Investigation of Coupling Reactions for the Synthesis of Valienamine Pseudodisaccharides

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Abstract: Amine-linked pseudodisaccharides based on valienamine were synthesised by C–N bond-forming reactions between valienol-derived C-1 electrophiles and carbohydrate nitrogen nucleophiles. Palladium-catalysed coupling with trichloroacetimidate leaving groups, Mitsunobu reactions with a nosylamide nucleophile, and alkylation of amines by C-1 bromides were investigated.

Key words: amination, carbohydrates, carbocycles, pseudodisaccharides, valienamine

Valienamine is a polyhydroxylated unsaturated carbocyclic amine that bears a resemblance to α-D-glucose, sharing its stereochemistry at C-1–C-4 (Figure 1).[1,2] It occurs in nature (in Actinobacteria) as a substructure of oligosaccharide-like structures in which it is linked by N-substitution to other carbohydrates (e.g. in acarbose, amylostatin, adiposins and salbostatin) or carbasugars (validomycins, validoxylamines).[3] These pseudooligosaccharides are inhibitors of various α-glucosidases, and can be more potent and more specific inhibitors than valienamine itself.[1,3] A current theory on the biosynthesis of valienamine-based pseudooligosaccharides is that the key coupling step occurs between a carbohydrate amine and a C-5=C-5a unsaturated carbocyclic electrophile bearing a leaving group at the allylic C-1,[4] taking advantage of the allylic reactivity enhancement.[5]

The synthesis of modified valienamine-based pseudodisaccharide or pseudooligosaccharide structures with different stereochemistry in the carbocycle and/or the carbohydrate moieties, and/or with different linkage positions on the carbohydrate ring, so altering the binding specificities of the pseudodisaccharides, has been described in the literature.[6] One of the most successful methods for coupling carbasugar and carbohydrate amine components by C–N bond formation is the epoxide-opening approach studied by Ogawa. 1,2-Epoxide-opening reactions have been used for the efficient synthesis of α-*lyxo* (2-*epi*-valienamine) pseudodisaccharides;[7] the corresponding reaction for the synthesis of β-*xylo* (1-*epi*-valienamine) pseudodisaccharides shows potential, but has hardly been investigated.[8] For α-*xylo* (valienamine) linkages, an indirect route based on 1,5a-epoxide opening followed by dehydration has been used.[9] More recently, Shing has developed a very efficient method based on palladium-catalysed coupling of C-1 chlorides, giving a more direct route to α-*xylo* pseudodisaccharides.[10]

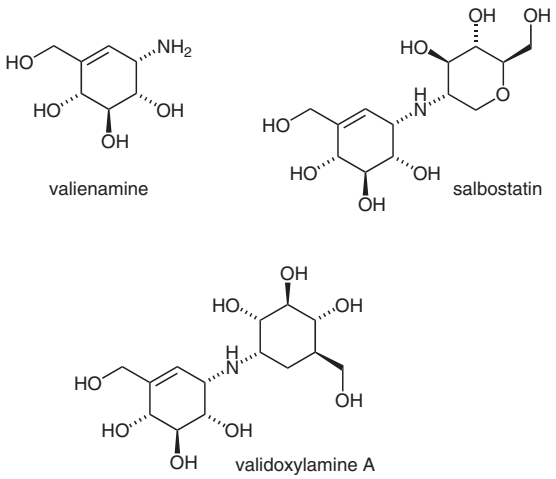

Figure 1 Valienamine and examples of natural valienamine pseudodisaccharides

As part of our ongoing project towards the synthesis of biologically relevant hydrolytically stable oligosaccharide analogues,[11] we describe in this letter our results on the coupling reactions of valienol-derived C-1 electrophiles with carbohydrate amine derived nucleophiles for valienamine pseudodisaccharide synthesis. We evaluated the potential of three types of C-1 electrophile in coupling reactions designed to give the C-1-substituted allylic amines, i.e. the (*epi*)valienamine pseudodisaccharides, using nucleophiles based on 6-amino-6-deoxyglucose.

Mitsunobu coupling[12] has been used for (protected) secondary amine synthesis using sulfonamides as an activating group. The 2-nitrosulfonyl (nosyl) group has the advantage of being easily deprotected by thiol nucleophiles to reveal the parent secondary amine.[13] We have previously used this reaction for amine-linked pseudodisaccharide synthesis.[14] The α **1** and β **2** carbasugar (valienol) C-1 alcohols were available by a published route,[15] and the nosylamide **4** was prepared by nosylation of amine **3** as described previously.[14] The α alcohol **1** coupled cleanly with the nosylamide **4** under Mitsunobu conditions to give the β-linked pseudodisaccharide **9** (Table 1, entry 1).[16,17] However, under the same condi-

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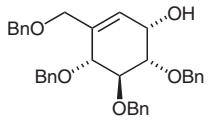
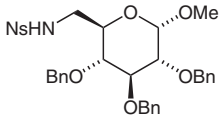
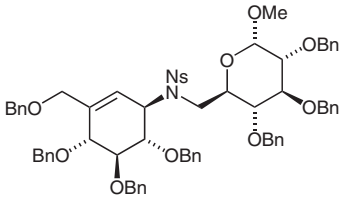
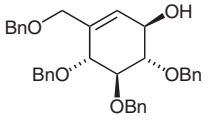
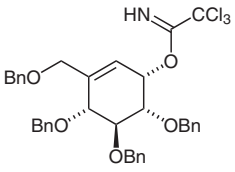
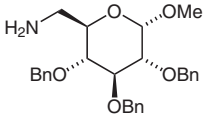
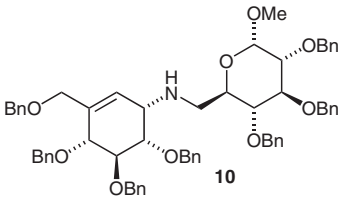
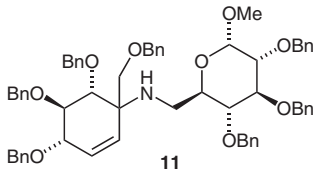
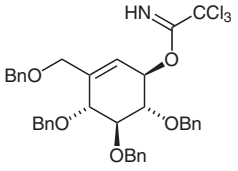
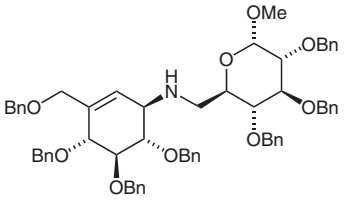
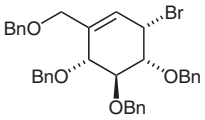
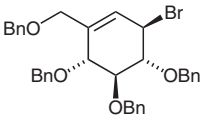
tions, the β alcohol **2** failed to give a useful quantity of the α-linked pseudodisaccharide, but rather the reaction resulted in the formation of multiple by-products (Table 1, entry 2).

Palladium-catalysed allylic amination has been used by Shing for the synthesis of valienamine pseudodisaccharides using valienol C-1 chlorides as electrophiles.[10] He found that C-1 leaving groups other than chloride (acetate, 1,2-epoxide and 1,2-cyclic-sulfite) failed to give coupling products.[18] We tested trichloroacetimidates, apparently a novel leaving group for this reaction. The imidates **5** and **6** were prepared easily (Cl_3CCN, DBU, CH_2Cl_2, r.t., 89–94%),[19] stereospecifically and in high yield from the corresponding alcohols. Under Shing's conditions, the α-imidate **5** and the C-6 amine **3** did not give a clean reaction (Table 1, entry 3). Two pseudodisaccharides were isolat-

Table 1 Coupling Reactions[a]

Entry	Electrophile	Nucleophile	Conditions	Product	Yield[b]
1	 **1**	 **4**	A	 **9**	**9** (64%)
2	 **2**	**4**	A	–[c]	–[c]
3	 **5**	 **3**	B	 **10** +  **11**	**10** (21%) + **11** (21%)
4	 **6**	**3**	B	 **12**	**12** (85%)
5	 **7**	**3**	C	**10** + **12**	**10** (51%) + **12** (14%)
6	 **8**	**3**	C	**10**	**10** (67%)

[a] Reaction condition: (A) PPh_3, DIAD, THF, 0 °C → r.t. (B) $Pd_2(dba)_3$, TMPP, Et_3N, MeCN, r.t. (C) *i*-Pr_2EtN, MeCN, 50 °C.
[b] Isolated yields.
[c] No pseudodisaccharide was isolated.

ed, the α-linked **10** and the S_N2' product **11**, whose newly formed stereogenic centre at C-5 was not assigned. Formation of the β-linked pseudodisaccharide **12** was not detected in this reaction. In contrast, the β-imidate **6** coupled with the C-6 amine **3** under the same conditions to give the β-linked pseudodisaccharide **12** in high yield as a single diastereomer (Table 1, entry 4).[17,20] Hence, these reactions apparently go by the usual double displacement mechanism[5] to give overall retention of configuration.

Direct displacement of C-1 halides by amines in the presence of stoichiometric base was among the first methods published (in the early 1980s) for valienamine-based pseudodisaccharide synthesis,[21] but this method has not been used since. We synthesised the C-1 bromides **7** and **8** by an Appel reaction[22] from the β-alcohol **2** (PPh_3, CBr_4, CH_2Cl_2, 0 °C → r.t., 45% total; separable by chromatography). Heating the β-bromide **8** with the amine **3** in the presence of *i*-Pr_2EtN gave the α coupling product **10** in 67% yield, with none of the β diastereomer detected (Table 1, entry 6).[17,23] However, the α-bromide **7** also coupled with the amine **3** to give the same α-linked pseudodisaccharide **10** as the major product (51%), along with a minor quantity (14%) of the product with inversion of configuration **12** (Table 1, entry 5). Kuzuhara has commented[21c] that the C-1 configurational instability of a related valienol C-1 bromide could be the cause of a non-stereospecific coupling reaction. We confirmed that while the bromides **7** and **8** are stable enough to be separated by column chromatography, they do interconvert in CH_2Cl_2 solution when treated with *n*-Bu_4NBr as a bromide source. Under these conditions each of the bromides **7** and **8** equilibrated to give the same thermodynamic mixture, **7**/**8** ca 2:1. It seems that the β-bromide **8** is relatively reactive towards displacement by the amine nucleophile **3** (with inversion), more so than the α-bromide **7**,[24] for which C-1 epimerisation (by S_N2 displacement by bromide ion) to the β diastereomer **8** and subsequent coupling with the amine **3** competes effectively.

The methods described here gave good results in some cases for the coupling reactions.[25] The palladium-catalysed method and the Mitsunobu method give superior results for the synthesis of the β-(1,2-*trans*)linkage; in fact, these methods probably represent the state of the art for the formation of such linkages by carbasugar-electrophile–carbohydrate-nucleophile couplings. Direct nucleophilic substitution of the C-1 bromide gave superior results for the synthesis of the α-(1,2-*cis*)linkage. Given the recognised relevance of valienamine pseudodisaccharides[26] and current interest in the synthesis of analogues with new application areas,[27] we hope that the findings described here can be useful. More generally, the trichloroacetimidate appears to be a functional leaving group in palladium-catalysed allylic amination reactions, having the advantage of a high-yielding and stereospecific formation.

Acknowledgment

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References and Notes

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(2) The lack of a stereogenic centre at C-5 means that the stereochemistry of valienamine is described by analogy to a pentose rather than as a hexose, hence it has the α-*xylo* configuration. 1-*epi*-Valienamine has a β-*xylo* configuration, and 2-*epi*-valienamine has an α-*lyxo* configuration. Valienamine derivatives are numbered with carbasugar numbering to stress the homomorphic relationship with carbohydrates.
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(15) Cumpstey, I.; Gehrke, S.; Erfan, S.; Cribiu, R. *Carbohydr. Res.* **2008**, *343*, 1675.
(16) **Mitsunobu Coupling**: α-Alcohol **1** (54 mg, 0.10 mmol) and nosylamide **4** (65 mg, 0.10 mmol) were dissolved in anhyd THF (2 mL) and the solution was cooled to 0 °C under N_2. PPh_3 (53 mg, 0.202 mmol) was added, then after 15 min, DIAD (39 μL, 0.198 mmol) was added dropwise. After 30 min, the ice-bath was removed, and the reaction was allowed to proceed at r.t. After TLC (pentane–EtOAc, 2:1) indicated the consumption of the alcohol (R_f 0.2) and the sulfonamide (R_f 0.1) and the formation of a product (R_f 0.15), the mixture was concentrated in vacuo. The residue was purified by flash column chromatography to give the β-linked pseudodisaccharide **9** (65 mg, 64%).

(17) The stereochemistry of the bromides (**7** and **8**) and pseudodisaccharides (**9**, **10** and **12**) was assigned using the $J_{1,2}$ and $J_{1,5a}$ coupling constants from the ^{1}H NMR spectra, in comparison with reported data.[28] In α-*xylo* compounds, $J_{1,5a}$ was in the range 4.4–5.8 Hz; $J_{1,2}$ was in the range 3.5–4.4 Hz. In β-*xylo* compounds, H-5a appeared as a singlet; $J_{1,2}$ was between 7.1–9.2 Hz (not determined for **9**). These $J_{1,2}$ values are consistent with the $^2H_3$ half-chair conformation expected for both diastereomers. For the nosylated pseudodisaccharide **9**, many of the NMR resonances were broad, possibly resulting from steric crowding and conformational change, which weakens an argument for configurational assignment of this compound based on coupling constants, but its configuration was confirmed by its deprotection (PhSH, K_2CO_3, DMF, 83%) to give **12**.

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(20) **Palladium-Catalysed Coupling**: β-Imidate **6** (94 mg, 0.14 mmol), trimethylolpropane phosphite (TMPP; 5 mg, 0.028 mmol) and $Pd_2(dba)_3$ (7 mg, 0.014 mmol) were placed in a round-bottomed flask with a magnetic stirrer bar. The flask was evacuated, then placed under Ar. Amine **3** (194 mg, 0.42 mmol) was suspended in MeCN (it was partially soluble), the solvent was degassed and the mixture was placed under Ar. The amine suspension was transferred to the reaction vessel by syringe. Et_3N (0.09 mL, 0.63 mmol) was added, and the mixture colour changed from a purple/brown suspension to a pale yellow solution. The reaction mixture was stirred at r.t. under Ar. After 15 h, TLC (pentane–EtOAc, 3:1) showed complete consumption of the imidate (R_f 0.8), amine remaining (R_f 0), and the formation of a major product (R_f 0.1). The mixture was concentrated in vacuo and the residue was purified by flash column chromatography to give the β-linked pseudodisaccharide **12** (115 mg, 85%).

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(23) **Coupling with C-1 Bromides**: β-Bromide **8** (42 mg, 0.070 mmol) and amine **3** (80 mg, 0.17 mmol) were dissolved in MeCN (1 mL) under Ar. *N*,*N*′-Diisopropylethylamine (35 μL, 0.20 mmol) was added and the reaction mixture was heated to 50 °C. After 24 h, TLC (pentane–EtOAc, 2:1) indicated the formation of a major product (R_f 0.3). The mixture was concentrated in vacuo, and the residue was purified by flash column chromatography to give the α-linked pseudodisaccharide **10** (46 mg, 67%).

(24) The β-bromide **8** does react at a higher rate with the amine **3** (reacting slowly at r.t.) than does its α epimer **7** (which needed heating for any reaction to take place).

(25) **Representative Data:**
2,3,4,6-Tetra-*O*-benzyl-5a-carba-β-D-*xylo*-hex-5(5a)-enopyranosyl Trichloroacetimidate (6): colourless oil; $[\alpha]_D^{21}$ –53.9 (*c* = 1.0, $CHCl_3$). IR (film): 1662 (C=N) cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.91–4.00 (m, 3 H, H-2, H-3, H-6), 4.23 (d, $J_{6,6'}$ = 12.2 Hz, 1 H, H-6′), 4.37 (d, $J_{3,4}$ = 7.5 Hz, 1 H, H-4), 4.49, 4.53 (2 × d, *J* = 11.9 Hz, 2 H, PhCH_2), 4.73 (d, *J* = 10.9 Hz, 1 H, PhC*H*H′), 4.82, 5.00 (2 × d, *J* = 11.0 Hz, 2 H, PhCH_2), 4.85–4.91 (m, 3 H, PhCH_2, PhCH*H*′), 5.75 (d, $J_{1,2}$ = 7.1 Hz, 1 H, H-1), 5.82 (s, 1 H, H-5a), 7.26–7.35 (m, 20 H, ArH), 8.48 (s, 1 H, NH). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 69.7, 72.5, 74.8, 75.3, 75.5, 79.5, 79.6, 81.7, 83.9, 91.4, 122.1, 127.6, 127.7, 127.7, 127.8, 127.9, 127.9, 128.3, 128.4, 128.4, 137.9, 138.2, 138.3, 138.4, 138.6, 162.1. HRMS–ESI: *m*/*z* [M + Na]$^+$ calcd for $C_{37}H_{36}O_5NCl_3Na$: 702.1551; found: 702.1521.
2,3,4,6-Tetra-*O*-benzyl-5a-carba-β-D-*xylo*-hex-5(5a)-enopyranosyl Bromide (8): colourless oil; $[\alpha]_D^{23}$ –73.3 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.75 (dd, $J_{2,3}$ = 10.2 Hz, $J_{3,4}$ = 8.0 Hz, 1 H, H-3), 3.94–3.98 (m, 2 H, H-2, H-6), 4.23 (d, $J_{6,6'}$ = 12.7 Hz, 1 H, H-6′), 4.37 (d, $J_{3,4}$ = 8.0 Hz, 1 H, H-4), 4.51, 4.54 (2 × d, *J* = 11.8 Hz, 2 H, PhCH_2), 4.73 (d, *J* = 10.8 Hz, 1 H, PhC*H*H′), 4.76 (d, $J_{1,2}$ = 7.9 Hz, 1 H, H-1), 4.82 (d, *J* = 11.0 Hz, 1 H, PhC*H*H′), 4.86 (d, *J* = 10.9 Hz, 1 H, PhCH*H*′), 4.93–4.98 (m, 3 H, PhCH_2, PhCH*H*′), 5.91 (s, 1 H, H-5a), 7.25–7.41 (m, 20 H, ArH). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 51.7, 69.5, 72.6, 75.4, 75.7, 76.2, 79.8, 85.0, 85.5, 125.9, 127.9, 127.9, 127.9, 127.9, 128.0, 128.0, 128.3, 128.5, 128.5, 128.6, 137.7, 138.1, 138.1, 138.3, 138.4. HRMS–ESI: *m*/*z* [M + Na]$^+$ calcd for $C_{35}H_{35}O_4BrNa$: 621.1611; found: 621.1610.
Methyl 6-[2,3,4,6-Tetra-*O*-benzyl-5a-carba-β-D-*xylo*-hex-5(5a)-enopyranosylamino]-2,3,4-tri-*O*-benzyl-6-deoxy-α-D-glucopyranoside (12): white solid; $[\alpha]_D^{25}$ –21.2 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.60 (dd, $J_{5,6}$ = 6.4 Hz, $J_{6,6'}$ = 11.7 Hz, 1 H, H-6^I), 3.01 (dd, $J_{5,6'}$ = 2.5 Hz, $J_{6,6'}$ = 11.7 Hz, 1 H, H-6′^{I}), 3.29 (s, 3 H, OMe), 3.36 (m, 1 H, H-1^{II}), 3.46–3.51 (m, 2 H, H-2^I, H-4^I), 3.59 (at *J* = 9.2 Hz, 1 H, H-2^{II}), 3.73 (m, 1 H, H-5^I), 3.87–3.90 (m, 2 H, H-3^{II}, H-6^{II}), 3.99 (at, *J* = 9.3 Hz, 1 H, H-3^I), 4.26 (d, $J_{6,6'}$ = 12.0 Hz, 1 H, H-6′^{II}), 4.33 (d, $J_{3,4}$ = 7.1 Hz, 1 H, H-4^{II}), 4.41–5.00 (m, 15 H, 7 × PhCH_2, H-1^I), 5.67 (s, 1 H, H-5a^{II}), 7.23–7.40 (m, 35 H, ArH). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 47.1, 55.3, 60.0, 70.3, 70.5, 72.3, 73.5, 74.7, 75.1, 75.2, 75.4, 75.9, 79.3, 80.2, 80.4, 82.0, 82.1, 85.2, 98.1, 127.2, 127.7, 127.8, 127.9, 127.9, 128.0, 128.1, 128.3, 128.5, 128.5, 128.5, 128.6, 135.6, 138.4, 138.4, 138.6. HRMS–ESI: *m*/*z* [M + Na]$^+$ calcd for $C_{63}H_{67}NO_9Na$: 1004.4708; found: 1004.4626.

(26) Acarbose is used as a diabetes type 2 drug; Validamycin A is used as an agrochemical fungicide against rice sheath blight.

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