Novel approach towards the morphine skeleton. Synthesis of 1-(5-benzyloxy-2-bromo-4-methoxybenzyl)-6-oxo-3,4,6,7,8,8a-hexahydro-1*H*-isoquinoline-2-carboxylic acid phenyl ester via *N*-acylpyridinium salt chemistry

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Abstract

A dihydropyridone-mediated approach to the morphine skeleton was investigated. The hexahydroisoquinoline **2** was synthesized in 9 steps using *N*-acylpyridinium chemistry and dihydropyridone functionalization methods. This new approach should be useful in the design of more efficient syntheses of morphine and its derivatives.

Graphical Abstract

Keywords

Alkaloid synthesis, Nitrogen heterocycles, 1-Acylpyridinium salts, Asymmetric synthesis

1. Introduction

Morphine (**1**) has been a target for total synthesis since its structure elucidation by Robinson in 1925. Many routes have been explored and are reported in the literature.¹ The rigidity of morphinans along with the axial orientation of the C9 substituent prompted us to investigate a new approach using asymmetric *N*-acylpyridinium salt chemistry.² The synthesis of intermediate hexahydroisoquinoline **2** was obtained in 9 linear steps from readily available materials and is reported herein along with an alternate route explored leading to spiro compound **3** (Fig. 1).

Figure 1.

2. Results and discussion

Chiral *N*-acylpyridinium salt chemistry has been extensively investigated in our laboratory.² Introduction of a substituent adjacent to the nitrogen atom of pyridine can be done stereoselectively by treatment of a chiral pyridinium salt with a Grignard or other organometallic reagent. Following an acidic workup, dihydropyridones are obtained in high yield and high diastereomeric ratio. An additional feature of this methodology is the presence of A^(1,3) strain between the carbamate group and the newly introduced C2 appendage. Consequently, the latter adopts preferentially an axial orientation. The target disconnection that would be amenable to this methodology in the case of morphine is the axial C9-C10 bond (**Fig. 1**). Bicyclic intermediate **2** was an initial target since it contains all the non-methyl carbon atoms present in morphine. Besides, structures similar to **2** have been converted into morphinans in the past.³ The synthesis of hexahydroisoquinoline **2** was initiated by the reaction of Grignard reagent **5**⁴ with the preformed salt of 3-triisopropylsilyl-4-methoxypyridine and (+/-)-*trans*-2-(α -cumyl)cyclohexyl chloroformate (TCC chloroformate) (**Scheme 1**). Upon acidic workup, a good yield (88%) of pure dihydropyridone **6** was obtained with excellent diastereoselectivity (92% de). Racemic TCC chloroformate was used in this preliminary study; however, both antipodes of the chloroformate are accessible by enzymatic resolution of the racemic alcohol precursor. Based upon previous studies in our laboratory, the use of the (-)-enantiomer of TCC chloroformate would lead to the desired absolute stereochemistry of natural morphine.² Exposure of the highly encumbered dihydropyridone **6** to one equivalent of bromine lead to the selective halogenation of the aromatic ring *para* to the benzyloxy group.⁵ No halogenation was observed on the dihydropyridone ring. At this stage the chiral auxiliary was removed by treatment under

basic conditions and recovered in near quantitative yield. The triisopropyl group was no longer needed as well and was removed under acidic conditions. Reprotection of the free amine **8** was accomplished either with benzyl or phenyl chloroformate.

Various conditions were then explored for the synthesis of compound **2**. Initially, it was thought that a Robinson annulation on dihydropyridone **9** would give rise directly to a tetrahydroisoquinoline intermediate.⁶ Unfortunately, no alkylation at the C3 position of dihydropyridone **9** was observed. Formation of a silyl enol ether of compound **9** also failed to give alkylation products upon reaction with methyl vinyl ketone.⁷ A slightly longer route was then envisioned. It involved the use of a strong electrophile such as 3-butenyltriflate. Under those conditions, alkylation of the C3 position of dihydropyridone **9** was observed in 43% yield.⁸ An equal quantity of starting material was recovered along with the expected product **10**.

Scheme 1. a) toluene, THF, -78 °C, 88%, 85% de; b) AcOH, AcONa, Br₂, 86%; c) MeONa, EtOH, reflux, followed by 10% HCl, 100%; d) LDA, THF, -78 °C then benzyl chloroformate (**9a**, 81%) or phenyl chloroformate (**9b**, 85%); e) KHMDS, THF, -78 °C then 3-butenyl triflate, **10a** (42%) or **10b** (37%)

At this point, an alternative approach was investigated. It aimed at the activation of the C3 position towards alkylation (Scheme 2). Enol **11** was obtained in good yield (86%) by deprotonation with sodium bis(trimethylsilyl)amide followed by treatment with trifluoroethylformate.⁹ Compound **11** reacted smoothly under mildly basic conditions to afford the highly substituted dihydropyridone **12** in good yield (88%).¹⁰ At this stage, various reduction conditions were attempted to obtain the piperidone ring. Unfortunately, the presence of the reactive carbonyl groups in compound **12** prevented the transformation. Obtaining the piperidone intermediate was critical to the success of this route. Indeed, cyclization of dihydropyridone **12** under acidic conditions yielded spiro compound **3** exclusively. The difference in electrophilicity between the aldehyde group and the C4 carbonyl moiety of the vinylgous amide accounts for this result. Reduction of the dihydropyridone to the piperidone ring was needed to remove the conjugation and

increase the electrophilicity of the C4 carbonyl. Basic cyclization conditions gave either retro Michael enol **11** or decomposition. The relative stereochemistry of compound **3** was assigned by NOE experiment. Irradiation of the benzylic CH₂ protons produced a positive NOE effect with the ethylenic proton of the cyclohexenone moiety (Fig. 2).

Scheme 2. a) NaHMDS, THF, -78 °C then CF₃CH₂CHO, 86%; b) MVK, Et₃N, EtOAc, cat. KOH, 88%; c) TsOH, benzene, 50 °C, 70%

Figure 2. Relative stereochemistry

The initial plan was then further explored. Dihydropyridone **10b** was reduced to the piperidone *via* a procedure previously reported by our laboratory (Scheme 3).¹¹ Wacker oxidation took place smoothly to afford diketone compound **14**.¹² The relative stereochemistry of this compound was also determined by an NOE experiment and confirmed to be *trans* (Fig. 2). As expected, molecular mechanics (MMFF) indicated that the C2, C3 substituents of **14** were *trans* diaxial due to A^(1,3) strain.^{2d} Irradiation of the CH₂ group attached to the C3 position yielded a positive NOE effect with the proton adjacent to the nitrogen atom. The desired relative stereochemistry being *cis*, we were hoping that epimerization would occur under the subsequent basic cyclization conditions. Prior estimation of the energy of the conformer distribution of both the *trans* and the *cis* compounds indicated that the *cis* compound was thermodynamically favored by a few kcal/mol. Diketone **14** was treated with base to yield tertiary alcohol **16** as a 3:1 inseparable mixture of isomers.¹³ The cyclization initially proceeded *via* the complete conversion of **14** to isolable bicyclononane compound **15**. Extended reaction times, however, afforded the complete disappearance of the bicyclononane to yield the expected octahydroisoquinoline **16**. No elimination was observed under these reaction conditions. However, dehydration occurred upon treatment with acid to afford compounds **2** and **17** in 23% and 13% yield, respectively, along with 27% of the major isomer of alcohol **16**. The relative stereochemistry of minor compound **17** was confirmed to be *trans* by X-ray analysis (Scheme 4). Careful monitoring of the dehydration reaction revealed that the minor isomer of alcohol **16** reacted first to produce compound **17**. Desired compound **2**

formed more slowly and originated from the major isomer of alcohol **16**. Dehydration of the recovered alcohol **16** would lead to a combined 50% of the desired hexahydroisoquinoline **2**. This observation suggests that epimerization of the C3 position to the desired *cis* configuration in **2** took place during the cyclization step.

Scheme 3. a) L-Selectride, THF, -78 °C, 74%; b) Cu(OAc)₂, PdCl₂, DMF/H₂O, 56%; c) Ba(OH)₂·8H₂O, THF, -5 °C for 2.5 h then 10 °C for 2 h, 75%; d) H₂SO₄, THF, 0 °C, 23% **2**, 13% **17**, 27% **16**.

Scheme 4. X-ray crystal structure of compound **17**.

3. Conclusions

In summary, hexahydroisoquinoline **2** was successfully synthesized via *N*-acylpyridinium salt chemistry. Hexahydroisoquinoline **2** represents a potential intermediate in the synthesis of (-)-morphine (**1**). All the non-methyl carbon atoms of morphine are present in compound **2**. Although the relative stereochemistry between the C2 and C3 carbons of compounds **10**, **13** and **14** was opposite to the required one, epimerization took place during the basic cyclization to afford the desired *cis*-hexahydroisoquinoline **2** as the major product. A racemic mixture of TCC chloroformate was used in this initial study; however, either enantiomer is available and

the (-)-enantiomer of TCC chloroformate would lead to the absolute stereochemistry present in natural morphine.

4. Experimental

4.1 General methods

All reactions were performed in oven-dried glassware under a nitrogen or argon atmosphere and stirred magnetically. THF and ether were distilled from sodium/benzophenone ketyl prior to use. Toluene was distilled from sodium. Triethylamine, diisopropylamine, and CH₂Cl₂ were distilled from calcium hydride and stored under argon over 4 Å molecular sieves. *n*-Butyllithium was titrated against biphenylmethanol. Sodium bis(trimethylsilyl)amide was titrated against 9-methylfluorene following the procedure reported by Mash and coworkers.¹⁴ Other reagents and solvents from commercial sources were stored under argon and used directly. Melting points were measured on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Radial preparative layer chromatography (radial PLC) was performed on a Chromatotron (Harrison Associates, Palo Alto, CA) using glass plates coated with 1, 2 or 4 mm layers of Kieselgel 60 PF254 containing gypsum. High-resolution mass spectral analysis (HRMS) was performed at North Carolina State University. NMR spectra were obtained using a Varian Gemini GN-300 (300 MHz), Varian Mercury 300 (300 MHz) or Varian Mercury 400 (400 MHz). Chemical shifts are in ppm units with TMS (0.0 ppm) used as the internal standard for ¹H NMR spectra and the CDCl₃ absorption of (77.23 ppm) for ¹³C NMR. Certain ¹³C NMR spectra display a mixture of rotamers (r) and all peaks observed are listed. IR spectra were recorded on a Perkin-Elmer 1430, MIDAC M2000, or JASCO FT/IR-410 spectrometer. X-Ray data was obtained at Wake Forest University X-Ray laboratory.

4.2 Experimental procedures

4.2.1 2-(5-Benzyloxy-4-methoxybenzyl)-4-oxo-5-(triisopropylsilyl)-3,4-dihydro-2H-pyridine-1-carboxylic acid 2-(1-methyl-1-phenylethyl)cyclohexyl ester (6). To a solution of 4-methoxy-3-(triisopropylsilyl)pyridine (1.0 g, 3.78 mmol) in 38 mL of freshly distilled toluene cooled to -23 °C was added a solution of (+/-)-TCC chloroformate (1 M in toluene, 3.78 mL). After 30 min, the solution was cooled to -78 °C and 15 mL of THF was added. The Grignard reagent **5** (5.65 mmol) (freshly prepared by the procedure described below) was added *via* a jacketed cannula maintained at -78 °C. The resulting mixture was stirred at -78 °C for 1.5 h. The reaction mixture was quenched by the addition of 13 mL of 10% HCl and warmed to rt over a period of 1 h. After usual workup the residue was purified by flash chromatography to yield 2.41 g (88%) of the major diastereomer and 93 mg (3.4%) of the minor diastereomer: 85% de. Major isomer: IR (thin film, neat, NaCl) 2938, 2861, 1717, 1655, 1571, 1514, 1383, 1323, 1251, 1136, 1018 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 7.74 (s, 1H), 7.48 (d, 2H, *J* = 7.6 Hz), 7.41-7.26 (m, 6H), 7.18-7.14 (m, 2H), 6.99-6.95 (m, 1H), 6.81 (d, 1H, *J* = 8.4 Hz), 6.50-6.48

(m, 1H), 5.21-5.13 (m, 2H), 4.85-4.78 (m, 1H), 3.87 (s, 3H), 2.81 (broad s, 1H), 2.44-1.70 (m, 9H), 1.35-0.86 (m, 31H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 197.1, 152.7, 152.3, 148.9, 148.2, 147.4, 137.4, 129.2, 128.8, 128.3, 128.1, 127.5, 125.1, 122.6, 115.9, 112.1, 110.7, 78.0, 71.4, 56.2, 53.1, 51.3, 39.5, 36.0, 33.6, 31.2, 26.9, 26.1, 24.8, 21.6, 19.1, 11.3; HRMS Calcd for $\text{C}_{45}\text{H}_{61}\text{NO}_5\text{Si}$: 724.4397 $[\text{M}+\text{H}]^+$. Found: 724.4398 $[\text{M}+\text{H}]^+$.

4.2.2 Procedure for the preparation of 3-benzyloxy-4-methoxybenzylmagnesium chloride. To a mixture of magnesium powder (2.75 g, 75.3 mmol) in 90 mL of anhydrous THF at rt was added 1,2-dibromoethane (0.3 mL, 3.5 mmol). After stirring for 15 min, a solution of 3-benzyloxy-4-methoxybenzyl chloride (5.93 g, 22.6 mmol) in 20 mL of anhydrous THF was added over a period of 50 min at rt. After completion of the addition, the Grignard reagent was stirred for an additional 1.5 h at rt to form a light brown solution. Stirring was stopped to allow for the excess magnesium to settle and the Grignard reagent was cooled to -78°C .

4.2.3 2-(5-Benzyloxy-2-bromo-4-methoxybenzyl)-4-oxo-5-(triisopropylsilyl)-3,4-dihydro-2H-pyridine-1-carboxylic acid 2-(1-methyl-1-phenylethyl)cyclohexyl ester (7). The starting material **6** (18.11 g, 25 mmol) was placed in a 1 L flask. NaOAc (3.1 g, 37.5 mmol) and 583 mL of glacial AcOH were added. To the mixture was slowly added a solution of Br_2 (1.28 mL, 25 mmol) in 50 mL glacial AcOH. The reaction mixture was allowed to stir at rt for 8 h. Some solid precipitated out. The acetic acid was evaporated and the crude oil was dissolved in CH_2Cl_2 , washed twice with H_2O (120 mL) and once with brine (120 mL). The organic phase was dried with Na_2SO_4 and concentrated *in vacuo*. Trituration in hexanes gave compound **7** as a white solid (16.01 g). Purification of the mother liquor by radial PLC (SiO_2 , EtOAc/hexanes) yielded an additional 1.22 g of product to bring the total amount to 17.2 g (86%). Some starting material was also recovered (1.37 g, 7.5%). Mp $159\text{--}161^\circ\text{C}$; IR (thin film, neat, NaCl) 2939, 2862, 1716, 1656, 1572, 1509, 1385, 1322, 1248, 1017 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 7.80 (s, 1H), 7.44-7.19 (m, 9H), 7.04-7.00 (m, 2H), 6.48 (s, 1H), 5.17-5.04 (m, 2H), 4.86-4.80 (m, 1H), 3.84 (s, 3H), 3.43-3.41 (broad m, 1H), 2.75-2.70 (m, 1H), 2.53-2.47 (m, 1H), 2.36-2.31 (m, 1H), 2.17-2.15 (broad m, 1H), 1.99-1.93 (broad m, 2H), 1.73-1.64 (m, 3H), 1.38-1.04 (m, 31H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 197.1, 152.3 and 152.1 (r), 149.4, 147.7 and 147.5 (r), 136.8, 128.7, 128.2, 128.1, 127.6, 125.5, 125.3, 117.3, 116.2, 115.1, 110.9, 78.1, 71.2, 56.5, 51.4, 51.0, 39.9 and 39.8 (r), 35.9, 33.3, 30.0, 27.0, 26.1, 24.8, 23.0, 19.2, 11.3; HRMS Calcd for $\text{C}_{45}\text{H}_{60}\text{BrNO}_5\text{Si}$: 802.3502 $[\text{M}+\text{H}]^+$. Found: 802.3481 $[\text{M}+\text{H}]^+$.

4.2.4 2-(5-Benzyloxy-2-bromo-4-methoxybenzyl)-2,3-dihydro-1H-pyridin-4-one (8). The starting material **7** (208 mg, 0.26 mmol) was dissolved in 10 mL of ethanol. Sodium methoxide (0.3 mL, 25w% solution in methanol) was added and the resulting solution was stirred at reflux overnight. The solvent was removed *in vacuo* and THF (10 mL) was added. A 10% aqueous solution of HCl (2.33 mL) was added and the mixture was stirred for 1 h at rt and then cooled down to 0°C . Solid K_2CO_3 was added carefully to the mixture. After usual workup and flash chromatography, the product **8** was obtained as a white solid (111 mg, 100%): mp $117.5\text{--}118.5^\circ\text{C}$; IR (thin film, neat, NaCl) 3250, 3032, 2955, 1623, 1576, 1507 1258, 1215, 1164, 1027 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 7.41-7.32 (m, 5H), 7.06 (s, 1H), 6.86-6.83 (m, 1H), 6.61 (s, 1H), 5.18 (dd, 2H, $J = 12.8$

and 37.2 Hz), 4.99 (d, 1H, $J = 7.6$ Hz), 4.40 (broad d, 1H, $J = 5.2$ Hz), 3.89 (s, 3H), 3.85-3.78 (m, 1H), 2.93-2.88 (m, 1H), 2.82 (dd, 1H, $J = 9.2$ and 14.0 Hz), 2.51 (dd, 1H, $J = 5.2$ and 16.0 Hz), 2.37 (dd, 1H, $J = 11.4$ and 16.2 Hz); ^{13}C NMR (CDCl_3 , 100 MHz) δ 192.5, 150.8, 149.6, 147.2, 136.6, 128.8, 128.2, 128.0, 127.5, 117.1, 116.5, 115.3, 99.3, 71.2, 56.4, 52.8, 41.9, 39.4; Anal. Calcd for $\text{C}_{20}\text{H}_{20}\text{BrNO}_3$: C, 59.71; H, 5.01; N, 3.48. Found: C, 59.42; H, 4.99; N, 3.69.

4.2.5 2-(5-Benzyloxy-2-bromo-4-methoxybenzyl)-4-oxo-3,4-dihydro-2H-pyridine-1-carboxylic acid benzyl ester (9a). Compound **8** (1.0 g, 2.49 mmol) was dissolved in THF and cooled down to -78°C . A preformed solution of LDA in THF at -78°C (diisopropylamine, 0.522 mL, 3.73 mmol; $n\text{-BuLi}$, 1.5 mL, 3.73 mmol) was then added *via* cannula. The resulting solution was stirred for 1 h and then allowed to warm up to -40°C . Freshly distilled benzyl chloroformate (0.426 mL, 3.00 mmol) was then quickly added and the reaction was stirred for 1.5 h at -40°C . The reaction mixture was quenched with a saturated aqueous solution of NaHCO_3 . After usual work up and purification of the residue by radial PLC, the product **9a** was isolated as a white solid (1.08 g, 81%): mp $91\text{--}93^\circ\text{C}$; IR (thin film, neat, NaCl) 3032, 2931, 1725, 1669, 1603, 1504, 1327, 1259, 1216, 1023 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz, $T = 55^\circ\text{C}$) δ 7.71 (d, 1H, $J = 8.0$ Hz), 7.40-7.24 (m, 10H), 6.94 (s, 1H), 6.59 (s, 1H), 5.35 (d, 1H, $J = 8.4$ Hz), 5.17-4.97 (m, 4H), 4.90-4.85 (m, 1H), 3.79 (s, 3H), 2.98 (dd, 1H, $J = 7.4$ and 13.4 Hz), 2.86 (dd, 1H, $J = 8.0$ and 13.6 Hz), 2.70 (m, 1H), 2.33 (d, 1H, $J = 16.8$ Hz); ^{13}C NMR (CDCl_3 , 100 MHz) δ 192.8, 149.3, 147.5, 141.7, 136.7, 134.8, 128.8, 128.7, 128.6, 128.0, 127.8, 127.5, 116.8, 116.0, 115.4, 107.6, 71.2, 69.1, 56.3, 52.9, 39.3, 35.9; HRMS Calcd for $\text{C}_{28}\text{H}_{26}\text{BrNO}_5$: 536.1073 $[\text{M}+\text{H}]^+$. Found: 536.1046 $[\text{M}+\text{H}]^+$. Anal. Calcd for $\text{C}_{28}\text{H}_{26}\text{BrNO}_5$: C, 62.69; H, 4.89; N, 2.61. Found: C, 62.48; H, 4.90; N, 2.78.

4.2.6 2-(5-Benzyloxy-2-bromo-4-methoxybenzyl)-4-oxo-3,4-dihydro-2H-pyridine-1-carboxylic acid phenyl ester (9b). The same procedure as described for the preparation of **9a** was used, with phenylchloroformate. After purification by radial PLC compound **9b** was obtained in 85% yield as a white solid: mp $110\text{--}112^\circ\text{C}$; IR (thin film, neat, NaCl) 3067, 2929, 1740, 1671, 1604, 1508, 1331, 1257, 1190, 1026 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz, $T = 55^\circ\text{C}$) δ 7.73 (d, 1H, $J = 8.0$ Hz), 7.40-7.20 (m, 8H), 6.98-6.93 (m, 3H), 6.65 (s, 1H), 5.45 (d, 1H, $J = 8.0$ Hz), 5.14-5.02 (m, 3H), 3.81 (s, 3H), 3.11 (dd, 1H, $J = 8.6$ and 13.4 Hz), 2.96 (dd, 1H, $J = 7.0$ and 13.4 Hz), 2.85 (dd, 1H, $J = 6.2$ and 16.6 Hz), 2.45 (d, 1H, $J = 16.4$ Hz); ^{13}C NMR (CDCl_3 , 100 MHz) δ 192.2, 150.5, 149.8, 147.9, 141.0, 136.9, 129.4, 128.6, 128.0, 127.9, 127.4, 126.1, 121.0, 117.5, 116.7, 115.7, 108.4, 71.6, 56.4, 53.3, 39.8, 36.1; HRMS Calcd for $\text{C}_{27}\text{H}_{24}\text{BrNO}_5$: 522.0916 $[\text{M}+\text{H}]^+$. Found: 522.0928 $[\text{M}+\text{H}]^+$.

4.2.7 2-(5-Benzyloxy-2-bromo-4-methoxybenzyl)-3-but-3-enyl-4-oxo-3,4-dihydro-2H-pyridine-1-carboxylic acid benzyl ester (10a). In a flask, purged with argon, were placed 3-butenol (0.347 mL, 4 mmol), pyridine (0.323 mL, 4 mmol) and 4 mL of anhydrous hexane. In a separate flask, trifluoromethanesulfonic anhydride (0.676 mL, 4 mmol) was diluted with 4 mL of anhydrous hexane and cooled to 0°C . The alcohol/pyridine solution was transferred to the anhydride *via* cannula, and the resulting heterogeneous mixture was stirred at 0°C for 20 min. The precipitate was filtered and the

clear, colorless filtrate was used as is, without concentration or purification. The starting material **9a** (200 mg, 0.37 mmol) was placed in a separate flask. Freshly distilled THF was added (20 mL) and the resulting mixture was cooled to -78 °C. A solution of KHMDS (3.73 mL, 1.86 mmol) was then added and the reaction mixture was stirred for 30 min at -78 °C. The crude triflate was then added quickly to the enolate, and the reaction mixture was stirred for 4 h at -78 °C. The reaction mixture was quenched with a saturated aqueous solution of NaHCO₃ and warmed to rt. After usual workup and purification by radial PLC, compound **10a** was isolated in a 42% yield (93 mg) as an oil. Some starting material was also recovered (68 mg, 34%). IR (thin film, neat, NaCl) 3071, 2931, 1726, 1666, 1604, 1503, 1327, 1260, 1214, 1117, 1028 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz, T = 55 °C) δ 7.65 (bs, 1H), 7.41-7.25 (m, 10H), 6.94 (s, 1H), 6.57 (s, 1H), 5.71-5.61 (m, 1H), 5.29 (d, 1H, *J* = 8.0 Hz), 5.18-4.89 (m, 6H), 4.75 (t, 1H, *J* = 7.2 Hz), 3.81 (s, 3H), 2.97 (dd, 1H, *J* = 8.0 and 13.6 Hz), 2.82 (dd, 1H, *J* = 7.2 and 13.6 Hz), 2.22 (t, 1H, *J* = 7.4 Hz), 2.12-1.92 (m, 2H), 1.64-1.46 (m, 2H); ¹³C NMR (CDCl₃, 100 MHz, T = 55 °C) δ 196.6, 149.8, 148.0, 140.5, 137.3, 137.1, 135.2, 128.9, 128.9, 128.8, 128.6, 128.4, 128.2, 127.6, 117.7, 116.8, 115.9, 106.4, 71.8, 69.3, 56.7 and 56.6 (r), 48.3, 36.3, 31.0, 30.0; HRMS Calcd for C₃₂H₃₂BrNO₅: 590.1542 [M+H]⁺. Found: 590.1555 [M+H]⁺.

4.2.8 2-(5-Benzyloxy-2-bromo-4-methoxybenzyl)-3-but-3-enyl-4-oxo-3,4-dihydro-2H-pyridine-1-carboxylic acid phenyl ester (10b). The procedure followed was the same as described for the preparation of compounds **10a**. Compound **10b** was obtained as an oil in 37% yield. IR (thin film, neat, NaCl) 2929, 1740, 1668, 1604, 1505, 1335, 1259, 1192 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz, T = 55 °C) δ 7.65 (d, 1H, *J* = 7.6 Hz), 7.39-7.17 (m, 8H), 6.97 (s, 1H), 6.91 (m, 2H), 6.63 (s, 1H), 5.78-5.68 (m, 1H), 5.37 (d, 1H, *J* = 6.8 Hz), 5.14-4.91 (m, 6H), 3.81 (s, 3H), 3.10-3.05 (m, 1H), 2.90 (dd, 1H, *J* = 6.8 and 13.6 Hz), 2.34-2.27 (m, 2H), 2.19-2.02 (m, 2H); ¹³C NMR (CDCl₃, 100 MHz, T = 55 °C) δ 196.4, 150.7, 150.0, 148.1, 140.2, 137.3-137.1 (r), 129.6, 128.9, 128.4, 128.2, 127.5, 126.4, 121.2, 117.7, 116.9, 116.1, 107.3, 71.9, 57.1, 56.7, 48.7, 36.5, 31.1, 30.1; HRMS Calcd for C₃₁H₃₀BrNO₅: 576.1386 [M+H]⁺. Found: 576.1365 [M+H]⁺.

4.2.9 2-(5-Benzyloxy-2-bromo-4-methoxybenzyl)-3-hydroxymethylene-4-oxo-3,4-dihydro-2H-pyridine-1-carboxylic acid benzyl ester (11). A solution of dihydropyridine **9a** (3.41 g, 6.36 mmol) was dissolved in THF (60 mL) and cooled to -78 °C. A solution of NaHMDS (0.7 M, 11.8 mL, 8.26 mmol) was then added and the solution was stirred at -78 °C for 45 min. Neat trifluoroethyl formate (3.66 mL, 38.3 mmol) was rapidly added and the mixture was stirred at -78 °C for 3 h and then warmed up to -40 °C prior to a quench with neat H₂SO₄ (0.636 mL). The reaction mixture was transferred to a separatory funnel with ether and water. The layers were separated, and the aqueous phase was extracted with ether. The combined organic extracts were washed with saturated aqueous NH₄Cl, dried over MgSO₄ and concentrated *in vacuo*. The residual yellow oil was dissolved in ether and extracted with cold 1% aqueous NaOH. The remaining organic phase was concentrated to give the starting dihydropyridone (407 mg, 12%). The aqueous extract was acidified to pH = 1 by addition of 10% HCl and extracted with CH₂Cl₂. The combined organic extract were dried over MgSO₄ and concentrated *in vacuo* to give **11** as a yellow foam (3.07 g, 86%). IR (thin film, neat, NaCl) 2931, 1728, 1609, 1508, 1240 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz, T = 55 °C) δ

14.00 (broad s, 1H), 7.52 (broad s, 1H), 7.40-7.27 (m, 10H), 6.96 (s, 1H), 6.92 (s, 1H), 6.53 (broad s, 1H), 5.40 (d, 1H, $J = 7.6$ Hz), 5.26-5.14 (m, 2H), 5.07-4.95 (m, 3H), 3.81 (s, 3H), 3.00-2.94 (m, 1H), 2.89 (dd, 1H, $J = 6.0$ and 12.8 Hz); ^{13}C NMR (CDCl_3 , 100 MHz, $T = 55^\circ\text{C}$) δ 182.9, 170.2, 150.0, 147.9, 139.6 (broad), 137.0, 135.1, 129.1, 129.0, 128.8, 128.2, 127.7, 127.3, 118.3, 116.6, 105.9, 105.7, 71.8, 69.4, 56.48, 54.5; HRMS Calcd for $\text{C}_{29}\text{H}_{26}\text{BrNO}_6$: 564.1022 $[\text{M}+\text{H}]^+$. Found: 564.1046 $[\text{M}+\text{H}]^+$.

4.2.10 2-(5-Benzyloxy-2-bromo-4-methoxybenzyl)-3-formyl-4-oxo-3-(3-oxo-butyl)-3,4-dihydro-2H-pyridine-1-carboxylic acid benzyl ester (12). The starting enol **11** (3.76 g, 6.65 mmol) was dissolved in 110 mL of dry EtOAc and cooled to 0°C . Triethylamine was added (1.37 mL, 9.85 mmol) and methylvinylketone (0.828 mL, 10 mmol) followed by a catalytic amount of KOH. The reaction mixture was stirred at 0°C for 6 h and quenched with water. The pH was adjusted to 2 with aqueous 1% HCl, and the aqueous phase was extracted with ether. The combined extracts were washed with brine and dried over MgSO_4 . Filtration and evaporation of the solvents afforded the crude diketone **12**. Flash chromatography gave 3.72g (88%) of product as a white foam. IR (thin film, neat, NaCl) 2933, 1716, 1660, 1600, 1504 1298, 1217 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz, $T = 55^\circ\text{C}$) δ 10.13 (s, 1H), 7.55-7.29 (m, 9H), 7.18-7.16 (m, 2H), 6.89 (s, 1H), 6.53 (s, 1H), 5.32 (broad s, 1H), 5.09-4.95 (m, 4H), 4.62 (broad s, 1H), 3.81 (s, 3H), 2.94 (dd, 1H, $J = 10.6$ and 13.8 Hz), 2.81 (d, 1H, $J = 14.0$ Hz), 2.32-2.26 (m, 2H), 2.07-2.00 (m, 5H); ^{13}C NMR (CDCl_3 , 100 MHz, $T = 55^\circ\text{C}$) δ 206.0, 201.8, 194.2, 149.9, 147.9, 141.5, 137.1, 134.8, 128.9, 128.8, 128.5, 128.3, 128.1, 127.3, 117.3, 116.4, 105.9, 71.7, 69.4, 58.1, 56.5, 37.4, 32.7, 30.0, 27.2; HRMS Calcd for $\text{C}_{33}\text{H}_{32}\text{BrNO}_7$: 634.1440 $[\text{M}+\text{H}]^+$. Found: 634.1414 $[\text{M}+\text{H}]^+$.

4.2.11 1-(5-Benzyloxy-2-bromo-4-methoxybenzyl)-5,9-dioxo-2-aza-spiro[5.5]undeca-3,7-diene-2-carboxylic acid benzyl ester (3). Compound **12** (214 mg, 0.34 mmol) was placed in benzene (4 mL). To this solution was added 64 mg of *p*-toluenesulfonic acid. The resulting reaction mixture was stirred overnight at 50°C . After usual workup, the residue was purified by radial PLC to yield 151 mg (70%) of compound **3** as a white solid: mp $167\text{--}168^\circ\text{C}$; IR (thin film, neat, NaCl) 2928, 1729, 1668, 1602, 1507, 1301, 1206 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz, $T = 55^\circ\text{C}$) δ 7.54-7.32 (m, 9H), 7.16-7.14 (m, 2H), 6.99 (d, 1H, $J = 9.6$ Hz), 6.89 (broad s, 1H), 6.49 (s, 1H), 6.22 (d, 1H, $J = 10.8$ Hz), 5.36 (broad s, 1H), 5.07-4.95 (m, 4H), 4.58 (broad s, 1H), 3.82 (s, 3H), 2.95-2.92 (m, 2H), 2.50 (broad s, 1H), 2.39 (dt, 1H, $J = 4.4$ and 20 Hz), 2.15 (dt, 1H, $J = 4.4$ and 14 Hz), 2.05-1.97 (m, 1H); ^{13}C NMR (CDCl_3 , 100 MHz, $T = 55^\circ\text{C}$) δ 197.5, 195.8, 152.7, 149.4, 147.4, 141.0, 140.3, 136.9, 134.4, 131.9, 129.0, 128.9, 128.3, 128.1, 127.1, 116.6, 115.8, 106.1, 105.4, 71.5, 69.3, 58.2, 57.5, 56.4, 49.3, 33.1, 32.6, 30.1; HRMS Calcd for $\text{C}_{33}\text{H}_{30}\text{BrNO}_6$: 616.1335 $[\text{M}+\text{H}]^+$. Found: 616.1349 $[\text{M}+\text{H}]^+$.

4.2.12 2-(5-Benzyloxy-2-bromo-4-methoxybenzyl)-3-but-3-enyl-4-oxo-piperidine-1-carboxylic acid phenyl ester (13). The starting dihydropyridone **10b** (625 mg, 1.08 mmol) was dissolved in freshly distilled THF and cooled to -78°C . A 1M solution of L-Selectride[®] (2.2 mL, 2.2 mmol) was added dropwise and the reaction mixture was allowed to stir for 4 h. The reaction was quenched with water. After usual workup, the residue was purified by radial PLC to yield 462 mg (74%) of piperidone **13** as an oil. IR

(thin film, neat, NaCl) 2932, 1711, 1504, 1416, 1205 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz, $T = 55^\circ\text{C}$) δ 7.38-7.24 (m, 7H), 7.16 (t, 1H, $J = 7.2$ Hz), 7.00-6.70 (m, 4H), 5.72-5.68 (m, 1H), 5.10-5.03 (m, 2H), 4.98-4.90 (m, 3H), 4.49-4.43 (m, 1H), 3.83 (s, 3H), 3.43-3.32 (m, 1H), 2.90-2.88 (m, 2H), 2.77-2.68 (m, 1H), 2.40 (t, 1H, $J = 7.2$ Hz), 2.33 (d, 1H, $J = 14.8$ Hz), 2.13-2.00 (m, 2H), 1.78-1.77 (m, 2H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 210.4, 154.4, 151.2, 149.5, 147.6, 136.9, 129.53, 129.46, 128.9, 128.8, 128.4, 128.2, 128.1, 127.5, 127.4, 125.7, 121.7, 121.5, 116.8, 116.4, 116.3, 116.12 and 116.08 (r), 115.4, 71.5 and 71.2 (r), 56.8 and 56.7 (r), 53.6 and 53.3 (r), 39.6 and 39.3 (r), 38.3 and 38.0 (r), 37.7, 31.4 and 30.3 (r); HRMS Calcd for $\text{C}_{31}\text{H}_{32}\text{BrNO}_5$: 578.1542 $[\text{M}+\text{H}]^+$. Found: 578.1544 $[\text{M}+\text{H}]^+$.

4.2.13 2-(5-Benzyloxy-2-bromo-4-methoxybenzyl)-4-oxo-3-(3-oxo-butyl)-piperidine-1-carboxylic acid phenyl ester (14). The starting alkene **13** (462mg, 0.8 mmol) was dissolved in DMF/ H_2O (14 mL / 2 mL). $\text{Cu}(\text{OAc})_2$ (30 mg, 0.17 mmol) and PdCl_2 (14 mg, 10 mol%) were then added. The resulting mixture was stirred under air for 2 h. The reaction mixture was quenched with water and extracted with ether. After usual workup the residue was purified by radial PLC to give **14** as an oil (268 mg, 56%). IR (thin film, neat, NaCl) 2926, 1713, 1699, 1600, 1505, 1207 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 7.41-7.26 (m, 7H), 7.21-7.14 (m, 1H), 7.03-6.97 (m, 2H), 6.85 (d, 1H, $J = 8.8$ Hz), 6.81-6.69 (m, 1H), 5.19-5.03 (m, 2H), 4.84 (t, 1H, $J = 7.2$ Hz), 4.47-4.35 (m, 1H), 3.86-3.82 (m, 3H), 3.43-3.28 (m, 1H), 2.90 (t, 2H, $J = 7.4$ Hz), 2.86-2.74 (m, 1H), 2.68-2.31 (m, 4H), 2.10 (d, 3H, $J = 6.8$ Hz), 2.06-1.83 (m, 2H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 210.2 and 210.0 (r), 207.5 and 207.2 (r), 154.3 and 154.2 (r), 151.2, 149.5 and 149.2 (r), 147.6, 136.8 and 136.7 (r), 129.5, 129.4, 129.2, 128.9, 128.8, 128.7, 128.2, 128.11, 128.08, 128.0, 127.5, 127.3, 125.7 and 125.6 (r), 121.7 and 121.5 (r), 116.7 and 116.3 (r), 116.2 and 116.0 (r), 115.5 and 115.4 (r), 71.4 and 71.2 (r), 57.7, 56.7 and 56.4 (r), 53.5 and 53.2 (r), 40.9 and 40.7 (r), 39.4 and 39.1 (r), 38.4, 37.8 and 37.7 (r), 30.3, 24.8 and 24.7 (r); HRMS Calcd for $\text{C}_{31}\text{H}_{32}\text{BrNO}_6$: 593.1413 $[\text{M}]^+$. Found: 593.1428 $[\text{M}]^+$.

4.2.14 1-(5-Benzyloxy-2-bromo-4-methoxybenzyl)-4a-hydroxy-6-oxo-octahydroisoquinoline-2-carboxylic acid phenyl ester (16). The starting diketone **14** (165 mg, 0.28 mmol) was dissolved in 10 mL of anhydrous THF and cooled to -5°C . To this solution was added $\text{Ba}(\text{OH})_2 \cdot 8\text{H}_2\text{O}$ (17 mg, 0.055 mmol). The resulting mixture was allowed to stir for 2.5 h at -5°C . TLC analysis at this point showed complete conversion of the starting material to the intermediate bicyclononane derivative **15**. The temperature was then raised to 10°C and an additional amount of $\text{Ba}(\text{OH})_2 \cdot 8\text{H}_2\text{O}$ (54 mg, 0.175 mmol) was added. After 2 h a TLC analysis showed the disappearance of the bicyclononane intermediate and formation of the bicyclic alcohol **17**. Methanol was evaporated and the crude mixture was dissolved in methylene chloride. Water and aqueous NH_4Cl were added and the pH was adjusted to neutrality. After usual workup, the residue was purified by radial PLC to yield compound **17**, a white solid, as an inseparable 3:1 mixture of epimers in a 75% yield. Mp $168\text{--}169^\circ\text{C}$; IR (thin film, neat, NaCl) 3438, 3064, 2949, 1694, 1504, 1416, 1207, 1162 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 7.39-6.70 (mixed signals, 11H), 6.58 (d, 1H, $J = 8.4$ Hz), 5.14-4.99 (m, 2H), 4.76-4.73 (m, 0.75H, epimer 1), 4.50-4.48 (m, 0.25H, epimer 2), 4.12-3.98 (m, 1H), 3.83-3.76 (m, 3H), 3.47-3.18 (m, 2H), 3.11-3.10 (m, 1H), 2.93 (dd, 0.75H, $J = 2.8$ and 14.4

Hz), 2.55-2.20 (m, 6H), 2.03-1.68 (m, 3.6H), 1.33-1.30 (m, 0.75H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 210.9, 210.8, 207.9, 154.1, 153.3, 151.2, 151.0, 148.8, 148.6, 147.5, 147.1, 136.8, 136.7, 130.5, 130.2, 129.1, 128.9, 128.7, 128.5, 127.8, 127.1, 127.0, 125.0, 124.9, 124.7, 121.4, 121.2, 121.0, 117.2, 117.0, 116.2, 116.0, 115.5, 115.2, 73.0, 72.3, 71.5, 71.2, 71.1, 56.1, 55.5, 54.5, 53.6, 44.6, 44.2, 43.1, 41.3, 39.5, 39.3, 38.8, 38.3, 35.1, 34.3, 33.2, 32.8, 32.2, 27.2, 24.9, 24.8; HRMS Calcd for $\text{C}_{31}\text{H}_{32}\text{BrNO}_6$: 594.1491 $[\text{M}+\text{H}]^+$. Found: 594.1464 $[\text{M}+\text{H}]^+$.

4.2.15 *Cis* 1-(5-Benzyloxy-2-bromo-4-methoxybenzyl)-6-oxo-3,4,6,7,8,8a-hexahydro-1H-isoquinoline-2-carboxylic acid phenyl ester (2). The tertiary alcohol **16** (88 mg, 0.15 mmol) was dissolved in THF (5 mL) and cooled to 0 °C. A few drops of concentrated H_2SO_4 were added and the reaction mixture was stirred at 0 °C. Careful monitoring by TLC and ^1H NMR showed that the minor isomer of the tertiary alcohol eliminated faster to yield the more polar product **17**. The major isomer cyclized at a much slower rate to yield the less polar product. After 8 h at 0 °C, 20 mg of the major *cis* compound **2** (23%) and 11 mg of the minor *trans* compound **17** (13%) were isolated after usual workup and purification by radial PLC (SiO_2 , EtOAc/hexanes). The major isomer of the starting alcohol **16** was also recovered in 27% yield (24 mg). Analysis for compound **2**: mp 160-163 °C; IR (thin film, neat, NaCl) 2931, 1711, 1671, 1508, 1414, 1256 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz, T = 55 °C) δ 7.37-7.22 (m, 7H), 7.15-7.09 (m, 1H), 7.03-6.97 (m, 1H), 6.86-6.84 (m, 1H), 6.71-6.69 (m, 2H), 6.06 (s, 1H), 5.13-5.01 (m, 3H), 4.20-4.06 (broad m, 1H), 3.85-3.80 (m, 3H), 3.20-2.96 (m, 3H), 2.78-2.50 (m, 4H), 2.44-2.32 (m, 1H), 2.27-1.98 (m, 2H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 198.9 and 198.7 (r), 159.6, 153.8 and 153.5 (r), 151.3 and 151.2 (r), 149.4 and 149.1 (r), 147.8 and 147.5 (r), 137.1 and 136.9 (r), 129.5, 129.3, 128.9, 128.8, 128.7, 128.2, 128.14, 128.09, 127.9, 127.6, 127.4, 127.2, 125.6 and 125.4 (r), 121.7 and 121.4 (r), 116.7 and 116.4 (r), 116.2 and 115.6 (r), 71.8 and 71.3 (r), 56.45 and 56.38 (r), 55.7 and 54.4 (r), 40.8 and 40.7 (r), 39.0 and 38.6 (r), 36.7 and 36.6 (r), 33.8 and 33.6 (r), 33.4 and 33.2 (r), 24.4 and 24.3 (r); HRMS Calcd for $\text{C}_{31}\text{H}_{30}\text{BrNO}_5$: 576.1386 $[\text{M}+\text{H}]^+$. Found: 576.1368 $[\text{M}+\text{H}]^+$. The structure of compound **17** was confirmed by X-ray analysis.

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