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Chemoselective deprotection and functional group interconversion of ring-fused 2*N*,3*O*-oxazolidinones of *N*-acetyl-D-glucosamine

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Abstract—These studies describe the chemoselective deprotection of *trans*-fused 2*N*,3*O*-oxazolidinone derivatives of *N*-acetyl-β-D-glucosamine. Selective opening of the oxazolidinone ring or *N*-deacetylation without ring opening is demonstrated. Certain amines are shown to efficiently afford C-2 ureido sugars under mild conditions. This work demonstrates the high degree of chemoselective manipulation possible with ring-fused 2*N*,3*O*-oxazolidinone derivatives of *N*-acetyl-D-glucosamine.

N-Substituted 2-amino-2-deoxy-D-hexopyranoside residues are important structural and functional components of numerous bioactive glycoconjugates. Protection and/or latentiation strategies for the 2-amino moiety of D-glucosaminyl donors play a critical role in stereoselective glycosylation reactions and post-glycosylation chemical manipulation to obtain target glycosides.[1] We previously reported ring-fused 2*N*,3*O*-oxazolidinone derivatives of phenyl 2-amino-2-deoxy-1-thio-D-glucopyranoside as glycosyl donors for the stereoselective synthesis of α-linked glycosides of D-glucosamine.[2,3] Oxazolidinone protection of the 2-*N* and 3-*O* positions facilitates differentiation of the 3-hydroxyl moiety from other hydroxyl groups. Hydrolytic ring opening (deprotection) of *N*-unsubstituted oxazolidinones (**1**) under mild conditions affords 2-amino products (**2**, Fig. 1).[2] *N*-acetylglucosamine derivatives have been obtained through selective *N*-acetylation following hydrolysis of 2*N*,3*O*-oxazolidinones (**3**, Fig. 1).[4] Treatment of the *N*-unsubstituted ring-fused oxazolidinones with alcohols in the presence of base affords ring-opening deprotection of the C-3 hydroxyl group with concomitant generation of the C-2 carbamate (**4**, Fig. 1).[2]

Certain inherent limitations of *N*-unsubstituted 2*N*,3*O*-oxazolidinone protected D-glucosaminyl donors have been overcome through acetyl substitution the oxazolidinone nitrogen.[5] Substitution of the oxazolidinone nitrogen precludes *N*-glycosylation and blocks reaction with donor activating reagents. Moreover, thioglycosides of these donors can be activated using mild activating systems. Unlike *N*-unsubstituted ring-fused oxazolidinones (**1**, Fig. 1), we initially found hydrolysis of ring-fused 2*N*,3*O*-oxazolidinones of *N*-acetyl-D-glucosamine (**5**, Fig. 1) to give product mixtures. These mixtures resulted from competition between *N*-deacetylation, *N*-deacetylation followed by oxazolidinone opening, and oxazolidinone opening with retention of the *N*-acetyl substituent (**1**, **2**, **3**, Fig. 1). Here we report studies investigating the chemoselective deprotection of 2*N*,3*O*-oxazolidinone protected *N*-acetyl-D-glucosamine and the selective formation of 2-carbamoyl and 2-ureido derivatives.

Chiral monocyclic *N*-acyl oxazolidinones are widely employed in asymmetric Aldol reactions. We initially envisioned established methods for selective *N*-deacylation of these monocyclic oxazolidinones might be applicable to selective *N*-deacetylation of the *trans*-fused oxazolidinones here. Initial attempts to selectively cleave the *N*-acetyl substituent from 4,6-di-*O*-acetyl protected derivatives of glycosides **5** afforded complex reaction mixtures. While *O*-acetyl cleavage was anticipated, mixtures obtained using various reaction conditions clearly demonstrated the carbonyl of these *trans*-fused *N*-acetyl substituted oxazolidinones are highly labile compared to monocyclic oxazolidinones. High torsion strain of

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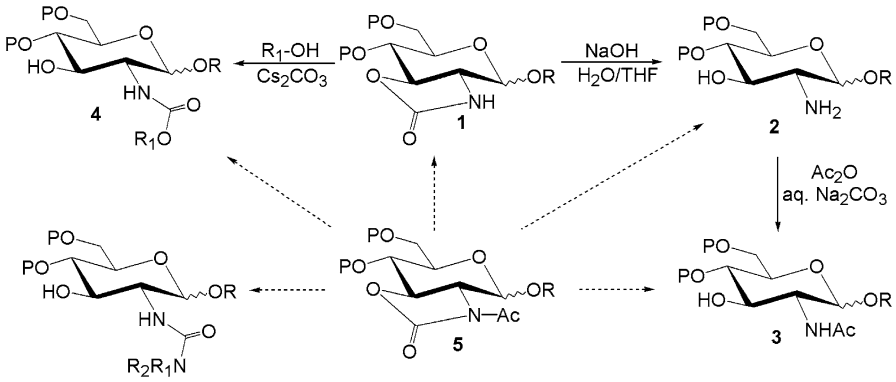


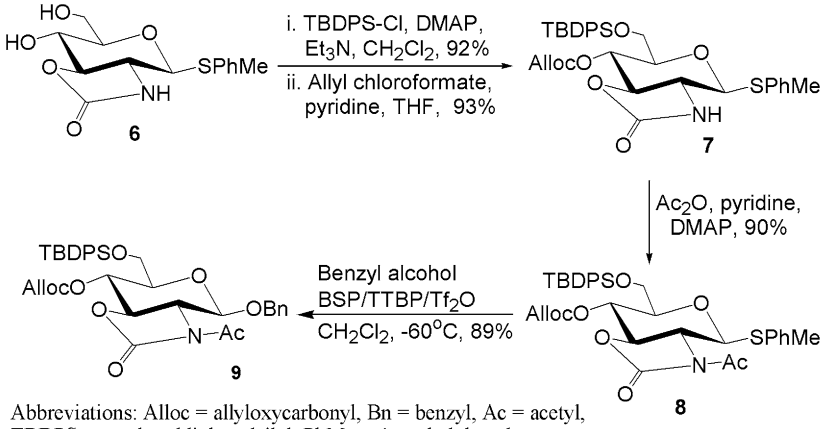
Figure 1. Known interconversions of *N*-unsubstituted 2*N*,3*O*-oxazolidinone protected D-glucosamine derivatives (solid arrows). Chemoselective manipulation of 2*N*,3*O*-oxazolidinone protected *N*-acetyl D-glucosamine derivatives investigated here (dashed arrows).

the *trans*-fused oxazolidinone resulted in competing reactivity of the *N*-acetyl carbonyl and the internal carbonyl of the oxazolidinone ring.

Benzyl glycoside **9** was prepared to facilitate studies toward identifying reagents and reaction conditions to selectively cleave the *N*-acetyl substituent and selectively open the oxazolidinone ring (Scheme 1). Synthesis of **9** began with 2*N*,3*O*-oxazolidinone protected thioglycoside **6**, which was prepared using procedures as previously reported.[2,5] Selective protection of the C-6 hydroxyl group as the silyl ether,[6] followed by allyloxycarbonyl protection of the C-4 hydroxyl group,[7] afforded **7**. Subsequent acetylation afforded *N*-acetyl donor **8**.[5] Glycosidation of **8** with benzyl alcohol employing 1-benzylsulfinylpiperidine (BSP) and trifluoromethanesulfonic anhydride (Tf_2O) as donor activating agents proceeded smoothly to afford **9** in high yield and stereoselectivity.[8]

We first investigated methods to hydrolyze oxazolidinone **9** by varying temperature and concentration of inorganic base. As shown at the top of Table 1, there are two discrete pathways for hydrolysis. Hydrolytic conditions that selectively remove the *N*-acetyl group first will afford *N*-unsubstituted oxazolidinone **10** (Pathway A). Further hydrolysis of oxazolidinone **10** then affords ring opening and yields complete deprotection of the 3-hydroxyl and 2-amine groups.[3] In contrast, hydrolytic conditions that selectively open the oxazolidinone ring first will afford the 2-*N*-acetyl sugar (Pathway B), which is stable to further hydrolysis and thus directly affords *N*-acetyl glucosamine derivatives. Simple hydrolysis of **9** employing excess NaOH at 0 °C, as well as many other hydroxide derivatives, afforded a mixture of products **11** and **12** (Table 1, entry 1).[9] Under these conditions hydroxide attack is non-specific. Attack on the internal carbonyl of the oxazolidinone ring is slightly favored. Selective *N*-acetylation of reaction mixtures containing **11** and **12** provided **12** in excellent overall yield. Thus non-specific hydrolysis followed by selective *N*-acetylation of the reaction mixture does provide an effective two-step route to the *N*-acetyl product.

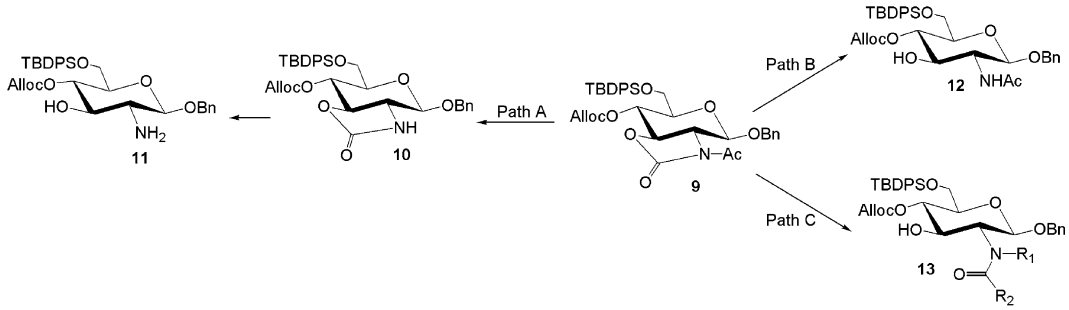
Crich and Vinod recently reported selective ring-opening cleavage of *N*-acetyl substituted 2*N*,3*O*-oxazolidinone protected glucosamine derivatives employing barium hydroxide in hot ethanol to give the *N*-acetyl-D-glucosamine products.[10] However, in our system these conditions afforded a product mixture (competing pathways A and B). Extensive screening of reaction conditions varying time, temperature, and concentration of inorganic bases revealed temperature and concentration of bases as important, if not more important, than the



Abbreviations: Alloc = allyloxycarbonyl, Bn = benzyl, Ac = acetyl, TBDPS = *tert*-butyldiphenylsilyl, PhMe = 4-methylphenyl

Scheme 1.

Table 1. Observed reaction pathways during hydrolysis and methanolysis



Entry	Substrate	Reaction conditions	Product(s), yield	Reaction pathway
1	**9**	1 N NaOH (excess), THF, 0 °C	**11**:**12**[a] = 2:3, 90% .	Pathways A ≈ B
2	**9**	1 N NaOH (4–8 equiv), THF, 0 °C	**10**:**12**[a] = 3:1, 90%	Pathway A > B
3	**9**	$LiBH_4$, THF, 0 °C	**10**:**12** = 4:1, 77%	Pathway A > B
4	**9**	$LiOH/H_2O_2$, THF/H_2O (3:1), −40 to 0 °C	**10**:**12** > 9:1, 95%, Pathway A	Pathway A ≫ B
5	**9**	LiCl–LiOH, ethanol/H_2O (3:1), rt	**12**,[a] 80%	Pathway B
6	**9**	NaOMe (1 equiv), toluene, −40 °C	**13a**, R_1 = Ac, R_2 = OCH_3, 90%,	Pathway C
7	**9**	Cs_2CO_3 (catalytic), CH_3OH, rt	**13a**, R_1 = Ac, R_2 = OCH_3, 95%	Pathway C
8	**9**	NaOMe (excess), CH_3OH, rt	**13b**,[a] R_1 = H, R_2 = OCH_3, 85%	Pathway C

[a] Complete loss of Alloc occurred under these reaction conditions.

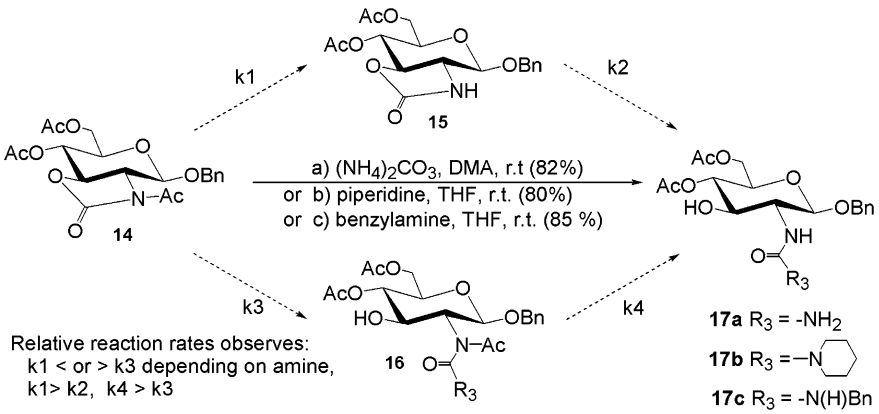
hydroxide counter ion present for controlling hydrolysis. Ultimately, we found that increasing the rate of *N*-deacetylation over cleavage of the oxazolidinone ring (Pathway A) is favored under mild hydrolysis conditions. For example, selective removal of the *N*-acetyl group was favored over cleavage of the oxazolidinone ring by employing slow addition of a 1 N sodium hydroxide solution (4–8 equiv total) to glycoside **9** in THF at 0 °C (Table 1, entry 2). Both temperature control and slow rate of hydroxide addition was necessary to achieve preferential cleavage of the acetyl group before oxazolidinone opening. Chemoselective cleavage of the *N*-acetyl substituent was also observed under reduction conditions using $LiBH_4$ (Table 1, entry 3).[11]

The greatest chemoselectivity achieved for cleavage of the *N*-acetyl group to afford **10** was found using LiOOH mediated hydrolysis (Table 1, entry 4, **10**:**12** > 9:1).[12] Here, substrate **9** in 3:1 THF/H_2O was treated with 4–8 equiv of 30% H_2O_2 at −40 °C (phase separation between H_2O and THF was observed), followed by addition of 2 equiv of LiOH. The reaction mixture was quickly brought to 0 °C and quenched within minutes by adding Na_2SO_3 solution. It was found essential to add lithium hydroxide at low temperature to minimize oxazolidinone ring opening prior to cleavage of the *N*-acetyl group. In situ treatment of *N*-unsubstituted oxazolidinone **10** with excess 1 N sodium hydroxide in THF afforded free amine **11** in high yield.[3]

Chemoselective cleavage of the oxazolidinone ring to preferentially afford *N*-acetyl product **12** was also achieved by employing LiCl–LiOH hydrolysis (Pathway B, Table 1, entry 5).[12] The addition of lithium chloride (3–5 equiv) to glycoside **9** prior to the addition of lithium hydroxide was required to cleave the oxazolidinone ring without affecting the *N*-acetyl moiety. These unique hydrolysis conditions provide a direct route to efficiently obtain the *N*-acetyl-D-glucosamine product.

We previously demonstrated *N*-unsubstituted 2*N*,3*O*-oxazolidinone protected derivatives of D-glucosamine undergo efficient ring opening with alkoxides to afford C-2 carbamates.[3] Here, we evaluated the reaction between methoxide and *N*-acetyl substituted 2*N*,3*O*-oxazolidinone **9** under forcing and non-forcing conditions. The addition of sodium methoxide to substrate **9** under non-forcing conditions was found to control the reaction of methoxide with substrate and provide high yields of *N*-acetyl methyl carbamate **13a** (Table 1, entries 6 and 7).[13] Under these reaction conditions the methoxide anion selectively attacks the carbonyl of the oxazolidinone ring leaving the *N*-acetyl group intact. When substrate **9** was treated with excess sodium methoxide in methanol over prolonged reaction time initial formation of the *N*-acetyl methyl carbamate **13a** was followed by deacetylation to afford **13b** (Table 1, entry 8). Methyl carbamates such as **13b** are readily hydrolyzed to the corresponding free amine using established methods.[14]

It is notable that during the preparation of this letter, Oscarson and co-workers reported mild methoxide treatment of glycosides of 2*N*,3*O*-oxazolidione protected 4,6,-di-*O*-benzyl-*N*-acetyl-D-glucosamine directly afforded *N*-acetyl-D-glucosamine derivatives having a free 3-hydroxyl group.[15] The high yields and clear chemoselective opening of the *trans*-fused oxazolidinone prior to acetyl cleavage by methoxide here contradict this result. However, anomeric configuration of substrates employed was not reported, and Crich and Vinod reported dramatic affects of anomeric configuration on oxazolidinone opening versus cleavage of the *N*-acetyl substituent for certain 2*N*,3*O*-oxazolidione protected derivatives of *N*-acetyl-D-glucosamine.[10]



Scheme 2.

Having observed chemoselective cleavage of the *N*-acetyl group, we anticipated it might be possible to exploit this differential reactivity to selectively remove the *N*-acetyl moiety in the presence of *O*-acetyl groups. To this end, we evaluated a number of amine-based reagents commonly employed for selective *O*-deacetylation of anomeric acetates in the presence of other primary and secondary *O*-acetyl groups.[16] To our surprise, these reactions provided *N*-deacetylated C-2 ureido sugars in excellent yield (Scheme 2). Monitoring the reactions and reaction intermediates by thin-layer chromatography and NMR revealed that these reactions proceed through two different pathways (Scheme 2). Intermediates **15** and **16** are both produced. The ratio of **15** to **16** depends on the amine nucleophile employed. Formation of intermediate **15** is followed by slow conversion of **15** to **17**. In contrast, **16** rapidly undergoes *N*-deacetylation under reaction conditions to afford **17**. Relative rates were determined by comparing conversion of **14** to **17** and intermediates **15** and **16** to **17** under identical reaction conditions.

Ichikawa and Pinter previously reported the use of *trans*-fused, *N*-unsubstituted, 1*N*,2*O*-oxazolidinones in the synthesis of C-1 urea glycosides.[17] Our studies here, in conjunction with previous reports employing thioglycosides of 2*N*,3*O*-oxazolidione protected *N*-acetyl-D-glucosamine as glycosyl donors,[5,15] reveals an efficient route for the synthesis of C-2 urea glycoconjugates, which are present in a number of antimicrobial natural products and *N*-deacetylase inhibitors.[18,19]

In summary, conditions for the chemoselective hydrolysis and methanolysis of highly strained *trans*-fused 2*N*,3*O*-oxazolidinone derivatives of *N*-acetyl-β-D-glucosamine have been investigated and identified. Selective cleavage of the oxazolidinone ring or *N*-deacetylation without ring cleavage has been achieved on the same substrate. Certain amine nucleophiles have been shown to efficiently open the *trans*-fused *N*-acetyl oxazolidinone ring under mild conditions to afford C-2 ureido sugars with concomitant removal of the *N*-acetyl moiety. This work demonstrates the high degree of chemoselective manipulation possible with 2*N*,3*O*-oxazolidinone derivatives of *N*-acetyl-D-glucosamine, and presents specific methods that will be valuable in elaborating sugar glycosides in the stereoselective synthesis of glycoconjugates containing variably substituted 2-amino-2-deoxy-D-hexopyranosides.

Acknowledgments

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8. Benzyl glycoside **9** was prepared from **5** in four steps, 68% overall yield. All products were characterized by mass spectroscopic (ESI) and NMR analysis. Select data for **8** and **9**: (**8**) $R_f = 0.59$ (2:5, EtOAc/hexanes); ^{1}H NMR ($CDCl_3$) δ 1.06 (s, 9H), 2.30 (s, 3H), 2.58 (s, 3H), 3.64 (m, 1H), 3.88 (m, 2H), 4.22 (m, 2H), 4.66 (d, 2H), 4.82 (d, 1H), 4.90 (m, 3H), 5.92 (m, 1H), 7.04 (d, 2H), 7.44 (m, 8H), 7.74 (dd, 4H). Mass spec. (ESI) *m*/*z* 698.1 ($M+Na^+$). Compound (**9**) $R_f = 0.55$ (2:5, EtOAc/hexanes); ^{1}H NMR ($CDCl_3$) δ 0.92 (s, 9H), 2.39 (s, 3H), 3.78–3.99 (m, 3H), 4.11 (d, 1H), 4.15 (d, 1H), 4.70 (d, 1H), 4.95 (d, 1H), 5.12–5.29 (m, 3H), 5.82 (m, 1H), 7.10–7.35 (m, 11H), 7.50–7.60 (m, 4H). Mass spec. (ESI) *m*/*z* 672.6 ($M+Na^+$).
9. All products were characterized by mass spectroscopic and NMR analyses. Selected data for **10**–**12**, **13a**–**b**, **17a**–**c**: Compound (**10**) $R_f = 0.32$ (2:5, EtOAc/hexanes); ^{1}H NMR ($CDCl_3$) δ 1.08 (s, 9H), 3.59–3.68 (m, 2H), 3.88 (d, 2H), 4.22 (dd, 1H), 4.58–4.71 (m, 4H), 4.89 (d, 1H), 5.10 (s, 1H), 5.27–5.41 (m, 3H), 5.86–5.97 (m, 1H), 7.31–7.45 (m, 11H), 7.65–7.78 (m, 4H). Mass spec. (ESI) *m*/*z* 640.4 ($M+Na^+$). Compound (**11**) $R_f = 0.36$ (15:1, EtOAc/MeOH); ^{1}H NMR ($CDCl_3$) δ 1.09 (s, 9H), 2.75 (t, 1H), 3.37–3.47 (m, 2H), 3.67 (t, 1H), 3.95–3.98 (dd, 2H), 4.25 (d, 1H), 4.53 (d,

1H), 4.85 (d, 1H), 7.30–7.50 (m, 11H), 7.71 (m, 4H). Mass spec. (ESI) m/z 508.3 ($M+H^+$).

Compound (**12**) $R_f = 0.27$ (EtOAc); ^1H NMR ($CDCl_3$) δ 1.08 (s, 9H), 1.96 (s, 3H), 3.45–3.52 (m, 2H), 3.63 (m, 2H), 3.91–4.04 (dd, dd, 2H), 4.14 (dd, 1H), 4.40 (d, 1H), 4.55 (d, 1H), 4.81 (d, 1H), 5.75 (s, 1H), 7.32–7.46 (m, 11H), 7.71 (m, 4H). Mass spec. (ESI) m/z 572.5 ($M+Na^+$).

Compound (**13a**) $R_f = 0.21$ (1:1, EtOAc/Hexanes); ^1H NMR ($CDCl_3$) δ 1.09 (s, 9H), 1.94 (s, 3H), 3.62–3.69 (m, 2H), 3.77 (s, 3H), 3.84–3.96 (m, 2H), 4.57 (dd, 2H), 4.71 (d, 1H), 4.89 (d, 1H), 5.06–5.34 (m, 4H), 5.51 (d, 1H), 5.84 (m, 1H), 7.31–7.48 (m, 11H), 7.71 (m, 4H). Mass spec. (ESI) m/z 714.5 ($M+Na^+$).

Compound (**13b**) $R_f = 0.44$ (3:1, EtOAc/Hexanes); ^1H NMR ($CDCl_3$) δ 1.09 (s, 9H), 3.36–3.47 (m, 2H), 3.65–3.69 (m, 4H), 3.96–4.14 (m, 2H), 4.12 (dd, 1H), 4.46 (d, 1H), 4.56 (d, 1H), 4.86 (d, 1H), 7.30–7.47 (m, 11H), 7.69 (m, 4H). Mass spec. (ESI) m/z 588.6 ($M+Na^+$).

Compound (**17a**) $R_f = 0.42$ (EtOAc); ^1H NMR ($CDCl_3$) δ 2.09 (s, 3H), 2.12 (s, 3H), 2.82 (s, 2H), 3.48–3.55 (m, 1H), 3.59–3.65 (m, 1H), 3.76 (t, 3H), 4.15–4.20 (dd, 1H), 4.26–4.32 (dd, 1H), 4.35–4.47 (m, 1H), 4.48 (d, 1H), 4.52 (d, 1H), 4.88 (d, 1H), 4.95 (dd, 1H), 5.78 (s, 1H), 7.34–7.40 (m, 5H). Mass spec. (ESI) m/z 419.4 ($M+Na^+$).

Compound (**17b**) $R_f = 0.46$ (EtOAc); ^1H NMR ($CDCl_3$) δ 1.50–1.59 (m, 5H), 2.09 (s, 3H), 2.15 (s, 3H), 3.01 (d, 1H), 3.19–3.28 (m, 4H), 3.44–3.65 (m, 2H), 3.89 (dd, 1H), 4.25–4.38 (dd, 1H), 4.48–4.64 (m, 3H), 4.88 (d, 1H), 4.96 (dd, 1H), 7.28–7.34 (m, 5H). Mass spec. (ESI) m/z 487.4 ($M+Na^+$).

Compound (**17c**) $R_f = 0.54$ (EtOAc); ^1H NMR ($CDCl_3$) δ 2.01 (s, 3H), 2.08 (s, 3H), 3.35 (m, 1H), 3.51–3.55 (m, 1H), 3.64 (t, 1H), 4.09–4.29 (m, 3H), 4.34 (d, 1H), 4.41 (d, 2H), 4.52 (d, 1H), 4.80 (d, 1H), 4.91 (t, 1H), 5.76 (s, 1H), 5.91 (m, 1H), 6.90–7.36 (m, 10H). Mass spec. (ESI) m/z 509.4 ($M+Na^+$).

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