Pergamon

Tetrahedron: *Asymmetry* 11 (2000) 4687–4691

TETRAHEDRON: *ASYMMETRY*

An efficient synthetic route to chiral 4-alkyl-1,2,3,4-tetrahydroquinolines: enantioselective synthesis of (*R*)-4-ethyl-1,2,3,4-tetrahydroquinoline

Neelakandha S. Mani* and Min Wu

Department of Medicinal Chemistry, Ligand Pharmaceuticals, Inc., 10275 Science Center Dr., San Diego, CA, 92121, USA

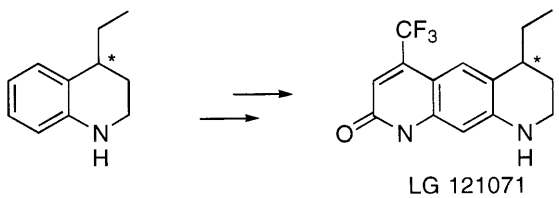
Received 9 October 2000; accepted 6 November 2000

Abstract

An efficient synthetic route to non-racemic chiral 4-alkyl-1,2,3,4-tetrahydroquinoline is described. (4*R*)-4-Ethyl-1,2,3,4-tetrahydroquinoline was obtained by the organoaluminum promoted modified Beckmann rearrangement involving the oxime sulfonate of (3*R*)-3-ethylindan-1-one. The required optically active indanone was obtained via an asymmetric conjugate reduction of (*E*)-ethyl 3-phenylpent-2-enoate.

1. Introduction

Although substituted 1,2,3,4-tetrahydroquinolines with one or more stereogenic centers due to substituents on the hydroaromatic ring are well known in the literature,[1] very little work has been reported on their preparation in optically active form.[2] In connection with our work on the nonsteroidal androgen receptor modulator LG 121071 and related analogs,[3,4] we needed an asymmetric route suitable to prepare these compounds in both enantiomeric forms. An efficient



Scheme 1.

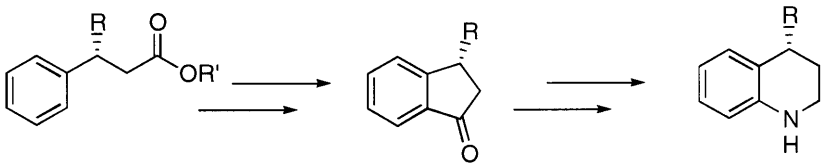
* Corresponding author. Present address: The R.W. Johnson Pharmaceutical Research Institute, 3210 Merryfield Row, San Diego, CA 92121, USA. Tel: (858) 784-3289; fax: (858) 450-2089; e-mail: nmani@prius.jnj.com

0957-4166/00/$ - see front matter
PII: S0957-4166(00)00468-7

synthesis of enantiopure 4-ethyl-1,2,3,4-tetrahydroquinoline with predetermined absolute configuration was thus required (Scheme 1). We were surprised to find that there are no methods on record for the synthesis of chiral 4-alkyl-tetrahydroquinolines with known absolute configuration. We wish to report herein the results of our studies in this direction. A preparatively useful synthetic route to obtain enantiopure 4-alkyl-1,2,3,4-tetrahydroquinolines is described, illustrated by the synthesis of (*R*)-4-ethyl-1,2,3,4-tetrahydroquinoline.

2. Results and discussion

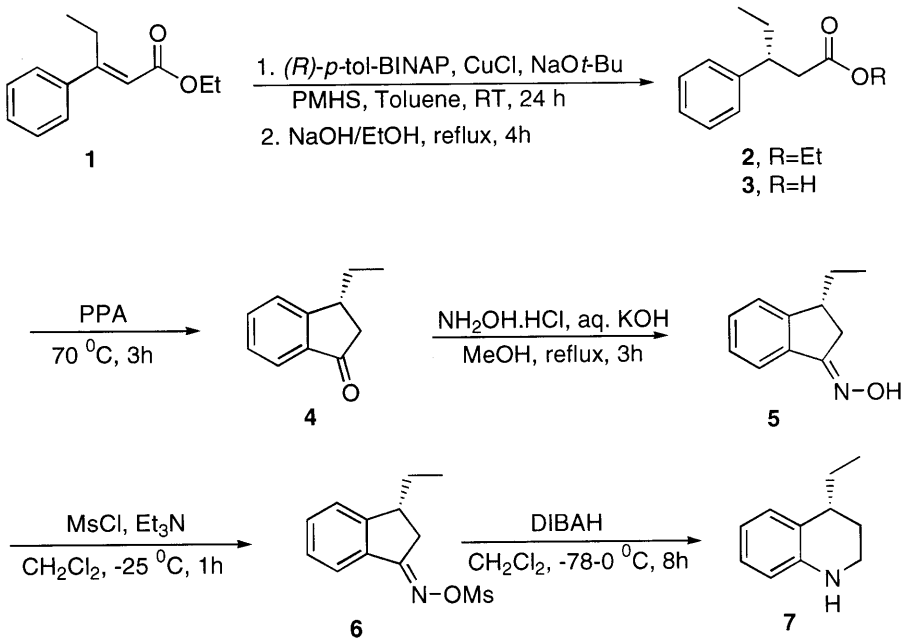
Since we were unable to find any non-racemic chiral 4-alkyl-1,2,3,4-tetrahydroquinolines with known absolute configuration in the literature, we focused our attention on a synthetic strategy, which would allow for direct correlation of stereochemistry with that of an intermediate of known absolute configuration. The synthetic pathway we designed consists of a modified Beckmann rearrangement involving a 3-substituted indanone oxime[5–7] (Scheme 2).



Scheme 2.

Optically active 3-substituted indanones of known stereochemistry have been reported in the literature.[8] Moreover, their absolute configuration could be easily determined by ORD.[9,10] Beckmann rearrangement of the unsubstituted indanone oxime has been shown to be highly regioselective.[5] More importantly, Yamamoto's organoaluminum promoted modified Beckmann rearrangement[6,7] of the unsubstituted 1-indanone oxime mesylate has been shown to yield 1,2,3,4-tetrahydroquinoline as the predominant product. Preparation of chiral 3-alkylindanones was envisaged through the classical cyclodehydration from the corresponding 3-alkylhydrocinnamic acid. Enantioselective synthesis of carboxylic acid derivatives with a stereocenter β to the carbonyl has been an area of intense investigation and several methods are now available for their preparation in high enantiomeric purity.[11–13] Asymmetric conjugate reduction of an α,β-unsaturated ester appeared most suitable, since Buchwald et al. have recently shown that conjugate reduction of α,β-unsaturated esters using copper hydride with *p*-tol-BINAP as a chiral ligand and polymethylhydrosiloxane as the hydride source gave products with a stereocenter β to the carbonyl in very good enantiomeric purity.[14] A Reformatsky reaction or a Horner–Emmons reaction with an aromatic ketone could easily furnish the required 3-alkyl cinnamic acid derivatives.[14,15] Synthesis of (*R*)-4-ethyl-1,2,3,4-tetrahydroquinoline using this methodology is outlined in Scheme 3.

Following Buchwald's procedure, asymmetric conjugate reduction of (*E*)-ethyl 3-phenylpent-2-enoate **1** using a catalyst formed from (*R*)-*p*-tol-BINAP, CuCl, and NaO*t*-Bu and an excess of polymethylhydrosiloxane (4 equiv.) furnished (*R*)-3-phenylpentanoate **2** (86% ee). Basic hydrolysis to the carboxylic acid followed by cyclization using polyphosphoric acid furnished (*R*)-3-ethyl-1-indanone in 80% yield. Treatment of this indanone with hydroxylamine hydrochloride in methanolic KOH furnished the oxime **5**. Treatment of **5** with methanesulfonyl chloride



Scheme 3.

and triethylamine furnished an unstable mesylate which was immediately treated with an excess of DIBAH to furnish (*R*)-(+)-4-ethyl-1,2,3,4-tetrahydroquinoline in very good overall yield.

In conclusion, an efficient enantioselective synthesis of 4-ethyl-1,2,3,4-tetrahydroquinoline correlating optical rotation and absolute configuration has been achieved. The methodology appears to be suitable for preparing various 4-alkyl-1,2,3,4-tetrahydroquinolines.

3. Experimental section

3.1. General methods

^{1}H NMR spectra were recorded at 400 or 500 MHz using $CDCl_3$ as solvent and TMS (0.00 ppm ^{1}H) or $CHCl_3$ (7.26 ppm ^{1}H) as internal standards. Chemical shifts (δ) are given in parts per million (ppm) and coupling constants (J) are given in hertz (Hz). Infrared spectra were taken on a Nicolet Impact 410 spectrometer. Optical rotations were measured on a Perkin–Elmer 241 polarimeter.

*3.2. (*R*)-3-Phenylpentanoic acid **3***

(*R*)-Ethyl 3-phenylpentanoate[14] (**2**) 800 mg, 3.87 mmol) was dissolved in ethanol (4 mL) Aqueous NaOH (10%, 2 mL) was added and the reaction mixture was refluxed for 4 h. The mixture was cooled to rt, acidified to pH 2 with 0.5N HCl and extracted with ethyl acetate (2×20 mL). The combined organic layer was washed with brine and dried over $MgSO_4$. After filtration, the solvents were evaporated and the crude product was purified by column chromatography (silica gel, ethyl acetate:hexanes 1:4) to yield the free acid as a colorless oil (680 mg, 91%); $[\alpha]_D^{25}$

−17.3 ($c=0.55$, ethanol) {lit.[8] $[\alpha]_D^{21}$ −18.4 ($c=1.6$, ethanol)}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.80 (3H, t, $J=7.5$), 1.61–1.78 (2H, m), 2.65 (2H, oct., $J=7.5$), 2.99 (1H, m), 7.17–7.23 (3H, m), 7.26–7.31 (2H, m).

3.3. (R)-3-Ethyl-1-indanone **4**

(*R*)-3-Phenylpentanoic acid (600 mg, 3.36 mmol) was treated with PPA (15 g) and the resulting mixture heated to 70°C. After 3 h, the reaction mixture was poured on to ice and extracted with ethyl acetate (2×25 mL). The combined organic layer was washed with water, saturated sodium bicarbonate, and brine and dried over $MgSO_4$. After filtration, the solvents were evaporated under reduced pressure and the crude product was purified by column chromatography (silica gel, ethyl acetate:hexanes 1:9) to yield the indanone **4** as a colorless oil (450 mg, 83%); $[\alpha]_D^{25}$ −15.5 ($c=0.67$, ethanol) {lit.[8] $[\alpha]_D^{19}$ −20.5 ($c=1.3$, ethanol)}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (3H, t, $J=7.5$), 1.51 (m, 1H), 1.98 (1H, m), 2.35 (1H, dd, $J=3.5$, 19.0), 2.83 (1H, dd, $J=3.5$, 19.0), 3.32 (1H, m), 7.36 (1H, t, $J=8.0$), 7.50 (1H, d, $J=8.0$), 7.59 (1H, t, $J=8.0$), 7.73 (1H, $J=7.5$).

3.4. (R)-3-Ethyl-1-indanone oxime **5**

To a solution of (*R*)-3-ethyl-1-indanone (250 mg, 1.56 mmol) in 5 mL of methanol was added hydroxylamine hydrochloride (162 mg, 2.33 mmol) and aq. KOH (50%, 0.53 mL, 4.72 mmol). The mixture was refluxed for 3 h when TLC indicated complete conversion. After cooling to room temperature, the reaction mixture was neutralized with dilute HCl and extracted with ethyl acetate (3×20 mL). The combined organic layer was washed with water, brine and dried over $MgSO_4$. After filtration, the solvents were evaporated under reduced pressure to obtain the crude oxime, which was purified by recrystallization from ethyl acetate–hexanes to yield a pale yellow solid (243 mg, 89%). Mp 81–83°C (lit.[16] for racemate 82–83°C); $[\alpha]_D^{25}$ +18.6 ($c=0.6$, ethanol)); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (3H, t, $J=7.5$), 1.51 (m, 1H), 1.88 (1H, m), 2.64 (1H, dd, $J=3.5$, 19.0), 3.13 (1H, dd, $J=8.1$, 19.0), 3.23 (1H, m), 7.26 (1H, t, $J=8.0$), 7.38 (2H, m), 7.69 (1H, d, $J=7.5$).

3.5. (R)-4-Ethyl-1,2,3,4-tetrahydroquinoline **7**

A solution of 4-ethyl-1-indanone oxime (300 mg, 1.83 mmol), triethylamine (0.51 mL, 3.66 mmol) in 10 mL of dry dichloromethane was cooled to −25°C. Methanesulfonyl chloride (0.17 mL, 2.19 mmol) was added over a period of 10 min. After stirring for 1 h, the reaction was diluted with dichloromethane (50 mL) and washed with ice-cold 1N hydrochloric acid followed by saturated sodium bicarbonate solution and brine. The dichloromethane solution was dried over $MgSO_4$ for 10 h. After filtration with aid of dry dichloromethane, the solution was concentrated under reduced pressure (maintaining the bath temperature at 20°C) to about 10–15 ml. The concentrated solution thus obtained was cooled to −78°C and DIBAH (1 M in hexanes, 6.4 mL) was added. After 10 min, the solution was warmed to 0°C and stirred for 8 h. The reaction mixture was diluted with dichloromethane (150 mL) and quenched with water. The organic layer was washed with brine and dried over $MgSO_4$. After filtration, the solvents were evaporated under reduced pressure and the crude product was purified by flash column chromatography (silica gel, ethyl acetate:hexanes 1:10) to furnish (*R*)-4-ethyl-1,2,3,4-tetra-

hydroquinoline **7** as pale yellow oil (216 mg, overall 73% in two steps); $[\alpha]_D^{25}$ +29.1 ($c=1.4$, ethanol); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.01 (3H, t, $J=7.5$), 1.51–1.94 (4H, m), 2.66 (1H, m), 3.24–3.36 (2H, m), 3.84 (1H, br), 6.50 (1H, d, $J=8.0$), 6.63 (1H, dt, $J=1.0$, 8.0), 6.98 (1H, dt, $J=1.0$, 8.0), 7.03 (1H, d, $J=8.0$); MS (70 eV) m/z 161 M^+, 132 $(M-CH_3CH_2)^{\bullet+}$. Spectroscopic data was consistent with previously reported[3] data for this compound.

Acknowledgements

We wish to thank Dr. Don Karanewsky for his very helpful suggestions and support.

References

1. Katritzky, A. R.; Rachwal, S.; Rachwal, B. *Tetrahedron* **1996**, *52*, 15031–15070.
2. Reichardt, C.; Aman, W.; Harms, K.; Schaefer, G.; Stein, J. *J. Prakt. Chem./Zhem-Ztg.* **1998**, *340*, 513–529.
3. Hamann, L. G.; Mani, N. S.; Davis, R. L.; Wang, X.-N.; Marschke, K. B.; Jones, T. K. *J. Med. Chem.* **1999**, *42*, 210–212.
4. Edwards, J. P.; Higuchi, R. I.; Winn, D. T.; Pooley, C. L. F.; Caferro, T. R.; Hamann, L. G.; Zhi, L.; Marschke, K. B.; Goldman, M. E.; Jones, T. K. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1003–1008.
5. Gawley, R. E. *Org. React.* **1988**, *35*, 1–420.
6. Hattori, K.; Matsumura, Y.; Miyazaki, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1981**, *103*, 7368–7370.
7. Maruoka, K.; Miyazaki, T.; Ando, M.; Matsumura, Y.; Sakane, S.; Hattori, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1983**, *105*, 2831–2843.
8. Brienne, M.-J.; Ouannes, C.; Jacques, J. *Bull. Soc. Chim. Fr.* **1967**, *2*, 613–623.
9. Smith, H. E.; Padilla, B. G.; Neergaard, J. R.; Chen, F.-M. *J. Am. Chem. Soc.* **1978**, *100*, 6035–6038.
10. Fontana, L. P.; Chandramouly, T.; Smith, H. E.; Polavarapu, P. L. *J. Org. Chem.* **1988**, *53*, 3379–3381.
11. Andersson, P. G.; Schink, H. E.; Osterlund, K. *J. Org. Chem.* **1998**, *63*, 8067–8070.
12. Romero, D. L.; Manninen, P. R.; Han, F.; Romero, A. G. *J. Org. Chem.* **1999**, *64*, 4980–4984.
13. Pippel, D. J.; Curtis, M. D.; Du., H.; Beak, P. *J. Org. Chem.* **1998**, *63*, 2–3.
14. Appella, D. H.; Moritani, Y.; Shintani, R.; Ferreira, E. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9473–9474.
15. Shriner, R. L. *Org. React.* **1942**, *1*, 1–37.
16. Bott, K. *Chem. Ber.* **1967**, *100*, 2791–2797.