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Thermodynamic equilibration of dihydropyridone enolates: application to the total synthesis of (+/–)-epiuleine

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Dedicated to Professor Dale Boger on the occasion of his 50th birthday.

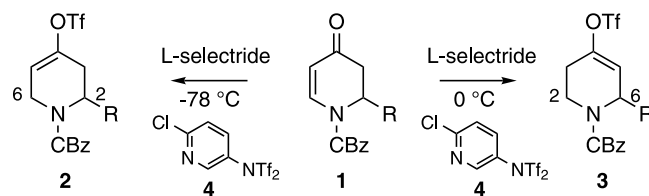
Abstract—Following 1,4-reduction of 2-substituted dihydropyridones (**1**), the requisite ‘kinetic’ enolate can be isomerized upon warming to allow the isolation of the thermodynamic enolate as its vinyl triflate (**3**). This enolate interconversion is dependent on the dihydropyridone C-2 substituent and can be interpreted in terms of conformational analysis. This novel scaffold (**3**) opens another avenue for the strategic deployment of dihydropyridones into both natural product synthesis and drug discovery. To this end, this method is highlighted by its use as a key step in a total synthesis of (+/–) epiuleine (**14**).

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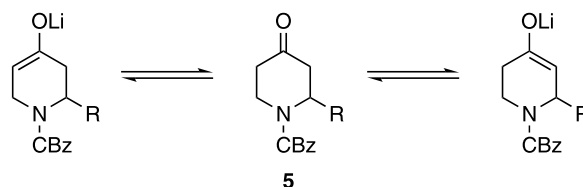
Dihydropyridones such as **1** are versatile synthetic building blocks that have found considerable use in both natural product synthesis and medicinal chemistry.^{1–5} These dihydropyridones are easily prepared via the addition of Grignard reagents or metallo-enolates to 1-acylpyridinium salts⁶ or by the hetero Diels Alder cyclocondensation of imines with siloxydienes,⁷ and have been extensively employed in the synthesis of substituted piperidines and tetrahydropiperidines.² We were interested in the 2,4-disubstituted-1,2,3,6-tetrahydropyridines which have been synthesized directly from 2-substituted dihydropyridones such as **1** (Scheme 1) by 1,4 reduction and in situ trap of the resulting enolate as its vinyl triflate (**2**).⁸ Vinyl triflate **2** is an excellent substrate for coupling reactions to generate diversity at C-4. The alternative olefin isomer, 4,6-disubstituted-1,2,3,6-tetrahydropyridine **3**, is also a desirable scaffold, but direct access to **3** from **1** had not been described. This report concerns a route to these isomeric 4,6-disubstituted tetrahydropyridines (**3**) via the thermodynamic equilibration of the enolate produced by 1,4-reduction of dihydropyridone **1**, and an application of this method to the total synthesis of (+/–)-epiuleine.

It was found that L-Selectride® (0.98 equiv.) mediated 1,4-reduction⁹ of **1** at –78°C followed by warming to

0°C allowed for enolate interconversion. The thermodynamic enolate thus produced could be efficiently trapped in situ with *N*-(5-chloro-2-pyridyl)triflimide (**4**) yielding isomeric vinyl triflate **3** in good yield with selectivity varying with the R group. Mechanistically, this interconversion requires small amounts of saturated ketone **5** to be produced as a proton shuttle between enolates (Scheme 2). We suggest that unreacted dihydropyridone **1** serves as the proton source (from C-3) to quench the enolate leading to **2**, thus producing a limited amount of ketone **5**. Supporting



Scheme 1.



Scheme 2.

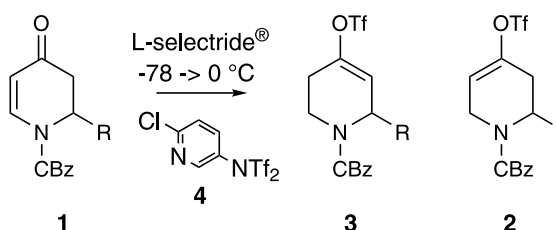
Keywords: dihydropyridone; tetrahydropyridine; enolate; epiuleine.

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this hypothesis, when the reaction is conducted with excess L-Selectride® (1.5 equiv.), ensuring complete consumption of the starting dihydropyridone **1**, this equilibration does not occur under the same conditions. Furthermore, direct enolization of the saturated ketone **5** (R=Ph, LHMDs, 0.98 equiv., –78°C), followed by equilibration (0°C) revealed the identical ratio for vinyl triflates **3b:2b** as was obtained for **1b** (Table 1).

To investigate the scope of this transformation, a brief study was undertaken to correlate the vinyl-triflate ratios with the R group at C-2, and to reveal the underlying source of selectivity (Table 1). Dihydropyridones (**1**) were synthesized in one step from 4-methoxypyridine, benzyl chloroformate and the appropriate Grignard according to literature procedures.⁶

Table 1.

			
Entry	R	3:2	Yield* (%)
1a	<i>t</i> -Butyl	20:1	60
1b	Phenyl	10:1	83
1c	<i>N</i> -Boc-indolyl	9:1	73
1d	Isopropyl	4:1	73
1e	<i>n</i> -Propyl	5:4	72

* Isolated yields.

It was observed that the selectivity increased with the size of the R group, with large R groups (**1a–c**) resulting in >9:1 selectivity, whereas small R groups (**1d**, **1e**) demonstrated reduced ratios.¹⁰ The observed trend is consistent with the A-values for these groups.

The origin of this thermodynamic enolate equilibration is likely found in relief of strain accompanying the ability of the R group to adopt a pseudo-axial orientation in a half-chair conformation to avoid interaction with the carbamate (see Fig. 1). A^(1,3) strain in *N*-acyl piperidines has been demonstrated to make 2-equatorially substituted amines less stable than the 2-axial isomers.^{11a} This same argument has also been invoked for the conformation of dihydropyridones,^{11b} and, for these two cases, may be even more pronounced as the axially disposed R group suffers only a single 1,3-diaxial interaction in the half-chair. Inspection of the competing half-chair conformations (Fig. 1) indicates that the thermodynamic enolate **A** enables the R group to occupy a pseudo-axial orientation to alleviate the interaction with the planar *N*-acyl group, although it must acquire a modest A^(1,2) strain from the adjacent olefin. In the kinetic half-chair **B**, a large R group will require a true axial orientation to avoid A^(1,3) strain. It appears

that the energy cost of pseudoaxial placement of large R groups in conformation **A** is significantly less than axial placement in conformation **B**. With diminishing size of R, the difference in relative energies can be expected to diminish as was observed. Molecular modeling was employed (Spartan)¹² and Monte Carlo conformational analysis (AM1) corroborated the enolic structures below as being global minimums. Relative energies for the competing half-chairs were estimated (MMFF) and these calculations revealed that the ΔG values increased with the size of R, and reflected the experimental order of selectivity for **1a–e**.

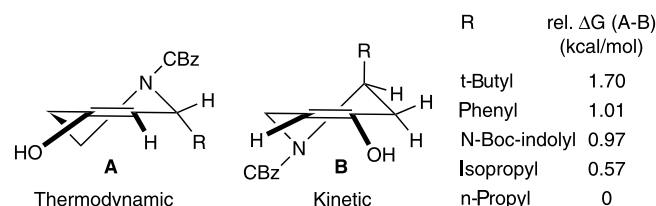
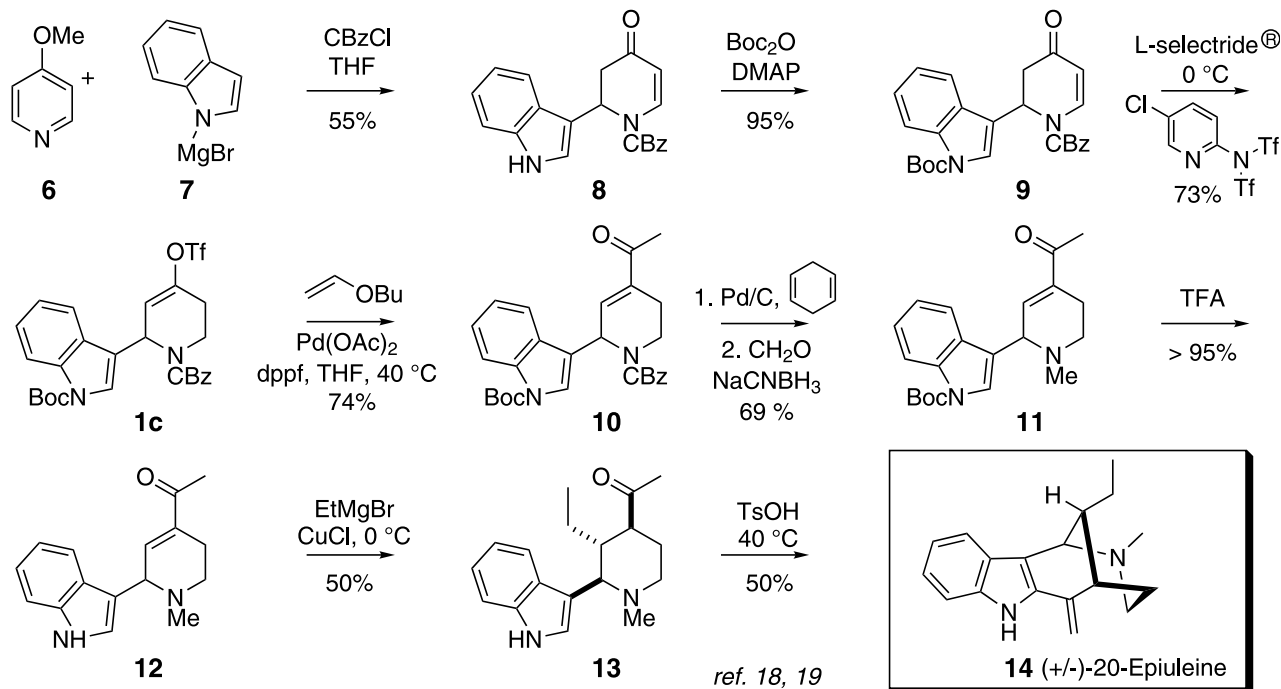


Figure 1.

To highlight the added advantage that results from this method, a concise total synthesis of (+/–)-epiuleine (**14**) was accomplished (Scheme 3). Epiulene (**14**) is a member of the *Strychnos* indole alkaloids, and was isolated from *Aspidosperma subincanum* in 1967.¹³ The total synthesis of epiuleine has been achieved in a number of laboratories with diverse synthetic routes and starting materials.^{14–21} We opted to initiate our efforts using the *N*-acylpyridinium salt route to dihydropyridones.

The addition of indole magnesium bromide (**7**)²² to 4-methoxypyridine (**6**) in the presence of benzylchloroformate gave 2-indolyl-dihydropyridone **8** in moderate yield.²³ Protection of the indole nitrogen to yield **9** was required prior to the key vinyl triflate formation. 1,4-Reduction was effected by L-Selectride® at –78°C accompanied by thermodynamic equilibration at 0°C and in situ trap as the vinyl triflate (**1c**). The ratio of vinyl triflates reproduced on scale at 9:1 favoring the thermodynamic product. Vinyl triflate **1c** was subjected to a Heck vinylation with *n*-butyl vinyl ether and was hydrolyzed in situ to produce the C-4 methyl ketone (**10**) that crystallized from the reaction mixture and thereby separated from the isomer arising from the minor vinyl triflate. This Heck coupling initially required some improvement, and the combination of THF, Pd(OAc)₂ and mild temperature proved to be optimal. The CBz group was removed by transfer hydrogenation, and the crude free amine was directly subjected to reductive amination with formaldehyde to provide **11**. Efforts to reduce this exchange to a single step by conducting the transfer hydrogenation in the presence of aq. formaldehyde were unsuccessful. Deprotection of the indole **11** yielded *N*-methylamine **12**²⁴ (>95%) that intersects with the total synthesis achieved by Husson and co-workers¹⁹ as well as the formal asymmetric route to epiulene as described by Tanaka and Katsumura.²¹ To complete this concise total synthesis, the established protocol was followed,^{18,19} and gave, in similar yields to those reported, (+/–)-epiuleine (**14**)²⁵ in 9 linear steps.



Scheme 3.

In conclusion, conditions were found that produce 4,6-disubstituted 1,2,3,6-tetrahydropyridines (**3**) from 2-substituted dihydropyridones (**1**). It was observed that the enolate resulting from 1,4-reduction of the 2-substituted dihydropyridones (**1**) could be thermodynamically equilibrated and that depending on the size of the R group at C-2, useful levels of selectivity in vinyl triflate production could be obtained. Such vinyl triflates can undergo a variety of transformations to effect diversity at C-4 producing molecules with properties that are not only of interest to medicinal chemists,¹ but also useful synthetic intermediates in natural product synthesis as was demonstrated for (+/-)-epiuleine.

Representative experimental procedure: To a flame dried flask equipped with stir bar was added benzyl 2-*tert*-butyl-4-oxo-3,4-dihydropyridine-1(2*H*)-carboxylate (**1a**, 0.25 g, 0.88 mmol) and anhydrous THF (5.0 mL). The resulting solution was cooled to -78°C under N_2 , and treated with L-Selectride® (1.0 M soln. in THF, 0.86 mL, 0.86 mmol) and then placed in a 0°C bath for 3 h. The yellow-tinted reaction was then cooled to -78°C , treated with *N*-(5-chloro-2-pyridyl)triflimide (**4**, 0.37 g, 0.95 mmol) and warmed to 25°C over 2 h. The reaction mixture was concentrated and subjected to flash chromatography (SiO_2 , 40 g RediSep® Column, 0–20% EtOAc/hexanes gradient) provided benzyl 6-*tert*-butyl-4-[[[(trifluoromethyl)sulfonyl]-oxy]-3,6-dihydropyridine-1(2*H*)-carboxylate (**3a**, 0.23 g, 60%). For **3a**: ^1H NMR (300 MHz, CDCl_3) δ rotamers 7.35 (m, 5H), 5.90 and 5.86 (s, 1H), 5.16 (m, 2H), 4.62 and 4.47 (s, 1H), 4.49 and 4.34 (dd, $J=13.7, 5.9$ Hz, 1H), 3.20 (m, 1H), 2.52 (br m, 1H), 2.22 and 2.16 (app s, 1H), 1.00 and 0.96 (s, 9H). FABHRMS m/z 422.1234 ($\text{M}+\text{H}^+$, $\text{C}_{18}\text{H}_{22}\text{F}_3\text{N}_1\text{O}_5\text{S}$ requires 422.1244).

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10. Ratios were determined from both the crude and purified ^1H NMR spectra. Isomeric vinyl triflates were inseparable using this purification, however they resolved easily following subsequent coupling reactions. The vinyl triflates can be stored neat under N_2 at 0°C for several days, but were found to partially decompose in CHCl_3 within hours at 25°C . Also, purification is not necessary for the subsequent coupling reaction.
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23. Freshly prepared indole Grignard **7** (3 M in THF, 178 mmol) was cooled to -78°C and treated dropwise with a solution of 4-methoxypyridine (**6**, 18.7 mL, 184 mmol) and warmed to -30°C over 30 min. Benzylchloroformate (62.1 mL, 50% in toluene, 184 mmol) was added dropwise and the reaction was kept at -20°C for 3 h. Aqueous HCl (1 M, 450 mL) was poured into the reaction and stirred for 30 min. The reaction was extracted with Et_2O (3×200 mL), washed with brine (500 mL) and dried over MgSO_4 . The reaction was filtered and concentrated under reduced pressure. The crude solid was recrystallized from EtOAc /hexanes to provide **8** as a white solid (34.8 g, 55%). For **8**: ^1H NMR (300 MHz, CDCl_3) δ 8.34 (s, 1H), 7.82 (d, $J=7.9$ Hz, 1H), 7.66 (d, $J=7.0$ Hz, 1H), 7.32 (m, 6H), 7.19 (dd, $J=8.1, 7.1$ Hz, 1H), 7.07 (dd, $J=7.9, 7.3$ Hz, 1H), 7.04 (d, $J=2.7$ Hz, 1H), 6.14 (d, $J=6.7$ Hz, 1H), 5.42 (d, $J=8.2$ Hz, 1H), 5.25 (s, 2H), 3.15 (dd, $J=16.5, 6.7$ Hz, 1H), 2.86 (d, $J=16.5$ Hz, 1H); FABHRMS m/z 347.1387 ($\text{M}+\text{H}^+$, $\text{C}_{21}\text{H}_{18}\text{N}_2\text{O}_3$ requires 347.13190). For **9**: ^1H NMR (300 MHz, CDCl_3) δ rotamers 8.10 and 8.08 (s, 1H), 7.94 (s, 1H), 7.55 (s, 1H), 7.40–7.20 (m, 8H), 6.06 and 6.04 (s, 1H), 5.44 (d, $J=8.3$ Hz, 1H), 5.24 (s, 2H), 3.15 (dd, $J=16.4, 7.1$ Hz, 1H), 2.84 (d, $J=16.4$ Hz, 1H), 1.65 (s, 9H); FABHRMS m/z 447.1888 ($\text{M}+\text{H}^+$, $\text{C}_{26}\text{H}_{26}\text{N}_2\text{O}_5$ requires 447.1915). See representative experimental above for **1c**: ^1H NMR (300 MHz, CDCl_3) δ rotamers 8.13 (d, $J=8.2$ Hz, 1H), 7.87 (br s, 1H), 7.36 (m, 7H), 7.05 (m, 1H), 6.27 (br s, 1H), 6.08 (br s, 1H), 5.22 (br m, 2H), 4.15 (br m, 1H), 3.11 (ddd, $J=14.0, 11.9, 4.3$ Hz, 1H), 2.76 (br m, 1H), 2.29 (dd, $J=17.1, 3.4$ Hz, 1H), 1.66 (s, 9H); FABHRMS m/z 603.1408 ($\text{M}+\text{Na}^+$, $\text{C}_{27}\text{H}_{27}\text{F}_3\text{N}_2\text{O}_7\text{S}$ requires 603.1386). In a flame dried flask equipped with a stir bar and activated molecular sieves (4 Å), vinyl triflate **1c** (2.94 g, 5.07 mmol) was dissolved in anhydrous THF (50 mL) under an N_2 atmosphere. *N*-Butylvinyl ether (6.56 mL, 50.6 mmol), dppf (0.28 g, 0.51 mmol) and $\text{Pd}(\text{OAc})_2$ (0.06 g, 0.25 mmol) were added successively and the reaction was de-oxygenated alternating between vacuum and nitrogen. Following the addition of Et_3N (1.06 mL, 7.6 mmol), the reaction was warmed to 40°C for 6 h under N_2 . Upon completion as judged by disappearance of **1c**, the reaction was concentrated under reduced pressure. The crude residue was dissolved in a 1:1 $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ solution containing 5% TFA and stirred for 2 h to effect complete conversion of the enol ether to the methyl ketone, and to cause precipitation. This mixture was filtered to provide **10** (1.78 g 74%) as a white solid. For **10**: ^1H NMR (300 MHz, CDCl_3) δ 8.08 (d, $J=8.5$ Hz, 1H), 7.93 (br s, 1H), 7.35 (m, 7H), 7.21 (br m, 1H), 7.00 (br s, 1H), 6.21 (br s, 1H), 5.23 (d, $J=12.3$ Hz, 1H), 5.16 (d, $J=12.3$ Hz, 1H), 4.15 (br m, 1H), 3.11 (ddd, $J=12.2, 12.2, 4.0$ Hz, 1H), 2.56 (d, $J=18.9$ Hz, 1H), 2.38 (s, 3H), 2.32 (m, 1H), 1.68 (s, 9H); FABHRMS m/z 475.2233 ($\text{M}+\text{H}^+$, $\text{C}_{28}\text{H}_{30}\text{N}_2\text{O}_5$ requires 475.2228). For **11**: ^1H NMR (300 MHz, CDCl_3) δ 8.14 (d, $J=7.6$ Hz, 1H), 7.64 (d, $J=7.9$ Hz, 1H), 7.55 (s, 1H), 7.33 (dd, $J=8.0, 7.1$ Hz, 1H), 7.23 (obs. by CDCl_3 dd, $J=7.5, 7.1$ Hz, 1H), 6.65 (s, 1H), 4.11 (br s, 1H), 3.09 (app dt, $J=10.9, 3.4$ Hz, 1H), 2.55 (m, 3H), 2.29 (s, 3H), 2.23 (s, 3H), 1.68 (s, 9H); FABHRMS m/z 355.1995 ($\text{M}+\text{H}^+$, $\text{C}_{21}\text{H}_{26}\text{N}_2\text{O}_3$ requires 355.2016).
24. ^1H NMR and FABHRMS spectra for **12** match those reported in Ref. 21.
25. ^1H NMR and FABHRMS spectra for **14** match those reported in Ref. 17.