REGIO-CONTROLLED CYCLIZATION OF 1-(3-METHYL-2-BUTENOYL)INDOLES AT THEIR 2 AND 7-POSITIONS

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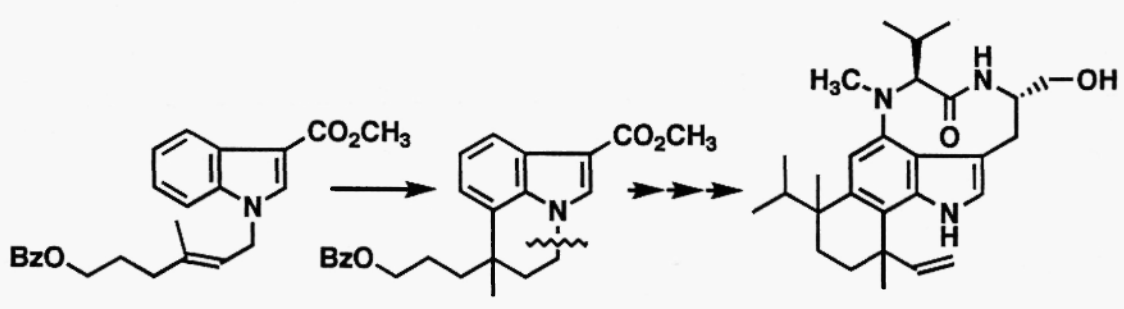
Abstract: A quarternary carbon substituent was efficiently introduced at their 2 and 7-positions of the indole nucleus by cyclization of 1-(3-methyl-2-butenoyl)-indole derivatives 4 and 7, and derived to a reversed prenyl group found in teleocidins 3 or echinulin 11.

Many important indole alkaloids such as tumor promoter: teleocidins 3(1), echinulin 11 (2) *etc.* contain several quarternary carbon substituents at the 2, 6 or 7-position(s) in their indole nucleus. However, introduction of such substituents on the indole nucleus is one of the most difficult problems in their chemical synthesis(3). We have reported unique methods (4) for direct

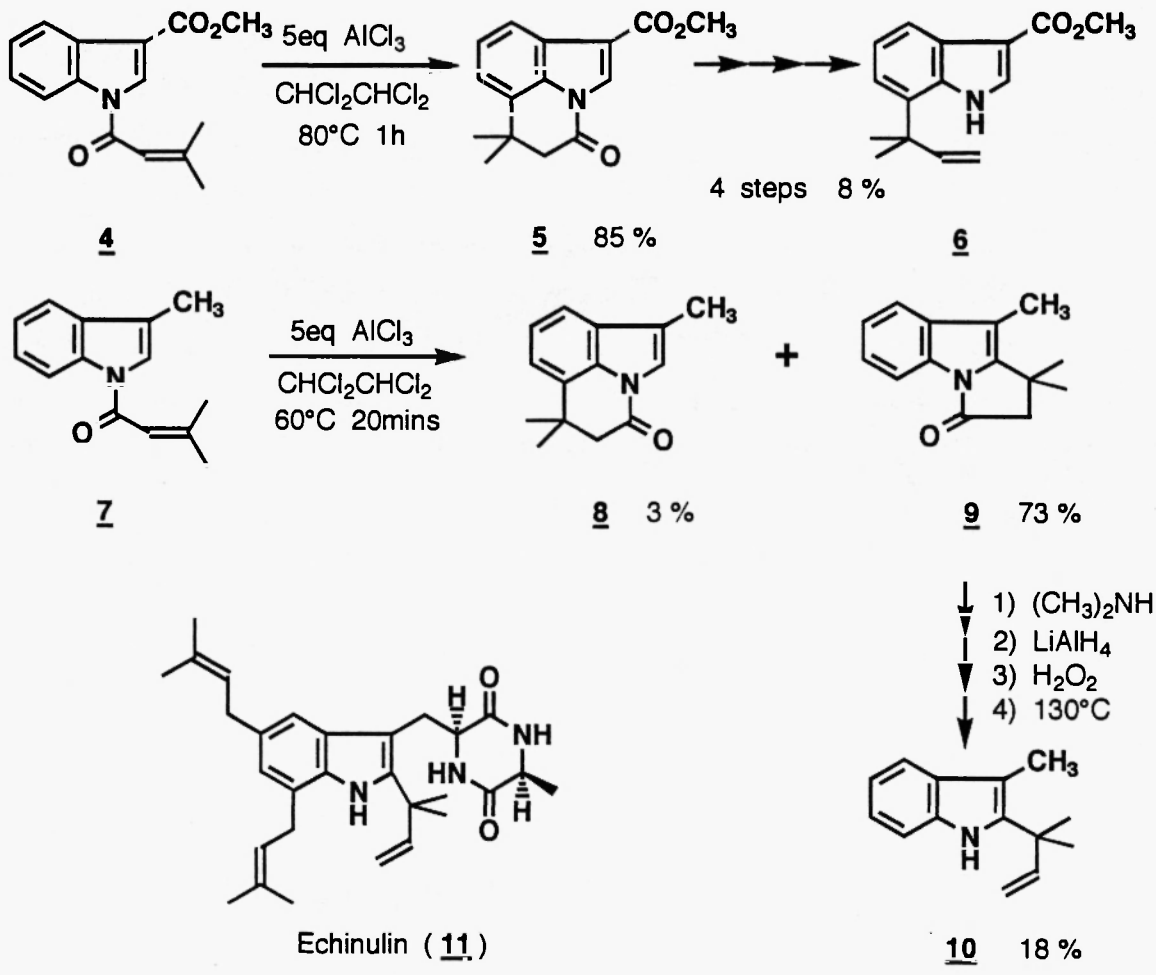


1 2 Teleocidin B (3)

introduction of substituent at benzene part of simple indole derivatives and applied them to the total synthesis of teleocidin B 3 (5). In our total synthesis of teleocidins, we developed novel regioselective cyclization of 1-substituted indole 1 at the 7-position of indole nucleus to give 2. One of the most crucial steps from 2 to teleocidins was cleavage of CH_2-N bond of 2 and transformation to the terminal olefin(5,6). Now, we report much more efficient method to introduce a quarternary carbon substituent at the 7 or 2-position of indole nucleus.

We had examined many reaction conditions for cyclization of 1-(3-methyl-2-butenoyl)indole derivative 4 (7,8) in the presence of various protic acid or Lewis acid such as $AlCl_3$ as a catalyst, but, the desired product 5 was never obtained in commonly used solvents such as dichloromethane, 1,2-dichloroethane, carbon tetrachloride *etc.* (6). In tetrachloroethane at 80℃ for 1 h, $AlCl_3$-catalyzed cyclization of 4 was found to give very desirable conditions to give a lactam 5 (9), which was the cyclization product at 7-position of indole nucleus in 85% yield. No product owing to cyclization at the 2-position of indole nucleus was observed in the reaction mixture. Since we have already succeeded in transformation of lactam 5 to 6 possessing a terminal olefin found in teleocidins in four steps (8% overall yield) in the model reactions of the total synthesis of teleocidins (6), now, we developed more efficient method to introduce a reversed prenyl group at 7-position of indole nucleus *via* *N*-acylation and cyclization at its 7-position(4→5→6).

To apply our novel method to the biomimetic synthesis of echinulin 11, we examined a similar $AlCl_3$-catalyzed cyclization of 1-(3-methyl-2-butenoyl)skatole 7(7, 10). 7 was also cleanly cyclized with $AlCl_3$ in tetrachloroethane at 60℃ for 20 min. to give two lactams 8 and 9 in 3% and 73% yields, respectively. In this case, regioselectivity for the 2-position was much more remarkable than the 7-position since the nucleophilicity of pyrrole part of usual indole 7 is more enhanced than that of benzene part(11, 12). Similarly to the transformation from 5 to 6, lactam 9 was transformed to a skatole derivative 10 containing a reversed prenyl group at 2-position in four steps[1) aminolysis with dimethylamine, 2) reduction of the amide group with $LiAlH_4$, 3) oxidation with H_2O_2, 4) elimination of *N*-oxide at 130℃] in 18% overall yield(13).



We believe that these novel methods for introduction of a reversed prenyl group into the 2 or 7-position in a biomimetic pathway is very important not only for their chemical synthesis but also for study of biosynthesis of the related natural products.

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(6) S. Nakatsuka *et al.*, unpublished results[1) $(CH_3)_2NH$, 2) $LiAlH_4$, 3) H_2O_2, 4) 130℃, 8% overall yield].

(7) These derivatives were obtained by *N*-acylation(NaH/RCOCl in DMF) of methyl indole-3-carboxylate in quant. yields.

(8) 4; mp 98-99℃, MS m/z 257(M^+), 175, 144. ^{1}H-NMR($CDCl_3$) δ 2.08(3H, br.s), 2.24 (3H, br.s), 3.96(3H, s), 6.42(1H, br.s), 7.39(2H, m), 8.15(1H, m), 8.23(1H, s), 8.45(1H, m).

(9) 5; mp 136℃, MS m/z 257(M^+), 242, 183, 154. ^{1}H-NMR($CDCl_3$) δ 1.45(6H, s), 2.88 (2H, s), 3.94(3H, s), 7.26(1H, br,d, J=8Hz), 7.35(1H, t, J=8Hz), 7.94(1H, br.d, J=8Hz), 8.31(1H, s).

(10) 7; mp 68℃, MS m/z 213(M^+), 131, 84. ^{1}H-NMR($CDCl_3$) δ 2.03(3H, br.s), 2.18 (3H, br.s), 2.28(3H, br.s), 6.34(1H, br.s), 7.28(1H, br.s), 7.33(2H, m), 7.50(1H, br.d, J=8Hz), 8.43(1H, br.d, J=8Hz).

(11) 8; mp 97-98℃, MS m/z 213(M^+), 198, 154. ^{1}H-NMR($CDCl_3$) δ 1.42(6H, s), 2.30 (3H, br.s), 2.80(2H, s), 7.18-7.29(2H, m), 7.38(1H, br.d,J=7Hz), 7.44(1H, br.s).

(12) 9; mp 101-102℃, MS m/z 213(M^+), 198, 170. ^{1}H-NMR($CDCl_3$) δ 1.54(6H, s), 2.28 (3H, s), 2.92(2H, s), 7.29(2H, m), 7.43(1H, m), 8.02(1H, m).

(13) 10; oil, MS m/z 199(M^+). ^{1}H-NMR($CDCl_3$) δ 1.53(6H, s), 2.33(3H, s), 5.10-5.16(2H, m), 6.10(1H, dd, J=16 & 10Hz), 7.09(2H, m), 7.29(1H, m), 7.49(1H, m), 7.82(1H, br.s).

Received August 6, 1996