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Synthesis of stagonolide C from Mulzer epoxide

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ABSTRACT

Total synthesis of stagonolide C using chiral pool strategy is described. The two key intermediates were prepared from L-glutamic acid and D-glucono-1,5-lactone, followed by Julia–Lythgoe olefination and Yamaguchi esterification to afford the target compound in an efficient way.

Naturally occurring macrolides, particularly 10-membered lactones (noneolides) have continued to attract synthetic chemists as well as biologists during recent years, because of their interesting structural features and various biological activities like plant growth inhibition, anti-feedant, anti-fungal and anti-bacterial activities.[1] For example, modiolide A and B have been shown to have anti-bacterial and anti-fungal activities.[2] Stagonolide C[3] represents another novel 10-membered ring lactone, and was the main phytotoxic metabolite of a fungal pathogen *Stagonospora cirsii*, *S. cirsii* was isolated from *Cirsium arvense*, and was proposed as a potential mycoherbicide by causing necrotic lesions on leaves. Other metabolites, namely stagonolide B–I[4] were structurally similar to stagonolide C, and were isolated from the same fungus.

All noneolides shown in Figure 1 possess some common interesting structural features, the olefinic moiety with well-defined geometry as well as stereochemically pure hydroxyl appendages make them very challenging synthetic targets. In 2009, Yadav and co-workers[5] reported the first total synthesis of stagonolide C. The key steps include the intramolecular ring-closing metathesis to construct the macrolide *trans* double bond. Sharpless asymmetric epoxidation was employed to control the hydroxyl stereochemistry. Later on, Nanda and co-workers[6] independently reported an alternative total synthesis route, which also involved the ring-closing metathesis reaction, while the hydroxyl stereo center was achieved by enzyme-catalyzed reaction.

In a previous study, a convenient route has been developed to achieve the chiral building blocks **2** and **3** from the commercially inexpensive D-glucolactone (Fig. 2).[8] Application of these chiral building blocks was exemplified to construct the stereochemically defined 1,3-diol motif of verbalactone and exophilin A.[8] Recently, the same chiral epoxide building blocks were employed to successfully achieve other naturally occurring products which contain the 1,3-diol fragments.[9,10] Herein, we wish to report our effort to

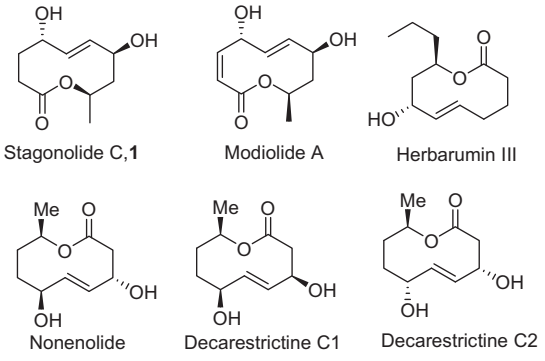

Figure 1. The structure of stagonolide C, modiolide A, herbarumin III, nonenolide, and decarestrictine C1 and C2.

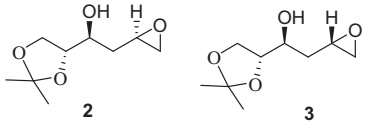

Figure 2. The structure of chiral building blocks Mulzer epoxide[7] **2** and **3**.

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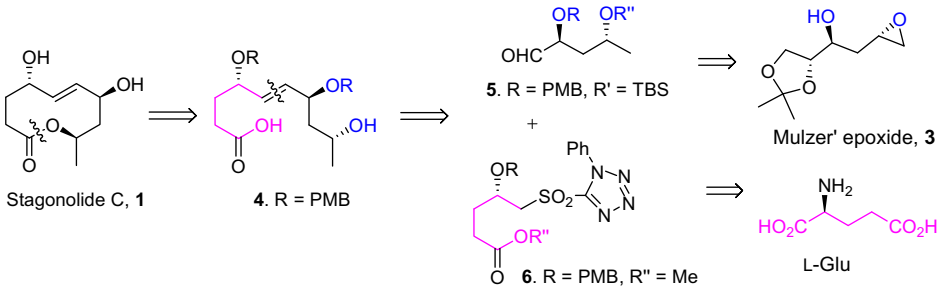


Scheme 1. Retrosynthetic analysis of stagonolide C.

exploit one molecular architecture as an excellent precursor for the total synthesis of stagonolide C.

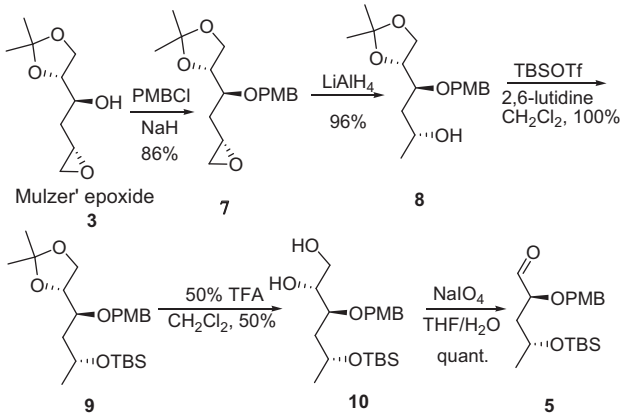
Retrosynthetic analysis of the target molecule stagonolide C is shown in Scheme 1. The target molecule can be achieved from seco acid **4**, the crucial ester linkage is planned to be constructed through Yamaguchi esterification,[11] The *trans* double bond can be formed from aldehyde **5** and sulfone **6** via Julia–Lythgoe olefination.[12] Fragments **5** and **6** would be prepared from the Mulzer epoxide and L-glutamic acid, respectively.

The synthesis of fragment **5** began with the Mulzer' epoxide, which was prepared from D-glucono-1,5-lactone according to the reported procedure.[8] As shown in Scheme 2, the hydroxyl group in epoxide **3** was protected as PMB ether **7** as reported previously.[13] Treatment of this intermediate with $LiAlH_4$ afforded the epoxy ring opening product **8** in a 96% yield. The newly-formed hydroxyl group was converted into a TBS ether **9** with TBSOTf/2,6-lutidine/CH_2Cl_2.[14] The acetonide was carefully hydrolyzed using[15] 50% aq F_3CCO_2H in CH_2Cl_2 to give **10**. Subsequent treatment of diol **10** with $NaIO_4/H_2O$–THF led to the required aldehyde **5** (Scheme 2).

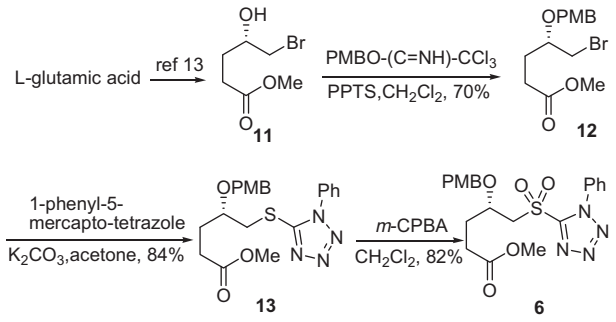
The synthesis of fragment **6** started from intermediate **11**,[16] which was prepared from commercially available L-glutamic acid in five steps. Protection of the hydroxyl group with PMBOC (=NH)CCl_3 in mild condition afforded **12**, subsequent thianation with *N*-phenyl-5-mercaptotetrazole/K_2CO_3 gave **13**, which was then subjected to *m*-CPBA oxidation to give fragment **6** in an 82% yield (Scheme 3).

With **5** and **6** in hand, our next task was to couple the two fragments. A careful survey of the critical Julia–Lythgoe olefination reaction condition was conducted. Accordingly, condensation of fragments **5** and **6** was achieved using sodium bis(trimethylsilyl)amide (NaHMDS) as base with hexamethylphosphoramide (HMPA) as additive in THF. In this reaction, prolonged deprotonation time by NaHMDS and slow addition of aldehyde would favor the formation of **14**[17] in moderate yield. Next, the TBS protecting group was cleaved with CSA/MeOH in a 90% yield. Subsequent treatment with LiOH/MeOH–H_2O afforded the seco acid **4**. The crucial ring-closing Yamaguchi esterification reaction failed in THF at 100 °C using 8 equiv Yamaguchi reagent **16**, finally, 20 equiv of **16** successfully furnished **17** as the sole product in a 63% yield (Scheme 4). Cleavage of PMB protecting groups using CAN[18] achieved the target molecule **1**,[19] with the spectroscopic data consistent with those reported in the literature.[4a]

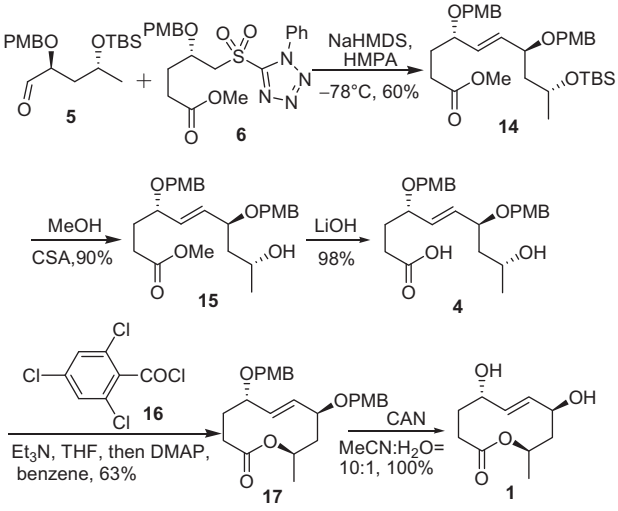
In conclusion, we have described an efficient synthesis route to construct stagonolide C. This protocol involved the utilization of previously developed chiral epoxide intermediate, Julia–Lythgoe coupling of two fragments and Yamaguchi esterification for intramolecular cyclization to achieve total synthesis of the target compound. This synthesis exemplified the usage of Mulzer epoxide



Scheme 2. Synthesis of fragment **5**.



Scheme 3. Synthesis of fragment **6**.



Scheme 4. Total synthesis of stagonolide C.

as chiral building blocks in efficient access to other 1,3-diols containing naturally occurring products.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.12.102.

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17. Analytical and spectral data of **14**: $[\alpha]_D^{26}$ −39.7 (*c* 0.33, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.40 Hz, 4H), 6.87 (dd, *J* = 8.40, 2.00 Hz, 4H), 5.59 (m, 2H), 4.54 (d, *J* = 8.40 Hz, 1H), 4.51 (d, *J* = 8.40 Hz, 1H), 4.29 (d, *J* = 4.00 Hz, 1H), 4.27 (d, *J* = 4.00 Hz, 1H), 4.08–4.00 (m, 2H), 3.90–3.80 (m, 1H), 3.80 (s, 6H), 3.63 (s, 3H), 2.42–2.37 (m, 2H), 2.00–1.78 (m, 2H), 1.72–1.67 (m, 1H), 1.59–1.55 (m, 1H), 1.13 (d, *J* = 6.40 Hz, 3H), 0.89 (s, 9H), 0.06 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 159.1 (2C), 134.9, 132.5, 130.8, 130.5, 129.3 (2C), 129.2 (2C), 113.9 (2C), 113.8 (2C), 78.0, 70.1, 69.9, 65.0, 55.26 (2C), 51.5, 46.5, 30.7, 30.1, 29.7, 25.9 (3C), 24.5, 18.0, −4.03, −4.70. ESI-MS: *m*/*z* 609.8 ($[M+Na]^+$). ESI-HRMS calcd for $C_{33}H_{50}O_7SiNa$ ($[M+Na]^+$): 609.3218; found: 609.3222.
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19. Analytical and spectral data of **1**: $[\alpha]_D^{26}$ +50 (*c* 0.2, $CHCl_3$). (lit.[4a] $[\alpha]_D^{25}$ +48 (*c* 0.2, $CHCl_3$).) ^1H NMR (400 MHz, $CDCl_3$): 5.59 (dd, *J* = 15.60, 9.20 Hz, 1H), 5.44 (dd, *J* = 15.60, 9.20 Hz, 1H), 5.18–5.13 (dq, *J* = 11.10, 6.30 Hz, 1H), 4.15–4.10 (m, 2H), 2.31–2.28 (m, 1H), 2.07–2.02 (m, 3H), 1.92–1.87 (m, 1H), 1.82–1.73 (m, 1H), 1.22 (d, *J* = 6.50 Hz, 3H). ^{13}C NMR: (100 MHz, $CDCl_3$): 174.2, 135.8, 133.1, 74.6, 72.3, 67.6, 43.6, 34.6, 31.5, 21.3. ESI-MS: *m*/*z* 222.9 ($[M+Na]^+$). ESI-HRMS calcd for $C_{10}H_{16}O_4Na$ ($[M+Na]^+$): 223.0941; found: 223.0948.