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Synthesis of the Putative Structure of Fistulosin Using the Ruthenium-Catalyzed Cycloisomerization of Diene

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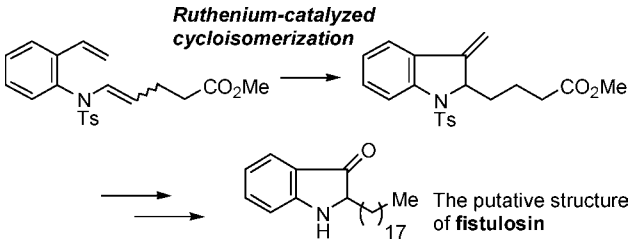
Received October 21, 2005



Fistulosin **1**, which was isolated from the root of the Welsh onion, is a novel indole alkaloid that has antifungal activity. The first total synthesis of the reported structure of fistulosin using our cycloisomerization of diene is described.

The antifungal indole fistulosin **1** (Figure 1) was isolated from the root of the Welsh onion (*Allium fistulosum* L.) by Tomita's group in 1999.[1] Vegetables among *Allium* species are known to be rich in flavonoids and alk(en)yl cysteine sulfoxides, which have perceived benefits for human health.[2] Since the late 1980s, biologically active products in *Allium* species have been investigated and the isolation of nematicidal and antibacterial agents has been reported by Tada's group.[3] Furthermore, Tomita's group reported the isolation of the new alkaloid fistulosin, which exhibited antifungal activities against the wilt-producing fungi *Fusarium oxysporum*.[1] In the field of agriculture, antifungal agents isolated from natural products, such as fistulosin, are expected to be useful as a result of their safety to animals, humans, and ecosystems.

We have been studying the development of new methods for the synthesis of nitrogen-containing heterocyclic compounds using ruthenium carbene catalysts[4] (**A** and **B**) (Figure 2) and have applied them to the synthesis of biologically active natural products.[5a−i] Recently, we developed the selective isomerization of terminal olefin (**2** → **4**) and the cycloisomerization of dienes

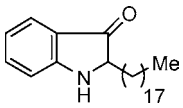


FIGURE 1. Reported structure of fistulosin (**1**).

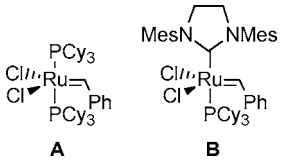


FIGURE 2. Ruthenium catalysts.

(**2** → **6**) by a combination of Grubbs catalyst **B** and vinyloxytrimethylsilane **3**.[5e,g,i] These novel reactions could be applied to the synthesis of a variety of substituted indoles **5**[5e] and 3-methylene-2,3-dihydroindoles **6**[5g] (Scheme 1). Indoles are a major class of alkaloids of great interest and significance because of their pharmacological activities.[6] Although the selective and catalytic cycloisomerizations[7] of dienes, in which a new ring is formed without the loss of carbon units, are highly atom-economical reactions, the application of this reaction to the synthesis of natural products or pharmaceutically useful compounds has not been reported because of limitations regarding the range of substrates and the tolerance of functional groups. We report here the first synthesis of the reported structure of fistulosin using our cycloisomerization of diene as a key step.

Initially, we planned to synthesize the key intermediate **8**, which has an octadecyl group at the 2-position of the indoline core, from *o*-vinylaniline derivative **7** by ruthenium-catalyzed cycloisomerization. Unfortunately, however, the reaction of **7** in the presence of catalyst **B** and **3** did not provide the desired cyclized product **8** at all but rather gave a complex mixture of regioisomers, which were produced by olefin migration of the nonadecenyl side chain (Scheme 2). Therefore, we next chose the enamide **12** as a substrate for cycloisomerization (Scheme 3). This substrate includes an olefin of an enamide group, which

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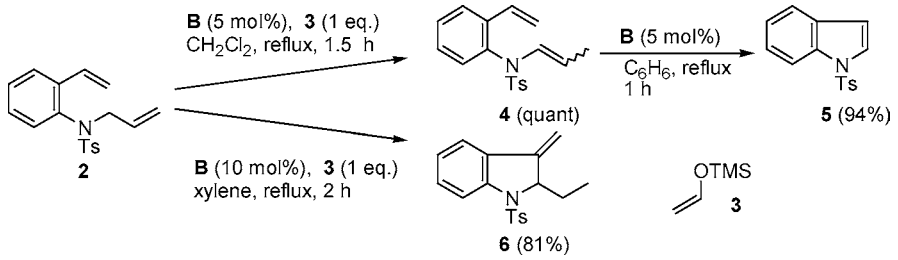
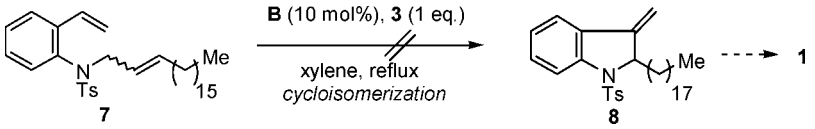
10.1021/jo0522005 CCC: $33.50
Published on Web 12/27/2005

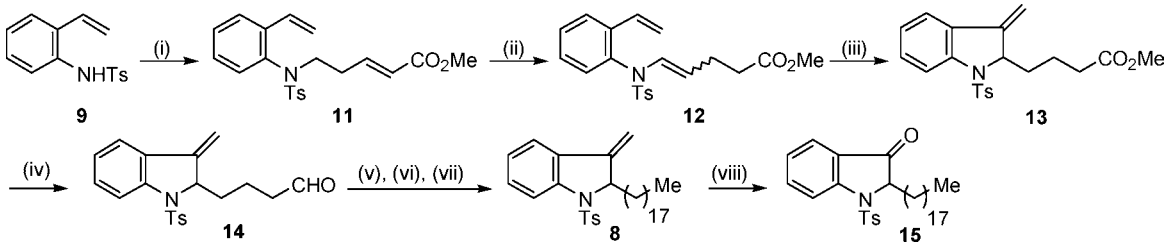
SCHEME 1. Synthesis of Substituted Indoles and 2,3-Dihydroindoles



SCHEME 2. Initial Approach to Fistulosin (1)

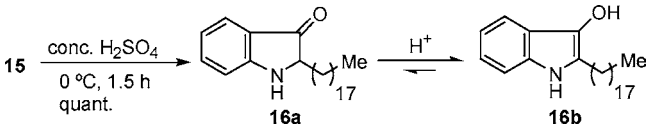


SCHEME 3. Synthesis of *N*-Tosyl-2-octadecyl-3-indolinone (15)[a]



[a] Reagents and conditions: (i) (*E*)-HO(CH$_2$)$_2$CH=CHCO$_2$Me (**10**), DEAD, PPh$_3$, THF, rt, 4 h, 99%; (ii) RuClH(CO)(PPh$_3$)$_3$, toluene, reflux, 23 h, 83%; (iii) **B** (10 mol %), **3** (1 equiv), xylene, reflux, 2 h, 87%; (iv) DIBAL, toluene, −78 °C, 20 min, 87%; (v) BrMg(CH$_2$)$_{13}$Me, THF, 0 °C, 20 min, 93%; (vi) MsCl, Et$_3$N, DMAP, CH$_2$Cl$_2$, rt, 30 min, 86%; (vii) NaBH$_4$, HMPA, 50 °C, 2 h, 71%; (viii) O$_3$, CH$_2$Cl$_2$, −78 °C, 15 min, then PPh$_3$, rt, 2 h, 70%.

SCHEME 4. Deprotection and Tautomerization



is expected to efficiently undergo our cycloisomerization, and an ester group for subsequent extension of the alkyl chain. The preparation of **12** was commenced with the Mitsunobu reaction of readily available **9** with alcohol **10**, and treatment of **11** with RuClH(CO)(PPh$_3$)$_3$[8] (10 mol %) provided enamide **12** in 83% yield. With substrate **12** in hand, cycloisomerization of **12** in the presence of Grubbs catalyst **B** (10 mol %) and **3** (1 equiv) gave cyclized product **13** as a stable colorless crystal in 87% yield. Installation of a tetradecyl group was achieved through a four-step procedure. Cyclized product **13** was reduced with DIBAL to give aldehyde **14**, and then treatment of **14** with Grignard reagent gave the secondary alcohol in 93% yield. Mesylation of the hydroxy group followed by the reduction of mesylate with NaBH$_4$ gave indoline **8**, which was converted to 3-indolinone **15** by ozonolysis. Finally, treatment of **15** with concentrated H$_2$SO$_4$ at 0 °C[9] gave the deprotected product **16a** quantitatively in crude form (Scheme 4). 3-Indolinone **16a** was pure and stable enough for the structure to be characterized by spectral analyses. However, further purifications of **16a** by column chromatography or recrystallization were unsuccessful, even though we used the same procedure reported by Tomita, since **16a** was gradually tautomerized to more thermodynamically stable 3-hydroxyindole **16b** in solution.[10a−c]

Next, we compared the spectral data of **16a** to those reported for natural fistulosin **1** (Table in Supporting Information). The IR spectrum of synthetic compound **16a** revealed a strong band at 1675 cm^{-1}, which was similar to the reported data (1684 cm^{-1}), and the reported characteristic mass peak at 133 [M − $C_{18}H_{36}^{+}$] was also observed in the spectrum of **16a**. On the other hand, the ^{1}H NMR spectra showed some remarkable differences. As for our synthetic **16a**, the chemical shift of methine proton at the 2-position was observed at 3.75 ppm, in contrast to 2.44 ppm reported by Tomita's group. In addition, conspicuous differences were seen in the ^{13}C NMR spectra. For example, the chemical shift of the carbonyl carbon of our sample was observed at 202.7 ppm, in contrast to the reported value of 171.5 ppm. Overall, the spectral data supported the structure of **16a**. Thus, we concluded that the spectral data of **16a** did not agree with those reported for fistulosin.

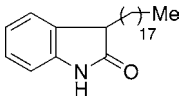


FIGURE 3. Structure of oxindole **17**.

We next compared the spectral data of the more stable tautomer **16b** and oxindole **17**, which are other candidates of the natural product "fistulosin". Tautomerization of **16a** occurred smoothly in an acidic medium, such as aqueous HCl or H$_2$SO$_4$,

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to give **16b**, which could be purified by recrystallization from *n*-hexane/AcOEt. Although the crystals of **16b** were not suitable for X-ray analysis, other spectra including 2D-NMR spectra (^{1}H−^{1}H COSY, HMBC, and HMQC) unambiguously confirmed the structure of **16b**. Oxindole **17** was synthesized by the procedures reported by Overman and co-workers.[11] However, the spectral data of both **16b** and **17** were also not consistent with the reported data of fistulosin (Table in Supporting Information). Further investigations are necessary to elucidate the structure of fistulosin.

In conclusion, we have achieved the first synthesis of the reported structure of fistulosin featuring our ruthenium-catalyzed cycloisomerization of diene. Further applications of our methodology to the syntheses of pharmacologically active products are currently in progress.

Experimental Section

***N*-*p*-Toluenesulfonyl-2-(3-methoxycarbonylpropyl)-3-methylene-2,3-dihydroindole (13).** To a stirred solution of **12** (262 mg, 0.68 mmol) and vinyloxytrimethylsilane **3** (79.0 mg, 0.68 mmol) in xylene (54.4 mL) was added ruthenium carbene catalyst **B** (57.7 mg, 0.068 mmol) under an Ar atmosphere, and the mixture was refluxed for 2 h. After the removal of solvent, the residue was purified by column chromatography (*n*-hexane/Et_2O = 5:1) to give **13** (229 mg, 87%) as a colorless prism. Mp 140−141 °C (*n*-hexane/AcOEt); ^{1}H NMR δ 7.75 (d, 1H, J = 8.1 Hz), 7.52 (d, 2H, J = 8.4 Hz), 7.26−7.31 (m, 2H), 7.14 (d, 2H, J = 8.6 Hz), 7.05 (dd, 1H, J = 7.7, 7.7 Hz), 5.37 (d,1H, J = 2.6 Hz), 4.88 (d, 1H, J = 2.0 Hz), 4.60−4.63 (m, 1H), 3.63 (s, 3H), 2.25−2.44 (m, 2H), 2.33 (s, 3H), 2.09−2.17 (m, 1H), 1.71−1.86 (m, 2H), 1.61−1.68 (m, 1H); ^{13}C NMR δ 173.8, 144.6, 144.0, 143.8, 134.1, 130.1, 130.0, 129.5, 127.2, 124.5, 120.9, 117.0, 103.0, 66.1, 51.5, 36.4, 33.8, 21.5, 18.6; IR (neat) cm^{-1} 2947, 1732, 1460, 1352, 1163, 662; LRMS (EI) *m*/*z* 385 (M^+, 41%), 230 (100%, base peak); HRMS (FAB) calcd for $C_{21}H_{24}NO_4S$ (M^+ + H) 386.1426, found 386.1420. Anal. Calcd for $C_{21}H_{23}NO_4S$: C 65.43 H 6.01 N 3.63. Found: C 65.48 H 6.09 N 3.62.

4-(*N*-*p*-Toluenesulfonyl-3-methylene-2,3-dihydroindolyl)butanal (14). To a cooled (−78 °C) solution of **13** (159 mg, 0.41 mmol) in toluene (25.0 mL) under Ar atmosphere was added DIBAL (1.01 M, toluene solution, 0.49 mL, 0.49 mmol). The mixture was stirred at −78 °C for 20 min, and the reaction was quenched by the addition of MeOH and saturated aqueous Rochelle's salt. Then the solution was allowed to stir at room temperature until separation of organic and water layers. The mixture was extracted with AcOEt, and the combined organic layers were washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was subjected to column chromatography (*n*-hexane/AcOEt = 4:1) to give **14** (126 mg, 87%) as a colorless oil. ^{1}H NMR δ 9.72 (t, 1H, J = 1.5 Hz), 7.75 (d, 1H, J = 8.1 Hz), 7.52 (d, 2H, J = 8.3 Hz), 7.26−7.31 (m, 2H), 7.14 (d, 2H, J = 8.5 Hz), 7.05 (dd, 1H, J = 7.6, 7.6 Hz), 5.38 (d, 1H, J = 2.4 Hz), 4.89 (d, 1H, J = 2.0 Hz), 4.60−4.62 (m, 1H), 2.40−2.48 (m, 2H), 2.33 (s, 3H), 2.10−2.16 (m, 1H), 1.75−1.85 (m, 2H), 1.60−1.70 (m, 1H); ^{13}C NMR δ 202.4, 144.6, 144.1, 143.8, 134.0, 130.13, 130.10, 129.6, 127.2, 124.6, 120.9, 117.1, 103.0, 66.1, 43.6, 36.5, 21.5, 15.8; IR (neat) cm^{-1} 1720, 1460, 1351, 1163, 661; LRMS (EI) *m*/*z* 355 (M^+, 36%), 200 (100%, base peak); HRMS (FAB) calcd for $C_{20}H_{22}NO_3S$ (M^+ + H) 356.1320, found 356.1309.

***N*-*p*-Toluenesulfonyl-2-octadecyl-3-methylene-2,3-dihydroindole (8).** To a cooled (−78 °C) solution of **14** (106 mg, 0.30 mmol) in THF (3.0 mL) was slowly dropped $C_{14}H_{29}MgBr$ (0.5 M, THF solution, 1.80 mL, 0.90 mmol). The mixture was stirred at 0 °C for 20 min, and the reaction was quenched by saturated aqueous NH_4Cl. The organic compounds were extracted with AcOEt, and the combined organic layers were washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was subjected to column chromatography (*n*-hexane/AcOEt = 6:1) to give the alcohol (153 mg, 93%) as a colorless oil.

To a solution of alcohol (209 mg, 0.38 mmol), DMAP (46.1 mg, 0.38 mmol), and Et_3N (0.26 mL, 1.89 mmol) in CH_2Cl_2 (9.0 mL) was added methanesulfonyl chloride (0.09 mL, 1.13 mmol) dropwise, and the mixture was stirred for 30 min at room temperature. After addition of saturated aqueous NH_4Cl, the organic compounds were extracted with CH_2Cl_2. The combined organic layers were washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was subjected to column chromatography (*n*-hexane/AcOEt = 5:1) to give the mesylate (204 mg, 86%) as a colorless oil.

To a solution of mesylate (104 mg, 0.17 mmol) in HMPA (2.2 mL) was added $NaBH_4$ (24.9 mg, 0.66 mmol), and the mixture was stirred at 50 °C for 2 h. After addition of saturated aqueous $NaHCO_3$, the organic compounds were extracted with AcOEt. The combined organic layers were washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was subjected to column chromatography (*n*-hexane/AcOEt = 40:1) to give **8** (62.6 mg, 71%) as a colorless oil. ^{1}H NMR δ 7.74 (d, 1H, J = 8.1 Hz), 7.53 (d, 2H, J = 8.1 Hz), 7.29 (d, 1H, J = 7.1 Hz), 7.27 (dd, 1H, J = 7.5, 7.5 Hz), 7.13 (d, 2H, J = 8.2 Hz), 7.04 (dd, 1H, J = 7.5, 7.5 Hz), 5.34 (d, 1H, J = 2.4 Hz), 4.85 (d, 1H, J = 1.8 Hz), 4.60−4.62 (m, 1H), 2.32 (s, 3H), 2.03−2.09 (m, 1H), 1.73−1.79 (m, 1H), 1.22−1.43 (m, 32H), 0.88 (t, 3H, J = 6.4 Hz); ^{13}C NMR δ 145.2, 144.0, 143.8, 134.4, 130.3, 129.9, 129.5, 127.1, 124.4, 120.7, 117.0, 102.6, 66.7, 37.2, 31.9, 29.4−29.7 (m), 22.8, 22.7, 21.5, 14.1; IR (neat) cm^{-1} 2920, 2850, 1457, 1353, 1167; LRMS (EI) *m*/*z* 537 (M^+, 100%, base peak), 382 (44%); HRMS (FAB) calcd for $C_{34}H_{52}NO_2S$ (M^+ + H) 538.3719, found 538.3732.

***N*-*p*-Toluenesulfonyl-2-octadecyl-3-indolinone (15).** To a cooled (−78 °C) solution of **8** (137 mg, 0.25 mmol) in CH_2Cl_2 (25.0 mL) was bubbled O_3 gas until the color of the solution turned to blue. After the addition of PPh_3 (200 mg, 0.76 mmol), the mixture was stirred at room temperature for 2 h. The solvent was removed under reduced pressure, and the residue was subjected to column chromatography (*n*-hexane/AcOEt = 30:1 to 8:1) to give **15** (94.0 mg, 70%) as a red oil. ^{1}H NMR δ 8.08 (d, 1H, J = 8.3 Hz), 7.67 (ddd, 1H, J = 7.3, 7.3, 1.5 Hz), 7.61 (d, 2H, J = 8.5 Hz), 7.61 (d, 1H, J = 8.5 Hz), 7.20 (d, 2H, J = 8.1 Hz), 7.19 (ddd, 1H, J = 7.1, 7.1, 0.7 Hz), 3.98 (dd, 1H, J = 6.1, 3.7 Hz), 2.35 (s, 3H), 2.08−2.27 (m, 2H), 1.06−1.44 (m, 32H), 0.88 (t, 3H, J = 6.6 Hz); ^{13}C NMR δ 198.8, 153.5, 144.9, 137.1, 133.5, 129.9, 127.2, 125.2, 124.5, 124.2, 117.1, 67.4, 32.0, 31.9, 29.3−29.7 (m), 23.0, 22.7, 21.5, 14.1; IR (neat) cm^{-1} 2915, 2848, 1733, 1604, 1355, 1151; LRMS (EI) *m*/*z* 539 (M^+, 12%), 433 (42%), 91 (100%, base peak); HRMS (FAB) calcd for $C_{33}H_{50}NO_3S$ (M^+ + H) 540.3511, found 540.3535.

2-Octadecyl-3-indolinone (16a). A mixture of **15** (90.0 mg, 0.17 mmol) and concentrated H_2SO_4 (2.0 mL) was stirred at 0 °C for 1.5 h. To the solution was slowly poured cooled water at 0 °C, and the aqueous layer was neutralized with saturated aqueous $NaHCO_3$. The organic compounds were extracted with AcOEt, and the combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated in vacuo to give **16a** (66.0 mg, 100%) as an orange solid. Mp 100−102 °C; ^{1}H NMR δ 7.61 (d, 1H, J = 7.9 Hz), 7.44 (dd, 1H, J = 8.2, 7.1 Hz), 6.88 (d, 1H, J = 8.6 Hz), 6.82 (dd, 1H, J = 7.3, 7.3 Hz), 4.70 (brs, 1H), 3.75 (dd, 1H, J = 8.4, 4.2 Hz), 1.83−1.96 (m, 1H), 1.55−1.64 (m, 1H), 1.25−1.40 (m, 32H), 0.88 (t, 3H, J = 6.8 Hz); ^{13}C

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NMR δ 202.7, 161.3, 136.9, 124.5, 121.5, 118.9, 112.6, 64.3, 32.0, 31.9, 29.3−29.7 (m), 25.8, 22.7, 14.1; IR (neat) cm^{-1} 3394, 2914, 2848, 1675, 1469, 1321, 734; LRMS (EI) *m*/*z* 385 (M^+, 18%), 161 (15%), 133 (10%), 84 (34%), 18 (100%, base peak).

2-Octadecyl-3-hydroxyindole (16b). A mixture of **15** (20.7 mg, 38.3 μmol) and concentrated H_2SO_4 (1.0 mL) was stirred at 0 °C for 1.5 h. To the solution was added cooled water (3.0 mL) and AcOEt (4.0 mL) at 0 °C slowly, and the mixture was stirred at room temperature for 1 h. After the aqueous layer was neutralized with saturated aqueous $NaHCO_3$, the organic compounds were extracted with AcOEt, and the combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated in vacuo to give **16b** (13.3 mg, 91%, estimated by ^1H NMR) as yellow needles. Mp 107−108 °C (*n*-hexane/AcOEt); ^1H NMR δ 7.56 (d, 1H, J = 7.7 Hz), 7.49 (dd, 1H, J = 8.1, 8.1 Hz), 6.95 (d, 1H, J = 8.2 Hz), 6.78 (dd, 1H, J = 7.1, 7.1 Hz), 6.08 (brs, 1H), 1.84−1.90 (m, 1H), 0.99−1.31 (m, 34H), 0.88 (t, 3H, J = 6.4 Hz), The peak at 6.08 ppm was disappeared in $CDCl_3/D_2O$ (10/1); ^{13}C NMR δ 204.6, 162.0, 138.1, 124.2, 121.5, 118.3, 112.0, 72.5, 32.0, 31.9, 29.3−29.8 (m), 23.0, 22.7, 14.1, IR (neat) cm^{-1} 2915, 2848, 1674, 1613, 1484, 1327, 740; LRMS (EI) *m*/*z* 385 (M^+, 20%), 383 (100%, base peak), 172 (45%), 146 (53%). Anal. Calcd for $C_{26}H_{43}NO$: C 80.98 H 11.24 N 3.63. Found: C 80.97 H 10.93 N 3.49.

Acknowledgment. This research was supported by Grants-in-Aid for the Encouragement of Young Scientists (A), for Scientific Research (B), for Priority Area (17035014), and for Exploratory Research from the Ministry of Education, Culture, Sports, Science and Technology (MEXT), Japan. We also thank the Naito Foundation and the Fujisawa Foundation for financial support.

Supporting Information Available: Experimental procedures of the synthesis of **11**, **12**, and **17**, and ^1H and ^{13}C NMR spectra of **8**, **11**, **13**−**15**, **16a**, and **16b**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0522005