Incorporation of Diarylbutylamine Pharmacophore into Indeno- or Naphtho[1,2-*b*]pyran Ring Systems

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Various conformationally constrained forms of the diarylbutylamine pharmacophore were accessed by incorporating it into heterocyclic ring systems, i.e., indeno[1,2-*b*]furan, indeno[1,2-*b*]pyran, naphtho[1,2-*b*]furan, and benzo[*h*]chromene. These compounds were formed by epoxidation of 2-alkenyl-substituted 1-indanols or 1-naphthalenols.

Introduction

The diarylbutylamine pharmacophore is found in several bioactive compounds, such as the dopamine receptor ligands **1** and the antihistamine difenhydramine **2** (Figure 1).[1–3] A general approach for improving the binding affinity and selectivity of such ligands toward receptor molecules is to constrain the bioactive conformation of the open-chain compounds in a (poly)cyclic framework. Typical examples of diarylbutylamine pharmacophores that are conformationally constrained by incorporation into an additional ring structure are the antidepressants dioxadrol **3**,[4] maprotiline **4**,[5] and the often-prescribed sertraline **5**.[6] The farnesyl transferase inhibitor **6**, which exhibits notable antitumor and antileukemic properties, can be regarded as both a diarylbutylamine and a diarylpropylamine constrained within a polycyclic framework.[7] In a similar manner, we conceived target compounds of type **7** — in which a diarylbutylamine-like pharmacophoric unit is incorporated in a tricyclic skeleton encompassing the fused ring systems indeno[1,2-*b*]furan, indeno[1,2-*b*]pyran, naphtho[1,2-*b*]furan, and benzo[*h*]chromene — to be constrained analogues of the acyclic models **1** and **2**. Our synthetic approach towards target compounds of type **7** consisted of regioselective opening of the epoxide ring by the tertiary alcohol center in each precursor **8**, which can be derived from the 2-alkenyl-substituted β-keto ester **9** by sequential Grignard and epoxidation reactions.

Results and Discussion

We describe separately the synthesis and structural and stereochemical analyses of the products.

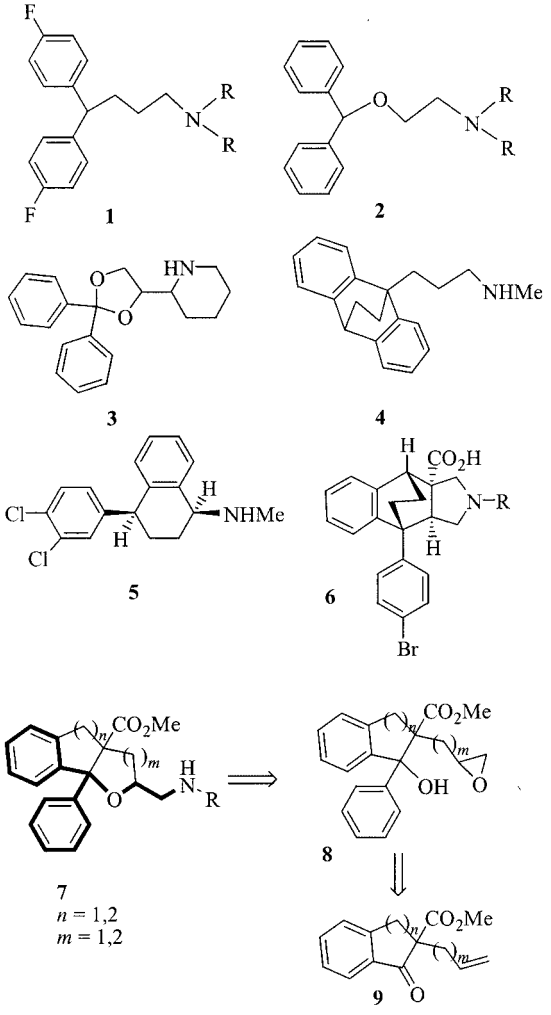

Figure 1. Structures of diarylbutylamine models and target compounds

Part 1. Synthesis

To construct the indeno[1,2-*b*]furan and indeno[1,2-*b*]pyran ring systems, the starting 1-indanone (**10**) was first

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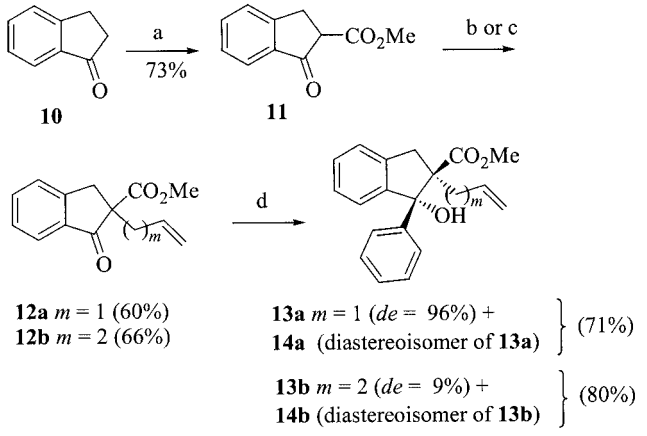
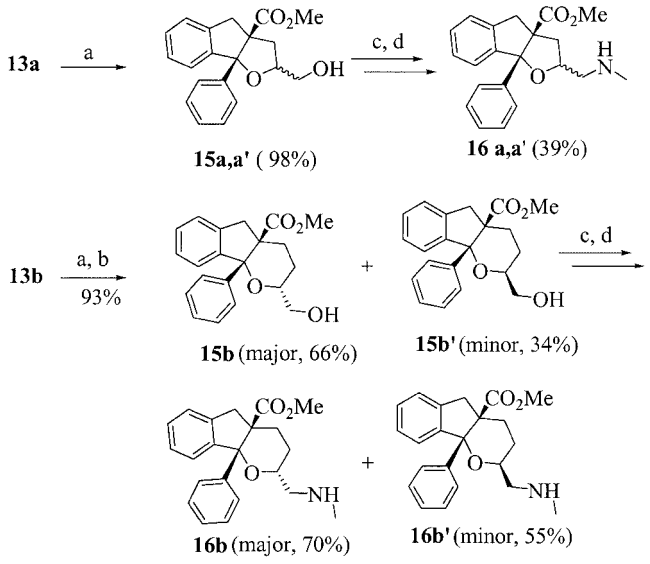
transformed into the corresponding β-keto ester **11**,[8] which was then alkylated using sodium hydride and either allyl bromide or 4-bromo-1-butene to give compounds **12a** and **12b**, respectively (Scheme 1).[9] Subsequent Grignard reaction using freshly prepared phenylmagnesium bromide at −78 °C afforded a mixture of the tertiary alcohols **13a**,**b** and their diastereoisomers **14a**,**b** in good yield, despite the steric hindrance resulting from the quaternary carbon atom adjacent to the ketone group, but the diastereomeric excess (*de*) values of the products formed were strikingly different: for **12a** the *de* was 96% (**13a** over **14a**) while that for **12b** was only 9% (**13b** over **14b**). We attribute the large *de* value found for **12a** to the formation of a cyclic Mg^{2+} chelate involving the β-keto ester moiety: indeed, as indicated by an MM+ model, this chelate presents the allyl side chain in a pseudoaxial orientation, which results in a preferential attack from the other side of the ring. In contrast, a similar cyclic Mg^{2+} chelate appears to be formed less readily from **12b** because it would require a pseudoaxial orientation of the sterically more demanding 2-butenyl side chain.



Scheme 1. Reagents and conditions: (a) NaH, $(CH_3O)_2CO$, reflux; (b) NaH, 3-bromo-1-propene, THF, 0 °C; (c) NaH, 4-bromo-1-butene, DMF, 70 °C; (d) PhMgBr, THF, −78 °C

To generate epoxide intermediates **8** and to effect concomitant cyclization (see Figure 1), each isolated compound **13a** and **13b** was subjected to epoxidation using *m*-chloroperbenzoic acid. Thus, from the reaction of **13a**, the corresponding primary alcohols **15a**,**a′** were obtained as an inseparable mixture of diastereoisomers in a 58:42 ratio (Scheme 2). NOESY analysis of this mixture (see below) confirmed the expected *cis* fusion existing within both diastereoisomers.

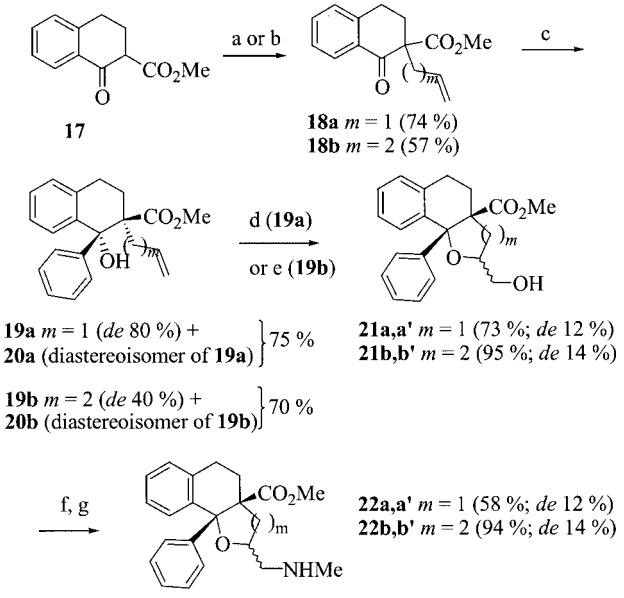
From the analogous reaction of compound **13b** with *m*-chloroperbenzoic acid, we obtained a mixture of epoxides and ring-closed products **15b**,**b′** (Scheme 2). This mixture was converted completely into the desired primary alcohols **15b**,**b′** by treatment with *t*BuOK in *t*BuOH (or, alternatively, by using *p*TSA in CH_2Cl_2; see below). The diastereoisomers **15b** and **15b′** (ratio 66:34) were separated by column chromatography. Again, NOESY analysis revealed a *cis* fusion within both diastereoisomers.



Scheme 2. Reagents and conditions: (a) *m*CPBA, CH_2Cl_2; (b) *t*BuOK, *t*BuOH; (c) Et_3N, MsCl, DMAP, CH_2Cl_2, 0 °C; (d) $MeNH_2$, H_2O, 120 °C, steel bomb

Finally, the mixture of alcohols **15a**,**a′** and the single compounds **15b** and **15b′** were converted into the corresponding amines **16a**,**a′**, **16b**, and **16b′**, respectively, by mesylation and then reaction with aqueous methylamine.

In an analogous sequence starting from β-ketoester **17**,[8] we prepared the alkylated tetralone analogues **18a** and **18b** (Scheme 3). Subsequent Grignard reactions afforded tertiary alcohols **19a**,**b** with a *de* of 80% (**19a** vs. **20a**) and 40% (**19b** vs. **20b**). Following isolation by column chromatography, the major diastereoisomers **19a** and **19b** were assigned again as the (Ph/alkenyl) *trans*-diaxial structures by



Scheme 3. Reagents and conditions: (a) NaH, 3-bromo-1-propene, DMF, 70 °C; (b) NaH, 4-bromo-1-butene, DMF, 70 °C; (c) PhMgBr, THF, −78 °C; (d) *m*CPBA, CH_2Cl_2; (e) *m*CPBA, CH_2Cl_2; then *p*TSA, CH_2Cl_2; (f) Et_3N, MsCl, DMAP, CH_2Cl_2, 0 °C; (g) $MeNH_2$, H_2O, 120 °C, steel bomb

NOESY analysis (*cis* relationships exists between the Ph and ester groups).

Epoxidation of compound **19a** using *m*-chloroperbenzoic acid afforded the ring-closed primary alcohols **21a**,**a′** as a mixture of diastereoisomers (ratio 56:44). NOESY analysis of the mixture confirmed the expected *cis* fusion within both diastereoisomers. A similar treatment of the 2-(3-butenyl)-substituted compound **19b** with *m*-chloroperbenzoic acid furnished a mixture of ring-closed diastereoisomeric alcohols **21b**,**b′** and epoxide intermediates. These compounds were converted completely into **21b**,**b′** upon treatment of the mixture with *p*-toluenesulfonic acid (*p*TSA) in CH_2Cl_2 (ratio 57:43). Finally, the mixtures of isomeric primary alcohols **21a**,**a′** and **21b**,**b′** were converted into the corresponding amines **22a**,**a′** and **22b**,**b′** by mesylation and then reaction with aqueous methylamine.

Part 2. Structural and Stereochemical Analyses

The relative stereochemistry and conformational structures of the alcohols obtained from the Grignard reactions, and those of the tricyclic products resulting from cyclization of the epoxide intermediates, was revealed by ^{1}H NMR spectroscopy experiments and were supported by MM+ molecular modeling studies.

Thus, following chromatographic separation of the 2-allyl-2-indanecarboxylates **13a** and **14a**, the structure of the major diastereoisomer **13a** was assigned on the basis of NOE correlations in the ^{1}H NMR spectrum. This study revealed an NOE between the vinylic proton $H^{2'}$ and one allylic proton H_d, which can be distinguished from H_c located in the plane of the alkene (Houk model).[10,11] Proton H_d further reveals a ^4J coupling of 1.5 Hz with the axial proton H^3_{ax} on the five-membered ring, which in turn shows an NOE correlation with the *ortho* protons of the axial phenyl group. These findings, particularly the axial positions of H^3_{ax} and the Ph group and the W-pattern observed for H^3_{ax} and H_d, can be accommodated by a *trans*-diaxial relationship between the phenyl and allyl substituents. This result is in accordance with model calculations that provided the conformational structure shown in Figure 2, and it also agrees with our previous report regarding the diastereoselectivity of the Grignard reaction in similar systems.[12]

In a similar manner, following the separation of the diastereoisomeric 2-(3-butenyl)-2-indanecarboxylates **13b** and **14b**, the major component **13b** was characterized also as the (Ph/alkenyl) *trans*-diaxial structure by applying NOESY analysis.

The relative stereochemistry of the indeno[1,2-*b*]furan isomers **15a**,**a′** was determined by ^{1}H NMR spectroscopy, including NOESY analysis. For both components, an NOE correlation is observed between the aromatic proton H^5 and the near-equatorial proton H^4_{eq}. The latter proton (H^4_{eq}) also correlates with H^3_b, while H^4_{ax} interacts with the *ortho* protons of the phenyl group. These data confirm the expected *cis* fusion of the two five-membered rings. We assigned the relative configurations of **15a** and **15a′** on the basis of the further NOE correlations indicated in Figure 3.

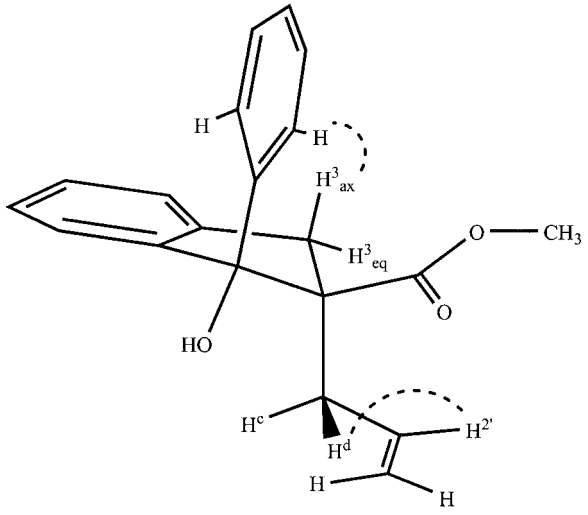


Figure 2. NOESY analysis of structure **13a**

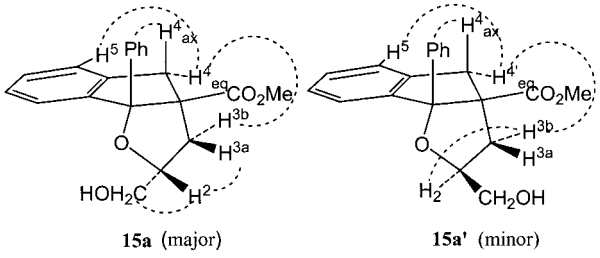


Figure 3. NOESY analysis of isomeric structures **15a** and **15a′**

From a conformational study of indeno[1,2-*b*]pyran compound **15b′** it appears that this compound can adopt a favorable chair conformation **15b′A** in which the Ph group is axial relative to the five-membered ring and equatorial to the six-membered ring (Figure 4). For **15b**, however, neither of the chair forms **15bB** or **15bC** is suitable because both of them experience severe 1,3-diaxial interactions. Moreover, the Ph group in **15bC** is equatorial to the five-membered ring and, therefore, it suffers further repulsive interactions with the coplanar benzene ring. From the model study, we

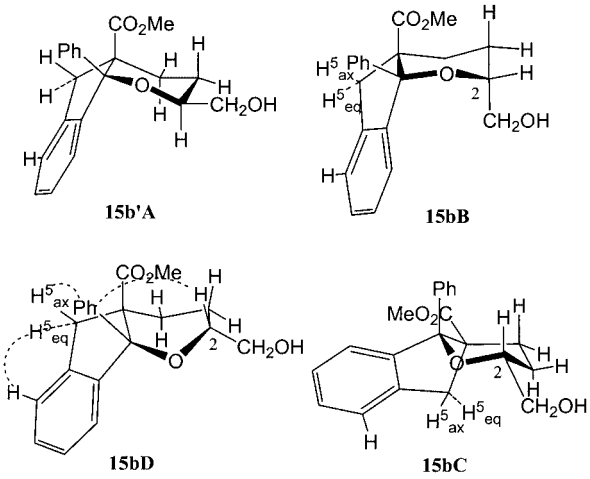


Figure 4. Conformational structures of **15b** and **15b′**

found a third, boat-like structure **15bD** to be the most favorable conformer. This structure was confirmed by NOESY analysis of **15b** in C_6D_6, which revealed correlations between the *ortho* protons of the Ph group and both H^5_{ax} and H^2: these two interactions cannot apply at the same time in either of conformers **15bB** or **15bC**.

In conclusion, we have developed a straightforward approach for the synthesis of conformationally constrained diphenylalkylamines, which have been incorporated into various heterocyclic ring systems, namely indeno[1,2-*b*]furan, indeno[1,2-*b*]pyran, naphtho[1,2-*b*]furan, and benzo[*h*]chromene.

Experimental Section

General Remarks: Infrared spectra were recorded using a Perkin−Elmer 1600 Fourier transform spectrometer. Mass spectra were obtained using a Hewlett−Packard MS-Engine 5989A apparatus for EI and CI spectra, and a Kratos MS50TC instrument for exact mass measurements performed in the EI mode at a resolution of 10,000. For the NMR spectra (δ, ppm), we used a Bruker AMX 400 and a Bruker Avance 300 spectrometer. Column chromatography was carried out using 70−230 mesh silica 60 (E.M. Merck) as the stationary phase.

For the synthesis and spectroscopic data of methyl 1-oxoindane-2-carboxylate (**11**) and methyl 1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (**17**), see ref.[8].

Methyl 2-Allyl-1-oxoindane-2-carboxylate (12a): A solution of **11** (2 g, 11 mmol) in THF (50 mL) was added at 0 °C to a solution of sodium hydride (60% dispersion in mineral oil; 0.69 g, 23 mmol) in THF (50 mL). The mixture was stirred at room temperature for 15 min before the addition of allyl bromide (1.09 mL, 13 mmol). After stirring at room temperature for 18 h, satd. aq. NH_4Cl (50 mL) was added. The aqueous layer was extracted three times with CH_2Cl_2. The combined organic phases were dried with $MgSO_4$ and filtered and then the solvents were evaporated. The residue was purified by column chromatography (silica gel; heptane/ethyl acetate, 4:1). Yield 60%. IR (NaCl): $\tilde{\nu}$ = 1727.5 (C=O), 1713.0 (C=O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.74 (d, *J* = 8 Hz, 1 H, H arom.), 7.58 (dd, *J* = 8, 7 Hz, 1 H, H arom.), 7.40 (d, *J* = 7 Hz, 1 H, H arom.), 7.37 (dd, *J* = 8, 7 Hz, 1 H, H arom.), 5.61 (m, 1 H, C*H*=CH_2), 5.08 (d, *J* = 17 Hz, 1 H, CH=CH_2), 5.01 (d, *J* = 10 Hz, 1 H, CH=CH_2), 3.71 (s, 3 H, OCH_3), 3.60 (d, *J* = 18 Hz, 1 H, H^3), 3.13 (d, *J* = 18 Hz, 1 H, H^3), 2.84 (dd, *J* = 14, 7 Hz, 1 H, CH_2−CH=CH_2), 2.61 (dd, *J* = 14, 7 Hz, 1 H, CH_2−CH=CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 202.4, 171.6, 153.5, 135.8, 135.5, 133.0, 128.1, 127.7, 124.1, 119.7, 60.3, 53.1, 36.3, 30.6 ppm. MS (EI): *m*/*z* (%) = 231 (100) [$M^{\cdot+}$], 199 (19) [$M^{\cdot+}$ − MeOH], 189 (74) [$M^{\cdot+}$ − CH_3CH=CH_2], 171 (39) [$M^{\cdot+}$ − HCO_2CH_3], 157 (75) [$C_{10}H_5O_2^+$]; exact mass calculated for $C_{14}H_{14}O_3$: 230.0943; found 230.0948.

General Procedure for the Synthesis of 12b, 18a, and 18b: 11 (1 g, 5 mmol), or **17**, in DMF (50 mL) was added dropwise over 10 min to a mixture of sodium hydride (60% dispersion in mineral oil; 0.32 g, 8 mmol) in DMF (20 mL) at 0 °C. The mixture was stirred at room temperature for 15 min. A solution of 4-bromo-1-butene (0.69 mL, 7 mmol), or allyl bromide, in DMF (20 mL) was added. After stirring at 70 °C for 18 h, the reaction mixture was cooled down and water (50 mL) was added. The aqueous layer was extracted three times with CH_2Cl_2. The combined organic phases were washed with brine, dried with $MgSO_4$, and filtered and then the solvents were evaporated. The residue was purified by column chromatrography (silica gel; heptane/ethyl acetate, 4:1).

Methyl 2-(3-Butenyl)-1-oxoindane-2-carboxylate (12b): Yield 66%. IR (NaCl): $\tilde{\nu}$ = 1715.3 (C=O), 1714.7 (C=O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.77 (d, *J* = 8 Hz, 1 H, H arom.), 7.64 (dd, *J* = 8, 1 Hz, 1 H, H arom.), 7.51 (d, *J* = 8 Hz, 1 H, H arom.), 7.40 (t, *J* = 8 Hz, 1 H, H arom.), 5.77 (m, 1 H, C*H*=CH_2), 5.02 (dd, *J* = 18, 2 Hz, 1 H, CH=CH_2), 4.96 (d, *J* = 9 Hz, 1 H, CH=CH_2), 3.78 (d, *J* = 18 Hz, 1 H, H^3), 3.70 (s, 3 H, OCH_3), 3.09 (d, *J* = 18 Hz, 1 H, H^3), 2.25−1.90 (m, 4 H, CH_2CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 204.4, 172.2, 154.9, 154.2, 138.6, 136.4, 128.0, 126.2, 124.9, 116.5, 60.8, 53.3, 37.4, 34.2, 28.7 ppm. MS (EI): *m*/*z* (%) = 245 (16) [MH^+], 213 (13) [MH^+ − MeOH], 190 (100) [MH^+ − CH_2CH_2CH=CH_2], 130 (63) [MH^+ − HCO_2CH_3 − CH_2CH_2CH=CH_2], 77 (12) [$C_6H_5^+$]; exact mass calculated for $C_{15}H_{16}O_3$: 244.1099; found 244.1095.

Methyl 2-Allyl-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (18a): Yield 74%. IR (NaCl): $\tilde{\nu}$ =1734.3 (C=O), 1688.0 (C=O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.98 (dt, *J* = 8, 1 Hz, 1 H, H arom.), 7.38 (ddd, *J* = 9, 8, 2 Hz, 1 H, H arom.), 7.22 (m, 1 H, H arom.), 7.15 (d, *J* = 8 Hz, 1 H, H arom.), 5.78 (m, 1 H, C*H*=CH_2), 5.11 (dd, *J* = 15, 2 Hz, 1 H, CH=CH_2), 5.03 (d, *J* = 8 Hz, 1 H, CH=CH_2), 3.54 (s, 3 H, OCH_3), 3.01 (ddd, *J* = 18, 10, 5 Hz, 1 H, H^4), 2.86 (ddd, *J* = 18, 11, 6 Hz, 1 H, H^4), 2.74−2.53 (m, 2 H, CH_2−CH=CH_2), 2.47 (ddd, *J* = 19, 10, 5 Hz, 1 H, H^3), 2.07 (m, 1 H, H^3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 195.3, 172.4, 143.7, 134.0, 133.8, 132.3, 129.2, 128.5, 127.2, 119.3, 57.8, 52.8, 39.1, 30.9, 26.2 ppm. MS (EI): *m*/*z* (%) = 245 (87) [MH^+], 226 (4) [$M^{\cdot+}$ − H_2O], 203 (80) [$M^{\cdot+}$ − CH_2CH=CH_2], 185 (41) [$M^{\cdot+}$ − CO_2CH_3], 171 (92) [$M^{\cdot+}$ − $CO_2CH_2CH_3$], 118 (100) [$C_6H_6O^+$], 90 (92) [$C_7H_6^+$], 77 (19) [$C_6H_5^+$]; exact mass calculated for $C_{15}H_{16}O_3$: 244.1099; found 244.1095.

Methyl 2-(3-Butenyl)-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (18b): Yield 57%. IR (NaCl): $\tilde{\nu}$ = 1735.2 (C=O), 1686.8 (C=O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.03 (d, *J* = 8 Hz, 1 H, H arom.), 7.42 (t, *J* = 8 Hz, 1 H, H arom.), 7.28 (t, *J* = 8 Hz, 1 H, H arom.), 7.18 (d, *J* = 8 Hz, 1 H, H arom.), 5.80 (m, 1 H, C*H*=CH_2), 5.07, (d, *J* = 17 Hz, 1 H, CH=CH_2), 4.94 (d, *J* = 10 Hz, 1 H, CH=CH_2), 3.67 (s, 3 H, OCH_3), 3.50 (ddd, *J* = 18, 9, 5 Hz, 1 H, H^4), 2.92 (dt, *J* = 18, 5 Hz, 1 H, H^4), 2.58 (m, 2 H, CH_2CH=CH_2), 2.21−1.90 (m, 4 H, H^3 + CH_2CH_2CH=CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 195.3, 175.3, 144.8, 140.4, 135.3, 134.9, 129.8, 129.5, 125.3, 115.2, 59.7, 50.4, 35.2, 30.3, 29.8, 25.2 ppm. MS (EI): *m*/*z* (%) = 259 (31) [MH^+], 204 (100) [MH^+ − CH_2CH_2CH=CH_2], 172 (60) [MH^+ − MeOH − CH_2CH_2CH=CH_2]; exact mass calculated for $C_{16}H_{18}O_3$: 258.1256; found 258.1253.

General Procedure for the Synthesis of 13a/14a, 13b/14b, 19a/20a, and 19b/20b: Bromobenzene (2.12 mL, 20 mmol) was added dropwise to magnesium turnings (0.63 g, 18 mmol) and a crystal of iodine in dry THF (40 mL) under argon. The mixture was heated under reflux for 60 min and then cooled to −78 °C. **12a** (2.63 g, 11 mmol) in dry THF (50 mL) was added and the mixture was stirred at room temperature for 16 h before satd. aq. NH_4Cl (50 mL) was added. The aqueous layer was extracted three times with CH_2Cl_2. The combined organic phases were dried with Na_2SO_4 and filtered and then the solvents were evaporated. The residue was purified by column chromatography (silica gel; CH_2Cl_2/ethyl acetate, 95:5).

Methyl (1*R,2*R**)-2-Allyl-1-hydroxy-1-phenylindane-2-carboxylate (13a):** Yield 71%. IR (KBr): $\tilde{\nu}$ = 3494.0 (OH), 1711.4 (C=O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.37−7.06 (m, 9 H, H arom.), 5.63 (m, 1 H, C*H*=CH_2), 5.09 (d, *J* = 18 Hz, 1 H, CH=CH_2), 5.04 (dd, *J* = 8, 1 Hz, 1 H, CH=CH_2), 3.60 (d, *J* = 16 Hz, 1 H, H^3), 3.27 (s, 3 H, OCH_3), 3.04 (d, *J* = 16 Hz, 1 H, H^3), 3.02 (ddd, *J* = 14, 6, 2 Hz, 1 H, CH_2CH=CH_2), 2.66 (s, 1 H, OH), 2.29 (dd, *J* = 14, 8 Hz, 1 H, CH_2CH=CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.7, 145.9, 143.0, 140.7, 134.4, 128.9, 127.7, 127.6, 127.4, 125.9, 124.8, 124.1, 118.7, 88.1, 64.7, 51.4, 37.5, 36.7 ppm. MS (EI): *m*/*z* (%) = 308 (37) [$M^{\cdot+}$], 291 (5) [$M^{\cdot+}$ − H_2O], 248 (63) [$M^{\cdot+}$ − HCO_2CH_3], 231 (11) [$M^{\cdot+}$ − H_2O − CO_2CH_3], 207 (100) [$M^{\cdot+}$ − HCO_2CH_3 − $CH_2CH=CH_2$]; exact mass calculated for $C_{20}H_{20}O_3$: 308.1412; found 308.1412.

Methyl (1*R,2*R**)-2-(3-Butenyl)-1-hydroxy-1-phenylindane-2-carboxylate (13b):** Yield 47%. IR (KBr): $\tilde{\nu}$ = 3456.7 (OH), 1708.0 (C=O), 1640.0 (C=O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.33−7.10 (m, 9 H, H arom.), 5.77 (m, 1 H, C*H*=CH_2), 5.00 (dd, *J* = 16, 2 Hz, 1 H, CH=CH_2), 4.93 (dd, *J* = 10, 2 Hz, 1 H, CH=CH_2), 3.62 (d, *J* = 16 Hz, 1 H, H^3), 3.24 (s, 3 H, OCH_3), 2.99 (d, *J* = 16 Hz, 1 H, H^3), 2.57 (s, 1 H, OH), 2.31 (dddd, *J* = 13, 12, 5, 1 Hz, 1 H, CH_2CH$_2$CH=CH_2), 2.08 (m, 1 H, CH_2CH=CH_2), 1.86 (m, 1 H, CH_2CH=CH_2), 1.64 (ddd, *J* = 13, 12, 5 Hz, 1 H, CH_2CH$_2$CH=CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.8, 146.2, 143.3, 141.1, 138.0, 128.9, 127.7, 127.5, 127.3, 126.0, 124.8, 124.1, 114.8, 88.5, 65.1, 51.3, 37.0, 31.7, 30.1 ppm. MS (EI): *m*/*z* (%) = 322 (13) [$M^{\cdot+}$], 281 (86) [$M^{\cdot+}$ − $CH_2CH=CH_2$], 249 (40) [$M^{\cdot+}$ − MeOH − $CH_2CH=CH_2$], 203 (60) [$M^{\cdot+}$ − H_2O − HCO_2CH_3 − $CH_2CH=CH_2$], 171 (62) [$M^{\cdot+}$ − H_2O − MeOH − HCO_2CH_3 − $CH_2CH=CH_2$], 105 (100) [$C_6H_5CO^+$]; exact mass calculated for $C_{21}H_2O_3$: 322.1569; found 322.1569.

Methyl (1*R,2*R**)-2-Allyl-1-hydroxy-1-phenyl-1,2,3,4-tetrahydronaphthalene-2-carboxylate (19a):** Yield 60%. IR (KBr): $\tilde{\nu}$ = 3537.2 (OH), 1736.4 (C=O), 1640.0 (C=O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.40 (d, *J* = 8 Hz, 1 H, H arom.), 7.21−7.12 (m, 6 H, H arom.), 6.99 (m, 2 H, H arom.), 5.63 (m, 1 H, C*H*=CH_2), 5.10 (dd, *J* = 17, 1 Hz, 1 H, CH=CH_2), 5.05 (d, *J* = 10 Hz, 1 H, CH=CH_2), 4.60 (s, 1 H, OH), 3.46 (s, 3 H, OCH_3), 3.07 (ddd, *J* = 14, 6, 1 Hz, 1 H, CH_2CH=CH_2), 2.93 (dd, *J* = 9, 4 Hz, 2 H, H^4), 2.25 (dd, *J* = 14, 8 Hz, 1 H, CH_2CH=CH_2), 2.13 (m, 1 H, H^3), 1.98 (ddd, *J* = 15, 5, 4 Hz, 1 H, H^3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.7, 145.5, 139.7, 134.4, 133.8, 127.7, 127.6, 127.3, 127.1, 126.8, 126.7, 118.3, 78.2, 53.9, 51.6, 35.6, 24.3, 21.9 ppm. MS (EI): *m*/*z* (%) = 322 (11) [$M^{\cdot+}$], 305 (5) [$M^{\cdot+}$ − OH], 262 (5) [$M^{\cdot+}$ − HCO_2CH_3], 245 (14) [$M^{\cdot+}$ − H_2O − CO_2CH_3], 195 (100) [$C_{14}H_{11}O^+$], 105 (27) [$C_6H_5CO^+$], 77 (33) [$C_6H_5^+$]; exact mass calculated for $C_{21}H_{22}O_3$: 322.1569; found 322.1565.

Methyl (1*R,2*R**)-2-(3-Butenyl)-1-hydroxy-1-phenyl-1,2,3,4-tetrahydronaphthalene-2-carboxylate (19b):** Yield 28%. IR (KBr): $\tilde{\nu}$ = 3530.3 (OH), 1705.9 (C=O), 1641.5 (C=O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.50 (d, *J* = 7 Hz, H arom.), 7.23 (m, 6 H, H arom.), 7.11 (dd, *J* = 7, 2 Hz, 2 H, H arom.), 5.82 (m, 1 H, C*H*=CH_2), 5.01 (dd, *J* = 17, 2 Hz, 1 H, CH=CH_2), 4.98 (dd, *J* = 12, 2 Hz, CH=CH_2), 4.69 (s, 1 H, OH), 3.52 (s, 3 H, OCH_3), 3.01 (m, 2 H, H^4), 2.52 (dt, *J* = 14, 5 Hz, 1 H, H^3), 2.24 (m, 2 H, CH_2CH=CH_2), 2.09 (m, 1 H, CH_2CH$_2$CH=CH_2), 1.90 (m, 1 H, CH_2CH$_2$CH=CH_2), 1.71 (ddd, *J* = 14, 12, 5 Hz, 1 H, H^3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.7, 146.3, 140.6, 138.3, 135.0, 128.4, 128.3, 128.0, 127.7, 127.4, 127.3, 115.5, 79.2, 54.3, 52.3, 30.6, 30.3, 25.2, 22.3 ppm. MS (EI): *m*/*z* (%) = 336 (10) [$M^{\cdot+}$], 295 (49) [$M^{\cdot+}$ − $CH_2CH=CH_2$], 259 (15) [$M^{\cdot+}$ − H_2O − CO_2CH_3], 195 (100) [$C_{14}H_{11}O^+$], 105 (80) [$C_6H_5CO^+$], 77 (36) [$C_6H_5^+$]; exact mass calculated for $C_{22}H_{24}O_3$: 336.1725; found 336.1726.

General Procedure for the Synthesis of 15a,a′ and 21a,a′: *m*CPBA (5.5 g, 32 mmol) was added to a mixture of **13a** (3.27 g, 11 mmol) in CH_2Cl_2 (70 mL). After stirring at room temperature for 19 h, satd. aq. Na_2CO_3 (50 mL) was added. The aqueous layer was extracted three times with CH_2Cl_2. The combined organic phases were dried with Na_2SO_4 and filtered and then the solvents were evaporated. The residue was purified by column chromatography (silica gel; heptane/ethyl acetate, 1:1).

Methyl (3a*S,8b*R**)-2-(Hydroxymethyl)-8b-phenyl-2,3,4,8-tetrahydro-3a*H*-indeno[1,2-*b*]furan-3a-carboxylate (15a,a′):** Mixture of diastereoisomers, *de* = 16%; yield 98%. IR (NaCl): $\tilde{\nu}$ = 3445.7 (OH), 1727.6 (C=O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.29−7.03 (m, 9 H, H arom.), 4.84 (m, 0.58 H, H^2), 3.86 (m, 2.26 H, 0.42 H^2 + 1 H^4 + 0.84 CH_2OH), 3.60 (dd, *J* = 12, 3 Hz, 0.58 H, CH_2OH), 3.32 (dd, *J* = 12, 5 Hz, 0.58 H, CH_2OH), 3.17 (s, 1.74 H, OCH_3), 3.07 (s, 1.26 H, OCH_3), 3.03 (d, *J* = 17 Hz, 0.42 H, H^4), 3.00 (d, *J* = 17 Hz, 0.58 H, H^4), 2.83 (dd, *J* = 13, 9 Hz, 0.42 H, H^3), 2.68 (dd, *J* = 13, 6 Hz, 0.58 H, H^3), 1.86 (2 × dd, *J* = 13, 10, 5 Hz, 1 H, H^3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.0, 173.3, 146.3, 143.4, 141.6, 141.4, 140.4, 139.4, 128.8, 128.6, 127.8, 127.5, 127.4, 127.3, 127.2, 127.1, 127.0, 126.3, 125.8, 125.3, 124.9, 124.7, 124.2, 100.9, 100.4, 81.9, 78.1, 66.3, 65.2, 64.3, 63.7, 51.4, 51.3, 40.7, 40.2, 39.9, 38.7 ppm. MS (EI): *m*/*z* (%) = 324 (4) [$M^{\cdot+}$], 306 (14) [$M^{\cdot+}$ − H_2O], 293 (42) [$M^{\cdot+}$ − OCH_3], 274 (8) [$M^{\cdot+}$ − MeOH − H_2], 264 (28) [$M^{\cdot+}$ − HCO_2CH_3], 233 (35) [$M^{\cdot+}$ − OCH_3 − HCO_2CH_3], 250 (100) [$C_{16}H_{13}^+$]; exact mass calculated for $C_{20}H_{20}O_4$: 324.1362; found 324.1362.

Methyl (3a*S,9b*S**)-2-(Hydroxymethyl)-9b-phenyl-2,3,5,9b-tetrahydronaphtho[1,2-*b*]furan-3a(4*H*)-carboxylate (21a,a′):** Mixture of diastereoisomers, *de* = 12%; yield 73%. IR (NaCl): $\tilde{\nu}$ = 3443.3 (OH), 1725.7 (C=O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.23−7.09 (m, 9 H, H arom.), 4.90 (m, 0.56 H, H^2), 4.02 (dd, *J* = 11, 5 Hz, 0.44 H, CH_2OH), 3.85 (dd, *J* = 11, 4 Hz, 0.44 H, CH_2OH), 3.82 (m, 0.44 H, H^2), 3.52 (dd, *J* = 12, 4 Hz, 0.56 H, CH_2OH), 3.21 (s, 1.68 H, OCH_3), 3.17 (dd, *J* = 12, 5 Hz, 0.56 H, CH_2OH), 3.11 (s, 1.31 H, OCH_3), 3.02 (m, 2 H, H^5), 2.56 (m, 1.44 H, 1 H^4 + 0.44 H^3), 2.34 (dd, *J* = 13, 7 Hz, 0.56 H, H^3), 2.26 (m, 0.44 H, H^4), 2.18 (dd, *J* = 13, 9 Hz, 0.56 H, H^3), 2.02 (m, 1 H, 0.56 H^4 + 0.44 H^3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.6, 174.8, 144.4, 143.3, 142.2, 139.8, 136.3, 134.4, 130.3, 130.2, 130.1, 128.5, 128.1, 127.9, 127.8, 127.7, 127.6, 126.5, 126.4, 126.2, 88.2, 88.1, 80.2, 76.4, 65.5, 64.2, 58.5, 57.8, 52.3, 52.0, 33.4, 32.9, 25.1, 24.9, 24.7, 24.3 ppm. MS (EI): *m*/*z* (%) = 339 (21) [MH^+], 320 (21) [$M^{\cdot+}$ − H_2O], 307 (51) [MH^+ − MeOH], 275 (90) [MH^+ − 2MeOH], 261 (28) [MH^+ − HCO_2CH_3 − MeOH], 105 (33) [$C_6H_5CO^+$], 77 (34) [$C_6H_5^+$]; exact mass calculated for $C_{21}H_{22}O_4$: 338.1518; found 338.1527.

General Procedure for the Synthesis of 15b/15b′, and 21b,b′: *m*CPBA (1.5 g, 8.9 mmol) was added to a mixture of **19b** (1 g, 3 mmol) in CH_2Cl_2 (20 mL). After stirring at room temperature for 19 h, satd. aq. Na_2CO_3 (30 mL) was added. The aqueous layer was extracted three times with CH_2Cl_2. The combined organic phases were dried with Na_2SO_4 and filtered and then the solvents were evaporated. The residue was dissolved in CH_2Cl_2 (50 mL) and then *p*TSA (0.28 g, 1.5 mmol) was added. After stirring at room temperature for 6 h, water (30 mL) was added. The aqueous layer was extracted three times with CH_2Cl_2. The combined organic phases were dried with Na_2SO_4 and filtered and then the solvents were evaporated. The residue was purified by column chromatography (silica gel; heptane/ethyl acetate, 7:3).

Methyl (2*R,4a*R**,9b*R**)-2-(Hydroxymethyl)-9b-phenyl-3,4,5,9b-tetrahydroindeno[1,2-*b*]pyran-4a(2*H*)-carboxylate (15b) and Methyl (2*S**,4a*R**,9b*R**)-2-Hydroxymethyl-9b-phenyl-3,4,5,9b-tetrahydroindeno[1,2-*b*]pyran-4a(2*H*)-carboxylate (15b′):** IR (NaCl): $\tilde{\nu}$ = 3440.8 (OH), 1724.9 (C=O) cm^{-1}. MS (EI): *m*/*z* (%) = 338 (7) [$M^{\cdot+}$], 307 (12) [$M^{\cdot+} - CH_3O$], 279 (100) [$M^{\cdot+} - CO_2CH_3$], 275 (17) [$M^{\cdot+} - C_2O_2H_2$], 205 (55) [$C_{16}H_{13}^+$], 105 (26) [$C_6H_5CO^+$]; exact mass calculated for $C_{21}H_{22}O_4$: 338.1518; found 338.1529. **Minor Isomer 15b′:** Yield 32%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37−7.04 (m, 9 H, H arom.), 3.81 (m, 2 H, H^2 + CH_2OH), 3.64 (d, *J* = 16 Hz, 1 H, H^5), 3.35 (s, 3 H, OCH_3), 2.67 (d, *J* = 16 Hz, 1 H, H^5), 2.50 (s, 1 H, OH), 2.18 (m, 2 H, CH_2OH + H^4), 1.65 (m, 1 H H^4), 1.29 (m, 2 H, H^3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.9, 146.5, 143.6, 139.2, 128.2, 127.7, 127.2, 126.8, 126.3, 125.3, 124.8, 124.4, 89.4, 72.3, 66.0, 57.8, 51.5, 42.1, 29.2, 21.2 ppm. **Major Isomer 15b:** Yield 61%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27−7.15 (m, 8 H, H arom.), 7.05 (d, *J* = 8 Hz, 1 H, H arom.), 4.38 (m, 1 H, H^2), 3.91 (d, *J* = 17 Hz, 1 H, H^5), 3.59 (dd, *J* = 12, 4 Hz, 1 H, CH_2OH), 3.47 (dd, *J* = 12, 7 Hz, 1 H, CH_2OH), 3.30 (s, 3 H, OCH_3), 3.08 (d, *J* = 17 Hz, 1 H, H^5), 2.50 (s, 1 H, OH), 2.18 (ddd, *J* = 15, 6, 6 Hz, 1 H, H^4), 1.93 (ddd, *J* = 15, 9, 6 Hz, 1 H, H^4), 1.76 (m, 1 H, H^3), 1.52 (m, 1 H, H^3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.9, 147.0, 143.7, 139.5, 128.6, 127.8, 127.4, 126.9, 126.5, 125.9, 125.0, 124.5, 89.6, 72.5, 66.2, 58.0, 42.6, 41.4, 29.5, 21.5 ppm.

Methyl (4a*S,10b*R**)-2-(Hydroxymethyl)-10b-phenyl-3,4,6,10b-tetrahydro-2*H*-benzo[*h*]chromene-4a(5*H*)-carboxylate (21b,b′):** Mixture of diastereoisomers, *de* = 14%; yield 70%. IR (NaCl): $\tilde{\nu}$ = 3342.9 (OH), 1726.0 (C=O) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27−7.08 (m, 9 H, H arom.), 4.32 (m, 0.43 H, H^2), 3.78 (dd, *J* = 11, 7 Hz, 0.57 H, CH_2OH), 3.72 (dd, *J* = 11, 3 Hz, 0.57 H, CH_2OH), 3.59 (m, 0.57 H, H^2), 3.50 (m, 0.86 H, CH_2OH), 3.42 (s, 1.29 H, OCH_3), 3.28 (s, 1.71 H, OCH_3), 3.21 (ddd, *J* = 18, 11, 6 Hz, 0.43 H, H^6), 3.02 (m, 1.14 H, H^6), 2.98 (ddd, *J* = 18, 6, 3 Hz, 0.43 H, H^6), 2.63−2.19 (m, 2 H, 0.57 H^3 + 0.57 H^4 + 0.86 H^5), 2.11 (m, 1.29 H, 0.43 H^3 + 0.86 H^4), 2.02 (dt, *J* = 14, 5 Hz, 0.57 H, H^5), 1.87 (ddd, *J* = 14, 5, 2 Hz, 0.57 H, H^5), 1.70 (ddd, *J* = 15, 6, 3 Hz, 0.57 H, H^4), 1.52−1.29 (m, 1 H, H^3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.4, 174.9, 145.9, 145.1, 143.8, 138.6, 136.8, 136.1, 129.5, 129.1, 128.8, 128.7, 128.5, 128.1, 127.8, 127.7, 127.6, 127.4, 126.8, 81.0, 79.7, 75.0, 71.3, 66.9, 66.8, 52.0, 51.6, 48.9, 47.2, 29.7, 27.4, 26.8, 26.7, 25.8, 25.1, 23.5, 22.7 ppm. MS (EI): *m*/*z* (%) = 353 (17) [MH^+], 321 (100)[MH^+ − MeOH], 292 (48)[$M^{\cdot+} - CO_2CH_3 - H_2$], 289 (61) MH^+ − 2MeOH], 261 [$MH^+ - HCO_2CH_3$ − MeOH], 105 (33) [$C_6H_5CO^+$], 77 (34) [$C_6H_5^+$]; exact mass calculated for $C_{22}H_{24}O_4$: 352.1675; found 352.1687.

General Procedure for the Mesylation of 15a,a′, 15b/15b′, 21a,a′ and 21b,b′: Et_3N (8.5 mL, 61 mmol) was added to a solution of **15a**,**a′** (1.98 g, 6 mmol) in CH_2Cl_2 (50 mL). MsCl (1.9 mL, 24 mmol) and DMAP (0.15 g, 1 mmol) were then added at 0 °C. After stirring at 0 °C for 2 h, water (50 mL) was added. The aqueous layer was extracted three times with CH_2Cl_2. The combined organic phases were dried with $MgSO_4$ and filtered and then the solvents were evaporated. The residue was purified by column chromatography (silica gel; heptane/ethyl acetate, 1:1).

Methyl (3a*S,8b*R**)-2-{[(Methylsulfonyl)oxy]methyl}-8b-phenyl-2,3,4,8b-tetrahydro-3a*H*-indeno[1,2-*b*]furan-3a-carboxylate (15a,a′ Mesylate):** Mixture of diastereoisomers, *de* = 16%; yield 78%. IR (KBr): $\tilde{\nu}$ = 1719.9 (C=O), 1353.2 + 1170.5 (SO_2O) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38−7.03 (m, 9 H, H arom.), 5.01 (m, 0.58 H, H^2), 4.58 (dd, *J* = 11, 6 Hz, 0.42 H, CH_2OMs), 4.44 (dd, *J* = 11, 4 Hz, 0.42 H, CH_2OMs), 4.15 (dd, *J* = 11, 4 Hz, 0.58 H, CH_2OMs), 4.09 (dd, *J* = 11, 6 Hz, 0.58 H, CH_2OMs), 4.06 (m, 0.42 H, H^2), 3.94 (d, *J* = 17 Hz, 0.42 H, H^4), 3.83 (d, *J* = 17 Hz, 0.58 H, H^4), 3.22 (s, 1.74 H, OCH_3), 3.12 (s, 1.26 H, SO_2CH_3), 3.10 (s, 1.26 H, OCH_3), 3.05 (d, *J* = 17 Hz, 0.42 H, H^4), 2.93 (s, 1.74 H, SO_2CH_3), 3.03 (d, *J* = 17 Hz, 0.58 H, H^4), 2.81 (m, 1 H, H^3), 2.01 (dd, *J* = 13, 7 Hz, 0.42 H, H^3), 1.83 (dd, *J* = 13, 10 Hz, 0.58 H, H^3) ppm. ^{13}C (100 MHz, $CDCl_3$): δ = 173.5, 173.1, 146.0, 143.2, 141.7, 141.1, 140.2, 139.5, 129.3, 129.0, 128.2, 128.0, 127.7, 127.6, 127.5, 127.4, 126.5, 126.4, 126.0, 125.6, 125.5, 125.2, 124.6, 101.9, 101.2, 78.6, 75.4, 70.9, 70.6, 66.2, 65.2, 51.8, 51.7, 40.9, 40.8, 40.6, 38.8, 37.8, 37.6 ppm. MS (EI): *m*/*z* (%) = 402 (9) [$M^{\cdot+}$], 384 (20) [$M^{\cdot+} - H_2O$], 370 (61) [$M^{\cdot+}$ − MeOH], 306 (2) [$M^{\cdot+} - CH_3SO_3H$], 288 (19) [$M^{\cdot+} - H_2O - CH_3SO_3H$], 264 (33) [$M^{\cdot+} - CH_3SO_3CH_2$-CHO], 229 (35) [$C_{18}H_{13}^+$], 205 (100) [$C_{16}H_{13}^+$]; exact mass calculated for $C_{21}H_{22}SO_6$: 402.1137; found 402.1136.

Methyl (2*R,4a*R**,9b*R**)-2-{[(Methylsulfonyl)oxy]methyl}-9b-phenyl-3,4,5,9b-tetrahydroindeno[1,2-*b*]pyran-4a(2*H*)-carboxylate (15b Mesylate) + Methyl (2*S**,4a*R**,9b*R**)-2-{[(Methylsulfonyl)-oxy]methyl}-9b-phenyl-3,4,5,9b-tetrahydroindeno[1,2-*b*]pyran-4a(2*H*)-carboxylate (15b′ Mesylate):** IR (KBr): $\tilde{\nu}$ = 1724.4 (C=O), 1451.9 + 1280.0 (SO_2O) cm^{-1}. MS (EI): *m*/*z* (%) = 416 (1) [$M^{\cdot+}$], 384 (11) [$M^{\cdot+}$ − MeOH], 357 (100) [$M^{\cdot+} - CH_3CO_2$], 321 (20) [$M^{\cdot+} - CH_3SO_3$], 302 (9) [$M^{\cdot+} - CH_2SO_3 - H_2O$]; exact mass calculated for $C_{22}H_{24}O_6S$: 416.1294; found 416.1284. **Minor Isomer 15b′ Mesylate:** Yield 32%. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.41−6.97 (m, 9 H, H arom.), 4.52 (dd, *J* = 11, 7 Hz, 1 H, CH_2OMs), 4.30 (dd, *J* = 11, 3 Hz, 1 H, CH_2OMs), 3.95 (m, 1 H, H^2), 3.62 (d, *J* = 16 Hz, 1 H, H^5), 3.35 (s, 3 H, OCH_3), 3.06 (s, 3 H, SO_2CH_3), 2.66 (d, *J* = 16 Hz, 1 H, H^5), 2.22 (m, 2 H, H^4), 1.66 (m, 2 H, H^3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.2, 143.7, 142.2, 139.5, 129.5, 129.2, 128.4, 128.0, 127.5, 126.5, 126.0, 125.6, 125.0, 90.3, 72.6, 69.9, 55.7, 51.9, 40.6, 38.1, 37.6, 21.9 ppm. **Major Isomer 15b Mesylate:** Yield 63%. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34−7.02 (m, 9 H, H arom.), 4.63 (m, 1 H, H^2), 4.20 (m, 2 H, CH_2OMs), 3.97 (d, *J* = 17 Hz, 1 H, H^5), 3.35 (s, 3 H, OCH_3), 3.08 (d, *J* = 17 Hz, 1 H, H^5), 3.02 (s, 3 H, SO_2CH_3), 2.20 (dt, *J* = 14, 6 Hz, 1 H, H^4), 1.92 (m, 2 H, H^4 + H^3), 1.54 (m, 1 H, H^3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.0, 146.9, 142.3, 141.4, 130.1, 129.3, 128.6, 128.1, 127.9, 126.8, 126.2, 125.7, 125.1, 90.9, 73.2, 70.0, 58.0, 52.2, 42.9, 38.2, 31.7, 23.6 ppm.

Methyl (3a*S,9b*R**)-2-{[(Methylsulfonyl)oxy]methyl}-9b-phenyl-2,3,5,9b-tetrahydronaphtho[1,2-*b*]furan-3a(4*H*)-carboxylate (21a,a′ Mesylate):** Mixture of diastereoisomers, *de* = 12%; yield 95%, IR (KBr): $\tilde{\nu}$ = 1721.4 (C=O) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.27−7.03 (m, 9 H, H arom.), 5.06 (m, 0.56 H, H^2), 4.83 (dd, *J* = 11, 8 Hz, 0.44 H, CH_2OMs), 4.48 (dd, *J* = 11, 4 Hz, 0.44 H, CH_2OMs), 4.03 (m, 0.44 H, H^2), 3.90 (dd, *J* = 11, 4 Hz, 0.56 H, CH_2OMs), 3.77 (dd, *J* = 11, 6 Hz, 0.56 H, CH_2OMs), 3.22 (s, 1.68 H, OCH_3), 3.20 (s, 1.32 H, SO_3CH_3), 3.10 (s, 1.32 H, OCH_3), 3.02 (m, 2 H, H^5), 2.78 (s, 1.68 H, SO_2CH_3), 2.52 (m, 1 H, H^4), 2.48 (dd, *J* = 13, 7 Hz, 0.57 H, H^3), 2.32 (m, 0.86 H, H^3), 2.08 (dd, *J* = 13, 9 Hz, 0.57 H, H^3), 1.99 (m, 1 H, H^4) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.0, 174.4, 144.0, 143.1, 141.5, 139.6, 136.1, 134.2, 131.1, 130.1, 128.4, 128.3, 128.1, 128.0, 127.9, 127.8, 127.5, 127.3, 127.1, 126.5, 89.2, 88.6, 76.6, 73.8, 72.3, 72.0, 58.1, 57.2, 52.1, 52.0, 38.1, 37.6, 34.2, 33.9, 25.0, 24.8, 24.6, 24.0 ppm. MS (EI): *m*/*z* (%) = 417 (9) [$MH^{\cdot+}$], 356 (30) [$M^{\cdot+} - CH_3CO_2H$], 339 (16) [$MH^{\cdot+} - CH_3CO_2H - H_2O$], 263 (100) [$MH^{\cdot+} - CH_3SO_3 - CH_3CO_2$], 243 (53) [$M^{\cdot+} - HCO_2CH_3 - CH_3SO_3H - H_2O$]; exact mass calculated for $C_{22}H_{24}O_6S$: 416.1294; found 416.1291.

Methyl (4a*S,10b*R**)-2-{[(Methylsulfonyl)oxy]methyl}-10b-phenyl-3,4,6,10b-tetrahydro-2*H*-benzo[*h*]chromene-4a(5*H*)-carboxylate**

(21b,b′ Mesylate): Mixture of diastereoisomers, *de* = 14%; yield 98%. IR (KBr): $\tilde{\nu}$ = 1725.9 (C=O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.30−7.08 (m, 9 H, H arom.), 4.61 (m, 0.43 H, H^2), 4.44 (dd, *J* = 11, 8 Hz, 0.57 H, CH_2OMs), 4.28 (dd, *J* = 11, 3 Hz, 0.57 H, CH_2OMs), 4.15 (dd, *J* = 10, 6 Hz, 0.43 H, CH_2OMs), 3.92 (dd, *J* = 10, 6 Hz, 0.43 H, CH_2OMs), 3.88 (m, 0.57 H, H^2), 3.35 (s, 1.29 H, OCH_3), 3.33 (s, 1.71 H, OCH_3), 3.05 (s, 1.71 H, SO_2CH_3), 3.00 (m, 2 H, H^6), 2.94 (s, 1.29 H, SO_2CH_3), 2.48 (m, 1.43 H, 1 H^3 + 0.43 H^4), 2.29 (m, 1 H, H^3), 2.09 (m, 1 H, H^5), 1.93 (m, 1.57 H, H^4), 1.74 (m, 1 H, H^5) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.1, 174.6, 145.5, 145.1, 143.2, 138.1, 136.9, 135.9, 135.8, 129.9, 128.9, 128.5, 128.4, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 127.4, 126.9, 81.4, 79.9, 73.6, 72.5, 72.0, 68.8, 52.1, 51.7, 48.7, 46.9, 38.0, 37.9, 29.3, 27.3, 26.6, 26.1, 25.6, 25.0, 23.5, 22.6 ppm. MS (EI): *m*/*z* (%) = 431 (28) [$M^{\cdot+}$], 412 (13) [$M^{\cdot+}$ − H_2O], 370 (100) [$M^{\cdot+}$ − CH_3CO_2 − H_2], 353 (50) [$M^{\cdot+}$ − CH_3CO_2H − H_2O]; exact mass calculated for $C_{23}H_{26}O_6S$: 430.1450; found 430.1458.

General Procedure for the Synthesis of 16a,a′, 16b and 16b′, 22a,a′ and 22b,b′: $MeNH_2$ (40% solution in water; 1.2 mL, 14 mmol) was added to a solution of the mesylate (1.22 g, 3 mmol) in methanol (20 mL). After heating at 120 °C in a steel bomb for 6 h, the reaction mixture was cooled and then water (30 mL) was added. The aqueous layer was extracted three times with CH_2Cl_2. The combined organic phases were dried with $MgSO_4$ and filtered and then the solvents were evaporated. The residue was purified by column chromatography (silica gel; methanol/CH_2Cl_2, 1:9).

Methyl (3a*S,8b*R**)-2-[(Methylamino)methyl]-8b-phenyl-2,3,4,8b-tetrahydro-3a*H*-indeno[1,2-*b*]furan-3a-carboxylate (16a,a′):** Mixture of diastereoisomers, *de* = 16%; yield 50%. IR (NaCl): $\tilde{\nu}$ = 3487.0 (NH), 1728.5 (C=O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.35−7.05 (m, 9 H, H arom.), 4.94 (m, 0.58 H, H^2), 4.51 (s, 1 H, NH), 3.99 (d, *J* = 17 Hz, 0.58 H, H^4), 3.98 (m, 0.42 H, H^2), 3.83 (d, *J* = 17 Hz, 0.42 H, H^4), 3.19 (s, 1.26 H, OCH_3), 3.09 (s, 1.74 H, OCH_3), 3.06 (m, 3 H, 1 H^4 + 2CH_2NHCH_3), 2.81 (dd, *J* = 13, 6 Hz, 0.42 H, H^3), 2.71 (dd, *J* = 13, 10 Hz, 0.58 H, H^3), 2.53 (s, 1.74 H, $NHCH_3$), 2.43 (s, 1.26 H, $NHCH_3$), 1.98 (dd, *J* = 13, 6 Hz, 0.58 H, H^3), 1.76 (dd, *J* = 13, 10 Hz, 0.42 H, H^3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.5, 173.9, 147.0, 143.9, 142.4, 142.0, 141.1, 139.9, 129.5, 129.2, 128.4, 128.2, 128.0, 127.8, 127.7, 127.0, 126.8, 126.4, 126.0, 125.6, 101.8, 101.0, 80.1, 76.5, 66.7, 65.8, 56.3, 54.8, 52.1, 52.0, 43.1, 43.0, 41.5, 39.5, 36.1, 36.0 ppm. MS (EI): *m*/*z* (%) = 337 (56) [$M^{\cdot+}$], 278 (19) [$M^{\cdot+}$ − CH_3CO_2], 205 (100) [$M^{\cdot+}$ − HCO_2CH_3 − H_2NCH_3 − CO]; exact mass calculated for $C_{21}H_{23}NO_3$: 337.1678; found 337.1676.

Methyl (2*R,4a*R**,9b*R**)-2-[(Methylamino)methyl]-9b-phenyl-3,4,5,9b-tetrahydroindeno[1,2-*b*]pyran-4a(2*H*)-carboxylate (16b) and Methyl (2*S**,4a*R**,9b*R**)-2-[(Methylamino)methyl]-9b-phenyl-3,4,5,9b-tetrahydroindeno[1,2-*b*]pyran-4a(2*H*)-carboxylate (16b′):** IR (NaCl): $\tilde{\nu}$ = 3485.4 (NH), 1729.3 (C=O) cm^{-1}. MS (EI): *m*/*z* (%) = 351 (100) [$M^{\cdot+}$], 320 (30) [$M^{\cdot+}$ − H_2NCH_3], 291 (33) [$M^{\cdot+}$ − HCO_2CH_3]; exact mass calculated for $C_{22}H_{25}O_3N$: 351.1834; found 351.1848. **Minor Isomer 16b′:** Yield 69%. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.48−6.92 (m, 9 H, H arom.), 3.83 (m, 2 H, NH + H^2), 3.60 (d, *J* = 16 Hz, 1 H, H^5), 3.32 (s, 3 H, OCH_3), 2.94 (dd, *J* = 12, 8 Hz, 1 H, CH_2NHCH_3), 2.78 (dd, *J* = 12, 2 Hz, 1 H, CH_2NHCH_3), 2.64 (d, *J* = 16 Hz, 1 H, H^5), 2.52 (s, 3 H, NCH_3), 2.17 (m, 2 H, H^4), 1.64 (m, 1 H, H^3), 1.39 (m, 1 H, H^3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.5, 144.1, 142.8, 140.3, 129.0, 128.1, 127.8, 126.9, 125.7, 124.9, 89.9, 70.0, 58.3, 56.8, 51.8, 40.7, 36.4, 29.8, 23.9 ppm. **Major Isomer 16b:** Yield 76%. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.30−7.02 (m, 9 H, H arom.), 4.40 (m, 1 H, H^2), 4.09 (d, *J* = 17 Hz, 1 H, H^5), 3.27 (s, 3 H, OCH_3), 3.11 (d, *J* = 17 Hz, H^5), 2.78 (s, 1 H, NH), 2.57 (m, 2 H, CH_2NHCH_3), 2.45 (s, 3 H, $NHCH_3$), 2.24 (dd, *J* = 13, 6 Hz, 1 H, H^4), 1.95 (ddd, *J* = 13, 8, 6 Hz, 1 H, H^4), 1.82 (m, 1 H, H^3), 1.49 (m, 1 H, H^3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.5, 147.6, 144.2, 140.2, 128.9, 128.1, 127.7, 127.2, 126.2, 125.5, 124.9, 89.9, 71.5, 58.4, 57.6, 52.0, 42.5, 36.7, 30.0, 24.0 ppm.

Methyl (3a*S,9b*R**)-2-[(Methylamino)methyl]-9b-phenyl-2,3,5,9b-tetrahydronaphtho[1,2-*b*]furan-3a(4*H*)-carboxylate (22a,a′):** Mixture of diastereoisomers, *de* = 12%; yield 61%. IR (NaCl): $\tilde{\nu}$ = 3476.9 (NH), 1721.5 (C=O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.23−7.04 (m, 9 H, H arom.), 4.87 (m, 0.56 H, H^2), 3.82 (m, 0.44 H, H^2), 3.18 (s, 1.68 H, OCH_3), 3.09 (s, 1.32 H, OCH_3), 2.96 (m, 2 H, H^5), 2.51 (m, 2 H, CH_2NHCH_3), 2.43 (dd, *J* = 13, 8 Hz, 0.56 H, H^3), 2.35 (s, 1 H, NH), 2.34 (s, 1.32 H, $NHCH_3$), 2.26 (s, 1.68 H, $NHCH_3$), 2.15 (dd, *J* = 14. 8 Hz, 0.56 H, H^3), 1.94 (m, 2.88 H, 0.88 H^3 + 2 H^4) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.6, 174.8, 144.5, 143.8, 142.3, 140.3, 136.5, 134.1, 130.5, 130.2, 128.1, 127.9, 127.8, 127.7, 127.6, 127.5, 127.4, 127.1, 88.2, 87.7, 78.1, 75.0, 58.2, 57.7, 56.0, 55.6, 53.9, 51.9, 36.8, 36.7, 36.0, 35.9, 25.7, 25.2, 24.9, 24.2 ppm. MS (EI): *m*/*z* (%) = 352 (57) [MH^+], 320 (7) [$M^{\cdot+}$ − H_2NCH_3], 275 (29) [$C_{19}H_{15}O_2^+$], 219 (43) [$C_{17}H_{15}^+$], 205 (100) [$C_{16}H_{13}^+$]; exact mass calculated for $C_{22}H_{25}NO_3$: 352.1913; found 352.1883.

Methyl (4a*S,10b*R**)-2-[(Methylamino)methyl]-10b-phenyl-3,4,6,10b-tetrahydro-2*H*-benzo[*h*]chromene-4a(5*H*)-carboxylate (22b,b′):** Mixture of diastereoisomers, *de* = 14%, yield 96%. IR (NaCl): $\tilde{\nu}$ = 3483.4 (NH), 1725.2 (C=O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.23−7.02 (m, 9 H, H arom.), 5.19 (s, 1 H, NH), 4.53 (m, 0.43 H, H^2), 3.71 (m, 0.57 H, H^2), 3.34 (s, 1.29 H, OCH_3), 3.30 (s, 1.71 H, OCH_3), 3.15−2.90 (m, 2.43 H, 2 H^6 + 0.43 CH_2NHCH_3), 2.78 (dd, *J* = 13, 3 Hz, 0.57 H, CH_2NHCH_3), 2.54 (s, 1.71 H, $NHCH_3$), 2.50 (s, 1.29 H, $NHCH_3$), 2.49−2.22 (m, 2.86 H, 1 CH_2NHCH_3 + 1 H^5 + 0.43 H^4 + 0.43 H^3), 2.02−1.66 (m, 3.14 H, 1 H^5 + 1.57 H^4 + 0.57 H^3), 1.42 (m, 1 H, H^3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.3, 174.8, 145.8, 145.2, 143.8, 138.5, 136.7, 136.1, 129.6, 129.0, 128.8, 128.5, 128.4, 128.1, 127.8, 127.7, 127.5, 127.3, 126.8, 81.1, 79.7, 72.2, 68.5, 56.5, 53.9, 52.1, 51.6, 48.8, 47.1, 36.2, 35.7, 29.7, 27.3, 26.9, 26.8, 15.7, 15.5, 25.1, 24.6 ppm. MS (EI): *m*/*z* (%) = 365 (42) [$M^{\cdot+}$], 321 (22) [$M^{\cdot+}$ − CH_2NHCH_3], 289 (75) [$M^{\cdot+}$ − $C_3H_{10}NO$], 261 (61) [$M^{\cdot+}$ − HCO_2CH_3 − CH_2NHCH_3], 219 (100) [$C_{17}H_{15}^+$]; exact mass calculated for $C_{23}H_{27}O_3N$: 365.1991; found 365.1985.

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