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A formal synthesis of both atropenantiomers of desertorin C

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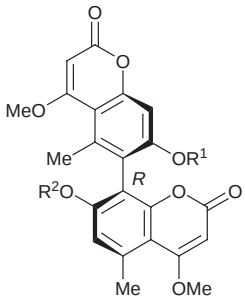
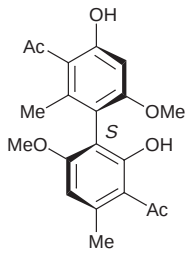
Asymmetric synthesis of both enantiomers of 1,1′-(2′,4-dihydroxy-6,6′-dimethoxy-2,4′-dimethylbiphenyl-3,3′-diyl)-bisethanone allows the formal synthesis of both enantiomers of 4,4′,7,7′-tetramethoxy-5,5′-dimethyl-6,8′- bicoumarin (desertorin C).

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 $R^1 = R^2 = H$
2 $R^1 = H$, $R^2 = Me$
3 $R^1 = R^2 = Me$
4 $R^1 = R^2 = Bz$



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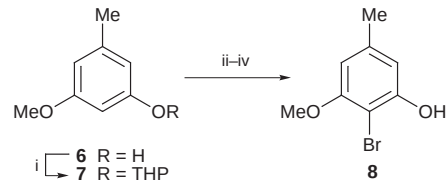
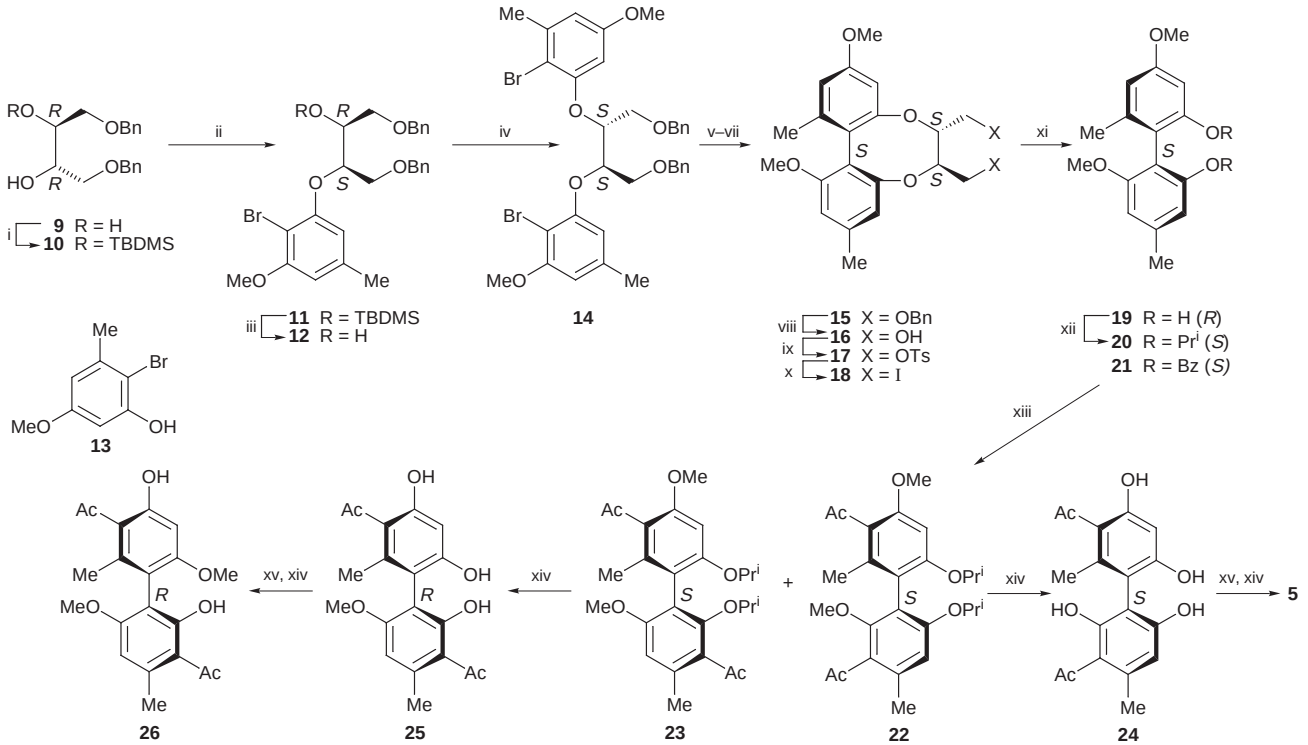


Scheme 1 *Reagents and conditions*: i, TsOH, dihydropyran, THF, 0 °C, 20 h; ii, BuLi, Ar, THF, TMEDA, 25 °C, 4 h; iii, $BrCF_2CF_2Br$, 25 °C, 1 h; iv, H^+, H_2O.

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**, Bu_3P, DEAD, THF, 25 °C, 24 h; iii, Bu_4NF, THF, 25 °C, 1 h; iv, **13**, Bu_3P, DEAD, THF, 25 °C, 48 h; v, BuLi, Ar,THF, −78 °C, 1 h; vi, CuCN, TMEDA, −78 to −40 °C, 15 min; vii, O_2, −78 °C, 3 h; viii, H_2, Pd/C, EtAc, 94%; ix, TsCl, C_5H_5N, 0 °C, 7 h, 78%; x, NaI, Me_2CO, reflux, 5 h, 91%; xi, Zn, EtOH, reflux, 1 h, 80%; xii, Pr^iBr, K_2CO_3, DMF, 45 °C, 48 h, 68%; xiii, TFAA, AcOH, CH_2Cl_2, 25 °C, 7h, 69%; xiv, BCl_3, CH_2Cl_2, 0 °C, 2 h; xv, MeI, K_2CO_3, 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 debenzylation 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, $[\alpha]_D^{20}$ −27 (*c* 0.67, $CHCl_3$).

In order for the intramolecular coupling **14**→**15** to occur the aryloxy substituents in the intermediate higher order cyanocuprate[7] 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 columns[8] nor did the ^1H and ^{19}F 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, $\Delta\varepsilon$ 24.3) and a negative second effect (λ 215 nm, $\Delta\varepsilon$ −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 diketones **22** and **23**. Selective dealkylation of this mixture with BCl_3 yielded the tetrol **24** (30%), mp 198–200 °C, $[\alpha]_D^{20}$ 32.8 (*c* 0.86, Me_2CO), $\delta_{OH}(CDCl_3)$ 8.46, 8.54, 11.80 and 13.42, and the triol **25** (35%), mp 120 °C decomp., $[\alpha]_D^{20}$ −61.0 (*c* 1.05, Me_2CO), $\delta_{OH}(CDCl_3)$ 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), $[\alpha]_D^{20}$ 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, $[\alpha]_D^{20}$ −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.

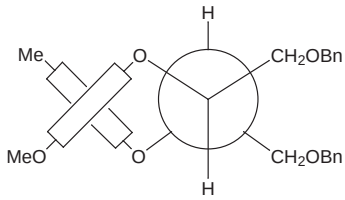


Fig. 1 Newman projection along the 2,3-bond of the D-threitol **14** in the conformation for the coupling reaction leading to **15**.

Notes and references

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10 CD spectra: Degradation product λ(MeOH)/nm 227 and 270 ($\Delta\varepsilon$ 7.7 and −6.5). Synthetic product λ(MeCN)/nm 196, 216, 231, 275, 296 and 340 ($\Delta\varepsilon$ 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: λ(MeCN)/nm 196, 216, 230, 276, 295 and 335 ($\Delta\varepsilon$ −19.8, 52.7, −33.5, 14.7, −7.5 and −5.2).

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