有机化学 DOI: 10.6023/cjoc202206034 研究简报
Chinese Journal of Organic Chemistry NOTE

秋水仙碱及其天然类似物(－)-*N*-乙酰秋水酚甲醚的不对称合成

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摘要 采用相对简单的不对称合成方法，完成了秋水仙碱及其天然类似物(－)-*N*-乙酰秋水酚甲醚(NCME)的形式全合成. 首先经简单醛、酮的 Aldol 缩合完成碳骨架的构筑，然后经手性亚磺酰胺诱导的不对称还原胺化反应，廉价、高效地合成了手性胺中间体；再经过高价碘试剂的氧化关环，构筑该类生物碱的三元环结构. 本策略为该类生物碱的简便、快速合成提供了有效方法.

关键词 秋水仙碱；(－)-*N*-乙酰秋水酚甲醚；叔丁基亚磺酰胺；不对称合成

Asymmetric Synthesis of (－)-Colchicine and Its Natural Analog (－)-*N*-Acetylcolchicine Methyl Ether

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Abstract (－)-Colchicine and its natural analogue (－)-*N*-acetylcolchinol methyl ether have been synthesized in a comparatively conciser asymmetric synthetic approach. Firstly, the carbon framework was constructed by Aldol condensation of simple aldehydes and ketones, and then the chiral amine intermediates were synthesized economically and efficiently through asymmetric reductive amination with chiral *tert*-butanesulfinamide. The 3-rings skeleton of colchicine and related alkaloids was then constructed by oxidation with hypervalent iodine reagent. Our strategy provides an efficient method for the convenient and economical synthesis of these alkaloids.

Keywords colchicine; (－)-*N*-acetylcolchinol methyl ether; *tert*-butanesulfinamide; asymmetric synthesis

1 Introduction

(－)-Colchicine (**1**, Figure 1) is a tricyclic alkaloid isolated from plants of the genus Colchicum (*autumn crocus*) and has been approved for the treatment of gout.[1] Besides, colchicine was reported to exert a variety of functions including anti-tumor, antiviral and anti-inflammatory activity.[2] Recently, new therapeutic uses of colchicine are being actively explored, the best example of which is colchicine clinical trials for treating coronavirus disease-2019 (COVID-19).[3] COVID-19 represents a worldwide infectious condition and paxlovid is a promising new drug

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Received June 20, 2022; revised July 26, 2022; published online September 1, 2022.
Project supported by the Shenzhen Science and Technology Innovation Commission (Nos. JSGG20210901145539016, JCYJ20190812171005713, JCYJ2021-0324121611032), the Shenzhen Baoan Chinese Medicine Development Foundation (No. 2020KJCX-KTYJ-215), the Shenzhen Excellent Scientific and Technological Innovation Talents Training Project-PhD Initiation Program (No. RCBS20210706092212002), and the Guangdong Basic and Applied Basic Research Foundation (Nos. 2020A1515011427, 2022A1515011777).
深圳市科技计划(Nos. JSGG20210901145539016, JCYJ20190812171005713, JCYJ20210324121611032)、深圳市宝安中医药发展基金会(No. 2020KJCX-KTYJ-215)、深圳市优秀科技创新人才培养-博士启动(No. RCBS20210706092212002)和广东省基础与应用基础研究基金(Nos. 2020A1515011427, 2022A1515011777)资助项目.
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combination that could reduce the risk of hospitalization and death by 89%.[4] The most critical mechanism that underlies the anti-viral effects of colchicine could be ascribed to the blockage of cytokine (interleukin-1β, interleukin-6, interleukin-8, tumor necrosis factor α) release[5] and the inhibition of Nod-like receptor protein 3 inflammasom,[6] as inflammatory response is blamed for several clinical manifestations of COVID-19. More importantly, colchicine could interfere with the formation, elongation, and polymerization of tubulin, a cytoskeletal protein on which coronaviruses depend to transport viral particle and replicate inside the host cells.[3a]

As such, colchicine shows potential applications as lead compound in drug discovery, and numerous modifications of the colchicine chemical structure have been made to develop new candidate drug molecules.[7] Since the sufficient quantity of (−)-colchicine is needed to support the drug discovery, (−)-colchicine and its natural analogues have attracted considerable attention from synthetic chemists, and several synthetic strategies have been reported since 1959 when Eschenmoser published the first synthesis of colchicine.[8-9] Futhermore, Li's work[9c] in 2017 and Yang's work[9e] in 2021 elegantly improved the efficiency to synthesize (−)-colchicine and its natural analogues.

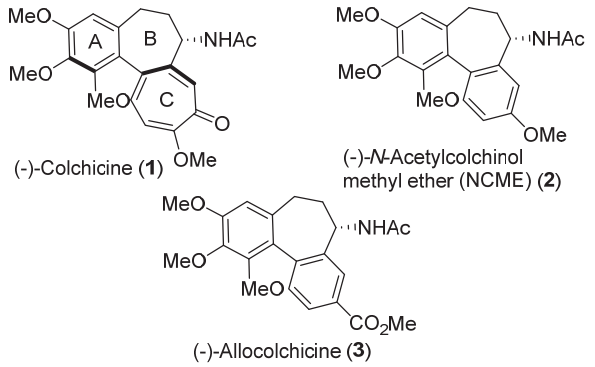
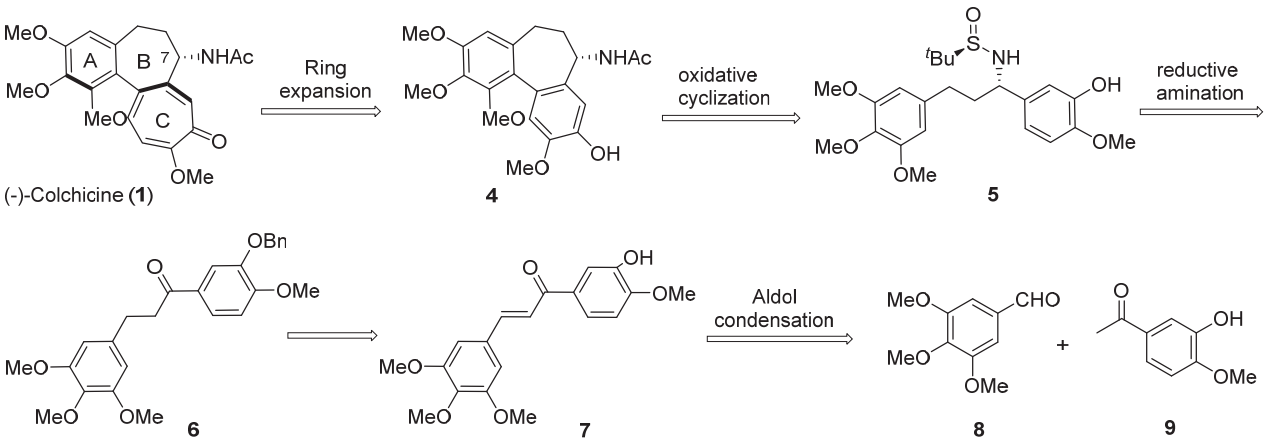


Figure 1 Molecular structures of colchicine **1** and natural allocolchicinoids **2** and **3**

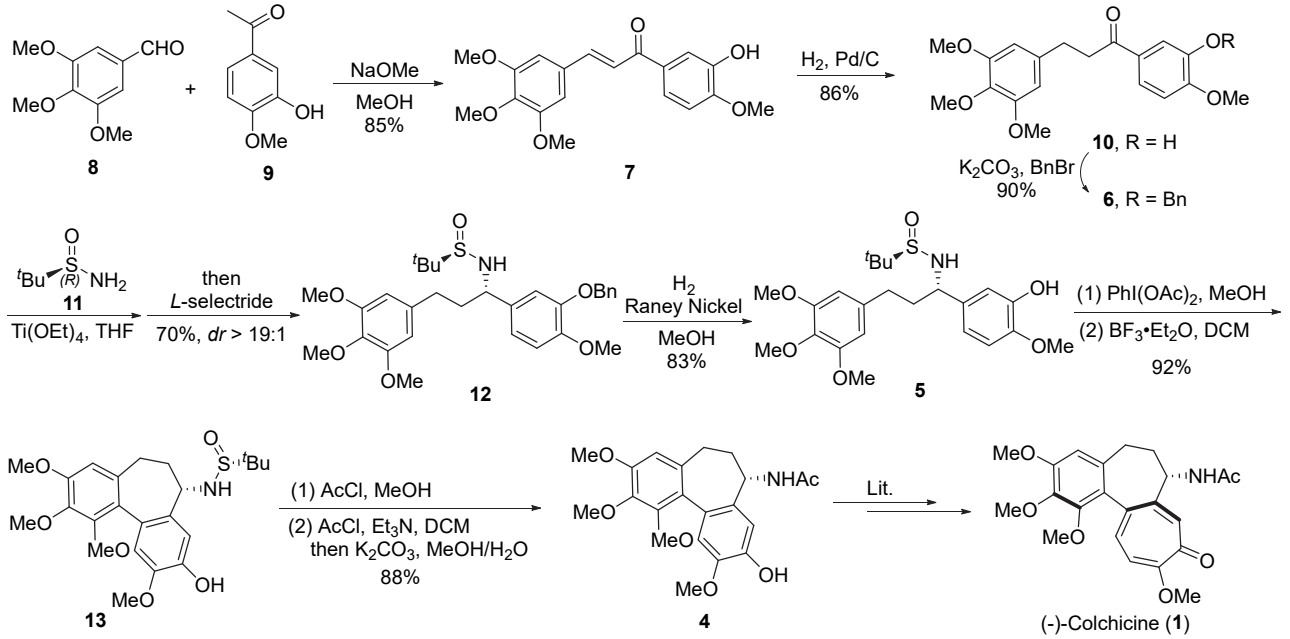
2 Results and discussion

Our retrosynthetic analysis is shown in Scheme 1. The C ring of colchicine molecular can be constructed based on compound **4** by a 3-steps ring expansion sequence which was demonstrated by Banwell[10] and modified by Yang.[9e] The advanced intermediate **4** can be synthesized under oxidative cyclization condition from compound **5**. As for compound **5**, the key point is the synthesis of the chiral amine functional group which controls the axial chirality configuration of colchicine molecule.[9a] And this problem can be solved efficiently by reductive amination of ketone **6** with the commercially available chiral *tert*-butanesulfinamide.[11] The ketone **6** can be easily prepared in large scale by aldol condensation of 3,4,5-methoxybenzaldehyde **8** and compound **9** followed by hydrogenating the carbon-carbon double bond and then protecting the phenol group with benzyl.

As shown in Scheme 2, our synthesis commenced with the aldol condensation of aldehyde **8** and ketone **9** which are all commercially available. The reaction worked well under NaOMe (sodium methoxide) condition in 48 h then the chalcone **7** can be prepared in decagram scale. However, acid promoted aldol reaction conditions was also be evaluated, but the reaction mixture was more complex and only moderate yield was provided. The carbon-carbon double bond was hydrogenated by Pd/C under H_2 atmosphere in 86% yield. Then the phenol was protected with benzyl group to yield compound **6** smoothly. The next key step was the reductive amination in which reaction chiral *tert*-butanesulfinamide **11** was applied as the amine source and controlling the chirality at the same time.[12] Firstly, ketone **6** and compound **11** were treated with $Ti(OEt)_4$ (titanium ethoxide) in tetrahydrofuran (THF) under reflux temperature for 48 h, and the imine intermediate was purified by flash column chromatography, then a reduction with *L*-selectride (lithium tri-*sec*-butylborohydride) generated the chiral amine **12**. Furthermore, this two-step sequence also worked well in one pot producing compound **12** in 70% yield without isolating the ketimine.



Scheme 1 Retrosynthetic analysis of (−)-colchicine

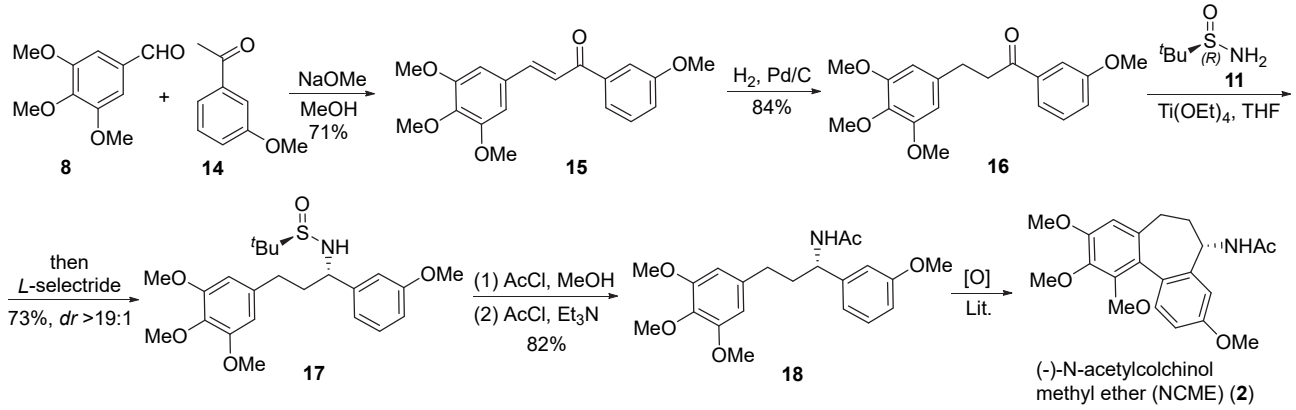


Scheme 2 Formal total synthesis of (−)-colchicine

With chiral amine **12** in hand, we planned to remove the benzyl protecting group with Pd/C and hydrogen gas. Nevertheless, the reaction didn't work with all the starting material recovered. Then Raney nickel was evaluated as catalyst in hydrogen atmosphere with MeOH as solvent, and the reaction was completed in 12 h to afford the product **5** in 83% yield. The oxidative cyclization of compound **5** was conducted with PIDA [(diacetoxyiodo)benzene], and this reaction worked smoothly generating the advanced intermediate **13** in 92% yield. Having successfully assembled the basic skeleton of A, B, C ring, the next step was converting the sulfinyl to acetyl group of the amine. Treatment of the compound **13** with HCl generated *in-situ* by AcCl (acetyl chloride) and MeOH at room temperature provided the desired amine salts smoothly. Without purification, the yielded amine was acetylated with AcCl/Et_3N, and at the same time was acetylated the phenol group which was released by further adding K_2CO_3 directly into the reaction mixture. The NMR spectra, optical rotation ($[\alpha]_D^{25}$ −45.0 (*c* 0.75, $CHCl_3$), lit.[9e] −45.32 (*c* 0.75, $CHCl_3$)) and melting point (128～130 ℃, lit.[9e] 130～133 ℃) of the synthetic compound **4** were identical to the compound reported in the literature. As mentioned in the retrosynthetic analysis, the established protocol reported by Yang could conveniently convert **4** to colchicine.[9e]

Having successfully completed the asymmetric synthesis of (−)-colchicine, we then turned our attention to its natural analogue (−)-*N*-acetylcolchinol methyl ether (NCME) **2**, for the reason that this special alkaloid was proved to be a better inhibitor than colchicine of cell growth and tubulin polymerization.[13] Interestingly, NCME was isolated from nature until 1991 by Feroz, and it was named as suhailamine, but incorrectly identified as (−)-allocolchicine **3**.[14] Eighteen years later, until 2019 this mystery was clarified by Davies who compared the characterization data carefully and completed the total synthesis of NCME [(−)-suhailamine] with Roberts.[15]

There were several approaches to synthesize NCME



Scheme 3 Formal total synthesis of (−)-*N*-acetylcolchinol methyl ether (NCME)

even before it was established as a naturally-occurring allocolchicinoid.[16] Herein we report our concise asymmetric synthesis of (−)-NCME. As shown in Scheme 3, chalcone **15** was synthesized by aldol condensation of aldehyde **8** and 3-methoxyacetophenone **14**. Then the carbon-carbon double bond was hydrogenated with Pd/C as catalyst to afford the ketone **16** in 84% yield. As used in the synthesis of (−)-colchicine, the chiral amine of **17** was also constructed by reductive amination of chiral *tert*-butanesulfinamide **11** and ketone **16**. To our delight, this reaction also worked smoothly to provide **17** in 73% yield with good diastereoselectivity (*dr*＞19∶1). The sulfinyl group of the amine **17** was easily transformed to Ac through being deprotected with AcCl/MeOH and acetylated with AcCl/Et_3N. The NMR spectra and optical rotation ($[\alpha]_D^{25}$−40.0 (*c* 1.0, $CHCl_3$); lit.[15b] −44.9 (*c* 1.0, $CHCl_3$)) of the synthetic compound **18** were identical to the compound reported in the literature. Furthermore, the amine **18** was converted to (−)-NCME **2** conveniently in one step under the oxidation of PIFA ((bis(trifluoroacetoxy)iodo)benzene).[15b]

3 Conclusions

In conclusion, we have established a comparatively conciser asymmetric synthetic approach to (−)-colchicine and its natural analogue (−)-*N*-acetylcolchinol methyl ether. The carbon framework was constructed by Aldol condensation of simple aldehydes and ketones, and then the chiral amine intermediates were synthesized economically and efficiently through asymmetric reductive amination with chiral *tert*-butanesulfinamide. The 3-rings skeleton of colchicine and related alkaloids was then constructed by oxidation with hypervalent iodine reagent. Our strategy provided a more convenient and economical method for the synthesis of these alkaloids. The discovery of anti-tumor and antiviral drugs based on these lead compounds is ongoing in our lab.

4 Experimental section

4.1 Reagents and instruments

All commercial chemicals and solvents were used as received without further purification unless otherwise noted. Petroleum ether (PE) refers to the fraction boiling in the 60～90 ℃ range. Anhydrous THF was distilled from sodium benzophenone ketyl. Anhydrous CH_2Cl_2, MeOH were distilled from calcium hydride. All reactions and manipulations which are sensitive to moisture or air were performed under inert atmosphere of nitrogen. NMR spectra were recorded on a Bruker AV 400 spectrometer at 400 MHz (^{1}H NMR), 101 MHz (^{13}C NMR). Chemical shifts were reported relative to internal TMS for ^{1}H NMR data, deuterated solvent for ^{13}C NMR data, respectively. Optical rotations were determined using a WXG-4 circular polarimeter. High-resolution mass spectra (HRMS) were obtained by electrospray ionization (ESI) on a Bruker Daltonics 7T mass spectrometer in positive ion mode.

4.2 Chemical synthesis procedures

4.2.1 Synthesis of compound **7**

To a solution of compound **8** (15 g, 76.5 mmol) and compound **9** (12.6 g, 76.5 mmol) in 300 mL of MeOH was added NaOMe solution (61 mL, 5 mol/L in MeOH) slowly at room temperature, and the resulting mixture was stirred for 48 h to complete the reaction. The mixture was concentrated, and water (100 mL) was added. After neutralization with aqueous 6 mol/L HCl solution, the mixture was then extracted with EtOAc (150 mL×3). The combined organic phase was dried with anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was chromatographed on silica-gel column with petroleum ether/ethyl acetate (*V*∶*V*=3∶1) to give product **7** (22.4 g, 85% yield) as a green yellow solid, m.p. 128～130 ℃; R_f=0.5 (petroleum ether/ethyl acetate, *V*∶*V*=1∶1). ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.65 (d, *J*=15.6 Hz, 1H), 7.58 (dd, *J*=8.0, 2.0 Hz, 2H), 7.33 (d, *J*=15.6 Hz, 1H), 6.88 (dt, *J*=8.2, 0.8 Hz, 1H), 6.79 (s, 2H), 5.67 (s, 1H), 3.92 (s, 3H), 3.86 (s, 6H), 3.83 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) *δ*: 188.9, 153.6, 150.7, 145.7, 144.4, 140.4, 132.0, 130.7, 122.2, 121.3, 114.9, 110.2, 105.8, 61.2, 56.4, 56.3; HRMS calcd for $C_{19}H_{20}NaO_6$ $[M+Na]^+$ 367.1152, found 367.1158.

4.2.2 Synthesis of compound **10**

To a solution of compound **7** (10 g, 29 mmol) in ethyl acetate (100 mL) was added Pd/C (0.5 g), and the suspension mixture was stirred at room temperature under ambient H_2 pressure for 3 h. The mixture was then filtered through a pad of Florisil and concentrated *in vacuo*. The residue was chromatographed on silica-gel column with petroleum ether/ethyl acetate (*V*∶*V*=3∶1) to give product **10** (8.6 g, 86% yield) as a white solid, m.p. 104～106 ℃; R_f=0.5 (petroleum ether/ethyl acetate, *V*∶*V*=1∶1). ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.55 (dq, *J*=4.0, 2.1 Hz, 2H), 6.92～6.84 (m, 1H), 6.46 (s, 2H), 5.66 (s, 1H), 3.96 (s, 3H), 3.85 (s, 6H), 3.82 (s, 3H), 3.23 (dd, *J*=8.5, 6.9 Hz, 2H), 2.99 (dd, *J*=8.4, 6.9 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) *δ*: 198.2, 153.3, 150.8, 145.6, 137.4, 136.4, 130.9, 121.7, 114.4, 110.1, 105.5, 61.0, 56.2, 40.4, 31.0; HRMS calcd for $C_{19}H_{22}NaO_6$ $[M+Na]^+$ 369.1309, found 369.1319.

4.2.3 Synthesis of compound **6**

To a solution of compound **10** (8.6 g, 24.8 mmol) in *N*,*N*-dimethylformamide (DMF) (60 mL) were added K_2CO_3 (10.3 g, 74.5 mmol) and BnBr (4.7 mL, 27.3 mmol). The solution was then heated at 60 ℃ for 1 h. When it was cooled to room temperature, the mixture was washed with H_2O (100 mL) and extracted with ethyl acetate (60 mL×4). The combined organic phase was washed with saturated NaCl solution and dried with anhydrous Na_2SO_4, then concentrated *in vacuo*. The residue was chromatographed on silica-gel column with petroleum ether/ethyl acetate (*V*∶*V*=2∶1) to give product **6** (9.7 g, 90% yield) as a white solid, m.p. 108～110 ℃; R_f=0.7 (petroleum ether/ethyl acetate, *V*∶*V*=1∶1). ^{1}H NMR

(400 MHz, $CDCl_3$) δ: 7.59 (dq, J=4.3, 2.1 Hz, 2H), 7.52～7.43 (m, 2H), 7.40～7.34 (m, 2H), 7.34～7.28 (m, 1H), 6.90 (d, J=9.0 Hz, 1H), 6.45 (s, 2H), 5.18 (s, 2H), 3.94 (s, 3H), 3.84 (s, 6H), 3.82 (s, 3H), 3.24～3.16 (m, 2H), 3.01～2.94 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 197.9, 154.1, 153.4, 148.3, 137.4, 136.7, 136.5, 130.1, 128.8, 128.2, 127.7, 123.2, 112.9, 110.6, 105.5, 71.1, 61.0, 56.3, 40.2, 31.0; HRMS calcd for $C_{26}H_{28}NaO_6^+$ $[M+Na]^+$ 459.1778, found 459.1787.

4.2.4 Synthesis of compound (−)-**12**

To the solution of compound **6** (5.3 g, 12.1 mmol) and *tert*-butanesulfinamide **11** (1.8 g, 14.5 mmol) in anhydrous THF (50 mL) was added $Ti(OEt)_4$ (5.1 mL, 24.2 mmol) under N_2 atmosphere. The mixture was refluxed for 48 h, then cooled to −78 ℃ followed by the addition of *L*-selectride (36.3 mL, 1.0 mol/L in THF). The reaction mixture was then warmed to room temperature naturally and stirred for 3 h, then quenched with H_2O (50 mL). The mixture was then filtered through a pad of Florisil before extracted with ethyl acetate (60 mL×3). The combined organic phase was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was chromatographed on silica-gel column with petroleum ether/ethyl acetate (V∶V=1∶1) to give product (−)-**12** (3.8 g, 73% yield, dr>19∶1) as a green yellow solid, m.p. 40～42 ℃; R_f= 0.4 (petroleum ether/ethyl acetate, V∶V=1∶2). $[\alpha]_D^{25}$− 42.5 (c 2.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.49～7.39 (m, 2H), 7.39～7.31 (m, 2H), 7.30～7.25 (m, 1H), 6.93～6.82 (m, 3H), 6.32 (s, 2H), 5.14 (dd, J=16.4, 12.0 Hz, 2H), 4.31 (ddd, J=8.3, 5.9, 2.7 Hz, 1H), 3.90 (s, 3H), 3.84 (s, 6H), 3.82 (s, 3H), 3.36 (d, J=2.8 Hz, 1H), 2.52～2.34 (m, 2H), 2.14～1.95 (m, 2H), 1.10 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 153.4, 149.5, 148.4, 137.2, 137.0, 136.4, 134.1, 128.7, 128.0, 127.5, 121.1, 113.6, 111.7, 105.5, 71.3, 61.0, 58.9, 56.3, 56.1, 55.5, 40.2, 32.9, 22.6; HRMS calcd for $C_{30}H_{39}NNaO_6S$ $[M+Na]^+$ 564.2390, found 564.2390.

4.2.5 Synthesis of compound (−)-**5**

To a solution of compound **12** (3.8 g, 7.0 mmol) in MeOH (80 mL) was added Raney Ni (0.4 g), and the suspension mixture was stirred at room temperature under ambient H_2 pressure for 12 h. The mixture was then filtered through a pad of Florisil and concentrated *in vacuo*. The residue was chromatographed on silica-gel column with petroleum ether/ethyl acetate (V∶V=1∶2) to give product (−)-**5** (2.6 g, 83% yield) as a white solid, m.p. 140～142 ℃; R_f=0.3 (petroleum ether/ethyl acetate, V∶V=1∶2). $[\alpha]_D^{25}$−40.0 (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, CD_3OD) δ: 6.89 (d, J=8.2 Hz, 1H), 6.83～6.67 (m, 2H), 6.46 (s, 2H), 4.15 (dd, J=8.1, 6.1 Hz, 1H), 3.85 (s, 3H), 3.81 (s, 6H), 3.72 (s, 3H), 2.52 (t, J=7.5 Hz, 2H), 2.32～2.16 (m, 1H), 2.13～1.98 (m, 1H), 1.14 (s, 9H); ^{13}C NMR (101 MHz, CD_3OD) δ: 154.4, 148.6, 147.7, 139.1, 137.2, 136.2, 120.3, 115.5, 112.5, 106.8, 61.1, 60.9, 56.7, 56.5, 56.4, 40.5, 33.8, 23.1; HRMS calcd for $C_{23}H_{33}NNaO_6S$ $[M+Na]^+$ 474.1921, found 474.1929.

4.2.6 Synthesis of compound (−)-**13**

To a solution of compound **5** (1.5 g, 3.3 mmol) in MeOH (10 mL) was added $PhI(OAc)_2$ (1.1 g, 6.6mmol) and stirred at room temperature for 5 min. The mixture was added to a solution of BF_3•Et_2O (1.2 mL, 9.9 mmol) in dichloromethane (250 mL). The resulting solution was stirred at room temperature for 3 h, quenched with saturated $NaHCO_3$ solution (50 mL), and extracted with dichloromethane (60 mL×3). The combined organic phase was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was chromatographed on silica-gel column with petroleum ether/ethyl acetate (V∶V=1∶2) to give product (−)-**13** (1.4 g, 92% yield) as a light brown solid, m.p. 102～104 ℃; R_f=0.3 (petroleum ether/ethyl acetate, 1∶2, V∶V). $[\alpha]_D^{25}$−85.0 (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, CD_3OD) δ: 7.02 (s, 1H), 6.98 (s, 1H), 6.73 (s, 1H), 4.13～4.06 (m, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.85 (s, 3H), 3.56 (s, 3H), 2.52～2.41 (m, 2H), 2.29～2.17 (m, 1H), 2.08～2.01 (m, 1H), 1.27 (s, 9H); ^{13}C NMR (101 MHz, CD_3OD) δ: 153.9, 151.8, 147.3, 146.8, 142.3, 136.9, 134.3, 126.5, 126.3, 114.6, 112.7, 109.1, 61.5, 61.2, 57.2, 56.6, 56.6, 43.1, 32.0, 23.3, 22.7; HRMS calcd for $C_{23}H_{31}NNaO_6S$ $[M+Na]^+$ 472.1764, found 472.1781.

4.2.7 Synthesis of compound (−)-**4**

To the solution of compound (−)-**13** (1.4 g, 3.1 mmol) in MeOH (30 mL) was added AcCl (442 μL, 6.2 mmol). The mixture was stirred at room temperature for 2 h followed by being concentrated *in vacuo*. The residue was dissolved in dichloromethane (DCM, 50 mL), then added Et_3N (2.1 mL, 15.5 mmol) and AcCl (465 μL, 6.5 mmol). The mixture was stirred at room temperature for 2 h, then added H_2O (15 mL), MeOH (15 mL) and K_2CO_3 (1.7 g, 12.4 mmol). The resulting mixture was stirred at 60 ℃ for 12 h then concentrated in vacuo. The residue was extracted with ethyl acetate (50 mL×3). The combined organic phase was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was chromatographed on silica-gel column with petroleum ether/ethyl acetate (1∶2, V∶V) to give product (−)-**4** (1.0 g, 88% yield) as an off-white solid, m.p. 128～130 ℃; R_f=0.25 (petroleum ether/ethyl acetate, 1∶2, V∶V); $[\alpha]_D^{25}$−45.0 (c 0.75, $CHCl_3$); ^{1}H NMR (400 MHz, CD_3OD) δ: 7.01 (s, 1H), 6.83 (s, 1H), 6.74 (s, 1H), 4.66～4.56 (m, 1H), 3.89 (s, 3H), 3.89 (s, 3H), 3.86 (s, 3H), 3.55 (s, 3H), 2.57～2.46 (m, 1H), 2.33～2.22 (m, 2H), 2.02 (s, 3H), 1.97～1.87 (m, 1H); ^{13}C NMR (101 MHz, CD_3OD) δ: 172.4, 153.8, 152.0, 147.3, 147.0, 142.3, 136.8, 134.0, 126.7, 126.6, 114.8, 111.2, 109.1, 61.6, 61.3, 56.7, 56.6, 50.0, 40.3, 31.6, 22.6; HRMS calcd for $C_{21}H_{25}NNaO_6$ $[M+Na]^+$ 410.1574, found 410.1595.

4.2.8 Synthesis of compound **15**

To a solution of compound **8** (15 g, 76.5 mmol) and compound **14** (12.6 g, 84.2 mmol) in 300 mL of MeOH was added NaOMe solution (61 mL, 5 mol/L in MeOH) slowly at room temperature, and the resulting mixture was

stirred for 36 h. The mixture was concentrated, and water (100 mL) was added. After neutralization with aqueous 6 mol/L HCl solution, the mixture was then extracted with EtOAc (150 mL×3). The combined organic phase was dried with anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was chromatographed on silica-gel column with petroleum ether/ethyl acetate (V∶V=4∶1) to give product **15** (17.8 g, 71% yield) as a green yellow paste: R_f=0.7 (petroleum ether/ethyl acetate, V∶V=2∶1); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.73 (d, J=15.7 Hz, 1H), 7.63～7.57 (m, 1H), 7.54 (dd, J=2.7, 1.6 Hz, 1H), 7.45～7.35 (m, 2H), 7.16～7.12 (m, 1H), 6.87 (s, 2H), 3.93 (s, 6H), 3.91 (s, 3H), 3.89 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 190.4, 160.0, 153.6, 145.2, 140.6, 139.8, 130.5 129.7, 121.6, 121.1, 119.2, 113.2, 105.8, 61.1, 56.4, 55.6; HRMS calcd for $C_{19}H_{20}NaO_5$ $[M+Na]^+$ 351.1203, found 351.1207.

4.2.9 Synthesis of compound **16**

To a solution of compound **15** (17.8 g, 54.2 mmol) in ethyl acetate (100 mL) was added Pd/C (0.89 g), and the suspension mixture was stirred at room temperature under ambient H_2 pressure for 3 h. The mixture was then filtered through a pad of Florisil and concentrated *in vacuo*. The residue was chromatographed on silica-gel column with petroleum ether/ethyl acetate (V∶V=4∶1) to give product **16** (15.0 g, 84% yield) as a white solid, m.p. 66～68 ℃; R_f =0.7 (petroleum ether/ethyl acetate, V∶V=2∶1); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.54 (dd, J=7.8, 1.1 Hz, 1H), 7.48 (t, J=2.1 Hz, 1H), 7.36 (t, J=8.0 Hz, 1H), 7.10 (dd, J=7.9, 2.7 Hz, 1H), 6.47 (s, 2H), 3.84 (s, 9H), 3.82 (s, 3H), 3.28 (t, J=7.6 Hz, 2H), 3.01 (t, J=7.6 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 199.1, 159.9, 153.3, 138.3, 137.1, 136.4, 129.7, 120.7, 119.5, 112.4, 105.5, 60.9, 56.1, 55.5, 40.7, 30.7; HRMS calcd for $C_{19}H_{22}NaO_5$ $[M+Na]^+$ 353.1359, found 353.1363.

4.2.10 Synthesis of compound (−)-**17**

To the solution of compound **16** (4.0 g, 12.1 mmol) and *tert*-butanesulfinamide **11** (1.8 g, 14.5 mmol) in anhydrous THF (50 mL) was added $Ti(OEt)_4$ (5.1 mL, 24.2 mmol) under N_2 atmosphere. The mixture was refluxed for 48 h, then cooled to −78 ℃ followed by the addition of *L*-selectride (36.3 mL, 1.0 mol/L in THF). The reaction mixture was then warmed to room temperature naturally and stirred for 3 h, then quenched with H_2O (50 mL). The mixture was filtered through a pad of Florisil before extracted with ethyl acetate (60 mL×3). The combined organic phase was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was chromatographed on silica-gel column with petroleum ether/ethyl acetate (V∶V=1∶2) to give product (−)-**17** (3.8 g, 73% yield, dr>19∶1, V∶V) as a green yellow paste: R_f=0.3 (petroleum ether/ethyl acetate, V∶V=1∶2); $[\alpha]_D^{25}$−65.0 (c 2.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.27 (t, J=7.9 Hz, 1H), 6.90 (dt, J=7.6, 1.2 Hz, 1H), 6.87 (t, J=2.1 Hz, 1H), 6.83 (ddd, J=8.1, 2.7, 0.9 Hz, 1H), 6.38 (s, 2H), 4.40 (td, J=6.9, 3.1 Hz, 1H), 3.84 (s, 6H), 3.81 (s, 3H), 3.80 (s, 3H), 3.50 (d, J=3.1 Hz, 1H), 2.60～2.49 (m, 2H), 2.22～2.06 (m, 2H), 1.15 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 159.7, 153.2, 143.5, 136.8, 136.2, 129.5, 119.9, 113.3, 112.9, 105.4, 60.8, 59.2, 56.0, 55.5, 55.1, 40.0, 32.8, 22.5; HRMS calcd for $C_{23}H_{33}NNaO_5S$ $[M+Na]^+$ 458.1972, found 458.2004.

4.2.11 Synthesis of compound (−)-**18**

To a solution of compound (−)-**17** (3.8 g, 8.7 mmol) in MeOH (50 mL) was added AcCl (1.2 mL.17.4 mmol). The mixture was stirred at room temperature for 2 h followed by being concentrated *in vacuo*. The residue was dissolved in DCM (50 mL), then added Et_3N (4.8 mL, 34.8 mL) and AcCl (652 μL, 9.1 mmol). The mixture was stirred at room temperature for 2 h, then washed with H_2O (50 mL). The aqueous phase was extracted with DCM (40 mL×3). The combined organic phase was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was chromatographed on silica-gel column with petroleum ether/ethyl acetate (V∶V=1∶2) to give product (−)-**4** (2.7 g, 82% yield) as a light green yellow paste: R_f=0.25 (petroleum ether/ethyl acetate, V∶V=1∶2); $[\alpha]_D^{25}$−40.0 (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.26 (t, J=7.8 Hz, 1H), 6.88 (d, J=7.6 Hz, 1H), 6.85～6.78 (m, 2H), 6.36 (s, 2H), 5.98 (d, J=8.4 Hz, 1H), 4.99 (dd, J=15.6, 7.6 Hz, 1H), 3.82 (s, 6H), 3.81 (s, 3H), 3.79 (s, 3H), 2.60～2.49 (m, 2H), 2.19～2.11 (m, 1H), 2.09～2.02 (m, 1H), 1.96 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 169.5, 160.0, 153.2, 143.7, 137.3, 136.2, 130.0, 119.0, 113.0, 112.6, 105.4, 60.9, 56.2, 55.3, 53.4, 37.6, 33.0, 23.5; HRMS calcd for $C_{21}H_{27}NNaO_5$ $[M+Na]^+$ 396.1781, found 396.1821.

Supporting Information ^{1}H NMR and ^{13}C NMR spectra of new compounds **7**, **10**, **6**, **12**, **5**, **13**, **4**, **15**, **16**, **17** and **18**. The Supporting Information is available free of charge via the Internet at http://sioc-journal.cn/.

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