Total Synthesis of (±)-Cephalosol via Silyl Enol Ether Acylation

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Abstract: An efficient total synthesis of (±)-cephalosol is reported. Key steps are the acylation of a silyl enol ether with monomethyl oxalyl chloride and the subsequent acid-mediated ring closure to the isocoumarin structure. A chemoselective allylation and the conversion of the olefin into a methyl acetate were applied to install the γ-lactone moiety.

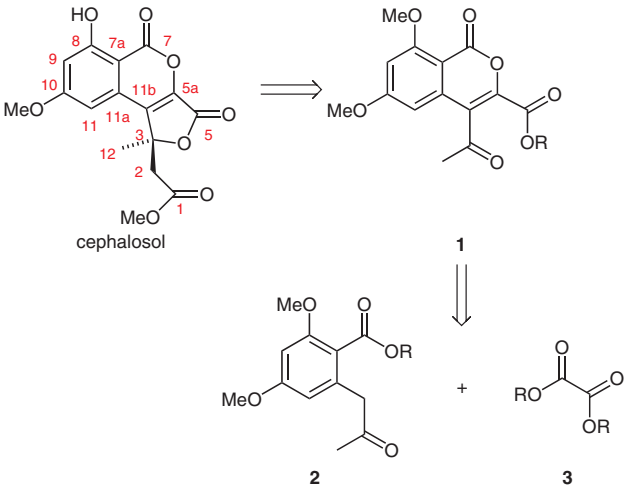
Key words: acylation, cephalosol, chemoselectivity, isocoumarins, lactones

Cephalosol was isolated from *Cephalosporium acremonium* IFB-E007, an endophytic fungal strain living in *Trachelospermun jasminoides*, well known in Chinese herbal medicine for the treatment of arthritis and other inflammatory diseases.[1] Its structure was determined by spectroscopic methods and the absolute configuration was proposed by a computational approach. The unprecedented skeleton of cephalosol consists of an isocoumarin annulated to an α,β unsaturated γ-lactone bearing a quaternary center (C3) with a methyl acetate side chain. The antibiotic activity of the novel natural product (MIC values μg mL^{-1}: *Escheria coli*/3.8, *Pseudomonas fluorescens*/3.9, *Trichophyton rubrum*/7.8, *Candida albicans*/1.95) was associated with the α,β unsaturated γ-lactone substructure. Here, we report our results on an efficient synthesis of cephalosol.

Our synthetic plan relied on an introduction of the C1–C2 methyl ester side chain at the late stage of the synthesis (Scheme 1). The ketone **1** could be a suitable precursor for such a transformation. This should allow the simultaneous introduction of a C1–C2 side-chain equivalent, the generation of the stereocenter, and the ring closure to the γ-lactone. Ketone **1** could be accessible from the reaction of benzyl methyl ketone **2** with an oxalic acid derivative **3**.

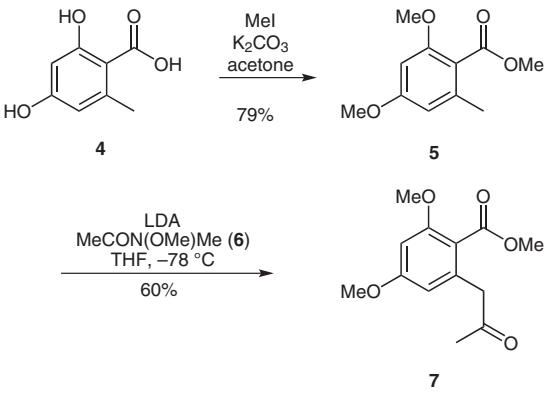
Among the various methods for the synthesis of isocoumarins[2] there are only a few examples for the preparation of 3-carboxyisocoumarins such as **1**: a Wittig approach,[3] the use of α-diazophosphonates,[4] and a Claisen approach of homophthalate with oxalate,[5] which is related to the proposed route **2** + **3** → **1**.

Starting point of the synthesis was the preparation of the ketone **7** (Scheme 2). Orsellinic acid (**4**) was converted in one step into its dimethyl ether methyl ester **5**. The latter gave the ketone **7** via deprotonation and reaction with the



Scheme 1 Retrosynthetic analysis of cephalosol

Weinreb amide **6**. Compared to the 82% yield for the same acylation of the corresponding ethyl ester,[6] a lower yield of 60% was achieved for the formation of **7**. Side reactions due to self condensation can occur more easily for the methyl ester than for the ethyl ester.



Scheme 2 Synthesis of the ketone **7**

The acylation of the ketone **7** with dimethyl oxalate (**9**) was examined next (Scheme 3). Different bases (NaH, LDA) and various oxalic acid equivalents (**9** and monomethyl oxalyl chloride **10**) did not give the desired product **11** but the isocoumarin **12**. The intramolecular attack of the enolate oxygen at the methyl ester dominated in all cases over the intermolecular acylation reaction.

In order to suppress the intramolecular side reaction by lowering the nucleophilicity of the enolate equivalent and by increasing the electrophilicity of the oxalate equiva-

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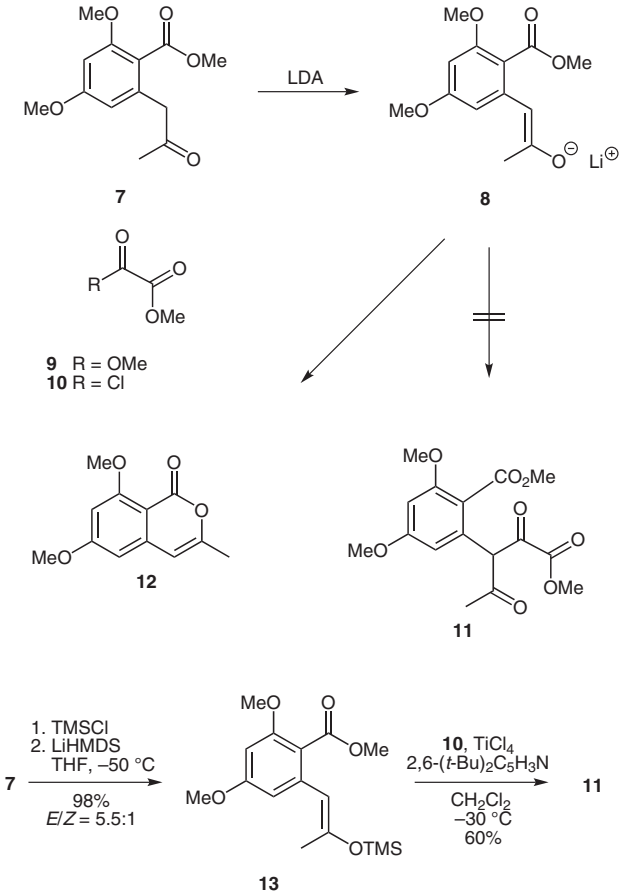
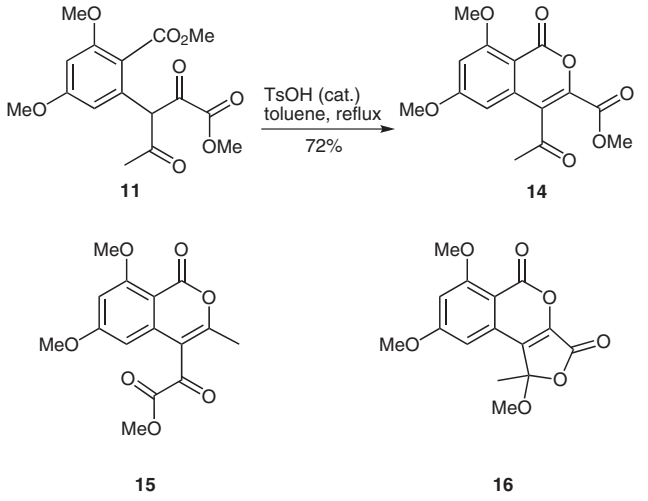


Scheme 3 The intermolecular acylation **7** → **8** → **11**

lent, the Lewis acid mediated reaction of the corresponding silyl enol ether with the acid chloride **10** was examined. The ketone **7** could be converted into the silyl enol ether **13** by addition of LiHDMS to a mixture of TMSCl and **7** at –50 °C.[7] $TiCl_4$ was found to be the most suitable Lewis acid for the reaction of **13** with **10** to produce the 1,3-diketone **11**. Because the diketone was formed as titanium enolate,[8] an excess of Lewis acid was necessary, 6 equivalents proved to be the best choice. The acid liberated in the titanium enolate formation protonated some silyl enol ether **13** and converted it back into the ketone **7**. This side reaction could be suppressed by addition of a base (1.1 equiv of 2,6-di-*tert*-butylpyridine[9]). Using these optimized conditions a 60% yield of the desired 1,3-diketone **11** was obtained.

The cyclization of the 1,3-diketone **11** to the isocoumarin **14** was achieved with catalytic amounts of TsOH in boiling toluene (Scheme 4). In the mixture of side products (19%), the regioisomeric cyclization product **15** was the main constituent. The assignment of the two regioisomers was possible by combined NMR techniques (HMBC, HMQC, NOESY). Using one equivalent of TfOH instead of TsOH for the cyclization gave 62% yield of the desired product **14** with the γ-lactone **16** as the main side product.

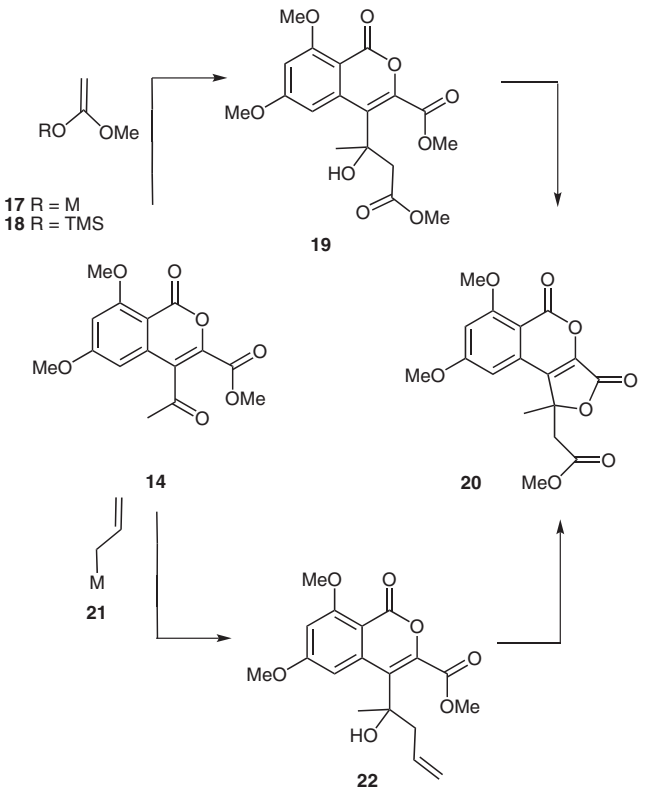
Basic cyclization conditions did not deliver compound **14**. One possible explanation for this failure could be the easy



Scheme 4 Cyclization of **11** to the isocoumarine **14**

enolate formation of the strong chelator **11**, which may adopt a conformation unfavorable for the cyclization.

The completion of the cephalosol skeleton synthesis required the addition of a C2 unit to the keto group in **14**. Towards this goal two synthetic routes were examined (Scheme 5). The shorter one included the addition of a methyl acetate enolate **17** to obtain the tertiary alcohol **19**, which should cyclize to the desired γ-lactone **20**. The presence of three carbonyl groups and two Michael acceptor positions in **14** complicated this reaction and no suit-

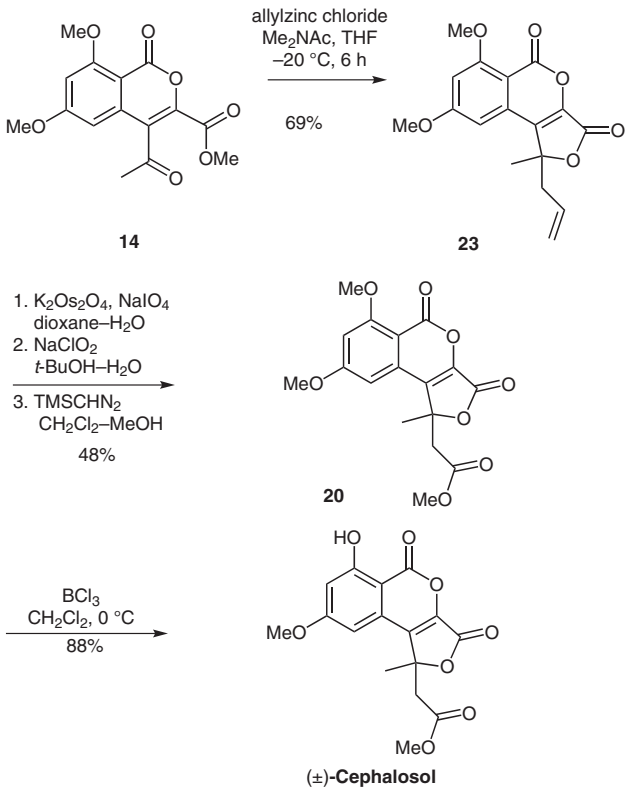


Scheme 5 Two possible strategies for the introduction of the methyl acetate side chain

able conditions for this reaction using a zinc/copper enolate could be found. The corresponding selective addition of the ketene acetal **18** to the desired carbonyl group in **14** was also unsuccessful.

The reactivity of allylmetal reagents can be tuned by proper choice of the metal. The addition of an allylmetal reagent **21** to **14** would lead to the homoallylic alcohol **22**. A subsequent oxidative cleavage of the double bond could deliver the required compound **20**. We investigated the addition of allylmagnesium, -tin, and -zinc reagents to the ketone **14**. No satisfying chemoselectivity was achieved with allylmagnesium chloride,[10] but considerable attack at the ester groups was observed. The reactivity of tetraallyltin/Ti(O*i*-Pr)$_4$[11] was too low to obtain any addition product **22**.

Allylzinc chloride (3.3 equiv) exhibited at –20 °C the desired reactivity[12] and delivered without detection of the intermediate γ-hydroxy ester **22** directly the γ-lactone **23** (Scheme 6). The attempted asymmetric addition of an allylzinc reagent in the presence of a chiral bisoxazoline[13] was unsuccessful because no turnover was observed under these conditions even at higher temperature. The conversion of the terminal alkene **23** into the methyl ester **20** was achieved using the standard reaction sequence of oxidative cleavage,[14] Pinnick oxidation[15] and methyl ester formation.



Scheme 6 Introduction of the methyl acetate side chain and completion of the synthesis

The final step of the synthesis required the selective cleavage of the C8 methyl ether. Using the precoordination of boron trichloride at the ortho carbonyl group[16] the selective conversion of the dimethyl ether **20** into the target compound (±)-cephalosol was possible in 88% yield. The analytical and spectral data of synthetic cephalosol (mp, NMR, IR) were identical to those reported.[1]

In conclusion, the first synthesis of (±)-cephalosol was accomplished in 10 steps from orsellinic acid with 5.8% overall yield. The total synthesis confirms the structural assignment of the natural product and opens synthetic access to derivatives with potential antibiotic applications.

All nonaqueous reactions were carried out using flame-dried glassware under argon. All solvents were distilled by rotary evaporation. Solvents for nonaqueous reactions were dried as follows prior to use: THF was dried with KOH and subsequently distilled from sodium/benzophenone; Et_2O was distilled from K/Na alloy (K/Na, 4:1). All commercially available reagents and reactants were used without purification, unless otherwise noted. Reactions were monitored by TLC using Merck Silica Gel 60 F_{245} plates and visualized by fluorescence quenching under UV light. In addition, TLC plates were stained using a $KMnO_4$ stain. Chromatographic purification of products was performed on Merck Silica Gel 60 (230–400 mesh) using a forced flow of eluents. Concentration under reduced pressure was performed by rotary evaporation at 40 °C and appropriate pressure. Yields refer to purified and spectroscopically pure products, unless otherwise noted. IR spectra were recorded on a Bruker IFS 200 or a Nicolet Magna-IR 750 spectrometer. The absorption bands are given in wave numbers (cm^{-1}). NMR spectra were recorded on a Bruker ARX300, DRX400, or DRX500 spectrometer at room temperature. Chemical shifts are reported in ppm with the solvent resonance as internal standard. Mass spectra were recorded on a Finnigan MAT TSQ 700 or MAT 95S spectrometer.

Methyl 2,4-Dimethoxy-6-methylbenzoate (5)

To a suspension of K_2CO_3 (25.6 g, 185 mmol) in acetone (60 mL) was added orsellinic acid (**4**; 4.96 g, 29.5 mmol). MeI (11.0 mL, 177 mmol) was added and the reaction mixture was refluxed for 7 h. After removal of the solvent and excess MeI in vacuo, H_2O (120 mL) was added and the resulting solution was extracted with Et_2O (5 × 60 mL). The combined organic layers were washed with $NaHCO_3$ (50 mL) and brine (50 mL). Drying (Na_2SO_4) and subsequent evaporation of the solvent gave the crude product. Purification by silica gel chromatography (pentane–Et_2O, 3:1) delivered the methyl ester **5** as a light yellow oil, which turned into a white solid upon storage at 4 °C.

Yield: 3.91 g (79%); mp 41 °C; R_f = 0.27 (pentane–Et_2O, 3:1).

IR (film): 2949, 2841, 1724, 1603, 1266, 1231, 1201, 1157, 1096, 1052, 831, 642, 611 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.28 (s, 3 H, CH_3), 3.79 (s, 3 H, OCH_3), 3.80 (s, 3 H, OCH_3), 3.88 (s, 3 H, OCH_3), 6.29–6.33 (m, 2 H, 3-H, 5-H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.1 (CH_3), 52.1 (OCH_3), 55.5 (OCH_3), 56.1 (OCH_3), 96.4 (CH), 106.9 (CH), 116.6 (C-1), 138.4 (C-6), 158.4 (*C*OCH_3), 161.5 (*C*OCH_3), 168.8 (*C*O_2CH_3).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_{14}O_4$ + Na: 233.0790; found: 233.0784.

Methyl 2,4-Dimethoxy-6-(2-oxopropyl)benzoate (7)

To *i*-Pr_2NH (3.9 mL, 28 mmol) in THF (56 mL) was added *n*-BuLi (10.5 mL of a 2.5 M solution in hexanes, 26.3 mmol) at 0 °C. After 30 min, the LDA solution thus obtained was cooled to –78 °C and transferred via a cannula to a solution of the ester **5** (5.00 g, 23.8 mmol) in THF (56 mL) at –78 °C. The reaction mixture was stirred

for 5 min at –78 °C and then the Weinreb amide **6** (2.8 mL, 26 mmol) was added via a syringe. After 80 min at –78 °C, aq 2 M HCl (60 mL) was added and the mixture was allowed to warm to r.t. The mixture was extracted with CH_2Cl_2 (3 × 100 mL) and the combined organic layers were dried (Na_2SO_4). After evaporation of the solvents, the crude product was purified by silica gel chromatography (pentane–Et_2O, 1:2) to afford the ketone **7**; as a yellow oil, which solidified upon storage at 4 °C.

Yield: 3.58 g (60%); mp 64 °C; R_f = 0.24 (pentane–Et_2O, 1:2).

IR (film): 2957, 2933, 2870, 1689, 1602, 1583, 1460, 1323, 1201, 1154, 831, 734, 643 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.15 (s, 3 H, CH_3), 3.68 (s, 2 H, CH_2), 3.81 (s, 3 H, OCH_3), 3.82 (s, 3 H, OCH_3), 3.84 (s, 3 H, OCH_3), 6.31 (d, *J* = 2.2 Hz, 1 H, CH), 6.41 (d, *J* = 2.2 Hz, 1 H, CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 29.4 (CH_3), 49.2 (CH_2), 52.2 (OCH_3), 55.6 (OCH_3), 56.2 (OCH_3), 97.9 (CH), 107.6 (CH), 116.2 (C-1), 135.9 (C-6), 159.3 (*C*OCH_3), 162.0 (*C*OCH_3), 168.1 (*C*O_2CH_3), 205.5 (CH_2*C*OCH_3).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{16}O_5$ + Na: 275.0895; found: 275.0890.

Methyl 2,4-Dimethoxy-6-[2-(trimethylsiloxy)prop-1-enyl]benzoate (13)

To a solution of ketone **7** (3.55 g, 14.2 mmol) and TMSCl (3.6 mL, 28 mmol) at –50 °C was added LiHMDS (20.5 mL 0.9 M solution in methylcyclohexane, 18.5 mmol) via a syringe during 30 min. The reaction mixture was stirred for 1 h at –50 °C. A 9:1 mixture of sat. aq NH_4Cl/25% NH_3 (30 mL) was added. The mixture was allowed to warm to r.t. and treated with H_2O (50 mL). The separated aqueous layer was extracted with Et_2O (2 × 40 mL), the combined organic layers were dried (Na_2SO_4), and the solvents removed in vacuo. After three-fold co-evaporation with toluene (30 mL) and 12 h drying in high vacuum, the silyl enol ether **13** was obtained. Analysis of the ^1H NMR spectrum showed a 5.5:1 *E*/*Z* mixture. The crude product was used for the following acylation step without further purification.

Light yellow oil; yield: 4.51 g (98%); R_f = 0.68 (pentane–Et_2O, 1:2).

IR (film): 2954, 1726, 1596, 1578, 1425, 1258, 1201, 1154, 1095, 839, 756, 688 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.17 [s, 9 H, $Si(CH_3)_3$-*Z*], 0.24 8s, 9 H, $Si(CH_3)_3$-*E*], 1.85 (d, *J* = 0.6 Hz, 3 H, CH_3-*E*), 1.93–1.97 (m, 3 H, CH_3-*Z*), 3.76 (s, 3 H, OCH_3-*Z*), 3.78 (s, 3 H, OCH_3-*E*), 3.79 (s, 3 H, OCH_3-*E*), 3.84 (s, 3 H, OCH_3-*E*), 3.87 (s, 3 H, OCH_3-*Z*), 5.31–5.34 (m, 1 H, CH-*Z*), 5.72–5.77 (m, 1 H, CH-*E*), 6.27 (d, *J* = 2.2 Hz, 1 H, CH_{arom}-*Z*), 6.29–6.34 (m, 2 H, CH_{arom}-*E*), 7.13 (d, *J* = 2.2 Hz, 1 H, CH_{arom}-*Z*).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 0.3 [$Si(CH_3)_3$-*E*], 0.9 [$Si(CH_3)_3$-*Z*], 19.7 (CH_3-*E*), 24.3 (CH_3-*Z*), 52.1 (OCH_3-*Z*), 52.1 (OCH_3-*E*), 55.4 (OCH_3-*E*), 55.8 (OCH_3-*Z*), 55.9 (OCH_3-*E*), 96.2 (CH_{arom}-*E*), 96.5 (CH_{arom}-*Z*), 104.6 (CH-*E*), 104.7 (CH-*Z*), 106.5 (CH-*Z*), 106.7 (CH-*E*), 115.3 (C-1-*Z*), 116.6 (C-1-*E*), 151.4 (CO-*Z*), 152.9 (CO-*E*), 157.5 (CO-*Z*), 157.8 (CO-*E*), 161.0 (CO-*Z*), 161.0 (CO-*E*), 168.5 (COSi-*E*), 169.1 (COSi-*Z*).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_{24}O_5Si$ + Na: 347.1291; found: 347.1285.

Methyl (*Z*)-2-(2-Hydroxy-1-methoxy-1,4-dioxopent-2-en-3-yl)-4,6-dimethoxybenzoate (11)

To a solution of monomethyl oxalyl chloride (1.2 mL, 13 mmol) in CH_2Cl_2 (60 mL) were added successively $TiCl_4$ (4.1 mL, 37 mmol) and 2,6-di-*tert*-butylpyridine (1.5 mL, 6.7 mmol) at –30 °C. To the dark red reaction mixture was added dropwise the silyl enol ether **13** (2.00 g, 6.16 mmol) in CH_2Cl_2 (18 mL) during 75 min. The mixture was stirred for 4 h at –30 °C. H_2O (80 mL) was added and the mixture was allowed to warm to r.t. The separated aqueous layer was extracted with CH_2Cl_2 (3 × 40 mL) and the combined organic layers were dried (Na_2SO_4). After evaporation of the solvents, a silica gel chromatography (pentane–EtOAc–HCO_2H, 8:4:0.3) gave the 1,3-diketone **11** as a yellow oil, which upon storage at –20 °C became a white solid.

Yield: 1.23 g (60%); mp 81 °C; R_f = 0.36 (pentane–EtOAc–HCO_2H, 8:4:0.3).

IR (film): 2953, 2845, 1727, 1598, 1577, 1261, 1207, 1157, 1046, 1016, 833, 732, 673 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.04 (s, 3 H, CH_3), 3.63 (s, 3 H, $COHCO_2CH_3$), 3.72 (s, 3 H, 1-CO_2CH_3), 3.80 (s, 3 H, 4-OCH_3), 3.82 (s, 3 H, 6-OCH_3), 6.32 (d, *J* = 2.2 Hz, 1 H, CH-3), 6.47 (d, *J* = 2.2 Hz, 1 H, CH-5), 15.68 (s, 1 H, OH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.9 (CH_3), 52.1 (1-CO_2CH_3), 52.6 ($COHCO_2CH_3$), 55.6 (4-OCH_3), 56.0 (6-OCH_3), 98.5 (CH-5), 108.0 (CH-3), 113.4 (CH_{benzyl}), 117.3 (C-1), 135.4 (C-2), 158.7 (C-6), 161.7 (C-4), 162.4 ($COHCO_2CH_3$), 167.4 (1-*C*O_2CH_3), 169.3 (COH), 199.4 (*C*OCH_3).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_{18}O_8$ + Na: 361.0899; found: 361.0894.

6,8-Dimethoxy-3-methyl-1*H*-isochromen-1-one (12)

To the ketone **7** (185 mg, 733 μmol) in THF (5 mL) was added dimethyl oxalate (1.15 mL, 0.69 mmol), followed by the dropwise addition of LiHMDS (0.69 mL of a 1 M solution in toluene, 0.69 mmol) at –50 °C. The reaction mixture was stirred for 2 h at –50 °C and then treated with aq 2 M HCl (2 mL). The aqueous layer was extracted with EtOAc (3 × 10 mL) and the combined organic layers were dried (Na_2SO_4). Evaporation of the solvents gave a mixture with isocoumarin **12** as the main component. An analytical sample was purified by silica gel chromatography.

R_f = 0.25 (EtOAc–pentane, 1:1).

IR (film): 2846, 1715, 1667, 1596, 1568, 1212, 1160, 971, 692 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.20 (d, *J* = 0.9 Hz, 1 H, CH_3), 3.87 (s, 3 H, OCH_3), 3.94 (s, 3 H, OCH_3), 6.08 (d, *J* = 0.9 Hz, 1 H, CH_{benzyl}), 6.28 (d, *J* = 2.3 Hz, 1 H, CH), 6.40 (d, *J* = 2.3 Hz, 1 H, CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.6 (CH_3), 55.7 (OCH_3), 56.4 (OCH_3), 98.3 (CH_{arom}), 99.5 (CH_{arom}), 103.0 (*C*C-3), 103.8 (CH_{benzyl}), 142.6 (*C*C-4), 155.6 (C-3), 159.7 (C-1), 163.5 (*C*OCH_3), 165.5 (*C*OCH_3).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{13}O_4$: 221.0814; found: 221.0808.

Cyclization of 11 with TsOH; Methyl 4-Acetyl-6,8-dimethoxy-1-oxo-1*H*-isochromene-3-carboxylate (14) and 6,8-Dimethoxy-4-(methyl-2-oxoacetate)-3-methyl-1-oxo-1*H*-isochromene (15)

To the 1,3 diketone **11** (386 mg, 1.14 mmol) in toluene (114 mL) was added TsOH (33 mg) and the reaction mixture was refluxed for 90 min. After evaporation of the solvent, a silica gel chromatography (pentane–acetone, 3:1 → 2:1) afforded the isocoumarin **14** (253 mg, 72%) and a mixture of side products with compound **15** as the main component (66 mg, 19%).

Isocoumarin 14

White powder; mp 185 °C; R_f = 0.33 (pentane–acetone, 2:1).

IR (film): 1710, 1593, 1457, 1431, 1310, 1253, 1206, 1167, 1029, 730, 700, 577 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.58 (s, 3 H, CH_3), 3.87 (s, 3 H, 6-OCH_3), 3.92 (s, 3 H, CO_2CH_3), 3.98 (s, 3 H, 8-OCH_3), 6.27 (d, *J* = 2.2 Hz, 1 H, H-5), 6.62 (d, *J* = 2.2 Hz, 1 H, H-7).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 32.1 (CH_3), 53.3 (CO_2CH_3), 56.0 (6-OCH_3), 56.7 (8-OCH_3), 100.7 (CH-5), 101.0 (CH-7), 104.7 (*C*C-1), 126.5 (C-4), 137.0 (*C*C-4), 138.7 (C-3), 155.9 (C-1), 161.0 (CO_2CH_3), 164.1 (C-8), 166.0 (C-6), 199.9 ($COCH_3$).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{14}O_7$ + Na: 329.0637, found: 329.0632.

Regioisomer 15

Colorless oil; R_f = 0.41 (pentane–acetone, 2:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.29 (s, 3 H, CH_3), 3.83 (s, 3 H, 8-OCH_3), 3.90 (s, 3 H, CO_2CH_3), 3.96 (s, 3 H, 6-OCH_3), 6.44 (d, *J* = 2.2 Hz, 1 H, H-5), 6.48 (d, *J* = 2.2 Hz, 1 H, H-7).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.0 (CH_3), 53.6 (CO_2CH_3), 55.8 (8-OCH_3), 56.5 (6-OCH_3), 98.4 (H-5), 99.0 (H-7), 102.1 (*C*C-1), 112.9 (C-4), 138.6 (*C*C-4), 156.8 (C-1), 161.1 (C-3), 163.2 (CO_2CH_3), 163.8 (C-6), 166.0 (C-8), 186.6 ($COCO_2CH_3$).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{14}O_7$ + Na: 329.0637; found: 329.0632.

Cyclization of 11 with TfOH; Methyl 4-Acetyl-6,8-dimethoxy-1-oxo-1*H*-isochromene-3-carboxylate (14) and 1,6,8-Trimethoxy-1-methyl-1*H*-furo[3,4-*c*]isochromene-3,5-dione (16)

To the 1,3-diketone **11** 1.56 g, 4.61 mmol) in CH_2Cl_2 (92 mL) was added TfOH (0.41 mL, 4.6 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 4.5 h and then treated with sat. aq $NaHCO_3$ (25 mL). After addition of H_2O (40 mL), the mixture was extracted with CH_2Cl_2 (4 × 25 mL) and the combined organic layers were dried (Na_2SO_4). After evaporation of the solvent, a silica gel chromatography (pentane–acetone, 3:1 → 2:1) afforded the isocoumarin **14** (874 mg, 62%) and the γ-lactone **16** (121 mg, 9%). The analytical data of compound **14** corresponded to the data from the TsOH-mediated cyclization (*vide supra*).

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White solid; mp 257 °C; R_f = 0.36 (pentane–acetone, 2:1).

IR (film): 2947, 1771, 1594, 1455, 1383, 1283, 1247, 1206, 1167, 990, 865 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.91 (s, 3 H, CH_3), 3.21 (s, 3 H, 1-OCH_3), 3.97 (s, 3 H, 8-OCH_3), 4.02 (s, 3 H, 6-OCH_3), 6.63 (d, *J* = 2.3 Hz, 1 H, H-9), 6.69 (d, *J* = 2.2 Hz, 1 H, H-7).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.5 (CH_3), 51.8 (1-OCH_3), 56.2 (8-OCH_3), 56.7 (6-OCH_3), 99.9 (C-9), 101.2 (C-7), 103.5 (*C*C-5), 106.6 (C-1), 128.2 (C_{benzyl}), 133.7 (C_qC_{benzyl}), 142.4 (C_qC-3), 156.3 (C-3), 160.8 (C-5), 165.0 (C-6), 166.6 (C-8).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{14}O_7$ + Na: 329.0637; found: 329.0632.

1-Allyl-6,8-dimethoxy-1-methyl-1*H*-furo[3,4-*c*]isochromene-3,5-dione (23)

Allylzinc Chloride Solution in THF: A solution of $ZnCl_2$ in THF (13.6 mL, 0.5 M, 6.80 mmol) was diluted with THF (3.4 mL). To this solution was added dropwise a THF solution of allylmagnesium chloride (4.0 mL, 1.7 M, 6.8 mmol) at 20 °C. The reaction mixture was stirred for 2 h at 20 °C. The allylzinc chloride solution thus obtained (0.32 M) was used directly in the following reaction.

*Addition of Allylzinc Chloride to the Isocoumarin **14***: To the isocoumarin **14** (500 mg, 1.63 mmol) in *N*,*N*-dimethylacetamide (18 mL) was added a THF solution of allylzinc chloride (17.0 mL, 0.32 M, 5.44 mmol) during 6 h at –20 °C. Half sat. aq NH_4Cl (40 mL) was added and the mixture was allowed to warm to r.t. After addition of H_2O (40 mL), the aqueous layer was extracted with CH_2Cl_2 (3 × 60 mL) and the combined organic layers were dried (Na_2SO_4). After evaporation of the solvents in vacuo, a silica gel chromatography (pentane–acetone, 3:1 → 2:1) gave the γ-lactone **23**; as a light yellow solid.

Yield: 358 mg (69%); mp 189 °C; R_f = 0.17 (pentane–acetone, 3:1).

IR (film): 1764, 1594, 1565, 1456, 1383, 1208, 1167, 992, 970, 838, 754 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.76 (s, 3 H, CH_3), 2.72 (dd, *J* = 14.6, 7.1 Hz, 1 H, CH_{2allyl}), 2.88 (dd, *J* = 14.6, 7.4 Hz, 1 H, CH_{2allyl}), 3.97 (s, 3 H, 8-OCH_3), 4.00 (s, 3 H, 6-OCH_3), 5.02 (d, *J* = 16.1 Hz, 1 H, CH_2), 5.03 (d, *J* = 11.0 Hz, 1 H, CH_2), 5.49 (dddd, *J* = 16.4, 11.7, 7.2, 7.2 Hz, 1 H, C*H*CH_{2allyl}), 6.48 (d, *J* = 2.2 Hz, 1 H, H-9), 6.68 (d, *J* = 2.1 Hz, 1 H, H-7).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.1 (CH_3), 42.7 (CH_{2allyl}), 56.1 (8-OCH_3), 56.7 (6-OCH_3), 84.9 (C-1), 100.0 (CH-7), 100.9 (CH-9), 103.7 (*C*C-5), 120.9 (CH_2), 129.9 (*C*HCH_{2allyl}), 133.4 (C_{benzyl}), 134.0 (C_q), 140.7 (C_q), 156.5 (C-5), 162.4 (C-3), 165.3 (C-6), 166.0 (C-8).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{16}O_6$ + Na: 339.0845; found: 339.0839.

Methyl 2-(6,8-Dimethoxy-1-methyl-3,5-dioxo-3,5-dihydro-1*H*-furo[3,4-*c*]isochromen-1-yl)acetate (20)

Oxidative Alkene Cleavage: To the alkene **23** (150 mg, 474 μmol) in dioxane–H_2O (3:1, 8.4 mL) was added 2,6-lutidine (0.22 mL, 1.9 mmol) at 20 °C. To this solution were added K_2OsO_4·2 H_2O (7.0 mg, 19 μmol) and $NaIO_4$ (406 mg, 1.90 mmol). The reaction mixture was stirred for 26 h at 20 °C. Solids formed were filtered off and H_2O (5 mL) was added to the filtrate. After extraction with CH_2Cl_2 (8 × 5 mL), the combined organic layers were washed with H_2O (5 mL), and dried (Na_2SO_4). Evaporation of the solvents in vacuo gave the corresponding aldehyde (168 mg).

Oxidation of the Aldehyde: The aldehyde was dissolved in *t*-BuOH–H_2O (5:2, 7.5 mL). NaH_2PO_4·2 H_2O (248 mg, 1.59 mmol) and 2-methylbut-2-ene (0.51 mL, 4.8 mmol) were added at 20 °C. After 5 min, $NaClO_2$ (286 mg, 3.16 mmol) was added and the reaction mixture was stirred for 25 h at 20 °C. After the addition of aq 10% Na_2SO_3 (10 mL) and aq 2 M HCl (6 mL), the mixture was extracted with CH_2Cl_2 (5 × 20 mL), and the combined organic layers were dried (Na_2SO_4). After evaporation of the solvents in vacuo the corresponding carboxylic acid (137 mg) was obtained.

Formation of the Methyl Ester: To the carboxylic acid in CH_2Cl_2–MeOH (4:1, 1.8 mL) was added dropwise $TMSCHN_2$ in Et_2O (0.25 mL, 2 M, 0.50 mmol) at 0 °C. After 5 min, H_2O–AcOH (10:1, 10 mL) was added. H_2O (6 mL) was added and the mixture was extracted with CH_2Cl_2 (8 × 10 mL) and the combined organic layers were dried (Na_2SO_4). After evaporation of the solvents in vacuo, a silica gel chromatography (CH_2Cl_2–acetone, 30:1 → 10:1) afforded the methyl ester **20**.

White solid; yield: 79.1 mg (48% from **23**); mp 202 °C; R_f = 0.55 (CH_2Cl_2–acetone, 10:1).

IR (film): 1760, 1596, 1564, 1456, 1384, 1253, 1204, 1163, 993, 967, 733 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.86 (s, 3 H, CH_3), 3.01 (d, *J* = 15.6 Hz, 1 H, CH_2), 3.19 (d, *J* = 15.7 Hz, 1 H, CH_2), 3.59 (s, 3 H, CO_2CH_3), 3.97 (s, 3 H, 8-OCH_3), 4.02 (s, 3 H, 6-OCH_3), 6.43 (d, *J* = 2.2 Hz, 1 H, H-9), 6.67 (d, *J* = 2.2 Hz, 1 H, H-7).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.7 (CH_3), 42.5 (CH_2), 52.3 (CO_2CH_3), 56.1 (8-OCH_3), 56.7 (6-OCH_3), 82.0 (C-1), 100.0 (C-7), 100.6 (C-9), 103.9 (*C*C-5), 132.8 (C_{benzyl}), 133.9 (C_q), 140.9 (C_q), 156.4 (C-5), 162.0 (C-2), 165.4 (C-6), 166.0 (C-8), 168.2 (CO_2CH_3).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{17}O_8$: 349.0923; found: 349.0918.

(±)-Cephalosol

To a solution of the dimethyl ether **20** (51 mg, 0.15 mmol) in CH_2Cl_2 (3 mL) was added BCl_3 in hexane (0.15 mL, 1 M, 0.15 mmol) at 0 °C. After 90 min at 0 °C, an additional amount of BCl_3 in hexane (0.15 mL, 1 M, 0.15 mmol) was added. After 10 min, aq 1 M HCl (7 mL) and H_2O (7 mL) were added. The mixture was extracted with CH_2Cl_2 (4 × 10 mL) and the combined organic layers were dried (Na_2SO_4). After evaporation of the solvents in vacuo, a silica gel chromatography (pentane–acetone, 3:1 → 2:1) afforded (±)-cephalosol.

White solid; yield: 44 mg (88%); mp 202–203 °C (Lit.[1] mp 206–208 °C); R_f = 0.77 (CH_2Cl_2–acetone, 10:1).

IR (film): 3519, 1775, 1724, 1694, 1615, 1565, 1516, 1465, 1428, 1364, 1222, 1010 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.84 (s, 3 H, H-12), 3.02 (d, *J* = 16.0 Hz, 1 H, H-2), 3.19 (d, *J* = 16.0 Hz, 1 H, H-2), 3.60 (s, 3 H, 1-OCH_3), 3.93 (s, 3 H, 10-OCH_3), 6.44 (d, *J* = 2.1 Hz, 1 H, H-11), 6.69 (d, *J* = 2.1 Hz, 1 H, H-9), 11.29 (s, 1 H, 8-OH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.4 (C-12), 42.6 (C-2), 52.9 (1-OCH_3), 56.9 (10-OCH_3), 82.6 (C-3), 100.9 (C-7a), 103.3 (C-9), 103.8 (C-11), 131.7 (C-11a), 135.4 (C-11b), 140.3 (C-5a), 162.3 (C-5), 165.3 (C-7), 166.8 (C-8), 167.9 (C-10), 168.7 (C-1).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_{14}O_8$ + Na: 357.0586; found: 357.0581.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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