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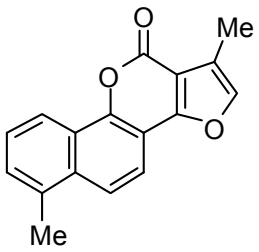
SYNTHESIS OF NEO-TANSHINLACTONE VIA THE PALLADIUM-MEDIATED INTRAMOLECULAR BIARYL COUPLING REACTION

Hitoshi Abe,[a]* Toshitaka Kawai,[a] Yoshinori Komatsu,[a] Mayu Kamimura,[a] Yasuo Takeuchi,[b] and Yoshikazu Horino[a]

a) Graduate School of Science and Engineering, University of Toyama, Gofuku, Toyama 930-8555, Japan, b) Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences, Okayama University, Okayama 700-8530, Japan
abeh@eng.u-toyama.ac.jp

Abstract – Neo-tanshinlactone (**1**) was synthesized by the intramolecular aryl-aryl coupling reaction of the precursor ester, which was prepared from the corresponding furan carboxylic acid (**13**) and naphthol (**3**), using a palladium reagent.

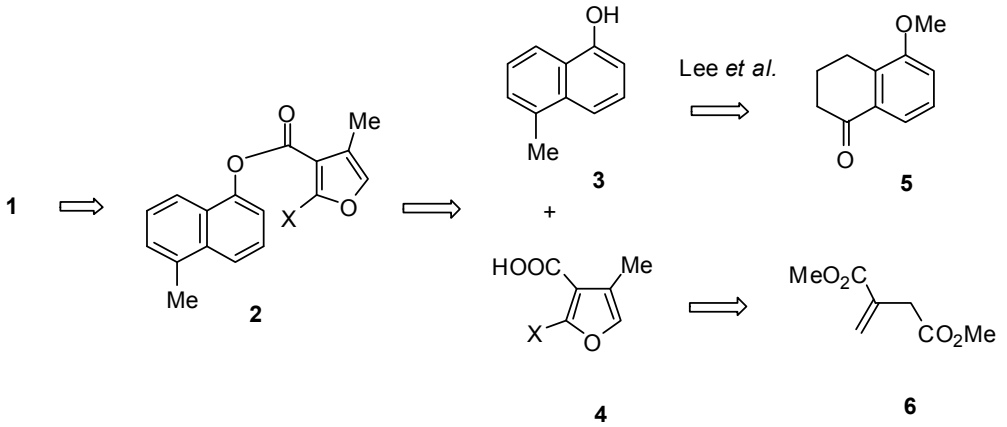
Neo-tanshinlactone (**1**) is a natural heterocyclic compound, which was isolated from the rhizome of *Salvia miltiorrhiza* Bunge, and its chemical structure was elucidated in 2004 by Lee and co-workers who also achieved the first synthesis of **1**.[1] As its biological activity, compound **1** exhibited a potent inhibition against several cancer cell lines.[2] Due to such a significant biological activity, the total synthesis of this compound is still an interesting theme in the field of both organic synthesis and medicinal chemistry.



neo-tanshinlactone (**1**)

Recently, we have intensively studied the palladium-mediated aryl-aryl coupling reaction in an intramolecular manner to conveniently prepare polycyclic aromatic compounds.[3] This method has been utilized for the synthesis of 6*H*-dibenzo[*b*,*d*]pyran-6-one type natural products,[4] such as graphislactones, alternariol, arnottin I, etc.[5] It was expected that this intramolecular aryl-aryl coupling could also be used as a key step for the total synthesis of neo-tanshinlactone **1**.

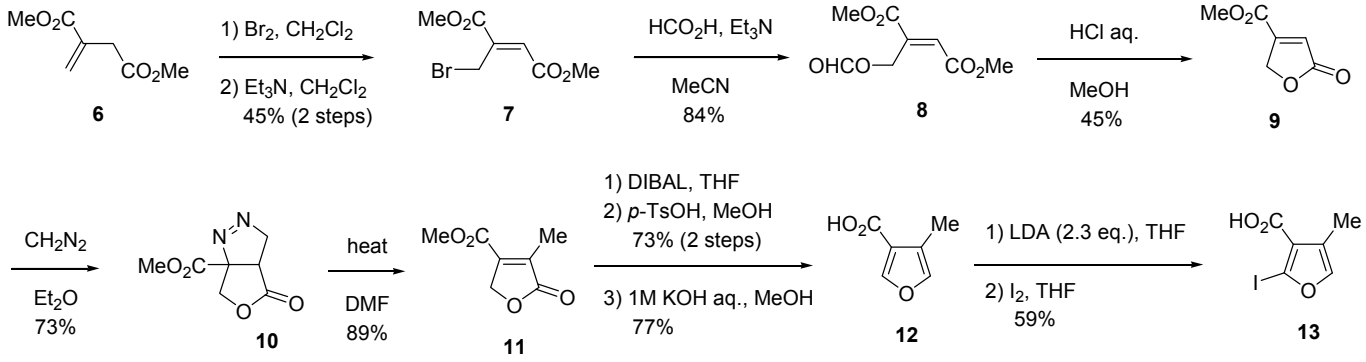
Our synthetic plan was straightforward as illustrated in Scheme 1 in which **1** would be synthesized by the intramolecular aryl-aryl coupling reaction of the precursor ester **2**. Compound **2** would be prepared by the simple esterification between the corresponding naphthol **3** and furan **4**. The two fragments **3** and **4** would easily be derived from 5-methoxytetralone **5** and itaconate ester **6**, respectively.



Scheme 1. Synthetic plan for neo-tanshinlactone (**1**)

We initially prepared the naphthol **3** from **5** by Lee's method.[1] On the other hand, for the synthesis of the 2,3,4-trisubstituted furan compound **4**, dimethyl itaconate **6** was selected as the starting material. According to the reported method,[6] **6** was successively treated with bromine and triethylamine to form the allylic bromide **7**, which was converted to the formate **8** by substitution with formic acid (Scheme 2).[7] The treatment of the formate **8** under acidic conditions afforded the five-membered lactone **9** in moderate yield.

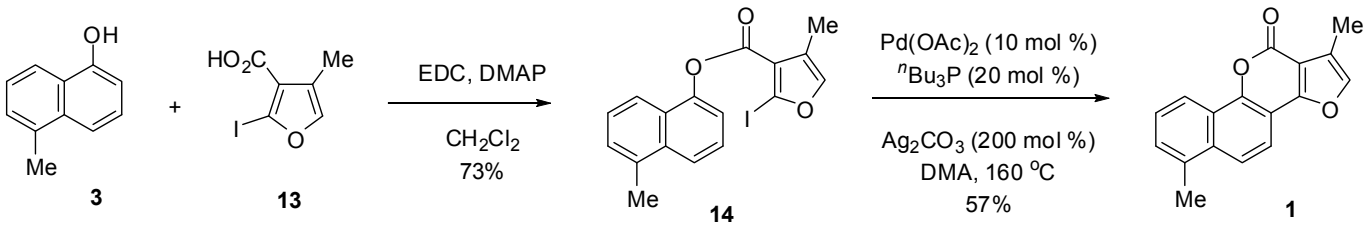
Introduction of the methyl group on the furan ring was performed via a series of a [3+2] cycloaddition of diazomethane and a denitrogenation process.[8] The cycloaddition between **9** and diazomethane successfully afforded the pyrazole **10**, which was transformed into the methyl product **11** under a heated condition. Aromatization of the furanone **11** was carried out by the two-step sequence of the DIBAL reduction and the acid treatment with TsOH. Hydrolysis of the methyl ester generated the furan carboxylic acid **12** which was iodinated at the 2-position using LDA and I_2 to produce the iodofuran **13**.[9]



Scheme 2. Preparation of 2-iodo-4-methyl-3-furancarboxylic acid (**13**)

After the conventional ester formation, the key ester **14** was obtained (Scheme 3). In the final step, the various reaction conditions were examined in detail for the intramolecular coupling. As a result, the

combination of $Pd(OAc)_2$ (10 mol %), $^nBu_3P$ (20 mol %), Ag_2CO_3, (200 mol %), and DMA provided the best yield (57%).



Scheme 3. Synthesis of neo-tanshinlactone (**1**)

Thus, the total synthesis of **1** was completed. The spectral data of the synthesized **1** matched those of the authentic sample.

In summary, the palladium-mediated aryl-aryl coupling reaction was effective for the total synthesis of neo-tanshinlactone (**1**). This technique will be useful for the construction of other polycyclic compounds containing a furan ring.

EXPERIMENTAL

General: Melting points were measured using a Yanaco micromelting point hot-plate apparatus (MP-500D) and are uncorrected. The IR spectra were recorded using a SHIMADZU FT-IR-8400 spectrophotometer. The NMR spectra were obtained using a JEOL α-400 instrument. The elemental analysis was performed by a Vario MICRO-cube or Perkin-Elmer 2400II analyzer. The silica gel column chromatography was carried out using a Wakogel C-200. All reactions were carried out under N_2 atmosphere.

5-Methylnaphthol (**3**),[1] **dimethyl 2-bromomethylfumarate** (**7**),[6] **dimethyl 2-formyloxymethylfumarate** (**8**),[7] **3-methoxycarbonyl-2,5-dihydrofuran-5-one** (**9**),[7] **6a-methoxycaronyl-3a,4,6,6a-tetrahydrofuro[3,4-*c*]pyrazole-4(1*H*)-one** (**10**),[8] **4-methyl-3-methoxycarbonyl-2,5-dihydrofuran-5-one** (**11**),[8] and **4-methyl-3-furancarboxylic acid** (**12**)[8,9] were prepared by the reported methods.

2-Iodo-4-methyl-3-furancarboxylic acid (**13**)

n-Butyllithium (16.4 mmol (hexane solution)) was dropwise added to a solution of diisopropylamine (2.30 mL, 16.4 mmol) in dry THF (20.0 mL) at -78 °C, then the mixture was stirred for 15 min. To the LDA solution, a solution of **12** (1.00 g, 7.14 mmol) in THF (20 mL) was dropwise added at -78 °C. The reaction mixture was warmed to rt and allowed to stand for 20 min. A solution of freshly sublimed I_2 (2.00 g, 7.88 mmol) in THF (40 mL) was added dropwise to the reaction mixture at -78 °C, and then the

mixture was warmed to rt. After 30 min, the reaction was quenched with water, then the mixture was acidified with a 10% aqueous HCl solution. After extractive work-up with ether, the organic layer was washed with a sat. aqueous $Na_2S_2O_3$ solution and brine, then dried over $MgSO_4$. Evaporation of the solvent gave a residue which was subjected silica gel column chromatography (hexane:Et_2O = 2:1), and then the obtained material was recrystallized from Et_2O-hexane to afford colorless needles of **13** (1.07 g, 59%), mp 150.8 - 151.3 ºC (Et_2O-hexane). ^{1}H-NMR (400 MHz, $(CD_3)_2CO$) δ : 2.18 (3H, d, *J* = 1.2 Hz, CH_3), 7.65 (1H, q, *J* = 1.2 Hz, 5-H). ^{13}C-NMR (100 MHz, $(CD_3)_2CO$) δ : 10.1, 101.1, 123.8, 124.8, 147.0, 163.9. IR (KBr) cm^{-1}: 769.5, 941.2, 1111, 1252, 1302, 1516, 1684, 2974. *Anal*. calcd for $C_6H_5IO_3$: C, 28.60 ; H, 2.00. Found: C, 28.87; H, 2.23.

2-Iodo-4-methyl-furan-3-carboxylic acid 5-methyl-naphthalen-1-yl ester (14)

A mixture of **3** (616 mg, 3.90 mmol), **13** (991 mg, 3.93 mmol), EDC (1.22 g, 6.36 mmol), DMAP (97.5 mg, 0.798 mmol), and CH_2Cl_2 (30 mL) was stirred for 1.5 h at rt. The mixture was diluted with CH_2Cl_2 and then washed with water and brine. After drying over $MgSO_4$, the solvent was evaporated to give a residue which was subjected to silica gel column chromatography (hexane:Et_2O = 5:1). Recrystallization from Et_2O afforded the colorless solid of **14** (1.12 g, 73%), mp 121.5 - 121.9ºC (Et_2O). ^{1}H-NMR (400 MHz, $(CD_3)_2CO$) δ : 2.32 (3H, d, *J* = 1.2 Hz, 4-Me), 2.73 (3H, s, 5'-Me), 7.42-7.44 (2H, m), 7.48 (1H, t, *J* = 7.2 Hz), 7.62 (1H, dd, *J* = 8.0, 8.8 Hz), 7.82 (1H, q, *J* = 1.2 Hz, 5-H), 7.89 (1H, d, *J* = 7.2 Hz), 8.02 (1H, d, *J* = 8.8 Hz). ^{13}C-NMR (100 MHz, $(CD_3)_2CO$) δ : 10.3, 19.7, 102.9, 119.4, 120.5, 123.2, 123.3, 124.1, 124.3, 126.2, 127.2, 128.0, 134.8, 135.4, 147.5, 147.6, 161.7. IR (KBr) cm^{-1}: 781, 943, 1051, 1074, 1140, 1219, 1281, 1404, 1495, 1599, 1726, 3121. *Anal*.calcd for $C_{17}H_{13}IO_3$: C, 52.06; H, 3.34. Found: C, 51.81 ; H, 3.39.

Neo-tanshinlactone (1)[1]

A mixture of **14** (49.8 mg, 0.127 mmol), $Pd(OAc)_2$ (3.5 mg, 0.016 mmol), $^nBu_3P$ (4.9 mg, 0.024 mmol), Ag_2CO_3 (70.1 mg, 0.254 mmol), and DMA (3 mL) was heated for 10 min at 160 ^{o}C. The mixture was diluted with AcOEt and the undissolved materials were filtered off. Water was added to the mixture, and the organic layer was collected. The solution was washed with brine and dried over $MgSO_4$, and then the solvent was evaporated. After purification by silica gel column chromatography (hexane:Et_2O = 10:1), pure **1** (19.1 mg, 57%) was obtained as a colorless solid, mp 228.6 - 229.0 ºC (hexane-AcOEt) [lit.,[1] 173-175 ^{o}C (hexane-AcOEt)]. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.41 (3H, d, *J* = 1.2 Hz), 2.74 (3H, s), 7.45 (1H, q, *J* = 1.2 Hz), 7.46 (1H, d, *J* = 8.4 Hz), 7.55 (1H, t, *J* = 8.4 Hz), 7.88 (1H, d, *J* = 8.8 Hz), 7.92 (1H, d, *J* = 8.8 Hz), 8.50 (1H, d, *J* = 8.4 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 8.7, 19.8, 108.2, 110.4, 116.8, 120.5, 120.9, 121.0, 123.6, 127.0, 129.0, 133.4, 134.7, 141.2, 149.7, 158.8. IR (KBr) cm^{-1}: 771.5, 1011, 1076, 1171, 1381, 1578, 1620, 1726, 2922, 2970.

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