Refinement

Refinement on F

$R = 0.039$

$wR = 0.048$

$S = 1.84$

1895 reflections

204 parameters

H atoms refined with individual U_{iso}

$w = 4F_o^2/\sigma^2(F_o^2)$

$(\Delta/\sigma)_{max} < 0.001$

$\Delta\rho_{max} = 0.22$ e Å^{-3}

$\Delta\rho_{min} = -0.17$ e Å^{-3}

Extinction correction: Stout & Jensen (1968)

Extinction coefficient: 0.13135×10^{-4}

Scattering factors from *International Tables for X-ray Crystallography* (Vol. IV)

Table 1. *Selected geometric parameters (Å, °)*

N1—C5	1.394 (2)	C4—C5	1.413 (2)
N1—C9	1.373 (2)	C10—C11	1.360 (2)
N1—C10	1.401 (2)		
C1—O1—C11	119.6 (1)	C3—C4—C11	119.5 (1)
C5—N1—C10	111.3 (1)	C5—C4—C11	105.9 (1)
O1—C1—O2	116.9 (1)	N1—C5—C4	106.1 (1)
O1—C1—C2	117.3 (1)	N1—C10—C11	104.7 (1)
O2—C1—C2	125.8 (2)	O1—C11—C4	122.5 (1)
C1—C2—C3	122.5 (1)	C4—C11—C10	112.0 (1)
C2—C3—C4	118.5 (1)		

Table 2. *Comparison of 2-pyrone ring geometries (Å)*
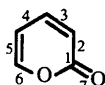
Bond							
1	2	3	4	5	6	7	Reference
1.385 (2)	1.456 (2)	1.371 (2)	1.385 (2)	1.409 (2)	1.372 (2)	1.202 (2)	(a)
1.414 (3)	1.445 (3)	1.382 (3)	1.375 (3)	1.411 (3)	1.358 (2)	1.200 (2)	(b)
1.367 (4)	1.448 (5)	1.344 (5)	1.431 (5)	1.395 (4)	1.378 (4)	1.204 (4)	(c)
1.373 (5)	1.462 (7)	1.355 (6)	1.429 (7)	1.391 (7)	1.383 (5)	1.203 (6)	(d)
1.383 (1)	1.432 (1)	1.351 (2)	1.432 (1)	1.383 (1)	1.380 (1)	1.213 (1)	(e)
1.394 (7)	1.438 (8)	1.400 (8)	1.406 (8)	1.348 (8)	1.364 (7)	1.205 (7)	(f)

References: (a) compound (2) (present work); (b) 3-acetyl-6-methyl-2H-pyrano[2,3-b]indolizin-2-one (Kakehi *et al.*, 1993); (c) coumarin (Gavuzzo *et al.*, 1974); (d) 3-bromoacetylcoumarin (Vasudevan *et al.*, 1991); (e) 7-ethoxycoumarin (Ueno, 1985); (f) 3-acetyl-4-hydroxy-6-phenyl-2-pyrone (Thailambal & Pattabhi, 1985).

Azimuthal scans of several reflections indicated no need for an absorption correction. The H atoms were located from a difference Fourier map and refined isotropically. The structure was solved by direct methods (*SIR*88; Burla *et al.*, 1989) utilizing the *TEXSAN* (Molecular Structure Corporation, 1985) system.

Data collection: *MSC/AFC Diffractometer Control Software* (Molecular Structure Corporation, 1992). Cell refinement: *MSC/AFC Diffractometer Control Software*. Data reduction: *TEXSAN*. Program(s) used to refine structure: *ORTEP*II (Johnson, 1976). Molecular graphics: *TEXSAN*. Software used to prepare material for publication: *TEXSAN*.

Lists of atomic coordinates, displacement parameters, structure factors and complete geometry have been deposited with the IUCr (Reference: CF1120). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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(1R*,3R*,4S*)-4-(tert-Butyldiphenylsilyl-oxy)-6,7-dimethoxy-1-methyl-3-phenyl-1,2,3,4-tetrahydroisoquinoline

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Abstract

Ambiguous information obtained from ^{1}H NMR spectroscopy has prompted an investigation of the correct stereochemistry of the title compound, $C_{34}H_{39}NO_3Si$, by X-ray diffraction analysis. An uncommon pseudo-axial–axial *trans* conformation was observed for the substituents linked to the C-4 and C-3 atoms (IUPAC numbering). The pseudo-equatorial conformation of the methyl group joined to the C-1 atom was also confirmed.

Comment

In connection with previous studies of the stereoselective preparation of different isoquinolinic derivatives, a convenient method for the stereoselective

synthesis of epimeric ($1R^*,3S^*,4R^*$)- and ($1R^*,3R^*,4S^*$)-4-(*tert*-butyldiphenylsilyloxy)-6,7-dimethoxy-1-methyl-3-phenyl-1,2,3,4-tetrahydroisoquinoline, (II) and (III), has recently been reported (Badía, Domínguez & Tellitu, 1992), including a critical reductive process of the corresponding dihydroisoquinoline derivative, (I), at the last step of the synthetic pathway. Thus, under catalytic hydrogenation conditions, precursor (I) yielded, with excellent diastereomeric excess, tetrahydroisoquinoline (II) (Tellitu, 1994), fully identified by spectroscopic determinations supported by X-ray diffraction analysis (Urtiaga *et al.*, 1995). On the other hand, the use of NBH$_4$ as reduction agent afforded a mixture of compounds (II) and (III) in a 1:1 ratio (see scheme below).

Conditions:
A: H$_2$/Pt, only (II)
B: NaBH$_4$, (II) and (III)
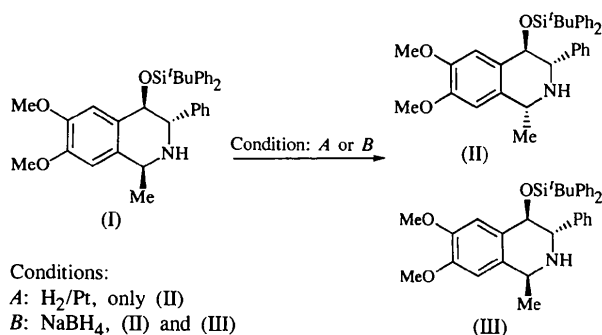
The relative configuration of the C9 and C11 atoms for compound (III) was established by performing different nuclear Overhauser effect (NOE) experiments (Kinns & Sanders, 1984) allowing the assignment of a *trans* relationship for the H9 and H11 protons (NOE between C91 protons and H11, but not between the H11 and H9 protons). The unexpected observation of a positive NOE between the H11 and H2 protons, however, could be in good agreement with either the ($1R^*,3R^*,4S^*$) or ($1R^*,3R^*,4R^*$) relative configurations, as shown below.
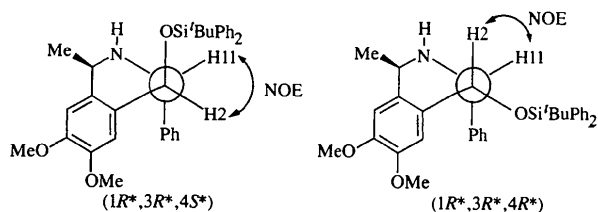
The spectroscopic studies were therefore of doubtful use for the determination of the relative stereochemistry of the selected chiral centres. In this context, X-ray analysis appeared to be essential for that purpose.

The molecular structure with atom-numbering scheme is shown in Fig. 1 (Johnson, 1976). The molecule consists of an aromatic ring condensed with a hydrogenated heterocyclic ring containing substituents bonded to the asymmetric C2, C9 and C11 atoms. The planes of both rings of the tetrahydroisoquinoline fragment form a dihedral angle of 5.31 (7)°.
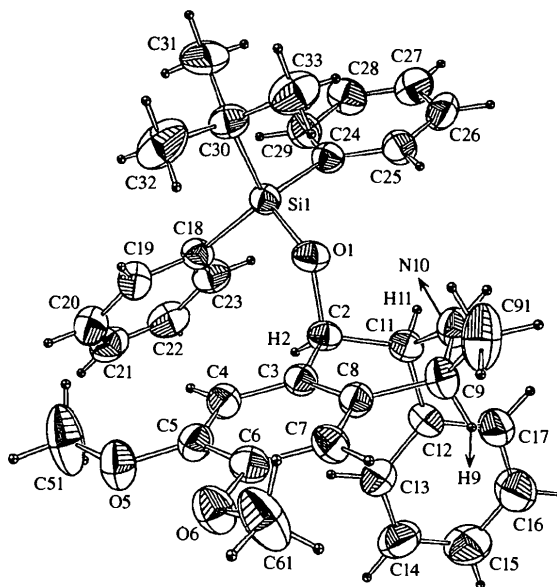

Fig. 1. The molecular structure of (III) showing the numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are displayed as spheres of arbitrary radii.

The molecule under study shows a *trans* configuration for the *tert*-butyldiphenylsilyloxy group ($'$BuSiPh$_2$O) bonded to C2 and the phenyl group bonded to C11, thus adopting pseudo-axial and axial conformations, respectively [O1—C2—C11—C12 -168.1 (2)°]; in consequence, the H2 and H11 atoms are in pseudo-equatorial and equatorial conformations, respectively [H2—C2—C11—H11 69.9 (3)°]. Moreover, the torsion angles C11—N10—C9—C91 of -164.2 (2) and C11—N10—C9—H9 of 80.2 (3)° indicate a pseudo-equatorial conformation for the methyl group at C9, which implies a *trans* configuration for the latter group and the phenyl group at C11 and a *cis* configuration between the group at C9 and the $'$BuSiPh$_2$O group at C2. From these data, a ($1R^*,3R^*,4S^*$) configuration may be proposed for the tetrahydroisoquinoline under study. It is noteworthy to point out that the same conformation has also been observed in CDCl$_3$ solution, as demonstrated by the observation of a positive NOE between the H2 and H11 protons.

On the other hand, the N10—C9 and C11—N10 bond lengths [1.470 (3) Å] show total single-bond character, which is typical for aminic N atoms in other isoquinoline derivatives also studied by the present research group (Arrieta, Badía, Domínguez, Lete, Igartua *et al.*, 1988; Arrieta, Badía, Domínguez, Lete, Martínez de Marigorta *et al.*, 1988). It may also be emphasized that the heterocyclic ring exhibits a sofa conformation, the C2—C3—C8—C9 and C2—C11—N10—C9 torsion angles being equal to -2.6 (3) and 62.2 (2)°, respectively; both values are consistent with the proposed conformation (Plywaczyk, Tykarska, Jaskóski & Kosturkiewicz, 1984).

The orientation of the methoxy groups in the aromatic condensed ring is as follows: the group bonded to C5 is approximately coplanar with the aromatic plane [C51 deviation is -0.091 (5) Å; C51—O5—C5—C6 176.2 (3)°]. On the contrary, the group bonded to C6 is not in this plane [C61 deviation is -0.382 (4) Å; C61—O6—C6—C7 15.3 (4)°]. The conformation, untypical of o-dimethoxybenzene derivatives, is probably the result of steric hindrances. All the other determined values for the angles and bond distances are similar to those already reported for different tetrahydroisoquinolines (Arrieta, Badía, Domínguez, Lete, Igartua et al., 1988; Arrieta, Badía, Domínguez, Lete, Martínez de Marigorta et al., 1988; González-Cameno et al., 1994).

Finally, a comparison with the $(1R*,3S*,4R*)$-epimer (Urtiaga et al., 1995) shows that the methyl group at C-1 (C9) is in the same conformation in both epimers. Nevertheless, the substituents at C-3 (C11) and C-4 (C2) are in a equatorial–pseudo-equatorial conformation in (II) and in an axial–pseudo-axial conformation in the epimer (III) under study.

Experimental

The isoquinoline derivative (III) was prepared by reduction of (I) with NaBH₄ at room temperature. The crude mixture was flash column chromatographed affording two compounds in a 1:1 ratio. Both derivatives were purified by crystallization from methanol. The more polar substance (m.p. 405–406 K) proved to be the epimeric derivative (III), as evidenced by NMR, IR and MS spectroscopy, together with elemental analysis (Badía, Domínguez & Tellitu, 1992).

Crystal data

$C_{34}H_{39}NO_3Si$	Mo $K\alpha$ radiation
$M_r = 537.773$	$\lambda = 0.71069$ Å
Orthorhombic	Cell parameters from 25
$Pna2_1$	reflections
$a = 8.181$ (3) Å	$\theta = 9–17°$
$b = 21.020$ (4) Å	$\mu = 0.113$ mm^{-1}
$c = 17.402$ (1) Å	$T = 293$ (2) K
$V = 2992$ (1) Å^3	Prism
$Z = 4$	$0.29 \times 0.21 \times 0.13$ mm
$D_x = 1.194$ Mg m^{-3}	Colourless
D_m not measured	

Data collection

Enraf–Nonius CAD-4	$R_{int} = 0.008$
diffractometer	$\theta_{max} = 27.26°$
ω–2θ scans	$h = 0 \rightarrow 9$
Absorption correction: none	$k = 0 \rightarrow 22$
2794 measured reflections	$l = 0 \rightarrow 18$
2643 independent reflections	4 standard reflections
2473 reflections with	frequency: 120 min
$I > 2\sigma(I)$	intensity decay: 3%

Refinement

Refinement on F^2	$(\Delta/\sigma)_{max} = 0.011$
$R(F) = 0.0305$	$\Delta\rho_{max} = 0.323$ e Å^{-3}
$wR(F^2) = 0.0925$	$\Delta\rho_{min} = -0.225$ e Å^{-3}

$S = 1.121$	Extinction correction: none
2628 reflections	Scattering factors from
352 parameters	*International Tables for*
H atoms riding on C atoms	*Crystallography* (Vol. C)
$[U_{iso}(H) = 1.2U_{eq}(C)]$	Absolute configuration:
$w = 1/[\sigma^2(F_o^2) + (0.0528P)^2$	Flack (1983)
$+ 0.428P]$	Flack parameter = 0.08 (13)
where $P = (F_o^2 + 2F_c^2)/3$	

Table 1. *Selected geometric parameters (Å, °)*

Si1—O1	1.653 (2)	O6—C6	1.370 (3)
Si1—C24	1.879 (3)	O6—C61	1.423 (4)
Si1—C18	1.882 (3)	C3—C8	1.398 (3)
Si1—C30	1.896 (3)	C33—C30	1.539 (4)
C2—O1	1.444 (3)	N10—C9	1.470 (3)
C2—C3	1.509 (3)	O5—C5	1.362 (3)
C2—C11	1.525 (4)	O5—C51	1.415 (4)
C11—N10	1.470 (3)	C30—C32	1.527 (5)
C11—C12	1.526 (3)	C8—C9	1.514 (4)
C31—C30	1.532 (4)	C9—C91	1.533 (4)
O1—Si1—C24	110.2 (1)	C6—O6—C61	117.3 (2)
O1—Si1—C18	108.0 (1)	C9—N10—C11	113.9 (2)
C24—Si1—C18	110.0 (1)	C5—O5—C51	117.0 (2)
O1—Si1—C30	104.3 (1)	C32—C30—C31	108.8 (3)
C24—Si1—C30	107.4 (1)	C32—C30—C33	108.1 (3)
C18—Si1—C30	116.7 (1)	C32—C30—Si1	113.7 (2)
O1—C2—C3	107.7 (2)	C31—C30—Si1	110.0 (2)
O1—C2—C11	108.0 (2)	C33—C30—Si1	107.7 (2)
C3—C2—C11	111.0 (2)	C2—O1—Si1	127.9 (1)
N10—C11—C2	109.9 (2)	N10—C9—C8	113.9 (2)
N10—C11—C12	111.6 (2)	N10—C9—C91	107.6 (2)
C2—C11—C12	115.1 (2)	C8—C9—C91	112.3 (2)

The title compound crystallized in the orthorhombic system; space group $Pna2_1$ or $Pnam$ (non-standard setting for $Pnma$) from the systematic absences. The structure solution was only possible in the $Pna2_1$ space group. The relatively large displacement parameters for the C31–C33, O5, C51, O6, C61 and C91 atoms can be attributed to slight disorder in these groups. H atoms were placed at calculated positions and included using a riding model, each with a fixed isotropic displacement parameter equal to 1.2 times that of the attached atom.

Data collection: *CAD-4 Software* (Enraf–Nonius, 1989). Cell refinement: *CAD-4 Software*. Data reduction: *Xtal3.2* (Hall, Flack & Stewart, 1992). Program(s) used to solve structure: *SHELXS86* (Sheldrick, 1990). Program(s) used to refine structure: *SHELXL93* (Sheldrick, 1993). Molecular graphics: *ORTEPII* (Johnson, 1976). Software used to prepare material for publication: *PARST* (Nardelli, 1983) and *SHELXL93*.

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angle of 120.6 (3)° with respect to one another, while the benzyl and thiophenyl rings attached to the N atom of the β-lactam ring are at an angle of 4.3 (2)° with respect to one another. The central β-lactam ring is bent, with a mean torsion-angle value of 4.3 (2)°.

Comment

β-Lactams with a substituent at the N atom which is easily removable under mild conditions find wide applicability in the synthesis of bicyclic β-lactam antibiotics and non-β-lactam molecules (Lukacs & Ohno, 1990). To achieve this goal, various moieties have been used as the nitrogen protective groups (George, 1993). In our on-going research on β-lactams, we have synthesized several β-lactams with various substituents on the N atom (Srirajan, Deshmukh, Puranik & Bhawal, 1996; Jayaraman, Puranik & Bhawal, 1996). We now report a novel protective group for the N atom of the β-lactam ring of the title compound, (I).

(I)
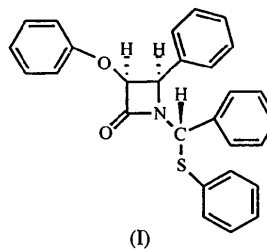
The deprotection of the novel protective group of (I) under mild conditions affords an N-unsubstituted β-lactam, which is an important synthon for various biologically active molecules. The X-ray structure determination was undertaken in order to establish unambiguously the stereochemistry at the C2 and C3 atoms of the β-lactam ring and at the C10 chiral centre.

The molecular structure of the title compound consists of a four-membered cyclic amide, with a *cis* disposition of phenoxy and phenyl groups at C2 and C3, and a thiophenylbenzyl group at the N atom of the β-lactam ring. The relative configurations at C2, C3 and C10 were established as S, R and R, respectively. The H atoms at C2 and C3 are *cis* with respect to one another [H2—C2—C3—H3 7.2 (3)°]. The geometry of the four-membered ring is similar to that reported for *cis* β-lactams (Jayaraman, Puranik & Bhawal, 1996; Jayaraman, Srirajan, Deshmukh & Bhawal, 1996; Srirajan, Puranik, Deshmukh & Bhawal, 1996; Chiaroni *et al.*, 1995). The β-lactam ring is bent with an average torsion-angle value of 4.3 (2)°, which is consistent with that observed in related structures (Spek, van der Steen, Johann, Jastrzebski & Koten, 1994; van der Steen, Kleijn, Spek & Koten, 1990). The internal angles of the four-membered ring vary from 85.6 (3) to 95.7 (3)°.

Novel Protective Group in β-Lactam Chemistry: 3-Phenoxy-4-phenyl-N-[α-(phenylthio)benzyl]azetidin-2-one

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Abstract

3-Phenoxy-4-phenyl-1-[phenyl(phenylthio)methyl]azetidin-2-one, $C_{28}H_{23}NO_2S$, with a novel protective group, was prepared from thiophenol. The single-crystal analysis of the compound reveals the H atoms at C2 and C3 of the β-lactam ring to be in a *cis* configuration. The relative configuration at the C2, C3 and C10 chiral centres are established as S, R and R, respectively. The phenoxy and phenyl substituents at C2 and C3 are at an