*Refinement*

Refinement on $F^2$
$R[F^2 > 2\sigma(F^2)] = 0.048$
$wR(F^2) = 0.118$
$S = 1.06$
4484 reflections
317 parameters
H atoms: see below
$w = 1/[\sigma^2(F_o^2) + (0.046P)^2 + 0.7746P]$
where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max} = 0.20$ e Å$^{-3}$
$\Delta\rho_{min} = -0.19$ e Å$^{-3}$
Extinction correction: none
Scattering factors from *International Tables for Crystallography* (Vol. C)

Table 2. *Selected geometric parameters (Å, °) for (2b)*

| | | | |
|---|---|---|---|
| C4a—C8e | 1.391 (2) | C8a—C8b | 1.474 (2) |
| C4a—C4b | 1.516 (2) | C8b—C8c | 1.501 (2) |
| C4b—C4c | 1.532 (2) | C8b—C8d | 1.559 (2) |
| C4b—C8c | 1.580 (2) | C8c—C8d | 1.517 (2) |
| C4c—C8a | 1.384 (2) | C8d—C8e | 1.492 (2) |
| C4—C4a—C4b | 128.6 (2) | C8c—C8b—C8d | 59.39 (10) |
| C8e—C4a—C4b | 109.79 (14) | C8b—C8c—C8d | 62.22 (11) |
| C4a—C4b—C4c | 103.50 (13) | C8b—C8c—C4b | 104.10 (13) |
| C4a—C4b—C8c | 103.42 (13) | C8d—C8c—C4b | 103.81 (13) |
| C4c—C4b—C8c | 102.80 (13) | C8e—C8d—C8c | 107.14 (14) |
| C8a—C4c—C4b | 110.18 (14) | C8e—C8d—C8b | 121.01 (14) |
| C4c—C8a—C8b | 110.09 (14) | C8c—C8d—C8b | 58.39 (10) |
| C8a—C8b—C8c | 108.51 (14) | C4a—C8c—C8d | 110.35 (14) |
| C8a—C8b—C8d | 120.03 (15) | | |

Data were collected by the double-pass method using a charge-coupled device area-detector system. The first 50 frames of data were recollected at the end of data collection to monitor crystal decay. The structures were solved by direct methods and refined successfully in the monoclinic space group $P2_1/c$. Full-matrix least-squares refinement was carried out by minimizing $w(F_o^2 - F_c^2)^2$. The non-H atoms were refined anisotropically to convergence. The H atoms were treated using appropriate riding models (*AFIX* = m3; *SHELXTL-Plus*; Sheldrick, 1995), except for the hydroxyl H atom of (2*a*) which was refined freely with an isotropic displacement parameter. One of the carbonyl O atoms (O3) in compound (2*b*) exhibits disorder, with two positions O3 and O3′ which are 0.23 (1) Å above and below the mean plane defined by atoms C8d, C16 and C17 and the midpoint of O3 and O3′. The refined occupancy factor for O3 is 0.58 (5).

For both compounds, data collection: *SMART* software (Siemens, 1995); cell refinement: *SAINT* (Siemens, 1995); data reduction: *SAINT*; program(s) used to solve structures: *SHELXTL-Plus* (Sheldrick, 1995); program(s) used to refine structures: *SHELXTL-Plus*; molecular graphics: *SHELXTL-Plus*; software used to prepare material for publication: *SHELX-Plus*.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: BK1278). Services for accessing these data are described at the back of the journal.



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# Tyrosinium-D-tetrahydroisoquinoline-3-carboxylate 1.5-Hydrate and Tyrosyl-D-tetrahydroisoquinoline-3-carboxamide Hydrate

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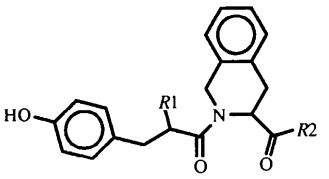
## Abstract

Crystals of the two dipeptide title compounds, Tyr-D-Tic, $C_{19}H_{20}N_2O_4.1.5H_2O$, and Tyr-D-Tic-$NH_2$, $C_{19}H_{21}N_3O_3.H_2O$, were prepared by the sitting-drop method. Tyr-D-Tic is orthorhombic ($P2_12_12_1$) and crystallizes as a zwitterion. The asymmetric unit contains two peptide molecules and three molecules of water.

Tyr-D-Tic-$NH_2$ crystals are monoclinic ($P2_1$), the asymmetric unit containing one peptide molecule and one molecule of water. Despite some differences in packing, the conformation of the two dipeptides is almost identical (r.m.s. deviation for non-H atoms is approximately 0.18 Å).

## Comment

A new class of potent opioid peptides contains a tetrahydroisoquinoline-3-carboxylic acid (Tic) residue in the second position. Peptides with the initial sequence Tyr-D-Tic-*X* are $\mu$-selective agonists (Schiller *et al.*, 1993). The dipeptide Tyr-D-Tic-$NH_2$ possesses activity similar to the tripeptide Tyr-D-Tic-Phe and tetrapeptide Tyr-D-Tic-Phe-Phe, both $\mu$-agonists (Temussi *et al.*, 1994), although the binding affinity of the dipeptide is 10–20-fold lower than that of the tripeptide (Wilkes & Schiller, 1995). Despite the lower binding affinity, Tyr-D-Tic-$NH_2$ still has measurable opioid activity (Temussi *et al.*, 1994). Thus, the selectivity and activity is at least partially dependent on the first two residues.




(1) $R1 = NH_3^+$, $R2 = O^-$
(2) $R1 = NH_2$, $R2 = NH_2$

The structure of Tyr-D-Tic, (1), is shown in Fig. 1. The two peptide molecules in the asymmetric unit of (1) are almost identical (r.m.s. deviation 0.207 Å for all non-H atoms, O2 matches with O4′ and O2′ matches with O4). The crystals of Tyr-D-Tic-$NH_2$, (2), contain one peptide molecule and one water molecule in the asymmetric unit (Fig. 2).

A comparison of all non-H atoms (except the *c*-terminal O atom and N atoms) in (1) with their corresponding atoms in (2) produces r.m.s. deviations of 0.181 and 0.150 Å for fits with the two molecules in the asymmetric unit of (1). The maximum deviations are seen in the Tic residue (*i.e.* 0.283 Å for C2*G*3 and 0.260 Å for C2′). Thus, the structures of (1) and (2) are superimposable.

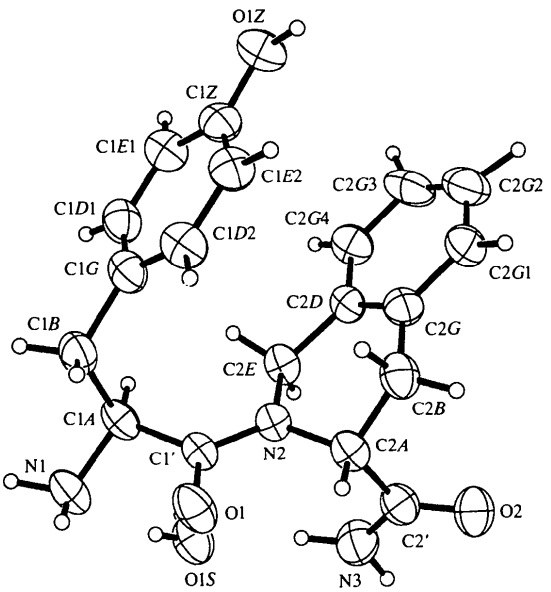



Fig. 1. View of Tyr-D-Tic, (1), showing the labeling of the non-H atoms and the relationship between the molecules in the asymmetric unit. Displacement ellipsoids are shown at 50% probability levels; H atoms are drawn as small circles of arbitrary radii.

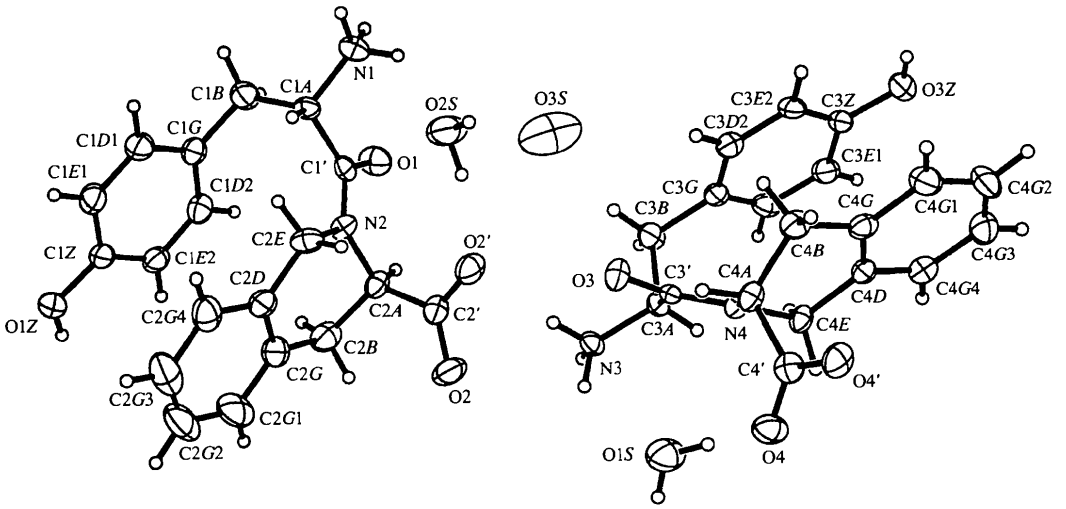



Fig. 2. View of Tyr-D-Tic-$NH_2$, (2), showing the labeling of the non-H atoms. Displacement ellipsoids are shown at 50% probability levels; H atoms are drawn as small circles of arbitrary radii.

Both (1) and (2) form three-dimensional networks *via* hydrogen bonds (Tables 2 and 4), although the attractions in (2) tend to be weaker. In (2), there are two three-centered hydrogen bonds formed by the N terminal amino group in each of the two molecules in the asymmetric unit and either a solvent molecule (in the same cell) or the tyrosine hydroxyl (in a symmetry related molecule). In both compounds, the planes formed by the aromatic rings are almost parallel [3.9 and 1.3° for the angle between the planes for each of the two molecules in (1), and 5.9° for (2)]. Because of the packing, this can be seen more clearly in (2) (Fig. 4). In (1), the three-dimensional network contains alternating hydrophobic and hydrophilic layers which are perpendicular to the *c* axis (Fig. 3). A layered structure is not observed in (2).

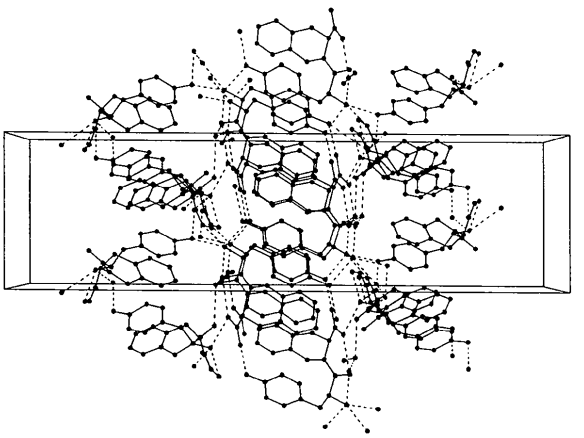


Fig. 3. Packing diagram of (1) viewed down the *a* axis. H atoms have been omitted for clarity; hydrogen bonds are shown as dashed lines. The alternating hydrophobic and hydrophilic (hydrogen-bonded) layers are clearly visible.

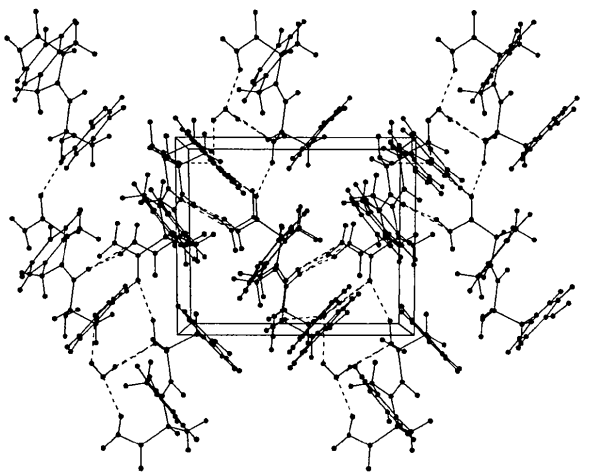


Fig. 4. Packing diagram of (2) viewed down the *c* axis. H atoms have been omitted for clarity; hydrogen bonds are shown as dashed lines.

## Experimental

Tyr-D-Tic, (1), and Tyr-D-Tic-$NH_2$, (2), were obtained from G. A. Brine (Research Triangle Institute, Research Triangle Park, NC, USA). Initial crystallization conditions were discovered using the Crystal Screen™ I kit (Hampton Research, Riverside, CA, USA). Diffraction quality crystals were prepared by equilibrating a sitting drop containing 3 $\mu$l of (1) (34.7 mg $ml^{-1}$) and 3 $\mu$l of reservoir solution against a 1 ml reservoir of 100 m*M* Tris (pH 8.5), 27% PEG 1000; crystals grew overnight. Crystals of (2) were prepared by equilibrating a sitting drop containing 3 $\mu$l of the dipeptide (25 mg $ml^{-1}$ in 29% methanol) and 2 $\mu$l of the reservoir solution against a 1 ml reservoir of 100 m*M* HEPES (pH 8.05), 1.3 *M* lithium sulfate; crystals grew overnight.

### Compound (1)

*Crystal data*

$C_{19}H_{20}N_2O_4.1.5H_2O$
$M_r$ = 367.39
Orthorhombic
$P2_12_12_1$
$a$ = 9.127 (1) Å
$b$ = 10.522 (1) Å
$c$ = 37.195 (2) Å
$V$ = 3572.0 (6) $Å^3$
$Z$ = 8
$D_x$ = 1.366 Mg $m^{-3}$
$D_m$ not measured

Cu $K\alpha$ radiation
$\lambda$ = 1.54178 Å
Cell parameters from 35 reflections
$\theta$ = 9.63–59.89°
$\mu$ = 0.838 $mm^{-1}$
$T$ = 223 (2) K
Plate
0.56 × 0.35 × 0.06 mm
Clear colorless

*Data collection*

Siemens *P*4 diffractometer
$2\theta/\omega$ scans
Absorption correction: face-indexed numerical
$T_{min}$ = 0.72, $T_{max}$ = 0.95
3258 measured reflections
3105 independent reflections
2770 reflections with $I > 2\sigma(I)$

$R_{int}$ = 0.022
$\theta_{max}$ = 57.00°
$h = -1 \rightarrow 9$
$k = 0 \rightarrow 11$
$l = 0 \rightarrow 40$
3 standard reflections every 97 reflections
intensity decay: 2.01%

*Refinement*

Refinement on $F^2$
$R[F^2 > 2\sigma(F^2)]$ = 0.046
$wR(F^2)$ = 0.127
$S$ = 1.063
3105 reflections
511 parameters
H atoms: coordinates only refined
$w = 1/[\sigma^2(F_o^2) + (0.0866P)^2 + 0.2685P]$
where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = −0.089

$\Delta\rho_{max}$ = 0.459 e $Å^{-3}$
$\Delta\rho_{min}$ = −0.233 e $Å^{-3}$
Extinction correction: *SHELXL*93 (Sheldrick, 1993)
Extinction coefficient: 0.0013 (2)
Scattering factors from *International Tables for Crystallography* (Vol. C)
Absolute configuration: Flack (1983)
Flack parameter = 0.0 (3)

Table 1. *Selected torsion angles (°)*

| | |
|---|---|
| N1—C1*A*—C1′—N2 | 131.8 (4) |
| C1*A*—C1′—N2—C2*A* | 177.1 (4) |
| C1′—N2—C2*A*—C2′ | 115.4 (4) |

| | |
|---|---|
| N3—C3*A*—C3′—N4 | 134.6 (4) |
| C3*A*—C3′—N4—C4*A* | −179.0 (4) |
| C3′—N4—C4*A*—C4′ | 127.1 (2) |
| N1—C1*A*—C1*B*—C1*G* | −172.5 (4) |
| C1*A*—C1*B*—C1*G*—C1*D*1 | 92.4 (5) |
| N3—C3*A*—C3*B*—C3*G* | −178.2 (3) |
| C3*A*—C3*B*—C3*G*—C3*D*1 | 86.2 (5) |
| C1′—N2—C2*E*—C2*D* | 131.7 (4) |
| C1′—N2—C2*A*—C2*B* | −118.0 (4) |
| N2—C2*A*—C2*B*—C2*G* | −46.5 (5) |
| C2*A*—C2*B*—C2*G*—C2*G*1 | −163.3 (4) |
| C2*B*—C2*G*—C2*G*1—C2*G*2 | −173.6 (5) |
| C3′—N4—C4*E*—C4*D* | 130.0 (4) |
| C3′—N4—C4*A*—C4*B* | −106.1 (4) |
| N4—C4*A*—C4*B*—C4*G* | −54.6 (4) |
| C4*A*—C4*B*—C4*G*—C4*G*1 | −158.2 (4) |
| C4*B*—C4*G*—C4*G*1—C4*G*2 | −179.4 (4) |

Table 2. *Hydrogen-bonding geometry (Å, °) for (1)*

| *D*—H···*A* | *D*—H | H···*A* | *D*···*A* | *D*—H···*A* |
|---|---|---|---|---|
| O1*S*—H1*SA*···O4 | 0.90 (4) | 2.06 (2) | 2.879 (5) | 150 (3) |
| O2*S*—H2*SA*···O2′ | 0.90 (1) | 1.91 (2) | 2.792 (5) | 166 (2) |
| N1—H1*B*···O4$^{i}$ | 0.86 (5) | 1.96 (5) | 2.755 (5) | 151 (4) |
| N1—H1*C*···O1*Z*$^{ii}$ | 1.00 (5) | 1.96 (5) | 2.901 (5) | 155 (4) |
| N1—H1*D*···O3*Z*$^{iii}$ | 0.91 (5) | 2.27 (5) | 2.892 (5) | 124 (4) |
| N1—H1*D*···O2*S* | 0.92 (5) | 2.17 (5) | 2.887 (6) | 133 (4) |
| N3—H3*B*···O4′$^{iv}$ | 0.90 (5) | 1.98 (5) | 2.847 (5) | 160 (4) |
| N3—H3*D*···O1*S* | 0.98 (4) | 2.24 (4) | 2.957 (6) | 128 (3) |
| N3—H3*D*···O1*Z*$^{v}$ | 0.98 (4) | 2.41 (4) | 3.125 (4) | 130 (3) |
| N3—H3*C*···O2′ | 0.88 (5) | 1.96 (5) | 2.781 (5) | 153 (4) |
| O3*Z*—H3*ZA*···O4′$^{vi}$ | 0.82 | 1.84 (4) | 2.630 (5) | 161 (1) |
| O1*Z*—H1*ZA*···O2$^{vii}$ | 0.82 | 1.78 (1) | 2.566 (5) | 159 (1) |
| O2*S*—H2*SB*···O3*S* | 0.90 (2) | 2.11 (2) | 2.963 (6) | 157 (1) |
| O3*S*···O1$^{viii}$ | – | – | 2.875 (6) | – |

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

## Compound (2)

*Crystal data*

| | |
|---|---|
| $C_{19}H_{21}N_3O_3.H_2O$ | Cu $K\alpha$ radiation |
| $M_r$ = 357.40 | $\lambda$ = 1.54178 Å |
| Monoclinic | Cell parameters from 67 reflections |
| $P2_1$ | $\theta$ = 12.43–63.56° |
| $a$ = 8.981 (1) Å | $\mu$ = 0.758 mm$^{-1}$ |
| $b$ = 10.597 Å | $T$ = 223 (2) K |
| $c$ = 9.703 (1) Å | Plate |
| $\beta$ = 98.76 (1)° | 0.40 × 0.20 × 0.08 mm |
| $V$ = 912.68 (14) Å$^3$ | Clear colorless |
| $Z$ = 2 | |
| $D_x$ = 1.301 Mg m$^{-3}$ | |
| $D_m$ not measured | |

*Data collection*

| | |
|---|---|
| Siemens *P*4 diffractometer | $R_{int}$ = 0.013 |
| $2\theta/\omega$ scans | $\theta_{max}$ = 56.41° |
| Absorption correction: face-indexed numerical | $h = -9 \rightarrow 0$ |
| $T_{min}$ = 0.81, $T_{max}$ = 0.90 | $k = -1 \rightarrow 11$ |
| 1608 measured reflections | $l = -10 \rightarrow 10$ |
| 1450 independent reflections | 3 standard reflections every 97 reflections |
| 1323 reflections with $I > 2\sigma(I)$ | intensity decay: 2.33% |

*Refinement*

| | |
|---|---|
| Refinement on $F^2$ | $\Delta\rho_{max}$ = 0.189 e Å$^{-3}$ |
| $R[F^2 > 2\sigma(F^2)]$ = 0.048 | $\Delta\rho_{min}$ = −0.199 e Å$^{-3}$ |
| $wR(F^2)$ = 0.141 | Extinction correction: *SHELXL*93 (Sheldrick, 1993) |
| $S$ = 1.044 | Extinction coefficient: 0.0071 (18) |
| 1450 reflections | Scattering factors from *International Tables for Crystallography* (Vol. C) |
| 257 parameters | Absolute configuration: Flack (1983) |
| H atoms: riding model or coordinates only | Flack parameter = 0.3 (5) |
| $w = 1/[\sigma^2(F_o^2) + (0.1086P)^2 + 0.0882P]$ where $P = (F_o^2 + 2F_c^2)/3$ | |
| $(\Delta/\sigma)_{max}$ = 0.005 | |

Table 3. *Selected torsion angles (°)*

| | |
|---|---|
| N1—C1*A*—C1′—N2 | 135.6 (5) |
| C1*A*—C1′—N2—C2*A* | 176.0 (5) |
| C1′—N2—C2*A*—C2′ | 111.5 (5) |
| N1—C1*A*—C1*B*—C1*G* | −169.3 (5) |
| C1*A*—C1*B*—C1*G*—C1*D*1 | 77.7 (6) |
| C1′—N2—C2*E*—C2*D* | 142.7 (5) |
| C1′—N2—C2*A*—C2*B* | −120.4 (5) |
| N2—C2*A*—C2*B*—C2*G* | −49.1 (6) |
| C2*A*—C2*B*—C2*G*—C2*G*1 | −159.6 (5) |
| C2*B*—C2*G*—C2*G*1—C2*G*2 | −178.2 (6) |

Table 4. *Hydrogen-bonding geometry (Å, °) for (2)*

| *D*—H···*A* | *D*—H | H···*A* | *D*···*A* | *D*—H···*A* |
|---|---|---|---|---|
| O1*S*—H1*S*1···N1 | 0.85 (4) | 2.09 (5) | 2.906 (7) | 159 (6) |
| N1—H1*B*···O2$^{i}$ | 1.04 (6) | 2.44 (6) | 3.188 (6) | 128 (4) |
| N3—H3*B*···O1*S* | 0.99 (7) | 2.10 (7) | 3.026 (7) | 154 (5) |
| N3—H3*A*···O1$^{ii}$ | 0.94 (7) | 1.94 (7) | 2.836 (6) | 158 (6) |
| O1*Z*—H1*Z*···O2$^{iii}$ | 1.01 (7) | 1.71 (7) | 2.706 (6) | 168 (6) |
| N1—H1*A*···O1*Z*$^{iv}$ | 0.89 (6) | 2.44 (7) | 3.305 (6) | 162 (6) |

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

For Tyr-D-Tic, the largest remaining difference peak (0.459 e Å$^{-3}$) is not located within covalent bonding distance of any atom. Attempts to refine with a water molecule in this position resulted in an occupancy of less than 10%. Several other difference peaks are located near O3*S* and are likely due to the H atoms, but the data were too weak to refine the positions of these atoms.

For both compounds, data collection: *XSCANS* (Siemens, 1994); cell refinement: *XSCANS*; data reduction: *XSCANS*; program(s) used to solve structures: *SHELXTL* (Sheldrick, 1994); program(s) used to refine structures: *SHELXTL*; molecular graphics: *SHELXTL*; software used to prepare material for publication: *SHELXTL*.

This research was supported in part by the National Institue for Drug Abuse (NIDA) and the Office of Naval Research (ONR).

Supplementary data for this paper are available from the IUCr electronic archives (Reference: BS1028). Services for accessing these data are described at the back of the journal.

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# Intermediates in the Synthesis of *Daphniphyllum* Alkaloids. I. A Tetracyclic Oxygen Analogue

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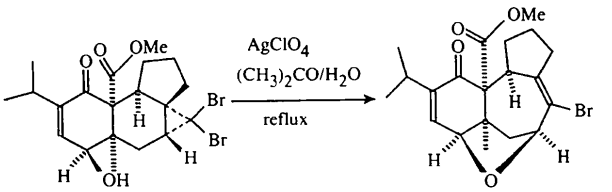
## Abstract

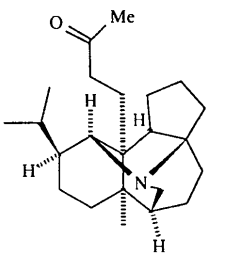
In methyl (3*S*,5*S*,6*S*,10*R*,11*R*)-2-bromo-3,6-epoxy-8-isopropyl-5-methyl-9-oxotricyclo[9.3.0.0$^{5,10}$]tetradeca-1,7-diene-10-carboxylate, $C_{20}H_{25}BrO_4$, the seven-membered ring is half-chair shaped, the six-membered ring adopts a boat conformation and the five-membered rings both adopt envelope conformations. The molecule adopts an overall hemispherical conformation.

## Comment

In our projected synthesis of *Daphniphyllum* alkaloids, such as methyl homodaphniphyllate, (1), we have developed a route to an oxygen analogue, (2), containing many of the same structural features. We have previously presented the X-ray structure determination of a tetracyclic intermediate, (3) (Castellano, Brocksom & Ceschi, 1994), and this compound undergoes a complex rearrangement reaction catalyzed by silver(I) salts in polar solvents (Brocksom, Pesquero & Lopes, 1990) leading to the crystalline product (2). Although the macroscopic sample is racemic, the crystal selected by hand turned out to be a single enantiomer and is the subject of the present paper. This three-dimensional structure determination is absolutely essential for successful planning of the total synthesis and cannot be accomplished by conventional spectroscopic means such as high-field NMR measurements.




(3) (2)




(1)

A *ZORTEP* (Zsolnai, 1995) illustration of the formula unit showing the relative stereochemistry is presented in Fig. 1 and selected bond distances and angles are given in Table 1. Compound (2) has an ether bridge in a tetracyclic structure containing fused six-, seven- and five-membered carbocyclic skeletons, analogous to the nitrogen-bridged *Daphniphyllum* alkaloids. The structure is heavily influenced by the ether bridge which forces the molecule to adopt an overall hemispherical conformation. The six-membered ring is in a slightly distorted boat conformation, with C6 and C9 lying at distances of 0.516 (6) and 0.408 (5) Å, respectively, from the least-squares plane through atoms C5, C7, C8 and C10; both five-membered rings adopt envelope conformations, with C13 and C5 occupying the flap positions at distances of 0.526 (7) and −0.696 (5) Å from the least-squares plane made up of the remaining four atoms in the cyclopentane and furan rings, respectively. The molecules are joined through C—H···O interactions: C11···O1$^{i}$ 3.410 (7), H11···O1$^{i}$ 2.53 Å and