Asymmetric Synthesis of Gonioheptolide A Analogues via an Organocatalytic Aldol Reaction as the Key Step

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Abstract: An efficient asymmetric synthesis of the potential antitumor agent (–)-gonioheptolide A derivatives is described. By employing an (*S*)-proline-catalyzed aldol reaction, the RAMP hydrazone α-alkylation methodology, and a diastereoselective reduction with zinc borohydride five stereocenters are established in the target compound. 4-*epi*-Methoxy-gonioheptolide A was obtained in ten steps in 15% overall yield and excellent diastereo- and enantiomeric excesses (de ≥95%, ee ≥99%).

Key words: dihydroxyacetone, aldol reaction, organocatalysis, proline, styryllactone

Styryllactones are secondary metabolites isolated from plants of the family annonaceae, genus *goniothalamus*.[1] Since the first isolation of goniothalamin in 1967,[2] more than 30 styryllactones[3] were discovered showing interesting cytotoxic, pesticidal, and antitumor activity.[4] A characteristic feature of the styryllactones is the presence of mono- or bicyclic tetrahydrofuran ring systems, densely decorated with oxygenated stereocenters.[1]

(–)-Gonioheptolide A (**1**) was first isolated in 1993 from the bark of *Goniothalamus giganteus* by McLaughlin et al.[5] The initially published structure was revised by McLaughlin and Hanaoka et al. in 1999.[6] The generally accepted structure of (–)-gonioheptolide A containing the furan alkyl ester skeleton **1** is shown in Figure 1. (–)-Gonioheptolide A shows interesting antitumor activities against lung, breast, and colon cancer cells.[5]

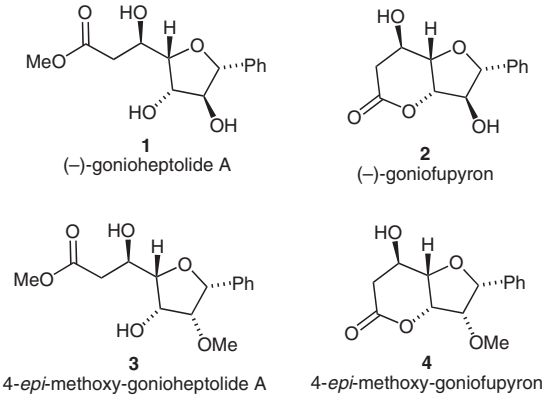

Figure 1 (–)-Gonioheptolide A (**1**), (–)-goniofupyron (**2**), and the epimeric methoxy compounds **3** and **4**

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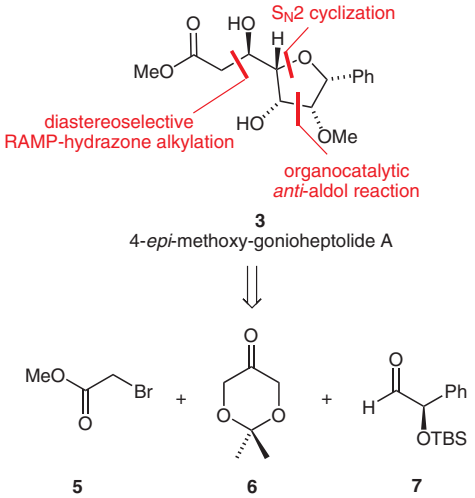
The first semi-synthesis of **1** was accomplished by McLaughlin et al. starting from (–)-goniofupyron (**2**), by opening the lactone moiety under acidic conditions to the corresponding methyl ester.[6]

To the best of our knowledge, the only total synthesis of **1** has been published by Hudson et al. in 2007.[7] Starting from L-(+)-tartaric acid, **1** was synthesized in 18 steps and an overall yield of 3%. The same group synthesized four different stereoisomers of **1**. These isomers showed even higher activity against breast cancer cells in biological studies.[8]

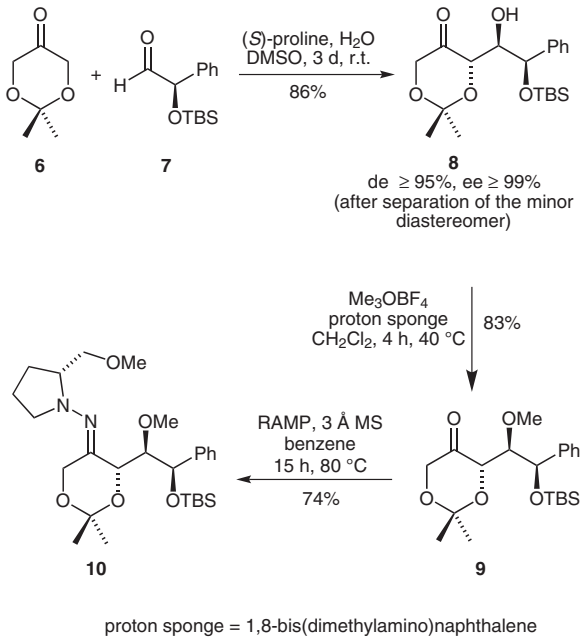
For a new access to this interesting class of compounds we envisaged a different route to synthesize new epimers and derivatives of **1** and **2** (Figure 1). Based on our previous experience in proline-catalyzed aldol reactions,[9] RAMP-hydrazone alkylations,[10] previous total syntheses of natural products and bioactive compounds starting from dioxanone,[11] we hoped that the epimeric gonioheptolide **3** could be prepared from three basic building blocks: commercially available methyl bromoacetate (**5**), 2,2-dimethyl-1,3-dioxan-5-one (**6**, dioxanone),[12] and aldehyde **7** (Scheme 1).



Scheme 1 Retrosynthetic analysis of 4-*epi*-methoxy-gonioheptolide A (**3**)

The envisaged route to 4-*epi*-methoxy-gonioheptolide A (**3**) consisted of an organocatalytic aldol reaction followed by diastereoselective RAMP-hydrazone alkylation. Subsequent reduction of the keto group and anionic ring closure should form the furan moiety.

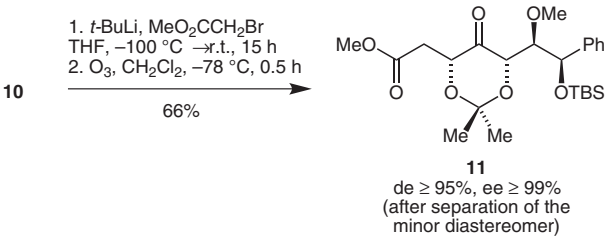
In the first stereogenic step, we employed an (*S*)-proline-catalyzed aldol reaction of dioxanone (**6**) with the TBS-protected aldehyde **7**, which could be easily synthesized from (*R*)-mandelic acid[13] (Scheme 2). The aldol product **8** was obtained with very good diastereoselectivity (de = 90%) and the minor diastereomer could be separated by column chromatography giving access to the diastereo- and enantiomerically pure aldol product **8** (de ≥95%, ee ≥99%) in very good yield (86%). Subsequent reaction of the free alcohol group with Meerwein's reagent in the presence of proton sponge [1,8-bis(dimethylamino)naphthalene] gave the methyl ether **9** in 83% yield and condensation of the ketone with RAMP resulted in 74% the desired hydrazone **10** in good yield.



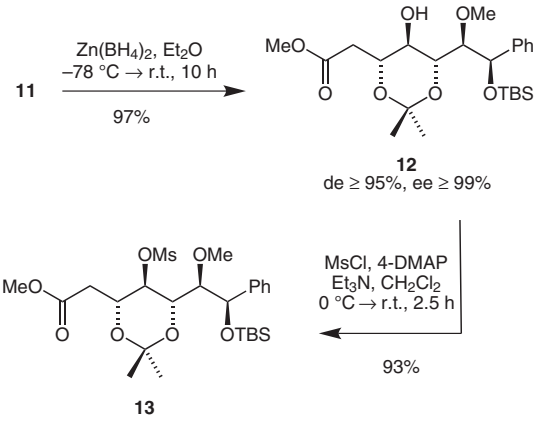
Scheme 2 Organocatalytic *anti*-aldol reaction as a key step

The RAMP-hydrazone α-alkylation methodology[14] was used to give the alkylated product **11** in a two-step sequence consisting of the alkylation of hydrazone **10** with *tert*-butyllithium and methyl bromoacetate (**5**) in THF at –100 °C and a subsequent ozonolysis to remove the chiral auxiliary. The alkylation proceeded with a diastereomeric excess of 94%. Column chromatography yielded the diastereo- and enantiomerically pure alkylation product in a one-pot fashion from **10** to **11** with 66% yield over 2 steps (Scheme 3).

Anti-diastereoselective reduction of ketone **11** with zinc borohydride gave the alcohol **12** in 97% yield (de ≥95%, ee ≥99%). In accordance with previous findings it should be noted that other reducing reagents, such as boron hydrides were not selective enough or led to the wrong diastereomer.[15] The cyclization precursor **13** was finally obtained by mesylation of the secondary alcohol under basic conditions (Scheme 4).

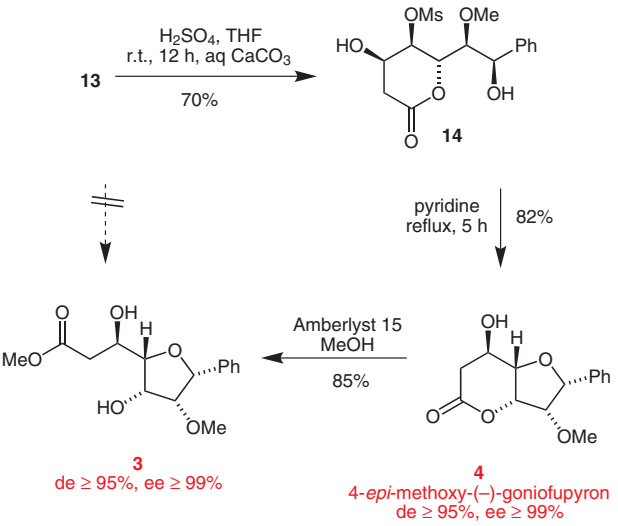


Scheme 3 α-Alkylation of **10** with methyl bromoacetate (**5**) as electrophile



Scheme 4 *Anti*-diastereoselective reduction with $Zn(BH)_4$ and mesylation

We initially thought that the acidic removal of the protection groups and subsequent treatment with $CaCO_3$ could provide the target compound **3** directly. However, only lactone **14** was obtained in 70% yield. By refluxing **14** in pyridine the cyclization to the bicyclic goniofupyron derivative could be achieved in 82% yield. Finally, in analogy to McLaughlin's synthesis the 4-*epi*-methoxy-goniofupyron (**4**) was opened under acidic conditions to the target compound **3** (Scheme 5).



Scheme 5 Final steps in the synthesis of the epimeric goniheptolide analogues **3** and **4**

Attempts to convert the methoxy group into the corresponding free secondary alcohol turned out to be difficult. Protocols with different Lewis acids and on different stages were tried without success. Thus, the epimeric natural product **2** could not be obtained via this route. To support our expectations for the stereochemical outcome of the synthesis the absolute configuration of the acyclic ester **15** was determined by X-ray crystal structure analysis. This compound was obtained by deprotection of **13** under methanolic acidic conditions. Additional NOE measurements of **3** confirmed the expected inversion of the stereocenter at C-2 during the cyclization step (Figure 2).

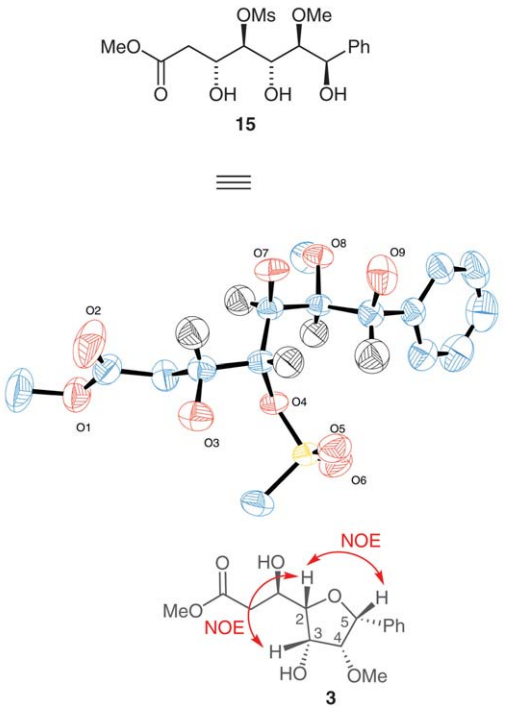


Figure 2 X-ray crystal structure of **15**[16] and NOE measurement of **3**

In summary, we have developed an asymmetric synthesis of new epimeric (–)-goniohеptolide A analogues using an organocatalytic aldol reaction with (*S*)-proline as the stereogenic key step. 4-*epi*-Methoxy-goniohеptolide A was obtained in ten steps in a good overall yield of 15% in diastereo- and enantiopure form starting from the dioxanone (**6**), aldehyde **7**, and methyl bromoacetate (**5**). Besides this key step an α-alkylation employing the RAMP-hydrazone methodology and an S_N2 ring closure gave us access to the epimeric methoxy-goniohеptolide A (**3**) and the epimeric methoxy-goniofupyron (**4**). This synthetic strategy could also lead to different stereoisomers and derivatives of (–)-goniohеptolide A (**1**). Compared to conventional strategies stereoisomers can be accessed by using (*S*)- or (*R*)-proline in the key step and/or the RAMP- or SAMP-hydrazone for the alkylation, respectively. Furthermore, the reduction of the ketone can be directed to the opposite diastereomer by using L-Selectride as the reducing agent.

All commercially available compounds were used without further purification. (*R*)-2-[(*tert*-Butyldimethylsilyl)oxy]-2-phenylacetaldehyde (**7**) was synthesized following a procedure published by Kobayashi et al.[13] For preparative column chromatography silica gel 60 (particle size 0.040–0.063 mm, 230–240 mesh, flash) was used. Yields are reported based on pure, separated diastereomers. Melting points were determined with a Büchi Melting Point B-540 and optical rotation values with a Perkin-Elmer P241 polarimeter. TLC was carried out with silica gel 60 F_{254} plates from Merck and visualization was achieved by staining with vanillin solution in EtOH with 1% concd H_2SO_4. IR spectra were acquired with a PerkinElmer Spectrum 100 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on Varian Mercury 300 or Inova 400 spectrometers with TMS as internal standard. Mass spectra were measured with a Finnigan SSQ7000 spectrometer (CI 100 eV; EI 70 eV). HRMS data were recorded with a ThermoFinnigan LCQ Deca XP plus (ESI) or a ThermoFisher Scientific LTQ-Orbitrap XL (ESI) instrument.

(*S*)-4-{(1*R*,2*R*)-2-[(*tert*-Butyldimethylsilyl)oxy]-1-hydroxy-2-phenylethyl}-2,2-dimethyl-1,3-dioxan-5-one (8)

To a solution of 2,2-dimethyl-1,3-dioxan-5-one (**6**; 781 mg, 6.0 mmol) and (*R*)-2-[(*tert*-butyldimethylsilyl)oxy]-2-phenylacetaldehyde (**7**; 500 mg, 2 mmol) in DMSO (8 mL) were added (*S*)-proline (69 mg, 0.3 mmol) and H_2O (180 mg, 10 mmol). The mixture was stirred at r.t. for 3 d, quenched with brine (5 mL), and extracted with Et_2O (3 × 10 mL). Drying of the combined Et_2O extracts ($MgSO_4$), evaporation of the solvent, and column chromatography (*n*-pentane–Et_2O, 15:1 to 6:1) of the crude product afforded **8** as a colorless oil; yield: 655 mg (86%); $[\alpha]_D^{26}$ –121.3 (*c* = 1.02, $CHCl_3$); R_f = 0.3 (*n*-pentane–EtOAc, 15:1).

IR (capillary): 3517, 3064, 3033, 2987, 2929, 2856, 1748, 1578, 1542, 1466, 1381, 1253, 1225, 1159, 1083, 1007, 938, 860, 838, 778, 702, 673, 635, 562, 537 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = –0.24 (s, 3 H, CH_3Si), 0.06 (s, 3 H, CH_3Si), 0.88 (s, 9 H, *t*-C_4H_9Si), 1.35 (s, 3 H, CH_3), 1.47 (s, 3 H, CH_3), 3.07 (d, *J* = 2.3 Hz, 1 H, OH), 3.80 (d, *J* = 16.6 Hz, 1 H, CH_2^a), 3.96 (dd, *J* = 16.6, 1.2 Hz, 1 H, CH_2^b), 4.07–4.10 (m, 1 H, H-4), 4.17–4.18 (m, 1 H, H-3), 4.99 (d, *J* = 7.2 Hz, 1 H, H-5), 7.26–7.38 (m, 5 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = –5.0, –4.4, 18.1, 23.0, 24.8, 25.8 (3 C), 67.0, 74.8, 75.6, 76.4, 100.4, 127.7 (2 C), 128.1 (2 C), 128.2, 140.4, 207.2.

MS (EI, 70 eV): *m*/*z* (%) = 59 (20), 72 (11), 73 (73), 75 (68), 91 (21), 105 (13), 115 (12), 117 (16), 129 (62), 131 (12), 159 (22), 193 (62), 194 (10), 221 (100), 222 (20).

HRMS-ESI: *m*/*z* [2 M + Na]$^+$ calcd for $C_{40}H_{64}O_{10}Si_2$ + Na: 783.3930; found: 783.3931.

(*S*)-4-{(1*R*,2*R*)-2-[(*tert*-Butyldimethylsilyl)oxy]-1-methoxy-2-phenylethyl}-2,2-dimethyl-1,3-dioxan-5-one (9)

To a solution of **8** (3.61 g, 9.49 mmol) in anhyd CH_2Cl_2 (94 mL) were added Me_3OBF_4 (2.10 g, 14.23 mmol) and proton sponge (5.08 g, 23.72 mmol). The mixture was refluxed under argon for 4 h. After cooling to r.t., the mixture was washed with HCl (1.5 N, 50 mL). The aqueous layer was extracted with Et_2O (2 × 30 mL). The combined organic layers were dried ($MgSO_4$) and the solvent was evaporated. The resulting solid was suspended in Et_2O (200 mL) and filtered over a short plug of silica gel. The filtrate was evaporated and purified by column chromatography (*n*-pentane–Et_2O, 8:1) to afford **9** as a colorless oil; yield: 3.11 g (83%); $[\alpha]_D^{26}$ –129.9 (*c* = 1.02, $CHCl_3$); R_f = 0.5 (*n*-pentane–Et_2O, 8:1).

IR (capillary): 3065, 3034, 2988, 2931, 2893, 2857, 1779, 1751, 1726, 1673, 1467, 1424, 1380, 1315, 1223, 1125, 1089, 1056, 986, 890, 863, 837, 779, 670, 626, 573, 541, 481 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = –0.18 (s, 3 H, CH_3Si), 0.06 (s, 3 H, CH_3Si), 0.92 (s, 9 H, *t*-C_4H_9Si), 1.28 (s, 3 H, CH_3), 1.43 (s, 3 H,

CH_3), 3.59 (s, 3 H, OCH_3), 3.61–3.63 (m, 2 H, CH_2), 3.73 (dd, J = 8.3, 1.8 Hz, 1 H, H-4), 4.09 (m, 1 H, H-3), 4.97 (d, J = 8.3 Hz, 1 H, H-5), 7.24–7.37 (m, 5 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = –4.9, –4.8, 18.1, 22.7, 25.0, 25.8 (3 C), 60.9, 66.9, 76.0, 76.7, 87.2, 100.1, 127.9 (2 C), 127.9, 128.4 (2 C), 140.9, 206.8.

MS (EI, 70 eV): m/z (%) = 59 (27), 73 (71), 75 (15), 89 (38), 91 (18), 115 (20), 129 (98), 130 (15), 131 (11), 147 (12), 173 (47), 195 (10), 203 (11), 205 (10), 219 (16), 221 (100), 222 (55), 223 (15), 231 (30), 247 (27), 263 (24), 265 (29), 279 (16), 337 (12), 395 (3, $[M + H]^+$).

HRMS-ESI: m/z $[M + Na]^+$ calcd for $C_{21}H_{34}O_5Si$ + Na: 417.2068; found: 417.2068.

(2*R*)-*N*-((*R*)-4-{(1*R*,2*R*)-2-[(*tert*-Butyldimethylsilyl)oxy]-1-methoxy-2-phenylethyl}-2,2-dimethyl-1,3-dioxan-5-ylidene)-2-(methoxymethyl)cyclopentanamine (RAMP Hydrazone 10)

To a solution of **9** (1.66 g, 4.20 mmol) and RAMP (2.18 g, 16.79 mmol) in benzene (21 mL) were added 3 Å molecular sieves. The mixture was heated at reflux for 15 h. After filtration of the molecular sieves, the solvent was removed under reduced pressure. Purification of the crude product by column chromatography (*n*-pentane–Et_2O, 4:1) afforded **10** as a yellow oil; yield: 1.58 g (74%); $[\alpha]_D^{23}$ –41.5 (c = 1.01, $CHCl_3$); R_f = 0.2 (*n*-pentane–Et_2O, 5:1).

IR (capillary): 3469, 2935, 1460, 1377, 1222, 1086, 933, 841, 760, 701, 669, 625, 572, 517 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = –0.16 (s, 3 H, CH_3Si), 0.05 (s, 3 H, CH_3Si), 0.84 (s, 9 H, t-C_4H_9Si), 1.28 (s, 3 H, CH_3), 1.38 (s, 3 H, CH_3), 1.59–1.74 (m, 1 H, RMP-H), 1.78–1.88 (m, 2 H, RMP-H), 1.92–2.03 (m, 1 H, RMP-H), 2.68–2.76 (m, 1 H, NCH_2^a), 2.85–2.92 (m, 1 H, NCH_2^b), 3.07–3.16 (m, 1 H, NCH), 3.23 (dd, J = 7.2, 9.3 Hz, 1 H, $MeOCH_2^a$), 3.36 (s, 3 H, OCH_3), 3.43 (s, 3 H, OCH_3), 3.48 (dd, J = 4.5, 9.3 Hz, 1 H, $MeOCH_2^b$), 3.60 (dd, J = 3.5, 6.9 Hz, 1 H, H-4), 4.12 (dd, J = 1.5, 15.8 Hz, 1 H, CH_2^a), 4.25 (dd, J = 1.5, 3.5 Hz, 1 H, H-3), 4.48 (d, J = 15.8 Hz 1 H, CH_2^b), 5.10 (d, J = 6.7 Hz, 1 H, H-5), 7.21–7.25 (m, 3 H, ArH), 7.41–7.45 (m, 2 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = –4.7 (2 C), 18.2, 22.7, 23.3, 25.8 (3 C), 26.6, 26.8, 55.4, 59.1, 60.7, 60.9, 66.8, 72.5, 74.6, 75.1, 88.1, 99.2, 127.1, 127.7 (2 C), 127.9 (2 C), 142.6, 159.0.

MS (EI, 70 eV): m/z (%) = 70 (13), 73 (21), 82 (6), 89 (20), 91 (6), 98 (16), 112 (5), 114 (7), 139 (8), 183 (100), 184 (27), 195 (14), 221 (9), 241 (6), 242 (12), 461 (6), 506 (1, $[M + H]^+$).

HRMS-ESI: m/z $[M + H]^+$ calcd for $C_{27}H_{47}O_5N_2Si$: 507.3249; found: 507.3247.

Methyl 2-((4*R*,6*S*)-6-{(1*R*,2*R*)-2-[(*tert*-Butyldimethylsilyl)oxy]-1-methoxy-2-phenylethyl}-2,2-dimethyl-5-oxo-1,3-dioxan-4-yl)acetate (11)

Under argon **10** (411 mg, 0.81 mmol) was dissolved in anhyd THF (3.2 mL) and cooled to –78 °C. *t*-BuLi (1.47 M in *n*-pentane, 0.61 mL, 0.89 mmol) was added dropwise and the mixture was stirred at –78 °C for 2 h. After cooling to –100 °C, methyl bromoacetate (**5**; 0.13 mL, 0.89 mmol) dissolved in anhyd THF (0.9 mL) was added subsequently. The mixture was stirred for 2 h and warmed to r.t. over 15 h. The reaction was quenched with pH 7 buffer solution (5.0 mL) and extracted with Et_2O (3 × 5 mL). The combined organic layers were dried ($MgSO_4$) and the solvent was evaporated. The crude product was dissolved in anhyd CH_2Cl_2 (50.0 mL) under argon and cooled to –78 °C. Ozone was bubbled through the solution for 15 min. Excess of ozone was removed by flushing the solution with argon while warming to r.t. The mixture was dried ($MgSO_4$) and the solvent was removed under vacuum. Purification of the crude product by column chromatography (*n*-pentane–Et_2O, 4:1) afforded **11** as a yellow oil; yield: 251 mg (66%); $[\alpha]_D^{23}$ –11.0 (c = 1.03, $CHCl_3$); R_f = 0.4 (*n*-pentane–Et_2O, 6:1).

IR (capillary): 2938, 2857, 1743, 1444, 1380, 1258, 1202, 1170, 1122, 1087, 920, 851, 776, 702 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = –0.19 (s, 3 H, CH_3Si), 0.03 (s, 3 H, CH_3Si), 0.81 (s, 9 H, t-C_4H_9Si), 1.42 (s, 3 H, CH_3), 1.50 (s, 3 H, CH_3), 2.32 (dd, J = 16.3, 8.9 Hz, 1 H, CH_2^a), 2.58 (dd, J = 16.3, 3.7 Hz, 1 H, CH_2^b), 3.59 (s, 3 H, OCH_3), 3.65–3.68 (m, 1 H, H-4), 3.70 (s, 3 H, CO_2CH_3), 4.15–4.16 (m, 1 H, H-3), 4.59–4.62 (m, 1 H, CHOH), 5.89 (d, J = 8.2 Hz, 1 H, H-5), 7.24–7.41 (m, 5 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = –4.9, –4.8, 18.1, 20.7, 25.7 (3 C), 28.9, 35.7, 52.0, 61.5, 74.5, 75.4, 78.3, 87.7, 98.7, 127.7 (4 C), 128.1, 141.3, 171.1, 205.8.

MS (EI, 70 eV): m/z (%) = 55 (11), 57 (15), 59 (29), 73 (83), 75 (19), 85 (24), 89 (54), 91 (25), 105 (11), 115 (27), 131 (10), 143 (19), 183 (20), 201 (15), 221 (100), 222 (19), 245 (19).

HRMS-ESI: m/z $[M + H]^+$ calcd for $C_{24}H_{39}O_7Si$: 467.2460; found: 467.2460.

Methyl 2-((4*R*,5*R*,6*R*)-6-{(1*R*,2*R*)-2-[(*tert*-Butyldimethylsilyl)oxy]-1-methoxy-2-phenylethyl}-5-hydroxy-2,2-dimethyl-1,3-dioxan-4-yl)acetate (12)

A solution of $Zn(BH_4)_2$ in dry Et_2O (0.14 M, 50.5 mL, 7.06 mmol) was added dropwise under argon to a solution of **11** (589 mg, 1.26 mmol) in anhyd Et_2O (9.0 mL) at –78 °C. The mixture was slowly warmed to r.t. and stirred for 10 h. After cooling to 0 °C, MeOH (10 mL) was added and the mixture was stirred for additional 30 min. The reaction was quenched with sat. aq NH_4Cl (30 mL) and extracted with CH_2Cl_2 (3 × 30 mL). Drying of the combined CH_2Cl_2 layers ($MgSO_4$), evaporation of the solvent, and column chromatography (*n*-pentane–Et_2O, 2:1) of the crude product afforded **12** as a colorless oil; yield: 574 mg (97%); $[\alpha]_D^{25}$ –10.1 (c = 1.00, $CHCl_3$); R_f = 0.5 (*n*-pentane–Et_2O 2:1).

IR (capillary): 3502, 2994, 2935, 2858, 1742, 1454, 1381, 1321, 1257, 1201, 1169, 1068, 933, 845, 760, 702 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = –0.19 (s, 3 H, CH_3Si), 0.05 (s, 3 H, CH_3Si), 0.90 (s, 9 H, t-C_4H_9Si), 1.28 (s, 3 H, CH_3), 1.36 (s, 3 H, CH_3), 2.40 (dd, J = 3.2, 15.6 Hz, 1 H, CH_2^a), 2.85 (dd, J = 8.9, 15.6 Hz, 1 H, CH_2^b), 3.20 (s, 3 H, OCH_3), 3.24–3.33 (m, 2 H, H-2, H-4), 3.58 (d, J = 1.0 Hz, 1 H, OH), 3.68 (s, 3 H, CO_2CH_3), 3.73 (dd, J = 7.2, 9.2 Hz, 1 H, H-3), 4.10 (dt, J = 3.2, 9.2 Hz, 1 H, C*H*OH), 4.81 (d, J = 3.5 Hz, 1 H, H-5), 7.24–7.39 (m, 5 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = –4.9, –4.4, 18.2, 19.4, 25.9 (3 C), 29.3, 37.7, 51.6, 61.7, 69.3, 70.0, 71.3, 74.5, 90.8, 98.7, 127.2 (2 C), 127.4, 127.9 (2 C), 141.8, 171.8.

MS (EI, 70 eV): m/z (%) = 59 (19), 73 (31), 89 (15), 113 (10), 115 (11), 145 (16), 185 (27), 221 (100), 222 (20).

HRMS-ESI: m/z [2 M + Na]$^+$ calcd for $C_{48}H_{80}O_{14}Si_2$ + Na: 959.4979; found: 959.4959.

Methyl 2-((4*R*,5*R*,6*S*)-6-{(1*R*,2*R*)-2-[(*tert*-butyldimethylsilyl)oxy]-1-methoxy-2-phenylethyl}-2,2-dimethyl-5-[(methylsulfonyl)oxy]-1,3-dioxan-4-yl)acetate (13)

Et_3N (0.43 mL, 3.06 mmol) and a catalytic amount of 4-DMAP were added to a solution of **12** (552 mg, 1.18 mmol) in CH_2Cl_2 (12.0 mL). After cooling to 0 °C, a solution of MsCl (0.13 mL, 1.65 mmol) in CH_2Cl_2 (1.0 mL) was added dropwise. The mixture was stirred for 30 min at 0 °C and for 2 h at r.t., then quenched with sat. aq NH_4Cl (10 mL), and extracted with CH_2Cl_2 (3 × 10 mL). Drying of the combined CH_2Cl_2 layers ($MgSO_4$), evaporation of the solvent, and column chromatography (*n*-pentane–Et_2O, 2:1) of the crude product afforded **13** as a colorless solid, yield: 598 mg (93%); mp 89–91 °C $[\alpha]_D^{24}$ –12.0 (c = 0.75, $CHCl_3$); R_f = 0.3 (*n*-pentane–Et_2O, 2:1).

IR (capillary): 3469, 2934, 2856, 1742, 1448, 1360, 1255, 1177, 1069, 956, 846, 763, 701, 629, 573, 531 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = –0.20 (s, 3 H, CH_3Si), 0.04 (s, 3 H, CH_3Si), 0.88 (s, 9 H, t-C_4H_9Si), 1.21 (s, 3 H, CH_3), 1.34 (s, 3 H,

CH_3), 2.44 (dd, J = 6.2, 16.1 Hz, 1 H, CH_2[a]), 2.89 (dd, J = 2.5, 16.1 Hz, 1 H, CH_2[b]), 3.13 (s, 3 H, SO_2CH_3), 3.41–3.45 (m, 1 H, H-4), 3.45 (s, 3 H, OCH_3), 3.68 (s, 3 H, CO_2CH_3), 3.85 (dd, J = 3.5, 8.2 Hz, 1 H, H-3), 4.16–4.29 (m, 2 H, H-2, C*H*OMs), 4.73 (d, J = 6.7 Hz, 1 H, H-5), 7.26–7.39 (m, 5 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = –4.9, –4.5, 18.1, 19.1, 25.7 (3 C), 29.1, 37.5, 39.3, 51.7, 61.4, 69.0, 71.6, 75.3, 75.9, 88.2, 99.1, 127.7 (2 C), 127.8, 128.2 (2 C), 141.3, 171.1.

MS (EI, 70 eV): *m*/*z* (%) = 59 (14), 73 (31), 89 (16), 153 (10), 221 (100), 222 (20), 223 (36).

HRMS-ESI: *m*/*z* $[M + Na]^+$ calcd for $C_{25}H_{42}O_9SSi$ + Na: 569.2211; found: 569.2201.

(2*S*,3*R*,4*R*)-4-Hydroxy-2-[(1*S*,2*R*)-2-hydroxy-1-methoxy-2-phenylethyl]-6-oxotetrahydro-2*H*-pyran-3-yl Methanesulfonate (14)

To a solution of **13** (583 mg, 1.07 mmol) in THF (10 mL) was added concd H_2SO_4 (0.46 mL, 8.53 mmol). The mixture was stirred at r.t. overnight and quenched with sat. aq $CaCO_3$ (1 mL). After extraction with EtOAc (3 × 10 mL), the combined organic layers were dried ($MgSO_4$). Evaporation of the solvent and column chromatography (*n*-pentane–EtOAc, 1:3) of the crude product mixture afforded **14** as a colorless solid; yield: 270 mg (70%); mp 26–27 °C; $[\alpha]_D^{24}$ –34.6 (*c* = 0.75, $CHCl_3$); R_f = 0.4 (*n*-pentane–EtOAc, 1:3).

IR (ATR): 3440, 3026, 2937, 1729, 1453, 1344, 1222, 1171, 1090, 936, 850, 816, 762, 705 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.69 (dd, J = 9.6, 17.5 Hz, 1 H, CH_2[a]), 2.86 (dd, J = 5.9, 17.5 Hz 1 H, CH_2[b]), 3.12 (s, 3 H, OCH_3), 3.28 (s, 3 H, SO_2CH_3), 3.67–3.73 (m, 1 H, H-4), 4.54–4.61 (m, 1 H, CH), 4.65–4.69 (m, 1 H, H-3), 4.80 (d, J = 4.7 Hz, 1 H, H-5), 5.34–5.39 (m, 1 H, C*H*OMs), 7.32–7.44 (m, 5 H, ArH).

The integrals at 2.86 ppm and 3.28 ppm were slightly larger than expected and it was assumed that the two missing alcohol protons overlap.

^{13}C NMR (75 MHz, $CDCl_3$): δ = 34.7, 38.8, 62.2, 63.7, 72.6, 76.1, 80.8, 85.9, 126.2 (2 C), 128.6 (2 C), 128.9, 140.0, 167.9.

MS (EI, 70 eV): *m*/*z* (%) = 107 (13), 127 (10), 135 (91), 145 (10), 155 (17), 159 (12), 161 (12), 215 (65), 229 (32), 233 (41), 247 (100), 248 (16), 265 (17), 343 (41, $[M – OH]^+$).

Anal. Calcd for $C_{15}H_{20}O_8S$ (360.09): C, 49.99; H, 5.59. Found: C, 50.13; H, 5.48.

Methyl (3*R*,4*R*,5*S*,6*S*,7*R*)-3,5,7-Trihydroxy-6-methoxy-4-[(methylsulfonyl)oxy]-7-phenylheptanoate (15)

Compound **13** (583 mg, 1.07 mmol) was deprotected with concd H_2SO_4 (0.46 mL) in MeOH–THF (1:1, 22 mL). The workup procedure was done as described above. Crystallization from EtOAc in the refrigerator resulted in suitable single crystals; yield: 192 mg (46%); mp 109–111 °C; $[\alpha]_D^{25}$ +5.6 (*c* = 0.75, MeOH); R_f = 0.5 (*n*-pentane–EtOAc, 1:3).

IR (ATR): 3491, 3188, 3027, 2914, 2828, 2076, 1720, 1498, 1443, 1386, 1337, 1291, 1236, 1172, 1063, 1014, 979, 914, 856, 823, 763, 731, 700, 675 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.63 (dd, J = 9.4, 16.8 Hz, 1 H, CH_2[a]), 2.86 (dd, J = 3.0, 16.8 Hz, 1 H, CH_2[b]), 3.08 (s, 3 H, $CHOCH_3$), 3.18 (s, 3 H, SO_2CH_3), 3.58 (dd, J = 1.7, 6.7 Hz, 1 H, H-4), 3.72 (m, 4 H, CO_2CH_3, OH), 3.97 (d, J = 4.3 Hz, 1 H, OH), 4.14–4.23 (m, 2 H, OH, H-3), 4.46–4.53 (m, 1 H, C*H*CH_2), 4.88 (dd, J = 4.2, 5.7 Hz, 1 H, C*H*OMs), 5.17 (d, J = 6.2 Hz, 1 H, H-4), 7.25–7.41 (m, 5 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 36.9, 38.8, 52.1, 60.1, 67.1, 70.7, 72.0, 83.5, 85.4, 125.9 (2 C), 127.5, 128.4 (2 C), 141.2, 173.2.

MS (EI, 70 eV): *m*/*z* (%) = 113 (7), 115 (13), 119 (9), 121 (17), 125 (10), 134 (29), 135 (15), 140 (18), 144 (10), 157 (26), 165 (29), 172 (11), 249 (17), 393 (1, [M + H]).

HRMS-ESI: *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{25}O_9S$: 393.1214; found: 393.1219.

(2*R*,3*S*,3a*S*,7*R*,7a*S*)-7-Hydroxy-3-methoxy-2-phenyltetrahydro-2*H*-furo[3,2-*b*]pyran-5(6*H*)-one (4)

Lactone **14** (150 mg, 0.4 mmol) was dissolved in pyridine (0.8 mL) and the mixture was heated at reflux for 5 h. After adding H_2O (20 mL), the aqueous phase was extracted with EtOAc (3 × 15 mL). The combined organic phases were washed with HCl (1.5 M, 5 mL) and brine (10 mL), dried ($MgSO_4$), and evaporated. Chromatographic purification on silica gel (eluent: CH_2Cl_2–MeOH, 20:1) afforded the title compound **4** as a colorless glassy solid; yield: 89 mg (82%); $[\alpha]_D^{25}$ –21.2 (*c* = 0.52, $CHCl_3$); R_f = 0.3 (CH_2Cl_2–MeOH, 20:1).

IR (ATR): 3404, 2923, 2853, 2322, 2190, 2098, 1728, 1496, 1454, 1397, 1354, 1256, 1225, 1192, 1130, 1059, 1009, 920, 841, 791, 763, 725, 702 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.66–2.76 (m, 1 H, CH_2[a]), 2.79–2.89 (br s, 1 H, OH), 3.03–2.89 (m, 4 H, CH_3, CH_2[b]), 3.87 (dd, J = 2.9, 5.7 Hz, 1 H, H-4), 4.18–4.28 (m, 1 H, H-2), 4.36–4.43 (m, 1 H, CH), 4.78 (d, J = 2.9 Hz, 1 H, H-5), 5.36 (dd, J = 5.7, 8.4 Hz, 1 H, H-3), 7.04–7.77 (m, 5 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 35.6, 60.6, 66.6, 74.6, 80.1, 81.5, 82.0, 126.9 (2 C), 127.0, 128.1 (2 C), 135.0, 170.2.

MS (EI, 70 eV): *m*/*z* (%) = 58 (100), 65 (11), 77 (21), 79 (12), 87 (61), 91 (51), 103 (12), 107 (26), 115 (11), 131 (13), 134 (48), 135 (11), 144 (29), 264 (22, $[M^+]$).

Anal. Calcd for $C_{14}H_{16}O_5$ (264.01): C, 63.63; H, 6.10. Found: C, 63.26; H, 5.96.

(*R*)-Methyl 3-Hydroxy-3-[(2*S*,3*S*,4*R*,5*R*)-3-hydroxy-4-methoxy-5-phenyltetrahydrofuran-2-yl]propanoate (3)

4-*epi*-Methoxy-(–)-goniofupyron (**4**; 45 mg, 0.17 mmol) was dissolved in MeOH (1 mL) and Amberlyst 15 (17 mg) was added. The mixture was stirred overnight. Direct chromatographic purification on silica gel (eluent: CH_2Cl_2–MeOH, 20:1) afforded 4-*epi*-methoxy-(–)-gonioheptolide (**3**) as a colorless solid; yield: 43 mg (85%); mp 92–93 °C, $[\alpha]_D^{25}$ –58.7 (*c* = 0.53, $CHCl_3$), R_f = 0.4 (CH_2Cl_2–MeOH, 20:1).

IR (ATR): 3447, 3037, 2927, 2861, 1894, 1727, 1605, 1542, 1495, 1437, 1367, 1262, 1148, 1101, 1068, 999, 957, 913, 873, 850, 757, 698 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.74–2.77 (m, 2 H, CH_2), 3.02 (s, 3 H, OCH_3), 3.29 (d, J = 9.2 Hz, 1 H, OH), 3.51 (d, J = 6.2 Hz, 1 H, OH), 3.71 (s, 3 H, CO_2CH_3), 3.84 (dd, J = 3.9, 5.1 Hz, 1 H, H-4), 4.04 (dd, J = 3.3, 7.0 Hz, 1 H, H-2), 4.37–4.46 (m, 1 H, CH), 4.55–4.65 (m, 1 H, H-3), 4.84 (d, J = 3.9 Hz, 1 H, H-5), 7.25–7.47 (m, 5 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 38.8, 51.7, 60.0, 67.3, 73.4, 80.5, 80.8, 82.8, 127.0 (2 C), 127.9, 128.1 (2 C), 136.1, 172.1.

MS (EI, 70 eV): *m*/*z* (%) = 103 (22), 135 (36), 145 (45), 163 (100), 229 (73), 230 (11), 233 (13), 247 (16), 265 (21, [M + H]).

Anal. Calcd for $C_{15}H_{20}O_6$ (264.01): C, 60.80; H, 6.80. Found: C, 60.83; H, 6.92.

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(16) Crystallographic data for **15** reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 818574. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif or on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: +44(1223)336033; e-mail: deposit@ccdc.cam.ac.uk].

