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A CONVENIENT ASYMMETRIC SYNTHESIS OF PYRROLO[2,1-a]ISOQUINOLINES

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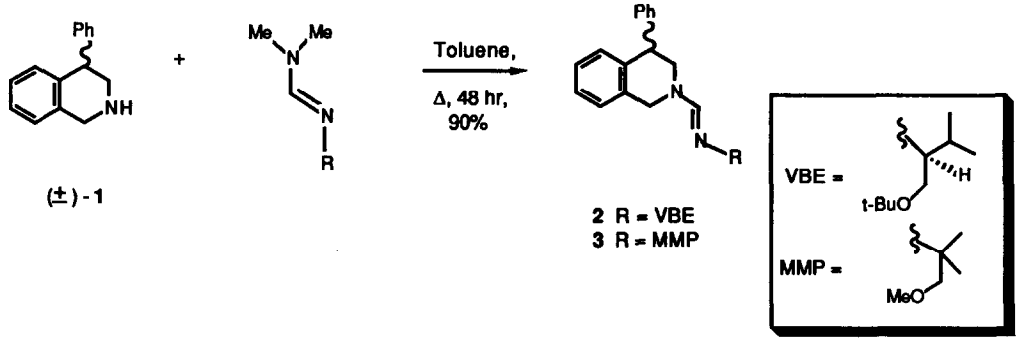
Summary: A four-step synthesis of optically pure 6α-phenyl pyrroloisoquinolines from chiral formamidines has been accomplished.

Pyrrolo[2,1-a]isoquinolines such as **4a**, **4b** have been shown to be an important class of compounds due to their significant anti-depressant activity.[1] Because of this, they have been the object of considerable synthetic activity primarily due to Maryanoff[2,3] who has described efficient routes to **4**. Asymmetric syntheses have also been described by these authors furnishing both diastereomers **4a**, **4b** in high enantiomeric excess.

We wish to describe a four-step, three-pot route to the 6α-phenylpyrroloisoquinoline **4a** which proceeds in good yield and high optical purity. The method is based upon the use of metalated chiral formamidines which are alkylated with a high degree of diastereoselectivity.[4]

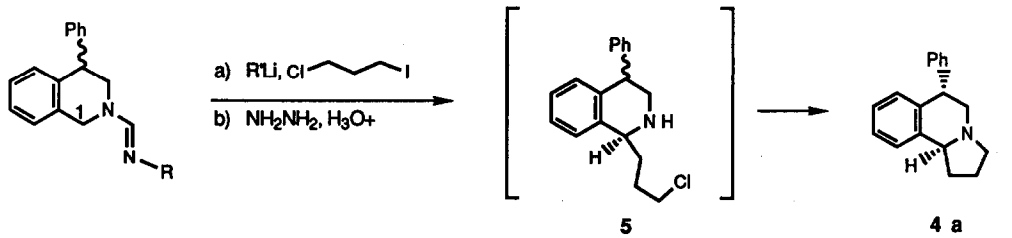
Starting with racemic 4-phenyl-1,2,3,4-tetrahydroisoquinoline **1**[5], reaction with the dimethylaminoformamidine transformed it into the chiral formamidine **2** by direct exchange. The

SCHEME 1



resulting diastereomeric mixture **2** was assured to be 1:1 by using excess chiral dimethylaminoformamidine and following the reaction until all of **1** was consumed. In a similar fashion, the achiral formamidine **3** was prepared using the 2-methyl-1-methoxypropyl amine as the formamidine component.[6]

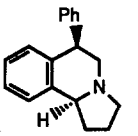
Metalation of formamidines **2** and **3** with s-BuLi or t-BuLi at -78°C resulted in a deep red solution, which after 30 minutes was alkylated at -100°C with 1-chloro-3-iodopropane. Removal of the formamidine auxiliary[7] (EtOH-H_2O-HOAc-NH_2NH_2, 8:1:1:2) at 0°C produced the secondary amine, **5** which spontaneously cyclized to a 2.2 : 1 ratio of diastereomers **4a**, **4b** (Table I) in greater than 80% yield over three steps. In an attempt to enhance the ratio of **4a** : **4b** the stoichiometry and nature of alkyl lithium base was varied (Table I). Most notable of these



2, R = VBE
3, R = MMP

5

4 a



4 b

results is (entry 5), wherein a deficiency of base resulted in a diastereomeric ratio of 13:1 for **4a** : **4b**, indicating a difference in the kinetic acidity of the C-1 protons for each formamidine diastereomer. Lithium diisopropylamide (entry 6) was found to be unsuitable as a base, most likely due to its weaker basicity.[8]

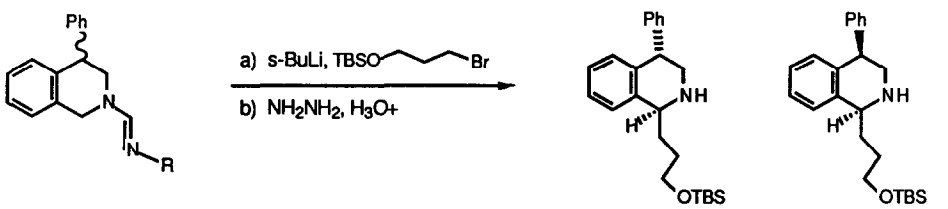
TABLE I

Entry	R'LI (eq.)[a]	R	YIELD(%)[b]	4a:4b[c]
1	*t*-BuLi(1.1)	VBE	58	1.1 : 1
2	*s*-BuLi(1.1)	VBE	86	2.2 : 1
3	*s*-BuLi(1.1)	MMP	53	1.1 : 1
4	*t*-BuLi(0.3)	VBE	25	1.1 : 1
5	*s*-BuLi(0.3)	VBE	25	13 : 1
6	LDA (0.5)	VBE	0	0

[a]All reactions run in tetrahydrofuran. [b]Yields after silica gel chromatography.
[c]Diastereomer ratio determined by capillary GC, (250°C, 5% phenyl methyl silicon)

Unfortunately, these high ratios were achieved at the expense of the chemical yield. The configurationally different formamidine diastereomers were undoubtedly metalating at different rates in the presence of a deficiency of base. In the case of the stronger base *t*-BuLi no such biased metalation was seen. The mixture **4a**, **4b** was separated by preparative HPLC [Waters Porasil;hexane (70%), ethyl acetate(28%), methanol(2%). The ^{1}H NMR spectrum of pure **4b** as its (R)-(+)-MTPA salt[9] indicated a large excess (>90%) of one enantiomer.

To further support the NMR assay, alkylated analogs of **1** were prepared. Formamidines **2** and **3** were individually metalated as outlined before, and then alkylated with the TBDMS ether of 3-bromo-propanol[10]. Removal of the formamidine auxiliary, produced the alkylated isoquinolines **6a** , **6b** in racemic and non-racemic form respectively. Pure **6a** and **6b**[11] were converted to their (S)-(-)-MTPA amides,[12] and the ^{19}F NMR spectra showed distinct signals for each enantiomer at -69.9, and -71.6 ppm ($CFCl_3$ internal standard). When **6a** was examined, an enantiomeric excess of >92%, was revealed.[13]



2 or 3 **6 a** **6 b**

The metalation/alkylation sequence of chiral formamidines provides a new method for the synthesis of pyrroloisoquinolines of type **4**, that occurs in >85% yield over the four steps and in high optical purity.

References and Notes

1. Maryanoff, B.E.; McComsey, D.F.; Constanzo, M.J.; Setler P.E.; Gardocki, J.F.; Shank R.P.; Schneider, C.R. *J.Med. Chem.* **1984**, *27*, 946.
2. Maryanoff, B.E.; McComsey, D.F.; Duhl-Emswiler *J.Org. Chem.* **1983**, *48*, 5062.
3. Maryanoff, B.E.; McComsey, D.F. *J.Heterocyclic Chem.* **1985**, *22*, 911. Maryanoff B.E.; McComsey, D.F.; Mutter, M.S.; Sorgi, K.L.; Maryanof, C.A. *Tet. Lett.* **1988**, *29*, 5073.
4. Meyers, A. I.; Miller, D. B.; White, F. H. *J. Am. Chem. Soc.* **1988**, *110*, 4778 and earlier references cited.
5. The authors thank Dr. Bruce E. Maryanoff, McNeil Pharmaceutical Co. for a sample of **1**.

6. Available from the condensation of 2-methyl-2-amino-1-propanol with DMF dimethyl acetal, followed by subsequent protection of the primary alcohol as its methyl ether using NaH and MeI. For further studies with this formamidine, see Meyers, A. I.; Du, B.; Gonzalez, M. *J. Org. Chem.* **1990**, in press.
7. Meyers, A.I.; Gulles, J.W. *Heterocycles* **1989**, *28*, 295, and earlier references cited.
8. LDA has been found to be a suitable base for deprotonation if the chiral auxiliary is protected as its methyl ether rather than t-butyl ether.
9. Villani, Jr., F.J.; Costanzo, M.J.; Inners, R.R.; Mutter, M.S.; McClure, D.E. *J.Org.Chem.* **1986**, *51*, 3715.
10. Available from the reaction of 3-bromopropanol with TBDMS chloride and triethylamine in methylene chloride.
11. **6a** and **6b** were assigned by correlation of their spectral data to that of **4a** and **4b**.
12. The amine was treated with 1.0 eq. of the acid chloride of (S)-(-)-α-Methoxy-α-(trifluoromethyl)-phenyl acetic acid (Aldrich Chem. Co.) and 1.0 eq. of triethylamine in methylene chloride. All spectra were recorded on a Bruker 300MHz NMR.
13. Physical data for new compounds: : **2** $[\alpha]_D$ -19.8° (c 1.1, $CHCl_3$); ^1H NMR 270 MHz ($CDCl_3$); δ 0.76-0.86(dd, 6H, J=6.71 Hz), 1.09-1.13(d, 9H, J=7.2Hz), 1.85(m,1H), 2.65(m, 1H), 3.15(m, 1H),3.45(m,2H), 3.78(m, 1H), 4.15(m, 1H), 4.7(m, 2H), 6.9-7.35(m, 10H) ppm; IR (film) 3062, 3025, 2974, 2870,1650, 1602, 1493, 1452, 1386, 1362, 1210, 1197, 1079, 1006, 886, 754, 701 cm^{-1}. **3** ^1H NMR 270 MHz ($CDCl_3$); δ 1.08(s,6H), 3.14(q, 2H, J=9,6.2 Hz), 3.31(s, 3H), 3.48(dd, 1H, 13,6 Hz), 3.80(dd, 1H, J=13, 4.5 Hz), 4.16(m, 1H), 4.56(ABq, 1H, J=17.7 Hz), 4.87(ABq, 1H, J=17.7 Hz), 6.9-7.35(m, 10H) ppm.^{13}C NMR 300 MHz ($CDCl_3$); δ 25.7, 25.9, 45.2, 45.8, 52.4, 55.9, 59.2, 82.6, 126.1, 126.2, 126.4, 126.5, 128.2, 128.6, 128.9, 129.4, 133.8, 137.2, 143.2, 151.0 ppm IR(film) 3061, 3025, 2964, 2874, 1645, 1493, 1451, 1385, 1280, 1158, 1108, 998, 963, 754, 702 cm^{-1}. **6a**: ^1H NMR 270 MHz ($CDCl_3$); δ 0.06(s, 6H), 0.91(s, 9H), 1.7-2.1(m, 6H), 3.01(dd, 1H, J=12.8, 7.5Hz), 3.44(dd, 1H, J=12.8, 5.1Hz), 3.7(m, 2H), 4.08-4.16(m, 2H), 6.8-7.3(m, 9H)ppm;^{13}C NMR 300 MHz ($CDCl_3$); δ 5.3, 18.3, 25.9, 32.8, 45.9, 49.8, 55.7, 63.1, 125.7, 125.9, 126.1, 126.3, 128.3, 128.8, 129.9, 138.1, 140.0, 144.8; IR (film) 3335, 3062, 3019, 2928, 2856, 1600, 1491, 1471,1451, 1387, 1360, 1255, 1100, 1004, 973, 836, 775, 750, 701 cm^{-1}; $[\alpha]_D$ -16.2° (c 1.6, $CHCl_3$). **6b** : ^1H NMR 270 MHz ($CDCl_3$); δ 0.64(s, 6H), 0.91(s, 9H), 1.69-2.1(m, 6H), 3.16-3.33(qd, 2H, J=15.0, 13.5, 5.0), 3.66-3.76(m, 2H), 4.05-4.1(m, 2H), 6.9-7.3(m, 9H). Compounds **4a**, **4b** are in agreement with that reported by Maryanoff, B.E.; McComsey, D.F.; Inners R.R.; Mutter, M.S.; Wooden, G.P.; Mayo, S.L.; Olofson, R.A. *J.Am.Chem. Soc.* **1989**, *111*, 2487.

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