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Cerium ammonium nitrate: a new catalyst for regioselective protection of glycols

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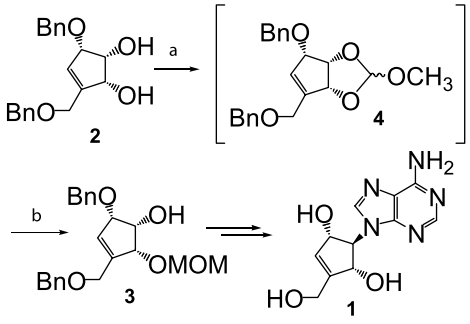
Abstract—The regioselective introduction of a methoxymethyl (MOM) group on different type of glycols via an orthoester intermediate was investigated. The novelty presented in this study is the use of ceric ammonium nitrate instead of the previously employed camphorsulfonic acid as catalyst. The monoprotection reaction was revealed to be highly selective when the glycol moiety was in the presence of an ether functionality.

1. Introduction

The selective monoprotection of polyhydroxylated compounds has been subject of research for many years because of its importance in the synthesis of complex natural products and their corresponding analogues.[1,2] In addition, the occurrence of 1,2-diols in macrolides, nucleosides and carbohydrates has led to the development of many protective groups of different stability to a range of reagents. For example, the selective protection of primary hydroxyl group versus a secondary alcohol,[3,4] the regioselective silylation of nucleosides,[5,6] and the selective monoprotection of carbohydrates[7] are some motivating cases in which regioselectivity may be necessary.

In the course of the enantioselective synthesis of (+)-neplanocin F (**1**), a synthetic challenge was the regioselective protection of the secondary allylic hydroxyl group over the secondary homoallylic hydroxyl group of the advanced synthetic intermediate **2**.[8] This problem was solved with the use of a methoxymethyl (MOM) protecting group that was able to discriminate between the allylic and homoallylic hydroxyl groups of a particular glycol. There were only two examples of this one-pot reaction reported in the literature based on orthoester formation of the corresponding diol by treatment with trimethyl orthoformate followed by in situ diisobutyl aluminum hydride reductive cleavage in methylene chloride at low temperature.[9,10] The former case illustrates the introduction of a MOM moiety onto the less sterically hindered hydroxyl group of a glycol.[9] In contrast to this report, a similar method describes the selective protection of a secondary alcohol with MOM groups in the presence of a primary alcohol.[10] These results suggested that the regioselectivity of this one pot reaction was strongly modulated by the nature of the substituents in the vicinity of the diol moiety. When **2** was reacted under these monoprotection conditions, in the presence of camphorsulfonic acid as catalyst as previously described,[9,10] only unreacted starting material was recovered. However, if the reaction is carried out employing cerium (IV) ammonium nitrate (CAN) instead of camphorsulfonic acid smoothly affords the desired MOM derivative **3** via the orthoester **4** (Scheme 1).[8] The use of a strong oxidant such as CAN as catalyst constitutes a surprising novelty for this type of reaction.[8]



Scheme 1. Reagents and conditions: (a) trimethyl orthoformate, CH_2Cl_2, CAN, rt, 2 h; (b) DIBAL, −78 °C 1 h→0 °C 10 min, 66%.

Keywords: Glycols; Regioselective monoprotection; Methoxymethyl protecting group; Diisobutyl aluminum hydride.
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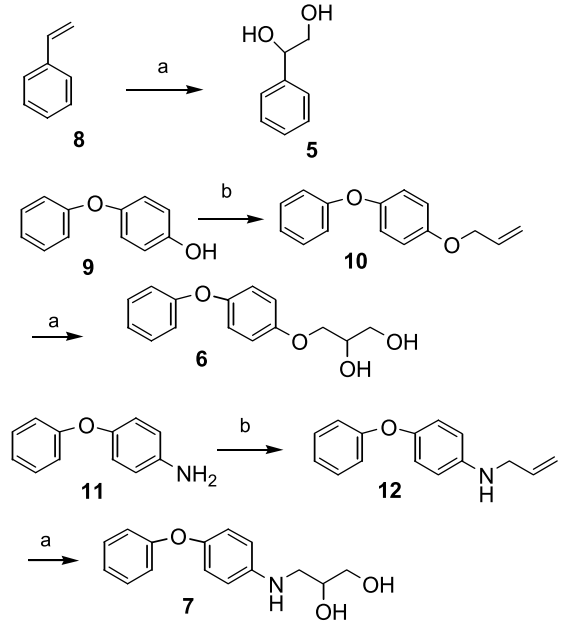
Consequently, it seems of interest to explore its scope as a general monoprotective protocol to introduce one MOM unit in glycols with vanishing environmental differences.

2. Results and discussion

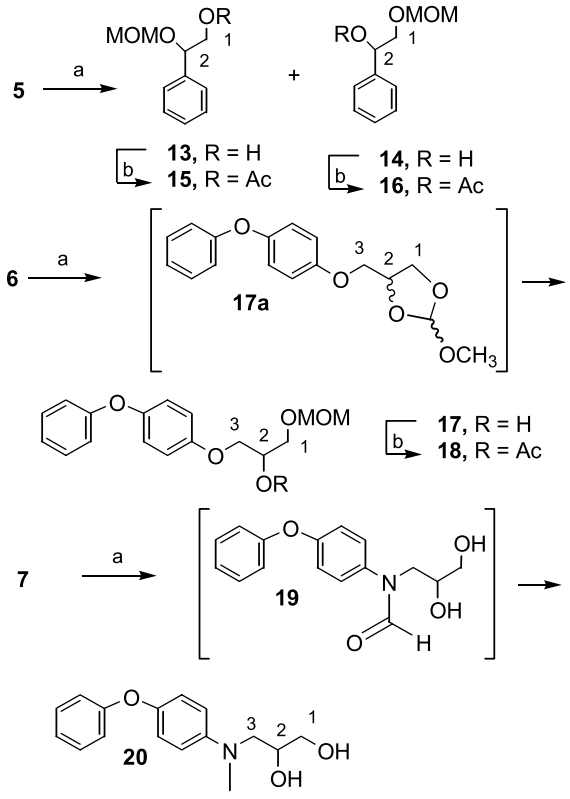
In order to investigate the reliability of this reaction, the syntheses of simple models that would mimic complex natural products were considered. Then, glycols possessing both a primary and a secondary alcohol were the first type of diols studied. The rationale for selecting the target glycols was to investigate the influence of a heteroatom in the vicinity of the glycol moiety on selectivity. The introduction of this heteroatom as an ether or amine functionality was motivated by their ability to coordinate with the aluminum atom of the diisobutyl aluminum hydride reagent improving selectivity. For this purpose, three glycols were envisioned (compounds **5**–**7**). Compound **5**, has no hetereoatoms in its chemical structure other than those of the glycol group and compounds **6** and **7** possess ether and amino groups at the α-carbon, respectively. Glycol **5** was straightforwardly prepared from styrene (**8**) via a perhydroxylation reaction[11] by treatment with potassium osmate and potassium ferricyanide in 90% yield. In a similar way, compound **6** was prepared from readily available 4-phenoxyphenyl allyl ether **10**, which in turn was prepared from 4-phenoxyphenol as described in a similar yield.[12,13] The nitrogen-containing derivative **7** was analogously prepared from 4-phenoxyaniline (compound **11**) via the allyl amine **12** (Scheme 2).

The monoprotection of glycol **5** exhibited low regioselectivity employing either CAN or CSA as catalysts. In the first case, compounds **13** and **14** were obtained in a (1.7:1) ratio favoring **13** in 81% overall yield. The regiochemistry observed for this reaction may be explained as a consequence of the hydride attack by the less hindered side of the corresponding orthoester intermediate. The chemical structure of **13** and **14** was unambiguously characterized by NMR analysis of their corresponding acetates **15** and **16**, respectively. For example, the peak centered at 4.90 ppm as a double of doublets in **13** corresponding to H-1 shifted downfield to 5.97 ppm in the acetyl derivative **15** with the same multiplicity. A similar behavior was experienced when **14** was acetylated. H-2 of **14** appeared as a multiplet centered at 3.69 ppm. This signal shifted downfield in the acetylated product **16**. This peak was observed as a double of doublets centered at 4.88 ppm. In addition, the use of the common catalyst (CSA) for this type of reaction slowed down the reaction rate as well as impaired the reaction yield without changing regioselectivity (Scheme 3).

The stereochemistry of this one-pot reaction was very encouraging when glycol **6** was used as a substrate. Certainly, **6** was reacted with trimethyl orthoformate in the presence of CAN to afford the corresponding orthoester intermediate that on reaction with DIBAL at −78 °C afforded solely the monoprotective MOM derivative **17** in 90% yield. Interestingly, when CSA was used as catalyst a similar high regioselectivity was observed but the reaction yield was lower (67% yield). In order to confirm the formation of this product, **17** was treated with acetic anhydride to yield **18**. The position of the MOM protecting group was confirmed by ^{1}H NMR analysis. The signal assigned to H-2 in **17**, which appeared as a sextet centered at 4.17 ppm, shifted downfield 1.15 ppm in **18**. The



Scheme 2. Reagents and conditions: (a) $K_2OsO_4 \cdot 2H_2O$, K_2CO_3, $K_3Fe(CN)_6$, py, *tert*-butanol–water, 90% for **5**, 87% for **6**, 89% for **7**; (b) Refs. 12,13 for **10**, KOH, $CH_2{=}CHCH_2Cl$, DMSO, rt, 72 h, 81% for **12**.



Scheme 3. Reagents and conditions: (a) i. trimethyl orthoformate, CH_2Cl_2, CAN (CSA), rt, 2 h, ii. DIBAL, −78 °C 1 h→0 °C 10 min, 81% for **13/14** (1.7:1) ratio, 32% if CSA was employed, 90% (CAN) or 67% (CSA) for **17**, 20% (CAN) for **20**; (b) Ac_2O, py, rt, 16 h, 94% for **15/16**, 97% for **18**.

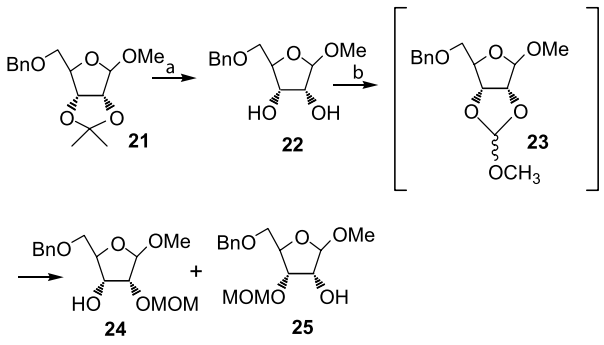
regiochemistry of this reaction was quite in agreement with our previous results on compound **2** that, under these conditions, gave rise to **3** as a single regioisomer (Scheme 3).[8] In addition, this result confirms a Block's previous work about the selective introduction of a MOM protecting group on a closely related compound.[14] Moreover, the neighboring group participation of an etherified oxygen atom has also been observed in ring-opening reaction on dioxolane-type acetals.[15,16] In addition, it has been reported that the configuration of the acetalic carbon atom strongly modulates the regiochemistry of closely related ring-cleavage reactions.[17,18] The exocyclic substituents of those acetals are two significantly different groups in size such as a phenyl (or naphtyl) group and a hydrogen atom. Therefore, the spatial orientation of the bulkier group can avoid coordination with the hydride donor through van der Waals forces, so the hydride attack occurs by the less hindered face of the molecule. In our case, the configuration of the orthoester intermediate **17a** that leads to **17** had no influence on regioselectivity. The proton NMR spectrum of this orthoester precursor showed the presence of both diastereomers as an equimolecular mixture. The characteristic peaks of this orthoester were observed as singlets at 5.80 and 5.83 ppm for the acetalic proton and at 3.35 and 3.36 ppm for the methoxy group of both diastereomers, respectively. Hence, the regioselectivity of this one-pot reaction is controlled by the presence of the vicinal ether functionality regardless of the acetalic-type carbon configuration.

The attempts for the regioselective introduction of one unit of a MOM protective group when the nitrogen-containing glycol **7** was used as a substrate were unsuccessful. It was not possible to isolate the corresponding mono-MOM derivative. Under these reaction conditions, the main product was the *N*-methyl derivative **20**. Apparently, the presence of the nitrogen atom in glycol **7** avoids formation of the corresponding orthoester intermediate. Interestingly, when diisobutyl aluminium hydride was not added to the reaction mixture, the formyl amide **19** was formed instead of the expected orthoester. Apparently, this transacetylation reaction may be catalyzed by CAN acting as a Lewis acid. Therefore, generation of the *N*-methyl derivative **20** can be rationalized by simple reduction of amide **19** by treatment with diisobutyl aluminium hydride (Scheme 3).

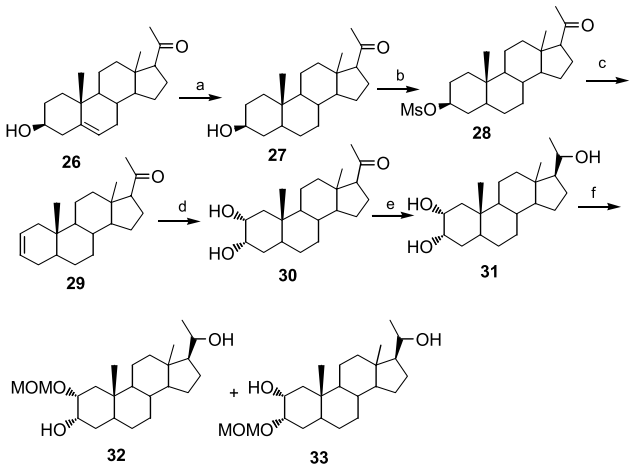
The free hydroxyl groups of methyl ribofuranoside **22** could not be regioselectively protected under this one-pot procedure as expected. The β-oriented methyl glycoside and benzyloxy groups prevent the aluminum atom of the DIBAL reagent to coordinate discriminatorily with any of the oxygen atoms present either at the anomeric center or at the C-5 position. Thus, **22** treated with trimethyl orthoformate followed by reductive ring opening with diisobutyl aluminium hydride afforded the respective MOM derivatives **24** and **25** in a (1:1) ratio. In this case, CAN also increased the reaction rate compared with CSA: 1 h after addition of diisobutyl aluminium hydride for CAN versus 5 h for CSA. At this point a valuable question rose. What is the role either of CAN or CSA? The orthoester intermediate **23** was isolated by reaction of **22** with trimethyl orthoformate employing CAN as catalyst without further addition of diisobutyl aluminium hydride. Interestingly, on treatment with diisobutyl aluminium hydride **23** was not converted into **24** and **25** in the absence of CAN, but produced the expected MOM derivatives, **24** and **25**, when this catalyst is present. That is, the catalyst is not only required for catalyzing the orthoester formation but is also essential for the reaction to complete. These results strongly suggested that CAN undoubtedly acts as a Lewis acid by catalyzing the second step of this reaction. To strength this idea, it has also been observed that the well-known electron acceptor 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) behaves as a Lewis acid in acetal removal reactions.[19,20] Compound **22** was readily prepared from **21** by isopropyliden cleavage by treatment with acetic acid, which was straightforwardly prepared from D-ribose (Scheme 4).[21]

A very similar behavior was observed when pregnan derivative **31** was employed as a substrate. In this case, only a poor selectivity was observed due to the lack of a vicinal heteroatom to coordinate with the aluminum atom present at the diisobutyl aluminium hydride reagent. Accordingly, **31** was reacted under these reaction conditions to produce **32** and **33** in a (1:1.5) ratio. Once again the absence of a heteroatom in the vicinity of the glycol group has a marked effect on regioselectivity. The use of CAN increased the reaction rate as well; in this case CAN resulted to be 3.5-fold faster than CSA. **31**, was synthesized starting from pregnenolone (**26**). Therefore, pregnenolone was treated with hydrogen in the presence of 10% palladium on activated carbon to give **27** quantitatively, which on reaction with mesyl chloride followed by an elimination reaction by treatment with lithium bromide in *N*,*N*-dimethylformamide at 120 °C[22] afforded exclusively the desired Δ-2 alkene **29** in good yield. This reaction occurred with high regioselectivity, the corresponding Δ-3 alkene was not detected. **29** was perhydroxylated by treatment with osmium tetroxide in the presence of *N*-methylmorpholine-*N*-oxide[23] to afford exclusively the α-glycol **30** in 70% yield. The stereochemical course of the reaction can be justified by the presence of the angular methyl group that blocks the β-face of the A ring. Finally, **30** was treated with diisobutyl aluminium hydride to give the 20-*S* isomer **31** with high diastereoselectivity in 97% yield (Scheme 5).

On the other hand, **38**, which contains an α-oriented glycol group at the C-1 and C-2 positions as well as a vicinal α-methoxy group at the C-3 position, could be regioselectively protected at C-1 as a MOM derivative **39** but in low

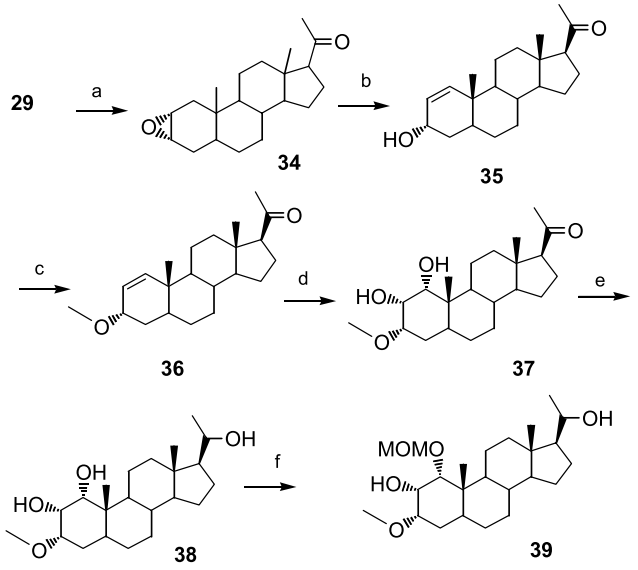


Scheme 4. Reagents and conditions: (a) 60% AcOH, 50 °C, 40 h, 63%; (b) i. trimethyl orthoformate, CH_2Cl_2, CAN, rt, 2 h, ii. DIBAL, −78 °C 1 h→ 0 °C 10 min, 92%.



Scheme 5. Reagents and conditions: (a) H_2, 10% Pd/C, EtOH, 100%; (b) ClMs, py, 0 °C, 90 min; (c) LiBr, DMF, 120 °C, 2 h, 64% from **27**; (d) $K_2OsO_4 \cdot 2H_2O$, K_2CO_3, $K_3Fe(CN)_6$, py, *tert*-butanol–water, 70%; (e) DIBAL, Cl_2CH_2, −78 °C, 45 min, 97%; (f) i. trimethyl orthoformate, CH_2Cl_2, CAN (CSA), rt, 2 h, ii. DIBAL, −78 °C 1 h→0 °C 10 min, 38% for **32** (CAN), 55% for **33** (CAN), 32% for **32** (CSA), 37% for **33** (CSA).

yields either with CAN or CSA. Compound **39** was unstable on standing but the fact that the presence of the methoxy group that is able to coordinate with the reducing agent strengthens the assumption that an oxygen atom in the surroundings of the glycol is required to warrant high regioselectivity. In connection with the reaction rate, once again CAN was more efficient than CSA as catalyst (2 h for CAN versus 4 h for CSA). **38** was prepared starting from **29** as illustrated in Scheme 6. Therefore, **29** treated with *m*-chloroperbenzoic acid gave rise to the α-epoxy derivative **34** in 59% yield, which on reaction with diphenyldiselenide[24] and sodium borohydride followed by treatment with *t*-butylhydroperoxide was converted into **35** in 48% yield. Compound **35** treated with sodium hydride and iodomethane led to the α-methoxy derivative **36** in 53% yield that was reacted with osmiun tetroxide/*N*-methylmorpholine-*N*-oxide to afford the corresponding α-1,2-glycol **37** in 52% yield. Finally, the target molecule **38** was obtained by treatment with diisobutyl aluminium hydride in 92% yield (Scheme 6).



Scheme 6. Reagents and conditions: (a) *m*-CPBA, Cl_2CH_2, 0 °C→rt, 1 h, 59%; (b) i. PhSeSePh, $NaBH_4$, EtOH–THF (1:1), reflux, 6 h, ii. 70% ^{t}BuOOH, reflux, 1 h, 48%; (c) NaH, IMe, THF, 0 °C, 53%; (d) $K_2OsO_4 \cdot 2H_2O$, K_2CO_3, $K_3Fe(CN)_6$, py, *tert*-butanol–water, 52%; (e) DIBAL, Cl_2CH_2, −78 °C, 1 h, 92%; (f)) i. trimethyl orthoformate, CH_2Cl_2, CAN, rt, 2 h, ii. DIBAL, −78 °C 1 h→0 °C 10 min, 17%.

In conclusion, we studied the scope of this interesting one-pot monoprotection reaction that employs ceric ammonium nitrate as catalyst. The use of CAN resulted in better yields than the employment of camphorsulfonic acid. Moreover, CAN notably accelerated the rate of the reaction compared with CSA in all cases but no differences in regioselectivity was observed between both catalysts. In addition, the presence of a heteroatom in the vicinity of a specific glycol such as oxygen had a profound effect on regioselectivity. It is worth to point out that hydride attack did not proceed in the absence of catalyst once the orthoester was formed. These evidences indicated that CAN is not only required to catalyze orthoester formation but is also essential for hydride attack to take place. Therefore, in this reaction, CAN works as a Lewis acid regardless its strong oxidant properties. Efforts to study the potential use of this reaction in more complex models as well as to investigate the reaction mechanism in detail are currently being pursued in our laboratory.

3. Experimental

3.1. General

Unless otherwise noted, all reagents were commercially available. All moisture sensitive reactions were performed under dry atmosphere of argon and all the glassware used in air and/or moisture sensitive reactions was flame-dried. Methylene chloride was distilled from P_2O_5 and stored over 4 Å molecular sieves.

Nuclear magnetic resonance spectra were recorded using a Bruker AC-200 MHz or a Bruker AM-500 MHz spectrometers. Chemical shifts are reported in parts per million (δ) relative to tetramethylsilane. The ^{1}H NMR spectra are referenced with respect to the residual $CHCl_3$ proton of the solvent $CDCl_3$ at 7.26 ppm. Coupling constants are reported in Hertz. ^{13}C NMR spectra were fully decoupled and are referenced to the middle peak of the solvent $CDCl_3$ at 77.0 ppm. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet.

Melting points were determined using a Fisher-Johns apparatus and are uncorrected. IR spectra were recorded using a Nicolet Magna 550 spectrometer. Low-resolution mass spectra were obtained on a VG TRIO 2 instrument in electron impact mode at 70 eV (direct inlet).

Column chromatography was performed on silica gel 60 (230–240 mesh) and analytical TLC was performed on commercial 0.2 mm aluminum coated silica gel plates (Kieselgel 60 F_{254}) and visualized by UV light (254 nm) or by immersion in ethanolic 5% H_2SO_4. Elemental analyses were conducted by Atlantic Microlab Inc., Norcross, Georgia.

3.1.1. 1-Phenyl-ethane-1,2-diol (5). A mixture of styrene (compound **8**; 500 mg, 4.80 mmol), *tert*-butanol–water (1:1) (20 mL), pyridine (3.8 μL, 0.05 mmol), potassium ferricyanide (10.9 g, 14.40 mmol), potassium carbonate (284 mg, 14.40 mmol), and potassium osmate dihydrate (3.6 mg, 0.01 mmol) was stirred at room temperature for 24 h. An aqueous saturated solution of sodium bisulfite was added until no evolution of bubbles was observed. The aqueous phase was extracted with ethyl acetate (5×10 mL). The combined organic layers were dried ($MgSO_4$), and the solvent was evaporated. The residue was purified by column chromatography (silica gel) using hexane–EtOAc (3:2) as eluent to afford 597 mg (90% yield) of pure glycol **5** as a white solid: R_f 0.13 (3:2, hexane–ethyl acetate); mp 63–64 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.37 (m, 5H), 4.82 (m, 1H), 3.72 (m, 2H), 2.58 (broad s, 1H), 2.14 (broad s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 140.5, 128.5, 128.0, 126.1, 74.7, 68.1.

3.1.2. 3-(4-Phenoxy-phenoxy)propane-1,2-diol (6). A mixture of compound **10** (500 mg, 2.21 mmol), *t*-butanol/water (1:1) (20 mL), pyridine (1.8 μL, 0.02 mmol), potassium ferricyanide (2.18 g, 6.64 mmol), potassium carbonate (1.10 g, 6.64 mmol) and potassium osmate dihydrate (1.6 mg, 0.005 mmol) was stirred at room temperature for 48 h. The reaction mixture was quenched as depicted for the preparation of compound **5**. The product was purified by column chromatography (silica gel) employing hexane–EtOAc (2:3) as eluent to afford 500 mg (87% yield) of pure diol **6** as a white solid: R_f 0.21 (hexane–EtOAc, 1:1); mp 86–87 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.31 (m, 2H), 6.96 (m, 7H), 4.11 (sxt, J=4.9 Hz, 1H), 4.04 (m, 2H), 3.87 (dd, J=11.2, 3.9 Hz, 1H), 3.87 (dd, J=11.2, 5.4 Hz, 1H), 2.79 (broad s, 1H), 2.26 (broad s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 158.2, 154.6, 150.7, 129.6, 122.6, 120.7, 117.7, 115.6, 70.4, 69.7, 63.6; MS (*m*/*z*, relative intensity) 260 (M^+, 28), 186 (100). Anal. calcd for $C_{15}H_{16}O_4$: C 69.22, H 6.20. Found: C 69.23, H 6.07.

3.1.3. *N*-Allyl [4-phenoxy]aniline (12). To a solution of *p*-phenoxyaniline (2.0 g, 10 mmol) in dimethylsulfoxide (20 mL) was added potassium hydroxide (2.5 g, 10 mmol). The mixture was stirred at room temperature for 10 min. Then, allyl chloride (0.9 mL, 10 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 72 h. The mixture was partitioned between water (50 mL) and methylene chloride (50 mL). The aqueous phase was extracted with methylene chloride (2×30 mL). The combined organic layers were washed with a saturated solution of sodium chloride (5×50 mL), dried ($MgSO_4$), and the solvent was removed. The residue was purified by column chromatography (silica gel) employing hexane–EtOAc (199:1) as eluent to afford 2.05 g (81% yield) of pure compound **12** as a colorless oil: R_f 0.36 (hexane–EtOAc, 17:1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.27 (m, 2H), 6.93 (m, 5H), 6.61 (d, J=9.2 Hz, 2H), 5.97 (ddt, J=17.2, 10.4, 5.1 Hz, 1H), 5.29 (dd, J=17.2, 1.5 Hz, 1H), 5.18 (dq, J=10.0, 1.5 Hz, 1H), 3.76 (dt, J=6.0, 2.0 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 159.1, 147.8, 144.7, 135.5, 129.7, 122.0, 121.2, 117.1, 116.3, 114.0, 47.1; MS (*m*/*z*, relative intensity) 225 (M^+, 77), 198 (21), 184 (54), 129 (36), 77 (100).

3.1.4. 3-(4-Phenoxy-phenylamino)propane-1,2-diol (7). A solution of compound **12** (408 mg, 1.81 mmol) in *tert*-butanol–tetrahydrofuran–water (10:3:1; 5.0 mL) was treated with *N*-methylmorpholine-*N*-oxide (233 mg, 1.99 mmol) and osmiun tetroxide (10 mg). The mixture was stirred at room temperature overnight. The reaction mixture was quenched by addition of an aqueous saturated solution of sodium bisulfite (5.0 mL) and was extracted with methylene chloride (3×15 mL). The combined organic phases were washed with brine (3×5 mL), dried ($MgSO_4$), and the solvent was evaporated. The product was purified by column chromatography (silica gel) employing hexane–EtOAc (6:1) as eluent to afford 420 mg (89% yield) of compound **7** as a brown solid: R_f 0.10 (1:1, hexane–EtOAc); mp 84–86 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.29–7.25 (m, 2H, aromatic protons), 6.96 (m, 5H, aromatic protons), 6.67 (m, 2H, aromatic protons), 3.99 (m, 1H, H-2), 3.82 (dd, J=11.2, 3.9 Hz, 1H, H-1_a), 3.67 (dd, J=11.2, 5.9 Hz, 1H, H-1_b), 3.30 (dd, J=13.9, 5.8 Hz, 1H, H-3_a), 3.19 (dd, J=13.9, 5.6 Hz, 1H, H-3_b), 2.55 (broad s, 2H, *OH*); ^{13}C NMR (50 MHz, $CDCl_3$) δ 158.8, 148.8, 144.8, 129.4, 122.0, 121.0, 117.0, 114.4, 70.3, 64.6, 47.1; MS (*m*/*z*, relative intensity) 259 (M^+, 22), 198 (100).

3.1.5. 2-Methoxymethoxy-2-phenyl-ethanol (13); 2-methoxymethoxy-1-phenyl-ethanol (14). *Method A*. A solution of compound **5** (108 mg, 0.78 mmol) in anhydrous methylene chloride (10 mL) was treated with trimethyl orthoformate (120 μL, 1.08 mmol) in the presence of cerium ammonium nitrate (5 mg) under argon atmosphere. The reaction mixture was stirred at room temperature for 2 h and then was cooled at −78 °C. Then, diisobutyl aluminium hydride was added (1.0 mL, 5.40 mmol). The mixture was stirred at −78 °C for 1 h. The reaction mixture was allowed to warm to 0 °C and was stirred for additional 10 min. The reaction was worked up by addition of an aqueous 1.0 N solution of hydrochloric acid (2 mL) and an aqueous saturated solution of sodium and potassium tartrate (10 mL). The resulting mixture was extracted with methylene chloride (3×10 mL). The combined organic layers were washed with brine (2×5 mL), dried ($MgSO_4$), and the solvent was evaporated. The residue was purified by column chromatography (silica gel) employing hexane–EtOAc (1:1) as eluent to give 115 mg (81% yield) of a mixture of regioisomers **13** and **14** in a (1:1.7) ratio as a colorless oil. Compound **13**: R_f 0.36 (hexane–EtOAc, 3:2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (m, 5H), 4.90 (dd, J=8.5, 3.0 Hz, 1H), 4.69 (m*AB*, 2H), 3.79 (dd, J=10.6, 3.1 Hz, 1H), 3.79 (dd, J=10.6, 8.4 Hz, 1H), 3.38 (s, 3H). Compound **14**: R_f 0.44 (3:2, hexane–EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (m, 5H), 4.70 (m, 1H), 4.66 (m*AB*, 2H), 3.69 (m, 2H), 3.40 (s, 3H).

Method B. A solution of compound **5** (88 mg, 0.64 mmol) in anhydrous methylene chloride (10 mL) was treated as described in method A but employing camphorsulfonic acid (CSA, 5 mg) instead of ceric ammonium nitrate as catalyst. The product was purified by column chromatography (silica gel) employing hexane–EtOAc (1:1) as eluent to afford 37 mg (32% yield) of a mixture of regioisomers **13** and **14** in a (1:1.6) ratio.

3.1.6. (2-Methoxymethoxy-2-phenyl)ethyl) acetate (15); [(2-methoxymethoxy-1-phenyl)ethyl] acetate (16). To a

solution of a mixture of compounds **13** and **14** (42 mg) in pyridine (1.0 mL) was added acetic anhydride (0.5 mL). The reaction mixture was stirred at room temperature overnight. Then, an aqueous 5% solution of hydrochloric acid was added and the mixture was stirred for an additional hour. The reaction mixture was partitioned between water (2.0 mL) and ethyl acetate (5.0 mL). The organic phase was washed with 5% HCl (2 mL) and brine (2×5 mL), dried ($MgSO_4$), and the solvent was evaporated. The residue was purified by column chromatography (silica gel) eluting with hexane–EtOAc (9:1) to afford 48 mg (94%) of an 1.2:1 ratio of a mixture of acetates **15** and **16** as a colorless oil. Compound **15**: R_f 0.53 (hexane–EtOAc, 4:1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.36 (m, 5H), 5.97 (dd, J=7.7, 4.4 Hz, 1H), 4.63 (m*AB*, 2H), 3.86 (dd, J=11.0, 7.7 Hz, 1H), 3.75 (dd, J=11.0, 4.4 Hz, 1H), 3.31 (s, 3H), 2.13 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 137.5, 128.5, 128.3, 126.7, 96.4, 74.6, 69.9, 55.3, 21.2. Compound **16**: R_f 0.45 (hexane–EtOAc, 4:1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.36 (m, 5H), 4.88 (dd, J=6.5, 5.1 Hz, 1H), 4.61 (m*AB*, 2H), 4.26 (m*AB*, 2H), 3.39 (s, 3H), 2.09 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 137.8, 128.6, 128.4, 127.1, 94.3, 75.6, 67.7, 55.4, 20.9.

3.1.7. 1-Methoxymethoxy-3-(4-phenoxy-phenoxy)propan-2-ol (17). A solution of compound **6** (230 mg, 0.88 mmol) in anhydrous methylene chloride (20 mL) was treated as depicted for the preparation of compound **13** (Method A). The crude product was purified by column chromatography (silica gel) eluting with a mixture of hexane–EtOAc (4:1) to afford 240 mg (90% yield) of pure compound **17** as a colorless oil: R_f 0.48 (hexane–EtOAc, 1:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (m, 2H), 6.98 (m, 7H), 4.70 (m*AB*, 2H), 4.17 (sxt, J=5.0 Hz, 1H), 4.02 (d, J=5.5 Hz, 2H), 3.79 (dd, J=10.5, 4.1 Hz, 1H), 3.72 (dd, J=10.5, 5.9 Hz, 1H), 3.40 (s, 3H), 2.80 (d, J=4.8 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 158.2, 154.7, 150.4, 129.5, 122.4, 120.6, 117.6, 115.5, 96.7, 69.4, 69.3, 69.1, 55.3; MS (*m*/*z*, relative intensity) 304 (M^+, 13), 186 (48), 45 (100). Anal. calcd for $C_{17}H_{20}O_5$: C 67.09, H 6.62. Found: C 67.00, H 6.70.

A solution of diol **6** (230 mg, 0.88 mmol) in anhydrous methylene chloride (20 mL) was treated as depicted for compound **13** (method B). The product was purified by column chromatography (silica gel) employing hexane–EtOAc (4:1) as eluent to give 180 mg (67% yield) of pure **17** as a colorless oil.

3.1.8. 2-Methoxy-4-(4-phenoxyphenoxymethyl)-[1,3]-dioxolane (17a). A solution of compound **6** (25 mg, 0.10 mmol) in anhydrous methylene chloride (5 mL) was treated with trimethyl orthoformate (21 μL, 0.20 mmol) and CAN (5 mg) under argon atmosphere. The mixture was stirred at room temperature for 2 h. The reaction was worked up by addition of an aqueous saturated solution of sodium bicarbonate (5 mL). The mixture was extracted with methylene chloride (3×5 mL). The combined organic layers were washed with water (2×5 mL), dried ($MgSO_4$), and the solvent was evaporated. The residue was purified by preparative TLC eluting with hexane–EtOAc (3:2) to afford 29 mg (95% yield) of **17a** as an equimolecular diastereomeric mixture as colorless oils: R_f 0.69, 0.66 (hexane–EtOAc, 1:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (m, 2H), 7.05 (m, 1H), 6.97 (m, 4H), 6.89 (m, 2H), 5.83, 5.80 (s, 1H), 4.65, 4.53 (p, J=6.5 Hz, 1H), 4.25, 4.20 (m, 2H), 4.04 (m, 2H), 4.04, 3.96 (m, 2H), 3.36, 3.35 (s, 3H).

3.1.9. 1-Methoxymethoxy-3-(4-phenoxy-phenoxy)propan-2-yl Acetate (18). To a solution of compound **17** (56 mg, 0.18 mmol) in pyridine (1 mL) was added acetic anhydride (0.5 mL) as depicted for compounds **15** and **16**. After the usual workup, the product was purified by column chromatography (silica gel) eluting with hexane–EtOAc (19:1) to afford 62 mg (97% yield) of pure compound **18** as a colorless oil: R_f 0.75 (hexane–EtOAc, 1:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (t, J=7.9 Hz, 2H), 7.04 (t, J=7.6 Hz, 1H), 6.96 (d, J=8.9 Hz, 2H), 6.94 (d, J=8.7 Hz, 2H), 6.89 (d, J=9.1 Hz, 2H), 5.32 (p, J=5.0 Hz, 1H), 4.65 (m*AB*, 2H), 4.15 (dd, J=10.2, 5.0 Hz, 1H), 4.12 (dd, J=10.2, 5.2 Hz, 1H), 3.82 (m*AB*, 2H), 3.36 (s, 3H), 2.12 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.4, 158.3, 154.7, 150.7, 129.6, 122.6, 120.7, 117.7, 115.8, 96.6, 71.0, 66.8, 65.8, 55.3, 21.0; MS (*m*/*z*, relative intensity) 346 (M^+, 5), 186 (9), 161 (54), 131 (38), 71 (32), 45 (100). Anal. calcd for $C_{19}H_{22}O_6$: C 65.88, H 6.40. Found: C 66.17, H 6.62.

3.1.10. *N*-(2,3-Dihydroxy-propyl)-*N*-(4-phenoxyphenyl)-formamide (19); 3-[methyl-(4-phenoxy-phenyl)-amino]-propane-1,2-diol (20). A solution of compound **7** (80 mg, 0.31 mmol) in methylene chloride (10 mL) was treated as described for the preparation of **13** (Method A). The product was purified by column chromatography (silica gel) eluting with hexane–EtOAc (4:1) to afford 16 mg (20% yield) of compound **20** as a colorless oil. In an independent experiment, compound **19** was isolated as a white solid in 90% yield when DIBAL was not added to the reaction mixture. Compound **19**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.35 (s, 1H), 7.37 (m, 2H), 7.17 (m, 3H), 7.03 (d, J=Hz, 2H), 3.93 (dd, J=15.9, 8.2 Hz, 1H), 3.87 (m, 2H), 3.66 (m, 1H), 3.59 (dd, J=11.6, 2.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.0, 157.0, 156.4, 135.9, 130.0, 126.4, 124.0, 119.42, 119.37, 70.1, 63.6, 49.2. Compound **20**: R_f 0.25 (hexane–EtOAc, 2:3); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.28 (m, 2H), 6.96 (m, 5H), 6.82 (m, 2H), 4.02 (ddt, J=8.0, 5.0, 3.4 Hz, 1H), 3.80 (dd, J=11.4, 3.3 Hz, 1H), 3.58 (dd, J=11.4, 5.1 Hz, 1H), 3.39 (dd, J=14.3, 8.1 Hz, 1H), 3.25 (dd, J=14.7, 5.1 Hz, 1H), 2.94 (s, 3H), 2.09 (broad s, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 158.7, 147.1, 142.6, 129.5, 122.2, 120.8, 117.4, 115.1, 69.4, 64.3, 56.9, 39.9; MS (*m*/*z*, relative intensity) 273 (M^+, 9), 212 (100), 197 (17).

3.1.11. Methyl 5-benzyloxy-β-D-ribofuranoside (22). Protected D-ribose derivative **21** (900 mg, 3.06 mmol) was treated with 60% acetic acid (5 mL). The reaction mixture was stirred at 50 °C for 40 h. The solvent was evaporated and the product was purified by column chromatography (silica gel) employing hexane–EtOAc (7:3) as eluent to afford 450 mg (63% yield) of pure compound **22** as a yellowish oil: R_f 0.15 (hexane–EtOAc, 3:2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (m, 5H, aromatic protons), 4.83 (s, 1H, H-1), 4.59 (m*AB*, 2H, OCH_2Ph), 4.19 (t, J=5.7 Hz, 1H, H-3), 4.09 (q, J=5.7 Hz, 1H, H-4), 4.00 (d, J=4.8 Hz, 1H, H-2), 3.63 (dd, J=10.0, 5.9 Hz, 1H, H-5$_a$), 3.60 (dd, J=10.0, 5.5 Hz, 1H, H-5$_b$), 3.33 (s, 3H, OCH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.9 (C-1′), 128.4 (C-3′), 127.8

(C-4′), 127.7 (C-2′), 108.3 (C-1), 81.8 (C-4), 75.1 (C-2), 73.5 (O*C*H$_2$Ph), 73.0 (C-3), 71.9 (C-5), 55.1 (O*C*H$_3$).

3.1.12. Methyl 5-benzyloxy-2,3-*O*-methoxymethylidene-β-D-ribofuranoside (23). A solution of compound **22** (110 mg, 0.43 mmol) in anhydrous methylene chloride (10 mL) was treated with trimethyl orthoformate (95 μL, 0.87 mmol) in the presence of ceric ammonium nitrate (30 mg) and the mixture was stirred at room temperature for 2 h. The solution was quenched by addition of an aqueous saturated solution of sodium bicarbonate (10 mL). The mixture was extracted with methylene chloride (3×10 mL). The combined organic layers were washed with water (2×10 mL), dried ($MgSO_4$) and the solvent was evaporated. The residue was purified by column chromatography (silica gel) eluting with hexane–EtOAc (19:1) to afford 90 mg (71% yield) of pure orthoester **23** as a colorless oil: R_f 0.61 (hexane–EtOAc, 7:3); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (M, 5H), 5.86 (s, 1H), 4.97 (s, 1H), 4.81 (d, J=6.0 Hz, 1H), 4.67 (d, J=6.0 Hz, 1H), 4.55 (m*AB*, 2H), 4.39 (dist t, J=7.2 Hz, 1H), 3.54 (dd, J=9.7, 6.4 Hz, 1H), 3.48 (dd, J=9.7, 8.2 Hz, 1H), 3.30 (s, 3H), 3.29 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.9, 128.4, 127.7, 117.4, 108.7, 84.6, 84.1, 81.5, 73.3, 70.7, 54.8, 51.4.

3.1.13. Methyl 5-benzyloxy-2-methoxymethoxy-β-D-ribofuranoside (24); methyl 5-benzyloxy-3-methoxymethoxy-β-D-ribofuranoside (25). A solution of compound **22** (125 mg, 0.50 mmol) in anhydrous methylene chloride (10 mL) was treated as depicted for compound **13** (Method A). Once DIBAL was added, the mixture was stirred at −78 °C for 1 h. After the usual workup, the product was purified by column chromatography (silica gel) eluting with a mixture of hexane–EtOAc (4:1) to give 135 mg (92% yield) of an equimolecular mixture of alcohols **24** and **25** as a colorless oil: Compound **24**: R_f 0.23 (hexane–EtOAc, 3:2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (m, 5H), 4.91 (s, 1H), 4.78 (s, 2H), 4.61 (m*AB*, 2H), 4.18 (m, 1H), 4.07 (m, 1H), 3.95 (d, 1H), 3.69–3.54 (m, 4H), 3.43 (s, 3H), 3.35 (s, 3H), 2.67 (s, 1H). Compound **25**: R_f 0.23 (3:2, hexane–ethyl acetate), ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (m, 5H), 4.87 (s, 1H), 4.68 (s, 2H), 4.60 (m*AB*, 2H), 4.18 (m, 2H), 4.07 (m, 1H), 3.69–3.54 (m, 2H), 3.37 (s, 3H), 3.34 (s, 3H), 2.67 (s, 1H).

A solution of compound **22** (125 mg, 0.50 mmol) in anhydrous methylene chloride (10 mL) was treated as depicted for compound **13** (Method B). After DIBAL addition, the mixture was stirred at −78 °C for 5 h. Purification of the product afforded 50 mg (34% yield) of an equimolecular mixture of compounds **24** and **25**.

3.1.14. 3α-Hydroxy-5α-pregnan-20-one (27). A solution of pregnenolone (compound **26**; 10.0 g, 31.60 mmol) in absolute ethanol (600 mL) was treated with hydrogen at atmospheric pressure in the presence of 10% palladium on activated carbon (1.0 g). The reaction mixture was stirred at room temperature for 4 h. The mixture was filtered through a celite column and the solvent was evaporated to afford 10.1 g (100% yield) of compound **27** as a white solid. The product was used as such in the next step without further purification: R_f 0.27 (hexane–EtOAc, 7:3), mp 182–185 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.58 (m, 1H), 2.51 (m, 1H), 2.10 (s, 3H), 0.79 (s, 3H), 0.59 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 209.5, 71.3, 63.9, 56.7, 54.2, 44.8, 44.3, 39.1, 38.1, 37.0, 35.5, 35.3, 32.0, 31.5, 28.9, 28.6, 24.4, 22.8, 21.3, 13.5, 12.3; MS (*m*/*z*, relative intensity) 318 (M^+, 40), 300 (25), 215 (37), 55 (100).

3.1.15. 3α-Methanesulphonyl-5α-pregn-2-en-20-one (28). To a solution of compound **27** (10.1 g, 31.60 mmol) in pyridine (100 mL) at 0 °C was added methanesulphonyl chloride (3.05 mL, 39.19 mmol) and the mixture was stirred at this temperature for 1.5 h. The reaction was quenched by addition of aqueous solution of 5% hydrochloric acid. The mixture was extracted with methylene chloride (3×70 mL) and the combined organic layers were washed with 5% HCl (3×50 mL), brine (50 mL) and dried (Na_2SO_4). The solvent was evaporated to afford crude compound **28**, which was used as such in the next step. An analytical sample was purified by column chromatography (silica gel) for characterization employing hexane–EtOAc (19:1) as eluent to afford pure compound **28** as a white solid: mp 110–112 °C; R_f 0.38 (hexane–EtOAc, 7:3); ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.62 (m, 1H), 2.99 (s, 3H), 2.49 (m, 1H), 2.10 (s, 3H), 0.82 (s, 3H), 0.60 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 209.5, 81.9, 63.7, 56.5, 53.9, 44.8, 44.2, 38.9, 38.8, 36.8, 35.4, 35.3, 35.1, 31.8, 31.5, 28.6, 28.3, 24.3, 22.8, 21.2, 13.4, 12.1; MS (*m*/*z*, relative intensity) 396 (M^+, 19), 378 (22), 300 (27), 215 (58), 79 (100).

3.1.16. 5α-Pregn-2-en-20-one (29). A solution of compound **28** in anhydrous *N*,*N*-dimethylformamide (100 mL) was treated with lithium bromide (9.93 g, 114.31 mmol). The reaction mixture was stirred at 120 °C for 2 h and the mixture was allowed to cool to 0 °C, and water (100 mL) was added. The mixture was extracted with ethyl acetate (3×100 mL). The organic phase was washed with brine (50 mL) and water (2×50 mL), dried (Na_2SO_4) and the solvent was evaporated in vacuo. The product was purified by column chromatography (silica gel) employing hexane–EtOAc (49:1) as eluent to afford 6.08 g (64% yield from **27**) of pure compound **29** as a white solid: mp 90–92 °C, R_f 0.56 (hexane–EtOAc, 9:1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.59 (m, 2H), 2.51 (m, 1H), 2.11 (s, 3H), 0.74 (s, 3H), 0.60 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 209.7, 125.9, 125.8, 63.8, 56.7, 53.9, 44.2, 41.4, 39.7, 39.1, 35.6, 34.6, 31.8, 31.6, 30.2, 28.6, 24.4, 22.7, 20.9, 13.4, 11.7; MS (*m*/*z*, relative intensity) 300 (M^+, 21), 285 (8), 257 (10), 246 (21), 215 (18), 55 (100).

3.1.17. 2α,3α-Dihydroxy-5α-pregnan-20-one (30). To a solution of compound **29** (309 mg, 1.03 mmol) in *tert*-butanol–tetrahydrofuran–water (10:3:1, 5 mL) was added *N*-methylmorpholine-*N*-oxide (132 mg, 1.13 mmol) and osmiun tetroxide (10 mg). The reaction mixture was stirred at room temperature overnight. Then, the reaction was quenched by addition of an aqueous saturated solution of sodium bisulfite (5 mL). The mixture was extracted with ethyl acetate (3×10 mL) and the combined organic phases were washed with an aqueous saturated solution of sodium bisulfite (5 mL), brine (2×5 mL), dried (Na_2SO_4) and the solvent was evaporated. The residue was purified by column chromatography (silica gel) eluting with a mixture of hexane–EtOAc (7:3) to afford 237 mg (70% yield) of compound **30** as a white solid: mp 190–193 °C; R_f 0.26

(hexane–EtOAc, 3:7); ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.96 (m, 1H), 3.82–3.72 (m, 1H), 2.53 (m, 1H), 2.11 (s, 3H), 0.80 (s, 3H), 0.60 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 209.8, 69.2, 69.0, 63.7, 56.6, 54.3, 44.3, 40.9, 39.0, 38.1, 36.9, 34.8, 34.2, 31.7, 31.5, 27.5, 24.4, 22.8, 20.8, 13.4, 12.4; MS (*m*/*z*, relative intensity) 334 (M^+, 55), 316 (82), 298 (25), 231 (44), 55 (100).

3.1.18. (20*S*)-2α,3α-Dihydroxy-5α-pregnan-20-ol (31). To a solution of diol **30** (564 mg, 1.69 mmol) in anhydrous methylene chloride (80 mL) cooled at −78 °C was added dropwise a solution of diisobutyl aluminium hydride (0.66 mL, 3.71 mmol) in methylene chloride (3 mL) under an argon atmosphere. The reaction mixture was stirred at −78 °C for 45 min. Then, the reaction was quenched by addition of 5% aqueous hydrochloric acid (10 mL) and an aqueous saturated solution of sodium potassium tartrate (20 mL). The aqueous layer was extracted with methylene chloride (2×30 mL). The combined organic layers were washed with brine (2×20 mL), dried ($MgSO_4$), and the solvent was evaporated. The residue was purified by column chromatography (silica gel) eluting with a mixture of hexane–EtOAc (7:3) to give 550 mg (97% yield) of compound **31** as a white solid: mp 200–203 °C, R_f 0.33 (hexane–EtOAc 1:4); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.96 (m, 1H), 3.78–3.69 (m, 2H), 1.13 (d, J=6.2 Hz, 3H), 0.81 (s, 3H), 0.74 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 70.5, 69.3, 69.1, 58.6, 55.9, 54.3, 42.6, 41.0, 40.1, 38.2, 37.0, 34.7, 34.2, 31.9, 27.7, 25.7, 24.5, 23.6, 20.8, 12.6, 12.4; MS (*m*/*z*, relative intensity) 336 (M^+, 1), 318 (27), 250 (31), 232 (91), 45 (100).

3.1.19. (20*S*)-3α-Hydroxy-2α-methoxymethoxy-5α-pregnan-20-ol (32); (20*S*)-2α-hydroxy-3α-methoxymethoxy-5α-pregnan-20-ol (33). A solution of compound **31** (105 mg, 0.31 mmol) in anhydrous methylene chloride (10 mL) was treated as depicted for compound **13** (Method A). Once DIBAL addition, the mixture was stirred at −78 °C for 2 h. After the usual workup, the product was purified by column chromatography (silica gel) eluting with hexane–EtOAc (7:3) to afford 45 mg (38% yield) of compound **32** and 64 mg (55% yield) of compound **33** as white solids. Compound **32**: mp 138–140 °C, R_f 0.37 (hexane–EtOAc, 1:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.68 (m*AB*, 2H, OCH_2OCH_3), 4.02 (m, 1H, H-3), 3.69 (m, 2H, H-2, H-20), 3.38 (s, 3H, OCH_3), 1.12 (d, J=6.2 Hz, 3H, H-21), 0.80 (s, 3H, H-19), 0.74 (m, 3H, H-18); ^{13}C NMR (50 MHz, $CDCl_3$) δ 94.7 (OCH_2O), 74.8 (C-2), 70.6 (C-20), 67.7 (C-3), 58.6 (C-17), 55.9 (C-14), 55.5 (OCH_3), 54.2 (C-9), 42.5 (C-13), 40.1 (C-12), 38.2 (C-5), 38.2 (C-1), 36.8 (C-10), 34.7 (C-8), 33.7 (C-4), 31.8 (C-7), 27.6 (C-6), 25.6 (C-16), 24.4 (C-15), 23.6 (C-21), 20.8 (C-11), 12.6 (C-18), 12.4 (C-19); MS (*m*/*z*, relative intensity) 381 (M^+, 1), 318 (23), 45 (100). Anal. calcd for $C_{23}H_{40}O_4$: C 72.59, H 10.59. Found: C 70.13, H 10.59. Compound **33**: mp 183–185 °C, R_f 0.25 (hexane–EtOAc, 1:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.72 (d, J=6.6 Hz, 1H, OCH_aHOCH_3), 4.70 (d, J=6.6 Hz, 1H, OCH_bHOCH_3), 3.82 (m, 1H, H-3), 3.72 (m, 1H, H-20), 3.64 (m, 1H, H-2), 3.42 (s, 3H, OCH_3), 1.13 (d, J=5.9 Hz, 3H, H-21), 0.81 (s, 3H, H-19), 0.74 (m, 3H, H-18); ^{13}C NMR (125 MHz, $CDCl_3$) δ 96.8 (OCH_2O), 78.7 (C-3), 70.5 (C-20), 68.5 (C-2), 58.6 (C-17), 56.0 (C-14), 55.7 (OCH_3), 54.4 (C-9), 42.6 (C-13, C-1), 40.1 (C-12), 39.1 (C-5), 36.9 (C-10), 34.7 (C-8), 33.4 (C-4), 32.0 (C-7), 27.8 (C-6), 25.7 (C-16), 24.5 (C-15), 23.6 (C-21), 20.8 (C-11), 12.6 (C-18), 12.5 (C-19); MS (*m*/*z*, relative intensity) 381 (M^+, 2), 349 (6), 302 (7), 45 (100). Anal. calcd. for $C_{23}H_{40}O_4.0.4H_2O$: C 71.29, H 10.61. Found C 71.29, H 10.44.

A solution of compound **31** (100 mg, 0.30 mmol) in anhydrous methylene chloride (10 mL) was treated as depicted for compound **13** (Method B). Once addition of DIBAL was performed, the reaction mixture was stirred at −78 °C for 7 h. After the usual workup, the product was purified by column chromatography (silica gel) employing hexane–EtOAc (7:3) as eluent to afford 36 mg (32% yield) of compound **32** and 42 mg (37% yield) of compound **33** as white solids.

3.1.20. 2α,3α-Epoxy-5α-pregnan-20-one (34). To a solution of compound **29** (5.2 g, 17.3 mmol) in methylene chloride (300 mL) cooled at 0 °C was added dropwise a solution of 80% *m*-chloroperbenzoic acid (4.48 g, 25.9 mmol) in methylene chloride (200 mL). The reaction mixture was stirred at room temperature for 1 h, and then it was washed with an aqueous saturated solution of sodium bicarbonate (3×100 mL). The organic phase was dried ($MgSO_4$), and the solvent was evaporated. The residue was purified by column chromatography (silica gel) employing hexane–EtOAc (99:1) as eluent to afford 3.15 g (59% yield) of compound **34** as a white solid: mp 153–154 °C; R_f 0.24 (hexane–EtOAc, 9:1), ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.12 (m, 2H), 2.51 (m, 1H), 2.11 (s, 3H), 0.75 (s, 3H), 0.59 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.6, 63.8, 56.5, 53.9, 52.4, 50.9, 44.0, 38.9, 38.3, 36.2, 35.6, 33.7, 31.6, 31.5, 29.0, 28.3, 24.4, 22.8, 20.9, 13.3, 13.0; MS (*m*/*z*, relative intensity) 316 (M^+, 19), 298 (25), 213 (24), 55 (100). Anal. calcd for $C_{21}H_{32}O_2 \cdot 2$EtOAc: C 70.70, H 9.82. Found C 70.25, H 10.19.

3.1.21. 3α-Hydroxy-5α-pregn-1-en-20-one (35). To a solution of diphenyldiselenide (3.11 g, 9.95 mmol) in a (1:1) mixture of absolute ethanol–tetrahydrofuran (50 mL) cooled at 0 °C under argon atmosphere was added sodium borohydride portionwise until the yellow solution turned clear. Then, a solution of compound **34** (3.15 g, 9.95 mmol) in tetrahydrofuran (20 mL) was added and the reaction mixture was refluxed for 6 h. The mixture was cooled at 0 °C and 70% *t*-butylhydroperoxide (17 mL, 119.4 mmol) was added dropwise. The reaction mixture was refluxed for an additional hour, and it was quenched by addition of water (100 mL). The aqueous layer was extracted with ethyl acetate (2×70 mL). The combined organic phases were washed with brine (2×40 mL), dried ($MgSO_4$), and the solvent was evaporated. The residue was purified by column chromatography (silica gel) eluting with a mixture of hexane–EtOAc (19:1) to afford 1.51 g (48% yield) of pure compound **35** as a white solid: mp 130–132 °C; R_f 0.31 (hexane–EtOAc, 15:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.08 (d, J=10.0 Hz, 1H, H-1), 5.67 (m, 1H, H-2), 4.11 (m, 1H, H-3), 2.53 (m, 1H, H-17), 2.11 (s, 3H, H-21), 0.80 (s, 3H, H-19), 0.63 (m, 3H, H-18); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.6, 140.2, 126.2, 64.4, 63.7, 56.8, 50.9, 44.3, 39.0, 38.9, 38.0, 35.8, 34.8, 31.9, 31.5, 27.9, 24.4, 22.8, 21.1, 13.8, 13.5; MS (*m*/*z*, relative intensity) 316 (M^+, 8), 298 (4), 246 (9), 43 (100). Anal. calcd for $C_{21}H_{32}O_2$: C 79.70, H 10.19. Found C 79.51, H 10.32.

3.1.22. 3α-Methoxy-5α-pregn-1-en-20-one (36). To a solution of compound **35** (1.51 g, 4.77 mmol) in anhydrous tetrahydrofuran (50 mL) was added sodium hydride (460 mg, 9.54 mmol) and iodomethane (3 mL, 47.7 mmol) at 0 °C under argon atmosphere. The reaction mixture was stirred at room temperature for 48 h. The reaction was quenched by addition of an aqueous saturated solution of ammonium chloride (20 mL). The aqueous layer was extracted with ethyl acetate (3×20 mL), dried ($MgSO_4$), and the solvent was evaporated. The residue was purified by column chromatography (silica gel) employing hexane–EtOAc (19:1) as eluent to afford 830 mg (53% yield) of pure compound **36** as a white solid: mp 69–72 °C; R_f 0.84 (hexane–EtOAc, 15:1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.08 (d, J=10.1 Hz, 1H), 5.70 (d, J=10.1, 4.2 Hz, 1H), 3.57 (m, 1H), 3.36 (s, 3H), 2.53 (m, 1H), 2.11 (s, 3H), 0.80 (s, 3H), 0.62 (m, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 209.7, 140.5, 124.0, 73.3, 63.7, 56.8, 56.3, 50.7, 44.3, 39.3, 39.0, 38.0, 35.8, 31.8, 31.5, 30.8, 27.9, 24.4, 22.8, 21.1, 13.8, 13.6; MS (*m*/*z*, relative intensity) 330 (M^+, 33), 301 (11), 246 (7), 203 (11), 85 (100). Anal. calcd for $C_{22}H_{34}O_2$: C 79.95, H 10.37. Found C 79.98, H 10.34.

3.1.23. 1α,2α-Dihydroxy-3α-methoxy-5α-pregnan-20-one (37). To a solution of compound **36** (157 mg, 0.48 mmol) in a (10:3:1) mixture of *tert*-butanol–tetrahydrofuran–water (5 mL) were added *N*-methylmorpholine-*N*-oxide (67 mg, 0.57 mmol) and osmiun tetroxide (10 mg). The reaction mixture was stirred at room temperature overnight. The reaction was worked up by addition of an aqueous saturated solution of sodium bisulfite (5 mL). The mixture was extracted with ethyl acetate (3×10 mL) and the organic phase was washed with saturated solution of $NaHSO_3$ (5 mL) and brine (2×5 mL), dried ($MgSO_4$), and the solvent was evaporated. The residue was purified by column chromatography (silica gel) eluting with a mixture of hexane–EtOAc (3:2) to afford 81 mg (52% yield) of pure compound **37** as a white solid: mp 190–193 °C, R_f 0.45 (hexane–EtOAc, 2:3), ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.90 (m, 1H, H-2), 3.56 (m, 1H, H-1), 3.48 (m, 1H, H-3), 3.35 (s, 3H, OCH_3), 2.50 (m, 1H, H-17), 2.10 (s, 3H, H-21), 0.94 (s, 3H, H-19), 0.59 (m, 3H, H-18); ^{13}C NMR (50 MHz, $CDCl_3$) δ 209.8, 79.0, 75.5, 72.4, 63.9, 56.6, 56.6, 55.3, 43.9, 42.1, 39.4, 38.0, 35.1, 31.8, 31.4, 28.0, 27.9, 24.6, 24.2, 22.6, 13.3, 8.3; MS (*m*/*z*, relative intensity) 364 (M^+, 13), 346 (29), 332 (15), 314 (23), 81 (100). Anal. calcd for $C_{21}H_{32}O_4$: C, 72.49; H, 9.95. Found: C, 72.08; H, 9.92.

3.1.24. (20*S*)-1α,2α-Dihydroxy-3α-methoxy-5α-pregnan-20-ol (38). To a solution of diol **37** (80 mg, 0.22 mmol) in anhydrous methylene chloride (10 mL) cooled at −78 °C was added dropwise a 0.96 M solution of diisobutyl aluminium hydride (0.50 mL) in anhydrous methylene chloride under argon atmosphere. The reaction mixture was stirred at −78 °C for 1 h. The reaction was quenched by addition of a 5% aqueous solution of hydrochloric acid (5 mL) and an aqueous saturated solution of sodium potassium tartrate (5 mL). The aqueous layer was extracted with methylene chloride (3×10 mL), and the combined organic phases were washed with brine (2×5 mL), dried ($MgSO_4$), and the solvent was evaporated. The residue was purified by column chromatography (silica gel) employing hexane–EtOAc (1:1) as eluent to give 74 mg (92% yield) of triol **38** as a white solid: mp 165–169 °C; R_f 0.25 (hexane–EtOAc, 2:3); ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.88 (m, 1H), 3.70 (m, 1H), 3.56 (m, 1H), 3.48 (m, 1H), 3.35 (s, 3H), 1.12 (d, J=6.2 Hz), 0.96 (s, 3H), 0.74 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 79.0, 75.5, 72.4, 70.6, 58.7, 56.7, 55.8, 55.4, 42.1, 40.4, 38.1, 35.0, 31.9, 28.2, 28.0, 25.5, 24.7, 24.3, 23.5, 12.5, 8.4. Anal. calcd for $C_{22}H_{38}O_4 \cdot 1/3$EtOAc: C 70.79, H 10.35. Found: C 71.17, H 9.81.

3.1.25. (20*S*)-2α-Hydroxy-1α-methoxymethoxy-3α-methoxy-5α-pregnan-20-ol (39). A solution of compound **38** (26 mg, 0.071 mmol) in anhydrous methylene chloride (10 mL) was treated as depicted for compound **13** (Method A). After DIBAL addition, the mixture was stirred at −78 °C for 2 h. The product was purified by column chromatography (silica gel) employing hexane–EtOAc (7:3) as eluent followed by further purification by preparative TLC eluting with hexane–EtOAc (1:1) to afford 15 mg of unreacted starting material and 5 mg (17% yield) of compound **39** as a white solid: R_f 0.36 (hexane–EtOAc, 1:1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.72 (m*AB*, 2H), 4.08 (m, 1H), 3.72 (m, 1H), 3.51 (m, 1H), 3.42 (s, 3H), 3.35 (s, 3H), 3.33 (m, 1H), 1.12 (d, J=6.2 Hz), 1.02 (s, 3H), 0.74 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 97.4, 85.3, 78.7, 77.2, 70.4, 58.8, 56.7, 55.8, 55.4, 42.1, 42.0, 40.7, 38.5, 35.5, 31.8, 28.0, 25.4, 24.7, 23.8, 23.5, 12.6, 9.1.

A solution of compound **38** (150 mg, 0.41 mmol) in anhydrous methylene chloride (10 mL) was treated as depicted for compound **13** (Method B). After DIBAL addition, the reaction mixture was stirred at −78 °C for 4 h. The residue was purified as depicted before affording 115 mg of the starting material (76%) and 2 mg (1% yield) of compound **39**.

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Supplementary data

General methods and ^{1}H and ^{13}C NMR spectra for all new compounds. DEPT spectra for compounds **6**, **7**, **17**, **19**, **20**, **22**, **32**–**36**, and **38**. ^{1}H–^{1}H COSY spectra for compounds **7**, **22**, **35**, and **37**. ^{1}H–^{13}C 2D correlation spectra for compounds **22**, **32**, **33**, and **37**.

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References and notes

1. Greene, T. W.; Wuts, P. G. M. In *Protective Groups in Organic Synthesis*, 3rd ed; Wiley: New York, 1999; pp 17–200.

2. Nicolaou, K. C.; Sorensen, E. J. In *Classics in Total Synthesis*; VCH: Weinheim, 1996.
3. Oikawa, M.; Wada, A.; Okazaki, F.; Kusumoto, S. *J. Org. Chem.* **1996**, *61*, 4469–4475.
4. Bailey, W. F.; Zarcone, L. M. J.; Rivera, A. D. *J. Org. Chem.* **1995**, *60*, 2532–2536.
5. Ogilvie, K. K.; Hakimelahi, G. H.; Proba, Z. A.; McGee, D. P. C. *Tetrahedron Lett.* **1982**, *23*, 1997–2000.
6. Ogilvie, K. K.; McGee, D. P. C.; Boisvert, S. M.; Hakimelahi, G. H.; Proba, Z. A. *Can. J. Chem.* **1983**, *61*, 1204–1209.
7. Chauchan, K.; Wheelan, P.; Murphy, R. C.; Falck, J. R. *J. Am. Chem. Soc.* **1994**, *116*, 5050–5056.
8. Comin, M. J.; Leitofuter, J.; Rodriguez, J. B. *Tetrahedron* **2002**, *58*, 3129–3136.
9. Friesen, R. W.; Vanderwal, C. *J. Org. Chem.* **1996**, *61*, 9103–9110.
10. Takasu, M.; Naruse, Y.; Yamamoto, H. *Tetrahedron Lett.* **1988**, *29*, 1947–1950.
11. Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z. M.; Xu, D.; Zhang, X.-Z. *J. Org. Chem.* **1992**, *57*, 2768–2771.
12. Schvartzapel, A. J.; Fichera, L.; Esteva, M.; Rodriguez, J. B.; Gros, E. G. *Helv. Chim. Acta* **1995**, *78*, 1207–1214.
13. Schvartzapel, A. J.; Zhong, L.; Docampo, R.; Rodriguez, J. B.; Gros, E. G. *J. Med. Chem.* **1997**, *40*, 2314–2322.
14. Block, M. H. *Tetrahedron Lett.* **1992**, *33*, 8149–8150.
15. Hajkó, J.; Borbás, A.; Lipták, A.; Kajtár-Peredy, M. *Carbohydr. Res.* **1991**, *216*, 413–420.
16. Borbás, A.; Hajkó, J.; Kajtár-Peredy, M.; Lipták, A. *J. Carbohydr. Chem.* **1993**, *12*, 191–200.
17. Lipták, A.; Borbás, A.; Jánossy, L.; Szilágyi, L. *Tetrahedron Lett.* **2000**, *41*, 4949–4953.
18. Lipták, A. *Tetrahedron Lett.* **1976**, *17*, 3551–3554.
19. Desruet, M.-D.; Morin, C.; Ogier, L. *Carbohydr. Res.* **1997**, *301*, 225–229.
20. García Fernández, J. M.; Ortiz Mellet, C.; Moreno Marín, A.; Fuentes, J. *Carbohydr. Res.* **1995**, *274*, 263–268.
21. Mashhood, S.; Ramesh, K.; Borchardt, R. T. *Tetrahedron Lett.* **1990**, *31*, 1509–1512.
22. Holysz, R. P. *J. Am. Chem. Soc.* **1953**, *75*, 4432–4437.
23. VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, *23*, 1973–1976.
24. Sharpless, K. B.; Lauer, R. F. *J. Am. Chem. Soc.* **1973**, *95*, 2697–2699.