Diastereoselective Synthesis of 2,5-Disubstituted Decahydroquinolines via Ring-Rearrangement Metathesis and Zirconium-Mediated Cyclization

Jürgen Neidhöfer, Siegfried Blechert*

Institut für Chemie, Technische Universität Berlin, Strasse des 17. Juni 135, 10623 Berlin, Germany
Fax +49(30)31423619; E-mail: blechert@chem.tu-berlin.de

Received 2 June 2004; revised 3 September 2004

Abstract: A diastereoselective approach to 2,5-substituted decahydroquinolines by zirconium-mediated cyclization of unsaturated \(a,a'-\)disubstituted piperidines \(\text{II}\) is described. The required piperidines could be obtained from secondary sulfonamides \(\text{III}\) via ruthenium-catalyzed ring-rearrangement metathesis (RRM) in high yields. Racemic \(\text{trans-195A}\) and \(\text{2-epi-trans-195A}\) were synthesized in 8 steps starting with butyraldehyde and cyclohex-2-enol.

Key words: metathesis, ruthenium, piperidines, zirconium, decahydroquinolines

Decahydroquinolines occur in nature in skin secretions of dendrobatid and mantelline frogs\(^1\) as well as in bufonid toads,\(^2\) ascidians,\(^3,4\) marine flatworms\(^5\) and myrmicine ants.\(^6\) These relatively nontoxic biologically active compounds have marked activity on ion channels.\(^6\) They have proved to be noncompetitive blockers of nicotinic receptor channels and are thus interesting agents for biomedical research and molecular pharmacology.\(^7\) Both \(\text{cis-}\) and \(\text{trans-}\)-fused decahydroquinolines have been found since discovery of the first representative \(\text{cis-195A}\), isolated from skin extracts of the panamanian frog \(\text{dendrobatus pumilio}\) in 1968.\(^8,9\) Many of these compounds cannot be obtained from their natural sources in sufficient quantities for NMR- or X-ray-analysis and their structure and stereochemistry has been only tentatively assigned.\(^9\) Synthesis is needed to confirm their structure by comparison with the natural material and to obtain these alkaloids, and derivatives thereof, in adequate amounts for biological screening.\(^10\)

2,5-Disubstituted decahydroquinolines are the major class with nearly 30 different representatives.\(^11\) In our work we tried to investigate an efficient and concise approach to these significant alkaloids. We focused on a strategy for synthesis of the \(\text{5-methyl substituted species by means of ring-rearrangement metathesis (RRM) and Negishi’s zirconium-mediated olefin-coupling}\)\(^12\) as key steps (Scheme 1). Application of zirconium-mediated olefin-coupling to natural product synthesis has been successfully established by Mori et al. for annulation of a \(\text{5,6-membered octahydroindole ring-system and subsequent carboxylation within the total synthesis of (→)Dendrobine.}\)\(^13\) To the best of our knowledge an application to \(\text{6,6-membered rings has never been performed. We have tried now for the first time to investigate this versatile reaction for annulation of a 6,6-membered decahydroquinoline ring-system I by conversion of adequate unsaturated \(a,a'-\)disubstituted piperidines II. The required piperidines II were expected to be accessible through RRM of III. RRM-processes have already been proven to be a powerful tool in natural product synthesis\(^14\) and in combination with a Negishi coupling reaction the desired decahydroquinolines I should readily be obtained in only a few steps.

SYNTHESIS 2004, No. 18, pp 3047–3054
Advanced online publication: 02.11.2004
DOI: 10.1055/s-2004-834904; Art ID: T06004SS
© Georg Thieme Verlag Stuttgart · New York
nitrobenzenesulfonamides under Mitsunobu conditions and subsequent chemoselective cleavage either of the carbamate or the sulfonamide moiety.\(^{17}\) Transformation of 3 with N-Boc-2-nitrobenzenesulfonamide, disisopropyl azodicarboxylate (DIAD) and PPh\(_3\) in THF yielded 6 in 65\% and cleavage of the resulting carbamate was achieved with 5\% TFA in THF to give 7 in 98\% yield.

In this context we were next interested in investigating the possibility of a kinetic resolution or a kinetic transformation by employing a diastereomeric 1:1 mixture of the metathesis precursor to the desired RRM-process. Conversion of 7 with cyclohex-2-enol under Mitsunobu conditions gave 8a and 8b in a 1:1 ratio in 46\% yield. Attempts to synthesize 8a and 8b by replacing the amine and alcohol functionality, employing cyclohex-2-enyl-2-nitrobenzenesulfonamide and hept-1-en-3-ol, respectively, under various conditions resulted in no conversion. Likewise, application of palladium-mediated allylic substitution, by treatment with cyclohex-2-enyl acetate or methylcarbonate, respectively, did not succeed. Subsequent metathesis was performed in CH\(_2\)Cl\(_2\) under ethylene atmosphere, using 5 mol\% benzylidene-bis(tricyclohexylphosphine)ruthenium dichloride (Grubbs catalyst). The transformation resulted in complete conversion to the desired tetrahydropyridine derivatives 9a and 9b, which could be separated by chromatographic purification in an overall yield of 96\%. Employment of ethylene was essential in this reaction in order to suppress the formation of dimeric byproducts.\(^{18}\) Contrary to our hopes both diastereomers were converted simultaneously as indicated by NMR-analysis of the reaction mixture.

---

**Scheme 2** Synthetic route to the tetrahydropyridines. **Reactions and conditions:** (a) AllylMgBr, Br(O-i-Pr), Et\(_2\)O; (b) MsCl, Et\(_3\)N, CH\(_2\)Cl\(_2\); (c) NaN\(_3\), DMSO; (d) LAH, Et\(_2\)O; (e) NsCl, K\(_2\)CO\(_3\), CH\(_2\)Cl\(_2\); (f) NsBocNH, DIAD, PPh\(_3\), THF; (g) 5\% TFA, THF; (h) cyclohex-2-enol, DIAD, PPh\(_3\), THF; (i) isolated as diastereomeric mixture (1:1) in 46\% yield; (j) 5 mol\% Grubbs’ catalyst, ethylene, CH\(_2\)Cl\(_2\)

---

**Scheme 3** Synthetic route to the decahydroquinolines. **Reactions and conditions:** (a) PhSH, K\(_2\)CO\(_3\), DMF, BnBr, TBAI; (b) Cp\(_2\)ZrCl\(_2\), BuLi, THF; (c) HCl; (d) H\(_2\), Pd/C, MeOH; (e) p-NO\(_2\)-BzCl, Et\(_3\)N, CH\(_2\)Cl\(_2\)
Whereas the cyclization of 9a with BuLi and dicyclopen-tadienylzirconium dichloride (Cp2ZrCl2) resulted in dimerization by coupling of the aromatic nitro group, cyclization to the desired decahydroquinolines could be achieved after transformation of sulfonamide 9a into the N-benzyl derivative 10a (Scheme 3). The deprotection- protection sequence was performed with thiophenol (PhSH) and K2CO3 in DMF and subsequent treatment with benzyl bromide (BnBr) in a one-pot procedure to give 10a in 90% yield. Subsequent zirconium mediated coupling afforded only decahydroquinoline 11a along with isomerized starting material 12a. The ratio of 11a to 12a was determined to be 7:2 by GC-analysis of the crude product. Compound 11a could be isolated in 74% yield and final hydrogenation with 10% palladium on charcoal gave 1 and final hydrogenation with 10% palladium on charcoal structure of the product configuration was not clear by NMR analysis, configuration was identical to the natural product and subsequent X-ray analysis (Figure 2). The found con- figuration of the propyl group of 11a, which still remains unknown, is currently under investigation in our laboratory.

In conclusion, we have presented a concise and highly diastereoselective approach to trans-fused 2,5-disubstituted decahydroquinolines. Racemic trans-195A (1) and 2-epi-trans-195A (15) were synthesized in 8 steps starting with butyraldehyde and cyclohex-2-enol. Enantioselective synthesis in order to determine the absolute configuration of trans-195A, which still remains unknown, is currently under investigation in our laboratory.

Figure 3 Postulated zirconacycle intermediates

Taber et al. have shown that cyclozirconations are reversible processes in which the stereochemistry of the products can be influenced by stereogenic centers in the employed substrate, either through kinetic or thermodynamic control. In our case, we assumed that the stereochemistry of the propyl group of 10a could have a remarkable influence on the high diastereoselectivity observed within the cyclization to decahydroquinoline 11a. To investigate the effect of a propyl group with contrary stereochemistry we transformed 9b into the corresponding N-benzyl derivative 10b. Surprisingly, cyclization of 10b also resulted in only one diastereomer 11b, which could be isolated with a negligible lower yield of 69% compared to 11a. In addition a less polar fraction was isolated with 25% yield, which could be identified as a 2:1 mixture of 12b with 13b. Final hydrogenation of 11b gave 15 in 89% yield. The configuration of 15 was established after transformation to the N-p-nitrobenzoyl derivative 16 and subsequent X-ray analysis (Figure 2). We presume that the observed lower rate of cyclization and the increased amount of isomerized starting material by employing 10b could be caused by destabilization of the corresponding zirconacycle B due to adverse interaction of the propyl group, which is expected to be in an unfavorable axial position for 10b and in an equatorial position for 10a with the corresponding zirconacycle A (Figure 3).

Figure 2 X-ray structures of 14 and 16

1H NMR spectra (500 MHz) and 13C NMR spectra (125 MHz) were recorded on a Bruker DRX 500 spectrometer using the indicated solvents. NMR chemical shifts are expressed in ppm upfield, relative to the internal solvent peak. HRMS were recorded on a Finnigan MAT 95 SQ spectrometer. IR spectra were measured on a Nicolet FT-IR 750 spectrometer. Melting points were determined on a Leica Galen III heater table microscope and are uncorrected. Elemental analyses were recorded on an Elementar Vario El Fa. (Analytik Jena). Analytical TLC was performed on Merck silica gel 60 (0.040–0.063 mm) or Fluka alumina (type 5016A basic, Brockmann activity grade 3) using the indicated solvents. Anhyd Et2O, anhyd DMSO and all chemicals were purchased from Aldrich and were used without further purification. THF was freshly distilled under N2 from sodium/benzophenone and CH2Cl2 was distilled from CaH2. All reactions were carried out under N2 using flame dried glassware with the exception of Negishi coupling which was carried out under Ar. Metathesis reactions were performed in a Braun MB 150B-G glove box under N2.

Hept-1-en-4-ol (3) A stirred solution of allylmagnesium bromide in hexane (90.0 mL, 1.0 M) was diluted with anhyd Et2O (150 mL) and cooled in an ice bath. Trisopropoxy borate (20.8 mL, 90.0 mmol) was added dropwise at 0 °C over 15 min. After stirring for 2 h at r.t. n-butanal (5.41 mL, 60.0 mmol) was added dropwise via a syringe and stirring was continued for 3 h. An aq solution of NaOH (30 mL, 3 M) was added and the mixture was refluxed for 3 h. The organic layer was washed with water (50 mL), brine (50 mL) and dried (MgSO4). The solvent was removed by distillation over a 10 cm Vigreux column at atmospheric pressure. Fractional distillation of the crude product at re-
duced pressure yielded 3 (5.76 g, 84%) as colorless liquid; bp 67–68 °C (24 mbar).

IR (film): 3453 (m), 2960 (m), 2932 (m), 1710 (s), 1435 (m), 1413 (m), 1360 (s), 1168 (s), 1124 (m), 854 (m), 783 (m), 742 (m), 730 (m), 655 (m) cm⁻¹.

1H NMR (500 MHz, CDCl₃): δ = 5.85–5.76 (m, 1 H), 5.12 (d, J = 15.2 Hz, 1 H), 5.12 (d, J = 11.0 Hz, 1 H), 3.65 (br s, 1 H), 2.33–2.25 (m, 1 H), 2.17–2.08 (m, 1 H), 1.65 (s, 1 H), 1.56–1.40 (m, 3 H), 1.40–1.30 (m, 1 H), 0.92 (t, J = 6.9 Hz, 3 H).

13C NMR (125 MHz, CDCl₃): δ = 135.0 (CH), 118.0 (CH₆), 70.5 (CH₂), 42.0 (CH₂), 39.0 (CH₂), 18.9 (CH₂), 14.1 (CH₃).

MS (EI): m/z (%) = 191 (1) [M – H]⁺, 151 (33), 105 (22), 97 (13), 96 (26), 81 (22), 79 (18), 67 (22), 55 (100), 54 (34).

HRMS: m/z [M⁺] calcd for C₇H₁₃N₃: 139.1109; found: 139.1124.

2-Nitro-N-(1-propyl-3-en-1-yl)-benzenesulfonamide (7)

From 5: To an ice-cold stirred solution of 3 (9.50 g, 83.2 mmol) and Et₃N (17.4 mL, 125 mmol) in CH₂Cl₂ (60 mL) was added dropwise MeCl₂ (7.73 mL, 99.8 mmol) over 15 min. The resulting mixture was allowed to warm to r.t. and stirred for 3 h. After diluting with CH₂Cl₂ (400 mL) the reaction mixture was washed with H₂O (3 × 100 mL), brine (100 mL) and dried (MgSO₄). The solvent was removed in vacuo and the crude product was purified by flash chromatography on silica gel (cyclohexane–MTBE, 3:1) to give 4 (12.8 g, 80%) as pale yellow oil; R₆ 0.40.

IR (film): 2960 (m), 2925 (m), 2875 (w), 2850 (w), 1355 (m), 1336 (m), 1258 (s), 972 (w), 913 (s), 802 (w) cm⁻¹.

IR (film): 2960 (m), 2925 (m), 2875 (w), 2850 (w), 1355 (m), 1336 (m), 1258 (s), 972 (w), 913 (s), 802 (w) cm⁻¹.

IR (film): 3453 (m), 3098 (w), 3077 (w), 2959 (m), 2931 (m), 2873 (m), 1710 (s), 1435 (m), 1413 (m), 1360 (s), 1168 (s), 1124 (m), 854 (m), 783 (m), 742 (m), 730 (m), 655 (m) cm⁻¹.

IR (film): 3453 (m), 3098 (w), 3077 (w), 2959 (m), 2931 (m), 2873 (m), 1710 (s), 1435 (m), 1413 (m), 1360 (s), 1168 (s), 1124 (m), 854 (m), 783 (m), 742 (m), 730 (m), 655 (m) cm⁻¹.


Anal Calcd for C₁₄H₁₇N₂O₅S: C, 54.28; H, 6.54; N, 7.16.

2-Nitro-N-(1-propyl-3-en-1-yl)-benzenesulfonamide (7)

From 5: To an ice-cold stirred solution of 3 (9.50 g, 83.2 mmol) and Et₃N (17.4 mL, 125 mmol) in CH₂Cl₂ (60 mL) was added dropwise MeCl₂ (7.73 mL, 99.8 mmol) over 15 min. The resulting mixture was allowed to warm to r.t. and stirred for 3 h. After diluting with NaOH (30 mL, 2.5 M) at 0 °C the resulting suspension was vigorously stirred at r.t. for 30 min. The solvent was decanted off, the remaining solid was washed with Et₂O (5 × 50 mL) and the combined extracts were dried (MgSO₄). The solvent was removed by distillation over a 10 cm Vigreux column at atmospheric pressure and the remaining liquid was diluted with CH₂Cl₂ (40 mL). After addition of K₂CO₃ (17.4 g, 123 mmol) the mixture was cooled to 0 °C and NaCl (16.4 g, 74.0 mmol) was added portionwise over 15 min. The ice bath was removed and the suspension was stirred at r.t. for 24 h. After diluting with CH₂Cl₂ (500 mL) the mixture was washed with H₂O (100 mL), brine (100 mL) and dried (MgSO₄). The solvent was evaporated and the crude product was purified by flash chromatography on silica gel (CH₂Cl₂–cyclohexane, 3:1) to give 7 (14.4 g, 78%) as pale yellow solid; R₆ 0.38, mp 30–32 °C.

From 6: To an ice-cold stirred solution of 6 (2.00 g, 5.02 mmol) in THF (500 mL) was added dropwise TFA (25.0 mL, 324 mmol) over 10 min. The mixture was allowed to warm to r.t., stirred for 1 h and cooled to 0 °C. Aq sat. NaHCO₃ (350 mL) was added until the aqueous phase showed pH 8. After separation of the organic layer, the aqueous layer was extracted with CH₂Cl₂ (3 × 100 mL) and the combined organic layers were dried (MgSO₄). The solvent was removed in vacuo and the remaining solid was purified by flash chromatography on silica gel (CH₂Cl₂–cyclohexane, 3:1) to give 7 as pale yellow solid (1.47 g, 98%); R₆ 0.38; mp 30–32 °C.
moved in vacuo. Flash chromatography of the remaining oil on silica gel (CH₂Cl₂–cyclohexane, 1:3) gave a yellow solid; mp 67–68 °C; Rf 0.27.

1H NMR (500 MHz, CDCl₃): δ = 147.8 (C), 135.4 (C), 133.3 (CH), 133.1 (CH), 132.9 (CH), 130.5 (CH), 125.4 (CH), 118.8 (CH₂), 54.8 (CH), 39.6 (CH₂), 37.0 (CH₂), 18.7 (CH₂), 13.8 (CH₃).

MS (EI): m/z (%) = 259 (60) [M – C₅H₅]+, 258 (8), 257 (60), 188 (6), 187 (8), 186 (100), 92 (8).

HRMS: m/z [M – C₅H₅]+ calcled for C₁₉H₂₆N₂O₄S: 378.1613; found: 378.1627.

Anal. Calcd for C₁₉H₂₆N₂O₄S: C, 60.09; H, 6.92; N, 7.40. Found: C, 60.16; H, 6.91; N, 7.41.

Diastereoselective Synthesis of 2,5-Disubstituted Decahydroquinolines

N-Cyclohex-2-en-1-yl-2-nitro-N-(1-propyl-but-3-enyl)-benzenesulfonamide (8a with 8b)

DIAD (3.41 mL, 17.3 mmol) was added dropwise over 15 min to an ice-cold stirred solution of 7 (3.97 g, 46%) as a pale yellow oil; Rf 0.24.

1H NMR (500 MHz, CDCl₃): δ = 8.09–8.92 (m, 2 H), 7.69–7.60 (m, 4 H), 7.56–7.74 (m, 2 H), 5.88–5.69 (m, 2 H), 5.77–5.63 (m, 2 H), 5.55 (d, J = 10.0 Hz, 1 H), 5.05 (d, J = 17.0 Hz, 1 H), 4.99 (d, J = 8.0 Hz, 1 H), 4.98 (d, J = 17.5 Hz, 1 H), 1.23–1.11 (m, 1 H), 4.85 (t, J = 7.3 Hz, 3 H).

MS (EI): m/z (%) = 337 (3) [M – C₅H₅]+, 310 (14), 309 (100), 186 (56), 94 (14), 80 (23).


Anal. Calcd for C₁₉H₂₆N₂O₄S: C, 60.30; H, 6.92; N, 7.40. Found: C, 60.09; H, 6.91; N, 7.39.
\[ J = 14.7 \text{ Hz, 1 H}, 3.71 (d, J = 14.7 \text{ Hz, 1 H}), 3.11-3.03 (m, 1 H), \\
2.83-2.75 (m, 1 H), 2.28-2.19 (m, 1 H), 1.95-1.87 (m, 2 H), 1.84- \\
1.76 (m, 1 H), 1.63-1.47 (m, 1 H), 1.47-1.22 (m, 5 H), 0.82 (t, J = \\
7.2 \text{ Hz, 3 H}). \]

\[ ^{1}C \text{ NMR (125 MHz, CDCl}_{3}: \delta = 142.0 (C), 139.1 (CH), 129.5 \\
(CH), 128.5 (CH), 128.0 (CH), 126.4 (CH), 123.9 (CH), 114.2 \\
(CH), 59.6 (CH), 56.9 (CH), 37.0 (CH), 34.8 (CH), 33.9 (CH), \\
26.3 (CH), 26.1 (CH), 20.2 (CH), 14.3 (CH). \]

MS (EI): \text{m/z (\%)} = 283 (1) [M]^+, 240 (15), 215 (12), 214 (100), 91 \\
(66).

HRMS: \text{m/z [M]}^+ \text{calcd for } C_{20}H_{30}N: 283.2300; \text{found: } 283.2300.

\( 10a \)

The preparation of \( 10b \) was similar to the procedure described for 
\( 10a \). After conversion of \( 9b \) (3.75 g, 9.11 mmol) and chromatographic 
reflux of the crude product on alumina (cyclohexane–CH2Cl2, 10:1) 
yielded \( 10b \) (3.75 g, 9.91 mmol) and chromato-
graphic purification of the crude product on alumina 
chromatographic purifica-

**PAPER**

Synthesis 2004, No. 18, 3047–3054 © Thieme Stuttgart · New York
12a with 13a

IR (film): 3283 (w), 2952 (s), 2922 (ss), 2855 (s), 2783 (w), 2666 (w). The mixture was stirred for 3 h. After distilling with MTBE (50 mL) the mixture was washed with H2O (2 × 10 mL), brine (10 mL) and dried (MgSO4). Evaporation of the solvent and flash chromatographic purification of the crude product on silica gel (EtOAc–cyclohexane, 1:4) afforded 14 (146 mg, 83%) as a pale yellow solid. 1H NMR (500 MHz, CDCl3): δ = 7.73 (d, J = 8.5 Hz, 2 H), 6.94 (d, J = 8.5 Hz, 2 H), 3.83–3.72 (m, 1 H), 3.37 (br s, 1 H), 2.58 (br s, 1 H), 1.56–1.87 (m, 3 H), 1.49–0.98 (m, 6 H), 0.90 (t, J = 6.6 Hz, 3 H), 0.70 (m, 1 H), 1.33–0.93 (m, 3 H), 0.77 (d, J = 6.4 Hz, 3 H), 0.68 (t, J = 7.1 Hz, 3 H).


rac-(2R,4aS,5R,8aS)-5-Methyl-2-propyl-decahydroquinoline (1)

Compound 11a (500 mg, 1.75 mmol) was added to a stirred suspension of palladium on charcoal (94 mg, 10% Pd/C) in MeOH (35 mL). The mixture was flushed with hydrogen and stirred under balloon pressure at r.t. for 16 h. After filtration through celite and washing with MeOH (2 × 20 mL) the combined filtrates were dried (MgSO4). The solvent was removed by distillation over a 10 cm Vigreux column at atmospheric pressure and the remaining liquid was purified by bulb to bulb distillation (0.05 mbar, 150 °C) to give 1 (302 mg, 88%) as a colorless solid; mp 27–28 °C.

IR (film): 3274 (w), 2954 (s), 2923 (ss), 2869 (s), 2855 (s), 2793 (m), 1650 (s), 1602 (s), 1531 (s), 1450 (s), 1410 (s), 1373 (m), 1343 (m), 1285 (s), 1243 (m), 1145 (s), 1054 (s), 752 (m) cm–1.


rac-(2R,4aS,5R,8aS)-5-Methyl-2-propyl-decahydroquinoline (15)

The preparation of 15 was similar to the procedure described for 14.

11b (235 mg, 0.82 mmol) and purification of the crude product by flash chromatography on silica gel (cyclohexane–EtOAc, 1:4) gave 16 (154 mg, 87%) as a pale yellow solid; mp 122–124 °C (after recrystallization from EtO2).


rac-[(2S,4aS,5R,8aS)-5-Methyl-2-propyl-octahydroquinoline-1-yl]-(4-nitro-phenyl)methane (16)

The preparation of 16 was similar to the procedure described for 14.

11b (235 mg, 0.82 mmol) and purification of the crude product by bulb to bulb distillation (0.05 mbar, 150 °C) yielded 16 (154 mg, 87%) as a pale yellow solid; mp 156–157 °C (after recrystallization from EtO2).


X-ray analysis in ref.20.
References


(15) Absolute configuration not known.


(20) Crystallographic data for both structures have been deposited with the Cambridge Crystallographic Data Centre under the depository numbers: CCDC-239791 (1), CCDC-239792 (16).