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Highly stereoselective synthesis of furano-oxepanes: intramolecular nitrone cycloaddition (INC) reactions on sugar derived 2-substituted allylic ethers☆

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Abstract—The stereoselective synthesis of furano-oxepanes has been achieved from sugar ethers by an intramolecular nitrone cycloaddition (INC) reaction. The substitution at the 2-position of the allylic group aided in the exclusive formation of oxepanes.

1. Introduction

Seven-membered oxacycles are structural fragments of a variety of bioactive natural products,[1] besides their use in pharmacological applications.[2] The presence of these systems in complex molecules such as ciguatoxin[3] and others make them challenging synthetic targets, thus resulting in the development of number of synthetic methods.[4] Nitrone–alkene cycloaddition[5] reactions are powerful synthetic routes for the preparation of isoxazolidines that can be converted into a variety of compounds. The intramolecular nitrone cycloaddition (INC) of *O*-allyl saccharides give furano-pyran, pyrano-pyran and furano-oxepane systems. Collins et al.,[6] Bhattacharjya et al.[6] and Shing et al.[6] reported the synthesis of tetrahydro-pyrans and oxepanes using INC reactions on sugar derived 3-*O*-allyl ethers. Further, Shing et al. discovered the detrimental effect of steric congestion on the formation of oxepane rings. Earlier we reported[7] substituent effects on the intramolecular 1,3-dipolar cycloaddition reaction of D-glucose-derived 3-*O*-prenyl and allylic ethers, which resulted new sugar-derived furano-pyranes as exclusive products. In continuation of our studies on the substituent effects on INC reactions, herein, we report the synthesis of chiral furano-oxepanes as exclusive products from the sugar derived 2-substituted allylic ethers (Fig. 1).

2. Results and discussion

The requisite 3-*O*-allyl ether–aldehydes **6** and **7** were obtained from diacetone glucose (DAG) **1** (Scheme 1). Accordingly **1** on reaction with allyl bromides **C** and **D** in the presence of NaH in DMF resulted in the formation of ethers **2** (66%) and **3** (68%), respectively. Acid hydrolysis of **2** and **3** with 60% aq. acetic acid at room temperature furnished the diols **4** and **5**, respectively, which on oxidative cleavage with $NaIO_4$ gave **6** and **7**. The thus made aldehydes **6** and **7** were independently subjected to INC reaction with $CH_3NHOH{\cdot}HCl$ in the presence of Et_3N to give **8** (75%) and **9** (50%), respectively, as exclusive products, whose structures were unambiguously assigned from NMR spectroscopic studies.

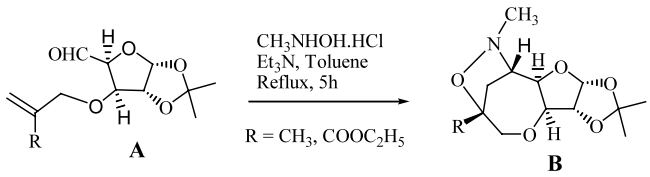

Figure 1.

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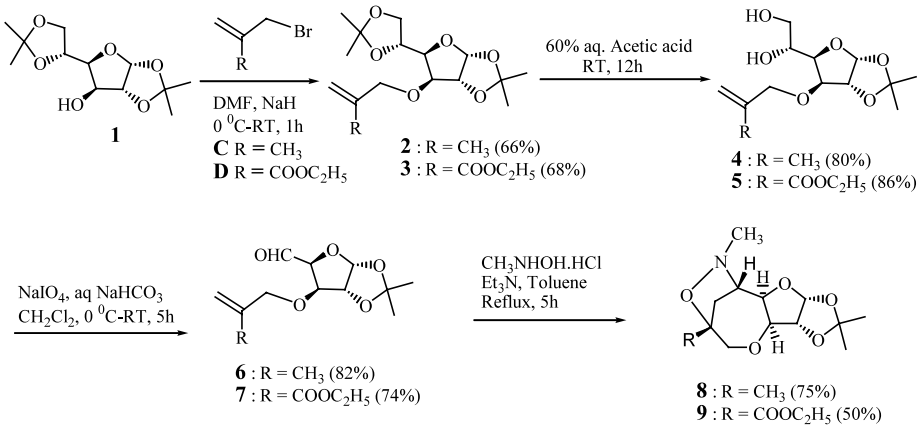


Scheme 1.

NMR studies on compound **9** showed NOE between H_{7b} and H_3 indicating their diaxial disposition in the seven-membered ring, which takes a chair form. Further long-range ω coupling $J_{H4-H6b} = 1.0$ Hz and $J_{H5-H6a} \approx 0$ Hz and weak NOE between H_{7a} and H_{6a} support the proposed conformation for the oxepane ring. Other characteristic NOE's as shown in Figure 2 confirmed the envelope conformation for isopropylidine ring and NOE between N-CH_3 with H_4 confirmed that azoxy ring is pointing below the average plane of seven-membered ring. The same was further confirmed from the energy minimized[8] structure as shown in Figure 2.

Thus, from the preceding discussion, it was evident that the substituent on the 2-position of allylic group, influences the cyclisation, resulting in oxepanes as exclusive products.

Therefore, the study on INC reactions was extended to the allyl ethers **18** and **19** derived from sorbose, wherein, in contrast to the case of **6** and **7**, the 1,2-*O*-isopropylidine group is on the top side, while the aldehyde/allyl ether groups are on the bottom side of furan ring. Accordingly, the known diacetonide **10**,[9] obtained from sorbose, was subjected to alkylation with CH_3I in dioxane in presence of KOH to give **11** (Scheme 2). Hydrolysis of **11** with aq. acetic acid followed by selective protection of diol **12** with TrCl gave **13** (87%). Allylation of **13** with **C** and **D** independently gave **14** (75%) and **15** (64%), which on hydrolysis with TFA in CH_2Cl_2 furnished **16** and **17**, respectively. Swern oxidation of **16** and **17** afforded **18** (84%) and **19** (60%), respectively, which on INC reaction under standard reaction conditions furnished oxepanes **20** (80%) and **21** (53%), respectively. Structures of **20** and **21** were unambiguously assigned from the spectral studies.

NMR studies on compound **21** (Fig. 3) showed NOE between H_{7a} and H_3 indicating their diaxial disposition in a seven-membered ring, which is in a chair conformation. Further long-range ω coupling $J_{H4-H6a} = 1.1$ Hz and $J_{H5-H6a} \approx 0$ Hz, and a weak NOE between H_{6b} and H_{7b} supported the proposed conformation for the seven-membered ring. Other characteristic NOE's between H_4 and CH_3(a) confirmed an envelope conformation for isopropylidine ring and NOE between *N*-CH_3 with H_4 confirms that the azoxy ring is pointing above the average plane of the seven-membered ring, which was further supported from the minimum energy structure (Fig. 3).

3. Conclusion

In conclusion, it is well demonstrated that the substituent on the 2-position of allylic group has a prominent role in defining the regiochemical outcome, thus resulting in seven-membered oxepane ring systems as exclusive products.

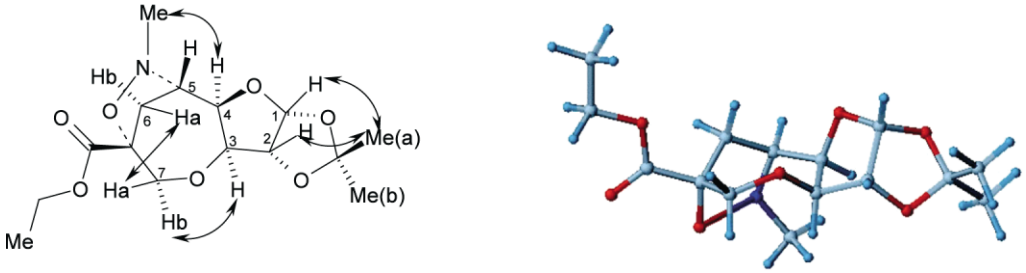
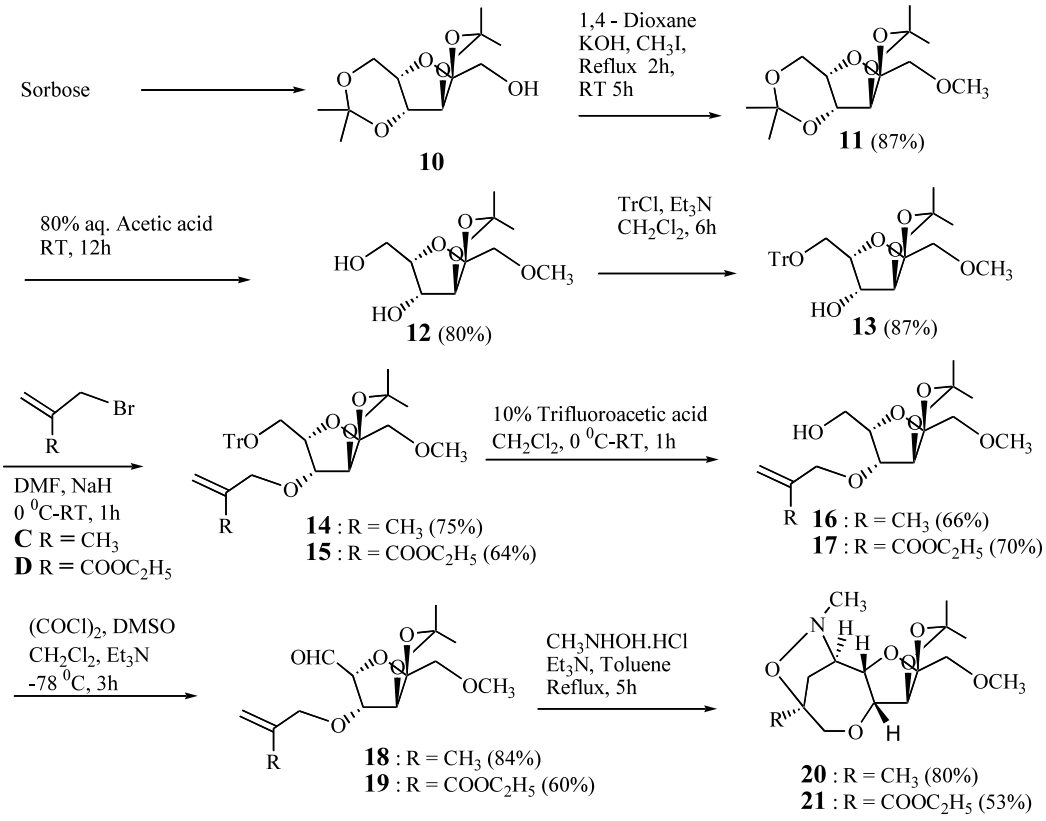


Figure 2. Characteristic NOE's and minimum energy structure for **9**.



Scheme 2.

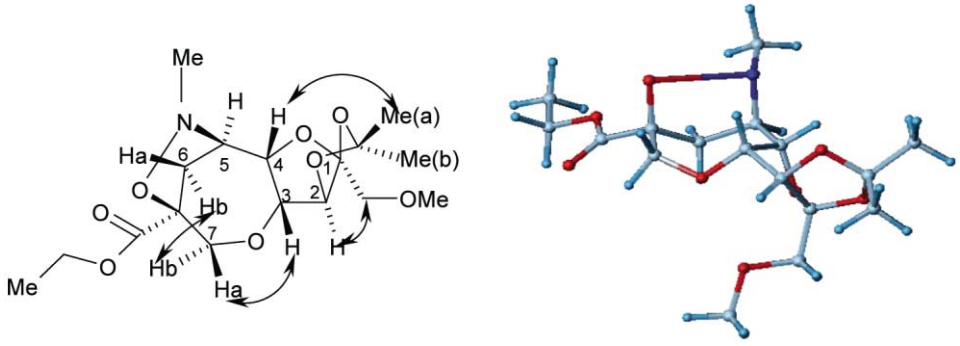


Figure 3. Characteristic NOE's and minimum energy structure for **21**.

4. Experimental

NMR spectra were recorded on Varian Gemini FT-200 MHz (21°C) with 7–10 mM solutions in appropriate solvents using TMS as internal standard. Solvents were dried over standard drying agents and freshly distilled prior to use. IR spectra were taken with a Perkin–Elmer 1310 spectrometer. Mass spectra were recorded on CEC-21-11013 or Finnigan Mat 1210 double focusing mass spectrometers operating at a direct inlet system and FABMS was measured using VG AUTOSPEC mass spectrometers at 5 or 7 k resolution using perflurokerosene as an internal reference. Nomenclature mentioned in this section was adopted from ACD/Name Version 1.0β, Advanced Chemistry Development Inc., Toronto, Canada, Organic solutions were dried over anhydrous Na_2SO_4 and concentrated below 40°C in vacuo.

4.1. 5-[2,2-Dimethyl-(4*R*)-1,3-dioxolan-4-yl]-2,2-dimethyl-(3a*R*,5*R*,6*S*,6a*R*)-perhydrofuro[2,3-*d*][1,3]-dioxol-6-yl 2-methylallyl ether 2

To a stirred solution of **1** (5 g, 19.23 mmol) in DMF (10 mL), sodium hydride (1.11 g, 46.15 mmol, 50% suspension) was added slowly at 0°C. After stirring at room temperature for 30 min, β-methyl allyl chloride (1.9 mL, 19.23 mmol) was added and reaction mixture was stirred for further 1 h. It was quenched with aqueous ammonium chloride solution (20 mL) and extracted with ether (3×50 mL). The ether layer was washed with water (25 mL), brine (25 mL) and dried

(Na_2SO_4). The organic layer was evaporated and residue obtained purified by column chromatography (silica gel, hexane–EtOAc, 19:1) to afford **2** (4 g, 66%) as a pale yellow syrup; $[\alpha]_D = -24.3$ (*c* 1.0, $CHCl_3$); IR (neat): 880, 1045, 1100, 1200, 1365, 2980 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 5.80 (d, 1H, $J = 3.7$ Hz, H-1), 4.90–4.88 (2s, 2H, olefinic), 4.48 (d, 1H, $J = 3.7$ Hz, H-2), 4.32–4.20 (m, 1H, H-4), 4.10–3.90 (m, 5H, H-5, 6a, 6b, 7a, 7b), 3.85 (d, 1H, $J = 1.70$ Hz, H-3), 1.70 (s, 3H, CH_3), 1.50 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 1.32 (s, 3H, CH_3), 1.29 (s, 3H, CH_3); EIMS (*m*/*z*, %): 299 (M^+–15, 20), 127 (10), 101 (43), 85 (11), 55 (100). Anal. calcd for $C_{16}H_{26}O_6$: C, 61.13; H, 8.34. Found: C, 61.07; H, 8.30.

4.2. Ethyl 2-[5-[2,2-dimethyl-(4*R*)-1,3-dioxolan-4-yl]-2,2-dimethyl-(3a*R*,5*R*,6*S*,6a*R*)-perhydrofuro[2,3-*d*][1,3]dioxol-6-yloxymethyl]acrylate 3

To a stirred solution of **1** (2.00 g, 7.69 mmol) in DMF (5 mL), sodium hydride (0.44 g, 18.46 mmol, 50% suspension) was added slowly at 0°C. After stirring at room temperature for 30 min, ethyl 2-bromo methyl acrylate (1.48 g, 7.69 mmol) was added and after 1 h, it was worked-up and purified as described for **2** to afford **3** (1.94 g, 68%) as a pale yellow syrup; $[\alpha]_D = -20.1$ (*c* 5.65, $CHCl_3$); IR (neat): 848, 1024, 1056, 1168, 1376, 1712, 2993 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 6.31–5.94 (2s, 2H, olefinic), 5.8 (d, 1H, $J = 3.5$ Hz, H-1), 4.58 (d, 1H, $J = 3.5$ Hz, H-2), 4.39–4.20 (m, 5H, H-3, 5, 4, -$OC\underline{H}_2CH_3$), 4.10–3.93 (m, 4H, H-6a, 6b, 7a, 7b), 1.52 (s, 3H, CH_3), 1.48 (s, 3H, CH_3), 1.40–1.25 (m, 9H, CH_3, CH_3, $OCH_2C\underline{H}_3$); FABMS (*m*/*z*, %): 372 (M^+, 8), 357 (48), 281 (12), 147 (100), 127 (36), 101 (52), 73 (76). Anal. calcd for $C_{18}H_{28}O_8$: C, 58.05; H, 7.58. Found: C, 58.01; H, 7.53.

4.3. 1-[2,2-Dimethyl-6-(2-methylallyloxy)-(3a*R*,5*R*,6*S*,6a*R*)-perhydrofuro[2,3-*d*][1,3]dioxol-5-yl]-(1*R*)-ethane-1,2-diol 4

A solution of compound **2** (3 g, 9.55 mmol) in 60% aq. acetic acid (15 mL) was stirred at room temperature for 12 h. It was neutralized with solid sodium bicarbonate (15 g), extracted into ethyl acetate (2×75 mL) and the organic layer was dried (Na_2SO_4). Evaporation of the solvent and purification of residue by column chromatography (silica gel, hexane–EtOAc, 3:2) afforded **4** (2.1 g, 80%) as a pale yellow syrup; $[\alpha]_D = -34.4$ (*c* 1.0, $CHCl_3$); IR (neat): 830, 1075, 1170, 2970, 3480 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 5.85 (d, 1H, $J = 3.65$ Hz, H-1), 4.98–4.90 (2s, 2H, olefinic), 4.51 (d, 1H, $J = 3.65$ Hz, H-2), 4.12–3.90 (m, 5H, H-4, 6a, 6b, 7a, 7b), 3.82–3.65 (m, 2H, H-3, 5), 2.86 (bs, 1H, -OH), 2.61 (bs, 1H, -OH), 1.78 (s, 3H, CH_3), 1.50 (s, 3H, CH_3), 1.25 (s, 3H, CH_3); EIMS (*m*/*z*, %): 259 (M^+–15, 4), 155 (10), 127 (50), 113 (60), 71 (57), 43 (100).

4.4. Ethyl 2-[5-[1,2-dihydroxy-(1*R*)-ethyl]-2,2-dimethyl-(3a*R*,5*R*,6*S*,6a*R*)-perhydrofuro[2,3-*d*][1,3]dioxol-6-yloxymethyl]acrylate 5

A solution of compound **3** (1.94 g, 5.20 mmol) in 60% aq. acetic acid (10 mL) was stirred at room temperature for 12 h, it was worked-up and purified as described for **4** to afford **5** (1.49 g, 86%) as a pale yellow syrup; $[\alpha]_D = -14.5$ (*c* 6.45, $CHCl_3$); IR (neat): 1024, 1072, 1168, 1376, 1712, 2976, 3488 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 6.32–5.90 (2s, 2H, olefinic), 5.85 (d, 1H, $J = 3.72$ Hz, H-1), 4.50 (d, 1H, $J = 3.72$ Hz, H-2), 4.30–4.18 (m, 3H, H-4, -$OC\underline{H}_2CH_3$), 4.16–4.0 (m, 2H, H-3, 5), 4.0–3.57 (m, 4H, H-6a, 6b, 7a, 7b), 1.48 (s, 3H, CH_3), 1.39–1.22 (m, 6H, CH_3, -$OCH_2C\underline{H}_3$); FABMS (*m*/*z*, %): 355 (M^++23, 12), 332 (M^+, 4), 275 (24), 127 (46), 85 (100), 59 (76).

4.5. 6,6,12,14-Tetramethyl-(1*S*,2*R*,4*R*,8*R*,9*S*,12*R*)-3,5,7,10,13-pentaoxa-14-azatetracyclo[10.2.1.$0^{2,9}$.$0^{4,8}$]-pentadecane 8

To a stirred solution of **4** (0.90 g, 3.28 mmol) in CH_2Cl_2 (10 mL), sat. sodium bicarbonate solution (0.4 mL) was added followed by sodium periodate (1.40 g, 6.56 mmol) at 0°C and reaction mixture stirred for 5 h. After completion of the reaction (TLC analysis), solid Na_2SO_4 (0.50 g) was added, stirred for further 20 min and extracted with CH_2Cl_2. Organic layer was dried (Na_2SO_4) and evaporated to afford 2,2-dimethyl-6-(2-methylallyloxy)-(3a*R*,5*S*,6*R*,6a*R*)-perhydrofuro[2,3-*d*]-[1,3]dioxole-5-carbaldehyde **6** (0.65 g, 82%) as a colourless syrup, which was used as such for the next reaction.

A mixture of **6** (0.65 g, 2.68 mmol), *N*-methyl hydroxylamine hydrochloride (0.22 g, 2.68 mmol) and Et_3N (0.75 mL, 5.37 mmol) in toluene (6 mL) was heated at reflux for 5 h. Toluene was removed and the residue obtained was purified by column chromatography (silica gel, hexane–EtOAc, 9:1) to afford **8** (0.545 g, 75%) as a white solid; mp 94–96°C; $[\alpha]_D = -17.25$ (*c* 0.75, $CHCl_3$); IR (KBr): 815, 1011, 1100, 1216, 1372, 1455, 2969 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 5.88 (d, 1H, $J = 3.7$ Hz, H-1), 4.41 (d, 1H, $J = 3.7$ Hz, H-2), 4.16 (ddd, 1H, $J = 1.0$, 1.7, 3.5 Hz, H-4), 4.09 (d, 1H, $J = 1.7$ Hz, H-3), 3.60 (dd, 1H, $J = 3.5$, 6.5 Hz, H-5), 3.44 (q, 2H, $J = 12.5$ Hz, H-7a, 7b), 2.76 (s, 3H, N-CH_3), 2.72 (d, 1H, $J = 12.5$ Hz, H-6a), 2.20 (ddd, 1H, $J = 1.0$, 6.5, 12.5 Hz, H-6b), 1.48 (s, 3H, CH_3), 1.39 (s, 3H, CH_3), 1.32 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) 111.57, 104.26, 85.80, 84.44, 82.35, 79.18, 76.65, 66.63, 46.58, 33.49, 26.56, 26.07, 25.34; EIMS (*m*/*z*, %): 271 (M^+, 10), 256 (8), 98 (40), 69 (36), 57 (30), 43 (100). Anal. calcd for $C_{13}H_{21}NO_5$: C, 57.55; H, 7.80. Found: C, 57.49; H, 7.77.

4.6. Ethyl 6,6,14-trimethyl-(1*S*,2*R*,4*R*,8*R*,9*S*,12*R*)-3,5,7,10,13-pentaoxa-14-azatetracyclo[10.2.1.$0^{2,9}$.$0^{4,8}$]-pentadecane-12-carboxylate 9

To a stirred solution of **5** (1.48 g, 4.46 mmol) in CH_2Cl_2 (15 mL), sat. sodium bicarbonate solution (0.6 mL) was added followed by sodium periodate (1.91 g, 8.92 mmol) at 0°C and reaction mixture stirred for 5 h. It

was worked-up as described for **6** to afford ethyl 2-[5-formyl-2,2-dimethyl-(3a*R*,5*S*,6*R*,6a*R*)-perhydrofuro-[2,3-*d*][1,3]dioxol-6-yloxymethyl]acrylate **7** (0.99 g, 74%) as a colourless syrup, which was used as such for the next reaction.

A mixture of **7** (0.99 g, 3.3 mmol), *N*-methyl hydroxylamine hydrochloride (0.275 g, 3.3 mmol) and Et_3N (0.92 mL, 6.6 mmol) in toluene (10 mL) was heated at reflux for 5 h. It was worked-up and purified as described for **8** to afford **9** (0.54 g, 50%) as a white solid; mp 65–67°C; $[\alpha]_D=+71.0$ (*c* 0.5, $CHCl_3$); IR (KBr): 1015, 1092, 1246, 1384, 1738, 2910, 2992 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 5.89 (d, 1H, $J=3.7$ Hz, H-1), 4.44 (d, 1H, $J=3.7$ Hz, H-2), 4.23 (q, 2H, $J=7.1$ Hz, $OC\underline{H}_2CH_3$), 4.17 (ddd, 1H, $J=1.0$, 1.8, 3.5 Hz, H-4), 4.09 (d, 1H, $J=1.8$ Hz, H-3), 3.68 (dd, 1H, $J=3.5$, 6.4 Hz, H-5), 3.94 (d, 1H, $J=12.7$ Hz, H-7a), 3.65 (d, 1H, $J=12.7$ Hz, H-7b), 2.77 (s, 3H, N-CH_3), 2.88 (d, 1H, $J=12.6$ Hz, H-6a), 2.68 (ddd, 1H, $J=1.0$, 6.4, 12.6 Hz, H-6b), 1.49 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 1.30 (t, 3H, $J=7.1$ Hz, $OCH_2C\underline{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) 170.87, 111.80, 104.26, 87.86, 84.39, 82.27, 79.91, 72.81, 66.52, 61.88, 45.81, 31.45, 26.60, 26.10, 13.99; FABMS (*m*/*z*, %): 330 (M^++1, 100), 156 (20), 109 (15), 95 (26), 83 (27), 55 (50). Anal. calcd for $C_{15}H_{23}NO_7$: C, 54.70; H, 7.04. Found: C, 54.61; H, 6.99.

4.7. 3a-Methoxymethyl-2,2,7,7-tetramethyl-(3a*S*,4a*S*,8a*R*,8b*S*)-perhydro[1,3]dioxolo[4′,5′:4,5]furo[3,2-*d*]-[1,3]dioxine 11

To a solution of **10** (13.0 g, 50.0 mmol) in 1,4-dioxane (65 mL), solid KOH (8.41 g, 150.0 mmol) was added and heated at reflux for 2 h. The reaction mixture was cooled to 0°C and CH_3I (6.4 mL, 100.0 mmol) was added. After 5 h, 1,4-dioxane was removed on rotavapor, the reaction mixture was treated with water (50 mL) and extracted with ether (3×75 mL). Ethereal layer was washed with water (50 mL), brine (50 mL), dried (Na_2SO_4) and evaporated. The residue obtained was purified by column chromatography (silica gel, hexane–EtOAc, 9:1) to afford **11** (11.91 g, 87%) as a pale yellow syrup; $[\alpha]_D=-5.25$ (*c* 6.35, $CHCl_3$); IR (neat): 1120, 1200, 1376, 2928, 2992 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 4.53 (s, 1H, H-2), 4.44 (ddd, 1H, $J=2.2$, 5.3 Hz, H-4), 4.31 (d, 1H, $J=2.2$ Hz, H-3), 3.96 (abq, 2H, $J=8.6$ Hz, -$C\underline{H}_2OCH_3$), 3.74 (m, 2H, H-5a, 5b), 3.48 (s, 3H, -OCH_3), 1.49 (s, 3H), 1.44 (s, 3H), 1.41 (s, 3H), 1.28 (s, 3H); EIMS (*m*/*z*, %): 259 (M^+−15, 20), 210 (10), 171 (15), 101 (40), 85 (43), 45 (100).

4.8. 5-Hydroxymethyl-3a-methoxymethyl-2,2-dimethyl-(3a*S*,5*S*,6*R*,6a*S*)-perhydrofuro[2,3-*d*][1,3]dioxol-6-ol 12

A solution of compound **11** (11.9 g, 43.4 mmol) in 80% aq. acetic acid (80 mL) was stirred at room temperature for 12 h. It was neutralised with solid sodium bicarbonate (90 g), extracted into ethyl acetate (2×75 mL) and the organic layer dried (Na_2SO_4). Evaporation of the solvent and purification of residue by column chromatography (silica gel, hexane–EtOAc, 1:1) afforded **12** (8.13 g, 80%) as a pale yellow syrup; $[\alpha]_D=+29.9$ (*c* 8.85, $CHCl_3$); IR (neat): 1104, 1200, 1360, 2944, 3424 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 4.42 (s, 1H, H-2), 4.35 (dt, 1H, $J=2.7$, 5.2, 5.2 Hz, H-4), 4.19 (dd, 1H, $J=2.7$, 10.5 Hz, H-3), 3.94 (m, 2H, H-5a, 5b), 3.82 (d, 1H, $J=10.5$, -OH), 3.66 (abq, 2H, $J=10.1$ Hz, -$C\underline{H}_2OCH_3$), 3.48 (s, 3H, -OCH_3), 1.52 (s, 3H), 1.35 (s, 3H); FABMS (*m*/*z*, %): 280 (M^++46, 20), 257 (M^++23, 40), 235 (M^++1, 12), 217 (38), 147 (44), 127 (54), 85 (89), 73 (100).

4.9. 3a-Methoxymethyl-2,2-dimethyl-5-trityloxymethyl-(3a*S*,5*S*,6*R*,6a*S*)-perhydrofuro[2,3-*d*][1,3]dioxol-6-ol 13

To a stirred solution of **12** (2.5 g, 10.6 mmol) in CH_2Cl_2 (10 mL), Et_3N (2.96 mL, 21.3 mmol) followed by trityl chloride (3.54 g, 12.72 mmol) were added at 0°C. After 6 h, it was diluted with CH_2Cl_2 (50 mL) and the organic layer was washed with water (50 mL), brine (50 mL) and dried (Na_2SO_4). Evaporation of the solvent and purification of residue by column chromatography (silica gel, hexane–EtOAc 19:1) afforded **13** (4.43 g, 87%) as a pale yellow syrup; $[\alpha]_D=+20.75$ (*c* 4.90, $CHCl_3$); IR (neat): 704, 1120, 1232, 1440, 2944, 3440 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.48 (m, 6H, Ar-H), 7.29 (m, 6H, Ar-H), 7.22 (m, 3H, Ar-H), 4.41 (s, 1H, H-2), 4.36 (dt, 1H, $J=2.4$, 5.6 Hz, H-4), 4.14 (dd, 1H, $J=2.4$, 10.5 Hz, H-3), 3.63 (abq, 2H, $J=10.1$ Hz, -$C\underline{H}_2OCH_3$), 3.42 (s, 3H, -OCH_3), 3.40 (m, 2H, H-5a, 5b), 1.53 (s, 3H), 1.35 (s, 3H); FABMS (*m*/*z*, %): 233 (M^+−243, 6), 243 (100), 165 (16).

4.10. 3a-Methoxymethyl-2,2-dimethyl-6-(2-methylallyloxy)-5-trityloxymethyl-(3a*S*,5*S*,6*R*,6a*S*)-perhydrofuro[2,3-*d*][1,3]dioxole 14

To a stirred solution of **13** (2 g, 4.2 mmol) in DMF (5 mL), sodium hydride (0.24 g, 10.00 mmol, 50% suspension) was added slowly at 0°C. After stirring at room temperature for 30 min, β-methyl allyl chloride (0.41 g, 4.2 mmol) was added and after 1 h, it was worked-up as described for **2** to afford **14** (1.67 g, 75%) as a white solid; mp 128–130°C; $[\alpha]_D=+29.6$ (*c* 6.30, $CHCl_3$); IR (KBr): 704, 1088, 1200, 1376, 1456, 2848, 2928 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.49 (m, 6H, Ar-H), 7.25 (m, 6H, Ar-H), 7.18 (m, 3H, Ar-H), 4.95–4.75 (m, 2H, olefinic), 4.42 (s, 1H, H-2), 4.39 (dt, 1H, $J=3.4$, 4.9, 4.9 Hz, H-4), 3.90 (td, 1H, $J=12.7$, 1.3 Hz, H-7a), 3.85 (d, 1H, $J=3.4$ Hz, H-3), 3.75 (td, 1H, $J=1.3$, 12.5, Hz, H-7b), 3.50 (dd, 1H, $J=5.4$, 9.1 Hz, H-5a), 3.42 (abq, 2H, $J=12.4$ Hz, -$C\underline{H}_2OCH_3$), 3.40 (s, 3H, -OCH_3), 3.2 (dd, 1H, $J=9.1$, 7.7 Hz, H-5b), 1.60 (s, 3H, CH_3), 1.57 (s, 3H), 1.37 (s, 3H); FABMS (*m*/*z*, %): 287 (M^+−243, 4), 243 (10), 109 (45), 95 (62), 55 (100).

4.11. Ethyl 2-[3a-methoxymethyl-2,2-dimethyl-5-trityloxymethyl-(3a*S*,5*S*,6*R*,6a*S*)-perhydrofuro[2,3-*d*][1,3]-dioxol-6-yloxymethyl]acrylate 15

To a stirred solution of **13** (1.6 g, 3.35 mmol) in DMF (5 mL), sodium hydride (0.19 g, 8.05 mmol, 50% sus-

pension) was added slowly at 0°C. After stirring at room temperature for 30 min, ethyl 2-bromo methyl acrylate (0.65 g, 3.35 mmol) was added. After 1 h, it was worked-up and purified as described for **2** to afford **15** (1.265 g, 64%) as a pale yellow syrup; $[\alpha]_D = +43.0$ (*c* 3.45, $CHCl_3$); IR (neat): 720, 1088, 1376, 1712, 2928 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.42 (m, 6H, Ar-H), 7.27 (m, 6H, Ar-H), 7.21 (m, 3H, Ar-H), 6.16 (dt, 1H, $J = 2.9$, 1.3, 1.3 Hz, olefinic), 5.58 (dt, 1H, $J = 2.9$, 1.3, 1.3 Hz, olefinic), 4.52 (s, 1H, H-2), 4.47 (ddd, 1H, $J = 3.1$, 5.5, 7.8 Hz, H-4), 4.31(td, 1H, $J = 14.0$, 1.3, 1.3 Hz, H-7a), 4.17 (q, 2H, $J = 7.2$ Hz, $-OC\underline{H}_2CH_3$), 4.12 (td, 1H, $J = 14.0$, 1.3, 1.3 Hz, H-7b), 4.05 (d, 1H, $J = 3.1$ Hz, H-3), 3.49 (abq, 2H, $J = 11.0$ Hz, $-C\underline{H}_2OCH_3$), 3.45 (dd, 1H, $J = 5.5$, 9.2 Hz H-5a), 3.38 (s, 3H, $-OCH_3$), 3.28 (dd, 1H, $J = 9.2$, 7.8 Hz, H-5b), 1.55 (s, 3H), 1.40 (s, 3H), 1.26 (t, 3H, $J = 7.2$ Hz, $OCH_2C\underline{H}_3$); FABMS (*m*/*z*, %): 345 (M^+–243, 10), 380 (20), 243 (100), 165 (24).

4.12. 3a-Methoxymethyl-2,2-dimethyl-6-(2-methylallyloxy)-(3a*S*,5*S*,6*R*,6a*S*)-perhydrofuro[2,3-*d*][1,3]dioxol-5-ylmethanol 16

To a stirred solution of **14** (1.67 g, 3.1 mmol) in CH_2Cl_2 (15 mL), trifluoroacetic acid (1.64 mL) was added at 0°C and stirred at room temperature for 1 h. It was quenched with aq. sodium bicarbonate solution (25 mL) and extracted with CH_2Cl_2 (3×30 mL). Organic layer was washed with water (25 mL), brine (25 mL) and dried (Na_2SO_4). Evaporation of solvent and purification of residue by column chromatography (silica gel, hexane–EtOAc, 3:2) afforded **16** (0.6 g, 66%) as a pale yellow syrup; $[\alpha]_D = +32.4$ (*c* 5.50, $CHCl_3$); IR (neat): 880, 1040, 1120, 1200, 1360, 1456, 2920, 3456 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 5.0–4.88 (m, 2H, olefinic), 4.54 (s, 1H, H-2), 4.40 (dt, 1H, $J = 3.3$, 4.8, 4.8 Hz, H-4), 4.04 (td, 1H, $J = 12.5$, 1.1 Hz, H-7a), 3.99 (d, 1H, $J = 3.3$ Hz, H-3), 3.94 (td, 1H, $J = 4.8$, 12.1 Hz, H-5a), 3.88 (td, 1H, $J = 12.5$, 1.1 Hz, H-7b), 3.86 (dd, 1H, $J = 4.8$, 12.1 Hz, H-5b), 3.61 (abq, 2H, $J = 12.4$ Hz, $-C\underline{H}_2OCH_3$), 3.44 (s, 3H, $-OCH_3$), 1.73 (s, 3H, CH_3), 1.51 (s, 3H), 1.41 (s, 3H); FABMS (*m*/*z*, %): 289 (M^++1, 20), 231 (12), 109 (32), 95 (45), 69 (62), 55 (100). Anal. calcd for $C_{14}H_{24}O_6$: C, 58.32; H, 8.39. Found: C, 58.25; H, 8.33.

4.13. Ethyl 2-[5-hydroxymethyl-3a-methoxymethyl-2,2-dimethyl-(3a*S*,5*S*,6*R*,6a*S*)-perhydrofuro[2,3-*d*][1,3]dioxol-6-yloxymethyl]acrylate 17

To a stirred solution of **15** (1.26 g, 2.13 mmol) in CH_2Cl_2 (10 mL), trifluoroacetic acid (1.2 mL) was added at 0°C, stirred at room temperature for 1 h and worked-up and purified as described for **16** to afford **17** (0.52 g, 70%) as a pale yellow syrup; $[\alpha]_D = +14.8$ (*c* 5.30, $CHCl_3$); IR (neat): 1120, 1200, 1376, 1712, 2944, 3472 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 6.32 (dt, 1H, $J = 2.8$, 1.2 Hz, olefinic), 5.82 (dt, 1H, $J = 2.8$, 1.2 Hz, olefinic), 4.57 (s, 1H, H-2), 4.43 (ddd, 1H, $J = 3.3$, 5.5, 7.7 Hz, H-4), 4.35 (td, 1H, $J = 12.9$, 1.2, 1.2 Hz, H-7a), 4.24 (q, 2H, $J = 7.1$ Hz, $-OC\underline{H}_2CH_3$), 4.18 (td, 1H, $J = 12.9$, 1.1, 1.1 Hz, H-7b), 4.05 (d, 1H, $J = 3.3$ Hz, H-3), 3.84 (m, 2H, H-5a, 5b), 3.57 (abq, 2H, $J = 10.5$ Hz, $-C\underline{H}_2OCH_3$), 3.43 (s, 3H, $-OCH_3$), 1.50 (s, 3H, $-CH_3$), 1.41 (s, 3H), 1.23 (t, 3H, $J = 7.1$ Hz, $OCH_2C\underline{H}_3$); FABMS (*m*/*z*, %): 346 (M^+, 4), 355 (8), 281 (29), 242 (40), 147 (60), 73 (100), 55 (60). Anal. calcd for $C_{16}H_{26}O_8$: C, 55.48; H, 7.57. Found: C, 55.40; H, 7.52.

4.14. 4-Methoxymethyl-6,6,12,14-tetramethyl-(1*R*,2*S*,4*S*,8*S*,9*R*,12*S*)-3,5,7,10,13-pentaoxa-14-azatetracyclo-[10.2.1.$0^{2,9}$.$0^{4,8}$]pentadecane 20

To a stirred solution of oxalyl chloride (0.20 mL, 2.28 mmol) in dry CH_2Cl_2 (5 mL), dry DMSO (0.32 mL, 4.57 mmol) was added at −78°C. After stirring at the same temperature for 20 min, a solution of **16** (0.60 g, 2.08 mmol) in dry CH_2Cl_2 (5 mL) was added dropwise and the reaction mixture stirred for further 3 h. It was quenched with Et_3N (1.73 mL, 12.48 mmol) and stirred till reaction mixture comes to room temperature. It was diluted with CH_2Cl_2 (25 mL) and organic layer was washed with water (25 mL), brine (25 mL), dried (Na_2SO_4) and evaporated to afford 3a-methoxymethyl-2,2-dimethyl-6-(2-methylallyloxy)-(3a*S*,5*R*,6*R*,6a*S*)-perhydrofuro[2,3-*d*][1,3]dioxole-5-carbaldehyde **18** (0.50 g, 84%) as a light brown syrup, which was used as such for the next reaction.

A mixture of **18** (0.50 g, 1.75 mmol), *N*-methyl hydroxylamine hydrochloride (0.146 g, 1.75 mmol) and Et_3N (0.49 mL, 3.50 mmol) in toluene (5 mL) was heated at reflux for 5 h and worked-up as described for **8** to afford **20** (0.44 g, 80%) as a white solid; mp 113–115°C; $[\alpha]_D = +21.3$ (*c* 0.5, $CHCl_3$); IR (KBr): 1030, 1107, 1369, 2912, 2995 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 4.34 (s, 1H, H-2), 4.26 (ddd, 1H, $J = 1.1$, 1.8, 3.1 Hz, H-4), 4.09 (d, 1H, $J = 1.8$ Hz, H-3), 3.64 (d, 1H, $J = 10.8$ Hz, H-7a), 3.57 (dd, 1H, $J = 3.1$, 6.4 Hz, H-5), 3.57 (d, 1H, $J = 10.8$ Hz, H-7b), 3.45 (s, 2H, $C\underline{H}_2OCH_3$), 3.45 (s, 3H, $-OCH_3$), 2.75 (s, 3H, $N-CH_3$), 2.67 (d, 1H, $J = 12.7$ Hz, H-6a), 2.19 (ddd, 1H, $J = 1.1$, 6.4, 12.7 Hz, H-6b), 1.50 (s, 3H, CH_3), 1.39 (s, 3H, CH_3), 1.38 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) 112.78, 112.22, 85.83, 84.42, 82.32, 79.81, 77.07, 72.75, 66.80, 59.72, 46.59, 33.58, 27.36, 26.26, 25.35; FABMS (*m*/*z*, %): 316 (M^++1, 96), 258 (22), 185 (40), 133 (22), 93 (84), 55 (100). Anal. calcd for $C_{15}H_{25}NO_6$: C, 57.13; H, 7.99. Found: C, 58.06; H, 7.93.

4.15. Ethyl-4-methoxymethyl-6,6,14-trimethyl-(1*R*,2*S*,4*S*,8*S*,9*R*,12*S*)-3,5,7,10,13-pentaoxa-14-azatetracyclo-[10.2.1.$0^{2,9}$.$0^{4,8}$]pentadecane-12-carboxylate 21

To a stirred solution of oxalyl chloride (0.12 mL, 1.43 mmol) in dry CH_2Cl_2 (5 mL), dry DMSO (0.2 mL, 2.86 mmol) was added at −78°C. After 20 min, a solution of **17** (0.45 g, 1.30 mmol) in dry CH_2Cl_2 (5 mL) was added dropwise. After 3 h, it was quenched with Et_3N (1.08 mL, 7.8 mmol) and worked-up as described for **18** to

afford ethyl 2-[5-formyl-3a-methoxymethyl-2,2-dimethyl - (3a*S*,5*R*,6*R*,6a*S*) - perhydrofuro[2,3 - *d*][1,3]-dioxol-6-yloxymethyl]acrylate **19** (0.27 g, 60%) as a light brown syrup, which was used as such for the next reaction.

A mixture of **19** (0.27 g, 0.78 mmol), *N*-methyl hydroxylamine hydrochloride (0.066 g, 0.78 mmol) and Et_3N (0.22 mL, 1.57 mmol) in toluene (5 mL) was heated at reflux for 5 h. It was worked-up as described for **8** to afford **21** (0.155 g, 53%) as a white solid; mp 66–68°C; $[\alpha]_D = -26.3$ (*c* 0.5, $CHCl_3$); IR (KBr): 1050, 1200, 1250, 1500, 1720, 2905, 2998 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 4.36 (s, 1H, H-2), 4.27 (ddd, 1H, $J = 1.1$, 2.1, 3.1 Hz, H-4), 4.22 (q, 2H, $J = 7.2$ Hz, $OC\underline{H}_2CH_3$), 4.09 (d, 1H, $J = 2.1$ Hz, H-3), 3.95 (d, 1H, $J = 12.8$ Hz, H-7a), 3.64 (dd, 1H, $J = 3.1$, 6.5 Hz, H-5), 3.62 (d, 1H, $J = 12.8$ Hz, H-7b), 3.61 (q, 2H, $J = 10.7$ Hz, $C\underline{H}_2OCH_3$), 3.45 (s, 3H, -OCH_3), 2.76 (s, 3H, N-CH_3), 2.83 (d, 1H, $J = 12.6$ Hz, H-6a), 2.66 (ddd, 1H, $J = 1.1$, 6.5, 12.6 Hz, H-6b), 1.50 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 1.29 (t, 3H, $J = 7.2$ Hz, $OCH_2C\underline{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) 170.90, 112.80, 112.41, 87.86, 84.33, 82.58, 79.48, 72.83, 72.67, 66.63, 61.86, 59.76, 45.79, 31.53, 27.36, 26.25, 13.99; FABMS (*m*/*z*, %): 374 (M^++ 1, 100), 316 (62), 270 (10), 188 (20), 129 (18), 113 (28). Anal. calcd for $C_{17}H_{27}NO_8$: C, 54.68; H, 7.29. Found: C, 54.62; H, 7.24.

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