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Synthesis of the Carbon Framework of Scholarisine A by Intramolecular Oxidative Coupling

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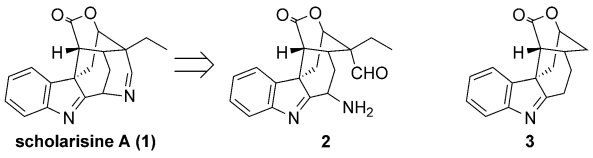
Abstract: Scholarisine A, isolated from the leaves of *Alstonia scholaris*, is a monoterpene indole alkaloid with an unprecedented cage-like structure. In this paper, preparation of the distinctive cage-like core skeleton of scholarisine A is described. The key feature of this synthetic strategy is an intramolecular oxidative coupling reaction at the late stage to construct a 10-oxa-tricyclo[5.3.1.$0^{3,8}$]undecan-9-one structure fused with indolenine. Intramolecular oxidative coupling by using *N*-iodosuccinimide gave the carbon framework of scholarisine A in moderate yield, which is the first example of intramolecular oxidative-coupling reaction between non-activated enolate and indole. This study lays the foundation for continued investigations towards the total synthesis of scholarisine A.

Keywords: cage compounds · C–C coupling · heterocyclic compounds · natural products · polycyclic compounds · synthetic methods

Introduction

Scholarisine A (**1**), which was isolated from the leaves of *Alstonia scholaris*, is a monoterpene indole alkaloid having an unprecedented cage-like structure fused with indolenine.[1] Several analogues of **1** have interesting biological activities.[2] The unprecedented molecular architecture of scholarisine A (**1**) has made it a challenging synthetic target, and the elegant first total synthesis of **1** was reported by the group of Smith in 2012.[3]

From the viewpoints of flexibility and convenience in the synthesis of **1**, we considered that it might be effective to construct the cyclic imine from amino aldehyde **2** at the last stage (Scheme 1). Accordingly, we needed to construct the 10-oxa-tricyclo[5.3.1.$0^{3,8}$]undecan-9-one structure fused with indolenine, as in compound **2**. To examine the feasibility of this approach, we set out to synthesize **3** as a model compound of **2**.



Scheme 1. Synthetic approach to scholarisine A.

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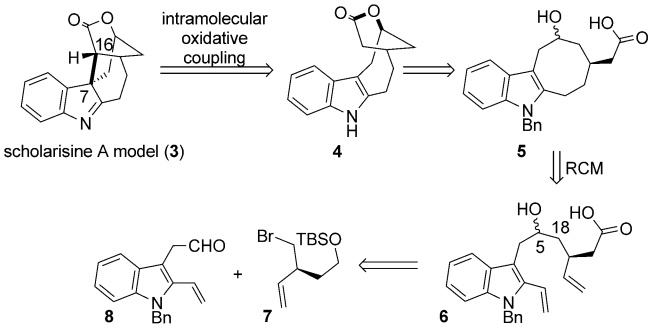
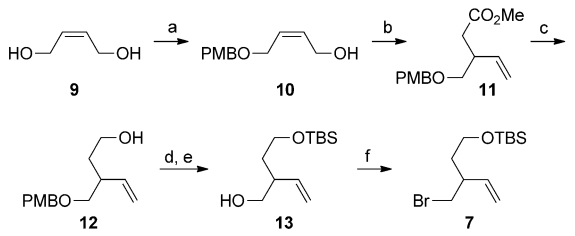


Scheme 2. Retrosynthetic analysis of scholarisine A model compound (**3**).

The retrosynthetic analysis of **3** is outlined in Scheme 2. We thought that the construction of **3** might be accomplished by linking C7 and C16 by using an intramolecular oxidative-coupling reaction. Direct intermolecular oxidative-coupling of indoles with carbonyl compounds was developed by Baran and co-workers.[4,5] Recently, Ma and co-workers have investigated the intramolecular oxidative-coupling between indole and α-carbonyl carbons, and utilized their methodology in the synthesis of complicated indole alkaloids.[6] But, although several examples of intramolecular oxidative coupling between activated α-carbonyl carbon and indole C3 have been reported, there is no case involving a non-activated lactone, as in **4**. The intermediate **4** could be obtained from the carboxylic acid **5** and the 8-membered ring could be constructed by the ring-closing metathesis of **6**. The intermediate **6** was split into two fragments, bromide **7** and aldehyde **8** by disconnection of the C5–C18 bond.

Results and Discussion

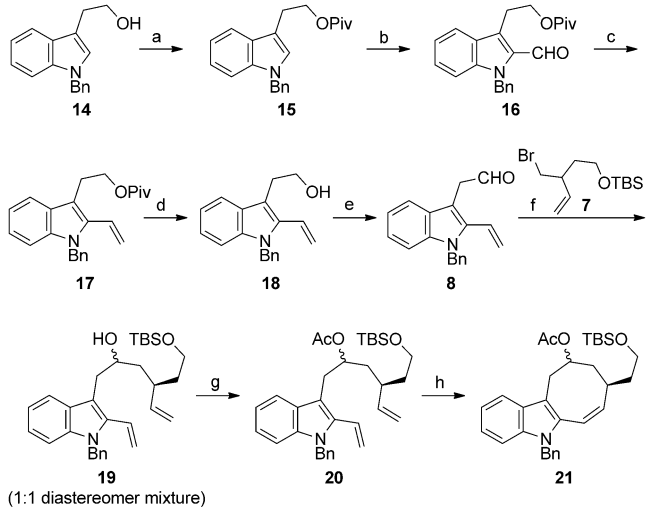
The synthesis of bromide **7** began with 2-butene-1,4-diol **9** (Scheme 3). Mono-PMB (*p*-methoxybenzyl ether) protec-



Scheme 3. Reagents and conditions: a) PMBCl, NaH, TBAI, THF, heated at reflux; b) $MeC(OMe)_3$, hydroquinone, toluene, reflux, 83% (2 steps); c) $LiAlH_4$, THF, 0°C to RT; d) TBSCl, imidazole, DMF; e) DDQ, CH_2Cl_2, pH 7 buffer, 88% (3 steps); f) PPh_3, CBr_4, Et_3N, CH_2Cl_2, quant.

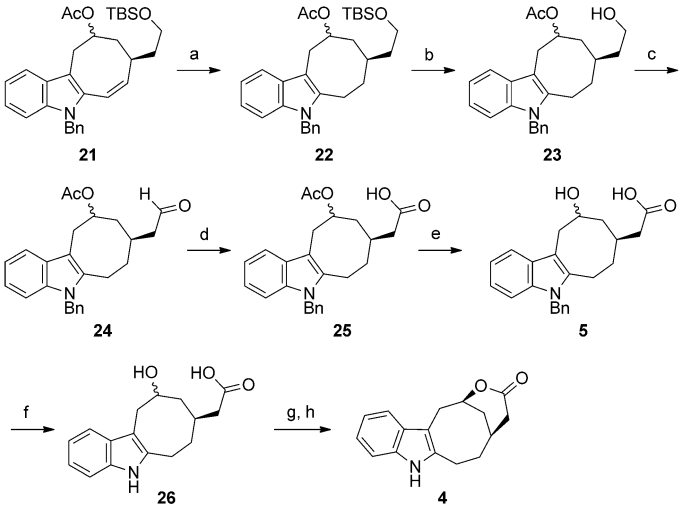
tion of 2-butene-1,4-diol **9**[7] and a subsequent Johnson–Claisen rearrangement[8] afforded methyl ester **11**. Reduction of the methyl ester with $LiAlH_4$ and protection of the resulting hydroxy group as a *tert*-butyldimethylsilyl (TBS) ether, followed by oxidative deprotection of PMB group with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ), gave the alcohol **13**. Finally, alcohol **13** was treated with PPh_3 and CBr_4 in the presence of Et_3N to afford bromide **7**.

Synthesis of olefin **21**, which has an eight-membered ring, is summarized in Scheme 4. Here, alcohol **14**, prepared from 3-indoleacetic acid according to the literature procedure[9] was treated with PivCl in the presence of Et_3N to afford the pivaloate (Piv) ester **15**. Formylation and subsequent introduction of the methylene group by using the Wittig reaction gave olefin **17**. Deprotection of the Piv group followed by *o*-iodoxybenzoic acid (IBX) oxidation[10] afforded aldehyde **8**. Bromide **7** was treated with *tert*-butyllithium and the resulting anion was immediately coupled to the aldehyde **8**, affording alcohol **19** as a 1:1 diastereomeric mixture. Acetylation and ring-closing metathesis by using the second-generation Grubbs catalyst[11] to construct the eight-membered ring gave cyclooctene **21**. In the ring-closing metathesis step with compound **19**, which has a free hydroxy group in the neighborhood of the olefin, the desired eight-membered ring compound was not obtained; the undesired dimer was obtained instead. It is crucial to protect the hydroxy group for ring-closing metathesis.[12] On the other hand, even when the hydroxy-protected diene **20** was used as a substrate, the eight-membered ring compound **21** could not be obtained by using the first-generation Grubbs catalyst.



Scheme 4. Reagents and conditions: a) PivCl, Et_3N, DMAP, CH_2Cl_2, 95%; b) $POCl_3$, DMF, 60°C, 88%; c) CH_3PPh_3Br, *n*-BuLi, THF, 0°C, 92%; d) $LiAlH_4$, THF, 0°C, 91%; e) IBX, DMSO, 69%; f) *t*BuLi, Et_2O, −95°C; compound **7**, −78°C; g) Ac_2O, DMAP, pyridine, CH_2Cl_2, −78°C to RT, 56% (2 steps); h) second-generation Grubbs catalyst, toluene, heated at reflux, 96%.

The synthesis of lactone **4**, which is the precursor for intramolecular oxidative coupling, is summarized in Scheme 5. The olefin of **21** was hydrogenated and then the TBS group

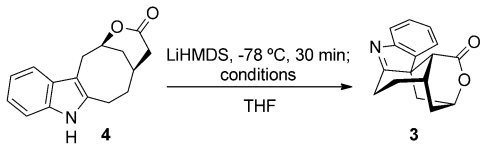


Scheme 5. Reagents and conditions: a) H_2, PtO_2, MeOH, benzene; b) HF, pyridine, THF, 62% (2 steps); c) IBX, DMSO; d) $AgNO_3$, NaOH, EtOH, THF, H_2O; e) K_2CO_3, MeOH, THF, 91% (3 steps); f) Na, NH_3, −78°C, 74%; g) Ac_2O, Et_3N, THF, 0°C to RT, 73%; h) PPh_3, DEAD, THF, 0°C, 33%.

was removed with HF in the presence of pyridine to afford alcohol **23**. IBX oxidation[10] gave aldehyde **24**, which was treated with $AgNO_3$ under basic conditions[13] to give carboxylic acid **25**. In the oxidation of aldehyde **24**, the use of $NaClO_2$ instead of $AgNO_3$ resulted in the formation of a complex mixture. Hydrolysis of the acetyl group and nitrogen deprotection furnished hydroxy carboxylic acid **26**. At this stage, diastereomers of *cis*-**26** and *trans*-**26** were separated by silica-gel column chromatography. The mixed-anhydride method using acetic anhydride was employed to convert *cis*-hydroxy carboxylic acid *cis*-**26** to lactone **4** in moderate yield. In contrast to *cis*-**26**, lactonization of *trans*-**26** was unsuccessful. Although we investigated the conditions of Mitsunobu lactonization[14] (temperature, solvent, and reagents) and the effect of various leaving groups on lactonization by intramolecular S_N2 reaction, the yield could not be improved. It is considered that *trans*-**26** does not readily adopt the conformation required for the intramolecular S_N2 lactonization reaction.

With the intramolecular oxidative coupling precursor **4** in hand, we investigated the construction of **3**, the 10-oxa-tricyclo[5.3.1.$0^{3,8}$]undecan-9-one structure fused with indolenine (Table 1). First, we examined $Fe(acac)_3$[5] and Cu(2-ethylhexanoate)$_2$,[4] which are commonly used oxidants for oxidative heterocoupling (Table 1, entries 1 and 2). The reaction did not proceed with $Fe(acac)_3$ (Table 1, entry 1). However, Cu(2-ethylhexanoate)$_2$ gave the desired intramolecular oxidative coupling product **3**, though the reaction yield was low (Table 1, entry 2). We next investigated I_2,[6,15] which is the best oxidant for intramolecular oxidative coupling between activated enolates and indoles (Table 1, entry 3). Fortunately, the yield was increased to 59%, even though the substrate was a non-activated simple lactone. It is considered that the key intermediate **4** is conformationally restricted and the enolate can easily approach the indole. We then screened various iodine reagents (Table 1, entries 4–6). The yield was slightly improved when *N*-iodosuccinimide (NIS) was used instead of I_2 (Table 1, entry 5). Iodine monochloride and hypervalent iodine reagents[16] were less effective (Table 1, entries 4 and 6). Nevertheless, this is the first example of intramolecular oxidative coupling reaction between non-activated enolate and indole, with moderate yield. The product was deduced to be **3** by detailed NMR analysis using HMBC (see the Experimental Section, Figure 1), HMQC, and NOE experiments.

Table 1. Intramolecular oxidative-coupling.



Entry	Oxidant	T [°C]	t	Yield [%]
1	$Fe(acac)_3$	RT[a]	1 h	0
2	Cu(2-ethylhexanoate)$_2$	RT[a]	2 h	7
3	I_2	−78	40 min	59
4	ICl	−78	2 h	28
5	NIS	−78	2 h	63
6	$PhI(OAc)_2$	−78	2 h	32

[a] Addition of oxidant at −78 °C.

Conclusion

A possible method for construction of the core carbon framework of scholarisine A was examined by using model compound **3** as a target. The ring-closing metathesis strategy successfully led to the key eight-membered ring structure **21**. The key reaction, intramolecular oxidative coupling of non-activated lactone **4**, proceeded in the desired manner to afford the 10-oxa-tricyclo[5.3.1.$0^{3,8}$]undecan-9-one structure fused with indolenine. Thus, the intramolecular oxidative coupling reaction is an effective tool for the construction of complex structures, and a non-activated lactone can also be employed as a substrate. Based on the chemistry described herein, further studies directed towards the total synthesis of scholarisine A are underway.

Experimental Section

PMB ether 10: Compound **9** (3.2 mL, 34.0 mmol) was added to a suspension of NaH (61% in oil, 816 mg, 34.0 mmol) in THF (68 mL) was added at 0 °C. The mixture was stirred for 2.5 h at 0 °C. PMBCl (4.6 mL, 34.0 mmol) was added and stirring was continued with heating at reflux for 17 h. Then, 10% aqueous K_2CO_3 was added and the mixture was extracted with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica-gel column chromatography (AcOEt/*n*-hexane = 1:5) to afford **10** (5.11 g, 72%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.85 (br s, 1H), 3.81 (s, 3H), 4.07 (d, J = 6.1 Hz, 2H), 4.18 (d, J = 6.1 Hz, 2H), 4.46 (s, 2H), 5.71–5.76 (m, 1H), 5.80–5.85 (m, 1H), 6.88 (d, J = 8.7 Hz, 2H), 7.27 ppm (d, J = 8.7 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 55.24, 58.70, 65.33, 113.82, 128.32, 129.46, 129.89, 132.28, 159.28 ppm; IR (Zn-Se): $\tilde{\nu}$ = 3447 cm^{-1} (br), 1613, 1514 cm^{-1}; MS (EI): m/z: 208 [M^+]; HRMS (EI): m/z: calcd for $C_{12}H_{16}O_3$: 208.1100 [M^+], found: 208.1102.

Methyl ester 11: Compound **10** (2.04 g, 9.80 mmol) and hydroquinone (324 mg, 2.94 mmol) were dissolved in toluene (15 mL) and $MeC(OMe)_3$ (4 mL). The mixture was stirred at reflux, and MeOH was removed in a Dean Stark apparatus with MS 4 Å. After 16 h, the solvent was removed under reduced pressure. The crude product was purified by silica-gel column chromatography (AcOEt/*n*-hexane = 1:9) to afford **11** (2.15 g, 83%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.35 (dd, J = 10.5, 8.5 Hz, 1H), 2.57 (dd, J = 10.5, 6.1 Hz, 1H), 2.90 (m, 1H), 3.35 (dd, J = 9.2, 7.1 Hz, 1H), 3.46 (dd, J = 9.2, 6.8 Hz, 1H), 3.63 (s, 3H), 3.80 (s, 3H), 4.42 (d, J = 11.6 Hz, 1H), 4.44 (d, J = 11.6 Hz, 1H), 5.08 (ddd, J = 10.5, 1.3, 1.0 Hz, 1H), 5.12 (ddd, J = 17.3, 1.3, 1.3 Hz, 1H), 5.75 (ddd, J = 17.3, 10.5, 7.6 Hz, 1H), 6.87 (d, J = 8.8 Hz, 2H), 7.24 (d, J = 8.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 36.40, 40.23, 51.45, 55.25, 72.39, 72.64, 113.71, 116.13, 129.18, 130.34, 137.94, 159.13, 172.90; IR (Zn-Se): $\tilde{\nu}$ = 1738, 1613, 1513 cm^{-1}; MS (EI): m/z: 264 [M^+]; HRMS (EI): m/z: calcd for $C_{15}H_{20}O_4$: 264.1362 [M^+]; found: 264.1363.

Alcohol 12: A solution of **11** (27.8 g, 99.7 mmol) in THF (150 mL) was added to a suspension of $LiAlH_4$ (80% in oil, 4.74 g, 125 mmol) in THF (400 mL) at 0 °C. The mixture was stirred for 40 min and then the reaction was quenched with saturated aqueous Rochelle salt. The mixture was extracted with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to afford **12** (22.9 g, mixture) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.63 (ddt, J = 13.5, 8.0, 6.0 Hz, 1H), 1.75 (ddt, J = 13.5, 7.8, 6.0 Hz, 1H), 2.09 (br s, 1H), 2.51 (m, 1H), 3.37 (dd, J = 9.5, 7.5 Hz, 1H), 3.44 (dd, J = 9.5, 5.5 Hz, 1H), 3.63 (m, 1H), 3.70 (dt, J = 11.0, 6.0 Hz, 1H), 3.81 (s, 3H), 4.46 (s, 2H), 5.06–5.12 (m, 2H), 5.71 (ddd, J = 17.3, 10.3, 8.3 Hz, 1H), 6.88 (d, J = 8.9 Hz, 2H), 7.25 (d, J = 8.9 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 35.16, 41.54, 55.25, 61.03, 72.82, 73.55, 113.80, 115.77, 129.30, 130.08, 139.55, 159.22; IR (Zn-Se): $\tilde{\nu}$ = 3399, 1614, 1514 cm^{-1}; MS (EI): m/z: 236 [M^+]; HRMS (EI): m/z: calcd for $C_{14}H_{20}O_3$: 236.1413 [M^+]; found: 236.1412.

TBS ether 13: TBSCl (16.8 g, 112 mmol) was added to a solution of **12** (22.9 g, mixture) and imidazole (16.8 g, 247 mmol) in DMF (200 mL). The mixture was stirred for 15 h and the reaction was quenched with H_2O. The mixture was extracted with *n*-hexane. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The corresponding silyl ether (34.8 g, mixture) was obtained and used for the next reaction without further purification.

DDQ (25.0 g, 110 mmol) was added to a solution of the silyl ether (34.8 g, mixture) in CH_2Cl_2 (300 mL) and pH 7 buffer (Na_2HPO_4/NaH_2PO_4, 30 mL). The reaction mixture was stirred for 1 h, then the re-

action was quenched with saturated aq. $NaHCO_3$ and the mixture was extracted with Et_2O. The combined organic layers were washed with H_2O and brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica-gel column chromatography (AcOEt/*n*-hexane = 1:9) to afford **13** (20.2 g, 3 steps 88%) as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = -0.06$ (s, 6H), 0.90 (s, 9H), 1.60 (ddt, $J = 14.0$, 7.5, 6.0 Hz, 1H), 1.65 (ddt, $J = 14.0$, 8.0, 6.0 Hz, 1H), 1.89 (brs, 1H), 2.41 (m, 1H), 3.52 (dt, $J = 11.0$, 6.0 Hz, 1H), 3.56 (dt, $J = 11.0$, 6.0 Hz, 1H), 3.63 (m, 1H), 3.72 (m, 1H), 5.12 (m, 2H), 5.67 ppm (ddd, $J = 17.0$, 11.0, 8.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta = -5.43$, −5.41, 18.24, 25.88, 34.38, 44.09, 61.12, 65.69, 116.66, 139.52 ppm; IR (Zn-Se) $\tilde{\nu} = 3447$ (br) cm^{-1}; MS (FAB): *m/z*: 231 [M^+]; HRMS (FAB): *m/z*: calcd for $C_{12}H_{27}O_2Si$: 231.1780 [$M+H^+$]; found: 231.1772.

Bromide 7: CBr_4 (46.0 mg, 139 μmol) and PPh_3 (36.2 mg, 138 μmol) were added to a solution of **13** (10.5 mg, 45.6 μmol) and TEA (38 μL, 274 μmol) in CH_2Cl_2 (500 μL). The reaction mixture was stirred for 3 h, then the reaction was quenched with saturated aqueous $NaHCO_3$ and the mixture was extracted with *n*-pentane. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to afford **7** (13.3 mg, crude) as a colorless oil. The crude product was used in the next step without purification. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.04$ (s, 6H), 0.89 (s, 9H), 1.57 (ddt, $J = 11.1$, 8.5, 5.9 Hz, 1H), 1.79 (m, 1H), 2.59 (m, 1H), 3.42 (dd, $J = 9.9$, 5.8 Hz, 1H), 3.44 (dd, $J = 9.9$, 5.8 Hz, 1H), 3.60 (m, 1H), 3.65 (dt, $J = 10.5$, 5.9 Hz, 1H), 5.10–5.16 (m, 2H), 5.66 ppm (ddd, $J = 17.0$, 10.5, 8.5 Hz, 1H).

Piv ester 15: PivCl (2.2 mL, 18.1 mmol) was added to a solution of **14** (4.17 g, 16.6 mmol), TEA (6.9 mL, 49.5 mmol), and DMAP (204 mg, 1.67 mmol) in CH_2Cl_2 (40 mL) was added at 0°C. The mixture was stirred at room temperature for 1 h, then a saturated aqueous solution of $NaHCO_3$ was added at 0°C. The mixture was separated and the water layer was extracted with *n*-hexane. The combined organic layers were dried over Na_2SO_4, and concentrated under reduced pressure. The residue was again dissolved in *n*-hexane and the solution was washed with saturated aqueous Na_2CO_3, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by silica-gel column chromatography (AcOEt/*n*-hexane = 1:20) to afford **15** (5.25 g, 95%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.16$ (s, 9H), 3.03 (t, $J = 7.0$ Hz, 2H), 4.33 (t, $J = 7.0$ Hz, 2H), 5.27 (s, 2H), 6.95 (s, 1H), 7.10–7.13 (m, 3H), 7.18 (t, $J = 7.6$ Hz, 1H), 7.22–7.30 (m, 4H), 7.64 ppm (d, $J = 7.8$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta = 24.68$, 27.19, 38.68, 49.88, 64.42, 109.62, 111.30, 118.99, 119.10, 121.80, 126.16, 126.83, 127.57, 128.11, 128.73, 136.55, 137.54, 178.61 ppm; IR (Zn-Se): $\tilde{\nu} = 1725$ cm^{-1}; MS (EI): *m/z*: 335 [M^+]; HRMS (EI): *m/z*: calcd for $C_{22}H_{25}NO_2$: 335.1885 [M^+]; found: 335.1883.

Aldehyde 16: A mixture of DMF (5 mL) and $POCl_3$ (2.9 mL, 32 mmol) was stirred at room temperature for 1 h, and a solution of **15** (33.3 g, 99.3 mmol) in DMF (160 mL) was added. The mixture was warmed to 60°C and stirred for 5 h. Then it was added to saturated aqueous Na_2CO_3 at 0°C and the whole was extracted with Et_2O. The combined organic layers were washed with H_2O, then brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica-gel column chromatography (AcOEt/*n*-hexane = 1:9) to afford **16** (31.7 g, 88%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.11$ (s, 9H), 3.46 (t, $J = 6.4$ Hz, 2H), 4.35 (t, $J = 6.4$ Hz, 2H), 5.82 (s, 2H), 7.05 (d, $J = 7.1$ Hz, 2H), 7.18–7.25 (m, 4H), 7.34–7.41 (m, 2H), 7.79 (d, $J = 8.2$ Hz, 1H), 10.16 ppm (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 23.33, 27.12, 38.68, 47.82, 64.39, 110.96, 120.85, 121.27, 126.45, 126.47, 126.61, 127.27, 127.60, 128.56, 131.28, 137.88, 139.53, 178.50, 181.38 ppm; IR (Zn-Se): $\tilde{\nu} = 1729$, 1660 cm^{-1}; MS (FAB): *m/z*: 364 [$M+H$]$^+$; HRMS (EI): *m/z*: calcd for $C_{23}H_{25}NO_3$: 363.1835 [M^+]; found: 363.1833.

Alkene 17: *n*-BuLi (1.63 M in *n*-hexane, 6.5 mL, 10.6 mmol) was added to a suspension of CH_3PPh_3Br (3.64 g, 10.2 mmol) in THF (10 mL) at 0°C. The mixture was stirred at room temperature for 15 min. The resulting orange solution was added to a solution of **16** (3.08 mg, 8.47 mmol) in THF (32 mL) at 0°C. Stirring was continued for 15 min at 0°C, then the reaction was quenched with saturated aq. NH_4Cl and the mixture was extracted with Et_2O. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica-gel column chromatography (AcOEt/*n*-hexane = 1:20) to afford **17** (2.97 g, 92%) as colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.17$ (s, 9H), 3.21 (t, $J = 7.5$ Hz, 2H), 4.31 (t, $J = 7.5$ Hz, 2H), 5.38 (s, 2H), 5.45 (dd, $J = 11.6$, 1.2 Hz, 1H), 5.58 (dd, $J = 17.6$, 1.2 Hz, 1H), 6.72 (dd, $J = 17.6$, 11.6 Hz, 1H), 7.01 (d, $J = 7.3$ Hz, 2H), 7.10–7.30 (m, 6H), 7.34–7.41 (m, 2H), 7.68 ppm (d, $J = 7.6$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta = 24.43$, 27.19, 38.70, 47.28, 64.37, 109.55, 110.04, 118.83, 119.03, 119.66, 122.50, 125.61, 125.91, 127.23, 128.03, 128.74, 135.12, 137.20, 137.91, 178.72 ppm; IR (Zn-Se): $\tilde{\nu} = 1719$ cm^{-1}; MS (EI): *m/z*: 361 [M^+]; HRMS (EI): *m/z*: calcd for $C_{24}H_{27}NO_2$: 361.2042 [M^+]; found: 361.2045.

Alcohol 18: A solution of **17** (2.97 g, 8.22 mmol) in THF (8 mL) was added to a suspension of $LiAlH_4$ (80% in oil, 368 mg, 7.76 mmol) in THF (17 mL) at 0°C. The reaction mixture was stirred for 20 min at 0°C and then the reaction was quenched with saturated aqueous Rochelle salt. The mixture was extracted with Et_2O. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica-gel column chromatography (AcOEt/*n*-hexane = 3:7) to afford **18** (2.07 g, 91%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.44$ (t, $J = 8.5$ Hz, 1H), 3.1 (t, $J = 6.2$ Hz, 2H), 3.94 (dt, $J = 8.5$, 6.2 Hz, 2H), 5.39 (s, 2H), 5.44 (dd, $J = 11.4$, 1.0 Hz, 1H), 5.58 (dd, $J = 17.5$, 1.0 Hz, 1H), 6.73 (dd, $J = 17.5$, 11.4 Hz, 1H), 7.04 (d, $J = 7.4$ Hz, 2H), 7.10–7.32 (m, 6H), 7.34–7.41 (m, 2H), 7.65 ppm (d, $J = 7.7$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta = 28.36$, 47.38, 63.18, 109.67, 110.50, 119.01, 119.73, 122.60, 125.64, 125.95, 127.27, 128.13, 128.77, 135.55, 137.36, 137.87 ppm; IR (Zn-Se): $\tilde{\nu} = 3357$ cm^{-1}; MS (EI): *m/z*: 277 [M^+]; HRMS (EI): *m/z*: calcd for $C_{19}H_{19}NO$: 277.1467 [M^+]; found: 277.1462.

Aldehyde 8: IBX (4.05 g, 1.45 mmol) was added to a solution of **18** (2.59 g, 7.16 mmol) in DMSO (50 mL). The mixture was stirred at room temperature for 3.5 h. The reaction was quenched with pH 7 buffer (KH_2PO_4/Na_2HPO_4) at 0°C. The mixture was filtered and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica-gel column chromatography (AcOEt/*n*-hexane = 1:9 (0.5% MeOH was added)) to afford **8** (1.36 g, 69%) as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 3.90$ (d, $J = 2.7$ Hz, 2H), 5.39 (s, 2H), 5.49–5.53 (m, 2H), 6.68 (dd, $J = 17.5$, 11.4 Hz, 1H), 7.02 (d, $J = 7.0$ Hz, 2H), 7.14–7.30 (m, 6H), 7.56 (d, $J = 7.7$ Hz, 1H), 9.73 ppm (t, $J = 2.7$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) $\delta = 40.40$, 47.38, 103.93, 109.82, 118.62, 120.20, 120.56, 122.92, 125.32, 125.95, 127.41, 128.05, 128.82, 136.56, 137.09, 137.53, 199.47 ppm; IR (Zn-Se): $\tilde{\nu} = 1720$ cm^{-1}; MS (EI): *m/z*: 275 [M^+]; HRMS (EI): *m/z*: calcd for $C_{19}H_{17}NO$: 275.1310 [M^+]; found: 275.1318.

Alcohol 19: A solution of *t*BuLi (1.59 M in *n*-pentane, 4.7 mL, 11.3 mmol) was added to a solution of **7** (1.60 g, 5.45 mmol) in Et_2O (23 mL) at −95°C. The mixture was stirred for 10 min at −95°C and a solution of **8** (1.04 g, 3.78 mmol) in THF (7.5 mL) was added to it. The reaction mixture was stirred at −75°C for 4 h, then the reaction was quenched with saturated aq. NH_4Cl and the mixture was extracted with AcOEt. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The non-reacted starting materials were removed by silica-gel column chromatography (AcOEt/*n*-hexane = 1:9) to afford **19** (1.21 g, mixture) as a pale yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.04$ (s, 6H), 0.89 (s, 9H), 1.42–1.55 (m, 1H), 1.62–1.74 (m, 3H), 2.46 (m, 1H), {2.90 (dd, $J = 14.2$, 9.0 Hz), 3.10 (dd, $J = 14.2$, 4.1 Hz), 1H}, {2.90 (dd, $J = 14.3$, 8.5 Hz), 3.10 (dd, $J = 14.3$, 6.5 Hz), 1H}, 3.55–3.67 (m, 2H), 3.96–4.09 (m, 1H), 4.98–5.14 (m, 2H), 5.40 (s, 2H), 5.38- 5.44 (m, 1H), 5.49–5.73 (m, 2H), 6.73 (dd, $J = 17.9$, 11.9 Hz, 1H), 7.03 (d, $J = 7.5$ Hz, 2H), 7.08–7.30 (m, 6H), {7.62 (d, $J = 5.0$ Hz), 7.63 ppm (d, $J = 5.1$ Hz), 1H}; ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta = -5.29$, −5.28, 18.31, 25.97, 32.73, 33.66, 37.55, 37.78, 38.10, 38.43, 42.40, 42.47, 47.43, 47.45, 60.88, 61.23, 69.94, 70.63, 76.74, 109.62, 109.63, 110.97, 111.13, 114.94, 115.33, 118.99, 119.07, 119.34, 119.35, 119.73, 122.58, 122.62, 125.71, 125.75, 125.91, 127.25, 128.24, 128.27, 128.77, 135.66, 135.76, 137.45, 137.48, 137.91, 142.10, 143.00 ppm; IR (Zn-Se): $\tilde{\nu} = 3565$, 3450 cm^{-1}; MS (EI): *m/z*: 489 [M^+]; HRMS (EI): *m/z*: calcd for $C_{31}H_{43}NO_2Si$: 489.306 [M^+]; found: 489.306.

Acetate 20: Ac_2O (14 mL) was added to a solution of **19** (1.21 g, mixture) and DMAP (60.3 mg 493 μmol) in pyridine (24 mL) and CH_2Cl_2 (25 mL) at −78 °C. The mixture was stirred for 3 h and warmed to room temperature. The solvents were removed under reduced pressure with toluene. The crude product was purified by silica-gel column chromatography (AcOEt/*n*-hexane = 3:97) to afford **20** (1.12 g, 2 steps 56 %) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.00–0.02 (m, 6H), {0.87 (s), 0.88 (s), 9H}, 1.26–1.76 (m, 4H), {1.85 (s), 1.94 (s), 3H}, 2.22–2.32 (m, 1H), 2.99–3.20 (m, 2H), 3.46–3.60 (m, 2H), 4.85- 5.02 (m, 2H), 5.16–5.25 (m, 1H), 5.30–5.63 (m, 3H), 5.39 (s, 2H), {6.72 (dd, J = 18.0, 10.9 Hz), 6.72 (dd, J = 17.9, 11.9 Hz), 1H}, 6.98 (d, J = 7.3 Hz, 2H), 7.08–7.30 (m, 6H), 7.68 ppm (d, J = 7.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = −5.35, −5.33, 14.17, 18.24, 21.18, 21.23, 25.91, 25.93, 29.80, 30. 21, 36.95, 37.66, 37.81, 38.18, 39.16, 39.58, 47.33, 47.34, 60.61, 60.76, 61.93, 72.75, 73.20, 109.44, 110.44, 110.57, 114.71, 115.77, 118.60, 118.64, 119.45, 119.62, 119.67, 122.40, 125.81, 127.14, 127.15, 128.36, 128.38, 128.71, 135.20, 135.22, 137.30, 137.33, 138.01, 138.02, 141.16, 141.97, 170.32, 170.43 ppm; IR (Zn-Se): $\tilde{\nu}$ = 1736 cm^{-1}; MS (EI): m/z: 531 [M^+]; HRMS (EI): m/z: calcd for $C_{33}H_{45}O_3NSi$: 531.3169 [M^+]; found: 531.3149.

Alkene 21: A solution of second-generation Grubbs catalyst (555 mg, 65.4 μmol) in toluene (10 mL) was added to a solution of **20** (5.69 g, 10.7 mmol) in toluene (500 mL). The mixture was stirred with heating at reflux for 13 h and the solvent was removed under reduced pressure. The crude product was purified by silica-gel column chromatography (AcOEt/*n*-hexane = 4:96) to afford **21** (5.26 g, 96 %) as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = {−0.03 (s), −0.02 (s), 6H}, {0.80 (s), 0.82 (s), 9H}, 1.56–1.97 (m, 4H), {2.00 (s), 2.09 (s), 3H}, 2.20–3.10 (m,2H), 3.21–3.57 (m, 3H), {4.95 (m), 5.45 (m), 1H}, 5.30 (m, 2H), {5.73 (m), 5.89 (m), 1H}, {6.34 (d, J = 11.2 Hz), 6.37 (d, J = 11.2 Hz), 1H}, 6.99 (d, J = 7.4 Hz, 2H), 7.08–7.25 (m, 6H), {7.52 (d, J = 7.9 Hz), 7.67 ppm (d, J = 7.2 Hz), 1H}; ^{13}C NMR ($CDCl_3$, 125 MHz): δ = −5.37, −5.32, 14.19, 18.18, 18.19, 21.04, 21.45, 21.57, 25.81, 25.85, 38.11, 41.19, 46.87, 47.16, 60.38, 60.88, 61.10, 73.23, 109.15, 109.24, 117.39, 118.43, 118.83, 119.33, 119.50, 121.98, 122.12, 126.04, 126.13, 127.24, 127.27, 128.18, 128.65, 128.67, 135.38, 136.69, 136.76, 137.91, 137.94, 170.58, 171.13 ppm; IR (Zn-Se): $\tilde{\nu}$ = 1730 cm^{-1}; MS (EI): m/z: 503 [M^+]; HRMS (EI): m/z: calcd for $C_{31}H_{41}O_3NSi$: 503.2856 [M^+]; found: 503.2848.

Cyclooctane 22: PtO_2 (474 mg, 2.09 mmol) was added to a solution of **21** (5.26 g, 10.4 mmol) in MeOH (150 mL) and benzene (50 mL). Hydrogen was admitted through a balloon and the reaction mixture was stirred for 22 h. The catalyst was removed by filtration through Celite, and the solvent was removed under reduced pressure. The crude product was purified by silica-gel column chromatography (AcOEt/*n*-hexane = 5:95) to afford **22** (5.27 g, mixture) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = {−0.04 (s), −0.03 (s), 0.01 (s), 6 H}, {0.79 (s), 0.85 (s), 9H}, 1.20–1.86 (m, 7H), {1.99 (s), 2.11 (s), 3H}, 2.73–3.30 (m, 4H), 3.45–3.58 (m, 2H), {4.82 (m), 5.26 (m), 1H}, {5.30 (d, J = 17.6 Hz), 5.34 (d, 17.5 Hz), 2H}, 6.97 (d, J = 7.8 Hz, 2H), 7.07–7.14 (m, 2H), 7.18–7.29 (m, 4H), {7.51 (m), 7.58 ppm (m), 1H}; ^{13}C NMR ($CDCl_3$, 125 MHz): δ = −5.40, −5.32, −5.28, 18.13, 18.25, 21.46, 21.58, 22.46, 23.63, 25.81, 25.89, 27.39, 29.02., 29.13, 30.12, 34.02, 38.39, 41.11, 41.49, 46.33, 46.34, 60.81, 61.19, 73.11, 74.66, 107.36, 107.88, 109.09, 109.13, 117.68, 118.01, 119.28, 119.31, 120.91, 120.97, 125.85, 125.88, 127.27, 127.92, 128.35, 128.72, 128.73, 136.35, 136.49, 136.89, 137.14, 138.18, 138.25, 170.34, 170.80 ppm; IR (Zn-Se): $\tilde{\nu}$ = 1731 cm^{-1}; MS (EI): m/z: 505 [M^+]; HRMS (EI): m/z: calcd for $C_{31}H_{43}O_3NSi$: 505.3012 [M^+]; found: 505.3026.

Alcohol 23: HF•pyridine (7:3, 3 mL) was added to a solution of **22** (5.27 g, mixture) and pyridine (10 mL) in THF (120 mL) at room temperature. The reaction mixture was stirred for 11 h, then the reaction was quenched with saturated aq. $CuSO_4$ and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The crude mixture was purified by silica-gel column chromatography (AcOEt/hexane = 1:9) to afford **23** (2.55 g, 2 steps 62 %) as a white amorphous solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.20–1.89 (m, 7H), {2.02 (s), 2.09 (s), 3H}, 2.76–2.88 (m, 1H), {2.90–3.02 (m), 3.12 (dd, J = 14.7, 4.1 Hz), 3.24 (dd, J = 14.7, 7.8 Hz), 3.28 (dd, J = 14.7, 2.6 Hz), 3H}, {4.78 (m), 5.29 (m), 1H}, 5.34 (d, J = 17.2 Hz, 2H), 6.98 (d, J = 7.1 Hz, 2H), 7.09–7.16 (m, 4H), 7.20–7.30 (m, 4H), {7.53 (m), 7.59 ppm (m), 1H}; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.39, 21.57, 22.28, 23.48, 27.27, 28.13, 29.31, 30.26, 34.09, 35.37, 35.63, 38.08, 40.55, 41.00, 46.31, 46.34, 60.21, 60.45, 73.39, 74.96, 107.28, 107.98, 109.17, 109.20, 117.63, 117.90, 119.32, 119.35, 120.97, 121.03, 125.82, 125.86, 127.28, 127.79, 128.17, 128.71, 128.72, 136.36, 136.47, 136.79, 137.13, 138.16, 138.19, 170. 62, 170.66 ppm; IR (Zn-Se): $\tilde{\nu}$ = 3423 (br), 1730 cm^{-1}; MS (EI): m/z: 391 [M^+]; HRMS (EI): m/z: calcd for $C_{25}H_{29}NO_3$: 391.2146 [M^+]; found: 391.2145.

Carboxylic acid 5: IBX (3.66 g, 13.1 mmol) was added to a solution of **23** (2.55 g, 6.51 mmol) in DMSO (45 mL). The mixture was stirred at room temperature for 2 h, then the reaction was quenched with pH 7 buffer. The mixture was filtered through Celite and extracted with CH_2Cl_2. The combined organic layers were concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 again and the solution was washed with H_2O. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to afford **24** (2.32 g, mixture). The crude product was used for the next reaction without further purification.

NaOH (898 mg, 22.4 mmol) in EtOH/H_2O = 9:1 (20 mL) was added to a solution of the above aldehyde **24** and $AgNO_3$ (1.52 g, 8.95 mmol) in EtOH/H_2O = 9:1 (30 mL) and THF (17 mL) was added at 0 °C. The mixture was stirred for 1 h at 0 °C. Brine and Et_2O were added and the whole solution was acidified with 2 M aqueous HCl (→pH 1) and extracted with Et_2O. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to afford **25** (2.42 g, mixture). The crude product was used for the next reaction without further purification.

K_2CO_3 (4.12 g, 29.8 mmol) was added to a solution of **25** (2.42 g, mixture) in MeOH (57 mL) and THF (34 mL). The reaction mixture was stirred at 50 °C for 2 h and the solvent was removed under reduced pressure. CH_2Cl_2 and water were added and the mixture was acidified with 2 M aqueous HCl (to pH 1). The organic layer was separated and the aqueous layer was extracted with AcOEt. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by silica-gel column chromatography (AcOEt/*n*-hexane = 1:3 (+0.5 % AcOH)) to afford **5** (2.16 g, 3 steps 91 %) as a yellow amorphous solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.24–1.36 (m, 1H), 1.42–1.70 (m, 3H), 2.08–2.26 (m, 3H), {2.76–3.02 (m), 3.10 (m), 3.28 (m), 4H}, {3.94 (m), 4.24 (m), 1H}, 5.32 (d, J = 17.2 Hz, 1H), 5.35 (d, J = 17.2 Hz, 1H), 6.96 (m, 2H), 7.11–7.16 (m, 2H), 7.20–7.29 (m, 4H), 7.59–7.66 ppm (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.28, 23.19, 27.71, 30.28, 30.32, 31.97, 33.65, 35.23, 39.22, 41.82, 42.29, 42.60, 46.29, 46.33, 70.02, 72.43, 107.71, 108.94, 109.17, 109.24, 117.80, 117.98, 119.38, 119.41, 121.03, 121.07, 125.80, 125.86, 127.30, 128.00, 128.17, 128.72, 136.38, 136.40, 136.49, 136.63, 138.16, 138.19, 177.89, 178.13 ppm; IR (Zn-Se): $\tilde{\nu}$ = 3362 (br), 1705 cm^{-1}; MS (FAB): m/z: 363 [M^+]; HRMS (EI): m/z: calcd for $C_{23}H_{25}NO_3$: 363.1835 [M^+]; found: 363.1832.

Hydroxycarboxylic acid 26: Compound **5** (1.42 g, 3.91 mmol) was added to a solution of Na (931 mg, 40.5 mmol) in liq. NH_3 (ca. 20 mL) in THF (14 mL) at −78 °C. The mixture was stirred at −78 °C for 3.5 h. The reaction was quenched with solid NH_4Cl and the whole was warmed up to room temperature. Then, H_2O and Et_2O were added and the mixture was acidified with 6 M HCl (→pH 1), then extracted with AcOEt. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica-gel column chromatography (AcOEt/*n*-hexane = 9:1 (0.5 % of AcOH was added)) to afford **26** (3.77 g, 96 %) as a white amorphous solid.

cis and *trans* isomers of **26** were partially separated by silica-gel column chromatography (MeOH/$CHCl_3$/AcOH = 10:200:1). ***cis*-26**: white amorphous solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.39–1.56 (m, 2H), 1.58–1.68 (m, 2H), 1.70 (m, 1H), 1.80 (m, 1H), 2.29 (d, J = 7.3 Hz, 2H), 2.83 (m, 1H), 2.92 (m, 1H), 2.96 (dd, J = 14.7, 6.9 Hz, 1H), 3.16 (dd, J = 14.7, 3.4 Hz, 1H), 3.95 (m, 1H), 7.11 (dt, J = 7.1, 1.1 Hz, 1H), 7.12 (dt, J = 7.2, 1.3 Hz, 1H), 7.28 (dd, J = 7.2, 1.1 Hz, 1H), 7.57 (dd, J = 7.1, 1.3 Hz, 1H), 7.89 (brs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.94, 30.90, 31.08, 34.44, 41.48, 42.82, 72.42, 107.09, 110.46, 117.75, 119.54, 121.11, 129.10, 135.02, 135.34, 177.55; IR (Zn-Se): $\tilde{\nu}$ = 3392 (br), 1704 cm^{-1}; MS (EI): m/z: 273 [M^+]; HRMS (EI): m/z: calcd for $C_{16}H_{19}NO_3$: 273.1365 [M^+]; found: 273.1359. ***trans*-26**: white amorphous solid. ^{1}H NMR (500 MHz,

$CDCl_3$): $\delta = 1.56$ (m, 1H), 1.61 (m, 2H), 1.90 (m, 1H), 2.22 (m, 1H), 2.28–2.40 (m, 2H), 2.86–3.00 (m, 3H), 3.10 (dd, $J = 14.4$, 4.6 Hz, 1H), 4.21 (m, 1H), 7.09 (t, $J = 7.1$ Hz, 1H), 7.12 (t, $J = 7.1$ Hz), 7.29 (d, $J = 7.1$ Hz, 1H), 7.54 (d, $J = 7.1$ Hz, 1H), 7.81 ppm (brs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 25.88$, 28.20, 29.99, 36.17, 39.41, 42.38, 70.21, 108.75, 110.42, 117.86, 119.45, 121.06, 128.95, 134.87, 135.42, 176.95 ppm; IR (Zn-Se): $\tilde{\nu} = 3390$–3000 (br), 1703 cm^{-1}; MS (EI): m/z: 273 [M^+]; HRMS (EI): m/z: calcd for $C_{16}H_{19}NO_3$: 273.1365 [M^+]; found: 273.1358.

Lactone 4 from *cis*-26: Ac_2O (150 μL, 1.6 μmol) was added to a solution of **26** (*cis*/*trans* = 67:33, 383 mg, 1.40 mmol) and TEA (220 μL, 1.6 mmol) in THF (10 mL) at 0 °C. The mixture was stirred for 11 h at the same temperature, and then allowed to warm to room temperature. The reaction was quenched by adding saturated aqueous $NaHCO_3$ and the mixture was extracted with Et_2O. The combined organic layers were dried with Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica-gel column chromatography (AcOEt/*n*-hexane = 6:4) to afford **4** (175 mg, 73 % as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.80$ (d, $J = 15.1$ Hz, 1H), 1.94 (dt, $J = 15.1$, 6.1 Hz, 1H), 2.04 (m, 1H), 2.13 (m, 1H), 2.45 (m, 1H), 2.48 (dd, $J = 17.9$, 4.8 Hz, 1H), 2.72 (dd, $J = 17.9$, 8.9 Hz, 1H), 2.85 (ddd, $J = 16.6$, 10.3, 3.0 Hz, 1H), 3.06 (dd, $J = 15.2$, 9.6 Hz, 1H), 3.18 (ddd, $J = 16.6$, 8.3, 2.4 Hz, 1H), 3.58 (dd, $J = 15.2$, 7.8 Hz, 1H), 4.92 (ddd, $J = 9.6$, 7.8, 6.1 Hz, 1H), 7.11 (dd, $J = 7.7$, 7.6 Hz, 1H), 7.14 (dd, $J = 7.7$, 7.6 Hz, 1H), 7.29 (d, $J = 7.7$ Hz, 1H), 7.49 (d, $J = 7.6$ Hz, 1H), 7.98 ppm (brs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 24.43$, 27.34, 28.77, 29.98, 31.49, 34.67, 79.08, 107.64, 110.36, 117.38, 119.66, 121.58, 128.53, 134.95, 135.73, 171.53 ppm; IR (KBr): $\tilde{\nu} = 3252$, 1716 cm^{-1}; MS (FAB): m/z: 256 [$M+H^+$]; HRMS (EI): m/z: calcd for $C_{16}H_{17}NO_2$: 255.1259 [M^+], found: 255.1258.

Lactone 4 from *trans*-26: DEAD (2.2 M in toluene, 20 μL, 43 μmol) was added to a solution of PPh_3 (11.4 mg, 43.4 μmol) in THF (400 μL) at 0 °C. The mixture was stirred at 0 °C for 30 min, and then a solution of *trans*-**26** (7.9 mg, 29 μmol) in THF (300 μL) was added to the mixture. The mixture was stirred at 0 °C for 1 h. The reaction was quenched with brine and the mixture was extracted with AcOEt. The organic layers were dried with Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by GPC to afford **4** (2.4 mg, 9.4 mmol, 33 %) as a white solid.

Intramolecular oxidative coupling product (3): *Preparation of LiHMDS*: *n*-BuLi (1.65 M in *n*-hexane, 430 μL, 710 μmol) was added to a solution of 1,1,1,3,3,3-hexamethyldisilazane (150 μL, 710 μmol) in THF (920 μL) at 0 °C. The mixture was stirred at room temperature for 30 min.

Oxidative coupling: The above solution of LiHMDS (160 μL, 75 μmol) was added to a solution of **4** (8.6 mg, 34 μmol) in THF (600 μL) at −78 °C and the mixture was stirred at −78 °C for 30 min. Then, a solution of NIS (11.4 mg, 50.6 μmol) in THF (100 μL) was added and the reaction mixture was stirred at −78 °C for 2 h. The reaction was quenched with saturated aqueous $Na_2S_2O_3$ and the mixture was extracted with AcOEt. The combined organic layers were washed with H_2O, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by PTLC (silica-gel, AcOEt/*n*-hexane = 90 %) to afford **3** (5.4 mg, 63 %) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.74$ (ddd, $J = 14.5$, 3.1, 0.8 Hz, 1H), 1.81 (dt, $J = 13.6$, 5.0 Hz, 1H), 1.92 (dd, $J = 15.1$, 1.3 Hz, 1H), 2.12 (d, $J = 3.1$ Hz, 1H), 2.16 (dddd, $J = 13.6$, 6.3, 3.1, 1.1 Hz, 1H), 2.30 (dt, $J = 15.1$, 3.3 Hz, 1H), 2.44 (dddd, $J = 14.5$, 11.7, 3.7, 3.3 Hz, 1H), 2.53 (dquin, $J = 11.7$, 3.1 Hz, 1H), 2.83 (ddd, $J = 14.5$, 13.6, 6.3 Hz, 1H), 2.97 (ddd, $J = 14.5$, 5.0, 1.1 Hz, 1H), 4.97 (dddd, $J = 3.7$, 3.3, 1.3, 0.8 Hz, 1H), 7.23 (t, $J = 7.4$ Hz, 1H), 7.26 (d, $J = 7.4$ Hz, 1H), 7.35 (d, $J = 7.6$, 7.4 Hz, 1H), 7.57 ppm (d, $J = 7.6$ Hz, 1H);^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 24.05$, 27.31, 29.25, 30.42, 34.03, 48.39, 51.85, 74.20, 120.42, 122.24, 126.19, 128.68, 142.68, 154.07, 172.44, 183.73 ppm; IR (Zn-Se): $\tilde{\nu} = 1753$ cm^{-1}; MS (FAB); m/z: 254 [$M+H^+$]; HRMS (EI): m/z: calcd for $C_{16}H_{15}NO_2$: 253.1103 [M^+]; found: 253.1111. Figure 1 shows the structural determination of **3**.

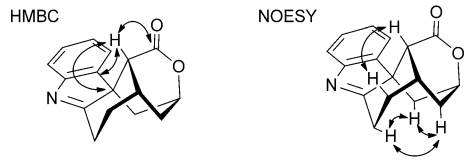


Figure 1. Structure determination of scholarisine A model compound (**3**)

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