First Total Synthesis and Absolute Configuration of the Styryl Lactone Gonioheptolide A

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Abstract: Efficient asymmetric syntheses of both naturally occurring and non-naturally occurring enantiomers of gonioheptolide A are reported. The absolute configuration of (+)-gonioheptolide A was established by NOESY, Mosher ester analysis, and comparison with the specific rotation of the isolated (+)-gonioheptolide A.

Key words: gonioheptolide A, styryl lactones, natural products, antitumor agents, stereoselective synthesis

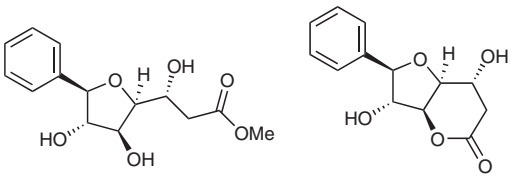

Figure 1

Gonioheptolide A (**1**, Figure 1) is representative of the styryl lactones, a structurally interesting, synthetically challenging and biologically important group of natural products derived from the plant family *Annonaceae* indigenous to Asia.[3] Considerable prior effort has focused on the isolation, characterization,[4] and synthesis of many different styryl lactones.[5] A number of total syntheses of different styryl lactones have also appeared.[6]

Gonioheptolide A has five contiguous stereocenters starting from a benzylic carbon and leading toward a carboxy terminal methyl ester. While racemic gonioheptolide A has been prepared by semi-synthesis from (±)-goniofupyrone,[7] no stereospecific total synthesis or semi-synthesis from other styryl lactones of known configuration has established the absolute configuration of gonioheptolide A unambiguously.

In addition to determining the absolute configuration of the natural product, a total stereoselective synthesis of gonioheptolide A could also provide an approach to the synthesis of any or all of its possible stereoisomers, and potentially to the stereoselective synthesis of other important styryl lactones,[8] as well as many non-naturally occurring analogues. Since they have considerable selective cytotoxic activity toward many cancer cell lines,[9] a versatile, general route to other styryl lactones as well as gonioheptolide A would further provide an enriched diversity of styryl lactones not available from natural sources, leading toward a more thoroughly defined structure–activity relationship. The styryl lactones act by stimulating apoptosis through an intrinsic-pathway-activation of caspases, causing a cascade of proteolytic activity, cell damage, and eventual cell death.[10] Clearly, analogues with enhanced selective cytotoxicity would be desirable.

Since the absolute configuration of (–)-goniofupyrone was established,[6g] it was assumed that (+)-gonioheptolide A,[7] the naturally occurring isomer, had the absolute configuration shown as **1** in Figure 1. However, no experimental evidence establishing that absolute configuration has been reported. Here, we report a stereospecific synthesis of both enantiomers of gonioheptolide A allowing for simultaneous determination of the absolute configurations.

Our general approach to the synthesis of gonioheptolide is shown in Scheme 1. Introduction of the terminal phenyl as the (*E*)-styrene in **5** subsequent to the selective elaboration of L-(+)-tartrate as the monobenzyl derivative **4** facilitated Sharpless asymmetric epoxidation to give intermediate **6**. Subsequent intramolecular cyclization of **6** was followed with conversion into **7** and final elaboration of **7** into **1** (Scheme 1).

In the first phase of our syntheses of **1** through intermediate **7** we prepared **5** as shown in Scheme 2. Conversion of **3** into **4** involved well-known reactions,[11] that have previously been applied in the stereoselective synthesis of monosaccharides.[12] Swern oxidation of **4** gave the known aldehyde intermediate **8**.[12] Subsequent Wittig alkenation gave a mixture of isomers that could be readily isomerized[13] to give the purified (*E*)-styryl isomer **9** in a good overall yield of 65% over two steps. Efficient removal of the ketal under acidic conditions gave intermediate **5** in excellent overall yield of 16% over the seven-step process.

In the subsequent conversion of **5** into **1** we first followed the route in Scheme 3 showing the seven step conversion of **5** into **13**, the C3 epimer of **1**. As predicted by the

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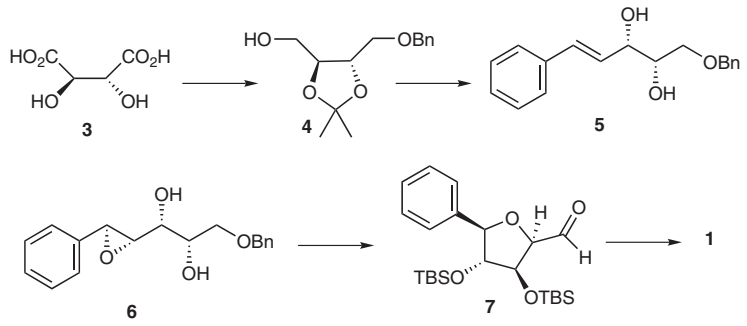
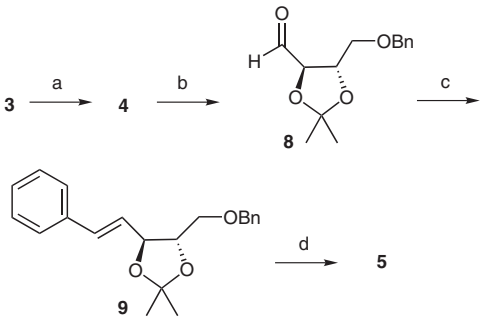


Scheme 1 General approach for the preparation of gonioheptolide A

Sharpless model,[14] using (+)-diethyl tartrate as the chiral ligand in epoxidation gave the desired *threo*-epoxide **6** in 87% yield. No attempts were made at this stage to determine the level of diastereoselectivity. The intramolecular cyclization of **6** under acidic conditions led to the formation of dihydroxytetrahydrofuran **10** in a 5-*endo* fashion. This reaction occurred in high yield and with great selectivity. Acid-catalyzed stereospecific conversion of β-hydroxy epoxides to hydroxytetrahydrofurans as well as the cyclization of epoxy esters to lactones are also well-known and have been employed elsewhere in the synthesis of other styryl lactones.[5b,6d,6m,8a,15]

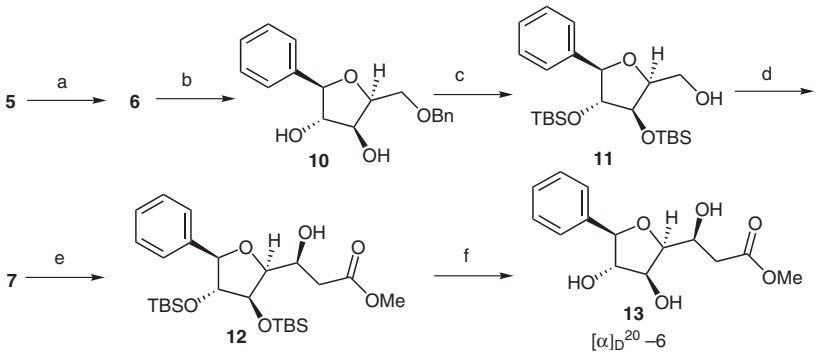
The conversion of **10** into **7**, a key intermediate in the last stage of the synthesis of **1**, was carried out by first protecting the secondary hydroxys, removing the benzyl group, and subsequently oxidizing the primary alcohol product to the aldehyde **7** using Dess–Martin periodinane. In the second step, selective debenzylation required the use of minimal amounts of catalyst, since excessive quantities led to ring opening due to hydrogenolysis of the secondary benzylic ether. By addition of the palladium catalyst portionwise and performing the hydrogenolysis at atmospheric pressure and room temperature, these byproducts could be suppressed at optimal conditions and **11** was obtained in 91% yield. Compound **11** was subsequently converted into **7** in 75% yield.



Scheme 2 *Reagents and conditions*: (a) (i) 2,2-dimethoxypropane, MeOH, cyclohexane, TsOH, reflux, 85%; (ii) $LiAlH_4$, THF, reflux, 60%; (iii) NaH, BnBr, THF, 0 °C to r.t., 63%; (b) Swern oxidation, –78 °C, 70%; (c) (i) $BnP^+Ph_3Br^-$, *n*-BuLi, THF, –40 °C; (ii) AIBN, PhSH, benzene, 80 °C, 76% (2 steps); (d) TFA, H_2O, 0 °C to r.t., 95%.

Finally, a stereoselective aldol reaction was carried out under kinetically controlled conditions using the lithium enolate of methyl acetate. Predominantly the undesired anti-Felkin–Anh stereoisomer **12** was obtained under these conditions with excellent diastereoselectivity (>96% de). The absolute configuration at the hydroxy carbon was observed to be *S* as confirmed by Mosher ester analysis (Figure 2).[16] Mild desilylation using tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF)[17] gave compound **13**, which was the C3 epimer of the target molecule **1**.

Alternative introduction of the aldol ester earlier in the synthesis led to difficulties that were insurmountable. Intermediate **9** was converted into aldol **14**. However, when the ketal was removed the stable lactone **15** was formed (Scheme 4). Thus, we chose to stage the aldol chemistry at the end of the overall sequence in the synthesis reported here.



Scheme 3 *Reagents and conditions*: (a) (+)-DET, Ti(O*i*-Pr)$_4$, *t*-BuOOH, MS 4 Å, CH_2Cl_2, –20 °C, 87%; (b) CSA, CH_2Cl_2, r.t., 85%; (c) (i) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 88%; (ii) H_2, Pd/C, MeOH, r.t., 91%; (d) DMP, CH_2Cl_2, 0 °C to r.t., 75%; (e) MeOAc, LDA, –78 °C, THF, 81%; (f) TASF, DMF, r.t., 90%.

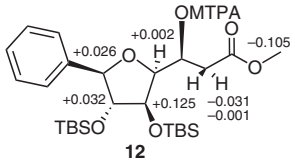


Figure 2

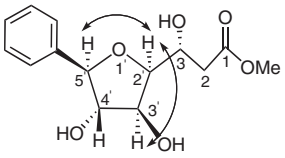
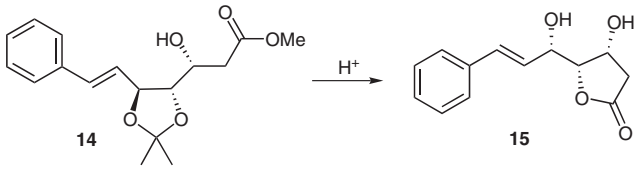


Figure 3

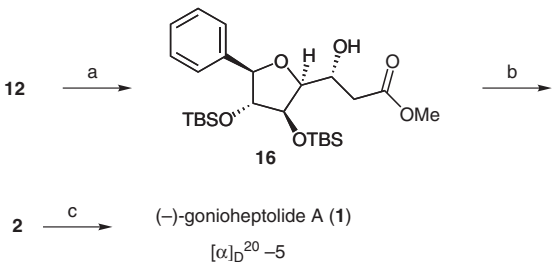


Scheme 4

Mitsunobu inversion[18] was attempted on intermediate **12**. This approach failed presumably due to the presence of the bulky *tert*-butyldimethylsilyl at C3 in the tetrahydrofuran ring. An alternative approach shown in Scheme 5 employed stereospecific reduction of the reoxidized aldol hydroxy using the Corey–Bakshi–Shibata (CBS)[19] reagent (*S*)-2-methyl-1,3,2-oxazaborolidine as a chiral catalyst. As predicted by the model for this reduction, the desired (*R*)-alcohol **16** was obtained in good yield with excellent diastereoselectivity (>98% by Mosher ester analysis). Subsequent desilylation using tris(dimethylamino)sulfonium difluorotrimethylsilicate led to the formation of (–)-goniofupyrone (**2**) along with small amounts of the (–)-enantiomer of gonioheptolide A. Conversion of **16** to (–)-gonioheptolide A in 70% yield was accomplished in two steps. (–)-Gonioheptolide A was identical (NMR, NOESY) to the natural product except for the reported specific rotation of +5.[3b,7] The observed specific rotation of –5 and not +5 suggested initially that the configurations of all stereocenters were opposite to those shown in (–)-gonioheptolide A (**1**, Figure 1) for the reported naturally occurring isomer.

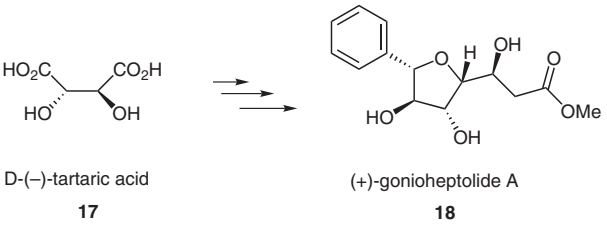
NOESY of (–)-gonioheptolide A (**1**) showed strong NOE signals between the C2′ and C3′, C2′ and C5′ protons in the furan ring (Figure 3). This also confirmed the *threo* stereochemistry of the epoxide **6**.

We also synthesized the (+)-isomer of gonioheptolide A in an analogous process to that shown starting from



Scheme 5 *Reagents and conditions*: (a) (i) DMP, CH_2Cl_2, r.t., 80%; (ii) (*S*)-2-methyl-1,3,2-oxazaborolidine, BH_3–THF, THF, r.t., 83%; (b) TASF, DMF, r.t.; (c) MeOH, THF, H_2SO_4, r.t., 70% (2 steps).

(–)-tartaric acid (**17**) (Scheme 6). In comparison to the strategy shown in Schemes 2, 3, and 5 for (–)-gonioheptolide A, we used (–)-diethyl tartrate in the Sharpless epoxidation instead of (+)-diethyl tartrate, and the (*R*)-2-methyl-1,3,2-oxazaborolidine catalyst in place of the corresponding (*S*)-isomer to synthesize (+)-gonioheptolide A (**18**). Since the specific rotation of synthesized gonioheptolide A was +5, there was little doubt that the absolute configuration of the naturally occurring (+)-gonioheptolide A (**18**) is opposite to the one proposed earlier (**1**, Figure 1).[3b,7]



Scheme 6

In conclusion, we have established the absolute configuration of the natural isomer of gonioheptolide A by synthesizing both isomers of gonioheptolide A. The synthetic strategy proved applicable for the synthesis of different isomers of gonioheptolide A and intermediates in the synthesis could be useful in the asymmetric synthesis of other styryl lactones.

All reactions were carried out under N_2 atmosphere using anhyd solvents and conditions, unless otherwise noted. THF and Et_2O were distilled under N_2 from Na–benzophenone. The solvents used were ACS grade from Fisher. Reagents were purchased from Aldrich and Acros, and used without further purification. Reactions were monitored by TLC carried out on 0.20 mm Polygram SIL silica gel plates (Art.-Nr. 805 023) with fluorescent indicator UV_{254} using UV light and 15% H_2SO_4–MeOH and heat as visualizing agents. Normal-phase flash column chromatography was carried out using Davisil silica gel (100–200 mesh, Fisher). NMR spectra were recorded on Varian INOVA 600 and Varian VXRS-400 instruments and calibrated using residual undeuterated solvent as an internal reference. Optical rotations were recorded on an AUTOPOL III 589/546 polarimeter. HRMS were recorded on a Micromass LCT Electrospray mass spectrometer performed at the Mass Spectrometry & Proteomics Facility (The Ohio State University).

Mosher Ester; General Procedure

To a stirred soln of alcohol (1 equiv), DMAP (0.5 equiv), and Et_3N (3 equiv) in CH_2Cl_2 was added (+)-(*S*)- or (–)-(*R*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (MTPACl) (3 equiv) at r.t. The resulting mixture was stirred overnight. The soln was diluted with EtOAc and washed with H_2O, dried, and concentrated in vacuo. Pu-

rification by column chromatography (silica gel) furnished the Mosher ester. *Note*: It should be noted that (*R*)- or (*S*)-MTPA esters are obtained from (*S*)- or (*R*)-MTPACl, respectively.

[(4*S*,5*S*)-5-(Benzyloxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl]methanol (4)

2,3-*O*-Isopropylidene-L-threitol was synthesized from (+)-tartaric acid **3** as reported earlier.[11] To a cooled suspension (0 °C) of NaH (0.541 g, 22.5 mmol) in THF (8 mL) was added dropwise 2,3-*O*-isopropylidene-L-threitol (2.0 g, 12.34 mmol) in THF (6 mL). The mixture was stirred at 0 °C for 1 h after which BnBr (2.1 g, 12.2 mmol) was added and the mixture was warmed to r.t. and stirred for 6 h. The reaction was then quenched with sat. NH_4Cl soln and extracted with Et_2O. The combined organic extracts were dried (anhyd Na_2SO_4), concentrated, and purified by flash chromatography (silica gel, 3–20% EtOAc–hexanes) to give **4** (1.9 g, 63%) as a colorless oil; R_f = 0.24 (silica gel, 25% EtOAc–hexanes).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.35–7.25 (m, 5 H), 4.57 (s, 2 H), 4.06–4.02 (m, 1 H), 3.94–3.91 (m, 1 H), 3.74–3.72 (m, 1 H), 3.68–3.65 (m, 2 H), 3.56–3.53 (m, 1 H), 1.41 (d, *J* = 3.6 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.9, 128.7, 128.1, 127.9, 109.6, 79.8, 76.8, 73.9, 70.6, 62.6, 27.2, 27.2.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{20}NaO_4$: 275.1259; found: 275.1262.

(4*R*,5*S*)-5-(Benzyloxymethyl)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde (8)[12]

To 2 M oxalyl chloride in CH_2Cl_2 (5.1 mL, 10.2 mmol) at –78 °C was added DMSO (1.63 g, 20.9 mmol) dropwise. After 10 min of stirring at –78 °C, **4** (1.29 g, 5.10 mmol) in CH_2Cl_2 (16 mL) was added dropwise and the resulting soln was stirred for 1 h. Et_3N (4.3 mL, 30.6 mmol) was added and the mixture was stirred at –78 °C for 30 min and then warmed to r.t. for 30 min. The mixture was quenched with H_2O and extracted with CH_2Cl_2. The combined organic extracts were dried (anhyd Na_2SO_4), concentrated, and purified by flash chromatography (silica gel, 9–16% EtOAc–hexanes) to give **8** (0.9 g, 70%) as a pale yellow oil; TLC as a streak (silica gel, 50% hexanes–EtOAc).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 9.75 (s, 1 H), 7.35–7.2 (m, 5 H), 4.59 (s, 2 H), 4.26–4.21 (m, 2 H), 3.68–3.62 (m, 2 H), 1.48 (s, 3 H), 1.41 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.9, 137.9, 128.7, 128.1, 127.9, 111.9, 82.3, 76.4, 73.8, 70.1, 27.1, 26.4.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{18}NaO_4$: 273.1103; found: 273.1090.

(4*S*,5*S*)-4-(Benzyloxymethyl)-2,2-dimethyl-5-[(*E*)-styryl]-1,3-dioxolane (9)

To a soln of $BnPh_3PBr$ (1.46 g, 3.38 mmol) in anhyd THF (14.1 mL) under N_2 at –40 °C was added 2.5 M *n*-BuLi in hexanes (1.35 mL, 3.38 mmol). After stirring at –40 °C for 15 min, **8** (0.71 g, 2.82 mmol) in THF (5.64 mL) was added slowly to the mixture when the orange color faded slowly. After stirring at r.t. for 4 h, the mixture was poured into aq NH_4Cl and extracted with Et_2O. The combined organic extracts were dried (Na_2SO_4) and concentrated to give an *E*/*Z* mixture of alkene products, which was subsequently equilibrated to the *E*-isomer as follows: To a soln of AIBN (119 mg, 8% by weight) in anhyd benzene (10 mL), PhSH (0.26 mg, 16% by weight) was added followed by the addition of the *E*/*Z* alkene mixture in benzene. The mixture was refluxed at 80 °C and the reaction was monitored by TLC. After 2 h the reaction was complete and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (silica gel, 2% EtOAc–hexanes) to give **9** as a pale yellow oil (0.7 g, 76% over 2 steps); R_f = 0.66 (silica gel, 25% EtOAc–hexanes).

$[\alpha]_D^{20}$ –34.55 (*c* 1.1, $CHCl_3$).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.25–7.38 (m, 10 H), 6.62 (d, *J* = 15.6 Hz, 1 H), 6.16 (dd, *J* = 6.5, 15.6 Hz, 1 H), 4.61 (q, *J* = 11.5 Hz, 2 H), 4.42 (t, *J* = 12 Hz, 1 H), 3.98–4.02 (m, 1 H), 3.69–3.60 (m, 2 H), 1.47 (br s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.3, 136.5, 133.9, 128.8, 128.6, 128.2, 127.9, 127.9, 126.9, 126.5, 80.5, 79.5, 73.8, 69.7, 27.3, 27.2.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{21}H_{24}NaO_3$: 347.1623; found: 347.1633.

(*E*,2*S*,3*S*)-1-(Benzyloxy)-5-phenylpent-4-ene-2,3-diol (5)

To a cooled (0 °C) soln of **9** (0.5 g, 1.54 mmol) in CH_2Cl_2 (38 mL) was added 90% TFA in H_2O (3 mL) and the mixture was stirred at 0 °C for 1 h. The mixture was diluted with CH_2Cl_2, washed with H_2O, sat. aq Na_2CO_3 soln, and again with H_2O. The organic layer was dried (anhyd Na_2SO_4), filtered, and concentrated. The crude product was purified by flash column chromatography (silica gel, 10–50% EtOAc–hexanes) to give **5** (0.42 g, 95%) as a white solid; R_f = 0.51 (silica gel, 66% EtOAc–hexanes).

$[\alpha]_D^{20}$ –25.25 (*c* 0.8, $CHCl_3$).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.36–7.27 (m, 10 H), 6.64 (d, *J* = 16.2 Hz, 1 H), 6.19 (dd, *J* = 6.5, 16.2 Hz, 1 H), 4.55 (q, *J* = 11.4 Hz, 2 H), 4.36–4.33 (m, 1 H), 3.78–3.75 (m, 1 H), 3.67–3.58 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.8, 136.6, 132.8, 128.8, 128.7, 128.2, 128.1, 128.0, 126.8, 73.9, 73.7, 73.5, 71.7.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{20}NaO_3$: 307.1310; found: 347.1308.

(1*R*,2*S*)-3-(Benzyloxy)-1-[(2*S*,3*S*)-3-phenyloxiran-2-yl]propane-1,2-diol (6)

Activated, powdered 4 Å molecular sieves (38 mg) and anhyd CH_2Cl_2 (10 mL) were placed in a 50-mL flame-dried flask. (+)-DET (218 mg, 1.05 mmol) was added to the above slurry and the mixture was cooled to –20 °C. Ti(O*i*-Pr)$_4$ (1.0 mL, 3.38 mmol) and anhyd 3.6 M *t*-BuOOH in CH_2Cl_2 (0.59 mL, 2.1 mmol) were added dropwise and the mixture was stirred at –20 °C for 40 min. A predried (4 Å MS) soln of **5** (200 mg, 0.704 mmol) in CH_2Cl_2 (8 mL) was added to it dropwise and the mixture was stirred at –20 °C for 7 h. The reaction was quenched by adding it to a cooled (0 °C) soln of $FeSO_4 \cdot 7H_2O$ (0.33 g per mmol of allylic alcohol) and tartaric acid (0.1 g per mmol of allylic alcohol) in H_2O (1 mL per mmol of allylic alcohol) and stirred for 10 min without a cooling bath. The aqueous layer was extracted with Et_2O and the combined organic extracts were stirred over 30% NaOH in brine (1 mL per mmol of allylic alcohol) at 0 °C for 1 h. The aqueous layer was again extracted with Et_2O and the combined organic extracts were dried (anhyd Na_2SO_4), filtered, and concentrated. The crude product was purified by flash column chromatography (silica gel, 50% EtOAc–hexanes) to give **6** (183 mg, 87%) as a white crystalline solid; R_f = 0.50 (silica gel, 66% EtOAc–hexanes).

$[\alpha]_D^{20}$ –41.30 (*c* 0.4, $CHCl_3$).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.34–7.29 (m, 10 H), 4.57 (q, *J* = 11.4 Hz, 2 H), 3.97–3.94 (m, 1 H), 3.90–3.89 (m, 1 H), 3.85–3.82 (m, 1 H), 3.69–3.63 (m, 2 H), 3.18–3.17 (m, 1 H), 2.66–2.64 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.8, 136.7, 128.8, 128.7, 128.6, 128.2, 128.1, 125.9, 73.9, 71.7, 71.5, 70.7, 63.1, 55.6.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{20}NaO_4$: 323.1259; found: 323.1253.

(2*S*,3*S*,4*S*,5*R*)-2-(Benzyloxymethyl)-5-phenyltetrahydrofuran-3,4-diol (10)

To a stirred soln of epoxide **6** (0.5 g, 1.67 mmol) in anhyd CH_2Cl_2 (8 mL) was added catalytic amount of 10-camphorsulfonic acid (37 mg, 0.16 mmol) and the soln was stirred for 4 h. The mixture was neutralized with sat. aq $NaHCO_3$ soln and extracted with EtOAc. The combined organic extracts were dried (anhyd Na_2SO_4), concentrated, and purified by flash chromatography (silica gel, 1% MeOH–CH_2Cl_2) to give **10** as a colorless oil (0.425 g, 85%); R_f = 0.32 (silica gel, 66% EtOAc–hexanes).

$[\alpha]_D^{20}$ +3.8 (*c* 0.5, $CHCl_3$).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.45 (d, *J* = 7.2 Hz, 1 H), 7.37–7.27 (m, 9 H), 4.67–4.59 (m, 3 H), 4.34–4.29 (m, 2 H), 4.09–4.07 (m, 1 H), 3.98–3.89 (m, 2 H), 3.22 (d, *J* = 6.6 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.9, 137.6, 128.8, 128.7, 128.2, 128.1, 128.0, 126.5, 85.0, 84.9, 80.2, 78.5, 74.3, 69.8.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{20}NaO_4$: 323.1259; found: 323.1279.

(2*S*,3*R*,4*R*,5*R*)-[3,4-Bis(*tert*-butyldimethylsiloxy)-5-phenyltetrahydrofuran-2-yl]methanol (11)

To a soln of alcohol **10** (0.1 g, 0.33 mmol) in CH_2Cl_2 (3.3 mL) at 0 °C was added 2,6-lutidine (0.30 mL, 2.64 mmol). After stirring for 5 min at this temperature, TBSOTf (0.30 mL, 1.32 mmol) was added dropwise and the mixture was stirred at 0 °C for 20 min, after which time no starting material was detected by TLC. Sat. aq NH_4Cl (3 mL) was added. The organic phase was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 6 mL). The combined organic extracts were dried (anhyd Na_2SO_4), concentrated, and purified by flash chromatography (silica gel, 2% EtOAc–hexanes) to afford the bis(*tert*-butyldimethylsilyl) ether (0.155 g, 88%) as a colorless oil; R_f = 0.74 (silica gel, 17% EtOAc–hexanes).

$[\alpha]_D^{20}$ +10.43 (*c* 0.7, $CHCl_3$).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.38–7.18 (m, 10 H), 4.75 (s, 1 H), 4.60 (q, *J* = 12 Hz, 2 H), 4.37–4.35 (m, 1 H), 3.99–3.98 (m, 2 H), 3.80–3.77 (m, 2 H), 0.88 (s, 9 H), 0.75 (s, 9 H), 0.02 (s, 3 H), 0.01 (s, 3 H), –0.01 (s, 3 H), –0.12 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.1, 138.4, 128.6, 128.3, 128.2, 127.8, 127.3, 126.9, 89.4, 85.4, 81.4, 79.6, 73.8, 69.1, 25.9, 25.8, 18.2, 18.0, –4.2, –4.3, –4.5, –4.9.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{30}H_{48}NaO_4Si_2$: 551.2989; found: 551.2991.

This intermediate product (0.155 g, 0.29 mmol) was hydrogenated over 5% Pd/C (8 mg) in MeOH (20 mL) at r.t. and H_2 (1 bar). After stirring for 30 min, another portion of 5% Pd/C (8 mg) was added to the mixture. After stirring overnight the catalyst was filtered and the filtrate was concentrated to give alcohol **11** (117 mg, 91%) as a colorless oil; R_f = 0.33 (silica gel, 20% EtOAc–hexanes).

$[\alpha]_D^{20}$ +3.67 (*c* 0.3, $CHCl_3$).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.42 (d, *J* = 7.8 Hz, 2 H), 7.29 (m, 2 H), 7.23–7.21 (m, 1 H), 4.72 (d, *J* = 3 Hz, 1 H), 4.26–4.23 (m, 1 H), 4.10–4.09 (m, 1 H), 4.04–3.99 (m, 2 H), 3.91–3.87 (m, 1 H), 0.87 (s, 9 H), 0.79 (s, 9 H), 0.05 (s, 3 H), 0.01 (s, 3 H), –0.06 (s, 3 H), –0.12 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.7, 128.4, 127.7, 127.0, 88.2, 85.3, 81.7, 80.2, 62.8, 25.9, 25.8, 18.1, 18.0, –4.2, –4.4, –4.4, –4.8.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{23}H_{42}NaO_4Si_2$: 461.2519; found: 461.2508.

(2*R*,3*R*,4*R*,5*R*)-3,4-Bis(*tert*-butyldimethylsiloxy)-5-phenyltetrahydrofuran-2-carbaldehyde (7)

Dess–Martin periodinane (164 mg, 0.39 mmol) was added to a soln of **11** (121 mg, 0.28 mmol) in CH_2Cl_2 (0.6 mL) at 0 °C. The resulting mixture was stirred at r.t. for 30 min before it was subjected to column chromatography (silica gel, 10% EtOAc–hexane) to give **7** as a colorless oil that was directly used in the next step.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 9.88 (d, *J* = 1.8 Hz, 1 H), 7.48–7.27 (m, 5 H), 4.97 (s, 1 H), 4.53–4.52 (m, 1 H), 4.32 (dd, *J* = 1.2, 3.6 Hz, 1 H), 4.09 (d, *J* = 1.2 Hz, 1 H), 0.89 (s, 9 H), 0.68 (s, 9 H), 0.06 (d, *J* = 5.4 Hz, 6 H), –0.03 (s, 3 H), –0.17 (s, 3 H).

Methyl (*S*)-3-[(2*S*,3*R*,4*R*,5*R*)-3,4-Bis(*tert*-butyldimethylsiloxy)-5-phenyltetrahydrofuran-2-yl]-3-hydroxypropanoate (12)

To a precooled soln of 1.8 M LDA in toluene (0.42 mL, 0.75 mmol) at –78 °C was added excess methyl acetate (56 mg, 0.75 mmol). After stirring at the same temperature for 30 min, aldehyde **7** (82 mg, 0.19 mmol) in THF (0.1 mL) was added dropwise to the mixture. It was stirred at –78 °C for 30 min and then it was quenched with sat. aq NH_4Cl soln. The aqueous layer was extracted with EtOAc and the combined organic extracts were dried (anhyd Na_2SO_4), concentrated, and purified by flash chromatography (silica gel, 6% EtOAc–hexanes) to afford **12** (78 mg, 81%) as a colorless oil; R_f = 0.38 (silica gel, 20% EtOAc–hexanes).

$[\alpha]_D^{20}$ +24.5 (*c* 0.6, $CHCl_3$).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.34 (d, *J* = 7.2 Hz, 2 H), 7.26 (t, *J* = 7.2 Hz, 2 H), 4.76 (s, 1 H), 4.45–4.40 (m, 1 H), 4.10 (d, *J* = 2.4 Hz, 1 H), 4.02 (s, 1 H), 3.98 (dd, *J* = 3.0, 8.4 Hz, 1 H), 3.72 (s, 3 H), 3.14 (d, *J* = 4.8 Hz, 1 H), 2.95 (dd, *J* = 3.0, 17.4 Hz, 1 H), 2.63 (dd, *J* = 9.6, 17.4 Hz, 1 H), 0.89 (s, 9 H), 0.75 (s, 9 H), 0.07 (s, 3 H), 0.06 (d, *J* = 4.8 Hz, 6 H), –0.10 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.2, 141.1, 128.3, 127.4, 126.6, 89.8, 85.4, 84.1, 79.0, 65.9, 51.9, 38.9, 25.9, 25.8, 18.2, 18.1, –4.2, –4.2, –4.5, –4.9.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{26}H_{46}NaO_6Si_2$: 533.2731; found: 533.2738.

Methyl (*S*)-3-[(2*S*,3*S*,4*S*,5*R*)-3,4-Dihydroxy-5-phenyltetrahydrofuran-2-yl]-3-hydroxypropanoate (13)

To a soln of aldol product **12** (6 mg, 0.012 mmol) in DMF (0.1 mL) was added dropwise a soln of TASF (8.1 mg, 0.029 mmol) in DMF (0.1 mL). The resulting mixture was stirred overnight and diluted with a phosphate buffer soln of pH 7. The organic phase was separated and the aqueous layer was extracted with EtOAc. The combined organic extracts were dried (anhyd Na_2SO_4), concentrated, and purified by flash chromatography (5% MeOH–CH_2Cl_2) to afford **13** (3 mg, 90%) as a white solid; R_f = 0.24 (silica gel, 10% MeOH–CH_2Cl_2).

$[\alpha]_D^{20}$ –6.0 (*c* 0.3, $CHCl_3$).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.41–7.35 (m, 5 H), 4.62 (d, 1 H), 4.47–4.45 (m, 1 H), 4.40–4.39 (m, 1 H), 4.12–4.10 (m, 1 H), 3.99–3.96 (m, 1 H), 3.72 (s, 3 H), 2.85 (dd, *J* = 3, 16.8 Hz, 1 H), 2.67 (dd, *J* = 9, 16.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.5, 139.5, 129.1, 128.8, 128.3, 126.5, 85.8, 84.9, 81.4, 79.6, 68.1, 52.2, 38.0.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{18}NaO_6$: 305.1001; found: 305.1001.

Methyl (*R*)-3-[(2*S*,3*R*,4*R*,5*R*)-3,4-Bis(*tert*-butyldimethylsiloxy)-5-phenyltetrahydrofuran-2-yl]-3-hydroxypropanoate (16)

Dess–Martin periodinane (93 mg, 0.22 mmol) was added to a soln of **12** (80 mg, 0.16 mmol) in CH_2Cl_2 (3 mL) at 0 °C. The resulting mixture was stirred at r.t. for 30 min before it was subjected to column chromatography (silica gel, 10% EtOAc–hexane) to give the

corresponding ketone (6.4 mg, 80%) as colorless oil, which was directly used in the next step. To a soln of the ketone (50 mg, 0.1 mmol) in THF (0.6 mL) was added 1 M (*S*)-2-methyl-1,3,2-oxazaborolidine in toluene (0.19 mL, 0.19 mmol) followed by addition of 1 M BH_3 in THF soln (0.19 mL, 0.19 mmol) dropwise. The resulting mixture was stirred at r.t. for 2 h after which it was cooled to 0 °C and quenched by slow addition of H_2O. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic extracts were dried (anhyd Na_2SO_4), concentrated, and purified by flash chromatography (silica gel, 6% EtOAc–hexanes) to give the desired product **16** (42 mg, 83%) as a colorless oil; R_f = 0.33 (silica gel, 20% EtOAc–hexanes).

$[\alpha]_D^{20}$ +7.9 (*c* 0.3, $CHCl_3$).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.44 (d, *J* = 7.8 Hz, 2 H), 7.29–7.21 (m, 3 H), 4.72 (s, 1 H), 4.49–4.46 (m, 1 H), 4.12–4.11 (m, 1 H), 4.09–4.08 (m, 2 H), 3.71 (s, 3 H), 3.25 (s, 1 H), 2.71 (dd, *J* = 8.4, 15.6 Hz, 1 H), 2.62 (dd, *J* = 4.2, 15.6 Hz, 1 H), 0.87 (s, 9 H), 0.78 (s, 9 H), 0.08 (s, 3 H), 0.01 (s, 3 H), –0.08 (s, 3 H), –0.13 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.3, 140.5, 128.4, 127.8, 126.9, 87.3, 84.8, 82.3, 80.4, 68.1, 51.9, 38.3, 25.9, 25.8, 18.0, 17.9, –4.1, –4.1, –4.4, –4.9.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{26}H_{46}NaO_6Si_2$: 533.2731; found: 533.2747.

(2*R*,3*R*,3a*S*,7*R*,7a*S*)-3,7-Dihydroxy-2-phenylhexahydro-5*H*-furo[3,2-*b*]pyran-5-one [(–)-Goniofupyrone, 2]

To a soln of **16** (5 mg, 0.01 mmol) in DMF (0.1 mL) was added dropwise a soln of TASF (13.5 mg, 0.05 mmol) in DMF (0.1 mL). The mixture was stirred overnight and diluted with a phosphate buffer soln (pH 7). The organic phase was separated and the aqueous layer was extracted with EtOAc. The combined organic extracts were dried (anhyd Na_2SO_4), concentrated, and purified by flash chromatography (silica gel, 50% EtOAc–hexanes) to afford (–)-goniofupyrone (**2**) (2 mg, 82%).

$[\alpha]_D^{20}$ –5.0 (*c* 0.2, $CHCl_3$) [Lit.[4d] $[\alpha]_D^{20}$ –5.0 (*c* 0.2, $CHCl_3$)].

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.37–7.30 (m, 5 H), 4.96 (dd, *J* = 3, 5.4 Hz, 1 H), 4.70 (d, *J* = 6.6 Hz), 4.44 (dt, 1 H, *J* = 3.9, 5.9 Hz), 4.34 (br t, 1 H, *J* = 5.2 Hz), 4.28 (dd, *J* = 2.4, 6.6 Hz, 1 H), 2.90 (dd, *J* = 3.6, 16.8 Hz, 1 H), 2.67 (dd, *J* = 6, 16.8 Hz, 1 H), 2.54 (br s, 1 H), 2.22 (br s, 1 H).

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{14}NaO_5$: 273.0739; found: 273.0762.

(–)-Methyl (*R*)-3-[(2*S*,3*S*,4*S*,5*R*)-3,4-Dihydroxy-5-phenyltetrahydrofuran-2-yl]-3-hydroxypropanoate [(–)-Gonioheptolide A, 1]

To a soln of **16** (5 mg, 0.01 mmol) in DMF (0.1 mL) was added dropwise a soln of TASF (13.5 mg, 0.05 mmol) in DMF (0.1 mL). The mixture was stirred overnight and diluted with a buffer soln (pH 7). The organic phase was separated and the aqueous layer was extracted with EtOAc. The crude was dissolved in THF (0.3 mL) and MeOH (0.3 mL) and a drop of concd H_2SO_4 was added.[7] The reaction was stirred at r.t. for 30 min, diluted with sat. aq soln of $CaCO_3$, and extracted with EtOAc. The solvent was evaporated and the crude product was purified by flash chromatography (silica gel, 50% EtOAc–hexanes) to afford (–)-gonioheptolide A (**1**) (2 mg, 70%) as a white solid; R_f = 0.21 (silica gel, 25% EtOAc–hexanes).

$[\alpha]_D^{20}$ –5.0 (*c* 0.3, $CHCl_3$).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.46 (d, *J* = 7.8 Hz, 2 H), 7.36–7.7.34 (m, 3 H), 4.59 (d, *J* = 6.6 Hz, 1 H), 4.47–4.43 (m, 1 H), 4.34 (dd, *J* = 4.8, 6.4 Hz, 1 H), 4.10–4.09 (m, 2 H), 3.71 (s, 3 H), 3.68 (d, *J* = 4.8 Hz, 1 H), 3.62 (d, *J* = 7.8 Hz, 1 H), 2.88 (dd, *J* = 9, 16.8 Hz, 1 H), 2.64 (dd, *J* = 4.2, 16.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.5, 139.6, 128.8, 128.3, 126.3, 84.6, 84.2, 80.1, 68.1, 52.3, 37.7.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{18}NaO_6$: 305.1001; found: 305.0989.

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