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Formation of a Novel 1-*Aza*-tricyclo[5.3.0.0^{4,8}]decane System via Tandem Radical Cyclization of a Tryptophan Derivative

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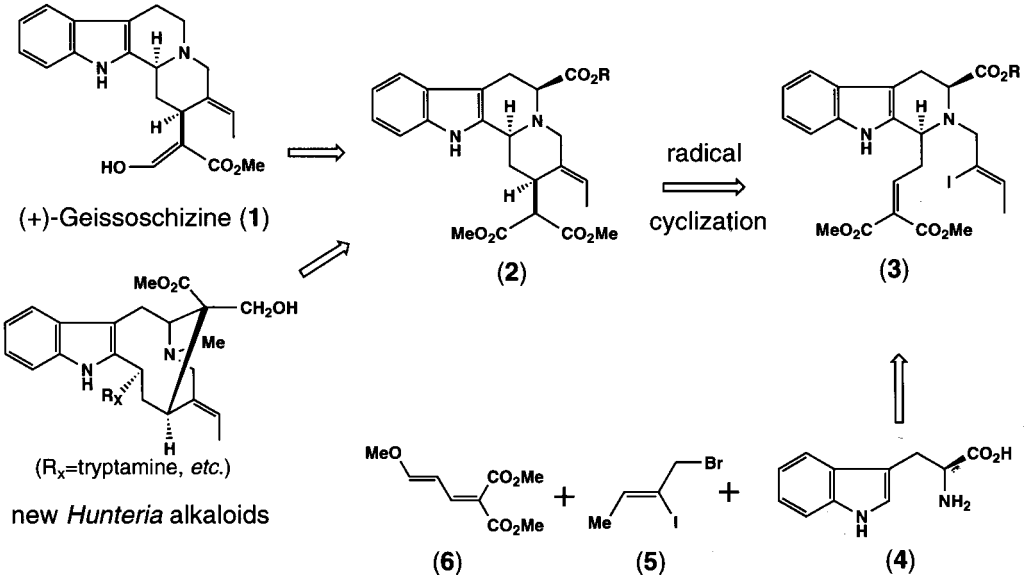
Abstract—Novel pentacyclic compounds containing a 1-*aza*-tricyclo[5.3.0.0^{4,8}]decane system in the molecule were formed exclusively by radical cyclization of the *N*b,*N*b-disubstituted tryptophan derivative.

Introduction

We have previously reported a concise total synthesis of (±)-geissoschizine,[1] which is an important biogenetic precursor for many structural types of monoterpenoid indole alkaloids.[2] In that synthesis we employed a radical cyclization strategy in the key step for the construction of the tetracyclic Corynanthe-skeleton. By utilizing this newly developed method, we next planned the total synthesis of optically active geissoschizine (**1**)[3] as well as new Sarpagine-type alkaloids,[4] which were isolated from *Hunteria zeylanica* by our group, starting from tryptophan. The synthetic plan is outlined in Scheme 1, which features the construction of the Corynantheoid compound (**2**) by radical cyclization of the vinyl iodide derivative (**3**), which would be easily prepared by assembly of three components, i.e. tryptophan (**4**), allyl bromide (**5**), and diene ester derivative (**6**).

Results and Discussion

Synthesis of the radical reaction substrate (**3**) began with the *N*b-monoalkylation of tryptophan *tert*-butyl ester (**7**).[5] Thus, *N*b-alkylation of **7** with 1 equiv. of allylbromide (**5**)[6] in CH_3CN followed by condensation of the resulting



Scheme 1.

Keywords: alkaloids; cyclization; indoles; radicals and radical reaction.

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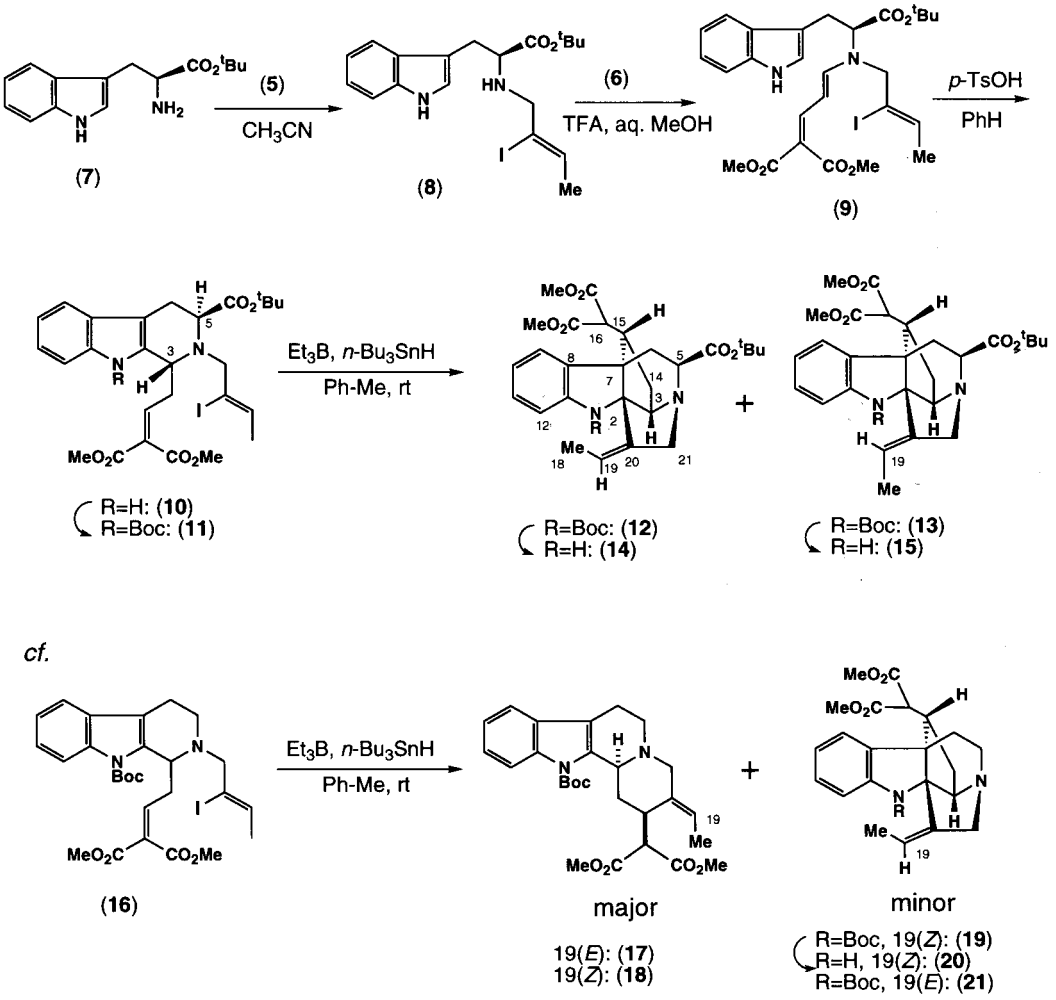
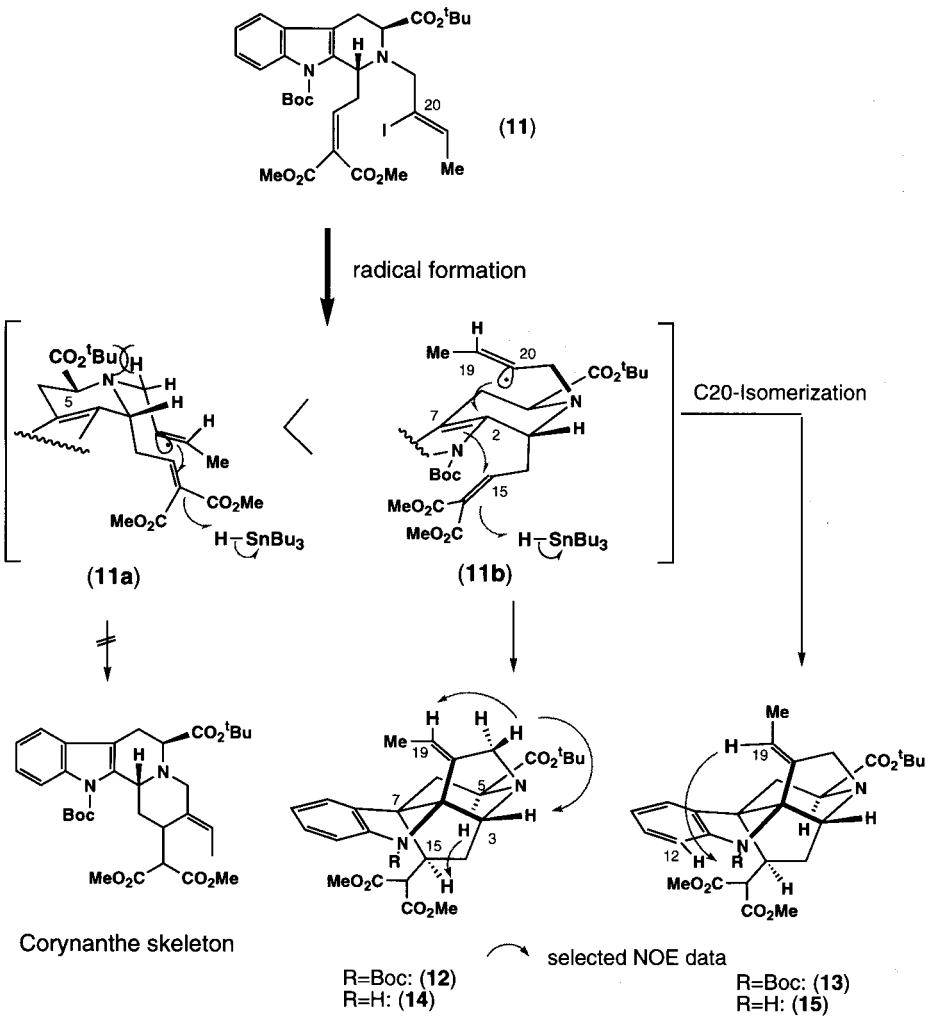
secondary amine (**8**) with the methoxy diene diester (**6**)[3b,7] in aqueous MeOH (1:5) in the presence of 2 equiv. of trifluoroacetic acid gave the enamine (**9**) in 54% overall yield. Acid-promoted C-ring formation was best accomplished when *p*-toluenesulfonic acid (1.1 equiv) was used in dry benzene to give tricyclic compound (**10**) in 57% yield. The relative stereochemistry between the C3 and C5 positions was first assumed to be *trans* based on Cook's studies[8] on Pictet–Spengler cyclization of tryptophan derivatives, and subsequently confirmed by the structural analysis of the radical cyclization products (vide infra).

With the requisite substrate for radical reaction in hand, compound (**10**) was allowed to react with common reagents for radical reaction, resulting in the formation of many inseparable products. The *N*a-Boc derivative (**11**) was then prepared by a conventional method and it was subjected to the radical cyclization with Et_3B and *n*-Bu_3SnH[9] in toluene at room temperature. Under these conditions in the previous study,[1] the Corynantheoid compounds (**17** and **18**) could have been obtained as the main products when tryptamine derivative (**16**) was used as a substrate. However, unusual compounds (**12** and **13**) having a pentacyclic skeleton were exclusively produced in 72% yield from tryptophan derivative (**11**). The structure of the pentacyclic compounds was fully characterized after separation as *des*-Boc derivatives [**14** (42% isolated yield) and **15** (11% isolated yield)]. Thus, the major compound (**14**) showed the typical UV absorption due to an indoline chromophore. Characteristically, the HMBC spectra exhibited long-range connectivities between H-16 and C7 and between H-19 and C2, revealing the presence of a 1-*aza*-tricyclo[5.3.0.$0^{4,8}$]decane system in the molecule. The ^1H and ^{13}C NMR spectra of 14 closely resemble those of compound (**20**),[1] which has been obtained from **16** as a minor product and whose structure was determined by X-ray analysis, except for the signals due to the presence of a *tert*-butoxycarbonyl group at the C5 position in **14**. The stereochemistry at the C15 and C19 positions were respectively determined by differential NOE spectra as shown in Scheme 3. The structure of the minor compound (**15**) was also confirmed by spectroscopic analysis as in the case of compound (**14**). Especially, the NOE observation between H-19 and both *N*a-H and H12 revealed the 19*E* configuration in compound (**15**) (Scheme 2).

The reason why the indoline compounds (**12**,**13**) formed exclusively by radical cyclization of **11**, although the Corynanthe skeleton was mainly produced from the tryptamine derivative (**16**), remains obscure. But, probably



Scheme 2.



Scheme 3.

owing to the steric repulsion between the bulky *tert*-butoxycarbonyl group and the *N*b-allyl group in the transition state (**11a**), which would bring about the formation of the desired Corynanthe structure, compound (**11**) would take a more favorable conformer (**11b**), resulting in the formation of pentacyclic compounds via tandem radical reaction as shown in Scheme 3. Further efforts for preparation of the Corynantheoid compounds in line with this strategy as well as the utilization of the novel cyclization reaction found in the present study to construct polycyclic nitrogen-containing molecules are underway in our laboratory.

Experimental

General

UV: recorded in MeOH. Hitachi U 3400. ^{1}H and ^{13}C NMR spectra: recorded at 500 and 125.65 MHz, respectively. (ppm, *J* in Hz with TMS as internal standard.) JEOL JNM A-500. EI-MS: direct probe insertion at 70 eV. JEOL JMS-AM20. FAB-MS: JEOL-HX110. CD: JASCO J-720WI. Optical Rotation: JASCO DIP-140. TLC: precoated Kieselgel 60 F254 plates (Merck, 0.25 mm thick). Column chromatography: Kieselgel [Merck, 70–230 mesh (for open chromatography) and 230–400 mesh (for flash chromatography). Medium pressure liquid chromatography (MPLC): silica gel prepacked column Kusano CPS-HS-221–05.

***N*b-allylation of tryptophan *tert*-butyl ester (7).** To a solution of L-tryptophan *tert*-butyl ester (**7**) (7.78 g, 0.03 mmol) in CH_3CN (80 ml), bromide (**5**) (7.82 g, 0.03 mmol) was added and the reaction mixture was stirred at room temperature for 16 h under argon atmosphere. The reaction mixture was then poured into the chilled saturated aq. $NaHCO_3$ solution and the whole was extracted with $CHCl_3$ three times. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The residue was separated by SiO_2 flash column chromatography (25% *n*-hexane/$CHCl_3$) to give **8** (8.41 g, 64%) as a colorless amorphous powder. UV (MeOH) λ_{max}: 290, 281, 220 nm. ^{1}H NMR ($CDCl_3$) δ: 8.05 (1H, br-s, *N*a-H), 7.64 (1H, d, J=8.0 Hz, C9–H),[10] 7.34 (1H, d, J=8.0 Hz, C12–H), 7.18 (1H, dd, J_1=J_2=8.0 Hz, C11–H), 7.11 (2H, m, C2–H, C10–H), 5.68 (1H, q, J=6.3 Hz, C19–H), 3.50 (1H, br-d, J=14.0 Hz, C5–H), 3.48 (1H, m, C5–H), 3.38 (1H, d, J=14.0 Hz, C21–H), 3.16 (1H, dd, J_1=6.1, J_2=14.4 Hz, C6–H), 3.05 (1H, dd, J_1=7.6, J_2=14.4 Hz, C6–H), 1.69 (3H, d, J=6.3 Hz, C18–H), 1.37 (9H, s, *tert*-Bu). ^{13}C NMR ($CDCl_3$) δ: 173.6 ($-CO_2{}^{t}Bu$), 136.2 (C13),[10] 131.7 (C19),

127.7 (C8), 122.9 (C2), 122.0 (C11), 119.3 (C10), 119.1 (C9), 111.7 (C7), 111.0 (C12), 109.7 (C20), 81.0 ($OC(CH_3)_3$), 60.2 (C5), 59.6 (C21), 29.2 (C6), 28.0 ($CO_2C(CH_3)_3$), 21.6 (C18). EIMS *m/z* (%): 440 (M^+, 2), 339 (73), 254 (100). HR-EIMS: Calcd For $C_{19}H_{25}O_2N_2I$; 440.0962, found; 440.0971.

Preparation of *N*b, *N*b-disubstitued tryptophan derivative (9). To a stirred mixture of **8** (6.84 g, 15.5 mmol) and **6** (13.1 g, 65.6 mmol) in aqueous MeOH (1:5, 100 ml), trifluoroacetic acid (2.4 ml, 31.2 mmol) was added dropwise at 0°C. The reaction mixture was warmed at 55°C for 8 h under argon atmosphere. The reaction mixture was then poured into the chilled saturated aq. $NaHCO_3$ solution and the whole was extracted with $CHCl_3$ three times. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The residue was separated by SiO_2 flash column chromatography (67% *n*-hexane/AcOEt) to give **9** (7.94 g, 84%) as a colorless amorphous powder. UV (MeOH) λ_{max}: 369, 220 nm. ^{1}H NMR ($CDCl_3$) δ: 8.10 (1H, br-s, *N*a-H), 7.67 (1H, d, *J*=12.4 Hz, C15–H), 7.57 (1H, d, *J*=8.0 Hz, C9–H), 7.38 (1H, d, *J*=8.0 Hz, C12–H), 7.22 (1H, t, *J*=8.0 Hz, C11–H), 7.15 (1H, t, *J*=8.0 Hz, C10–H), 7.01 (1H, d, *J*=2.1 Hz, C2–H), 6.19 (1H, t, *J*=12.4 Hz, C14–H), 5.54 (1H, br-q, *J*=6.0 Hz, C19–H), 4.14 (1H, m, C5–H), 4.03 (1H, d, *J*=15.9 Hz, C21–H), 3.86 (1H, d, *J*=15.9 Hz, C21–H), 3.79 (3H, s, $-CO_2CH_3$), 3.77 (3H, s, $-CO_2CH_3$), 3.47 (1H, dd, *J*=6.6, 14.1 Hz, C6–H), 3.22 (1H, dd, *J*=9.0, 14.1 Hz, C6–H), 1.62 (3H, d, *J*=6.0 Hz, C18–H_3), 1.42 (9H, s, *tert*-Bu). ^{13}C NMR ($CDCl_3$) δ: 169.2 ($-CO_2{}^t$Bu), 167.1 (CO_2CH_3), 167.0 (CO_2CH_3), 153.4 (C15), 152.5 (C3), 136.2 (C13), 133.6 (C19), 126.7 (C8), 123.5 (C2), 122.1 (C11), 119.5 (C10), 118.3 (C9), 111.5 (C12), 109.6 (C7), 108.8 (C16), 99.8 (C14), 99.8 (C20), 82.8 ($OC(CH_3)_3$), 65.8 (C5), 62.4 (C21), 51.6 (CO_2CH_3), 51.3 (CO_2CH_3), 27.9 ($CO_2C(CH_3)_3$), 27.9 (C6), 21.5 (C18). FABMS (NBA) *m/z*: 609 $[M+H]^+$. HR-FABMS (NBA): Calcd For $C_{27}H_{34}O_6N_2I$; 609.1462, found; 609.1470.

Preparation of tetrahydro-β-carboline derivative (10). *p*-TsOH·H_2O was added portionwise to a stirred solution of compound **9** (42.6 mg, 0.0701 mmol) in benzene (2 ml) at 0°C in the following manner: 0 min, 3.6 mg (0.0189 mmol); 13 h, 3.5 mg (0.0184 mmol); 21 h, 3.5 mg (0.0184 mmol); 26 h, 3.6 mg (0.0189 mmol). In the intervals between addition of *p*-TsOH·H_2O, the reaction mixture was stirred at room temperature under argon atmosphere. After the final addition of the reagent, the reaction mixture was further stirred for 4 h at room temperature under argon atmosphere. The reaction mixture was then poured into the chilled saturated aq. $NaHCO_3$ solution and the whole was extracted with $CHCl_3$ three times. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The residue was separated by SiO_2 flash column chromatography (75% *n*-hexane/AcOEt) to give **10** (24.3 mg, 57%) as a colorless amorphous powder. UV (MeOH) λ_{max}: 274, 223 nm. ^{1}H NMR ($CDCl_3$) δ: 7.92 (1H, s, *N*a-H), 7.49 (1H, d, *J*=7.8 Hz, C9–H), 7.39 (1H, t, *J*=7.8 Hz, C15–H), 7.31 (1H, d, *J*=7.8 Hz, C12–H), 7.16 (1H, dt, *J*=1.0, 7.8 Hz, C11–H), 7.09 (1H, dt, *J*=1.0, 7.8 Hz, C10–H), 5.91 (1H, q, *J*=6.3 Hz, C19–H), 4.30 (1H, br-t, *J*=5.8 Hz, C3–H), 3.88 (1H, dd, *J*=5.1, 7.1 Hz, C5–H), 3.79 (3H, s, $-CO_2CH_3$), 3.75 (3H, s, $-CO_2CH_3$), 3.61 (1H, d, *J*=14.9 Hz, C21–H), 3.48 (1H, d, *J*=14.9 Hz, C21–H), 3.10 (1H, dd, *J*=7.1, 15.9 Hz, C6–H), 2.95 (1H, ddd, *J*=4.6, 7.5, 15.8 Hz, C14–H), 2.86 (1H, td, *J*=7.5, 15.8 Hz, C14–H), 2.97 (1H, dd, *J*=5.1, 15.9 Hz, C6–H), 1.78 (3H, d, *J*=6.3 Hz, C18–H_3), 1.39 (9H, s, *tert*-Bu). ^{13}C NMR ($CDCl_3$) δ: 171.8 ($-CO_2{}^t$Bu), 165.9 (CO_2CH_3), 164.4 (CO_2CH_3), 149.3 (C15), 136.4 (C13), 133.2 (C2), 132.7 (C19), 128.3 (C16), 126.9 (C8), 121.9 (C11), 119.5 (C10), 118.2 (C9), 110.9 (C12), 108.6 (C20), 108.0 (C7), 81.2 ($OC(CH_3)_3$), 61.7 (C21), 57.2 (C5), 54.9 (C3), 52.3 (CO_2CH_3), 52.3 (CO_2CH_3), 33.9 (C14), 28.1 ($CO_2C(CH_3)_3$), 22.3 (C6), 21.7 (C18). CD (0.39 mM, MeOH, 24°C), λ_{nm} ($\Delta\epsilon$): 345 (0), 297 (−1.2), 292 (−0.8), 289 (−0.9), 282 (−0.5), 262 (0), 249 (+0.1), 228 (+8.2), 219 (0), 210 (−5.1), 203 (0). FABMS (NBA) *m/z*: 609 $[M+H]^+$. HR-FABMS (NBA): Calcd For $C_{27}H_{34}O_6N_2I$; 609.1462, found; 609.1471.

Preparation of *N*a-Boc derivative (11). To a stirred solution of **10** (27.4 mg, 0.045 mmol) in CH_3CN (1 ml) was successively added *p*-dimethylaminopyridine (1.5 mg, 0.012 mmol) and di-*tert*-butyl dicarbonate (0.012 ml, 0.052 mmol), and the reaction mixture was stirred at room temperature for 37 h under argon atmosphere. The reaction mixture was concentrated under reduced pressure and the residue was separated by SiO_2 flash column chromatography (12% Et_2O/*n*-hexane) to give **11** (21.0 mg, 66%) as a colorless amorphous powder. UV (MeOH) λ_{max}: 294, 266, 227 nm. ^{1}H NMR ($CDCl_3$) δ: 8.14 (1H, d, *J*=7.3 Hz, C12–H), 7.60 (1H, dd, *J*=5.9, 8.1 Hz, C15–H), 7.46 (1H, d, *J*=7.3 Hz, C9–H), 7.31 (1H, dt, *J*=1.2, 7.3 Hz, C10–H), 7.25 (1H, dt, *J*=1.2, 7.3 Hz, C11–H), 5.92 (1H, q, *J*=6.4 Hz, C19–H), 4.58 (1H, dd, *J*=4.1, 10.5 Hz, C3–H), 3.94 (1H, dd, *J*=5.1, 11.2 Hz, C5–H), 3.78 (3H, s, $-CO_2CH_3$), 3.77 (3H, s, $-CO_2CH_3$), 3.46 (1H, br-d, *J*=14.2 Hz, C21–H), 3.34 (1H, d, *J*=14.2 Hz, C21–H), 3.02 (1H, overlapped, C14–H), 3.01 (1H, dd, *J*=11.2, 16.9 Hz, C6–H), 2.81 (1H, dd, *J*=5.1, 16.9 Hz, C6–H), 2.78 (1H, overlapped, C14–H), 1.80 (3H, dd, *J*=1.5, 6.4 Hz, C18–H_3), 1.63 (9H, s, *tert*-Bu), 1.50 (9H, s, *tert*-Bu). ^{13}C NMR ($CDCl_3$) δ: 171.3 ($-CO_2{}^t$Bu), 165.9 (CO_2CH_3), 164.5 (CO_2CH_3), 149.9 (-$NCO_2{}^t$Bu), 149.7 (C15), 136.1 (C13), 134.8 (C16), 133.5 (C19), 128.9 (C8), 127.4 (C2), 124.5 (C11), 122.9 (C10), 118.2 (C9), 115.8 (C12), 114.7 (C7), 107.6 (C20), 84.1 ($OC(CH_3)_3$), 81.4 ($OC(CH_3)_3$), 60.5 (C21), 55.3 (C3), 54.8 (C5), 52.1 (CO_2CH_3), 33.7 (C14), 28.2 ($CO_2C(CH_3)_3$), 28.0 ($CO_2C(CH_3)_3$), 21.8 (C18), 19.9 (C6). CD (0.39 mM, MeOH, 24°C), λ_{nm} ($\Delta\epsilon$): 300 (0), 290 (+0.1), 284 (+0.4), 282 (+0.38), 250 (+2.0), 242 (+3.1), 231 (0), 225 (−1.9), 216 (−2.5), 210 (−3.4), 200 (0). FABMS (NBA) *m/z*: 709 $[M+H]^+$. HR-FABMS (NBA): Calcd For $C_{32}H_{42}O_8N_2I$; 709.1986, found; 709.1964.

Radical reaction of 11. To a stirred solution of **11** (36.6 mg, 0.0517 mmol) was successively added *n*-Bu_3SnH (0.021 ml, 0.078 mmol) and a solution of Et_3B in *n*-hexane (1.04 mol/l, 0.01 ml, 0.0104 mmol), and the mixture was stirred at room temperature for 30 min. To this reaction mixture was further added a solution of Et_3B in *n*-hexane (1.04 mol/l, 0.014 ml, 0.0146 mmol). The resulting mixture was stirred for 30 min and then diluted with AcOEt. To this solution was added a

saturated aq. KF solution (0.1 ml) and KF (86 mg), and the whole mixture was stirred for 1 h. The insoluble material was filtrated off by suction filtration and the mother liquid was poured into the saturated aq. $NaHCO_3$ solution. The whole was extracted with $CHCl_3$ three times, and the combined organic layer was washed with brine, dried over $MgSO_4$, and evaporated. The residue was separated by SiO_2 flash column chromatography ($CHCl_3$) to give **12** and **13** (21.5 mg, 72%) as an inseparable mixture.

Removal of *N*a-protecting group from 12 and 13. A mixture of **12** and **13** (118 mg, 0.203 mmol) was dissolved in formic acid (2 ml) and the mixture was stirred at room temperature for 13 h under argon atmosphere. After evaporation of formic acid under reduced pressure, the residue was dissolved in $CHCl_3$. The organic layer was washed with 10% aq. $NaHCO_3$ solution. The aqueous layer was extracted with $CHCl_3$ two times. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The residue was separated by MPLC (1% MeOH/$CHCl_3$) to give **14** (41.5 mg, 42%) and **15** (10.9 mg, 11%) as a colorless amorphous powder, respectively. Major isomer **14**: $[\alpha]_D^{22}=+68.4$ (*c* 0.88, $CHCl_3$). UV (MeOH) λ_{max}: 298, 262, 256, 250, 245, 214 nm. ^{1}H NMR ($CDCl_3$) δ: 7.08 (1H, dt, *J*=1.0, 7.6 Hz, C11–H), 6.83 (1H, br-d, *J*=7.3 Hz, C9–H), 6.68 (1H, dt, *J*=1.0, 7.3 Hz, C10–H), 6.66 (1H, d, *J*=7.8 Hz, C12–H), 5.30 (1H, tq, *J*=1.4, 7.1 Hz, C19–H), 3.97 (1H, s, *N*–H), 3.93 (1H, dd, *J*=4.6, 12.2 Hz, C5–H), 3.72 (1H, d, *J*=5.3 Hz, C3–H), 3.69 (3H, s, $-CO_2CH_3$), 3.61 (1H, td, *J*=1.4, 16.1Hz, C21–Hβ), 3.39 (3H, s, $-CO_2CH_3$), 3.37 (1H, overlapped, C21–Hα), 3.02 (2H, overlapped, C15–H and C16–H), 2.41 (1H, dd, *J*=4.6, 12.2 Hz, C6–H), 2.32 (1H, ddd, *J*=3.2, 5.6, 14.9 Hz, C14–H), 2.13 (1H, t, *J*=12.2 Hz, C6–H), 1.86 (1H, m, C14–H), 1.50 (9H, s, *tert*-Bu), 1.13 (3H, td, *J*=1.4, 7.1 Hz, C18–H_3). ^{13}C NMR ($CDCl_3$) δ: 171.3 (CO_2^tBu), 169.5 (CO_2CH_3), 168.6 (CO_2CH_3), 151.6 (C13), 139.4 (C20), 129.6 (C8), 128.4 (C11), 125.3 (C9), 118.6 (C10), 116.0 (C19), 110.7 (C12), 87.7 (C2), 81.4 ($OC(CH_3)_3$), 72.3 (C3), 60.0 (C7), 58.7 (C5), 56.4 (C16), 55.9 (C21), 52.6 (CO_2CH_3), 52.2 (CO_2CH_3), 47.8 (C15), 35.2 (C6), 31.3 (C14), 28.1 ($CO_2C(CH_3)_3$), 12.0 (C18). FABMS (NBA) *m/z*: 483 $[M+H]^+$. HR-FABMS (NBA): Calcd For $C_{27}H_{35}O_6N_2$; 483.2495, found; 483.2484. Minor isomer **15**: $[\alpha]_D^{22}=+43.0$ (*c* 0.59, $CHCl_3$). UV (MeOH) λ_{max}: 297, 261, 256, 250, 245, 214 nm. ^{1}H NMR ($CDCl_3$) δ: 7.06 (1H, dt, *J*=1.2, 7.8 Hz, C11–H), 6.82 (1H, d, *J*=7.3 Hz, C9–H), 6.73 (1H, d, *J*=7.3 Hz, C12–H), 6.69 (1H, t, *J*=7.3 Hz, C10–H), 4.91 (1H, tq, *J*=2.5, 6.9 Hz, C19–H), 3.74 (1H, s, *N*–H), 3.92 (1H, dd, *J*=4.4, 12.4 Hz, C5–H), 3.69 (3H, s, $-CO_2CH_3$), 3.63 (1H, d, *J*=5.6 Hz, C3–H), 3.55 (1H, br-d, *J*=16.9 Hz, C21–Hβ), 3.49 (1H, br-d, *J*=16.9Hz, C21–Hα), 3.38 (3H, s, $-CO_2CH_3$), 3.04 (2H, overlapped, C15–H and C16–H), 2.39 (1H, dd, *J*=4.4, 12.4 Hz, C6–H), 2.35 (1H, overlapped, C14–H), 1.98 (1H, t, *J*=12.4 Hz, C6–H), 1.82 (1H, m, C14–H), 1.51 (9H, s, *tert*-Bu), 1.46 (3H, d, *J*=6.9 Hz, C18–H_3). ^{13}C NMR ($CDCl_3$) δ: 171.4 ($-CO_2^tBu$), 169.4 (CO_2CH_3), 168.7 (CO_2CH_3), 151.3 (C13), 141.7 (C20), 128.6 (C8), 128.4 (C11), 126.4 (C9), 118.7 (C10), 114.0 (C19), 109.6 (C12), 86.3 (C2), 81.5 ($OC(CH_3)_3$), 71.2 (C3), 59.9 (C7), 58.5 (C5), 56.1 (C16), 52.6 (CO_2CH_3), 52.3 (CO_2CH_3), 51.8 (C21), 47.7 (C15), 35.1 (C6), 31.1 (C14), 28.1 ($CO_2C(CH_3)_3$), 14.0 (C18). FABMS (NBA) *m/z*: 483 $[M+H]^+$. HR-FABMS (NBA): Calcd For $C_{27}H_{35}O_6N_2$; 483.2495, found; 483.2484.

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10. The numbering of the synthetic intermediates and final products corresponds to the biogenetic numbering of the monoterpenoid indole alkaloids, which is used throughout.