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Synthesis of the Tagetitoxin Core via Photo-Stevens Rearrangement

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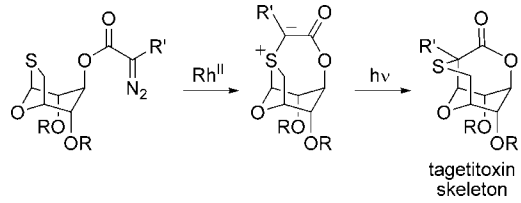
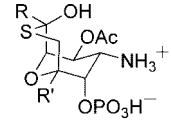
ABSTRACT



The core structure of the RNA polymerase inhibitor tagetitoxin has been synthesized by one-carbon ring expansion of bridged bicyclic monothioacetals. The key steps are intramolecular ylide formation by reaction between the sulfur atom and a pendant diazoester, followed by an efficient photochemical 1,2-rearrangement to give the desired 9-oxa-3-thiabicyclo[3.3.1]nonane ring system.

Tagetitoxin is a phytotoxin of unique structure and biological activity that was isolated from the bacterium *Pseudomonas syringae* pv. *tagetis* in 1981.[1] The compound is an inhibitor of RNA polymerase in chloroplasts[2] and bacteria[3] and a specific inhibitor of eukaryotic RNA polymerase III.[3] The structure initially proposed for tagetitoxin[4] was later revised to a bicyclic framework[5] for which two isomeric structures, **1** and **2**, were suggested (Figure 1). Isomer **1** was believed to be the more likely, but structure **2** could not be ruled out with the spectroscopic data available, nor could the relative stereochemistry at the hemithioacetal center or the absolute configuration be proved. A recent publication[6] questioned the mass spectrometry data used in the structural assignment, but no alternative structure was put forward.

The biological activity of tagetitoxin and the ambiguities surrounding its structure make it an intriguing target for synthesis. Recently, we completed the first synthesis of the tagetitoxin skeleton, employing as a key step the intramolecular reaction of a thiol with an α-ketoester.[7,8] In this paper, we present an alternative strategy for the synthesis of the tagetitoxin core, utilizing the rearrangement of a sulfur ylide.



1 R = $CONH_2$, R' = COOH
2 R = COOH, R' = $CONH_2$

Figure 1. Proposed structures for tagetitoxin.

Our strategy for construction of the bicyclic system was to employ a metallocarbenoid-mediated ring expansion of

(1) Mitchell, R. E.; Durbin, R. D. *Physiol. Plant Pathol.* **1981**, *18*, 157.
(2) Matthews, D. E.; Durbin, R. D. *J. Biol. Chem.* **1990**, *265*, 493.
(3) Steinberg, T. H.; Matthews, D. E.; Durbin, R. D.; Burgess, R. R. *J. Biol. Chem.* **1990**, *265*, 499.
(4) Mitchell, R. E.; Durbin, R. D. *Phytochemistry* **1983**, *22*, 1425.
(5) Mitchell, R. E.; Coddington, J. M.; Young, H. *Tetrahedron Lett.* **1989**, *30*, 501.
(6) Gronwald, J. W.; Plaisance, K. L.; Marimanikkuppam, S.; Ostrowski, B. G. *Physiol. Mol. Plant Pathol.* **2005**, *67*, 23.
(7) For other approaches to the synthesis of tagetitoxin, see: (a) Sammakia, T.; Hurley, T. B.; Sammond, D. M.; Smith, R. S.; Sobolov, S. B.; Oeschger, T. R. *Tetrahedron Lett.* **1996**, *37*, 4427. (b) Dent, B. R.; Furneaux, R. H.; Gainsford, G. J.; Lynch, G. P. *Tetrahedron* **1999**, *55*, 6977.
(8) Plet, J. R. H.; Porter, M. J. *Chem. Commun.* **2006**, 1197.

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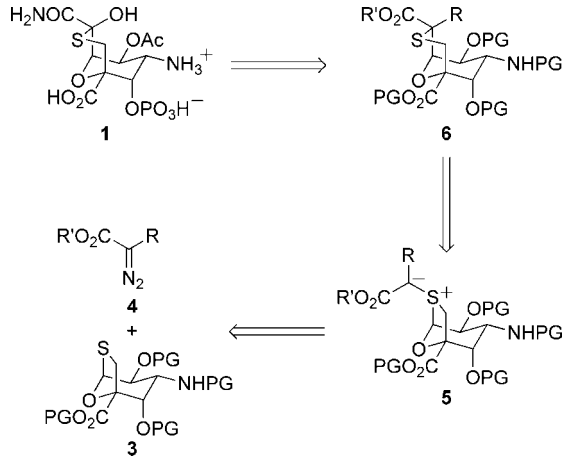
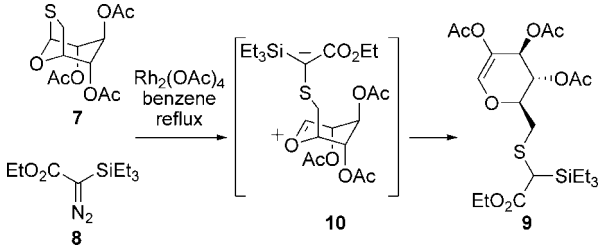
Scheme 1. Retrosynthesis of Tagetitoxin



1,3-oxathiolanes.[9] Thus, a bicyclic thioacetal substrate **3** would be treated with a diazoester **4** in the presence of a rhodium carboxylate catalyst to afford ylide intermediate **5**. It was envisaged that this ylide would undergo Stevens rearrangement to the bridged 6,6-system **6**, ready for final transformation to the target **1** (Scheme 1). Although such reactions proved successful with simple monocyclic systems,[9] initial studies[8] with bicyclic substrates were fruitless; products originating from ylide intermediates were observed, but the desired ring expansion products were not detected. For example, reaction of monothioacetal **7** with ethyl diazo(triethylsilyl)acetate **8** gave glycal **9** as the only isolable product (Scheme 2).

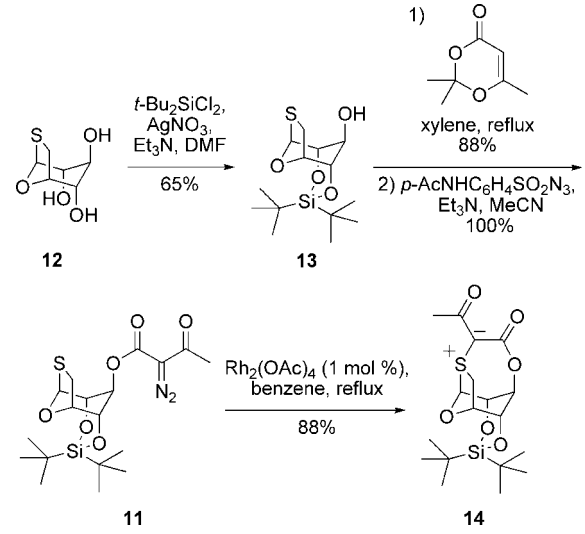
Scheme 2. Attempted Ring Expansion of a Bicyclic Substrate[8]



We considered that the failure of the anticipated ring expansion was likely due to the conformational flexibility of a monocyclic intermediate **10** and postulated that carrying out the ylide formation in an intramolecular fashion should lead to a more constrained intermediate, from which the desired C−C bond formation would be favored.

Glucose-derived C(3)-diazo esters such as **11** were chosen as the initial test system for this hypothesis (Scheme 3). Thus D-glucose was converted to 1,6-thioanhydroglucose (**12**) in good yield over four steps,[10] and the C(2) and C(4) hydroxyl groups were selectively protected using a di-*tert*-butylsilylene bridge,[11] giving **13**. Acetoacetylation[12] and diazo transfer proceeded smoothly to afford model substrate **11**, which on exposure to 1 mol % rhodium(II) acetate dimer was converted to isolable tetracyclic ylide **14**. The structure of ylide **14** was confirmed by X-ray crystallography.[13]

Scheme 3. Synthesis of Ylide **14**



A number of cyclic sulfonium ylides have previously been shown to be relatively stable[14] but to undergo [1,2]-rearrangement at elevated temperatures. Hence a range of conditions, using solvents of varying polarities, was tested in order to induce rearrangement of **14** to **15**. Heating ylide **14** in refluxing xylene, methanol or DMSO all led to the recovery of starting material, with decomposition being observed after extended reaction times. Microwave heating of ylide **14** in a range of solvents also proved ineffective. Indeed, ylide **14** proved to have remarkable thermal stability, melting at 243−245 °C without appreciable decomposition.

(9) (a) Ioannou, M.; Porter, M. J.; Saez, F. *Chem. Commun.* **2002**, 346. (b) Ioannou, M.; Porter, M. J.; Saez, F. *Tetrahedron* **2005**, *61*, 43. (c) Zhu, S.; Xing, C.; Zhu, S. *Tetrahedron* **2006**, *62*, 829. (d) Stepakov, A. V.; Molchanov, A. P.; Magull, J.; Vidović, D.; Starova, G. L.; Kopf, J.; Kostikov, R. R. *Tetrahedron* **2006**, *62*, 3610.

(10) (a) Akagi, M.; Tejima, S.; Haga, M. *Chem. Pharm. Bull.* **1963**, *11*, 58. (b) Chu, C. K.; Beach, J. W.; Jeong, L. S.; Choi, B. G.; Comer, F. I.; Alves, A. J.; Schinazi, R. F. *J. Org. Chem.* **1991**, *56*, 6503.

(11) Furusawa, K.; Ueno, K.; Katsua, T. *Chem. Lett.* **1990**, 97.

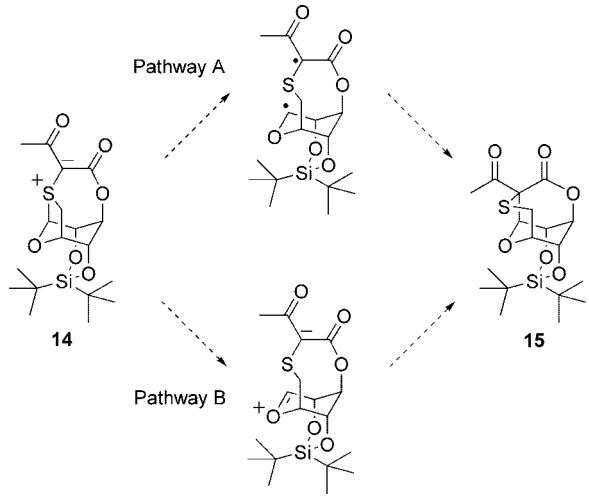
(12) Clemmens, R. J.; Hyatt, J. A. *J. Org. Chem.* **1985**, *50*, 2431.

(13) Single crystal structure of **14**. $C_{18}H_{28}O_6SSi$, M_r 400.55, orthorhombic, space group $P2_12_12_1$, a = 6.4058(8), b = 11.0838(14), c = 28.504(4) Å, V = 2023.8(4) Å^3, Z = 4, ρ_{calc} = 1.315 Mg m^{-3}, Mo Kα radiation (λ = 0.71073 Å, μ = 0.249 mm^{-1}), T = 150(2) K, a total of 4829 (R_{int} = 0.0518) independent reflections with $2\theta < 55°$ were collected. The structure was solved by direct methods and refined by full matrix least-squares using the SHELXL-97. The resulting 235 parameters were refined to converge at R_1 = 0.0485 and wR_2 = 0.1083 ($I > 2\sigma(I)$), max/min residual electron density 0.398/−0.261 Å^{-3}, GOF 1.036. CCDC 697726 contains the supplementary crystallographic data, which can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(14) Moody, C. J.; Taylor, R. J. *Tetrahedron* **1990**, *46*, 6501.

Two mechanisms for thermal rearrangement of ylide **14** to give the desired tetracycle **15** can be conceived (Scheme 4). Homolysis pathway A is the usual mechanism of the Stevens rearrangement,[15] but it was believed that heterolytic mechanism B might be favored in this case. The isolation of glycal **9** from the reaction of substrate **7** seems to indicate the feasibility of the heterolytic process, and so the stability of ylide **14** was quite surprising.

Scheme 4. Mechanistic Pathways for Thermal Rearrangement

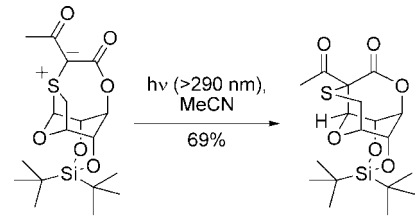


Attempts were made to promote heterolysis by addition of protic (TFA, TfOH) or Lewis [Cu(acac)$_2$] acids to ylide **14**, with the expectation that this would increase the polarization of the C−S bond; these attempts, however, were unsuccessful, with no ring-expansion product being formed.

After these unsuccessful attempts to induce rearrangement of the ylide thermally or with acid catalysis, our attention turned to the photochemical variant of the Stevens rearrangement. Although first reported almost 40 years ago,[16] this reaction has received limited attention and has been studied only with relatively simple substrates.[17] While a mechanism involving a concerted 1,2-shift is conceivable, the isolation of radical homocoupling products indicates that, like its thermal counterpart, the photo-Stevens reaction occurs via a homolytic pathway.[17c] However, low yields are commonly obtained due to further photochemical reactions of the products, and the competitive (or exclusive) formation of products derived from carbenes has also been observed on photolysis of sulfur ylides.[17a,b,18]

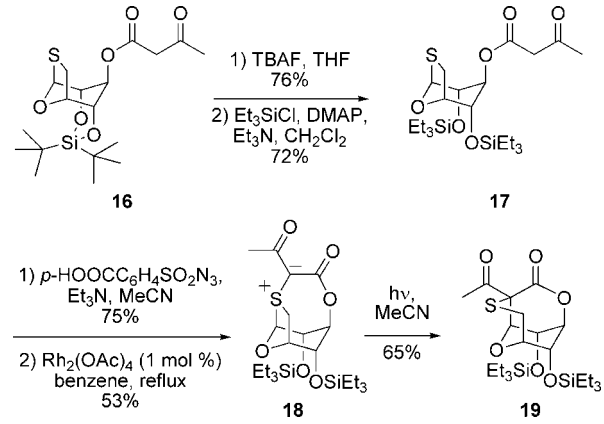
Ylide **14** was subjected to photolysis in acetonitrile (medium pressure Hg lamp, Pyrex filter). Pleasingly, complete conversion to tetracycle **15** was observed within 2 h (Scheme 5), completing the synthesis of the core bicyclic structure of tagetitoxin. The transformation of **14** to **15** was confirmed both by significant changes in the IR absorption spectra (**14**: ν_{max} 1682 and 1597 cm^{-1}; **15**: ν_{max} 1744 and 1717 cm^{-1}), and by long-range ^{1}H−^{13}C NMR correlation experiments.

Scheme 5. Photo-Stevens Reaction



Having validated our strategy toward the tagetitoxin core, attention then turned to assessing which structural elements were essential for successful ylide formation and photo-Stevens reaction. To this end, acetoacetate **16** was deprotected with TBAF, and the resulting diol reprotected as its bis-triethylsilyl ether **17** (Scheme 6). Diazo transfer and rhodium-catalyzed diazodecomposition afforded ylide **18**; upon photolysis, **18** was smoothly converted to tricyclic ring-expansion product **19**, with no significant changes in rate or yield to the previous example.

Scheme 6. Bis-Triethylsilyl-Protected Substrate



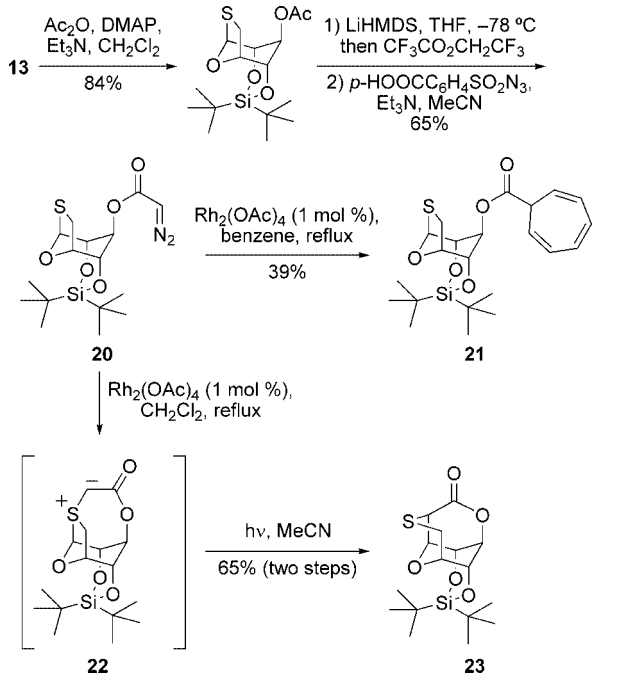
Diazoacetate **20** was also synthesized from alcohol **13** (Scheme 7).[19] Treatment with rhodium(II) acetate in

(15) (a) Schöllkopf, U.; Ostermann, G.; Schossig, J. *Tetrahedron* **1969**, *10*, 2619. (b) Baldwin, J. E.; Erickson, W. F.; Hackler, R. E.; Scott, R. M. *J. Chem. Soc., Chem. Commun.* **1970**, 576. (c) Ollis, W. D.; Rey, M.; Sutherland, I. O. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1009.

(16) Fish, R. H.; Chow, L. C.; Caserio, M. C. *Tetrahedron Lett.* **1969**, *10*, 1259.

(17) (a) Trost, B. M.; LaRochelle, R. W. *J. Am. Chem. Soc.* **1970**, *92*, 5804. (b) LaRochelle, R. W.; Trost, B. M.; Krepski, L. *J. Org. Chem.* **1971**, *36*, 1126. (c) Zhang, J.-J.; Schuster, G. B. *J. Org. Chem.* **1988**, *53*, 716. (d) Fujii, T.; Sakuragi, H.; Furukawa, N. *Tetrahedron Lett.* **1995**, *36*, 8039. (e) Shevchenko, V. V.; Khimich, N. N.; Platz, M. S.; Nikolaev, V. A. *Tetrahedron Lett.* **2005**, *46*, 435. (f) Nikolaev, V. A.; Shevchenko, V. V.; Platz, M. S.; Khimich, N. N. *Russ. J. Org. Chem.* **2006**, *42*, 815. (g) Shevchenko, V. V.; Zhegalova, N. G.; Borzenko, A. O.; Nikolaev, V. A. *Helv. Chim. Acta* **2008**, *91*, 501.

Scheme 7. Diazoacetate Substrate



benzene led to cycloheptatriene **21** as the major product;[20] on switching to dichloromethane, ylide **22** was produced. This ylide was unstable to chromatography, and so the crude reaction mixture was immediately subjected to photolysis, affording tetracycle **23** in 65% yield over two steps.

In summary, a concise route to the core structure of tagetitoxin has been developed, employing rhodium-catalyzed ylide formation and photo-Stevens rearrangement. The scope of this methodology has been explored to assess its suitability for adaptation to a total synthesis, which will be the focus of our future studies. The subtle mechanistic factors that allow this Stevens rearrangement to occur photochemically, but not thermally, will also be investigated.

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Supporting Information Available: Experimental procedures and compound characterization data for compounds **7** and **11**−**23**; CIF file for compound **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) (a) Trost, B. M. *J. Am. Chem. Soc.* **1967**, *89*, 138. (b) Johnson, A. W.; Amel, R. T. *J. Org. Chem.* **1969**, *34*, 1240.

(19) Danheiser, R. L.; Miller, R. F.; Brisbois, R. G.; Park, S. Z. *J. Org. Chem.* **1990**, *55*, 1959.

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