Synthetic Studies Towards the B,C,D,E Fragment of Antibiotic CP44, 161

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Abstract: The synthesis of polyethers **32** and **33** from tricyclic bis-spiroacetal aldehyde **27** and *E*-bromide **7** are described. A key step in the synthetic strategy involved the oxidative cyclisation of a bicyclic hydroxyspiroacetal **22a,b** to a *cis* bis-spiroacetal unit, which resulted in preferential formation of *cis* aldehyde **27**. A Barbier reacton of bromide **7** and tricyclic aldehyde **27** then afforded *erythro* alcohol **28** which after epoxidation and acid catalysed cyclisation completed the synthesis of polyethers **32** and **33** providing an effective framework on which to synthesise the B,C,D and E rings of antibiotic CP44,161 **1**.

Key words: bis-spiroacetal, polyether, oxidative cyclisation

Antibiotic CP44,161 **1**[1] is a polyether antibiotic extracted from three strains of a *Dactylsporangiumin* species which contains a complex 1,6,8-trioxadispiro[4.1.5.3]pentadec-13-ene moiety (like salinomycin **2**[2]) and an A ring which is similar to that found in lasalocid A.[3] Whilst several synthetic approaches to salinomycin **2** have been published,[4-10] no chemical synthesis of antibiotic CP44,161 **1** has been reported. Like salinomycin **2**, antibiotic CP44,161 **1** has been reported to exhibit activity against coccidiosis in poultry and enhance feed utilisation in ruminants.[11]

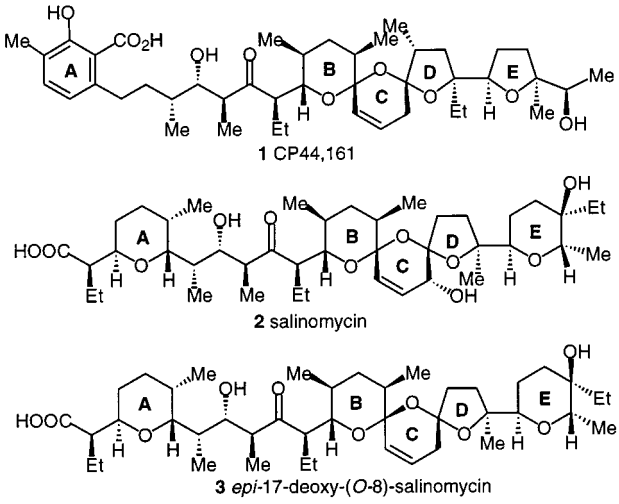
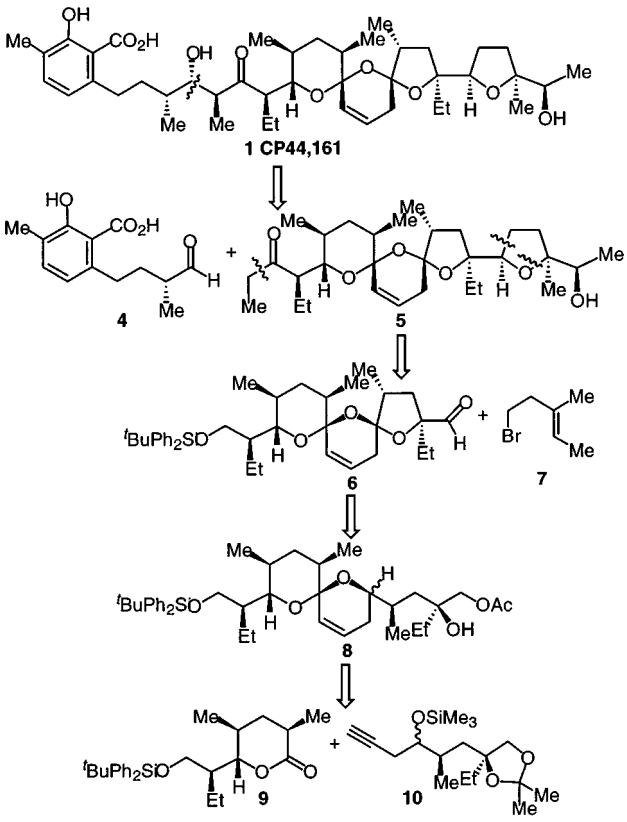


Figure 1

Our synthetic approach to antibiotic CP44,161 **1** focuses on the addition of the A and E rings after construction of the central bis-spiroacetal unit whilst related syntheses of salinomycin **2** have involved late assembly of ring C after appending the D,E rings to ring B.

With these thoughts in mind, a synthesis of antibiotic CP44,161 **1** was proposed making use of an initial aldol disconnection to afford aldehyde **4** and ketone **5** followed by a second disconnection of ketone **5** to aldehyde **6** and bromide **7** (Scheme 1).



Scheme 1

The synthesis of aldehyde **4** has been previously reported by Kishi and Ireland *et al*.[12,13] whilst construction of tricyclic bis-spiroacetal aldehyde **6** was anticipated to occur by oxidative cyclisation of bicyclic hydroxyspiroketal **8** following methodology established in synthetic approaches to the bis-spiroacetal core in *epi*-17-deoxy-(*O*-8)-salinomycin **3**.[14,15] Further disconnection of bicyclic hydroxyspiroketal **8** required the synthesis of lactone **9** and acetylene **10**.

The synthesis of lactone **9** has been previously reported[10,14] hence initial construction of acetylene **10** and bromide **7** was required.

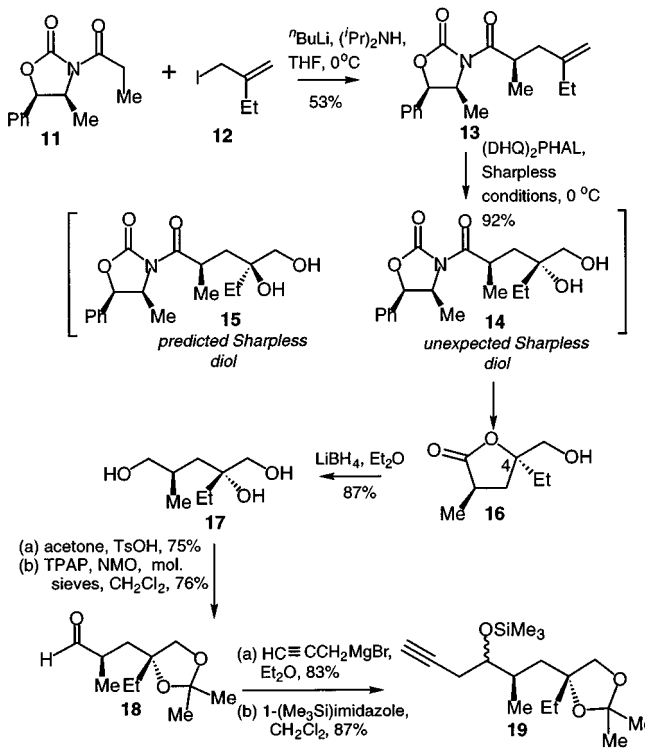
Synthesis of Acetylene 10 (Scheme 2) and Bromide 7. The synthesis of acetylene **10** commenced with the alkylation of propanoyloxazolidinone **11** with allyl iodide **12**[16] to form alkene **13**. Based on the Sharpless mnemonic, asymmetric dihydroxylation[17] of the terminal olefin using potassium osmate and $(DHQ)_2PHAL$, was expected to afford diol **15**, however, in the final stages of this work, X-ray diffraction studies subsequently revealed that lactone **16**, produced by cyclisation of the unexpected diol **14**, was in fact the major product. Lactone **16** contains the incorrect stereochemistry at C-4 to that required for the formation of acetylene **10**. It is unclear why the facial selectivity of dihydroquinine ligands did not follow the Sharpless mnemonic, however, the presence of the chiral oxazolidinone moiety may have been a contributing factor. The development of methodology to reverse this stereochemical outcome in order to obtain the correct diol **15** is currently being investigated. Work reported herein provides methodology to produce a fragment resembling the B,C,D and E rings of antibiotic CP44,161 using acetylene **19**.

The synthesis of acetylene **19** was completed by reduction of lactone **16** with lithium borohydride to afford triol **17** which, after protection of the 1,2-diol as an acetonide, was oxidised at the remaining primary alcohol to afford aldehyde **18**. Grignard reaction of aldehyde **18** with propargylmagnesium bromide resulted in the formation of an alcohol which, after protection as a silyl ether afforded acetylene **19** as a 1:1 mixture of diastereomers.

Synthesis of Aldehyde 27 (Scheme 3). With acetylene **19** and lactone **9** in hand, assembly of the bis-spiroacetal core was effected based on related work.[15] Addition of the lithium acetylide derived from acetylene **19** to lactone **9** followed by treatment with acidic methanol afforded acetal **20**. After protection of the primary hydroxyl group as an acetate **21**, partial hydrogenation to a *cis* olefin followed by acid catalysed cyclisation resulted in a 1:1 mixture of spiroacetals **22a** and **22b**.

Spiroacetals **22a** and **22b** were treated with iodobenzene diacetate and iodine[18] to afford a 1:3.3 mixture of tricyclic bis-spiroacetals **23** and **24**. The preference for *cis* bis-spiroacetal **24** in this cyclisation reaction can be attributed to the presence of the C-4 methyl group, which causes unfavourable steric interactions upon formation of the minor *trans* bis-spiroacetal **23**. *trans* Bis-spiroacetal **23** therefore undergoes rapid epimerisation at the allylic spirocentre to *cis* bis-spiroacetal **25**. The presence of the C-4 methyl group exhibited a marked effect on the stereochemical outcome of the oxidative cyclisation in that earlier studies on the oxidative cyclisation of spiroacetals which lack this methyl group provided the *trans* isomer as the major product.

Hydrolysis of the bis-spiroacetal acetate **24** afforded alcohol **26** which upon oxidation using tetrapropylammonium perruthenate afforded aldehyde **27**.



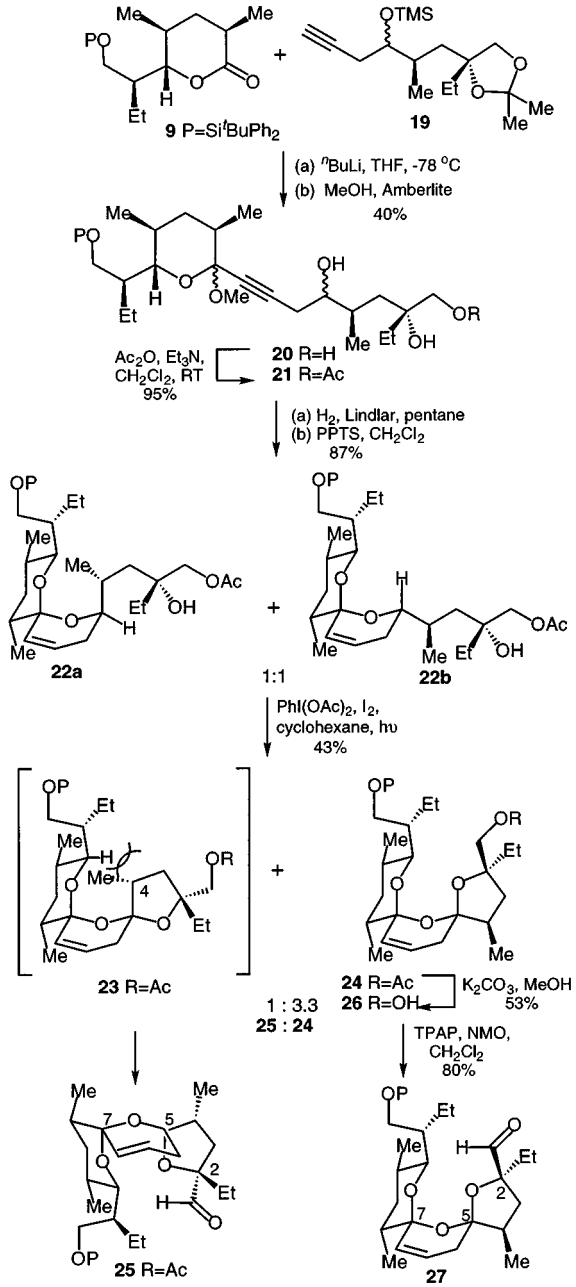
Scheme 2

The major aldehyde **27** prepared in Scheme 3 is epimeric at C-2, C-5 and C-7 to that required for the bis-spiroacetal portion of the right hand fragment **5** of antibiotic CP44,161 **1** while acetate **25** has the correct stereochemistry for the bis-spiroacetal moiety but is epimeric at C-2. Conversion of the epimeric bis-spiroacetal centres (C-5, C-7) in aldehyde **27** to the naturally occurring *cis* bis-spiroacetal conformation present in acetate **25** (which is also found in salinomycin **2**) may be achieved by acid catalysed equilibration at a later stage in the synthesis as demonstrated by Kocienski *et al.*[10] in the synthesis of salinomycin **2**. In order to obtain the correct stereochemistry at C-2 however, a synthesis of acetylene **10** is required.

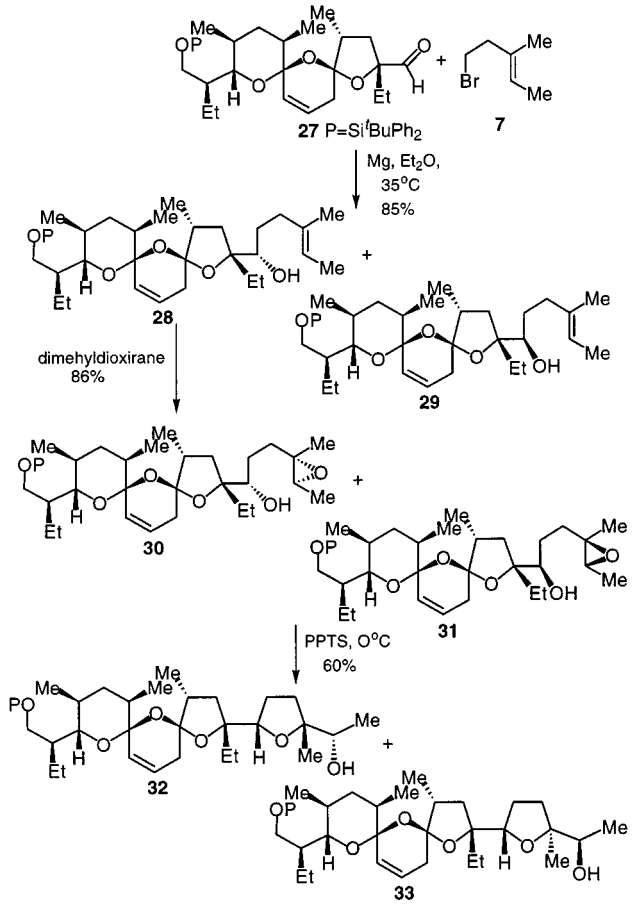
Synthesis of Bromide 7. Bromide **7** was prepared in six steps from 2-acetyl-γ-butyrolactone following Julia olefination methodology previously used in the synthesis of a related bromide.[19]

Synthesis of Polyether 32 - a Fragment Resembling the B,C,D and E rings of Antibiotic CP44,161 1 (Scheme 4).

Applying methodology established in synthetic approaches to the D and E rings of salinomycin **2**,[19] the union of bromide **7** and aldehyde **27** using a Barbier reaction resulted in the successful synthesis of alcohols **28** and **29** as a 4.7:1 mixture of *erythro* and *threo* isomers in 85% yield. After separation of *erythro* alcohol **28**, treatment with dimethyl dioxirane resulted in a 1:1 mixture of epoxides **30** and **31** which, after treatment with a catalytic quantity of PPTS cyclised in 60% overall yield to afford polyethers **32** and **33** which were separated by HPLC.



Scheme 3



Scheme 4

In conclusion, polyethers **32** and **33** were synthesised from aldehyde **27** and bromide **7** using the methodology described above. Noteworthy features of this synthetic strategy include the oxidative cyclisation of a bicyclic hydroxyspiroacetal **22a,b** to a bis-spiroacetal unit which provides *cis* aldehyde **27** preferentially; the addition of a bis-homoallylic bromide **7** to a neopentylic like aldehyde **27**; and acid catalysed cyclisation of a γ-hydroxyepoxide to a disubstituted tetrahydrofuran in the presence of a sensitive bis-spiroacetal. The work reported herein provides a framework on which to synthesise the B,C,D and E rings of antibiotic CP44,161 **1** after synthesising diol **15** which provides access to aldehyde **6**.

Acknowledgement

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