Regiocontrolled Cyclohexenone Annulation via Acylation of a Ketone Carbonyl

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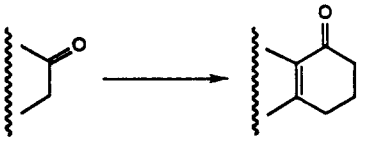
1-(1-Ethoxyvinyl)cycloalkenes, readily available by palladium-catalyzed condensation of enol triflates with ethyl vinyl ether or its α-trimethylstannyl derivative, enter into Diels–Alder reaction with (*Z*)-1,2-bis(phenylsulfonyl)ethylene. These adducts undergo smooth reductive desulfonylation to provide cyclohexenones after enol ether hydrolysis. Migration of the double bond into the thermodynamically more stable internal conjugated position completes the annulation scheme.

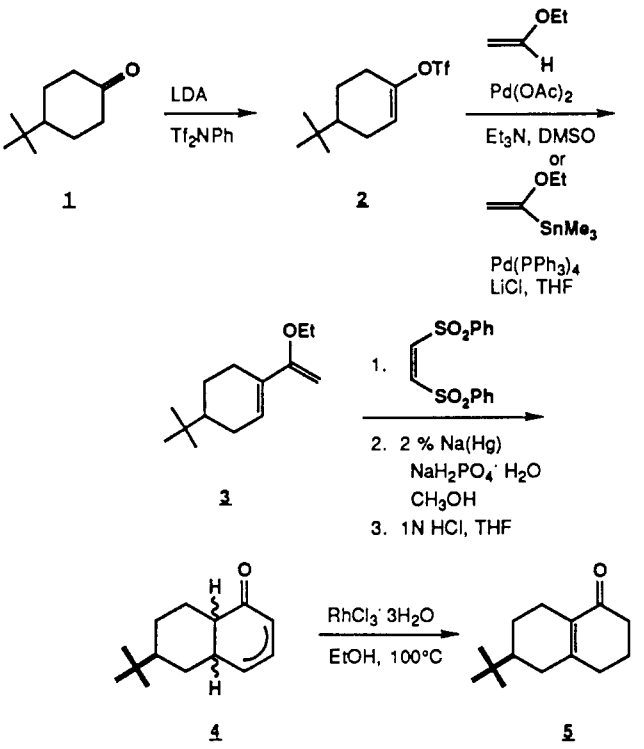
While developing a synthetic entry to a complex natural product, we had need for effecting the following conversion smoothly under mild conditions. This transformation has been accorded surprisingly little attention.[2-5] In fact, the only effective pathway known to us is a seven-step transformation developed by House.[6] However, this process includes steps that precluded its use for our purpose.[7]



As a potentially serviceable alternative strategy, we envisioned milder indirect acylation of the carbonyl group so as to allow for six-membered ring construction via subsequent [4 + 2] cycloaddition. Introduction of the desired double bond would then be implemented via controlled reductive elimination conditions.[8] We focused on 3-ethoxybutadienes such as **3** (Scheme I) because of the ready availability of ethyl vinyl ether and its α-trimethylstannyl derivative,[9,10] and the striking ease with which these reagents can be coupled to vinyl triflates.[11,12]

The advantages offered by the new protocol were considered to be the chemospecific and regiospecific C–C coupling exemplified by **2** → **3**, the activation inherent in

Scheme I



dienes such as **3** for facilitating cycloaddition to the acetylene equivalent (*Z*)-1,2-bis(phenylsulfonyl)ethylene,[13] the lack of concern for stereochemistry during the conversion of **3** into **5**, and the reliability offered by Rh(III) salts for isomerizing the unsaturated linkage into the thermodynamically favored location central to the two rings.[14]

Direct arrival at **3** was possible by two methods. The first involved carbon–carbon bond formation by means of (α-ethoxyvinyl)stannane and tetrakis(triphenylphosphine)palladium.[9] The alternative use of ethyl vinyl ether and palladium acetate as co-reagents[12] proved somewhat more simple and expedient, although the yield of product in both instances was notably high (97%). A lesser amount of noble metal catalyst is required (3 mol % $Pd(OAc)_2$ vs 5 mol % $Pd(PPh_3)_4$). Also, the product

(1) Undergraduate Research Participant, Summer 1989.

(2) The reader will recognize that the desired *overall chemical change* is the equivalent of a homo-Nazarov sequence although the sequences are totally unrelated mechanistically. For recent work in the Nazarov area, see refs 3–5.

(3) Paquette, L. A.; Fristad, W. E.; Dime, D. S.; Bailey, T. R. *J. Org. Chem.* **1980**, 45, 3017 and references cited therein.

(4) (a) Santelli-Rouvier, C.; Santelli, M. *Synthesis* **1983**, 429. (b) Ramaiah, M. *Ibid.* **1984**, 529. (c) Ono, M. J. *Syn. Org. Chem. Jpn.* **1981**, *39*, 872.

(5) Denmark, S. E. *Comprehensive Organic Synthesis*, Vol. 5; Pergamon Press, in press.

(6) House, H. O.; Giese, R. W.; Kronberger, K.; Kaplan, J. P.; Simeone, J. F. *J. Am. Chem. Soc.* **1970**, *92*, 2800.

(7) A reaction scheme that might be adaptable to this purpose has been developed by Chan, T. H.; Prasad, C. V. C. *J. Org. Chem.* **1987**, *52*, 110.

(8) Trost, B. M.; Arndt, H. C.; Strege, P. W.; Verhoeven, T. R. *Tetrahedron Lett.* **1976**, 3477.

(9) Cheney, D. L.; Paquette, L. A. *J. Org. Chem.* **1989**, *54*, 3334.

(10) Analogous chemistry has previously been effected with (α-alkoxyvinyl)zinc chlorides [Negishi, E.; Luo, F.-T. *J. Org. Chem.* **1983**, *48*, 1560], (α-ethoxyvinyl)tributylstannane [Kosugi, M.; Sumiya, T.; Obara, Y.; Suzuki, M.; Sano, H.; Migita, T. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 767], and (α-ethoxyvinyl)trimethylsilane [Hatanaka, Y.; Hiyama, T. *J. Org. Chem.* **1988**, 53, 918].

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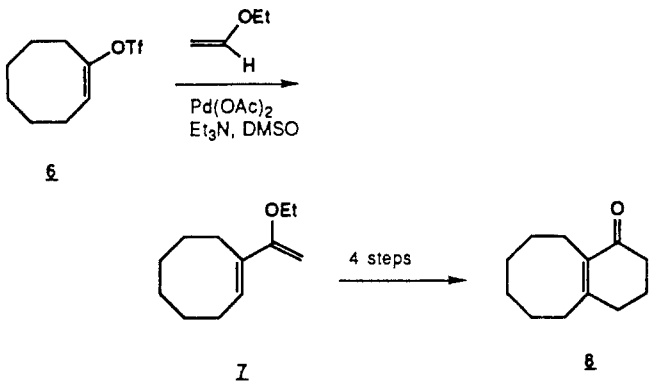
0022-3263/90/1955-2443$02.50/0

Scheme II



as directly isolated is already colorless and does not possess the pale yellow-green hue that materializes when (α-ethoxyvinyl)trimethylstannane is utilized. These observations and the relatively high cost of the tin reagent prompted use of the Andersson–Halberg procedure for the duration of this investigation.

Usefully, the Diels–Alder addition of (*Z*)-1,2-bis(phenylsulfonyl)ethylene to **3** can be effected thermally (refluxing CH_2Cl_2 or THF for 5 days) or at high pressure (120 000 psi)[15] under ambient conditions for 2–3 days. The efficiency of the first procedure averaged 20% less than that realized when heating was not applied (~100%).

The resulting adduct was directly subjected to reductive desulfonylation without purification. Best results were achieved when the 2.25% sodium amalgam was freshly prepared and contained no free mercury. Furthermore, *slow* addition of this reducing agent to a solution of the reactant in buffered methanol[8] was notably beneficial. Otherwise, overreduction of the diene product was noted. Addition of the amalgam in one portion gave rise (after acidic hydrolysis) to levels of saturated ketone in excess of 60%. Use of dimethylformamide as solvent[16] caused aromatization of the diene intermediate to become dominant.

Heating of the reduction product with 1 N hydrochloric acid in tetrahydrofuran gave the expected conjugated ketone predominantly, but never free of the β,γ-isomer. This was of no consequence since heating of this mixture with rhodium trichloride and a small amount of ethanol transformed all of the constituents into **5**. This isomerization was best achieved at 100 °C in a closed vessel. The overall conversion of **3** to **5** proceeds in 32% yield. Beginning with 4-*tert*-butylcyclohexanone, a total effiicency of 29% was routinely achieved.

In order to assess the feasibility of annulating a medium-sized ring, we turned to cyclooctanone. Its conversion to **6** (Scheme II) has previously been reported.[17] This enol triflate behaved well under the typical conditions for conversion to dienyl ether **7** (79%). With this intermediate in hand, the four-step annulation sequence was carried out in the predescribed manner. Pure **8**[18] was obtained in 27% overall yield. Thus, the Diels–Alder reativity of **7** can be directly correlated to that of **3**.

Finally, recourse was made to (−)-methone (**9**) for the purpose of determining whether chiral centers in close proximity to the double bond of the product enone (see **12**, Scheme III) would retain their stereochemical integrity. Regiospecific enolization and O-triflation were easily realized to give **10** (87%). The subsequent coupling reaction leading to **11** gave no evidence for being sterically impeded, since the diene was reproducibly isolated in 92% yield. During the conversion to **12**, the Diels–Alder cycloaddition, reductive removal of the pair of phenylsulfonyl groups, and acidic hydrolysis were uneventful. On the other hand the Rh(III)-promoted isomerization proved more sluggish than usual. Complete migration of the double bond to the interior of the molecule required a minimum of two periods of heating with this catalyst. Although the yield of **12** was not adversely affected (32% from **11**), a mixture of two inseparable conjugated ketones was produced. Since all of the ^1H NMR signals for the two isomers are coincident except for the doublets associated with the ring methyl substituent ($\Delta\delta = 0.03$), we conclude that some modest loss of configuration (ca. 35%; ^1H NMR analysis) had occurred at C-5 and that **13** was not formed competitively.

The present strategy concisely accomplishes the desired cyclohexenone annulation. The requisite reaction conditions are sufficiently mild to be useful in a wide variety of applications. While the generality of this sequence has not yet been extensively explored, the present findings suggest that it might well be a general approach for regiocontrolled joining of a 2-cyclcohexenone to an existing carbonyl functionality.

Experimental Section

1-(1-Ethoxyvinyl)-4-*tert*-butylcyclohexene (3). A. Pd(II)-Catalyzed Condensation with Ethyl Vinyl Ether. Ethyl vinyl ether (1.94 g, 26.9 mmol), Et_3N (817 mg, 8.07 mmol), enol triflate **2**[17] (1.54 g, 5.38 mmol), and $Pd(OAc)_2$ (36 mg, 0.16 mmol) were placed in a Pyrex tube containing dry DMSO (10 mL). The orange-colored mixture was heated at 60–65 °C for 1.5 h while being stirred, allowed to cool, poured into ice water (70 mL), and extracted with petroleum ether (3 × 50 mL). The combined organic layers were washed with 1 N NaOH solution (40 mL), dried, and concentrated. Filtration through a column of basic alumina (40 g, elution with petroleum ether) and concentration in vacuo gave **3** as a colorless oil (1.02 g, 97%): IR (neat, cm^{-1}) 3030, 2960, 1655, 1625, 1575, 1480; ^1H NMR (300 MHz, C_6D_6) δ 6.57–6.55 (m, 1 H), 4.29 (d, J = 1.8 Hz, 1 H), 4.02 (d, J = 1.8 Hz, 1 H), 3.57 (q, J = 7.0 Hz, 2 H), 2.39–2.32 (m, 1 H), 2.16–2.00 (m, 2 H), 1.83–1.51 (m, 2 H), 1.22–1.11 (m, 2 H), 1.15 (t, J = 7.0 Hz, 3 H), 0.78 (s, 9 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 161.19, 132.35, 125.25, 80.75, 62.70, 44.20, 32.10, 27.28, 27.12, 24.49, 14.67 (one C not observed); MS m/z (M^+) calcd 208.1827, obsd 208.1815.

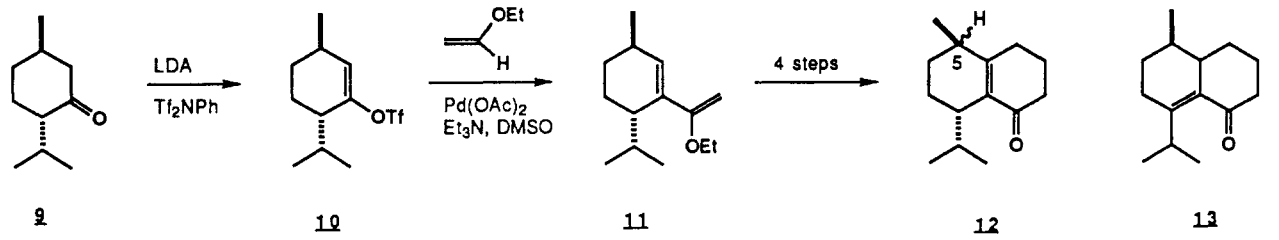
Anal. Calcd for $C_{14}H_{24}O$: C, 80.71; H, 11.61. Found: C, 80.66; H, 11.56.

B. Pd(0)-Catalyzed Condensation with (α-Ethoxyvinyl)trimethylstannane. A mixture of anhydrous LiCl (331 mg, 7.80 mmol) and $(Ph_3P)_4Pd$ (90 mg, 0.078 mmol) in THF (5 mL) was treated under nitrogen with a solution of (α-ethoxyvinyl)trimethylstannane (366 mg, 1.56 mmol) and enol triflate **2** (448 mg, 1.56 mmol) in the same solvent (5 mL). The magnetically stirred mixture was heated at reflux for 15 h, diluted with petroleum ether (60 mL), and poured into 10% NH_4OH solution (15 mL). The separated organic phase was washed with 10% NH_4OH solution (3 × 10 mL), filtered through a short pad of Florisil, and concentrated in vacuo to give 315 mg (97%) of **3**, spectroscopically identical with the material prepared above.

(α-Ethoxyvinyl)trimethylstannane.[9] A solution of freshly distilled ethyl vinyl ether (94 mmol) in dry THF (100 mL) was cooled to −78 °C, and *tert*-butyllithium (96 mmol, 1.5 M in hexanes) was added dropwise over a 25-min period. After 45 min of stirring at −78 °C, the reaction mixture was allowed to warm to −15 °C over 1 h. A bright yellow suspension formed. While at −15 °C, the mixture was transferred via cannula to a solution of trimethyltin chloride (17.8 g, 67.9 mmol) in THF (−78 °C) over 15 min, warmed to 15 °C, and quenched with saturated NH_4Cl solution. The product was extracted into ether, dried, and distilled to give 12.2 g (58%) of colorless liquid: bp 68–70 °C (15 Torr); ^1H NMR (300 MHz, C_6D_6) δ 4.67 (d, J = 1.7 Hz, 1 H), 4.08 (d,

(15) Use was made of a Leco Corporation instrument.
(16) Mirsadeghid, S.; Rickborn, B. *J. Org. Chem.* **1985**, *50*, 4340.
(17) McMurry, J. E.; Scott, W. J. *Tetrahedron Lett.* **1983**, 979.
(18) (a) Fujita, S.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 2827. (b) Hirano, S.; Hiyama, T.; Nozaki, H. *Tetrahedron Lett.* **1973**, 1331; *Tetrahedron* **1976**, *32*, 2381.

Scheme III



9 10 11 12 13

J = 1.8 Hz, 1 H), 3.71 (q, J = 7.0 Hz, 2 H), 1.27 (t, J = 7.0 Hz, 3 H), 0.19 (s with satellites, 9 H); MS m/z ($M^+ - CH_3$) calcd 218.9983, obsd 218.9981.

6-*tert*-Butyl-9(10)-octal-1-one (5).[6] A solution of **3** (388 mg, 1.86 mmol) and (*Z*)-1,2-bis(phenylsulfonyl)ethylene (574 mg, 1.86 mmol) in CH_2Cl_2 (3 mL) was placed under 120 000 psi at room temperature for 3 days. Concentration in vacuo afforded the Diels–Alder adduct (0.96 g, 100%) as a pale yellow foam.

The above cycloadduct was dissolved in anhydrous CH_3OH (20 mL) containing $NaH_2PO_4 \cdot H_2O$ (1.03 g, 7.44 mmol) and stirred vigorously while 2.25% sodium amalgam (11.4 g, 11.2 mmol) was added portionwise under nitrogen during 8 h. The rate was adjusted so that 0.5–1.0 g was introduced every 30 min. Following completion of the addition, the mixture was stirred for 12 h, filtered, and extracted with petroleum ether (3 × 70 mL). The combined organic phases were washed with water (2 × 20 mL) and brine (2 × 30 mL) and then concentrated. The residue was taken up in THF (30 mL) containing 1 N HCl (3 mL), refluxed for 2.5 h, cooled, and extracted with ether (3 × 30 mL). The combined ethereal layers were dried, concentrated, and purified by MPLC on silica gel (elution with 10% ethyl acetate in petroleum ether) to give **4** (195 mg, 51%).

The ketone mixture was placed in a heavy-walled tube, which was charged with absolute EtOH (500 μL) containing rhodium trichloride trihydrate (15.0 mg, 0.057 mmol). After three freeze–thaw cycles, the tube was sealed and heated at 100 °C for 15 h. The cooled reaction mixture was diluted with ether (1 mL), filtered through a short silica gel column, and concentrated. The residue was purified by MPLC (silica gel, elution with 10% EtOAc in petroleum ether) to give 121 mg (32% from **3**) of **5** as a clear oil that crystallized at room temperature; IR (neat, cm^{-1}) 3300, 2980, 1658, 1452, 1380; ^1H NMR (300 MHz, $CDCl_3$) δ 2.56–1.85 (series of m, 10 H), 1.45–0.93 (m, 3 H), 0.87 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 196.06, 157.41, 132.14, 43.73, 37.79, 33.51, 32.03, 31.50, 27.05, 23.46, 22.45 (one C not observed); MS m/z (M^+) calcd 206.1653, obsd 206.1671.

Anal. Calcd for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found: C, 81.14, H, 10.71.

1-(1-Ethoxyvinyl)cyclooctene (7). Enol triflate **6**[17] (1.29 g, 5.00 mmol), when treated as described above for **2**, gave 712 mg (79%) of **7** as a pale yellowish oil. The analytical sample was purified by preparative VPC: IR (neat, cm^{-1}) 2993, 2943, 2860, 1713, 1643, 1630, 1453; ^1H NMR (300 MHz, $CDCl_3$) δ 6.28 (t, J = 8.4 Hz, 1 H), 4.23 (d, J = 2.1 Hz, 1 H), 4.01 (d, J = 2.1 Hz, 1 H), 3.77 (q, J = 7.0 Hz, 2 H), 2.48 (m, 2 H), 2.20 (m, 2 H), 1.58 (m, 8 H), 1.34 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 160.51, 135.62, 127.63, 81.55, 62.82, 56.15, 30.08, 29.32, 27.01, 26.00, 25.67, 14.57; MS m/z (M^+) calcd 180.1504, obsd 180.1488.

Anal. Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 79.62; H, 11.17.

Bicyclo[6.4.0]dodec-1(8)-en-9-one (8).[18] The reaction conditions described earlier were employed in each step. From 532 mg (2.95 mmol) of **7** there was isolated 140 mg (27% overall) of **8** as a colorless oil: IR (neat, cm^{-1}) 2910, 2843, 1665, 1630, 1470, 1448; ^1H NMR (300 MHz, $CDCl_3$) δ 2.46 (m, 2 H), 2.38 (m, 6 H), 1.95 (m, 2 H), 1.75 (m, 2 H), 1.45 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 198.46, 159.80, 135.46, 37.84, 33.88, 31.03, 29.70, 28.67, 26.63, 26.50, 23.19, 22.64; MS m/z (M^+) calcd 178.1358, obsd 178.1344.

Anal. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.64; H, 10.21.

1-(((Trifluoromethyl)sulfonyl)oxy)-3(*R*)-methyl-6(*S*)-isopropylcyclohexene (10). A cold (−78 °C) solution of (−)-methone (3.09 g, 20.0 mmol) in THF (20 mL) was added slowly to a magnetically stirred solution of lithium diisopropylamide (22.0 mmol) in the same solvent (50 mL) at −78 °C. After 1.5 h, a cold (−20 °C) solution of *N*-phenyltrifluoromethanesulfonimide[19] (7.86 g, 22.0 mmol) in THF (50 mL) was introduced, and the reaction mixture was allowed to warm slowly to room temperature overnight. The usual workup and MPLC purification (silica gel, elution with petroleum ether) gave **10** as a colorless oil (4.97 g, 87%): IR (neat, cm^{-1}) 2960, 2870, 1675, 1450, 1416; ^1H NMR (300 MHz, $CDCl_3$) δ 5.64 (s, 1 H), 2.49 (m, 1 H), 2.35 (m, 1 H), 2.28 (m, 1 H), 1.82 (m, 2 H), 1.42 (m, 1 H), 1.15 (m, 1 H), 1.04 (d, J = 7.0 Hz, 3 H), 0.95 (d, J = 7.0 Hz, 3 H), 0.82 (d, J = 6.7 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 151.79, 125.90, 115.36, (q), 43.12, 30.64, 29.98, 27.36, 22.51, 21.25, 19.85, 16.39; MS m/z (M^+) calcd 286.0850, obsd 286.0839.

1-(1-Ethoxyvinyl)-3(*R*)-methyl-6(*S*)-isopropylcyclohexene (11). Homologation of enol triflate **10** as before furnished 830 mg (92%) of **11** as a colorless oil after preparative GC: IR (neat, cm^{-1}) 2952, 2922, 2863, 1642, 1590, 1462, 1283; ^1H NMR (300 MHz, $CDCl_3$) δ 5.90 (s, 1 H), 4.07 (d, J = 1.6 Hz, 1 H), 3.91 (d, J = 1.6 Hz, 1 H), 3.75 (m, 2 H), 2.42 (m, 1 H), 2.23 (m, 1 H), 2.00 (m, 1 H), 1.75 (m, 2 H), 1.31 (t, J = 7.0 Hz, 3 H), 1.11 (m, 1 H), 0.93 (d, J = 7.0 Hz, 3 H), 0.90 (d, J = 7.0 Hz, 3 H), 0.88 (m, 1 H), 0.70 (d, J = 6.9 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 163.66, 138.62, 134.48, 81.72, 62.81, 39.83, 30.59, 30.40, 28.94, 21.79, 21.32, 20.82, 16.75, 14.57; MS m/z (M^+) calcd 208.1827, obsd 208.1833.

Anal. Calcd for $C_{14}H_{24}O$: C, 80.71; H, 11.61. Found: C, 80.76; H, 11.67.

Mixture of 5(*R*)- and 5(*S*)-Methyl-8(*S*)-isopropyl-9(10)-octal-1-one (12). The reaction conditions described earlier were utilized without modification. From 416 mg (2.00 mmol) of **11** there was isolated 132 mg (32% overall) of **12**. The diastereomers (very similar retention times by capillary GC) were not separated: IR (neat, cm^{-1}) 2947, 2869, 1659, 1617, 1462, 1385; ^1H NMR (300 MHz, $CDCl_3$) δ 2.72 (m, 1 H), 2.48 (m, 2 H), 2.25 (m, 3 H), 1.95 (m, 4 H), 1.55 (m, 3 H), 1.14 (d, J = 7.3 Hz) and 1.11 (d, J = 7.2 Hz, total 3 H), 0.84 (d, J = 6.8 Hz, 2 H), 0.74 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm (major isomer) 199.30, 161.16, 136.09, 38.51, 36.73, 35.12, 29.87, 29.64, 27.69, 22.61, 21.03, 20.61, 19.08, 18.57; (minor isomer) 198.86, 161.30, 136.04, 38.23, 36.55, 35.51, 30.29, 27.94, 21.96, 21.11, 20.18, 19.52, 18.64 (one C not observed); MS m/z (M^+) calcd 206.1670, obsd 206.1657.

Anal. Calcd for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found: C, 81.16; H, 10.72.

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