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(2S*R*,3S*R*,4*RS*)-*tert*-Butyl 2,3-dihydroxy 4-(*tert*-butoxycarbonyl)aminohexanoate

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Key indicators

Single-crystal X-ray study
T = 293 K
Mean σ(C–C) = 0.003 Å
R factor = 0.046
wR factor = 0.066
Data-to-parameter ratio = 16.0

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

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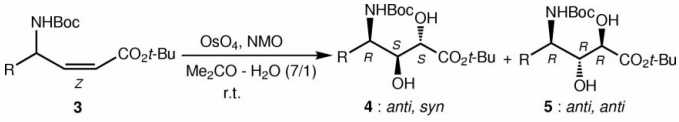
The reaction of γ-(*N*-*t*-butoxycarbonyl)amino-α,β-ethylenic esters with OsO_4 yields the corresponding α,β-dihydroxy compounds with good diastereoselectivity. The crystal structure of the major stereomer, (2*SR*,3*SR*,4*RS*)-Me_2CHC\\-forcelb]H($NHCO_2{}^tBu$)CHOHCHOH$CO_2{}^tBu$, $C_{16}H_{31}NO_6$, shows that the relative stereochemistry of the CHO–CHO–CHN sequence is *anti–syn*.

Comment

For many years, our group has focused on the synthesis of γ-amino acid fragments obtained *via* addition of alkyl 3-lithiopropiolates to nitrones (Dagoneau *et al.*, 1999, 2001; Denis *et al.*, 1997). The γ-*N*-hydroxyamino-α,β-acetylenic esters formed during this process are highly functionalized synthetic intermediates. We have developed original approaches leading to γ-amino-α,β-saturated esters (Dagoneau *et al.*, 2001), γ-(*N*-benzyl)amino-α,β-ethylenic esters and/or α,β-ethylenic γ-lactames (Denis *et al.*, 1997). On the basis of this methodology, we have recently described the synthesis of the (*Z*)-γ-(*N*-*t*-butoxycarbonyl)amino-α,β-ethylenic esters 3 (Dagoneau *et al.*, 1999), which may be easily dihydroxylated to afford the corresponding γ-(*N*-*t*-butoxycarbonyl)amino-α,β-dihydroxy esters (Dondoni *et al.*, 1993; Imashiro *et al.*, 1998; Reetz *et al.*, 1996). In this paper, we describe the dihydroxylation of the (*Z*)-γ-(*N*-*t*-butoxycarbonyl)amino-α,β-ethylenic *tert*-butyl esters 3 by osmium tetroxide in the presence of *N*-methylmorpholine *N*-oxide (NMO), yielding the corresponding γ-(*N*-*t*-butoxycarbonyl)amino-α,β-dihydroxy esters 4 and 5 (Scheme 1). We also discuss the crystal structure analysis of compound 4*b* (Fig. 1).

As shown in Scheme 1, the two hydroxy groups have been introduced stereoselectively. The aminodiols have been obtained as a mixture of the two diastereomers, *anti–syn*, 4, and *anti–anti*, 5, in more than 3:1 ratios. In the dihydroxylation of a heterosubstituted allylic double bond (in particular of *Z* stereochemistry) by osmium tetroxide, which is sensitive to the steric effect (allylic 1.3-strain; Cha *et al.*, 1984; Cha & Kim, 1995; Hoffmann, 1989; Koskinen & Chen, 1991), we expected the formation of the *anti–anti* aminodiols resulting in the dihydroxylation reaction from the less hindered face of the double bond. However, a crystallographic study of the major stereomer 4*b* (Scheme 1) showed that the relative stereochemistry of the C2–C4 sequence is *anti–syn.* This result clearly points to the approach of the reagent to the C—C π face bearing the *N*-*t*-butoxycarbonyl group, *i.e.* the most hindered face. One of the main features of this atomic arrangement is the existence of three hydrogen bonds. One is intramolecular (O3—H2···O5; Fig. 1), while the other two [N1—H1···$O1^i$ and O4—H3···$O3^i$; symmetry code (i) as in

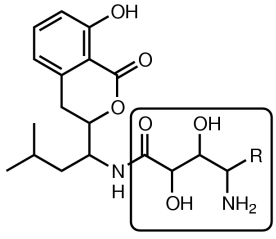
Table 2] are intermolecular and connect the organic entities to build an infinite chain extending along the *c*-axis direction. Table 2 reports the main geometric features of this hydrogen-bond network, while Fig. 2 gives a perspective view of it. A similar *anti–syn* stereoselectivity has been described by Imashiro *et al.* (1998). It has been speculated that *syn* selectivity might be explained by the existence of a hydrogen bond between osmium tetroxide and the *N*-*t*-butoxycarbonyl H atom, leading to the formation of the *anti–syn* aminodiols (Imashiro *et al.*, 1998). By extrapolation, we expect that the major compounds 4*a* and 4*c* also possess the same *anti–syn* stereochemistry. The γ-(*N*-*t*-butoxycarbonyl)amino-α,β-dihydroxy esters 4 and 5 represent the protected side chains, respectively, of the antitumour compounds Y-05460M-A (Sato *et al.*, 1992) and PM-94128 (Canedo *et al.*, 1997; Scheme 2).



3 **4** : *anti, syn* **5** : *anti, anti*

R = **a** : Et, **4**/**5** : 75/25, 85%; **b** : *i*-Pr, **4**/**5** : 80/20, 86%; **c** : *i*-Bu, **4**/**5** : 85/15, 98%

Scheme 1



R = *i*-Pr : Y-05460M-A

R = *i*-Bu : PM-94128

Scheme 2

Experimental

γ-(*N*-*t*-Butoxycarbonyl)amino-α,β-dihydroxy *tert*-butyl esters 4 and 5 were prepared according to the following procedure. To a stirred solution of γ-(*N*-*t*-butoxycarbonyl)amino-α,β-ethylenic *tert*-butyl ester 3*b* (108 mg, 0.36 mmol) in an acetone/water mixture (12 ml, 7/1) under argon were added successively *N*-methylmorpholine *N*-oxide (NMO, 55 mg, 0.54 mmol) and OsO_4 (14 mg, 0.05 mmol). The resulting mixture was stirred at room temperature for 36 h and sodium bisulfite was added slowly. After 5 min of stirring, the solution was diluted with ethyl acetate and water. After separation of the two phases, the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and filtered. The filtrate was concentrated under vacuum to yield the crude product. Chromatography on silica gel (eluant ethyl acetate–pentane, 4/1) afforded 68 mg (0.2 mmol) of the major diastereomer 4*b*, 16 mg (0.05 mmol) of the minor diastereomer 5*b* and 20 mg (0.06 mmol) of a mixture of 4*b* and 5*b*. The overall yield was 86%. Scheme 1 shows the experimental process for the preparation of γ-(*N*-*t*-butoxycarbonyl)amino-α,β-dihydroxy *tert*-butyl esters 4 and 5. For 4*b*: m.p. 393–394 K; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.98 (*t*, *J* = 6.1 and 6.2 Hz, 6H), 1.43 (*s*, 9H), 1.52 (*s*, 9H), 1.82–1.90 (*m*, 1H), 3.27 (*s*, 1H), 3.47 (*t*, *J* = 9.0 and 9.5 Hz, 1H), 3.85 (*s*, 2H), 4.35 (*s*, 1H), 4.73 (*d*, *J* = 9.5 Hz, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 19.6, 19.7, 28.0, 28.3, 29.7, 56.4, 71.8, 71.9, 80.0, 83.2, 157.6, 172.8; IR (neat): 3445 (ν_{OH}), 3370 (ν_{NH}), 1725 [$\nu_{C=O}$ ester], 1675 cm^{-1} [$\nu_{C=O}$ carbamate; mass spectrum (CI, NH_3 + isobutane) *m*/*z* 334 (MH^+). Analysis calculated for $C_{16}H_{31}NO_6$: C 57.64, H 9.37, N 4.20%; found: C 57.57, H,9.38, N 4.14%. For 5*b*: ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.88 (*d*, *J* = 6.9 Hz, 3H), 0.95 (*d*, *J* = 6.9 Hz, 3H), 1.44 (*s*, 9H), 1.49 (*s*, 9H), 2.10–2.32 (*m*, 1H), 2.43 (*d*, *J* = 8.6 Hz, 1H), 3.56–3.96 (*m*, 3H), 4.12–4.24 (*m*, 1H), 4.28 (*d*, *J* = 9.2 Hz, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 15.7, 20.0, 27.5, 28.2, 28.4, 56.1, 73.4, 74.0, 80.2, 82.4, 156.6, 171.0; mass spectrum (CI, NH_3 + isobutane) *m*/*z* 334 (MH^+).

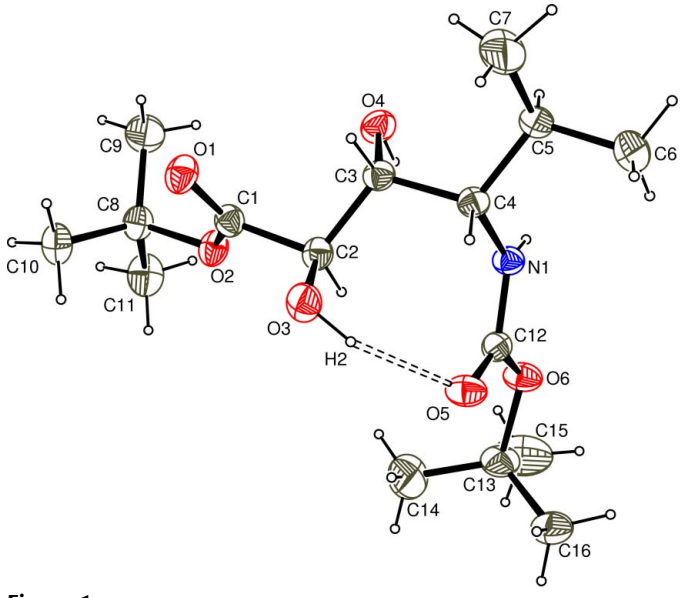


Figure 1
A view of the molecule, with displacement ellipsoids shown at the 30% probability level. H atoms are shown as spheres of arbitrary radii.

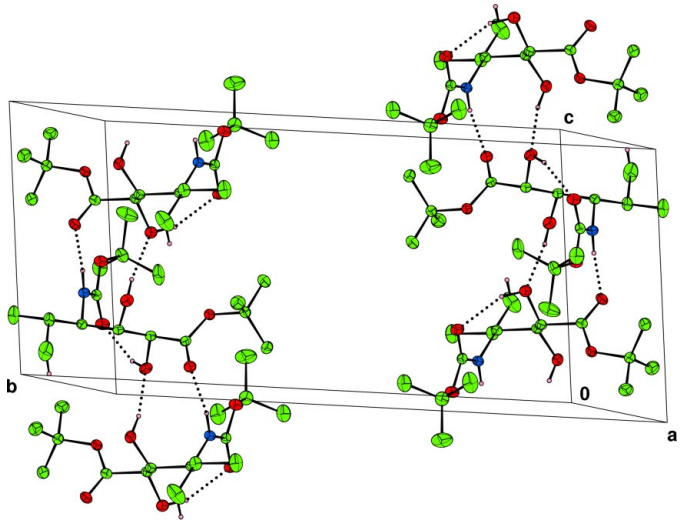


Figure 2
The N—H···O and O—H···O hydrogen bonding and the infinite chain extending along the *c*-axis direction. H atoms not involved in hydrogen bonding have been omitted. Displacement ellipsoids are drawn at the 20% probability level.

Crystal data

$C_{16}H_{31}NO_6$	D_x = 1.150 Mg m^{-3}
M_r = 333.42	Mo $K\alpha$ radiation
Monoclinic, $P2_1/c$	Cell parameters from 25 reflections
a = 9.077 (4) Å	θ = 10.0–11.8°
b = 21.777 (5) Å	μ = 0.09 mm^{-1}
c = 10.19 (1) Å	T = 293.2 K
β = 107.02 (6)°	Prism, colourless
V = 1926 (2) Å^3	0.20 × 0.13 × 0.10 mm
Z = 4	

Data collection

Enraf–Nonius CAD-4 diffractometer	θ_{max} = 30.0°
ω scans	$h = 0 \rightarrow 12$
Absorption correction: none	$k = -30 \rightarrow 30$
6037 measured reflections	$l = -14 \rightarrow 13$
5752 independent reflections	2 standard reflections every 120 reflections
3323 reflections with $I > 2.5\sigma(I)$	intensity decay: 0.8%
R_{int} = 0.011	

Refinement

Refinement on F	H-atom parameters not refined
R = 0.046	$w = 1/[\sigma^2(F_o) + 0.00063\|F_o\|^2]$
wR = 0.066	$(\Delta/\sigma)_{max}$ = 0.007
S = 1.69	$\Delta\rho_{max}$ = 0.21 e Å^{-3}
3323 reflections	$\Delta\rho_{min}$ = −0.18 e Å^{-3}
208 parameters	

Table 1
Selected geometric parameters (Å, °).

O1—C1	1.2058 (19)	C2—C3	1.528 (2)
O2—C1	1.3245 (19)	C3—C4	1.535 (2)
O2—C8	1.485 (2)	C4—C5	1.531 (2)
O3—C2	1.424 (2)	C5—C6	1.514 (3)
O4—C3	1.419 (2)	C5—C7	1.508 (3)
O5—C12	1.227 (2)	C8—C9	1.503 (3)
O6—C12	1.3385 (19)	C8—C10	1.518 (3)
O6—C13	1.476 (2)	C8—C11	1.515 (3)
N1—C4	1.456 (2)	C13—C14	1.507 (4)
N1—C12	1.340 (2)	C13—C15	1.504 (3)
C1—C2	1.517 (2)	C13—C16	1.503 (3)
C1—O2—C8	121.98 (12)	C6—C5—C7	109.60 (18)
C12—O6—C13	121.62 (14)	O2—C8—C9	108.55 (15)
C4—N1—C12	123.20 (14)	O2—C8—C10	110.97 (14)
O1—C1—O2	125.88 (16)	O2—C8—C11	102.09 (14)
O1—C1—C2	123.01 (15)	C9—C8—C10	112.81 (16)
O2—C1—C2	111.11 (13)	C9—C8—C11	111.76 (17)
O3—C2—C1	106.76 (13)	C10—C8—C11	110.14 (16)
O3—C2—C3	111.20 (13)	O5—C12—O6	125.36 (15)
C1—C2—C3	108.92 (14)	O5—C12—N1	124.49 (15)
O4—C3—C2	109.27 (13)	O6—C12—N1	110.15 (14)
O4—C3—C4	112.57 (13)	O6—C13—C14	110.77 (16)
C2—C3—C4	112.85 (13)	O6—C13—C15	102.40 (17)
N1—C4—C3	110.24 (12)	O6—C13—C16	109.65 (16)
N1—C4—C5	109.62 (13)	C14—C13—C15	111.1 (2)
C3—C4—C5	113.08 (14)	C14—C13—C16	111.2 (2)
C4—C5—C6	111.23 (15)	C15—C13—C16	111.4 (2)
C4—C5—C7	112.11 (18)		

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

D—H···A	D—H	H···A	D···A	D—H···A
O3—H2···O5	0.90	2.02	2.8551 (19)	154
N1—H1···O1^{i}	0.88	2.17	3.012 (2)	163
O4—H3···O3^{i}	0.93	2.03	2.943 (2)	169

Symmetry code: (i) $x, \frac{1}{2} - y, z - \frac{1}{2}$.

The H atoms were set geometrically or using difference Fourier maps. They were recalculated before the last refinement cycle.

Data collection: *CAD*-4 *Software* (Enraf–Nonius, 1989); cell refinement: *CAD*-4 *Software*; data reduction: *TEXSAN* (Molecular Structure Corporation, 1992–1997); program(s) used to solve structure: *SIR*92 (Altomare *et al.*, 1993); program(s) used to refine structure: *TEXSAN*; molecular graphics: *ORTEP*III (Burnett & Johnson, 1996), *ORTEP*-3 *for Windows* (Farrugia, 1997) and *CAMERON* (Watkin *et al.*, 1993); software used to prepare material for publication: *TEXSAN*.

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