Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.082$
$wR(F^2) = 0.245$
$S = 1.058$
2141 reflections
264 parameters
H atoms: see below
$w = 1/[\sigma^2(F_o^2) + (0.12P)^2 + 1.51P]$
where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} = 0.013$
$\Delta\rho_{max} = 0.33$ e Å^{-3}
$\Delta\rho_{min} = -0.27$ e Å^{-3}
Extinction correction: *SHELXL*97 (Sheldrick, 1997)
Extinction coefficient: 0.013 (4)
Scattering factors from *International Tables for Crystallography* (Vol. C)

One atom (C18) was found to be affected by disorder: this was modelled in terms of two unequal sites of occupancies 0.71 (6) and 0.29 (6). Residual disorder is thought to be largely responsible for the high conventional R values. The distances between these isotropic components and C19 were restrained to be 1.52 (1) Å. H atoms were included at geometrically calculated positions, except for the hydroxy H atom (H5O) on O5 which was found from a circular Fourier synthesis. They were then allowed to ride on their parent atoms with $U_{iso} = xU_{eq}$(parent), where $x = 1.5$ for methyl and hydroxy H atoms and $x = 1.2$ for all others. Standard uncertainties on C—C distances range from 0.009 to 0.014 Å.

Data collection: *CAD*-4 *Software* (Enraf–Nonius, 1989). Cell refinement: *CAD*-4 *Software*. Data reduction: *CAD*-4 *Software*. Program(s) used to solve structure: *MULTAN*78 (Main *et al.*, 1978). Program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997). Molecular graphics: *SHELXTL/PC* (Sheldrick, 1994). Software used to prepare material for publication: *SHELXL*97 and *PARST* (Nardelli, 1983).

We wish to thank Professor S. P. SenGupta, Department of Materials Science, Indian Association for the Cultivation of Science, Calcutta, for extending the facilities and for his keen interest in our work. We are also grateful to the Council of Scientific and Industrial Research, Government of India, for financial assistance.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: BM1144). Services for accessing these data are described at the back of the journal.

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6-Allyl-8,8-dimethyl-3-oxo-2-(1-phenylethyl)-2-azabicyclo[4.3.0]non-1(9)-ene-5-carboxylic Acid, a Key Compound in the Asymmetric Synthesis of Quadrone

ANGÈLE CHIARONI,[a] CLAUDE RICHE,[a] DUMAS FRANÇOISE,[b] MARC MAUDUIT[b] AND CHRISTINE MIET[b]

[a]*Institut de Chimie des Substances Naturelles, CNRS, 91198 Gif sur Yvette CEDEX, France, and* [b]*BIOCIS, Université de Paris Sud, Centre d'études pharmaceutiques, Laboratoire de Synthèse Organique, 5 rue Jean-Baptiste Clément, 92296 Châtenay-Malabry CEDEX, France. E-mail: claude.riche@icsn.cnrs-gif.fr*

(*Received 30 April 1997; accepted 4 November 1997*)

Abstract

The X-ray structure analysis of the title compound, $C_{22}H_{27}NO_3$, establishes unambiguously the relative and absolute configurations of the two asymmetric C atoms, C5 (*S*) and C6 (*S*), based on the known *R* absolute configuration of the C10 atom, and provides essential information on the transition state of the Michael reaction leading to its formation.

Comment

The enantioselective synthesis of quaternary carbon centres through the Michael addition of chiral imines to electrophilic alkenes under neutral conditions (d'Angelo *et al.*, 1992) has been used for the asymmetric synthesis of a large number of biologically active compounds (d'Angelo *et al.*, 1993). For our part, we were interested in the asymmetric synthesis of (−)-quadrone, (1), an antitumour compound isolated from the fungus

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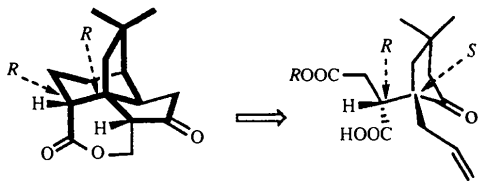
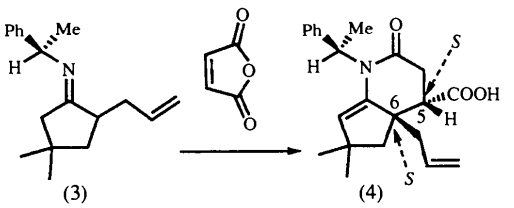
Aspergilus terreus (Ranieri & Calton, 1978). The retrosynthetic analysis based on the aforementioned Michael addition of chiral imines led us to consider that the key cyclopentanone adduct (2), having 14 of the 15 C atoms required and two adjacent asymmetric centres (the quaternary carbon centre and the carbon centre bearing the axial carboxylic function), might be obtained with a high degree of regio- and stereocontrol (Dumas & Miet, 1995).

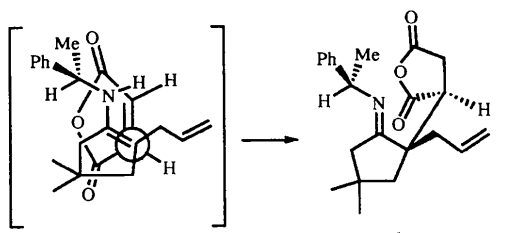


(1) (−)-Quadrone (2)

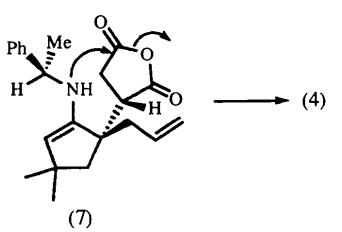
In this paper, we report the stereochemical results obtained by using maleic anhydride as β-substituted electrophilic alkene and the chiral imine (3) derived from 2-allyl-4,4-dimethylcyclopentanone and (*R*)-1-phenylethylamine. Thus, addition of imine (3) to maleic anhydride produced a single adduct, (5*S*,6*S*,10*R*)-(4), resulting from the alkylation at the more substituted α-side of imine (3) and subsequent lactamization of the intermediary tautomeric enamine (6).



(3) (4)



(5) (6)



(7)

The relative and absolute configurations of the stereogenic centres C5 (*S*) and C6 (*S*) in acid (4) were established from an X-ray structure analysis, based on the known *R* absolute configuration of the benzyl carbon centre of the chiral auxiliary amine, which became the C10 atom in adduct (4).

The observed diastereoselectivity can be explained by considering the practical general rule enabling the prediction of the predominant facial selectivity. According to this rule, which has been recently rationalized by calculating the two transition states of the reaction involving chiral enaminones and methyl acrylate (Tran Huu Dau *et al.*, 1998), the alkylation takes place preferentially on the less hindered π-face of the enamine depicted in its energetically preferred conformation, *anti* to the bulky phenyl group [(5)], thus leading to the observed *S* configuration of the quaternary carbon centre C6 in adduct (4), corresponding to the one required for the synthesis of natural (−)-quadrone, (1).

The absolute *S* configuration at C5 in adduct (4) implies that the electrophile is engaged in a compact *endo* approach, (5), in which one of the electron-withdrawing groups of maleic anhydride faced the N atom of the enamine. Such an *endo* approach (Cavé *et al.*, 1996) largely prevails over the corresponding *exo* approach (d'Angelo *et al.*, 1988). It should be noted that, as expected, a high degree of regio- and diastereoselectivity was encountered in this Michael addition, allowing the direct control of two adjacent asymmetric centres. Work is in progress in order to ensure the correct crucial *R* configuration of the tertiary carbon centre bearing the carboxylic function.

The crystal structure with atomic labelling of compound (4) is given in Fig. 1. The double bond C1=C9 of 1.322 (3) Å confers to the five-membered ring (C1, C6–C9) a quasi-planarity, with atom C7 only 0.173 (3) Å

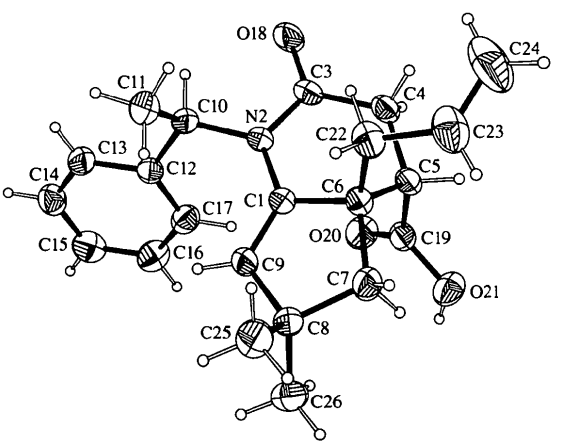


Fig. 1. The molecular structure of (4) with displacement ellipsoids at the 30% probability level.

from the mean plane of the other four atoms. Torsion-angle values show that the phenyl ring is nearly perpendicular to the lactam ring [dihedral angle of 97.1 (1)°]. That ring adopts an envelope conformation, with atom C6 as the flap, lying 0.693 (2) Å from the mean plane of the other five atoms. In the crystal, the molecules are linked in chains through strong hydrogen bonds between the hydroxyl group O21—H and the O18 atom of the nearest molecule [O21···O18($-x$, $1-y$, $\frac{1}{2}+z$) 2.629 (4), H···O18 1.82 Å and O21—H···O18 169.5°].

Experimental

The enantiomerically pure adduct (4) was synthesized in 86% yield *via* the asymmetric Michael addition of the chiral imine (3) (2.0 g, 7.8 mmol), derived from 2-allyl-4,4-dimethylcyclopentanone and (*R*)-1-phenylethylamine ($[\alpha]_D^{20}$ = +39.1, neat), with maleic anhydride (0.92 g, 9.4 mmol) in THF (4 ml) at room temperature for 10 min. After removal of the solvent, the crude product was chromatographed (silica gel; cyclohexane–ethyl acetate 4:1) to give pure (4), which was recrystallized from dry acetone (m.p. 422–423 K).

Crystal data

$C_{22}H_{27}NO_3$
M_r = 353.45
Tetragonal
$P4_1$
a = 13.154 (7) Å
c = 11.869 (8) Å
V = 2054 (2) Å^3
Z = 4
D_x = 1.143 Mg m^{-3}
D_m not measured

Mo $K\alpha$ radiation
λ = 0.71070 Å
Cell parameters from 25 reflections
θ = 8.7–12.2°
μ = 0.075 mm^{-1}
T = 293 (2) K
Prism
0.80 × 0.54 × 0.54 mm
Colourless

Data collection

Philips PW1100 diffractometer
$\theta/2\theta$ scans
Absorption correction: none
3951 measured reflections
1899 independent reflections
1682 reflections with $I > 2\sigma(I)$
R_{int} = 0.039

θ_{max} = 25°
$h = -15 \rightarrow 15$
$k = 0 \rightarrow 15$
$l = 0 \rightarrow 14$
3 standard reflections
every 600 reflections
frequency: 180 min
intensity decay: none

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.031
$wR(F^2)$ = 0.095
S = 1.083
1897 reflections
239 parameters
H atoms: see below
$w = 1/[\sigma^2(F_o^2) + (0.0349P)^2 + 0.0942P]$
where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = −0.006

$\Delta\rho_{max}$ = 0.121 e Å^{-3}
$\Delta\rho_{min}$ = −0.092 e Å^{-3}
Extinction correction: *SHELXL*93
Extinction coefficient: 0.045 (3)
Scattering factors from *International Tables for Crystallography* (Vol. C)
Absolute configuration: given by chemistry

Table 1. *Selected geometric parameters (Å, °)*

C1—C9	1.322 (3)	C4—C5	1.523 (3)
C1—N2	1.419 (3)	C5—C6	1.554 (3)
C1—C6	1.510 (3)	C6—C7	1.540 (3)
N2—C3	1.361 (3)	C7—C8	1.551 (3)
C3—C4	1.508 (3)	C8—C9	1.508 (3)
C9—C1—N2	128.8 (2)	C1—C6—C7	102.1 (2)
C9—C1—C6	113.3 (2)	C1—C6—C5	107.5 (2)
N2—C1—C6	117.9 (2)	C7—C6—C5	116.1 (2)
C3—N2—C1	120.8 (2)	C6—C7—C8	108.4 (2)
N2—C3—C4	120.2 (2)	C9—C8—C7	102.1 (2)
C3—C4—C5	117.3 (2)	C1—C9—C8	113.0 (2)
C4—C5—C6	108.1 (2)		
C1—N2—C3—C4	9.1 (3)	C6—C7—C8—C9	10.0 (2)
N2—C3—C4—C5	3.3 (3)	C7—C8—C9—C1	−5.3 (2)
C3—C4—C5—C6	−37.5 (2)	C8—C9—C1—C6	−1.6 (2)
C4—C5—C6—C1	58.3 (2)	C9—C1—C6—C7	7.9 (2)
C5—C6—C1—N2	−50.8 (2)	C1—N2—C10—C12	−74.3 (2)
C6—C1—N2—C3	16.3 (3)	C3—N2—C10—C12	112.1 (2)
C1—C6—C7—C8	−10.8 (2)	N2—C10—C12—C13	178.0 (2)

All the H atoms, located in difference Fourier maps, were fitted geometrically and refined with a riding model according to *SHELXL*93 (Sheldrick, 1993). The combination of atom types and X-ray wavelength does not permit a reliable determination of absolute configuration from anomalous dispersion effects

Data collection: Philips PW1100/20 software. Cell refinement: Philips PW1100/20 software. Data reduction: *PHIL* (Riche, 1981). Program(s) used to solve structure: *SHELXS*86 (Sheldrick, 1985). Program(s) used to refine structure: *SHELXL*93. Molecular graphics: *R3M* (Riche, 1983) and *ORTEP* (Johnson, 1965). Software used to prepare material for publication: *ACTACIF* (Riche, 1992).

Supplementary data for this paper are available from the IUCr electronic archives (Reference: CF1188). Services for accessing these data are described at the back of the journal.

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