Synthetic Study of Versipelostatin A: Synthesis of the Spirotetronate Unit Starting from Pulegone

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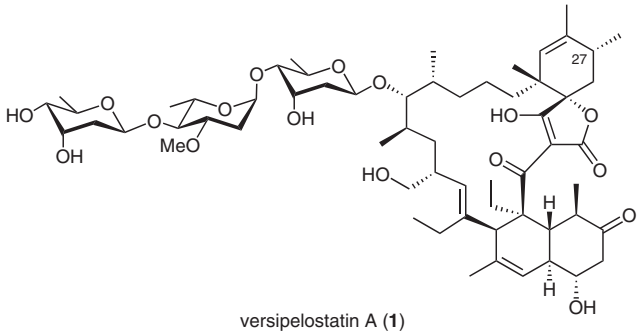
Abstract: The synthesis of the spirotetronate unit of versipelostatin A, a down-regulator of molecular chaperone GRP78, was achieved in ten steps starting from pulegone, via the Johnson–Claisen rearrangement. A model study of the coupling reaction with the octalin unit was also performed.

Key words: versipelostatin A, natural products, spiro compounds, Claisen rearrangement

In 2002, Shin-ya and co-workers isolated versipelostatin A (**1**; Figure 1) from the culture broth of *Streptomyces versipellis* and identified it as a down-regulator of *grp78* gene expression.[1] In the endoplasmic reticulum (ER) of solid tumor cells, the expression of the GRP78 protein enhances the ER stress response, which plays a role in the resistance to chemotherapy and hypoglycaemic stress.[2] Thus, a specific down-regulator of GRP78 would hold promise as an alternative to cancer chemotherapy.[3] The structure of versipelostatin A, including its stereochemistry, was determined to be that of **1** by analysis of its spectroscopic data and on the basis of synthetic studies of the sugar moieties.[4,5] Versipelostatin A consists of a trisaccharide attached to a seventeen-membered macrocycle fused to spirotetronate and octalin units. Our interest in the unique structure and biological activity of versipelostatin A led us to pursue its synthesis. Herein, we report the efficient synthesis of the spirotetronate unit of versipelostatin A. To date, several synthetic studies of spirotetronate-related compounds,[6,7] such as tetronolide,[8–11] quartromicin,[12,13] and spirohexenolide,[14] have been reported, and some of these synthetic approaches are currently used for the total synthesis of natural products.

Our synthetic plan for **1** is illustrated in Scheme 1. The synthetic features include anion-mediated coupling reactions of fragments **B**, **C**, and **D**, macrocyclization by ring-closing metathesis (RCM) between C-10 and C-11, followed by formation of the octalin system by an intramolecular Diels–Alder reaction of **A**. The spirotetronate fragment **B** was envisioned to be prepared from allylic alcohol **E** via a [3,3]-sigmatropic rearrangement. Compound **E**, in turn, was thought to be accessible from spirolactone **F**, which could be synthesized from (*S*)-pulegone by introduction of the tetronate ring and oxidative cleavage of the double bond.



versipelostatin A (**1**)

Figure 1 Structure of versipelostatin A (**1**)

We synthesized the enantiomeric spirotetronate unit *ent*-**B**, with the aim of establishing a synthetic route towards versipelostatin A. Although the stereochemistry of the natural spirotetronate unit is 27*R*, which corresponds to 9*R* in the intermediate **B**, we selected the more economical (*R*)-pulegone as the starting material for our model study.

The initial stage of the synthesis is shown in Scheme 2. Alkylation of lithiated methyl propiolate with (*R*)-pulegone afforded the adduct **3** stereoselectively via axial attack.[15] The sequential 1,4-addition of the methoxide ion followed by spirolactone formation[13] gave the desired tetronate derivative **4**. The yield of **4** was 69% for the two steps based on (*R*)-pulegone; elimination of the methyl propiolate group under basic conditions caused regeneration of (*R*)-pulegone (16%).[15] Tetronate derivative **4** was converted into ketone **5** by ozonolysis of the isopropylidene moiety. The α,β-dehydrogenation of ketone **5** proved to be somewhat challenging. Saegusa oxidation, 2-iodoxybenzoic acid (IBX) oxidation, phenylsulfanylation, or phenylselenenylation and oxidation were all attempted, but in each case either no or very little of the desired enone was obtained. However, dehydrogenation following Mukaiyama's protocol [LHMDS, PhS(Cl)=N(*t*-Bu)][16] afforded enone **6** in satisfactory yield. The 1,2-addition of methylmagnesium bromide to 7-en-6-one **6** gave the corresponding allylic alcohol as a single isomer.[17] Subsequent oxidation and allylic rearrangement was achieved simultaneously using pyridinium chlorochromate (PCC) and silica gel to give 6-en-8-one **8**. This enone was further treated with methylmagnesium bromide to give two diastereomeric adducts, **9** and **10**, in an approximately 2:1 ra-

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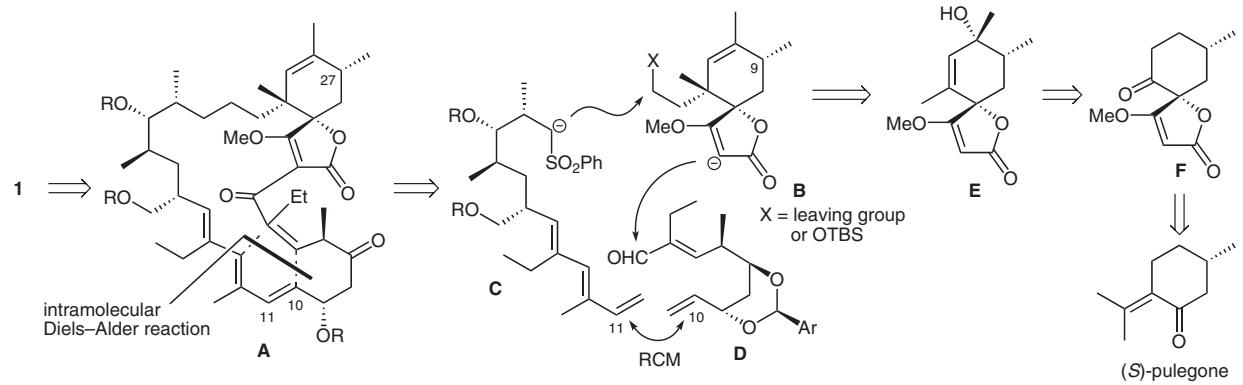
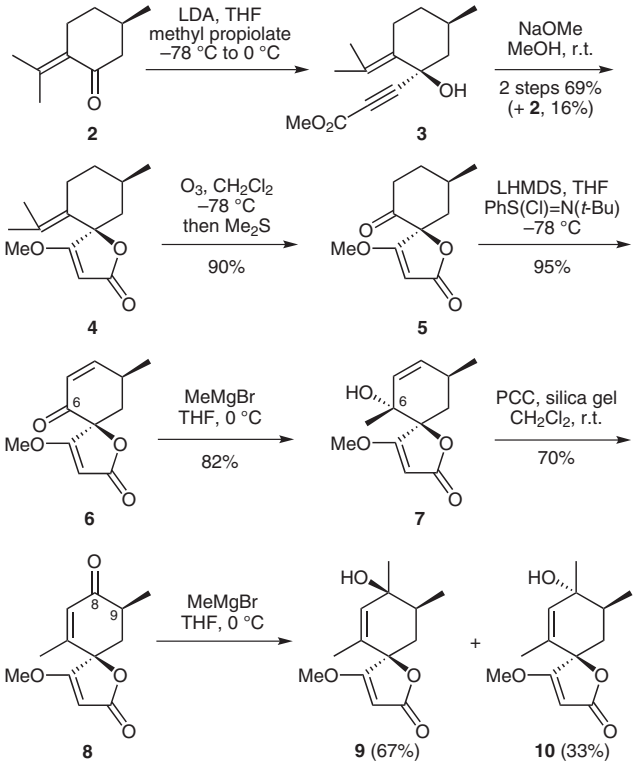


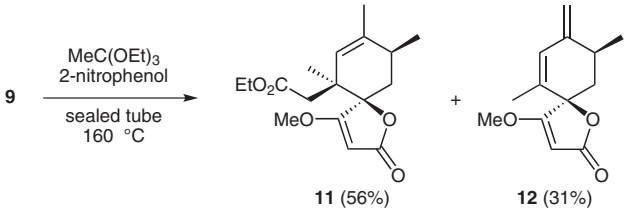
Scheme 1 Synthetic route to versipelostatin A (**1**) and its spirotetronate unit

tio. Nucleophilic attack from the opposite side of the C-9 methyl group gave the major adduct **9**, which was the desired product. Unfortunately, the use of methyllithium as a nucleophile accelerated an axial attack and decreased the formation of **9** (**9**/**10** = 1:3).



Scheme 2 Synthesis of allylic alcohol **9**

The stereochemistries of the adducts were confirmed by NOE experiments (vide infra). After chromatographic separation of the two diastereomers, the required compound **9** was subjected to [3,3]-sigmatropic rearrangement to install a C_2 unit at the C-6 position. Attempted vinyl ether formation, oxy-Michael addition to vinyl sulfone and acetylation followed by Ireland–Claisen rearrangement[18] were all unsuccessful. Refluxing in triethyl orthoacetate with propionic acid as a catalyst only resulted in the formation of the undesired *exo*-selective dehydration product **12**. In contrast, using 2-nitrophenol instead of propionic acid afforded the desired Johnson–Claisen rearrangement product **11** (36%), accompanied by **12** (36%) and unreacted **9** (23%) within 16 hours. The yield of **11** was not improved by extending the reaction time. Microwave irradiation accelerated both the rearrangement and the elimination (**11**: 33%, **12**: 36%, **9**: 36% in 15 min). The best result was obtained when the reaction was carried out in a sealed tube at a high temperature (Scheme 3).[19–22]



Scheme 3 Synthesis of **11** by Johnson–Claisen rearrangement

The synthesis of key intermediate **14** (*ent*-**B**) is shown in Scheme 4. The synthesized ester **11** was treated with $LiAlH_4$, followed by protection of the hydroxy group as a TBS ether to give **14**, the stereochemistry of which was confirmed by NOE experiments (Figure 2) and by the similarity of the ^{1}H NMR spectra of the synthesized compound **14** to the reported spectra of related spirotetronates.[11,23,24] Following the stereoselective construction of the spirotetoronate unit, we subsequently addressed the coupling reaction using synthesized **14** and benzaldehyde as a model compound for the acylated octalin unit.

Using established protocols,[9,14] spirotetronate **14** was lithiated with *t*-BuLi, followed by treatment with benzaldehyde to afford a product predicted to be **15**.[25]

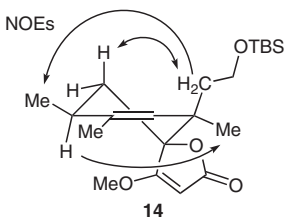
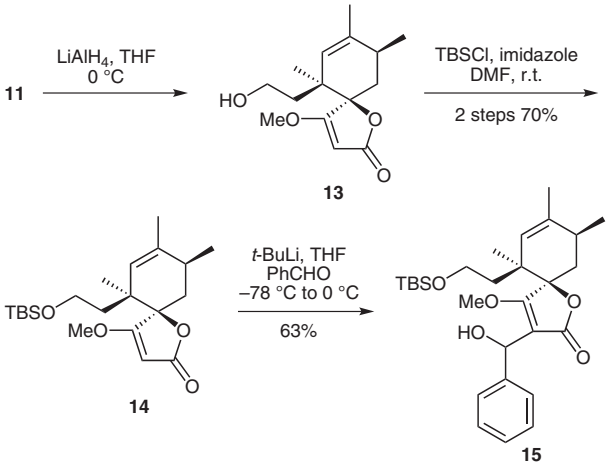


Figure 2 NOE study of compound **14**



Scheme 4 Synthesis of key intermediate **14** and its alkylation

In summary, we have achieved an efficient stereoselective synthesis of the enantiomeric spirotetronate unit **14** of versipelostatin A (**1**). The overall yield was 8.9% in ten steps starting from commercially available (*R*)-pulegone. This synthetic method is thought to be applicable to other spirotetronate-based natural products. In addition, we performed a model study of the coupling reaction of the spirotetronate unit and the acylated octalin unit using benzaldehyde as an electrophile. Our continuing research towards the synthesis of versipelostatin A, including the synthesis of other coupling partners and studies on cyclizations, is in progress.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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0.88 (s, 3.6 H, TBS), 0.89 (s, 5.4 H, TBS), 0.95 (s, 1.2 H, 6-Me), 0.97 (s, 1.8 H, 6-Me), 1.05 (d, *J* = 7.3 Hz, 1.8 H, 9-Me), 1.05 (d, *J* = 6.9 Hz, 1.2 H, 9-Me), 1.63–1.68 (m, 3 H, 8-Me), 1.74–1.83 (m, 2 H, 6-CH_2-), 1.88 (dd, *J* = 13.7, 6.8 Hz, 0.6 H, 10-Ha), 1.94 (dd, *J* = 13.8, 6.9 Hz, 0.4 H, 10-Ha), 2.05 (m, 1 H, 10-Hb), 2.38 (m, 1 H, 9-H), 3.69–3.77 (m, 2 H, 6-CH_2-C*H*$_2$-), 3.88 (s, 1.8 H, 4-OMe), 3.94 (s, 1.2 H, 4-OMe), 4.14 (d, *J* = 10.0 Hz, 0.6 H), 4.33 (d, *J* = 10.0 Hz, 0.4 H), 5.10 (m, 1 H, 7-H), 5.96 (s, 0.6 H, OH), 5.98 (s, 0.4, OH), 7.25–7.43 (m, 5 H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.3 (1.2 C), –5.3 (0.8 C), 18.2 (0.4 C), 18.2 (0.6 C), 19.5 (0.4 C), 19.6 (0.6 C), 20.9 (1 C), 21.6 (0.6 C), 21.6 (0.4 C), 25.9 (3 C), 32.6 (1 C), 37.7 (0.6 C), 37.9 (0.4 C), 49.2 (1 C), 42.3 (0.4 C), 42.4 (0.6 C), 59.9 (0.4 C), 59.9 (0.6 C), 60.3 (0.6 C), 60.4 (0.4 C), 67.2 (0.6 C), 67.7 (0.4 C), 87.7 (0.6 C), 87.9 (0.4 C), 103.1 (0.4 C), 103.2 (0.6 C), 125.8 (1.2 C), 125.9 (0.8 C), 127.2 (0.4 C), 127.3 (0.6 C), 127.5 (0.6 C), 127.6 (0.4 C), 128.6 (2 C), 136.0 (0.6 C), 136.2 (0.4 C), 142.9 (0.4 C), 143.1 (0.6 C), 173.5 (0.4 C), 173.7 (0.6 C), 177.9 (0.4 C), 178.4 (0.6 C); MS (ESI-TOF): *m*/*z* $[M + Na]^+$ calcd for $C_{28}H_{42}N_2NaO_5Si$: 509.2694; found: 509.2661

