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Asymmetric Synthesis of the *m*C7N Core of the Manumycin Family: Preparation of (+)-MT 35214 and a Formal Total Synthesis of (-)-Alisamycin

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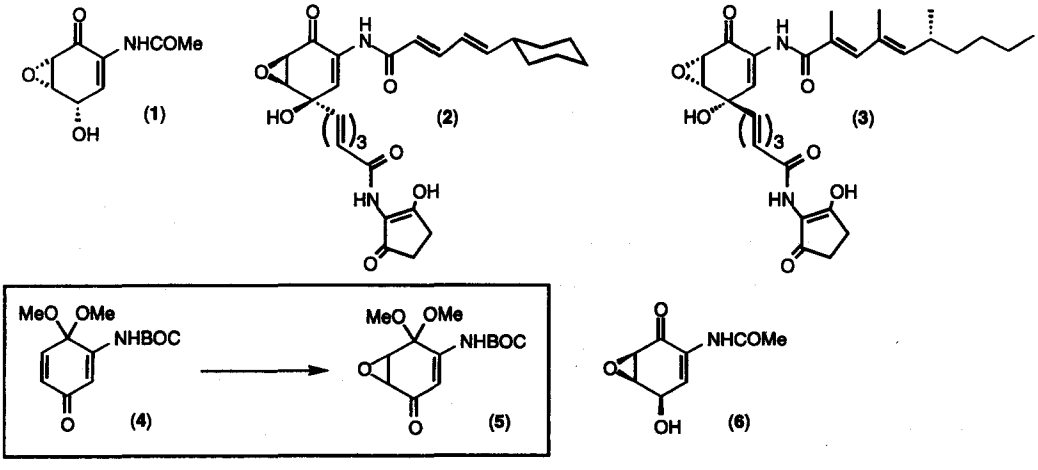
Abstract: An asymmetric approach to the *m*C7N epoxyquinone central unit of the manumycin antibiotics is described based on the enantioselective (89% ee) chiral phase transfer epoxidation of a substituted cyclohexenone. The chiral epoxide is employed in the first syntheses of the title compounds in enantiomerically pure form.

Tremendous advances have been made in recent years concerning the asymmetric epoxidation of alkenes.[1] Most success has been achieved with electron rich alkenes, the Sharpless[2] and Jacobsen/Katsuki[3] procedures being of particular note. There have also been significant discoveries in the asymmetric epoxidation of acyclic enones of the chalcone type.[4] The asymmetric epoxidation of cyclic enones, however, has proved much more challenging.[5,6] Our interest in this area stems from a synthetic programme concerned with the total synthesis and biological evaluation of epoxycyclohexenone natural products and novel analogues.[7-13] We have reported total syntheses, in racemic form, of the anti-tumour agent LL-C10037α **1**[8,10] and the antibiotic alisamycin **2**,[9,10] which is closely related to manumycin **3**. The key step in these syntheses is the conversion of enone **4** into epoxide **5**, which constitutes the *m*C7N core of all these natural products. In order to prepare such compounds in enantiomerically pure form we therefore required an asymmetric synthesis of epoxide **5**. It should be noted that Wipf *et al.* have prepared related epoxides in enantioenriched form using chiral acetal methodology.[14] We decided, however, not to employ chiral auxiliaries but to develop a procedure based on chiral catalysts or reagents. We have recently described the successful implementation of this approach during the synthesis of the (+)-enantiomer of manumycin A **3**.[13] Herein, we provide more details of the asymmetric epoxidation of **4** to produce (-) -**5**, and describe its utility for the preparation of alisamycin **2** and (+)-MT 35214 **6**.



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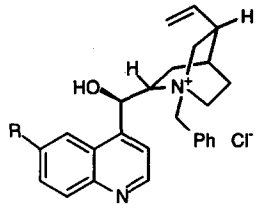
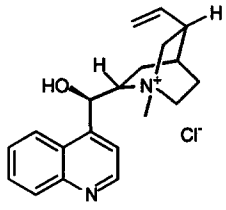
We were attracted by the simplicity of Wynberg's phase transfer epoxidation procedure[5] in which *N*-benzylquininium chloride **7** was employed as the chiral catalyst with *t*-butyl hydroperoxide as oxidant and catalytic sodium hydroxide as base. Using these conditions with cyclohexenone, (2*S*,3*S*)-epoxycyclohexenone was obtained in *ca.* 20% enantiomeric excess (ee).[5a] We therefore used Wynberg's procedure (but with 12 mol % of **7**) for the epoxidation of dienone **4** (Table, entry i). Under these conditions we were delighted to obtain epoxide (-)-**5** with an ee of 66% as determined by HPLC using a Chiralcel OJ column. To our knowledge, this is the highest ee obtained for the epoxidation of cyclohexenones using chiral phase transfer methodology. However, with the same conditions but leaving the reaction for 7 days (entry ii) there was a slight increase in ee to 69%, and a significant increase to 77% ee was obtained when a stoichiometric quantity of the quininium salt was employed (entry iii). We then turned our attention to the use of other ammonium salts,[5b,16] the best proving to be commercially available *N*-benzylcinchonidinium chloride **8** which gave (-)-**5** in 89% ee (entry iv). The yield of (-)-**5** based on starting material consumed was satisfactory but the actual conversion was rather low (32%). A range of solvents, oxidants and bases were employed with *N*-benzylcinchonidinium chloride **8** at a variety of reaction temperatures in order to improve the conversion, but with no success. *N*-Methyl cinchonidinium chloride **9** was prepared and utilised under the optimum conditions. This catalyst did give a marginally higher yield (entry v) but unfortunately epoxide (-)-**5** was formed with a disappointing ee (35%). We had hoped, based on literature precedence,[5b,d] that the use of the pseudoenantiomeric *N*-benzylcinchoninium chloride **10** would produce (+)-**5** but surprisingly this catalyst also gave (-)-**5**, albeit in only 10% ee (entry vi)

The predominant (-)-enantiomer was assigned the (2*S*, 3*R*)-configuration by analogy with Wynberg's studies on epoxycyclohexenone[5a] and this was subsequently confirmed by conversion into known compounds (see later). Wynberg's transition state model,[5d] in which the *N*-benzyl substituent discriminates between the *re* and *si* faces of the cyclohexenone during the enantioselective epoxidation process, is compatible with the high ee's obtained in this study: the 5-*t*-butoxycarbonylamino substituent leads to a marked increase in the unfavourable interactions in the transition state leading to the minor enantiomer.

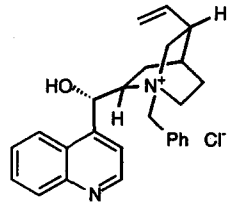
Table Epoxidation of **4** using *t*-BuOOH/cat. NaOH in toluene at rt with chiral phase transfer agents **7-10**



(7), R = OMe (8), R = H



(9)



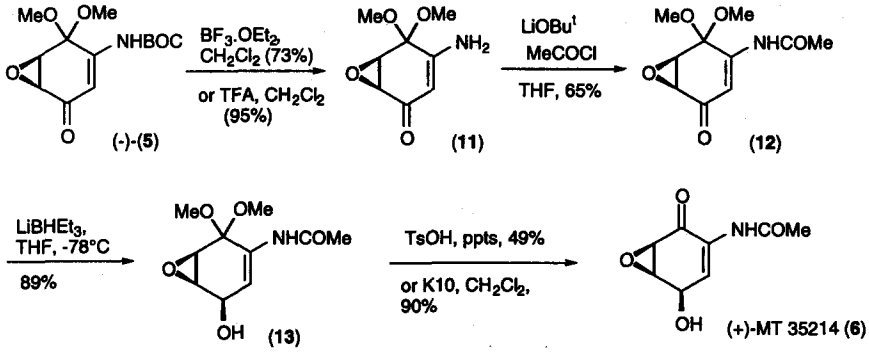
(10)

Entry	Catalyst	Conditions[a]	Yield of **5** (%)[b,c]	ee (%)[d]
i	**7**	12 mol % **7**, rt, 2d	55 (22)	66
ii	**7**	12 mol % **7**, rt, 7d	57 (28)	69
iii	**7**	100 mol % **7**, rt, 7d	74 (28)	77
iv	**8**	100 mol % **8**, rt, 7d	71[a,e] (32)	89
v	**9**	100 mol % **9**, rt, 7d	93 (39)	35
vi	**10**	100 mol % **10**, rt, 7d	48 (15)	10

[a]See experimental procedure for details[17] [b]With the (-)-enantiomer (2*S*, 3*R*) predominating
[c]The yield of **5** based on recovered **4** is shown (the absolute yield is given in parentheses)
[d]Determined by HPLC using a Chiracel OJ column [hexane-IPA (98:2) @ 1 mL/min as eluant]
[e]On a subsequent run,[13] the yield based on recovered starting material was 82%

A single recrystallisation of (-)-**5** (entry iv) from dichloromethane-hexane increased the ee from 89% to 94%, and after two recrystallisations a sample with an ee of 99.5% was obtained. We have previously converted racemic **5** into racemic LL-C10037α **1**.[8,10] The availability of (-)-**5** in high enantiomeric purity has allowed us to complete the first asymmetric synthesis of the enantiomer of **1**, that is (+)-MT 35214 **6**, as shown in Scheme 1. The sequence is essentially the same as that employed in our published synthesis of the racemate[8,10] but three improvements deserve mention. Removal of the BOC group using boron trifluoride diethyl etherate and molecular sieves in DCM[18] proceeded in reasonable yield to give amine **11** but the use of trifluoroacetic acid gave a near quantitative conversion. The crystalline amine **11** was acetylated in moderate yield with acetyl chloride to give **12** which, in the earlier approach, was reduced with sodium borohydride in methanol to give a mixture (*ca.* 4 : 1) of *syn* and *anti* alcohols. We have since found that the use of Super-Hydride® ($LiBHEt_3$) in THF at low temperature gives exclusively the *syn* isomer **13** in excellent yield. Finally, cleavage of the acetal, originally performed in 49% yield using *para*-toluenesulfonic acid and pyridinium *para*-toluenesulfonate, was achieved more efficiently using the montmorillonite K10 procedure developed in our laboratories.[19] The NMR, IR and mass spectral data, as well as mp (148-149°C; lit.[20] mp 149-151°C, dec.) and R_f, of (+)-MT 35214 **6** were in accord with literature values.[20] The optical rotation value determined for our synthetic sample of (+)-**6** {$[\alpha]_D$ +186.7 (*c* 0.35, MeOH)} corresponded well to the reported value for the enantiomer **1** {$[\alpha]_D$ -202 (*c* 0.3, MeOH)}[14] although it differed in magnitude, but not sign, from the reported value for (+)-MT 35214 itself {$[\alpha]_D$ +104 (*c* 1, MeOH)}.[20] This synthesis confirmed the absolute stereochemistry of (-)-**5** obtained in the asymmetric epoxidation step. The overall yield of (+)-**6**, obtained in 7 steps from 2-amino-1,4-dimethoxybenzene, is over 10%; this compares well with Wipf's asymmetric route to (-)- LL-C10037α (12 steps, *ca.* 1.3% overall yield[14]).

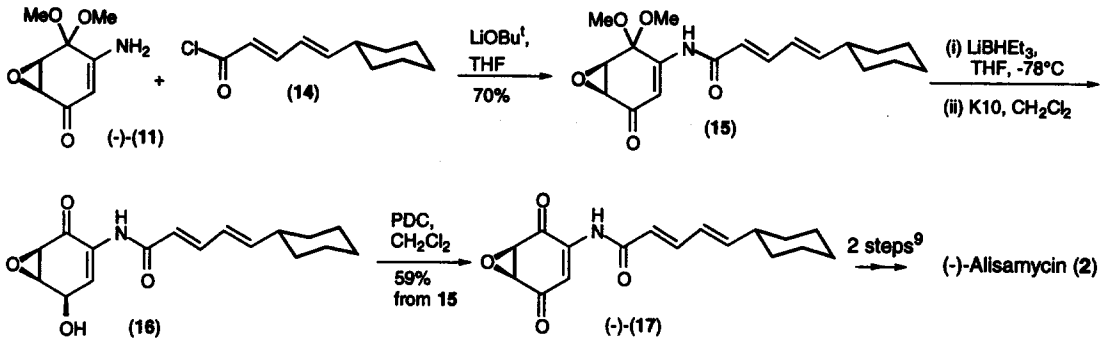
Scheme 1



Similar chemistry was employed to prepare, for the first time and in enantiomerically pure form, alisamycin epoxyquinone (-)-**17** as shown in Scheme 2. Thus acylation of **11** with acid chloride **14**[8-10] proceeded in good yield to give amide **15** which was reduced and deprotected as before to produce the secondary alcohol **16**, which is a novel, enantiomerically pure analogue of alisamycin **2** lacking the complete lower side chain. Oxidation with PDC then converted **16** efficiently into (-)-alisamycin epoxyquinone **17**. This is the first synthesis of this alisamycin degradation product[21] and the spectroscopic data were entirely consistent with literature values {$[\alpha]_D$ -55 (*c* 0.6, $CHCl_3$); lit.[21] $[\alpha]_D$ -50 (*c* 0.12, $CHCl_3$)}. The preparation of (-)-**17** also constitutes a formal total synthesis of (-)-alisamycin as we have reported a two step procedure for the conversion of racemic **17** into the natural product.[9,10]

We are currently optimising this methodology, exploring ways to prepare (+)-**5**, and utilising (-)-**5** in the synthesis of other members of the manumycin family.

Scheme 2



Acknowledgements

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17. To dienone **4** (0.37 mmol), powdered NaOH (0.062 mmol) and *N*-benzylcinchonidinium chloride **8** (0.37 mmol) in toluene (1.5 mL) was added *t*-BuOOH in toluene (3.2*M*, 1.85 mmol) at 0°C under N_2. The reaction was stirred at rt for 7d, then quenched with sat. aq. sodium sulfite (10 mL) and extracted (5 x CH_2Cl_2). The combined organic layers were washed with water, dried (Na_2SO_4) and concentrated *in vacuo*. Purification on silica gel (CH_2Cl_2-EtOAc, 95:5) gave **5** (32%) which was recrystallised twice (CH_2Cl_2-hexane) to give (-)-**5** (26 mg, 25%) as colourless needles, mp 116-117°C; $[\alpha]_D$ -189.4 (*c* 1, $CHCl_3$) (> 99 % ee by HPLC on Chiracel OJ column; R_t 28.8 min) followed by recovered **4** (55%).
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