Revision of the Absolute Configuration of (−)-Bostrycin

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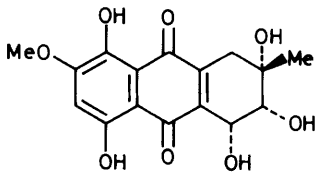
The stereostructure (**2**) is established for (−)-bostrycin, based upon an asymmetric synthesis of its enantiomer and an *X*-ray structure of an intermediate, *i.e.* (**7b**), in that synthesis.

(−)-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**).

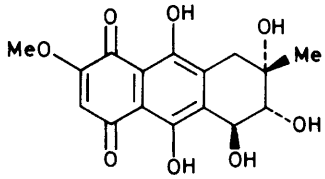
Based upon the diastereofacial reactivity of the diene (**4a**)[4] and our interpretation of the behaviour,[5] we expected that the diene (**4b**) would serve as a precursor of bostrycin (**3**). Thus, guided by the protocol developed by the Boston College workers, we envisaged that the diene (**4b**) 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.

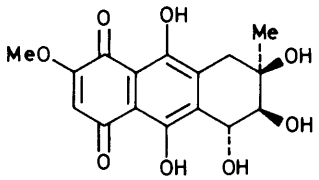
The conversion of compound (**10**) into the quinone (**7b**) presented problems because of the base sensitivity of the reactant. However, the reaction was achieved by the use of activated manganese(IV) oxide in boiling benzene. Following silica-gel fractionation of the product, the quinone (**7b**), 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 ^1H n.m.r. spectrum (CD_3SOCD_3) which matched that of an authentic sample of (−)-bostrycin {which



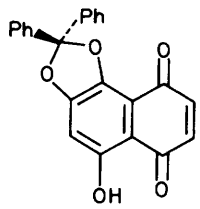
(**1**)



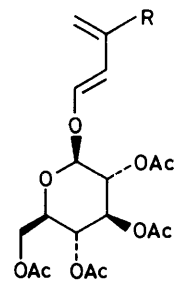
(**2**)



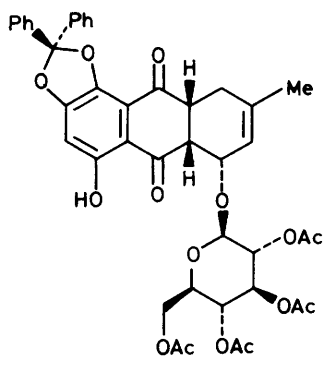
(**3**)



(**5**)



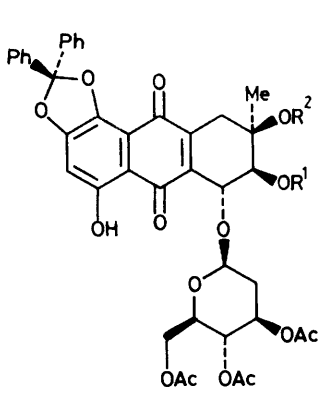
(**4**)
a; R = $OSiMe_3$
b; R = Me



(**6**)

† 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.

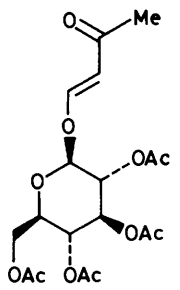
‡ This additional step was necessary because the diol precursor of compound (**10**) was a somewhat unstable entity and conditions to effect its conversion into the quinone (**7a**) could not be devised.



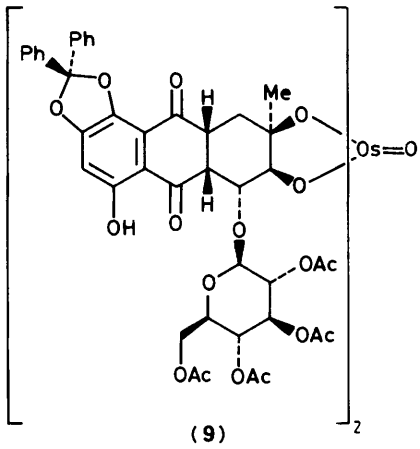
(7)

a; $R^1 = R^2 = H$

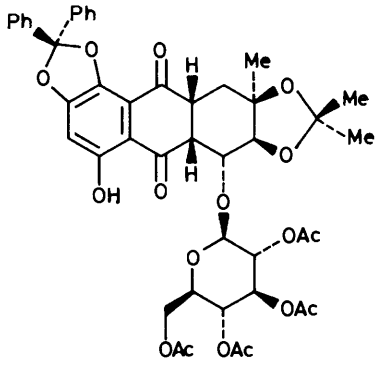
b; $R^1, R^2 = CMe_2$



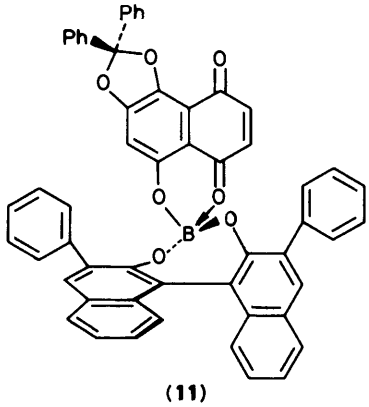
(8)



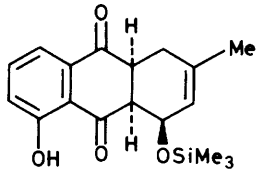
(9)



(10)



(11)



(12)

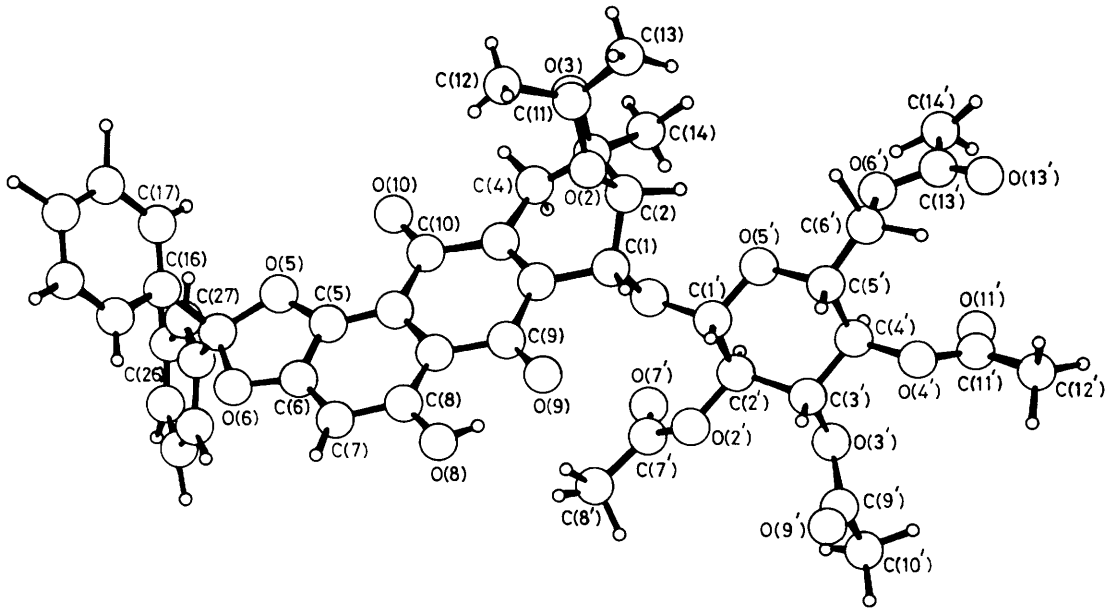


Figure 1. Molecular structure of compound (**7b**).

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-trimethylsilyoxybuta-1,3-diene to the 'bottom' face of the presumed complex (**11**) [generated by sequential treatment of (*S*)-3,3′-diphenyl-(1,1′-binaphthalene)-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}, μ(Mo-K_α) = 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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