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SYNTHETIC STUDIES ON TAXOL. PART II.[1b]
β-FRAGMENTATION OF ALKOXY RADICALS IN MEDIUM-SIZED CARBOCYCLE SYNTHESIS.

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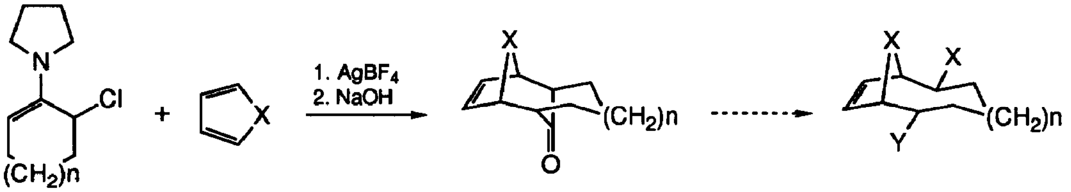
Abstract: An efficient excision of the keto bridge present in tricyclo[4.3.1.1^{2,5}]undecanones or tricyclo[5.3.1.1^{2,6}]dodecanones has been accomplished by β-fragmentation of an alkoxy radical under the procedure of Suárez [PhI(OAc)$_2$ - I$_2$].

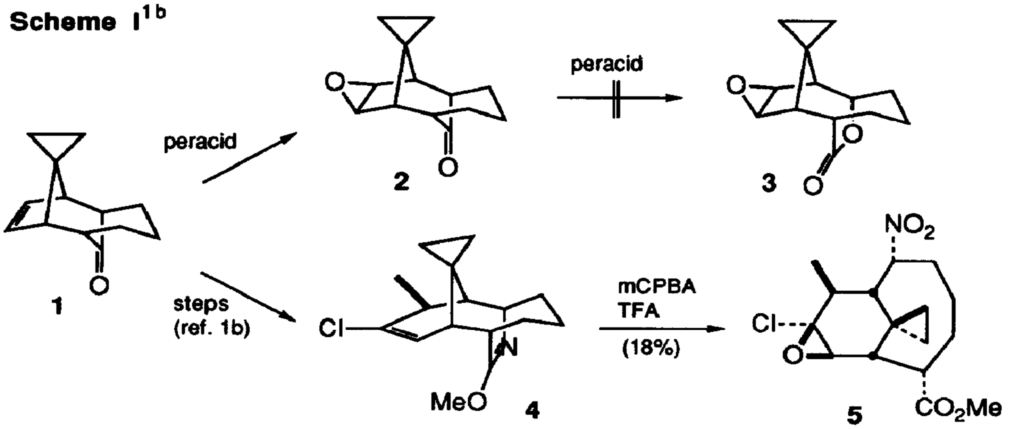
Recently we reported a new synthetic approach toward taxol involving a cyclic azaallyl [4+3] cycloaddition by the procedure of Schmid.[1b,2] This Schmid cycloaddition protocol represents a general synthetic method for many medium-sized carbocycles and heterocycles. The cycloadduct contains the keto bridge which would be useful in not only providing suitable functionality for further elaboration, but also rigidifying the otherwise flexible conformation of the medium-sized ring. At the same time, central to the successful implementation of the Schmid cycloaddition to natural product synthesis is an efficient method for excision of the keto bridge to furnish the requisite ring system. Herein we report a practical solution for oxidative cleavage of the keto bridge by the Suárez protocol, which involves a facile β-fragmentation of an alkoxy radical.[3]



Although a Baeyer-Villiger oxidation of the keto bridge was initially thought to provide an expedient solution, the cycloadduct 1 was found to be recalcitrant toward Baeyer-Villiger oxidation (Scheme I).[4] Thus, an interim solution was found in oxidative cleavage of the cyclic imidates **2a** and **2b**, which were readily prepared by a facile Beckmann rearrangement.[1b] Unfortunately, the final oxidation of the imidate functionality suffers from a disappointingly low yield.[5,6]

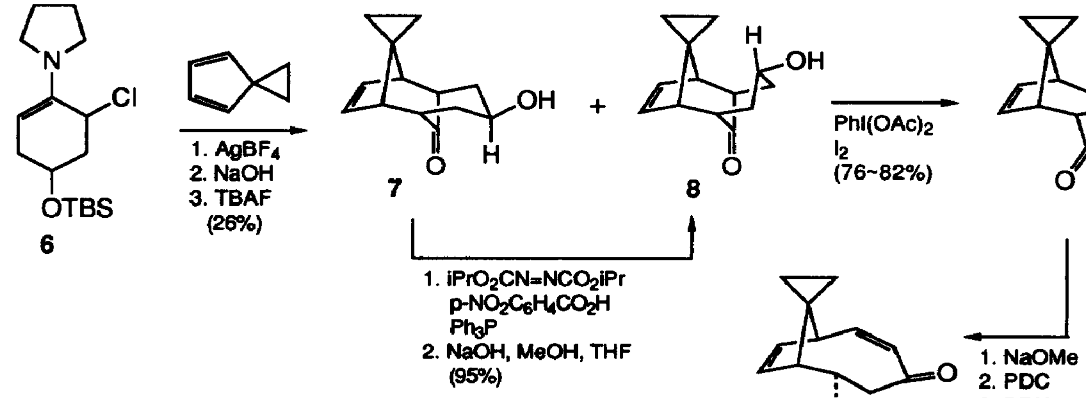
In our search of a general, efficient method for excising the keto bridge, we became intrigued with the possibility of applying the Suárez procedure [PhI(OAc)$_2$ - I$_2$] to a hydroxy ketone so as to induce β-fragmentation of an alkoxy radical.[3] Thus, we decided to prepare a hydroxy-substituted cycloadduct; the Schmid cycloaddition of 5-*t*-butyldimethylsiloxy-3-chloro-2-pyrrolidino-cyclohexene 6 with spiro[2.4]hepta-4,6-diene, followed by desilylation gave a 4:1 mixture of cycloadducts 7 and 8 in 26% overall yield (Scheme II).[7] Although the ^{1}H NMR analysis of 8 indicated the absence of the corresponding hemiacetal, treatment with PhI(OAc)$_2$ - I$_2$ (100W lamp,

Scheme I^{1b}



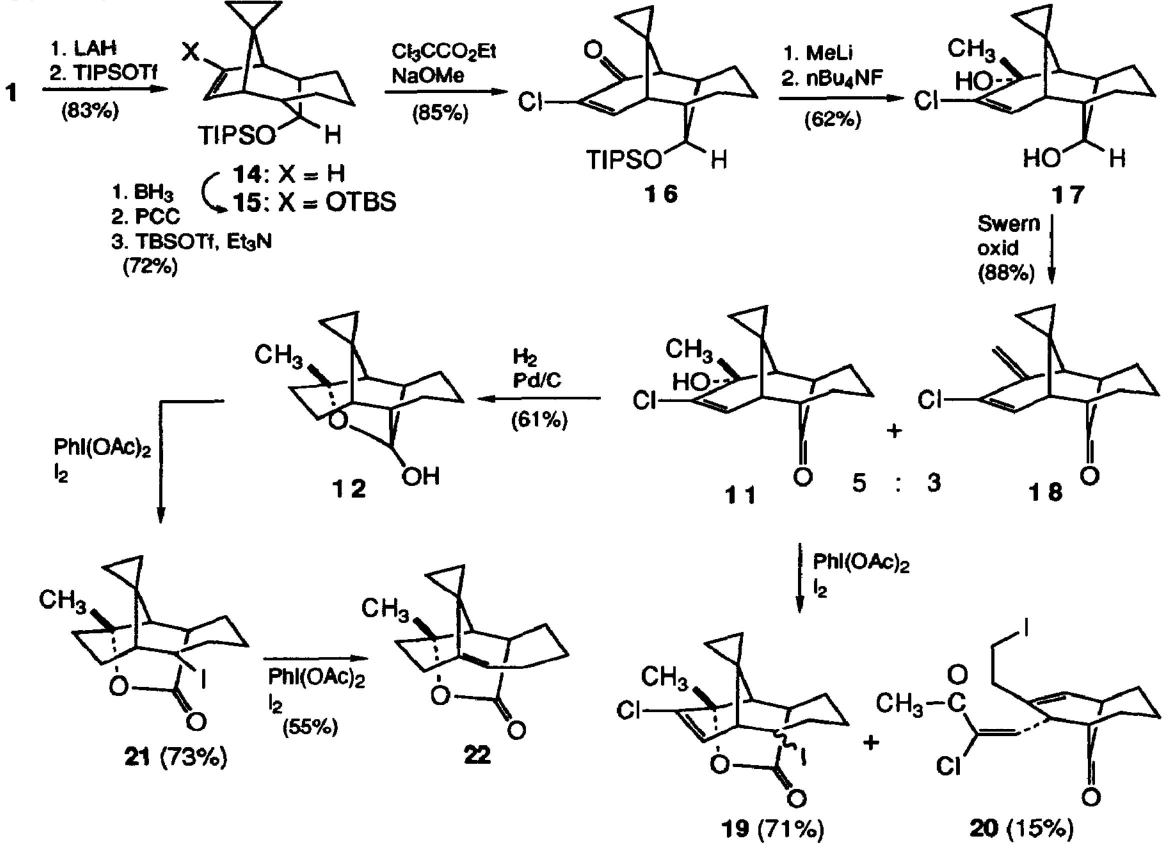
40 °C) afforded the iodolactone 9 (IR 1770 cm^{-1}), as a 4:1 diastereomeric mixture, in 76~82% yield. Lactone 9 was then converted to the enone ester 10 (IR 1735, 1680, 1605 cm^{-1}) by standard transformations. When a 4:1 mixture of cycloadducts 7 and 8 were directly subjected to the action of PhI(OAc)$_2$ - I$_2$, the *trans* hydroxy ketone 7 remained unreacted, whereas 8 was converted smoothly into 9. Thus, the Suárez cleavage provides a practical solution to the otherwise difficult separation of a diastereomeric mixture of 7 and 8. Subsequently, the requisite inversion of the hydroxy configuration of 7 was achieved by the Mitsunobu inversion and subsequent hydrolysis of the resulting *p*-nitrobenzoate in 95% overall yield.[8]

Scheme II



We also decided to examine the Suárez cleavage with the hydroxy group preinstalled onto the six-membered A-ring. The requisite compounds 11 and 12 were prepared from the cycloadduct 1, as outlined in Scheme III. The hydroboration - oxidation sequence of the olefin 14, followed by treatment of the resulting ketone with TBSOTf and Et$_3$N gave the silyl enol ether 15.[9] The one-carbon ring enlargement was then accomplished in excellent overall yield by the use of dichlorocarbene to furnish the α,β-unsaturated ketone 16.[10] Subsequent treatment with MeLi, followed by desilylation (nBu$_4$NF) gave the diol **17** in 62% yield. Finally, Swern oxidation gave rise to a 5 : 3 mixture of the desired ketone **11** and the dehydration product **18**. Hydrogenation of the ketone **11** took place readily to afford the ketone **12**, which exists predominantly as the corresponding hemiketal.[11]

Scheme III



As summarized above, the Suárez cleavage of both compounds **11** and **12** took place smoothly to give rise to the desired iodolactones in good yield. Not surprisingly, in the case of **11**, in competition with the formation of **19** (as a 5:3 diastereomeric mixture), β-scission of the tertiary alkoxy radical in the A-ring also occurred to give the bicyclic diketone **20**, following a facile cyclopropane ring opening of the resulting carbon-centered radical intermediate. Such a bifurcate pathway was completely suppressed in the case of **12**, as the latter compound exists as the corresponding hemiketal; the iodolactone **21** was obtained (73%) virtually as a single diastereomer. No other product was found in the reaction mixture.[12]

In conclusion, we have developed a general synthetic method for functionalized medium-sized carbocycles and heterocycles by a tandem application of the Schmid cycloaddition and the Suárez cleavage.[13] Further synthetic applications in natural product synthesis are currently in progress.[14]

References and Footnotes

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5. For clarity, only one regioisomer is shown in Scheme I, although treatment of ketone **1** with hydroxylamine gave a 3:2 mixture of two oximes, which in turn furnished the identical ratio of the two regioisomers in the subsequent transformations.
6. We were able to accomplish a Baeyer-Villiger-type oxidation by the use of an α-methoxy hydroperoxide, followed by the Criegee rearrangement. However, preparation of the requisite α-methoxy hydroperoxide was somewhat cumbersome.
7. (a) Unoptimized yield. (b) Although the chemical yield is not high, a simple experimental procedure, coupled with the ready availability of the starting materials, allowed us to prepare multi-gram quantities of the cycloadducts **7** and **8**.
8. For reviews, see: (a) Mitsunobu, O. *Synthesis* **1981**, 1. (b) Castro, B. R. *Org. React.* **1983**, *29*, 1. (c) Hughes, D. L. *Org. React.* **1992**, *42*, 335.
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10. *Cf.* Jefford, C. W.; Gunsher, J.; Hill, D. T.; Brun, P.; Le Gras, J.; Waegell, B. *Organic Syntheses;* Wiley: New York, 1988; Collect. Vol. VI, p.142.
11. Alternatively, **12** was prepared by dichlorocarbene-mediated ring expansion of **14**, followed by dehalogenation (Na, NH_3) and allylic oxidation (CrO_3-DMP). Subsequent standard transformations analogous to **11** provided an easy access to **12**.
12. Upon prolonged exposure the formation of the bridgehead olefin **22** was observed. No other regioisomeric olefin was found in the reaction mixture. The olefin **22** results from the further action of Suárez's reagent on the iodolactone **21**. Indeed, treatment of pure **21** with Suárez's reagent provided the former compound. *Syn* elimination of the corresponding iodoso intermediate might be involved [*Cf.* Reich, H.; Peake, S. L. *J. Am. Chem. Soc.* **1978**, *100*, 4888]. On the other hand, iodo compounds **9** and **19** seem to be unreactive toward Suárez's reagent. Further mechanistic studies, as well as the stereochemical determination of **21**, are currently underway.
13. Related application of Suárez's cleavage on the Schmid cycloadduct derived from furan provides a new, conceptually appealing route to oxocane natural products: Kim, H.; Ziani-Cherif, C.; Cha, J. K. unpublished results.
14. We are grateful to Sterling-Winthrop, the National Institutes of Health (GM 35956), and The University of Alabama for generous financial support. J. K. C. also thanks the National Institutes of Health for a Research Career Development Award (GM00575), and J. O. acknowledges a graduate fellowship from The University of Alabama.

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