EFFICIENT SYNTHESIS OF BENZ[*c,d*]INDOL-3(1*H*)-ONE DERIVATIVES BY INTRAMOLECULAR CYCLIZATION OF 3-(4'-METHYLCINNAMOYL)INDOLES AND SUBSEQUENT ELIMINATION OF TOLUENE.

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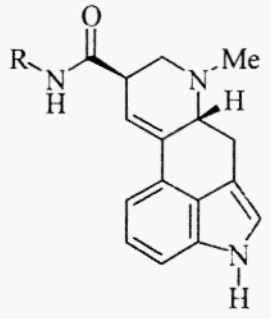
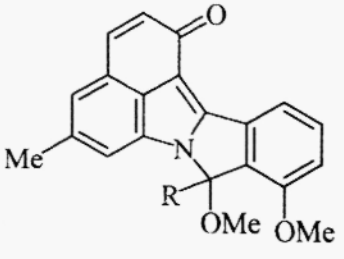
Abstract: Benz[*c,d*]indol-3(1*H*)-one **10** and **11**, a major part of indole alkaloids 0231A **2** and 0231B **3** produced by *Streptomyces sp.* HKI0231, new enzyme inhibitors of 3α-hydroxysteroid dehydrogenase, were efficiently synthesized by cyclization of 3-(4'-methylcinnamoyl)indole derivatives **6c** and **7c** and elimination of toluene.

In the biosynthesis of ergot alkaloids **1**, a phenyl group is first introduced at 4-position of tryptophan.[1] Although many attempts introducing such substituent at the position of indole nucleolus have been studied for a long time, no successful method was reported[2] except a few cases.[3-5]



1 Ergot alkaloids



2 : R = OMe 0231A
3 : R = H 0231B

Figure 1.

In our synthetic studies on indole alkaloids, we have found intra- and intermolecular cyclization toward the 4-position of indole nucleus in cases of dehydrotryptophan and *N*-acylindole derivatives.[5] Recently, we found a novel synthetic method of benz[*c,d*]indol-3(1*H*)-one derivatives **5**, whose common structure was found in enzyme inhibitor 0231A **2** and 0231B **3** from *Streptomyces sp.* HKI0231,[6] *via* intramolecular cyclization of substituted 3-cinnamoylindoles **4** and subsequent elimination of benzene (Fig. 2).[7]

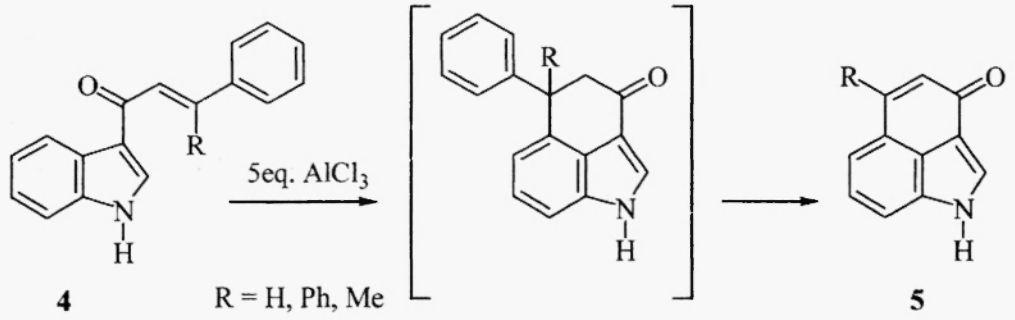


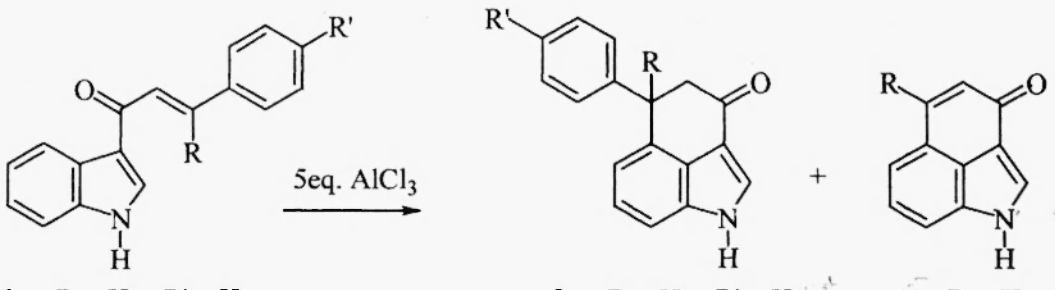
Figure 2. Cyclo-elimination of 3-cinnamoylindole derivatives.

In this reaction, a phenyl group was used as a promoter of the cyclization and also as a protective group of a double bond because its elimination gave aromatized benz[*c,d*]indol-3(1*H*)-one derivatives. Although the benz[*c,d*]indol-3(1*H*)-one derivatives were expected to be useful key intermediates for indole alkaloids containing substituent at the 4-position, the reaction yields were insufficient (45-79%). In this paper, we report much more efficient synthetic method for the substituted benz[*c,d*]indol-3(1*H*)-one **10** and **11** by studies on the efficiency of several substituted benzene as a promoter and eliminator.

The starting materials **6a-c** and **7a-d** were prepared from 1-pivaloylindole by Friedel-Crafts acylation[8] with corresponding 3-cinnamoyl chlorides and subsequent de-protection of the pivaloyl group. Reaction conditions and results of $AlCl_3$ catalyzed cyclo-elimination of substituted 3-cinnamoylindole derivatives **6a-c** and **7a-d** are shown in the Table 1.

An electron withdrawing nitro group at 4'-position of benzene ring completely obstructed the cyclization (entry 7 and 8). Although a stronger electron donating methoxy group is expected to be a suitable function for cyclo-elimination, cyclization and also elimination were delayed to afford the intermediates **8b**[9] or **9b**[10] (entry 2 and 5). The elimination of 4'-methoxyphenyl group of **9b** was completely impeded and no eliminated product **11** was detected in the reaction mixture (entry 5). House *et al.* reported that the excess $AlCl_3$ converted methoxy group to complex compound with positive charge and it inactivates phenyl group.[11] Our results agree with their theory.

On the other hands, an electron donating methyl group accelerated cyclization and also elimination of the phenyl group (entry 3 and 6). Typical reaction in entry 3 is as follows: 5 eq. $AlCl_3$ was added to a stirred solution of **6c** in $CHCl_2CHCl_2$ at 80°C and stirred for 10 min. The cooled reaction mixture was poured into saturated aq. NaCl, and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4, and the solvent was removed in *vacuo*. Purification of the residue by silica gel chromatography (100% ethyl acetate) gave benz[*c,d*]indol-3(1*H*)-one **10** (85%). [**10**: m.p. 157-162°C (dec.);^{1}H-NMR δ ppm(500MHz, 10%CD_3OD in $CDCl_3$) 6.71(1H, d, *J*=9.4Hz), 7.40(1H, dd, *J*=7.3 and 8.0Hz), 7.58(1H, d, *J*=7.3Hz), 7.66(1H, d, *J*=8.0Hz), 7.79(1H, d, *J*=9.4Hz), 8.31(1H, s); ^{13}C-NMR δ ppm(100MHz, 10%CD_3OD in $CDCl_3$) 115.5, 115.8, 123.6, 123.7, 124.3, 125.8, 131.8, 133.4, 133.9, 139.1, 182.3; UV λ_{max} (MeOH) 232(ε=20000), 340(ε=7600), 381(ε=7100), 398(ε=9000), 419(ε=6500)nm; IR ν_{max} (KBr) 3147, 3094, 3054, 2931, 2850, 2795, 1640, 1590, 1565, 1500, 1321, 1186, 1137, 821, 740cm^{-1}; EIMS (70eV, *m/z*) 169(M^+, base peak), 141, 114; HREIMS Calcd for $C_{11}H_7NO$: 169.0528. Found 169.0536].



6a : R = H, R' = H
6b : R = H, R' = OMe
6c : R = H, R' = Me
7a : R = Me, R' = H
7b : R = Me, R' = OMe
7c : R = Me, R' = Me
7d : R = Me, R' = NO_2

8a : R = H, R' = H
8b : R = H, R' = OMe
8c : R = H, R' = Me
9a : R = Me, R' = H
9b : R = Me, R' = OMe
9c : R = Me, R' = Me
9d : R = Me, R' = NO_2

10 : R = H
11 : R = Me

Table 1. Cyclo-elimination of substituted 3-cinnamolylindole derivatives **6a-c** and **7a-d**.

Entry	S. M.	Conditions	Time (min)	Products (Yield%)	
1	**6a**	$CHCl_2CHCl_2$, 80°C	20	**8a** (-)	**10** (45)[7]
2	**6b**	$CHCl_2CHCl_2$, 80°C	20	**8b** (16)	**10** (11)
3	**6c**	$CHCl_2CHCl_2$, 80°C	10	**8c** (-)	**10** (85)
4	**7a**	CH_2Cl_2, r. t.	30	**9a** (-)	**11** (79)[7]
5	**7b**	CH_2Cl_2, r. t.	120	**9b** (84)	**11** (-)
6	**7c**	CH_2Cl_2, r. t.	10	**9c** (-)	**11** (93)
7	**7d**	CH_2Cl_2, r. t.	30	No Reaction	
8	**7d**	$CHCl_2CHCl_2$, 120°C	30	No Reaction	

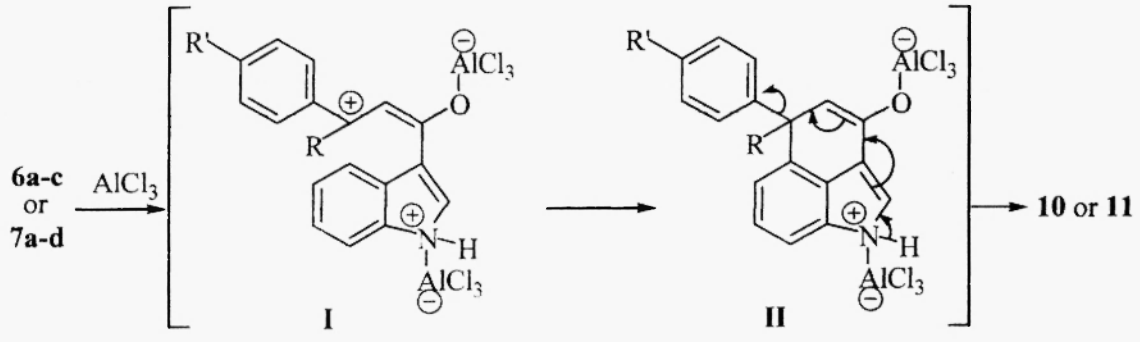


Figure 3. Cyclo-elimination mechanism of **6a-c** and **7a-d**.

Thus, we could develop an efficient synthesis of benz[*c,d*]indol-3(1*H*)-one derivatives **10** and **11**[12] by intramolecular cyclization of 3-(4'-methylcinnamoyl)indoles **6c** and **7c** and subsequent elimination of toluene. Application of this cyclo-elimination to total synthesis of ergot alkaloids **1** and enzyme inhibitor 0231A **2** and B **3** are now in progress.

References and Notes

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7) Very recently, our preliminary results on cyclo-elimination of 3-cinnamoylindole derivatives **4** were submitted for publication.
8) (a) D. M. Ketcha and G. W. Gribble, *J. Org. Chem.*, **50**, 5451(1985); (b) S. Nakatsuka, K. Teranishi and T. Goto, *Tetrahedron Lett.*, **35**, 2699(1994).
9) **8b**: ^{1}H-NMR δ ppm (200MHz, 10%CD_3OD in $CDCl_3$) 3.08(2H, d, *J*=8.1Hz), 3.81(3H, s), 4.70(1H, t, *J*=8.1Hz), 6.80-6.89(3H, m), 7.15-7.23(3H, m), 7.33(1H, d, *J*=6.8Hz), 7.83(1H, s).
10) **9b**: ^{1}H-NMR δ ppm(400MHz, $CDCl_3$) 1.80(3H, s), 2.94(1H, d, *J*=15.9Hz), 3.27(1H, d, *J*=15.9Hz), 3.76(3H, s), 6.79(2H, br.d, *J*=8.8Hz), 7.02(1H, d, *J*=7.0Hz), 7.20-7.32(4H, m), 7.73(1H, d, *J*=2.9Hz), 9.03(1H, br.d, *J*=2.9Hz).
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12) **11**: m.p. 159-164°C (dec.); ^{1}H-NMR δ ppm(500MHz, 10%CD_3OD in $CDCl_3$) 2.54(3H, d, *J*=1.1Hz), 6.52(1H, q, *J*=1.1Hz), 7.42(1H, dd, *J*=7.6 and 8.0Hz), 7.63(1H, d, *J*=8.0Hz), 7.64(1H, d, *J*=7.6Hz), 8.23(1H, s); ^{13}C-NMR δ ppm(100MHz, 10%CD_3OD in $CDCl_3$) 18.3, 115.4, 115.7, 121.0, 124.0, 124.9, 126.1, 130.2, 133.2, 133.5, 149.5, 182.6; UV λ_{max} (MeOH) 233(ε=18000), 321(ε=7300), 378(ε=6000), 395(ε=7600), 415(ε=5600)nm; IR ν_{max} (KBr) 3386, 3081, 3040, 2936, 2846, 1633, 1565, 1502, 1440, 1362, 1307, 1130, 950, 848, 755cm^{-1}; EIMS (70eV, *m/z*) 183(M^+), 154(base peak), 127; HREIMS Calcd for $C_{12}H_9NO$: 183.0684. Found 183.0680.

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