The first total synthesis of a type II manumycin antibiotic, (+)-TMC-1 A: the total syntheses of (−)-LL-C10037β and (+)-manumycin B

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Received (in Cambridge, UK) 8th January 1999, Accepted 22nd January 1999

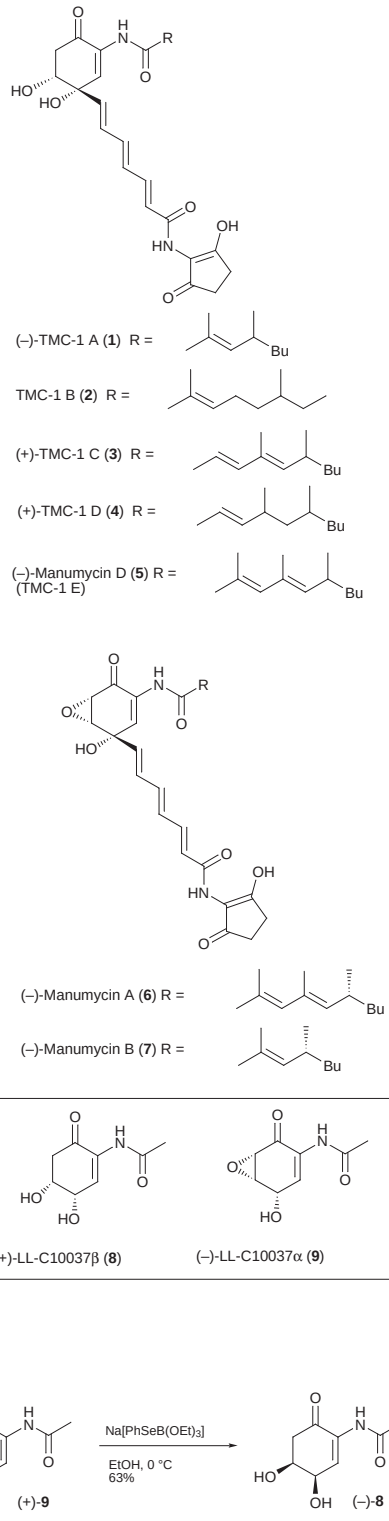
A procedure using Na[PhSeB(OEt)$_3$] is reported for conversion of the type I epoxy ketone manumycins into the type II β-hydroxyketone variants; using this procedure, (−)-LL-C10037β and (+)-TMC-1A have been prepared for the first time; the first synthesis of (+)-manumycin B, which provides full stereochemical clarification of the natural product, is also described.

The most recent additions to the manumycin family of antibiotics are the TMC-1 natural products **1**–**5** which were isolated from *streptomyces* sp. A-230 in 1996 by Kohno and co-workers and shown to be cytotoxic to a range of tumour cell lines *in vitro*.[1] This new group of compounds differ from most of the manumycin family,[2–6] *e.g.* manumycin A **6** and manumycin B **7**,† in that they possess a β-hydroxy ketone in place of the more common epoxy ketone unit. Sattler, Thiericke and Zeeck have termed[3] the β-hydroxy ketone subset, which also includes manumycin D **5**,[1,4] type II manumycins and the epoxy ketone subset type I manumycins. The same structural relationship is seen in the less complex anti-tumour natural products LL-C10037β **8** and LL-C10037α **9**.[7]

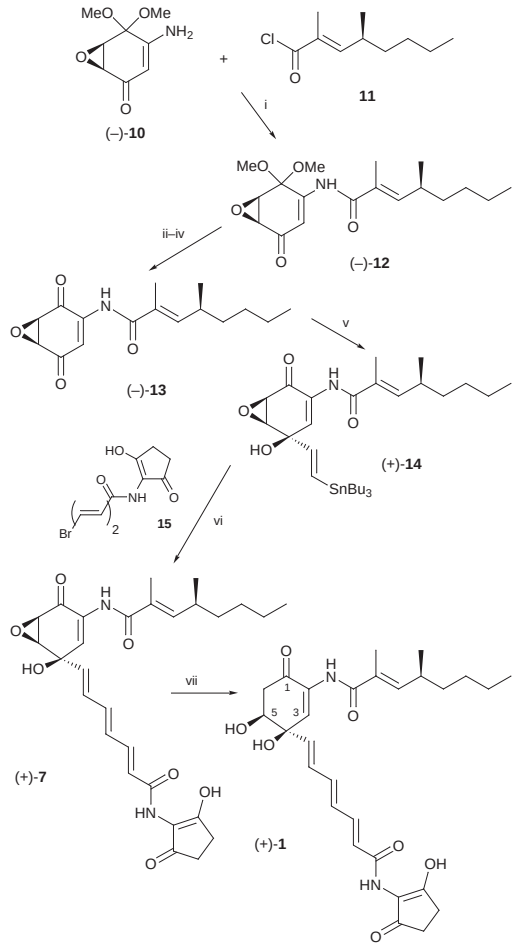
Despite their promising biological properties and interesting structures, synthetic approaches to the TMC-1 antibiotics have not been reported to date. We have recently developed a synthetic route to the type I manumycins and utilised it to prepare (+)-manumycin A[5] and other members of the family.[2,6] Regioselective reduction of the α,β-epoxy ketone group of the type I manumycins should produce the type II variants. Thus, TMC-1A **1** should be available by the reduction of manumycin B **7**.†

In order to establish the validity of this strategy, we first investigated the conversion of LL-C10037α **9** into LL-C10037β **8** as shown in Scheme 1.

The (+)-enantiomer of LL-C10037α (also known as MT 35214) was prepared using our published procedure.[6] The reagent of choice for the epoxy ketone reduction proved to be Na[PhSeB(OEt)$_3$],[8] generated *in situ* by $NaBH_4$ reduction of PhSeSePh. Model studies showed that this reagent displays exceptional tolerance towards the sensitive functional groups present within the target molecules. Treatment of (+)-**9** with a freshly prepared solution of Na[PhSeB(OEt)$_3$] in EtOH at 0 °C resulted in the formation of (−)-LL-C10037β **8**, after oxidative work-up, in an unoptimised but respectable yield of 63%.‡ Compound **8** is extremely sensitive to acid and readily undergoes dehydration–aromatisation. All spectroscopic data (IR, UV, NMR) for **8** were entirely consistent with those published[7] for the natural product. In addition, the optical rotation of (−)-**8** corresponded well to the literature data for the enantiomeric natural product {$[\alpha]_D$ −34.8 (*c* 0.9, MeOH); lit.,[7] +26.3 (*c* 0.26, MeOH)} and satisfactory HRMS data were obtained [Found: MH^+, 186.07681. $C_8H_{12}NO_4$ requires 186.07663 (1 ppm error)]. This study therefore produced the first synthesis of LL-C10037β and established the methodology for an assault on TMC-1 A. Due to the ready availability of the enantiomerically pure amine (−)-**10**, prepared utilising the Wynberg chiral phase transfer technology developed for our synthesis of (+)-manumycin A,[5,6] the (+)-enantiomer of TMC-1 A was targeted (Scheme 2).



Scheme 1



Scheme 2 *Reagents and conditions*: i, Bu^{t}OLi, THF (89%); ii, $LiEt_3BH$, THF, −78 °C (95%); iii, montmorillonite K10, CH_2Cl_2, room temp. (90%); iv, PDC, CH_2Cl_2, room temp (76%); v, (*E*)-$Bu_3SnCH{=}CHLi$, THF, −78 °C (28%); vi, [5% $PdCl_2(Ph_3P)_2$, DIBAL-H], THF–DMF, room temp. (71%); vii, Ph_2Se_2, $NaBH_4$, EtOH, 0 °C (66%).

Evans' oxazolidinone methodology was employed to prepare (*S*)-(+)-2-methylpropanal which was converted into acid chloride **11** using standard methodology.[5] Acylation of (−)-**10** in the presence of lithium *tert*-butoxide[2] afforded amide (−)-**12** in an excellent yield of 89%. Direct deprotection of the acetal was attempted but was unsuccessful due to aromatisation; amide (−)-**12** was therefore converted into the corresponding epoxy quinone (−)-**13** *via* a three step reduction–deprotection–oxidation sequence in good overall yield. The enantiomeric quinone, (+)-**13**, was obtained by Hara *et al.* by chromic acid degradation of manumycin B.[9] The NMR data and optical rotation of quinone (−)-**13** corresponded well to those of its enantiomer {*e.g.* $[\alpha]_D$ −16.5 (*c* 1.1, $CHCl_3$); lit.,[9b] +16.0 (*c* 0.2, $CHCl_3$)}.

Quinone (−)-**13** was elaborated *via* the addition of (*E*)-$Bu_3SnCH{=}CHLi$:[10] a mixture of mono- and di-adducts was obtained from which vinylstannane (+)-**14** was isolated in 28% yield after chromatography. The expected[2,5] *syn*-hydroxy epoxide structure was confirmed by the diagnostic coupling constant between H-3 and H-5 (*J* 2.7 Hz). Stille coupling between vinylstannane (+)-**14** and dienyl bromide **15**[11] proceeded efficiently (71%) to give (+)-manumycin B **7** as a bright yellow solid (mp 96–97 °C; lit.,[4] 94 °C) which displayed spectroscopic, chromatographic and polarimetric data entirely consistent with it being the enantiomer of the natural product. This is the first synthesis of manumycin B and it confirms that, as proposed,[5] it does indeed have the *syn*-hydroxy epoxide configuration illustrated (rather than the corresponding *anti*-arrangement described in the original structure elucidation[4]).

Treatment of (+)-manumycin B **7** with $Na[PhSeB(OEt)_3]$ using the reaction conditions developed in the model studies resulted in the formation of a polar, light sensitive, dark yellow solid in an isolated yield of 66%. All spectroscopic and chromatographic data proved to be consistent with the literature[1] values for the natural antibiotic, TMC-1 A [*e.g.* $\delta_C(CDCl_3$, 500 MHz) 191.8 (C-1), 132.0 (C-2), 126.2 (C-3), 73.5 (C-4), 71.8 (C-5), 40.5 (C-6); lit.,[1] ($CDCl_3$, 400 MHz) 191.8 (C-1), 132.2 (C-2), 126.0 (C-3), 73.6 (C-4), 71.9 (C-5), 40.6 (C-6)]. The optical rotation of the product {$[\alpha]_D$ +58.6 (*c* 0.5, $CHCl_3$) was consistent with it being the enantiomer of (−)-TMC-1 A **1** {lit.[1] −55.0 (*c* 0.1, $CHCl_3$)}. This study therefore confirms structure **1** for (−)-TMC-1 A and establishes the 4′*R* configuration for the side chain methyl group.

In summary, we have devised a procedure for converting the type I epoxy ketone manumycins into the type II β-hydroxy ketone variants. Using this procedure, (−)-LL-C10037β and (+)-TMC-1A have been prepared for the first time and the structures of the natural products confirmed. The first synthesis of (+)-manumycin B is also reported, thereby correcting the published stereochemical assignment and confirming the *syn*-hydroxy epoxide structure. It seems likely that manumycin B is the biosynthetic proecursor of TMC-1 A, and therefore that the chemical synthesis described above is biomimetic.

We thank the Foundation for Research Development (South Africa) and the EPSRC for research fellowships (J. J. C. G. and X. W., respectively). We are also grateful to Dr T. A. Dransfield and Miss H. Fish (University of York) for their expert assistance with mass spectrometry and NMR spectroscopy, and to Dr S.-i. Ikeda[9b] for spectra and physical data for epoxyquinone (+)-**13**.

Notes and references

† Manumycin B (ref. 4) is shown with the revised *syn*-hydroxy epoxide stereochemistry suggested in ref. 5 and the 4′*R* configuration of the side chain methyl substituent established in ref. 5(*b*).

‡ All new compounds were fully characterised spectroscopically and by HRMS/elemental analysis.

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Communication 9/00261H