Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 46 (2005) 31–35
Tetrahedron Letters

A novel simple pyrolytic approach towards anhydronucleosides

Alya Al-Etaibi, Saad Makhseed, Nouria A. Al-Awadi* and Yehia A. Ibrahim*

Chemistry Department, Faculty of Science, Kuwait University, PO Box 5969, Safat 13060, Kuwait

Received 8 September 2004; revised 2 November 2004; accepted 8 November 2004

Abstract—An interesting novel gas phase thermal intramolecular substitution reaction was discovered, which led to the conversion of the 2-β-D-*N*-glucosyl, 2-β-D-*N*-galactosyl and 2-β-D-*N*-ribosyl derivatives of 3-thioxo-2,3-dihydro-1,2,4-triazin-5(4*H*)-ones into their corresponding 3,2′-anhydro-β-D-mannosyl, 3,2′-anhydro-β-D-talosyl and 3,2′-anhydro-β-D-arabinosyl derivatives. The structures of these new anhydroglycosyls were determined by NMR experiments and by X-ray crystallography.

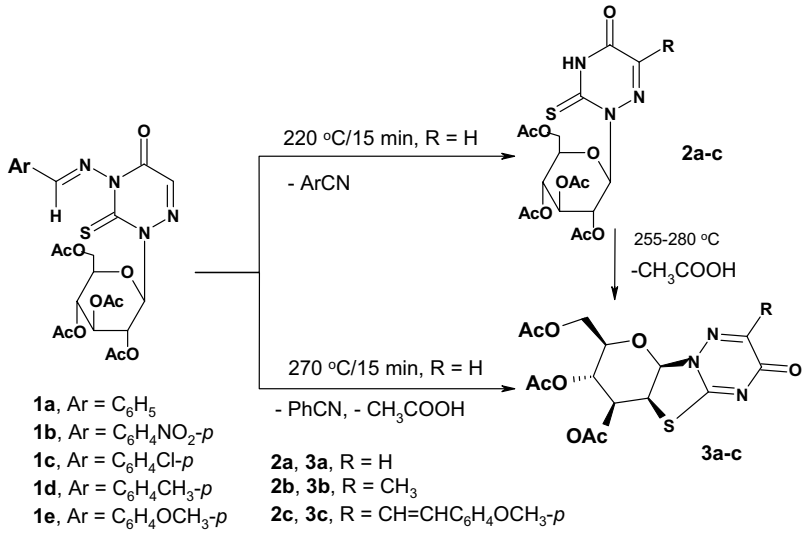
There exists considerable interest in the synthesis of 2,2′- and 2,3′-anhydronucleosides due to the possibility that these compounds can be attacked by nucleophiles at the C-2′ or C-3′ positions affording compounds with anti-AIDS activity.[1] To the best of our knowledge the first reported method for the synthesis of 2,2′-anhydronucleosides involved treating 1-3′,5′-*O*-isopropylidene-2′-*O*-methanesulfonyl-β-D-xylofuranosylthymine with sodium hydroxide in refluxing ethanol to afford the corresponding 2,2′-anhydronucleoside.[2] Recently,[1d,f,g,3–5] the action of bases ($NaHCO_3$/DMF, PhCOONa or DBU) on the the appropriate 2′-*O*-phenyloxycarbonyl or 2′-*O*-methanesulfonyl derivatives of nucleosides have been used to promote anhydrization. Additionally, heating 2′-deoxy-2′-iodonucleosides in DMF with di-*n*-butyltin oxide gave the corresponding anhydronucleosides.[6] 2,2′-Anhydrothionucleosides have also been investigated and some synthetic methods have been reported.[7a,b] Moreover, a method has been reported for the synthesis of arabino-6-aza-2-thio-2,2′-anhydrouridine.[8]

The chemistry and diverse applications of heterocyclic glycosyl derivatives have received much attention due to their pronounced biological activity. Recently[9] we reported a simple selective synthesis of 2-glycosyl derivatives of 1,2,4-triazine-3,5(2*H*,4*H*)-diones and their thiones (6-azauracil derivatives), which possess potential biological activity as cytotoxic, antiviral, enzyme inhibiting, immunosuppressive, antiphlogestic and bacteriostatic agents.[10,11] Extension of this methodology enabled a direct selective synthesis of 2-*N*-glycosyls of 1,2,4-triazole-3(2*H*)-thione, which are also of considerable biological interest.[12] Scheme 1 illustrates the crucial step in our synthetic methods, which depends on selective protection–deprotection via the arylideneamino group. In our previous work we have shown that removal of the benzonitrile leads to efficient selective synthesis of the desired 2-glycosyl derivatives (e.g., **2a**) upon pyrolysis of the arylideneamino derivatives (e.g., **1**, Scheme 1) at ca. 180–200 °C. We have also studied the kinetics of the triazole derivatives, which involves six-membered transition state concerted hetero-retro-ene elimination reactions.[13] During our kinetic studies of the pyrolysis of the 2-glucosyl-4-arylideneamino-3-thioxo-2,3-dihydro-1,2,4-triazin-4(5*H*)-ones **1** we found that heating **1** at a temperature above 220 °C led to the formation of the expected *N*-glucosyl derivative **2a** in addition to another product, which was identified as 3,2′-anhydro-2-(3,4,6-tri-*O*-acetyl-β-D-mannosyl)-3-mercapto-1,2,4-triazin-5(2*H*)-one **3a**. The yield of the latter was optimal at 270 °C. This finding represents an interesting, new, easy pyrolytic synthetic access to anhydroglycosyl derivatives. This gas phase pyrolytic approach has been extended to the synthesis of 3,2′-anhydro-β-D-talosyl and 3,2′-anhydro-β-D-arabinosyl derivatives of 3-mercapto-1,2,4-triazin-5(2*H*)-ones.

The formation of **3a** presumably involves elimination of acetic acid from **2a**. This presumption was substantiated by pyrolyzing **2a** and this indeed gave **3a** with the optimum yield (87%) obtained by heating at 270 °C for

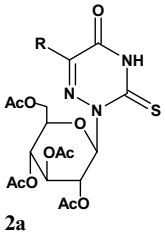
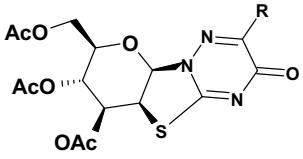
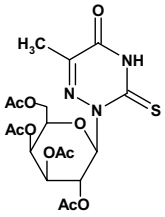
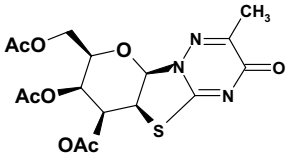
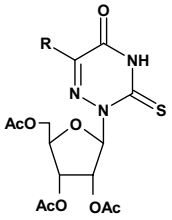
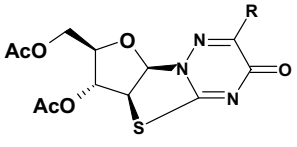
Keywords: Pyrolysis; Nucleosides; Anhydronucleosides; 1,2,4-Triazines.
* Corresponding authors. Tel.: +965 9464215; fax: +965 4816482; e-mail addresses: nouria@kuc01.kuniv.edu.kw; yehiaai@kuc01.kuniv.edu.kw

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.11.050



Scheme 1.

Table 1. Pyrolytic conditions for the reactions of **2a–c**, **6**, **9a**,**b**, yields and characteristic ^{1}H NMR data

Entry	Substrate[16]	Conditions[a] (yield %)[b]	Products[c]	^{1}H NMR δ (J Hz) substrate	Anomeric H product
					
1	**2a**	270 °C/20 min (87)	**3a**	6.69 (9.2)	5.80 (3.6)
2	**2b**	255 °C/20 min (60)	**3b**	6.66 (9.0)	5.74 (3.7)
3	**2c**	280 °C/20 min (85)	**3c**	6.67 (9.2)	5.79 (3.6)
					
4	**6**	280 °C/40 min (87)	**7**	6.64 (9.1)	5.72(4)
					
5	**9a**	260 °C/20 min (30)	**10a**	7.08 (2.0)	6.33 (7.2)
6	**9b**	275 °C/20 min (16)	**10b**	7.11 (2.6)	6.31 (7.3)

[a] The substrate (50–150 mg) was introduced into a pyrex tube (1.5 × 12 cm), cooled in liquid nitrogen, sealed under vacuum (0.06 mbar) and heated at the appropriate temperature for the time indicated in a custom-made pyrolyzer.[14]

[b] The conversion (as indicated by complete disappearance of the starting material) was 100% in each case. The yield was determined by ^{1}H NMR spectroscopy.[15]

[c] Compound **3a**, yellow crystals, mp 234 °C, LCMS: m/z = 400 (M+1); Anal. Cald for $C_{15}H_{17}N_3O_8S$ (399.4): C 45.11, H 4.29, N 10.52%. Found: C 45.31, H 4.29, N 10.62%. Compound **3b**, yellow crystals, mp 209 °C, LCMS: m/z = 414 (M+1), Anal. Cald for $C_{16}H_{19}N_3O_8S$ (413.4): C 46.49, H 4.63, N 10.16%. Found: C 46.53, H 4.71, N 10.14%. Compound **3c**, brownish crystals, mp 229 °C, LCMS: m/z = 532 (M+1), Anal. Cald for $C_{24}H_{25}N_3O_9S$ (531.5): C 54.23, H 4.74, N 7.91%. Found: C 54.46, H 5.02, N 7.91%. Compound **7**, colourless crystals, mp 271 °C, LCMS: m/z = 414 (M+1), Anal. Cald for $C_{16}H_{19}N_3O_8S$ (413.4): C 46.49, H 4.63, N 10.16%. Found: C 46.66, H 4.77, N 10.26%. Compound **10a**, brown syrup, LCMS: m/z = 328 (M+1), Anal. Cald for $C_{12}H_{13}N_3O_6S$ (327.3): C 44.03, H 4.00, N 12.84%. Found: C 44.15, H 4.20, N 12.65%. Compound **10b**, brown syrup, LCMS: m/z = 342 (M+1), Anal. Cald for $C_{13}H_{15}N_3O_6S$ (341.4): C 45.74, H 4.43, N 12.31%. Found: C 45.56, H 4.52, N 12.45%.

20 min. The procedure was extended to the synthesis of the anhydromannosyls **3b**,**c** by heating the corresponding glucosyl derivatives **2b**,**c**. Table 1 summarizes the results. The structure of the anhydromannosyl derivative **3a** was determined by MS, LCMS, ^{1}H, ^{13}C NMR, H,H-COSY, HMQC and HMBC spectral data.[18a] Thus, whereas the anomeric protons of β-*N*-glycosyls **1** and **2** appear downfield with large J values ($J \approx 9$ Hz), the anhydro products **3** have anomeric proton signals shifted upfield with small coupling constants ($J = 3.6$, 3.7 Hz) (Table 1). This upfield shift is attributed to the removal of the acetoxy group with its inductive and anisotropic effect. The change of the coupling constant depends on the dihedral angle, which is large (1,2-axial, axial) in **1**, **2** and small (1,2-axial, equatorial) in **3**. The X-ray analysis of compound **3a** (Fig. 1)[19] confirmed its structure and stereochemistry.

Extension of this methodology to other glycosyls was investigated. Thus, heating of 2-β-D-galactosyl **6** was studied at different temperatures and the optimum conversion (100%) was achieved at 280 °C (87% yield) to the corresponding 3,2′-anhydro-2-(3,4,6-tri-*O*-acetyl-β-D-talosyl)-3-mercapto-1,2,4-triazin-5(2*H*)-one **7**. Compound **6** was obtained as shown in Scheme 2. Thus, treatment of 4-amino-6-methyl-3(2*H*)-thioxo-1,2,4-triazin-5(4*H*)-one **4** with 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl bromide in DMF and triethylamine gave the corresponding 2-β-D-galactopyranosyl derivative **5**. The latter was treated with nitrous acid in acetic acid to give the desired deaminated derivative **6**.

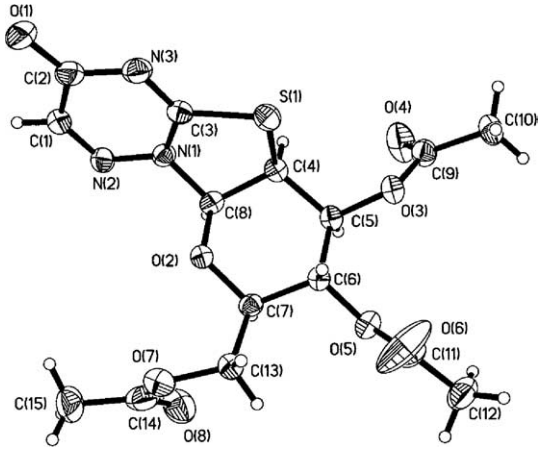


Figure 1. ORTEP drawing of compound **3a**.

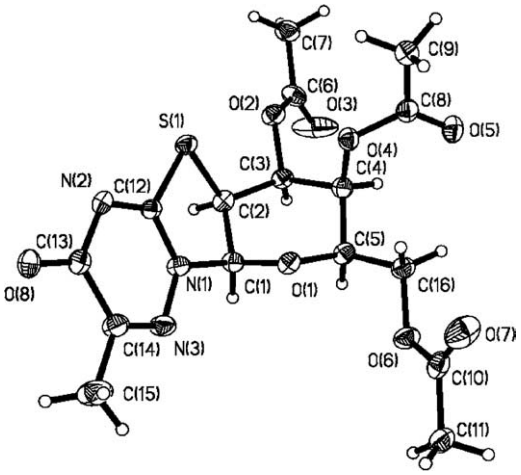
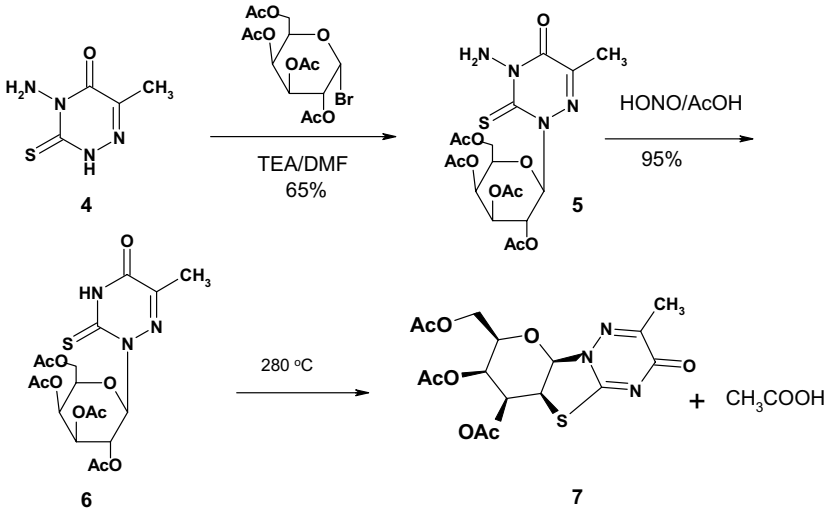


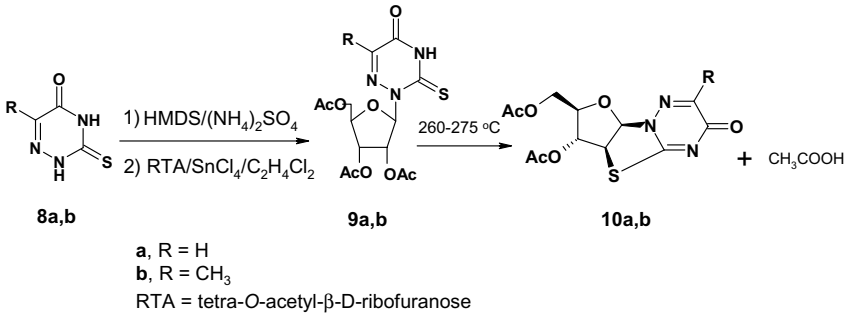
Figure 2. ORTEP drawing of compound **7**.

A full assignment of the ^{1}H and ^{13}C NMR signals of **7** was made[18b] using H,H-COSY, HMQC and HMBC spectral data, and the X-ray analysis of compound **7** (Fig. 2)[19] confirmed its structure and stereochemistry.

Application of this methodology to the synthesis of the anhydroarabinosyl derivatives from their corresponding ribosyl derivatives required 2-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-3(2*H*)-thioxo-1,2,4-triazin-5(4*H*)-ones **9a**,**b**, which were prepared as shown in Scheme 3 following the procedure described by Niedballa and Vorbrüggen[17] for the synthesis of **9a**. Thus, heating



Scheme 2.



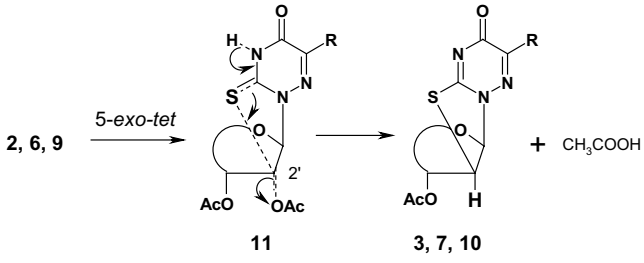
Scheme 3.

3(2*H*)-thioxo-1,2,4-triazin-5(4*H*)-ones **8a**,**b** with HMDS and a catalytic amount of ammonium sulfate gave the corresponding 3,5-*S, O*-bis(trimethylsilyl)-1,2,4-triazine derivatives, which were treated with 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose and $SnCl_4$ in 1,2-dichloroethane to give the required starting 2-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-3(2*H*)-thioxo-1,2,4-triazin-5(4*H*)-ones **9a**,**b**. Pyrolysis of **9a** and **9b** was optimized to give the corresponding 3,2′-anhydro-β-D-arabinosyl derivatives **10a**,**b**. The optimum conditions were 260 °C/20 min for complete conversion of **9a** to give a 30% isolated yield of **10a** and 270 °C/20 min for complete conversion of **9b** to give a 16% isolated yield of **10b**. The structures of **10a**,**b** were confirmed by MS and NMR data.[18c]

The proposed mechanism for the thermal conversion of these acylated glycosyls **2**, **6** and **9** into their anhydro derivatives **3**, **7** and **10** is illustrated in Scheme 4. This involves the intramolecular S_N2 (5-*exo-tet*) attack by the sulfur on C-2′ of the glycosyl moiety followed by elimination of acetate (CH_3COO^-) and H^+, which ultimately produce acetic acid.

Pyrolysis of each of **1a–e**, **2a**,**b**, **6**, **9a** were studied kinetically following our recently reported experimental procedures.[20] Each compound gave excellent reproducible first order kinetics to 98% reaction, the rates of which were independent of the initial concentration of the compounds. The kinetic data (which will be published separately) gave excellent Arrhenius plots with no deviant points, as indicated by the correlation coefficient. This is the most reliable indication of the absence surface catalyzed elimination.[21]

The present work describes the development of a new simple access for the synthesis of anhydronucleosides by means of pyrolysis of per-*O*-acylated glycosides in which the 2-acetoxy group acted as leaving group in the formation of the anhydro linkage. Therefore, the present method is expected to stimulate many interesting applications since anhydronucleosides are potential starting materials for the synthesis of modified nucleosides of potential biological activity. Further applications of this novel synthesis of anhydronucleosides and their synthetic transformation are under current investigation in our laboratory.



Scheme 4.

Acknowledgements

The support of Kuwait University received through research Grant no. SC03/00 and the facilities of Analab/SAF (Grants no. GS01/01, GS02/01, GS03/01) are gratefully acknowledged.

References and notes

1. (a) Mitsuya, H.; Yarchoan, R.; Broder, S. *Science* **1990**, *249*, 1533–1544; (b) DeClerck, E. *Design of Anti-AIDS Drugs*; Elsevier: New York, 1990; (c) Herdewijn, P.; Balzarini, J.; DeClerck, E.; Pauwels, R.; Baba, M.; Broder, S.; Vander-Heghe, H. *J. Med. Chem.* **1987**, *30*, 1270–1278; (d) Warshaw, J. A.; Watanabe, K. A. *J. Med. Chem.* **1990**, *33*, 1663–1666; (e) Huang, J.-T.; Chen, L.-C.; Wang, L.; Kim, M.-H.; Warshaw, J. A.; Armstrong, D.; Zhu, Q.-Y.; Chou, T.-C.; Watanabe, K. A.; Matulic-Adamic, J.; Su, T.-L.; Fox, J. J.; Polsky, B.; Baron, P. A.; Gold, J. W. M.; Hardy, W. D.; Zuckerman, E. *J. Med. Chem.* **1991**, *34*, 1640–1646; (f) Rama Rao, A. V.; Gurjar, M. K.; Lalitha, S. V. S. *J. Chem. Soc., Chem. Commun.* **1994**, *10*, 1255–1256; (g) Chen, B. C.; Quinlan, S. L.; Stark, D. R.; Reid, J. G.; Audia, W. H.; George, J. G.; Eisenreich, E.; Brundidge, S. P. H.; Racha, S.; Spector, R. H. *Tetrahedron Lett.* **1995**, *36*, 7957–7960; (h) Xi, Z.; Agback, P.; Plavec, J.; Sandström, A.; Chattopadhyaya, J. *Tetrahedron* **1992**, *48*, 359–370; (i) Chambert, S.; Gautier-Luneau, I.; Fontecave, M.; Decout, J. L. *J. Org. Chem.* **2000**, *65*, 249–253.
2. Fox, J. J.; Condington, J. F.; Yung, N. C.; Kaplan, L.; Lampen, J. O. *J. Am. Chem. Soc.* **1958**, *80*, 5155–5160.
3. Tolstikov, G. A.; Mustafin, A. G.; Gataullin, R. R.; Spirikhin, L. V.; Sultanova, V. S.; Abdrakhmanov, I. B. *Russ. Chem. Bull.* **1993**, 1137–1141.
4. Mustafin, A. G.; Suyundukova, M. V.; Gataullin, R. R.; Spirikhin, L. V.; Abdrakhmanov, I. B.; Tolstikov, G. A. *Izv. Akad. Nauk. Ser. Khim.* **1997**, 1420–1421.
5. Hrebabecky, H.; Holy, A. *Carbohydr. Res.* **1991**, *216*, 179–186.

6. Robles, R.; Rodrigues, C.; Izquierdo, I.; Plaza, M. T.; Mota, A.; de Cienfuegos, L. A. *Tetrahedron: Asymmetry* **2000**, *11*, 3069–3077.
7. (a) Shaw, G.; Warrener, R. N. *J. Chem. Soc.* **1959**, 50–55; (b) Ueda, T.; Shibuya, S. *Chem. Pharm. Bull.* **1970**, *18*, 1076–1078.
8. Fu, Y. L.; Parthasarathy, R.; Bobek, M. *J. Carbohydr. Nucleosides Nucleotides* **1978**, *5*, 79–87.
9. (a) Ibrahim, Y. A. *Carbohydr. Lett.* **1996**, *1*, 425–432; (b) Ibrahim, Y. A. *Carbohydr. Lett.* **1996**, *2*, 189–195; (c) Mansour, A. K.; Ibrahim, Y. A.; Khalil, N. A. S. M. *Nucleosides Nucleotides* **1999**, *18*, 2265–2283.
10. Roy Durman, P. *Analogues of Nucleic Acid Compounds*; Springer Verlag: Berlin–Heidelberg–New York, 1970; pp. 42–45.
11. Robins, R. K. *Chem. Eng. News* **1986**, *64*, 28.
12. Ibrahim, Y. A.; Abbas, A. A.; Elwahy, A. H. M. *Carbohydr. Lett.* **1999**, *3*, 331–338, and references cited therein.
13. (a) Al-Awadi, N. A.; Ibrahim, Y. A.; Kaul, K.; Dib, H. *J. Phys. Org. Chem.* **2002**, *15*, 324–329; (b) Al-Etaibi, A.; Abdallah, M.; Al-Awadi, N.; Ibrahim, Y.; Hasan, M. *J. Phys. Org. Chem.* **2004**, *17*, 49–55.
14. Al-Juwaiser, I. A.; Al-Awadi, N. A.; El-Dusouqui, O. M. E. *Can. J. Chem.* **2002**, *80*, 499–503.
15. Behbehani, H.; Ibrahim, M. R.; Ibrahim, Y. A. *Tetrahedron Lett.* **2002**, *43*, 6421–6426.
16. Compounds **1** and **2** were prepared as described.[9] Compound **6** was prepared in a similar way to that described for **2** using acetobromogalactose. Compound **9a** was prepared as reported[17] with slight modification and compound **9b** was similarly prepared.
17. Niedballa, U.; Vorbrüggen, H. *J. Org. Chem.* **1974**, *39*, 2654–3660.
18. (a) Compound **3a**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.08, 2.10, 2.13 (3s, 9H, CH_3CO), 3.87 (ddd, 1H, *J* 2.0, 4.6, 9.6, H-5′), 4.16 (dd, 1H, *J* 2.0, 12.5, H-6′), 4.35 (dd, 1H, *J* 4.6, 12.5, H-6′), 4.76 (dd, 1H, *J* 3.6, 5.7, H-2′), 5.39 (t, 1H, *J* 9.6, H-4′), 5.55 (dd, 1H, *J* 5.7, 9.6, H-3′), 5.80 (d, 1H, *J* 3.6, H-1′), 7.59 (s, 1H, H-6); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.5, 20.7, 20.8 ($3CH_3$), 46.9 (C-2′), 61.4 (C-6′), 64.9 (C-4′), 69.3 (C-3′), 72.7 (C-5′), 88.6 (C-1′), 142.7 (C-6), 159.9 (C-5), 168.8 (C-3), 169.2, 169.6, 170.6 ($3COCH_3$); (b) Compound **7**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.09, 2.12, 2.19 (3s, 9H, CH_3CO), 2.33 (s, 3H, CH_3-6), 4.07 (t, 1H, *J* 6.0, H-5′), 4.21 (m, 2H, H-6′), 4.45 (dd, 1H, *J* 4.0, 6.0, H-2′), 5.41 (d, 1H, *J* 4, H-4′), 5.56 (dd, 1H, *J* 4.0, 6.0, H-3′), 5.72 (d, 1H, *J* 4.0, H-1′); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 17.4 (CH_3-6), 20.4, 20.6 ($3CO\,CH_3$), 42.6 (C-2′), 61.0 (C-6′), 63.8 (C-4′), 66.3 (C-3′), 72.0 (C-5′), 89.0 (C-1′), 151.9 (C-6), 160.9 (C-5), 169.1 (C-3), 169.1, 170.1, 170.3 ($3COCH_3$); (c) Compound **10a**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.07, 2.19 (2s, 6H), 4.20 (dd, 1H, *J* 5.0, 12.0, H-5′), 4.33 (d, 1H, *J* 7.0, H-2′), 4.42 (dd, 1H, *J* 3.7, 12.0, H-5′), 4.58 (dd, 1H, *J* 3.4, 7.2, H-3′), 5.23 (br, 1H, H-4′), 6.33 (d, 1H, *J* 7.2, H-1′), 7.63 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.2, 21.3 ($2CH_3$), 49.8 (C-2′), 63.5 (CH_2), 81.5 (CH-4′), 84.2 (CH-3′), 96.5 (CH-1′), 142.9 (CH-6), 160.9 (C-5), 167.6 (C-3), 170.9 ($2CH_3CO$).
19. Crystal data for **3a** (ref. CCDC 253346) and **7** (ref. CCDC 253347) can be obtained on request from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EW, UK.
20. Dib, H. H.; Al-Awadi, N. A.; Ibrahim, Y. A.; El-Dusouqui, O. S. M. *Tetrahedron* **2003**, *59*, 9455–9464.
21. Taylor, R. *J. Chem. Soc., Perkin Trans.* **1983**, *2*, 809–811.