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A direct efficient diastereoselective synthesis of enantiopure 3-substituted-isobenzofuranones

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Abstract—Condensation of (−)-8-benzylaminomenthol with *o*-phthaldehyde lead to the chiral perhydro-1,3-benzoxazine **2** as single diastereoisomer. That compound reacted with different organometallics leading to **3** in excellent de. Hydrolysis of carbinols, followed by oxidation of the intermediates allowed for the synthesis of enantiopure phthalides.

1. Introduction

Phthalides (1(3*H*)-isobenzofuranones) are valuable synthetic intermediates[1] and a class of compounds possessing significant biological properties.[2] For example, some 3-alkyl substituted phthalides exhibit pharmacological applications,[3] and some others have been used as starting materials for the synthesis of carbo- and heterocycles.[4] These facts led to an increased interest in the synthesis of these compounds.[5] Specially interesting are the methodologies leading to optically active 3-alkyl substituted phthalides and, in this way, asymmetric hydrogenations[6] or alkylations,[7] enantioselective additions of alkylzinc,[8] asymmetric reductions of ketoesters,[9] and the use of chiral templates[10] have been successfully developed.

Herein we report on a versatile diastereoselective synthesis of chiral 3-substituted phthalides in excellent enantiomeric excess (ee) by using a chiral perhydro-1,3-benzoxazine derived from (−)-8-benzylaminomenthol.[11] This template has been successfully used in diastereoselective synthesis of aza-heterocycles by intramolecular cyclizations,[12] and now we envisaged that it can be used in a different diastereoselective approach. In this way, the perhydro-1,3-benzoxazine nucleus is now used as a chiral inductor in diastereoselective additions of different organometallics to a carbonyl group and a masked formyl substituent. The hydrolysis of the template, with recovering of the starting aminoalcohol, after the creation of a novel stereocenter and further elaboration of the intermediate allowed for the synthesis of a great variety of enantioenriched 3-substituted phthalides.

The versatility of the method is based on the possibility to introduce different substituents at C-3 in the final phthalides starting from a single compound by simply changing the nature of the nucleophile.

2. Results and discussion

The starting perhydro-1,3-benzoxazine **2**[13] was prepared as previously described by condensation of (−)-8-benzylaminomenthol and *o*-phthaldehyde in excellent yield and total diastereoselectivity, and transformed into the corresponding alcohols **3a**–**k** by reaction with different organometallics (Scheme 1). To this end, a solution of **2** in an ethereal solvent was reacted with excess of Grignard, organolithium, organozinc, and organocerium reagents[14] to afford alcohols **3a**–**k** as single diastereomers or with good diastereomeric excesses except for allylmagnesium or allylzinc derivatives (Table 1).

The chemical yields are excellent except for the reactions with ethyl-, isopropyl-, and *n*-butylmagnesium bromides. In these cases significant amount of the reduction derivative **4** was isolated (entries 3–6), but this problem was circumvented by using organollithium reagents, which lead to alkylation products, and no reduction derivatives were formed (compare entries 1 and 6, vs 2 and 7, respectively). The organocerium derivatives[15] also provided better yields than those obtained with Grignard or lithium reagents maintaining the degree of diastereoselection (compare entry 11 vs 9). Trifluromethylated alcohol **3i** was obtained in very good yield by addition

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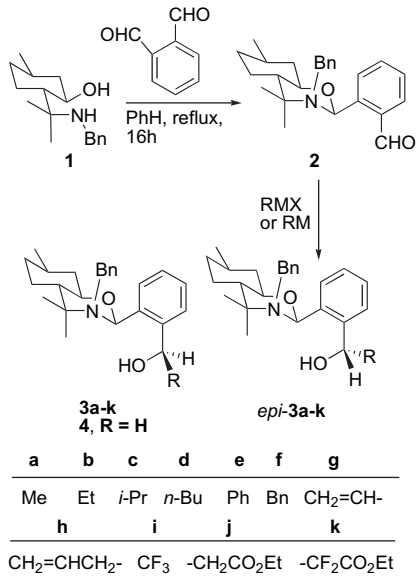


Scheme 1. Synthesis of **2** and reaction with organometallics.

of $TMSCF_3$ catalyzed by anhydrous TBAF.[16] Treatment of **2** with 4 equiv of Reformatsky reagents[17] gave alcohols **3j** and **3k** in good to excellent yields, but they highly decreased when less than 4 equiv of organometallic was used.

The nucleophilic addition of organometallics to aldehyde **2** is also stereochemically noteworthy. In most cases only one diastereoisomer was detected in the ^1H NMR of the reaction mixtures, and the stereochemistry of the novel created stereocenter is independent on the organometallic used in the reaction. An exception to this general behavior was the reactions with allylmagnesium bromide in Et_2O (entries 14 and 15 in Table 1), but a significant improvement in the stereoselection was observed when allylmagnesium chloride, in THF, was used instead (entry 16 in Table 1). The reaction with allylzinc bromide occurred also with moderate diastereoselection.

Table 1. Nucleophilic addition of organometallic reagents to **2**

Entry	Reagent	Temp (°C)	Solvent	Time (h)	Products (%)[a]
1	MeMgI	0	Et_2O	0.5	**3a**:*epi*-**3a** (93:3)
2	MeLi	0	THF	0.5	**3a**:*epi*-**3a** (96:3)
3	EtMgBr	0	THF	1	**3b**:*epi*-**3b** (85:2) **4** (11)
4	*i*-PrMgBr	−30	Et_2O	1.5	**3c** (47) **4**(39)
5	*i*-PrMgBr	−30	Et_2O	1.5	**3c** (52) **4**(43)
6	*n*-BuMgBr	−30	Et_2O	2.3	**3d** (70) **4**(13)
7	*n*-BuLi	−30	THF	0.5	**3d** (98)[b]
8	*n*-BuLi–$CeCl_3$	−78	THF	3	**3d** (96)[b]
9	PhMgBr	25	Et_2O	1.5	**3e** (82)[b]
10	PhLi	−78	THF	0.75	**3e**:*epi*-**3** (95:3)
11	PhMgBr–$CeCl_3$	0	THF	0.5	**3e** (94)[b]
12	$PhCH_2MgBr$	−30	Et_2O	0.75	**3f** (87)[b]
13	CH_2=CHMgBr	25	Et_2O	3	**3g** (96)[b]
14	CH_2=$CHCH_2MgBr$	−30	Et_2O	0.5	**3h**:*epi*-**3h** (43:39)
15	CH_2=$CHCH_2MgBr$	−78	Et_2O	0.5	**3h**:*epi*-**3h** (48:46)
16	CH_2=$CHCH_2MgCl$	−78	THF	0.5	**3h**:*epi*-**3h** (78:14)
17	CH_2=$CHCH_2ZnBr$	25	THF	1.5	**3h**:*epi*-**3h** (77:15)
18	CF_3TMS	0	THF	0.75	**3i** (96)[b]
19	$BrZnCH_2CO_2Et$	0	THF	24	**3j** (72)[b,c]
20	$BrZnCF_2CO_2Et$	0	THF	2	**3k** (95)[b,c]

[a] Yields in parenthesis refer to pure and isolated compounds.
[b] Only one diastereoisomer was observed in the ^1H NMR spectra of the reaction mixtures.
[c] It was necessary to use 4 equiv of the organometallic to achieve complete conversion.

The configuration of the formed quaternary stereocenter was determined as *R* for compound **3a** and *S* for the difluoroacetate derivative **3k** by X-ray diffraction analysis,[18] extended for all the alcohols, and later confirmed after elimination of the chiral auxiliary.

The sense of the excellent 1,4-stereoinduction observed is coincident with that previously observed for related compounds[13] and the described 1,2-stereoinduction for the addition to carbonyl groups placed at the same chiral inductor.[19] It can be explained by accepting that the addition occurs in the conformation shown in Figure 1, determined by the strong (9%) NOE observed between the hydrogen atoms placed at the formyl group and the C-2 of the template. The major adducts are formed by the preferred nucleophilic attack from the less hindered *Re* face of the carbonyl group according to a Felkin–Anh model. Probably a coordination of the organometallic to the oxygen atom of the template occurred prior to the addition of the carbonyl group.[19]

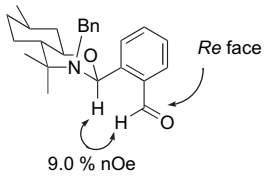
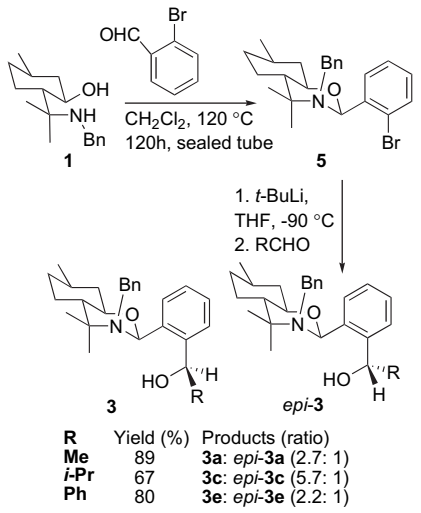


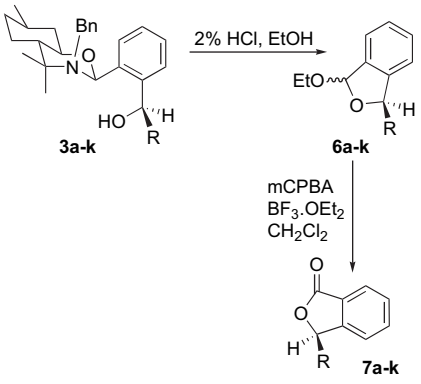
Figure 1. Preferred conformation in $CDCl_3$ solution for compound **2**.

In order to gain further information concerning 1,4-stereoinduction with perhydro-1,3-benzoxazines as chiral templates we explore the chiral aryllithium derived from **5** in an alternative preparation of carbinols **3**. Some chirons bearing a chiral acetal appendage have been previously used in diastereoselective additions to carbonyl compounds.[7d,20] Compound **5** was prepared in 65% yield, as a single diastereoisomer, by condensation of **1** with *o*-bromobenzaldehyde and converting into the organolithium derivative by treatment with 2.2 equiv of *t*-BuLi at −90 °C in THF. Addition of the appropriate aldehyde (1.5 equiv) at that temperature afforded alcohols **3a**, **3c**, and **3e** as major diastereoisomers but in lower yield and diastereoselectivity than those above described (Scheme 2).

The transformation of the benzylic alcohols into the final phthalides **7a–k** was performed in two steps as depicted in Scheme 3. Hydrolytic cleavage of the *N*,*O*-ketal by reaction with dilute (2%) aqueous alcoholic HCl solution allows for the regeneration of the carbonyl group and the formation of the acetals **6a–k** as an equimolar mixture of cis and trans isomers in good to excellent yield. The mixture of these isomers was not isolated but used in the next step after purification. The 3-alkyl derivatives were easily hydrolyzed and transformed into **6a–d** after 12–48 h of reaction (entries 1–4 in Table 2) but in these conditions, the hydrolysis of perhydrobenzoxazines **6e–k** occurred very slowly, and long periods of reaction or refluxing conditions were necessary to obtain the ketals (entries 5–7). The benzyl derivative **3f** was hydrolyzed at rt very slowly (entry 6), but the transformation



Scheme 2. Reaction of the aryllithium derived from **5** with aldehydes.



Scheme 3. Synthesis of phthalides **7a–k**.

Table 2. Hydrolysis of **3a–k** and oxidation to 3*H*-isobenzofuran-1-ones **7a–k**

Entry	Hydrolysis time (h)	Product (%)[a]	Oxidation time (h)	Product (%)[b]
1	12	**6a** (96)	3	**7a** (72)
2	12	**6b** (91)	4	**7b** (71)
3	12	**6c** (97)	4	**7c** (52)[d]
4	48	**6d** (84)	3	**7d** (76)
5	720	**6e** (97)	0.5	**7e** (90)
6	192	**6f** (95)	3.5	**7f** (83)
7	720	**6g** (70)	3	**7g** (—)[e]
8	14[c]	**6h** (95)	3	**7h** (58)
9	12[c]	**6i** (85)	72	**7i** (80)
10	7[c]	**6j** (65)[f]	24	**7j** (62)
11	7[c]	**6k** (62)[f]	48	**7k** (60)

[a] Yields in parenthesis refer to isolated compounds.
[b] Yields in parenthesis refer to total yields, and were calculated from alcohols **3**.
[c] Reflux.
[d] Conversion was total in the oxidation step.
[e] Compound **7g** could not be purified.
[f] As a mixture of 1-ethoxy- and 1-hydroxy-1,3-dihydroisobenzofurans.

of **3h–k** was only possible at reflux of ethanol. The hydrolysis of alcohols **3e** (R=Ph) and **3g** (R=vinyl) was performed at rt for 30 days because under refluxing conditions they lead to a complex mixture of reaction and the desired isobenzofuranes could not be isolated.

Treatment of compounds **6a–k** with MCPBA and $BF_3\cdot OEt_2$[21] in CH_2Cl_2 at rt gave the enantiopure isobenzofuran-1-ones **7a–k** in good to excellent yields (Table 2). All the phthalides were purified by column chromatography or recrystallization, except the vinyl derivative **7g**, which could not be isolated from the reaction crude. The optical rotations of compounds **7a**,[22] **7b**,[23] **7d**,[24] **7e**,[9] and **7h**[25] were compared with those previously described, allowing to confirm the absolute configuration of the stereocenter formed as *R*. This result was consistent with the absolute configuration determined for the alcohols **3a** and **3k**, and therefore, essentially no racemization is taking place during the hydrolysis and oxidation conditions. Enantiomeric excesses for compounds **7a–h** were determined as >99% by HPLC analysis (see Section 3).

In summary, our methodology allows for the preparation of enantiopure 3-substituted phthalides starting from easily accesible compounds. In addition, a great variety of substituents can be introduced merely by changing the nucleophile acting on the formyl group of the aryl substituent at C-2 in the starting chiral perhydro-1,3-benzoxazine.

3. Experimental

3.1. General

All reactions were carried out under an argon atmosphere in an 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. (Trifluoromethyl)trimethylsilane was used as 2 M solution in THF. ^1H NMR (300 MHz), ^{13}C NMR (75 MHz), and ^{19}F (282.38 MHz) spectra were registered in $CDCl_3$ as solvent and TMS or $CFCl_3$ as internal reference, and chemical shifts are given in parts per million. Specific rotations were determined on a digital polarimeter using Na lamp, and concentration is given in grams per 100 mL. Melting points were obtained with open capillary tubes and are uncorrected. TLC was performed on 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 out on silica gel (230–240 mesh).

3.1.1. Synthesis of alcohols 3a–k. General method. To a solution of the aldehyde **2** (5.3 mmol) in the appropriate ethereal solvent (Table 1, 5 mL) under argon and at the temperature showed in Table 1 was slowly added a solution of the appropriate organometallic reagent (5.83 mmol) and the mixture was stirred at that temperature until disappearance of the starting material (TLC). 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 over anhydrous $MgSO_4$, and the solvent was evaporated in vacuo. The residue was purified by flash chromatography on silica gel using hexanes–ethyl acetate as eluent.

3.1.1.1. (1*R*,2′*S*,4a′*S*,7′*R*,8a′*R*)-1-(2-(*N*-Benzyl-4′,4′,7′-trimethyl-octahydro-2*H*-benzo[*e*][1,3]oxazin-2′-yl)phenyl)-ethanol (3a). White solid. Mp: 88–90 °C (from hexane). $[\alpha]_D^{23}$ +9.9 (*c* 1.20, $CHCl_3$); $[\alpha]_D^{23}$ +10.2 (*c* 1.0, CH_2Cl_2).

^{1}H NMR (δ): 0.93 (d, 3H, J=6.5 Hz); 0.97–1.24 (m, 3H); 1.21 (s, 3H); 1.28 (d, 3H, J=6.5 Hz); 1.38 (s, 3H); 1.42–1.60 (m, 1H); 1.62–1.74 (m, 3H); 1.98 (m, 1H); 3.52 (d, 1H, J=16.2 Hz); 3.67 (td, 1H, J_1=10.5 Hz, J_2=4.2 Hz); 3.84 (s, 1H); 3.90 (d, 1H, J=16.2 Hz); 5.33 (q, 1H, J=6.5 Hz); 5.84 (s, 1H); 6.73–6.76 (m, 2H); 6.93–6.99 (m, 3H); 7.10–7.21 (m, 3H); 7.56 (d, 1H, J=7.0 Hz). ^{13}C NMR (δ): 19.0; 20.9; 22.2; 25.0; 28.3; 31.3; 34.9; 41.3; 46.3; 47.1; 58.4; 63.9; 76.2; 86.3; 124.6; 125.7; 126.8; 127.5 (2C); 127.7 (3C); 128.3; 136.8; 142.1; 143.3. IR (Nujol): 3200; 1600; 1590; 820; 780; 750 cm^{-1}. CI/MS (*m*/*z*, %): 394 (M+1, 100). Anal. Calcd for $C_{26}H_{35}NO_2$ (393.56): C, 79.33; H, 8.97; N, 3.56. Found: C, 79.51; H, 8.82; N, 3.44.

3.1.1.2. (1*S*,2′*S*,4a′*S*,7′*R*,8a′*R*)-1-(2-(*N*-Benzyl-4′,4′,7′-trimethyl-octahydro-2*H*-benzo[*e*][1,3] oxazin-2′-yl)phenyl)-ethanol (*epi*-3a). Colorless oil. $[\alpha]_D^{23}$ +8.5 (*c* 0.29, CH_2Cl_2). ^{1}H NMR (δ): 0.83–0.92 (m, 1H); 0.95 (d, 3H, J=6.5 Hz); 0.98–1.16 (m, 3H); 1.25 (s, 3H); 1.31 (s, 3H); 1.32 (d, 3H, J=6.8 Hz); 1.33–1.77 (m, 3H); 1.99 (m, 1H); 3.23 (d, 1H, J=16.0 Hz); 3.61 (td, 1H, J_1=10.5 Hz, J_2=4.2 Hz); 3.87 (d, 1H, J=16.0 Hz); 5.51–5.55 (m, 1H); 5.55 (s, 1H); 6.75–6.79 (m, 2H); 6.97–7.18 (m, 6H); 7.39–7.42 (m, 1H). ^{13}C NMR (δ): 15.1; 22.2; 24.3; 25.2; 28.2; 31.2; 34.9; 41.3; 48.3; 48.7; 58.0; 66.5; 75.6; 90.7; 125.8; 126.2; 126.3; 127.5 (2C); 127.8 (2C); 128.6; 128.9; 135.9; 142.6; 146.5. IR (Film): 3520; 3400; 3060; 3020; 1600; 1590; 750; 720; 700 cm^{-1}. CI/MS (*m*/*z*, %): 394 (M+1, 34); 133(100). Anal. Calcd for $C_{26}H_{35}NO_2$ (393.56): C, 79.33; H, 8.97; N, 3.56. Found: C, 72.25; H, 9.09; N, 3.68.

3.1.1.3. (1*R*,2′*S*,4a′*S*,7′*R*,8a′*R*)-1-(2-(*N*-Benzyl-4′,4′,7′-trimethyl-octahydro-2*H*-benzo[*e*][1,3] oxazin-2′-yl)phenyl)-propan-1-ol (3b). Colorless oil. $[\alpha]_D^{23}$ +3.3 (*c* 1.08, $CHCl_3$). ^{1}H NMR (δ): 0.95–1.12 (m, 2H); 0.97 (t, 3H, J=7.5 Hz); 0.97 (d, 3H, J=6.5 Hz); 1.18–1.38 (m, 1H); 1.25 (s, 3H); 1.47 (s, 3H); 1.50–1.78 (m, 6H); 2.02 (m, 1H); 2.82 (s, 1H); 3.68 (d, 1H, J=16.2 Hz); 3.73 (td, 1H, J_1=10.5 Hz, J_2=4.0 Hz); 3.90 (d, 1H, J=16.2 Hz); 5.10 (dd, 1H, J_1=8.1 Hz, J_2=5.0 Hz); 5.93 (s, 1H); 6.77–6.80 (m, 2H); 6.97–7.10 (m, 3H); 7.10–7.24 (m, 3H); 7.65 (d, 1H, J=7.5 Hz). ^{13}C NMR (δ): 11.0; 20.3; 22.3; 25.0; 28.3; 29.1; 31.4; 35.0; 41.4; 45.9; 46.5; 58.2; 68.2; 76.6; 85.3; 125.0; 125.7; 126.7; 127.2; 127.6 (2C); 127.7 (2C); 128.2; 136.7; 143.0 (2C). IR (Film): 3560; 3420; 3210; 3060; 1600; 1590; 1570; 820; 750; 730; 710 cm^{-1}. CI/MS (*m*/*z*, %): 408 (M+1, 100). Anal. Calcd for $C_{27}H_{37}NO_2$ (407.59): C, 79.56; H, 9.15; N, 3.44. Found: C, 79.70; H, 9.28; N, 3.32.

3.1.1.4. (1*S*,2′*S*,4a′*S*,7′*R*,8a′*R*)-1-(2-(*N*-Benzyl-4′,4′,7′-trimethyl-octahydro-2*H*-benzo[*e*][1,3] oxazin-2′-yl)phenyl)-propan-1-ol (*epi*-3b). Colorless oil. $[\alpha]_D^{23}$ +0.9 (*c* 1.62, $CHCl_3$). ^{1}H NMR (δ): 0.97 (d, 3H, J=6.9 Hz); 1.00–1.20 (m, 3H); 1.28 (s, 3H); 1.32 (s, 3H); 1.39–1.77 (m, 6H); 2.00 (m, 1H); 3.00 (br s, 1H); 3.38 (d, 1H, J=16.0 Hz); 3.64 (td, 1H, J_1=10.7 Hz, J_2=4.0 Hz); 3.90 (d, 1H, J=16.0 Hz); 5.09 (m, 1H); 5.71 (s, 1H); 6.80–6.83 (m, 2H); 7.00–7.10 (m, 4H); 7.12–7.25 (m, 2H); 7.49 (dd, 1H, J_1=7.3 Hz, J_2= 1.2 Hz). ^{13}C NMR (δ): 11.1; 16.8; 22.3; 25.1; 28.3; 31.2; 31.4; 34.9; 41.3; 47.8; 47.9; 58.3; 73.2; 75.8; 91.0; 125.8; 126.4; 127.1; 127.5 (2C); 127.8 (2C); 128.3; 128.7; 136.2; 142.4 (2C). IR (Film): 3550; 3400; 3050; 1590; 1450; 750; 720; 690 cm^{-1}. CI/MS (*m*/*z*, %): 408 (M+1, 100). Anal. Calcd for $C_{27}H_{37}NO_2$ (407.59): C, 79.56; H, 9.15; N, 3.44. Found: C, 79.62; H, 9.02; N, 3.31.

3.1.1.5. (1*R*,2′*S*,4a′*S*,7′*R*,8a′*R*)-1-(2-(*N*-Benzyl-4′,4′,7′-trimethyl-octahydro-2*H*-benzo[*e*][1,3] oxazin-2′-yl)phenyl)-2-methylpropan-1-ol (3c). Colorless oil. $[\alpha]_D^{23}$ +1.1 (*c* 0.50, $CHCl_3$). ^{1}H NMR (δ): 0.67–1.00 (m, 2H); 0.70 (d, 3H, J=6.7 Hz); 0.89 (d, 3H, J=6.2 Hz); 0.91 (d, 3H, J=6.4 Hz); 1.10–1.24 (m, 1H); 1.22 (s, 3H); 1.42 (s, 3H); 1.44–1.78 (m, 5H); 1.94 (m, 1H); 2.82 (s, 1H); 3.63 (td, 1H, J_1=10.5 Hz, J_2=4.1 Hz); 3.65 (d, 1H, J=16.4 Hz); 3.77 (d, 1H, J=16.4 Hz); 4.79 (d, 1H, J=7.5 Hz); 5.91 (s, 1H); 6.73–6.77 (m, 2H); 6.90–7.16 (m, 6H); 7.62 (dd, 1H, J_1=7.7 Hz, J_2=1.1 Hz). ^{13}C NMR (δ): 18.4; 19.6; 21.4; 22.3; 25.0; 28.2; 31.4; 34.1; 35.1; 41.4; 45.5; 45.8; 57.8; 73.3; 76.6; 83.8; 125.5; 125.7; 126.4; 126.6; 127.5 (4C); 127.7; 136.7; 142.0; 142.4. IR (Nujol): 3360; 3060; 3020; 1600; 1590; 1450; 780; 750 cm^{-1}. CI/MS (*m*/*z*, %): 422 (M+1, 100). EI/MS (*m*/*z*, %): 421 (M, 0.1); 148 (72); 91 (100). Anal. Calcd for $C_{28}H_{39}NO_2$ (421.61): C, 79.76; H, 9.32; N, 3.32. Found: C, 79.85; H, 9.43; N, 3.21.

3.1.1.6. (1*R*,2′*S*,4a′*S*,7′*R*,8a′*R*)-1-(2-(*N*-Benzyl-4′,4′,7′-trimethyl-octahydro-2*H*-benzo[*e*][1,3] oxazin-2′-yl)phenyl)-pentan-1-ol (3d). Colorless oil. $[\alpha]_D^{23}$ +17.6 (*c* 1.44, $CHCl_3$). ^{1}H NMR (δ): 0.95 (t, 3H, J=7.5 Hz); 0.97–1.10 (m, 1H); 1.02 (d, 3H, J=6.5 Hz); 1.13–1.49 (m, 5H); 1.30 (s, 3H); 1.50 (s, 3H); 1.50–1.78 (m, 7H); 2.08 (m, 1H); 2.92 (s, 1H); 3.68 (d, 1H, J=16.2 Hz); 3.76 (td, 1H, J_1=10.5 Hz, J_2=4.0 Hz); 3.95 (d, 1H, J=16.2 Hz); 5.25 (m, 1H); 5.97 (s, 1H); 6.81–6.84 (m, 2H); 6.97–7.07 (m, 3H); 7.15–7.28 (m, 3H); 7.68 (d, 1H, J=8.0 Hz). ^{13}C NMR (δ): 14.2; 20.1; 22.3; 22.9; 25.0; 28.3; 28.7; 31.4; 35.0; 36.0; 41.4; 46.0; 46.6; 58.2; 68.2; 76.6; 85.3; 125.0; 125.7; 126.7; 127.2; 127.6 (2C); 127.7 (2C); 128.2; 136.7; 142.7; 143.0. IR (Film): 3560; 3420; 3210; 3060; 3020; 1600; 1590; 1570; 1450; 820; 750; 730; 710 cm^{-1}. CI/MS (*m*/*z*, %): 436 (M+1, 100). Anal. Calcd for $C_{29}H_{41}NO_2$ (435.64): C, 79.95; H, 9.49; N, 3.22. Found: C, 80.07; H, 9.60; N, 3.34.

3.1.1.7. (1*R*,2′*S*,4a′*S*,7′*R*,8a′*R*)-1-(2-(*N*-Benzyl-4′,4′,7′-trimethyl-octahydro-2*H*-benzo[*e*][1,3] oxazin-2′-yl)phenyl) phenyl-methanol (3e). Colorless oil. $[\alpha]_D^{23}$ +14.0 (*c* 0.80, $CHCl_3$). ^{1}H NMR (δ): 1.07–1.12 (m, 1H); 1.07 (d, 3H, J=6.5 Hz); 1.24–1.47 (m, 2H); 1.26 (s, 3H); 1.53 (s, 3H); 1.64–1.81 (m, 4H); 2.06 (m, 1H); 3.76 (d, 1H, J= 16.2 Hz); 3.78 (td, 1H, J_1=10.5 Hz, J_2=4.1 Hz); 4.00 (d, 1H, J=16.2 Hz); 5.07 (s, 1H); 6.18 (s, 1H); 6.30 (s, 1H); 6.70 (d, 1H, J=7.7 Hz); 6.89–6.96 (m, 2H); 7.06–7.18 (m, 3H); 7.20–7.36 (m, 7H); 7.76 (d, 1H, J=7.4 Hz). ^{13}C NMR (δ): 20.8; 22.3; 24.9; 28.5; 31.4; 35.0; 41.3; 42.5; 46.6; 58.9; 71.2; 76.8; 85.0; 125.9; 127.1 (2C); 127.3 (2C); 127.5; 127.6; 127.7 (2C); 128.1 (3C); 128.2 (2C); 137.5; 142.0; 142.2 (2C). IR (Film): 3580; 3220; 3060; 3020; 1720; 1690; 1600; 1570; 1450; 750; 730; 690 cm^{-1}. CI/MS (*m*/*z*, %): 456 (M+1, 92); 195 (100). Anal. Calcd for $C_{31}H_{37}NO_2$ (455.63): C, 81.72; H, 8.19; N, 3.07. Found: C, 81.52; H, 8.30; N, 2.87.

3.1.1.8. (1*S*,2′*S*,4a′*S*,7′*R*,8*a*′*R*)-1-(2-(*N*-Benzyl-4′,4′,7′-trimethyl-octahydro-2*H*-benzo[*e*][1,3] oxazin-2′-yl)phenyl) phenyl-methanol (*epi*-3e). Colorless oil. $[\alpha]_D^{23}$ −1.6 (*c* 0.61, $CHCl_3$). ^{1}H NMR (δ): 0.87–1.08 (m, 1H); 0.90 (d,

3H, J=6.5 Hz); 1.10–1.37 (m, 2H); 1.13 (s, 3H); 1.18 (s, 3H); 1.39–1.73 (m, 4H); 1.94 (m, 1H); 3.38 (td, 1H, J_1=10.5 Hz, J_2=4.0 Hz); 3.65 (d, 1H, J=16.2 Hz); 4.00 (d, 1H, J=16.2 Hz); 5.62 (s, 1H); 5.90 (s, 1H); 6.89–6.96 (m, 2H); 7.02–7.13 (m, 4H); 7.15–7.33 (m, 8H); 7.76 (d, 1H, J=7.4 Hz). ^{13}C NMR (δ): 20.1; 22.3; 24.7; 28.5; 31.2; 34.9; 41.0; 44.9; 47.2; 59.5; 75.7; 77.5; 85.7; 126.1; 126.4 (2C); 126.6; 127.5; 127.8 (2C); 127.9 (2C); 128.2 (3C); 128.9; 130.2; 137.4; 140.9; 141.2; 144.6. IR (Film): 3253; 3060; 3030; 1603; 1451; 756; 732; 692 cm^{-1}. Anal. Calcd for $C_{31}H_{37}NO_2$ (455.63): C, 81.72; H, 8.19; N, 3.07. Found: C, 81.84; H, 8.30; N, 3.19.

3.1.1.9. (1*R*,2′*S*,4a′*S*,7′*R*,8a′*R*)-1-(2-(*N*-Benzyl-4′,4′,7′-trimethyl-octahydro-2*H*-benzo[*e*][1,3] oxazin-2′-yl)phenyl)-2-phenylethanol (3f). Colorless oil. $[\alpha]_D^{23}$ +9.7 (*c* 3.10, $CHCl_3$). ^{1}H NMR (δ): 0.96 (d, 3H, J=6.4 Hz); 0.98–1.12 (m, 2H); 1.18–1.26 (m, 1H); 1.21 (s, 3H); 1.37 (s, 3H); 1.40–1.53 (m, 2H); 1.68–1.75 (m, 2H); 1.95 (m, 1H); 2.19 (br s, 1H); 2.78 (dd, 1H, J_1=13.6 Hz, J_2=5.0 Hz); 2.97 (dd, 1H, J_1=13.6 Hz, J_2=8.1 Hz); 3.52 (td, 1H, J_1= 10.4 Hz, J_2=3.8 Hz); 3.62 (d, 1H, J=16.3 Hz); 3.84 (d, 1H, J=16.3 Hz); 5.46 (dd, 1H, J_1=8.1 Hz, J_2=5.0 Hz); 5.57 (s, 1H); 6.77–6.80 (m, 2H); 6.96–7.02 (m, 3H); 7.12–7.24 (m, 8H); 7.62 (d, 1H, J=7.0 Hz). ^{13}C NMR (δ): 20.6; 22.4; 24.9; 25.0; 28.3; 31.4; 35.1; 41.4; 43.9; 46.1; 46.5; 57.9; 69.2; 76.3; 84.9; 125.2; 125.7; 126.2; 126.9; 127.0; 127.5 (4C); 128.2 (3C); 129.4 (2C); 136.6; 138.9; 142.4; 143.2. IR (Film): 3530; 3200; 3060; 3020; 1720; 1600; 1580; 1490; 1450; 760; 730; 700 cm^{-1}. CI/MS (*m*/*z*, %): 470 (M+1, 100). Anal. Calcd for $C_{32}H_{39}NO_2$ (469.66): C, 81.83; H, 8.37; N, 2.98. Found: C, 81.70; H, 8.48; N, 3.09.

3.1.1.10. (1*R*,2′*S*,4a′*S*,7′*R*,8a′*R*)-1-(2-(*N*-Benzyl-4′,4′,7′-trimethyl-octahydro-2*H*-benzo[*e*][1,3] oxazin-2′-yl)phenyl)-prop-2-en-1-ol (3g). White solid. Mp: 102–103 °C (from ethanol). $[\alpha]_D^{23}$ +29.0 (*c* 0.80, $CHCl_3$). ^{1}H NMR (δ): 0.88 (d, 3H, J=6.5 Hz); 0.92–1.00 (m, 1H); 1.10–1.37 (m, 1H); 1.21 (s, 3H); 1.30 (s, 3H); 1.44–1.45 (m, 1H); 1.56–1.68 (m, 4H); 1.94 (m, 1H); 3.38 (d, 1H, J=16.0 Hz); 3.62 (td, 1H, J_1=10.5 Hz, J_2=4.1 Hz); 3.84 (d, 1H, J=16.0 Hz); 3.87 (s, 1H); 5.11 (dt, 1H, J_1=10.5 Hz, J_2=1.7 Hz), 5.29 (dt, 1H, J_1=17.2 Hz, J_2=1.7 Hz); 5.40–5.65 (m, 1H); 5.67 (s, 1H); 5.80 (br s, 1H); 6.71–6.88 (m, 2H); 6.90–6.97 (m, 4H); 7.06 (dt, 1H, J_1=7.5 Hz, J_2=1.5 Hz); 7.15 (dt, 1H, J_1=6.5 Hz, J_2=1.5 Hz); 7.48 (d, 1H, J=7.3 Hz). ^{13}C NMR (δ): 18.0; 22.2; 25.1; 28.3; 31.3; 34.8; 41.2; 46.7; 46.8; 58.3; 68.9; 76.4; 88.1; 114.4; 125.7; 126.9; 127.1; 127.6 (3C); 127.7 (2C); 128.5; 137.1; 138.6; 141.6; 141.9. IR (Film): 3560; 3400; 3060; 3020; 1635; 1600; 1570; 1450; 750; 730; 710; 690 cm^{-1}. CI/MS (*m*/*z*, %): 406 (M+1, 96); 145 (100). Anal. Calcd for $C_{27}H_{35}NO_2$ (405.57): C, 79.96; H, 8.70; N, 3.45. Found: C, 79.32; H, 8.70; N, 3.01.

3.1.1.11. (1*R*,2′*S*,4a′*S*,7′*R*,8a′*R*)-1-(2-(*N*-Benzyl-4′,4′,7′-trimethyl-octahydro-2*H*-benzo[*e*][1,3] oxazin-2′-yl)phenyl)-but-3-en-1-ol (3h). Colorless oil. $[\alpha]_D^{23}$ +17.0 (*c* 1.97, $CHCl_3$). ^{1}H NMR (δ): 1.03–1.26 (m, 2H); 1.04 (d, 3H, J=6.5 Hz); 1.28–1.40 (m, 1H); 1.31 (s, 3H); 1.50 (s, 3H); 1.57–1.69 (m, 2H); 1.74–1.83 (m, 2H); 2.02 (m, 1H); 2.30–2.35 (m, 1H); 2.41–2.59 (m, 1H); 2.93 (br s, 1H); 3.68 (d, 1H, J=16.0 Hz); 3.75 (td, 1H, J_1=10.6 Hz, J_2=4.1 Hz); 3.96 (d, 1H, J=16.0 Hz); 5.13 (dt, 1H, J_1=10.0 Hz, J_2=1.0 Hz); 5.18 (dd, 1H, J_1=17.7 Hz, J_2=1.7 Hz); 5.26–5.40 (m, 1H); 5.60–5.88 (m, 1H); 5.95 (s, 1H); 6.84–6.87 (m, 2H); 7.00–7.09 (m, 3H); 7.10–7.28 (m, 3H); 7.71 (d, 1H, J=7.3 Hz). ^{13}C NMR (δ): 20.3; 22.4; 25.1; 28.3; 31.4; 35.1; 40.9; 41.4; 46.1; 46.7; 58.2; 67.8; 76.6; 85.5; 116.8; 124.5; 125.7; 126.9; 127.4; 127.6 (2C); 127.7 (2C); 128.2; 135.8; 136.6; 142.3; 142.7. IR (Film): 3560; 3420; 3060; 3020; 1640; 1600; 1580; 1450; 760; 740; 710 cm^{-1}. CI/MS (*m*/*z*, %): 420 (M+1, 100); 159 (59). Anal. Calcd for $C_{28}H_{37}NO_2$ (419.60): C, 80.15; H, 8.89; N, 3.34. Found: C, 79.42; H, 8.32; N, 3.19.

3.1.1.12. (1*S*,2′*S*,4a′*S*,7′*R*,8a′*R*)-1-(2-(*N*-Benzyl-4′,4′,7′-trimethyl-octahydro-2*H*-benzo[*e*][1,3] oxazin-2′-yl)phenyl)-but-3-en-1-ol (*epi*-3h). Colorless oil. $[\alpha]_D^{23}$ −12.0 (*c* 1.60, $CHCl_3$). ^{1}H NMR (δ): 0.98 (d, 3H, J=6.5 Hz); 1.01–1.21 (m, 2H); 1.29 (s, 3H); 1.33 (s, 3H); 1.40–1.68 (m, 2H); 1.76–1.80 (m, 2H); 1.95 (m, 1H); 2.22–2.32 (m, 1H); 2.43–2.49 (m, 1H); 3.27 (d, 1H, J=16 Hz); 3.64 (td, 1H, J_1=10.5 Hz, J_2=4.0 Hz); 3.80 (d, 1H, J=16 Hz); 5.08–5.18 (m, 2H); 5.39–5.42 (m, 1H); 5.61 (s, 1H); 5.86–5.99 (m, 1H); 6.79–6.81 (m, 2H); 6.99–7.12 (m, 4H); 7.13–7.27 (m, 2H); 7.46 (d, 1H, J=7.2 Hz). ^{13}C NMR (δ): 15.5; 22.3; 25.2; 28.23; 31.2; 34.9; 41.3; 42.9; 43.2; 46.4; 58.1; 70.2; 75.7; 90.1; 116.3; 125.8; 126.7; 126.9; 127.5 (2C); 127.8 (2C); 128.5; 128.9; 136.1; 136.5; 142.4 (2C). IR (Film): 3580; 3410; 3060; 3020; 1640; 1600; 1580; 1450; 760; 720; 700 cm^{-1}. CI/MS (*m*/*z*, %): 420 (M+1, 100). Anal. Calcd for $C_{28}H_{37}NO_2$ (419.60): C, 80.15; H, 8.89; N, 3.34. Found: C, 79.64; H, 8.27; N, 3.63.

3.1.1.13. (1*S*,2′*S*,4a′*S*,7′*R*,8a′*R*)-1-(2-(*N*-Benzyl-4′,4′,7′-trimethyl-octahydro-2*H*-benzo[*e*][1,3] oxazin-2′-yl)phenyl)-2,2,2-trifluoroethanol (3i). White solid. Mp: 103–104 °C (from methanol). $[\alpha]_D^{23}$ −25.5 (*c* 1.00, $CHCl_3$). ^{1}H NMR (δ): 0.96–1.14 (m, 2H); 1.03 (d, 3H, J=6.5 Hz); 1.26 (q, 1H, J=11.8 Hz); 1.39 (s, 3H); 1.52 (s, 3H); 1.54–1.62 (m, 2H); 1.73–1.83 (m, 2H); 2.08 (m, 1H); 3.77 (td, 1H, J_1=10.5 Hz, J_2=6.0 Hz); 3.82 (s, 2H); 5.92 (q, 1H, J_1=17.1 Hz); 5.96 (s, 1H); 6.80–6.83 (m, 2H); 7.04–7.09 (m, 3H); 7.19–7.26 (m, 2H); 7.31–7.42 (m, 1H); 7.82 (d, 1H, J=7.0 Hz). ^{19}F NMR (δ): −77.1 (br s, 3F). ^{13}C NMR (δ): 20.8; 22.3; 25.1; 28.3; 31.4; 35.2; 41.3; 46.1; 46.48; 57.9; 67.2 (q, $^2J_{CF}$=31.6 Hz); 76.5; 84.1; 126.0; 127.6 (2C); 127.8 (2C); 128.1; 128.2; 128.7; 129.1; 133.4; 137.9; 143.1. IR (KBr): 3554; 3080; 3060; 3030; 1726; 1600; 1493; 1455; 1243; 1154; 1103; 764; 714 cm^{-1}. CI/MS (*m*/*z*, %): 448 (M+1, 100); 447 (M, 11); 428 (23). Anal. Calcd for $C_{26}H_{32}F_3NO_2$ (447.53): C, 69.78; H, 7.21; N, 3.13. Found: C, 69.70; H, 7.34; N, 3.05.

3.1.1.14. (3*R*,2′*S*,4a′*S*,7′*R*,8a′*R*)-Ethyl 3-(2-(*N*-benzyl-4′,4′,7′-trimethyl-octahydro-2*H*-benzo[*e*][1,3] oxazin-2′-yl)phenyl)-3-hydroxypropanoate (3j). Yellow solid. Mp: 131–132 °C (from hexane). $[\alpha]_D^{23}$ +9.7 (*c* 0.34, $CHCl_3$). ^{1}H NMR (δ): 0.97 (d, 3H, J=6.5 Hz); 1.00–1.09 (m, 2H); 1.21–1.30 (m, 1H); 1.28 (t, 3H, J=7.1 Hz); 1.28 (s, 3H); 1.44 (s, 3H); 1.48–1.55 (m, 1H); 1.62–1.78 (m, 3H); 2.01 (m, 1H); 2.36 (d, 1H, J=15.4 Hz); 2.71 (dd, 1H, J_1=15.4 Hz, J_2=9.9 Hz); 3.45 (br s, 1H); 3.54 (d, 1H, J=16.2 Hz); 3.72 (td, 1H, J_1=10.5 Hz, J_2=4.0 Hz); 3.91 (d, 1H, J=16.2 Hz); 4.14–4.23 (m, 2H); 5.82 (d, 1H, J=9.9 Hz); 5.86 (s, 1H); 6.78–6.80 (m, 2H); 6.79–7.00 (m,

3H); 7.05 (d, 1H, J=7.5 Hz); 7.16 (dt, 1H, J_1=7.5 Hz, J_2=1.3 Hz); 7.23 (dt, 1H, J_1=7.5 Hz, J_2=1.3 Hz); 7.60 (d, 1H, J=7.5 Hz). ^{13}C NMR (δ): 14.2; 22.2; 25.0; 28.2; 31.3; 34.9; 41.4; 41.3; 47.1; 58.2; 60.4; 65.1; 76.5; 86.3; 124.9; 125.7; 127.2; 127.5 (3C); 127.7 (2C); 128.4; 136.7; 141.2; 142.3; 171.7. IR (Nujol): 3460; 3040; 1680; 1600; 1580; 1370; 1320; 770; 730; 700 cm^{-1}. CI/MS (*m*/*z*, %): 466 (M+1, 100). Anal. Calcd for $C_{29}H_{39}NO_4$ (465.62): C, 74.81; H, 8.44; N, 3.00. Found: C, 74.12; H, 8.21; N, 3.02.

3.1.1.15. (3*S*,2′*S*,4a′*S*,7′*R*,8a′*R*)-Ethyl 3-(2-(*N*-benzyl-4′,4′,7′-trimethyl-octahydro-2*H*-benzo[*e*][1,3] oxazin-2′-yl)phenyl)-2,2-difluoro-3-hydroxypropanoate (3k). White solid. Mp: 140–141 °C (from hexane). $[\alpha]_D^{23}$ −30.0 (*c* 0.83, $CHCl_3$). ^{1}H NMR (δ): 0.96–1.12 (m, 2H); 1.01 (d, 3H, J=6.5 Hz); 1.23–1.30 (m, 1H); 1.36 (s, 3H); 1.37 (t, 3H, J=7.1 Hz); 1.50–1.70 (m, 2H); 1.59 (s, 3H); 1.72–1.81 (m, 2H); 2.08 (m, 1H); 3.76 (td, 1H, J_1=10.5 Hz, J_2=4.0 Hz); 3.81 (s, 2H); 4.32–4.42 (m, 2H); 6.05 (s, 1H); 6.09 (dd, 1H, $^2J_{HF}$=19.6 Hz, $^2J_{HF}$=3.1 Hz); 6.81 (m, 2H); 6.97–7.07 (m, 3H); 7.17–7.27 (m, 2H); 7.32–7.37 (m, 1H); 7.83 (d, 1H, J=7.7 Hz). ^{19}F NMR (δ): −110.3 (d, 1F, J=260.6 Hz); −124.6 (dd, 1F, J_1=260.6 Hz, $^2J_{HF}$=19.6 Hz). ^{13}C NMR (δ): 13.9; 21.4; 22.4; 25.1; 28.3; 31.4; 35.19; 41.4; 45.9; 46.1; 57.7; 62.9; 67.7 (dd, $^2J_{CF}$=32.5 Hz, $^2J_{CF}$= 21.7 Hz); 76.4; 83.7; 114.0 (dd); 125.9; 126.7; 127.4; 127.5 (2C); 127.6 (2C); 127.7; 128.5; 133.4; 138.3; 143.7; 163.5 (dd). IR (Nujol): 3520; 3060; 1770; 1730; 1600; 1590; 1320; 770; 740; 710; 700 cm^{-1}. CI/MS (*m*/*z*, %): 502 (M+1, 100). Anal. Calcd for $C_{29}H_{37}F_2NO_4$ (501.61): C, 69.44; H, 7.43; N, 2.79. Found: C, 68.92; H, 6.97; N, 2.36.

3.1.2. Synthesis of (2*S*,4a*S*,7*R*,8a*R*)-3-benzyl-2-(2-bromophenyl)-4,4,7-trimethyl-octahydro-2*H*-benzo[*e*][1,3] oxazine (5). A solution of (−)-8-*N*-benzylaminomenthol (11.5 mmol) and 2-bromobenzaldehyde (23 mmol) was stirred in a sealed tube at 120 °C until disappearance of the starting aminoalcohol (TLC, 5 days). Then 50 mL of ethanol was added and the mixture ethanol–water was evaporated in vacuo. The residue was chromatographed on silica gel with hexanes–ethyl acetate 1:60 as eluent. Yield 65%. White solid. Mp: 71 °C (from hexane). $[\alpha]_D^{23}$ +54.9 (*c* 1.20, $CHCl_3$). ^{1}H NMR (δ): 0.97–1.16 (m, 2H); 0.98 (d, 3H, J=6.5 Hz); 1.06 (s, 3H); 1.23 (q, 1H, J=11.7 Hz); 1.48 (s, 3H); 1.54–1.70 (m, 3H); 1.75–1.78 (m, 1H); 1.99 (m, 1H); 3.67 (d, 1H, J=17.1 Hz); 3.73 (td, 1H, J_1=10.5 Hz, J_2=4.1 Hz); 3.95 (d, 1H, J=17.1 Hz); 5.99 (s, 1H); 6.90–7.14 (m, 7H); 7.34 (dd, 1H, J_1=7.9 Hz, J_2=1.2 Hz); 7.60 (dd, 1H, J_1=7.8 Hz, J_2=1.7 Hz). ^{13}C NMR (δ): 19.8; 22.4; 25.1; 27.8; 31.5; 35.2; 41.6; 46.0; 46.6; 58.2; 76.7; 87.3; 123.3; 125.4; 126.8; 127.0 (2C); 129.1; 130.2; 132.3; 138.8; 143.7. IR (Film): 3060; 3020; 1600; 1590; 1450; 750; 720; 690 cm^{-1}. CI/MS (*m*/*z*, %): 428 (M+1, 100), 430 (M+2, 90). Anal. Calcd for $C_{24}H_{30}BrNO$ (428.41): C, 67.29; H, 7.06; N, 3.27. Found: C, 67.20; H, 7.21; N, 3.18.

3.1.3. Synthesis of 3*H*-isobenzofuran-1-ones (7a–k). General method. A solution of the corresponding perhydrobenzoxazines **3a–k** (4 mmol) in ethanol (60 mL) and 2% aqueous hydrochloric acid (30 mL) was stirred at rt or refluxing (see experimental conditions in Table 2) 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 resulting 1,3-dihydroisobenzofurans **6a–k** were redissolved in anhydrous CH_2Cl_2 (10 mL), MCPBA (4.07 mmol) and $BF_3{\cdot}Et_2O$ (0.74 mmol) were added under argon and the mixture was stirred at rt until the oxidation was finished (TLC, Table 2). The reaction mixture was quenched and made alkaline by addition of a saturated solution of sodium bicarbonate. The aqueous layer was extracted with diethyl ether (3×5 mL). The organic extracts were washed with brine and dried over anhydrous $MgSO_4$, and the solvent was evaporated in vacuo. The residue was purified by flash chromatography on silica gel using hexanes–ethyl acetate as eluent. The enantiomeric excesses for compounds **7a–h** were determined as >99% by HPLC (Chiralcel OD column 0.46×25 cm; solvent ratio (hexane/IPA) 99:1 except for **7e**,**f** (90/10) and **7d** (98/2); flow rate: 1.1 mL/min for **7a**,**b**,**e**,**f**; 1.0 mL/min for **7c**,**d** and 1.2 mL/min for **7h**; and UV detection at 225 nm for **7a–d**,**h** and at 208 nm for **7e** and **7f**).

The (−)-8-benzylaminomenthol can be recovered in 90–95% from the aqueous phase of the hydrolysis simply by adding a solution of sodium carbonate to pH=8 and extraction with diethyl ether (4×50 mL). The ethereal solution was dried over anhydrous $MgSO_4$, and the solvent was evaporated in vacuo giving a white solid, which was recrystallized from hexanes.

3.1.3.1. (*R*)-3-Methylisobenzofuran-1(3*H*)-one (7a). White solid. Mp: 47–49 °C (from hexane). $[\alpha]_D^{23}$ +41.4 (*c* 1.39, CH_2Cl_2). ^{1}H NMR (δ): 1.65 (d, 3H, J=6.7 Hz); 5.58 (q, 1H, J=6.7 Hz), 7.45 (dd, 1H, J_1=7.5 Hz, J_2=0.7 Hz); 7.53 (t, 1H, J=7.5 Hz); 7.69 (dt, 1H, J_1=7.6 Hz, J_2= 1.1 Hz); 7.91 (d, 1H, J=7.6 Hz). ^{13}C NMR (δ): 20.3; 77.7; 121.7; 125.3; 125.5; 129.0; 134.1; 151.1; 170.4. IR (Film): 1780; 1600; 1590; 1450; 770; 740; 700 cm^{-1}. MS (*m*/*z*, %): 149 (M+1, 100). EI/MS (*m*/*z*, %): 105 (100); 133 (56). Anal. Calcd for $C_9H_8O_2$ (148.16): C, 72.96; H, 5.44. Found: C, 73.08; H, 5.52. HPLC analysis: 3*S* isomer 24.59 min, 3*R* isomer 25.84 min.

3.1.3.2. (*R*)-3-Ethylisobenzofuran-1(3*H*)-one (7b). Colorless oil. $[\alpha]_D^{23}$ +78.7 (*c* 1.37, $CHCl_3$). ^{1}H NMR (δ): 1.00 (t, 3H, J=7.3 Hz); 1.83 (dq, 1H, J_1=14.5 Hz, J_2= 7.2 Hz); 2.14 (ddq, 1H, J_1=14.5 Hz, J_2=7.2 Hz, J_3= 4.3 Hz); 5.47 (dd, 1H, J_1=7.1 Hz, J_2=4.3 Hz); 7.45 (dd, 1H, J_1=7.5 Hz, J_2=1.0 Hz); 7.53 (t, 1H, J=7.5 Hz); 7.69 (dt, 1H, J_1=7.5 Hz, J_2=1.0 Hz); 7.88 (d, 1H, J=7.5 Hz). ^{13}C NMR (δ): 8.7; 27.5; 82.3; 121.7; 125.4; 126.1; 129.0; 133.9; 149.6; 170.7. IR (Film): 1770; 1600; 1590; 1450; 760; 740; 700; 690 cm^{-1}. EI/MS (*m*/*z*, %): 162 (M, 10); 133 (100); 105 (35). Anal. Calcd for $C_{10}H_{10}O_2$ (162.19): C, 74.06; H, 6.21. Found: C, 74.00; H, 6.02. HPLC analysis: 3*S* isomer 18.74 min, 3*R* isomer 20.16 min.

3.1.3.3. (*R*)-3-Isopropylisobenzofuran-1(3*H*)-one (7c). White solid. Mp: 59–60 °C (from hexane). $[\alpha]_D^{23}$ +73.0 (*c* 1.03, $CHCl_3$). ^{1}H NMR (δ): 0.80 (d, 3H, J=6.8 Hz); 1.13 (d, 3H, J=6.8 Hz); 2.24–2.35 (m, 1H); 5.38 (d, 1H, J=3.7 Hz); 7.47 (dd, 1H, J_1=7.4 Hz, J_2=0.9 Hz); 7.54 (t, 1H, J=7.4 Hz); 7.68 (dt, 1H, J_1=7.4 Hz, J_2=0.9 Hz); 7.88 (d, 1H, J=7.4 Hz). ^{13}C NMR (δ): 15.5; 18.6; 32.2; 85.6; 122.1; 125.5; 126.5; 128.9; 133.8; 149.8; 170.8. IR (Nujol): 1740; 1600; 730; 690 cm^{-1}. CI/MS (*m*/*z*, %): 177 (M+1,

100). Anal. Calcd for $C_{11}H_{12}O_2$ (176.21): C, 74.98; H, 6.86. Found: C, 74.79; H, 6.57. HPLC analysis: 3*S* isomer 11.37 min, 3*R* isomer 12.30 min.

3.1.3.4. (*R*)-3-Butylisobenzofuran-1(3*H*)-one (7d). Colorless oil. $[\alpha]_D^{23}$ +49.1 (*c* 0.65, $CHCl_3$). ^1H NMR (δ): 0.88 (t, 3H, *J*=7.0 Hz); 1.23–1.48 (m, 4H); 1.71–1.76 (m, 1H); 2.00–2.05 (m, 1H); 5.46 (dd, 1H, J_1=7.8 Hz, J_2=4.0 Hz); 7.42 (dd, 1H, J_1=7.5 Hz, J_2=1.0 Hz); 7.50 (t, 1H, *J*=7.5 Hz); 7.66 (dt, 1H, J_1=7.5 Hz, J_2=1.0 Hz); 7.88 (d, 1H, *J*=7.5 Hz). ^{13}C NMR (δ): 13.8; 22.4; 26.8; 34.4; 81.5; 122.7; 125.6; 125.7; 129.0; 134.0; 150.1; 180.7. IR (Film): 1740; 1610; 1590; 1450; 730; 710; 690 cm^{-1}. EI/MS (*m*/*z*, %): 190 (M, 1); 41 (100); 133 (39); 77 (27); 105 (13). Anal. Calcd for $C_{12}H_{14}O_2$ (190.24): C, 75.76; H, 7.42. Found: C, 75.90; H, 7.52. HPLC analysis: 3*S* isomer 11.79 min, 3*R* isomer 12.43 min.

3.1.3.5. (*R*)-3-Phenylisobenzofuran-1(3*H*)-one (7e). White solid. Mp: 152–153 °C (from hexane). $[\alpha]_D^{23}$ −45.5 (*c* 0.4, $CHCl_3$). ^1H NMR (δ): 6.41 (s, 1H); 7.27–7.41 (m, 6H); 7.57 (t, 1H, *J*=7.5 Hz); 7.65 (dt, 1H, J_1=7.5 Hz, J_2=1.1 Hz); 7.98 (d, 1H, *J*=7.5 Hz). ^{13}C NMR (δ): 82.6; 122.8; 125.6; 126.9 (2C); 128.9 (2C); 129.3; 134.3; 136.3; 149.6; 170.5. IR (Nujol): 1760; 1600; 1590; 770; 750; 700 cm^{-1}. CI/MS (*m*/*z*, %): 211 (M+1, 100); 133 (16). Anal. Calcd for $C_{14}H_{10}O_2$ (210.23): C, 79.98; H, 4.79. Found: C, 79.66; H, 5.07. HPLC analysis: 3*S* isomer 9.87 min, 3*R* isomer 12.76 min.

3.1.3.6. (*R*)-3-Benzylisobenzofuran-1(3*H*)-one (7f). White solid. Mp: 93–94 °C (from hexane). $[\alpha]_D^{23}$ +56.0 (*c* 1.12, $CHCl_3$). ^1H NMR (δ): 3.15 (dd, 1H, J_1=14.0 Hz, J_2=7.5 Hz); 3.23 (dd, 1H, J_1=14.0 Hz, J_2=7.5 Hz); 5.67 (t, 1H, *J*=6.4 Hz); 7.18–7.29 (m, 6H); 7.45 (t, 1H, *J*=7.5 Hz); 7.58 (t, 1H, *J*=7.5 Hz); 7.80 (d, 1H, *J*=7.5 Hz). ^{13}C NMR (δ): 40.8; 81.3; 122.4; 125.6; 126.1; 127.1; 128.5 (2C); 129.2; 129.7 (2C); 133.8; 135.0; 149.1; 170.4. IR (Nujol): 1730; 1600; 730; 700 cm^{-1}. CI/MS (*m*/*z*, %): 225 (M+1, 100); 133 (5). Anal. Calcd for $C_{15}H_{12}O_2$ (224.25): C, 80.34; H, 5.39. Found: C, 80.02; H, 5.28. HPLC analysis: 3*S* isomer 16.81 min, 3*R* isomer 17.38 min.

3.1.3.7. (*R*)-3-Allylisobenzofuran-1(3*H*)-one (7h). Colorless oil. $[\alpha]_D^{23}$ +74.5 (*c* 0.55, $CHCl_3$). ^1H NMR (δ): 2.62–2.75 (m, 2H); 5.12–5.16 (m, 1H); 5.20–5.21 (m, 1H); 5.52 (t, 1H, *J*=5.9 Hz); 5.75 (ddt, 1H, J_1=11.0 Hz, J_2=9.7 Hz, J_3=6.7 Hz); 7.27–7.52 (m, 2H); 7.67 (dt, 1H, J_1=7.4 Hz, J_2=1.0 Hz); 7.90 (d, 1H, *J*=7.5 Hz). ^{13}C NMR (δ): 38.6; 80.1; 119.6; 121.9; 125.6; 126.1; 129.1; 131.1; 133.9; 149.3; 170.3. IR (Film): 1750; 1640; 1620; 1600; 1470; 750; 720; 700 cm^{-1}. CI/MS (*m*/*z*, %): 175 (M+1, 100); 133 (31). Anal. Calcd for $C_{11}H_{10}O_2$ (174.20): C, 75.85; H, 5.79. Found: C, 75.67; H, 5.81. HPLC analysis: 3*S* isomer 22.21 min, 3*R* isomer 24.93 min.

3.1.3.8. (*S*)-3-Trifluoromethylisobenzofuran-1(3*H*)-one (7i). White solid. Mp: 44–45 °C (from hexane). $[\alpha]_D^{23}$ +32.7 (*c* 1.13, $CHCl_3$). ^1H NMR (δ): 5.53 (q, 1H, $^2J_{HF}$=5.8 Hz); 7.57 (dt, 2H, J_1=7.5 Hz, J_2=0.7 Hz); 7.68 (dt, 1H, J_1=7.5 Hz, J_2=1.1 Hz); 7.89 (d, 1H, *J*=7.5 Hz). ^{19}F NMR (δ): −77.1 (d, 3F, $^2J_{HF}$=5.8 Hz). ^{13}C NMR (δ): 76.4 (q, $^2J_{CF}$=35.7 Hz); 123.4; 126.3; 131.1; 134.9; 140.6; 168.3; 170.5. IR (Nujol): 1760; 1600; 1590; 1450; 770; 720; 700 cm^{-1}. CI/MS (*m*/*z*, %): 203 (M+1, 100). Anal. Calcd for $C_9H_5F_3O_2$ (202.13): C, 53.48; H, 2.49. Found: C, 53.08; H, 2.79.

3.1.3.9. (*R*)-Ethyl 2-(3-oxo-1,3-dihydroisobenzofuran-1-yl)acetate (7j). Yellow oil. $[\alpha]_D^{23}$ +4.8 (*c* 0.92, $CHCl_3$). ^1H NMR (δ): 1.27 (t, 3H, *J*=7.2 Hz); 2.91 (d, 2H, *J*=6.7 Hz); 4.21 (q, 2H, *J*=7.2 Hz); 5.89 (t, 1H, *J*=6.7 Hz); 7.50 (d, 1H, *J*=7.5 Hz); 7.55 (t, 1H, *J*=7.5 Hz); 7.69 (t, 1H, *J*=7.5 Hz); 7.90 (d, 1H, *J*=7.5 Hz). ^{13}C NMR (δ): 14.1; 39.5; 61.2; 77.0; 122.1; 125.7; 125.8; 129.5; 134.3; 148.7; 169.2; 169.9. IR (Film): 1760; 1730; 1600; 1590; 1450; 770; 740; 700 cm^{-1}. CI/MS (*m*/*z*, %): 221 (M+1, 100). Anal. Calcd for $C_{12}H_{12}O_4$ (220.22): C, 65.45; H, 5.49. Found: C, 65.56; H, 5.59.

3.1.3.10. (*S*)-Ethyl 2,2-difluoro-2-(3-oxo-1,3-dihydroisobenzofuran-1-yl)acetate (7k). Yellow oil. $[\alpha]_D^{23}$ +47.6 (*c* 0.84, $CHCl_3$). ^1H NMR (δ): 1.30 (t, 3H, *J*=7.1 Hz); 4.34 (q, 2H, *J*=7.1 Hz); 5.87 (dd, 1H, $^2J_{1HF}$=14.0 Hz, $^2J_{2HF}$=4.5 Hz); 7.64 (m, 2H); 7.75 (t, 1H, *J*=7.5 Hz); 7.95 (d, 1H, *J*=7.5 Hz). ^{19}F NMR (δ): −121.4 (dd, 1F, J_1=274.8 Hz, $^2J_{HF}$=14.0 Hz); −112.4 (dd, 1F, J_1=274.8 Hz, $^2J_{HF}$=4.5 Hz). ^{13}C NMR (δ): 13.8; 63.8; 76.6 (t, $^2J_{CF}$=32.2 Hz); 112.0 (dd); 123.8; 126.1; 126.3; 130.8; 134.7; 141.6; 161.5 (t); 168.6. IR (Film): 1776; 1760; 1602; 1468; 740; 726; 690 cm^{-1}. CI/MS (*m*/*z*, %): 257 (M+1, 100). Anal. Calcd for $C_{12}H_{10}F_2O_4$ (256.2): C, 56.26; H, 3.93. Found: C, 56.37; H, 4.05.

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