Manumycin A: Synthesis of the (+)-Enantiomer and Revision of Stereochemical Assignment

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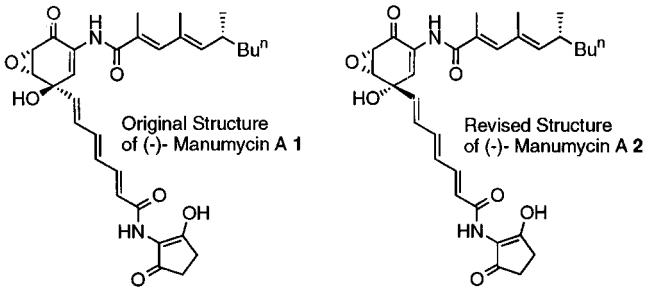
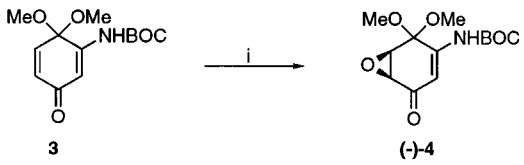
In 1963, Buzzetti, Prelog, and colleagues described the isolation of a structurally unique antibiotic from *Streptomyces parvulus* (Tü 64) which they christened manumycin A.[1] Subsequently, Zeeck's group reported degradation, NMR, and CD studies to establish the absolute structure of manumycin A as **1**.[2] Other representatives of the manumycin family were soon discovered[3] (e.g., asukamycin[3a] and alisamycin[3b]), and the family was shown to possess a wide range of biological properties. From a structural viewpoint, the fact that manumycin A (**1**), manumycin B,[3c] and EI-1625-2[3d] have been assigned as *anti*-hydroxy epoxides, whereas all other members of the family have been assigned the *syn* relationship, is rather surprising. This difference has attracted recent attention in terms of its biosynthetic origin:[4] research by Gould, Floss et al. calls into question the validity of the stereochemical assignment to manumycin A (**1**). Herein, we describe the first total synthesis of manumycin A, as its (+)-enantiomer, confirm that it does indeed possess the *syn*-hydroxy epoxide arrangement, and therefore, report that natural manumycin A has the revised structure **2**.



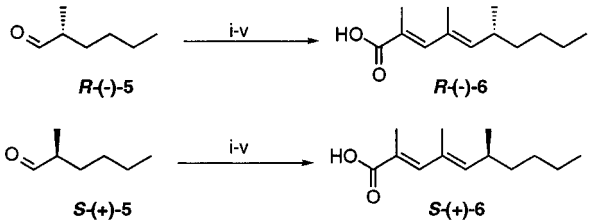
To date, the only successful preparation of a member of the manumycin family is our synthesis, in racemic form, of alisamycin.[5] Extension of this methodology would lead to "*syn*-manumycin A".

Scheme 1[a]



[a] Reagents: (i) *N*-Benzylcinchonidinium chloride, TBHP, cat. NaOH, rt, 6 d [32% (82% based on recovered **3**); 89% ee].

Scheme 2[a]



[a] Reagents: (i) $Ph_3P{=}C(Me)CO_2Et$, toluene, Δ; (ii) Dibal-H, THF, −78 °C; (iii) MnO_2, CH_2Cl_2, Δ; (iv) $Ph_3P{=}C(Me)CO_2Et$, CH_2Cl_2, Δ; (v) LiOH, aq THF−MeOH. Overall yields: (−)-**6**, 55%; (+)-**6**, 60%.

In order for chiroptical comparisons with natural manumycin A to be made, the crucial starting material **4** was required as a single enantiomer. Chiral acetal methodology has been used to prepare related epoxides in enantioenriched form,[6] but we decided to develop a non-auxiliary-based approach. We therefore investigated the epoxidation of the readily available enone **3**[5] using Wynberg's chiral phase-transfer catalysis procedure (Scheme 1).[7] The use of 1 molar equiv of *N*-benzylcinchonidinium chloride and *tert*-butyl hydroperoxide (TBHP) in toluene with catalytic sodium hydroxide and gave the desired epoxide (−)-**4** in 32% yield (82% based on recovered **3**) and high ee (89%). To our knowledge, this is the highest ee ever obtained for the epoxidation of cyclohexenones using chiral phase-transfer catalysis. Two recrystallizations of the reaction product from dichloromethane−hexane gave enantiomerically pure **4** [>99.5% ee as determined by HPLC using a Chiralcel OJ column: $[\alpha]_D$ −189.4 (*c* 1, $CHCl_3$); mp 116−117 °C]. The predominant (−)-enantiomer was assigned the 2*S*,3*R* configuration by conversion into a known[8,9] compound, (+)-MT 35214, and comparison of optical rotations. The 2*S*,3*R* configuration also predominated in the preparation of cyclohexenone oxide by similar procedures.[7a] We had hoped, on the basis of literature precedent,[7b] that the pseudoenantiomeric *N*-benzylcinchoninium chloride would give a predominance of (+)-**4**, but surprisingly, under the optimum conditions, its use again gave (−)-**4**, albeit in only 10% ee. The (+)-enantiomer is required for the synthesis of natural manumycin but we decided to proceed with (−)-**4**

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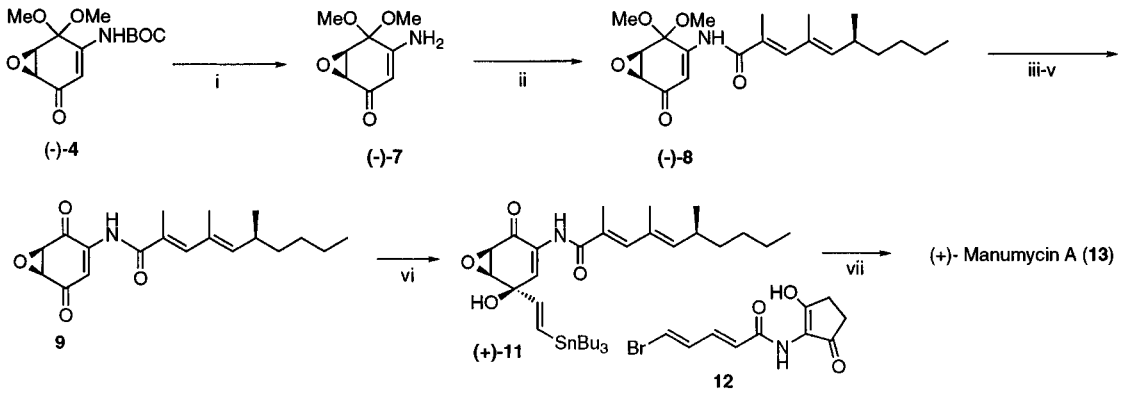
Scheme 3[a]



[a] Reagents: (i) TFA−CH_2Cl_2 (1:4) (98%); (ii) *t*-BuOLi, THF then acid chloride derived from (+)-**6** (91%); (iii) $LiEt_3BH$, THF, −78 °C (95%); (iv) Montmorillonite K10, CH_2Cl_2, rt (89%); (v) PDC, CH_2Cl_2, rt (91%); (vi) *E*-$Bu_3SnCH{=}CHLi$ (**10**) THF, −78 °C (25%); (vii) **12**, [5% $PdCl_2(Ph_3P)_2$, Dibal-H], THF−DMF, rt (71%).

and prepare *ent*-manumycin. The top side chains **6** were prepared from (*R*)-[10] and (*S*)-2-methylpropanal (**5**) via the sequence shown in Scheme 2. (*R*)-(−)-**6** gave data fully consistent with those reported from the natural product degradation studies [$[\alpha]_D$ −76.3 (*c* 1.9, $CHCl_3$) (lit.[2] $[\alpha]_D$ −75.8 (*c* 1.6, $CHCl_3$))], thus confirming the absolute stereochemistry of the top side chain of manumycin A. Acid (*S*)-(+)-**6** was utilized for the preparation of *ent*-manumycin A.

The elaboration of the enantiomerically pure epoxide (−)-**4** is shown in Scheme 3. The BOC group was removed by treatment with TFA, and the resultant crystalline amine **7** was acylated with the acid chloride produced from (+)-**6** [$(COCl)_2$, CH_2Cl_2, 0 °C]. Amide **8** was then converted into the corresponding quinone via a three-step reduction−deprotection−oxidation sequence as shown (attempts to effect the direct deprotection of **8** were unsuccessful). Quinone **9** was obtained in a good overall yield (68%) and gave consistent spectroscopic data that corresponded well to those reported by Zeeck et al.[2] for the enantiomeric system obtained by the chromic acid degradation of manumycin A. The optical rotation of **9** is close to zero [lit.[2] $[\alpha]_D$ −8.0] but its CD spectrum correlated well to the published values for its enantiomer. This study therefore confirms the absolute stereochemistry of the epoxide moiety of manumycin A, initially proposed on the basis of comparative CD studies.[2]

It is now well established[5] that the addition of organometallic reagents to epoxyquinones such as **9** proceeds with complete stereoselectivity, the organometallic reagent attacking from the face opposite the epoxide to generate *syn*-hydroxy epoxides. Addition of vinyllithium reagent **10**[11] to quinone **9** gave a mixture of products with monoadduct **11** predominating. NMR spectroscopy provided convincing evidence that adduct **11** was, as expected,[5] a *syn*-hydroxy epoxide **11** [H-3 is particularly diagnostic: δ_H 7.38 (d, 1H, J = 2.5 Hz); this is consistent with published[5] values for closely related systems, one of which was characterized by X-ray crystallography[5b]]. Confident of the stereochemistry of **11**, we proceeded with the Stille reaction.[12,13] Stannane **11** was coupled to bromo diene **12**[14] using Negishi's catalyst[13] [$PdCl_2$-$(Ph_3P)_2$, Dibal-H] to give (+)-**13** in 71% yield as a bright yellow solid [mp 134−136 °C (lit.[2] 139−141 °C dec)]. The spectroscopic and chromatographic data were entirely consistent with the literature[2] values and with those obtained from authentic[15] samples of manumycin A. The optical rotation obtained for **13** is also consistent with the value obtained from commercial material [$[\alpha]_D$ (synthetic) +193.0 (*c* 0.1, $CHCl_3$); $[\alpha]_D$ (commercial) −191.4 (*c* 0.07, $CHCl_3$)] and the CD data (see Supporting Information) provides convincing evidence that **13** is the enantiomer of natural manumycin A. *Our study therefore indicates that the structure of manumycin A should be revised to* ***2****.*

The assignment of C-4 stereochemistry to the manumycin family of natural products was made using the exciton chirality procedure and is based on the conclusion that a positive CD couplet indicates the presence of a 4*S*-stereocenter. This deduction was first made with asukamycin[3a] and then extended to manumycin A[2d] and other members of the family.[3] It should be noted that **13** exhibits a positive CD couplet but, from its method of synthesis, has the 4*R*-configuration. It would therefore appear that variations in the substitution pattern of the upper side chain can result in exceptions to this exciton chirality rule, presumably due to conformational changes resulting in a realignment of the coupled chromophores.

In summary, the first total synthesis of (+)-manumycin A (**13**) has been achieved, leading to a revision of the published structure of the natural product. The revised *syn*-hydroxy epoxide stereochemistry is now in accord with the biosynthetic mechanism proposed by Gould, Floss et al.[4] It seems likely that the structures of manumycin B and EI-1625-2, which were also assigned as *anti*-hydroxy epoxides by use of the exciton chirality method,[3c,d] will also need to be revised. Further refinements of the synthetic route, and the preparation and biological evaluation of novel manumycin A analogues, will be reported in due course.[16]

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Supporting Information Available: ^1H NMR and ^{13}C NMR spectra for compounds **4**, **6**−**9**, chiral HPLC data for (−)-**4**; UV and CD spectra for **9**; experimental procedure for the preparation of (+)-manumycin A (**13**); ^1H NMR, ^{13}C NMR, UV, and CD spectra of (+)-manumycin A (**13**) (with authentic comparisons); IR spectrum and MS and HRMS data for (+)-manumycin A (**13**) (22 pages).

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