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A *DE NOVO* ASYMMETRIC SYNTHESIS OF PHOMOPSOLIDE E: A PRACTICAL CONVERSION FROM PHOMOPSOLIDE D

Joel M. Harris,‡ Miaosheng Li,‡ and George A. O'Doherty*

Department of Chemistry and Chemical Biology, Northeastern University, Boston, MA 02115, USA. E-mail: g.odoherty@neu.edu

This paper is dedicated to Professor Tohru Fukuyama on the occasion of his 70th birthday, who is widely regarded as a synthetic organic chemist's chemist.

Abstract – A practical three-step synthesis of phomopsolide E has been developed from a synthetic sample of phomopsolide D in three steps at 62% yield. A *de novo* asymmetric synthesis of phomopsolide D was accomplished in 8 steps from an achiral dienone in 47% yield. The initial asymmetry of phomopsolide E was installed by a Sharpless asymmetric dihydroxylation, whereas, a highly diastereoselective reagent control iterative asymmetric hydrogenation reaction was used to diastereoselectively install the pyranone stereochemistry. The net synthetic effort of phomopsolide E was accomplished in a total 11 steps in 40% overall yield. The route as devised provided for the first-time access to synthetic material for biological analysis and established both the absolute and relative stereochemistry for this natural product.

INTRODUCTION

Traditionally, the American elm, which thrives on a wide range of soils and can endure root disturbance, drought and extreme cold, was one of the most widely-planted street tree in the US.[1] Unfortunately, the preeminence of the American elm tree has been challenged by the arrival of Dutch elm disease to North America.[2] Once infected by Dutch elm disease a healthy 100-year-old American elm can be killed in as little as two weeks.[2] Since the 1980s, over 40 million elm trees have been killed in the US alone.[3,4] It was reported that Des Moines, Iowa, lost a quarter of a million trees in as little as a six-year window.[4]

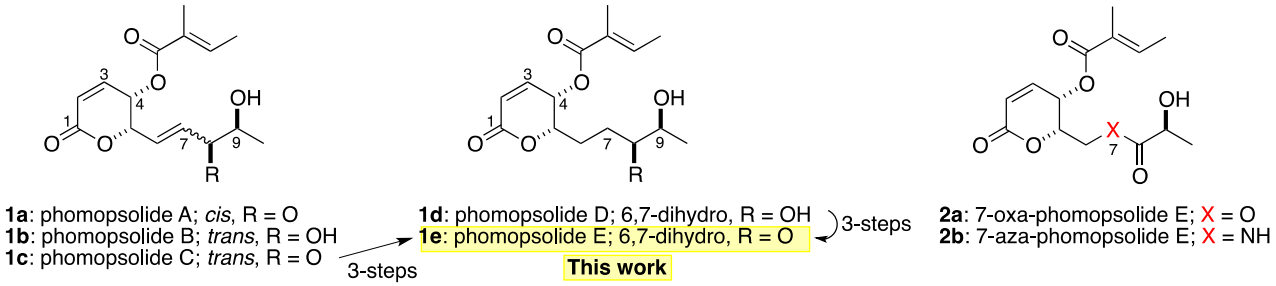
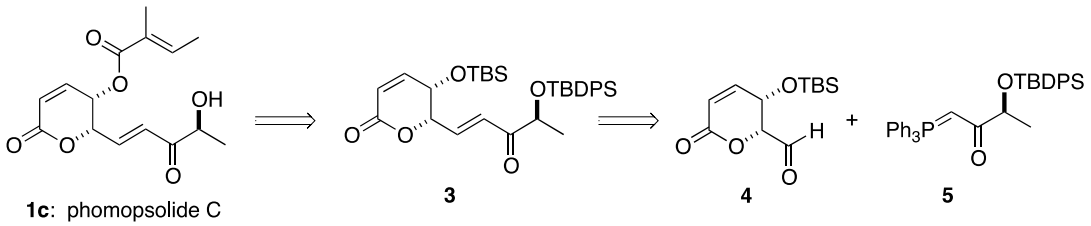


Figure 1. The phomopsolides and related analogues

Dutch elm disease is caused by a fungus, *Ophiostoma ulmi*, which would be quite innocuous if it were not for its vector, the elm bark beetle (*e.g.*, *Hylurgopinus rufipes*), which spreads the fungus as it flies from infected trees to healthy trees to feed and deposit its eggs. This seemingly innocuous behavior, by the beetle, unfortunately becomes a very effective delivery mechanism for the spores of the fungus.[5] In an effort to fight this suburban pandemic, there has been an ongoing search for antiboring/antifeeding compounds that can effectively deter the beetle form the American elm. Along these lines, Grove,[6] and later Stierle,[7] found a series of related 6-substituted 5,6-dihydro-5-hydroxypyran-2-ones, the phomopsolides, which appeared to dissuade the *Scolytid beetles* from feeding. Interestingly, both phomopsolides A and B were discovered from the fungus *Phomopsis oblonga*, which in known to cohabitate with the elm tree. A decade later, three new phomopsolides (C-E) were isolated from fungi associated with the bark of the Pacific yew (*Taxus brevifolia*) along with phomopsolides A and B. All five of these compounds were found to have antimicrobial activity against *S. aureus*.[8]

Inspired by the potent biological activity, in addition to the synthetic challenge, chemists have sought after the total synthesis of the phomopsolides. To date, there have been nine successful syntheses of the phomopsolides and analogues. Phomopsolide B was the first to succumb to total synthesis, by the efforts of Noshita (1994).[8] About a decade later, we synthesized phomopsolide C[9] and phomopsolide D[10] in 2002 and 2004 respectively.[11] In 2005, Blechert reported a synthesis of phomopsolide C.[12] In 2012 and 2015, phomopsolide B was synthesized by Prasad[13] and Sabitha.[14] Finally in 2014, the *C*-4,5-bisepimer of phomopsolide B was synthesized by Atmakur.[15] As part of a medicinal chemistry effort aimed at exploring the stereochemical structure activity relationship (S-SAR) study of pyranone containing polyketide natural products,[16-19] like the phomopsolides, we synthesized a 7-oxo- and 7-aza-analogues of phomopsolide E, as well as, their *C*-4 epimers (in 2004[11] and in 2018[20]). As the nomenclature suggests, both of these synthetic analogues, 7-oxo- and 7-aza-analogues of phomopsolide E, were envisioned to be isosteres of phomopsolide E and as such intended to mimic its biological activity. To be able to quantify the effectiveness of this structural analogy, we required access to the natural product. Unfortunately, we were not able to obtain a sample from natural sources, so we turned to its synthesis. Herein we describe

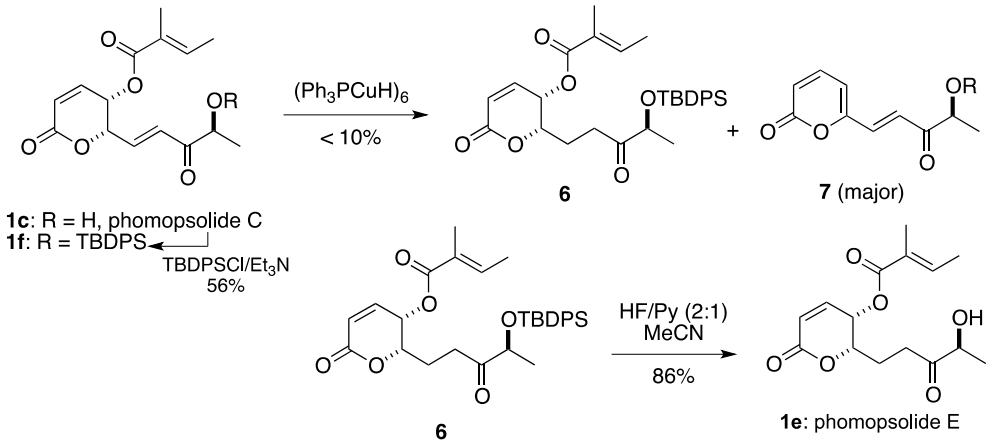
our successful effort to synthesize phomopsolide E from synthetically prepared phomopsolide D, which constitutes the first synthesis of phomopsolide E and establishes in absolute and relative stereochemistry.



Scheme 1. Synthesis of phomopsolide C

RESULTS AND DISCUSSION

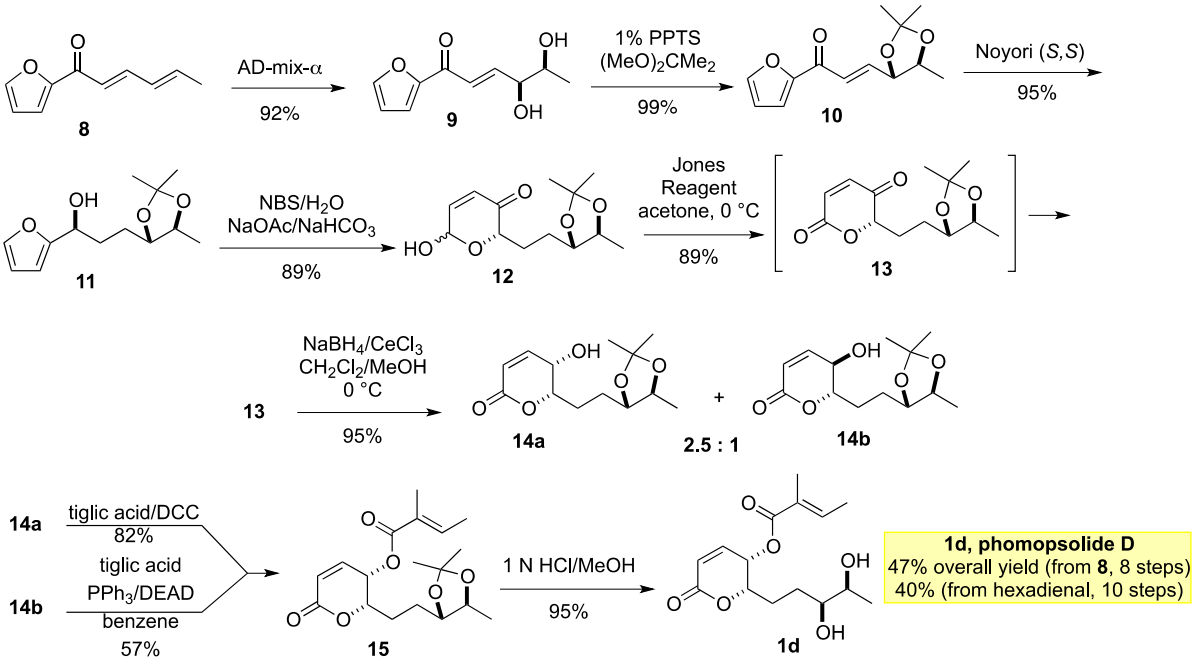
Previously, we disclosed our successful approach to phomopsolide C, the convergent route involved a stabilized Wittig olefination approach to enone **3** from chiral fragments aldehyde **4** and ylide **5** (Scheme 1). A three- step deprotection, acylation and deprotection sequence on **3** provides the natural product **1c**. With phomopsolide C (**1c)** in hand, we explored its direct conversion into the reduced congener natural products phomospolide E (**1e**). This required the selective 1,4-reduction of the enone functionality in the presence of α,β-unsaturated ester and α,β-unsaturated lactone functionality (Scheme 2). Our efforts to find suitably selective conditions centered upon the use of various reducing reagents on both phomopsolide C (**1c**) and its TBDPS-ether **1f**. The silyl ether **1f** was our pent-ultimate intermediate in our phomopsolide C synthesis and a compound that could be prepared from phomopsolide C (TBDPSCl/Et_3N, 10% DMAP; 56%). Unfortunately, we found that the base sensitivity of both **1c** and **1f**, significantly limited the types of reducing reagents that could be used. For example, exposure of either phomopsolide **1c** and **1f** to the basic reactions of typical 1,4-reducing agents (*e.g.*, $LiHBEt_3$, Dibal-H/CuMe, etc.) led exclusively to elimination products like pyranone **7**. Based upon the success Chiu *et al*. found with its use in the 1,4-reduction of enones in the context of complex molecule synthesis,[21] we turned to the use of the Striker reagent.[22] A modicum of success was achieved with the use of the Striker reagent on the TBDPS-enol ether **1f**, however, only a small amount of the desired reduction product **6** was formed along with a greater amount of elimination products, like **7**. We were able to isolate enough of the reduction product **6** (~3 mg) from the reaction mixture to allow for the subsequent TBDPS-deprotection reaction (2:1 HF/Py, MeCN, 86%) to supply phomopsolide E, which had a ^1H NMR consistent with the spectral isolated for the natural product.[6,7]



Scheme 2. Synthesis of phomopsolide E from phomopsolide C

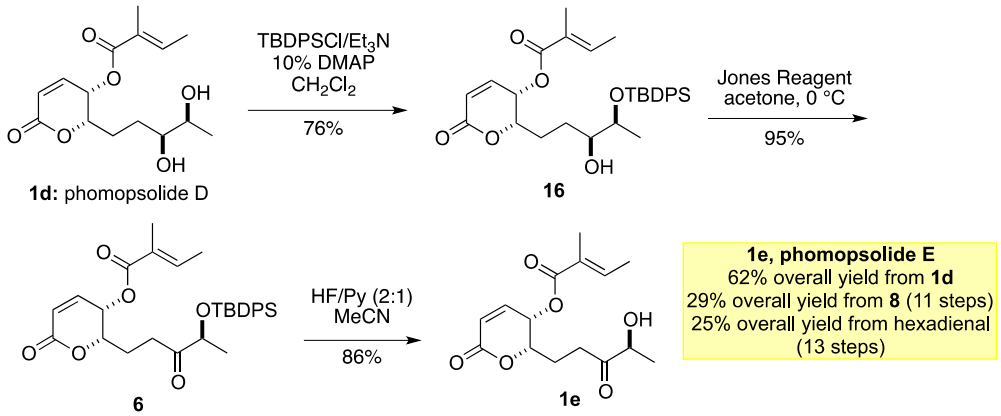
While formally, we had accomplished a route to phomopsolide E, the route as it existed was impractical, as it did not provide significant quantities of the natural product for biological studies. Because this route did not satisfy our need for material, we continued our search for an alternative approach to phomopsolide E. Our synthesis of phomopsolide D differed from our synthesis of phomopsolide C in that we were particularly interested in being able to control all the stereochemistry by the use of asymmetric catalysis (Scheme 3). Next, we decided to look into the possibility of accessing phomopsolide E from phomopsolide D. In contrast to the reductive route to phomopsolide E from phomopsolide C, the route to phomopsolide E from phomopsolide D would be oxidative.

Previously we demonstrated that phomopsolide D could be prepared from dienone **8**, via furan alcohol **11** and pyranones **14a**/**14b**. A three step Sharpless asymmetric oxidation, protection and Noyori asymmetric reduction sequence was used to install the asymmetry of furan alcohol **11** (87%). A subsequent three-step Achmatowicz oxidation, Jones oxidation and Luche reduction reaction sequence was used to convert **11** in to a 2:1 mixture of pyranones **14a/b** (75%). A combination of retentive (tigilic Acid/DCC, 82%) and invertive (tiglic Acid PPh_3/DEAD) ester formations converts the mixture of diastereomer **14a/b** into acetonide protected natural product, which can be easily deprotected to form phomopsolide D (HCl(aq), 95%).



Scheme 3. Synthesis of phomopsolide D

With adequate quantities of phomopsolide D (**1d**) in hand, we returned to the idea of synthesizing phomopsolide E (**1e**) (Scheme 4). Specifically, the notion that the 1,2-diol of phomopsolide D could be regioselectively oxidized to directly give phomopsolide E. Despite considerable effort at screening various oxidative conditions, these labors were universally unsuccessful. Thus, we turned to a protection, oxidation, deprotection strategy. As we had an inkling of success with the *C*-8 TBDPS group, were turned to it. To our delight, the less hinder hydroxyl group of phomopsolide D was selectively protected as a TBDPS ether **16**.[23] The unprotected alcohol in **16** was oxidized to ketone **6** with Jones reagent. Finally, a TBDPS deprotection gave the natural product phomopsolide E (**1e**) (62% yield in 3 steps) whose spectral data matched that of the isolated natural product in terms of IR, ^{1}H, ^{13}C NMR, and optical rotation.[6,7]



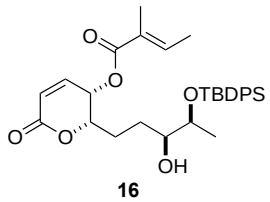
Scheme 4. Synthesis of phomopsolide E from phomopsolide D

In conclusion, two routes to phomopsolide E (**1e**) was reported. One, a reductive approach from phomopsolide C (**1c**) and the other, an oxidative approach from phomopsolide D (**1d**), in three steps at 62% yield. Of the two approaches, the oxidative approach from phomopsolide D, was the more practical. The *de novo* asymmetric synthesis of phomopsolide D was accomplished in 8 steps from an achiral dienone **8** in 47% yield. In sum, a net *de novo* asymmetric synthesis of phomopsolide E (**1e**) from achiral dienone **8** was established in a total of 11 steps and occurred in 29% overall yield.

EXPERIMENTAL

General Methods and Materials: Commercial reagents were used without further purification. Dry methylene dichloride, (DCM) was obtained from an in-house dry solvent system which employs nitrogen gas pressure to pass solvent through activated alumina columns. Air and moisture sensitive reactions were carried out under nitrogen atmosphere with help of septa and syringes. Silica coated glass backed thin layer chromatography plates were developed in solvents (% by volume) and stained with *p*-anisaldehyde or potassium permanganate. For compound purification flash column chromatography was performed using 60-200 mesh silica gel. ^{1}H NMR and ^{13}C NMR spectra were recorded on 600 MHz spectrometers. Chemical shift for internal standard $CDCl_3$ was set to δ 7.26 for ^{1}H NMR and δ 77.36 for ^{13}C NMR. For IR, samples were analyzed neat on a Bruker Alpha-P FT-IR spectrometer. High-resolution mass spectrometry data were obtained from the mass spectrometry center at Barnett Institute at Northeastern. Optical rotations were measured on a Jasco P-2000 digital polarimeter, concentration and solvent of choice are mentioned in parentheses.

(5*S*,6*S*)-5-(2-Methyl-2-butenoyloxy)-6-[(3*S*,4*S*)-4-(*tert*-butyldiphenylsilanyloxy)-3-hydroxypentyl]-5,6-dihydropyran-2-one (16):

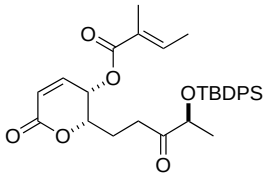


16

To a stirred solution of phomopsolide D (**1d**) (0.263 g, 0.88 mmol) in CH_2Cl_2 (3 mL) were added TBDPSCl (0.267 g, 0.97 mmol), triethylamine (45 mg, 0.44 mmol), and DMAP (54 mg, 0.44 mmol). The reaction mixture was stirred at rt for 24 h and then diluted with Et_2O (50 mL). The organic layer was washed with diluted HCl (1 M, 20 mL), sat. aq. $NaHCO_3$ (20 mL), brine (100 mL) and dried over Na_2SO_4. After removal of the solvent *in vacuo*, flash chromatography (3:7 EtOAc/hexanes) on silica gel afforded TBDPS-ether **16** (0.360 g, 76%) as a colorless oil and the starting material phomopsolide D (40 mg, 15%). R_f (30% EtOAc) = 0.40; $[\alpha]^{25}_D$ +120 (*c* 1.02, MeOH); IR (thin film, cm^{-1}) 3494, 3074, 2957, 2932, 2858,

1732, 1651, 1428, 1255, 1112, 824; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.68 (m, 4H), 7.40 (m, 6H), 7.01 (dd, *J* = 9.6, 6.0 Hz, 1H), 6.91 (qq, *J* = 7.2, 1.2 Hz, 1H), 6.20 (d, *J* = 9.6 Hz, 1H), 5.22 (dd, *J* = 6.0, 2.4 Hz, 1H), 4.54 (ddd, *J* = 9.0, 6.4, 3.2 Hz, 1H), 3.72 (dq, *J* = 6.0, 5.4 Hz, 1H), 3.43 (ddd, *J* = 8.4, 5.4, 5.4 Hz, 1H), 2.49 (d, *J* = 4.8 Hz, 1H), 2.04 (m, 1H), 1.82 (dd, *J* = 1.2, 1.2 Hz, 3H), 1.80 (dd, *J* = 6.6, 1.2 Hz, 3H), 1.74 (m, 1H), 1.58 (m, 2H), 1.07 (s, 9H), 1.03 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.7, 163.0, 140.8, 139.4, 135.8, 135.7, 133.9, 133.2, 129.8, 129.7, 127.7, 127.5, 127.4, 124.7, 78.5, 75.0, 72.9, 63.0, 27.8, 27.0, 26.4, 19.6, 19.2, 14.4, 11.9; ESI HRMS Calcd for $[C_{31}H_{40}O_6Si + Na]^+$: 559.2486, Found: 559.2504.

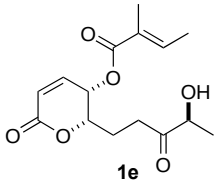
(5*S*,6*S*)-5-(2-Methyl-2-butenoyloxy)-6-[(4*S*)-4-(*tert*-butyldiphenylsilanyloxy)-3-oxopentyl]-5,6-dihydropyran-2-one (6):



6

Alcohol **16** (145 mg, 0.27 mmol) was dissolved in acetone (4 mL) and cooled to 0 °C. Jones reagent (2.97 M, 91 μL, 0.27 mmol) was added dropwise into the solution. After 15 min the starting material was no longer visible by TLC and the solution was filtered through a pad of celite and washed with Et_2O (50 mL). The organic layer was washed with sat. aq. $NaHCO_3$ (30 mL) and brine (30 mL), dried ($NaSO_4$), and concentrated to afford ketone **6** (134 mg, 95%) as a colorless oil: R_f (30% EtOAc/hexanes) = 0.48; $[\alpha]^{25}_D$ +124 (*c* 2.11, CH_2Cl_2); IR (thin film, cm^{-1}) 2930, 1717, 1428, 1253, 1111, 823, 740, 703; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.63 (m, 4H), 7.38 (m, 6H), 7.00 (dd, *J* = 9.6, 6.0 Hz, 1H), 6.91 (qq, *J* = 7.2, 1.2 Hz, 1H), 6.19 (d, *J* = 10.2 Hz, 1H), 5.18 (q, *J* = 6.0 Hz, 1H), 4.42 (ddd, *J* = 9.6, 3.6, 3.6 Hz, 1H), 4.24 (dd, *J* = 7.2, 7.2 Hz, 1H), 2.80 (m, 2H), 2.02 (m, 1H), 1.82 (m, 7H), 1.23 (d, *J* = 6.6 Hz, 3H), 1.12 (s); ^{13}C NMR (150 MHz, $CDCl_3$) δ 212.2, 166.6, 162.7, 140.7, 139.5, 135.7, 135.6, 135.3, 133.3, 132.8, 129.9, 129.8, 127.8, 127.6, 127.5, 124.7, 78.0, 75.4, 63.1, 32.1, 26.9, 23.8, 20.8, 19.1, 14.5, 12.0; ESI HRMS Calcd for $[C_{31}H_{38}O_6Si + Na]^+$: 557.2330, Found: 557.2325.

Phomopsolide E (1e):



1e

Ketone **6** (126 mg, 0.24 mmol), MeCN (1 mL), and HF-Py (2:1) (2.5 M, 2 mL, ~4.9 mmol) were added to a plastic vial and stirred at rt for 12 h. The reaction was quenched with sat. aq. $NaHCO_3$ (5 mL), and the aqueous layer was extracted with EtOAc (2 x 60 mL). The organic layer was washed with HCl (1 M, 10 mL), dried over Na_2SO_4, and concentrated under reduced pressure to afford the crude alcohol. Flash chromatography (3:7 EtOAc/hexanes) on silica gel yielded 60 mg (0.20 mmol, 86%) of phomopsolide E (**1e**) as a colorless oil: R_f (100% EtOAc) 0.63; $[\alpha]^{25}_D$ +246 (*c* 1.20, MeOH); IR (thin film, cm^{-1}) 3494, 2977, 2932, 1713, 1650, 1381, 1256, 1130, 1089, 829; ^1H NMR (600 MHz, $CDCl_3$) δ 7.00 (dd, *J* = 10.2, 6.0 Hz, 1H), 6.89 (qq, *J* = 6.6, 1.2 Hz, 1H), 6.18 (d, *J* = 9.6 Hz, 1H), 5.27 (dd, *J* = 6.0, 2.4 Hz, 1H), 4.57 (ddd, *J* = 10.2, 3.6, 3.6 Hz, 1H), 4.26 (dq, *J* = 6.6, 4.2 Hz, 1H), 3.43 (d, *J* = 4.8 Hz, 1H), 2.76 (m, 2H), 2.12 (m, 1H), 2.00 (m, 1H), 1.81 (dd, *J* = 1.2, 1.2 Hz, 3H), 1.79 (dd, *J* = 7.2, 1.2 Hz, 3 H), 1.38 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 211.6, 166.7, 162.6, 140.8, 139.7, 127.4, 124.6, 77.8, 72.7, 63.0, 32.4, 24.0, 19.8, 14.5, 12.0; ESI HRMS Calcd for $[C_{15}H_{20}O_6 + Na]^+$: 319.1152, Found: 319.1154.

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