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A NEW TOTAL SYNTHESIS OF (±)-*α*-NOSCAPINE

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Abstract – A new, convergent total synthesis of (±)-*α*-noscapine was developed on a grams scale through the condensation of 3-trimethylsilyl-meconin derivative **9** and the iodized salt cotarnine derivative **20** as the key step. Staring from simple 2,3-dimethoxybenzoic acid, piperonal and 2,2-dimethoxyethanamine, through the traditional chemical processes to give the final product in 11.6% yield over 14 steps.

(–)-*α*-Noscapine (**1**, also known as narcotine, nectodon, nospen) (Figure 1) is a benzylisoquinoline alkaloid without significant painkilling properties, which was originally isolated from *Papaver somniferum* L.[1] This agent is primarily used for its antitussive (cough-suppressing) effects,[2] which appears to be primarily mediated by its sigma receptor agonist activity.[3] It has been also found that (–)-*α*-noscapine displays other potential clinical utilities for the treatment of cancer,[4] stroke,[5] anxiety,[6] cerebral edema,[7] and so on.

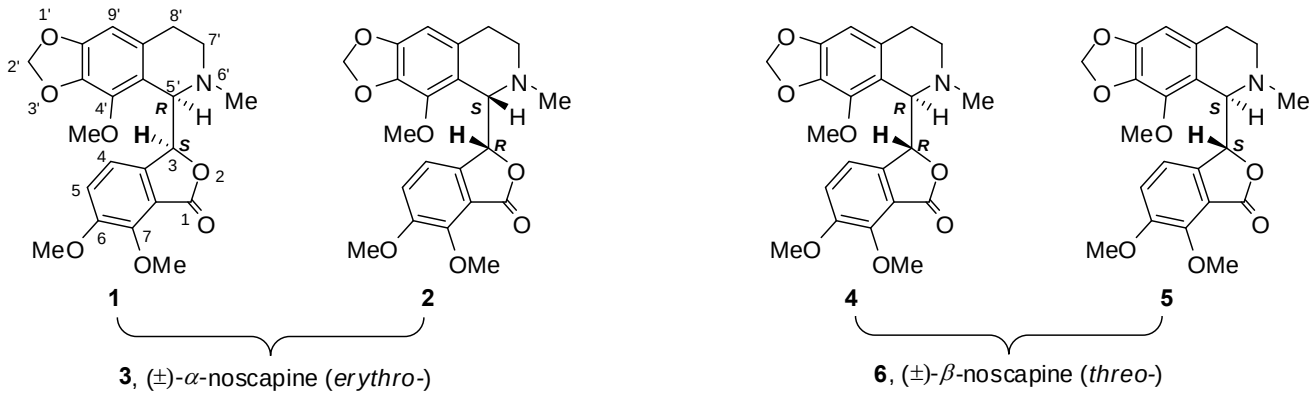
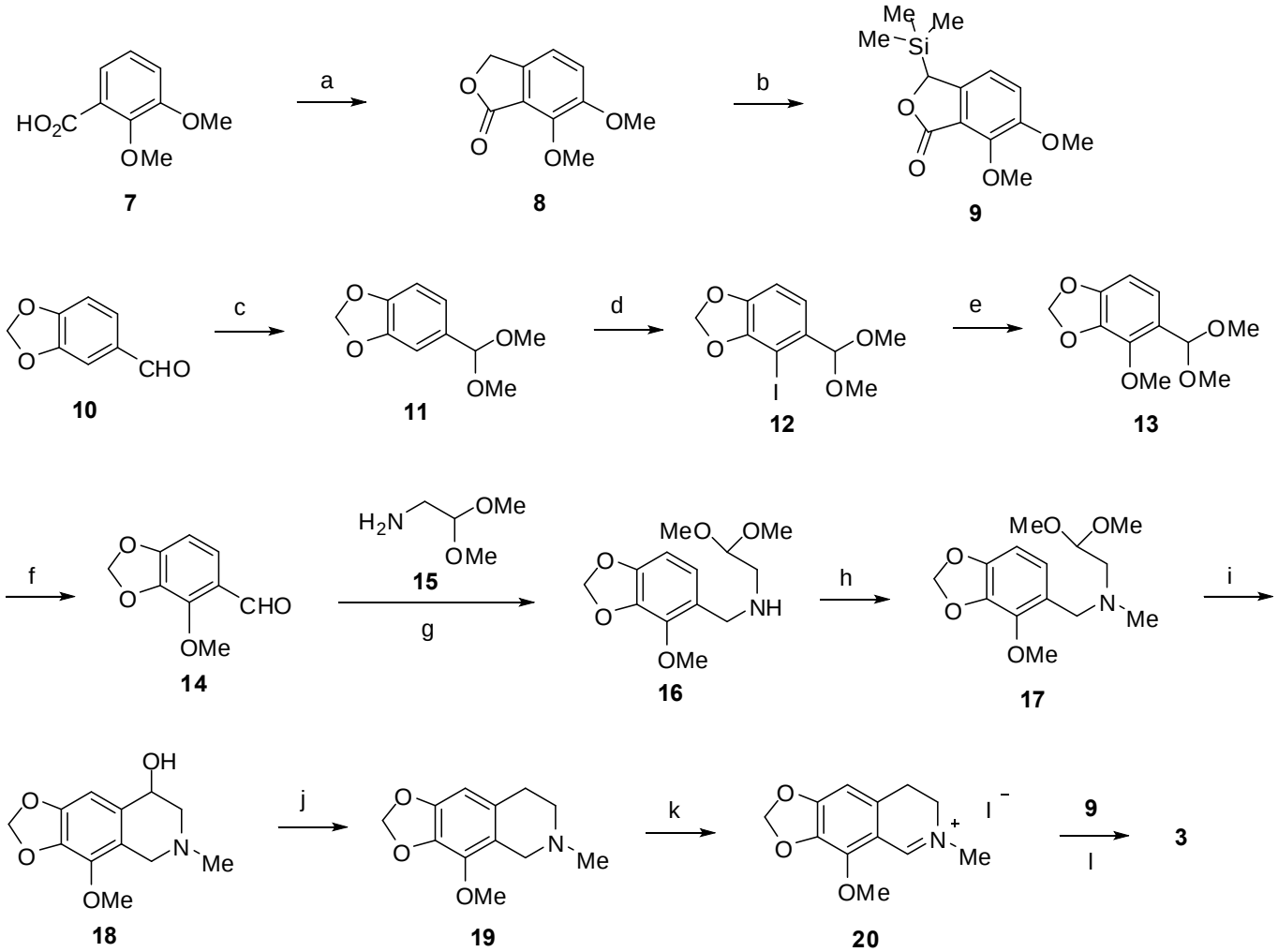


Figure 1. Stereochemical Structures of Noscapine

Natural (–)-*α*-noscapine (or *erythro*-) contains two contiguous chiral carbon centers: C-5’ at tetrahydroisoquinoline ring and C-3 at phthalide framework (Figure 1). In contrast, its diastereoisomers

(±)-*β*-noscapine (**6**, or *threo*-noscapine) exhibits less biological activities.

Clinically used narcotine can be provided through extraction from plant resource[8] or possible resolution of synthetic (±)-*α*-noscapine (**3**). So far, the total synthesis of narcotine or (±)-*α*-noscapine is still limited.[9] The pioneer work was reported by Robinson and Perkin[10] who constructed C5'-C3 bond through direct condensation between meconin (**8**) and cotarnine (**18**) (Scheme 1), which were produced by degradation of natural narcotine. Shono[11] developed zinc-promoted reductive coupling of 3-bromo-meconin to the iminium salt of cotarnine to construct C5'-C3 bond. Alternatively, Kerekes[12] and Szántay[13] synthesized tetrahydroisoquinoline skeleton through Bischler-Napieralski reaction after formation of C5'-C3 bond. In recent years Xu *et al*.[14] also developed a new blocking group-directed diastereoselective synthetic method based on the Bischler-Napieralski cyclization.



Scheme 1. Reagents and conditions: (a) 37% aq. HCl, 37% aq. HCHO, AcOH, 50 ~ 60 ºC, 24 h, 74%; (b) i) LDA, THF, −70 ~ −50 ºC, 1 h; ii) TMSCl, −70 ~ 0 ºC, 2 h, 96%; (c) $CH(OMe)_3$, MeOH, 50 ~ 60 ºC, 1 h; (d) i) *n*-BuLi, THF, −10 ~ −5 ºC, 1 h; ii) I_2, −10 ~ −5 ºC, 1 h, 89%; (e) NaOMe, CuI, DMF, 60 ~ 70 ºC, 12 h; (f) 10% aq. HCl, CH_2Cl_2, rt, 4 h, 69%; (g) MeOH, $NaBH_4$, 0 ºC ~ rt, 1 h; (h) MeOH, 37% aq. HCHO, $NaBH_4$, 0 ºC ~ rt, 1 h; (i) 20% aq. HCl, rt, 24 h, 77%; (j) TFA, $NaBH_4$, 0 ºC ~ rt, 24 h, 98%; (k) AcOK, I_2, EtOH, 80 ºC, 3 h, 84%; (l) KHF_2, DMF, rt, 24 h, 42%.

Herein, we report a new approach to synthesis of (±)-*α*-noscapine (**3**), which constructs the C5'-C3 bond through the condensation of meconin derivative **9** and cotarnine derivative **20** as the key step (Scheme 1). Meconin (**8**) was produced from the easier available material 2,3-dimethoxybenzoic acid (**7**) with good isolated yield.[15] Then it was treated with LDA and TMSCl respectively at low temperature to give the 3-trimethylsilyl derivative **9** in high yield,[16] which was used directly at the last step for the synthesis of noscapine.

The second fragment **20** was synthesized from piperonal (**10**) through several steps (Scheme 1). The acetal protected product **11** was treated with *n*-BuLi and I_2 respectively to give the 4-iodo product **12**,[17] which was substituted by –OMe, deprotected of the acetal to give the key intermediate **14** in 61% yield over five steps.[18] 2,2-Dimethoxyethanamine (**15**) and 37% aq. HCHO were used successively in the next reductive amination steps,[19] **17** was obtained in quantitative yield, which was then conducted the intramolecular cyclization in 20% aq. HCl to give cotarnine **18** in 77% yield over three steps.[20] The 4-OH of **18** was eliminated using TFA/$NaBH_4$ condition[20a] to give the tetrahydroisoquinoline **19** in 98% yield, which was then treated with AcOK and I_2 to give the cotarnine iodized salt derivative **20** in 84% isolated yield.[21] At the last step, adopting KHF_2 to cut the C-Si bond of **9**, it was coupled with **20** in DMF to give noscapine.[21] The crude products should contain all of the four configurations, that were (±)-*α*-noscapine (**3**) and (±)-*β*-noscapine (**6**), while the ratio was *not* detected by us. Resolution of **3** from the crude product was conducted by simple recrystalization from MeOH in 42% overall yield, which was identified by comparison with the natural narcotine sample.

In summary, we have developed a new total synthetic route for (±)-*α*-noscapine on a grams scale through the condensation of 3-trimethylsilyl-meconin derivative **9** and the iodized salt cotarnine derivative **20** as the key step. Starting from the easy commercial available materials including 2,3-dimethoxybenzoic acid (**7**), piperonal (**10**) and 2,2-dimethoxyethanamine (**15**), through the traditional chemical processes to give the final product **3** in 16.3% yield over 11 steps (from **10**). Most of the intermediates were purified by recrystallization.

EXPERIMENTAL

All commercially available materials and solvents were used as received without any further purification. ^{1}H NMR spectra were recorded on a Bruker ARX-300 spectrometer using TMS as an internal standard. Mass spectra were obtained from a Finnigan MAT-95/711 spectrometer. Melting points were measured on a Buchi B-540 melting point apparatus, which are uncorrected.

6,7-Dimethoxyisobenzofuran-1(3*H*)-one (8). A stirred mixture of **7** (91.0 g, 0.5 mol), 37% aq. HCHO solution (81 g, 1.0 mol), 37% aq. HCl (80 g, 0.8 mol) and AcOH (200 g) was heated at 50 ~ 60 ºC for 24

h to give a clear solution, which was then poured into chilled water (1 kg). The resulting solid was collected by suction filtration, washed by water (60 g × 3), and dried at 50 ºC to give the crude **8** (95 g) as a tan solid, which was purified by recrystallization from 90% MeOH/H_2O (180 g) to give **8** (71.8 g, 74%) as a white solid. mp 100 ~ 101 ºC (ref.,[22] 102 ~ 103 ºC). ^{1}H NMR (300 Hz, $CDCl_3$): δ 3.92 (s, 3H), 4.11 (s, 3H), 5.20 (s, 2H), 7.09 (d, 1H, J = 8.2 Hz), 7.25 (d, 1H, J = 8.2 Hz). ESI-MS (*m/z*): 217.0 (M + Na), 411.0 (2M + Na).

6,7-Dimethoxy-3-(trimethylsilyl)isobenzofuran-1(3*H*)-one (9). A 2 M LDA/THF solution (165 mL, 0.33 mol) was added slowly to the cooled solution of **8** (58.2 g, 0.3 mol) in dry THF (500 g) over 1 h under nitrogen atmosphere to keep the reaction temperature between –70 ~ –50 ºC. The reaction solution was stirred at the temperature for another 30 min and an orange solution was obtained, which was treated dropwise with TMSCl (60.0 g, 0.55 mol) over 1 h. The resulting faint yellow solution was stirred for another 2 h and the reaction temperature was raised to ~0 ºC. The volatile materials were removed and the residuum was triturated with CH_2Cl_2 (900 g), washed with water (600 g × 3), dried over anhydrous Na_2SO_4. The solvent was recovered to give **9** (76.7 g, 96%) as a white solid, which was used directly at the next step. mp 107 ~ 110 ºC (ref.,[16] 110 ~ 112 ºC). ^{1}H NMR (300 Hz, $CDCl_3$): δ 0.10 (s, 9H), 3.91 (s, 3H), 4.10 (s, 3H), 5.16 (s, 1H), 6.92 (d, 1H, J = 8.2 Hz), 7.22 (d, 1H, J = 8.2 Hz). ESI-MS (*m/z*): 267.0 (M + H), 288.9 (M + Na), 554.9 (2M + Na).

4-Methoxybenzo[*d*][1,3]dioxole-5-carbaldehyde (14). A mixture of piperonal (150.1 g, 1.0 mol), $CH(OMe)_3$ (138.0 g, 1.3 mol) and anhydrous MeOH (400 g) was stirred and heated at 50 ~ 60 ºC for 1 h. The volatile materials were removed to give 5-(dimethoxymethyl)benzo[*d*][1,3]dioxole (**11**) as a faint yellow oil.

A 2.5 M *n*-BuLi/THF solution (440 mL, 1.1 mol) was added slowly to the cooled solution of **11** (196 g, 1.0 mol) in dry THF (800 g) over 1 h under nitrogen atmosphere to keep the reaction temperature between –10 ~ –5 ºC. The reaction solution was stirred at the temperature for another 30 min and a red solution was obtained. I_2 (280.0 g, 1.1 mol) was added portionwise into the reaction mixture over 1 h to keep the reaction temperature below 0 ºC. The resulting dark red solution was stirred for another 30 min at 0 ºC. The volatile materials were removed and the residuum was dissolved in CH_2Cl_2 (2 kg), washed with 10% aq. Na_2SO_3 (1.5 kg × 2), water (1.5 kg × 2), dried over anhydrous Na_2SO_4. The solvent was recovered to give 5-(dimethoxymethyl)-4-iodobenzo[*d*][1,3]dioxole **12** (287 g, 89%) as a tan solid.

A mixture of **12** (287 g, 0.89 mol), NaOMe (96.0 g, 1.78 mol) and CuI (17.1 g, 0.09 mol) in dry DMF (1 kg) was stirred and heated at 60 ~ 70 ºC for 12 h to give a dark brown solution. The reaction solution was cooled to rt and filtered through a celite pad. The filtrate was concentrated under reduced pressure and

around 600 g DMF was recovered. The residuum was dissolved in CH_2Cl_2 (1.5 kg) and washed with water (1 kg × 3). The CH_2Cl_2 solution was stirred rapidly with 10% aq. HCl solution (600 g) at rt for 4 h. The organic layer was separated, washed with water (1 kg × 2), 5% aq. $NaHCO_3$ (1 kg × 2) respectively, dried over anhydrous Na_2SO_4. The solvent was recovered to give crude **14** (146 g) as a yellow-brown solid, which was purified by recrystallization from 85% MeOH/H_2O (290 g) one time to give the pure **14** (110 g, 69%) as a grey needle. mp 101 ~ 103 ºC (ref.,[23] 101 ~ 102 ºC). ^{1}H NMR (300 Hz, $CDCl_3$): δ 4.13 (s, 3H), 6.04 (s, 2H), 6.59 (d, 1H, J = 8.1 Hz), 7.47 (d, 1H, J = 8.1 Hz), 10.22 (s, 1H). ESI-MS (*m/z*): 203.0 (M + Na), 383.0 (2M + Na).

4-Methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-*g*]isoquinolin-8-ol (18). A mixture of compound **14** (90.0 g, 0.5 mol) and **15** (55.2 g, 0.53 mol) in anhydrous MeOH (500 g) was stirred at rt for 1 h before it was cooled to 0 ~ 10 ºC. $NaBH_4$ (11.5 g, 0.3 mol) was added portionwise into the reaction mixture over 1 h to keep the reaction temperature below 20 ºC. The reaction solution was stirred for another 30 min at rt. The volatile materials were removed and the residuum was dissolved in CH_2Cl_2 (1 kg), washed with water (1 kg × 3). The solvent was recovered to give 2,2-dimethoxy-*N*-((4-methoxybenzo[*d*][1,3]dioxol-5-yl)methyl)ethanamine **16** (135 g) as a faint yellow oil.

A mixture of compound **16** (135 g, 0.5 mol) and 37% aq. HCHO solution (61 g, 0.75 mol) in MeOH (600 g) was stirred at rt for 1 h before it was cooled to 0 ~ 10 ºC. $NaBH_4$ (15.0 g, 0.4 mol) was added portionwise into the reaction mixture over 1 h to keep the reaction temperature below 20 ºC. The reaction solution was stirred for another 1 h at rt. The volatile materials were removed and the residuum was dissolved in CH_2Cl_2 (1 kg), washed with water (1 kg × 3). The solvent was recovered to give 2,2-dimethoxy-*N*-((4-methoxybenzo[*d*][1,3]dioxol-5-yl)methyl)-*N*-methylethanamine **17** (142 g) as a faint yellow oil.

Compound **17** (142 g, 0.5 mol) was mixed with 20% aq. HCl (600 g) and stirred at rt for 24 h. 50% aq. NaOH solution was then added slowly into the reaction mixture to adjust the solution pH 10 ~ 11, and keep the solution temperature below 40 ºC. The resulting brown-yellow solid was collected by suction filtration, washed by water (100 g × 3), and dried at 50 ºC to give the crude **18** (114 g) as a tan solid, which was purified by recrystallization from 90% EtOH/H_2O (230 g) to give pure **18** (91.2 g, 77%) as a white solid. mp 151 ~ 153 ºC (ref.,[20] 153 ~ 154 ºC). ^{1}H NMR (300 Hz, $CDCl_3$): δ 2.45 (s, 3H), 2.87-3.11 (m, 3H), 3.71 (m, 1H), 3.99 (s, 3H), 4.46 (m, 1H), 5.89 (s, 2H), 6.59 (s, 1H). ESI-MS (*m/z*): 238.0 (M + H), 497.0 (2M + Na).

4-Methoxy-6-methyl-5,6,7,8-tetrahydro[1,3]dioxolo[4,5-*g*]isoquinoline (19). $NaHB_4$ (15.1 g, 0.4 mol) was added portionwise into a stirred solution of compound **18** (71.2 g, 0.3 mol) and TFA (137 g, 1.2 mol)

in CH_2Cl_2 (600 g) over 1 h to keep the reaction temperature below 25 ºC and the reaction mixture was stirred at rt for another 24 h. Then it was cooled to 0 ~ 10 ºC and 20% aq. NaOH solution was added slowly into the reaction mixture to adjust the solution pH 10~11, and keep the solution temperature below 40 ºC. The organic layer was separated, washed by water (600 g × 4), dried over anhydrous Na_2SO_4. The solvent was recovered to give **19** (64.7 g, 98%) as a faint-yellow solid. mp 43 ~ 46 ºC (ref.,[20a] 44 ~ 45 ºC). ^{1}H NMR (300 Hz, $CDCl_3$): δ 2.45 (s, 3H), 2.59 (t, 2H, J = 5.9 Hz), 2.79 (t, 2H, J = 5.9 Hz), 3.44 (s, 2H), 3.97 (s, 3H), 5.84 (s, 2H), 6.30 (s, 1H). ESI-MS (*m/z*): 220.0 (M + H).

4-Methoxy-6-methyl-7,8-dihydro[1,3]dioxolo[4,5-*g*]isoquinolin-6-ium iodide (20). A mixture of compound **19** (60 g, 0.27 mol), anhydrous AcOK (29.4 g, 0.3 mol) and I_2 (77.4 g, 0.3 mol) in anhydrous EtOH (500 g) was heated to reflux for 3 h before it was cooled to 0 ~ 10 ºC. The resulting faint-yellow solid was collected by suction filtration, washed by cooled EtOH (60 g × 3), and dried at 50 ºC to give the crude **20** (89 g), which was purified by recrystallization from anhydrous EtOH (380 g) to give pure **20** (79.5 g, 84%) as a faint-yellow solid. mp 178 ~ 181 ºC (ref.,[23] 183 ~ 184 ºC). ^{1}H NMR (300 Hz, DMSO-d_6): δ 3.06 (t, 2H, J = 8.1 Hz), 3.67 (s, 3H), 3.85 (t, 2H, J = 8.1 Hz), 4.11 (s, 3H), 6.20 (s, 2H), 6.83 (s, 1H), 8.99 (s, 1H).

(±)-*α*-Noscapine (3). A mixture of **9** (53.3 g, 0.2 mol), **20** (69.4 g, 0.2 mol) and anhydrous KHF_2 (19.5 g, 0.25 mol) in dry DMF (700 g) was stirred at rt for 24 h under nitrogen atmosphere to give a orange solution. The reaction solution was filtered through a celite pad. The filtrate was concentrated under reduced pressure and around 500 g DMF was recovered. The residuum was triturated with water (600 g), stirred at rt for 1 h, the resulting brown-yellow solid was collected by suction filtration, washed by water (60 g × 3), and dried at 50 ºC to give the noscapine diastereoisomers (77 g, 92%), which was purified by recrystallization from anhydrous MeOH (390 g) to give **3** (34.7 g, 42%) as a white solid. mp 228 ~ 230 ºC (ref.,[24] 232 ºC). ^{1}H NMR (300 Hz, $CDCl_3$): δ 1.95 (br s, 1H), 2.37 (br s, 2H), 2.56 (s, 3H), 2.58 (br s, 1H), 3.86 (s, 3H), 4.02 (br s, 3H), 4.09 (s, 3H), 4.41 (br s, 1H), 5.59 (br s, 1H), 5.93 (s, 2H), 6.11 (br s, 1H), 6.31 (s, 1H), 6.96 (m, 1H). ESI-MS (*m/z*): 414.1 (M + H), 436.0 (M + Na), 452.0 (M + K), 849.1 (2M + Na).

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