7476-11-1; 1,1,3,3-tetraphenyl-2-propanone (metalation product), 109283-56-9; *p*-methylacetophenone, 122-00-9; *p*-methylacetophenone (metalation product), 54731-27-0; 2,2-diphenylethanal, 947-91-1; 2,2-diphenylethanal (metalation product), 107365-24-2; phenylacetonitrile, 140-29-4; phenylacetonitrile (metalation product), 17983-40-3; *tert*-butyl acetate, 540-88-5; ethyl phenylacetate, 101-97-3; ethyl phenylacetate (metalation product), 31491-20-0; ethyl dithioacetate, 870-73-5; ethyl dithioacetate (metalation product), 109283-57-0; dimethyl sulfoxide, 67-68-5; 3-ethyl-3-pentanol, 597-49-9; 3-ethyl-3-pentanol (metalation product), 6689-17-4; 4-methyl-2-pentanone, 108-10-1; 4-methyl-2-pentanone (metalation product), 2346-32-9; 4-methyl-2-pentanone (reduction product), 109283-58-1; cyclohexanone, 108-94-1; cyclohexanone (metalation product), 6651-36-1; cyclohexanone (reduction product), 13871-89-1; 2-methylcyclohexanone, 583-60-8; 2-methylcyclohexanone (reduction product), 109283-59-2; *d*-(+)-camphor, 464-49-3; *d*-(+)-camphor (metalation product), 70982-26-2; *d*-(+)-camphor (reduction product), 74472-21-2; methyl cyclopropyl ketone, 765-43-5; methyl cyclopropyl ketone (metalation product), 42161-96-6; methyl cyclopropyl ketone (reduction production), 85696-56-6; phenyl propyl ketone, 495-40-9; phenyl propyl ketone (metalation product), 84839-88-3; phenyl propyl ketone (reduction product), 72812-50-1; octanal, 124-13-0; octanal (metalation product), 70109-89-6; octanal (reduction product), 14246-16-3; cyclohexanaldehyde, 2043-61-0; cyclohexanaldehyde (metalation product), 53282-55-6; cyclohexanaldehyde (reduction product), 88773-80-2; *trans*-1-phenyl-1-buten-3-one, 1896-62-4; *trans*-1-phenyl-1-buten-3-one (metalation product), 61140-47-4; *trans*-1-phenyl-1-buten-3-one (reduction product), 76987-16-1; benzophenone, 119-61-9.

Synthesis of the Oudemansins, Naturally Occurring β-Methoxyacrylates from Basidomycetes

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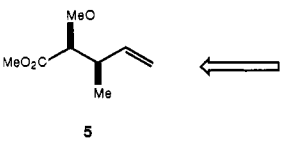
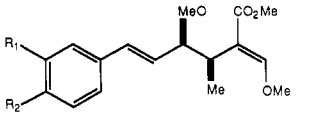
Short, stereocontrolled syntheses of the antifungal metabolites oudemansins A (**1**) and B (**2**) from a common precursor (**5**) are described. Stereospecific olefination of **5** via the β-keto phosphine oxides **12** and **21** affords dienes (*E*)-**7** and (*E*)-**22**, which are transformed to the corresponding styryl esters **14** and **23**. Introduction of the β-methoxyacrylate group by acylation of **14** and **23** with *N*-formylimidazole affords the title compounds exclusively.

Studies of basidomycetes have resulted in the identification of novel metabolites with a broad spectrum of biological activities.[1] Recently, Steglich and co-workers reported the isolation and characterization of four structurally related antibiotics, oudemansins A (**1**)[2] and B (**2**)[3] from mycelial cultures of *Oudemansiella mucida* and strobilurins A (**3**) and B (**4**) from cultures of *Strobilurus tenacellus*.[4] These compounds exhibit antifungal and antibiotic activity and inhibit eukaryotic respiration by blocking cytochrome b–c_1 electron transfer, an activity attributed to the presence of the characteristic β-methoxyacrylate group.[5] This novel biological activity has fostered interest in the oudemansins as synthetic targets, and several routes to oudemansin A have been recorded.[6]

An analysis of the structures of oudemansins A and B suggests that the requisite (*E*)-styryl- and β-methoxyacrylate groups of each could be derived by selective transformation of the terminal functionality of a common synthetic intermediate, ester **5**. This approach has the advantage of allowing a straightforward preparative route to analogues differing at either the styryl or acrylate unit and would facilitate an evaluation of the role of these groups in the biological activity of the parent compounds.

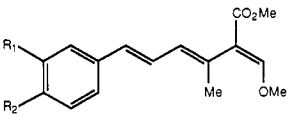


5



1; R_1=R_2=H, oudemansin A

2; R_1=OCH_3, R_2=Cl, oudemansin B



3; R_1=R_2=H, strobilurin A

4; R_1=OCH_3, R_2=Cl, strobilurin B

Our synthetic plan called for initial introduction of the styryl subunit followed by elaboration of the sensitive acrylate system. Herein we detail our studies on the synthesis of the oudemansins, which have resulted in expedient, stereocontrolled routes to **1** and the previously unprepared **2**.[7]

Results and Discussion

Early attempts at introduction of the (*E*)-styryl group of the oudemansins were frustrated by our inability to control the olefin geometry using standard olefination

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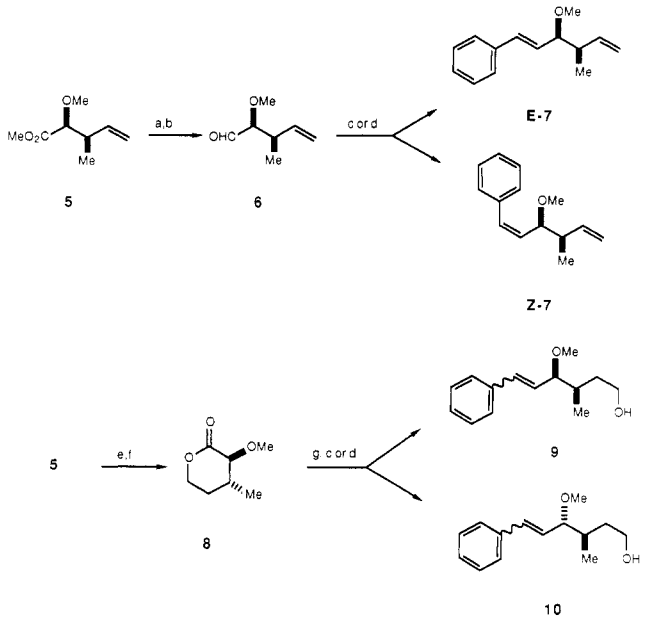
0022-3263/87/1952-4303$01.50/0

Table I. Stereochemistry of Styrene Formation

substrate	reagent	conditions	product	$E:Z^a$
6	Ph_3PCH_2Ph Br	*n*-BuLi, THF, 0 °C	7	2:1 (N)
8	Ph_3PCH_2Ph Br	*n*-BuLi, THF, reflux	9, 10	10:1 (G)[b]
8	Ph_3PCH_2Ph Br	KH, DMSO, reflux	9, 10	>40:1 (G)[b]
6	$(EtO)_2P(O)CH_2Ph$	*t*-BuOK, THF, 25 °C	7	2.5:1 (N)
6	$(EtO)_2P(O)CH_2Ph$	*t*-BuOK, THF, HMPA	7	3:1 (N)
6	$(EtO)_2P(O)CH_2Ph$	KHMDS, THF, 0 °C	7	2:1 (N)
6	$(EtO)_2P(O)CH_2Ph$	KHMDS, THF, −40 °C	7	1.5:1 (N)
8	$(EtO)_2P(O)CH_2Ph$	KH, THF, 80 °C	9, 10	3:1 (N)[b]
5	$Ph_2P(O)CH_2Ph$	*n*-BuLi, THF, −78 °C	7	>100:1 (G, N)
8	$Ph_2P(O)CH_2Ph$	*n*-BuLi, THF, −78 to 0 °C	c	

[a] Ratios determined by GC (G) or 500-MHz NMR (N). [b] Products are epimeric mixtures at C_3. [c] No olefin products were obtained in this reaction.

Scheme I[a]



[a] Reagents: (a) $LiAlH_4$, Et_2O, 0 °C; (b) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, −78 °C; (c) $Ph_3P^+CH_2Ph^-Br$, *n*-BuLi, THF; (d) $(EtO)_2POCH_2Ph$, KH, THF; (e) 9-BBN, then aqueous H_2O_2, NaOH; (f) TsOH, CH_2Cl_2; (g) DIBAL, toluene, 0 °C.

procedures (Scheme I). Ester **5**, available as a 7:1 mixture of syn:anti diastereomers[8] was transformed to the corresponding aldehyde **6** by reduction and reoxidation using the Swern[9] conditions. No effort was made at this juncture to separate the anti diastereomer, as this minor contaminant could be conveniently removed at a later synthetic stage. Attempts to convert **6** to the desired diene (*E*)-**7** by using Wittig or Emmons–Horner conditions invariably led to a mixture of *E* and *Z* products (Table I). Alternatively, hydroboration[10] of **5** followed by acid-catalyzed lactonization afforded *O*-methyl verrucarinolactone, **8**. Interestingly, the material obtained from this sequence was diastereomerically pure, indicating a kinetic preference for lactonization of the syn γ-hydroxy ester derived from **5** (relative to the anti ester resulting from hydroboration of the minor anti contaminant). Reduction of **8** to the lactol and attempted olefination again yielded mixtures of *E* and *Z* dienes **9**; as an added complication, significant epimerization at the C_2 methoxy center was observed in these reactions, presumably a result of intramolecular proton abstraction by the γ-alkoxy substituent.

Table II. Hydride Reduction of β-Keto Phosphine Oxide 12

conditions	ratio (*E*)-**7**/(*Z*)-**7**[a]	yield,[b,c] %
$NaBH_4$, EtOH, 25 °C, 48 h	>100:1	15%
$NaBH_4$, EtOH, 50 °C, 4 h	3.9:1	33
$LiAlH_4$, THF, −78 to 0 °C, 1 h	3.6:1	60
i-Bu_2AlH, toluene, −20 °C[d]	11.9:1	10
$LiBH_4$, THF, 0–25 °C, 12 h	>100:1	61

[a] Ratios determined by gas chromatography; limits of detection 100:1. [b] Based on crude **12**. [c] Combined yield for chromatographed olefin isomers. [d] Intermediate β-hydroxy phosphine oxide was treated with NaH (THF, 25 °C) to effect conversion to **7**.

A more satisfactory solution to the problem of introduction of the styryl unit utilizes the olefination procedure of Warren.[11] Lithiation of phosphine oxide **11**[12] and addition to ester **5** gave the β-keto phosphine oxide **12** (Scheme II). Reduction of **12** with hydride reagents affords diene mixtures in which the desired *E* isomer predominates. In our hands, superior *E*:*Z* ratios were obtained with borohydride reagents (Table II) which provide olefin (*E*)-**7** as the only detectable isomer, albeit in rather low yield (32% from **5** for $LiBH_4$). In view of the reported stability of β-phosphino lithium alkoxides,[11] the isolation of olefinic products directly from reduction of **12** with hydride reagents was somewhat surprising.[13] Of the hydride reagents examined, only diisobutylaluminum hydride afforded an intermediate β-hydroxy phosphine oxide.

With the (*E*)-styryl unit in place, we turned our attention to introduction of the sensitive β-methoxyacrylate group. Hydroboration of diene (*E*)-**7** afforded alcohol **13**; at this stage, the anti diastereomer (carried over from **5**) was conveniently removed by flash chromatography.[14] Oxidation of **13** with Jones reagent and treatment with diazomethane afforded methyl ester **14**. The literature procedure for formylation of **14** by acylation of the enolate with methyl formate[6b] was a capricious reaction in our hands, affording only low yields of the acylated product. In contrast, generation of the dianion[15] of acid **15** (2 equiv of *t*-BuLi) followed by treatment with methyl formate and dimethyl sulfate afforded a mixture consisting predominantly (52%) of (*Z*)-acrylate **16**,[16] accompanied by small

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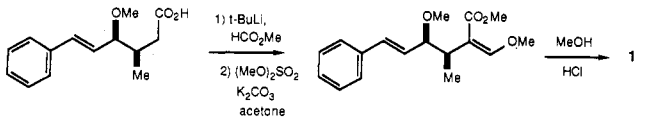
(16) Physical and spectral data for **16** were identical with literature values; see ref 6b.



15 16

amounts (<3%) of the desired **1**. Exposure of this mixture to acidic methanol results in the rapid isomerization[17] of the undesired *E* isomer to give **1** as the only product (37% from **15**). A more direct route to **1** consisted of acylation of the enolate of **14** with *N*-formylimidazole[18] followed by *O*-alkylation of the resulting β-formyl ester with K_2CO_3/dimethyl sulfate[6e] to give **1** in 57% yield from **14**. Although the yield for the conversion of **14** to **1** is somewhat low, we note that the above procedure represents a significant improvement over previous reports for this conversion.[6b,e]

For our synthesis of the previously unprepared oudemansin B, **2**, we required the functionalized phosphine oxide **17**. We were able to prepare **17** directly by a modified Arbuzov procedure[12] using ethyl diphenylphosphinite and 5-(bromomethyl)-2-chloroanisole in refluxing THF. This procedure is a convenient, high-yielding method for preparing substituted phosphine oxides which contain functionality incompatible with conditions for metalation and/or oxidation. With phosphine oxide **17** in hand, the synthesis of **2** was carried out essentially as described above for oudemansin A. Lithiation of **17** and addition to **5** gave β-keto phosphine oxide **21**, which was reduced with $LiBH_4$ to give diene (*E*)-**22**. Hydroboration afforded alcohol **23** which was subjected to oxidation and esterification to give **24**. Acylation of **24** using the *N*-formylimidazole protocol gave, as the only product, oudemansin B, **2**. Both synthetic oudemansins **1** and **2** exhibited physical and spectral properties in excellent agreement with reported data for the natural[2,3] and synthetic[6] material.

Our synthesis of oudemansins A and B from common glycolate Claisen product **5** demonstrates the utility of this and related substrates for selective development at either the carboxylic or olefinic terminus. The procedures reported herein for stereoselective development of the styryl and β-alkoxy acrylate groups of the oudemansins should be applicable to the synthesis of other members of this class of antibiotics. Finally, the brevity of our synthetic route and the availability of starting ester **5** in quantity is expected to facilitate the preparation of analogues at both the aromatic and acrylate sites, in order to define structure–activity and mechanistic relationships for the oudemansins and related compounds. These studies are in progress and will be reported in due course.

Experimental Section

Melting points were determined on a Thomas Hoover Unimelt capillary melting apparatus. Nuclear magnetic resonance spectra were determined on a General Electric GN-500 or a Bruker WM-360 spectrometer. All NMR spectra were recorded in $CDCl_3$ solvent with tetramethylsilane as an internal reference. IR spectra were recorded on a Beckman IR 4220. Gas chromatographic analyses were performed on a Varian 3700 equipped with thermal conductivity detectors and 10-m OV-225 (10%) or Carbowax 20 M (10%) columns. High-pressure liquid chromatographic analyses were performed on an IBM 934 ternary system equipped with an IBM 250 × 10 mm silica gel column. Elemental analyses were performed by E + R Microanalytical Laboratory, Inc., Corona, NY.

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(*E*)-(3*S,4*R**)-3-Methoxy-4-methyl-1-phenylhexa-1,5-diene ((*E*)-7).** To a solution of ester **5**[8] (7:1 mixture with anti diastereomer, 156 mg, 0.986 mmol) and $MgBr_2{\cdot}Et_2O$ (258 mg, 1.00 mmol) in THF (10 mL) at −78° C was added a solution of benzyl diphenylphosphine oxide[12] (568 mg, 1.94 mmol) and *n*-BuLi (0.75 mL, 2.5 M in hexane, 1.87 mmol) in THF (10 mL) over a 30-min period. The reaction was quenched with water (5 mL), diluted with ether, and washed with brine (20 mL). The organic fraction was dried (Na_2SO_4) and the solvent was evaporated in vacuo to give β-keto phosphine oxide **12** as a white solid.

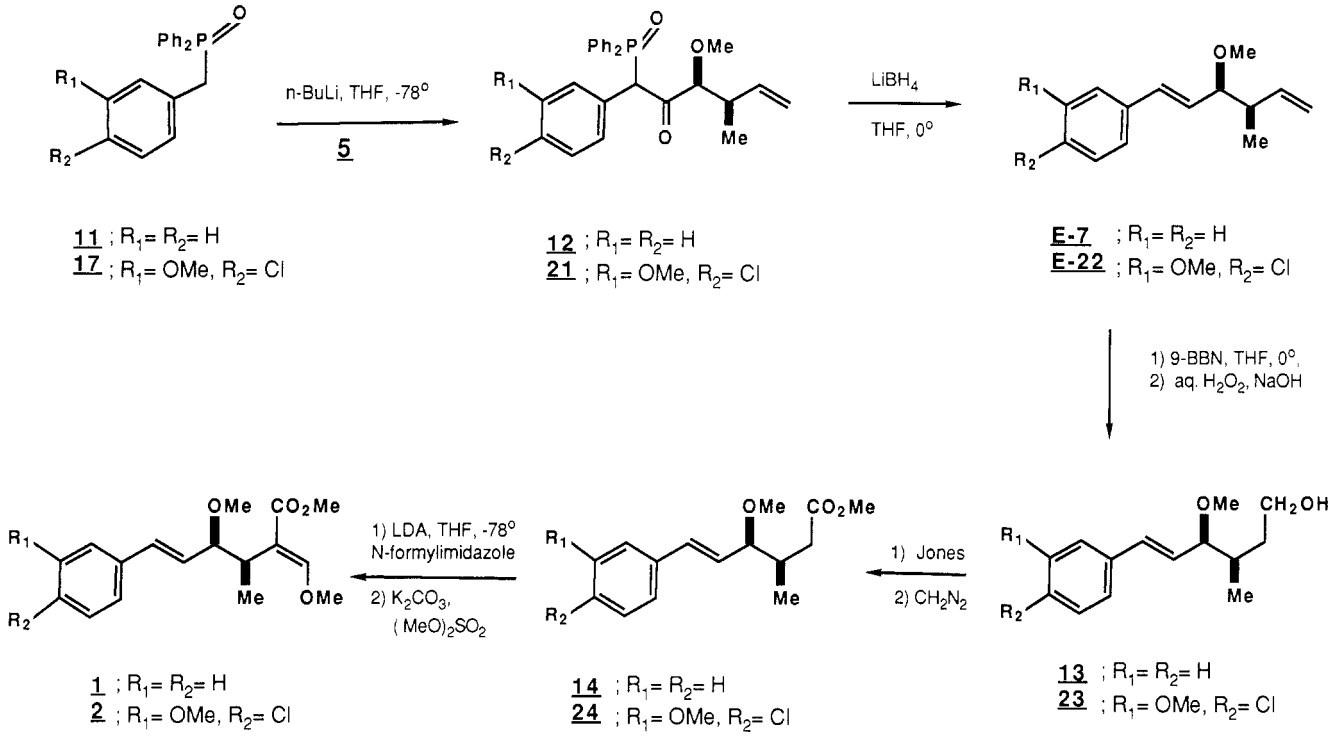
Without further purification, the crude **12** was dissolved in 10 mL of THF and added to a solution of $LiBH_4$ (267 mg, 12.3 mmol) in THF (10 mL) at 0 °C, and the mixture was allowed to warm to ambient temperature overnight. The reaction was quenched with 15% NaOH (10 mL) and extracted with ether (2 × 10 mL). The ether fractions were dried ($MgSO_4$), evaporated in vacuo, and chromatographed on silica gel (20:1 pentane/ether) to yield a 7:1 mixture of (*E*)-**7** (64 mg 32%) and its anti diastereomer as a clear oil. An analytical sample of (*E*)-**7** was prepared by preparative HPLC and bulb-to-bulb distillation (120 °C, 15 mmHg): IR (neat oil) 1090 cm^{-1}; ^1H NMR (500 MHz) δ 7.39 (d, *J* = 7.4 Hz, 2 H), 7.31 (t, *J* = 7.4 Hz, 2 H), 7.24 (t, *J* = 7.4 Hz, 1 H), 6.51 (d, *J* = 15.9 Hz, 1 H), 6.05 (dd, *J* = 15.9, 8.1 Hz, 1 H), 5.86 (m, 1 H), 5.07 (m, 2 H), 3.56 (dd, *J* = 8.1, 5.8 Hz, 1 H), 3.32 (s, 3 H), 2.49 (m, 1 H), 1.07 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (125.8 MHz) δ 140.2, 136.6, 133.2, 128.5, 128.2, 127.6, 126.5, 114.7, 86.3, 56.6, 42.5, 15.6. Anal. Calcd for $C_{14}H_{18}O$; C, 83.12; H, 8.97. Found: C, 83.05; H, 8.96.

(*E*)-(3*R,4*S**)-4-Methoxy-3-methyl-6-phenylhex-5-enol (13).** To a solution of (*E*)-**7** (82 mg, 0.40 mmol) in THF (10 mL) at 0 °C was added 9-BBN (4.9 mL, 0.5 M in THF, 2.5 mmol) over 5 min. The reaction temperature was held at 0 °C for 2 h and then allowed to warm to ambient temperature overnight. The reaction was quenched by sequential addition of ethanol (4 mL), 15% NaOH (5 mL), and 30% aqueous H_2O_2 (4 mL). The resulting mixture was stirred 4 h, washed with saturated K_2CO_3 (3 × 15 mL), dried over $MgSO_4$, and the solvent was evaporated in vacuo. The residual oil was chromatographed on silica gel (5:1 hexane/ethyl acetate) to yield **13** (54 mg, 60%) as a clear oil. An analytical sample was prepared by bulb-to-bulb distillation (120 °C, 0.1 mmHg): IR (neat oil) 3400 (br), 1090 cm^{-1}; ^1H NMR (500 MHz) δ 7.40 (d, *J* = 7.3 Hz, 2 H), 7.33 (t, *J* = 7.3 Hz, 2 H), 7.25 (m, 1 H), 6.53 (d, *J* = 16.0 Hz, 1 H), 6.12 (dd, *J* = 16.0, 8.2 Hz, 1 H), 3.75 (m, 1 H), 3.64 (m, 2 H), 3.33 (s, 3 H), 2.56 (br s, 1 H), 1.98 (m, 1 H), 1.76 (m, 1 H), 1.45 (m, 1 H), 0.96 (d, *J* = 6.9 Hz, 3 H); ^{13}C NMR (125.8 MHz) δ 136.5, 133.8, 128.6, 127.7, 127.2, 126.5, 86.8, 61.4, 56.5, 35.9, 35.7, 16.6. Anal. Calcd for $C_{14}H_{20}O_2$; C, 76.33; H, 9.15. Found: C, 76.18; H, 9.21.

Methyl (*E*)-(3*R,4*S**)-4-Methoxy-3-methyl-6-phenylhex-5-enoate (14).** To a solution of **13** (20 mg, 0.09 mmol) in acetone (6 mL) at 0 °C was added 8 N Jones reagent (0.5 mL, 0.32 mmol). After 2 h the reaction was diluted with ether (5 Ml), filtered through Celite, and washed with brine. The solution was dried ($MgSO_4$), evaporated in vacuo, and chromatographed on silica gel (3:1 hexane/ethyl acetate) to yield acid **15** (21 mg, quantitative) as a clear oil. The acid was treated with excess diazomethane to yield the methyl ester **14**: IR (neat oil) 1750, 1090, cm^{-1}; ^1H NMR (500 MHz) δ 7.32 (d, *J* = 7.4 Hz, 2 H), 7.25 (t, *J* = 7.4 Hz, 2 H), 7.17 (m, 1 H), 6.46 (d, *J* = 16.0 Hz, 1 H), 5.97 (dd, *J* = 16.0, 7.8 Hz, 1 H), 3.56 (s, 3 H), 3.52 (dd, *J* = 7.8, 5.5 Hz, 1 H), 3.24 (s, 3 H), 2.46 (dd, *J* = 15.2, 5.5 Hz, 1 H), 2.22 (m, 1 H), 2.07 (dd, *J* = 15.2, 8.4 Hz, 1 H), 0.96 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (125.8 MHz) δ 173.6, 136.4, 133.4, 128.6, 127.7, 126.5, 85.6, 56.7, 51.5, 37.5, 35.2, 15.7.

(±)-Oudemansin A (1). To a solution of **14** (9.0 mg, 0.036 mmol) in THF (2 mL) at −78 °C was added LDA (1.0 mL, 0.18 M in THF). After 5 min a solution of *N*-formylimidazole[17] (1.0 mL, 0.26 M in THF) was added and the reaction was allowed to warm to ambient temperature over 35 min. The reaction was partitioned between ether (4 mL) and 5% HCl (3 mL). After extraction of the aqueous fraction with 10 mL of ether, the combined organic fractions were dried ($MgSO_4$) and evaporated in vacuo. The residue was dissolved in 5 mL of acetone with K_2CO_3 (20 mg) and dimethyl sulfate (0.08 mL, 0.80 mmol). After 12 h the solution was diluted with 5 mL of ether, washed with 10 mL of water, and dried with $MgSO_4$. The solvent was evap-

Scheme II. Synthesis of Oudemansins A and B



11 ; R_1= R_2= H
17 ; R_1= OMe, R_2= Cl

12 ; R_1= R_2= H
21 ; R_1= OMe, R_2= Cl

E-7 ; R_1= R_2= H
E-22 ; R_1= OMe, R_2= Cl

1 ; R_1= R_2= H
2 ; R_1= OMe, R_2= Cl

14 ; R_1= R_2= H
24 ; R_1= OMe, R_2= Cl

13 ; R_1= R_2= H
23 ; R_1= OMe, R_2= Cl

orated in vacuo and the residue chromatographed on silica gel (20:1 hexane/ethyl acetate) to yield 6 mg of (±)-oudemansin A (57%) in addition to recovered **14** (0.5 mg). **1**: IR (neat oil) 1700, 1640, 1090 cm^{-1}; ^1H NMR (500 MHz) δ 7.34–7.20 (m, 5 H), 7.18 (s, 1 H), 6.40 (d, J = 15.9 Hz, 1 H), 5.92 (dd, J = 15.9, 8.9 Hz, 1 H), 3.95 (dd, J = 9.6, 8.9 Hz, 1 H), 3.77 (s, 3 H), 3.63 (s, 3 H), 3.32 (s, 3 H), 3.00 (dq, J = 9.6, 7.0 Hz, 1 H), 1.26 (d, J = 7.0 Hz, 3 H); ^{13}C NMR (125.8 MHz) δ 168.1, 159.4, 137.0, 132.5, 129.5, 128.4, 127.3, 126.4, 112.2, 85.0, 61.3, 56.5, 50.9, 35.6, 15.7.

[(4-Chloro-3-methoxyphenyl)methyl]diphenylphosphine Oxide (17). To a solution of 2-chloro-5-methylanisole (**18**)[19] (5.49 g, 38.0 mmol) in CCl_4 (200 mL) was added *N*-bromosuccinimide (7.84 g, 44.0 mmol) and benzoyl peroxide (25 mg). The solution was heated to 100 °C for 90 min, cooled, and filtered to remove precipitated succinimide. The solvent was evaporated in vacuo and the residue was chromatographed on silica gel (50:1 hexane/ether) to give 8.20 g of 5-(bromomethyl)-2-chloroanisole (**19**) contaminated with ca. 30% of the dimer, which was used without further purification: IR (neat oil) 1600, 1410, 1290 cm^{-1}; ^1H NMR (250 MHz) δ 7.30 (m, 1 H), 6.92 (m, 2 H), 4.44 (s, 2 H), 3.90 (s, 3 H); ^{13}C NMR (90.6 MHz) δ 155.2, 141.7, 137.7, 130.3, 121.8, 112.9, 56.2, 32.7.

To a mixture of ethanol (1.72 g, 38.4 mmol) and pyridine (2.9 mL, 35.8 mmol) in THF (100 mL) was added a solution of diphenylchlorophosphine (7.69 g, 34.9 mmol) in THF (20 mL). After 3 h the reaction was filtered and the filtrate was added to **19** (8.2 g, 24 mmol), and the resulting mixture was heated to 80 °C for 2 days. The solvent was evaporated in vacuo and the residual solid recrystallized from ethyl acetate to yield **17** (5.72 g, 42% from **18**) as a white solid, mp 202–203 °C: IR (KBr) 1190, 720, 690 cm^{-1}; ^1H NMR (250 MHz) δ 7.74–7.66 (m, 4 H), 7.53–7.41 (m, 6 H), 7.14 (d, J = 8.0 Hz, 1 H), 6.69 (t, J = 2.0 Hz, 1 H), 6.58 (dt, J = 8.0, 2.0 Hz, 2 H), 3.69 (s, 3 H), 3.62 (d, J = 14.0 Hz, 2 H); ^{13}C NMR (90.6 MHz) δ 154.7, 131.7, 131.3, 131.1, 131.0, 129.7, 128.5, 128.4, 123.0, 114.3, 55.9, 38.3 (d, J = 66.6 Hz). Anal. Calcd for $C_{20}H_{18}ClO_2P$; C, 67.33; H, 5.09; Cl, 9.94; P, 8.68. Found: C, 67.20; H, 4.85; Cl, 10.14; P, 8.95.

(*E*)-(3*S,4*R**)-3-Methoxy-4-methyl-1-(4-chloro-3-methoxyphenyl)hexa-1,5-diene ((*E*)-22).** To a solution of **5** (296 mg, 1.87 mmol) and $MgBr_2$·Et_2O (482 mg, 1.87 mmol) in 15 mL of THF at −78 °C was added a solution of **17** (1.00 g, 2.8 mmol) and *n*-BuLi (1.1 mL, 2.5 M in hexanes, 2.75 mmol) in THF (20 mL) over 30 min. The reaction was held at −78 °C for 1 h and then warmed to 0 °C and quenched with H_2O (5 mL). The organic fraction was washed with 50 mL of water, dried over $MgSO_4$, and concentrated in vacuo to yield β-keto phosphine oxide **21** as a white solid.

The crude **21** was dissolved in 10 mL of THF and added to a solution of $LiBH_4$ (352 mg, 16.2 mmol) in THF (20 mL). The reaction was stirred overnight, quenched with 15% NaOH (5 mL), and washed with water. The organic fraction was dried with $MgSO_4$, evaporated in vacuo, and chromatographed on silica gel (50:1 pentane/ether) to give a 7:1 mixture of (*E*)-**22** and its anti diasteromer (146 mg, 30%) as a clear oil. An analytical sample of (*E*)-**22** was prepared by preparative HPLC and bulb-to-bulb distillation (120 °C, 0.1 mmHg): IR (neat oil) 1490, 1410, 1060 cm^{-1}; ^1H NMR (500 MHz) δ 7.23 (d, J = 8.6 Hz, 1 H), 6.88 (m, 2 H), 6.43 (d, J = 16.1 Hz, 1 H), 5.99 (dd, J = 16.1, 7.8 Hz, 1 H), 5.81 (m, 1 H), 5.02 (m, 2 H), 3.85 (s, 3 H), 3.50 (dd, J = 7.8, 6.2 Hz, 1 H), 3.28 (s, 3 H), 2.44 (m, 1 H), 1.02 (d, J = 7.0 Hz, 3 H); ^{13}C NMR (125.8 MHz) δ 154.9, 140.0, 136.5, 132.1, 130.0, 128.9, 121.5, 119.4, 114.7, 109.7, 86.0, 56.6, 55.9, 42.4, 15.5. Anal. Calcd for $C_{15}H_{19}ClO_2$: C, 67.54; H, 7.18. Found: C, 67.50; H, 7.25.

(*E*)-(3*R,4*S**)-4-Methoxy-3-methyl-6-(4-chloro-3-methoxyphenyl)hex-5-enol (23).** With use of a procedure identical with that for **13**, (*E*)-**22** (380 mg, 1.42 mmol) was treated with 9-BBN (23 mL, 0.5 M in THF, 11.5 mmol). The reaction was allowed to warm to ambient temperature overnight. Following workup and flash chromatography on silica gel (3:1 hexane/ethyl acetate), **23** (387 mg, 95%) was obtained as a clear oil: IR (neat oil) 3400 (br) cm^{-1}; ^1H NMR (500 MHz) δ 7.30 (d, J = 8.6 Hz, 1 H), 6.93 (m, 2 H), 6.49 (d, J = 16.0 Hz, 1 H), 6.10 (dd, J = 16.0, 8.1 Hz, 1 H), 3.93 (s, 3 H), 3.79–3.59 (m, 3 H), 3.34 (s, 3 H), 2.61 (br s, 1 H), 1.98 (m, 1 H), 1.77 (m, 1 H), 1.45 (m, 1 H), 0.97 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (125.8 MHz) δ 154.9, 136.3, 132.7, 130.0, 128.0, 121.7, 119.4, 109.7, 86.6, 61.2, 56.6, 56.0, 35.7, 35.5, 16.4. An analytical sample was prepared by bulb-to-bulb distillation (180 °C, 0.1 mmHg). Anal. Calcd for $C_{15}H_{21}ClO_3$: C, 63.26; H, 7.43; Cl, 12.45. Found: C, 63.45; H, 7.61; Cl, 12.31.

Methyl (*E*)-(3*R,4*S**)-4-Methoxy-3-methyl-6-(4-chloro-3-methoxyphenyl)hex-5-enoate (24).** Following the procedure used to prepare **14**, alcohol **23** (86 mg, 0.30 mmol) was oxidized with Jones reagent and treated with excess diazomethane to yield **24** (81 mg, 86%) as a pale oil. An analytical sample was prepared by bulb-to-bulb distillation (120 °C, 0.1 mmHg): IR (neat oil) 1730, 1460, 1290, 1060 cm^{-1}; ^1H NMR (500 MHz) δ 7.30 (d, J =

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8.3 Hz, 1 H), 6.93 (m, 2 H), 6.50 (d, J = 16.2 Hz, 1 H), 6.04 (dd, J = 16.2, 7.6 Hz, 1 H), 3.93 (s, 3 H), 3.64 (s, 3 H), 3.59 (dd, J = 7.6, 5.1 Hz, 1 H), 3.31 (s, 3 H), 2.53 (dd, J = 15.3, 5.7 Hz, 1 H), 2.30 (m, 1 H), 2.16 (dd, J = 15.3, 8.3 Hz, 1 H), 1.01 (d, J = 7.0 Hz, 3 H): ^{13}C NMR (125.8 MHz) 173.4, 154.9, 136.4, 132.3, 130.1, 128.6, 121.7, 119.5, 109.7, 85.4, 56.8, 56.0, 51.5, 37.4, 35.1, 15.6. Anal. Calcd for $C_{16}H_{21}ClO_4$: C, 61.44; H, 6.78. Found: C, 61.38; H, 6.64.

(±)-Oudemansin B (2). To a solution of **24** (38 mg, 0.12 mmol) in THF (2 mL) at −78 °C was added LDA (2.0 mL, 0.13 M). After 5 min a solution of *N*-formylimidazole (0.75 mL, 0.53 M in THF, 0.40 mmol) was added to the orange reaction mixture. The orange color immediately dissipated. The reaction was allowed to warm to ambient temperature over 35 min. The reaction was partitioned between 5% HCl (3 mL) and ether (5 mL). The aqueous fraction was extracted with 5 mL of ether and the combined organic fractions were dried with $MgSO_4$ and concentrated in vacuo. The residue was combined with K_2CO_3 (30 mg, 0.22 mmol) and dimethyl sulfate (0.125 mL, 1.32 mmol) in 4 mL of acetone. After 12 h the reaction was diluted with ether (5 mL), washed with water (5 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed on silica gel (15:1 hexane/ethyl acetate) to yield (±)-oudemansin B (19 mg, 44%) as a clear oil, in addition to recovered **24** (5 mg). **2**: IR (neat oil) 1700, 1640, 1080 cm^{-1}; ^{1}H NMR (500 MHz) δ 7.26 (m, 1 H), 7.20 (s, 1 H), 6.86 (m, 2 H), 6.35 (d, J = 15.9 Hz, 1 H), 5.91 (dd, J = 15.9, 8.5 Hz, 1 H), 3.93 (dd, J = 9.5, 8.5 Hz, 1 H), 3.90 (s, 3 H), 3.77 (s, 3 H), 3.64 (s, 3 H), 3.32 (s, 3 H), 2.99 (dq, J = 9.5, 6.9 Hz, 1 H), 1.26 (d, J = 6.9 Hz, 3 H); ^{13}C NMR (125.8 MHz) δ 168.1, 159.5, 154.8, 136.9, 131.5, 130.4, 130.0, 121.3, 119.4, 112.1, 109.8, 84.8, 61.4, 56.7, 56.0, 51.0, 35.6, 15.7.

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Selective Monofluorination of β-Diketones

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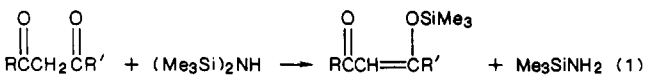
Treatment of silyl enol ethers of β-diketones with 5% F_2 in N_2 results in the formation of 2-fluoro 1,3-diketones. The acyclic derivatives exist as keto tautomers, while the dimedone derivative is enolic. Similarly, the silyl enol ethers of β-keto esters give rise to α-fluoro-β-keto esters.

There have been few attempts to prepare 2-fluoro 1,3-diketones. In special cases, 5-fluoro-5-alkylbarbituric acids can be formed from monofluoromalonates.[1,2] It has also been noted that *trans*-perfluoro-2-pentene can be converted to a 2-fluoro 1,3-diketone.[3] Acid hydrolysis of fluorinated enones has also been shown to give rise to these monofluoro diketones.[4] The lamellar compound, $C_{19}XeF_6$, formed when XeF_6 is absorbed on graphite, reacts with β-diketones to give 40–60% yields of the monofluoro derivatives.[5]

Difluorination can be a complicating factor; for example, the action of xenon difluoride on β-diketones resulted mainly in 2,2-difluoro-1,3-diketones.[6] The monofluoro derivatives could be isolated in low yields when the reaction was performed in dilute solutions with a large substrate to reagent ratio. Similarly, perchloryl fluoride reacted with 2,4-pentanedione in the presence of alkoxide to give the difluoro adduct in 77% yield.[2] However, monofluorination was observed under similar conditions for 2-acylcycloalkanones, cyclic β-keto esters, and diketones.[7] Many of these reactions were complicated by subsequent ring opening. Lerman and Rozen[8] were able to monofluorinate β-keto esters with acetyl hypofluorite, but they did not study β-diketones.

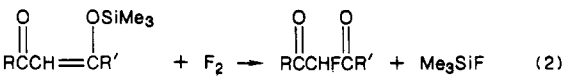
Results

Since the reagents used for fluorination of β-diketones are either expensive or explosive, investigation of the use of dilute fluorine was undertaken. Recently, we have found that trimethylsilyl enol ethers can be selectively fluorinated to give α-fluoro ketones using dilute fluorine.[9] Since trimethylsilyl enol ethers of β-diketones are readily formed[10] as indicated in eq 1, their fluorination was



a, R = R′ = Ph; **b**, R = Me; R′ = Ph; **c**, R = R′ = *t*-Bu; **d**, R = R′ = *n*-Pr; **e**, R = Et; R′ = *n*-Bu

studied. Treatment of these silyl enol ethers with 5% F_2 in N_2 at −78 °C in $CFCl_3$ results in the monofluoro diketone in 26–53% yield (eq 2). Table I summarizes the results and indicates the scope of the reaction. Although the yields are not spectacular, the method does provide only the monofluorinated derivatives and constitutes the only general pathway now available to these compounds.



In our earlier study of α-fluoro ketones,[9] di- and trifluorination of methyl ketones was observed. Thus, not surprisingly, the fluorination of 2-(trimethylsiloxy)-2-penten-4-one (R = R′ = CH_3) resulted in an inseparable complex mixture containing at least five compounds, as

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