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Taichi KOMODA[a], Yoshihiko SHINODA[a] & Shin-ichi NAKATSUKA[a]
[a] The United Graduate School of Agricultural Science, Gifu University1-1 Yanagido, Gifu 501-1193, Japan
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Preliminary Communication

Total Synthesis of 0231B, an Inhibitor of 3α-Hydroxysteroid Dehydrogenase Produced by *Streptomyces sp.* HKI0231

Taichi KOMODA, Yoshihiko SHINODA, and Shin-ichi NAKATSUKA†

The United Graduate School of Agricultural Science, Gifu University, 1-1 Yanagido, Gifu 501-1193, Japan

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The new inhibitors of 3α-hydroxysteroid dehydrogenase, 0231A 1 and 0231B 2, have a unique benz[*c*,*d*]indol-3(1*H*)-one structure in their molecules. In our advanced studies on indole chemistry, we have developed an efficient synthetic method for benz[*c*,*d*]indol-3(1*H*)-one derivatives. We report here its application to the synthesis of 0231B in 10 steps (8.1% overall yield) from 6-methylindole 8 by introducing an acyl group into the 3-position of the indole nucleus, cyclization of the side chain at the 3-position to the 4-position and subsequent elimination of the phenyl group, and conjugate addition of the substituted phenyl group.

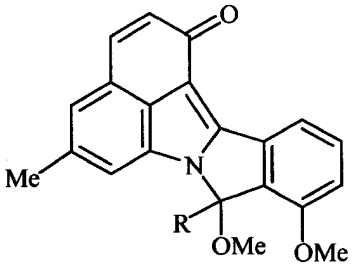
Key words: inhibitor; 3α-hydroxysteroid dehydrogenase; anti-inflammatory agent; indole

The new inhibitors of 3α-hydroxysteroid dehydrogenase, 0231A **1** and 0231B **2**, were isolated from a fermentation broth of *Streptomyces sp.* HKI0231 (Fig. 1).[1] Since 3α-hydroxysteroid dehydrogenase is an enzyme concerned with inflammatory processes, these compounds are promising as lead structures for anti-inflammatory agents. We report in this paper a successful total synthesis of 0231B **2**.

In our advanced studies on indole chemistry,[2–8] we have developed an efficient synthesis of benz[*c*,*d*]indol-3(1*H*)-one derivatives **5** (R = H, Me, Ph), a major constituent of natural inhibitors 0231A and 0231B, by efficient regioselective cyclization of 3-cinnamoylindoles **4** toward the 4-position of the indole nucleus (Fig. 2) (Komoda, T., and Nakatsuka, S., submitted for publication).

Hegedus *et al.* have synthesized benz[*c*,*d*]indol-3(1*H*)-one derivative **6** from 4-bromoindole by [Pd^0]-catalyzed cyclization and found **6** to be a highly electrophilic and conjugate addition of **6** with H^- or CH_3^- giving benz[*c*,*d*]indoline derivative **7** (Fig. 3).[9] We therefore conducted our synthesis of **1** or **2** *via* benz[*c*,*d*]indol-3-one **11** as a key intermediate (Scheme 1).

We chose 6-methylindole **8** as the starting material. After protecting the nitrogen with a pivaloyl group, a *trans-p*-methylcinnamoyl group(*) was introduced at



1, 0231A: R=OMe
2, 0231B: R=H

Fig. 1. Structures of 0231A and 0231B.

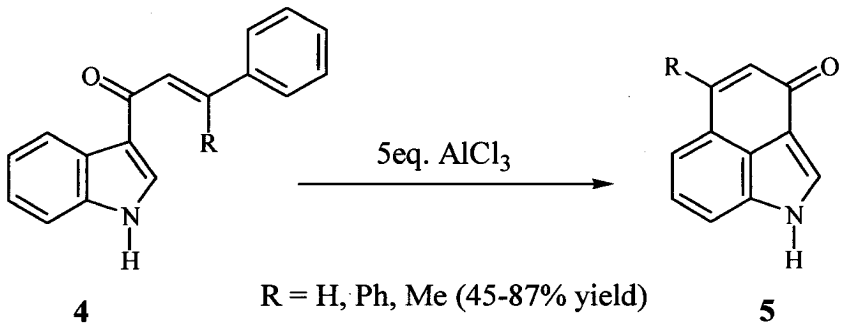
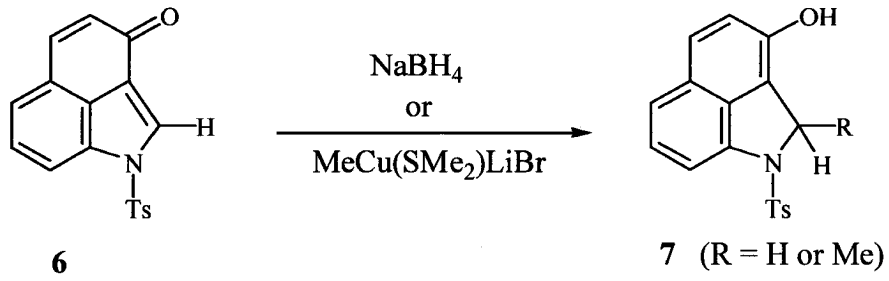


Fig. 2. Synthesis of Benz[*c*,*d*]indol-3(1*H*)-one Derivatives with $AlCl_3$.

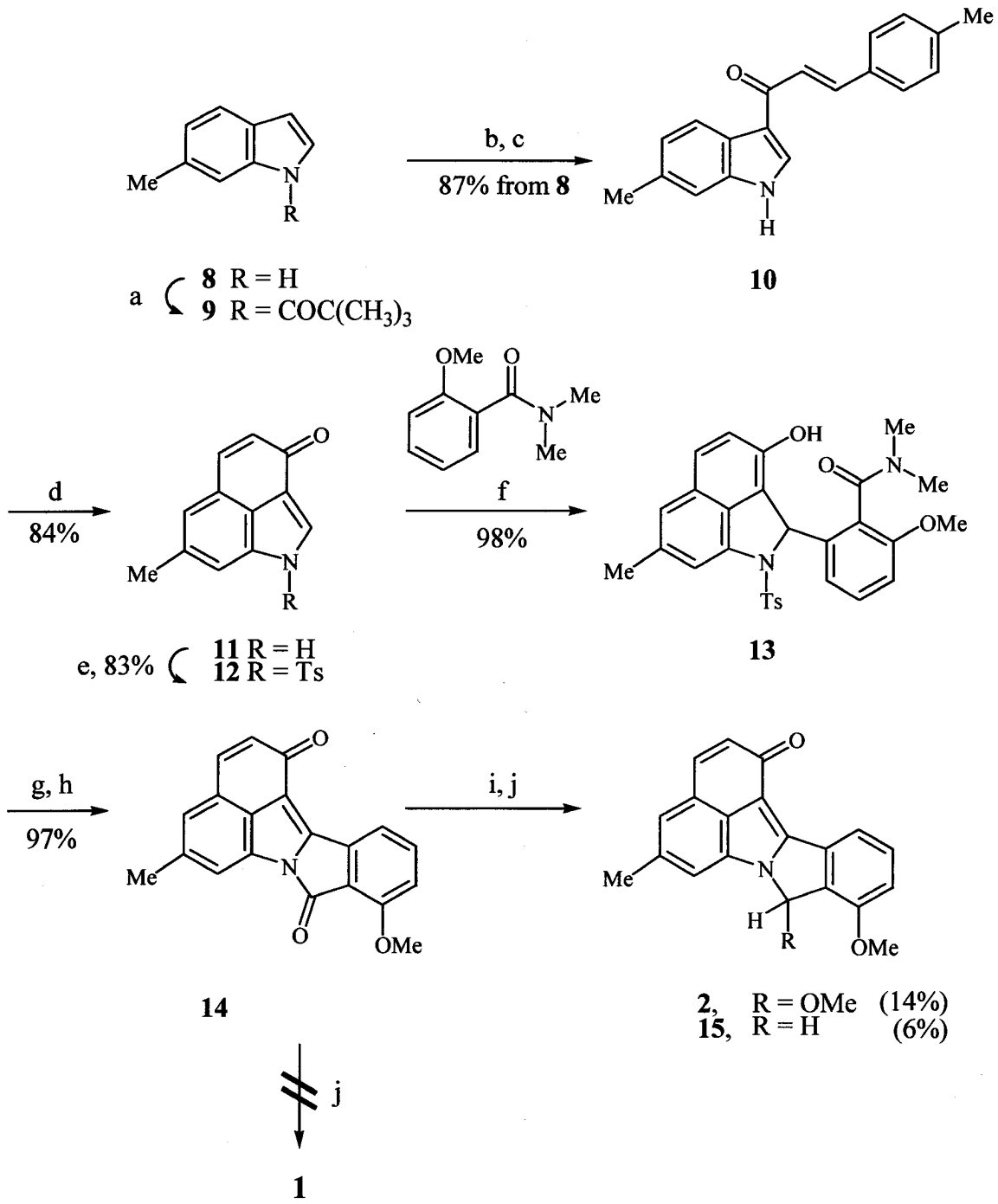
† To whom correspondence should be addressed. Fax: +81-58-293-2919; E-mail: nakatsu@cc.gifu-u.ac.jp

* In our recent study on cyclo-elimination, the *trans-p*-methylcinnamoyl derivative was found to be superior to cinnamoyl derivatives (unpublished result).



6 **7** (R = H or Me)

Fig. 3. Conjugate Addition of 1-Tosylbenz[*c*,*d*]indol-3(1*H*)-one (Hegedus *et al.*[9]).



Scheme 1. a) Trimethylacetyl Chloride, DMAP, Et_3N, CH_2Cl_2; b) *trans-p*-Methylcinnamoyl Chloride, $AlCl_3$, CH_2Cl_2; c) 1*N*-NaOH, MeOH; d) $AlCl_3$, $CHCl_2CHCl_2$, 80°C; e) TsCl, Py; f) *sec*-BuLi, TMEDA, THF; g) O_2, KOH, CuCl, MeOH; h) PhMe, Refl.; i) $LiAlH_4$, THF, −40°C; j) CSA, MeOH, Refl.

the 3-position by Friedel-Crafts acylation,[10,11] and subsequent de-protection of the pivaloyl group afforded *trans-p*-methylcinnamoyl derivative **10** in an 87% overall yield from **8**. The *trans* configuration of the side chain was determined from the coupling constant ($J=15.7$ Hz) in the ^{1}H-NMR spectrum of **10**.

Cyclo-elimination of **10** was next achieved. To a stirred suspension of 5eq. $AlCl_3$ in $CHCl_2CHCl_2$ heated to 80°C for 30 min, a solution of **10** in $CHCl_2CHCl_2$ was added drop-wise over 15 min, and the mixture stirred for 30 min at 80°C. Purification of the reaction mixture by silica gel column chromatography (100% ethyl acetate) afforded 7-methylbenz[*c*,*d*]indol-3(1*H*)-one **11** (84%) [**11**: NMR δ (400 MHz, 10% CD_3OD in $CDCl_3$): 2.55 (3H, s, 7-CH_3), 7.68 (1H, d, $J=9.4$ Hz, 4-H), 7.40 (1H, s, 6-H), 7.46 (1H, s, 8-H), 7.73 (1H, d, $J=9.4$ Hz, 5-H), 8.24 (1H, s, 2-H); EIMS *m*/*z*: 183 (M^+, base peak), 154, 149, 139, 127].(*) The structure of **11** was determined by ^{1}H- and ^{13}C-NMR, HMBC, HMQC and MS data.

N-Tosylate **12** was prepared from **11** [TsCl/Py, 83%]. Conjugate addition of 7-methyl-1-tosylbenz[*c*,*d*]indol-3-(1*H*)-one **12** with lithiated *N*, *N*-dimethyl-*O*-methylsalicylamide[12] was achieved in THF at −78°C to give benz[*c*,*d*]indoline derivative **13** (98%) [**13**: NMR δ (500 MHz, $CDCl_3$): 2.28 (3H, s, Ts-CH_3), 2.50 (3H, s, 7-CH_3), 3.17 (3H, s, N-CH_3), 3.32 (3H, s, N-CH_3), 3.81 (3H, s, O-CH_3), 6.17 (1H, s, 2-H), 6.76 (1H, d, $J=8.0$ Hz), 6.83 (1H, d, $J=8.0$ Hz), 6.93 (1H, d, $J=8.7$ Hz, 4-H), 7.11 (1H, s, 6-H), 7.15 (2H, d, $J=8.2$ Hz), 7.18 (1H, t, $J=8.0$ Hz), 7.36 (1H, s, 8-H), 7.37 (1H, d, $J=8.7$ Hz, 5-H), 7.56 (2H, d, $J=8.2$ Hz), 10.6 (1H, s, O-H); EIMS *m*/*z*: 516 (M^+), 361, 316 (base peak)]. The ^{1}H-NMR spectrum of **13** clearly indicated the naphthol structure as previously reported.[3]

Hydrolysis of the *N*-tosyl group of **13** and subsequent oxidation was achieved by stirring in a sat. KOH-MeOH solution under O_2 in the presence of CuCl for 3 days to give the benz[*c*,*d*]indol-3(1*H*)-one derivative.(*) The crude product was refluxed overnight in toluene to afford lactam **14** in a 97% overall yield [**14**: NMR δ (500 MHz, $CDCl_3$): 2.54 (3H, s, 5-CH_3), 4.05 (3H, s, 8-OCH_3), 6.59 (1H, d, $J=9.6$ Hz, 2-H), 7.02 (1H, d, $J=8.5$ Hz, 10-H), 7.25 (1H, s, 4-H), 7.59 (1H, d, $J=9.6$ Hz, 3-H), 7.63 (1H, dd, $J=7.3$, 8.5 Hz, 11-H), 7.70 (1H, s, 6-H), 7.96 (1H, d, $J=7.3$ Hz, 12-H); EIMS *m*/*z*: 315 (M^+, base peak), 286].

Partial reduction of lactam **14** with $LiAlH_4$ was achieved at −40°C in THF, and the crude product obtained by the usual work up was immediately treated with CSA in methanol under reflux for 4 h under nitrogen. Purification of the crude reaction mixture by silica gel chromatography (1% MeOH in CH_2Cl_2) gave 0231B **2** (14%) as a yellow crystal, over-reduced compound **15** (6%) and starting material **14** (45%) [**2**: NMR δ (500 MHz, $CDCl_3$): 2.58 (3H, s, 5-CH_3), 2.96 (3H, s, 8-OCH_3), 4.00 (3H, s, 9-OCH_3), 6.71 (1H, *d*, $J=9.6$ Hz, 2-H), 6.77 (1H, s, 8-H), 7.04 (1H, d, $J=8.1$ Hz, 10-H), 7.33 (1H, s, 4-H), 7.45 (1H, s, 6-H), 7.57 (1H, dd, $J=7.7$, 8.1 Hz, 11-H), 7.65 (1H, d, $J=9.6$ Hz, 3-H), 8.22 (1H, d, $J=7.7$ Hz, 12-H); EIMS *m*/*z*: 331(M^+), 300 (base peak), 285, 257, 228], [**15**: NMR δ (500 MHz, $CDCl_3$): 2.66 (3H, s, 5-CH_3), 3.96 (3H, s, 9-OCH_3), 5.69 (2H, s, 8-H), 7.12 (1H, d, $J=8.0$ Hz, 10-H), 7.22 (1H, d, $J=8.5$ Hz, 2-H), 7.49 (1H, t, $J=8.0$ Hz, 11-H), 7.61 (1H, br.s), 7.88 (1H, br.s), 7.93 (1H, d, $J=8.5$ Hz, 3-H), 8.09 (1H, d, $J=8.0$ Hz, 12-H); EIMS *m*/*z*: 301 (M^+, base peak), 286, 258, 228]. The ^{1}H-NMR, ^{13}C-NMR, MS, UV and IR data for synthetic **2** were identical with the reported data.[1] We thus achieved the first complete synthesis of 0231B in 10 steps (8.1%).

Unfortunately, 0231A **1** could not be obtained by an acid treatment of **14** in MeOH. A synthetic study of 0231A **1** is now in progress.

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