# Enantioselective Cascade Sequence to Indoloquinolizidines and Its Application in the Synthesis of *epi*-Geissochizol

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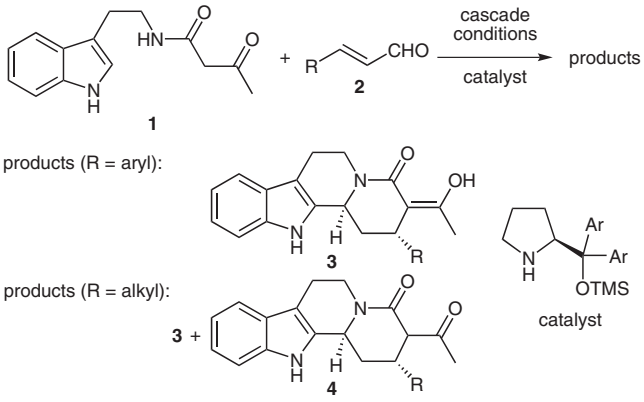
**Abstract:** An organocatalyzed one-pot Michael addition and Pictet–Spengler sequence utilizing β-keto amide and aliphatic α,β-unsaturated aldehydes was developed, which provided access to highly substituted indolo[2,3-*a*]quinolizidines as a mixture of keto and enol tautomers. Such tautomeric pairs were transformed into stable compounds with an *E*-ethylidenyl group in telescoped steps. This method was successfully applied in the synthesis of *epi*-geissoschizol.

**Key words:** Michael addition, organocatalysis, cyclization, enantioselectivity, reduction

During our continuous development of stereoselective synthetic methods for highly substituted quinolizidines,[1] we have recently discovered a cascade reaction[2] between aromatic nucleophile-tethered activated methylene compound **1** and α,β-unsaturated aldehydes **2** catalyzed by prolinol TMS ether[3] (Scheme 1). When an aromatic aldehyde was used, the conjugate addition of **1** to **2** and subsequent acid-catalyzed Pictet–Spengler (PS) cyclization provided polycyclic enol **3** as a sole diastereomer. Moderate to good yields and good to excellent enantioselectivities were achieved.[2] However, when an aliphatic aldehyde was employed, this cascade sequence resulted in a pair of inseparable keto–enol tautomers.




**Scheme 1** Cascade reactions between indole-tethered activated methylene compounds **1** and α,β-unsaturated aldehydes **2**

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To our knowledge, quite a few indoloquinolizidine alkaloids bear alkyl substituents at C-15 and an ethyl or ethylidenyl group at C-16 (Figure 1).[4] We envisioned that the tautomers obtained from our cascade reaction could be further transformed into compounds **6** with an ethylidenyl group at C-16 via a sequence of reduction, dehydration, and reduction (Scheme 2).[5] The fully functionalized compounds **6** might be very useful in the total synthesis of indoloquinolizidine alkaloids bearing an ethylidenyl group at C-16, if properly handled.

To test the feasibility of these transformations, pure compound **3a**, which was obtained from the cascade reaction between β-keto amide **1** and cinnamaldehyde (**2a**), was subjected to reduction and elimination (Scheme 3). Al-

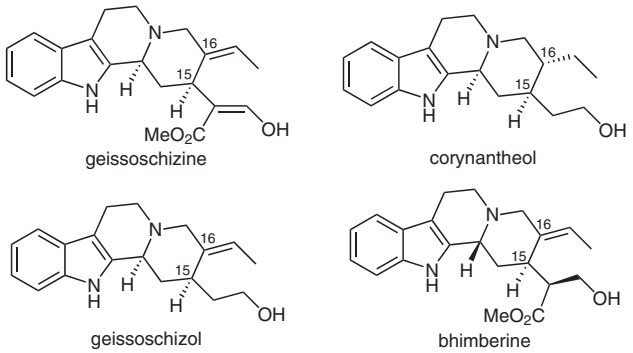
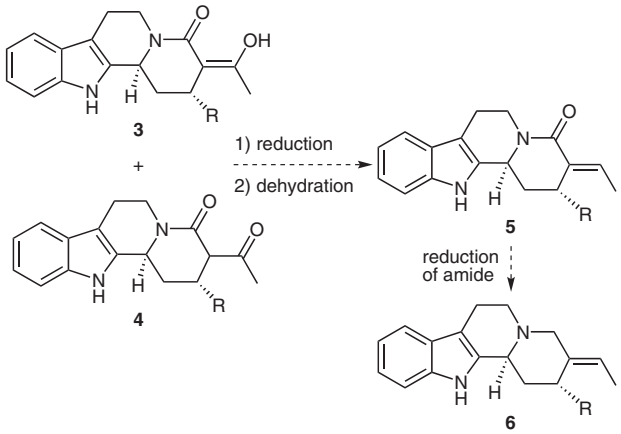
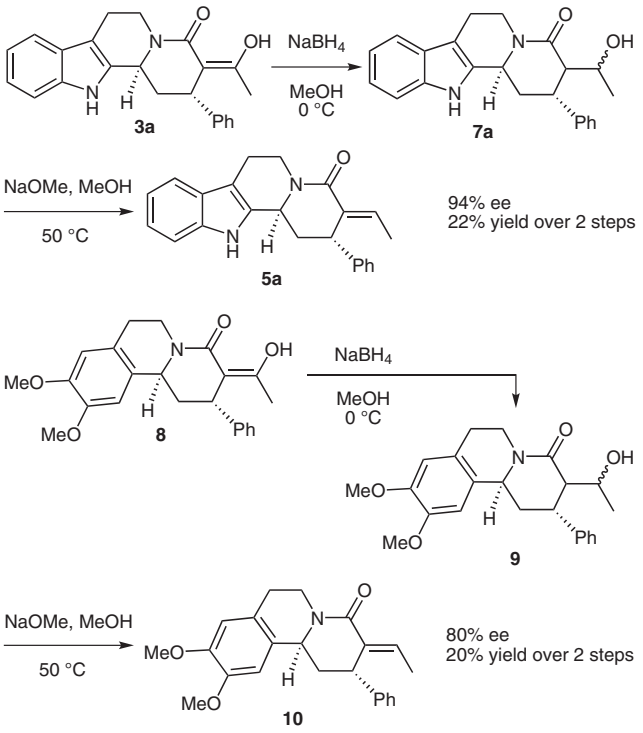



**Figure 1** Examples of indoloquinolizidine-based alkaloids with an ethyl or ethylidenyl group at C-16




**Scheme 2** Conceptual functional group transformations of tautomers **3** and **4** leading to ethylidenyl indoloquinolizidines

though a stable enol form of **3a** was observed by $^1$H NMR analysis, the presence of keto–enol equilibrium in the solution of **3a** in methanol was possible, and the keto tautomer was reduced to alcohol as expected when treated with $NaBH_4$. The mixture of diastereomers **7a** underwent elimination by following a protocol developed by Martin et al.[5h] affording the dehydrated product **5a** bearing an *E*-ethylidenyl group. The yield over three steps (cascade reaction, reduction, and elimination) was 22%. Using the same strategy, pure compound **8**, which was also obtained by the cascade reaction, was transformed into compound **10** in 20% yield.

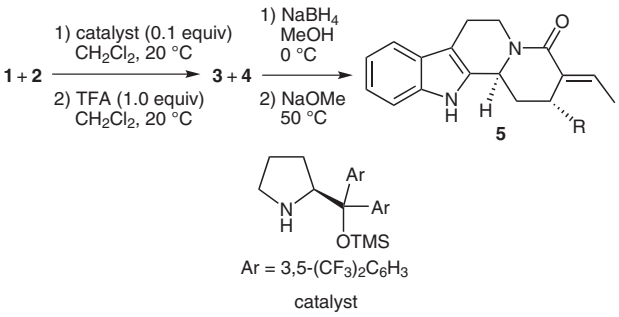



**Scheme 3** Reduction and elimination of compound **3a** and **8**

Next a selected set of aliphatic aldehydes **2b**–**g** was studied in the cascade reaction, followed by telescoped reduction and elimination steps to afford indoloquinolizidines **5b**–**g** with an *E*-ethylidenyl substituent at C-16 position.[6] As shown in Table 1, the enantioselectivity was quite dependent on the bulkiness of the R group in aldehydes **2**; better enantioselectivities were achieved when aldehydes with relatively bulkier groups were employed (Table 1, entries 4–7). The yields over three steps ranged from 20–26%, thus the average yield of each step was about 60%. It should also be noted that only one column chromatographic operation was required to afford the pure **5**.

In order to demonstrate the synthetic value of the present methodology, *epi*-geissoschizol was targeted for our synthetic attempt.[7] As illustrated in Scheme 4, our synthesis of *epi*-geissoschizol began with reduction of propargyl alcohol **11** with lithium aluminum hydride. The crude allylic alcohol thus obtained was directly subjected to oxidation by pyridine·$SO_3$–DMSO and the yield over two

**Table 1** Reduction of Keto–Enol Tautomers and Subsequent Elimination[a]

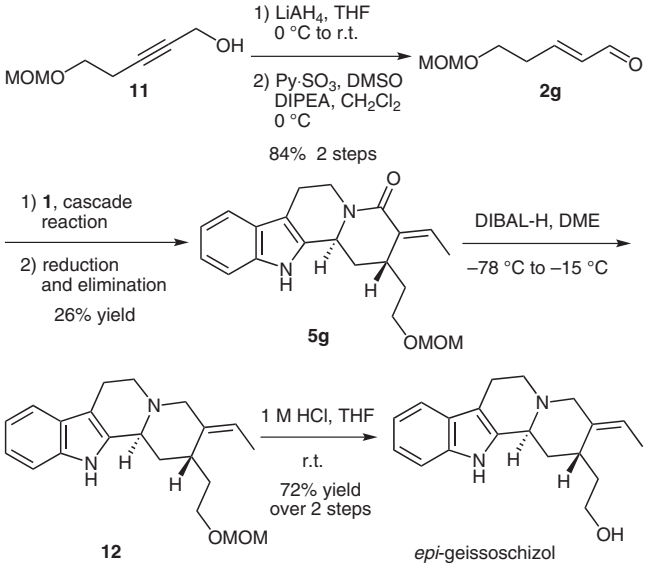



| Entry | 5 | Yield (%)[b] | ee (%)[c] |
|---|---|---|---|
| 1 | **5a**, R = Ph | 22 | 94 |
| 2 | **5b**, R = Me | 20 | 70 |
| 3 | **5c**, R = Et | 22 | 82 |
| 4 | **5d**, R = *n*-Pr | 22 | 98 |
| 5 | **5e**, R = $(CH_2)_4Me$ | 21 | 92 |
| 6 | **5f**, R = $(CH_2)_6Me$ | 23 | 94 |
| 7 | **5g**, R = $(CH_2)_2OMOM$ | 26 | 97 |

[a] Reaction conditions: see experimental part for details.
[b] Calculated over 3 steps.
[c] Determined by chiral HPLC analysis.

steps was 84%. A cascade reaction between **1** and **2g** under the promotion of the chiral amine catalyst and an acid additive provided a pair of keto–enol tautomers, which was subjected to telescoped reduction and dehydration steps to afford compound **5g** bearing geissoschizol's framework (Table 1, entry 7). With **5g** in hand, reduction of the lactam group became our focus. Borch's protocol[8] for selective reduction of the lactam functionality worked well in the synthesis of geissochizine by Martin et al.[5h] and the synthesis of racemic geissoschizol by Winterfeldt et al.[5a] However, in our case, when compound **5g** was treated with trimethyloxonium tetrafluoroborate and 2,6-di-*tert*-butylpyridine in dichloromethane followed by reduction with $NaBH_4$, no formation of the reduced product was observed and most of the starting material was recovered. To our delight, the lactam in **5g** was readily reduced by DIBAL-H at –15 °C in DME to afford compound **12**. Removal of MOM group by 1.0 M HCl in THF delivered *epi*-geissoschizol in 72% yield over two steps. Thus *epi*-geissochizol was obtained enantioselectively in only five steps and by two column chromatographic operations.

In summary, we have developed an operationally convenient asymmetric organocatalyzed cascade process for the preparation of indoloquinolizidines with aliphatic substituents at C-15 and *E*-ethylidenyl substituent at C-16. The highly functionalized products were obtained from readily available reagents by telescoping three steps in 20–26% yield with good to excellent enantioselectivities. Using **5g** as the starting material, *epi*-geissoschizol was obtained in




**Scheme 4** Synthesis of *epi*-geissoschizol

72% yield over two steps. The method reported herein would find more applications in the synthesis of indoloquinolizidine alkaloids.

TLC analyses were carried out on 0.25 mm silica gel plates visualized with UV light and/or by staining with ethanolic phosphomolybdic acid (PMA) or $I_2$. Flash column chromatography was performed on silica gel H (10–40 μ). NMR spectra were recorded on Bruker spectrometers (500 MHz or 400 MHz). Chemical shifts (δ) are given in ppm relative to TMS; coupling constants (*J*) in Hz. Optical rotations were taken on JASCO P1030. High-resolution mass spectra were recorded on Bruker ApeXIII 7.0 TESLA FTMS. Enantiomeric excesses were determined by chiral HPLC using a Waters or Shimadzu instrument.

**Telescoping Steps; 1,2,3,6,7,12b-Hexahydroindolo[2,3-*a*]quinolizin-4(12*H*)-ones 5; General Procedure**

To a mixture of prolinol catalyst (0.01 mmol, 0.1 equiv) and benzoic acid (0.01 mmol, 0.1 equiv) in $CH_2Cl_2$ (0.2 mL) was added β-keto amide **1** (0.1 mmol, 1 equiv) under an atmosphere of $N_2$, followed by the addition of α,β-unsaturated aldehyde **2** (0.15 mmol, 1.5 equiv). The reaction mixture was stirred at 20 °C and the progress of the reaction was followed by TLC (eluent: EtOAc; $R_f$ = 0.5). After full consumption of β-keto amide **1**, the mixture was diluted with $CH_2Cl_2$ (0.3 mL). Then, TFA (0.1 mmol, 1.0 equiv) was added and the mixture was stirred at 20 °C for 0.5 h. The mixture was diluted with $CH_2Cl_2$ (5 mL) and washed with sat. aq $NaHCO_3$ (3 mL). The aqueous phase was extracted with $CH_2Cl_2$ (2 × 5 mL). The combined organic phases were dried ($Na_2SO_4$) and concentrated in vacuo to afford a crude keto–enol mixture of **3** and **4**, which was used directly in the next step. The crude keto–enol mixture from cascade reaction was dissolved in MeOH (4 mL for 0.3 mmol **1**) and cooled in an ice-salt bath. Then $NaBH_4$ (4 equiv) was added in one portion. The reaction mixture was stirred at r.t. for 30 min and quenched by the addition of sat. aq $NaHCO_3$ (4 mL). The aqueous layer was extracted with $CH_2Cl_2$ (2 × 10 mL). The combined organic layers were dried ($Na_2SO_4$). After evaporation of the solvent and drying under high vacuo, the crude alcohol product was redissolved in anhyd MeOH (5 mL). NaOMe (10 equiv) was added in one portion. The mixture was heated at 50 °C for 24 h. After cooling to r.t., $H_2O$ (10 mL) was added, and the mixture was extracted with $CH_2Cl_2$ (3 × 10 mL). The combined organic phases were dried ($Na_2SO_4$) and concentrated in vacuo to afford the crude product, which was purified by flash silica gel chromatography to afford pure product **5**.

**(2*R*,12b*S*,*E*)-3-Ethylidene-2-phenyl-1,2,3,6,7,12b-hexahydroindolo[2,3-*a*]quinolizin-4(12*H*)-one (5a)**

HPLC [Phenomenex Chiralpak amylose-2, hexane–*i*-PrOH (4:1); flow rate = 1.00 mL/min, λ = 220 nm]: $t_R$ = 7.56 min (minor enantiomer), $t_R$ = 11.85 min (major enantiomer); $[\alpha]_D^{25}$ –121.9 (*c* 0.28, $CHCl_3$).

$^1$H NMR (500 MHz, $CDCl_3$): δ = 7.84 (s, 1 H), 7.49 (d, *J* = 7 Hz, 1 H), 7.31–7.37 (m, 3 H), 7.26–7.30 (m, 3 H), 7.13–7.17 (m, 1 H), 7.09–7.12 (m, 1 H), 5.23–5.27 (m, 1 H), 4.55–4.58 (m, 1 H), 4.30–4.31 (m, 1 H), 2.77–2.88 (m, 3 H), 2.59 (dt, *J* = 13, 3 Hz, 1 H), 2.20 (td, *J* = 13, 3.5 Hz, 1 H), 1.67 (d, *J* = 7 Hz, 3 H).

$^{13}$C NMR (125 MHz, $CDCl_3$): δ = 164.3, 141.5, 137.6, 136.4, 133.2, 130.6, 129.0, 127.6, 127.0, 127.0, 122.1, 119.8, 118.4, 111.0, 110.1, 49.5, 40.6, 37.8, 36.5, 21.3, 14.0.

HRMS (ESI): *m*/*z* calcd for $(C_{23}H_{23}N_2O)^+$: 343.1805; found: 343.1815.

**(2*R*,12b*S*,*E*)-3-Ethylidene-2-methyl-1,2,3,6,7,12b-hexahydroindolo[2,3-*a*]quinolizin-4(12*H*)-one (5b)**

HPLC [Daicel Chiralpak ADH, hexane–*i*-PrOH (4:1); flow rate = 0.65 mL/min, λ = 220 nm]: $t_R$ = 11.40 min (minor enantiomer), $t_R$ = 15.40 min (major enantiomer); $[\alpha]_D^{25}$ –129.0 (*c* 0.42, $CHCl_3$).

$^1$H NMR (500 MHz, $CDCl_3$): δ = 8.58 (s, 1 H), 7.51 (d, *J* = 8 Hz, 1 H), 7.33 (d, *J* = 8 Hz, 1 H), 7.17 (t, *J* = 8 Hz, 1 H), 7.12 (t, *J* = 8 Hz, 1 H), 7.03 (q, *J* = 7 Hz, 1 H), 5.20–5.27 (m, 1 H), 5.01–5.05 (m, 1 H), 3.14–3.17 (m, 1 H), 2.79–2.98 (m, 3 H), 2.36–2.40 (m, 1 H), 1.92 (td, *J* = 12, 4 Hz, 1 H), 1.80 (d, *J* = 7 Hz, 3 H), 1.23 (d, *J* = 7 Hz, 3 H).

$^{13}$C NMR (125 MHz, $CDCl_3$): δ = 164.0, 136.5, 134.1, 133.9, 133.7, 127.0, 122.0, 119.7, 118.4, 111.1, 109.6, 49.6, 40.8, 34.7, 26.7, 21.3, 18.3, 13.5.

HRMS (ESI): *m*/*z* calcd for $(C_{18}H_{21}N_2O)^+$: 281.1648; found: 281.1658.

**(2*R*,12b*S*,*E*)-3-Ethylidene-2-ethyl-1,2,3,6,7,12b-hexahydroindolo[2,3-*a*]quinolizin-4(12*H*)-one (5c)**

HPLC [Phenomenex Chiralpak amylose-2, hexane–*i*-PrOH (4:1); flow rate = 1.00 mL/min, λ = 220 nm]: $t_R$ = 7.85 min (minor enantiomer), $t_R$ = 11.65 min (major enantiomer); $[\alpha]_D^{25}$ –5.9 (*c* 0.37, $CHCl_3$).

$^1$H NMR (500 MHz, $CDCl_3$): δ = 8.17 (s, 1 H), 7.50 (d, *J* = 8 Hz, 1 H), 7.32 (d, *J* = 8 Hz, 1 H), 7.17 (t, *J* = 8 Hz, 1 H), 7.12 (t, *J* = 8 Hz, 1 H), 7.02 (q, *J* = 7.5 Hz, 1 H), 5.19–5.25 (m, 1 H), 4.94 (dd, *J* = 13, 4.5 Hz, 1 H), 2.84–2.94 (m, 3 H), 2.76–2.82 (m, 1 H), 2.48–2.52 (m, 1 H), 1.87 (td, *J* = 13, 3.5 Hz, 1 H), 1.78 (d, *J* = 7.5 Hz, 3 H), 1.55–1.66 (m, 2 H), 1.02 (t, *J* = 7.5 Hz, 3 H).

$^{13}$C NMR (125 MHz, $CDCl_3$): δ = 164.1, 136.4, 134.3, 133.8, 133.2, 127.0, 122.1, 119.8, 118.5, 111.0, 110.0, 49.8, 40.8, 33.6, 32.2, 25.5, 21.3, 14.0, 12.2.

HRMS (ESI): *m*/*z* calcd for $(C_{19}H_{23}N_2O)^+$: 295.1805; found: 295.1816.

**(2*R*,12b*S*,*E*)-3-Ethylidene-2-propyl-1,2,3,6,7,12b-hexahydroindolo[2,3-*a*]quinolizin-4(12*H*)-one (5d)**

HPLC [Phenomenex Chiralpak amylose-2, hexane–*i*-PrOH (4:1); flow rate = 1.00 mL/min, λ = 220 nm]: $t_R$ = 7.17 min (minor enantiomer), $t_R$ = 11.80 min (major enantiomer); $[\alpha]_D^{25}$ –9.1 (*c* 0.57, $CHCl_3$).

$^1$H NMR (500 MHz, $CDCl_3$): δ = 8.56 (s, 1 H), 7.50 (d, *J* = 8 Hz, 1 H), 7.33 (d, *J* = 8 Hz, 1 H), 7.10–7.18 (m, 2 H), 7.01 (q, *J* = 7 Hz, 1 H), 5.23–5.26 (m, 1 H), 4.97 (dd, *J* = 12, 4 Hz, 1 H), 2.78–2.98 (m, 4 H), 2.52 (dt, *J* = 12, 4 Hz, 1 H), 1.86–1.89 (m, 1 H), 1.77 (d, *J* = 7 Hz, 3 H), 1.36–1.62 (m, 4 H), 0.97 (t, *J* = 7 Hz, 3 H).

$^{13}$C NMR (125 MHz, $CDCl_3$): δ = 164.2, 136.5, 134.0, 133.9, 133.4, 127.0, 122.0, 119.7, 118.4, 111.1, 109.5, 50.0, 40.9, 34.8, 32.4, 31.6, 21.3, 20.7, 14.3, 13.9.

HRMS (ESI): *m*/*z* calcd for $(C_{20}H_{25}N_2O)^+$: 309.1961; found: 309.1973.

**(2*R*,12b*S*,*E*)-3-Ethylidene-2-pentyl-1,2,3,6,7,12b-hexahydroindolo[2,3-*a*]quinolizin-4(12*H*)-one (5e)**

HPLC [Daicel Chiralpak AS-H, hexane–*i*-PrOH (4:1); flow rate = 0.70 mL/min, λ = 220 nm]: $t_R$ = 8.5 min (major enantiomer), $t_R$ = 16.1 min (minor enantiomer); $[\alpha]_D^{25}$ –111.6 (*c* 0.45, $CHCl_3$).

$^1$H NMR (400 MHz, $CDCl_3$): δ = 7.86 (s, 1 H), 7.50 (d, *J* = 7 Hz, 1 H), 7.32 (d, *J* = 7 Hz, 1 H), 7.17 (t, *J* = 7 Hz, 1 H), 7.11 (t, *J* = 7 Hz, 1 H), 6.99 (q, *J* = 7.2 Hz, 1 H), 5.16–5.27 (m, 1 H), 4.91–4.98 (m, 1 H), 2.73–3.00 (m, 4 H), 2.43 (dt, *J* = 12.6, 4 Hz, 1 H), 1.87 (td, *J* = 12.6, 4 Hz, 1 H), 1.78 (d, *J* = 7.2 Hz, 3 H), 1.32–1.62 (m, 8 H), 0.91 (t, *J* = 7 Hz, 3 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 164.1, 136.5, 134.0, 133.8, 133.6, 127.2, 122.2, 120.0, 118.6, 111.0, 110.1, 49.9, 40.8, 32.5, 32.0, 31.9, 29.8, 27.3, 22.8, 21.3, 20.7, 14.2, 13.9.

HRMS (ESI): *m*/*z* calcd for $(C_{22}H_{29}N_2O)^+$: 337.2274; found: 337.2279.

**(2*R*,12b*S*,*E*)-3-Ethylidene-2-heptyl-1,2,3,6,7,12b-hexahydroindolo[2,3-*a*]quinolizin-4(12*H*)-one (5f)**

HPLC [Daicel Chiralpak AS-H, hexane–*i*-PrOH (4:1); flow rate = 0.70 mL/min, λ = 220 nm]: $t_R$ = 8.04 min (major enantiomer), $t_R$ = 13.6 min (minor enantiomer); $[\alpha]_D^{25}$ –112.9 (*c* 0.3, $CHCl_3$).

$^1$H NMR (400 MHz, $CDCl_3$): δ = 7.85 (s, 1 H), 7.50 (d, *J* = 8 Hz, 1 H), 7.32 (d, *J* = 8 Hz, 1 H), 7.17 (t, *J* = 8 Hz, 1 H), 7.12 (t, *J* = 8 Hz, 1 H), 6.99 (q, *J* = 7.2 Hz, 1 H), 5.17–5.27 (m, 1 H), 4.91–4.98 (m, 1 H), 2.71–3.01 (m, 4 H), 2.43 (dt, *J* = 12.8, 3.2 Hz, 1 H), 1.87 (td, *J* = 12.4, 4 Hz, 1 H), 1.78 (d, *J* = 7.2 Hz, 3 H), 1.32–1.62 (m, 12 H), 0.91 (t, *J* = 6.8 Hz, 3 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 164.1, 136.5, 134.0, 133.8, 133.6, 127.2, 122.2, 120.0, 118.5, 111.0, 110.1, 49.8, 40.8, 32.6, 32.5, 32.0, 31.9, 29.8, 29.5, 27.7, 22.8, 21.3, 14.2, 13.9.

HRMS (ESI): *m*/*z* calcd for $(C_{24}H_{33}N_2O)^+$: 365.2587; found: 337.2596.

**(2*S*,12b*S*,*E*)-3-Ethylidene-2-[2-(methoxymethoxy)ethyl]-1,2,3,6,7,12b-hexahydroindolo[2,3-*a*]quinolizin-4(12*H*)-one (5g)**

HPLC [Daicel Chiralpak AS-H, hexane–*i*-PrOH (3:1); flow rate = 0.60 mL/min, λ = 220 nm]: $t_R$ = 17.3 min (major enantiomer), $t_R$ = 47.0 min (minor enantiomer); $[\alpha]_D^{25}$ –114.1 (*c* 1.0, MeOH).

$^1$H NMR (400 MHz, $CDCl_3$): δ = 8.48 (s, 1 H), 7.40 (d, *J* = 8.0 Hz 1 H), 7.21 (d, *J* = 8.0 Hz, 1 H), 6.99–7.00 (m, 2 H), 6.95 (q, *J* = 7.2 Hz, 1 H), 5.13 (d, *J* = 9.6 Hz, 1 H), 4.90 (d, *J* = 11.2 Hz, 1 H), 4.56 (s, 1 H), 3.54–3.61 (m, 1 H), 3.42–3.50 (m, 1 H), 3.31 (s, 3 H), 3.04–3.14 (m, 1 H), 2.66–2.99 (m, 3 H), 2.47 (dt, *J* = 12.8, 1.6 Hz, 1 H), 1.80–1.88 (m, 2 H), 1.71 (d, *J* = 7.2 Hz, 3 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 163.9, 136.4, 134.6, 133.7, 132.8, 126.9, 122.0, 119.7, 118.3, 111.0, 109.5, 96.8, 65.5, 55.5, 49.9, 40.8, 32.5, 32.3, 28.8, 21.2, 13.7.

HRMS (ESI): *m*/*z* calcd for $(C_{21}H_{26}N_2O_3 + Na)^+$: 377.1943; found: 377.1996.

**(2*S*,11b*S*,*E*)-3-Ethylidene-9,10-dimethoxy-2-phenyl-2,3,6,7-tetrahydro-1*H*-pyrido[2,1-*a*]isoquinolin-4(11b*H*)-one (10)**

HPLC [Phenomenex Chiralpak amylose-2, hexane–*i*-PrOH (4:1); flow rate = 1.00 mL/min, λ = 220 nm]: $t_R$ = 17.34 min (minor enantiomer), $t_R$ = 22.23 min (major enantiomer); $[\alpha]_D^{25}$ –19.1 (*c* 0.37, $CHCl_3$).

$^1$H NMR (500 MHz, $CDCl_3$): δ = 7.33–7.37 (m, 2 H), 7.24–7.30 (m, 4 H), 6.60 (s, 1 H), 6.43 (s, 1 H), 4.96 (dt, *J* = 11, 3 Hz, 1 H), 4.39 (dd, *J* = 11.5, 3 Hz, 1 H), 4.24–4.26 (m, 1 H), 3.84 (s, 3 H), 3.81 (s, 3 H), 2.78–2.93 (m, 2 H), 2.58–2.64 (m, 2 H), 2.06–2.10 (m, 1 H), 1.66 (d, *J* = 7 Hz, 3 H).

$^{13}$C NMR (125 MHz, $CDCl_3$): δ = 164.2, 147.8, 147.7, 141.8, 136.8, 130.8, 128.9, 128.9, 127.9, 127.6, 126.8, 111.6, 108.5, 56.3, 56.0, 51.8, 40.2, 38.5, 38.1, 28.9, 13.9.

HRMS (ESI): *m*/*z* calcd for $(C_{23}H_{26}NO_3)^+$: 364.1907; found: 364.1919.

**(*E*)-5-(Methoxymethoxy)pent-2-enal (2g)**

To a stirred solution of $LiAlH_4$ (102 mg, 3 mmol) in THF (5mL) was added a solution of **11**[9] (288 mg, 2 mmol) in THF (2 mL) dropwise at 0 °C. The reaction mixture was allowed to stir at r.t. for 6 h and the progress of the reaction was followed by TLC (eluent: PE–EtOAc, 1:1; $R_f$ = 0.65). The mixture was quenched with $H_2O$ (0.1 mL) and 2.5 M aq NaOH (0.1 mL), and diluted with EtOAc (20 mL). $Al(OH)_3$ was removed by filtration. The organic layer was concentrated to afford the crude allylic alcohol, which was used directly in the next step. To a solution of crude allylic alcohol in $CH_2Cl_2$ was added DIPEA (1.5 mL) and DMSO (1.5 mL) at 0 °C. Pyridine·$SO_3$ complex (1.6 g, 8 mmol) was added in portions. The reaction mixture was stirred at 0 °C for 30 min, then quenched with $H_2O$ (10 mL), and diluted with $Et_2O$ (15 mL). The organic layer was washed with $H_2O$ (15 mL) and brine (15 mL), and dried ($Na_2SO_4$). The crude product obtained after concentrating under reduced pressure was purified by flash silica gel chromatography to provide aldehyde **2g** as a colorless oil; yield: 240 mg (84%).

$^1$H NMR (400 MHz, $CDCl_3$): δ = 9.51 (d, *J* = 7.8 Hz, 1 H), 6.88 (dt, *J* = 15.6, 6.2 Hz, 1 H), 6.19 (dd, *J* = 15.6, 7.8 Hz, 1 H), 4.63 (s, 2 H), 3.70 (t, *J* = 12.3 Hz, 2 H), 3.36 (s, 3 H), 2.62–2.65 (m, 2 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 193.8, 154.9, 134.3, 96.5, 65.5, 55.3, 33.0.

HRMS (ESI): *m*/*z* calcd for $(C_7H_{12}O_3 + Na)^+$ 167.0606; found: 167.0623.

***epi*-Geissoschizol**

To a solution of compound **5g** (180 mg, 0.51 mmol) in DME (5 mL) was added DIBAL-H (1 M in toluene) dropwise at –70 °C and the reaction mixture was allowed to stir at –15 °C for 4 h (TLC monitoring, eluent: PE–EtOAc, 2:1; $R_f$ = 0.45). After quenching with aq NaOH (2 M, 1 mL), the reaction mixture was diluted with $CHCl_3$ (20 mL) and $H_2O$ (10 mL). The combined organic layers were washed with $H_2O$ (15 mL) and brine (20 mL), dried ($Na_2SO_4$), and concentrated in vacuo to afford crude **12**. The O-MOM ether derivative **12** formed was dissolved in THF (5 mL), and aq HCl (1 M, 5 mL) was added via a syringe. The mixture was stirred at r.t. overnight. $Et_3N$ (1 mL) was added and the mixture was diluted with $CHCl_3$ (25 mL). The organic layer was separated and washed sequentially with $H_2O$ (10 mL) and brine (15 mL). After drying ($Na_2SO_4$), and concentration under reduced pressure, the residue was purified by flash chromatography on silica gel eluting with 30:1 $CH_2Cl_2$–MeOH to afford 112 mg (72%) of *epi*-geissochizol as a white solid; mp 151–153 °C; $[\alpha]_D^{25}$ –29.4 (*c* 1.0, MeOH).

$^1$H NMR (400 MHz, $CD_3OD$): δ = 7.40 (d, *J* = 8.0 Hz, 1 H), 7.32 (d, *J* = 8.0 Hz, 1 H), 7.08 (t, *J* = 8.0 Hz, 1 H), 7.00 (t, *J* = 8.0 Hz, 1 H), 5.56 (q, *J* = 7.2 Hz, 1 H), 3.83 (d, *J* = 12.0 Hz, 1 H), 3.60–3.72 (m, 2 H), 3.10–3.40 (m, 5 H), 2.95–3.06 (m, 1 H), 2.70–2.80 (m, 2 H), 2.47 (d, *J* = 12.8 Hz, 1 H), 1.75–1.95 (m, 3 H), 1.71 (d, *J* = 7.2 Hz, 3 H).

$^{13}$C NMR (100 MHz, $CD_3OD$): δ = 136.8, 135.6, 133.6, 126.9, 121.9, 120.8, 118.5, 117.3, 110.6, 106.6, 59.5, 59.2, 55.5, 52.1, 34.5, 33.5, 30.1, 29.4, 20.6, 11.6.

HRMS (ESI): *m*/*z* calcd for $(C_{19}H_{25}N_2O)^+$: 297.1892; found: 297.1903.

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

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