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A pair of epimeric 13-hydroxy-2,3,6,7-tetramethoxy-8b,11,12,12a,13,13a-hexahydro-9*H*-9a-azacyclopenta[*b*]-triphenylene-10-ones

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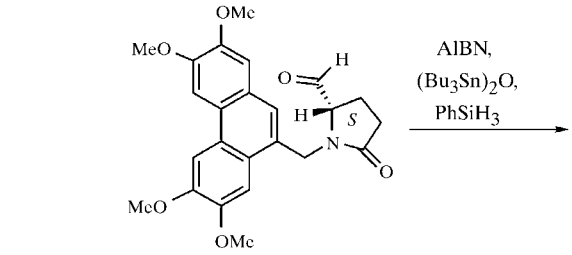
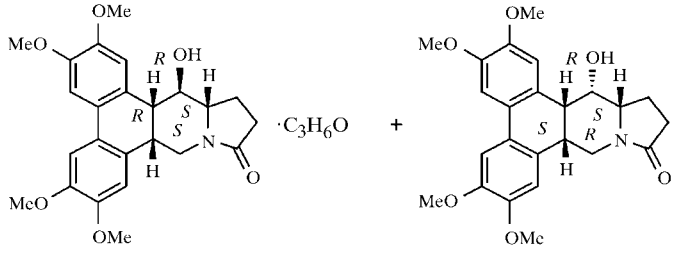
The structures of two compounds which are intermediates in the synthesis of phenanthroindolizidine alkaloids have been determined. (8b*S*,13a*S*,14*R*,14a*R*)-8b,9,11,12,13,13a,14,-14a-Octahydro-14-hydroxy-2,3,6,7-tetramethoxydibenzo[*f*,*h*]-pyrrolo[1,2-*b*]isoquinolin-11-one acetone solvate, $C_{24}H_{27}NO_6\cdot C_3H_6O$, (II), crystallizes in a chiral space group with one solvent molecule (acetone) present in the asymmetric unit. On the other hand, (8b*S*,13a*S*,14*S*,14a*R*)-8b,9,11,12,13,13a,14,14a-octahydro-14-hydroxy-2,3,6,7-tetramethoxydibenzo[*f*,*h*]pyrrolo[1,2-*b*]isoquinolin-11-one, $C_{24}H_{27}NO_6$, (III), crystallizes in a centrosymmetric space group with two molecules in the asymmetric unit and with no solvent present. The two molecules in the asymmetric unit of (III) are structurally the same. Compounds (II) and (III) are epimers at the C atom carrying the OH group; otherwise they are very similar in structure.

Comment

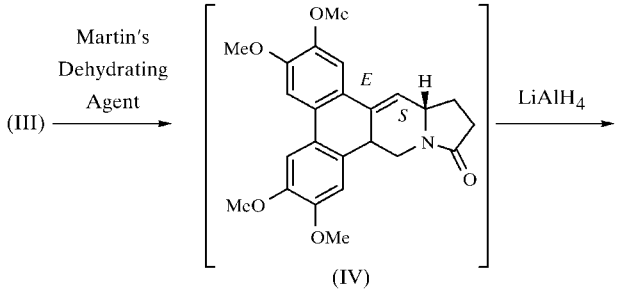
In a project involving the synthesis and evaluation of a number of phenanthroindolizidine alkaloids (Li *et al.*, 2001) that are of interest as potential cancer chemotherapeutic agents, we have developed a synthetic route (Zhong *et al.*, 2004; see scheme) to this group of alkaloids *via* a pair of epimeric intermediates, *viz*. the title compounds, (II) and (III). Reductive ring closure of optically active (I) using free-radical chemistry (Hays & Fu, 1996, 1999) gives the intermediates (II) and (III) in an approximate 2.3:1 ratio. The key issue in this work was the determination of the relative stereochemistries for (II) and (III), as those epimers did not lend themselves to definitive NMR spectral analyses. Compound (III), with its *trans* H—C—C—OH arrangement that is necessary for the elimination of water, is readily converted to the 14–14a double-bonded intermediate (IV) (not analyzed due to instability). Reduction of the amide function and concomitant rearrangement of the double bond in (IV) produces the natural product tylophorine, (V), which is an antitumor agent (Gao *et al.*, 2004). Optical rotation measurements of bulk samples of (II) and (III) indicate that optical activity is maintained, giving the final product as (*S*)-(+)-tylophorine (Buckley & Rapoport, 1983; Norlander & Njoroge, 1987), with a single chiral center at the 13a position. However, the crystal of (II) was obtained as a racemate (see *Experimental*), indicating that at least a portion of the sample had racemized during ring closure or that the starting material, (I), was partially racemized at the outset. The issue of this apparent partial racemization is presently under study.



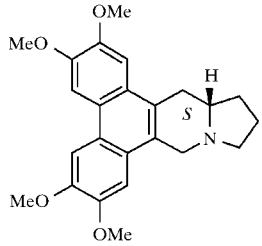
(I)



(II) (III)



(IV)



(*S*)-(+)-Tylophorine, (V)

The structure of the molecule consists of a semiplanar aromatic system that is torsionally distorted, with an azacyclohexane ring in a chair configuration fused *cis* to atoms C14 and C17 of a dihydrophenanthrene system. The molecular structures of (II) and (III), apart from their epimeric relationship at C19, are very similar.

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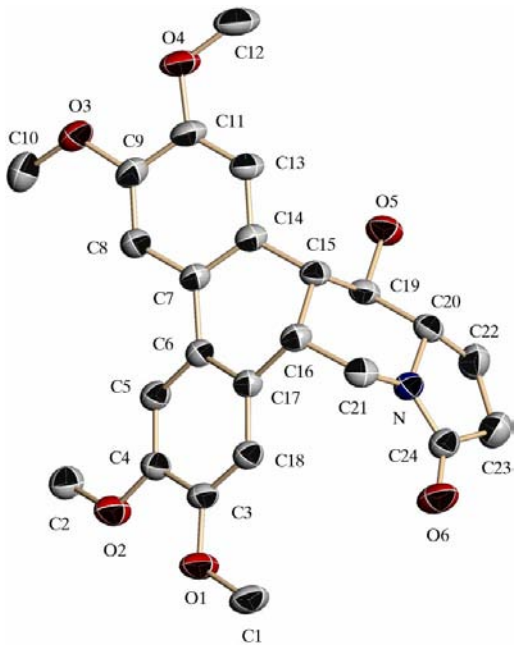

Figure 1
A view of the structure of (II), showing the atomic numbering scheme. Displacement ellipsoids are drawn at the 50% probability level. H atoms and the acetone solvent molecule have been omitted for clarity.

One major structural difference between (II) and (III) is the torsion angle between the aromatic rings, defined as the angle between the C5—C6 and C7—C8 bonds. For (II), this angle is 20.0 (3)°, whereas in (III), the corresponding value is found to be 11.0 (3)°. The torsion angles between the C14—C15 and C16—C17 bonds are 53.2 (2) and 48.18 (19)° for (II) and (III), respectively. Taken together, these values are in accord with the statistically observed relationship between these two parameters in these types of systems (Allen, 2002; Bruno *et al.*, 2002). Given the difference in unit-cell contents and the inclusion of acetone in the structure of (II), no straightforward comparison of the torsion angles may be made, although the values are not atypical for the dihydrophenanthrene ring system. We note that, in the presence of acetone in the lattice of (II), the number of intermolecular contacts is lower, and we speculate that this leads to the higher torsion value.

While the presence of a solvent of crystallization in (II) disturbs the intermolecular contacts, a direct comparison may be made between the interbond angles and lengths of the two structures. Inspection of the structures of (II) and (III) shows that all bond lengths and angles in the two structures are well within the normal reported ranges and are similar in both structures.

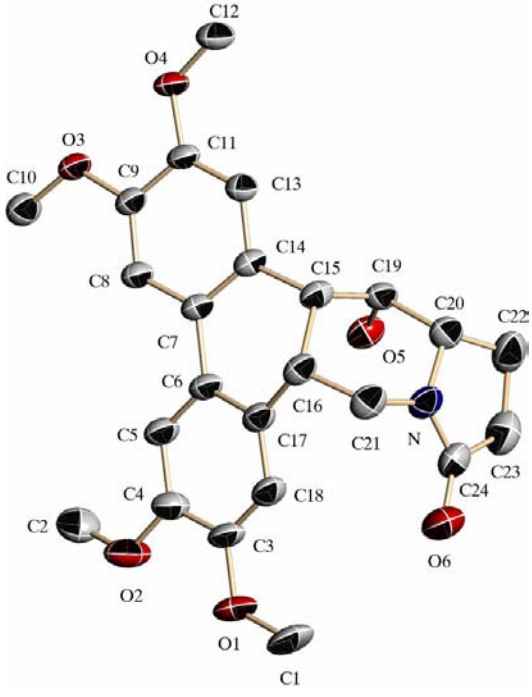

Figure 2
A view of the structure of (III), illustrating one of the two crystallographically independent molecules and showing the atomic numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms have been omitted for clarity.

Experimental

To a solution of (I) (2.12 g, 5.00 mmol) in dry benzene (15 ml) in a 100 ml Schlenk tube were added bis(tributyltin) oxide [$(Bu_3Sn)_2O$, 0.38 ml, 0.75 mmol], $PhSiH_3$ (0.31 ml, 2.50 mmol), EtOH (0.585 ml, 2.00 mmol) and 2,2′-azobis(isobutyro)nitrile (90 mg, 0.548 mmol; AIBN) in benzene (2.0 ml). The vessel was sealed, shaken and placed in an oil bath at 353–358 K. After 12 h, thin-layer chromatographic analysis indicated that all of the starting material had been consumed. The mixture was allowed to cool to room temperature and tetrabutylammonium fluoride (30.0 ml of a 1.0 *M* solution in tetrahydrofuran, 30.0 mmol) was added with stirring for 2 h, at the end of which time 2 *M* HCl (15 ml) was added. The reaction mixture was extracted with CH_2Cl_2 (3 × 50 ml), and the combined organic extracts were dried ($MgSO_4$), filtered and concentrated. The residue was purified by flash chromatography (eluting with 3:1:0.01 CH_2Cl_2–EtOAc–MeOH) to give 827 mg (69%) of compound (II) in the non-solvated form. Analysis: $[\alpha]_D^{22}$ 78.3° (*c* 0.48, $CHCl_3$); HREIMS, calculated for $C_{24}H_{27}NO_6$: 425.1838; found: *m*/*z* 425.1842. Compound (III) was obtained as 30% of the final product. Analysis: $[\alpha]_D^{22}$ −84.5° (*c* 1.0, $CHCl_3$); HREIMS, calculated for $C_{24}H_{27}NO_6$: 425.1838; found: *m*/*z* 425.1842. Single crystals of (II) as the acetone solvate and of (III) were obtained from 2:1 acetone–methanol solutions after partial evaporation. The crystal of (II) was shown to be a racemic mixture, a fact which indicates that either the ring closure of (I) to (II) is accompanied by racemization, or that the starting material, (I), was partially racemized.

Compound (II)

Crystal data

$C_{24}H_{27}NO_6·C_3H_6O$
M_r = 483.54
Monoclinic, $P2_1/c$
a = 11.5790 (10) Å
b = 17.4011 (15) Å
c = 13.0453 (11) Å
β = 110.488 (2)°
V = 2462.2 (4) Å^3
Z = 4
D_x = 1.304 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 3948 reflections
θ = 2.2–22.1°
μ = 0.09 mm^{-1}
T = 295 (2) K
Block, colorless
0.50 × 0.20 × 0.15 mm

Data collection

Bruker SMART 1000 CCD area-detector diffractometer
φ and ω scans
Absorption correction: multi-scan (*SADABS*; Sheldrick, 1996)
T_{min} = 0.881, T_{max} = 0.986
24 264 measured reflections

5059 independent reflections
2927 reflections with $I > 2\sigma(I)$
R_{int} = 0.053
θ_{max} = 26.4°
$h = -14 \rightarrow 14$
$k = -21 \rightarrow 21$
$l = -16 \rightarrow 16$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.046
$wR(F^2)$ = 0.127
S = 1.01
5059 reflections
323 parameters
H-atom parameters constrained

$w = 1/[\sigma^2(F_o^2) + (0.0429P)^2 + 0.9647P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.18 e Å^{-3}
$\Delta\rho_{min}$ = −0.19 e Å^{-3}

Table 1
Selected geometric parameters (Å, °) for (II).

C15—C19	1.534 (3)	C19—C20	1.517 (3)
C19—O5	1.421 (2)		
C5—C6—C7	121.80 (18)	C17—C16—C15	110.27 (16)
C8—C7—C6	122.32 (19)	C18—C17—C16	121.90 (18)
C14—C15—C16	110.11 (17)	O5—C19—C20	109.32 (16)
C21—C16—C17	115.18 (16)	O5—C19—C15	108.68 (16)
C5—C6—C7—C8	20.0 (3)	C14—C15—C16—C17	53.2 (2)

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

D—H···A	D—H	H···A	D···A	D—H···A
O5—H5···O6^{i}	0.82	1.92	2.737 (2)	174

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

Compound (III)

Crystal data

$C_{24}H_{27}NO_6$
M_r = 425.47
Orthorhombic, $P2_12_12_1$
a = 13.0534 (16) Å
b = 14.9664 (18) Å
c = 21.356 (3) Å
V = 4172.1 (9) Å^3
Z = 8
D_x = 1.355 Mg m^{-3}

Mo $K\alpha$ radiation
Cell parameters from 8864 reflections
θ = 2.3–25.0°
μ = 0.10 mm^{-1}
T = 293 (2) K
Fragment, colorless
0.50 × 0.42 × 0.40 mm

Data collection

Bruker SMART 1000 CCD area-detector diffractometer
φ and ω scans
Absorption correction: multi-scan (*SADABS*; Sheldrick, 1996)
T_{min} = 0.953, T_{max} = 0.962
45 934 measured reflections

5663 independent reflections
4458 reflections with $I > 2\sigma(I)$
R_{int} = 0.035
θ_{max} = 28.3°
$h = -17 \rightarrow 17$
$k = -19 \rightarrow 19$
$l = -27 \rightarrow 28$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.033
$wR(F^2)$ = 0.086
S = 0.98
5663 reflections
567 parameters

H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0549P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.19 e Å^{-3}
$\Delta\rho_{min}$ = −0.18 e Å^{-3}

Table 3
Selected geometric parameters (Å, °) for (III).

C15—C19	1.544 (3)	C19—C20	1.526 (3)
C19—O5	1.417 (2)		
C5—C6—C7	121.28 (16)	C17—C16—C15	112.09 (15)
C8—C7—C6	121.10 (16)	C18—C17—C6	118.88 (18)
C14—C15—C16	110.63 (15)	O5—C19—C20	108.21 (15)
C17—C16—C21	115.78 (15)	O5—C19—C15	112.80 (15)
C5—C6—C7—C8	11.0 (3)	C14—C15—C16—C17	48.18 (19)

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

D—H···A	D—H	H···A	D···A	D—H···A
O5—H5A···O12	0.82	2.00	2.818 (2)	179

Most H atoms were introduced at calculated positions and refined by applying a riding model [C—H = 0.93–0.98 Å and U_{iso}(H) = 1.2U_{eq}(C); O—H = 0.82 Å and U_{iso}(H) = 1.5U_{eq}(O)]. The hydroxyl H atoms in (III) were located in difference Fourier maps and were refined with constraints on their positions and U_{iso} values. Friedel equivalents were merged before the final refinement.

For both compounds, data collection: *SMART* (Bruker, 1997); cell refinement: *SAINT* (Bruker, 1997); data reduction: *SAINT*; program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *SHELXTL* (Sheldrick, 1997); software used to prepare material for publication: *SHELXTL*.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: FR1452). Services for accessing these data are described at the back of the journal.

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