Asymmetric Synthesis of (–)-9-*epi*-Metazocine

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Abstract: (–)-9-*epi*-Metazocine was synthesized through an Evans *syn* aldol reaction, ring-closing metathesis reaction and intramolecular radical cyclization.

Key word: asymmetric, drug development, aldol, ring-closing metathesis, radical cyclization

The natural alkaloid (–)-morphine is an important narcotic analgesic but it exhibits undesired addictive side effects.[1] Structural modification can reduce this problem to a considerable extent, such as the clinically used (–)-pentazocine (**1**) and (–)-9-*epi*-metazocine (**2b**) (Figure 1).[2] Most analogues of (–)-morphine feature a benzylic quaternary carbon center, and the construction of such a center in an enantioselective manner is an ongoing challenge for organic chemists. Methods for the enantioselective construction of this center include Grewe-type cyclization,[3] radical reaction,[4] palladium-catalyzed asymmetric allylic alkylation (AAA),[5] Heck reaction,[6] and Claisen rearrangement.[7] Recently, our group reported that the synthesis of a rigid benzobicyclo[3.3.1] lactone proceeds through an intramolecular Friedel–Crafts type Michael addition of the corresponding α,β-unsaturated lactone.[8] However, application of the strategy to the synthesis of (–)-9-*epi*-metazocine was not efficient. Herein, we report an asymmetric synthesis of (–)-9-*epi*-metazocine through the application of intramolecular radical cyclization.

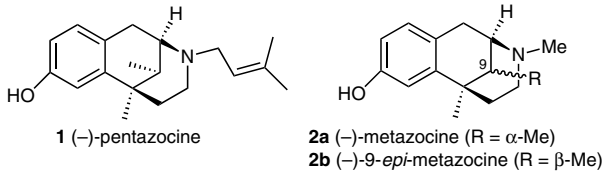
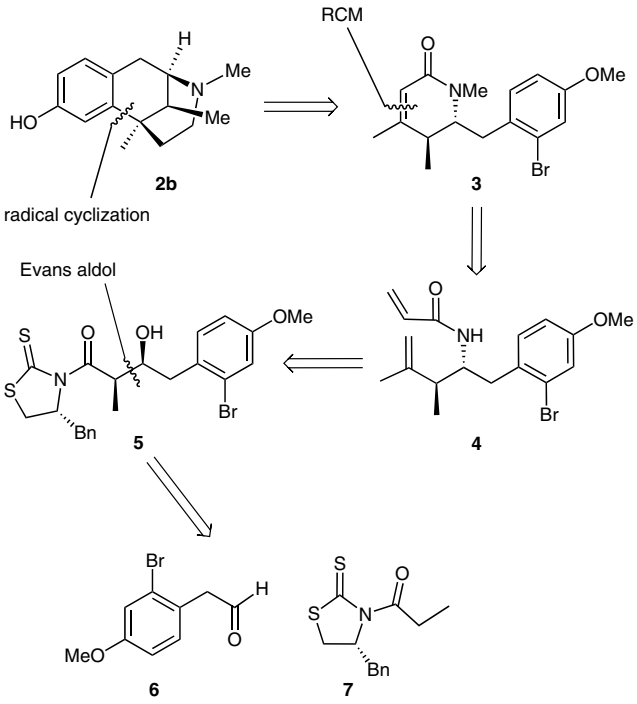


Figure 1

Our retrosynthetic analysis is outlined in Scheme 1. The framework of **2b** may be accessed stereoselectively through intramolecular radical cyclization of the α,β-unsaturated lactam **3**. The formation of **3** could be accomplished by using ring-closing metathesis (RCM) from amide **4**, which, in turn, was derived from **5**. The preparation of **5** could be achieved from aldehyde **6** and *N*-propionylthiazolidinethione (**7**) by an Evans aldol reaction.



Scheme 1 Retrosynthetic analysis

The synthesis of intermediate **5** is shown in Scheme 2. Starting from the commercially available 3-bromoanisole (**8**), 2-bromo-4-methoxyacetophenone (**9**) was obtained in 70% yield through a Friedel–Crafts reaction.[9] Upon treatment of **9** with bromine, the substituted phenacyl bromide **10** was obtained in nearly quantitative yield. Reduction of **10** with $NaBH_4$ followed by intramolecular S_N2 reaction generated the epoxy compound, which was transformed into aldehyde **6** upon treatment with a catalytic amount of $BF_3{\cdot}OEt_2$[10] in 81% overall yield for the three steps. Generation of **5** through an Evans *syn* aldol reaction[11] between aldehyde **6** and *N*-propionylthiazolidinethione (**7**) in 76% yield with excellent diastereoselectivity (>20:1 dr) completed the synthesis.[12]

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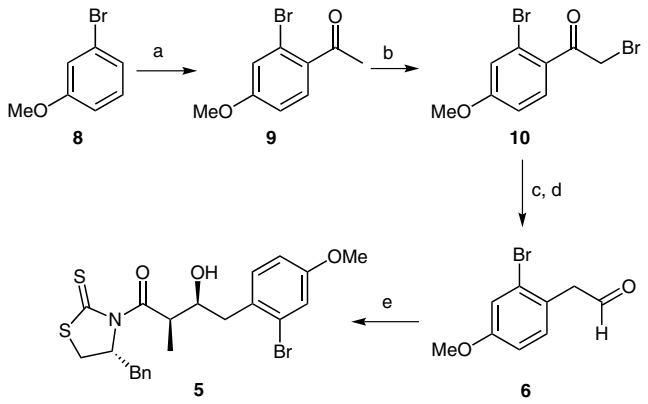

Scheme 2 *Reagents and conditions*: (a) $AlCl_3$·AcCl, CH_2Cl_2, 0 °C, 70%; (b) Br_2, Et_2O, r.t., 96%; (c) $NaBH_4$, MeOH, then K_2CO_3, r.t., 93%; (d) BF_3·Et_2O, THF, r.t., 91%; (e) $TiCl_4$, (–)-sparteine, 0 °C, NMP, **7**, CH_2Cl_2, –78 °C, 76%.

With the key intermediate **5** in hand, it was smoothly converted into the corresponding Weinreb amide **11**,[13] and its free hydroxy group was protected as the TBS ether to afford **12** (Scheme 3). Treatment of **12** with excess methyl magnesium iodide gave the corresponding ketone **13** in 92% yield. Subsequent Wittig reaction led to olefin **14** in 85% yield. Deprotection of **14** afforded **15**, which was converted into the corresponding azide **16** by the use of $(PhO)_2P(O)N_3$.[14,15] Under Staudinger reaction conditions[16] (PPh_3, THF–H_2O), azide **16** was reduced to the primary amine, which was directly acylated with acryloyl chloride in the present of Et_3N to give **4** in 50% yield over two steps. The substituted α,β-unsaturated lactam **17** was generated by ring-closing metathesis (RCM)[17] utilizing Hoveyda second-generation Grubbs catalyst, in 25% yield (60% recovery of material, 40% brsm).[18] In this process, other Grubbs catalysts were also examined, but the yields were low. Methylation (NaH, MeI) of **17**, followed by radical cyclization with Bu_3SnH in the presence of AIBN in benzene at reflux, led to aryl radical cyclization[19] and the exclusive formation of 6-*exo* cyclization product **18** in 87% yield.[20] Upon reduction and subsequent demethylation, (–)-9-*epi*-metazocine (**2b**)[21] was obtained in 90% yield over two steps.

In conclusion, we have finished the total synthesis of (–)-9-*epi*-metazocine (**2b**) using an Evans *syn* aldol reaction, ring-closing metathesis, and radical cyclization as key steps. The benzylic quaternary carbon center was established through intramolecular radical cyclization with high stereoselectivity.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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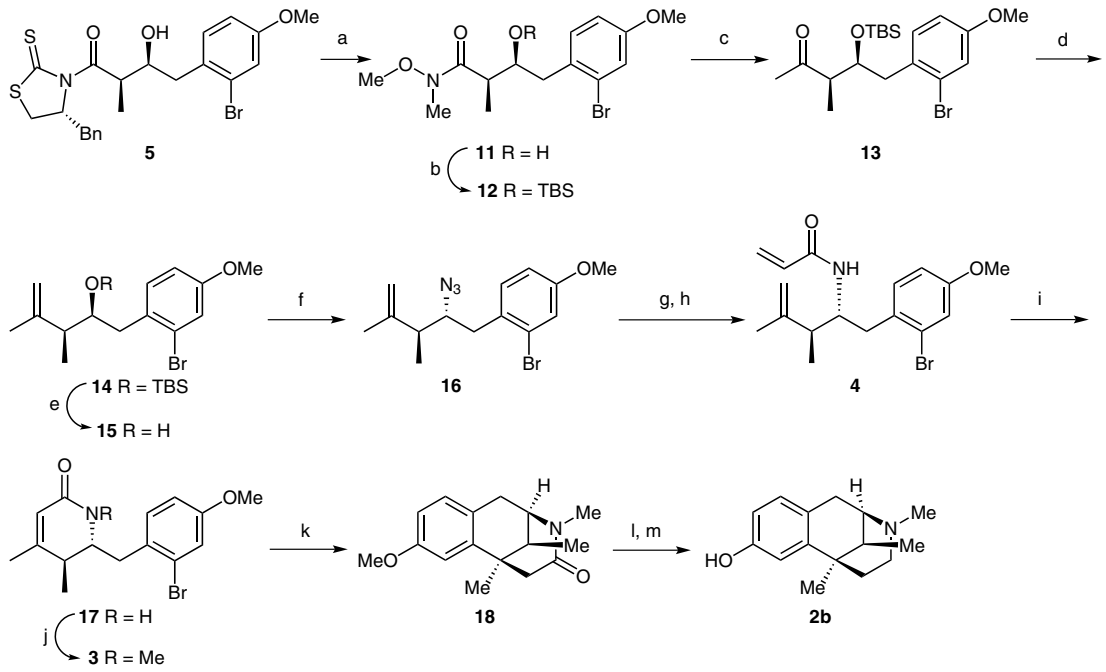

Scheme 3 *Reagents and conditions*: (a) MeO(H)NMe·HCl, Imidazole, CH_2Cl_2, r.t., 90%; (b) TBSCl, Imidazole, DMF, r.t., 95%; (c) MeMgI, THF, 0 °C, 92%; (d) $MePPh_3I$, *n*-BuLi, THF, 0 °C, 85%; (e) TBAF·$3H_2O$, THF, r.t., 84%; (f) PPh_3, DIAD, DPPA, THF, 0 °C, 80%; (g) PPh_3, H_2O, THF, 45 °C; (h) acryloyl chloride, Et_3N, CH_2Cl_2, 0 °C, 50% for two steps; (i) Hoveyda–Grubbs II (8 mol%), CH_2Cl_2, reflux, 40% (brsm); (j) NaH, MeI, r.t., 90%; (k) Bu_3SnH, AIBN, benzene, reflux, 87%; (l) $LiAlH_4$, THF, reflux; (m) BBr_3, CH_2Cl_2, 90% for two steps.

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(12) **Compound 5**: To a solution of thiazolidinethione propionate **7** (4.27 g, 16.1 mmol) in CH_2Cl_2 (100 mL) at 0 °C, was added $TiCl_4$ (1.86 mL, 16.9 mmol); a characteristic orange slurry formed. After 10 min, (–)-sparteine (3.78 g, 16.1 mmol) was added, and the color changed to a deep red. After stirring for 30 min, the mixture was cooled to –78 °C, *N*-methylpyrrolidinone (NMP; 1.6 mL, 16.1 mmol) was added and the mixture was stirred for an additional 10 min. Aldehyde **6** (4.06 g, 17.7 mmol) in CH_2Cl_2 (20 mL) was added and the mixture was stirred at –78 °C for 1 h. After a further 2.5 hours stirring at 0 °C, the reaction was quenched with sat. NH_4Cl. After separation of layers, the aqueous layer was further extracted with CH_2Cl_2 (2 × 30 mL) and the combined organic extract was dried over anhydrous Na_2SO_4 and evaporated in vacuo. The residue was purified by chromatography (petroleum ether–EtOAc, 10:1) to afford **5** (6.0 g, 76%) as yellow liquid; $[\alpha]_D^{18}$ –79.3 (*c* 2.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.37–7.33 (m, 2 H), 7.29–7.27 (m, 3 H), 7.19 (d, *J* = 8.4 Hz, 1 H), 7.11 (d, *J* = 2.8 Hz, 1 H), 6.82 (dd, *J* = 2.4, 8.4 Hz, 1 H), 5.37–5.31 (m, 1 H), 4.62–4.56 (m, 1 H), 4.24 (br s, 1 H), 3.77 (s, 3 H), 3.37 (dd, *J* = 6.8, 11.2 Hz, 1 H), 3.21 (dd, *J* = 3.6, 13.2 Hz, 1 H), 3.07–3.00 (m, 1 H), 2.90–2.86 (m, 3 H), 1.38 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 201.0, 177.6, 158.8, 136.3, 131.9, 129.3, 129.2, 128.8, 127.1, 124.9, 118.0, 113.5, 71.9, 68.6, 55.4, 42.7, 39.6, 36.7, 31.9, 10.8; HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{22}H_{25}BrNO_3S_2$: 494.0454; found: 494.0463.

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(15) **Compound 16**: To a solution of alcohol **15** (0.68 g, 2.3 mmol) in THF (30 mL) was added Ph_3P (0.65 g, 2.5 mmol), DIAD (0.51 g, 2.5 mmol), and diphenylphosphoryl azide (0.96 g, 2.7 mmol) at 0 °C and stirring was continued for 12 h. The solvent was removed in vacuo and the residue was purified by chromatography (petroleum ether–EtOAc,100:1) to afford **16** (0.6 g, 80%) as a colorless liquid; $[\alpha]_D^{18}$ +74.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.21 (d, *J* = 8.4 Hz, 1 H), 7.12 (d, *J* = 2.8 Hz, 1 H), 6.84 (dd, *J* = 2.8, 8.4 Hz, 1 H), 4.91 (s, 1 H), 4.90 (s, 1 H), 3.80 (s, 3 H), 3.62–3.57 (m, 1 H), 3.12 (dd, *J* = 2.8, 14.0 Hz, 1 H), 2.58 (dd, *J* = 10.8, 14.4 Hz, 1 H), 2.52–2.45 (m, 1 H), 1.81 (s, 3 H), 1.22 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 159.0, 146.3, 132.3, 129.5, 124.5, 118.0, 113.6, 112.7, 65.5, 55.5, 45.7, 37.6, 20.0, 16.1; IR: 3366, 2961, 2925, 2853, 2102, 1604, 1492, 1243, 1034 cm^{-1}; HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{19}BrN_3O$: 324.0706; found: 324.0718.

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(19) **Compound 17**: To a stirred solution of **4** (200 mg, 0.57 mmol) in CH_2Cl_2 (60 mL) Hoveyda–Grubbs II (28 mg, 0.045 mmol, 8 mol%) was added under an argon atmosphere. The mixture was heated at reflux for 24 h, then the solvent was removed in vacuum and the residue was purified by chromatography (EtOAc) to afford **17** (46 mg, 25%) as a colorless solid; $[\alpha]_D^{16}$ +172 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.11 (d, *J* = 2.4 Hz, 1 H), 7.03 (d, *J* = 8.8 Hz, 1 H), 6.81 (dd, *J* = 2.4, 8.8 Hz, 1 H), 5.71 (s, 1 H), 5.49 (s, 1 H), 3.78 (s, 3 H), 3.50–3.45 (m, 1 H), 2.96–2.84 (m, 2 H), 2.18 (q, *J* = 6.8 Hz, 1 H), 1.96 (s, 3 H), 1.19 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 165.2, 159.0, 156.0, 132.0, 128.8, 124.8, 118.8, 118.4, 113.7, 55.6, 55.5, 40.6, 37.6, 22.0, 17.7; IR: 3242, 2965, 2929, 2866, 1675, 1606, 1492, 1241, 1031 cm^{-1}; HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{19}BrNO_2$: 324.0594; found: 324.0596.

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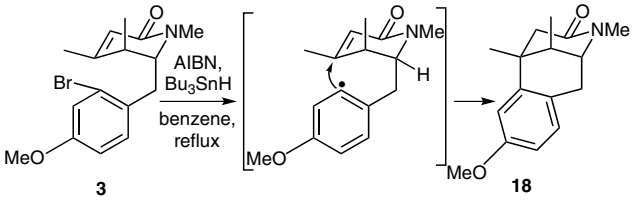
(21) Preparation of compound **18** (Scheme 4): To a solution of **3** (43 mg, 0.12 mmol) in benzene (10 mL) at reflux, was added dropwise a solution of Bu_3SnH (51 mg, 0.18 mmol) and AIBN (30 mg, 0.18 mmol) in benzene (10 mL) over 1 h by using a syringe. The mixture was then heated at reflux for 3 h. After evaporation of the solvent, the residue was purified by chromatography on silica gel (hexane–EtOAc, 2:1) to give **18** (27 mg, 87%); $[\alpha]_D^{22}$ –77 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 6.96 (d, *J* = 8.0 Hz, 1 H), 6.90 (d, *J* = 2.4 Hz, 1 H), 6.72 (dd, *J* = 2.4, 8.0 Hz, 1 H), 3.78 (s, 3 H), 3.53 (s, 1 H), 2.96 (s, 2 H), 2.93 (s, 3 H), 2.48 (d, *J* = 17.6 Hz, 1 H), 2.30 (d, *J* = 19.2 Hz, 1 H), 2.04 (q, *J* = 6.8 Hz, 1 H), 1.38 (s, 3 H), 1.19 (d, *J* = 7.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 169.0, 158.6, 145.3, 130.6, 123.7, 112.4, 111.5, 61.0, 55.3, 43.4, 36.9, 36.9, 34.2,

33.8, 24.1, 14.4; HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{22}NO_2$: 260.1645; found: 260.1657.



Scheme 4

(22) **(–)-9-*epi*-metazocine (2b)**: $[\alpha]_D^{17}$ +22.0 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 6.95 (d, *J* = 8.0 Hz, 1 H), 6.80 (d, *J* = 2.4 Hz, 1 H), 6.61 (dd, *J* = 2.4, 8.0 Hz, 1 H), 3.13 (d, *J* = 17.6 Hz, 1 H), 2.92 (d, *J* = 5.6 Hz, 1 H), 2.67 (dd, *J* = 5.6, 17.6 Hz, 1 H), 2.44 (d, *J* = 6.8 Hz, 1 H), 2.36 (s, 3 H), 2.03 (d, *J* = 8.4 Hz, 2 H), 1.88 (q, *J* = 6.8 Hz, 1 H), 1.29 (s, 3 H), 1.26 (d, *J* = 7.2 Hz, 3 H), 1.10 (d, *J* = 9.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 154.1, 146.4, 129.1, 128.6, 113.0, 111.5, 60.1, 47.6, 43.0, 38.2, 34.9, 34.8, 27.3, 24.0, 15.0; IR: 3254, 2932, 2865, 1610, 1496, 1485, 1360, 769 cm^{-1}; HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{22}NO$: 232.1696; found: 232.1692.

