COMMUNICATION

Lewis-acid catalysed arylation of the hydroxyamino sugar moiety of the natural product SB-219383

John M. Berge,* Catherine S. V. Houge-Frydrych and Richard L. Jarvest

GlaxoSmithKline, Third Avenue, Harlow, Essex, UK CM21 5AJ

Received (in Cambridge, UK) 5th July 2001, Accepted 7th September 2001
First published as an Advance Article on the web 21st September 2001

The natural product SB-219383 1a contains an unique bicyclic hydroxyamino sugar moiety. Novel *C*-glycosidation reactions of this hydroxyamino sugar moiety are reported. The formation of a sugar nitrone intermediate is postulated which is subsequently trapped by electron-rich aromatic rings to yield *C*-aryl hydroxyamino sugars.

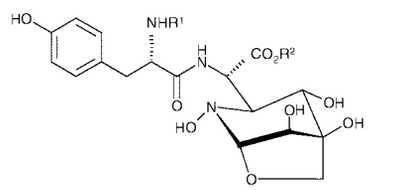
Introduction

The natural product SB-219383 **1a**, isolated from a *Micromonospora* sp. NCIMB 40684, is a potent and selective inhibitor of bacterial tyrosyl tRNA synthetase (YRS) and as such is a potential lead for new antibacterial agents.[1,2] SB-219383 contains a unique bicyclic hydroxyamino sugar moiety. Herein we report novel *C*-glycosidation reactions of the hydroxyamino sugar moiety of SB-219383. We have already reported that the bicyclic system of SB-219383 is ring-opened with sodium borohydride and that the monocyclic product **1b** maintains good inhibition against bacterial tyrosyl tRNA synthetase.[3] The reduction probably proceeds *via* a nitrone-like species, a potentially valuable intermediate for other novel reactions. We were interested in the Lewis-acid catalysed reaction of SB-219383 with electron-rich aromatic substrates as a route to *C*-glycosidated derivatives, thus giving access to previously unavailable analogues of SB-219383 for biological evaluation. Reaction of exocyclic nitrones, derived from carbohydrates, with organolithium reagents have been used extensively to prepare complex sugars[4] and this provided encouragement to investigate the nitrone chemistry of SB-219383. Furthermore, this reaction would have some novelty as *C*-glycosidation of piperidine-derived sugars have been rarely reported,[5] although an example of the addition of silylketene acetal to a pyrrolidine nitrone was reported recently.[6]

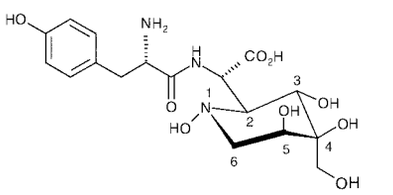
Results and discussion

The substrate for the arylation reactions was the *N*-Cbz (benzyloxycarbonyl) protected *n*-butyl ester **3**.[2] Treatment of **3** with tetrachlorostannane–ethyl acetate in the presence of the electron-rich aromatics 2,4,6-trimethoxybenzene, 2,4-dimethoxybenzene or furan yielded the corresponding 2-aryl derivatives **4a**, **5a**, **6a** and **6b** in moderate yields, presumably *via* the nitrone **7** (Scheme 1).

The more sterically demanding aryl groups gave only one stereoisomer **4a** or **5a** in which the aryl group had reacted at C-6, determined by HMBC correlations between H-6 of the piperidine ring and the C-1 of the aromatic ring. In addition, the piperidine ring of the sugar had undergone conformational inversion, allowing the aryl substituent to adopt an equatorial orientation, as established by examination of the ^{1}H NMR vicinal coupling constants.† Thus, $J_{5,6}$ = 8.6 Hz in **5a** is consistent with an ax–ax disposition of these protons. The larger than predicted value of $J_{2,3}$ = 5.2 Hz for eq–eq disposition is possibly caused by some distortion of the piperidine ring by the large axial amino acid substituent at C-2. However, this is still a significantly smaller coupling than $J_{2,3}$ = 11.1 Hz in **1** where both protons are axial. Similar arguments apply to the identification of **4a**. The formation of products **4a** and **5a** thus results from attack at the less hindered face of the nitrone double bond *via* route A (Fig. 1). Conversely, when furan was employed as the nucleophile two stereoisomers were formed, **6a** and **6b** in a 3 : 1 ratio. ^{1}H NMR analysis indicated that both isomers retained the original conformation of the piperidine ring. The major isomer **6a** was shown to have an equatorial

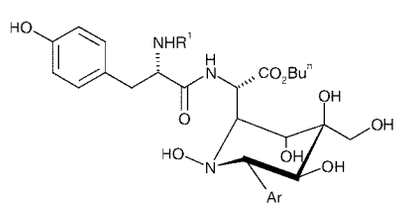


1a R^1 = H, R^2 = H
2 R^1 = Cbz R^2 = H
3 R^1 = Cbz R^2 = Bu^n

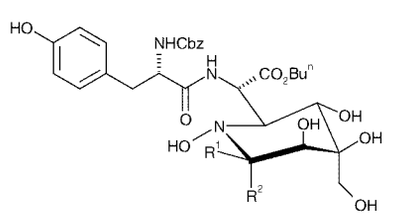


1b

i (**4a**), (**5a**)
ii (**4b**), (**5b**)



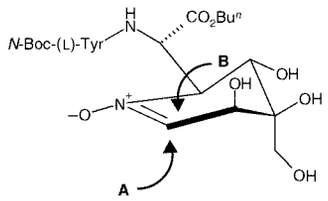
4a R^1 = Cbz, Ar = 2,4,6-trimethoxyphenyl (42%)
4b R^1 = H, Ar = 2,4,6-trimethoxyphenyl (40%)
5a R^1 = Cbz, Ar = 2,4-dimethoxyphenyl (41%)
5b R^1 = H, Ar = 2,4-dimethoxyphenyl (41%)



6a R^1 = 2-furyl, R^2 = H (45%)
6b R^1 = H, R^2 = 2-furyl (15%)

Scheme 1 *Reagents*: i) ArH, $SnCl_4$, EtOAc, RT, 48 h; ii) 10% Pd–C, H_2, MeOH, 1 atmosphere, RT, 8 h.

DOI: 10.1039/b105965n



7

Fig. 1

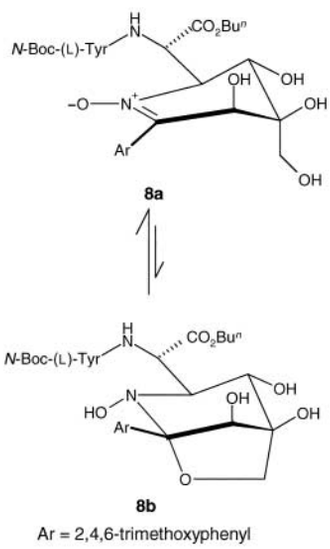


Fig. 2

furan substituent on the basis of $J_{5,6}$ = 6.0 Hz, consistent with an eq–ax arrangement of these two protons, although $J_{2,3}$ = 6.4 Hz is low for an ax–ax coupling constant. The minor component was shown to have an axial furan substituent, $J_{2,3}$ = 8.4 Hz (ax–ax) and $J_{5,6}$ = 5.1 Hz (eq–eq). These observations suggest that the smaller furan nucleophile is less sterically demanding in its approach to the sugar nitrone **7** and the major pathway is attack *via* route B to give the more thermodynamically stable β-anomer **6a**. The minor component **6b** results from attack *via* route A and in this case the resultant axial furan substituent is not large enough to cause conformational inversion of the piperidine ring.

The product ratios contrast with those obtained in pyranoglucose α-trichloroacetimidate chemistry from which β-anomers are formed with the methoxybenzenes, but the α-anomer is strongly preferred from furan.[7,8] However, in both chemistries the methoxylated benzenes result in addition *trans* to the adjacent hydroxy, whereas the furan gives predominantly a product *cis* to the adjacent hydroxy group.

Catalytic hydrogenation[2] of **4a** or **5a** resulted in removal of the Cbz group to yield **4b** or **5b** respectively. Compounds **4b** or **5b** were incubated in DMSO in air and monitored by negative ion LC-MS. The parent $[M]^-$ ion of **4b** was gradually replaced over 48 h by an $[M - 2H]^-$ ion, consistent with aerial oxidation to the nitrone **8a**, facilitated by the adjacent aryl substituent. Formation of the nitrone is most likely followed by equilibration to the cyclic 6-aryl SB-219383 analogue **8b** (Fig. 2). The reduced retention time of the product was consistent with the cyclised form **8b** being the major isomer. The instability in DMSO solution precluded the determination of reliable YRS inhibition constants.

In conclusion, we have proposed the facile formation of the endocyclic sugar nitrone **7** from SB-219383 and shown that it is a useful intermediate for effecting *C*-glycosidation under mild conditions, requiring minimal use of protecting groups. Characterisation of the *C*-glycosidation products by NMR has established the stereochemical outcome of the reaction and a tentative rationalisation for the observed stereoselectivity is proposed.

Experimental

NMR experiments were performed on Bruker AM250 or Avance 400, mass spectra were obtained on a VG Platform spectrometer. Organic solutions were dried over magnesium sulfate. HPLC data were generated on a Beckmann System Gold machine using a C18 column gradient, eluting with methanol–ammonium formate buffer. Grad 1 refers to a gradient of 0–95% methanol over 30 minutes and Grad 2 refers to a gradient of 25–75% methanol over 20 minutes.

(2*S*,3*S*,4*S*,5*S*,6*S*)-[4-Hydroxymethyl-1,3,4,5-tetrahydroxy-6-(2,4,6-trimethoxyphenyl)piperidin-2-yl][(*N*-benzyloxycarbonyl)-tyrosylamino]acetic acid *n*-butyl ester 4a

To a solution of (3*S*,4*S*,5*R*,8*R*)-2-(2,4,5,8-tetrahydroxy-7-oxa-2-azabicyclo[3.2.1]octan-3-yl)-2-(tyrosylamino)acetic acid *n*-butyl ester hydrochloride **3** (36 mg, 0.06 mmol) and 2,4,6-trimethoxybenzene (20.4 mg, 0.12 mmol) in ethyl acetate (2.5 cm^3) under argon at room temperature was added tetrachlorostannane (42 μL, 0.36 mmol). After stirring for 17 h the reaction was quenched with water (5 cm^3) and the organic material was extracted with ethyl acetate (2 × 10 cm^3). The combined organic extracts were dried and evaporated to yield 47 mg of crude product. Chromatography over silica gel eluting with dichloromethane containing increasing amounts of methanol (0 ⟶ 5%) gave **4a** as a white solid (19.6 mg, 42%). HPLC (Grad 1) R_t = 13 min, 95%. δ_H ($CDCl_3$) 0.86 (3H, t, *J* = 7.2, Me of butyl); 1.21–1.37 (3H, m, CH_2 of butyl and 1H exchangeable); 1.46–1.57 (2H, m, CH_2 of butyl); 1.80–2.09 (2H, br m, 2 × exchangeable H); 2.59 (1H, br s, exchangeable H); 2.88–3.04 (2H, m, CH_2 of tyrosine); 3.60–3.75 (2H, 4-CH_2OH); 3.68 (6H, s, 2-OMe and 6-OMe); 3.75 (3H, s, OMe); 3.79 (1H, d, *J* = 6.9, H-2); 3.96 (1H, br d, *J* = 6.9, H-3); 3.91–3.99 (2H, m, CO_2CH_2 and H-3); 4.08–4.16 (1H, m, CO_2CH_2); 4.35–4.44 (1H, m, ZNH*CH*CON); 4.53 (1H, d, *J* = 10.5, H-5); 4.72 (1H, d, *J* = 10.3, H-6); 4.92 (1H, t, *J* = 6.9, NH*CH*CO_2); 4.97–5.08 (2H, m, CH_2 of C_6H_5); 5.57 (1H, br s, NH of Z group); 6.09 (2H, s, H-3 and H-5 of trimethoxyphenyl); 6.62–6.71 (2H, m, H-6′ and H-8′); 6.96 (2H, d, *J* = 6.96, H5′ and H9′); 7.22–7.35 (5H, m, C_6H_5); *m*/*z* $(FAB)^+$ 795 (MNa^+, 40%), 773 (MH^+, 100).

(2*S*,3*S*,4*S*,5*S*,6*S*)-[4-Hydroxymethyl-1,3,4,5-tetrahydroxy-6-(2,4,6-trimethoxyphenyl)piperidin-2-yl](tyrosylamino)acetic acid *n*-butyl ester 4b

Compound **4a** (14 mg, 0.018 mmol) was dissolved in ethyl acetate (5 cm^3) and hydrogenated over 10% palladium charcoal (27 mg) at atmosphere pressure. After 7 h the mixture was filtered and the filtrate evaporated to yield the crude product. Chromatography over silica gel eluting with dichloromethane containing increasing amounts of methanol (0 ⟶ 25%) gave **4b** as a white solid (10 mg, 40%). HPLC (Grad 2) R_t = 13.1 min, 76%. δ_H (CD_3OD) 0.78 (3H, t, *J* = 7.2, Me of butyl); 1.17–1.26 (2H, m, CH_2 of butyl); 1.37–1.42 (2H, m, CH_2 of butyl); 2.51 (1H, dd, *J* = 13.6 and 8.5, CH_2 of tyrosine); 2.97 (1H, dd, *J* = 13.9 and 4.3, CH_2 of tyrosine); 3.45 (1H, dd, *J* = 8.6 and 4.6, H-2); 3.70 (12H, m, H-3, 4-CH_2OH and 3 × OMe of trimethoxyphenyl); 3.86–4.05 (4H, m, H_2N*CH*CO, CO2*CH*2 and H-5); 4.51 (1H, d, *J* = 9.9, H-6); 4.80 (NH*CH*CO under water peak); 6.12 (2H, s, H-3 and H-5 of trimethoxyphenyl); 6.63 (2H, d, *J* = 6.6, H-6′ and H-8′); 6.95 (2H, d, *J* = 8.2, H-5′ and H-9′). *m*/*z* $(FAB)^+$ 661 (MNa^+, 11%), 639 (MH^+, 100).

(2*S*,3*S*,4*S*,5*S*,6*S*)-[4-Hydroxymethyl-1,3,4,5-tetrahydroxy-6-(2,4-dimethoxyphenyl)piperidin-2-yl][(*N*-benzyloxycarbonyl)-tyrosylamino]acetic acid *n*-butyl ester 5a

From **3** (60 mg, 0.1 mmol) using an identical methodology to that described above, but with 2,4-dimethoxybenzene as the nucleophile, **5a** was obtained after 48 h (38 mg, 51%). HPLC (Grad 1) R_t = 12.8 min, 97%. δ_H (CD_3OD) 0.96 (3H, t, *J* = 7.2, Me of butyl); 1.34–1.49 (2H, m, CH_2 of butyl); 1.57–1.69 (2H, m, CH_2 of butyl); 2.80 (1H, dd, *J* = 13.9 and 9.4, CH_2 of tyrosine); 3.15 (1H, dd, *J* = 13.9 and 4.7, CH_2 of tyrosine); 3.65

(1H, d, J = 11.2, 4-CH_2OH); 3.72 (3H, s, OMe); 3.77 (3H, s, OMe); 3.84 (1H, d, J = 11.4, 4-CH_2OH); 3.91 (1H, dd, J = 7.0 and 5.9, H-2); 3.96 (1H, d, J = 5.2, H-3); 4.06–4.14 (2H, m, CO_2CH_2); 4.38 (1H, d, J = 8.6, H-5); 4.39–4.42 (1H, m, ZNH-*CH*CON); 4.43 (1H, d, J = 8.6, H-6); 5.00 (1H, d, J = 14.2, CH_2 of Z); 5.14 (1H, d, J = 7.0, NH*CH*CO_2); 6.51–6.55 (2H, m, H-3 and H-5 of dimethoxyphenyl); 6.70 (2H, d, J = 8.4, H-6′ and H-8′); 7.07 (2H, d, J = 8.4, H-5′ and H-9′); 7.22–7.35 (5H, aromatics of C_6H_5); 7.44 (1H, d, J = 8.3, H-6 of dimethoxyphenyl). *m*/*z* (FAB)$^+$ 764 (MNa^+, 24%), 742 (MH^+, 100).

(2*S*,3*S*,4*S*,5*S*,6*S*)-[4-Hydroxymethyl-1,3,4,5-tetrahydroxy-6-(2,4-dimethoxyphenyl)piperidin-2-yl](tyrosylamino)acetic acid *n*-butyl ester 5b

Compound **5a** (30 mg, 0.04 mmol) was hydrogenated in an identical way to that described above to give **5b** as a white solid (10 mg, 41%). HPLC (Grad 2) R_t = 13.1 min, 96%. δ_H ($CDCl_3$) 0.99 (3H, t, J = 7.3, Me of butyl); 1.40–1.52 (2H, m, CH_2 of butyl); 1.60–1.68 (2H, m, CH_2 of butyl); 2.73 (1H, dd, J = 13.6 and 8.2, CH_2 of tyrosine); 3.11 (1H, dd, J = 13.6 and 8.2, CH_2 of tyrosine); 3.62 (1H, dd, J = 8.1 and 4.9, H_2N*CH*CO); 3.72 (1H, d, J = 11.2, CH_2OH); 3.83 (1H, d, J = 11.2, 4-CH_2OH); 3.84 (6H, s, 2 × OMe); 3.88 (1H, dd, J = 6.0 and 5.9, H-2); 3.94 (1H, d, J = 5.9, H-3); 4.08–4.20 (2H, m, CO_2CH_2); 4.41 (1H, d, J = 8.4, H-5); 4.71 (1H, d, J = 8.5, H-6); 5.11 (1H, d, J = 6.6, NH*CH*CO); 6.54–6.58 (2H, m, H-3 and H-5 of dimethoxyphenyl); 6.57 (2H, d, J = H-6′ and H-8′); 6.78 (2H, d, J = 7.9, H-5′ and H-9′); 7.13 (1H, d, J = 8.4, H-3 of dimethoxyphenyl); 7.47 (1H, d, J = 8.5, H-6 of dimethoxyphenyl). *m*/*z* (FAB)$^+$ 608 (MH^+, 100%).

(2*S*,3*S*,4*R*,5*S*,6*S*)-[4-Hydroxymethyl-6-(2-furyl)-1,3,4,5-tetrahydroxypiperidin-2-yl]-2-[(*N*-benzyloxycarbonyl)tyrosylamino]-acetic acid *n*-butyl ester 6a and (2*S*,3*S*,4*R*,5*S*,6*R*)-[4-hydroxymethyl-6-(2-furyl)-1,3,4,5-tetrahydroxypiperidin-2-yl]-2-[(*N*-benzyloxycarbonyl)tyrosylamino]acetic acid *n*-butyl ester 6b

From **3** (58 mg 0.096 mmol) using an identical methodology to that described above but with furan as the nucleophile a 3 : 1 mixture of **6a** and **6b** was obtained after 48 h in 60% yield. Chromatographic separation gave **6a** (30 mg, 45%). HPLC (Grad 2) R_t = 12.2 min, 90%. δ_H (CD_3OD) 0.94 (3H, t, J = 7.4, *Me* of butyl); 1.37–1.45 (2H, m, CH_2 of butyl); 1.59–1.66 (2H, m, CH_2 of butyl); 2.82 (1H, 14.0 and 9.2); 3.12 (1H, dd, J = 13.8 and 5.6); 3.40 (1H, d, J = 10.8, 4-CH_2OH); 3.71 (1H, d, J = 10.0, 4-CH_2OH); 3.94 (1H, d, J = 6.3, H-3); 4.04 (1H, dd, J = 6.4 and 5.6, H-2); 4.11 (2H, t, J = 7.0, $CO_2CH_2CH_2$); 4.38 (1H, dd, J = 8.6 and 5.6, ZNH*CH*CON); 4.43 (1H, d, J = 6.0, H-5); 4.68 (1H, d, J = 5.9, H-6); 5.08 (2H, m, CH_2 of Z); 5.23 (1H, d, J = 4.1, NH*CH*CO_2); 6.38 (1H, dd, J = 3.1 and 1.5, H-4 of furan); 6.50 (1H, d, J = 2.6, H-3 of furan); 6.90 (2H, d, J = 8.4, H-6′ and 8′); 7.07 (2H, d, J = 8.4, H-5′ and H-7′); 7.30–7.34 (5H, m, C_6H_5); 7.47 (1H, d, J = 4.1, H-1.5, H-5 of furan). *m*/*z* (FAB)$^+$ 672 (MH^+, 100%); and **6b** (10 mg, 15%) of HPLC (Grad 2) R_t = 12.2 min, 86%. δ_H (CD_3OD) 0.92 (3H, t, J = 7.2, *Me* of butyl); 1.35–1.47 (2H, m, CH_2 of butyl); 1.56–1.64 (2H, m, CH_2 of butyl); 2.82 (1H, dd, J = 14.0 and 4.5, H-3′); 3.17 (1H, dd, J = 14.2 and 4.8, H-3′); 3.82 (1H, d, J = 8.4, H-3); 3.96 (1H, d, J = 11.6, 4-CH_2OH, other H under MeOH peak); 3.98 (1H, dd, J = 8.2 and 3.9, H-2); 4.07–4.18 (2H, m, $CO_2CH_2CH_2$); 4.38 (1H, d, J = 5.1, H-5); 4.45 (1H, dd, J = 8.4 and 3.6, ZNH-*CH*CON); 4.48 (1H, dd, J = 9.5 and 4.8, H-2′); 4.51 (1H, d, J = 5.1, H-6); 4.96 (1H, d, J = 12.5, CH_2 of Z group); 5.09 (1H, d, J = 3.9, NH*CH*CO_2); 6.34 (1H, dd, J = 3.0 and 1.9, H-4 furan); 6.43 (1H, d, J = 3.1, H-3 furan); 6.68 (2H, d, J = 8.33, H-6′ and H-8′); 7.06 (2H, d, J = 8.44, H-5′ and H-9′); 7.21–7.31 (5H, m, C_6H_5); 7.41 (1H, d, J = 1.9, H-5 furan). *m*/*z* (FAB)$^+$ 672 (MH^+, 100%).

Acknowledgements

We thank Anthony Beck, Analytical Sciences, GlaxoSmith-Kline, Harlow for the NMR experiments.

Notes and references

† The alternative boat conformation, enabling both the aryl and amino acid substituents to be equatorial, was discounted as there was no observable NOE between H-2 and H-5 or H-3 and H-6.

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