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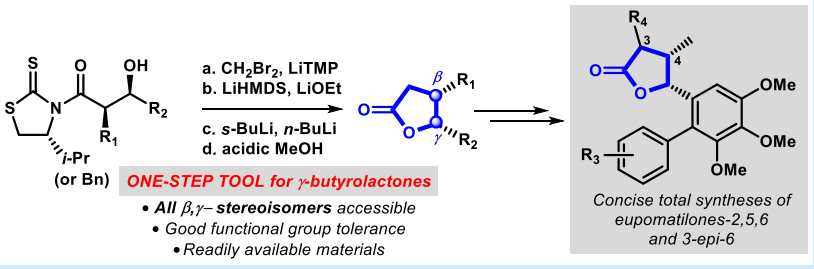
Synthesis of γ-Lactones via the Kowalski Homologation Reaction: Protecting-Group-Free Divergent Total Syntheses of Eupomatilones-2,5,6, and 3-*epi*-Eupomatilone-6

Hosam Choi,[†] Hanho Jang,[†] Hyoungsu Kim,[‡] and Kiyoun Lee*[,†]

[†]Department of Chemistry, The Catholic University of Korea, Bucheon 14662, Korea

[‡]College of Pharmacy, Ajou University, Suwon 16499, Korea

Supporting Information



ABSTRACT: A highly efficient synthesis of functionalized chiral γ-butyrolactone scaffolds has been described. The basis of the approach is the Kowalski ester homologation that is modified for our proposed transformation. The newly developed methodology combines a divergent synthetic strategy to permit a straightforward protecting-group-free asymmetric total syntheses of eupomatilones-2,5,6, and 3-*epi*-eupomatilone-6 in five or six steps from commercial starting materials, making it one of the shortest syntheses reported to date.

Many structurally complex chiral γ-butyrolactones exhibit a wide range of biological properties[1] and often serve as key synthetic intermediates within the context of natural product syntheses (Figure 1).[2] Intrigued by the diversity of this

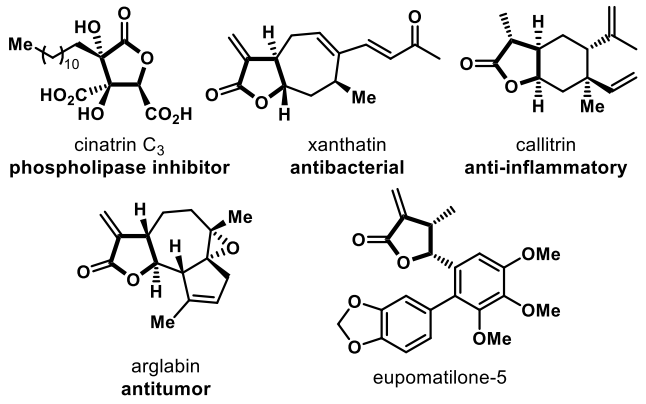


Figure 1. Natural products containing γ-butyrolactones.

naturally occurring motif, in the past decades, significant efforts have been made on the development of synthetic approaches toward the enantioselective construction of γ-butyrolactones.[1a,3] There are several representative conventional methods for the synthesis of γ-butyrolactones, including intramolecular substitutions or halolactonization based on either inherent electrophilic or nucleophilic characteristics of substituents at the γ-position.[4] Despite impressive advances in the field of γ-butyrolactone synthesis, successful protocols are thus far largely limited in terms of substrate scope diversity, stereoselectivity, and starting material availability. Moreover, to date, many asymmetric methods have focused on the generation of one stereogenic center, while strategies providing access to optically active γ-butyrolactones possessing β,γ-two vicinal stereogenic centers have rarely been reported.[5]

Consequently, further developments are needed to address the generally limited substrate scope and moderate stereoselectivity. In order to access a broader range of structurally diverse chiral lactones in a step-economical and versatile fashion, a new synthetic approach is required. Herein, we disclose studies on the development of a concise synthesis of γ-butyrolactones with access to two chiral functional groups with the necessary stereochemistry based on a slightly modified Kowalski ester homologation reaction in which an effective intramolecular ring closure occurs.

This efficient approach was applied to the synthesis of protecting-group-free divergent total syntheses of three members of natural eupomatilones-2,5,6 and one 3-*epi*-eupomatilone-6. Even though the Kowalski ester homologation reaction is a robust and valuable method for new carbon–carbon bond forming reactions,[6,7] its application in natural product synthesis is extremely rare.[8] Additionally, to the best of

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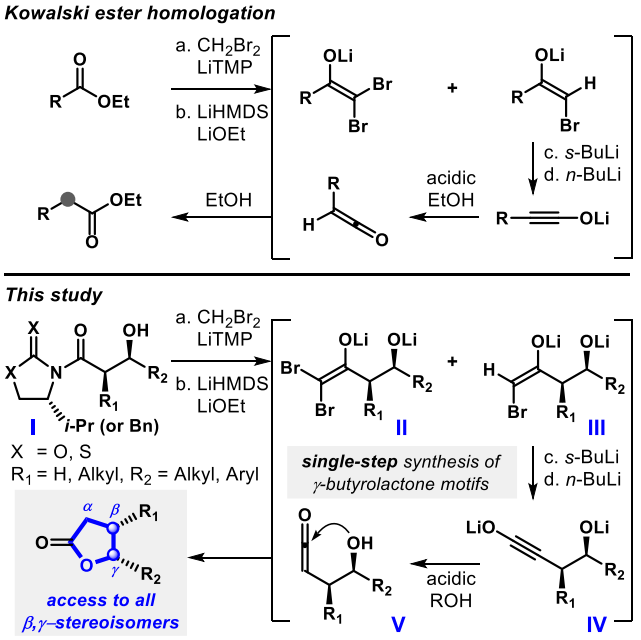
our knowledge, this work presents one of the shortest asymmetric total syntheses of eupomatilones reported to date.

On the basis of a simplified mechanism of the Kowalski reaction, as depicted in Scheme 1, we hypothesized that it

Scheme 1. Proposed Strategy for the Synthesis of the γ-Butyrolactone Framework

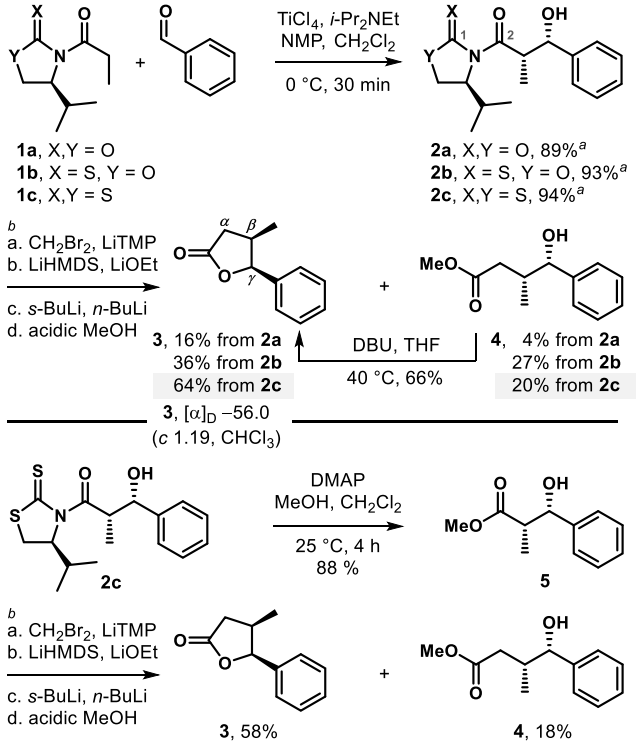


would be possible to accomplish the construction of an optically active β,γ-disubstituted γ-butyrolactone motif if the Kowalski ester homologation reaction was combined with a chiral auxiliary-mediated asymmetric aldol reaction, followed by in situ intramolecular ring closure in a tandem manner.

The proposed transformation mechanism is as follows[9,10] (Scheme 1): upon treatment with dibromomethyllithium, the chiral auxiliary bearing starting material **I** could be converted to a tetrahedral intermediate. Subsequent treatment with silazide base (LiHMDS) and lithium ethoxide results in the formation of di- and monobromoketone enolates **II** and **III**. The key halogen−metal exchange rearrangement occurs upon treatment with *sec*-butyllithium leading to ynolate anion **IV** at low temperature. This is followed by the addition of *n*-butyllithium, which acts as a base to regenerate LiTMP and deprotonate the remaining enolate **III** to complete the rearrangement and convert residual enolate **III** to ynolate **IV**. In turn, quenching the resulting ynolate anion by acidic alcohol might generate the desired chiral γ-butyrolactone, presumably through the intramolecular ring closure of the ketene intermediacy **V**. Additionally, it was anticipated that the stereochemical outcome of the two vicinal stereogenic centers in γ-butyrolactones would be retained under those reaction conditions. Furthermore, it should be noted that all β,γ-stereoisomers would be accessible by taking advantage of the high stereofacial selectivity of auxiliary-mediated asymmetric aldol reactions.

To test this hypothesis, *syn*-aldol adduct **2a** was prepared using an Evans type auxiliary-mediated aldol protocol,[11−14] following the procedure described by Crimmins.[15,16] Compound **2a** was then subjected to the modified Kowalski ester homologation reaction conditions (Scheme 2). While this

Scheme 2. Synthesis of γ-Lactones via the Aldol/Kowalski Homologation Sequence



[a]Isolated yield of major diastereomer. [b]Reaction conditions: 0.3−0.6 mmol of **2a−c** and **5**. (i) LiTMP (4.0 equiv), CH_2Br_2 (4.4 equiv), −78 °C, (ii) LiHMDS (2.0 equiv), LiOEt (1.0 equiv), −78 to −20 °C, (iii) *s*-BuLi (2.0 equiv), −78 to −20 °C, (iv) *n*-BuLi (4.0 equiv), −78 °C, (v) acidic MeOH. NMP = *N*-methyl-2-pyrrolidone; LiHMDS = lithium bis(trimethylsilyl)amide.

initial attempt was successful, it afforded the desired γ-butyrolactone **3** in an unsatisfactory yield (16%). Replacing the *N*-acyloxazolidinone with an oxazolidinethione in *syn*-aldol product **2b** and subsequently subjecting it to the one-carbon homologated intramolecular lactonization improved the yield but only to 36%.

We hypothesized that these results could be attributed to the inherent electrophilic nature of the C1 carbonyl carbon in **2a−c** and the consequent inhibition of the initial dibromoketone enolate formation. Therefore, we expected that substrates with reduced electrophilic character at C1 and auxiliaries, which could be cleaved more easily than oxazolidinones or oxazolidinethiones, would be advantageous in achieving more effective ring closure.[11,15,17] After searching for alternative chiral auxiliaries and fine-tuning the reaction parameters, including bases and temperature, we were delighted to find that the use of asymmetric *syn*-aldol products bearing *N*-acylthiazolidinethione with a Bn or an *i*-Pr (Scheme 2) moiety proved to be more effective leading to a higher conversion (64%) along with **4** in 20% yield. It is of note that the developed reaction proceeds with complete retention of the stereochemistry in **3** (see the Supporting Information). An additional attribute of this approach is that the isolated **4**, the one-carbon homologated intermediate γ-hydroxy ester, underwent cyclization upon treatment with DBU in THF to deliver the desired **3** (66%), revealing a significant benefit of the present methodology.

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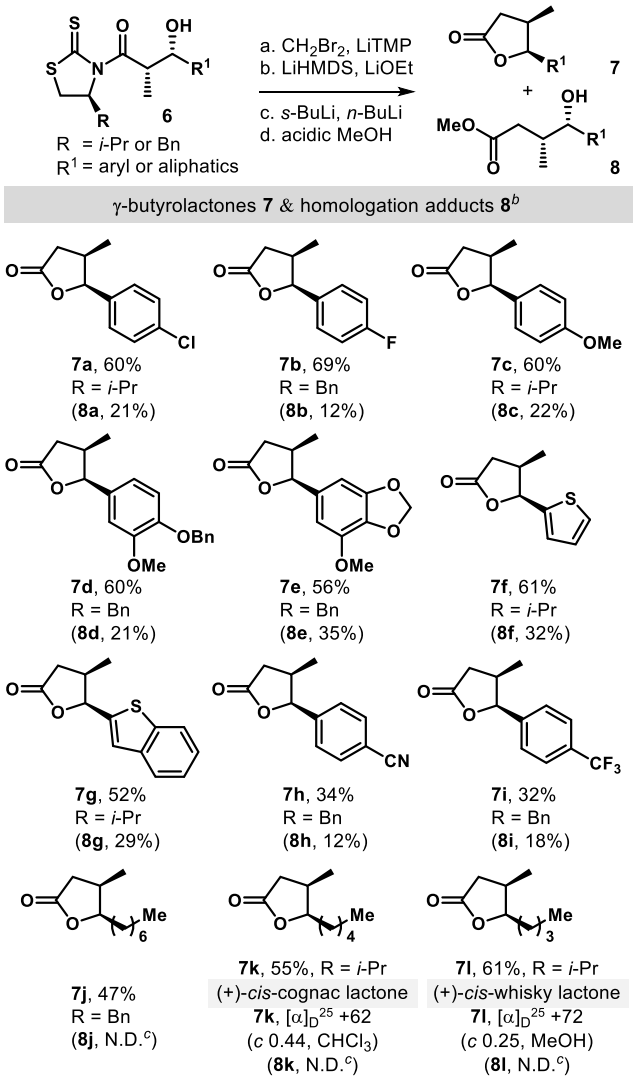
Now that the chiral auxiliary had served its intended purpose in the formation of the *syn*-aldol product **2c**, we sought to address the intramolecular ring closure with a simpler ester functionality by removal of the chiral auxiliary. This was performed by methanolysis (DMAP (20 mol %), MeOH (1.5 equiv), CH_2Cl_2, 25 °C, 4 h, 88%) and subsequent one-carbon homologated intramolecular cyclization, which proceeded to provide **3** in 58% yield, suggesting that a direct mode of homologated ring closure from an intermediate such as **2c** may constitute a more effective approach than a two-step process through intermediate **5**.

Given the interest in facilitating access to the desired γ-butyrolactone **3**, we set out to explore the scope and the limitations of this transformation. Representative examples are summarized in Scheme 3. A series of β-hydroxy carbonyl compounds bearing aryl and aliphatic substituents was prepared and found to undergo the desired γ-butyrolactonization in good to moderate conversions. Electron-neutral and electron-rich aryl substituents were well tolerated (Scheme 3, **7a–g**), while slightly lower yields were observed with substrates containing electron-deficient substituents (4-CN (**7h**) and 4-CF_3 (**7i**)).

These experiments have shown that the reaction conditions were compatible with a range of functional groups and that aromatic substrates were generally slightly more effective than aliphatics (**7j–l**). It is of note that the current strategy produced the shortest total synthesis of the optically active natural products (+)-*cis*-cognac lactone (**7k**) and (+)-*cis*-whisky lactone (**7l**) reported to date[18,19] (two steps in total from commercially available **1c**), demonstrating the applicability of this strategy in natural product synthesis.

To demonstrate the synthetic utility of this methodology, we tackled the synthesis of three members of the eupomatilone family (eupomatilones-2,5,6) and one 3-*epi*-eupomatilone-6. Eupomatilones 1–7 (Figure 2) are natural products isolated from the Australian shrub *Eupomatia bennettii* in 1991 by Carroll and Taylor, and they are members of a structurally intriguing class of lignans.[20]

Scheme 3. Substrate Scope of the Kowalski One-Carbon Homologative Lactonization.[a]



[a]Reaction conditions: (i) LiTMP (4.0 equiv), CH_2Br_2 (4.4 equiv), −78 °C, (ii) LiHMDS (2.0–4.0 equiv), LiOEt (1.0 equiv for **7a–i** and no LiOEt was used for **7j–l**), −78 to −20 °C, (iii) *s*-BuLi (2.0–4.0 equiv), −78 to −20 °C, (iv) *n*-BuLi (2.0–4.0 equiv), −78 °C, (v) acidic MeOH. (For details, see the Supporting Information.) [b]Isolated yields of **7** and **8**. [c]Not determined.

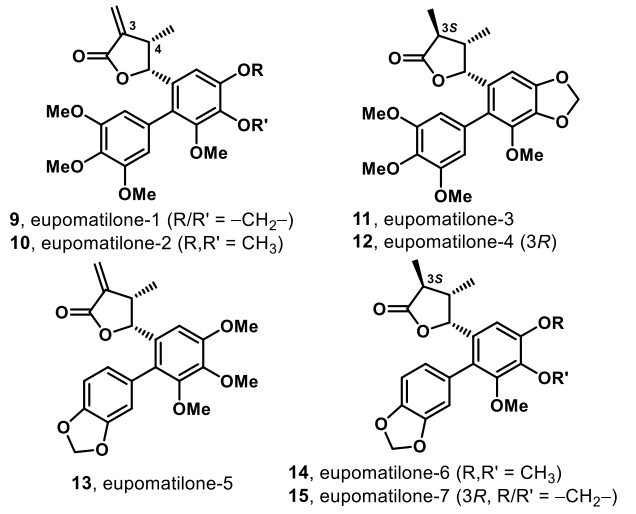


Figure 2. Eupomatilones 1–7.

Due to their unique structural features, including the chiral γ-butyrolactone motifs and the highly oxygenated biaryl skeletons, several elegant and concise syntheses have been accomplished by different groups, such as the Hall group's efficient construction of γ-butyrolactone in (±)-eupomatilone-6 employing a Brønsted acid catalyzed allylboration,[21e] the Buchwald group's asymmetric synthesis of eupomatilone-3 via dynamic kinetic resolution,[21f] and the Rovis group's asymmetric synthesis of eupomatilones-4,7 and 3-*epi*-eupomatilone-6 utilizing the rhodium catalyzed desymmetrization of succinic anhydrides.[21i]

While there have been a number of prior syntheses reported,[21] many utilize a biaryl linkage via a cross-coupling reaction in the first stage of the synthesis and a late stage stereoselective formation of the γ-lactone core.[21c,d,f–h,j–l] It should be noted that our synthetic route, in contrast, provides the rapid stereoselective formation of the γ-lactone core and potentially allows ready manipulation of the biaryl functionality

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which ultimately permits a concise divergent assembly of eupomatilones, thereby effectively enhancing the synthetic utility of the present methodology.

The total syntheses of eupomatilone-2 (**10**) and eupomatilone-5 (**13**) is illustrated in Scheme 4. An asymmetric aldol addition of chlorotitanium enolate of thiazolidinethione propionate *ent*-(+)-**1c** with 3,4,5-trimethoxybenzaldehyde afforded the *syn*-aldol adduct **16** in 98% yield, which was subjected to a modified Kowalski ester homologation reaction to provide the desired γ-butyrolactone **17** (66%) along with the γ-hydroxy ester **18** (19%). The isolated intermediate **18** underwent ring closure upon treatment with DBU in THF to provide **17** (67%).

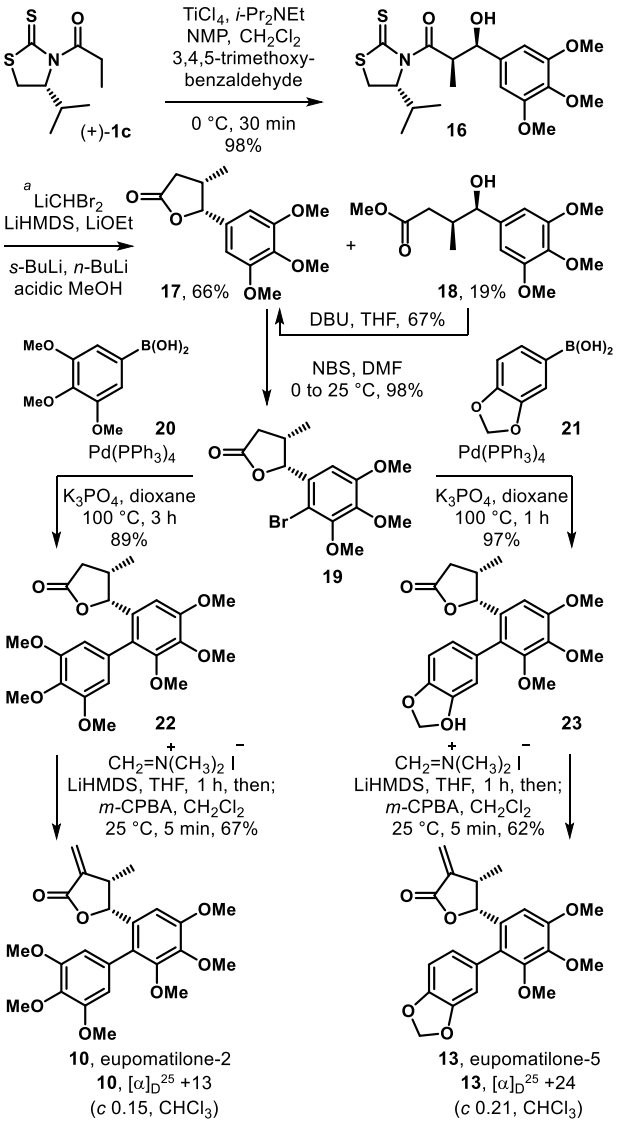
Having successfully secured the γ-butyrolactone **17**, we continued our investigation to the formation of the biaryl skeleton and completion of four members of the eupomatilones family of lignans. Toward this end, bromination of **17** by treatment with NBS in DMF provided the aryl bromide **19** in high yield (98%). The Suzuki cross-coupling of the resulting common intermediate **19** and 3,4,5-trimethoxyphenylboronic acid (**20**) ($Pd(PPh_3)_4$, K_3PO_4, dioxane, 100 °C) smoothly proceeded to provide **22** (89%).

Similarly, the Suzuki coupling of **19** with 3,4-(methylenedioxy)phenylboronic acid **21** resulted in **23** in excellent yield (97%). Subsequent installation of the α-*exo*-methylene moiety of **10** upon treatment of **22** with Eschenmoser's salt (LiHMDS, THF, −78 °C, 1 h) and its subsequent in situ elimination (*m*-CPBA, CH_2Cl_2, 25 °C, 5 min) afforded the eupomatilone-2 (**10**) in 67% yield. The synthesis of eupomatilone-5 (**13**) was accomplished in a similar fashion in 62% yield which proved to be identical in all respects with the reported properties of the natural product (Scheme 4).

With straightforward access to (+)-eupomatilones-2 and -5, the synthesis of eupomatilone-6 (**14**) was realized upon treatment of the lactone enolate of **23** with iodomethane (LiHMDS, THF, 5 min, −78 °C) as a single diastereomer (Scheme 5). Furthermore, the diastereoselective hydrogenation of the α-*exo*-methylene lactone **13** was best effected with Wilkinson's catalyst in toluene, in which the facial selectivity is governed by the C-4 methyl, providing 3-*epi*-eupomatilone-6 (**24**) in good conversion and diastereoselectivity (95%, dr >8.8:1), thereby providing access to three members of eupomatilones family and one 3-*epi*-analogue in only five steps (for eupomatilones-2,5,6) and six steps (for 3-*epi*-eupomatilone-6) from commercially available thiazolidinethione propionate (+)-**1c**, which proved our approach is comparable in length to the shortest asymmetric syntheses of eupomatilones reported by the Rovis group,[21i] highlighting the efficiency of our approach.

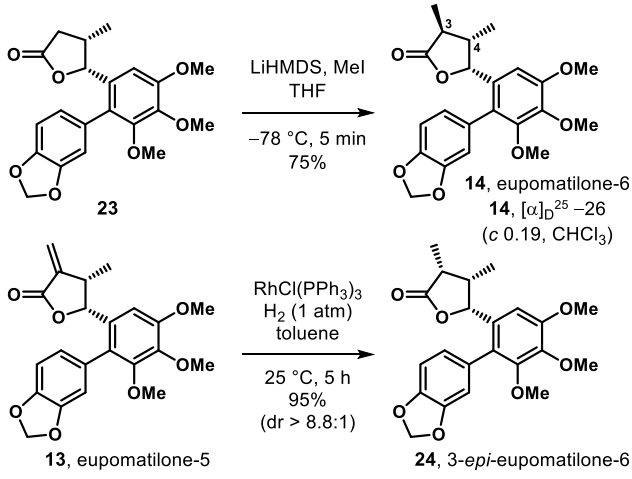
In summary, we have demonstrated an efficient synthesis of γ-butyrolactones via a combination of the asymmetric aldol/Kowalski ester homologation reaction. The strategy enables the straightforward preparation of a range of γ-butyrolactones bearing two vicinal functional groups and requisite stereochemistry in a single step. The applicability of this transformation was demonstrated in a protecting-group-free divergent total syntheses of eupomatilones-2,5,6 and 3-*epi*-

Scheme 4. Divergent Total Synthesis of Eupomatilone-2 and Eupomatilone-5



[a]Reaction conditions: 0.5−1.0 mmol of **16**. (i) LiTMP (4.0 equiv), CH_2Br_2 (4.4 equiv), −78 °C, (ii) LiHMDS (4.0 equiv), LiOEt (1.0 equiv), −78 to −20 °C, (iii) *s*-BuLi (4.0 equiv), −78 to −20 °C, (iv) *n*-BuLi (4.0 equiv), −78 °C, (v) acidic MeOH.

Scheme 5. Total Synthesis of Eupomatilone-6 and 3-*epi*-Eupomatilone-6



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eupomatilone-6. This represents one of the shortest asymmetric syntheses of eupomatilones family of lignans reported to date. The extension of this transformation in furthering the exploration of natural products is in progress, and the continued examination for more concise and facile access to chiral γ-lactones and tetrahydrofurans will be disclosed in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02848.

Full experimental details and copies of ^{1}H and ^{13}C NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: kiyoun@catholic.ac.kr.

ORCID

Hyoungsu Kim: 0000-0002-2774-8727

Kiyoun Lee: 0000-0003-4940-5044

Notes

The authors declare no competing financial interest.

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