First Total Synthesis of a Novel Monoterpenoid Isoquinoline Alkaloid, (±)-Alangine

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The structure including the stereochemistry of a novel monoterpenoid isoquinoline alkaloid, alangine, was confirmed by total synthesis *via N*-acyliminium cyclization to construct the isoquinoline skeleton and reductive cleavage of vinyl epoxide with Pd(0) catalyst.

Key words *Alangium*; alkaloid; total synthesis; isoquinoline

Recently, a new type of monoterpenoid isoquinoline alkaloid, alangine (**1**), was isolated from *Alangium lamarckii* (Alangiaceae) by Tanahashi and co-workers.[1] Its novel skeleton, probably derived from a biogenetic intermediate common to normal monoterpenoid isoquinoline alkaloids by the elimination of one carbon unit, was proposed based on the results of spectroscopic analyses. In particular, the relative stereochemistry of the vicinal positions at C2 and C14 in **1** was assumed based on nuclear Overhauser effect (NOE) correlations between H_2-15 and H_α-1 and those between H-11b and H-14. In the course of chemical and pharmacological studies on monoterpenoid indole[2] and isoquinoline[3] alkaloids, we were interested in the structure and the synthesis of this new type of alkaloid. Thus, we attempted the total synthesis of compound **1** and its 14-epimer (**2**) to clarify the relative stereochemistry of alangine. In this communication, we describe a concise total synthesis of **1** and **2**, and confirm that the structure of alangine is indeed **1** as proposed in the previous paper.[1]

Our basic approach to alangine synthesis, which features the construction of isoquinoline skeleton (**3**) *via N*-acyliminium ion prepared from cyclic imide (**4**)[4,5] and the regioselective preparation of homoallyl alcohol residue in **1** and **2** from a 1,3-dienyl side chain, is outlined in Fig. 1.

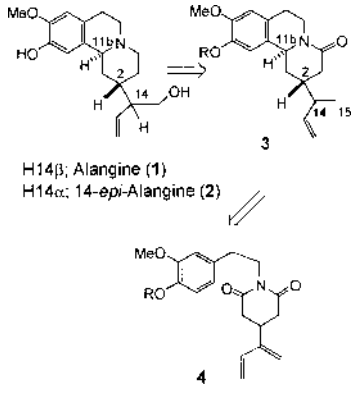

Fig. 1

First, we started with the preparation of cyclic anhydride (**7**) possessing an appropriate side chain that is subsequently convertible to the homoallyl alcohol. Conjugate addition of Grignard reagent prepared from chloroprene[6,7] to *trans*-glutaconic acid dimethyl ester (**5**) in the presence of 0.1 eq of $CuBr \cdot Me_2S$ and 2 eq of $TMSCl$[8] afforded adduct (**6**) in 48% yield (Chart 1). The esters in **6** were hydrolyzed with sodium hydroxide in 96% yield, followed by the treatment of the resultant acids with acetic anhydride in hot tetrahydrofuran (THF) to give cyclic anhydride (**7**) quantitatively. The thus obtained anhydride (**7**) was condensed with phenetylamine derivative (**8**), which was prepared from vanillin *via* a three-step reaction (protection of the phenol with an MEM group, condensation of the aldehyde with nitromethane, and $LiAlH_4$ reduction of the α,β-unsaturated nitro group), to give amide (**9**) in 91% yield, which was again heated with acetic anhydride in THF to afford cyclic imide (**10**) in 82% yield. Acid-assisted partial reduction of imide (**10**) ($NaBH_4$, molecular sieves, Dowex 50WX8, EtOH, CH_2Cl_2) yielded aminoacetal intermediate (**11**), that was then treated with CF_3CO_2H in CH_2Cl_2 to afford isoquinoline derivatives in 87% overall yield, probably *via N*-acyliminium ion cyclization. The product contained two diastereomers, namely, the H-11b/H-2 *trans* isomer (**12**) and its *cis* diastereomer in the ratio of 3.7 : 1. Their structures including the relative stereochemistry were determined by NMR analyses including differential NOE experiments.

Attempts at hydroboration-oxidation using various borane reagents to introduce a hydroxy group regioselectively at C-15 in **12** were unsuccessful. Therefore, we altered the synthetic route that utilized the 14,15-epoxy derivative of **13**, which was derived from **12** after removal of the protection on the phenol. Exposure of diene (**13**) to *m*-CPBA (1.1 eq, phosphate buffer, CH_2Cl_2, 0—5 °C) gave two desired epoxides (**14**, **15**) in 24% and 32% yields, respectively, together with 12,13-epoxide (**16**) in 26% yield, which could be converted to the starting material **13** by treatment with SmI_2 (2 eq 0 °C)[9] in 47% yield. The relative stereochemistry of the epoxy function in **14** and **15** was tentatively assigned as shown in Chart 2, based on the results obtained by the following reactions. Cleavage of the major epoxide (**15**) with hydride under conventional conditions[10] ($AlCl_3$, $LiAlH_4$, 0 °C, THF) afforded homoallyl alcohol (**19**) in low yield (4%), which could be converted to **2** (*vide infra*), indicating that the relative stereochemistry at C14 in epoxide (**15**) was the β form as shown in Chart 2, based on the consideration of the reaction mechanism that the hydride attack would occur *via* the *SN*2 type process.[10] DIBAH reduction[11] of the same epoxide (**15**) gave mainly a unique product (**17**) possessing a cyclopropane ring. The structure including the stereochemistry at C14 was determined from heteronuclear multiple bond connectivity (HMBC) spectrum and differential NOE experiments. Accordingly, reductive cleavage of the epoxy ring in **14** and **15** was carried out by employing the conditions developed by Tsuji *et al.*[12] When major epoxide (**15**) was treated with 0.2 eq of $Pd_2(dba)_3$–$CHCl_3$ and 0.2 eq of n-Bu_3P in 1,4-dioxane in the presence of Et_3N and HCO_2H, two homoallyl alcohols (**18**) and (**19**) were obtained in 22% and 64% yields, respectively. Under the same conditions, diastereomeric epoxide (**14**) gave **18** and **19** in 22% and 34%

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yields, respectively, whose relative stereochemistries at C14 were unambiguously determined by the following experiments (*vide infra*). The reaction would proceed *via* the π-allylpalladium alkoxide complex, that was equilibrated under thermodynamically controlled conditions *via* σ-palladium intermediates,[12] resulting in the formation of **19** predominantly over **18** from the two starting materials with different stereochemistries. The thus obtained homoallyl alcohols (**18**, **19**) possessing the lactam function in the molecule were reduced with DIBAH to furnish target compounds **1** and **2**, respectively. The stereochemistry at C14 in **1** and **2** was confirmed by NOE experiments (see Fig. 2) using the sterically rigid derivatives (**20**, **21**), that were obtained by mesylation of the primary alcohols in **1** and **2**. The synthetic compound **1**, not the 14-epimer (**2**), was completely identical with the natural product by comparison of their chromatographic behavior, as well as their mass, and ^{1}H- and ^{13}C-NMR spectra.[13] In conclusion, the structure of alangine was concluded to be **1** as was proposed originally.[1]

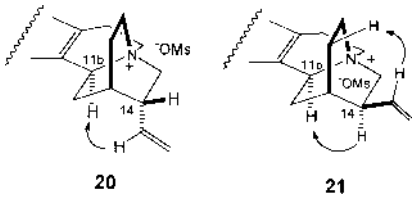

Fig. 2. NOE Correlations

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References and Notes

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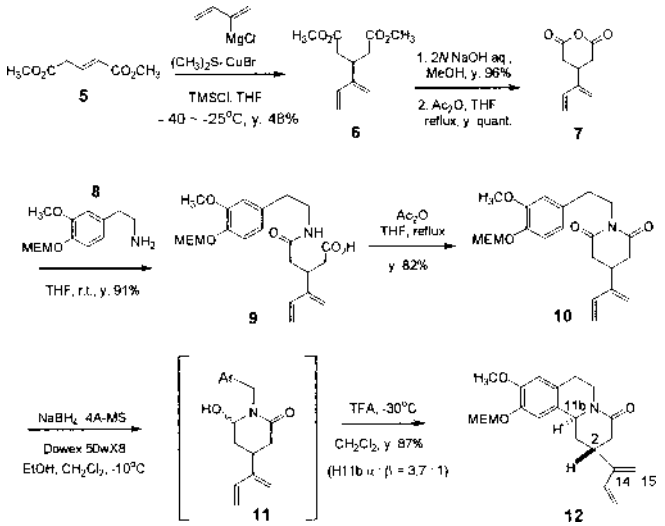

Chart 1

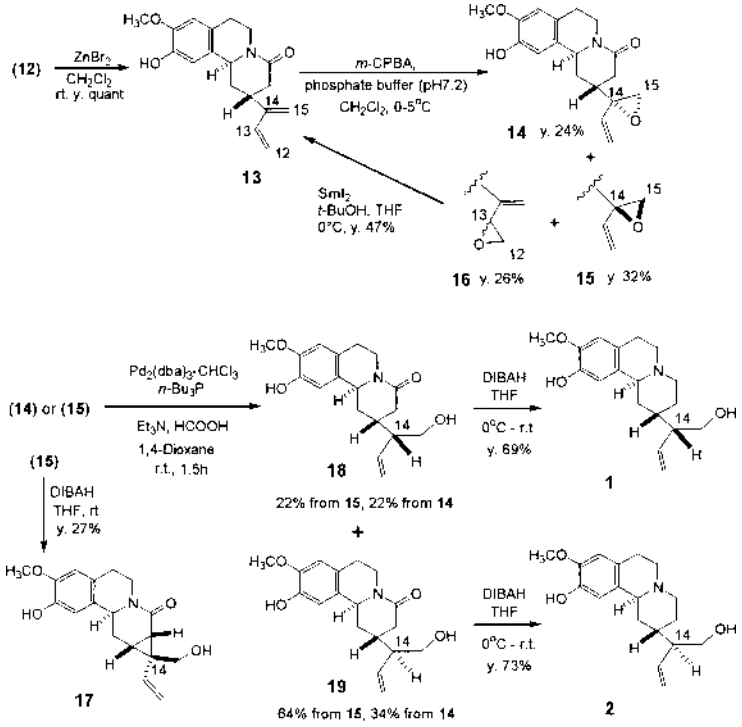

Chart 2

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13) In the ^{1}H- and ^{13}C-NMR spectra, the chemical shifts of synthetic alangine, particularly those of atoms neighboring nitrogen, *i.e*., C4, C6, C11b, were different from those of natural product originally reported in ref. 1. Thus, the natural product, which was kindly provided by Professor T. Tanahashi, was rechromatographed on Al_2O_3 and its NMR spectra were recorded again. The thus obtained data were completely identical with those of the synthetic compound described below. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.59 (1H, m, H-3), 1.69 (1H, m, H-2), 1.76 (1H, m, H-3), 1.87 (1H, m, H-1), 2.06 (1H, m, H-1), 2.45 (1H, m, H-14), 2.50—2.56 (2H, H-4, H-7 overlapped), 2.72 (1H, m, H-4), 2.78 (1H, m, H-6), 3.02 (1H, m, H-6), 3.08 (1H, m, H-7), 3.49 (1H, dd, J=8.7, 10.5 Hz, H-15), 3.60 (1H, m, H-11b), 3.84 (1H, m, H-15), 3.85 (3H, s, Ar-OCH_3), 5.19 (1H, dd, J=1.7, 17.2 Hz, H-12), 5.25 (1H, dd, J=2.0, 10.2 Hz, H-12), 5.59 (1H, ddd, J=9.8, 9.8, 17.1 Hz, H-13), 6.55 (1H, s, H-8), 6.74 (1H, s, H-11). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 26.8 (C7), 28.3 (C3), 32.0 (C2), 32.6 (C1), 48.4 (C14), 49.3 (C4), 52.2 (C6), 55.9 (Ar-OCH_3), 57.1 (C11b), 63.5 (C15), 110.9 (C8)*, 111.0 (C11)*, 118.7 (C12), 126.2 (C7a), 130.1 (C11a), 138.9 (C13), 143.8 (C10), 145.0 (C9) *=interchangeable. Compound (**2**): ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 1.66 (2H, H-2, H-3 overlapped), 1.81 (1H, m, H-1), 1.85 (1H, m, H-3), 2.06 (1H, m, H-1), 2.47 (1H, m, H-14), 2.53—2.59 (2H, H-4, H-7 overlapped), 2.74—2.78 (2H, H-4, H-6 overlapped), 3.01 (1H, dd, J=6.5, 11.7 Hz, H-6), 3.08 (1H, m, H-7), 3.39 (1H, dd, J=8.8, 10.7 Hz, H-15), 3.51 (1H, m, H-11b), 3.77 (1H, dd, J=4.1, 10.4 Hz, H-15), 3.84 (3H, s, Ar-OCH_3), 5.24 (1H, ddd, J=0.6, 1.9, 17.0 Hz, H-12), 5.34 (1H, dd, J=1.9, 10.2 Hz, H-12), 5.65 (1H, ddd, J=9.9, 9.9, 17.3 Hz, H-13), 6.55 (1H, s, H-8), 6.68 (1H, s, H-11). ^{13}C-NMR (150 MHz, $CDCl_3$) δ: 27.2 (C7), 28.0 (C3), 31.8 (C2), 33.5 (C1), 48.4 (C14), 49.7 (C4), 52.2 (C6), 56.0 (Ar-OCH_3), 57.1 (C11b), 63.7 (C15), 111.0 (C8, C11), 119.2 (C12), 126.2 (C7a), 130.4 (C11a), 139.0 (C13), 143.4 (C10), 145.0 (C9).