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Synthesis and Biological Activity of Enantiomers of Antitumor Irofulven

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Stereoselective synthesis of (−)-irofulven has been achieved by cycloaddition of (*R*)-5-chloro-5-methyl-2-cyclopentenone to the 1,3-dipolar intermediate from 1-acetyl-1-(diazoacetyl)cyclopropane. The enantiomer, (+)-irofulven, was prepared in a similar way starting with (*S*)-5-chloro-5-methyl-2-cyclopentenone. (+)-Irofulven was 5 to 6 times less toxic than (−)-irofulven to adenocarcinoma (MV 522) cells.

Introduction

The toxic mushroom *Omphalotus illudens* (formerly *Clitocybe illudens*) is the source of highly toxic sesquiterpenes illudin S and M (**1**, **2**).[1] The compounds were tested many years ago by the National Cancer Institute and were found to possess antitumor activity but with a poor therapeutic index. However, certain derivatives of these compounds have greatly improved efficacy as antitumor agents. In particular, the derivative irofulven (hydroxymethylacylfulvene, **4**)[2] has been extensively investigated and is currently in phase II clinical trials against ovarian, prostate, and gastrointestinal cancers, both as a monotherapy[3] and in combination with well-known anticancer drugs.

Irofulven is best prepared by semisynthesis from illudin S, which is readily obtained from fermentation of *O. illudens*. Treatment with dilute H_2SO_4 converts **1** to acylfulvene **3** in a reverse Prins reaction. Reaction of **3** with formaldehyde in dilute H_2SO_4 gives irofulven in a yield of 40% from **1**.

The total synthesis of (±)-acylfulvene has been achieved by means of the Padwa carbonyl ylide 1,3-dipolar cycloaddition methodology.[4] More recently a synthetic approach to either enantiomer of acylfulvene, utilizing the allenic Pauson−Khand reaction, has been reported by Brummond et al.[5] We now disclose an alternative

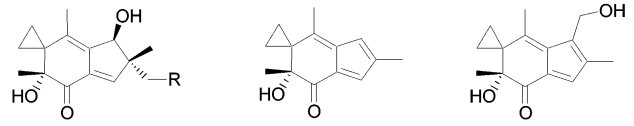
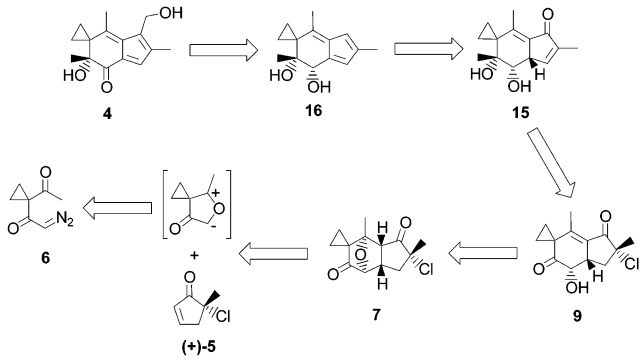


FIGURE 1. Structures of illudins and derivatives.

SCHEME 1. Retroanalysis of the Irofulven Total Synthesis



synthesis that was designed to furnish either enantiomer of irofulven. The retrosynthesis is outlined in Scheme 1. We planned to establish the chirality in the first step by using 5-chloro-5-methyl-2-cyclopentenone (**5**) of known absolute configuration. Cycloaddition of **5** with the dipolar intermediate from diazoketone (**6**) would give a product whose absolute configuration could be deduced.

Assuming the stereochemistry of the oxygen bridge to be thus established we believed it would be possible to control formation of the chiral center of irofulven. That center would be constructed by a Grignard reaction. Having served its purpose the chloro substituent would be removed by dehydrohalogenation, thus setting the stage for creating the fulvene structure.

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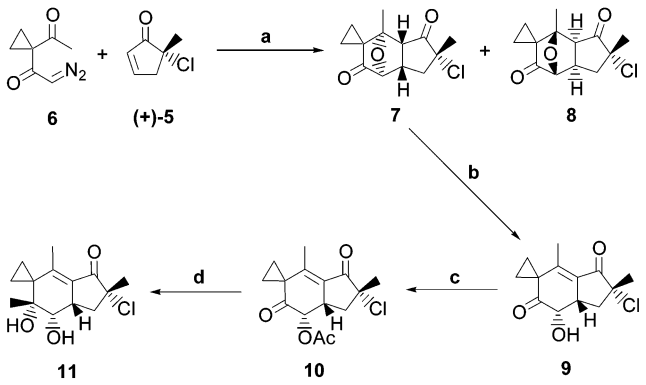
SCHEME 2[a]



[a] Reagents and conditions: (a) cat. $Rh_2(OAc)_4$, CH_2Cl_2, reflux, 1 h (54% **7**, 20% **8**); (b) K_2CO_3, 90% *i*-PrOH/H_2O, rt, 6 h (70%); (c) Ac_2O, Py, rt, 2 h (90%); (d) MeMgCl, THF, −78 °C, 2 h, then 0 °C, 2 h (87%).

Synthesis

Racemic 5-chloro-5-methyl-2-cyclopentenone (±)-**5** was readily prepared according to the literature procedure.[6] Resolution of the enantiomers was achieved by asymmetric reduction of (±)-**5** with BH_3·THF and catalytic (*S*)-2-methyl-CBS-oxazaborolidine. This furnished a diastereomeric mixture of the (*R*)-cyclopentenols which were readily separated and reoxidized to give (+)-**5** (98% ee) and (−)-**5** (82% ee). Likewise, reduction of (±)-**5** with catalytic (*R*)-2-methyl-CBS-oxazaborolidine afforded diastereomeric (*S*)-cyclopentenols which after separation and reoxidation gave (−)-**5** (98% ee) and (+)-**5** (83% ee).[7]

Cycloaddition reaction of cyclopentenone (+)-**5** with diazoketone **6** and a catalytic amount of $Rh_2(OAc)_4$ in refluxing CH_2Cl_2 yielded a mixture of diastereomers **7** and **8** (54% and 20%, respectively, Scheme 2). The exo products were the only ones isolated. X-ray crystallographic analysis established the relative configuration of the chiral centers depicted in **7**.[8]

The oxo bridge in diastereomer **7** was cleaved under mild basic conditions (K_2CO_3, 2-propanol−H_2O 9:1; the best yields were obtained with this solvent system). Acetylation of alcohol **9** to give **10** followed by Grignard reaction with methylmagnesium chloride at low temperature gave a high yield (87%) of a single cis glycol **11** with the indicated stereochemistry (Scheme 2). This structure was confirmed by forming crystalline acetonide **12** (83%, Scheme 3) whose absolute configuration was firmly established by X-ray crystallographic analysis (Figure 2). Noteworthy features of the Grignard reaction were (a) complete regioselectivity (the cyclopentenone was unreactive) and (b) complete stereoselectivity: only one tertiary alcohol was obtained, indicating the directive influence of the adjacent α-acetoxy group.[9] Thus the stereochemistry at the new chiral center was firmly established.

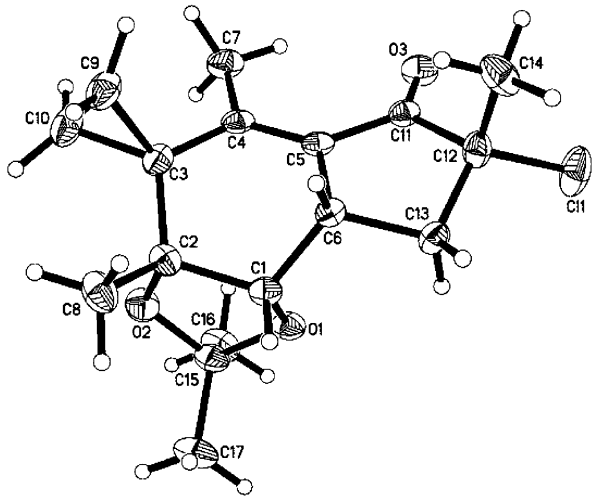
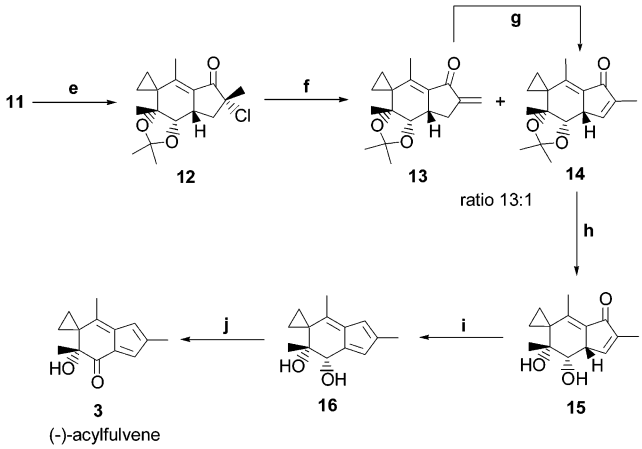


FIGURE 2. X-ray structure of compound **12**.

SCHEME 3[a]



[a] Reagents and conditions: (e) 2,2-dimethoxypropane, cat. *p*-TsOH, DMF, rt, 24 h (83%); (f) DBU, benzene, rt, 1.5 h; (g) cat. $RhCl_3$·$3H_2O$, EtOH, reflux, 20 min (62%, 2 steps); (h) 80% AcOH/H_2O, 90 °C, 2 h (78%); (i) DIBALH, CH_2Cl_2, −78 °C, 30 min (49%); (j) IBX, DMSO, rt, 2 h (53%).

Dehydrohalogenation of intermediate **12** was achieved by treatment with DBU in benzene.[10] A mixture of exocyclic and endocyclic enones **13** and **14** was formed in a 13:1 ratio. Without separation, the mixture was refluxed in EtOH with rhodium chloride,[11] which caused isomerization of the exocyclic to the more stable endocyclic isomer with overall yield of 62%.

Removal of the acetonide protecting group gave glycol **15**, which on DIBALH reduction of the ketone and concomitant 1,4-elimination of the resulting hydroxy group yielded fulvene **16** in 49% yield. On oxidation with *o*-iodoxybenzoic acid (IBX) **16** gave (−)-acylfulvene **3**, which was identical with the compound derived from illudin S in all respects including optical rotation.[12]

Starting from cyclopentenone (−)-**5** and employing the same set of reactions, the enantiomer of acylfulvene (+)-**3** was prepared in 10 steps in an overall yield of 3.1%. The

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(8) Relative configuration was established by analysis of the racemate corresponding to **7**, which was obtained in an earlier experiment from the cycloaddition of diazoketone **6** with (±)-**5**.
(9) Reaction of unprotected **9** with MeMgCl under similar conditions gives the stereoisomeric trans diol in low yield (30%). Cis diol **11** was not detected.
(10) Jean-Baptiste, W.; Francois, R. *Bull. Soc. Chim. Fr.* **1979**, *5*−*6*, II−273.
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SCHEME 4. Mechanism of Biological Action of Irofulven

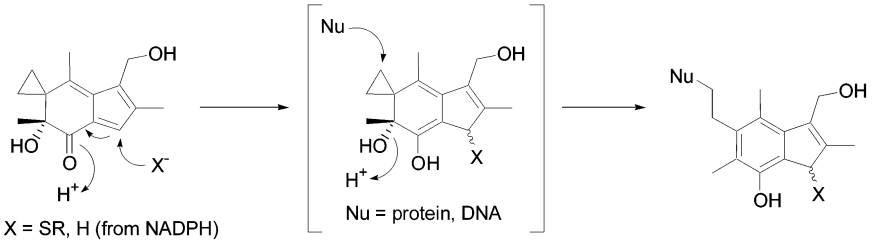

TABLE 1. Comparison of Toxicity of (−)-Acylfulvene with (+)-Acylfulvene and (−)-Irofulven with (+)-Irofulven in MV 522 Adenocarcinoma Cells[a]

	2 h	48 h
(−)-acylfulvene	300 ± 50	350 ± 20
(+)-acylfulvene	1700 ± 600	1900 ± 300
(−)-irofulven	200 ± 20	170 ± 20
(+)-irofulven	1300 ± 400	900 ± 200

[a] IC_{50} values (nM) after 2 h and 48 h exposure to compounds. IC_{50} is the concentration of the fulvene at which 50% inhibition occurred in the Trypan blue assay (48 h) or 50% inhibition of thymidine incorporation into cellular DNA (in the 2 h assay).

acylfulvene enantiomers were converted to the corresponding (−)-irofulven and (+)-irofulven via the known method.[2]

Biological Activity

The mechanism of action of irofulven is thought to involve an activation step in which nucleophilic attack on the α,*β*-unsaturated ketone by thiol or NADPH (Scheme 4) leads to a highly reactive intermediate.[13] Opening of the cyclopropane ring, accompanied by loss of the tertiary hydroxyl, results in alkylation of protein and DNA.[14] It was of interest to determine if the stereochemistry of the tertiary hydroxyl was critical to the hypothesized activation step or to the alkylation step. Therefore the toxicity of (+)-acylfulvene and (+)-irofulven against a lung adenocarcinoma cell line MV522 was compared to that of their (−)-enantiomers. The results are shown in Table 1.

IC_{50} values were obtained for 2 and 48 h exposure times. Previous studies have shown that sensitive cell lines possess an energy-dependent transport mechanism for taking up the drug. This results in toxicity at 2 h being comparable to that after 48 h. In nonsensitive cells toxicity at 2 h is less than that at 48 h.[15]

(+)-Acylfulvene was about 6 to 5 times less toxic than (−)-acylfulvene after 2 or 48 h, respectively. Likewise, (+)-irofulven was about 6 to 5 times less toxic than (−)-irofulven after 2 or 48 h of exposure. Thus the (+)-enantiomers do possess inherent toxicity, which, though comparatively low, cannot be attributed to contamination by the (−)-enantiomers. The difference in toxicity can possibly be explained by differences in either the activation rate or the rate of the alkylation. The former would appear to be more likely since the activated intermediate is so unstable. One might thus conclude that the stereochemistry of the tertiary hydroxyl does play a role in the enzyme-catalyzed activation step.

It is interesting to note that an NADPH-dependent alkenone oxidoreductase (AOR) enzyme has been reported to reduce the α,*β*-unsaturated ketone of irofulven.[16] This follows our earlier report of a similar reduction by a cytosolic NADPH enzyme.[13] Human embryonic kidney cells that overexpress AOR are 20-fold more sensitive to irofulven-induced cytotoxicity than control cells.[16]

Experimental Section

Compound 7. A solution of **6**[17] (550 mg, 4.21 mmol) in CH_2Cl_2 (12 mL) was added dropwise over a period of 40 min to a refluxing solution of (+)-**5**[7] (98% ee, 1.31 g, 10.0 mmol), rhodium(II) acetate (39 mg), and DMF (125 μL) in CH_2Cl_2 (12 mL). The solution was refluxed for an additional 20 min, then concentrated and chromatographed (10:3 hexanes−ethyl acetate) to give 452 mg of **7** (54%) and 167 mg of **8** (20%) as white solids.

Major diastereomer (**7**): $[\alpha]^{25}_D$ −85.0 (*c* 19.5 mg/mL, $CHCl_3$); mp 141−2 °C; ^{1}H NMR ($CDCl_3$) *δ* 0.72−0.78 (m, 1H), 1.03−1.10 (m, 1H), 1.15−1.21 (m, 1H), 1.36−1.42 (m, 4H), 1.61 (s, 3H), 2.33 (dd, *J* = 7.8, 13.8 Hz, 1H), 2.64 (dd, *J* = 8.8, 14.0 Hz, 1H), 2.76 (d, *J* = 8.4 Hz, 1H), 2.85 (q, *J* = 8.1 Hz, 1H), 4.35 (s, 1H); ^{13}C NMR ($CDCl_3$) *δ* 12.2, 13.6, 15.0, 27.5, 38.5, 39.9, 42.1, 54.5, 69.1, 84.9, 88.2, 208.7, 211.2; IR (NaCl, thin film) 3001, 2978, 1759, 1454 cm^{-1}; MS (DEI) *m*/*z* (% rel intensity) 256 (M^+ + 2, 6), 254 (M^+, 18), 225 (99), 197 (56), 124 (100), 43 (48); HRMS for $C_{13}H_{15}ClO_3$ calcd 254.0710, found 254.0718. The relative configuration was confirmed by X-ray crystallography.[8]

Minor diastereomer (**8**): $[\alpha]^{25}_D$ −121.3 (*c* 20.3 mg/mL, $CHCl_3$); mp 131−2 °C; ^{1}H NMR ($CDCl_3$) *δ* 0.74−0.80 (m, 1H), 1.02−1.09 (m, 1H), 1.17−1.23 (m, 1H), 1.34−1.40 (m, 4H), 1.63 (s, 3H), 1.93 (dd, *J* = 8.6, 14.8 Hz, 1H), 2.71 (dd, *J* = 7.8, 15.0 Hz, 1H), 3.00−3.12 (m, 2H), 4.28 (s, 1H); ^{13}C NMR ($CDCl_3$) *δ* 12.1, 13.6, 14.8, 22.7, 39.5, 39.6, 41.5, 54.1, 71.2, 83.9, 87.6, 206.0, 211.2; IR (NaCl, thin film) 2988, 1749, 1445 cm^{-1}; MS (DEI) *m*/*z* (% rel intensity) 256 (M^+ + 2, 12), 254 (M^+, 36), 225 (79), 191 (50), 124 (100), 43 (41); HRMS for $C_{13}H_{15}ClO_3$ calcd 254.0710, found 254.0716.

Compound 9. To a solution of **7** (972 mg, 3.82 mmol) in 90% 2-propanol (250 mL) was added K_2CO_3 (3.75 g) at room temperature. The mixture was stirred for 6 h then poured into a mixture of ethyl acetate and water. The aqueous layer was extracted with ethyl acetate and the combined organic layers were washed with brine and dried with $MgSO_4$. The solvent

(12) The optical rotation of the synthetic sample **3** compares with that of a naturally derived authentic sample: $[\alpha]^{25}_D$ −494.2 (*c* 2.9 mg/mL, EtOH). This value differs from the value reported in ref 2.

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was evaporated and the crude product chromatographed (10:3 hexanes−ethyl acetate) to give 681 mg of **9** (70%) as a white solid: $[\alpha]^{25}_D$ −23.8 (*c* 10.4 mg/mL, ethyl acetate); mp 140−1 °C; ^{1}H NMR ($CDCl_3$) δ 1.25−1.34 (m, 1H), 1.40−1.50 (m, 1H), 1.65 (s, 3H), 1.71−1.80 (m, 1H), 1.92−2.00 (m, 1H), 2.06 (d, J = 2.8 Hz, 3H), 2.38 (dd, J = 7.2, 12.8 Hz, 1H), 2.48 (br, 1H), 2.66 (t, J = 12.1 Hz, 1H), 3.09−3.21 (m, 1H), 4.03 (d, J = 2.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 12.7, 19.7, 22.6, 26.9, 32.9, 37.7, 38.4, 70.9, 71.8, 123.7, 153.1, 198.1, 204.6; IR (NaCl, thin film) 3421, 2922, 1714, 1698, 1613, 1464 cm^{-1}; MS (DEI) *m*/*z* (% rel intensity) 256 (M^+ + 2, 4), 254 (M^+, 12), 218 (23), 161 (100), 91 (62), 77 (53); HRMS for $C_{13}H_{15}ClO_3$ calcd 254.0710, found 254.0710; UV λ_{max} (EtOH) 279 nm (ϵ 11 130).

Compound 10. To a solution of **9** (450 mg, 1.52 mmol) in acetic anhydride (15 mL) was added 0.6 mL of pyridine at room temperature. The solution was stirred for 2 h then poured into water. $NaHCO_3$ was then added until bubbling ceased. The aqueous layer was extracted with ethyl acetate and the combined organic layers were washed with saturated $NaHCO_3$ solution and brine. The solution was dried with $MgSO_4$ and concentrated. The crude product was chromatographed (10:3 hexanes−ethyl acetate) to give 473 mg of **10** (90%) as a white solid: $[\alpha]^{25}_D$ −19.4 (*c* 14.6 mg/mL, $CHCl_3$); mp 143−5 °C; ^{1}H NMR ($CDCl_3$) δ 1.26−1.40 (m, 2H), 1.63 (s, 3H), 1.67−1.73 (m, 1H), 1.98−2.04 (m, 1H), 2.04 (d, J = 2.8 Hz, 3H), 2.08 (s, 3H), 2.24 (t, J = 12.0 Hz, 1H), 2.43 (dd, J = 7.2, 12.8 Hz, 1H), 3.18−3.26 (m, 1H), 5.19 (d, J = 3.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 13.8, 20.1, 22.1, 23.6, 27.9, 35.0, 38.9, 39.9, 71.8, 72.9, 125.2, 154.5, 170.7, 198.7, 201.3; IR (NaCl, thin film) 2984, 1749, 1716, 1704, 1612, 1439 cm^{-1}; MS (DEI) *m*/*z* (% rel intensity) 299 (MH^+ + 2, 1), 297 (MH^+, 3), 236 (20), 201 (100), 173 (21), 161 (37) 43 (73); HRMS for $C_{15}H_{18}ClO_4$ (MH^+) calcd 297.0893, found 297.0881.

Compound 11. To a solution of **10** (477 mg, 1.62 mmol) in THF (40 mL) was added a solution of MeMgCl (3.0 M in THF, 2.25 mL, 6.75 mmol) at −78 °C. The solution was stirred for 2 h, warmed to 0 °C, stirred for an additional 2 h, and then quenched with saturated NH_4Cl solution. The aqueous layer was extracted with ethyl acetate and the combined organic layers were washed with brine and dried with $MgSO_4$. The solvent was evaporated and the crude product chromatographed (2:1 hexanes−ethyl acetate) to give 377 mg of **11** (87%) as a colorless gum: $[\delta]^{25}_D$ −19.2 (*c* 12.4 mg/mL, ethyl acetate); ^{1}H NMR ($CDCl_3$) δ 0.88−0.95 (m, 1H), 0.98−1.09 (m, 2H), 1.20 (s, 3H), 1.24−1.31 (m, 1H), 1.66 (s, 3H), 1.94 (d, J = 2.0 Hz, 3H), 2.34−2.47 (m, 2H), 2.92−3.00 (m, 1H), 3.70 (d, J = 3.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 6.4, 12.5, 13.1, 24.7, 26.7, 29.9, 38.6, 40.1, 70.5, 71.4, 73.4, 123.5, 156.2, 198.7; IR (NaCl, thin film) 3528, 3397, 3009, 2975, 2927, 1706, 1604, 1439 cm^{-1}; MS (DEI) *m*/*z* (% rel intensity) 272 (M^+ + 2, 2), 270 (M^+, 5), 235 (22), 217 (25), 189 (28), 133 (30), 91 (32), 43 (100); HRMS for $C_{14}H_{19}ClO_3$ calcd 270.1023, found 270.1019.

Compound 12. To a solution of **11** (120 mg, 0.443 mmol) and *p*-TsOH (20 mg) in DMF (3 mL) was added 2,2-dimethoxypropane (500 μL, 4.07 mmol) at room temperature. The solution was stirred for 25 h, and then quenched with saturated $NaHCO_3$ solution. The aqueous layer was extracted with ether and the combined organic layers were washed with water and brine. The solution was dried with $MgSO_4$ and concentrated. The crude product was chromatographed (5:1 hexanes−ethyl acetate) to give 115 mg of **12** (83%) as a white solid: $[\alpha]^{25}_D$ +50.0 (*c* 12.9 mg/mL, $CHCl_3$); mp 128 °C dec; ^{1}H NMR ($CDCl_3$) δ 0.44−0.50 (m, 1H), 0.95−1.02 (m, 1H), 1.13−1.20 (m, 4H), 1.22 (s, 3H), 1.29−1.36 (m, 4H), 1.59 (s, 3H), 2.06 (d, J = 2.0 Hz, 3H), 2.39 (dd, J = 7.6, 12.8 Hz, 1H), 2.52 (t, J = 11.4 Hz, 1H), 2.71−2.79 (m, 1H), 4.20 (d, J = 2.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 9.1, 13.9, 14.3, 23.5, 27.2, 27.4, 27.6, 32.6, 39.8, 71.5, 82.6, 83.3, 108.6, 126.3, 158.1, 198.8; IR (NaCl, thin film) 2985, 2881, 1715, 1631, 1439 cm^{-1}; MS (DCI/NH_3) *m*/*z* (% rel intensity) 313 (MH^+ + 2, 4), 311 (MH^+, 13), 277 (100); HRMS for $C_{17}H_{24}ClO_3$ (MH^+) calcd 311.1414, found 311.1423. The absolute configuration was confirmed by X-ray crystallography.

Compound 14. To a solution of **12** (400 mg, 1.29 mmol) in benzene (15 mL) was added DBU (400 μL, 2.67 mmol) at room temperature. The mixture was stirred for 1.75 h, during which time a white precipitate formed. The reaction was quenched with acetic acid (0.5 mL) and the mixture added to water. The aqueous layer was extracted with ether and the combined organic layers were washed with water and brine. The solution was dried with $MgSO_4$ and concentrated to give 317 mg of **13** and **14** in a 13:1 ratio as a pale yellow liquid. Exocyclic double bond isomer (**13**): ^{1}H NMR ($CDCl_3$) δ 0.37−0.43 (m, 1H), 0.90−0.97 (m, 1H), 1.07−1.13 (s, 3H), 1.15 (s, 3H), 1.20 (s, 3H), 1.24−1.33 (m, 1H), 1.34 (s, 3H), 2.14 (d, J = 1.6 Hz, 3H), 2.75−2.86 (m, 3H), 4.23 (d, J = 2.4 Hz, 1H), 5.33−5.37 (m, 1H), 6.00−6.04 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 7.9, 12.6, 14.4, 23.1, 27.2, 27.6, 28.0, 32.5, 36.3, 83.5, 85.2, 108.5, 116.9, 133.0, 147.5, 154.6, 193.2; IR (NaCl, thin film) 2984, 1694, 1623, 1433 cm^{-1}; MS (20 eV) *m*/*z* (% rel intensity) 274 (M^+, 29), 259 (14), 216 (60), 201 (100), 187 (28), 173 (58), 159 (26), 145 (24); HRMS for $C_{17}H_{22}O_3$ calcd 274.1569, found 274.1571.

The crude mixture of **13** and **14** was dissolved in 95% ethanol (35 mL) to which $RhCl_3 \cdot 3H_2O$ (30.5 mg, 0.116 mmol) was added. The mixture was refluxed at 90 °C for 20 min then diluted with ether. The solid was filtered off and the filtrate concentrated. The crude product was chromatographed (5:1 hexanes−ethyl acetate) to give 213 mg of endocyclic double bond isomer **14** (62%) as a pale yellow liquid, which solidified upon freezing: $[\alpha]^{25}_D$ +121.8 (*c* 10.7 mg/mL, $CHCl_3$); mp 64−66 °C; ^{1}H NMR ($CDCl_3$) δ 0.38−0.45 (m, 1H), 0.84−0.92 (m, 1H), 1.02−1.08 (m, 1H), 1.166 (s, 3H), 1.173 (s, 3H), 1.20−1.26 (m, 1H), 1.34 (s, 3H), 1.87 (s, 3H), 2.10 (s, 3H), 3.22 (br s, 1H), 4.42 (d, J = 2.8 Hz, 1H), 6.97 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 7.0, 11.3, 12.5, 14.0, 23.3, 27.1, 27.5, 31.6, 42.5, 83.0, 86.3, 109.3, 130.6, 145.9, 146.4, 148.4, 195.9; IR (NaCl, thin film) 2984, 2934, 2874, 1686, 1650, 1632, 1452, 1440 cm^{-1}; MS (20 eV) *m*/*z* (% rel intensity) 274 (M^+, 46), 259 (15), 216 (82), 201 (50), 173 (77), 159 (40), 146 (52), 109 (100); HRMS for $C_{17}H_{22}O_3$ calcd 274.1569, found 274.1569.

Compound 15. A solution of **14** (127 mg, 0.541 mmol) in 80% acetic acid (45 mL) was heated at 90 °C for 2 h. The solution was poured into saturated $NaHCO_3$ solution and extracted with ethyl acetate. The combined organic layers were washed with water and brine then dried with $MgSO_4$. The crude product was chromatographed (1:1 hexanes−ethyl acetate) to give 84 mg of **15** (78%) as a white solid: $[\alpha]^{25}_D$ −246.6 (*c* 9.7 mg/mL, ethyl acetate); mp 131−2 °C; ^{1}H NMR ($CDCl_3$) δ 0.80−1.10 (m, 3H), 1.18−1.24 (m, 1H), 1.26 (s, 3H), 1.60 (br, 1H), 1.85 (s, 3H), 1.95 (s, 3H), 2.30 (br, 1H), 3.54 (br s, 1H), 3.94 (d, J = 4.8 Hz, 1H), 7.08 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 6.6, 11.2, 11.3, 11.7, 25.0, 29.9, 44.2, 71.5, 74.6, 126.4, 145.8, 147.1, 147.6, 195.0; IR (NaCl, thin film) 3439, 1666, 1632, 1612 cm^{-1}; MS (20 eV) *m*/*z* (% rel intensity) 234 (M^+, 51), 216 (35), 201 (31), 173 (82), 159 (63), 145 (71), 43(100); HRMS for $C_{14}H_{18}O_3$ calcd 234.1256, found 234.1257; UV λ_{max} (EtOH) 286 nm (ϵ 11 396).

Compound 16.[5] To a mixture of **15** (9.0 mg, 38.4 μmol) and CH_2Cl_2 (0.5 mL) at −78 °C was added DIBALH (1.5 M in toluene, 150 μL, 225 μmol) slowly dropwise. The mixture was stirred for 30 min then quenched with methanol (0.1 mL). Potassium sodium tartrate solution (5%) was then added and the mixture extracted with ethyl acetate. The combined organic layers were washed with water and brine then dried with $MgSO_4$. The crude product was chromatographed (5:1 hexanes−ethyl acetate) to give 4.1 mg of **16** (49%) as a yellow gum: $[\alpha]^{25}_D$ −13.2 (*c* 1.7 mg/mL, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.80−1.05 (m, 3H), 1.15 (s, 3H), 1.20−1.28 (m, 1H), 1.61 (d, J = 7.8 Hz, 1H), 1.84 (s, 3H), 2.06 (d, J = 1.2 Hz, 3H), 2.85 (s, 1H), 4.32 (d, J = 7.8 Hz, 1H), 6.07 (t, J = 1.6 Hz, 1H), 6.33 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 6.5, 13.1, 15.8, 16.3, 23.3, 29.8, 72.4, 73.0, 114.2, 130.8, 133.0, 138.2, 141.5, 150.7; IR (NaCl, thin

film) 3407, 2973, 2926, 1629, 1445 cm^{-1}; MS (20 eV) *m*/*z* (% rel intensity) 234 (M^+, 51), 216 (35), 201 (31), 173 (82), 159 (63), 145 (71), 43 (100); HRMS for $C_{14}H_{18}O_2$ calcd 218.1307, found 218.1310.

(−)-Acylfulvene (3). To a solution of **16** (15.0 mg, 64.4 μmol) in DMSO (1.0 mL) was added IBX (29.6 mg, 0.105 mmol) at room temperature. The mixture was stirred for 2 h then diluted with water. The aqueous layer was extracted with ethyl acetate and the combined organic layers were washed with water and brine. The solution was dried with $MgSO_4$ and the crude product chromatographed (10:1 hexanes−ethyl acetate) to give 7.8 mg of **3** (53%) as an orange gum: $[\alpha]^{25}_D$ −493.4 (*c* 2.1 mg/mL, EtOH);[11] ^{1}H NMR ($CDCl_3$) δ 0.68−0.75 (m, 1H), 1.04−1.11 (m, 1H), 1.24−1.33 (m, 1H), 1.38 (s, 3H), 1.48−1.56 (m, 1H), 2.00 (s, 3H), 2.15 (s, 3H), 3.92 (br s, 1H), 6.43 (s, 1H), 7.17 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 9.9, 14.6, 15.4, 17.1, 28.0, 37.4, 76.4, 120.7, 126.4, 136.1, 140.6, 142.6, 158.5, 197.9; IR (NaCl, thin film) 3420, 1641 cm^{-1}; MS (20 eV) *m*/*z* (% rel intensity) 216 (M^+, 58), 201 (21), 188 (54), 173 (71), 159 (26), 145 (42), 43 (100); HRMS for $C_{14}H_{16}O_2$ calcd 216.1150, found 216.1148.

The enantiomer, (+)-acylfulvene, was prepared in the same manner: $[\alpha]^{25}_D$ +476.0 (*c* 6.6 mg/mL, EtOH).

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Supporting Information Available: ^{1}H NMR spectra of compounds **7**−**16**, **3**, and **4**, and X-ray data for **7** and **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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