Total Synthesis and Structural Revision of Incargutines A and B

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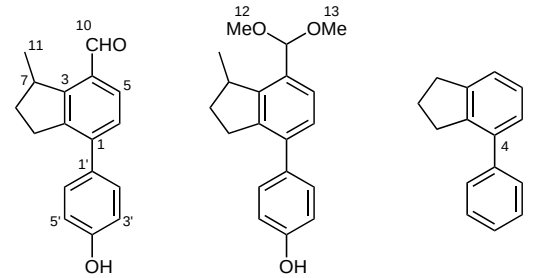
Abstract: We achieved the first total synthesis of (±)-incargutines A and B, which were isolated from the roots of *Incarvillea arguta*, utilizing $In(OTf)_3$-catalyzed enolization of cyclohexenone derivatives subsequent to an intramolecular Alder–Rickert reaction. At first, we synthesized the proposed structures of incargutines A and B. The spectral data of the synthetic proposed compounds did not correspond to those of the natural products. Then, we synthesized the methyl regioisomers of the proposed structures. Spectral data of these synthetic compounds were identical to those of natural incargutines A and B. Therefore, the structures of incargutines A and B were clearly established to be the methyl regioisomers.

Key words: total synthesis, incargutine, enols, Alder–Rickert reaction, indium

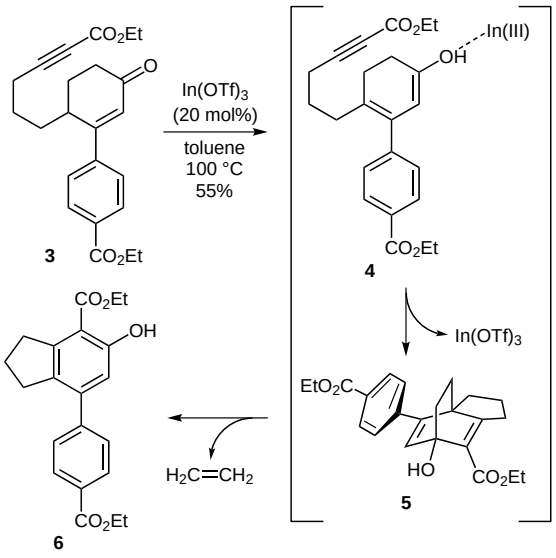
Incargutines A and B were isolated as novel biphenyl natural products from the roots of *Incarvillea arguta* in 2009.[1] The proposed structures, except for the absolute configuration of C-7, were elucidated to be **1** and **2** by 1D and 2D NMR spectroscopy and mass spectrometry (Figure 1). Biphenyl natural products possessing a 4-phenylindane moiety have rarely been isolated.[1–3] The biosynthesis of incargutines has attracted attention given their unique structures.[4] It was revealed that incargutines possess moderate cytotoxicity against tumor cell lines, where incargutine A in particular demonstrated equivalent cytotoxicity against LOVO cells (IC_{50} 0.47 μg/mL) as observed with doxorubicin.[1]



incargutine A (**1**) incargutine B (**2**) 4-phenylindane

Figure 1 Proposed structures of incargutines A, B and structure of 4-phenylindane

The authors have recently demonstrated a one-pot synthesis of phenol derivatives from cyclohexenone derivatives by a Lewis acid catalyzed enolization and subsequent intramolecular Alder–Rickert reaction.[5,6] For example, the reaction of cyclohexenone **3** in the presence of 20 mol% of $In(OTf)_3$ gave 4-phenylindane derivative **6** in 55% yield (Scheme 1).[6] The reaction pathway is estimated to involve the $In(OTf)_3$-catalyzed enolization of **3** to generate dienol intermediate **4** in situ, followed by an intramolecular Alder–Rickert reaction via diene **5** with extrusion of ethylene gas. By utilizing this cascade reaction, the authors anticipated that the synthesis of (±)-incargutines A and B could be achieved.



Scheme 1 $In(OTf)_3$-catalyzed one-pot synthesis of 4-phenylindane derivative **6**

Our retrosynthetic plan is indicated in Scheme 2. (±)-Incargutines A (**1**) and B (**2**) would be synthesized from phenylindane **A** by conversion of the ethoxycarbonyl group at C-4 into a formyl group, conversion of the alkoxycarbonyl group into a hydroxy group at C-4′, and deoxygenation of the phenolic hydroxy group at C-5. Phenylindane **A** would be obtained by utilizing the aforementioned $In(OTf)_3$-catalyzed one-pot synthesis of the 4-phenylindane derivative from cyclohexenone **B** as a key step. Cyclohexenone **B** would be obtained by the arylation of cyclohexenone **C**. Cyclohexenone **C** would be provided by alkylation of cyclohexenone **D** with alkyl iodide **E**.

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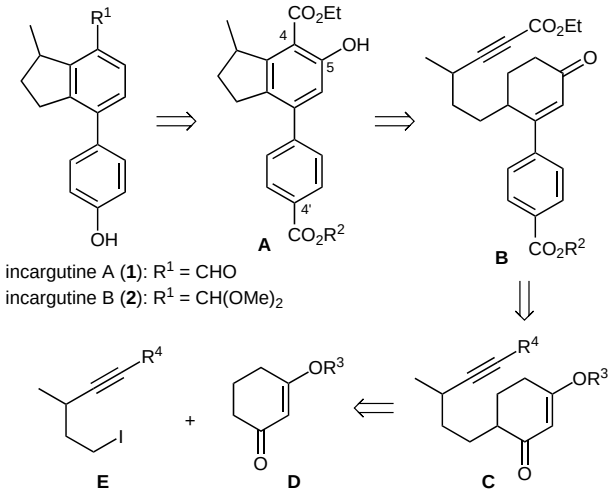
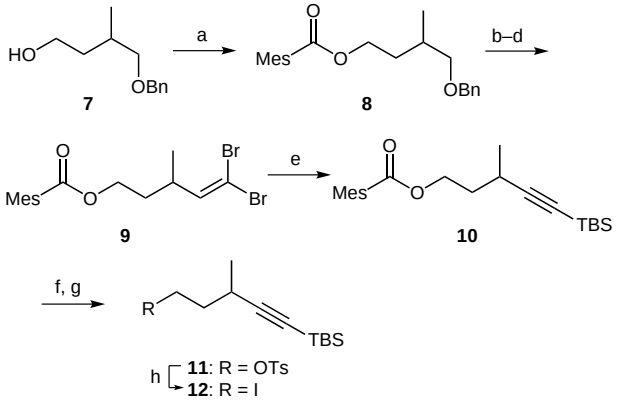


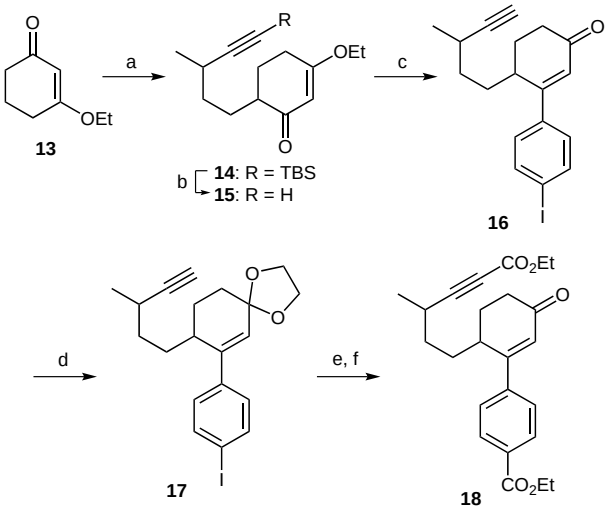
Scheme 2 Retrosynthetic analysis of incargutines A and B

Iodide **12** corresponding to **E** in the synthetic plan was prepared from known alcohol **7**[7] (Scheme 3). The primary hydroxy group of alcohol **7** was protected in the form of a mesitoate ester by treatment with 2,4,6-$Me_3C_6H_2COCl$, Et_3N, and DMAP to give **8** in 77% yield. The benzyl ether **8** was subjected to hydrogenolysis in the presence of 10% Pd/C. Swern oxidation of the primary alcohol, and Corey–Fuchs dibromoolefination of the resulting aldehyde afforded dibromoolefin **9** in 93% yield (3 steps). Treatment of dibromoolefin **9** with *n*-BuLi and then TBSCl gave alkyne **10** in 91% yield. Deprotection of the mesitoyl group in **10** using LAH and tosylation of the primary alcohol by treatment with TsCl, Et_3N, and DMAP afforded tosylate **11** in 84% (2 steps). Iodide **12** was prepared by treatment of tosylate **11** with NaI in 91% yield.



Scheme 3 *Reagents and conditions*: (a) 2,4,6-$Me_3C_6H_2COCl$, Et_3N, DMAP, CH_2Cl_2, r.t., 77%; (b) H_2, 10% Pd/C, MeOH, 40 °C; (c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –78 °C to 0 °C; (d) CBr_4, Ph_3P, pyridine, CH_2Cl_2, r.t., 93% (3 steps); (e) *n*-BuLi, TBSCl, THF, –78 °C to r.t., 91%; (f) LAH, THF, r.t.; (g) TsCl, Et_3N, DMAP, CH_2Cl_2, r.t., 84% (2 steps); (h) NaI, acetone, reflux, 91%.

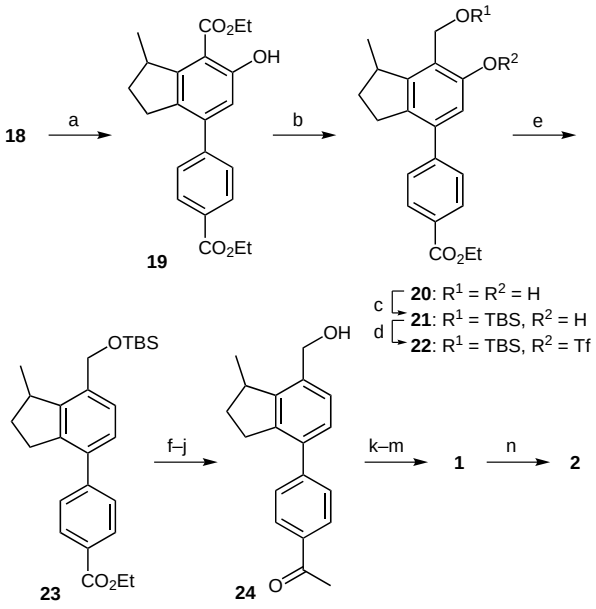
Cyclohexenone **18** corresponding to **B** in the synthetic plan was prepared from commercially available 3-ethoxycyclohex-2-enone (**13**, Scheme 4). Cyclohexenone **13** was treated with LDA and then iodide **12** in the presence of HMPA to afford 6-alkylcyclohexenone **14** in 74% yield. The TBS group in **14** was deprotected using TBAF to give enone **15** in 99% yield. Enone **15** was converted into iodide **16** in 87% yield by treatment with 4-iodophenylmagnesium chloride[8] in situ prepared from 1,4-diiodobenzene with *i*-PrMgCl, followed by workup with 10% HCl. Protection of the ketone in **16** with 1,2-bis(trimethylsilyloxy)ethane and TMSOTf[9] gave acetal **17** in 75% yield. Acetal **17** was treated with *i*-PrMgCl to generate the alkynyl and aryl dianion intermediate, followed by treatment with $ClCO_2Et$ to give the diester. The acetal moiety was hydrolyzed with $TsOH{\cdot}H_2O$ in acetone and water to give cyclohexenone **18** in 54% yield (2 steps). Cyclohexenone **18** is a substrate of the $In(OTf)_3$-catalyzed one-pot synthesis of the 4-phenylindane derivative. The compounds **14**–**18** were diastereomeric mixtures, their diastereomeric ratio and stereochemistry could not be determined.



Scheme 4 *Reagents and conditions*: (a) LDA, then **12**, HMPA, THF, –78 °C to r.t., 74%; (b) TBAF, THF, 30 °C, 99%; (c) 1,4-diiodobenzene, *i*-PrMgCl, THF, r.t. then 10% HCl aq, 87%; (d) 1,2-bis(trimethylsilyloxy)ethane, TMSOTf, CH_2Cl_2, –70 °C, 75%; (e) *i*-PrMgCl, then $ClCO_2Et$, THF, 40 °C; (f) $TsOH{\cdot}H_2O$, H_2O, acetone, r.t., 54% (2 steps).

Examination of the $In(OTf)_3$-catalyzed one-pot synthesis of 4-arylindane **19** from cyclohexene **18** was performed (Scheme 5). Treatment of **18** with 20 mol% of $In(OTf)_3$ in xylene at 130 °C for five hours afforded 4-arylindane **19** in 56% yield.[6] Investigation of the proposed structures of incargutines A and B from 4-arylindane **19** was performed. The regioselective reduction of 4-arylindane **19** with $BH_3{\cdot}SMe_2$ afforded diol **20** in 84% yield. Following protection of the primary hydroxy group in **20** with TBSCl and Et_3N (89%), the phenolic hydroxy group in **21** was converted into the triflate with Tf_2O and Et_3N to give triflate **22** in 80% yield. The Pd(0)-catalyzed hydrogenolysis[10] of triflate **22** with formic acid afforded ethyl ester **23** in 79% yield. Reduction of ester **23** with $LiBH_4$ gave a primary alcohol, which was oxidized with Dess–Martin periodinane to give the aldehyde. The alde-

hyde was treated with MeMgBr to afford the secondary alcohol, which was oxidized with Dess–Martin periodinane to give the ketone. Deprotection of the TBS group with TBAF afforded alcohol **24** in 84% yield (5 steps). The Baeyer–Villiger reaction of methyl ketone **24** with MCPBA and $Sc(OTf)_3$[11] gave the acetate, and Dess–Martin oxidation of the primary alcohol to give the aldehyde followed by hydrolysis of the acetyl group with 10% HCl afforded the proposed structure of incargutine A (**1**) in 41% yield (3 steps). The proposed structure of incargutine B (**2**) was synthesized by treatment of **1** with $CH(OMe)_3$ and Amberlyst-15[12] in 82% yield.



Scheme 5 *Reagents and conditions*: (a) $In(OTf)_3$ (20 mol%), xylene, 130 °C, 56%; (b) $BH_3{\cdot}SMe_2$, THF, r.t., 84%; (c) TBSCl, Et_3N, CH_2Cl_2, r.t., 89%; (d) Tf_2O, Et_3N, CH_2Cl_2, r.t., 80%; (e) $Pd(OAc)_2$, Ph_3P, HCO_2H, Et_3N, DMF, 60 °C, 79%; (f) $LiBH_4$, THF, 50 °C; (g) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, r.t.; (h) MeMgBr, THF, r.t.; (i) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, r.t.; (j) TBAF, THF, r.t., 84% (5 steps); (k) MCPBA, $Sc(OTf)_3$, CH_2Cl_2, r.t.; (l) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, r.t.; (m) 10% HCl aq, THF, r.t., 41% (3 steps); (n) $CH(OMe)_3$, Amberlyst-15, MeCN, r.t., 82%.

The spectral data of synthetic compounds **1** and **2** were not identical with those of natural incargutines A and B, respectively. In the ^1H NMR spectra, the chemical shift at H-11 of the synthetic compounds was observed markedly downfield compared with that of the natural products (Table 1). Thus, discrepancies in the spectroscopic data of synthetic and natural incargutines A and B led to the conclusion that the proposed structures of the natural compounds were incorrect.

The actual structures of incargutines A and B may be concluded to be **25** and **26**, respectively, on the basis of a comparison of the ^1H NMR data (Figure 2). The synthesis

Table 1 Comparison of ^1H NMR Data for Natural Incargutines A, B and **1**, **2** at H-11[a]

Position	**1**	Incargutine A	**2**	Incargutine B
H-11	1.29	0.80	1.26	0.80

[a] 400 MHz, $CDCl_3$, δ (ppm).

of **25** and **26** was subsequently performed according to a scheme similar to that employed for the synthesis of compounds **1** and **2**.

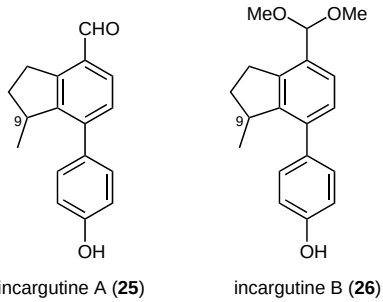
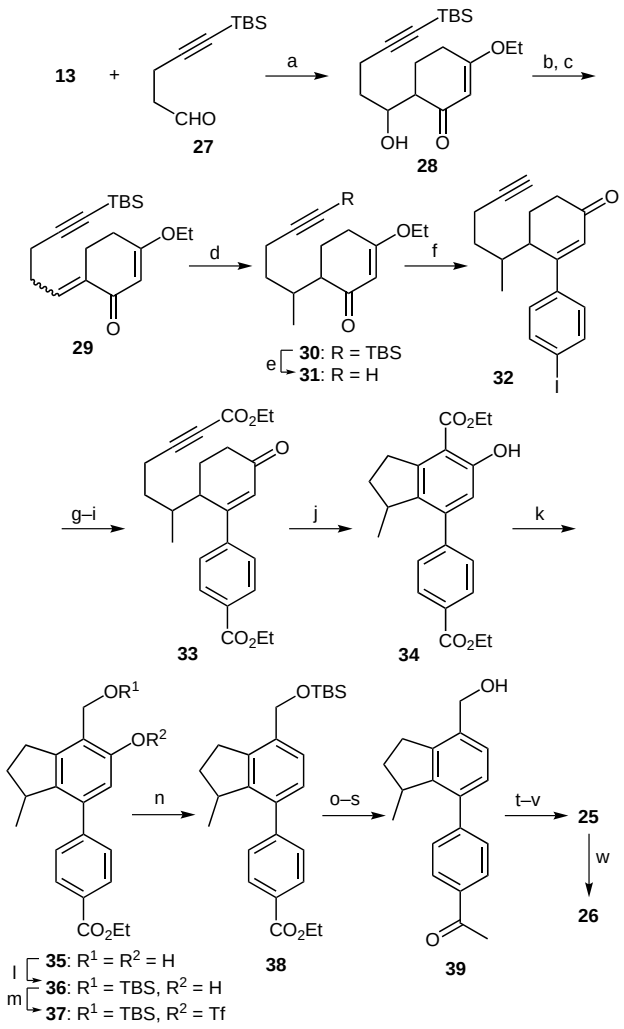


Figure 2 Revised structures of incargutines A and B

Cyclohexenone **13** was treated with LDA and then known aldehyde **27**[13] in the presence of DMPU to afford alcohol **28** in 74% yield (Scheme 6). Alcohol **28** was converted into the mesylate followed by treatment with DBU to afford α,β-unsaturated enone **29** as a sole product in 72% yield (2 steps). The stereochemistry of **29** was not determined. α,β-Unsaturated enone **29** was treated with MeMgBr in the presence of CuI and DMPU to give methylated enone **30** as a mixture of two diastereomers (2.2:1) in 91% yield. The TBS group in **30** were deprotected using TBAF to give enone **31** in 91% yield. Enone **31** was converted into cyclohexenone **33**, a substrate of the $In(OTf)_3$-catalyzed one-pot synthesis of a 4-phenylindane derivative, according to our developed synthetic method. $In(OTf)_3$-catalyzed enolization and subsequent intramolecular Alder–Rickert reaction was carried out by treatment of enone **33** with 20 mol% of $In(OTf)_3$ in xylene at 130 °C to afford 4-arylindane **34** in 52% yield. Incidentally, the compounds **30**–**33** were used as diastereomeric mixtures in Scheme 6, their diastereomeric ratio besides compound **30** and stereochemistry was not determined. Synthesis of compounds **25**[14] and **26**[15] from 4-arylindane **34** was subsequently performed according to the developed synthetic method of compounds **1** and **2**. Spectral data of synthetic compounds **25** and **26** were identical to those of natural incargutines A and B, respectively. Therefore, the structures of incargutines A and B have clearly been determined to be those presented as **25** and **26**, respectively.



Scheme 6 *Reagents and conditions*: (a) LDA, then **27**, DMPU, THF, –78 °C, 74%; (b) MsCl, Et_3N, CH_2Cl_2, 0 °C; (c) DBU, toluene, 60 °C, 72% (2 steps); (d) MeMgBr, CuI, DMPU, THF, 0 °C, 91%; (e) TBAF, THF, 30 °C, 91%; (f) 1,4-diiodobenzene, *i*-PrMgCl, 1,4-dioxane, 80 °C then 10% HCl aq, 77%; (g) 1,2-bis(trimethylsilyloxy)ethane, TMSOTf, CH_2Cl_2, –70 °C; (h) *i*-PrMgCl, then $ClCO_2Et$, THF, 40 °C; (i) $TsOH·H_2O$, H_2O, acetone, r.t., 42% (3 steps); (j) $In(OTf)_3$ (20 mol%), xylene, 130 °C, 52%; (k) $BH_3·SMe_2$, THF, r.t., 96%; (l) TBSCl, Et_3N, CH_2Cl_2, r.t., 97%; (m) Tf_2O, pyridine, CH_2Cl_2, r.t., 95%; (n) $Pd(OAc)_2$, Ph_3P, HCO_2H, Et_3N, DMF, 60 °C, 83%; (o) $LiBH_4$, THF, 50 °C; (p) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, r.t.; (q) MeMgBr, THF, r.t.; (r) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, r.t.; (s) TBAF, THF, r.t., 73% (5 steps); (t) MCPBA, $Sc(OTf)_3$, CH_2Cl_2, r.t.; (u) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, r.t.; (v) 10% HCl aq, THF, r.t., 40% (3 steps); (w) $CH(OMe)_3$, Amberlyst-15, MeCN, r.t., 93%.

In conclusion, the authors achieved the first total synthesis of (±)-incargutines A and B using our developed $In(OTf)_3$-catalyzed one-pot synthesis of a 4-phenylindane derivative. Our findings reveal that the actual structures of incargutines A and B are **25** and **26**, respectively, which represent the methyl regioisomers of **1** and **2**, respectively.

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

References and Notes

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(14) **Experimental Procedure and Analytical Data of (±)-Incargutine A (25)**
To a solution of alcohol **39** (85.5 mg, 0.305 mmol) in CH_2Cl_2 (5.0 mL) were added MCPBA (65%, 306 mg, 2.75 mmol) and $Sc(OTf)_3$ (75.1 mg, 0.153 mmol) at 0 °C under Ar atmosphere, and the mixture was stirred at r.t. for 96 h. The reaction mixture was extracted with CH_2Cl_2, and the organic layer was washed with sat. aq $NaHCO_3$ solution (3×) and 10% $Na_2S_2O_3$ aq solution. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by a silica gel column chromatography (hexane–EtOAc, 4:1) to give a mixture of the product and unidentified contaminants, which was used for the next reaction without further purification. To a suspension of the above mixture and $NaHCO_3$ (156 mg, 1.86 mmol) in CH_2Cl_2 (5.0 mL) was added Dess–Martin periodinane (157 mg, 0.371 mmol) at 0 °C, and the mixture was stirred at r.t. for 1 h. The reaction was quenched by addition of a mixture of sat. aq $Na_2S_2O_3$ solution and sat. aq $NaHCO_3$ solution (1:1), and the mixture was extracted with EtOAc. The organic layer was washed with H_2O and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was used for the next reaction without further purification. To a solution of the above crude product in THF (3.0 mL) was added 10% HCl aq solution (3.0 mL) at 0 °C, and the mixture was stirred at r.t. for 12 h. The reaction mixture was extracted with EtOAc. The organic layer was washed with sat. aq $NaHCO_3$ solution, H_2O and brine, and then dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by a preparative TLC (hexane–EtOAc, 8:1) to give (±)-incargutine A (**25**, 30.8 mg, 40% yield, 3 steps) as a white solid; mp 166–167 °C. IR (neat): 3259, 1663, 1610, 1585, 1515, 1438 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 10.18 (1 H, s), 7.69 (1 H, d, *J* = 7.8 Hz), 7.31 (2 H, d, *J* = 8.5 Hz), 7.24 (1 H, m), 6.91 (2 H, d, *J* = 8.5 Hz), 4.91 (1 H, m), 3.59 (1 H, m), 3.26–3.40 (2 H, m), 2.36 (1 H, m), 1.79 (1 H, m), 0.82 (3 H, d, *J* = 6.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 192.7,

155.3, 148.4, 146.5, 144.3, 133.0, 130.9, 129.9, 129.7, 129.7, 128.4, 115.4, 115.4, 37.7, 33.3, 29.9, 19.7. MS–FAB: *m/z* = 253 $[M + H]^+$. HRMS–FAB: *m/z* $[M + H]^+$ calcd for $C_{17}H_{17}O_2$: 253.1229; found: 253.1218.

(15) **Experimental Procedure and Analytical Data of (±)-Incargutine B (26)**

To a solution of (±)-incargutine A (**25**, 10.5 mg, 0.0416 mmol) and $CH(OMe)_3$ (0.050 mL, 0.440 mmol) in MeCN (2.0 mL) was added Amberlyst-15 (7.3 mg) at 0 °C, and the mixture was stirred at r.t. for 1 h. The reaction was quenched by addition of a sat. aq $NaHCO_3$ solution. The mixture was filtered and then extracted with EtOAc. The organic layer was washed with H_2O and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by a preparative TLC (hexane–EtOAc, 5:1) to give (±)-incargutine B (**26**, 11.5 mg, 93% yield) as a colorless oil. IR (neat): 3375, 1612, 1592, 1519, 1214, 1108 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.36 (1 H, d, *J* = 7.8 Hz), 7.27 (2 H, m), 7.08 (1 H, d, *J* = 7.8 Hz), 6.86 (2 H, d, *J* = 8.4 Hz), 5.41 (1 H, s), 4.81 (1 H, m), 3.55 (1 H, m), 3.37 (6 H, s), 2.92–3.04 (2 H, m), 2.30 (1 H, m), 1.71 (1 H, m), 0.80 (3 H, d, *J* = 6.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.6, 146.9, 142.0, 138.7, 134.1, 132.2, 129.8, 129.8, 127.6, 124.6, 115.1, 115.1, 102.7, 53.2, 53.2, 38.2, 33.3, 29.3, 19.9. MS–FAB: *m/z* = 267, 298 $[M]^+$. HRMS–FAB: *m/z* $[M]^+$ calcd for $C_{19}H_{22}O_3$: 298.1569; found: 298.1579.

