Synthetic Studies toward Illudins and Ptaquilosin. A Highly Convergent Approach via the Dipolar Cycloaddition of Carbonyl Ylides

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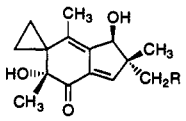
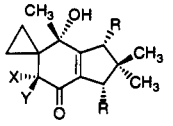
Received December 13, 1993

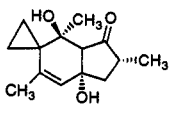
Illudins M (**1**) and S (**2**) are extremely toxic sesquiterpenes produced by *Omphalotus illudens*, the jack-o'-lantern mushroom.[1-4] Recently, two new members of this family (**3** and **4**) have been isolated from a closely related fungus.[5] Illudins and the related ptaquilosin (**5**), the aglycon of the carcinogen ptaquiloside,[6] have been evaluated for antitumor activity at the NCI and show selective toxicity for human myelocytic leukemia and other carcinoma cells of various species of origin.[7] As a consequence of their biological activity, it is not surprising that these compounds have received considerable attention as synthetic targets. The synthesis of illudin M and S was achieved by Matsomoto in 1971.[8] This past year, Kigoshi and co-workers reported the total synthesis of (−)-ptaquilosin in 20 steps (2.9% overall yield).[9]



1; Illudin M (R=H)
2; Illudin S (R=OH)



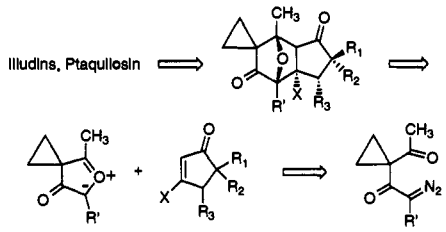
3; Illudin A (R=H, X=OH, Y=CH_3)
4; Illudin B (R=OH, X=CH_3, Y=OH)



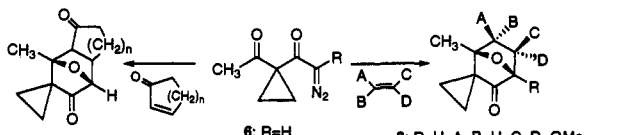
5; Ptaquilosin

In light of the interest in this class of antitumor agents, we undertook a study designed to provide a general means for the synthesis of the core skeleton of the target molecules. In addition, because of their extreme toxicity and consequent low therapeutic index, it seemed reasonable to us to modify the basic skeleton so as to reduce cytotoxicity without compromising antitumor activity.[10] Specifically, we envisioned the use of a dipolar-cycloaddition reaction of a cyclic carbonyl ylide dipole as the key step for the construction of the illudin/ptaquilosin skeleton. This strategy provides for a rapid assembly of the basic core unit of the target molecules having most of the functionality in place (Scheme 1). As shown in the retrosynthetic scheme, opening of the oxy bridge of the cycloadduct would ultimately lead to the core structure of the target molecules in a highly convergent manner. Herein we report our preliminary results dealing with the bimolecular dipolar-cycloaddition and subsequent oxy-bridge ring-opening studies.

Scheme 1



Scheme 2



14; n=1
15; n=2

6; R=H
7; R=CO_2Et

8; R=H, A=B=H, C=D=OMe
9; R=H, A=Cl, B=CN, C=D=H
10; R=CO_2Et, A=B=H, C=D=OMe
11; R=CO_2Et, A=Cl, B=CN, C=D=H
12; R=H, A=C=CO_2Me, B=D=H
13; R=CO_2Et, A=B=C=H, D=SO_2Ph

In earlier papers we described the formation of bridged oxabicyclo[3.2.1]octanes from the rhodium(II)-catalyzed reaction of 1-diazopentanediones.[11] 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.[12] Five-membered-ring carbonyl ylides could also be generated on treating 1-diazobutanediones with Rh(II) carboxylates.[13] Thus, the Rh(II)-catalyzed reaction of cyclopropyl-substituted α-diazo ketones **6** and **7** resulted in cycloaddition to a variety of acyclic and cyclic alkenes. The cycloaddition proceeded readily with 1,1-dimethoxyethylene, producing cycloadducts **8** and **10** in 82% and 81% yields, respectively (Scheme 2). Reaction with α-chloroacrylonitrile gave the alternate regioisomeric cycloadducts **9** and **11** in 68% and 60% yields as a 3:1 mixture of diastereomers. The assigned regiochemistry of the products follows from their characteristic NMR spectra.[14] When dimethyl maleate and phenyl vinyl sulfone were used as trapping agents, cycloadducts **12** and **13** were obtained as the exclusive products in 76% and 68% yields, respectively. Cyclic alkenes also participated in these tandem cyclization–cycloaddition reactions. Among the cyclic alkenes used, the reaction of cyclopentenone with **6** is noteworthy, giving cycloadduct **14** (74%) as a 4:1 mixture of *exo* and *endo* isomers. A similar reaction occurred with cyclohexenone, producing **15** as a 5:1 mixture of diastereomers. Isolation of *exo*-**14** as the major stereoisomer establishes the feasibility of the planned convergent approach to the illudin family as outlined in Scheme 1. The regiochemical results encountered can be rationalized on the basis of FMO considerations. For carbonyl ylides, the HOMO dipole is dominant for reactions with electron deficient dipolarophiles, while the LUMO becomes important for cycloaddition to more electron rich species.[15]

Having established that the dipolar cycloaddition occurred with ease, we next addressed the issue of whether the oxy bridge

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(14) The assigned regiochemistry follows from the NMR spectra, which show a coupling constant of the bridgehead hydrogen with the adjacent geminal protons of 6.0 and 1.4 Hz with compound **9**. The bridgehead proton corresponds to a singlet with the regioisomeric set of cycloadducts (*i.e.*, **8**).
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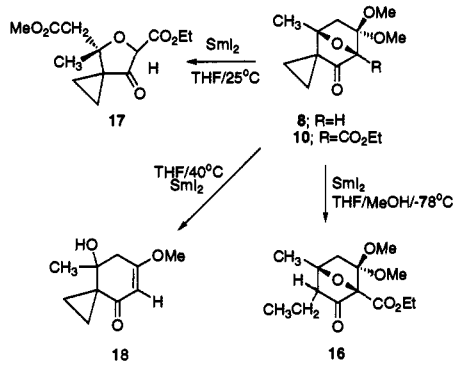
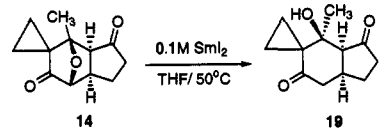
Scheme 3

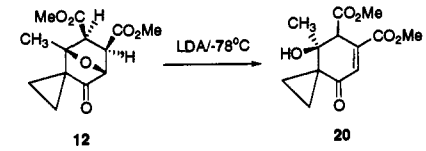


can be opened in the presence of other sensitive functionalities. In recent years samarium(II) iodide has emerged as a powerful, yet highly selective, reducing agent.[16] Molander has utilized the selective nature of SmI_2 to effect reduction of functionalized vinyloxirane derivatives,[17] and that report prompted us to explore the use of this reagent in the present study. Overwhelming evidence exists that free radicals are formed during SmI_2 reductions.[16] Consequently, a major concern associated with the planned illudin approach was that the cyclopropyl ring present in the cycloadduct would be cleaved by the powerful one-electron reducing agent.[18] Indeed, treatment of cycloadduct **10** with SmI_2/THF/MeOH at −78 °C produced the cyclopropyl ring opened product **16** in 61% yield (2:1 mixture of diastereomers) (Scheme 3). Apparently, the SmI_2–MeOH combination is a sufficiently powerful reducing agent that rapidly donates an additional electron to the putative ring-opened carbon-centered radical, thereby generating an organosamarium intermediate that is irreversibly protonated.

Cyclopropyl ketyl anions, whose only substituents on the cyclopropyl ring are alkyl or hydrogen, are known to undergo a reversible ring-opening reaction.[19] This observation suggested that if the SmI_2-promoted cyclopropyl carbinyl ketyl ring opening reaction proceeded in a kinetic manner, then cleavage of the oxy bridge might occur under thermodynamic conditions. Toward this end, we examined the SmI_2-induced reaction of **10** without MeOH (proton source) and at 25 °C. However, the only product formed corresponded to furanone **17** (5:1 mixture of diastereomers, 85%). Under these conditions, SmI_2 acts as a Lewis acid[16] and induces a retro-Claisen-type fragmentation *via* a dimethoxy carbenium ion. In support of this suggestion, the reaction of **10** with 1 equiv of $SnCl_2$ gave **17** in 79% yield. Realizing that the presence of the carbethoxy group promotes the retro-Claisen fragmentation, we turned our attention to cycloadduct **8** wherein the ester functionality is replaced by a hydrogen. As indicated in Scheme 3, this substrate underwent efficient oxy bridge ring opening to give **18** (62%) when treated with SmI_2 in THF at 40 °C. No signs of any cyclopropyl ring opened product was detected in the crude reaction mixture. Under the thermodynamic conditions, cleavage of the oxy bridge is followed by a subsequent elimination of methoxide from the resulting samarium enolate, producing **18** as the exclusive product. An alternate explanation, which is also consistent with the product crossover, assumes that SmI_2 is less strongly solvated in THF and therefore is a more selective reducing agent with respect to C–O bond cleavage. Indeed, the reducing power of SmI_2 has been shown to be closely related to the *coordinating power* of the reaction medium.[20,21]

In an analogous manner, treatment of cycloadduct **14** with SmI_2 at 50 °C for 13 h gave the desired ring-opened product **19** in 62% yield. We have also found that a carbanionic center





adjacent to the oxy bridge can also be used to induce the ring opening. Thus, the reaction of cycloadduct **12** with LDA at −78 °C produced hydroxy enone **20** in 78% yield as an 8:3 mixture of diastereomers. This base-induced elimination provides an alternate approach to the construction of the illudin M and S skeleton.

In summary, a new strategy has been described for the synthesis of the core skeleton of the illudins and ptaquilosin. Further studies are now in progress to develop and optimize the reductive-cycloaddition strategy using alternative precursor molecules and containing additional oxygen functionality and stereochemical detail.

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.

Supplementary Material Available: Experimental details for the preparation and spectroscopic characterization of compounds **6–20** (9 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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