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Note

A convenient synthesis of *endo*-H ethylidene acetals

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In this paper, we report a stereoselective approach to 5-membered ethylidene cyclic acetals with *endo*-H configuration. Acetals are useful protecting groups in carbohydrate chemistry [1–4]. Direct acetalation is generally an acid-catalysed procedure [5,6], providing efficient methods for isopropylidenation or benzylidenation of carbohydrates [5,6]. Ethylidene acetals can easily be prepared under equilibrium conditions by acid-catalysed acetalation (e.g., treatment of suitable sugars with paraldehyde–*p*-toluenesulfonic acid). These are, however, less useful protecting groups in comparison to acetonides [1] because, in the case of 5-membered cyclic acetals, mixtures of the *endo*-H and *exo*-H dioxolane diastereomers are formed. When the acetalation is equilibrium-controlled, the 1,3-dioxolane systems show a strong preference for the *exo*-H (*endo*-alkyl) isomers. This was rationalised by assuming that the 1,3-dioxolane ring adopts a suitable half-chair (or twist) conformation (refs. [7,8] and references cited therein).

Clode [3] postulated that acid-catalysed acetal formation may be divided into a kinetic and a thermodynamic phase; the products of each of these may differ considerably from each other. Thus, the *endo*-phenyl diastereomer was formed by benzylidenation of 1,4-anhydroerythritol under kinetically controlled conditions ([3] and references cited therein); acid-catalysed equilibration led to an equimolar mixture of the two diastereomers.

Recently, we found a convenient one-pot method for acetalation of various pyranosides which follows a different nonclassical pathway (refs. [9–11] and references cited therein). Thus, pyranosides having a *cis,trans* sequence of three contiguous hydroxyl groups react under relatively mild conditions and in the absence of any acidic catalysts

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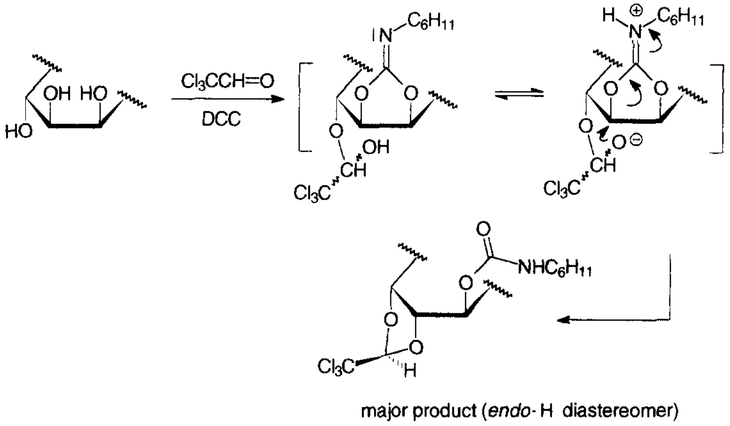

Scheme 1.

with the reagent system trichloroacetaldehyde (chloral)–dicyclohexylcarbodiimide (DCC) to form cyclic 2,2,2-trichloroethylidene acetals. These acetalations are generally accompanied by inversion of the configuration at the middle chiral carbon atom of the triol unit [12]; Scheme 1. In contrast to acid-catalysed ethylidenations [1], the cyclic chloral acetals, formed in this way, are predominantly *endo*-H diastereomers, since one of the reaction steps (probably the irreversible cyclisation step) is kinetically controlled [10]. Molecular models indicate that the interaction of the trichloromethyl substituent with the sugar moiety in the S_N2 cyclic transition states leading to the *endo*-H and *exo*-H diastereomers favours the *endo*-H isomer.

Various *endo*-H diastereomeric trichloroethylidene acetals were obtained in pure form using column chromatography or, in some cases, fractional crystallisation. Thus, methyl α-L-rhamnopyranoside (**1**) gives an *endo*-H/*exo*-H diastereomeric mixture (17:1) of the methyl 2-*O*-cyclohexylcarbamoyl-6-deoxy-3,4-*O*-(2,2,2-trichloroethylidene)-α-L-altropyranosides (**2a**/**2b**) [13]. Scheme 2 shows the *endo*-H diastereomer **2a**. This compound could be obtained in pure form [1] by repeated fractional crystallisation from 2-propanol–heptane [14].

There are only two examples in the literature which deal with the conversion of trichloroethylidene acetals into ethylidene acetals [15,16]. Raney-nickel [15] and tributylstannane–α,α'-azobisisobutyronitrile (AIBN) [16], respectively, were used for hydrogenation/dehalogenation. We examined both reducing reagents and also the palladium–charcoal–hydrogen system. Raney-nickel afforded the desired products but only in very poor yield. Hydrogenation of the choral acetals in the presence of palladium–charcoal required a long reaction time (more than 48 h) and gave poor yields. In both cases a mixture of monochloroethylidene and ethylidene acetals was obtained.

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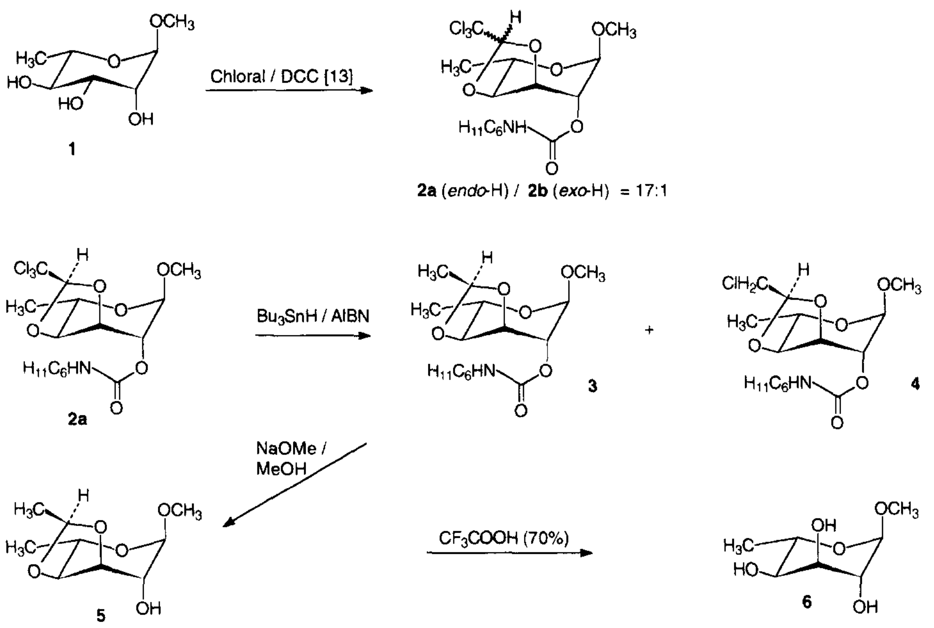
[1] Properties of the pure *endo*-H diastereomer **2a**: mp 117–118 °C (2-propanol–heptane), $[\alpha]_D^{25}$ −84.23° (*c* 1.3, $CHCl_3$) [14].



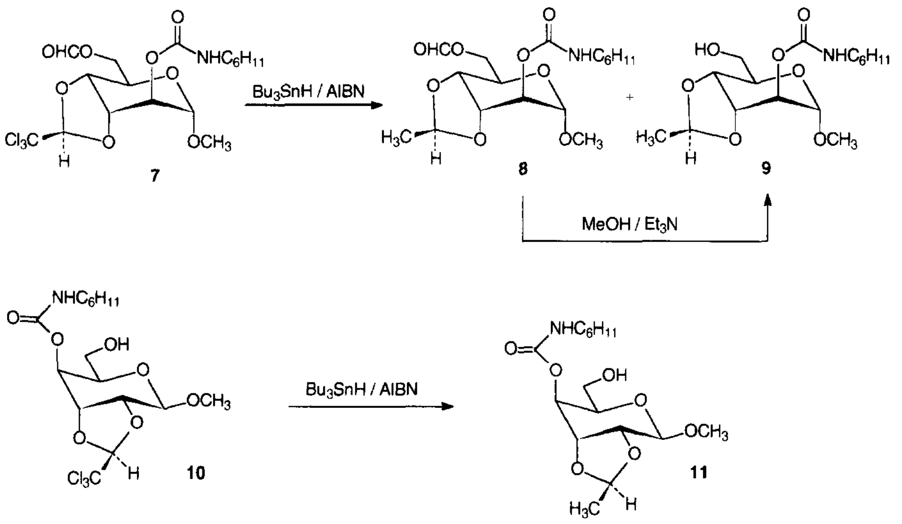
Scheme 2.

In contrast, very satisfactory results were achieved by treatment of the chloral acetals with tributylstannane–AIBN according to Jacobsen and Sløk [16] (see also [17]). Thus, refluxing the *endo*-H L-altroside **2a** in toluene in the presence of a threefold excess of Bu_3SnH and a catalytic amount of AIBN during a period of 6 h gave the desired ethylidene derivative **3** in excellent yield (92%). In addition, the monochlorosubstituted byproduct **4** was isolated (3%). Longer reaction times decreased the amounts of the byproduct **4** but decarbamoylation then took place, forming the new byproduct **5** detectable by TLC (Scheme 2).

The *endo*-H ethylidene acetal protecting groups can be removed by acid-catalysed hydrolysis, as easily as in the case of acetonides. Thus, the L-altropyranoside **5**, prepared by decarbamoylation from **3** (methanolysis), was treated for 30 min at room temperature with aqueous trifluoroacetic acid (70%), giving methyl 6-deoxy-α-L-altropyranoside (**6**) in high yield (88%) (Scheme 2).

The formylated D-altroside **7**, prepared from methyl α-D-mannopyranoside–chloral–DCC in a one-step reaction [13], was reduced with Bu_3SnH–AIBN. A mixture of the ethylidene acetal **8** and the deformylated product **9** was obtained (ratio **8**/**9** ≈ 9:11 determined by NMR spectroscopy). Heating the mixture for 10 min in MeOH–Et_3N gave the pure methyl 2-*O*-cyclohexylcarbamoyl-[(*S*)-3,4-*O*-ethylidene]-α-D-altropyranoside (**9**) in 84% yield (Scheme 3).

The D-guloside **10** [9] was converted into the corresponding ethylidene acetal **11** in a similar matter. The product **11** (92%) formed a stable gel with hydrocarbons (e.g., toluene, hexane) and crystallisation was induced by ultrasonification of the gel for 5 h; Scheme 3.



Scheme 3.

In conclusion, an efficient way has been found to prepare ethylidene acetals with *endo*-H configuration. The latter can be cleaved easily under mild acid-catalysed conditions. Furthermore, it is important to mention that the conversion of chloral acetals into ethylidene acetals can be simultaneously combined with the Barton procedure of reduction [18] to prepare deoxy sugars. Thus, ethylidene acetal-protected α-linked L-digitoxosides were synthesised by reduction of the corresponding 2-xanthate of various 6-deoxy-3,4-*O*-(2,2,2-trichloroethylidene)-α-L-altrosides with Bu_3SnH–AIBN [19].

The structures of all compounds are supported by their ^1H and ^{13}C NMR spectral data. The ^1H NMR spectra of the ethylidene acetals **3**, **9**, and **11** show characteristic doublets for the methyl groups between δ 1.25 and 1.29, and quartets for the acetal protons between δ 5.34 and 5.44. The range of the chemical shifts of the ethylidene acetal protons is typical of *endo*-H signals [7]. Compared to the corresponding protons of the chloral acetals **2** (δ 5.46, s), **7** (δ 5.49, s), and **10** (δ 5.78, s) the corresponding signals of **3**, **9**, and **11** are, as expected, shifted to higher field. Moreover, significant shifts to higher field of the acetal C-atoms were observed in ^{13}C NMR spectra of the ethylidene acetals (**3**: δ 20.9, 101.2; **9**: δ 20.9, 101.7; **11**: δ 21.4, 102.2) compared with the trichloroethylidene acetals (**2**: δ 99.5, 107.1; **7**: δ 99.1, 107.1; **10**: δ 99.3, 106.7). This can be explained by the substitution of the electron-withdrawing chlorine atoms by hydrogen.

1. Experimental

General.—Column chromatography: Silica Gel 60 (63–200 μm) [Merck]. Thin-layer chromatography (TLC): Silica Gel foils 60 F_{254} [Merck]. NMR: Bruker AC 250 and

ARX 300; internal standard Me_4Si. Melting points were determined using a polarising microscope Leitz (Laborlux 12 Pol) equipped with a hot-stage (Mettler FP 90).

Methyl 2-O-cyclohexylcarbamoyl-6-deoxy-[(R)-3,4-O-ethylidene]-α-L-altropyranoside (**3**) and *methyl [(R)-3,4-O-(2-chloroethylidene)]-2-O-cyclohexylcarbamoyl-6-deoxy-α-L-altropyranoside* (**4**).—A solution of **2a** (1.0 g, 2.3 mmol), Bu_3SnH (2.35 g, 6.9 mmol), and AIBN (20 mg) in dry toluene (40 mL) was refluxed for 4 h under an inert gas atmosphere. After addition of a second portion of AIBN (10 mg), refluxing of the mixture was continued for 2 h. TLC control (1:1 EtOAc–toluene) showed the major product **3** at R_f 0.55 and the byproduct **4** at R_f 0.62.

The solution was concentrated under reduced pressure to a third of its volume and hexane (10 mL) was added. At reduced temperature, 0.63 g (83%) of crystalline **3** was separated by filtration and washed with hexane. The filtrate was concentrated under reduced pressure and hexane was added (20 mL). After allowing the solution to stand overnight in a refrigerator, the precipitate was isolated and purified by column chromatography (1:3 EtOAc–toluene) giving 50 mg (9%) of **3**; mp 152.3–153.5 °C (hexane); $[\alpha]_D^{25}$ −57° (*c* 1.0, $CHCl_3$); and 26 mg (3%) of **4**; mp 157.8–158.2 °C (hexane); $[\alpha]_D^{25}$ −59° (*c* 1.0, $CHCl_3$).

3: ^1H NMR data ($CDCl_3$): δ 1.22 (m, 5 H, cyclohexyl-CH_2), 1.29 (d, 3 H, *J* 4.9 Hz, *Me*CH), 1.31 (d, 3 H, $J_{5,6}$ 6.3 Hz, H-6), 1.64 (m, 3 H, cyclohexyl-CH_2), 1.92 (m, 2 H, cyclohexyl-CH_2), 3.37 (s, 3 H, OMe), 3.47 (m, 1 H, cyclohexyl-CH), ~ 3.84 (m, 2 H, H-4, H-5), 4.17 (dd, 1 H, $J_{2,3}$ 4.3 Hz, $J_{3,4}$ 5.8 Hz, H-3), 4.53 (d, 1 H, $J_{1,2}$ 3.4 Hz, H-1), 4.64 (d, 1 H, $J_{NH,CH}$ 7.6 Hz, NH), 5.06 (dd, 1 H, H-2), 5.34 (q, 1 H, MeC*H*); ^{13}C NMR data ($CDCl_3$): δ 18.9 (C-6), 20.9 (*Me*CH), 24.7, 25.5, 33.3 (cyclohexyl-CH_2), 50.1 (cyclohexyl-CH), 55.4 (OMe), 63.4 (C-5), 69.6 (C-2), 70.5, 77.2 (C-3, C-4), 99.5 (C-1), 101.2 (Me*C*H), 154.2 (C=O). Anal. Calcd for $C_{16}H_{27}NO_6$ (326.4): C, 58.89; H, 8.34; N, 4.29. Found: C, 58.64; H, 8.21; N, 4.29.

4: ^1H NMR data ($CDCl_3$): δ 1.23 (m, 5 H, cyclohexyl-CH_2), 1.30 (d, 3 H, $J_{5,6}$ 6.3 Hz, H-6), 1.64 (m, 3 H, cyclohexyl-CH_2), 1.91 (m, 2 H, cyclohexyl-CH_2), 3.39 (s, 3 H, OMe), 3.47 (m, 1 H, cyclohexyl-CH), 3.52 (m, 2 H, CH_2Cl), 3.83 (dq, 1 H, $J_{4,5}$ 8.9 Hz), 4.01 (dd, 1 H, $J_{3,4}$ 5.8 Hz, H-4), 4.25 (dd, 1 H, $J_{2,3}$ 4.6 Hz, H-3), 4.58 (d, 1 H, $J_{1,2}$ 2.8 Hz, H-1), 4.70 (d, 1 H, $J_{NH,CH}$ 7.6 Hz, NH), 5.06 (dd, 1 H, H-2), 5.42 (dd, 1 H, $J_{H,Ha} \approx J_{H,Hb} \approx 3.7$ Hz, C*H*CH_2Cl); ^{13}C NMR data ($CDCl_3$): δ 18.7 (C-6), 24.7, 25.4, 33.2 (cyclohexyl-CH_2), 44.9 (CH*C*H_2Cl), 50.2 (cyclohexyl-CH), 55.5 (OMe), 62.9 (C-5), 69.2 (C-2), 75.4, 77.3 (C-3, C-4), 99.2 (C-1), 101.9 (*C*HCH_2Cl), 154.0 (C=O). Anal. Calcd for $C_{16}H_{26}ClNO_6$ (360.8): C, 53.26; H, 7.26; N, 3.88. Found: C, 53.20; H, 7.20; N, 3.88.

Methyl 6-deoxy-[(S)-3,4-O-ethylidene]-α-L-altropyranoside (**5**).—A solution of **3** (0.5 g, 1.53 mmol) and NaOMe (4.6 mmol) in dry MeOH (5 mL) was refluxed for 2 h. TLC control (1:1 EtOAc–toluene) showed product **5** at R_f 0.25. After neutralisation with an acidic exchanger resin, the solution was concentrated under reduced pressure. The syrupy residue was purified by column chromatography (1:1 EtOAc–toluene) to give **5** as a colourless oil (0.29 g, 94%); $[\alpha]_D^{21}$ −59° (*c* 1.1, $CHCl_3$); ^1H NMR data ($CDCl_3$): δ 1.28 (d, 3 H, *J* 4.9 Hz, *Me*CH), 1.33 (d, 3 H, $J_{5,6}$ 6.1 Hz, H-6), 2.78 (d, 1 H, $J_{2,OH}$ 4.0 Hz, 2-OH), 3.41 (s, 3 H, OMe), 3.77 (dq, 1 H, $J_{4,5}$ 9.2 Hz, H-5), 3.86 (ddd, 1 H, $J_{1,2}$ 5.8 Hz, $J_{2,3}$ 7.0 Hz, H-2), 3.94 (dd, 1 H, $J_{3,4}$ 7.0 Hz, H-4), 4.22 (dd, H-3), 4.43 (d, 1 H, H-1), 5.24 (q, 1 H, MeC*H*); ^{13}C NMR data ($CDCl_3$): δ 19.3 (C-6), 20.0 (*Me*CH), 55.5 (OMe), 65.5 (C-5), 67.1 (C-2), 70.1, 78.2 (C-3, C-4), 100.1 (C-1), 102.0 (Me*C*H). Anal. Calcd for $C_9H_{16}O_5$ (204.1): C, 52.96; H, 7.90. Found: C, 52.86; H, 7.74.

Methyl 6-deoxy-α-L-altropyranoside (**6**).—Compound **5** (0.150 g, 0.73 mmol) was dissolved in aqueous trifluoroacetic acid (70%, 3 mL) and the solution was allowed to stand at room temperature for 30 min. TLC control (EtOAc) showed **6** at R_f 0.21. After concentrating the mixture under reduced pressure, toluene (5 mL) was added and the solution once more concentrated to give a crude product which was purified by column chromatography (EtOAc). Compound **6** (0.115 g, 88%) was obtained as a colourless oil; $[\alpha]_D^{21}$ −107° (*c* 0.49, $CHCl_3$); ^{1}H NMR data ($CDCl_3$): δ 1.31 (d, 3 H, $J_{5,6}$ 6.4 Hz, H-6), ~ 3.53 (m, H-4), 3.78 (dq, 1 H, $J_{4,5}$ 8.9 Hz, H-5), ~ 3.87 (m, 2 H, H-2, H-3), 4.58 (dd, 1 H, $J_{1,2}$ 1.8 Hz, H-1); ^{13}C NMR data ($CDCl_3$): δ 19.3 (C-6), 55.5 (OMe), 65.6 (C-5), 69.6, 69.9, 78.2 (C-2, C-3, C-4), 100.1 (C-1). Anal. Calcd for $C_7H_{14}O_5$ (178.2): C, 47.18; H, 7.92. Found: C, 47.23; H, 8.10.

Methyl 2-O-cyclohexylcarbamoyl-[(S)-3,4-O-ethylidene]-α-D-altropyranoside (**9**).—A solution of **7** (1.0 g, 2.1 mmol), Bu_3SnH (2.13 g, 6.3 mmol), and AIBN (20 mg) in dry toluene (40 mL) was refluxed for 4 h under N_2. After addition of a second portion of AIBN (10 mg), refluxing of the mixture was continued for 3 h. TLC control (1:3 EtOAc–toluene) showed the major product **9** at R_f 0.15 and the 6-*O*-formyl derivative **8** at R_f 0.52. After cooling, MeOH (5 mL) and Et_3N (0.25 mL) were added and the mixture was refluxed for 10 min. Then the solution was concentrated to half its volume, hexane (10 mL) was added, and the mixture was allowed to stand overnight in a refrigerator. The precipitate was separated and washed with hexane to give 0.60 g (84%) of **9**; mp 158–160.1 °C (hexane); $[\alpha]_D^{21}$ +66° (*c* 1.0, $CHCl_3$); ^{1}H NMR data ($CDCl_3$): δ 1.20 (m, 5 H, cyclohexyl-CH_2), 1.28 (d, 3 H, *J* 4.9 Hz, *Me*CH), 1.62 (m, 3 H, cyclohexyl-CH_2), 1.89 (m, 2 H, cyclohexyl-CH_2), 2.29 (broad, 1 H, 6-OH), 3.36 (s, 3 H, OMe), 3.42 (m, 1 H, cyclohexyl-CH), ~ 3.75 (m, 3 H, H-5, H-6a, H-6b), ~ 4.18 (m, 2 H, H-3, H-4), 4.60 (d, 1 H, $J_{1,2}$ 2.7 Hz, H-1), 4.84 (d, 1 H, $J_{NH,CH}$ 7.9 Hz, NH), 5.03 (dd, 1 H, $J_{2,3}$ 4.0 Hz, H-2), 5.36 (q, 1 H, MeC*H*); ^{13}C NMR data ($CDCl_3$): δ 20.9 (*Me*CH), 25.0, 25.6, 33.4 (cyclohexyl-CH_2), 50.4 (cyclohexyl-CH), 55.8 (OMe), 63.0 (C-6), 67.5, 69.2 (C-2, C-5), 70.7, 74.4 (C-3, C-4), 99.3 (C-1), 101.7 (Me*C*H), 154.1 (C=O). Anal. Calcd for $C_{16}H_{27}NO_7$ (345.4): C, 55.64; H, 7.88; N, 4.06. Found: C, 55.26; H, 7.71; N, 4.22.

Methyl 4-O-cyclohexylcarbamoyl-[(S)-2,3-O-ethylidene]-β-D-gulopyranoside (**11**).—A solution of **10** (1.0 g, 2.2 mmol), Bu_3SnH (2.27 g, 6.6 mmol), and AIBN (20 mg) in dry toluene (40 mL) was refluxed for 4 h under an inert gas atmosphere (N_2). After addition of a second portion of AIBN (10 mg), refluxing of the mixture was continued for 2 h. TLC control showed compound **11** at R_f 0.39 (1:3 EtOAc–toluene). After cooling, the solution was concentrated under reduced pressure to half its volume and then hexane (10 mL) was added. The gel which formed was sonicated for 5 h in an ultrasonic bath (120 W, 35 kHz). The precipitate was isolated and washed with hexane to give 0.70 g (92%) of **11**; mp 158–166.9 °C (hexane); $[\alpha]_D^{22}$ +48° (*c* 1.05, $CHCl_3$); ^{1}H NMR data ($CDCl_3$): δ 1.22 (m, 5 H, cyclohexyl-CH_2), 1.25 (d, 3 H, *J* 4.9 Hz, *Me*CH), 1.65 (m, 3 H, cyclohexyl-CH_2), 1.92 (m, 2 H, cyclohexyl-CH_2), 3.10 (dd, 1 H,

$J_{6a,OH}$ 8.1 Hz, $J_{6b,OH}$ 6.1 Hz, 6-OH), 3.42 (m, 1 H, cyclohexyl-CH), 3.52 (ddd, 1 H, $J_{5,6a}$ 6.4 Hz, $J_{6a,6b}$ 11.9 Hz, H-6a), 3.53 (s, 3 H, OMe), 3.69 (ddd, 1 H, $J_{5,6b}$ 6.4 Hz, H-6b), 3.86 (ddd, 1 H, $J_{4,5}$ 1.2 Hz, H-5), 4.02 (dd, 1 H, $J_{1,2}$ 7.0 Hz, $J_{2,3}$ 4.9 Hz, H-2), 4.17 (dd, 1 H, $J_{3,4}$ 2.7 Hz, H-3), 4.36 (d, 1 H, H-1), 4.88 (d, 1 H, $J_{NH,CH}$ 7.9 Hz, NH), 5.10 (dd, 1 H, H-4), 5.44 (q, 1 H, MeC*H*); ^{13}C NMR data ($CDCl_3$): δ 21.4 (*Me*CH), 24.6, 25.3, 33.0, 33.1 (cyclohexyl-CH_2), 50.2 (cyclohexyl-CH), 56.9 (OMe), 60.1 (C-6), 67.1, 72.8, 74.3, 75.2 (C-2, C-3, C-4, C-5), 101.3 (C-1), 102.2 (Me*C*H), 155.3 (C=O). Anal. Calcd for $C_{16}H_{27}NO_7$ (345.4): C, 55.64; H, 7.88; N, 4.06. Found: C, 55.92; H, 8.11; N, 3.96.

Acknowledgements

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