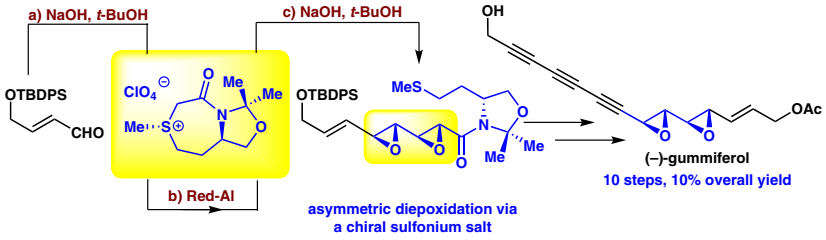
Synthesis C. García-Ruiz et al. Special Topic

Synthesis of (–)- and (+)-Gummiferol via Asymmetric Synthesis of Glycidic Amides

Cristina García-Ruiz
Iván Cheng-Sánchez
Francisco Sarabia*

Department of Organic Chemistry, Faculty of Sciences, University of Málaga, Campus de Teatinos s/n, 29071 Málaga, Spain
frsarabia@uma.es



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Abstract An efficient synthesis of the natural product (–)-gummiferol is achieved according to a novel asymmetric methodology of epoxide formation based on a new class of chiral sulfonium salts. This new methodology allows the rapid and efficient construction of the diepoxide system contained within the natural product.

Key words asymmetric synthesis, glycidic amides, chiral sulfonium salts, natural products, diepoxides

(–)-Gummiferol (**1**) was isolated from *Adenia gummifera* in 1995 by Wall et al.,[1] after the identification of cytotoxic activity exhibited by the organic extracts obtained from its leaves. Following the recognition of gummiferol as being responsible for this biological activity, its cytotoxicity was then evaluated against various cancer cell lines, revealing strong activity against P388 murine leukemia and U373 human glioma cell lines with ED_{50} values of 0.03 μg/mL and 0.05 μg/mL, respectively.[1] Extensive spectroscopic analyses allowed the establishment of the planar structure of (–)-gummiferol, featuring the presence of a conjugated triacetylene and a diepoxy moiety, however, its absolute configuration was not determined. Despite the prominent cytotoxic activity of gummiferol and the lack of certainty regarding its absolute configuration, only one total synthesis has been reported so far by Takamura and co-workers in 2011, which allowed the absolute configuration to be established[2] According to this synthesis, the construction of the contiguous epoxide unit was undertaken by sequential Sharpless asymmetric epoxidations,[3] which secured the stereochemistry of the oxirane rings and also provided the synthesis of the other possible stereoisomers, including the enantiomer (+)-gummiferol (*ent*-**1**). On the other hand, the conjugated triacetylenic moiety was installed via a Cadiot–Chodkiewicz[4] reaction between a bromoacetylene derivative and a diacetylene. As a consequence of this synthetic work, the absolute configuration was unambiguously established for (–)-gummiferol as depicted in Figure 1.

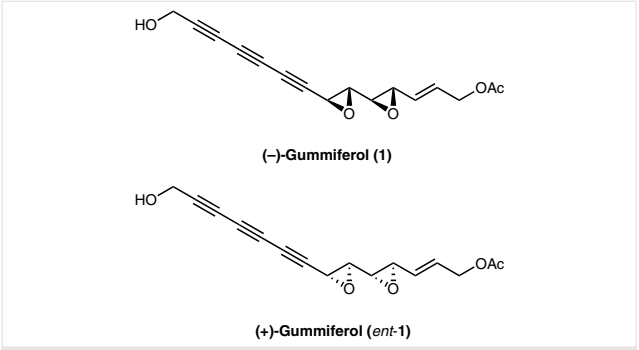
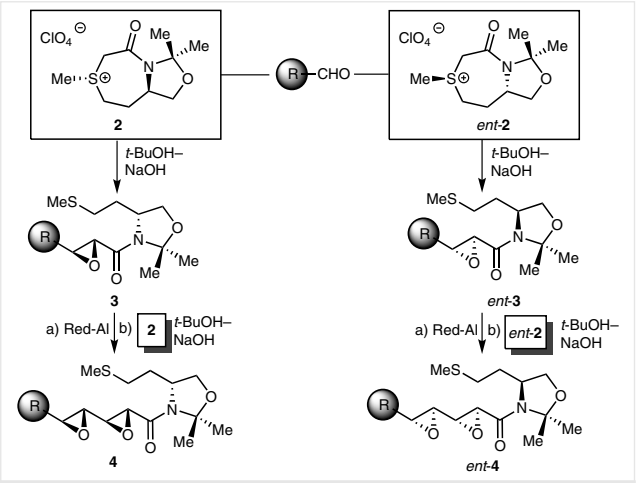


Figure 1 Structures of natural gummiferol (**1**) and its enantiomer

Furthermore, a series of gummiferol analogues was synthesized that enabled a detailed structure–activity relationship study. The growth-inhibitory activity of all these synthetic products, including natural gummiferol (**1**), against HL60 and HeLa S3 cells revealed that the presence of both the triacetylenic and diepoxide systems was essential for cytotoxic activity. Interestingly, the stereochemistry of the diepoxide unit did not seem to have an important effect on the cytotoxic activity as the four diastereoisomers of gummiferol exhibited very similar antitumor activities with IC_{50} values in the low μM range for both cancer cell lines.[5]

The reported total synthesis of gummiferol constitutes an efficient and general method capable of producing a wide range of gummiferol-type molecules and opens new opportunities in the search for new antitumor agents. Considering the promising biological profile displayed by gummiferol and with the aim of offering a synthetic alternative

to the previously reported synthesis, we decided to engage in a more efficient and readily accessible route toward the gummiferols. To this aim, the use of a novel asymmetric synthesis of glycidic amides based on the chiral sulfonium salts **2** and *ent*-**2**, recently developed in our laboratories, represents a synthetic alternative for the stereoselective construction of the oxirane rings. This methodology has proven to be highly efficient in terms of generality, scope, and stereoselectivity.[6,7] As proof of the utility of such methodology, various natural products of biological interest, including bengamides,[8] the cyclodepsipeptides globomycin and SF-1902 A_5,[9] and sphingoid-type bases,[10] have been efficiently prepared. Recently, this synthetic methodology was expanded to the stereoselective synthesis of diepoxy amides and has been applied in the synthesis of the natural product, (–)-depudecin.[11] The synthesis of contiguous diepoxides in a stereoselective fashion, via sulfonium salts **2** or *ent*-**2**, is accomplished in a three-step sequence under very mild conditions, making this methodology very suitable for the construction of this type of structural unit (Scheme 1).



Scheme 1 Cyclic sulfonium salts **2** and *ent*-**2** and their applications in the synthesis of diepoxy amides **4** and *ent*-**4**

It is important to highlight that the absolute configurations of sulfonium salts **2** and *ent*-**2** were recently established according to X-ray analyses of their crystals (Figure 2).[12] The obtained X-ray crystal structures revealed that the stereochemistry at the sulfur atom was opposite that which we had initially proposed according to NMR and conformational studies.[7]

Based on these precedents, we propose a synthesis of (–)-gummiferol (**1**) based on chiral sulfur ylide methodology for the sequential construction of the oxirane rings. Thus, according to the retrosynthetic analysis depicted in Scheme 2, (–)-gummiferol (**1**) would be obtained through a Cadiot–Chodkiewicz coupling between diepoxy alkyne **5** and the iodo diacetylene **6**.[13] The alkyne present in **5** would

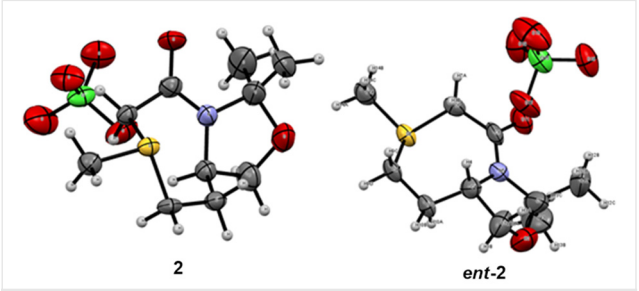
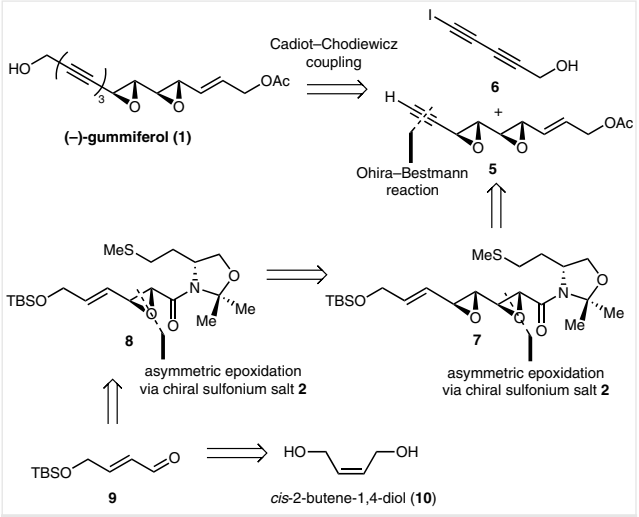


Figure 2 X-ray crystal structures (ORTEP) of sulfonium salts **2** and *ent*-**2**

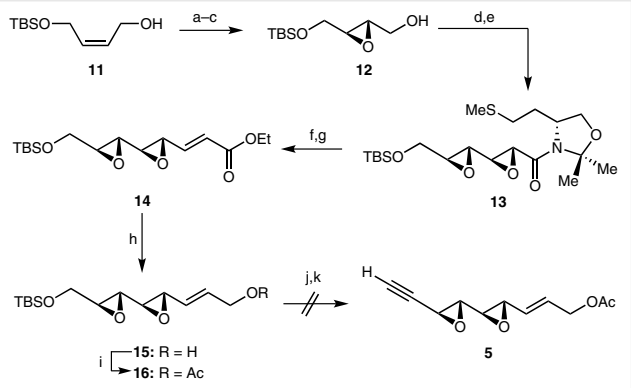
be introduced via an Ohira–Bestmann reaction[14] on diepoxy amide **7**, which, in turn, would be prepared from epoxy amide **8** via asymmetric epoxidation mediated by the sulfonium salt **2**. The epoxy amide **8** would be generated from the α,β-unsaturated aldehyde **9**, itself readily accessible from commercially available *cis*-2-butene-1,4-diol (**10**).[15]



Scheme 2 Retrosynthetic analysis of (–)-gummiferol (**1**)

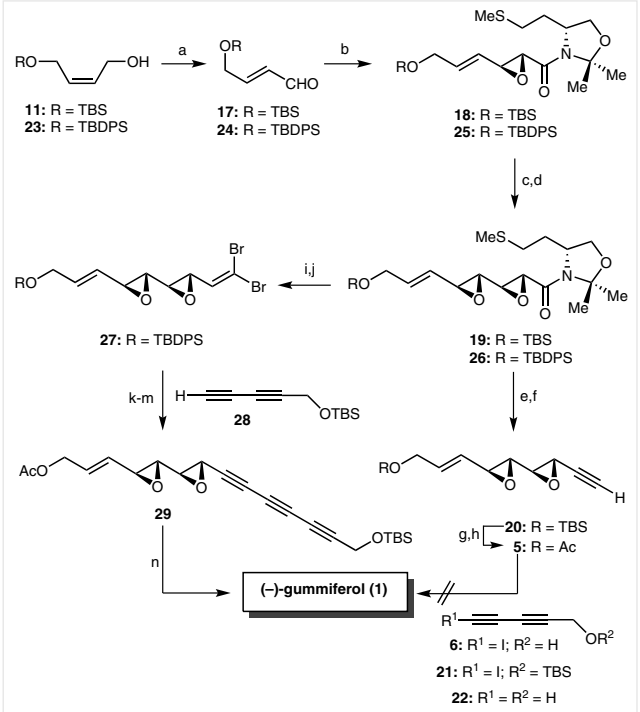
We initially envisioned the synthesis of the diepoxy alkyne **5** from allylic alcohol **11** in a strategy that would combine a Sharpless asymmetric epoxidation (SAE) and the use of our chiral sulfur ylide methodology. Thus, from **11**, we prepared the known epoxy alcohol **12**,[16] which was subjected to a Parikh–Doering oxidation.[17] The resulting crude aldehyde was then treated with the sulfonium salt **2** to afford diepoxy amide **13** in 73% yield over two steps. This diepoxy amide **13** was transformed into the corresponding aldehyde by treatment with Red-Al, and the crude aldehyde was subjected to a Wittig reaction to generate the corresponding diepoxy α,β-unsaturated ester **14** in a 60% yield over two steps. Subsequent reduction of **14** to give allylic alcohol **15**, by treatment with DIBAL-H, was followed by protection of the alcohol as an acetate, by reaction with

Ac_2O in pyridine, to afford diepoxy alkene **16** in 55% overall yield (Scheme 3). In this way, the chiral sulfur ylide methodology enabled us to synthesize the diepoxide **16** in a reasonably good overall yield and in a highly stereoselective fashion, reducing the number of synthetic steps versus Takamura's synthesis. At this point, however, we encountered serious problems when we attempted the installation of the alkyne group. Thus, despite the fact that deprotection of silyl ether **16** proceeded in a very good yield, by treatment with TBAF, subsequent oxidation on treatment with sulfur trioxide–pyridine complex (SO_3·py) resulted in no formation of the desired aldehyde. Attempts via other oxidation methods, including Swern, 2,2,6,6-tetramethylpiperidine 1-oxyl–[bis(acetoxy)iodo]benzene (TEMPO–BAIB), Dess–Martin periodinane, 2-iodoxybenzoic acid (IBX), tetrapropylammonium perruthenate (TPAP) and PCC were also unsuccessful. The failure of this key step directed us to consider a new approach.



Scheme 3 First approach to the synthesis of diepoxy alkyne **5**. *Reagents and conditions*: (a) PCC, NaOAc, CH_2Cl_2, 25 °C, 16 h; (b) DIBAL-H, CH_2Cl_2, –78 °C, 45 min; (c) (+)-DET, Ti(O*i*-Pr)$_4$, TBHP, 4 Å MS, CH_2Cl_2, –50 °C, 8 h, 65% over 3 steps; (d) SO_3·py, CH_2Cl_2, DMSO, 0 °C → 25 °C; (e) **2**, NaOH (5.0 M), *t*-BuOH, 73% over 2 steps; (f) Red-Al, THF, 0 °C, 1 h; (g) $Ph_3P{=}CHCO_2Et$, CH_2Cl_2, 25 °C, 60% over 2 steps; (h) DIBAL-H, CH_2Cl_2, –78 °C, 30 min, 76%; (i) Ac_2O, py, 25 °C, 12 h, 73%; (j) TBAF, THF; (k) SO_3·py, CH_2Cl_2, DMSO, 0 °C → 25 °C; or Swern oxidation; or TEMPO–BAIB, MeCN–H_2O, 25 °C, 16 h; or PCC, NaOAc, CH_2Cl_2, 25 °C, 16 h, then Ohira–Bestmann reagent, K_2CO_3.

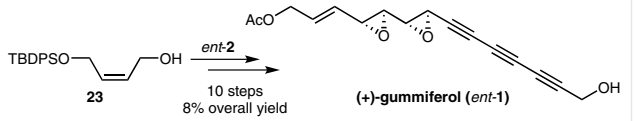
Starting again from alcohol **11**, oxidation with PCC afforded aldehyde **17**, which was treated with sulfonium salt **2** under basic conditions to provide epoxy amide **18** in a 40% yield over two steps. Reduction with Red-Al, followed again by treatment with chiral sulfonium salt **2** of the resulting epoxy aldehyde supplied diepoxy amide **19** in an excellent 95% overall yield from **18** (Scheme 4). With diepoxy olefin **19** in hand, we proceeded with the introduction of the alkynyl group through successive reduction with Red-Al and an Ohira–Bestmann reaction to obtain alkyne **20** in a modest 44% yield. Replacement of the TBS group by an acetyl was carried out without difficulty to provide the gummiferol precursor **5** in an 85% yield over two steps from **20**. Despite the overall moderate yield to reach fragment **5**, we studied the coupling with iodo dialkyne **6** under Cadiot–Chodkiewicz conditions. Unfortunately, we were unable to obtain the desired coupling product that corresponded to gummiferol. The failure of this coupling prompted us to attempt other reaction conditions [$Cu(OAc)_2$/piperidine; $(Ph_3P)PdCl_2$/CuI/DIPA; CuI/piperidine, among others] and different diacetylene derivatives (**21** or **22**). However, the result in all cases was decomposition of the reaction mixtures and no detection of the formation of (–)-gummiferol. In light of these discouraging results, we finally decided to surmount the problem of the coupling reaction by using the conditions employed by Takamura in the total synthesis of gummiferol. On the other hand, the low yields obtained for some steps during the synthesis of **5** was attributed to the possible instability of the TBS group under certain reaction conditions employed in the route. For this reason, we also investigated replacement of the TBS group by the more robust TBDPS group. Thus, starting from the TBDPS derivative **23**, we repeated the synthetic scheme delineated for **5** to obtain diepoxy amide **26**, via epoxy amide **25**, with better yields being obtained compared with those for the TBS de-



Scheme 4 Synthesis of (–)-gummiferol. *Reagents and conditions*: (a) PCC, NaOAc, CH_2Cl_2, 25 °C, 16 h; (b) **2**, NaOH (3.0 M), *t*-BuOH, 25 °C, 12 h, 40% for **18**, 54% for **25** (both over 2 steps); (c) Red-Al, THF, 0 °C, 1 h; (d) **2**, NaOH (5.0 M), *t*-BuOH, 25 °C, 95% for **19** and 95% for **26** (both over 2 steps); (e) Red-Al, THF, 0 °C, 45 min; (f) Ohira–Bestmann reagent, K_2CO_3, MeOH, 25 °C, 16 h, 44% over 2 steps; (g) TBAF, THF, 25 °C, 12 h; (h) Ac_2O, py, 25 °C, 2 h, 85% over 2 steps; (i) Red-Al, THF, 0 °C, 45 min; (j) CBr_4, Ph_3P, Et_3N, 0 °C → –78 °C, 40% over 2 steps; (k) TBAF, THF, 0 °C, 1 h; (l) **28**, CuCl, NH_2OH·HCl, MeOH, –78 °C; (m) Ac_2O, py, DMAP, 51% over 3 steps; (n) HF·py, THF, 0 °C, 2 h, 95%.

rivatives. Reduction of **26** with Red-Al, followed by a Corey–Fuchs reaction[18] provided dibromo alkene **27** in a 40% overall yield. Next, we proceeded with the final coupling reaction between dibromo alkene **27** and dialkyne **28** by sequential treatment with TBAF and $CuCl/NH_2OH{\cdot}HCl/EtNH_2$ to afford the corresponding coupling product, which, after acetylation, was transformed into the precursor **29** of (–)-gummiferol in a 51% overall yield. Final desilylation according to the Takamura protocol provided natural gummiferol. The desired product was obtained in 10 steps with a 10% overall yield from alcohol **23** (Scheme 4).

In addition, the application of the synthetic strategy employing the sulfonium salt *ent*-**2** instead of **2** allowed access to (+)-gummiferol (*ent*-**1**) in 10 steps with an 8% overall yield from alcohol **23** (Scheme 5).



Scheme 5 Synthesis of (+)-gummiferol

In conclusion, new syntheses of natural and non-natural gummiferols have been described. In particular, the development of an alternative more efficient route to construct the diepoxy alkyne has been demonstrated. From readily available starting materials, the new route is in principle suitable to provide rapid access to all the diastereoisomers of gummiferol, together with various analogues that are expected to be of biological interest in virtue of their potential antitumor properties.

All reactions were carried out under an argon atmosphere with dry, freshly distilled solvents under anhydrous conditions, unless using aqueous reagents or if otherwise noted. All solvents used in reactions were dried and distilled using standard procedures. Tetrahydrofuran (THF) was distilled from sodium benzophenone, and CH_2Cl_2 and benzene from calcium hydride. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, unless otherwise stated. All solutions used in work-up procedures were saturated unless otherwise noted. All reagents were purchased at highest commercial quality and used without further purification unless otherwise stated. All reactions were monitored by thin-layer chromatography (TLC) using Merck silica gel plates (0.25 mm, 60F-254) and made visual with UV light (254 nm); acidic ceric ammonium molybdate/phosphomolybdic acid or potassium permanganate solutions and heat were used as developing agents. Flash column chromatography (FCC) was performed using Merck silica gel (60 Å, particle size 230-400 mesh) under air pressure. All solvents used for chromatographic purifications were distilled prior to use. Specific optical rotations were recorded on a Perkin-Elmer 241 polarimeter with a sodium halogen lamp (λ = 589 nm) and a cell path length of 100 mm (*c* is given in g/100 mL). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX-400 MHz instrument and calibrated using residual undeuterated solvent as an internal reference. Chemical shifts are reported in ppm with the resonance resulting from incomplete deuteration of the solvent as the internal standard [$^{13}CDCl_3$: 7.26 ppm (s) and 77.0 ppm (t)]. ^{1}H NMR assignments were accomplished based on COSY 2D NMR experiments (cosygp experiment). ^{1}H NMR data are reported as follows: chemical shift (ppm) [multiplicity, coupling constant(s) (*J*) (Hz), integration, assignment]. The following abbreviations are used to explain the multiplicities: s = singlet; d = doublet; t = triplet; q = quartet; br = broad; m = multiplet, or combinations thereof. ^{13}C NMR signals are singlets, unless otherwise stated. High-resolution mass spectrometry (HRMS) was performed on a Bruker HCT-ULTRA ESI-TOF and APCI mass spectrometer in positive mode. HRMS signals are reported to four decimal places and are within ±5 ppm of theoretical values.

Diepoxy Amide 13

Epoxy alcohol **12** (320 mg, 1.47 mmol, 1.0 equiv) was dissolved in a mixture of CH_2Cl_2–DMSO (1:1) (6 mL) and cooled to 0 °C. At this temperature, Et_3N (0.6 mL, 4.4 mmol, 3.0 equiv) was added followed by $SO_3{\cdot}py$ (420 mg, 2.6 mmol, 1.8 equiv). The mixture was allowed to reach r.t. and 5 h later was quenched by the addition of buffer (pH 7) and diluted with Et_2O. The aqueous phase was extracted with Et_2O and the combined organic extracts were washed with H_2O and brine, dried over anhydrous $MgSO_4$ and the solvent removed under reduced pressure. The resulting crude aldehyde was used in the next step without further purification. To a suspension of sulfonium salt **2** (530 mg, 1.7 mmol, 1.1 equiv) in *t*-BuOH (20 mL) was added NaOH (0.31 mL, 5.0 M aq solution, 1.53 mmol, 1.0 equiv) at 25 °C. After 1 h at this temperature, a solution of the crude aldehyde in *t*-BuOH (5 mL) was added and the resulting mixture was stirred overnight. The crude mixture was then diluted with CH_2Cl_2 and H_2O and, after decantation, the aqueous phase was extracted with CH_2Cl_2 three times. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (silica gel, 20% EtOAc in hexanes) to afford diepoxy amide **13** (460 mg, 73% over 2 steps) as a pale yellow oil.

$[\alpha]_D^{25}$ –19.2 (*c* 0.4, CH_2Cl_2); R_f = 0.20 [silica gel, 40% EtOAc in hexanes].

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.27 (ddd, *J* = 8.8, 4.7, 3.5 Hz, 1 H, CONC*H*), 3.97 (ddd, *J* = 9.1, 5.2, 1.3 Hz, 1 H, OCH_2CH), 3.89–3.86 (m, 1 H, OCH_2CH), 3.85 (d, *J* = 2.0 Hz, 1 H, SiOCH_2), 3.69 [dd, *J* = 12.3, 3.7 Hz, 1 H, CH_2CH(O)CH], 3.54 [d, *J* = 2.0 Hz, 1 H, CH(O)*CH*CO], 3.30 [dd, *J* = 3.4, 2.0 Hz, 1 H, *CH*(O)CHCO], 3.11–3.06 [m, 2 H, SiOCH_2 and CH_2CH(O)*CH*], 2.59–2.50 (m, 1 H, SCH_2CH_2), 2.48–2.39 (m, 1 H, SCH_2CH_2), 2.08 (s, 3 H, CH_3S), 2.05–2.00 (m, 1 H, SCH_2CH_2), 1.83–1.73 (m, 1 H, SCH_2CH_2), 1.59 (s, 3 H, CH_3C), 1.48 (s, 3 H, CH_3C), 0.84 [s, 9 H, $(CH_3)_3$CSi], 0.02 [s, 3 H, $(CH_3)_2$Si], 0.00 [s, 3 H, $(CH_3)_2$Si].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.92, 95.87, 67.03, 61.59, 56.29, 55.96, 55.50, 51.73, 51.25, 34.42, 30.64, 26.19, 25.80, 22.93, 18.28, 15.73, –5.39, –5.41.

HRMS (H-ESI): *m*/*z* $[M + H]^+$ calcd for $C_{20}H_{38}NO_5SSi$: 432.2240; found: 432.2227.

γ,δ-Diepoxy α,β-Unsaturated Ester 14

A solution of diepoxy amide **13** (213 mg, 0.5 mmol, 1.0 equiv) in dry THF (8 mL) was treated dropwise with Red-Al (0.31 mL, 60% w/v in toluene, 1.08 mmol, 2.2 equiv) at 0 °C. After 1 h at this temperature, the reaction mixture was diluted with sat. aq NH_4Cl solution. The aqueous phase was then separated, extracted twice with EtOAc and the combined organic phase washed with H_2O and brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The resulting crude aldehyde was used in the next step without further purification. A solution of the crude aldehyde in CH_2Cl_2 (10 mL) was treated with the phosphorus ylide, $Ph_3P{=}CHCO_2Et$ (260 mg, 0.75

mmol 1.5 equiv). After 30 min, the reaction was complete and the solvent was removed under reduced pressure. The resulting crude residue was purified by flash column chromatography (silica gel, 20% EtOAc in hexanes) to provide the α,β-unsaturated diepoxy ester **14** (100 mg, 60% over 2 steps) as a pale yellow oil.

$[\alpha]_D^{25}$ –12.4 (*c* 0.7, CH_2Cl_2); R_f = 0.64 [silica gel, 40% EtOAc in hexanes].

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.64 (dd, *J* = 15.7, 7.2 Hz, 1 H, C*H*=CH-CO), 6.15 (dd, *J* = 15.7, 0.7 Hz, 1 H, CH=C*H*CO), 4.19 (q, *J* = 7.1 Hz, 2 H, CH_2CH_3), 3.87 (dd, *J* = 12.3, 2.8 Hz, 1 H, SiOCH_2), 3.74 (dd, *J* = 12.3, 3.9 Hz, 1 H, SiOCH_2), 3.47 [ddd, *J* = 7.2, 2.0, 0.7 Hz, 1 H, CH(O)C*H*CH=], 3.10 [ddd, *J* = 3.9, 2.7, 2.1 Hz, 1 H, CH_2CH(O)], 3.04 [dd, *J* = 4.0, 2.1 Hz, 1 H, CH_2CH(O)C*H*], 3.01 [dd, *J* = 4.0, 2.0 Hz, 1 H, C*H*(O)CHCH=], 1.28 (t, *J* = 7.1 Hz, 3 H, CH_2CH_3), 0.88 [s, 9 H, $(CH_3)_3$CSi], 0.06 [s, 3 H, $(CH_3)_2$Si], 0.05 [s, 3 H, $(CH_3)_2$Si].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.41, 143.02, 124.71, 61.82, 60.69, 58.50, 56.24, 53.77, 52.62, 25.82, 18.32, 14.18, –5.37, –5.39.

HRMS (H-ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{29}O_5Si$: 329.1784; found: 329.1780.

Allylic Alcohol 15

At –78 °C, DIBAL-H (1.15 mL, 1.0 M in toluene, 1.15 mmol, 2.5 equiv) was added to a solution of ester **14** (151 mg, 0.46 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL). After 30 min, the reaction was complete and was allowed to warm to 0 °C. At this temperature, the mixture was diluted with EtOAc and sat. aq Na^+/K^+ tartrate solution. After 2 h of vigorous stirring, the aqueous phase was extracted twice with EtOAc and the organic layer washed with H_2O and brine, then dried over anhydrous $MgSO_4$ and filtered. The solvent was then removed carefully under reduced pressure at low temperature. Purification by flash column chromatography (silica gel, 20% EtOAc in hexanes) of the resulting crude residue rendered the allylic alcohol **15** (100 mg, 76% yield) as a pale yellow oil.

$[\alpha]_D^{25}$ –20.2 (*c* 0.4, CH_2Cl_2); R_f = 0.35 [silica gel, 30% EtOAc in hexanes].

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.11 (dt, *J* = 15.6, 5.1 Hz, 1 H, CH=C*H*CH_2), 5.49 (ddt, *J* = 15.6, 7.9, 1.7 Hz, 1 H, C*H*=CHCH_2), 4.19 (d, *J* = 3.9 Hz, 2 H, =CHCH_2OH), 3.88 (dd, *J* = 12.2, 2.8 Hz, 1 H, SiOCH_2), 3.74 (dd, *J* = 12.2, 4.0 Hz, 1 H, SiOCH_2), 3.40 [dd, *J* = 7.9, 2.1 Hz, 1 H, (O)C*H*CH=], 3.09 [ddd, *J* = 4.0, 2.8, 2.1 Hz, 1 H, CH_2CH(O)CH], 3.00 [dd, *J* = 4.3, 2.1 Hz, 1 H, CH_2CH(O)C*H*], 2.93 [dd, *J* = 4.3, 2.1 Hz, 1 H, C*H*(O)CHCH=], 1.61 (br s, 1 H, O*H*), 0.89 [s, 9 H, $(CH_3)_3$CSi], 0.06 [s, 3 H, $(CH_3)_2$Si], 0.05 [s, 3 H, $(CH_3)_2$Si].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.29, 127.24, 62.57, 62.05, 58.00, 56.05, 55.25, 53.25, 25.84, 18.34, –5.35, –5.36.

HRMS (H-ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{27}O_4Si$: 287.1679; found: 287.1685.

Acetyl Derivative 16

To a solution of the allylic alcohol **15** (32 mg, 0.1 mmol, 1.0 equiv) in py (3 mL) was added Ac_2O (0.4 mL, 4.5 mmol, 40 equiv) at r.t. After 12 h at the same temperature, the solvent was removed under vacuum and the crude residue was purified by flash column chromatography (silica gel, 10% EtOAc in hexanes) to furnish acetate **16** (27 mg, 73% yield) as a pale yellow oil.

$[\alpha]_D^{25}$ –15.3 (*c* 0.4, CH_2Cl_2); R_f = 0.91 [silica gel, 40% EtOAc in hexanes].

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.03 (dtd, *J* = 15.6, 5.8, 0.6 Hz, 1 H, CH=C*H*CH_2), 5.51 (ddt, *J* = 15.6, 7.8, 1.5 Hz, 1 H, C*H*=CHCH_2), 4.58 (dd, *J* = 5.8, 1.5 Hz, 2 H, =CHCH_2OH), 3.92–3.83 (m, 1 H, SiOCH_2), 3.74 (dd, *J* = 12.2, 4.0 Hz, 1 H, SiOCH_2), 3.38 [dd, *J* = 8.0, 1.9 Hz, 1 H, CH(O)C*H*CH=], 3.09 [ddd, *J* = 4.0, 2.8, 2.1 Hz, 1 H, CH_2CH(O)CH], 2.99 [dd, *J* = 4.3, 2.1 Hz, 1 H, CH_2CH(O)C*H*], 2.93 [dd, *J* = 4.3, 2.1 Hz, 1 H, C*H*(O)CHCH=], 2.17 (s, 3 H, OCOCH_3), 0.89 [s, 9 H, $(CH_3)_3$CSi], 0.07 [s, 3 H, $(CH_3)_2$Si], 0.06 [s, 3 H, $(CH_3)_2$Si].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 130.19, 129.83, 63.61, 61.98, 57.97, 56.07, 54.93, 53.10, 30.91, 25.84, 20.93, 18.33, –5.36, –5.37.

HRMS (H-ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{29}O_5Si$: 329.1784; found: 329.1776.

Epoxy Amide 18

To a suspension of PCC (1.6 g, 7.4 mmol, 1.5 equiv) in CH_2Cl_2 (20 mL) was added anhydrous NaOAc (1.6 g, 19.8 mmol, 4.0 equiv) followed by a solution of *cis*-alcohol **11** (1.0 g, 4.94 mmol, 1.0 equiv) in CH_2Cl_2 (15 mL). The reaction mixture was stirred at r.t. for 6 h and the resulting crude was filtered off through a pad of SiO_2 and washed with Et_2O. The solvent was removed under vacuum and the crude aldehyde **17** was used in the next step without further purification. The crude aldehyde was reacted with sulfonium salt **2** (1.3 g, 4.0 mmol, 1.1 equiv) and NaOH (1.2 mL, 3.0 M aq solution, 3.6 mmol, 1.0 equiv), according to the procedure described above for the synthesis of diepoxy amide **13**, to yield epoxy amide **18** (800 mg, 40% over two steps) as a pale yellow oil.

$[\alpha]_D^{25}$ –11.1 (*c* 0.8, CH_2Cl_2); R_f = 0.43 [silica gel, 40% EtOAc in hexanes].

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.09 (ddd, *J* = 15.4, 4.4, 4.0 Hz, 1 H, CH_2C*H*=CH), 5.48 (ddt, *J* = 15.4, 8.1, 2.0 Hz, 1 H, CH_2CH=C*H*), 4.27 (ddd, *J* = 10.2, 4.9, 3.1 Hz, 1 H, CONC*H*), 4.17 (dt, *J* = 3.7, 1.7 Hz, 2 H, SiOCH_2), 3.99 (ddd, *J* = 9.1, 5.2, 1.4 Hz, 1 H, OCH_2CH), 3.89–3.84 (m, 1 H, OCH_2CH), 3.58 [dd, *J* = 8.1, 1.7 Hz, 1 H, =CHC*H*(O)CH], 3.51 [d, *J* = 1.9 Hz, 1 H, CH(O)C*H*CO], 2.53 (ddd, *J* = 13.2, 7.0, 5.1 Hz, 1 H, SC$H_2$$CH_2$), 2.40 (ddd, *J* = 13.4, 8.9, 6.6 Hz, 1 H, SC$H_2$$CH_2$), 2.05 (s, 3 H, CH_3S), 2.03–1.96 (m, 1 H, SCH_2CH_2), 1.78–1.71 (m, 1 H, SCH_2CH_2), 1.61 (s, 3 H, CH_3C), 1.51 (s, 3 H, CH_3C), 0.87 [s, 9 H, $(CH_3)_3$CSi], 0.03 [s, 6 H, $(CH_3)_2$Si].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.42, 137.15, 124.45, 95.89, 67.01, 62.51, 57.82, 55.85, 55.44, 34.27, 30.79, 26.27, 25.88, 22.99, 18.32, 15.81, –5.37, –5.38.

HRMS (H-ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{38}NO_4SSi$: 416.2291; found: 416.2286.

Diepoxy Amide 19

To a solution of epoxy amide **18** (100 mg, 0.24 mmol, 1.0 equiv) in dry THF (6 mL) was added dropwise Red-Al (0.15 mL, 60% w/v, 0.53 mmol, 2.2 equiv) at 0 °C. After 1 h at 0 °C, the reaction mixture was quenched by the addition of sat. aq NH_4Cl solution. After separation of both layers, the aqueous phase was extracted with EtOAc, the organic extracts were washed with brine and dried over $MgSO_4$, and the solvent was evaporated under reduced pressure. The resulting crude epoxy aldehyde was used in the next step without further purification The crude aldehyde was reacted with sulfonium salt **2** (85 mg, 0.26 mmol, 1.1 equiv) and NaOH (0.04 mL, 5.0 M aq solution, 0.24 mmol, 1.0 equiv), according to the general procedure described above for the synthesis of diepoxy amide **13**, to yield diepoxy amide **19** (36 mg, 95% over two steps) as a yellow oil.

$[\alpha]_D^{25}$ –21.4 (*c* 1.0, CH_2Cl_2); R_f = 0.26 [silica gel, 40% EtOAc in hexanes].

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.04 (dt, *J* = 15.4, 4.3 Hz, 1 H, CH_2C*H*=CH), 5.50–5.40 (m, 1 H, CH_2CH=C*H*), 4.34–4.27 (m, 1 H, CONC*H*), 4.18 (dd, *J* = 4.2, 1.9 Hz, 2 H, SiOCH_2), 4.01 (dd, *J* = 8.7, 5.7 Hz, 1 H, OCH_2CH), 3.90 (d, *J* = 9.2 Hz, 1 H, OCH_2CH), 3.58 [d, *J* = 1.9 Hz, 1 H, CH(O)C*H*CO], 3.43 [dd, *J* = 8.0, 1.9 Hz, 1 H, =CHC*H*(O)CH], 3.36 [dd, *J* = 3.3, 1.9 Hz, 1 H, C*H*(O)CHCO], 3.05–3.02 [m, 1 H, =CHCH(O)C*H*], 2.58

(ddd, J = 12.9, 7.7, 5.2 Hz, 1 H, SCH_2CH$_2$), 2.52–2.41 (m, 1 H, SCH_2CH$_2$), 2.11 (s, 3 H, CH_3S), 2.05 (ddd, J = 20.8, 9.3, 5.1 Hz, 1 H, SCH$_2$CH_2), 1.81–1.70 (m, 1 H, SCH$_2$CH_2), 1.63 [s, 3 H, (CH_3)$_2$C], 1.52 [s, 3 H, (CH_3)$_2$C], 0.89 [s, 9 H, (CH$_3$)$_3$CSi], 0.05 [s, 6 H, (CH$_3$)$_2$Si].

^{13}C NMR (100 MHz, CDCl$_3$): δ = 162.92, 136.24, 125.09, 95.94, 67.05, 62.64, 56.56, 55.99, 55.67, 55.40, 51.24, 34.46, 30.69, 26.21, 25.89, 22.95, 18.36, 15.83, –5.32, –5.34.

HRMS (H-ESI): m/z [M + H]$^+$ calcd for $C_{22}H_{40}NO_5SSi$: 458.2397; found: 458.2391.

Diepoxy Alkyne 20

To a solution of epoxy amide **19** (76 mg, 0.17 mmol, 1.0 equiv) in dry THF (5 mL) was added dropwise Red-Al (0.1 mL, 60% w/v, 0.37 mmol, 2.2 equiv) at 0 °C. After 1 h at 0 °C, the reaction mixture was quenched by the addition of sat. aq NH$_4$Cl solution. After separation of both layers, the aqueous phase was extracted with EtOAc, the organic extracts were washed with brine and dried over MgSO$_4$, and the solvent was evaporated under reduced pressure. The resulting crude epoxy aldehyde was used in the next step without further purification. To a solution of the crude aldehyde in dry MeOH (5 mL) was added K$_2$CO$_3$ (50 mg, 0.33 mmol, 2.0 equiv), followed by a solution of the Ohira–Bestmann reagent [dimethyl-1-diazo-2-oxopropylphosphonate; MeCOC(N$_2$)PO(OMe)$_2$] (70 mg, 0.33 mmol, 2.0 equiv) in MeOH (2 mL) at r.t. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was diluted with H$_2$O and Et$_2$O. The aqueous phase was extracted with Et$_2$O twice, and the organic solution separated, dried over MgSO$_4$ and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 20% EtOAc in hexanes) of the resulting crude residue rendered the alkyne **20** (20 mg, 44% over 2 steps) as a pale yellow oil.

[α]$_D^{25}$ –38.0 (c 0.2, CH$_2$Cl$_2$); R_f = 0.54 [silica gel, 20% EtOAc in hexanes].

^{1}H NMR (400 MHz, CDCl$_3$): δ = 6.05 (dtd, J = 15.4, 4.3, 0.6 Hz, 1 H, CH$_2$CH=CH), 5.45 (ddt, J = 15.4, 8.0, 1.9 Hz, 1 H, CH$_2$CH=CH), 4.20 (dd, J = 4.2, 1.8 Hz, 2 H, SiOCH_2), 3.40 [dd, J = 8.0, 1.6 Hz, 1 H, =CHCH(O)CH], 3.36 [dt, J = 3.3, 1.6 Hz, 1 H, CH(O)CHCCH], 3.26 [dd, J = 3.5, 2.1 Hz, 1 H, CH(O)CHCCH], 2.97 [dd, J = 3.5, 2.1 Hz, 1 H, =CHCH(O)CH], 2.34 (d, J = 1.7 Hz, 1 H, CCH), 0.91 [s, 9 H, (CH_3)$_3$CSi], 0.07 [s, 6 H, (CH_3)$_2$Si].

^{13}C NMR (100 MHz, CDCl$_3$): δ = 136.24, 125.14, 79.29, 72.30, 62.66, 57.25, 56.61, 55.52, 42.59, 25.90, 18.20, –5.31, –5.33.

HRMS (H-ESI): m/z [M + H]$^+$ calcd for $C_{15}H_{25}O_3Si$: 281.1573; found: 281.1569.

Acetate 5

Alkyne **20** (20 mg, 0.07 mmol, 1.0 equiv) was dissolved in THF (5 mL) and to this solution was added TBAF (0.11 mL, 1.0 M in THF, 0.11 mmol, 1.5 equiv) at r.t. After 45 min, the reaction mixture was diluted with Et$_2$O and sat. aq NH$_4$Cl solution. The aqueous phase was then extracted with EtOAc and the organic extract washed with H$_2$O and brine and dried over MgSO$_4$. The solvent was removed under vacuum and the crude alcohol was used in the next step without further purification. To a solution of the allylic alcohol in py (2 mL) was added Ac$_2$O (0.2 mL, 2.0 mmol, 40 equiv) at r.t. After 12 h at the same temperature, the solvent was removed under vacuum and the crude residue was purified by flash column chromatography (silica gel, 10% EtOAc in hexanes) to furnish acetate **5** (12.5 mg, 85% yield over 2 steps) as a pale yellow oil.

[α]$_D^{25}$ –45.3 (c 0.5, CH$_2$Cl$_2$); R_f = 0.52 [silica gel, 20% EtOAc in hexanes].

^{1}H NMR (400 MHz, CDCl$_3$): δ = 6.04 (dtd, J = 15.6, 5.8, 0.7 Hz, 1 H, CH$_2$CH=CH), 5.59–5.42 (m, 1 H, CH$_2$CH=CH), 4.61 (dd, J = 5.8, 1.6 Hz, 2 H, OCH_2), 3.42–3.33 [m, 2 H, CH=CHCH(O)CH and CH(O)CHC], 3.27 [dd, J = 3.4, 2.0 Hz, 1 H, CH(O)CHC], 2.99 [dd, J = 3.4, 2.0 Hz, 1 H, =CHCH(O)CH], 2.34 (d, J = 1.7 Hz, 1 H, CCH), 2.13–2.03 (s, 3 H, CH_3CO).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 170.53, 130.34, 129.59, 79.18, 72.50, 63.51, 56.98, 56.53, 54.93, 42.65, 20.83.

HRMS (H-ESI): m/z [M + H]$^+$ calcd for $C_{11}H_{13}O_4$: 209.0814; found: 209.0787.

Epoxy Amide 25

To a suspension of PCC (1.6 g, 7.4 mmol, 1.5 equiv) in CH$_2$Cl$_2$ (20 mL) was added anhydrous NaOAc (1.6 g, 20.0 mmol, 4.0 equiv) followed by *cis*-allylic alcohol **23** (0.9 mL, 5.0 mmol, 1.0 equiv) dissolved in CH$_2$Cl$_2$ (10 mL). The reaction mixture was stirred at r.t. for 6 h and the resulting crude was filtered off through a pad of SiO$_2$ and washed with Et$_2$O. The solvent was then removed under vacuum and the crude aldehyde was used in the next step without further purification. The crude aldehyde was reacted with sulfonium salt **2** (1.7 g, 5.4 mmol, 1.1 equiv) and NaOH (1.7 mL, 3.0 M aq solution, 5.0 mmol, 1.0 equiv), according to the procedure described above for the synthesis of epoxy amide **18**, to yield epoxy amide **25** (1.46 g, 54% over two steps) as a pale yellow oil.

[α]$_D^{25}$ –9.4 (c 1.0, CH$_2$Cl$_2$); R_f = 0.6 [silica gel, 40% EtOAc in hexanes].

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.67–7.64 (m, 4 H, CH$_{arom}$), 7.44–7.36 (m, 6 H, CH$_{arom}$), 6.12 (dt, J = 15.4, 4.0 Hz, 1 H, CH$_2$CH=CH), 5.65 (ddt, J = 15.4, 8.1, 1.9 Hz, 1 H, CH$_2$CH=CH), 4.31 (dt, J = 8.2, 5.0 Hz, 1 H, CONCH), 4.23 (dt, J = 3.6, 1.7 Hz, 2 H, SiOCH_2), 4.03 (ddd, J = 9.1, 5.2, 1.3 Hz, 1 H, OCH_2CH), 3.90 (d, J = 9.2 Hz, 1 H, OCH_2CH) 3.63 [dd, J = 8.1, 1.8 Hz, 1 H, =CHCH(O)CH], 3.56 [d, J = 1.9 Hz, 1 H, CH(O)CHCO], 2.61–2.51 (m, 1 H, SCH_2CH$_2$), 2.43 (ddd, J = 13.4, 9.0, 6.6 Hz, 1 H, SCH_2CH$_2$), 2.14–2.07 (m, 1 H, SCH$_2$CH_2), 2.04 (s, 3 H, CH$_3$S), 1.84–1.70 (m, 1 H, SCH$_2$CH_2), 1.66 [s, 3 H, (CH_3)$_2$C], 1.56 [s, 3 H, (CH_3)$_2$C], 1.06 [s, 9 H, (CH_3)$_3$Si].

^{13}C NMR (100 MHz, CDCl$_3$): δ = 163.46, 136.74, 135.48, 133.32, 133.23, 129.79, 127.76, 124.52, 95.95, 67.07, 63.29, 60.37, 57.89, 55.87, 55.57, 34.33, 30.84, 26.82, 26.31, 23.04, 19.25, 15.83.

HRMS (H-ESI): m/z [M + H]$^+$ calcd for $C_{30}H_{42}NO_4SSi$: 540.2604; found: 540.2594.

Diepoxy Amide 26

To a solution of epoxy amide **25** (166 mg, 0.31 mmol, 1.0 equiv) in dry THF (10 mL) was added dropwise Red-Al (0.2 mL, 60% w/v, 0.62 mmol, 2.2 equiv) at 0 °C. After 1 h at 0 °C, the reaction mixture was quenched by the addition of sat. aq NH$_4$Cl solution. After separation of both layers, the aqueous phase was extracted with EtOAc, the organic extracts were washed with brine and dried over MgSO$_4$, and the solvent was evaporated under reduced pressure. The resulting crude epoxy aldehyde was used in the next step without further purification. The crude aldehyde was reacted with sulfonium salt **2** (110 mg, 0.34 mmol, 1.1 equiv) and NaOH (0.01 mL, 5.0 M aq solution, 0.31 mmol, 1.0 equiv), according to the procedure described above for the synthesis of diepoxy amide **19**, to yield diepoxy amide **26** (170 mg, 95% over two steps) as a pale yellow oil.

[α]$_D^{25}$ –23.0 (c 1.0, CH$_2$Cl$_2$); R_f = 0.40 [silica gel, 40% EtOAc in hexanes].

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.68–7.64 (m, 4 H, CH$_{arom}$), 7.44–7.36 (m, 6 H, CH$_{arom}$), 6.05 (ddd, J = 15.4, 4.5, 3.9 Hz, 1 H, CH$_2$CH=CH), 5.56 (ddt, J = 15.4, 7.9, 1.9 Hz, 1 H, CH$_2$CH=CH), 4.36–4.29 (m, 1 H, CONCH), 4.23 (dd, J = 4.2, 1.9 Hz, 2 H, SiOCH_2), 4.06–4.00 (ddd, J = 9.2, 5.3, 1.4

Hz, 1 H, OCH_2CH), 3.92 (dd, *J* = 9.2, 0.8 Hz, 1 H, OCH_2CH), 3.60 [d, *J* = 1.9 Hz, 1 H, CH(O)C*H*CO], 3.44 [dd, *J* = 7.9, 1.9 Hz, 1 H, =CHC*H*(O)CH], 3.40 [dd, *J* = 3.3, 2.0 Hz, 1 H, C*H*(O)CHCO], 3.04 [dd, *J* = 3.3, 2.1 Hz, 1 H, =CHC*H*(O)C*H*], 2.65–2.55 (m, 1 H, SCH_2CH_2), 2.49 (dt, *J* = 12.4, 6.6 Hz, 1 H, SCH_2CH_2), 2.12 (s, 3 H, CH_3S), 2.11–2.05 (m, 1 H, SCH$_2$CH_2), 1.90–1.76 (m,1 H, SCH$_2$CH_2), 1.66 [s, 3 H, (CH_3)$_2$C], 1.54 [s, 3 H, (CH_3)$_2$C], 1.09–1.03 [s, 9 H, (CH_3)$_3$CSi].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.94, 135.79, 135.50, 133.39, 129.77, 127.74, 125.15, 95.98, 67.08, 63.39, 56.61, 56.01, 55.74, 55.40, 51.31, 34.49, 30.74, 26.82, 26.24, 22.98, 19.24, 15.86.

HRMS (H-ESI): *m*/*z* [M + H]$^+$ calcd for $C_{32}H_{44}NO_5SSi$: 582.2709; found: 582.2706.

Dibromo Alkene 27

To a solution of diepoxy amide **26** (100 mg, 0.17 mmol, 1.0 equiv) in dry THF (10 mL) was added dropwise Red-Al (0.12 mL, 60% w/v, 0.38 mmol, 2.2 equiv) at 0 °C. After 1 h at 0 °C, the reaction mixture was quenched by the addition of sat. aq NH_4Cl solution. After separation of both layers, the aqueous phase was extracted with EtOAc, the organic extracts were washed with brine and dried over $MgSO_4$, and the solvent was evaporated under reduced pressure. The resulting crude epoxy aldehyde was used in the next step without further purification. To a solution of CBr_4 (115 mg, 0.34 mmol, 2.0 equiv) in CH_2Cl_2 (10 mL) was added Ph_3P (90 mg, 0.34 mmol) at 0 °C. The mixture was stirred at the same temperature for 15 min, and Et_3N (0.02 mL, 0.17 mmol, 1.0 equiv) was added. After stirring for 5 min at 0 °C, a solution of the crude epoxy aldehyde (obtained above) in CH_2Cl_2 (5 mL) was added at –78 °C. The mixture was stirred at the same temperature for 2 h. After this time, the reaction mixture was quenched with sat. aq $NaHCO_3$ solution. The mixture was then diluted with EtOAc, washed with H_2O and brine, and then dried over $MgSO_4$ and concentrated under reduced pressure. The resulting crude residue was purified by flash column chromatography (silica gel, 10% EtOAc in hexanes) to afford the corresponding dibromo alkene **27** (40 mg, 40% yield) as a pale yellow oil.

$[\alpha]_D^{25}$ –35.1 (*c* 0.7, CH_2Cl_2); R_f = 0.75 [silica gel, 10% EtOAc in hexanes].

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.68–7.64 (m, 2 H, CH_{arom}), 7.44–7.36 (m, 8 H, CH_{arom}), 6.16 (d, *J* = 7.8 Hz, 1 H, C*H*=CBr$_2$), 6.07–6.00 (m, 1 H, CH$_2$C*H*=), 5.55 (ddt, *J* = 15.4, 7.8, 1.9 Hz, 1 H, CH$_2$CH=C*H*), 4.23 (dd, *J* = 4.2, 1.9 Hz, 2 H, CH_2CH=), 3.64 [dd, *J* = 7.8, 2.0 Hz, 1 H, (O)C*H*CH=CBr$_2$], 3.40 [dd, *J* = 7.9, 2.0 Hz, 1 H, CH=CHC*H*(O)CH], 3.07 [dd, *J* = 3.9, 2.0 Hz, 1 H, C*H*(O)CHCH=CBr$_2$], 2.97 [dd, *J* = 3.9, 2.1 Hz, 1 H, CH=CHCH(O)C*H*], 1.06 [s, 9 H, (CH_3)$_3$CSi].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.63, 135.57, 135.51, 134.80, 134.47, 129.77, 127.74, 125.24, 63.41, 57.18, 56.68, 55.61, 54.99, 26.84, 19.27.

HRMS (H-ESI): *m*/*z* [M + H]$^+$ calcd for $C_{25}H_{29}Br_2O_3Si$: 563.0253; found: 563.0251.

Trialkyne 29

To a solution of the dibromo alkene **27** (51 mg, 0.09 mmol, 1.0 equiv) in THF (5 mL) was added TBAF (0.4 mL, 1.0 M solution in THF, 0.36 mmol, 4.0 equiv) at 0 °C. The mixture was stirred at r.t. for 1 h and the solvent was then removed under vacuum. The corresponding bromo alkyne was obtained as a colorless amorphous solid and was used in the next step without further purification. To a solution of $EtNH_2$ (2.25 mL, 70% aq) in MeOH (3 mL) was added CuCl (4 mg, 45.0 µmol, 0.5 equiv) at r.t. resulting in the formation of a blue solution. To the resulting mixture was added NH_2OH·HCl (19 mg, 270.0 µmol, 3.0 equiv) at the same temperature to discharge the blue color. To the resulting mixture was added dialkyne **28** (19 mg, 99.0 µmol, 1.1 equiv) in MeOH (1.0 mL) at r.t., and the mixture was stirred at the same temperature for 20 min. To the resulting yellow suspension was added a solution of the above-obtained bromoacetylene in MeOH (1.0 mL) at –78 °C, and the mixture was stirred at the same temperature for 20 min. The mixture was then diluted with Et_2O, washed with H_2O and brine, dried over $MgSO_4$ and the solvent was removed under vacuum. The resulting trialkyne was used in the next step without further purification. To a solution of the obtained trialkyne in CH_2Cl_2 (4 mL) was added py (0.05 mL, 0.63 mmol, 7.0 equiv), Ac_2O (0.04 mL, 0.45 mmol, 5.0 equiv) and DMAP (4 mg, 0.03 mmol, 0.3 equiv) at 0 °C. The mixture was stirred at the same temperature for 20 min, then diluted with Et_2O, washed with H_2O and brine, and dried over $MgSO_4$. Concentration under reduced pressure, followed by purification of the resulting crude residue by flash column chromatography (silica gel, 30% EtOAc in hexanes) provided trialkyne **29** (20 mg, 51% yield over 3 steps) as a yellow oil.

$[\alpha]_D^{25}$ –11.2 (*c* 0.5, CH_2Cl_2); R_f = 0.7 [silica gel, 60% EtOAc in hexanes].

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.04 (ddd, *J* = 15.2, 6.1, 5.5 Hz, 1 H, AcOCH$_2$C*H*=), 5.49 (ddt, *J* = 15.6, 7.8, 1.5 Hz, 1 H, AcOCH$_2$CH=C*H*), 4.59 (dd, *J* = 5.7, 1.5 Hz, 2 H, AcOCH_2), 4.39 (s, 2 H, CH_2OTBS), 3.44 [d, *J* = 2.0 Hz, 1 H, C*H*(O)CHC], 3.38 [dd, *J* = 8.1, 1.8 Hz, 1 H, =CHC*H*(O)], 3.33 [dd, *J* = 3.2, 2.0 Hz, 1 H, C*H*(O)CHC], 3.01 [dd, *J* = 3.2, 2.0 Hz, 1 H, =CHCH(O)C*H*], 2.08 (s, 3 H, CH_3CO), 0.90 [s, 9 H, (CH_3)$_3$CSi], 0.12 [s, 6H (CH_3)$_2$Si].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.54, 130.50, 129.43, 77.80, 73.63, 69.49, 69.14, 63.48, 63.14, 62.01, 57.48, 56.24, 55.07, 52.11, 43.05, 25.72, 20.83, 18.25, –5.22.

HRMS (H-ESI): *m*/*z* [M – $CH_3C(O)$ + 2 H]$^+$ calcd for $C_{20}H_{27}O_4Si$: 359.31559; found: 359.31555.

(–)-Gummiferol (1)

Dialkyne **29** (3.0 mg, 7.5 µmol) was treated with HF·py (15 µL) in THF (2.0 mL) in exactly the same way as described by Takamura et al.,[2] yielding (–)-gummiferol (**1**) (2.0 mg, 95%), the spectroscopic and physical properties of which matched with those reported for the natural product.

$[\alpha]_D^{25}$ –59.8 (*c* 0.05, MeOH).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.03 (ddd, *J* = 15.5, 6.1, 5.6 Hz, 1 H, AcOCH$_2$C*H*=), 5.49 (ddt, *J* = 15.6, 7.8, 1.5 Hz, 1 H, AcOCH$_2$CH=C*H*), 4.57 (dd, *J* = 5.7, 1.5 Hz, 2 H, AcOCH_2), 4.37 (s, 2 H, CH_2OH), 3.42 [d, *J* = 2.0 Hz, 1 H, C*H*(O)CHC], 3.37 [dd, *J* = 8.0, 2.0 Hz, 1 H, =CHC*H*(O)], 3.33 [dd, *J* = 3.2, 2.0 Hz, 1 H, C*H*(O)CHC], 3.00 [dd, *J* = 3.2, 2.0 Hz, 1 H, =CHCH(O)C*H*], 2.06 (s, 3 H, CH_3CO).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.56, 130.53, 129.46, 77.24, 73.66, 69.51, 69.17, 63.51, 63.17, 62.04, 57.51, 56.27, 55.09, 52.14, 43.08, 20.86.

HRMS (H-ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{15}O_5$: 287.0919; found: 287.0915.

(+)-Gummiferol (*ent*-1)

(+)-Gummiferol (*ent*-**1**) (1.5 mg, 95%) was prepared according to the same synthetic scheme previously described for (–)-gummiferol (**1**), through compounds *ent*-**25**, *ent*-**26**, *ent*-**27** and *ent*-**29**, and its spectroscopic and physical properties matched with those reported in the literature.[5] Compounds *ent*-**25**, *ent*-**26**, *ent*-**27** and *ent*-**29** were prepared in the exactly same way as their corresponding enantiomers

(as previously described), and exhibited identical spectroscopic and physical properties as those of compounds **25**, **26**, **27** and **29**, respectively, except for their specific rotations.

Epoxy Amide *ent*-25

Yield: 2.1 g (48% over 2 steps from **23**); $[\alpha]_D^{25}$ +23.0 (*c* 0.4, CH_2Cl_2).

HRMS (H-ESI): *m*/*z* $[M + H]^+$ calcd for $C_{30}H_{42}NO_4SSi$: 540.2604; found: 540.2602.

Diepoxy Amide *ent*-26

Yield: 155 mg (92% over 2 steps from *ent*-**25**); $[\alpha]_D^{25}$ +35.1 (*c* 0.4, CH_2Cl_2).

HRMS (H-ESI): *m*/*z* $[M + H]^+$ calcd for $C_{32}H_{44}NO_5SSi$: 582.2709; found: 582.2694.

Dibromo Alkene *ent*-27

Yield: 32 mg (40% over 2 steps from *ent*-**26**); $[\alpha]_D^{25}$ +26.6 (*c* 0.8, CH_2Cl_2).

HRMS (H-ESI): *m*/*z* $[M + H]^+$ calcd for $C_{25}H_{29}Br_2O_3Si$: 563.0253; found: 563.0249.

Trialkyne *ent*-29

Yield: 12 mg (49% over 3 steps from *ent*-**27**); $[\alpha]_D^{25}$ +8.5 (*c* 0.2, CH_2Cl_2).

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1561606.

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