Hydroxyarylketones via Ring-Opening of Lactones with Aryllithium Reagents: An Expedient Synthesis of (±)-Anabasamine

Lei Miao, Stassi C. DiMaggio,[1] Mark L. Trudell*

Department of Chemistry, University of New Orleans, New Orleans, LA 70148, USA
Fax +1(504)2806860; E-mail: mtrudell@uno.edu

Received 1 July 2009; revised 18 August 2009

Abstract: The regioselective ring-opening of lactones (δ-valerolactone and γ-butyrolactone) with aryllithium reagents is reported for the construction of a series of δ-hydroxy aryl ketones and γ-hydroxy aryl ketones. Application of this method for the expeditious syntheses of (±)-anabasamine and its nicotine-related analogue are also described.

Key words: ketones, lactones, nucleophilic addition, ring-opening, natural products

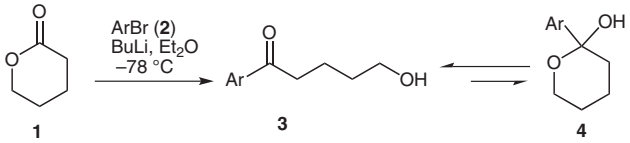
δ-Hydroxy ketones have been reported to be useful building blocks for the construction of both natural and non-natural compounds.[2,3] Synthesis of these versatile intermediates has been achieved via a variety of methods that include the photooxidation of aryldihydropyrans,[4] oxidation of β-hydroxy sulfones,[5] and nucleophilic ring-opening of δ-valerolactone (**1**).[2,3,6–8] Of these methods, the latter has been the most widely used. However, an investigation of the scope and limitations of organolithium nucleophiles has not been previously reported.

Previous work in our laboratories led to the development of a synthetic process for the construction of δ-hydroxy pyridinyl ketone derivatives via the addition of pryridinyllithium reagents with δ-valerolactone.[6] The success of this reaction has prompted a broader study of its scope and limitations. Herein, we report the reactivity of a series of aryllithium and heteroaryllithium reagents with δ-valerolactone and γ-butyrolactone for the preparation of δ-hydroxy aryl ketone and γ-hydroxy aryl ketone derivatives.

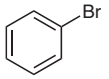
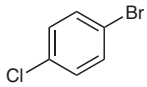
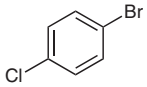
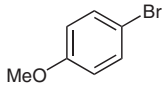
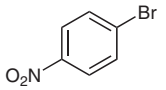
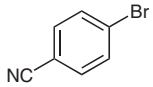
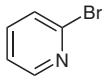
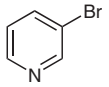
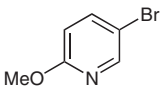
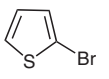
As summarized Table 1, a series of δ-hydroxy ketones **3** were readily prepared from the reaction of **1** with a variety of aryllithium and heteroaryllithium reagents (General Method A). The organolithium reagents were initially generated in situ by treatment of the corresponding bromide with either *n*-butyllithium or *tert*-butyllithium in diethyl ether at –78 °C. The lactone **1** was then added to the organolithium solution and the reaction was quenched with brine to furnish the δ-hydroxy ketones **3** in high yields (Table 1). The δ-hydroxy ketones generally existed as a mixture of chain–ring tautomers (**3**:**4**, >90:10), with the equilibrium favoring the open-chain form **3**.[9]

It is noteworthy that the reaction conditions did not tolerate strong electron-withdrawing groups on the aryl bromide [Table 1, entry 5 (NO_2) and entry 6 (CN)]. Presumably, the sensitivity of these groups to the strongly basic and nucleophilic organolithium reagents led to the formation of intractable mixtures. Furthermore, no diol products, which could be formed from the subsequent ad-

Table 1 Ring-Opening of δ-Valerolactone (**1**)



1 **3** **4**

Entry	Compd	**2**	BuLi (1.2 equiv)	Yield of **3** (%)[a]
1	**a**		*t*-BuLi	79
2	**b**		*t*-BuLi	87
3	**c**		*t*-BuLi	72
4	**d**		*t*-BuLi	90
5	**e**		*t*-BuLi	–[b]
6	**f**		*t*-BuLi	–[b]
7	**g**		*n*-BuLi	81
8	**h**		*n*-BuLi	63
9	**i**		*n*-BuLi	98[c]
10	**j**		*n*-BuLi	79

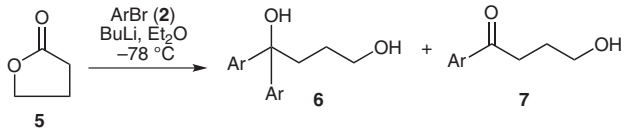
[a] General Method A; isolated yield.
[b] Intractable mixture.
[c] Using **1** (1.33 equiv); see Miao et al.[6]

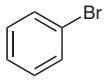
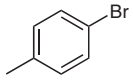
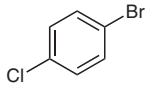
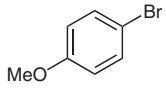
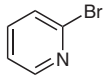
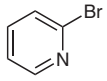
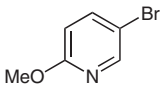
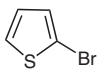
SYNTHESIS 2010, No. 1, pp 0091–0097
Advanced online publication: 19.10.2009
DOI: 10.1055/s-0029-1217047; Art ID: M03509SS

dition of the organolithium to the hydroxy ketones, were observed. These results suggest that, under the low temperature conditions, nucleophilic attack on the lactone **1** was significantly more favorable than reaction with the newly formed ketones **3**. As such, it is possible to obtain the δ-hydroxy aryl ketones in high yield by simple control of the reaction stoichiometry.

The ring-opening reaction was also explored with γ-butyrolactone (**5**; Table 2). Using the reaction conditions established for **1** (General Method A), the reactivity of **5** differed significantly from that of the homologous lactone **1**. In general, the major products from the reaction of **5** with the various aryllithium reagents were the 1,1-diarylbutane-1,4-diols **6**,[10] while the corresponding γ-hydroxy ketones **7** were the minor products.

Table 2 Ring-Opening of γ-Butyrolactone (**5**)



Entry	Compd	2	BuLi	6/7[a]	6/7[b]
1	**a**		*t*-BuLi	65:16	9:71
2	**b**		*t*-BuLi	72:18	10:67
3	**c**		*t*-BuLi	68:13	11:63
4	**d**		*t*-BuLi	77:15	14:68
5	**g**		*n*-BuLi	–:70[c]	
6	**h**		*n*-BuLi	–:66[c]	
7	**i**		*n*-BuLi	–:89[c]	
8	**j**		*n*-BuLi	70:20	23:75

[a] General Method A; isolated yield.
[b] General Method B; isolated yield.
[c] Trace amounts of **6** (<10%) observed by NMR.

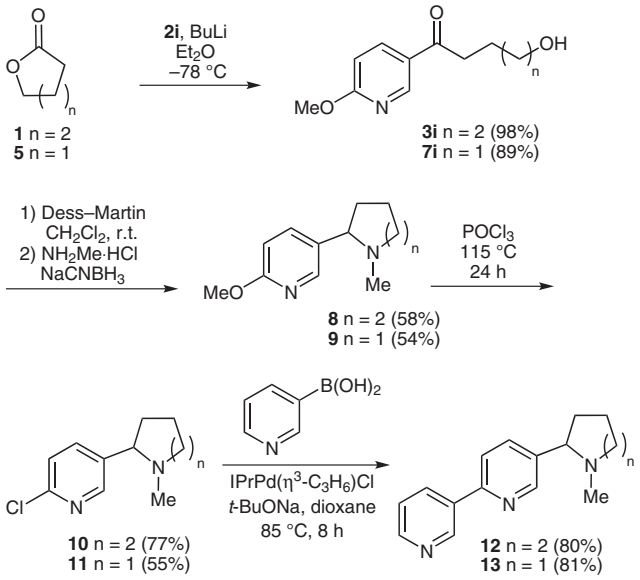
The formation of diols **6a–d** and **6j** resulted from a second addition of the organolithium reagent to the corresponding ketone that was formed initially. These results are consistent with the fact that the γ-hydroxy ketones **7a–d** and **6j** are more reactive toward nucleophilic addition than the lactone **5**. Furthermore, the difference in the product distributions of lactones **1** and **5** can be explained by the reactivity of the different ring systems toward nucleophiles.[11] Previous studies have shown **1** to be much more susceptible toward ring-opening than **5**. As such, in the reaction of **1** with the aryllithium reagents, the newly formed hydroxy ketone **3** does not readily compete with the reactive lactone **1**, thus, none of the corresponding diol was formed. Alternatively, in the five-membered-ring system, the lower relative reactivity of **5** allows the hydroxy ketone **7** to compete for the aryllithium reagent and thus leads to the formation of the diol **6**.

It was interesting to discover that the pyridinyllithium reagents **2g**, **2h** and **2i** did not readily undergo the secondary addition reaction. Only the corresponding γ-hydroxy ketones **7** were obtained in good yield, with only trace amounts (<10%) of the diols **6** present. Presumably, the pyridinyl moiety of ketones **7g**, **7h** and **7i** deactivates the carbonyl towards addition of a second equivalent the organolithium reagent by formation of stabilized aggregate intermediate species.[12] As a result, the more reactive lactone **5** is consumed prior to the competing second addition. Even employing an excess of the pyridinyllithium reagents (2.0 equiv) did not lead to increased production of the corresponding diols **6**.

With these results in hand, it was envisaged that the order of addition of the lactone **5** may affect the product **6/7** distribution. To this end, the order of addition was reversed by addition of a pre-cooled (–78 °C) solution of the aryllithium reagent in diethyl ether to a solution of **5** in the same solvent at –78 °C (General Procedure B). For the aryl bromides **2a–d** and **2j** that were tested, all gave improved yields of the γ-hydroxy aryl ketone **7** over the corresponding diols **6** (Table 2). The γ-hydroxy aryl ketones **7** existed nearly exclusively in the open-chain tautomer form. Only trace amounts of the ring tautomers could be observed by NMR for **7g** and **7h**.

In order to demonstrate the utility of this method for the construction of more complex molecular scaffolds we have completed the syntheses of the piperidine alkaloid anabasamine **12**[13] and its unnatural nicotine analogue **13**. Anabasamine was of interest due to its structural similarity to the tobacco alkaloids and its novel pharmacological profile of cholinergic and anti-inflammatory activity.[14]

As illustrated in Scheme 1, the nucleophilic ring-opening of lactones **1** and **5** by **2i** gave the prerequisite hydroxy pyridinyl ketones **3i** and **7i**, respectively, in good yields (Table 1 and Table 2). Generation of the piperidine (**8**) and the pyrrolidine (**9**) ring systems were then readily achieved by oxidation of the alcohols with Dess–Martin reagent to furnish the corresponding aldehydes, followed by reductive amination with methylamine hydrochloride/sodium cyanoborohydride in methanol.[15] The anabasine derivative **8** (58%) and nicotine derivative **9** (54%) were obtained in good overall yields for the two-step processes. The 6-methoxypyridinyl moieties were then converted in 77% and 55% yield, respectively, into the 6-chloropyridi-



Scheme 1 Synthesis of (±)-anabasamine (**12**) and nicotine analogue **13**

nyl derivatives **10** and **11**, with phosphorous oxychloride in a sealed pressure tube at 115 °C for 24 hours.

Finally, Suzuki–Miyaura coupling of the chloro derivatives **10** and **11** with 3-pyridineboronic acid using a variety of palladium/ligand systems and conditions, afforded the target natural product (±)-anabasamine (**12**) and the corresponding nicotine derivative **13** in modest yields (40–50%).[16] However, the catalytic system reported by Nolan and co-workers was found to be superior for this system, providing **12** in 80% yield and **13** in 81% yield.[17] Overall, this first total synthesis of the alkaloid (±)-anabasamine (**12**) was achieved in 35% yield via the five-step sequence from **1**. The nicotine derivative **13** was obtained in 21% overall yield from **5**.

All chemicals were purchased from Aldrich Chemical Company and used as received unless otherwise noted. Proton and carbon NMR were recorded on a Varian 400 MHz spectrometer at ambient temperature in $CDCl_3$ from Cambridge Isotope Laboratories, Inc. ^{1}H NMR chemical shifts are reported as δ values (ppm) relative to tetramethylsilane. ^{13}C NMR chemical shifts are reported as δ values (ppm) relative to $CDCl_3$ (77.0 ppm). Melting points (mp) were measured with an Electrothermal R Mel-Temp apparatus and are uncorrected. Atlantic Microlab, Inc., Norcross, GA performed all CHN microanalyses.

Nucleophilic Ring-Opening of 1 or 5; General Method A

Under an atmosphere of nitrogen, to a stirred solution of aryl bromide **2** (5 mmol, 1 equiv) in anhydrous Et_2O (80 mL), was added a solution of BuLi (1.6 M in hexanes, 6 mmol, 1.2 equiv) dropwise over 15 min at –78 °C. The solution was stirred for an additional 15 min at –78 °C and then a solution of lactone (**1** or **5**; 5 mmol, 1 equiv) in Et_2O (20 mL) was added dropwise. The reaction was allowed to warm to r.t. and stirred for 2 h. Brine (75 mL) was added to quench the reaction and the organic layer was taken. The aqueous layer was extracted with EtOAc (2 × 50 mL) and CH_2Cl_2 (2 × 50 mL). The combined organic portions were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2; hexanes–EtOAc) to afford hydroxy aryl ketone **3** or **7**.

5-Hydroxy-1-phenylpentan-1-one (3a)[3]

Prepared by Method A.

Yield: 565 mg (79%); light-yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.61–1.68 (m, 2 H), 1.79–1.87 (m, 2 H), 1.99 (s, 1 H), 3.02 (t, *J* = 7.1 Hz, 2 H), 3.66 (t, *J* = 6.3 Hz, 2 H), 7.45 (t, *J* = 7.9 Hz, 2 H), 7.55 (t, *J* = 7.4 Hz, 1 H), 7.95 (m, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 20.4, 32.4, 38.3, 62.6, 128.3, 128.8, 133.3, 137.1, 200.7.

Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 73.63; H, 7.98.

5-Hydroxy-1-*p*-tolylpentan-1-one (3b)[2c]

Prepared by Method A.

Yield: 837 mg (87%); white solid; mp 36–38 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.56–1.75 (m, 3 H), 1.84 (m, 2 H), 2.38 (s, 3 H), 3.00 (t, *J* = 7.1 Hz, 2 H), 3.67 (dd, *J* = 11.6, 6 Hz, 2 H), 7.26 (d, *J* = 7.3 Hz, 2 H), 7.87 (d, *J* = 8.2 Hz, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 20.5, 21.9, 32.5, 38.2, 62.5, 128.4, 129.5, 134.6, 144.1, 200.5.

Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.75; H, 8.49.

1-(4-Chlorophenyl)-5-hydroxypentan-1-one (3c)

Prepared by Method A.

Yield: 0.77 g (72%); white solid; mp 59–61 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.61–1.69 (m, 3 H), 1.80–1.88 (m, 2 H), 3.00 (t, *J* = 7.1 Hz, 2 H), 3.68 (dd, *J* = 11.6, 5.8 Hz, 2 H), 7.43 (d, *J* = 8.4 Hz, 1 H), 7.90 (d, *J* = 8.5 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.4, 32.4, 38.3, 62.6, 129.1, 129.7, 135.4, 139.7, 199.3.

Anal. Calcd for $C_{11}H_{13}ClO_2$: C, 62.12; H, 6.16. Found: C, 62.17; H, 6.10.

5-Hydroxy-1-(4-methoxyphenyl)pentan-1-one (3d)[4]

Prepared by Method A.

Yield: 933 mg (90%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.60–1.68 (m, 2 H), 1.77–1.85 (m, 2 H), 2.01 (s, 1 H), 2.96 (t, *J* = 7.1 Hz, 2 H), 3.65 (dd, *J* = 10.7, 5.9 Hz, 2 H), 3.85 (s, 3 H), 6.89–6.93 (m, 2 H), 7.91–7.95 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.6, 32.5, 38.0, 55.7, 62.5, 113.9, 127.5, 130.5, 163.7, 199.3.

Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.63; H, 7.74.

5-Hydroxy-1-(pyridin-2-yl)pentan-1-one (3g)[18]

Prepared by Method A.

Yield: 730 mg (81%); yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.63–1.71 (m, 2 H), 1.77–1.87 (m, 2 H), 1.92 (s, 1 H), 3.25 (t, *J* = 7.3 Hz, 2 H), 3.69 (t, *J* = 6.1 Hz, 2 H), 7.46 (ddd, *J* = 7.5, 4.8, 1.0 Hz, 1 H), 7.83 (td, *J* = 7.7, 1.7 Hz, 1 H), 8.03 (d, *J* = 7.9 Hz, 1 H), 8.66 (d, *J* = 4.7 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.5, 20.3, 25.5, 32.4, 35.8, 37.4, 62.5, 62.6, 95.1, 120.2, 122.1, 123.6, 127.3, 137.2, 137.6, 147.7, 149.1, 153.5, 161.1, 202.1.

Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82. Found: C, 66.96; H, 7.46; N, 7.73.

5-Hydroxy-1-(pyridin-3-yl)pentan-1-one (3h)[2d]
Prepared by Method A.

Yield: 350 mg (63%); yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.64–1.72 (m, 2 H), 1.83–1.99 (m, 3 H), 3.06 (t, *J* = 7.1 Hz, 2 H), 3.70 (t, *J* = 6.1 Hz, 2 H), 7.43 (dd, *J* = 8.0, 4.8 Hz, 1 H), 8.25 (m, 1 H), 8.77 (dd, *J* = 4.8, 0.8 Hz, 1 H), 9.17 (d, *J* = 2.1 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 20.3, 32.2, 38.7, 62.3, 124.0, 132.4, 135.8, 149.6, 153.4, 199.4.

Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82. Found: C, 65.74; H, 7.39; N, 7.67.

4-Hydroxy-1-(6-methoxypyridin-3-yl)butan-1-one (3i)[6]
Prepared by General Method A.

Yield: 1.0 g (98%); pale-yellow solid; mp 42–44 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.80 (d, *J* = 2.4 Hz, 1 H), 8.14 (dd, *J* = 8.7, 2.4 Hz, 1 H), 6.79 (d, *J* = 8.7 Hz, 1 H), 4.01 (s, 3 H), 3.68 (t, *J* = 6.3 Hz, 2 H), 2.97 (t, *J* = 7.1 Hz, 2 H), 1.92 (br s, 1 H), 1.81–1.87 (m, 2 H), 1.64–1.70 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.3, 166.9, 149.2, 138.4, 126.8, 111.4, 62.5, 54.3, 38.2, 32.4, 20.4.

Anal. Calcd for $C_{10}H_{15}NO_3$: C, 63.14; H, 7.23; N, 6.69. Found: C, 62.97; H, 7.19; N, 6.64.

5-Hydroxy-1-(thiophen-2-yl)pentan-1-one (3j)
Prepared by Method A.

Yield: 726 mg (79%); yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.62–1.71 (m, 3 H), 1.82–1.90 (m, 2 H), 2.97 (t, *J* = 7.2 Hz, 2 H), 3.67 (dd, *J* = 10.4, 6 Hz, 2 H), 7.13 (dd, *J* = 4.9, 3.8 Hz, 1 H), 7.63 (dd, *J* = 4.9, 1.1 Hz, 1 H), 7.73 (dd, *J* = 3.8, 1.1 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.9, 32.3, 39.1, 62.4, 128.4, 132.2, 133.9, 144.4, 193.8.

Anal. Calcd for $C_9H_{12}O_2S$: C, 58.67; H, 6.56. Found: C, 58.50; H, 6.70.

1,1-Diphenylbutane-1,4-diol (6a)[2a]

Prepared by Method A.

Yield: 393 mg (65%); white solid; mp 104–106 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.54–1.61 (m, 2 H), 1.94 (s, 1 H), 2.41 (t, *J* = 7.2 Hz, 2 H), 3.24 (s, 1 H), 3.63 (t, *J* = 5.6 Hz, 2 H), 7.18–7.23 (m, 2 H), 7.27–7.32 (m, 4 H), 7.39–7.43 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.4, 39.2, 63.3, 78.1, 126.3, 127.0, 128.4, 147.3.

Anal. Calcd for $C_{16}H_{18}O_2$: C, 79.31; H, 7.49. Found: C, 79.06; H, 7.55.

1,1-Di-*p*-tolylbutane-1,4-diol (6b)
Prepared by Method A.

Yield: 486 mg (72%); white solid; mp 106–108 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.53–1.62 (m, 2 H), 1.83 (s, 1 H), 2.31 (s, 6 H), 2.38 (t, *J* = 7.2 Hz, 2 H), 2.94 (s, 1 H), 3.64 (s, 2 H), 7.10 (d, *J* = 8.0 Hz, 4 H), 7.29 (d, *J* = 8.2 Hz, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.2, 27.5, 39.2, 63.4, 78.0, 126.2, 129.1, 136.5, 144.5.

Anal. Calcd for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 79.66; H, 8.19.

1,1-Di(4-chlorophenyl)butane-1,4-diol (6c)[10b]
Prepared by Method A.

Yield: 529 mg (68%); white solid; mp 125–127 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.50–1.60 (m, 2 H), 2.11 (s, 1 H), 2.37 (t, *J* = 7.1 Hz, 2 H), 3.64 (t, *J* = 5.6 Hz, 2 H), 3.83 (s, 1 H), 7.24–7.28 (m, 4 H), 7.30–7.34 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.0, 39.3, 63.2, 76.5, 127.7, 128.6, 133.0, 145.6.

Anal. Calcd for $C_{16}H_{16}Cl_2O_2$: C, 61.75; H, 5.18. Found: C, 61.76; H, 5.36.

1,1-Di(4-methoxyphenyl)butane-1,4-diol (6d)
Prepared by Method A.

Yield: 584 mg (77%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.54–1.61 (m, 2 H), 1.73 (s, 1 H), 2.36 (t, *J* = 7.6 Hz, 2 H), 2.83 (s, 1 H), 3.66 (m, 2 H), 3.78 (d, *J* = 6.0 Hz, 6 H), 6.80–6.85 (m, 4 H), 7.29–7.33 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.5, 39.4, 55.5, 63.4, 100.2, 113.6, 127.5, 139.8, 158.5.

Anal. Calcd for $C_{18}H_{22}O_4$: C, 71.50; H, 7.33. Found: C, 70.69; H, 7.26.

1,1-Di(thiophen-2-yl)butane-1,4-diol (6j)
Prepared by Method A.

Yield: 445 mg (70%); white solid; mp 94–96 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.67–1.74 (m, 2 H), 1.92 (t, *J* = 4.9 Hz, 1 H), 2.48 (t, *J* = 7.0 Hz, 2 H), 3.70 (dd, *J* = 10.8, 5.7 Hz, 2 H), 4.33 (s, 1 H), 6.93–6.97 (m, 4 H), 7.22 (dd, *J* = 4.9, 1.4 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.5, 42.9, 63.2, 76.1, 123.9, 124.8, 126.9, 152.4.

Anal. Calcd for $C_{12}H_{14}O_2S_2$: C, 56.66; H, 5.55. Found: C, 56.91; H, 5.83.

General Method B
Under an atmosphere of nitrogen, to a stirred solution of aryl bromide **2** (5 mmol, 1 equiv) in anhydrous Et_2O (40 mL), was added a solution of BuLi (1.6 M in hexanes, 6 mmol, 1.2 equiv) dropwise over 15 min at –78 °C. The solution was stirred for an additional 15 min at –78 °C and then added slowly via cannula to a solution of lactone **5** (5 mmol, 1 equiv) in Et_2O (40 mL) at –78 °C. The reaction was allowed to warm to r.t. and stirred for 2 h. Brine (75 mL) was added to quench the reaction and the organic layer was taken. The aqueous layer was extracted with EtOAc (2 × 50 mL) and CH_2Cl_2 (2 × 50 mL). The combined organic portions were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2; hexanes–EtOAc) to afford the γ-hydroxy aryl ketone **7**.

4-Hydroxy-1-phenylbutan-1-one (7a)[7]
Prepared by Method B.

Yield: 582 mg (71%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.84 (t, *J* = 5.3 Hz, 1 H), 1.99–2.06 (m, 2 H), 3.14 (t, *J* = 6.9 Hz, 2 H), 3.75 (dd, *J* = 5.9, 11.3 Hz, 2 H), 7.43–7.48 (m, 2 H), 7.54–7.59 (m, 1 H), 7.96–7.99 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.1, 35.5, 62.6, 128.3, 128.8, 133.4, 137.1, 200.8.

Anal. Calcd for $C_{10}H_{12}O_2$: C, 73.15; H, 7.37. Found: C, 72.88; H, 7.42.

4-Hydroxy-1-*p*-tolylbutan-1-one (7b)[5b]
Prepared by Method B.

Yield: 593 mg (67%); white solid; mp 42–44 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.86 (s, 1 H), 1.98–2.05 (m, 2 H), 2.41 (s, 3 H), 3.11 (t, *J* = 6.9 Hz, 2 H), 3.75 (s, 2 H), 7.27 (d, *J* = 8.0 Hz, 2 H), 7.88 (d, *J* = 8.2 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.9, 27.2, 35.5, 62.6, 128.4, 129.5, 134.6, 144.2, 200.4.

Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 73.98; H, 7.98.

1-(4-Chlorophenyl)-4-hydroxybutan-1-one (7c)[19]
Prepared by Method B.

Yield: 628 mg (63%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.77 (s, 1 H), 1.96–2.04 (m, 2 H), 3.10 (t, *J* = 6.9 Hz, 2 H), 3.74 (t, *J* = 6.0 Hz, 2 H), 7.44 (d, *J* = 8.5 Hz, 2 H), 7.92 (d, *J* = 8.5 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.0, 35.4, 62.4, 129.1, 129.7, 135.4, 139.8, 199.5.

Anal. Calcd for $C_{10}H_{11}ClO_2$: C, 60.46; H, 5.58. Found: C, 60.66; H, 5.81.

4-Hydroxy-1-(4-methoxyphenyl)butan-1-one (7d)[20]
Prepared by Method B.

Yield: 660 mg (68%); white solid; mp 46–48 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.93 (t, *J* = 5.2 Hz, 1 H), 1.97–2.04 (m, 2 H), 3.08 (t, *J* = 6.9 Hz, 2 H), 3.74 (q, *J* = 5.7 Hz, 2 H), 3.87 (s, 3 H), 6.93 (d, *J* = 9.0 Hz, 2 H), 7.96 (d, *J* = 9.0 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.3, 35.2, 55.7, 62.6, 114.0, 127.5, 130.6, 163.7, 199.4.

Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 67.97; H, 7.37.

4-Hydroxy-1-(pyridin-2-yl)butan-1-one (7g)[8]
Prepared by Method A.

Yield: 577 mg (70%); yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.98–2.05 (m, 2 H), 2.57 (t, *J* = 5.7 Hz, 1 H), 3.31 (t, *J* = 7.0 Hz, 2 H), 3.70 (q, *J* = 6.0 Hz, 2 H), 7.48 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1 H), 7.84 (td, *J* = 7.7, 1.7 Hz, 1 H), 8.03 (d, *J* = 7.9 Hz, 1 H), 8.66 (d, *J* = 4.7 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 27.8, 34.5, 62.2, 122.1, 127.5, 137.3, 149.1, 153.6, 202.7.

Anal. Calcd for $C_9H_{11}NO_2$: C, 65.44; H, 6.71; N, 8.48. Found: C, 64.76; H, 7.04; N, 8.29.

4-Hydroxy-1-(pyridin-3-yl)butan-1-one (7h)[2d]
Prepared by Method A.

Yield: 545 mg (66%); light-yellow solid; mp 36–38 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.98–2.05 (m, 2 H), 2.40 (t, *J* = 5.1 Hz, 1 H), 3.13 (t, *J* = 7.0 Hz, 2 H), 3.74 (dd, *J* = 11.3, 5.8 Hz, 2 H), 7.40 (dd, *J* = 8.0, 4.8 Hz, 1 H), 8.23 (dt, *J* = 8.0, 2.0 Hz, 1 H), 8.74 (dd, *J* = 4.8, 1.7 Hz, 1 H), 9.16 (d, *J* = 2.2 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.8, 35.6, 61.7, 124.0, 132.4, 135.8, 149.6, 153.4, 199.4.

Anal. Calcd for $C_9H_{11}NO_2$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.85; H, 6.82; N, 8.45.

4-Hydroxy-1-(6-methoxypyridin-3-yl)butan-1-one (7i)
Prepared by Method A.

Yield: 870 mg (89%); pale-yellow solid; mp 35–37 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.82 (d, *J* = 2.4 Hz, 1 H), 8.15 (dd, *J* = 8.7, 2.5 Hz, 1 H), 6.79 (d, *J* = 8.7 Hz, 1 H), 4.01 (s, 3 H), 3.75 (d, *J* = 4.4 Hz, 2 H), 3.08 (t, *J* = 6.9 Hz, 2 H), 2.14 (s, 1 H), 1.98–2.05 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.5, 167.0, 149.3, 138.4, 126.8, 111.4, 62.3, 54.3, 35.3, 27.0.

Anal. Calcd for $C_{10}H_{13}NO_3$: C, 61.53; H, 6.71; N, 7.18. Found: C, 61.70; H, 6.82; N, 7.03.

4-Hydroxy-1-(thiophen-2-yl)butan-1-one (7j)[21]
Prepared by Method B.

Yield: 641 mg (75%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.87 (t, *J* = 5.3 Hz, 1 H), 1.99–2.06 (m, 2 H), 3.08 (t, *J* = 7.0 Hz, 2 H), 3.75 (q, *J* = 5.8 Hz, 2 H), 7.12–7.15 (m, 1 H), 7.64 (dd, *J* = 4.9, 1.0 Hz, 1 H), 7.75 (dd, *J* = 3.8, 1.0 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.4, 36.2, 62.4, 128.4, 132.3, 133.9, 144.4, 193.7.

Anal. Calcd for $C_8H_{10}O_2S$: C, 56.44; H, 5.92. Found: C, 56.05; H, 6.10.

6′-Methoxy-1-methylanabasine (8)
To a solution of the δ-hydroxy aryl ketone **3i** (1.25 g, 6 mmol) in CH_2Cl_2 (60 mL) at r.t. under an atmosphere of nitrogen, was added a solution of Dess–Martin reagent in CH_2Cl_2 (3.80 g, 9.0 mmol, 12 mL). The mixture was stirred for 1.5 h, then diluted with Et_2O (50 mL) and poured into a solution of $Na_2S_2O_3$ (8.5 g) in sat. $NaHCO_3$ (60 mL) and stirred for 5 min until clear. The organic layer was taken and the aqueous mixture was extracted with Et_2O (3 × 50 mL). The combined organic portions were washed with sat. $NaHCO_3$ (50 mL), H_2O (50 mL) and dried over Na_2SO_4. The solids were filtered and the solvent was removed under reduced pressure to afford the corresponding aldehyde in nearly quantitative yield. The aldehyde was then used in the next step without further purification. The aldehyde (1.2 g, 6.0 mmol), $MeNH_2$·HCl (400 mg, 6.0 mmol) and $NaCNBH_3$ (400 mg, 9.0 mmol) were dissolved in anhydrous MeOH (25 mL) and stirred under nitrogen at r.t. for 48 h. The solvent was removed under reduced pressure followed by addition of sat. Na_2CO_3 (100 mL) to the residue. The mixture was exacted with CH_2Cl_2 (3 × 100 mL) and the combined extracts were dried over Na_2SO_4. The solids were filtered, the solvent removed under reduced pressure and the residue purified by column chromatography (SiO_2; MeOH–CH_2Cl_2, 1:9) to afford **8**.

Yield: 720 mg (58%); oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.02 (d, *J* = 2.0 Hz, 1 H), 7.61 (dd, *J* = 8.6, 2.4 Hz, 1 H), 6.71 (d, *J* = 8.4 Hz, 1 H), 3.93 (s, 3 H), 3.02 (d, *J* = 11.6 Hz, 1 H), 2.75 (dd, *J* = 11.0, 2.4 Hz, 1 H), 2.14 (m, 1 H), 1.99 (s, 3 H), 1.81 (d, *J* = 12.8 Hz, 1 H), 1.73–1.52 (m, 4 H), 1.42–1.30 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.6, 145.8, 137.7, 111.0, 67.5, 57.5, 53.4, 44.4, 35.7, 26.0, 24.9.

Anal. Calcd for $C_{12}H_{18}N_2O$: C, 69.87; H, 8.80; N, 13.58. Found: C, 69.90; H, 8.71; N, 13.42.

6′-Methoxynicotine (9)[22]
The nicotine derivative was prepared from **7i** (1.2 g, 6.0 mmol) in similar fashion to that of **8**, to furnish **9**.

Yield: 670 mg (54%); yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03 (d, *J* = 2.4 Hz, 1 H), 7.62 (dd, *J* = 8.6, 2.4 Hz, 1 H), 6.74 (d, *J* = 8.8 Hz, 1 H), 3.93 (s, 3 H), 3.24 (t, *J* = 8.0 Hz, 1 H), 3.01 (t, *J* = 8.4 Hz, 1 H), 2.28 (m, 1 H), 2.15 (s, 3 H), 2.01–1.68 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.8, 146.1, 137.8, 131.0, 111.1, 68.4, 57.0, 53.4, 40.2, 34.7, 22.4.

Anal. Calcd for $C_{11}H_{16}N_2O$: C, 68.72; H, 8.39; N, 14.57. Found: C, 68.57; H, 8.70; N, 14.40.

6′-Chloro-1-methylanabasine (10)

The methoxy derivative **8** (500 mg, 2.4 mmol) was dissolved in $POCl_3$ (10 mL) and sealed in a glass pressure tube. The reaction was stirred at 115 °C for 24 h. The reaction mixture was cooled to 0 °C then the excess $POCl_3$ was removed under reduced pressure. The viscous residue was added to ice-water (50 mL), then the aqueous solution was slowly added to sat. Na_2CO_3 (50 mL) at 0 °C. The mixture was extracted with CH_2Cl_2 (5 × 50 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by gravity column chromatography (SiO_2; MeOH–CH_2Cl_2, 1:9) to afford **10**.

Yield: 404 mg (77%); yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.29 (d, *J* = 2.0 Hz, 1 H), 7.67 (dd, *J* = 8.0, 2.4 Hz, 1 H), 7.29 (d, *J* = 8.4 Hz, 1 H), 3.02 (d, *J* = 11.6 Hz, 1 H), 2.82 (dd, *J* = 12.0, 3.2 Hz, 1 H), 2.14–2.08 (m, 1 H), 1.98 (s, 3 H), 1.82 (d, *J* = 12.0 Hz, 1 H), 1.73–1.66 (m, 3 H), 1.55–1.33 (m, 2 H).

^{13}C NMR (100 MHz, $CDC1_3$): δ = 150.1, 149.1, 139.5, 137.9, 124.4, 65.5, 57.3, 44.6, 36.2, 26.0, 24.8.

Anal. Calcd for $C_{11}H_{15}N_2Cl$: C, 62.70; H, 7.18; N, 13.30. Found: C, 62.57; H, 7.30; N, 13.40.

6′-Chloronicotine (11)

Prepared from **9** (460 mg, 2.4 mmol) in a similar fashion to that of **10**, to furnish **11**.

Yield: 280 mg (55%); yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.30 (d, *J* = 2.0 Hz, 1 H), 7.68 (dd, *J* = 8.4, 2.2 Hz, 1 H), 7.29 (d, *J* = 8.4 Hz, 1 H), 3.23 (m, 1 H), 3.09 (t, *J* = 8.0 Hz, 1 H), 2.31 (m, 2 H), 2.16 (s, 3 H), 2.01–1.91 (m, 1 H), 1.90–1.78 (m, 1 H), 1.72–1.64 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.2, 149.3, 138.0, 137.5, 124.4, 68.2, 57.1, 40.5, 35.5, 22.7.

Anal. Calcd for $C_{10}H_{13}N_2Cl$: C, 61.07; H, 6.66; N, 14.24. Found: C, 60.87; H, 6.86; N, 14.10.

(±)-Anabasamine (12)[13]

Under an atmosphere of argon, **10** (125 mg, 0.60 mmol, 1.0 equiv), pyridine-3-boronic acid (110 mg, 0.90 mmol, 1.5 equiv), η^3-allyl[1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene]palladium(II) chloride (35 mg, 0.060 mmol, 0.1 equiv) and sodium *tert*-butoxide (118 mg, 1.2 mmol, 2.0 equiv) were added to anhydrous dioxane (10 mL). The reaction mixture was stirred vigorously at 85 °C for 8 h. The cooled reaction mixture was filtered through Celite 545 (2 g) and rinsed with EtOAc (5 mL) and CH_2Cl_2 (5 mL). The filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2; hexanes–EtOAc, 30:70) to afford **12**.

Yield: 120 mg (80%); yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.20 (d, *J* = 1.6 Hz, 1 H), 8.65 (d, *J* = 1.6 Hz, 1 H), 8.63 (s, 1 H), 8.33 (dd, *J* = 8.0, 1.2 Hz, 1 H), 7.81 (dd, *J* = 8.0, 2.0 Hz, 1 H), 7.73 (d, *J* = 8.0 Hz, 1 H), 7.40 (m, 1 H), 3.06 (d, *J* = 11.6 Hz, 1 H), 2.89 (dd, *J* = 11.2, 2.4 Hz, 1 H), 2.18–2.12 (m, 1 H), 2.04 (s, 3 H), 1.86–1.54 (m, 6 H). ^{1}H NMR data were consistent with previously reported values.[13]

^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.9, 149.9, 149.8, 148.3, 139.8, 136.1, 135.0, 134.4, 123.8, 120.7, 68.1, 57.5, 44.8, 36.1, 26.1, 24.9.

Anal. Calcd for $C_{16}H_{19}N_3$: C, 75.85; H, 7.56; N, 16.59. Found: C, 75.77; H, 7.86; N, 16.20.

6′-(3-Pyridinyl)nicotine (13)[23]

Prepared from **11** (118 mg, 0.60 mmol) in a similar fashion to that of **12**, to furnish **13**.

Yield: 116 mg (81%); pale-yellow oil.

^{1}H NMR (400 MHz, $CDC1_3$): δ = 9.19 (s, 1 H), 8.64 (s, 2 H), 8.32 (d, *J* = 8.4 Hz, 1 H), 7.84 (dd, *J* = 8.0, 1.6 Hz, 1 H), 7.74 (d, *J* = 8.4 Hz, 1 H), 7.41 (m, 1 H), 3.29 (t, *J* = 8.0 Hz, 1 H), 3.18 (t, *J* = 8.4 Hz, 1 H), 2.39–2.33 (m, 2 H), 2.22 (s, 3 H), 2.07–1.74 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.1, 150.1, 150.0, 148.4, 139.5, 136.2, 135.5, 134.5, 123.8, 120.8, 68.8, 57.2, 40.6, 35.4, 22.8.

Anal. Calcd for $C_{15}H_{17}N_3$: C, 75.28; H, 7.16; N, 17.56. Found: C, 75.01; H, 7.47; N, 17.31.

Acknowledgment

This research was funded by the National Institute on Drug Abuse (DA11528), the Louisiana Board of Regents and the University of New Orleans.

References

(1) New address: S. C. DiMaggio, Department of Chemistry, Xavier University of Louisiana, New Orleans, LA 70118, USA
(2) (a) Descotes, G.; Soula, J.-C. *Bull. Soc. Chim. Fr.* **1964**, 2636. (b) Crich, D.; Huang, X.; Newcomb, M. *Org. Lett.* **1999**, *1*, 225. (c) Bailey, W. F.; Khanolkar, A. D. *Tetrahedron* **1991**, *47*, 7727. (d) Ohkawa, S.; Terao, S.; Terashita, Z.; Shibouta, Y.; Nishikawa, K. *J. Med. Chem.* **1991**, *34*, 267.
(3) Rosenblum, S. B.; Bihovsky, R. *J. Am. Chem. Soc.* **1990**, *112*, 2746.
(4) (a) Atkinson, R. S. *Chem. Commun.* **1970**, 177. (b) Atkinson, R. S. *J. Chem. Soc.* **1971**, 784.
(5) (a) Fuji, K.; Node, M.; Usami, Y.; Kiryu, Y. *J. Chem. Soc., Chem. Commun.* **1987**, 449. (b) Fuji, K.; Usami, Y.; Kiryu, Y.; Node, M. *Synthesis* **1992**, 852.
(6) Miao, L.; DiMaggio, S. C.; Shu, H.; Trudell, M. L. *Org. Lett.* **2009**, *11*, 1579.
(7) Yang, S.-B.; Gan, F.-F.; Chen, G.-J.; Xu, P.-F. *Synlett* **2008**, 2532.
(8) Gómez, I.; Alonso, E.; Ramón, D. J.; Yus, M. *Tetrahedron* **2000**, *56*, 4043.
(9) Whiting, J. E.; Edward, J. T. *Can. J. Chem.* **1971**, *49*, 3799.
(10) (a) Vozza, J. F. *J. Org. Chem.* **1959**, *24*, 720. (b) Umio, S.; Ueda, I.; Nojima, H. *J. Med. Chem.* **1972**, *15*, 855.
(11) Brown, H. C.; Brewster, J. H.; Shechter, H. *J. Am. Chem. Soc.* **1954**, *76*, 467.
(12) Gossage, R. A.; Jastrzebski, J. T. B. H.; van Koten, G. *Angew. Chem. Int. Ed.* **2005**, *44*, 1448.
(13) Mukhamedzhanova, S. Z.; Aslanov, Kh. A.; Sadykov, A. S.; Leont'ev, V. B.; Kiryukhin, V. K. *Khim. Prir. Soedin.* **1968**, *24*, 158.
(14) (a) Tilyabaev, Z.; Abduvakhabov, A. A. *Chem. Nat. Compd.* **1998**, *34*, 295; *Khim. Prir. Soedin.* **1998**, *3*, 327. (b) Mukhamedzhanova, Kh. S.; Nasirov, S. K. h. *Dokl. Akad. Nauk. USSR* **1984**, *8*, 45. (c) Sapronov, N. S.; Khnychenko, L. K. *Farmakol. Toksikol.* **1982**, *45*, 25.
(15) Baxendale, I. R.; Brusotti, G.; Matsuoka, M.; Ley, S. V. *J. Chem. Soc., Perkin Trans. 1* **2002**, 143.
(16) (a) Zhang, C.; Huang, J.; Nolan, S. P.; Trudell, M. L. *J. Org. Chem.* **1999**, *64*, 3804. (b) Zhang, C.; Trudell, M. L. *Tetrahedron Lett.* **2000**, *41*, 595. (c) Grasa, G. A.; Viciu, M. S.; Huang, J.; Zhang, C.; Trudell, M. L.; Nolan, S. P. *Organometallics* **2002**, *21*, 2866.

(17) Viciu, M. S.; Germaneau, R. F.; Navarro-Fernandez, O.; Stevens, E. D.; Nolan, S. P. *Organometallics* **2002**, *21*, 5470.
(18) Shimizu, J.; Tsurki, T.; Yamagishi, Y.; Inchino, T. Japanese Patent JP06157459, **1994**; *Chem. Abstr.* **1994**, *121*, 179498.
(19) Huang, N.; Xu, L. *Youji Huaxue* **1989**, *9*, 436; *Chem. Abstr.* **1989**, *113*, 5301.
(20) Ramadas, S. R.; Sukumaran, K. B. *Ind. J. Chem.* **1970**, *8*, 470.
(21) Acheson, R. M.; Cooper, M. W. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1185.
(22) Dukat, M.; Fiedler, W.; Dumas, D.; Damaj, M. I.; Martin, B. R.; Rosencrans, J. A.; James, J. R.; Glennon, R. A. *Eur. J. Med. Chem.* **1996**, *331*, 875.
(23) Schmidt, B.; Neitemeier, V. *Synthesis* **1998**, 42.