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Preparation of Polysubstituted Isochromanes by Addition of *ortho*-Lithiated Aryloxiranes to Enaminones

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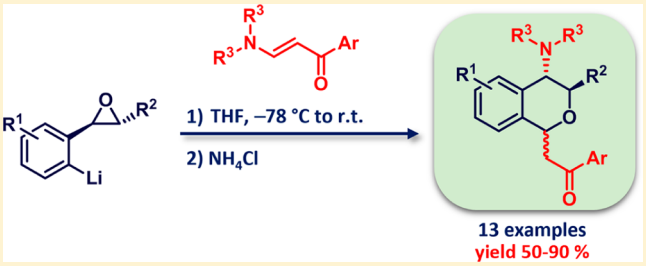
Supporting Information

ABSTRACT: The reaction of *ortho*-lithiated aryloxiranes with various enaminones straightforwardly affords new functionalized isochromanes as mixtures of two epimeric stereoisomers in reasonable to very good yields (50−90%). The two diastereomers, which show a high structural variability, can be easily separated by column chromatography.



Isochromanes enjoy a special interest in the field of heterocyclic chemistry because they occur frequently in a wide variety of natural products with variegated biological activities. Indeed, some isochromane derivatives exhibit hypotensive,[1] antitumor,[2] and growth-regulating[3] activities; some others have a specific effect on the dopaminergic system.[4]

The most commonly used approaches to the formation of the pyran ring of isochromanes are based on the cyclization of *β*-phenylethanols with aldehydes[5−7] and base-catalyzed cyclizations of 2-allylbenzylic alcohols.[8,9] In both methods, high temperatures are required, and in several cases the yields are quite disappointing. A more convenient method based on the reaction of methyleugenol with methyl trifluoromethyl pyruvate has recently been developed.[10] A stereoselective synthesis of alkylamino-substituted isochromanes[11] based on the lateral lithiation of *N*-alkyl-(*o*-tolyl)aziridines followed by trapping with carbonyl compounds has recently been reported.[12] An enantiospecific synthesis of isochromanes using a variant of the intramolecular Nicholas reaction has also been described,[13] as well as a gold-catalyzed intramolecular furan/alkyne reaction.[14] Because of the importance of isochromane derivatives for their biological activities, the development of new methods of synthesis of such compounds is actively being pursued.

In the present paper, we report a novel one-pot synthetic procedure for isochromanes simply based on the addition of *ortho*-lithiated aryloxiranes[15] to enaminones, which are versatile building blocks in the synthesis of many heterocyclic systems, including natural products and their analogues.[16]

Addition of *ortho*-lithiated *trans*-stilbene oxide (**1a-Li**) (Figure 1), obtainable by Li−Br exchange of the corresponding *o*-bromo-*trans*-stilbene oxide (**1a**) upon treatment with PhLi in THF at −78 °C (Scheme 1),[17] to the Michael acceptor 1-phenyl-3-dimethylaminopropenone (**2a**) resulted in the unexpected formation of a couple of diastereomers with poor stereoselectivity (d.r. 66/34), as assessed by ^{1}H NMR analysis. Indeed, the same *ortho*-lithiated aryloxiranes have been reported to react with other Michael acceptors to give clean 1,4-addition.[15a,b] The two diastereomers could be easily separated by column chromatography. A detailed NMR investigation was successively carried out on the major diastereomer in order to unequivocally elucidate its structure. The absence of vinylic protons in the ^{1}H NMR spectrum led us to rule out the formation of the addition−elimination compound **3** (Figure 1).

Furthermore, although the ^{1}H NMR spectrum of the above major diastereomer showed an ABX spin system typical of a CH−CH$_2$ residue,[18] which could be consistent with the structure of Michael adduct **4**, this compound was ruled out because of the two doublets detected at 4.71 and 4.09 ppm with a coupling constant ($^3J_{H-H}$) of 8.9 Hz, which is not compatible with a *trans*-configured epoxide (^3J < 3 Hz). Moreover, both the 2,3-dihydro-1*H*-indene **5** and the 1,2,3,4-tetrahydronaphthol **6**, which in principle could originate from a Michael addition of **1a-Li** to **2a** followed by a cyclization on the epoxide ring, in analogy to our previous studies,[15] can be excluded as well because a methylene unit is not present in their structures (Figure 1).[19]

On the basis of the above evidence, we conclude that the final product of the reaction between **1a-Li** and **2a** has the structure of isochromanes **8a**/*epi*-**8a** (mixture of diaster-

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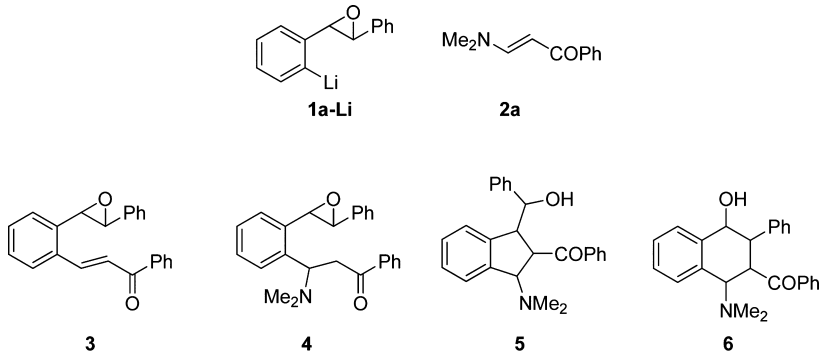
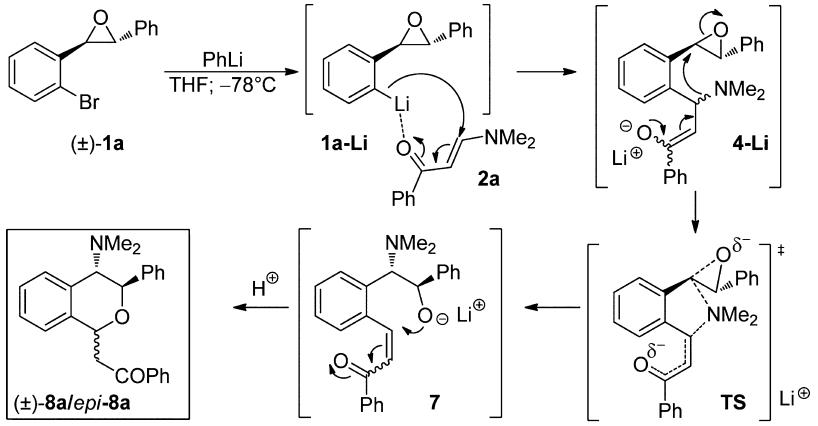


Figure 1. Plausible products from the conjugate addition of **1a-Li** to enaminone **2a**.

Scheme 1. Proposed Mechanism for the Multistep Formation of Isochromane Derivatives (±)-8a/*epi*-8a



eomers), which may form at the end of a multistep process including inter- and intramolecular Michael additions and regio- and stereoselective ring-opening and ring-closing steps, as in the proposed synchronous concerted mechanism depicted in Scheme 1. Isochromanes **8a**/*epi*-**8a** proved to be interconvertible under basic conditions.[20]

The highly regioselective epoxide ring opening can be justified since the delivery of the very poor leaving group Me_2NLi in **4-Li** should occur only in a concerted fashion to the closest benzylic carbon via the kinetically favored five-membered cyclic transition state **TS** (Scheme 1). A 2D NOESY experiment was then performed on the major stereoisomer in order to obtain information about the spatial arrangement of the groups in the molecule (Figure 2). Strong

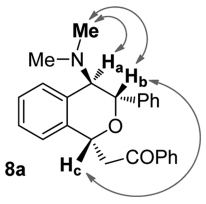


Figure 2. NOEs observed in the major diastereomer **8a**.

NOEs were detected between the dimethylamino group and the two benzylic protons H_a and H_a (originally belonging to the epoxide moiety) as well as between H_b and H_c. Such evidence on the one hand strongly supports the assigned stereochemistry of **8a** (Figure 2)[21] but on the other hand suggests that the Me_2N group migrates from its original position (β with respect to the carbonyl group in the electrophile **2a**), thereby triggering a nucleophilic intramolecular epoxide ring-opening reaction. The structure of the major diastereoisomer was also confirmed by X-ray analysis on the derivative **8j** (vide infra).

A further experiment established that the two diastereomers isolated from the crude reaction mixture were epimeric at the C1 position. Indeed, a mixture of two stereoisomers in a 64/36 ratio was recovered after treatment of **8a** with LDA in THF at 0 °C followed by acidic quenching (Scheme 2). The spectral data for the minor stereoisomer completely fitted those of *epi*-**8a** obtained from the Michael addition reaction of **1a-Li** to propenone **2a** (Scheme 1). The proposed mechanism shown in Scheme 1 is also consistent with the formation of two diastereomers epimeric at C1, as the nucleophilic attack at the epoxide moiety in a basic medium presumably occurs via a stereospecific S_N2 reaction,[15] whereas the addition of the resulting alkoxide to the planar C−C double bond of **7** is most likely not stereoselective.

Comparable results were obtained when *ortho*-lithiated *trans*-stilbene oxide **1a-Li** was reacted with enaminones **2b−g** to give the corresponding isochromanes **8b−g**/*epi*-**8b−g** in reasonable yields (50−65%; Table 1, entries 2−7). The relative configuration of the diastereoisomers *epi*-**8** was confirmed by a 2D NOESY experiment carried out on the model compound *epi*-**8b** (see the Supporting Information).

The reaction proved to be of general applicability with reference to the amino group of the used enaminone and the structural features of the *ortho*-lithiated *trans*-aryloxirane. Indeed, it worked equally well when different sterically hindered enaminones (dimethylamino-, diethylamino-, and pyrrolidinyl-substituted propenones **2a**,**b**,**h**,**i**) were reacted with *ortho*-lithiated aryloxiranes **1b-Li**, **1c-Li**, and **1d-Li**; the

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Scheme 2. Equilibration between 8a and *epi*-8a in a Basic Medium

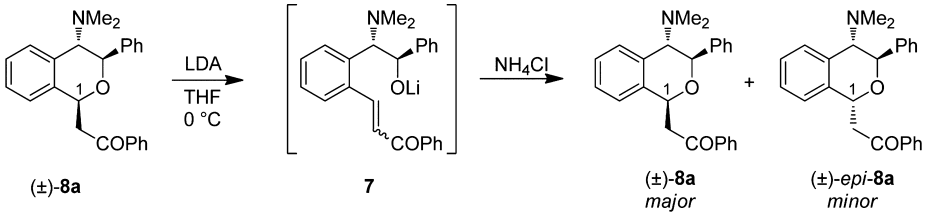
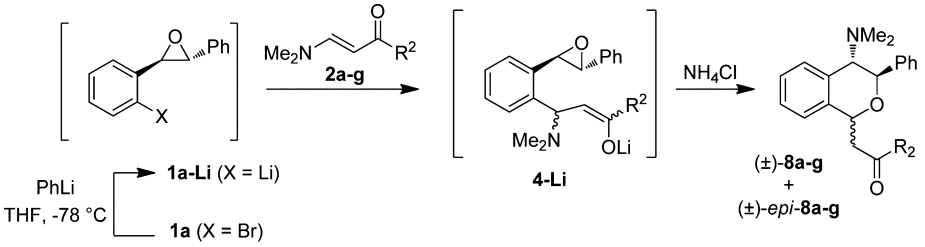
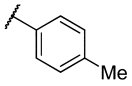
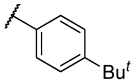
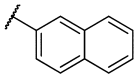
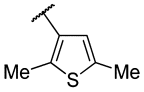


Table 1. Synthesis of Isochromane Derivatives 8a–g/*epi*-8a–g[a]



entry	enaminone **2**	R^2	isochromane **8**, yield (%)[b,c]	d.r.[d,e]
1	**2a**		**8a**/*epi*-**8a** (60)	66:34[f]
2	**2b**		**8b**/*epi*-**8b** (60)	50:50
3	**2c**		**8c**/*epi*-**8c** (60)	50:50
4	**2d**		**8d**/*epi*-**8d** (65)	70:30[f]
5	**2e**		**8e**/*epi*-**8e** (50)	50:50
6	**2f**		**8f**/*epi*-**8f** (50)	50:50
7	**2g**		**8g**/*epi*-**8g** (63)	66:34[f]

[a]Subjected to the lithiation–trapping sequence, *cis*-configured *o*-bromostilbene oxide did not lead to any isochromane derivative but to a mixture of unidentified compounds. [b]Isolated yields after column chromatography. [c]Overall isolated yields of both diastereomers. [d]Calculated by ^{1}H NMR analysis of the crude reaction mixture. [e]Separable by column chromatography on silica gel (see the Experimental Section). [f]The relative configuration of the major diastereomer was 1*R**,3*S**,4*R**.

resulting isochromane derivatives **8h–m**/*epi*-**8h–m** were isolated in reasonable to very good yields (50–90%; Table 2).

In conclusion, this paper has reported a new one-pot method of synthesis of isochromane derivatives, which are of interest in several fields for their biological properties and synthetic utility, simply based on the reaction of *ortho*-lithiated aryloxiranes with enaminones. A plausible mechanism for their formation has also been proposed on the basis of spectroscopic and crystallographic evidence.

EXPERIMENTAL SECTION

General Methods. Oxiranes **1a–d** were prepared according to the Durst's methodology.[22] Enaminones **2a–i** were prepared by aminomethylenation of commercially available acetophenones.[23]

Synthesis of Isochromanes 8a–m/*epi*-8a–m. *General Procedure.* A solution of PhLi (1.5 mmol; or 1 mmol of *n*-BuLi for **1d**) was added to a solution of the appropriate oxirane **1** (1.8 mmol; or 1.0 mmol for **1d**) in THF (6 mL) under N_2 with stirring at −78 °C (or −98 °C for **1d**). After 20 min (or 5 min for **1d**) at this temperature, a solution of enaminone **2** (1.0 mmol; or 0.9 mmol for **1d**) in THF (2 mL) was added dropwise. The resulting mixture was stirred and allowed to warm to rt, quenched with aq NH_4Cl (10 mL), and extracted with Et_2O (3 × 20 mL). The solvent was removed under reduced pressure, and the crude residue was purified by column chromatography (silica gel; hexane/Et_2O 5–7/5–3) to give compounds **8**.

2-[(1R,3S*,4R*)-4-(Dimethylamino)-3-phenylisochroman-1-yl]-1-phenylethanone (**8a**).* Brown oil, 150 mg, 40% yield. ^{1}H NMR (400 MHz): δ 2.16 (s, 6H), 3.43 (dd, ^2J = 11.4 Hz, ^3J = 5.0 Hz, 1H), 3.58 (dd, ^2J = 11.4 Hz, ^3J = 6.5 Hz, 1H), 4.09 (d, J = 9.1 Hz, 1H), 4.71 (d, J = 9.1 Hz, 1H), 5.60 (dd-like t, J = 5.7 Hz, 1H), 7.08–7.11 (m, 1H), 7.19–7.62 (m, 11H), 7.95–7.97 (m, 2H). ^{13}C NMR (100 MHz): δ 41.2, 45.7, 66.3, 73.9, 78.0.1, 123.6, 126.7, 126.8, 127.4, 127.8, 127.9, 128.2, 128.3[6], 128.4[2], 133.0, 137.1, 137.3, 139.2, 142.0, 198.2. ESI-MS (m/z): 394 [M^+ + 23 (Na)]. FT-IR (film, cm^{-1}): 3030, 2922, 2856,

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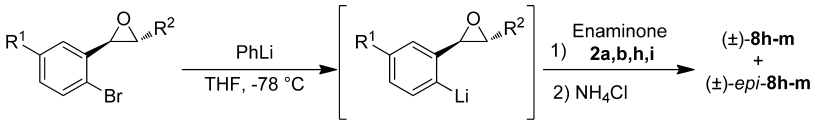
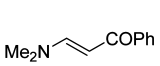
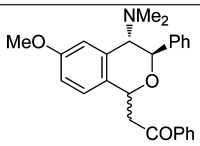
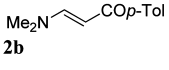
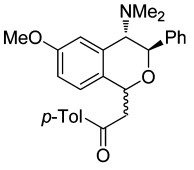
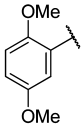
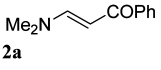
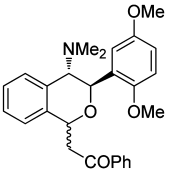
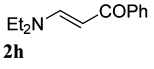
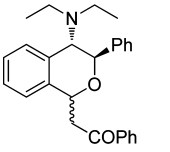
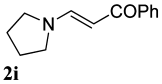
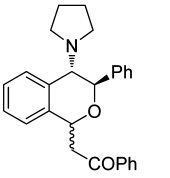
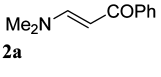
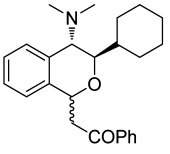
Table 2. Synthesis of Isochromane Derivatives 8h−m/*epi*-8h−m



1a-d **1a-d-Li**

entry	R^1	R^2	Oxirane **1**	Enaminone **2**	Isochromane **8**	Yield **8**/epi-**8** (%)[a,b] dr[c,d]
1	MeO	Ph	**1b**	 **2a**		**8h**/*epi*-**8h** (50) dr = 60/40[e]
2	″	″	**1b**	 **2b**		**8i**/*epi*-**8i** (50) dr = 66:34[e]
3	H		**1c**	 **2a**		**8j**/*epi*-**8j** (70) dr = 50:50
4	″	Ph	**1a**	 **2h**		**8k**/*epi*-**8k** (90) dr = 50:50
5	″	″	**1a**	 **2i**		**8l**/*epi*-**8l** (60) dr = 66:34[e]
6	H	*c*-Hex	**1d**	 **2a**		**8m**/*epi*-**8m** (50)[f] dr = 55:45

[a]Isolated yields after column chromatography. [b]Overall isolated yields of both diastereomers. [c]Calculated by ^{1}H NMR analysis of the crude reaction mixture. [d]Separable by column chromatography on silica gel (see the Experimental Section). [e]The relative configuration of the major diastereomer is 1*R**,3*S**,4*R**. [f]Lithiation was performed using *n*-BuLi at −98 °C.

1683, 1597, 1448, 848, 751, 700. Anal. Calcd for $C_{25}H_{25}NO_2$: C, 80.83; H, 6.78; N, 3.77. Found: C, 80.90; H, 6.90; N, 3.85.

2-[(1R,3R*,4S*)-4-(Dimethylamino)-3-phenylisochroman-1-yl]-1-phenylethanone (epi-**8a**).* Brown oil, 77 mg, 20% yield. ^{1}H NMR (400 MHz): δ 2.43 (s, 6H), 3.38 (dd, ^2J = 11.9 Hz, ^3J = 4.0 Hz, 1H), 3.68 (dd, ^2J = 11.9 Hz, ^3J = 8.6 Hz, 1H), 4.12 (d, J = 2.6 Hz, 1H), 5.24 (dd, J = 8.6, 4.0 Hz, 1H), 5.27 (d, J = 2.6 Hz, 1H), 7.08−7.10 (m, 1H), 7.23−7.60 (m, 11H), 7.98−8.00 (m, 2H). ^{13}C NMR (150 MHz): δ 41.8, 45.4, 62.0, 68.5, 71.9, 124.0, 127.1, 127.6, 127.7, 127.8, 128.4, 128.6, 130.2, 133.1, 137.3, 138.6, 139.0, 198.0. ESI-MS (m/z): 394 [M^+ + 23 (Na)]. FT-IR (film, cm^{-1}): 3062, 2926, 2783, 1682, 1634, 1449, 752, 697. Anal. Calcd for $C_{25}H_{25}NO_2$: C, 80.83; H, 6.78; N, 3.77. Found: C, 80.93; H, 6.93; N, 3.90.

2-[(1R,3S*,4R*)-4-(Dimethylamino)-3-phenylisochroman-1-yl]-1-(p-tolyl)ethanone (**8b**).* Yellow oil, 117 mg, 30% yield. ^{1}H NMR (400 MHz): δ 2.15 (s, 6H), 2.38 (s, 3H), 3.40 (dd, ^2J = 16.4 Hz, ^3J = 5.1 Hz, 1H), 3.56 (dd, ^2J = 16.4 Hz, ^3J = 6.4 Hz, 1H), 4.09 (d, J = 9.0 Hz, 1H), 4.70 (d, J = 9.0 Hz, 1H), 5.59 (dd-like t, J = 5.6 Hz, 1H), 7.06−7.08 (m, 1H), 7.18−7.39 (m, 9H), 7.58−7.60 (m, 1H), 7.85−7.87 (m, 2H). ^{13}C NMR (150 MHz): δ 21.6, 41.3, 45.7, 66.3, 73.9, 78.1 123.7, 126.7, 126.8, 127.5, 127.8, 128.0, 128.2, 128.5, 129.0, 129.1, 134.9, 139.4, 142.1, 143.8, 197.8. ESI-MS (m/z): 408 [M^+ + 23 (Na)]. FT-IR (film, cm^{-1}): 3030, 2923, 2855, 1682, 1606, 1450, 810, 756, 699. Anal. Calcd for $C_{26}H_{27}NO_2$: C, 81.01; H, 7.06; N, 3.63. Found: C, 81.17; H, 7.28; N, 3.78.

2-[(1R,3R*,4S*)-4-(Dimethylamino)-3-phenylisochroman-1-yl]-1-(p-tolyl)ethanone (epi-**8b**).* Yellow oil, 114 mg, 30% yield. ^{1}H NMR (600 MHz): δ 2.40 (s, 6H), 2.43 (s, 3H), 3.35 (dd, ^2J = 15.8 Hz, ^3J = 3.9 Hz, 1H), 3.67 (dd, ^2J = 15.8 Hz, ^3J = 8.4 Hz, 1H), 4.06 (d, J = 3.0 Hz, 1H), 5.24 (d, J = 3.0 Hz, 1H), 5.27 (dd, J = 8.4, 3.9 Hz, 1H), 7.08−7.09 (m, 1H), 7.24−7.32 (m, 9H), 7.56−7.58 (m, 1H), 7.89−7.91 (m, 2H). ^{13}C NMR (150 MHz): δ 21.6, 41.8, 45.3, 62.1, 68.6, 71.9, 124.0, 126.9, 127.4, 127.7, 128.3, 128.5, 129.2, 130.0, 134.9, 138.7, 139.3, 143.8, 197.6. ESI-MS (m/z): 408 [M^+ + 23 (Na)]. FT-IR

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(film, cm^{-1}): 3061, 2924, 2782, 1682, 1606, 755, 736, 700. Anal. Calcd for $C_{26}H_{27}NO_2$: C, 81.01; H, 7.06; N, 3.63. Found: C, 81.21; H, 7.30; N, 3.76.

1-(4-tert-Butylphenyl)-2-[(1R,3S*,4R*)-4-(dimethylamino)-3-phenylisochroman-1-yl]ethanone (**8c**).* Brown oil, 125 mg, 30% yield. ^{1}H NMR (400 MHz): δ 1.36 (s, 9H), 2.16 (s, 6H), 3.45 (dd, ^2J = 11.3 Hz, ^3J = 5.6 Hz, 1H), 3.57 (dd, ^2J = 11.3 Hz, ^3J = 6.4 Hz, 1H), 4.09 (d, J = 9.3 Hz, 1H), 4.70 (d, J = 9.3 Hz, 1H), 5.62 (dd-like t, J = 5.8 Hz, 1H), 7.23−7.51 (m, 11H), 7.91−7.91 (m, 2H). ^{13}C NMR (100 MHz): δ 31.0, 41.2, 45.6, 62.7, 66.3, 73.9, 123.6, 125.4, 125.6, 127.4, 128.1, 128.2, 128.3, 128.5, 128.8, 132.2, 137.0, 139.3, 142.1, 156.6, 197.7. ESI-MS (m/z): 450 [M^+ + 23 (Na)]. FT-IR (film, cm^{-1}): 3063, 2964, 1681, 1605, 1451, 1334, 1026, 839, 751, 697. Anal. Calcd for $C_{29}H_{33}NO_2$: C, 81.46; H, 7.78; N, 3.28. Found: C, 81.50; H, 7.85; N, 3.30.

1-(4-tert-Butylphenyl)-2-[(1R,3R*,4S*)-4-(dimethylamino)-3-phenylisochroman-1-yl]ethanone (epi-**8c**).* Brown oil, 129 mg, 30% yield. ^{1}H NMR (400 MHz): δ 1.32 (s, 9H), 2.36 (s, 6H), 3.30 (dd, ^2J = 11.8 Hz, ^3J = 4.0 Hz, 1H), 3.63 (dd, ^2J = 11.8 Hz, ^3J = 8.5 Hz, 1H), 4.03 (d, J = 3.2 Hz, 1H), 5.21 (d, J = 3.2 Hz, 1H), 5.23 (dd, J = 8.5, 4.0 Hz, 1H), 7.03−7.06 (m, 1H), 7.15−7.28 (m, 7H), 7.42−7.45 (m, 2H), 7.52−7.54 (m, 1H), 7.88−7.91 (m, 2H). ^{13}C NMR (100 MHz): δ 31.1, 41.8, 45.3, 62.1, 68.7, 71.8, 123.9, 125.4, 126.9, 127.3, 127.6, 127.7, 128.2, 128.3, 129.9, 134.0, 134.7, 138.6, 139.4, 156.7, 197.7. ESI-MS (m/z): 450 [M^+ + 23 (Na)]. FT-IR (film, cm^{-1}): 3061, 2964, 2783, 1682, 1605, 1450, 1285, 1030, 844, 737, 699. Anal. Calcd for $C_{29}H_{33}NO_2$: C, 81.46; H, 7.78; N, 3.28. Found: C, 81.50; H, 7.90; N, 3.50.

2-[(1R,3S*,4R*)-4-(Dimethylamino)-3-phenylisochroman-1-yl]-1-(naphthalen-2-yl)ethanone (**8d**).* Brown oil, 170 mg, 40% yield. ^{1}H NMR (600 MHz): δ 2.21 (s, 6H), 3.60 (dd, ^2J = 11.3 Hz, ^3J = 4.7 Hz, 1H), 3.78 (dd, ^2J = 11.3 Hz, ^3J = 6.7 Hz, 1H), 4.15 (d, J = 8.8 Hz, 1H), 4.77 (d, J = 8.8 Hz, 1H), 5.69 (dd-like t, J = 5.7 Hz, 1H), 7.18−7.20 (m, 1H), 7.27−7.42 (m, 7H), 7.55−7.67 (m, 3H), 7.88−7.96 (m, 3H), 8.06−8.08 (m, 1H), 8.54 (s, 1H). ^{13}C NMR (150 MHz): δ 41.3, 45.8, 66.3, 74.1, 78.1, 123.7, 124.1, 126.6, 126.7, 126.9, 127.5, 127.7, 127.8, 128.0, 128.2, 128.3, 128.4, 129.6, 130.4, 132.4, 134.8, 135.6, 137.1, 139.2, 142.0, 198.2. ESI-MS (m/z): 444 [M^+ + 23 (Na)]. FT-IR (film, cm^{-1}): 3030, 2920, 2786, 1681, 1597, 1469, 1449, 821, 756, 699. Anal. Calcd for $C_{29}H_{27}NO_2$: C, 82.63; H, 6.46; N, 3.32. Found: C, 82.76; H, 6.53; N, 3.42.

2-[(1R,3R*,4S*)-4-(Dimethylamino)-3-phenylisochroman-1-yl]-1-(naphthalen-2-yl)ethanone (epi-**8d**).* Brown oil, 104 mg, 25% yield. ^{1}H NMR (600 MHz): δ 2.43 (s, 6H), 3.49 (dd, ^2J = 11.7 Hz, ^3J = 4.0 Hz, 1H), 3.85 (dd, ^2J = 11.7 Hz, ^3J = 8.6 Hz, 1H), 4.08 (d, J = 3.1 Hz, 1H), 5.27 (d, J = 3.1 Hz, 1H), 5.31 (dd, J = 8.5, 4.0 Hz, 1H), 7.13−7.15 (m, 1H), 7.22−7.35 (m, 7H), 7.55−7.63 (m, 3H), 7.89−7.94 (m, 3H), 8.07−8.09 (m, 1H), 8.51 (s, 1H). ^{13}C NMR (150 MHz): δ 41.8, 45.4, 62.1, 68.7, 71.9, 124.0, 124.1, 126.7, 127.0, 127.4, 127.6, 127.7, 128.3, 128.4, 129.6, 130.1, 130.2, 132.5, 133.8, 134.7, 135.6, 138.6, 139.1, 198.0. ESI-MS (m/z): 444 [M^+ + 23 (Na)]. FT-IR (film, cm^{-1}): 3059, 2929, 2860, 1678, 1627, 1449, 1287, 1029, 823, 755, 699. Anal. Calcd for $C_{29}H_{27}NO_2$: C, 82.63; H, 6.46; N, 3.32. Found: C, 82.78; H, 6.76; N, 3.40.

2-[(1R,3S*,4R*)-4-(Dimethylamino)-3-phenylisochroman-1-yl]-1-(thiophen-3-yl)ethanone (**8e**).* Brown oil, 93 mg, 25% yield. ^{1}H NMR (400 MHz): δ 2.19 (s, 6H), 3.38 (dd, ^2J = 13.5 Hz, ^3J = 6.0 Hz, 1H), 3.49 (dd, ^2J = 13.5 Hz, ^3J = 6.7 Hz, 1H), 4.16 (br s, 1H), 4.73 (br s, 1H), 5.57−5.59 (m, 1H), 7.12−7.14 (m, 1H), 7.12−7.68 (m, 10H), 8.08−8.10 (m, 1H). ^{13}C NMR (100 MHz): δ 41.2, 46.9, 66.1, 68.2, 73.7, 123.7, 126.1, 126.9, 127.1, 127.5, 127.9, 128.2, 128.3, 132.6, 139.1, 139.2, 142.7, 192.3. ESI-MS (m/z): 400 [M^+ + 23 (Na)]. FT-IR (film, cm^{-1}): 3031, 2923, 2855, 1674, 1510, 1412, 791, 754, 699. Anal. Calcd for $C_{23}H_{23}NO_2S$: C, 73.18; H, 6.14; N, 3.71. Found: C, 73.25; H, 6.30; N, 3.80.

2-[(1R,3R*,4S*)-4-(Dimethylamino)-3-phenylisochroman-1-yl]-1-(thiophen-3-yl)ethanone (epi-**8e**).* Brown oil, 95 mg, 25% yield. ^{1}H NMR (600 MHz): δ 2.37 (s, 6H), 3.23 (dd, ^2J = 11.7 Hz, ^3J = 3.9 Hz, 1H), 3.48 (dd, ^2J = 11.7 Hz, ^3J = 8.5 Hz, 1H), 4.07 (br s, 1H), 5.12 (dd, J = 8.5, 3.9 Hz, 1H), 5.20 (br s, 1H), 6.99−7.25 (m, 9H), 7.50−7.52 (m, 2H), 8.00−8.01 (m, 1H). ^{13}C NMR (150 MHz): δ 41.7, 46.6, 61.9, 68.4, 71.9, 124.0, 126.3, 127.0, 127.1, 127.4, 127.6, 127.8, 127.9, 128.2, 128.3, 130.3, 132.5, 138.4, 142.6, 192.0. ESI-MS (m/z): 400 [M^+ + 23 (Na)]. FT-IR (film, cm^{-1}): 2925, 1668, 1450, 1262, 1030, 755, 700. Anal. Calcd for $C_{23}H_{23}NO_2S$: C, 73.18; H, 6.14; N, 3.71. Found: C, 73.23; H, 6.19; N, 3.89.

2-[(1R,3S*,4R*)-4-(Dimethylamino)-3-phenylisochroman-1-yl]-1-(2,5-dimethylthiophen-3-yl)ethanone (**8f**).* Brown oil, 101 mg, 25% yield. ^{1}H NMR (400 MHz): δ 2.12 (s, 6H), 2.32 (s, 3H), 2.57 (s, 3H), 3.22 (dd, ^2J = 11.2 Hz, ^3J = 5.2 Hz, 1H), 3.30 (dd, ^2J = 11.2 Hz, ^3J = 6.3 Hz, 1H), 4.04 (d, J = 8.4 Hz, 1H), 4.67 (d, J = 8.4 Hz, 1H), 5.48 (dd-like t, J = 5.7 Hz, 1H), 7.00−7.02 (m, 1H), 7.04−7.36 (m, 8H), 7.54−7.56 (m, 1H). ^{13}C NMR (100 MHz): δ 14.9, 15.9, 41.2, 48.7, 66.3, 73.7, 78.1, 123.7, 126.4, 126.7, 127.5, 127.8, 127.9, 128.2, 134.8, 136.0, 139.4, 142.1, 147.4, 194.1. ESI-MS (m/z): 428 [M^+ + 23 (Na)]. FT-IR (film, cm^{-1}): 3030, 2920, 2786, 1667, 1549, 1480, 1450, 832, 756, 699. Anal. Calcd for $C_{25}H_{27}NO_2S$: C, 74.04; H, 6.71; N, 3.45. Found: C, 74.10; H, 6.80; N, 3.50.

2-[(1R,3R*,4S*)-4-(Dimethylamino)-3-phenylisochroman-1-yl]-1-(2,5-dimethylthiophen-3-yl)ethanone (epi-**8f**).* Brown oil, 103 mg, 25% yield. ^{1}H NMR (600 MHz): δ 2.35 (s, 9H), 2.62 (s, 3H), 3.18 (dd, ^2J = 11.6 Hz, ^3J = 4.2 Hz, 1H), 3.42 (dd, ^2J = 11.6 Hz, ^3J = 8.5 Hz, 1H), 4.03 (d, J = 3.5 Hz, 1H), 5.17 (d, J = 3.5 Hz, 1H), 5.20 (dd, J = 8.5, 4.2 Hz, 1H), 6.95−6.96 (m, 1H), 7.00−7.02 (m, 1H), 7.17−7.27 (m, 7H), 7.51−7.53 (m, 1H). ^{13}C NMR (150 MHz): δ 14.9, 15.9, 41.7, 48.5, 62.2, 68.6, 71.9, 124.0, 126.1, 126.9, 127.4, 127.6, 127.7 128.3, 129.9, 133.5, 135.0, 135.8, 138.8, 139.2, 147.6, 193.8. ESI-MS (m/z): 428 [M^+ + 23 (Na)]. FT-IR (film, cm^{-1}): 2922, 1667, 1478, 1262, 1136, 698. Anal. Calcd for $C_{25}H_{27}NO_2S$: C, 74.04; H, 6.71; N, 3.45. Found: C, 74.10; H, 6.80; N, 3.63.

2-[(1R,3S*,4R*)-4-(Dimethylamino)-3-phenylisochroman-1-yl]-1-(pyridin-2-yl)ethanone (**8g**).* Brown oil, 150 mg, 40% yield. ^{1}H NMR (400 MHz): δ 2.15 (s, 6H), 3.75 (dd, ^2J = 12.1 Hz, ^3J = 4.6 Hz, 1H), 3.84 (dd, ^2J = 12.1 Hz, ^3J = 7.4 Hz, 1H), 4.06 (d, J = 9.0 Hz, 1H), 4.67 (d, J = 9.0 Hz, 1H), 5.61 (dd, J = 4.6, 7.4 Hz, 1H), 7.13−7.43 (m, 9H), 7.57−7.59 (m, 1H), 7.74−7.78 (m, 1H), 7.97−7.99 (m, 1H), 8.62−8.65 (m, 1H). ^{13}C NMR (100 MHz): δ 41.3, 44.6, 66.4, 73.7, 77.9, 121.9, 123.6, 126.6, 126.7, 127.0, 127.5, 127.7, 127.8, 128.1, 136.8, 139.3, 142.2, 148.8, 153.5, 199.4. ESI-MS (m/z): 395 [M^+ + 23 (Na)]. FT-IR (film, cm^{-1}): 3028, 2922, 2852, 1672, 1583, 1336, 1031, 800, 753, 699. Anal. Calcd for $C_{24}H_{24}N_2O_2$: C, 77.39; H, 6.49; N, 7.52. Found: C, 77.48; H, 6.60; N, 7.68.

2-[(1R,3R*,4S*)-4-(Dimethylamino)-3-phenylisochroman-1-yl]-1-(pyridin-2-yl)ethanone (epi-**8g**).* Brown oil, 84 mg, 23% yield. ^{1}H NMR (400 MHz): δ 2.33 (s, 6H), 3.65 (dd, ^2J = 11.9 Hz, ^3J = 3.8 Hz, 1H), 3.89 (dd, ^2J = 11.9 Hz, ^3J = 9.5 Hz, 1H), 4.05 (d, J = 4.6 Hz, 1H), 5.20 (d, J = 4.6 Hz, 1H), 5.33 (dd, J = 9.5, 3.8 Hz, 1H), 7.11−7.59 (m, 10H), 7.76−7.80 (m, 1H), 8.00−8.03 (m, 1H), 8.59−8.61 (m, 1H). ^{13}C NMR (150 MHz): δ 41.5, 44.3, 62.1, 69.1, 71.5, 122.0, 124.2, 127.0, 127.1, 127.4, 127.7, 127.8, 128.2, 129.8, 136.8, 138.8, 148.8, 153.3, 199.1. ESI-MS (m/z): 395 [M^+ + 23 (Na)]. FT-IR (film, cm^{-1}): 3060, 2921, 2784, 1698, 1583, 1450, 1286, 1030, 830, 756, 700. Anal. Calcd for $C_{24}H_{24}N_2O_2$: C, 77.39; H, 6.49; N, 7.52. Found: C, 77.47; H, 6.56; N, 7.60.

2-[(1R,3S*,4R*)-4-(Dimethylamino)-6-methoxy-3-phenylisochroman-1-yl]-1-phenylethanone (**8h**).* Brown oil, 121 mg, 30% yield. ^{1}H NMR (400 MHz): δ 2.14 (s, 6H), 3.38 (dd, ^2J = 11.2 Hz, ^3J = 5.0 Hz, 1H), 3.55 (dd, ^2J = 11.2 Hz, ^3J = 6.5 Hz, 1H), 3.78 (s, 3H), 4.03 (d, J = 9.2 Hz, 1H), 4.66 (d, J = 9.2 Hz, 1H), 5.52 (dd-like t, J = 5.7 Hz, 1H), 6.75−6.77 (m, 1H), 6.98−7.01 (m, 1H), 7.18−7.41 (m, 8H), 7.49−7.52 (m, 1H), 7.94−7.96 (m, 2H). ^{13}C NMR (150 MHz): δ 41.2, 46.0, 55.3, 66.5, 73.9, 78.2, 112.5, 112.9, 124.9, 127.5, 127.9, 128.2, 128.3, 128.4, 131.5, 133.0, 137.5, 138.9, 142.1, 158.7, 198.4. ESI-MS (m/z): 424 [M^+ + 23 (Na)]. FT-IR (film, cm^{-1}): 3055, 2930, 1683, 1580, 1496, 1265, 1035, 813, 736, 701. Anal. Calcd for $C_{26}H_{27}NO_3$: C, 77.78; H, 6.78; N, 3.49. Found: C, 77.94; H, 6.90; N, 3.63.

2-[(1R,3R*,4S*)-4-(Dimethylamino)-6-methoxy-3-phenylisochroman-1-yl]-1-phenylethanone (epi-**8h**).* Brown oil, 82 mg, 20% yield. ^{1}H NMR (400 MHz): δ 2.33 (s, 6H), 3.28 (dd, ^2J = 11.6 Hz, ^3J

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= 4.1 Hz, 1H), 3.59 (dd, ^2J = 11.6 Hz, ^3J = 8.4 Hz, 1H), 3.80 (s, 3H), 3.97 (d, J = 3.6 Hz, 1H), 5.15 (d, J = 3.6 Hz, 1H), 5.17 (dd, J = 8.4, 4.1 Hz, 1H), 6.76−6.79 (m, 1H), 6.94−6.96 (m, 1H), 7.07−7.08 (m, 1H), 7.21−7.24 (m, 5H), 7.40−7.43 (m, 2H), 7.49−7.52 (m, 1H), 7.92−7.94 (m, 2H). ^{13}C NMR (150 MHz): δ 41.7, 45.6, 55.3, 62.4, 68.7, 71.8, 114.0, 114.1, 125.1, 127.8, 128.3, 128.4, 128.5, 130.8, 133.0, 135.4, 137.4, 139.4, 144.4, 158.6, 198.2. ESI-MS (m/z): 424 [M^+ + 23 (Na)]. FT-IR (film, cm^{-1}): 3055, 2930, 2835, 1683, 1608, 1496, 1449, 1265, 1035, 736, 701. Anal. Calcd for $C_{26}H_{27}NO_3$: C, 77.78; H, 6.78; N, 3.49. Found: C, 77.80; H, 6.90; N, 3.62.

2-[(1R,3S*,4R*)-4-(Dimethylamino)-6-methoxy-3-phenylisochroman-1-yl]-1-(p-tolyl)ethanone (**8i**).* Brown oil, 144 mg, 35% yield. ^{1}H NMR (600 MHz): δ 2.18 (s, 6H), 2.42 (s, 3H), 3.41 (dd, ^2J = 12.2 Hz, ^3J = 4.0 Hz, 1H), 3.57 (dd, ^2J = 12.2 Hz, ^3J = 5.3 Hz, 1H), 3.83 (s, 3H), 4.08 (d, J = 9.0 Hz, 1H), 4.70 (d, J = 9.0 Hz, 1H), 5.57 (dd-like t, J = 5.6 Hz, 1H), 6.79−6.81 (m, 1H), 7.02−7.04 (m, 1H), 7.12−7.42 (m, 8H), 7.89−7.91 (m, 2H). ^{13}C NMR (150 MHz): δ 41.2, 45.9, 55.3, 60.3, 66.5, 73.8, 78.1, 112.5, 112.9, 124.9, 127.5, 127.8, 128.2, 128.5, 129.1, 131.6, 135.0, 138.8, 142.1, 143.7, 158.6, 197.9. ESI-MS (m/z): 438 [M^+ + 23 (Na)]. FT-IR (film, cm^{-1}): 3062, 2924, 1682, 1607, 1496, 1282, 1034, 808, 756, 700. Anal. Calcd for $C_{27}H_{29}NO_3$: C, 78.04; H, 7.03; N, 3.37. Found: C, 78.12; H, 7.10; N, 3.52.

2-[(1R,3R*,4S*)-4-(Dimethylamino)-6-methoxy-3-phenylisochroman-1-yl]-1-(p-tolyl)ethanone (epi-**8i**).* Brown oil, 64 mg, 15% yield. ^{1}H NMR (400 MHz): δ 2.38 (s, 6H), 2.42 (s, 3H), 3.31 (dd, ^2J = 11.6 Hz, ^3J = 4.1 Hz, 1H), 3.62 (dd, ^2J = 11.6 Hz, ^3J = 8.3 Hz, 1H), 3.85 (s, 3H), 4.02 (d, J = 3.4 Hz, 1H), 5.19 (d, J = 3.4 Hz, 1H), 5.22 (dd, J = 8.3, 4.1 Hz, 1H), 6.81−6.83 (m, 1H), 6.99−7.01 (m, 1H), 7.12−7.28 (m, 8H), 7.87−7.89 (m, 2H). ^{13}C NMR (150 MHz): δ 41.7, 45.5, 55.3, 60.3, 62.5, 68.7, 71.8, 113.9, 114.0, 125.2, 127.7, 127.8, 128.2, 128.5, 129.2, 130.9, 134.9, 135.5, 139.5, 143.7, 158.5, 197.8. ESI-MS (m/z): 438 [M^+ + 23 (Na)]. FT-IR (film, cm^{-1}): 3060, 2930, 2783, 1680, 1607, 1499, 1442, 1284, 1034, 808, 757, 699. Anal. Calcd for $C_{27}H_{29}NO_3$: C, 78.04; H, 7.03; N, 3.37. Found: C, 78.11; H, 7.20; N, 3.50.

2-[(1R,3S*,4R*)-3-(2,5-Dimethoxyphenyl)-4-(dimethylamino)-isochroman-1-yl]-1-phenylethanone (**8j**).* Brown solid, 152 mg, 35% yield. Mp = 95−96 °C (Et_2O). ^{1}H NMR (400 MHz): δ 2.15 (s, 6H), 3.41 (dd, ^2J = 11.4 Hz, ^3J = 5.2 Hz, 1H), 3.58 (dd, ^2J = 11.4 Hz, ^3J = 6.3 Hz, 1H), 3.67 (s, 3H), 3.75 (s, 3H), 4.11 (d, J = 8.7 Hz, 1H), 5.25 (d, J = 8.7 Hz, 1H), 5.64 (dd-like t, J = 5.7 Hz, 1H), 6.73−6.75 (m, 2H), 6.88 (br s, 1H), 7.05−7.07 (m, 1H), 7.18−7.24 (m, 2H), 7.38−7.42 (m, 2H), 7.49−7.53 (m, 1H), 7.62−7.65 (m, 1H), 7.94−7.97 (m, 2H). ^{13}C NMR (100 MHz): δ 41.3, 45.8, 55.7, 56.1, 66.4, 70.6, 73.8, 112.1, 113.6, 114.1, 123.5, 126.6, 126.8, 128.1, 128.3, 128.4, 131.7, 133.0, 137.4, 137.7, 139.4, 150.8, 153.7, 198.3. ESI-MS (m/z): 454 [M^+ + 23 (Na)]. FT-IR (film, cm^{-1}): 3059, 2932, 1682, 1597, 1449, 1359, 1049, 849, 753, 691. Anal. Calcd for $C_{27}H_{29}NO_4$: C, 75.15; H, 6.77; N, 3.25. Found: C, 75.23; H, 6.83; N, 3.28.

2-[(1R,3R*,4S*)-3-(2,5-Dimethoxyphenyl)-4-(dimethylamino)-isochroman-1-yl]-1-phenylethanone (epi-**8j**).* Brown oil, 150 mg, 35% yield. ^{1}H NMR (400 MHz): δ 2.36 (s, 6H), 3.31 (dd, ^2J = 11.7 Hz, ^3J = 4.3 Hz, 1H), 3.61 (s, 3H), 3.76 (s, 3H), 3.87 (dd, ^2J = 11.7 Hz, ^3J = 7.9 Hz, 1H), 3.96 (d, J = 4.5 Hz, 1H), 5.41 (dd, J = 7.9, 4.3 Hz, 1H), 5.65 (d, J = 4.5 Hz, 1H), 6.62−6.63 (m, 1H), 6.76−6.82 (m, 2H), 7.13−7.14 (m, 1H), 7.25−7.31 (m, 2H), 7.42−7.45 (m, 2H), 7.54−7.58 (m, 2H), 7.99−8.00 (m, 2H). ^{13}C NMR (100 MHz): δ 41.7, 45.6, 55.5, 56.3, 63.4, 65.9, 70.1, 112.2, 113.6, 114.3, 124.3, 127.0, 127.2, 128.3, 128.4, 129.5, 132.9, 137.4, 138.8, 151.5, 153.3, 198.2. ESI-MS (m/z): 454 [M^+ + 23 (Na)]. FT-IR (film, cm^{-1}): 3061, 2932, 2833, 1682, 1596, 1499, 1449, 1280, 1047, 807, 752, 690. Anal. Calcd for $C_{27}H_{29}NO_4$: C, 75.15; H, 6.77; N, 3.25. Found: C, 75.22; H, 6.89; N, 3.44.

2-[(1R,3S*,4R*)-4-(Diethylamino)-3-phenylisochroman-1-yl]-1-phenylethanone (**8k**).* Brown oil, 179 mg, 45% yield. ^{1}H NMR (400 MHz): δ 0.90 (t, J = 7.04 Hz, 6H), 2.31−2.37 (m, 2H), 2.51−2.58 (m, 2H), 3.48 (dd, ^2J = 11.3 Hz, ^3J = 5.0 Hz, 1H), 3.66 (dd, ^2J = 11.3 Hz, ^3J = 6.6 Hz, 1H), 4.27 (d, J = 9.4 Hz, 1H), 4.67 (d, J = 9.4 Hz, 1H), 5.67 (dd-like t, J = 5.8 Hz, 1H), 7.06−7.75 (m, 12H), 8.01−8.04 (m, 2H). ^{13}C NMR (150 MHz): δ 15.5, 45.0, 46.0, 62.1, 74.4, 79.5, 123.7, 127.6, 127.7, 127.8, 128.0, 128.3, 128.5, 128.6, 129.4, 133.0, 137.5, 138.6, 139.3, 198.3. ESI-MS (m/z): 422 [M^+ + 23 (Na)]. FT-IR (film, cm^{-1}): 3063, 2927, 1685, 1603, 1451, 1284, 1027, 798, 747, 696. Anal. Calcd for $C_{27}H_{29}NO_2$: C, 81.17; H, 7.32; N, 3.51. Found: C, 81.25; H, 7.50; N, 3.60.

2-[(1R,3R*,4S*)-4-(Diethylamino)-3-phenylisochroman-1-yl]-1-phenylethanone (epi-**8k**).* Brown oil, 181 mg, 45% yield. ^{1}H NMR (400 MHz): δ 0.96 (t, J = 7.0 Hz, 6H), 2.42−2.47 (m, 2H), 2.64−2.69 (m, 2H), 3.40 (dd, ^2J = 11.3 Hz, ^3J = 4.4 Hz, 1H), 3.75 (dd, ^2J = 11.3 Hz, ^3J = 8.3 Hz, 1H), 4.24 (d, J = 6.2 Hz, 1H), 5.02 (d, J = 6.2 Hz, 1H), 5.22 (dd, J = 8.3, 4.4 Hz, 1H), 7.11−7.13 (m, 1H), 7.23−7.70 (m, 11H), 7.96−7.98 (m, 2H). ^{13}C NMR (100 MHz): δ 14.1, 14.8, 44.6, 45.4, 59.6, 70.3, 72.8, 124.2, 126.8, 126.9, 127.8, 128.2, 128.3, 128.5, 128.6, 129.0, 133.1, 137.3, 138.8, 197.9. ESI-MS (m/z): 422 [M^+ + 23 (Na)]. FT-IR (film, cm^{-1}): 3060, 2926, 2780, 1685, 1599, 1448, 1265, 1076, 805, 753, 700. Anal. Calcd for $C_{27}H_{29}NO_2$: C, 81.17; H, 7.32; N, 3.51. Found: C, 81.30; H, 7.51; N, 3.60.

1-Phenyl-2-[(1R,3S*,4R*)-3-phenyl-4-(pyrrolidin-1-yl)-isochroman-1-yl]ethanone (**8l**).* Brown oil, 160 mg, 40% yield. ^{1}H NMR (400 MHz): δ 1.63 (br s, 4H), 2.45 (br s, 2H), 2.66 (br s, 2H), 3.45 (dd, ^2J = 9.5 Hz, ^3J = 4.6 Hz, 1H), 3.62 (dd, ^2J = 9.5 Hz, ^3J = 6.9 Hz, 1H), 4.17 (d, J = 6.7 Hz, 1H), 4.88 (d, J = 6.7 Hz, 1H), 5.67 (dd, J = 4.6, 6.9 Hz, 1H), 7.05−7.56 (m, 12H), 7.97−7.99 (m, 2H). ^{13}C NMR (100 MHz): δ 24.2, 45.1, 48.8, 63.1, 73.1, 78.0, 123.5, 126.8, 127.0, 127.5, 128.0, 128.1, 128.2, 128.3, 128.4, 128.5, 133.0, 137.4, 139.3, 142.2, 198.3. ESI-MS (m/z): 420 [M^+ + 23 (Na)]. FT-IR (film, cm^{-1}): 3062, 2964, 1682, 1597, 1448, 1280, 1028, 751, 698. Anal. Calcd for $C_{27}H_{27}NO_2$: C, 81.58; H, 6.85; N, 3.52. Found: C, 81.65; H, 6.90; N, 3.69.

1-Phenyl-2-[(1R,3R*,4S*)-3-phenyl-4-(pyrrolidin-1-yl)-isochroman-1-yl]ethanone (epi-**8l**).* Brown oil, 80 mg, 20% yield. ^{1}H NMR (400 MHz): δ 1.69 (br s, 4H), 2.69 (br s, 4H), 3.20 (dd, ^2J = 11.8 Hz, ^3J = 3.9 Hz, 1H), 3.85 (dd, ^2J = 11.8 Hz, ^3J = 8.8 Hz, 1H), 3.95 (br s, 1H), 5.27 (d, J = 2.4 Hz, 1H), 5.37 (dd, J = 8.8, 3.9 Hz, 1H), 7.00−7.50 (m, 12H), 7.95−7.97 (m, 2H). ^{13}C NMR (100 MHz): δ 23.6, 46.5, 50.5, 61.7, 70.1, 75.0, 124.7, 126.5, 126.9, 127.1, 127.5, 128.1, 128.4, 128.5, 130.1, 133.0, 137.6, 138.3, 140.1, 198.7. ESI-MS (m/z): 420 [M^+ + 23 (Na)]. FT-IR (film, cm^{-1}): 3060, 2928, 1684, 1597, 1448, 1283, 1023, 751, 695. Anal. Calcd for $C_{27}H_{27}NO_2$: C, 81.58; H, 6.85; N, 3.52. Found: C, 81.70; H, 6.93; N, 3.60.

2-[(1R,3S*,4R*)-3-Cyclohexyl-4-(dimethylamino)isochroman-1-yl]-1-phenylethanone (**8m**).* Yellow oil, 89 mg, 28% yield. ^{1}H NMR (400 MHz): δ 0.92−1.18 (m, 6H), 1.39−1.58 (m, 5H), 2.72 (s, 6H), 3.22 (dd, ^2J = 14.7 Hz, ^3J = 4.1 Hz, 1H), 3.37 (m, 1H), 3.48 (dd, ^2J = 14.7 Hz, ^3J = 8.4 Hz, 1H), 3.80 (d, J = 8.1 Hz, 1H), 5.11 (dd, J = 8.4, 4.1 Hz, 1H), 7.02−7.04 (m, 1H), 7.11−7.52 (m, 6H), 7.94−7.96 (m, 2H). ^{13}C NMR (100 MHz): δ 25.8, 26.3, 26.4, 26.6, 30.4, 40.8, 41.6, 44.3, 61.6, 74.1, 81.0, 123.2, 126.5, 126.6, 128.3, 128.6, 128.7, 132.9, 136.3, 137.8, 140.2, 199.4. ESI-MS (m/z): 378 [M^+ + 1 (H)]. FT-IR (film, cm^{-1}): 3029, 2926, 2852, 1685, 1598, 1449, 1265, 738, 703, 689. Anal. Calcd for $C_{25}H_{31}NO_2$: C, 79.54; H, 8.28; N, 3.71. Found: C, 79.70; H,.8.40; N, 3.80.

2-[(1R,3R*,4S*)-3-Cyclohexyl-4-(dimethylamino)isochroman-1-yl]-1-phenylethanone (epi-**8m**).* Yellow oil, 71 mg, 22% yield. ^{1}H NMR (600 MHz): δ 1.22−1.43 (m, 6H), 1.60−1.76 (m, 4H), 2.04−2.09 (m, 1H), 2.40 (s, 6H), 3.34 (dd, ^2J = 16.1 Hz, ^3J = 3.1 Hz, 1H), 3.58 (dd, ^2J = 16.1 Hz, ^3J = 8.8 Hz, 1H), 3.64 (m, 1H), 3.83 (d, J = 3.0 Hz, 1H), 5.42 (dd, J = 8.8, 3.1 Hz, 1H), 7.28−7.30 (m, 2H), 7.42−7.59 (m, 5H), 8.00−8.02 (m, 2H). ^{13}C NMR (125 MHz): δ 25.8, 25.9, 26.4, 29.7, 30.2, 37.0, 41.8, 45.8, 59.4, 66.8, 75.4, 123.6, 126.8, 127.5, 128.4, 128.5, 131.4, 132.4, 133.1, 137.4, 138.5, 198.3. ESI-MS (m/z): 378 [M^+ + 1 (H)]. FT-IR (film, cm^{-1}): 3062, 2923, 2780, 1688, 1597, 1449, 1283, 749, 690. Anal. Calcd for $C_{25}H_{31}NO_2$: C, 79.54; H, 8.28; N, 3.71. Found: C, 79.58; H, 8.32; N, 3.78.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

General methods, copies of ^{1}H/^{13}C NMR spectra for compounds **8a−m** and *epi*-**8a−m**, 2D NOESY experiment for

epi-**8b**, X-ray ellipsoid plot of compound **8j**, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(18) A doublet-of-doublets-like triplet at 5.60 ppm ($^3J_{H-H}$ = 5.7 Hz) and doublets of doublets at 3.59 and 3.43 ppm ($^3J_{H-H}$ = 5.0 and 6.5 Hz, $^2J_{H-H}$ = 16.6 Hz).

(19) The presence of a CH_2 in the structure of the major diastereomer was also confirmed by a ^{13}C NMR DEPT analysis.

(20) Equilibration between **8a** and *epi*-**8a** was achieved by treating a pure sample of **8a** with LDA in THF at 0 °C.

(21) Support for the structure of **8a** came from the X-ray analysis (CCDC 953462) carried out on the major diastereomer **8j** obtained by reacting **1c-Li** with **2a**. It is noteworthy that all of the bond lengths and bond angles are completely in agreement with those of other isochromane structures known in the literature. See: Orue, A.; Reyes, E.; Vicario, J. L.; Carrillo, L.; Uria, U. *Org. Lett.* **2012**, *14*, 3740.

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