FORMAL TOTAL SYNTHESIS OF EUPOLAURAMINE

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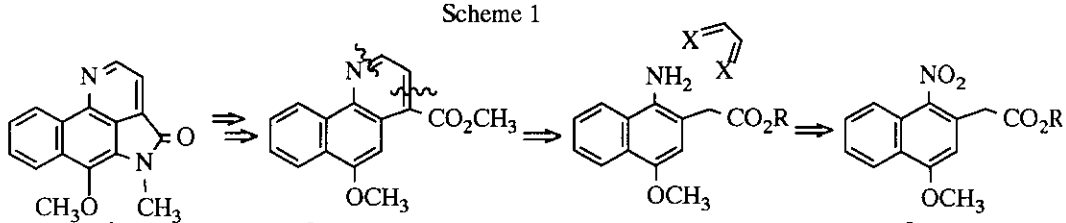
Abstract *The key intermediate for eupolauramine synthesis was obtained in a short reaction sequence in which vicarious nucleophilic substitution of hydrogen was the key step.*

Total synthesis of eupolauramine 1, an azaphenanthrene alkaloid isolated by Taylor *et al.*[1] from the bark of *Eupomatia laurina* was already a subject of four papers.[2-5] In the last of them a very efficient synthesis based on 10-step reaction sequence was described.[5] The key intermediate in this synthesis, benzo[4]quinoline derivative 2a, was constructed from commercial methyl 2-naphthylacetate in 7 steps, of which crucial steps were formation of C-N and C-OMe bonds, and aromatization of dihydrocarbostyril moiety *via* thiolactam formation. Vicarious nucleophilic substitution of hydrogen (VNS) discovered and developed in our laboratory is already a powerful tool in organic synthesis,[6] particularly heterocyclic compounds.[7] In this paper it will be shown that this reaction can be also efficiently used in synthesis of 2 and therefore 1.

Scheme 1



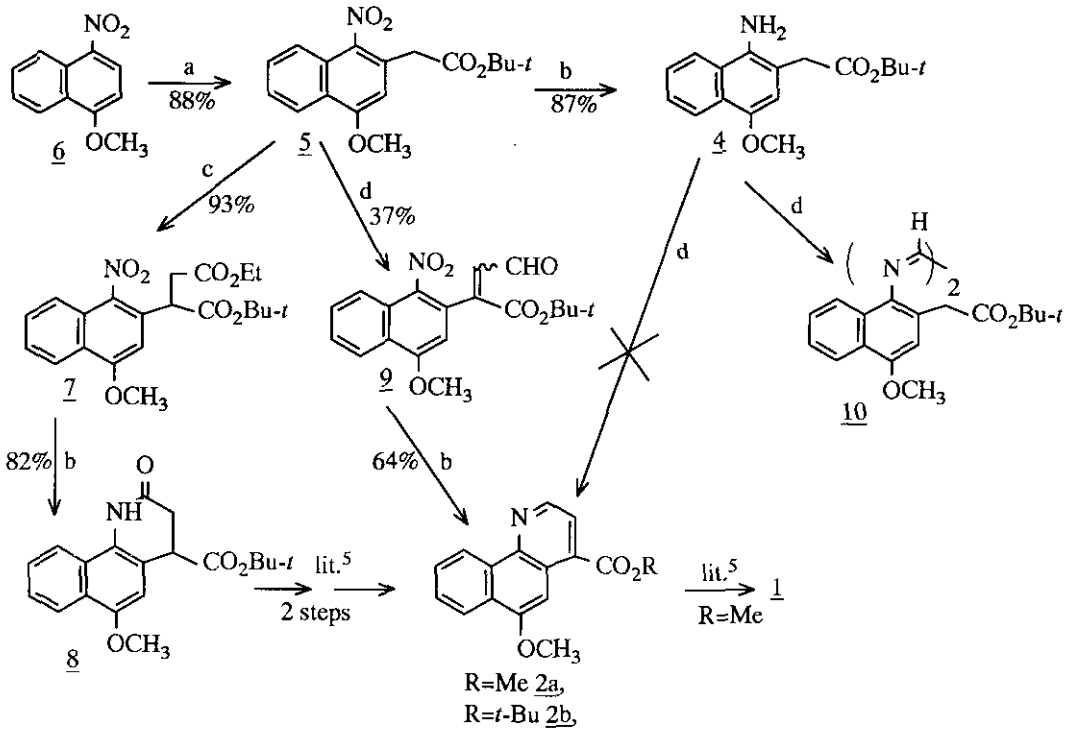
1 2a 4 5

Retrosynthetic analysis of structure 2 shows possibility of disconnection onto 3-(1-methoxy)naphthylacetic acid moiety and a two-carbon unit (shown on Scheme 1). The former fragment can be efficiently prepared from commercially available 4-nitromethoxynaphthalene 6 *via* the VNS reaction with carbanion of alkyl chloroacetate giving 5.[8] There are a few ways of conversion of the VNS product 5 into desired intermediate 2 as shown on Scheme 2.

Treating of 6 with 1.1 eq. of *t*-butyl chloroacetate in the presence of 5 eq. of *t*-BuOK in DMF at -20° (typical VNS conditions) gave expected product 5 in 88% yield which was subjected to catalytic hydrogenation on 10% Pd/C to give 4. *t*-Butyl ester was selected in order to avoid transesterfication with *t*-butoxide. Several attempts of transformation of 4 directly to target molecule 2 by the reaction with glyoxal (40% aq, or polymeric dihydrate) under a variety of conditions were unsuccessful. The reaction with 40% glyoxal in aq. EtOH catalyzed by piperidine gave dimeric product 10 even when five fold excess of the aldehyde was used, whereas in the presence of stronger bases, like *t*-BuOK or KOH only tars were produced.

Dedicated to Professor Masatomo Hamana on the occasion of his 75th birthday

Scheme 2



a. $ClCH_2CO_2Bu$-*t*/ 5 eq. *t*-BuOK, /DMF; -20°C/1 h

b. H_2 60 psi/10% Pd/C/EtOH; room temperature

c. $BrCH_2CO_2Et$, 5 eq. K_2CO_3, /DMF; room temperature/overnight

d. 40% glyoxal/cat. DBU/DMF;room temperature /1 h

Since condensation of glyoxal with amine 4 to give 2b was unsuccesfull we attempted its condensation with 5 in which the benzylic position is efficiently activated by the *ortho*-nitro group. After a few unsuccessful attempts under a variety of conditions (Et_3N, piperidine or K_2CO_3 with 40% aq. glyoxal or its polymer in DMF, MeCN, EtOH or pyridine) we have found that the reaction worked satisfactorilly when an excess of 40% aq. glyoxal in DMF and catalytic amount of DBU as a base were used. Desired unsaturated aldehyde 9 was obtained in 37% yield as a single isomer. Geometry of this unsaturated aldehyde was not determined, but it was subjected directly to hydrogenation which resulted in spontaneous cyclization to 2 as the only isolable product in 64% yield .

Thus the key intermediate in eupolauramine synthesis 2 was synthesized in a 3-steps process in which VNS was the key reaction. Lower owerall yield, as compared with the approach described by Kikugawa was compensated by convenience and briefness of the described above methodology.

Alternative, somewhat longer approach to synthesis of 2 from 5 consists in its alkylation with methyl bromoacetate in DMF and an excess of K_2CO_3 as a base to give bisester 7 almost quantitatively. This ester, subjected to catalytic reduction on 10% Pd/C underwent also spontaneous cyclization to lactam 8. Another way of the ring closure resulting in 5-membered ring product, was not observed. Analogous compound 8 but as methyl ester was described by Kikugawa as advanced intermediate in the total synthesis of 1. It can be aromatized to 2 (also methyl ester) in 2 steps.[5] Our route to 8 is comparative considering overall yield but

seems to be more convenient.

EXPERIMENTAL

Melting points are uncorrected. The ir spectra were taken in KBr with Acculab 1 spectrophotometer and only noteworthy absorptions were listed. ^{1}H-Nmr spectra were recorded on Varian Gemini 200 spectrometer in $CDCl_3$ in reference to TMS. Chemical shifts are given in ppm, coupling constants in Hertz. High-resolution mass spectra were measured on AMD 604 spectrometer. Column chromatography was performed on silica gel 240-400 mesh (Merck) using hexane-ethyl acetate mixtures as eluents. All reagents and solvents were commercial.

t-Butyl 3-(1-methoxy-4-nitronaphtyl) acetate (5):
To a stirred solution of *t*-BuOK (8.4 g, 75 mmol) in 30 ml of dry DMF, a solution of 1-methoxy-4-nitronaphthalene (3.05 g, 15 mmol) and *t*-butyl chloroacetate (2.8 g, 20 mmol) in dry DMF (10 ml) was added at -20°C during 10 min. After the addition was completed the deep-red mixture was stirred for additional hour at -20°C, then poured into 200 ml of dil. cold HCl. After extraction with CH_2Cl_2 (3 x 20 ml) and evaporation of the solvent the residue was recrystallized from methanol to yield 5, 4.2 g (88 %), mp 93-95°C. Ir: 1735 (CO_2), 1520, 1340 (NO_2); ^{1}H-nmr: δ 1.16(s, 9H, Bu-*t*), 3.77(s, 2H, CH_2), 4.07(s, 3H, OCH_3), 6.70(s, 1H, H-2), 7.51-7.69(m, 2H, H-6,7), 7.89(ddd, J=8.27, 1.43, 0.71, 1H, H-8), 8.29(ddd, J=8.06, 1.76, 0.78, 1H, H-5). Anal. Calcd for $C_{17}H_{19}NO_5$: C, 64.33; H, 6.05; N, 4.41. Found: C, 64.31; H, 6.13; N, 4.34.

t-Butyl 3-(1-methoxy-4-aminonaphthyl)acetate (4):
5 (1.58 g, 5 mmol) was dissloved in 96% EtOH (150 ml), 10% Pd/C (100 mg) was added and the resulted mixture was shaken in the Parr apparatus under hydrogen at 60 psi pressure. After completion of the reduction (tlc control) the catalyst was filtered off, solvent evaporated and the residue was purified by column chromatography (hexane-ethyl acetate, 8:1)to yield 4, 1.25 g (87%) mp 64-65°C (hexane-EtOH). Ir: 3410, 3350 (NH_2), 1695 (CO_2); ^{1}H-nmr: δ 1.43(s, 9H, Bu-*t*), 3,62(s, 2H, CH_2), 3.95(s, 3H, OCH_3), 6.64(s, 1H, H-2), 7.48(m, 2H, H-6.7), 7.83(m, 1H, H-8), 8.23(m, 1H, H-5); hrms(m/z): 287.1520(M^+,$C_{17}H_{21}NO_3$, calcd 287.1521). Anal. Calcd for $C_{17}H_{21}NO_3$: C, 71.05; H, 7.35; N, 4.88. Found: C, 70.63; H, 7.21; N, 4.65.

Bis[N-4-(1-methoxy-3-*t*-butoxycarbonylmethyl)naphthyl]glyoxalimine (10):
4 (287 mg, 1 mmol) was dissolved in 96% EtOH (25 ml). Glyoxal (0.3 ml, 5 mmol) was added as 40% aq. solution followed by the addition of 1 drop of piperidine. Solid product precipitated immediately. After 1 h the mixture was poured into cold water (100 ml) and extracted with CH_2Cl_2 (3x20 ml), solvent was evaporated and the crude product was recrystallized from hexane - CCl_4 to give 155 mg orange crystals of 10 (51%), mp 183-184°C. Ir: 1730 (CO_2), 1625(N=C); ^{1}H-nmr: δ 1.46(s, 18H, Bu-*t*), 3.70(s, 4H, CH_2), 4.05(s, 6H, OCH_3), 6.82(s, 2H, H-2), 7.48-7.57(m, 4H, H-6,7), 7.88(m, 2H, H-8), 8.28(m, 2H, H-5), 8.47(s, 2H, N=CH). Anal.Calcd for $C_{36}H_{40}N_2O_6$: C, 72.46; H, 6.76; N, 4.70. Found: C, 72.70; H, 6.69; N, 4.33.

t-Butyl 2-[3-(1-methoxy-4-nitronaphthyl)]-3-ethoxycarbonyl propionate (7):
5 (1.59 g, 5 mmol), ethyl bromoacetate (0.84 ml, 7.5 mmol) and K_2CO_3 (1.7g, 12.5 mmol) were stirred in dry DMF (10 ml) during 2 days. After diluting with water (100 ml), extraction with CH_2Cl_2 (3x20 ml), evaporation of the solvent, the residue was recrystallized from hexane-EtOH to give 1.84 g of 7 (91%), mp 85.5-87.5°C. Ir: 1725(CO_2), 1525,1390(NO_2); ^{1}H-nmr: δ 1.25(t, J=7.14, 3H, CH_3), 1.40(s, 9H, Bu-*t*), 2.78(dd, J=16.75, 4.88, 1H, CH_2CO_2), 3.17(dd, J=16.75, 10.18, 1H, CH_2CO_2), 4.03(s, 3H, OCH_3), 4.16(q, J=7.14, 2H, OCH_2), 4.27(dd, J=10.18, 4.88, 1H, H-2), 7.53-7.69(m, 2H, H-6.7), 7.78(m, 1H, H-8), 8.27(m, 1H, H-5). Anal. Calcd for $C_{21}H_{25}NO_7$: C, 62.52; H, 6.25; N, 3.47. Found: C, 62.56; H, 6.21; N, 3.59.

t-Butyl 6-methoxy-2-oxy-1,2,3,4-tetrahydrobenzo[h]quinoline-4-carboxylate (8):
7 (1.21 g, 3 mmol) was dissloved in 96% EtOH (200 ml), 10% Pd/C (100 mg) was added and resulted mixture was shaked in the Parr apparatus under hydrogen at 60 psi pressure until the substrate was consumed (tlc control). The catalyst was filtered off, the solution was left for 5 days, then the solvent was evaporated. The residue was purified by column chromatography (AcOEt-hexane, 1:4) followed by recrystallization from 96% EtOH to give 8, 0.81 g (82%), mp 221°C (decomp.). Ir: 1725(CO_2), 1675(CONH); ^{1}H-nmr: δ 1.40(s, 9H, Bu-t), 2.88(dd, J=16.11, 6.60, 1H, CH_2CON), 3.02(dd, J=16.11, 3.68, 1H, CH_2CON), 3.89(dd, J=6.60, 3.68, 1H, $CHCO_2$), 4.00(s, 3H, OCH_3), 6.76(s, 1H, H-5), 7.48-7.64(m, 2H, H-8,9), 7.84(m, 1H, H-7), 8.28(m, 1H, H-10), 8.49(s, 1H, NH); hrms (m/z): 327.1470(M^+, $C_{19}H_{21}NO_4$, calcd 327.1471). Anal.Calcd for $C_{19}H_{21}NO_4$: C, 69.70; H, 6.47; N, 4.29. Found: C, 69.35; H, 6.30; N, 4.09.

t-Butyl 3-(1-methoxy-4-nitronaphthyl)propen-2-al-3-carboxylate (9):
To 5 (158 mg,0.5 mmol) dissolved in DMF (2 ml), 40% aq. glyoxal (0.6 ml, 5 mmol) and 1 drop of DBU were added. After stirring at 20°C for 1 h the reaction mixture was poured into 50 ml of dil. cold HCl and extracted with CH_2Cl_2 (3x10 ml). The solvent was evaporated and the residue was filtered through silica gel using AcOEt-hexane (1:4) mixture as eluent to yield pure 9, 67 mg (37%), mp 137-140°C (hexane-EtOH). Ir: 1725(CO_2), 1690(CHO), 1525, 1350(NO_2); ^{1}H-nmr: δ 1.49(s, 9H, Bu-*t*), 4.09(s, 3H, OCH_3), 6.62(s, 1H, H-2), 7.02(d, J=8.00, 1H, H-vinyl), 7.61-7.80(m, 2H, H-6,7), 8.22(ddd, J=8.30, 1.14, 0.80, 1H, H-8), 8.38(ddd, J=8.14, 1.80, 0.80, 1H, H-5), 9.58(d, J=8.6, 1H, CHO). Anal.Calcd for $C_{19}H_{19}NO_6$: C, 63.85; H, 5.36; N, 3.92. Found: C, 63.49; H, 5.30; N, 3.52.

t-Butyl 6-methoxybenzo[4]quinoline-4-carboxylate (2b):
9 (58 mg, 0.162 mmol) was dissolved in 50 ml of 96% EtOH, 10% Pd/C (10 mg) was added and resulted mixture was hydrogenated in the Parr apparatus. After completion of the reaction (tlc control) the catalyst was filtered off, the solvent was evaporated and the residue was chromatographed on silica gel (AcOEt-hexane, 1:4 as eluent) to give 2b, 32 mg (64%), mp 77-78.5°C (hexane-EtOH). Ir: 1705(CO_2), 1295; ^{1}H-nmr: δ 1.71(s, 9H, Bu-t), 4.15(s, 3H, OCH_3), 7.76(m, 2H, H-8.9), 7.92(d, J=4.70, 1H, H-3), 8.04(s, 1H, H-5), 8.34(m, 1H, H-7), 8.89(d, J=4.70, 1H, H-2), 9.27(m, 1H, H-10). Anal. Calcd for $C_{19}H_{19}NO_3$: C, 73.76; H, 6.19; N, 4.53. Found: C, 73.56; H, 6.16; N, 4.36

REFERENCES

1. B. F. Bowden, E. Ritchie, and W. C. Taylor, Aust. J. Chem., 1972, 25, 2659.
2. J. I. Lewin and S. M. Weinreb, J. Org. Chem., 1984, 49, 4325.
3. P. Karuso and W. C. Taylor, Aust. J. Chem., 1984, 37, 1271.
4. Y. Murakami, T. Watanabe, M. Saka, and Y. Yokoyama, Chem. Pharm. Bull., 1988, 36, 3732.
5. M. Kawase, Y. Miyake, T. Sakamoto, M. Shimada, and Y. Kikugawa, Tetrahedron, 1989, 45, 1653.
6. M. Mąkosza and J. Winiarski, Acc. Chem. Res., 1987, 20, 282
7. M. Mąkosza, Synthesis, 1991, 103.
8. B. Mudryk and M. Mąkosza, Synthesis, 1988, 1007

Received, 28th October, 1991