HETEROCYCLES, Vol. 106, No. 1, 2023, pp. 166 - 173. © 2023 The Japan Institute of Heterocyclic Chemistry
Received, 29th October, 2022, Accepted, 30th November, 2022, Published online, 6th December, 2022
DOI: 10.3987/COM-22-14774

CONCISE SYNTHESIS OF (±)-CEPHALOTAXINE

Jian Zhang,[a,b,c]* Huili Ding,[a] Yuxue Fan,[a] Hui Chen,[a,b] Hongxia Dai,[a,b]* and Ming Jing[a,b]

[a]School of Pharmacy, Gansu University of Chinese Medicine, Lanzhou 730000, P. R. China; [b]Northwest Collaborative Innovation Center for Traditional Chinese Medicine Co-Constructed by Gansu Province & MOE of PRC, Lanzhou 730000, P. R. China. [c]Key Laboratory of Chemistry and Quality for TCM of the College of Gansu Province, Lanzhou 730000, P. R. China.

*Corresponding Author: zhangjian@gszy.edu.cn; daihongxia007@163.com;

Abstract – The construction of 1-azaspiro[4.4]nonane framework was achieved via the key Stevens rearrangement reaction of the Weinreb amide. And the subsequent steps mediated by the carbonyl of Weinreb amide led to the concise formal synthesis of (±)-cephalotaxine. Further development and application of asymmetric Stevens rearrangement of the Weinreb amide are underway.

Cephalotaxine (CET, **1**) represents the parent polycyclic core of a series of *Cephalotaxus* alkaloids.[1] Particularly, homoharringtonine (HTT, **2**) was approved by FDA in 2012 for treatment of chronic myeloid leukemia.[2] Structurally, *Cephalotaxus* alkaloids are characterized with a 1-azaspiro[4.4]nonane ring system featuring a crucial azaquaternary carbon center (Figure 1). Cephalotaxine's absolute configuration was determined by X-ray analysis of the corresponding *p*-bromobenzoate by Powell in 1974.[3] The unique 1-azaspiro[4,4]nonane fused to a benzazepine rendered cephalotaxine as an intriguing synthetic target. Since the first total synthesis of cephalotaxine reported by the Weinreb and the Semmelhack groups in 1972,[4] more than 30 synthetic routes have been reported.

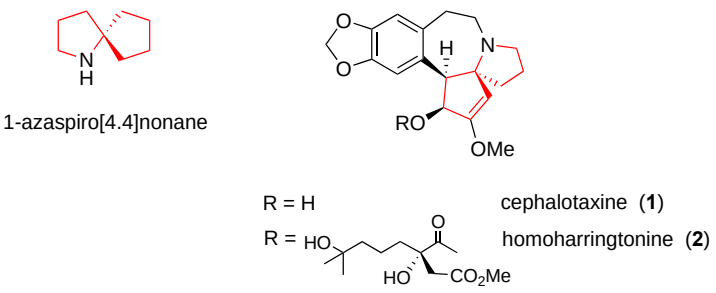


Figure 1

And the first enantioselective synthesis of (-)-cephalotaxine was reported by Mori group[5] which was based on the construction of the 1-azaspiro[4,4]nonane ring system (**3**). In Mori's report, upon treatment with neat polyphosphoric acid (PPA), **3** cyclized to give the desired product **4** via the Friedel-Crafts cyclization. But the cyclization of compound **5** with PPA was unsuccessful. So the dimethoxy groups of **4** were transformed into a methylenedioxy group in order to produce the tetrahydroazepine **6**. Mori prepared the intermediate **6** from the dimethoxyaromatic derivative **3** in a two-step process on the way to the total synthesis of cephalotaxine (Figure 2) and the research results inspired the followup synthesis works. Many research groups have completed the synthesis of cephalotaxine via the Mori's intermediate **6**.[6] In particular, Hayes's group[7] completed the asymmetric synthesis of cephalotaxine through the key intermediate **6** in 2008. It is worth mentioning that Hayes's group realized the one step conversion from the 1-azaspiro[4.4]nonane framework **5** to the Mori's intermediate **6** via $SnCl_4$.

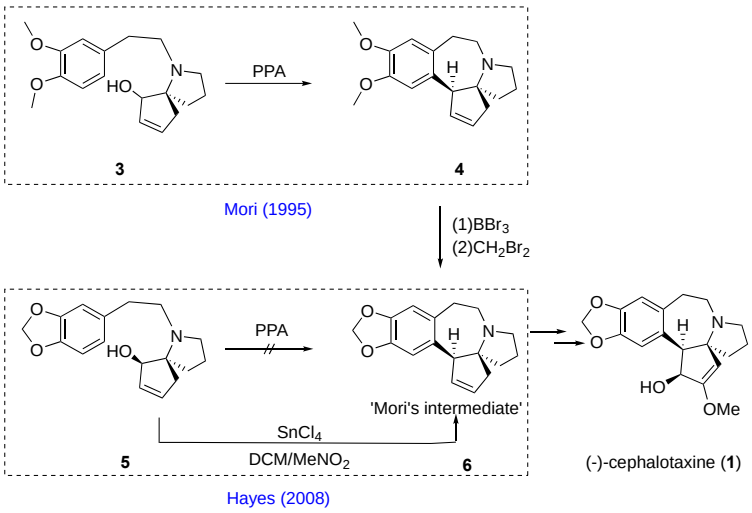
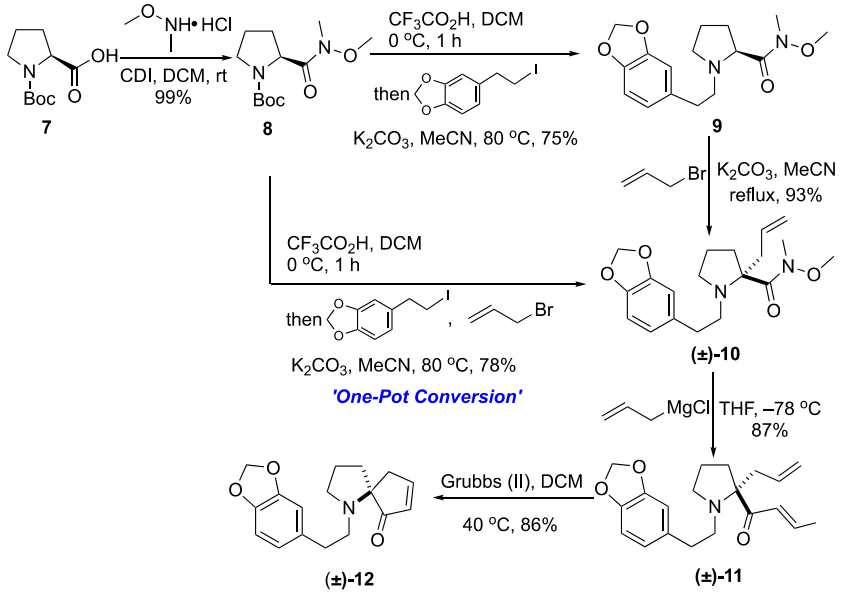


Figure 2

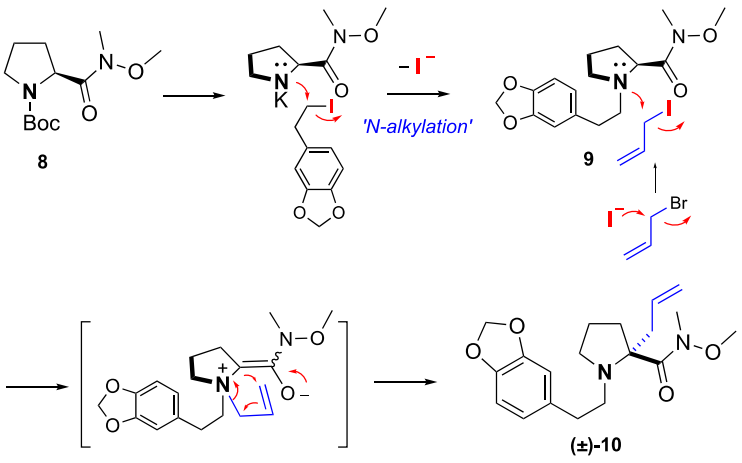
In recent years, different construction strategies of 1-azaspiro[4.4]nonane framework have been developed and it also aroused our research interest. Recently, we developed the [2,3]-Stevens rearrangement of the 'Weinreb amide' and applied it successfully to the construction of 1-azaspiro[4.4]nonane and 6-azaspiro[4.5]decane frameworks. Base on our new synthetic strategy, we got the key intermediate **4** by the concise method and the formal total synthesis of (±)-cephalotaxine could be completed in 13 steps.[8] In this report, we synthesized the compound **6** through an efficient strategy and the formal synthesis of (±)-cephalotaxine could be shortened by 3 steps.

As outlined in Scheme 1, the synthesis commenced from a raw material **7**, and the 'Weinreb amide' **8** could be easily obtained with a high yield.[9] Further deprotection via CF_3CO_2H and *N*-alkylation afforded compound **9** in 75% yield. Based on our previous application,[10] allyl derivative **10** was obtained in almost quantitative yield from **9** via [2,3]-Stevens rearrangement under the mild K_2CO_3/MeCN condition.

Through further study, we found that compound **10** could be synthesized in 'one-pot' from compound **8** with a yield of 78%. Compared with the previous two steps conversion, the tandem reaction of *N*-alkylation and Stevens rearrangement made the reaction with a higher yield. As depicted in Scheme 2, the iodine ion which generated by the *N*-alkylation step promoted the Stevens rearrangement reaction. First, the iodine ion and allyl bromide underwent nucleophilic substitution reaction to generate allyl iodide. Then the *N*-quaternization step between compound **9** and allyl iodide could smoothly produce the quaternary ammonium salt intermediate. Allyl derivative **10** could be obtained via [2,3]-rearrangement under the alkalescency condition. The one-pot *N*-alkylation and Stevens rearrangement sequence make this synthesis route more simple and efficient.



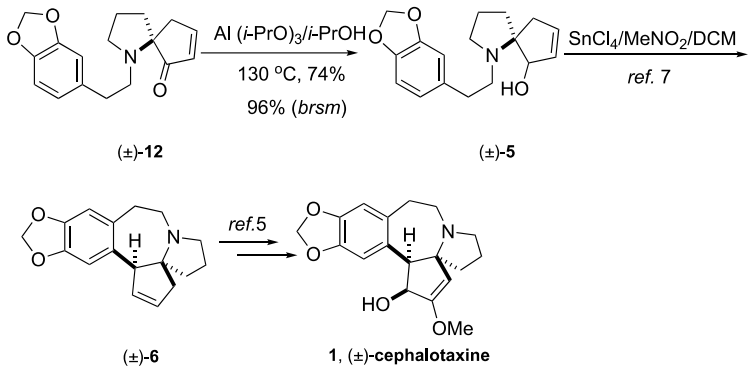
Scheme 1



Scheme 2

Sequential application of nucleophilic substitution of 'Weinreb amide' and ring closing metathesis reaction provided a rapid entry to construct the 1-azaspiro[4.4]nonane skeleton. The nucleophilic substitution reaction of allyl derivative **10** could be proceed with allylmagnesium chloride successfully and the conjugated ketone compound **11** was obtained in 87% yield. Further cyclization of **11** with Grubbs(II) catalyst[11] yielded the spirocyclopentenone **12** in a high yield. In this way, we efficiently constructed the 1-azaspiro[4.4]nonane framework starting from compound **7** by 4 steps.

As expected, the good yield formation of the allylic alcohol **5** was obtained with the classic M-P-V reaction under aluminum isopropoxide/2-propanol conditions. The reduction process of similar substrates have been reported in the previous literature.[8,12] According to Hayes's report, upon treatment **5** with $SnCl_4$, the desired Friedel-Crafts cyclization product **6** was obtained in 48% yield, whose spectroscopic and analytical data were identical to those previously reported.[6,7] Since it has been shown that the Mori's intermediate **6** can be converted into cephalotaxine (1) in 4 steps,[5] we have successfully completed the formal synthesis of (±)-cephalotaxine in 10 steps via a new and facile construction of 1-azaspiro[4.4]nonane framework (Scheme 3).



Scheme 3

In summary, we set out the study of construction of the 1-azaspiro[4.4]nonane skeleton starting from the readily assemble 'Weinreb amide'. The carbonyl group of 'Weinreb amide' mediated the subsequent key steps to the synthesis of cephalotaxine. In our previous work, starting from compound **7**, the Mori's intermediate **6** could be obtained in a total yield of 12.9% by 9 steps.[8] In this work, starting from the same starting materials, the synthesis route was shortened to 6 steps and the total yield was increased to 20.5%. In this way, we can easily and efficiently complete the synthesis of cephalotaxine in 10 steps. This is also one of the shortest synthetic routes reported so far. Studies along this line and development of an asymmetric synthesis application of this method are underway.

EXPERIMENTAL

Synthesis of compound 8. To a solution of **7** (2.15 g, 10 mmol) in DCM was added CDI (1.95 g, 12 mmol). The mixture was stirred at room temperature for 1 h, upon which time MeNHOMe·HCl (1.17 g, 12 mmol) was added. The reaction mixture was stirred for 4 h and quenched with water. The phases were separated and the organic phase was added 4 M HCl (0.44 mL) and water (8.6 mL). The combined organic layer was dried over Na_2SO_4 and concentrated under reduce pressure. The residue was purified by flash chromatography on silica gel (PET/EtOAc = 3:1) to yield Weinreb amide **8** (2.56 g, yield 99%) as a clear oil, R_f = 0.33 (PET : EtOAc = 3:1). IR (film): ν_{max} 2975, 2937, 2879, 1698, 1399, 1164, 1122, 999 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.36 (s, 5H), 1.40 (s, 4H), 1.76-1.96 (m, 3H), 2.08-2.19 (m, 1H), 3.14 (s, 3H), 3.34-3.45 (m, 1H), 3.47-3.55 (m, 1H), 3.67 (s, 2H), 3.73 (s, 1H), 4.53-4.57 (m, 0.52H), 4.63-4.66 (m, 0.46H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 23.3, 23.9, 28.3, 28.4, 29.5, 30.4, 32.2, 32.3, 46.5, 46.8, 56.4, 56.7, 61.1, 61.2, 79.2, 79.4, 153.8, 154.4, 173.2, 173.8; HRMS (ESI) *m/z* calcd for $C_{12}H_{22}N_2O_4Na$ $[M+Na]^+$: 281.1477, found: 281.1467.

Synthesis of compound 9. To a solution of **8** (98 mg, 0.38 mmol) in DCM was added CF_3CO_2H (0.2 mL) at 0 °C. The mixture was stirred for 1.5 h and concentrated in vacuo to remove CF_3CO_2H and then utilized in next step. The above mixture was dissolved in MeCN and added in the flask after the K_2CO_3 (131 mg, 0.95 mmol) and iodide (157 mg, 0.57 mmol) were suspended in MeCN under nitrogen atmosphere. The resulting solution was refluxed for 4 h and filtered. The filtrate was evaporated, diluteded with H_2O, and extracted with DCM. The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by flash column chromatography on silica gel (DCM/MeOH = 30:1) gave **9** (87 mg, yield 75%) as a light-yellow oil, R_f = 0.5 (DCM : MeOH = 10:1); IR (film): ν_{max}2938, 1667, 1503, 1490, 1443, 1388, 1247, 1187, 1039, 1001, 926, 810; ^1H NMR (400 MHz, $CDCl_3$) δ 1.79-1.89 (m, 2H), 1.92-2.03 (m, 1H), 2.11-2.19 (m, 1H), 2.40 (q, 1H, *J* = 8.0 Hz), 2.51-2.57 (m, 1H), 2.75 (t, 2H, *J* = 8.0 Hz), 2.83-2.90 (m, 1H), 3.19 (s, 3H), 3.28-3.33 (m, 1H), 3.51-3.54 (m, 1H), 3.67 (s, 3H), 5.90 (s, 2H), 6.63-6.72 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.2, 29.2, 32.5, 35.2, 53.4, 56.9, 61.4, 63.5, 100.7, 108.1, 109.2, 121.4, 134.2, 145.7, 147.5, 175.0. HRMS (ESI) *m/z* calcd for $C_{16}H_{22}N_2NaO_4$$[M+Na]^+$ 329.1477, found 329.1462.

Synthesis of compound 10. To a suspension of K_2CO_3 (87 mg, 0.62 mmol) was added the solution of **9** (87 mg, 0.28 mmol) in MeCN under nitrogen atmosphere, followed by the addition of allyl bromide (0.05 mL, 0.56 mmol). The mixture was stirred for 21 h, filtered, and evaporated. After diluting with H_2O, the filtrate was extracted with DCM. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. Purification by flash column chromatography on silica gel (PET/EtOAc = 3:1) yielded **10** (104 mg, yield 93%) as a light yellow oil. R_f = 0.38 (DCM : MeOH = 10:1); IR (film): ν_{max} 2937, 1647, 1503, 1490, 1442, 1360, 1247, 1187, 1040, 1002, 926, 809 cm^{-1}; ^1H

NMR (400 MHz, $CDCl_3$) δ 1.76-1.87 (m, 2H), 1.88-1.95 (m, 1H), 2.10-2.17 (m, 1H), 2.24-2.29 (m, 1H), 2.64-2.79 (m, 5H), 3.00-3.12 (m, 2H), 3.15 (s, 3H), 3.62 (s, 3H), 5.01-5.06 (m, 2H), 5.77-5.86 (m, 1H), 5.89 (s, 2H), 6.62 (q, 1H, *J* = 4.0 Hz), 6.66-6.71 (m, 2H); ^{13}C NMR (100MHz, $CDCl_3$) δ 22.6, 32.9, 34.2, 35.8, 37.6, 51.0, 51.2, 60.2, 70.8, 100.7, 108.0, 109.2, 117.1, 121.4, 134.6, 135.9, 145.6, 147.4, 175.6. HRMS (ESI) *m/z* calcd for $C_{19}H_{26}N_2NaO_4[M+Na]^+$ 369.1790, found 369.1792.

Synthesis of compound 10 in 'One-Pot' method. To a solution of **8** (122 mg, 0.47 mmol) in DCM was added CF_3CO_2H (0.3 mL) and stirred for 1.5 h at 0 °C. Then the reaction mixture was concentrated in vacuo to remove CF_3CO_2H and the residue was dissolved in MeCN. K_2CO_3 (228 mg, 1.65 mmol) and iodide (196 mg, 0.71 mmol) were added in order under nitrogen atmosphere. The resulting solution was refluxed for 4 h and then the allyl bromide (0.08 mL, 0.94 mmol) was added. The mixture was stirred for additional 21 h, filtered, and evaporated. After diluting with H_2O, the filtrate was extracted with DCM. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. Purification by flash column chromatography on silica gel (PET/EtOAc = 3:1) yielded **10** (127 mg, yield 78%) as a light yellow oil.

Synthesis of compound 11. To a solution of **10** (527 mg, 1.52 mmol) in anhydrous THF was added a solution of allylmagnesium chloride (1.0 M in THF, 4.57 mL, 4.57 mmol) slowly using a syringe pump at –78 °C. After being stirred for 30 min, the solution was quenched with saturated NH_4Cl solution and warmed to room temperature. The reaction was then diluted with EtOAc, washed with water and brine, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (DCM/MeOH = 50:1) to yield **11** (431 mg, yield 87%) as a yellow oil, R_f = 0.63 (DCM : MeOH = 10:1); IR (film): ν_{max} 2947, 1688, 1628, 1503, 1490, 1442, 1247, 1187, 1041, 916; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.80-1.82 (m, 3H), 1.84-1.91 (m, 4H), 2.13-2.18 (m, 1H), 2.51-2.79 (m, 6H), 3.20-3.25 (m, 1H), 4.99-5.06 (m, 2H), 5.79-5.86 (m, 1H), 5.90 (s, 2H), 6.42 (q, 1H, *J* = 4.0 Hz), 6.57-6.62 (m, 2H), 6.69 (d, *J* = 8.0 Hz, 1H), 6.80-6.89 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.2, 23.1, 32.9, 35.4, 35.6, 50.9, 51.2, 72.8, 100.7, 108.0, 109.2, 117.1, 121.5, 126.7, 134.3, 135.9, 141.8, 145.6, 147.3, 202.2. HRMS (ESI) *m/z* calcd. for $C_{20}H_{25}NNaO_3[M+Na]^+$ 350.1732, found 350.1739.

Synthesis of compound 12. The solution of **11** (28 mg, 0.08 mmol) in DCM was added to a suspension of Grubbs(II) catalyst (7.3 mg, 0.008 mmol) in DCM under nitrogen atmosphere and the mixture was refluxed for 30 min. The reaction solution was concentrated under reduced pressure and purified by flash column chromatography on silica gel (DCM : MeOH = 30:1) to afford **12** (21 mg, yield 86%) as a yellow oil. R_f = 0.5 (DCM : MeOH = 15:1); IR (film): ν_{max} 2934, 1701, 1503, 1490, 1442, 1247, 1038, 808 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.76-1.82 (m, 1H), 1.87-1.94 (m, 1H), 1.99-2.11 (m, 2H), 2.49-2.75 (m, 6H), 2.97-3.02 (m, 1H), 3.11-3.17 (m, 1H), 5.88 (s, 2H), 6.08-6.10 (m, 1H), 6.59 (d, 1H, *J* = 8.0 Hz), 6.65 (d, *J* = 4.0 Hz, 1H), 6.70 (d, 1H, *J* = 8.0 Hz), 7.61 (q, 1H, *J* = 4.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ

21.8, 35.8, 36.8, 39.4, 51.5, 51.9, 70.9, 100.7, 108.0, 109.1, 121.4, 133.4, 134.1, 145.7, 147.4, 162.4, 212.6; HRMS(ESI) *m/z* calcd for $C_{17}H_{19}NNaO_3[M+Na]^+$ 308.1263, found 308.1262.

Synthesis of compound 5. The aluminium isopropoxide (753 mg, 3.6 mmol) was dissolved in isopropanol and was refluxed for 5 min. Before being refluxed for an additional 1 h, a solution of **12** (35 mg, 0.12 mmol) in isopropanol was added to the mixture. The reaction solution was distilled for 3 h and cooled to room temperature. The residue was diluted with water and adjusted to pH = 7 with 1 M HCl at 0 °C. The solution was extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated. Purification by flash column chromatography on silica gel (DCM/MeOH = 20:1) yielded **5** (26 mg, yield 74%) as a brown oil, R_f = 0.2 (DCM : MeOH = 10:1); IR (film): ν_{max}3439, 2924, 1635, 1503, 1490, 1443, 1247, 1192, 1039, 925, 808; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.88-2.05 (m, 3H), 2.12-2.21 (m, 2H), 2.40-2.45 (m, 1H), 2.80-2.97 (m, 4H), 3.19 (m, 1H), 3.58 (s, 1H), 3.80 (s, 1H), 4.81 (s, 1H), 5.85-5.90 (m, 2H), 5.93 (s, 2H), 6.68-6.75 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.4, 34.0, 38.1, 38.3, 52.9, 53.7, 74.5, 80.4, 100.9, 108.4, 109.1, 121.7, 130.9, 132.1, 133.6, 146.2, 147.7; HRMS (ESI) *m/z* calcd. for $C_{17}H_{22}NO_3$ $[M+H]^+$ 288.1600, found 288.1585.

Synthesis of compound 6. To the solution of **5** (33 mg, 0.115 mmol) in DCM/$MeNO_2$ (1:1, 2 mL) was added $SnCl_4$ (0.135 mL, 1.15 mmol) dropwise under inert atmosphere at –78 °C, and the mixture was then warmed to 50 °C and stirred at this temperature for 4 h. The reaction mixture was cooled to room temperature and diluted with EtOAc (5 mL). Then, 1 N HCl (1 mL) was added, and the pH was adjusted to 14 by addition solution of NaOH. The layers were separated, and the aqueous solution was extracted with DCM (10 mL × 5). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel chromatography (DCM/MeOH, 80:1-20:1) to give **6** (15 mg, 48% yield) as a light yellow oil. R_f = 0.33 (DCM : MeOH = 8:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.69-1.81 (m, 2H), 1.95-2.03 (m, 3H), 2.31-2.43 (m, 2H), 2.54-2.59 (m, 1H), 2.76 (d, 1H, *J* = 16.0 Hz), 2.93-2.97 (m, 1H), 3.08-3.20 (m, 2H), 3.88 (s, 1H), 5.53 (t, 1H, *J* = 3.2 Hz), 5.85 (dd, 1H, *J* = 8.0, 4.0 Hz), 5.88 (d, 2H, *J* = 4.8 Hz), 6.59 (s, 1H), 6.66 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 19.8, 30.4, 34.8, 43.0, 48.9, 53.4, 62.2, 68.1, 100.7, 109.8, 110.7, 128.5, 131.6, 132.0, 132.2, 145.9, 146.2. HRMS (ESI) *m/z* calcd for $C_{17}H_{20}NO_2$ $[M+H]^+$ 270.1489, found 270.1498.

ACKNOWLEDGEMENTS

This work was supported by the National Natural Science Foundation of China (21562001), the Natural Science Foundation of Gansu Province (22JR5RA586) and the Educational Science and Technology Innovation Program of Gansu Province (2021CYZC-13).

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