Pyrroles and Indolizidines from Deprotonated α-(Alkylideneamino)nitriles

Ines Schäfer,[a,b] Till Opatz*[b]

[a] Department of Chemistry, University of Hamburg, Martin-Luther-King-Platz 6, 20146 Hamburg, Germany

[b] Institute of Organic Chemistry, University of Mainz, Duesbergweg 10–14, 55128 Mainz, Germany
Fax +49(6131)3922338; E-mail: opatz@uni-mainz.de

Received 10 March 2011; revised 5 April 2011

Dedicated to Professor Dieter Enders on the occasion of his 65th birthday

Abstract: Their ready availability from simple starting materials in only two synthetic steps and their versatility as building blocks for the construction of highly substituted amines and N-heterocycles renders α-(alkylideneamino)nitriles useful synthetic intermediates. Herein, short syntheses of tri- and tetrasubstituted pyrroles including the northern half of the HMG-CoA reductase inhibitor atorvastatin as well as an access to 3-substituted indolizidines will be described.

Key words: heterocycles, carbanions, pyrroles, Umpolung, Michael addition

Introduction

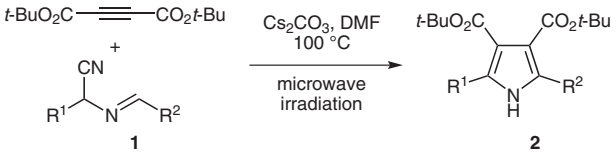
The powerful anion-stabilizing capacity of the cyano group allows Strecker products derived from aromatic or heteroaromatic aldehydes and secondary amines to be deprotonated under relatively mild conditions.[1–4] More surprisingly, even those α-aminonitriles derived from primary amines or ammonia can be α-deprotonated without inducing the impending retro-Strecker reaction, i.e. base-induced dehydrocyanation, if the correct base, such as potassium hexamethyldisilazanide, is employed at low temperatures.[4–6] The resulting keteniminates can serve as stabilized α-aminocarbanion equivalents in one-pot syntheses of highly substituted α-branched amines,[7] pyrrolidines,[8] 1,2-diamines,[9] β-amino alcohols,[10] or γ-amino acids.[11] After reaction with a suitable electrophile, the nitrile substituent can be removed under mild conditions as delocalization of the amine nitrogen lone pair into the σ*-orbital of the C–CN bond leads to its scission with formation of an iminium ion which can subsequently be trapped by suitable nucleophiles.[12]

The more effective charge delocalization in the resulting carbanions confers an increased CH acidity to α-(alkylideneamino)nitriles, which can even be deprotonated with cesium carbonate or amidine bases like DBU or 1,1,3,3-tetramethylguanidine (TMG).[13–15] The products obtained by alkylation or vinylogous addition of these stabilized 2-azaallyl anions are not susceptible to spontaneous elimination of cyanide, nevertheless, decyanation can be effected after removal of the C=N bond, e.g. by reduction or ring closure. The former option permits the preparation of γ-amino acids and pyrrolidines,[16,17] the latter process is a key step in a modular synthesis of tetrasubstituted pyrroles.[18]

Results and Discussion

Pyrroles belong to the most abundant aromatic N-heterocycles and new methods for their preparation are constantly being developed.[19–27] As demonstrated by Tsuge and Ueno, the thermal reaction of α-(alkylideneamino)nitriles **1** with acetylenedicarboxylates furnishes pyrrole-3,4-dicarboxylates **2** via the intermediate formation of N-protonated azomethine ylides in a prototropic shift.[28] The anionic variant of this reaction provides the same products in even higher yield if cesium carbonate as a base is combined with microwave irradiation of the reaction mixture (Table 1).

Table 1 Pyrroles from Acetylenedicarboxylates



1 2

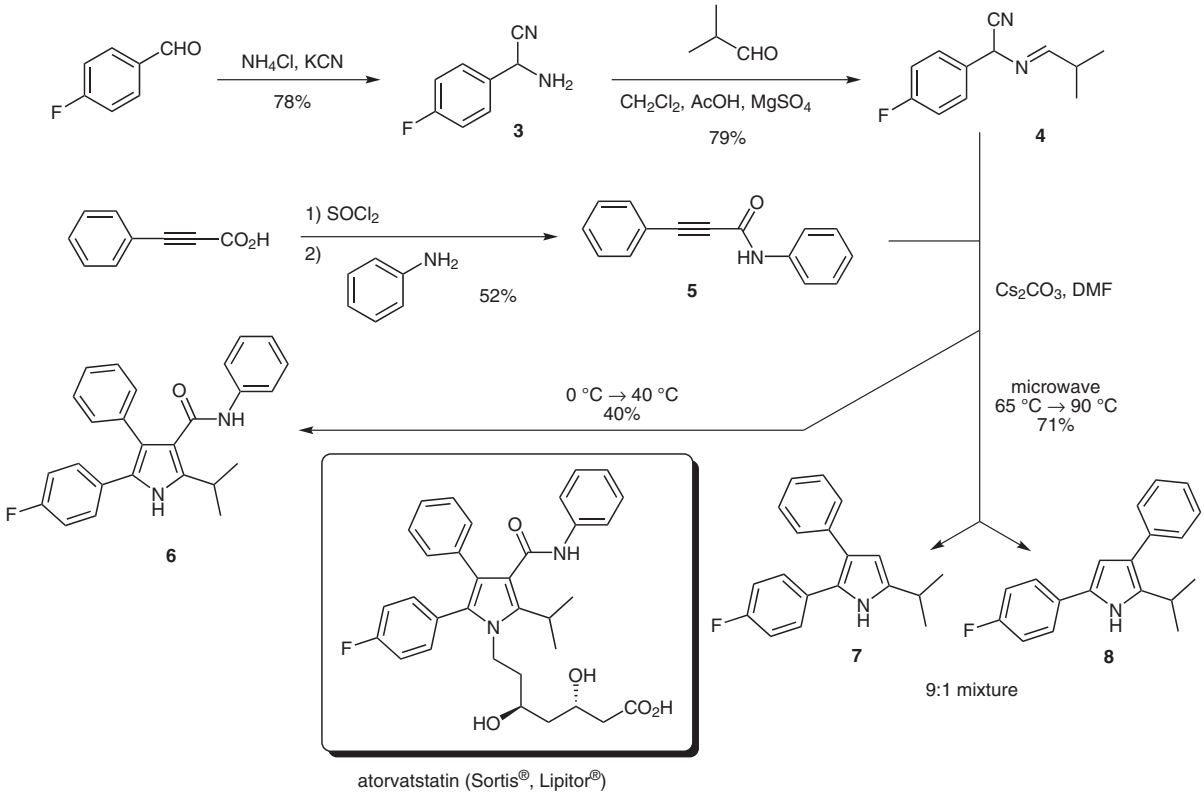
Imine	R^1	R^2	Pyrrole	Yield (%)
1a	Me	2-naphthyl	**2a**	67
1b	Bn	2-naphthyl	**2b**	51
1c	Bn	3,4-$(MeO)_2C_6H_3$	**2c**	56
1d	Ph	3,4-$(MeO)_2C_6H_3$	**2d**	62
1e	Cy	2-naphthyl	**2e**	55
1f	Cy	4-$O_2NC_6H_4$	**2f**	86

Moreover, alkynes with a single acceptor group turned out to be sufficiently reactive substrates under identical conditions. The products are formed in regioselective fashion and we chose the pyrrole portion of the top-selling antihyperlipidemic agent atorvastatin (Lipitor®, Sortis®, sales in 2008: 12.4 billion US$) as a test case.[29,30]

The pronucleophile was prepared by Strecker reaction of 4-fluorobenzaldehyde with ammonium chloride. The resulting aminonitrile **3** was condensed with isobutyraldehyde to furnish the α-(alkylideneamino)nitrile **4**. Reaction

SYNTHESIS 2011, No. 11, pp 1691–1704
Advanced online publication: 29.04.2011
DOI: 10.1055/s-0030-1260415; Art ID: Z26111SS
© Georg Thieme Verlag Stuttgart · New York

Downloaded by: University of Pittsburgh. Copyrighted material.



Scheme 1 Synthesis of the pyrrole portion of atorvastatin

of phenylpropiolic acid chloride with aniline gave the unsymmetrical electrophile **5**, the reaction of which with **4** surprisingly gave the highest yield of the target pyrrole **6** when the temperature of the reaction with cesium carbonate in *N*,*N*-dimethylformamide was low. In contrast, the conditions optimized for the reaction with acetylenedicarboxylates resulted in the formation of a 9:1 isomeric mixture of the decarbamoylated trisubstituted pyrroles **7** and **8** in 71% combined yield. The mechanism of their formation presumably involves the initial formation of pyrrolecarboxanilide **6** and its regioisomer which eliminate phenyl isocyanate in a retro-Friedel–Crafts reaction (Scheme 1).

For the formation of pyrrole **6** from **4** and **5**, two mechanistic alternatives may be discussed. One (path A) in-

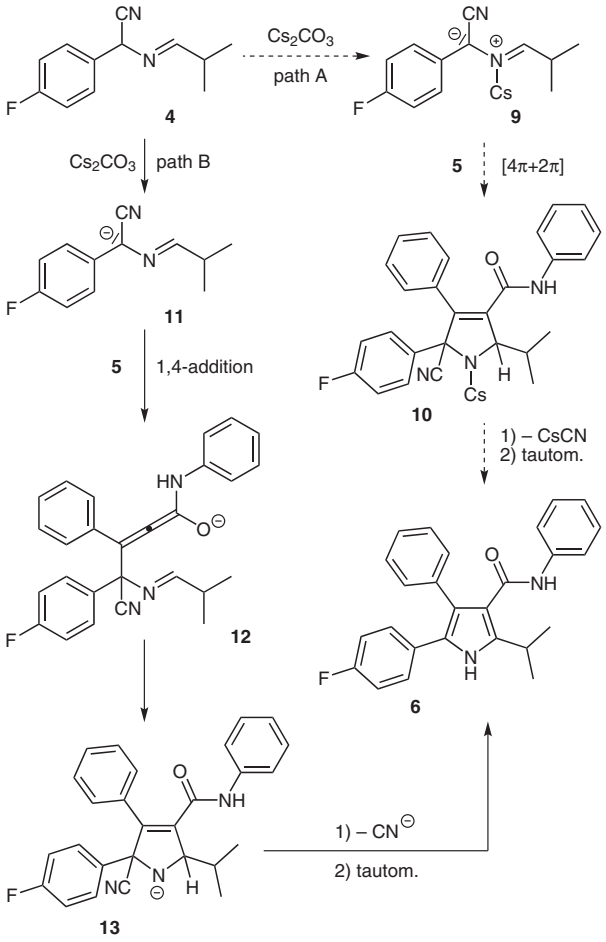
Biographical Sketches

Ines Schäfer (née Bergner) was born 1975 in Pritzwalk, Germany. After professional training as a laboratory assistant, she studied chemistry at the University of Mainz to earn her diploma degree in 2005. She performed her graduate studies at the University of Mainz and at the University of Hamburg under the supervision of Professor Till Opatz and received her Ph.D. in 2009. Her research projects focused on 1,4-additions of deprotonated α-aminonitriles and α-(alkylideneamino)nitriles. Currently, she is employed at Merck KGaA, Darmstadt.

Till Opatz was born in 1973 in Bad Homburg v. d. Höhe, Germany. He received his diploma in chemistry at the University of Frankfurt/M. and his Ph.D. at the University of Mainz. After a postdoctoral stay with Prof. Rob M. J. Liskamp in Utrecht, The Netherlands, he completed his habilitation under the supervision of Prof. Horst Kunz in 2006. In 2007, he was appointed Professor in Organic Chemistry at the University of Hamburg, and accepted an offer of chair at the University of Mainz in 2010. His research interests are the chemistry of natural products and the development of new synthetic methods.

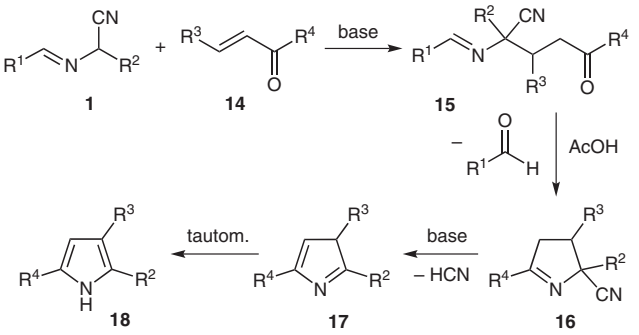
Downloaded by: University of Pittsburgh. Copyrighted material.

volves the intermediate formation of an N-metalated azomethine ylide **9** which adds to alkyne **5** in a 1,3-dipolar cycloaddition. Alternatively (path B), the anion of **4** reacts in a Michael addition with **5** and the resulting enolate **12** cyclizes to anion **13**, from which cyanide is eliminated, followed by tautomerization to the thermodynamically favored 1*H*-pyrrole.[31–34] Since the same reaction can be effected by amidine and guanidine bases, path B appears most likely and intermediates of the 1,4-addition derived from similar electrophiles have been characterized.[35] This, however, would mean that the 5-*endo*-trig cyclization involved in the latter process is proceeding efficiently (Scheme 2).



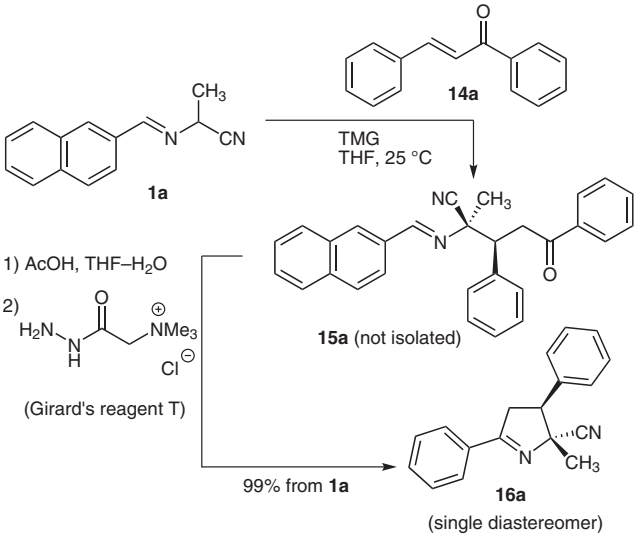
Scheme 2 1,4-Addition (path B) versus 1,3-dipolar cycloaddition (path A)

Vinylogous additions of α-(alkylideneamino)nitriles to enones may proceed very cleanly when amidine or guanidine bases are used in tetrahydrofuran at ambient temperature.[15] The addition products **15** represent imines of γ-aminocarbonyl compounds and should be prone to cyclization in acidic medium.[36] Indeed, the action of aqueous acetic acid liberates aldehydes from compounds **15** and leads to the entropy-driven formation of 3,4-dihydro-2*H*-pyrrole-2-carbonitriles **16**, which can in turn be dehydrocyanated to pyrroles **18** upon treatment with potassium *tert*-butoxide (Scheme 3).[37]



Scheme 3 Preparation of pyrroles by 1,4-addition and cyclization

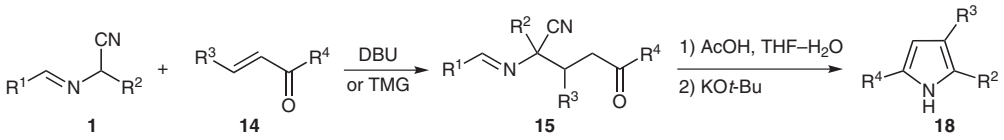
Cyanopyrrolines of type **16** can alternatively be obtained by condensation of enones with N-unsubstituted aminonitriles and subsequent base-induced electrocyclization of their conjugate anions. This procedure has already been employed by us for the synthesis of di- to tetrasubstituted pyrroles but turned out to be limited to products with an aromatic 5-substituent.[38] In contrast, the hydrolysis/cyclization sequence presented here readily provides 2,5-dialkyl-substituted pyrrolines **16**. Unfortunately, their dehydrocyanation is much less efficient than their formation and the yields of pyrroles **18** over three steps from α-(alkylideneamino)nitriles **1** are in the 20–40% range. For the removal of the aldehyde liberated in the cyclization step, Girard's reagent T[39] in combination with an aqueous extraction proved useful and was at least equally effective as a the chromatographic purification of intermediates **16**. For example, 2-methyl-3,5-diphenyl-3,4-dihydro-2*H*-pyrrole-2-carbonitrile (**16a**) could be obtained as a single diastereomer in 99% yield over two steps using the extractive procedure without any additional purification (Scheme 4). In contrast, the presence of the aldehyde in the dehydrocyanation led to the formation of addition products and diminished the overall yield. The obtained results are summarized in Table 2.

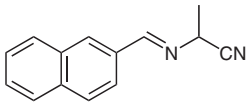
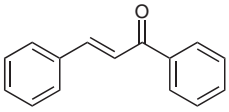
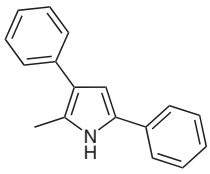
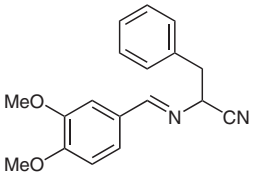
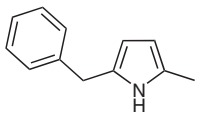
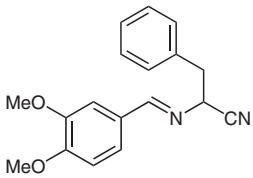
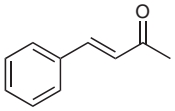
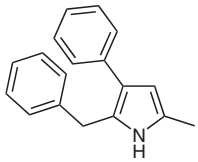
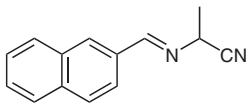
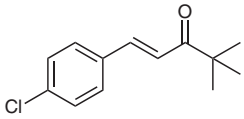
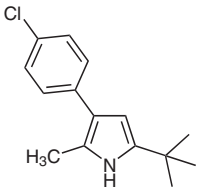


Scheme 4 Synthesis of the cyanopyrroline **16a**

Downloaded by: University of Pittsburgh. Copyrighted material.

Table 2 Pyrroles from α-(Alkylideneamino)nitriles and Enones



α-(Alkylideneamino)nitrile **1**		Enone **14**		Pyrrole **18**		Yield (%)
1a		14a		**18a**		30[a]
1c		14b		**18b**		36[b] 28[c]
1c		14c		**18c**		30[a]
1a		14d		**18d**		18[a]

[a] Girard's reagent T was used to remove the aldehyde after cyclization.
[b] Chromatographic purification of the cyanopyrroline intermediate.
[c] Crude cyanopyrroline was used.

The introduction of alkyl substituents to positions 2 and/or 5 of the intermediates **16** provides the opportunity to prepare fused bicyclic systems such as indolizidines from bifunctional electrophiles. 7-Bromohept-1-en-3-one (**19**), prepared from 5-bromopentanoic acid via the acid chloride and reaction with trimethyl(vinyl)silane,[40] was reacted with α-(alkylideneamino)nitrile **1d** in the presence of DBU. The addition product **20** was obtained in 97% yield and was cyclized in acid medium followed by reduction with sodium cyanoborohydride without isolation of the intermediate cyanopyrroline. The resulting diastereomeric 3-phenylindolizidines **21a** and **21b** were obtained in 24 and 18% yield, respectively, after chromatographic separation. The minor diastereomer could be crystallized as its picrate salt; its crystal structure is shown in Figure 1. Attempts to isolate the intermediate of type **16** were unsuccessful and dinitrile **22** and pyrrole **23** turned out to be the major isolated products when the reduction step was omitted (Scheme 5).

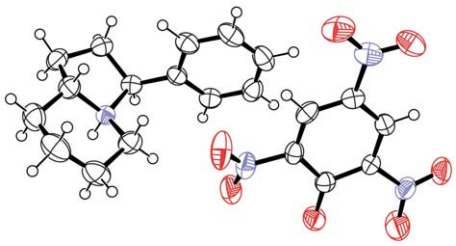
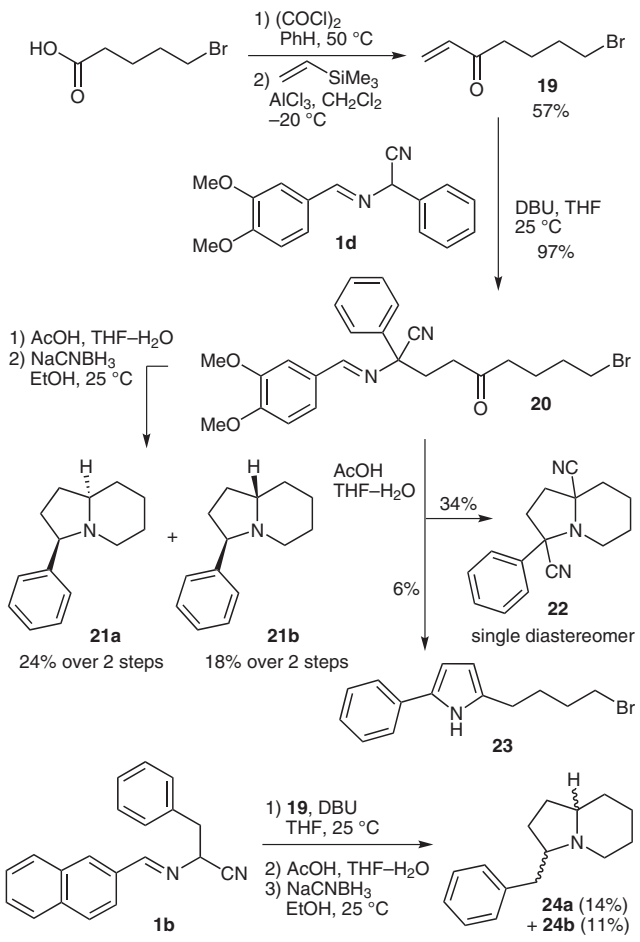


Figure 1 Crystal structure of the picrate of **21b**

When the same method was applied to α-(alkylideneamino)nitrile **1b**, the diastereomeric indolizidines **24a** and **24b** could be isolated in 14 and 11% yield (over 3 steps from **1b**) after chromatographic separation. Unfortunately, NOESY data did not help to assign their relative configuration and attempts to prepare crystalline salts were unsuccessful.

Solvents were dried and distilled before use: THF and benzene (K/benzophenone), CH_2Cl_2 (CaH_2), and EtOAc (K_2CO_3), and petroleum ether (bp 40–70 °C, PE) (CaH_2). The preparation of **1a–d** is described elsewhere.[8,17] All other solvents and reagents were purchased from commercial suppliers and were used without further purification. TLC was performed on TLC aluminum sheets (silica gel 60 F_{254}, KGaA Merck). Flash chromatography was carried out on silica gel (35–70 μm, Acros). ^1H and ^{13}C NMR spectra were re-

Downloaded by: University of Pittsburgh. Copyrighted material.



Scheme 5 Preparation of indolizidines

corded on a Bruker AC 300, AV 400, AMX 400, or DMX 500 instrument. Chemical shifts were referenced to the residual solvent signal ($CDCl_3$: $\delta_H = 7.26$, $\delta_C = 77.0$; CD_3OD: $\delta_H = 3.31$, $\delta_C = 49.0$; DMSO-d_6: $\delta_H = 2.70$, $\delta_C = 39.5$).[41] IR spectra were recorded on a Perkin-Elmer 1760X FTIR spectrophotometer or a Bruker Alpha-P FTIR spectrophotometer. Melting points were measured on a Dr. Tottoli apparatus and are uncorrected. MS spectra were recorded on a Finnigan MAT 95 (FD-MS), VG70S (FAB-MS and FAB-HRMS) or a Varian MAT 311A (EI-MS). ESI-HRMS spectra were recorded on a Waters Q-ToF-Ultima 3-Instrument. Elemental analyses were performed on a VarioMicro Cube (Elementar) or a CHN-O-Rapid (Heraeus).

Crystal data of **21b** picrate were obtained on a Siemens/Bruker AXS Smart diffractometer. CCDC-818238 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(1223)336033; e-mail: deposit@ccdc.cam.ac.uk.

2-Amino-2-cyclohexylacetonitrile

According to a modified protocol by Taillades et al.,[42] the title compound was prepared by addition of a soln of cyclohexanecarbaldehyde (12.00 g, 0.107 mol) in EtOH (40 mL) to a soln of KCN (8.52 g, 0.131 mol) and NH_4Cl (11.35 g, 0.212 mol) in 25% NH_3 (150 mL). After stirring at r.t. for 1.5 h, the mixture was extracted with Et_2O (2 × 100 mL). The combined organic layers were concentrated in vacuo to furnish a colorless oil. The crude product (14.86 g) was filtered over silica gel (cyclohexane–EtOAc, 4:1) to yield the product (9.33 g, 0.068 mol, 63%) as colorless crystals; mp 42–43 °C (Lit.[43] 44–45 °C); $R_f = 0.17$ (cyclohexane–EtOAc, 1:1 + 1% Me_2NEt), ninhydrin.

IR (ATR): 3338 (m), 2924 (s), 2851 (m), 2223 (w, CN), 1624 (m), 1453 (m), 971 (s), 949 (m), 916 (m), 887 cm^{-1} (m).

^1H NMR (300 MHz, $CDCl_3$): $\delta = 3.51$ (d, $J = 5.9$ Hz, 1 H, CHCN), 1.94–1.43 (m, 8 H, CH_2, NH_2), 1.36–1.00 (m, 5 H, CH_2).

^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 121.4$ (CN), 49.0 (*C*HCN), 42.0 ($C1_{Cy}$), 29.2, 28.2, 25.9, 25.6, 25.5 (C_{Cy}).

MS (EI): *m*/*z* (%) = 138 (4) $[M]^+$, 112 (11) $[M - CN]^+$, 83 (7) [cyclohexyl]$^+$, 56 (100) $[M - cyclohexyl]^+$, 41 (22).

Anal. Calcd for $C_8H_{14}N_2$: C, 69.52; H, 10.21; N, 20.27. Found: C, 69.74; H, 10.22; N, 20.34.

2-Cyclohexyl-2-[(2-naphthylmethylene)amino]acetonitrile (1e); Typical Procedure

2-Amino-2-cyclohexylacetonitrile (2.00 g, 14.5 mmol) was dissolved in anhyd $CHCl_2$. 2-Naphthaldehyde (2.49 g, 15.9 mmol), $MgSO_4$ (5.20 g, 43.2 mmol), and AcOH (4.15 mL, 72.5 mmol) were added. The mixture was stirred for 6 h at r.t. under an argon atmosphere. The $MgSO_4$ was filtered off and was washed with CH_2Cl_2. The filtrate was washed with sat. aq $NaHCO_3$, dried (Na_2SO_4), and concentrated in vacuo. The crude product (3.68 g) was recrystallized (Et_2O) to furnish colorless crystals (1.99 g, 7.20 mmol, 50%); the mother liquor yielded a further crop (0.94 g, 3.40 mmol, 23%). Product as colorless crystals: total yield: 2.93 g (10.6 mmol, 73%); mp 89–90 °C; $R_f = 0.72$ (cyclohexane–EtOAc, 4:1).

IR (ATR): 2925 (m), 2853 (m), 1646 (m), 1453 (w), 1343 (w), 1122 (w), 1014 (w), 974 (m), 890 (w), 869 (m), 835 (s), 750 (s), 484 cm^{-1} (m).

^1H NMR (400 MHz, $CDCl_3$): $\delta = 8.62$ (d, $J = 1.4$ Hz, 1 H, HC=N), 8.13 (s, 1 H, $H1_{Naphthyl}$), 8.01 (dd, $J = 8.6$, 1.6 Hz, 1 H, $H_{Naphthyl}$), 7.95–7.91 (m, 1 H, $H_{Naphthyl}$), 7.90–7.85 (m, 2 H, $H_{Naphthyl}$), 7.60–7.51 (m, 2 H, $H_{Naphthyl}$), 4.57 (dd, $J = 5.6$, 1.4 Hz, 1 H, HCCN), 2.04–1.66 (m, 6 H, H_{Cy}), 1.39–1.15 (m, 5 H, H_{Cy}).

^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 162.9$ (CH=N), 135.3 (Cq), 133.2 (Cq), 133.0 (Cq), 131.5, 129.0, 128.9, 128.1, 127.9, 126.9, 123.9, 117.5 (CN), 64.6 (*C*HCN), 42.2 ($C1_{Cy}$), 30.0, 28.9, 26.2, 26.1, 25.9.

MS (EI): *m*/*z* (%) = 276 (100) $[M]^+$, 194 (98), 167 (96), 155 (43).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{21}N_2$: 277.1705; found: 277.1707.

Anal. Calcd for $C_{19}H_{20}N_2$: C, 82.57; H, 7.29; N, 10.14. Found: C, 82.53; H, 7.29; N, 9.86.

2-Cyclohexyl-2-(4-nitrobenzylideneamino)acetonitrile (1f)

Following the typical procedure for **1e** using 2-amino-2-cyclohexylacetonitrile (2.00 g, 14.5 mmol), and anhyd CH_2Cl_2, 4-nitrobenzaldehyde (2.20 g, 14.6 mmol), $MgSO_4$ (5.24 g, 43.5 mmol), and AcOH (5 drops). The $MgSO_4$ was filtered off and was washed with CH_2Cl_2. The filtrate was washed with sat. aq $NaHCO_3$, dried (Na_2SO_4), and concentrated in vacuo. Recrystallization (Et_2O) gave colorless crystals (3.26 g, 12.0 mmol, 83%); the mother liquor yielded further crystals (0.29 g, 1.1 mmol, 7%). Product as colorless crystals; total yield: 3.55 g (13.1 mmol, 90%); mp 76–77 °C; $R_f = 0.70$ (cyclohexane–EtOAc, 2:1).

IR (ATR): 2929 (m), 1650 (m), 1522 (s), 1345 (s), 1292 (m), 1012 (m), 850 (s), 827 (m), 745 (m), 676 cm^{-1} (m).

^1H NMR (400 MHz, $CDCl_3$): $\delta = 8.56$ (d, $J = 1.7$ Hz, 1 H, HC=N), 8.30 (AA′-part of AA′BB′-system, 2 H, $H3_{Ar}$, $H5_{Ar}$), 7.97 (BB′-part of AA′BB′-system, 2 H, $H2_{Ar}$, $H6_{Ar}$), 4.60 (dd, $J = 5.5$, 1.7 Hz, 1 H, CH), 2.07–1.66 (m, 6 H, H_{Cy}), 1.39–1.12 (m, 5 H, H_{Cy}).

Downloaded by: University of Pittsburgh. Copyrighted material.

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 160.5 (HC=N), 149.8 ($C4_{Ar}$), 140.5 ($C1_{Ar}$), 129.6 (2 C, $C2_{Ar}$, $C6_{Ar}$), 124.2 (2 C, $C3_{Ar}$, $C5_{Ar}$), 116.8 (CN), 64.5 (CH), 42.1 ($C1_{Cy}$), 30.0, 28.8, 26.1, 25.99, 25.9 (C_{Cy}).

MS (EI): *m/z* (%) = 271 (8) $[M]^+$, 189 (100), 83 (34), 55 (49).

Anal. Calcd for $C_{15}H_{17}N_3O_2$: C, 66.40; H, 6.32; N, 15.49. Found: C, 66.39; H, 6.42; N, 15.39.

Pyrroles 2 from α-(Alkylideneamino)nitriles and Di-*tert*-butyl Acetylenedicarboxylate; General Procedure

To an argon-flushed microwave reaction vessel was added a mixture of imine **1**, di-*tert*-butyl acetylenedicarboxylate (1–1.2 equiv), and Cs_2CO_3 (2 equiv) in DMF (20 mL/mmol). The mixture was heated to 100 °C for 1 min by irradiation with microwaves (CEM Discover, air cooling, IR-temperature control, maximum power 100 W). After pressure equilibration, the mixture was diluted with sat. aq $NaHCO_3$ (5 mL/100 mg imine) and the mixture was extracted with EtOAc (3 × 5 mL/100 mg imine). The combined organic layers were washed with H_2O (10 mL/100 mg imine) and brine (10 mL/100 mg imine) and dried (Na_2SO_4). After removal of the solvent in vacuo, the crude product was purified by column chromatography.

Di-*tert*-butyl 5-Methyl-2-(2-naphthyl)-1*H*-pyrrole-3,4-dicarboxylate (2a)

According to the general procedure using **1a** (100.1 mg, 0.481 mmol), di-*tert*-butyl acetylenedicarboxylate (130.1 mg, 0.575 mmol), and Cs_2CO_3 (311.9 mg, 0.957 mmol) in DMF (1.5 mL). A portion (238.6 mg) of the crude product (251.8 mg) was purified by column chromatography (silica gel, PE–EtOAc, 5:1) to furnish **2a** (123.9 mg, 0.304 mmol, 67%) as a yellow foam; R_f = 0.26 (PE–EtOAc, 4.5:1).

IR (KBr): 3290 (m), 2977 (m), 1698 (vs), 1478 (m), 1429 (m), 1392 (m), 1230 (m), 1170 (s), 1139 (m), 1117 (s), 1099 (s), 848 (m), 747 cm^{-1} (m).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 11.75 (br s, 1 H, NH), 7.99–7.85 (m, 4 H, $H_{Naphthyl}$), 7.62 (dd, *J* = 8.6, 1.7 Hz, 1 H, $H_{Naphthyl}$), 7.53 (mc, 2 H, $H_{Naphthyl}$), 2.41 (s, 3 H, CH_3), 1.50 [s, 9 H, $C(CH_3)_3$], 1.40 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 165.0 (C=O), 163.2 (C=O), 134.0 (Cq), 132.6 (Cq), 131.9 (Cq), 129.2 (Cq), 128.8 (Cq), 127.7, 127.6, 127.5, 126.6, 126.1, 125.3, 125.2, 116.3 (Cq), 113.3 (Cq), 79.7 [*C*$(CH_3)_3$], 79.1 [*C*$(CH_3)_3$], 28.0 [3 C, C(*C*$H_3)_3$], 27.6 [3 C, C(*C*$H_3)_3$], 12.5 (CH_3).

MS (ESI): *m/z* (%) = 471.3 (60) $[M + CH_3CN + Na]^+$, 430.2 (35) $[M + Na]^+$, 408.2 (88) $[M + H]^+$, 352.2 (43), 296.1 (100), 278.1 (63).

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{25}H_{30}NO_4$: 408.2175; found: 408.2185.

Di-*tert*-butyl 5-Benzyl-2-(2-naphthyl)-1*H*-pyrrole-3,4-dicarboxylate (2b)

According to the general procedure using **1b** (200.4 mg, 0.705 mmol), di-*tert*-butyl acetylenedicarboxylate (161.4 mg, 0.713 mmol), and Cs_2CO_3 (460.4 mg, 1.413 mmol) in DMF (1.46 mL). A part (382.4 mg) of the crude product (393.5 mg) was purified by column chromatography (silica gel, PE–EtOAc, 5:1) to furnish **2b** (167.6 mg, 0.347 mmol, 51%) as a light-brown foam; R_f = 0.42 (PE–EtOAc, 4.5:1).

IR (KBr): 2976 (m), 1698 (vs), 1455 (m), 1427 (m), 1367 (s), 1230 (m), 1167 (s), 1139 (m), 1118 (m), 1091 (s), 847 cm^{-1} (m).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 11.95 (br s, 1 H, NH), 8.00–7.86 (m, 4 H, $H_{Naphthyl}$), 7.62 (dd, *J* = 8.5, 1.7 Hz, 1 H, $H_{Naphthyl}$), 7.53 (mc, 2 H, $H_{Naphthyl}$), 7.32–7.25 (m, 4 H, Ph), 7.22–7.16 (m, 1 H, $H4_{Ph}$), 4.20 (s, 2 H, CH_2Ph), 1.42 [s, 9 H, $C(CH_3)_3$], 1.39 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (125.8 MHz, DMSO-d_6): δ = 164.8 (C=O), 163. 4 (C=O), 139.5 (Cq), 135.8 (Cq), 132.6 (Cq), 132.1 (Cq), 130.4 (Cq), 128.7 (Cq), 128.3 (2 C, Ph), 128.1 (2 C, Ph), 127.7, 127.7, 127.6, 126.6, 126.2, 126.1, 125.8, 125.7, 116.3 (Cq), 113.9 (Cq), 79.9 [*C*$(CH_3)_3$], 79.5 [*C*$(CH_3)_3$], 31.7 (CH_2), 27.9 [C(*C*$H_3)_3$], 27.7 [C(*C*$H_3)_3$].

MS (ESI): *m/z* (%) = 484.4 (65) $[M + H]^+$, 372.2 (100), 354.2 (52), 260.2 (40).

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{31}H_{34}NO_4$: 484.2488; found: 484.2494.

Di-*tert*-butyl 5-Benzyl-2-(3,4-dimethoxyphenyl)-1*H*-pyrrole-3,4-dicarboxylate (2c)

According to the general procedure using **1c** (100.5 mg, 0.341 mmol), di-*tert*-butyl acetylenedicarboxylate (77.9 mg, 0.344 mmol), and Cs_2CO_3 (222.9 mg, 0.684 mmol) in DMF (0.71 mL). A part (151.0 mg) of the crude product (160.8 mg) was purified by column chromatography (silica gel, PE–EtOAc, 4:1) to furnish **2c** (89.0 mg, 0.180 mmol, 56%) as light-yellow foam; R_f = 0.26 (PE–EtOAc, 4:1).

IR (KBr): 3316 (m), 2976 (m), 1703 (vs), 1505 (s), 1457 (m), 1367 (m), 1252 (s), 1228 (s), 1166 (s), 1122 (m), 1090 (m), 1026 (m), 848 cm^{-1} (m).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 11.64 (br s, 1 H, NH), 7.33–7.15 (m, 5 H), 7.09 (d, *J* = 1.6 Hz, 1 H), 7.05–6.99 (m, 2 H), 4.15 (s, 2 H, CH_2Ph), 3.77 (6 H, 2 OCH_3), 1.40 [s, 9 H, $C(CH_3)_3$], 1.39 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 165.0 (C=O), 163.3 (C=O), 148.4 (*C*OCH_3), 148.2 (*C*OCH_3), 139.5 (Cq), 134.6 (Cq), 130.7 (Cq), 128.2 (2 C, Ph), 127.9 (2 C, Ph), 126.0, 123.8 (Cq), 119.9, 115.0 (Cq), 113.7 (Cq), 111.5, 111.3, 79.5 [*C*$(CH_3)_3$], 79.2 [*C*$(CH_3)_3$], 55.5 (OCH_3), 55.4 (OCH_3), 31.6 (*C*H_2Ph), 27.8 [3 C, C(*C*$H_3)_3$], 27.6 [3 C, C(*C*$H_3)_3$].

MS (ESI): *m/z* (%) = 494.3 (87) $[M + H]^+$, 382.2 (100), 364.2 (68).

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{29}H_{36}NO_6$: 494.2543; found: 494.2560.

Di-*tert*-butyl 2-(3,4-Dimethoxyphenyl)-5-phenyl-1*H*-pyrrole-3,4-dicarboxylate (2d)

According to the general procedure using **1d** (199.8 mg, 0.713 mmol), di-*tert*-butyl acetylenedicarboxylate (194.1 mg, 0.858 mmol), and Cs_2CO_3 (465.1 mg, 1.427 mmol) in DMF (1.49 mL). A part (361.9 mg) of the crude product (381.9 mg) was purified by column chromatography (silica gel, PE–EtOAc, 3:1) to obtain pure **2d** (201.3 mg, 0.420 mmol, 62%) as a light-yellow foam; R_f = 0.10 (PE–EtOAc, 4:1).

IR (KBr): 3318 (m), 2976 (m), 1704 (vs), 1504 (s), 1455 (m), 1440 (m), 1367 (m), 1250 (s), 1169 (s), 1127 (s), 1058 (m), 1026 (m), 848 (m), 697 cm^{-1} (m).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 11.76 (br s, 1 H, NH), 7.55–7.35 (m, 5 H, Ph), 7.17 (d, *J* = 1.9 Hz, 1 H, H2), 7.11 (dd, *J* = 8.4, 1.9 Hz, 1 H, H6), 7.02 (d, *J* = 8.4 Hz, 1 H, H5), 3.79 (s, 6 H, 2 OCH_3), 1.40 [s, 9 H, $C(CH_3)_3$], 1.34 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR, PENDANT (100.6 MHz, DMSO-d_6): δ = 164.3 (C=O), 163.8 (C=O), 148.5 (*C*OCH_3), 148.1 (*C*OCH_3), 132.9 (2 Cq), 141.4 (Cq), 128.6 (2 C), 127.8 (2 C), 127.7, 123.7 (Cq), 120.8, 115.3 (Cq), 115.0 (Cq), 112.1, 111.3, 79.5 [*C*$(CH_3)_3$], 79.5 [*C*$(CH_3)_3$], 55.5 (OCH_3), 55.4 (OCH_3), 27.6 [3 C, C(*C*$H_3)_3$], 27.5 [3 C, C(*C*$H_3)_3$].

MS (ESI): *m/z* (%) = 480.4 (97) $[M + H]^+$, 368.2 (100), 350.1 (68).

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{28}H_{34}NO_6$: 480.2386; found: 480.2393.

Downloaded by: University of Pittsburgh. Copyrighted material.

Di-*tert*-butyl 5-Cyclohexyl-2-(2-naphthyl)-1*H*-pyrrole-3,4-dicarboxylate (2e)

According to the general procedure using **1e** (200 mg, 0.724 mmol), di-*tert*-butyl acetylenedicarboxylate (164.0 mg, 0.725 mmol), and Cs_2CO_3 (471.0 mg, 1.446 mmol) in DMF (1.5 mL). The crude product (434 mg) was purified by column chromatography (silica gel, PE–EtOAc, 8:1) to furnish **2e** (188 mg, 0.395 mmol, 55%) as a yellow foam; R_f = 0.19 (PE–EtOAc, 8:1).

IR (KBr): 2927 (m), 1693 (s), 1450 (m), 1365 (m), 1223 (m), 1166 (s), 1130 (s), 1116 (m), 1082 (m), 746 cm^{-1} (m).

^1H NMR (300 MHz, DMSO-d_6): δ = 11.39 (br s, 1 H, NH), 8.00–7.86 (m, 4 H, $H_{Naphthyl}$), 7.63–7.48 (m, 3 H, $H_{Naphthyl}$), 3.20 (pseudo-t, J_{app} ≈ 11.5 Hz, 1 H, CH_{Cy}), 1.91–1.61 (m, 7 H, H_{Cy}), 1.61–1.12 {m, 21 H, contained in this multiplet: 1.50 [s, 9 H, $C(CH_3)_3$], 1.35 [s, 9 H, $C(CH_3)_3$]}.

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 164.7 (C=O), 163.5 (C=O), 142.1 (Cq), 132.5 (Cq), 132.0 (Cq), 130.5 (Cq), 128.8 (Cq), 127.6, 127.5, 127.2, 126.4, 126.3 (2 C), 126.0, 115.7 (Cq), 112.5 (Cq), 79.5 [$C(CH_3)_3$], 79.2 [$C(CH_3)_3$], 35.5 (C_{Cy}), 31.6 (2 C, C_{Cy}), 27.9 [3 C, $C(CH_3)_3$], 27.5 [3 C, $C(CH_3)_3$], 26.3 (2 C, C_{Cy})), 25.4 (C_{Cy}).

MS (EI): *m*/*z* (%) = 475 (39) $[M]^+$, 346 (55), 345 (100), 249 (30), 56 (32).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{30}H_{38}NO_4$: 476.2801; found: 476.2810.

Di-*tert*-butyl 5-Cyclohexyl-2-(4-nitrophenyl)-1*H*-pyrrole-3,4-dicarboxylate (2f)

According to the general procedure using **1f** (200.0 mg, 0.737 mmol), di-*tert*-butyl acetylenedicarboxylate (200.2 mg, 0.885 mmol), and Cs_2CO_3 (480.0 mg, 1.47 mmol) in DMF (1.54 mL). A part (440.0 mg) of the crude product (450.0 mg) was purified by column chromatography (silica gel, PE–EtOAc, 11:2) to furnish **2f** (298.0 mg, 0.633 mmol, 86%) as a yellow foam; R_f = 0.27 (PE–EtOAc, 8:1).

IR (KBr): 1698 (s), 1518 (m), 1451 (m), 1366 (m), 1230 (m), 1161 (s), 1120 (s), 1109 (m), 1084 (m), 847 cm^{-1} (m).

^1H NMR (300 MHz, DMSO-d_6): δ = 11.52 (br s, 1 H, NH), 8.29 (AA′-part of AA′BB′-system, J_{app} ≈ 8.8 Hz, 2 H, H3, H5), 7.72 (BB′-part of AA′BB′-system, J_{app} ≈ 8.8 Hz, 2 H, H2, H6), 3.18 (tt, *J* = 11.9, 3.4 Hz, 1 H, CH_{Cy}), 1.87–1.57 (m, 7 H, H_{Cy}), 1.50 [s, 9 H, $C(CH_3)_3$], 1.40 [s, 9 H, $C(CH_3)_3$], 1.35–1.19 (m, 3 H, H_{Cy}).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 164.4 (C=O), 163.2 (C=O), 146.0 ($COCH_3$), 143.4 ($COCH_3$), 137.5 (Cq), 128.3 (2 C), 127.8 (Cq), 123.3 (2 C), 117.6 (Cq), 113.3 (Cq), 80.2 [$C(CH_3)_3$], 79.5 [$C(CH_3)_3$], 35.6 (C_{Cy}), 31.5 (2 C, C_{Cy}), 27.9 [3 C, $C(CH_3)_3$], 27.5 [3 C, $C(CH_3)_3$], 26.2 (2 C, C_{Cy}), 25.4 (C_{Cy}).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{26}H_{35}N_2O_6$: 471.2495; found: 471.2498.

Anal. Calcd for $C_{26}H_{34}N_2O_6$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.34; H, 7.26; N, 5.81.

2-Amino-2-(4-fluorophenyl)acetonitrile (3)

To a soln of KCN (5.04 g, 77.35 mmol) and NH_4Cl (6.90 g, 0.129 mol) in 25% aq NH_3 (95 mL) was added a soln of 4-fluorobenzaldehyde (8.12 g, 65.4 mmol) in EtOH (25 mL) over 10 min. After 105 min stirring at r.t., the slightly yellow soln was extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with half-sat. brine, dried (Na_2SO_4), and the solvent was removed in vacuo. The crude product (9.83 g) still contained minor impurities and was recrystallized (EtOH) to give colorless crystals (5.31 g, 35.4 mmol, 54%); a further crop of crystals could be obtained from the mother liquor (2.32 g, 15.5 mmol, 24%). Product **3** was obtained as colorless crystals; combined yield: 7.63 g (50.8 mmol, 78%); mp 72–73.5 °C; R_f = 0.38 (PE–EtOAc, 1:1).

IR (KBr): 3334 (m), 3274 (m), 3185 (m), 2227 (m, CN), 1607 (m), 1516 (s), 1247 (s), 1160 (m), 1084 (m), 979 (m), 962 (s), 936 (m), 881 (m), 835 cm^{-1} (s).

^1H NMR (300 MHz, $CDCl_3$): δ = 7.56–7.48 (m, 2 H, $H2_{Ar}$, $H6_{Ar}$), 7.15–7.06 (m, 2 H, $H3_{Ar}$, $H5_{Ar}$), 4.90 (t, *J* = 7.5 Hz, 1 H, CH), 1.95 (br s, 2 H, NH_2).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 162.9 (d, ^1J = 247.5 Hz, 1 C, $C4_{Ar}$), 132.1 (d, ^4J = 3.4 Hz, 1 C, $C1_{Ar}$), 128.4 (d, ^3J = 9.1 Hz, 2 C, $C2_{Ar}$, $C6_{Ar}$), 120.7 (CN), 116.0 (d, ^2J = 21.4 Hz, 2 C, $C3_{Ar}$, $C5_{Ar}$), 46.6 (CH).

MS (FD): *m*/*z* (%) = 150.1 (100) $[M]^+$.

Anal. Calcd for $C_8H_7FN_2$: C, 63.99; H, 4.70; N, 18.66. Found: C, 64.01; H, 4.58; N, 18.87.

2-(4-Fluorophenyl)-2-[(2-methylpropylidene)amino]acetonitrile (4)

To a stirred soln of **3** (2.00 g, 13.32 mmol) in anhyd CH_2Cl_2 (5 mL) were added $MgSO_4$, (2.4 g, 20.0 mmol), isobutyraldehyde (1.34 mL, 14.65 mmol), and AcOH (10 drops) under an argon atmosphere. The mixture was stirred for 17 h at r.t. Due to incomplete conversion, further AcOH (12 drops) was added and stirring was continued for 4 h. After addition of further AcOH (12 drops), the mixture was heated to reflux for 4 h and stirred overnight at r.t. The $MgSO_4$ was filtered off and washed with CH_2Cl_2. The combined filtrates were washed with sat. aq $NaHCO_3$ (20 mL) and brine (20 mL), dried ($MgSO_4$), and concentrated in vacuo to furnish a light-yellow oil (2.15 g, 10.5 mmol, 79%), which was sufficiently pure for the next synthetic transformation; R_f = 0.69 (PE–EtOAc, 2:1).

IR (film): 2970 (s), 2933 (m), 2875 (m), 2244 (w, CN), 1662 (s), 1606 (s), 1510 (s), 1468 (m), 1234 (s), 1160 (m), 837 cm^{-1} (s).

^1H NMR (300 MHz, $CDCl_3$): δ = 7.97 (dd, *J* = 4.7, 1.6 Hz, 1 H, HC=N), 7.42–7.36 (m, 2 H, $H2_{Ar}$, $H6_{Ar}$), 7.14–7.06 (m, 2 H, $H3_{Ar}$, $H5_{Ar}$), 5.52 (br s, 1 H, HCCN), 2.60 [mc, 1 H, $CH(CH_3)_2$], 1.14 [d, *J* = 6.9 Hz, 6 H, $CH(CH_3)_2$].

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 172.9 (HC=N), 161.1 (d, $^1J_{C\text{-}F}$ = 248.4 Hz, 1 C, $C4_{Ar}$), 130.7 (d, $^4J_{C\text{-}F}$ = 3.3 Hz, 1 C, $C1_{Ar}$), 128.9 (d, $^3J_{C\text{-}F}$ = 8.5 Hz, 2 C, $C2_{Ar}$, $C6_{Ar}$), 116.8 (CN), 115.7 (d, $^2J_{C\text{-}F}$ = 22.0 Hz, 2 C, $C3_{Ar}$, $C5_{Ar}$), 60.8 (CH), 34.3 [$CH(CH_3)_2$], 18.9 [2 C, $CH(CH_3)_2$].

MS (FD): *m*/*z* (%) = 256.1 (100), 204.2 (90) $[M]^+$.

Anal. Calcd for $C_{12}H_{13}FN_2$: C, 70.57; H, 6.42; N, 13.72. Found: C, 70.21; H, 6.49; N, 13.45.

***N*,3-Diphenylpropiolamide (5)**

A suspension of phenylpropiolic acid (2.50 g, 17.1 mmol) and $SOCl_2$ (1.49 mL, 20.5 mmol) in anhyd benzene (9 mL) was stirred for 3 h at 70 °C. After 30 min, a clear soln resulted. Excess $SOCl_2$ and benzene were removed in vacuo. The oily residue was dissolved in anhyd benzene (9 mL) and cooled to 0 °C. A soln of aniline (3.19 g, 34.2 mmol) in anhyd benzene (9 mL) was added over 10 min. The ice bath was removed and the mixture was stirred for 80 min at r.t. The beige and turbid mixture was poured into ice-cold water (40 mL), the organic layer was separated, and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with 5% HCl, H_2O, 5% aq Na_2CO_3, and again with H_2O (30 mL each) After drying (Na_2SO_4), the solvent was removed in vacuo and the crude product (2.68 g, light beige solid) was recrystallized (EtOH, 10 mL) to obtain a colorless solid (1.16 g, 5.24 mmol, 31%); the mother liquor gave a further crop of colorless crystals (0.80 g, 3.62 mmol, 21%). Product **5** was obtained as colorless crystals;

Downloaded by: University of Pittsburgh. Copyrighted material.

combined yield: 1.96 g (8.89 mmol, 52%); mp 124–125 °C (Lit.[44] 125–126 °C); R_f = 0.45 (PE–EtOAc, 2:1).

IR (KBr): 2212 (m), 1625 (m), 1604 (m), 1593 (m), 1542 (s), 1497 (m), 1487 (m), 1441 (s), 1327 (m), 1319 (m), 1249 (m), 751 (s), 720 (m), 687 (s), 508 cm^{-1} (m).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.87 (br s, 1 H, NH), 7.77–7.62 (m, 4 H, Ph), 7.58–7.44 (m, 3 H, Ph), 7.34 (pseudo-t, J_{app} ≈ 7.4 Hz, 2 H, Ph), 7.17 (pseudo-t, J_{app} ≈ 6.9 Hz, 1 H, Ph).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 151.1 (C=O), 137.4 (C1′), 132.6 (2 C), 130.3, 129.1 (2 C), 128.6 (2 C), 124.9, 120.0 (2 C), 119.9 (C1″), 85.8 (C3), 83.4 (C2).

MS (FAB): *m*/*z* (%) = 222.1 $[M + H]^+$.

HRMS (FAB): *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{12}NO$: 222.0919; found: 222.0922.

5-(4-Fluorophenyl)-2-isopropyl-4-phenyl-1*H*-pyrrole-3-carboxanilide (6)

To a soln of **4** (53.0 mg, 0.259 mmol) and **5** (63.2 mg, 0.285 mmol) in DMF (490 μL) was added, under an argon atmosphere, Cs_2CO_3 (169.1 mg, 0.519 mmol). The mixture was stirred for 135 min at 0 °C, for 170 min at r.t. and for 75 min at 40 °C. TLC indicated complete consumption of **4**. The mixture was partitioned between sat. aq $NaHCO_3$ (5 mL) and EtOAc (5 mL). The aqueous phase was extracted with EtOAc (3 × 5 mL) and the combined organic layers were washed with H_2O and brine (10 mL each) and dried (Na_2SO_4), and the solvent was removed in vacuo. A part (108.7 mg) of the viscous yellow material (125.7 mg) was purified by column chromatography (silica gel, toluene) to furnish **6** (35.4 mg, 0.089 mmol, 40%) as a slightly yellowish solid; mp 199–200.5 °C. The starting material **5** (28.3 mg, 0.128 mmol, 57%) was also recovered; R_f = 0.47 (PE–EtOAc, 4:1); R_f = 0.13 (toluene).

IR (KBr): 3407 (m), 3249 (m), 1639 (s), 1597 (m), 1510 (s), 1439 (m), 1221 (m), 750 (m), 691 cm^{-1} (m).

^{1}H NMR, COSY, HMBC (400 MHz, 100.6 MHz, DMSO-d_6): δ = 11.14 (br s, 1 H, NH), 9.21 (br s, 1 H, NHCO), 7.44–7.38 (m, 2 H, H2″$_{Ar}$, H6″$_{Ar}$), 7.27–7.16 (m, 9 H), 7.15–7.08 (m, 2 H, H3′$_{Ar}$, H5′$_{Ar}$), 6.96 (pseudo-t, J_{app} ≈ 7.3 Hz, 1 H, H4″$_{Ar}$), 3.33 (sept, *J* = 7.0 Hz, 1 H, CH, partly buried under the H_2O signal), 1.32 [d, *J* = 7.0 Hz, 6 H, $CH(CH_3)_2$].

^{13}C NMR, HMBC, HSQC (100.6 MHz, 400 MHz, DMSO-d_6): δ = 164.8 (C=O), 159.1 (d, $^1J_{C-F}$ = 243.7 Hz, 1 C, C4′), 139.4 (C1″), 139.2 (C2), 135.2 (C1‴$_{Ar}$), 130.0 (2 C, Ar‴), 129.4 (d, $^3J_{C-F}$ = 8.0 Hz, 2 C, C2′, C6′), 129.0 (d, $^4J_{C-F}$ = 3.2 Hz, 1 C, C1′), 128.5 (2 C, C3″$_{Ar}$, C5″$_{Ar}$), 128.1 (2 C, Ar‴), 126.2 (C4‴$_{Ar}$), 125.7 (C4), 122.8 (C4″$_{Ar}$), 119.3 (C3), 119.0 (2 C, C2″$_{Ar}$, C6″$_{Ar}$), 117.2 (C5), 114.8 (d, $^2J_{C-F}$ = 21.4 Hz, 2 C, C3′, C5′), 25.9 (CH), 22.4 [2 C, $CH(CH_3)_2$].

Transient NOE: Irradiation on δ = 1.32 [$CH(CH_3)_2$] enhances the signals at δ = 11.14 (NH, 1.4%), 9.21 (NHCO, 0.2%), and 3.33 (CH, 4.3%); irradiation on δ = 3.33 (CH) enhances the signals at δ = 11.14 (NH, 0.1%), 9.21 (NHCO, 0.1%), and 1.32 [$CH(CH_3)_2$, 0.7%]; irradiation on δ = 9.21 (NHCO) enhances the signals at δ = 7.44–7.38 (H2″$_{Ar}$, H6″$_{Ar}$, 10.4%), 7.27–7.16 (1.6%), 3.33 (CH, 0.2%), and 1.32 [$CH(CH_3)_2$, 0.3%]; irradiation on δ = 11.14 (NH) enhances the signals at δ = 7.27–7.16 (H2′$_{Ar}$, H6′$_{Ar}$, 11.6%), 3.33 (CH, 0.2%), and 1.32 [$CH(CH_3)_2$, 5.8%].

MS (ESI): *m*/*z* (%) = 399.31 (100) $[M + H]^+$, 355.33 (21) [M – *i*-Pr + H]$^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{26}H_{24}FN_2O$: 399.1873; found: 399.1874.

2-(4-Fluorophenyl)-5-isopropyl-3-phenyl-1*H*-pyrrole (7) and 5-(4-Fluorophenyl)-2-isopropyl-3-phenyl-1*H*-pyrrole (8)

An argon-flushed microwave reaction vessel was charged with **4** (300.3 mg, 1.47 mmol), **5** (357.7 mg, 1.62 mmol), and Cs_2CO_3 (962.1 mg, 2.95 mmol). After addition of anhyd DMF (3.0 mL), the mixture was heated under stirring to 65 °C for 2 min (CEM Discover, air cooling, IR temperature control, maximum power 100 W) and then to 90 °C for 2 min (maximum power 150 W). After pressure equilibration, sat. aq $NaHCO_3$ (15 mL) and EtOAc (15 mL) were added. The aqueous layer was extracted with EtOAc (3 × 15 mL), the combined organic layers were washed with H_2O and brine (30 mL each) and dried (Na_2SO_4). After removal of the solvent in vacuo, a part (621.2 mg) of the crude product (664.5 mg) was purified by column chromatography (silica gel, PE–EtOAc, 4:1) to furnish a 9:1 isomeric mixture of **7** and **8** as a light-brown oil (273.9 mg, 0.98 mmol, 71%) which crystallized later to give a light-brown solid; R_f = 0.56 (PE–EtOAc, 4:1).

IR (KBr): 3420 (m), 2966 (m), 1603 (m), 1525 (m), 1510 (s), 1220 (m), 835 (s), 803 (m), 770 (s), 705 cm^{-1} (m).

MS (FD): *m*/*z* (%) = 279.2 (100) $[M]^+$.

HRMS (FAB): *m*/*z* $[M]^+$ calcd for $C_{19}H_{18}FN$: 279.1423; found: 279.1425.

Compound 7

^{1}H NMR, COSY, HMBC (400 MHz, 100.6 MHz, DMSO-d_6): δ = 10.83 (br s, 1 H, NH), 7.36–7.28 (m, 2 H, H2′, H6′), 7.28–7.14 (m, 4 H, H2″, H6″, H3″, H5″), 7.16–7.10 (m, 3 H, H3′, H5′, H4″), 5.94 (dd, *J* = 2.7, 0.6 Hz, 1 H, =CH), 2.90 (sept, *J* = 6.9 Hz, 1 H, CH), 1.25 [d, *J* = 6.9 Hz, 6 H, $CH(CH_3)_2$].

^{13}C NMR, HMBC, HSQC (100.6 MHz, 400 MHz, DMSO-d_6): δ = 160.7 (d, $^1J_{C-F}$ = 243.1 Hz, 1 C, C4′), 139.6 (C5), 137.2 (C1″), 130.1 (d, $^4J_{C-F}$ = 3.0 Hz, 1 C, C1′), 129.3 (d, $^3J_{C-F}$ = 7.9 Hz, 2 C, C2′, C6′), 128.3, 127.8 (2 × 2 C, C2″, C6″; C3″, C5″), 125.2 (C4″), 125.1 (C2), 120.4 (C3), 115.1 (d, $^2J_{C-F}$ = 21.4 Hz, 2 C, C3′, C5′), 105.0 (=CH), 26.6 (CH), 22.7 [2 C, $CH(CH_3)_2$].

Compound 8

Characteristic NMR shifts.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.8 (br s, 1 H, NH), 6.49 (d, *J* = 2.8 Hz, 1 H, =CH), 3.20 (sept, *J* = 7.0 Hz, 1 H, CH), 1.31 [d, *J* = 7.0 Hz, 6 H, $CH(CH_3)_2$].

^{13}C NMR (100.7 MHz, DMSO-d_6): δ = 105.7 (HC=), 25.2 (CH), 22.9 [2 C, $CH(CH_3)_2$].

2-Methyl-2-[(2-naphthylmethylene)amino]-5-oxo-3,5-diphenylpentanenitrile (15a)

Under an argon atmosphere, **1a** (249.7 mg, 2.00 mmol) was dissolved in anhyd THF (2 mL). After addition of TMG (158 μL, 1.26 mmol), the mixture was stirred for 1 min at r.t. A soln of chalcone (**14a**, 250.4 mg, 1.20 mmol) in anhyd THF (0.5 mL) was added and the mixture was stirred for 3.5 h at r.t. The mixture was washed with sat. aq $NaHCO_3$ (2 × 5 mL) and the combined aqueous phases were re-extracted with EtOAc (2 × 5 mL). The combined organic layers were dried (Na_2SO_4) and the solvent was removed in vacuo to yield a light-yellow oil (541.2 mg, quant.) which was used without further purification for the next synthetic step; R_f = 0.66 (PE–EtOAc, 1:1); bright-orange color after ninhydrin treatment.

2-Methyl-3,5-diphenyl-3,4-dihydro-2*H*-pyrrole-2-carbonitrile (16a)

Under an argon atmosphere, crude **15a** (515.6 mg) was dissolved in THF (1.5 mL). H_2O (1.5 mL) and AcOH (412 μL, 7.20 mmol) were added and the mixture was stirred for 17.5 h at r.t. The mixture was partitioned between sat. aq $NaHCO_3$ (10 mL) and EtOAc (5 mL). The aqueous layer was extracted with EtOAc (2 × 5 mL), the com-

Downloaded by: University of Pittsburgh. Copyrighted material.

bined organic layers were washed H_2O and brine (10 mL each) and dried (Na_2SO_4), and the solvent was removed in vacuo to furnish a light-brown oil (409.7 mg). A portion (394 mg) of the crude product was dissolved in EtOH (5 mL), Girard's reagent T (317.2 mg, 1.89 mmol) and AcOH (5 drops) were added. The mixture was stirred for 20 h under an argon atmosphere. After partitioning between sat. aq $NaHCO_3$ (15 mL) and EtOAc (10 mL), the aqueous phase was extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with H_2O (4 × 10 mL) and brine (10 mL) and dried (Na_2SO_4), and the solvent was removed in vacuo. The resulting residue was dissolved in EtOAc (10 mL), washed with H_2O (4 × 10 mL), and dried (Na_2SO_4), and the solvent was removed in vacuo to furnish **16a** (282.3 mg, 1.08 mmol, 99% over 2 steps) as a yellow oil that gave yellow crystals; mp 96–98 °C; R_f = 0.43 (PE–EtOAc, 5:1).

IR (ATR): 1606 (m), 1572 (w), 1446 (m), 1339 (m), 1179 (w), 1121 (w), 762 (s), 692 (s), 669 (w), 566 (w), 495 (w), 477 cm^{-1} (w).

^1H NMR (300 MHz, $CDCl_3$): δ = 7.98–7.90 (m, 2 H, H2′$_{Ph}$, H6′$_{Ph}$), 7.58–7.44 (m, 3 H, Ph), 7.41–7.28 (m, 5 H, Ph), 4.11 (t, J = 8.6 Hz, 1 H, CH), 3.49 (dq, J_q = 17.1, J_d = 8.6 Hz, 2 H, CH_2), 1.23 (s, 3 H, CH_3).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 175.3 (C=N), 136.6 (Cq), 132.9 (Cq), 131.8, 128.8 (2 C), 128.7 (2 C), 128.1 (2 C), 127.9 (3 C), 122.7 (CN), 71.8 (*C*CN), 52.1 (CH_2), 39.6 (CH), 22.0 (CH_3).

Transient NOE: Irradiation at δ = 4.11 (CH) enhances the signals at δ = 7.31 (C_6H_5, 3.3%), 3.49 (CH_2, 2.6%), and 1.23 (CH_3, 0.4%); irradiation at δ = 1.23 (CH_3) enhances the signals at δ = 7.94 (C_6H_5, 0.2%), 7.31 (C_6H_5, 0.8%), 4.11 (CH, 0.4%), and 3.49 (CH_2, 0.8%).

MS (FAB): m/z (%) = 261.2 (33) $[M + H]^+$.

HRMS (FAB): m/z $[M + H]^+$ calcd for $C_{18}H_{17}N_2$: 261.1391; found: 261.1394.

2-Methyl-3,5-diphenyl-1*H*-pyrrole (18a)

Under an argon atmosphere, **16a** (199.2 mg, 0.765 mmol) was dissolved in anhyd THF (2 mL), KO*t*-Bu (90.2 mg, 0.803 mmol) was added and the mixture was stirred for 125 min at r.t. Since TLC indicated incomplete conversion, another portion of KO*t*-Bu (45.1 mg, 0.402 mmol) was added and the mixture was stirred for 19 h at r.t. After addition of further KO*t*-Bu (45.3 mg, 0.404 mmol) stirring was continued for 3 h. The brown mixture was partitioned between sat. aq $NaHCO_3$ (10 mL) and EtOAc (5 mL). The aqueous layer was extracted with EtOAc (3 × 5 mL), the combined organic layers were washed with H_2O (3 × 5 mL) and dried (Na_2SO_4), and the solvent was removed in vacuo to furnish a light-brown oil (179.0 mg). A portion (167.7 mg) of the crude product was purified by column chromatography (silica gel, PE–EtOAc, 5:1) to furnish **18a** as a light-yellow oil; yield: 50.1 mg (0.215 mmol, 30%); yield over 3 steps: 30%; R_f = 0.44 (CH_2Cl_2–PE–EtOAc, 3:3:0.1).

IR (ATR): 1604 (m), 1495 (m), 1449 (m), 1439 (m), 1152 (m), 753 (s), 733 (m), 690 (s), 669 (m), 647 (m), 527 (m), 491 cm^{-1} (m).

^1H NMR (300 MHz, DMSO-d_6): δ = 11.14 (br s, 1 H, NH), 7.64 (pseudo-d, J_{app} ≈ 8.2 Hz, 2 H, Ph), 7.47–7.41 (m, 2 H, Ph), 7.39–7.30 (m, 4 H, Ph), 7.20–7.09 (m, 2 H, Ph), 6.71 (d, J = 2.6 Hz, 1 H, =CH), 2.41 (s, 3 H, CH_3).

^{13}C NMR (100.6 MHz, DMSO-d_6): δ = 136.9 (Cq), 132.7 (Cq), 129.3 (Cq), 128.6 (2 C), 128.4 (2 C), 126.6 (2 C), 125.9 (Cq), 125.2, 124.7, 123.0 (2 C), 121.2 (Cq), 105.3 (=CH), 12.7 (CH_3).

HRMS (ESI): m/z $[M]^+$ calcd for $C_{17}H_{15}N$: 233.1204; found: 233.1215.

2-Benzyl-2-[(3,4-dimethoxybenzylidene)amino]-5-oxohexanenitrile (15b)

Under an argon atmosphere, **1c** (1.008 g, 3.43 mmol) was dissolved in anhyd THF (10 mL). After the addition of DBU (533 μL, 3.57 mmol), the mixture was stirred for 1 min at r.t. Methyl vinyl ketone (**14b**, 283 μL, 3.40 mmol) was added and the mixture was stirred for a further 135 min. The organic layer was washed with sat. aq $NaHCO_3$ (2 × 10 mL). The combined aqueous layers were re-extracted with EtOAc (2 × 10 mL), the combined organic layers were dried (Na_2SO_4), and the solvent was removed in vacuo to furnish a viscous yellow oil (1.22 g, 3.35 mmol, 99%), which was used without further purification; R_f = 0.45 (PE–EtOAc, 1:1).

IR (NaCl): 1716 (m), 1642 (m), 1601 (m), 1586 (m), 1514 (s), 1455 (m), 1422 (m), 1269 (s), 1241 (m), 1164 (m), 1141 (m), 1025 cm^{-1} (m).

^1H NMR (300 MHz, $CDCl_3$): δ = 7.97 (s, 1 H, HC=N), 7.38 (d, J = 1.8 Hz, 1 H, H2′), 7.25–7.14 (m, 6 H, H$_{Bn}$, H6′), 6.89 (d, J = 8.3 Hz, 1 H, H5′), 3.96 (s, 3 H, OCH_3), 3.94 (s, 3 H, OCH_3), 3.16 (AB-system, J = 13.6 Hz, 2 H, CH_2Ph), 2.64–2.22 (m, 4 H, 2 CH_2), 2.12 (s, 3 H, CH_3).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 206.7 (C=O), 160.6 (HC=N), 152.1, 149.3 (C3′/C4′), 134.0 (Cq), 130.9 (2 C, C$_{Bn}$), 128.1 (2 C, C$_{Bn}$), 127.8 (Cq), 127.4, 123.9 (C6′), 118.4 (CN), 110.5, 109.2 (C2′/C6′), 67.8 (*C*CN), 56.0 (2 C, 2 OCH_3), 46.5 (*C*H_2Ph), 38.8, 33.9, 30.1.

HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{22}H_{24}NaN_2O_3$: 387.1685; found: 387.1682.

2-Benzyl-5-methyl-3,4-dihydro-2*H*-pyrrole-2-carbonitrile (16b)

Under an argon atmosphere, **15b** (1.015 g, 2.78 mmol) was dissolved in THF (5 mL) and after the addition of H_2O (5 mL) and AcOH (956 μL, 16.70 mmol), the mixture was stirred for 21 h at r.t. The mixture was partitioned between sat. aq $NaHCO_3$ (10 mL) and EtOAc (10 mL). The aqueous layer was extracted with EtOAc (2 × 10 mL), the combined organic layers were washed with H_2O (10 mL) and dried (Na_2SO_4), and the solvent was removed in vacuo to furnish a light-brown oil (878.4 mg). A portion (868.4 mg) of the crude product was purified by column chromatography (silica gel, PE–EtOAc, 3:1) to furnish **16b** as a yellow oil which solidified later to give a yellow solid; yield: 345.2 mg (1.74 mmol, 63%); mp 61–62 °C; R_f = 0.32 (PE–EtOAc, 1:1), brown spot (ninhydrin).

IR (film/NaCl): 3030 (m), 2922 (m), 2237 (w, CN), 1643 (s), 1497 (m), 1456 (m), 1430 (m), 1380 (m), 1322 (m), 1032 (m), 740 (m), 704 cm^{-1} (s).

^1H NMR (300 MHz, $CDCl_3$): δ = 7.33–7.23 (m, 5 H, Ph), 3.23 (d, J = 13.5 Hz, 1 H, $PhCH_2$-Hα), 3.12 (d, J = 13.5 Hz, 1 H, $PhCH_2$-Hβ), 2.63–2.49 (m, 1 H), 2.32–2.07 (m, 3 H), 2.05 (s, 3 H, CH_3).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 179.7 (C=N), 134.3 (C1$_{Ph}$), 130.5 (2 C, Ph), 128.3 (2 C, Ph), 127.4 (C4$_{Ph}$), 121.7 (CN), 73.5 (*C*CN), 44.9 (*C*H_2Ph), 39.3, 33.1, 19.5 (CH_3).

HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{13}H_{14}NaN_2$: 221.1055; found: 221.1051.

2-Benzyl-5-methyl-1*H*-pyrrole (18b)

Under an argon atmosphere, **16b** (5.0 mg, 0.025 mmol) was dissolved in anhyd THF (50 μL), KO*t*-Bu (3.2 mg, 0.029 mmol) was added and the mixture was stirred for 17.5 h at 45 °C. The dark brown mixture was partitioned between sat. aq $NaHCO_3$ (2 mL) and EtOAc (2 mL). The organic layer was dried (Na_2SO_4) and the solvent was removed in vacuo to furnish **18b** (2.5 mg, 0.015 mmol, 58%) as a brown oil; yield over 3 steps: 36%; R_f = 0.44 (PE–EtOAc, 5:1), spot turned pink in air.

Downloaded by: University of Pittsburgh. Copyrighted material.

IR (film/NaCl): 3421 (m), 3367 (m), 2923 (m), 2854 (m), 1494 (m), 1454 (m), 1036 (m), 769 (s), 715 (m), 696 cm^{-1} (m).

^1H NMR (300 MHz, $CDCl_3$): δ = 7.47 (br s, 1 H, NH), 7.34–7.29 (m, 2 H, Ph), 7.25–7.21 (m, 3 H, Ph), 5.86 (t, *J* = 2.8 Hz, 1 H, =CH), 5.79 (t, *J* = 2.8 Hz, 1 H, =CH), 3.94 (s, 2 H, CH_2Ph), 2.21 (s, 3 H, CH_3).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 139.8 ($C1_{Ph}$), 129.2 (C2), 128.7 (2 C, Ph), 128.6 (2 C, Ph), 127.0 (C5), 126.3 ($C4_{Ph}$), 106.5 (=CH), 105.8 (=CH), 34.2 (CH_2), 13.0 (CH_3).

MS (ESI): *m*/*z* (%) = 341.24 (90) $[2 M - H]^+$, 250.18 (63), 170.07 (100) $[M - H]^+$.

HRMS (ESI): *m*/*z* $[M]^+$ calcd for $C_{12}H_{13}N$: 171.1048; found: 171.1051.

2-Benzyl-2-[(3,4-dimethoxybenzylidene)amino]-5-oxo-3-phenylhexanenitrile (15c)

Under an argon atmosphere, **1c** (250.3 mg, 0.850 mmol) was dissolved in anhyd THF (2.0 mL). After addition of DBU (133 μL, 0.892 mmol), the mixture was stirred for 1 min at r.t. Benzylideneacetone (**14c**, 124.4 mg, 0.851 mmol) in anhyd THF (0.5 mL) was added and the mixture was stirred for 20 h at r.t. The mixture was washed with sat. aq $NaHCO_3$ (2 × 5 mL) and the combined aqueous phases were extracted with EtOAc (2 × 5 mL). The combined organic layers were dried (Na_2SO_4) and the solvent was removed in vacuo to furnish a viscous orange oil (418.9 mg, quant.) which was subjected to the next step without further purification; R_f = 0.17 (PE–EtOAc, 4:1).

2-Benzyl-5-methyl-3-phenyl-3,4-dihydro-2*H*-pyrrole-2-carbonitrile (16c)

Under an argon atmosphere, crude **15c** (402.7 mg) was dissolved in THF (1.5 mL), H_2O (1.5 mL) and AcOH (583 μL, 10.2 mmol) were added and the mixture was stirred for 21.5 h at r.t. The mixture was partitioned between sat. aq $NaHCO_3$ (15 mL) and EtOAc (10 mL), the aqueous layer was extracted with EtOAc (2 × 5 mL), the combined organic layers were washed with H_2O (10 mL) and dried (Na_2SO_4), and the solvent was removed in vacuo to furnish a viscous orange oil (351.2 mg). A portion (338.4 mg) of the crude product was dissolved in EtOH (5 mL), Girard's reagent T (257.6 mg, 1.536 mmol) and AcOH (5 drops) were added. After stirring for 22 h under an argon atmosphere at r.t., the mixture was partitioned between sat. aq $NaHCO_3$ (15 mL) and EtOAc (10 mL). The aqueous layer was extracted with EtOAc (2 × 5 mL) and the combined organic layers were washed with H_2O (5 × 5 mL) and brine (10 mL) and dried (Na_2SO_4), and the solvent was removed in vacuo to furnish a viscous orange material (245.2 mg), which partially crystallized and was subjected to the subsequent reaction without further purification; R_f = 0.35 (PE–EtOAc, 2:1), ochre color (ninhydrin).

2-Benzyl-5-methyl-3-phenyl-1*H*-pyrrole (18c)

Under an argon atmosphere, crude **16c** (217.6 mg, 0.793 mmol) was dissolved in anhyd THF (2.0 mL) and KO*t*-Bu (93.5 mg, 0.833 mmol) was added. The mixture was stirred for 1.5 h at r.t. The dark brown mixture was partitioned between sat. aq $NaHCO_3$ (10 mL) and EtOAc (5 mL) and the aqueous layer was extracted with EtOAc (3 × 5 mL), the combined organic layers were washed with H_2O (4 × 5 mL) and dried (Na_2SO_4), and the solvent was removed in vacuo to furnish a light-brown foam (164.5 mg). A portion (153 mg) of the crude product was purified by column chromatography (silica gel, cyclohexane–EtOAc, 5:1) to furnish **18c** (48.3 mg, 0.195 mmol) as a red-brown resin; yield over 3 steps: 30%; R_f = 0.45 (PE–EtOAc, 5:1), spot turns pink in air.

IR (ATR): 1599 (m), 1492 (m), 1451 (m), 1439 (m), 760 (s), 730 (m), 695 (s), 648 (m), 525 (m), 459 cm^{-1} (m).

^1H NMR (300 MHz, DMSO-d_6): δ = 10.6 (br s, 1 H, NH), 7.31–7.22 (m, 6 H, Ph), 7.20–7.06 (m, 4 H, Ph), 5.92 (d, *J* = 2.4 Hz, 1 H, =CH), 4.00 (s, 2 H, CH_2Ph), 2.17 (s, 3 H, CH_3).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 140.8 ($C1_{Bn}$), 137.3 ($C1_{Ph}$), 128.3 (2 C), 128.3 (2 C), 127.9 (2 C), 126.6 (2 C), 126.1 (Cq), 125.8, 124.5, 124.4 (Cq), 120.5 (Cq), 105.5 (=CH), 31.9 (*C*H_2Ph), 12.7 (CH_3).

MS (ESI): *m*/*z* (%) = 248.2 (60) $[M + H]^+$, 247.17 (63) $[M]^{\cdot+}$, 246.15 (100) $[M - H]^+$.

HRMS (ESI): *m*/*z* $[M]^+$ calcd for $C_{18}H_{17}N$: 247.1361; found: 247.1357.

(*E*)-1-(4-Chlorophenyl)-4,4-dimethylpent-1-en-3-one (14d)

Pinacolone (8.00 g, 79.9 mmol) and 4-chlorobenzaldehyde (12.52 g, 89.1 mmol) were dissolved in EtOH (30 mL) and H_2O (10 mL) and 10% aq NaOH (8 mL) were added. The mixture was stirred overnight at r.t. The light-yellow crystals were removed by filtration, washed with 50% EtOH and dried in vacuo (14.82 g, 66.5 mmol, 83%); from the mother liquor, another crop (0.92 g, 4.1 mmol, 5%) of crystals was obtained. The product was obtained as light-yellow crystals; combined yield: 15.74 g (70.7 mmol, 88%); mp 85–86 °C (Lit.[45] 85–85.5 °C); R_f = 0.60 (PE–EtOAc, 5:1).

IR (ATR): 1678 (m), 1608 (m), 1487 (m), 1075 (s), 1004 (m), 983 (s), 815 (s), 776 (m), 524 (m), 488 cm^{-1} (m).

^1H NMR (300 MHz, $CDCl_3$): δ = 7.59 (d, J_{trans} = 15.6 Hz, 1 H, H1), 7.47 (AA′-part of AA′BB′-system, 2 H, $H2_{Ph}$, $H6_{Ph}$), 7.32 (BB′-part of AA′BB′-system, 2 H, $H3_{Ph}$, $H5_{Ph}$), 7.07 (d, J_{trans} = 15.6 Hz, 1 H, H2), 1.20 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR, PENDANT (125.8 MHz, $CDCl_3$): δ = 203.9 (C=O), 141.4 (=CHAr), 136.0 (Cq), 133.4 (Cq), 129.4 (2 C), 129.1 (2 C), 121.1 (=CHCO), 43.3 [Cq, $C(CH_3)_3$], 26.2 [3 C, $C(CH_3)_3$].

MS (FAB): *m*/*z* (%) = 223.2 (100) $[M + H]^+$.

Anal. Calcd for $C_{13}H_{15}ClO$: C, 70.11; H, 6.79. Found: C, 70.26; H, 6.92.

3-(4-Chlorophenyl)-2,6,6-trimethyl-2-[(2-naphthylmethylene)amino]-5-oxoheptanenitrile (15d)

Under an argon atmosphere, **1a** (249.0 mg, 1.12 mmol) was dissolved in anhyd THF (2 mL). After addition of TMG (158 μL, 1.26 mmol), the mixture was stirred for 1 min at r.t. A soln of **14d** (267.1 mg, 1.2 mmol) in anhyd THF (0.5 mL) was quickly added and the mixture was stirred for 6 h at r.t. The mixture was washed with sat. aq $NaHCO_3$ (5 mL), the combined aqueous layers were re-extracted with EtOAc (2 × 5 mL). The combined organic layers were dried (Na_2SO_4) and the solvent was removed in vacuo to furnish a light-yellow oil (541.2 mg, quant.) which was subjected to the subsequent reaction without further purification; yield: 541.2 mg (quant.); R_f = 0.43 (PE–EtOAc, 5:1).

5-*tert*-Butyl-3-(4-chlorophenyl)-2-methyl-3,4-dihydro-2*H*-pyrrole-2-carbonitrile (16d)

Under an argon atmosphere, crude **15d** (517.1 mg, 1.20 mmol) was dissolved in THF (1.5 mL), H_2O (1.5 mL) and AcOH (412 μL, 7.20 mmol) were added and the mixture was stirred for 16.5 h at r.t. The mixture was partitioned between sat. aq $NaHCO_3$ (10 mL) and EtOAc (5 mL). The aqueous layer was extracted with EtOAc (2 × 5 mL), the combined organic layers were washed with H_2O and brine (10 mL each) and dried (Na_2SO_4), and the solvent was removed in vacuo to furnish a yellow oil (428.8 mg). A portion (412.2 mg) of the crude product was dissolved in EtOH (5 mL), Girard's reagent T (320.7 mg, 1.91 mmol) and AcOH (5 drops) were added and the mixture was stirred for 18 h at r.t. The mixture was partitioned between sat. aq $NaHCO_3$ (15 mL) and EtOAc (10 mL), the aqueous layer was extracted with EtOAc (2 × 10 mL), the combined organic

Downloaded by: University of Pittsburgh. Copyrighted material.

layers were washed with H_2O (4 × 10 mL) and brine (10 mL) and dried (Na_2SO_4), and the solvent was removed in vacuo to furnish a yellow oil (286.0 mg); R_f = 0.31 (PE–EtOAc, 5:1), pink color (ninhydrin).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.33 (AA′-part of AA′BB′-system, 2 H, $H3_{Ph}$, $H5_{Ph}$), 7.19 (BB′-part of AA′BB′-system, 2 H, $H2_{Ph}$, $H6_{Ph}$), 3.86 (t, *J* = 8.8 Hz, 1 H, CH), 3.11 (dd, *J* = 17.2, 8.6 Hz, 1 H, CH_2-Ha), 2.92 (dd, *J* = 17.2, 9.1 Hz, 1 H, CH_2-Hb), 1.24 [s, 9 H, $C(CH_3)_3$], 1.09 (s, 3 H, CH_3).

5-*tert*-Butyl-3-(4-chlorophenyl)-2-methyl-1*H*-pyrrole (18d)

Under an argon atmosphere, crude **16d** (205.1 mg, 0.746 mmol) was dissolved in anhyd THF (2 mL), KO*t*-Bu (89.1 mg, 0.794 mmol) was added and the mixture was stirred for 50 min at r.t. The brown mixture was partitioned between sat. aq $NaHCO_3$ (10 mL) and EtOAc (5 mL) and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with H_2O (3 × 5 mL) and dried (Na_2SO_4), and the solvent was removed in vacuo to furnish a light-yellow oil (192.3 mg). ^{1}H NMR indicated the presence of unreacted starting material and a portion (177.3 mg) of the crude product was dissolved in anhyd THF (1.7 mL), KO*t*-Bu (87.9 mg, 0.783 mmol) was added and the mixture was stirred for 24 h at r.t. The workup procedure was repeated to furnish a light-brown and partially crystalline material (148.6 mg), a portion (139.0 mg) of which was purified by column chromatography (silica gel, PE–EtOAc, 8:1) to furnish a yellow oil (30.2 mg, 0.122 mmol) which still contained minor impurities; yield: 30.2 mg (0.122 mmol); yield over 3 steps: 18%; R_f = 0.41 (PE–EtOAc, 5:1).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.41 (br s, 1 H, NH), 7.33 (br s, 4 H, Ph), 5.87 (d, *J* = 2.7 Hz, 1 H, =CH), 2.30 (s, 3 H, CH_3), 1.24 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 139.7 ($C4_{Ph}$), 136.6 (Cq), 128.2 (2 C), 127.8 (2 C), 122.9 (Cq), 117.0 (Cq), 101.5 (=CH), 30.9 [*C*$(CH_3)_3$], 30.3 [3 C, C(*C*$H_3)_3$], 12.6 (CH_3).

MS (ESI): *m*/*z* (%) = 264.15 (100) $[M + OH]^+$, 247.1 (15) $[M]^+$, 207.99 (18).

HRMS (ESI): *m*/*z* $[M]^+$ calcd for $C_{15}H_{18}ClN$: 247.1128; found: 247.1132.

5-Bromopentanoyl Chloride[46]

In a flame-dried round bottom flask, 5-bromopentanoic acid (5.00 g, 27.6 mmol) was dissolved in anhyd benzene (10 mL) under an argon atmosphere. The mixture was warmed to 50 °C and oxalyl chloride (3.44 mL, 40.1 mmol) was added over 150 min. Stirring was continued for a further 60 min at 50 °C and overnight at r.t. The solvent and excess oxalyl chloride were removed in vacuo and the resulting light-yellow liquid (5.41 g, 27.1 mmol, 98%) was used without further purification.

7-Bromohept-1-en-3-one (19)[47]

The title compound was synthesized according to a modified procedure by Calas et al.,[40] the workup was performed according to a procedure by Andersen et al.[48] An argon-flushed flame-dried round-bottom flask was charged with anhyd CH_2Cl_2 (32.5 mL) and $AlCl_3$ (3.80 g, 28.5 mmol) The mixture was cooled to –20 °C and a soln of trimethyl(vinyl)silane (2.72 g, 27.1 mmol) and 5-brompentanoyl chloride (5.41 g, 27.1 mmol) was added over 45 min. Stirring was continued for 105 min at –20 °C. The reaction was quenched by pouring the mixture onto a mixture of ice and NH_4Cl (100 g/20 g). The aqueous phase was extracted with CH_2Cl_2 (2 × 60 mL) and the combined organic layers were washed with sat. aq $NaHCO_3$, H_2O and brine (60 mL each) and dried (Na_2SO_4); after the addition of a small amount of hydroquinone, the solvent was removed in vacuo to furnish an orange turbid liquid (5.22 g). Chromatographic purification (silica gel, PE–EtOAc, 10:1 to 7:1) furnished **19** (2.95 g, 15.44 mmol, 57%) as a light-yellow liquid. A small quantity of hydroquinone was added before concentration in vacuo. The product was stored at –18 °C to prevent polymerization; R_f = 0.45 (PE–Et_2O, 1:1).

IR (ATR): 1698 (m), 1678 (s), 1614 (m), 1401 (m), 1251 (m), 1201 (m), 984 (m), 963 (s), 559 cm^{-1} (m).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.35 (dd, *J* = 17.7, 10.5 Hz, 1 H, H2), 6.22 (dd, *J* = 17.7, 1.2 Hz, 1 H, $=CH_2$-H_{trans}), 5.83 (dd, *J* = 10.5 Hz, 1.2 Hz, 1 H, $=CH_2$-H_{cis}), 3.41 (t, *J* = 6.6 Hz, 2 H, CH_2Br), 2.63 (t, *J* = 7.1 Hz, 2 H, CH_2CO), 1.93–1.84 (m, 2 H, CH_2-6), 1.82–1.73 (m, 2 H, CH_2-5).

^{13}C NMR, PENDANT (100.7 MHz, $CDCl_3$): δ = 200.0 (C=O), 136.4 (=CH), 128.2 ($=CH_2$), 38.4 (C4), 33.2 (C7), 32.1 (C6), 22.4 (C5).

MS (EI): *m*/*z* (%) = 191 (3) $[M]^+$, 111 (29) $[M – Br]^+$, 55 (100) $[C_3H_5O]^+$.

(*E*)-9-Bromo-2-[(3,4-dimethoxybenzylidene)amino]-5-oxo-2-phenylnonanenitrile (20)

Under an argon atmosphere, **1d** (734.7 mg, 2.62 mmol) was dissolved in anhyd THF (7.5 mL). After addition of DBU (430 μL, 2.88 mmol), the mixture was stirred for 1 min at r.t. To the deep red soln was added **19** (502.1 mg, 2.63 mmol) in anhyd THF (2.5 mL) over 2 min. The orange-colored soln was stirred for 90 min at r.t. Sat. aq $NaHCO_3$ (50 mL) was added and the mixture was extracted with EtOAc (4 × 25 mL). The combined organic layers were dried (Na_2SO_4) and the solvent was removed in vacuo to furnish a light-brown resin (1.195 g, 2.53 mmol, 97%) which was subjected to the next step without further purification; R_f = 0.37 (PE–EtOAc, 2:1).

IR (ATR): 1510 (s), 1448 (m), 1420 (m), 1265 (s), 1239 (s), 1162 (m), 1139 (m), 1021 (s), 761 (m), 698 cm^{-1} (m).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.53 (s, 1 H, HC=N), 7.65–7.61 (m, 2 H, H2″, H6″), 7.48 (d, *J* = 1.9 Hz, 1 H, H2′), 7.44–7.38 (m, 2 H, H3″, H5″), 7.37–7.32 (m, 2 H, H4″, H6′), 6.93 (d, *J* = 8.3 Hz, 1 H, H5′), 3.97 (s, 3 H, OCH_3), 3.94 (s, 3 H, OCH_3), 3.34 (t, *J* = 6.6 Hz, 2 H, CH_2-9), 2.55–2.48 (m, 4 H), 2.40 (td, *J* = 7.1, 2.3 Hz, 2 H), 1.82–1.74 (m, 2 H, CH_2-8), 1.70–1.61 (m, 2 H, CH_2-7).

^{13}C NMR (100.7 MHz, $CDCl_3$): δ = 208.0 (C=O), 160.2 (HC=N), 152.4, 149.4 (C3′/C4′), 139.7 (C1″), 128.9 (2 C, C3″,5″), 128.7 (C4″), 128.0 (C1′), 125.9 (2 C, C2″, C6″), 124.2 (C6′), 118.9 (CN), 110.6 (C2′), 109.5 (C5′), 70.0 (*C*CN), 56.0, 56.0 (2 OCH_3), 41.8 (C6), 37.9, 37.6, 33.1, 31.9, 22.1 (C7).

MS (FAB): *m*/*z* (%) = 471.1 (72) $[M + H]^+$.

HRMS (FAB): *m*/*z* $[M + H]^+$ calcd for $C_{24}H_{28}{}^{79}BrN_2O_3$: 471.1283; found: 471.1277.

***rel*-(3*R*,8a*R*)-3-Phenyloctahydroindolizine (21a) and *rel*-(3*R*,8a*S*)-3-Phenyloctahydroindolizine (21b)**

To a soln of **20** (1.17 g, 2.49 mmol) in THF (2 mL) was added H_2O (1 mL) and AcOH (900 μL, 15.7 mmol) and the mixture was stirred for 2 h at r.t. EtOH (9.20 mL, 157 mmol) and $NaCNBH_3$ (994.2 mg, 15.8 mmol) were added to the yellow mixture which was stirred for 17.5 h at r.t. Ethanolamine (2 mL) was added to destroy the borane–amine complexes and stirring was continued for 6 h. The mixture was partitioned between sat. aq $NaHCO_3$ and EtOAc (80 mL each), the aqueous layer was extracted with EtOAc (3 × 40 mL), the combined organic layers were washed with half-sat. brine (2 × 80 mL) and extracted with 1 M HCl (4 × 20 mL). The combined acidic extracts were made alkaline with sat. aq Na_2CO_3 (50 mL) and extracted with Et_2O (4 × 40 mL). The combined ethereal extracts were dried (Na_2SO_4) and the solvent was removed in vacuo to furnish a light-brown liquid (438.4 mg) which consisted of the diastereomeric products **21a** and **21b** in a 1.2:1 ratio. Separation of both diastereomers was achieved by column chromatography (silica gel, PE–

Downloaded by: University of Pittsburgh. Copyrighted material.

EtOAc, 5:1 + 1% Me_2NEt) to furnish pure **21a** (colorless liquid, 116.3 mg, 0.578 mmol, 24% over 2 steps) and pure **21b** (colorless liquid, 89.7 mg, 0.446 mmol, 18% over 2 steps).

Major Diastereomer 21a

R_f = 0.83 (PE–EtOAc, 1:1), greenish color (ninhydrin).

IR (ATR): 2930 (m), 2787 (w), 1450 (w), 1257 (w), 1141 (w), 1120 (w), 1077 (w), 1047 (w), 755 (m), 698 (s), 543 cm^{-1} (w).

^1H NMR, COSY, HMBC (400 MHz, 100.6 MHz, CD_3OD): δ = 7.36–7.27 (m, 4 H, $H2_{Ph}$, $H6_{Ph}$, $H3_{Ph}$, $H5_{Ph}$), 7.25–7.20 (m, 1 H, $H4_{Ph}$), 3.12 (t, *J* = 8.5 Hz, 1 H, H3), 2.75 (pseudo-d, J_{app} ≈ 10.9 Hz, 1 H, H4a), 2.14–2.00 (m, 2 H, H2a, H8a), 1.94–1.74 (m, 4 H, H1a, H5a, H7a, H4b), 1.71–1.61 (m, 1 H, H2b), 1.60–1.50 (m, 2 H, H6a, H1b), 1.49–1.41 (m, 1 H, H5b), 1.40–1.25 (m, 2 H, H6b, H7b).

^{13}C NMR, HSQC, HMBC (100.6 MHz, 400 MHz, CD_3OD): δ = 143.8 (C1′), 129.3 (2 C, C3′, C5′), 128.9 (2 C, C2′, C6′), 128.2 (C4′), 71.9 (C3), 66.8 (C8a), 52.5 (C4), 32.8 (C2), 31.9 (C7), 30.4 (C1), 26.2 (C5), 25.4 (C6).

MS (EI): *m*/*z* (%) = 201 (65) $[M]^+$, 200 (76) $[M – H]^+$, 172 (35) $[M – C_2H_4]^+$, 124 (100) $[M – Ph]^+$.

HRMS (ESI): *m*/*z* $[M + 2 H]^+$ calcd for $C_{14}H_{21}N$: 203.1674; found: 203.1675.

Minor Diastereomer 21b

R_f = 0.24 (PE–EtOAc, 1:1), greenish color (ninhydrin).

IR (ATR): 2926 (m), 2850 (m), 1686 (w), 1455 (m), 1358 (w), 1306 (w), 1181 (w), 1136 (w), 1109 (w), 1065 (w), 1027 (w), 754 (m), 699 cm^{-1} (s).

^1H NMR, COSY, HMBC (400 MHz, 100.6 MHz, CD_3OD): δ = 7.35–7.29 (m, 2 H, $H2_{Ph}$, $H6_{Ph}$), 7.28–7.23 (m, 3 H, $H3_{Ph}$, $H5_{Ph}$, $H4_{Ph}$), 4.20 (dd, *J* = 8.4, 4.8 Hz, 1 H, H3), 2.83 (mc, 1 H, H8a), 2.70 (pseudo-d, J_{app} ≈ 12.3 Hz, 1 H, H4a), 2.34 (mc, 1 H, H2a), 2.18 (mc, 1 H, H1a), 2.00 (dt, *J* = 12.5, 3.2 Hz, 1 H, H4b), 1.96–1.88 (m, 1 H, H2b), 1.80–1.66 (m, 2 H, H6a, H7a), 1.57 (mc, 2 H, H5a, H1b), 1.42–1.28 (m, 2 H, H5b, H7b), 1.27–1.16 (m, 1 H, H6b).

^{13}C NMR, HSQC, HMBC (100.7 MHz, 400 MHz, CD_3OD): δ = 142.6 (C1′), 129.6 (2 C), 129.2 (2 C), 128.4 (C4′), 65.6 (C3), 60.8 (C8a), 48.4 (C4), 31.3, 31.2 (C1/C2), 30.9 (C7), 25.3 (C6), 23.6 (C5).

MS (EI): *m*/*z* (%) = 201 (58) $[M]^+$, 200 (67) $[M – H]^+$, 172 (35) $[M – C_2H_4]^+$, 124 (100) $[M – Ph]^+$.

HRMS (ESI): *m*/*z* $[M]^+$ calcd for $C_{14}H_{19}N$: 201.1517; found: 201.1515.

3-Phenyloctahydroindolizine-3,8a-dicarbonitrile (22) and 2-(4-Bromobutyl)-5-phenyl-1*H*-pyrrole (23)

To a soln of **20** (137.0 mg, 0.291 mmol) in THF (1 mL) was added H_2O (1 mL) and AcOH (100 μL, 1.75 mmol). The mixture was stirred for 17 h at r.t. before sat. aq $NaHCO_3$ (10 mL) was added and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with H_2O and brine (10 mL each), dried (Na_2SO_4) and the solvent was removed in vacuo. A portion (142.4 mg) of the resulting resin (149.8 mg) was purified by column chromatography (silica gel, PE–EtOAc, 4:1) to furnish **23** (5.0 mg, 0.018 mmol, 6%) as a light-yellow oil and **22** (23.5 mg, 0.094 mmol, 34%) as a light-orange oil.

Compound 22

R_f = 0.42 (PE–EtOAc, 2:1); orange/green color (ninhydrin).

IR (ATR): 2946 (m), 1447 (m), 1256 (m), 1210 (m), 1150 (m), 1140 (m), 1104 (m), 957 (m), 760 (s), 698 cm^{-1} (s).

^1H NMR, COSY, HMBC (400 MHz, 100.6 MHz, $CDCl_3$): δ = 7.58–7.54 (m, 2 H, $H2_{Ph}$, $H6_{Ph}$), 7.43–7.33 (m, 3 H, $H3_{Ph}$, $H5_{Ph}$, $H4_{Ph}$), 2.89 (ddd, *J* = 13.9, 10.3, 8.7 Hz, 1 H, H2a), 2.80 (td, *J* = 11.9, 2.8 Hz, 1 H, H4a), 2.71 (mc, 1 H, H4b), 2.44 (ddd, *J* = 12.6, 8.7, 1.9 Hz, 1 H, H1a), 2.27 (mc, 1 H, H7a), 2.19 (ddd, *J* = 13.9, 9.8, 1.9 Hz, 1 H, H2b), 1.97 (dt, *J* = 12.6, 10.3 Hz, 1 H, H1b), 1.91–1.83 (m, 1 H, H6a), 1.80–1.71 (m, 2 H, H5a, H6b), 1.68–1.60 (m, 1 H, H7b), 1.54–1.42 (m, 1 H, H5b).

^{13}C NMR, HSQC, HMBC (100.7 MHz, 400 MHz, $CDCl_3$): δ = 139.7 (C1′), 129.0 (2 C, C3′, C5′), 128.9 (C4′), 125.4 (2 C, C2′, C6′), 117.9 (CN), 117.9 (CN), 67.0 (C3), 63.0 (C8a), 43.5 (C4), 39.4 (C2), 36.0 (C7), 35.7 (C1), 24.5 (C5), 20.9 (C6).

MS (EI): *m*/*z* (%) = 251 (50) $[M]^+$, 224 (45), 197 (60), 174 (74) $[M – Ph]^+$, 122 (100), 106 (83), 82 (62), 78 (68), 55 (56), 51 (72), 41 (75).

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{16}H_{17}NaN_3$: 274.1320; found: 274.1331.

Compound 23

R_f = 0.67 (PE–EtOAc, 2:1).

^1H NMR (400 MHz, MHz, $CDCl_3$): δ = 7.43–7.34 (m, 5 H, $H2_{Ph}$, $H6_{Ph}$, $H3_{Ph}$, $H5_{Ph}$, NH), 7.28–7.23 (m, 1 H, $H4_{Ph}$), 6.20 (d, *J* = 3.5 Hz, 1 H, H4), 5.94 (dt, *J* = 3.5, 1.1 Hz, 1 H, H3), 3.95 (t, *J* = 5.9 Hz, 2 H, CH_2-4′), 2.89 (t, *J* = 6.2 Hz, 2 H, CH_2-1′), 1.95–1.88 (m, 2 H, CH_2-3′), 1.87–1.80 (m, 2 H, CH_2-2′). The spectrum showed the presence of impurities.

^{13}C NMR (100.7 MHz, $CDCl_3$): δ = 132.7 (Cq), 130.7 (Cq), 128.8 (2 C, Ph), 128.5 (2 C, Ph), 126.5 ($C4_{Ph}$), 125.7 (Cq), 108.3 (=CH), 104.9 (=CH), 30.6, 24.3, 24.0, 21.2.

HRMS (ESI): *m*/*z* $[M]^+$ calcd for $C_{14}H_{16}{}^{79}BrN$: 277.0466; found: 277.0476.

(*E*)-2-Benzyl-9-bromo-2-[(2-naphthylmethylene)amino]-5-oxononanenitrile

Under an argon atmosphere, **1b** (399.7 mg, 1.41 mmol) was dissolved in anhyd THF (4 mL) and DBU (231 μL, 1.55 mmol) was added. The mixture was stirred for 1 min at r.t. before **19** (269.1 mg, 1.41 mmol) in anhyd THF (2.5 mL) was added over 1 min. Since TLC revealed only incomplete conversion after 2 h stirring at r.t., another portion of **19** (49.0 mg, 0.256 mmol) was added and stirring was continued for 70 min. To the dark-blue mixture was added sat. aq $NaHCO_3$ (30 mL) and the mixture was extracted with EtOAc (4 × 15 mL). The combined organic layers were dried (Na_2SO_4) and the solvent was removed in vacuo to furnish a brown resin (709.0 mg, quant.) which was subjected to the next step without further purification; R_f = 0.27 (PE–EtOAc, 5:1).

IR (ATR): 1712 (m), 1638 (m), 1454 (m), 1371 (m), 1269 (m), 1241 (m), 820 (m), 752 (s), 701 (s), 476 cm^{-1} (s).

^1H NMR (400 MHz, $CDCl_3$): δ = 8.21 (s, 1 H, HC=N), 8.02 (br s, 1 H, $H1_{Naphthyl}$), 7.99 (dd, *J* = 8.6, 1.6 Hz, 1 H, $H3_{Naphthyl}$), 7.92–7.86 (m, 3 H, $H4_{Naphthyl}$, $H5_{Naphthyl}$, $H8_{Naphthyl}$), 7.56 (tt, *J* = 12.6, 3.5 Hz, 2 H, $H6_{Naphthyl}$, $H7_{Naphthyl}$), 7.24–7.18 (m, 5 H, Ph), 3.32 (t, *J* = 6.6 Hz, 2 H, H2–H9), 3.22 (AB-system, *J* ≈ 13.6 Hz, 2 H, CH_2Ph), 2.60–2.29 (m, 6 H), 1.87–1.73 (m, 2 H), 1.71–1.61 (m, 2 H).

^{13}C NMR, PENDANT (100.7 MHz, $CDCl_3$): δ = 208.1 (C=O), 161.5 (HC=N), 135.1 (Cq), 133.9 (Cq), 132.9 (Cq), 132.3 (Cq), 131.4, 130.9 (2 C), 128.8, 128.7, 128.2 (2 C), 127.9, 127.8, 127.5, 126.8, 123.6, 118.3 (CN), 68.2 (*C*CN), 46.4, 41.8, 37.9, 34.0, 33.1, 32.0, 22.1.

MS (FAB): *m*/*z* (%) = 475.2 (100) $[M]^+$, 385.2 (45).

HRMS (FAB): *m*/*z* $[M + H]^+$ calcd for $C_{27}H_{28}{}^{79}BrN_2O$: 475.1385; found: 475.1387.

Downloaded by: University of Pittsburgh. Copyrighted material.

***rel*-(3*R*,8a*R*)-3-Benzyloctahydroindolizine and *rel*-(3*R*,8a*S*)-3-Benzyloctahydroindolizine (24a, 24b)**

To a soln of crude (*E*)-2-benzyl-9-bromo-2-[(2-naphthylmethylene)amino]-5-oxononanenitrile (657.8 mg, 1.384 mmol) in THF (1 mL) was added H_2O (0.5 mL) and AcOH (475 μL, 8.30 mmol) and the mixture was stirred for 19 h at r.t. EtOH (4.9 mL, 83.5 mmol) and $NaCNBH_3$ (540.3 mg, 8.60 mmol) were added to the yellow mixture which was stirred for another 3 h at r.t. Ethanolamine (1 mL) was added to destroy borane complexes and the mixture was stirred for 75 min. After addition of sat. aq $NaHCO_3$ (40 mL), the brown mixture was extracted with EtOAc (4 × 20 mL), the combined organic layers were washed with half-sat. brine (2 × 40 mL) and extracted with 1 M HCl (5 × 15 mL). The combined acidic extracts were made alkaline by addition of sat. aq Na_2CO_3 and were extracted with CH_2Cl_2 (5 × 20 mL). The combined organic layers were dried (Na_2SO_4) and the solvent was removed in vacuo to furnish a brownish liquid (99.6 mg). A portion (97.1 mg) of the crude product was purified by column chromatography (silica gel, PE–EtOAc, 6:1 + 1% Me_2NEt) to yield **24a** (37.5 mg, 0.174 mmol, 14% over 2 steps) as a colorless liquid and **24b** (30.1 mg, 0.140 mmol, 11% over 2 steps) also as a colorless liquid. Care should be taken to prevent evaporation of the products during removal of solvent and/or eluent in vacuo. The relative configuration of both products could not be determined by ROESY experiments and attempts to obtain single crystals of the salts failed.

Compound 24a

R_f = 0.35 (PE–EtOAc, 6:1 + 1% Me_2NEt), grayish color (ninhydrin).

IR (ATR): 2930 (m), 2856 (w), 2787 (w), 1495 (w), 1452 (m), 1362 (w), 1336 (w), 1273 (w), 1206 (s), 1139 (m), 1117 (m), 739 (m), 698 (s), 496 cm^{-1} (m).

^1H NMR, COSY, HMBC (400 MHz, 100.6 MHz, CD_3OD): δ = 7.26–7.23 (m, 2 H, $H3_{Ph}$, $H5_{Ph}$), 7.19–7.13 (m, 3 H, $H2_{Ph}$, $H6_{Ph}$, $H4_{Ph}$), 3.26 (mc, 1 H, H4a), 3.09 (dd, *J* = 11.4, 2.6 Hz, 1 H, $PhCH_2$-Ha), 2.46–2.35 (m, 2 H, $PhCH_2$-Hb, H3), 2.00–1.90 (m, 2 H, H4b, H8a), 1.80–1.76 (m, 2 H, H6a, H7a), 1.75–1.68 (m, 2 H, H1a, H6b), 1.66–1.53 (m, 2 H, H2a, H5a), 1.48–1.39 (m, 1 H, H2b), 1.38–1.33 (m, 1 H, H1b), 1.31–1.26 (m, 2 H, H5b, H7b).

^{13}C NMR, HSQC, HMBC (100.7 MHz, 400 MHz, CD_3OD): δ = 141.0 (C1′), 130.1 (2 C, C2′, C6′), 129.4 (2 C, C3′, C5′), 127.2 (C4′), 68.4 (C3), 67.2 (C8a), 52.9 (C4), 40.5 (CH_2Ph), 31.7 (C7), 29.5 (C1), 29.2 (C2), 26.1 (C5), 25.4 (C6).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{22}N$: 216.1752; found: 216.1761.

Compound 24b

R_f = 0.11 (PE–EtOAc, 6:1 + 1% Me_2NEt), grayish color (ninhydrin).

IR (ATR): 2926 (m), 2851 (w), 1496 (w), 1451 (w), 1330 (w), 1196 (w), 1138 (w), 1115 (w), 1085 (w), 735 (m), 698 (s), 505 cm^{-1} (w).

^1H NMR, COSY, HMBC (400 MHz, 100.6 MHz, CD_3OD): δ = 7.27–7.23 (m, 2 H, $H3_{Ph}$, $H5_{Ph}$), 7.18–7.13 (m, 3 H, $H2_{Ph}$, $H6_{Ph}$, $H4_{Ph}$), 3.40 (ddd, *J* = 14.8, 8.2, 4.1 Hz, 1 H, H3), 3.07–2.98 [m, 2 H, H4a, contained in this multiplet: 3.00 (dd, *J* = 12.9, 4.1 Hz, 1 H, $PhCH_2$-Ha)], 2.80 (mc, 1 H, H8a), 2.72–2.65 (m, 1 H, H4b), 2.35 (dd, *J* = 12.9, 10.7 Hz, 1 H, $PhCH_2$-Hb), 1.94 (mc, 1 H, H7a), 1.81–1.72 (m, 2 H, H2a, H5a), 1.70–1.65 (m, 1 H, H1a), 1.61–1.48 (m, 3 H, H2b, H5b, H6a), 1.42–1.33 (m, 2 H, H6b, H7b), 1.29–1.22 (m, 1 H, H1b).

^{13}C NMR, HSQC, HMBC (100.7 MHz, 400 MHz, CD_3OD): δ = 141.1 (C1′), 130.3 (2 C, C2′, C6′), 129.5 (2 C, C3′, C5′), 127.1 (C4′), 62.8 (C3), 60.9 (C8a), 48.2 (C4), 37.6 (CH_2Ph), 31.0 (C1), 30.4 (C7), 28.2 (C2), 25.3 (C5), 24.1 (C6).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{22}N$: 216.1752; found: 216.1761.

Acknowledgment

This work was supported by the Deutsche Forschungsgemeinschaft. We thank I. Nevoigt (University of Hamburg) for the crystallographic analysis and Dr. S. Franke (late, University of Hamburg) and Dr. N. Hanold (University of Mainz) for mass spectrometry.

References

(1) Seebach, D.; Enders, D. *Angew. Chem.* **1975**, *87*, 1.
(2) Albright, J. D. *Tetrahedron* **1983**, *39*, 3207.
(3) Enders, D.; Shilvock, J. P. *Chem. Soc. Rev.* **2000**, *29*, 359.
(4) Opatz, T. *Synthesis* **2009**, 1941.
(5) Meyer, N.; Opatz, T. *Synlett* **2003**, 1427.
(6) von Miller, W.; Plöchl, J. *Ber. Dtsch. Chem. Ges.* **1898**, *31*, 2718.
(7) Werner, F.; Blank, N.; Opatz, T. *Eur. J. Org. Chem.* **2007**, 3911.
(8) Meyer, N.; Werner, F.; Opatz, T. *Synthesis* **2005**, 945.
(9) Kison, C.; Meyer, N.; Opatz, T. *Angew. Chem. Int. Ed.* **2005**, *44*, 5662.
(10) Kison, C.; Opatz, T. *Eur. J. Org. Chem.* **2008**, 2740.
(11) Bergner, I.; Opatz, T. *Synthesis* **2007**, 918.
(12) Bruylants, P. *Bull. Soc. Chim. Belg.* **1924**, *33*, 467.
(13) Tsuge, O.; Ueno, K.; Kanemasa, S.; Yorozu, K. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 1809.
(14) Tsuge, O.; Kanemasa, S.; Yamada, T.; Matsuda, K. *J. Org. Chem.* **1987**, *52*, 2523.
(15) Tsuge, O.; Ueno, K.; Kanemasa, S.; Yorozu, K. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 3347.
(16) Meyer, N.; Opatz, T. *Synlett* **2004**, 787.
(17) Bergner, I.; Opatz, T. *Synthesis* **2007**, 918.
(18) Bergner, I.; Opatz, T. *J. Org. Chem.* **2007**, *72*, 7083.
(19) Estevez, V.; Villacampa, M.; Menendez, J. C. *Chem. Soc. Rev.* **2010**, *39*, 4402.
(20) Joshi, U.; Pipelier, M.; Naud, S.; Dubreuil, D. *Curr. Org. Chem.* **2005**, *9*, 261.
(21) St. Cyr, D. J.; Martin, N.; Arndtsen, B. A. *Org. Lett.* **2007**, *9*, 449.
(22) Milgram, B. C.; Eskildsen, K.; Richter, S. M.; Scheidt, W. R.; Scheidt, K. A. *J. Org. Chem.* **2007**, *72*, 3941.
(23) Agarwal, S.; Knölker, H.-J. *Org. Biomol. Chem.* **2004**, *2*, 3060.
(24) Balme, G. *Angew. Chem. Int. Ed.* **2004**, *43*, 6238.
(25) Trofimov, B. A.; Mikhaleva, A. I.; Schmidt, E. Y.; Sobenina, L. N. *Adv. Heterocycl. Chem.* **2010**, *99*, 209.
(26) Russel, J. S.; Pelkey, E. T.; Yoon-Miller, S. J. P. *Prog. Heterocycl. Chem.* **2009**, *21*, 145.
(27) Russel, J. S.; Pelkey, E. T. *Prog. Heterocycl. Chem.* **2009**, *20*, 122.
(28) Tsuge, O.; Ueno, K. *Heterocycles* **1982**, *19*, 1411.
(29) Roth, B. D. (Warner-Lambert Co., USA) EP 0409281, **1991**.
(30) Pandey, P. S.; Srinivasa Rao, T. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 129.
(31) Tsuge, O.; Kanemasa, S.; Yorozu, K.; Ueno, K. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 3359.
(32) Kanemasa, S.; Tsuge, O. *Adv. Cycloaddit.* **1993**, *3*, 99.
(33) Pearson, W. H.; Stoy, P. *Synlett* **2003**, 903.
(34) Vivanco, S.; Lecea, B.; Arrieta, A.; Prieto, P.; Morao, I.; Linden, A.; Cossio, F. P. *J. Am. Chem. Soc.* **2000**, *122*, 6078.
(35) Bergner, I. *Dissertation*; University of Hamburg: Germany, **2009**.

Downloaded by: University of Pittsburgh. Copyrighted material.

(36) van der Werf, A.; Kellogg, R. M. *Tetrahedron Lett.* **1991**, *32*, 3727.
(37) Tasheva, D.; Petrova, A.; Simova, S. *Synth. Commun.* **2007**, *37*, 3971.
(38) Bergner, I.; Wiebe, C.; Meyer, N.; Opatz, T. *J. Org. Chem.* **2009**, *74*, 8243.
(39) Girard, A.; Sandulesco, G. *Helv. Chim. Acta* **1936**, *19*, 1095.
(40) Pillot, J. P.; Dumogues, J.; Calas, R. *C. R. Acad. Sci., Ser. C* **1974**, *278*, 789.
(41) Gottlieb, H. E.; Kotlyar, V.; Nudelman, A. *J. Org. Chem.* **1997**, *62*, 7512.
(42) Lagriffoul, P.-H.; Tadros, Z.; Taillades, J.; Commeyras, A. *J. Chem. Soc., Perkin Trans. 2* **1992**, 1279.
(43) Kurtz, P.; Disselnkoetter, H. *Justus Liebigs Ann. Chem.* **1972**, *764*, 69.
(44) Wright, S. W.; Petraitis, J. J.; Freimark, B.; Giannaras, J. V.; Pratta, M. A.; Sherk, S. R.; Williams, J. M.; Magolda, R. L.; Arner, E. C. *Bioorg. Med. Chem.* **1996**, *4*, 851.
(45) Weinstock, H. H. Jr.; Fuson, R. C. *J. Am. Chem. Soc.* **1934**, *56*, 1241.
(46) Collman, J. P.; Brauman, J. I.; Doxsee, K. M.; Halbert, T. R.; Bunnenberg, E.; Linder, R. E.; LaMar, G. N.; Del Gaudio, J.; Lang, G.; Spartalian, K. *J. Am. Chem. Soc.* **1980**, *102*, 4182.
(47) Bajgrowicz, J. A.; El Hallaoui, A.; Jacquier, R.; Pigiere, C.; Viallefont, P. *Tetrahedron* **1985**, *41*, 1833.
(48) Andersen, S. H.; Sharma, K. K.; Torssell, K. B. G. *Tetrahedron* **1983**, *39*, 2241.

Downloaded by: University of Pittsburgh. Copyrighted material.