An enantioselective approach to (+)-laurencin

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A convergent enantioselective route to an advanced intermediate for the synthesis of the marine natural product (+)-laurencin has been developed. The methodology employs ring-opening of an ephedrine-based spiro-epoxide with a chiral secondary alcohol, hemiacetal allylation and ring closing metathesis as the key steps for elaboration of the functionalized medium-ring ether moiety in laurencin.

Introduction

The stereoselective construction of medium-sized oxacycles[1] continues to be an area of active interest and target-oriented[2] as well as general[3] strategies for assembling such ring systems have been extensively investigated in recent years. In particular, medium-ring ether containing marine natural products[4] isolated from red algae have attracted considerable synthetic effort. The halogenated oxocines laurencin (**1**),[5] laurenyne (**2**)[6] and prelaureatin (**3**)[7] (Fig. 1) are representative examples of the impressive array of red algae metabolites that have been the focus of intense synthetic investigations in recent years. Above all, the synthesis of laurencin has served to showcase new methodology for the stereoselective construction of substituted eight-membered oxacycles and several successful strategies targeting laurencin have been reported.[8] Herein, we describe a concise and enantioselective formal synthesis of laurencin.

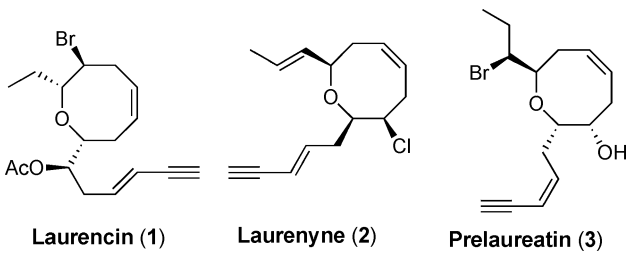

Fig. 1 Medium-ring ether containing halogenated marine natural products.

Results and discussion

For the purposes of this investigation, we chose to examine a new route to the α,α′-disubstituted oxocine core of laurencin. Specifically, we targeted the ketone (+)-**4** (Fig. 2), which is an advanced intermediate in an earlier approach to laurencin.[8h] At the outset, we reasoned that a direct entry to the α,α′-disubstituted ether motif in **4** could be achieved by an epoxide ring-opening with a secondary alcohol, the oxocine ring system would be accessible by a ring closing metathesis reaction and the ketone

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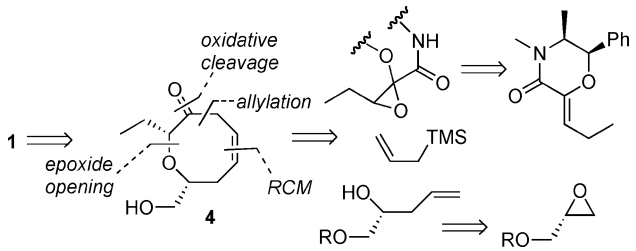
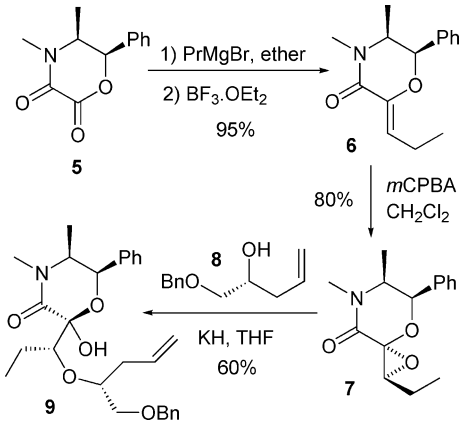


Fig. 2 Retrosynthetic strategy for laurencin intermediate (+)-**4**.

could be derived from an aminoalcohol (Fig. 2). The proposed disconnections appeared to suit our methodology based on ephedrine-derived templates.[9] Consequently, an ephedrine-derived alkylidene morpholinone was identified as a precursor to a chiral epoxide intermediate while a glycidol derivative seemed suitable for obtaining the required secondary alcohol (Fig. 2).

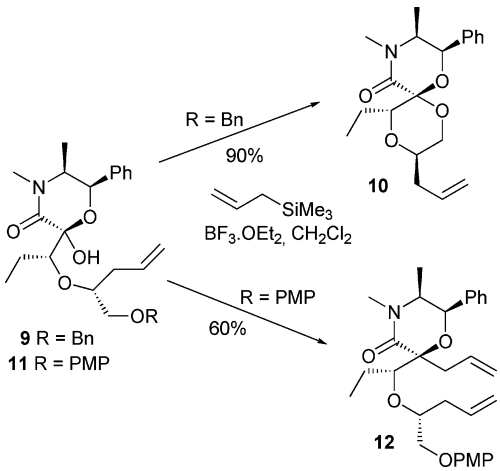
Our approach to the functionalized oxocine core in laurencin begins with the morpholine-dione **5**[10] which is readily prepared (85%) from commercially available (1*R*,2*S*)-ephedrine hydrochloride and ethyloxalyl chloride. Treatment of **5** with propylmagnesium bromide and dehydration of the resulting hemiacetal cleanly generated the alkylidene morpholinone **6**[11] (95%, Scheme 1). Reaction of **6** with *m*CPBA provided the epoxide **7** (85%) as a single diastereomer, which was stable to chromatography. At this stage, the stereochemistry of **7** was assigned by analogy to the epoxidation of a similar substrate.[9a] While the ring opening of substituted epoxides[12] with secondary alkoxides is uncommon, it was gratifying to see that epoxide **7** reacted with the potassium salt of alcohol **8**[13] to furnish the hemiacetal **9** (60%). This key step assembled the two stereocenters adjacent to the oxygen in the oxocine core of laurencin (Scheme 1).

We anticipated that allylation of the hemiacetal in **9** would provide the diene precursor for the required oxocine. However, subjecting **9** to BF_3 etherate–allyltrimethylsilane provided the spiro-acetal **10** (90%, Scheme 2) and only a trace of the allylation product. Changing the Lewis acid to $TiCl_4$ was not beneficial and provided debenzylated **9** as the only isolable product in low yield. The spiro-acetal **10** could not be allylated under these conditions. Clearly, the benzyl ether in **9** was unsuitable for the required transformation and an alternative was necessary. We chose to employ the *p*-methoxyphenyl (PMP) protecting group which was expected to be relatively unreactive under the allylation conditions. Accordingly, the hemiacetal **11** was prepared from epoxide **7**



Scheme 1

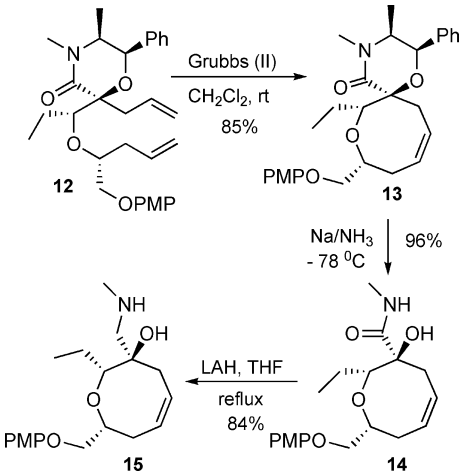
and the potassium salt of (*R*)-1-(4-methoxyphenoxy)-3-buten-2-ol[14] following the procedure for **9**. As projected, allylation of **11** proceeded smoothly to provide the diene **12** (60%, Scheme 2) as a single diastereomer.



Scheme 2

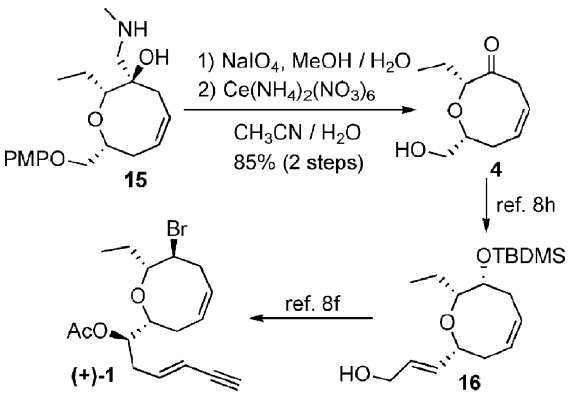
Medium-ring ether construction from the diene **12** was readily achieved by ring closing metathesis with the Grubbs(II) catalyst at ambient temperature and the spiro-oxocine **13** was obtained in good yield (85%). Attention to experimental detail was necessary in the following step. Normally, removal of the ephedrine portion in morpholinones such as **13** is readily effected with dissolving metal reduction (Na–NH_3).[9] In the present case, competing, albeit slow reduction of the *p*-methoxyphenyl protecting group was a distinct possibility. Indeed, we observed that benzylic C–O bond cleavage was faster than reduction of the *p*-methoxyphenyl group and a rapid quenching of the reaction (1 min) provided the hydroxy amide **14** in excellent yield (96%, Scheme 3). Longer reaction times resulted in partial reduction of the *p*-methoxyphenyl protecting group as well. Reduction of **14** with LAH provided the amino alcohol **15** (84%).

The target ketone (+)-**4** was readily prepared from the amino alcohol **15** by treatment with $NaIO_4$ (98%) followed by removal of the *p*-methoxyphenyl protection with ceric ammonium nitrate (87%). Ketone **4** provided spectroscopic data that was in agreement with that reported[8h] in the literature and has previously been



Scheme 3

converted[8h] to oxocine **16**[8f] which is an advanced intermediate in the total synthesis of (+)-laurencin (Scheme 4).



Scheme 4

Conclusion

In conclusion, we have established an efficient enantioselective route to an advanced intermediate in the synthesis of (+)-laurencin. The present route is shorter (10 steps) and provides **4** in higher overall yield (11.3%) compared to the reported synthesis[8h] (21 steps, 4.3% overall yield from commercially available starting materials). A notable advantage of the methodology is the ready availability of both enantiomers of ephedrine and glycidol. This should enable the assembly of all possible stereoisomers of disubstituted oxocines such as **4** to provide access to analogues of laurencin and its congeners.

Experimental section

General

All reactions requiring anhydrous conditions were performed under a positive pressure of nitrogen using oven-dried glassware (120 °C) that was cooled under nitrogen. THF was distilled from sodium benzophenone ketyl and dichloromethane was distilled from calcium hydride. Commercial precoated silica gel (Merck 60F-254) plates were used for TLC. Silica gel for column chromatography was 230–400 mesh. All melting points are

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uncorrected. IR spectra were recorded on a Bruker TENSOR 27 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AVANCE-500 instrument. Coupling constants (J) are given in Hz. Mass spectra were obtained on an Agilent 1100 series LC/MSD chromatographic system. High-resolution mass spectra were obtained on a Waters GCT Premier Micromass mass spectrometer. Optical rotations were measured at the sodium D line on a JASCO-DIP 370 digital polarimeter at ambient temperature.

(5*S*,6*R*)-4,5-Dimethyl-6-phenyl-morpholin-2,3-dione (5). To a cold (0 °C), stirred solution of (1*R*,2*S*)-(−)-ephedrine hydrochloride (10 g, 0.05 mol) in dichloromethane (40 mL) was added DMAP (0.3 g, 2.5 mmol). Triethylamine (21.1 mL, 0.15 mol) was added, followed by dropwise addition of ethyloxalyl chloride (6.7 mL, 0.06 mol). The mixture was stirred at 0 °C for 1 h and then at ambient temperature for 48 h. Cold water was added and the mixture was extracted with dichloromethane (3 × 50 mL). The combined organic layers were washed with HCl (2 M, 3 × 25 mL), dried (Na_2SO_4) and concentrated under reduced pressure to yield a pale yellow solid. This was triturated with dichloromethane–hexane (7 : 2, 3 × 15 mL) to provide 9.3 g (85%) of the dione as a crystalline white solid that was pure by ^{1}H NMR. This material was used without further purification. If necessary, it can be recrystallized from ethyl acetate–hexane. Mp: 183–184 °C; $[\alpha]_D^{23} = -202$ (c 1, $CHCl_3$); spectroscopic data consistent with that reported in the literature.[10b]

(2*S*,3*S*,5*R*,6*S*)-2-Ethyl-6,7-dimethyl-5-phenyl-1,4-dioxa-7-azaspiro[2.5]octan-8-one (7). To a solution of **6**[9b] (2 g, 8.2 mmol) in dichloromethane (30 mL) was added *m*CPBA (1.83 g, 10.6 mmol) at −78 °C and the mixture was warmed to ambient temperature and stirred for 40 min. Saturated aqueous $NaHCO_3$ was added, the mixture was extracted with ethyl acetate (3 × 20 mL) and the combined organic layers were dried and concentrated under reduced pressure. The residue obtained was immediately subjected to purification by flash chromatography on silica gel (3 : 1 ethyl acetate–hexane) to give 1.7 g (80%) of **7** as a colourless gum. IR (neat): 2976, 1669, 1294, 1195, 930, 700 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39–7.36 (m, 2H), 7.33–7.27 (m, 3H), 5.47 (d, 1H, $J = 3$), 3.69 (t, 1H, $J = 6.5$), 3.65 (dq, 1H, $J = 3$, 6.5), 3.11 (s, 3H), 1.91–1.80 (m, 2H), 1.12 (t, 3H, $J = 7.5$), 1.03 (d, 3H, $J = 6.5$); ^{13}C NMR (125.77 MHz, $CDCl_3$): δ 163.6, 136.7, 128.7, 128.2, 125.5, 82.2, 76.03, 63.5, 59.4, 34.0, 21.0, 12.5, 10.3; $[\alpha]_D^{23} = -115.5$ (c 2, $CHCl_3$); MS (APCI): 262.1 (M + 1, 100); HRMS (CI): m/z 262.1451 (262.1443 calc. for $C_{15}H_{20}NO_3$, M + H).

(2*S*,5*S*,6*R*)-2-((*R*)-1-((*R*)-1-(Benzyloxy)pent-4-en-2-yloxy)propyl)-2-hydroxy-4,5-dimethyl-6-phenylmorpholin-3-one (9). To a solution of the alcohol **8** (0.88 g, 4.2 mmol) in THF (20 mL) at 0 °C was added KH (252 mg (obtained by washing a 30 wt% dispersion in mineral oil with hexane), 6.3 mmol, as a suspension in THF (2 mL)). The mixture was then stirred for 10 min at 0 °C and a solution of the epoxide **7** (1.1 g, 4.2 mmol) in THF (5 mL) was added. The reaction mixture was then warmed up to ambient temperature, stirred for 4.5 h, cold water (10 mL) was added, and the mixture was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (2 : 1 ethyl acetate–hexane) to provide 1 g (50%) of **9** as a yellow oil. IR (neat): 3326, 2976, 1739, 1636, 1242, 1086 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36–7.22 (m, 10H), 5.85–5.78 (m, 1H), 5.44 (d, 1H, $J = 2.7$), 5.08–5.02 (m, 2H), 4.90 (br s, 1H), 4.59–4.50 (AB, 2H, $J = 12.1$), 3.86–3.82 (m, 1H), 3.67–3.64 (m, 1H), 3.52–3.49 (m, 1H), 3.43–3.38 (m, 2H), 2.94 (s, 3H), 2.36–2.34 (m, 2H), 1.92–1.87 (m, 1H), 1.71–1.65 (m, 1H), 1.11 (t, 3H, $J = 7.3$), 0.98 (d, 3H, $J = 7$); ^{13}C NMR (125.77 MHz, $CDCl_3$): δ 168.3, 138.3, 137.8, 134.5, 128.5, 128.4, 127.9, 127.8, 127.7, 126, 117.5, 98.4, 83.9, 79.1, 73.6, 72.5, 72, 59.4, 37, 33.5, 23.2, 12.3, 11.6; $[\alpha]_D^{23} = -105.6$ (c 1, $CHCl_3$); MS (APCI): 454.2 (M + 1, 100); HRMS (EI): m/z 453.2509 (453.2515 calc. for $C_{27}H_{35}NO_5$, M+).

(3*R*,5*R*,6*S*,8*R*,9*S*)-3-Allyl-9,10-dimethyl-5-ethyl-8-phenyl-1,4,7-trioxa-10-azaspiro[5.5]undecan-11-one (10). To a solution of **9** (320 mg, 0.7 mmol) in dichloromethane (15 mL) at −78 °C was added allyltrimethylsilane (0.67 mL, 4.2 mmol) followed by BF_3 etherate (0.52 mL, 4.2 mmol). The mixture was stirred at −78 °C for 15 min and then warmed to ambient temperature and stirred for 22 h. Cold water was added and the mixture was extracted with dichloromethane (3 × 25 mL). The combined organic layers were dried and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (1 : 3 ethyl acetate–hexane) to provide 220 mg (90%) of **10** as a colourless oil. IR (neat): 2925, 1663, 1496, 1042, 700 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40–7.36 (m, 3H), 7.34–7.31 (m, 1H), 5.89–5.83 (m, 1H), 5.21 (d, 1H, $J = 2.3$), 5.16–5.07 (m, 2H), 4.21 (dd, 1H, $J = 7.3$, 5.5), 4.05–4.00 (apparent t, 1H, $J = 10$), 3.88–3.82 (m, 1H), 3.67 (dd, 1H, $J = 11.2$, 2.7), 3.46 (dq, 1H, $J = 13.2$, 3), 3.07 (s, 3H), 2.40–2.34 (m, 1H), 2.22–2.16 (m, 1H), 1.55–1.49 (m, 2H), 1.12 (d, 3H, $J = 5.9$), 0.98 (t, $J = 7.3$, 3H); ^{13}C NMR (125.77 MHz, $CDCl_3$): δ 165.1, 138, 133.8, 128.6, 128.1, 126.1, 117.3, 95.32, 80.5, 78.0, 74.7, 64.6, 59.4, 36.3, 34.1, 23.3, 12.3, 10.3; $[\alpha]_D^{23} = -45.9$ (c 1, $CHCl_3$); MS (APCI): 346.3 (M + 1, 100); HRMS (EI): m/z 345.1940 (345.1940 calc. for $C_{20}H_{27}NO_4$, M+).

(2*S*,5*S*,6*R*)-2-((*R*)-1-((*R*)-1-(4-Methoxyphenoxy)pent-4-en-2-yloxy)propyl)-2-hydroxy-4,5-dimethyl-6 phenylmorpholin-3-one (11). To a solution of (*R*)-1-(4-methoxyphenoxy)-3-buten-2-ol[14] (0.70 g, 3.6 mmol) in THF (18 mL) at 0 °C was added KH (252 mg, 6.3 mmol). The mixture was then stirred for 10 min at 0 °C and a solution of the epoxide **7** (0.80 g, 3.1 mmol) in THF (5 mL) was added. The reaction mixture was then warmed up to ambient temperature, stirred for 4.5 h, cold water (10 mL) was added, and the mixture was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (2 : 1 ethyl acetate–hexane) to provide 0.73 g (50%) of **11** as a yellow oil. IR (neat): 3327, 2936, 1633, 1507, 1230, 756 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37–7.31 (m, 4H), 7.30–7.26 (m, 1H), 6.85–6.81 (m, 4H), 5.82–5.74 (m, 1H), 5.40 (br s, 1H), 5.09–5.02 (m, 2H), 3.95–3.91 (m, 3H), 3.87–3.84 (m, 1H), 3.75 (s, 3H), 3.47 (dq, 1H, $J = 6$, 2.5), 3.06 (s, 3H), 2.42–2.32 (m, 2H), 2.03–1.97 (m, 1H), 1.85–1.79 (m, 1H), 1.10 (t, 3H, $J = 8$), 1.08 (d, 3H, $J = 7$). ^{13}C NMR (125.77 MHz, $CDCl_3$): δ 169, 154.0, 153.3, 137.7, 134.4, 128.5, 127.9, 126.1, 117.9, 115.7, 114.8, 98.6, 83.3, 78.0, 72.8, 69.9, 59.9, 55.9, 36.5, 33.9, 22.3, 12.4, 11.2; $[\alpha]_D^{23} = -60$ (c 1, $CHCl_3$); MS (APCI): 470.2 (M + 1, 100); HRMS (EI): m/z 469.2467 (469.2464 calc. for $C_{27}H_{35}NO_6$, M+).

(2*S*,5*S*,6*R*)-2-Allyl-((*R*)-1-((*R*)-1-(4-Methoxyphenoxy)pent-4-en-2-yloxy)propyl)-4,5-dimethyl-6-phenylmorpholin-3-one (12). To a solution of **11** (660 mg, 1.4 mmol) in dichloromethane (15 mL) at −78 °C was added allyltrimethylsilane (1.4 mL, 8.5 mmol) followed by BF_3 etherate (1.1 mL, 8.5 mmol). The mixture was stirred at −78 °C for 15 min and then warmed to ambient temperature and stirred for 18 h. Cold water was added and the mixture was extracted with dichloromethane (3 × 25 mL). The combined organic layers were dried and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (1 : 3 ethyl acetate–hexane) to provide 232 mg (60%) of **12** as a colourless oil. IR (neat): 2934, 1643, 1508, 1230, 1043, 823 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.36–7.32 (m, 3H), 7.29–7.26 (m, 2H), 6.85–6.80 (m, 4H), 6.04–5.95 (m, 1H), 5.83–5.75 (m, 1H), 5.31 (d, 1H, $J = 3.5$), 5.11–5.01 (m, 4H), 3.96–3.90 (m, 3H), 3.83 (m, 1H), 3.76 (s, 3H), 3.43 (dq, 1H, $J = 3.5, 7$), 3.05 (s, 3H), 2.68 (dd, 1H, $J = 14, 7.5$), 2.59 (dd, 1H, $J = 14, 7.5$), 2.40–2.37 (m, 2H), 1.95–1.88 (m, 1H), 1.87–1.78 (m, 1H), 1.09 (t, 3H, $J = 7$), 1.06 (d, 3H, $J = 7$); ^{13}C NMR (125.77 MHz, $CDCl_3$): δ 170.2, 154.0, 153.4, 138.8, 134.6, 134.5, 128.4, 127.6, 126.1, 117.9, 117.6, 115.7, 114.8, 85.4, 84.0, 77.4, 73.7, 69.8, 59.7, 55.9, 41.4, 36.2, 34.0, 22.8, 12.7, 11.3; $[a]_D^{23} = -63$ (*c* 1, $CHCl_3$); MS (APCI): 494.2 (M + 1, 100); HRMS (EI): *m/z* 493.2824 (493.2828 calc. for $C_{30}H_{39}NO_5$, M+).

(2*R*,3*S*,6*S*,7*R*,9*R*,11*Z*)-3,4-Dimethyl-7-ethyl-9((4-methoxyphenoxy)methyl)-2-phenyl-1,8-dioxa-4-azaspiro[5.7]tridec-11-en-5-one (13). To a solution of **12** (350 mg, 0.5 mmol) in dichloromethane (290 mL) was added the Grubbs(II) catalyst (43 mg, 0.05 mmol, 10 mol%). The reaction mixture was stirred at room temperature for 28 h and the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel (1 : 1 ethyl acetate–hexane) to give 280 mg (85%) of **13** as a white solid. Mp: 67–69 °C; IR (neat): 2958, 1646, 1507, 1230, 823 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.41–7.35 (m, 2H), 7.33–7.31 (m, 3H), 6.86–6.82 (m, 4H), 6.02–5.97 (m, 1H), 5.62–5.59 (m, 1H), 5.28 (d, 1H, $J = 3$), 4.19 (dd, 1H, $J = 9, 5$), 3.86 (dd, 1H, $J = 9, 7.5$), 3.77 (s, 3H), 3.74–3.72 (m, 1H), 3.56–3.52 (m, 2H), 3.32 (dd, 1H, $J = 13, 5.5$), 3.01 (s, 3H), 2.68 (dd, 1H, $J = 13, 5.5$), 2.51–2.47 (m, 1H), 2.43–2.38 (m, 1H), 1.78–1.75 (m, 1H), 1.42–1.37 (m, 1H), 1.10 (t, 3H, $J = 7.5$), 0.96 (d, 3H, $J = 7$); ^{13}C NMR (125.77 MHz, $CDCl_3$): δ 170.3, 154.0, 153.1, 138.1, 130.2, 128.7, 128.6, 127.8, 125.7, 115.4, 115.0, 87.7, 85.7, 83.4, 72.0, 71.5, 58.9, 56.0, 33.6, 32.1, 30.0, 24.9, 13.0, 11.3; $[a]_D^{23} = +13.5$ (*c* 1, $CHCl_3$); MS (APCI): 466.2 (M + 1, 100); HRMS (EI): *m/z* 465.2524 (465.2515 calc. for $C_{28}H_{35}NO_5$, M+).

(2*R*,3*S*,5*Z*,8*R*)-2-Ethyl-8-((4-methoxyphenoxy)methyl)-3,4,7,8-tetrahydro-3-hydroxy-*N*-methyl-2*H*-oxocine-3-carboxamide (14). To anhydrous liquid ammonia (15 mL, distilled over sodium) was added Na metal (87 mg, 3.8 mmol) at −78 °C and the mixture was stirred for 15 min. To the resulting blue solution was added rapidly a solution of **13** (250 mg, 0.54 mmol) in anhydrous THF (3 mL) and the mixture was stirred for 1 min. A mixture of methanol–water (3 : 1, 5 mL) was added and the reaction mixture was brought to ambient temperature and stirred for 30 min to remove ammonia. The resulting solution was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (ethyl acetate) to provide 180 mg (96%) of **14** as a colourless gum. IR (neat): 3392, 2928, 1663, 1507, 1231, 1068, 1035, 824 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 6.88–6.84 (m, 4H), 6.54 (br s, 1H), 6.07–6.02 (m, 1H), 5.91–5.85 (m, 1H), 4.27 (s, 1H), 4.03 (dd, 1H, $J = 5, 9.5$), 3.95 (dd, 1H, $J = 4.5, 9.5$), 3.85–3.81 (m, 1H), 3.78 (s, 3H), 3.63 (m, 1H), 2.85 (d, 3H, $J = 4$), 2.85–2.82 (m, 1H), 2.57–2.51 (m, 1H), 2.35–2.31 (m, 1H), 2.26–2.22 (m, 1H), 1.68–1.63 (m, 1H), 1.16–1.08 (m, 1H), 1.01 (t, 3H, $J = 7$); ^{13}C NMR (125.77 MHz, $CDCl_3$): δ 176.3, 154.2, 153.2, 129.7, 129.4, 115.6, 115.0, 84.1, 82.3, 79.1, 71.9, 56.0, 37.8, 31.4, 26.7, 23.6, 10.9; $[a]_D^{23} = +27$ (*c* 1, $CHCl_3$); MS (APCI): 350.1 (M + 1, 100); HRMS (EI): *m/z* 349.1897 (349.1889 calc. for $C_{19}H_{27}NO_5$, M+).

(2*R*,3*S*,5*Z*,8*R*)-8-((4-Methoxyphenoxy)methyl)-2-ethyl-3,4,7,8-tetrahydro-3-((methylamino)methyl)-2*H*-oxocin-3-ol (15). To a stirred solution of **14** (180 mg, 0.52 mmol) in THF (10 mL) at 0 °C was slowly added lithium aluminium hydride (157 mg, 4.1 mmol). The mixture was then brought to room temperature and heated to reflux for 50 h. The reaction mixture was then cooled to room temperature and 3 N HCl (5 mL) was added. The resulting solution was washed with ethyl acetate (2 × 15 mL). The aqueous layer was cooled (<5 °C), basified (pH = 10) with 6 N sodium hydroxide and concentrated under reduced pressure. The residual solids were extracted with ethyl acetate (5 × 15 mL) and the combined organic layers were dried and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (1 : 3 ethyl acetate–hexane) to provide 145 mg (84%) of **15** as a colourless oil. IR (neat): 2930, 1737, 1507, 1231, 1039, 823 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 6.85–6.81 (m, 4H), 5.98–5.93 (m, 1H), 5.89–5.84 (m, 1H), 3.99 (m, 1H), 3.77–3.75 (m, 2H), 3.72 (s, 3H), 3.50 (dd, 1H, $J = 1.1, 10.8$), 2.70 (d, 1H, $J = 13$), 2.69 (m, 1H), 2.58 (d, 1H, $J = 13$), 2.46 (s, 3H), 2.38–2.27 (m, 2H), 2.14 (dd, 1H, $J = 12.5, 6.5$), 1.69–1.65 (m, 1H), 1.27–1.19 (m, 1H), 1.04 (t, 3H, $J = 7$); ^{13}C NMR (125.77 MHz, $CDCl_3$): δ 154.0, 153.2, 130.1, 129.2, 115.5, 114.8, 85.4, 80.6, 76.9, 71.7, 56.5, 55.9, 37.7, 36.6, 31.4, 24.0, 11.4; $[a]_D^{23} = +85$ (*c* 1, $CHCl_3$); MS (APCI): 336.2 (M + 1, 100); HRMS (CI): *m/z* 336.2193 (336.2175 calc. for $C_{19}H_{30}NO_4$, M + H).

(2*R*,5*Z*,8*R*)-2-Ethyl-7,8-dihydro-8-(hydroxymethyl)-2*H*-oxocin-3(4*H*)-one (4). [8h]To a stirred solution of **15** (100 mg, 0.3 mmol) in a mixture of methanol–water (100 : 1, 4 mL) at 0 °C was added $NaIO_4$ (255 mg, 1.2 mmol). The reaction mixture was maintained at this temperature for 15 min and then warmed to room temperature and stirred for 2.5 h. A cold saturated aqueous solution of sodium bicarbonate was added and the mixture was extracted with ethyl acetate (3 × 15 mL). The combined organic layers were dried (sodium sulfate) and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (1 : 3 ethyl acetate–hexane) to provide 85 mg (98%) of the ketone as a colourless gum. IR (neat): 2930, 1715, 1508, 1231, 1044, 823 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 6.87–6.83 (m, 4H), 5.89–5.84 (m, 1H), 5.71–5.66 (m, 1H), 4.06 (dd, 1H, $J = 9.1, 5.9$), 3.97–3.90 (m, 2H), 3.82–3.78 (m, 2H), 3.78 (s, 3H), 2.82 (dd, 1H, $J = 12, 4.5$), 2.45 (dd, 2H, $J = 7.1, 4.5$), 1.79–1.73 (m, 1H), 1.63–1.57 (m, 1H), 1.02 (t, 3H, $J = 7$); ^{13}C NMR (125.77 MHz, $CDCl_3$): δ 213.8, 154.3, 153.0, 128.4, 126.5, 115.7, 114.9, 87.6, 82.1, 71.1, 56.0, 41.3, 30.4, 26.4, 10.4; $[a]_D^{23} = +513$ (*c* 1, $CHCl_3$); MS (APCI): 291.1 (M + 1, 100) HRMS (CI): *m/z* 290.1519 (290.1518 calc. for $C_{17}H_{22}NO_4$, M+).

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To a stirred solution of the ketone (30 mg, 0.1 mmol) in acetonitrile–water (4 : 1, 2.5 mL) at 0 °C was added ceric ammonium nitrate (164 mg, 0.3 mmol). The resulting orange coloured reaction mixture was stirred at 0 °C for 10 min and then diluted with dichloromethane (10 mL). The aqueous layer was extracted with dichloromethane (2 × 10 mL) and the combined organic layers were dried (sodium sulfate) and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (1 : 2 ethyl acetate–hexane) to provide 20 mg (87%) of **4** as a white solid. Mp: 71–72 °C; IR (solid): 3440, 3026, 1710, 1645, 1095, 1063, 755 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.86–5.81 (m, 1H), 5.68–5.63 (m, 1H), 3.89 (dd, 1H, $J = 12.5, 7.5$), 3.83 (dd, 1H, $J = 8, 4.5$), 3.69–3.62 (m, 2H), 3.60–3.56 (m, 1H), 2.83 (dd, 1H, $J = 12.5, 7.5$), 2.36–2.34 (m, 2H), 2.00 (m, 1H), 1.81–1.74 (m, 1H), 1.73–1.63 (m, 1H), 1.00 (t, 3H, $J = 7.5$); ^{13}C NMR (125.77 MHz, $CDCl_3$): δ 213.2, 128.3, 126.2, 87.0, 84.3, 66.1, 41.2, 30.2, 26.3, 10.2; $[a]_D^{23} = +610$ (*c* 1, $CHCl_3$) (lit.[8h] $[a]_D^{25} = +568$ (*c* 0.81, $CHCl_3$); MS (APCI): 183.1 (M − 1, 100).

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