The first total synthesis of (±)-colabomycin D

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Received (in Cambridge) 1st March 1999, Accepted 17th March 1999

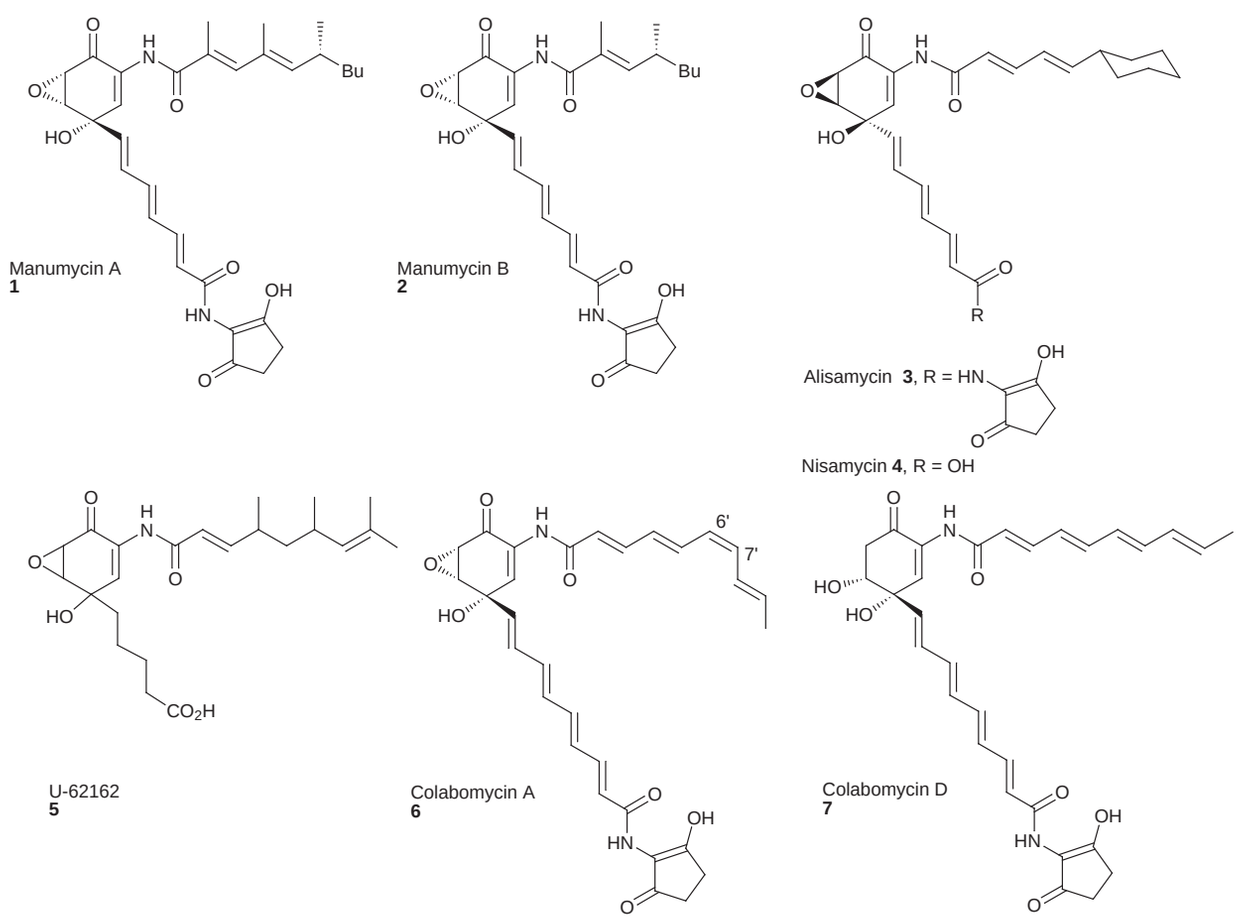
The first total synthesis of a colabomycin antibiotic, colabomycin D, in racemic form, is reported. In addition, (±)-6′*E*-colabomycin A has been prepared and valuable spectroscopic information gained to confirm the structural assignment of colabomycin A.

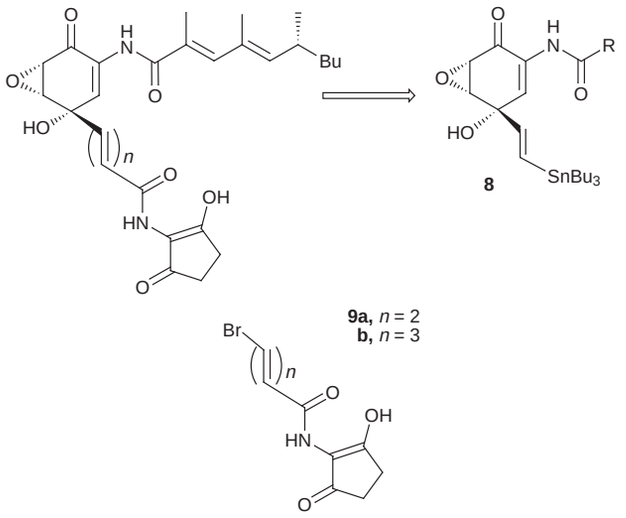
The antibiotic, antitumour and enzyme inhibitory properties of the manumycin family of natural products have stimulated considerable interest in their synthesis.[1] In structural terms, the 2-amino-3-hydroxycyclopentenone trienamide lower side-chain is common to the majority of the family members, *e.g.* manumycin A **1**,† manumycin B **2**† and alisamycin **3**. Nisamycin **4**, however, is the carboxylic acid analogue of alisamycin, and U-62162 **5** has a saturated five carbon lower side-chain. Synthetic routes have now been devised to prepare all of these compounds.[1–4] By contrast, there have been no reports of synthetic studies on colabomycin A **6**,[5] a member of the manumycin family isolated from *Streptomyces griseoflavus* (strain Tü 2880) by Zeeck's group in Göttingen. Colabomycin A **6**, an antibiotic which also possesses anti-leukaemic activity, is distinguished structurally by its tetraenamide lower side-chain and the unusual *E*,*E*,*Z*,*E*-tetraene present in the upper side-chain. Two other metabolites, colabomycin B and colabomycin C, were also isolated in the original study but their structures were not elucidated.[5] The only other related compound, which was also isolated from *Streptomyces griseoflavus*, is colabomycin D **7**.[6] Colabomycin D contains a β-hydroxy ketone in place of the more common epoxy ketone unit (a so-called[6] type II manumycin).

In addition to the synthetic challenge posed by their complex structure, colabomycins are extremely light-sensitive and are insoluble in most common organic solvents. We now report the successful syntheses of 6′*E*-colabomycin A and colabomycin D **7**.

The synthetic route adopted for this venture is based on the methodology we developed to prepare alisamycin,[1] (+)-manumycin A[2] and other members of the family[3,4] in which the lower side-chain is constructed by the Stille coupling of a vinylstannane **8** with a highly functionalised bromodiene **9a** (Scheme 1).

For the colabomycins, the same strategy necessitated the use of the corresponding bromotriene **9b**, which we have previously





Scheme 1

employed in natural product synthesis.[7] Our first target was 6′*E*-colabomycin A **14** (Scheme 2) which we intended to convert into colabomycin D **7** using Na[PhSeB(OEt)$_3$].[4,8]

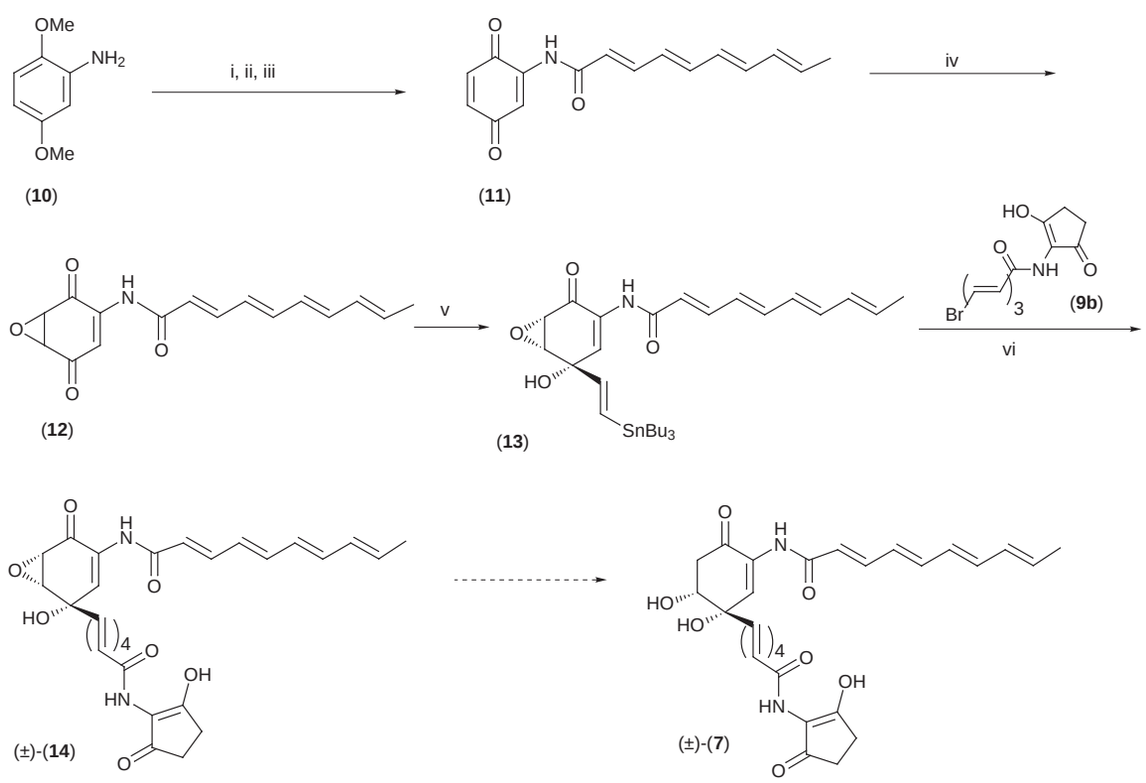
Aniline **10** was elaborated to give quinone **11** by an efficient three step procedure involving acylation with (2*E*,4*E*,6*E*,8*E*)-deca-2,4,6,8-tetraenoic acid chloride, hypervalent iodine oxidation and acetal hydrolysis.‡ Epoxidation to **12** followed by addition of *E*-Bu$_3$SnCH=CHLi[9] gave a mixture of a single mono-adduct together with di-adducts from which vinylstannane **13** was isolated in 21% yield after chromatography. The expected[1–4] *syn*-hydroxy epoxide structure was confirmed by the diagnostic coupling constant between H-3 and H-5 (*J* 2.5 Hz). All of the subsequent operations were carried out in the dark. Stille coupling between vinylstannane **13** and trienyl bromide **9b**[7] gave (±)-6′*E*-colabomycin A **14** as a yellow solid (mp > 280 °C). This compound, which was fully characterised by NMR spectroscopy,‡ is an alkene isomer of colabomycin A **6** which exhibited almost identical ^{13}C-NMR absorptions (±0.5 ppm) apart from the C4–C8 portion of the upper side-chain [**14**: δ_C (d_7-DMF, 500 MHz) 132.5 (C-4), 137.6 (C-5), 130.3 (C-6), 141.0 (C-7), 130.6 (C-8). Colabomycin A **6**:[5] δ_C (d_7-DMF, 500 MHz) 131.1 (C-4), 136.1 (C-5), 127.1 (C-6), 134.1 (C-7), 128.2 (C-8)]. It should be noted that the assignment of the 6′*Z*-stereochemistry to colabomycin A **6** was based on coupling constant data only ($J_{6',7'}$ = 12.6 Hz).§ Given that all of the other manumycin analogues, including colabomycin D **7**, only contain *trans*-disubstituted alkenes in their upper side chains, we felt that there was a possibility that colabomycin A actually possessed the all *trans*-alkenyl structure **14.** The synthesis of **14** rules out that possibility and the assignment of structure **6** to colabomycin A seems secure.

Our initial plan was to treat keto epoxide **14** with Na[PhSeB(OEt)$_3$],[4,8] generated *in situ* by sodium borohydride reduction of diphenyl diselenide, in order to effect the reduction to colabomycin D **7**. Unfortunately, keto epoxide **14** proved to be extremely insoluble in a range of organic solvents and the reduction reaction could not be accomplished efficiently. We therefore adopted the alternative strategy, shown in Scheme 3, in which epoxide ring opening was carried out prior to the Stille coupling.

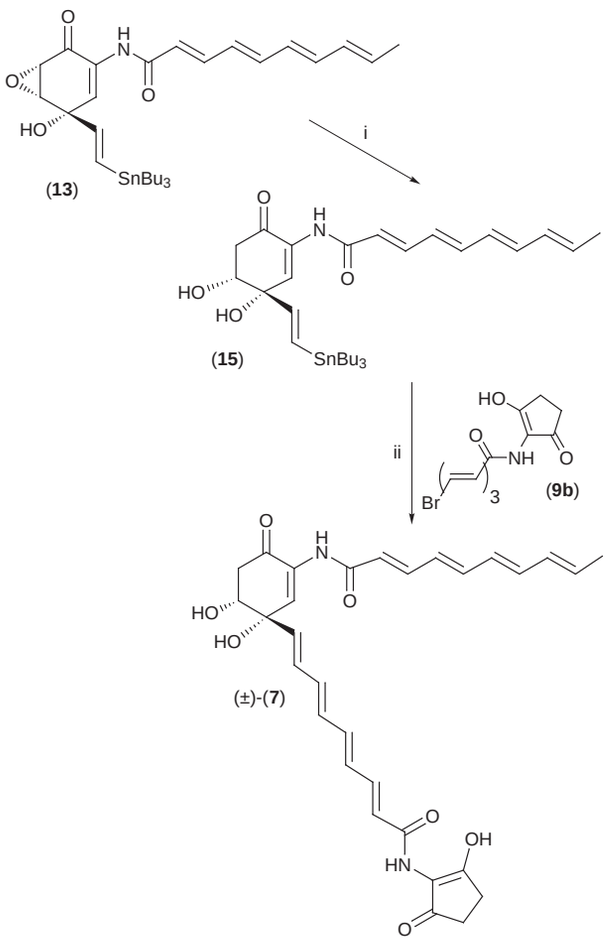
Thus, treatment of keto epoxide **13** with Na[PhSeB(OEt)$_3$], generated β-hydroxy ketone **15** in 63% yield. Stille coupling between **15** and **9b** (with exclusion of light during the reaction and work-up) then proceeded smoothly to give colabomycin D **7**, in racemic form. The authenticity of the synthetic sample was confirmed by comparison of a number of physical measurements with the published[6] values [*e.g.* δ_C (C_5D_5N, 500 MHz) 193.3 (C-1), 133.0 (C-2), 130.4 (C-3), 74.4 (C-4), 73.0 (C-5), 42.8 (C-6); these values are identical to those published[6]]. In summary, we have completed the first synthesis of colabomycin D **7**, in racemic form, thereby confirming its structure, and have also prepared (±)-6′*E*-colabomycin A **14**. We are currently applying the methodology described herein to complete the synthesis of (+)-colabomycin A.

Acknowledgements

We thank the EPSRC and the Foundation for Research Development (South Africa) for research fellowships (X. W. and J. J. C. G., respectively). We are also grateful to Dr T. A.



Scheme 2 *Reagents and conditions*: (i) $C_9H_{11}COCl$, py, DMAP; (ii) $PhI(OAc)_2$, MeOH; (iii) Amberlyst 15 (42% over 3 steps); (iv) ^{t}BuOOH, DBU, EtOAc, 30 s (60%); (v) *E*-Bu$_3$SnCH=CHLi, THF, −78 °C (21%); (vi) [5% $PdCl_2(Ph_3P)_2$, DIBAL-H], THF–DMF, rt (80%).



Scheme 3 *Reagents and conditions*: (i) $Na[PhSeB(OEt)_3]$, EtOH, 0 °C (63%); (ii) [5% $PdCl_2(Ph_3P)_2$, DIBAL-H], THF–DMF, rt (54%).

Dransfield and Miss H. Fish (University of York) for their expert assistance with mass spectrometry and NMR spectroscopy, respectively, and to Dr I. Sattler and Professor A. Zeeck for unpublished spectroscopic data for colabomycin D.

Notes and references

† Manumycin A and manumycin B are shown with the revised *syn*-hydroxy epoxide stereochemistry (see references 2 and 4).
‡ All new compounds were fully characterised spectroscopically and by HRMS/elemental analysis with the exception of (±)-6′*E*-colabomycin A **14** for which a weak $(M + 1)^+$ ion was observed by FAB-MS but an accurate mass could not be obtained.
§ Unfortunately, even at 500 MHz, the corresponding $J_{6',7'}$ coupling constant for **14** was obscured by adjacent signals.

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Communication 9/01618J