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The first asymmetric synthesis of marliolide from readily accessible carbohydrate as chiral template

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ABSTRACT

A simple and efficient strategy for the first asymmetric total synthesis of marliolide was accomplished by using stereoselective alkylation of the dianion of the β-hydroxy lactone enolate with myristyl aldehyde as a key step. The key intermediate, β-hydroxyl γ-methyl butyrolactone was prepared by transformation of L-lyxonolactone starting from D-ribose, a naturally abundant chiral carbohydrate.

1. Introduction

Since the first isolation and identification of structure of Litsenolides from *Litsea japonica* [1], a variety of γ-butyrolactone derivatives were discovered and their individual biological activities were investigated [2–4].

Looking at the structural features of γ-butyrolactones, aliphatic chain is connected to α position of lactone ring by single or double bond in various forms of saturation, carbon length and E/Z-isomerism. At β position, hydroxyl group is generally located, and methyl or methylene at γ position (Fig. 1). The biological activities of these derivatives are influenced not only by characteristics of α-positioned substituents, but also by the functionalities and stereochemistry of the β and γ substituents. Inspired by the relationship between structure and biological activity, efforts have been dedicated to develop general methods to construct skeletons of γ-butyrolactone analogues by employing iodolactonization with appropriate acetylenic or olefinic acids [5], transesterification-based enzymatic resolution of secondary allylic alcohols [6], photooxygenation of chiral allylic alcohols followed by reduction and acid-catalyzed cyclization [7], cycloalkenylation of tungsten-alkynol species with aldehydes [8], asymmetric Sharpless dihydroxylation reaction of α,β′,β,γ-unsaturated esters using AD-mix [9], Ag (I)-mediated alkyne-lactonization [10], enatioselective tandem Michael-aldol reaction [11], and so on.

Among the many kinds of γ-lactone derivatives, we focused on marliolide, a natural product extracted for the first time from the leaves of *Mollinedia marliae* and the bark of *Cinnamomum cambodianum*, which exhibited variety of biological activities ranging from anti-spasmodic, anti-allergic, anti-inflammatory to anti-oxidant activities [12,13]. Recently, Chin et al. reported that extractives in chloroform potion from the bark of *Cinnamomum cambodianum* exhibited remarkable inflammatory activity by inhibiting the production of interleukin-6, the expression of COX-2, and the main component of that extractant was identified as marliolide [14,15]. So far, only racemic synthesis of marliolide has been reported and many papers have only dealt with the syntheses of its structural derivatives [5–11]. In our ongoing efforts on synthesis of new chemical entities derived from D-ribose [16] and their biological activities, we report here the first asymmetric synthesis of marliolide.

We envisaged that the butyrolactone **2** could be connected with an aldehyde by using lactone enolate alkylation, and the β-hydroxyl γ-methyl butyrolactone could be prepared from the L-(2,3-isopropylidene)lyxono-1,4-lactone **3**. Joullie and Chen have demonstrated that a dianion derived from **2** can undergo aldol reaction with various aldehydes, which upon dehydration deliver 2-alkylidenelactones [17]. D-Ribose was identified as an

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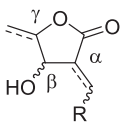

Fig. 1. Representative of γ-butyrolactone derivatives.

appropriate starting material for the synthesis of marliolide because it contains the whole chirality that is required for the construction of our desired skeleton except for the reverse configuration at γ-position of the lactone ring (Fig. 2). L-Lyxonolactone is readily accessible from D-ribose via D-ribonolactone by a known simple process reported previously [18].

2. Results and discussion

Our synthesis of marliolide commenced with the construction of (4*S*,5*S*)-dihydro-4-hydroxy-5-methylfuran-2(3*H*)-one **2** as a precursor for coupling reaction with lauraldehyde. We prepared L-lyxonolactone **3** starting from D-ribose through a number of steps referring to the former reports [18].

But, our initial attempts to convert the primary alcohol into a removable group as a halide or a sulfonate proved to be failure because of unexpected decomposition of the starting material under the general halogenation [19] or conservation of the sulfonate under reductive deoxgenation [20]. So, we came up with the detouring deoxygenation method by means of selenylation of alcohol and subsequent deselenylation of resulting selenide.

As shown in Scheme 1, treatment of the primary alcohol **3** with PhSeCN in the presence of nBu$_3$P [21] followed by conventional radical deselenylation of phenylselenide **4** by using tributyltin hydride (nBu$_3$SnH) [22] afforded the corresponding γ-methyl butyrolactone **5** in 59% yield for 2 steps.

Removal of acetonide protecting group with 1M HCl and treatment of diol **6** with phenylchlorothionoformate resulted in the selective formation of thionocarbonate at α-hydroxyl group, which was readily removed according to Barton-McCombie condition (nBu$_3$SnH, AIBN) [23] to furnish the deoxygenated mono-alcohol **2** [6,24].

Ester enolate aldol reaction of dianion derived from β-hydroxy ester without protection of alcohol is well known process [17,25]. Therefore, coupling of dianion derived from β-hydroxy lactone **2** by treatment of excess LDA was conducted with myristyl aldehyde to produce an inseparable diasteromeric mixture **7** in 4:1 ratio (Scheme 2). Elucidated from the plausible transition state geometry **A** during the aldol reaction, the existence of methyl group and alkoxide-metal chelated moiety on the same face would favor the approaching of the aldehyde from the opposite face, which is in agreement with Prestwich's work [26]. Hence only **R** conformers at α carbon were the predominant aldol adducts in spite of *syn*/*anti*-isomerism of two secondary alcohols. At this point, we did not make much effort to separate this mixture and to improve the ratio because the selective dehydration of alcohol in aliphatic chain would produce the double bond that meant the disappearance of stereocenter at α position. According to the previous report [25], the β-hydroxyl group in lactone ring was protected regioselectively to give the mono-silyl ether **8**. Mesylation of the remaining hydroxyl group followed by warming to 45 °C afforded spontaneously the desired olefin **9a** with *E* geometry as the major isomer, along with **9b** in a 3.7: 1 ratio in 90% total yield. Finally, deprotection of the silyl ethers, **9a** and **9b**, under acidic condition gave marliolide **1** and **10**, respectively. Our synthesized marliolide **1** had the same spectroscopic characteristics ([α], mp, NMR, etc), identical with those reported for the natural product, and the whole data were in good agreement with those kindly provided by Professor Chin from Dongguk University.

3. Conclusion

We constructed the γ-butyrolactone skeleton started from the D-(2,3-isopropylidene)lyxono-1,4-lactone derived from D-ribose and introduced aliphatic side chain by using lactone enolate alkylation with lauraldehyde. Throughout this synthetic work, we can now turn our attention to further elaboration which would lead to an asymmetric synthesis of a variety of naturally occurring products. Biological activities of marliolide are under investigation and the result will be announced elsewhere in the near future.

4. Experimental section

4.1. Materials

Except where noted, all the materials were purchased from commercial suppliers and were used without further purification. All reactions were routinely carried out under an inert atmosphere of dried nitrogen. ^{1}H-NMR Spectra (CDCl$_3$, DMSO-d_6) were recorded on a Varian (400 MHz) spectrometer (Varian Medical Systems, Inc., Palo Alto, CA, USA). The ^{1}H-NMR data are reported as peak multiplicities: s for singlet, d for doublet, dd for doublet of doublets, t for triplet, q for quartet, bs for broad singlet and m for multiplet. ^{13}C-NMR spectra (CDCl$_3$, DMSO-d_6) were recorded on Varian (100 MHz) spectrometer. The chemical shifts are reported as parts per million (δ) relative to the solvent peak with coupling constants in hertz (Hz). Optical rotations were determined on Jasco P-2000 polarimeter in appropriate solvent. Infrared spectra were recorded on FT-IR (NICOLET-iS5). Melting points were measured on Thermoscientific-9200. Elemental analyses (C, H) were used to determine purity of all synthesized compounds, and the results were within ±0.4% of the calculated values, confirming ≥ 95% purity. Reactions were monitored with TLC (Merck precoated 60F$_{254}$ plates). Spots were detected by viewing under a UV light, colorizing with charring after dipping in anisaldehyde solution or basic KMnO$_4$ solution. Column chromatography was performed on silica gel 60 (230–400 mesh Kieselgel 60). The mass spectra were recorded using LRMS (electron ionization MS) obtained on a Shimadzu-2020 or using HRMS

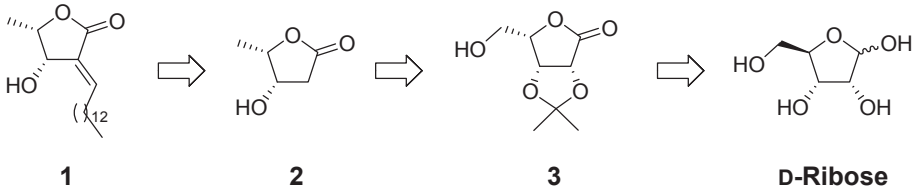

Fig. 2. Retrosynthetic analysis of Marliolide **1**.