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Lithiation of *N*-Alkyl-(*o*-tolyl)aziridine: Stereoselective Synthesis of Isochromans[§]

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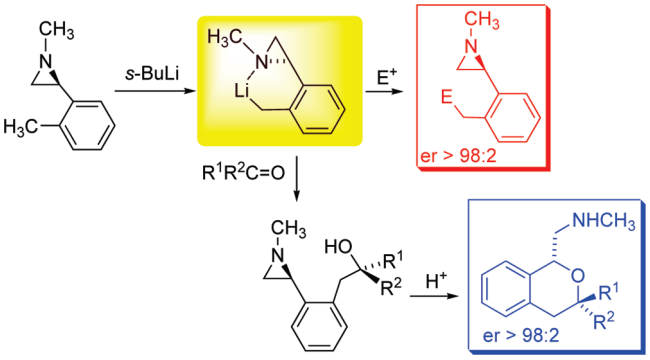
Received June 8, 2009



The lithiation reaction of *o*-tolylaziridine **1** has been investigated by using the aziridine ring capability to act as a directing metalation group. Trapped with electrophiles, the resulting *o*-aziridinyl benzyllithium **1-Li** gives access to several functionalized aziridines **2a**−**j**. The hydroxyalkylated derivatives **2d**−**j** were converted into important scaffolds such as isochromans **3a**−**d**. A stereoselective preparation of isochromans (*R*)-**3b**, (1*R*,3*S*)-**3d**, and (1*R*,3*R*)-**3d** has been developed starting from enantioenriched *o*-tolylaziridine.

Synthesizing substituted aziridines and their derivatives by using the lithiation/electrophile trapping sequence is a useful synthetic methodology.[1] Within this context, we have recently reported that *N*-alkylarylaziridines are smoothly α- and/or *o*-lithiated depending upon the aziridine ring substitution, solvent, and temperature.[2,3] Specifically, the previously described directing-metalation ability of the aziridine group, combined with its bias to give nucleophilic ring-opening, has been successfully exploited for the preparation of phthalans.[4,5]

Six-membered-ring oxygen-bearing aromatic heterocycles with isochroman and related skeletons occur in nature and among bioactive compounds of interest, including drugs (medicines, agrochemicals, etc.) and drug candidates.[6] D_1 dopaminergic agonists with 1,3-disubstituted isochroman skeletons are among the few D_1 agonists known to date. The synthesis of 1,3-disubstituted isochromans with an aminomethyl substituent typically requires multistep oxa-Pictet−Spengler cyclizations.[7]

In exploiting the lithiation-trapping sequence of arylaziridines, we thought that 1-aminomethyl-3-alkyl(or aryl)-substituted isochromans could be prepared simply by lateral-lithiation of *o*-tolyl-substituted *N*-alkyl-arylaziridines, trapping with carbonyl compounds, and finally cyclization (Scheme 1).[8]

The reaction of 1-methyl-2-(*o*-tolyl)aziridine **1** with *s*-BuLi in THF at −78 °C in the presence of TMEDA gave exclusively the thermodynamically favored[9,10] lithiated intermediate **1-Li** as proved by trapping with D_2O to furnish deuterated derivative **2a** (>98% D) (Table 1). Additionally, lithiated intermediate **1-Li** reacted with other electrophiles (Table 1) to give ortho-functionalized aziridines **2b**−**j**.

[§] Dedicated to Professor Peter Stanetty of the Vienna University of Technology for his 65th birthday.

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(8) Some recent examples on lateral lithiation: (a) Aliyenne, A. O.; Kraiem, J.; Kacem, Y.; Hassine, B. B. *Tetrahedron Lett.* **2008**, *49*, 1473–1475. (b) Wilkinson, J. A.; Raiber, E. A.; Ducki, S. *Tetrahedron* **2008**, *64*, 6329–6333. (c) Clayden, J.; Turner, H.; Helliwell, M.; Moir, E. *J. Org. Chem.* **2008**, *73*, 4415–4423. (d) Hogan, A.-M. L.; Tricotet, T.; Meek, A.; Khokhar, S. S.; O'Shea, D. *J. Org. Chem.* **2008**, *73*, 6041–6044. (e) Uchida, K.; Fukuda, T.; Iwao, M. *Tetrahedron* **2007**, *63*, 7178–7186. (f) Sae-Lao, P.; Kittakoop, P.; Rajivroongit, S. *Tetrahedron Lett.* **2006**, *47*, 345–348. (g) Burkhart, D. J.; Zhou, P.; Blumenfeld, A.; Twamley, B.; Natale, N. R. *Tetrahedron* **2001**, *57*, 8039–8046. (h) Kowalczyk, B. A. *Synthesis* **2000**, 1113–1116. (i) Wang, C.-C.; Li, J. J.; Huang, H.-C.; Lee, L. F.; Reitz, D. B. *J. Org. Chem.* **2000**, *65*, 2711–2715.

(9) It is likely that the nitrogen-induced stabilization in the six-membered cyclic lithiated intermediated **1-Li**, and Complex Induced Proximity Effect could act sinergically making the lateral benzylic position the kinetically and thermodynamically favored one, see: (a) Clayden J., In *Organolithiums: Selectivity for Synthesis*; Pergamon: Oxford, UK, 2002; Chapter 2. (b) Whisler, M. C.; MacNeil, S.; Snieckus, V.; Beak, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 2206–2225.

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DOI: 10.1021/jo9011943 Published on Web 07/17/2009

SCHEME 1. Retrosynthetic Approach to Isochromans

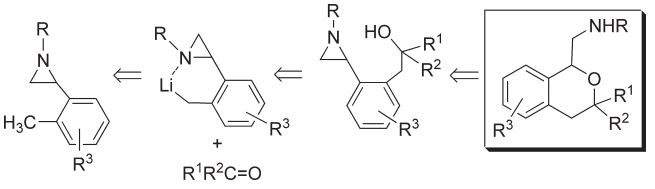
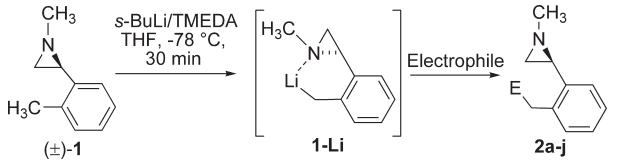


TABLE 1. Lithiation/Electrophile Trapping of *o*-Tolylaziridine 1



aziridine **2**	electrophile	yield (%)[a]	dr[b]
2a	D_2O	95	
2b	CH_3I	95	
2c	$CH_3(CH_2)_2I$	95	
2d	acetone	57	
2e	cyclohexanone	21	
2f	benzophenone	73	
2g	propiophenone	52[c]	70/30
2h	*t*-BuCHO	82[d]	80/20
2i	4-Cl-C_6H_4CHO	85[d]	70/30
2j	furfural	80[d]	70/30

[a]Isolated yield. [b]Diastereomeric ratio calculated on the ^{1}H NMR of the crude reaction mixture. [c]Only the major diastereoisomer was isolated. [d]Overall yield of a separable mixture of stereoisomers.

The reaction with carbonyl compounds gave hydroxyalkylated derivatives **2d**−**j** with a low stereoselectivity. Fortunately the diastereoisomers could be easily separated by flash chromatography.

The results of the lithiation/trapping sequence above clearly demonstrate the directing group ability of the aziridine ring. It is, indeed, worth pointing out that the lithiation of the related acyclic derivative, 2-*N*,*N*-dimethylaminomethyltoluene, is comparatively much slower requiring more than 6 h at room temperature for complete deprotonation.[8f,9]

The *ortho*-hydroxyalkylated aziridines **2e**−**j** were cyclized to prepare a range of isochromans (Scheme 2).[11]

Several proton sources [TFA, $(COOH)_2$, HCOOH, H_2SO_4] and solvents (THF, CH_3CN, Et_2O, dioxane/H_2O 4/1) were examined in order to find the best conditions. Acetic acid either as proton source or reaction solvent at room temperature proved to be superior with better yields and cleaner reactions for the preparation of the isochromans **3a**−**d** (Table 2). In the case of compounds **2h** and **2i** both diastereoisomers were cyclized and the relative configurations of the isochromans and the corresponding hydroxyalkylated aziridines were determined.[12]

(11) Vaulx, R. L.; Jones, F. N.; Hauser, C. R. *J. Org. Chem.* **1964**, *29*, 1387–1391.

(12) Following a referee's suggestion, the one-pot cyclization was performed by addition of 2 mL of acetic acid to the reaction mixture (1 mmol scale) obtained after quenching of the lithiated intermediate with benzophenone. The complete conversion of **2f** into **3b** was observed and the isochroman was isolated with 40% yield.

SCHEME 2. Acid-Catalyzed Cyclization to Isochromans

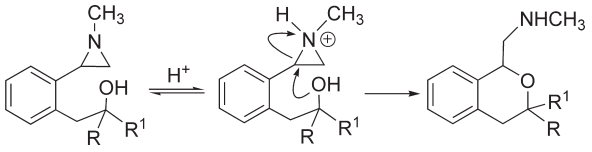
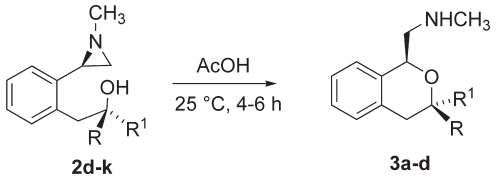


TABLE 2. Preparation of Isochromans 3



aziridine **2**	benzopyrane **3**	R	R^1	yield (%)[a]
2e	**3a**	$-(CH_2)_5-$		80
2f	**3b**[b]	Ph	Ph	98
(*R**,*R**)-**2h**[c]	(*R**,*S**)-**3c**	*t*-Bu	H	80
(*R**,*S**)-**2h**[d]	(*R**,*R**)-**3c**	H	*t*-Bu	80
(*R**,*R**)-**2i**[c]	(*R**,*S**)-**3d**	4-Cl-C_6H_4	H	85
(*R**,*S**)-**2i**[d]	(*R**,*R**)-**3d**	H	4-Cl-C_6H_4	60

[a]Calculated by ^{1}H NMR analysis of the crude. [b]See ref 12. [c]Major diastereoisomer. [d]Minor diastereoisomer.

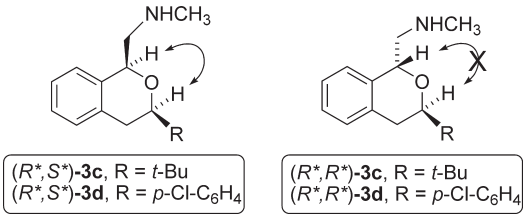


FIGURE 1. Selected NOE interactions for stereochemical assignment.

The relative stereochemistry of isochromans (*R**,*S**)-**3c**,**d** and (*R**,*R**)-**3c**,**d** was ascertained by selective 1D NOESY experiments,[13] the major isomers having an (*R**,*S**) relative configuration (Figure 1).

As illustrated in Scheme 3, considering that the reaction occurs exclusively with an S_N2 mechanism,[14] two possible pathways could be hypothesized: the first involves nitrogen protonation and ring-opening by nucleophilic addition of the hydroxy group to the benzylic α-carbon (path a, Scheme 3), and the second involves the intermediacy of an acetate followed by nucleophilic displacement of acetic acid by the hydroxy group (path b, Scheme 3).[15]

These mechanistic pathways were distinguished by determining the stereochemistry of the major isomer **2i** by X-ray analysis.[16] When diastereomerically pure (*R**,*R**)-**2i** was

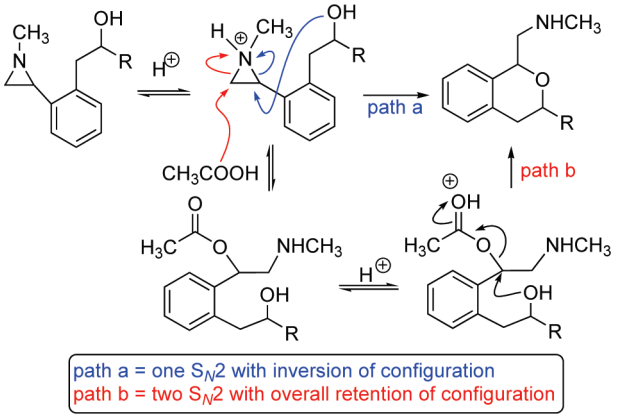
(13) Neuhaus, D.; Williamson, M. In *The Nuclear Overhauser Effect in Structural and Conformational Analysis*; VCH: New York, 1989; p 264.

(14) This assumption rises considering that the reaction on pure diastereomers of (*R**,*R**)-**2h**,**i** and (*R**,*S**)-**2h**,**i** is highly stereospecific giving only one isochroman. Likely, a mixture of diastereomeric isochromans should have been obtained with an S_N1 mechanism.

(15) Such hypothesis could be put forward since the GC-MS analysis of the crude reaction mixture showed a side product deriving from the addition of CH_3COOH to the starting aziridine **2**.

(16) CCDC 733354 contains the supplementary crystallographic data for compound (*R**,*R**)-**2i**. These data have been deposited with the Cambridge Crystallographic Data Centre and can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif.

SCHEME 3. Reaction Pathways for the Intramolecular Cyclization of Hydroxyalkylated Aziridines



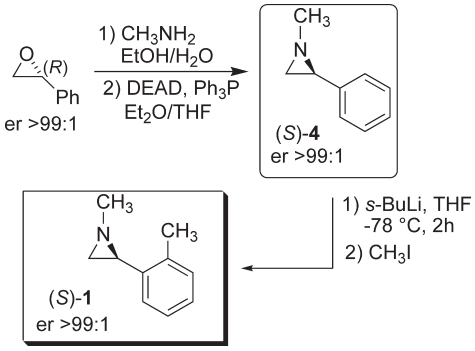
dissolved in acetic acid only isochroman (*R**,*S**)-**3d** was obtained, likely as the result of a single S_N2 reaction with one inversion of configuration (path a, Scheme 3). This result, with NMR evidence, allowed the assignment of the relative configuration (*R**,*R**) to the major isomers of the hydroxyalkylated aziridines **2h**−**j**.

Aware of the importance of the biological activities of some isochroman derivatives,[17] and that the control of their stereochemistry could be an important goal in planning a synthesis of such a scaffold, we turned our attention to the chiral version of this lateral-lithiation/electrophile trapping sequence.

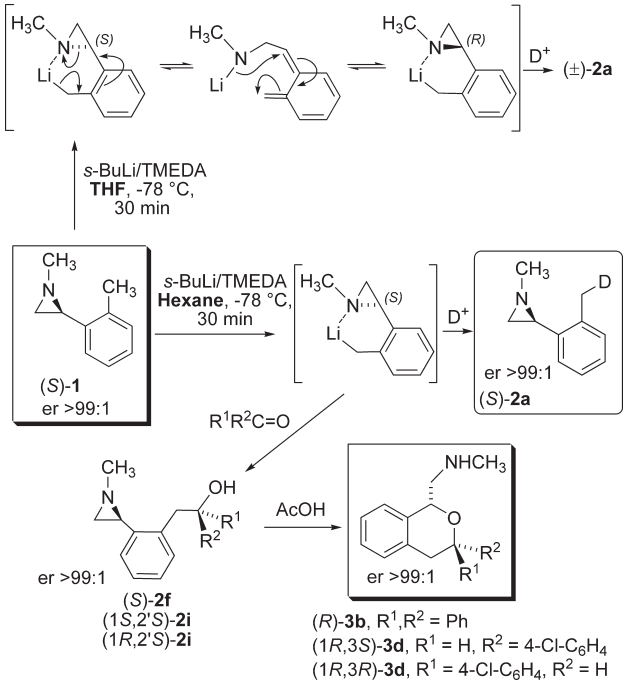
The first step was the synthesis of the enantioenriched aziridine (*S*)-**4** ($[\alpha]_D$ +178 (*c* 1.5, $CHCl_3$)),[18] which was obtained in >98:2 er starting from commercially available (*R*)-(−)-styreneoxide (Scheme 4). Enantioenriched aziridine (*S*)-**4** was subjected to an ortho-lithiation/methylation sequence to give enantioenriched *o*-tolylaziridine (*S*)-**1**.[4] Surprisingly, when aziridine (*S*)-**1** was subjected to lithiation under the same conditions (*s*-BuLi/TMEDA THF, −78 °C, 30 min) used for (±)-**1**, a completely racemic sample was obtained upon quenching with a deuterium source (Scheme 5).

A possible explanation for the observed racemization could be an aziridine ring-opening-promoted resonance (Scheme 4).[19] Reclosing to the aziridine might then occur on both the enantiotopic faces of the double bond causing racemization. In striking contrast, it was found that when the same lithiation/electrophile trapping sequence was performed in a less polar solvent such as hexane, no racemization occurred and highly enantioenriched (*S*)-**2a** was obtained. Likely the solvent could affect the nature and the

SCHEME 4. Preparation of Optically Active *o*-Tolylaziridine (*S*)-1



SCHEME 5. Lateral Lithiation of Chiral *o*-Tolylaziridine (*S*)-1



aggregation state of the lithiated intermediate disfavoring racemization.[20] The trapping reaction with carbonyl compounds gave chiral derivatives (*S*)-**2f**, (1*S*,2′*S*)-**2i**, and (1*R*,2′*S*)-**2i** which were subsequently converted into the corresponding enantioenriched isochromans (*R*)-**3b**, (1*R*,3*S*)-**3d**, and (1*R*,3*R*)-**3d**.[21]

In conclusion, this work reports a new and convenient methodology for the preparation of ortho-functionalized aziridines based on the benzylic lithiation of simple and easily available *o*-tolylaziridines. The role of the aziridine ring as a directing group is significant in showing a higher efficiency relative to open chain benzylamines. The usefulness of the hydroxyalkylated aziridines has been demonstrated with the preparation of isochroman derivatives with controlled stereochemistry and in highly enantioenriched form.

(17) (a) Schoenleber, R. W.; DeNinno, M. P.; Basha, F. Z.; Ehrlich, P. P.; Perner, R. J.; Meyer, M. D.; Campbell, J. R.; Martin, Y. C.; Stout, D. M.; De Bernardis, J. F.; Morton, H. E.; Michaelides, M. Patent WO 96/38435, **1996**. (b) Len, C.; Pilard, S.; Lipka, E.; Vaccher, C.; Dubois, M. P.; Shrinska, Y.; Tran, V.; Rabiller, C. *Tetrahedron* **2005**, *61*, 10583–10595. (c) TenBrink, R. E.; Bergh, C. L.; Duncan, J. N.; Harris, D. W.; Huff, R. M.; Lahti, R. A.; Lawson, C. F.; Lutzke, B. S.; Martin, I. J.; Rees, S. A.; Schlachter, S. K.; Sih, J. C.; Smith, M. W. *J. Med. Chem.* **1996**, *39*, 2435–2437. (d) DeNinno, M. P.; Schoenleber, R. W.; Asin, K. E.; MacKenzie, R.; Kababian, J. W. *J. Med. Chem.* **1990**, *33*, 2950–2952.

(18) Fujita, S.; Imamura, K.; Nozaki, H. *Bull. Soc. Chem. Jpn.* **1971**, *44*, 1975–1977.

(19) The resonance effect is often invoked for this kind of intermediate even if their structures are still unknown, see: (a) Clark, R. D.; Jahangir, A. *Org. React.* **1995**, *47*, 1–314. (b) Ito, Y.; Nakatsuka, M.; Saegusa, T. *J. Am. Chem. Soc.* **1982**, *104*, 7609–7622.

(20) A NMR investigation could help to shed light on this isomerization process; for a related example on the solvent effect, see: Capriati, V.; Florio, S.; Luisi, R.; Mazzanti, A.; Musio, B. *J. Org. Chem.* **2008**, *73*, 3197–3204.

(21) The absolute configuration could be assigned considering that the intramolecular cyclization is highly stereospecific (see infra).

Experimental Section

General Procedure for the Lithiation/Trapping Sequence of Aziridine (*S*)-1. To a stirred solution of (*o*-tolyl)aziridine (*S*)-**1** (100 mg, 0.68 mmol) and TMEDA (204.0 μL, 1.36 mmol) in hexane (4 mL) at −78 °C was added dropwise a solution of *sec*-BuLi (1.4 M in hexane, 972 μL, 1.36 mmol). After 30 min at −78 °C the electrophile (1.36 mmol) was added neat if liquid and in 2.0 mL of solvent if solid. After 2 h at −78 °C, the mixture was allowed to warm slowly to room temperature and the reaction mixture was poured into saturated aqueous NH_4Cl (10 mL) and extracted with Et_2O (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo. Flash chromatography afforded the substituted aziridines **2**.

2-(2-Deuteriomethylphenyl)-1-methylaziridine (*S*)-2a: colorless oil, 98% (98% D); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.60 (d, J = 6.2 Hz, 1 H), 1.84 (d, J = 3.7 Hz, 1 H), 2.33 (dd, J = 3.5, 6.5 Hz, 1 H), 2.37 (t, CH_2D, J = 1.8 Hz, 2 H), 2.50 (s, 3 H), 7.10−7.24 (m, 4 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.2 (t, J_{C-D} = 37 Hz), 37.6, 40.4, 48.0, 125.7, 125.9, 126.6, 129.5, 136.4, 138.0; GC-MS m/z (%) 147 [M^+, 100], 132 (45), 117 (19), 106 (16), 91 (9); FT-IR (film, cm^{-1}) 3025, 2967, 2944, 2848, 2779, 1491, 1454, 1383, 752, 732. Enantiomeric purity of (*S*)-**2a** determined by ^{1}H NMR in the presence of Mosher's acid (er > 99:1) ($[\alpha]^{20}_D$ +104 (*c* 1.1, $CHCl_3$)).

2-[2-(1-Methylaziridin-2-yl)phenyl]-1,1-diphenylethanol (*S*)-2f: white solid, mp 154−156 °C, 73%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.67 (d, J = 6.6 Hz, 1 H), 2.14 (d overlapping s at 2.16 ppm, J = 3.7 Hz, 1 H), 2.16 (s, 3 H), 2.46 (dd, J = 3.6, 7.0 Hz, 1 H), 3.80 (s, 2 H), 6.16 (d, J = 8.0 Hz, 1 H), 6.91 (t, J = 8.0 Hz, 1 H), 7.08−7.18 (m, 3 H), 7.20−7.24 (m, 3 H), 7.33−7.34 (m, 4H), 7.70 (d, J = 7.5 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 35.5, 42.2, 45.2, 45.5, 75.7, 124.8, 126.0, 126.1, 126.3, 126.6, 126.7, 127.5, 128.0, 128.7, 130.6, 136.7, 138.3, 147.1, 151.0; GC-MS m/z (%) 329 [M^+, 1], 299 (17), 146 (100), 104 (35), 77 (14); FT-IR (KBr, cm^{-1}) 3424, 3063, 2940, 2850, 1447, 1080, 1059, 770, 755, 699. Anal. Calcd for $C_{23}H_{23}NO$: C, 83.44; H, 7.88; N, 4.05. Found: C, 83.02; H, 7.75; N, 4.28. Enantiomeric purity of (*S*)-**2f** (er > 99:1) determined by HPLC analysis (OD-H chiral column; hexane:*i*PrOH 99:1; flow 1.0 mL/min; for (±)-**2f** t_1 = 9.7 min, t_2 = 10.9 min; for (*S*)-**2f** t = 10.9 min) ($[\alpha]^{20}_D$ +319 (*c* 1, CH_3CN)).

General Procedure for the Preparation of Isochroman 3. The hydroxyalkylated phenylaziridine **2** (1.0 mmol) in 3.0 mL of acetic acid was stirred at room temperature until the disappearance of the starting material (TLC monitoring, AcOEt/petroleum ether, 8/2). The resulting reaction mixture was poured into 20 mL of aqueous NaOH (10%) and extracted with CH_2Cl_2 (3 × 10 mL), then the combined organic extracts were dried (Na_2SO_4) and evaporated in vacuo. The crude was purified by flash chromatography (silica gel; CH_2Cl_2/MeOH, 9/1) to obtain the pure isochroman **3**.

1-Methylaminomethyl-3,3-diphenyl-3,4-dihydro-1*H*-isochromene (*R*)-3b: white solid, mp 123−126 °C, 77%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.15 (br s, 1 H), 2.56 (s, 3 H), 3.04 (dd, J = 12.2, 8.5 Hz, 1 H), 3.15 (dd, J = 12.2, 2.5 Hz, 1 H), 3.30 (d, J = 16.5 Hz, 1 H), 3.66 (d, J = 16.5 Hz, 1H), 4.68 (d, br, J = 7.7 Hz, 1 H), 6.9 (d, J = 7.5 Hz, 1 H), 7.07−7.31 (m, 12 H), 7.37 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 36.1, 39.4, 56.9, 71.0, 78.8, 123.9, 125.1, 126.2, 126.6, 126.7, 127.0, 127.9, 128.0, 128.1, 128.3, 133.5, 135.2, 141.6, 148.2; ESI-MS m/z (%) 330 [M − H]$^+$ (100); FT-IR (KBr, cm^{-1}) 3430, 1600, 1447, 1073, 752, 700. Anal. Calcd for $C_{23}H_{23}NO$: C, 83.85; H, 7.04; N, 4.25. Found: C, 84.05; H, 7.07; N, 4.15. Enantiomeric purity of (*R*)-**3b** determined by HPLC analysis (OD-H chiral column; hexane: *i*PrOH 99:1; flow 0.5 mL/min; for (±)-**3b** t_1 = 55.1 min, t_2 = 108.5 min; for (*R*)-**3b** t = 55.1 min); ($[\alpha]_D$ −226.2 (*c* 0.5, $CHCl_3$)).

Acknowledgment. This work was carried out under the framework of the National Project "Stereoselezione in Sintesi Organica. Metodologie ed Applicazioni" and supported by the University of Bari.

Supporting Information Available: Experimental procedures, spectra of the new compounds, and copies of 1D and 2D NMR experiments. This material is available free of charge via the Internet at http://pubs.acs.org.