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(3*R*,4*R*,5*S*)-5-(Acetamidomethyl)-*N*-benzyl-3,4-dihydroxytetrahydrofuran-3-carboxamide

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Key indicators

Single-crystal X-ray study
T = 120 K
Mean σ(C–C) = 0.003 Å
R factor = 0.034
wR factor = 0.077
Data-to-parameter ratio = 9.9

For details of how these key indicators were automatically derived from the article, see http://journals.iucr.org/e.

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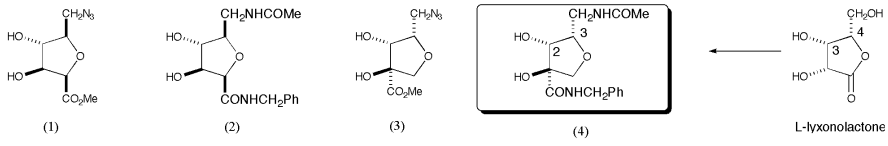
The title compound, $C_{15}H_{20}N_2O_5$, is the first example of a branched tetrahydrofuran sugar amino acid dipeptide isostere incorporated into a peptidomimetic. The crystal structure contains intermolecular N—H···O and O—H···O hydrogen bonds.

Comment

δ-Tetrahydrofuran (THF) sugar amino acids (SAA) have been extensively investigated as dipeptide isosteres (Baron *et al.*, 2004; Grotenberg *et al.*, 2004; Raunkjr *et al.*, 2004). Introduction of δ-THF SAA building blocks has been shown to induce secondary structural features such as β-turn-like structures (Chakraborty *et al.*, 2004; Smith *et al.*, 2003; Hungerford *et al.*, 2000) and helices (Claridge *et al.*, 1999; Osterkamp *et al.*, 2000) in small peptidomimetics. All the previously reported δ-THF SAA scaffolds have linear carbon chains, as in (1), which has been incorporated into peptidomimetics such as (2). The synthesis of branched sugar lactones (Hotchkiss *et al.*, 2004) has allowed ready access to a new class of δ-THF SAA building blocks, such as (3), which contain a branched carbon chain. The monomer (3) was prepared as an oil from L-lyxonolactone in a sequence in which the branched carbon chain was introduced by the Ho (1978, 1985*a*,*b*) crossed aldol procedure, and the δ-THF ring was subsequently formed by an intramolecular alkylation. The branched scaffold (3) was transformed into the crystalline branched peptidomimetic (4).



The structure of (4) has been determined in order to remove any ambiguity in the stereochemical outcomes of either the aldol or the ring closure reactions. Additionally, the crystal structure of (4) may give some indication of the

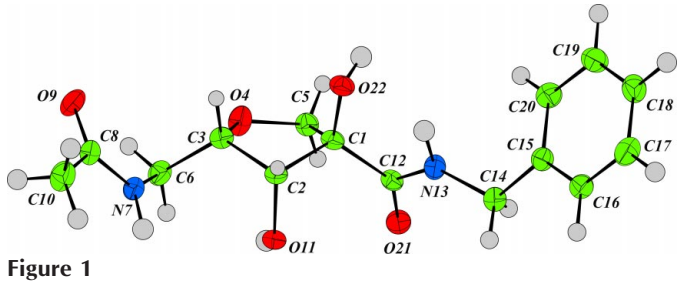


Figure 1
The molecular structure of (4), with displacement ellipsoids drawn at the 50% probability level.

secondary structural motif likely to be induced by the incorporation of the monomer (3) into peptidomimetics. The molecular structure of (4) is shown in Fig. 1. As usually expected for sugar derivatives, there are intermolecular hydrogen bonds (Table 2 and Fig. 2).

Experimental

Compound (4) was dissolved in acetone in a small glass cylinder and then crystallized as the solvent evaporated slowly to give colourless needle-like crystals.

Crystal data

$C_{15}H_{20}N_2O_5$
M_r = 308.33
Orthorhombic, $P2_12_12_1$
a = 15.3802 (6) Å
b = 5.4473 (2) Å
c = 18.0635 (8) Å
V = 1513.37 (10) Å^3
Z = 4
D_x = 1.353 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 3224 reflections
θ = 5–27°
μ = 0.10 mm^{-1}
T = 120 K
Needle, colourless
0.40 × 0.04 × 0.02 mm

Data collection

Nonius KappaCCD diffractometer
ω scans
Absorption correction: multi-scan (*DENZO/SCALEPACK*; Otwinowski & Minor, 1997)
T_{min} = 0.820, T_{max} = 0.998
5747 measured reflections
1973 independent reflections
1594 reflections with $I > 2\sigma(I)$
R_{int} = 0.048
θ_{max} = 27.4°
$h = -19 \rightarrow 19$
$k = -7 \rightarrow 5$
$l = -23 \rightarrow 23$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.034
$wR(F^2)$ = 0.077
S = 0.93
1973 reflections
200 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F^2) + 0.02 + 0.04P]$, where $P = [\max(F_o^2, 0) + 2F_c^2]/3$
$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.27 e Å^{-3}
$\Delta\rho_{min}$ = −0.23 e Å^{-3}
Extinction correction: Larson (1970)
Extinction coefficient: 16 (5)

Table 1
Selected bond lengths (Å).

C1—C2	1.551 (2)	C6—N7	1.453 (2)
C1—C5	1.525 (3)	N7—C8	1.334 (2)
C1—C12	1.531 (3)	C8—O9	1.236 (2)
C1—O22	1.421 (2)	C8—C10	1.501 (3)
C2—C3	1.518 (3)	C12—N13	1.333 (2)
C2—O11	1.421 (2)	C12—O21	1.235 (2)
C3—O4	1.438 (2)	N13—C14	1.454 (2)
C3—C6	1.522 (3)	C14—C15	1.515 (3)
O4—C5	1.436 (2)		

Table 2
Hydrogen-bond geometry (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
O22—H6···O9^{i}	0.95	1.75	2.649 (2)	158
N7—H12···O21^{ii}	1.00	1.95	2.953 (2)	177
O11—H1···O11^{iii}	0.95	1.95	2.886 (2)	166

Symmetry codes: (i) $x-\frac{1}{2}, -y+\frac{3}{2}, -z+2$; (ii) $-x+2, y+\frac{1}{2}, -z+\frac{3}{2}$; (iii) $-x+2, y-\frac{1}{2}, -z+\frac{3}{2}$.

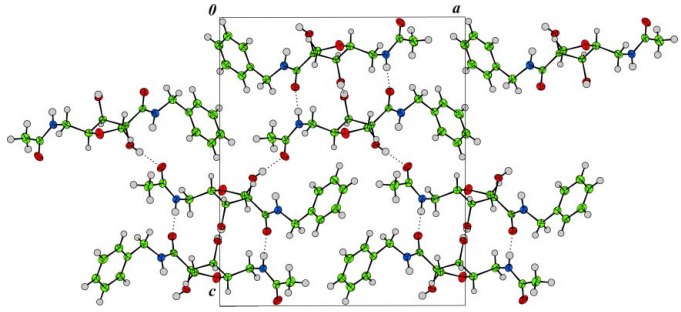


Figure 2
A packing diagram of (4), viewed down the b axis. Hydrogen bonds are indicated by dashed lines.

In the absence of significant anomalous scattering, Friedel pairs were merged. The absolute configuration of (4) was assigned since the starting material was L-lyxonolactone with known absolute configuration and two of the chiral centres are retained (see scheme). H atoms were located in difference density maps. Those attached to C atoms were repositioned geometrically. The H atoms were initially refined with soft restraints on the bond lengths and angles to regularize their geometry (C—H = 0.98–1.01 Å, O—H = 0.95 Å and N—H = 0.95–1.00 Å), after which they were refined as riding, with U_{iso}(H) = 1.2U_{eq}(C), and U_{iso}(H) = 0.05 Å^2 for those bonded to N and O atoms.

Data collection: *COLLECT* (Nonius, 2001); cell refinement: *DENZO/SCALEPACK* (Otwinowski & Minor, 1997); data reduction: *DENZO/SCALEPACK*; program(s) used to solve structure: *SIR92* (Altomare *et al.*, 1994); program(s) used to refine structure: *CRYSTALS* (Betteridge *et al.*, 2003); molecular graphics: *CAMERON* (Watkin *et al.*, 1996); software used to prepare material for publication: *CRYSTALS*.

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References

Altomare, A., Cascarano, G., Giacovazzo, G., Guagliardi, A., Burla, M. C., Polidori, G. & Camalli, M. (1994). *J. Appl. Cryst.* **27**, 435–435.
Baron, R., Bakowies, D. & van Gunsteren, W. F. (2004). *Angew. Chem. Int. Ed.* **43**, 4055–4059.
Betteridge, P. W., Carruthers, J. R., Cooper, R. I., Prout, K. & Watkin, D. J. (2003). *J. Appl. Cryst.* **36**, 1487.
Chakraborty, T. K., Srinivasi, P., Tapadar, S. & Mohan, B. K. (2004). *J. Chem. Sci.* **116**, 187–207.
Claridge, T. D. W., Long, D. D., Hungerford, N. L., Aplin, R. T., Smith, M. D., Marquess, D. G. & Fleet, G. W. J. (1999). *Tetrahedron Lett.* **40**, 2199–2202.
Grotenberg, G. M., Timmerj, M. S. M., Llamas-Saiz, A. L., Verdoes, M., van der Marel, G. A., van Raaij, M. J., Overkleeft, H. S. & Overhand, M. (2004). *J. Am. Chem. Soc.* **126**, 3444–3446.
Ho, P. T. (1978). *Tetrahedron Lett.* **19**, 1623–1626.
Ho, P. T. (1985*a*). *Can. J. Chem.* **57**, 381–381.
Ho, P. T. (1985*b*). *Can. J. Chem.* **63**, 2221–2224.
Hotchkiss, D., Soengas, R., Simone, M. I., van Ameijde, J., Hunter, S., Cowley, A. R. & Fleet, G. W. J. (2004). *Tetrahedron Lett.* **45**, 9461–9464.
Hungerford, N. L., Claridge, T. D. W., Watterson, M. P., Aplin, R. T., Moreno, A. & Fleet, G. W. J. (2000). *J. Chem. Soc. Perkin Trans.* 1, **21**, 3666–3679.
Larson, A. C. (1970). *Crystallographic Computing*, edited by F. R. Ahmed, pp. 291–294. Copenhagen: Munksgaard.

Nonius (2001). *COLLECT*. Nonius BV, Delft, The Netherlands.
Osterkamp, F., Ziemer, B., Koert, U., Wiesner, M., Raddatz, P. & Goodman, S. L. (2000). *Chem. Eur. J.* **6**, 666–683.
Otwinowski, Z. & Minor, W. (1997). *Methods in Enzymology*, Vol. 276, *Macromolecular Crystallography*, Part A, edited by C. W. Carter Jr & R. M. Sweet, pp. 307–326. New York: Academic Press.
Raunkjr, M., El Oualid, F., van der Marel, G. A., Overkleeft, H. S. & Overhand, M. (2004). *Org. Lett.* **6**, 3167–3170.
Smith, M. D., Claridge, T. D. W., Sansom, M. P. & Fleet, G. W. J. (2003). *Org. Biomol. Chem.* **1**, 3647–3655.
Watkin, D. J., Prout, C. K. & Pearce, L. J. (1996). *CAMERON*. Chemical Crystallography Laboratory, Oxford, England.

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$h = -19\rightarrow19$
$k = -7\rightarrow5$
$l = -23\rightarrow23$

Refinement

Refinement on F^2
Least-squares matrix: full
$R[F^2 > 2\sigma(F^2)] = 0.034$
$wR(F^2) = 0.077$
$S = 0.93$
1973 reflections
200 parameters
0 restraints
Primary atom site location: structure-invariant direct methods
Hydrogen site location: inferred from neighbouring sites
H-atom parameters constrained
$w = 1/[\sigma^2(F^2) + 0.02 + 0.04P]$, where $P = (\max(F_o^2, 0) + 2F_c^2)/3$
$(\Delta/\sigma)_{max} = 0.001$
$\Delta\rho_{max} = 0.27$ e Å^{-3}
$\Delta\rho_{min} = -0.23$ e Å^{-3}
Extinction correction: Larson (1970)
Extinction coefficient: 16 (5)
Absolute structure: see text

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å²)

	x	*y*	*z*	U_{iso}*/U_{eq}
C1	0.88317 (12)	0.7829 (4)	0.87417 (9)	0.0223
C2	0.97505 (11)	0.8760 (3)	0.85276 (9)	0.0218

C3	1.03223 (13)	0.7093 (3)	0.89934 (10)	0.0236
O4	0.98853 (9)	0.4761 (2)	0.90166 (8)	0.0325
C5	0.89837 (13)	0.5078 (4)	0.88312 (11)	0.0253
C6	1.12326 (12)	0.6622 (4)	0.86972 (10)	0.0280
N7	1.17646 (10)	0.8825 (3)	0.87016 (8)	0.0265
C8	1.23146 (13)	0.9302 (4)	0.92556 (10)	0.0277
O9	1.23594 (9)	0.7976 (3)	0.98096 (7)	0.0359
C10	1.28844 (14)	1.1520 (4)	0.91690 (12)	0.0382
O11	0.99245 (8)	0.8649 (2)	0.77563 (6)	0.0260
C12	0.81349 (12)	0.8364 (3)	0.81569 (9)	0.0223
N13	0.76255 (10)	1.0272 (3)	0.83168 (8)	0.0270
C14	0.69186 (12)	1.1100 (4)	0.78430 (10)	0.0302
C15	0.62532 (12)	1.2545 (4)	0.82810 (10)	0.0258
C16	0.59055 (13)	1.4675 (4)	0.79875 (11)	0.0290
C17	0.52648 (15)	1.5955 (4)	0.83627 (11)	0.0364
C18	0.49727 (14)	1.5138 (4)	0.90401 (11)	0.0369
C19	0.53254 (14)	1.3028 (4)	0.93495 (12)	0.0344
C20	0.59632 (13)	1.1732 (4)	0.89712 (11)	0.0308
O21	0.80707 (9)	0.7148 (3)	0.75824 (7)	0.0310
O22	0.86476 (8)	0.9015 (3)	0.94242 (6)	0.0267
H21	0.9824	1.0484	0.8695	0.0249*
H31	1.0346	0.7770	0.9505	0.0275*
H51	0.8628	0.4350	0.9230	0.0314*
H52	0.8863	0.4194	0.8351	0.0314*
H61	1.1528	0.5378	0.9019	0.0351*
H62	1.1197	0.6002	0.8182	0.0351*
H101	1.3496	1.1069	0.9211	0.0460*
H102	1.2828	1.2342	0.8676	0.0460*
H103	1.2789	1.2808	0.9548	0.0460*
H141	0.7154	1.2151	0.7437	0.0369*
H142	0.6659	0.9606	0.7617	0.0369*
H161	0.6108	1.5234	0.7492	0.0370*
H171	0.5021	1.7491	0.8141	0.0440*
H181	0.4517	1.6088	0.9321	0.0440*
H191	0.5124	1.2389	0.9851	0.0400*
H201	0.6219	1.0239	0.9186	0.0366*
H3	0.7724	1.0854	0.8803	0.0500*
H6	0.8250	0.7940	0.9658	0.0500*
H12	1.1800	0.9957	0.8266	0.0500*
H1	0.9932	0.6928	0.7664	0.0500*

Atomic displacement parameters (Å²)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
C1	0.0245 (10)	0.0238 (9)	0.0187 (8)	−0.0028 (9)	0.0037 (8)	−0.0028 (8)
C2	0.0248 (10)	0.0213 (8)	0.0192 (8)	−0.0016 (9)	0.0011 (8)	−0.0008 (8)
C3	0.0272 (10)	0.0211 (8)	0.0226 (9)	−0.0026 (9)	−0.0003 (8)	0.0003 (8)
O4	0.0278 (8)	0.0248 (7)	0.0450 (8)	−0.0026 (7)	−0.0068 (7)	0.0071 (7)

C5	0.0249 (10)	0.0249 (10)	0.0263 (10)	−0.0029 (9)	0.0005 (8)	0.0003 (9)
C6	0.0288 (10)	0.0282 (10)	0.0270 (10)	0.0034 (10)	−0.0045 (9)	−0.0033 (9)
N7	0.0221 (8)	0.0322 (8)	0.0252 (8)	−0.0006 (8)	−0.0029 (7)	0.0027 (8)
C8	0.0217 (10)	0.0331 (11)	0.0284 (10)	0.0027 (9)	−0.0032 (8)	0.0007 (10)
O9	0.0339 (8)	0.0421 (9)	0.0316 (7)	−0.0004 (8)	−0.0118 (6)	0.0080 (7)
C10	0.0323 (12)	0.0396 (12)	0.0428 (12)	−0.0034 (11)	−0.0087 (10)	0.0039 (11)
O11	0.0267 (7)	0.0315 (7)	0.0198 (6)	0.0008 (7)	0.0037 (6)	0.0033 (6)
C12	0.0216 (9)	0.0232 (9)	0.0222 (10)	−0.0032 (9)	0.0032 (8)	−0.0013 (8)
N13	0.0239 (8)	0.0292 (8)	0.0278 (8)	0.0028 (8)	−0.0027 (7)	−0.0039 (8)
C14	0.0256 (10)	0.0372 (10)	0.0276 (10)	0.0032 (10)	−0.0002 (8)	0.0000 (9)
C15	0.0228 (10)	0.0295 (9)	0.0252 (9)	−0.0032 (9)	−0.0023 (8)	−0.0022 (9)
C16	0.0284 (11)	0.0308 (10)	0.0279 (10)	0.0009 (10)	−0.0012 (9)	−0.0004 (9)
C17	0.0377 (12)	0.0365 (11)	0.0351 (11)	0.0071 (11)	−0.0083 (10)	−0.0029 (10)
C18	0.0291 (11)	0.0471 (13)	0.0344 (11)	0.0054 (11)	−0.0015 (10)	−0.0111 (11)
C19	0.0324 (11)	0.0405 (11)	0.0304 (10)	−0.0035 (11)	0.0039 (9)	−0.0016 (10)
C20	0.0327 (11)	0.0298 (10)	0.0299 (10)	−0.0009 (9)	−0.0014 (9)	0.0010 (9)
O21	0.0299 (8)	0.0380 (7)	0.0251 (7)	0.0014 (7)	−0.0014 (6)	−0.0076 (7)
O22	0.0281 (7)	0.0316 (7)	0.0204 (6)	−0.0023 (7)	0.0040 (6)	−0.0042 (6)

Geometric parameters (Å, º)

C1—C2	1.551 (2)	C10—H103	0.992
C1—C5	1.525 (3)	O11—H1	0.952
C1—C12	1.531 (3)	C12—N13	1.333 (2)
C1—O22	1.421 (2)	C12—O21	1.235 (2)
C2—C3	1.518 (3)	N13—C14	1.454 (2)
C2—O11	1.421 (2)	N13—H3	0.946
C2—H21	0.993	C14—C15	1.515 (3)
C3—O4	1.438 (2)	C14—H141	0.998
C3—C6	1.522 (3)	C14—H142	0.994
C3—H31	0.996	C15—C16	1.383 (3)
O4—C5	1.436 (2)	C15—C20	1.397 (3)
C5—H51	0.988	C16—C17	1.386 (3)
C5—H52	1.009	C16—H161	0.996
C6—N7	1.453 (2)	C17—C18	1.378 (3)
C6—H61	1.001	C17—H171	1.000
C6—H62	0.991	C18—C19	1.388 (3)
N7—C8	1.334 (2)	C18—H181	1.009
N7—H12	1.001	C19—C20	1.389 (3)
C8—O9	1.236 (2)	C19—H191	1.020
C8—C10	1.501 (3)	C20—H201	0.983
C10—H101	0.975	O22—H6	0.947
C10—H102	1.001		

C2—C1—C5	102.01 (15)	C8—C10—H102	113.8
C2—C1—C12	113.72 (14)	H101—C10—H102	105.3
C5—C1—C12	111.54 (15)	C8—C10—H103	114.2
C2—C1—O22	104.54 (14)	H101—C10—H103	105.6

C5—C1—O22	112.69 (15)	H102—C10—H103	106.6
C12—C1—O22	111.80 (15)	C2—O11—H1	102.4
C1—C2—C3	101.14 (14)	C1—C12—N13	114.19 (15)
C1—C2—O11	113.85 (14)	C1—C12—O21	122.15 (16)
C3—C2—O11	114.10 (15)	N13—C12—O21	123.65 (17)
C1—C2—H21	109.7	C12—N13—C14	123.60 (16)
C3—C2—H21	109.4	C12—N13—H3	111.7
O11—C2—H21	108.5	C14—N13—H3	124.1
C2—C3—O4	105.93 (15)	N13—C14—C15	111.03 (15)
C2—C3—C6	116.01 (15)	N13—C14—H141	109.7
O4—C3—C6	106.97 (15)	C15—C14—H141	109.4
C2—C3—H31	108.3	N13—C14—H142	106.7
O4—C3—H31	108.5	C15—C14—H142	111.6
C6—C3—H31	110.9	H141—C14—H142	108.3
C3—O4—C5	109.77 (14)	C14—C15—C16	119.78 (17)
C1—C5—O4	106.88 (16)	C14—C15—C20	121.25 (17)
C1—C5—H51	112.7	C16—C15—C20	118.95 (19)
O4—C5—H51	108.5	C15—C16—C17	120.64 (19)
C1—C5—H52	110.5	C15—C16—H161	118.6
O4—C5—H52	108.6	C17—C16—H161	120.7
H51—C5—H52	109.6	C16—C17—C18	120.4 (2)
C3—C6—N7	112.17 (15)	C16—C17—H171	119.5
C3—C6—H61	109.1	C18—C17—H171	120.1
N7—C6—H61	107.5	C17—C18—C19	119.8 (2)
C3—C6—H62	109.7	C17—C18—H181	120.6
N7—C6—H62	108.5	C19—C18—H181	119.6
H61—C6—H62	109.8	C18—C19—C20	119.90 (19)
C6—N7—C8	121.40 (16)	C18—C19—H191	121.4
C6—N7—H12	122.4	C20—C19—H191	118.7
C8—N7—H12	115.7	C15—C20—C19	120.33 (19)
N7—C8—O9	121.84 (19)	C15—C20—H201	119.1
N7—C8—C10	116.61 (17)	C19—C20—H201	120.6
O9—C8—C10	121.55 (18)	C1—O22—H6	103.7
C8—C10—H101	110.7		

Hydrogen-bond geometry (Å, º)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O22—H6···O9^{i}	0.95	1.75	2.649 (2)	158
N7—H12···O21^{ii}	1.00	1.95	2.953 (2)	177
O11—H1···O11^{iii}	0.95	1.95	2.886 (2)	166

Symmetry codes: (i) $x-1/2, -y+3/2, -z+2$; (ii) $-x+2, y+1/2, -z+3/2$; (iii) $-x+2, y-1/2, -z+3/2$.