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Furans in Synthesis 9. [1] Approaches to the Syntheses of Guaianolides and Pseudoguaianolides

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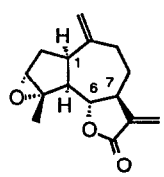
Abstract : The bicyclo[5.3.0]decane containing **23**, which should serve as a precursor to a variety of guaianolides and pseudoguaianolides has been constructed in 5 steps and 36% overall yield *via* a furan terminated cationic cyclization.

Bicyclo[5.3.0]decane subunits occur in nature as integral parts of complex bioactive natural products such as guaianolides [2] and pseudoguaianolides [2]. These functionally and stereochemically complex compounds have attracted considerable attention from the chemical community, due in large part to potent and diverse biological activities which have been associated with various members of these classes. These include antitumor , antineoplastic , antileukemic , allergenic , antihelmentic , antifeedant , contraceptive , molluscicidal , and antiinflammatory properties. As a result of these potent activities and the small quantities of material generally available from plant sources the less complex guaianolides and pseudoguaianolides have been popular targets of total chemical synthesis [3,4]. The guaianolides may be represented by estafiatin **1** and compressanolide **2**. These compounds generally possess a cis-ring fusion and a butyrolactone moiety fused to the seven-membered ring *via* either positions C6-C7 or C7-C8. The pseudoguaianolides are divided into the ambrosanolides (β-CH_3 at C-10) and the helananolides (α-CH_3 at C-10). Relatively simple ambrosanolides are represented by damsin **3** , ambrosin **4** , and parthenin **5** .



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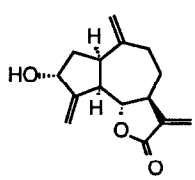

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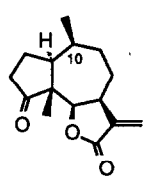

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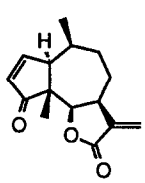

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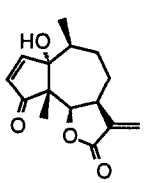

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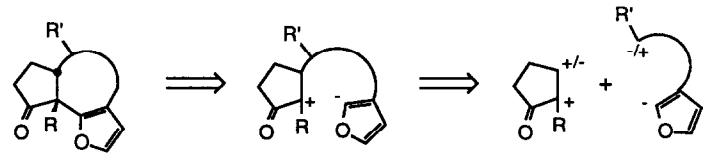
Compounds **1** - **5** have a butyrolactone ring fused to the common bicyclo[5.3.0]decane skeleton at C6-C7 fused in either a cis- or trans-fashion. They also possess 2-3 additional stereocenters about the periphery of the generally conformationally mobile seven-membered ring. Given the potential problems in stereochemical control posed by this flexibility, significant conformational rigidity and thus control of stereochemistry might be achieved through the introduction of a double bond into the seven membered B-ring. Central to our approach to the synthesis of molecules **1** - **5** is the use of a furan as a terminator function in cationic cyclization sequences [1,5]. The furan will supply the requisite double bond equivalent, enabling the B-ring to adopt a stable chair conformation, and yielding the desired butyrolactone after chemical manipulation. In this letter we will describe a general strategy which should permit the construction of **1** - **5**.

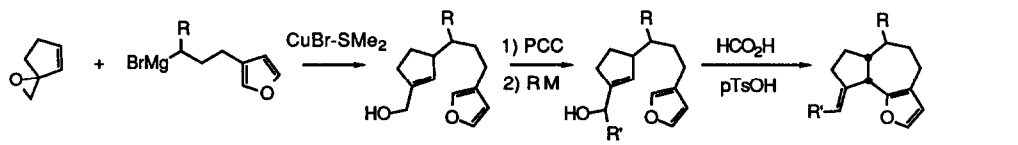
Our experience in the field of furan terminated cationic cyclizations [1,5] suggested the approach outlined in Scheme I for the syntheses of compounds **1** - **5**. Selective reaction at the side chain of a 3-substituted furan nucleophile or electrophile with the depicted cyclopentanone dication or anion/cation equivalent would give the hypothetical intermediate **6**. Unmasking a latent α-keto-carbenium ion equivalent would afford **7** after electrophilic aromatic substitution [1,5]. With proper choice of R- and R' one could approach either the guaianolides **1** - **2** or the pseudoguaianolides **3** - **5**. We have successfully utilized vinyl-spiroepoxides as cyclohexanone dication equivalents [5] which suggested employing the vinyl spiro-epoxides prepared from cyclopentenone [5f] and 2-methyl-cyclopentenone [5f] for the present application. Scheme II describes our initial studies.

Scheme I

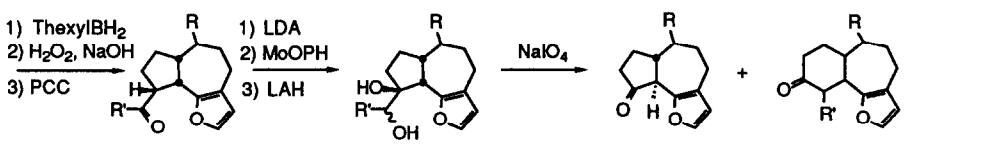


7 **6**

Scheme II



8	**9**	**10** R	Yield	**11** R	R'	Yield	**12** R	R'	Yield
		H	85%	H	Me	84%	H	Me	92%
		$=CH_2$	69%	H	Ph	64%	H	Ph	87%
				H	pMeOPh	63%	H	pMeOPh	74%



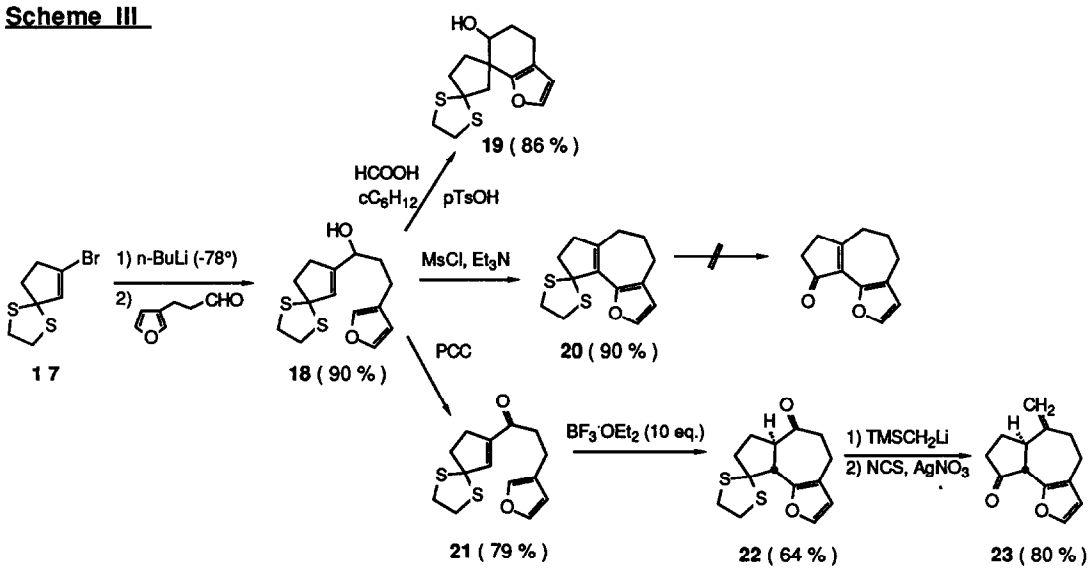
13 R	R'	Yield	**14** R	R'	Yield	**15** R	Yield	**16** R	R'	Yield
H	Me	42%	H	pMeOPh	60%	H	35%	H	pMeOPh	51%
H	Ph	45%								
H	pMeOPh	40%								

In principal either the guaianolides or pseudoguaianolides could be prepared from spiro-epoxides **8** [5f], in practice we were unable to realize this goal, for every attempt to react **8** (R' = Me) in Sn_2' fashion with Grignard reagents **9** (Cu [1])[5] resulted in epoxide opening and addition of the organometallic to the β,γ-unsaturated aldehyde. However **8** [5f] (R = H) reacted smoothly with organometallics **9** affording allylic alcohols **10** (Scheme II, 69 - 85 % yields). Alcohols **10** would not cyclize, but oxidation (PCC) and organometallic addition provided the corresponding 2°-allylic alcohols which were readily cyclized (HCO_2H , cC_6H_{12} ; followed by pTsOH) furnishing olefins **12**[6a] in 74 - 92 % yield. We envisioned an olefin cleavage, in either 1 or 2-steps, to give the desired ketone **7**.

Toward that end we exposed **12** (R = H; R" = Me) to a variety of reagents designed to vicinally hydroxylate the double bond or directly yield the ketone. These included: a) OsO_4 (catalytic or stoichiometric)[7a-e]; b) $KMnO_4$ [7f-g]; c) RuO_4 (catalytic or stoichiometric) [7h-j]; d) O_3 ; or e) MCPBA followed by acidic aq. periodate. With the exception of conditions e) (3%) we were unable to obtain **15**. We next examined the conversion of **12** to ketones **13** (40 - 45% yield) by hydroboration, and oxidation (H_2O_2, base; followed by PCC). At this point a number of alternatives were explored including Baeyer-Villiger oxidation and enol ether ozonolysis to no avail. In each of these cases we observed either no reaction, or furan destruction. We finally obtained ketone **15** as described in the lower portion of Scheme II. Ketone **13** (R = pMeOPh) was treated with LDA and MoOPH [8] to give a single diol **14** (60%, stereochemistry not determined) after reduction (LAH). Diol cleavage ($NaIO_4$, aq. tBuOH) afforded a mixture of **15** (35%) and **16** (51%), the latter a product of a pinacol-type rearrangement.

The Scheme II route does give **15**, however it is altogether too long (10 steps) and the overall yield is an abysmal 3.3%. As an alternative we examined the chemistry outlined in Scheme III. In this sequence we hoped to avoid the troublesome C=C cleavage by carrying the C=O center into the scheme in a protected form.

Scheme III



The dithioketal **17** [9a,b], prepared from 1,3-cyclopentane dione, was metallated (nBuLi) and reacted with 3-(3-furyl)-propanal to give alcohol **18** (90%). Exposure of **18** to our "standard" allylic alcohol cyclization conditions (i. HCO_2H, cC_6H_{12}; ii. pTsOH) provided spirocycle **19** (86%) as the only isolated product. The desired mode of reaction was observed after specific C-O bond activation (MsCl, Et_3N) [9c] to furnish **20** (90%), a compound in which the double bond had migrated to the 1,5-position. At this stage we examined the conversion of **20** to ketone **15**. We were unable, despite numerous attempts, to effect this transformation. These difficulties and the stranding of the double bond in the 1,5-position caused us to consider the "safer" alternative presented in the lower portion of Scheme III.

Alcohol **18** was oxidized (PCC) furnishing enone **21** (79%); which was smoothly cyclized with $BF_3{\cdot}OEt_2$ to provide almost exclusively the trans fused **22** (64%; 6:1 trans to cis)[6b]. Ketone **22** was reacted with $TMSCH_2Li$ [9d-i] to provide an

intermediate silylmethyl carbinol. Exposure of this alcohol to NCS , $AgNO_3$ [9j] gave only trans fused **23**[6b] (80%) which had not only suffered deprotection but had also been converted to the desired 10-exo-methylene derivative. We are now examining the conversion of **23** to compounds **1** - **5**, these results will be reported in due course.

In summary; we have extended our furan terminated cationic cyclization studies to the synthesis of bicyclo[5.3.0]decane ring systems. Our route to the nicely functionalized ketone **23** is short (5 steps) and affords the target in a respectable 34% overall yield. Our studies of the conversion of **23** to compounds **1** - **5** are expected to provide the information on the control of stereochemistry in the normally flexible 7-membered ring needed for an assault on the more functionally and stereochemically complex pseudoguaianolides such as fastigilin-C as well as the daphnane and tigliane diterpenes.

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6) a) Although not specifically demonstrated the obtention of a *cis* - fused product is expected from the method of synthesis, and literature precedent (see ref. 5c and references cited therein); b) Vandewalle has reported (ref. 6c,d) that the $J_{1,5}$ values for trans and cis-fused perhydroazulenes are ca. $J_{1,5}$ (cis) 12-13Hz and $J_{1,5}$ (trans) 10-11Hz. Compound **15** exhibits a resonance attributed to H-5 at 3.71ppm (d, J= 6.6Hz); we have performed MM2 calculations which suggest that **15** should be more stable than its cis counterpart by ca. 1.9kcal. Further support for the thermodynamic preference of related trans-fused bicyclo[5.3.0]decane ring systems have been reported by Rigby (ref. 6e) and Seebach (ref. 6f). Compound **22** exhibits 5-H resonances at 3.66(brd, J= 8.5Hz, 0.85H), and 3.12(d, J= 13.1Hz, 0.15H) attributed to trans and cis-**22** respectively; **23** 3.75ppm(d, J= 8.7Hz, 1); MM2 calculations suggest trans-**23** is more stable than its cis counterpart by >2kcal; c) Devreese, A.A.; Demunyck, M.; DeClercq, P.J.; Vandewalle, M. *Tetrahedron* **1983**, *39*, 3039; d) *ibid* , *idem* **1983**, *39* , 3049; e) Rigby, J.H.; Wilson, J.Z. *J. Am. Chem. Soc.* **1984**, *106* , 8217; f) Weller, T.; Seebach, D.; Davis, R.E.; Laird, B.B. *Helv. Chim. Acta* **1981**, *64* , 736.

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