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Ethyl 12b-allyl-1-hydroxy-3,6,7,12b-tetrahydro-4*H*-1,3-dioxolo[4,5-*g*]pyrido[2,1-*a*]isoquinoline-2-carboxylate

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Key indicators

Single-crystal X-ray study
T = 294 K
Mean σ(C–C) = 0.006 Å
R factor = 0.084
wR factor = 0.180
Data-to-parameter ratio = 14.1

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

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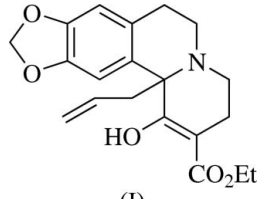
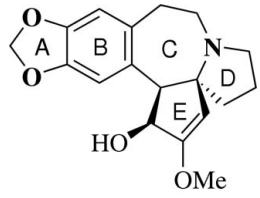
The title compound, $C_{20}H_{23}NO_5$, is an advanced intermediate used in the total synthesis of cephalotaxine. An intramolecular O—H···O hydrogen bond exists in the crystal structure.

Comment

Cephalotaxine (CET), parent of the cephalotaxus alkaloids (Huang & Xue, 1984; Jalil Miah *et al.*, 1998), possesses a unique benzazepine-bearing pentacyclic *ABCDE* ring skeleton. Naturally occurring esters of CET (harringtonine and homoharringtonine) have been found to be highly effective in the treatment of actute human leukaemia and are currently undergoing advanced clinical trials (Kantarjian *et al.*, 2001). Homoharringtonine is also a potent agent against strains of the chloroquinine-resistant *Plasmodium f.* malaria parasite *in vitro* (Whaun & Brown, 1990). The unique structure and therapeutic potential of this group of alkaloids have stimulated much synthetic research, which has produced several elegant total syntheses of CET (Tietze & Schirok, 1999; Koseki *et al.*, 2002; Suga *et al.*, 2002), and numerous studies of the construction of the pentacyclic ring system.



(I)



(-)-Cephalotaxine

The title enol ester, (I), an advanced intermediate used in the total synthesis of CET, was obtained from a Dieckmann cyclization of the corresponding diester precursor (Wang, 2003). As shown in (Fig. 1), the molecule has reactive side groups that could serve as handles for further conversion to cephalotaxine (CET). The two six-membered heterocylic rings are *trans*-fused. The six-membered heterocyle bearing the CO_2Et group adops a twist conformation, while the other adopts a half-chair conformation. In the molecule, atom O5 acts as an intramolecular hydrogen-bond donor, forming an

O—H···O bond with the carbonyl atom O3. The displacement parameters for C16 and C17 are quite large, which could explain the too short C16—C17 distance (1.093 Å).

Experimental

To a refluxing mixture of KO^{t}Bu (134 mg, 1.2 mmol) in 10 ml of toluene was added the corresponding allyl diester of the title compound (403 mg, 1.0 mmol) in 2 ml of toluene. After 30 min, the reaction mixture was diluted with 20 ml of EtOAc, washed with water (5 ml) and brine (5 ml), dried, and evaporated under reduced pressure. The residue was purified by silica-gel column chromatography, eluted with petroleum ether–EtOAc (5:1 *v*/*v*), to give the corresponding enol ester, (I) (268 mg, 75%), as colourless needles. Single crystals suitable for X-ray determination were obtained by slow evaporation of an AcOEt solution over a period of several days (m.p. 395–396 K). HRMS (EI) *m*/*z* calculated for [*M* + H] $C_{20}H_{24}NO_5$: 358.1649; found: 358.1653.

Crystal data

$C_{20}H_{23}NO_5$
M_r = 357.39
Monoclinic, $P2_1/c$
a = 8.5365 (7) Å
b = 20.0523 (18) Å
c = 10.6574 (9) Å
β = 99.854 (4)°
V = 1797.4 (3) Å^3
Z = 4
D_x = 1.321 Mg m^{-3}
Mo $K\alpha$ radiation
μ = 0.10 mm^{-1}
T = 294 (2) K
Plate, colourless
0.29 × 0.13 × 0.06 mm

Data collection

Bruker SMART CCD area-detector diffractometer
φ and ω scans
Absorption correction: none
9495 measured reflections
3350 independent reflections
1915 reflections with $I > 2\sigma(I)$
R_{int} = 0.054
θ_{max} = 25.5°

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.084
$wR(F^2)$ = 0.180
S = 1.16
3350 reflections
238 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0336P)^2 + 2.3489P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.60 e Å^{-3}
$\Delta\rho_{min}$ = −0.40 e Å^{-3}
Extinction correction: *SHELXL97*
Extinction coefficient: 0.0022 (9)

Table 1
Hydrogen-bond geometry (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
O5—H5···O3	0.82	1.83	2.556 (4)	147

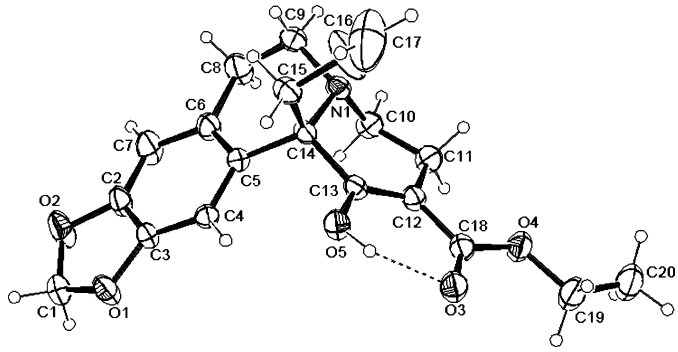


Figure 1
The structure of (I), showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 30% probability level. The dashed line indicates the intramolecular hydrogen bond.

All H atoms were positioned geometrically (C—H values were set at 0.97, 0.96, 0.93 and 0.82 Å for CH_2, CH_3, CH and OH H atoms, respectively) and refined with a riding model, with U_{iso}(H) = 1.2 or 1.5 times U_{eq}(C), or 1.5U_{eq}(O). No attempt was made to model a disorder for the $CH_2CH{=}CH_2$ group.

Data collection: *SMART* (Bruker, 2000); cell refinement: *SAINT* (Bruker, 2000); data reduction: *SAINT*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *SHELXTL* (Bruker, 2000); software used to prepare material for publication: *SHELXTL*.

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