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Synthesis and spectroscopic NMR studies of a highly stable cross-ozonide product derived from a carbohydrate system

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Abstract—Ozonolysis of a carbohydrate derived norbornene system afforded a stable intramolecular cross-ozonide through a stereocontrolled pathway involving a regioselective fragmentation of the primary ozonide.

1. Introduction

The chemistry of endoperoxides and trioxolane systems has gained much popularity over the last decade because they were recognized as structures widely distributed in nature, mostly due to their inherent biological properties.[1] A great deal of effort has been directed towards studying the chemistry and biological mode of action of artemisinin **1** (Fig. 1) and a plethora of analogues. Artemisinin[2] is a natural product from a traditional Chinese herbal remedy and has shown a potent antimalarial activity.[3] The fact that this type of compound has been used as a model for the design of new therapeutic agents against resistant forms of *Plasmodium falciparum* led to the development of simpler cyclic peroxide structures with important antimalarial activity.[4]

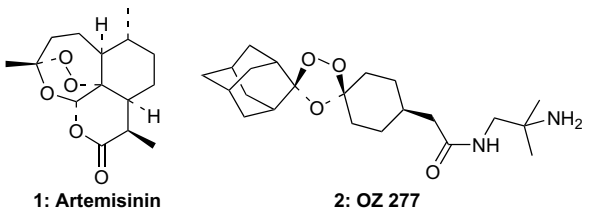

Figure 1.

More recently, a new drug candidate named OZ 277 **2** has strongly emerged as a new antimalarial agent.[5] The unique structural similarity that this synthetic ozonide exhibits with artemisinin is the peroxide bridge, which is critical for the pharmacological activity.

The synthesis of 1,2,4-trioxolane rings is usually achieved through ozonolysis of a carbon–carbon double bond. The mechanism of the ozonolysis reaction proposed by Criegee consists of three steps: (i) a [3+2] cycloaddition reaction of ozone with the alkene leading to the formation of a primary ozonide or 1,2,3-trioxolane **3**, (ii) a cycloreversion process providing the transient carbonyl oxide and a stable carbonyl compound, which may proceed in two different ways in the case of unsymmetrically substituted alkenes **4a** and **4b**, (iii) recombination of the carbonyl oxide and the newly formed carbonyl group derivative to give 1,2,4-trioxolane **5**.[6] In the case where the transient carbonyl oxide is trapped by another carbonyl derivative present in the reaction medium, the product is a cross-ozonide **6a** and **6b**[7] (see Scheme 1).

Alternatively, when the ozonolysis reaction is performed in a participating solvent, such as an alcohol, the carbonyl oxide can react with the solvent to give an alkoxy hydroperoxide, which upon the appropriate workup yields the corresponding ester.[8] In the last two cases, the reaction products provide useful information regarding the regioselectivity of the primary ozonide cleavage.[9]

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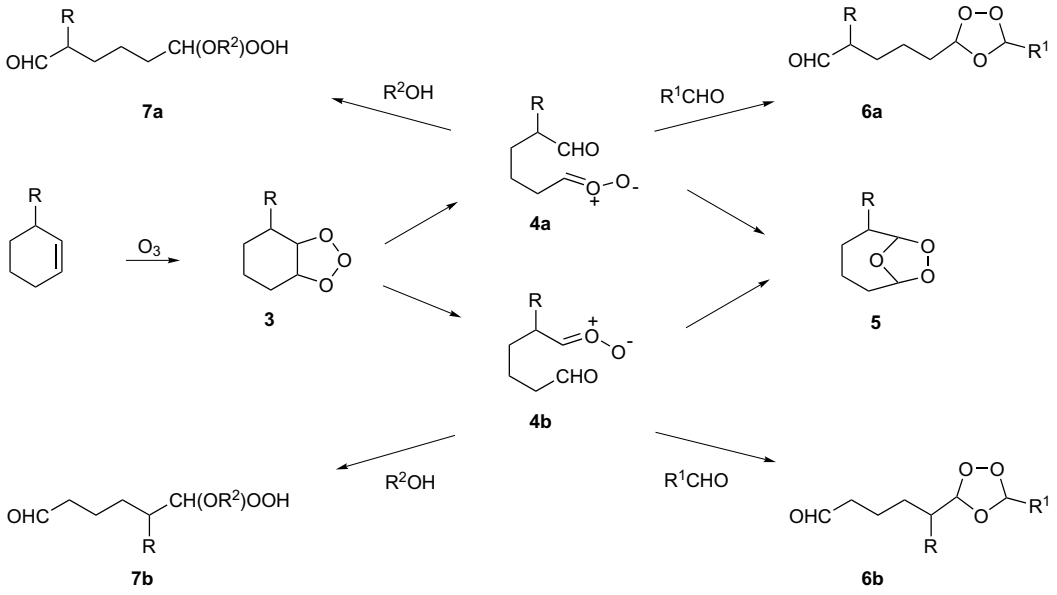


Scheme 1.

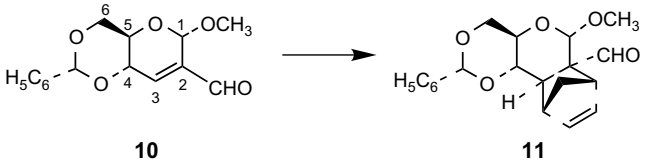
2. Results and discussion

In this context, we report the synthesis of an enantiomerically pure and highly stable intramolecular cross-ozonide structure. The product was obtained by means of a non-symmetric ozonolysis of a norbornene type skeleton derived from a carbohydrate system.

Our enantiospecific route relies on the use of D-glucose as source of chirality and employed the pyranoside ring as the initial scaffolding for constructing a dienophile with an exocyclic electron withdrawing group. In a simple and efficient synthetic sequence, methyl-α-D-glucopyranoside **8** was converted into a cyclic α,β-unsaturated aldehyde **10** (Scheme 2).[10]

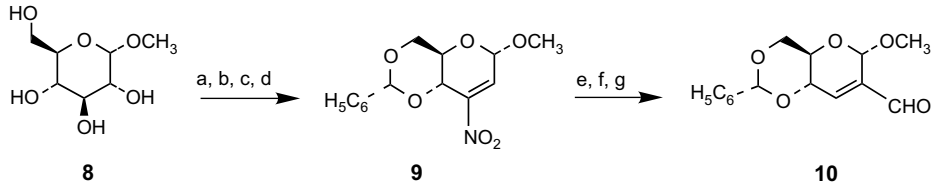
The reaction of aldehyde **10** with freshly cracked cyclopentadiene afforded the cycloadduct **11** in 26% yield as the major adduct (Scheme 3). The product was the result of the diene approach from the β face of dienophile **10** in an *endo* manner. We were surprised with the outcome and low yield of this reaction, since the isomeric dienophile (with the carbonyl group attached at C-3) afforded the corresponding β-*exo* adduct in 85% yield as a single product under similar reaction conditions.[11,12]

The structure assignment of **11** was based on spectroscopic evidence. All its ^{1}H and ^{13}C NMR signals were unequivocally assigned by using homo and heteronuclear 2D NMR techniques and NOE experiments.



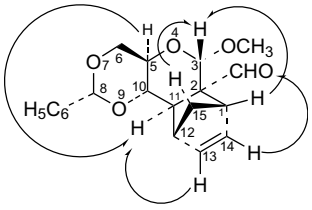
Scheme 3. Reagents and conditions: $LiClO_4$ anhydrous 5 M in Et_2O, cyclopentadiene, rt.

The proton spectrum showed four sharp singlets at 3.42, 4.84, 5.51, and 9.53 ppm that were assigned as the methoxy group, the anomeric proton H-3, the benzylic proton H-8, and the aldehyde proton, respectively. Two broad singlets at 2.96 and 3.14 ppm correspond to the bridge head protons H-1 and H-12. A well defined double doublet at 4.33 ppm was attributed to the equatorial H-6 and two other double doublets centered at 6.08 and 6.19 ppm were assigned to the vinylic protons H-13 and H-14. Another characteristic multiplet that integrated for two protons appeared at 1.63 ppm and was attributed to the methylene group C-15. A coupling constant of 9.18 Hz between the vicinal protons H-10 and H-11 clearly showed a *trans* relationship, suggesting that the product was formed by the approach of the cyclopentadiene from the β face of the



Scheme 2. Reagents and conditions: (a) $NaIO_4$, H_2O, pH 5–6; (b) CH_3NO_2, $NaOCH_3$, CH_3OH; (c) $C_6H_5CH(OCH_3)_2$, CSA, $CHCl_3$; (d) MsCl, Et_3N, CH_2Cl_2; (e) KCN, H_2O, Amberlite, CH_3CN; (f) Et_3N, acetone/H_2O; (g) DiBAL-H, CH_2Cl_2.

dienophile. The NOE observed between H-5↔H-11 and H-1↔H-3 also corroborated the attack of the diene from the β face of the dienophile. The NOE observed between H-11↔H-13 and H-14↔H–CHO showed the *endo* character of the addition. The NOE between H-3↔H-15 also confirmed that compound **12** is a β-*endo* adduct (Fig. 2).

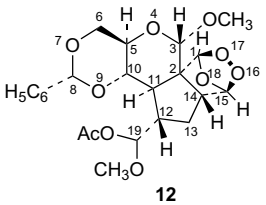


11

Figure 2. Significant NOE correlations.

The ozonolysis reaction of cycloadduct **11** was carried out in a dichloromethane–methanol solution with solid $NaHCO_3$ in suspension. The crude reaction mixture was then treated with acetic anhydride and triethylamine in dichloromethane. The TLC analysis of the crude material showed only one product, which after flash chromatography purification afforded product **12** in 54% yield.

The IR spectrum of **12** showed typical absorption bands at 1733 and 1761 cm^{-1} assigned to the carbonyl of the acetate group and the peroxide linkage, respectively. The ^1H NMR spectrum showed five distinctive sharp singlets at 4.63, 4.92, 5.55, 5.94, and 6.50 ppm that integrated for one proton each and correspond to protons attached at carbon atoms bearing two oxygenated functions. There were also three other neat singlets that integrated for three protons each at 2.11, 3.43, and 3.51 ppm, which were assigned to a methyl group from the acetate and two methoxy groups, respectively. No aldehyde proton signal was observed at low fields. The pyranose backbone was confirmed by the signals of the methoxy group at 3.43 ppm and the anomeric proton at 4.92 ppm. The benzylidene acetal structure was evident from the aromatic protons between 7.38 and 7.53 ppm, the presence of the acetal proton at 5.55 ppm and the characteristic coupling constant of the geminal protons H-6_{eq} and H-6_{ax} plus the vicinal coupling constant with H-5 (Fig. 3). The signals of the ^{13}C NMR spectrum also denoted the existence of a methyl group at 21.3 ppm, a carbonyl carbon at 169.6 ppm both from the acetate group, two methoxyl carbons at 55.2 and 57.5 ppm and five acetal carbons at 97.3, 102.4, 106.6, 107.8, and 111.4 ppm. The complete set of signals in the ^1H and ^{13}C NMR spectra were assigned by using homo and heteronuclear 2D NMR techniques and NOE experiments.



12

Figure 3. Compound **12** rings numbering.

Due to the number of oxygen atoms that are part of the ring system, it was difficult to establish a complete proton/carbon connectivity in the structure. For this reason, in order to confirm the presence and regioselective formation of the 1,2,4-trioxolane ring we performed selected gradient experiments of heteronuclear multiple bond correlation (HMBC). The ^2J and ^3J coupling constants correlations were of great utility in providing the following evidence:

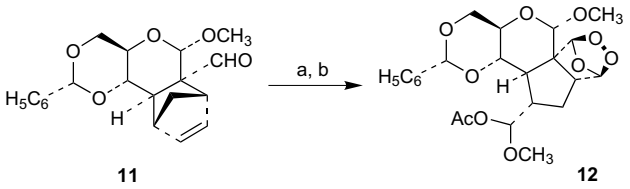
(a) The cross-peaks between C-1/H-11, C-1/H-15, and C-3/H-1 allowed the C-1 signal to be identified; (b) the cross peaks between C-1/H-15, C-15/H-13α, and C-15/H-13β determined the remaining carbon peak of the trioxolane ring; (c) the cross-peaks between C-2/H-14, C-14/H-3, and C-15/H-14 were used to assign the signal for C-14; (d) the cross-peaks between C-11/H-12, C-12/H-10, C-14/H-12, and C-19/H-12 helped to establish the chemical shift of C-12.

The NOESY experiments were useful to corroborate part of the chemical shift assignments and provide extra stereochemical information. The correlation found between H-3↔H-14 and H-10↔H-14 showed that the ozonide ring is located on the α face of the fused ring system; the correlation between H-1↔H-11 and H-1↔OCH_3 also corroborated this ring system and confirmed that the signal at 111.4 ppm corresponded to the carbon adjacent to C-2; the correlation between H-13α↔H-15 helped to clearly identify the H-13α; the correlation between H-3↔H-14 and H-10↔H-14 defined the orientation of H-14 towards the β face of the molecule and the correlation between H-10↔H-12 and H-11↔H-19 demonstrated that there was no epimerization of the C-12 configuration during the treatment with triethylamine.

The stereochemistry of C-1 and C-15 was proposed based on the value of ^1H NMR coupling constants between H-14 and H-15 in comparison with computer-generated 3D structures obtained by CHEM 3D™ Pro V.4.0, with MM2 force-field calculations for energy minimization for the two possible orientations of the 1,2,4-trioxolane ring. The calculated dihedral angle between H-14/C-14/C-15/H-15 for the model with the peroxide bridge oriented toward the β face is $\Phi = 78.3°$, while for the other isomer it is $\Phi = 44.4°$. The coupling constants calculated according to the Karplus equation[13] for both dihedral angles were $J_{H\text{-}14/H\text{-}15} = 0.1$ and 4.1 Hz, respectively. Considering that the signal of H-15 is a singlet, the only model that showed a good agreement between the calculated and the observed coupling constant is the diastereoisomer with the peroxide bridge oriented toward the β face. Similar results were obtained with the corresponding epimers at C-19.

Unfortunately, no spectroscopic evidence was found to establish the configuration of C-19 and we were unable to obtain a crystalline material suitable for X-ray diffraction analysis. For this reason, the stereochemistry of C-19 is not shown in Figure 3. It is worth to mention that the reaction afforded only one of the two possible diastereoisomers at C-19. The HRMS showed a peak for the $[M+NH_4]^+ = 482.2032$ that is in agreement with the $C_{23}H_{28}O_{10}$ calculated molecular formula.

In addition to the spectroscopic studies, the positive peroxide test using the iodide method[14] was chemical evidence for the peroxide structure. All these data were consistent with the structure of ozonide **12** (Scheme 4).

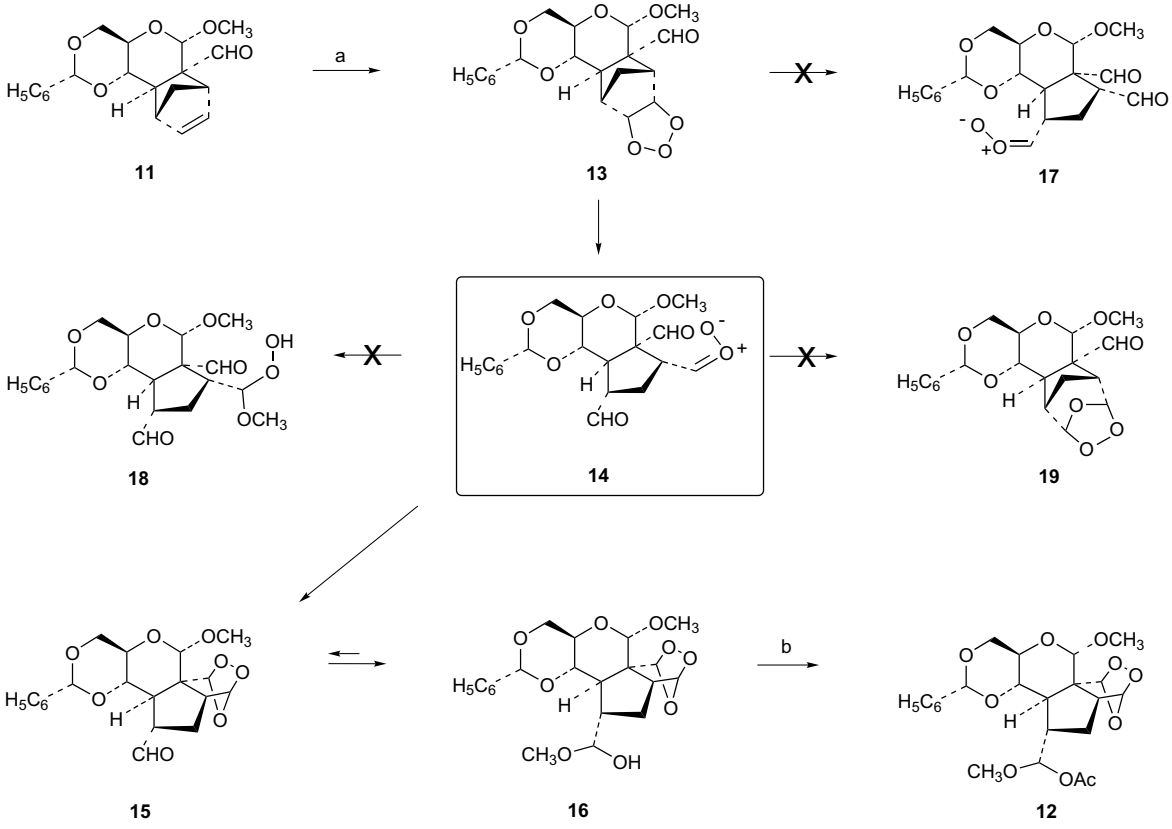


Scheme 4. Reagents and conditions: (a) O_3, $MeOH/CH_2Cl_2$, $NaHCO_3$, −78 °C; (b) $(CH_3CO)_2O$, Et_3N, CH_2Cl_2, rt.

The analysis of the reaction product obtained and the possible alternative pathway that the ozonolysis reaction could undergo showed a high degree of regio- and stereocontrol. The reaction of cycloadduct **11** with ozone yielded the primary ozonide **13**, which upon regioselective fragmentation afforded only one of the two possible transient carbonyl oxide intermediates. Carbonyl oxide **14** was trapped by one of the two aldehyde groups present in the molecule at this stage and formed the 1,2,4-trioxolane intermediate **15**. It was not possible to detect any by-products derived from the other two possible competing processes: reaction of the carbonyl oxide with methanol and concomitant formation of the methoxy hydroperoxide **18**, nor its recombination with the carbonyl group generated at the other termini of the double bond to generate ozonide **19**. Further diastereoselective reaction of the carbonyl group at C-19 with methanol afforded hemiacetal **16**, which upon acetylation yielded the final product **12**. The fact that the reaction afforded only one diastereoisomer at C-19 allowed us to speculate that the result could be due to an intramolecular hydrogen bond formation between the hemiacetal and the oxygen of the trioxolane ring, which is suitably oriented, thus stabilizing preferentially one of the epimers (Scheme 5).

3. Conclusion

A 1,2,4-trioxolane system was synthesized in a regio- and stereocontrolled tandem reaction process. This nonsymmetric ozonolysis is most likely controlled by the effect of remote substituents.[9] As proposed by Wu,[15] in this case, the aldehyde group in the norbornene system has a favorable spatial arrangement to induce the regioselective ozonide fragmentation through space. Furthermore, its proximity to the reacting double bond is made evident by the formation of the cross-ozonide in 54% yield as the only detectable reaction product. The material was stable to flash column chromatography and other normal laboratory manipulations; furthermore, after storage at −20 °C for several months it showed no evidence of decomposition.



Scheme 5. Reagents and conditions: (a) O_3, $MeOH/CH_2Cl_2$, $NaHCO_3$, −78 °C; (b) $(CH_3CO)_2O$, Et_3N, CH_2Cl_2, rt.

4. Experimental

4.1. General

Melting points were taken on a Leitz Wetzlar Microscope Heating Stage, Model 350 apparatus, and are uncorrected. Optical rotations were recorded with a Jasco DIP 1000 polarimeter. IR spectra were recorded on a Nicolet Impact Model 410 instrument. Room temperature ^{1}H and ^{13}C NMR spectra using homo- and heteronuclear 2D NMR techniques and NOE experiments (including heteronuclear multiple bond correlation (HMBC) and NOESY) were recorded on Bruker AC 200 and DMX 500 spectrometers with Me_4Si as internal standard and chloroform-*d* as solvent. High resolution mass spectrometry measurements were performed using a Waters AutoSpect equipment or Applied Biosystems MS. The reactions were monitored by TLC on 0.25 mm E. Merck silica gel plates ($60F_{254}$), using UV light and anisaldehyde–H_2SO_4–AcOH as detecting agent. Flash column chromatography, using Merck silica gel 60H, was performed by gradient elution created by mixtures of hexanes and increasing amounts of EtOAc. The reactions were performed under 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. Preparation of 3-methoxy-8-phenyl-4,7,9-trioxatetracyclo[10.2.1.0^{2,11}.0^{5,10}]-pentadec-13-ene-2-carbaldehyde 11

Methyl 4,6-*O*-benzylidene-2,3-dideoxy-2-*C*-formyl-α-D-*erythro*-hex-2-enopyranoside **10** (583 mg, 2.1 mmol) was azeotropically dried with dry benzene under vacuum and dissolved in anhydrous petroleum ether (35 mL) at room temperature under an argon atmosphere. Anhydrous lithium perchlorate (18.6 g, 0.2 mol) and freshly cracked cyclopentadiene (1.4 mL, 21.2 mmol) were added sequentially under an inert atmosphere at room temperature to the magnetically stirred solution. Stirring was continued for 7 days at rt. At this time, fresh amounts of anhydrous petroleum ether and cyclopentadiene were added and the reaction mixture was stirred for seven more days. The mixture was diluted with ethyl acetate, washed with distilled water, dried (Na_2SO_4), and concentrated. The crude product was purified by flash chromatography to yield pure **11** (189 mg, 26%) as a colorless oil. Compound **11**: $[\alpha]_D^{23} = +35.8$ (*c* 8.24, $CHCl_3$); IR (NaCl) ν_{max}: 699, 755, 850, 974, 1086, 1212, 1374, 1454, 1721 (C=O), 2854, 2972 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.63 (m, 2H, H-15, H-15′), 2.36 (dd, 1H, $J_{10,11}$ 9.2, $J_{11,12}$ 1.8 Hz, H-11), 2.96 (bs, 1H, H-12), 3.14 (bs, 1H, H-1), 3.42 (s, 3H, OCH_3), 3.49 (dd, 1H, $J_{10,11} = J_{5,10}$ 9.5 Hz, H-10), 3.65 (dd, 1H, $J_{gem} = J_{5,6ax}$ 10.0, H-6ax), 3.81 (m, 1H, H-5), 4.33 (dd, 1H, J_{gem} 10.0, $J_{5,6eq}$ 4.6 Hz, H-6eq), 4.84 (s, 1H, H-3), 5.53 (s, 1H, H-8), 6.08 (dd, 1H, $J_{13,14}$ 5.6, $J_{12,13}$ 3.2 Hz, H-13), 6.19 (dd, 1H, $J_{13,14}$ 5.6, $J_{1,14}$ 2.8 Hz, H-14), 7.30–7.55 (m, 5H, aromatics), 9.53 (s, 1H, C*H*O); ^{13}C NMR (50 MHz, $CDCl_3$): δ44.3 (C-15), 45.0 (C-12), 45.2 (C-11), 47.7 (C-1), 56.3 (O*C*H$_3$), 62.4 (C-2), 65.5 (C-5), 69.6 (C-6), 79.7 (C-10), 101.6 (C-8), 104.7 (C-3), 126.1 (2C, aromatics, C_{ortho}), 128.1 (2C, aromatics, C_{meta}), 128.9 (1C, aromatic, C_{para}), 132.3 (C-14), 137.3 (1C, aromatic, C_{ipso}), 139.2 (C-13), 199.6 (*C*HO); HRMS (EI) observed mass: 341.139010 (for $[M-H]^+$ calculated mass: 341.138899).

4.3. Preparation of 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 12

Aldehyde **11** (121.3 mg, 0.4 mmol) was dissolved in a 5:1 mixture of CH_2Cl_2–CH_3OH (6 mL) and solid $NaHCO_3$ (120 mg, 1.4 mmol) was added. The suspension was cooled down to −78 °C and an ozone stream was bubbled through the stirred suspension. Ozone addition was stopped when complete consumption of **11** was observed by TLC analysis. The mixture was then flushed with argon, and $NaHCO_3$ was removed by filtration. The filtrate was concentrated under vacuum to give the crude as colorless oil, which was taken up in CH_2Cl_2 (6 mL). The mixture was cooled down to 0 °C, and acetic anhydride (170 μL, 1.8 mmol) and triethylamine (75 μL, 0.4 mmol) were added. The mixture was stirred at room temperature overnight and then partitioned between ethyl acetate 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 under vacuum. Chromatography of the crude product afforded pure **12** (87.3 mg, 54%) as a colorless oil. Compound **12**: $[\alpha]_D^{25} = +21.5$ (*c* 0.44, $CHCl_3$); IR (NaCl) ν_{max}: 700, 755, 941, 978, 1018, 1053, 1076, 1122, 1161, 1229, 1376, 1456, 1733 (COOC), 1761 (COOC), 2854, 2931 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.08 (dd, 1H, J_{gem} 14.9, J_{vic} 6.6 Hz, H-13β), 2.11 (s, 3H, CH_3CO), 2.31 (dm, 1H, J_{gem} 14.9 Hz, H-13α), 2.55 (d, 1H, $J_{10,11}$ 10.1 Hz, H-11), 2.71 (d, 1H, $J_{11,12}$ 7.9 Hz, H-12), 2.77 (dd, 1H, $J_{14,13\beta}$ 11.8, $J_{14,13\alpha}$ 3.2 Hz, H-14), 3.25 (dd, 1H, $J_{10,11} = J_{10,5}$ 10.0 Hz, H-10), 3.43 (s, 3H, OCH_3 anomeric), 3.51 (s, 3H, OCH_3 acetalic), 3.71 (dd, 1H, $J_{gem} = J_{5,6ax}$ 10.4 Hz, H-6ax), 3.92 (m, 1H, H-5), 4.33 (dd, 1H, J_{gem} 10,3, $J_{5,6eq}$ 5,0 Hz, H-6eq), 4.63 (s, 1H, H-3), 4.92 (s, 1H, H-19), 5.55 (s, 1H, H-8), 5.94 (s, 1H, H-1), 6.50 (s, 1H, H-15), 7.38–7.44 (m, 3H aromatics), 7.49–7.53 (m, 2H aromatics); ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.3 (*C*H$_3$CO), 26.6 (C-13), 43.6 (C-11), 46.7 (C-12), 50.9 (C-14), 55.2 (OCH_3 anomeric), 57.5 (OCH_3 acetalic), 60.8 (C-5), 62.4 (C-2), 69.2 (C-6), 78.2 (C-10), 97.3 (C-3), 102.4 (C-8), 106.6 (C-15), 107.8 (C-19), 111.4 (C-1), 126.2 (2C aromatics, C_{ortho}), 128.4 (2C aromatics, C_{meta}), 129.3 (1C aromatic, C_{para}), 137.2 (1C aromatic, C_{ipso}), 169.7 (CH$_3$*C*O); HRMS (CI) observed mass: 482.2032 (for $[M+NH_4]^+$ calculated mass: 482.2026).

Acknowledgements

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