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Novel Methods for the Construction of 3-(2H) Furanone Spiroketals.

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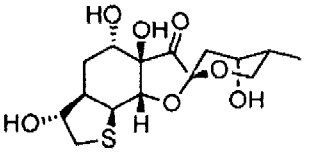
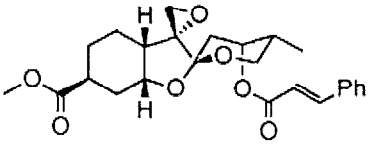
Abstract: Two stereoselective routes to the 3-(2 H) furanone spiroketal **1** have been achieved.

The 3-(2H) furanone moiety is found in a wide range of natural products including the anticarcinogen phyllanthoside[2] and the hypocholesterolemic breynins.[3] The total synthesis of phyllanthoside[4] and several approaches to phyllanthocin[5] have been reported Breynolide, the aglycon of the breynins has just recently been synthesized by the Williams[6] and Smith[7] groups. We report here two novel approaches to the construction of the furanone backbone of breynolide and phyllanthocin based on α-alkoxystannanes.



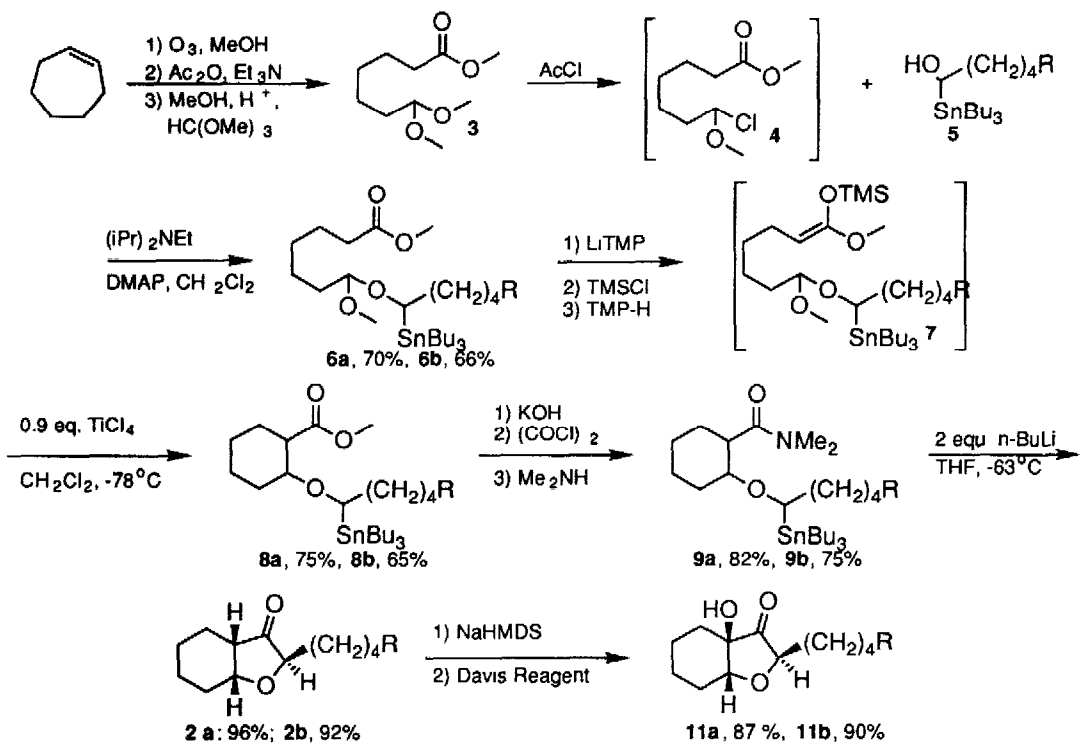
Breynolide



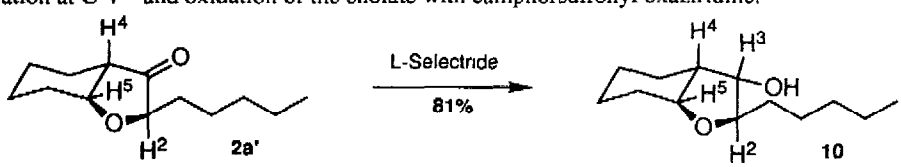
Phyllanthocin

Initially, a model study for the construction of bicyclic furanone **2** (**a**, R = Me; **b**, R = OMOM) was carried out as shown in Scheme 1 Ozonolysis of cycloheptene employing the conditions reported by the Schreiber group[8] provided the ester aldehyde in excellent yield. Although the ester acetal product may be obtained directly from the ozonolysis reaction, better results were obtained by transforming the aldehyde to the dimethyl acetal **3** in a second step. Conversion of **3** to the α-chloro ether **4**[9] and subsequent coupling with the α-hydroxyalkylstannane **5**[10] gave the mixed stannyl acetal **6** in 66 - 70% overall yield. Enolization using lithium tetramethylpiperidide (LiTMP), and subsequent O-silylation using Me_3SiCl, and a second equivalent of tetramethylpiperidine (required) provided **7**. Treatment of the crude silyl ketene acetal with 0.9 eq $TiCl_4$ at -78°C in CH_2Cl_2 induced the 6-$exo_n$$exo_e$[11] intramolecular Mukaiyama reaction with complete regioselectivity to provide the cyclohexane **8** in 65-75% overall yield from **6** Conversion of the ester to the dimethylamide **9** was straightforward Intramolecular nucleophilic addition of the α-alkoxylithio species (generated in situ by the addition of 2 eq BuLi at -63°C)[12] provided the furanone **2** in >90% yield. The relative stereochemistry of the major isomer of furanone **2a** (crude product ratio 8.6 1.1:1) was assigned by 1D and 2D NOE experiments as that shown in Scheme 1. This observation was surprising in light of MM2 calculations which indicated that the *cis* ring fused isomer with the C-2 alkyl group α was favored by nearly 4 kcal/mol relative to the C-2 alkyl β isomer **2a** isolated. Further verification of the stereochemical assignment was obtained by stereospecific reduction of the furanone carbonyl of **2a** to alcohol **10** with L-Selectride. Irradiation of H^4 in **10** revealed an NOE enhancement for H^3 and H^5 indicating that hydride addition had occurred from the top face of the

Scheme 1

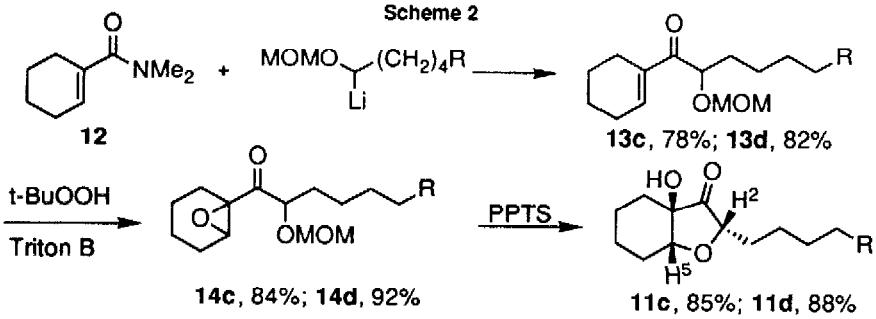


molecule. In agreement with this result, no NOE enhancement was observed between H^3 and H^2 of **10**. The regiochemistry and stereochemistry of the intramolecular aldol reaction is influenced by the trialkylstannane substituent.[12] The relative stereochemistry of H^5 and the C-2 alkyl substituent results from preferential addition of the ketene silyl acetal on an intermediary oxocarbenium ion from the face opposite the bulky stannane.[13] Introduction of oxygen at C-4 to provide furanone **11** was readily accomplished via regiospecific deprotonation at C-4[14] and oxidation of the enolate with camphorsulfonyl oxaziridine.[15]



An alternative approach to furanone **11** is illustrated in Scheme 2. Nucleophilic addition[16] of an α-alkoxylithio anion to unsaturated amide **12** provided the α-alkoxy ketone **13** (**c**, R = H; **d**, R = OTBS) Nucleophilic epoxidation of the double bond using t-butylhydroperoxide and Triton B gave the keto epoxides **14c** and **14d** as an 85:15 or 87:13 mixture of isomers, respectively. The selectivity of the epoxidation may arise via a preferred eclipsed conformation of the carbonyl and the α-alkoxy group resulting in stereoselective approach of the hydroperoxide anion away from the bulkier alkyl substituent. Reaction of the isomeric mixture of **14** in ethanol with pyridinium *p*-toluene sulfonate removed the methoxymethyl acetal protecting group and

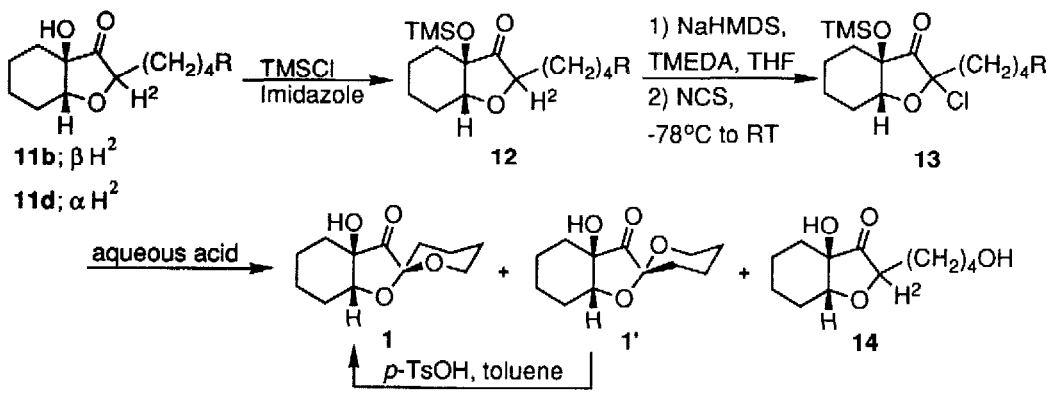
Scheme 2



afforded the ring closed furanone **11c** in 85% yield. Acid catalyzed cleavage of the TBDS group was also observed for **14d**. Regiospecific reprotection of the primary alcohol was accomplished in 92% yield. The relative stereochemistry of bicyclic furanone **11c** was clearly not identical to **11a**. MM2 calculations of the possible isomers of **11** revealed that the most stable isomer exhibited *cis* ring fusion with the C-4 hydroxy β and the C-2 alkyl group α, i. e., furanone **11c**. Confirmation of the stereochemical assignment of **11c** was obtained by comparison of the calculated coupling constants for H^5 and H^2 (dihedral angles obtained from the calculated MM2 structures) with the spectral data observed. Furthermore, acetylation of the C-4 hydroxy group in **11c** resulted in a downfield shift of both H^2 and H^5. Thus, the two approaches to furanone **11** in Schemes 1 and 3 provide products with complementary stereochemistry at the C-2 site.

Oxidation and spiroketalization of **11** is shown in Scheme 3. Deprotonation at C-2 of **11** was substantially more difficult than enolization of **2** at C-4. Several attempts to generate a dianion by direct

Scheme 3



deprotonation of **11** were unsuccessful. Derivatization of the tertiary alcohol with Me_3SiCl was readily accomplished to provide the TMS/TBDS bis silyl ether **12d** in 93% yield. The initial plan was to form the silyl enol ether and oxidize C-2 by epoxidation; however, generation of the enolate and attempted O-silylation only resulted in the C-silylated product in modest yield. Oxidation of C-2 was best accomplished by reaction of the enolate with N-chlorosuccinimide and direct treatment of the crude α-chloro ketone **13** with methanolic HCl. *In situ* deprotection of the TBDS ether of **13d** and spiroketalization with 10% HCl in MeOH provided the ketal **1** in 55% overall yield from **12** along with 25% of the diol **14**. The ketal **1** was obtained as a 1 9:1 (**1**:**1'**)

mixture of isomers. The stereochemistry of **1** was assigned by ^{13}C NMR chemical shifts (ketone and C-11) in analogy with a similar spiroketal reported by Smith and co-workers[4]. Acid catalyzed equilibration of the mixture of isomers (TsOH, benzene, reflux 28 h)[4] provided a 6:1 ratio of **1**:**1'**. Furanone **13b**, on the other hand, required harsher conditions to remove the MOM group. Deprotection of the MOM with 6 N HCl/ THF at reflux resulted in a 35% yield of **1** and a 5% yield of **14**.

In summary, we have presented two new and stereochemically complementary approaches to cyclic furanones. A furanone spirocyclic ketal model system for the synthesis of breynolide has also been successfully carried out.

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References and Footnotes

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13. These results are in agreement with recent computational studies by Houk and coworkers (Broeker, J L.; Hoffmann, R. W.; Houk, K. N. *J Am Chem. Soc.* **1991**, *113*, 5006 - 5017). For a review of 1, 3 - allylic strain in stereoselective transformations of heteroatom double bonds, see Hoffman, R. W. *Chem. Rev* , **1989**, *89*, 1841. We are currently pursuing more detailed studies of this novel method for stereocontrol.
14. Deprotonation studies indicated that the kinetic and thermodynamic enolates are formed at C-4 Therefore, the ring closure of **9** to **2** may also result in epimerization at C-4 to provide only the *cis* ring fusion; however, epimerization at C-2 is not possible. Indeed, subsequent studies using **11b** indicate that epimerization at C-2 results in preferential formation of the C-2 alkyl β isomer, i. e , the relative stereochemistry at C-2/ C-5 in **2** arises from the aldol reaction.
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