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A Very Rapid Stereocontrolled Entry to Highly Functionalized [5-8-5] Ring Systems Using the Saegusa Reaction

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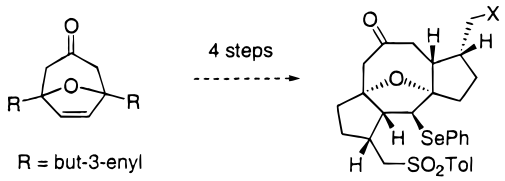
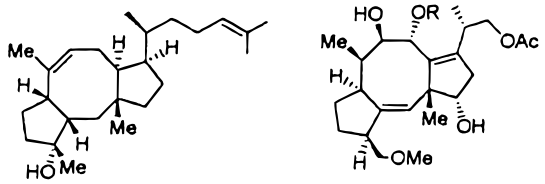
ABSTRACT



A highly functionalized dicyclopenta[*a*,*d*]cyclooctanone product, representing the basic [5-8-5] skeleton found in natural products such as the ophiobolins and fusicoccins, was prepared in only four synthetic steps from a readily available bridged ketone. The highly stereoselective sequence involves use of the Saegusa ring-expansion protocol to effect initial ring expansion–cyclization and a subsequent radical cyclization using $TolSO_2SePh$.

A number of complex cyclooctane-containing natural products have attracted synthetic attention because of their challenging structures, combined with wide-ranging biological activities.[1] Members of the ophiobolin and fussicoccin families, for example, ophiobolin F **1** and fusicoccin A **2**, Figure 1, possessing a fused [5-8-5] ring system, have proved to be of particular interest and have been the focus of several very recent studies.[2]

Our interest in developing total synthesis strategies involving symmetry-breaking operations of oxa-bridged ketones,[3,4] and also in the use of the Saegusa protocol for effecting ring expansion,[5] led us to devise a potentially very concise, stereocontrolled entry to the type of [5-8-5] system present in natural products such as **1** and **2**.



1 **2**

Figure 1. Structures of ophiobolin F and fusicoccin A.

According to this plan, outlined in Scheme 1, the highly functionalized [5-8-5] system **3** would be available by

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(1) For revews, see: (a) Petasis, N. A.; Patane, M. A. *Tetrahedron* **1992**, *48*, 5757. (b) Mehta, G.; Singh, V. *Chem. Rev.* **1999**, *99*, 881.

(2) For recent efforts, see: (a) Randall, M. L.; Lo, P. C−K.; Bonitatebus, P. J., Jr.; Snapper, M. L. *J. Am. Chem. Soc.* **1999**, *121*, 4534. (b) Sieburth, S. McN.; McGee, K. F., Jr.; Al-Tel, T. H. *Tetrahedron Lett.* **1999**, *40*, 4007.

(3) See, for example: Gethin, D. M.; Simpkins, N. S. *Tetrahedron* **1997**, *53*, 14417.

(4) For relevant reviews, see: (a) Molander, G. A. *Acc. Chem. Res.* **1998**, *31*, 603. (b) Chiu, P.; Lautens, M. *Top. Curr. Chem.* **1997**, *190*, 1.

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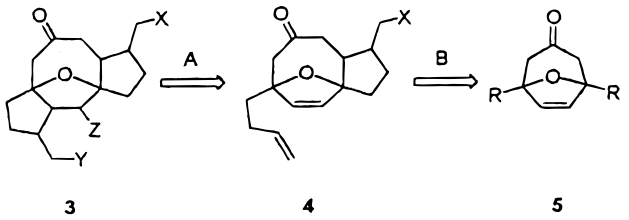
Scheme 1



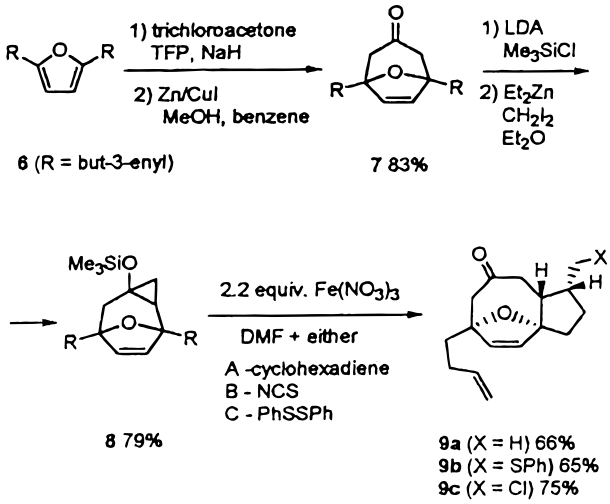
cyclization of 1,6-dienyl precursor **4**, using a bifunctional reagent YZ (step A).

Intermediate **4** would be formed from symmetrical ketone **5**, in which R represents an unsaturated appendage (here but-3-enyl), by a process involving ring expansion with concomitant cyclization onto one of the R groups (step B).

Since the sequence evolves around the conformationally predictable ketone template **5**, a high degree of diastereocontrol was anticipated. In addition, we planned to initiate the key sequence by enolization of **5**, which ultimately could be expected to produce nonracemic intermediates through the use of chiral lithium amide reagents.[6]

Here we present our preliminary realization of the approach shown in Scheme 1, which demonstrates that this strategy has substantial potential for the stereoselective construction of complex polycyclic frameworks, Scheme 2.

Scheme 2



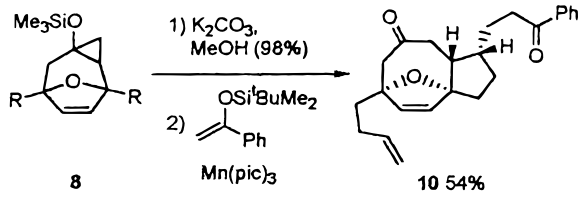
The readily available furan **6** was subjected to the Föhlisch conditions for [4 + 3] cycloaddition using an excess of trichloroacetone in 2,2,3,3-tetrafluoropropan-1-ol (TFP),[7] followed by dehalogenation, to give the key bicyclic ketone **7** in excellent overall yield.

Enol silane formation in the usual way, followed by cyclopropanation under Furukawa conditions, then provided trimethylsilyloxycyclopropane **8** in 79% overall.[8] This intermediate was then subjected to reaction conditions developed by Booker-Milburn for effecting regioselective cyclopropane cleavage, followed by *5-exo-trig* mode of cyclization onto an unsaturated appendage.[9] This is a modification of the initial Saegusa protocol which involves ring cleavage using $FeCl_3$, resulting in simple ring expansion.[10]

Under the modified conditions, which involve the use of $Fe(NO_3)_3$ in combination with cyclohexadiene, *N*-chlorosuccinimide (NCS), or diphenyl disulfide as the radical terminator, cyclopropane **8** was smoothly converted into the desired tricyclic products **9a**−**c**. These products were formed as single diastereomers, the stereochemistry shown being assigned on the basis of ample precedent from the Booker-Milburn work and using predictive models for such radical cyclization reactions.

In addition to the above Fe(III) method for cyclization, we also explored the alternative Mn(III) method developed by Narasaka and co-workers.[11] Initial desilylation of **8** using K_2CO_3 in methanol was followed by reaction with $Mn(pic)_3$ (pic = 2-pyridinecarboxylate) in the presence of an enol silane partner derived from acetophenone, Scheme 3.

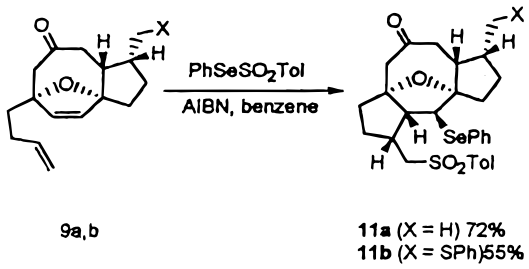
Scheme 3



This sequence furnished diketone **10**, in which the product radical resulting from cyclopropane ring cleavage and *5-exo-trig* cyclization has undergone a subsequent intermolecular addition to the enol silane. This side chain forming reaction appears particularly attractive, bearing in mind the type of substituents present at this position in the natural products **1** and **2**.

Completion of the full [5-8-5] ring system required only one further synthetic step, carried out on the dienyl ketone intermediates **9a** and **9b**, Scheme 4.

Scheme 4



Reaction of either **9a** or **9b** with $TolSO_2SePh$ under typical radical cyclization conditions gave the desired tetracyclic products **11a** and **11b** in good yield.[12] This reaction proceeds by addition of a sulfonyl radical to the terminus of the butenyl

side chain, subsequent rapid *5-exo-trig* cyclization onto the cyclic alkene, and then reaction of the product radical with $TolSO_2SePh$.

Since at this stage the stereochemistry of these products could not be predicted with absolute certainty, we were prompted to conduct an X-ray structure determination of the crystalline ketosulfone **11a** (Figure 2).

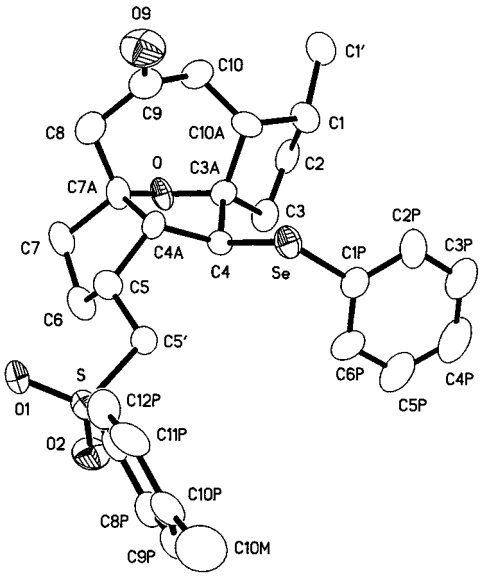


Figure 2. X-ray structure of **11a**.

The resulting structure shows that both of the butenyl appendages have cyclized in an *exo*-orientation with respect to the core oxabicyclic ketone. Somewhat surprisingly, the selenenyl substituent resides in an *endo*-orientation with respect to this core, but this can be seen to be a result of a high level of crowding on the other face due to the newly formed five-membered ring carrying a bulky sulfonyl substituent.

Although we have yet to probe the chemistry of these intermediates in any detail, a few preliminary reactions have been carried out. For example, treatment of selenide **11a** with H_2O_2 in THF resulted in *syn*-elimination to give alkene **12**, Figure 3. However, cleavage of the ether bridge of **11b** by

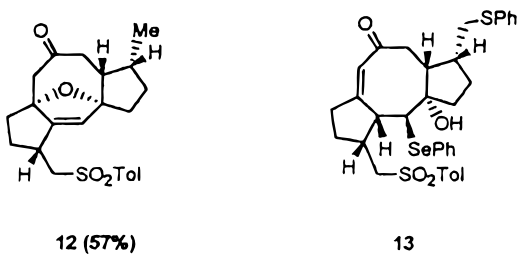
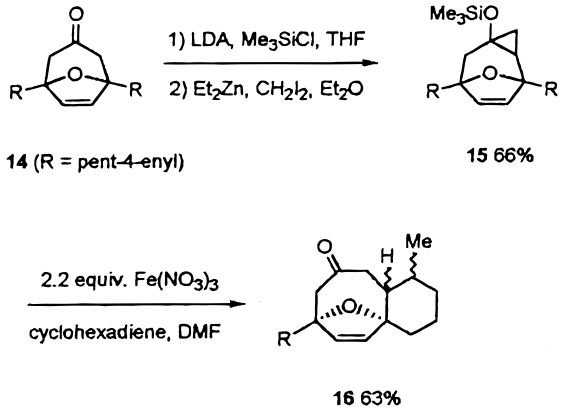


Figure 3. Structures of **12** and **13**.

a seemingly straightforward elimination to give **13** has so far proved elusive under various acidic and Lewis acidic and basic conditions. Further exploration of this process, along with alternative strategies for ether cleavage, are ongoing.

Finally we have established that it should be possible to apply this type of approach for the synthesis of polycyclic products containing six-membered rings, as indicated in Scheme 5.

Scheme 5



Thus, an analogous series of reactions to those described above was carried out, starting with ketone **14**, having pent-4-enyl side chains, Scheme 5. Enol silane formation and cyclopropanation to give **15** proved straightforward, and the crucial ring cleavage cyclization then gave ketone **16** in 63% yield. Although this compound proved to be a mixture of three diastereomers in a 7:4:1 ratio, this result demonstrates for the first time that the Booker-Milburn approach can be used for the synthesis of six-membered rings.[13]

In conclusion, we have demonstrated a rapid new entry to highly functionalized polycyclic products, starting from symmetrical oxa-bridged ketones. The availability of tetracyclic structures such as **11**, by means of a fully stereocontrolled route, in only seven steps from furan, suggests that this should be a fruitful approach for target synthesis. Further efforts are being devoted to examining these opportunities.

Acknowledgment. We thank The University of Nottingham and Rhône-Poulenc Rorer for support of A.J.H.

Supporting Information Available: Figures giving ^1H and ^{13}C NMR spectra of **9b**, **11a**, **11b**, and **12** and crystal structure coordinates for **11a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) We are aware of only one related example using the $Mn(pic)_3$ system, see ref 11.