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Synthesis of Polycyclic Frameworks through Iron-Catalyzed Intramolecular [5+2] Cycloaddition

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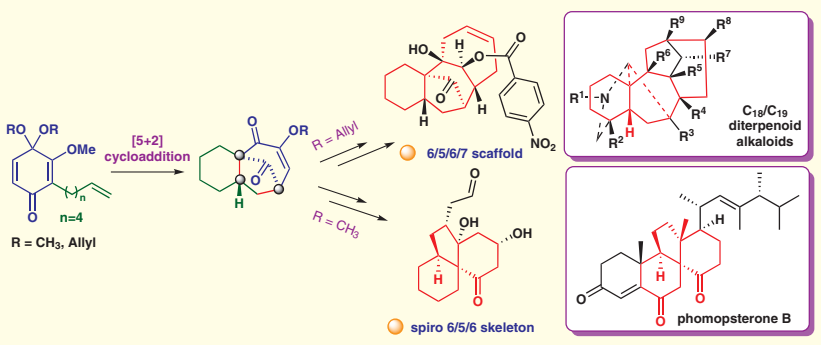

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Abstract A concise and efficient approach to the core of the C_{18}/C_{19} diterpenoid alkaloids and phomopsterone B is reported. Both syntheses share the same iron-catalyzed intramolecular [5+2] cycloaddition to assemble the tricyclo[6.3.1.0^{1,6}]dodecane skeleton. The following approach to the 6/5/6/7 tetracyclic core scaffold of C_{18}/C_{19} diterpenoid alkaloids features a regioselective Grignard addition/thermal Claisen rearrangement/RCM cyclization. Meanwhile the synthetic steps to access the spiro 6/5/6 tricyclic subunits of phomopsterone B were characterized as intramolecular aldol reaction, Wacker oxidation, and Criegee reaction.

Key words C_{18}/C_{19}-diterpenoid alkaloids, phomopsterone B, Iron-catalyzed, [5+2] cycloaddition

C_{18}/C_{19}-diterpenoid alkaloids embodying the 6/5/6/7 tetracyclic skeleton have great diversity in their biological activities.[1,2] As demonstrated in Figure 1, Sepaconitine (**1**)[3] and *N*-acetylsepaconitine (**2**)[3b] (Figure 1a), isolated from *A. septentrionale Koelle* and *A. leucostomum*, respectively, possess strong antiarrhythmic activity.[4] Guayewuanine A (**3**), a novel C_{19}-diterpenoid alkaloid isolated from *A. hemslevanum*, was reported to exhibit good analgesic activity.[5] Although C_{18}/C_{19}-diterpenoid alkaloids have fascinating structures with diverse biological activity, only a few groups (Weisner,[6] Gin,[7] Sarpong,[8] and Fukuyama[9]) have completed the total synthesis of C_{18}/C_{19}-diterpenoid alkaloids. Synthetic studies toward the skeleton of C_{18}/C_{19}-diterpenoid alkaloids have been conducted by a raft of research groups.[10,11] Nevertheless, most of their work involved the construction of fragments with an azacyclic subunit.

Meanwhile, phomopsterone B (**4**), a functionalized ergostane-type steroid with spiro 6/6/5/6 tetracyclic core scaffold, was originally isolated from the medically important plant *Phyllathus glaucus* (Figure 1b). Biological investigations indicate that **4** functioned as an iNOS enzyme inhibitor that exhibits remarkable anti-inflammatory activity (IC_{50} = 1.49 μM).[12] Unfortunately, no group has completed the total synthesis of phomopsterone B. Meanwhile, synthetic investigation toward the scaffold of phomopsterone B is scarce. Rajagopalan reported tin-mediated vinyl radical cyclization to construct the spiro 6/5/6 tricyclic subunit.[13] Matsuo developed ethylaluminium dichloride-promoted intramolecular formal [4+2] cycloaddition to afford the 6/5/6 tricyclic scaffold.[14] Mattay also documented oxidative photoinduced electron transfer (PET) reactions of cyclic cyclopropyl(vinyl) silyl ethers bearing an olefinic or acety-

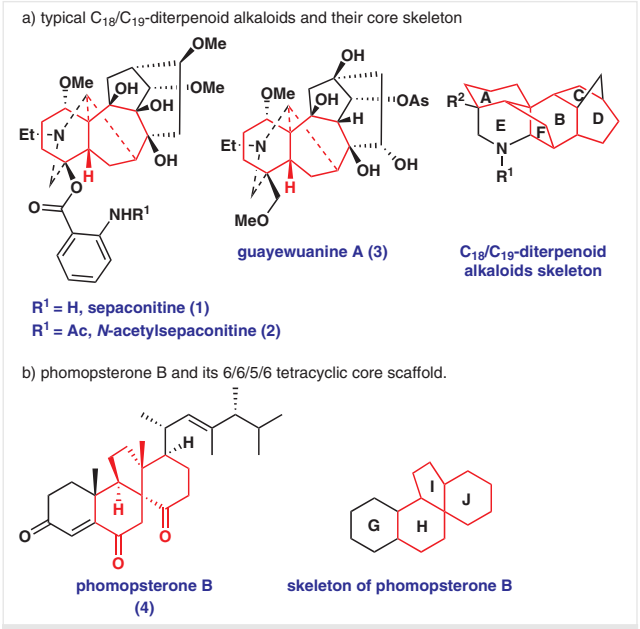


Figure 1 Typical C_{18}/C_{19}-diterpenoid alkaloids and phomopsterone B and their core skeletons

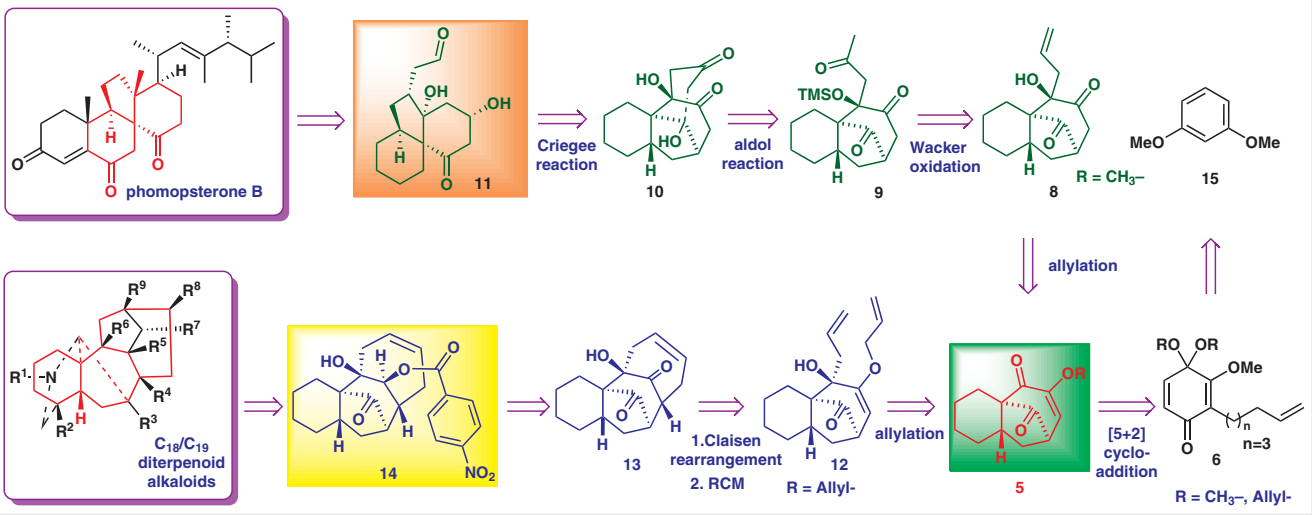
lenic side chain to give spiro 6/5/6 tricyclic compounds. However, this reaction only delivered the product with low yield (22%).[15]

Recently, we developed an efficient methodology for accessing the tricyclo[6.3.1.0^{1,6}]dodecane skeleton via iron-catalyzed intramolecular perezone-type [5+2] cycloaddition.[16] Notably, this methodology features an inexpensive and environmentally friendly catalyst ($FeCl_3$), broad substrate scope (>18 examples), efficient reaction conditions (CH_2Cl_2, 0 °C, <10 min), good yields (up to 91%), decent diastereoselectivities (up to 20:1 dr) and scalability (>2 g). To our knowledge, utilization of intramolecular [5+2] cycloaddition strategy to construct the core skeleton of the C_{18}/C_{19}-diterpenoid alkaloids and phomopsterone B remain unknown. Herein, we describe our achievement in implementing the [5+2] cycloadducts for the rapid and efficient synthesis of the 6/5/6/7 tetracyclic skeleton of C_{18}/C_{19}-diterpenoid alkaloids and the spiro 6/5/6 tricyclic subunit of phomopsterone B. Thus, we could achieve divergent synthesis of different core skeletons of natural products from [5+2] cycloadducts, which will contribute to the development of future related research projects.

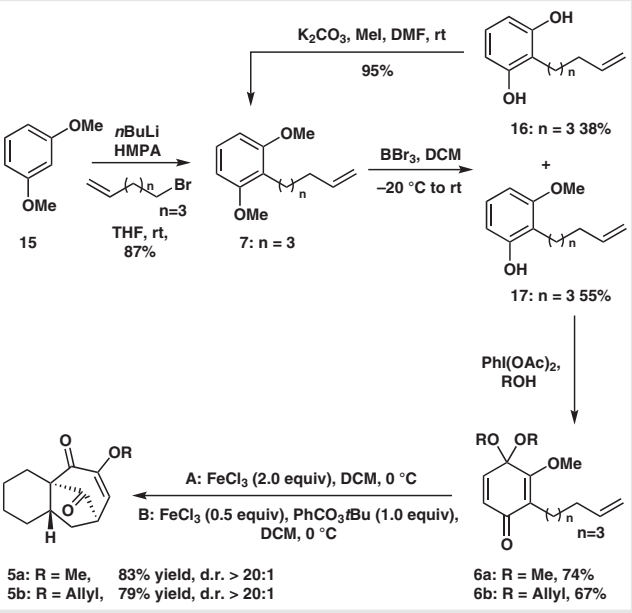
Retrosynthetically, compound **11**, which embodies the 6/5/6 tricyclic subunit of phomopsterone B, could be constructed from **10** via Criegee reaction (Scheme 1). Compound **10** was accessible from **9** through the aldol reaction. The acetyl in **9** can be generated from **8** via Wacker oxidation. Allylic alcohol **8** could be made by [5+2] adducts **5** via regioselective Grignard addition. Meanwhile, compound **14**, which consists of the 6/5/6/7 tetracyclic skeleton of C_{18}/C_{19}-diterpenoid alkaloids, could be achieved by regioselective reduction of diketone **13** followed by protection with esters. Diketone compound **13** was obtained from **12** by thermal Claisen rearrangement and cross-metathesis reaction. Compound **12** was then generated from **5** via Grignard addition and allylation. Compound **5** could be accessible from our reported iron-catalyzed intramolecular perezone-type [5+2] cycloaddition.[16]

In our previous work,[16] the approach required six steps to access the [5+2] cycloaddition precursor. So, we investigated steps to shorten the synthetic route to the initial cycloaddition precursor. Our revised synthetic approach to [5+2] cycloaddition substrate commenced by reacting 1,3-dimethoxybenzene with *n*-BuLi, followed by alkylation with 6-bromo-1-hexene to provide the desired **7** in 87% yield (Scheme 2). Monodemethylation of **7** with BBr_3 afforded a mixture of the desired phenol **17** and the doubly O-demethylated compound **16** (**16**/**17** ratio 9:11, ca. 1.5:1 ratio, 93% combined yield). Chromatographic separation of **16** and **17** allowed recycling of the undesirable **16** to **7** in 95% yield. Treatment of phenol **17** with $PhI(OAc)_2$ under alcoholic solvent furnished the corresponding precursor **6a** (74% yield with MeOH) and **6b** (67% yield with allyl alcohol).[17] Notably, the revised synthetic route to the cycloaddition precursor is three steps fewer than our previous synthetic route.[16] Compounds **6a** and **6b** were then subjected to our reported iron-catalyzed intramolecular [5 + 2] cycloaddition conditions to give the corresponding cycloadducts **5a** and **5b** in good yield (83% and 79%, respectively) with decent diastereoselectivities (>20:1).

Equipped with cycloadduct **5a**, we geared up for constructing the spiro 6/5/6 skeleton of phomopsterone B. Exposure of cycloadduct **5a** to Grignard reagent would lead to selective attack on the conjugated ketone, presumably via chelation of a magnesium species with both the carbonyl and methoxyl group, followed by acidic hydrolysis to afford **8** in 75% yield. Protection of the tertiary alcohol in **8** to TMS ether **18**, followed by Wacker oxidation, furnished methyl ketone **9** in 69% yield over two steps.



Scheme 1 Retrosynthetic analysis of the spiro 6/5/6 core scaffold of phomopsterone B and the tetracyclic 6/5/6/7 core skeleton of C_{18}/C_{19}-diterpenoid alkaloids

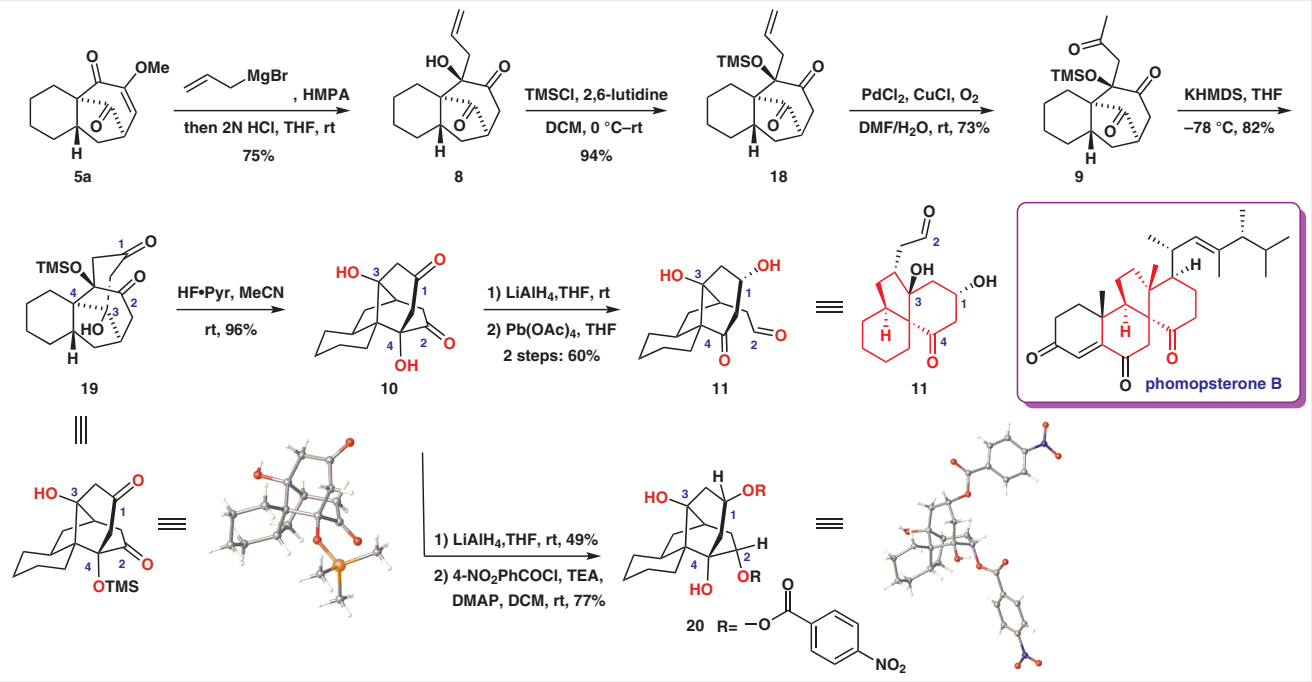


Scheme 2 Synthesis of tricyclo[6.3.1.0^{1,6}] dodecane **5a** and **5b**

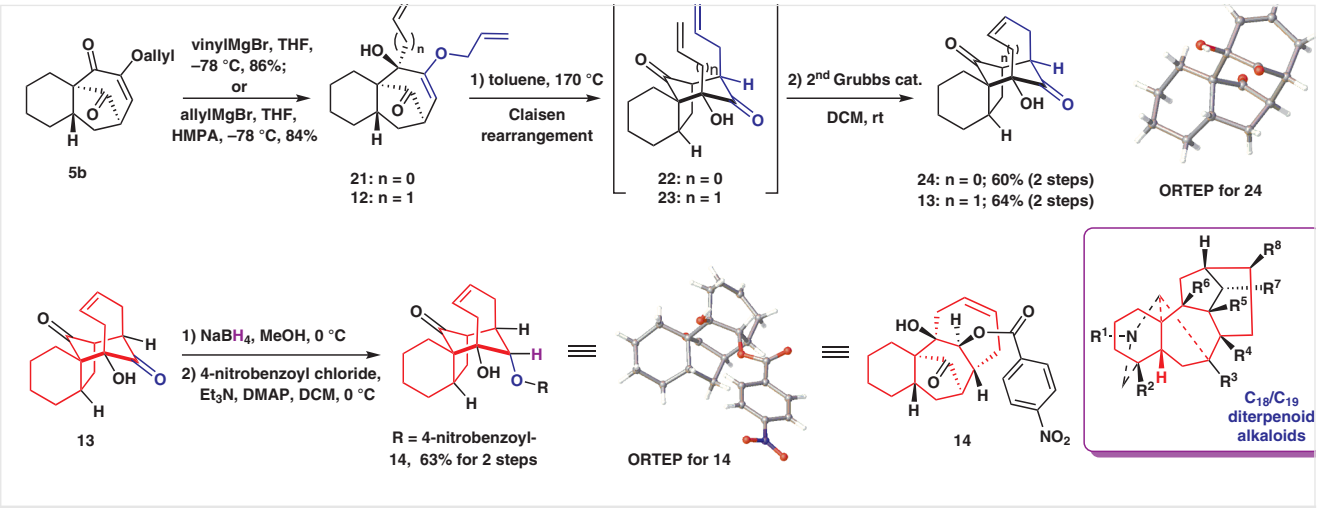
After that, an initial attempt to react methyl ketone **9** with KOH/MeOH only resulted in eliminated byproduct, and no aldol product **19** was detected. Inspired by Hanessian's work,[18] treatment of **9** under Mukaiyama type aldol condensation condition [$TiCl_4$/DIPEA/TMSCl] gave compound **19** in 49% yield. Delightfully, using KHMDS as base at –78 °C boosted the production of the product to 82% yield. The structure of compound **19** was further confirmed by X-ray crystallography, which showed that the aldol condensation occurred site-selectively at C3 instead of C2.

We also assessed a series of conditions to forge the five-membered ring, but the approach failed.[19] Desilylation of **19** under HF·Pyr afforded alcohol **10** in 96% yield. To forge the spiro 6/5/6 skeleton of phomopsterone B, we investigated various conditions ($NaIO_4$, HIO_4, $Pb(OAc)_4$, *m*CPBA, etc.) to cleave the C–C bonds of α-hydroxy ketones. However, the reaction gave rise to no reaction or led to decomposition of the starting material. Fortunately, the target compound **11** could be acquired via $LiAlH_4$-mediated reduction of compound **10** followed by $Pb(OAc)_4$ promoted oxidative cleavage in 60% yield over two steps. Notably, the stereochemistry of the hydroxyl group at C1 in compound **11** was identified by derivatization of compound **10** to give compound **20**, the structure of which was confirmed by X-ray crystallography (Scheme 3).[20]

Inspired by our success in construction of the spiro 6/5/6 subunit of phomopsterone B, we turned our attention to forging the 6/5/6/7 ring system of C_{18}/C_{19}-diterpenoid alkaloids. Reaction of cycloadduct **5b** with Grignard reagent resulted in selective attack on the conjugated ketone to afford **21** in 86% yield and **12** in 84% yield (Scheme 4). Thermal Claisen rearrangement of **21** and **12** gave **22** and **23** with excellent facial selectivity; the resulting mixture was subsequently subjected to ring-closing metathesis (RCM),[21] which furnished **24** and **13** over two steps in 60% and 64% yield, respectively.[22] The structure of **24** was confirmed by X-ray crystallography. Meanwhile, compound **13** could be



Scheme 3 Synthesis of the spiro 6/5/6 tricyclic compound **11**



Scheme 4 Synthesis of the tetracyclic 6/5/6/7 core skeleton of C_{18}/C_{19}-diterpenoid alkaloids

transformed into **14** in a two-step derivatization. The structure of compound **14** was characterized by X-ray crystallography, which completed our successful application of [5+2] cycloadducts for the construction of the 6/5/6/7 ring system of C_{18}/C_{19}-diterpenoid alkaloids.

In summary, we have successfully utilized iron-catalyzed intramolecular perezone-type [5+2] cycloadducts to forge the spiro 6/5/6 tricyclic subunit of phomopsterone B and the 6/5/6/7 tetracyclic ring system of the C_{18}/C_{19} diterpenoid alkaloids. Notably, the revised pathway to the [5+2] cycloaddition precursor has been shortened to three steps. We look forward to further exploring these successful applications in related total synthesis campaign.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1610258.

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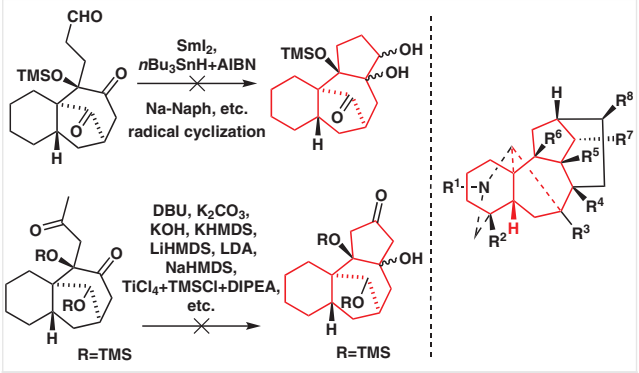
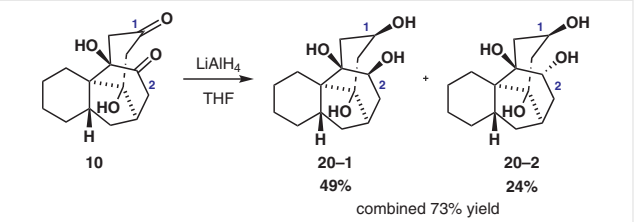
(19) We also tried to construct the 6/5/6/5 tetracyclic core skeleton of the C_{18}/C_{19}-diterpenoid alkaloids, but failed (Scheme 5).



Scheme 5

(20) Reduction of compound **10** under $LiAlH_4$ gave two diastereoisomers, **20-1** and **20-2** in 49% yield and 24% yield, respectively. Compound **20-1** was further transformed into compound **20**, the structure of which was confirmed by X-ray crystallography. The stereochemistry of hydroxyl group at C1 in target compound **11** could be identified from X-ray crystallographic analysis of compound **20** (Scheme 6).



Scheme 6

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(22) **Experimental Procedure and Characteristic Data for Ketone (24)**: Compound **21** (22.3 mg, 0.08 mmol) was added to toluene (0.5 mL) in a sealed tube and stirred at 170 °C overnight. The solvent was then removed in vacuo to afford the crude product, which was used in the next step without further purification. To a solution of Grubbs II (17.5 mg, 0.02 mmol) in CH_2Cl_2 (8.0 mL) at room temperature was added the above product in CH_2Cl_2 (2.5 mL) and the mixture was stirred at room temperature for 10 h. The solvent was then removed in vacuo and the crude product was purified by column chromatography (EtOAc/petroleum ether = 1:5) to afford the product **24** (12.1 mg, 60% for two steps) as a white solid; mp 119–121 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.65–5.59 (m, 2 H), 3.87 (s, 1 H), 2.88 (t, *J* = 5.2 Hz, 1 H), 2.73–2.60 (m, 2 H), 2.46 (dd, *J* = 5.2, 7.2 Hz, 1 H), 2.04–1.98 (m, 2 H), 1.90–1.81 (m, 2 H), 1.70 (dd, *J* = 5.2, 13.2 Hz, 1 H), 1.66–1.59 (m, 1 H), 1.52–1.47 (m, 1 H), 1.42 (ddd, *J* = 2.8, 7.6, 14.0 Hz, 1 H), 1.15 (dddd, *J* = 2.8, 4.0, 12.4, 25.2 Hz, 1 H), 1.03 (ddt, *J* = 2.8, 12.8, 25.6 Hz, 1 H), 0.72 (ddd, *J* = 3.2, 13.2, 25.6 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 211.8, 211.0, 132.7, 127.9, 78.9, 60.5, 50.6, 48.5, 35.2, 34.8, 31.6, 30.6, 24.0, 22.7, 20.6. IR (neat): 2925, 2850, 1735, 1448, 1369, 1239, 1141, 1030 cm^{-1}. HRMS (ESI): *m*/*z* [M+Na]$^+$ calcd for $C_{15}H_{18}NaO_3$: 269.1154; found: 269.1151.