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A tetrahydropentaleno[1,6a-*a*]-naphthalen-4(2*H*)-one of defined relative stereochemistry for use towards Agariblazeispirol C

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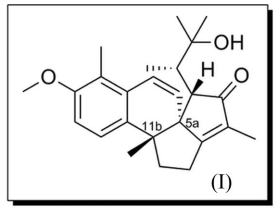
Towards the synthesis of the novel natural product Agariblazeispirol C, (5a*R**,11b*R**)-9-methoxy-3,8,11b-trimethyl-5,6,7,11b-tetrahydro-1*H*-pentaleno[1,6a-*a*]naphthalen-4(2*H*)-one, $C_{20}H_{24}O_2$, has been prepared at a key stage of the preparative programme. The structure shows the desired stereochemical outcome of the central cyclization protocol, *viz*. a *syn*-relationship between the aliphatic methyl group on the 11b-position and the methylene group on the 5a-position [C—C—C—C = −34.57 (18)°].

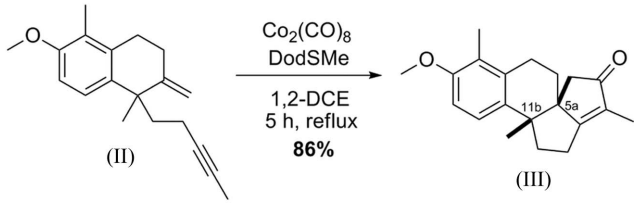
Comment

Over recent years, studies within our laboratory have focused on the development of a series of metal-mediated methods and their application in organic synthesis. In this regard, a selection of these techniques have found direct application within the arena of natural product synthesis (Crawford *et al.*, 2006; Caldwell *et al.*, 2005; Kerr *et al.*, 2001). More recently, these studies have targeted the total synthesis of Agariblazeispirol C, (I), which was isolated from the cultured mycelia of *Agaricus blazei* (Hirotani *et al.*, 2005). Our specific approach towards the synthesis of this target includes the development of an intramolecular Pauson–Khand cyclization to expediently construct the tetracyclic core of the natural product.

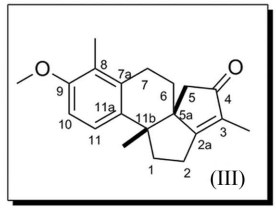
The cyclization precursor, (II), an advanced intermediate within our synthetic programme, was employed in the key Pauson–Khand cyclization, under sulfide-promoted conditions (Brown *et al.*, 2005), to yield the cyclopentenone product in an excellent 86% yield. A crucial feature of the desired angularly fused ring skeleton of Agariblazeispirol C is the relative stereochemical arrangement across the C atoms at positions 5a and 11b (see Scheme). Despite NMR spectroscopic studies only showing one diastereoisomer of product, the required *syn*-arrangement at the two adjacent stereogenic centres could not be established with certainty. In an attempt to confirm the desired relative configuration, colourless crystals were grown by slow diffusion of light petroleum ether into a near-saturated diethyl ether solution of (III) at room temperature. The resulting structure (Fig. 1) allowed the elucidation of the *syn*-relationship between the aliphatic methyl group on C11b and the methylene on C5a [C5—C5a—C11b—C15 = −34.57 (18)°] confirming that the key Pauson–Khand annulation provides the stereochemistry required in the final natural product.



(I)



(II) (III)



(III)

In order to assess the relative frequency of *syn*- and *anti*-arrangements in similar systems, a search of the Cambridge Structural Database (CSD; Allen, 2002) was undertaken. However, suprisingly few relevant structures were found. There were only two structures with a similar system of three fused aliphatic rings (Prakash & Mohanakrishnan, 2008; Sha *et al.*, 1999) and, similarly, only two structures with fused five-

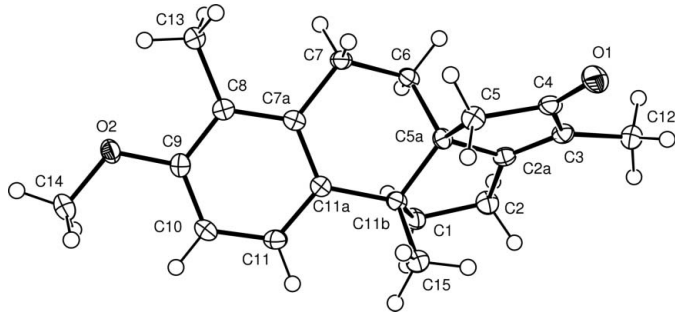


Figure 1
The molecular structure of (III), showing the atom-labelling scheme and 50% probability displacement ellipsoids.

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membered rings with substitution equivalent to (III) (Simonen & Kivekäs, 1984; Inoue *et al.*, 2006). The bond lengths and angles found for (III) (see Table 1) closely match the comparable parameters in these literature structures. In the absence of any strong hydrogen-bond donors, the structure adopted is essentially discrete with the shortest intermolecular contact taking place between the carbonyl O atom and a methylene group [O1$\cdots$H2b^{i} = 2.47 Å; symmetry code: (i) $1-x, -\frac{1}{2}+y, \frac{1}{2}-z$].

Table 1
Selected geometric parameters (Å, °).

O1—C4	1.2206 (17)	C3—C4	1.473 (2)
C2a—C3	1.337 (2)	C4—C5	1.519 (2)
C2a—C5a	1.508 (2)	C5—C5a	1.538 (2)
C3—C2a—C5a	114.12 (13)	C3—C4—C5	108.57 (13)
C2a—C3—C4	107.64 (13)	C4—C5—C5a	104.12 (12)
O1—C4—C3	126.20 (14)	C2a—C5a—C5	102.09 (11)
O1—C4—C5	125.01 (14)		

Experimental

A round-bottomed flask was flame dried under vacuum prior to cooling under a blanket of nitrogen. The vessel was charged with alkyne, (II) (0.175 g, 0.316 mmol), as a solution in 1,2-dichloroethane (15 ml). To this was added octacarbonyldicobalt (0.151 g, 0.442 mmol) and the resulting mixture was stirred at room temperature for 1 h. After this time, dodecylmethyl sulfide (0.29 ml, 1.106 mmol) was added and the resulting mixture was refluxed for 5 h before filtering through a plug of celite. The filtrate was concentrated under reduced pressure, and the resulting residue was purified by column chromatography (0–20% diethyl ether in petroleum ether) to afford (III) (0.08 g, 86% yield; m.p. 421–423 K) as a white solid. IR (CH_2Cl_2) major peaks (cm^{-1}): 1664, 1701; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.15 (*s*, 3H, alkyl CH_3), 1.46 (*ddd*, ^2J = 13.3 Hz, J = 5.1 Hz, J = 2.0 Hz, 1H, alkyl CH_2), 1.75 (*s*, 3H, vinylic CH_3), 1.98–2.08 (*m*, 2H, alkyl CH_2), 2.14 (*s*, 3H, $ArCH_3$), 2.26–2.42 (*m*, 3H, alkyl protons), 2.54–2.71 (*m*, 3H, alkyl protons), 2.84 (*ddd*, ^2J = 14.0 Hz, J = 5.1 Hz, J = 2.0 Hz, 1H, alkyl CH_2), 3.82 (*s*, 3H, OCH_3), 6.77 (*d*, J = 8.6 Hz, 1H, ArH), 7.17 (*d*, J = 8.6 Hz, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 8.4, 11.3, 23.6, 23.6, 25.4, 31.2, 42.8, 43.1, 43.4, 53.7, 55.6, 108.6, 124.1, 124.6, 132.1, 134.0, 135.7, 155.4, 186.8, 210.9; HRMS *m*/*z* (ESI): calculated for $C_{20}H_{25}O_2$ (M^+ + H): 297.1851. Found: 297.1849.

Crystal data

$C_{20}H_{24}O_2$
M_r = 296.39
Monoclinic, $P2_1/c$
a = 10.4995 (4) Å
b = 15.4913 (5) Å
c = 9.8227 (3) Å
β = 101.117 (3)°
V = 1567.69 (9) Å^3
Z = 4
Mo $K\alpha$ radiation
μ = 0.08 mm^{-1}
T = 123 K
0.25 × 0.22 × 0.22 mm

Data collection

Oxford Diffraction Gemini S diffractometer
10529 measured reflections
3593 independent reflections
2387 reflections with $I > 2\sigma(I)$
R_{int} = 0.037
Standard reflections: 0

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.047
$wR(F^2)$ = 0.100
S = 0.96
3593 reflections
203 parameters
H-atom parameters constrained
$\Delta\rho_{max}$ = 0.29 e Å^{-3}
$\Delta\rho_{min}$ = −0.24 e Å^{-3}

H atoms were positioned geometrically and refined in riding mode, with C—H distances set at 0.95, 0.98 and 0.99 Å for aromatic, CH_2 and CH_3 groups, respectively, and with U_{iso}(H) values set at $1.5U_{eq}$(C) for methyl groups and at $1.2U_{eq}$(C) for all other groups.

Data collection: *CrysAlis CCD* (Oxford Diffraction, 2009); cell refinement: *CrysAlis CCD*; data reduction: *CrysAlis RED* (Oxford Diffraction, 2009); program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *ORTEPII* (Johnson, 1976); software used to prepare material for publication: *SHELXL97*.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: EG3057). Services for accessing these data are described at the back of the journal.

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