

A SHORT STEP SYNTHESIS OF CLAVICIPITIC ACIDS FROM 4-CYANOMETHYLINDOLE

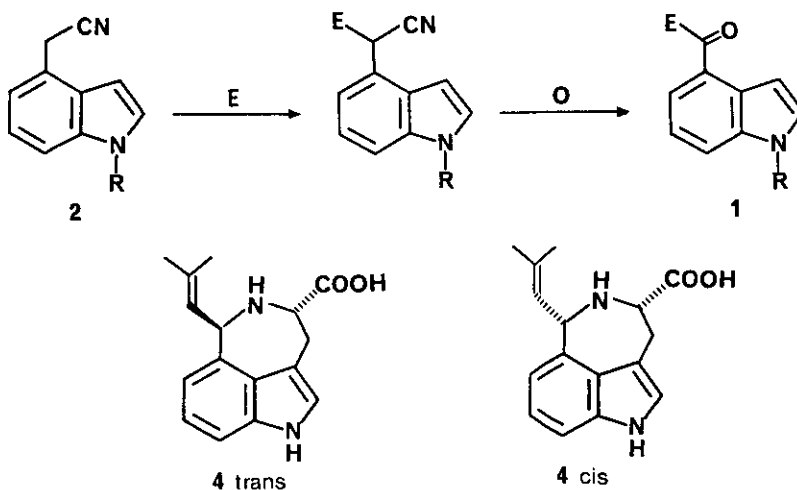
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Abstract — 4-(3-methyl-1-oxo-2-buten-1-yl)indole (3) was efficiently synthesized from 4-cyanomethyl-1-(p-toluenesulfonyl)indole by alkylation with 2-methyl-2-buten-1-yl tosylate and by successive aerobic oxidation and deprotection of N-tosyl group. 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}

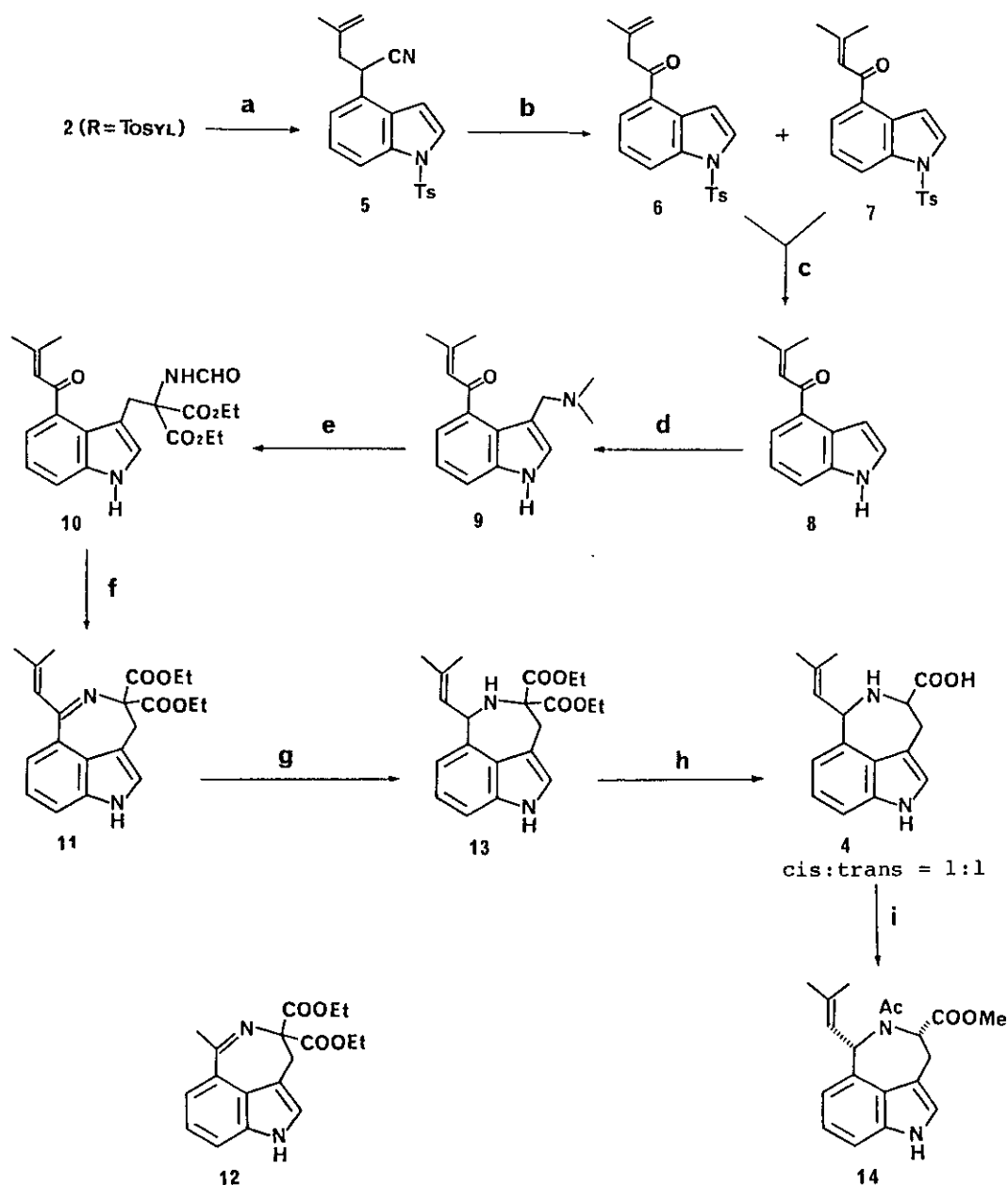
First, a methallyl (2-methyl-2-propen-1-yl) group was introduced to α -position of the side chain in 2 (R=tosyl). Anion of 2 (500 mg, 1.61 mmol) prepared with butyllithium (1.64 mmol) was reacted with methallyl tosylate (1.62 mmol) in dry THF (5 mL) under argon atmosphere at -78 °C for 2 h. After usual workup, the mixture was chromatographed on silica gel and eluted with CH₂Cl₂ 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. MoO₅.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 (CH₃)₂N=CH₂.⁸ The condensation of 8 with diethyl N-formylaminomalonate was effected by dimethyl acetylenedicarboxylate⁹ (THF/0°C/5.5 h) to yield the desired 3,4-disubstituted indole 9¹⁰ 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/TsOCH₂C(Me)=CH₂, b) Bu^tOK/-78°C-O₂, c) NaOH/MeOH, d) Me₂N⁺CH₂·Cl⁻,
 e) OHNHCH(CO₂Et)₂/MeOCOC=CCO₂Me, f) 1.2N HCl/DME, g) C₆H₄O₂BH,
 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/H₂O/DME (1.2N HCl:DME = 1:1) under argon atmosphere at refluxing temperature for 1.5 h, the Schiff's base 10¹² 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 (CHCl₃/0°C/30 min) to give diester 12¹³ 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.

ACKNOWLEDGEMENT

The authors express their appreciation to Professor M. Natsume and Dr. Muratake of Research Foundation Itsuu Laboratory for generous gifts of precious specimens and spectra, and helpful discussions. They also express thanks to Dr. M. Tanimoto, Messrs. Hikita and Mohara of their institute for measurement of NMR and Mass spectra and their analyses.

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- (7) Pale yellow flakes (from hexane-CH₂Cl₂) melted at 113–114°C. NMR(CDCl₃) δ 2.00(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.(C₁₃H₁₃NO): 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(CDCl₃) δ 1.18(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.(C₂₂H₂₆N₂O₆): 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(CDCl₃) δ 0.52–0.90(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. ($\text{C}_{21}\text{H}_{24}\text{N}_2\text{O}_4$): 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) δ 1.23(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. ($\text{C}_{21}\text{H}_{26}\text{N}_2\text{O}_4$): 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 ($\text{RNH}_2^+\text{CR}'\text{COO}^-$) 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 ($\text{RNHCR}'\text{COOH}$). 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: δ 1.96(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: δ 1.89(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.

Received, 20th January, 1987