Asymmetric Synthesis of Bicyclic β -Lactones via the Intramolecular, Nucleophile-Catalyzed Aldol-Lactonization (NCAL) Reaction: Improved Efficiency and Expanded Scope

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Supporting Information

Experimental details and characterization data (including ^1H and ^{13}C NMR spectra) for pyridinium salt **2b**, aldehyde acid **1a**, and bicyclic β -lactones **3f** and **4c** obtained via the intramolecular NCAL reaction. This material is available free of charge via the Internet at <http://pubs.acs.org>

General

Mukaiyama's reagent **2a** and 2-bromopyridine was purchased from Acros and used as received. Methyl triflate and triflic anhydride were purchased from Aldrich and used as received. Pyridinium salts **2c**¹ and **2d**² were prepared according to literature procedures. *O*-Acetylquinidine³, caged-QND⁴, and *O*-trimethylsilylquinine⁵ were prepared according to literature procedures. Aldehyde acid substrates⁶ were obtained by ozonolysis of the corresponding trimethylsilylenol ethers (**1a**, **1b**, **1d**, **1e**)⁷ or alkene acids (**1c**, **1f**, **1g**).⁸ All aldehyde acids were purified by MPLC (RT Scientific, Inc., 40 mm x 350 mm EL 170 g Silica). Chiral GC analyses were performed using a 30 m Chiraldex β -DA column or a 2,3-di-OAc-6-TBS β -cyclodextrin column at the indicated oven temperatures and H₂ carrier pressures.

N-Propyl-2-bromopyridinium triflate (**2b**):

In a resealable tube was placed a solution of 2-bromopyridine (1.92 mL, 20.0 mmol) in 6 mL of CH₂Cl₂. The solution was degassed by three freeze/thaw cycles and the tube was then finally purged with nitrogen. The colorless solution was cooled to -78 °C, and then *n*-propyl trifluoromethanesulfonate⁹ (3.80 g, 20.0 mmol) was added slowly with stirring under nitrogen. The cooling bath was removed, the tube was sealed, and the reaction mixture was stirred for 16 h at 25 °C. After concentration in *vacuo*, toluene (20 mL) was added to the yellow oil, and after stirring for 30 mins, the reaction mixture was stored in a refrigerator overnight to precipitate the pyridinium salt. The clear supernatant was

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removed via syringe and an additional 20 mL of dry diethyl ether was added to wash the precipitate. The diethyl ether was removed via syringe and all subsequent operations were done under a stream of nitrogen to exclude moisture and prevent hydrolysis. The washed solid was dried under high vacuum for 48 h at 25 °C to afford 6.5 g (93%) of *N*-propyl-2-bromopyridinium triflate (**2b**). On a smaller reaction scale, a crystalline solid was obtained, rather than a precipitate, after storage in the refrigerator overnight. Both forms of the pyridinium salt **2b** gave comparable yields in the NCAL process: mp 162-164 °C; IR (thin film) 3092, 2976, 1614, 1258 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 9.32 (dd, *J*= 4.5, 1.5 Hz, 1H), 8.44 (dd, *J*= 8.0, 1.5 Hz, 1H), 8.28 (dd, *J*= 8.0, 1.5 Hz, 1H), 8.14 (dt, *J*= 6.5, 1.5 Hz, 1H), 4.84 (t, *J*= 8.0 Hz, 2H), 2.06 (tq, *J*= 8.0 Hz, 2H), 1.09 (t, *J*= 8.0 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 149.0, 147.0, 137.4, 134.9, 128.0, 120.9 (q, *J*= 314 Hz, CF₃), 65.0, 23.7, 10.6.

Note: For optimal yields in the NCAL process, it is imperative to use aldehyde acid substrates of very high purity.

Representative Procedures for the Racemic NCAL Process as Described for Bicyclic β-lactone (±)-3f** (Method C):**

To a solution of pyridinium salt **2b** (350 mg, 1.0 mmol) and triethylamine (281 μl, 2.0 mmol) in 6 mL of CH₂Cl₂ was added via syringe pump a solution of aldehyde acid **1f** (123.0 mg, 0.5 mmol) in 4 mL of CH₂Cl₂ over 1 h. The resulting dark yellow solution was stirred for another 11 h, at which point the volatiles were removed under reduced pressure to give a dark red residue. The crude reaction mixture was then partitioned between ethyl acetate and sat. NH₄Cl solution (50 mL each). The phases were separated, and the organic phase was washed with brine (30 mL), dried over MgSO₄, filtered, and concentrated to afford a light red residue that was purified by flash chromatography on SiO₂ (CH₂Cl₂ with 1% triethylamine) to afford β-lactone **3f** (95.2 mg, 84%) as a light

yellow oil. Spectroscopic data matched that provided for the optically active β -lactone **3f** provided in the text.

β -Lactone (±)-4c This racemic β -lactone was prepared from aldehyde acid **1c** (130 mg, 0.5 mmol) according to the representative procedure (Method C). Purification by flash chromatography (3:7 $\rightarrow$ 2:3, EtOAc:hexanes with 1% triethylamine) gave β -lactone **4c** as a colorless oil (100 mg, 84%): R_f 0.43 (3:2, hexanes:EtOAc); IR (thin film) 1830, 1740 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 4.73 (ddd, J = 6.0, 5.0, 2.5 Hz, 1H), 3.86 (ddd, J = 10.5, 6.5, 5.0 Hz, 1H), 3.79 (s, 6H), 2.53 (dd, J = 15.0, 10.0 Hz, 1H), 2.25 (dd, J = 15.0, 10.0 Hz, 1H), 2.09 (m, 3H), 1.80 (dddd, J = 16.0, 11.5, 7.5, 5.0 Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 171.9, 171.8, 171.6, 69.0, 53.3, 53.2, 51.9, 45.0, 25.5, 24.1, 23.7; LRMS (APCI) Calcd for $\text{C}_{11}\text{H}_{15}\text{O}_4$ $[\text{M}+\text{H}]$: 243.0. Found: 243.0.

(+)-(1*R*, 2*S*)- β -lactone 4c. Prepared according to the representative asymmetric procedure (Method B) using aldehyde acid **1c** (130 mg, 0.5 mmol, 1.0 equiv), pyridinium salt **2b** (525 mg, 1.5 mmol), *O*-acetyl quinidine (17 mg, 0.05 mmol), and diisopropylethylamine (281 μl , 2.0 mmol) in 6 mL of CH_2Cl_2 . Purification by flash chromatography on SiO_2 (7:3, hexanes:EtOAc with 1% triethylamine) gave β -lactone **4c** (92 mg, 76%) as a colorless oil: $[\alpha]_{\text{D}}^{25} +83.8$ (c 0.0179, CHCl_3). Enantiomeric excess was determined to be 98% by chiral GC analysis using a 2,3-di-OAc-6-TBS β -CD

column (140 °C, 11psi); $t_{(1S,2R)} = 22.5$ min (minor), $t_{(1R,2S)} = 23.6$ min (major). All other spectroscopic data matched that of the racemic compound prepared using triethylamine as nucleophile.

All other bicyclic β -lactones (**3a-3e**, **4a**, **4b**) matched characterization data described previously.¹⁰

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1a

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