JOC The Journal of Organic Chemistry

Subscriber access provided by UNIVERSITY OF ADELAIDE LIBRARIES

Note

A Radical Based Synthesis of Lingzhiol

Lea-Marina Mehl, and Martin E. Maier

J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.7b01416 • Publication Date (Web): 18 Aug 2017

ACS Publications

The Journal of Organic Chemistry is published by the American Chemical Society.
1155 Sixteenth Street N.W., Washington, DC 20036

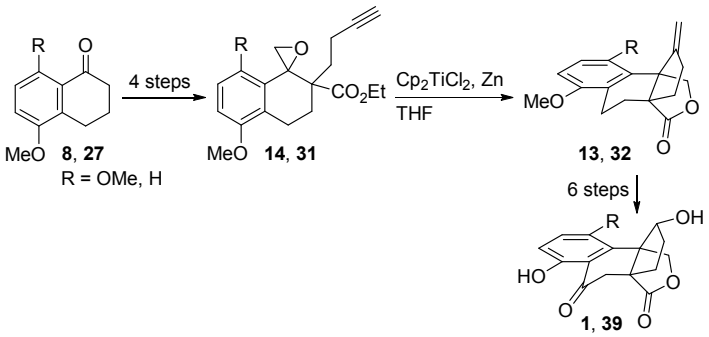
A Radical Based Synthesis of Lingzhiol

Lea-Marina Mehl and Martin E. Maier*

Institut für Organische Chemie, Eberhard Karls Universität Tübingen, Auf der Morgenstelle 18, 72076 Tübingen, Germany

martin.e.maier@uni-tuebingen.de

TOC graphic



ABSTRACT: The polycyclic natural product lingzhiol [(±)-**1**] was synthesized from dimethoxytetralone **8** via cyclization of an intermediate benzylic radical, generated from spiroepoxide **14**, onto an alkynyl substituent generating the tetracyclic compound **13** with an exocyclic double bond. After oxidative cleavage of the double bond of **13** and reduction of the keto function of **23**, the correct diastereomer **12**-*syn* was converted to lingzhiol (**1**) via known steps. In a similar manner, lingzhiol analog **39** was synthesized from 5-methoxy-tetralone (**27**).

Due to the extensive medicinal use of mushrooms belonging to the genus *Ganoderma*, these species are promising sources of novel natural products. For example, quite recently the polycyclic compounds lingzhiol[1] (**1**) and sinensilactam[2] (**2**) were isolated from *Ganoderma lucidum* and *Ganoderma sinensis*, respectively (Figure 1). Interestingly, both compounds appear as racemates in these mushrooms.

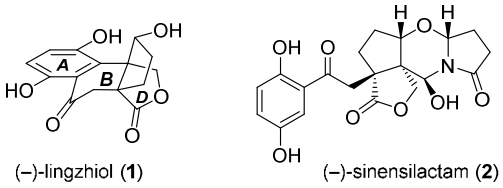
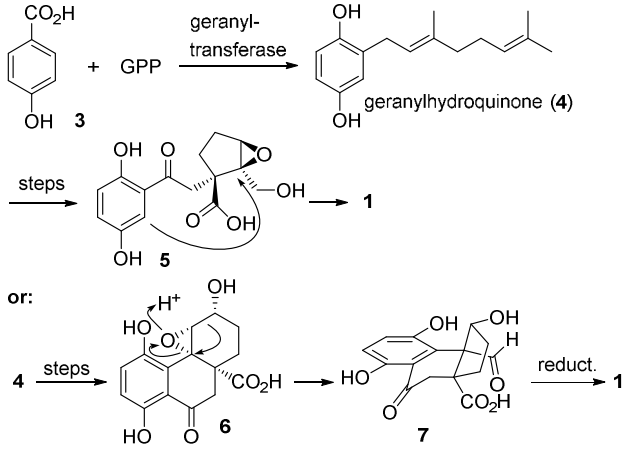


Figure 1. Structures of the polycyclic natural products (–)-lingzhiol (**1**) and (–)-sinensilactam (**2**).

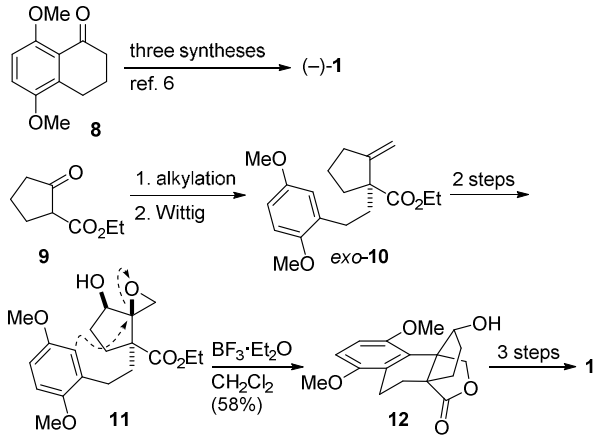
It was suggested that these compounds are biosynthesized in plants from 4-hydroxybenzoic acid (**3**), a product of the shikimic acid pathway, and geranyl diphosphate (Scheme 1).[3] In a second proposal, geranylhydroquinone would be cyclized and oxidized to polycycle **6**. A subsequent semipinacol rearrangement of the epoxyalcohol function would lead to advanced intermediate **7**. Regarding the biosynthesis of these compounds it is not sure whether a cyclase phase precedes the oxidation phase or vice versa.[4] Both **1** and **2** were found to be inhibitors of Smad3 phosphorylation in TGF-β1 induced cellular assays. Smad3 is a transcription protein implicated in renal fibrosis.[5] Common structural features for **1** and **2** are an acylated hydroquinone and a central cyclopentane ring featuring two vicinal quaternary centers.

Scheme 1. Possible key intermediates and key steps in the biosynthesis of lingzhiol (**1**).



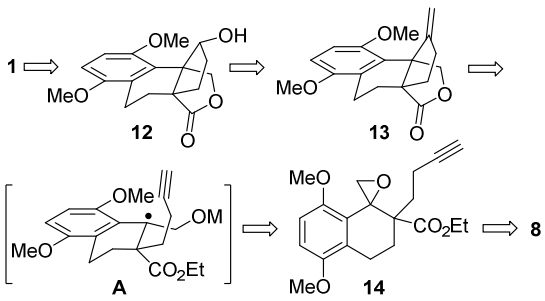
Due to the interesting structure lingzhiol (**1**) has attracted significant interest from synthetic groups. Up to now five total syntheses from other groups were reported. Three of them start from 5,8-dimethoxy-tetralone[6] (**8**) and two use 2-oxo-cyclopentanecarboxylate[7] **9** as starting material. Our own group contributed with a synthesis of lingzhiol and some analogs where an alkylation and Wittig reaction on ethyl 2–oxocyclopentancarboxylate (**9**) to *exo*-alkene **10** allowed for a short route to epoxide **11** which underwent a Lewis acid promoted intramolecular Friedel-Crafts alkylation[7a] to key tetracyclic intermediate **12** (Scheme 2).[8]

Scheme 2. Published routes to lingzhiol either start from tetralone **8** or oxocyclopentane carboxylate **9**.



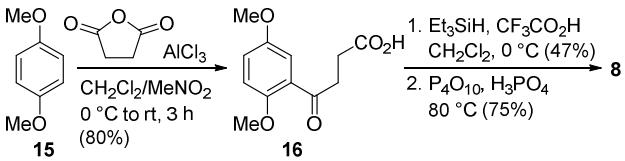
In our retrosynthetic plan tetracyclic intermediate **12** would originate from exocyclic alkene **13** (Scheme 3). After this key FGI, a radical cyclization of benzylic radical **A** to its alkyne function becomes obvious. The benzylic radical **A** would be generated from spiroepoxide **14**, which in turn can be traced back to tetralone **8**.[9,10] In this paper we detail the implementation of this plan, the associated difficulties and how this strategy led to lingzhiol (±-**1**) and the deoxy analog **39**.

Scheme 3. Retrosynthesis for lingzhiol featuring a radical cyclization to form the cyclopentane ring.



Dimethoxytetralone **8** was prepared from *p*-dimethoxybenzene (**15**) by the classical Haworth strategy. Here we could improve the yield for the Friedel-Crafts acylation[11] with succinic anhydride by running the $AlCl_3$ induced reaction in a mixture of nitromethane and dichloromethane (Scheme 4). This way ketoacid **16** was obtained in 80% yield. For the subsequent reductive removal of the keto function we relied on ionic reduction using triethylsilane in presence of trifluoroacetic acid in dichloromethane.[12] The second Friedel-Crafts reaction to tetralone was performed as described[11] yielding ketone **8** in 75% yield.

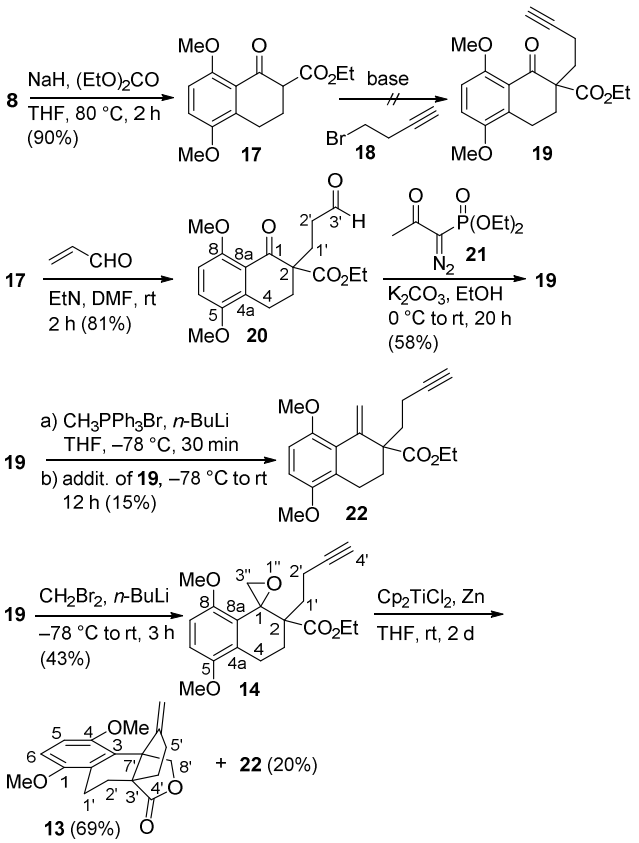
Scheme 4. Synthesis of tetralone **8** via Haworth strategy.



In the next step a carboxylation reaction[13] on tetralone **8** using diethyl carbonate in presence of sodium hydride delivered β-ketoester **17** (Scheme 5). The plan was then to alkylate ketoester **17** with 4-bromo-1-

butyne[14] (**18**). However, the desired product **19** could not be observed [NaH (1.6 equiv), **18** (1.4 equiv), THF, 0 to 80 °C, 20 h]. We therefore prepared aldehyde **20** by base induced Michael addition of ketoester **17** to acrolein.[15] Subsequently, aldehyde **20** was reacted with the Ohira-Bestmann reagent, the diazo compound **21**, in ethanol in presence of potassium carbonate,[16] giving rise to alkyne **19** in 58% yield. For the synthesis of spiroepoxide **14** we first considered an olefination reaction on ketone **19** followed by epoxidation of the exocyclic double bound. However, neither Wittig (Ph_3PCH_3Br, *n*-BuLi, THF; Ph_3PCH_3Br, KO*t*-Bu, *t*-BuOH) nor Lombardo conditions[17] (20% of **22**) nor Peterson olefination led to the desired alkene **22** in satisfactory yields. Therefore, we focused on a formal carbene addition to the keto function of **19**. While epoxidation with the Corey-Chaykowski reagent ($(CH_3)_3S^+ I^-$, NaH, DMSO) was not successful, the intended transformation could be realized with (bromomethyl) lithium,[18,19] generated from dibromomethane (1.5 equiv) and *n*-BuLi (1.2 equiv) in THF at –78 °C. Epoxide **14** was obtained essentially as a single diastereomer (~ 6:1). In the ^{1}H NMR spectrum epoxide **14** shows a characteristic peak at δ = 3.25 ppm (d, *J* = 4.3 Hz) which can be assigned to one of the CH_2 epoxide protons. The diastereomeric ratio of the epoxides was determined by integration of the OCH_2CH_3 triplets at δ = 1.04 and 0.99 ppm, respectively. A small amount of starting ketone **19** (~ 20%) could be separated by chromatography. Unfortunately, we were not able to obtain epoxide **14** in very pure form. Alternatively, it was possible to use the crude mixture from the epoxidation reaction, containing some ketone **19**, for the subsequent radical cyclization reaction. In these cases the yield of **14** was determined by integration of the aromatic protons. It seems that epoxide formation on ketone **19** is hampered by steric hindrance and electronic deactivation of the keto function by the 8-OCH_3 substituent. For the radical cyclization epoxide **14** was subjected to a preformed mixture of zinc (9 equiv) and Cp_2TiCl_2 (3 equiv) in THF at 0˚C followed by stirring of the mixture for 2 d. This gave tetracyclic lactone **13** in 69% yield as yellow powder. In addition to tetracycle **13** around 20% of alkene **22** was formed under these conditions.

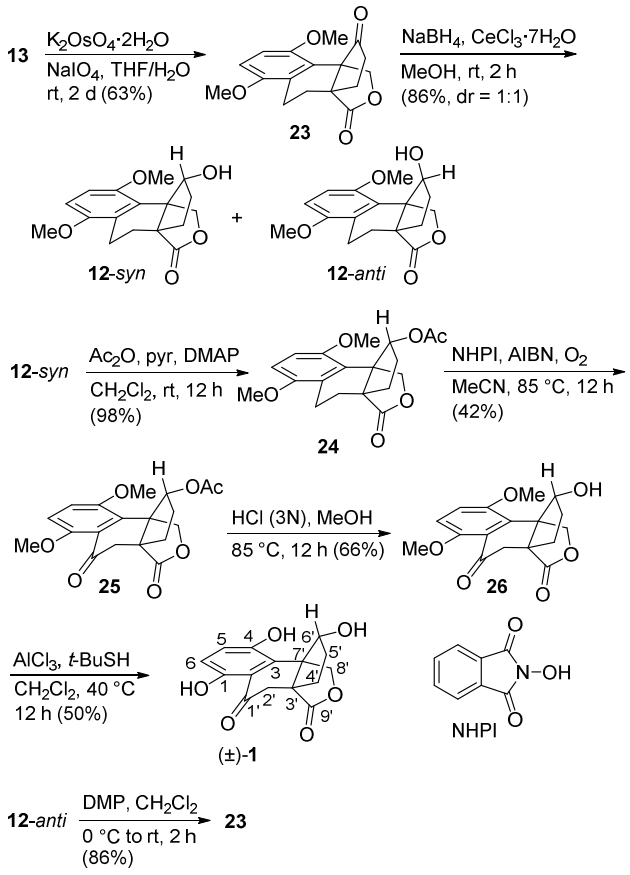
Scheme 5. Synthesis of tetracycle **13**.



The subsequent oxidative cleavage of the exocyclic double bond was best performed as a one pot process. Thus, alkene **13** was stirred in an aqueous solution of THF in presence of catalytic amounts of potassium osmate(VI) dihydrate ($K_2OsO_4 \cdot 2H_2O$) and sodium periodate ($NaIO_4$, 4 equiv)[20] to give ketone **23** in 63% yield (Scheme 6). Its spectral data were in accordance with a sample that was prepared by oxidation of the corresponding alcohol.[8] As a final challenge, the diastereoselective reduction of ketone **23** remained. Using sodium borohydride in methanol a 1:2 mixture of **12**-*syn* and **12**-*anti* was obtained. Here *syn* refers to the isomer where the hydroxyl group points towards the butyrolactone part. Other conditions ($NaBH_4$, EtOH, 0 °C to rt, 1.5 h, *syn*/*anti* = 25:75, 75% yield; Et_3SiH, $TiCl_4$, CH_2Cl_2, –40 °C, 30 min, no reaction; L-Selectride, THF, –78 °C to rt, 3 h, *syn*/*anti* = 33:67) also preferentially led to **12**-*anti*. However, in presence of cerium trichloride hydrate ($CeCl_3 \cdot 7H_2O$, 1 equiv) a 1:1 mixture of **12**-*syn* and **12**-*anti* was formed.[21] Both isomers could be separated by chromatography. It was possible to recycle the

12-*anti* isomer by oxidation to ketone **23** using the Dess-Martin periodinane[22] reagent. Inversion of the stereochemistry at C-6' of **12**-*anti* under Mitsunobu conditions remained fruitless. For the conversion of alcohol **12**-*syn* to lingzhiol we followed literature precedence.[6,8] Thus, acetylation of **12**-*syn* to acetate **24** was followed by benzylic oxidation with oxygen in presence of *N*-hydroxyphthalimide and AIBN which gave phenone **25** in a decent yield of 42%. An X-ray analysis of acetate **24** (see Supporting Information) proved the relative stereochemistry of the reduction step. Subsequent hydrolysis of the acetate led to hydroxyphenone **26**. A final cleavage of the aromatic ether functions with aluminium chloride in presence of *tert*-butyl mercaptan provided racemic lingzhiol **1**. Its spectral data fully matched the literature values.

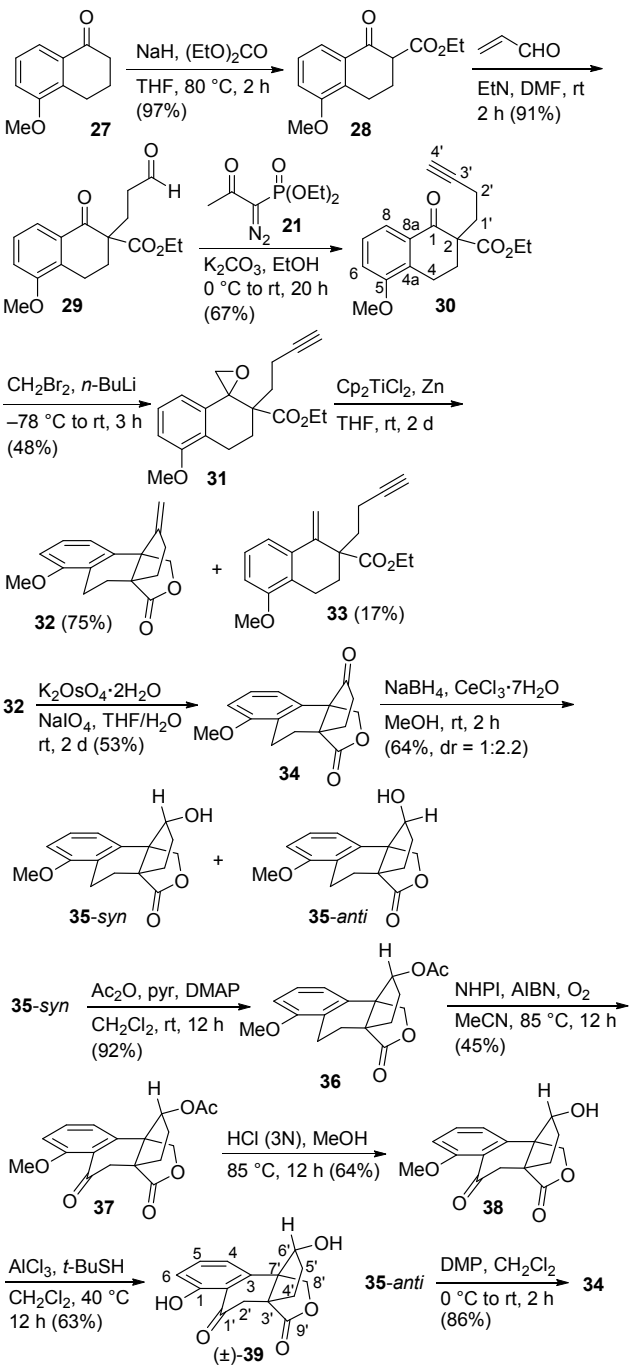
Scheme 6. Conversion of exocyclic alkene **13** to lingzhiol (**1**).



In order to elucidate the stereoelectronic influence of the 4-OCH_3 group (lingzhiol numbering) on the reactivity of the tetralone carbonyl group and to shed light on the role of the corresponding hydroxyl function in lingzhiol we designed analog **39** (Scheme 7). The synthesis of **39** was patterned along the route shown for (±)-**1** (Scheme 5 and 6). Even though 5-methoxy-1-tetralone (**27**) is commercially available, we prepared it from naphthalene-1,5-diol via catalytic hydrogenation which led to 5-hydroxy-1-tetralone[23] followed by a Williamson ether synthesis (K_2CO_3, MeI, acetone, 56% yield).

Following the route of Schemes 5 and 6, **27** was carboxylated to ketoester[24] **28** and then added to acrolein under basic conditions (Scheme 7). Aldehyde **29** could be converted to alkyne **30** using the Ohira-Bestmann reagent. Reaction of ketone **30** with lithiated dibromomethane furnished epoxide **31** in 48% yield. The reductive cyclization provided tetracycle **32** in 75% yield. Again, some deoxygenation of the epoxide to the corresponding alkene **33** (17%) was observed. While the transformations up to **32** proceeded with somewhat higher yields as compared to the sequence for (±)-**1**, the oxidative cleavage of the double bond was less efficient providing ketone **34** in 53% yield. Moreover, the reduction of ketone **34** favored the wrong isomer, even in presence of $CeCl_3 \cdot 7H_2O$ (**35**-*syn*/**35**-*anti* = 1:2). Four further steps converted alcohol **35**-*syn* via acetate **36**, phenone **37**, and hydroxyketone **38** to lingzhiol analog **39**.

Scheme 7. Synthesis of lingzhiol analog (±)-**39**.



Starting from tetralone **8** we developed a novel strategy to the polycyclic natural product lingzhiol (**1**). The key reaction was a radical cyclization of epoxyalkyne **14** under reductive conditions using *in situ* generated Cp_2TiCl leading to polycycle **13**. Oxidative cleavage of the exocyclic double bond furnished

ketone **23**. Reduction of ketone **23** with sodium borohydride in presence of cerium trichloride delivered a 1:1 mixture of alcohols **12**-*syn* and **12**-*anti*. Using an established sequence of reactions alcohol **12**-*syn* could be converted to lingzhiol (±)-**1**. In a similar strategy 5-methoxy-1-tetralone (**27**) was converted to lingzhiol analog (±)-**39**.

Experimental Section

General. Reactions were generally run under nitrogen atmosphere in oven dried glassware. Progress of the reactions was followed using TLC plates "POLYGRAM SIL G/UV254", petroleum ether, ethyl acetate (EtOAc), dichloromethane, methanol and mixtures of them as an eluent. Dry diethyl ether (Et_2O) and tetrahydrofuran were distilled from sodium and benzophenone, whereas dry CH_2Cl_2, methanol and EtOAc were distilled from CaH_2. Distilled petroleum ether with a boiling range of 40–60 °C was used. ^{1}H NMR (400.160 MHz) and ^{13}C NMR (100.620 MHz) spectra were measured on a "Bruker Avance 400" spectrometer using $CDCl_3$ as solvent at room temperature. Peak assignments were done by NMR spectroscopy (^{1}H, ^{13}C, DEPT-135, H,H-COSY, HSQC, and HMBC). High-resolution mass spectra (HRMS) were recorded on a "Bruker maXis 4G" instrument with electron spray ionization (ESI) and TOF mass detector. Not all the compound names may correspond to IUPAC nomenclature.

4-(2',5'-Dimethoxyphenyl)-4-oxobutyric acid (**16**). Succinic anhydride (11.25 g, 11.25 mmol) and *p*-dimethoxybenzene (**15**) (13.88 g,10.04 mmol) were added to a solution of $AlCl_3$ (30.0 g, 0.23 mol) in a mixture of CH_2Cl_2/nitromethane (1:1, each 125 mL) at 0 °C. The mixture was allowed to warm from 0 °C to rt and stirred over 3 h, after which the solution was poured into ice-water (about 500 mL). This mixture was acidified to pH 1 using concentrated HCl while cooling the mixture in an ice bath. The mixture was extracted with EtOAc (3 × 250 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was recrystallized from a mixture of $CHCl_3$ (about 15 mL) and petroleum ether (few drops). The resulting very pale yellow solid was filtered

and dried (19.0 g, 80%). R_f = 0.32 (petroleum ether/EtOAc, 2:1). ^{1}H NMR data for keto acid **16** matched those reported in the literature.[11]

Ethyl 5,8-dimethoxy-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate[13] (**17**). A solution of tetralone **8** (13.8 g, 66.9 mmol, 1 equiv) in THF (335 mL) was dropped into a suspension of NaH (3.30 g, 83.6 mmol, 1.25 equiv, 60% in mineral oil) and freshly distilled diethyl carbonate (80.9 g, 83.0 mL, 0.685 mol) in THF (220 mL) under a nitrogen atmosphere. The mixture was then heated to 70 °C for additional 2 h. The color of the reaction mixture turned from yellow to dark red. The mixture was diluted with a saturated aqueous solution of NH_4Cl (450 mL) and extracted with Et_2O (3 × 140 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was crystallized from a mixture of Et_2O and petroleum ether (10:1; about 20 mL) to give ketoester **17** (16.7 g, 90%) as fawn solid. R_f = 0.48 (petroleum ether/EtOAc, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.01 (d, *J* = 8.8 Hz, 1H, 6-H), 6.82 (d, *J* = 9.1 Hz, 1H, 7-H), 4.23 (q, *J* = 7.1 Hz, 2H, OC*H*$_2$CH$_3$), 3.86 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 3.58 (dd, *J* = 10.9, 4.8 Hz, 1H, 2-H), 3.10 (dt, J = 18.2, 5.3 Hz, 1H, 4-H), 2.83-2.74 (m, 1H, 4-H), 2.47-2.28 (m, 2H, 3-H), 1.26 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 192.7 (C-2), 170.4 (CO_2Et), 154.3 (C-8), 150.1 (C-5), 134.1 (C-4a), 122.2 (C-8a), 115.7 (C-6), 110.2 (C-7), 61.0 (O*C*H$_2$CH$_3$), 56.4 (C-2), 55.9, 55.7 (OCH_3), 25.1 (C-3), 22.0 (C-4), 14.2 (OCH$_2$*C*H$_3$).

Ethyl 5,8-dimethoxy-1-oxo-2-(3-oxopropyl)-1,2,3,4-tetrahydro¬naphthalene-2-carboxylate (**20**). Acrolein (5.2 g, 6.2 mL, 93 mmol, 1.5 equiv) and NEt_3 (0.88 g, 1.2 mL, 8.7 mmol, 0.14 equiv) were added to a solution of ester **17** (16.7 g, 60.0 mmol, 1 equiv) in DMF (120 mL) under a nitrogen atmosphere. The mixture was stirred at rt for 2 h. The reaction was quenched using HCl (1N, 140 mL) and extracted with Et_2O (3 × 120 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude aldehyde **20** (17.0 g, 81%), obtained as a light yellow oil, was used in the next step without further purification. R_f = 0.26 (petroleum ether/EtOAc, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.79 (t, *J* = 1.1 Hz, 1H, CHO), 6.96 (d, *J* = 9.1 Hz, 1H, 6-H), 6.70 (d, *J* = 9.1 Hz, 1 H, 7-H), 4.06-

4.16 (m, 2H, OC*H*$_2$CH$_3$), 3.86 (s, 3H, OCH$_3$), 3.81 (s, 3H, OCH$_3$), 2.87-2.97 (m, 2H, 4-H), 2.71-2.76 (m, 1H, 2'-H), 2.51-2.61 (m, 2H, 3-H, 2'-H), 2.23-2.31 (m, 1H, 1'-H), 2.09-2.15 (m, 1H, 1'-H), 1.96-2.04 (m, 1H, 3-H), 1.12 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 201.4 (CHO), 194.7 (C-1), 171.6 (CO$_2$Et), 153.9 (C-8), 150.1 (C-5), 132.9 (C-4a), 122.9 (C-8a), 114.9 (C-6), 110.2 (C-7), 61.1 (O*C*H$_2$CH$_3$), 57.1 (C-2), 56.4, 55.7 (OCH$_3$), 39.7 (C-2'), 30.3 (C-3), 26.1 (C-1'), 20.5 (C-4), 13.9 (OCH$_2$*C*H$_3$); HRMS (ESI-TOF) *m/z*: [M + Na + MeOH]$^+$ calcd for C$_{19}$H$_{26}$O$_7$Na 389.15707; found 389.15717.

Ethyl 2-(but-3-yn-1-yl)-5,8-dimethoxy-1-oxo-1,2,3,4-tetrahydro¬naphthalene-2-carboxylate (**19**). Anhydrous K$_2$CO$_3$ (7.10 g, 51.4 mmol, 2 equiv) was added to a solution of aldehyde **20** (8.60 g, 25.7 mmol, 1 equiv) in EtOH (150 mL) under a nitrogen atmosphere at 0 °C. The diazophosphonate[16] **21** (7.36 g, 33.4 mmol, 1.3 equiv) was added dropwise as a solution in EtOH (100 mL). The mixture was allowed to gradually warm to rt over 20 h. The reaction mixture was diluted using a saturated aqueous solution of NaHCO$_3$ (300 mL) followed by extraction with EtOAc (2 × 180 mL). The combined organic extracts were dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (petroleum ether/EtOAc, 2:1) to afford alkyne **19** (4.82 g, 58%) as a pale yellow solid. R$_f$ = 0.55 (petroleum ether/EtOAc, 1:1); mp 78.1 °C (EtOAc); ^{1}H NMR (400 MHz, CDCl$_3$): δ = 6.95 (d, *J* = 9.1 Hz, 1H, 6-H), 6.79 (d, *J* = 9.1 Hz, 1H, 7-H), 4.07-4.17 (m, 2H, OC*H*$_2$CH$_3$), 3.85 (s, 3H, OCH$_3$), 3.81 (s, 3H, OCH$_3$), 2.89-2.93 (m, 2H, 4-H), 2.54-2.60 (m, 1H, 3-H), 2.36-2.46 (m, 1H, 2'-H), 2.23-2.34 (m, 2H, 1'-H, 2'-H), 2.00-2.08 (m, 2H, 3-H, 1'-H), 1.95 (t, *J* = 2.5 Hz, 1H, 4'-H), 1.12 (t, *J* = 7.3 Hz, 3H, OCH$_2$C*H*$_3$); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 194.5 (C-1), 171.3 (CO$_2$Et), 153.9 (C-8), 150.0 (C-5), 132.9 (C-4a), 122.9 (C-8a), 114.8 (C-6), 110.1 (C-7), 84.0 (C-3'), 68.4 (C-4'), 61.1 (O*C*H$_2$CH$_3$), 57.5 (C-2), 56.4, 55.7 (OCH$_3$), 32.8 (C-1'), 29.6 (C-3), 20.4 (C-4), 14.4 (C-2'), 13.9 (OCH$_2$*C*H$_3$); HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ calcd for C$_{19}$H$_{22}$O$_5$Na 353.13594; found 353.13618.

Ethyl 2-(but-3-yn-1-yl)-5,8-dimethoxy-1-methylene-1,2,3,4-tetrahydronaphthalene-2-carboxylate (**22**).

a) Wittig reaction: To a suspension of methyltriphenylphosphonium iodide (365 mg, 0.903 mmol, 3 equiv) in THF (3 mL) was added *n*-BuLi (0.13 mL, 0.33 mmol, 2.5 M, 1.01 equiv) at –78 °C slowly. The reaction mixture turned to deep yellow and was stirred for 30 min at –78 °C. Then ketone **19** (100 mg, 0.303 mmol, 1 equiv), dissolved in THF (1 mL) was added dropwise. The reaction mixture was brought to room temperature and stirred overnight. Then it was quenched with saturated NH_4Cl solution (20 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (petroleum ether/EtOAc, 4:1) to give alkene **22** (15 mg, 15%) as colorless oil.

b) Takai-Lombardo reaction: Zinc powder (86 mg, 1.3 mmol, 4.3 equiv) was submitted in a Schlenk-flask and dried 30 min with a heat gun (300 °C) under vacuo. After cooling, dry THF (10 mL) and CH_2Cl_2 (5 mL) were added. The suspension was cooled to -40 °C before $TiCl_4$ (0.3 mL, 0.3 mmol, 1M in THF, 1 equiv) was added dropwise. Afterwards the mixture was brought to 5 °C and kept at this temperature for 3 d under N_2-atomosphere. The solution turned from green to brown. The stirred mixture was diluted with dry CH_2Cl_2 (4 mL) and then ketone **19** (100 mg, 0.303 mmol), dissolved in dry CH_2Cl_2 (2 mL), was added dropwise. The cooling bath was removed and the mixture was stirred for 1.5 h. The reaction was quenched with saturated $NaHCO_3$ solution (15 mL), the organic layer was separated and the aqueous layer was extracted with petroleum ether (3 × 10 mL). The combined organic extracts were washed with saturated NaCl solution (15 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (petroleum ether/EtOAc, 5:1). The product **22** (20 mg, 20%) was obtained as colorless oil.

R_f = 0.56 (petroleum ether/EtOAc, 4:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.74 (d, *J* = 8.8 Hz, 1H, 6-H), 6.67 (d, *J* = 8.8 Hz, 1H, 7-H), 5.91 (s, 1H, 1-CH_2), 5.35 (s, 1H, 1-CH_2), 4.06-4.18 (m, 2H, OC*H*$_2$CH$_3$), 3.78 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 2.69-2.90 (m, 2H, 4-H), 2.35-2.42 (m, 1H, 3-H), 2.17-2.32 (m, 3H, 1'-H, 2'-H), 1.96-2.00 (m, 1H, 1'-H), 1.71-178 (m, 1H, 3-H), 1.94 (t, *J* = 2.3 Hz, 1H, 4'-H), 1.14 (t, *J* = 7.3 Hz, 3H,

OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.6 (CO_2Et), 151.5 (C-1), 150.8 (C-8), 141.2 (C-5), 127.2, 126.0 (C-4a, C-8a), 114.7 (C-7), 110.0 (C-6), 108.7 (1-CH_2), 84.3 (C-3'), 68.2 (C-4'), 60.6 (OCH_2CH_3), 56.3, 55.7 (OCH_3), 51.5 (C-2), 35.0 (C-1'), 30.1 (C-3), 20.7 (C-4), 14.4 (C-2'), 14.0 (OCH_2CH_3); HRMS (ESI-TOF**)**: *m/z*: [M + Na]$^+$ calcd for $C_{20}H_{24}O_4Na$ 351.15668; found 351.15678.

Ethyl 2-(but-3-yn-1-yl)-5,8-dimethoxy-3,4-dihydro-2*H*-spiro[naphthalene-1,2'-oxirane]-2-carboxylate (**14**). A solution of *n*-BuLi (2.5M in hexane, 2.61 mL, 6.54 mmol, 1.2 equiv) was added dropwise to a solution of dibromomethane (1.42 g, 8.17 mmol, 1.5 equiv) and alkyne **19** (1.80 g, 5.45 mmol, 1 equiv) in freshly distilled, dry THF (70 mL) at –78 °C under argon atmosphere. The mixture was stirred for 10 min at –78 °C, then brought to room temperature and stirred for 1 h. The solvent was removed under reduced pressure and the residue filtered through a pad of silica gel. The filtrate was concentrated in vacuo and the residue subjected to flash chromatography (petroleum ether/EtOAc, 2:1) which provided spiroepoxide **14** (810 mg, 43%) as a light yellow oil. Despite the chromatography it was not possible to obtain pure **14**. R_f = 0.60 (petroleum ether/EtOAc, 1:1); ^1H NMR (400 MHz, $CDCl_3$): δ = 6.70 (d, *J* = 8.9 Hz, 1H, ArH), 6.63 (d, *J* = 9.0 Hz, 1H, ArH), 3.93-4.02 (m, 2H, OCH_2CH_3), 3.74 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3), 3.26 (d, *J* = 4.3 Hz, 1H, CH_2 epoxide), 2.96-3.04 (m, 1H), 2.66-2.74 (m, 1H), 2.36-2.42 (m, 1H), 2.21-2.30 (m, 1H), 2.08-2.15 (m, 1H), 1.99-2.05 (m, 1H), 1.92 (t, *J* = 2.6 Hz, 1H), 1.87-1.97 (m, 1H), 1.70-1.78 (m, 1H), 1.04 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3); HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ calcd for $C_{20}H_{24}O_5Na$ 367.15159; found 367.15137.

Lingzhiol precursor **13**. Zinc (584 mg, 8.94 mmol, 9.0 equiv) and Cp_2TiCl_2 (742 mg, 2.98 mmol, 3.0 equiv) were suspended in freshly distilled THF (100 mL) in a flame dried round bottom flask, followed by stirring of the slurry for 1 h at rt (the color changed from deep red to green). Meanwhile epoxide **14** (342 mg, 0.993 mmol, 1 equiv) was dissolved in THF (50 mL) under argon atmosphere and cooled to 0 °C. Then the titanocene dichloride/zinc solution was added dropwise. The reaction mixture was brought to room temperature and stirred for 72 h. The mixture was diluted with HCl (1N, 45 mL), stirred for 2 h at rt and

extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure to provide polycycle **13** (240 mg, 69%) as light yellow crystals. R_f = 0.40 (petroleum ether/EtOAc, 4:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.70 (s, 2H, 5-H, 6-H), 5.12 (t, *J* = 1.8 Hz, 1H, 6'-CH_2), 4.97 (t, *J* = 1.9 Hz, 1H, 6'-CH_2), 4.90 (d, *J* = 10.0 Hz, 1H, 8'-H), 4.43 (d, *J* = 10.0 Hz, 1H, 8'-H), 3.77 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 2.99 (dt, *J* = 17.5, 4.9 Hz, 1H, 1'-H), 2.55-2.46 (m, 1H, 1'-H), 2.35-2.17 (m, 2H, 5'-H), 2.13-2.05 (m, 1H, 4'-H), 2.01 (dt, *J* = 13.3, 4.4 Hz, 1H, 2'-H), 1.92-1.85 (m, 1H, 4'-H), 1.67-1.60 (m, 1H, 2'-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 182.2 (C-9'), 152.8 (C-6'), 151.9 (C-4), 150.9 (C-1), 127.2, 127.0 (C-2, C-3), 108.7, 108.6 (C-5, C-6), 108.6 (6-CH_2), 75.3 (C-8'), 55.8 (OCH_3), 55.2 (OCH_3), 53.7, 53.3 (C-3', C-7'), 32.9 (C-5'), 32.2 (C-4'), 26.9 (C-2'), 18.8 (C-1'); HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{18}H_{20}O_4Na$ 323.12538; found 323.12537.

Ketone **23**. $K_2OsO_4 \cdot 2H_2O$ (5.9 mg, 0.016 mmol, 5.5 mol%) was added in one portion to a mixture of olefin **13** (96 mg, 0.32 mmol, 1 equiv) and $NaIO_4$ (2745 mg, 1.28 mmol, 4 equiv) in THF (5.5 mL) and water (5.5 mL). The reaction mixture was stirred for 2 d at rt. The mixture was diluted using a saturated aqueous solution of NaOH (1N, 30 mL). The aqueous layer was extracted with EtOAc (4 × 20 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography to give ketone **23** (60 mg, 63%) as fawn-colored solid. Its spectral data were identical to a sample prepared by oxidation of the corresponding alcohol.[8] R_f = 0.35 (petroleum ether/EtOAc, 2:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.74 (s, 2H, 5-H, 6-H), 5.09 (d, *J* = 10.1 Hz, 1H, 8'-H), 4.38 (d, *J* = 10.1 Hz, 1H, 8'-H), 3,78 (s, 6H, OCH_3), 3.02 (dt, *J* = 17.7, 4.5 Hz, 1H, 1'-H), 2.54-2.63 (m, 1H, 1'-H), 2.28-2.42 (m, 3H, 4'-H, 5'-H), 2.09-2.15 (m, 2H, 2'-H, 4'-H), 1.75-1.82 (m, 1H, 2'-H); ^{13}C NMR (400 MHz, $CDCl_3$): δ = 210.3 (C-6'), 180.6 (C-9'), 152.8, 150.9 (C-1, C-4), 126.5 (C-2), 121.4 (C-3), 109.8, 109.6 (C-5, C-6), 72.8 (C-8'), 56.6 (C-7'), 56.2 (OCH_3), 55.8 (OCH_3), 49.7 (C-3') 36.0 (C-5'), 26.0 (C-2'), 25.9 (C-4'), 18.7 (C-1'); HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{17}H_{18}O_5Na$ 325.10464; found 325.10460.

Alcohols **12**-*syn* and **12**-*anti*. A solution of ketone **23** (45 mg, 0.15 mmol, 1 equiv) in MeOH (7 mL) was treated with $CeCl_3 \cdot 7H_2O$ (55.5 mg, 0.149 mmol, 1 equiv) and $NaBH_4$ (8.5 mg, 0.22 mmol, 1.5 equiv) at rt. After 2 h stirring at rt, the reaction mixture was diluted with EtOAc (9 mL) and washed with saturated NaCl solution (6 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo to give a mixture of diastereomeric alcohols **12**. The isomers were separated by flash chromatography (CH_2Cl_2/EtOAc, 12:1) to give 19 mg (43%) of **12**-*syn* and 19 mg (43%) of **12**-*anti*, both as colorless solid.

12-*syn*:[6b,6c,7a,8] R_f = 0.29 (CH_2Cl_2/EtOAc, 12:1); mp 205.3 °C ($CDCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.73 (d, *J* = 9.0 Hz, 1H, ArH), 6.68 (d, *J* = 8.9 Hz, 1H, ArH), 5.19 (d, *J* = 9.9 Hz, 1H, 8'-H), 4.14 (t, *J* = 6.2 Hz, 1H, 6'-H), 4.08 (d, *J* = 9.8 Hz, 1H, 8'-H), 3.81 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 3.04 (dt, *J* = 17.4, 4.0 Hz, 1H, 1'-H), 2.83 (s, 1H, OH), 2.42 (ddd, *J* = 17.2, 12.6, 4.4 Hz, 1H, 1'-H), 2.18-2.25 (m, 1H, 4'-H), 2.11 (dt, *J* = 13.6, 3.9 Hz, 1H, 2'-H), 1.82-1.94 (m, 2H, 4'-H, 5'-H), 1.66 (dd, *J* = 13.2, 4.8 Hz, 1H, 2'-H), 1.52-1.58 (m, 1H, 5'-H); ^{13}C NMR (400 MHz, $CDCl_3$): δ = 182.2 (C-9'), 151.3, 151.2 (C-1, C-4), 129.4 (C-2), 126.2 (C-3), 108.7, 108.2 (C-5, C-6), 81.8 (C-6'), 71.0 (C-8'), 55.9, 55.8 (OCH_3), 53.6 (C-7'), 52.7 (C-3'), 32.4 (C-5'), 30.1 (C-4'), 26.7 (C-2'), 18.5 (C-1').

12-*anti*: R_f = 0.36 (CH_2Cl_2/EtOAc, 12:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.74 (s, 2H, 5-H, 6-H), 4.66 (t, *J* = 3.1 Hz, 1H, 6'-H), 4.38 (d, *J* = 10.3 Hz, 1H, 8'-H), 4.29 (d, *J* = 10.3 Hz, 1H, 8'-H), 3.80 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 2.65-2.69 (m, 2H, 1'-H), 2.16-2.20 (m, 2H, 4'-H), 1.94-2.00 (m, 2H, 2'-H), 1.87-1.92 (m, 2H, 5'-H); ^{13}C NMR (400 MHz, $CDCl_3$): δ = 182.0 (C-9'), 151.2, 150.7 (C-1, C-4), 129.4 (C-2), 125.7 (C-3), 109.3, 108.3 (C-5, C-6), 80.6 (C-6'), 76.9 (C-8'), 56.6 (C-7'), 55.9, 55.6 (OCH_3), 52.7 (C-3'), 34.6 (C-4'), 31.6 (C-5'), 28.2 (C-2'), 19.4 (C-1'); HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{17}H_{20}O_5Na$ 327.12029; found 327.12070.

Ketone **23** from alcohol **12**-*anti*. A suspension of DMP (25 mg, 0.059 mmol, 1.3 equiv) in CH_2Cl_2 (2.1 mL) was cooled to 0 °C. Alcohol **12**-*anti* (15 mg, 0.049 mmol, 1 equiv) dissolved in CH_2Cl_2 (0.9 mL) was added slowly. The mixture was stirred for 2 h at room temperature before it was treated with a solution of NaOH (1N, 4.5 mL) and extracted with diethyl ether (2 × 4.5 mL). The ethereal extracts were dried with

Na_2SO_4, filtered and concentrated in vacuo. Ketone **23** (13 mg, 86%) was obtained without purification as a light brown solid.

Acetate **24**.[6b,8] Acetic anhydride (19.1 mg, 0.187 mmol, 3 equiv), pyridine (14.8 mg, 15.1 μL, 0.187 mmol, 3 equiv) and DMAP (1.3 mg, 0.011 mmol, 0.17 equiv) were added successively to a solution of alcohol **12**-*syn* (19 mg, 0.060 mmol, 1 equiv) in CH_2Cl_2 (0.8 mL) at 0 °C. The reaction mixture was allowed to warm to rt and subsequently stirred overnight. It was then diluted with CH_2Cl_2 (1.5 mL), washed with HCl solution (1N, 0.5 mL) and once with a saturated NaCl solution (1.5 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Flash chromatography (petroleum ether/EtOAc, 1:1) gave acetate **24** (21 mg, 98%) as colorless solid. R_f = 0.61 (petroleum ether/EtOAc, 1:1); mp 191.5 °C (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.71 (d, *J* = 8.9 Hz, 1H, 6-H), 6.67 (d, *J* = 8.9 Hz, 1H, 5-H), 5.42 (s, 1H, 6'-H), 4.90 (d, *J* = 10.1 Hz, 1H, 8'-H), 4.09 (d, *J* = 10.2 Hz, 1H, 8'-H), 3.78 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 3.08 (ddd, *J* = 17.0, 4.4, 2.4 Hz, 1H, 1'-H), 2.30-2.48 (m, 2H, 1'-H, 5'-H), 2.16-2.21 (m, 1H, 2'-H), 2.11 (s, 3H, $C(=O)CH_3$), 1.94-2.02 (m, 1H, 5'-H), 1.60-1.76 (m, 3H, 4'-H, 2'-H); ^{13}C NMR (400 MHz, $CDCl_3$): δ = 182.5 (C-9'), 170.2 ($C(=O)CH_3$), 151.4, 150.7 (C-1, C-4), 127.2, 125.7 (C-2, C-3), 109.0, 108.4 (C-5, C-6), 82.2 (C-6'), 72.2 (C-8'), 55.8, 55.4 (OCH_3), 54.9, 51.6 (C-3', C7'), 32.3 (C-4'), 31.3 (C-5'), 27.4 (C-2'), 21.4 ($C(=O)CH_3$), 18.3 (C-1'); HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{19}H_{22}O_6Na$ 369.13086; found 369.13098.

Phenone **25**.[6b,8] *N*-hydroxyphthalimide (24.7 mg, 0.152 mmol, 2.5 equiv) and AIBN (5.0 mg, 0.03 mmol, 0.5 equiv) were added to a solution of acetate **24** (21 mg, 0.061 mmol, 1 equiv) in acetonitrile (1.8 mL) at rt. Through a steel needle oxygen was continuously bubbled through the solution. The reaction mixture was stirred overnight at 85 °C. Afterwards it was cooled to room temperature and the solvent removed under reduced pressure. The crude product was purified by flash chromatography (petroleum ether/EtOAc, 1:1) to give phenone **25** (9.2 mg, 42%) as colorless solid. R_f = 0.22 (petroleum ether/EtOAc, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.08 (d, *J* = 9.3 Hz, 1H, 5-H), 6.93 (d, *J* = 9.3 Hz, 1H, 6-H), 5.48 (broad,

1H, 6'-H), 4.99 (d, *J* = 10.4 Hz, 1H, 8'-H), 4.29 (d, *J* = 10.4 Hz, 1H, 8'-H), 3.84 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 2.87 and 2.79 (AB system, *J* = 12.8 Hz, 2H, 2'-H), 2.44-2.53 (m, 1H, 4'-H), 2.12 (s, 3H, $C(=O)CH_3$), 1.92-1.99 (m, 1H, 4'-H), 1.63-1.74 (m, 2H, 5'-H); ^{13}C NMR (400 MHz, $CDCl_3$): δ = 194.1 (C-1'), 179.4 (C-9'), 170.0 ($C(=O)CH_3$), 152.3 (C-3), 150.3 (C-2), 130.2 (C-1), 122.9 (C-4), 117.0 (C-5), 112.5 (C-6), 81.6 (C-6'), 71.1 (C-8'), 56.6, 56.0 (OCH_3), 55.2 (C-3') 52.8 (C-7'), 44.3 (C-2'), 31.8 (C-4'), 31.5 (C-5'), 21.3 ($C(=O)CH_3$); HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{19}H_{20}O_7Na$ 383.11012; found 383.11028.

Hydroxyphenone **26**.[6a,6b,6c,7a,8] To a stirred solution of acetate **25** (8.5 mg, 0.024 mmol, 1 equiv) in methanol (1.3 mL) was added HCl (3N, 1.3 mL). The mixture was heated to 85 °C overnight then cooled to rt before the solvent was removed under reduced pressure. The residue was dissolved in water (4 mL) and extracted with CH_2Cl_2 (3 × 3 mL). The combined organic extracts were dried with Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by flash chromatography (petroleum ether/EtOAc, 1:1) to give hydroxyphenone **26** (5 mg, 66%) as colorless solid. R_f = 0.12 (petroleum ether/EtOAc, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.09 (d, *J* = 9.2 Hz, 1H, 5-H), 6.88 (d, *J* = 9.2 Hz, 1H, 6-H), 5.30 (d, *J* = 10.0 Hz, 1H, 8'-H), 4.27 (t, *J* = 6.2, 1H, 6'-H), 4.26 (d, *J* = 10.0 Hz, 1H, 8'-H), 3.87 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 2.79 and 2.86 (AB system, *J* = 13.1 Hz, 1H, 2'-H), 2.35-2.38 (m, 1H, 4'-H), 1.90-1.94 (m, 1H, 5'-H), 1.75-1.79 (m, 1H, 4'-H), 1.51-1.56 (m, 1H, 5'-H); ^{13}C NMR (400 MHz, $CDCl_3$): δ = 194.8 (C-1'), 179.6 (C-9'), 152.5 (C-1), 150.1 (C-4), 134.0 (C-3), 122.3 (C-2), 117.0 (C-5), 111.4 (C-6), 81.6 (C-6'), 70.1 (C-8'), 56.5, 56.4 (OCH_3), 53.4 (C-7' or C-3'), 53.4 (C-7' or C-3'), 44.1 (C-2'), 32.2 (C-5'), 31.4 (C-4'); HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{17}H_{18}O_6Na$ 341.09956; found 341.09977.

Lingzhiol (±-**1**).[6,7,8] To a solution of $AlCl_3$ (4.2 mg, 0.031 mmol, 2 equiv) in abs. CH_2Cl_2 (1.25 mL) was added *t*-BuSH (0.6 mL, 0.471 g, 5.22 mmol) at 0 °C. The reaction mixture was stirred for 15 min at 0 °C. A solution of aryl methyl ether **26** (5.0 mg, 0.016 mmol, 1 equiv) in dry CH_2Cl_2 (1 mL) was then added dropwise at 0 °C. The resulting mixture was refluxed overnight. Thereafter, it was treated with a saturated solution of NaH_2PO_4 (1.1 mL). The organic layer was separated and the aqueous layer was

extracted with EtOAc (3 × 1.5 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (petroleum ether/EtOAc, 1:1) to yield lingzhiol (±-**1**) (2.3 mg, 50%) as light yellow solid. R_f = 0.2 (petroleum ether/EtOAc, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.6 (s, 1H, 1-OH), 7.27 (d, *J* = 9.0 Hz, 1H, 5-H), 6.82 (d, *J* = 8.9 Hz, 1H, 6-H), 5.26 (d, *J* = 9.7 Hz, 1H, 8'-H), 4.94 (s, 1H, 6'-OH), 4.67 (t, *J* = 4.1 Hz, 1H, 6'-H), 4.49 (d, *J* = 9.7 Hz, 1H, 8'-H), 3.14 (d, *J* = 16.1 Hz, 1H, 2'-H), 2.83 (d, *J* = 15.9 Hz, 1H, 2'-H), 2.47-2.51 (m, 1H, 4'-H or 5'-H), 1.72-1.84 (m, 3H, 4'-H, 5'-H); ^{13}C NMR (400 MHz, $CDCl_3$): δ = 202.4 (C-1'), 180.1 (C-9'), 156.3 (C-3), 148.0 (C-2), 129.0 (C-1), 127.6 (C-5), 117.9 (C-6), 116.5 (C-4), 80.6 (C-6'), 71.0 (C-8'), 56.2 (C-7'), 52.5 (C-3'), 42.3 (C-2'), 33.8 (C-4' or C-5'), 33.3 (C-4' or C-5'); HRMS (ESI-TOF) *m/z*: $[M - H]^-$ calcd for $C_{15}H_{13}O_6$ 289.07176; found 289.07203.

ASSOCIATED CONTENT

Supporting Information

Experimental details for the synthesis of analog **39** (compounds **27** – **39**). Copies of NMR spectra. X-ray crystallography data, CIF file, and thermal ellipsoid plot for acetate **24**. The Supporting Information is available free of charge on the ACS Publications website.

AUTHOR INFORMATION

Corresponding Author

* E-mail: martin.e.maier@uni-tuebingen.de

Present Addresses

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

This work was supported by the Deutsche Forschungsgemeinschaft (Grant No. Ma 1012/33-1) and the state of Baden-Württemberg. The authors would like to acknowledge networking contribution by the COST Action CM1407 "Challenging organic syntheses inspired by nature - from natural products chemistry to drug discovery". We also thank the students Fabio Mazzotta, Felix Preusch, and Philipp Weiß for contributions to this project.

REFERENCES

1 Yan, Y.-M.; Ai, J.; Zhou, L.-L.; Chung, A. C. K.; Li, R.; Nie, J.; Fang, P.; Wang, X.-L.; Luo, J.; Hu, Q.; Hou, F.-F.; Cheng, Y.-X. *Org. Lett.* **2013**, *15*, 5488.

2 Luo, Q.; Tian, L.; Di, L.; Yan, Y.-M.; Wei, X.-Y.; Wang, X.-F.; Cheng, Y.-X. *Org. Lett.* **2015**, *17*, 1565.

3 Inouye, H.; Ueda, S.; Inoue, K.; Matsumura, H. *Phytochemistry* **1979**, *18*, 1301.

4 Chen, K.; Baran, P. S. *Nature* **2009**, *459*, 824.

5 Massague, J. *Nat. Rev. Mol. Cell Biol.* **2012**, *13*, 616.

6 (a) Long, R.; Huang, J.; Shao, W.; Liu, S.; Lan, Y.; Gong, J.; Yang, Z. *Nat. Commun.* **2014**, *5*, 5707. (b) Sharmah Gautam, K.; Birman, V. B. *Org. Lett.* **2016**, *18*, 1499. (c) Li, X.; Liu, X.; Jiao, X.; Yang, H.; Yao, Y.; Xie, P. *Org. Lett.* **2016**, *18*, 1944.

7 (a) Chen, D.; Liu, H.-M.; Li, M.-M.; Yan, Y.-M.; Xu, W.-D.; Li, X.-N.; Cheng, Y.-X.; Qin, H.-B. *Chem. Commun.* **2015**, *51*, 14594. (b) Chen, D.; Xu, W.-D.; Liu, H.-M.; Li, M.-M.; Yan, Y.-M.; Li, X.-N.; Li, Y.; Cheng, Y.-X.; Qin, H.-B. *Chem. Commun.* **2016**, *52*, 8561.

8 Rengarasu, R.; Maier, M. E. *Asian J. Org. Chem.* **2017**, *6*, 108.

9 For some examples of such cyclization reactions, see: (a) Shi, L.; Meyer, K.; Greaney, M. F. *Angew. Chem. Int. Ed.* **2010**, *49*, 9250. (b) Das, D.; Kant, R.; Chakraborty, T. K. *Org. Lett.* **2014**, *16*, 2618. (c) Das, D.; Chakraborty, T. K. *Org. Lett.* **2017**, *19*, 682.

10 For reviews, see: (a) Justicia, J.; Alvarez de Cienfuegos, L.; Campana, A. G.; Miguel, D.; Jakoby, V.; Gansäuer, A.; Cuerva, J. M. *Chem. Soc. Rev.* **2011**, *40*, 3525. (b) Morcillo, S. P.; Miguel, D.; Campaña, A. G.; Álvarez de Cienfuegos, L.; Justicia, J.; Cuerva, J. M. *Org. Chem. Front.* **2014**, *1*, 15-33.

11 Wipf, P.; Jae-Kyu, J. *J. Org. Chem.* **2000**, *65*, 6319.

12 Chen, C. P.; Swenton, J. S. *J. Org. Chem.* **1985**, *50*, 4569.

13 Johnson, D. W.; Mander, L. N. *Aust. J. Chem.* **1978**, *31*, 1561.

14 (a) Schulte, K. E.; Reiss, K. P. *Chem. Ber.* **1953**, *86*, 777. (b) Daniels, S. B.; Cooney, E.; Sofia, M. J.; Chakravarty, P. K.; Katzenellenbogen, J. A. *J. Biol. Chem.* **1983**, *258*, 15046.

15 (a) Bensa, D.; Rodriguez, J. *Synth. Commun.* **2004**, *34*, 1515. (b) Schopohl, M. C.; Faust, A.; Mirk, D.; Fröhlich, R.; Kataeva, O.; Waldvogel, S. R. *Eur. J. Org. Chem.* **2005**, 2987.

16 Pietruszka, J.; Witt, A. *Synthesis* **2006**, 4266.

17 Lombardo, L. *Org. Synth.* **1987**, *65*, 81.

18 Michnick, T. J.; Matteson, D. S. *Synlett* **1991**, *31*, 631.

19 For a recent review, see: Pace, V.; Castoldi, L.; Monticelli, S.; Rui, M.; Collina, S. *Synlett* **2017**, *28*, 879.

20 See for example: (a) Yu, W.; Mei, Y.; Kang, Y.; Hua, Z.; Jin, Z. *Org. Lett.* **2004**, *6*, 3217. (b) Nicolaou, K. C.; Adsool, V. A.; Hale, C. R. H. *Org. Lett.* **2010**, *12*, 1552 and references therein.

21 Gemal, A. L.; Luche, J. L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.

22 (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155. (b) Boeckman, R. K., Jr.; Shao, P.; Mullins, J. J. *Org. Synth.* **2000**, *77*, 141.

23 Blanc, J.-B.; Chen, L.; Firooznia, F.; Gillespie, P.; Goodnow, R. A., Jr.; He, Y.; Lin, T.-A.; So, S.-S.; Yun, H.; Zhang, Z.; F. Switzerland Pat. Appl. Publ. WO 2010018113 A2, 2010.

24 For the corresponding methyl ester, see: Cívicos, J. F.; Ribeiro, C. M. R.; Costa, P. R. R.; Nájera, C. *Tetrahedron* **2016**, *72*, 1897.