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Remote stereochemical control in asymmetric Diels–Alder reactions: synthesis of the angucycline antibiotics, (−)-tetrangomycin and MM 47755

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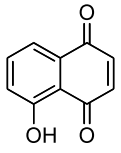
Abstract—The first asymmetric syntheses of the angucycline antibiotics, (−)-tetrangomycin and MM 47755, are achieved via a short efficient sequence starting from the chiral Lewis acid promoted Diels–Alder reaction of 5-hydroxy-1,4-naphthoquinone and (±)-(*E*)-5-dimethylphenylsilyl-5-methyl-1-(2′-trimethylsiloxyvinyl)cyclohexene **7** where an effective kinetic resolution of the latter, controlled by its remote stereocentre, is described.

The asymmetric Diels–Alder cycloaddition is one of the most useful reactions available to the synthetic organic chemist because of its ability to create four contiguous chiral centres in one step.[1] The source of asymmetry is often incorporated into either the diene or dienophile, or is from an asymmetric catalyst. Other stereogenic centres in the cycloadduct are usually derived from either of the reactants or are subsequently formed by post-addition modifications. The former approach is generally reliant on the availability of either dienes or dienophiles in enantiomerically enriched or pure form. We have previously demonstrated an alternative where a chiral Lewis acid, derived from (*S*)-3,3′-diphenyl-1,1′-binaphthalene-2,2′-diol and borane, promoted the Diels–Alder reaction of 5-hydroxy-1,4-naphthoquinone **1** and the racemic diene (±)-**2**.[2] The reaction gave an effective kinetic resolution of the racemic diene partner and the cycloadduct, obtained with 98% ee, was subsequently transformed into the angucyclinone antibiotics, (+)-emycin A and (+)-ochromycinone **3**. The stereochemical outcome was explained by a double induction process based on the facial reactivity of each of the reactants. The facial selectivity of dienophile–Lewis acid complex had been documented by Kelly et al.[3] and that of the diene was controlled by an allylic hydroxyl group at the stereogenic centre adjacent to the dienyl unit. Carreño et al. have adapted this approach for the syntheses (+)-**3** and (+)-rubiginone B_2 **4**, both achieved in 80% ee, using the cycloaddition of an enantiomerically pure sulfinylquinone dienophile as the source of asymmetry to affect a kinetic resolution of a racemic diene.[4] The facial selectivity of the diene was also controlled by an allylic substituent. In a further extension of this work, Carreño et al.[5] have investigated the kinetic resolution of a vinyl cyclohexene, possessing protected tertiary hydroxyl functionality at the remote C-5 position but lacking a C-3 allylic substituent, using the same dienophile. After a series of transformations they produced the angucyclinone analogue (−)-8-deoxytetrangomycin **5** with 50% ee.



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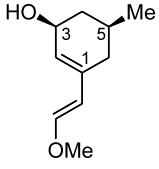
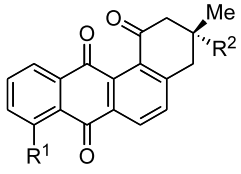
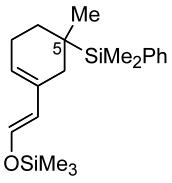


(±)-**2**



3 R^1 = OH, R^2 = H
4 R^1 = OMe, R^2 = H
5 R^1 = H, R^2 = OH
6 R^1 = R^2 = OH
13 R^1 = OMe, R^2 = OH



(±)-**7**

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Krohn et al.[6,7] have reported a concise synthesis of the angucyclinone, (±)-tetrangomycin **6**, which relied on the thermally promoted Diels–Alder reaction of 5-hydroxy-1,4-naphthoquinone **1** and diene (±)-**7** to construct the benz[*a*]anthraquinone ring system. They assumed that the Diels–Alder reaction between **1** and **7** gave a mixture of diastereoisomeric cycloadducts, however, our examination of their reported experimental data indicated the possibility that only one of the *endo* diastereoisomers had been formed. This being the case, the facial selectivity of diene **7** is presumed to arise from the substituents at the remote C-5 chiral centre. We now report a chiral Lewis acid promoted Diels–Alder reaction of quinone **1** in which an effective kinetic resolution of the diene partner (±)-**7**, controlled by the remote C-5 stereogenic centre, resulted.

Our initial aim was to determine the facial selectivity exhibited by (±)-**7**. The thermal Diels–Alder reaction of **1** and **7** gave an 88:12 mixture of cycloadducts (±)-**8a** and (±)-**8b** in 84% yield. This ratio was readily determined by integration of the signals for the 8-OH, H-5 and OTMS protons in the ^{1}H NMR spectrum. A similar ratio (91:9) of (±)-**8a** and (±)-**8b** was obtained for the tetra-*O*-acetyl diborate promoted cycloaddition. The structure of the major cycloadduct was consistent with all NMR data and the relative stereochemistry at C-3 was evident from strong NOE correlations between the C-3 methyl group to H-2$_\beta$ and -4$_\beta$ and a weaker correlation to H-12b. On this basis the more reactive face of **7** is that *syn* to the 'large' phenyldimethylsilyl group. The favoured approach of the dienophile is *anti* to the pseudo-axial methyl group of **7**, as depicted in Figure 1, which minimises steric interactions in the transition state.

Reaction of **1**, via the chiral complex **9**, and diene (±)-**7** in dichloromethane at −78°C also gave 91:9 to 94:6 (de 82 to 88%) mixtures of **8a** and **8b** over repeated experiments (Scheme 1). The ligand, (*S*)-3,3′-diphenyl-1,1′-binaphthalene-2,2′-diol, was recovered from the reaction mixture in near quantitative yield. The structure of the major adduct **8a** was based upon the premise that the matched enantiomer of **7** reacted preferentially to the less hindered *Re* face of **9** as depicted in Figure 1. Aromatisation of the mixtures gave optically active angucyclinone **10**, $[\alpha]_D$ −42 to −52 (*c* 0.5, CH_2Cl_2), in 82% yield. The ee was determined by ^{1}H NMR experiments using the chiral solvating agent, (*S*)-2,2,2-trifluoro-1-(9-anthryl)ethanol, and ranged from 67–78% depending on the ratio of **8a** to **8b**. The fact that the ee was less than the de for the Diels–Alder reaction suggests that either the facial selectivity of complex **9** was not complete and the diene was reacting, to a small extent, from its upper more hindered *Si* face or a competing thermal reaction of **1** and (±)-**7** was occurring on workup. The next step in the sequence involved the treatment of **10** with boron trifluoride etherate which gave silyl fluoride **11** (90%). Subsequent oxidation with hydrogen peroxide and potassium fluoride gave tertiary alcohol **12** in 57% yield. Photochemical oxidation of **12** in methanol gave tetrangomycin **6** in a 78% yield. The spectroscopic data were identical to those reported by Krohn et al.[6,7] for the racemate. The ee was determined using NMR spectroscopy and found to range from 68–78%. The specific rotation measured on a chloroform solution of **6** (68% ee) was $[\alpha]_D$ −67 (*c* 0.4, $CHCl_3$). Of concern was the

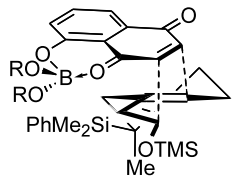
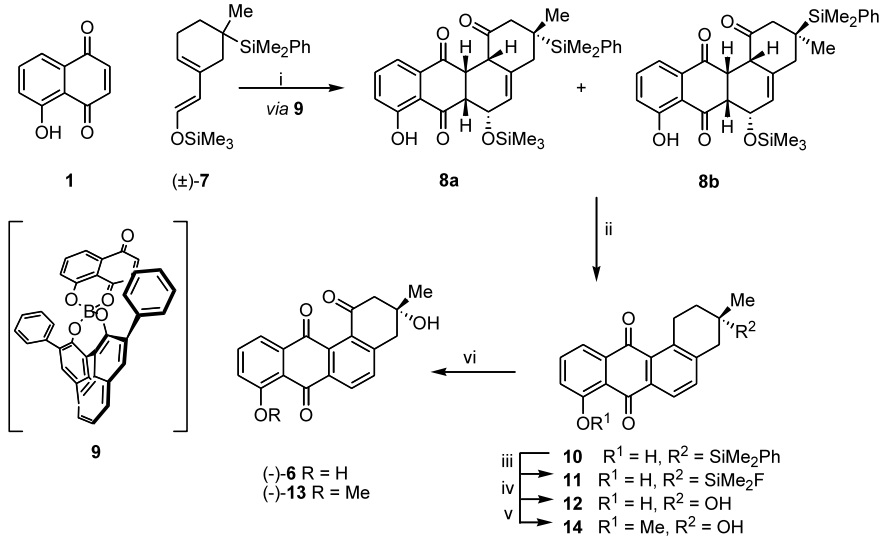


Figure 1.



Scheme 1. *Reagents, conditions and yields*: (i) (*S*)-3,3′-diphenyl-1,1′-binaphthalene-2,2′-diol, BH_3·THF, HOAc, CH_2Cl_2, −78°C, 94% (82–88% de); (ii) DBU, air, CH_2Cl_2, 82% (67–78% ee); (iii) BF_3·Et_2O, CH_2Cl_2, 90%; (iv) H_2O_2, KF, $NaHCO_3$, THF–MeOH, 57%; (v) MeI, Ag_2O, CH_2Cl_2, 25°C; (vi) *hv*, MeOH, 78% (68–78% ee).

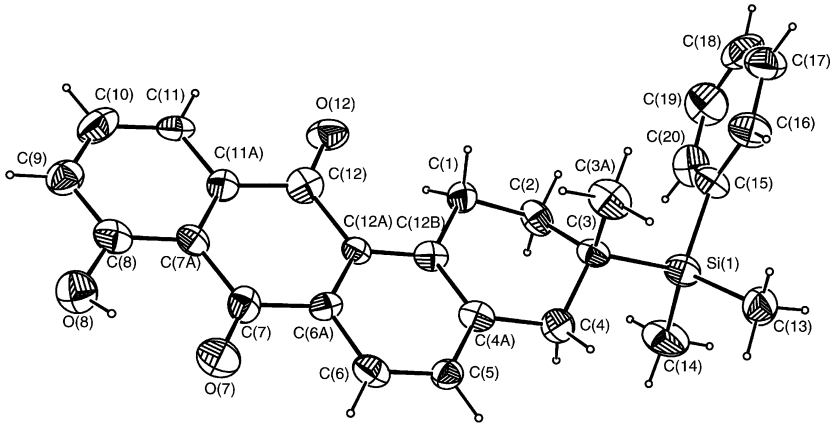


Figure 2. The molecular structure of **10**.

fact that the specific rotation for the natural product had a reported value of $[\alpha]_D$ +42 (*c* 0.9, $CHCl_3$).[8,9] The sign and the magnitude of this rotation, in comparison to that measured by us, brings into doubt either the original assignment of the structure of natural **6** or the reporting of these data.

The related angucyclinone MM 47755 **13**, which is the 8-*O*-methyl congener of **6**, has been independently isolated by two groups.[10,11] They reported the specific rotations for **13** as $[\alpha]_D$ −107 (*c* 0.5, MeOH) and −136 (*c* 0.04, MeOH), respectively. Treatment of the angucyclinone **12** (ee 70%) with methyl iodide and silver(I) oxide gave, after photochemical oxidation of methyl ether **14** in methanol, (−)-**13** in a 70% yield for the two steps. The specific rotation was measured as $[\alpha]_D$ −69 (*c* 0.7, MeOH) and the ee was assessed as 70% by NMR methods.

The stereochemical outcome of the cycloaddition was based on the model for asymmetric induction for the Diels–Alder reactions of **9** proposed by Kelly et al.[3] in conjunction with that for the facial selectivity of diene **7** determined from NMR data of adduct **8a**. This in turn led to the assignment of the absolute configurations of (−)-**6** and (−)-**13** both as 3*R*. Unambiguous confirmation for these assignments came from minor modifications to the reaction sequence. Recrystallisation of **10** from hot hexanes increased the ee to 90%. A further crystallisation of a small amount of this material gave crystals suitable for an X-ray crystallographic study[12] the solution of which is shown in Figure 2. On the basis of the crystallographic data the configuration of **10** was determined as 3*S* and thus, those of (−)-**6** and (−)-**13** as 3*R*. Continuation of the synthesis outlined in Scheme 1 using **10** (90% ee), with recrystallisation of each intermediate, gave (−)-tetrangomycin **6** with an optical rotation $[\alpha]_D$ −100 (*c* 0.26, MeOH) and with an ee of 98%.

In summary, we have shown that enantiomerically enriched cycloadducts can be obtained from a chiral Lewis acid Diels–Alder reaction of **1** and diene (±)-**7**. The facial selectivity of (±)-**7** is controlled by the remote C-5 stereogenic centre which, in conjunction with the high facial selectivity of complex **9**, results in an effective kinetic resolution of the diene component. We have demonstrated the utility of this approach with the first asymmetric syntheses of (−)-tetrangomycin **6** in 31% overall yield with ee ranging from 68 to 78% and (−)-MM 47755 **13** in 28% overall yield with a 70% ee. Recrystallisation of the reaction intermediates resulted in an increase in their ee's and gave (−)-**6** with 98% ee. An X-ray crystallographic study of **10** unambiguously established the absolute configurations of (−)-**6** and (−)-**13** as 3*R*. This synthesis required a stoichiometric amount of the chiral Lewis acid to promote the pivotal asymmetric Diels–Alder reaction. Further work investigating the use of chiral Lewis acid *catalysts* to effect kinetic resolutions of racemic dienes using Diels–Alder reactions of the type described is warranted.

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12. *Crystal data and structure refinement for* **10**: $C_{27}H_{26}O_3Si$, M=426.57, monoclinic, space group $P2(1)$, a=

17.597(16), $b=7.211(6)$, $c=18.494(17)$ Å, $\beta=107.333(12)°$, $V=2240(3)$ Å^3, $Z=4$, $T=163(2)$ K, λ(Mo-Kα)=0.71073 Å, 21414 reflections measured, 5706 unique (R(int)=0.1093), Bruker SMART CCD diffractometer, empirical absorption correction (SADABS), $\mu=0.131$ mm^{-1}. Final R indices $R_1[I>2\sigma(I)]=0.0453$, final w$R2(F^2)=0.0812$ (all data), absolute structure parameter 0.0(2); Flack, H. D. *Acta Crystallogr*. **1983**, *A39*, 876. Atomic coordinates, thermal parameters, and bond lengths and angles have been deposited at the Cambridge Crystallographic Data Centre (CCDC). Any request to the CCDC for this material should quote the full literature citation and deposition number CCDC 172389.