A General Synthesis of N-Reverse-Prenyl Indoles

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Abstract: A general method for the construction of N-reverse-prenyl indoles was established using copper catalyzed N-propargylation, the Lindlar hydrogenation of the acetylenic bond, and dehydrogenation with chemical manganese dioxide as key steps. The antifungal indole alkaloids (1 and 2) and N-reverse-prenyl tryptophan (3) were efficiently synthesized by this method.

Key words: N-reverse-prenyl indole, N-propargylation, Lindlar hydrogenation, dehydrogenation

The N-reverse-prenyl (N-1,1-dimethyl-2-propenyl) indole skeleton is a constituent of some biologically interesting natural products that are not commonly found in nature.1–4 In connection with the synthetic studies for cycloamarin A,2 isolated from a marine bacterium, we needed to explore a general entry to the efficient synthesis of the N-reverse-prenyl indole derivatives. There were no reports of synthetic efforts directed toward the N-reverse-prenyl indole skeleton when we initiated our program. After our work was completed,5 related works6 whose strategies are quite analogous to ours were reported.7 We now describe the details of a general method for the construction of this unique skeleton utilizing copper catalyzed N-propargylation of indoline, the Lindlar hydrogenation of the acetylenic bond,8 and dehydrogenation with chemical manganese dioxide (CMD).7 The targets are shown in Figure 1.

![Figure 1](image_url)

Figure 1

Our first targets were simple antifungal N-reverse-prenyl indole alkaloids 1 and 2, isolated from the basidomycete Aporpium caryae.2 Initially, indole (4) was attempted to undergo the propargylation with propargyl acetate (5) by using copper (I) salts,10 as shown in Scheme 1. The reaction did not proceed at all because of the low nucleophilicity of indole-nitrogen. However, indoline (7) whose nitrogen is more nucleophilic easily reacted with propargyl acetate (5) under analogous conditions to give the propargylated indoline 8 though 0.5 equivalents of Cul were needed.11 After partial reduction over Lindlar’s catalyst, the resulting indoline 9 was dehydrogenated by use of CMD9 to yield the N-reverse-prenyl indole derivative 10. Bromination of 10 with N-bromosuccinimide (NBS) afforded the 3-bromo derivative 11, which was transformed to the desired indole 1 by lithiation with tert-BuLi followed by methoxylation. In general, the 3-lithiated indoles are easily rearranged to the corresponding 2-lithiated derivatives. However, no 2-methyl ester derivative was detected in the above case, which might be due to the steric hindrance of the bulky reverse-prenyl function.12

Transformation of 1 to the corresponding diol derivative 2 was accomplished by use of Sharpless asymmetric dihydroxylation (AD).13 It is known that Sharpless AD of the terminal olefin proceeds sluggishly with lower enantioselectivity because of no sulfonamide effect. Since Sharpless AD of 1 with commercially available AD-mix proceeded slowly, the quantity of both osmium and the ligand was increased to 0.1 equivalents to accelerate the reaction. However, the ligand in AD-mix showed low selectivity as shown in entry 1 (Table 1). So far, pyrimidine based chiral ligands (DHQD)2PYR and (DHQ)2PYR gave the best result to give (R)-2 with 89% ee (entry 3) and (S)-2 with 69% ee (entry 5), respectively. Common lower selectivity in AD was observed by changing the ligand from DHQD to DHQ (see entries 3 and 5; 4 and 7). Thus we could achieve the synthesis of the antifungal indole alkaloids 1 and (S)-2 in an overall yield of about 60% from indoline (7).

Our next target was the tryptophan derivative 3, which is the constituent of rufomycins. After methyl esterification of carbobenzoxy-L-tryptophan (12), reduction of the indole nucleus with (CF3CO2)2BH-THE14 afforded the indole 13. Propargylation followed by dehydrogenation of 14 with CMD afforded the indole 15 in good yield, which smoothly underwent the Lindlar reduction to give the
tryptophan derivative 3. In this case, the reduction of the propargyl derivative 14, followed by dehydrogenation with CMD afforded 3 in lower yield. Corey and co-workers synthesized the Boc derivative of 3 utilizing our method for the total synthesis of okaramine N.6a Incidentally, direct attachment of the side chain to 10 with the aziridine derivative 16 by use of scandium triflate15 was attempted but failed to give 3 (Scheme 2).

Thus, we were able to establish a general entry into the construction of the N-reverse-prenyl indole skeleton. The method will be useful for the synthesis of other com-
Melting points were determined on a YANAGIMOTO micro melting point apparatus (hot plate) and are uncorrected. IR spectra were measured on a SHIMADZU FTIR-8100 spectrometer. Analytical TLC was performed on a Merck silica gel BW-820MH, 120 g, hexane–Et2O, 200:1–50:1 to give 9 (2.46 g, 91%) as a pale yellow oil.

IR (neat): 3291, 1605, 1485, 1256, 1225, 747 cm⁻¹.

HRMS (EI): m/z calcd for C13H15N: 185.1204; found: 185.1211.

HRMS (EI): m/z calcd for C13H15N: 185.1204; found: 185.1195.


1-(1,1-Dimethylallyl)-2,3-dihydro-1H-indole (9); Typical Procedure

To a solution of 8 (2.68 g, 14.44 mmol) in MeOH (40 mL) was added Lindlar’s catalyst (260 mg) under Ar, and hydrogen gas was introduced (balloon with needle through three-way stopcock). The black slurry was stirred under 1 atm of H₂ at r.t. for 10 h. The mixture was filtered through a pad of Celite⁶ and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (silica gel BW-820MH, 120 g, hexane–Et₂O, 100:1–50:1) to give 9 (2.46 g, 91%) as a pale yellow oil.

IR (neat): 3291, 1605, 1485, 1256, 1225, 747 cm⁻¹.

HRMS (EI): m/z calcd for C₁₁H₁₂N: 185.1204; found: 185.1211.

1-(1,1-Dimethyl-2-propynyl)-2,3-dihydro-1H-indole (8); Typical Procedure

To a stirred solution of S²⁰ (2.80 g, 20 mmol) in THF (40 mL) were added indoline (7) (2.24 mL, 20 mmol), Cul (380 mg, 2.0 mmol), and i-Pr₂NEt (7.0 mL, 40 mmol) at r.t., and the mixture was stirred at 50 °C for 13 h. To the reaction mixture was added CuI (380 mg, 2.0 mmol) since TLC indicated that the reaction had not gone to completion. After 5 h, additional Cul (380 mg, 2.0 mmol) was added, and the mixture was stirred at 50 °C for 3 h. Upon cooling, the mixture was filtered through a pad of Celite⁶ (washed with Et₂O). The filtrate was washed with 1 M aq KH₂SO₄ (2 ×) and sat. brine, dried over MgSO₄, filtered and concentrated in vacuo. The residue was purified by column chromatography (silica gel BW-820MH, 150 g, hexane–Et₂O, 200:1→50:1→30:1) to give 8 (3.34 g, 90%) as a pale yellow oil.

IR (neat): 3291, 1605, 1485, 1256, 1225, 747 cm⁻¹.

HRMS (EI): m/z calcd for C₁₃H₁₅N: 185.1204; found: 185.1211.

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To a stirred solution of 10 (444 mg, 2.40 mmol) in DMF (8.0 mL) was added NBS (223 mg, 1.20 mmol) at 0 °C, and the mixture was added dropwise to a stirred solution of Cbz-L-Trp-OMe (421 mg, 1.20 mmol) in THF (12.8 mL). The reaction was quenched with sat. aq Na2SO4, and concentrated in vacuo. The residue was purified by column chromatography (silica gel BW-820MH, 25 g. hexane–Et2O, 12:1) to give 11 (600 mg, 95%) as a colorless oil.

IR (neat): 3375, 1717, 1215, 1047, 733 cm⁻¹.

HRMS (EI): m/z calcd for C10H10NO2: 182.0658; found: 182.0657.

Methyl 1-(1,1-Dimethylallyl)-1H-indole-2-carboxylate [11]; Typical Procedure

To a stirred solution of 11 (507 mg, 1.92 mmol) in THF (12.8 mL) was added dropwise t-BuLi (1.62 M in pentane, 2.49 mL, 4.03 mmol) at −78 °C under N2, and the mixture was stirred for 30 min. The reaction was quenched with H2O, and the mixture was extracted with Et2O. The extract was washed with 1 M aq KHSO4 and sat. brine, dried over MgSO4, filtered, and concentrated in vacuo. The residue was purified by column chromatography (silica gel BW-820MH, 25 g. hexane–Et2O, 12:1) to give 12 (600 mg, 95%) as a colorless oil.

IR (neat): 1703, 1538, 1458, 1351, 1215, 1107, 769 cm⁻¹.

HRMS (EI): m/z calcd for C12H12NO2: 182.0871; found: 182.0870.

Methyl 1-(1,1-Dimethylallyl)-1H-indole-3-carboxylate [12]; Typical Procedure

To a stirred solution of 11 (507 mg, 1.92 mmol) in THF (12.8 mL) was added dropwise t-BuLi (1.62 M in pentane, 2.49 mL, 4.03 mmol) at −78 °C under N2, and the mixture was stirred for 30 min. The reaction was quenched with sat. aq NH4Cl, and the mixture was extracted with Et2O. The extract was washed with sat. brine, dried over MgSO4, filtered, and concentrated in vacuo. The residue was purified by column chromatography (silica gel BW-820MH, 20 g. hexane–Et2O, 12:1) to give 13 (415 mg, 96%) as a colorless oil.

IR (neat): 3375, 1717, 1215, 1047, 733 cm⁻¹.

HRMS (EI): m/z calcd for C12H12NO2: 182.0871; found: 182.0870.

Methyl 1-(2S,2,3-Dihydroxy-1,1-dimethylpropyl)-1H-indole-3-carboxylate [13, Entry 5 in Table 1]; Typical Procedure

To a well-stirred solution of (DHQ)2PYR (12.8 mg, 0.0145 mmol), K2CO3 (60.1 mg, 0.435 mmol), KF (9 mg, 0.145 mmol) and l (353 mg, 1.45 mmol) in t-BuOH-H2O (0.750.75 mL) was added K2[OsO2(OH)4] (5.3 mg, 0.0145 mmol) at 0 °C. The mixture was stirred at 4 °C for 24 h, and then Na2SO4 (250 mg) was added. The suspension was warmed up to r.t. EtOAc and sat. brine were added, and the aqueous layer was further extracted with EtOAc (2 ×). The combined extracts were dried over Na2SO4 and concentrated in vacuo. The residue was purified by column chromatography (silica gel BW-820MH, 10 g, hexane–EtOAc, 1:1–1:3) to give 14 (240.5 mg, quantitative) as a colorless oil; [α]24D = 27.62 (c = 1.0, CHCl3).

IR (neat): 3418, 1694, 1539, 1456, 1385, 1210, 1163, 1120, 1092, 1067, 909, 735 cm⁻¹.

Methyl 2-(2-Benzoxycarbonylamino-3-(2,3-dihydro-1H-indol-3-yl)propionate [14]; Typical Procedure

To a stirred solution of Cbz-L-Trp-OMe (421 mg, 1.20 mmol) in DMF (20 mL) were added 2-Ph-CyMe (444 mg, 2.40 mmol) at 0 °C, and the mixture was stirred at r.t. for 6 h. After dilution with Et2O, the mixture was washed with H2O (2 ×), Me2S, and sat. brine. The mixture was stirred at 4 °C for 24 h, and then Na2SO4, Me2S, and concentrated in vacuo. The residue was purified by column chromatography (silica gel BW-820MH, 20 g. hexane–EtOAc, 2:1–1:1) to give 15 (420 mg, 96% from Cbz-L-Trp-OMe) as a white wax; [α]24D = 27.62 (c = 1.0, CHCl3).

IR (neat): 3375, 1717, 1215, 1047, 733 cm⁻¹.

HRMS (EI): m/z calcd for C20H22N2O4: 354.1580; found: 354.1579.

The enantiomeric purity of 15 determined to be 69% ee.

HRMS (EI): m/z calcd for C15H11NO2: 277.1314; found: 277.1275. HPLC analysis of 2 was carried out as follows. Column: Daicel CHIRALPAK AD; Solvent: hexane–iPrOH, 9:1; Flow Rate: 1.0 mL/min; Detector: 254 nm; Retention Time: 16.3 min ([S]-isomer) and 18.2 min ([R]-isomer). The enantiomeric purity of 2 was determined to be 96% ee.
hexane–EtOAc, 5:1–4:1–3:1) to give 14 (121 mg, 75%) as a green oil. Because 14 was labile, this material was immediately used for the next step without further purification.

To a stirred solution of 14 (35 mg, 0.083 mmol) was added MnO2 (CMD, 36.2 mg, 0.416 mmol) at r.t., and the mixture was stirred for 12 h. The mixture was filtered through a pad of Celite® and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (silica gel BW-820MH, 9 g, hexane–EtOAc, 6:1→5:1→4:1→3:1) to give 15 (30 mg, 86%) as a colorless oil; [a]D 26 +39.89 (c = 0.9, CHCl3).

IR (neat): 3345, 1725, 1510, 1456, 1211, 1059, 734 cm–1.

IR (neat): 3345, 1725, 1510, 1456, 1211, 1059, 734 cm–1.

HRMS (EI): m/z calc for C23H22N2O4: 418.1893; found: 418.1895.

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HRMS (EI): m/z calc for C23H22N2O4: 418.1893; found: 418.1895.

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References


(9) CMD is produced for battery manufacture. It is quite active and useful for various oxidations and dehydrogenations. See: (a) Aoyama, T.; Sonoda, N.; Yamachi, M.; Toriyama, K.; Anzai, M.; Ando, A.; Shioiri, T. Synlett 1998, 35; and references therein. (b) Yokokawa, F.; Sameshima, H.; Shioiri, T. Synlett 2001, 986; and references therein. (c) CMD is commercially available from Wako Pure Chemical Industries, Ltd. [Fax: +81(6)62105964].


(11) According to the ref. 19, the propargylation reaction proceeded with 0.1 equiv of CuCl. In our case, the reaction proceeded with CuCl but with less efficiency.


