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Synthesis of novel isoxazole-linked steroidal glycoconjugates—an application of a novel steroidal nitrile oxide

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Abstract

Isoxazole-linked steroidal glycoconjugates are prepared by 1,3-dipolar cycloaddition reactions of an in situ generated and hitherto unknown steroidal nitrile oxide with appropriate propargyl ethers of sugars. The methodology provides a novel vector in the form of an easily accessible nitrile oxide having the ability to couple with many biomolecules, thus offering a new pathway to construct biologically significant novel steroidal conjugates.

Keywords: Bioconjugation; Glycoconjugates; Cycloaddition; Isoxazole; Steroid; Propargyl ethers of sugars

Bioconjugation has emerged as a fast growing technology providing a simple method to couple two or more molecular entities with distinct properties to form novel conjugates possessing the combined properties of its individual components.[1] The medicinal applications of this are based on the fact that several new conjugates arising through such bioconjugation have been found to exhibit unusual biological properties and activities as the different molecular segments act cooperatively.

Steroids, due to their rigid framework and potential for varying levels of functionalization, broad biological activity profile and ability to penetrate the cell membrane and bind to specific hormonal receptors, have become preferred synthons for the development of diverse bioconjugates. Several conjugates derived from diverse steroids through integration and/or linkage with other biomolecules, drugs and other functional molecules along with their pharmacological applications have been reported.[2] Some steroidal framework conjugates are steroid–polyamine conjugates,[3] steroid–anthraquinone hybrids,[4] steroid–carbohydrate conjugates[5] and many other steroidal conjugates.[6] Steroidal glycosides are used as agents for combating cholesterol, microbes, fungi, viruses, tumours and molluscs.[7] Amongst several steroidal glycosides one well-known example is digitoxin, a cardiac glycoside.

Recently, the so-called 'Click chemistry' has been used in the synthesis of a wide variety of glycoconjugates.[8–10] This has been attributed to the ease of reaction and relative stability of the 1,2,3-triazole linker. However, the use of an isoxazole moiety in a similar sense has yet to be realized fully. Based on the stability of nitroalkanes and in view of the availability of several efficient methods of transforming nitroalkanes into their respective nitrile oxides[11] and the utility of carbohydrates in cycloaddition reactions,[12] it appeared of interest to employ an isoxazole moiety in the aforementioned sense. In the present Letter, we report the application of a novel steroidal nitrile oxide, as a

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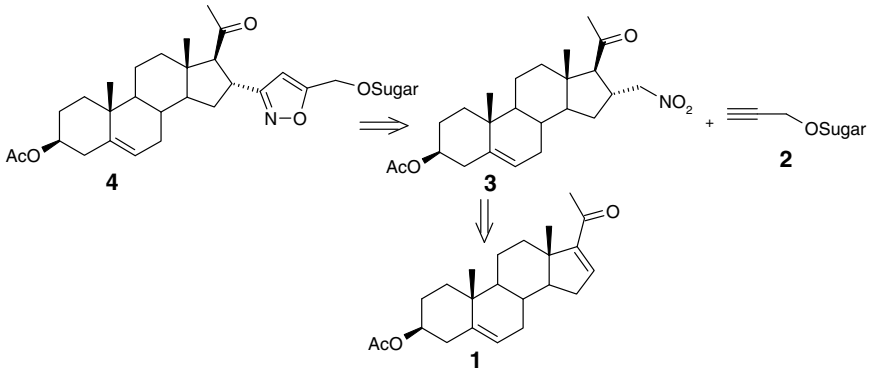


Scheme 1. Retrosynthetic analysis.

variant in 'Click'-like chemistry, for the synthesis of isoxazole-linked steroidal glycoconjugates.

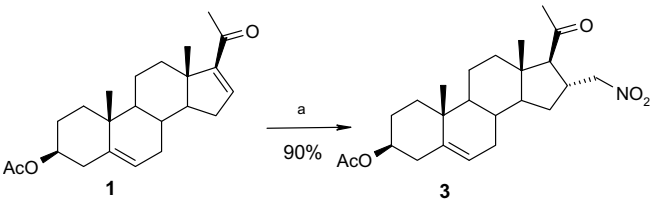
Towards a target such as **4**, a retrosynthetic analysis (Scheme 1) was carried out by taking into account the ready access to propargyl ether sugars **2** and steroidal nitroalkane **3**.

The synthetic phase of our investigation started with the synthesis of 3β-acetoxy-16α-nitromethyl-5-pregnen-20-one **3**, starting from readily available 16-dehydropregnenolone acetate (16-DPA) (**1**) using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as a base and nitromethane in dry dichloromethane. The reaction was complete in 12 h affording the desired product in 90% yield as shown in Scheme 2.[13] To the best of our knowledge, the only report available for the preparation of this compound is by employing piperidine as a base and the reaction takes 5 days to complete.[14]

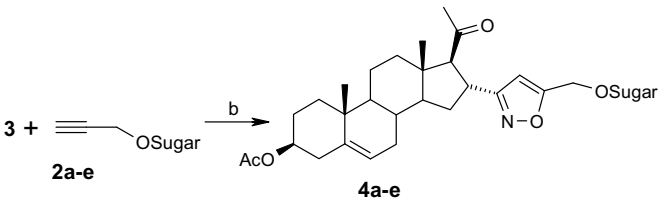
The propargyl ethers of the sugars were prepared from readily available sugars such as D-glucose, D-mannitol and D-galactose. All the monosaccharides were transformed into the respective alcohols followed by treatment with NaH, propargyl bromide and tetrabutylammonium bromide in THF as a solvent affording the respective propargyl ethers **2a**, **2b**, **2c** and **2e**. Propargyl ether **2d** was obtained by conversion of D-glucose into the D-glucal, which on Ferrier rearrangement with propargyl alcohol using bismuth nitrate in acetonitrile, following a literature procedure,[15] afforded the required product.

In our approach, nitroalkane **3** was treated with propargyl ethers **2a**–**e** in the presence of phenyl isocyanate (PhNCO) and triethylamine in dry benzene at room temperature utilizing Mukaiyama's conditions.[11a] The one-pot reaction proceeds completely regioselectively affording 3,5-disubstituted isoxazoles **4a**–**e** as shown in Scheme 3.[16] All the newly formed glycoconjugates (Table 1) were purified by column chromatography over silica gel to furnish the desired products in 58–65% yield.

The regioselective formation of the cycloadduct was confirmed by the appearance of characteristic ^{1}H NMR signals at δ 6.03–6.10 ppm as singlets for 4′-H. Other signals such as that at δ 5.36–5.37 ppm (broad singlet for 6-H), δ 3.00 ppm as a doublet (17-H) and the remaining signals were in accordance with the assigned structures.[16]



Scheme 2. Reagents and conditions: (a) DBU, CH_3NO_2, CH_2Cl_2, −15 °C to rt, 12 h.

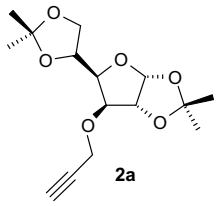
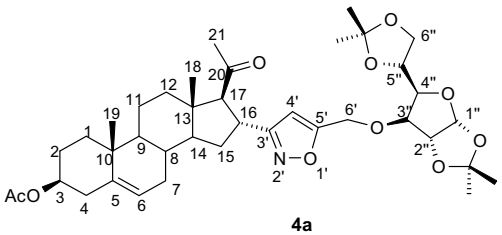
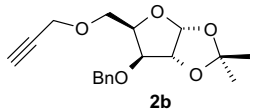
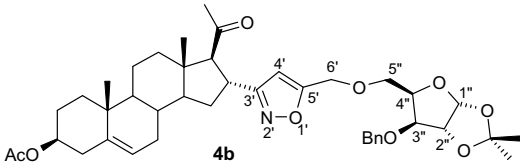
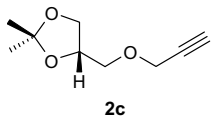
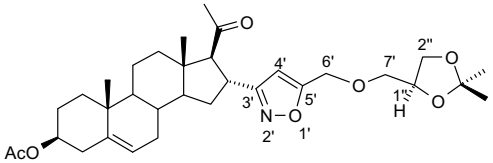
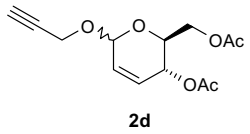
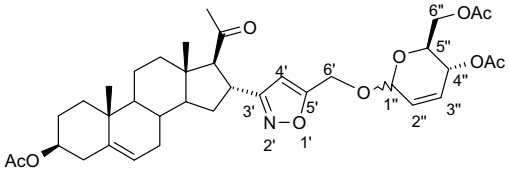
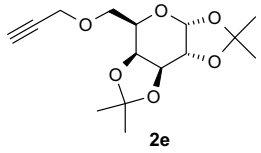
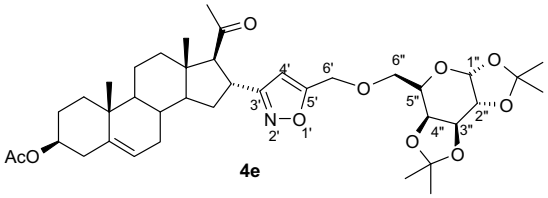


Scheme 3. Reagents and conditions: (b) PhNCO, Et_3N, dry benzene, rt.

^{13}C NMR signals were observed[17] at δ 102 ppm for C-4′, δ 167 ppm for C-5′, δ 168 ppm for C-3′, δ 170 ppm for the acetate carbonyl and at δ 207 ppm for C-20, which lent further support to the assigned structures.[16] Since the stereochemical outcome of the conjugate addition has been shown to be dependent on the nature of the nucleophile employed and the stereoselectivity varies from highly *syn* selective to highly *anti* selective,[18] it was expedient to ascertain the stereostructure of steroidal nitroalkane **3** on the one hand, and that of the derived cycloadduct on the other. Therefore, single crystal X-ray analysis of the cycloadduct derived from propargyl ether **2a** and nitroalkane **3** was performed. The ORTEP diagram of the steroidal glycoconjugate **4a** is given in Figure 1.[19] From the molecular geometry of **4a** it can safely be concluded that the conjugate addition of nitromethane to 16-DPA is *anti*-selective and that the 1,3-dipolar cycloaddition is regioselective.

In conclusion, we have developed a very simple and convenient [3+2] cycloaddition route for the synthesis of a new class of steroidal conjugates **4a**–**e**, featuring an isoxazole moiety between the sugar and the steroid entities. We have in turn, provided a novel vector in the form of an easily

Table 1
Cycloaddition of steroidal nitrile oxide **3** with sugar propargyl ethers

Entry	Sugar propargyl ethers	Cycloadduct	Yield[a] (%)
1	 **2a**	 **4a**	65
2	 **2b**	 **4b**	62
3	 **2c**	 **4c**	60
4	 **2d**	 **4d**	58
5	 **2e**	 **4e**	64

[a] Yields after column chromatography.

accessible nitrile oxide having the ability to couple with a host of biomolecules, thus offering a new pathway to construct novel molecular entities bearing the pregnenolone framework. The developed methodology may prove beneficial in the synthesis of other biologically significant steroidal conjugates, studies on which are in progress.

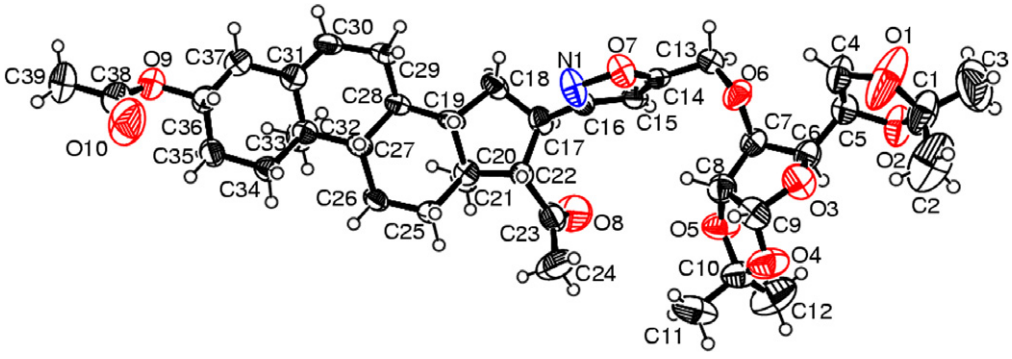


Fig. 1. ORTEP representation of the X-ray structure of **4a**.

Acknowledgements

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13. *Procedure for the preparation of 3β-acetoxy-16α-nitromethyl-5-pregnen-20-one* (**3**): To a stirred solution of 16-DPA (0.178 g, 0.5 mmol) and freshly distilled nitromethane (0.25 mL, 5 mmol) in dry dichloromethane (10 mL), DBU (0.37 mL, 2.5 mmol) was added at −15 °C. The reaction mixture was then stirred at room temperature. After 12 h 2 N HCl (10 mL) was added, the layers were partitioned, and the acidic layer was extracted with dichloromethane (3 × 15 mL). The combined extracts were dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. The product obtained was purified by recrystallization using petroleum ether and dichloromethane (9:1) to afford nitro compound **3** in 90% yield.
Spectral data of compound **3**: White crystalline solid, mp 149 °C. IR ($CHCl_3$): $\nu_{max} = 2938, 1729, 1701, 1552, 1438, 1381, 1363\ cm^{-1}$. ^1H NMR (300 MHz, $CDCl_3$): δ 0.68 (s, 3H, 18-H_3), 1.02 (s, 3H, 19-H_3), 1.11–1.29 (m, 2H), 1.33–1.65 (m, 10H), 1.85–1.94 (m, 3H), 2.04 (s, 3H, acetyl-Me), 2.16 (s, 3H, 21-H_3), 2.31–2.33 (m, 2H), 2.48 (d, 1H, $J = 9$ Hz, 17-H), 3.37 (m, 1H, 16-H), 4.28 (d, 2H, $J = 6$ Hz, nitromethyl), 4.58 (m, 1H, 3-H), 5.37 (br s, 1H, 6-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.79 (C-18), 19.26 (C-19), 20.79, 21.44 (acetyl-CH_3), 27.64, 28.95, 31.48 (C-21), 35.34, 36.52, 36.88, 37.97, 38.67, 44.96, 49.60, 55.32, 67.36 (C-17), 73.68 (C-3), 79.59, 121.93 (C-6), 139.66 (C-5), 170.57 (acetate-CO), 206.89 (C-20) ppm.
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16. *General procedure for the cycloaddition*: To 25 mL of dry benzene containing 1 mmol of PhNCO and 0.55 mmol of propargyl ether **2** were added a solution of 0.55 mmol of nitro compound **3** and 10 drops of Et_3N in 15 mL of dry benzene. The reaction started, evolving CO_2 and diphenylurea precipitated. After stirring the reaction mixture overnight, the solution was filtered. The brownish yellow benzene solution was evaporated under reduced pressure, the residue was dissolved in diethyl ether and filtered and the filtrate washed with dil HCl and then with water and dried over anhydrous Na_2SO_4. The product was purified by column chromatography over silica gel using a mixture of petroleum ether and ethyl acetate (70:30).
Spectral data of compounds: (i) *Compound* **4a**: White crystalline solid, mp 168–170 °C. IR ($CHCl_3$): $\nu_{max} = 3100, 1734, 1710, 1240, 760\ cm^{-1}$. ^1H NMR (300 MHz, $CDCl_3$): δ 0.74 (s, 3H, 18-H_3), 1.03 (s, 3H, 19-H_3), 1.15 (m, 2H), 1.31 (s, 3H), 1.36 (s, 3H), 1.43 (s, 3H), 1.49 (s, 3H), 1.57–1.90 (m, 13H), 2.04 (s, 3H, acetyl-Me), 2.18 (s, 3H, 21-H_3), 2.33 (m, 2H), 3.00 (d, 1H, $J = 9$Hz, 17-H), 3.92–4.11 (m, 5H, 16-H, 6″-H_2, 4″-H, 3″-H), 4.29 (m, 1H, 5″-H), 4.54 (d, 1H, $J = 3.6$ Hz, 2″-H), 4.59 (m, 1H, 3-H), 4.69 (s, 2H, 6′-H_2), 5.36 (br s, 1H, 6-H), 5.88 (d, 1H, $J = 3.6$ Hz, 1″-H), 6.10 (s, 1H, 4′-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.67 (C-18), 19.30 (C-19), 20.87, 21.44 (acetyl-CH_3), 25.41, 26.22, 26.79, 26.87, 27.67, 31.37, 31.55, 31.64, 31.69 (C-21), 34.30, 36.57, 36.94, 38.01, 38.59, 45.11, 49.67, 55.68, 63.51, 67.50 (C-17), 69.02, 72.23, 73.72 (C-3), 81.11, 82.47, 82.75, 102.60 (C-4′), 105.22 (C-1′), 109.21 (>$C(CH_3)_2$, sugar), 118.98 (>$C(CH_3)_2$, sugar), 122.08 (C-6), 139.66 (C-5), 167.50 (C-5′), 168.46 (C-3′), 170.55 (acetate-CO), 207.70 (C-20) ppm. HRMS (TOF, ES^+): calcd for $C_{39}H_{56}NO_{10}$: 698.3904 [M^++H]; found, 698.3910 [M^++H].
(ii) *Compound* **4b**: Yellowish sticky mass. IR ($CHCl_3$): $\nu_{max} = 2932, 1732, 1707, 1372, 1243, 760\ cm^{-1}$. ^1H NMR (300 MHz, $CDCl_3$): δ 0.73 (s, 3H, 18-H_3), 1.03 (s, 3H, 19-H_3), 1.15 (m, 2H), 1.31 (s, 3H), 1.48 (s, 3H), 1.55–1.89 (m, 13H), 2.03 (s, 3H, acetyl-Me), 2.16 (s, 3H, 21-H_3), 2.34 (m, 2H), 3.00 (d, 1H, $J = 9$Hz, 17-H), 3.78(d, 1H, $J = 5.4$ Hz), 3.91–3.95 (m, 2H), 4.36 (m, 1H), 4.47–4.68 (m, 6H), 5.36 (br s, 1H, 6-H), 5.94 (d, 2H, $J = 3.6$Hz, 1″-H), 6.03 (s, 1H, 4′-H), 7.28–7.33 (m, 5H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.67 (C-18), 19.29 (C-19), 20.86, 21.42 (acetyl Me), 26.27, 26.79, 27.67, 31.35, 31.53, 31.62, 31.70 (C-21), 34.24, 36.55, 36.91, 38.00, 38.56, 45.07, 49.64, 55.65, 64.25, 68.73 (C-17), 69.07, 71.93 (–O*C*H_2Ph), 73.76 (C-3), 79.08, 81.65, 82.15, 102.49 (C-4′), 105.12 (C-1″), 111.76 (>$C(CH_3)_2$, sugar), 122.13 (C-6), 127.64 (Ar-C), 128.00 (Ar-C), 128.52 (Ar-C), 137.33 (Ar-C), 139.58 (C-5), 167.47 (C-5′), 168.94 (C-3′), 170.55 (acetate-CO), 207.73 (C-20) ppm. HRMS (TOF, ES^+): calcd for $C_{42}H_{56}NO_9$: 718.3955 [M^++H], found, 718.3953 [M^++H].
(iii) *Compound* **4c**: Yellowish sticky mass. IR ($CHCl_3$): $\nu_{max} = 2932, 1734, 1710, 1240, 760\ cm^{-1}$. ^1H NMR (300 MHz, $CDCl_3$): δ 0.73 (s, 3H, 18-H_3), 0.86 (m, 2H), 1.03 (s, 3H, 19-H_3), 1.25 (s, 6H, >$C(CH_3)_2$), 1.52–1.89 (complex m, 13H), 2.03 (s, 3H, –COCH_3), 2.17 (s, 3H, 21-Me), 2.34 (m, 2H), 3.00 (d, 1H, $J = 9$ Hz, 17-H), 3.57 (m, 2H, 7′-H), 3.72 (t, 1H, $J = 7$ Hz, 2″-H_a-H), 3.92 (t, 1H, $J = 9.3$ Hz, 16-H), 4.05 (t, 1H, $J = 7.2$ Hz, 2″-H_b-H), 4.28 (m, 1H, 1″-H), 4.59 (br s, 3H, 3-H, 6′-H_2), 5.37 (br s, 1H, 6-H), 6.04 (s, 1H, 4′-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.65 (C-18), 19.28 (C-19), 20.86, 21.39 (acetyl CH_3), 25.32, 26.73, 27.67, 31.39, 31.52, 31.62, 31.66 (C-21), 34.34, 36.54, 36.91, 38.00, 38.57, 45.07, 49.66, 55.67, 64.24, 66.44 (C-17), 69.11, 71.92, 73.72 (C-3), 74.55, 102.59 (C-4′), 109.58 (>$C(CH_3)_2$, sugar), 122.09 (C-6), 139.61 (C-5), 167.48 (C-5′), 168.64 (C-3′), 170.48

(acetate-CO), 207.67 (C-20) ppm. HRMS (TOF, ES^+): calcd for $C_{33}H_{48}NO_7$: 570.3431 [M^++H]; found, 570.3424 [M^++H].

(iv) *Compound* **4d**: Yellowish sticky mass, IR ($CHCl_3$): $\nu_{max} = 2921$, 2851, 1742, 1705, 1240, 760 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 0.74 (s, 3H, 18-H_3), 1.03 (s, 3H, 19-H_3), 1.16–1.91 (complex m, 15H), 2.03 (s, 3H, acetyl-Me, steroid), 2.10 (s, 6H, acetyl-Me, sugar), 2.18 (s, 3H, 21-H_3), 2.33 (m, 2H), 3.00 (d, 1H, $J = 9$ Hz, 17-H), 3.92 (t, 1H, $J = 9$ Hz, 16-H), 4.13-4.24 (m, 3H, 6′-H_2, 5″-H), 4.63–4.67 (m, 2H, 3-H, 6″-H_a), 4.77 (d, 1H, $J = 13.5$ Hz, 6″-H_b), 5.14 (s, 1H, 1″-H), 5.32 (s, 1H, 6-H), 5.36 (s, 1H, 4″-H), 5.84 (d, 1H, $J = 10.2$ Hz, 3″-H), 5.93 (d, 1H, $J = 10.2$ Hz, 2″-H), 6.06 (s, 1H, 4′-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.64 (C-18), 19.28 (C-19), 20.78, 20.85, 20.95, 21.41 (acetyl-Me), 27.65, 31.28, 31.51, 31.60, 31.63 (C-21), 36.89, 37.99, 38.55, 45.07, 49.63, 55.67, 60.56, 62.66, 65.03, 67.20 (C-17), 69.09, 73.71 (C-3), 94.00, 102.78 (C-4′), 122.07 (C-6), 126.90, 129.94, 139.62 (C-5), 167.50 (C-5′), 168.41 (C-3′), 170.23 (acetate-CO), 170.52 (acetate-CO), 170.73 (acetate-CO), 207.71 (C-20) ppm. HRMS (TOF, ES^+): calcd for $C_{37}H_{50}NO_{10}$: 668.3435 [M^++H]; found, 668.3435 [M^++H].

(v) *Compound* **4e**: White crystalline solid, mp 90–92 °C. IR ($CHCl_3$): $\nu_{max} = 2930$, 1735, 1710, 1240, 760 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 0.73 (s, 3H, 18-H_3), 0.85 (m, 2H), 1.03 (s, 3H, 19-H_3), 1.10–1.25 (m, 2H), 1.33 (s, 6H, $>C(CH_3)_2$), 1.44 (s, 3H), 1.54 (s, 3H), 1.59–1.86 (complex m, 11H), 2.03 (s, 3H, acetyl-Me), 2.17 (s, 3H, 21-H_3), 2.34 (m, 2H), 3.00 (d, 1H, $J = 9$ Hz, 17-H), 3.67–3.69 (m, 2H), 3.98 (m, 2H), 4.23 (d, 1H, $J = 9.1$ Hz), 4.31 (m, 1H), 4.60 (m, 4H), 5.37 (br s, 1H, 6-H), 5.54 (d, 1H, $J = 5.1$ Hz, 1″-H), 6.05 (s, 1H, 4′-H) ppm.^{13}C NMR (75 MHz, $CDCl_3$): δ 13.68 (C-18), 19.30 (C-19), 20.88, 21.43 (acetyl CH_3), 24.45, 24.92, 25.98, 26.09, 27.68, 31.38, 31.55, 31.65, 31.72, 34.28, 36.57, 36.94, 38.02, 38.59, 45.09, 49.68, 55.67, 64.25, 66.89 (C-17), 69.08, 69.90, 70.46, 70.64, 71.10, 73.76 (C-3), 96.33, 102.46 (C-4′), 108.66 (anomeric C, sugar), 109.36 ($>C(CH_3)_2$, sugar), 122.14 (C-6), 139.62 (C-5), 167.47 (C-5′), 169.19 (C-3′), 170.55 (acetate-CO), 207.75 (C-20) ppm. HRMS (TOF, ES^+): calcd for $C_{39}H_{56}NO_{10}$: 698.3904 [M^++H]; found, 698.3882 [M^++H].

17. (a) Weinig, H. G.; Passacantilli, P.; Colapietro, M.; Piancatelli, G. *Tetrahedron Lett.* **2002**, *43*, 4613; (b) Baskaran, S.; Baskaran, C.; Trivedi, G. K. *J. Chem. Res. (S)* **1997**, 394.
18. Patrocinio, V. L.; Costa, P. R. R.; Correia, C. R. D. *Synthesis* **1994**, 474.
19. Crystallographic data for the structure in this Letter have been deposited with the Cambridge Crystallographic Data Centre as Supplementary Publication Number CCDC 674216. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(1223)336033 or e-mail: deposit@ccdc.cam.ac.uk]. Some selected crystallographic data: empirical formula $C_{39}H_{55}N\ O_{10}$, crystal system, space group: monoclinic, *P*21; some of the important bond lengths: N(1)–C(16), 1.302; C(14)–C(15), 1.335(7); O(7)–C(14), 1.354; O(7)–N(1), 1.414(4).