd, *J* = 7.7, 3.3 Hz, 2H), 2.25 (m, 2H), 1.44–1.98 (m, 16H). ^{13}C NMR (50 MHz, C_6D_6) δ: 117.6, 80.0, 70.1, 48.1, 43.4, 31.6, 28.6, 23.5, 23.3.

Hydroxy lactone 9

Yield: 16% (formed during chromatography), colourless crystals, mp 129°C. IR (neat, KBr) (cm^{-1}): 3420 (br), 2972, 2879, 1769, 1439, 1372, 1211, 1161, 1011, 970. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 4.40 (dd, *J* = 8.6, 7.0 Hz, 1H), 4.05

(dd, J = 8.6, 7.5 Hz, 1H), 2.68 (br s 1H), 2.50 (m 1H), 1.32–1.93 (m, 8H). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 179.1, 73.2, 69.2, 41.0, 31.6, 23.6, 21.8, 21.0. EI-MS *m/z* (%): molecular ion not observed, 154 (13), 112 (42), 97 (57), 83 (78), 55 (100). CI-MS (NH_3) *m/z*: 174 ($[M + NH_4]^+$, 100). The connectivity and stereochemistry of **9** were established by means of single crystal X-ray diffraction.

Synthesis of 3b

A solution in CH_2Cl_2 of 2-acetoxy-2-methoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (**1**), containing about 40% of an acyclic isomer (19), was treated with hydroxy ketone **2b** and trifluoroacetic acid in dichloromethane. After washing with dilute base, the organic layer was dried and the solvent was evaporated. Chromatography of the residue gave pure oxadiazoline **3b** (57%) as a colorless oil. IR (neat) (cm^{-1}): 2961, 2885, 1744, 1449, 1212, 1136, 1125, 1108, 921. ^{1}H NMR (300 MHz, $CDCl_3$, 1:1 mixture of two diastereomers) δ: 3.70–3.85 (m, 4H, -OCH_2), 3.43 (s, 3H, -OCH_3), 3.42 (s, 3H, -OCH_3), 2.43–1.50 (m, 18H), 1.53 (s, 12H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 220.7, 137.1, 119.2, 63.1, 52.0, 46.4, 38.0, 29.8, 29.6, 24.3, 24.2, 20.9. EI-MS *m/z* (%): molecular ion not observed, 181, 153 (100), 129, 112, 111, 83 (100). CI-MS (NH_3) *m/z*: 274 ($[M + NH_4]^+$).

Thermolysis of 3b

A solution of **3b** (0.51 g, 2 mmol) in benzene (20 mL) in a sealed tube was heated at 110°C for 20 h. Evaporation of the solvent left a residue that was chromatographed on silica (hexane:ethyl acetate, 90:10) to afford bicyclic ketone **17** (33%), hydroxyorthoester **18** (~10% after thermolysis), and dimer **19** (ca. 4%).

Product 17

Yield: 33%, colourless oil. IR (neat) (cm^{-1}): 2946, 2861, 1740, 1464, 1452, 1164, 1064, 1044. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.09 (dd, J = 11.8, 6.1 Hz, 1H), 3.60 (d, J = 12.2, J = 4.4, Hz, 1H), 3.39 (s 3H), 2.86 (m, 1H), 1.51–2.26 (m, 8H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 212.8, 102.5, 65.0, 50.4, 45.4, 40.5, 35.9, 32.0, 17.9. HR-MS *m/z* calcd. for $C_9H_{14}O_3$: 170.0943; found: 170.0969.

Product 18

Only a few colourless crystals could be obtained for X-ray diffraction. The compound hydrolysed spontaneously to the corresponding hydroxylactone.

Product 19

Colourless crystals, yield ca. 3%. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.77 (m, 4H), 3.28 (s, 6H, -OCH_3), 2.73 (m, 2H), 2.18–1.32 (m, 16H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 108.9, 84.9, 61.4, 47.9, 42.6, 33.5, 27.8, 27.2, 20.9. The structure and stereochemistry were confirmed by means of single crystal X-ray diffraction.

Synthesis of 3c

A solution in CH_2Cl_2 of 2-acetoxy-2-methoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (**1**), containing about 40% of an acyclic isomer (19), was treated with hydroxy ketone **2c** and trifluoroacetic acid in dichloromethane. After washing with dilute base, the organic layer was dried and the solvent was evaporated. Chromatography of the residue gave pure oxadiazoline **3c** (60%) as a colorless oil. IR (neat) (cm^{-1}): 2959, 2888, 1742, 1458, 1211, 1140, 1104, 917. ^{1}H NMR (300 MHz, $CDCl_3$, mixture of two diastereoisomers) δ: 3.81–4.02 (overlapping multiplets, 4H), 3.43 (s, 3H), 3.42 (s, 3H), 1.60–2.42 (m, 14H), 1.54 (s, 6H), 1.53 (s, 3H), 1.52 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 218.5, 136.9, 119.5, 63.6, 63.5, 52.0, 48.8, 38.7, 27.0, 24,3, 24.1, 20.9. EI-MS *m/z* (%): molecular ion not observed, 211 ($[M - OMe]^+$, 9), 173 (38), 139 (11), 129 (10), 97 (100), 84 (26), 69 (100). CI-MS (NH_3) *m/z*: 260 ($[M + NH_4]^+$, 58).

Thermolysis of 3c

A solution of **3c** (0.51 g, 2 mmol) in benzene (20 mL) in a sealed tube was heated at 110°C for 20 h. Evaporation of the solvent left a residue that was chromatographed on silica (hexane:ethyl acetate, 90:10) to afford bicyclic ketone **28** (28%), **25** (10% isolated, unstable compound, hydrolysing, in part, to hydroxylactone **26** during the separation procedure), product **22** (2% isolated, undergoes hydrolyses to α-hydroxylactone **26**), hydroxylactone **26**, product **27**, some of which could have hydrolysed to **26** during TLC separation (5% isolated), and dimers **29** and **30** (about 3% each).

Product 22

Colourless oil. ^{1}H NMR (200 MHz, C_6D_6) δ: 4.09 (dd, J = 9.0 Hz, J = 6.4 Hz, 1H), 3.62 (s, 3H), 3.47 (dd, J = 9.0, J = 2.9 Hz, 1H), 2.57 (m, 1H), 2.32 (m, 1H), 2.0–1.55 (m, 4H), 1.54 (s, 3H), 1.50 (s, 3H), 1.27 (m, 1H). ^{13}C NMR (50 MHz, C_6 D_6) δ: 124.8, 109.4, 98.1, 70.9, 51.1, 50.1, 34.2, 31.3, 28.1, 27.7, 25.5. Product **22** hydrolysed easily to **26**.

Product 25

Colourless oil. IR (neat) (cm^{-1}): 3510 (br), 2954, 2881, 1449, 1365, 1168, 1135, 1113, 1045, 982. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.92 (t, J = 10.1 Hz, 1H), 3.37 (dd, J = 10.2, J = 5.6 Hz, 1H), 3.34 (s, 3H), 3.31 (s, 3H), 2.88 (br. s, 1H), 2.34 (m, 1H), 1.98–2.10 (m, 2H), 1.72–1.80 (m, 3H), 1.45 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 118.2, 90.6, 69.6, 51.5, 50.7, 47.9, 35.1, 32.6, 26.1. EI-MS *m/z* (%): 189 ($[M + 1]^+$, 5), 157 ($[M - OMe]^+$, 100), 98 (10), 75 (8).

Product 26

Colourless oil. IR (neat) (cm^{-1}): 3425 (br), 2962, 2876, 1765, 1446, 1383, 1211, 1156, 1008, 978. ^{1}H NMR (200 MHz, C_6D_6) δ: 3.74 (t, J = 9.3 Hz, 1H), 3.04 (dd, J = 9.4, J = 5.8 Hz, 1H), 2.91 (br s, 1H), 2.29 (m, 1H), 2.00–0.85 (m, 6H). ^{13}C NMR (50 MHz, C_6D_6) δ: 179.5, 83.6, 71.1, 46.4, 39.0, 31.3, 24.8. EI-MS *m/z* (%): 143 ($[M + 1]^+$, 41), 112 (10), 98 (94), 97 (100), 83 (19). CI-MS (NH_3) *m/z*: 160 ($[M + NH_4]^+$, 100).

Product 27

Colourless oil. IR (neat) (cm^{-1}): 3051, 2954, 2875, 1754, 1642, 1441, 1364, 1202, 1074, 1018, 929. ^{1}H NMR (200 MHz, C_6D_6) δ: 5.69 (m, 1H), 4.97 (m, 2H), 4.04 (dd, J = 9.1, J = 6.2 Hz, 1H), 3.69 (s, 3H), 3.43 (dd, J = 9.1, J = 1.6 Hz, 1H), 3.37 (s, 3H), 2.47 (m, 1H), 1.50–2.25 (m, 12H). ^{13}C NMR (125 MHz, C_6D_6) δ: 171.1, 138.4, 127.1, 115.2, 106.8, 98.7, 71.7, 51.7, 50.1, 36.0, 33.8, 32.7, 31.6, 25.9, 22.1. EI-MS *m/z* (%): 264 (9), 254 (100), 253 ([M – CO-

$(OCH_3)]^+$, 45). HR-MS *m/z* calcd. for $C_{16}H_{24}O_6$: 312.1573; found: 312.1555. Compound **27** hydrolysed readily to **26**.

Product 28

Colourless oil. IR (neat) (cm^{-1}): 2947, 2888, 1774, 1449, 1330, 1178, 1094, 959, 721. ^1H NMR (200 MHz, $CDCl_3$) δ: 4.28 (dd, *J* = 8.4 Hz, *J* = 4.5 Hz, 1H), 4.21 (t, *J* = 8.4 Hz, 1H), 3.36 (s, 3H), 2.60 (m, 1H), 1.60–2.15 (m, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 211.9, 102.5, 67.8, 52.0, 45.3, 40.8, 34.6, 18.6. EI-MS *m/z* (%): 157 ($[M + 1]^+$, 5), 128 (58), 113 (10), 97 (32), 84 (20), 74 (100). CI-MS (NH_3) *m/z*: 174 ($[M + NH_4]^+$, 100).

Product 29

^1H NMR (200 MHz, C_6D_6) δ: 4.22 (t, *J* = 8.6 Hz, 2H), 3.38 (s, 6H), 3.32 (dd, *J* = 8.6, *J* = 5.3 Hz, 2H), 2.87 (m, 2H), 2.27 (m, 2H), 1.45–2.05 (m, 10H). ^{13}C NMR (50 MHz, C_6D_6) δ: 115.2, 92.1, 69.6, 49.2, 47.3, 36.4, 31.5, 25.4. EI-MS *m/z* (%): 312 ($[M]^+$, 2), 281 ($[M - OCH_3]^+$, 9), 141 (81), 140 (100), 139 (63), 112 (62), 111 (42), 79 (27). The structure and stereochemistry were secured by means of single crystal X-ray diffraction. The structure of **30**, an isomer of **29**, was also determined by means of single crystal X-ray diffraction.

Thermolysis of 3a in the presence of dimethyl acetylenedicarboxylate (DMAD)

A solution of **3a** (0.26 g, 1 mmol) and DMAD (1.3 mmol) in benzene (10 mL) in a sealed tube was heated at 110°C for 20 h. Evaporation of the solvent left a residue that was chromatographed on silica (hexane:ethyl acetate, 90:10) to afford a mixture of diastereomers **32** and **33**. The diastereomers were separated with a Merck (LOBAR, MPLC) silica column, eluent EtOAc–hexane, 10:90).

Product 32

Colourless oil, yield: 3%. IR (neat) (cm^{-1}): 2950, 2860, 2248, 1724, 1439, 1254, 1062, 909. ^1H NMR (300 MHz, $CDCl_3$) δ: 4.28 (dd, *J* = 8.5, *J* = 4.6 Hz, 1H), 3.77 (s, 3H), 2.69 (d, *J* = 8.5 Hz, 1H), 3.34 (s, 3H), 3.55 (s, 3H), 3.47 (s, 3H), 2.3 (br. m, 1H), 2.12 (m, 1H), 1.30–1.85 (m, 8H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 153.2, 126.8, 111.5, 90.2, 80.9, 72.8, 71.8, 52.9, 51.8, 51.4, 43.4, 29.8, 27.8, 23.1, 22.6. EI-MS *m/z* (%): molecular ion not observed, 281 ($[M - CO]^+$, 32), 229 (13), 140 (35), 111 (100), 93 (64).

Product 33

Colourless crystals, yield: 3%, mp 68°C. ^1H NMR (300 MHz, $CDCl_3$) δ: 4.19 (dd, *J* = 8.6, *J* = 4.3 Hz, 1H), 3.77 (s, 3H), 3.61 (d, *J* = 8.7 Hz, 1H), 3.56 (s, 3H), 3.40 (s, 3H), 2.25 (br m, 1H), 2.14 (m, 1H), 1.30–1.90 (m, 8H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 153.0, 127.0, 112.0, 88.8, 79.5, 72.8, 71.3, 52.9, 52.0, 51.5, 43.8, 30.6, 27.7, 23.1, 22.7. The structure of **33** (Scheme 12) was determined by means of single crystal X-ray diffraction.

Acknowledgments

Financial support from the Natural Sciences and Engineering Research Council of Canada (NSERC) is gratefully acknowledged. We thank Dr. Jim Britten for the X-ray crystallography and Professor Paul Harrison for the use of his MPLC equipment.

References

1. (*a*) R.W. Hoffmann and H. Häuser. Tetrahedron, **21**, 891 (1965); (*b*) D.M. Lemal, E.P. Gosselink, and S.D. McGregor. J. Am. Chem. Soc. **88**, 582 (1966); (*c*) R.W. Hoffmann. Angew. Chem. Int. Ed. Engl. **10**, 529 (1971); (*d*) R.W. Hoffmann, K. Steinbach, and B. Dittrich. Chem. Ber. **106**, 2174 (1973); (*e*) R.W. Hoffmann and M. Reiffen. Chem. Ber. **109**, 2565 (1976); (*f*) R.A. Moss and J.K. Huselton. J. Chem. Soc., Chem. Commun. 950 (1976); (*g*) G. Hömberger, W. Kirmse, and R. Lelgemann. Chem. Ber. **124**, 1867 (1991); (*h*) G. Frenzen, M. Rischke, and G. Seitz. Chem. Ber. **126**, 2317 (1993); (*i*) C. Gerninghaus, A. Kümmell, and G. Seitz. Chem. Ber. **126**, 733 (1993); (*j*) P. Couture, D.L. Pole, and J. Warkentin. J. Chem. Soc., Perkin Trans. 2, 1565 (1997); (*k*) J. Warkentin. J. Chem. Soc., Perkin Trans. 1, 2161 (2000).
2. (*a*) R.A. Moss, C.B. Mallon, and C.-T. Ho. J. Am. Chem. Soc. **99**, 4105 (1977); (*b*) R.A. Moss. Acc. Chem. Res. **13**, 58 (1980); (*c*) R.A. Moss, C.M. Young, L.A. Perez, K. Krogh-Jespersen. J. Am. Chem. Soc. **103**, 2413 (1981).
3. N.G. Rondan, K.N. Houk, and R.A. Moss. J. Am. Chem. Soc. **102**, 1770 (1980).
4. N. Kuhn, J. Fahl, R. Boese, G. Henkel. Z. Naturforsch. **53b**, 881 (1998).
5. J.A. Dunn, J.P. Pezacki, M.J. McGlinchey, and J. Warkentin. J. Org. Chem. **64**, 4344 (1999).
6. J.P. Ross, P. Couture, and J. Warkentin. Can. J. Chem. **75**, 1331 (1997).
7. (*a*) H.-W. Wanzlick. Angew. Chem. Int. Ed. Engl. **1**, 75 (1962); (*b*) G. Doleschall. Tetrahedron Lett. **21**, 4183 (1980).
8. R.A. Braun. J. Am. Chem. Soc. **87**, 5516 (1965).
9. D.L. Pole and J. Warkentin. J. Org. Chem. **62**, 4065 (1997).
10. (*a*) M. Dawid, P.C. Venneri, and J. Warkentin. Can. J. Chem. **79**, 110 (2001); (*b*) M. Dawid, P.C. Venneri, and J. Warkentin. Can. J. Chem. **79**, 1294 (2001).
11. D.L. Pole and J. Warkentin. Liebigs Ann. 1907 (1995).
12. P.C. Venneri and J. Warkentin. Can. J. Chem. **78**, 1194 (2000).
13. M. Dawid, G. Mloston, and J. Warkentin. Org. Lett. **3**, 2455 (2001).
14. N. Kuhn, H. Bohnen, and G. Henkel. Z. Naturforsch. **49b**, 1473 (1994).
15. N. Kuhn, M. Steimann, and G. Weyers. Z. Naturforsch. **54b**, 427 (1999).
16. N. Kuhn, K. Eichele, and M. Walker. Z. Anorg. Allg. Chem. **627**, 2565 (2001).
17. D.L. Boger and C.E. Brotherton. Tetrahedron Lett. **25**, 5611 (1984).
18. K. Kassam and J. Warkentin. J. Org. Chem. **59**, 5071 (1994).
19. K. Kassam, D.L. Pole, M. El-Saidi, and J. Warkentin. J. Am. Chem. Soc. **116**, 1161 (1994).
20. H.N.C. Wong. Houben-Weyl: Methods of organic chemistry. Vol. E17e. *Edited by* A. deMeijere. Georg Thieme Verlag, Stuttgart. 1998. pp. 513–514.
21. H.E. Zimmerman and J. English. J. Am. Chem. Soc. **76**, 2285 (1954).