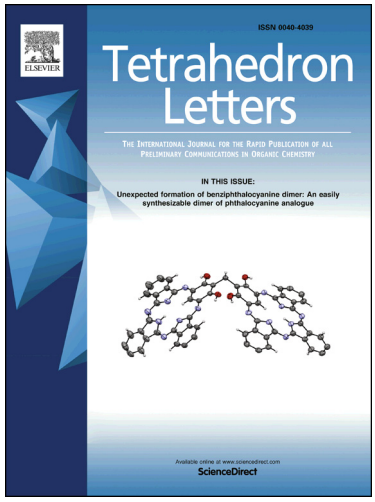

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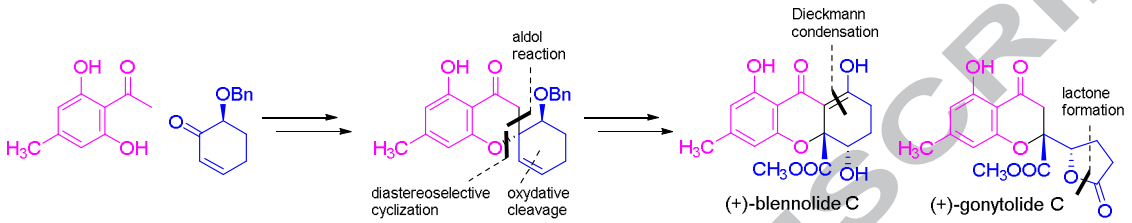

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Total synthesis of (+)-blennolide C and (+)-gonytolide C via spirochromanone

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This article is dedicated to the late Professor István E Markó, Université catholique de Louvain, deceased on July 31, 2017.

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ABSTRACT

We report the asymmetric total synthesis of (+)-blennolide C and (+)-gonytolide C isolated from endophytic fungi. The synthesis involved construction of a spirochromanone with a chiral quaternary carbon by the aldol reaction of o-hydroxyacetophenones and optically active α-oxygenated cyclohexenone, followed by cyclization under acidic conditions. Oxidative cleavage of the alkene moiety of the spirochromanone furnished the chromanone diester. Through treating the diester with a Lewis acid, the first total synthesis of (+)-blennolide C was achieved by deprotecting the oxygen functionality of the diester and simultaneous Dieckmann condensation. Total synthesis of (+)-gonytolide C was also achieved by lactone formation from the deprotected diester.

Naturally occurring xanthones[1] and their biogenetically related chromanones with γ-butyrolactones have been isolated from a wide range of plants, bacteria, fungi, and lichens as monomeric and dimeric structures. Some of these compounds exhibit antibacterial, antifungal, and antialgal activities. Monomeric xanthones (+)-blennolides A (**1**) and C (**2**) were isolated with dimeric (+)-secalonic acid B (**1**)[2] from the fungus *Blennoria* sp., an endophytic fungus from *Carpobrotus edulis*.[3] Biogenetically related (+)-gonytolide C (**4**), monomeric chromanone with γ-lactone moiety was isolated from the fungus *Gonytrichum* sp. with dimeric (+)-gonytolide A (**5**) which shows innate immune promoter activity[4] (**Figure 1**).

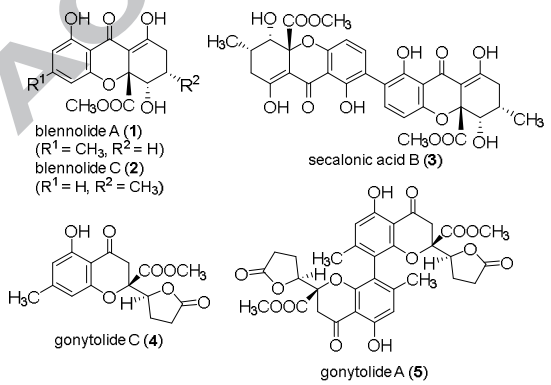
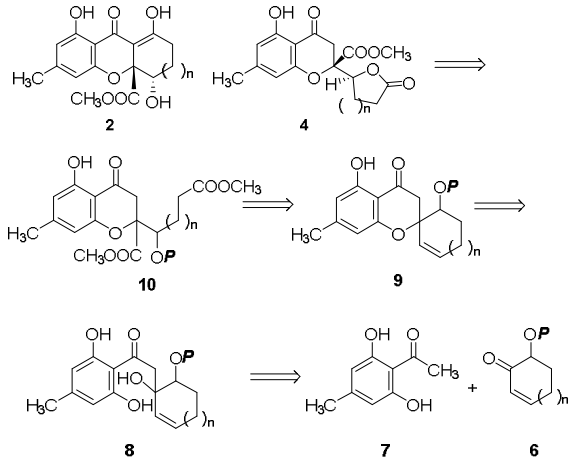


Figure 1. Representative xanthones **1–3** and chromanones **4–5** from endophytic fungi.

Synthetic studies towards these xanthones and related chromanones have been performed, and the total syntheses of some of monomeric[5] and dimeric derivatives[6] have been reported. Asymmetric total syntheses of natural (+)-gonytolide C (**4**) was reported,[7] however synthesis of natural (+)-blennolide C (**2**) has not been reported yet. Moreover, these syntheses are target-oriented using γ-lactone derivatives and development of more flexible synthetic methods is expected toward synthesis of natural products as well as their derivatives.

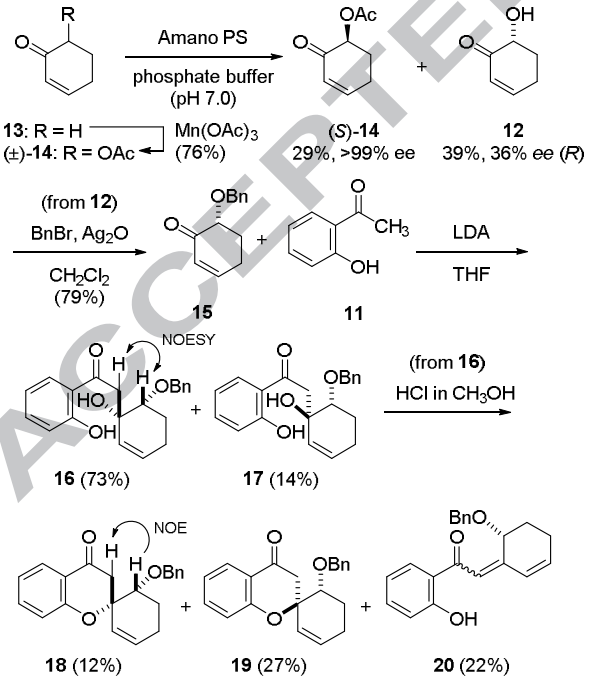
In our ongoing synthetic studies of biologically active natural products,[8] we planned to develop a new methodology for asymmetric total synthesis of (+)-blennolide C (**2**), (+)-gonytolide C (**4**) and their derivatives with other ring sizes. We assumed that optically active α-oxygenated cyclohexenone **6** (n = 1) derived from cyclohexanone or cyclohexene oxide can be used as the source of cyclohexene and γ-lactone in **2** and **4**. Aldol reaction with *o*-hydroxyacetophenone **7** and cyclization of the aldol adducts **8** should give spirochromanones **9** with a chiral quaternary center.[9] Target natural products **2** and **4** could be obtained by oxidative cleavage of the alkene moiety in **9** followed by cyclization. Derivatives with other sizes of cycloalkene or lactone in **2** and **4** can be accessed using another ring sizes of cycloalkenones **6** (n = 0, 2, 3,…). Based on this analysis, we examined the total synthesis of (+)-blennolide C (**2**) and (+)-gonytolide C (**4**) via spirochromanone using optically active α-oxygenated cyclohexenone and o-hydroxyacetophenone (**Scheme 1**).

A model synthetic study using simple o-hydroxyacetophenone (**11**) and α-oxygenated cyclohexenone **12** was performed. **12**



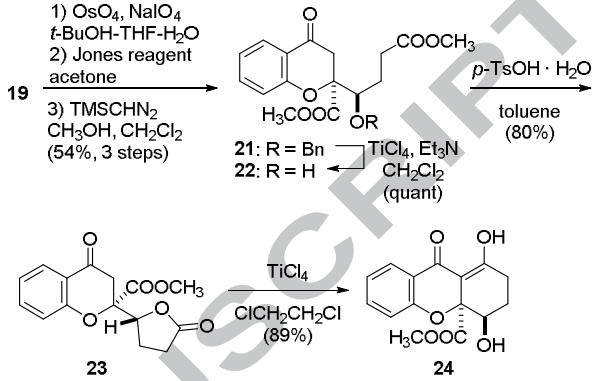
Scheme 1. Retrosynthesis for blennolide C (**2**) and gonytolide C (**4**) via spirochromanone intermediates **9**. P: protecting groups.

(36% ee with *R* configuration as the major isomer) was prepared by acetoxylation of cyclohexenone (**13**) with $Mn(OAc)_3$ followed by enzymatic hydrolysis of acetate (±)-**14**.[10] After the benzylation of **12**, cyclohexenone **15**[11] was subjected to an aldol reaction with **11** in the presence of 2 equivalents of LDA[12] to give the aldol adducts **16** and **17** as a mixture of diastereomers. Less polar **16** was obtained as a major isomer. After separation, **16** was cyclized under acidic conditions (HCl in CH_3OH, reflux, 33 h)[13] to afford diastereomeric spirochromanones **18** (12%) and **19** (27%) and dehydrated dienone **20**. Less polar **19** was obtained as the major isomer in this reaction. The relative stereochemistry of **16** and **18** was determined as *cis* for the two oxygen functionalities on cyclohexene ring by NOE experiments, which showed a correlation between the methylene protons derived from **11** and the proton of the methyne bearing the benzyloxy group (**Scheme 2**).



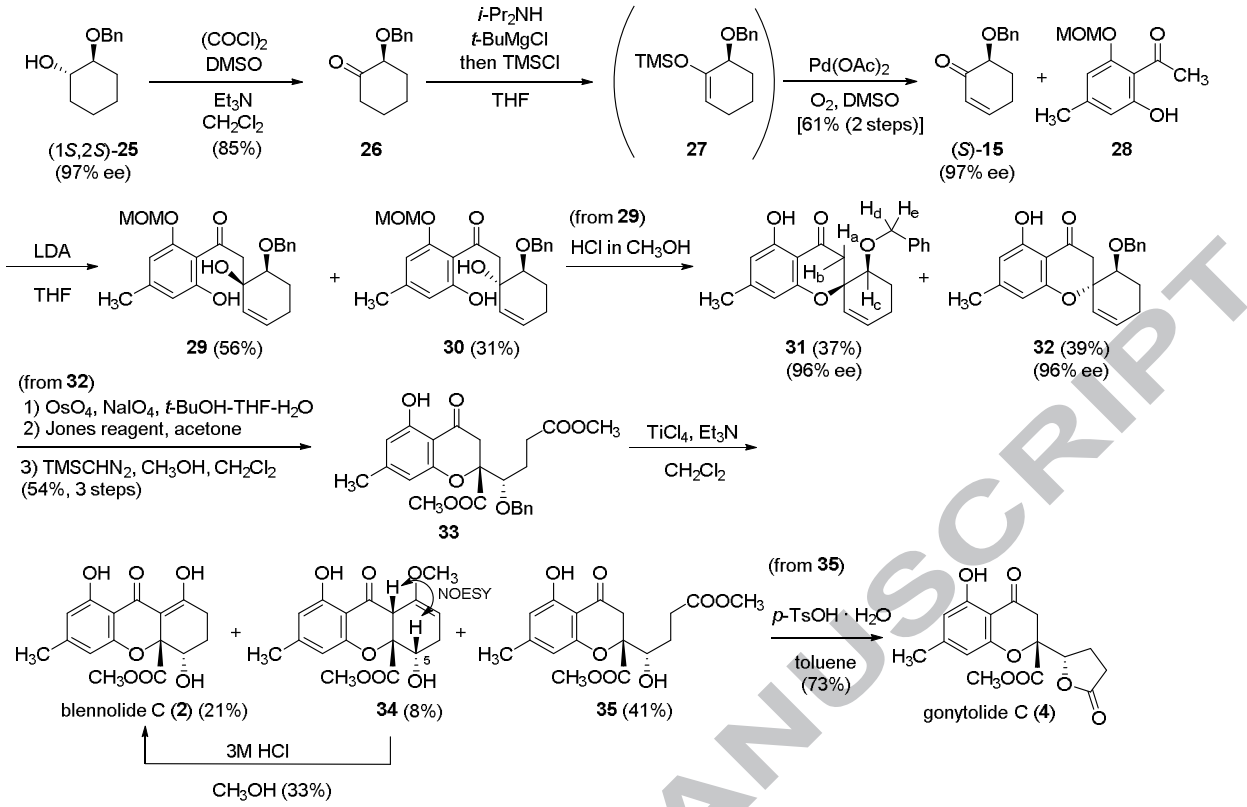
Scheme 2. Synthesis of model spirochromanones **18** and **19**.

Lemieux-Johnson oxidation of the alkene in **19** with the desired relative stereochemistry, followed by Jones oxidation and esterification, gave diester **21**. Trial for Claisen condensation of **21** using $TiCl_4/Et_3N$ system[14] gave deprotected alcohol **22**, which was treated with *p*-TsOH gave γ-lactone **23**, the model chromanone of gonytolide C (**4**) with γ-lactone moiety. The Dieckmann condensation reaction of **23** under basic conditions (NaH or LDA) gave complex mixtures. No reaction occurred when **23** was treated with $TiCl_4$ in the presence of Et_3N in refluxed CH_2Cl_2.[14] Reaction in the absence of Et_3N gave desired **24**, the model xanthone of blennolide C (**2**), in 17% yield with the recovery of **23** in 33% yield. The yield of **24** was improved to 89% when 1,2-dichloroethane was used instead of CH_2Cl_2 (**Scheme 3**).



Scheme 3. Synthesis of model chromanone **23** and xanthone **24**.

Next, we performed the asymmetric total synthesis of (+)-blennolide C (**2**) and (+)-gonytolide C (**4**) with functionalized acetophenone **7** and optically active cyclohexenone (*S*)-**15** with correct stereochemistry (**Scheme 4**). (1*S*,2*S*)-1,2-Cyclohexanediol monobenzyl ether (**25**, 97% ee) prepared by PLE-catalyzed resolution of (±)-**25** using vinyl acetate[15] was used as a key synthetic intermediate. Swern oxidation of (1*S*,2*S*)-**25**, regioselective conversion of the resultant ketone **26** to silyl enol ether **27** using magnesium amide,[16] followed by palladium-catalyzed oxidation of **27** mediated by oxygen (O_2),[17] afforded optically active enone (*S*)-**15**. The optical purity of (*S*)-**15** was estimated as 97% ee. The aldol reaction of mono-MOM-protected acetophenone **28**, derived from dihydroxyacetophenone **7**,[5b] and enone (*S*)-**15**, gave adducts **29** and **30**.[18] After isolation, treatment of major isomer **29** with HCl in CH_3OH gave spirochromanones **31** and less polar **32** in 37% and 39% yields, respectively. When the crude product of the aldol reaction of **28** and (*S*)-**15** was subjected directly to the cyclization conditions, **31** and **32** were obtained in 42% and 34% yields in 2 steps, respectively. Sufficient information for the relative configuration of **31** and **32** was not obtained by the NOE experiment. Therefore, the relative stereochemistry of **31** and **32** were deduced by correlation of the ^1H NMR data and the polarity of **18** and **19**. The chemical shifts of the protons around the stereocenters in more polar **18** and **31** generally showed a greater upfield shift than those of less polar **19** and **32**. The Δδ values of the two benzylic protons (H_d and H_e) were similar between those of **18** and **31**, and **19** and **32**, respectively (**Table 1**). Based on these data, the absolute configurations of **31** and **32** were deduced as (1*R*,2*S*) and (1*S*,2*S*), respectively. Optical purity was estimated for **31** and **32** as 96% ee, which shows that these compounds were obtained without any loss of optical purity during the reaction course.[19] After the diastereomers were separated by column chromatography, **32** with the desired configuration was subjected to similar treatment to **19** to give diester **33**. Trial for the catalytic hydrogenation of **33** recovered the starting material. Treatment of **33** with $TiCl_4$ and Et_3N gave (+)-blennolide C (**2**), xanthone with methyl enol ether **34**, and deprotected alcohol **35**.[4a] The NOESY spectrum of **34** showed the *cis* relationship between the proton at the ring juncture and C5-H. Enol ether **34** can be converted to blennolide C (**2**) under acidic conditions. Alcohol **35** was treated with *p*-TsOH under reflux in toluene to give (+)-



Scheme 4. Total synthesis of (+)-blennolide C (**2**) and (+)-gonytolide C (**4**).

Table 1. Comparison of ^{1}H NMR data and polarity of **18**, **19**, **31**, and **32** (unit: ppm).[a]

	18 (more polar)	**19** (less polar)	**31** (more polar)	**32** (less polar)
H_a, H_b	2.59, 3.15 (0.56)	2.77, 3.28 (0.51)	2.49, 3.23 (0.74)	2.73, 3.27 (0.54)
H_c	3.50	3.90	3.48	3.87
H_d, H_e	4.49, 4.66 (0.17)	4.55, 4.63 (0.08)	4.49, 4.73 (0.24)	4.55, 4.64 (0.09)

[a] $\Delta\delta$ of the two protons is shown in parentheses.

gonytolide C (**4**). The spectral data for synthesized (+)-blennolide C (**2**) and (+)-gonytolide C (**4**) were identical to those of the natural products. The optical rotations of synthesized blennolide C (**2**) and gonytolide C (**4**) were estimated as $[\alpha]_D^{22.6}$ +180.7 (*c* 0.07, $CHCl_3$) and $[\alpha]_D^{23.7}$ +25.6 (*c* 0.18, $CHCl_3$), which were identical with the natural products [lit. **2**: $[\alpha]_D^{25}$ +181.7 (*c* 0.06, $CHCl_3$),[3] **4**: $[\alpha]_D$ +25.1 (*c* 0.184, $CHCl_3$)].[4a]

In summary, first total syntheses of (+)-blennolide C (**2**) and synthesis of (+)-gonytolide C (**4**) were achieved. Key spirochromanone **31** was obtained by the aldol reaction of *o*-hydroxyacetophenone and optically active α-oxygenated cyclohexenone and cyclization in acidic condition. Oxidative cleavage of the alkene moiety in the spirochromanone gave diester **32**, which was subjected to Dieckmann condensation resulted in the total synthesis of (+)-blennolide C (**2**). Lactone formation of hydroxyester **34** derived from diester **32** furnished (+)-gonytolide C (**4**). Extension of this methodology to the synthesis of other natural products and the derivatives are currently being examined using a variety of acetophenones and α-oxygenated cycloalkenones with another substituents and ring sizes.

Acknowledgments

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18. The diastereoselectivity was improved when toluene was used as a solvent with adding HMPA to give *ca.* 5 : 1 of **29** and **30** (52% and 11%, respectively).
19. The undesired chromanone **31** can be isomerized to desired **32** when **31** was heated in toluene in a sealed tube under microwave irradiation at 150 ºC in the presence of pyrrolidine to give a 1 : 1 mixture of **31** and **32**.

Supplementary Material

Supplementary material that may be helpful in the review process should be prepared and provided as a separate electronic file. That file can then be transformed into PDF format and submitted along with the manuscript and graphic files to the appropriate editorial office.

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Highlights

- First total synthesis of natural (+)-blennolide C was achieved.
- Synthesis of (+)-gonytolide C was also achieved via spirochromanone.
- Adduct of acetophenone and cyclohexenone is a good substrate for spirochromanone.
- Xanthones were constructed via alkene cleavage in spirochromanone and cyclization.