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Short Communication

Synthesis of New 1-C-(2-Furyl)- and 3-C-(2-Furyl)-hexopyranosides and 3-C-(2-Furyl)-daunorubicin Analogs

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Summary. Reaction of furan with 3,4-di-O-acetyl-*L*-rhamnal (**1**) afforded a mixture of epimeric 3-C-(2-furyl) glycals **3** and **4** and 1-C-(2-furyl)-hex-2-enopyranoses **5** and **6**. Glycals **3** and **4** were transformed to 2-deoxy-glycosides **9**–**13** and 3′-deamino-3′-C-(2-furyl)daunorubicines **15** and **16**. Hex-2-enopyranosyl **5** was *cis* hydroxylated with osmium tetroxide/N-methylmorpholine N-oxide to C-glycoside **14**.

Keywords. Daunorubicin analogs; Electrophilic substitution; Furan; Glycals; Unsaturated carbohydrates; C-Glycosides.

Synthese neuer 1-C-(2-Furyl)- und 3-C-(2-Furyl)-hexapyranoside und 3-C-(2-Furyl)-daunorubicin-Analoge (Kurze Mitt.)

Zusammenfassung. Die Reaktion von Furan mit 3,4-Di-O-acetyl-*L*-rhamnal (**1**) ergab eine Mischung von epimeren 3-C-(2-Furyl)-glycalen **3** und **4** und 1-C-(2-Furyl)-hex-2-enopyranosen **5** und **6**. Die Glycale **3** und **4** wurden zu den 2-Deoxy-glycosiden **9**–**13** und 3′-Deamino-3′-C-(2-furyl)-daunorubicinen **15** und **16** transformiert. Hex-2-enopyranosyl **5** wurde mit Osmiumtetroxid/N-methylmorpholin-N-oxid zum C-Glycosid *cis*-hydroxyliert.

The 3-C-(2-furyl)-glycals seemed to be attractive and unexplored substrates for the synthesis of 3′-modified carbohydrates. Similarly, the 1-C-(2-furyl)-hex-2-enopyranosides are interesting synthons for the synthesis of different 1-C-substituted sugars. Synthetic transformations of furan [1] and its derivatives [2, 3] are well known and indicate that synthesis of higher sugars and branch chain monosaccharides from 1-C-(2-furyl)-hex-2-enopyranosides and 3-C-(2-furyl)-glycals is possible.

The choice of 3,4-di-O-acetyl-*L*-rhamnal (**1**) as a substrate stemmed from our interest in anthracycline antibiotics and the structural requirements for their biological activity: (a) deoxygenation at C-6′ position; (b) *L*-configuration of sugar

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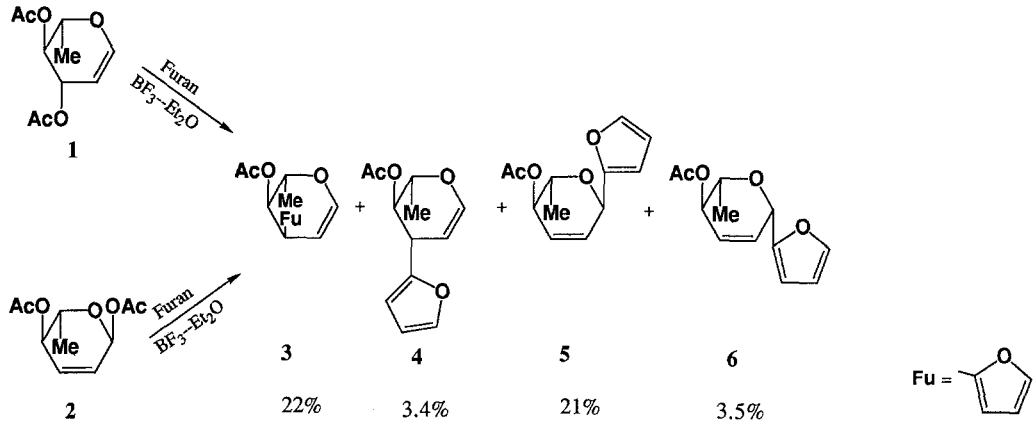
portion. The earlier studies [4, 5] of the reaction of 3,4,6-tri-O-acetyl-*D*-glucal with furan served as an example of the electrophilic substitution reaction of furan with glycals. The 3,4-di-O-acetyl-*L*-rhamnal (**1**) reaction with furan in methylene chloride in the presence of a catalytic amount of $BF_3 \cdot Et_2O$ gave a mixture of C-3 substituted glycals **3** [6] and **4** [7] and the epimeric mixture of unsaturated C-glycosides **5** and **6** in an overall yield of 50%. The proposed structures of compounds **3**–**6** were confirmed by ^1H and ^{13}C nuclear magnetic resonance (Table 1), and assigned configurations were further supported by subsequent chemical transformations.



The interesting aspect of this reaction was the product distribution. It is generally accepted that the first step of the reaction involves formation of allylic carbocation at C-3, which easily rearranges to carbocation at C-1, which is then followed by the reaction of carbocationic center with a base. Previously studied reactions of glycals (e.g., reaction with alcohols) catalyzed by Lewis acids were usually carried out in conditions that resulted in the formation of thermodynamically controlled products. On the other hand compounds **3**–**6** obtained by electrophilic substitution of furan cannot be rearranged or equilibrated; therefore their proportions might be regarded as a reflection of charge distribution in the intermediate formed in the reaction of 3,4-di-O-acetyl-*L*-rhamnal (**1**) with BF_3. Unless there is a significant difference in the rate of reaction at C-1 and C-3 [8], the equal proportion of 3-C-(2-furyl)-glycals **3** and **4** and 1-C-(2-furyl)-hex-2-enopyranosides **5** and **6** suggests similar charge distribution at position C-1 and C-3.

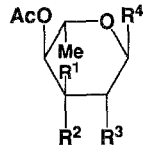
Table 1. ^{13}C-NMR (75 MHz, $CDCl_3$) data for compounds **3**–**6**

Compound	C-1	C-2	C-3	C-4	C-5	C-6	OCO*Me*	OCO*Me*
3	143.7	97.6	33.4	71.9[a]	68.8[a]	16.8	20.3	169.5
4	143.4	99.3	37.8	72.8[a]	72.1[a]	16.8	20.3	169.5
5	70.0[b]	128.1[a]	126.6[a]	67.3[b]	66.6[b]	17.4	20.5	169.9
6[c]	72.4[b]	128.8[a]	126.8[a]	70.2[b]	70.0[b]	17.9	20.5	169.9

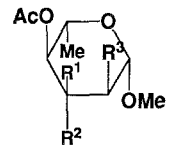
[a, b] Signals can be interchanged

[c] ^{13}C-NMR data for **6** were obtained from the spectrum containing a mixture of **5** and **6**

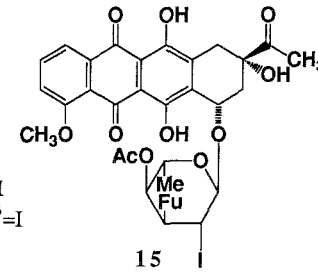
To determine whether the formation of fully equilibrated allylic carbocations takes place before electrophilic attack, we have synthesized 1,4-di-O-acetyl-α-*L*-erythro-hex-enopyranose (**2**), an isomer of **1** which has a leaving group at C-1 instead of C-3. The previously unreported **2** [9] was then reacted with furan in the same conditions as for **1**, and an analogous product distribution was noticed. This suggested that in both reactions the initial step of the reaction was formation of allylic carbocations with charge distribution similar for both substrates.



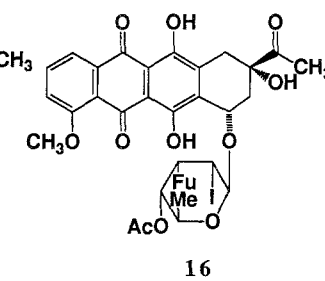
9: R^1=furyl; R^2=R^3=H; R^4=OMe
11: R^1=furyl; R^2=H; R^3=I; R^4=OMe
13: R^1=H; R^2=furyl; R^3=I; R^4=OMe
14: R^1=H; R^2=OAc; R^3=OAc; R^4=furyl



10: R^1=furyl; R^2=R^3=H
12: R^1=furyl; R^2=H; R^3=I



15



16

Glycals **3** and **4** were explored as substrates for 2-deoxy glycosides. Two different reactions were used toward synthesis of 2-deoxy and 2-deoxy-2-iodo methyl glycosides. The treatment of glycal **3** with methanol containing 2% hydrogen chloride gave the 4 : 1 mixture of α and β methyl glycosides **9** and **10**. Similarly good yields were obtained in the reaction of the mixture of glycals **3** and **4** (6 : 1) with methanol in the presence of N-iodosuccinimide (*NIS*) [10]. The methyl 2-iodo-α-*L*-altropyranoside **11** [11] was a major product and respectively smaller quantities of β-*L*-allo-(**12**) [12] and α-*L*-manno-glycoside (**13**) [13] were also isolated. The ^{1}H-NMR data indicated that compound **11** adopted the conformation $^4C_1$ (*L*) in chloroform solution [11].

The *cis*-hydroxylation of 2-(4-O-acetyl-2,3,6-trideoxy-α-*L*-erythro-hex-2-enopyranosyl)furan (**5**) with osmium tetroxide and N-methylmorpholine N-oxide (*NMMO*) [14] and subsequent acetylation of the dihydroxy intermediate gave 2-(2,3,4-tri-O-acetyl-6-deoxy-α-*L*-manno-pyranosyl)furan (**14**) [15], which confirmed the initial assignment of the configuration at C-1 for hex-2-enopyranose **5**.

Having established a pattern of reactivity for 3-C-(2-furyl)-glycals, the usefulness of these derivatives was further demonstrated by the synthesis of novel anthracycline antibiotics. The reaction of glycal **3** with daunomycinone (*DNM*) and *NIS* led to formation of two *trans* addition products, one with an α-*L*-altro configuration (**15**) [16] and the other with a β-*L*-allo configuration (**16**) [17]. Both compounds were separated and purified by column chromatography with a solution of toluene-acetone (10 : 1) as an eluent, and their configuration assignments were based on ^{1}H-NMR data. Antitumor properties of anthracycline analogs **15** and **16** are under evaluation.

References and Notes

[1] Lipshutz B. H. (1986) Chem. Rev. **86**: 795
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[3] Schmidt R. R., Effenberger G. (1987) Liebigs Ann. Chem.: 825

[4] Grynkiewicz G., BeMiller J. N. (1982) Carbohydr. Res. **108**: C1

[5] Ichikawa Y., Isoboe M., Konobe M., Goto T. (1987) Carbohydr. Res. **171**: 193

[6] ^{1}H-NMR ($CDCl_3$, 300 MHz) for **3**: δ 7.36, 6.33, 6.12 (1 H each, m, furyl), 6.48 (1 H, dd, $J_{1,2}$ = 6.0 Hz, $J_{1,3}$ = 1.7 Hz, H-1), 4.76 (1 H, dd, $J_{2,3}$ = 4.8 Hz, H-2), 3.96 (1 H, m, H-3), 4.82 (1 H, dd, $J_{3,4}$ = 5.8 Hz, H-4), 4.06 (1 H, dq, $J_{4,5}$ = 8.8 Hz, H-5), 1.98 (3 H, s, O*Ac*), 1.29 (3 H, d, $J_{5,6}$ = 6.3 Hz, H-6)

[7] ^{1}H-NMR ($CDCl_3$, 300 MHz) for **4**: δ 7.33, 6.28, 6.10 (1 H each, m, furyl), 6.44 (1 H,dd, $J_{1,2}$ = 6.1 Hz, $J_{1,3}$ = 2.5 Hz, H-1), 4.78 (1 H, dd, $J_{2,3}$ = 2.1 Hz, H-2), 3.65 (1 H, dt, H-3), 5.07 (1 H, t, $J_{3,4}$ = 8.6 Hz, H-4), 3.99 (1 H, dq, $J_{4,5}$ = 9.1 Hz, H-5), 2.05 (3 H, s, O*Ac*), 1.26 (3 H, d, $J_{5,6}$ = 6.4 Hz, H-6)

[8] Priebe W., Zamojski A. (1980) Tetrahedron **36**: 287

[9] 1,4-Di-O-acetyl-α-*L*-erythro-hexenopyranose (**2**) was prepared by heating 3,4-di-O-acetyl-*L*-rhamnal (**1**) in water at 80°C for 1 h. Extraction of water layer with chloroform, evaporation, and subsequent acetylation with acetic anhydride in pyridine followed by chromatography gave **2** in 40% yield as a distillable oil (Kugelrohr, 200°C/1 Torr). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 6.21 (1 H, s, H-1), 5.95 (1 H, d, $J_{2,3}$ = 10.2 Hz, H-2), 5.78 (1 H, dt, H-3), 5.05 (1 H, dq, $J_{4,5}$ = 9.3 Hz, H-4), 3.92 (1 H, dq, H-5), 2.07, 2.06 (3 H each, s, O*Ac*), 1.21 (3 H, d, $J_{5,6}$ = 6.2 Hz, H-6); ^{13}C-NMR (75 MHz, $CDCl_3$): 130.9, 125.7 (C-2, C-3), 88.1 (C-1), 70.0, 67.0 (C-4, C-5), 17.7 (C-6)

[10] Thiem J., Karl H., Schwentner J. (1978) Synthesis: 696

[11] ^{1}H-NMR $CDCl_3$, 300 MHz) for **11**: δ 4.96 (1 H, d, $J_{1,2}$ = 7.5 Hz, H-1), 4.92 (1 H, t, H-4), 4.42 (1 H, dd, $J_{2,3}$ = 11.5 Hz, H-2), 4.24 (1 H, qd, $J_{4,5}$ = 3.4 Hz, $J_{5,6}$ = 7.0 Hz, H-5), 3.69 (1 H, dd, $J_{3,4}$ = 3.6 Hz, H-3), 3.50 (3 H, s, O*Me*), 1.99 (3 H, s, O*Ac*), 1.42 (3 H, d, H-6); ^{13}C-NMR ($CDCl_3$, 75 MHZ): δ 169.5 (CO), 152.1, 141.5, 110.3, 108.0 (furyl), 101.7 (C-1), 72.7, 70.0 (C-4, C-5), 56.3 (O*Me*), 43.8 (C-3), 27.9 (C-2), 20.6 (O*Ac*), 16.4 (C-6)

[12] ^{1}H-NMR ($CDCl_3$, 300 MHz) for **12**: δ 5.08 (1 H, d, $J_{1,2}$ = 9.2 Hz, H-1), 4.58 (1 H, dd, $J_{3,4}$ = 5.7 Hz, $J_{4,5}$ = 10.0 Hz, H-4), 4.26 (1 H, dd, $J_{2,3}$ = 6.0 Hz, H-2), 4.26 (1 H, qd, H-5), 4.03 (1 H, t, H-3), 3.56 (3 H, s, O*Me*), 1.90 (3 H, s, O*Ac*), 1.23 (3 H, d, $J_{5,6}$ = 6.1 Hz, H-6); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 169.8 (CO), 152.1, 142.3, 111.2, 110.0 (furyl), 101.4 (C-1), 73.8, 69.5 (C-4, C-5), 57.0 (O*Me*), 44.2 (C-3), 28.7 (C-2), 20.7 (O*Ac*), 18.0 (C-6)

[13] ^{1}H-NMR ($CDCl_3$, 300 MHz) for **13**: δ 5.31 (1 H, t, H-4), 5.08 (1 H, s, H-1), 4.52 (1 H, d, $J_{2,3}$ = 3.6 Hz, H-2), 3.96 (1 H, qd, $J_{4,5}$ = 9.5 Hz, H-5), 3.47 (3 H, s, O*Me*), 3.32 (1 H, dd, $J_{3,4}$ = 10.8 Hz, H-3), 2.00 (3 H, s, O*Ac*), 1.29 (3 H, d, $J_{5,6}$ = 6.1 Hz, H-6)

[14] Van Rheenen V., Kelly R. C., Cha D. Y. (1976) Tetrahedron Lett.: 1973

[15] ^{1}H-NMR ($CDCl_3$, 300 MHz) for **14**: δ 7.53, 6.60, 6.46 (1 H each, m, furyl), 5.79 (1 H, dd, $J_{1,2}$ = 1.5 Hz, H-2), 5.44 (1 H, dd, $J_{2,3}$ = 3.4 Hz, $J_{3,4}$ = 9.9 Hz, H-3), 5.21 (1 H, t, H-4), 5.05 (1 H, s, H-1), 3.70 (1 H, qd, $J_{4,5}$ = 9.2 Hz, H-5), 2.24, 2.09, 2.08 (3 H each, s, O*Ac*), 1.29 (3 H, d, $J_{5,6}$ = 6.2 Hz, H-6); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 169.9, 169.8, 169.5 (CO), 148.7, 142.9, 110.1, 109.6 (furyl), 71.4, 70.7, 69.8, 69.1, 68.9, (C-1, C-2, C-3, C-4, C-5), 20.4, 20.3, 20.2 (O*Ac*), 17.1 (C-6)

[16] ^{1}H-NMR ($CDCl_3$, 300 MHz) for **15**: δ 5.73 (1 H, d, $J_{1,2}$ = 6.6 Hz, H-1′), 5.47 (1 H, m, H-7), 4.99 (1 H, t, H-4′), 4.61 (1 H, s, 9-OH), 4.36 (1 H, dd, $J_{2',3'}$ = 10.5 Hz, H-2′), 4.35 (1 H, m, H-5′), 4.11 (3 H, s, O*Me*), 3.66 (1 H, dd, $J_{3',4'}$ = 3.6 Hz, H-3′), 3.27 (1 H, d, H-10 e), 3.05 (1 H, d, $J_{10\,ax,\ 10e}$ = 19.0 Hz, H-10 ax), 2.47 (1 H, bd, H-8 e), 2.44 (1 H, s, H-14), 2.12 (1 H, dd, $J_{7,8ax}$ = 3.9 Hz, $J_{8\,ax,\ 8e}$ = 14.7 Hz, H-8 ax), 2.01 (3 H, s, O*Ac*), 1.49 (d, $J_{5,6}$ = 6.9 Hz, H-6′); ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 212.5 (CO), 186.9 (C-5, C-12), 169.8, (CO), 160.9 (C-4), 156.2, 155.6 (C-6, C-11), 151.8, 141.8, 110.3, 108.2 (furyl), 135.7, 135.4, 135.3, 133.3 (C-2, C-6 a, C-10 a, C-12 a), 120.8 (C-4 a), 119.8 (C-1), 111.4, 111.3 (C-5 a, C-11 a), 101.9 (C-1′), 76.4 (C-9), 72.7 (C-4′), 70.2 (C-5′), 68.6 (C-7), 56.6 (O*Me*), 43.7 (C-3′), 35.2 (C-8), 33.6 (C-10), 26.7 (C-2′), 24.9 (C-14), 20.8 (O*Ac*), 16.9 (C-6′); The ^{13}C-NMR assignments were confirmed by 2 D-NMR experiment (the CSCMBB spectra were acquired as 576 × ½ K blocks with Nicolet NT 300)

[17] ^{1}H-NMR ($CDCl_3$, 300 MHz) for **16**: δ 5.77 (1 H, d, $J_{1,2}$ = 9.4 Hz, H-1′), 5.62 (1 H, m, H-7), 4.65 (1 H, s, 9-OH), 4.47 (1 H, dd, $J_{3',4'}$ = 5.6 Hz, $J_{4',5'}$ = 10.0 Hz, H-4′), 4.24 (1 H, dd, $J_{2',3'}$ = 6.1 Hz, H-2′), 4.11 (3 H, s, O*Me*), 4.05 (1 H, t, H-3′), 3.28 (1 H, d, H-10 e), 3.11 (1 H, d, $J_{10\,ax,10\,e}$ = 19.4 Hz, H-10 ax), 2.62 (1 H, bd, H-8 e), 2.45 (1 H, s, H-14), 2.06 (1 H, dd, $J_{7,8\,ax}$ = 3.6 Hz, $J_{8\,ax,8\,e}$ = 14.9 Hz, H-8 ax), 1.87 (3 H, s, O*Ac*), 0.95 (d, $J_{5,6}$ = 6.0 Hz, H-6′)

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