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A convergent asymmetric synthesis of γ-butenolides

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Au Professeur H. B. Kagan, avec toute mon admiration

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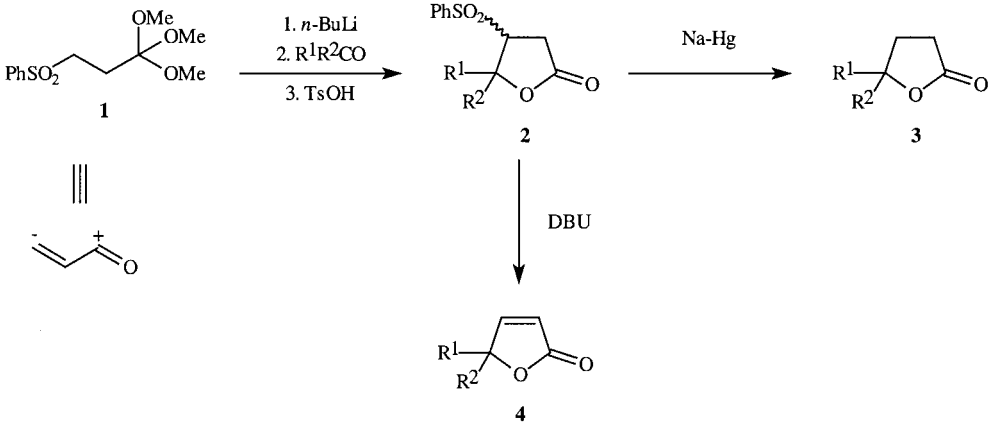
Abstract—The addition of aldehydes to the new enantiomerically pure lithiated sulfoxide-orthoester 13 yielded γ-butenolides of high enantiomeric purities after elimination of phenylsulfinic acid. The cyclocondensation with ketones was less stereoselective. This new asymmetric synthesis of γ-butenolides has been applied to a convergent preparation of the antifungal antibiotic (+)-cerulenin.

1. Introduction

γ-Lactones and butenolides (γ-substituted-2(5*H*)-furanones) form an important class of compounds which appear as substructures in many natural products and also constitute pivotal building blocks for the synthesis of a wide range of biologically active compounds. Consequently, the development of efficient routes towards enantiomerically pure butenolides has received considerable attention. They have been obtained by resolution,[1] by transformation of products of the chiral pool,[2] or by asymmetric syntheses using microbial[3] or chiral reagents.[4]

Recently, a convergent and general method of synthesis of γ-lactones and butenolides has been reported from our laboratory.[5] It involved the cyclocondensation of aldehydes or ketones with a C_3 reagent **1** acting as a 1,3 dipole equivalent (Scheme 1). The wide scope of the method prompted us to study an asymmetric version of the sequence.[6] We now report the full details of these studies and their application to



Scheme 1.

Keywords: sulfoxides; asymmetric synthesis; cyclocondensation; γ-butenolides; cerulenin.

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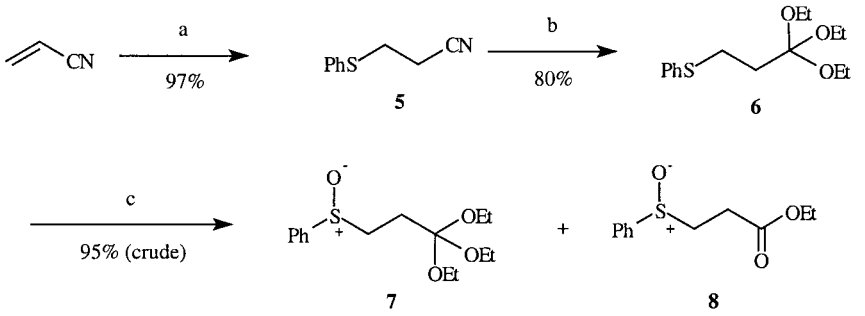
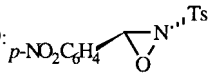
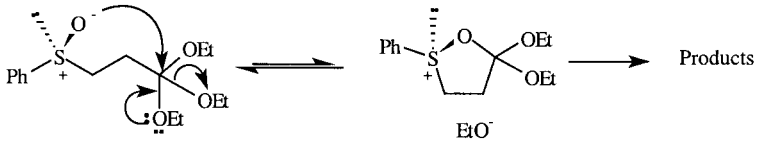


Scheme 2. Conditions: (a) PhSH, Et_3N in MeOH, rt; (b) HCl_g in EtOH (sat.), rt; (c) (±)-**9** in CH_2Cl_2. **9**: 



Scheme 3.

an enantioselective synthesis of the antifungal antibiotic (+)-cerulenin.

2. Synthesis of the C_3 reagent

Arylsulfoxide-stabilised carbanions have been shown to add to aldehydes with high stereoselectivities[7] with the exception of the dianion derived from γ-phenylsulfinylpropionic acid.[8] We felt that the replacement of the carboxyl group by an orthoester would generate a monoanion adding to prochiral carbonyl compounds with higher facial selectivity. The corresponding C_3 reagent **7** could not be prepared by the obvious method consisting of the reaction of menthyl tolylsulfinate with a Grignard reagent (Anderson's method[9]) because the orthoesters were unstable under these conditions.

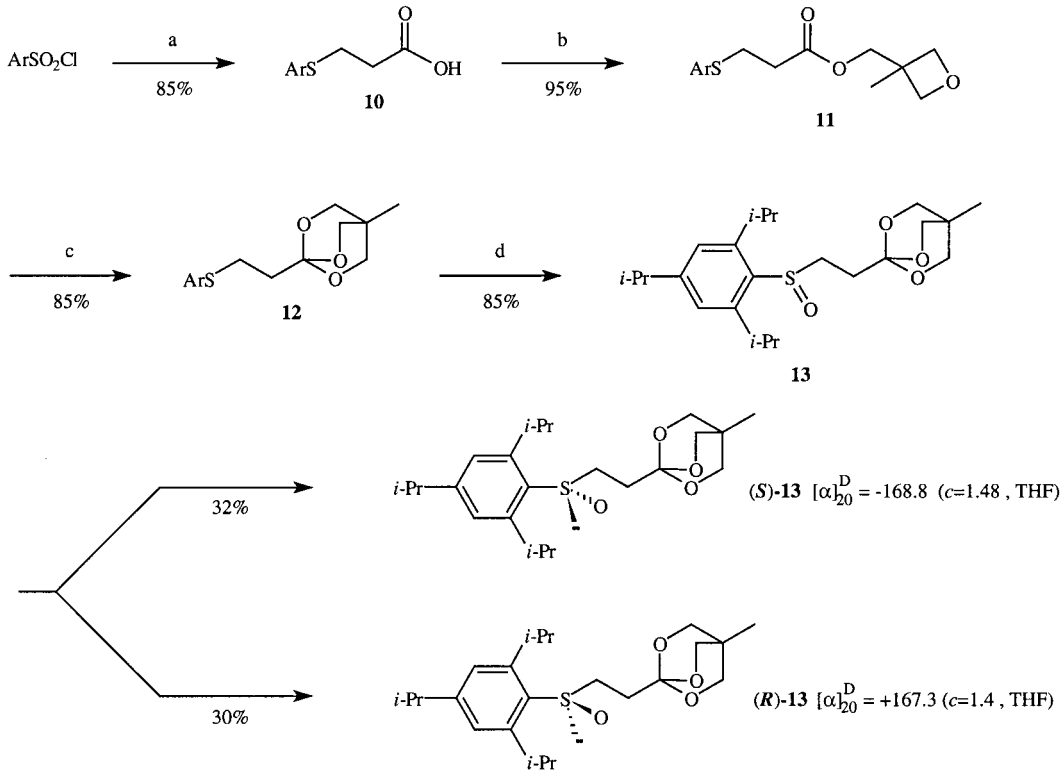
A conventional sequence of reaction gave the sulfide-orthoester **6** which was oxidised to the corresponding sulfoxide with (±)-oxaziridine **9**[10] (Scheme 2). The corresponding sulfoxide was obtained in good yields, but was always contaminated by ±10% of the corresponding ester **8**. All attempts to purify **7** led to increasing amount of ester **8** accompanied by unidentified products. The intrinsic instability of **7** probably resulted from an anchimeric assistance of the ionisation of the orthoester by sulfoxide (Scheme 3).

We then selected the bicyclic orthoester described by Corey et al. for its greater stability and its easy preparation from the corresponding carboxylic acid.[11] A bulky aryl substituent was selected (a) to hinder the sulfoxide group which would be less prone to assist the ionisation of the orthoester, (b) to enhance the facial selectivity in both the asymmetric oxidation of the sulfide precursor and the addition of the sulfoxide-stabilised anion to a carbonyl group.

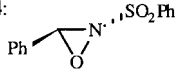
The sulfide-orthoester **12** was readily prepared in three steps from simple starting materials (Scheme 4). It was cleanly converted into the corresponding racemic sulfoxide **13** by reaction with *rac*-oxaziridine **14** under strictly anhydrous conditions. There was no contamination by the corresponding ester. The moisture-sensitive orthoester-sulfoxide **13** could be kept for several weeks at rt under dry atmosphere.

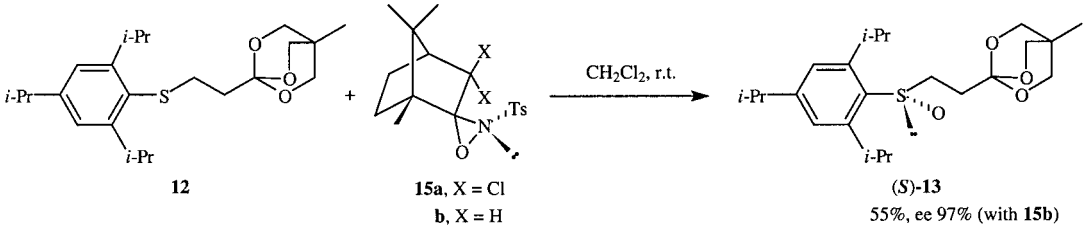
Resolution of *rac*-**13** was readily effected by preparative hplc followed by recrystallisation of the enantiomers in ethyl acetate. Both enantiomers were obtained in good yields and high enantiomeric purities (≥99.9%). The absolute configuration of the (−)-enantiomer **13** was shown to be (*S*) by an X-ray diffraction analysis.[12]

The need for a resolution by hplc led us to examine an alternative route for the synthesis of individual enantiomers of **13**. We considered the asymmetric oxidation of sulfides to sulfoxides which has already been widely explored with many different oxidants.[13] However, we found that very few of these reagents have general application and even fewer would be compatible with the presence of the sensitive orthoester function. In earlier experiments, we had selected Kagan's modification of the Sharpless epoxidation system.[13a] However, the bulky triisopropylphenyl-substituted sulfide group of **12** could not be oxidised by Kagan's reagent even after 48 h at rt. The inertness of **12** towards oxidants was further confirmed by the slow rate of its reaction with Davis' camphorsulfonyloxaziridine reagents **15a** and **b**[14] (Scheme 5). The reactions had to be conducted at rt for c.a. 2–3 days with the more reactive **15a** and for c.a. 5 days with **15b**. We used **15b** in most cases because it was easier to prepare. With (+)-**15b**, yields of pure (*S*)-**13** were reproducibly 50–55% with an ee of 97%. This method represents a convenient asymmetric synthesis of both enantiomers (*S*)- and (*R*)-**13** in high enantiomeric purity.



Scheme 4. *Conditions*: (a) $LiAlH_4$, Et_2O, Δ then methylacrylate (3 equiv.), Et_3N 5% in MeOH followed by LiOH in aqueous THF; (b) *N*,*N*-carbonyldiimidazole (1.07 equiv.) in CH_2Cl_2 then 3-methyl-3-oxetanemethanol (1.2 equiv.); (c) $BF_3{\cdot}OEt_2$ (0.25 equiv.), CH_2Cl_2; (d) **14**, CH_2Cl_2; (e) preparative hplc on Chiralpak-AD column, elution with dry *n*-hexane/*i*-propanol (9:1), recrystallisation in dry AcOEt. **14**:





Scheme 5.

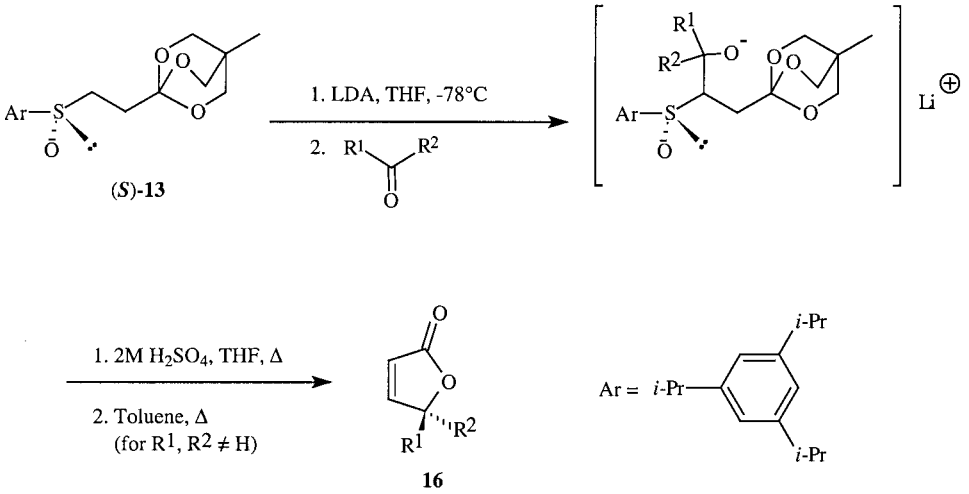
3. Asymmetric synthesis of γ-butenolides

Treatment of enantiomerically pure (*S*)-**13** C_3-reagent with LDA gave the corresponding sulfoxide-stabilised carbanion (Scheme 6). At −78°C over a period of 6 h, it quantitatively added to both aldehydes and ketones. At −40°C, the reaction was not complete, probably as a result of a less favourable equilibrium or/and a competitive enolisation of the carbonyl compound under these strongly basic conditions. The crude adducts were directly refluxed in THF containing aqueous 2 M H_2SO_4. With the aldehyde adducts **16** (R^2=H), both cyclisation and elimination of phenylsulfenic acid were complete after 12 h. With the ketone adducts **16** (R^1, R^2≠H), the elimination step was slower: additional reflux of the worked-up mixture in toluene was needed.

A representative series of carbonyl compounds was then converted into the corresponding γ-butenolides by this one pot, three-step sequence using enantiomerically pure (*S*)-**13** as C_3 component. Table 1 shows that: (a) yields were good. As a matter of fact the total yield is higher with sulfoxide reagent **13** than with the corresponding sulfone reagent **1**.[5] Thus, even for the production of racemic γ-butenolide, we recommend the racemic sulfoxide reagent **13** instead of the phenylsulfone **1**; (b) enantiomeric excesses vary. They were high with aliphatic and aromatic aldehydes. *trans*-Crotonaldehyde gave a much lower ee, but this was the result of partial racemisation under the reaction conditions. As expected, facial selectivity was much lower with ketones.

The absolute configuration of the known butenolides **16a**,[8] **b**,[15] **c**[3a] and **g**[8] were assigned by comparison of their optical rotations with those reported earlier. Absolute configurations of **16d–f** were assigned by analogy.

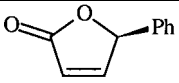
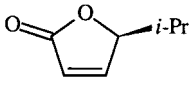
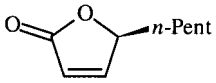
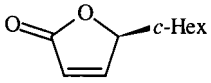
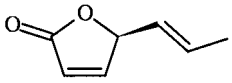
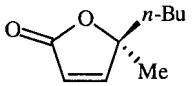
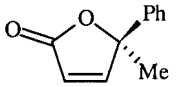
The absolute configuration of all butenolides **16a–f** (major



Scheme 6.

isomer) can be explained or (and) predicted on the basis of a six-membered ring transition state with a lithium cation coordinated to the oxygen atom of the carbonyl and sulfinyl groups (Figs. 1 and 2).[9a,16] There are four possible transition states for the addition of the lithium carbanion derived from (*S*)-**13** to a prochiral carbonyl compound. Both transition states B and C should be disregarded, since they involve an approach of the carbonyl compound on the face containing the very bulky aryl substituent of the sulfur atom.

Table 1. Asymmetric synthesis of γ-butenolides **16**

Entry	γ-Butenolide **16**	Yield (%)	ee[a] (%)	$[\alpha]^{20}_D$ ($CHCl_3$)
1	 **16a**	79	93	+271.2 (*c* 1.02) (*R*)
2	 **16b**	78	90	+109.5 (*c* 1.02) (*S*)
3	 **16c**	79	85	+71.1 (*c* 1.48) (*S*)
4	 **16d**	82	89	+127.7 (*c* 1.01) (*S*)
5	 **16e**	70	53	+55.0 (*c* 0.60) (*S*)
6	 **16f**	95	29	+4.6 (*c* 1.42) (*S*)
7	 **16g**	65	32	+67.9 (*c* 1.22) (*R*)

[a] Measured by chiral GC with racemic mixture of butenolide as reference.

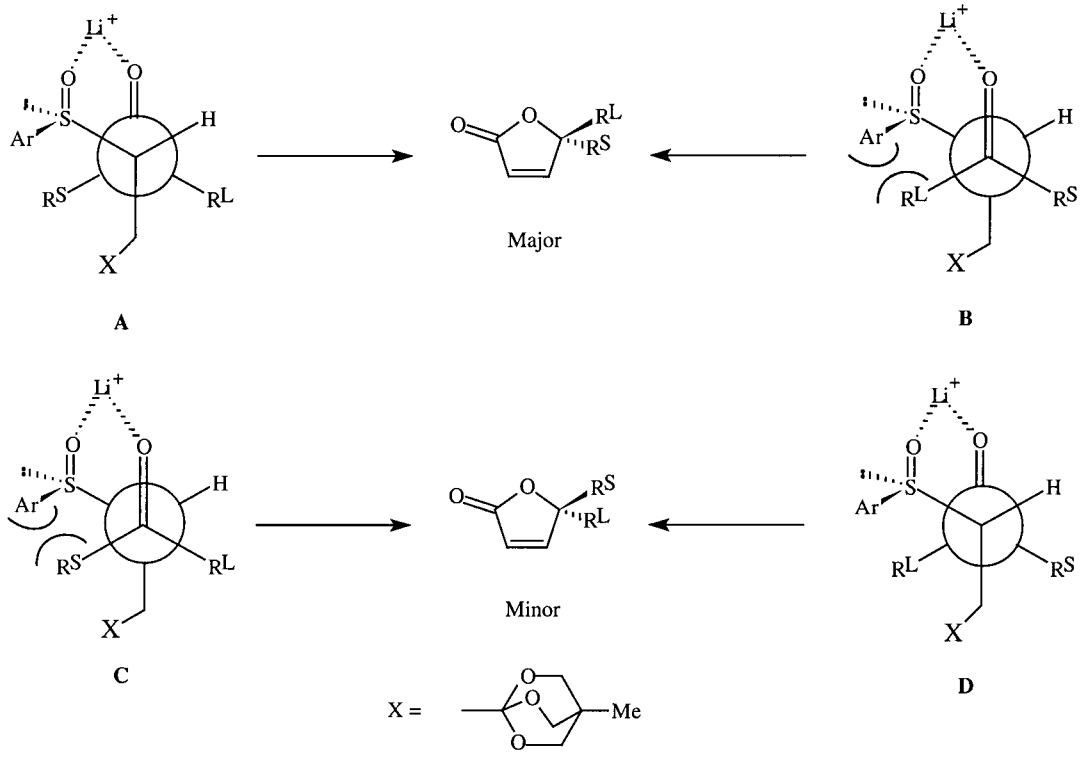


Figure 1.

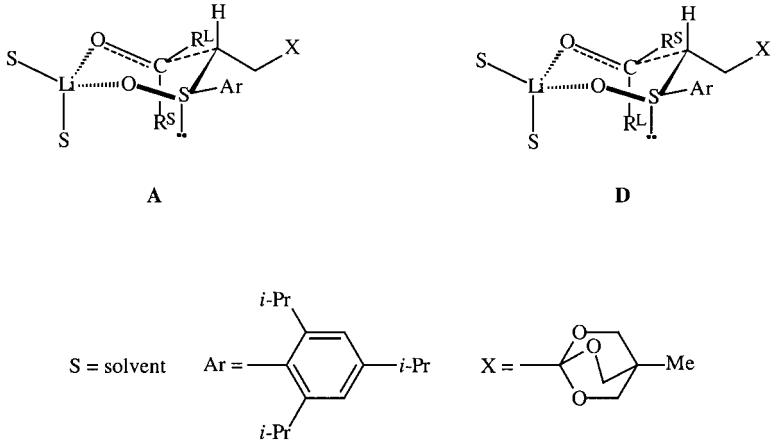


Figure 2.

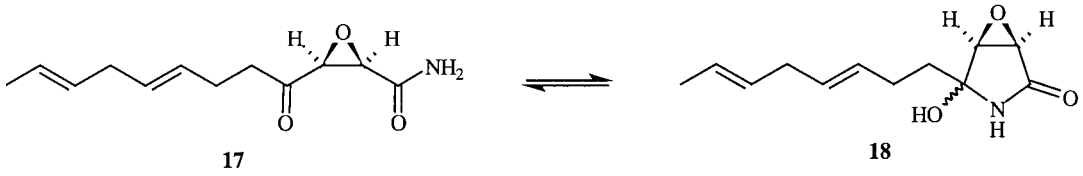
Examination of the most probable chair conformation of transition states, A and D, easily explain the observed facial selectivities. A has all large groups equatorial whereas, in D, the largest substituent of the aldehyde is axial. Thus A should be of lower energy than D. This explains the good facial selectivity with aldehydes (R_S much smaller than R_L) and the poor selectivity with ketones (R_S not very different from R_L).

4. Application to the total asymmetric synthesis of (+)-cerulenin

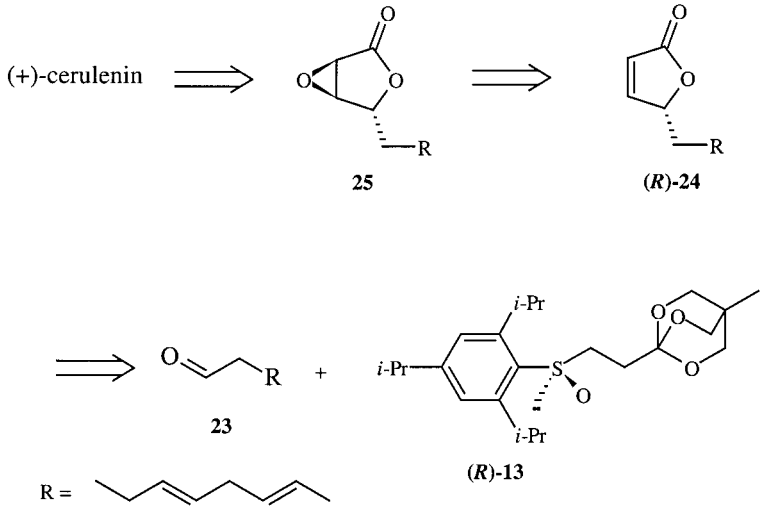
(+)-Cerulenin **17** is an antifungal antibiotic which was first isolated from the culture filtered of *Cephalosporium caerulens*.[17] This natural product is a powerful inhibitor of fatty acid biosynthesis in a variety of yeast cells.[18] It was also found to be inhibitory for various bacteria, fungi and yeasts.[19] In protic conditions, the molecule can cyclise to a mixture of diastereomeric γ-lactams **18** (Scheme 7). The actual active tautomer of **17** is still unknown.

As a result of its interesting biological activity and its peculiar structural features, this natural product has attracted much interest in the community of synthetic chemists.[20] Still, only six syntheses lead to the optically active natural compound.[21] Several are rather long and linear. The best yields were obtained by the convergent routes developed by Yoda et al.[21c] (19.5%, 7 steps) and Townsend et al.[21e] (26%, 10 steps).

Our retrosynthetic Scheme 8 involved butenolide (*R*)-**24** as



Scheme 7.

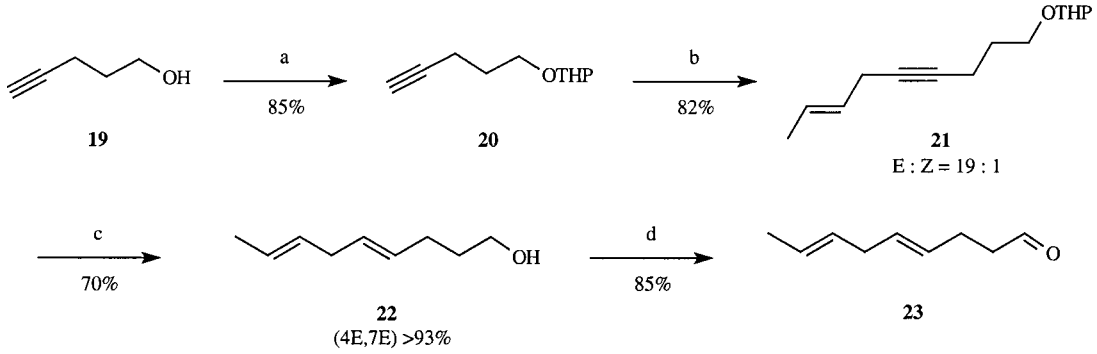


Scheme 8.

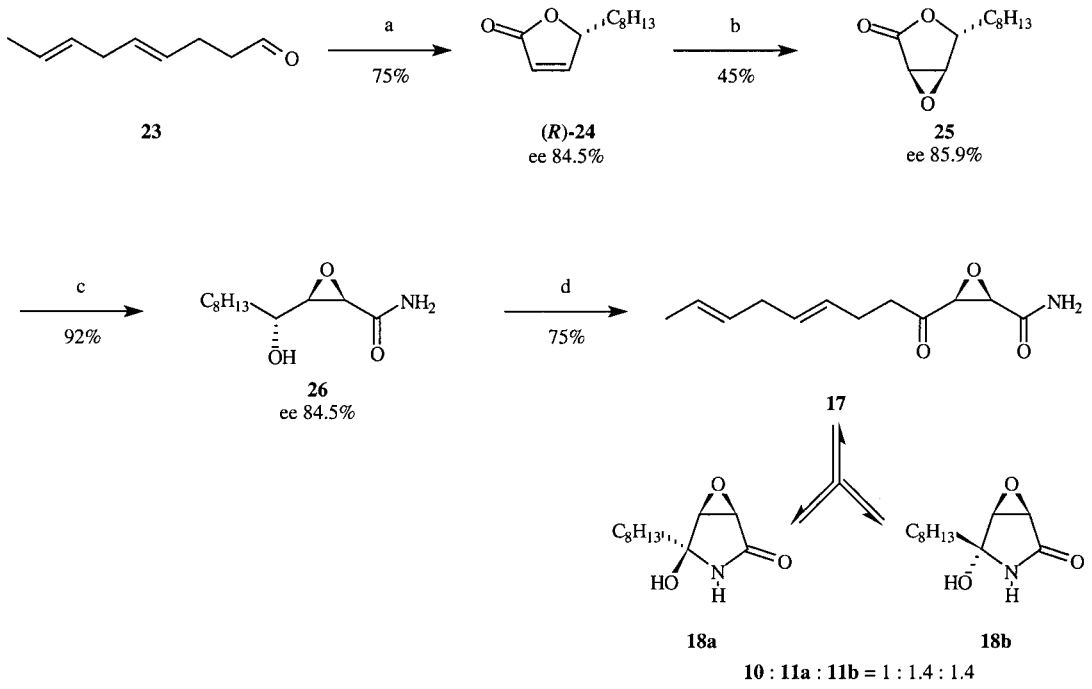
key intermediate. This compound has already been converted into (+)-cerulenin.[20b] It should be easily prepared by the one-pot asymmetric synthesis of butenolides described above, starting from the (*R*) enantiomer of the C_3 reagent.

The aldehyde compound is (4*E*,7*E*)-nonadienal **23** which had been prepared earlier by Townsend et al.[21e] Having experienced some problems in scaling up the described synthesis, we devised another route shown in Scheme 9. The protected pentynol **20** was coupled with *trans*-crotyl bromide to yield 82% of **21** (*E*/*Z*=19:1). Reduction of the triple bond by lithium in liquid ammonia followed by methanolysis gave (4*E*,7*E*)-nonadienal **22** (isomeric purity≥93%). Swern oxidation gave aldehyde **23**, which was not stable and was therefore, immediately used in the butenolide synthesis. This synthetic route compares well with that of Townsend et al. in terms of yields (±42%) and selectivity (≥93% of *E*,*E* isomer).

The aldehyde **23** was then reacted with the enantiomerically pure C_3-reagent (*R*)-**13** as described above (Scheme 10). The butenolide (*R*)-**24** was obtained in 75% yield and 84.5% ee (chiral hplc). It was converted in three steps into (+)-cerulenin: stereoselective oxidation to the epoxylactone **25** was effected following the procedure described by Hegedus et al.,[21d] aminolysis of **25** as described before, and oxidation of the resulting alcohol **26** to (+)-cerulenin was performed as described by Townsend et al.[21e] The natural product was obtained as a mixture of three tautomers. Intermediates **25** and **26** were obtained with ee≅84–85% showing that all transformations had occurred



Scheme 9. *Conditions*: (a) 2,3-dihydropyrane, PTSA, CH_2Cl_2, Δ; (b) *n*-BuLi, CuBr·DMS, THF, −78°C then *trans*-crotyl bromide, −78°C → rt, 8 h; (c) Li, NH_3, *t*-BuOH, $(NH_4)_2SO_4$, −78°C then MeOH, PPTS, 40°C; (d) DMSO, oxalyl chloride, Et_3N in CH_2Cl_2, −78°C.



Scheme 10. *Conditions*: (a) LDA, THF, −78°C+(*R*)-**13**, add **23**, 6 h, −78°C, then H_2SO_4, Δ, 12 h; (b) NaClO, Et_2O–DMF, 0°C; (c) NH_3 in MeOH, 0°C; (d) $TPAP_{cat}$, NMO, CH_2Cl_2, MS 4 Å, rt, 1 h.

without epimerisation. It is therefore reasonable to assume that the ees of each of the tautomer of (+)-cerulenin is also in the range 84–85%.

This nine-step asymmetric synthesis of (+)-cerulenin is rather short and practical although, it gives lower yield (9%, 10 steps) than Yoda's and Townsend's previous syntheses. However, its highly convergent character makes it uniquely suited for the synthesis of analogs of (+)-cerulenin for agrochemical and pharmacological studies.

5. Experimental

5.1. General

^1H and ^{13}C NMR spectra were recorded with a Varian Gemini-200, VXR-200, Gemini-300 or Brucker AM-500; $CDCl_3$ was used as solvent and tetramethylsilane as internal reference, δ_H values are in ppm. IR spectra were registered on a BIO-RAD TFS 135 FT-IR spectrometer. All absorption values are expressed in wavenumbers (cm^{-1}). Mass spectra were recorded with a Finnigan MAT-TSQ 700 apparatus. $[\alpha]_D$ values were obtained on a Perkin–Elmer 241 MC polarimeter. Melting points are uncorrected. Enantiomeric excesses were measured on hplc with a Millipore Waters 600 Controller, UV Millipore Waters 486 as detector and fitted with Diacel Chiralpak-AD, -AS, OD-H analytical column. A Carlo Erba Fractovap GC apparatus was used fitted with a polymethoxysiloxane RSL-150 column (achiral phase) or Chrompack CP-Chirasil-Dex-Cb (Chiral phase). Resolution on preparative hplc were run on an apparatus developed by Dr E. Cavoy (UCB-Pharma, Belgium) and fitted with a Diacel Chiralpak-AD column (L=25 cm, ϕ=5 cm). TLC were run on silicagel $60F_{254}$; column chromatography was performed with gel 60 (60–200 μm, Merck) or with gel 40 (230–400 μm, Merck). THF, Et_2O were dried on Na/benzophenone and distilled; CH_2Cl_2, 1,2-dichloroethane, AcOEt, *n*-hexane, petroleum ether, *i*-Pr_2NH were dried on CaH_2 then distilled, EtOH was dried on magnesium ethoxide and distilled. Aldehydes and ketones were distilled before use.

5.1.1. 3-(Phenylsulfenyl)propanenitrile 5. 5.8 mL (88 mmol) of acrylonitrile was added dropwise to a solution containing 10 mL of thiophenol (97 mmol) and 0.6 mL of Et_3N (4 mmol) in 180 mL of methanol. The reaction mixture was stirred overnight then concentrated under reduced pressure. The oily residue was purified by bulb-to-bulb distillation (120°C, 10^{-3} mmHg) to give pure sulfide **5**. Yield: 13.65 g (95%). ^1H NMR: 2.58 (t, 2H, J=7.5 Hz), 3.12 (t, 2H, J=7.5 Hz), 7.26–7.45 (m, 5H). ^{13}C NMR: 17.9, 29.8, 117.8, 127.3, 129.1, 131, 133. IR (CH_2Cl_2): 3050, 2929, 2240, 1590. Mass (EI+Q1MS): 163, 123, 109, 77, 54.

5.1.2. 1,1-Diethoxy-3-(phenylsulfenyl)propyl ethyl ether 6. *Step A*. A cooled solution (−35°C) of 10 g (61.26 mmol) of nitrile **5** and 5.35 mL of dry ethanol in 50 mL of methylene chloride was saturated with anhydrous gaseous hydrogen chloride. The solution was kept at 5°C for 20 h then concentrated in vacuo. The residue was washed with dry ether and the solvent was removed under reduced pressure. The iminoester salt was obtained in quantitative yield and used without purification. ^1H NMR: 1.44 (t, 3H, J=7.1 Hz), 3.06 (t, 2H, J=7.0 Hz), 3.30 (t, 2H, J=7.0 Hz), 4.56 (q, 6H, J=7.1 Hz), 7.2–7.5 (m, 5H), 11.5 (s_{broad}, 1H), 12.4 (s_{broad}, 1H). ^{13}C NMR: 13.5, 30.0, 33.5, 71.0, 127.3, 129.2, 131, 134, 177, I.R.: 3300, 2400, 1655, 1590, 1090.

Step B. A solution of the iminoester salt (17 g, 59.8 mmol) in 55 mL of anhydrous methylene chloride and 33 mL of ethanol was kept at rt for 60 h. The precipitate was filtered

and solvents were removed in vacuo. The residual oil was treated with dry ether and insoluble materials were filtered off. The oily residue was purified by flash chromatography using silicagel (petroleum ether/diethyl ether, 20:80), which had been treated with an eluent containing 5% of Et_3N or by bulb-to-bulb distillation (bp 150°C, 0.5 mmHg). Yield: 13.6 g (80%). ^{1}H NMR: 1.19 (t, 9H, J=7.1 Hz), 2.1–2.18 (m, 2H), 3.11–3.19 (m, 2H), 3.7 (q, 6H, J=7.1 Hz), 7.5–8.0 (m, 5H). ^{13}C NMR: 14.8, 27.4, 32, 56.9, 113.9, 125.8, 128.5, 129.1, 136.1. I.R. (CH_2Cl_2): 3060, 2990, 2950, 2895, 1590, 1480, 1170. Mass (EI+Q1MS): 239, 147, 123, 109, 137, 284. Anal. calcd for $C_{15}H_{24}O_3S$: C 63.34%, H 8.50%, S 11.27%; found: C 63.21%, H 8.58%, S 10.70%.

5.1.3. Phenyl 3,3,3-triethoxypropyl sulfoxide 7. To a solution of sulfide **6** (500 mg, 1.75 mmol) in anhydrous methylene chloride (5 mL) was added dropwise 560 mg of oxaziridine **9** (1.75 mmol) in CH_2Cl_2 (3 mL). After 2 min, the solvent was removed in vacuo and the resulting solid was triturated in dry ether. The suspension was filtered off and the solvent was removed under reduced pressure to yield crude sulfoxide **7** which could not be separated from ester **8**. Yield: 493 mg (95%). ^{1}H NMR (crude): 1.12–1.25 (m, 9H), 1.89 (ddd, 1H, J=14.7, 11.3, 5 Hz), 2.22 (ddd, 1H, J=14.6, 11.2, 4.9 Hz), 2.72 (ddd, 1H, J=13.5, 11.2, 4.9 Hz), 2.98 (ddd, 1H, J=13.6, 11.3, 4.9), 3.34–3.53 (m, 6H), 7.48–7.64 (m, 5H). ^{13}C NMR (crude): 14.8, 32.1, 38.9, 57.1, 114.1, 124.1, 129.4, 130.9, 141.2. IR (neat): 3062, 2991, 1590, 1170, 1050.

5.1.4. Ethyl 3-phenylsulfinylpropionate 8.[22] ^{1}H NMR: 1.25 (t, 3H, J=7.1 Hz), 2.50–2.60 (m, 1H), 2.85–2.97 (m, 2H), 3.17–3.28 (m, 1H), 4.12 (q, 2H, J=7.1 Hz), 7.5–7.7 (m, 5H). ^{13}C NMR: 13.9, 25.9, 50.8, 60.8, 123.8, 129, 130.9, 142.6, 170.9. IR (CH_2Cl_2): 3060, 2990, 2950, 2920, 1740, 1590, 1490, 1450, 1050.

5.1.5. 2,4,6-Triisopropylbenzenethiol 27.[23] To a suspension of $LiAlH_4$ (115.5 g, 2.89 mol) in anhydrous ether (2 L) was added slowly a solution of 2,4,6-triisopropylbenzensulfonyl chloride (300 g, 0.96 mol) in ether (2 L). The reaction mixture was refluxed for 4 h, cooled to 0°C and neutralised by careful addition of aqueous 2N HCl. Extraction with diethyl ether gave the crude thiol in quantitative yield (227 g). It could be further purified by bulb-to-bulb distillation (110°C, 1.3×10^{-3} Bar) or used without any purification. ^{1}H NMR: 1.24 (d, 6H, J=6.9 Hz), 1.26 (d, 12H, J=7.0 Hz), 2.87 (hept, 1H, J=6.9 Hz), 3.07 (s, 1H), 3.51 (hept, 1H, J=7.0 Hz), 7.01 (s, 2H). ^{13}C NMR: 23.3, 24.1, 31.8, 34.2, 121.3, 124.0, 147.1, 148.2. Mass (EI+Q1MS): 221, 236, 193, 203.

5.1.6. Methyl 3-[(2,4,6-triisopropylphenyl)sulfenyl]propionate 28. A solution of thiol **27** (100 g, 423 mmol) and methyl acrylate (76 mL, 846 mmol) in methanol (428 mL) containing 3 mL of Et_3N was stirred overnight. Evaporation of the solvent gave quantitatively the methyl ester (136.5 g), which could be used without any purification. ^{1}H NMR: 1.23 (d, 12H, J=6.9 Hz), 1.25 (d, 6H, J=6.9 Hz), 2.55 (t, 2H, J=7.6 Hz), 2.87 (t, 2H, J=7.6 Hz), 2.81–2.94 (m, 1H), 3.65 (s, 3H), 3.89 (hept, 2H, J=6.9 Hz), 7.01 (s, 2H). ^{13}C NMR: 23.9, 24.4, 31.4, 32.3, 34.2, 34.2, 51.6, 121.8, 127.4, 149.7, 153.1, 172.3. IR (neat): 3043, 2962, 2929, 2869, 1745, 1169. Mass (EI+Q1MS): 203, 189, 322. HRMS (EI): calcd for $C_{19}H_{30}O_2S$: 322.1966; found: 322.1974.

5.1.7. 3-[(2,4,6-Triisopropylphenyl)sulfenyl]propionic acid 10. A biphasic mixture of methyl ester **28** (207 g, 609 mmol), LiOH (137 g, 1.830 mol), THF (2.6 L) and water (1.8 L) was stirred at rt for 7 h. After acidification by addition of 6N HCl (pH 1) and extraction by CH_2Cl_2, the combined organic phases were concentrated under reduced pressure. The crude acid was purified by recrystallisation in hot *n*-hexane to give needles (mp: 122–124°C). Yield: 159.7 g (85%). ^{1}H NMR: 1.23 (d, 12H, J=6.8 Hz), 1.25 (d, 6H, J=6.9 Hz), 2.59 (t, 2H, J=7.3 Hz), 2.87 (hept, 1H, J=6.9 Hz), 2.87 (t, 2H, J=7.3 Hz), 3.89 (hept, 2H, J=6.9 Hz), 7.00 (s, 2H), 10.2 (s_{broad}, 1H). ^{13}C NMR: 23.8, 24.4, 31.5, 31.9, 34.1, 34.2, 121.9, 127.3, 149.8, 153.2, 178.3. IR (KBr,): 3044, 2964, 2656, 1701. Mass (CI+Q1MS): 309, 267, 249, 203. Anal. calcd for $C_{18}H_{28}O_2S$: C 70.08%, H 9.15%, S 10.39%; found: C 70.20%, H 9.13%, S 10.17%.

5.1.8. (3-Methyl-3-oxethanyl)methyl 3-[(2,4,6-triisopropylphenyl)sulfenyl]propionate 11. A solution of 50 g of acid **10** (0.163 mol) in 210 mL of anhydrous methylene chloride was added dropwise to a suspension of *N*,*N*′-carbonyldiimidazole (28.3 g, 0.175 mol) in methylene chloride (210 mL). After 30 min, 3-methyl-3-oxetanemethanol (20 mL, 0.2 mol) was added. After 36 h at rt, the mixture was concentrated in vacuo and the crude product was purified by flash chromatography (petroleum ether/AcOEt, 4:1) on silicagel, pretreated with a mixture of petroleum ether/ethyl acetate (4:1) containing 5% of Et_3N. Yield: 60.8 g (95%) (colourless oil). ^{1}H NMR: 1.23 (d, 12H, J=6.9 Hz), 1.25 (d, 6H, J=6.9 Hz), 1.34 (s, 3H), 2.60 (t, 2H, J=7 Hz), 2.88 (t, 2H, J=7.3 Hz), 2.77–2.98 (m, 1H), 3.88 (hept, 2H, J=6.8 Hz), 4.19 (s, 2H), 4.44 (AB, 4H, J=26.2 Hz), 7.01 (s_{broad}, 2H). ^{13}C NMR: 21.1, 23.8, 24.4, 31.4, 32.5, 34.2, 34.3, 39.1, 68.8, 79.4, 121.8, 127.6, 149.7, 153.0, 171.8. IR (neat): 3047, 2960, 2930, 2869, 1741, 1167, 1017, 985. Mass (EI+Q1MS): 43, 85, 203, 235. HRMS (EI): calcd for $C_{23}H_{36}O_3S$: 392.2385; found: 392.2379.

5.1.9. 2-(4-Methyl-2,6,7-trioxabicyclo[2,2,2]oct-1-yl)ethyl 2,4,6-triisopropylphenyl sulfide 12. 5.84 mL (46.5 mmol) of $BF_3{\cdot}OEt_2$ was added dropwise to a solution of ester **11** (73 g, 186 mmol) in dry methylene chloride (186 mL) at 0°C. The solution was stirred at 0°C for 2 h. Addition of 130 mL of dry Et_3N in ether gave a precipitate, which was filtered off. The solvent was removed under reduced pressure and the crude orthoester was purified by flash chromatography (AcOEt/*n*-hexane, 1:1) using silicagel, which had been treated with an eluent containing 5% of Et_3N. Yield: 62 g (85%). Mp: 148–150°C. ^{1}H NMR: 0.77 (s, 3H), 1.22 (d, 12H, J=6.9 Hz), 1.24 (d, 6H, J=6.9 Hz), 1.89–1.94 (m, 2H), 2.68–2.74 (m, 2H), 2.86 (hept, 2H, J=6.9 Hz), 3.84 (s, 6H), 3.92 (hept, 2H, J=7.3 Hz), 6.98 (s, 2H). ^{13}C NMR: 14.5, 23.9, 24.5, 31.3, 31.4, 31.4, 34.2, 36.9, 72.6, 108.3, 128.3, 128.3, 149.2, 153.1. IR (KBr): 3045, 2958, 2877, 1054. Mass (CI+Q1MS): 393.3, 249.2, 234.2, 157.1. Anal. calcd for $C_{23}H_{36}O_3S$: C 70.36%, H 9.24%, S 8.17%. Found: C 70.45%, H 9.37%, S 8.54%.

5.1.10. 2-(4-Methyl-2,6,7-trioxabicyclo[2,2,2]oct-1-yl)ethyl 2,4,6-triisopropylphenyl sulfoxide 13. *Racemic serie*. To a solution of sulfide **12** (10 g, 25.47 mmol) in anhydrous methylene chloride (20 mL) was added 6.65 g (25.47 mmol) of (±)-*trans*-3-phenyl-2-phenylsulfonyloxaziridine **14**[24] in 20 mL of CH_2Cl_2. After 1 h, the solvent was removed under reduced pressure and the crude mixture was purified by recrystallisation in hot anhydrous AcOEt (30 mL) to yield pure sulfoxide as colourless crystals (mp:145–148°C). Yield: 8.3 g (80%).

Resolution on chiral hplc. 40 mL of a solution of 5 g (25.47 mmol) sulfoxide (±)-**13** in 1 L of an anhydrous mixture of *i*-PrOH/*n*-hexane (10:90) was injected every 12 min on a hplc apparatus fitted with a Chiralpak-AD column (L=25 cm, ϕ=5 cm). The column was eluted with a dry mixture of *i*-PrOH/*n*-hexane (10:90). Each enantiomer was collected, the solvents were removed in vacuo and the enantiomers were recrystallised from anhydrous ethyl acetate. *S enantiomer*: yield 1.6 g (32%). >99.9% ee. $[\alpha]^{20}_D$=−168.8 (*c* 1.48, THF). *R enantiomer*: yield 1.5 g (30%). >99.9% ee. $[\alpha]^{20}_D$=+167.3 (*c* 1.4, THF).

Asymmetric oxidation. In a 25 mL round bottomed flask were introduced 1 g (2.547 mmol) of sulfide **12**, 0.783 g (2.547 mmol) of (+)-*N*-(phenylsulfonyl)camphoroxaziridine **15a**[14] and 3 mL of dry methylene chloride. The solution was stirred for 6 days. Removal of the solvent under high vacuum left a residue which was recrystallised from anhydrous AcOEt to give pure sulfoxide as white solid (mp 145–148°C) in 55% yield (0.572 g). 97% ee (*S* enantiomer), $[\alpha]^{20}_D$=−163.5 (*c* 1.48, THF). ^{1}H NMR: 0.78 (s, 3H), 1.23 (d, 6H, J=6.2 Hz), 1.24 (d, 6H, J=6.7 Hz), 1.24 (d, 6H, J=6.8 Hz), 2.00 (ddd,, 1H, J=6, 10.3, 14 Hz), 2.17 (ddd,, 1H, J=5.2, 10.4, 14.1 Hz), 2.87 (hept, 1H, J=6.8 Hz), 3.03 (ddd, 1H, J=6.1, 10.4, 13.1 Hz), 3.45 (ddd, 1H, J=5.2, 10.4, 13.1 Hz), 3.85–4.09 (m, 2H), 3.86 (s, 6H), 7.05 (s_{broad}, 2H). ^{13}C NMR: 14.3, 23.6, 24.2, 24.4, 27.9, 30.3, 31.4, 34.2, 48.9, 72.7, 108.4, 123, 134.3, 150, 152. IR (cm^{-1}): 3048, 2959, 2879, 1598, 1460, 1398, 1047, 934, 887, 730. MS (CI-Q1MS): 157, 209, 203, 234, 252, 393, 409, 437. Anal. calcd for $C_{23}H_{36}O_4S$: C 67.61%, H 8.88%, S 7.85%; found: C 67.39%, H 9.00%, S 8.10%.

5.2. General procedure for the preparation of γ-butenolides 19

A solution of the sulfoxide (*S*)-**13** (0.5 g, 1.224 mmol) in THF was added dropwise to a solution of LDA (1.1 equiv.) in THF at −78°C. The mixture was stirred for 1 h. The carbonyl compound (1.2 equiv.) was then added dropwise and the reaction mixture was stirred for 6 h at −78°C. The mixture was quenched by 6 mL of H_2SO_4 (2 M) at −78°C. The resulting mixture was then refluxed overnight. Extraction with methylene chloride gave a crude product, which was purified by chromatography on silica gel to yield pure butenolides **16** when starting from aldehydes. With ketones, the product consisted of a mixture of butenolide and the corresponding phenylsulfinyl lactones. It was diluted in 10 mL of toluene and refluxed for 6 h. Addition of water, extraction with methylene chloride and concentration of the combined organic phases yielded crude butenolides, which were purified by chromatography on silicagel. Enantiomeric purities were determined by GC analysis on a 25 m×0.25 mm (ID) CHROMPACK CP-CHIRASIL-DEX-CB column.

5.2.1. (5*R*)-5-Phenyl-2(5*H*)-furanone 16a.[8] Colourless oil. Yield: 155 mg (79%). ee: 93%. $[\alpha]^{20}_D$=+271.2 (*c* 1.02, $CHCl_3$) {Lit.[8] $[\alpha]^{20}_D$=+304 (*c* 1.0, $CHCl_3$)}. ^{1}H NMR: 6.02 (dd, 1H, J=2.1, 1.9 Hz), 6.22 (dd, 1H, J=5.6, 2.1 Hz), 7.25–7.29 (m, 2H), 7.37–7.41 (m, 3H), 7.54 (dd, 1H, J=5.6, 1.9 Hz). ^{13}C NMR: 84.3, 120.9, 126.5, 129, 129.3, 134.3, 155.8, 173.1. IR (CH_2Cl_2): 3057, 1760, 1160, 1090, 1080, 855, 815.

5.2.2. (5*S*)-5-Isopropyl-2(5*H*)-furanone 16b.[15] Colourless oil. Yield: 120 mg (78%). ee: 90%. $[\alpha]^{20}_D$=+109.51 (*c* 1.02, $CHCl_3$), $[\alpha]^{20}_D$=+111.5 (*c* 1.56, dioxane) {Lit.[15] $[\alpha]^{20}_D$=+121 (*c* 2, dioxane)}. ^{1}H NMR: 1.00 (d, 6H, J=6.9 Hz), 1.95–2.11 (m, 1H), 4.84–4.88 (m, 1H), 6.17 (dd, 1H, J=5.7, 2 Hz), 7.46 (dd, 1H, J=5.7, 2 Hz). ^{13}C NMR: 17.6, 17.9, 31.6, 87.9, 122.2, 154.8, 170.5. IR (CH_2Cl_2): 2998, 1760, 1160, 1090, 1080, 855, 815.

5.2.3. (5*S*)-5-Pentyl-2(5*H*)-furanone 16c.[3a] Colourless oil. Yield: 149 mg (79%). ee: 79%. $[\alpha]^{20}_D$=+71.1 (*c* 1.48, $CHCl_3$) {Lit.[3a] (*R*) $[\alpha]^{20}_D$=−85.55 (*c* 1.35, $CHCl_3$)}. ^{1}H NMR:, 0.82–0.88 (m, 3H), 1.19–1.43 (m, 6H), 1.6–1.76 (m, H), 4.97–5.05 (m, 1H), 6.07 (dd, 1H, J=5.7, 2 Hz), 7.44 (dd, 1H, J=5.7, 2 Hz). ^{13}C NMR: 13.8, 22.3, 24.5, 31.3, 33, 83.4, 121.4, 156.4, 173.1. IR (CH_2Cl_2): 2935, 1755, 1163, 1032, 820.

5.2.4. (5*S*)-5-Cyclohexyl-2(5*H*)-furanone 16d.[25] White solid. Mp 45–48°C. Yield: 167 mg (82%). ee: 89%. $[\alpha]^{20}_D$=+127.7 (*c* 1.01, $CHCl_3$). ^{1}H NMR: 1.1–1.3 (m, 5H), 1.7–1.8 (m, 6H), 4.8–4.9 (m, 1H), 6.1 (dd, 1H, J=5.7, 2 Hz), 7.5, 6.1 (dd, 1H, J=5.7, 2 Hz). ^{13}C NMR: 25.6, 25.7, 25.9, 28.0, 28.4, 41.1, 87.4, 121.7, 155.4, 173.1. IR (CH_2Cl_2): 2940, 2860, 1752.

5.2.5. (5*S*)-5-[(*E*)-1-Propenyl]-2(5*H*)-furanone 16e.[25] Colourless oil. Yield: 106 mg (70%). ee: 53%. $[\alpha]^{20}_D$=+55.04 (*c* 0.60, $CHCl_3$). ^{1}H NMR: 1.76 (dd, 3H, J=6.6, 1.6 Hz), 5.35 (ddq, 1H, J=14.8, 7.9, 1.6 Hz), 5.38–5.43 (m, 1H), 5.93 (dq, 1H, J=14.8, 6.6 Hz), 6.12 (dd, 1H, J=5.7, 1.9 Hz), 7.37 (dd, 1H, J=5.7, 1.9). ^{13}C NMR: 17.7, 83.8, 121.4, 124.6, 132.7, 155.2, 172.8. IR ($CHCl_3$): 2950, 1755, 1290, 1075, 1020, 970, 820.

5.2.6. (5*S*)-5-Methyl-5-butyl-2(5*H*)-furanone 16f.[26] Colourless oil. Yield: 179 mg (95%). ee: 29%. $[\alpha]^{20}_D$=+4.57 (*c* 1.42, $CHCl_3$). ^{1}H NMR: 0.89 (t, 3H, J=7.0 Hz), 1.16–1.39 (m, 4H), 1.47 (s, 3H), 1.70–1.78 (m, 2H), 6.01 (d, 1H, J=5.7 Hz), 7.39 (d, 1H, J=5.7 Hz). ^{13}C NMR: 13.7, 22.6, 23.8, 25.7, 37.9, 89.0, 120.3, 160.6, 172.7. IR (CH_2Cl_2): 2935, 1753, 1163, 1032, 816.

5.2.7. (5*R*)-5-Methyl-5-phenyl-2(5*H*)-furanone 16g.[8] Colourless oil. Yield: 139 mg (65%). ee: 32%. $[\alpha]^{20}_D$=+67.97 (*c* 1.22, $CHCl_3$) {Lit.[8] $[\alpha]^{20}_D$=+276 (*c* 3.7, $CHCl_3$)}. ^{1}H NMR: 1.83 (s, 3H), 6.06 (d, 1H, J=5.6 Hz), 7.3–7.45 (m, 5H), 7.64 (d, 1H, J=5.6 Hz). ^{13}C NMR: 26.3, 88.9, 119.4, 124.8, 128.3, 130.8, 149.8, 160.3, 173.2. IR

(CH_2Cl_2): 3012, 2993, 2987, 1760, 1600, 1450, 1235, 1120, 1080.

5.2.8. 4-Pentynyl tetrahydro-2*H*-pyran-2yl ether 20.[20b] 6.38 mL (69.19 mmol) of dihydropyran was added dropwise to a solution of 4-pentyn-1-ol (5 mL, 57.66 mmol) and *p*-toluenesulfonic acid (10 mg, 0.06 mmol) in anhydrous methylene chloride (150 mL) at 0°C. The mixture was then stirred for 3 h at 0°C. Removal of the solvent in vacuo gave the crude ether **20** which was purified by distillation (46–49°C, 0.1 mmHg). Yield: 7.52 g (84%) as a colourless oil. ^{1}H NMR: 1.48–1.90 (m, 6H), 1.96 (t, 1H, *J*=2.6 Hz), 3.44–3.55 (m, 2H), 3.79–3.90 (m, 2H), 4.61 (t, 1H, *J*=3.3 Hz). ^{13}C NMR: 15.3, 19.4, 25.4, 28.6, 30.6, 62.1, 65.7, 68.3, 83.9, 98.7. IR (neat): 3295, 2944, 2873, 2118.

5.2.9. (*E*)-7-Nonen-4-ynyl tetrahydro-2*H*-pyran-2-yl ether 21.[27] 7.77 mL of a solution of 2.25 M *n*-BuLi in hexanes (17.49 mmol) was added dropwise to a stirred solution of the pyranyl ether 20 (2.675 g, 15.9 mmol) and CuBr·DMS (0.650 g, 3.16 mmol) in 80 mL of THF at −78°C. After 1.5 h, freshly distilled crotyl bromide (2.31 mL, 19.08 mmol) was added dropwise. The temperature was slowly raised to rt and the mixture was stirred overnight. An aqueous solution of ammonium chloride was added and the aqueous phase was extracted with diethyl ether. The collected organic phases were dried over $MgSO_4$, filtered off and concentrated in vacuo. The oily residue was purified by flash chromatography on silicagel (AcOEt/*n*-hexane, 10:90) to give pure **21** as a colourless oil. Yield: 2.68 g (80.5%). ^{1}H NMR: 1.47–1.86 (m, 6H), 1.68 (dd, 3H, *J*=2, 3 Hz), 2.26–2.35 (m, 2H), 2.84–2.87 (m, 2H), 3.42–3.55 (m, 2H), 3.77–3.93 (m, 2H), 4.62 (t, 1H, *J*=3 Hz), 5.29–5.73 (m, 2H). ^{13}C NMR: 15.7, 17.6, 19.5, 21.9, 25.5, 29.2, 30.7, 62.1, 66.1, 98.8, 105.3, 105.5, 125.9, 126.3. IR (neat): 2944, 2873, 2212.

5.2.10. (4*E*,7*E*)-4,7-Nonadienyl-1-ol 22.[20e] *Step A*. 95 mg of lithium wire (13.66 mmol) was added smoothly to a solution of acetylene **21** (1 g, 4.50 mmol), *t*-butanol (1.06 mL, 14.36 mmol) and ammonium sulphate (1.261 g, 10.25 mmol) in liquid NH_3. Stirring was maintained for 30 min then 1.35 g of ammonium chloride was added. Ammonia was slowly evaporated at rt. Addition of water, extraction with diethyl ether and concentration in vacuo gave a colourless oil (**29**), which was directly used in the next step.

Step B. A solution of the crude olefin **29** (3.5 g, 15.6 mmol) and PPTS (0.4 g, 1.56 mmol) in MeOH (140 mL) was heated at 40°C for 4 h. The solvent was removed in vacuo and the oily residue was flash chromatographed (AcOEt/*n*-hexane, 10:90) to give pure alcohol **22** as a colourless oil. Yield: 1.57 g (72%). ^{1}H NMR: 1.62–1.67 (m, 3H), 2.06–2.14 (m, 2H), 2.67–2.75 (m, 2H), 3.66 (t, 2H, *J*=6.6 Hz), 5.40–5.47 (m, 4H). ^{13}C NMR: 17.8, 28.9, 32.5, 35.6, 62.6, 125.5, 129.4, 129.7, 130.1.

5.2.11. (4*E*,7*E*)-4,7-Nonadienal 23.[21e] A solution of DMSO (3.04 mL, 42.78 mmol) in 22.5 mL of anhydrous methylene chloride was added dropwise at −78°C into a solution of oxalyl chloride (1.86 mL, 21.39 mmol) in 37.5 mL of methylene chloride. After 5 min, a solution of alcohol **22** (1.5 g, 10.69 mmol) in methylene chloride (22.5 mL) was added dropwise at −78°C and the stirring was maintained for 15 min before adding 11.9 mL of Et_3N. Care should be taken not to raise the temperature above −60°C during addition of the successive reagents. Then, the mixture was brought up to rt. Addition of 30 mL of 1N HCl solution followed by extraction with methylene chloride gave the crude aldehyde **23** which was flash chromatographed (AcOEt/*n*-hexane, 5:95). Pure (4*E*,7*E*)-4,7-nonadienal was obtained as a colourless oil. Yield: 1.25 g (84.5%). Bp 85°C (4.5 mmHg). ^{1}H NMR: 1.66 (d, 3H, *J*=4.7 Hz), 2.31–2.38 (m, 2H), 2.48–2.53 (m, 2H), 2.65–2.59 (m, 2H), 5.34–5.53 (m, 4H), 9.77 (s, 1H). ^{13}C NMR: 17.9, 25.1, 35.5, 43.4, 125.7, 128.3, 129.3, 130.7, 201.2. IR (CH_2Cl_2): 2959, 2718, 1727, 969.

5.2.12. (5*R*)-5-[(3*E*,6*E*)-3,6-Octadienyl]-2(5*H*)-furanone 24.[20e] A procedure similar to the one described above for the preparation of butenolides **16** was used for the synthesis of (5*R*)-5-[(3*E*,6*E*)-3,6-octadienyl]-2(5*H*)-furanone **24** starting from 1 g (2.45 mmol) of sulfoxide (*R*)-**13** and 0.372 g (2.69 mmol) of (4*E*,7*E*)-nonadienal. Yield: 353 mg (75%). ee: 84.5%. $[\alpha]^{20}_D$=−53.08 (*c* 0.83, $CHCl_3$). ^{1}H NMR: 1.66 (m, 3H), 1.69–1.88 (m, 2H), 2.19 (m, 2H), 2.66–2.68 (m, 2H), 5.03–5.06 (m, 1H), 5.35–5.55 (m, 4H), 6.11 (dd, 1H, *J*=5.7, 2 Hz), 7.47 (dd, *J*=5.7, 2 Hz). ^{13}C NMR: 17.8, 28.0, 33.0, 35.5, 82.7, 121.5, 126.7, 128.4, 129.2, 130.8, 156.2, 173.1. IR (CH_2Cl_2): 2970, 2890, 1755.

5.2.13. (1*R*,4*R*,5*S*)-4-[(3*E*,6*E*)-3,6-Octadienyl]-3,6-dioxabicyclo[3.1.0]hexan-2-one 25.[21e] A 13% aqueous solution of NaClO (0.65 mL, 1.37 mmol) was added dropwise at 0°C into a solution of butenolide **24** (140 mg, 0.69 mmol) in 28 mL of a mixture of ether/DMF (1:1). The mixture was stirred for 1 h at 0°C; then, the reaction was quenched by addition of 5 mL of 10% $Na_2S_2O_3$ solution. The aqueous phase was extracted three times with ether and the collected organic phases concentrated in vacuo. The oily residue was flash chromatographed (hexane/ether, 5:1) to yield a colourless oil. Yield: 65 mg (45%). ee: 85.9%. $[\alpha]^{20}_D$=+46.0 (*c* 0.5, $CHCl_3$) {Lit.[21e] $[\alpha]^{20}_D$=+56.7 (*c* 0.025, $CHCl_3$)}. ^{1}H NMR: 1.66 (d, 3H, *J*=4.5 Hz), 1.72–1.79 (m, 2H), 2.10–2.29 (m, 2H), 2.66–2.70 (m, 2H), 3.77 (d, 1H, *J*=2.6 Hz), 3.98 (d, 1H, *J*=2.6 Hz), 4.57–4.62 (m, 1H), 5.33–5.56 (m, 4H). ^{13}C NMR: 17.8, 27.2, 31.8, 35.5, 49.8, 57.9, 79.1, 125.8, 128.0, 129.1, 131.0, 170.2. IR (neat): 2980, 1789, 1191, 967, 855.

5.2.14. (2*R*,3*R*)-3-[(1*R*,4*E*,7*E*)-1-Hydroxy-4,7-nonadienyl]-2-oxiranecarboxamide 26.[21e] 75 μL of a 25% aqueous ammonia solution (0.48 mmol) was added dropwise into a solution of epoxylactone **25** (50 mg, 0.24 mmol) in 1 mL of methanol at 0°C. After stirring 3 h, the reaction was stopped by addition of 2 mL of 0.5N HCl solution. The aqueous phase was extracted three times with methylene chloride and the combined organic phases were concentrated in vacuo. The solid residue was flash chromatographed (AcOEt/hexane, 1:1) to give amide **26** as a white solid. Yield: 50 mg (92%) (Lit.[21e] 90%). ee: 84.5%. $[\alpha]^{20}_D$=+55.5 (*c* 0.72, $CHCl_3$) {Lit.[21e] $[\alpha]^{20}_D$=+67.4 (*c* 0.24, $CHCl_3$)}. ^{1}H NMR: 1.65–1.67 (m, 3H), 1.70–1.78 (m, 2H), 2.07–2.30 (m, 2H), 2.65–2.68 (m, 2H), 3.12 (dd, 1H,

J=4.6, 8.2 Hz), 3.45–3.54 (m, 1H), 3.53 (d, 1H, J=4.6 Hz), 6.33–6.57 (m, 4H), 6.33 (s_{broad}, 1H), 6.57 (s_{broad}, 1H). ^{13}C NMR: 17.8, 27.8, 34.6, 35.5, 54.3, 60.1, 68.1, 125.5, 128.1, 128.6, 129.7, 170.5. IR: 3386, 1678, 1595, 1426, 1119, 1072.

5.2.15. (+)-Cerulenin 17.[21e] 8 mg (22 μmol) of TPAP was added at once to a solution of alcohol **26** (50 mg, 0.23 mmol), NMO (95 mg, 0.68 mmol) in anhydrous methylene chloride on 4 Å molecular sieves. The reaction mixture was stirred for 1 h then diluted with anhydrous ether and filtered through a short column of Celite®. The organic phase was washed with water and the aqueous phase was extracted with methylene chloride. The crude product was purified on silicagel (AcOEt/hexane, 2:3) to give a white solid corresponding to tautomers of cerulenin. Yield: 39 mg (75%) (Lit.[21e] 80%). ee: 85%. $[\alpha]^{20}_D$=+57.2 (*c* 0.2, MeOH) {Lit.[21e] $[\alpha]^{20}_D$=+62.0 (*c* 0.15, MeOH)}. *Linear isomer*: ^1H NMR: 1.64–1.67 (m, 3H), 2.18–2.36 (m, 2H), 2.62–2.71 (m, 4H), 3.73 (d, 1H, J=5.3 Hz), 3.87 (d, 1H, J=5.3 Hz), 5.37–5.59 (m, 4H), 6.33 (s_{broad}, 1H), 6.57 (s_{broad}, 1H). ^{13}C NMR: 17.9 (C_1), 25.9, 29.7, 35.4, 40.8, 55.3, 125.8, 127.7, 129.2, 130.7, 167.2, 202. *Cyclic isomers*: ^1H NMR: 1.64–1.67 (m, 6H), 1.76–2.05 (m, 4H), 2.18–2.36 (m, 4H), 2.62–2.71 (m, 4H), 3.59 (d, 1H, J=2.5 Hz), 3.61 (d, 1H, J=2.5 Hz), 3.65 (s_{broad}, 1H), 3.82 (d, 1H, J=2.5 Hz), 3.83 (d, 1H, J=2.5 Hz), 5.37–5.59 (m, 8H), 6.33 (s_{broad}, 1H).

5.2.16. Registry numbers. 3055-87-6, 53075-94-8, 22693-41-0, 70404-21-6, 90366-21-5, 98878-30-9, 98878-24-1, 101836-41-3, 118917-42-3, 60112-29-0, 104923-70-8, 137449-38-8, 137449-41-3, 67596-41-2, 52264-9-34435-19-2, 62992-46-5, 79532-17-5, 62964-98-1, 62499-92-7, 64807-39-2, 72301-01-0, 72301-02-1, 17397-89-6.

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