Pergamon

Tetrahedron Letters, Vol. 36, No. 12, pp. 1989-1992, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)00209-X

An Efficient Dipolar-Cycloaddition Route to the Pterosin Family of Sesquiterpenes

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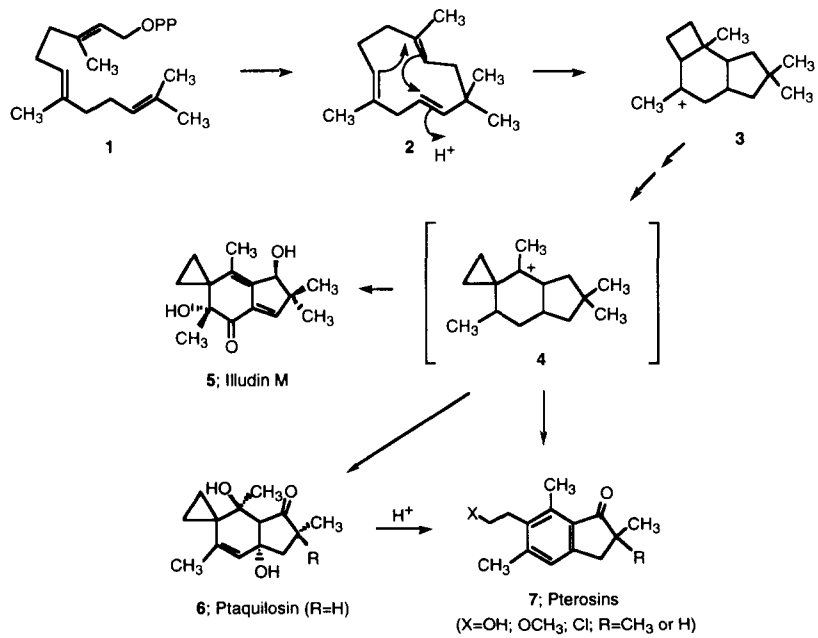
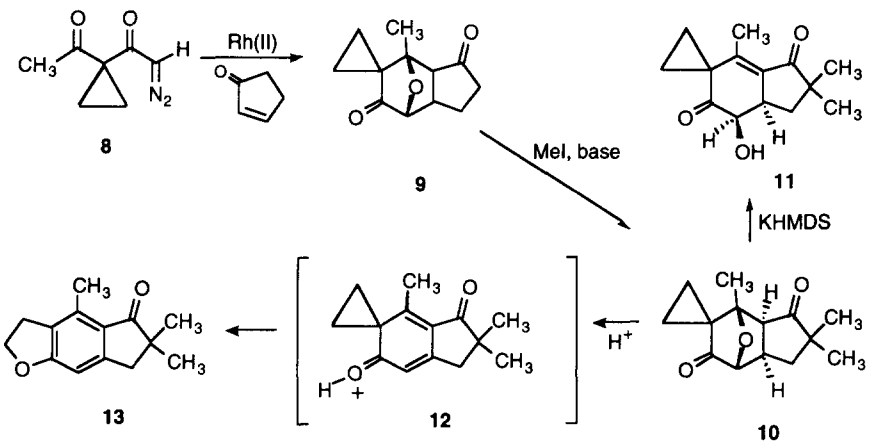
Abstract: A short synthesis of several members of the pterosin family of sesquiterpenes is described in which the key step involves a dipolar-cycloaddition using a carbonyl ylide.

The pterosins (**7**) are a large group of biologically active sesquiterpenes isolated from the bracken fern *Pteridium aquilinium*.[1,2] The carcinogenicity of bracken fern was discovered in 1960 in connection with cattle poisoning[3] which had been reported as early as the 19th century.[4] The major pterosin found in bracken fern is pterosin B (**7**; R=H, X=OH). This compound has been theorized to be formed by decomposition of an unstable precursor, ptaquilosin (**6**) which has also been isolated from bracken.[5] The structures of the pterosins have led to the suggestion[6] that they are derived from farnesyl pyrophosphate (**1**) *via* the same protoilludane precursor **4** which was proposed for the basidiomycete metabolite illudin-M.[7] Evidence for this connection stems from the fact that these natural products are often isolated from the same species[8,9] and that the pterosins can easily be formed by treating ptaquilosin with mild acid.[10]



A major obstacle to the synthesis of the pterosins is the problem of regioselective construction of the penta-substituted aromatic ring. To date, synthetic approaches have relied heavily on classical electrophilic substitution reactions with their inherent problems of regiocontrol.[11-13] In this communication we wish to report the facile preparation of pterosins H, I, and Z which relies on a dipolar cycloaddition of a cyclic carbonyl ylide dipole as the key step of the synthesis.

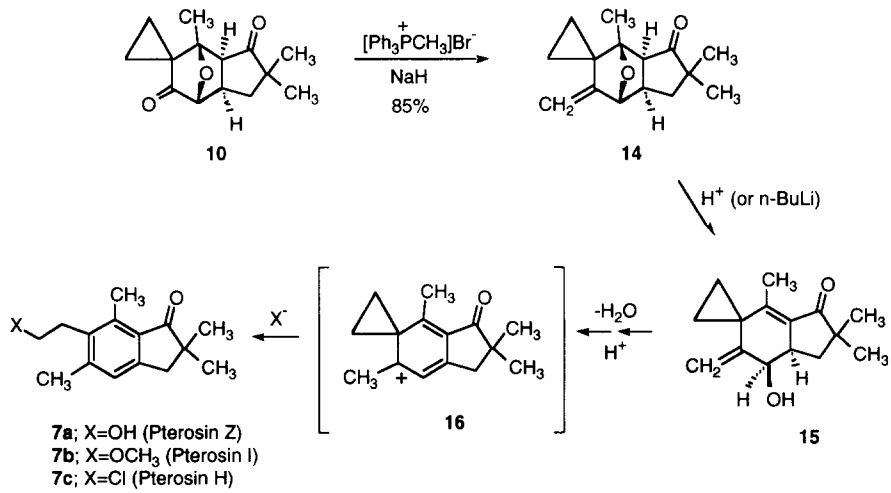
Our own interest in the pterosins evolved from our earlier work with the structurally related illudin family,[14] and the strategy that evolved for our approach to the pterosin H, I, and Z was derived from that effort. In our illudin effort, we described the formation of a bridged oxabicyclo[2.2.1]octane from the rhodium(II) catalyzed reaction of the cyclopropyl substituted α-diazo ketone **8**.[14] The reaction involves the formation of a rhodium carbenoid and subsequent transannular cyclization of the electrophilic carbon onto the adjacent keto group to generate a cyclic carbonyl ylide, followed by 1,3-dipolar cycloaddition.[15] The cycloaddition proceeded readily with cyclopentenone giving cycloadduct **9** as a 4:1-mixture of *exo* and *endo* isomers in 86% yield. The reaction of *exo*-**9** with 2.2 equiv of methyl iodide using potassium hexamethylsilazide as the base provided the dimethylated product **10**



in 79% yield. Our expectation was that the regiospecificity of oxy-bridge cleavage could be controlled to give either the illudin or ptaquilosin skeleton based on the reaction conditions employed. Using compound **10** as a model system, we were successfully able to convert it into **11** (illudin skeleton) upon treatment with base. Further reaction of **10** with *p*-toluenesulfonic acid in THF produced dihydrobenzofuran **13** in 70% yield. The overall sequence of reactions can best be described as proceeding by an initial oxy-bridge ring opening followed by dehydration and a subsequent acid-catalyzed cyclopropyl ketone rearrangement.[16] The facility of the process is undoubtedly related to the aromaticity gained in the final step.

With this observation in hand, we reasoned that several members of the pterosin family would

be readily accessible from the corresponding methylene derivative **14**. The synthesis began by treating **10** with triphenylmethylphosphonium bromide in the presence of sodium hydride and isolating the expected Wittig product **14** in 85% yield. By using the appropriate acid-solvent combination, we were able to obtain each of the pterosins in one step from the key reactive intermediate **16**. It was even possible to isolate precursor **15** using either gentle acidic conditions or by treating **14** with



n-BuLi in THF at 0°C. Thus, pterosin I (**7b**; X=OCH_3) was formed in quantitative yield by treating **14** with *p*-toluenesulfonic acid in methanol at 25°C. Pterosin H (**7c**; X=Cl) was obtained in 80% yield from the reaction of **14** with HCl in dry DMF, whereas pterosin Z (**7a**; X=OH) was formed (75%) by treating **14** with *p*-toluenesulfonic acid and HCl in ethyl acetate.

In summary, a dipolar-cycloaddition strategy has been successfully applied toward the synthesis of several members of the pterosin family. Other aspects of this approach and its application to the more complex members of the illudalane class of sesquiterpenes will be reported in due course.

Acknowledgment: We gratefully acknowledge support of this work by the National Institutes of Health (CA-26751). Use of the high-field NMR spectrometer used in these studies was made possible through equipment grants from the NIH and NSF.

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(*Received in USA* 3 *January* 1995; *accepted* 25 *January* 1995)