Tetrahedron Letters,Vol.25,No.9,pp 969-972,1984 0040-4039/84 $3.00 + .00
Printed in Great Britain

TOTAL SYNTHESIS OF (±)-CANNABISATIVINE

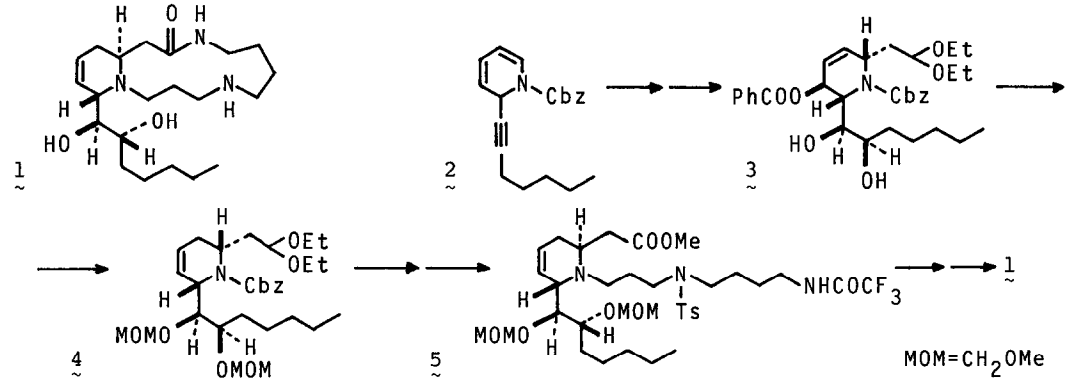
Masashi Ogawa, Naoko Kuriya, and Mitsutaka Natsume*
Research Foundation Itsuu Laboratory
2-28-10 Tamagawa, Setagaya-ku, Tokyo 158, Japan

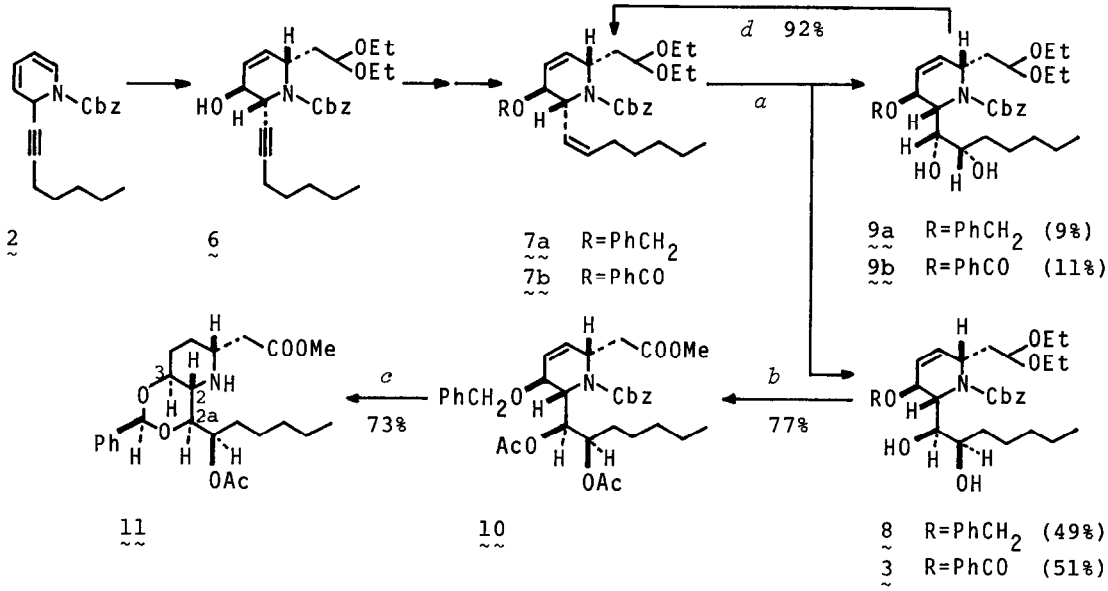
Abstract: Total synthesis of the *Cannabis* alkaloid cannabisativine (1) was stereoselectively achieved for the first time in a racemic form starting from a dihydropyridine derivative (2) by way of 3, 4, and 5.

Cannabisativine is an alkaloid isolated from *Cannabis sativa* L. and its structure has been established by single crystal X-ray analysis to be 1, whose polyamine function consists of spermidine and is incorporated into a thirteen-membered lactam ring condensed with a tetrahydropyridine moiety.[1)]

Here, we report a stereoselective synthesis of (±)-cannabisativine (1) starting from 1-benzyloxycarbonyl-2-(1-heptynyl)-1,2-dihydropyridine (2) according to our synthetic plan: i) stereo-predominant formation of the compound (3) bearing the C-seven side chain with correct stereochemistry (2→3), ii) regioselective introduction of the double bond in the piperidine part (3→4), iii) formation of the spermidine unit, followed by isomerization and oxidation of the C-two side chain (4→5), and iv) construction of the thirteen-membered lactam ring.

For the first step of the plan, compounds (7a) and (7b), prepared from 2 by way of 6 as reported previously,[2)] were oxidized with OsO_4 at low temperature, keeping in mind that the bulky *O*-substituents such as the $PhCH_2$ and PhCO groups are essential to discriminate between the reactivity of the two double bonds against OsO_4.[3)] Products (8) and (9a) were produced with $PhCH_2$ and (3) and (9b) with PhCO. The stereochemistry of the α-glycol system was verified by converting the major product (8) into the benzylidene derivative (11) [^{1}H-NMR





2 6 7a R=$PhCH_2$ 7b R=PhCO

9a R=$PhCH_2$ (9%) 9b R=PhCO (11%)

11 10 8 R=$PhCH_2$ (49%) 3 R=PhCO (51%)

a: OsO_4 in hexane-Et_2O-Py (10:10:1), -75→ -5°C.

b: i) Ac_2O, Py, r.t.; ii) 2% HCl in DME-H_2O (4:1), r.t.; iii) Jones reagent in Me_2CO, 0°C; iv) CH_2N_2 in MeOH-Et_2O.

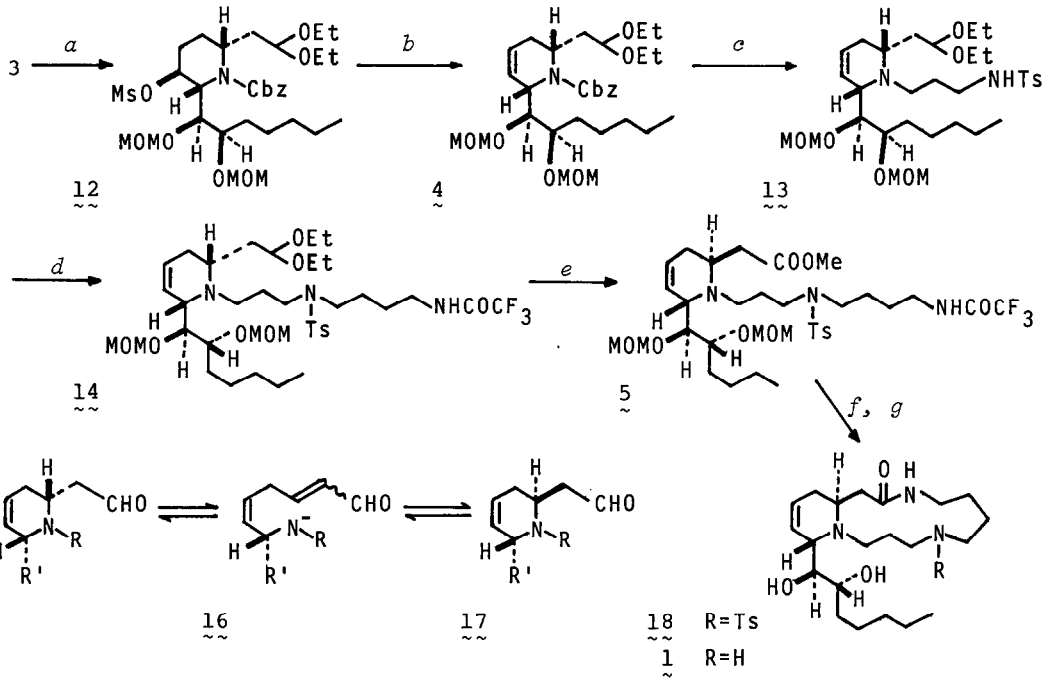
c: i) H_2, 10% Pd-C, 0.3% HCl in MeOH; ii) 6% NaOMe in MeOH, 0°C; iii) $ZnCl_2$ in PhCHO, r.t.; iv) Ac_2O, Py, r.t.

d: i) $NaIO_4$, MeOH-H_2O (4:1), r.t.; ii) $Ph_3P{=}CH{-}C_5H_{11}$, THF, 0°C.

Chart 1

($CDCl_3$) δ: 2.57 (dd, *J*=9, 9 Hz, H-2), 3.48 (ddd, *J*=9, 9, 4.5 Hz, H-3), 3.80 (dd, *J*=9, 4.5 Hz, H-2a)]. The diethyl acetal grouping of 8 was transformed at first into the methyl acetate moiety in 10 to simplify analysis of the ^{1}H-NMR signals around the ether region of the compound (11). The coupling pattern of $J_{2,3}=J_{2,2a}=9$ Hz clearly demonstrates that the stereochemical arrangement is expressed as shown. Therefore, 8 and 3 can serve as suitable intermediates for cannabisativine synthesis. The undesired product (9a) was converted back to 7a in a high yield, indicating that vicinal diol formation can be carried out stereoselectively. On a preparative scale, 7b was oxidized by a modified procedure[4] [catalytic amount of OsO_4, $Me_3N{\rightarrow}O$, THF-H_2O (5:1), 0→10°C] to afford 3 and 9b in 50% and 11% yields, respectively.

The next step was the regioselective introduction of the double bond in the piperidine ring and it was attainable in a high yield only by treating the methanesulfonate (12) with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).[5] For the preparation of 12, the vicinal diols in the compound (3) were protected by the methoxymethyl (MOM) group, the *O*-benzoate group was hydrolyzed, and the double bond was catalytically reduced over Pt in DME. This was followed by treatment with methanesulfonyl chloride in pyridine as usual. For the DBU



a: i) $MeOCH_2Cl$, *i*-Pr_2NEt-CH_2Cl_2 (1:4), r.t., 85%; ii) K_2CO_3 suspended in MeOH, r.t., 100%; iii) H_2, Pt, DME, r.t.; iv) $MeSO_2Cl$, Py, r.t., 80%.

b: DBU-toluene (1:1), 110-115°C, 81%.

c: i) Na, NH_3-THF, -70– -60°C; ii) $ClCOCH_2CH_2NHTs$, K_2CO_3 in PhH-PhMe-H_2O (3:1:1), 0→10°C, 87%; iii) $LiAlH_4$, THF, reflux, 85%.

d: i) 4-bromo-*N*,*N*-phthaloyl-1-aminobutane, K_2CO_3, DMF, r.t., 96%; ii) 80% NH_2NH_2-H_2O, EtOH, r.t., iii) $(CF_3CO)_2O$, Et_3N-CH_2Cl_2 (1:4), -78°C, 70%.

e: i) *p*-TsOH, Me_2CO, 0°C→r.t.; ii) K_2CO_3 suspended in MeOH, 0°C; iii) Jones reagent, Me_2CO, 0°C; iii) CH_2N_2 in MeOH-Et_2O, 0°C, 80%.

f: i) 3% $Ba(OH)_2$ in MeOH-H_2O (3:1), r.t.; ii) HCl salt; iii) $(COCl)_2$, 0°C; iv) K_2CO_3 suspended in CH_3CN, r.t.; v) 10% HCl in MeOH-H_2O (3:1), 43%.

g: Na, NH_3-THF, -78°C, 82%.

Chart 2

treatment, a toluene solution of 12 was heated to 110-115°C (bath temperature) for *ca.* 20 h.

The spermidine side chain was constructed by applying two successive elongations to the nitrogen atom of the compound (4) through 13 to 14. The nitrogen-protecting group of 4 was removed with Na in liquid ammonia and the resulting amine was acylated with β-tosylaminopropionic chloride in the presence of K_2CO_3, followed by reduction of the amide function with $LiAlH_4$ to yield 13. 4-Bromo-*N*,*N*-phthaloyl-1-aminobutane was reacted with 13 using K_2CO_3 in DMF, and the terminal nitrogen function was changed to trifluoroacetamide group as in 14. An aldehyde obtained from 14 by ketal exchange procedure was next submitted to epimerization reaction of the C-two side chain. This is

based on an equilibrium between 15 and 17 (R=R'=alkyl groups) with a *retro*-Michael compound (16) as a possible intermediate.[5] Brief exposure of the aldehyde derived from 14 to a saturated solution of K_2CO_3 in MeOH at 0°C furnished a 2,6-*trans* derivative exclusively,[5] which was isolated in the form of methyl carboxylate (5) after Jones oxidation and esterification with CH_2N_2.

The final stage of the synthesis, cyclization to the thirteen-membered lactam ring, was accomplished as follows. The compound (5) was hydrolyzed with $Ba(OH)_2$ and the resulting amino acid was directly converted to its acid chloride HCl salt. A cold solution of the acid chloride in CH_3CN was added dropwise to a suspension of K_2CO_3 in a large amount of CH_3CN using a dry ice jacketed dropping funnel, with vigorous stirring at room temperature. The methoxymethyl group was removed by acid treatment and the desired compound (18) was obtained in 43% yield from 5. Cleavage of the *N*-tosyl group completed the synthesis of (±)-1, mp 150-151°C (Me_2CO-Et_2O). This was identified by comparing it with natural cannabisativine by TLC [Al_2O_3, CH_2Cl_2-EtOH (24:1); CH_2Cl_2-DME (3:2)] and by the MS, IR ($CHCl_3$), ^{1}H-NMR (400 MHz, CD_3OD, 50°C), and ^{13}C-NMR (100 MHz, $CDCl_3$) spectra.[6]

Acknowledgment —— We wish to thank Professors D. J. Slatkin, University of Pittsburgh and M. ElSohly, University of Mississippi for generous gifts of cannabisativine. We are also grateful to Meiji Seika Kaisha Ltd., for measurement of the NMR spectra.

REFERENCES AND NOTES

1) H. L. Lotter, D. J. Abraham, C. E. Turner, J. E. Knapp, P. L. Schiff, Jr., and D. J. Slatkin, *Tetrahedron Lett.*, 1975, 2815.
2) M. Natsume and M. Ogawa, *Heterocycles*, 20, 601 (1983).
3) a) M. Natsume and M. Ogawa, *Heterocycles*, 16, 973 (1981); b) M. Natsume and M. Ogawa, *Chem. Pharm. Bull.*, 30, 3442 (1982).
4) *cf.* V. VanRheenen, R. C. Kelly, and D. Y. Cha, *Tetrahedron Lett.*, 1976, 1973.
5) M. Ogawa, J. Nakajima, and M. Natsume, *Heterocycles*, 19, 1247 (1982).
6) ^{13}C-NMR ($CDCl_3$, 27°C) of (±)-1 δ: 14.4, 23.0, 24.4, 25.6, 25.8, 26.1, 27.3, 29.9, 32.3, 33.6, 38.5, 39.9, 43.6, 48.6, 49.3, 51.9, 59.5, 74.1, 123.4, 128.2, 170.1.

(Received in Japan 3 December 1983)