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Selective Partial Reduction of Various Heteroaromatic Compounds with Bridgehead Nitrogen via Birch Reduction Protocol

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Abstract

For the first time various heteroaromatic compounds with bridgehead nitrogen, including indolizines, bispyrrolopyrimidines, pyrroloquinolines, pyrroloisoquinolines, and bispyrrolopyrazines, were selectively partially reduced under Birch reduction conditions. It was found that the double bond in the fused heterocycles which possesses the highest LUMO density can be selectively reduced under these conditions. Indolizine **6**, containing an ester group at C-6, was reductively alkylated to give dihydroindolizines **8** and **9** possessing a quaternary carbon center in good yield. It was found that ambident substrate **12**, under Birch reduction conditions, underwent smooth partial reduction to give 4,5-dihydroquinoline **14** as a sole product with no evidence of reduction of the side chain olefin. It was also shown that electron-rich pyrroloisoquinoline **15**, which cannot be reduced via catalytic hydrogenation conditions, was efficiently transformed into its dihydrocounterpart **16** by using the Birch reduction protocol. Finally, it was shown that various fused diazines were smoothly and stereoselectively reduced under Birch reduction conditions to give *trans*-4,5-disubstituted dihydropyrimidines **30** and **32** in virtually quantitative yields.

Introduction

We have recently developed a set of novel transition metalcatalyzed cycloisomerization methods for the efficient synthesis of furans,¹ pyrroles,^{1b,2} and fused pyrroloheterocycles.^{2,3} Although we have shown that exhaustive catalytic hydrogenation/reduction of certain fused heteroaromatic compounds can serve as an expeditious approach toward bicyclic and tricyclic alkaloids and their derivatives,^{2,3} no general methods for selective partial reduction of pyrroloheterocycles exist.⁴ We found this rather unfortunate, as various types of partially reduced heteroaromatic compounds of this type are very attractive synthetic targets due to

their diverse biological activities (Figure 1). For example, various dihydroindolo[2,1-*a*]-isoquinolines have been shown to inhibit the growth of human mammary carcinoma cells.⁵ It is also known that some pyrrolofused tricyclic heterocycles, such as dihydroquinolines and dihydroisoquinolines, show *in vivo* activity against P388 leukemia.⁶ Particularly, we are interested in the synthesis and partial selective reduction of the pyridine ring of the pyrroloisoquinoline core of lamellarins, polycyclic natural products with profound cytotoxic⁷ and anti-HIV⁸ activities. Herein we report a general and selective method for partial reduction of pyridine, pyrimidine, and pyrazine rings of various heteroaromatic compounds with bridgehead nitrogen via a Birch reduction motif.

Results and Discussion

Initially, we attempted partial Birch reduction of the pyridine ring of indolizines. Although some reports exist on the Birch reduction of a nonfused pyridine nucleus,⁹ there are no examples of such reduction of a fused pyridine ring. Accordingly, we examined reduction of activated indolizines **1–6**, possessing an ester functionality at different positions of the heterocycle (Scheme 1). All attempts on the reduction of indolizines **1–3** resulted in their total decomposition. It was found, however, that indolizine **4**, possessing an ester group at C-6, underwent smooth partial reduction to give **5** in good yield. It should be mentioned that this partial Birch reduction of indolizine **4** is highly regioselective and no other reduced compounds were observed besides **5**.¹⁰ When a bulky *tert*-butyl ester was introduced into the ring (**6**), partially reduced product **7** was obtained in a slightly improved yield (Scheme 1).

Inspired by the successful reduction of indolizines, we attempted reductive alkylation of **6** as an attractive approach for generation of a quaternary carbon center¹¹ at C-6 of indolizine (Scheme 2). Our initial reductive alkylation reaction was attempted by quenching a reaction mixture with excess MeI. Reduction under these conditions resulted in a complex mixture of products with the desired alkylated product **8** not exceeding 30%. Remarkably, the yield was dramatically improved by adding (CH₃OCH₂CH₂)₂NH as an additive.¹² The reductive alkylation reaction with a bulkier electrophile, BuBr, proceeded equally well to give **9** in 92% yield (Scheme 2).

Encouraged by these results, we attempted the Birch reduction of nonactivated fused tricyclic heteroaromatic systems. Gratifyingly, pyrroloquinoline **10** underwent selective reduction to furnish 4,5-dihydropyrroloquinoline **11** quantitatively (Scheme 3). Next, we tested the chemoselectivity of the Birch reduction vs catalytic hydrogenation on ambident substrate **12**, possessing an alkenyl functionality in the side chain. It was found that this pyrroloquinoline, under Birch reduction conditions, underwent smooth partial reduction to give 4,5-dihydroquinoline **14** as a sole product with no traces of reduction of the side chain olefin. Expectedly, catalytic hydrogenation of **12** selectively reduced the terminal olefin moiety to produce heteroaromatic **13** quantitatively (Scheme 3).

Next, we drew our attention to the selective reduction of the pyridine ring of pyrroloisoquinolines, as model studies toward lamellarins I, K, and L.¹³ It deserves mentioning that there is a precedent on successful hydrogenation of the pyridine ring of electron-neutral indoloisoquinolines.^{4a} However, attempts on hydrogenation of an electron-rich alkoxy-substituted indoloisoquinoline gave a disappointingly low yield (6%) of the desired product.^{4b} These results posed a potential problem for the partial hydrogenation of the pyrroloisoquinoline core of lamellarins, as all of them possess requisite hydroxy or alkoxy groups. To verify whether catalytic hydrogenation of electron-rich pyrroloisoquinolines, like their indoloisoquinoline counterparts,^{4b} is problematic, we first tested hydrogenation of 8-dimethylamino pyrroloisoquinoline **15** (Scheme 4). Not

surprisingly, all our efforts to achieve the partial reduction of **15** via catalytic hydrogenation even with high loading of catalyst and under high hydrogen pressure failed. In contrast, Birch reduction of **15** proceeded smoothly to furnish the desired product **16** quantitatively (Scheme 4).

Next, partial Birch reduction of alkoxy-substituted pyrroloisoquinolines under Birch reduction conditions was tested (Scheme 5). In a similar fashion, C-7 methoxy-substituted isoquinoline **17** was converted to the corresponding 5,6-dihydropyrroloisoquinoline **18** in excellent yield. However, when C-9 methoxy-substituted compound **19** was subjected to Birch reduction conditions, the reaction was not selective, affording the desired **20** in only 50% yield.

To understand this outcome, we performed DFT calculations (B3LYP/6-31G*) of pyrroloisoquinolines **17** and **19**. Our calculations indicated that the highest LUMO density of **17** resides at C-5 and C-6, thus securing selective reduction, whereas that of **19** was located at C-7 of the aryl ring thereby causing unselective reduction (Figure 2).

At this point, it occurred to us that switching the methoxy group with the phenoxide may make the benzene ring more electron-rich, thereby suppressing the undesired over-reduction process.¹⁴ To this end, sodium phenoxide **22**, generated in situ by the addition of 1.2 equiv of NaH to the phenol **21**, was subjected to the standard Birch reduction conditions. Partial reduction of this sodium salt proceeded substantially more sluggishly though very selectively¹⁵ affording the desired phenol **23** quantitatively. In contrast, phenol **21** did not give clean conversion under the former conditions, resulting in a mixture of over-reduced products (Scheme 6).¹⁶

Next, we examined the reduction of silyl-protected phenol **24**, which is appealing as a superior substrate over the sodium phenoxide as it can be easily handled throughout the syntheses. Silyl ether **24** was prepared directly from **19** in 90% yield, using B(C₆F₅)₃-catalyzed cleavage of alkyl aryl ethers with triethylsilane.¹⁷ To our delight, the reduction of silyl-protected phenol **24** was both quick and selective, producing phenol **23** in virtually quantitative yield (Scheme 7).

We envisioned that this unusual selectivity of the reduction of silyl ether **24** could be explained by a plausible mechanism depicted in Scheme 8. Isoquinoline **24** undergoes 1,6-reduction, acquiring two electrons, followed by protonation at C-5 to form methylene-cyclohexadienone **25**. A second 1,6-reduction of the latter followed by second electron transfer and protonation at C-6 produces phenoxide **26**, the formation of which suppresses the over-reduction.¹⁵ The reaction product, phenol **23**, is produced upon quenching **26** with aq NH₄-Cl.

Finally, we examined Birch reduction of various fused diazines (Scheme 9). During our investigation toward (±)-tetraoponerine T6 and its analogues, exhaustive reduction of bispyrrolopyrimidine **27** was accomplished in a two-step sequence.³ First, catalytic hydrogenation of **27** over PtO₂ in acidic media was *cis*-diastereoselective and stopped at the formation of a stable amidinium salt, which, in turn, was further reduced by lithium aluminum hydride.³ In contrast, Birch reduction of **27** selectively reduced its middle ring to give **28** quantitatively. Furthermore, the reduction of 4,5-disubstituted bispyrrolopyrimidines **29** and **31** selectively produced *trans*-4,5-disubstituted dihydrobispyrrolopyrimidines¹⁸ as sole diastereomers in excellent yields. Likewise, the middle ring of bispyrrolopyrazine **33** was selectively reduced to give **34** in a good yield under similar conditions (Scheme 9).

Conclusions

In summary, we developed a mild and general method for selective partial reduction of various heteroaromatic compounds with bridgehead nitrogen, which included electron-deficient indolizines, neutral- and electron-rich pyrroloisoquinolines, pyrroloquinolines, bispyrrolopyrimidines, and bispyrrolopyrazines. It is believed that this method can serve as a new and effective tool for quick and easy access toward various partially reduced fused heterocyclic compounds.

Experimental Sections

Compounds **1**, **4**, **27**, **29**, and **31** are known and were prepared according to the published procedures.^{3b,19} Compounds **2**, **3**, **6**, **10**, **12**, **15**, **17**, **19**, **21**, **24**, and **33** were synthesized from alkynyl heterocycles, employing the Cu-assisted cycloisomerization method.^{2,3,19b} See the Supporting Information for details.

Representative Procedure for Birch Reduction (**11**)

Ammonia (25 mL) was condensed with Na (110 mg, 4.78 mmol) in a three-neck flask equipped with a rubber septum and a drying tube (anhydrous Ca(OH)₂) at –78 °C. A solution of 1-propylpyrrolo[1,2-*a*]quinoline **10** (200 mg, 0.96 mmol) in THF (4 mL) was added to the blue mixture, which was then stirred at –78 °C for 30 min. Aqueous NH₄Cl (5 mL) was added to the mixture and the solution was allowed to warm to room temperature. The reaction mixture was thoroughly extracted with hexanes. The combined extracts were washed (brine), dried (anhydrous Na₂SO₄), and concentrated under reduced pressure. The residue was purified by silica gel chromatography with 5% EtOAc/hexanes to give 1-propyl-4,5-dihydropyrrolo[1,2-*a*]quinoline **11** as an oil (203 mg, >99%).

Representative Procedure for Reductive Alkylation (**8**)

Ammonia (20 mL) was condensed with Na (53 mg, 2.30 mmol) in a three-neck flask equipped with a rubber septum and a drying tube (anhydrous Ca(OH)₂) at –78 °C. A solution of 3-propylindolizine-6-carboxylic acid *tert*-butyl ester **6** (120 mg, 0.46 mmol) and bis(2-methoxyethyl)amine (0.5 mL, 3.42 mmol) in THF (4 mL) was added to the blue mixture and the solution was stirred at –78 °C for 30 min. MeI (0.3 mL, 4.65 mmol) was added to the mixture. After an additional 1 h, aqueous NH₄Cl (5 mL) was added to the mixture and the solution was allowed to warm to room temperature. The reaction mixture was thoroughly extracted with hexanes. The combined extracts were washed (brine), dried (anhydrous Na₂SO₄), and concentrated under reduced pressure. The residue was purified by silica gel chromatography with 2% EtOAc/hexanes to give 6-methyl-3-propyl-5,6-dihydroindolizine-6-carboxylic acid *tert*-butyl ester **8** as an oil (118 mg, 93%).

5: ¹H NMR (500 MHz, C₆D₆) δ 6.36 (2H, m), 6.23 (1H, t, *J* = 3.1 Hz), 6.15 (1H, d, *J* = 2.6 Hz), 5.72 (1H, dd, *J* = 9.9, 4.0 Hz), 3.88 (1H, dd, *J* = 12.5, 9.2 Hz), 3.84–3.77 (2H, m), 3.59 (1H, dd, *J* = 12.3, 6.4 Hz), 3.07–3.03 (1H, m), 0.84 (3H, t, *J* = 7.2 Hz). ¹³C NMR (125 MHz, C₆D₆) δ 170.9, 128.5, 121.8, 121.3, 116.5, 108.9, 107.6, 60.8, 45.1, 41.0, 14.0. MS *m/z* (rel intensity) 191 (M⁺, 31), 161 (7), 118 (100), 89 (9). HRMS (EI) calcd for C₁₁H₁₃NO₂ (M⁺) 191.0946, found 191.0944.

7: ¹H NMR (500 MHz, C₆D₆) δ 6.43 (1H, dd, *J* = 9.9, 2.2 Hz), 6.15 (1H, d, *J* = 3.3 Hz), 6.00 (1H, d, *J* = 3.7 Hz), 5.70 (1H, dd, *J* = 9.7, 4.2 Hz), 3.91–3.87 (1H, m), 3.66 (1H, dd, *J* = 12.5, 6.2 Hz), 3.16–3.12 (1H, m), 2.32 (2H, t, *J* = 7.7 Hz), 1.54–1.49 (2H, m), 1.29 (9H, s), 0.85 (3H, t, *J* = 7.3 Hz). ¹³C NMR (125 MHz, C₆D₆) δ 170.7, 134.4, 128.5, 121.6, 115.1, 107.1, 106.9, 80.7, 42.1, 41.9, 28.3, 27.9 (×3), 22.5, 14.0. MS *m/z* (rel intensity) 261 (M⁺, 29), 205

(17), 160 (100), 130 (56). HRMS (EI) calcd for $C_{16}H_{23}NO_2$ (M^+) 261.1729, found 261.1745.

8: 1H NMR (500 MHz, C_6D_6) δ 6.38 (1H, d, J = 9.5 Hz), 6.15 (1H, d, J = 3.7 Hz), 6.00 (1H, d, J = 3.3 Hz), 5.64 (1H, d, J = 9.5 Hz), 4.12 (1H, d, J = 12.5 Hz), 3.43 (1H, d, J = 12.1 Hz), 2.42–2.38 (2H, m), 1.63–1.58 (2H, m), 1.26 (9H, s), 1.22 (3H, s), 0.85 (3H, t, J = 7.3 Hz). ^{13}C NMR (125 MHz, C_6D_6) δ 173.7, 138.4, 128.5, 122.0, 120.3, 107.0, 106.8, 80.4, 48.8, 45.0, 28.3, 27.8 ($\times 3$), 23.3, 22.8, 14.0. MS m/z (rel intensity) 275 (M^+ , 11), 174 (100), 144 (60), 130 (30). HRMS (EI) calcd for $C_{17}H_{25}NO_2$ (M^+) 275.1885, found 275.1869.

9: 1H NMR (400 MHz, C_6D_6) δ 6.42 (1H, d, J = 9.9 Hz), 6.16 (1H, d, J = 3.5 Hz), 6.02 (1H, d, J = 3.5 Hz), 5.73 (1H, d, J = 9.4 Hz), 4.14 (1H, d, J = 12.9 Hz), 3.64 (1H, d, J = 12.3 Hz), 2.44 (2H, t, J = 7.7 Hz), 1.79–1.72 (1H, m), 1.67–1.54 (3H, m), 1.36–1.23 (2H, m), 1.29 (9H, s), 1.18–1.09 (2H, m), 0.88 (3H, t, J = 7.3 Hz), 0.79 (3H, t, J = 7.3 Hz). ^{13}C NMR (100 MHz, C_6D_6) δ 173.1, 134.3, 128.5, 121.6, 120.3, 107.0, 106.8, 80.5, 48.9, 47.0, 37.0, 28.4, 27.9 ($\times 3$), 27.1, 23.3, 22.6, 14.1, 14.0. MS m/z (rel intensity) 317 (M^+ , 21), 261 (100), 186 (48), 130 (58). HRMS (EI) calcd for $C_{20}H_{31}NO_2$ (M^+) 317.2355, found 317.2367.

11: 1H NMR (400 MHz, C_6D_6) δ 7.36 (1H, d, J = 3.6 Hz), 7.04 (1H, dt, J = 7.6, 1.6 Hz), 6.97 (1H, d, J = 6.5 Hz), 6.88 (1H, dt, J = 7.6, 1.0 Hz), 6.15 (1H, d, J = 2.9 Hz), 6.05 (1H, d, J = 3.5 Hz), 2.77 (2H, t, J = 7.5 Hz), 2.59–2.56 (2H, m), 2.49–2.45 (2H, m), 1.69–1.60 (2H, m), 0.87 (3H, t, J = 7.3 Hz). ^{13}C NMR (100 MHz, C_6D_6) δ 138.0, 131.2, 131.1, 130.5, 129.1, 127.2, 123.7, 118.6, 108.7, 104.6, 31.8, 29.0, 23.9, 22.6, 14.2. MS m/z (rel intensity) 221 (M^+ , 48), 182 (100), 167 (50), 154 (11). HRMS (EI) calcd for $C_{15}H_{17}N$ (M^+) 211.1361, found 211.1345.

13: Mp 57 °C. 1H NMR (400 MHz, C_6D_6) δ 8.15 (1H, d, J = 8.8 Hz), 7.45 (1H, dd, J = 7.7, 1.5 Hz), 7.25 (1H, dt, J = 7.1, 1.7 Hz), 7.19 (1H, d, J = 9.2 Hz), 7.14 (1H, dt, J = 7.7, 1.0 Hz), 6.73 (1H, d, J = 8.8 Hz), 6.66–6.62 (2H, m), 3.06 (2H, t, J = 7.6 Hz), 1.76–1.72 (2H, m), 1.34–1.30 (4H, m), 0.93 (3H, t, J = 7.1 Hz). ^{13}C NMR (100 MHz, C_6D_6) δ 136.2, 132.6, 131.6, 128.6, 126.5, 126.2, 123.1, 120.0, 117.9, 116.7, 113.1, 102.8, 31.9, 31.8, 28.6, 22.9, 14.3. MS m/z (rel intensity) 237 (M^+ , 22), 191 (9), 180 (100). HRMS (EI) calcd for $C_{17}H_{19}N$ (M^+) 237.1517, found 237.1529.

14: 1H NMR (400 MHz, C_6D_6) δ 7.36 (1H, d, J = 3.6 Hz), 7.04 (1H, dt, J = 7.6, 1.6 Hz), 6.97 (1H, d, J = 6.5 Hz), 6.88 (1H, dt, J = 7.5, 0.9 Hz), 6.15 (1H, d, J = 3.5 Hz), 6.06 (1H, d, J = 3.5 Hz), 5.74–5.61 (1H, m), 5.00–4.93 (2H, m), 2.80 (2H, t, J = 7.6 Hz), 2.60–2.55 (2H, m), 2.48–2.45 (2H, m), 1.98 (2H, q, J = 7.0 Hz), 1.75–1.67 (2H, m). ^{13}C NMR (100 MHz, C_6D_6) δ 138.6, 138.0, 131.1, 131.0, 130.6, 129.1, 127.2, 123.8, 118.6, 115.0, 108.8, 104.6, 33.8, 29.0, 28.9, 28.6, 23.9. MS m/z (rel intensity) 237 (M^+ , 21), 182 (100), 167 (34). HRMS (EI) calcd for $C_{17}H_{19}N$ (M^+) 237.1517, found 237.1521.

16: Mp 119 °C. 1H NMR (500 MHz, C_6D_6) δ 7.60 (1H, d, J = 8.8 Hz), 6.66 (1H, d, J = 3.7 Hz), 6.60 (1H, dd, J = 8.6, 2.8 Hz), 6.47 (1H, d, J = 2.6 Hz), 6.20 (1H, d, J = 3.3 Hz), 3.42 (2H, t, J = 6.4 Hz), 2.61 (2H, t, J = 6.6 Hz), 2.59 (6H, s), 2.38 (2H, t, J = 7.5 Hz), 1.60–1.52 (2H, m), 0.94 (3H, t, J = 7.4 Hz). ^{13}C NMR (125 MHz, C_6D_6) δ 148.9, 131.7, 131.3, 130.1, 123.6, 120.8, 112.5, 112.3, 106.9, 101.4, 40.7, 40.5 ($\times 2$), 30.4, 28.8, 22.8, 14.1. MS m/z (rel intensity) 254 (M^+ , 38), 225 (100), 209 (21), 112 (27). HRMS (EI) calcd for $C_{17}H_{22}N_2$ (M^+) 254.1783, found 254.1778.

18: Mp 71 °C. 1H NMR (500 MHz, C_6D_6) δ 7.31 (1H, d, J = 7.7 Hz), 7.11 (1H, t, J = 7.9 Hz), 6.72 (1H, d, J = 3.7 Hz), 6.40 (1H, d, J = 8.4 Hz), 6.14 (1H, d, J = 3.3 Hz), 3.38 (3H, s), 3.37 (2H, t, J = 6.7 Hz), 2.92 (2H, t, J = 6.8 Hz), 2.27 (2H, t, J = 7.6 Hz), 1.52–1.45 (2H, m), 0.88 (3H, t, J = 7.3 Hz). ^{13}C NMR (125 MHz, C_6D_6) δ 156.9, 133.4, 132.0, 129.2, 128.3,

118.2, 115.3, 107.3, 107.0, 104.4, 54.9, 40.1, 28.5, 22.6, 22.4, 14.1. MS m/z (rel intensity) 241 (M^+ , 30), 212 (100), 196 (36), 167 (8). HRMS (EI) calcd for $C_{16}H_{19}NO$ (M^+) 241.1467, found 241.1466.

23: Mp 82 °C. 1H NMR (500 MHz, C_6D_6) δ 6.86 (1H, d, J = 2.6 Hz), 6.81 (1H, d, J = 8.1 Hz), 6.63 (1H, d, J = 3.7 Hz), 6.52 (1H, dd, J = 8.1, 2.6 Hz), 6.14 (1H, d, J = 3.3 Hz), 4.42 (1H, bs), 3.28 (2H, t, J = 6.5 Hz), 2.45 (2H, t, J = 6.6 Hz), 2.28 (2H, t, J = 7.5 Hz), 1.53–1.46 (2H, m), 0.89 (3H, t, J = 7.3 Hz). ^{13}C NMR (125 MHz, C_6D_6) δ 156.6, 133.4, 131.8, 129.3, 129.1, 122.3, 112.5, 108.9, 107.2, 104.0, 40.8, 28.7, 28.5, 22.6, 14.0. MS m/z (rel intensity) 227 (M^+ , 52), 202 (27), 198 (100), 98 (10). HRMS (EI) calcd for $C_{15}H_{17}NO$ (M^+) 227.1310, found 227.1320.

28: 1H NMR (500 MHz, C_6D_6) δ 6.18 (1H, d, J = 3.4 Hz), 6.17 (1H, dd, J = 3.4, 0.9 Hz), 6.06 (1H, d, J = 3.7 Hz), 6.02 (1H, d, J = 3.7 Hz), 3.80 (1H, m), 2.80–2.76 (3H, m), 2.67 (1H, dd, J = 15.0, 1.7 Hz), 2.40 (2H, t, J = 7.9 Hz), 1.74–1.60 (4H, m), 1.36–1.24 (2H, m), 1.11–1.02 (4H, m), 0.97 (3H, t, J = 7.3 Hz), 0.92 (3H, t, J = 7.3 Hz), 0.95–0.89 (2H, m), 0.75 (3H, t, J = 7.3 Hz). ^{13}C NMR (125 MHz, C_6D_6) δ 131.0, 127.6, 126.9, 123.0, 106.6, 105.7, 104.4, 93.2, 50.9, 34.2, 31.7, 30.4, 30.2, 28.6, 27.9, 26.1, 22.8, 22.4, 22.1, 14.2, 14.1. MS m/z (rel intensity) 312 (M^+ , 50), 283 (100), 241 (8). HRMS (EI) calcd for $C_{21}H_{32}N_2$ (M^+) 312.2566, found 312.2563.

30: 1H NMR (500 MHz, C_6D_6) δ 7.25–7.14 (5H, m), 6.22 (1H, d, J = 3.3 Hz), 6.16 (1H, d, J = 3.3 Hz), 6.10 (1H, d, J = 3.7 Hz), 6.07 (1H, d, J = 3.7 Hz), 3.86–3.81 (1H, m), 3.29–3.17 (2H, m), 3.13–3.02 (3H, m), 2.42 (2H, m), 1.70 (2H, sext, J = 7.4 Hz), 1.12 (3H, d, J = 7.0 Hz), 1.04 (3H, t, J = 7.3 Hz), 0.83 (3H, d, J = 6.6 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.7, 130.5, 128.7, 128.4 ($\times 2$), 128.3 ($\times 2$), 126.8, 126.7, 125.9, 105.7, 103.4, 103.3, 92.2, 51.0, 34.6, 33.2, 29.7, 28.2, 21.8, 14.8, 14.1, 13.9. MS m/z (rel intensity) 332 (M^+ , 33), 303 (14), 241 (100), 91 (79). HRMS (EI) calcd for $C_{23}H_{28}N_2$ (M^+) 332.2253, found 332.2245.

32: Mp 98 °C. 1H NMR (500 MHz, C_6D_6) δ 7.15–7.04 (5H, m), 6.56 (1H, d, J = 3.7 Hz), 6.09 (1H, d, J = 3.7 Hz), 5.91 (1H, dd, J = 3.7, 1.5 Hz), 5.31 (1H, d, J = 3.7 Hz), 3.54–3.49 (1H, m), 3.42 (3H, s), 2.91–2.80 (3H, m), 2.72–2.59 (2H, m), 0.97 (3H, d, J = 7.0 Hz), 0.67 (3H, d, J = 6.6 Hz). ^{13}C NMR (125 MHz, C_6D_6) δ 146.5, 142.1, 128.8 ($\times 2$), 128.7 ($\times 2$), 126.3, 125.8, 125.6, 120.4, 105.0, 101.7, 93.4, 83.6, 57.3, 51.5, 36.0, 32.9, 28.6, 14.8, 13.4. MS m/z (rel intensity) 320 (M^+ , 24), 229 (100), 199 (50), 91 (88). HRMS (EI) calcd for $C_{21}H_{24}N_2O$ (M^+) 320.1889, found 320.1883.

34: Mp 150 °C. 1H NMR (400 MHz, C_6D_6) δ 6.49 (2H, d, J = 3.5 Hz), 6.10 (2H, d, J = 3.5 Hz), 3.15 (4H, s), 2.30 (4H, t, J = 7.3 Hz), 1.56–1.46 (4H, m), 0.93 (6H, t, J = 7.3 Hz). ^{13}C NMR (100 MHz, C_6D_6) δ 130.1 ($\times 2$), 125.6 ($\times 2$), 107.1 ($\times 2$), 101.1 ($\times 2$), 40.9 ($\times 2$), 28.5 ($\times 2$), 22.8 ($\times 2$), 14.0 ($\times 2$). MS m/z (rel intensity) 242 (M^+ , 31), 213 (100), 184 (37), 92 (8). HRMS (EI) calcd for $C_{16}H_{22}N_2$ (M^+) 242.1783, found 242.1790.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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10. 73% yield of **5** was due to the highly acid-sensitive nature of **5**
11. For the installation of a quaternary carbon center in the Birch reduction, see for examples: Schultz AG, Sundararaman P. *Tetrahedron Lett.* 1984; 25:4591. Donohoe TJ, Guyo PM. *J Org Chem.* 1996; 61:7664. [PubMed: 11667718]
12. This additive has been recently introduced by Donohoe, who showed that this secondary amine could serve not only as a mild proton source in Birch reductions, but also after the deprotonation, as an efficient chelating agent for Na⁺ thereby enhancing the nucleophilicity of the enolate; see for an example: Donohoe TJ, Guyo PM, Harji RR, Helliwell M. *Tetrahedron Lett.* 1998; 39:3075.
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15. Introduction of alkoxide had dramatically increased the energy of LUMO (3.55 eV in **22** vs -0.17 eV and -0.48 eV for **17** and **19**, respectively), which resulted in significantly slower reduction (6 h for **22** vs 10–20 min for **17** and **19**).
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18. The relative configuration of **32** was confirmed by a NOESY experiment. NOE was observed between the hydrogen at C-4 and the methyl group at C-5 (so it was between the methyl group at the C-4 position and the hydrogen at the C-5 position).
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Figure 1.
Selected examples of biologically important partially reduced pyrrolo-heterocycles.

Figure 2.
LUMO density distribution in 3-methyl analogues of **17** and **19**.

Scheme 1. Partial Birch Reduction of Indolizines^a

^a Reagents and conditions: (i) Na, NH₃, -78 °C, then aq NH₄Cl.

Scheme 2. Reductive Alkylation of Indolizine 6

Scheme 3. Partial Reduction of Pyrroloquinolines

Scheme 4. Partial Reduction of Electron-Rich Pyrroloisoquinoline 15^a

^a Reagents and conditions: (i) Pd/C(20%), H₂ (10 Mpa), 12 h, (ii) Na, NH₃, -78 °C, 10 min, then aq NH₄Cl.

Scheme 5. Partial Reduction of Alkoxy-Substituted Pyrroloisoquinolines^a

^a Reagents and conditions: (i) Na, NH₃, -78 °C, then aq NH₃Cl.

Scheme 6. Partial Reduction of Sodium Salt 22

Scheme 7. Partial Reduction of Silyl-Protected Alcohol 24

Scheme 8. Proposed Mechanism for Partial Reduction of 24

Scheme 9. Partial Reduction of Fused Diazines^a

^a Reagents and conditions: (i) Na, NH₃, -78 °C, then aq NH₃Cl.