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# Expedient synthesis of aminooxylated-carbohydrates for chemoselective access of glycoconjugates

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**Abstract**—Herein, we describe an efficient preparation of various biologically important carbohydrate motifs bearing an aminooxy group at the anomeric position. These nucleophilic sugar analogues represent useful intermediates for the chemoselective preparation of glycoconjugates. The key glycosylation step involves the coupling of fluoro-activated protected sugar and *N*-hydroxyphthalimide in the presence of $BF_3{\cdot}Et_2O$. Final deprotection and cleavage of the phthalimide moiety with methylhydrazine afforded new Glc-β-$ONH_2$ **3**, GalNAc-β-$ONH_2$ **9**, Glc-α-$ONH_2$ **14**, Gal-α-$ONH_2$ **17** and Man-α-$ONH_2$ **20** derivatives with good yields. Compared to the literature results, the preparation of Gal-β-$ONH_2$ **6**, GalNAc-α-$ONH_2$ **11** and Lac-β-$ONH_2$ **23** proved to be more efficient. 

Glycoproteins play important roles in biological processes, such as cell adhesion, cell differentiation or cell growth, wherein carbohydrates represent key recognition elements.[1] In order to study and elucidate the biochemical and physiopathological involvement of such constructions, extensive investigations are in progress to access synthetic glycopeptides. However, due to the multifunctionalities of peptides or sugars, the difficulty in forming the *O*-glycosidic linkage constitutes a major problem for the classical chemical approach.[2] Recently, a number of examples have demonstrated the efficiency of chemoselective ligation as an alternative strategy for building complex glycoconjugates.[3] Particularly, oxime bond formation constitutes an attractive route for conjugation of glycopeptides.[4] In this context, carbohydrate motifs glycosylated with an aminooxy function are of great interest and some of these have been described and used successfully.[4b–d] Most notably, these aminooxy analogues are also tolerated by some glycosyltransferases and can be used as substrates for the synthesis of more complex oligosaccharides through enzymatic reaction. Herein, we report a general and efficient method for the preparation of these sugar analogues based on the coupling of glycosylfluoride and *N*-hydroxyphthalimide (Fig. 1) in the presence of $BF_3{\cdot}Et_2O$ followed by adapted deprotection steps. This represents a synthetic improvement to known compounds (e.g. Gal-β-$ONH_2$ **6**,[5] GalNAc-α-$ONH_2$ **11**[4b–d] and Lac-β-$ONH_2$ **23**[4b–d]). It also provides ready access to new derivatives, such as Glc-β-$ONH_2$ **3**, GalNAc-β-$ONH_2$ **9**, Glc-α-$ONH_2$ **14**, Gal-α-$ONH_2$ **17** and Man-α-$ONH_2$ **20**. Altogether, these compounds are of great importance for installing carbohydrate-recognition motifs in a user-defined position within any scaffold molecule through oxime bond formation, thus providing ideal chemical access to complex glycoconjugates without protecting-group manipulation or coupling reagents.

To date, only few methods using *N*-hydroxysuccinimide (HOSuc) or *N*-hydroxyphthalimide (HOPht) as the nucleophilic reagent in glycosylation reactions have been described in the literature.[6] Recently, direct incor-

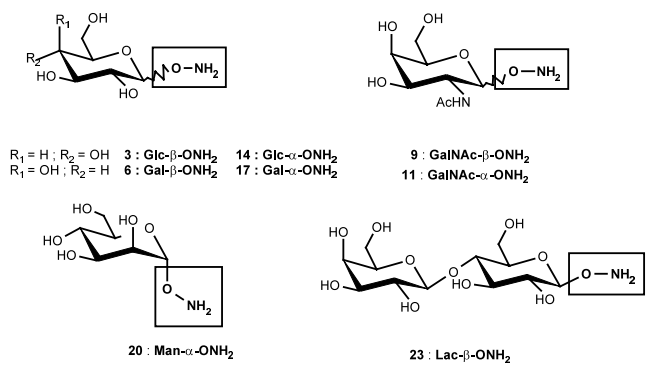


**Figure 1.** Structures of the various α- and β-aminooxy-glycosylated sugar analogues prepared.

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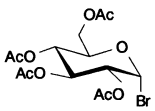
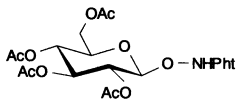
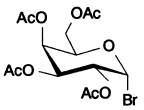
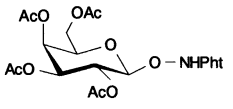
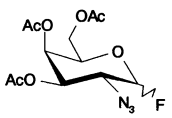
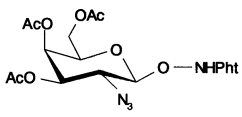
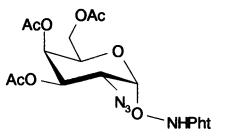
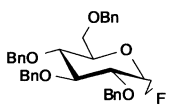
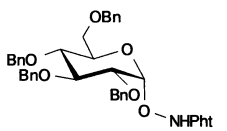
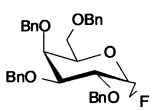
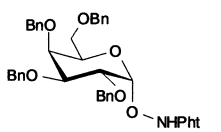
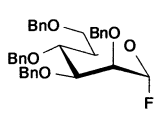
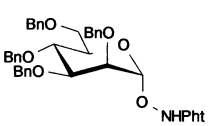
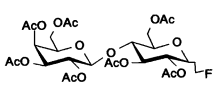
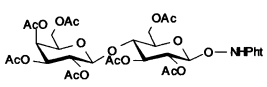
poration of *N*-hydroxysuccinimide has been described by Roy[5] starting from penta-*O*-acetylated gluco- and galactobromides **1** and **4** using phase-transfer catalysis (PTC). This glycosylation occurs at room temperature using 4 equiv. of HOSuc and 1 equiv. of tetrabutylammonium hydrogen sulphate as catalyst in a $CH_2Cl_2/Na_2CO_3$ 1 M biphasic system and was found to be stereoselective for β-gluco- and β-galactosyloxysuccinimide due to the presence of an anchimeric acetate participating group on C-2. This method was adopted by Bertozzi to prepare compound **11**[4d] bearing an α-linkage starting from 2-azido-galactosylchloride.[7]

In most cases, the *O*-Glycosyl-Suc are converted into glycosylhydroxamic esters by ring opening providing a linking arm suitable for glycoconjugate preparation.[5,6a] More occasionally, the highly efficient conversion of -OSuc or -OPht moieties into the corresponding free *O*-substituted hydroxylamines with hydrazine[8] could be used in the preparation of acceptors for chemoselective oxime bond formation.[4,9] In comparison with Roy's PTC method, we have found that the use of the more stable glycosylfluoride with a non-participating azide (Table 1, entry 3) or benzyl protecting groups (Table 1, entries 4–6) on C-2 afford both α- and β-linkages very

**Table 1.** Reaction conditions for the preparation of α- and β-aminooxy linkages

| Entry | Glycosyl donor | Glycosylation conditions, yield | Intermediate | Deprotection conditions, yield | Product |
|---|---|---|---|---|---|
| 1 |  **1** | *Pht-OH*[a], TBAHS, $CH_2Cl_2$, r.t, 4h, 71% |  **2** | $MeNHNH_2$, EtOH, r.t, 4h, Quant. | **3 : Glc-β-ONH$_2$** |
| 2 |  **4** | *Pht-OH*, TBAHS, $CH_2Cl_2$, r.t, 3h, 80% |  **5** | $MeNHNH_2$, EtOH, r.t, 4h, Quant. | **6 : Gal-β-ONH$_2$** |
| 3 |  **7** | *Pht-OH*, $BF_3$:$Et_2O$, $Et_3N$, r.t, 30 min, 50% |  **8** | a) $H_2$ Pd/C 1atm, MeOH/$Ac_2O$, r.t, 1h<br>b) $MeNHNH_2$, EtOH, r.t, 4h, 90% | **9 : GalNAc-β-ONH$_2$** |
| | | *Pht-OH*, $BF_3$:$Et_2O$, $Et_3N$, r.t, 30 min, 38% |  **10** | a) $H_2$ Pd/C 1atm, MeOH/$Ac_2O$, r.t, 1h<br>b) $MeNHNH_2$, EtOH, r.t, 4h, 90% | **11 : GalNAc-α-ONH$_2$** |
| 4 |  **12** | *Pht-OH*, $BF_3$:$Et_2O$, $Et_3N$, r.t, 30 min, 60% (+ 30% β) |  **13** | a) $H_2$ Pd/C 1atm, MeOH, r.t, 1h<br>b) $MeNHNH_2$, EtOH, r.t, 4h, 55% | **14 : Glc-α-ONH$_2$** |
| 5 |  **15** | *Pht-OH*, $BF_3$:$Et_2O$, $Et_3N$, r.t, 30 min, 60% (+ 30% β) |  **16** | a) $H_2$ Pd/C 1atm, MeOH, r.t, 1h<br>b) $MeNHNH_2$, EtOH, r.t, 4h, 55% | **17 : Gal-α-ONH$_2$** |
| 6 |  **18** | *Pht-OH*, $BF_3$:$Et_2O$, $Et_3N$, r.t, 30 min, 75% |  **19** | a) $H_2$ Pd/C 1atm, MeOH, r.t, 1h<br>b) $MeNHNH_2$, EtOH, r.t, 4h, 44% | **20 : Man-α-ONH$_2$** |
| 7 |  **21** | *Pht-OH*, $BF_3$:$Et_2O$, $Et_3N$, r.t, 30 min, 70% |  **22** | $MeNHNH_2$, EtOH, r.t, 4h, Quant. | **23 : Lac-β-ONH$_2$** |

[a] Pht-OH denotes N-hydroxyphtalimide.

efficiently with $BF_3{\cdot}Et_2O$ as a promoter. On the other hand, our experiments have shown that *N*-hydroxyphthalimide is much more reactive for glycosylation and more easily cleaved than the *N*-hydroxysuccinimide moiety. In addition, we demonstrated the efficiency of our method through several examples, such as the Glc, Gal, GalNAc and Man series, as well as for functionalisation of more complex oligosaccharides, such as lactose (Table 1, entry 7).

In entries 1 and 2 of Table 1, we report the stereoselective β-glycosylation with *N*-hydroxyphthalimide from per-*O*-acetate bromide derivatives **1** and **4** using PTC in very good yield (71–80%). However, for compound **10**, this method proved to be non-reproducible in our hands and also instability observed for 3,4,6-tri-*O*-acetyl-2-azido-2-deoxy-α-D-galactosylchloride during the PTC-coupling reaction led to a much lower yield (22%, not shown). Therefore, we were interested in fluoride activation of the anomeric position as a more direct and general approach.

Glycosylfluorides **7**, **12**, **15**, **18** and **21** were prepared very easily using diethylaminosulfur trifluoride (DAST) as a fluorine donor in THF.[10] Convenient denitration (Table 1, entry 3) of 3,4,6-tri-*O*-acetyl-2-azido-2-deoxy-α-D-galactopyranosyl nitrate was achieved with sodium nitrite in aqueous dioxane at 80°C.[11] Selective deacetylation of per-*O*-acetyl lactose (Table 1, entry 7) at the anomeric centre was realised using an ethylenediamine/acetic acid mixture in THF at room temperature.[12]

Glycosylfluorides represent very reactive donors in glycosylation reactions with HOPht using $BF_3{\cdot}Et_2O$[13] as a promoter. Typically, stoichiometric amounts of *N*-hydroxyphthalimide and triethylamine were reacted in the presence of glycosylfluoride and the promoter (5 equiv.) in $CH_2Cl_2$ at room temperature.[14] The reaction is usually fast and complete within 15–30 min (Table 1). After classical work-up, separation of the α and β anomers (Table 1, entries 3–5) is easily performed by silica-gel chromatography.

First, we have obtained the two anomers **8** and **10** (50 and 38%, respectively) from fluoride compound **7**. The α stereochemistry of compound **10** was confirmed by crystallographic structure.[15] Starting from compounds **12** and **15** (Table 1, entries 4 and 5), we were able to prepare 90% of α/β anomer mixture (ratio 2/1) to give gluco- and galacto-derivatives, **13** and **16**, respectively. Moreover, the glycosylation of tetrabenzylmannofluoride derivative **18** (Table 1, entry 6) by the same method stereoselectively afforded the mannosyl-α-*N*-oxyphthalimide **19** with high yield (75%). Finally, we have also demonstrated that this method is suitable for the easy transformation of more complex oligosaccharides. In Table 1, entry 7, we have shown the stereoselective β-incorporation of PhtOH starting from lactose fluoride derivative **21** with good yield (70%) according to the same procedure.

The final acetate deprotection and cleavage of the phthalimide group was realised using a large excess of methylhydrazine in ethanol at room temperature[16] for compounds **2**, **5** and **22**. Pure and ninhydrine-active free aminooxy derivatives **3**, **6** and **23** were obtained as white powders after purification and lyophilisation. It is noteworthy that previous attempts to access mannose derivative **20** using acetate protection failed completely probably because of an elimination reaction occurring during the final deprotection. On the other hand, deprotection of benzyl groups for compounds **13**, **16** and **19** by palladium hydrogenation in methanol and reductive acetylation of the azide moiety for derivatives **8** and **10** by palladium hydrogenation in methanol/acetic anhydride at room temperature is more tricky due to the fragility of the N–O bond under reductive conditions. According to NMR and X-ray structural analysis (not shown[15]), we have demonstrated, in the case of compound **10**, that reduced and acetylated compounds at the anomeric position are mainly obtained after several hours under these conditions. Consequently, the evolution of the reaction of benzyl deprotection or azide reduction should be carefully controlled with a short reaction time to avoid any risk of N–O bond breaking.[17] Further, phthalimide cleavage was performed following the procedure described for **2**, **5** and **22** to give compounds **14**, **17**, **11**, **9** and **20**. All these compounds, and previously unknown derivatives **3**, **14**, **17**, **9** and **20**, were fully characterised by NMR and MS analysis.[18]

In conclusion, we have described a convenient preparation of various aminooxy sugars analogues **3**, **9**, **14**, **17**, **20** and **23** using glycosylfluoride as a donor and $BF_3{\cdot}Et_2O$ as a promoter. α- or β-Analogues of the corresponding sugar are obtained, which is important for assessing the influence of the anomeric configuration in biological processes. Compared to the literature,[4b–d,5] compounds **6** and **11** were obtained more efficiently and easily using *N*-hydroxyphthalimide. A further advantage of this approach that it provides carbohydrate-based compounds readily accessible to a broader community for the construction of various glycoconjugates. These compounds represent the structural base for most of the carbohydrate-recognition motifs found in glycoconjugates. Therefore, their manipulation for chemoselective preparation of the corresponding glycoconjugates should provide useful tools for glycobiology, as well as new therapeutics. Work in this direction is currently underway in our laboratory and will be reported in the near future.

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10. (a) Rosenbrook, Jr., Wm.; Riley, D. A.; Lartey, P. A. *Tetrahedron Lett.* **1985**, *26*, 3–4; (b) Posner, G. J.; Haines, S. R. *Tetrahedron Lett.* **1985**, *26*, 5–8.
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14. A typical procedure follows for mannose analogue **19**: To a stirring solution of compound **18** (1.27 g, 2.33 mmol), *N*-hydroxyphthalimide (0.38 g, 2.33 mmol) and triethylamine (325 μL, 2.33 mmol) in $CH_2Cl_2$ (20 mL) was added $BF_3{\cdot}Et_2O$ (1.47 mL, 11.6 mmol) and the reaction was stirred at room temperature for 15 min. After classical work-up, the residue was purified by silica-gel chromatography (AcOEt/Hexane, 3/7) to give pure compound **19** (1.20 g, 75%). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ ppm 7.74–7.63 (m, 4H, $H_{(ar.)Pht}$), 7.37–7.10 (m, 20H, $H_{(ar.)Bn}$), 5.48 (d, 1H, $^3J_{1,2}=1.8$ Hz, H-1), 4.81–4.33 (m, 8H, $4CH_2$), 4.50 (m, 1H, H-5), 4.13–4.03 (m, 2H, H-2, H-4), 3.91 (dd, 1H, $^3J_{2,3}=3.2$ Hz, $^3J_{3,4}=8.9$ Hz, H-3), 3.81 (dd, 1H, $^3J_{5,6a}=3.7$ Hz, $^2J_{6a,6b}=11.2$ Hz, H-6a), 3.61 (dd, 1H, $^3J_{5,6b}=1.9$ Hz, H-6b); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ ppm 163.6 (C=O), 138.9 ($C_{(ar.)Bn}$), 138.8 ($C_{(ar.)Bn}$), 138.7 ($C_{(ar.)Bn}$), 138.2 ($C_{(ar.)Bn}$), 134.9 ($CH_{(ar.)Pht}$), 128.8 ($C_{(ar.)Pht}$), 128.7 ($CH_{(ar.)Bn}$), 128.7 ($CH_{(ar.)Bn}$), 128.6 ($CH_{(ar.)Bn}$), 128.5 ($CH_{(ar.)Bn}$), 128.3 ($CH_{(ar.)Bn}$), 128.2 ($CH_{(ar.)bn}$), 128.0 ($CH_{(ar.)Bn}$), 128.0 ($CH_{(ar.)Bn}$), 127.9 ($CH_{(ar.)Bn}$), 127.8 ($CH_{(ar.)Bn}$), 123.9 ($CH_{(ar.)Pht}$), 104.1(C-1), 79.7 (C-3), 75.3 ($CH_2$), 74.6, 74.1, 73.6 ($CH_2$), 73.5, 73.3 ($CH_2$), 72.7 ($CH_2$), 69.0 (C-6).
15. Crystallographic data (excluding structural factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 167839 and 167794. Copies of the data can be obtained, free of charge, on application to: The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk]
16. The use of methylhydrazine instead of hydrazine was found to be more efficient and facilitated the subsequent purification of the final compounds.
17. A mixture of compound **19** (2.23 g, 3.25 mmol) and Pd/C 10% (0.14 g, 1.3 mmol) in methanol (20 mL) was stirred at room temperature under an atmosphere of hydrogen for 2 h. The catalyst was removed by filtration and the solvent was evaporated in vacuo. The residue was taken up with water, the aqueous layer was extracted several times with ethyl acetate and it was then lyophilised. The residual white powder was diluted in an ethanol/methylhydrazine (1/1) mixture (10 mL) and the solution was stirred overnight at room temperature. Chromatographic purification ($CH_2Cl_2$/EtOH 10/1→1/1) afforded pure compound **20** (270 mg, 44%).
18. All these compounds were identified by one- and two-dimensional NMR techniques ($^1$H, $^{13}$C, GCOSY, GHMQC) as well as mass spectrometry (DCI $NH_3$/isobutane). Compound **3**: $^1$H NMR (300 MHz, $D_2O$) $\delta$ 4.59 (d, 1H, $^3J_{1,2}=8.3$ Hz, H-1), 3.96 (dd, 1H, $^3J_{5,6a}=2.3$ Hz, $^2J_{6a,6b}=12.2$ Hz, H-6a), 3.76 (dd, 1H, $^3J_{5,6b}=5.7$ Hz, H-6b), 3.57–3.30 (m, 4H, H-2, H-3, H-4, H-5); $^{13}$C NMR (75 MHz, $D_2O$) $\delta$ 105.4 (C-1), 76.2, 76.1 (C-3, C-4), 72.0 (C-2), 69.9 (C-5), 61.1 (C-6); $M_{calcd}=195.2$; $m/z=196.0$ $[M+H]^+$, 212.9 $[M+NH_4]^+$, 180.1 $[M-ONH_2]^+$, 147.2 $[M-OH-ONH_2]^+$, 132.1 $[M-2OH-ONH_2]^+$, 115.2 $[M-3OH-ONH_2]^+$. Compound **6**: $^1$H NMR (300 MHz, $D_2O$) $\delta$ 4.54 (d, 1H, $^3J_{1,2}=8.1$ Hz, H-1), 3.94 (bd, 1H, $^3J_{3,4}=3.4$ Hz, H-4), 3.87–3.73 (m, 3H, H-5, H-6a, H-6b), 3.69 (dd, 1H, $^3J_{2,3}=9.8$ Hz, H-3), 3.55 (dd, 1H, H-2); $^{13}$C NMR (75 MHz, $D_2O$) $\delta$ 105.9 (C-1), 75.5 (C-3), 73.2 (C-2), 69.7 (C-4), 69.0 (C-5), 61.4 (C-6); $M_{calcd}=195.2$; $m/z=196.0$ $[M+H]^+$, 212.9 $[M+NH_4]^+$, 180.1 $[M-ONH_2]^+$, 147.2 $[M-OH-ONH_2]^+$, 132.1 $[M-2OH-ONH_2]^+$, 115.2 $[M-3OH-ONH_2]^+$. Compound **9**: $^1$H NMR (300 MHz, $D_2O$) $\delta$ 4.57 (d, 1H, $^3J_{1,2}=8.7$ Hz, H-1), 3.98–3.89 (m, 2H, H-4, H-2), 3.86–3.70 (m, 4H, H-3, H-5, H-6a, H-6b), 2.07 (s, 3H, $HNCOCH_3$); $^{13}$C NMR (75 MHz, $D_2O$) $\delta$ 175.3 ($HNCOCH_3$), 104.5 (C-1), 75.5, 71.4 (C-3, C-5), 68.2 (C-4), 61.4 (C-6), 51.1 (C-2), 22.5 ($HNCOCH_3$); $M_{calcd}=357.3$; $m/z=237.0$ $[M+H]^+$, 204.1 $[M-ONH_2]^+$. Compound **14**: $^1$H NMR (300 MHz, $D_2O$) $\delta$ 5.06 (d, 1H, $^3J_{1,2}=3.3$ Hz, H-1), 3.94 (dd, 1H, $^3J_{5,6a}=1.9$ Hz, $^2J_{6a,6b}=12.2$ Hz, H-6a), 3.85 (dd, 1H, $^3J_{5,6b}=4.7$ Hz, H-6b), 3.80–3.77 (m, 1H, H-5), 3.72–3.62 (m, 2H, H-2, H-3), 3.48 (t, 1H, $^3J_{3,4}=^3J_{4,5}=9.0$ Hz, H-4); $^{13}$C NMR (75 MHz, $D_2O$) $\delta$ 102.0 (C-1), 73.2, 72.1, 71.2, 69.8 (C-2, C-3, C-4, C-5), 60.7 (C-6); $M_{calcd}=195.2$; $m/z=196.0$ $[M+H]^+$, 212.9 $[M+NH_4]^+$, 180.1 $[M-ONH_2]^+$. Compound **17**: $^1$H NMR (300 MHz, $D_2O$) $\delta$ 5.11 (d, 1H, $^3J_{1,2}=3.9$ Hz, H-1), 4.07–4.00 (m, 2H, H-6a, H-6b), 3.93 (dd, 1H, $^3J_{2,3}=10.4$ Hz, H-2), 3.89–3.78 (m, 3H, H-3, H-4, H-5); $^{13}$C NMR (75 MHz, $D_2O$) $\delta$ 102.0 (C-1), 71.4, 69.7, 69.6, 68.2 (C-2, C-3, C-4, C-5), 61.5 (C-6); $M_{calcd}=195.2$; $m/z=196.1$ $[M+H]^+$, 212.9 $[M+NH_4]^+$. Compound **20**: $^1$H NMR (300 MHz, $D_2O$) $\delta$ 5.00 (d, 1H, $^3J_{1,2}=1.7$ Hz, H-1), 4.03 (dd, 1H, $^3J_{2,3}=2.8$ Hz, H-2), 3.97 (dd, 1H, $^3J_{5,6a}=1.3$ Hz, $^2J_{6a,6b}=12.3$ Hz, H-6a), 3.88 (dd, $^3J_{5,6b}=3.7$ Hz, H-6b), 3.76–3.72 (m, 3H, H-3, H-4, H-5); $^{13}$C NMR (75 MHz, $D_2O$) $\delta$ 103.8 (C-1), 73.4, 71.2, 69.4 (C-2), 67.2, 61.4 (C-6); $M_{calcd}=195.2$; $m/z=196.1$ $[M+H]^+$, 212.8 $[M+NH_4]^+$. For NMR data of **11** and **23**, see Ref. 4d.