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Studies on the Synthesis of Highly Substituted Furans: The Synthesis of Calicogorgins A and C

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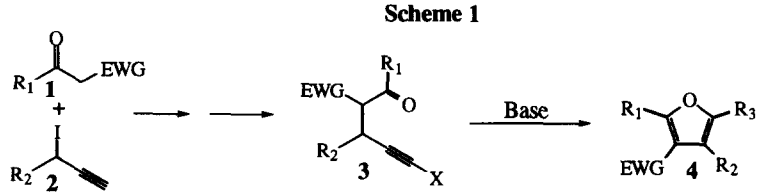
Abstract: A short and highly efficient synthesis of calicogorgin A and C has been accomplished. The key features include a rapid assembly of the furanyl moieties, a sulfonyl anion alkylation to join the two halves and a bis-reductive desulfurization. © 1997 Elsevier Science Ltd. All rights reserved.

We have recently developed a synthetic strategy that allows for the rapid assembly of highly substituted furans from malonate and acetoacetate precursors, Scheme 1.[1] This methodology allowed for the facile construction of di-, tri-, and tetrasubstituted furans with multiple functionality present. With the culmination of this work, it was our intent to demonstrate the utility of this methodology in natural product synthesis. The calicogorgins (**5-7**), isolated from marine invertebrates, are 3-ketosphinganine derivatives which show lethal and repellent activities against the gastropod *D. fragum*, Scheme 2.[2] At 30 ppm, they exhibited 100% mortality in the snail within 24 hours, as well as a marked activity to the snail at 45 μm/cm^2 in the bioassay for repellent activity.[2] The structure of these compounds was primarily determined on the basis of spectroscopic evidence.

A retrosynthetic analysis for two members of this family, calicogorgin A and C, is given in Scheme 2. It was envisioned that they could be efficiently constructed by alkylation of furyl sulfone **8a/b** with bromide **9**.[3] Simultaneous reductive removal of the sulfone and sulfonamide, followed by functional group manipulation would furnish the natural product. Furyl sulfone **8a/b** could be created from the appropriate acetoacetate (**10**) and alkynyl sulfide (**11**), while bromide **9** could be produced by Grignard addition of a suitable nonanol derivative (**12**) to N-phenylsulfonyl serine (**13**) following the Rapoport protocol.[4]

Scheme 1

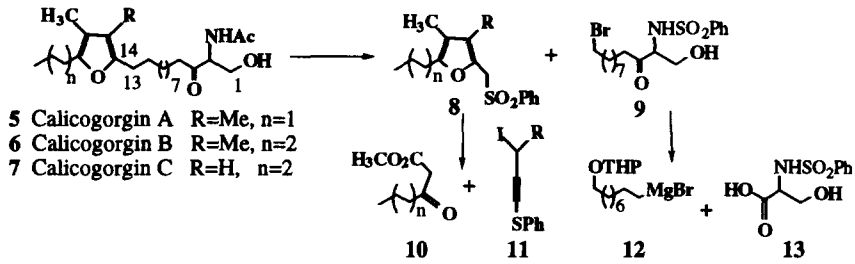


R_1 = alkyl, aryl, ether
R_2 = H, alkyl
EWG = ester, ketone

X = SOPh, SO_2Ph, CO_2CH_3, CH_2Br, CO_2H, CHO

R_3 = CH_2SOPh, CH_2SO_2Ph, $CH_2CO_2CH_3$, $CHCH_2$, CH_2CO_2H, CH_2CHO

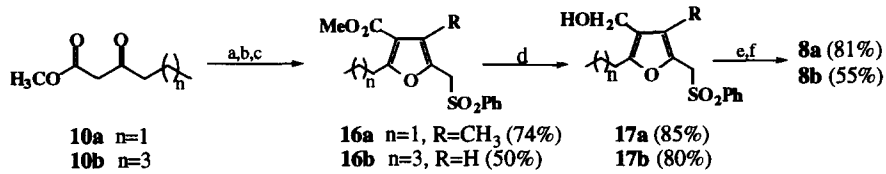
Scheme 2



The synthesis of calicogorgin A and C[5] began with construction of the furyl sulfone, Scheme 3. Alkylation of acetoacetates **10a/b**[6] with 3-iodo-1-thiophenyl-1-butyne (**14**)[7] or 3-iodo-1-thiophenyl-1-propyne (**15**),[7] followed by oxidation with mCPBA, and isomerization with benzyltrimethylammonium methoxide (BTMAOMe) in methanol, spawned furans **16a/b** in excellent overall yields, as expected. This alkylation was a slight modification from our original protocol[1] in that the alkynyl sulfide moiety was fully intact and did not have to be introduced in a separate step after the alkylation. Although nucleophilic additions are known to occur readily at the β-carbon of alkynyl sulfides,[8] there was no evidence of such additions in these reactions.

With the furan skeleton intact, completion of the "left portion" of the molecule required exhaustive reduction of the ester group. Although methods exist for this direct transformation, they did not prove useful in this synthesis, consequently reduction *via* the alcohol was pursued. Treatment of esters **16a/b** with DIBAL gave the corresponding alcohols (**17a/b**) in good yields, however, all endeavours to directly reduce these alcohols to methyl groups failed. Fortunately, when **17a/b** were converted to their iodides (PPh_3, I_2 and imidazole),[9] and the unstable iodides were directly subjected to hydride reduction, ($NaCNBH_3$, HMPA),[10] the desired furans (**8a/b**) were obtained in 81% and 55% respectively.

Scheme 3



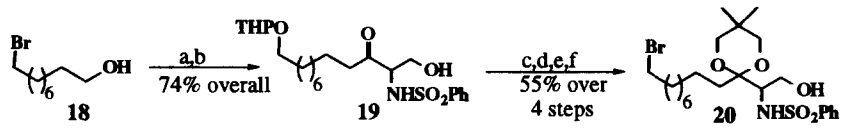
Reagents: a) NaH, **14** or **15**, THF; b) mCPBA (2 eq.), CH_2Cl_2; c) BTMAOMe (25 mol %), MeOH, 14 h; d) DIBAL (2 eq.), CH_2Cl_2, -78°C; e) PPh_3, I_2, imidazole, CH_3CN, Et_2O; f) $NaCNBH_3$, HMPA, 50°C.

Synthesis of the "right half" began with 9-bromo-1-nonanol (**18**), Scheme 4. Protection of the alcohol as its THP-ether, ensued by treatment with magnesium metal generated the Grignard reagent (**12**). Addition of 5 mole equiv. of this reagent to (±)-N-phenylsulfonyl serine **13**, pretreated with 2 mole equiv. of n-BuLi, furnished ketone **19** in 80% yield.[4] The use of 2 mole equiv. of n-BuLi and a large excess of Grignard reagent is crucial to the success of this reaction. Since the reaction is presumed to proceed *via* the trianion of

N-phenylsulfonyl serine, the n-BuLi serves two purposes: 1) it reduces the amount of Grignard reagent required to effect reaction, and 2) the lithium counterion improves the yield of the adduct; that is, with only magnesium salts the rate of reaction is slow and the yield of ketone adduct is low.[11]

Manipulation of the various functional groups such that the desired C-C bond could be formed and that the substrate could be easily transformed into the natural product was now the requirement, Scheme 4. This task began with the protection of the primary alcohol as its *tert.*-butyldiphenylsilyl ether,[12] THP-ether deprotection with acidic methanol to produce the primary alcohol,[13] followed by direct conversion to the bromide.[14] Unfortunately, attempted ketalization of the TBDPS-ether under a variety of conditions produced disappointing yields of the desired compound (ca 36%) along with significant decomposition of the starting substrate. It appeared that the bulky *tert.*-butyldiphenylsilyl protecting group, perhaps in conjunction with the benzene sulfonyl group, made the carbonyl carbon so hindered that ketalization was next to impossible. Consequently, recourse to deprotection of the alcohol followed by ketalization was taken to generate ketal **20**.

Scheme 4



Reagents: a) DHP, pTSA, CH_2Cl_2; b) 1. Mg(m), THF; 2. **13**, nBuLi (2 eq.), THF, -78°C; then add Grignard reagent, -78°C-RT, 40 h; c) TBDPSiCl, imidazole, CH_2Cl_2; d) NBS, PPh_3, CH_2Cl_2; e) TBAF, THF; f) 2,2-dimethyl-1,3-propanediol, pTSA, C_6H_6, reflux.

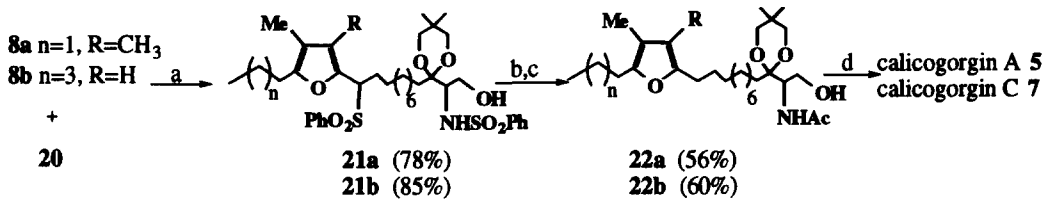
At this point, it was felt that reprotection of the alcohol so that it would not interfere in the subsequent coupling step was unattractive since it would introduce two additional steps into the synthesis. A more pleasing scenario was to simply add sufficient base to abstract all the acidic hydrogens (i.e. 3 mole equiv.) and allow the reaction to proceed, the premise being that alkylation of the sulfonyl anion would be faster than any of several undesired side reactions. This strategy was not without precedent.[3]

To test the feasibility of this approach, Scheme 5, furyl sulfones **8a/b** and bromide **20** were mixed and cooled to -78°C, at which time 3 mole equiv. of NaHMDS was added. After 1/2 hour at -78°C no change was observed, however, upon warming to 0°C (ca 2 h) most of the starting materials were consumed. After conventional work-up and SiO_2 chromatography, the coupled products (**21a/b**) were obtained in excellent yields, with no evidence of any elimination or ether products (alkylation of the alkoxide anion of **20** with itself in either an intramolecular or intermolecular reaction). This was contrary to the results of Olson, where upon warming their alkylation reaction to room temperature a significant amount of elimination products was observed.[3]

With coupling of the two fragments now completed, two tasks remained to complete the synthesis: 1) removal of the sulfonyl groups, and 2) functional group manipulation. Efforts to reduce the sulfonyl groups in **21a/b** with sodium naphthalenide under a variety of conditions[15] only led to complex mixtures, of which the major compound (ca 50%) was simply the C-desulfonylated product. However, treatment with 35 mole equiv. of freshly prepared Na/Hg in refluxing buffered methanol (Na_2HPO_4) gave the desired amino alcohols,[16] which were chemoselectively converted with Ac_2O in pyridine to the amido alcohols (**22a/b**) in respectable 56% and 60% yields, respectively. As expected, when these ketals were treated with PPTS in wet refluxing

acetone for 24 hours, calicogorgins A and C (**5**, **7**) were obtained in 90% and 92% yields after silica gel chromatography. These synthetic compounds had all spectral and physical data in complete agreement with that reported by Ochi.[2]

Scheme 5



Reagents: a) **8a** or **8b**, **20**, THF, -78°C, then NaHMDS (3 eq.), warm to 0°C; b) Na/Hg (35 eq.), Na_2HPO_4, MeOH, reflux; c) Ac_2O, Py, 0°C; d) PPTS, acetone, reflux.

In conclusion, an efficient synthesis of calicogorgin A (16% overall) and calicogorgin C (17.6% overall) has been accomplished (longest linear sequence being 10 steps in both syntheses). This represents the first total synthesis of these natural products, and displays the potential utility of our furan synthesis for the rapid assembly of natural products.

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