A Versatile Diquinane from Fulvene as a Building Block in Natural Product Synthesis. 1. A Facile Synthesis of the Iridoids Loganin and Sarracenin

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Introduction

Iridoid monoterpenes,[1] a class of cyclopentanoid natural products, are not only important for biosynthesis of some indole alkaloids but also have significant biological activities.[2] These characteristics elicited widespread interest from synthetic chemists.[3] Among the various iridoid monoterpenes, the cyclopenta[*c*]pyran bearing the 2-oxo-*cis*-bicyclo[4.3.0]nonane moiety **1** (Figure 1) as a fundamental ring system is the most widely distributed including loganin (**2**),[4] mussaenoside (**3**),[5] mitsugashiwalactone (**4**),[6] and boschnialactone (**5**).[7] Some iridoid natural products with a C_7-C_8 *seco* ring (e.g., sarracenin (**6**)[8] and xylomollin (**7**)[9]) have received the attention of synthetic chemists due to their biological activities and the challenge posed by the high degree of functionalization with attendant stereochemical intricacies. Here, we wish to describe a formal total synthesis of loganin (**2**) and sarracenin (**6**) from the versatile diquinane **8** (Figure 2). We believe that our approach to these iridoid monoterpenes is notable for its generality, preparative simplicity, and conceptual novelty.

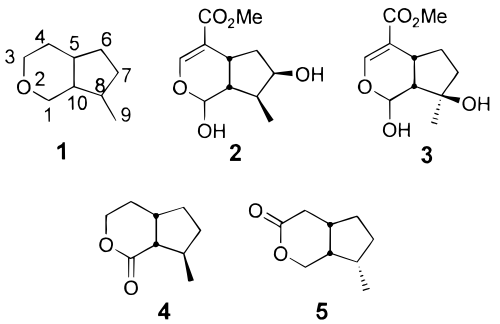

Figure 1.

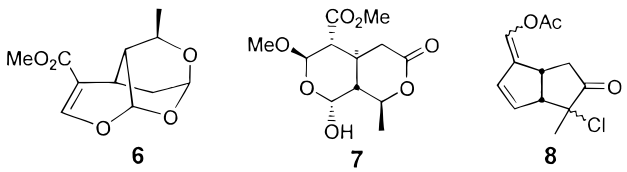

Figure 2.

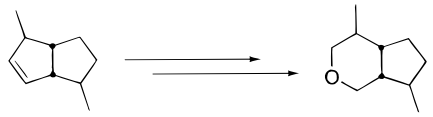

Figure 3.

Results and Discussion

In the synthesis of iridoid monoterpenes, construction of the cyclopenta[*c*]pyran ring system from a more stable *cis*-bicyclo[3.3.0]octene precursor in the final stage is an important strategy (Figure 3).[4,5c,d,10] Recently, we found that fulvene **9** undergoes a three-carbon annulation to afford diquinane **8**.[11] We believe diquinane **8** is a potential intermediate for the synthesis of iridoid natural products. Our strategy for the synthesis of the title compounds is illustrated in Scheme 1.

The key intermediate **8** was easily prepared from fulvene **9** on a molar scale from cyclopentadiene in a one-pot reaction.[12] The cycloaddition step proceeded well by reaction of fulvene **9** and in situ generation of methyl chloroketene from α-chloropropionyl chloride and triethylamine to produce the regioselective cycloadducts **10a** and **10b** (as shown in Scheme 2).[13] Treatment of the

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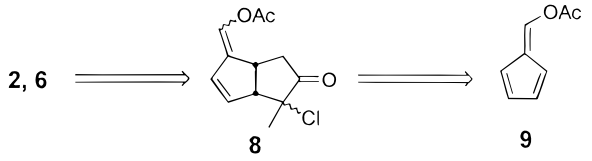
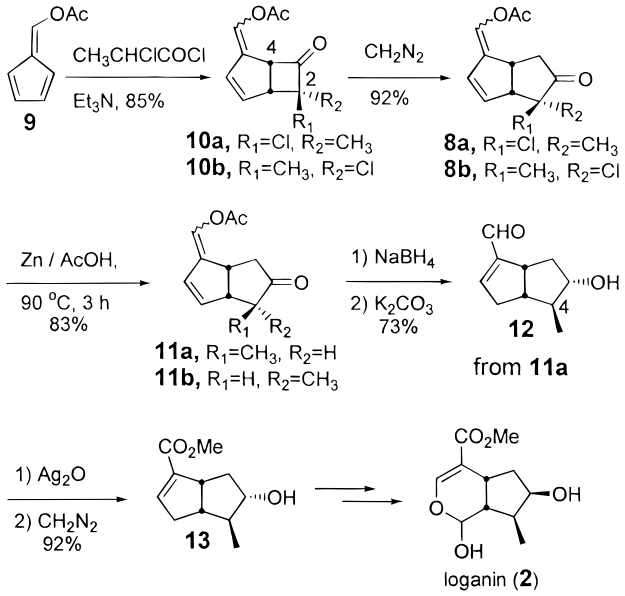
Scheme 1



Scheme 2



mixture **10** with 1.2 equiv of ethereal diazomethane (generated from Diazald) in ether gave diquinanes **8**.[14] In the one-carbon ring expansion reaction, the presence of the electron-withdrawing chlorine substituent at C_2 affected the migratory aptitudes and thus favored the migration of the more electron rich C_4 as expected. Diquinanes **8** provide *cis*-ring junction and the contain the same number of carbons as the iridoid monoterpenes.

Chlorodiquinane **8** was dechlorinated by reaction of zinc powder in acetic acid at 90 °C for 1.5 h to form a 3:2 mixture of **11a** and **11b** (83%).[14] However, at room temperature dechlorination was completed after 4 h and produced a 1:9 mixture of **11a** and **11b**. The relative stereochemistry of C_4 in **11a** and **11b** was established by NOE experiments. **11b** has a significant nuclear Overhauser effect (6.32%) between the methyl group and vinyl proton in the ^{1}H NMR spectra, and **11a** has no significant nuclear Overhauser effect between these protons (Figure 4). Ketone **11a** has the indicated stereochemical orientation of the C_4 methyl group, i.e., *exo* to the *cis*-fused bicyclo[3.3.0]octene system, which is required for the successful synthesis of loganin (**2**). With **11a** in hand, sodium borohydride was used to reduce the keto group at 0 °C in methanol, and after 30 min, the excess sodium borohydride was destroyed with acetone and the resulting mixture was treated with aqueous saturated potassium carbonate to furnish hydroxy aldehyde **12** as a single isomer in 73% yield. Oxidation of the formyl group in **12** with silver oxide and subsequent esterification of the resulting hydroxy acid with diazomethane afforded hydroxy ester **13** in 92% yield. Since **13** was converted into loganin (**2**) previously, this work constitutes a formal total synthesis of racemic loganin (**2**).[4a,b]

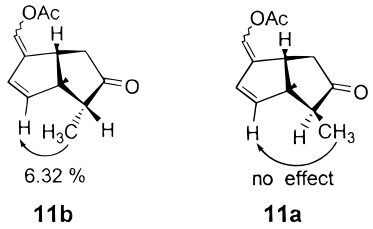
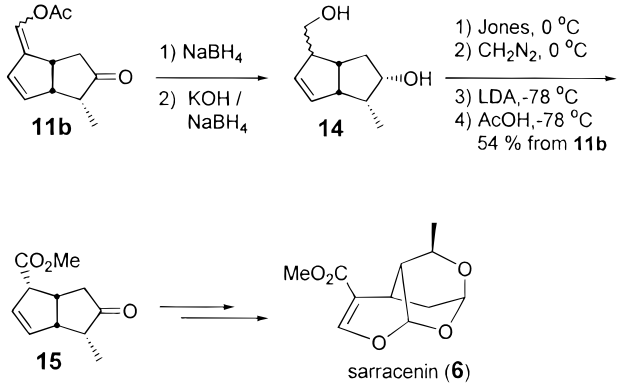


Figure 4.

Scheme 3



The route used to synthesize sarracenin (**6**) is shown in Scheme 3. Reduction of **11b** with excess sodium borohydride in methanol at 0 °C followed by addition of aqueous potassium hydroxide to hydrolyze the vinyl acetate in **11b** and subsequent reduction of the resulting formyl group furnished the diols **14**. Diols **14** were then oxidized by using Jones reagent, and the resulting keto acids were treated with diazomethane. Without purification, the resulting crude keto esters were treated with lithium diisopropylamide in THF at −78 °C followed by quenching of the dienolate with acetic acid to give the keto ester **15** as a single product (54% overall yield from **11b**). The ^{1}H and ^{13}C NMR spectra of **15** are identical to those of an authentic sample previously produced in our laboratory.[8] Since compound **15** has been transformed into sarracenin (**6**) previously,[8] this work constitutes a formal total synthesis of racemic sarracenin (**6**).

In summary, the successful synthesis of loganin (**2**) and sarracenin (**6**) demonstrate the utility of the versatile diquinane **8** for the synthesis of iridoids. Efforts directed toward the synthesis of other naturally occurring cyclopentanoid products are currently underway in our laboratory.

Experimental Section

General. THF was distilled before use from a deep blue solution resulting from sodium and benzophenone under nitrogen. All other reagents and solvents were obtained from commercial sources and used without further purification. TLC was performed with precoated silica gel (60 F_{254} plates). Column chromatography was carried out on silica (70−230 mesh). All reactions were performed under an atmosphere of nitrogen in dried (except those concerned with aqueous solutions) spherical flasks and stirred with magnetic bars.

(1*R,5*R**,6*S**)- and (1*R**,5*R**,6*R**)-Acetic Acid (6-Chloro-6-methyl-7-oxobicyclo[3.2.0]hept-3-en-2-ylidene)methyl Ester (10a and 10b)**. To a stirred solution of **9** (13.6 g, 0.10 mol)

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and triethylamine (20.9 mL, 0.15 mol) in cyclohexane (400 mL) was added dropwise 2-chloropropinoyl chloride (14.6 mL, 0.15 mol) at reflux temperature. After 2 h, the precipitate was removed by filtration, and the solvent was stripped in vacuo. The residue was purified by column chromatography with silica gel (hexane/ethyl acetate = 4:1) to provide a ca. 8:1 ratio of cycloadducts **10a** and **10b** (19.20 g, 85%).

For 10a: light yellow oil; IR (neat) 1794, 1760 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40 (d, J = 1.8 Hz, 0.5H), 7.16 (s, 0.5H), 6.67 (d, J = 5.7 Hz, 0.5H), 6.35 (dd, J = 5.4, 1.5 Hz, 0.5H), 6.08−5.95 (m, 1H), 4.95 (dd, J = 7.2, 1.2 Hz, 0.5H), 4.66 (d, J = 7.2 Hz, 0.5H), 3.90−3.80 (m, 1H), 2.20 (s, 1.5H), 2.15 (s, 1.5H), 1.53 (s, 1.5H), 1.52 (s, 1.5H); mass (EI, 70 eV) 228 (M^+, 1.7, Cl = 37), 226 (M^+, 5.1, Cl = 35), 43 (100); HRMS calcd for $C_{11}H_{11}O_3Cl$ 226.0397 (Cl = 35), found 226.0403. Anal. Calcd for $C_{11}H_{11}O_3$-Cl: C, 58.29; H, 4.89. Found: C, 58.52; H, 4.67.

For 10b: light yellow oil; IR (neat) 1798, 1759 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40 (d, J = 1.8 Hz, 0.5H), 7.14 (s, 0.5H), 6.63 (d, J = 5.7, 0.5 Hz), 6.32 (dd, J = 5.7, 1.2 Hz, 0.5H), 6.10−6.00 (m, 1H), 4.72 (dd, J = 6.0, 1.2 Hz, 0.5H), 4.40 (d, J = 6.9 Hz, 0.5H), 3.80−3.70 (m, 1H), 2.19 (s, 1.5H), 2.16 (s, 1.5H), 1.82 (s, 1.5H), 1.81 (s, 1.5H); mass (EI, 70 eV) 228 (M^+, 1.4, Cl = 37), 226 (M^+, 4.3, Cl = 35), 43 (100); HRMS calcd for $C_{11}H_{11}O_3Cl$ 226.0397 (Cl = 35), found 226.0393. Anal. Calcd for $C_{11}H_{11}O_3$-Cl: C, 58.29; H, 4.89. Found: C, 57.93; H, 5.10.

(3a*R,4*S**,6a*R**)-Acetic Acid (4-Chloro-4-methyl-5-oxo-3a,5,6,6a-tetrahydro-4*H*-pentalen-1-ylidene)methyl Ester (8a).** A solution of **10a** (10.0 g, 41.6 mmol) and methanol (10 mL) in ether (40 mL) was treated with diazomethane (generated from 20 g of Diazald) at 0 °C. After 2 h, nitrogen was bubbled into the solution to remove excess diazomethane. The ether solution was concentrated and chromatographed on silica gel (elution with 4:1 hexane/ethyl acetate) to afford **8a** (9.77 g, 92%) as a light yellow oil: IR (neat) 1756 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.39 (d, J = 1.5 Hz, 0.5H), 6.89 (s, 0.5H), 6.74 (dd, J = 5.7, 0.9 Hz, 0.5H), 6.40 (dd, J = 6.3, 0.9 Hz, 0.5H), 6.10−6.00 (m, 1H), 4.30 (d, J = 7.2 Hz, 0.5H), 4.06 (d, J = 6.9 Hz, 0.5H), 3.85−3.70 (m, 1H), 2.95−2.80 (m, 2H), 2.15 (s, 1.5H), 2.09 (s, 1.5H), 1.38 (s, 1.5H), 1.37 (s, 1.5H); mass (EI, 70 eV) 242 (M^+, 6.5, Cl = 37), 240 (M^+, 19.2, Cl = 35), 43 (100); HRMS calcd for $C_{12}H_{13}O_3Cl$ 240.0554 (Cl = 35), found 240.0555. Anal. Calcd for $C_{12}H_{13}O_3Cl$: C, 59.88; H, 5.44. Found: C, 59.72; H, 5.21.

(3a*R,4*S**,6a*R**)- and (3a*R**,4*R**,6a*R**)-Acetic Acid (4-Methyl-5-oxo-3a,5,6,6a-tetrahydro-4*H*-pentalen-1-ylidene)-methyl Ester (11a and 11b).** A suspension of **8a** or **8b** (2.0 g, 8.3 mmol) and zinc powder (3.0 g) in acetic acid (4 mL) was stirred at 90 °C for 1.5 h. CH_2Cl_2 (100 mL) was added to the reaction mixture, and the excess Zn was filtered off. The organic solution was alkalized with an aqueous solution of saturated sodium bicarbonate at 0 °C, and the layers were separated. The organic layer was washed with brine and dried over anhydrous $MgSO_4$. After the evaporation of the solvent, the residue was chromatographed on silica gel (hexane/ethyl acetate = 4:1) to obtain a 3:2 mixture of **11a** and **11b** (1.42 g, 83%).

For 11a: light yellow oil; IR (neat) 1739 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.30 (d, J = 2.1 Hz, 0.5H), 7.01 (br s, 0.5H), 6.50 (d, J = 5.7 Hz, 0.5H), 6.20−6.05 (m, 1.5H), 3.62−3.40 (m, 1H), 3.14−3.06 (m, 1H), 2.82 (dd, J = 18.9, 10.5 Hz, 0.5H), 2.73 (dd, J = 18.9, 10.5 Hz, 0.5H), 2.41−2.38 (m, 1H), 2.16 (s, 3H), 2.19−2.05 (m, 1H), 1.18 (d, J = 7.5 Hz, 1.5H), 1.17 (d, J = 7.2 Hz, 1.5H); mass (EI, 70 eV) 206 (M^+, 0.3), 151 (100); HRMS calcd for $C_{12}H_{14}O_3$ 206.0943, found 206.0936.

For 11b: light yellow oil; IR (neat) 1739 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.28 (d, J = 3.9 Hz, 0.5H), 7.05 (d, J = 0.9 Hz, 0.5H), 6.51 (dd, J = 6.0, 2.4 Hz, 0.5H), 6.15 (dd, J = 5.7, 2.1 Hz, 0.5H), 5.98 (dt, J = 5.7, 2.1 Hz, 0.5H), 5.94 (dd, J = 5.7, 2.1 Hz, 0.5H), 3.74−3.56 (m, 1.5H), 3.48−3.38 (m, 0.5H), 2.92−2.72 (m, 1H), 2.65−2.45 (m, 1H), 2.17 (s, 3H), 2.15−2.00 (m, 1H), 1.15 (d, J = 7.2 Hz, 1.5H), 1.10 (d, J = 6.9 Hz, 1.5H); mass (EI, 70 eV) 206 (M^+, 1.8), 43 (100); HRMS calcd for $C_{12}H_{14}O_3$ 206.0943, found 206.0935. Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 70.00; H, 7.03.

(3a*R,4*S**,5*S**,6a*R**)-5-Hydroxy-4-methyl-3,3a,4,5,6,6a-hexahydropentalene-1-carbaldehyde (12).** To a solution of **11a** (500 mg, 2.43 mmol) in methanol (10 mL) was added sodium borohydride (100 mg, 2.86 mmol) at 0 °C under nitrogen. The mixture was stirred for 30 min, and then the excess sodium borohydride was destroyed by adding 1 mL of acetone. After 30 min, saturated aqueous potassium carbonate (1 mL) was added and the resulting mixture was stirred at room temperature for an additional 2.5 h. The mixture was concentrated to about 3 mL under reduced pressure and diluted with ethyl acetate (100 mL). The organic phase was washed with saturated aqueous ammonium chloride and brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (hexane/ethyl acetate = 4:1) to yield **12** (294 mg, 73%) as a colorless oil: IR (neat) 3358, 1727 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.77 (s, 1H), 6.74 (dd, J = 4.2, 2.4 Hz, 1H), 3.66 (dt, J = 6.3, 8.7 Hz, 1H), 3.27−3.14 (m, 1H), 2.80 (ddt, J = 20.1, 9.3, 2.1 Hz, 1H), 2.57−2.40 (m, 2H), 2.28 (ddd, J = 18.3, 9.3, 2.4 Hz, 1H), 2.10−1.85 (br s, 1H), 1.48−1.26 (m, 2H), 1.06 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.90 (d), 151.16 (d), 150.68 (s), 78.97 (d), 48.76 (d), 46.30 (d), 42.73 (d), 39.39 (t), 38.83 (t), 16.23 (q); mass (EI, 70 eV) 166 (M^+, 3.2), 105 (100); HRMS calcd for $C_{10}H_{14}O_2$ 166.0993, found 166.0992.

(3a*R,4*S**,5*S**,6a*R**)-5-Hydroxy-4-methyl-3,3a,4,5,6,6a-hexahydropentalene-1-carboxylic Acid Methyl Ester (13).** A suspension of **12** (300 mg, 1.81 mmol), silver oxide (500 mg, 2.17 mmol) in methanol (2 mL), and water (4 mL) was stirred at room temperature for 36 h. The reaction mixture was acidified with 10% HCl and extracted with ethyl acetate. The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated to leave a residue that was dissolved in ether and treated with excess diazomethane at 0 °C. After 15 min, the remaining diazomethane was destroyed with a few drops of acetic acid, the solution was washed with saturated sodium bicarbonate and brine and dried ($MgSO_4$), and the solvent was evaporated. Column chromatography of the residue on silica gel (hexane/ethyl acetate = 4:1) furnished 325 mg (92%) of **13** as a colorless oil: IR (neat) 3330, 1716 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.66 (d, J = 2.1 Hz, 1H), 3.73 (s, 3H), 3.64 (dt, J = 6.6, 9.0 Hz, 1H), 3.28−3.15 (m, 1H), 2.70 (ddt, J = 19.2, 9.0, 2.4 Hz, 1H), 2.49 (ddd, J = 12.9, 9.0, 6.6 Hz, 1H), 2.32 (dq, J = 19.2, 3.0 Hz, 1H), 2.22 (ddd, J = 19.2, 9.6, 2.4 Hz, 1H), 1.65 (br s, 1H), 1.48−1.43 (m, 2H), 1.06 (d, J = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.52 (s), 141.76 (d), 139.61 (s), 79.01 (d), 51.37 (d), 48.99 (d), 45.99 (d), 44.87 (t), 40.30 (t), 38.26 (t), 16.19 (q); mass (EI, 30 eV) 196 (M^+, 6.1), 119 (100); HRMS calcd for $C_{11}H_{16}O_3$ 196.1099, found 196.1096. Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.70; H, 7.98.

(1S*,3a*R,4*R**,6a*R**)-4-Methyl-5-oxo-1,3a,4,5,6,6a-hexahydropentalene-1-carboxylic Acid Methyl Ester (15).** To a stirred solution of **11b** (300 mg, 1.46 mmol) in methanol (10 mL) was added sodium borohydride (200 mg, 5.71 mmol) at 0 °C under nitrogen for 30 min. Aqueous sodium hydroxide (1 mL, 50%) was added, and the resulting mixture was stirred at 0 °C for an additional 2.5 h. The reaction was quenched with acetone, and the mixture was concentrated to about 3 mL under reduced pressure and diluted with ethyl acetate (100 mL). The organic phase was washed with aqueous NH_4Cl and brine, dried ($MgSO_4$), and concentrated to yield diols **14** as a 3:2 mixture of diasteromers. Major product: ^1H NMR (300 MHz, $CDCl_3$) δ 5.95−5.85 (m, 1H), 5.65−5.60 (m, 1H), 3.96 (t, J = 3.9 Hz, 1H), 3.90−3.80 (m, 2H), 3.25−3.19 (m, 1H), 3.19−3.05 (m, 1H), 3.00−2.90 (m, 1H), 2.5 (br s, 2H), 2.05−1.80 (m, 3H), 1.11 (d, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 133.93 (d), 131.70 (d), 77.32 (d), 61.71 (t), 55.29 (d), 51.15 (d), 43.00 (d), 40.36 (d), 35.56 (t), 38.26 (t), 10.79 (q). Minor product: ^1H NMR (300 MHz, $CDCl_3$) δ 6.05−5.90 (m, 1H), 5.70−5.60 (m, 1H), 3.97 (dt, J = 1.8, 4.8 Hz, 1H), 3.60−3.40 (m, 2H), 3.25−3.10 (m, 1H), 2.95−2.85 (m, 1H), 2.60−2.50 (m, 1H), 2.25−2.14 (m, 1H), 2.10−1.90 (m, 3H), 1.75−1.65 (m, 1H), 1.10 (d, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.09 (d), 131.51 (d), 77.76 (d), 66.42 (t), 58.57 (d), 54.37 (d), 42.85 (t), 42.28 (d), 42.04 (d), 11.29 (q). Without further purification, excess Jones reagent was added to a stirred solution of crude **14** in acetone at 0 °C. The mixture was stirred for 30 min and treated with 2-propanol to destroy the unreacted oxidant. After the solvent was removed, the residue was diluted with water and extracted with ethyl acetate. The organic extracts were washed with brine, dried, and concentrated. The residue was dissolved in ether and treated with excess diazomethane at 0 °C. After 15 min, nitrogen was bubbled into the solution to remove excess diazomethane followed by concentration. The residue, dissolved in dried THF (5

mL), was added into a solution of LDA which was generated in situ from diisopropylamine (0.8 mL) in dried THF (15 mL) and *n*-butyllithium (1.6 M, 3.5 mL) at −78 °C. After storage of this mixture for 30 min, acetic acid (0.5 mL) in THF (5 mL) was added. The reaction mixture was stirred at −78 °C for an additional 5 min, and the reaction was quenched with saturated aqueous sodium bicarbonate (15 mL). The liquid layers were separated, and aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried, and concentrated. The residue was chromatographed on silica gel, eluting with hexane/ethyl acetate (4:1), to give keto ester **15** (162 mg, 54%) as an oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.91−5.88 (m, 1H), 5.84−5.81 (m,1H), 3.83−3.79 (m, 1H), 3.68 (s, 3H), 3.31−3.20 (m, 1H), 3.04−2.99 (m, 1H), 2.36 (dd, J = 18.6, 9.6 Hz, 1H), 2.31−2.29 (m, 1H), 2.14 (dd, J = 18.6, 5.4 Hz, 1H), 1.15 (d, J = 5.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 219.96 (s), 173.13 (s), 136.20 (d), 128.71 (d), 54.97 (d), 53.91 (d), 51.75 (t), 47.41 (d), 39.45 (t), 38.54 (d), 15.96 (q); mass (EI, 70 eV) 194 (M^+, 16.9), 93 (100); HRMS calcd for $C_{11}H_{14}O_3$ 194.0943, found 194.0947.

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