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A New Approach to Pyranofuranones, Advanced Intermediates for the Synthesis of Manoalide, Cacospongionolides and their Analogues

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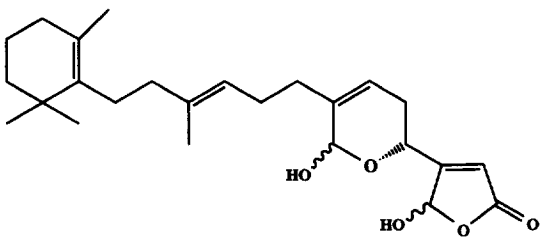
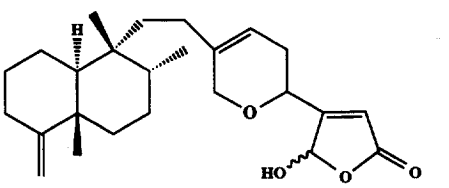
Abstract: The pyranofuranone fragment, main structural feature of many bioactive sesterterpenes of marin origin, is accessible through a simple and convenient synthetic sequence.

Manoalide[1] (**1**), a sesterpenoid metabolite isolated from the sponge *Luffariella variabilis*, is a potent anti-inflammatory agent and inhibitor of various forms of phospholipase A_2[2]. These important activites have stimulated the interest of many groups leading to several total syntheses of the natural product[3-7]. Attempts have also been made[8] to synthesize the pyranofuranone moiety which is considered a potentially pharmacophoric group of manoalide and related compounds, since the methyl manoalide analogue **3** is also biologically active[2]. Among the manoalide congeners, particularly interesting is cacospongionolide B (**2**)[9] which exhibits specific inhibition of human phospholipase A_2[10] while is consistently more stable than manoalide[11].



1

Manoalide

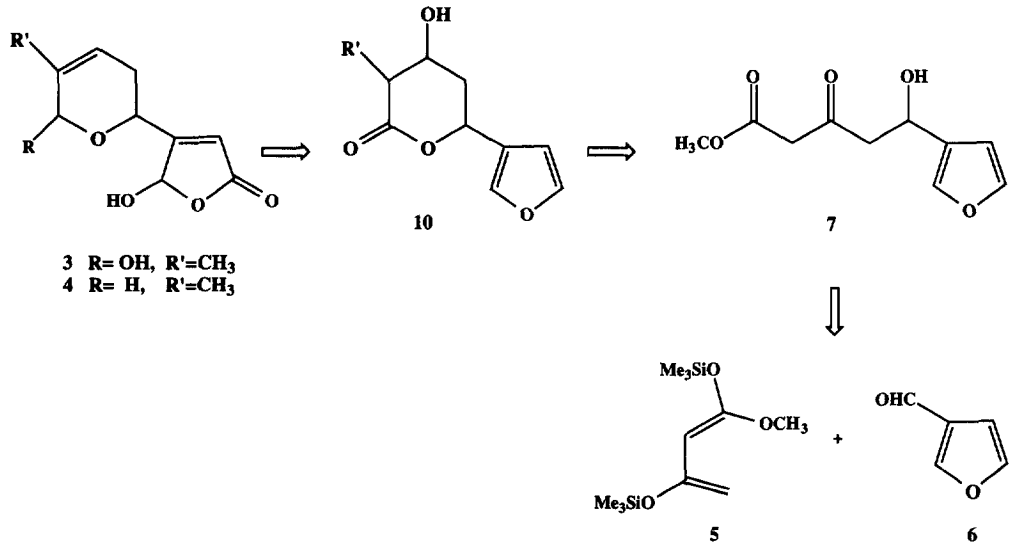


2

Cacospongionolide B

We report here a new general strategy for the synthesis of pyranofuranones of type **3** and **4** according to the following retrosynthetic scheme (Scheme 1).

Scheme 1



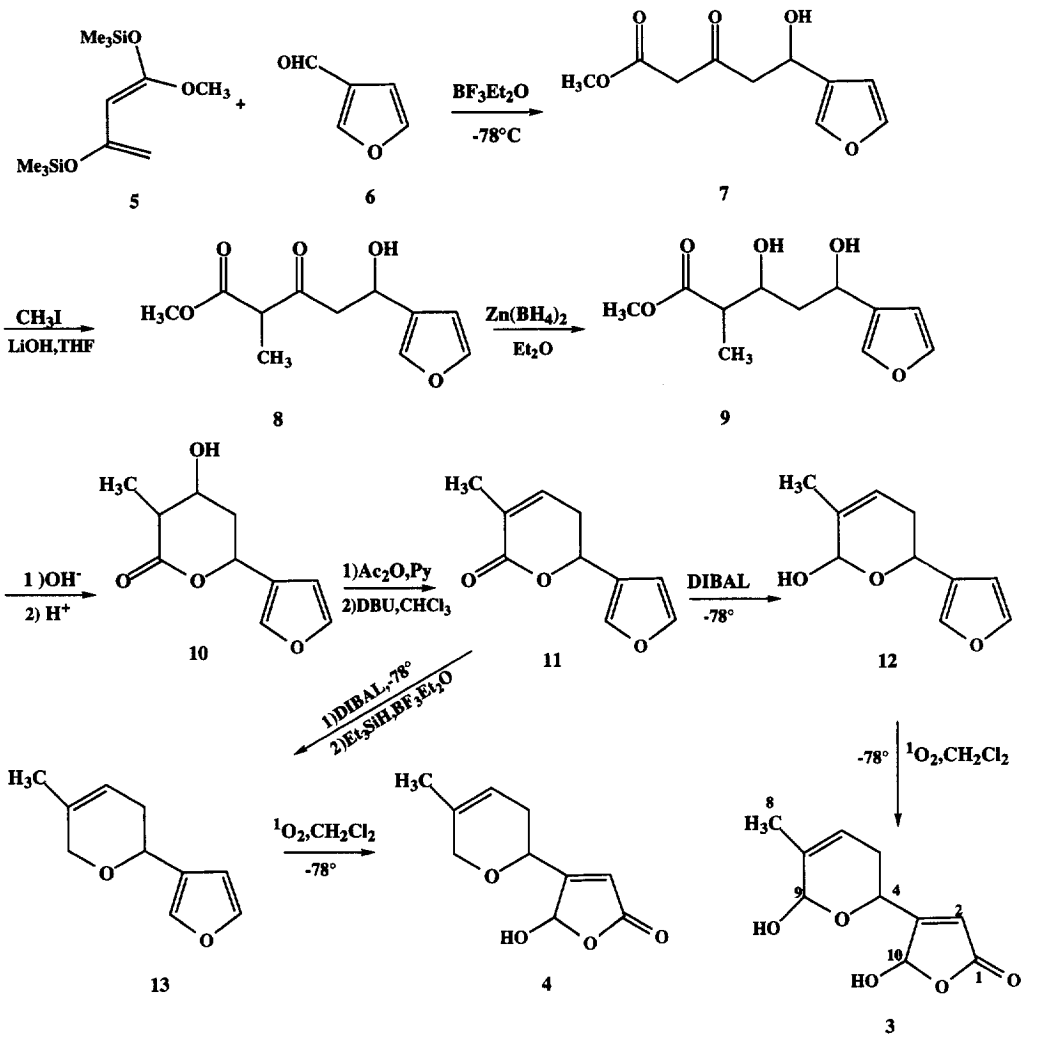
The approach is essentially based on: a) generation of the sensitive hydroxybutenolide moiety by photo-oxidation of the furan nucleus with $^1O_2$; b) formation of the six-membered heterocyclic ring by lactonization of the appropriate 5-hydroxyester; c) introduction of the desired R' substituent by alkylation of a 1,3-dicarbonyl compound, deriving from an aldol-type condensation on 3-formylfuran.

In fact, (Scheme 2), **7** has been obtained in 82% isolated yield by reaction of aldehyde **6** (1 eq.) with Brassard diene **5**[12] (1.5 eq.) in ether solution at -78° for 1h. Alkylation of **7** with CH_3I (1.5 eq.) in the presence of $LiOH{\cdot}H_2O$ (1 eq.)[13] in anhydrous THF solution (40°C, 3h) has afforded **8** in 70% yield as diastereomeric mixture (^1H NMR data).

Crude **9**, obtained by treatment of **8** with $Zn(BH_4)_2$ in ether solution for 0.5h at 0°C[14], has been converted into the hydroxylactone **10** by controlled hydrolysis with aqueous 0.1N NaOH (rt, 16h) and subsequent acidification with 2N H_2SO_4. Acetylation of **10** with Ac_2O/Py (rt, 1h) and elimination reaction, performed by DBU (rt, 5 min), have afforded **11** (total yield of six steps, **7->11**, 38%). **12** (98% yield) and **13** (78% yield) have been then respectively obtained from **11** by partial or complete reduction of the carbonyl function[15]. Finally, photo-sensitized oxidation of furan derivatives **12** and **13**, according to Faulkner's procedure[16], has given the manoalide methyl analogue **3**, identified by its NMR data[2,17] (68% yield), and the cacospongionolide methyl analogue **4**[18] (66 % yield), respectively.

This sequence is of synthetic value not only because it could allow a convergent synthesis of manoalide, cacospongionolide B and congeners, but gives also access to simple bioactive manoalide and cacospongionolide analogues of type **3** and **4** by the easy introduction of different R' substituents in the alkylation key-step. The synthesis of other manoalide and cacospongionolide B analogues and of cacospongionolide B itself are in progress.

Scheme 2



5 6 7 8 9 10 11 12 13 4 3

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17. In the ^{13}C NMR spectrum (CD_3OD, 100.6 MHz) the presence of a mixture of diastereomers was evident by the splitting of several signals, as previously observed for similar compounds[19].
18. ^{1}H NMR δ ($CDCl_3$, 250 MHz), 6.16 (s, H-10), 6.05 (s, H-2), 5.54 (bs, H-6), 4.42 (bt, J = 6.6 Hz, H-4), 4.12 (ABq, J = 15.8 Hz, H-9), 2.27 (bm, H-5), 1.64 (s, H-8). ^{13}C NMR δ ($CDCl_3$, 62.9 MHz) 171.5 (C-1), 168.3 (C-3), 133.0 (C-7), 117.4 (C-2), 117.1 (C-6), 98.6 (C-10), 69.3 (C-4), 69.0 (C-9), 28.9 (C-5), 18.4 (C-8).
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