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NEW SIGMATROPIC SEQUENCES BASED ON THE [2,3]-WITTIG REARRANGEMENT OF THE BIS-ALLYLIC ETHER SYSTEM

A GENERAL APPROACH TO REGIOCONTROLLED C—C BOND FORMATION OF ALLYLIC MOIETIES LEADING TO UNSATURATED CARBONYL COMPOUNDS

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Abstract—Four new sigmatropic sequences triggered by the regiocontrolled [2,3]-Wittig rearrangement of unsymmetrical bis-allylic ethers (**1**) to the 1,5-dien-3-ols (**2**) are described, which provide unique, regiocontrolled methods for the synthesis of a wide variety of unsaturated carbonyl compounds possessing interesting molecular frameworks. The newly developed sequences include the [2,3]-Wittig–Claisen, the tandem [2,3]-Wittig–oxy-Cope, the tandem oxy-Cope–Claisen, and the tandem oxy-Cope–Cope sequences.

Recently a number of tandem [3,3]–[3,3]-sigmatropic sequences such as Claisen–Cope and Cope–Claisen rearrangements have been developed and have found substantial utility in the methodology for organic synthesis.[1-3] In contrast, however, only a few [2,3]-sigmatropic rearrangements have been exploited in tandem or in series, particularly for effecting C—C bond formations.[1,4] We have recently found that the [2,3]-Wittig sigmatropic rearrangement of unsymmetrical bis-allylic ethers (**1**) is exceedingly useful for regio- and stereoselective preparations of 1,5-dien-3-ols (**2**).[5] To expand its synthetic potential further, our efforts have been directed towards the development of sigmatropic sequences triggered by the particular [2,3]-Wittig variant.

Herein we describe four new sigmatropic sequences based on the [2,3]-Wittig process which provide unique, facile methods for the synthesis of various classes of unsaturated carbonyl compounds possessing interesting molecular frameworks.[6] The overall bond reorganizations are shown in Scheme 1. Particularly noteworthy is that the net effect of these sequences allows two or three allylic moieties initially linked by a readily formed ether bond(s) to be recombined by a newly created C—C bond(s) in a regiospecific fashion.

RESULTS AND DISCUSSION

Tandem [2,3]-*Wittig–oxy-Cope sequence* (*Eq.* 2)

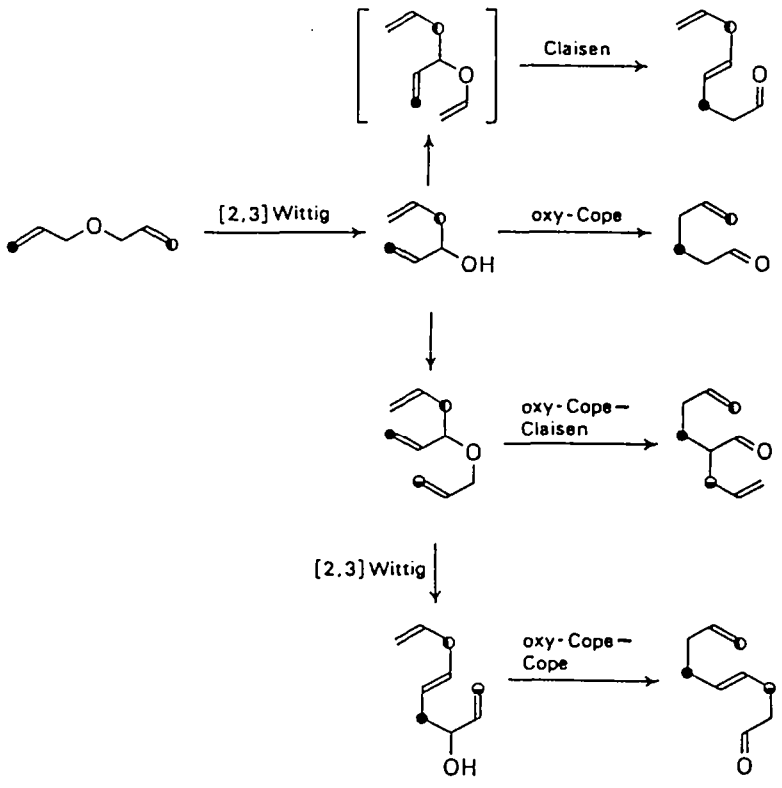
First, the accessibility of diastereomerically defined 1,5-dien-3-ols (**2**) by virtue of the [2,3]-Wittig rearrangement[5] prompted us to investigate the unresolved stereochemistry of the acyclic oxy-Cope process.[7] Thus we examined the rearrangement of *erythro*- and *threo*-rich mixtures of **2a** and **b** (Scheme 2) by applying the current procedures including thermolysis in N-methylpyrrolidone (NMP)[8] and the anionic oxy-Cope[9] and the siloxy-Cope modifications[10] (Table 1).

Inspection of the data in Table 1 reveals stereo-

Table 1. Oxy-Cope rearrangement of **2**

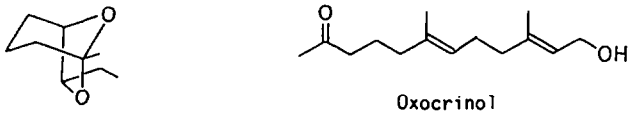
Entry	Substrate[a] (*threo*:*erythro*)	Condition[b] (time, h)	Product (% Yield,[c] *E*:*Z*[d])
1	**2a** (79:21)	A (6)	**4a** (56,[e] 71:29)
2		B (10)	**4a** (79, 67:33)
3		C (60)	**4a** (63, 95:5)
4	**3a** (79:21)	C (43)	**4a** (84, 71:29)
5	**2a** (12:88)	A (4)	**4a** (48,[e] 72:28)
6		B (11)	**4a** (77, 79:21)
7		C (43)	**4a** (61, 92:8)
8	**2b** (80:20)	C (72)	**4b** (42,[e] 95:5)

[a] Prepared via [2,3]-Wittig rearrangement of the corresponding bis-allylic ether (Ref. 5).
[b] (A) The potassium alkoxide (prepared with KH) was heated in DME at 85°; (B) heated in NMP at 204°; (C) heated in n-decane at 174°.
[c] GLC yield.
[d] Determined by GLC.
[e] Distilled yield.

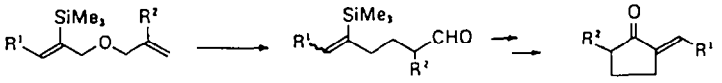


Scheme 1.

chemical features of the acyclic oxy-Cope process. Both the *erythro*- and *threo*-rich substrate afford essentially the same degree (67–95%) of *E*-selectivity, depending on the reaction procedures. Of synthetic value is the high stereoselection observed with the thermolysis in decane. It thus appears that the olefinic ations.[12] Recently we have demonstrated the utility of this sequence in the context of the synthesis[13] of insect pheromone (±)-*exo*-brevicomin and oxocrinol (isolated from a Mediterranean algae[14]) and also of the otherwise difficult preparations of functionalized vinylsilanes as exemplified by Eq. (5).[15]



(±)-exo-Brevicomin

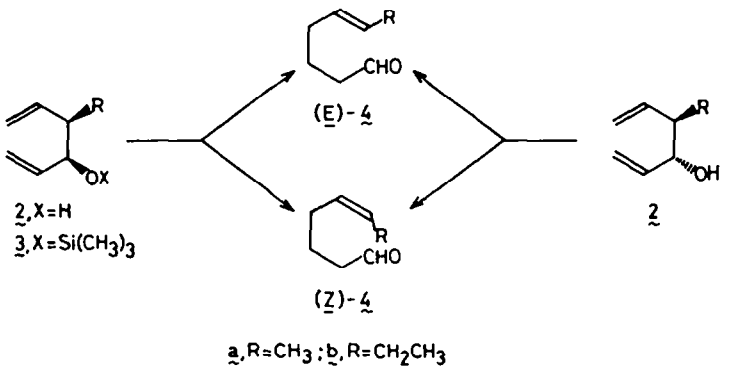


stereochemistry of the product is independent of the relative stereochemistry of the substrate, in sharp contrast to the high stereospecificity reported for the cyclic oxy-Cope processes.[9]

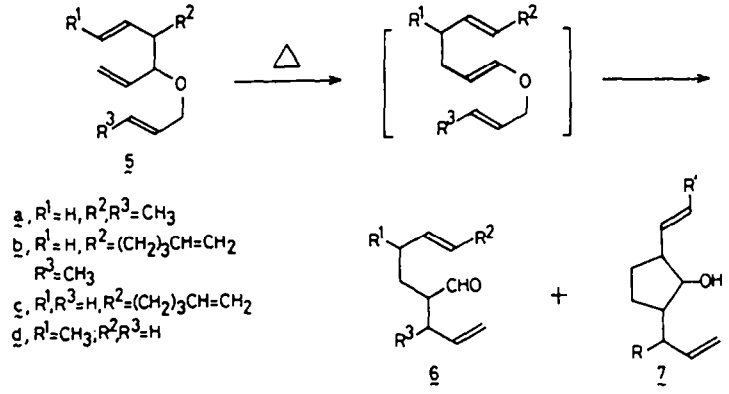
From the synthetic viewpoint, the tandem [2,3]-Wittig–oxy-Cope sequence is of special interest since the net effect allows the allyloxy moiety to serve as a homoenolate equivalent,[11] thereby achieving the otherwise difficult S_N2-type C—C bond formations. Therefore, this sequence provides a versatile synthetic route to δ,ε-unsaturated carbonyl compounds which have found widespread use in synthetic transform-

[2,3]-Wittig–allylation–tandem oxy-Cope–Claisen sequence (Eq. 3)

Secondly, we studied thermolysis of the allylic ethers **5** which were readily obtainable via etherification of the [2,3]-Wittig products (**2**). Thus **5** was heated at 200–250° to afford the dienal **6** as the major product. The formation of **6** is best explained by the tandem oxy-Cope–Claisen sequence (Scheme 3). Table 2 shows the representative examples. In certain cases, the cyclic alcohol **7** was also formed which was independently shown to arise from **6** via an intramolecular ene reaction.[16] Interestingly, the use of NMP as the



Scheme 2.

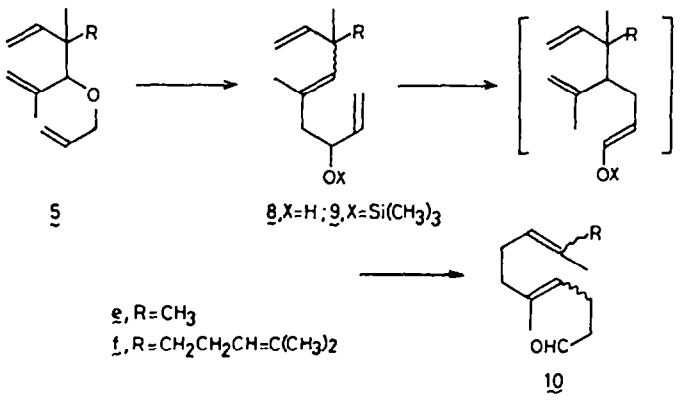


Scheme 3.

Table 2. Tandem oxy-Cope–Claisen rearrangement of **5**

Entry	Substrate[a] (*threo* : *erythro*)[b]	Conditions[c] Temp,°; time, h	Product (% Yield)[d]
1	**5a** (79 : 21)	250; 10	**6a** (36); **7** (R = CH_3, R′ = H) (20)
2[e]	**5a** (79 : 21)	250; 5	**6a** (46); **7** (R = CH_3, R′ = H) (12)
3	**5b**[f] (80 : 20)	200; 4	**6b** (45)
4	**5c**[f] (80 : 20)	200; 4	**6c** (45)
			7 (R = H, R′ = $(CH_2)_2CH{=}CH_2$) (13)
5	**5d**	250; 10	**6d** (41)

[a] Prepared by etherification of **2** with an allylic halide.
[b] The diastereomeric ratio refers to that of **2**.
[c] All reactions were run in a sealed tube.
[d] Isolated yield.
[e] Thermolysis was conducted in NMP.
[f] Prepared from (*E*)-2,7-octadienol as the starting material. We thank Professor J. Tsuji for providing the butadiene telomer; cf. J. Tsuji, *Pure Appl. Chem.* **51**, 5070 (1979).



Scheme 4.

reaction medium depresses the subsequent ene reaction (entry 2).

The transformation offers the first example of the tandem sequence in which the oxy-Cope triggers the Claisen process. The stereochemical outcome of the sequence, although not extensively studied, appears predictable from a combination of the known stereochemistry of each sigmatropic process involved. In fact, the newly created olefinic bond possesses exclusively the *E*-geometry (entries 1–4).

[2,3] - *Wittig–allylation*–[2,3] - *Wittig–tandem oxy - Cope–Cope sequence* (*Eq.* 4)

Thirdly, we examined thermolysis of the trienols **8** which were readily prepared via the regiocontrolled [2,3]-Wittig process of the bis-allylic ethers **5**. Thus triol **8e** was heated in NMP at 202° to produce a geometric mixture (*E*/*Z* ratio of 2.0)[17] of geranylacetaldehyde (**10e**) in 41% isolated yield. Significantly, an increased yield (86%) was obtained when the siloxytriene **9e** was heated neat at 250°. The formation of **10e** is explained by the tandem (sil)oxy-Cope–Cope rearrangement (Scheme 4). A similar thermolysis of a diastereomeric mixture (72:28)† of **8f**, derived from geraniol via the aforementioned sequence, afforded a geometric mixture of farnesylacetaldehyde (**10f**) in 46% isolated yield.‡ The stereomixture was found to be a mixture of the four possible geometric isomers through GLC comparisons with a stereomixture (4*E*/4*Z*, 2:1) of (8*E*)-**10f** independently prepared from (6*E*)-neroridol via the Claisen rearrangement.§

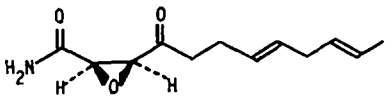
The transformation includes the first example of the tandem sequence in which the oxy-Cope triggers the Cope process. Furthermore, the new sequence provides a novel, versatile method for the synthesis of functionalized 1,5-diene derivatives which are commonly found in many terpenoid natural products. In particular, farnesylacetaldehyde obtained above is a promising precursor of geranyl farnesylacetate (so-called Gefarnate), a commercial antiulcer agent.[18]

[2,3]-*Wittig–Claisen sequence* (*Eq.* 1)

Finally, we explored the Claisen rearrangement[19] of the [2,3]-Wittig products (**2**). Thus, 1,5-dien-3-ols (**2**) were subjected to the three modifications of the Claisen process to afford 1,4-dienes with different functionalities (Scheme 5). First, we found that the enol ether Claisen process[20] of **2c** afforded (*E*,*E*)-4,7-nonadienal (**11c**) in 66% distilled yield.‖ Second, the orthoester Claisen modification[21] of **2d** gave exclusively the (*E*,*E*)-isomer of ethyl 4,7-tridecanoate (**12d**) in 86% yield. Third, the acetate of **2e** was subjected to the enolate Claisen modification[22] to give, after hydrolysis, the (*E*)-4,7-octadienoic acid (**13e**) in 79% yield.

A notable feature in this approach to 1,4-dienes[23] is that the geometry of the two olefinic bonds can be fully controlled by the high *E*-selectivity of the [2,3]-Wittig[5] and Claisen processes.[19] Furthermore, the remarkable flexibility inherent in this approach permits ready access to a wide variety of functionalized 1,4-dienes which are frequently found in natural products and synthetic intermediates thereof.

In order to illustrate the synthetic potential of the [2,3]-Wittig–Claisen sequence, our effort was directed towards the total synthesis of cerulenin (**14**), which has been reported to exhibit both antibiotic and antifungal activities and to inhibit the biosynthesis of lipids and steroids.[24] Recently (*E*,*E*)-4,7-nonadienal (**11c**) (or the



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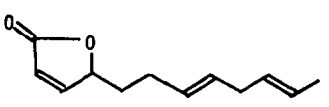

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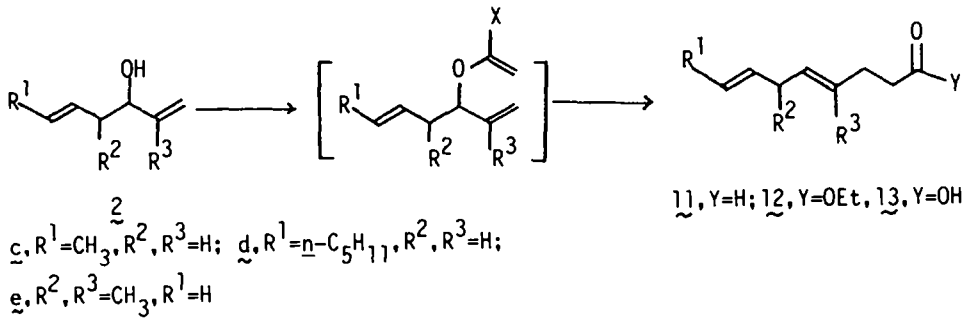
† The stereochemistry of the major diastereomer has not yet been determined.

‡ In this case, no increased yield was obtained with the attempted siloxy-Cope rearrangement.

§ A similar Claisen process of (6*Z*)-neroridol gave another authentic mixture (4*E*/4*Z*, 2:1) of **10f**.

‖ It may be noted that the Claisen process proceeded cleanly without occurrence of the oxy-Cope process, indicating that the transition state for the Claisen shift is of lower energy than that for the oxy-Cope shift in these systems.



Scheme 5.

dienol) has been shown to serve as the side-chain component which has, however, been prepared via tedious, lengthy sequences of reactions using less accessible acetylenic alcohols.[25a–c] With a satisfactory quantity of **11c** in hand, we set out to develop a new, more facile method for conversion of **11c** to the butenolide **15**, which is the most widely used precursor of **14**.[25] Scheme 6 depicts the newly developed sequence.

Dienal **11c** was first converted to epoxide **16** in 88% yield via the standard ylide procedure, which was then converted to the α-phenylthiolactone **17** in 82% yield according to the synthetic procedure of Uda and co-workers.[26] Oxidation of **17** followed by thermolysis of the resulting sulfoxide furnished the desired butenolide **15** in 76% yield. Since **15** has been elaborated to **14** in three simple steps,[25a] this synthesis of **15** constitutes a new formal synthesis of (±)-**14**. Notably, the straightforward synthesis of **15**, coupled with the easy availability of **11c**, makes the overall process an attractive method of choice for the relatively large-scale synthesis of (±)-cerulenin.

EXPERIMENTAL

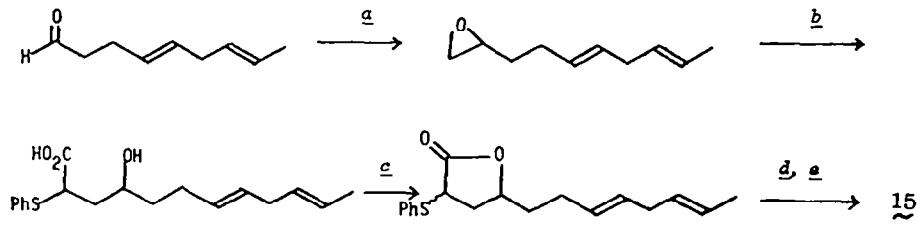
B.ps are uncorrected. IR spectra were recorded on a JASCO A-102 spectrometer. NMR spectra were taken on a Varian EM-390 spectrometer and are reported in ppm downfield from internal TMS. GC analyses were run on a Shimazu GC-3BT chromatograph using He as the carrier gas (1 kg cm^{-2}) and a 3 mm × 3 m column [20% PEG 20M on Chromosorb W (60–80 mesh) or 1% OV 1 on Shimalite W (60–80 mesh)] at the indicated temp. THF was dried by distillation from $LiAlH_4$ immediately prior to use. All reactions except for etherification using the phase transfer technique were performed under N_2 atmosphere. BuLi was used as a soln in hexane (*ca* 1.3 M) purchased from Ventron Co. The term "usual workup" is used in the following product isolation procedure: dilution of the reaction mixture with Et_2O and H_2O, successive extraction with Et_2O and brine; treatment of the organic extracts with anhyd $MgSO_4$; and solvent removal under reduced pressure. The term "chemical purity" stands for the freedom of a stereoisomeric mixture of the indicated compound from contaminants.

Preparations of allylic ethers (**1**)

The preparation of **1a** is described as a representative. Allyl bromide (17.0 ml, 220 mmol) was added dropwise to a rigorously stirred mixture of crotyl alcohol (93% *E* by GC assay) (14.4 g, 200 mmol), n-Bu_4NHSO_4 (3.7 g, 10 mmol), NaOH (16.0 g, 400 mmol) and H_2O (4 ml) at ambient temp. The solid formed was filtered off. Usual workup of the filtrate followed by distillation gave ether (*E*)-**1a** (16.2 g, 73%): b.p. 58–62°/57 mmHg (> 98% chemical purity by GC assay); IR (neat) 1380, 1095, 990, 960, 920 cm^{-1}; ^{1}H-NMR (CCl_4) δ 1.69 (d, J = 5.4 Hz, 3H), 3.74–4.00 (m, 4H), 4.97–5.37 (m, 2H), 5.43–6.07 (m, 3H). A similar reaction of crotyl alcohol (95% *Z*) (1.44 g, 20 mmol) gave (*Z*)-**1a** (1.30 g, 63%): b.p. 108–110° (> 98% chemical purity by GC assay); IR (neat) 1380, 1095, 990, 920, 770 cm^{-1}; ^{1}H-NMR (CCl_4) δ 1.67 (d, J = 5.4 Hz, 3H), 3.83–4.27 (m, 4H), 5.05–5.48 (m, 2H), 5.53–6.24 (m, 3H).

[2,3]-*Wittig rearrangement of allylic ethers* (**1**)

A typical procedure is shown in the preparation of **2a**. A hexane soln of n-BuLi (50 ml, 70 mmol) was added dropwise to



a: $(CH_3)_3S^+I^-$/NaH, DMSO, 0°C; *b*: $PhSCH_2COOH$/LDA (2 equiv), THF, −60°C; *c*: PhH, 80°C; *d*: MCPBA, CH_2Cl_2, −78°C; *e*: reflux, toluene ($CaCO_3$, 2 equiv)

Scheme 6.

a cold (−85°) THF soln of **1a** (*E*/*Z* = 93:7) (5.6 g, 50 mmol) (using an EtOH/liquid N_2/dry ice bath). The resulting mixture was stirred at that temp for several hours, allowed to warm to 0°, and quenched with sat NH_4Cl. Usual workup followed by distillation afforded *threo*-**2a** (*threo*/*erythro* = 79:21) (4.42 g, 79%): b.p. 72–74°/35 mmHg [lit.[27] 55–56°/14 mmHg]; IR (neat) 3350, 990, 910 cm^{-1}; ^{1}H-NMR (CCl_4) δ 0.97 (d, J = 7.0 Hz, 3H), 1.74 (s, 1H), 2.07–2.36 (m, 1H), 3.73–3.94 (dd, 1H), 4.90–5.33 (m, 4H), 5.53–6.03 (m, 2H). Upon addition of Eu-fod, the methyl signals at 0.97 ppm were shifted downfield to 4.37 and 5.14 ppm (0.63 and 2.37 H).

Similar treatment of *Z*-**1a** (*E*/*Z* = 5:95) (2.24 g, 20 mmol) with n-BuLi (15 ml, 29 mmol) afforded *erythro*-**2a** (*threo*/*erythro* = 12:88) (1.81 g, 81%). Upon addition of Eu-fod to the NMR (CCl_4) sample, the methyl signals at 0.97 ppm were shifted downfield to 3.42 and 3.66 ppm (2.64 and 0.36 H).

Oxy-Cope rearrangement of 1,5-*dien*-3-*ols* (**2**)

The oxy-Cope rearrangements shown in Table 1 were carried out following the literature procedures. For example, the anionic oxy-Cope rearrangement was carried out as follows. A soln of *threo*-**2a** (*threo*/*erythro* = 79:21) (0.2 g, 2 mmol) in 50 ml of dimethoxyethane was treated with KH (0.09 g, 2.2 mmol). The resulting mixture was heated under reflux for 6 h to give, after usual workup followed by distillation, a geometric mixture of 5-hepten-1-al (**4a**) (0.21 g, 56%): b.p. 50–52°/9 mmHg [lit.[27] 157°]. The (*E*)- and (*Z*)-isomers were separated by preparative GLC (PEG 20 M, 100°).

(*E*)-**4a**: GLC (PEG 20M, 120°) R_t = 14.8 min; IR (neat) 1730, 970 cm^{-1}; ^{1}H-NMR (CCl_4) δ 1.50–1.83 (m, 5H), 1.83–2.13 (m, 2H), 2.34 (t, J = 7.5 Hz, 2H), 5.20–5.57 (m, 2H), 9.87 (t, J = 3 Hz, 9H). Decoupling the multiplet at 5.20–5.57 ppm caused the multiplet at 1.50–1.83 ppm to collapse to a singlet at 1.64 ppm.

(*Z*)-**4a**: GLC (PEG 20M, 120°) R_t = 16.1 min; IR (neat) 1720, 740 cm^{-1}; ^{1}H-NMR (CCl_4) δ 1.49–1.87 (m, 5H), 1.87–2.23 (m, 2H), 2.36 (t, J = 7.5 Hz, 2H), 5.20–5.53 (m, 2H), 9.87 (t, J = 3 Hz, 1H). Decoupling the multiplet at 5.20–5.53 ppm caused the multiplet at 1.49–1.87 ppm to collapse to a singlet at 1.61 ppm.

Preparation of allylic ethers **5a–f**

The ethers **5a–f** were prepared as described for the preparation of **1a**.

Ether **5a**: 5.7 g (76%); b.p. 64–66°/12 mmHg; IR (neat) 1085, 990, 965, 920 cm^{-1}; ^{1}H-NMR (CCl_4) δ 1.00 (d, J = 6.6 Hz, 3H), 1.70 (d, J = 4.5 Hz, 3H), 2.00–2.50 (m, 1H), 3.30–4.10 (m, 3H), 4.90–6.10 (m, 8H).

Ether **5b**: 3.2 g (83%); IR (neat) 3075, 2925, 2850, 1640, 1440, 990, 965, 910 cm^{-1}, GC/MS (CI), *m*/*z* (rel. int.) 111 (21.4), 93 (17.3), 81 (8.3), 79 (12.7), 67 (38.5), 57 (44.7), 55 (100).

Ether **5c**: 30 g (73%); IR (neat) 3000, 2940, 2850, 1640, 1420, 1075, 990, 915 cm^{-1}; GC/MS (CI), *m*/*z* (rel. int.) 97 (2.9), 79 (6.4), 77 (7.7), 67 (29.8), 55 (90.0), 41 (100).

Ether **5d**: 4.4 g (72%); b.p. 67–70°/8 mmHg; IR (neat) 3000, 2920, 2850, 1640, 1420, 1085, 990, 965, 920 cm^{-1}; ^{1}H-NMR (CCl_4) δ 1.63 (m, 1H), 2.03–2.23 (m, 2H), 3.50–4.12 (m, 3H), 4.90–6.10 (m, 8H).

Ether **5e**: 1.52 g (84%); IR (neat) 1070, 990, 910, 895 cm^{-1}; ^{1}H-NMR (CCl_4) δ 1.00 (s, 3H), 1.03 (s, 1H), 1.67 (s, 3H), 3.37 (s, 1H), 3.67 (dd, J = 13.5 and 6 Hz, 1H), 3.97 (dd, J = 13.5 and 4.5 Hz, 1H), 4.66–6.55 (m, 8H). Decoupling the multiplet at 6.00 ppm caused the multiplet at 3.67 and 3.97 ppm to collapse to doublets (J = 13.5 Hz).

Ether **5f** (derived from geraniol): 8.27 g (86%); b.p. 90–97°/1 mmHg; IR (neat) 1080, 990, 910 cm^{-1}; ^{1}H-NMR (CCl_4) δ 0.93 and 1.00 (2s, 2.3 and 0.7 H), 1.56 (s, 3H), 1.66 (s, 6H), 1.17–2.17 (4H), 3.42 (s, 1H), 3.63 (dd, J = 12.6 and 6 Hz, 1H), 3.95 (dd, J = 12.6 and 4.2 Hz, 1H), 4.62–4.67 (m, 9H).

Ether **5f** (derived from nerol): 7.20 g (87%); b.p. 92–98°/1 mmHg; IR (neat) 1070, 1000, 910 cm^{-1}; ^{1}H-NMR (CCl_4) δ 0.93 and 1.00 (2s, 1.35 and 1.65H), 1.56 (s, 3H), 1.66 (s, 6H), 1.17–2.17 (4H), 3.42 (s, 1H), 3.63 (dd, J = 12.6 and 6 Hz, 1H), 3.95 (dd, J = 12.6 and 4.2 Hz, 1H), 4.62–4.67 (m, 9H).

Tandem oxy-Cope–Claisen rearrangement of allylic ethers (**5**)

Allylic ethers **5** were thermolyzed in a sealed tube with or without NMP under the conditions indicated in Table 2. Aldehydes **6** and/or alcohols **7** were isolated after usual workup followed by silica-gel column chromatography.

Aldehyde **6a**: 0.52 g (36%); IR (neat) 1720, 995, 965, 915 cm^{-1}; ^{1}H-NMR (CCl_4) δ 1.03 (d, J = 6.3 Hz, 3H), 1.65 (d, J = 3.6 Hz, 3H), 1.10–2.30 (m, 5H), 2.55 (dt, J = 6.9 Hz, 1H), 4.90–6.10 (m, 5H), 9.67 (m, 1H).

Alcohol **7** (R = CH_3, R′ = H): 0.29 g (20%); IR (neat) 3300, 995, 915 cm^{-1}; ^{1}H-NMR (CCl_4) δ 1.00 and 1.05 (2d, J = 4.8 Hz, 3H), 1.10–2.50 (m, 7H), 3.80 (m, 1H), 4.80–6.10 (m, 7H).

Aldehyde **6b**: 0.9 g (45%); IR (neat) 1725, 990, 970, 915 cm^{-1}; ^{1}H-NMR (CCl_4) δ 0.97 (d, J = 7 Hz, 3H), 1.20–2.50 (m, 12H), 4.82–5.03 (m, 4H), 5.30–6.00 (m, 4H), 9.60 (s, 1H).

Aldehyde **6c**: 0.92 g (46%); IR (neat) 1725, 990, 915 cm^{-1}; ^{1}H-NMR (CCl_4) δ 1.26–2.30 (m, 13H), 4.28–5.97 (m, 8H), 9.60 (s, 1H).

Aldehyde **6d**: 0.37 g (41%); IR (neat) 1725, 990, 915 cm^{-1}; ^{1}H-NMR (CCl_4) δ 1.00 (d, J = 6.3 Hz, 3H), 1.30–2.70 (m, 6H), 4.70–6.00 (m, 6H), 9.57 (m, 1H).

[2,3]-*Wittig–oxy-Cope–Cope sequence of allylic ethers* (**5**)

[2,3]-*Wittig rearrangement of* **5**. The [2,3]-Wittig rearrangement of ethers **5** was carried out as described for the rearrangement of **2a**. The rearranged alcohols **8** were purified by distillation.

Alcohol **8e**: 4.48 g (84%); b.p. 79–81°/10 mmHg; IR (neat) 3380, 990, 915, 820 cm^{-1}; ^{1}H-NMR (CCl_4) δ 1.16 (s, 6H), 1.67 (s, 3H), 2.00 (br s, 1H), 2.08 (d, J = 8.7 Hz, 2H), 4.11 (dt, J = 8.7 Hz, 1H), 4.80–6.20 (m, 7H).

Alcohol **8f**: 1.00 g (81%); b.p. 100–103°/0.05 mmHg; IR (neat) 3350, 985, 905, 830 cm^{-1}; ^{1}H-NMR (CCl_4) δ 1.17 (s, 3H), 1.57 (s, 3H), 1.67 (s, 6H), 1.33–2.17 (m, 7H), 4.17 (dt, J = 6.3 Hz, 1H), 4.83–6.17 (m, 8H).

Silylation of alcohols **8**

Alcohol **8** was heated at 150° for 1 h in hexamethyldisilazane in the presence of a catalytic amount of imidazole. Fractional distillation from the reaction vessel provided the trimethylsilyl ether **9** in the indicated yields.

Trimethylsilyl ether **9e**: 0.72 g (84%); b.p. 67–69°/5 mmHg; IR (neat) 990, 915, 840 cm^{-1}; ^{1}H-NMR (CCl_4) δ 0.05 (s, 9H), 1.13 (s, 6H), 1.62 (2s, 3H), 2.03 (d, J = 6.9 Hz, 2H), 4.13 (dd, J = 6.9 Hz, 1H), 4.80–6.20 (m, 7H).

Trimethylsilyl ether **9f**: 1.52 g (85%); b.p. 100–110°/0.05 mmHg; IR (neat) 990, 910, 840 cm^{-1}; ^{1}H-NMR (CCl_4) δ 0.05 (s, 9H), 1.17 (s, 3H), 1.57 (s, 3H), 1.67 (s, 6H), 1.33–2.17 (m, 6H), 4.17 (dt, J = 6.3 Hz, 1H), 4.83–6.17 (m, 8H).

Tandem oxy-Cope–Cope rearrangement of **8** *or* **9**

Alcohol **8** or trimethylsilyl ether **9** was heated neat in a sealed tube at 250° or under reflex in NMP. The rearrangement was monitored by GLC and TLC until complete. The rearranged aldehyde **10** was isolated after usual workup followed by silica-gel column chromatography. The geometrical assignment was made by GLC comparison with an authentic mixture prepared from linalool or (6*E*)- or (6*Z*)-neroridol via Saucy–Marbet rearrangement.[20]

Geranylacetaldehyde **10e**: IR (neat) 1725, 835 cm^{-1}; ^{1}H-NMR (CCl_4) δ 1.57 and 1.67 (2s, 9H), 1.83–2.10 (m, 6H), 2.20–2.47 (m, 2H), 5.07 (m, 2H), 9.80 (br s, 1H); GLC (PEG 20M, 180°), R_t = 29.3 and 31.6 min (33:67).

Farnesylacetaldehyde **10f**: IR (neat) 1730, 840 cm^{-1}; ^{1}H-NMR (CCl_4) δ 1.56–1.65 (2s, 12H), 1.83–2.17 (m, 10H), 2.20–2.47 (m, 2H), 5.07 (m, 3H), 9.77 (br s, 1H); GLC (OV 1, 150°) R_t = 14.6, 17.0 and 18.3 min (18:57:25).

Sequential [2,3]-*Wittig–Claisen rearrangement*

Preparation of 4,7-*nonadienal* (**11c**) *via Saucy–Marbet rearrangement.*[20] 1,5-Heptadien-3-ol (**2c**) (5.44 g, 48 mmol) in ethylvinyl ether (46.8 ml, 484 mmol) was heated at 140° for 2 h in the presence of mercuric acetate (2.96 g, 9.2 mmol). Potassium carbonate was then added to the reaction mixture.

The ppt was filtered off using Et_2O. The filtrate was chromatographed through Florisil using hexane as an eluent. The resultant filtrate was evaporated and then distilled to give 4,7-nonadienal **11c** (3.8 g, 56%): b.p. 36–38°/0.1 mmHg (> 98% chemical purity by GC assay); IR (neat) 2820, 2720, 1730, 970 cm^{-1}; ^{1}H-NMR (CCl_4) δ 1.66 (m, 3H), 2.25–2.53 (m, 4H), 2.53–2.78 (m, 2H), 5.28–5.53 (m, 4H), 9.90 (m, 1H).

Ethyl 4,7-tridecadienoate (**12d**). The orthoester Claisen modification of **2d** was carried out according to the literature procedure[21] to give the ester **12d** in 87% yield: b.p. 124–127°/3 mmHg (> 98% chemical purity by GC assay); IR (neat) 1740, 1375, 1250, 1180, 1160, 1040, 970 cm^{-1}; ^{1}H-NMR (CCl_4) δ 0.80–1.00 (m, 3H), 1.10–1.50 (m, 6H), 1.23 (t, J = 7.2 Hz, 3H), 1.82–2.16 (m, 2H), 2.22–2.40 (m, 4H), 2.57–2.79 (m, 2H), 4.11 (q, J = 7.2 Hz, 2H), 5.15–5.69 (m, 4H).

4,6-Dimethyl-4,7-octadienoic acid (**13e**). The [2,3]-Wittig rearrangement of 1-(2-methyl-2-propenyloxy)-2-butene (**1e**) was carried out as described above and then acetyl chloride was added to the resultant soln to give 2,4-dimethyl-3-acetoxy-1,5-hexadiene in 68% yield (b.p. 75–83°/25 mmHg). The Ireland–Claisen modification of the acetate thus obtained according to the literature procedure[22] afforded the ester **13e** in 79% yield: b.p. 67–74°/3 mmHg (> 95% chemical purity by GC assay); IR (neat) 3700, 2800, 1710, 1635, 995, 810 cm^{-1}; ^{1}H-NMR (CCl_4) δ 1.03 (d, J = 6.6 Hz, 3H), 1.66 (s, 3H), 2.09–2.61 (m, 4H), 2.81–3.30 (m, 1H), 4.79–5.23 (m, 3H), 5.73 (ddd, J = 17.7, 9.9 and 5.7 Hz, 1H), 9.60 (br s, 1H).

Formal total synthesis of (±)-cerulenin (**14**)

Preparation of epoxide **16**. Treatment of **11c** (2.78 g, 20.1 mmol) with NaH (0.96 g, 20 mmol) and trimethylsulfonium iodide (4.08 g, 20 mmol) in 20 ml of DMSO according to the standard procedure[28] gave 1,2-epoxy-(*E,E*)-5,8-decadiene **16** (2.68 g, 88%): b.p. 54–57°/2 mmHg: IR (neat) 3000, 2950, 2900, 2850, 1450, 1260, 960, 915, 840 cm^{-1}; ^{1}H-NMR (CCl_4) δ 1.62 (m, 5H), 2.10 (m, 2H), 2.30 (dd, J = 5.7 and 3.4 Hz, 1H), 2.50–3.00 (m, 4H), 5.40 (m, 4H).

Preparation of the butenolide **15**. Compound **15** was prepared according to essentially the same procedure as that reported by Uda and co-workers.[26] Treatment of **16** (0.754 g, 4.95 mmol) with a dilithium species derived from phenylthioacetic acid (0.756 g, 4.50 mmol) and LDA in 10 ml of THF. The reaction mixture was quenched with H_2O. The aq phase was separated, acidified with 3 N HCl and saturated with NaCl. After usual workup, evaporation gave the hydroxycarboxylic acid (1.12 g, 78%). The hydroxy acid (0.906 g, 2.82 mmol) was heated in C_6H_6 to give the α-phenylthio-γ-butyrolactone **17** (0.855 g, quant) after evaporation: IR (neat) 3070, 3040, 2950, 2860, 1770, 1450, 1360, 1200, 1095, 1060, 975, 790, 765, 699 cm^{-1}; ^{1}H-NMR (CCl_4) δ 1.40–1.90 (m, 5H), 1.90–2.40 (m, 4H), 2.50–2.90 (m, 2H), 3.40–4.70 (m, 2H), 5.40 (m, 4H), 7.00–7.67 (m, 5H). The lactone **17** (0.46 g, 1.52 mmol) was treated with MCPBA (0.262 g, 1.52 mmol) in CH_2Cl_2 at −78° to give α-sulfinyl-γ-butyrolactone (0.485 g, quant): IR (neat) 3070, 3040, 2950, 2860, 1770, 1450, 1360, 1200, 1095, 1060, 975, 790, 765, 699 cm^{-1}; ^{1}H-NMR (CCl_4) δ 1.40–2.90 (m, 11H), 3.70–4.70 (m, 2H), 5.40 (m, 4H), 7.20–7.90 (m, 5H). The resultant lactone (0.477 g, 1.5 mmol) was heated at 110° in xylene in the presence of $CaCO_3$ (3 mmol) to afford the butenolide **15** in 76% yield after silica-gel column chromatography: IR (neat) 3050, 3000, 2900, 2830, 1750, 1440, 1320, 1160, 1100, 1020, 965 cm^{-1}; ^{1}H-NMR (CCl_4) δ 1.50 1.90 (m, 5H), 1.90–2.40 (m, 2H), 2.50–2.90 (m, 2H), 4.80–5.20 (m, 1H), 5.40 (m, 4H), 6.00 (dd, J = 6.0 and 1.5 Hz, 1H), 7.45 (dd, J = 6.0 and 1.5 Hz, 1H). The spectral data are in good agreement with those reported.[25]

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