A convenient synthetic method for 4-nitro-1,3,4,5-tetra-hydrobenz[cd]indoles and its application for an alternative synthesis of (±)-6,7-secoagroclavine

A CONVENIENT SYNTHETIC METHOD FOR 4-NITRO-1,3,4,5-TETRAHYDROBENZ[cd]INDOLES AND ITS APPLICATION FOR AN ALTERNATIVE SYNTHESIS OF (±)-6,7-SECOAGROCLAVINE[1]

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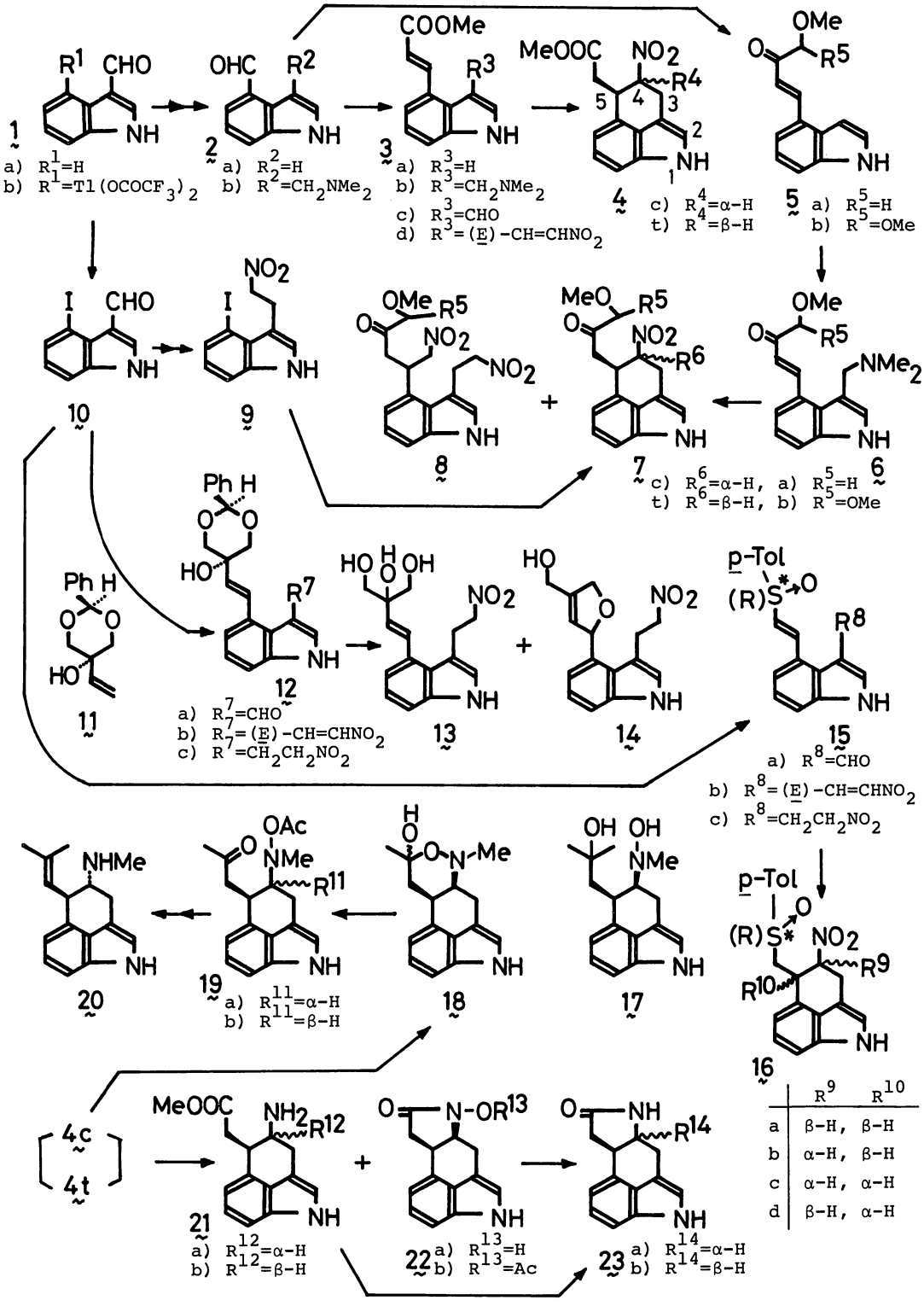
Abstract ——— Various 4-substituted indoles are prepared and a simple synthetic method for 4-nitro-1,3,4,5-tetrahydrobenz[cd]-indole derivatives is elaborated using intramolecular Michael addition reaction as a key step. Syntheses of new tetracyclic 4H-indolo[6,5,4-cd]indole derivatives and (±)-6,7-secoagroclavine are also included.

In recent years, there has been a rapid increase in reports of synthetic study directed toward ergot alkaloids.[2-8] One of the key facing problems for their syntheses is the construction of suitably substituted 1,3,4,5-tetrahydrobenz[cd]indole nucleus. Many efforts have been focused on their syntheses[2] and various methods have been developed such as 1,3-dipolar nitrone approach,[3] nitrile oxide cyclization,[4] intramolecular aldol condensation,[5] Friedel-Crafts acylation,[6] Photo-irradiated enamide cyclization,[7] and intramolecular S_N2' type cyclization of allyl alcohol.[8]
In this report, we wish to describe that an intramolecular Michael approach is also a versatile method for obtaining 4-nitro-1,3,4,5-tetrahydrobenz[cd]indoles and its optically active derivatives. Application for an alternative synthesis of (±)-6,7-secoagroclavine and 4H-indolo[6,5,4-cd]indole derivatives are also reported.

I. Syntheses of Various 4-Substituted Indoles and 4-Nitro-1,3,4,5-tetrahydrobenz[cd]indole Derivatives

Wittig reaction of 4-indolecarboxaldehyde (2a), which is now readily available from 3-indolecarboxaldehyde[9] (1a) via (3-formylindol-4-yl)thallium bis-trifluoroacetate (1b),[10] with methoxycarbonylmethylenetriphenylphosphorane afforded a 99% yield of



	R9	R10
a	β-H,	β-H
b	α-H,	β-H
c	α-H,	α-H
d	β-H,	α-H

methyl 3-(indol-4-yl)acrylate (3a, mp 128.5-129°C). Subsequent Mannich reaction using AcOH-Me_2NH-HCHO converted 3a to the gramine derivative (3b, oil) in 95% yield. Treatment of 3b with KF and 18-crown-6 in refluxing CH_3CN-CH_3NO_2 (1:1, v/v) afforded 4,5-cis- (4c, oil) and 4,5-trans-5-methoxycarbonylmethyl-4-nitro-1,3,4,5-tetrahydrobenz[cd]indole (4t, oil) in 16% and 71% yields, respectively.

By the following short step route, 4c and 4t were alternatively prepared from methyl 3-(3-formylindol-4-yl)acrylate (3c), which was readily available in one pot operation from 1a via 1b in 70% yield as described before.[11] Nitroaldol reaction of 3c with CH_3NO_2 in the presence of NH_4OAc gave the (E)-nitrovinyl compound [3d, mp 194-197°C (dec.)] in 82% yield. Reduction of the vinyl moiety of 3d with $NaBH_4$ in MeOH and a successive brief heating of the reaction mixture produced stereoselectively 4c in 79% yield. The 4,5-trans-compound (4t) could be obtained in 65% yield by the epimerization of 4c by the action of NEt_3 in refluxing benzene together with 33% yield of 4c. It should be noted that the ratio of 4t to 4c depended on the used solvent and base, and we could not find the optimum reaction conditions for obtaining 4t exclusively. The stereochemistries of 4c and 4t were determined by the coupling constant between C_4- and C_5-H in their proton nuclear magnetic resonance (^{1}H-nmr) spectra, where the cis-compound (4c) had 4 Hz while the trans-compound (4t) had 6 Hz.

Treatment of 2a with either methoxymethylcarbonylmethylenetriphenylphosphorane[12] or pyruvaldehyde dimethyl acetal in the presence of 1% aqueous K_2CO_3 afforded 1-methoxy- (5a, mp 156-157°C) or 1,1-dimethoxy-4-(indol-4-yl)-3-buten-2-one (5b, mp 103-104°C) in 82% and 49% yields, respectively. Mannich reaction of 5a and 5b with AcOH-Me_2NH-HCHO afforded the gramines, 6a (mp 161-163°C) and 6b (mp 124-125°C), in 90% and 44% yields, respectively. The yield of 6b was greatly improved by changing the order of the above reactions. Thus, 2a was first led to the gramine[13] (2b, oil) by the Mannich reaction in 78% yield. The compound (2b) underwent aldol condensation reaction with pyruvaldehyde dimethyl acetal to give 6b in 86% yield. Subsequent treatment of 6a with KF and 18-crown-6 in CH_3CN-CH_3NO_2 (1:1, v/v) produced the 4,5-cis- (7ac, mp 162-164°C), 4,5-trans-5-(3-methoxyacetonyl)-4-nitro-1,3,4,5-tetrahydrobenz[cd]indole (7at, oil), and 8a (mp 107-108°C) in 21%, 63%, and 8% yields, respectively. Under similar reaction conditions, 6b afforded an inseparable mixture of 7bc and 7bt as an oil (ratio of 7bc:7bt=1:8, determined based on its ^{1}H-nmr spectrum), and 8b (oil) in 74% and 22% yields, respectively. The compound (7ac) could also be obtained by the following route. Thus, 4-iodo-3-nitroethylindole (9),

prepared from 4-iodo-3-indolecarboxaldehyde (10) as reported previously,[14] was reacted with 1-methoxy-3-buten-2-one[15] in DMF and NEt_3 in the presence of a catalytic amount of $Pd(OAc)_2$ to afford 7ac in a single step in 31% yield.

Heck reaction of 10 with 2,5-trans-2-phenyl-5-vinyl-1,3-dioxan-5-ol[16] (11) gave a 86% yield of 12a (mp 146-148°C), which was further converted to 12b (mp 203-204°C) in 95% yield by the nitroaldol reaction with CH_3NO_2. Reduction of 12b with $NaBH_4$ afforded 12c (mp 203-205°C) in 84% yield. Treatment of 12c with aqueous 2N-HCl produced 13 (mp 101-102°C) and 14 (oil) in 54% and 35% yields, respectively. Attempts to convert 13 and 14 to the corresponding 4-nitro-1,3,4,5-tetrahydrobenz[cd]indole derivatives is in progress.

II. Syntheses of Optically Active 4-Nitro-1,3,4,5-tetrahydrobenz[cd]indoles

Heck reaction of 10 with optically active (+)-(R)-p-tolylvinylsulfoxide[17] in DMF gave a 45% yield of (-)-(R)-2-(3-formylindol-4-yl)vinyl-p-tolylsulfoxide [15a, mp 99-104°C, $[\alpha]_D^{17}$-257.7° (c 0.466, EtOH)], which was subsequently led to the (+)-(R)-(E)-nitrovinyl compound [15b, mp 218-223°C, $[\alpha]_D^{13}$+694.5° (c 0.099, DMF)] in 56% yield by the nitroaldol reaction. Reduction of 15b with $NaBH_4$ at room temperature afforded (+)-(R)-nitroethyl compound [15c, mp 168.5-171.5°C, $[\alpha]_D^{13}$+209.4° (c 1.015, CH_3CN)] in 74% yield. Treatment of 15b with $NaBH_4$ in refluxing $CHCl_3$-MeOH produced possible four kinds of cyclized products, 16a [mp 174-176°C, $[\alpha]_D^{13}$+238.3° (c 0.194, CH_3CN)], 16b [mp 187-189°C, $[\alpha]_D^{13}$+225.6° (c 0.321, CH_3CN)], 16c, and 16d (mp 176-182°C)] in 26%, 33%, 4%, and 9% yields, respectively, in the order of elution on silica gel column chromatography. Although, 16c could not be isolated, its content was calculated based on the 400MHz ^{1}H-nmr spectrum of a mixture consisting of 16c and 16d. On the other hand, similar treatment of 15c with $NaBH_4$ produced 16a, 16b, and 16d in 14%, 37%, and 10% yields, respectively, without formation of any detectable amount of 16c.

The fact that the treatment of pure 16a or 16b with $NaBH_4$ in refluxing $CHCl_3$-MeOH produced 2:3 mixture of 16a and 16b without formation of 16c and 16d clearly proved that these compounds were epimers at the 4-position. By the comparison of their ^{1}H-nmr spectra with those of 4c, 4t, 7c, and 7t, 16a was deduced to be 4,5-cis while 16b being 4,5-trans-isomer. Similarly, 16c and 16d were assigned to be 4,5-cis- and 4,5-trans-isomer, respectively. Optical purity of 16b was determined to be pure (100% de), comparing with the corresponding (±)-16b, based on 400MHz ^{1}H-NMR analysis using (+)-Eu-DPPM as a chiral shift reagent. Althogh investigations for establishing absolute configuration of the 5-position are currently in progress,

the structures of 16a-d were tentatively assigned as shown in the Chart. Thus, the intramolecular Michael type cyclization of chiral vinyl sulfoxide was found to be an efficient method for constructing optically active 4-nitro-1,3,4,5-tetrahydrobenz[cd]indole nucleus.

III. An Alternative Synthesis of (±)-6,7-Secoagroclavine

With an expectation to obtain 4,5-cis-4-N-methylhydroxyamino-5-(2-methylpropen-1-yl)-1,3,4,5-tetrahydrobenz[cd]indole (17), 4c was reacted with an excess amount of MeMgI in THF-Et_2O to afford a 69% yield of 4,5-cis-N-methylhydroxylaminohemiketal compound [18, mp 181-183°C (dec.)] as a single product, whose configuration of hydroxyl group was not certain. Treatment of 18 with Ac_2O-pyridine gave 4,5-cis-N-methyl-N-acetoxy compound (19a, oil) in 93% yield. Based on these data, 4t was reacted successively with excess MeMgI and then with Ac_2O-pyridine to produce a 69% yield of the 4,5-trans-N-methyl-N-acetoxy compound (19b, mp 137.5-139.5°C), which was identical with the sample prepared as described before.[8] Since 19b had already been derived to (±)-6,7-secoagroclavine (20), an alternative synthetic route for 20 was thus established.

IV. Syntheses of Tetracyclic 4H-Indolo[6,5,4-cd]indole Derivatives

Reduction of 4c with zinc amalgam and 2N-HCl produced the amino compound (21a, oil) and unstable 6a,9a-cis-6,6a,7,8,9,9a-hexahydro-7-hydroxy-4H-indolo[6,5,4-cd]indole-8-one [22a, mp >300°C (dec.)] in 57% and 41% yields, respectively. Mild alkaline treatment of 21a with aqueous $NaHCO_3$ easily afforded 6a,9a,-cis-6,6a,7,8,9,9a-hexahydro-4H-indolo[6,5,4-cd]indole-8-one [23a, mp 263-266°C (dec.)] in 80% yield. The hydroxamic acid structure of 22a was proved by the following reactions. Thus, acetylation of 22a with Ac_2O-pyridine gave the corresponding O-acetyl derivative (22b, mp 182-184°C) in 87% yield. Furthermore, titanium (III) chloride reduction of 22a produced 23a in 87% yield.

On the other hand, reduction of 4t with zinc amalgam and 2N-HCl cleanly generated 21b (oil) in 77% yield. Treatment of 21b with aqueous $NaHCO_3$ gave 6a,9a-trans-6,6a,7,8,9,9a-hexahydro-4H-indolo[6,5,4-cd]indole-8-one (23b, mp >300°C) in 87% yield. In conclusion, 4H-indolo[6,5,4-cd]indole derivatives[18] are now readily accessible from 3-indolecarboxaldehyde (1a) in five steps with high overall yield.

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