HETEROCYCLES, Vol. 69, 2006, pp. 217 - 222. © The Japan Institute of Heterocyclic Chemistry
Received, 10th May, 2006, Accepted, 9th June, 2006, Published online, 20th June, 2006. COM-06-S(O)10

SYNTHESES OF ULOCLADOL

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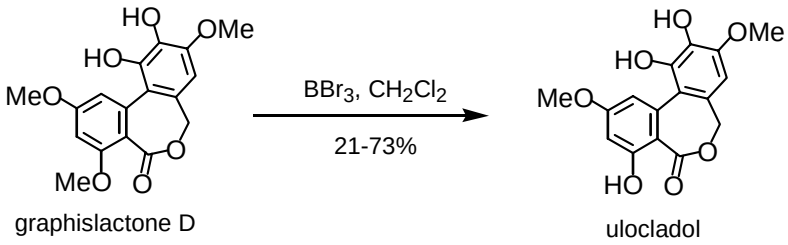
Abstract – Several synthetic routes to produce ulocladol were established through a short-step transformation involving the selective demethylation or a lactone transformation process.

Ulocladol was isolated from the marine fungi *Ulocladium botrytis* in 1999.[1] The structural determination was carried out using an NMR technique and other spectrum analyses. Because of its interesting biological activity, such as a tyrosine kinase inhibitor,[1,2] we have been attracted to its total synthesis. The unique structural feature of ulocladol is that this compound has a 7*H*-dibenzo[*c*,*e*]oxepin-5-one core[3] and the two fused aromatic rings in the core are highly oxygenated. To our knowledge, there are few examples of natural products[4] which possess such a heterocyclic system, and the general synthesis of this type of compound has never been reported.

Recently, the total synthesis of graphislactone D through a palladium-assisted biaryl coupling reaction and a lactone reconstruction method was demonstrated.[5] In this report, we present the short-step synthesis of ulocladol, which is structurally related to graphislactone D.

Initially, the selective demethylation reaction of graphislactone D was examined with the combination system of aluminum chloride and sodium iodide.[6] Although all attempts were unsuccessful using this reagent system, it was found that boron tribromide was effective for the methyl ether cleavage reaction[7] of graphislactone D (Scheme 1). The NMR data indicate that our synthetic product is consistent with the reported natural product as summarized in Table 1. However, the chemical yields in this transformation from graphislactone D into ulocladol varied in the range between 21-73%. In spite of our intensive efforts to improve the reproducibility of the chemical yields, we could not find any good reaction conditions when graphislactone D was used as the precursor. Thus, we needed another route for the synthesis of

ulocladol.



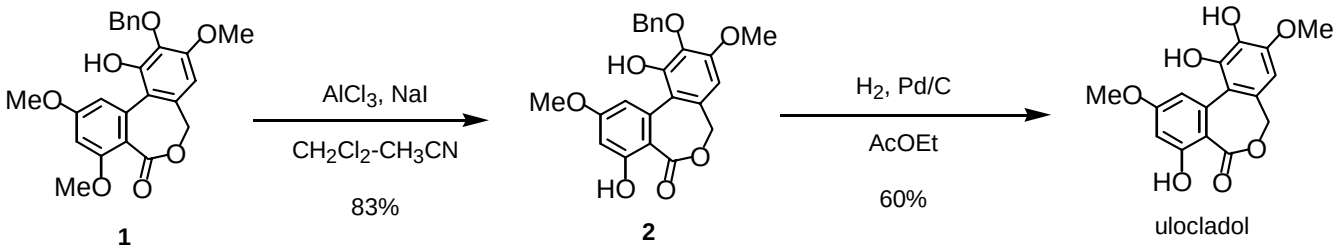
Scheme 1. Selective demethylation of graphislactone D

Table 1. Comparison of NMR data

^{1}H (δ ppm)		^{13}C (δ ppm)	
synthetic	reported[1]	synthetic	reported[1]
3.87 (3H, s)	3.87 (3H, s)	55.5	55.5
3.95 (3H, s)	3.95 (3H, s)	56.3	56.3
4.79 (1H, d, *J* = 12.0 Hz)	4.79 (1H, d, *J* = 11.7 Hz)	70.3	70.3
5.11 (1H, d, *J* = 12.0 Hz)	5.11 (1H, d, *J* = 11.7 Hz)	100.8	100.8
5.68 (1H, s)	5.68 (1H, br. s)	103.0	103.1
5.77 (1H, s)	5.77 (1H, br. s)	106.8	106.9
6.56 (1H, d, *J* = 2.4 Hz)	6.55 (1H, d, *J* = 2.5 Hz)	110.2	110.2
6.58 (1H, s)	6.58 (1H, s)	118.7	118.8
6.91 (1H, d, *J* = 2.4 Hz)	6.92 (1H, d, *J* = 2.5 Hz)	127.0	127.1
		133.7	133.8
		135.9	135.9
		142.0	142.1
		146.3	146.3
		163.0	163.0
		163.2	163.2
		172.5	172.5

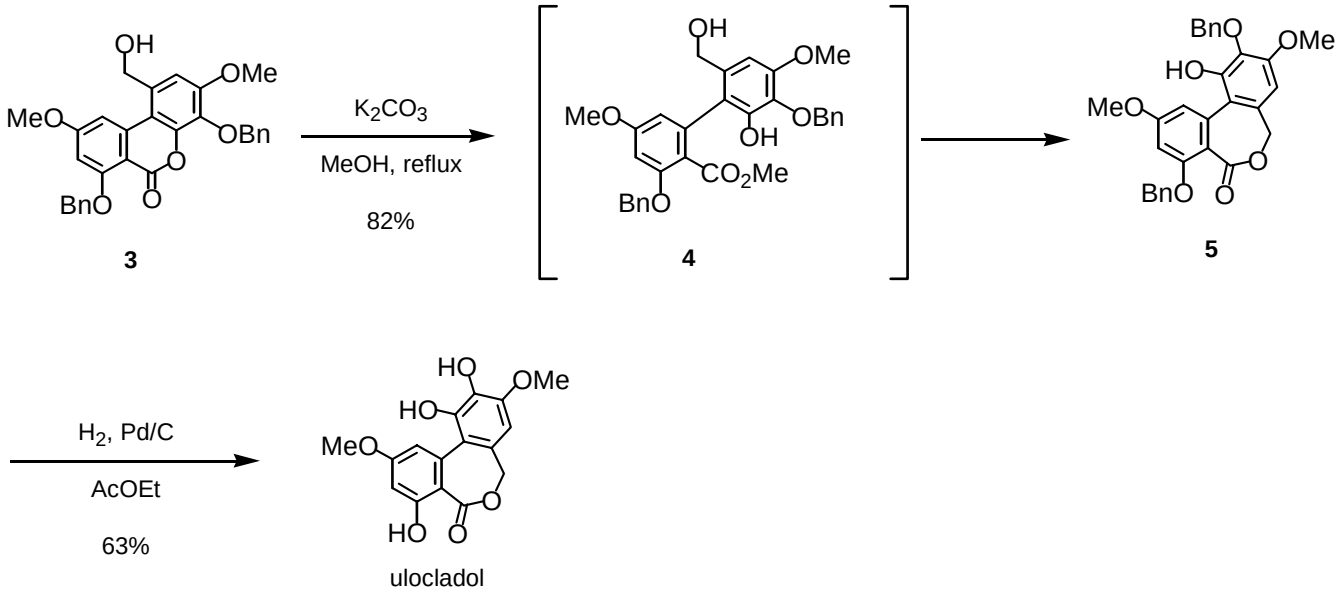
As the next scheme to synthesize our target molecule, we tried a two-step transformation from the seven-membered ring lactone compound (**1**),[5] which is an important intermediate for the synthesis of graphislactones (Scheme 2). In this case, the aluminum chloride-sodium iodide system[6] was efficient for the selective demethylation of the methoxy group by the neighboring participation of the lactone carbonyl group. The final deprotection of the phenolic alcohol of **2** was achieved by the catalytic hydrogenolysis conditions.

The third synthetic route for the synthesis of ulocladol is shown in Scheme 3. In this scheme, the six-membered ring lactone (**3**)[5] was successfully transformed into the seven-membered ring lactone (**5**) in a single step using a methanolysis protocol. This transformation must proceed through a lactone-opened intermediate (**4**). With the seven-membered ring lactone (**5**) in hand, employing the conventional hydrogenolysis technique lead to the completion of the synthesis of ulocladol.



Scheme 2. The second route to ulocladol

In conclusion, we achieved three different routes for the synthesis of ulocladol using several lactones, which were intermediates utilized in the synthesis of the graphislactones.



Scheme 3. The third synthesis of ulocladol involving a lactone reconsrtuction process

EXPERIMENTAL

General: Melting points were measured using a Yanagimoto micro melting point hot-plate apparatus and are uncorrected. The IR spectra were recorded using a JASCO FTIR-350 spectrophotometer. The NMR spectra were obtained using a Varian INOVA-600 or MERCURY-300 instrument with the chemical shifts being reported as δ ppm and the couplings expressed in Hertz. The FAB-MS was obtained using a VG-70SE instrument with *m*-nitrobenzyl alcohol as the matrix. Silica gel column chromatography was carried out using Daisogel 1002W. All reactions were carried out under an argon atmosphere.

Selective demethylation reaction of graphislactone D

To a solution of graphislactone D (10 mg, 0.03 mmol) in CH_2Cl_2 (1 mL) was added BBr_3 (1 mol/L in CH_2Cl_2) (31μL, 0.03 mmol) at -40ºC, and then the mixture was stirred for 16h at the same temperature. The reaction mixture was poured into ice water and extracted with CH_2Cl_2. The organic layer was washed with brine and dried over anhydrous $MgSO_4$. After evaporation, the resulting yellow solid was subjected to a silica-gel column chromatography with AcOEt-hexane (3:2) as the eluent. Ulocladol was then obtained in a pure form (7 mg, 73%).

Ulocladol: Colorless needles, mp 169.5-180.5ºC (decomp)(CH_2Cl_2-Et_2O)[lit.,[1] mp 110-111ºC].[8] IR (KBr) cm^{-1}: 3389, 2940, 1660, 1620, 1570, 1340, 1160, 1095. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.87 (3H, s, 10-OCH_3), 3.95 (3H, s, 3-OMe), 4.79 (1H, A of AB, d, J = 12.0 Hz, Ar$CH_AH_BCO_2$), 5.11 (1H, B of AB, d, J = 12.0 Hz, Ar$CH_AH_BCO_2$), 5.68 (1H, s, 2-OH, exchangeable with D_2O), 5.77 (1H, s, 1-OH, exchangeable with D_2O), 6.56 (1H, d, J = 2.4 Hz, H-9), 6.58 (1H, s, H-4), 6.91 (1H, d, J = 2.4 Hz, H-11), 10.32 (1H, s, 8-OH, exchangeable with D_2O). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 55.5, 56.3, 70.3, 100.8, 103.0, 106.8, 110.2, 118.7, 127.0, 133.7, 135.9, 142.0, 146.3, 163.0, 163.2, 172.5. *Anal.* Calcd for $C_{16}H_{14}O_7$・1/4 H_2O: C, 59.54; H, 4.53. Found: C, 59.56; H, 4.45. MS (FAB, positive ion mode) *m/z*: 319 [M+1].

2-Benzyloxy-1,8-dihydroxy-3,10-dimethoxy-5*H*,7*H*-dibenzo[*c*,*e*]oxepin-7-one (**2**)

To a solution of **1** (156 mg, 0.37 mmol) in a mixture of CH_3CN (8 mL) and CH_2Cl_2 (4 mL), $AlCl_3$ (247 mg, 1.85 mmol) and NaI (195 mg, 1.30 mmol) were successively added at 0 ºC. After the mixture was stirred for 1 h at 0ºC, 10% $Na_2S_2O_3$ aq. and CH_2Cl_2 were added. The organic layer was separated, washed with brine and dried over anhydrous $MgSO_4$. After evaporation, the resulting residue was subjected to silica-gel column chromatography using AcOEt-hexane (1:1) as the eluent to give **2** (126 mg, 83%): Colorless needles, mp 139.5-140.5℃ (CH_2Cl_2 - Et_2O). IR (KBr) cm^{-1}: 3440 (OH), 1655 (CO), 1615, 1160, 1100. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.83 (3H, s, 3-OCH_3), 3.97 (3H, s, 10-OMe), 4.80 (1H, A of AB, d, J = 12.0 Hz, Ar$CH_AH_BCO_2$), 5.05 (1H, B of AB, d, J = 11.1 Hz, ArCH_AH_BPh), 5.11 (1H, A of AB, d, J = 12.0 Hz, ArCH_AH_BPh), 5.19 (1H, B of AB, d, J = 11.1 Hz, ArCH_AH_BPh), 6.14 (1H, s, 1-OH), 6.52 (1H, d, J = 2.4 Hz, H-9), 6.59 (1H, s, H-4), 6.80 (1H, d, J = 2.4, Hz, H-11), 7.37 - 7.40 (5H, m, C_6H_5) 10.28 (1H, s, 8-OH). ^{13}C-NMR (150 MHz, $CDCl_3$) δ: 55.4, 55.6, 70.2, 75.6, 100.6, 103.7, 106.6, 110.3, 117.9, 128.6, 128.7, 131.1, 135.3, 135.9, 136.5, 147.7, 151.8, 162.8, 163.0, 172.4. *Anal.* Calcd for $C_{23}H_{20}O_7$: C, 67.64; H, 4.94. Found: C, 67.39 ; H, 4.78.

Debenzylation of 2

A mixture of **2** (87 mg, 0.21 mmol) and 10% Pd/C (8 mg) in AcOEt (10 mL) was stirred under an H_2 atmosphere for 3 h at rt. After filtration, the solvent was evaporated off to give a crystalline residue, which was subjected to silica-gel column chromatography using AcOEt-hexane (1:1) as the eluent. Ulocladol (40 mg, 60%) was obtained in a pure form.

2,8-Dibenzyloxy-1-hydroxy-3,10-dimethoxy-5*H*,7*H*-dibenzo[*c*,*e*]oxepin-7-one (**5**)

A mixture of **3** (101 mg, 0.20 mmol), K_2CO_3 (112 mg, 0.81 mmol), and MeOH (6 mL) was heated under reflux for 8 h. After extraction with CH_2Cl_2, the obtained organic layer was washed with brine, dried over anhydrous $MgSO_4$, and evaporated to give a residual oil. Silica-gel column chromatography with AcOEt-hexane (1:2) gave **5** (82 mg, 82%): white amorphous. IR (KBr) cm^{-1}: 3500 (OH), 1720 (CO), 1600, 1160, 1130. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.78 (3H, s, 10-OCH_3), 3.96 (3H, s, 3-OMe), 4.73 (1H, A of AB, d, J = 11.7 Hz, ArCH_AH$_B$CO$_2$), 4.95 (1H, B of AB, d, J = 11.7 Hz, ArCH$_A$$H_BCO_2$), 5.03 (1H, A of AB, d, J = 11.1 Hz, 2-CH_AH$_B$Ph), 5.03 (1H, A of AB, d, J = 12.3 Hz, 8-CH_AH$_B$Ph), 5.20 (1H, B of AB, d, J = 11.1 Hz, 2-CH$_A$$H_B$Ph), 5.23 (1H, B of AB, d, J = 12.3 Hz, 8-CH$_A$$H_B$Ph), 6.12 (1H, s, OH, exchangeable with D_2O), 6.55 (1H, d, J = 2.4 Hz, H-9), 6.61 (1H, s, H-4), 6.86 (1H, d, J = 2.4 Hz, H-11), 7.29 - 7.50 (10H, m, 2×C_6H_5). ^{13}C-NMR (150 MHz, $CDCl_3$) δ: 55.4, 55.0, 68.9, 71.0, 75.7, 100.4, 104.3, 106.5, 114.1, 117.7, 127.0, 127.7, 128.5, 128.6, 128.7, 128.8, 132.5, 135.2, 135.6, 136.5, 136.7, 147.7, 151.7, 158.5, 161.3, 166.6. MS (FAB, positive ion mode) *m/z*: 499 [M+1].

Debenzylation of 5

A mixture of **5** (80 mg, 0.16 mmol) and 10% Pd/C (11 mg) in AcOEt (10 mL) was stirred under an H_2 atmosphere for 3 h at rt. After filtration, the solvent was evaporated off to give a crystalline residue, which was subjected to silica-gel column chromatography using AcOEt-hexane (1:1) as the eluent. Ulocladol (32 mg, 63%) was obtained in a pure form.

ACKNOWLEDGEMENTS

The authors are indebted to Prof. G. M. König (University of Bonn) for providing the spectral data for ulocladol. We thank the SC-NMR Laboratory of Okayama University for performing the NMR experiments. Part of this work was supported by the Japan Society for the Promotion of Science for H. A. (Grant No. 18590005).

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8. The reason why the observed mp is quite different from the reported one is unclear. Comparing both the ^{1}H and ^{13}C NMR data between the synthetic and reported ones, it is unambiguous that these substrates are identical. See Table 1.