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FURANS IN SYNTHESIS 10.[1] AN EFFICIENT CONSTRUCTION OF THE BICYCLO[5.3.0]DECANE RING SYSTEM OF FASTIGILIN-C

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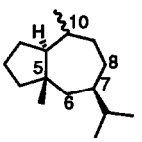
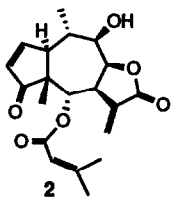
Abstract: *The efficient preparation of an advanced intermediate for the synthesis of Fastigilin-C 2, via a furan terminated cationic cyclization, is described.*

For the past several years we have been investigating furan terminated cationic cyclizations as the key step in the construction of linearly fused-, bridged-, and spirocyclic-alkaloid and terpenoid ring systems.[3] Recently our attention has focused upon the facile preparation of the bicyclo[5.3.0]decane ring system present in the pseudoguaianolides. The pseudoguaianolides, a group of butyrolactone containing sesquiterpenes, are divided into the ambrosanolides **1a** (10β-CH_3, lactone fused *via* C-6 -C-7 or C-7 - C-8) and the helenanolides **1b** (10α-CH_3, lactone fused C-7 - C-8). The helenanolides are more highly oxygenated, stereochemically complex, and have been associated with diverse biological activities. [4,5] Fastigilin-C **2**[6a,b] is one of the most intriguing of the helenanolides; exhibiting substitution at each of the carbon atoms of the cycloheptane ring, and it has been reported to exhibit extremely potent cytotoxic and antineoplastic activity,[6a] thus making it an attractive target for total synthesis.[7] Lansbury[6c] has recently reported an approach to **2** which provides 2,3-dihydro fastigilin-C. Unfortunately the Lansbury group was unable to complete the synthesis of **2**; being foiled by the A-ring enone double bond during the final stages of the synthesis. Our interest in this area and the recent report of Lansbury[6c] have prompted us to disclose our efforts directed toward the synthesis of **2**.

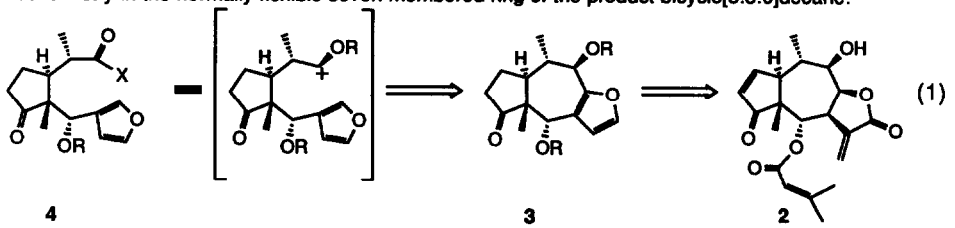


1a 10-β-CH_3 Ambrosanolides
1b 10-α-CH_3 Helenanolides



2

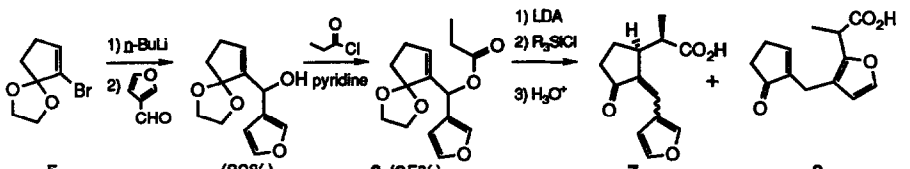
Based upon our earlier work[1,3] we envisioned constructing the furan containing bicyclo[5.3.0]decane nucleus from a cyclopentanone **4** which possessed a cyclization initiator (stabilized carbocation) and terminator (furan) which would afford a stereochemically complex tricycle (equation 1). Furan represents the operational equivalent of a variety of useful functionalities,[1,3,8,9] including a butyrolactone,[8,9] and its incorporation will allow excellent control of regiochemistry in the introduction of this subunit, and will also provide routine control of stereochemistry in the normally flexible seven membered ring of the product bicyclo[5.3.0]decane.



4 **3** **2** (1)

Equation 1 outlines our plan for the preparation of an advanced fastigilin-C **2** intermediate. We would introduce the 2,3-double bond late in the sequence and *hide* it while the butyrolactone was being produced. The numerous methods available for the introduction of this double bond afforded to us by the utilization of robust protecting groups for the C-6 and C-9 oxygens and a masked butyrolactone; together with the flattening and chair like conformation of the B-ring make **3** a desirable target. We envision **3** resulting from furan attack upon the oxo-stabilized cation depicted in equation 1; with ketone **4** serving as the latent operational equivalent of the illustrated cyclization intermediate. Our first approach to the synthesis of **4** is presented in equation 2.

The Ireland[10] ester enolate Claisen rearrangement was first examined for its ability to construct a cyclization precursor. Toward that end 2-bromo-cyclopentenone dioxolane **5**[11] was treated with n-BuLi, followed by 3-furaldehyde to give the corresponding furyl carbinol (89%, eq.2). Acylation (propionyl chloride, pyridine) furnished propionate **6** (95%) which was treated with LDA and TBDMS-Cl (-78°C) followed by warming to room temperature, provided a 69% yield of a 95:5 mixture (after hydrolysis) of the desired furan **7**[12] and a disubstituted furan **8** which results from a competitive Claisen rearrangement through a double bond of the furan. [13] We found that this ratio of desired to undesired rearrangement products could be profoundly influenced by the nature of the alkyl groups on the silylating reagent, as illustrated in equation 2. With **7** in hand we were required to introduce a 5-CH_3, 10-OH (with proper relative stereochemistry) and examine the crucial cyclization. We found that modification of these two centers was quite difficult; therefore we resorted to the approach described in Scheme I.



5 (89%) **6** (95%) **7** + **8**

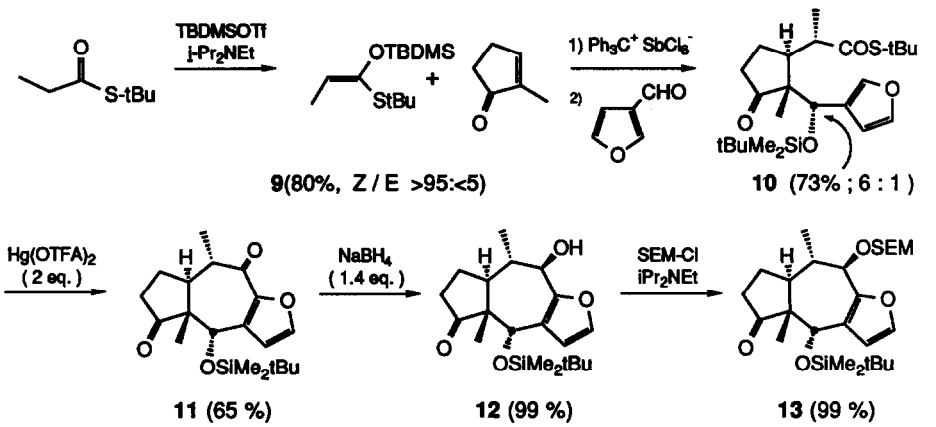
R_3SiCl	Yield	Ratio (7/8)
t-$BuMe_2$	69%	95 : 5
$(Me)_3$	79%	75 : 25
(i-Pr)$_3$	73%	20 : 80

Mukaiyama has recently described a trityl salt catalyzed tandem conjugate addition-Aldol condensation sequence[14] to form a trans-disubstituted cyclopentanone with predictable exo-cyclic stereochemistry. Such a protocol seemed to be ideally suited to the synthesis of our target cyclopentanone **4**. Toward that end t-butyl thiopropionate was treated (Scheme I) with TBDMSOTf (iPr_2NEt) to give the related silyl ether **9** (80%, Z/E = >95:<5[14,15]) which was combined with 2-methyl-2-cyclopentenone (CH_2Cl_2, -95°C) followed by 5 mole% of Ph_3CSbCl_6.[14] After stirring for 20 minutes at -95°C 3-furaldehyde (in CH_2Cl_2) was added and the mixture was allowed to warm to room temperature over 12 hours to furnish a mixture of **10** and pro-C-6-iso-**10** (73%, 6:1) that was difficult to separate.[16] We were unable to detect the presence of any materials with alternative relative stereochemistries at pro-C-1, -5, and -10; the ratio of 6:1 at pro-C-6 is in agreement with the reports of Mukaiyama[14] and is temperature dependant. The ratio of **10** to 6β-**10**, which has been optimized at ca. 6:1 (-95°C), falls to ca. 2.5:1 at -80°C.

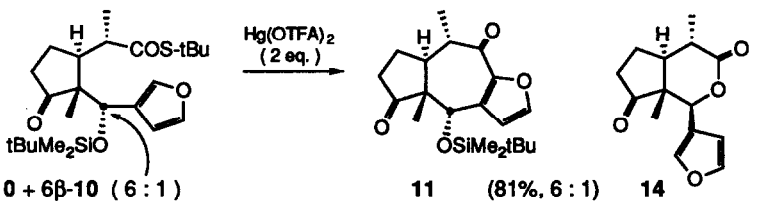
With our cyclization substrate in hand we turned our attention to the ring closing reaction. After several attempts (CuOTf[17a], $(Me)_3OBF_4$) we found that we could smoothly effect the desired cyclization by exposing **10** to $Hg(OTFA)_2$[17b,c] (2 eq., in anh. CH_3CN, room temperature) to furnish the bicyclo[5.3.0]decane containing furan **11** (65%) as a white crystalline solid (mp = 119-121°C). The facility of this closure coupled with the difficult separation of **10**

from 6β-**10** caused us to consider cyclizing the mixture of **10** and its pro-C-6 stereoisomer. In the event (eq. 3) a 6:1 mixture of **10** and 6β-**10** were treated with $Hg(OTFA)_2$ to provide an 81% yield of a 6:1 ratio of ketone **11** and lactone **14**. These two materials are readily separated; thus negating the need for the tedious purification of **10**. In a separate experiment 6β-**10** was exposed to $Hg(OTFA)_2$ to give, exclusively, lactone **14**.

Scheme I: The Synthesis of 13, a Fastigilin-C Precursor



The fifth of the seven B-ring stereocenters of fastigilin-C **2** was then smoothly and selectively introduced (Scheme I) by reduction of the 9-one with $NaBH_4$ (MeOH) to give 9β-alcohol **12** (99%) as a single stereoisomer. Alcohol **12** was then protected as the related SEM-ether[19] giving **13** (99%). Our assignment of the reduction stereochemistry as 9β-OR is based upon a comparison of the ^{1}H-NMR spectrum of **12** with a related furan prepared by Schultz in his synthesis of aromatin.[9] The vicinal C-9 - C-10 coupling (C-9 d, J = 9.69Hz) is close to that reported by Schultz (C-9 d, J = 9.4Hz); and is in good agreement with the coupling values expected from the energy minimized conformation of **12** (C-9 - C-10 dihedral angle = 170°).[18] Support for the relative stereochemical assignments depicted in Scheme I was realized after a rigorous analysis of ^{1}H- spectra of alcohol **12**.[20]



(3)

In conclusion, we have reported an efficient (4 steps from enol ether **9**, 40% overall yield) and stereoselective synthesis of an advanced intermediate (**13**) in a projected construction of the pseudoguaianolide fastigilin-C **2**. Worthy of note is the excellent control of stereochemistry about the periphery of the seven-membered B-ring and the facility of preparation *via* a furan terminated-cationic cyclization. Efforts directed toward the conversion of **13** to fastigilin-C **2** are underway and will be reported in due course.

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12) The stereochemistry indicated for **7** has not been rigorously established; however it is expected based upon literature precedent (see ref. 10 and references cited therein).
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16) At this juncture the relative stereochemistry at pro-carbons -1,-5,-6, and -10 has not been established, however it is anticipated to be as drawn based upon the precedent of Mukaiyama (see ref. 14). The ratios observed at these centers are in good agreement with the observations of Mukaiyama.
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20) Extensive NOE studies were performed on alcohol **12** at 500 MHz with a Bruker AM-500 spectrometer. These included: 2-D NOESY and selective 1-D NOE difference experiments. The relative stereochemistry at the 1-, 10-, and 9-positions is supported since proton 9-H shows strong NOEs to H-1 (*cis*), and to the C-10 methyl (*cis*). However only a very weak NOE is observed to the 10-H (*trans*). The relative stereochemistry depicted at the 1-, 5-, and 6-positions is supported by the NOE observed from the 6-H to the C-5 methyl (*cis*), but no NOE is seen to the 1-H (*trans*). If the alternative C-9 stereochemistry had been obtained, a strong NOE would have been expected from 9-H - 10-H and a weak NOE to the 1-H.

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