Absolute stereochemistry of 1,2′-linked bi(naphthoquinone)s

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Asymmetric syntheses of the enantiomers of the naturally occurring atropisomerically chiral 1,2′-linked bi(naphthoquinone)s 8′-hydroxyisodiospyrin and isodiospyrin have allowed their absolute configurations to be assigned by X-ray and circular dichroism spectral studies of synthetic intermediates.

There is a small number of naturally occurring bi(naphthoquinone)s which exhibit axial chirality.[1] Two of these compounds, (−)-8′-hydroxyisodiospyrin **1**[2,3] (which also occurs naturally in racemic form)[3] and (−)-isodiospyrin **2**,[1] are both 1,2′-linked and are of unknown but identical absolute configuration since isodiospyrin has been converted into 8′-hydroxyisodiospyrin in poor yield.[2]

We now report the synthesis of the enantiomers of both of these compounds which have been previously synthesised in racemic form.[4]

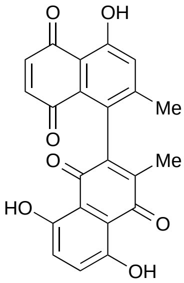
The known hydroxymethyl compound **2**,[5] on treatment with Schlosser's base[6] followed by 1,2-dibromo-1,1,2,2-tetrafluoroethane, afforded the bromo compound **4** (Scheme 1), and hence the bromo compound **5**. The known nitrile **6**[5] was converted into the amide **7** which under standard conditions[7] gave the dihydrooxazole **8**.

When the dihydrooxazole **8** was allowed to react with an excess of the Grignard reagent derived from the bromo compound **5** (Scheme 2), a 45% yield of the coupled product resulted which consisted of an inseparable mixture of two diastereoisomers, as shown by the ^{1}H NMR spectrum, in the ratio 7 : 1. The major diastereoisomer was predicted to possess structure **9** (*i.e. R*) since the stereochemical outcome of the coupling is controlled by the chelating ability of the *ortho*-substituents (Fig. 1).[8]This stereochemistry was confirmed by an X-ray study† of a sample of the derived iodide **10** (Fig. 2) obtained by crystallisation of the diastereoisomeric mixture to constant specific rotation.

The iodide, enriched in the diastereoisomer **10**, was converted sequentially into the aldehyde **11**, the hydroxymethyl compound **12** and finally into the methyl compound **13**. The Mosher ester[9] of the hydroxymethyl compound indicated the presence of two diastereoisomers in the ratio 7 : 1, thus confirming that no racemisation has occurred during these transformations.

The circular dichroism (CD) spectrum[10] of the methyl compound **13** indicated the *S*-configuration in agreement with both mechanistic prediction and the X-ray study.

The methyl compound was oxidatively demethylated by treatment with ammonium cerium(iv) nitrate and the crude mixture of quinones so obtained was completely demethylated by exposure to aluminium chloride. Fractional crystallisation of the crude product allowed the separation of the (+)-(*S*)



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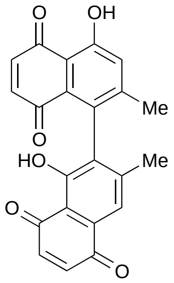

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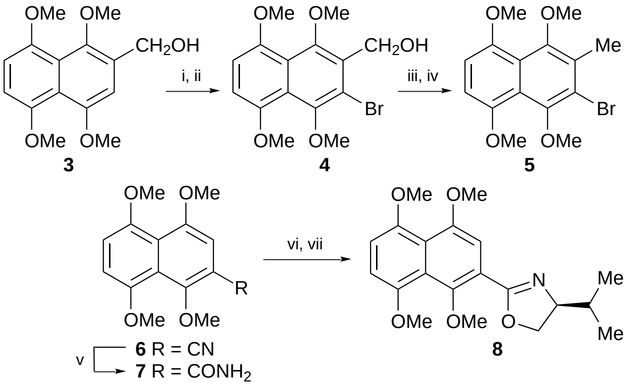
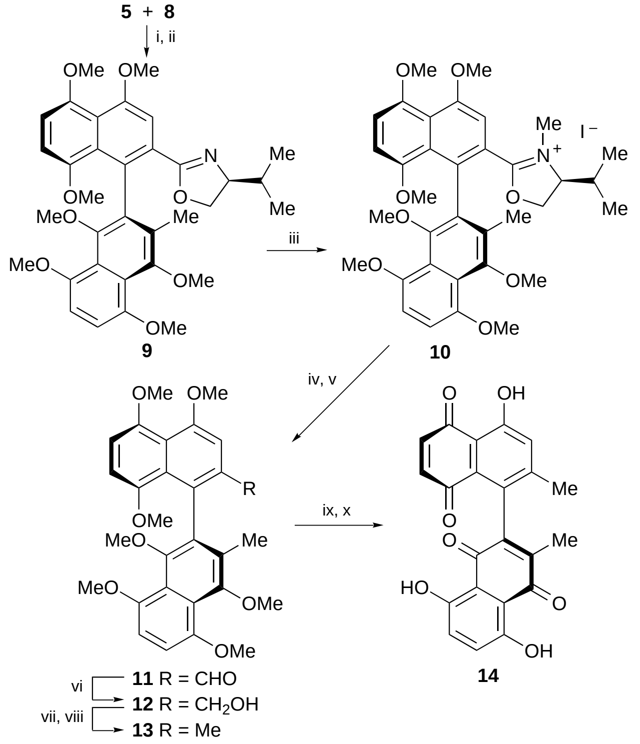


Scheme 1 *Reagents and conditions*: i, Bu^{t}OK, BuLi, THF, −78 °C, Ar, 5 h; ii, BrCF$_2$CF$_2$Br, −78 °C, Ar, 38%; iii, MeSO$_2$Cl, NEt$_3$, CH$_2$Cl$_2$, 25 °C, Ar, 3.5 h; iv, NaBH$_3$CN, ZnCl$_2$, Et$_2$O, 25 °C, Ar, 2 h, 67%; v, KOH, Bu^{t}OH, reflux, Ar, 2 h, 94%; vi, Et$_3$OBF$_4$, (ClCH$_2$)$_2$, 25 °C, Ar, 24 h; vii, (*S*)-valinol, reflux, Ar, 48 h, 45%



Scheme 2 *Reagents and conditions*: i, 1.5 equiv. **5**, Mg, THF, reflux, Ar, 3 h; ii, **8**, THF, reflux, Ar, 5 h, 45%; iii, MeI, MeNO$_2$, 60 °C, Ar, 24 h, 100%; iv, NaBH$_4$, THF, MeOH, 0 °C, Ar, 1 h; v, H$^+$, 25 °C, Ar, 2 h, 67%; vi, NaBH$_4$, aq. NaOH, THF, 0 °C, Ar, 1 h, 100%; vii, MeSO$_2$Cl, NEt$_3$, CH$_2$Cl$_2$, 25 °C, Ar, 3.5 h; viii, LiAlH$_4$, THF, reflux, Ar, 3 h, 83%; ix, aq. CAN, MeCN, 0–25 °C, 30 min; x, AlCl$_3$, CH$_2$Cl$_2$, 0–25 °C, 1 h, 45%

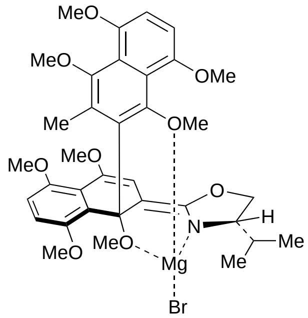


Fig. 1 Preferred transition state for the coupling reaction leading to diastereoisomer **9**

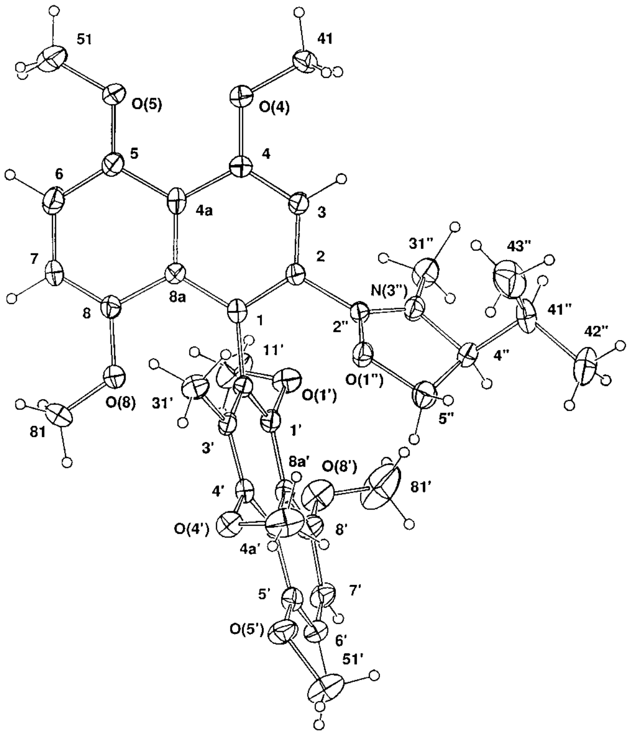
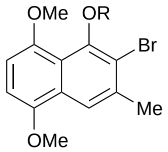


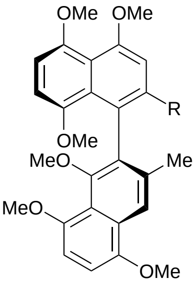
Fig. 2 The cation of **10** as derived from the X-ray study; 20% thermal ellipsoids are shown for the non-hydrogen atoms, hydrogen atoms having arbitrary radii of 0.1 Å. Carbon atom labelling is shown by numbers only. Dihedral angles between central (unprimed) and pendant (fused) ring skeletal planes (prime and double prime): 81.2(2), 54.0(2)°.

enantiomer **14** of 8′-hydroxyisodiospyrin, mp 274 °C, from its less soluble racemate **1**. The spectroscopic properties of these compounds were identical with those of the natural materials.[2–4] Since the (+)-(*S*) enantiomer **14** absorbs strongly at the D-line it was not possible to obtain a precise value for the specific rotation; the CD spectrum (dioxane), however, exhibited maxima at λ 298, 354 and 480 nm (Δε 11.3, 6.9 and 2.4) and minima at λ 265 and 419 nm (Δε −22.8 and −1.4). The natural product thus possesses the *R* configuration.

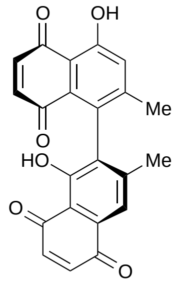
The synthesis of isodiospyrin followed similar methodology. The required bromo compound **16**, obtained by methylation of the naphthol **15**,[11] was allowed to react as its Grignard reagent with the dihydrooxazole **8**. In this case the diastereoisomeric ratio of the coupled products was 10 : 1. At the stage of the aldehyde **17** in the synthetic sequence optical purification could readily be achieved by crystallisation, as shown by the ^{1}H and ^{19}F NMR spectra of the Mosher ester of the derived alcohol **18** when compared with those of the derivative of the racemic alcohol. These spectral data and those for the Mosher ester of



15 R = H
16 R = Me



17 R = CHO
18 R = CH$_2$OH
19 R = Me



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the alcohol **12** allowed the configuration of the alcohol **18** to be assigned as *S*,[12] which was confirmed by the CD spectrum of the methyl compound **19**. Synthetic (+)-(*S*)-isodiospyrin **20**, mp 233 °C (lit.[13] for enantiomer, 233 °C), proved to be identical in physical properties, except rotation $\{[\alpha]_D^{20}$ +138 (*c* 0.38, CHCl$_3$) [lit.[13] for enantiomer, −150 (*c* 0.27, CHCl$_3$)]$\}$, with those of an authentic sample of the racemate.‡ The natural product thus possesses the *R* configuration.

Footnotes

† *Crystal data* for **10**: $C_{35}H_{42}NO_8{}^+I^-\cdot H_2O$, M = 749.6. Orthorhombic, $P2_12_12_1$, a = 33.27(1), b = 10.473(8), c = 10.247(3) Å, V = 3570 Å^3, D_c (Z = 4) = 1.39$_5$ g cm^{-3}. N_0 Independent 'observed' [$I > 3\sigma(I)$] out of N measured absorption-corrected diffractometer reflections [$2\theta_{max}$ = 50°; 2θ–θ scan mode (extended counter arm); monochromatic Mo–$K\alpha$ radiation, λ = 0.7107$_3$ Å, μ_{Mo} = 9.5 cm^{-1}, specimen: 0.53 × 0.70 × 0.37 mm, $A^*_{min,\,max}$ = 1.39, 1.46] were refined by full-matrix least-squares to convergence [anisotropic thermal parameter forms for non-hydrogen atoms $(x,y,z,U_{iso})_H$ (cation) constrained at estimated values, difference map residue modelled as water molecule O (H$_O$ not observed)]. Conventional R,R_w (statistical weights) on $|F|$: for *hkl* (N,N_0 = 3564, 2723) 0.050, 0.055 (alternative hand: 0.055, 0.061); for $\bar{h}\bar{k}\bar{l}$ (N,N_0 = 3563, 2730) 0.050, 0.055 (0.057, 0.062); for all data (N,N_0 = 6589, 5731) Flack 'x' = −0.02(4). The assigned chirality is harmonious with that of the internal l-valine reference.

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