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Branched tetrahydrofuran α,α-disubstituted-δ-sugar amino acid scaffolds from branched sugar lactones: a new family of foldamers?

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Abstract—Efficient S_N2 ring closure of open chain trihydroxytriflates—in which the leaving group is on a primary carbon adjacent to a quaternary centre—provides access to tetrahydrofurans with branched carbon chains from branched carbohydrate lactones; the first examples of a new class of branched chain tetrahydrofuran α,α-disubstituted-δ-sugar amino acid scaffolds are described.

1. Introduction

Sugar amino acids (SAAs) are an important class of peptidomimetics[1] as building blocks in combinatorial chemistry[2] and as an extensive class of foldamers.[3] Their predisposition to induce novel secondary structures is well established.[4] Although pyranose[5] and oxetanose[6] δ-SAAs have been widely studied, furanose tetrahydrofuran (THF) δ-SAAs[7] are the most thoroughly investigated dipeptide isosteres with significant biological activity.[8]

Almost all SAAs have linear carbon chains, since the only carbohydrates from which they may be derived also have unbranched chains;[9] the rare examples of SAA, which have a branched carbon chain[10] require substantial synthetic effort. Recently, the Kiliani reaction on ketohexoses, followed by acetonation, has provided a number of easily accessible diacetonides[11,12] containing branched chains, which may allow ready access to a new class of α,α-disubstituted-δ-SAAs.

In the synthesis of a series of THF δ-SAAs, the THF ring was generated by a nucleophilic displacement of a triflate at C-2 of a lactone by conversion into an open chain hydroxymethyl ester [not isolated], which closed in situ to the THF carboxylate;[13] for example, the lactone triflate **1** in methanol in the presence of pyridine gave the open chain ester **2**, which closed to form the δ-SAA scaffold **3**.[14] The combination of the excellent triflate leaving group and of an α-carbonyl functionality makes this an efficient S_N2 reaction. This letter reports the synthesis of branched THF δ-SAA scaffolds by an unexpectedly efficient [presumably] S_N2 closure of trihydroxytriflates in which the leaving group is on a primary carbon adjacent to a quaternary centre. Thus, the azidolactones **4** and **7** were converted in good isolated yields to the carbon branched THF esters **6** (77%) and **9** (79%), respectively, by reaction with hydrogen chloride in methanol; the sequence involves removal of the acetonide protecting group and ester exchange to give the open chain trihydroxy triflates **5** and **8**, which undergo spontaneous closure to the branched carbon chain δ-SAA scaffolds (Scheme 1).

2. Synthesis of *trans*-THF δ-SAA scaffold 6 from D-ribonolactone

For the synthesis of the δ-SAA scaffold **6**, in which the azide component on the THF is *trans* to the ester function, the primary alcohol in the protected D-ribonolactone[15] **10** was esterified with triflic anhydride in dichloromethane in the presence of pyridine, and the resulting triflate treated with sodium azide in ethyl acetate to afford the azide **11** {[mp 36 °C, $[\alpha]_D^{23}$ +18.9 (*c*, 1.66 in $CHCl_3$) [Lit., [16] mp 39 °C, $[\alpha]_D$ +15.0 (*c*, 1.00 in $CHCl_3$)]]} (Scheme 2).

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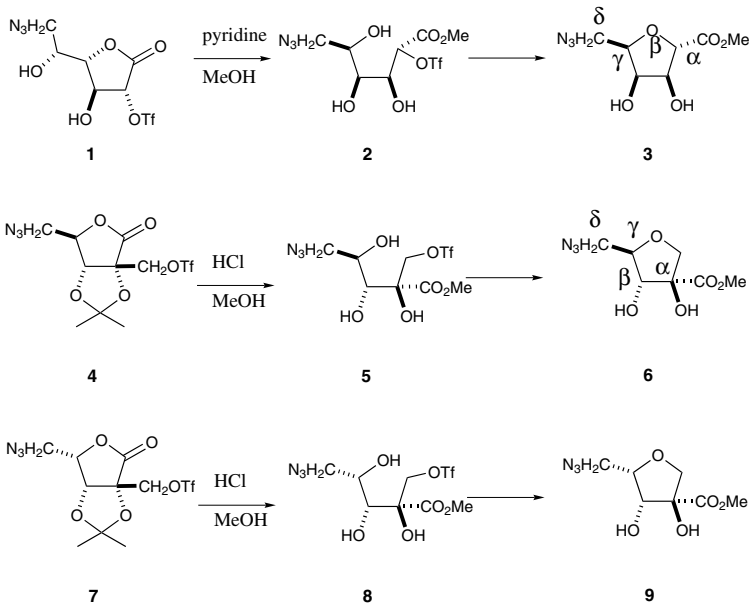
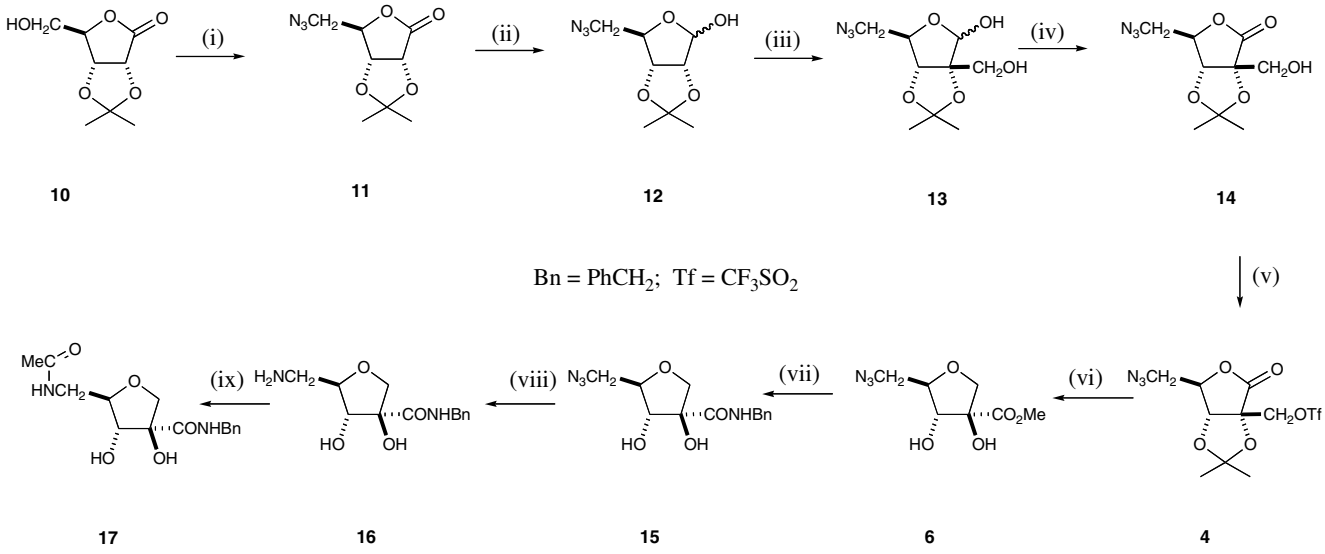


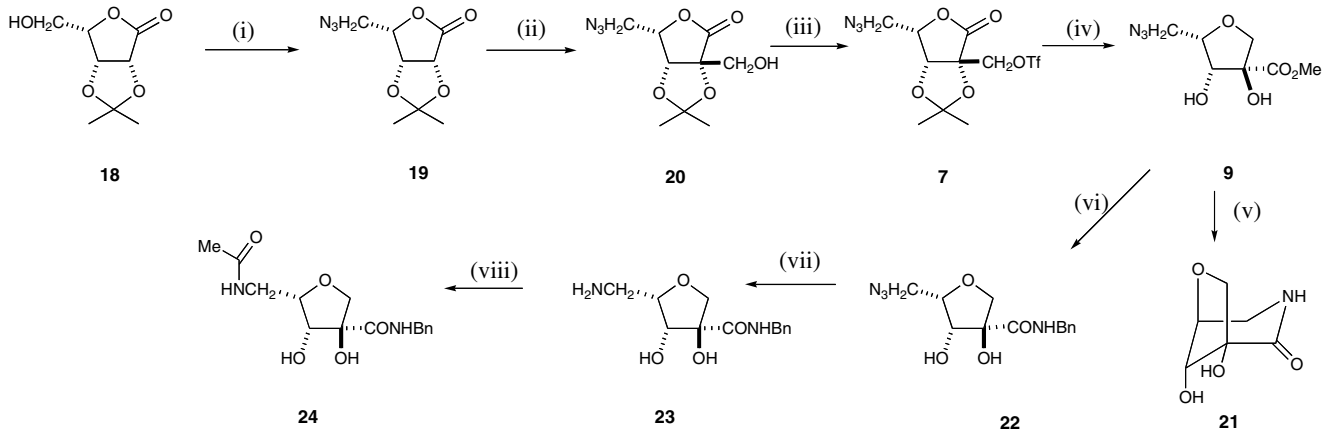
Scheme 1. Synthesis of branched THF δ-SAAs.



Scheme 2. Reagents and conditions: (i) Tf_2O, pyridine, CH_2Cl_2; then NaN_3, EtOAc (77%); (ii) DIBAL, CH_2Cl_2 −78 °C (93%); (iii) CH_2O, K_2CO_3, H_2O (92%); (iv) Br_2, $BaCO_3$, H_2O (92%); (v) Tf_2O, pyridine, CH_2Cl_2 (100%); (vi) HCl, MeOH (77%); (vii) $BnNH_2$, 120 °C (83%); (viii) H_2, 10% Pd/C, dioxane (91%); (ix) $(MeCO)_2O$, pyridine; then K_2CO_3, MeOH (82%).

Reduction of the azidolactone **11** with diisobutylaluminium hydride (DIBAL) in dichloromethane gave **12**, which underwent an efficient Ho crossed aldol condensation[17] with aqueous formaldehyde in the presence of potassium carbonate to afford the carbon branched lactol **13** [mp 115–117 °C, $[\alpha]_D^{25}$ +23.1 (*c*, 0.95 in MeCN)]. Oxidation of the lactol **13** by aqueous bromine in the presence of barium carbonate gave the azido lactone **14**,[18] the structure of which was confirmed by X-ray analysis.[19] Esterification of the primary alcohol in **14** with triflic anhydride in dichloromethane in the presence of pyridine gave the triflate **4** [an oil, $[\alpha]_D^{21}$ +58.9 (*c*, 0.52 in CH_2Cl_2)]. Reaction of **4** with hydrogen chloride in methanol caused removal of the acetonide protecting group, ring opening to the trihydroxy triflate ester and subsequent ring closure to give the key azido ester **6**.[20]

The sterically hindered carbonyl group in **6** underwent relatively easy nucleophilic attack; treatment of **6** with benzylamine at 120 °C gave the corresponding benzylamide **15** [mp 109–110 °C, $[\alpha]_D^{21}$ +61.1 (*c*, 0.44 in methanol)], which on hydrogenation in 1,4-dioxane in the presence of 10% palladium on carbon afforded the amine **16** [mp 85–85.5 °C, $[\alpha]_D^{23}$ +8.5 (*c*, 2.49 in MeOH)]. Peracetylation of **16** with acetic anhydride in pyridine, followed by removal of the esters by ester exchange with potassium carbonate in methanol, gave the bis-amide **17**



Scheme 3. Reagents and conditions: (i) Tf_2O, pyridine, CH_2Cl_2; then NaN_3, Me_2CO (74%); (ii) DIBAL, CH_2Cl_2; then CH_2O, K_2CO_3, H_2O; then Br_2, $BaCO_3$, H_2O (68%); (iii) Tf_2O, pyridine, CH_2Cl_2 (100%); (iv) HCl, MeOH (79%); (v) H_2, 10% Pd/C, dioxane (72%); (vi) $BnNH_2$, 120 °C (95%); (vii) H_2, 10% Pd/C, dioxane (89%); (ix) $(MeCO)_2O$, pyridine; then K_2CO_3, MeOH (74%).

[mp 155–155.5 °C; $[\alpha]_D^{23}$ +0.64 (*c*, 0.70 in methanol)] as a novel dipeptide isostere.

The ease of these reactions suggests that, together with the overall yield for the formation of **6** from **10** of 47% allowing significant quantities to be prepared, **6** can be studied as a member of a potential new class of foldamer.

3. Synthesis of *cis*-THF δ-SAA scaffold 9 from L-lyxonolactone

A similar sequence was followed from the readily available protected L-lyxonolactone **18**[21] for the epimeric δ-SAA scaffold **9**, in which the azide component in the THF ring is *cis* to the ester function. The alcohol **18** was converted by triflation and azide displacement to the azide **19** [mp 72–74 °C, $[\alpha]_D^{22}$ −76.8 (*c*, 0.52 in $CHCl_3$)] by an identical procedure to that for the preparation from D-lyxonolactone[22] of the corresponding enantiomer [mp 59.7 °C, $[\alpha]_D$ −71.0 (*c*, 2.0 in $CHCl_3$)].[23] DIBAL reduction of the lactone **19**, followed by a Ho crossed aldol condensation to the branched lactol,[24] and subsequent oxidation by aqueous bromine afforded the branched lyxonolactone **20**.[25] Esterification of the primary alcohol in **20** with triflic anhydride in dichloromethane in the presence of pyridine gave the triflate **7** [mp 33.5–34 °C; $[\alpha]_D^{21}$ −29.4 (*c*, 0.70 in EtOAc)], which on treatment with hydrogen chloride in methanol gave the branched scaffold **9**.[26] The overall yield of **9** from the protected lyxonolactone **18** was 40% (Scheme 3).

Hydrogenation of the azido ester **9** in the presence of a palladium catalyst in dioxane produced the corresponding amine, which spontaneously cyclized to the bicyclic lactam **21** [mp 194–197 °C (dec.); $[\alpha]_D^{23}$ −5.2 (*c*, 0.22 in MeOH)], the structure of which was firmly established by X-ray crystallographic analysis.[27] The ease of the ring closure indicated that nucleophilic attack on the carbonyl group is not particularly hindered. The azido ester scaffold **9** was also treated with benzylamine to afford the amide **22** [oil, $[\alpha]_D^{21}$ −0.82 (*c*, 0.52 in MeOH)], which on catalytic hydrogenation gave the corresponding amine **23** [mp 112–113 °C; $[\alpha]_D^{21}$ −6.7 (*c*, 0.39 in MeOH)]. Treatment of the amine **23** with acetic anhydride in pyridine, followed by removal of the esters by transesterification with potassium carbonate in methanol afforded the dipeptide mimetic **24** [mp 164–166 °C; $[\alpha]_D^{23}$ −6.7 (*c*, 0.39 in MeOH)], the structure of which was confirmed by X-ray crystallographic analysis.[28]

4. Summary

This letter reports the first examples of the efficient generation of THF rings with branched carbon chains from branched sugar lactones, producing carboxylates with quaternary centres adjacent to the acid functionality. More efficient routes to these and other such THF SAA scaffolds should be available from the diacetonides generated from the Kiliani reaction on ketohexoses.[11,12] This will allow studies on the structure of homooligomers from this new class of potential foldamer.

Acknowledgements

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18. Data for the azido hamamelonolactone **14**: mp 100.5–102 °C; $[\alpha]_D^{25}$ +11.3 (*c*, 0.31 in MeCN); m/z (AutoSpec-ETOF CI^+): 261.0 ($M + NH_4^+$, 100%), found: 261.1197 $[M + NH_4^+]$ $C_9H_{17}N_4O_5$ requires 261.1199; ν_{max} (thin film): 3430 (OH), 2129 (N_3), 1782 (C=O) cm^{-1}; δ_H ($CDCl_3$, 400 MHz): 1.45, 1.47 (6H, 2 × s, $C(CH_3)_2$), 2.30 (1H, b, OH), 3.70 (2H, m, H-5′ and H-5), 3.94 (1H, d, $J_{H\text{-}2',H\text{-}2}$ 11.7 Hz, H-2′), 4.08 (1H, d, H-2′), 4.66 (1H, a-t, $J_{H\text{-}4,H\text{-}5'}$, $J_{H\text{-}4,H\text{-}5}$ 5.58 Hz, H-4), 4.64 (1H, s, H-3); δ_C ($CDCl_3$, 100 MHz): 26.7, 26.9 ($C(CH_3)_2$), 51.9 (C-5), 61.5 (C-2′), 79.7 (C-3), 81.7 (C-4), 85.3 (C-2), 114.0 ($C(CH_3)_2$), 174.4 (C=O). $C_9H_{17}N_4O_5$ requires: C 44.44, H 5.39, N 17.28; found C 44.39, H 5.37, N 17.32.
19. Cambridge Crystallographic Data Centre deposition number for **14**: CCDC 267517 [http://www.ccdc.cam.ac.uk.
20. Data for the *trans*-azido ester **6**: viscous oil, $[\alpha]_D^{21}$ +24.5 (*c*, 4.38 in MeOH); *m/z* (AutoSpecETOF CI^+): 235.1 ($M + NH_4^+$, 28%), found: 235.1048 $[M + NH_4^+]$ $C_7H_{15}N_4O_5$ requires 235.1042; ν_{max} (thin film): 3428 (OH), 2106 (N_3), 1735 (C=O) cm^{-1}; δ_H ($CDCl_3$, 400 MHz): 3.44 (1H, dd, $J_{H\text{-}6,H\text{-}6'}$ 13.4 Hz, $J_{H\text{-}6,H\text{-}5}$ 5.0 Hz, H-6), 3.60 (1H, dd, $J_{H\text{-}6',H\text{-}5}$ 3.6 Hz, H-6′), 3.71 (1H, d, $J_{OH\text{-}4,H\text{-}4}$ 5.5 Hz, OH-4), 3.86 (3H, s, OMe), 3.96 (1H, d, $J_{H\text{-}2,H\text{-}2'}$ 9.7 Hz, H-2), 4.02-4.08 (1H, m, H-5), 4.18 (1H, a-t, H-4), 4.21 (1H, s, OH-3), 4.26 (1H, d, $J_{H\text{-}2',H\text{-}2}$ 9.7 Hz, H-2′); δ_C ($CDCl_3$, 100 MHz): 51.7 (C-5), 53.4 (OMe), 74.5 (C-2), 81.2 (C-4), 82.6 (C-5), 84.0 (C-3), 172.9 (C=O).
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25. Data for branched lyxonolactone **20**: mp 98–99 °C; $[\alpha]_D^{21}$ −0.11 (*c*, 0.73 in $CHCl_3$); *m/z* (AutoSpeC CI^+): 261.1 ($[M+NH_4]^+$, 100%), found: 261.1204 $(M+NH_4)^+$ $C_9H_{17}N_4O_5$ requires 261.1199; ν_{max} (thin film): 3221 (OH), 2101 (N_3), 1784 (C=O) cm^{-1}; δ_H ($CDCl_3$, 400 MHz): 1.43 and 1.49 (6H, 2 × s, $C(CH_3)_2$), 2.19–2.25 (1H, m, $J_{OH\text{-}2',H\text{-}2 \text{ and } H\text{-}2'}$ 3.9 Hz, O*H*), 3.65 (1H, dd, $J_{H\text{-}5,H\text{-}5'}$ 13.1 Hz, $J_{H\text{-}5,H\text{-}4}$ 6.1 Hz, H-5), 3.73 (1H, dd, $J_{H\text{-}5',H\text{-}4}$ 7.3 Hz, H-5′), 3.94 (1H, a-dd, $J_{H\text{-}2,H\text{-}2'}$ 11.4 Hz, H-2), 4.03 (1H, a-dd, H-2′), 4.58 (1H, ddd, $J_{H\text{-}4,H\text{-}3}$ 3.4 Hz, H-4), 4.79 (1H, d, H-3); δ_C ($CDCl_3$, 125 MHz): 26.4, 26.9 ($C(CH_3)_2$), 49.5 (C-5), 61.4 (C-2′), 77.2 (C-4), 78.4 (C-3), 86.0 (C-2), 114.2 (*C* $(CH_3)_2$), 174.7 (C=O); $C_9H_{17}N_4O_5$ requires: C 44.44, H 5.39, N 17.28; found: C 44.41, H 5.39, N 17.10.
26. Data for the *cis*-azido ester **9**: yellow oil, *m/z* (AutoSpec-E CI^+): 218.0 ($[M + H]^+$, 100%), found: 218.0776 $[M + H]^+$ $C_7H_{12}N_3O_5$ requires 218.0777; $[\alpha]_D^{21}$ −39.5 (c, 0.61 in MeOH); ν_{max} (thin film): 3418 (OH), 2107 (N_3), 1732 (C=O) cm^{-1}; δ_H (CD_3CN, 400 MHz): 2.85 (1H, dd, $J_{H\text{-}6',H\text{-}6}$ 12.8 Hz, $J_{H\text{-}6',H\text{-}5}$ 5.0 Hz, H-6), 2.92 (1H, dd, $J_{H\text{-}6,H\text{-}5}$ 7.7 Hz, H-6), 3.18 (1H, d, $J_{H\text{-}2,H\text{-}2'}$ 9.8 Hz, H-2), 3.19 (3H, s, OMe), 3.38 (1H, d, $J_{OH\text{-}4,H\text{-}4}$ 5.9 Hz, OH-4), 3.47-3.52 (1H, dd, $J_{H\text{-}4,H\text{-}5}$ 3.5 Hz, H-4), 3.65 (1H, ddd, H-5), 3.79 (1H, d, H-2′), 3.80 (1H, br, OH-3); δ_C (CD_3CN, 100 MHz): 49.83 (C-6), 51.81 (OMe), 73.42 (C-2), 77.92 (C-4), 80.04 (C-5), 84.39 (C-3), 170.93 (C=O).
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