A SHORT STEP SYNTHESIS OF CLAVICIPITIC ACIDS FROM 4-CYANOMETHYLINDOLE

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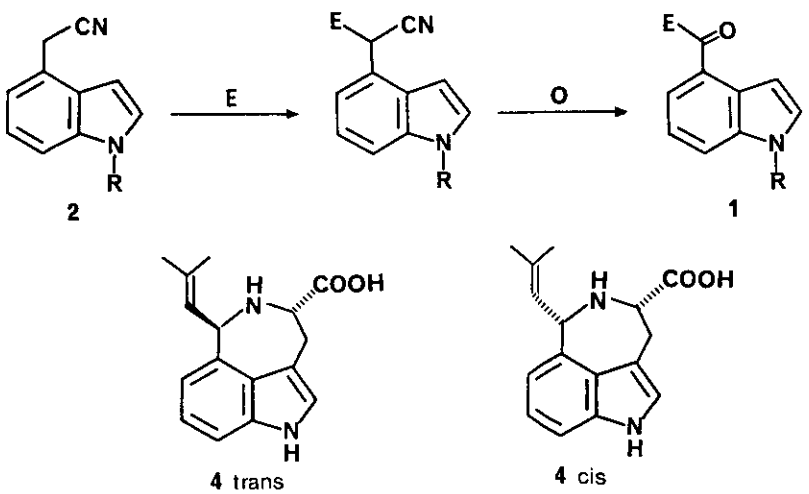
Abstract —— 4-(3-methyl-1-oxo-2-buten-1-yl)indole (3) was efficiently synthesized from 4-cyanomethyl-1-(p-toluenesulfonyl)indole by alkylation with 2-methyl-2-buten-1-yl tosylate and by successive aerobic oxidation and deprotection of N-tosyl group. The acylindole 3 was used for a short step synthesis of clavicipitic acids (4).

Ergot alkaloids and their related compounds have got a considerable attention owing to their interesting biological activities, and much efforts have been made to synthesize them efficiently. These alkaloids commonly comprise of the indole skeleton with an α-substituted C_5 isoprene unit at the 4-position.[1] For their synthesis, 4-acylindoles 1 should convincingly be a versatile intermediate. There have, however, been few examples starting from 1 except for 4-formylindole,[2] because that any precursors leading to 1 have probably been known with easy availability and versatility.



It occurred to us that 4-cyanomethylindole (2)[3] would just fit above situation for the reasons that (i) the indole 2 has become easily available in a large scale, (ii) 2 possesses an active methylene to extend a carbon chain, and (iii) also its cyano group is able to suffer oxidative extrusion. We wish to describe here that the idea was proved by the synthesis of 4-(3-methyl-1-oxo-2-buten-1-yl)indole (3) as a representative, and that the indole 3 provided a short-step synthesis of clavicipitic acids (4), which are interesting derailment product in the biosynthesis of ergot alkaloids.[4,5]

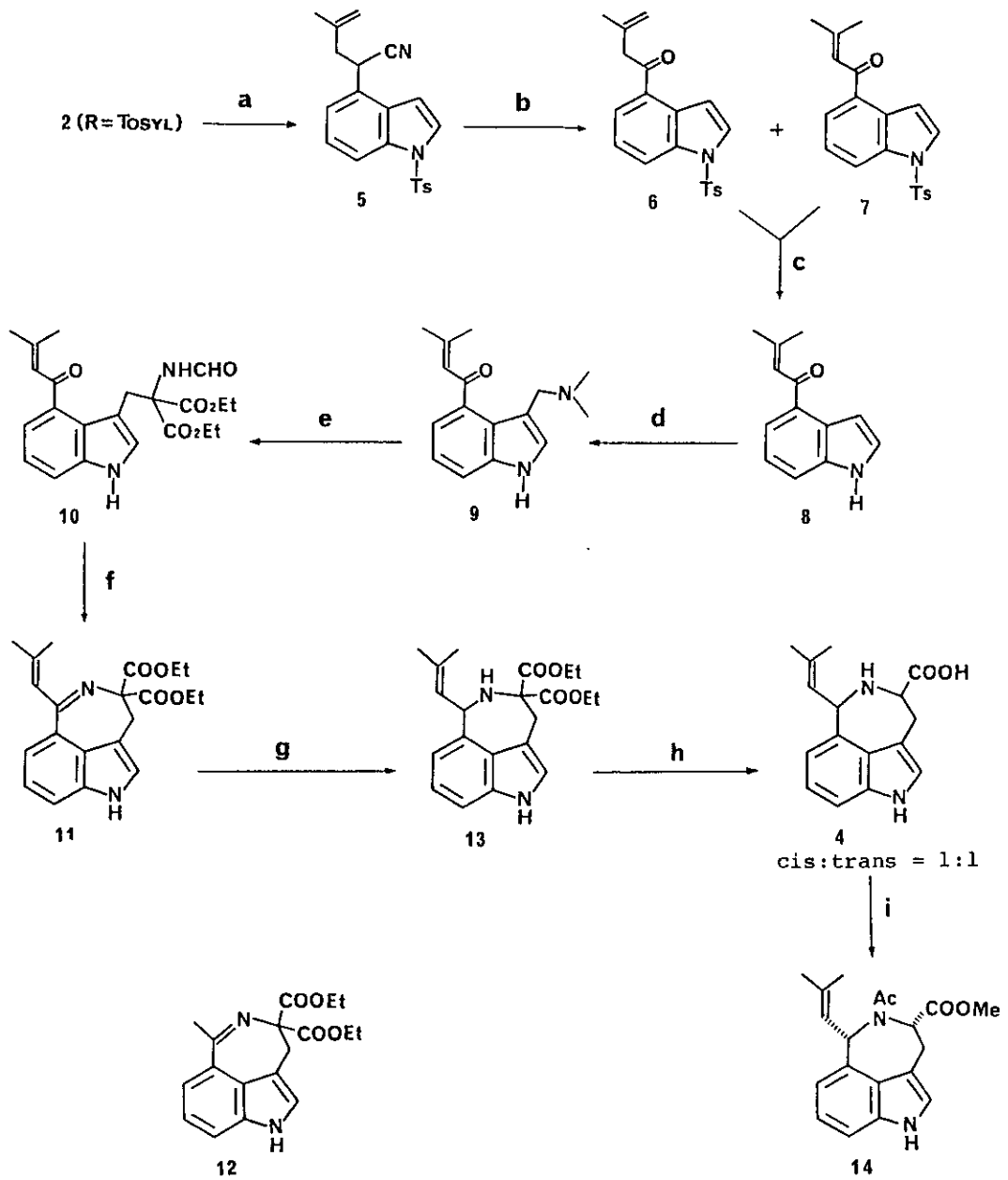
First, a methallyl (2-methyl-2-propen-1-yl) group was introduced to α-position of the side chain in 2 (R=tosyl). Anion of 2 (500 mg, 1.61 mmol) prepared with butyllithium (1.64 mmol) was reacted with methallyl tosylate (1.62 mmol) in dry THF (5 mL) under argon atmosphere at -78 °C for 2 h. After usual workup, the mixture was chromatographed on silica gel and eluted with CH_2Cl_2 to give the desired indole 5 in 85% yield (selectivity 91%).

In order to remove the cyano group of the indole 5, we used aerobic oxidation of anion of 5. The indole 5 (1.29 mmol) was stirred with potassium t-butoxide (1.30 mmol) in dry dimethoxyethane (DME) (5 mL) under argon at -78°C for 30 min to yield a red colored solution of the anion, which was in turn exposed to dry dioxygen at -78°C until the red color disappeared (<1 h). The reaction mixture gave ketones 6 and 7 (6/7 = 58/42) in 74% yield. The formation of the mixture 6 and 7 did not disturb our work at all (vide infra). The aerobic oxidation of 5 was further examined under various conditions (NaH or BuLi/ THF or dioxane/ -78°C - room temperature), where none exceeded the system of t-BuOK/DME/-78°C. MoO_5.Py.(HMPA)[6] was also less effective as an oxidant for the present purpose.

Deprotection of the N-tosyl group of 6 accompanied with double bond isomerization (NaOH/MeOH): the mixture of 6 and 7 gave solely a conjugated ketone 3.[7] The deprotection was also able to be done without isolation of 6 and 7 after the oxidation of 5.

The starting acylindole 3 was now in our hand, so that we started to synthesize clavicipitic acids (4). Introduction of an alanine equivalent at the 3-position of 3 was required in the first place, and was attained by the standard procedure through a gramine 8, which was quantitatively obtained from 3 and $(CH_3)_2N{=}CH_2{}^{+}Cl^{-}$.[8] The condensation of 8 with diethyl N-formylaminomalonate was effected by dimethyl acetylenedicarboxylate[9] (THF/0°C/5.5 h) to yield the desired 3,4-disubstituted indole 9[10] in 87% yield.

The step that we felt the most anxious was the intramolecular formation of Schiff's base 10 from 9 after hydrolysis of N-formyl group, since the reaction of α,β-unsaturated ketones



a) BuLi/$TsOCH_2C(Me)=CH_2$, b) Bu^tOK/-78°C-O_2, c) NaOH/MeOH, d) $Me_2N^{\pm}=CH_2 \cdot Cl^-$,
e) $OHONHCH(CO_2Et)_2$/$MeOCOC=CCO_2Me$, f) 1.2N HCl/DME, g) $C_6H_4O_2BH$,
h) KOH/MeOH, i) MeCOOCOMe/MeOH.

with primary amine give in general conjugate addition products, β-aminoketones.[11] On the other hand, we expected that the steric factors of 9 would favor the desired cyclization. When the indole 9 was treated in HCl/H_2O/DME (1.2N HCl:DME = 1:1) under argon atmosphere at refluxing temperature for 1.5 h, the Schiff's base 10[12] formed in 52% yield together with 11 (16%). The latter was likely produced by the retro-aldol reaction of 10 or 9.

The compound 10 was an ethyl analogue of Kozikowski's intermediate, so that further transformation was made in accord with his method.[5c] Catecholborane reduced selectively the C-N double bond of 10 ($CHCl_3$/0°C/30 min) to give diester 12[13] in 72% yield. Finally, the diester 12 was hydrolyzed with KOH/MeOH at room temperature for 6 h, and successive treatment of the mixture with ion-exchanger resin (IRC-50, H^+-form), as shown by Natsume,[5b] gave clavicipitic acids (4) (cis/trans = 1).[14] Direct comparison of our product 4 with Natsume's synthetic sample (pure cis- and trans-form) confirmed the above results. Furthermore, our compound (cis and trans mixture) was transformed into the cis-isomer of N-acetyl methyl ester 13, whose physical properties were identical with those reported by Kozikowski and Natsume.[5]

4-Cyanomethylindole (2) was shown to be useful as a precursor of 4-acylindoles which was applied to a short step synthesis of clavicipitic acids. Further application of 2 to synthesis of valuable indoles is now progress.

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(7) Pale yellow flakes (from hexane-CH_2Cl_2) melted at 113-114°C. NMR($CDCl_3$)δ2.00(s, 3H), 2.21(s, 3H), 6.80-6.88(m, 1H), 7.11-7.34(m, 3H), 7.54(d, J=8.0Hz, 1H), 7.70(d, J=8.0Hz, 1H), and 8.78-9.10(broad s, 1H)ppm. IR(KBr) 3285, 1637, 1590, and 1500 cm^{-1}. Mass(m/z, %) 199(M^+, 100), 184(83), 170(18), 167(16), 156(16), 144(47), and 116(62). Anal. Calcd.($C_{13}H_{13}NO$): C,78.36; H,6.58; N,7.03. Found: C,78.21; H,6.67; N,6.98.

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(10)Colorless prisms (from hexane-ethyl acetate) melted at 147-148.5°C. NMR($CDCl_3$)δ1.18(t, J=7.1Hz, 6H), 2.01(d, J=1.3Hz, 3H), 2.27(d, J=1.3Hz, 3H), 3.90(s, 2H), 4.12-4.19(four q, J=7.1Hz, 4H), 6.61(qq, J=1.3 and 1.3Hz, 1H), 7.01-7.06(m, 1H), 7.15(dd, J=8.1 and 7.4Hz, 1H), 7.15-7.17(m, 1H), 7.35(dd, J=7.4 and 1.0Hz, 1H), 7.44(dd, J=8.1 and 1.0Hz, 1H), 7.97(d, J=1.4Hz, 1H), 8.78-8.85(m, 1H)ppm. IR(KBr) 3355, 3210, 1745, 1670, 1600, and 1494 cm^{-1}. Mass(m/z, %) 414(M^+,9), 212(62), and 170(100). Anal. Calcd.($C_{22}H_{26}N_2O_6$): C,63.75; H,6.32; N,6.76. Found: C,63.58; H,6.38; N,6.62.

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(12)Pale yellow prisms (from hexane-ethyl acetate) melted at 153.5-155°C. NMR($CDCl_3$) δ0.52-0.90(m, 3H), 1.08-1.48(m,3H), 1.96(d, J=1.3Hz, 3H), 2.01(d, J=1.3Hz, 3H), 3.39-4.47(m, 6H), 6.36(qq, J=1.3 and 1.3Hz, 1H), 7.06(ddd, J=2.3, 1.1, and 1.1Hz, 1H), 7.18(dd, J=8.1

and 7.5Hz, 1H), 7.37(dd, J=8.1 and 0.8Hz, 1H), 7.40(dd, J=7.5 and 0.8Hz, 1H), and 8.25–8.35(m, 1H)ppm. IR(KBr) 1745, 1590, and 1505 cm^{-1}. Mass(m/z,%) 368(M^+, 94), 367(100), 295(74), 293(40), 222(37), 221(91), 207(39), and 206(41). Anal. Calcd.($C_{21}H_{24}N_2O_4$): C,68.46; H,6.57; N,7.60. Found: C,68.43; H,6.64; N,7.51.

(13)Colorless prisms (from hexane-ethyl acetate) melted at 125–126.5°C. NMR($CDCl_3$) δ1.23(t, J=7.1Hz, 3H), 1.26(t, J=7.1Hz, 3H), 1.74(d, J=1.2Hz, 3H), 1.88(d, J=1.2Hz, 3H), 3.06–3.14(m, 1H), 3.48(d, J=15.6Hz, 1H), 3.93(dd, J=15.5 and 1.3Hz, 1H), 4.11–4.32(m, 4H), 5.30(broad d, J=8.8Hz, 1H), 5.45(dqq, J=8.8, 1.2, and 1.2Hz, 1H), 6.77(d, J=7.2Hz, 1H), 6.93–6.97(m, 1H), 7.03(dd, J=8.2 and 7.2Hz, 1H), 7.17(d, J=8.2Hz, 1H), and 7.91–7.99(m, 1H)ppm. IR(KBr) 3330, 1747, and 1725 cm^{-1}. Mass(m/z,%) 370(M^+,44), 297(100), 241(28), 223(56), 196(40), 182(30), 167(41), and 154(32). Anal. Calcd.($C_{21}H_{26}N_2O_4$): C,68.09; H,7.07; N,7.56. Found: C,68.27; H,7.19; N,7.49.

(14)The NMR(400MHz) spectra showed that 4 obtained here existed in betain form ($RNH_2^+CR'COO^-$)in neutral CD_3OD. On the other hand, the NMR spectra of 4 in basic CD_3OD exhibited similar pattern to those of 4 with the amino acid structure (RNHCR'COOH). These trend was further confirmed by the NMR spectral analysis of Natsume's sample.

The NMR(400MHz) spectra of 4 in CD_3OD with betain form were as follows:

trans-4: δ1.96(d, J=1.1Hz, 3H), 1.99(d, J=1.1Hz, 3H), 3.21(ddd, J=16.6, 11.5, and 1.3Hz, 1H), 3.85(dd, J=16.6 and 3.4Hz, 1H), 4.14(dd, J=11.5 and 3.4Hz, 1H), 5.58(d with fine coupling, J=9.5Hz, 1H), 5.62(d, J=9.5Hz, 1H), 6.85(d, J=7.4Hz, 1H), 7.12(dd, J=8.1 and 7.4Hz, 1H), 7.24(broad s, 1H), and 7.37(d, J=8.1Hz, 1H)ppm.

cis-4: δ1.89(d, J=1.3Hz, 3H), 1.94(d, J=1.3Hz, 3H), 3.41(ddd, J=16.4, 12.4, and 1.5Hz, 1H), 3.72(dd, J=16.4 and 3.8Hz, 1H), 4.19(dd, J=12.4 and 3.8Hz, 1H), 5.49(d with fine coupling, J=9.0Hz, 1H), 5.92(d, J=9.0Hz, 1H), 6.84(d, J=7.4Hz, 1H), 7.10(dd, J=8.4 and 7.4Hz, 1H), 7.22(broad s, 1H), and 7.34(d, J=8.4Hz, 1H)ppm.

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