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A Radical Cyclization Strategy for the Concise Total Synthesis of (±)-Geissoschizine

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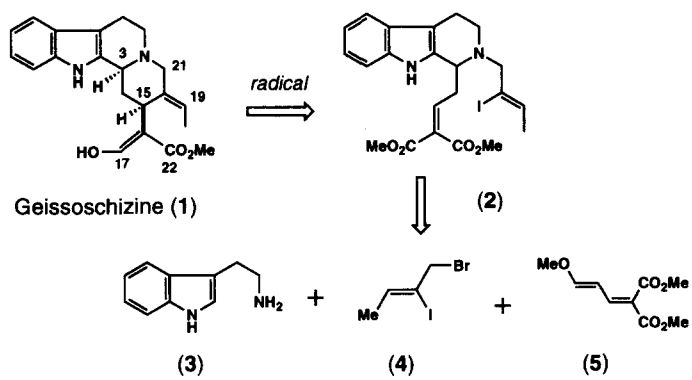
Abstract A short synthetic route to (±)-geissoschizine (**1**) was developed that features the construction of a Corynanthe-skeleton via radical cyclization of vinyl iodide, which was easily prepared by assembly of three fragments. New pentacyclic molecules formed by the radical cyclization were also reported.

A Corynanthe-type alkaloid, geissoschizine (**1**), is a universal biogenetic key intermediate leading to many skeletal types of monoterpenoid indole alkaloids, and we recently proposed a most plausible stereostructure of (**1**).[1] From 1976 to 1996, total syntheses of geissoschizine have been reported by eight groups.[2] In some syntheses developed in the early years, there were problems concerning the control over the relative stereochemistry between the C3 and C15 positions and/or the stereoselective construction of the 19(*E*) ethylidene side chain. Although recent new synthetic methodologies overcame these problems elegantly, many of them still required operation involving long steps, introduction of a C1-unit (C17 or C22 positions) in the last stage of the synthesis, and/or reduction of the lactam function at the C21 position. Geissoschizine is a very important natural product for biosynthetic studies[3] as well as a useful precursor for biomimetic transformation to many other skeletal types of indole alkaloids, therefore, we aimed to develop a facile and practical synthetic route for (**1**). Here, we report a new concise total synthesis of (±)-geissoschizine (**1**). Our basic approach to geissoschizine is outlined in Scheme 1 and features stereoselective construction of the Corynantheoid compound (**9**) having a C3/C15 *cis*-relationship via radical cyclization of the vinyl iodide (**2**), which can be prepared by assembly of three components, i.e., tryptamine (**3**) , (*Z*)-vinyl iodide (**4**), and diene diester (**5**).

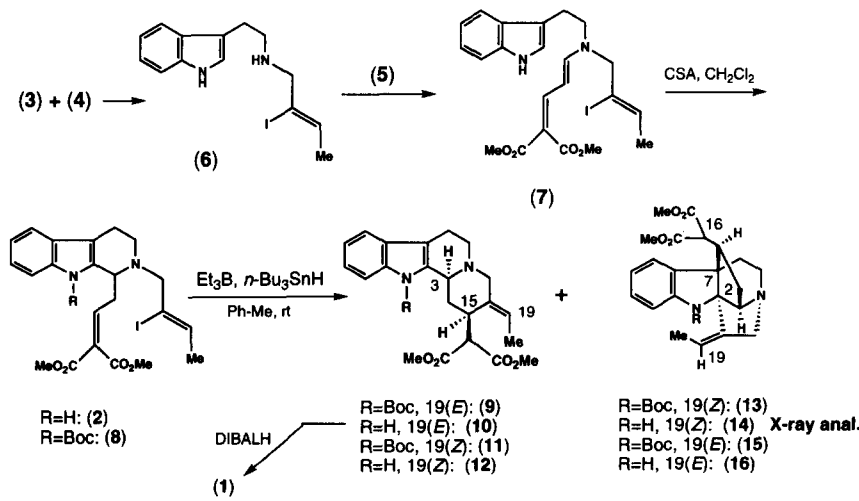


Scheme 1

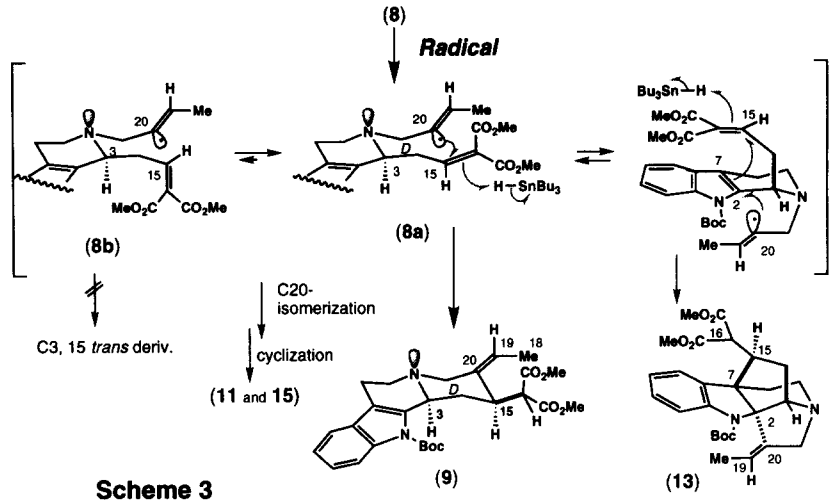
Our synthesis started with the preparation of the N_b-monosubstituted tryptamine derivative (**6**). Thus, alkylation of **3** in MeCN with the bromide (**4**), which was prepared from known allylic alcohol[4] by treatment with NBS/PPh_3 in CH_2Cl_2, gave the secondary amine (**6**) in 82% yield. Condensation of **6** with the alkoxy diene diester (**5**)[2g, 5, 6] in MeOH afforded the enamine (**7**) in 90% yield, which was then subjected to Pictet-Spengler cyclization with 1.4 equiv. of camphor sulfonic acid in CH_2Cl_2 to give the tetrahydro-β-carboline derivative (**2**) in 60% yield. Compound **2** was, however, unstable and changed gradually to the C3-N_b *seco*, $\Delta^{3,14}$ derivative in the solution or during storage under vacuum. To stabilize the indole derivative (**2**), the N_a function was protected with $(Boc)_2O$ and DMAP in CH_2Cl_2 to give **8** in 44% yield from **7**.

With the requisite substrate **8** for the radical cyclization in hand, we then turned our attention to the construction of the Corynantheoid skeleton. Radical cyclization of the vinyl iodide (**8**) according to the conditions developed by Oshima[7] (n-Bu_3SnH, 1.5 eq; Et_3B, 0.4 eq, toluene, room temperature, 75 min.) afforded the desired tetracyclic product (**9**)[8] possessing the C3/C15 *cis*-relationship as a major product in 33% yield, along with the 19(*Z*) isomer (**11**)[8] (17% yield), and two indoline derivatives (**13** and **15**) (32% total yield). The use of Ph_3SnH in place of *n*-Bu_3SnH slightly improved the product ratio of **9** and **11** to 2.5:1 (44% total yield). Employment of nickel-promoted cyclization[9] [1. bis(1,5-cyclooctadiene)nickel(0), Et_3N, MeCN, 2. Et_3SiH] with **8** afforded the compound (**9**) as a sole isolable product, although the isolated yield was poor (10% yield). High diastereoselectivity regarding C3/C15 *cis*-relationship observed in the above reactions can be comprehended using the chair-like transition state models (**8a**) and (**8b**) (Scheme 3). The intermediate (**8a**), in which a large malonate residue assumes an equatorial orientation, would be predominant over the conformer (**8b**), resulting in the formation of the compound (**9**). The 19(*Z*) isomer (**11**) would be formed through the isomerization of the vinyl radical intermediate (**8a**).

The structure of side-products (**13** and **15**) having an indoline nucleus produced in the radical cyclization could be elucidated using the *des*-Boc derivatives (**14** and **16**).[10] Characteristically, the HMBC spectra of **14** and **16** 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 molecules. The novel pentacyclic structure including the stereochemistry at C15 was confirmed by a single-crystal X-ray analysis of compound (**14**). The



Scheme 2



Scheme 3

tandem radical cyclization mechanism as shown in Scheme 3 could be considered for the formation of these new skeletal types of compounds.

Finally, deprotection of the N_a-Boc group in **9** with formic acid and subsequent partial reduction of the resultant diester (**10**) to the monoaldehyde with DIBALH furnished (±)-geissoschizine (**1**) in 72% yield (based on 50% recovered starting material) (mp. 195-197°C; lit[2b] mp. 187-189°C), which was identical with the natural product by comparison of TLC, IR, ^{1}H- and ^{13}C-NMR, and HRMS.

In conclusion, a concise synthetic route for (±)-geissoschizine was developed that requires only seven steps from tryptamine.[11] Application of this chemistry to the total synthesis of other indole alkaloids is currently being investigated in our laboratory.

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8. (**9**): HR-FABMS m/z (NBA) : calcd. for $C_{27}H_{35}N_2O_6$ (M+H), 483.2495, found 483.2477. ^{1}H-NMR (500MHz, $CDCl_3$) δ: 1.65 (9H, s, $C(CH_3)_3$), 1.66 (4H, C18-H_3, C14-Hβ), 2.47 (1H, ddd, *J* =4.9, 8.5, 13.4 Hz, C14-Hα), 2.65-2.70 (2H, C5-Hα, C6-H), 2.85 (1H, m, C6-H), 3.02 (1H, m, C5-Hβ), 3.19 (1H, d, *J* =12.5 Hz, C21-Hα), 3.63 (3H, s, $-CO_2CH_3$), 3.65 (1H, m, C15-H), 3.67 (3H, s, $-CO_2CH_3$), 3.70 (1H, d, *J* =12.5 Hz, C21-Hβ), 3.93 (1H, d, *J* =11.0 Hz, C16-H), 4.09 (1H, br-s, C3-H), 5.53 (1H, q, *J* =6.6 Hz, C19-H), 7.22 (1H, t, *J* =7.6 Hz, C10-H), 7.26 (1H, t, *J* =7.6 Hz, C11-H), 7.41 (1H, d, *J* =7.6 Hz, C9-H), 8.07 (1H, d, *J* =7.6 Hz, C12-H). ^{13}C-NMR (125MHz, $CDCl_3$) δ: 136.62 (C2), 54.55 (C3), 48.77 (C5), 21.15 (C6), 116.18 (C7), 129.08 (C8), 117.96 (C9), 122.66 (C10), 124.04 (C11), 115.40 (C12), 136.93 (C13), 33.36 (C14), 34.06 (C15), 56.04 (C16), 13.03 (C18), 122.25 (C19), 133.49 (C20), 58.18 (C21), 52.17 and 52.40 (CO_2CH_3), 168.97 and 168.98 (CO_2CH_3), 28.14 $C(CH_3)_3$, 83.85 $C(CH_3)_3$, 150.14 (CO_2tBu). The detailed NOE experiments revealed that the D-ring in **9** assumes a boat-form conformation. (**11**): ^{13}C-NMR (125MHz, $CDCl_3$) δ: 136.26 (C2), 56.71 (C3), 43.81 (C5), 21.67 (C6), 114.75 (C7), 129.13 (C8), 117.93 (C9), 122.62 (C10), 123.99 (C11), 115.75 (C12), 136.40 (C13), 32.37 (C14), 41.78 (C15), 54.42 (C16), 13.06 (C18), 117.29 (C19), 133.73 (C20), 54.98 (C21), 52.51 and 52.67 (CO_2CH_3), 168.77 and 168.95 (CO_2CH_3), 28.11 ($CH_3)_3$, 83.97 $C(CH_3)_3$, 150.05 (CO_2tBu).
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10. (**14**): mp. 185-186°C (AcOEt). Anal. calcd. for $C_{22}H_{26}N_2O_4$: C; 69.09, H; 6.85, N; 7.32, found: C; 68.83, H; 6.81, N; 7.32. ^{1}H-NMR (400MHz, $CDCl_3$) δ: 1.14 (3H, d, *J* =7.4 Hz, C18-H), 1.84 (1H, td, *J* =6.1, 14.4 Hz, C14-Hβ), 2.04-2.10 (2H, m, C6-H), 2.30 (1H, dd, *J* =8.8, 14.4 Hz, C14-Hα), 2.78 (1H, ddd, *J* =2.2, 4.4, 14.7 Hz, C5-Hα), 2.98 (1H, d, *J* =12.0 Hz, C16-H), 3.05 (1H, m, C15-H), 3.16 (1H, d, *J* =14.4 Hz, C21-Hα), 3.26 (1H, m, C5-Hβ), 3.39 (3H, s, $-CO_2CH_3$), 3.60 (1H, d, *J* =6.1 Hz, C3-H), 3.69 (3H, s, $-CO_2CH_3$), 3.69 (1H, d, *J* =14.4 Hz, C21-Hβ), 3.96 (1H, s, N_a-H), 5.30 (1H, q, *J* =7.4 Hz, C19-H), 6.65 (1H, d, *J* =7.5 Hz, C12-H), 6.67 (1H, t, *J* =7.5 Hz, C10-H), 6.80 (1H, d, *J* =7.5 Hz, C9-H), 7.07 (1H, t, *J* =7.5 Hz, C11-H). ^{13}C-NMR (125MHz, $CDCl_3$) δ: 87.72 (C2), 72.00 (C3), 47.76 (C5), 32.89 (C6), 60.18 (C7), 130.41 (C8), 125.29 (C9), 118.38 (C10), 128.28 (C11), 110.54 (C12), 151.40 (C13), 31.48 (C14), 47.38 (C15), 56.32 (C16), 12.11 (C18), 115.87 (C19), 140.41 (C20), 60.32 (C21), 52.17 and 52.56 (CO_2CH_3), 168.73 and 169.58 (CO_2CH_3). Crystallographic data for compound **14**. The space group of the colorless prismatic crystal is P1. Cell constants are a=9.8554(7), b=12.1915(9), c=8.8033(8)Å, α=105.862(6)°, β=90.656(8)°, γ=74.071(6)°, V=976.1(1)Å^3, Z=2. Of the 3699 reflections which were collected, 3483 were unique. The final R factor is 0.043 (Rw=0.039).The refined fractional atomic coordinates, the bond lengths, the bond angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. (**16**): mp. 201-203°C (AcOEt). ^{13}C-NMR (125MHz, $CDCl_3$) δ: 86.19 (C2), 70.93 (C3), 47.71 (C5), 32.67 (C6), 60.19 (C7), 129.39 (C8), 126.42 (C9), 118.60 (C10), 128.20 (C11), 109.47 (C12), 151.10 (C13), 31.26 (C14), 47.30 (C15), 56.14 (C16), 14.01 (C18), 113.94 (C19),142.51 (C20), 56.14 (C21), 52.22 and 52.57 (CO_2CH_3), 168.75 and 169.55 (CO_2CH_3).
11. On exposure to the radical cyclization conditions, the unstable indole derivative **2** gave **10** in 12% yield. In this case, the production of the pentacyclic indoline derivatives (**14** or **16**) could not be observed. By applying this pathway, a five-step total synthesis of (±)-**1** could be achieved, although it is not practical.

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