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Templated scaffolds of *cis*- and *trans*-tetrahydrofuran γ-amino acids: γ-azido-β-hydroxy-tetrahydrofuran-2-carboxylates from pentono-δ-lactones

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Abstract—Short syntheses of enantiomeric templated scaffolds of *cis*- and *trans*-tetrahydrofuran γ-amino acids from pentono-δ-lactones derived from arabinose and ribose are reported; an unexpectedly efficient synthesis of a templated tetrahydrofuran β-amino acid by azide displacement of a triflate β to an ester function proceeds with remarkably little elimination. These materials should allow evaluation of such peptidomimetics to induce predisposition towards secondary structures.
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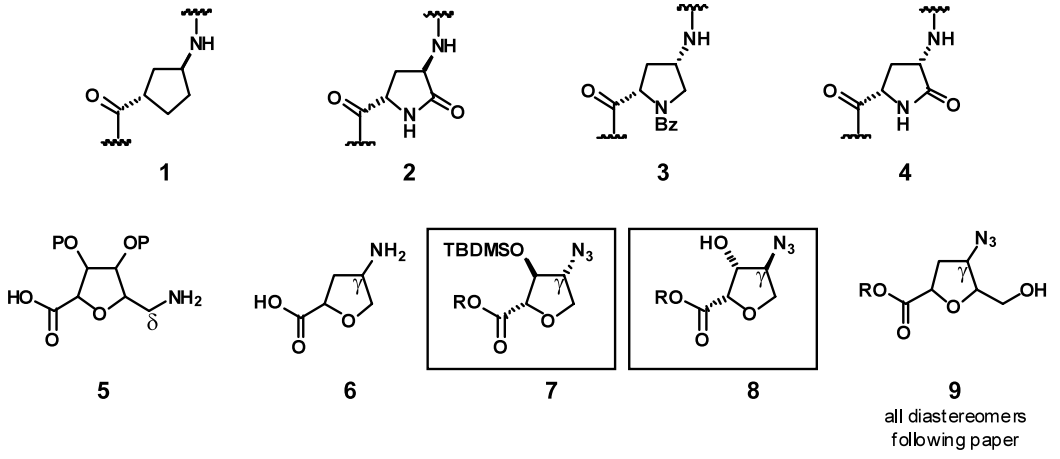
1. Introduction

The design of molecules that mimic the secondary and tertiary structures of proteins and RNA, yet that are composed of non-natural building blocks is a compelling challenge, offering the possibility of reproducing and extending the functional capabilities of Nature's macromolecules. Although to date this 'foldamer'[1] approach has not achieved the successes of de novo protein design[2] and protein redesign,[3] protein-like secondary folding has been demonstrated for homo- and heterooligomers derived from a diverse array of peptidic and non-peptidic templates.[4] For β-peptides [which constitute the most extensively characterised class of foldamer], the controlled assembly of compact tertiary structures (helical bundles) is likely be achieved soon.[5] Structural studies via solution NMR have identified a multitude of helical, turn and sheet structures in organic and aqueous solvents.[6] Resistance of these molecules to degradation by proteolytic enzymes[7] has led to a variety of studies of their biological properties, including: antimicrobial action;[8,9] inhibition of small-intestinal fat and cholesterol absorption;[10] as β-peptide based somatostatin mimics;[11] as anti-proliferatives against human cancer cell growth;[12] their cellular uptake;[13] and their biodegradability.[14]



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Like β-peptides, γ-peptides built from acyclic residues form stable helical,[15] turn[16] and sheet[15a] structures in organic solvents (together with some, as yet, uncharacterised structures[17]), and display resistance to proteolytic enzymes.[7] However, in contrast to the extensive studies on β-peptides built from residues containing 5- or 6-membered rings, there are only limited reports of γ-peptides based on cyclic templates. This is somewhat surprising given that for β-peptides, the use of cyclically constrained residues resulted in increased population of folded states in aqueous media.[18] Gellman has reported parallel sheet formation between extended strands built from *trans*-3-amino-cyclopentanecarboxylic acid residues **1** and a non-γ-peptide linker.[19] In addition Toniolo predicts an extended left-handed helix (with 13 Å pitch length) for homooligomers of the structurally related γ-lactam building block **2** on the basis of the X-ray crystal structure of a homotrimer.[20] Studies of the conformational preferences of single *cis*-configured γ-amino acids based on proline and γ-lactam scaffolds **3**[21] and **4**[22] indicate propensities to act as γ-turn and type IVa β-turn mimetics respectively. However, it is not clear that the nearest neighbour hydrogen bonds present in these examples will dominate in oligomeric derivatives. Oligomers of tetrahydrofuran and oxetane templated β-and δ-amino acids derived from carbohydrates can form novel peptidic structures that fold predictably. Examples include repeating β-turn structures[23] (reminiscent of the β-bend ribbon spiral[24]) and a 16-helix[25] from diastereomers of the δ-amino acid template **5**, and 10-helices for hexapeptides of *cis*-oxetane β-amino acids.[26]

Previous syntheses of THF γ-amino acids building blocks are limited. *cis*- And *trans*-forms of the simplest THF γ-amino acid framework **6** were synthesised from diethyl allylmalonate as potential GABA mimics,[27] whereas Vogel generated a C-5 substituted γ-azido acid en route to a *C*-nucleoside analogue of AZT.[28]

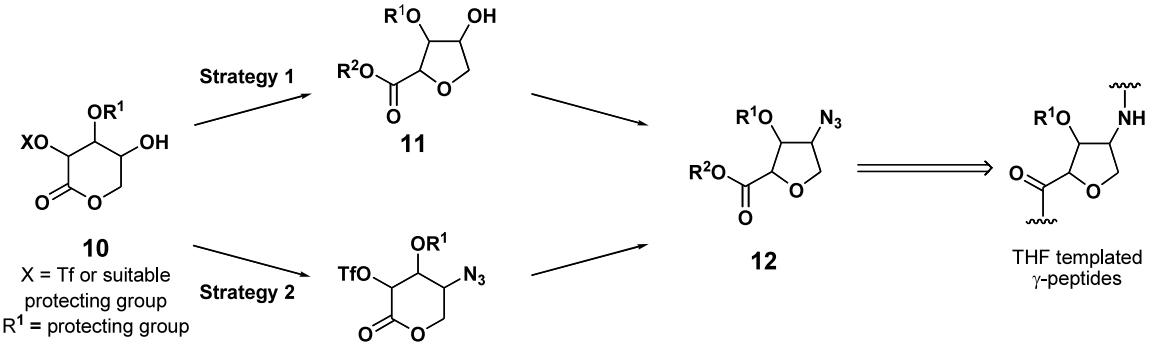
2. Synthesis

This and the following paper[29] describe short syntheses of protected γ-amino acids based on THF templates to allow studies on the conformational properties of γ-peptides bearing cyclically constrained residues. In this first paper, the synthesis of the 2,4-*cis*- and 2,4-*trans*-substituted β-hydroxy THF γ-azido esters **7** and **8** is described from pentono-δ-lactones. The following paper highlights routes to all diastereomeric 3-deoxy analogues **9** bearing C-5 hydroxymethyl side chains from hexono-γ-lactones.

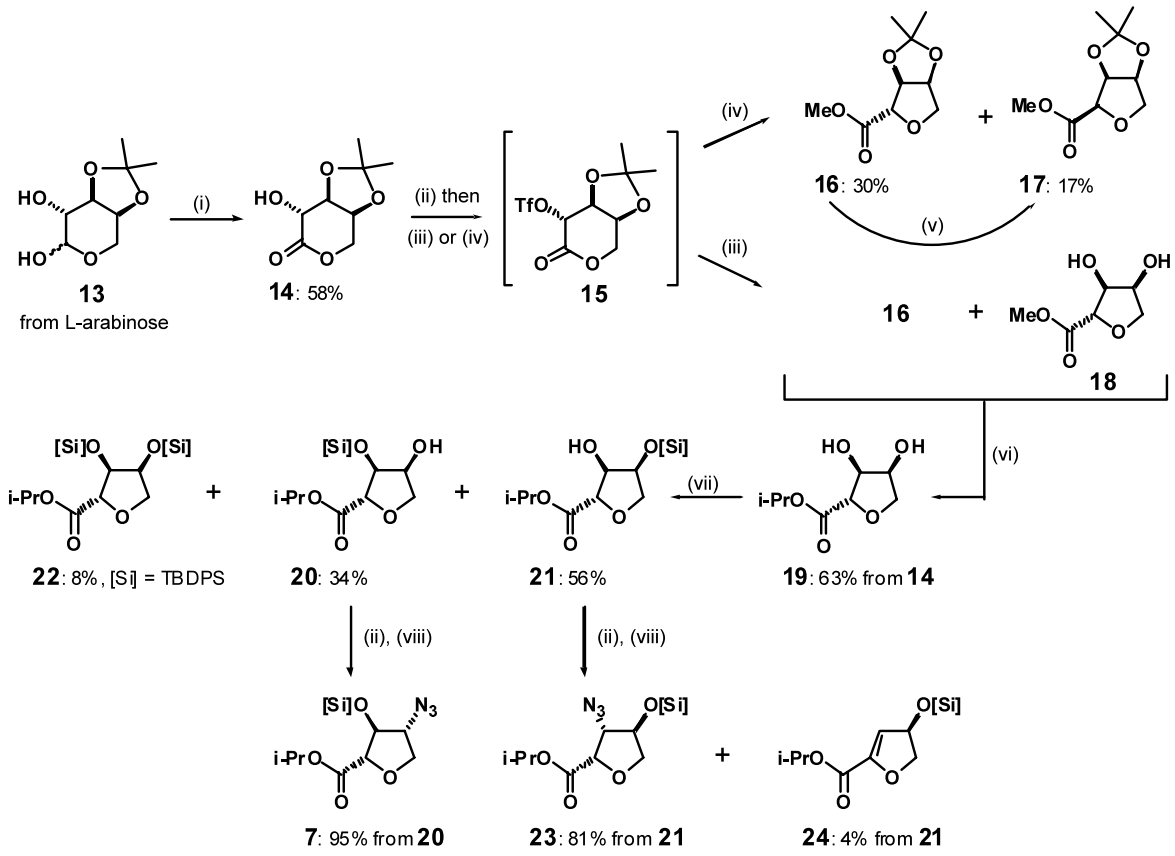
2-*O*-Trifluoromethanesulfonate derivatives (triflates) of carbohydrate δ-lactones **10** undergo efficient ring contraction to highly substituted tetrahydrofuran-2-carboxylates **11** when treated with methanol in the presence of either an acid[30] or base[31] catalyst. Initial nucleophilic opening of the lactone ring by methanol, followed by subsequent S_N2-type ring closure of an intermediate hydroxy triflate (or the corresponding alkoxide anion) forms the THF ring with inversion of configuration at the C-2 position. In applying this methodology to the synthesis of THF γ-azido esters **12** there is scope for introduction of the C-4 azido group either after [Strategy 1] or before [Strategy 2] formation of the THF ring in Scheme 1. Such flexibility is not available when γ-lactone starting materials are employed (see the following paper[29]).

2.1. Synthesis of 2,4-*cis* (L-*lyxo*) γ-azido ester 7 and 2,3-*cis* (D-*xylo*) β-azido ester 23 from arabinose

The 2,5-anhydro-L-ribonate **19**, available from L-*arabino*-configured precursors, served as the key intermediate in the synthesis of the 2,4-*cis* γ-azido ester **7** and its regioisomer **23** (Scheme 2). Oxidation of the kinetic acetonide of L-arabinose **13** using *N*-bromosuccinimide and pyridine in dichloromethane (DCM) gave the known δ-lactone product **14** in 58% yield[32] {mp 94–96°C (ethyl acetate/hexane), lit.[33] 95–97°C; $[\alpha]_D^{23}$ −28.0 (*c*, 1.0), lit.[33] $[\alpha]_D$ −1.0 (*c*, 3.0)}. Esterification of the free C-2 hydroxyl group with triflic anhydride in DCM in the presence of pyridine afforded the corresponding triflate **15**, which after aqueous extraction and concentration was used crude in subsequent steps. Ring contraction of the triflate intermediate to tetrahydrofuran products was investigated under both basic and acidic conditions. Treatment of **15** with potassium carbonate in methanol gave a mixture of two isopropylidene-containing products: the expected L-*ribo* THF carboxylate



Scheme 1. Synthetic routes to THF-templated γ-amino acids from pentono-1,5-lactones.



Scheme 2. *Reagents and conditions*: (i) *N*-bromosuccinimide, pyridine, CH_2Cl_2, 0°C to rt, 14 h; (ii) Tf_2O, pyridine, DCM, –20°C; (iii) 1% v/v AcCl in MeOH, rt, 13 h; (iv) 1.1 equiv. K_2CO_3, MeOH, 0°C, 1.5 h; (v) 0.3 equiv. K_2CO_3, MeOH, rt, 14 h; (vi) 5% v/v AcCl in Me_2CHOH, 80°C, 48 h; (vii) TBDPSCl, imidazole, DMF, 0°C to rt, 10 h; (viii) 4 equiv. NaN_3, DMF, rt, 10 h.

16 {30%; oil; $[\alpha]_D^{23}$ +64.6 (*c*, 1.2)} and a second product, assumed to be the C-2 epimer **17** {17%; oil; mp 61–62°C; $[\alpha]_D^{23}$ +88.5 (*c*, 1.1)}. Smooth conversion of **16** to the thermodynamically more stable all-*cis* product **17** (in 89% yield) under basic conditions confirmed that the two products differ only in C-2 stereochemistry; the proportion of **16** to **17** under basic conditions depends on the length of time of the reaction. In contrast, while treatment of the triflate **15** with hydrogen chloride in methanol at room temperature gave a mixture of the acetonide **16** together with the diol **18**, *no epimerisation at C-2 of the THF was observed*. When the methanol reaction mixture was heated to 70°C, only **18** was formed. Transesterification of **18** by reaction with acidic *iso*-propanol at 80°C gave the L-*ribo* isopropyl ester **19** {oil; $[\alpha]_D^{23}$ +44.3 (*c*, 1.0)} in 63% yield from **14**.

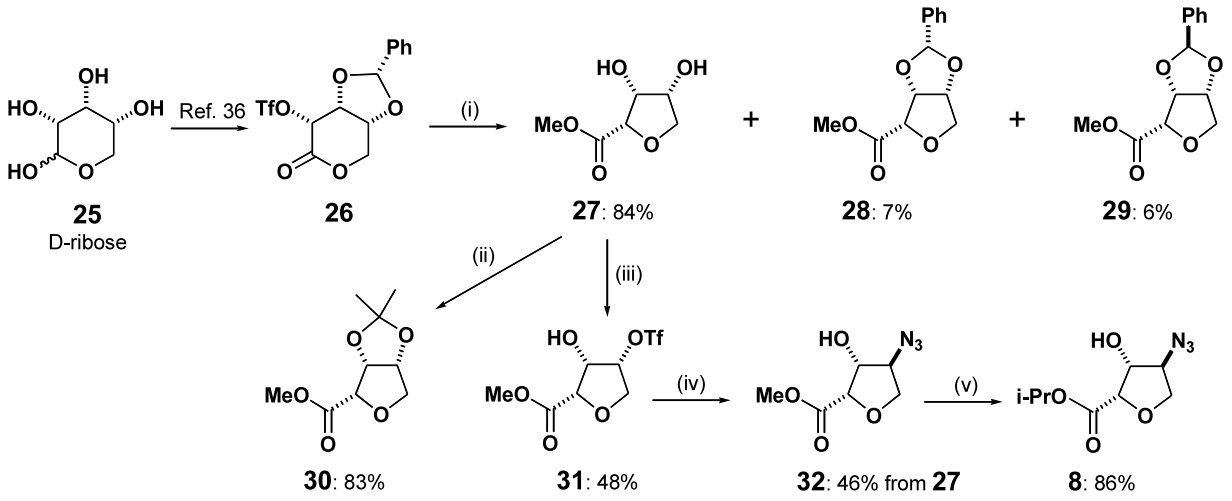
Reaction of the diol **19** with *tert*-butyldiphenylsilyl chloride in dimethylformamide (DMF) afforded an easily separable mixture of the 3-*O*-silyl and 4-*O*-silyl derivatives **20** {oil; $[\alpha]_D^{23}$ –28.9 (*c*, 1.9)} and **21** {oil $[\alpha]_D^{24}$ –16.5 (*c*, 1.6)}, in 34% and 56% yields, respectively. The crystalline disilyl compound **22** {mp 135–136°C (ethyl acetate/hexane); $[\alpha]_D^{24}$ +15.1 (*c*, 0.5)} was isolated from the reaction mixture in 8% yield; the structure of **22** was firmly established by X-ray crystallographic analysis which confirmed that the acid-mediated ring contraction of **15** proceeded with complete inversion of configuration at C-2.

Triflation of the remaining free hydroxyl group in **20**, followed by reaction of the crude triflate with sodium azide gave the D-*lyxo* γ-azido ester **7**[34] in an overall yield of 95%. More surprisingly, the L-*xylo* β-azido ester **23**[35] {oil; $[\alpha]_D^{23}$ –12.6 (*c*, 1.0)},was formed in 81% yield by similar treatment of **21**; only a very small amount of the β-elimination product **24** {4%; oil; $[\alpha]_D^{23}$ –22.3 (*c*, 1.8)} was isolated. The effective substitution [with little elimination] in this case is contrasted with the complete absence of substitution products for a related example reported in the following paper; in general, sodium azide is an excellent base for inducing elimination rather than substitution of β-triflates of carboxylic esters in THF rings.[29]

2.2. Synthesis of 2,4-*trans* (L-*xylo*) γ-azido ester 8 from D-ribose

The synthesis of the enantiomeric 2,4-*trans* γ-azido ester **8** from the L-*lyxo* THF carboxylate **27** generated from the easily accessible benzylidene D-ribonolactone **25** uses essentially the same strategy (Scheme 3). The 2-*O*-triflate **26**, available in three steps from D-ribose **25**,[36] was purified on a multigram scale via crystallisation from acetonitrile.

Reaction of **26** with a methanolic solution of hydrogen chloride under reflux afforded the diol-2-carboxylate **27**



Scheme 3. *Reagents and conditions*: (i) 5% v/v AcCl in MeOH, rt to 70°C, 3 h then aq. HCl added, 70°C, 15 h; (ii) CSA, acetone, rt, 24 h; (iii) 1.5 equiv. Tf_2O, pyridine, DCM, −25°C, 4 h then rt, 3 h; (iv) 5 equiv. NaN_3, DMF, rt, 15 h; (v) *p*-toluenesulfonic acid, Me_2CHOH, 80°C, 24 h.

{mp 72–73°C; $[\alpha]_D^{23}$ −22.3 (*c*, 1.8)} in 84% yield, together with small quantities of the epimeric benzylidene protected products **28** {7%; mp 79–80°C (ethyl acetate/hexane); $[\alpha]_D^{24}$ −160.5 (*c*, 1.0)} and **29** {6%; mp 125–126°C; $[\alpha]_D^{23}$ −71.9 (*c*, 1.0)}.[37] Reaction of the diol **27** into a single isopropylidene derivative **30** {mp 60–61°C; $[\alpha]_D^{24}$ confirmed the 2,3-*cis* stereochemistry of the diol. The optical rotation of **30** [which otherwise had identical NMR and other physical data to that of its enantiomer **17**] confirms the stereochemistry of the acid catalysed ring contraction.

Selective esterification of the unprotected C-4 hydroxyl group of the diol **27** with triflic anhydride gave the triflate **31** {mp 101–102°C; $[\alpha]_D^{24}$ −4.6 (*c*, 0.5)} in 48% yield. Treatment of crude **31** with sodium azide in DMF generated the inverted γ-azido ester product **32** in 46% yield from **27** {mp 115–116°C; $[\alpha]_D^{24}$ +35.9 (*c*, 1.0)}. Finally subjecting the azide **32** to *p*-toluenesulfonic acid in *iso*-propanol gave the L-*xylo* γ-azido isopropyl ester target **8** in 86% yield.[38]

3. Summary

This paper has described short routes to β-hydroxy γ-azido esters bearing both *cis*- and *trans*-stereochemistries with respect to the azide and ester moieties. The results of structural studies on γ-peptides generated from each of these protected γ-amino acids will be reported in due course. Additionally an efficient displacement of the β-triflate of a THF carboxylate provides easy access to some THF templated β-amino amino acid building blocks.

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34. **D-*lyxo* γ-Azido ester 7**: oil. $[\alpha]_D^{23}$ +11.3 (*c*, 1.2). δ_H (500 MHz): 1.16 (9H, s, SiC(CH_3)$_3$), 1.19 (3H, d, J 6.2, CH(CH_3)$_2$), 1.23 (3H, d, J 6.2, CH(CH_3)$_2$), 3.80 (1H, d, J 3.5, H-4), 4.11 (1H, d, $J_{5,5'}$ 10.0, H-5), 4.30 (1H, dd, $J_{5',4}$ 4.5 Hz, $J_{5',5}$ 10.0, H-5′), 4.50 (1H, b-s, H-2), 4.58 (1H, b-s, H-3), 5.05 (1H, sept, J 6.2 Hz, CHMe$_2$), 7.43–7.67 (10H, m, Ar-H). δ_C (50.3 MHz): 19.1 (C, SiCMe$_3$), 21.6 (2×CH$_3$, CH(CH$_3$)$_2$), 26.8 (3×CH$_3$, SiC(CH$_3$)$_3$), 66.4 (CH, CHMe$_2$), 68.9 (CH, C-4), 71.5 (CH$_2$, C-5), 80.7 (CH, C-3), 84.3 (CH, C-2), 127.9, 128.0, 130.2, 130.3 (Ar-CH), 132.2, 132.7 (Ar-C), 135.6, 135.8 (Ar-CH), 169.1 (C, C-1).
35. **L-*xylo* β-Azido ester 23**: oil. $[\alpha]_D^{23}$ −12.6 (*c*, 1.0). δ_H (500 MHz): 1.15 (9H, s, SiC(CH_3)$_3$), 1.34 (6H, d, J 6.2, CH(CH_3)$_2$), 3.90 (1H, dd, $J_{5,4}$ 0.9, $J_{5,5'}$ 9.8, H-5), 4.03 (1H, app-t, J 4.4 Hz, H-3), 4.08 (1H, dd, $J_{5',4}$ 3.8 Hz, $J_{5',5}$ 9.5 Hz, H-5′), 4.40 (1H, m, H-4), 4.81 (1H, d, $J_{2,3}$ 4.9 Hz, H-2), 5.20 (1H, sept, J 6.4 Hz, CHMe$_2$), 7.42–7.70 (10H, m, Ar-H). δ_C (50.3 MHz): 19.0 (C, SiCMe$_3$), 21.7, 21.8 (2×CH$_3$, CH(CH$_3$)$_2$), 26.8 (3×CH$_3$, SiC(CH$_3$)$_3$), 69.3 (CH, CHMe$_2$), 69.7 (CH, C-4), 74.8 (CH$_2$, C-5), 77.0 (CH, C-3), 79.1 (CH, C-2), 128.0, 128.1, 130.2, 130.3 (Ar-CH), 132.6 (Ar-C), 135.6 (Ar-CH), 168.3 (C, C-1).
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37. The stereochemistries at the asymmetric centres of the benzylidene groups in **28** and **29** were assigned on the basis of NOESY cross-peaks between each benzylidene methine proton and protons of the THF ring.
38. **L-*xylo* γ-azido ester 8**: mp 78–80°C; $[\alpha]_D^{24}$ +28.9 (*c*, 1.1); δ_H (400 MHz) 1.31 (6H, d, J 6.2, CH(CH_3)$_2$), 2.71 (1H, d, $J_{OH,3}$ 5.1, OH), 3.92 (1H, dd, $J_{4,5'}$ 2.1, $J_{5,5'}$ 9.9, H-5′), 4.12 (1H, m, H-4), 4.34 (1H, dd, $J_{4,5}$ 4.6, $J_{5,5'}$ 9.9, H-5), 4.49–4.51 (1H, m, H-3), 4.56 (1H, d, $J_{2,3}$ 4.3 Hz, H-2), 5.16 (1H, sept, J 6.2, CHMe$_2$). δ_C (50.3 MHz) 22.0 (2×CH$_3$, CH(CH$_3$)$_2$), 66.9 (CH, C-4), 69.8 (CH, CHMe$_2$), 71.3 (CH$_2$, C-5), 76.8 (CH, C-3), 80.3 (CH, C-2), 169.4 (C, C-1).