

A formal synthesis of both atropenantiomers of desertorin C

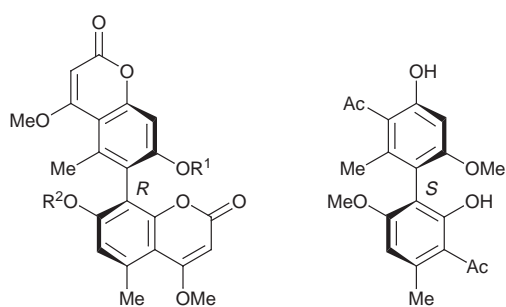
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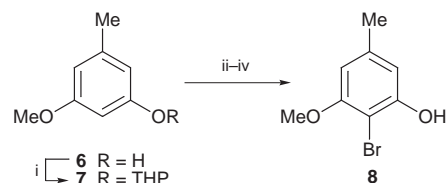
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Asymmetric synthesis of both enantiomers of 1,1'-(2',4'-dihydroxy-6,6'-dimethoxy-2,4'-dimethylbiphenyl-3,3'-diyl)-bisethanone allows the formal synthesis of both enantiomers of 4,4',7,7'-tetramethoxy-5,5'-dimethyl-6,8'-bicoumarin (desertorin C).

The desertorins A **1**, B **2** and C **3** are a family of unsymmetrical coumarin dimers of fungal origin which are optically active on account of restricted rotation about their stereogenic axes.¹



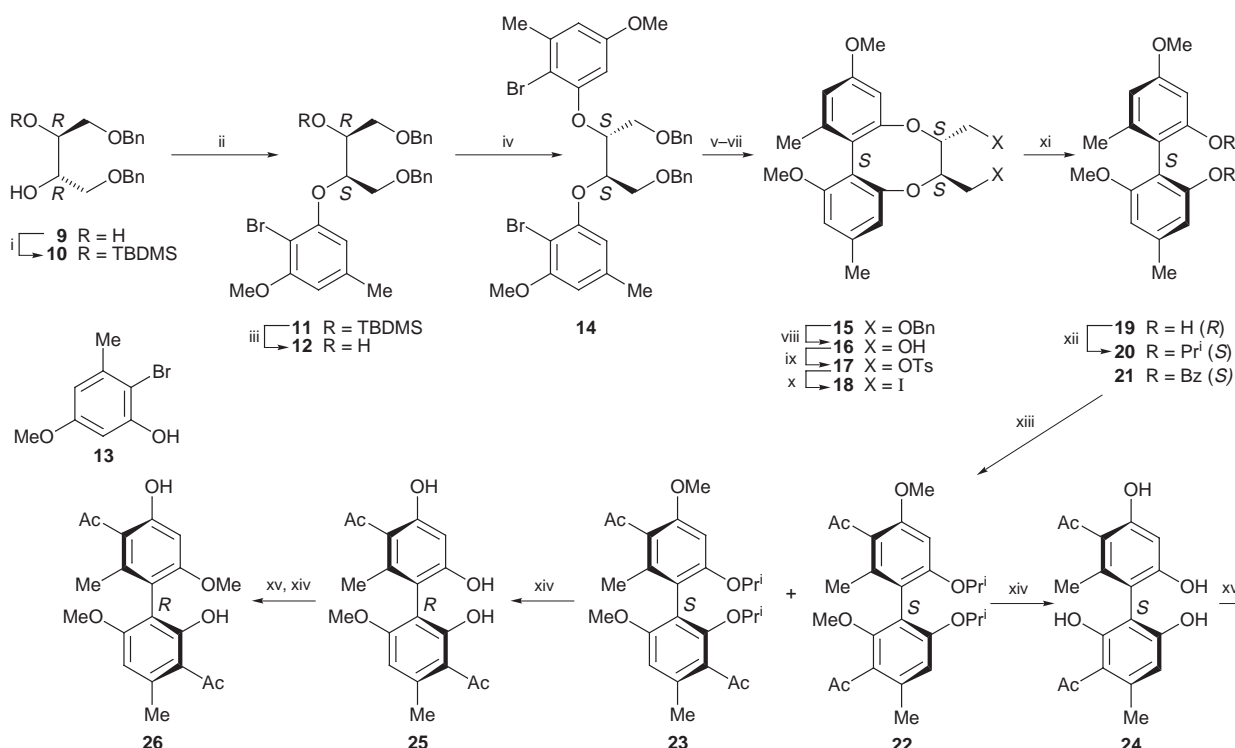
- 1** R¹ = R² = H
2 R¹ = H, R² = Me
3 R¹ = R² = Me
4 R¹ = R² = Bz



Scheme 1 Reagents and conditions: i, TsOH, dihydropyran, THF, 0 °C, 20 h; ii, BuLi, Ar, THF, TMEDA, 25 °C, 4 h; iii, BrCF₂CF₂Br, 25 °C, 1 h; iv, H⁺, H₂O.

Methylation of both desertorins A and B provides desertorin C which on base hydrolysis yields the diketone **5**.¹ We have previously synthesized desertorin C in racemic form using the (±)-diketone **5** as the key intermediate.² Subsequently the absolute configuration of the desertorins was established as *R* by an X-ray crystal structure determination of the bis-bromobenzoate **4**.³ We now describe a synthetic approach to both enantiomers of desertorin C.

O-Methylorcinol **6** (Scheme 1) was protected as its tetrahydropyranyl ether **7** which on lithiation and subsequent treatment with 1,2-dibromotetrafluoroethane and acidic work-up gave the bromophenol **8**,⁴ mp 71–72 °C, in 60% overall yield. Mitsunobu reaction (Scheme 2) between this bromo-



Scheme 2 Reagents and conditions: i, TBDMSCl, imidazole, DMF, 25 °C, 15 h, 76%; ii, **8**, Bu₃P, DEAD, THF, 25 °C, 24 h; iii, Bu₄NF, THF, 25 °C, 1 h; iv, **13**, Bu₃P, DEAD, THF, 25 °C, 48 h; v, BuLi, Ar, THF, –78 °C, 1 h; vi, CuCN, TMEDA, –78 to –40 °C, 15 min; vii, O₂, –78 °C, 3 h; viii, H₂, Pd/C, EtAc, 94%; ix, TsCl, C₅H₅N, 0 °C, 7 h, 78%; x, NaI, Me₂CO, reflux, 5 h, 91%; xi, Zn, EtOH, reflux, 1 h, 80%; xii, PrⁱBr, K₂CO₃, DMF, 45 °C, 48 h, 68%; xiii, TFAA, AcOH, CH₂Cl₂, 25 °C, 7 h, 69%; xiv, BCl₃, CH₂Cl₂, 0 °C, 2 h; xv, MeI, K₂CO₃, DMF, 40 °C, 15 h.

phenol **8** and the mono(*tert*-butyldimethylsilyl)ether **10** of 1,4-di-*O*-benzyl-L-threitol **9**⁵ gave the ether **11** (68%) which on deprotection afforded the alcohol **12** (90%). This alcohol was caused to react in another Mitsunobu reaction with the bromophenol **13**.⁶ The resultant D-threitol derivative **14**, mp 54–56 °C (45%), was subjected sequentially to lithiation, copper(I) cyanide and dry oxygen after the manner of Lipschutz *et al.*,⁷ which gave the cyclized product **15** (40%). Deprotection was achieved by hydrogenolytic debenzoylation and tosylation of the resultant diol **16**. The tosylate **17** was converted into the iodide **18**, mp 155–157 °C, which on reductive elimination with activated zinc supplied the diol **19**, mp 134–136 °C, $[\alpha]_{\text{D}}^{20} -27$ (*c* 0.67, CHCl_3).

In order for the intramolecular coupling **14**→**15** to occur the aryloxy substituents in the intermediate higher order cyanocuprate⁷ are predicted to adopt, on account of the anomeric effect, the *gauche* conformation depicted in Fig. 1. Hence the axial configuration of the intermediate cyclic compound **15** is *S* and that of the diol **19** is *R*. The diol appeared to be enantiomerically pure since it was not resolved on HPLC on two chiral columns⁸ nor did the ¹H and ¹⁹F NMR spectra of the derived Mosher diester show the presence of the other enantiomer even in the presence of a lanthanide shift reagent. The CD spectrum (MeCN) of the derived dibenzoate **21** showed exciton splitting centred at λ 226 nm with a positive first Cotton effect (λ 237 nm, $\Delta\epsilon$ 24.3) and a negative second effect (λ 215 nm, $\Delta\epsilon$ -9.0) in keeping with the *R* configuration of the diol **19**.⁹

Since *O*-methylorcinol **6** undergoes *C*-monoacetylation at both positions *ortho* to the hydroxy group, the diol **19** was isopropylated and the resultant ether **20** was acetylated with AcOH and TFAA, which supplied an inseparable mixture of the

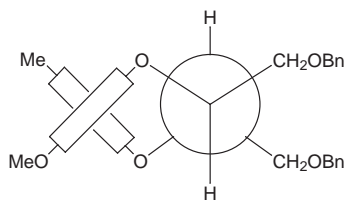


Fig. 1 Newman projection along the 2,3-bond of the D-threitol **14** in the conformation for the coupling reaction leading to **15**.

diketones **22** and **23**. Selective dealkylation of this mixture with BCl_3 yielded the tetrol **24** (30%), mp 198–200 °C, $[\alpha]_{\text{D}}^{20} 32.8$ (*c* 0.86, Me_2CO), $\delta_{\text{OH}}(\text{CDCl}_3)$ 8.46, 8.54, 11.80 and 13.42, and the triol **25** (35%), mp 120 °C decomp., $[\alpha]_{\text{D}}^{20} -61.0$ (*c* 1.05, Me_2CO), $\delta_{\text{OH}}(\text{CDCl}_3)$ 8.36, 11.87 and 12.45. Methylation and selective demethylation of the tetrol **24** gave the (*S*)-diketone **5** (69%), mp 147–149 °C (lit.,¹ 149–150 °C), $[\alpha]_{\text{D}}^{20} 34.0$ (*c* 0.94, Me_2CO),¹⁰ which had previously been obtained by basic hydrolysis of desertorin C.¹ The (*R*)-diketone **26** (82%), mp 145–146 °C, $[\alpha]_{\text{D}}^{20} -53.0$ (*c* 0.80, Me_2CO),¹¹ was obtained in a similar fashion from the triol **25**. Since the racemic diketone has been converted into desertorin C this constitutes a formal synthesis of both of the enantiomers of this metabolite.

Both the synthetic diketone **5** and the degradation product **5** appear to have undergone some racemisation, the former presumably at the tetrol stage, and the latter under the harsh conditions of the hydrolysis.

Notes and references

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- 10 CD spectra: Degradation product $\lambda(\text{MeOH})/\text{nm}$ 227 and 270 ($\Delta\epsilon$ 7.7 and -6.5). Synthetic product $\lambda(\text{MeCN})/\text{nm}$ 196, 216, 231, 275, 296 and 340 ($\Delta\epsilon$ 10.4, -31.8, 18.3, -9.0, 3.8 and 1.9). The racemic diketone was not resolved on HPLC nor was its ¹H NMR spectrum resolved in the presence of (*S*)-1-(anthracen-9-yl)-2,2,2-trifluoroethanol.
- 11 CD spectrum: $\lambda(\text{MeCN})/\text{nm}$ 196, 216, 230, 276, 295 and 335 ($\Delta\epsilon$ -19.8, 52.7, -33.5, 14.7, -7.5 and -5.2).

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