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TETRAHEDRON: *ASYMMETRY*

Synthesis of a new isoxazolidine from diacetone glucose †

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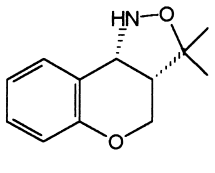
Abstract

The synthesis of a new furo-pyran-based isoxazolidine, making use of an intramolecular oxime–olefin cycloaddition (IOOC) reaction, is reported here, starting from diacetone glucose.

1. Introduction

Auxiliary-based asymmetric organic synthesis[1] is of paramount importance since it is a most flexible and predictable method in achieving stereocontrols in chemical transformations. In spite of tremendous developments made in the area of asymmetric catalysis,[2] the stoichiometric use of chiral auxiliaries is of primary interest to many researchers for the formation of new C–C bond-forming reactions. The use of chiral isoxazolidine[3] as an auxiliary was first reported by Masamune,[4] using a benzo-pyran-based system (**A**), which was later followed by reports on the amino acid[5] (**B**) as well as glycidol-derived isoxazolidines.[6] Due to availability and low cost, carbohydrates have been used for the development of successful chiral auxiliaries[7] and used in asymmetric transformations. Continuing our interest in the use of carbohydrates for the synthesis of natural products and bioactive carbohydrates, we describe our efforts for the synthesis of carbohydrate-derived furo-pyran-based isoxazolidine **1**, starting from diacetone glucose.



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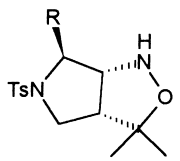

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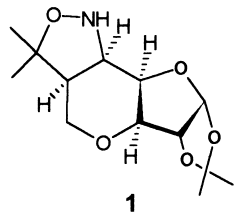

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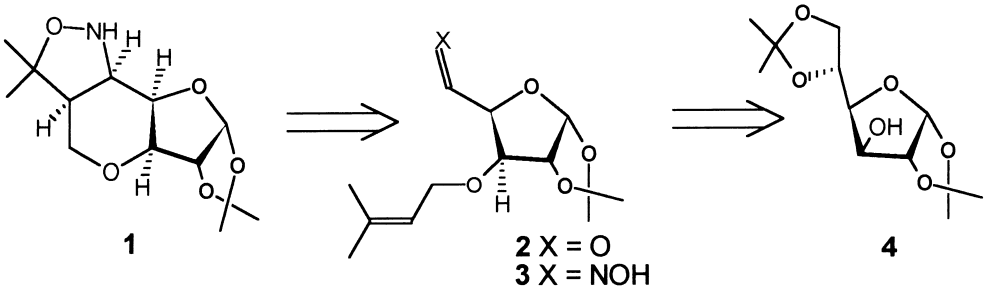
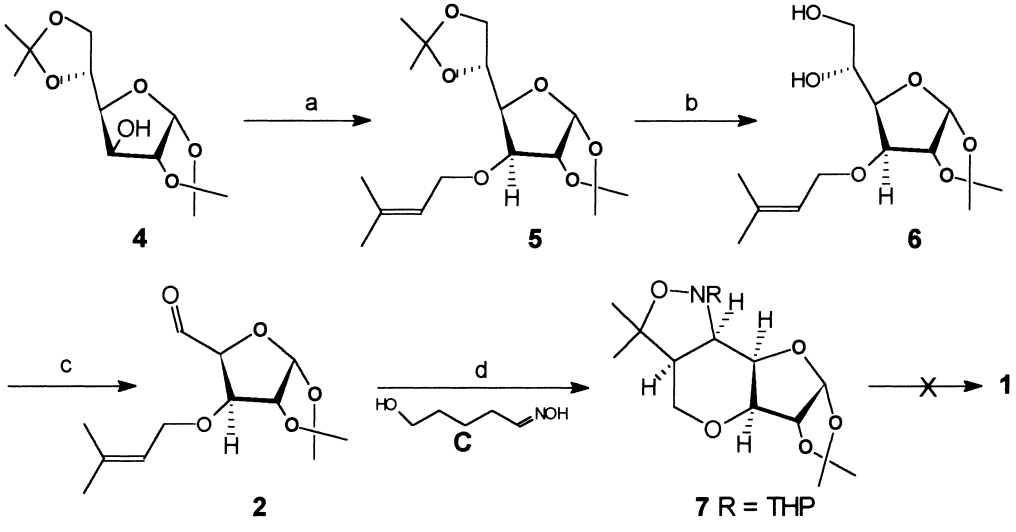
As shown in Scheme 1, the construction of a fused isoxazolidine ring system in **1** was envisaged from a [3+2] cycloaddition reaction involving a nitrone or nitrile oxide addition on the internal olefin, while templates for such cyclisation could be conveniently realised from diacetone glucose (**4**).



Scheme 1.

2. Results and discussion

Accordingly, alkylation of **4** (Scheme 2) with prenyl bromide in the presence of NaH gave **5** in 84% yield, $[\alpha]_D$ −21.6 (*c* 1.0, $CHCl_3$). Acid (60% aq. AcOH) hydrolysis of **5** at room temperature, followed by oxidative cleavage of resultant **6** with $NaIO_4$, furnished aldehyde **2**, $[\alpha]_D$ −54.1 (*c* 1.0, $CHCl_3$). The isoxazolidine formation was essentially planned to effect through an intramolecular [3+2] cycloaddition reaction involving a nitrone.[4,8] Thus, reaction of aldehyde **2** with oxime (**C**)[9] in the presence of Bu_2SnO in toluene at reflux gave a diastereomeric mixture of **7** (50%). However, attempts to convert **7** into **1** using a variety of reaction conditions met with failure.

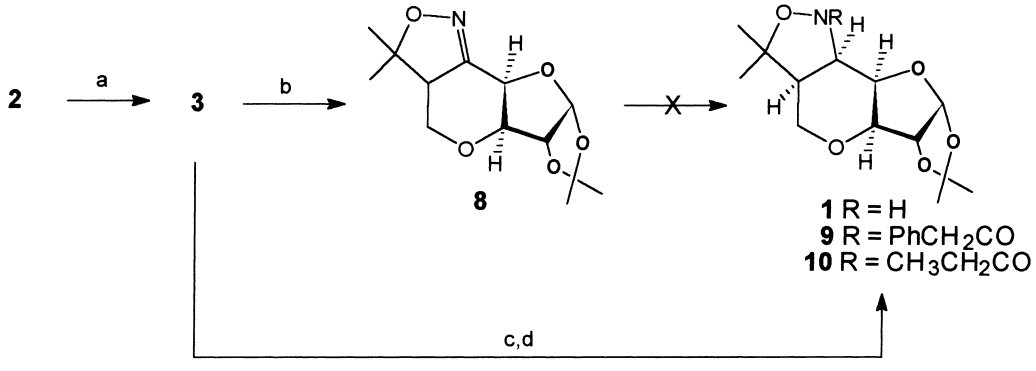


Reagents : a) NaH, prenyl bromide, DMF, 0°-RT; b) 60% aq. AcOH, 30°C; c) $NaIO_4$, aq. THF, 30°C; d) Bu_2SnO, Toluene, reflux.

Scheme 2.

Alternatively, it was planned to prepare **1**, through an intramolecular nitrile oxide–olefin cycloaddition (INOC) process.[10] Thus, treatment of **2** (Scheme 3) with $NH_2OH{\cdot}HCl$ in the presence of Et_3N in EtOH gave the corresponding oxime **3**. Further, on oxidation with sodium hypochlorite in CH_2Cl_2 (1:1), **3**

underwent a facile INOC reaction through the corresponding nitrile oxide and afforded isoxazoline **8** in a 90% yield, $[\alpha]_D$ +82.0 (*c* 0.5, $CHCl_3$). But attempts to convert **8** into **1** using several reaction conditions met with failure. Finally, however, oxime **3**, under thermal conditions, while heating in toluene at 180°C in a sealed tube for 18 h, underwent an intramolecular oxime–olefin cycloaddition (IOOC) reaction[11] and afforded *cis–syn* stereoisomer **1** in 55% yield as a solid. The new isoxazolidine system **1** was thoroughly characterised from the ^{1}H NMR and other spectral data. The stereochemical outcome of the isoxazolidine ring is in accordance with previous literature[12,13] as is evident from the ^{1}H NMR spectrum of **1**, where the stereochemistry was determined from the coupling constants H-3 to H-4, H-4 to H-5, and H-5 to H-6. H-5 was observed as a doublet at δ 3.95 ($J_{5,6}$=5.5 Hz), while H-3 appeared as a doublet at δ 3.88 ($J_{3,4}$=2.0 Hz). This data amply indicates that H-5 and H-6 are *cis* to each other, while H-4 is *syn* to the ring junction, hence it does not show appreciable coupling constants for $J_{4,5}$ in the present system. Thus, the *cis–syn* stereoselectivity[14,15] for the formation of **1** through IOOC reactions can be attributed to the cyclisation through the most stable conformation as shown in Fig. 1. The most stable conformer for the cyclisation resembles a thermodynamically stable *E*-nitrone-*s-trans*-allyl ether transition state, in which the oxime side chain exists in a pseudo-equatorial position, thereby resulting in the formation of *cis–syn* stereoisomer **1**. Compound **1** was subjected to acylation independently with phenacyl chloride and propionyl chloride in the presence of Et_3N in CH_2Cl_2 to afford the amides **9** and **10**, respectively.



Reagents: a) $NH_2OH{\cdot}HCl$, Et_3N, EtOH, reflux; b) 30% NaOCl, CH_2Cl_2, 30°C; c) Toluene, reflux in a sealed tube; d) $PhCH_2COCl$ or CH_3CH_2COCl, Et_3N, CH_2Cl_2

Scheme 3.

In conclusion, we have reported that the synthesis of a new carbohydrate-derived fused isoxazolidine from diacetone glucose. The amide derivatives of the new furo-pyran-based isoxazolidine could be used in a variety of asymmetric reactions.

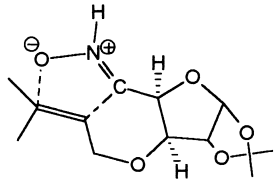


Figure 1.

3. Experimental section

All moisture sensitive reactions were performed under a nitrogen atmosphere using flame-dried glassware. Solvents were dried over standard drying agents and freshly distilled prior to use. ^{1}H NMR spectra were measured with a Varian Gemini (200 MHz) spectrometer, with tetramethylsilane as internal standard for solutions in deuteriochloroform. J values are given in hertz. Optical rotations were measured with a JASCO DIP-370 instrument, and $[\alpha]_D$ values are in units of 10^{-1} deg cm^2 g^{-1}. The IR spectra were taken using a Perkin–Elmer 1310 spectrometer. Organic solutions were dried over anhydrous Na_2SO_4 and concentrated below 40°C in vacuo.

*3.1. 1,2:5,6-Di-*O*-isopropylidene-3-*O*-(3′-methyl-2′-butenyl)-α-*D*-glucofuranose* **5**

To a stirred suspension of sodium hydride (1.1 g, 46 mmol, 50% suspension) in dry DMF (3 mL) at 0°C, a solution of **4** (5 g, 19.2 mmol) in DMF (10 mL) was added. After stirring at room temperature for 30 min, prenyl bromide (2.86 g, 19.2 mmol) was added and the reaction mixture stirred for a further 8 h. It was quenched with an aqueous ammonium chloride solution and extracted with ether (3×50 mL). The ethereal solution was washed with water and brine, dried (Na_2SO_4) and evaporated, and the residue obtained was purified by column chromatography [Si gel, hexane:ethyl acetate (20:1)] to afford **5** (5.3 g, 84%) as a syrup. $[\alpha]_D$ −21.6 (*c*=1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 5.8 (d, 1H, $J_{1,2}$=4.5 Hz, H-1), 5.3 (t, 1H, $J_{2',3'}$=6.7 Hz, olefinic), 4.5 (d, 1H, $J_{1,2}$=4.5 Hz, H-2), 4.3–3.9 (m, 6H, H-4,5,6,6′), 3.85 (d, 1H, $J_{3,4}$=3.5 Hz, H-3), 1.8, 1.7, 1.5, 1.43, 1.36, 1.3 (6s, 18H, –CH_3). Anal. calcd for $C_{17}H_{28}O_6$: C, 62.17; H, 8.59. Found: C, 62.02; H, 8.47.

*3.2. 1,2-*O*-Isopropylidene-3-*O*-(3′-methyl-2′-butenyl)-α-*D*-glucofuranose* **6**

A solution of compound **5** (3.2 g, 9.7 mmol) in 60% aq. acetic acid (16 mL) was stirred at room temperature for 12 h. It was neutralised with aq. sodium bicarbonate solution, extracted into ethylacetate (2×75 mL) and the organic layer washed with water and brine and dried (Na_2SO_4). Evaporation of the solvent and purification by column chromatography [Si gel, hexane:ethyl acetate (1:1)] afforded **6** (1.9 g, 67.8%) as a syrup. $[\alpha]_D$ −40.13 (*c*=1.0, $CHCl_3$); IR (neat): 3560, 3460, 1490, 720 cm^{-1}: ^{1}H NMR ($CDCl_3$): δ 5.85 (d, 1H, $J_{1,2}$=4.5 Hz, H-1), 5.35 (brt, 1H, $J_{2',3'}$=6.7 Hz, olefinic), 4.55 (d, 1H, $J_{1,2}$=4.5 Hz, H-2), 4.22–3.92 (m, 4H, H-3, 4, allylic CH_2), 3.9–3.65 (m, 3H, H-5, 6, 6′), 1.8, 1.7, 1.5, 1.3 (4s, 12H, –CH_3).

*3.3. 1,2-*O*-Isopropylidene-3-*O*-(3′-methyl-2′-butenyl)-α-*D*-xylopentadialdo-1,4-furanose* **2**

A solution of **6** (2.3 g, 7.9 mmol) in 60% aq. THF (15 mL) was treated with sodium metaperiodate (3.4 g, 15.9 mmol) in one portion and stirred at room temperature for 3 h. After completion of reaction, the solvent was removed to obtain the residue which was dissolved in dichloromethane (50 mL), filtered through Celite and washed with dichloromethane (3×25 mL). Combined organic layers were washed with water and brine, dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography [Si gel, hexane:ethyl acetate (3:1)] to afford aldehyde **2** (1.5 g, 73.5%) as a syrup. $[\alpha]_D$ −54.1 (*c*=1.0, $CHCl_3$); IR (neat): 1745, 1490, 725 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 9.6 (s, 1H, CHO), 6.05 (d, 1H, $J_{1,2}$=4.5 Hz, H-1), 5.9–5.7 (m, 1H, olefinic), 5.35–5.1 (m, 1H, H-4), 4.55–4.35 (m, 2H, H-2,3), 4.2–3.8 (m, 2H, allylic CH_2), 1.7, 1.65, 1.45, 1.25 (4s, 12H, –CH_3). Anal. calcd for $C_{13}H_{20}O_5$: C, 60.92; H, 7.86. Found: C, 60.73; H, 7.71.

3.4. N-*Tetrahydropyranyl-3,3,7,7-tetramethyl-(3a*S,*5a*S,*5b*R,*8a*R,*9a*R,*9b*R*)-perhydro-[1,3]-dioxolo-[5′′,4′′:4′,5′]-furo-[2′,3′:5,6]-pyrano-[4,3-*c*]-isoxazole **7** (R=THP)*

A stirred solution of **2** (0.6 g, 2.34 mmol) and 5-hydroxy pentanaloxime (**C**: 0.386 g, 3.3 mmol) in toluene (20 mL) containing a catalytic amount of Bu_2SnO was heated at reflux for 8 h. It was cooled to room temperature, filtered and evaporated and then the residue was purified by column chromatography [Si gel, hexane:ethyl acetate (9:1)] to give **7** (0.42 g, 50%) as a syrup. IR (neat): 2930, 1370, 1220 cm^{-1}; ^1H NMR ($CDCl_3$): δ 5.82 (d, 1H, $J_{1,2}$=4.5 Hz, H-1), 4.5 (d, 1H, $J_{1,2}$=4.5 Hz, H-2), 4.16 (t, 1H, $J_{8,9}$=5.2 Hz, H-8), 4.05 (m, 2H, H-12), 3.96 (d, 1H, $J_{3,4}$=2.0 Hz, H-4), 3.85 (d, 1H, $J_{3,4}$=2.0 Hz, H-3), 3.75 (d, 1H, $J_{5,6}$=5.6 Hz, H-5), 3.6–3.4 (m, 2H, H-7, 7′), 2.4–2.2 (m, 1H, H-6), 2.0–1.5 (m, 6H, H-9, 10, 11), 1.48, 1.3, 1.13 (3s, 12H, $–CH_3$). Anal. calcd for $C_{18}H_{29}NO_6$: C, 60.82; H, 8.22. Found: C, 60.61; H, 8.09.

3.5. *5-Deoxy-1,2-*O*-isopropylidene-3-*O*-(3′-methyl-2′-butenyl)-5-C-(oxime)-α-*D*-xylofuranose **3***

A mixture of **2** (1.5 g, 5.8 mmol), triethylamine (0.8 mL, 5.8 mmol) and hydroxylamine hydrochloride (0.4 g, 5.8 mmol) in ethanol (25 mL) was heated at reflux for 1 h. Ethanol was removed and the residue obtained was dissolved in ether (50 mL), the ethereal layer was washed with water (2×30 mL) and brine, then dried (Na_2SO_4) and evaporated and the residue obtained was purified by column chromatography [Si gel, hexane:ethyl acetate (9:1)] to give **3** (1.42 g, 90%) as a syrup. $[\alpha]_D$ −136.6 (*c*=1.2, $CHCl_3$); IR (neat): 3360, 3460, 1490, 725 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.32 (brs, 1H, N–OH), 6.88 (d, 1H, $J_{4,5}$=4.5 Hz, H-5), 5.8 (d, 1H, $J_{1,2}$=4.5 Hz, H-1), 5.25 (brt, 1H, $J_{2',3'}$=7.0 Hz, olefinic), 5.15 (t, 1H, $J_{3,4}$=5 Hz, H-4), 4.52 (d, 1H, $J_{1,2}$=4.5 Hz, H-2), 4.2 (d, 1H, $J_{3,4}$=5.0 Hz, H-3), 3.98 (m, 2H, allylic CH_2), 1.75, 1.65 (2s, 6H, $–CH_3$), 1.5, 1.3 (2s, 6H, $–CH_3$). Anal. calcd for $C_{13}H_{21}NO_5$: C, 57.55; H, 7.80. Found: C, 57.40; H, 7.68.

3.6. *3,3,7,7-Tetramethyl-perhydro-[1,3]-dioxolo-[5′′,4′′:4′,5′]-furo-[2′,3′:5,6]-pyrano-[4,3-*c*]-isoxazoline **8***

A 30% sodium hypochlorite solution (150 mL) was added to a stirred solution of **3** (1.3 g, 4.8 mmol) in CH_2Cl_2 (150 mL) at 0°C. After 30 min the reaction mixture was stirred at room temperature for 1 h and the two layers were then separated. The organic layer was dried (Na_2SO_4), evaporated and the residue obtained was purified by column chromatography [Si gel, hexane:ethyl acetate (9:1)] to give **8** (1.16 g, 90%) as a syrup. $[\alpha]_D$ +82.0 (*c*=0.5, $CHCl_3$); IR (neat): 3013, 2971, 1369, 1230, 1151, 1093, 1056, 755 cm^{-1}; ^1H NMR ($CDCl_3$): δ 5.9 (d, 1H, $J_{1,2}$=4.5 Hz, H-1), 4.85 (d, 1H, $J_{3,4}$=3.0 Hz, H-4), 4.5 (d, 1H, $J_{1,2}$=4.5 Hz, H-2), 3.98 (dd, 1H, $J_{6,7}$=9.0 Hz, $J_{7,7'}$=13.3 Hz, H-7), 3.88 (d, 1H, $J_{3,4}$=3.0 Hz, H-3), 3.35 (dd, 1H, $J_{7,7'}$=11.35 Hz, $J_{6,7'}$=13.5 Hz, H-7′), 3.18 (dd, 1H, $J_{6,7}$=9.0 Hz, $J_{6,7'}$=13.5 Hz, H-6), 1.48, 1.40, 1.30, 1.20 (4s, 12H, $–CH_3$). Anal. calcd for $C_{13}H_{19}NO_5$: C, 57.98; H, 7.11. Found: C, 57.75; H, 7.02.

3.7. *3,3,7,7-Tetramethyl-(3a*S,*5a*S,*5b*R,*8a*R,*9a*R,*9b*R*)-perhydro-[1,3]-dioxolo-[5′′,4′′:4′,5′]-furo-[2′,3′:5,6]-pyrano-[4,3-*c*]-isoxazole **1***

A solution of **3** (0.5 g, 1.8 mmol) in toluene (20 mL) was heated at 180°C for 18 h in a sealed tube. Toluene was evaporated and the residue was purified by column chromatography [Si gel, hexane:ethyl acetate (1:1)] to afford **1** (0.275 g, 55%) as a solid. Mp 180°C; $[\alpha]_D$ +7.99 (*c*=0.37, CH_3OH); IR (KBr): 3323, 2930, 1370, 1220 cm^{-1}; ^1H NMR ($CDCl_3$): δ 5.75 (d, 1H, $J_{1,2}$=4.0 Hz, H-1), 4.45 (d, 1H, $J_{1,2}$=4.0 Hz, H-2), 4.08 (d, 1H, $J_{3,4}$=2.0 Hz, H-4), 3.95 (brd, 1H, $J_{5,6}$=5.5 Hz, H-5), 3.88 (d, 1H, $J_{3,4}$=2.0 Hz,

H-3), 3.75 (dd, 1H, $J_{6,7}$=6.6 Hz, $J_{7.7'}$=11.0 Hz, H-7), 3.32 (brt, 1H, $J_{6,7'}$=13.0 Hz, H-7′), 2.32–2.2 (m, 1H, H-6), 1.42, 1.3, 1.25, 1.15 (4s, 12H, –CH_3). Anal. calcd for $C_{13}H_{21}NO_5$: C, 57.55; H, 7.80. Found: C, 57.34; H, 7.64.

3.8. N-*Phenylacetyl-3,3,7,7-tetramethyl-(3a*S,*5a*S,*5b*R,*8a*R,*9a*R,*9b*R*)-perhydro-[1,3]-dioxolo-[5′′, 4′′:4′,5′]-furo-[2′,3′:5,6]-pyrano-[4,3-*c*]-isoxazole* ***9***

Phenacyl chloride (0.13 mL, 1 mmol) was added to a stirred solution of **1** (0.25 g, 0.92 mmol) and triethylamine (0.16 mL, 1.2 mmol) in CH_2Cl_2 (5 mL) at 0°C and stirred at room temperature for 12 h. The reaction mixture was diluted with CH_2Cl_2 (20 mL), washed with water and brine and dried (Na_2SO_4). The organic layer was evaporated and the residue purified by column chromatography [Si gel, hexane:ethyl acetate (4:1)] to afford **9** (0.25 g, 71%) as a syrup. $[\alpha]_D$ −76.15 (*c*=0.78, $CHCl_3$); IR (neat): 2942, 1665, 1161, 1066 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.25 (brs, 5H, -Ph), 5.75 (d, 1H, $J_{1,2}$=4.0 Hz, H-1), 4.55 (d, 1H, $J_{3,4}$=2.0 Hz, H-4), 4.48 (d, 1H, $J_{1,2}$=4.0 Hz, H-2), 4.33 (d, 1H, $J_{5,6}$=5.5 Hz, H-5), 3.9 (d, 1H, $J_{3,4}$=2.0 Hz, H-3), 3.8 (t, 1H, $J_{6,7}$=7.0 Hz, $J_{7,7'}$=13.2 Hz, H-7), 3.72 (brs, 2H, Ph–CH_2–), 3.3 (brt, 1H, $J_{6,7'}$=11.3 Hz, $J_{7,7'}$=13.2 Hz, H-7′), 2.45–2.3 (m, 1H, H-6), 1.45, 1.32, 1.12, 0.9 (4s, 12H, –CH_3). Anal. calcd for $C_{21}H_{27}NO_6$: C, 64.76; H, 6.98. Found: C, 64.58; H, 6.87.

3.9. N-*Propionyl-3,3,7,7-tetramethyl-(3a*S,*5a*S,*5b*R,*8a*R,*9a*R,*9b*R*)-perhydro-[1,3]-dioxolo-[5′′,4′′:4′, 5′]-furo-[2′,3′:5,6]-pyrano-[4,3-*c*]-isoxazole* ***10***

Propionyl chloride (0.08 mL, 1 mmol) was added to a stirred solution of **1** (0.25 g, 0.92 mmol) and triethylamine (0.16 mL, 1.2 mmol) in CH_2Cl_2 (5 mL) at 0°C. After the completion of reaction (TLC analysis), the reaction was worked up as described for **9** and purified by column chromatography [Si gel, hexane:ethyl acetate (4:1)] to afford **10** (0.22 g, 75%) as a syrup. $[\alpha]_D$ −48.08 (*c*=0.85, $CHCl_3$); IR (neat): 2942, 1665, 1161, 1066 cm^{-1}; ^1H NMR ($CDCl_3$): δ 5.8 (d, 1H, $J_{1,2}$=4.2 Hz, H-1), 4.5–4.4 (m, 3H, H-2, 4, 5), 3.9 (dd, 1H, $J_{6,7}$=6.8 Hz, $J_{7.7'}$=13.0 Hz, H-7), 3.8 (d, 1H, $J_{3,4}$=2.0 Hz, H-3), 3.3 (brt, 1H, $J_{6,7'}$=11.3 Hz, $J_{7.7'}$=13.0 Hz, H-7′), 2.45–2.3 (m, 3H, H-6, –CH_2), 1.5, 1.3, 1.25, 1.15 (4s, 12H, –CH_3), 1.1 (t, 3H, –CH_3). Anal. calcd for $C_{16}H_{25}NO_6$: C, 58.70; H, 7.69. Found: C, 58.47; H, 7.55.

Acknowledgements

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