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Tandem Michael addition and intramolecular aldol cyclization of 1,2-dideoxy-1-nitroheptitols derived from sugars

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Abstract—The base-catalyzed Michael addition of primary nitro compounds derived from sugars with 2 equiv of methyl vinyl ketone or acrolein was followed, in situ, by an asymmetric intramolecular aldol cyclization, thus yielding 2-acyl-4-glyco-4-nitrocyclohexanol derivatives with high diastereoselectivity.

Despite of its longevity, the Michael reaction with aliphatic nitro compounds holds a crucial role in modern synthetic organic chemistry.[1] In some cases, when a primary nitroalkane reacts with 2 equiv of an electron-deficient olefin in the presence of a base, it may occur a double Michael addition, then followed by in situ intramolecular aldol cyclization of the initially formed bis-adducts. As far as we are aware, the first account on such type of process was reported by Feuer and Harmetz,[2] who described that by using sodium hydroxide as base and methyl vinyl ketone as acceptor, the formed products were 2-acyl-4-nitrocyclohexanol derivatives, an interesting class of polyfunctionalized molecules bearing three stereogenic centres. Later,[3] other authors have performed similar cyclizations by using a variety of conditions and, furthermore, some highly diastereoselective syntheses have been achieved.[4] However, due to the achirality of the starting materials, solvents and catalysts, the products were obtained in all cases as racemic mixtures. To the best of our knowledge, there had not been any studies before in which optically pure products could be produced.

Following our research work on asymmetric synthesis with sugar-derived nitro compounds,[5] we report herein our preliminary results about Michael reactions between 3,4,5,6,7-penta-*O*-acetyl-D-*galacto*- or D-*manno*-1,2-dideoxy-1-nitroheptitols **3c** or **3d**, and methyl vinyl ketone or acrolein. The starting nitrosugars **3c** and **3d** were prepared as previously described, from D-galactose or D-mannose **1a** or **1b**, respectively, by sequential treatment of each one of these with nitromethane, then acetylation of the resulting mixture of epimeric nitroheptitols and, finally, selective elimination of acetate group on C-2 from peracetylated **2c** or **2d** (Scheme 1).[6,7]

Treatment of **3c** with methyl vinyl ketone (MVK, 2.26 equiv) and 1,1,3,3-tetramethylguanidine (TMG, 2.00 equiv) in acetonitrile solvent yielded, after 30 min at room temperature, a crude oily mixture in which 7,8,9,10,11-penta-*O*-acetyl-1,3,4,5,6-pentadeoxy-5-nitro-5-(3′-oxobutyl)-D-*galacto*-2-ketoundeculose **4c**, and the nitrocyclohexanols **5c** and **6c** were clearly predominant (~90%, 44:25:31 ^{1}H NMR respective ratio[8]). Each one of these three major products was isolated as an analytically pure solid, after separation by preparative thin layer chromatography and crystallization from 96% ethanol. When the above reaction was carried out under identical conditions, but using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 2.00 equiv), instead of TMG, the crude product consisted in a mixture of (1*R*,2*S*,4*R*)- and (1*S*,2*R*,4*S*)-2-acetyl-4-(2′,3′,4′,5′,6′-penta-*O*-acetyl-1′-deoxy-D-*galacto*-hexitol-1′-yl)-1-methyl-4-nitrocyclohexanols **5c** and **6c** (44:51 ^{1}H NMR respective ratio), accompanied with a small percentage (ca. 5%) of the same minor compounds that were detected[8]

Keywords: Michael addition; Aldol cyclization; Nitro compounds; Sugars.
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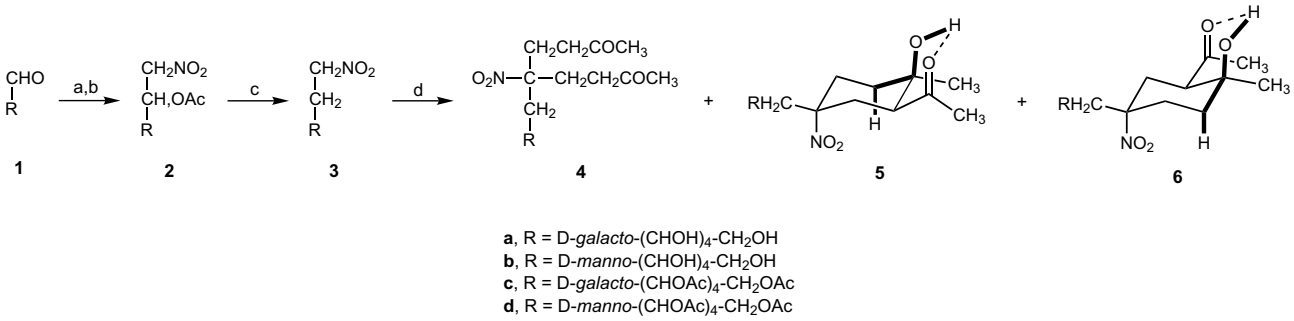


Scheme 1. Reaction conditions: (a) $MeNO_2$, NaOMe, MeOH; (b) Ac_2O, H_2SO_4; (c) $NaBH_4$, EtOH; (d) $CH_2{=}CHCOCH_3$, MeCN, TMG or DBU, rt, 30 min.

in the aforementioned reaction by using TMG. No acyclic **4c** was detected in this case. As was pointed above, the apparition of nitrocyclohexanols **5c** and **6c** can be explained through intramolecular aldol reactions from the double Michael adduct **4c**. In agreement with preceding results[4a,b] for reactions between achiral nitroalkanes and MVK, our major products are those with lower conformational energy values for substituents at cyclohexane ring,[9] and could present an intramolecular hydrogen bonding between the hydroxyl proton and the oxygen atom of acetyl group. Considering the cyclization could originate up to eight possible diastereoisomers, it is noteworthy the high degree of stereoselectivity which is achieved.

The structural characterization of the new compounds **4c**, **5c** and **6c** are supported by elemental analysis, spectral data (IR, 400 MHz ^{1}H NMR, 75 MHz ^{13}C NMR, HRMS),[10] and the X-ray single crystallographic analysis of **5c**[11] (Fig. 1). Both nitrocyclohexanols **5c** and **6c** evidenced their hydroxyl groups from bands at ca. 3510 cm^{-1}, and from D_2O exchangeable doublets at 3.82 ppm and 3.70 ppm, respectively. Irradiation of each one of these signals revealed long-range coupling (J^4 = 2.5 Hz) with its corresponding H-6ax proton, thus indicating[4a,4c] a fixed planar zig-zag arrangement that is made possible through chelation between the hydroxyl and the acetyl group (see Fig. 1); also supporting this hydrogen bonding, **5c** and **6c** showed, at rather low field (ca. 213 ppm) the ^{13}C NMR signals for their ketone carbonyls. Besides the close similarity of their spectra, the coincidence between chemical shifts for the signals of C-1′ carbons (in both nitrocyclohexanols at 42.4 ppm), strongly suggests that the side-chain at C-4 of **6c** occupies an equatorial position, as it was found for **5c**.

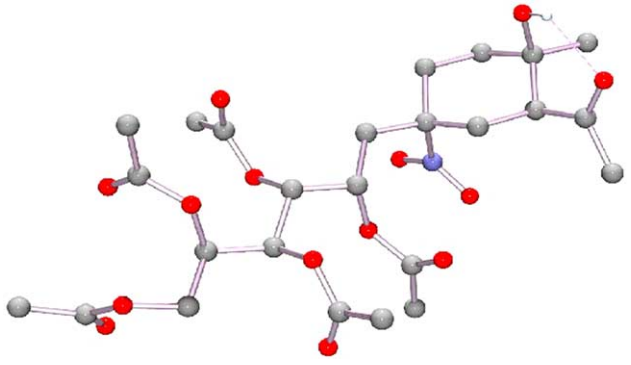


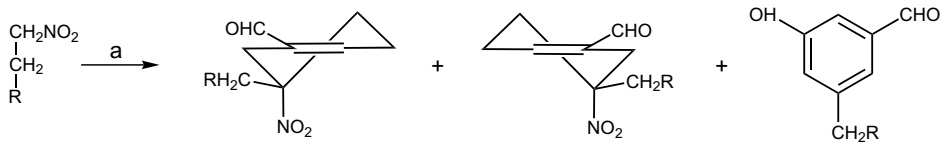
Figure 1. X-ray crystal structure of nitrocyclohexanol **5c**. Discontinuous line shows the hydrogen bonding between carbonyl oxygen at C-2 and hydroxyl proton; except for this one, all the other hydrogen atoms have been omitted for clarity.

In a similar way with the above described for **3c**, the reaction of 1,2-dideoxy-D-*manno*-nitroheptitol **3d** with MVK and DBU led, almost quantitatively, to an inseparable ~1:1 mixture of **5d** and **6d**.[12] Even though the relative configurations at C-1 and C-2 chiral centres in these new D-*manno*-nitrocyclohexanols are secure from NMR data, absolute configurations at C-1, C-2 and C-4 have been tentatively assigned, being based on comparison of the chemicals shifts which are the more different between these compounds, with those of the corresponding hydrogen or carbon atoms in their D-*galacto* analogues (see Table 1). Thus, we propose that compound **5d** should present the same (1*R*,2*S*,4*R*) configurations found by X-ray analysis from **5c**, whereas the (1*S*,2*R*,4*S*) configurations could be assigned for **6d** and **6c**.

Following the same procedure above described for the reactions with MVK, treatment of **3c** with acrolein and DBU, afforded (5*R*)- and (5*S*)-(2′,3′,4′,5′,6′-penta-*O*-acetyl-1′-deoxy-D-*galacto*-hexitol-1′-yl)-5-nitrocyclohex-1-enecarbaldehyde **7c** and **8c** as major compounds (1:1, ca. 90%),[13] accompanied with a small quantity (ca. 7%), of 5-(2′,3′,4′,5′,6′-penta-*O*-acetyl-1′-deoxy-D-*galacto*-hexitol-1′-yl)-3-hydroxy-benzenecarbaldehyde **9c** (Scheme 2), and some unidentified impurities. No evidence of the possible bis-adducts or nitrocyclohexanols was found in this case. The formation of **7c** and **8c** could be easily explained through double Michael addition, intramolecular aldol reaction and loss of water from

Table 1. Comparisons of ^{1}H and ^{13}C NMR chemical shifts of 2-acyl-4-glyco-1-methyl-4-nitrocyclohexanols **5c**, **5d**, **6c** and **6d**

Compound	O*H*	COC*H*$_3$	*H*-6ax	C-3	C-5	C-6
5c	3.82	2.29	1.11	34.2	31.4	30.4
5d	3.90	2.29	1.13	34.2	31.2	30.5
6c	3.70	2.21	1.37	34.4	34.0	27.5
6d	3.74	2.23	1.35	34.4	33.7	27.7



3 7 8 9

c, R = D-*galacto*-$(CHOAc)_4$-CH_2OAc
d, R = D-*manno*-$(CHOAc)_4$-CH_2OAc

Scheme 2. Reaction conditions: (a) CH_2=CHCHO, MeCN, DBU, rt, 30 min.

intermediate 2-formyl-4-nitrocyclohexanols; however, we have not found neither antecedents nor a reasonable mechanism to justify the formation of compounds as **9c** from nitro compounds and acrolein.[14] Parallel results were achieved for the reaction of **3d** with acrolein, being the product in this case a mixture of **7d**, **8d**[15] and **9d**.[16]

In conclusion, we have developed a simple and convenient method, based in tandem Michael addition and aldol intramolecular cyclization, for the asymmetric synthesis of 2-acyl-4-nitrocyclohexanol derivatives from nitroalkanes derived from sugars. Our further efforts will involve elaboration of this new methodology, as well as investigation of transformations of obtained new chiral products.

Acknowledgments

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8. The only noticeable presence of two small doublets (D_2O exchangeable, J = 2.5 Hz) at ca. 3.8 ppm suggests that the minor products could be another two stereoisomeric 2-acyl-1-methyl-4-glyco-4-nitrocyclohexanols.
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10. Selected data for **4c**: white solid, mp 105 °C. $[\alpha]_D^{22}$ +7.0 (*c* 0.50, $CHCl_3$). R_f 0.13 (4:1 ethyl ether:light petroleum). IR (KBr) ν_{max}: 1750 (C=O ester), 1715 (C=O ketone), 1545, 1371 (NO_2) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 2.44–1.80 (m, 10H, H-3a, H-3b, H-4a, H-4b, H-6a, H-6b, H-1′a, H-1′b, H-2′a, H-2′b), 2.18, 2.16, 2.15, 2.13, 2.08, 2.01, 2.00 (each s, each 3H, $2\times COCH_3$ $5\times OCOCH_3$). ^{13}C NMR ($CDCl_3$): δ = 205.8, 205.7 (C-2, C-3′), 91.0 (C-5), 70.4, 67.8, 67.6, 65.6 (C-7, C-8, C-9, C-10), 62.4 (C-11), 37.7, 37.4, 37.0 (C-3, C-6, C-2′), 29.9 (C-1), 29.8, 27.6 (C-4, C-1′). Selected data for **5c**: colourless solid, mp 167 °C. $[\alpha]_D^{22}$ −14.0 (*c* 0.50, $CHCl_3$). R_f 0.40 (4:1 ethyl ether:light petroleum). IR (KBr) ν_{max}: 3509 (OH), 1751 (C=O ester), 1712 (C=O ketone), 1547, 1369 (NO_2) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 3.82 (d, 1 D_2O exchangeable OH, $J_{6ax,OH}$=2.4 Hz, OH-1), 2.76 (dd, 1H, $J_{2,3ax}$ = 12.9 Hz, H-2), 2.65 (dt, 1H, $J_{3ax,3eq}$ = 14.3 Hz, $J_{3eq,5eq}$ = 2.9 Hz, H-3 eq), 2.31 (m, 1H, H-5eq), 2.29, 2.13, 2.12, 2.06, 2.00, 1.99 (each s, each 3 H, $1\times COCH_3$ $5\times OCOCH_3$), 2.06 (m, 1H, $J_{5ax,5eq}$ = 13.6 Hz, $J_{5ax,6eq}$ = 4.2 Hz, H-5ax), 1.84 (t, 1H, H-3ax), 1.61 (dt, 1H, $J_{5eq,6eq}$ = 3.1 Hz, $J_{6eq,6ax}$ = 14.4 Hz, H-6eq), 1.16 (s, 3H, CH_3-1), 1.11 (m, 1H, $J_{5eq,6ax}$ = 3.2 Hz, $J_{5ax,6ax}$ = 11.1 Hz, H-6ax). ^{13}C NMR ($CDCl_3$): δ = 212.9 (CH_3CO-2), 88.1 (C-4), 68.4 (C-1), 70.1, 67.8, 67.6, 64.9 (C-2′, C-3′, C-4′, C-5′), 62.5 (C-6′), 52.1 (C-2), 42.4 (C-1′), 34.2, 31.4, 30.5 (C-3, C-5, C-6), 31.5 (C_3CO-2), 28.3 (C_3-1). Selected data for **6c**: colourless solid, mp 153 °C. $[\alpha]_D^{22}$ +15.0 (*c* 0.30, $CHCl_3$). R_f 0.33 (4:1 ethyl ether:light petroleum). IR (KBr) ν_{max}: 3505 (OH), 1749 (C=O ester), 1710 (C=O ketone), 1545, 1371 (NO_2) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 3.70 (d, 1 D_2O exchangeable OH, $J_{6ax,OH}$ = 2.5 Hz, OH-1), 2.47 (m, 1H, $J_{2,3eq}$ = 2.9 Hz, H-3 eq), 2.46 (m, 1H, H-5eq), 2.43 (dd, 1H, $J_{2,3ax}$ = 11.9 Hz, H-2), 2.21, 2.13, 2.11, 2.06, 2.01, 1.99, (each s, each 3H, $1\times COCH_3$ $5\times OCOCH_3$), 1.95 (m, 2H, H-3ax, H-5ax), 1.67 (m, 1H, $J_{5eq,6eq}$ = 2.3 Hz, $J_{5ax,6eq}$ = 4.1 Hz, $J_{6eq,6ax}$ = 14.6 Hz, H-6eq), 1.37 (m, 1H, $J_{5ax,6ax}$ = 10.6 Hz, H-6ax), 1.16 (s, 3H, CH_3-1). ^{13}C NMR ($CDCl_3$): δ = 213.8 (CH_3CO-2), 88.3 (C-4), 68.6 (C-1), 70.2, 67.9, 67.6, 65.0 (C-2′, C-3′, C-4′, C-5′), 62.5 (C-6′), 52.2 (C-2), 42.4 (C-1′), 34.4, 34.0, 27.5 (C-3, C-5, C-6), 31.3 (C_3CO-2), 28.2 (C_3-1).
11. A single crystal of **5c**, crystallizing from ethanol by slow evaporation of the solvent, with approximate size of $0.30\times0.20\times0.07$ mm^3 was employed. The compound crystallized in the monoclinic space group $P2_1$ with a = 8.95930(10) Å, b = 11.7185(2) Å, c = 13.7627(2) Å β = 97.517(3)°, V = 1432.52(4) $Å^3$, Z = 2, D_c = 1.334 Mg/m^3, μ = 0.110 mm^{-1}. The intensities were measured on an Enraf Nonius Kappa CCD area detector diffractometer (ϕ and ω scans to fill Ewald sphere). A total of 6653 reflections were collected in the range θ 3.10–25.02°

utilizing Mo Kα radiation ($\lambda = 0.71073$ Å), and of these 4466 were independent ($R_{int} = 0.1293$). The structure was solved by direct methods with SHELXS97 (Sheldrick, G. M. *Acta Cryst.* **1990**, *A* 46, 467) and refined by full matrix least squares using SHELXL97 (Sheldrick, G. M. Program for Crystal Structure Refinement; University of Göttingen: Germany, 1997). X-ray crystallographic data have been deposited with the Cambridge Crystallographic Data Centre (CCDC 166186), which are available free of charge from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK.

12. Preparative thin layer chromatography of the reaction crude product afforded oily samples in which each one of compounds **5d** and **6d** was clearly predominant. IR (film) ν_{max}: 3497 (OH), 1749 (C=O ester), 1712 (C=O ketone), 1543, 1371 (NO_2) cm^{-1}. HRMS CI calcd for $C_{25}H_{37}NO_{14}$+H: 576.2292. Found $(M+H)^+$: 576.2287. Selected NMR data for **5d**: ^1H ($CDCl_3$): $\delta = 3.90$ (d, 1 D_2O exchangeable OH, $J_{6ax,OH} = 2.4$ Hz, OH-1), 2.73 (dd, 1H, $J_{2,3ax} = 12.9$ Hz, $J_{2,3eq} = 3.7$ Hz, H-2), 2.61 (dt, 1H, $J_{3ax,3eq} = 15.1$ Hz, $J_{3eq,5eq} = 3.0$ Hz, H-3eq), 2.50–1.90 (m, 3H, H-1′a, H-5ax, H-5eq), 2.29, 2.11, 2.10, 2.08, 2.05, 1.96 (each s, each 3H, $1 \times COCH_3 5 \times OCOCH_3$), 1.83 (t, 1H, H-3ax), 1.82 (br d, 1H, $J_{1'a,1'b} = 15.1$ Hz, H-1′b), 1.66 (dq, 1H, $J_{5eq,6eq}$=4.1 Hz, $J_{6eq,6ax} = 15.0$ Hz, H-6eq), 1.17 (s, 3H, CH_3-1), 1.13 (m, 1H, $J_{5ax,6ax} = 12.9$ Hz, H-6ax). ^{13}C ($CDCl_3$): $\delta = 214.5$ (CH_3CO-2), 88.1 (C-4), 68.2 (C-1), 70.5, 68.3, 68.2, 66.2 (C-2′, C-3′, C-4′, C-5′), 61.5 (C-6′), 52.1 (C-2), 41.3 (C-1′), 34.2, 31.2, 30.5 (C-3, C-5, C-6), 31.4 (CH_3CO-2), 28.3 (CH_3-1). Selected NMR data for **6d**: ^1H ($CDCl_3$): $\delta = 3.74$ (d, 1 D_2O exchangeable OH, $J_{6ax,OH} = 2.5$ Hz, OH-1), 2.75–1.80 (m, 7H, H-1′a, H-1′b, H-2, H-3ax, H-3eq, H-5ax, H-5eq), 2.23, 2.12, 2.07, 2.06, 2.05, 1.94 (each s, each 3H, $1 \times COCH_3$ $5 \times OCOCH_3$), 1.62 (dt, 1H, H-6eq), 1.35 (m, 1H, $J_{5ax,6ax} = 12.8$ Hz, $J_{5eq,6ax} = 3.3$ Hz, H-6ax), 1.17 (s, 3H, CH_3-1). ^{13}C ($CDCl_3$): $\delta = 213.8$ (CH_3CO-2), 88.4 (C-4), 68.3 (C-1), 70.5, 68.4, 67.5, 66.4 (C-2′, C-3′, C-4′, C-5′), 61.5 (C-6′), 52.2 (C-2), 41.2 (C-1′), 34.4, 33.7, 27.7 (C-3, C-5, C-6), 31.2 (C_3-1), 28.2 (C_3CO-2).
13. Although one of both cyclohexene nitroaldehydes **7c** and **8c** was isolated as a crystalline solid from 96% ethanol, we could not distinguish between these two structural possibilities. Selected data for **7c** (or **8c**): colourless solid, mp 156 °C. $[\alpha]_D^{22}$ −50.0 (*c* 0.50, $CHCl_3$). R_f 0.22 (1:1 ethyl acetate:hexane). IR (KBr) ν_{max}: 2738 (CH aldehyde), 1744 (C=O ester), 1682 (C=O aldehyde), 1539, 1373 (NO_2) cm^{-1}. ^1H NMR ($CDCl_3$): $\delta = 9.47$ (s, 1H, C*H*O), 6.77 (br s, 1H, H-2), 3.42 (d, 1H, $J_{6a,6b} = 18.3$ Hz, H-6a), 2.36 (d, 1H, H-6b), 2.6–1.8 (m, 6H, H-3a, H-3b, H-4a, H-4b, H-1′a, H-1′b), 2.16, 2.14, 2.07, 2.01, 1.98, (each s, each 3H, $5 \times OCOCH_3$). ^{13}C NMR ($CDCl_3$): $\delta = 192.1$ (*C*HO), 147.4 (C-2), 137.7 (C-1), 86.5 (C-5), 70.3, 67.8, 67.5, 64.9 (C-2′, C-3′, C-4′, C-5′), 62.5 (C-6′), 41.1 (C-4), 32.5 (C-1′), 28.3 (C-6), 22.9 (C-3), 20.6, 20.3 ($OCOC_3$). Anal. Calcd for $C_{23}H_{31}NO_{13}$: C, 52.17; H, 5.90; N, 2.64. Found: C, 52.45; H, 6.01; N, 2.57.
14. We observed that when the pure crystalline nitroaldehyde **7c** (or **8c**) was treated for 30 min in acetonitrile, at room temperature, with 1 equiv of DBU, the resulting product consisted in a ca. 1:1 mixture of the starting material and aromatic **9c**.
15. Selected data for **7d** (or **8d**): colourless oil, isolated by preparative thin layer chromatography; R_f 0.17 (4:1 ethyl ether:light petroleum). IR (film) ν_{max}: 2749 (CH aldehyde), 1747 (C=O ester), 1685 (C=O aldehyde), 1541, 1373 (NO_2) cm^{-1}. ^1H NMR ($CDCl_3$): $\delta = 9.43$ (s, 1H, C*H*O), 6.78 (br s, 1H, H-2), 3.30 (d, 1H, $J_{6a,6b} = 18.0$ Hz, H-6a), 2.66 (dd, 1H, $J_{1'a,1'b}$ = H-1′a), 2.34 (d, 1H, H-6b), 2.6–2.3 (m, 5H, H-3a, H-3b, H-4a, H-4b, H-1′b), 2.07, 2.05, 2.04, 1.96, 1.91, (each s, each 3H, $5 \times OCOCH_3$). ^{13}C NMR ($CDCl_3$): $\delta = 192.1$ (*C*HO), 147.6 (C-2), 137.5 (C-1), 86.5 (C-5), 70.4, 68.5, 67.7, 66.5 (C-2′, C-3′, C-4′, C-5′), 61.3 (C-6′), 39.3 (C-4), 32.3 (C-1′), 28.2 (C-6), 23.0 (C-3), 20.6, 20.5, 20.3 ($OCOC_3$). HRMS CI calcd for $C_{23}H_{31}NO_{13}$+H: 530.1873. Found $(M+H)^+$; 530.1880.
16. Selected data for **9d**: colourless oil, isolated by preparative thin layer chromatography; R_f 0.30 (4:1 ethyl ether:light petroleum). IR (film) ν_{max}: 3396 (OH), 2738 (CH aldehyde), 1747 (C=O ester), 1682 (C=O aldehyde) cm^{-1}. ^1H NMR ($CDCl_3$): $\delta = 9.87$ (s, 1H, C*H*O), 7.22, 7.17, 6.97 (each s, each 1H, H-2, H-4, H-6), 2.92 (dd, 1H, $J_{1'a,1'b} = 14.3$ Hz, H-1′a), 2.85 (dd, 1H, H-1′b), 2.09, 2.08, 2.06, 2.05, 1.90, (each s, each 3H, $5 \times OCOCH_3$). ^{13}C NMR ($CDCl_3$): $\delta = 192.1$ (*C*HO), 156.8 (C-3), 139.0, 137.8 (C-1, C-5), 123.6, 122.6 (C-4, C-6), 113.8 (C-2), 70.5, 70.4, 68.1, 67.5 (C-2′, C-3′, C-4′, C-5′), 61.7 (C-6′), 36.6 (C-1′), 20.7, 20.6 ($OCOC_3$). HRMS CI calcd for $C_{23}H_{28}O_{12}$+H; 497.1659. Found $(M+H)^+$: 497.1670.