DOI: 10.1002/ejoc.200600585

Short and Efficient Diastereoselective Synthesis of Enantiopure 1-Substituted 1*H*-2-Benzopyrans

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Keywords: Asymmetric synthesis / 1,3-Amino alcohols / Benzopyrans / Isochromanes / Isochromenes

The reaction of homophthaldehyde with (–)-8-(benzylamino)-menthol is regio- and diastereo-selective, leading to the chiral perhydro-1,3-benzoxazine **3** as a single diastereoisomer. The addition of different organometallics to **3** yielded alcohols **4** in excellent yields. Hydrolysis of carbinols, with 2 % HCl in methanol or ethanol, allowed for the synthesis of 1,3-disubstituted isochromanes, but hydrolysis in toluene led to enantiopure 1-substituted isochromenes.

Introduction

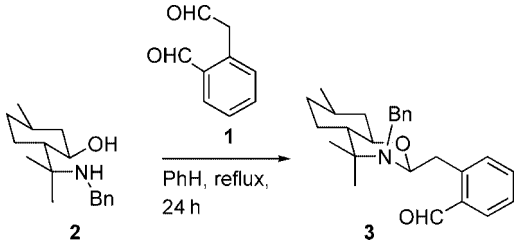
In contrast to chromanes or chromenes that possess significant biological properties,[1] 1*H*-2-benzopyrans (1*H*-isochromenes) are less common natural metabolites.[2] Their synthesis has been studied less probably because they are not very stable and show a tendency towards oxidation and polymerization.[3]

Earlier preparations of 1*H*-isochromenes consisted of the dehydration of isochromanols[4] or the heating of 1-acylbenzocyclobutanes to form the corresponding acyl-*o*-quinodimethanes followed by their cyclization.[5] 3-Alkyl-2-amino-substituted isochromenes have also been synthesized by thermolysis of aryl α-diazo ketones,[6] whereas 1-substituted 1*H*-2-benzopyrans have also been prepared from aryllithium derivatives.[7] More recently, 3-vinyl-substituted 1*H*-isochromenes have been prepared by the palladium-catalyzed reactions of ketones with *o*-bromophenyl allyl ethers,[8] or cycloisomerizations of *o*-alkynyl benzyl alcohols catalyzed by palladium iodide.[9] 2-Allyl-3-hydroxyalkyl-1,4-naphthoquinone also cyclizes to form benzoisochromenequinone by reaction with a palladium(II) complex.[10] Highly substituted 1*H*-isochromenes are obtained by cyclization of *o*-(1-alkynyl) aryl ketones or aldehydes promoted by Pd^{II},[11] bis(pyridine)iodonium tetrafluoroborate,[12] or iodine, bromine, sulfur, or selenium derivatives,[13] but to the best of our knowledge, there are no prior reports of the asymmetric synthesis of 2-substituted 1*H*-isochromenes.

Based on previous work on the diastereoselective alkylation[14] of imines attached to a chiral perhydrobenzoxazine, derived from (–)-8-(benzylamino)menthol,[15] we now present a novel diastereoselective synthesis of enantioenriched 1*H*-isochromenes. The method is based on that used for the perhydrobenzoxazine system as a chiral template to promote diastereoselective addition to a benzaldehyde derivative, recovery of the masked formyl group by hydrolysis and cyclization to form the final products. In this way, different chiral 1-substituted 1*H*-isochromenes are prepared from a common dialdehyde (homophthaladehyde), obtained by ozonolysis of indene.[16]

Results and Discussion

Condensation of 2-(*o*-formylphenyl)acetaldehyde (**1**) with (–)-8-(benzylamino)menthol (**2**) in refluxing benzene, under Dean–Stark conditions, for 24 h led to the starting material perhydrobenzoxazine (**3**) in 40% yield after column chromatography. The reaction is totally regio- and stereo-selective. The condensation only occurs with the aliphatic formyl group, leading to a single diastereoisomer with *S* configuration at C-2 in the perhydrobenzoxazine ring (Scheme 1).



Scheme 1. Synthesis of perhydrobenzoxazine **3**.

Aldehyde **3** was transformed into a mixture of diastereomeric secondary alcohols **4a**–**g** and *epi*-**4ag** by reaction with different organometallics at –90 °C in diethyl ether or THF in an argon atmosphere (Scheme 2 and

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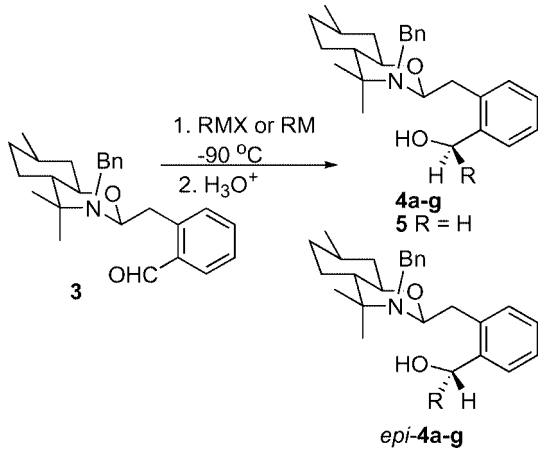
Table 1). Diastereoisomeric alcohols were isolated and purified by flash chromatography except for compounds **4b** and *epi*-**4b** which could not be separated.



Scheme 2. Addition of organometallics to aldehyde **3**.

Table 1. Nucleophilic addition of organometallics to aldehyde **3**.

	Reagent (equiv.)	R	Solvent	Time [min]	Product ratio [%][a]
1	MeMgI (2)	Me	Et_2O	60	**4a**/*epi*-**4a** (52:44)
2	MeMgCl (2)	Me	Et_2O	120	**4a**/*epi*-**4a** (55:41)
3	MeMgCl (2)	Me	THF	90	**4a**/*epi*-**4a** (66:30)
4	MeLi (1.1)	Me	Et_2O	45	**4a**/*epi*-**4a** (74:22)
5	MeLi (1.1)	Me	THF	45	**4a**/*epi*-**4a** (75:21)
6	*i*PrMgCl (2)	*i*Pr	Et_2O	60	**4b**/*epi*-**4b** (33:16)[b]
7	*n*BuMgI (2)	*n*Bu	Et_2O	30	**4c**/*epi*-**4c** (60:32)[c]
8	*n*BuMgCl (2)	*n*Bu	THF	30	**4c**/*epi*-**4c** (56:15)[c]
9	*n*BuLi (2)	*n*Bu	Et_2O	30	**4c**/*epi*-**4c** (68:27)
10	*n*BuLi (2)	*n*Bu	THF	30	**4c**/*epi*-**4c** (76:22)
11	PhMgBr (1.1)	Ph	Et_2O	120	**4d**/*epi*-**4d** (52:44)
12	PhMgBr (1.1)	Ph	THF	120	**4d**/*epi*-**4d** (53:43)
13	PhMgCl (1.1)	Ph	THF	120	**4d**/*epi*-**4d** (55:42)
14	CH_2=$CHMgBr$ (2)	vinyl	Et_2O	30	**4e**/*epi*-**4e** (64:32)
15	CH_2=$CHCH_2MgBr$ (2)	allyl	Et_2O	30	**4f**/*epi*-**4f** (74:22)
16	CH_2=$CHCH_2MgBr$ (2)	allyl	THF	15	**4f**/*epi*-**4a** (76:19)
17	CH_2=$CHCH_2MgCl$ (2)	allyl	THF	15	**4f**/*epi*-**4f** (74:21)
18	*t*BuLi (2)	*t*Bu	Et_2O	120[d]	**4g**/*epi*-**4g** (51:32)
19	*t*BuLi (2)	*t*Bu	THF	90	**4g**/*epi*-**4g** (85:9)

[a] Yields refer to isolated products after flash chromatography. [b] Determined by integration of the signals of ^{1}H NMR spectra of the mixture, 50% of the reduction product **5** was detected. [c] 4% (entry 5) and 25% (entry 6) of product **5** was isolated, respectively. [d] The reaction was allowed to reach room temp., but 15% of the starting compound was recovered.

The feasibility of the reaction was explored using Grignard and lithium reagents. The reactions were quantitative in most cases but the ratio of diastereoisomers is dependent on either the nature of the organometallic or the solvent. The reactions with methylmagnesium iodide or chloride in diethyl ether (entries 1 and 2 in Table 1) or with phenylmagnesium bromide or chloride (entries 11–13 in Table 1) give a near equimolar mixture of diastereoisomers using diethyl ether or THF as the solvent. The ratio of diastereoisomers increased to ca. 2:1 in the reaction using methylmagnesium chloride in THF (entry 3). The diastereoselection increased to 3:1 when methyllithium was used as the nucleophile in diethyl ether or THF (entries 4, 5).

The use of bulkier magnesium reagents, such as isopropyl or butyl derivatives, increased the diastereomeric ratios to ca. 2:1 and 4:1 (entries 6–8 in Table 1), respectively, but 50% of product **5**[17] was formed in the reaction with isopropylmagnesium chloride in diethyl ether or 25% with *n*-butylmagnesium chloride in THF, as a consequence of a competitive reduction process.[18] The reduced alcohol **5** was not formed when *n*-butyllithium was used in either diethyl ether or THF, although by using THF the ratio of diastereoisomers was better (entries 9 and 10).

Vinylmagnesium bromide also reacted quantitatively with **3** yielding a mixture (2:1) of diastereoisomers **4e** and *epi*-**4e**, and allylmagnesium reagents led to mixtures of **4f** and *epi*-**4f** with diastereomeric ratios that varied from ca. 3:1 (entries 15 and 17 in Table 1) to 4:1 for reactions with allylmagnesium bromide in THF (entry 16), respectively.

The bulkiest *tert*-butyllithium led to the best *dr* in the addition to **3** when the reaction was carried out in THF (entry 19). However, the process is slow at –90 °C when the solvent is changed to diethyl ether, and the starting aldehydes were recovered even at room temp. In these conditions the *dr* decreased to 5:3 (entry 18).

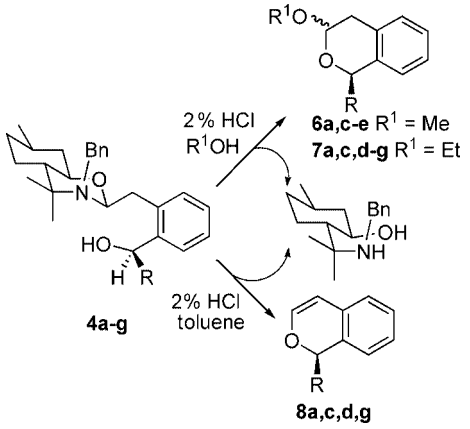
Aldehyde **3** was also reacted in THF at –78 °C, with organocerium compounds[19] but the yields and *dr* were very similar to those obtained in the reactions with their precursors magnesium or lithium reagents.

The stereochemistry at the new stereocenter in the major diastereoisomers was determined as *R* by X-ray diffraction analysis for compound **4d**[20] and extended to all the alcohols on the basis of their ^{1}H NMR and ^{13}C NMR spectroscopic data. For instance, in the ^{13}C NMR spectra the hydroxylic carbon for the *R* diastereoisomer appears 4.6–6.6 ppm at higher field than for the *S* epimer, except for compounds **4g** and *epi*-**4g** where the difference is only of 0.2 ppm.

The formation of the major diastereoisomer can be explained as a consequence of a preferred addition to the oxygen face of the heterocycle, probably because it is the less hindered face or because the coordination of the organometallic to the oxygen of the template, occurs prior to the reaction as described previously.[14,21]

Alcohols **4** were transformed into the final products in two different ways (Scheme 3 and Table 2). Isochromanes **6** were obtained in good to excellent yields, as a mixture of *cis* and *trans* isomers, by refluxing in methanol with a 2% solution of hydrochloric acid (entries 1–4 in Table 2). The hydrolytic cleavage was also carried out using ethanol as the solvent. The corresponding ethyl ketals **7** were also obtained as a *cis*/*trans* mixture of isomers (entries 5–9 in Table 2).

Attempts at further transformations of compounds **6** and **7** into the corresponding isochromanones by oxidation with *m*-CPBA,[22] sodium hypochlorite,[21b] or Bismuth(III) nitrate[23] failed, and unidentifiable mixtures of compounds were observed. However, compounds **4** were cleanly transformed into enantiopure 2-substituted isochromenes **8** after



Scheme 3. Preparation of isochromanes **6**–**7** and isochromenes **8**.

Table 2. Transformation of alcohols **4** into isochromanes **6**–**7** and isochromenes **8**.

	Solvent	R	Product [%][a]	Time [h]	*cis*/*trans* Ratio [%][b]
1	MeOH	Me	**6a** (68)	5	(67:33)
2	MeOH	*n*Bu	**6c** (65)	24	(66:34)
3	MeOH	Ph	**6d** (98)	5	(68:32)
4	MeOH	vinyl	**6e** (98)	24	(54:46)
5	EtOH	Me	**7a** (76)	72	(60:40)
6	EtOH	*n*Bu	**7c** (50)	24	(65:35)
7	EtOH	Ph	**7d** (98)	4	(62:38)
8	EtOH	allyl	**7f** (81)	23	(85:15)
9	EtOH	*t*Bu	**7g** (50)[c]	30	(74:26)
10	toluene	Me	**8a** (43)[c]	30	
11	toluene	*n*Bu	**8c** (85)	20	
12	toluene	Ph	**8d** (87)	25	
13	toluene	*t*Bu	**8g** (45)[c]	20	

[a] Yields refer to isolated products after flash chromatography. [b] Determined by integration of the signals of ^{1}H NMR spectra of the mixture. [c] Partially decompose during flash chromatography.

boiling in toluene with 2% HCl solution for 20–30 h. The reaction is nearly quantitative, and the moderate yields of **8a** and **8g** are due to partial decomposition of these isochromenes during purification by flash chromatography (entries 10–13 in Table 2). The transformation of **4** into **8** can also be carried out by using THF as the solvent and 5% solution of sulfuric acid. The reaction is faster (5–7 h of reflux) but the yields of the isolated isochromenes are lower. In these cases hydrolytic cleavage of the chiral (–)-8-(benzylamino)menthol, used as chiral template, was recovered in 90–95% simply by neutralization of the aqueous phase and extraction with chloroform.

In summary, the described methodology allows for the preparation of enantiopure 1-substituted isochromenes starting from easily accessible compounds. In addition, different substituents can be introduced merely by changing the nucleophile acting on the formyl group of the substituent at C-2 in the starting chiral perhydro-1,3-benzoxazine.

Experimental Section

General: All reactions were carried out in an argon atmosphere using oven-dried glassware. Solvents and bases were dried by standard methods: CH_2Cl_2 was distilled from CaH_2 and benzene, THF and Et_2O from Na. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded using $CDCl_3$ as the solvent and TMS as an internal reference, and chemical shifts are given in ppm. Specific rotations were determined using a digital polarimeter using a Na lamp, and the concentration is given in g per 100 mL. Melting points were obtained using open capillary tubes and are uncorrected. TLC was performed using glass-backed plates coated with silica gel 60 with an F_{254} indicator; the chromatograms were visualized under UV light and/or by staining with I_2 or phosphomolybdic acid. Flash chromatography was carried using silica gel (230–240 mesh).

Synthesis of (2*S*,4a*S*,7*R*,8a*R*)-2-[(*N*-Benzyl-4,4,7-trimethyloctahydro-2*H*-benzo[*e*][1,3]oxazin-2-yl)methyl]benzaldehyde (3): A solution of (–)-8-(benzylamino)menthol **2** (1.68 g, 6.5 mmol) and 2-(*o*-formylphenyl)acetaldehyde (**1**) (0.64 g, 4.3 mmol) in benzene (100 mL) was heated at reflux with a Dean–Stark trap for 24 h. The solvent was removed in vacuo and the residue was purified by flash chromatography using silica gel and toluene as the eluent. Aldehyde **3** was isolated as a pale yellow oil (0.67 g, 40%). $[\alpha]_D^{23}$ = –32.8 (*c* = 0.70, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.84–1.06 (m, 3 H), 0.87 (d, *J* = 6.4 Hz, 3 H), 1.09 (s, 3 H), 1.18 (s, 3 H), 1.19–1.32 (m, 1 H), 1.43–1.75 (m, 4 H), 2.99 (d, *J* = 6.8 Hz, 1 H), 3.00 (d, *J* = 4.4 Hz, 1 H), 3.25 (td, J_1 = 10.5 Hz, J_2 = 4.0 Hz, 1 H), 3.92 (d, *J* = 17.9 Hz, 1 H), 4.17 (d, *J* = 17.9 Hz, 1 H), 4.70 (dd, J_1 = 6.8 Hz, J_2 = 4.4 Hz, 1 H), 7.13–7.31 (m, 5 H), 7.37–7.47 (m, 3 H), 7.78 (dd, J_1 = 7.7 Hz, J_2 = 1.3 Hz, 1 H), 10.23 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.8, 22.2, 25.0, 27.2, 31.2, 35.0, 41.2, 37.5, 41.0, 46.6, 46.7, 57.4, 75.9, 88.3, 126.0, 126.7, 126.8 (2 C), 128.1 (2 C), 129.7, 132.0, 133.2, 134.6, 141.7, 143.9, 192.5 ppm. IR (film): $\tilde{\nu}$ = 3060, 3020, 1685, 1600, 1570, 1450, 770, 730, 700 cm^{-1}. $C_{26}H_{33}NO_2$ (391.55): calcd. C 79.76, H 8.50, N 3.58; found C 79.69, H 8.61, N 3.61.

Synthesis of Alcohols 4a–g. General Method: To a solution of the aldehyde **3** (5.3 mmol), in the appropriate ethereal solvent (Table 1, 5 mL) at –90 °C in an argon atmosphere, a solution of the organometallic reagent (5.83 mmol) was slowly added and the mixture was stirred at that temperature until the starting material has disappeared (TLC, Table 1). The reaction mixture was quenched with saturated ammonium chloride, and the product was extracted with diethyl ether (3 × 5 mL). The organic extracts were washed with brine and dried with anhydrous $MgSO_4$, and the solvent was evaporated in vacuo. The residue was purified by flash chromatography using silica gel and hexanes/ethyl acetate as the eluent.

(1*R*,2′*S*,4a′*S*,7′*R*,8a′*R*)-1-{2-[(*N*-Benzyl-4′,4′,7′-trimethyloctahydro-2*H*-benzo[*e*][1,3]oxazin-2′-yl)methyl]phenyl}ethanol (4a): 1.08 g, 49.9%. $[\alpha]_D^{23}$ = –15.9 (*c* = 0.38, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.84 (d, *J* = 6.5 Hz, 3 H), 0.86–1.02 (m, 2 H), 1.02–1.10 (m, 1 H),1.12 (s, 3 H), 1.28 (s, 3 H), 1.31–1.35 (m, 2 H), 1.54 (d, *J* = 6.4 Hz, 3 H), 1.58–1.66 (m, 2 H), 1.75 (m, 1 H), 2.51 (dd, J_1 = 14.0 Hz, J_2 = 1.6 Hz, 1 H), 3.04 (dd, J_1 = 14.0 Hz, J_2 = 9.5 Hz, 1 H), 3.36 (td, J_1 = 10.7 Hz, J_2 = 4.0 Hz, 1 H), 3.95 (d, *J* = 18.0 Hz, 1 H), 4.23 (d, *J* = 18.0 Hz, 1 H), 4.66 (s, 1 H), 4.81 (dd, J_1 = 9.5 Hz, J_2 = 1.6 Hz, 1 H), 5.05 (q, *J* = 6.4 Hz, 1 H), 7.16–7.25 (m, 4 H), 7.30–7.41 (m, 2 H), 7.41–7.50 (m, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.4, 21.0, 22.1, 24.9, 27.2, 31.2, 34.9, 37.5, 40.4, 45.9, 46.6, 57.2, 63.7, 76.3, 89.9, 125.0, 126.1, 126.7 (2 C), 126.8, 127.6, 128.3 (2 C), 130.3, 137.2, 142.9, 143.8 ppm. IR (Nujol): $\tilde{\nu}$ = 3400, 3060, 3020, 1590, 730, 710 cm^{-1}. $C_{27}H_{37}NO_2$ (407.59): calcd. C 79.56, H 9.15, N 3.44; found C 78.97, H 8.46, N 3.36.

(1*S*,2′*S*,4a′*S*,7′*R*,8a′*R*)-1-{2-[(*N*-Benzyl-4′,4′,7′-trimethyloctahydro-2*H*-benzo[*e*][1,3]oxazin-2′-yl)methyl]phenyl}ethanol (*epi*-4a):

0.91 g, 42.2%. $[\alpha]_D^{23}$ = –39.2 (*c* = 0.94, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.79–0.97 (m, 2 H), 0.88 (d, *J* = 6.5 Hz, 3 H), 1.01–1.17 (m, 1 H), 1.08 (s, 3 H), 1.28 (s, 3 H), 1.35 (d, *J* = 6.5 Hz, 3 H), 1.38–1.66 (m, 4 H), 1.80 (m, 1 H), 2.60 (dd, J_1 = 14.2 Hz, J_2 = 3.2 Hz, 1 H), 3.03 (dd, J_1 = 14.2 Hz, J_2 = 8.2 Hz, 1 H), 3.15 (br. s, 1 H), 3.39 (td, J_1 = 10.7 Hz, J_2 = 4.0 Hz, 1 H), 3.93 (d, *J* = 18.0 Hz, 1 H), 4.21 (d, *J* = 18.0 Hz, 1 H), 4.86–4.92 (m, 2 H), 7.11–7.19 (m, 4 H), 7.21–7.34 (m, 3 H), 7.38–7.40 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.2, 22.3, 25.0 (2 C), 27.3, 31.4, 35.1, 37.3, 41.1, 45.9, 46.5, 57.3, 68.8, 76.3, 89.2, 125.9, 126.4, 126.5, 126.9 (2 C), 127.1, 128.1 (2 C), 130.5, 136.0, 144.0, 144.2 ppm. IR (Nujol): ṽ = 3385, 3060, 3020, 1595, 760, 730 cm^{-1}. $C_{27}H_{37}NO_2$ (407.59): calcd. C 79.56, H 9.15, N 3.44; found C 79.14, H 8.94, N 3.17.

(1*R*,2′*S*,4a′*S*,7′*R*,8a′*R*)-1-{2-[(*N*-Benzyl-4′,4′,7′-trimethyloctahydro-2*H*-benzo[*e*][1,3]oxazin-2′-yl)methyl]phenyl}pentan-1-ol (4c): 1.64 g, 69%. $[\alpha]_D^{23}$ = +7.17 (*c* = 1.00, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.84–0.94 (m, 1 H), 0.85 (d, *J* = 6.5 Hz, 3 H), 0.89 (t, *J* = 7.1 Hz, 3 H), 1.07–1.15 (m, 1 H), 1.11 (s, 3 H), 1.24–1.47 (m, 5 H), 1.28 (s, 3 H), 1.51–1.85 (m, 6 H), 1.98 (m, 1 H), 2.50 (dd, J_1 = 14.0 Hz, J_2 = 1.7 Hz, 1 H), 3.05 (dd, J_1 = 14.0 Hz, J_2 = 9.6 Hz, 1 H), 3.35 (td, J_1 = 10.6 Hz, J_2 = 4.0 Hz, 1 H), 3.96 (d, *J* = 18 Hz, 1 H), 4.23 (d, *J* = 18 Hz, 1 H), 4.28 (s, 1 H), 4.79 (m, 2 H), 7.17–7.26 (m, 4 H), 7.33 (t, *J* = 7.5 Hz, 2 H), 7.41 (m, 1 H), 7.49 (d, *J* = 7.2 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0, 20.9, 22.0, 22.8, 24.9, 27.1, 28.7, 31.2, 34.2, 34.9, 37.3, 40.4, 45.9, 46.6, 57.2, 68.1, 76.4, 89.4, 125.5, 126.0, 126.7 (2 C), 126.8, 127.4, 128.2 (2 C), 130.2, 137.5, 142.4, 143.9 ppm. IR (film): ṽ = 3420, 3060, 3020, 1710, 1600, 1590, 1450, 750, 730, 710 cm^{-1}. $C_{30}H_{43}NO_2$ (449.67): calcd. C 80.13, H 9.64, N 3.11; found C 79.64, H 9.11, N 3.08.

(1*S*,2′*S*,4a′*S*,7′*R*,8a′*R*)-1-{2-[(*N*-Benzyl-4′,4′,7′-trimethyloctahydro-2*H*-benzo[*e*][1,3]oxazin-2′-yl)methyl]phenyl}pentan-1-ol (*epi*-4c): 0.51 g, 21.5%. $[\alpha]_D^{23}$ = –34.9 (*c* = 0.83, $CHCl_3$). ^1H NMR (300 MHz, $CHCl_3$): δ = 0.85 (t, *J* = 6.9 Hz, 3 H), 0.89 (d, *J* = 6.4 Hz, 3 H), 0.91–0.97 (m, 2 H), 1.04–1.28 (m, 5 H), 1.10 (s, 3 H), 1.29 (s, 3 H), 1.31–1.71 (m, 6 H), 1.81 (m, 1 H), 2.57 (dd, J_1 = 14.2 Hz, J_2 = 3.0 Hz, 1 H), 3.05 (dd, J_1 = 14.2 Hz, J_2 = 8.4 Hz, 1 H), 3.26 (br. s, 1 H), 3.39 (td, J_1 = 10.7 Hz, J_2 = 4.1 Hz, 1 H), 3.94 (d, *J* = 17.8 Hz, 1 H), 4.22 (d, *J* = 17.8 Hz, 1 H), 4.66 (dd, J_1 = 7.9 Hz, J_2 = 5.1 Hz, 1 H), 4.91 (dd, J_1 = 8.4 Hz, J_2 = 3.0 Hz, 1 H), 7.15–7.23 (m, 5 H), 7.25–7.30 (m, 2 H), 7.41 (d, *J* = 7.1 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CHCl_3$): δ = 14.0, 21.1, 22.1, 22.7, 24.9, 27.2, 28.5, 31.2, 35.0, 37.3, 38.7, 40.9, 45.8, 46.3, 57.2, 73.6, 76.3, 89.1, 125.8, 126.2, 126.8 (2 C), 127.0, 127.3, 128.0 (2 C), 130.5, 136.2, 143.2, 144.0 ppm. IR (film): ṽ = 3400, 3060, 3020, 1720, 1600, 1590, 1450, 750, 720, 700, 690 cm^{-1}. $C_{30}H_{43}NO_2$ (449.67): calcd. C 80.13, H 9.64, N 3.11; found C 79.84, H 9.48, N 2.91.

(1*R*,2′*S*,4a′*S*,7′*R*,8a′*R*)-1-{2-[(*N*-Benzyl-4′,4′,7′-trimethyloctahydro-2*H*-benzo[*e*][1,3]oxazin-2′-yl)methyl]phenyl}(phenyl)methanol (4d): White solid m.p. 146–147 °C (hexanes). 1.32 g, 53.3%. $[\alpha]_D^{23}$ = +10.8 (*c* = 0.20, $CHCl_3$). ^1H NMR (300 MHz, $CHCl_3$): δ = 0.81–1.10 (m, 2 H), 0.87 (d, *J* = 6.5 Hz, 3 H), 1.13 (s, 3 H), 1.16–1.25 (m, 2 H), 1.30 (s, 3 H), 1.49–1.68 (m, 3 H), 1.83 (m, 1 H), 2.62 (dd, J_1 = 14.0 Hz, J_2 = 1.6 Hz, 1 H), 3.21 (dd, J_1 = 14.0 Hz, J_2 = 9.5 Hz, 1 H), 3.40 (td, J_1 = 10.6 Hz, J_2 = 4.0 Hz, 1 H), 3.99 (d, *J* = 18 Hz, 1 H), 4.26 (d, *J* = 18 Hz, 1 H), 4.87 (dd, J_1 = 9.5 Hz, J_2 = 1.6 Hz, 1 H), 4.90 (s, 1 H), 6.09 (s, 1 H), 6.79 (dd, J_1 = 7.4 Hz, J_2 = 1.2 Hz, 1 H), 7.02–7.08 (m, 1 H), 7.15–7.29 (m, 4 H), 7.30–7.47 (m, 6 H), 7.50 (d, *J* = 7.4 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CHCl_3$): δ = 21.0, 22.0, 24.8, 27.1, 31.2, 34.8, 37.6, 40.4, 45.8, 46.4, 57.1, 70.3, 76.5, 89.7, 126.0, 126.6 (3 C), 126.7 (3 C), 127.6, 127.8 (2 C), 128.1 (2 C), 128.2, 130.0, 137.4, 142.5, 143.4, 143.7 ppm. IR (film): ṽ = 3300, 3040, 3020, 1600, 1590, 1450, 740, 690 cm^{-1}. $C_{32}H_{39}NO_2$ (469.66): calcd. C 81.83, H 8.37, N 2.98; found C 81.13, H 8.45, N 2.70.

(1*S*,2′*S*,4a′*S*,7′*R*,8a′*R*)-1-{2-[(*N*-Benzyl-4′,4′,7′-trimethyloctahydro-2*H*-benzo[*e*][1,3]oxazin-2′-yl)methyl]phenyl}(phenyl)methanol (*epi*-4d): Colorless oil. 1.01 g, 40.7%. $[\alpha]_D^{23}$ = +12.5 (*c* = 0.14, $CHCl_3$). ^1H NMR (300 MHz, $CHCl_3$): δ = 0.92 (d, *J* = 6.0 Hz, 3 H), 0.96–1.07 (m, 2 H), 1.14 (s, 3 H), 1.19–1.25 (m, 1 H), 1.29 (s, 3 H), 1.40–1.48 (m, 2 H), 1.51–1.72 (m, 2 H), 1.89 (m, 1 H), 2.14 (d, *J* = 14 Hz, 1 H), 2.66 (dd, J_1 = 14.0 Hz, J_2 = 9.3 Hz, 1 H), 3.41 (td, J_1 = 10.6 Hz, J_2 = 4.0 Hz, 1 H), 3.85 (d, *J* = 16.8 Hz, 1 H), 3.95 (d, *J* = 16.8 Hz, 1 H), 4.86 (d, *J* = 9.3 Hz, 1 H), 5.20 (br. s, 1 H), 5.77 (s, 1 H), 7.08–7.37 (m, 14 H) ppm. ^{13}C NMR (75 MHz, $CHCl_3$): δ = 21.3, 22.1, 24.9, 27.3, 31.2, 34.9, 38.0, 40.5, 45.9, 46.0, 57.1, 76.3, 76.6, 89.5, 125.5 (2 C), 125.7, 126.4 (2 C), 126.8 (2 C), 127.9 (2 C), 128.1 (3 C), 130.8, 131.6, 137.4, 142.3, 143.5, 145.2 ppm. IR (film): ṽ = 3350, 3060, 3020, 1600, 1590, 1450, 760, 720, 700 cm^{-1}. $C_{32}H_{39}NO_2$ (469.66): calcd. C 81.83, H 8.37, N 2.98; found C 81.49, H 7.96, N 2.69.

(1*R*,2′*S*,4a′*S*,7′*R*,8a′*R*)-1-{2-[(*N*-Benzyl-4′,4′,7′-trimethyloctahydro-2*H*-benzo[*e*][1,3]oxazin-2′-yl)methyl]phenyl}(phenyl)prop-2-en-1-ol (4e): 1.36 g, 61.4%. $[\alpha]_D^{23}$ = +1.5 (*c* = 0.92, $CHCl_3$). ^1H NMR (300 MHz, $CHCl_3$): δ = 0.85 (d, *J* = 6.5 Hz, 3 H), 0.89–0.95 (m, 1 H), 1.08–1.23 (m, 2 H), 1.12 (s, 3 H), 1.25–1.42 (m, 1 H), 1.28 (s, 3 H), 1.46–1.67 (m, 3 H), 1.77 (m, 1 H), 2.53 (d, *J* = 13.9 Hz, 1 H), 3.04 (dd, J_1 = 13.9 Hz, J_2 = 9.6 Hz, 1 H), 3.35 (td, J_1 = 10.5 Hz, J_2 = 3.9 Hz, 1 H), 3.95 (d, *J* = 17.9 Hz, 1 H), 4.22 (d, *J* = 17.9 Hz, 1 H), 4.71 (s, 1 H), 4.81 (d, *J* = 9.6 Hz, 1 H), 5.32 (dd, J_1 = 10.6 Hz, J_2 = 1.7 Hz, 1 H), 5.40–5.41 (m, 1 H), 5.53 (dd, J_1 = 17.1 Hz, J_2 = 1.7 Hz, 1 H), 6.07 (ddd, J_1 = 17.1 Hz, J_2 = 10.6 Hz, J_3 = 4.4 Hz, 1 H), 7.16–7.24 (m, 4 H), 7.29–7.34 (m, 3 H), 7.48 (d, *J* = 7.6 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CHCl_3$): δ = 21.1, 22.1, 24.9, 27.2, 31.3, 34.9, 37.6, 40.4, 46.0, 46.6, 57.3, 68.9, 77.5, 89.7, 114.9, 126.1, 126.7 (2 C), 126.8, 127.3, 127.9, 128.3 (2 C), 130.3, 137.3, 138.4, 141.6, 143.8 ppm. IR (film): ṽ = 3400, 3060, 3020, 1645, 1600, 1590, 1450, 990, 750, 730, 715, 690 cm^{-1}. $C_{28}H_{37}NO_2$ (419.60): calcd. C 80.15, H 8.89, N 3.34; found C 79.98, H 9.04, N 3.49.

(1*S*,2′*S*,4a′*S*,7′*R*,8a′*R*)-1-{2-[(*N*-Benzyl-4′,4′,7′-trimethyloctahydro-2*H*-benzo[*e*][1,3]oxazin-2′-yl)methyl]phenyl}(phenyl)prop-2-en-1-ol (*epi*-4e): 0.68 g, 30.7%. $[\alpha]_D^{23}$ = –13.5 (*c* = 0.92, $CHCl_3$). ^1H NMR (300 MHz, $CHCl_3$): δ = 0.89–1.27 (m, 3 H), 0.89 (d, *J* = 6.5 Hz, 3 H), 1.12 (s, 3 H), 1.30 (s, 3 H), 1.38–1.68 (m, 4 H), 1.82 (m, 1 H), 2.45 (dd, J_1 = 14.2 Hz, J_2 = 2.1 Hz, 1 H), 3.19 (dd, J_1 = 14.2 Hz, J_2 = 9.2 Hz, 1 H), 3.39 (td, J_1 = 10.6 Hz, J_2 = 4.0 Hz, 1 H), 3.95 (d, *J* = 17.9 Hz, 1 H), 4.17 (d, *J* = 17.9 Hz, 1 H), 4.53 (d, *J* = 5.9 Hz, 1 H), 4.87 (dd, J_1 = 9.2 Hz, J_2 = 2.1 Hz, 1 H), 5.09 (td, J_1 = 10.5 Hz, J_2 = 2.0 Hz, 1 H), 5.16 (m, 1 H), 5.34 (ddd, J_1 = 17.2 Hz, J_2 = 3.8 Hz, J_3 = 2.0 Hz, 1 H), 5.99 (ddd, J_1 = 17.2 Hz, J_2 = 10.5 Hz, J_3 = 3.8 Hz, 1 H), 7.16–7.33 (m, 7 H), 7.44 (d, *J* = 7.4 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CHCl_3$): δ = 21.2, 22.2, 24.9, 27.3, 31.3, 35.0, 37.8, 40.7, 45.9, 46.4, 57.2, 75.5, 76.4, 89.5, 113.5, 126.0, 126.6, 126.8 (2 C), 127.9, 128.1 (2 C), 129.4, 131.2, 137.4 (2 C), 141.3, 143.9 ppm. IR (film): ṽ = 3400, 3060, 3020, 1720, 1600, 1590, 1450, 995, 740, 700 cm^{-1}. $C_{28}H_{37}NO_2$ (419.60): calcd. C 80.15, H 8.89, N 3.34; found C 80.28, H 8.72, N 3.47.

(1*R*,2′*S*,4a′*S*,7′*R*,8a′*R*)-1-{2-[(*N*-Benzyl-4′,4′,7′-trimethyloctahydro-2*H*-benzo[*e*][1,3]oxazin-2′-yl)methyl]phenyl}(phenyl)but-3-en-1-ol (4f): 1.65 g, 72.2%. $[\alpha]_D^{23}$ = –3.7 (*c* = 1.19, $CHCl_3$). ^1H NMR (300 MHz, $CHCl_3$): δ = 0.86 (d, *J* = 6.5 Hz, 3 H), 0.90–1.00 (m, 2 H), 1.04–1.16 (m, 1 H), 1.12 (s, 3 H), 1.29 (s, 3 H), 1.33–1.77 (m, 5 H), 2.53 (dd, J_1 = 14 Hz, J_2 = 2 Hz, 1 H), 2.61 (td, J_1 = 14.1 Hz,

J_2 = 7 Hz, 1 H), 2.78 (td, J_1 = 14.1 Hz, J_2 = 7 Hz, 1 H), 3.04 (dd, J_1 = 14 Hz, J_2 = 9.6 Hz, 1 H), 3.36 (td, J_1 = 10.6 Hz, J_2 = 4.1 Hz, 1 H), 3.96 (d, J = 17.9 Hz, 1 H), 4.23 (d, J = 17.9 Hz, 1 H), 4.34 (s, 1 H), 4.80 (dd, J = 8.4 Hz, 1 H), 4.89 (t, J = 7 Hz, 1 H), 5.05 (dd, J_1 = 11 Hz, J_2 = 1.6 Hz, 1 H), 5.14 (dd, J_1 = 17.1 Hz, J_2 = 1.6 Hz, 1 H), 5.84 (ddt, J_1 = 17.1 Hz, J_2 = 11 Hz, J_3 = 7 Hz, 1 H), 7.18–7.27 (m, 4 H), 7.29–7.40 (m, 2 H), 7.43 (m, 1 H), 7.50 (d, J = 7.6 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CHCl_3$): δ = 21.0, 24.9, 27.2, 31.3, 34.9, 37.3, 39.0, 40.5, 45.9, 46.6, 57.3, 68.0, 76.4, 89.8, 117.0, 125.6, 126.0, 126.7 (2 C), 126.8, 127.6, 128.2 (2 C), 130.3, 135.6, 137.5, 141.6, 143.8 ppm. IR (film): $\tilde{\nu}$ = 3400, 3060, 3020, 1630, 1600, 1590, 1450, 750, 720, 700 cm^{-1}. $C_{29}H_{39}NO_2$ (433.63): calcd. C 80.33, H 9.07, N 3.23; found C 79.81, H 8.78, N 3.01.

(1*S*,2′*S*,4a′*S*,7′*R*,8a′*R*)-1-{2-[(*N*-Benzyl-4′,4′,7′-trimethyloctahydro-2*H*-benzo[*e*][1,3]oxazin-2′-yl)methyl]phenyl}(phenyl)but-3-en-1-ol (*epi*-4f): 0.41 g, 18%. $[\alpha]_D^{23}$ = –40.5 (c = 0.19, $CHCl_3$). ^{1}H NMR (300 MHz, $CHCl_3$): δ = 0.03–0.99 (m, 2 H), 0.91 (d, J = 6.5 Hz, 3 H), 1.03–1.16 (m, 1 H), 1.12 (s, 3 H), 1.31 (s, 3 H), 1.39–1.54 (m, 2 H), 1.60–1.70 (m, 2 H), 1.82 (m, 1 H), 2.39 (td, J_1 = 14.4 Hz, J_2 = 7.3 Hz, 2 H), 2.43 (dd, J_1 = 14.4 Hz, J_2 = 7.3 Hz, 1 H), 2.61 (dd, J_1 = 14.2 Hz, J_2 = 2.8 Hz, 1 H), 3.04 (dd, J_1 = 14.2 Hz, J_2 = 8.4 Hz, 1 H), 3.32 (br. s, 1 H), 3.40 (td, J_1 = 7.3 Hz, J_2 = 5.4 Hz, 1 H), 4.92 (dd, J_1 = 8.4 Hz, J_2 = 2.8 Hz, 1 H), 5.07 (d, J = 10.1 Hz, 1 H), 5.08 (d, J = 16.9 Hz, 1 H), 5.79 (ddt, J_1 = 16.9 Hz, J_2 = 10.1 Hz, J_3 = 7.3 Hz, 1 H), 7.16–7.34 (m, 7 H), 7.43 (d, J = 7.6 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CHCl_3$): δ = 21.1, 22.2, 24.9, 27.2, 31.3, 34.9, 37.4, 41.0, 43.4, 45.9, 46.3, 57.2, 72.6, 76.3, 89.1, 117.3, 125.9, 126.3, 126.8 (2 C), 127.2 (2 C), 128.1 (2 C), 130.5, 135.3, 136.2, 142.2, 143.9 ppm. IR (film): $\tilde{\nu}$ = 3420, 3060, 3020, 1635, 1600, 1590, 1450, 755, 730, 715, 690 cm^{-1}. $C_{29}H_{39}NO_2$ (433.63): calcd. C 80.33, H 9.07, N 3.23; found C 79.98, H 8.97, N 3.24.

(1*R*,2′*S*,4a′*S*,7′*R*,8a′*R*)-1-{2-[(*N*-Benzyl-4′,4′,7′-trimethyloctahydro-2*H*-benzo[*e*][1,3]oxazin-2′-yl)methyl]phenyl}-2,2-dimethylpropan-1-ol (4g): 1.98 g, 79.9%. $[\alpha]_D^{23}$ = –27.0 (c = 0.18, $CHCl_3$). ^{1}H NMR (300 MHz, $CHCl_3$): δ = 0.98 (s, 9 H), 0.99 (d, J = 4.6 Hz, 3 H), 0.93–1.07 (m, 2 H), 1.14–1.21 (m, 1 H),1.21 (s, 3 H), 1.30 (s, 3 H), 1.39–1.87 (m, 5 H), 2.03 (br. s, 1 H), 2.53 (d, J = 14.4 Hz, 1 H), 1.58–1.66 (m, 2 H), 1.75 (m, 1 H), 2.51 (dd, J_1 = 14.0 Hz, J_2 = 1.6 Hz, 1 H), 3.05 (dd, J_1 = 14.0 Hz, J_2 = 9.0 Hz, 1 H), 3.43 (td, J_1 = 10.6 Hz, J_2 = 4.0 Hz, 1 H), 4.05 (d, J = 17.8 Hz, 1 H), 4.28 (d, J = 17.8 Hz, 1 H), 4.84 (d, J = 9 Hz, 1 H), 4.88 (s, 1 H), 7.24–7.33 (m, 4 H), 7.41 (t, J = 7.5 Hz, 2 H), 7.54 (d, J = 7.4 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CHCl_3$): δ = 21.0, 22.3, 25.0, 26.4 (3 C), 27.4, 31.4, 35.1, 36.0, 37.9, 41.3, 46.1, 46.7, 57.3, 76.1, 76.2, 89.3, 125.7, 126.0, 126.8 (3 C), 127.6, 128.2 (2 C), 129.2, 137.3, 141.9, 144.3 ppm. IR (film): $\tilde{\nu}$ = 3450, 3060, 3020, 1600, 1590, 1450, 770, 730, 690 cm^{-1}. $C_{30}H_{43}NO_2$ (449.67): calcd. C 80.13, H 9.64, N 3.11, found C 80.27, H 9.50, N 3.24.

(1*S*,2′*S*,4a′*S*,7′*R*,8a′*R*)-1-{2-[(*N*-Benzyl-4′,4′,7′-trimethyloctahydro-2*H*-benzo[*e*][1,3]oxazin-2′-yl)methyl]phenyl}-2,2-dimethylpropan-1-ol (*epi*-4g): 0.20 g, 8.0%. $[\alpha]_D^{23}$ = –31.9 (c = 0.20, $CHCl_3$). ^{1}H NMR (300 MHz, $CHCl_3$): δ = 0.85 (s, 9 H), 0.90–1.08 (m, 2 H), 0.97 (d, J = 6.6 Hz, 3 H), 1.13 (s, 3 H), 1.17–1.27 (m, 1 H), 1.36 (s, 3 H), 1.39–1.59 (m, 2 H), 1.64–1.74 (m, 2 H), 1.90 (m, 1 H), 2.71 (d, J = 13.2 Hz, 1 H), 3.13 (br. s, 1 H), 3.48 (td, J_1 = 10.5 Hz, J_2 = 4.0 Hz, 1 H), 3.98 (d, J = 18 Hz, 1 H), 4.27 (d, J = 18 Hz, 1 H), 4.54 (s, 1 H), 5.00 (dd, J_1 = 7.8 Hz, J_2 = 3.3 Hz, 1 H), 7.17–7.34 (m, 7 H), 7.37–7.43 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CHCl_3$): δ = 21.3, 22.2, 24.9, 26.3 (3 C), 27.1, 31.3, 35.0, 36.7, 37.8, 41.0, 45.8, 46.0, 57.1, 76.3 (2 C), 89.0, 125.1, 125.7, 126.7 (3 C), 127.9 (2 C), 129.2, 130.1, 137.1, 140.3, 143.9 ppm. IR (film): $\tilde{\nu}$ = 3400, 3060, 3020, 1600, 1450, 740, 720 cm^{-1}. $C_{30}H_{43}NO_2$ (449.67): calcd. C 80.13, H 9.64, N 3.11; found C 80.28, H 9.76, N 3.13.

(2′*S*,4a′*S*,7′*R*,8a′*R*)-1-{2-[(*N*-Benzyl-4′,4′,7′-trimethyloctahydro-2*H*-benzo[*e*][1,3]oxazin-2′-yl)methyl]phenyl}methanol (5): 1.04 g, 50%. $[\alpha]_D^{23}$ = –11.3 (c = 0.17, $CHCl_3$). ^{1}H NMR (300 MHz, $CHCl_3$): δ = 0.86 (d, J = 6.5 Hz, 3 H),0.90–1.11 (m, 3 H), 1.15 (s, 3 H), 1.32 (s, 3 H), 1.35–1.49 (m, 2 H), 1.52–1.70 (m, 2 H), 1.77 (m, 1 H), 2.59 (d, J = 13.8 Hz, 1 H), 2.95 (dd, J_1 = 13.8 Hz, J_2 = 9.1 Hz, 1 H), 3.40 (td, J_1 = 10.6 Hz, J_2 = 4.0 Hz, 1 H), 3.99 (d, J = 18 Hz, 1 H), 4.24 (d, J = 18 Hz, 1 H), 4.31 (d, J = 11.9 Hz, 1 H), 4.60 (br. s, 1 H), 4.80 (d, J = 11.9 Hz, 1 H), 4.86 (d, J = 9.1 Hz, 1 H), 6.85–7.50 (m, 7 H), 7.52 (d, J = 7.8 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CHCl_3$): δ = 20.9, 22.0, 24.9, 27.2, 31.2, 34.8, 38.0, 40.3, 45.9, 46.5, 57.2, 63.6, 76.4, 89.5, 126.1, 126.7 (2 C), 126.8, 128.2 (3 C), 130.3, 130.5, 137.8, 139.5, 143.7 ppm. IR (film): $\tilde{\nu}$ = 3350, 3060, 3020, 1600, 1590, 1450, 1020, 740, 690 cm^{-1}. HRMS (CI+, *m*/*z*, %): 394 (M + 1, 66), 272 (100) cm^{-1}. $C_{26}H_{35}NO_2$ (393.56): calcd. C 79.35, H 8.96, N 3.56; found C 79.05, H 9.10, N 3.14.

Synthesis of Isochromanes 6–7. General Method: A solution of the corresponding perhydrobenzoxazine **4** (1 mmol) in methanol or ethanol (15 mL) and 2% aqueous hydrochloric acid (7 mL) was refluxed until the hydrolysis was complete (TLC). The aqueous layer was extracted with hexane (3×20 mL). The organic extracts were washed with brine, dried with anhydrous $MgSO_4$, and concentrated in vacuo. The residues were purified by flash chromatography on silica gel using hexanes/ethyl acetate as the eluent to obtain acetals **6** and **7** as an inseparable mixture of *cis* and *trans* diastereoisomers.

(1*R*)-3-Methoxy-1-methylisochromane (6a): Colourless oil. 121 mg, 68%. Mixture of *cis* and *trans* diastereoisomers. ^{1}H NMR (300 MHz, $CHCl_3$): δ = 1.58 (d, J = 7.1 Hz, 3 H), 1.63 (d, J = 7.1 Hz, 3 H), 2.79 (dd, J_1 = 16.0 Hz, J_2 = 2.5 Hz, 1 H), 2.92 (m, 2 H), 3.14 (dd, J_1 = 11.9 Hz, J_2 = 4.6 Hz, 1 H), 3.51 (s, 3 H), 3.59 (s, 3 H), 4.77 (dd, J_1 = 8.0 Hz, J_2 = 3.5 Hz, 1 H), 4.95 (m, 2 H), 5.08 (dd, J_1 = 4.7 Hz, J_2 = 2.3 Hz, 1 H), 7.08–7.16 (m, 4 H), 7.16–7.22 (m, 4 H) ppm.

(1*R*)-1-Butyl-3-methoxyisochromane (6c): Yellowish oil. 143 mg, 65%. Mixture of *cis* and *trans* diastereoisomers. ^{1}H NMR (300 MHz, $CHCl_3$): δ = 0.91 (t, J = 7.1 Hz, 3 H), 0.92 (t, J = 7.1 Hz, 3 H), 1.30–1.50 (m, 8 H), 1.75–1.90 (m, 2 H), 1.90–2.10 (m, 2 H), 2.76 (dd, J_1 = 15.8 Hz, J_2 = 2.5 Hz, 1 H), 2.92 (m, 2 H), 3.15 (dd, J_1 = 11.7 Hz, J_2 = 4.4 Hz, 1 H), 3.49 (s, 3 H), 3.58 (s, 3 H), 4.74 (dd, J_1 = 7.9 Hz, J_2 = 3.5 Hz, 1 H), 4.85 (m, 2 H), 5.06 (dd, J_1 = 4.7 Hz, J_2 = 2.4 Hz, 1 H), 7.08–7.16 (m, 4 H), 7.16–7.22 (m, 4 H) ppm.

(1*R*)-3-Methoxy-1-phenylisochromane (6d): Yellowish oil. 235 mg, 98%. Mixture of *cis* and *trans* diastereoisomers. ^{1}H NMR (300 MHz, $CHCl_3$): δ = 2.90 (d, J = 16.4 Hz, 1 H), 3.08 (m, 2 H), 3.35 (dd, J_1 = 10.9 Hz, J_2 = 4.6 Hz, 1 H), 3.51 (s, 3 H), 3.54 (s, 3 H), 4.93 (dd, J_1 = 7.6 Hz, J_2 = 3.1 Hz, 1 H), 5.15 (dd, J_1 = 4.5 Hz, J_2 = 2.2 Hz, 1 H), 5.80 (s, 2 H), 7.05–7.40 (m, 18 H) ppm.

(1*R*)-3-Methoxy-1-vinylisochromane (6e): Yellowish oil. 186 mg, 98%. Mixture of *cis* and *trans* diastereoisomers. ^{1}H NMR (300 MHz, $CHCl_3$): δ = 2.74 (dd, J_1 = 16.2 Hz, J_2 = 2.4 Hz, 1 H), 3.05 (m, 2 H), 3.20 (dd, J_1 = 11.9 Hz, J_2 = 4.6 Hz, 1 H), 3.36 (s, 3 H), 3.54 (s, 3 H), 4.12 (m, 2 H), 4.56 (t, J_1 = 8.0 Hz, 1 H), 5.12 (m, 1 H), 5.23 (m, 1 H), 5.38–5.50 (m, 1 H), 5.92–6.08 (m, 1 H), 6.14–6.24 (m, 1 H), 7.12–7.30 (m, 8 H) ppm.

(1*R*)-3-Ethoxyl-1-methylisochromane (7a): Yellowish oil. 146 mg, 76%. Mixture of *cis* and *trans* diastereoisomers. ^{1}H NMR (300 MHz, $CHCl_3$): δ = 1.23 (t, J = 7.1 Hz, 3 H), 1.29 (t, J = 7.1 Hz, 3 H), 1.58 (d, J = 6.6 Hz, 3 H), 1.60 (d, J = 6.5 Hz, 3 H), 2.71 (dd, J_1 = 16.5 Hz, J_2 = 2.3 Hz, 1 H), 2.93 (m, 2 H), 3.17 (dd, J_1 =

11.7 Hz, J_2 = 4.7 Hz, 1 H), 3.55–3.66 (m, 2 H), 3.83–3.91 (m, 1 H), 4.0–4.1 (m, 1 H), 4.82 (dd, J_1 = 8.0 Hz, J_2 = 3.7 Hz, 1 H), 4.93 (m, 2 H), 5.14 (dd, J_1 = 4.7 Hz, J_2 = 2.4 Hz, 1 H), 7.09–7.16 (m, 4 H), 7.16–7.22 (m, 4 H) ppm.

(1*R*)-1-Butyl-3-ethoxyisochromane (7c): Yellowish oil. 167 mg, 50%. Mixture of *cis* and *trans* diastereoisomers. ^{1}H NMR (300 MHz, $CHCl_3$): δ = 0.93 (t, J = 7.1 Hz, 6 H), 1.22 (t, J = 7.1 Hz, 3 H), 1.29 (t, J = 7.1 Hz, 3 H), 1.35–1.60 (m, 8 H), 1.75–1.90 (m, 2 H), 1.90–2.10 (m, 2 H), 2.77 (dd, J_1 = 16.4 Hz, J_2 = 2.3 Hz, 1 H), 2.93 (m, 1 H), 3.15 (dd, J_1 = 11.7 Hz, J_2 = 4.7 Hz, 1 H), 3.54–3.66 (m, 2 H), 3.83–3.91 (m, 2 H), 4.82 (m, 2 H), 5.15 (dd, J_1 = 4.7 Hz, J_2 = 2.2 Hz, 1 H), 7.09–7.16 (m, 4 H), 7.16–7.22 (m, 4 H) ppm.

(1*R*)-3-Ethoxy-1-phenylisochromane (7d): Yellowish oil. 249 mg, 98%. Mixture of *cis* and *trans* diastereoisomers. ^{1}H NMR (300 MHz, $CHCl_3$): δ = 1.26 (t, J = 6.9 Hz, 3 H), 1.29 (t, J = 7.3 Hz, 3 H), 2.92 (dd, J_1 = 16.3 Hz, J_2 = 2.1 Hz, 1 H), 3.05–3.25 (m, 2 H), 3.35 (dd, J_1 = 11.8 Hz, J_2 = 4.5 Hz, 1 H), 3.55–3.65 (m, 2 H), 3.93–4.01 (m, 2 H), 5.05 (dd, J_1 = 7.8 Hz, J_2 = 3.2 Hz, 1 H), 5.28 (dd, J_1 = 4.6 Hz, J_2 = 2.4 Hz, 1 H), 5.82 (s, 2 H), 7.05–7.46 (m, 18 H) ppm.

(1*R*)-1-Allyl-3-Methoxyisochromane (7f): Yellowish oil. 177 mg, 81%. Mixture of *cis* and *trans* diastereoisomers. ^{1}H NMR (300 MHz, $CHCl_3$): δ = 1.26 (t, J = 7.0 Hz, 3 H), 1.27 (t, J = 7.0 Hz, 3 H), 2.60–2.90 (m, 6 H), 2.90–3.20 (m, 2 H), 3.48–3.58 (m, 2 H), 3.82–3.92 (m, 2 H), 4.82 (dd, J_1 = 4.7 Hz, J_2 = 2.3 Hz, 1 H), 4.90–5.02 (m, 1 H), 5.10–5.25 (m, 8 H), 7.10–7.35 (m, 8 H) ppm.

(1*R*)-1-*tert*-Butyl-3-ethoxyisochromane (7g): Yellowish oil. 167 mg, 50%. Mixture of *cis* and *trans* diastereoisomers. ^{1}H NMR (300 MHz, $CHCl_3$): δ = 0.95 (s, 9 H), 0.96 (t, J = 7.1 Hz, 3 H), 0.97 (s, 9 H), 1.12 (t, J = 7.1 Hz, 3 H), 2.71 (dd, J_1 = 16.7 Hz, J_2 = 2.3 Hz, 1 H), 2.89–2.96 (m, 2 H), 3.06 (dd, J_1 = 11.8 Hz, J_2 = 4.7 Hz, 1 H), 3.54–3.61 (m, 2 H), 3.68–3.77 (m, 2 H), 4.44 (s, 1 H), 4.55–4.72 (m, 1 H) 4.88 (s, 1 H), 5.22 (dd, J_1 = 4.6 Hz, J_2 = 2.4 Hz, 1 H),7.12–7.28 (m, 8 H) ppm.

Synthesis of Isochromenes 8a, c, d, g. General Method: A solution of the corresponding perhydrobenzoxazine **4** (4 mmol) in toluene (60 mL) and 2% aqueous hydrochloric acid (30 mL) was refluxed until the hydrolysis was complete (TLC). The aqueous layer was extracted with hexane (3×60 mL). The organic extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash chromatography on silica gel using hexanes/ethyl acetate as the eluent.

(*R*)-1-Methyl-1*H*-isochromene (8a): Colorless oil. 0.25 g, 43%. $[\alpha]_D^{23}$ = +15.0 (c = 0.50, $CHCl_3$). ^{1}H NMR (300 MHz, $CHCl_3$): δ = 1.59 (d, J = 6.5 Hz, 3 H), 5.21 (q, J = 6.5 Hz, 1 H), 5.75 (d, J = 7.5 Hz, 1 H), 6.50 (d, J = 5.7 Hz, 1 H), 6.93–7.11 (m, 2 H), 7.12–7.22 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CHCl_3$): δ = 19.7, 73.5, 104.7, 123.0, 123.3, 126.6, 127.8, 129.6, 132.4, 144.8 ppm. IR (film): $\tilde{\nu}$ = 3066, 3020, 1626, 1452, 1092, 1054, 768 cm^{-1}. $C_{10}H_{10}O$ (146.19): calcd. C 82.16, H 6.89; found C 82.29, H 7.02.

(*R*)-1-Butyl-1*H*-isochromene (8c): Colorless oil. 0.64 g, 85%. $[\alpha]_D^{23}$ = +66.1 (c = 0.87, $CHCl_3$). ^{1}H NMR (300 MHz, $CHCl_3$): δ = 0.91 (t, J = 7.1 Hz, 3 H), 1.30–1.66 (m, 4 H), 1.65–1.76 (m, 1 H), 1.97–2.09 (m, 1 H), 5.07 (dd, J_1 = 8.5 Hz, J_2 = 4.7 Hz, 1 H), 5.72 (d, J = 5.7 Hz, 1 H), 6.48 (d, J = 5.7 Hz, 1 H), 6.86–7.00 (m, 2 H), 7.03–7.22 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CHCl_3$): δ = 14.0, 22.5, 27.6, 33.8, 77.4, 104.4, 123.1, 124.0, 126.4, 127.7, 129.6, 131.6, 144.3 ppm. IR (film): $\tilde{\nu}$ = 3067, 3020, 1626, 1600, 1453, 1052, 768 cm^{-1}. $C_{13}H_{16}O$ (188.27): calcd. C 82.94, H 8.57; found C 83.10, H 8.69.

(*R*)-1-Phenyl-1*H*-isochromene (8d):[7] White solid. M.p. 51–53 °C (from hexanes). 0.72 g, 87%. $[\alpha]_D^{23}$ = +9.2 (c = 0.50, $CHCl_3$). ^{1}H NMR (300 MHz, $CHCl_3$): δ = 5.84 (d, J = 5.7 Hz, 1 H), 6.10 (s, 1 H), 6.59 (d, J = 5.7 Hz, 1 H), 6.69 (dd, J_1 = 7.5 Hz, J_2 = 0.7 Hz, 2 H), 7.02 (d, J = 7.5 Hz, 1 H), 7.09 (dt, J_1 = 7.5 Hz, J_2 = 1.2 Hz, 1 H), 7.22 (dt, J_1 = 7.5 Hz, J_2 = 1.2 Hz, 1 H), 7.30–7.43 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CHCl_3$): δ = 79.5, 105.3, 123.1, 125.5, 126.7, 128.0 (2 C), 128.2, 128.4 (3 C), 130.2 (2 C), 140.0, 145.0 ppm. IR (film): $\tilde{\nu}$ = 3065, 3032, 1628, 1600, 1486, 1454, 1048, 754, 699 cm^{-1}. $C_{15}H_{12}NO$ (208.26): calcd. C 86.51, H 5.81; found C 86.64, H 5.95.

(*R*)-1-*tert*-Butyl-1*H*-isochromene (8g): Colorless oil. 0.34 g, 45%. $[\alpha]_D^{23}$ = +134.1 (c = 1.29, $CHCl_3$). ^{1}H NMR (300 MHz, $CHCl_3$): δ = 0.90 (d, J = 6.5 Hz, 9 H), 4.78 (s, 1 H), 5.46 (d, J = 5.7 Hz, 1 H), 6.44 (d, J = 5.7 Hz, 1 H), 6.81 (d, J = 7.5 Hz, 2 H), 7.01 (dt, J_1 = 7.5 Hz, J_2 = 1.5 Hz, 1 H), 7.09 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CHCl_3$): δ = 26.0 (3 C), 39.3, 85.0, 103.3, 122.9, 125.5, 127.1, 127.8, 130.6 (2 C), 145.7 ppm. IR (film): $\tilde{\nu}$ = 3067, 3025, 1633, 1452, 1394, 1365, 1052, 766 cm^{-1}. $C_{13}H_{16}O$ (188.27): calcd. C 82.94, H 8.57; found C 83.80, H 8.73.

Acknowledgments

Authors thank the Spanish Ministerio de Educación y Ciencia (DGI, Projects BQU2002-01046 and CTQ2005-01191/BQU) for financial support.

[1] a) J. M. Grisar, M. A. Petty, F. N. Bolkenius, J. Dow, J. Wagner, E. R. Wagner, K. D. Haegele, W. D. Jung, *J. Med. Chem.* **1991**, *34*, 257; b) H. Laatsch, *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 422; c) N. P. Seeran, H. Jacobs, S. McLean, W. F. Reynolds, *Phytochemistry* **1998**, *49*, 1389; d) T. Tanaka, F. Asai, M. Iinuma, *Phytochemistry* **1998**, *49*, 229.
[2] a) O. Potterat, H. Zahner, C. Volkmann, A. Zeeck, *J. Antibiotic* **1993**, *46*, 346; b) A. Ali, R. W. Read, S. Sotheeswaran, *Phytochemistry* **1994**, *35*, 1029; c) L. Hari, L. F. de Buyck, H. L. de Pooter, *Phytochemistry* **1991**, *30*, 1726; d) G. K. Poch, J. B. Gloer, *Tetrahedron Lett.* **1989**, *30*, 3483.
[3] J. D. Hepworth in *Comprehensive Heterocyclic Chemistry* (Ed.: A. R. Katritzky), Pergamon, **1984**, vol. 3, chapter 2, p. 765.
[4] J. Thibault, *Ann. Chim.* **1971**, *6*, 381.
[5] R. Hug, H.-J. Hansen, H. Schmid, *Helv. Chim. Acta* **1972**, *55*, 10.
[6] F. Léost, B. Chantegrel, C. Deshayes, *Tetrahedron* **1998**, *54*, 6457.
[7] B. Wünsch, *Arch. Pharm.* **1990**, *323*, 493.
[8] R. Mutter, I. B. Campbell, E. M. Martin, A. T. Merritt, M. Wills, *J. Org. Chem.* **2001**, *66*, 3284.
[9] B. Gabriele, G. Salerno, A. Fazio, R. Pittelli, *Tetrahedron* **2003**, *59*, 6251.
[10] R. G. F. Gilet, I. R. Green, C. P. Taylor, *Tetrahedron Lett.* **1999**, *40*, 4871.
[11] N. Asao, T. Nogami, K. Takahashi, Y. Yamamoto, *J. Am. Chem. Soc.* **2002**, *124*, 764.
[12] J. Barluenga, H. Vázquez-Villa, A. Ballesteros, J. M. González, *J. Am. Chem. Soc.* **2003**, *125*, 9028.
[13] D. Yue, N. Della Cá, R. C. Larock, *J. Org. Chem.* **2006**, *71*, 3381.
[14] R. Pedrosa, S. Sayalero, M. Vicente, B. Casado, *J. Org. Chem.* **2005**, *70*, 7273.
[15] A. Rassat, P. Rey, *Tetrahedron* **1974**, *30*, 3315.
[16] W. S. Knowles, Q. E. Thompson, *J. Org. Chem.* **1960**, *25*, 1031.

[17] Compound **5** was quantitatively obtained from **3** by reduction with sodium borohydride.
[18] M. S. Karasch, O. Reinmuth in *Grignard Reactions of Nonmetallic Substances*, Prentice Hall, New York, **1954**.
[19] H.-J. Liu, K.-S. Shia, X. Shang, B.-Y. Zhu, *Tetrahedron* **1999**, *55*, 3803.
[20] CCDC-619877 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
[21] a) E. L. Eliel, S. Morris-Natschke, *J. Am. Chem. Soc.* **1984**, *106*, 2937; b) X.-C. He, E. L. Eliel, *Tetrahedron* **1987**, *43*, 4979; c) E. L. Eliel, X.-C. He, *J. Org. Chem.* **1990**, *55*, 2144.
[22] J. Barluenga, J. R. Fernández, C. M. Rubiera, M. A. Yus, *J. Chem. Soc. Perkin Trans. 1* **1988**, 3113.
[23] K. J. Eash, M. S. Pulia, L. C. Wieland, R. S. Mohan, *J. Org. Chem.* **2000**, *65*, 8399.

Received: July 10, 2006
Published Online: September 18, 2006

