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(3a*S*,4*S*,4a*S*,7*R*,9*S*,9a*S*)-Methyl 4-benzyloxy-9-methylsulfonyloxy-2,2-dimethyl-8-oxo-octahydro-1,3-dioxa-5-thia-7a-azacyclopenta[*f*]azulene-7-carboxylate toluene solvate

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Key indicators

Single-crystal X-ray study
T = 193 K
Mean σ(C–C) = 0.003 Å
R factor = 0.027
wR factor = 0.049
Data-to-parameter ratio = 13.4

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

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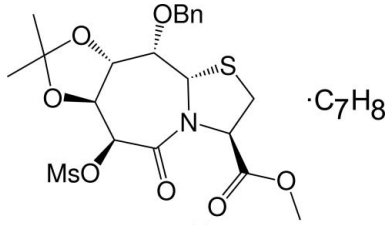
The absolute configuration has been determined for the title compound, $C_{21}H_{27}NO_9S_2\cdot C_7H_8$. The compound is a precurser in the synthesis of bicyclic dipeptide isosteres based on mannuronic acid. The seven-membered lactam ring adopts a rigid chair conformation.

Comment

Bicyclic dipeptide mimetics can induce and stabilize hairpin turns in peptide strands (Nagai & Sato, 1985). The originally proposed mechanism has been challenged by recent X-ray and NMR studies (Tremmel & Geyer, 2004). Polyhydroxylated 7,5-fused bicyclic thiazolidine lactams have been inserted into both cyclic and linear oligopeptides (Tremmel & Geyer, 2002). The title compound, (I), is a precurser for a class of carbohydrate-based dipeptide derivatives. The mesyl group can be exchanged for an azido group and subsequent reduction forms the amino group of the dipeptide mimetic. After cleavage of the isopropylidene and methyl ester protecting groups, a hydrophilic bicyclic dipeptide mimetic with an aromatic side chain is obtained. It can serve as a rigid substituent of a D-Phe-Pro dipeptide.



(I)

The starting reaction for the synthesis of the mesylated 7,5-fused bicyclic thiazolidine lactam, (I) (Fig. 1), is the condensation of D-γ-mannuronolactone with the methyl ester of L-cysteine. After protection of two hydroxy groups with 2,2-dimethoxypropane, the alcohol in position 9 is selectively activated with mesyl chloride. Finally, the benzylation of the remaining free hydroxyl group is performed with benzyl bromide and sodium hydride.

In both the crystalline state and in solution the seven-membered lactam ring of (I) adopts a rigid chair conformation, as found in the *gluco* derivatives (Geyer *et al.*, 1999).

Experimental

The title compound was prepared from (3a*S*,4*S*,4a*S*,7*R*,9*S*,9a*S*)-4-hydroxy-9-methanesulfonyloxy-2,2-dimethyl-8-oxo-octahydro-1,3-dioxa-5-thia-7a-azacyclopenta[*f*]azulene-7-carboxylic acid methyl ester (1.33 g, 3.25 mmol) by treatment with benzyl bromide (1.67 g, 9.75 mmol), sodium hydride (0.12 g, 4.88 mmol) and tetrabutylammonium iodide (20 mg, 0.05 mmol) in dimethylformamide (70 ml)

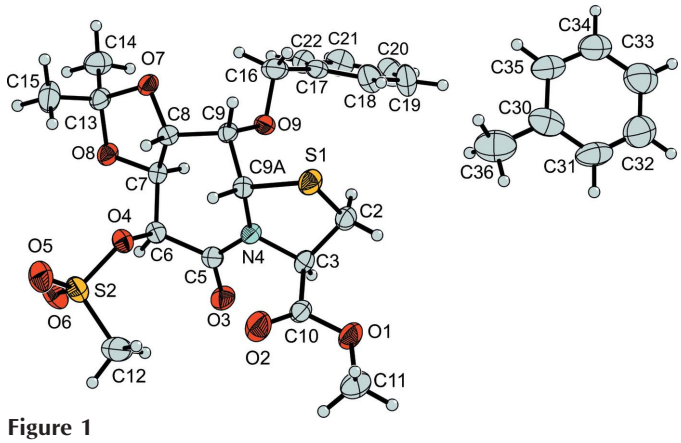


Figure 1
A view of (I), with 50% probability displacement ellipsoids.

for 3 h at room temperature. Water (200 ml) was added and the reaction mixture was extracted twice with toluene. After removal of the organic solvent, the desired product was purified by flash chromatography. Colourless crystals of (I) were obtained by recrystallization from ethyl acetate (yield: 1.06 g, 2.11 mmol, 65%). Spectroscopic analysis: ^{1}H NMR (500 MHz, DMSO-d_6, δ, p.p.m.): 7.38–7.28 (*m*, 5H, Ph), 5.30 (*s*, 1H, 9a-H), 5.27 (*s*, 1H, 6-H), 5.06 (*d*, $^3J_{3\text{-H},2'\text{-H}}$ = 6.80 Hz, 1H, 3-H), 4.90 (*d*, $^2J_{\text{Bn}}$ = 11.21 Hz, 1H, Ph—CH_2), 4.73 (*d*, $^2J_{\text{Bn}}$ = 11.21 Hz, 1H, Ph—CH_2), 4.30 (*d*, $^3J_{9\text{-H},8\text{-H}}$ = 2.24 Hz, 1H, 9-H), 4.26 (*dd*, $^3J_{8\text{-H},7\text{-H}}$ = 9.45 Hz, $^3J_{8\text{-H},9\text{-H}}$ = 2.24 Hz, 1H, 8-H), 4.15 (*dd*, $^3J_{7\text{-H},8\text{-H}}$ = 9.45 Hz, $^3J_{7\text{-H},6\text{-H}}$ = 1 Hz, 1H, 7-H), 3.64 (*s*, 3H, OCH_3), 3.37 (*dd*, $^2J_{2'\text{-H},2\text{-H}}$ = 11.76 Hz, $^3J_{2'\text{-H},3\text{-H}}$ = 7.00 Hz, 1H, 2′-H), 3.29 (*s*, 3H, SCH_3), 3.09 (*d*, $^2J_{2\text{-H},2'\text{-H}}$ = 11.76 Hz, 1H, 2-H), 1.39 (*ps*, 6H, CH_3). ^{13}C NMR (125 MHz, DMSO-d_6, δ, p.p.m.): 169.24, 163.02 (CO), 137.93, 128.30, 127.82, 127.71 (Ph), 108.61 (C_q^{Isopr}), 80.51 (9-C), 78.10 (6-C), 76.23 (8-C), 75.11 (CH_2—Ph), 70.47 (7-C), 65.63 (3-C), 60.84 (9a-C), 52.43 (OCH_3), 38.59 (SCH_3), 30.47 (2-C), 26.33, 26.24 (CH_3^{Isopr}).

Crystal data

$C_{21}H_{27}NO_9S_2{\cdot}C_7H_8$
M_r = 593.69
Orthorhombic, $P2_12_12_1$
a = 10.1251 (6) Å
b = 11.4082 (5) Å
c = 25.4972 (15) Å
V = 2945.2 (3) Å^3
Z = 4
D_x = 1.339 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 21120 reflections
θ = 1.6–26.2°
μ = 0.23 mm^{-1}
T = 193 (2) K
Plate, colourless
0.4 × 0.4 × 0.05 mm

Data collection

Stoe IPDS 2 diffractometer
ω scans
Absorption correction: none
29561 measured reflections
5724 independent reflections
4668 reflections with $I > 2\sigma(I)$
R_{int} = 0.037
θ_{max} = 26.0°
$h = -12 \rightarrow 12$
$k = -14 \rightarrow 14$
$l = -31 \rightarrow 31$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.027
$wR(F^2)$ = 0.049
S = 0.89
5724 reflections
426 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0245P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{\text{max}}$ = 0.001
$\Delta\rho_{\text{max}}$ = 0.14 e Å^{-3}
$\Delta\rho_{\text{min}}$ = −0.18 e Å^{-3}
Absolute structure: Flack (1983), with 2479 Friedel pairs
Flack parameter: 0.02 (4)

Table 1
Selected geometric parameters (Å, °).

C2—C3	1.511 (2)	C7—C8	1.513 (2)
C2—S1	1.8046 (19)	C8—O7	1.4195 (19)
C3—N4	1.462 (2)	C8—C9	1.508 (2)
C5—N4	1.360 (2)	C9—C9*A*	1.526 (2)
C5—C6	1.525 (2)	C9*A*—N4	1.491 (2)
C6—C7	1.509 (2)	C9*A*—S1	1.8249 (17)
C7—O8	1.426 (2)		
C3—C2—S1	103.08 (12)	N4—C9*A*—C9	114.01 (12)
N4—C3—C2	106.19 (14)	N4—C9*A*—S1	105.22 (11)
N4—C5—C6	120.77 (14)	C9—C9*A*—S1	111.06 (11)
C7—C6—C5	113.13 (14)	O7—C13—O8	105.69 (13)
O8—C7—C6	112.34 (14)	C5—N4—C3	117.25 (14)
O8—C7—C8	102.92 (13)	C5—N4—C9*A*	127.52 (14)
C6—C7—C8	114.53 (14)	C3—N4—C9*A*	114.03 (13)
O7—C8—C9	113.58 (13)	C8—O7—C13	105.45 (11)
O7—C8—C7	101.84 (12)	C7—O8—C13	107.76 (12)
C9—C8—C7	114.59 (14)	C2—S1—C9*A*	91.98 (8)
C8—C9—C9*A*	108.29 (13)		
S1—C2—C3—N4	44.96 (15)	C2—C3—N4—C5	159.54 (14)
N4—C5—C6—C7	49.6 (2)	C2—C3—N4—C9*A*	−32.03 (18)
C5—C6—C7—O8	164.96 (13)	C9—C9*A*—N4—C5	−67.5 (2)
C5—C6—C7—C8	−78.08 (18)	S1—C9*A*—N4—C5	170.54 (13)
O8—C7—C8—O7	−37.25 (15)	C9—C9*A*—N4—C3	125.47 (15)
C6—C7—C8—O7	−159.49 (14)	S1—C9*A*—N4—C3	3.54 (16)
O8—C7—C8—C9	−160.31 (14)	C9—C8—O7—C13	163.38 (13)
C6—C7—C8—C9	77.46 (18)	C7—C8—O7—C13	39.64 (15)
O7—C8—C9—O9	−67.30 (17)	O8—C13—O7—C8	−27.26 (15)
O7—C8—C9—C9*A*	172.24 (13)	C6—C7—O8—C13	144.76 (13)
C7—C8—C9—C9*A*	−71.28 (17)	C8—C7—O8—C13	21.06 (16)
C8—C9—C9*A*—N4	76.45 (17)	O7—C13—O8—C7	2.65 (16)
C8—C9—C9*A*—S1	−164.90 (11)	C3—C2—S1—C9*A*	−37.91 (13)
C6—C5—N4—C3	177.82 (14)	N4—C9*A*—S1—C2	20.48 (12)
C6—C5—N4—C9*A*	11.2 (2)	C9—C9*A*—S1—C2	−103.33 (12)

Methyl groups and solvent aromatic H atoms were refined with idealized geometry [for Me H, C—H = 0.98 Å, H—C—H = 109.5° and U_{iso}(H) = 1.5U_{eq}(C), with torsion angles from the electron density; for solvent CH, C—H = 0.98 Å, H on the external bisector, U_{iso}(H) = 1.2U_{eq}(C)]. All other H atoms were located and refined isotropically. The bond length range is 0.87 (2)–1.07 (2) Å.

Data collection: *X-AREA* (Stoe & Cie, 2005); cell refinement: *X-AREA*; data reduction: *X-AREA*; program(s) used to solve structure: *SIR92* (Altomare *et al.*, 1993); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *DIAMOND* (Brandenburg, 2004); software used to prepare material for publication: *WinGX* (Farrugia, 1999).

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