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

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’-diox.

We have recently reported the syntheses of the natural products rubigineone B1, 1 and B2, 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 stereoselective 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 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. One 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 coworkers4 reported a similar approach to anthracyclanes 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 achiral benzylidene acetals, naphthalene and 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, BH3,THF, and AcOH) to the extent that dienes could only react from the back face.4 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 diene 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

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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 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 1H 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 ([α]D21 +402 (c 0.1%, CH2Cl2) was identical in all respects to an authentic sample of the natural product. Likewise, synthetic 4 ([α]D21 +197 (c 0.1%, CH2Cl2), cf. lit.5 [α]D25 +204.5 (CHCl3)] gave data matching that of the product of photooxidation of natural 3.

In conclusion we have reported the first asymmetric syntheses of the angucycline antibiotics emycin A 3 and oochromycinone 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
1 Email Dlarsen@alkali.otago.ac.nz
2 Crystal data: C29H30O7, colourless rectangular prism, 0.1 x 0.2 x 0.4 mm, monoclinic, space group P21/a, a = 5.462(1), b = 20.141(1), c = 11.323(1), β = 95.45(1), U = 1239.9(1) Å2, Z = 2, μ = 0.77 mm−1.

References

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