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Synthesis of New β-Hydroxy Nitrate Esters as Potential Glycomimetics or Vasodilators

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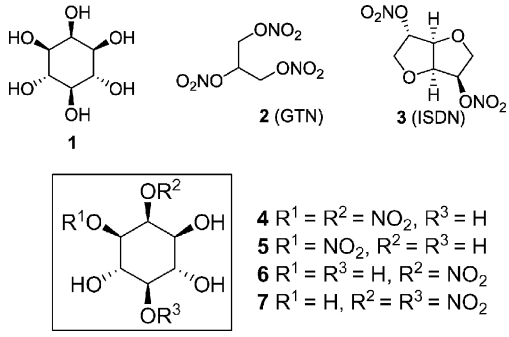
New β-hydroxy nitrates have been synthesized by the ring-opening reaction of epoxides with $Bi(NO_3)_3 \cdot 5H_2O$, which was used both as a catalyst and reagent. The synthesized molecules are both potential cyclitol mimetics and vasodilators as a result of their hydroxy groups and nitrate esters.

Introduction

Highly hydroxylated cycloalkanes are often referred to as cyclitols. Cyclitols are important compounds due to their potential use as glycosidase inhibitors, which are receiving considerable attention for their chemotherapeutic applications against diabetes, cancer, and viral infections.[1] For instance, inositols and, in particular, *myo*-inositol (**1**) derivatives play a central role in the cellular signal of various glycosidase enzymes and may have therapeutic applications.[2] Owing to the fundamental importance of cyclitols, there has been considerable interest in recent years in the design of new-generation cyclitol mimetics containing multiple hydroxy groups.[3] Organic nitrates[4] ($RONO_2$) are an important class of compounds that are widely used to treat a number of cardiovascular diseases,[5] including congestive and coronary heart failure, and are also of particular benefit in the treatment of angina pectoris attacks,[6] unstable angina[6a,7] and acute myocardial infection.[6a,8] Because the use of glyceryl trinitrate[9] (**2**, GTN) in the treatment of *Angina pectoris* has been shown to cause several adverse effects, the search for new organic nitrates with reduced side-effects and improved oral bioavailability has greatly increased in recent years. Isosorbide dinitrate (**3**, ISDN) and mononitrate are clinically used as vasodilators.[10] The synthesis of four selectively nitrated derivatives **4**–**7**[11] of *myo*-inositol has been reported in studies of hypotensive and cardiovascular activity.



Epoxides are versatile organic synthetic intermediates. For instance, 1,2-substituted β-hydroxy nitrates can be prepared through the facile ring-opening of epoxides. As a first approach to the synthesis of hydroxy nitrates, the classic methods used involve either the reaction of epoxides in nitric acid[12] or the nitration of halohydrins with $AgNO_3$.[13]

These methods require highly acidic conditions and the use of an expensive silver salt, respectively. A second approach involves the ring-opening of the epoxides by the nitrate ion prepared from NH_4NO_3, Bu_4NNO_3 or $NaNO_3$ in the presence of Lewis acids.[14] The use of NO in air,[15] $(NH_4)_2Ce(NO_3)_6$[16] and $ZrO(NO_3)_2$[17] in equivalent amounts has also been reported for the direct preparation of hydroxy nitrates from epoxides. Recently, the ring-opening of various epoxides using $Bi(NO_3)_3 \cdot 5H_2O$ to give β-hydroxy nitrates has been accomplished by Das et al.[18] and Salvador and co-workers.[19]

Functionalized organic nitrates are also intermediates in organic transformations. In fact, nitrates are the protected form of hydroxy groups and can be reduced to the corresponding alcohols by using catalytic hydrogenation[20] or reduction reagents.[21] Herein, we report the formation of new nitrate esters as possible glycomimetics and vasodilators by

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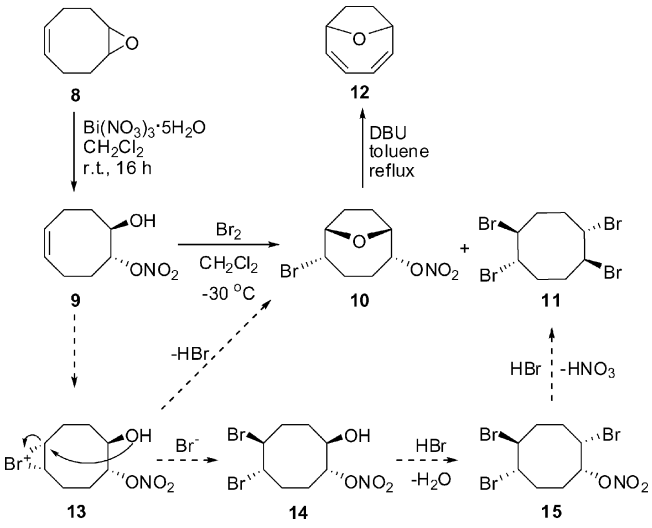
bismuth(III) nitrate mediated ring-opening of various mono- and diepoxides under mild reaction conditions. We selected bismuth nitrate pentahydrate, $Bi(NO_3)_3{\cdot}5H_2O$, as it is relatively non-toxic, readily available at low cost, insensitive to air and requires no special care during its handling.[22]

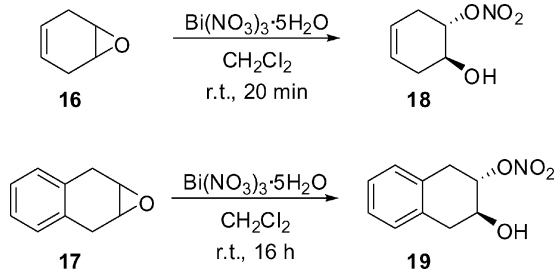
Results and Discussion

In our focused efforts to synthesize new-generation cyclitols or vasodilators through epoxide ring-opening reactions with $Bi(NO_3)_3{\cdot}5H_2O$, three types of epoxides were selected: (i) carbocyclic mono-epoxides, (ii) diepoxides, and (iii) epoxides with a tricyclic framework. Initially, the reaction of cyclooctene epoxide **8** (1 equiv.) and bismuth nitrate pentahydrate (1 equiv.), both as a nitrating agent and as a catalyst, was investigated at room temperature with dichloromethane as the solvent. The corresponding β-hydroxy nitrate **9** was obtained as the single reaction product and was characterized by ^1H and ^{13}C NMR (Scheme 1). The cyclooctene epoxide **8** was selected due to its double bond which can be easily functionalized. Then we turned our attention to the bromination reaction of **9** to observe the behaviour of the double bond and the free alcohol group in the molecule.[23] Compound **9** was treated with bromine in dichloromethane at –30 °C (Scheme 1). After purification by column chromatography and crystallization, two products were obtained. As the major product, we isolated the bicyclic ether-bridged product **10**. The structure of the second product was determined to be the tetrabromide **11**[24] by NMR and elemental analysis. The structure of **10** was confirmed by chemical transformation; the bromine and nitrate of **10** were eliminated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to afford 9-oxabicyclo[4.2.1]nona-2,4-diene (**12**).[25] For the formation of **10** and **11**, we propose the mechanism depicted in Scheme 1. The formation of **10** and **11** from **9** might well be explained by the formation of intermediate **13**. The *exo* attack of the hydroxy group on the bromonium ion **13** produces **10**. The addition of bromine to intermediate **13** yields **14**. Substitution of the hydroxy and nitrate groups of **14** by HBr results in the formation of **11**.



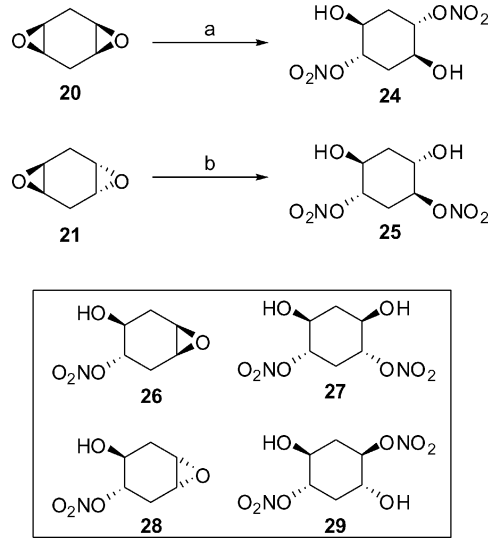
Scheme 1.

In an analogous manner, the epoxides **16**[26] and **17**[27] were selected as substrates to combine the tremendous ring-opening power of the oxiranes with bismuth nitrate. The reactions were performed at room temperature in CH_2Cl_2 and these epoxides underwent stereoselective ring-opening to the corresponding products **18** and **19** as single products in yields of 85 and 73%, respectively (Scheme 2).



Scheme 2.

Owing to the fundamental importance of the two organic nitrates, isosorbide dinitrate (**3**) and polyhydroxylated cycloalkanes, we shifted our attention to the synthesis of molecules with two nitrate functionalities. For this reason, *syn*- and *anti*-diepoxides (**20** and **21**) were first synthesized by oxidation of 1,4-cyclohexadiene with excess *m*-chloroperbenzoic acid (*m*-CPBA) and separation by silica gel column chromatography (Scheme 3).[28] As the *syn*-diepoxide **20** has electrophilic centres, two isomeric *trans*-β-hydroxy nitrates could be expected to form. To introduce two nitrate groups through the ring-opening reaction of epoxides, we treated the diepoxide **20** with bismuth nitrate in dichloromethane at room temperature. After completion of the reaction in 20 min, the spectroscopic data of the crude product revealed that only one dinitrate ring-opened product **24** was formed upon nitrate addition from the initially formed mono-nitrate adduct **26** in quantitative yield (Scheme 3). In particular, the three aliphatic carbon signals observed for **24** support the predicted symmetrical structure; the other possible isomer **27** should have four carbon resonance signals because of its axis of symmetry. The ring-opening reaction of the *anti* isomer **21** by a similar procedure yielded the dinitrate product **25** as a single product. The structure of **25** was determined by four carbon resonance signals. The other possible isomer **29** was not observed. The regiochemical outcome of the ring-opening reactions of these cyclohexene oxide type systems can be understood on the basis of the usual stereoelectronic factors that favour a *trans*-diaxial ring-opening mode. Figure 1 shows the AM1-calculated optimized geometries of the mono-epoxides **26** and **28**, in which both have steric effects on the axial position due to the hydrogen atom in **26** and the hydroxy groups in **28**. These could control the regioselectivity of the addition of the second nitrate.



Scheme 3. Reagents and conditions: (a) $Bi(NO_3)_3{\cdot}5H_2O$, room temp., 20 min, 74%; (b) $Bi(NO_3)_3{\cdot}5H_2O$, room temp., 20 min, 71%.

So as to obtain new di-β-hydroxy nitrates as potential glycosidases or vasodilators, we also used the *syn*-1,5-cyclooctadiene diepoxide **30**, prepared from *m*-CPBA oxidation, as a substrate for the ring-opening reaction with bismuth nitrate in CH_2Cl_2; we isolated only one product in quantitative yield (Scheme 4).[29] We presumed that the isolated product was the dinitrate **31**. Because of the steric hindrance of the first added nitrate functionality, we concluded that the second nitrate group attacks to form *syn*-1,5-dinitrate **31** instead of 1,4-dinitrate **32** due to axial interactions. We carried out AM1 and PM3 calculations on both possible products and found that the isomer **31** (–133.47 and –125.79 kcal/mol, by the AM1 and PM3 methods, respectively) is thermodynamically more stable than the isomer **32** (125.50l and –119.61 kcal/mol for the AM1 and PM3 methods, respectively). Furthermore, we prepared *syn*-diepoxide **33** by photo-oxygenation using tetraphenylporphyrin (TPP) as a sensitizer of 1,3-cyclohexadiene followed by the CoTPP-catalyzed reaction (Scheme 4).[30] The diepoxide **33** prepared was submitted to the ring-opening reaction with bismuth nitrate. Theoretically, the formation of three products (two symmetrical and one unsymmetrical) could be expected. However, the nitrated toxocarol derivative **34** was obtained as the sole product (Scheme 4). Although the three carbon signals observed for the molecule clearly indicate the formation of a symmetrical product, the alkoxy protons (C*H*OH) in molecule **34** resonate at δ = 4.04 ppm as a doublet (d, J = 5.6 Hz). The multiplet at δ = 5.30–5.19 ppm relating to C*H*ONO_2 shows that these protons are adjacent to both alkoxy and methylenic protons.

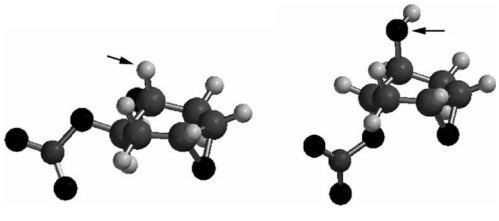
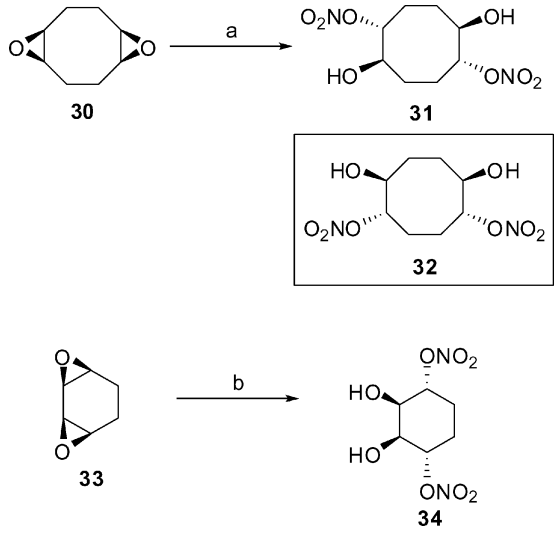
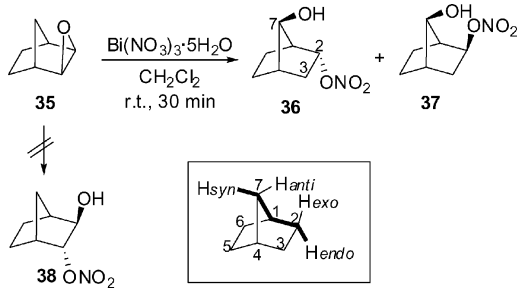


Figure 1. Optimized geometries of the mono-epoxides **26** and **28**.



Scheme 4. Reagents and conditions: (a) $Bi(NO_3)_3{\cdot}5H_2O$, room temp., 16 h, 70%; (b) $Bi(NO_3)_3{\cdot}5H_2O$, room temp., 30 min, 85%.

After the successful formation of the mono- and di-β-hydroxy nitrates from the rigid carbocyclic epoxides we investigated the ring-opening activity of bismuth nitrate towards epoxides in bicyclic skeletons. Norbornene epoxide (**35**)[31] was selected as a test molecule. After the reaction of **35** with bismuth nitrate in CH_2Cl_2, the reaction mixture was purified by chromatography on silica gel to give two isomeric products (Scheme 5). Careful examination of the reaction products revealed the formation of Wagner–Meerwein rearrangement products instead of the expected *trans* ring-opened product **38**.

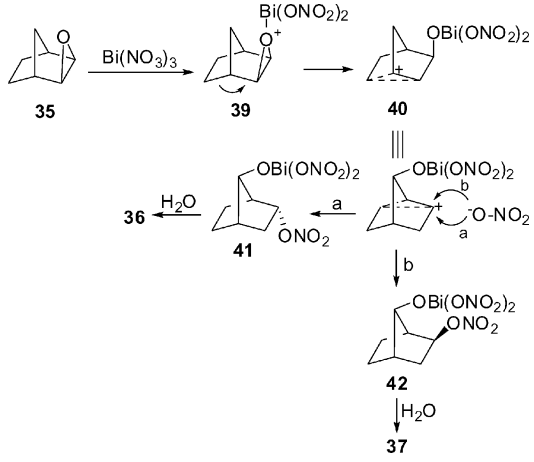


Scheme 5.

The structural assignments of the products were revealed by ^{1}H NMR spectroscopy. For both products, the relative configurations of the nitrate and skeleton structure of the molecules were determined from the coupling constants of the relevant protons. Whereas the methine proton connected to the nitrate (C*H*ONO_2) in molecule **37** resonates at δ = 4.98 ppm as a doublet of doublet of doublets (ddd, J = 7.1, 3.6, 2.8 Hz), the corresponding resonance in **36** at δ = 4.98 ppm is a doublet of doublets (dd, J = 7.9, 2.9 Hz). The long-distance coupling constant (J = 2.8 Hz) in mole-

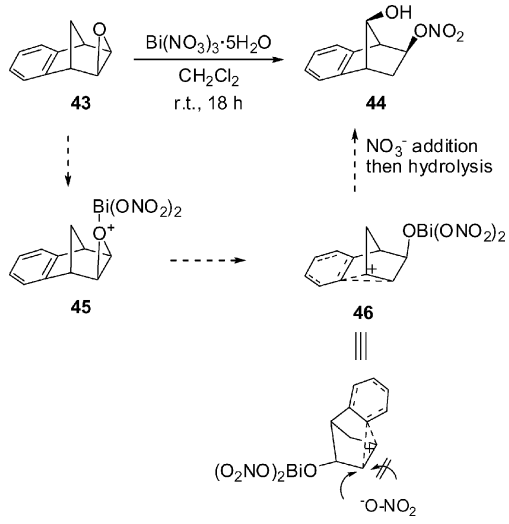
cule **37** (M or **W** orientation; the long-range coupling between 7*syn*-H and 2*endo*-H) supports the *exo* position of the nitrate, whereas there is no long-range coupling in the *endo*-nitrate structure **36**. Double resonance experiments were also used for the characterization of **36** and **37**. Irradiation of the bridge alkoxy proton converted the signal of the C*H*ONO$_2$ proton into a doublet of doublets in **37**. However, no similar behaviour was observed for **36** due to the *endo*-nitrate. Moreover, the large coupling constants (J = 13.9 Hz for **37** and J = 14.5 Hz for **26**) for the geminal 3 and 3′ protons are in agreement with the proposed structures.

In this reaction, the products **36** and **37** are Wagner–Meerwein rearrangement products, possibly obtained via intermediate **39** (Scheme 6). It is not possible to explain the products by the classic addition of nitrate to the epi ion **39**. In short, this mode of reaction shows a non-classic carbocation rearrangement.



Scheme 6.

Comparison of the results obtained during the final experiment with the others indicates that the structure of the carbocycle containing the epoxide ring affects the reaction outcome. We assume that steric effects in the intermediate **39** force the system to undergo a skeleton rearrangement. In this manner, to investigate the effect of the double bond on the skeleton rearrangement, the *exo*-benzonorbornadiene epoxide (**43**)[32] was treated with bismuth nitrate in CH_2Cl_2. A sole ring-opened product **44** was obtained in quantitative yield. A reasonable mechanism for the formation of **44** is shown in Scheme 7. The reaction may well proceed via non-classic carbocation intermediate **46**. The structure of **44** was elucidated on the basis of ^{1}H NMR spectroscopic data. The coupling constants relating to the methylenic protons (ddd, J = 13.4, 7.3, 3.3 Hz) and methine proton (dd, J = 7.3, 3.3 Hz) adjacent to the nitrate fully support the rearrangement product **44**. Although the methylenic protons of **44** resonate as an AB system at δ = 2.33 and 2.12 ppm, the large coupling constants show that these protons are in an ethano bridge, not in a methano bridge. Extensive NMR studies did not reveal the formation of any second product. These observations indicate that the *exo* face of the cation **46** is more accessible than the *endo* face, which is blocked by the benzene ring. Thus, the existence of a double bond (or aromatic ring) in the bicyclic carbon skeleton affects the product number, as well as the reaction outcome.



Scheme 7.

Conclusions

The present study using epoxides and bismuth nitrate produced not only new mono- and di-β-hydroxy nitrates as possible glycomimetics and vasodilators as well as synthetic precursors, but also led to insights into the reaction mechanisms. Monocarbocyclic oxiranes open to give products with *trans* stereo- and regioselectivity, whereas the epoxides fused to a bicyclic carbon framework are exposed to skeleton rearrangement through a non-classic carbocation mechanism.

Experimental Section

General Methods: Melting points were determined with a Büchi 539 capillary melting apparatus and are uncorrected. Infrared spectra were recorded with a Mattson 1000 FT-IR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded with 200 (50) and 400 (100) MHz Varian spectrometers and are reported in δ units with $SiMe_4$ as the internal standard. Elemental analyses were carried out with a Leco CHNS-932 instrument.

Calculation Methods: All calculations were performed by using SPARTAN04 software for Windows, version 1.0.0.[33] Energies were refined by using the semiempirical AM1 and PM3 methods.

Typical Procedure for the Synthesis of β-Hydroxy Nitrates: $Bi(NO_3)_3 \cdot 5H_2O$ (1 mmol) was added to a solution of the epoxide (1 mmol) in CH_2Cl_2 (1 mL) at room temperature. The reaction was completed in 5 min–18 h as verified by TLC. Then the reaction mixture was filtered through filter paper and the solvent was concentrated under reduced pressure. The crude product was purified by column chromatography or crystallization.

***trans*-[1*S*(*R*),8*S*(*R*),*Z*]-8-Hydroxycyclooct-4-enyl Nitrate (9):** The product **9** was obtained from **8** (250 mg, 2.02 mmol) and $Bi(NO_3)_3 \cdot$

$5H_2O$ (978 mg, 2.02 mmol) as described above by a typical procedure for 16 h. After filtration, the residue was purified by column chromatography (silica gel, 30 g), eluting with ethyl acetate/hexane (15:85). Elution gave the product **9** as a colourless oil (280 mg, 74%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.71 (ddd, J = 17.3, 11.2, 7.3 Hz, 1 H, A part of AB system, =CH), 5.62 (ddd, J = 17.3, 11.2, 7.3 Hz, 1 H, B part of AB system, =CH), 5.18 (ddd, J = 13.0, 8.8, 3.9 Hz, 1 H, $CHONO_2$), 3.96 (ddd, J = 13.0, 8.8, 3.9 Hz, 1 H, CHOH), 2.48–2.37 (m, 2 H, CH_2), 2.28–2.08 (m, 4 H, CH_2), 1.84–1.23 (m, 2 H, CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 130.2, 128.5, 86.0, 71.8, 33.2, 28.6, 23.0, 22.7 ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 3418, 3018, 2937, 2867, 1722, 1629, 1576, 1482, 1467, 1449, 1318, 1283, 1209, 1138, 1122, 1059, 1014, 973, 863, 737 cm^{-1}. $C_8H_{13}NO_4$ (187.19): calcd. C 51.33, H 7.00, N 7.48; found C 51.02, H 7.18, N 7.60.

Bromination of *trans*-[1*S*(*R*),8*S*(*R*),*Z*]-8-Hydroxycyclooct-4-enyl Nitrate (9): A solution of Br_2 (427 mg, 2.67 mmol) in CH_2Cl_2 (5 mL) was added dropwise to a solution of **9** (500 mg, 2.67 mmol) in CH_2Cl_2 (7 mL) at –30 °C and the mixture was stirred for 1 h. The reaction mixture was warmed to room temperature and the solvent of the mixture was removed under pressure. The residue was purified by column chromatography (silica gel, 30 g), eluting with ethyl acetate/hexane (3:97). The first elution gave the tetrabromide **11** (350 mg, 30%) and the second fraction provided **10** (485 mg, 68%).

[1*S*(*R*),2*S*(*R*),5*R*(*S*),6*R*(*S*)]-5-Bromo-9-oxabicyclo[4.2.1]nonan-2-yl Nitrate (10): Yield 360 mg, 51%, recrystallized from CH_2Cl_2/hexane as white crystals, m.p. 61–62 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 5.38–5.31 (m, 1 H, $CHONO_2$), 4.83–4.75 (m, 1 H, OCH), 4.64–4.61 (m, 1 H, CHBr), 4.20–4.10 (m, 1 H, OCH), 2.30–1.90 (m, 8 H, CH_2) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 85.10, 84.11, 79.34, 54.59, 31.50, 30.12, 28.22, 27.66 ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 2958, 1630, 1280, 1062, 936, 857 cm^{-1}. $C_8H_{12}BrNO_4$ (266.09): calcd. C 36.11, H 4.55, N 5.26; found C 35.99, H 4.52, N 5.25.

[1*S*(*R*),2*S*(*R*),5*S*(*R*),6*S*(*R*)]-1,2,5,6-Tetrabromocyclooctane (11): Yield 260 mg, 22%, recrystallized from CH_2Cl_2/hexane as white crystals, m.p. 129–130 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.78–4.75 (m, 4 H, CHBr), 2.86–2.79 (m, 4 H, CH_2), 2.15–2.08 (m, 4 H, CH_2) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 59.2, 28.8 ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 2922, 1426, 1217, 1065, 994, 762 cm^{-1}. $C_8H_{12}Br_4$ (427.80): calcd. C 22.46, H 2.83; found C 22.68, H 2.59.

(2*Z*,4*Z*)-9-Oxabicyclo[4.2.1]nona-2,4-diene (12): DBU (1.15 g, 7.57 mmol) was added to a solution of **10** (100 mg, 0.38 mmol) in toluene (3 mL) and the mixture was heated at reflux for 3 h. After cooling, H_2O was added to the reaction mixture and the mixture was extracted with diethyl ether. The organic layer was washed with water and dried with $MgSO_4$. After removal of the solvent in vacuo, the residue was purified by silica gel thin-layer chromatography. Elution with diethyl ether/hexane (25:75) gave **12** (40 mg, 87%, oil at room temperature). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.14–6.06 (m, 2 H, AA′ part of AA′BB′ system, =CH), 5.85–5.75 (m, 2 H, BB′ part of AA′BB′ system, =CH), 4.71–4.63 (m, 2 H, OCH), 2.24–2.12 (m, 4 H, CH_2) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 140.6, 126.4, 80.1, 41.9 ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 2925, 1732, 1633, 1067, 913, 744 cm^{-1}. $C_8H_{10}O$ (122.16): calcd. C 78.65, H 8.25; found C 79.01, H 8.08.

***trans*-[1*S*(*R*),6*S*(*R*)]-6-Hydroxycyclohex-3-enyl Nitrate (18):** The reaction was performed following the typical procedure described above for 20 min starting from **16** (200 mg, 2.08 mmol) and $Bi(NO_3)_3{\cdot}5H_2O$ (1.01 g, 2.09 mmol). The mixture was filtered and the residue purified by column chromatography (silica gel, 30 g), eluting with ethyl acetate/hexane (5:95). Elution gave the product **18** as a colourless oil (280 mg, 85%). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 5.65–5.49 (m, 2 H, =CH), 5.10 (ddd, J = 15.3, 8.9, 6.3 Hz, 1 H, $CHONO_2$), 3.98 (ddd, J = 15.3, 8.9, 6.3 Hz, 1 H, CHOH), 2.78–2.50 (m, 2 H, CH_2), 2.30–2.03 (m, 2 H, CH_2) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 126.4, 124.9, 85.2, 69.1, 35.0, 31.1 ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 3570, 3392, 3040, 2908, 2854, 1631, 1557, 1441, 1422, 1348, 1314, 1278, 1213, 1159, 1100, 1070, 1040, 997, 973, 867, 792, 755 cm^{-1}. $C_6H_9NO_4$ (159.14): calcd. C 45.28, H 5.70, N 8.80; found C 44.93, H 5.53, N 8.70.

***trans*-[2*S*(*R*),3*S*(*R*)]-3-Hydroxy-1,2,3,4-tetrahydronaphthalen-2-yl Nitrate (19):** The reaction was performed following the typical procedure described for 16 h starting from **17** (140 mg, 0.96 mmol) and $Bi(NO_3)_3{\cdot}5H_2O$ (465 mg, 0.96 mmol). The product **19** was recrystallized from CH_2Cl_2/hexane as yellow crystals (145 mg, 73%, m.p. 54–55 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26–7.20, (m, 2 H, aryl), 7.19–7.07 (m, 2 H, aryl), 5.27 (ddd, J = 12.9, 8.3, 5.4 Hz, 1 H, $CHONO_2$), 4.16 (ddd, J = 12.9, 8.3, 5.4 Hz, 1 H, CHOH), 3.25 (dd, J = 16.8, 5.4 Hz, 1 H, A part of AB system, CH_2), 2.97 (dd, J = 16.8, 8.3 Hz, 1 H, A part of AB system, CH_2), 2.92–1.30 (m, 2 H, CH_2), 2.82 (m, 1 H, OH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 132.9, 132.0, 129.2, 129.0, 127.2, 127.0, 83.4, 67.7, 36.3, 32.4 ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 3565, 3402, 3066, 3025, 2908, 2853, 1717, 1635, 1585, 1496, 1455, 1440, 1423, 131, 1321, 1276, 1217, 1161, 1111, 1059, 983, 953, 871, 749 cm^{-1}. $C_{10}H_{11}NO_4$ (209.20): calcd. C 57.41, H 5.30, N 6.70; found C 57.51, H 5.08, N 6.63.

Reaction of 1,4-Cyclohexadiene with *m*-CPBA: A mixture of 1,4-cyclohexadiene (2.50 g, 31.25 mmol) and *m*-CPBA [15.54 g (70%), 62.50 mmol] in dichloromethane (100 mL) was cooled in a salt–ice bath and stirred for 2 h. Dichloromethane (50 mL) was added and the reaction mixture was then washed with 10% NaOH (3 × 100 mL) and water (50 mL), dried with $MgSO_4$, filtered and the solvent removed under reduced pressure. The residue (3.42 g) was subjected to silica gel chromatography using ethyl acetate/hexane (10:90). The first fraction gave **21** (2.35 g, 67%). Then the column was eluted with CH_2Cl_2 to give **20** (850 mg, 24%).

***syn*-1,4-Cyclohexadiene Diepoxide (20):** Yield 625 mg, 18%, colourless crystals from CH_2Cl_2/hexane, m.p. 61–62 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.02 (d, J = 1.4 Hz, 4 H, OCH), 2.68 (d, J = 16.5 Hz, 2 H, A part of AB system, CH_2), 2.24 (dd, J = 16.5, 1.4 Hz, 2 H, B part of AB system, CH_2) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 51.1, 25.5 ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 3009, 2990, 2929, 1470, 1424, 1353, 1279, 1266, 1095, 1023, 933, 897, 835, 810, 788, 771 cm^{-1}. $C_6H_8O_2$ (112.13): calcd. C 64.27, H 7.19; found C 64.01, H 6.99.

***anti*-1,4-Cyclohexadiene Diepoxide (21):** Yield 1.95 g, 56%, colourless crystals from CH_2Cl_2/hexane, m.p. 181–182 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.07–3.05 (m, 4 H, OCH), 232–2.30 (m, 4 H, CH_2) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 50.9, 25.9 ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 2925, 2854, 1729, 1464, 127, 1074, 750 cm^{-1}. $C_6H_8O_2$ (112.13): calcd. C 64.27, H 7.19; found C 64.30, H 7.38.

[1*R*(*S*),2*R*(*S*),4*R*(*S*),5*R*(*S*)]-2,5-Dihydroxycyclohexane-1,4-diyl Dinitrate (24): The product **24** was prepared following the typical procedure described above for 20 min starting from **20** (250 mg, 2.23 mmol) and $Bi(NO_3)_3{\cdot}5H_2O$ (2.18 g, 4.46 mmol). The product **24** was recrystallized from CH_2Cl_2/hexane as white crystals (395 mg, 74%, m.p. 113–114 °C). ^{1}H NMR (200 MHz, CD_3COCD_3): δ = 5.25 (ddd, J = 10.7, 7.1, 4.0 Hz, 2 H, $CHONO_2$), 5.86 (d, J = 4.0 Hz, 2 H, OH), 4.05 (ddd, J = 10.7, 7.1, 4.0 Hz, 2 H, CHOH), 2.25 (ddd, J = 10.7, 7.1, 4.0 Hz, 2 H, A part of AB system, CH_2), 2.02 (ddd, J = 10.7, 7.1, 4.0 Hz, 2 H, B part of AB system, CH_2) ppm. ^{13}C NMR (50 MHz, CD_3COCD_3): δ = 84.8, 68.6, 34.3 ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 3398, 2925, 2856, 1716, 1635,

1442, 1276, 1181, 1067, 1015, 961, 854, 751 cm^{-1}. $C_6H_{10}N_2O_8$ (238.15): calcd. C 30.26, H 4.23, N 11.76; found C 30.50, H 4.08, N 11.67.

[1*S*(*R*),3*S*(*R*),4*S*(*R*),6*S*(*R*)]-4,6-Dihydroxycyclohexane-1,3-diyl Dinitrate (25): The product **25** was prepared following the typical procedure described above for 20 min starting from **21** (850 mg, 7.59 mmol) and $Bi(NO_3)_3·5H_2O$ (7.36 g, 15.18 mmol). The product **25** was recrystallized from CH_2Cl_2/hexane as white crystals (1.29 g, 71%, m.p. 172–173 °C). ^1H NMR (200 MHz, $CDCl_3$): δ = 5.10 (q, J = 5.8 Hz, 2 H, $CHONO_2$), 4.18 (q, J = 5.8 Hz, 2 H, CHOH), 2.31 (t, J = 5.8 Hz, 2 H, CH_2), 2.07 (t, J = 5.8 Hz, 2 H, CH_2) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 83.1, 67.7, 37.7, 29.2 ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 3753, 3378, 2931, 1638, 1441, 1326, 1279, 1181, 1090, 1069, 1015, 950, 862, 752 cm^{-1}. $C_6H_{10}N_2O_8$ (238.15): calcd. C 30.26, H 4.23, N 11.76; found C 30.41, H 4.20, N 11.70.

[1*R*(*S*),2*R*(*S*),5*R*(*S*),6*R*(*S*)]-2,6-Dihydroxycyclooctane-1,5-diyl Dinitrate (31): The product **31** was prepared following the typical procedure described above for 16 h starting from **30** (600 mg, 4.29 mmol) and $Bi(NO_3)_3·5H_2O$ (4.16 g, 8.57 mmol). The residue was purified by column chromatography (silica gel, 30 g), eluting with ethyl acetate/hexane (40:60). Elution gave the product **31** (800 mg, 70%, recrystallized from CH_2Cl_2/hexane as white crystals, m.p. 91–92 °C). ^1H NMR (400 MHz, CD_3OD): δ = 5.05 (ddd, J = 10.5, 8.0, 2.3 Hz, 2 H, $CHONO_2$), 3.79 (ddd, J = 10.5, 8.0, 2.3 Hz, 2 H, CHOH), 2.12–2.00 (m, 4 H, CH_2), 1.98–1.84 (m, 4 H, CH_2) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 87.9, 70.8, 28.5, 24.3 ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 3386, 2941, 1629, 1365, 1278, 1086, 1008, 977, 860, 755 cm^{-1}. $C_8H_{14}N_2O_8$ (266.21): calcd. C 36.09, H 5.30, N 10.52; found C 35.99, H 5.38, N 10.65.

[1*R*(*S*),2*R*(*S*),3*S*(*R*),4*S*(*R*)]-2,3-Dihydroxycyclohexane-1,4-diyl Dinitrate (34): The product **34** was prepared following the typical procedure described above for 30 min starting from **33** (500 mg, 4.46 mmol) and $Bi(NO_3)_3·5H_2O$ (4.34 g, 8.94 mmol). The product **34** was recrystallized from CH_2Cl_2/hexane as white crystals (900 mg, 85%, m.p. 88–89 °C). ^1H NMR (200 MHz, $CDCl_3$): δ = 5.30–5.19 (m, 2 H, $CHONO_2$), 4.04 (d, J = 5.6 Hz, 2 H, CHOH), 3.04–2.91 (m, 2 H, OH), 2.22–2.03 (m, 2 H, AA′ part of AA′BB′ system, CH_2), 1.97–1.26 (m, 2 H, BB′ part of AA′BB′ system, CH_2) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 82.4, 71.6, 24.7 ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 3403, 2940, 1634, 1440, 1315, 1276, 1068, 996, 853, 755 cm^{-1}. $C_6H_{10}N_2O_8$ (238.04): calcd. C 30.26, H 4.23, N 11.76; found C 30.03, H 4.40, N 11.75.

Reaction of Norbornene Epoxide (35) with $Bi(NO_3)_3·5H_2O$: The reaction was performed following the typical procedure described above for 30 min starting from **35** (800 mg, 7.27 mmol) and $Bi(NO_3)_3·5H_2O$ (3.53 g, 7.27 mmol). The mixture was filtered and the residue was purified by column chromatography (silica gel, 30 g), eluting with ethyl acetate/hexane (5:95). The first elution gave the product **36** as a colourless oil (380 mg, 30%). Then the column was eluted by ethyl acetate/hexane (7:93) to give **37** (850 mg, 68%).

[2*R*(*S*),7*R*(*S*)]-7-Hydroxybicyclo[2.2.1]heptan-2-yl Nitrate (36): ^1H NMR (200 MHz, $CDCl_3$): δ = 4.78 (dd, J = 7.9, 2.9 Hz, 1 H, $CHONO_2$), 4.25 (m, 1 H, CHOH), 2.31–2.29 (m, 1 H, CH), 2.18–2.13 (m, 1 H, CH), 2.05–1.95 (m, 2 H, CH_2), 1.87 (dd, J = 14.5, 7.9 Hz, 1 H, A part of AB system, CH_2), 1.69–1.53 (m, 1 H, CH_2), 1.27–1.20 (m, 2 H, CH_2) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 86.5, 78.7, 46.6, 41.2, 37.2, 26.8, 23.6 ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 3375, 2967, 2882, 1618, 1282, 1148, 1037, 1005, 935, 867, 758 cm^{-1}. $C_7H_{11}NO_4$ (173.17): calcd. C 48.55, H 6.40, N 8.09; found C 48.82, H 6.55, N 8.45.

[2*S*(*R*),7*R*(*S*)]-7-Hydroxybicyclo[2.2.1]heptan-2-yl Nitrate (37): Yield 730 mg, 58%, colourless crystals from CH_2Cl_2/hexane, m.p. 47–48 °C. ^1H NMR (200 MHz, $CDCl_3$): δ = 4.98 (ddd, J = 7.1, 3.6, 2.8 Hz, 1 H, $CHONO_2$), 4.05 (br. s, 1 H, CHOH), 2.35 (d, J = 4.4 Hz, 1 H, CH), 2.26–2.20 (m, 1 H, CH), 2.14–2.11 (m, 1 H, CH_2), 2.03 (dd, J = 13.9, 7.1 Hz, 1 H, A part of AB system, CH_2), 1.98–1.54 (m, 2 H, CH_2), 1.28–1.16 (m, 2 H, CH_2) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 88.7, 81.3, 46.4, 42.6, 37.4, 26.7, 24.4 ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 3343, 2965, 2925, 1625, 1279, 1157, 1085, 1068, 966, 865, 757 cm^{-1}. $C_7H_{11}NO_4$ (173.17): calcd. C 48.55, H 6.40, N 8.09; found C 48.77, H 6.35, N 8.23.

[2*R*(*S*),9*R*(*S*)]-9-Hydroxy-1,2,3,4-tetrahydro-1,4-methanonaphthalen-2-yl Nitrate (44): The product **44** was prepared following the typical procedure described above for 18 h starting from **43** (400 mg, 2.53 mmol) and $Bi(NO_3)_3·5H_2O$ (1.23 g, 2.53 mmol). The residue was purified by column chromatography (silica gel, 10 g), eluting with ethyl acetate. Elution gave the product **44** (350 mg, 63%, recrystallized from CH_2Cl_2/hexane as white crystals, m.p. 102–103 °C). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.29–7.21 (m, 1 H, aryl), 7.20–7.15 (m, 3 H, aryl), 4.95 (dd, J = 7.3, 3.3 Hz, 1 H, $CHONO_2$), 4.08 (m, 1 H, CHOH), 3.53 (m, 1 H, CH), 3.36–3.35 (m, 1 H, CH), 2.35 (m, 1 H, OH), 2.33 (ddd, J = 13.4, 7.3, 3.3 Hz, 1 H, A part of AB system, CH_2), 2.12 (dd, J = 13.4, 7.3 Hz, 1 H, B part of AB system, CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.0, 139.0, 128.0, 123.3, 122.4, 85.3, 83.8, 52.4, 48.2, 32.3 ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 3386, 2941, 1629, 1365, 1278, 1086, 1008, 977, 860, 755 cm^{-1}. $C_{11}H_{11}NO_4$ (221.21): calcd. C 59.73, H 5.01, N 6.33; found C 60.03, H 4.82, N 6.25.

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