Preparation of 1,4-Dihydroquinolines Bearing a Chiral Sulfoxide Group: New Highly Enantioselective Recyclable NADH Mimics

Stéphane Gaillard, Cyril Papamicaël, Francis Marsais, Georges Dupas, Vincent Levacher*

Laboratoire de Chimie Organique Fine et Hétérocyclique, UMR 6014, IRCOF, CNRS, Université et INSA de Rouen, B.P. 08, 76131 Mont Saint Aignan Cédex, France
Fax +33(2)35522962; E-mail: vincent.levacher@insa-rouen.fr
Received 22 November 2004

Abstract: The stereoselective preparation of 1,4-dihydroquinolines possessing a chiral sulfoxide group at C-3 is reported. These novel biomimetic NADH models (*R*)-**1a**,**b** have been shown to be highly enantioselective in the reduction of methyl benzoylformate, producing (*R*)-methyl mandelate in up to 95% ee. The corresponding quinolinium salts **4a**,**b** have been recovered in good yields. The regenerated models **1a**,**b** could be reused without any significant erosion of the enantioselectivity.

Key words: chiral sulfoxide, NADH models, quinoline, asymmetric reduction

Biomimetic NADH models possessing a sulfoxide group as a chiral inducer have proved to be highly efficient, allowing the reduction of various prochiral substrates with a high level of induction.[1] The main drawback of these coenzyme mimics is their poor stability towards nucleophiles and water, making them difficult to handle and hampering the possibility of being used in catalytic process. To circumvent this problem and further extend the potential of these mimics, we report herein the synthesis of annelated models **1a**,**b** in the quinoline series.[2] The presence of an additional fused phenyl ring is thereby expected to improve the stability of the reagent by masking the reactivity of the enamine double bond (Figure 1).

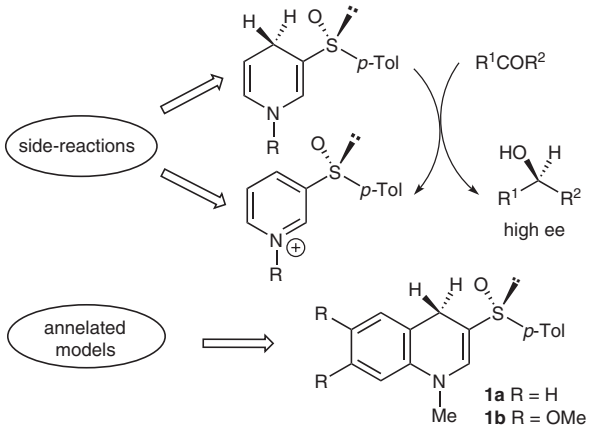
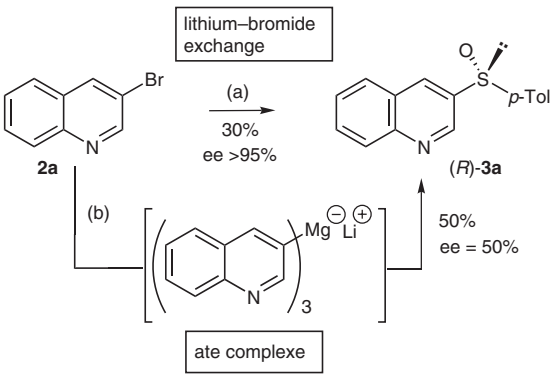


Figure 1 Simple biomimetic NADH models bearing a sulfoxide group as chiral inducer and their annelated analogues.

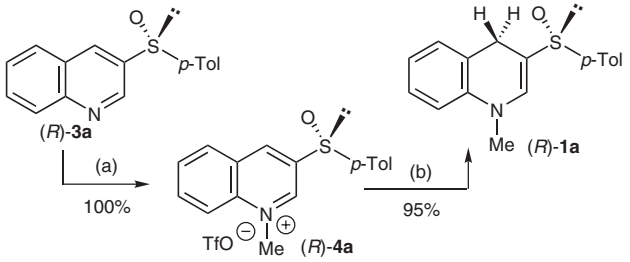
SYNLETT 2005, No. 3, pp 0441–0444
Advanced online publication: 17.01.2005
DOI: 10.1055/s-2005-862350; Art ID: D34304ST

We first focused on the preparation of **1a** by halogen–metal exchange reaction of 3-bromoquinoline (**2a**) followed by treatment of the resulting 3-metallated quinoline with (1*R*,2*S*,5*R*)-(–)-(*S*)-menthyl *p*-toluenesulfinate. Preliminary attempts to achieve bromide–magnesium exchange with isopropylmagnesium bromide at different temperatures (–78 °C to 0 °C) failed. In any case, 3-bromoquinoline and (*S*)-menthyl *p*-toluenesulfinate were recovered together with isopropyl phenyl sulfoxide. The desired (*R*)-3-*p*-tolyl sulfoxide quinoline (**3a**) was finally obtained in modest yield (30%) and excellent stereoselectivity (ee >95%)[3,4] by lithium–bromide exchange using *t*-BuLi in Et_2O at –78 °C (Scheme 1). Attempts to improve the yield by means of ate complexes[5] afforded **3a** in somewhat higher yield (55%). However, the stereoselectivity is significantly affected under these conditions, limiting seriously the synthetic interest of these ate complexes in the stereoselective preparation of sulfoxides from chiral sulfinates esters (Scheme 1).



Scheme 1 *Reagents and conditions*: (a) *t*-BuLi, Et_2O, –78 °C, then (1*R*,2*S*,5*R*)-(–)-(*S*)-menthyl *p*-toluenesulfinate; (b) Bu_3MgLi, toluene, –10 °C, 2.5 h, then (1*R*,2*S*,5*R*)-(–)-(*S*)-menthyl *p*-toluenesulfinate.

Quaternization of (*R*)-**3a** with methyl triflate in CH_2Cl_2 afforded quinolinium salt (*R*)-**4a**[6] in quantitative yield. At this stage, first attempts to reduce regioselectively quinolinium salt (*R*)-**4a** under classical conditions ($Na_2S_2O_4$/Na_2CO_3) failed, resulting in the formation of tarry materials presumably due to desulfination side reactions.[7] While the reduction conducted with $NaBH_4$ gave rise to an inseparable mixture of 1,2- and 1,4-regioisomers, we were pleased to observe the exclusive formation of 1,4-di-

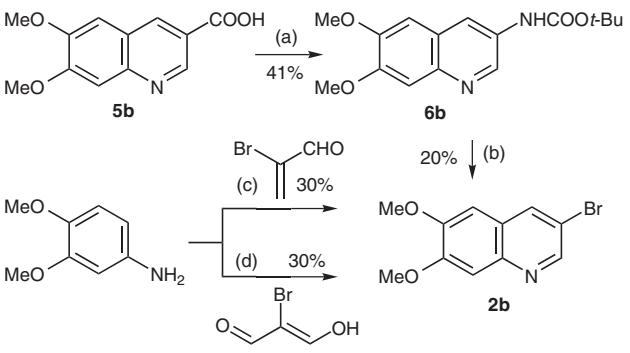


Scheme 2 *Reagents and conditions*: (a) MeOTf, CH_2Cl_2, 20 °C, 2 h; (b) BNAH, CH_2Cl_2, 20 °C, 2 h.

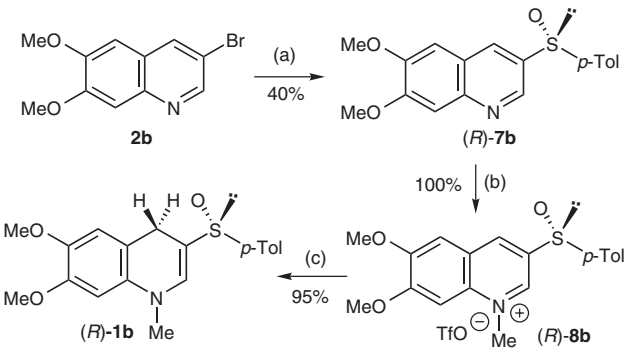
hydroquinoline **1a**[8] in high yield and under mild conditions by using *N*-benzyl-1,4-dihydronicotinamide (BNAH, Scheme 2).

We then turned our attention to the preparation of model **1b**. We anticipated that the presence of two strong electron-donating methoxy groups might increase the reducing properties of the 1,4-dihydroquinoline ring and thereby should improve the performance of these annelated models. To this end, various methods were investigated for the synthesis of the new 3-bromo-6,7-dimethoxyquinoline **2b** (Scheme 3). We first considered the possibility to have access to this key intermediate **2b** via a Curtius rearrangement of the known carboxylic acid **5b**.[9] This was accomplished by treatment of the former with diphenylphosphorazide (DPPA) in refluxing *t*-BuOH affording **6b** in 41% yield. Diazotization of **6b** with HBr–$NaNO_2$ followed by addition of molecular bromine provided the required key intermediate **2b**,[10] however, in modest yield (20%). In search of a more straightforward route, we next investigated an alternative approach by construction of the quinoline ring from 3,4-dimethoxyaniline and an appropriate 1,3-dielectrophile such as α-bromoacrolein[11] or 2-bromomalondialdehyde.[12] In both cases, bromoquinoline **2b** was isolated in 30% yield. Although the yield remains rather modest, this approach presents the advantage of furnishing the key intermediate **2b** in a single step process from readily available reagents (Scheme 3).

In contrast to 3-bromoquinoline, when 3-bromo-6,7-dimethoxyquinoline (**2b**) was treated with isopropylmagnesium bromide in THF at room temperature, metal–halogen exchange reaction took place smoothly to furnish the corresponding Grignard intermediate which was subsequently quenched with MeOD. An optimization of the reaction conditions showed that 3 equivalents of isopropylmagnesium bromide are required to drive the reaction to completion, providing 3-deuterated-6,7-dimethoxyquinoline in 100% yield. Treatment of the Grignard intermediate with (1*R*,2*S*,5*R*)-(–)-(*S*)-menthyl *p*-toluenesulfinate resulted in the formation of (*R*)-**7b**[13] in 40% yield as a single enantiomer (ee >98%).[14] Quinoline **7b** was further converted into 1,4-dihydroquinoline **1b**[16] by quaternization to give **8b**[15] which was regioselectively reduced with BNAH (Scheme 4).

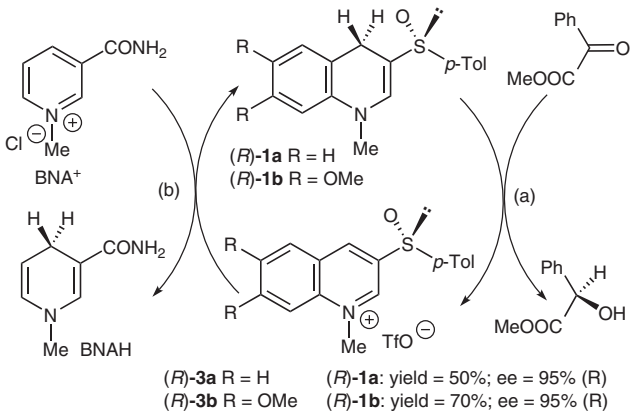


Scheme 3 *Reagents and conditions*: (a) $(PhO)_2PON_3$, Et_3N, *t*-BuOH, reflux, 24 h; (b) HBr (48%), Br_2, $NaNO_2$, –5 °C, 1 h; (c) Br_2, glacial acetic acid, reflux 1 h; (d) EtOH, HCl, reflux, 12h.



Scheme 4 *Reagents and conditions*: (a) *i*-PrMgCl (3 equiv), THF, 20 °C, 3 h, then (*1R*,*2S*,*5R*)-(–)-(*S*)-menthyl *p*-toluenesulfinate, 24 h; (b) MeOTf, CH_2Cl_2, 20 °C, 2 h; (c) BNAH, CH_2Cl_2, 20 °C, 2 h.

Performances of models **1a**,**b** were assessed in the course of the reduction of methyl benzoylformate (Scheme 5). For comparison purpose with literature data,[1] models were tested under standard conditions, i.e. in the presence of magnesium perchlorate in acetonitrile.[9] Under these conditions, both models **1a**,**b** produced (*R*)-methyl mandelate in 50% and 70% yield, respectively. As anticipated above, the presence of electron donating groups in **1b** improves to some extent the reducing properties of the model. More importantly, one may notice that the level of enantioselectivity of these new 1,4-dihydroquinolines is as high as those observed with non-annelated NADH models, affording (*R*)-methyl mandelate in up to 95% ee. One can conclude that an additional phenyl ring does not affect the high degree of stereocontrol already observed with dihydropyridine NADH mimics developed earlier.[1] Additionally, this annelation process offers the main advantage of stabilizing the reagent and hence to recycle the models. Thus, quinolinium salts (*R*)-**4a** and (*R*)-**8b** recovery was accomplished in 90% and 85% yields, respectively, after flash chromatography. Both recovered quinolinium salts were subsequently reduced to give models **1a**,**b**[17] in 95% yields. The recycled reagents were involved in the reduction of methyl benzoylformate without significant lost of their performances in terms of reactivity and enantioselectivity. One attractive perspective of this work is the potential for immobilization of these reagents on insoluble support, which should make recycling easier (Scheme 5).



Scheme 5 *Reagents and conditions*: (a) $Mg(ClO_4)_2$, MeCN, r.t., 24 h; (b) MeOTf, CH_2Cl_2, 20 °C, 2 h; (c) BNAH, CH_2Cl_2, 20 °C, 2 h.

Acknowledgment

We thank the CNRS, the région Haute-Normandie and the CRIHAN for financial and technical support.

References

(1) For leading references of NADH models bearing a sulfoxide group, see: (a) Li, J.; Liu, Y.-C.; Deng, J.-G. *Tetrahedron: Asymmetry* **1999**, *10*, 4343. (b) Kazuyuki, M.; Nishimoto, N.; Hidenobu, M.; Asuka, M.; Satoshi, O.; Yasuko, I.; Toshimasa, I.; Takeshi, I. *Chem. Commun.* **1996**, 2535. (c) Obika, S.; Nishiyama, T.; Tatematsu, S.; Miyashita, K.; Iwata, C.; Imanishi, T. *Tetrahedron* **1997**, *53*, 593. (d) Obika, S.; Nishiyama, T.; Tatematsu, S.; Miyashita, K.; Imanishi, T. *Chem. Lett.* **1996**, 853. (e) Obika, S.; Nishiyama, T.; Tatematsu, S.; Nishimoto, M.; Miyashita, K.; Imanishi, T. *Heterocycles* **1998**, 261. (f) Imanishi, T.; Obika, T.; Nishiyama, T.; Nishimoto, M.; Hamano, Y.; Miyashita, K.; Iwata, C. *Chem. Pharm. Bull.* **1996**, *44*, 267.

(2) For early reports on annelated NADH models, see: (a) Levacher, V.; Dupas, G.; Quéguiner, G.; Bourguignon, J. *Trends Heterocycl. Chem.* **1995**, *4*, 293. (b) Dupas, G.; Levacher, V.; Quéguiner, G.; Bourguignon, J. *Heterocycles* **1994**, *39*, 405. (c) Vitry, C.; Vasse, J.-L.; Levacher, V.; Dupas, G.; Quéguiner, G.; Bourguignon, J. *Tetrahedron* **2001**, *57*, 3087.

(3) Analytical data for (*R*)-**3a**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.30 (3 H, s), 7.21 (2 H, d, *J* = 8 Hz), 7.51 (3 H, m), 7.73 (1 H, m), 7.85 (1 H, d, *J* = 8 Hz), 8.05 (1 H, d, *J* = 8 Hz), 8.53 (1 H, s), 8.76 (1 H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.8, 125.6, 127.7, 128.3, 128.8, 129.9, 130.7, 131.7, 133.2, 139.5, 141.7, 142.9, 146.2, 149.1. Anal. Calcd for $C_{16}H_{13}NOS$: C, 71.88; H, 4.90; N, 5.24. Found: C, 71.78; H, 4.82; N, 5.10.

(4) Enantiomeric excesses were determined by HPLC analysis using a Chiracel OJ column (250 × 4.6 mm; 10 μm). Chromatographic conditions: eluent: heptane–2-propanol = 90:10; flow rate: 1 mL min^{-1}; pressure: 300 psi; temperature: 19 °C; UV detection: λ = 230 nm; t_R: 22 min [(*S*)-enantiomer] and 26 min [(*R*)-enantiomer].

(5) (a) Dumouchel, S.; Mongin, F.; Trécourt, F.; Quéguiner, G. *Tetrahedron Lett.* **2003**, *44*, 2033. (b) Dumouchel, S.; Mongin, F.; Trécourt, F.; Quéguiner, G. *Tetrahedron* **2003**, *44*, 8629.

(6) Analytical data for (*R*)-**4a**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.39 (3 H, s), 4.73 (3 H, s), 7.43 (2 H, d, *J* = 8 Hz), 7.81 (2 H, d, *J* = 8 Hz), 8.12 (1 H, t, *J* = 9 Hz), 8.36 (1 H, t, *J* = 9 Hz), 8.52 (2 H, m), 9.42 (1 H, s), 9.62 (1 H, s). ^{13}C NMR (75 MHz, MeOD): δ = 21.8, 47.5, 120.6, 124.3, 127.2, 131.1, 132.4, 132.8, 132.9, 139.2, 141.3, 141.7, 142.8, 144.9, 145.8, 147.8. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –80.5. HRMS (CI): *m/z* calcd for $C_{17}H_{16}NOS$: 282.0953. Found: 282.0957.

(7) Similar side reactions have already been observed during the reduction of 3-sulfoxide pyridinium salt under these conditions. See: Imanishi, T.; Hamano, Y.; Yoshikawa, H. T.; Iwata, C. *J. Chem. Soc., Chem. Commun.* **1988**, 473.

(8) Analytical data for (*R*)-**1a**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.76 (3 H, s), 3.45 (1 H, d, *J* = 19 Hz), 3.59 (3 H, s), 4.13 (1 H, d, *J* = 19 Hz), 7.05 (1 H, d, *J* = 8 Hz), 7.27 (2 H, d, *J* = 8 Hz), 7.47 (1 H, m), 7.65 (3 H, m), 7.87 (2 H, d, *J* = 8Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.7, 23.2, 38.9, 109.7, 112.9, 121.7, 123.3, 125.3, 127.7, 130.0, 130.2, 139.2, 139.3, 140.7, 140.8. HRMS (CI): *m/z* calcd for $C_{17}H_{17}NOS$: 283.1031. Found: 283.1035.

(9) Charpentier, P.; Lobrégat, V.; Levacher, V.; Dupas, G.; Quéguiner, G.; Bourguignon, J. *Tetrahedron Lett.* **1998**, *39*, 4013.

(10) Analytical data for **2b**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.98 (3 H, s), 4.00 (3 H, s), 6.92 (1 H, s), 7.34 (1 H, s), 8.10 (1 H, s), 8.68 (1 H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 56.5, 56.6, 104.5, 108.3, 115.6, 125.3, 135.8, 143.9, 149.2, 150.9, 153.0. Anal. Calcd for $C_{11}H_{10}BrNO_2$: C, 49.28; H, 3.76; N, 5.22. Found: C, 49.35; H, 3.82; N, 5.21.

(11) Smith, A. B.; Levenberg, P. A.; Jerris, P. J.; Scarborough, R. M.; Wovkulich, P. M. *J. Am. Chem. Soc.* **1981**, *103*, 1501.

(12) Trofimenko, S. *J. Org. Chem.* **1963**, *28*, 3243.

(13) Analytical data for (*R*)-**7b**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.29 (3 H, s), 3.93 (6 H, s), 7.02 (1 H, s), 7.20 (2 H, d, *J* = 8 Hz), 7.33 (1 H, s), 7.51 (2 H, d, *J* = 8 Hz), 8.29 (1 H, s), 8.62 (1 H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.8, 56.6, 56.7, 105.8, 108.3, 123.6, 125.4, 130.6, 131.4, 137.5, 142.1, 142.5, 144.2, 146.7, 151.1, 154.3. HRMS: *m/z* calcd for $C_{18}H_{17}NO_3S$: 327.0929. Found: 327.0933..

(14) Enantiomeric excesses were determined by HPLC analysis using a Chiralpak AD column (250 × 4.6 mm; 10 μm). Chromatographic conditions: eluent: heptane–2-propanol = 85:15; flow rate: 1 mL min^{-1}; pressure: 300 psi; temperature: 19 °C; UV detection: λ = 230 nm; t_R = 36 min [(*S*)-enantiomer] and 40 min [(*R*)-enantiomer].

(15) Analytical data for (*R*)-**8b**: ^{1}H NMR (300 MHz, MeOD): δ = 2.39 (3 H, s), 4.06 (3 H, s), 4.20 (3 H, s), 4.62 (3 H, s), 7.42 (2 H, d, *J* = 8Hz), 7.61 (1 H, s), 7.76 (3 H, m), 9.09 (1 H, s), 9.28 (1 H, s). ^{13}C NMR (75 MHz, MeOD): δ = 26.7, 51.7, 62.4, 63.3, 130.7, 113.6, 130.8, 132.3, 136.5, 143.7, 143.9, 144.8, 145.5, 146.6, 149.4, 158.6, 165.2. ^{19}F NMR (282 MHz, $CDCl_3$): δ = – 80.25. HRMS: *m/z* calcd for $C_{19}H_{20}NO_3S$: 342.1164. Found: 342.1165.

(16) Analytical data for (*R*)-**1b**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.32 (3 H, s), 2.94 (1 H, d, *J* = 18 Hz), 3.17 (3 H, s), 3.63 (1 H, d, *J* = 18 Hz), 3.67 (3 H, s), 3.78 (3 H, s), 6.24 (1 H, s), 6.33 (1 H, s), 6.84 (1 H, s), 7.21 (2 H, d, *J* = 8Hz), 7.43 (2 H, d, *J* = 8Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.8, 21.9, 39.2, 56.5, 56.6, 98.6, 108.5, 113.1, 113.4, 125.4, 130.0, 132.7, 139.2, 140.6, 140.9, 154.2, 148.3. HRMS (CI): *m/z* calcd for $C_{19}H_{21}NO_3S$: 343.1242. Found: 343.1249.

(17) **Typical Procedure for the Reduction of Methyl Benzoylformate with Mimics 1a,b:**
In a flask, flushed with argon, were introduced model **1b** (0.283 g, 1 mmol), MeCN (3 mL), methyl benzoylformate (142 μL, 1 mmol) and $Mg(ClO_4)_2$ (224 mg, 1 mmol). The

resulting solution was stirred at r.t. for 24 h in the dark. After addition of H_2O (10 mL), the organic solvent was evaporated under reduced pressure and the resulting aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). After drying ($MgSO_4$) and evaporation of the solvent, the residue was purified by chromatography on silica gel (eluent: Et_2O–cyclohexane = 2:1). Yield: 50%. Enantiomeric excesses were determined by HPLC analysis using a Chiracel OD column (250 × 4.6 mm; 10 μm). Chromatographic conditions: injection: 20 μl (0.5 mg of methyl mandelate in 10 mL of hexane); eluent: hexane–2-propanol = 90:10; flow rate: 1 mL min^{-1}; pressure: 300 psi; temperature: 22 °C; UV detection: λ = 235 nm; t_R = 9.2 min [(*S*)-enantiomer] and 14.8 min [(*R*)-enantiomer].