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Unsymmetrical ozonolysis of carbohydrate derived norbornene systems

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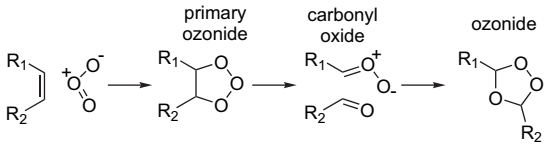
Abstract—The ozonolysis of carbohydrate derived norbornene systems in participating solvents demonstrated that different remote controlling factors could induce the regioselective fragmentation of the primary ozonide. The *exo* norbornene series afforded a complete regioselective process.

1. Introduction

Ozonolysis is a widely applied organic reaction in academic research and industrial developments. It is used to cleave multiple carbon–carbon or carbon–heteroatom bonds and even though there are many alternatives to this reaction, it is still a clean and cost effective option to perform a sustainable oxidative cleavage.[1] Extensive investigation of the mechanism of alkene ozonolysis has confirmed the basic pathway originally proposed by Criegee[2] in his seminal work several decades ago.

The most thoroughly developed proposal view the ozonolysis reaction as a three-step mechanism: (i) a [3+2] dipolar cycloaddition reaction of ozone with the alkene leading to formation of a primary ozonide (PO) (1,2,3-trioxolane), (ii) a cycloreversion process to provide the transient carbonyl oxide and a stable carbonyl compound, which may proceed in two different ways in the case of unsymmetrically substituted alkenes, and (iii) recombination of the carbonyl oxide and the carbonyl compound gives the ozonide (1,2,4-trioxolane) (Scheme 1).



Scheme 1. Overview of alkene ozonolysis.

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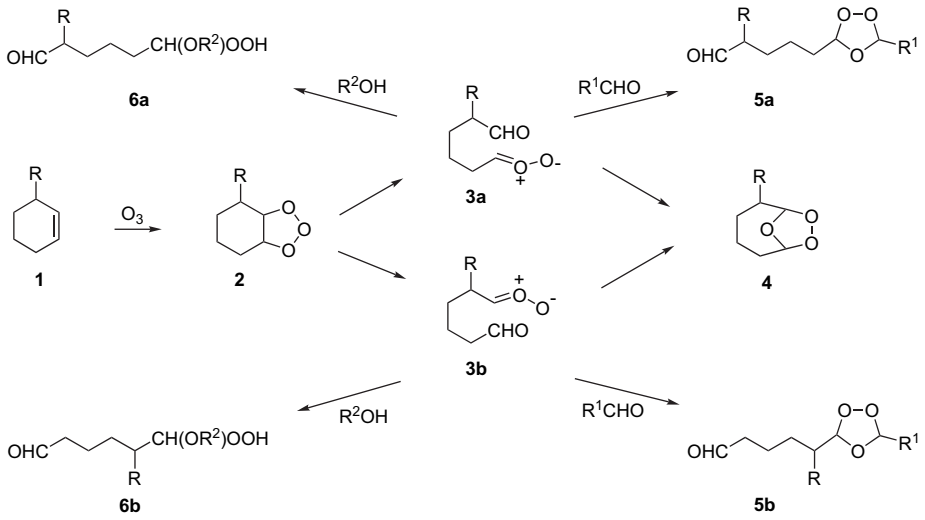
The primary concern with the ozonolysis reaction rests on safety issues. Ozonolysis initially generates ozonides and other unstable peroxides species often capable of spontaneous and explosive decomposition reactions.[3] To achieve the direct production of the desired carbonyl products, avoiding the formation of the high-energy ozonide intermediates generated in non-participating solvents, different methods have been reported as safer alternatives.[4]

In a recent report, Dussault et al.[5] suggested intercepting one of the three intermediates but the ozonide appeared too stable to be a target and the primary ozonides cannot react with nucleophiles in the presence of ozone. These facts leave only the carbonyl oxides as suitable targets for in situ trapping in order to develop a safer ozonolysis procedure.

Carbonyl oxides, produced by a spontaneous fragmentation of the primary ozonides even at low temperatures, are considered as the central species to the mechanism of ozonolysis. Even though the intermediates could never be directly detected in situ, sufficient evidences were accumulated in support of their role in the Criegee mechanism.[6] Although their structural and electronic features have aroused considerable interest in this research area, all the efforts devoted to study these transient intermediates still did not clarify their zwitterionic or diradical character.[7] Throughout this work the zwitterionic representation will be used.

In a typical procedure, the carbonyl oxide is trapped by the newly formed carbonyl group derivative to give the 1,2,4-trioxolane **4** (Scheme 2). However, the transient carbonyl oxide could also be trapped by another carbonyl derivative present in the reaction medium, producing a cross ozonide



Scheme 2.

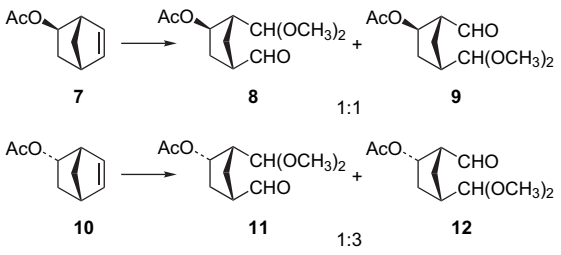
5a,**b**. Alternatively, when participating protic solvents such as alcohols are used, the reactive intermediate is intercepted by the nucleophilic attack of the solvent, yielding an α-alkoxy hydroperoxide **6a**,**b** (Scheme 2).

Schreiber et al.[8] was the first to take advantage of the symmetry breaking property of cyclic alkene ozonolysis in participating solvents, providing a simple entry to linear molecules with different functional groups at each terminus. For non-symmetric alkenes, one could make use of the different possible fragmentation pathway of a primary ozonide to generate new functionality in a regioselective manner. In the case of cyclic or polycyclic compounds the process could unveil a completely different carbon skeleton connectivity with a very useful functional group arrangement.[9,10]

Since the PO fragmentation defines the regioselectivity of the reaction course, much of the current interest in this process centers on the factors that affect the direction of the PO cleavage. Intense research activity has been pursued during the past years to clarify the effect of different types or number of substituents attached to the sp^2 carbons[11] on the fragmentation process. Many examples reported in the literature had led to understand at least three well known factors that play an important role in determining the regiochemistry of the PO cleavage: (i) the electronic effect of the substituent attached to the C–C double bond, (ii) the electronic effect of the heteroatom substituent at the allylic position, and (iii) the steric effect of the allylic dialkyl substituent.

In the first case, it has been established that the cleavage of the PO tends to occur along the path, which results in the placement of electron-donating substituents on the carbonyl oxide fragment.[12] This observation means that the carbonyl oxide will be formed on the carbon whose substituents are better suited to stabilize a developing positive charge.[13] Literature reports[8,9a,14] indicated that simple inductive arguments should reliably predict the electronic effect of the heteroatom substituent at the allylic position of an unsymmetrical cycloalkene. The steric effect of the allylic dialkyl substituents plays an important role in the cycloreversion process of the PO, since it yields the carbonyl oxide product with the geminal dialkyl groups most remote from the carbonyl oxide fragment.[15]

Remote factors have also been reported to control the regioselectivity of the PO fragmentation, but it is not clear how do they affect the process. Schreiber's report[8] on the ozonolysis of the *endo*-5-norbornen-2-ol acetate **10** is the first example of the effect of a remote substituent on the regiochemical outcome of the reaction (Scheme 3).

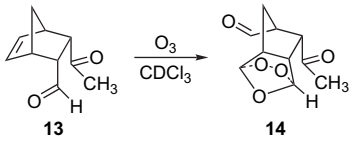


Scheme 3.

The workup procedure initially yielded the dimethyl acetal of the carbonyl terminal and subsequently the reduction of the alkoxy hydroperoxide afforded the free aldehyde group. Taking into account that the preferred direction of cleavage of **10** is opposite to that predicted by consideration of the inductive effects of the acetyloxy substituent, the former results suggested that the cleavage of the PO is not governed by the electronic effect of the remote substituent. Since this unsymmetrical ozonolysis published in 1982, we could only find a few examples reported in the literature with moderate regiocontrol and yielding in all cases variable mixtures of compounds.[16]

The first observation of an exclusive fragmentation of the PO controlled by remote carbonyl groups and stereoselective formation of final cross ozonides through the ozonolysis of

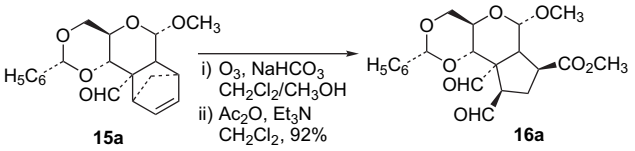
norbornene derivatives was reported by Wu et al.[12,17] (Scheme 4).



Scheme 4.

The competitive studies made by Wu's group with different series of *endo* substituted norbonene derivatives allowed them to propose that the fragmentation of the trioxolane ring was induced by the *endo* formyl group through space rather than through bond.

This regioselective process could find a wide variety of applications in organic synthesis if it could afford only one isomer instead of a mixture of the two possible ones. In the course of our ongoing research on the synthesis of pentalenolactone,[18] we found that the non-symmetric ozonolysis of a carbohydrate derived norbornene system (**15a**) showed an exceptional high regioselectivity of the PO fragmentation, which after workup afforded a polyfunctionalized cyclopentane moiety bearing two aldehyde groups (one from the original starting material attached at the quaternary center and other from the newly formed one) and a methyl ester as the unique product in 92% isolated yield (Scheme 5).



Scheme 5.

This highly non-symmetric process is evidently controlled by substituents that are at least a distance of two carbons from the double bond. A noteworthy observation is the fact that the carbonyl group attached at the quaternary center is in an *exo* position with respect to the olefin in this norbornene system.

Comparison of Wu's norbornene system **13** with **15a** suggests that, at least in our example, the carbonyl group does not have a favorable spatial arrangement to induce the ozonide fragmentation (Fig. 1). In this case, the carbonyl interaction through the space could not be the factor that controls the cleavage of the PO, as in the study reported by Wu and co-workers. Hence, there must be also other remote factors that control the outcome of this reaction.

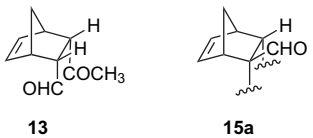


Figure 1. Comparison between *endo* and *exo* norbornene systems.

2. Results and discussion

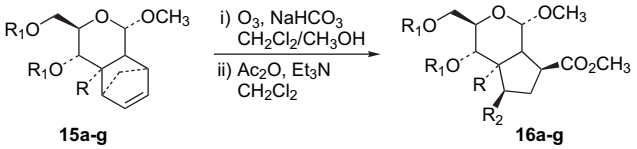
This result encourages us to further investigate the directing effects of other factors. In order to do so, we used cycloadduct **15a** as starting material to prepare several analogs, in which we replaced the aldehyde group by other functional groups with different steric and electronic demands. We also released part of the cyclic system tension by removing the benzylidene acetal group. The ozonolysis reactions of cycloadducts **15a–g** were carried out in a dichloromethane–methanol solution with solid $NaHCO_3$ in suspension. The crude reaction mixtures were then treated with acetic anhydride and triethylamine in dichloromethane.

The structure determination of all products was based on spectroscopic evidences. The ^1H and ^{13}C NMR signals were assigned by using homo and heteronuclear 2D NMR techniques and NOE experiments.[19] In all cases, we found the same regioselectivitiy and only one of the two possible regioisomers was isolated in good to very good yields. The results in Table 1 showed that the PO fragmentation regioselectivity is independent of the nature of the functional group attached at the quaternary carbon.

Ozonolysis of norbornenes **15a–g** may proceed through the mechanism depicted in Scheme 6. Since the isomeric products were not detected, formation of the carbonyl oxides **19a–g** from the primary ozonides **17a–g** should be excluded. Once the carbonyl oxide is formed, it would be quickly trapped by methanol to produce the corresponding α-alkoxy hydroperoxide. Finally, the hydroperoxide would be dehydrated with acetic anhydride and triethylamine to afford the corresponding ester derivative.

One of the common structural features among all these molecular moieties is the quaternary carbon. Based on these results, it seems reasonable to suggest that this quaternary center rather than any of the susbtituents could have a major influence on the regioselective fragmentation of the PO.

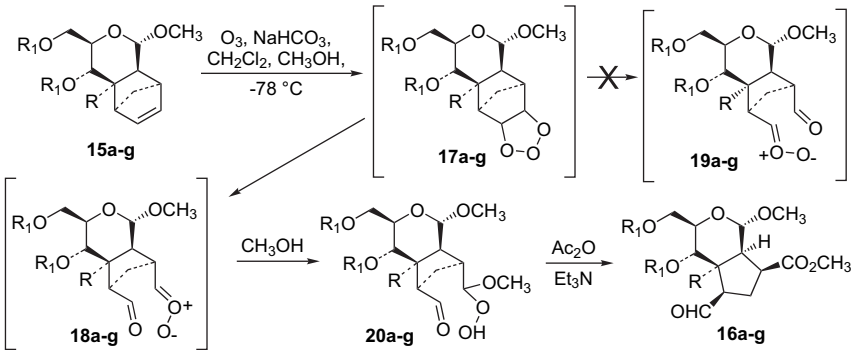
Table 1. Ozonolysis of *exo* norbornene systems



Entry	Starting material	R	R_1	R_2	Yield (%)
1	**15a**	CHO	Benzylidene acetal	CHO	92
2	**15b**	CH_2OH	Benzylidene acetal	CHO	69
3	**15c**	CO_2CH_3	Benzylidene acetal	CHO	95
4	**15d**	$CH(OH)CH_2CH_3$[a]	Benzylidene acetal	CHO	62
5	**15e**	$COCH_2CH_3$	Benzylidene acetal	CHO	45
6	**15f**	CH_2OAc	Benzylidene acetal	CHO	96
7	**15g**	CH_2OAc	Acetate	=CHOAc[b]	86

[a] Configuration of the secondary alcohol was not determined, only one of the epimers was ozonized (the more polar one).

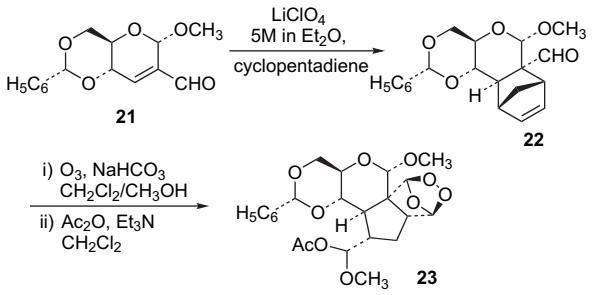
[b] The ozonolysis of the norbornene **15g** afforded the enol acetate derivative as the only product, the stereochemistry of the double bond was not determined.



Scheme 6.

To test this hypothesis, we planned to synthesize a new norbornene skeleton with a susbtituent attached at the other ring fusion position.

In order to achieve our goal, we first prepared the dienophile **21** in an efficient manner.[20] Reaction of aldehyde **21** with cyclopentadiene provided cycloadduct **22** in only 26% yield as the major adduct (Scheme 7).

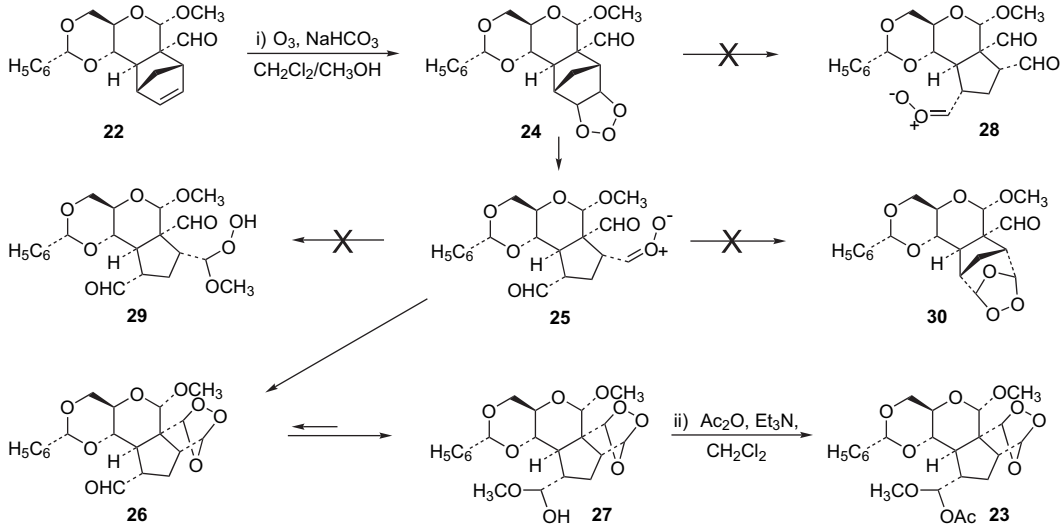


Scheme 7.

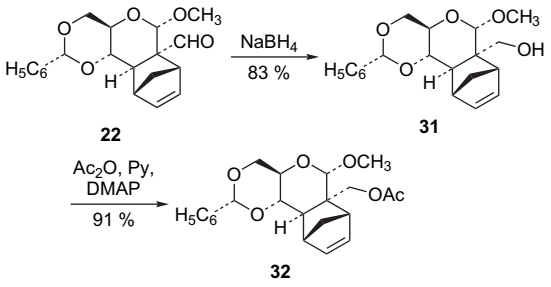
Unfortunately, the product was the result of the diene approach from the β face of the dienophile **21** in an *endo* manner. Despite of this result that positioned the carbonyl group in an *endo* mode with respect to the norbornene system and hence, could not discard the interaction of the carbonyl group through the space, we decided to explore the ozonolysis of this *endo* cycloadduct.

The ozonolysis reaction of cycloadduct **22** afforded product **23** in 54% yield.[21] We verified through the ^{1}H NMR spectrum of the crude material that it was the only product formed.

The analysis of the reaction outcome and the possible alternative pathway that the ozonolysis reaction could undergo, showed a high degree of regio- and stereocontrol. The reaction of cycloadduct **22** with ozone yielded the primary ozonide **24**, which upon regioselective fragmentation afforded only one of the two possible transient carbonyl oxide intermediates. The carbonyl oxide **25** was trapped by one of the two aldehyde groups present in the molecule at this stage and formed the 1,2,4-trioxolane intermediate **26**. It was not possible to detect any by-products derived from the other two possible competing processes: neither the reaction of the carbonyl oxide with methanol and concomitant formation of the methoxy hydroperoxide **29** nor its recombination



Scheme 8.



Scheme 9.

with the carbonyl group generated at the other terminus of the double bond to produce the ozonide **30**. Further diastereoselective reaction of the carbonyl group at C-19 with methanol afforded a hemiacetal **27**, which upon acetylation yielded the final product **23** (Scheme 8).

As it could be expected, it seems evident from this result that the carbonyl interaction through the space could be the dominating effect in the regioselective fragmentation of the PO. At this point, we wonder which could be the ozonolysis outcome if we replace the carbonyl group by other functional group. Reduction of the aldehyde **22** to the corresponding alcohol **31** and subsequent acetylation of the primary hydroxyl group afforded the acetate **32** (Scheme 9). Ozonolysis of the primary alcohol **31** under previously described conditions afforded a mixture of two products in a ratio of 2:1. After purification, the structure of the less polar and minor compound was identified as the lactone **36**, derived from the intramolecular carbonyl oxide trapping by the adjacent primary hydroxyl group (Scheme 10). The major and more polar compound was identified as the hemiacetal **35** derived from the attack of the primary alcohol on the newly formed aldehyde.

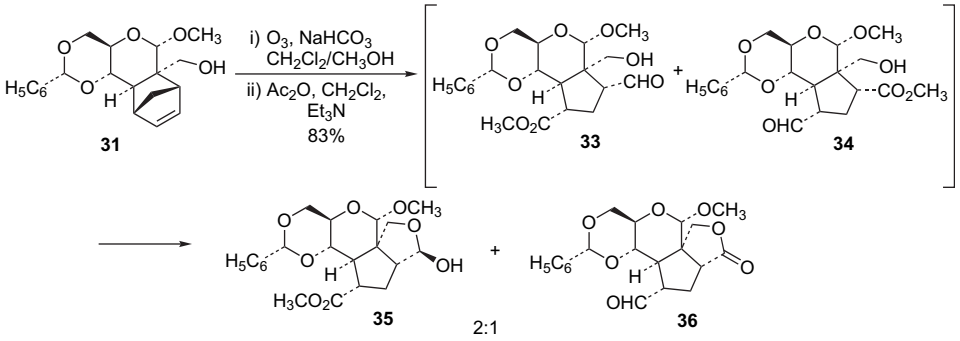
This example may demonstrate that the ability of an alcohol group to control the PO fragmentation through the space is lower than the aldehyde group, even though it could act as an intramolecular trapping agent of the carbonyl oxide once it is formed. Again, like in the previous series of compounds, the major product is the regioisomer derived from the generation of the carbonyl oxide at the more distant position from the quaternary center.

The acetylated derivative **32** also yielded a mixture of two isomeric products in a ratio of 3:1 determined by ^{1}H NMR integration. The mixture was inseparable by flash chromatography although its spectrum revealed that each compound was bearing an aldehyde and a methyl ester group besides the original acetate group. This data allowed us to assume that the mixture was formed by the two possible regioisomers (Scheme 11).

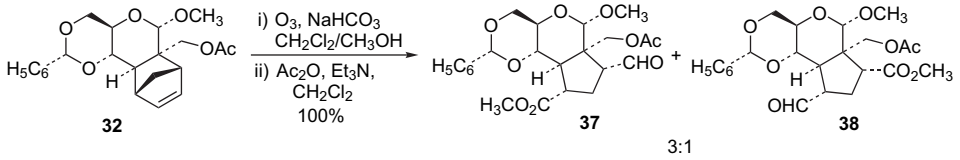
To determine the regioselectivity of this reaction, it was necessary to assign the structure to each isomer. For this reason, we transformed both compounds into the corresponding primary alcohols, by reducing the aldehyde groups with sodium borohydride.

The reaction afforded two primary alcohols: **39** as major and **40** as minor products (Scheme 12).

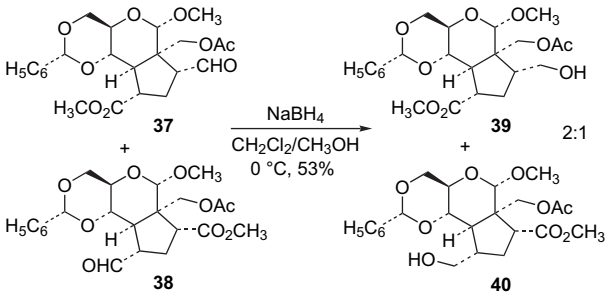
The major fraction was rather unstable to be isolated. This product was quickly converted into a less polar compound, which was identified without ambiguity as the lactone **41**, which was generated by the intramolecular attack of the primary alcohol to the methyl ester (Scheme 13). Therefore, the major isomer obtained from the ozonolysis reaction was compound **37**. This case made evident that the directing effect of an acetate group is lower than the hydroxyl group and much lower than the aldehyde group.



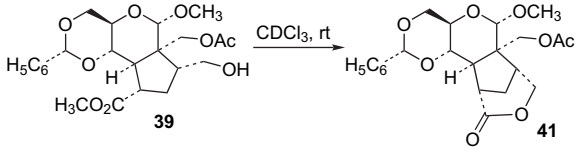
Scheme 10.



Scheme 11.



Scheme 12.



Scheme 13.

3. Conclusion

It is interesting to notice that according to these results, in a norbornene system with substituents in an *exo* position, the methyl ester and consequently the carbonyl oxide are always formed in the carbon more distant from the quaternary carbon. In the case of the norbornene system with substituents in an *endo* position, the carbonyl group probably exerts a dominant effect in the regioselectivity of the PO fragmentation as proposed by Wu, but when this functional group is replaced by probably less interacting groups (in our case an hydroxyl or an acetate) the regioselectivity is reversed showing that at least two opposing factors are taking place and the position of the quaternary center could be the dominating one. More studies are needed to draw a better interpretation of the remote factors that affect the PO fragmentation pathway but in any case these results are a starting point for further studies that will be reported in due course.

4. Experimental section

4.1. General

Melting points were taken on a Microscope Heating Stage apparatus and are uncorrected. Optical rotations were recorded with a digital polarimeter. IR spectra were recorded on a FTIR or dispersive spectrometer. Nuclear magnetic resonance spectra were recorded on a 200 MHz spectrometer with Me_4Si as internal standard and chloroform-*d* as solvent. Reactions were monitored by TLC on 0.25 mm Silica Gel plates (60F254), using UV light and anisaldehyde–H_2SO_4–AcOH as detecting agents. Flash column chromatography, using Silica Gel 60H, was performed by gradient elution created by mixtures of hexanes and increasing amounts of EtOAc. Reactions were performed under an argon atmosphere with dry, freshly distilled solvents under anhydrous conditions, unless otherwise noted. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, unless otherwise stated.

4.2. Synthesis of the *exo* norbornene systems

4.2.1. (1*S*,2*S*,3*S*,5*R*,8*R*,10*S*,11*S*,12*R*) 10-Methoxy-5-phenyl-4,6,9-trioxatetracyclo [10.2.1.0^{2,11}.0^{3,8}]pentadec-13-ene-2-carbaldehyde (15a). It was prepared according to the procedure described in Ref. 18.

4.2.2. (1*S*,2*S*,3*S*,5*R*,8*R*,10*S*,11*S*,12*R*) 2-Hydroxymethyl-10-methoxy-5-phenyl-4,6,9-trioxatetracyclo [10.2.1.0^{2,11}.0^{3,8}]pentadec-13-ene (15b). Cycloadduct **15a** (100.5 mg, 0.294 mmol) was dissolved in MeOH (3 mL) and cooled to 0 °C. Sodium borohydride (15.0 mg, 0.40 mmol) was added, followed by stirring at 0 °C for 20 min. Solution was diluted with ethyl acetate, washed with water, dried over Na_2SO_4, and concentrated in vacuo. The resulting crude product was purified by flash chromatography to furnish the alcohol **15b** (80.5 mg, 0.29 mmol, 79.6%). Colorless oil; $[\alpha]_D^{20}$ +41.7 (*c* 1.34, $CHCl_3$); IR (film): ν_{max} (cm^{-1}) 3556, 2956, 2887, 1450, 1406, 1368, 1095, 1057, 747, 699; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.45–7.34 (m, 5H), 6.43 (m, 1H), 6.35 (m, 1H), 5.42 (s, 1H), 4.32–4.22 (m, 3H), 3.93–3.81 (m, 1H), 3.60–3.50 (m, 3H), 3.36 (br s, 1H), 3.30 (s, 3H), 2.95 (br s, 1H), 2.87 (br s, 1H), 1.84 (t, *J*=3.0 Hz, 1H), 1.65 (d, *J*=9.0 Hz, 1H), 1.47 (br d, *J*=9.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 139.0, 137.2, 136.3, 129.1, 128.3, 125.9, 102.0, 101.9, 82.9, 69.7, 67.7, 59.3, 54.6, 51.0, 51.0, 46.7, 46.0, 45.2; HRMS *m*/*z* 362.1979 [(M+NH$_4^+$); calcd for $C_{20}H_{24}O_5$: 362.1967)].

4.2.3. (1*S*,2*S*,3*S*,5*R*,8*R*,10*S*,11*S*,12*R*) 10-Methoxy-5-phenyl-4,6,9-trioxatetracyclo [10.2.1.0^{2,11}.0^{3,8}]pentadec-13-ene-2-carboxylic acid methyl ester (15c). To a solution of cycloadduct **15a** (111 mg, 0.326 mmol) in *t*-BuOH (1 mL) were added aqueous NaH_2PO_4 (0.65 M, 0.3 mL, 0.195 mmol) and 28% H_2O_2 (0.08 mL, 0.648 mmol). The mixture was cooled to 0 °C, and $NaClO_2$ (1 M, 0.65 mL, 0.65 mmol) was added. The mixture was stirred at room temperature for 20 h, then the solution was extracted with ethyl acetate and washed with water. The aqueous phase was treated with HCl (0.1 M) until acidic reaction to pH paper and was extracted with ethyl acetate. The combined organic extract was dried (Na_2SO_4) and the volatiles removed under reduced pressure. The crude product was dissolved in a 2:3 mixture of Et_2O/$CHCl_3$ (20 mL) and the resulting solution was cooled at 0 °C. Ethereal solution of diazomethane was added dropwise until the reaction mixture turned light yellow. After stirring for 30 min at 0 °C, acetic acid was slowly added until disappearance of the yellow coloration. The volatiles were removed in vacuo, and the residual oil was purified by flash chromatography to furnish the methyl ester **15c** (92.1 mg, 0.25 mmol, 76%). Colorless oil; $[\alpha]_D^{27}$ +41.4 (*c* 1.10, $CHCl_3$); IR (film): ν_{max} (cm^{-1}) 2940, 2870, 1735, 1465, 1455, 1380, 1370, 1240, 1220, 1100, 1065, 1035, 920, 745, 705; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.34–7.31 (m, 5H), 6.38 (br s, 2H), 5.43 (s, 1H), 4.33 (d, *J*=2.81 Hz, 1H), 4.29–4.10 (m, 2H), 3.76 (s, 3H), 3.64–3.47 (m, 2H), 3.26 (d, *J*=9.36 Hz, 1H), 3.36 (s, 3H), 2.96 (br s, 1H), 2.76 (t, *J*=3.18 Hz, 1H), 1.60 (br d, *J*=9.0 Hz, 1H), 1.31 (br d, *J*=9.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 174.1, 137.5, 137.2, 129.0, 128.9, 128.1, 126.1, 102.1, 101.4, 79.5, 69.5, 59.3, 58.5, 55.0, 52.1, 51.0, 48.7, 47.5, 46.2. Anal. Calcd for $C_{21}H_{24}O_6$: C 67.73, H 6.50, O 25.78. Found: C 67.66, H 6.54.

4.2.4. (1*S*,1′undefined,2*R*,3*S*,5*R*,8*R*,10*S*,11*S*,12*R*) 10-Methoxy-5-phenyl-2-(1′-hydroxy) propyl-4,6,9-trioxatetracyclo [10.2.1.0^{2,11}.0^{3,8}]pentadec-13-ene (15d$_{\text{less polar}}$ and 15d$_{\text{more polar}}$). Li wire (945 mg, 135 mmol) in anhydrous THF (100 mL) was sonicated in an ultrasound cleaning bath while a mixture of aldehyde **15a** (2.716 g, 7.94 mmol) and EtBr (8.89 mL, 119.1 mmol) in anhydrous THF (60 mL) was slowly added at room temperature. After 2 h the reaction was completed, diluted with Et_2O, poured onto a 10% solution of NH_4Cl at 0 °C, and successively extracted with Et_2O. The combined organic layer was washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The crude product was purified by flash chromatography to furnish the two separated epimeric alcohols **15d** in a combined amount (2.068 g, 70%) and a 1:1 ratio.

4.2.4.1. Compound 15d$_{\text{(less polar)}}$. Colorless oil; $[\alpha]_D^{20}$ +36.4 (*c* 1.00, $CHCl_3$); IR (film): ν_{max} (cm^{-1}) 3550, 2970, 2875, 1475, 1410, 1375, 1162, 1096, 1064, 1012, 973, 925, 757, 704; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.48–7.36 (m, 5H), 6.46 (m, 1H), 6.34 (m, 1H), 5.38 (s, 1H), 4.41 (s, 1H), 4.25 (dd, J_1=10.3 Hz, J_2=5.1 Hz, 1H), 3.98 (dt, J_1=9.8 Hz, J_2=5.1 Hz, 1H), 3.63 (d, J=10.3 Hz, 1H), 3.58 (br s, 1H), 3.49 (t, J=10.2 Hz, 1H), 3.37 (m, 1H), 3.30 (s, 3H), 2.94 (br s, 1H), 2.76 (d, J=11.8 Hz, 1H), 2.20 (m, 1H), 1.98 (d, J=3.5 Hz, 1H), 1.90 (m, 1H), 1.63 (d, J=9.4 Hz, 1H), 1.41 (d, J=9.2 Hz, 1H), 1.09 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 140.1, 137.2, 135.9, 129.3, 128.5, 126.0, 102.6, 102.1, 83.9, 82.3, 70.2, 59.1, 54.5, 53.5, 51.0, 48.0, 46.1, 26.6, 12.7. Anal. Calcd for $C_{22}H_{28}O_5$: C 70.95, H 7.58, O 21.48. Found: C 71.00, H 7.52.

4.2.4.2. Compound 15d$_{\text{(more polar)}}$. Colorless oil; $[\alpha]_D^{18}$ +52.9 (*c* 1.00, $CHCl_3$); IR (film): ν_{max} (cm^{-1}) 3540, 2970, 2890, 1460, 1378, 1150, 1100, 1068, 1037, 988, 754, 703; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.45–7.37 (m, 5H), 6.42 (br s, 2H), 5.38 (s, 1H), 4.34 (d, J=2.6 Hz, 1H), 4.30–4.10 (m, 2H), 3.81 (m, 1H), 3.60 (d, J=9.7 Hz, 1H), 3.50 (t, J=9.7 Hz, 1H), 3.34 (s, 3H), 3.19 (br s, 1H), 2.98 (br s, 1H), 2.78 (d, J=6.9 Hz, 1H), 2.41 (t, J=3.2 Hz, 1H), 1.95–1.65 (m, 2H), 1.65 (d, J=8.9 Hz, 1H), 1.38 (d, J=8.9 Hz, 1H), 1.01 (t, J=7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 139.9, 137.3, 137.0, 129.0, 128.3, 125.9, 102.1, 102.0, 83.5, 81.5, 70.1, 60.5, 54.9, 53.5, 52.9, 47.4, 46.8, 46.3, 27.2, 12.1; HRMS *m*/*z* 390.2287 [(M+NH_4^+); calcd for $C_{22}H_{28}O_5$: 390.2281].

4.2.5. (1*S*,2*S*,3*S*,5*R*,8*R*,10*S*,11*S*,12*R*) 10-Methoxy-5-phenyl-2-(1′-oxo) propyl-4,6,9-trioxatetracyclo [10.2.1.0^{2,11}.0^{3,8}]pentadec-13-ene (15e). Jones reagent was added dropwise to a cooled (0 °C) solution of the mixture of epimeric alcohols **15d** (217 mg, 0.58 mmol) in acetone (20 mL) until the reaction mixture turned light orange. The reaction was stirred 15 min at 0 °C and isopropyl alcohol was added to reduce the excess Jones reagent until the reaction mixture turned green. Water was added to the mixture, which was vigorously stirred to dissolve the chromium salts and concentrated under reduced pressure (to remove the acetone). Solution was extracted with ethyl acetate, washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The resulting crude product was purified by flash chromatography to furnish the ketone **15e** (163 mg, 76%). Colorless oil; $[\alpha]_D^{24}$ +34.8 (*c* 1.07, $CHCl_3$); IR (film): ν_{max} (cm^{-1}) 2980, 2925, 2882, 1708, 1460, 1382, 1150, 1094, 1022, 981, 768, 753, 706; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.39–7.31 (m, 5H), 6.41 (t, J=1.7 Hz, 2H), 5.38 (s, 1H), 4.32 (d, J=3.3 Hz, 1H), 4.22 (dd, J_1=10.5 Hz, J_2=5.2 Hz, 1H), 3.92 (m, 1H), 3.70–3.30 (m, 4H), 3.37 (s, 3H), 2.92 (br s, 1H), 2.82 (d, J=3.2 Hz, 1H), 2.55 (m, 1H), 1.56 (d, J=8.8 Hz, 1H), 1.05 (d, J=8.5 Hz, 1H), 1.04 (t, J=8.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 211.7, 137.8, 137.2, 136.9, 128.8, 128.0, 126.0, 102.0, 101.7, 80.5, 69.4, 63.4, 59.5, 54.8, 49.5, 48.0, 47.0, 45.8, 34.2, 7.7; HRMS *m*/*z* 388.1131 [(M+NH_4^+); calcd for $C_{22}H_{26}O_5$: 388.1124].

4.2.6. (1*S*,2*S*,3*S*,5*R*,8*R*,10*S*,11*S*,12*R*) 2-Acetoxymethyl-10-methoxy-5-phenyl-4,6,9-trioxatetracyclo [10.2.1.0^{2,11}.0^{3,8}]pentadec-13-ene (15f). Alcohol **15b** (112 mg, 0.327 mmol) was dissolved in anhydrous CH_2Cl_2 (5 mL) and cooled to 0 °C. DMAP (9.0 mg, 0.072 mmol), pyridine (0.148 mL, 1.83 mmol), and acetic anhydride (0.089 mL, 0.944 mmol) were sequentially added. The resulting mixture was stirred at room temperature for 16 h and then diluted with ethyl acetate, washed with water, dried with Na_2SO_4, and concentrated in vacuo. The crude product was purified by flash chromatography to furnish pure **15f** (100.7 mg, 80%). Colorless oil; $[\alpha]_D^{23}$ +90.36 (*c* 1.91, $CHCl_3$); IR (film): ν_{max} (cm^{-1}) 2980, 1745, 1475, 1460, 1385, 1375, 1290, 1250, 1150, 1110, 1070, 1050, 1040, 760, 710; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.48–7.33 (m, 5H), 6.38 (br s, 2H), 5.43 (s, 1H), 4.44 (s, 2H), 4.35 (d, J=2.24 Hz, 1H), 4.24 (dd, J_1=10.3 Hz, J_2=5.24 Hz, 1H), 3.97 (m, 1H), 3.49 (dd, J_1=J_2=10.3 Hz, 1H), 3.37 (d, J=10.3 Hz, 1H), 3.31 (s, 3H), 2.98 (br s, 1H), 2.88 (br s, 1H), 2.28 (t, J=2.43 Hz, 1H), 2.05 (s, 3H), 1.67 (d, J=9.0 Hz, 1H), 1.48 (br d, J=9.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 171.0, 138.7, 137.7, 136.2, 128.9, 128.1, 126.1, 101.7, 101.6, 80.1, 70.0, 67.6, 59.8, 54.6, 50.0, 49.3, 47.5, 47.3, 47.0, 20.9; HRMS *m*/*z* 409.163714 [(M+Na^+); calcd for $C_{22}H_{26}O_6$: 409.162709].

4.2.7. (1*S*,2*S*,3*S*,4*R*,6*S*,7*S*,8*R*) 3-Acetoxy-2,4 bisacetoxymethyl-6-methoxy-5-oxatricyclo[6.2.1.0^{2,7}] undec-9-ene (15g). A solution of the acetylated alcohol **15f** (100 mg, 0.26 mmol) and pyridinium *p*-toluenesulfonate (20 mg, 0.08 mmol) in a 1:1 mixture of MeOH–$CHCl_3$ (40 mL) was heated at 40 °C for 96 h. The volatiles were removed in vacuo and the residue was dissolved in ethyl acetate, washed with water, and dried (Na_2SO_4). Evaporation under reduced pressure furnished 100 mg of the crude product, which was used without further purification in the next step.

The crude diol mixture (100 mg) was dissolved in anhydrous CH_2Cl_2 (10 mL) and the solution was cooled in an ice bath. Anhydrous pyridine (0.290 mL, 3.59 mmol), DMAP (19 mg, 0.152 mmol), and acetic anhydride (0.175 mL, 1.86 mmol) were sequentially added to the solution at 0 °C. After stirring 3 h at room temperature, the mixture was diluted with ethyl acetate, washed with brine, dried (Na_2SO_4), and concentrated. The crude product was purified by flash chromatography furnished pure **15g** (46.8 mg, 47%, two steps). Colorless oil; $[\alpha]_D^{21}$ +104.88 (*c* 2.95, $CHCl_3$); IR (film): ν_{max} (cm^{-1}) 3020, 1782 (CO, br), 1415, 1275, 1194; ^1H NMR ($CDCl_3$, 200 MHz) δ 6.50 (dd, J_1=5.62 Hz, J_2=3.19 Hz, 1H), 6.33 (dd, J_1=5.62 Hz, J_2=3.0 Hz, 1H), 4.72 (d, J=10.1 Hz, 1H), 4.33 (d, J=3.93 Hz, 1H), 4.27 (d,

J=6.55 Hz, 2H), 4.28–3.99 (m, 3H, C-5 H), 3.34 (s, 3H), 2.94 (br s, 1H), 2.77 (br s, 1H), 2.20 (t, J=3.56 Hz, 1H), 2.09 (s, 3H), 2.08 (s, 3H), 2.05 (s, 3H), 1.59 (d, J=9.17 Hz, 1H), 1.44 (br d, J=9.17 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 170.6, 170.5, 169.9, 138.8, 135.9, 101.5, 70.6, 68.0, 67.2, 63.5, 54.9, 51.5, 49.7, 48.5, 46.5, 46.4, 20.8, 20.6, 20.5; HRMS m/z 405.152577 [(M+Na$^+$); calcd for $C_{19}H_{26}O_8$: 405.152538].

4.3. Methyl 4,6-*O*-benzylidene-2,3-dideoxy-2-*C*-formyl-α-D-*erythro*-hex-2-enopyranoside (21)

Methyl 4,6-*O*-benzylidene-2-*C*-cyano-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside[20] (579 mg, 2.1 mmol) was azeotropically dried with dry benzene under vacuum, dissolved in anhydrous CH_2Cl_2 (43 mL), and cooled at −80 °C under an argon atmosphere. Diisobutylaluminum hydride (1 M solution in hexane, 4.8 mL, 4.8 mmol) was slowly added to the magnetically stirred solution. The reaction mixture was stirred for additionally 90 min at −80 °C and then quenched with 1:1 HOAc–water solution (3.4 mL). Stirring was continued for 30 min while the temperature rose to 0 °C. The mixture was extracted with CH_2Cl_2, washed with H_2O, 5% $NaHCO_3$ solution, and brine, dried (Na_2SO_4), and concentrated to furnish compound **6** (506 mg, 86%) as a white solid. Recrystallization afforded crystals as white needles mp 195.0–196.0 °C (CH_2Cl_2–petroleum ether); $[\alpha]_D^{20}$ +131.6 (c 0.80, $CHCl_3$); reported[22] mp 190–192 °C; $[\alpha]_D$ 100.4 (c 0.25, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 9.47 (s, 1H), 7.55–7.30 (m, 5H), 6.97 (s, 1H), 5.63 (s, 1H), 5.21 (s, 1H), 4.45–4.35 (m, 2H), 4.15–4.00 (m, 1H), 3.85 (dd, 1H, J_{gem}=$J_{5,6}$=10.2 Hz), 3.54 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 189.8, 146.5, 139.5, 136.8, 129.3, 128.3, 126.1, 102.6, 94.6, 75.4, 69.3, 63.3, 56.5.

4.4. Synthesis of the *endo* norbornene systems

4.4.1. (1*S*,2*S*,3*S*,5*R*,8*R*,10*S*,11*R*,12*R*) 3-Methoxy-8-phenyl-4,7,9-trioxatetracyclo[10.2.1.0^{2,11}.0^{5,10}] pentadec-13-ene-2-carbaldehyde (22). Methyl 4,6-*O*-benzylidene-2,3-dideoxy-2-*C*-formyl-α-D-*erythro*-hex-2-enopyranoside (**21**) (583.0 mg, 2.10 mmol) was azeotropically dried with dry benzene under vacuum and dissolved in anhydrous ethyl ether (35 mL) at room temperature under argon atmosphere. Anhydrous lithium perchlorate (18.6 g, 0.17 mol) and freshly cracked cyclopentadiene (1.4 mL, 21.20 mmol) were sequentially added under argon atmosphere at room temperature to the stirred solution. After seven days of stirring at room temperature, extra ethyl ether (35 mL) and cyclopentadiene (1.4 mL, 21.20 mmol) were added to the reaction mixture and stirred for seven additional days at the same temperature. The mixture was diluted with ethyl acetate, washed with water, dried (Na_2SO_4), and concentrated in vacuo. The crude product was purified by flash chromatography to furnish pure **22** (189 mg, 26%). Colorless oil; $[\alpha]_D^{23}$ +35.8 (c 8.24, $CHCl_3$); IR (film): ν_{max} (cm^{-1}) 2972, 2854, 1721, 1454, 1374, 1212, 1086, 974, 850, 755, 699; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 9.53 (s, 1H), 7.55–7.30 (m, 5H), 6.19 (dd, J_1=5.6 Hz, J_2=2.8 Hz, 1H), 6.08 (dd, J_1=5.6 Hz, J_2=3.2 Hz, 1H), 5.53 (s, 1H), 4.84 (s, 1H), 4.33 (dd, J_1=10.0 Hz, J_2=4.6 Hz, 1H), 3.81 (m, 1H), 3.65 (dd, J_1=J_2=10.0, 1H), 3.49 (dd, J_1=J_2=9.5 Hz, 1H), 3.42 (s, 3H), 3.14 (br s, 1H), 2.96 (br s, 1H), 2.36 (dd, J_1=9.2 Hz, J_2=1.8 Hz, 1H), 1.63 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 199.6, 139.2, 137.3, 132.3, 128.9, 128.1, 126.1, 104.7, 101.6, 79.7, 69.6, 65.5, 62.4, 56.3, 47.7, 45.2, 45.0, 44.3; HRMS m/z 341.139010 [(M−H$^+$); calcd for $C_{20}H_{21}O_5$: 341.138899].

4.4.2. (1*S*,2*S*,3*S*,5*R*,8*R*,10*S*,11*R*,12*R*) 2-Hydroxymethyl-3-methoxy-8-phenyl-4,7,9-trioxatetracyclo [10.2.1.0^{2,11}.0^{5,10}]pentadec-13-ene (31). Cycloadduct **22** (284 mg, 0.8 mmol) was dissolved in a 1:1 mixture of CH_2Cl_2–MeOH (32 mL) and cooled to 0 °C. Sodium borohydride (320 mg, 8.5 mmol) was added and the resulting mixture was stirred at 0 °C for 40 min. Acetone was added, the solution was stirred for 15 min, and concentrated in vacuo. The oil residue was dissolved in ethyl acetate, washed with water and brine, and concentrated. The crude product was purified by flash chromatography to furnish pure **31** (287 mg, 100%). Colorless oil; $[\alpha]_D^{19}$ +22.0 (c 0.79, $CHCl_3$); IR (film): ν_{max} (cm^{-1}) 3555, 2963, 2874, 1723, 1457, 1372, 1294, 1201, 1072, 754, 699; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.55–7.30 (m, 5H), 6.19 (m, 2H), 5.50 (s, 1H), 4.79 (s, 1H), 4.36 (dd, J=9.8 Hz, 1H), 3.85 (d, J=10.9 Hz, 1H), 3.73–3.64 (m, 2H), 3.58–3.43 (m, 2H), 3.50 (s, 3H), 3.22–2.90 (m, 3H), 2.94 (br s, 1H), 1.65 (d, J=9.4 Hz, 1H), 1.52 (d, J=9.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 137.4, 136.2, 135.2, 129.0, 128.2, 126.1, 105.5, 101.6, 78.9, 70.1, 67.3, 67.0, 57.0, 52.2, 46.9, 46.8, 44.1, 43.5.

4.4.3. (1*S*,2*S*,3*S*,5*R*,8*R*,10*S*,11*R*,12*R*) 2-Acetoxymethyl-3-methoxy-8-phenyl-4,7,9-trioxatetracyclo [10.2.1.0^{2,11}.0^{5,10}]pentadec-13-ene (32). The hydroxymethyl derivative **31** (136.3 mg, 0.4 mmol) was dissolved in anhydrous CH_2Cl_2 (4 mL) and the solution was cooled in an ice bath. Anhydrous pyridine (0.48 mL, 5.9 mmol), DMAP (catalytic amount), and acetic anhydride (0.34 mL, 3.6 mmol) were sequentially added to the solution at 0 °C. The mixture was stirred overnight at room temperature. MeOH was added; the mixture was diluted with ethyl acetate, washed with brine, dried (Na_2SO_4), and concentrated. The crude product was purified by flash chromatography furnished pure **32** (138.8 mg, 91%). Colorless oil; $[\alpha]_D^{20}$ +11.6 (c 1.17, $CHCl_3$); IR (film): ν_{max} (cm^{-1}) 2970, 1734, 1453, 1372, 1243, 1084, 755, 696; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.60–7.25 (m, 5H), 6.20 (dd, J_1=5.6 Hz, J_2=3.0 Hz, 1H), 6.06 (dd, J_1=5.6 Hz, J_2=3.0 Hz, 1H), 5.52 (s, 1H), 4.69 (s, 1H), 4.36 (dd, J_1=10.2 Hz, J_2=4.6 Hz, 1H), 4.12 (d, J=10.1 Hz, 1H), 3.97 (d, J=11.1 Hz, 1H), 3.85 (m, 1H), 3.66 (dd, J_1=J_2=10.0 Hz, 1H), 3.55 (dd, J_1=J_2=9.6 Hz, 1H), 3.45 (s, 3H), 2.98 (br s, 1H), 2.75 (br s, 1H), 2.04 (s, 3H), 1.73 (d, J=9.2 Hz, 1H), 1.59 (d, J=9.6 Hz, 1H), 1.53 (d, J=9.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 170.6, 137.5, 137.1, 134.6, 128.9, 128.2, 126.1, 103.7, 101.6, 79.6, 70.3, 66.8, 66.2, 57.0, 50.7, 48.3, 46.0, 45.1, 44.5, 21.1; HRMS m/z 404.2087 [(M+NH$_4^+$); calcd for $C_{22}H_{26}O_6$: 404.2072].

4.5. Representative experimental procedure for the ozonolysis of norbornenes

The cycloadduct **15a** (880.5 mg, 2.57 mmol) was dissolved in a 5:1 mixture of CH_2Cl_2–MeOH (5 mL) and solid $NaHCO_3$ (865 mg, 10.3 mmol) was added. The suspension was cooled to −78 °C and an ozone stream was

bubbled through the stirred suspension. Ozone addition was stopped when complete consumption of **15a** was observed by TLC analysis. The mixture was then flushed with argon, and $NaHCO_3$ was removed by filtration. The filtrate was concentrated in vacuo to give the crude material as a colorless oil, which was taken up in CH_2Cl_2 (13 mL). The mixture was cooled to 0 °C, and acetic anhydride (1.2 mL, 12.85 mmol) and triethylamine (0.5 mL, 3.08 mmol) were added. The mixture was stirred at room temperature for 1 h and then partitioned between diethyl ether and, sequentially, 0.5 M aqueous HCl, 0.625 M aqueous KOH, and brine. The combined organic extract was dried (Na_2SO_4) and concentrated in vacuo to give essentially pure **16a**. This crude material was purified by column chromatography (hexane–AcOEt) to provide 960.5 mg (92.3%) of **16a**.

4.5.1. (1*S*,2*S*,4*R*,7*R*,9*S*,10*S*,11*S*,13*R*) 1,13-Dicarbaldehyde-9-methoxy-4-phenyl-3,5,8-trioxatricyclo [8.3.0^{1,10}.0^{2,7}]tridecane-11-carboxylic acid methyl ester (16a). Colorless oil; $[\alpha]_D^{21}$ −20.4 (*c* 1.13, $CHCl_3$); IR (film): ν_{max} (cm^{-1}) 2926, 2864, 1724 (br), 1452, 1438, 1372, 1212, 1174, 1130, 1086, 962, 758; ^1H NMR ($CDCl_3$, 200 MHz) δ 10.23 (s, 1H), 9.65 (s, 1H), 7.37–7.31 (m, 5H), 5.48 (s, 1H), 4.90 (s, 1H), 4.33–4.21 (m, 2H), 4.08 (d, *J*=9.7 Hz, 1H), 3.72 (s, 3H), 3.73–3.66 (m, 1H), 3.65–3.41 (m, 1H), 3.39 (s, 3H), 3.35–2.96 (m, 2H), 2.70 (d, *J*=11.4 Hz, 1H), 2.16–1.97 (m, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 200.8, 198.6, 173.9, 136.7, 128.9, 128.1, 125.7, 102.0, 96.8, 73.9, 69.2, 59.8, 58.8, 56.2, 55.0, 52.8, 52.3, 41.6, 23.6; HRMS *m/z* 427.13585 [(M+Na+); calcd for $C_{21}H_{24}O_8$: 427.13688].

4.5.2. (1*S*,2*S*,4*R*,7*R*,9*S*,10*S*,11*S*,13*R*) 13-Formyl-1-(hydroxy) methyl-9-methoxy-4-phenyl-3,5,8-trioxatricyclo [8.3.0.0^{2,7}]tridecane-11-carboxylic acid methyl ester (16b). Colorless oil; 69% yield; $[\alpha]_D^{25}$ +14.52 (*c* 1.12, $CHCl_3$); IR (film): ν_{max} (cm^{-1}) 3502, 2937, 2853, 1727 (br), 1457, 1376, 1369, 1281, 1208, 1200, 1171, 1134, 1091, 1047, 966, 915, 732, 702; ^1H NMR ($CDCl_3$, 200 MHz) δ 9.96 (d, *J*=1.31 Hz, 1H), 7.34 (m, 5H), 5.45 (s, 1H), 4.85 (s, 1H), 4.35–4.12 (m, 3H), 4.03–3.91 (m, 1H), 3.71 (s, 3H), 3.81–3.58 (m, 2H), 3.36 (s, 3H), 3.25–2.95 (m, 3H), 2.57 (d, *J*=11.2 Hz, 1H), 2.09–1.90 (m, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 201.4, 174.6, 136.9, 128.8, 128.1, 125.7, 101.8, 97.4, 76.1, 69.2, 64.5, 59.4, 57.4, 55.0, 52.3, 52.2, 48.8, 42.0, 24.6; HRMS *m/z* 429.154574 [(M+Na$^+$); calcd for $C_{21}H_{26}O_8$: 429.152538].

4.5.3. (1*S*,2*S*,4*R*,7*R*,9*S*,10*S*,11*S*,13*R*) 13-Formyl-9-methoxy-4-phenyl-3,5,8-trioxatricyclo [8.3.0.0^{2,7}]tridecane-1,11-carboxylic acid methyl ester (16c). Colorless oil; 95% yield; $[\alpha]_D^{26}$ +14.45 (*c* 1.61, $CHCl_3$); IR (film): ν_{max} (cm^{-1}) 2860, 2760, 1675 (br), 1390, 1330, 1315, 1230, 1150, 1135, 1080, 1040, 995, 970, 890, 705, 650; ^1H NMR ($CDCl_3$, 200 MHz) δ 9.71 (s, 1H), 7.42–7.30 (m, 5H), 5.43 (s, 1H), 4.83 (s, 1H), 4.49–4.37 (m, 1H), 4.27–4.19 (m, 1H), 3.88 (d, *J*=9.5 Hz, 1H), 3.80 (s, 3H), 3.72 (s, 3H), 3.60–3.47 (m, 2H), 3.32 (s, 3H), 3.29–3.19 (m, 1H), 3.05 (d, *J*=12.7 Hz, 1H), 3.04–2.88 (m, 1H), 2.19–2.03 (m, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 198.5, 173.8, 172.4, 137.2, 128.7, 128.0, 125.9, 102.0, 96.8, 73.7, 69.4, 59.8, 59.0, 54.8, 54.4, 53.0, 52.4, 52.3, 41.8, 24.6; HRMS *m/z* 457.147448 [(M+Na$^+$); calcd for $C_{22}H_{26}O_9$: 457.147453].

4.5.4. (1*S*,2*S*,4*R*,7*R*,9*S*,10*S*,11*S*,13*R*) 13-Formyl-1-(1′-hydroxy)propyl-9-methoxy-4-phenyl-3,5,8-trioxatricyclo [8.3.0.0^{2,7}]tridecane-11-carboxylic acid methyl ester (16d). Colorless oil; 62% yield; $[\alpha]_D^{25}$ +35.21 (*c* 2.14, $CHCl_3$); IR (film): ν_{max} (cm^{-1}) 3533, 2947, 2863, 1731 (br), 1460, 1372, 1365, 1314, 1227, 1211, 1175, 1131, 1094, 1050, 1006, 977, 918, 845, 735, 699; ^1H NMR ($CDCl_3$, 200 MHz) δ 10.02 (d, *J*=1.12 Hz, 1H), 7.38–7.27 (m, 5H), 5.47 (s, 1H), 4.80 (br s, 1H), 4.39 (d, *J*=10.3 Hz, 1H), 4.33 (d, *J*=9.73 Hz, 1H), 4.24 (dd, J_1=10.11 Hz, J_2=4.68 Hz, 1H), 4.09 (m, 1H), 3.70 (s, 3H), 3.65 (dd, J_1=J_2=9.92 Hz, 1H), 3.41 (br s, 1H), 3.33 (s, 3H), 3.21–2.96 (m, 3H), 2.66 (d, *J*=11.04 Hz, 1H), 2.03–1.90 (m, 1H), 1.78–1.64 (m, 1H), 1.51–1.36 (m, 1H), 1,04 (t, *J*=7.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 201.8, 174.8, 136.9, 128.8, 128.1, 125.8, 102.1, 97.2, 77.7, 73.0, 69.1, 59.3, 55.9, 55.4, 54.9, 52.1, 49.0, 42.3, 24.5, 23.0, 10.8; HRMS *m/z* 457.184886 [(M+Na$^+$); calcd for $C_{23}H_{30}O_8$: 457.183838].

4.5.5. (1*S*,2*S*,4*R*,7*R*,9*S*,10*S*,11*S*,13*R*) 13-Formyl-9-methoxy-1-(1′-oxo) propyl-4-phenyl-3,5,8-trioxatricyclo [8.3.0.0^{2,7}]tridecane-11-carboxylic acid methyl ester (16e). Colorless oil; 45% yield; $[\alpha]_D^{20}$ +24.04 (*c* 1.60, $CHCl_3$); IR (film): ν_{max} (cm^{-1}) 3460, 2937, 2853, 1735 (br), 1698, 1457, 1435, 1376, 1208, 1178, 1134, 1091, 1047, 1010, 922, 739, 695, 651; ^1H NMR ($CDCl_3$, 200 MHz) δ 9.63 (s, 1H), 7.42–7.32 (m, 5H), 5.49 (s, 1H), 4.80 (br s, 1H), 4.31–4.16 (m, 2H), 4.05 (d, *J*=10.11 Hz, 1H), 3.71 (s, 3H), 3.69 (dd, J_1=J_2=11.4 Hz, 1H), 3.31 (s, 3H), 3.43–3.20 (m, 2H), 3.11 (dd, J_1=10.8 Hz, J_2=1.1 Hz, 1H), 3.07–2.87 (m, 3H), 2.17–2.01 (m, 1H), 1.07 (t, *J*=7.11 Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 211.1, 198.6, 174.2, 136.7, 128.9, 128.2, 125.6, 102.5, 97.1, 74.2, 69.5, 61.0, 60.4, 60.3, 54.8, 53.6, 52.2, 41.7, 35.8, 24.6, 8.2; HRMS *m/z* 455.168139 [(M+Na$^+$); calcd for $C_{23}H_{28}O_8$: 455.168188].

4.5.6. (1*S*,2*S*,4*R*,7*R*,9*S*,10*S*,11*S*,13*R*) 1-Acetoxymethyl-13-formyl-9-methoxy-4-phenyl-3,5,8-trioxatricyclo [8.3.0.0^{2,7}]tridecane-11-carboxylic acid methyl ester (16f). Colorless oil; 96% yield; $[\alpha]_D^{22}$ +16.43 (*c* 5.18, $CHCl_3$); IR (film): ν_{max} (cm^{-1}) 2940, 2880, 1745 (br), 1470, 1445, 1390, 1380, 1245, 1100, 1060, 940, 930, 765, 715; ^1H NMR ($CDCl_3$, 200 MHz) δ 9.86 (d, *J*=1.68 Hz, 1H), 7.42–7.30 (m, 5H), 5.44 (s, 1H), 4.86 (s, 1H), 4.78 (d, *J*=12.0 Hz, 1H), 4.42 (d, *J*=12.0 Hz, 1H), 4.21 (dd, J_1=10.1 Hz, J_2=4.68 Hz, 1H), 4.08 (d, *J*=9.74 Hz, 1H), 3.92 (ddd, J_1=9.74 Hz, J_2=9.73 Hz, J_3=4.68 Hz, 1H), 3.72 (s, 3H), 3.61 (dd, J_1=10.11 Hz, J_2=9.73 Hz, 1H), 3.33 (s, 3H), 3.21–2.88 (m, 3H), 2.72 (d, *J*=11.8 Hz, 1H), 2.09–2.00 (m, 1H), 1.96 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 200.5, 174.4, 170.3, 137.0, 128.7, 127.9, 125.8, 101.7, 97.5, 74.7, 69.1, 63.7, 59.1, 55.9, 55.0, 52.1, 50.0, 48.0, 41.9, 24.5, 20.6; HRMS *m/z* 471.161544 [(M+Na$^+$); calcd for $C_{23}H_{28}O_9$: 471.163103].

4.5.7. (1*S*,2*S*,3*R*,5*S*,6*S*,7*S*) 2-Acetoxy-1,3-bisacetoxymethyl-5-methoxy-4-oxabicyclo [6.3.0^{1,6}]-9-acetoxymethylene-nonane-7-carboxylic acid methyl ester (16g).

Colorless oil; 86% yield; $[\alpha]_D^{20}$ +68.09 (*c* 3.21, $CHCl_3$); IR (film): ν_{max} (cm^{-1}) 2940, 1750 (br), 1683, 1460, 1445, 1365, 1250, 1220, 1045; ^1H NMR ($CDCl_3$, 200 MHz) δ 6.97 (t, *J*=2.4 Hz, 1H), 5.34 (d, *J*=9.8 Hz, 1H), 4.95 (s, 1H), 4.49 (d, *J*=11.34 Hz, 1H), 4.40 (d, *J*=11.34 Hz, 1H), 4.17–3.89 (m, 3H), 3.74 (s, 3H), 3.34 (s, 3H), 3.19–3.04 (m, 2H), 2.83 (d, *J*=9.18 Hz, 1H), 2.60 (m, 1H), 2.12 (s, 3H), 2.10 (s, 3H), 2.07 (s, 3H), 2.04 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 174.2, 170.5, 170.4, 169.3, 167.3, 126.9, 126.4, 97.4, 67.4, 65.4, 63.3, 62.9, 55.0, 52.0, 48.3, 47.4, 42.7, 29.2, 20.6, 20.5, 20.4, 20.3; HRMS *m/z* 509.164747 [(M+Na^+); calcd for $C_{22}H_{30}O_{12}$: 509.163497].

4.5.8. (1*S*,2*S*,3*S*,5*R*,8*R*,10*S*,11*R*,12*S*,14*R*,15*S*,19undefined) 12-Acetoxymethoxy-methyl-3-methoxy-8-phenyl-4,7,9,16,17,18-hexoxapentacyclo [13.2.1.$0^{2,11}$.$0^{2,14}$.$0^{5,10}$]-octadecane (23). Colorless oil; 54% yield; $[\alpha]_D^{25}$ +21.5 (*c* 0.44, $CHCl_3$); IR (film): ν_{max} (cm^{-1}) 2931, 2854, 1761, 1733, 1456, 1376, 1229, 1161, 1122, 1076, 1053, 1018, 978, 941, 755, 700; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.53–7.49 (m, 2H), 7.44–7.38 (m, 3H), 6.50 (s, 1H), 5.94 (s, 1H), 5.55 (s, 1H), 4.92 (s, 1H), 4.63 (s, 1H), 4.33 (dd, J_1=10.3, J_2=5.0 Hz, 1H), 3.92 (m, 1H), 3.71 (dd, J_1=J_2=10.4 Hz, 1H), 3.51 (s, 3H), 3.43 (s, 3H), 3.25 (dd, J_1=J_2=10.0 Hz, 1H), 2.77 (dd, J_1=11.8, J_2=3.2 Hz, 1H), 2.71 (d, *J*=7.9 Hz, 1H), 2.55 (d, *J*=10.1 Hz, 1H), 2.31 (dm, *J*=14.9 Hz, 1H), 2.11 (s, 3H), 2.08 (dd, J_1=14.9, J_2=6.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 169.7, 137.2, 129.3, 128.4, 126.2, 111.4, 107.8, 106.6, 102.4, 97.3, 78.2, 69.2, 62.4, 60.8, 57.5, 55.2, 50.9, 46.7, 43.6, 26.6, 21.3; HRMS *m/z* 482.2032 [(M+NH_4^+); calcd for $C_{23}H_{28}O_{10}$: 482.2026].

4.5.9. Ozonolysis of 31, preparation of hemiacetal 35, and lactone 36.

4.5.9.1. (1*R*,2*S*,4*R*,7*R*,9*S*,10*R*,11*S*,13*R*,14*R*) 14-Hydroxy-2-methoxy-7-phenyl-3,6,8,15-tetraoxatetracyclo [10.3.2.$0^{1,10}$.$0^{1,13}$.$0^{4,9}$]hexadecane-11-carboxylic acid methyl ester (35). Colorless oil; 54% yield; $[\alpha]_D^{24}$ +4.7 (*c* 1.61, $CHCl_3$); IR (film): ν_{max} (cm^{-1}) 3437, 2948, 2926, 1730, 1457, 1372, 1213, 1117, 1091, 973, 755, 699; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.52–7.29 (m, 5H), 5.49 (s, 1H), 5.32 (s, 1H), 4.81 (s, 1H), 4.28 (dd, J_1=10.0 Hz, J_2=4.8 Hz, 1H), 4.11 (d, *J*=9.9 Hz, 1H), 3.91 (m, 1H), 3.80 (d, *J*=10.1 Hz, 1H), 3.72–3.60 (dd overlap, 1H), 3.65 (s, 3H), 3.38 (s, 3H), 3.17 (dd, J_1=J_2=9.8 Hz, 1H), 3.01 (m, 2H), 2.70 (br s, 1H), 2.59 (dd, J_1=10.4 Hz, J_2=3.8 Hz, 1H), 2.34 (m, 1H), 2.17 (m, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 173.7, 137.4, 128.9, 128.1, 126.1, 104.5, 102.07, 101.7, 78.9, 73.3, 69.4, 61.3, 58.3, 55.1, 51.7, 51.5, 48.2, 45.8, 30.1; HRMS *m/z* 407.1695 [(M+H^+); calcd for $C_{21}H_{26}O_8$: 407.1706].

4.5.9.2. (1*R*,2*S*,4*R*,7*R*,9*S*,10*R*,11*S*,13*R*) 2-Methoxy-14-oxo-7-phenyl-3,6,8,15-tetraoxatetracyclo [10.3.2.$0^{1,10}$.$0^{1,13}$.$0^{4,9}$]hexadecane-11-carbaldehyde (36). Colorless oil; 29% yield; $[\alpha]_D^{21}$ +20.8 (*c* 0.95, $CHCl_3$); IR (film): ν_{max} (cm^{-1}) 3422, 3015, 2926, 1771, 1719, 1453, 1372, 1287, 1213, 1113, 1087, 755, 699, 662; ^1H NMR ($CDCl_3$, 200 MHz) δ 9.73 (s, 1H), 7.52–7.29 (m, 5H), 5.53 (s, 1H), 4.59 (d, *J*=11.2 Hz, 1H), 4.56 (s, 1H), 4.31 (dd, J_1=10.1 Hz, J_2=4.9 Hz, 1H), 3.93 (m, 1H), 3.69 (dd, J_1=J_2=10.2 Hz, 1H), 3.65 (d, *J*=10.9 Hz, 1H), 3.42 (s, 3H), 3.28 (dd, J_1=J_2=9.7 Hz, 1H), 3.22 (dd, J_1=9.3 Hz, J_2=3.1 Hz, 1H), 3.03 (dd, J_1=11.5 Hz, J_2=5.3 Hz, 1H), 2.82 (d, *J*=9.9 Hz, 1H), 2.67–2.48 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 200.3, 177.5, 136.9, 129.2, 128.2, 126.1, 102.4, 98.7, 78.5, 71.5, 69.0, 61.2, 56.7, 55.3, 55.1, 46.5, 44.8, 26.0; HRMS *m/z* 375.1437 [(M+H^+); calcd for $C_{20}H_{22}O_7$: 375.1444].

4.5.10. Ozonolysis of 32. The crude product (141.2 mg, 100%) was analyzed by ^1H NMR as a 3:1 mixture of compounds **37** and **38**. The isomeric mixture was used without further purification in the next reaction step.

4.6. Preparation of 39 and 40

The mixture of **37**/**38** (90 mg, 0.2 mmol) was dissolved in a 1:1 mixture of CH_2Cl_2–MeOH (8 mL). The solution was cooled in an ice bath. Sodium borohydride (44 mg, 1.2 mmol) was added and the resulting mixture was stirred at 0 °C for 15 min. Acetone was added; the solution was stirred for additional 15 min and concentrated in vacuo. The oil residue was dissolved in ethyl acetate, washed with water, brine, and concentrated in vacuo. The crude product was purified by flash chromatography to furnish pure **39** (32.8 mg, 36%) and pure **40** (15.2 mg, 17%) as colorless oils. Compound **39** was unstable when it was dissolved in chloroform-*d* at room temperature and was gradually converted into lactone **41**.

4.6.1. (1*R*,2*S*,4*R*,7*R*,9*S*,10*R*,11*S*,13*R*) 1-Acetoxymethyl-11-hydroxymethyl-2-ethoxy-7-phenyl-3,6,8-trioxatricyclo [10.3.$0^{1,10}$.$0^{4,9}$]tridecane-13-carboxylic acid methyl ester (40). Colorless oil; 17% yield; $[\alpha]_D^{21}$ +11.3 (*c* 0.55, $CHCl_3$); IR (film): ν_{max} (cm^{-1}) 3462, 2924, 2853, 2359, 2342, 1738, 1732, 1456, 1368, 1244, 1109, 1080, 1038, 1005, 758; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.52–7.31 (m, 5H), 5.52 (s, 1H), 5.02 (s, 1H), 4.29 (dd, J_1=9.9 Hz, J_2=4.8 Hz, 1H), 4.11 (br s, 2H), 3.92 (m, 1H), 3.77–3.63 (m, 1H), 3.72 (s, 3H), 3.54 (m, 2H), 3.37 (dd, J_1=J_2=4.8 Hz, 1H), 3.37 (s, 3H), 3.16 (dd, J_1=7.9 Hz, J_2=11.8 Hz, 1H), 2.29 (m, 1H), 2.21 (d, *J*=8.1 Hz, 1H), 2.11 (m, 1H), 1.98 (dd, J_1=J_2=4.5 Hz, 1H), 1.98 (s, 3H), 1.60 (br s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 172.4, 169.8, 137.2, 128.9, 128.2, 126.0, 102.1, 98.9, 80.5, 69.3, 66.5, 64.3, 61.7, 55.4, 53.0, 51.6, 46.9, 45.3, 43.6, 28.3, 20.5; HRMS *m/z* 451.1971 [(M+H^+); calcd for $C_{23}H_{30}O_9$: 451.1967].

4.6.2. (1*S*,2*S*,4*R*,7*R*,9*R*,10*S*,11*R*,15*R*) 1-Acetoxymethyl-2-methoxy-12-oxo-7-phenyl-3,6,8,13-tetraoxatetracyclo[10.3.1.$0^{1,10}$.$0^{4,9}$]hexadecadene (41). Colorless oil; $[\alpha]_D^{24}$ +1.3 (*c* 0.55, $CHCl_3$); IR (film): ν_{max} (cm^{-1}) 2924, 2853, 2342, 1746 (C=O), 1454, 1371, 1231, 1125, 1092, 1055, 974, 756, 700; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.55–7.30 (m, 5H), 5.53 (s, 1H), 4.70 (s, 1H), 4.50–4.10 (m, 5H), 3.88 (m, 1H), 3.75 (dd, J_1=J_2=9.9 Hz, 1H), 3.49 (dd, J_1=J_2=9.7 Hz, 1H), 3.39 (s, 3H), 3.11 (d, *J*=6.7 Hz, 1H), 2.82 (m, 1H), 2.63 (d, *J*=10.3 Hz, 1H), 2.48 (m, 1H), 2.07 (s, 3H), 1.68 (dd, J_1=14.6 Hz, J_2=4.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 172.2, 170.3, 136.9, 129.1, 128.2, 125.9, 101.9, 98.1, 73.8, 71.8, 69.0, 64.2, 62.0, 55.3, 48.6, 45.2, 42.2, 37.9, 30.2, 20.7; HRMS *m/z* 419.1717 [(M+H^+); calcd for $C_{22}H_{26}O_8$: 419.1705].

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Supplementary data

^{1}H and ^{13}C NMR spectra and complete assignment of all NMR data are available online. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.08.070.

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