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Synthetic studies towards the *Lycopodium* alkaloid paniculatine†

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Two bridging tetracyclic products have been observed while attempting to construct the final C-ring of the *Lycopodium* alkaloid, paniculatine, by an intramolecular addition of enolates to unactivated *N*-alkyl pyridinium salts.

Introduction

The addition of enolates and their equivalents to *N*-alkyl pyridinium salts is well documented.[1] Due to the less electrophilic properties of *N*-alkyl pyridinium salts than their *N*-acyl counterparts, and the instability of the resultant dihydropyridine intermediates, electron-withdrawing substituents are usually introduced at the *meta*-position of the pyridine moiety to activate the pyridinium salts and meanwhile to stabilize the products. Not surprisingly, the majority of these studies has been focused on the addition reaction of activated *N*-alkyl pyridinium salts. The examples that involve straightforward addition to unactivated variants are limited especially in the context of natural product synthesis. We report herein the results of our study on the development of a novel approach to paniculatine (Fig. 1), which is based on an intramolecular unactivated *N*-alkyl pyridinium enolate addition reaction.[2]

Paniculatine (**1**) was isolated in 1975 by Castillo and co-workers from *Lycopodium paniculatum*.[3] The same group also reported the isolation of magellanine (**2**) and magellaninone (**3**) (Fig. 1) from *Lycopodium magellanicum*.[3c,4] These three alkaloids possess similar 6-5-5-6 tetracyclic frameworks with 5–7 stereogenic centers, one of which is quaternary. Their unique core structure stimulated interest amongst synthetic chemists. In 1993, Overman *et al.* reported the first total synthesis of (−)-**2** and (+)-**3** *via* a Prins–pinacol rearrangement.[5] In the same year, Paquette and co-workers, by using a tandem Michael–Michael addition, accomplished the total synthesis of (±)-**2** and (±)-**3**.[6] The first total synthesis of (+)-**1** was achieved by Sha's group based on a tandem radical cyclization.[7] The masked Diels–Alder approach to (±)-**2** was completed by Yen and Liao.[8] Using an intramolecular Pauson–Khand protocol,[9] Ishizaki *et al.* completed the formal total synthesis of (±)-**2**. Mukai's group synthesized (+)-**1**, (−)-**2** and (+)-**3** from a common intermediate based on two intramolecular Pauson–Khand reactions.[10] In addition to the completed syntheses, several synthetic studies on the formation of the tetracyclic framework of these alkaloids have been published in the literature.[11]

Results and discussion

A retrosynthetic analysis, as shown in Fig. 2, was proposed. By analogy to Sandham and Meyers' approach,[11d] we envisioned that **1** may be prepared *via* elaboration of the tetracyclic endione **4**, which may also be used as an advanced intermediate for the synthesis of the other two *Lycopodium* alkaloids. Intermediate **4** could in turn arise from *N*-methyl pyridinium salt **5** *via* an intramolecular enolate addition.[2] Two problems need to be addressed for the synthesis of **4**. First, it is unclear which position, either C-3 or C-9, of the pyridine moiety will be the preferred reaction site. It is well established that the *para*-position is attacked preferably by soft enolate nucleophiles in the intermolecular mode,[1] while the intramolecular precedents are rather rare.[2,12] Second, three different enolates (at the C-4, C-6 and C-14 positions of **5**) may be generated during the reaction, there is no guarantee that the

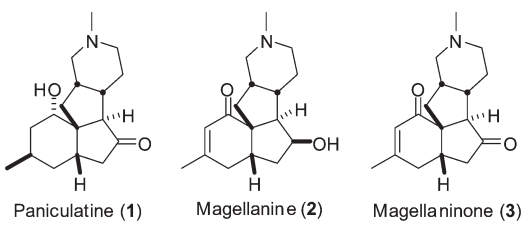

Fig. 1 *Lycopodium* alkaloids.

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† Electronic supplementary information (ESI) available: Copies of ^{1}H and ^{13}C NMR spectra of all new compounds, and X-ray crystallographic data (CIF) for compounds **14**, **17** and **21**·HCl·H_2O are provided. CCDC reference numbers 907561–907563. See DOI: 10.1039/c3ra41467a

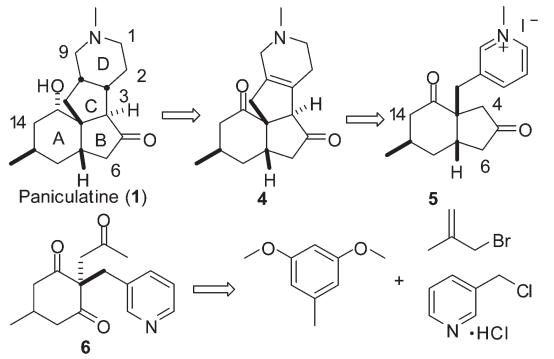


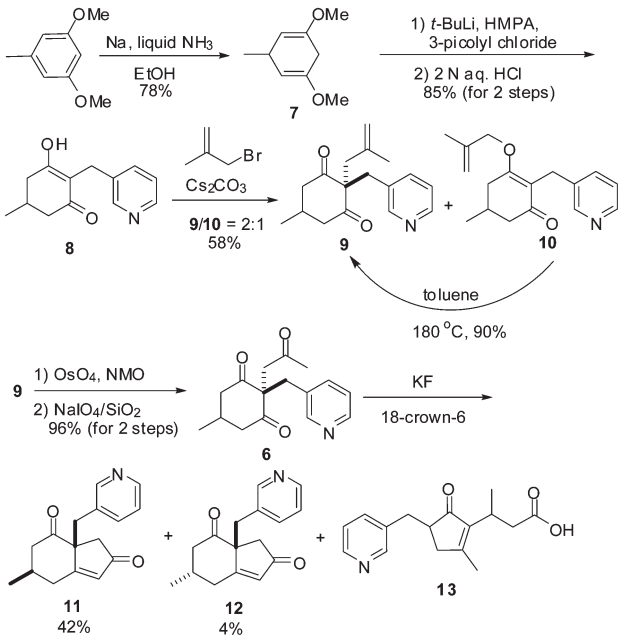
Fig. 2 Retrosynthetic analysis.

desired C-4 enolate addition will be the major one. At this stage, this regioselectivity still remained unclear.[13] *N*-Methyl pyridinium salt **5** may be accessible from triketone **6**, which may be synthesized from commercially available 3,5-dimethoxytoluene, 3-picolyl chloride hydrochloride, and 3-bromo-2-methyl-propene.

In order to test the proposed synthetic plan, intermediate **11** was prepared. As shown in Scheme 1, the synthesis commenced with a Birch reduction of 3,5-dimethoxytoluene to afford 1,5-dimethoxy-3-methyl-1,4-cyclohexadiene **7** in a yield of 78%.[14] Lithiation of **7** with *t*-BuLi in THF at −70 °C, followed by treatment with HMPA, and then with 3-chloromethylpyridine generated from 3-picolyl chloride hydrochloride[15] furnished the alkylated product, which was immediately hydrolyzed with 2 N HCl in THF to give enol ketone **8** in an overall yield of 85%.[14a,16] Next, our attention was turned to the construction of the all-carbon quaternary carbon center. Since direct introduction of a 2-oxopropyl to **8** was unsuccessful, a stepwise approach was examined. After extensive experimentation, it was found that treatment of **8** with Cs_2CO_3 in DMF at 0 °C, and then with 3-bromo-2-methylpropene afforded the desired product **9** as a mixture of two isomers, along with the *O*-alkylation product **10** (**9** : **10** = 2 : 1 in ratio) which was conveniently converted into **9** through a Claisen rearrangement.[17] The combined overall yield of **9** was 58%. Separation of the two isomers was tedious, so we carried the two isomers into the next stage.

Dihydroxylation[18] of **9** using OsO_4–NMO, followed by cleavage[19] with $NaIO_4$–SiO_2 provided triketone **6** in a yield of 96% for two steps (Scheme 1). When triketone **6** was subjected to the Yoshikoshi cyclization conditions (NaH, benzene),[20] enone **11** was obtained in a low yield (*ca.* 7%) accompanied by a significant amount of keto acid **13**.[21] The Dauben conditions (anhydrous KF, dibenzo-18-crown-6, xylene)[21] proved unsuccessful. However, it was discovered that when 18-crown-6 was used instead of dibenzo-18-crown-6, the yield of enone **11** was improved to 42%. At this point, the orientation of the methyl group was not determined. It is notable that the same transformation employing either of the two stereoisomers of **6** afforded the same ratio of products. Fig. 3 is a plausible rationale for the observed stereochemistry. Deprotonation of triketone **6** and the subsequent nucleophilic attack of the resulting enolate **A** on the carbonyl carbon shall afford intermediate **B** which undergoes rapid ring-opening and ring-closure to give **D** (major) and **E** (minor). Finally, **D** and **E** are converted into **11** and **12** by protonation and subsequent water elimination, respectively.

Stereoselective hydrogenation of enone **11** using Pd/C in ethyl acetate provided a single stereoisomer **14** (Scheme 2). The structure of **14** was unambiguously confirmed through X-ray crystallographic analysis.[22] It was found that the relative stereochemistry of **14** is consistent with what is required for



Scheme 1 Synthesis of compound **11**.

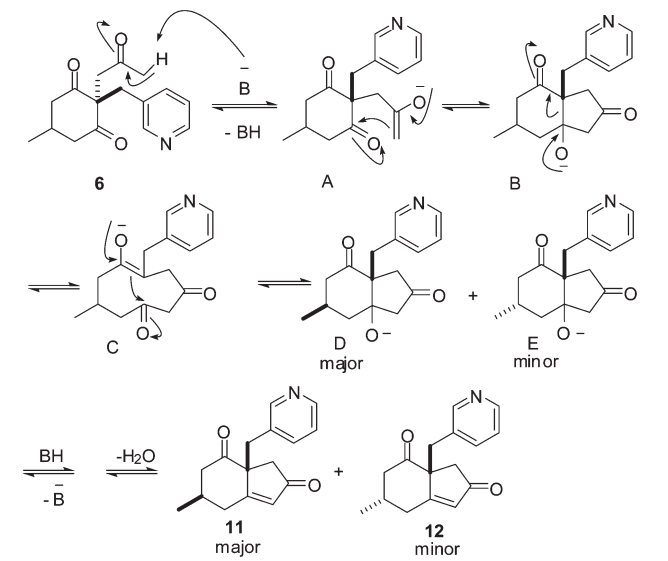
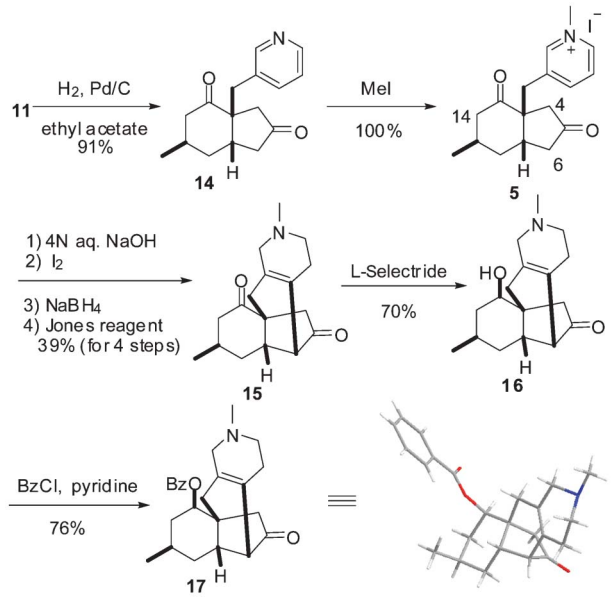


Fig. 3 A possible rationale for the observed stereochemistry.

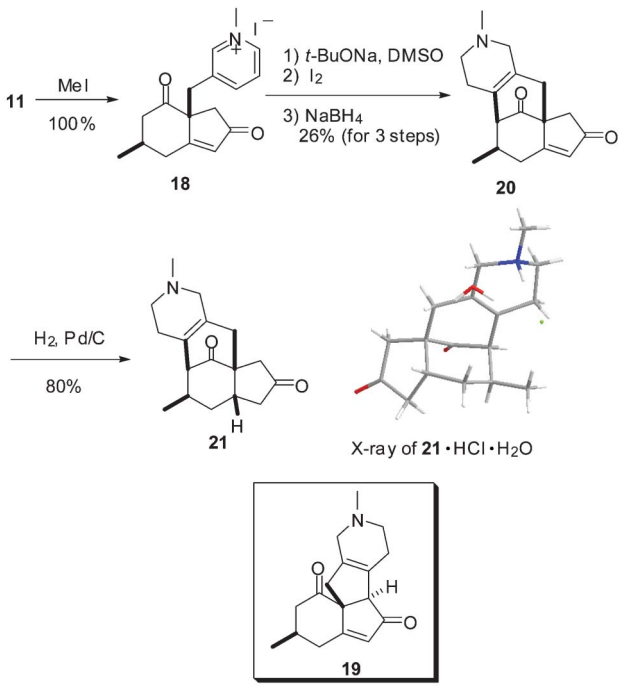


Scheme 2 Synthesis of compound **17**.

paniculatine. Intermediate **14** was methylated with methyl iodide to afford *N*-methyl pyridinium salt **5** in a quantitative yield, which bears all the carbon and oxygen atoms of the natural product.

With *N*-methyl pyridinium salt **5** in hand, we examined the intramolecular enolate addition reaction to construct the last ring of paniculatine (Scheme 2). By using a modified Weller procedure,[2] **5** underwent cyclization by treatment with 4 N aq. NaOH in toluene to afford the labile dihydropyridine,[23] which was immediately oxidized with iodine.[24] Reduction[11d] of the resulting pyridinium salt with $NaBH_4$ was accompanied by non-stereoselective reduction of the two carbonyl groups. Re-oxidation employing Jones reagent gave tetracyclic diketone **15** instead of the desired intermediate **4**, in a yield of 39% for four steps. The structure of **15** was confirmed following conversion into alcohol **16** and by X-ray crystallographic analysis of benzol ester **17**.[25] Attempts to alter the regioselectivity by changing the reaction temperature and the bases were unsuccessful.

Although the desired product was not obtained, it was found that the C-3 position of the pyridine moiety is the preferred reactive site. In order to facilitate the desired cyclization reaction, it was desirable to block the C-6 position of intermediate **5**. To achieve this goal, enone **11**, whose C-6 position was blocked by a double bond, was methylated using methyl iodide to give **18** in a quantitative yield (Scheme 3). Unfortunately, under the above cyclization conditions, **18** decomposed completely due to competing side reactions involving the α,β-unsaturated ketone moiety. After screening other non-nucleophilic bases, a DMSO solution of **18** was treated with *t*-BuONa at room temperature for one minute, the reaction mixture was extracted with toluene–*n*-hexane (1 : 1 v/v) and the extract was dried and directly oxidized with iodine.[24] It was found that the only isolated product after reduction[11d] with $NaBH_4$ was not the expected **19**, but the unexpected cyclization product **20**, whose structure was confirmed following transformation into saturated ketone **21** and by X-ray crystallographic analysis of the monohydrate of the hydrochloride salt of **21**.[26]



Scheme 3 Synthesis of compound **21**.

Conclusions

In conclusion, nucleophilic addition at the C-3 position of the pyridine moiety of the pyridinium salt is favorable, and the C-4 enolate of **5** or **18** is not the preferred reaction site. Therefore, the intramolecular pyridinium enolate addition produced two bridge-fused tetracyclic products **15** and **20**, instead of what was desired.

Experimental section

General information

All commercial reagents were used as received. Solvents were dried and distilled prior to use when deemed necessary: tetrahydrofuran (THF) and xylene (from sodium benzophenone ketyl); *N*,*N*-dimethylformamide (DMF), benzene, dimethyl sulfoxide (DMSO) and pyridine (from calcium hydride); ethanol (EtOH) and methanol (MeOH) (from magnesium ethoxide and magnesium methoxide, respectively); hexamethylphosphoramide (HMPA) (from lithium aluminium hydride). ^{1}H NMR spectra were recorded on a Bruker AV 400 (400 MHz) spectrometer and reported in ppm with the solvent resonance as the internal standard. ^{13}C NMR spectra were recorded on a Bruker AV 400 (100 MHz) or 500

(125 MHz) spectrometer and reported in ppm with the solvent resonance as the internal standard. All coupling constants (*J* values) were reported in Hertz (Hz). High resolution mass spectra (HRMS) were measured on a Thermo Scientific LTQ Orbitrap Discovery mass spectrometer using ESI (electrospray ionization). Melting points were determined with digital apparatus and were uncorrected.

Synthesis of compound 8. Preparation of 3-(chloromethyl)-pyridine: A portion of 3-picolyl chloride hydrochloride (8.1976 g, 0.0506 mol) was dissolved in a minimum amount of water (*ca.* 4 mL) and covered with diethyl ether (50 mL). To the above biphasic mixture was added a solution of NaOH (2.4901 g, 0.0623 mol) in water (4 mL) with vigorous stirring at 0 °C. After 2 min, the ether was separated and the aqueous portion was extracted with ether (2 × 50 mL). The combined organics were washed with brine (3 × 10 mL), dried over $MgSO_4$, filtered and concentrated. The resulting residue was then added directly to the carbanion reaction mixture (prepared as below).

Preparation of compound **8**: 1,5-Dimethoxy-3-methyl-1,4-cyclohexadiene (6 g, 0.0389 mol) was added to a stirred and cooled solution of *t*-BuLi (1.3 M in pentane, 31 mL, 0.0409 mol) in anhydrous THF (200 mL) under argon at −70 °C. Then stirring was continued for 1 h at −70 °C. HMPA (9.5 mL, 0.0548 mol) was added and stirring was further continued for 3 h at −70 °C. To the above reaction mixture was added 3-(chloromethyl)pyridine (prepared as above). The mixture was stirred for 4 h at −70 °C. The reaction was quenched by addition of saturated aq. NH_4Cl (120 mL) and brine (120 mL). The reaction temperature was allowed to rise to room temperature and the organic layer was separated. The aqueous layer was extracted with ether (3 × 50 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was dissolved in THF (100 mL) under argon and cooled to 0 °C. To the above solution was added 2 N aqueous HCl (52 mL). After that, the solution was allowed to rise to room temperature and stirred for 12 h. THF was concentrated. The residue was basified with solid $NaHCO_3$ to pH = 5–6, then with pyridine to pH = 7–8, and saturated with NaCl. The resulting mixture was thoroughly extracted with a 1 : 10 mixture of pyridine and ether. The combined organics were dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (CH_2Cl_2 : MeOH = 15 : 1) to give **8** as a brown amorphous solid (7.199 g, yield: 85%). ^{1}H NMR (400 MHz, CD_3OD) δ = 8.38 (d, *J* = 1.6 Hz, 1H), 8.26 (dd, *J* = 1.6, 4.8 Hz, 1H), 7.68 (dt, *J* = 1.6, 7.6 Hz, 1H), 7.27 (dd, *J* = 4.8, 7.6 Hz, 1H), 3.59 (s, 2H), 2.49–2.42 (m, 2H), 2.21–2.16 (m, 3H), 1.05 (d, *J* = 5.6 Hz, 3H) ppm; ^{13}C NMR (100 MHz, CD_3OD) δ = 187.10, 148.60, 145.33, 138.35, 137.09, 123.43, 113.52, 40.52, 28.34, 24.47, 19.66 ppm; HRMS (ESI) calcd. for $C_{13}H_{15}NO_2H^+$ $[M + H^+]$ 218.1176, found 218.1174.

Synthesis of compound 9. To a solution of **8** (3.9247 g, 18.065 mmol) in dry DMF (240 mL) was added Cs_2CO_3 (7.0629 g, 21.677 mmol) at 0 °C, and the resulting mixture was stirred for an additional 2 h. To the above mixture was added 3-bromo-2-methylpropene (2 mL, 19.871 mmol) in one portion. The mixture was stirred for 13 h at 0 °C. The solid was filtered off. The filtrate was concentrated under reduced pressure. The residue was dissolved in a mixture of ether (100 mL) and saturated aqueous NH_4Cl (20 mL). The organic layer was separated, and the aqueous layer was extracted with ether (3 × 30 mL). The combined organics were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (ethyl acetate (EA) : petroleum ether (PET) : Et_3N = 2 : 1 : 0.01) to give **9** as a mixture of stereoisomers (a pale yellow oil, 1.931 g, yield: 40%) and **10** as a brown oil (1.0138 g, yield: 20%).

A solution of **10** (1.0138 g, 3.736 mmol) in toluene (10 mL) was stirred at 180 °C (oil bath) in a sealed tube for 8 h. After evaporating the solvent, the residue was purified by chromatography on silica gel (EA : PET : Et_3N = 1 : 1 : 0.01) to give **9** as a mixture of stereoisomers (0.9124 g, yield: 90%, **9a**/**9b** = 1.28 : 1, the determination of isomer ratio was done by ^{1}H NMR). **9a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.41 (dd, *J* = 1.6, 4.8 Hz, 1H), 8.27 (d, *J* = 1.6 Hz, 1H), 7.34 (d, *J* = 7.7 Hz, 1H), 7.12 (dd, *J* = 4.8, 7.7 Hz, H), 4.87 (s, 1H), 4.66 (s, 1H), 3.12 (s, 2H), 2.61 (s, 2H), 2.47–2.42 (m, 2H), 2.05–1.98 (m, 2H), 1.62 (s, 3H), 0.93 (m, 1H), 0.85 (d, *J* = 6.2 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ = 211.32, 151.31, 148.30, 140.19, 137.84, 132.52, 123.12, 116.68, 67.97, 49.40, 48.06, 39.86, 24.15, 22.77, 21.27 ppm; HRMS (ESI) calcd. for $C_{17}H_{21}NO_2H^+$ $[M + H^+]$ 272.1645, found 272.1642. **9b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.44 (dd, *J* = 1.6, 4.8 Hz, 1H), 8.26 (d, *J* = 1.6 Hz, 1H), 7.32 (dt, *J* = 1.6, 6.0 Hz, 1H), 7.14 (dd, *J* = 4.8, 6.0 Hz, 1H), 4.82 (s, 1H), 4.63 (s, 1H), 3.08 (s, 2H), 2.63 (s, 3H), 2.59 (d, *J* = 4.0, 1 H), 2.03 (m, 1H), 1.62 (s, 3H), 1.61–1.56 (m, 2H), 0.77 (d, *J* = 6.6, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ = 211.19, 151.24, 148.44, 140.55, 137.70, 131.93, 123.19, 116.43, 68.02, 49.03, 46.19, 41.24, 24.36, 23.31, 21.01 ppm; HRMS (ESI) calcd. for $C_{17}H_{21}NO_2H^+$ $[M + H^+]$ 272.1645, found 272.1642. **10**: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.46 (d, *J* = 1.6 Hz, 1H), 8.34 (dd, *J* = 1.6, 4.8 Hz, 1H), 7.54 (dt, *J* = 1.6, 7.8 Hz, 1H), 7.10 (dd, *J* = 4.8, 7.6 Hz, 1H),4.95 (s, 1H), 4.91 (s, 1H), 4.45 (d, *J* = 6.8 Hz, 2H), 3.62 (s, 2H), 2.64 (m, 1H), 2.46 (m, 1H), 2.22–2.02 (m, 3H), 1.72 (s, 3H), 1.07 (d, *J* = 6.0 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 197.44, 171.37, 150.17, 146.83, 140.23, 137.02, 136.18, 122.99, 118.02, 113.08, 71.26, 44.61, 33.37, 28.53, 25.4, 21.07, 19.11 ppm; HRMS (ESI) calcd. for $C_{17}H_{21}NO_2H^+$ $[M + H^+]$ 272.1645, found 272.1643.

Synthesis of compound 6. Olefin **9** (2.9712 g, 10.950 mmol) was dissolved in a mixed solvent of THF (30 mL), *t*-BuOH (30 mL) and water (12 mL). *N*-Methylmorpholine *N*-oxide (3.8479 g, 32.849 mmol) was added at rt, followed by OsO_4 (0.0557 g, 0.219 mmol). The mixture was vigorously stirred for 20 h at rt. The reaction was quenched by addition of 20% aqueous $Na_2S_2O_3$ (60 mL). Stirring was continued for an additional 2 h, then brine (60 mL) was added. The resulting mixture was extracted with EA (3 × 40 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated. The crude diol obtained was dissolved in CH_2Cl_2 (120 mL) at rt, and silica gel-supported $NaIO_4$ (19.4186 g, 13.254 mmol) was added portionwise over a period of 30 min. Stirring was continued until disappearance of the diol occurred. The mixture was filtered through a sintered glass funnel, and the silica gel was thoroughly washed with a 1 : 10 mixture of methanol and methylene chloride (3 × 70 mL). Removal of the solvent afforded the crude triketone **6** that was purified by column chromatography on silica gel (EA : PET : Et_3N =

3 : 1 : 0.01) to give **6** as a light yellow amorphous solid (2.8819 g, yield: 96%). **6a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.51 (dd, J = 1.6, 4.8 Hz, 1H), 8.26 (d, J = 1.6 Hz, 1H), 7.28 (dt, J = 1.6, 8.0 Hz, 1H), 7.20 (dd, J = 4.8, 8.0 Hz, 1H), 2.92 (s, 2H), 3.26 (s, 2H), 2.57–2.44 (m, 4H), 2.04 (s, 3H), 1.27 (m, 1H), 0.95 (d, J = 6.5 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ = 210.95, 206.18, 150.72, 149.02, 137.26, 130.97, 123.36, 62.59, 52.54, 46.58, 40.15, 28.77, 23.01, 21.37 ppm; HRMS (ESI) calcd. for $C_{16}H_{19}NO_3H^+$ [M + H$^+$] 274.1438, found 274.1434. **6b**: ^{1}H NMR (400 MHz, CD_3OD) δ = 8.43 (dd, J = 1.6, 4.8 Hz, 1H), 8.24 (d, J = 1.6 Hz, 1H), 7.55 (dt, J = 1.6, 7.9 Hz, 1H), 7.37 (dd, J = 4.8, 7.8 Hz, 1H), 3.15 (s, 2H), 3.02 (s, 2H), 2.63–2.61 (m, 4H), 2.42 (m, 1H), 2.02 (s, 3H), 1.14 (d, J = 6.4 Hz, 3H) ppm; ^{13}C NMR (125 MHz, CD_3OD) δ = 210.59, 208.24, 151.30, 148.99, 130.98, 133.12, 124.93, 65.15, 48.73, 47.93, 39.70, 28.85, 26.65, 21.77 ppm; HRMS (ESI) calcd. for $C_{16}H_{19}NO_3H^+$ [M + H$^+$] 274.1438, found 274.1437.

Synthesis of compound 11. A mixture of triketone **6** (0.8960 g, 3.278 mmol), KF·2H$_2$O (0.9257 g, 9.834 mmol) and 18-crown-6 (0.4072 g, 1.541 mmol) in 50 mL of benzene was heated under refluxing for 3 h with continuous removal of water using a Dean–Stark trap filled with Linde 4 Å molecular sieves. After that, the solvent was removed and xylene (60 mL) was added. Refluxing was further continued for 16 h. The solvent was removed at reduced pressure. The residue was dissolved in EA (30 mL), washed with brine (3 × 2 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (EA : PET : Et_3N = 3 : 1 : 0.01) to give **11** as a white amorphous solid (0.3530 g, yield: 42%), **12** as an oil (0.0363 g, yield: 4%) and **13** as a pale yellow oil which is an inseparable mixture of epimers. **11**: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.50 (dd, J = 1.6, 4.8 Hz, 1H), 8.31 (d, J = 1.6 Hz, 1H), 7.36 (dt, J = 1.6, 7.6 Hz, 1H), 7.20 (dd, J = 4.8, 7.6 Hz, 1H), 5.84 (d, J = 1.6 Hz, 1H), 3.12 (d, J = 1.2 Hz, 2H), 3.12–3.00 (m, 1H), 2.99 (d, J = 18.8 Hz, 1H), 2.69–2.57 (m, 3H), 2.22 (d, J = 18.8 Hz, 1H), 2.04 (m, 1H), 1.26 (d, J = 6.4 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ = 207.36, 204.76, 177.54, 150.67, 149.01, 136.94, 130.28, 129.82, 123.33, 62.44, 46.18, 40.54, 39.72, 35.60, 33.95, 22.19 ppm; HRMS (ESI) calcd. for $C_{16}H_{17}NO_2H^+$ [M + H$^+$] 256.1332, found 256.1330. **12**: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.46 (dd, J = 1.6, 4.8 Hz, 1H), 8.29 (d, J = 1.6 Hz, 1H), 7.34 (dt, J = 1.6, 7.6 Hz, 1H), 7.17 (dd, J = 4.8, 7.6 Hz, 1H), 5.85 (d, J = 1.6 Hz, 1H), 3.18–3.07 (m, 4H), 2.95 (d, J = 18.8 Hz, 1H), 2.72 (m, 2H), 2.34 (dt, J = 2.4, 19.2 Hz, 1H), 2.20 (d, J = 18.8 Hz, 1H), 0.89 (d, J = 6.8 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 208.08, 204.04, 176.69, 150.72, 148.94, 136.87, 132.13, 130.40, 123.21, 63.35, 44.49, 40.83, 39.72, 33.62, 30.05, 19.38 ppm; HRMS (ESI) calcd. for $C_{16}H_{17}NO_2H^+$ [M + H$^+$] 256.1332, found 256.1330. **13**: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 11.27 (br, 1H), 8.43–8.37 (m, 2H), 7.57–7.55 (m, 1H), 7.26–7.22 (m, 1H), 3.11–3.04 (m, 1H), 2.82–2.74 (m, 1H), 2.70–2.50 (m, 4H), 2.15 (s, 0.54H), 2.10 (s, 0.42H), 1.99 (s, 3H), 1.19 (d, J = 6.8 Hz, 1.7H), 1.15 (d, J = 7.2 Hz, 1.2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 208.97, 176.16, 175.90, 169.40, 169.30, 149.22, 149.02, 146.83, 146.62, 141.67, 141.56, 137.40, 137.23, 135.38, 135.29, 123.65, 123.52, 45.65, 45.61, 38.43, 38.34, 37.68, 37.55, 34.48, 33.92, 33.88, 27.35, 27.24, 18.45, 18.29, 17.13 ppm; HRMS (ESI) calcd. for $C_{16}H_{19}NO_3H^+$ [M + H$^+$] 274.1438, found 274.1436.

Synthesis of compound 14. A suspension of enone **11** (0.3193 g, 1.251 mmol) and Pd/C (10%, 0.3512 g) in ethyl acetate (25 mL) was stirred under a hydrogen atmosphere at rt for 3 h. After the catalyst was removed by filtration, the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EA : PET : Et_3N = 3 : 1 : 0.01) to give **14** as a white solid (0.2929 g, yield: 91%); mp 125–126 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.50 (dd, J = 1.6, 4.8 Hz, 1H), 8.36 (d, J = 1.6 Hz, 1H), 7.37 (dt, J = 1.6, 8.0 Hz, 1H), 7.22 (dd, J = 4.8, 7.6 Hz, 1H), 3.18 (d, J = 14.0 Hz, 1H), 3.04 (d, J = 14.4 Hz, 1H), 2.99 (d, J = 18.4 Hz, 1H), 2.69 (m, 1 H), 2.55–2.43 (m, 2H), 2.29–2.19 (m, 2H), 2.11–1.87 (m, 4H), 1.10 (d, J = 6.4 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ = 213.88, 211.22, 150.46, 148.71, 136.86, 131.83, 123.40, 56.82, 46.49, 44.76, 42.88, 41.34, 38.88, 31.81, 30.07, 21.98 ppm; HRMS (ESI) calcd. for $C_{16}H_{19}NO_2H^+$ [M + H$^+$] 258.1489, found 258.1486.

Synthesis of compound 5. To a solution of **14** (0.1 g, 0.389 mmol) in acetone (5 mL) was added methyl iodide (0.1655 g, 1.166 mmol). The reaction was heated under reflux for 3 h, then removal of the solvent gave **5** as a pale yellow amorphous solid (0.1552 g, 100%): ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ = 8.88–8.86 (m, 2H), 8.28 (d, J = 8.0 Hz, 1H), 8.04 (t, J = 7.6 Hz, 1H), 4.32 (s, 3H), 3.63 (d, J = 13.6 Hz, 1H), 3.22 (d, J = 14.0 Hz, 1H), 2.87–2.76 (m, 2H), 2.61 (d, J = 18.0 Hz, 1H), 2.26–1.99 (m, 6H), 1.77 (d, J = 13.2, 1H), 1.06 (d, J = 6.0 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $(CD_3)_2SO$) δ = 214.25, 211.86, 145.43, 145.14, 143.98, 137.84, 127.11, 56.36, 47.94, 46.02, 44.43, 43.23, 40.83, 36.98, 30.61, 29.35, 21.63 ppm; HRMS (ESI) calcd. for $C_{17}H_{22}NO_2^+$ [M − I$^-$] 272.1645, found 272.1644.

Synthesis of compound 15. To a vigorously stirred suspension of **5** (0.15 g, 0.376 mmol) in toluene (40 mL) was added 4 N aqueous NaOH (0.75 mL, 3.005 mmol) at rt. The reaction mixture was stirred until the solid was dissolved completely. The organic phase was separated, and the aqueous phase was extracted with toluene (2 × 10 mL). The combined organic layers were dried over Na_2SO_4 for 10 min and filtered. The filtrate was treated with a solution of iodine (0.1430 g, 0.564 mmol) in toluene (5 mL) immediately at rt. After stirring for 10 h, to the reaction mixture was added saturated aqueous Na_2SO_3 until a colorless mixture was obtained. The reaction mixture was concentrated to dryness. The resulting solid was suspended in methanol (10 mL) and cooled to −10 °C. To the above mixture was added $NaBH_4$ (0.0213 g, 0.564 mmol). The reaction mixture was stirred for 20 min at −10 °C, quenched with 1 N aqueous HCl and basified with saturated aqueous $NaHCO_3$. Methanol was removed under reduced pressure and the aqueous layer was extracted with chloroform (4 × 5 mL). The extracts were dried over Na_2SO_4, filtered and concentrated. The residue was dissolved in acetone (5 mL) and cooled to 0 °C. Jones reagent was added to the above solution until the persistence of the orange color. Stirring was continued for an additional 2 h. The reaction was quenched with isopropanol, basified with saturated aqueous $NaHCO_3$ and concentrated. The resulting aqueous layer was extracted with CH_2Cl_2 (4 × 5 mL). The extracts were dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (CH_2Cl_2 : MeOH = 10 : 1) to give

15 as a wax solid (40 mg, yield: 39%): ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.96 (d, J = 15.6 Hz, 1H), 2.82 (dd, J = 5.6, 15.6 Hz, 1H), 2.68–2.52 (m, 5H), 2.43 (m, 1H), 2.37–2.04 (m, 10H), 1.64 (dt, J = 14.0, 2.4 Hz, 1H), 1.53 (td, J = 4.0, 13.8 Hz, 1H), 0.94 (d, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 211.28, 207.17, 128.61, 125.56, 58.22, 57.82, 52.05, 51.01, 45.42, 43.24, 43.09, 43.07, 37.45, 31.72, 30.66, 28.96, 18.61 ppm; HRMS (ESI) calcd. for $C_{17}H_{23}NO_2H^+$ [M + H$^+$] 274.1802, found 274.1802.

Synthesis of compound 16. To a solution of diketone **15** (50 mg, 0.183 mmol) in anhydrous THF (6 mL) was added dropwise L-Selectride (1 M in THF, 0.37 mL, 0.366 mmol) at −20 °C over a period of 10 min. The reaction mixture was stirred for an additional 3 h at the same temperature, quenched by the addition of water and extracted with CH_2Cl_2 (3 × 10 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on basic alumina (CH_2Cl_2 : MeOH = 75 : 1) to give alcohol **16** as a wax solid (35.3 mg, yield: 70%): ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.75 (s, 1H), 2.95 (s, 1H), 2.91 (s, 1H), 2.64–2.55 (m, 2H), 2.36 (s, 1H), 2.30 (s, 3H), 2.28–1.94 (m, 9H), 1.80 (s, 1H), 1.62 (S, 1H), 1.58 (s, 1H), 1.51–1.46 (m, 1H), 1.17 (d, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ = 210.01, 128.83, 124.85, 69.82, 59.76, 57.97, 52.15, 45.55, 43.45, 42.45, 39.04, 35.26, 34.31, 32.17, 28.90, 26.18, 20.82 ppm; HRMS (ESI) calcd. for $C_{17}H_{25}NO_2H^+$ [M + H$^+$] 276.1958, found 276.1956.

Synthesis of compound 17. To a solution of alcohol **16** (21.5 mg, 0.078 mmol) in dry pyridine (3 mL) was added benzoyl chloride (32.9 mg, 0.234 mmol) at rt. The reaction mixture was stirred for 12 h at 55 °C (oil bath). The solvent was removed under reduced pressure and the residue was dissolved in a mixture of methylene chloride (10 mL) and saturated aqueous $NaHCO_3$ (5 mL). The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (CH_2Cl_2 : MeOH = 15 : 1) to give **17** as a white solid (22.7 mg, yield: 76%); mp 110–111 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.04 (d, J = 7.6 Hz, 2H), 7.58 (d, J = 7.6 Hz, 1H), 7.47 (t, J = 8.0 Hz, 2H), 5.26 (s, 1H), 2.91 (d, J = 15.6 Hz, 1H), 2.73 (m, 1H), 2.65 (d, J = 17.2 Hz, 1H), 2.53–2.42 (m, 3H), 2.35–2.06 (m, 11H), 1.85 (d, J = 13.6 Hz, 1H), 1.69 (d, J = 17.6 Hz, 1H), 1.64–1.59 (m, 1H), 1.18 (d, J = 6.8 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 208.45, 165.70, 132.98, 130.34, 129.56, 128.48, 125.40, 72.17, 59.60, 57.73, 52.11, 45.33, 42.93, 41.60, 39.15, 35.74, 31.99, 30.87, 28.86, 25.87, 20.35 ppm; HRMS (ESI) calcd. for $C_{24}H_{29}NO_3H^+$ [M + H$^+$] 380.2220, found 380.2215.

Synthesis of compound 18. To a solution of enone **11** (0.1024 g, 0.401 mmol) in acetone (5 mL) was added methyl iodide (0.1708 g, 1.203 mmol). The reaction was heated under reflux for 3 h and removal of the solvent gave **18** as a pale yellow amorphous solid (0.1595 g, 100%): ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ = 8.94 (s, 1H), 8.89 (d, J = 6.0 Hz, 1H), 8.28 (d, J = 8.0 Hz, 1H), 8.05 (dd, J = 8.0, 6.0 Hz, 1H), 5.92 (s, 1H), 4.32 (s, 3 H), 3.53 (d, J = 14.0 Hz, 1H), 3.44 (d, J = 13.6 Hz, 1H), 3.07–2.81 (m, 3H), 2.67 (d, J = 18.8 Hz, 1H), 2.39 (dd, J = 2.7, 14.0 Hz, 1H), 2.30 (d, J = 18.8 Hz, 1H), 2.01–1.87 (m, 1H), 1.20 (d, J = 6.5 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $(CD_3)_2SO$) δ = 207.65, 204.24, 179.05, 145.75, 144.40, 136.30, 128.89, 126.94, 61.63, 48.00, 45.44, 37.25, 34.29, 33.44, 21.43 ppm; HRMS (ESI) calcd. for $C_{17}H_{20}NO_2^+$ [M − I$^-$] 270.1489, found 270.1494.

Synthesis of compound 20. To a stirred solution of **18** (0.0901 g, 0.227 mmol) in dry DMSO (1.5 mL) was added sodium *tert*-butoxide (0.0283 g, 0.295 mmol) at rt. The reaction mixture was stirred for 1 min, and then extracted with a 1 : 1 solution of toluene and *n*-hexane (6 × 8 mL). The extracts were combined, dried over Na_2SO_4 for 10 min and filtered. The filtrate was treated with a solution of iodine (0.0863 g, 0.340 mmol) in toluene (1 mL) immediately at rt. After stirring for 10 h, to the reaction mixture was added saturated aqueous Na_2SO_3 until a colorless mixture was obtained. The reaction mixture was concentrated to dryness. The resulting solid was suspended in methanol (5 mL) and cooled to −10 °C. To the above mixture was added $NaBH_4$ (0.0129 g, 0.340 mmol). The reaction mixture was stirred for 20 min at −10 °C, quenched with 1 N aqueous HCl and basified with saturated aqueous $NaHCO_3$. Methanol was removed under reduced pressure and the aqueous layer was extracted with chloroform (4 × 5 mL). The extracts were dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (CH_2Cl_2 : MeOH = 10 : 1) to give **20** as a white amorphous solid (16.2 mg, yield: 26%): ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.71 (d, J = 1.5 Hz, 1H), 3.44 (d, J = 18.8 Hz, 1H), 3.02 (d, J = 15.8 Hz, 1H), 2.79(d, J = 3.0 Hz, 1H), 2.73–2.45 (m, 7H), 2.36 (s, 3H), 2.36–2.33 (m, 1H), 2.14–2.03 (m, 2H), 1.95 (d, J = 18.9 Hz, 1H), 1.18 (d, J = 6.9 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 206.75, 206.21, 180.50, 129.82, 126.27, 126.15, 58.16, 57.16, 57.14, 51.77, 45.51, 45.08, 41.43, 38.95, 33.01, 32.89, 19.99 ppm; HRMS (ESI) calcd. for $C_{17}H_{21}NO_2H^+$ [M + H$^+$] 272.1645, found 272.1642.

Synthesis of compound 21. A suspension of enone **20** (0.015 g, 0.055 mmol) and Pd–C (10%, 0.348 g) in THF (5 mL) was stirred under a hydrogen atmosphere at rt for 4 h. After the catalyst was removed by filtration, the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (CH_2Cl_2 : MeOH = 10 : 1) to give **21** as a white amorphous solid (0.012 g, yield: 80%): ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.08–2.99 (m, 2H), 2.66–2.13 (m, 13H), 2.03–1.93 (m, 3H), 1.76 (d, J = 18.0 Hz, 1H), 1.58 (dd, J = 14.2, 3.3 Hz, 1H), 1.08 (d, J = 6.8 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ = 214.55, 213.07, 129.90, 125.30, 57.84, 57.50, 52.02, 51.83, 48.89, 45.59, 45.30, 43.22, 41.82, 34.97, 32.73, 28.78, 20.44 ppm; HRMS (ESI) calcd. for $C_{17}H_{23}NO_2H^+$ [M + H$^+$] 274.1802, found 274.1799.

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