Divergent Total Syntheses of Enmein-Type Natural Products: (–)-Enmein, (–)-Isodocarpin and (–)-Sculponin R

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Abstract: *Divergent total syntheses of enmein-type natural products, (–)-enmein, (–)-isodocarpin and (–)-sculponin R, have been achieved in a concise fashion. Key features of the strategy include (a) an efficient early-stage cage formation to control succeeding diastereoselectivity, (b) an one-pot acylation/akylation/lactonization to construct the C-ring and C8 quarternary center, (c) a reductive alkenylation approach to construct enmain D/E rings and (d) a flexible route to allow divergent syntheses of three natural products.*

The *ent*-kaurene diterpenoids, isolated from the *isodon* genus, have been an important family of natural products that exhibit rich biological activities and intriguing chemical structures.[1] Due to the limited supply from natural sources, these diterpenoids have attracted significant interests from the synthetic community for efficient chemical synthesis (Figure 1a).[2,3] Among various *ent*-kaurenoids, enmein (**1**) holds a unique position. It was the first *isodon* family member that was investigated for biological potency.[4] It is also the key compoent of *enmei-so*, namely "the grass effective for prolonging human life", which is a common herbal medicine used in Asia.[5] Enmein was first isolated from *I. japonica* in 1958,[6] and its structure was determined in 1966.[7] Unlike a regular *ent*-kaurene, enmein exhibits a more oxidized scaffold with C6,7 positions being cleaved, as well as a C1,7-lactone–type skeleton. Until now, more than 90 enmein-type natural products have been discovered, such as isodocarpin (**2**), sculponin R (**3**), macrocalyxin A, isorothornin G, etc (Figure 1b). Despite the great interest of this type of natural products from both biological and synthetic prospects, there has been only one relay synthesis of enmein by Fujita and coworkers in 1972,[8] whereas 42 steps were used from intermediate **4** (Figure 1c). Herein, we describe our efforts towards divergent total syntheses of three enmein-type *ent*-kaurenoids: (–)-enmein, (–)-isodocarpin and (–)-sculponin R.

Due to the distinct structure of enmein–type natural products, the challenge for their synthesis is *three-fold*. First, they contain various oxygen-based functional groups, such as free alcohols, acetals or hemi-acetals, lactones and ketones, at different oxidation levels. Thus, minimizing the use of protecting groups (PGs) would not be trivial. Second, construction of the C8-10 stereocenters could be challenging as two of them are all-carbon quarternary centers. Third, developing a divergent synthesis of more than one natural product would require identification of a common intermediate,[9] which might be complicated owing to the different substitution patterns of the D/E rings.

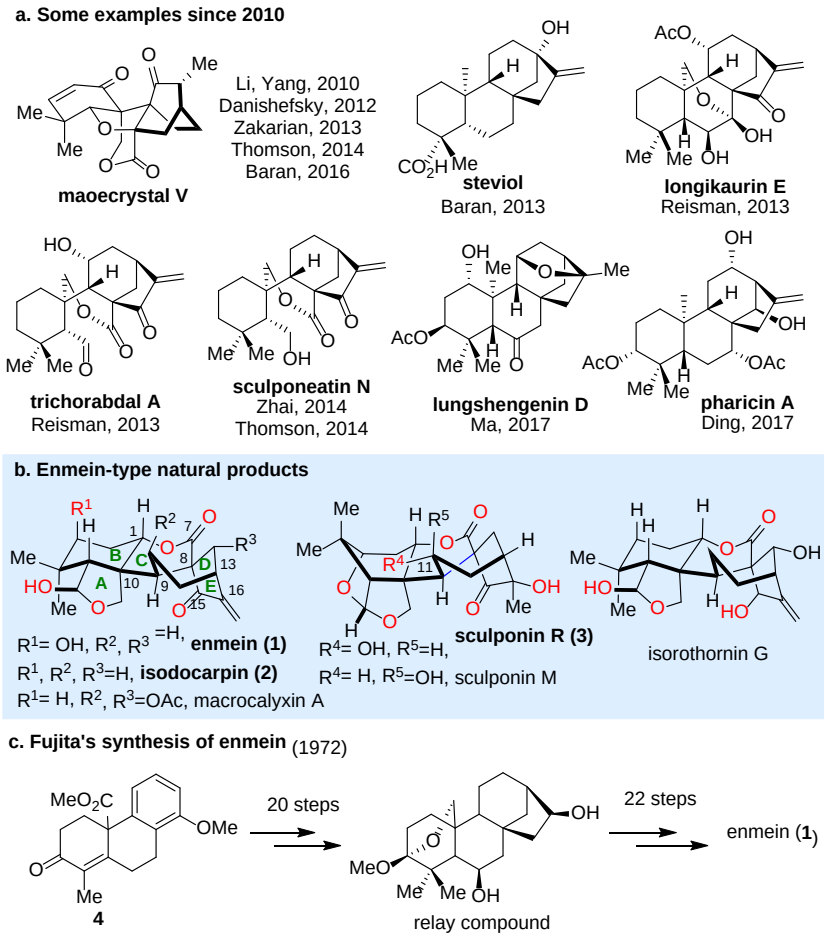
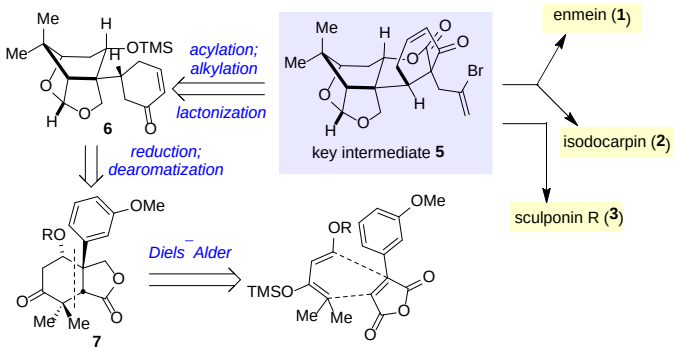


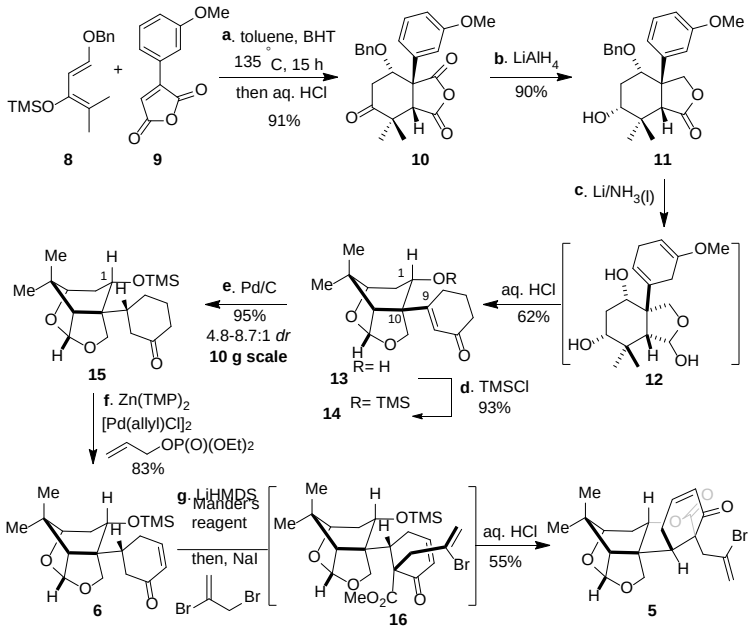
Figure 1. The *isodon ent*-kaurene diterpenoids.

To address these challenges, we conceived a strategy that is depicted in Scheme 1. Advanced intermdiate **5** containing a cyclohexenone ring was anticipated to serve as a common intermediate to access enmein, isodocarpin and sculponin R in similar numbers of steps. The enone moiety was envisioned to provide a handle to contruct the E ring and introduce the C11 hydroxy group in sculponin R at a late stage. The C8 quarternary center in intermediate **5** can be established by a consecutive acylation, alkylation and lactonization sequence from intermediate **6**. We postulated that building a cage ketal saffold at an early stage would have two benefits: 1) it protects both the C3 hydroxyl group and the hemi-acetal, thereby reducing PG usages; and 2) the rigid cage structure would facilitate subsequent diastereo-control for generating the C8 and C9 centers. Cage compound **6** is expected to be eventually prepared from a Diels–Alder adduct (**7**) through oxidation-state adjustment and dearomatization.



Scheme 1. Retro-synthetic analysis of enmein-type natural products.

The synthesis commenced with the Diels–Alder cycloaddition between Danishefsky-type diene **8**[10] and anhydride **9**, each prepared in three steps from commercially available chemicals (Scheme 2). Upon refluxing the mixture in toluene for 15 hours, followed by an acid workup, the bicyclic ketone product (**10**) was isolated in 91% yield. Treatment of **10** with $LiAlH_4$ led to selective reduction of the bulkier carbonyl group in the anhydride[11] as well as the ketone to afford lactone **11** in 90% yield. It is noteworthy that the lactone moiety remained intact even with prolonged reaction time or more $LiAlH_4$, which is likely due to the shielding effect by the arene ring. Subjecting lactone **11** to the Li/NH_3 conditions promoted (a) the Birch reduction to give the 1,4-diene, (b) reduction of the lactone to a hemi-acetal and (c) removal of the benzyl PG. Upon workup with aqueous HCl, the cyclohexenone moiety was afforded via enol ether hydrolysis and olefin isomerization; concurrently, the caged acetal was efficiently formed, which *matches well with the western hemisphere of sculponins R and M.*

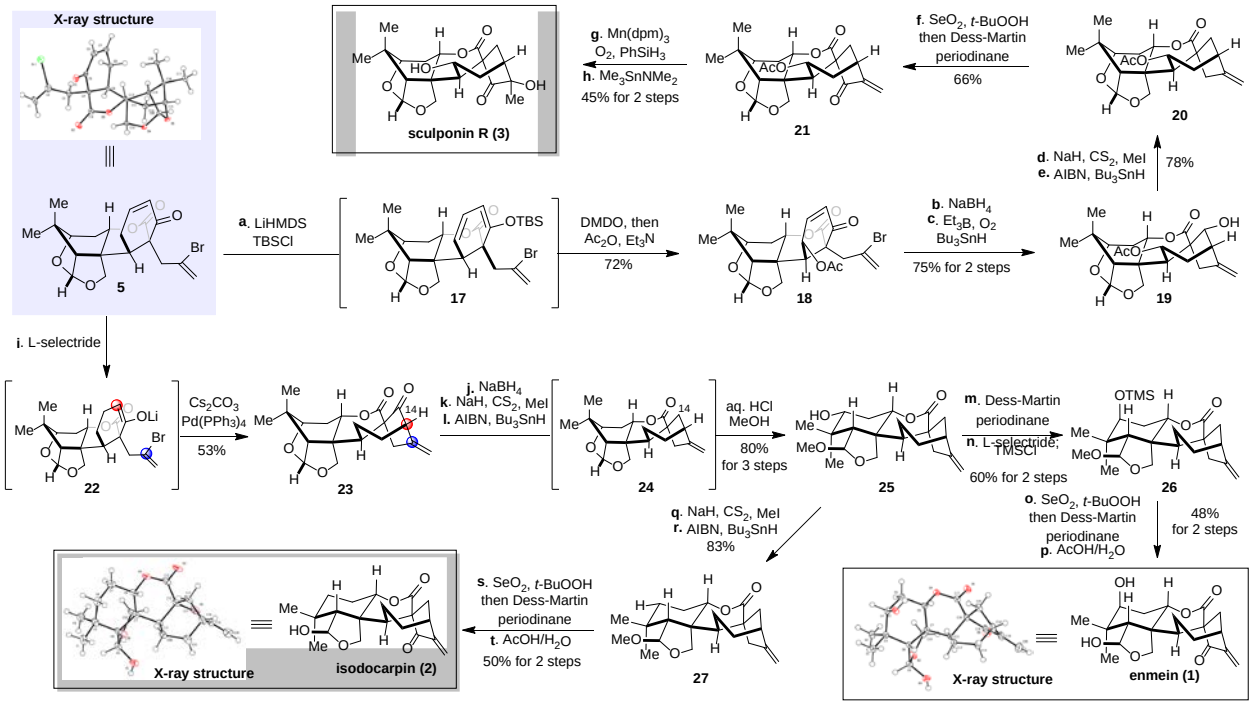


Scheme 2. Synthesis of key intermediate **5**.

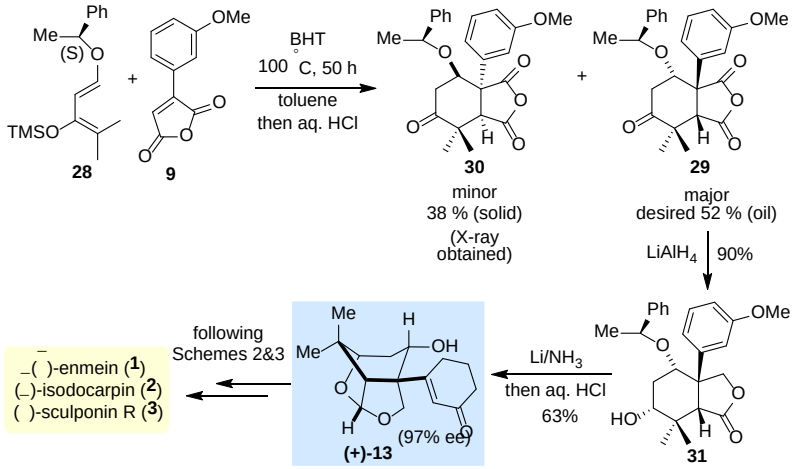
Direct hydrogenation of compound **13** under various conditions resulted in nearly no diastereoselectivity, likely due to that the cyclohexenone ring can undergo free rotation. We hypothesized that protection of the C1 hydroxyl group would restrict the rotation of the C9-C10 bond, which would in turn enhance the steric bias around the enone olefin. Indeed, TMS protection of the C1 alcohol following by hydrogenation with Pd/C afforded the C9 stereocenter with 4.8-8.7:1 dr. It is worthy to mention that the reaction can be scaled up to a 10-gram scale. Subsequently, enone **6** was synthesized using Newhouse's palladium-catalyzed dehydrogenation method,[12] though conventional two-step Saegusa oxidation also worked well. To furnish the C8 quaternary center and δ-lactone, a one-pot α-acylation/alkylation/lactonization was pursued. Treatment of enone **6** with LiHMDS/Mander's reagent[13] smoothly gave the β-keto ester intermediate; however, the α-alkylation with 2,3-dibromopropene proved to be a non-trivial challenge in this case as the *O*-alkylation was found dominant under most alkylation conditions. Ultimately, we found that, using NaH as the base and HMPA:THF=1:5 as the mixed solvent, the *C*-alkylation became the major reaction pathway (in a 6:1 ratio for *C* vs *O*-alkylation) and excellent diasteroselectivity (>10:1) was observed. To our delight, after removal of the TMS group with an acidic workup, lactonization took place simultaneously to provide compound **5** as a white solid in 55% yield from enone **6**. The structure and stereochemistry of lactone **5** were unambiguously determined by X-ray crystallography (Scheme 3).

With key intermediate **5** in hand, we turned our attention towards divergent syntheses of sculponin R, isodocarpin and enmein (Scheme 3). Vinylogous enol ether formation via treatment with LiHMDS/TBSCl, followed by DMDO oxidation, resulted in chemo- and diastereoselective[14] epoxidation at the β,γ-olefin, which collapsed *in situ* to give the γ-hydroxyl enone.[15] Subsequent one-pot acyl protection afforded ester **18** in 72% yield. Notably, attempts with other allylic oxidation methods were unfruitful for this transformation. Luche reduction of the enone moiety, followed by the radical conditions at room temperature trigered the 5-*exo* radical annulation to construct the [3.2.1] scaffold;[3j,3k] Subject compound **19** under the Barton–McCombie deoxygenation conditions promoted deoxygenation to eventually afford compound **20** in 78% yield.[16] Allylic oxidation by selenium dioxide followed by treatment with Dess–Martin periodinane gave enone **21**. Subsequent Mukaiyama hydration[17] followed by deacetylation using Me_3SnNMe_2[18] completed the total synthesis of sculponin R, which is spectroscopically identical to the natural sample reported by Sun and coworkers.[19]

To synthesize enmein and isodocarpin, a distinct reductive alkenylation approach was developed to build the D/E rings. L-selectride reduction of **5** led to fomation of lithium enolate **22**, followed by palladium-catalyzed alkenylation[20], smoothly provided the [3.2.1] bicycle **23**. An efficient reduction/Barton–McCombie deoxygenation sequence was adopted to remove the C14 oxygen, and, upon acidic workup in methanol, the cage structure was opened to release alcohol **25** in 83% overall yield. Compound **25** can serve as a common intermediate to prepare enmein and isodocarpin through late-stage functional group manipulations. Epimerization of the C3 hydroxyl group was realized through Dess–Martin oxidation and then L-selectride reduction. Finally, allylic oxidation followed by acid-mediated acetal hydrolysis and silyl removal completed the total synthesis of enmein (**1**). On the other hand, Barton–McCombie deoxygenation of intermediate **25** removed the C3 hydroxyl group. A similar allylic oxidatin/acetal hydrolysis protocol yielded isodocarpin (**2**). The structures of synthetic enmein and isodocarpin were further confirmed by X-ray crystallography (Scheme 3).



Scheme 3. Divergent total syntheses of racemic enmein, isodocarpin and sculponin R.[22]



Scheme 4. Syntheses of (–)-enmein, (–)-isodocarpin and (–)-sculponin R

To realize a *practical* route for the asymmetric syntheses of these natural products, we conceived the idea of using chiral diene **28**, prepared from (*S*)-1-phenylethanol, to influence the stereochemistry in the Diels–Alder reaction (Scheme 4). While the diastereoselectivity obtained was not ideal, the two diastereomers **29** and **30** can nevertheless be easily separated, and the major compound (**29**) was the desired isomer to access the natural enantiomers of these natual products. Starting from anhydride **29**, a similar reduction and acid treatment sequence was utilized to provide cage compound (+)-**13**, which is the same intermediate employed in the racemic synthesis. Given

the relatively low cost of (*S*)-1-phenylethanol, this route provides a rapid and inexpensive approach to access enantioenriched synthetic intermediates. Following the identical synthetic routes described in Schemes 2 and 3, syntheses of (–)-enmein, (–)-isodocarpin and (–)-sculponin R were eventually achieved, of which the optical rotation data match well with the reported ones for the natural samples.[7,19,21]

In summary, syntheses of (–)-enmein, (–)-isodocarpin and (–)-sculponin R have been achieved in a concise fashion. The key features of the strategy include (a) an efficient early-stage cage formation to control succeeding diastereoselectivity, (b) an one-pot acylation/akylation/lactonization to construct the C-ring and C8 quarternary center, (c) a reductive alkenylation approach to construct enmain D/E rings and (d) a flexible route to allow divergent syntheses of three natural products. We anticipate that the practicality and conciseness of this strategy should have important implications for preparing other *ent*-kaurene diterpenoids. Investigation of the anticancer activity of these natural products and their synthetic intermediates are ongoing.

Acknowledgements

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Keywords: terpene • enmein • divergent synthesis • cage formation• total synthesis

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