Efficient Synthesis of a Hexasubstituted Aromatic Ring via an Intramolecular Michael-Aldol Process: Preparation of a Late Tricyclic Intermediate for the Synthesis of Pseudopterosin A

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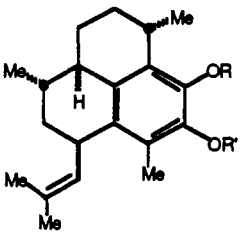
Isolation of the pseudopterosins A-L and secopseudopterosins A-D, marine metabolites from Caribbean sea whips of the genus *Pseudopterogorgia*, was described recently.[2] These compounds have been reported to exhibit potent antiinflammatory and analgesic activity. Among them, pseudopterosin A (**1**) and pseudopterosin E (**2**) have shown the most promise as therapeutic

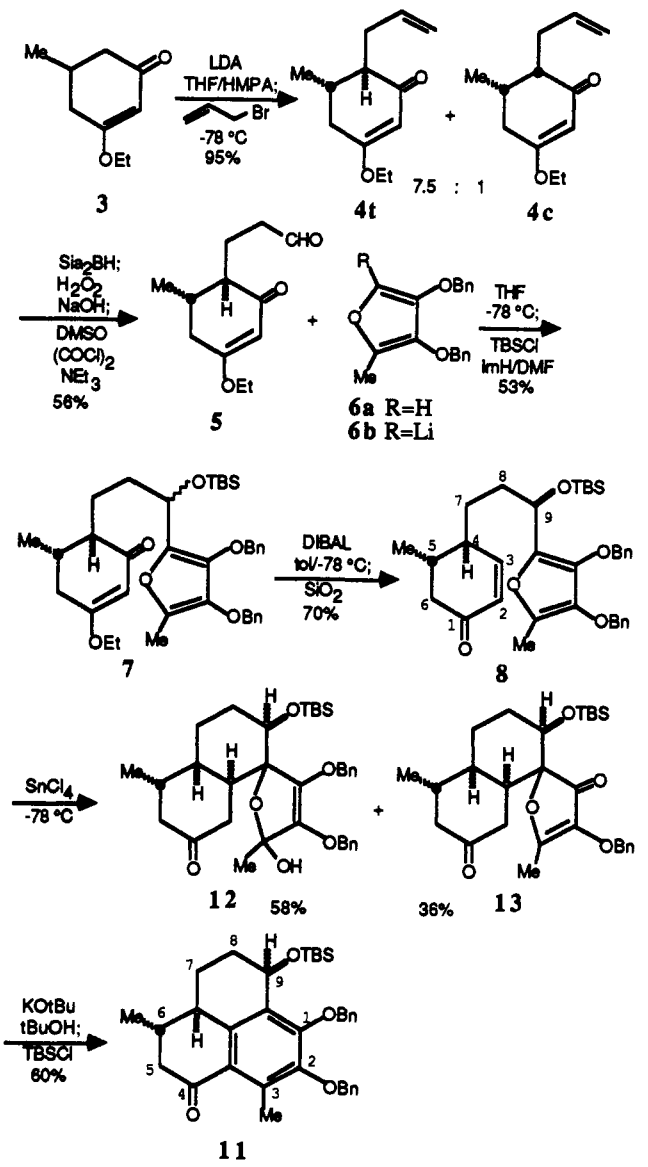


1 R = β-D-xylose R' = H
2 R = H R' = α-L-fucose

agents for inflammation, each exceeding the potency of the drug industry standard indomethacin.[2a,d,e] Their biological activity as well as their interesting structure, containing a substituted phenalene unit (with a hexasubstituted aromatic ring), has spurred interest in their synthesis, with two total syntheses of pseudopterosin A,[3,4] and several other approaches to the tricyclic pseudopterosin skeleton having been reported.[5] We report here an unusual approach to the substituted phenalene ring system, in which a two-step process for hexasubstituted aromatic ring formation is used, namely an intramolecular Michael addition of an electron-rich furan onto a cyclohexenone followed by an aldol condensation to generate efficiently a late tricyclic intermediate (**11**) for the synthesis of pseudopterosin A (**1**).

Our original idea was to carry out an intramolecular Diels-Alder cycloaddition of a properly functionalized 3-(2-furanyl)-propylcyclohexenone (e.g., **8**) which should proceed to give the oxanorbornene product from which water should be easily lost to generate the aromatic system. We prepared the desired substrate **8** in a straightforward manner as follows (Scheme I).

Scheme I



Alkylation of the readily available 5-methyl-3-ethoxycyclohexenone **3**[6] under the normal conditions[7] with allyl bromide afforded a 7.5:1 mixture of diastereomers favoring the desired trans product **4t** in 95% yield. Hydroboration-oxidation of the alkene with disiamylborane followed by Swern oxidation of the primary alcohol furnished the aldehyde **5** in 56% yield. The lithium anion **6b** was prepared from the known furan **6a**[8] by treatment with *n*-butyllithium at 0 °C, and then the aldehyde **5** was added in THF at −78 °C to give the secondary alcohol as a 1:1 diastereomeric mixture, which was silylated to give **7**. Conversion of the β-ethoxyenone into the transposed enone was accomplished by careful reduction with DIBAL at −78 °C followed by elimination on silica gel to give the desired enone **8** in 70% yield. It is remarkable that in this process the benzylic center α to the furan ring (the carbon bearing the silyloxy group) has undergone an equilibration to give only one diastereomeric silyl ether.[9] We believe that under the slightly acidic conditions, an allylic carbocation formed by dehydration of the allylic alcohol can be

(1) UCLA McCoy Award recipient, 1991-92; UCLA Hanson-Dow Teaching Award recipient, 1992.

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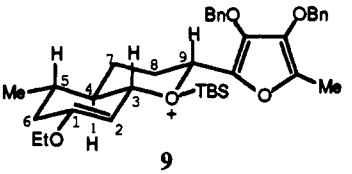
attacked by the silyl ether to give a bicyclic intermediate, which may equilibrate via a stabilized furfuryl carbocation, with subsequent hydrolysis giving the enone **8**.[10] The preference of the furan to be equatorial in **9** results in overall epimerization of



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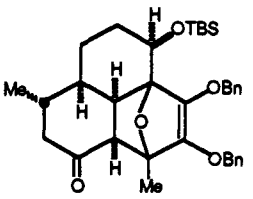

10

the C_9 center. With the enone **8** in hand, we attempted to effect the intramolecular Diels–Alder but were unable to isolate the initial adduct, the oxanorbornene **10**, or the dehydrated product, the desired phenalene **11**, under both thermal and Lewis acid-catalyzed conditions. The major products of the acid-catalyzed reactions were the novel intramolecular Michael adducts **12** and **13**. Thus treatment of the furyl enone **8** with stannic chloride in toluene at −78 °C for 1 h gave the hemiacetal **12** in 58% isolated yield accompanied by the elimination product **13** in 36% yield. Presumably the methyl substituent on the furyl ring is too sterically hindering to allow the concerted Diels–Alder reaction to occur easily, and a Lewis acid-catalyzed Michael addition of the very electron-rich furan occurs instead.[11] Addition of water in the workup produces the hemiacetal and the enone. However, the hemiacetal **12** is perfectly set up for conversion to the desired phenalene **11** if an aldol reaction followed by elimination of 2 equiv of water could be effected. Treatment of **12** with potassium *tert*-butoxide in *tert*-butyl alcohol gave a mixture of the desired product **11** and its desilylated analogue, which was subjected to silylation to give the desired phenalene **11** in an overall yield of 60%.[12]

Thus we have developed a new route to substituted phenalenes via a Michael-aldol sequence which permitted the preparation of the tricyclic intermediate **11** for the synthesis of pseudopterosin A **1** in only six steps. Further studies in this area are in progress.

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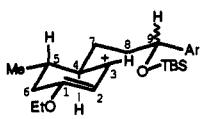
(9) The characteristic doubling of peaks in the ^1H and the ^{13}C NMR spectra similar to that seen for the enol ether **7** was not observed for these compounds, thus clearly establishing the presence of only one diastereomer. The assignment of the relative stereochemistry was made on the basis of the coupling constants for H_9 in the ^1H NMR spectra of ketone **11** and enone **12** (**11**: $J_{8a,9}$ = 11.8 Hz, $J_{8e,9}$ = 4.4 Hz; **12**: $J_{8a,9}$ = 11.5 Hz, $J_{8e,9}$ = 5.0 Hz), which place the silyl ether function in an equatorial position. This unanticipated epimerization occurred directly from the enol ether **7** upon treatment with DIBAL and also upon treatment of the intermediate allylic alcohol with *p*-toluenesulfonic acid. The allylic alcohol was clearly an epimeric mixture at C_9, since its ^1H NMR spectrum showed the characteristic doubling of peaks due to two diastereomers.

(10) We postulate that the allylic alcohol formed from **7** affords the cation **i** which is internally trapped by the silyl ether to give the diastereomeric mixture of bicyclic cations **ii**. This mixture can then be equilibrated to the more stable **9**, having the furyl group equatorial via the very stable benzylic cation **iii** in which the very electron-rich furan ring stabilizes the secondary cation. Final opening of the bicyclic ring by the ethoxyalkene and hydrolysis generates **8**.



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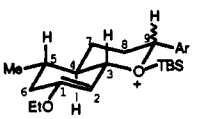

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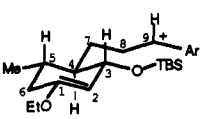
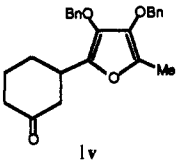


iii

(11) It is possible that the Michael addition of the electron-rich furan is just much faster than the Diels–Alder reaction or that the Diels–Alder adduct **10** does indeed form but is rapidly opened to relieve ring strain by a retro aldol-type reaction to give, after hydrolysis, the observed products **12** and **13**. All attempts to trap **10**, e.g., by reduction with borohydride, failed to show any evidence for this adduct. Other Michael adducts could also be easily prepared by this route, e.g., compound **iv** was formed when a solution of the furan **6a** and cyclohexenone was treated with $MeAlCl_2$.



iv

(12) We also tried to convert the enone **13** to the tricyclic aromatic ketone analogous to **11** (with OH at the 1-position instead of OBn), hoping that under basic conditions an intramolecular Michael addition would occur followed by elimination of the bridging oxygen atom. However, treatment of enone **13** with potassium *tert*-butoxide in *tert*-butyl alcohol did not provide any of the desired aromatic ketone. TLC established the formation of a new compound, which reverted back to **13** upon workup and isolation. This compound may be the corresponding Michael adduct, which undergoes retro-Michael reaction to break the more labile C–C bond in favor of β-elimination of the bridging oxygen. Further experiments to convert **13** to analogues of **11** are underway.