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cis- and *trans*-3-Azido-oxetane-2-carboxylate scaffolds: hexamers of oxetane *cis*-β-amino acids

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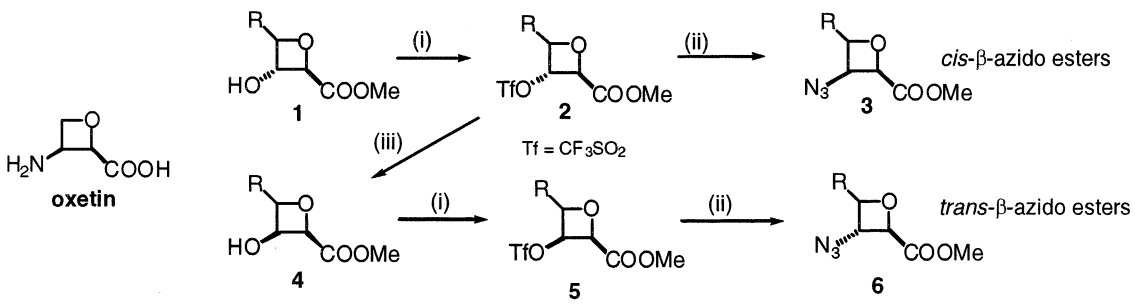
Abstract—Efficient synthesis of both *cis*- and *trans*-3-azido-oxetane-2-carboxylates relies upon efficient nucleophilic displacements of 3-*O*-triflates of oxetanes by trifluoroacetate and azide. Such structures are scaffolds for incorporation of oxetane-β-amino acids into oligomers; the synthesis of a series of protected β-hexapeptides and the X-ray crystal structure of methyl 2,4-anhydro-6-deoxy-5-*O*-benzyl-L-altronate are reported. © 2001 Elsevier Science Ltd. All rights reserved.

The challenge of designing unnatural oligomers ('foldamers'[1]) with propensities to adopt specific, compact conformations has received considerable attention in recent years.[2] Amongst the most extensively studied classes of foldamers are the β-peptides.[3] Short β-peptides based on both acyclic and cyclic residues have revealed helices, sheets and turn structures in the solid state, organic media and most significantly aqueous solution.[4,5] These endeavours have also highlighted potential clinical applications of β-peptide foldamers including antimicrobial activity in designed mimics of natural antibiotic peptides,[6] and inhibition of small-intestinal cholesterol and fat absorption.[7] The thorough structural investigations conducted on β-peptides incorporating 2-aminocyclopentane- and 2-aminocyclohexane-carboxylic acids,[8] and their pyrrolidine and piperidine-based analogues,[4] contrast with only limited reports on β-peptides containing four-membered cyclic residues.[9] The antibiotic oxetin[10,11] is the only naturally occurring β-amino acid yet reported that contains an oxetane ring. In order to study the potential of oxetane amino acids as a new family of foldamers, efficient routes to suitable oxetane scaffolds are required. This paper reports the synthesis of *cis*- and *trans*-3-azido-oxetane-2-carboxylates and of hexamers of *cis*-β-amino acids containing the oxetane structural motif.

Oxetanes **1** in which the hydroxyl group at C-3 is free and *trans* to the carboxylate are accessible from carbohydrate lactones.[12] Esterification of the alcohol group in **1** with triflic anhydride affords stable triflates **2**, even though the triflate is β to an ester function (Scheme 1). Reaction of **2** with sodium azide results in high yields of *cis*-β-azido esters **3**.[13] Alternatively, reaction of the triflates **2** with caesium trifluoroacetate in butanone[14] forms *cis*-β-hydroxy esters **4**. Conversion of **4** to the



Scheme 1. (i) $(CF_3SO_2)_2O$, pyridine, CH_2Cl_2; (ii) NaN_3, DMF; (iii) CF_3COOCs, MeCOEt.

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triflates **5**, followed by treatment with azide anion, provides access to the *trans*-β-azido esters **6**. The highly efficient S_N2 displacements of stable oxetane triflates by both nitrogen and oxygen nucleophiles allows the generation of a family of β-azidooxetane carboxylates for their study as building blocks for potential foldamers.

An example of such a strategy is shown in Scheme 2. Oxidation of L-rhamnose **7** with bromine water, followed by treatment with benzaldehyde formed the lactone **8** in 41% yield; esterification of the remaining alcohol in **8** with triflic anhydride and subsequent reaction with potassium carbonate in methanol gave the oxetane **9** with overall *retention* of configuration at C-2 in 55% yield as previously reported.[15]

Methanolysis of **9** with hydrogen chloride in methanol gave the diol **10** {oil, $[\alpha]_D^{22}$ +49.0 (*c*, 1.5)}[16] in 74% yield. Silylation of the diol **10** with *tert*-butyldimethylsilyl chloride in DMF in the presence of imidazole gave the 5-*O*-silyl derivative **11** {mp 49–51°C, $[\alpha]_D^{22}$ +0.65 (*c*, 0.8)} in 31% isolated yield (77% based on unrecovered starting material), together with some disilylated material. Esterification of the alcohol **11** with triflic anhydride formed the corresponding triflate (76% yield) which, with sodium azide in DMF, afforded the silylated *cis*-β-azidoester[17] **18** in 96% yield.

The synthesis of the benzylated azidoesters **16** and **17**, required a regioselective reduction of the benzylidene acetal **9**. Reaction of **9** with triethylsilane and trifluoroacetic acid[18] afforded the 5-*O*-benzylether **12** {$[\alpha]_D^{22}$ +69.7 (*c*, 1.1)} as the only isolated product in 76% yield. Esterification of the remaining free hydroxyl group at C-3 in **12** with triflic anhydride gave the stable triflate **13** {oil, $[\alpha]_D^{22}$ +13.4 (*c*, 1.1)} in 96% yield. Reaction of the triflate **13** with sodium azide in DMF afforded the benzyl-protected *cis*-β-azidoester **17**[19] in 97% yield. Treatment of **13** with caesium trifluoroacetate in butanone formed the inverted alcohol **14** {mp 93–94°C; $[\alpha]_D^{22}$ +30.5 (*c*, 0.5)} in 90% yield; the structure of the benzyl ether **14** was firmly established by X-ray crystallographic analysis (Fig. 1).[20] Subsequent triflation of **14** gave the triflate **15** (99% yield) which on reaction with sodium azide gave the protected *trans*-β-azidoester **16**.[21] The *cis*-β-azidoesters **17** and **18** have the same absolute configuration at C-2 and C-3 of the oxetane ring as does oxetin.

An analogous sequence starting from D-xylose **19** is shown in Scheme 3. Thus, bromine oxidation of xylose[22] followed by treatment with benzaldehyde afforded the lactone **20** in 60% overall yield. Sequential treatment of **20** with triflic anhydride in dichloromethane in the presence of pyridine, and reaction with potassium carbonate in methanol, resulted in inversion of configuration at C-2 to give the oxetane **21** {mp 121–126°C (Lit.[23] mp 122–124°C)} in 73% yield; this synthesis is superior to that previously reported from D-lyxonolactone.[23] A highly regioselective ring opening of the benzylidene acetal **21** with triethylsilane and trifluoroacetic acid gave **22** {mp 62–63°C, $[\alpha]_D^{25}$ −5.6 (*c*, 0.9)} in 83% yield. Formation of the stable triflate **25** {mp 29–31°C; $[\alpha]_D^{23}$ +24.6 (*c*, 1.05)} [97% yield] allowed access to the azide **26**[24] in 93% yield and to the epimeric alcohol **24** {mp 83–84°C; $[\alpha]_D^{24}$ −17.2 (*c*, 1.03)} in 99% yield. Esterification of **24** with triflic anhydride, followed by treatment with sodium azide gave the *trans*-β-azidoester **23**[25] in 84% overall yield.

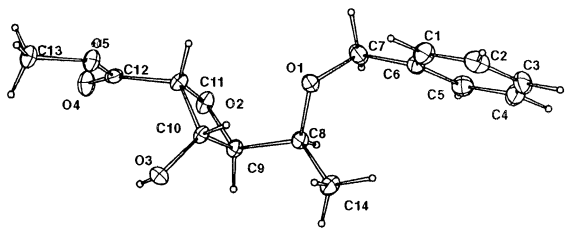
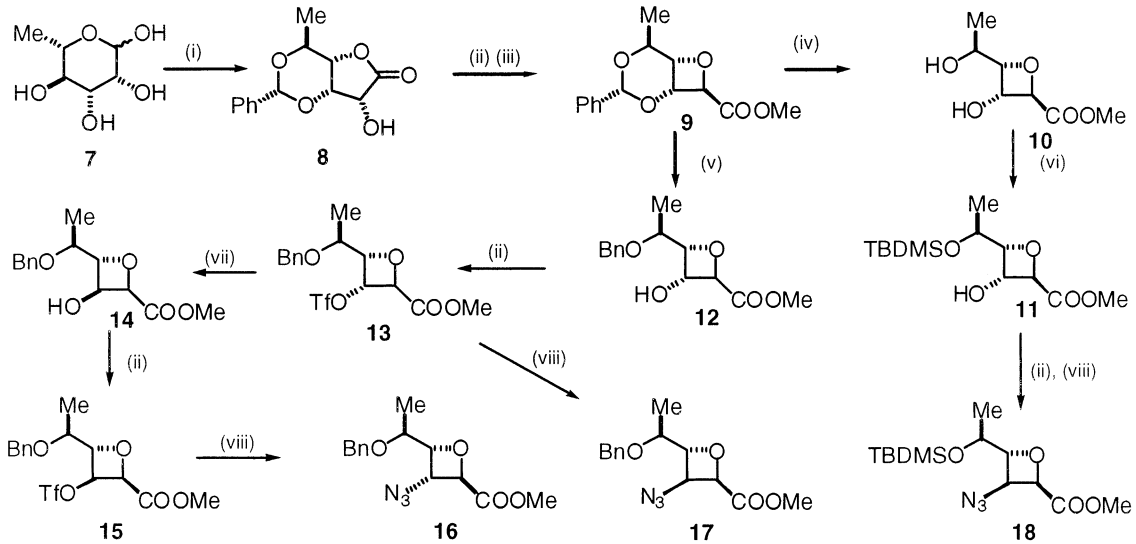
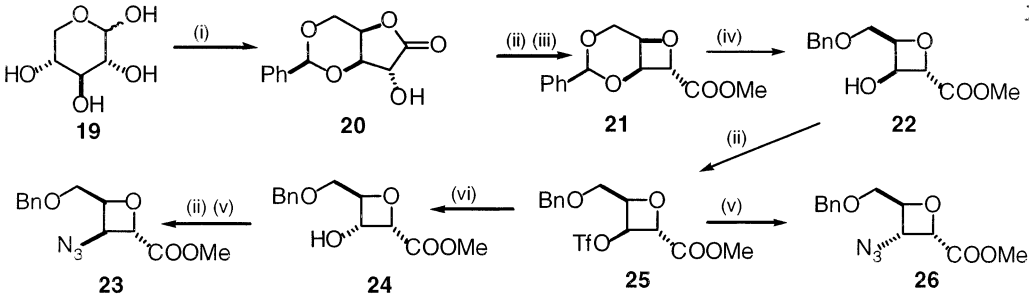


Fig. 1. X-Ray crystal structure of methyl 2,4-anhydro-6-deoxy-5-*O*-benzyl-L-altronate **14**.

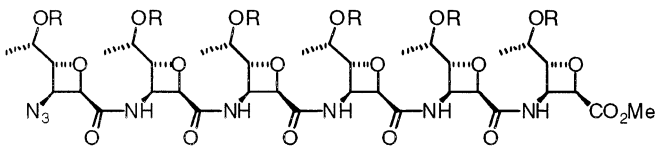


Scheme 2. (i) Br_2; then PhCHO, HCl; (ii) $(CF_3SO_2)_2O$, pyridine; (iii) K_2CO_3, MeOH; (iv) HCl, MeOH; (v) Et_3SiH, CF_3COOH; (vi) $^tBuMe_2SiCl$, imidazole, DMF; (vii) CF_3COOCs, MeCOEt; (viii) NaN_3, DMF.

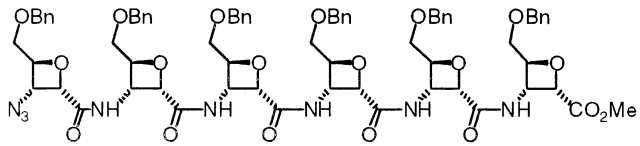


Scheme 3. (i) Br_2; then PhCHO, HCl; (ii) $(CF_3SO_2)_2O$, pyridine; (iii) K_2CO_3, MeOH; (iv) Et_3SiH, CF_3COOH; (v) NaN_3, DMF; (vi) CF_3COOCs, MeCOEt.

The *cis*-β-azidoester **26** has the opposite absolute configuration at C-2 and C-3 of the oxetane ring to that of oxetin.



27 R = Bn; **28** R = TBDMS



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Each of the *cis*-β-azidoesters **17**, **18** and **26** was hydrolysed to the corresponding acid and reduced to the corresponding amine which were then converted by standard peptide coupling techniques[26] into the corresponding hexamers **27**, **28** and **29** in good yields. The following paper[27] provides substantial evidence that the hexamers **27** and **28** with the *same* absolute configuration at C-2 and C-3 in each of the residues as oxetin form a left-handed helix stabilised by the formation of ten-membered inter-residue amide-carbonyl hydrogen-bonded rings. This is in contrast to the six-membered ring intra-residue hydrogen bond formed in the case of a dipeptide incorporating a cyclobutane β-amino-acid.[9] The hexamer **29** (having the *opposite* absolute configuration at C-2 and C-3 as oxetin) induces formation of a right-handed helix. In summary, this paper provides viable syntheses of both *cis* and *trans*-β-azido-oxetane-2-carboxylates by a series of very high yield S_N2 displacements of triflate at C-3 of an oxetane ring; such procedures should allow the evaluation of the oxetane ring as a candidate for the development of a new family of foldamers.

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19. Benzyl *cis*-β-azidoester **17**, oil; $[\alpha]_D^{22}$ −106.3 (*c*, 1.4); ν_{max} (thin film) 2116 (N_3), 1760 (C=O) cm^{-1}; δ_H ($CDCl_3$, 400 MHz): 1.14 (d, 3H, $J_{5,6}$ 6.6 Hz, H-6), 3.80 (dq, 1H, $J_{5,6}$ 6.6, $J_{4,5}$ 3.7 Hz, H-5), 3.87 (s, 3H, CO_2CH_3), 4.59 (ddd, 1H, $J_{2,4}$ 0.6, $J_{3,4}$ 5.4, $J_{4.5}$ 3.7 Hz, H-4), 4.68 (d, 1H, J_{gem} 11.5 Hz, CHPh), 4.72 (d, 1H, J_{gem} 11.5 Hz, CHPh), 4.84 (dd, 1H, $J_{2.3}$ 7.3, $J_{3.4}$ 5.4 Hz, H-3), 5.14 (br d, 1H, $J_{2,3}$ 7.3, H-2), 7.27–7.38 (m, 5H, PhH); δ_C ($CDCl_3$, 100.6 MHz): 14.8 (C-6), 52.3 (CO_2CH_3), 56.2 (C-3), 72.2 (CH_2Ph), 73.6 (C-5), 79.2 (C-2), 92.3 (C-4), 127.6, 127.7, 127.8, 128.4 (5C, Ph), 138.3 (C_{ipso}), 169.5 (C-1); m/z (APCI+) 264 (M+H$^+$−N_2, 95%), 206 (90), 157 (50), 121 (100).
20. The atomic coordinates for methyl 2,4-anhydro-6-deoxy-5-*O*-benzyl-L-altronate **14** are available on request from the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW; the crystallographic numbering system differs from that used elsewhere in the text. Any request should be accompanied by the full literature citation for this paper.
21. Benzyl *trans*-β-azidoester **16**, oil; $[\alpha]_D^{22}$ −30.0 (*c*, 1.0); ν_{max} (thin film) 2117 (N_3), 1758 (C=O) cm^{-1}; δ_H ($CDCl_3$, 500 MHz): 1.28 (d, 3H, $J_{5,6}$ 5.8 Hz, H-6), 3.85 (s, 3H, CO_2CH_3), 4.10 (dq, 1H, $J_{5,6}$ 5.8, $J_{4,5}$ 8.3 Hz, H-5), 4.56 (d, 1H, J_{gem} 10.9 Hz, CHPh), 4.61 (dd, 1H, $J_{3,4}$ 6.8, $J_{4.5}$ 8.3 Hz, H-4), 4.67 (d, 1H, J_{gem} 11.0 Hz, CHPh), 4.73 (dd, 1H, $J_{2.3}$ 5.6, $J_{3.4}$ 6.8 Hz, H-3), 4.85 (d, 1H, $J_{2,3}$ 5.6 Hz, H-2), 7.28–7.40 (m, 5H, PhH); δ_C ($CDCl_3$, 50.3 MHz): 15.3 (C-6), 53.2 (CO_2CH_3), 59.7 (C-3), 71.5 (CH_2Ph), 73.7 (C-5), 81.5 (C-2), 85.2 (C-4), 128.3, 128.6, 128.9 (5C, Ph), 138.4 (C_{ipso}), 170.7 (C-1); m/z (APCI+) 265 (17%), 264 (M+H$^+$−N_2, 100), 220 (17), 158 (80).
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24. Benzyl *cis*-β-azidoester **26**, oil; $[\alpha]_D^{25}$ +128.8 (*c*, 1.05); ν_{max} (thin film) 2116 (N_3), 1756 (C=O) cm^{-1}; δ_H ($CDCl_3$, 400 MHz): 3.67 (dd, 1H, J_{gem} 11.9, $J_{4,5}$ 2.9 Hz, H-5), 3.72 (dd, 1H, J_{gem} 11.9, $J_{4,5'}$ 3.0 Hz, H-5′), 3.89 (s, 3H, CO_2CH_3), 4.61 (d, 1H, J_{gem} 12.1 Hz, CHPh), 4.69 (d, 1H, J_{gem} 12.1 Hz, CHPh), 4.79–4.81 (m, 1H, H-4), 4.93 (dd, 1H, $J_{2,3}$ 7.6, $J_{3,4}$ 5.6 Hz, H-3), 5.22 (d, 1H, $J_{2,3}$ 7.6 Hz, H-2), 7.29–7.41 (m, 5H, PhH); δ_C ($CDCl_3$, 100.6 MHz): 52.3 (CO_2CH_3), 56.7 (C-3), 69.4 (C-5), 73.8 (CH_2Ph), 79.4 (C-2), 86.2 (C-4), 127.7, 127.9, 128.5 (5C, Ph), 137.6 (C_{ipso}), 169.4 (C-1); m/z (APCI+) 295 (M+NH_4^+, 35%), 250 (M+H$^+$−N_2, 100%).
25. Benzyl *trans*-β-azidoester **23**, oil; $[\alpha]_D^{26}$ +44.1 (*c*, 0.95); ν_{max} (thin film) 2112 (N_3), 1760 (C=O) cm^{-1}; δ_H ($CDCl_3$, 400 MHz): 3.78 (dd, 1H, J_{gem} 10.8, $J_{4,5}$ 5.1 Hz, H-5), 3.85 (s, 3H, CO_2CH_3), 3.91 (dd, 1H, J_{gem} 10.8, $J_{4,5'}$ 6.0, H-5′), 4.62 (s, 2H, CH_2Ph), 4.71–4.74 (m, 1H, H-3), 4.96–5.01 (m, 2H, H-2, H-4), 7.30–7.45 (m, 5H, PhH); δ_C ($CDCl_3$, 100.6 MHz): 52.6 (CO_2CH_3), 58.8 (C-3), 68.6 (C-5), 73.7 (CH_2Ph), 81.6 (C-2), 81.8 (C-4), 127.8, 128.4 (5C, Ph), 137.6 (C_{ipso}), 170.0 (C-1); m/z (APCI+) 250 (M+H$^+$−N_2, 75%), 144 (100%).
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