Revision of the Absolute Configuration of (−)-Bostrycin

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The stereostructure (**2**) is established for (−)-bostrycin, based upon an asymmetric synthesis of its enantiomer and an X-ray structure of an intermediate, *i.e.* (**7b**), in that synthesis.

(−)-Bostrycin, a red pigment first isolated from *Bostrychonema alpestre*,[1] shows activity against Gram-positive bacteria. The structure (**1**), initially proposed for the antibiotic,[1] was revised by Kelly and his co-workers[2] to the structure (**2**) on the basis of synthetic studies [which led to (±)-bostrycin] and an X-ray crystal structure of the O-isopropylidene derivative [prepared from (±)-bostrycin]. Recently, Kelly's group has recorded an elegant asymmetric synthesis of (−)-bostrycin and assigned the absolute configuration (**3**) to the antibiotic.[3] We now describe an asymmetric synthesis of (+)-bostrycin which establishes that it possesses the absolute configuration (**3**). Clearly, the natural product is the enantiomer of that suggested by Kelly and possesses the stereostructure (**2**).

Based upon the diastereofacial reactivity of the diene (**4a**)[4] and our interpretation of the behaviour,[5] we expected that the diene (**4b**) would serve as a precursor of bostrycin (**3**). Thus, guided by the protocol developed by the Boston College workers, we envisaged that the diene (**4b**) would react with the quinone (**5**) to give mainly the cycloadduct (**6**) which would be convertible into compound (**7a**) by *cis*-hydroxylation and dehydrogenation steps. After acidic hydrolysis and selective O-methylation, the last-cited material would afford bostrycin (**3**).

The diene (**4b**), m.p. 108—109 °C, $[\alpha]_D$ −14° (CH_2Cl_2), was prepared (45% yield after SiO_2 chromatography and recrystallisation) from the butenone (**8**)[6] using the Lombardo modification[7] of the Oshima methylenation procedure [$Zn/CH_2Br_2/TiCl_4$ in dry tetrahydrofuran (THF)]. It reacted with the quinone (**5**) in boiling benzene to give a 63 : 21 : 13 : 3 mixture of cycloadducts; addition of diethyl ether to the mixture induced the crystallisation of the major cycloadduct [presumed to possess the structure (**6**)], m.p. 160 °C (decomp.), $[\alpha]_D$ +159° (CH_2Cl_2), in 54% yield. When treated with osmium(VIII) oxide (1.5 mol. equiv. in CH_2Cl_2/CCl_4) followed by sodium metabisulphite (in THF/H_2O), compound (**6**) was transformed in 86% yield into the osmium dimer (**9**),† m.p. 167 °C (decomp.), $[\alpha]_D$ +119° (CH_2Cl_2), which underwent reaction with hydrogen sulphide in dichloromethane followed by 2,2-dimethoxypropane acidified with toluene-*p*-sulphonic acid to give the acetonide (**10**),‡ m.p. 105 °C (decomp.), $[\alpha]_D$ −47° (CH_2Cl_2), in 81% yield.

The conversion of compound (**10**) into the quinone (**7b**) presented problems because of the base sensitivity of the reactant. However, the reaction was achieved by the use of activated manganese(IV) oxide in boiling benzene. Following silica-gel fractionation of the product, the quinone (**7b**), m.p. 220—223 °C, $[\alpha]_D$ +147° (CH_2Cl_2), was isolated as red crystals in 50% yield. Acidic hydrolysis of the last-cited compound and

methylation of the product with diazomethane gave a red solid, m.p. 210 °C (decomp.), $[\alpha]_D$ +225° (Me_2SO), in 61% yield which was presumed to possess the structure (**3**). Although containing small amounts of impurities, the sample possessed a 300 MHz [1]H n.m.r. spectrum (CD_3SOCD_3) which matched that of an authentic sample of (−)-bostrycin {which

(**1**)

(**2**)

(**3**)

(**4**)

a; R = $OSiMe_3$
b; R = Me

(**5**)

(**6**)

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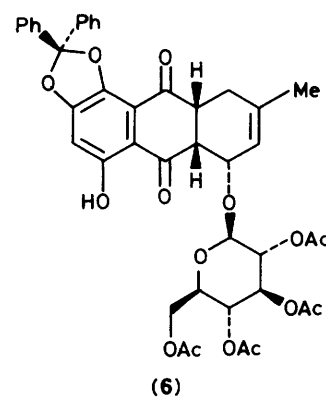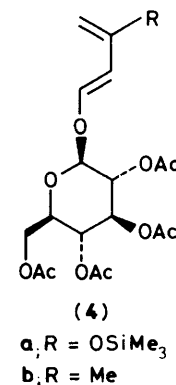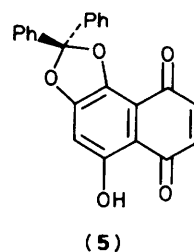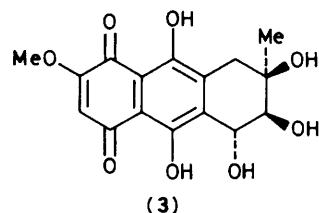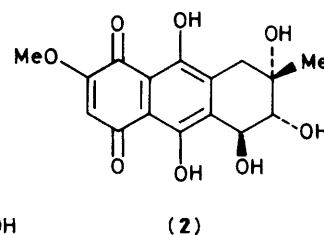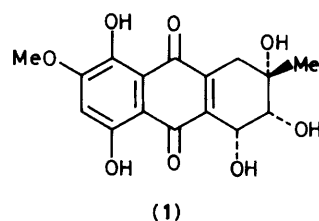
† For related structures, see: R. J. Collin, J. Jones, and W. P. Griffith, *J. Chem. Soc., Dalton Trans.*, 1974, 1094; F. L. Phillips and A. C. Skapski, *ibid.*, 1975, 2586.

‡ This additional step was necessary because the diol precursor of compound (**10**) was a somewhat unstable entity and conditions to effect its conversion into the quinone (**7a**) could not be devised.
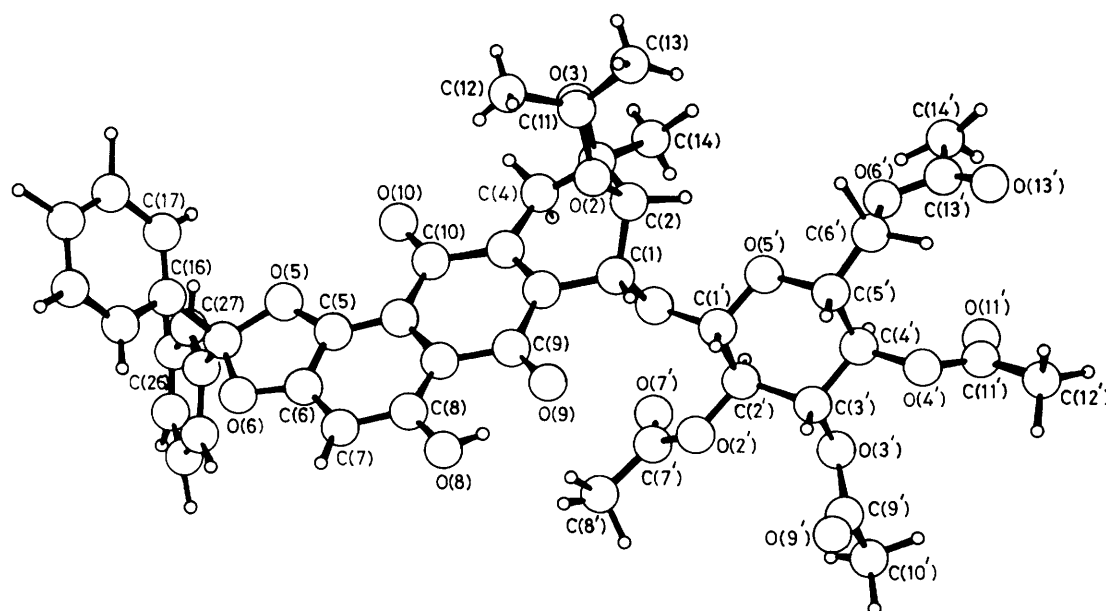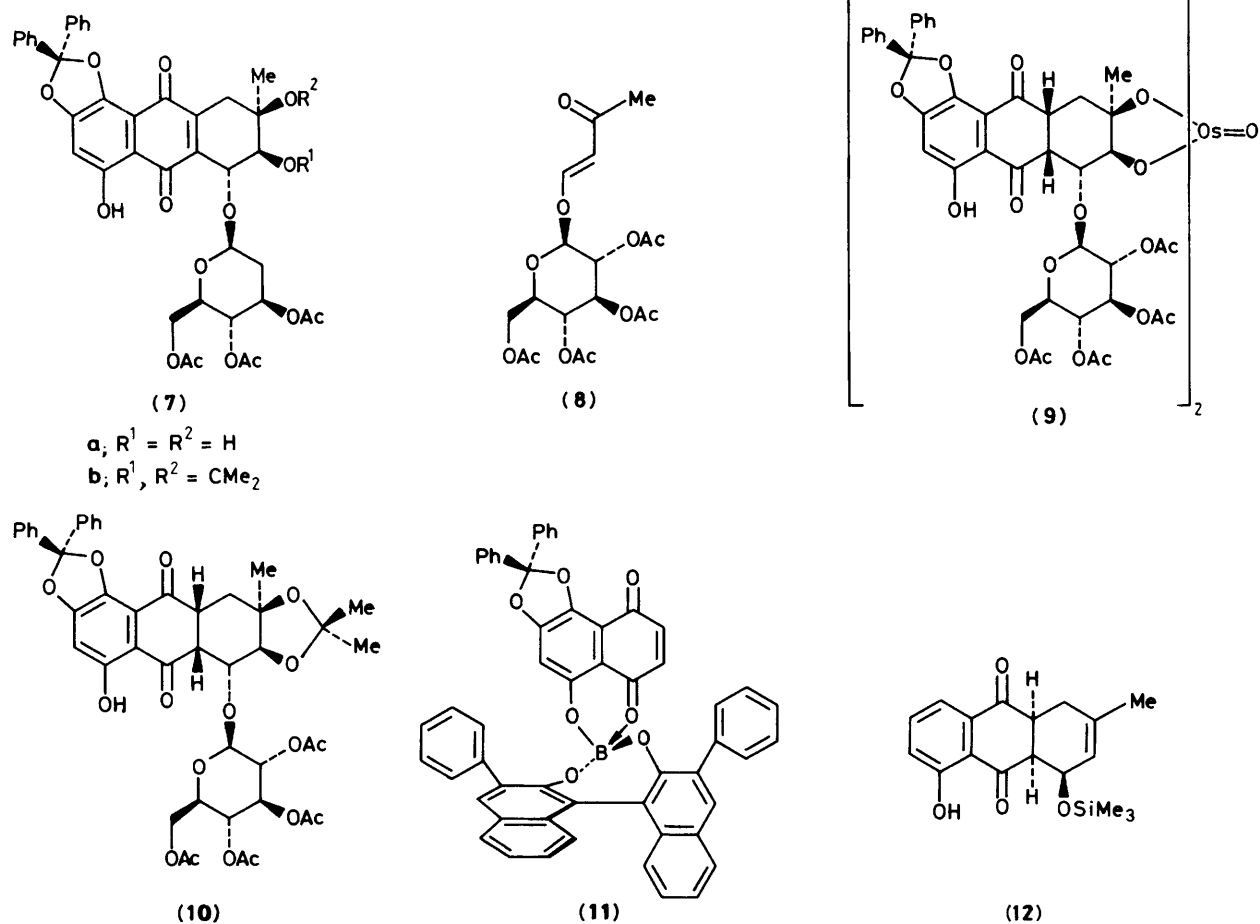
(7)

a; R^1 = R^2 = H
b; R^1, R^2 = CMe$_2$

(8)

(9)

(10)

(11)

(12)

Figure 1. Molecular structure of compound (**7b**).

also contained contaminants and showed $[\alpha]_D$ $-275°$ (Me_2SO).§

Clearly, our synthesis has led to the enantiomer of (−)-bostrycin and therefore either the expectations based upon our model were not realized or Kelly's assignments were in error. That the latter situation was the case was established by a single crystal X-ray structure analysis of compound (7b).¶ The molecular structure, shown in Figure 1, confirmed that the material possessed the absolute configuration that we had anticipated and therefore corroborated our structural assignments. In consequence, (−)-bostrycin must possess the absolute configuration (2).

A key step in Kelly's synthesis of (−)-bostrycin involved the addition of (E)-3-methyl-1-trimethylsilyloxybuta-1,3-diene to the 'bottom' face of the presumed complex (11) [generated by sequential treatment of (S)-3,3'-diphenyl-(1,1'-bi-naphthalene)-2,2'-diol with BH_3·THF, $MeCO_2H$, and the dienophile (5)]. Clearly, the cycloadduct obtained must possess the stereostructure (12) and be the enantiomer of that claimed. As a consequence of this work, Professor Kelly has re-examined his synthesis. It appears that the (R)-binaphthol [and not the (S)-binaphthol as claimed in the paper] is required to generate (−)-bostrycin.

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§ Kelly and his co-workers[3] quote $[\alpha]_D$ $-295°$ (Me_2SO) for bostrycin isolated from *Bostrychonema alpestre* and for their synthetic material; $[\alpha]_D$ $-81°$ (Me_2SO) is claimed for the antibiotic isolated from *Alternaria eichhorniae* (K. L. Stevens, Bader-Un-Din, A. Ahmad, and M. Ahmad, *Phytochemistry*, 1979, **18**, 1579).

¶ (−)-Bostrycin was originally assigned the absolute configuration (1) on the basis of an X-ray study of a derivative.[1] However, as pointed out by Kelly,[3] the poor discrepancy index ($R = 0.138$) of the analysis makes such an assignment tenuous.

Crystal data: $C_{45}H_{44}O_{17}$, $M = 856.8$, monoclinic, $a = 11.000(1)$, $b = 8.545(1)$, $c = 23.110(2)$ Å, $\beta = 94.85(1)°$, $U = 2164$ Å^3, space group $P2_1$, $Z = 2$, $D_c = 1.31$ g cm^{-3}, $\mu(Mo-K_\alpha) = 0.63$ cm^{-1}. An Enraf-Nonius CAD-4 diffractometer, employing Mo-K_α radiation ($\lambda = 0.71069$ Å; graphite monochromator) in the ω–2θ scan mode, was used to record 4379 reflections ($0 < \theta < 25°$). Lorentz–polarisation corrections were applied but absorption effects were ignored. The structure was solved by direct methods[8] and refined by block-matrix least-squares procedures[9] to final residuals of $R = 0.044$ and $R_w = 0.047$ for 2440 observed reflections with $F > 3\sigma$ (F). Atomic co-ordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

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