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# Stereoselective Radical-Mediated Cyclization of Norephedrine Derived *o*-Bromobenzamides: Enantioselective Synthesis of 4-Substituted 1,2,3,4-Tetrahydroisoquinolines

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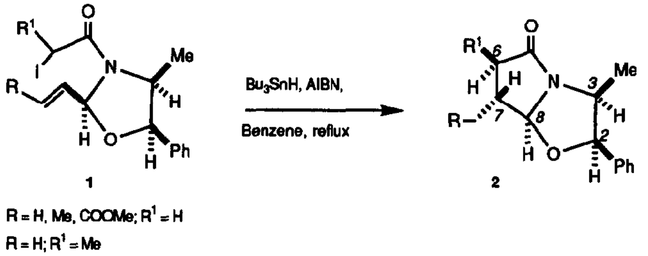
***Abstract:*** *Radical-mediated cyclization of norephedrine derived o-bromobenzamide 5 was found to be fairly stereoselective (85:15) favouring diastereoisomer trans-6. Tricyclic δ-lactams 6 were transformed in high yield into enantiomerically enriched (R)-1,2,3,4-tetrahydro-2,4-dimethylisoquinoline 8. Transition state modelling with a force field developed* ad hoc *(see also: Belvisi, L. et al. Tetrahedron 1992, 48, 3945) nicely predicts the stereochemical results.*

The understanding of the factors that control relative stereochemistry in radical cyclization reactions is a topic of continuous interest.[1,2] We recently showed that the radical mediated cyclization of norephedrine derived α-iodoamides 1 is highly stereoselective (≥97:3) favouring diastereoisomer 2 (Scheme 1).[3a,b]

**Scheme 1. Radical mediated cyclizations to give bicyclic γ-lactams 2.**

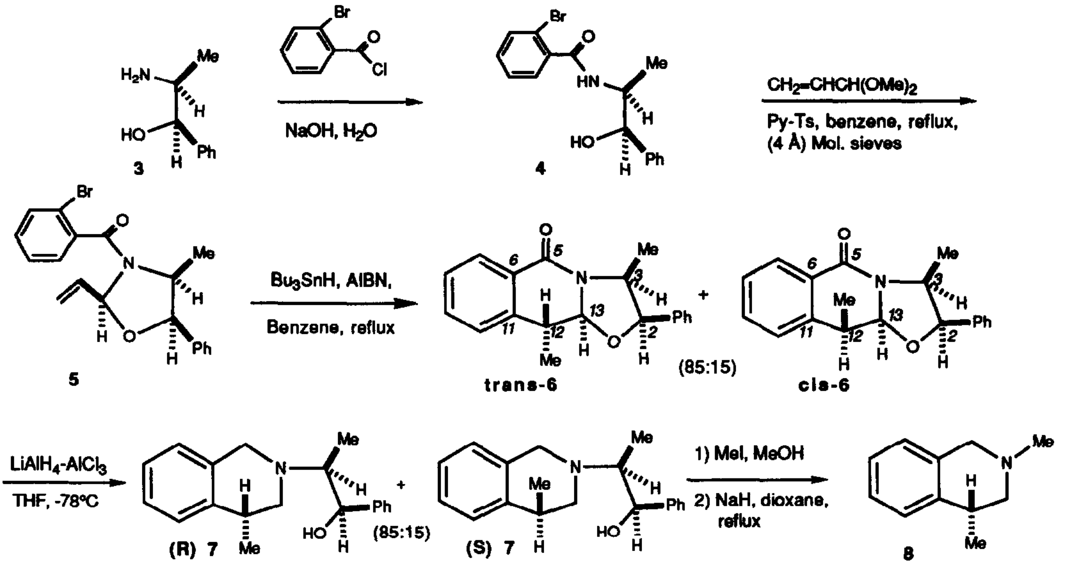


In this paper we report on the radical cyclization reaction of norephedrine derived *o*-bromobenzamide 5 to give tricyclic δ-lactams 6 and on the subsequent transformation of 6 into enantiomerically enriched (R)-1,2,3,4-tetrahydro-2,4-dimethylisoquinoline 8 (Scheme 2). The stereochemical outcome of the cyclization reaction was rationalized using a "radical force field" developed *ad hoc*, which models the transition state for the radical addition to the double bond.[3b,4]

*o*-Bromobenzamide 5 was synthesized as outlined in Scheme 2. Norephedrine 3 was treated with *ortho*-bromobenzoyl chloride (Shotten Baumann) to give benzamide 4 (95% yield). Subsequent reaction with acrolein dimethylacetal [refluxing benzene, pyridinium tosylate (Py-Ts), 4-Å mol. sieves] gave the corresponding oxazolidine 5 in very good yield (80-85%) and high *cis* selectivity (*trans* product not detected).[5]

Slow addition (7 hr) of a 0.08 M solution of Bu$_3$SnH (1.2 mol.eq.) in benzene containing a catalytic amount of AIBN (0.1 mol.eq.) to a 0.02 M refluxing benzene solution of *o*-bromobenzamide 5 (1 mol.eq.) gave, after work-up (KF-H$_2$O) and chromatography, tricyclic compounds 6 (50% yield).[6-8] The major side-product of the Bu$_3$SnH mediated reaction was the reduction product (benzamide): slower addition of Bu$_3$SnH (*e.g.* 10 h) and/or higher reaction temperature (*e.g.* refluxing toluene) did not improve the cyclization yield with respect to the competing reduction process.

**Scheme 2. Enantioselective synthesis of (R)-1,2,3,4-tetrahydro-2,4-dimethylisoquinoline 8.**



Aryl radicals are known to cyclize to alkenes with fair to good 5-*exo* : 6-*endo* selectivity,[7] and usually high 6-*exo* : 7-*endo* selectivity.[8] In our case no 7-*endo* ring closure product was detected. The ratio between the two diastereomers (**trans-6** vs. **cis-6**) was 85:15, which compares favourably with the 68.5 : 31.5 previously obtained at the same stereocentre in an attempted asymmetric synthesis of a chiral dihydroisoquinolone derivative *via* aryl radical cyclization.[8]

All new compounds have been fully characterized by $^{1}H$- and $^{13}C$-n.m.r. spectroscopy, IR, MS, and elemental analysis. Stereochemical ratios were checked by $^{1}H$ and $^{13}C$ n.m.r. analysis of the crude mixtures, and by capillary VPC. The stereostructure of tricyclic compounds **6** was proved by careful analysis of the $^{1}H$-$^{1}H$ coupling constants, and by n.O.e. difference experiments (both mono and bidimensional). This analysis was assisted by comparison with the calculated atomic distances, dihedral angles, and coupling constants of tricyclic compounds **6**, obtained using molecular mechanics in conjunction with Altona's equation[9] as implemented by MacroModel[10] (see Experimental Section). **Trans-6** shows a coupling constant $J(C_{12}\text{-}H)\text{-}(C_{13}\text{-}H) = 10.6$ Hz [calculated = 9.6] , while **cis-6** shows a value of 4.1 Hz [calculated = 3.9].

Unseparable tricyclic lactams **6** were treated with $LiAlH_4$-$AlCl_3$ ($AlH_3$) in THF at -78°C to reduce the carbonyl group and simultaneously cleave the oxazolidine ring (82-85% yield).[3a,b;11] Tetrahydroisoquinolines **7** were treated with methyl iodide (MeI) in methanol to give the corresponding N-methyl ammonium iodides (100%), which were cleaved to tetrahydroisoquinoline **8** (80%) and (1R, 2R)-*trans* -β-methylstirene oxide using sodium hydride in boiling dioxane. The enantiomeric excess (70%) of (R)-1,2,3,4-tetrahydro-2,4-

dimethylisoquinoline **8** was determined by $H^1$-NMR on the corresponding diastereomeric salts obtained with Mosher acid.[12] Fractional crystallization from n-hexane of tetrahydroisoquinolines **7** gave pure **(R) 7** (62 mg from 100 mg of 85:15 mixture), which was transformed into enantiomerically pure **8** *via* the above described procedure.

Chiral 1,2,3,4-tetrahydroisoquinolines have been the target of intense synthetic efforts:[8,13] while the 1-substituted ones are important intermediates for the synthesis of isoquinoline alkaloids, many simple 4-substituted 1,2,3,4-tetrahydroisoquinolines exhibit interesting and important pharmacological activities.[13i]

## Application of MM-Force Field Calculations to Model Transition Structures

Our approach was based on a completely "flexible model" in which all atoms are free to move and optimized in the calculation.[3b] Standard MM2 parameters as available in MacroModel[10] were used for atoms not involved in the bond breaking or bond making process. Most of the parameters for bond lengths, bond angles, and torsional angles regarding atoms involved in the reaction process were taken directly from the Spellmeyer-Houk parameter set.[4c] Parameters newly developed or modified for this force field are discussed in the following text: (a) The equilibrium bond length for the C(radical)-C(alkene) forming bond was assigned a value of 2.25 Å on the basis of the *ab initio* calculated value for the methyl radical addition to ethylene.[4i] (b) The H-$C_{sp}3$-$C_{alkene}$-$C_{alkene}$ torsional parameters were assigned values of $V_1$= 0.0; $V_2$=0.0; $V_3$= - 0.3 (atom type 5-1-2-2) and the $C_{sp}3$-$C_{sp}3$-$C_{alkene}$-$C_{alkene}$ values of $V_1$= -0.54; $V_2$=0.44; $V_3$= - 0.6 (atom type 1-1-2-2).[14b] These values were recently proposed by Houk *et al.*[14b] and Pettersson *et al.*[14c] in order to fit the *ab initio* potential energy surfaces for a series of alkenes. (c) The atom type equivalence for C(rad)-C(alkene)-C(alkene) was changed from atom type 1-atom type 1-atom type 2 to atom type 2-atom type 2-atom type 2. That is, all parameters for C(rad), C(alkene), C(alkene) not defined were assigned values equal to the analogous parameters for atom type 2. (d) The X-C(stereocentre)-C(alkene)-C(alkene) torsional parameters (X = O, N) were assigned values of $V_1$= 0.0; $V_2$=0.0; $V_3$= -1.0 for both X = N and O to improve allylic hydrogen eclipsing with the double bond.[14a]

As a result, a *6-exo* : *7-endo* ratio = 100:0 was calculated with this force field, in good agreement with the experimental result (no *7-endo* product detected). The *trans-cis* (C-12/C-13) ratio for compound **6** was predicted to be 97:3 [Boltzmann distribution at 353°K (+80°C, refluxing benzene)] using this modified force field, while the experimental ratio is only 85:15. The *trans-cis* (C-12/C-13) ratio is particularly influenced by the C(arom)-C(rad)-C(alkene)-C(alkene) torsional parameters which were assigned values of $V_1$= 0.0; $V_2$=1.25; $V_3$= 0.0 on the basis of the aforementioned equivalence to C(arom)-C(alkene)-C(alkene)-C(alkene). By changing $V_2$ from 1.25 to 0.00 the *trans-cis* ratio changes from 97:3 to 60:40. The experimental *trans-cis* ratio (85:15) can therefore be reproduced using an intermediate $V_2$ value (0.6). The transition structure models of the radical cyclization leading to compounds **6** are shown in Scheme 3.

The construction of an improved force field suitable for all radical cyclization reactions is currently underway in our laboratory.

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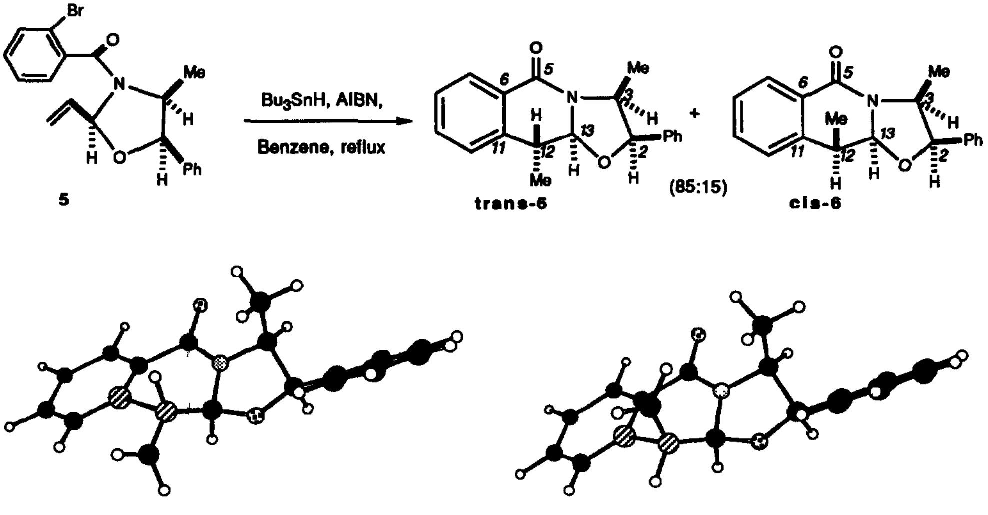
**Scheme 3. Transition structure models of the radical cyclization leading to compounds 6.**



*trans* 0.0 kcal $mol^{-1}$  *cis* 1.28 kcal $mol^{-1}$

## Computational Section

Using the Spellmeyer-Houk parameter set,[4c] modified as described in the main text, MacroModel[10] was used to generate accessible transition structures for the radical cyclization reaction of interest. The conformational space was searched with the Still-Chang-Guida usage-directed torsional Monte Carlo search[15] as implemented by the BATCHMIN program.[16] Two separate Monte Carlo runs were necessary: one for the structures leading to the *trans* compound and the other for the ones leading to the *cis* compound. An alternative procedure made use of Multiconformer[17] using a 30° or 60° resolution for each dihedral angle. The two methods usually gave comparable results and were used in concert to make sure that our conformational analysis was not dependent on the search method used.[18] The transition structures found by these searches were analyzed by a Boltzmann distribution at +80°C (353°K) of the various conformers leading to each of the possible stereoisomers. 7-*Endo* transition structures were all higher in energy (> 7 kcal $mol^{-1}$), and are not reported.

## Experimental Section

All new compounds were fully characterized by $^{1}H$ and $^{13}C$ n.m.r. spectroscopy (reported), IR, MS, and elemental analysis (reported only for selected compounds).

**Synthesis of *ortho*-bromobenzamide** 4. A solution of L-Norefedrine 3 (3.30 g, 21.8 mmol) in water (33 ml) was treated at 0°C with 2 N NaOH in water (10.0 ml, 20.0 mmol) and 2–bromobenzoyl chloride (4.0 g, 18.22 mmol). The two reagents were added slowly, simultaneously, and under vigorous stirring, so that the pH was kept constantly around 7. At the end of the addition the temperature was raised to 25°C, and the mixture was stirred overnight at room temperature. The white precipitate (Norefedrine *ortho*-bromobenzamide) was filtered under vacuum, washed with water, and dried under vacuum in the presence of $P_2O_5$ (5.79 g, 95% yield). $^1$H-NMR (200 MHz, $CDCl_3$) $\delta$: 1.05 (3H, $CH_3$, d, J=6.5 Hz), 3.1 (1H, OH, br.s), 4.55 (1H, NCH, m), 5.05 (1H, CHO, d, J=3.5 Hz), 6.18 (1H, NH, d, J=6.0 Hz), 7.20-7.65 (9H, Ar-H, m). Anal. Calcd for $C_{16}H_{16}NO_2Br$: C, 57.50; H,4.83 ; N,4.19 . Found: C,57.40 ; H,4.89; N,4.11.

**Oxazolidine 5.** A solution of Norefedrine *ortho*-bromobenzamide (4.0 g, 12.0 mmol) in dry benzene (75 ml) was treated with acrolein dimethylacetal (4.24 ml, 36.0 mmol) and pyridinium tosylate (0.75 g, 3.0 mmol). The mixture was stirred and heated at reflux under nitrogen for 10 hr using a reflux condenser equipped with 4-Å molecular sieves. The crude mixture was then evaporated, and the residue purified by flash-chromatography (n-hexane/ethyl acetate 4:1) to give the corresponding oxazolidine **5** (3.8 g, 85%). $^1$H-NMR (200 MHz, $CDCl_3$) $\delta$: 0.70 (50% 3H, $CH_3$-C-N, d, J=6.0 Hz), 1.0 (50% 3H, $CH_3$-C-N, d, J=6.0 Hz), 3.83 (50% 1H, CH-N, quint, J=6.0 Hz), 4.64 (50% 1H,CH=C,d,J=17.0 Hz), 4.84 (50% 1H, CH-N, quint, J=6.0 Hz), 4.99 (50% 1H,CH=C,d, J=10.0 Hz), 5.23 (50% 1H, CH-O, d,J=4.5 Hz), 5.24 (50% 1H, CH-O, d,J=8.5 Hz), 5.37 (50% 1H, N-CH-O, d, J=7.5 Hz), 5.49 (50% 1H,CH=C,d, J=10.0 Hz), 5.78 (50% 1H, CH=C, d, J=17.0 Hz), 6.01 (50% 1H, N-CH-O, d, J=5.5 Hz), 6.16 (50% 1H,C*H*=$CH_2$, dd, J=10.0, 17.0 Hz), 6.18 (50% 1H,C*H*=$CH_2$, dd, J=10.0, 17.0 Hz), 7.20-7.40 (9H, Ar-H, m). The $^1$H-NMR spectrum was recorded in $C_5D_5N$ at 80°C: at this temperature coalescence of the signals due to the presence of Z (50%) and E (50%) amide bond was observed. Anal. Calcd for $C_{19}H_{18}NO_2Br$: C, 61.30; H, 4.87; N, 3.76. Found: C, 61.19; H, 4.90; N, 3.70.

### $Bu_3SnH$ Mediated Radical Cyclization. Synthesis of Tricyclic Lactams 6.

A 0.08 M solution of $Bu_3SnH$ (1.46 ml, 5.5 mmol) in benzene (69.0 ml) containing AIBN (75.5 mg, 0.46 mmol) was slowly added via syringe pump (7 hr) to a boiling 0.02 M solution of oxazolidine **5** (1.70 g, 4.6 mmol) in benzene (230 ml), under nitrogen, with stirring. At the end of the addition, the mixture was cooled to room temperature, treated with a saturated aqueous solution of KF (150 ml) and stirred for 2 hr. The two layers were separated, the aqueous phase extracted with ethyl ether, and the combined organic extracts were dried ($Na_2SO_4$) and evaporated. The crude product was purified by flash-chromatography (benzene 100%; benzene : *i*-$Pr_2O$ 90:10) to give an inseparable mixture (1.1 g) of the tricyclic lactams **6** and of the reduction product (benzamide). A solution of this mixture (1.1 g) in dichloromethane (74 ml) was treated at room temperature, under nitrogen, with stirring, with $Me_3NO$-$2H_2O$ (0.832 g, 7.42 mmol) and $OsCl_3$ (110 mg, 0.375 mmol). The reaction mixture was then treated with a $NaHSO_3$ saturated aqueous solution, the two layers were separated, the aqueous phase extracted with ethyl ether, and the combined organic extracts were dried ($Na_2SO_4$) and evaporated. The crude product was purified by flash-chromatography (n-hexane-ethyl acetate 6:4) to give **tricyclic lactams 6** (0.688 g, 51%) as an inseparable mixture of ***trans*-6** and ***cis*-6** (85:15). ***Trans*-6** $^1$H-NMR (200 MHz, $CDCl_3$) $\delta$: 0.96 (3H, $CH_3$-C-N, d, J=6.3 Hz), 1.58 (3H, C*H*$_3$-CH-C=, d, J=6.0 Hz), 3.17 (1H, $CH_3$-C*H*-C=, dq, J=6.0, 10.6 Hz), 4.54 (1H, CH-N, dq, J=6.1, 6.3 Hz), 4.87 (1H, O-CH-N, d, J=10.6 Hz), 5.19 (1H, CH-O, d, J=6.1 Hz), 7.25-8.20 (9H, Ar-H, m). N.O.E. difference experiments, positive response: C(2)-H and C(13)-H; C(2)-H and C(12)-Me; C(3)-Me and C(12)-H. ***Cis*-6** $^1$H-NMR (200 MHz, $CDCl_3$) $\delta$: 1.29 (3H, $CH_3$-C-N, d, J=6.8 Hz), 1.61 (3H, C*H*$_3$-CH-C=, d, J=6.0 Hz), 3.3 (1H, $CH_3$-C*H*-C=, dq, J=6.0, 4.1 Hz), 4.54 (1H, CH-N, m), 5.25 (1H, CH-O, d, J=6.4 Hz), 5.40 (1H, O-CH-N, d, J=4.1 Hz), 7.25-8.20 (9H, Ar-H, m). ***Trans*-6 and *cis*-6 mixture** $^{13}$C-NMR (200 MHz, $CDCl_3$) δ: 12.847 (85% $CH_3$), 13.79 (15% $CH_3$), 14.71 (15% $CH_3$), 15.17 (85% $CH_3$), 37.25 (15% CH), 38.88 (85% CH), 53.88 (15% CH), 54.82 (85% CH), 81.60 (85% CH), 81.82 (15% CH), 87.52 (15% CH), 90.47 (85% CH), 124.83-132.27 (C=). IR ($CHCl_3$) ν (selected data): 3400, 3000, 2940, 2880, 1650, 1610, 1470, 1430, 1090, 980, 810 cm$^{-1}$. Calculated[9,10] and experimental coupling constants: Expt. J [C(12)-H / C(13)-H/ trans] = 10.6 Hz; calcd. J [C(12)-H / C(13)-H/ trans] = 9.6 Hz; Expt. J [C(12)-H / C(13)-H/ cis] = 4.1 Hz; calcd. J [C(12)-H / C(13)-H/ cis] = 3.9 Hz. Anal. Calcd for $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53; N, 4.77. Found: C, 77.65; H, 6.68; N, 4.70. MS (CI, butane): *m/e* 294 ($M^+$+1).

**Synthesis of tetrahydroisoquinolines 7 and 8.**

A suspension of $LiAlH_4$ (0.082 g, 2.15 mmol) in dry THF (10 ml) was treated under nitrogen, with stirring, with $AlCl_3$ (0.095 g, 0.712 mmol). The mixture was stirred at room temperature until LiCl precipitation was completed. To this mixture, cooled to -78°C, a solution of tricyclic lactams **6** (0.28 g, 0.95 mmol) in THF (9 ml) was added dropwise. After 4 hr at -78°C, the reaction was quenched by subsequent addition of water (0.107 ml), 15% NaOH (0.107 ml), and water (0.214 ml). The resulting mixture was treated with $Na_2SO_4$, diluted with ethyl ether, and stirred for 1 hr. Filtration of the various salts and evaporation of the organic phase gave a crude product which was purified by flash chromatography (n-hexane:ethyl acetate 90:10) to yield **tetrahydroisoquinolines 7** (0.230 g, 85%) as a 85:15 mixture. Fractional crystallization from n-hexane of tetrahydroisoquinolines **7** gave pure **(R) 7** (142 mg from 230 mg of 85:15 mixture). $^1$H-NMR (200 MHz, $CDCl_3$) δ: 0.98 (3H, $CH_3$-C-N, d, J=6.8 Hz), 1.35 (3H, $CH_3$-CH-C=, d, J=6.7 Hz), 2.58 (2H, MeCH-$CH_2$-N, m), 2.90 (1H, CH-N, dq, J=4.0, 6.8 Hz), 3.05 (1H, Me-*CH*-C=, m), 3.65 (1H, OH), 3.81 (1H, N-CH*H*-C=, d, J=15.0 Hz), 3.90 (1H, N-CH*H*-C=, d, J=15.0 Hz), 5.05 (1H, CHO, d, J=4.0 Hz), 7.0-7.5 (9H, Ar-H, m). $^{13}$C-NMR (200 MHz, $CDCl_3$) δ: 10.0 ($CH_3$), 20.9 ($CH_3$), 33.5 (CH), 54.2 ($CH_2N$), 55.2 ($CH_2N$), 64.0 (CHN), 72.5 (CHO), 126-128 (CH=), 140 (C=), 141.1 (C=). IR ($CHCl_3$) ν (selected data): 3400, 3000-2800, 1490, 1380, 900 cm$^{-1}$. Anal. Calcd for $C_{19}H_{23}NO$: C, 81.10; H, 8.24; N, 4.98. Found: C, 80.78; H, 8.00; N, 5.09. MS (F.A.B.$^+$) = *m/e* 282 ($M^+$+1, 85%), 280 (M-1, 79%), 174 (M-$C_7H_8O$, 100%).

(S) 7 $^1$H-NMR (200 MHz, $CDCl_3$) δ (selected data): 4.97 (1H, CHO, d, J=4.0 Hz). $^{13}$C-NMR (200 MHz, $CDCl_3$) δ (selected data): 33.4 (CH), 54.5 ($CH_2N$), 55.5 ($CH_2N$), 64.1 (CHN), 72.6 (CHO).

A solution of tetrahydroisoquinoline **(R) 7** (0.085 g, 0.3 mmol) in methanol (3.0 ml) was treated with methyl iodide (0.187 ml, 3.0 mmol). After stirring at room temperature for 48 hr, the solvent was evaporated under reduced pressure to yield the corresponding **N-methyl ammonium iodide** (0.128 g, 100%). Anal. Calcd for $C_{20}H_{26}INO$: C, 56.74; H, 6.19; N, 3.31. Found: C, 56.54; H, 6.30; N, 3.30.

A suspension of **N-methyl ammonium iodide** (0.126 g, 0.3 mmol) in dioxane (6.0 ml) was treated with NaH (50% in oil, 0.017 g, 0.36 mmol). The mixture was stirred at reflux for 3 hr, then cooled to room temperature, diluted with ethyl ether (15 ml) and washed with 5% $Na_2SO_4$ aqueous solution (2 x 5 ml). Evaporation of the solvent gave a crude mixture which was purified by flash chromatography (n-hexane-EtOAc 8:2 to 4:6) to yield (1R, 2R)-*trans* -β-methylstirene oxide and **(R)-1,2,3,4-tetrahydro-2,4-dimethylisoquinoline 8**, which was further purified by chromatography on [70-230 mesh ASTM]-neutral alumina (n-hexane-ethyl acetate 7:3) (0.038 g, 80%). $^1$H-NMR (200 MHz, $CDCl_3$) δ: 1.29 (3H, $CH_3$-C, d, J=6.9 Hz), 2.30 (1H, MeCH-CH*H*-N, dd, J=11.4, 7.1 Hz), 2.40 (3H, $CH_3$-N, s), 2.77 (1H, MeCH-CH*H*-N, dd, J=11.4, 5.15 Hz), 3.06 (1H, $CH_3$-C*H*-$CH_2$N, ddq, J=6.9, 5.15, 7.1 Hz), 3.50 (2H, N-$CH_2$-C=, s), 6.9-7.3 (4H, Ar-H, m). $^{13}$C-NMR (200 MHz, $CDCl_3$) δ: 20.59 ($CH_3$), 32.92 (CH), 46.21 ($CH_3$-N), 59.61 ($CH_2$-N), 60.79 ($CH_2$-N), 125.54 (CH=), 126.22 (CH=), 126.28 (CH=), 127.38 (CH=). IR ($CHCl_3$) ν (selected data): 2940, 2780, 1460, 1445 $cm^{-1}$. Anal. Calcd for $C_{11}H_{15}N$: C, 81.94; H, 9.38; N, 8.69. Found: C, 81.90; H, 9.50; N, 8.60. Tetrahydroisoquinoline **8** obtained starting from pure **(R)** **7** : $[\alpha]_D^{25}$= +35.5 (c 1.1, $CHCl_3$). Tetrahydroisoquinoline **8** obtained starting from 85:15 **(R)** **7**:**(S)** **7** : $[\alpha]_D^{25}$= +24.8 (c 1.6, $CHCl_3$). **Tetrahydroisoquinoline 8-HCl** MS (F.A.B.$^+$) = *m/e* 162 ($M^+$, 100%), 91 ($C_7H_7$, 31%).

### Enantiomeric purity of (R)-1,2,3,4-tetrahydro-2,4-dimethylisoquinoline 8.

An equimolar amount of **tetrahydroisoquinoline 8** (6.5 mg, 0.040 mmol) and Mosher acid[12] (9.4 mg, 0.040 mmol) were mixed in ethyl acetate (0.1 ml). Evaporation of the solvent under reduced pressure gave a salt (15.9 mg, 0.040 mmol).

(a) Using tetrahydroisoquinoline **8** [**70%** e.e., $[\alpha]_D^{25}$= +24.8 (c 1.6, $CHCl_3$)], obtained starting from 85:15 **(R)** **7**:**(S)** **7**. $^1$H-NMR (200 MHz, $CDCl_3$) δ: 1.31 (3H, C*H3*-CH, d, J=6.5 Hz), 2.70-2.75 (1H, CH-CH*H*-$N^+$, m, and 85% 3H, $CH_3N^+$, s), 2.80 (15% 3H, $CH_3N^+$, s), 3.3-3.5 (3H, $CH_3O$, s, and 1H, CH-CH*H*-N, m, and 1H, $CH_3$C*H*, m), 4.07 (1H, NCH*H*-C=, AB system, J=14.1 Hz), 4.27 (1H, NCH*H*-C=, AB system, J=14.1 Hz), 7.0-7.6 (9H, ArH,m).

(b) Using tetrahydroisoquinoline **8** [**100%** e.e., $[\alpha]_D^{25}$= +35.5 (c 1.1, $CHCl_3$)], obtained starting from pure **(R)** **7**. $^1$H-NMR (200 MHz, $CDCl_3$) δ: 1.31 (3H, C*H3*-CH, d, J=6.5 Hz), 2.70-2.75 (1H, CH-CH*H*-$N^+$, m, and 100% 3H, $CH_3N^+$, s), 3.3-3.5 (3H, $CH_3O$, s, and 1H, CH-CH*H*-N, m, and 1H, $CH_3$C*H*, m), 4.07 (1H, NCH*H*-C=, AB system, J=14.1 Hz), 4.27 (1H, NCH*H*-C=, AB system, J=14.1 Hz), 7.0-7.6 (9H, ArH,m).

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