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

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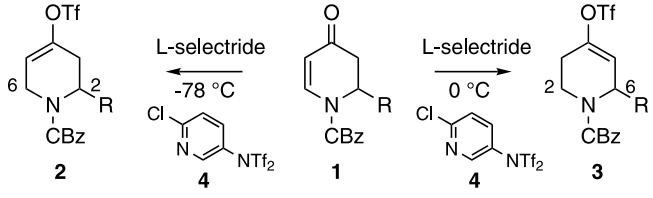
Dedicated to Professor Dale Boger on the occasion of his 50th birthday.

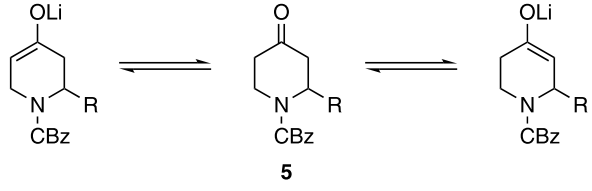
Abstract—Following 1,4-reduction of 2-substituted dihydropyridones (**1**), the requisite 'kinetic' enolate can be isomerized upon warming to allow the isolation of the thermodynamic enolate as its vinyl triflate (**3**). This enolate interconversion is dependent on the dihydropyridone C-2 substituent 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**).

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 salts[6] 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-reduction[9] 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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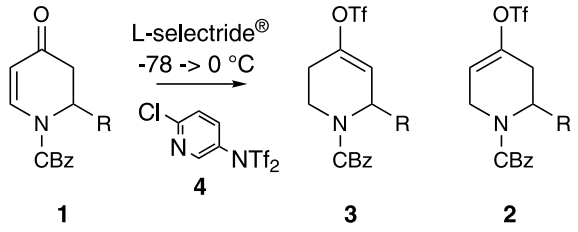
this hypothesis, when the reaction is conducted with excess L-Selectride® (1.5 equiv.), ensuring complete consumption of the starting dihydropyridone **1**, this equilibration does not occur under the same conditions. Furthermore, direct enolization of the saturated ketone **5** (R = Ph, LHMDS, 0.98 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	*t*-Butyl	20:1	60
1b	Phenyl	10:1	83
1c	*N*-Boc-indolyl	9:1	73
1d	Isopropyl	4:1	73
1e	*n*-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**.

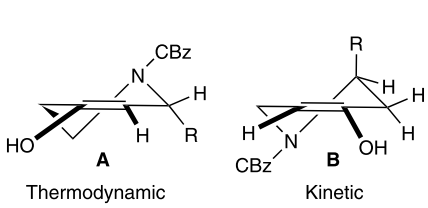
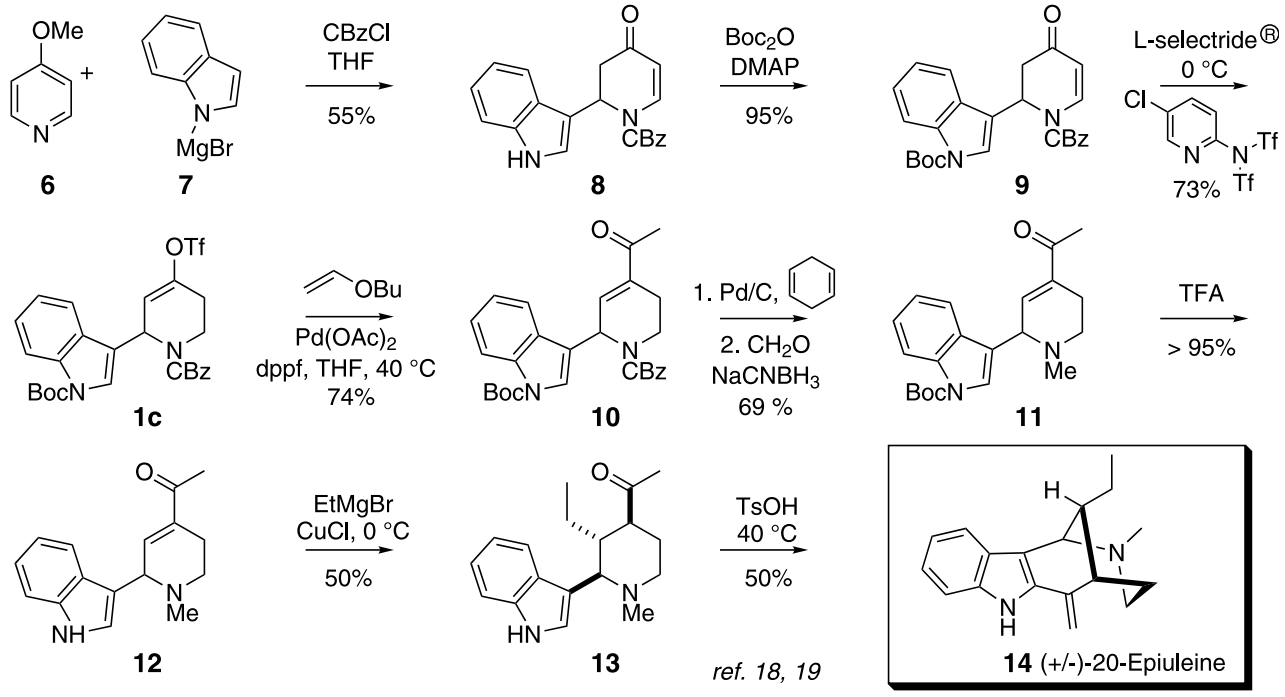


Figure 1.

To highlight the added advantage that results from this method, a concise total synthesis of (+/−)-epiuleine (**14**) was accomplished (Scheme 3). Epiuliene (**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-workers[19] as well as the formal asymmetric route to epiuliene 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**: ^{1}H 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 (M+H$^+$, $C_{18}H_{22}F_3N_1O_5S$ requires 422.1244).

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10. Ratios were determined from both the crude and purified ^{1}H 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**: ^{1}H 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 (M+H$^+$, $C_{21}H_{18}N_2O_3$ requires 437.3190).
For **9**: ^{1}H 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 (M+H$^+$, $C_{26}H_{26}N_2O_5$ requires 447.1915).
See representative experimental above for **1c**: ^{1}H 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 (M+Na$^+$, $C_{27}H_{27}F_3N_2O_7S$ 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 $Pd(OAc)_2$ (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 CH_3CN/H_2O 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**: ^{1}H 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 (M+H$^+$, $C_{28}H_{30}N_2O_5$ requires 475.2228).
For **11**: ^{1}H 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 (M+H$^+$, $C_{21}H_{26}N_2O_3$ requires 355.2016).
24. ^{1}H NMR and FABHRMS spectra for **12** match those reported in Ref. 21.
25. ^{1}H NMR and FABHRMS spectra for **14** match those reported in Ref. 17.