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Stereoselective total synthesis of cananginones (D–I) using Ireland–Claisen rearrangement as a key step

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ABSTRACT

A strategy for stereoselective total synthesis of α-substituted γ-hydroxymethyl γ-butyrolactone containing bioactive natural products cananginones (D–I) has been developed using cheap and commercially available D-mannitol as a chiral pool. The Ireland–Claisen rearrangement is utilized as a key step to generate the α-substituted chiral center of the core lactone moiety, while the elongation of aliphatic side chain by different C-8 hydrocarbon groups have been achieved by alkylation, Cadiot–Chodkiewicz, and Sonogashira reactions.

1. Introduction

Functionalized chiral γ-butyrolactone[1] is an important subunit of biologically active compounds. Examples of natural products having such γ-butyrolactone moiety include cananginones (A–I)[2] (**1**–**9**), goniothalamusin[3] (**10**), saccopetrin A[4] (**11**), debilisones (A-F)[5] (**12**–**17**), and oropheolide[6] (**18**), which belong to a family of linear acetogenins[7] (Fig. 1). The common skeleton of these type natural products is most often characterized by α-substituted unbranched unsaturated fatty acid chain terminated with a saturated γ-hydroxymethyl γ-butyrolactone. The substituted γ-butyrolactone groups in this class of natural products remains either in cis- or trans-configuration. Cananginones (A–I) (**1**–**9**) were first discovered by Kanokmedhakul and co-workers[2] from crude hexane extract of the stem bark of traditional Thai medicinal tree *Cananga latifolia*. Stereochemically, the embedded α-substituted long aliphatic side chain and γ-hydroxymethyl group on lactone ring are in trans-orientation (Fig. 1). Most of these compounds show cytotoxicity to human carcinoma cell lines KB, MCF7, and NCI-H187 in micromolar range. In addition some of these members exhibit moderate antimalarial and antifungal activities. Their potential as therapeutic agents as well as the interesting architectural feature (substituted chiral γ-butyrolactone containing polyunsaturated skeleton) of this class of linear acetogenins has rendered them attractive targets for the synthetic organic chemistry community.[8]

A common and very obvious approach[8] to prepare this α-substituted γ-hydroxymethyl γ-butyrolactone skeleton involves stereoselective alkylation at the enolizable α-position of the core γ-lactone moiety by long chain aliphatic halide (Scheme 1). The inherent chirality derived from the substituted parent lactone moiety usually plays a key role for this type diastereoselectivity. Barua and co-workers[8b] adopted this strategy proficiently to prepare debilisone[5] C; a member of the same family (**14**) (Fig. 1). In debilisone C both α- and γ-substituents specifically are in a cis-orientation. However, this synthetic route does not allow synthesis of molecules (**1**–**11**, **18**) where both the α- and γ-substituents on lactone ring are in trans-configuration. The major drawback[8b] of this strategy is that the synthesis of *trans*-α,γ-substituted γ-butyrolactone moiety offers low yield, due to the incomplete consumption or decomposition of starting γ-lactone and the poor diastereoselectivity, due to inefficient chiral induction exerted by remote γ-substituent of parent lactone moiety.

Thus the challenge is in the development of an effective route for the synthesis of *trans*-substituted γ-butyrolactone skeleton. We sought to pursue a very flexible strategy for the stereoselective

Abbreviations: TBAI, tetrabutyl ammonium iodide; TMSI, trimethyl sulphonium iodide; DCC, *N*,*N*′-dicyclohexylcarbodiimide; DMAP, 4-dimethylaminopyridine; LiHMDS, lithium bis(trimethylsilyl)amide; DMPU, *N*,*N*′-dimethylpropylene urea; HMPA, hexamethylphosphoramide; CH_2N_2, diazomethane; CSA, camphorsulfonic acid; NaHMDS, sodium bis(trimethylsilyl)amide; KHMDS, potassium bis(trimethylsilyl)amide; LDA, lithium diisopropylamide; DIBAL-H, diisobutylaluminum hydride; TMS-acetylene, ethynyltrimethylsilane; TBAF, tetrabutyl ammonium fluoride; DMP, Dess–Martin periodinane.

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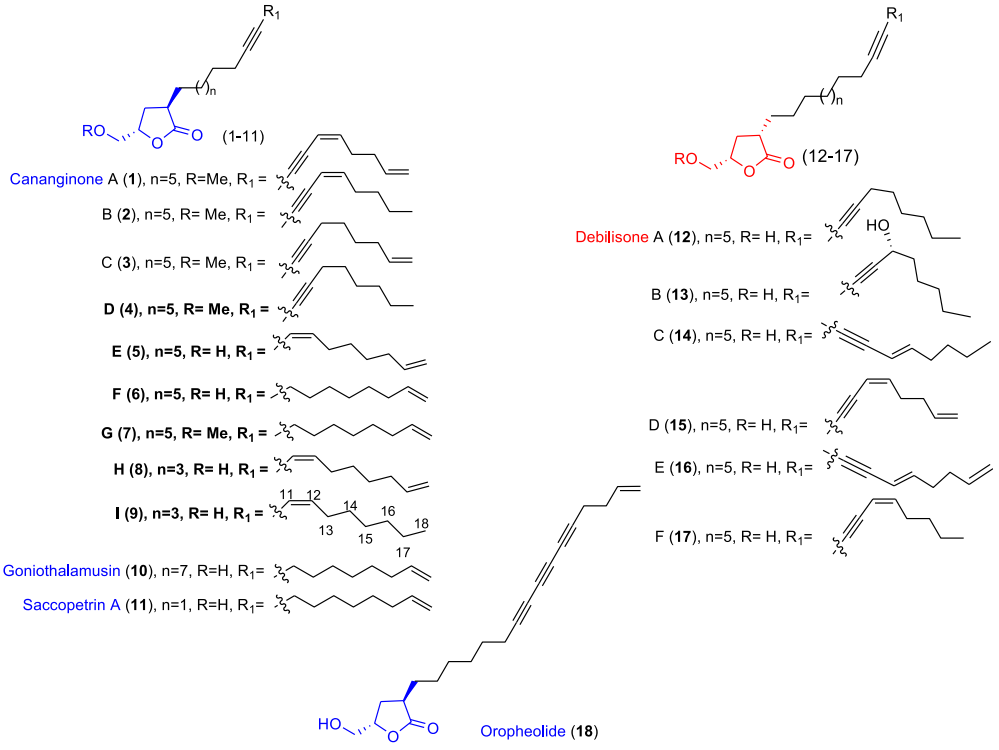
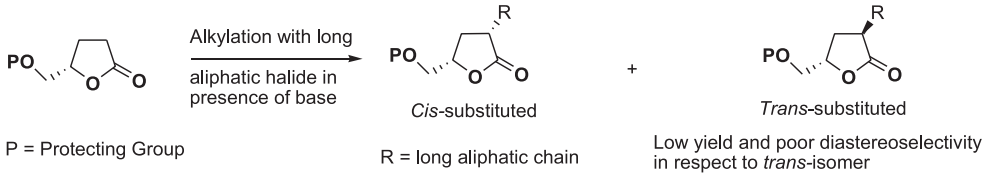


Fig. 1. Natural products with α-substituted γ-hydroxymethyl γ-lactone moiety.



Scheme 1. Known strategy for synthesis of α-substituted γ-hydroxymethyl γ-butyrolactone.

synthesis of γ-butyrolactone containing bioactive natural products using the Ireland–Claisen rearrangement[9] as a key step. The stereochemical outcome of this rearrangement can be ascertained by the predictable relay of chirality of the allylic center (present in the allylester surrogate) in an acyclic system through a well-understood transition state structure.[9,10] Our continual interest[11] in the asymmetric synthesis of bioactive natural products prompted us to embark upon the total synthesis of cananginones. To the best of our knowledge, total synthesis of any member of cananginones has not been reported till the date. Herein we describe the total synthesis of cananginones (D–I) for the first time (**4**–**9**). We believe this strategy can be used for successful stereoselective synthesis of a large number of natural products having the *trans*-α-substituted γ-hydroxymethyl γ-butyrolactone core.

2. Results and discussion

Retrosynthetic analysis of cananginones (D–I) is outlined in Scheme 2. We envisaged that the cananginones (D, E, H, I) (**4**, **5**, **8**, **9**) could be derived from the γ-lactones **22** and **23** by coupling it with the corresponding C-8 hydrocarbon counterparts (**19**–**21**) using Cadiot–Chodkiewicz reaction[12] or Sonogashira reaction.[13] The lactones **22** and **23** could be prepared from the intermediates **24** and **25**, respectively, involving regioselective γ-lactonization as one of the key steps. The construction of the alkynes **24** and **25** could be achieved from the common intermediate **26** utilizing the Ireland–Claisen rearrangement. Compound **26** then could be prepared by esterification of the acid **27** using the allylic alcohol **28**. Both the acid **27** and the allylic alcohol **28** could be synthesized from a single chiral pool; D-mannitol. For the cananginones (F and G) (**6** and **7**), we planned for a little alteration of above reaction sequences to preclude epimerization of the α-alkyl center during installation of the C-8 hydrocarbon part under basic conditions (Scheme 2). Both the cananginone F (**6**) and its methylated analogue cananginone G (**7**) could be prepared from the ester **29** by acid catalyzed γ-lactonization. The ester **29** in turn could be derived from the alkyne **24** by alkylation with the alkyl iodide **30**.

Our synthetic endeavor began with the preparation of known acid **27** and allylic alcohol **28** from commercially available, and cheap, D-mannitol (Scheme 3). The known α,β-unsaturated ester **31**,[14] derived from D-mannitol, was used to synthesize the epoxide **32** in four steps. First, the ester (**31**) was reduced to a saturated alcohol[14b] in the presence of $NaBH_4$/LiCl, which was subsequently benzylated with BnBr/NaH to get the corresponding benzyl ether.[15] Then the resultant benzyl ether was treated with 80% AcOH/H_2O to deprotect the acetonide and finally reacted with tosyl-imidazole in the presence of NaH[16] to afford the known epoxide **32**[15,17a] in good overall yield. The epoxide **32** was then transformed to the known allylic alcohol **28** by $Me_3SI/^nBuLi$ following the literature procedure.[17] The required acid **27**[18] was synthesized from the known ester **31** in two steps: hydrogenation followed by saponification in the presence of LiOH.