Total syntheses of the angucyclinone antibiotics (+)-emycin A and (+)-ochromycinone

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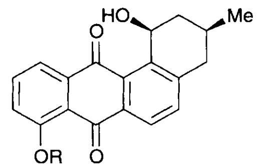
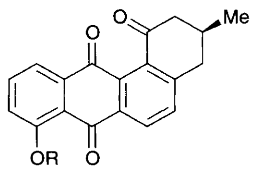
The first asymmetric synthesis of the angucyclinone antibiotics, emycin A and ochromycinone, is achieved *via* a short, efficient sequence from 5-hydroxy-1,4-naphthoquinone with the key step being an effective kinetic resolution of a racemic diene in a Diels–Alder reaction promoted by a chiral Lewis acid derived from (*S*)-3,3′-diphenyl-1,1′-binaphthalene-2,2′-diol.

We have recently reported the syntheses of the natural products rubiginone B_1 **1** and B_2 **2**, emycin A **3** and ochromycinone **4**, albeit in racemic form, as an initial part of a programme aimed at the development of a versatile synthetic strategy to bioactive members of the angucycline group of antibiotics.[1b,2] The key step in the syntheses was the Diels–Alder cycloaddition of 5-hydroxy-1,4-naphthoquinone **5** and the racemic form of the chiral 'semicyclic' diene **6a**. The reaction proceeded with high regio- and stereo-selectivity to afford the adduct (±)-**7a** as the sole cycloaddition product. The excellent facial selectivity of diene **6a** was attributed to steric effects in the *endo* transition state in which the dienophile **5** approaches the face of the diene which is *anti* to the allylic oxygenated substituent (Fig. 1).[2] Owing to the high degree of stereochemical control exhibited in this reaction, the use of diene **6a** in either enantiomeric form would provide a simple synthetic route to both enantiomers of angucyclinones **1–4**. Unfortunately all our attempts at an asymmetric synthesis of the diene system have so far been unsuccessful and thus our attention was diverted towards the dienophile (*i.e.* **5**).

The asymmetric Diels–Alder reaction of **5** and various achiral oxygenated dienes promoted by chiral Lewis acid complexes



1 R = Me
3 R = H



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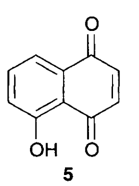
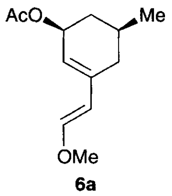
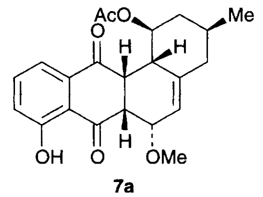


5



6a



7a

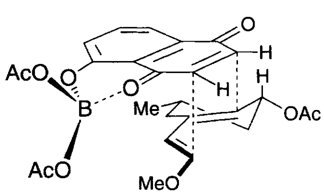


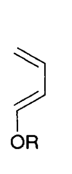
Fig. 1

has been studied by several groups.[3,4,5] The development of such methodology was aimed at the syntheses of naturally occurring anthraquinones and anthracyclines. A notable and early example was reported by Kelly *et al.*[3] who used the cycloaddition reaction of **5** and the diene **8a** promoted by a chiral Lewis acid derived from (*S*)-**9**, borane. THF, and acetic acid to give the cycloadduct **10a** with an impressive level of asymmetric induction (>98% ee). Yamamoto and coworkers[4] reported a similar approach to anthracycline intermediates using a chiral Lewis acid derived from (*R*,*R*)-tartaric acid diamides and trimethyl borate to promote the cycloaddition reaction of **5** and 1-trimethylsiloxybutadiene **8b** to give the enantiomer of adduct **10b** with ee's of 75–84%. Both approaches require either an equivalent or an excess of the Lewis acid for complete reaction, however, in each case the chiral ligand was easily recovered. A recent advance in this area reported by Mikami *et al.*[5] has resulted in a catalytic variant of this reaction. Treatment of **5** with 1-acetoxybutadiene **8a** with molecular sieve free (*S*)-binaphthol–titanium dichloride complex (10 mol%) gave the corresponding cycloadduct **10a** with ee in the range 76–96%.

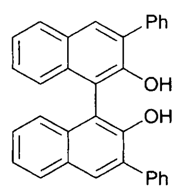
Despite the existence of these methods the only reported example of their use in targeted synthesis was in the formation of (−)-bostrycin by Kelly.[3] Furthermore the diene components in each of the studies were limited to simple achiral oxygenated butadienes. Here we report an extension of the Kelly system to reactions of 5-hydroxy-1,4-naphthoquinone **5** with chiral 'semicyclic' diene systems to produce the first asymmetric syntheses of the angucyclinone antibiotics **3** and **4**.

We felt that the high facial selectivity exhibited by racemic dienes such as **6a** in their cycloadditions with **5** would facilitate the control of absolute stereochemistry when used in conjunction with chiral Lewis acids. Kelly proposed for his system that the asymmetric induction arose because the front face of the dienophile was blocked in the complex **11** [formed from **5**, (*S*)-**9**, BH_3.THF, and AcOH] to the extent that dienes could only react from the back face.[3] We envisaged that use of complex **11** as the dienophile in our system would lead to a kinetic resolution of the racemic dienes **6**. The facial selectivity of the dienophile formed from (*S*)-**9** (*i.e.* **11**) and the (*S*,*S*)-enantiomers of **6** would be matched whereas **11** and (*R*,*R*)-**6** would be mismatched.

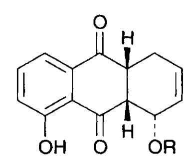
To test this theory the reaction of the dienol **6b** with **11** was investigated. The reaction proved problematic and after some initial success it was found to be variable, yielding little or no trace of cycloaddition products. It was ascertained that the problem lay with the formation of the chiral Lewis acid and it



8a R = Ac
8b R = TMS

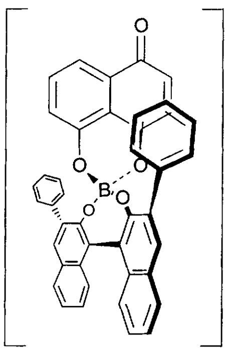


9



10a R = Ac
10b R = TMS

was found that the use of freshly prepared borane–tetrahydrofuran complex was essential for the success of the reaction. Once this had been addressed, reaction of **5** and greater than 2 equiv. of the diene (±)-**6b** promoted by (*S*)-**9**, freshly prepared borane–THF, and acetic acid in dry THF at −78 °C proceeded rapidly (< 2 min) to give the adduct (+)-**7b** in 69% yield after



11

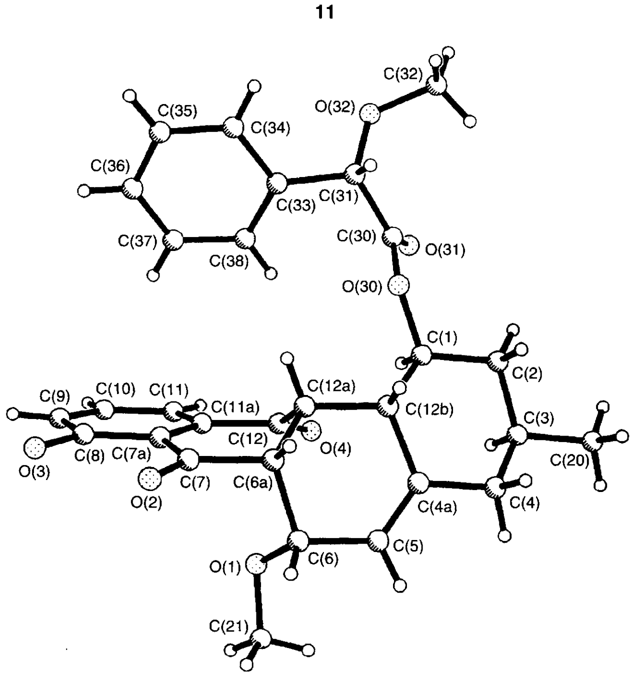
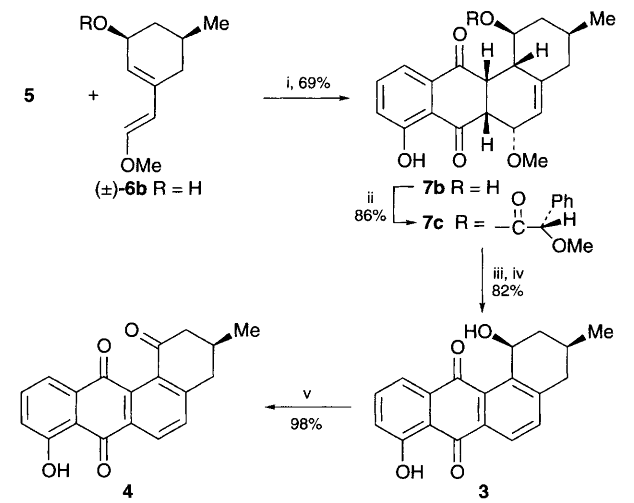


Fig. 2 Molecular structure of **7c**



Scheme 1 *Reagents and conditions*: i, BH_3.THF, (*S*)-**9**, HOAc, THF, −78 °C; ii, (*S*)-*O*-methylmandeloyl chloride, py, CH_2Cl_2; iii, DBU, CH_2Cl_2, air; iv, NaOMe, MeOH–THF; v, hν, CH_2Cl_2, O_2

column chromatography. The ligand (*S*)-**9** was easily recovered, however the excess diene, presumably rich in the (*R*,*R*)-enantiomer, did not survive the workup and purification processes. The asymmetric induction was found to be high (> 98% ee) by derivatisation of (+)-**7b** as its (*S*)-*O*-methylmandeloyl ester **7c**. This was easily established by comparison of the ^{1}H NMR spectrum of this reaction product after purification by column chromatography to that of the (*S*)-*O*-methylmandeloyl esters derived from (±)-**7b**. Furthermore, the absolute stereochemistry of **7c** [and hence of (+)-**7b**] was unequivocally determined by a single crystal X-ray diffraction study‡ (Fig. 2).

The stereochemical integrity of **7c** was also demonstrated by its conversion into (+)-emycin A **3** and (+)-ochromycinone **4** (Scheme 1). Synthetic **3** {$[\alpha]_D^{21}$ +402 (*c* 0.1%, CH_2Cl_2)} was identical in all respects to an authentic sample of the natural product. Likewise, synthetic **4** {$[\alpha]_D^{21}$ + 197 (*c* 0.1%, CH_2Cl_2), *cf.* lit,[6] $[\alpha]_D^{25}$ +204.5 ($CHCl_3$)} gave data matching that of the product of photooxidation of natural **3**.

In conclusion we have reported the first asymmetric syntheses of the angucyclinone antibiotics emycin A **3** and ochromycinone **4** in overall yields from **5** of 49 and 48% respectively. Although double stereodifferentiation in Diels–Alder reactions promoted by chiral Lewis acids has been well documented,[7,8] to our knowledge there have been no examples reported of efficient kinetic resolutions of racemic dienes using this type of approach. The kinetic resolution of the diene (±)-**6b** in this work proved to be remarkably efficient resulting in complete control of absolute stereochemistry at C-1 and C-3 of **3**, and at C-3 of **4**.

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Footnotes

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‡ Crystal data: $C_{29}H_{30}O_7$, colourless rectangular prism, 0.1 × 0.2 × 0.4 mm, monoclinic, space group $P2_1$, a = 5.462(1), b = 20.141(1), c = 11.323(1) Å, β = 95.45(1)°, U = 1239.9(1) Å^3, Z = 2, μ = 0.77 mm^{-1}. Data were collected at 130 K on a Siemens four circle diffractometer using graphite monochromated Cu-Kα radiaton. 1604 Reflections were collected in the range $4 < 2\theta < 110°$ and the 1602 independent reflections were used in the structural analysis. The structure was solved by direct methods (SHELXS-86)[9] and refined against all F^2 data (SHELXL-93)[10] to R_1 = 0.107 [for 1228 F > 4σ(F); wR_2 = 0.300 and goodness of fit = 1.04 for all 1602 F^2; 178 parameters; O(1), O(2), O(3), O(4), O(31), O(32) anisotropic]. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Information for Authors, Issue No. 1.

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