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A Versatile, Diels–Alder Reaction-Based Approach to Prenyleudesmane Diterpenoids: A Concise Total Synthesis of Sinupol

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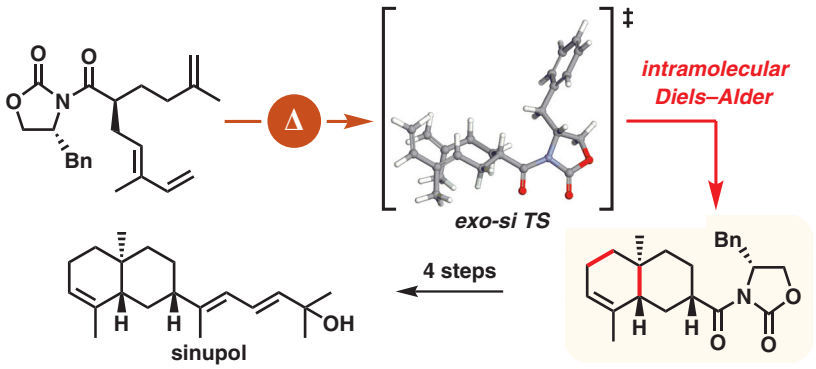

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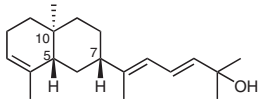
Abstract Herein, a concise strategy designed to provide general and diversifiable access to various prenyleudesmane terpenoids is described and utilized in the asymmetric synthesis of a biologically active prenyleudesmane diterpenoid, sinupol, which is accomplished in a seven-step procedure.

Key words prenyleudesmane diterpenoid, sinupol, PTP1B inhibitor, Diels–Alder reaction, total synthesis

Type 2 diabetes, which accounts for 90% of diabetes, is a chronic disease characterized by hyperglycemia, the common symptoms of which include polydipsia, polyuria, and unexplained weight loss.[1] Long-term complications from hyperglycemia include heart disease, stroke, and diabetic retinopathy, which can lead to blindness, renal failure, and reduced blood flow that can require subsequent limb amputation. Type 2 diabetes is caused by environmental factors such as overeating, lack of exercise, obesity and stress, and aging, in addition to a plurality of genetic factors including a predisposition to decrease insulin sensitivity and/or insulin secretion. Initial treatment begins with diet and exercise; however, if blood glucose levels are not sufficiently reduced, drug therapy involving injectable insulin and oral hypoglycemic agents such as sulfonylureas, α-glucosidase inhibitors, biguanides, thiazolidinediones, DPP4 inhibitors, and SGLT2 inhibitors is necessary.[2] Unfortunately, these clinically used diabetes drugs suffer from certain drawbacks such as side effects and the existence of nonresponders, which renders the development of more efficacious agents particularly important. Protein tyrosine phosphatase 1B (PTP1B) is a negative regulator of the tyrosine phosphorylation cascade integral to the insulin signaling pathway,[3] and is one of the most notable molecular targets for the development of novel therapeutic agents for type 2 diabetes.[4] PTP1B inhibitors are currently undergoing clinical trials as novel therapeutics for insulin-resistant type 2 diabetes by enhancing insulin signaling, but have not reached clinical application because of their low activity and selectivity.[5] In recent years, a search for more active PTP1B inhibitors from marine resources has been conducted.[6] In 2018, to identify novel diterpenoids as potential medicinal leads, Guo and co-workers launched an investigation on the extract of the soft coral *Sinularia polydactyla*, which led to the discovery of sinupol (**1**) as a novel prenyleudesmane diterpenoid (Figure 1).[7] The relative configuration of sinupol (**1**) was determined on the basis of ^{1}H NMR, ^{13}C NMR, COSY, HSQC, HMBC, and NOESY spectroscopic experiments, and the absolute configuration of the *trans*-fused decalin moiety was deduced by using time-dependent density functional theory electronic circular dichroism (TDDFT ECD) calculations. Compound **1** displayed moderate inhibitory activity against PTP1B, exhibiting IC_{50} values of 63.9 μM with oleanolic acid as positive control (IC_{50} = 2.56 μM). Herein, we describe a short and concise synthesis of sinupol (**1**), in which an intramolecular Diels–Alder reaction was used as a key step.



sinupol (**1**)

Figure 1 Structure of sinupol (**1**)

Our retrosynthetic analysis is depicted in Scheme 1. Assuming that sinupol (**1**) could be obtained from *trans*-fused decalin **2** through the removal of the chiral auxiliary followed by *E*-selective Horner–Wadsworth–Emmons reaction and methylation, we designed the construction of the

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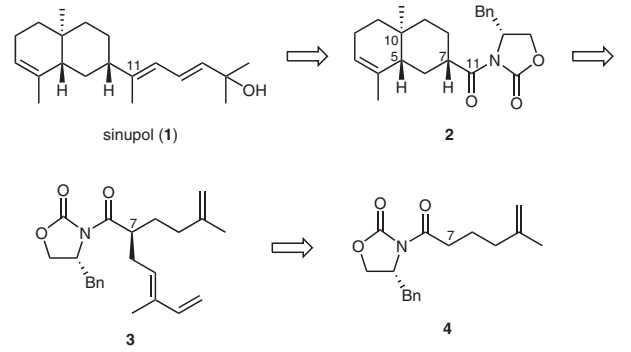
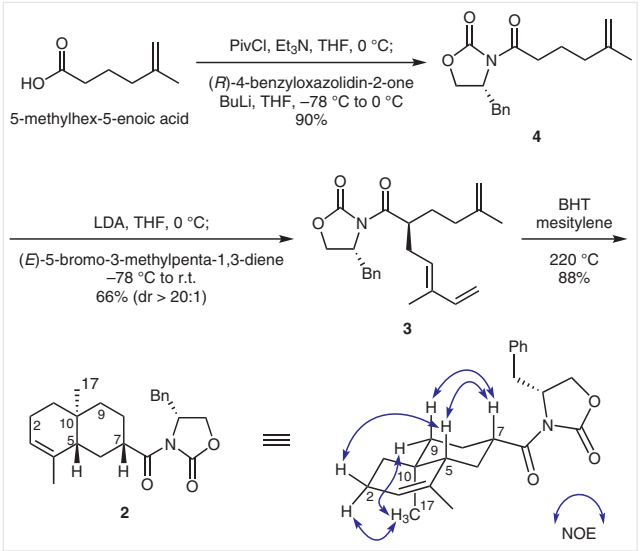
trans-fused decalin core as a key step by an intramolecular Diels–Alder reaction of triene **3**. We predicted that the conjugated diene moiety in triene **3** could be installed via Evans asymmetric alkylation[8] from imide **4**, which was prepared from 5-methylhex-5-enoic acid and (*R*)-4-benzyloxazolidin-2-one through amide coupling.



Scheme 1 Retrosynthetic analysis of sinupol (**1**)

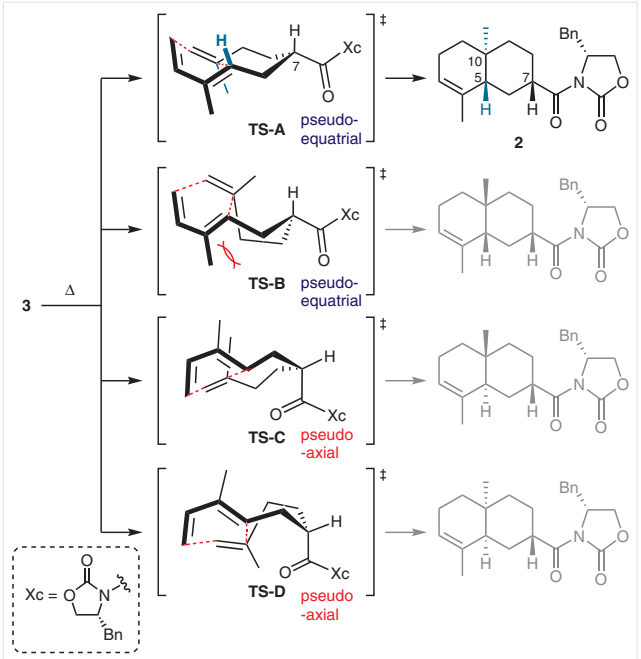
Our synthesis commenced with the preparation of *trans*-fused decalin **2** (Scheme 2). Commercial (*R*)-4-benzyloxazolidin-2-one was sequentially treated with BuLi and acid anhydride, which was prepared from 5-methylhex-5-enoic acid and pivaloyl chloride,[9] to give imide **4** in 90% yield. The LDA-generated enolate of **4** was alkylated with (*E*)-5-bromo-3-methylpenta-1,3-diene,[10] providing triene **3** in 66% yield. The absence of diastereomers in the ^{1}H NMR spectrum of the product confirmed the formation of **3** with the desired *S* configuration with high diastereoselectivity.[11] The thermal intramolecular Diels–Alder (IMDA) reaction of triene **3** in mesitylene at 220 °C for 168 h proceeded stereoselectively to provide the desired *trans*-fused decalin **2** in 88% yield along with unidentified diastereomers in 8% yield. The correlations between the H_α-2 and CH_3-17, H_β-2 and H-5, H-5 and H-7, H-7 and H_β-9, H_α-9 and H_3-17 atoms in the NOESY spectrum confirmed the *trans*-configuration between CH_3-17 and H-5. Since the absolute configuration of C-7 was determined to be *S* according to the stereoselectivity of the Evans asymmetric alkylation, the absolute configuration of the C-5, C-7, and C-10 atoms in cycloadduct **2** were defined as *S*, *S*, and *S*, respectively.

To better understand the high π-facial- and *endo*/*exo*-selectivity of this reaction, it is necessary to consider a possible chair-like transition state, namely, *exo-Si* (**TS-A**), *endo-Si* (**TS-B**), *exo-Re* (**TS-C**), and *endo-Re* (**TS-D**), as shown in Scheme 3. The two transition states *exo-Re* (**TS-C**) and *endo-Re* (**TS-D**) are clearly disadvantageous because the bulky chiral oxazolidinone group is oriented in the pseudo-axial position. In the case of *endo-Si* (**TS-B**), a severe nonbonded interaction would occur between the methyl substituent in the diene moiety and the tether methylene unit, making it unfavorable. Therefore, the structural elements of



Scheme 2 Synthesis of *trans*-fused decalin **2**

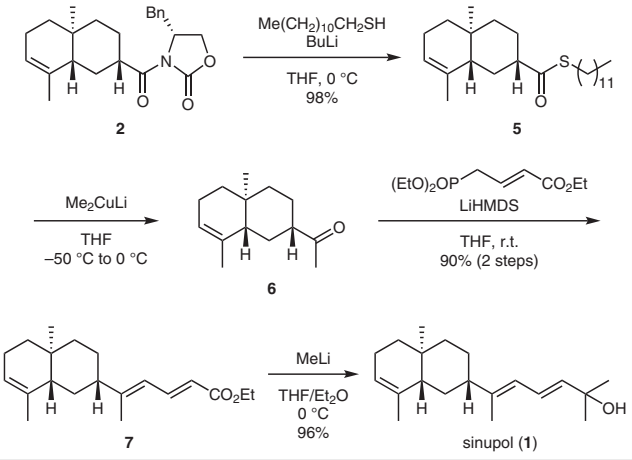
exo-Si (**TS-A**), which have minimal steric factors, can be expected to contribute favorably to the formation of *trans*-fused decalin **2**.



Scheme 3 Proposed transition states for the Diels–Alder reaction of compound **3**

With *trans*-fused decalin **2** in hand, we turned our attention to the late-stage synthesis of sinupol (**1**). First, we examined the conversion of **2** into Weinreb amide. Treatment with MeNHOMe·HCl and Me_3Al under classical conditions[12] was attempted, but Weinreb amide was not formed, and only the starting material was recovered. Other condi-

tions were investigated;[13] however, all efforts to perform the conversion into Weinreb amide failed, prompting us to evaluate alternative means for removing the chiral auxiliary moiety. Gratifyingly, when lithium thiolate derived from dodecane-1-thiol[14] was reacted with **2**, the exocyclic cleavage of the imide moiety[15] proceeded, and thioester **5** was obtained in 98% yield (Scheme 4). Thioester **5** was then converted into the corresponding methyl ketone **6** using Me_2CuLi,[16] which was subsequently subjected to a Horner–Wadsworth–Emmons reaction using LiHMDS and ethyl (*E*)-4-(diethoxyphosphoryl)but-2-enoate[17] to give (*E*,*E*)-α,β,γ,δ-unsaturated ester **7** as a single geometric isomer in 90% yield over two steps. Finally, we converted ester **7** into the desired tertiary alcohol **1** in 96% yield. To our delight, the spectroscopic data including ^{1}H and ^{13}C NMR spectra, IR spectrum, and high-resolution MS (HRMS) results of the as-synthesized **1** match those reported for sinupol, except for one outlier in the ^{13}C NMR data.[7]



Scheme 4 Synthesis of sinupol (**1**)

As a premise, since the reference signal was not defined in the isolation reported by Guo, all the reported chemical shifts are uniformly upfield-shifted by 0.3–0.5 ppm from our measured values with reference to the solvent signal (for the ^{13}C NMR, pyridine-d_5 C2 signal was calibrated at δ = 123.87 ppm) (Table 1). Then, upon comparison of the ^{13}C NMR of synthetic **1** and natural sinupol, a difference in the chemical shift for C-4 was observed. Since the signal of C-4 is close to the solvent signal, it seems reasonable to assume that this signal might have been overlooked in the report by Guo and co-workers. Although we could not obtain the original spectrum of sinupol, considering that all the other ^{13}C chemical shifts are essentially identical between synthetic **1** and natural sinupol, we are confident that the reported chemical shift for C-4 is a typographical error.

The optical rotation of the synthesized **1** was $[\alpha]_D^{25}$ +7.5 (*c* 0.10, MeOH), and the sign matched the reported value ($[\alpha]_D^{25}$ +13.1 (*c* 0.1, MeOH));[7] however, the absolute values

Table 1 Comparison of the ^{13}C NMR (in Pyridine-d_5) Spectroscopic Data for Synthetic **1** and Natural Sinupol

Position	Synthetic **1** δ [ppm][a]	Natural sinupol δ [ppm][a]	Δδ [ppm][b]
1	38.6	38.1	0.5
2	23.7	23.2	0.5
3	121.7	121.2	0.5
4	**135.6**	**135.9**	**–0.3**
5	47.3	46.8	0.5
6	29.4	29.0	0.4
7	49.3	48.9	0.4
8	27.3	26.8	0.5
9	40.8	40.3	0.5
10	32.8	32.4	0.4
11	142.6	142.2	0.4
12	124.3	123.8	0.5
13	123.4	123.0	0.4
14	142.3	141.9	0.4
15	70.4	69.9	0.5
16	21.7	21.2	0.5
17	16.2	15.7	0.5
18	15.4	14.9	0.5
19	31.3	30.9	0.4
20	31.3	30.9	0.4

[a] Spectrum recorded at 125 MHz.
[b] Synthetic **1** – Natural sinupol.

were different, indicating that the absolute configuration was not definitive. Therefore, we compared the ECD spectra of synthetic **1** and natural sinupol. The ECD spectrum of synthetic **1** showed a positive Cotton effect at 211 nm (Δε +4.63) as well as a negative Cotton effect at 233 nm (Δε –2.37), which were consistent with the ECD spectrum of natural sinupol [211 nm (Δε +4.83), 234 nm (Δε –1.98)].[7] As a result, the absolute configuration of synthetic sinupol (**1**) was determined to be 5*S*, 7*S*, and 10*S*.

In conclusion, a concise asymmetric total synthesis of sinupol (**1**) has been developed. Our synthetic strategy involves an Evans asymmetric alkylation and an intramolecular Diels–Alder reaction for the construction of *trans*-fused decalin **2**.[18] The synthesis of sinupol (**1**) was achieved in 44% yield in seven steps starting from commercially available 5-methylhex-5-enoic acid.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1610757.

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(18) **(*R*)-4-Benzyl-3-((2*S*,4a*S*,8a*S*)-4a,8-dimethyl-1,2,3,4,4a,5,6,8a-octahydronaphthalene-2-carbonyl)oxazolidin-2-one (2):** BHT (65.4 mg, 0.297 mmol) was added to a solution of triene **3** (1.09 g, 2.97 mmol) in mesitylene (29.7 mL) in a sealed tube. The solution was degassed and heated at 220 °C for 168 h. The reaction mixture was cooled to ambient temperature over a period of 1 h, concentrated in vacuo, and the residue was filtered through a thin pad of silica gel. Concentration of the filtrate followed by flash column chromatography on silica gel (hexane/EtOAc = 5:1) gave *trans*-fused decalin **2** (959 mg, 88% yield) as an amorphous solid along with an unidentified diastereomeric mixture (87.2 mg, 8% yield). R_f 0.25 (hexane/EtOAc = 4:1); $[\alpha]_D^{25}$ –52.6 (*c* 0.81, $CHCl_3$); IR (KBr): 2913, 2847, 1780, 1698, 1386, 1212 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.36–7.24 (m, 3 H), 7.24–7.19 (m, 2 H), 5.34 (m, 1 H), 4.68 (ddt, *J* = 7.4, 9.4, 3.2 Hz, 1 H), 4.21 (dd, *J* = 7.4, 9.0 Hz, 1 H), 4.18 (dd, *J* = 3.2, 9.0 Hz, 1 H), 3.57 (tt, *J* = 3.9, 12.1 Hz, 1 H), 3.27 (dd, *J* = 3.2, 13.4 Hz, 1 H), 2.81 (dd, *J* = 9.4, 13.4 Hz, 1 H), 2.13 (m, 1 H), 2.05 (m, 1 H), 2.02 (m, 1 H), 1.98 (m, 1 H), 1.89 (dq, *J* = 4.0, 13.4 Hz, 1 H), 1.70 (m, 1 H), 1.64 (s, 3 H), 1.50 (ddd, *J* = 2.8, 4.0, 13.2 Hz, 1 H), 1.44 (d, *J* = 11.9 Hz, 1 H), 1.41–1.34 (m, 2 H), 1.28 (dt, *J* = 4.2, 13.4 Hz, 1 H), 0.87 (s, 3 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 176.4 (C), 153.0 (C), 135.3 (C), 134.3 (C), 129.4 (CH)×2, 128.9 (CH)×2, 127.3 (CH), 121.3 (CH), 66.0 (CH_2), 55.3 (CH), 45.9 (CH), 43.2 (CH), 39.1 (CH_2), 38.0 (CH_2), 37.7 (CH_2), 32.2 (C), 26.4 (CH_2), 23.8 (CH_2), 22.8 (CH_2), 21.0 (CH_3), 15.5 (CH_3). MS (ESI-TOF): *m*/*z* (%) = 390 (100) $[M + Na]^+$. HRMS (ESI-TOF): *m*/*z* $[M + Na]^+$ calcd for $C_{23}H_{29}NO_3Na$: 390.2045; found: 390.2038