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Synthesis of a C-15/C-27 Segment of Venturicidine

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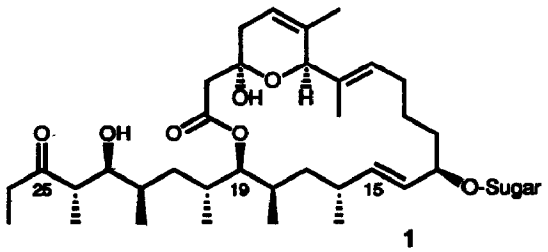
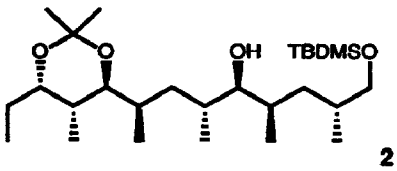
Abstract: *The C-15/C-27 segment of venturicidine contains a 1,3,5,n-anti-methylated alkyl chain, which resembles syndiotactic polypropylene and should therefore favor an extended conformation. A synthetic scheme is presented, by which such structures are generated in a cycle of four steps per three stereogenic centers. This allowed the synthesis of the above mentioned venturicidine fragment in 15 steps from propionaldehyde.*

The venturicidines A and B are antifungal antibiotics isolated in the sixties.[1,2] Their structure, including the absolute configuration, was elucidated by X-ray crystallography.[2,3] Several congeners of venturicidine have since been isolated.[4] Despite the fact that the venturicidines were among the first polyketide derived macrolides of known constitution and configuration, it was only in the late eighties that the first synthesis of the venturicidine aglycon was reported.[5] More recently, a second synthesis of the aglycon has been completed.[6]



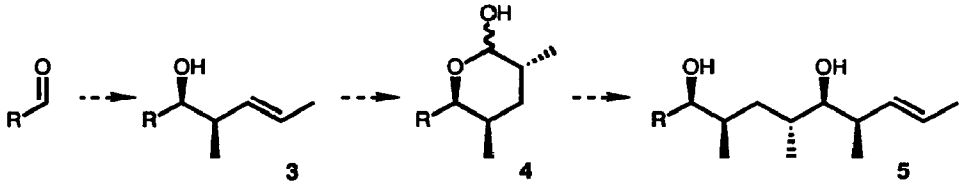
1



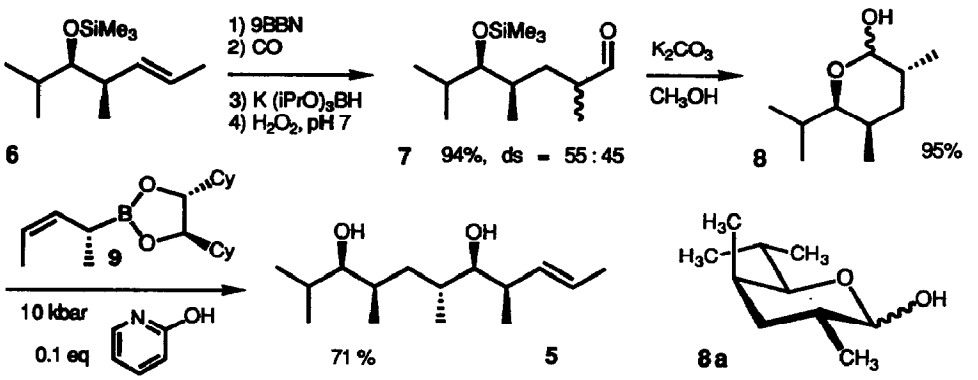
2

Our interest in the venturicidine aglycon arose from the peculiar 1,3,5-*anti*-methyl-substitution pattern in the C-15/C-27 segment, which should foster the population of an extended conformation,[7] as is indeed found in the crystal structure.[3] For more detailed conformational studies, we were interested in a concise approach to structures of this type. We thus developed a stereoselective route to 1,3,5,n-*anti*-methylated alkane chains based on the allylboration reaction with chiral pentenyl boronates.[8] For other routes to 1,3,5-*anti*-methylsubstituted alkane chains see ref. [9]. We tested our route in a synthesis of the known [5] building block **2**, comprising the C-15/C-27 segment of the venturicidines. This resulted in a considerable decrease in the number of steps required, cf. ref. [5,6,10].

The plan was to use a two stage homologation sequence, by which an aldehyde is first converted into a homoallylic alcohol **3**. By addition of a one carbon moiety, the latter should be converted to the tetrahydropyranol **4**. Simple homoallylic alcohols have been homologated to δ-lactols by hydroformylation [11] or by hydroboration based techniques.[12] When applied to **3**, problems of regio- as well as stereoselectivity arise.

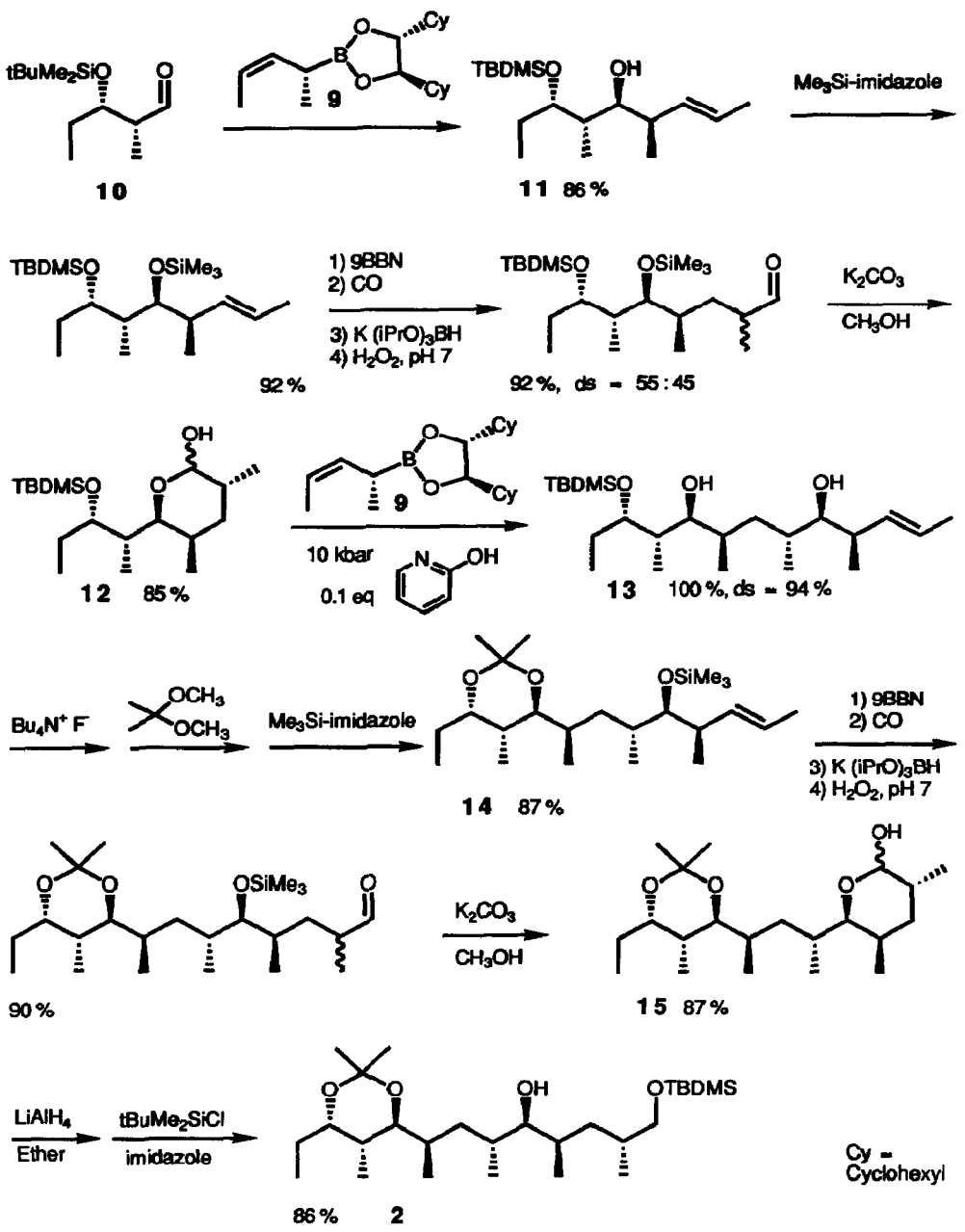


Hydroboration of **6** with 9-BBN was found to be fully regioselective but not at all stereoselective. Thus, when the hydroboration/homologation sequence developed by H.C. Brown [13] was applied to **6**, a 1:1 diastereomeric mixture of the aldehydes **7** (90-95%) was obtained. This lack of stereoselectivity is not detrimental, as epimerisation is possible at the stage of the δ-lactol.[14] Thus, treatment of **7** with K_2CO_3 in methanol resulted in desilylation,[15] lactolisation and epimerisation, such that the C-2 equatorial epimer was obtained selectively as an anomeric mixture. Key is the C-5-isopropyl group, which anchors the chair conformation, and the axial C-4 methyl group, which forces the C-2 methyl group into the equatorial position, cf. **8a**.



The epimerisation reaction shows that **8** is an equilibrium with the corresponding aldehyde. We hoped therefore, that the stationary concentration of the aldehyde would be high enough to allow a reaction with the pentenylboronate **9**. In fact, allylboration of a γ-lactol has been reported recently.[16] Nevertheless, the reactivity of both partners, **8** and **9**, was so low, that 10 kbar of pressure had to be applied to realize a 53% yield of **5**. If the equilibration of **8** with the aldehyde were rate limiting, this step could be accelerated by addition of a catalyst. Indeed, reaction of **8** and **9** at 10 kbar in the presence of 0.1 equivalent of 2-hydroxypyridine [17] increased the yield of **5** to 71%. This completes one cycle of the four step chain elaboration (**3** → **5**) protocol in which three new stereocenters are generated.

This technique has then been applied to the synthesis of the venturicidine-segment **2**: The starting point was the aldehyde **10**, obtained in three steps from propionaldehyde and the enantiomeric pentenyl boronate ent-**9**, as described in ref. [18]. Reaction of the aldehyde **10** with the pentenylboronate **9** furnished 86% of the homoallylic alcohol **11**. Silylation (92%), hydroboration/carbonylation (92%), followed by selective desilylation/epimerisation could be accomplished, as described above, to furnish 85% of the lactol **12** as an anomeric mixture.



The next chain extension to give **13** proceeded readily at 10 kbar under hydroxypyridine catalysis. Some protective group interchanges were necessary to introduce the acetonide function present in **2**. Starting from **14**, the next cycle of the chain extension protocol could be started. This led, in two steps, to the lactol **15**. With all stereocenters in place, the synthesis of **2** was completed by reduction and selective silylation of the primary alcohol function. The ^{1}H-NMR and mass spectra of the material obtained were identical to spectra

kindly provided by Dr. Akita (Toho-University, Chiba, Japan). The synthesis of **2** was thus realized in 12 steps from **10**, in an overall yield of 36%. This demonstrated the efficiency and reliability of our new protocol to generate 1,3,5,n-*anti*-methylated alkyl chains.

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