ORGANIC LETTERS

2007
Vol. 9, No. 18
3507−3510

Intramolecular Vinylsilane–Oxocarbenium Condensations: Concise Assembly of Cis-Bicyclic Ether Arrays†

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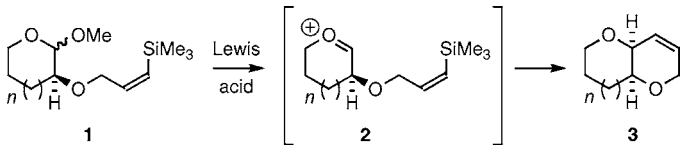
Received June 7, 2007

ABSTRACT



Lewis acid-mediated intramolecular attack of vinylsilanes at tethered oxonium precursors 1 results in a rapid assembly of the cis-fused bicyclic ether species 3, with complete regio- and stereospecific control, and in some cases near-quantitative yield. Continued investigation suggests a general approach to a variety of such ether frameworks.

In recent years a large number of natural products containing fused polycyclic ether arrays have surfaced and synthetic endeavors to address these complex and often biologically potent targets have quite rightly attracted much effort and attention. Foremost among these are the brevetoxins,[1] which themselves have inspired a profusion of approaches to systems of this overall type and pattern.[2]

However, as a result, efforts to date have focused primarily on ether arrays with an all-trans-arrangement, whereas strategies and thereby general methodologies for construction of the corresponding cis-systems have proved less prevalent.[3] This is not to say that many structurally complex and/or bioactive examples of this distinct subclass do not exist per se. In fact, these include a number of valid bicyclic natural product targets, as illustrated by Figure 1, with this feature further extrapolated to such intricate polycyclic architectures as the halichondrins and maitotoxin.

We recently chose to develop a general route to this common structural motif, involving the intramolecular attack of a proximally tethered vinylsilane at an oxocarbenium moiety, generated in situ from the corresponding cyclic acetal under appropriate Lewis acid activation, Scheme 1. We envisaged that the constrained intramolecular nature of the delivery would yield cis-ring junctions in exclusive fashion. Similar reactions utilizing a variety of equivalent electrophilic species[4] provide ample precedent, in particular the elegant studies of Overman.[5] By direct comparison, this particular

† Dedicated to the memory of Professor Shawn B. Allin [1966−2006]—scholar, scientist, and friend.

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(1) For example, Nicolau's landmark synthesis of brevetoxin B: Nicolau, K. C.; Theodorakis, E. A.; Rutjes, F. P. J. T.; Tiebes, J.; Sato, M.; Untersteller, E.; Xiao, X.-Y. *J. Am. Chem. Soc.* **1995**, *117*, 1171−1172. Nicolau, K. C.; Rutjes, F. P. J. T.; Theodorakis, E. A.; Tiebes, J.; Sato, M.; Untersteller, E. *J. Am. Chem. Soc.* **1995**, *117*, 1173−1174. For an intriguing personalized account of these efforts see: Nicolau, K. C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 589−607.

(2) (a) Alvarez, E.; Candenas, M. L.; Peréz, R.; Ravelo, J. L.; Martin, J. D. *Chem. Rev.* **1995**, *95*, 1953−1980. (b) Marmsäter, F. P.; West, F. G. *Chem. Eur. J.* **2002**, *8*, 4347−4353. (c) Evans, P. A.; Delouvrié, B. *Curr. Opin. Drug Discovery Dev.* **2002**, *5*, 986−998.

(3) One such example with potential for broader application features ring-closing metathesis in carbohydrate-derived systems: (a) Leeuwenburgh, M. A.; Overkleeft, H. S.; van der Marel, G. A.; van Boom, J. H. *Synlett* **1997**, 1263−1264. (b) Leeuwenburgh, M. A.; Kulker, C.; Duynstee, H. I.; Overkleeft, H. S.; van der Marel, G. A.; van Boom, J. H. *Tetrahedron* **1999**, *55*, 8253−8262.

10.1021/ol071349v CCC: $37.00
Published on Web 08/04/2007

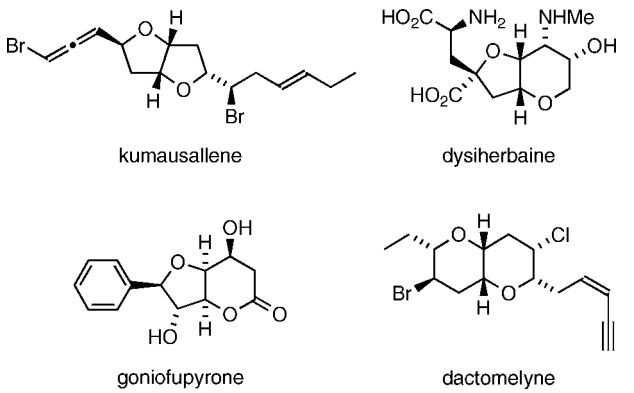
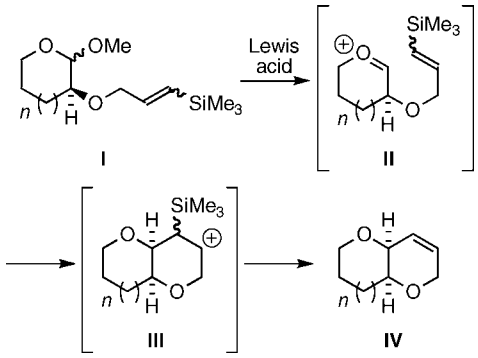


Figure 1. Representative cis-fused bicyclic ether natural products.

proposed cyclization would represent a 6-*exo*-trig closure at an exocyclic oxocarbenium initiator with endocyclic vinylsilane as the terminating group.[6]

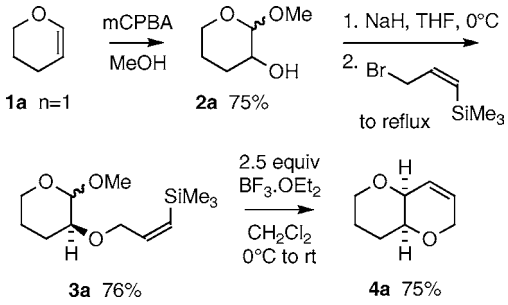
Scheme 1. Generalized Approach to Cis-Bicyclic Ether Arrays



Surprisingly, this class of cyclization has not previously been utilized in synthesis,[7] although an early example of monocyclic reactivity was investigated by Fleming.[8] This study exposed one plausible reason for the scarcity of examples of this type—the instability of the resulting allylic ether products to the prevailing reaction conditions.[9] We predicted that construction of bicyclic systems would allay this problem, due to increased resilience arising from the usual inherent entropic factors.

Proof of concept required a facile construction of the requisite precursors, via simple Williamson-type ether coupling of the appropriate α-hydroxylated acetal with corresponding vinylsilane fragments. The first example in our study employed the synthesis of a [6,6]-cis-fused pyranopyran system, and is illustrative of our overall strategy, Scheme 2. Mild epoxidation of dihydropyran in the presence of

Scheme 2. Precursor Synthesis and Cyclization



methanol yielded the 3-hydroxy-2-methoxyacetal **2a** as essentially pure trans isomer.[10] Well aware of the oft-times critical role of olefin stereochemistry in these processes,[11] we chose to proceed directly via the *Z*-silane in order to expedite our investigation; this fragment was readily constructed by using a modification of the known literature procedure.[12] Coupling ensued to afford the key substrate **3a** in overall satisfactory yield,[13] and cyclization studies could begin.

In the event, a brief survey of Lewis acid vs reaction conditions revealed BF_3-promoted cyclization to be both sufficiently rapid and essentially quantitative (GC-MS analysis). Furthermore, the reaction proceeded in exclusive fashion to furnish a single diastereomeric product, though isolated yield did drop somewhat due to inherent volatility.[14]

Although comparison with similar known trans compounds proved suggestive of a cis system, stereochemistry was not

(4) Acid chlorides: Burke, S. D.; Murtiashaw, C. W.; Dike, M. S.; Smith Strickland, S. M.; Saunders, J. O. *J. Org. Chem.* **1981**, *46*, 2400−2402. Nakamura, E.; Fukuzaki, K.; Kuwajima, I. *J. Chem. Soc., Chem. Commun.* **1983**, 499−501. Mikami, K.; Kishi, N.; Nakai, T. *Tetrahedron Lett.* **1983**, *24*, 795−798. Denmark, S. E.; Germanas, J. P. *Tetrahedron Lett.* **1984**, *25*, 1231−1234. Fukuzaki, K.; Nakamura, E.; Kuwajima, I. *Tetrahedron Lett.* **1984**, *25*, 3591−3594. Aldehydes: McIntosh, M. C.; Weinreb, S. M. *J. Org. Chem.* **1991**, *56*, 5010−5012. McIntosh, M. C.; Weinreb, S. M. *J. Org. Chem.* **1993**, *58*, 4823−4832. Ketones: Hoflack, J.; De Clercq, P. J. *Bull. Soc. Chim. Belg.* **1983**, *92*, 407−408. Thioacetals: Trost, B. M.; Murayama, E. *J. Am. Chem. Soc.* **1981**, *103*, 6529−6530.

(5) Overman, L. E.; Casteñada, A.; Blumenkopf, T. A. *J. Am. Chem. Soc.* **1986**, *108*, 1303−1304. Overman, L. E.; Blumenkopf, T. A.; Casteñada, A.; Thompson, A. S. *J. Am. Chem. Soc.* **1986**, *108*, 3516−3517. However, these latter studies have not always involved full participation of the silyl moiety, having invoked an alternative polar ene mechanism.

(6) A recent analogous approach to bridged oxabicyclics, employing both silicon- and sulfur-activated olefins, proceeded via ene and Prins pathways, respectively: Sasmal, P. K.; Maier, M. E. *Org. Lett.* **2002**, *4*, 1271−1274.

(7) By contrast the related reaction of iminium ions is a well-established strategy for alkaloid synthesis: Blumenkopf, T.; Overman, L. E. *Chem. Rev.* **1986**, *86*, 857−873.

(8) Chow, H.-F.; Fleming, I. *J. Chem. Soc., Perkin Trans. I* **1984**, 1815−1819.

(9) This possibility has not been overlooked, as elegantly exploited by Tius in a novel benzene annulation process: Tius, M. A. *Tetrahedron Lett.* **1981**, *22*, 3335−3338. Tius, M. A.; Ali, S. *J. Org. Chem.* **1982**, *47*, 3163−3166.

(10) Sweet, F.; Brown, R. K. *Can. J. Chem.* **1966**, *44*, 1571−1576.

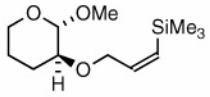
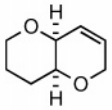
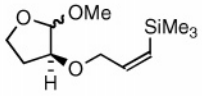
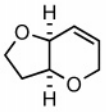
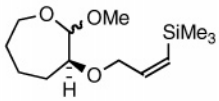
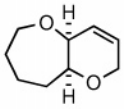
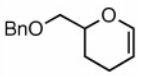
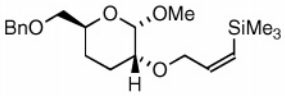
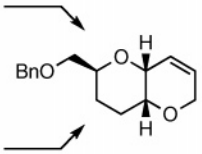
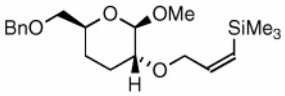
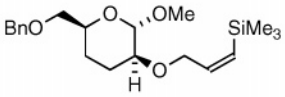
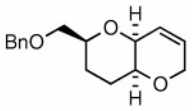
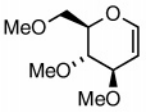
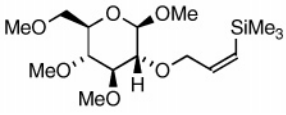
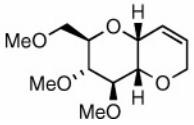
(11) In one rate study, an *E*-vinylsilane reacted >7000 times faster than its corresponding *Z*-counterpart: Overman, L. E.; Burk, R. M. *Tetrahedron Lett.* **1984**, *25*, 5739−5742. A similar observation was noted by Fleming, see ref 7.

(12) Heimstra, H.; Klaver, W. J.; Speckamp, W. N. *Recl. Trav. Chim. Pays-Bas* **1986**, *105*, 299−306.

(13) All new compounds were fully characterized by a wide range of analytical techniques, including ^{1}H and ^{13}C NMR, IR, MS, combustion analysis, and/or HRMS AMM.

(14) Similar low isolated yields (40%) have been reported in the trans-series: Alvarez, E.; Delgado, M.; Diaz, M. T.; Hanxing, L.; Pérez, R.; Martin, J. D. *Tetrahedron Lett.* **1996**, *37*, 2865−2868.

Table 1. Synthesis of Cis-Fused Bicyclic Ether Arrays—Initial Representative Survey[a]

entry	initial substrate, **1**	cyclization precursor, **3**	yield of **3**	bicycle, **4**	isolated yield of **4**[b]
a			76%		75%
b			64%		73%
c			63%		74%
d			64%		93%
e			61%		97%
f			68%		35%[c]
g			60%		75%[c]

[a] Depicted stereochemistry of all products is relative, except for entry g. [b] General procedure: dropwise addition of $BF_3{\cdot}OEt_2$ [2.5 equiv] to a stirred solution of precursor in CH_2Cl_2 at 0 °C, followed by warming to rt. [c] Cyclization performed at reflux.

readily obvious due to occluded signals in the initial NMR analysis, further complicated by long-range allylic interactions. Only after extensive decoupling studies in d_5-pyridine was a 2.6 Hz ^3J coupling revealed across the newly formed ring junction, thus allowing confirmation as cis.

Suitably encouraged, we subsequently adapted this method to a typical range of oxacyclic systems by simple exchange of the initial enol ether framework, Table 1. Similar exposure of dihydrofuran **1b** and tetrahydrooxepine **1c**[15] to our oxidation−etherification protocol afforded the requisite precursors. These underwent smooth cyclization to the [5,6] and [7,6] bicyclic arrays accordingly. In each case the cis-ring junction proved exclusive and was confirmed by subsequent NMR studies, with typical coupling values in the 2.5−4.6 Hz range.

Introduction of a simple substituent into the initial heterocyclic moiety served to probe overall potential for stereodivergent control of the process. Readily available benzyl ether **1d**[16] was subjected to nonspecific epoxidation with peracetic acid, yielding a mixture of three alcohol diastereoisomers.[17] Careful separation followed by etherification of each yielded both *anti*-anomers, **3d** and **3e**, along with *syn*-precursor **3f**. Cyclization thus allowed access to both cis-fused ether arrays accordingly, with overall complementary stereochemistry, albeit differing degree of success. Whereas both *anti*-precursors cyclized in near quantitative yield, *syn*-**3f** required more forcing conditions, under which competitive debenzylation led to formation of an anhydropyranose derivative as the major byproduct. Therefore it does appear evident the scope of the reaction will be susceptible

(15) Synthesis of the oxepin system: Oakes, F. T.; Yang, F.-A.; Sebastian, J. F. *J. Org. Chem.* **1982**, *47*, 3094−3097.

(16) Synthesis of the benzyl ether: Boschi, A.; Chiappe, C.; De Rubertis, A.; Ruasse, M. F. *J. Org. Chem.* **2000**, *65*, 8470−8477.

(17) These were obtained after acetylation of the initial crude mix, separation by flash chromatography, identification by extensive ^{1}H and ^{13}C NMR studies (including ^1J C−H anomeric coupling values), and finally, hydrolysis to re-yield each diastereoisomeric alcohol as a single isomer.

to the usual stereoelectronic factors prevalent in pyranose-type systems.[18]

Extension of this methodology to carbohydrate-type candidates was successfully demonstrated with trimethyl-D-glucal derivative **1g**.[19] Cyclization once again proceeded smoothly to yield pyranoglucose-system **4g**.[20] In this case the key cis-ring junction coupling rose to 6.2 Hz, indicative of a slightly flattened $^4C_1$ cis-fused chair, as previously observed in the related pyranoisochroman systems.[21]

In these latter examples, it is important to note that in each case the relative stereochemistry of the ring junction is a direct consequence of the epoxidation step, for which many selective technologies have arisen in recent years.[22]

(18) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Baldwin, J. E., Ed.; Pergamon Press: Oxford, U.K., 1983.

(19) Synthesized from D-glucal in two steps: (a) Permethylation: Dunkerton, L. V.; Adair, N. K.; Euske, J. M.; Brady, K. T.; Robinson, P. D. *J. Org. Chem.* **1988**, *53*, 845−850. (b) Epoxidation/methanolysis: Chiappe, C.; Lo Moro, G.; Munforte, P. *Tetrahedron*: *Asymmetry* **1997**, *8*, 2311−2317.

(20) The analogous perbenzylated compound has been reported (ref 3b).

(21) Verlhac, P.; Leteux, C.; Toupet, L.; Veyrières, A. *Carbohydr. Res.* **1996**, *291*, 11−20. Bürli, R.; Vasella, A. *Helv. Chim. Acta* **1996**, *79*, 1159−1168.

(22) For example, Gin's complementary sulfonium-mediated oxidative glycosylations: Kim, J-Y.; Di Bussolo, V.; Gin, D. Y. *Org. Lett.* **2001**, *3*, 303−306.

In summary, we have demonstrated an expeditious entry to cis-fused [*n*,6] bicyclic ether arrays from cyclic enol ethers, in complete regio- and stereospecific fashion. We are currently developing this methodology further to the complementary [*n*,*m*] systems by simple increase of tether length accordingly. In addition we hope to apply this strategy to the total synthesis of several bioactive natural products containing these important structural motifs.

Acknowledgment. We thank The Robert A. Welch Foundation for generous support of this work (Individual Award V-1450). S.P.F. is also grateful to the Gill Foundation for a Science Faculty Development Award, and The City University of New York for provision of start-up funds (Vice-Chancellor's Award).

Supporting Information Available: General experimental procedure for cyclization; ^{1}H and ^{13}C NMR spectra and data and confirmatory analyses for all cis-fused bicyclic ether products (**4a** through **4g**). This material is available free of charge via the Internet at http://pubs.acs.org.

OL071349V