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TETRAHEDRON: *ASYMMETRY*

Synthesis of (−)-(1′*S*,4a*S*,8a*R*)- and (+)-(1′*S*,4a*R*,8a*S*)-4a-ethyl-1-(1′-phenylethyl)-octahydroquinolin-7-ones

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Abstract—A synthesis of the enamine (−)-(1′*S*)-5-ethyl-1-(1′-phenylethyl)-1,2,3,4-tetrahydropyridine **4** and its application in a synthesis of (−)-(1′*S*,4a*S*,8a*R*)- and (+)-(1′*S*,4a*R*,8a*S*)-4a-ethyl-1-(1′-phenylethyl)-octahydroquinolin-7-ones **5** and **6** is described. In addition, an X-ray study of **6** is reported. Finally, the preparation of (+)-(4a*S*,8a*R*)-4a-ethyl-octahydroquinolin-7-one **7** is described.

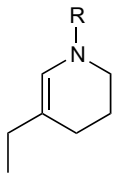
1. Introduction

The endocyclic enamine 5-ethyl-1,2,3,4-tetrahydropyridine[1–5] **I** and 3-(1-ethyl-4-oxo-cyclohex-2-enyl)-propionamide[6–10] **II** have both been used in the preparation of 4a-ethyl-octahydroquinolin-7-one **III**. Compound **III** is a versatile starting structure, which is commonly used in the synthesis of aspidosperma alkaloids.[1,6–8] Stevens et al.,[4] observed that treatment of non-chiral endocyclic enamines with methyl vinyl ketone affords racemic *cis*-fused cycles, but it is not known if this is due to kinetic or thermodynamic control.

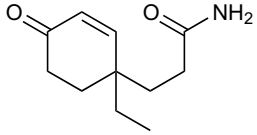
In a preliminary communication we reported[11] the preparation of (−)-(1′*R*)-1-(2′-hydroxy-1′-phenylethyl)-3,4-dihydro-1*H*-pyridin-2-one and its application in the synthesis of (*S*)-(+)-coniine. To explore other applications of 3,4-dihydro-1*H*-pyridin-2-ones in asymmetric synthesis, we prepared the (−)-(1′*S*)-5-ethyl-1-(1′-phenylethyl)-3,4-dihydro-1*H*-pyridin-2-one **3**, which was transformed into the corresponding enantiopure enamine **4** and then used for the synthesis of 4a-ethyl-1-(1′-phenylethyl)-octahydroquinolin-7-ones **5** and **6**.

The first step of this synthesis was the condensation[12] of (−)-(*S*)-1-phenylethylamine **1** with 4-formyl-hexanoic acid methyl ester **2** in dry toluene to give (−)-(1′*S*)-5-ethyl-1-(1′-phenylethyl)-3,4-dihydro-1*H*-pyridin-2-one **3** (90% yield, after purification on column Al_2O_3, *n*-hexane; *n*-hexane/CH_2Cl_2). Compound **3** was reduced with $LiAlH_4$/THF affording **4** (90% yield, after purification on column Al_2O_3, *n*-hexane) (Scheme 1). Assignments of the ^1H NMR of **3**[13] and **4**[14] were confirmed via ^{13}C–^1H correlation techniques.

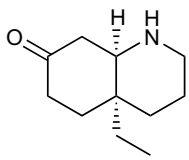
Condensation of enamine **4** with methyl vinyl ketone (MVK) in the presence of KOH/18-crown-6/methanol led to a mixture of compounds **5** and **6** in 85% overall yield.[15] The ^1H and ^{13}C NMR spectral data of the crude reaction showed only two diastereoisomers and only two compounds were observed by TLC analysis. The mixture was easily separated by chromatography



I



II



III

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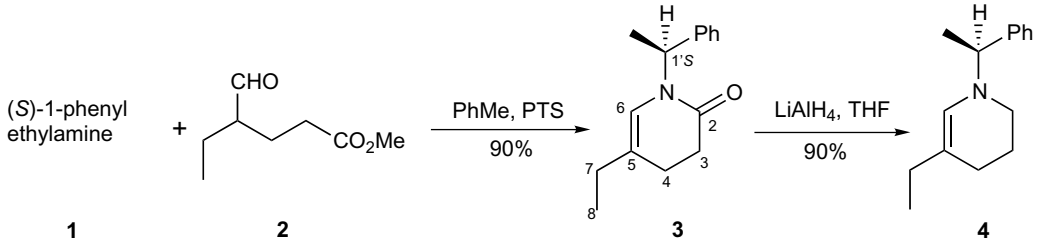


Scheme 1.

(Al_2O_3, 1% Et_3N, *n*-hexane) obtaining **5**[16] ($[\alpha]_D^{20}$ –98) and **6**[17] ($[\alpha]_D^{20}$ +5.0) in a 2:1 ratio (Scheme 2). The diastereomeric enhancement (33%) is particularly high compared to that from a similar study reported by Jankowski et al.[18]

Compound **5** becomes synthetically useful after removal of the 2-phenylethyl auxiliary. Catalytic hydrogenation of **5** with MeOH/HCl/Pd/C at pH ca. 5–6 led to **7** without complication. The crude material was purified by chromatography (SiO_2, 1% Et_3N, CH_2Cl_2/MeOH) giving **7** ($[\alpha]_D^{20}$ +27.6) in 90% yield. The specific rotation, ^1H and ^{13}C NMR spectral data for **7**[19] are comparable to those data reported for the same compound prepared by Meyers[9] (Scheme 3).

2. Results and discussion

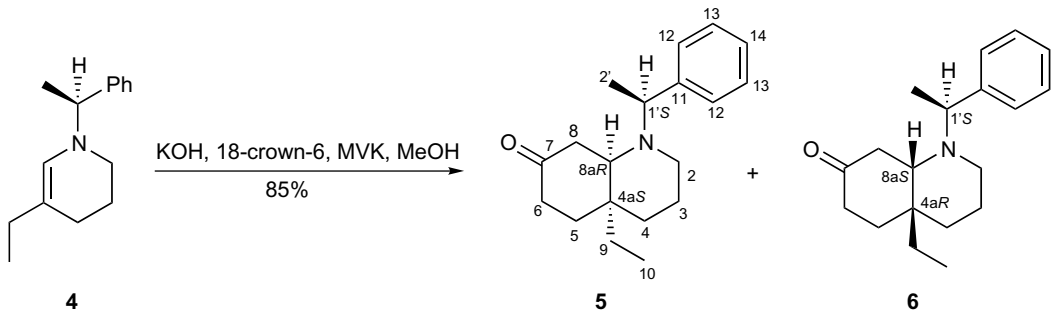
The ^1H NMR (400 MHz, $CDCl_3$) spectral data for **5** and **6** showed important differences. For example, the spectrum of **5** showed a doublet–doublet at 2.61 ppm for H-8a and a triplet at 0.72 ppm for CH_3 of the angular ethyl group, while for **6** these signals appeared at 3.15 and 0.89 ppm. Assignments in ^1H NMR for **5** and **6** were confirmed via ^{13}C–^1H correlation techniques.

To confirm the *cis*-fused ring for **5** and **6** we carried out ^1H NMR ($CDCl_3$) 1D NOE and ROESY experiments and only a strong enhancement between the CH_2 of the angular ethyl group and C(8a)H was observed for compound **5**.

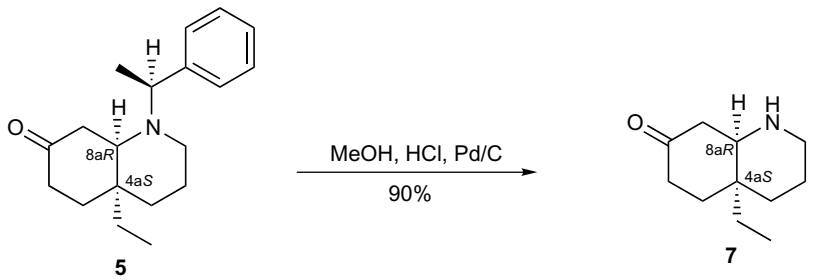
Fortunately, **6** can be crystallised from benzene/*n*-hexane and its X-ray diffraction analysis was performed and confirmed the *cis*-fused ring for **6**. The absolute configuration of the stereogenic centers C(4a) and C(8a) were determined as (*R*) and (*S*), respectively, based on the configuration of the auxiliary stereocenter, which is C(1′*S*) (source of chirality: (–)-(*S*)-1-phenylethylamine **1**) (Fig. 1). These results permitted us to assign the absolute configurations of the stereocenters of **5** as C(1′*S*), C(4a*S*) and C(8a*R*).

3. Conclusion

We have prepared the octahydroquinolin-7-ones **5** and **6** in good yields starting from the enantiopure endocy-



Scheme 2.



Scheme 3.

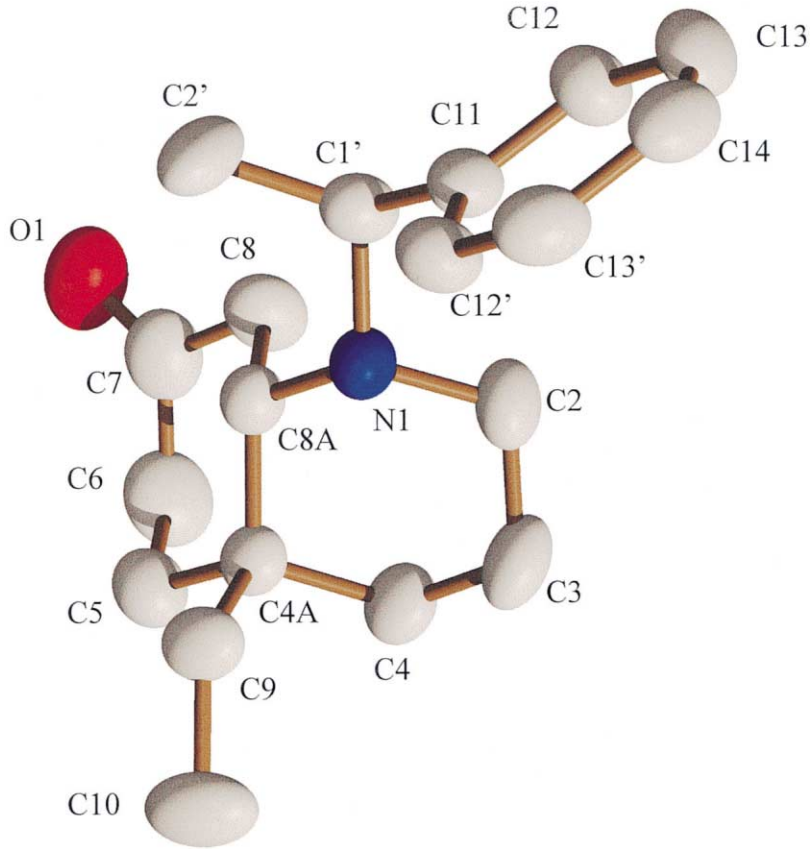


Figure 1. Crystal structure of **6**. The hydrogens are omitted for clarity.

cle enamine **4** and demonstrated by ^{1}H NMR, 1D NOE, and ROESY experiments on **5**, and by X-ray analysis of **6**, that both structures have *cis*-fused ring stereochemistries.

Acknowledgements

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13. **Compound 3**. R_f=0.46 (Al_2O_3/CH_2Cl_2); (90%) pale yellow liquid. IR (film, cm^{-1}): 3061, 2967, 1661; $[\alpha]_D^{20}$ −75 (*c* 1.0, CH_2Cl_2); ^{1}H NMR: δ (ppm, $CDCl_3$, *J* Hz): 0.91 (t, 3H-8, 7.32, 7.68); 1.51 (d, 3H-2′, 7.32); 1.96 (q, 2H-7, 7.32, 7.68); 2.17 (m, 2H-4, 7.68, 8.05, 8.42); 2.55 (t, 2H-3, 8.05); 5.60 (s, 1H-6); 6.02 (q, 1H-1′, 6.95); 7.20–7.40 (m, 5H, ϕ-H). ^{13}C NMR: δ (ppm, $CDCl_3$): 12.50 (C-8); 17.47 (C-2′); 23.83 (C-4); 27.12 (C-7); 31.72 (C-3); 49.35 (C-1′); 118.92 (C-6); 122.39 (C-5); 127.14 (2C-10); 127.31 (C-12); 128.54 (2C-11); 140.89 (C-9); 168.70 (C-2).
14. **Compound 4**. R_f=0.52 (Al_2O_3/*n*-hexane); (90%) colorless liquid. IR (film, cm^{-1}): 2960, 2929, 1452; $[\alpha]_D^{20}$ −23 (*c* 1.0, CH_2Cl_2); ^{1}H NMR: δ (ppm, $CDCl_3$, *J* Hz): 0.96 (t, 3H-8, 7.32, 7.68); 1.46 (d, 3H-2′, 6.95); 1.78 (m, 2H-3, 5.49, 5.86); 1.92 (m, 2H-4, 2H-7, 4.76, 6.56, 7.32); 2.72 (m, 2H-2, 4.39, 4.76, 5.86); 4.01 (q, 1H-1′, 6.95); 5.89 (s, 1H-6), 7.15–7.40 (m, 5H, ϕ-H). ^{13}C NMR: δ (ppm, $CDCl_3$): 13.36 (C-8); 18.05 (C-2′); 22.90 (C-3); 25.00

(C-7); 28.61 (C-4); 44.84 (C-2); 61.69 (C-1′); 112.00 (C-5); 126.80 (C-12); 127.30 (2C-10); 128.10 (C-6); 128.21 (2C-11); 143.45 (C-9). HRMS. $C_{15}H_{21}N$. Calcd 215.1674 (M^+), found 215.1664.

15. Condensation of non-chiral enamine 1-benzyl-5-ethyl-1,2,3,4-tetrahydropyridine with MVK led to a racemic mixture of 1-benzyl-4a-ethyl-octahydroquinolin-7-one: $[\alpha]_D^{20}$ 0 in 90% overall yield.
16. **Compound 5**. $R_f=0.32$ (Al_2O_3/*n*-hexane:ethyl acetate = 92:8); (56.6%) pale yellow oil. IR (film, cm^{-1}): 3050, 2934, 1713; $[\alpha]_D^{20}$ −98 (*c* 1.0, CH_2Cl_2); ^1H NMR: δ (ppm, $CDCl_3$): 0.72 (t, 3H-10, 7.70); 1.15–1.25 (m, 1H-4, 1H-3, 1H-9); 1.27 (d, 3H-2′, 6.60); 1.55–1.85 (m, 1H-3, 2H-5, 1H-4); 2.00–2.12 (m, 1H-6); 2.15 (hept, 1H-9, 7.70); 2.28–2.45 (m, 1H-8, 1H-6, 1H-2); 2.61 (dd, 1H-8a, 4.40, 11.20); 2.75 (t, 1H-8, 11.70); 2.96 (dt, 1H-2, 3.30, 12.0); 3.55 (q, 1H-1′, 6.60); 7.20–7.40 (m, 5H, ϕ-H); ^{13}C NMR: δ (ppm, $CDCl_3$): 7.50 (C-10); 21.72 (C-5); 22.47 (C-2′); 24.79 (C-5); 29.56 (C-9); 33.67 (C-3); 34.61 (C-8); 35.78 (C-4a); 37.15 (C-6); 41.11 (C-2); 59.58 (C-1′); 61.62 (C-8a); 126.90 (C-14); 127.27 (2C-12); 128.42 (2C-13); 145.25 (C-11); 212.80 (C-7). EI/MS: 285 (9); 270 (11); 256 (11); 228 (10) 215 (21); 214 (28); 105 (100); 104 (30); 103 (22); 79 (51); 77 (49); 42 (50). HRMS $C_{19}H_{27}NO$. Calcd 285.2093 (M^+), found 285.2077.
17. **Compound 6**. $R_f=0.40$ (Al_2O_3/*n*-hexane:ethyl acetate = 92:8); (28.4%). Mp 76–78°C. IR (film, cm^{-1}): 3050, 2933, 1711; $[\alpha]_D^{20}$ +5 (*c* 1.0, CH_2Cl_2); ^1H NMR: δ (ppm, $CDCl_3$): 0.89 (t, 3H-10, 7.70); 1.21 (d, 3H-2′, 6.60); 1.30 (dt, 1H-4, 4.40, 13.56); 1.38 (dt, 1H-5, 4.40, 13.56); 1.48–1.65 (m, 1H-3, 1H-5, 1H-9); 1.77 (td, 1H-4, 4.40, 11.70); 1.93 (dt, 1H-3, 4.47, 13.56); 2.06 (hept, 1H-9, 7.70); 2.18–2.36 (m, 2H-2, 1H-6); 2.38 (dd, 1H-8, 1.83, 2.20); 2.45 (td, 1H-6, 6.23, 11.56); 2.86 (dd, 1H-8, 12.04); 3.15 (dd, 1H-8a, 4.40, 10.45); 3.54 (q, H-1′, 6.60); 7.15–7.40 (m, 5H, ϕ-H); ^{13}C NMR: δ (ppm, $CDCl_3$): 7.45 (C-10); 19.48 (C-2′); 21.28 (C-5); 26.16 (C-4); 29.93 (C-9); 33.61 (C-3); 35.38 (C-8); 35.85 (C-4a); 37.40 (C-6); 43.78 (C-2); 59.51 (C-1′); 60.60 (C-8a); 126.58 (C-14); 127.00 (2C-10); 128.26 (2C-12); 146.83 (C-11); 212.64 (C-7). EI/MS: 285 (9); 270 (11); 256 (10); 228 (10); 215 (18); 214 (22); 105 (100); 104 (24); 103 (21); 79 (46); 77 (48); 42 (37). HRMS. $C_{19}H_{27}NO$. Calcd 285.2093 (M^+), found 285.2077.

    X-Ray analysis of 6. Crystallised from benzene/*n*-hexane. Colourless, irregular crystal, 0.7×0.6×0.6 mm^3, $C_{19}H_{27}NO$, orthorhombic, $P2_12_12_1$, $a=6.3490(10)$, $b=13.6643(17)$, $c=19.468(3)$ Å, $Z=4$. Bruker P4 diffractometer using Mo Kα radiation, $T=298(2)$ K, 5058 reflections measured up to $2\theta=57.50°$, 4264 independent data ($R_{int}=5.64\%$) for 3641 refined parameters. The structure was refined on basis on non absorption-corrected data, using standard methods[20] without neither restraints nor constraints. Final *R* indices: $R_1=4.24\%$ for 3641 data having $F_o>4\sigma$ (F_o) and $wR_2=11.62\%$ for all data. The crystallographic data have been deposited in CDCC, UK (deposition number 171160).
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