Convergent Synthesis of the Spiroacetal Fragment of Milbemycin β_1

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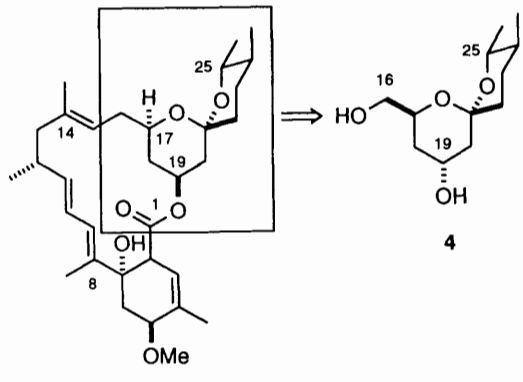
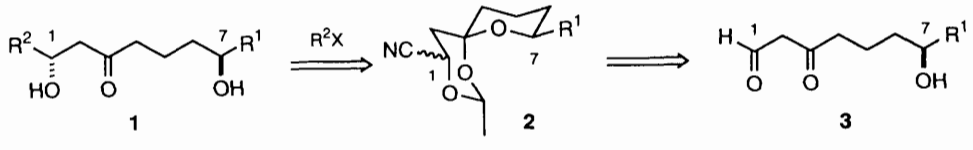
Milbemycin spiroacetal **4** was prepared from (4*S*,5*R*)-4,5-dimethylpentan-5-olide **5** and (*R*)-1-(benzyloxymethyl)oxirane by alkylation and stereoselective reductive decyanation of the intermediate spiroacetal cyanohydrin **7**.

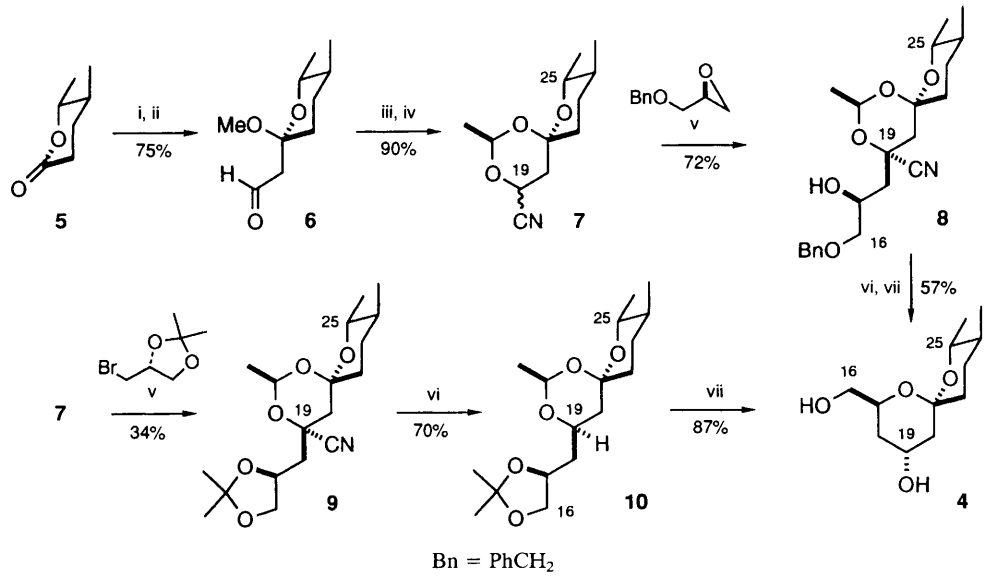
Interest in the synthesis of stereochemically complex polyol chains continues to stimulate the development of new strategies and methods for polyol chain synthesis. In work directed towards the total synthesis of a polyene macrolide antibiotic, our strategy called for coupling two fragments (Scheme 1) by alkylation and reductive decyanation of a cyanohydrin derived from β-keto aldehyde **3**. We have shown that similar alkylation and reductive decyanation protocols for convergent polyol chain syntheses can be very effective when an adjacent secondary alcohol is present to control the configuration at the newly formed stereogenic centre.[1] However, aldehyde **3** has an adjacent ketone rather than an alcohol, and one must look elsewhere for stereochemical induction. We considered that a remote secondary alcohol might be used to induce stereochemistry at the aldehyde centre by relaying stereochemical information through a



Milbemycin β_1



Scheme 1



Scheme 2 *Reagents and conditions*: i, AllylMgBr, then $CeCl_3$, $CH(MeO)_3$; ii, O_3, CH_2Cl_2, −78 °C, then Ph_3P; iii, Me_3SiCN, cat. KCN (18-crown-6), then MeOH, Dowex W50-1X; iv, MeCHO, camphorsulfonic acid (CSA), CH_2Cl_2; v, Li(pyrrolidide), tetrahydrofuran (THF), −78 °C, then dimethylpropyleneurea [DMPU; 1,3-dimethyl-3,4,5,6-tetrahydropyrimidin-2(1*H*)-one] and alkylating agent; vi, Li, NH_3, −78 °C; vii, MeOH, Dowex W50-1X

spiroacetal ring system **2**, and now report the successful development of this strategy in a short synthesis of a spiroacetal precursor of milbemycin β_1.

Milbemycins and avermectins have great potential as broad spectrum antiparasitic agents and have, as a result, been popular targets for total synthesis.[2] Spiroacetal fragments are key intermediates in syntheses of milbemycins and avermectins, and they have been prepared by a number of research groups.[2] Based on a standard chain elaboration[2] and Mitsunobu macrolactonization,[3] we identified spiroacetal diol **4** as a key intermediate for the synthesis of milbemycin β_1.

We began our synthesis of spiroacetal **4** with optially pure (4*S*,5*R*)-4,5-dimethylpentan-5-olide **5** which was prepared from (+)-β-citronellene by the method of Barrett.[3] Treatment of the lactone **5** (Scheme 2) with allylmagnesium bromide followed by trimethyl orthoformate and cerium trichloride gave the expected methyl acetal,[5] and subsequent ozonolysis gave the protected β-keto aldehyde **6** in 75% overall yield. The corresponding cyanohydrin was prepared by treatment with Me_3SiCN and catalytic KCN–18-crown-6 complex followed by methanolysis of the trimethylsilyl ether. Synthesis of the spiroacetal ring system was accomplished by treating the cyanohydrin acetal with acetaldehyde and catalytic CSA for 2 days in dry CH_2Cl_2. A small amount of isomeric material was reequilibrated to give the two major cyanohydrin spiroacetals **7** in a combined yield of 90%. We found in a model system that acetone was not incorporated into the spiroacetal structure, presumably owing to excessive steric strain. Formaldehyde was incorporated into a similar spiroacetal structure, but difficulties expected in the deprotection led to the selection of acetaldehyde.

Spiroacetal cyanohydrin **7** could in theory be coupled with an electrophile incorporating the remaining carbon skeleton of milbemycin β_1, but our immediate goal was the synthesis of spiroacetal **4**. Deprotonation of spiroacetal cyanohydrin **7** with lithium pyrrolidide in THF at −70 °C and alkylation with (*R*)-(2,2-dimethyl-1,3-dioxolan-4-yl)methyl bromide gave the coupled product **9** as a single isomer in 34% yield. The disappointing yield was due to the low reactivity of the β-alkoxy alkyl bromide. Reductive decyanation at an anomeric position is believed to proceed *via* an axial radical, and results in the stereoselective introduction of an axial hydrogen.[6] The C-25 stereogenic centre in cyanohydrin **9** locks the spiroacetal rings into a conformation that defines the C-19 axial and equatorial positions. Reductive decyanation gave spiroacetal **10** as a single isomer in 70% yield with the expected C-19 axial hydrogen configuration. Deprotection gave an 87% yield of the desired spiroacetal **4** which had the same spectral properties and optical rotation as previously reported.[4] The low yield in the alkylation of cyanohydrin **7** could be avoided by using commercially available (*R*)-1-(benzyloxymethyl)oxirane. Alkylation with the oxirane gave hydroxy cyanohydrin **8** in 72% yield. Treatment of cyanohydrin **8** with Li in NH_3 led to stereoselective removal of the cyano group with concomitant loss of the benzyl ether, and acidic workup gave spiroacetal **4** as a single isomer in 57% yield. Milbemycin spiroacetal **4** was thus prepared in six steps and 28% overall yield from the lactone **5**, and the remote stereochemical induction strategy developed here will be applied to the convergent synthesis of other natural products.

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