Enantio- and Diastereoselective Synthesis of Tetrahydrofurochromenes by Sequential Asymmetric Homoaldol Reaction and a Mukaiyama-Type Tetrahydrofuran Cyclization

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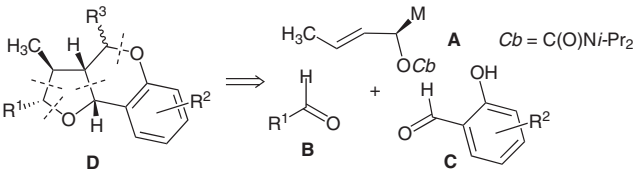
Abstract: Herein, we report on a flexible strategy for the stereoselective construction of highly substituted tetrahydrofurochromene derivatives by Mukaiyama-type cyclizations of enantioenriched enol carbamates with O-protected salicylaldehydes. The chromenes are generated as pure diastereomers and under complete chirality transfer.

Key words: heterocycles, homoaldol reaction, lithiation, salicylaldehydes, stereoselective synthesis



Scheme 1 Retrosynthetic route for the construction of tetrahydrofurochromenes.

The development of synthetic methods for the construction of tetrahydrofuran and tetrahydropyran rings as well as their polycyclic analogues has attracted considerable attention in recent years.[2] These structures are present in a number of biologically active natural products and functional molecules such as cordigol (**1**)[3] or the pterocarpane indigocarpan (**2**),[4] which contain the tetrahydrofurochromene structure and exhibit fungicidal or COX-inhibitory activity, respectively (Figure 1).

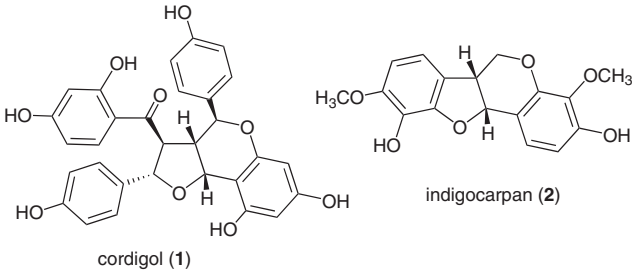
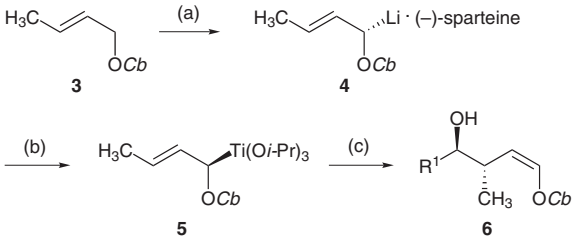


Figure 1 Tetrahydrofurochromenes occurring in nature.

Herein, we report a method for the synthesis of substituted tetrahydrofurochromenes of type **D** that has a wide degree of versatility (Scheme 1). An enantioenriched α-metallocrotyl carbamate (building block **A**), an aldehyde **B**, and a substituted salicylaldehyde **C** are sequentially attached to form the stereochemically homogeneous framework of **D**.

The key step of this reaction sequence is the boron trifluoride mediated synthesis of tetrahydrofuran carbaldehydes,[5] based on *O*-(4-hydroxyalk-1-enyl)-substituted carbamates **6**, which are readily accessible by the (–)-sparteine-mediated, asymmetric homoaldol reaction (Scheme 2).[6,7] Enantioselective α-deprotonation of (*E*)-but-2-enyl *N*,*N*-diisopropylcarbamate (**3**) gives (–)-sparteine–lithium compound **4**, which reacts with inversion of configuration with titanium(IV) isopropoxide.[8] The configurationally stable titanate **5** undergoes addition to aldehydes in a highly stereoselective manner with complete 1,3-transfer of chirality to form the (*Z*)-*anti*-4-hydroxyalk-1-enyl carbamates **6** with an enantiomeric ratio of up to 97:3 (Table 1).



Scheme 2 (–)-Sparteine-mediated homoaldol reaction of allyl carbamate **3**. *Reagents and conditions*: (a) *n*-BuLi, (–)-sparteine, *n*-pentane–cyclohexane (7:1), –78 °C, 2 h; (b) $Ti(O\textit{i}\text{-}Pr)_4$, –78 °C, 30 min; (c) (i) R^1CHO, –78 °C, 2 h, then –78 °C to r.t.; (ii) 2 M HCl.

As published in our initial report,[5a] enol carbamates of type **6** condense with aldehydes or ketones under the influence of $BF_3{\cdot}OEt_2$ in a Mukaiyama-type[10] reaction to form diastereomerically pure 2,3-*cis*-3,4-*trans*-4,5-*trans*-tetrahydrofurans; during this reaction the chiral information of **6** is completely retained.[11]

By applying the above-described method for the condensation of homoaldol adducts **6** with O-protected, substituted salicylaldehydes **7**, we established a new entry to tetrahydrofurochromenes (Scheme 3, Table 2). In the presence of 1.1 equivalents of $BF_3{\cdot}OEt_2$, *O*-TBDPS-protected salicylaldehyde **7a** and some ring-substituted de-

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Table 1 Synthesis of (*Z*)-*anti*-4-Hydroxyalk-1-enyl Carbamates **6**[a]

Entry	R^1	Product	Yield[b] (%)	Ratio[c] *anti*/*syn*	er[d]
1	*i*-Pr	**6a**[e]	91	95:5	97:3
2	*t*-Bu	**6b**	67	95:5	93:7
3	Cy	**6c**[e]	78	95:5	96:4
4	Bn	**6d**	78	95:5	95:5
5	Ph	**6e**[e]	76	95:5	95:5
6	2-BrC_6H_4	**6f**	45	94:6	75:25
7	2-naphthyl	**6g**	69	95:5	94:6

[a] For reaction conditions, see Scheme 2.
[b] Ratio *Z*/*E* ≥98:2; determined by GC.
[c] Determined by ^{1}H NMR.
[d] Determined for the major diastereomer by chiral HPLC (column: ChiraGrom 1, solvent: *n*-hexane–*i*-PrOH 50:1 to 200:1).
[e] Known compounds: **6a**,[6] **6c**,[9] and **6e**.[6]

rivatives **7b–h** and carbamates **6** were converted into the diastereomerically pure tetrahydrofurancarbaldehydes **10**. Subsequent desilylation at the aromatic hydroxy group using tetrabutylammonium fluoride led to spontaneous lactolization of the intermediate aldehydes **11** to give the chromenols **12** as mixtures of anomers in 73–99% yield over two steps.[12] Further diastereomers could not be detected by ^{1}H NMR. The high double diastereofacial selection can be explained by the (*E*)-oxonium ion intermediate **8** that adopts the depicted conformation, which avoids 1,3-allylic strain[13] and is therefore highly favored over the *Z*-isomer. Due to signal overlap of the anomers in chiral HPLC analysis, the determination of the enantiomeric ratios of chromenols **12** were carried out at the stage of the oxidized products **13**.

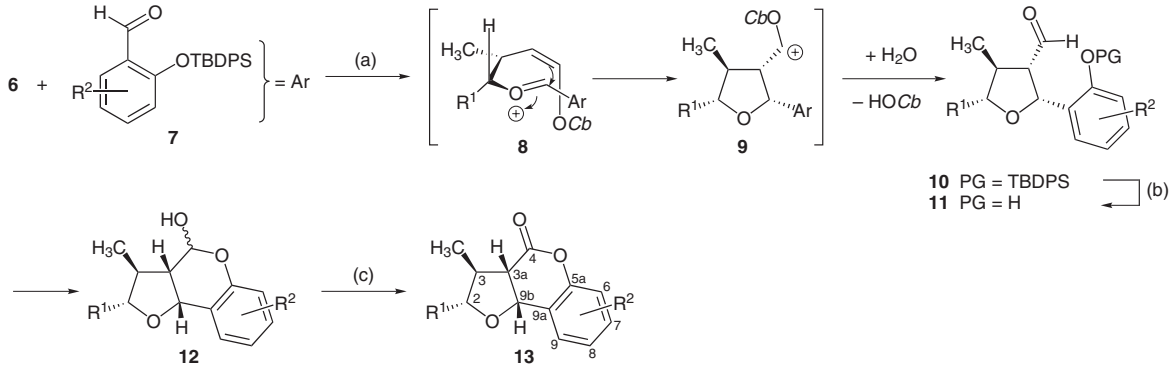
Compounds **12** were purified by silica gel chromatography and then oxidized to the corresponding chromenones **13**. While pyridinium chlorochromate and pyridinium dichromate oxidation of **12** under various conditions was less efficient, the mild conditions of the Ley oxidation[14] with tetra-*n*-propylammonium perruthenate (TPAP) and *N*-methylmorpholine *N*-oxide furnished diastereomerically pure chromenones **13**, as expected, with the enantiomeric enrichment of the starting homoaldol adducts **6** (er 75:25 to 97:3, dr ≥93:7, 63–97% yield).

The relative configuration of chromenol *rac*-**12ea** and chromenone **13ba** was elucidated by single-crystal X-ray analysis (Figures 2 and 3).[15] The absolute configuration is concluded from starting material **6**, since the methyl-bearing C3 carbon atom does not change its configuration during the reaction sequence.

Table 2 Synthesis of Tetrahydrofurochromenols **12** and Tetrahydrofurochromenones **13**[a]

Entry	Substrate (er)	R^1	Aldehyde	R^2	Chromenol	Yield (%) of **12**	Chromenone	Yield (%) of **13**	dr[b] of **13**	er[c] of **13**
1	**6a** (97:3)	*i*-Pr	**7a**	H	**12aa**	95	**13aa**	93	95:5	97:3
2	**6b** (93:7)	*t*-Bu	**7a**	H	**12ba**	89	**13ba**	95	95:5	93:7
3	**6c** (96:4)	Cy	**7a**	H	**12ca**	91	**13ca**	92	95:5	96:4
4	**6d** (95:5)	Bn	**7a**	H	**12da**	94	**13da**	92	95:5	95:5
5	**6e** (95:5)	Ph	**7a**	H	**12ea**	92[d]	**13ea**	96	95:5	94:6
6	**6f** (75:25)	2-BrC_6H_4	**7a**	H	**12fa**	91[d]	**13fa**	75	95:5	75:25
7	**6g** (94:6)	2-naphthyl	**7a**	H	**12ga**	95	**13ga**	76	95:5	94:6
8	**6a** (97:3)	*i*-Pr	**7b**	3-Me	**12ab**	92	**13ab**	86	95:5	97:3
9	**6a** (97:3)	*i*-Pr	**7c**	5-Me	**12ac**	99	**13ac**	92	95:5	97:3
10	**6a** (97:3)	*i*-Pr	**7d**	3-Ph	**12ad**	83	**13ad**	84	95:5	97:3
11	**6a** (97:3)	*i*-Pr	**7e**	5-Br-3-OMe	**12ae**	74[d]	**13ae**	96	93:7	>95:5
12	**6a** (97:3)	*i*-Pr	**7f**	4-OMe	**12af**	73[d]	**13af**	97	95:5	97:3
13	**6a** (97:3)	*i*-Pr	**7g**	5-Cl	**12ag**	98	**13ag**	65	95:5	97:3
14	**6a** (97:3)	*i*-Pr	**7h**	5-Br	**12ah**	94	**13ah**	63	95:5	97:3

[a] For reaction conditions, see Scheme 3.
[b] Ratio between major diastereomer and the sum of all minor diastereomers; determined by ^{1}H NMR.
[c] Determined by chiral HPLC (column: ChiraGrom 2, solvent: *n*-hexane–*i*-PrOH, 100:1 to 400:1).
[d] For entries 5 and 6: 30 min reaction time; for entries 11 and 12: 90 min reaction time.



Scheme 3 Synthesis of tetrahydrofurochromenones **13** by Mukaiyama-type cyclizations of (*Z*)-*anti*-4-hydroxyalk-1-enyl carbamates **6** and subsequent lactolization–oxidation. *Reagents and conditions*: (a) $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0 °C to r.t., 1 h; (b) TBAF, THF, r.t., 1 h; (c) TPAP, NMO, activated MS 3Å, MeCN, r.t., 4 h.

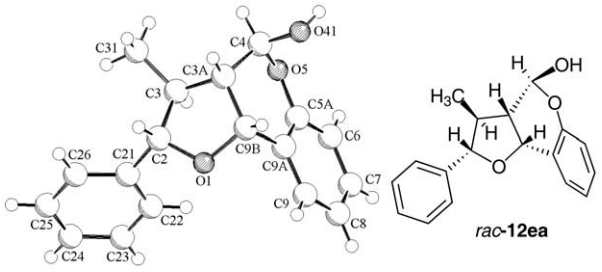


Figure 2 Single-crystal X-ray analysis of chromenol *rac*-**12ea**.

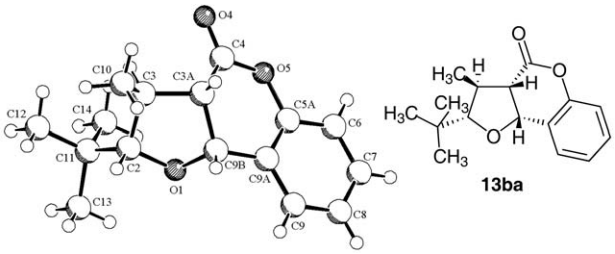
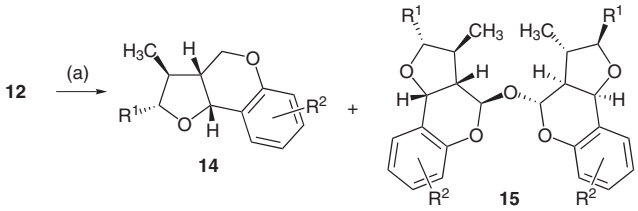


Figure 3 Single-crystal X-ray analysis of chromenone **13ba**.



Scheme 4 Reduction of chromenols **12** by ionic hydrogenation. *Reagents and conditions*: (a) Et_3SiH, $BF_3{\cdot}OEt_2$, MeCN, 0 °C to r.t., 30 min.

Reduction of the tetrahydrofurochromenols **12** by ionic hydrogenation[16] with triethylsilane/boron trifluoride–diethyl ether complex proceeded smoothly to yield the diastereomerically pure chromenes **14** (Scheme 4, Table 3). Surprisingly, the enantiomeric ratios differed from those of the starting homoaldol adducts **6**; they were slightly decreased. In addition, the optically active dimeric acetals **15** were isolated as single diastereomers in 13–31% yield.

Fortunately, suitable single-crystals for an X-ray analysis were obtained from *rac*-**15ea** (Figure 4),[15,17] which was isolated as single side product in the reduction of *rac*-**14ea**. It revealed that **15** consists of two homochiral parts, being connected by an oxido bridge over both the *exo* faces of the subunits. As expected, due to mutual kinetic resolution, the enantiomeric ratios of dimers **15** are higher than those of the starting materials **12**. Consequently, the decreased enantiomeric ratios of products **14** are due to the dimerization of the major enantiomers of the homochiral 'dimerization precursors'.

In conclusion, an elegant and powerful approach to complex tetrahydrofurochromene derivatives, starting from allyl carbamates and aldehydes, has been developed. A sequential asymmetric homoaldol reaction, followed by a Mukaiyama-type tetrahydrofuran cyclization with O-protected salicylaldehydes, gave anomeric chromenols in high yields and with high diastereoselectivities with complete transfer of chirality. Subsequent oxidation or ionic hydrogenation leads to tetrahydrofurochromenones or -chromenes, respectively. An expansion of this protocol for the synthesis of the aza-analogous heterocycles is currently under investigation and will be reported in due course.

All reactions were performed in flame-dried glassware under argon atmosphere. Unless otherwise specified, materials were obtained from commercial sources and used without purification. All solvents were dried according to standard procedures and purified by distillation prior to use. Flash column chromatography was performed on Merck 60 silica gel, 40–63 μm, or on ICN Biomedicals aluminum oxide B, activity 1, and monitored by TLC on Merck 60 F_{254} silica gel. Chiral HPLC analyses were carried out with the columns ChiraGrom 1 and ChiraGrom 2, 2 × 250 mm and 2 × 60 mm, purchased from Grom Analytic and HPLC GmbH, with *n*-hexane–*i*-PrOH solvent mixtures (50:1 to 400:1). Melting points were measured on a MFB 595 melting point apparatus from Gallenkamp, UK, and are uncorrected. IR absorption spectra were recorded on a Nicolet FT-IR 5DXC spectrophotometer. NMR spectra were recorded in $CDCl_3$ on a Bruker ARX 300 or AMX 400 spectrometer

Table 3 Ionic Hydrogenation of Tetrahydrofurochromenols **12**[a]

Entry	Substrate (er of **6**)	R^1	Products					
				Yield (%)	er[b]		Yield (%)	er[b]
1	**12aa** (97:3)	*i*-Pr	**14aa**	73	96:4	**15aa**	22	99:1
2	**12ba** (93:7)	*t*-Bu	**14ba**	81	92:8	**15ba**	16	98:2
3	**12ca** (96:4)	Cy	**14ca**	78	94:6	**15ca**	13	–[c]
4	**12da** (95:5)	Bn	**14da**	63	92:8	**15da**	31	99:1
5	**12ea** (95:5)	Ph	**14ea**	65	92:8	**15ea**	32	>97:3

[a] For reaction conditions, see Scheme 4.
[b] Determined by chiral HPLC [column: ChiraGrom 2, solvent: *n*-hexane–*i*-PrOH 100:1 (**14**), 100:1 to 200:1 (**15**)].
[c] Not determined.

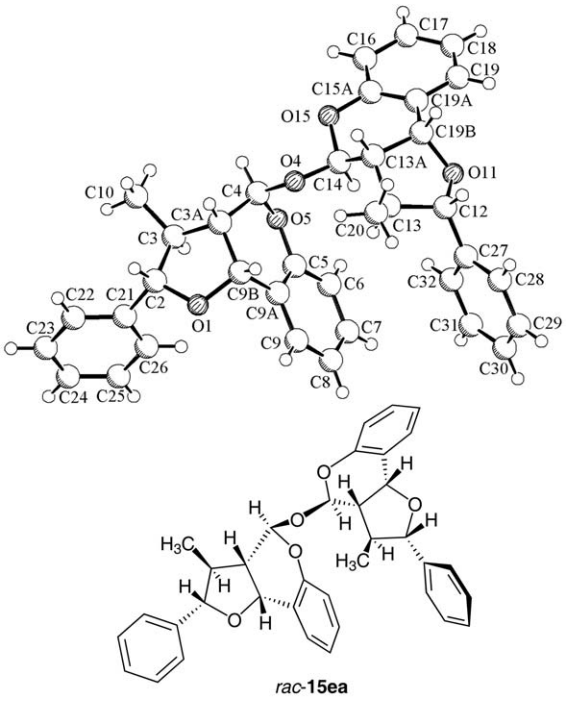


Figure 4 Single-crystal X-ray analysis of 'dimeric' acetal *rac*-**15ea**.

with TMS as internal standard. Elemental analyses were performed on an Elementar Analysensysteme Vario El III analyzer. Optical rotations were measured using a Perkin-Elmer 341 polarimeter, exact mass measurements were carried out on a Micromass Quattro LCZ.

Homoaldol Reaction of 3; General Procedure

In a 3-necked flask with cooled dropping funnel and mechanical stirrer carbamate **3**[6] (0.997 g, 5.0 mmol) and (–)-sparteine (1.23 g, 5.25 mmol) were dissolved in a mixture of *n*-pentane (7 mL) and cyclohexane (1 mL) and cooled to –78 °C; 1.6 M *n*-BuLi in *n*-hexane (3.44 mL, 5.5 mmol) was added dropwise. The mixture was stirred for 2 h and a soln of $Ti(O\textit{i}\text{-}Pr)_4$ (4.26 g, 15.0 mmol) in *n*-pentane (15 mL), precooled to –78 °C, was added. After a transmetalation time of 30 min, a soln of the aldehyde (10.0 mmol) in *n*-pentane (2 mL) was added at –78 °C, and stirring was continued for an additional 2 h. The soln was warmed to r.t., *t*-BuOMe (10 mL) was added and the mixture was poured into 2 M HCl (50 mL). The aqueous layer was separated and extracted with *t*-BuOMe (3 × 50 mL). The combined organic extracts were washed with sat. $NaHCO_3$ soln (20 mL) and dried ($MgSO_4$). The crude product was subjected to flash column chromatography (silica gel, Et_2O–pentane mixtures) to yield the pure homoaldol adduct **6**.

(1*Z*,3*S*,4*S*)-4-Hydroxy-3,5,5-trimethylhex-1-enyl *N*,*N*-Diisopropylcarbamate (6b)

White solid; yield: 0.95 g (67%); mp 62–63 °C; $[\alpha]_D^{20}$ –12.4 (*c* 0.82, $CHCl_3$); er 93:7.

IR (KBr): 3509, 2976, 1684, 1446, 1295, 1065 cm^{-1}.

^1H NMR (300 MHz): δ = 0.93 (s, 9 H), 1.12 (d, *J* = 7.0 Hz, 3 H), 1.26/1.27 (d, *J* = 6.5 Hz, 12 H), 1.58 (d, *J* = 5.0 Hz, 1 H), 3.02 (m, 1 H), 3.18 (br s, 1 H), 3.96 (br d, 2 H), 4.95 (dd, *J* = 10.0, 6.5 Hz, 1 H), 6.98 (d, *J* = 6.5 Hz, 1 H).

^{13}C NMR (75 MHz): δ = 20.5, 20.6, 21.3, 26.5, 31.6, 35.7, 45.9, 46.6, 83.0, 112.4, 134.2, 152.9.

Anal. Calcd for $C_{16}H_{31}NO_3$ (285.42): C, 67.33; H, 10.95; N, 4.91. Found: C, 67.33; H, 11.01; N, 4.82.

(1*Z*,3*S*,4*R*)-4-Cyclohexyl-4-hydroxy-3-methylbut-1-enyl *N*,*N*-Diisopropylcarbamate (6c)[9]

Colorless oil; yield: 1.22 g (78%); $[\alpha]_D^{20}$ +16.1 (*c* 0.95, $CHCl_3$); er 96:4.

IR (film): 3482, 2923, 1702, 1440, 1306, 1061 cm^{-1}.

^1H NMR (300 MHz): δ = 1.04 (d, *J* = 6.9 Hz, 3 H), 1.07–2.00 (m, 23 H), 2.09 (m, 1 H), 3.14 (t, *J* = 5.8 Hz, 1 H), 3.95 (br d, 2 H), 4.72 (dd, *J* = 10.0, 6.5 Hz, 1 H), 7.08 (dd, *J* = 6.5, 0.7 Hz, 1 H).

^{13}C NMR (75 MHz): δ = 17.9, 20.5, 21.3, 26.1, 26.4, 26.5, 27.1, 30.0, 33.0, 40.6, 46.0, 46.6, 79.4, 112.5, 136.0, 152.8.

Anal. Calcd for $C_{18}H_{33}NO_3$ (311.46): C, 69.41; H, 10.68; N, 4.50. Found: C, 69.34; H, 10.79; N, 4.42.

(1*Z*,3*S*,4*R*)-4-Hydroxy-3-methyl-5-phenylpent-1-enyl *N*,*N*-Diisopropylcarbamate (6d)

Colorless oil; yield: 1.24 g (78%); $[\alpha]_D^{20}$ +29.0 (*c* 1.25, $CHCl_3$); er 95:5.

IR (film): 3455, 2971, 1715, 1301, 1066, 762 cm^{-1}.

^1H NMR (300 MHz): δ = 1.12 (d, *J* = 7.0 Hz, 3 H), 1.21/1.23 (d, *J* = 6.7 Hz, 12 H), 1.59 (br s, 1 H), 2.68 (dd, *J* = 13.8, 8.6 Hz, 1 H), 2.73–2.90 (m, 2 H), 3.73 (m, *J* = 8.6, 4.4 Hz, 1 H), 3.88 (br d, 2 H), 4.80 (dd, *J* = 9.9, 6.5 Hz, 1 H), 7.13 (d, *J* = 6.5 Hz, 1 H), 7.15–7.35 (m, 5 H).

^{13}C NMR (75 MHz): δ = 17.5, 20.5, 21.5, 35.6, 41.2, 45.9, 46.6, 75.8, 111.8, 126.3, 128.4, 129.5, 136.1, 138.7, 152.8.

Anal. Calcd for $C_{19}H_{29}NO_3$ (319.44): C, 71.44; H, 9.15; N, 4.38. Found: C, 71.81; H, 9.52; N, 4.54.

(1*Z*,3*S*,4*S*)-4-(2-Bromophenyl)-4-hydroxy-3-methylbut-1-enyl *N*,*N*-Diisopropylcarbamate (6f)

Pale yellow solid; yield: 0.89 g (45%); mp 63–65 °C; $[\alpha]_D^{20}$ –15.3 (*c* 0.17, $CHCl_3$); er 75:25.

IR (film): 3447, 2966, 1682, 1323, 1059, 756 cm^{-1}.

^1H NMR (300 MHz): δ = 1.11 (d, *J* = 6.9 Hz, 3 H), 1.19 (d, *J* = 6.8 Hz, 12 H), 2.22 (d, *J* = 3.0 Hz, 1 H), 3.10 (m, 1 H), 3.82 (br d, 2 H), 4.80 (dd, *J* = 10.1, 6.5 Hz, 1 H), 4.97 (dd, *J* = 5.3, 3.0 Hz, 1 H), 7.01 (dd, *J* = 6.5, 0.8 Hz, 1 H), 7.08 (m, 1 H), 7.30 (m, 1 H), 7.45–7.50 (m, 2 H).

^{13}C NMR (75 MHz): δ = 18.1, 20.3, 21.4, 37.2, 46.0, 46.6, 76.2, 111.0, 122.6, 127.4, 128.2, 128.6, 132.3, 136.4, 142.2, 152.5.

Anal. Calcd for $C_{18}H_{26}BrNO_3$ (384.31): C, 56.26; H, 6.82; N, 3.64. Found: C, 55.89; H, 6.56; N, 3.38.

(1*Z*,3*S*,4*S*)-4-Hydroxy-3-methyl-4-(2-naphthyl)but-1-enyl *N*,*N*-Diisopropylcarbamate (6g)

Colorless oil; yield: 1.22 g (69%); $[\alpha]_D^{20}$ –46.8 (*c* 0.90, $CHCl_3$); er 94:6.

IR (film): 3442, 2979, 1682, 1308, 1057, 758 cm^{-1}.

^1H NMR (400 MHz): δ = 1.07 (d, *J* = 6.9 Hz, 3 H), 1.20 (br d, 12 H), 2.40 (br s, 1 H), 3.15 (m, 1 H), 3.87 (br d, 2 H), 4.64 (dd, *J* = 9.8, 6.5 Hz, 1 H), 4.73 (d, *J* = 6.0 Hz, 1 H), 6.91 (d, *J* = 6.5 Hz, 1 H), 7.36–7.51 (m, 3 H), 7.70–7.85 (m, 4 H).

^{13}C NMR (100 MHz): δ = 16.0, 20.3, 21.4, 37.6, 45.8, 46.7, 77.7, 112.7, 124.6, 125.1, 125.6, 125.9, 127.5, 127.5, 127.9, 132.8, 133.0, 135.1, 140.4, 152.6.

Anal. Calcd for $C_{22}H_{29}NO_3$ (355.47): C, 74.33; H, 8.22; N, 3.94. Found: C, 74.32; H, 8.40; N, 3.78.

***O*-*tert*-Butyldiphenylsilyl Protection of Salicylaldehydes; General Procedure, Method A**

A stirred soln of the salicylaldehyde (5.0 mmol), DMAP (0.064 g, 0.5 mmol), and Et_3N (1.1 mL, 7.5 mmol) in CH_2Cl_2 (10 mL) at 0 °C was treated dropwise with TBDPSCl (1.38 mL, 5.25 mmol). The mixture was stirred at r.t. for 12 h and then sat. $NaHCO_3$ soln (10 mL) was added. The aqueous layer was extracted with *t*-BuOMe (3 × 30 mL) and the combined organic extracts were dried (Na_2SO_4). The crude product was purified by flash column chromatography on aluminum oxide B (Et_2O–pentane mixtures).

2-(*tert*-Butyldiphenylsilyloxy)benzaldehyde (7a)

White solid; yield: 1.78 g (99%); mp 84 °C.

IR (KBr): 3048, 2930, 1688, 1247, 1106, 922, 703 cm^{-1}.

^1H NMR (300 MHz): δ = 1.13 (s, 9 H), 6.52 (dd, *J* = 8.4, 0.9 Hz, 1 H), 6.92 (ddd, *J* = 7.8, 7.3, 0.8 Hz, 1 H), 7.11 (ddd, *J* = 8.4, 7.3, 1.9 Hz, 1 H), 7.33–7.49 (m, 6 H), 7.73 (dd, 4 H), 7.83 (dd, *J* = 7.8, 1.9 Hz, 1 H), 10.79 (d, *J* = 0.8 Hz, 1 H).

^{13}C NMR (75 MHz): δ = 16.6, 26.4, 120.3, 121.3, 126.7, 128.0, 128.3, 130.3, 131.7, 135.3, 135.3, 158.6, 189.8.

Anal. Calcd for $C_{23}H_{24}O_2Si$ (360.52): C, 76.62; H, 6.71. Found: C, 76.28; H, 6.67.

2-(*tert*-Butyldiphenylsilyloxy)-5-methylbenzaldehyde (7c)

White solid; yield: 1.55 g (83%); mp 56–57 °C.

IR (KBr): 3050, 2929, 1680, 1246, 1115, 903, 699 cm^{-1}.

^1H NMR (300 MHz): δ = 1.11 (s, 9 H); 2.22 (s, 3 H), 6.41 (d, *J* = 8.5 Hz, 1 H), 6.94 (dd, *J* = 8.5, 2.3 Hz, 1 H), 7.33–7.49 (m, 6 H), 7.62 (d, *J* = 2.3 Hz, 1 H), 7.72 (dd, 4 H), 11.75 (s, 1 H).

^{13}C NMR (75 MHz): δ = 19.6, 20.3, 26.5, 120.1, 126.3, 128.0, 128.1, 130.2, 131.9, 135.4, 136.2, 156.7, 190.1.

Anal. Calcd for $C_{24}H_{26}O_2Si$ (374.55): C, 76.96; H, 7.00. Found: C, 76.99; H, 7.01.

2-(*tert*-Butyldiphenylsilyloxy)-4-methoxybenzaldehyde (7f)

White solid; yield: 1.54 g (79%); mp 118 °C.

IR (KBr): 2943, 1681, 1594, 1260, 1102, 982, 826 cm^{-1}.

^1H NMR (300 MHz): δ = 1.14 (s, 9 H), 3.33 (s, 3 H), 5.94 (d, *J* = 2.3 Hz, 1 H), 6.47 (ddd, *J* = 8.8, 2.3, 0.8 Hz, 1 H), 7.36–7.50 (m, 6 H), 7.74 (dd, 4 H), 7.78 (d, *J* = 8.8 Hz, 1 H), 10.61 (d, *J* = 0.8 Hz, 1 H).

^{13}C NMR (100 MHz): δ = 19.7, 26.4, 55.1, 104.5, 108.9, 120.6, 128.1, 129.8, 130.4, 131.8, 135.4, 160.7, 165.3, 188.4.

Anal. Calcd for $C_{24}H_{26}O_3Si$ (390.55): C, 73.81; H, 6.71. Found: C, 73.80; H, 6.76.

2-(*tert*-Butyldiphenylsilyloxy)-5-chlorobenzaldehyde (7g)

White solid; yield: 1.51 g (77%); mp 111 °C.

IR (KBr): 2956, 1687, 1472, 1273, 1115, 873, 703 cm^{-1}.

^1H NMR (400 MHz): δ = 1.12 (s, 9 H), 6.44 (d, *J* = 8.9 Hz, 1 H), 7.06 (dd, *J* = 8.9, 2.8 Hz, 1 H), 7.37–7.50 (m, 6 H), 7.70 (dd, 4 H), 7.77 (d, *J* = 2.8 Hz, 1 H), 10.68 (s, 1 H).

^{13}C NMR (100 MHz): δ = 19.6, 26.4, 121.3, 126.9, 127.5 127.8, 128.2, 130.5, 131.2, 135.0, 135.3, 157.1, 188.6.

Anal. Calcd for $C_{23}H_{23}ClO_2Si$ (394.97): C, 69.94; H, 5.87. Found: C, 69.88; H, 5.84.

5-Bromo-2-(*tert*-butyldiphenylsilyloxy)benzaldehyde (7h)

White solid; yield: 1.81 g (82%); mp 106 °C.

IR (KBr): 2959, 1683, 1470, 1267, 1118, 815, 701 cm^{-1}.

^1H NMR (400 MHz): δ = 1.11 (s, 9 H), 6.39 (d, *J* = 8.9 Hz, 1 H), 7.20 (dd, *J* = 8.9, 2.7 Hz, 1 H), 7.37–7.50 (m, 6 H), 7.70 (dd, 4 H), 7.92 (d, *J* = 2.7 Hz, 1 H), 10.68 (s, 1 H).

^{13}C NMR (100 MHz): δ = 19.6, 26.4, 114.1, 122.2, 128.9, 128.2, 130.5, 130.9, 131.2, 135.3, 137.8, 157.6, 188.5.

Anal. Calcd for $C_{23}H_{23}BrO_2Si$ (439.42): C, 62.87; H, 5.28. Found: C, 62.71; H, 5.28.

***O*-*tert*-Butyldiphenylsilyl Protection of Salicylaldehydes; General Procedure, Method B**

To a stirred soln of salicylaldehyde (5.0 mmol), imidazole (0.375 g, 5.5 mmol), and Et_3N (1.1 mL, 7.5 mmol) in DMF (10 mL) was added dropwise TBDPSCl (1.38 mL, 5.25 mmol). The mixture was stirred at r.t. for 16–24 h until TLC analysis showed complete conversion. Workup and purification was performed as described in Method A.

2-(*tert*-Butyldiphenylsilyloxy)-3-methylbenzaldehyde (7b)

Colorless oil; yield: 1.05 g (56%).

IR (film): 2959, 1678, 1470, 1222, 1115, 920, 704 cm^{-1}.

^1H NMR (400 MHz): δ = 1.13 (s, 9 H), 2.10 (s, 3 H), 6.91 (dd, *J* = 7.9, 7.4 Hz, 1 H), 7.28 (dd, *J* = 7.4, 1.9 Hz, 1 H), 7.32–7.46 (m, 6 H), 7.58 (dd, *J* = 7.9, 1.9 Hz, 1 H), 7.69 (dd, 4 H), 10.21 (d, 1 H).

^{13}C NMR (100 MHz): δ = 18.2, 20.4, 26.7, 121.7, 126.1, 127.1, 127.2, 127.9, 130.2, 132.0, 135.3, 137.4, 157.0, 189.5.

Anal. Calcd for $C_{24}H_{26}O_2Si$ (374.55): C, 76.96; H, 7.00. Found: C, 76.93; H, 6.99.

2-(*tert*-Butyldiphenylsilyloxy)-3-phenylbenzaldehyde (7d)[18]

White solid; yield: 1.43 g (66%); mp 171–172 °C.

IR (KBr): 2950, 1681, 1401, 1246, 1114, 920, 699 cm^{-1}.

^1H NMR (400 MHz): δ = 0.78 (s, 9 H), 7.07 (ddd, *J* = 7.7, 7.5, 0.8 Hz, 1 H), 7.23–7.54 (m, 15 H), 7.50 (dd, *J* = 7.5, 2.0 Hz, 1 H), 7.58 (dd, *J* = 7.7, 2.0 Hz, 1 H), 9.86 (d, *J* = 0.8 Hz, 1 H).

^{13}C NMR (100 MHz): δ = 19.1, 26.2, 122.1, 127.3, 127.5, 127.8, 128.2, 128.4, 130.0, 130.2, 131.2, 135.4, 135.6, 137.2, 138.3, 155.4, 188.0.

Anal. Calcd for $C_{29}H_{28}O_2Si$ (436.62): C, 79.77; H, 6.48. Found: C, 79.59; H, 6.52.

5-Bromo-2-(*tert*-butyldiphenylsilyloxy)-3-methoxybenzaldehyde (7e)
Pale yellow solid; yield: 0.93 g (40%); mp 102 °C.

IR (KBr): 2956, 1692, 1485, 1263, 1117, 845, 699 cm^{-1}.

^1H NMR (400 MHz): δ = 1.06 (s, 9 H), 2.90 (s, 3 H), 6.84 (d, *J* = 2.4 Hz, 1 H), 7.32–7.43 (m, 6 H), 7.54 (d, *J* = 2.4 Hz, 1 H), 7.66 (dd, 4 H), 10.68 (s, 1 H).

^{13}C NMR (100 MHz): δ = 20.3, 26.6, 54.3, 113.7, 119.9, 121.7, 127.5, 127.9, 129.6, 133.4, 134.3, 148.4, 150.9, 188.5.

Anal. Calcd for $C_{24}H_{25}BrO_3Si$ (469.44): C, 61.40; H, 5.37. Found: C, 61.01; H, 5.41.

Mukaiyama-Type Cyclization of Homoaldol Adducts 6; General Procedure
A soln of homoaldol adduct **6** (2.0 mmol) and *O*-TBDPS-protected salicylaldehyde **7** (2.2 mmol) in CH_2Cl_2 (3 mL) at 0 °C was treated dropwise with $BF_3{\cdot}OEt_2$ (0.28 mL, 2.2 mmol). The mixture was then warmed to r.t. and stirred for 60 min. Sat. NaCl soln (20 mL) was added and the aqueous layer was extracted with *t*-BuOMe (3 × 40 mL) and the combined organic extracts were dried ($MgSO_4$). The solvents were evaporated in vacuo and the crude product was dissolved in THF (10 mL). The soln was treated with 1 M TBAF in THF (4.0 mL, 4.0 mmol) at r.t. and stirred for 1 h. Then H_2O (10 mL) and *t*-BuOMe (10 mL) were added, the aqueous layer was extracted with *t*-BuOMe (3 × 20 mL), the combined organic phases were dried ($MgSO_4$), and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (silica gel, Et_2O–pentane mixtures) to give chromenol **12**.[19]

(2*R*,3*S*,3a*S*,9b*R*)-2-Isopropyl-3-methyl-2,3,3a,9b-tetrahydro-4*H*-furo[3,2-*c*]chromen-4-ol (12aa)
Colorless liquid; yield: 0.471 g (95%); $[\alpha]_D^{20}$ +23.8 (*c* 1.04, $CHCl_3$).

IR (film): 3377, 2963, 1455, 1239, 1146, 1031, 759 cm^{-1}.

^1H NMR (400 MHz): δ = 0.89/0.90 (d, *J* = 6.9 Hz, 6 H), 1.18 (d, *J* = 6.6 Hz, 3 H), 1.65 (m, 1 H), 2.06 (m, 2 H), 3.32 (dd, *J* = 7.1, 6.4 Hz, 1 H), 3.64 (br d, 1 H), 4.86 (d, *J* = 5.9 Hz, 1 H), 5.10 (br d, 1 H), 6.83–7.45 (m, 4 H).

^{13}C NMR (100 MHz): δ = 18.8, 18.9, 18.9, 32.2, 38.3, 51.3, 72.6, 91.3, 94.7, 116.9, 121.6, 121.6, 129.3, 130.4, 151.7.

Anal. Calcd for $C_{15}H_{20}O_3$ (248.32): C, 72.55; H, 8.12. Found: C, 72.15; H, 8.20.

(2*S*,3*S*,3a*S*,9b*R*)-2-*tert*-Butyl-3-methyl-2,3,3a,9b-tetrahydro-4*H*-furo[3,2-*c*]chromen-4-ol (12ba)
White solid; yield: 0.465 g (89%); mp 100 °C; $[\alpha]_D^{20}$ +46.0 (*c* 1.07, $CHCl_3$).

IR (KBr): 3359, 2973, 1466, 1241, 1148, 999, 757 cm^{-1}.

^1H NMR (400 MHz): δ = 0.88 (s, 9 H), 1.20 (d, *J* = 6.9 Hz, 3 H), 1.98 (m, 1 H), 2.18 (sext, *J* = 7.4 Hz, 1 H), 3.28 (d, *J* = 7.4 Hz, 1 H), 3.95 (br s, 1 H), 4.78 (d, *J* = 5.9 Hz, 1 H), 5.03 (d, *J* = 7.9 Hz, 1 H), 6.80–7.50 (m, 4 H).

^{13}C NMR (100 MHz): δ = 20.5, 26.3, 33.5, 36.0, 51.9, 72.7, 94.2, 94.8, 116.9, 121.5, 121.7, 129.3, 130.4, 152.3.

Anal. Calcd for $C_{16}H_{22}O_3$ (262.34): C, 73.25; H, 8.45. Found: C, 73.21; H, 8.48.

(2*R*,3*S*,3a*S*,9b*R*)-2-Cyclohexyl-3-methyl-2,3,3a,9b-tetrahydro-4*H*-furo[3,2-*c*]chromen-4-ol (12ca)
White solid; yield: 0.526 g (91%); mp 135 °C; $[\alpha]_D^{20}$ +11.7 (*c* 0.98, $CHCl_3$).

IR (KBr): 3313, 2929, 1451, 1242, 1159, 1057, 755 cm^{-1}.

^1H NMR (400 MHz): δ = 0.90–2.05 (m, 12 H), 1.18 (d, *J* = 6.8 Hz, 3 H), 2.00 (m, *J* = 7.4, 6.1 Hz, 1 H), 3.31 (d, *J* = 7.0 Hz, 1 H), 3.33 (br s, 1 H), 4.82 (d, *J* = 6.1 Hz, 1 H), 5.07 (d, *J* = 7.4 Hz, 1 H), 6.83–7.45 (m, 4 H).

^{13}C NMR (100 MHz): δ = 19.2, 26.0, 26.2, 26.5, 29.3, 29.4, 38.2, 42.2, 51.4, 72.7, 90.5, 94.9, 116.9, 121.6, 122.0, 129.4, 130.5, 152.0.

Anal. Calcd for $C_{18}H_{24}O_3$ (288.38): C, 74.97; H, 8.39. Found: C, 74.79; H, 8.56.

(2*R*,3*S*,3a*S*,9b*R*)-2-Benzyl-3-methyl-2,3,3a,9b-tetrahydro-4*H*-furo[3,2-*c*]chromen-4-ol (12da)
Colorless oil; yield: 0.556 g (94%); $[\alpha]_D^{20}$ +35.3 (*c* 0.97, $CHCl_3$).

IR (film): 3339, 2961, 1460, 1235, 1136, 949, 754 cm^{-1}.

^1H NMR (400 MHz): δ = 1.01 (d, *J* = 6.8 Hz, 3 H), 1.99 (m, 1 H), 2.10 (q, *J* = 6.8 Hz, 1 H), 2.75 (dd, *J* = 13.8, 5.4 Hz, 1 H), 2.85 (dd, *J* = 13.8, 6.9 Hz, 1 H), 3.23 (d, *J* = 4.5 Hz, 1 H), 3.77 (m, 1 H), 4.90 (d, *J* = 6.9 Hz, 1 H), 5.06 (d, *J* = 5.8 Hz, 1 H), 6.83–7.47 (m, 9 H).

^{13}C NMR (100 MHz): δ = 17.2, 40.1, 41.0, 41.1, 50.8, 72.6, 86.6, 94.9, 117.1, 121.8, 122.6, 126.3, 128.2, 129.4, 129.3, 130.2, 138.3, 151.3.

Anal. Calcd for $C_{19}H_{20}O_3$ (296.36): C, 77.00; H, 6.80. Found: C, 76.78; H, 7.81.

(2*S*,3*S*,3a*S*,9b*R*)-3-Methyl-2-phenyl-2,3,3a,9b-tetrahydro-4*H*-furo[3,2-*c*]chromen-4-ol (12ea)
White solid; yield: 0.521 g (92%); mp 159–161 °C; $[\alpha]_D^{20}$ –48.7 (*c* 0.98, $CHCl_3$).

IR (KBr): 3408, 2919, 1454, 1112, 1011, 871, 757 cm^{-1}.

^1H NMR (400 MHz): δ = 1.20 (d, *J* = 6.7 Hz, 3 H), 2.13 (m, 1 H), 2.35 (dt, *J* = 7.5, 5.0 Hz, 1 H), 3.09 (d, *J* = 4.8 Hz, 1 H), 4.40 (d, *J* = 9.0 Hz, 1 H), 5.15 (d, *J* = 7.5 Hz, 1 H), 5.30 (d, *J* = 5.0 Hz, 1 H), 6.88–7.53 (m, 9 H).

^{13}C NMR (100 MHz): δ = 15.8, 44.9, 50.6, 73.0, 88.4, 94.7, 117.2, 122.1, 122.7, 127.8, 126.4, 128.3, 129.4, 130.3, 140.6, 150.9.

Anal. Calcd for $C_{18}H_{18}O_3$ (282.33): C, 76.57; H, 6.43. Found: C, 76.28; H, 6.27.

X-ray crystal structure analysis for rac-**12ea***:* formula $C_{18}H_{18}O_3$, *M* = 282.32, colorless crystal 0.45 × 0.30 × 0.25 mm, *a* = 10.474(1), *b* = 16.381(1), *c* = 9.189(1) Å, β = 113.82(1)°, *V* = 1442.3(2) $Å^3$, ρ_{calc} = 1.300 g cm^{-3}, μ = 0.705 mm^{-1}, empirical absorption correction (0.742 ≤ *T* ≤ 0.844), *Z* = 4, monoclinic, space group $P2_1/c$ (No. 14), λ = 1.54178 Å, *T* = 223 K, ω and φ scans, 3678 reflections collected (±*h*, ±*k*, ±*l*), [(sinθ)/λ] = 0.58 $Å^{-1}$, 2348 independent (R_{int} = 0.023) and 2020 observed reflections [$I \geq 2\sigma(I)$], 193 refined parameters, *R* = 0.042, wR^2 = 0.127, max. residual electron density 0.19 (–0.20) e $Å^{-3}$, hydrogen atoms calculated and refined as riding atoms.

(2*S*,3*S*,3a*S*,9b*R*)-2-(2-Bromophenyl)-3-methyl-2,3,3a,9b-tetrahydro-4*H*-furo[3,2-*c*]chromen-4-ol (12fa)
White solid; yield: 0.659 g (91%); mp 118 °C; $[\alpha]_D^{20}$ –24.7 (*c* 1.21, $CHCl_3$).

IR (KBr): 3437, 2927, 1456, 1195, 1107, 1013, 754 cm^{-1}.

^1H NMR (400 MHz): δ = 1.29 (d, *J* = 6.8 Hz, 3 H), 2.17 (m, 1 H), 2.32–2.39 (m, *J* = 7.5 Hz, 1 H), 3.61 (d, *J* = 4.9 Hz, 1 H), 5.10 (d, *J* = 8.4 Hz, 1 H), 5.18 (d, *J* = 7.5 Hz, 1 H), 5.25 (d, *J* = 5.2 Hz, 1 H), 6.87–7.55 (m, 8 H).

^{13}C NMR (100 MHz): δ = 16.3, 45.9, 50.6, 73.2, 85.8, 94.5, 117.3, 122.1, 122.5, 122.9, 128.6, 129.0, 129.5, 130.3, 132.5, 132.5, 140.1, 150.9.

Anal. Calcd for $C_{18}H_{17}BrO_3$ (361.23): C, 59.85; H, 4.74. Found: C, 59.84; H, 4.72.

(2*S*,3*S*,3a*S*,9b*R*)-3-Methyl-2-(2-naphthyl)-2,3,3a,9b-tetrahydro-4*H*-furo[3,2-*c*]chromen-4-ol (12ga)
Colorless oil; yield: 0.629 g (95%); $[\alpha]_D^{20}$ –20.8 (*c* 0.90, $CHCl_3$).

IR (film): 3383, 3052, 1458, 1215, 1111, 990, 757 cm^{-1}.

^1H NMR (400 MHz): δ = 1.18 (d, *J* = 6.7 Hz, 3 H), 2.18 (m, 1 H), 2.35 (dt, *J* = 6.4, 5.5 Hz, 1 H), 3.51 (d, *J* = 5.0 Hz, 1 H), 4.66 (d, *J* = 8.9 Hz, 1 H), 5.18 (d, *J* = 7.4 Hz, 1 H), 5.28 (d, *J* = 5.5 Hz, 1 H), 6.87–7.84 (m, 11 H).

^{13}C NMR (100 MHz): δ = 15.8, 44.8, 50.6, 73.2, 88.5, 94.6, 117.2, 122.1, 122.7, 124.2, 125.5, 125.8, 126.0, 127.6, 127.8, 128.3, 129.5, 130.4, 133.1, 133.1, 138.0, 151.0.

Anal. Calcd for $C_{22}H_{20}O_3$ (332.39): C, 79.50; H, 6.06. Found: C, 79.43; H, 6.07.

(2*R*,3*S*,3a*S*,9b*R*)-2-Isopropyl-3,6-dimethyl-2,3,3a,9b-tetrahydro-4*H*-furo[3,2-*c*]chromen-4-ol (12ab)
White solid; yield: 0.241 g (92%) from 1.0 mmol of **6a**; mp 92–93 °C; $[\alpha]_D^{20}$ +25.9 (*c* 0.93, $CHCl_3$).

IR (KBr): 3403, 2966, 1472, 1222, 1150, 977, 749 cm^{-1}.

^1H NMR (400 MHz): δ = 0.91/0.92 (d, *J* = 6.2 Hz, 6 H), 1.19 (d, *J* = 6.9 Hz, 3 H), 1.67 (sext, *J* = 6.7 Hz, 1 H), 1.99 (m, 1 H), 2.09 (m, 1 H), 2.21 (s, 3 H), 3.30 (dd, *J* = 7.2, 6.7 Hz, 1 H), 3.49 (br s, 1 H), 4.82 (d, *J* = 6.2 Hz, 1 H), 5.07 (d, *J* = 7.4 Hz, 1 H), 6.87 (t, *J* = 7.0 Hz, 1 H), 7.07 (d, 1 H), 7.25 (d, *J* = 7.8 Hz, 1 H).

^{13}C NMR (100 MHz): δ = 16.0, 18.9, 18.9, 19.2, 32.3, 38.4, 51.5, 73.0, 91.2, 95.0, 120.9, 121.4, 126.0, 127.9, 130.4, 150.2.

Anal. Calcd for $C_{16}H_{22}O_3$ (262.34): C, 73.25; H, 8.45. Found: C, 73.01; H, 8.46.

(2*R*,3*S*,3a*S*,9b*R*)-2-Isopropyl-3,8-dimethyl-2,3,3a,9b-tetrahydro-4*H*-furo[3,2-*c*]chromen-4-ol (12ac)
Colorless oil; yield: 0.260 g (99%) from 1.0 mmol of **6a**; $[\alpha]_D^{20}$ –9.1 (*c* 0.99, $CHCl_3$).

IR (film): 3384, 2962, 1465, 1236, 1144, 1020, 817 cm^{-1}.

^1H NMR (400 MHz): δ = 0.91 (t, *J* = 6.8 Hz, 6 H), 1.19 (d, *J* = 6.8 Hz, 3 H), 1.68 (m, *J* = 6.8, 6.4 Hz, 1 H), 2.01 (m, 1 H), 2.08 (m, 1 H), 2.27 (s, 3 H), 3.31 (dd, *J* = 7.4, 6.4 Hz, 1 H), 3.32 (br s, 1 H), 4.80 (d, *J* = 6.2 Hz, 1 H), 5.05 (d, *J* = 7.2 Hz, 1 H), 6.77 (d, *J* = 8.5 Hz, 1 H), 7.01 (dd, *J* = 8.5, 2.2 Hz, 1 H), 7.22 (d, *J* = 2.2 Hz, 1 H).

^{13}C NMR (100 MHz): δ = 18.8, 19.1, 19.1, 20.5, 32.1, 38.3, 51.6, 72.8, 91.3, 94.9, 116.7, 121.7, 130.1, 130.6, 131.2, 149.7.

Anal. Calcd for $C_{16}H_{22}O_3$ (262.34): C, 73.25; H, 8.45. Found: C, 73.13; H, 8.49.

(2*R*,3*S*,3a*S*,9b*R*)-2-Isopropyl-3-methyl-6-phenyl-2,3,3a,9b-tetrahydro-4*H*-furo[3,2-*c*]chromen-4-ol (12ad)
Colorless oil; yield: 0.268 g (83%) from 1.0 mmol of **6a**; $[\alpha]_D^{20}$ +50.9 (*c* 0.47, $CHCl_3$).

IR (film): 3357, 2958, 1459, 1228, 1079, 989, 758 cm^{-1}.

^1H NMR (400 MHz): δ = 0.89/0.91 (d, *J* = 6.8 Hz, 6 H), 1.15 (d, *J* = 6.7 Hz, 3 H), 1.66 (sext, *J* = 6.8 Hz, 1 H), 1.96–2.13 (m, 2 H), 3.29 (t, *J* = 6.8 Hz, 1 H), 3.58 (br s, 1 H), 4.86 (d, *J* = 6.1 Hz, 1 H), 4.95 (d, *J* = 6.9 Hz, 1 H), 6.99–7.60 (m, 8 H).

^{13}C NMR (100 MHz): δ = 18.8, 19.0, 19.0, 32.2, 38.7, 51.2, 72.9, 91.2, 95.1, 121.4, 122.7, 126.9, 127.9, 129.5, 129.7, 130.5, 131.4, 138.1, 150.2.

HRMS-ESI: *m*/*z* $[M + Na]^+$ calcd for $C_{21}H_{24}NaO_3$: 347.1623; found: 347.1618.

(2*R*,3*S*,3a*S*,9b*R*)-8-Bromo-2-isopropyl-6-methoxy-3-methyl-2,3,3a,9b-tetrahydro-4*H*-furo[3,2-*c*]chromen-4-ol (12ae)
White solid; yield: 0.198 g (74%) from 0.75 mmol of **6a**; $[\alpha]_D^{20}$ –14.1 (*c* 0.56, $CHCl_3$).

IR (KBr): 3480, 2957, 1487, 1228, 1154, 1024, 838 cm^{-1}.

^1H NMR (400 MHz): δ = 0.87/0.91 (d, *J* = 6.7 Hz, 6 H), 1.17 (d, *J* = 6.7 Hz, 3 H), 1.60 (sext, *J* = 6.2 Hz, 1 H), 2.03 (m, 1 H), 2.13 (m, 1 H), 3.33 (dd, *J* = 7.8, 6.2 Hz, 1 H), 3.83 (s, 3 H), 4.48 (br s, 1 H), 4.85 (d, *J* = 6.7 Hz, 1 H), 5.24 (d, *J* = 5.9 Hz, 1 H), 6.89 (d, *J* = 2.2 Hz, 1 H), 7.17 (d, *J* = 2.2 Hz, 1 H).

^{13}C NMR (100 MHz): δ = 18.4, 18.5, 19.1, 32.1, 38.2, 51.7, 56.1, 71.7, 91.4, 94.9, 113.2, 114.2, 122.8, 124.4, 139.9, 148.9.

Anal. Calcd for $C_{16}H_{21}BrO_4$ (357.27): C, 53.79; H, 5.93. Found: C, 53.89; H, 6.07.

(2*R*,3*S*,3a*S*,9b*R*)-2-Isopropyl-7-methoxy-3-methyl-2,3,3a,9b-tetrahydro-4*H*-furo[3,2-*c*]chromen-4-ol (12af)
White solid; yield: 0.203 g (73%) from 1.0 mmol of **6a**; mp 89 °C; $[\alpha]_D^{20}$ +14.4 (*c* 0.96, $CHCl_3$).

IR (KBr): 3384, 2963, 1625, 1508, 1441, 1282, 1143, 991, 829 cm^{-1}.

^1H NMR (400 MHz): δ = 0.89/0.90 (d, *J* = 6.7 Hz, 6 H), 1.17 (d, *J* = 6.8 Hz, 3 H), 1.66 (sext, *J* = 6.7 Hz, 1 H), 1.98 (m, 1 H), 2.06 (m, 1 H), 3.29 (dd, *J* = 7.0, 6.7 Hz, 1 H), 3.74 (s, 3 H), 3.74 (br s, 1 H), 4.79 (d, *J* = 6.1 Hz, 1 H), 5.06 (d, *J* = 7.2 Hz, 1 H), 6.39 (d, *J* = 2.5 Hz, 1 H), 6.54 (dd, *J* = 8.5, 2.5 Hz, 1 H), 7.29 (d, *J* = 8.5 Hz, 1 H).

^{13}C NMR (100 MHz): δ = 18.8, 18.9, 19.1, 32.2, 38.3, 51.3, 55.2, 72.5, 91.2, 95.0, 101.5, 108.6, 114.4, 131.1, 153.0, 161.3.

Anal. Calcd for $C_{16}H_{22}O_4$ (278.34): C, 69.04; H, 7.97. Found: C, 68.69; H, 8.00.

(2*R*,3*S*,3a*S*,9b*R*)-8-Chloro-2-isopropyl-3-methyl-2,3,3a,9b-tetrahydro-4*H*-furo[3,2-*c*]chromen-4-ol (12ag)
Colorless oil; yield: 0.276 g (98%) from 1.0 mmol of **6a**; $[\alpha]_D^{20}$ –13.4 (*c* 1.00, $CHCl_3$).

IR (film): 3356, 2959, 1481, 1214, 1105, 1011, 825 cm^{-1}.

^1H NMR (400 MHz): δ = 0.87/0.91 (d, *J* = 6.7 Hz, 6 H), 1.17 (d, *J* = 6.5 Hz, 3 H), 1.64 (sext, *J* = 6.7 Hz, 1 H), 1.99–2.10 (m, 2 H), 3.33 (dd, *J* = 7.3, 6.3 Hz, 1 H), 3.64 (d, *J* = 4.7 Hz, 1 H), 4.82 (d, *J* = 6.1 Hz, 1 H), 5.11 (d, *J* = 5.9 Hz, 1 H), 6.79 (d, *J* = 8.8 Hz, 1 H), 7.14 (dd, *J* = 8.8, 2.6 Hz, 1 H), 7.39 (d, *J* = 2.6 Hz, 1 H).

^{13}C NMR (100 MHz): δ = 18.6, 18.6, 19.0, 32.1, 38.2, 51.0, 72.0, 91.4, 94.8, 118.4, 124.0, 126.5, 129.4, 129.9, 150.1.

Anal. Calcd for $C_{15}H_{19}ClO_3$ (282.76): C, 63.71; H, 6.77. Found: C, 63.66; H, 6.81.

(2*R*,3*S*,3a*S*,9b*R*)-8-Bromo-2-isopropyl-3-methyl-2,3,3a,9b-tetrahydro-4*H*-furo[3,2-*c*]chromen-4-ol (12ah)
Colorless oil; yield: 0.306 g (94%) from 1.0 mmol of **6a**; $[\alpha]_D^{20}$ –20.2 (*c* 0.82, $CHCl_3$).

IR (film): 3377, 2961, 1478, 1239, 1147, 1014, 818 cm^{-1}.

^1H NMR (400 MHz): δ = 0.87/0.91 (d, *J* = 6.9 Hz, 6 H), 1.18 (d, *J* = 6.6 Hz, 3 H), 1.64 (sext, *J* = 6.2 Hz, 1 H), 1.99–2.10 (m, 2 H), 3.32 (dd, *J* = 6.9, 6.2 Hz, 1 H), 3.40 (br s, 1 H), 4.82 (d, *J* = 6.0 Hz, 1 H), 5.11 (d, *J* = 6.1 Hz, 1 H), 6.74 (d, *J* = 8.7 Hz, 1 H), 7.23 (dd, *J* = 8.7, 2.4 Hz, 1 H), 7.53 (d, *J* = 2.4 Hz, 1 H).

^{13}C NMR (100 MHz): δ = 18.6, 18.7, 19.0, 32.1, 38.2, 51.0, 72.0, 91.4, 94.8, 113.8, 118.9, 124.5, 132.3, 132.9, 150.7.

Anal. Calcd for $C_{15}H_{19}BrO_3$ (327.21): C, 55.06; H, 5.85. Found: C, 55.24; H, 6.10.

Tetra-*n*-propylammonium Perruthenate/*N*-Methylmorpholine *N*-Oxide Oxidation of Chromenols 12; General Procedure
The tetrahydrofurochromenol **12** (0.3 mmol), NMO (0.053 g, 0.45 mmol), and freshly activated, powdered MS 3Å were suspended in MeCN and treated with TPAP (0.011 g, 0.03 mmol). The resulting mixture was stirred at r.t. for 4 h and was then directly transferred onto a silica gel column for purification by flash column chromatography (Et_2O–pentane mixtures).

(2*R*,3*S*,3a*S*,9b*R*)-2-Isopropyl-3-methyl-2,3,3a,9b-tetrahydro-4*H*-furo[3,2-*c*]chromen-4-one (13aa)
Colorless oil; yield: 0.069 g (93%); $[\alpha]_D^{20}$ –34.3 (*c* 1.06, $CHCl_3$); er 97:3.

IR (film): 2962, 1766, 1461, 1368, 1227, 1154, 760 cm^{-1}.

^1H NMR (400 MHz): δ = 0.87/0.90 (d, *J* = 6.7 Hz, 6 H), 1.27 (d, *J* = 7.0 Hz, 3 H), 1.66 (sext, *J* = 6.7 Hz, 1 H), 2.63 (m, 1 H), 2.89 (dd, *J* = 6.4, 5.7 Hz, 1 H), 3.38 (d, *J* = 6.6 Hz, 1 H), 5.00 (d, *J* = 6.4 Hz, 1 H), 7.05 (dd, *J* = 8.2, 1.0 Hz, 1 H), 7.18 (dt, *J* = 7.6, 7.4 Hz, 1 H), 7.34 (dt, *J* = 8.2, 7.4, 1.6 Hz, 1 H), 7.46 (dd, *J* = 7.6, 1.6 Hz, 1 H).

^{13}C NMR (100 MHz): δ = 18.4, 18.7, 18.8, 32.0, 41.1, 51.1, 73.5, 91.6, 116.8, 120.4, 124.6, 129.6, 130.3, 150.2, 168.4.

Anal. Calcd for $C_{15}H_{18}O_3$ (246.30): C, 73.15; H, 7.37. Found: C, 73.21; H, 7.58.

(2*S*,3*S*,3a*S*,9b*R*)-2-*tert*-Butyl-3-methyl-2,3,3a,9b-tetrahydro-4*H*-furo[3,2-*c*]chromen-4-one (13ba)
White solid; yield: 0.074 g (95%); mp 123 °C; $[\alpha]_D^{20}$ +0.3 (*c* 1.07, $CHCl_3$); er 93:7.

IR (KBr): 2958, 1758, 1457, 1375, 1225, 1161, 764 cm^{-1}.

^1H NMR (300 MHz): δ = 0.87 (s, 9 H), 1.29 (d, *J* = 6.9 Hz, 3 H), 2.79 (dd, *J* = 5.6, 3.0 Hz, 1 H), 2.87 (m, 1 H), 3.30 (d, *J* = 6.2 Hz, 1 H), 4.86 (d, *J* = 5.6 Hz, 1 H), 7.07 (dd, *J* = 8.1, 1.1 Hz, 1 H), 7.18 (dt, *J* = 7.5, 1.1 Hz, 1 H), 7.36 (m, *J* = 1.7 Hz, 1 H), 7.45 (dd, *J* = 7.5, 1.7 Hz, 1 H).

^{13}C NMR (75 MHz): δ = 20.7, 25.9, 33.4, 39.2, 51.3, 73.4, 94.9, 116.9, 119.5, 124.5, 130.2, 130.6, 151.1, 168.6.

Anal. Calcd for $C_{16}H_{20}O_3$ (260.33): C, 73.82; H, 7.74. Found: C, 73.85; H, 7.79.

X-ray crystal structure analysis: formula $C_{16}H_{20}O_3$, *M* = 260.32, colorless crystal 0.35 × 0.25 × 0.25 mm, *a* = 9.474(1), *b* = 6.560(1), *c* = 11.925(3) Å, β = 105.27(1)°, *V* = 715.0(2) $Å^3$, ρ_{calc} = 1.209 g cm^{-3}, μ = 0.661 mm^{-1}, empirical absorption correction ($0.802 \le T \le 0.852$), *Z* = 2, monoclinic, space group $P2_1$ (No. 4), λ = 1.54178 Å, *T* = 223 K, ω/2θ scans, 3047 reflections collected (±*h*, ±*k*, +*l*), [(sinθ)/λ] = 0.62 $Å^{-1}$, 2909 independent (R_{int} = 0.026) and 2763 observed reflections [$I \ge 2\ \sigma(I)$], 177 refined parameters, *R* = 0.031, wR^2 = 0.094, Flack parameter 0.01(17), max. residual electron density 0.17 (–0.11) e $Å^{-3}$, hydrogen atoms calculated and refined as riding atoms.

(2*R*,3*S*,3a*S*,9b*R*)-2-Cyclohexyl-3-methyl-2,3,3a,9b-tetrahydro-4*H*-furo[3,2-*c*]chromen-4-one (13ca)
White solid; yield: 0.079 g (92%); mp 119 °C; $[\alpha]_D^{20}$ –21.6 (*c* 0.64, $CHCl_3$); er 96:4.

IR (KBr): 2927, 1755, 1463, 1222, 1161, 1015, 769 cm^{-1}.

^1H NMR (400 MHz): δ = 0.86–1.83 (m, 11 H), 1.26 (d, *J* = 6.9 Hz, 3 H), 2.69 (m, 1 H), 2.86 (dd, *J* = 6.2, 5.2 Hz, 1 H), 3.37 (t, *J* = 6.6 Hz, 1 H), 4.95 (d, *J* = 6.2 Hz, 1 H), 7.06 (dd, *J* = 8.1, 1.1 Hz, 1 H), 7.18 (dt, *J* = 7.5, 1.1 Hz, 1 H), 7.35 (m, 1 H), 7.46 (dd, *J* = 7.5, 1.7 Hz, 1 H).

^{13}C NMR (100 MHz): δ = 19.0, 25.9, 26.0, 26.4, 29.0, 29.1, 41.0, 41.9, 51.0, 73.4, 90.9, 116.8, 120.2, 124.6, 129.7, 130.3, 150.4, 168.5.

Anal. Calcd for $C_{18}H_{22}O_3$ (286.37): C, 75.50; H, 7.74. Found: C, 75.21; H, 7.77.

(2*R*,3*S*,3a*S*,9b*R*)-2-Benzyl-3-methyl-2,3,3a,9b-tetrahydro-4*H*-furo[3,2-*c*]chromen-4-one (13da)
Colorless oil; yield: 0.081 g (92%); $[\alpha]_D^{20}$ +6.2 (*c* 1.23, $CHCl_3$), er 95:5.

IR (film): 2927, 1764, 1456, 1368, 1226, 1192, 759 cm^{-1}.

^1H NMR (400 MHz): δ = 1.12 (d, *J* = 6.8 Hz, 3 H), 2.48 (m, 1 H), 2.73 (dd, *J* = 13.8, 5.6 Hz, 1 H), 2.83 (dd, *J* = 13.8, 7.2 Hz, 1 H), 2.96 (t, *J* = 7.2 Hz, 1 H), 3.84 (m, 1 H), 5.09 (d, *J* = 7.0 Hz, 1 H), 7.02–7.55 (m, 9 H).

^{13}C NMR (75 MHz): δ = 16.9, 41.1, 43.8, 50.6, 73.7, 86.9, 116.8, 120.9, 124.8, 126.5, 128.4, 129.2, 129.4, 130.2, 137.8, 149.7, 168.0.

Anal. Calcd for $C_{19}H_{18}O_3$ (294.34): C, 77.53; H, 6.16. Found: C, 77.32; H, 6.24.

(2*S*,3*S*,3a*S*,9b*R*)-3-Methyl-2-phenyl-2,3,3a,9b-tetrahydro-4*H*-furo[3,2-*c*]chromen-4-one (13ea)
Colorless oil; yield: 0.081 g (96%); $[\alpha]_D^{20}$ –92.6 (*c* 0.68, $CHCl_3$); er 94:6.

IR (film): 2967, 1769, 1457, 1348, 1192, 1021, 760 cm^{-1}.

^1H NMR (300 MHz): δ = 1.26 (d, *J* = 6.7 Hz, 3 H), 2.51 (m, 1 H), 3.18 (dd, *J* = 8.7, 7.7 Hz, 1 H), 4.54 (d, *J* = 8.8 Hz, 1 H), 5.31 (d, *J* = 7.7 Hz, 1 H), 7.04–7.63 (m, 9 H).

^{13}C NMR (75 MHz): δ = 15.3, 47.4, 50.7, 74.0, 88.5, 116.8, 120.8, 125.0, 128.2, 126.6, 128.5, 129.5, 130.4, 139.1, 149.3, 167.5.

Anal. Calcd for $C_{18}H_{16}O_3$ (280.32): C, 77.17; H, 5.75. Found: C, 76.74; H, 5.84.

(2*S*,3*S*,3a*S*,9b*R*)-2-(2-Bromophenyl)-3-methyl-2,3,3a,9b-tetrahydro-4*H*-furo[3,2-*c*]chromen-4-one (13fa)
Pale yellow solid; yield: 0.081 g (75%); mp 147 °C; $[\alpha]_D^{20}$ –39.2 (*c* 1.12, $CHCl_3$); er 75:25.

IR (KBr): 2888, 1767, 1458, 1371, 1228, 1160, 751 cm^{-1}.

^1H NMR (400 MHz): δ = 1.44 (d, *J* = 6.9 Hz, 3 H), 2.77 (m, 1 H), 3.13 (t, *J* = 7.1 Hz, 1 H), 5.14 (d, *J* = 7.0 Hz, 1 H), 5.32 (d, *J* = 7.1 Hz, 1 H), 7.05–7.59 (m, 8 H).

^{13}C NMR (100 MHz): δ = 16.9, 47.7, 50.3, 74.4, 85.9, 117.0, 119.9, 122.7, 125.0, 127.8, 128.0, 129.4, 129.9, 130.6, 132.7, 139.1, 150.0, 167.5.

Anal. Calcd for $C_{18}H_{15}BrO_3$ (359.21): C, 60.18; H, 4.21. Found: C, 60.05; H, 4.23.

(2*S*,3*S*,3a*S*,9b*R*)-3-Methyl-2-(2-naphthyl)-2,3,3a,9b-tetrahydro-4*H*-furo[3,2-*c*]chromen-4-one (13ga)
Colorless oil; yield: 0.075 g (76%); $[\alpha]_D^{20}$ –59.5 (*c* 1.10, $CHCl_3$); er 94:6.

IR (film): 2960, 1755, 1464, 1217, 1160, 823, 763 cm^{-1}.

^1H NMR (400 MHz): δ = 1.29 (d, *J* = 6.7 Hz, 3 H), 2.62 (m, 1 H), 3.23 (dd, *J* = 8.7, 7.6 Hz, 1 H), 4.71 (d, *J* = 8.8 Hz, 1 H), 5.37 (d, *J* = 7.6 Hz, 1 H), 7.07–7.85 (m, 11 H).

^{13}C NMR (100 MHz): δ = 15.4, 47.3, 50.8, 74.2, 88.7, 116.9, 120.8, 124.0, 125.0, 126.0, 126.1, 126.2, 127.7, 127.9, 128.5, 129.6, 130.3, 133.1, 133.3, 136.5, 149.3, 167.6.

HRMS-ESI: *m*/*z* [M + MeOH + Na]$^+$ calcd for $C_{23}H_{22}NaO_4$: 385.1416; found: 385.1415.

(2*R*,3*S*,3a*S*,9b*R*)-2-Isopropyl-3,6-dimethyl-2,3,3a,9b-tetrahydro-4*H*-furo[3,2-*c*]chromen-4-one (13ab)
Colorless oil; yield: 0.067 g (86%); $[\alpha]_D^{20}$ –9.9 (*c* 0.78, $CHCl_3$); er 97:3.

IR (film): 2960, 1759, 1473, 1385, 1214, 1152, 779 cm^{-1}.

^1H NMR (300 MHz): δ = 0.88/0.90 (d, *J* = 6.6 Hz, 6 H), 1.27 (d, *J* = 6.9 Hz, 3 H), 1.67 (m, 1 H), 2.32 (s, 3 H), 2.67 (m, 1 H), 2.84 (dd, *J* = 6.2, 5.2 Hz, 1 H), 3.35 (t, *J* = 6.6 Hz, 1 H), 4.94 (d, *J* = 6.2 Hz, 1 H), 7.02–7.32 (m, 3 H).

^{13}C NMR (75 MHz): δ = 15.7, 18.6, 18.6, 19.0, 32.0, 41.1, 51.0, 73.8, 91.7, 119.9, 124.1, 126.0, 127.2, 131.8, 148.6, 168.5.

Anal. Calcd for $C_{16}H_{20}O_3$ (260.33): C, 73.82; H, 7.74. Found: C, 73.62; H, 7.78.

(2*R*,3*S*,3a*S*,9b*R*)-2-Isopropyl-3,8-dimethyl-2,3,3a,9b-tetrahydro-4*H*-furo[3,2-*c*]chromen-4-one (13ac)
White solid; yield: 0.072 g (92%); $[\alpha]_D^{20}$ –50.6 (*c* 0.90, $CHCl_3$); er 97:3.

IR (KBr): 2962, 1747, 1501, 1391, 1216, 1174, 826 cm^{-1}.

^1H NMR (300 MHz): δ = 0.89 (t, *J* = 6.6, 6 H), 1.26 (d, *J* = 6.8 Hz, 3 H), 1.67 (sext, *J* = 6.6 Hz, 1 H), 2.33 (s, 3 H), 2.64 (m, 1 H), 2.85 (m, *J* = 5.3 Hz, 1 H), 3.36 (t, *J* = 6.6 Hz, 1 H), 4.93 (d, *J* = 6.2 Hz, 1 H), 6.88–7.31 (m, 3 H).

^{13}C NMR (100 MHz): δ = 18.6, 18.9, 18.4, 20.6, 31.9, 41.1, 51.1, 73.6, 91.6, 116.5, 119.8, 129.9, 130.9, 134.2, 148.3, 168.6.

Anal. Calcd for $C_{16}H_{20}O_3$ (260.33): C, 73.82; H, 7.74. Found: C, 73.83; H, 7.83.

(2*R*,3*S*,3a*S*,9b*R*)-2-Isopropyl-3-methyl-6-phenyl-2,3,3a,9b-tetrahydro-4*H*-furo[3,2-*c*]chromen-4-one (13ad)
Colorless oil; yield: 0.081 g (84%); $[\alpha]_D^{20}$ +13.5 (*c* 0.26, $CHCl_3$); er 97:3.

IR (film): 2965, 1768, 1462, 1385, 1155, 763, 699 cm^{-1}.

^1H NMR (400 MHz): δ = 0.90/0.91 (d, *J* = 6.7 Hz, 6 H), 1.27 (d, *J* = 6.9 Hz, 3 H), 1.69 (m, 1 H), 2.69 (m, *J* = 6.6, 5.2 Hz, 1 H), 2.88 (dd, *J* = 6.0, 5.2 Hz, 1 H), 3.83 (t, *J* = 6.6 Hz, 1 H), 5.02 (d, *J* = 6.0 Hz, 1 H), 7.23–7.54 (m, 8 H).

^{13}C NMR (100 MHz): δ = 18.6, 18.7, 19.0, 32.0, 41.1, 50.9, 73.9, 91.8, 120.7, 129.4, 128.3, 129.5, 124.5, 127.2, 129.0, 132.0, 136.4, 147.2, 168.0.

HRMS-ESI: *m*/*z* [M + MeOH + Na]$^+$ calcd for $C_{25}H_{23}NaO_4$: 377.1729; found: 377.1740.

(2*R*,3*S*,3a*S*,9b*R*)-8-Bromo-2-isopropyl-6-methoxy-3-methyl-2,3,3a,9b-tetrahydro-4*H*-furo[3,2-*c*]chromen-4-one (13ae)
Slightly yellow oil; yield: 0.102 g (96%); $[\alpha]_D^{20}$ –41.9 (*c* 0.42, $CHCl_3$); er 95:5.

IR (film): 2968, 1768, 1488, 1364, 1271, 1155, 856 cm^{-1}.

^1H NMR (300 MHz): δ = 0.87/0.90 (d, *J* = 6.8 Hz, 6 H), 1.25 (d, *J* = 6.8 Hz, 3 H), 1.64 (m, 1 H), 2.58 (sext, *J* = 6.9 Hz, 1 H), 2.89 (t, *J* = 6.6 Hz, 1 H), 3.37 (dd, *J* = 6.9, 6.4 Hz, 1 H), 3.88 (s, 3 H), 4.95 (d, *J* = 6.6 Hz, 1 H), 7.03 (d, *J* = 2.2 Hz, 1 H), 7.19 (d, *J* = 2.2 Hz, 1 H).

^{13}C NMR (75 MHz): δ = 18.3, 18.4, 18.8, 31.9, 41.2, 50.8, 56.4, 73.2, 91.7, 113.4, 116.0, 122.0, 123.4, 138.7, 148.0, 167.0.

HRMS-ESI: *m*/*z* [M + MeOH + Na]$^+$ calcd for $C_{17}H_{23}BrNaO_5$: 409.0627; found: 409.0617.

(2*R*,3*S*,3a*S*,9b*R*)-2-Isopropyl-7-methoxy-3-methyl-2,3,3a,9b-tetrahydro-4*H*-furo[3,2-*c*]chromen-4-one (13af)
White solid; yield: 0.080 g (97%); mp 69 °C; $[\alpha]_D^{20}$ –26.6 (*c* 1.04, $CHCl_3$); er 97:3.

IR (KBr): 2964, 1756, 1661, 1513, 1440, 1157, 849 cm^{-1}.

^1H NMR (400 MHz): δ = 0.88 (t, *J* = 6.9 Hz, 6 H), 1.26 (d, *J* = 6.9 Hz, 3 H), 1.67 (m, 1 H), 2.65 (m, 1 H), 2.84 (m, *J* = 6.1 Hz, 1 H), 3.34 (dd, *J* = 6.7, 6.5 Hz, 1 H), 3.80 (s, 3 H), 4.93 (d, *J* = 6.1 Hz, 1 H), 6.58 (d, *J* = 2.5 Hz, 1 H), 6.73 (dd, *J* = 8.5, 2.5 Hz, 1 H), 7.35 (d, *J* = 8.5 Hz, 1 H).

^{13}C NMR (100 MHz): δ = 18.5, 18.6, 19.0, 32.0, 41.1, 51.1, 55.5, 73.3, 91.5, 101.9, 111.1, 112.4, 130.5, 151.4, 161.2, 168.6.

Anal. Calcd for $C_{16}H_{20}O_4$ (276.33): C, 69.54; H, 7.30. Found: C, 69.47; H, 7.37.

(2*R*,3*S*,3a*S*,9b*R*)-8-Chloro-2-isopropyl-3-methyl-2,3,3a,9b-tetrahydro-4*H*-furo[3,2-*c*]chromen-4-one (13ag)
White solid; yield: 0.055 g (65%); mp 92 °C; $[\alpha]_D^{20}$ –48.3 (*c* 0.30, $CHCl_3$); er 97:3.

IR (KBr): 2968, 1764, 1474, 1226, 1190, 1154, 815 cm^{-1}.

^1H NMR (400 MHz): δ = 0.87/0.91 (d, *J* = 6.7 Hz, 6 H), 1.27 (d, *J* = 6.8 Hz, 3 H), 1.65 (m, 1 H), 2.57 (m, 1 H), 2.91 (t, *J* = 6.3 Hz, 1 H), 3.39 (dd, *J* = 6.9, 6.3 Hz, 1 H), 4.97 (d, *J* = 6.5 Hz, 1 H), 7.00 (d, *J* = 8.7 Hz, 1 H), 7.30 (dd, *J* = 8.7, 2.6 Hz, 1 H), 7.45 (d, *J* = 2.6 Hz, 1 H).

^{13}C NMR (100 MHz): δ = 18.3, 18.4, 18.8, 31.9, 41.2, 50.8, 73.0, 91.7, 118.2, 122.2, 129.9, 129.4, 130.3, 148.6, 167.7.

Anal. Calcd for $C_{15}H_{17}ClO_3$ (280.75): C, 64.17; H, 6.10. Found: C, 63.81; H, 6.17.

(2*R*,3*S*,3a*S*,9b*R*)-8-Bromo-2-isopropyl-3-methyl-2,3,3a,9b-tetrahydro-4*H*-furo[3,2-*c*]chromen-4-one (13ah)
White solid; yield: 0.061 g (63%); mp 102 °C; $[\alpha]_D^{20}$ –91.3 (*c* 0.39, $CHCl_3$); er 97:3.

IR (KBr): 2970, 1763, 1474, 1227, 1153, 928, 814 cm^{-1}.

^1H NMR (400 MHz): δ = 0.87/0.91 (d, *J* = 6.9 Hz, 6 H), 1.26 (d, *J* = 6.8 Hz, 3 H), 1.65 (m, 1 H), 2.57 (m, 1 H), 2.90 (dd, *J* = 6.4, 6.1 Hz, 1 H), 3.38 (dd, *J* = 6.7, 6.5 Hz, 1 H), 4.96 (d, *J* = 6.5 Hz, 1 H), 6.94 (d, *J* = 8.7 Hz, 1 H), 7.45 (dd, *J* = 8.7, 2.4 Hz, 1 H), 7.60 (d, *J* = 2.4 Hz, 1 H).

^{13}C NMR (100 MHz): δ = 18.3, 18.5, 18.8, 31.9, 41.2, 50.8, 73.0, 91.7, 117.1, 118.6, 122.6, 132.4, 133.2, 149.2, 167.6.

Anal. Calcd for $C_{15}H_{17}BrO_3$ (325.20): C, 55.40; H, 5.27. Found: C, 55.52; H, 5.39.

Ionic Hydrogenation of Chromenols 12 with Boron Trifluoride–Diethyl Ether/Triethylsilane; General Procedure
To a stirred soln of the tetrahydrofurochromenol **6** (0.3 mmol) and Et_3SiH (0.19 mL, 1.2 mmol) in MeCN (5 mL) at 0 °C was added dropwise $BF_3{\cdot}OEt_2$ (0.08 mL, 0.6 mmol). The mixture was warmed to r.t. and stirred for 30 min, and then sat. $NaHCO_3$ soln (5 mL) was

added. The aqueous layer was extracted with *t*-BuOMe (3 × 15 mL), the combined organic extracts were dried ($MgSO_4$), and the solvents were removed in vacuo. Flash column chromatography (silica gel, Et_2O–pentane mixtures) gave the purified chromenes **14** along with the dimeric products **15**.

(2*R*,3*S*,3a*R*,9b*R*)-2-Isopropyl-3-methyl-2,3,3a,9b-tetrahydro-4*H*-furo[3,2-*c*]chromene (14aa)
Colorless oil; yield: 0.051 g (73%); R_f = 0.67 (Et_2O–pentane, 1:5); $[\alpha]_D^{20}$ –27.4 (*c* 0.95, $CHCl_3$); er 96:4).

IR (film): 2960, 1488, 1456, 1224, 1094, 1011, 757 cm^{-1}.

^1H NMR (400 MHz): δ = 0.91 (d, *J* = 6.8 Hz, 6 H), 1.17 (d, *J* = 6.8 Hz, 3 H), 1.54–1.77 (m, 2 H), 2.08 (m, 1 H), 3.29 (t, *J* = 6.8 Hz, 1 H), 3.71 (t, *J* = 10.7 Hz, 1 H), 4.11 (t, *J* = 10.7 Hz, 1 H), 4.71 (d, *J* = 5.6 Hz, 1 H), 6.77–7.58 (m, 4 H).

^{13}C NMR (100 MHz): δ = 18.9, 19.0, 19.0, 32.4, 38.1, 45.0, 65.4, 71.9, 91.2, 116.7, 120.9, 121.9, 129.2, 131.3, 154.9.

Anal. Calcd for $C_{15}H_{20}O_2$ (232.32): C, 77.55; H, 8.68. Found: C, 77.19; H, 8.76.

4,4′-Oxidobis[(2*R*,3*S*,3a*S*,4*R*,9b*R*)-2-isopropyl-3-methyl-2,3,3a,9b-tetrahydro-4*H*-furo[3,2-*c*]chromene] (15aa)
Colorless oil; yield: 0.016 g (22%); R_f = 0.57 (Et_2O–pentane, 1:5).

^1H NMR (300 MHz): δ = 0.81/0.82 (d, *J* = 6.7 Hz, 12 H), 1.04 (d, *J* = 6.7 Hz, 6 H), 1.53 (m, 2 H), 1.83 (m, 2 H), 2.14 (q, *J* = 6.5 Hz, 2 H), 3.27 (dd, *J* = 7.8, 6.3 Hz, 2 H), 4.87 (d, *J* = 6.8 Hz, 2 H), 5.34 (d, *J* = 6.2 Hz, 2 H), 6.85 (dd, *J* = 8.2, 1.1 Hz, 2 H), 6.98 (dt, *J* = 7.6, 1.1 Hz, 2 H), 7.19 (m, 2 H), 7.39 (dd, *J* = 7.6, 1.7 Hz, 2 H).

^{13}C NMR (100 MHz): δ = 18.3, 18.6, 19.1, 32.2, 38.1, 49.9, 72.2, 91.3, 96.0, 116.9, 121.9, 123.2, 129.2, 130.3, 151.1.

(2*S*,3*S*,3a*R*,9b*R*)-2-*tert*-Butyl-3-methyl-2,3,3a,9b-tetrahydro-4*H*-furo[3,2-*c*]chromen (14ba)
Colorless oil; yield: 0.060 g (81%); R_f = 0.76 (Et_2O–pentane, 1:5); $[\alpha]_D^{20}$ –3.6 (*c* 0.77, $CHCl_3$); er 92:8.

IR (film): 2957, 1491, 1467, 1223, 1096, 1009, 753 cm^{-1}.

^1H NMR (400 MHz): δ = 0.89 (s, 9 H), 1.18 (d, *J* = 6.8 Hz, 3 H), 1.73 (m, 1 H), 2.05 (m, 1 H), 3.25 (d, *J* = 7.1 Hz, 1 H), 3.68 (t, *J* = 11.0 Hz, 1 H), 4.08 (dd, *J* = 11.0, 5.0 Hz, 1 H), 4.65 (d, *J* = 5.2 Hz, 1 H), 6.86 (dd, *J* = 8.2, 1.2 Hz, 1 H), 6.94 (dt, *J* = 7.7, 1.2 Hz, 1 H), 7.19 (m, 1 H), 7.40 (dd, *J* = 7.7, 1.8 Hz, 1 H).

^{13}C NMR (100 MHz): δ = 20.3, 26.4, 33.4, 36.0, 45.2, 65.2, 71.6, 94.0, 116.6, 120.8, 122.8, 129.2, 131.6, 155.1.

Anal. Calcd for $C_{16}H_{22}O_2$ (246.34): C, 78.01; H, 9.00. Found: C, 77.96; H, 9.03.

4,4′-Oxidobis[(2*S*,3*S*,3a*S*,4*R*,9b*R*)-2-*tert*-butyl-3-methyl-2,3,3a,9b-tetrahydro-4*H*-furo[3,2-*c*]chromene] (15ba)
Colorless oil; yield: 0.012 g (16%); R_f = 0.79 (Et_2O–pentane, 1:5).

^1H NMR (300 MHz): δ = 0.92 (s, 18 H), 1.27 (d, *J* = 6.7 Hz, 6 H), 2.14–2.27 (m, 4 H), 3.29 (d, *J* = 7.2 Hz, 2 H), 4.77 (d, *J* = 5.7 Hz, 2 H), 5.06 (d, *J* = 8.1 Hz, 2 H), 6.91 (dd, *J* = 8.3, 1.0 Hz, 2 H), 6.97 (dt, *J* = 7.6, 7.5 Hz, 2 H), 7.22 (m, *J* = 1.6 Hz, 2 H), 7.39 (dd, *J* = 7.6, 1.6 Hz, 2 H).

^{13}C NMR (100 MHz): δ = 20.2, 26.4, 33.6, 35.9, 50.4, 72.6, 94.2, 97.2, 116.9, 121.6, 122.2, 129.3, 130.7, 152.0.

(2*R*,3*S*,3a*R*,9b*R*)-2-Cyclohexyl-3-methyl-2,3,3a,9b-tetrahydro-4*H*-furo[3,2-*c*]chromene (14ca)
Colorless liquid; yield: 0.064 g (78%); R_f = 0.75 (Et_2O–pentane, 1:5); $[\alpha]_D^{20}$ –4.6 (*c* 1.04, $CHCl_3$); er 94:6.

IR (film): 2926, 2850, 1488, 1451, 1221, 1012, 754 cm^{-1}.

^1H NMR (400 MHz): δ = 0.90–1.90 (m, 12 H), 1.15 (d, *J* = 6.9 Hz, 3 H), 2.05 (m, 1 H), 3.28 (t, *J* = 6.8 Hz, 1 H), 3.67 (t, *J* = 10.8 Hz, 1 H), 4.09 (m, *J* = 10.8 Hz, 1 H), 4.66 (d, *J* = 5.4 Hz, 1 H), 6.85 (dd, *J* = 8.3, 1.1 Hz, 1 H), 6.93 (dt, *J* = 7.5, 1.1 Hz, 1 H), 7.18 (m, 1 H), 7.39 (dd, *J* = 7.6, 1.7 Hz, 1 H).

^{13}C NMR (100 MHz): δ = 19.2, 26.0, 26.2, 26.5, 29.3, 29.6, 38.2, 42.4, 44.8, 65.5, 71.8, 90.3, 116.7, 120.9, 121.7, 129.2, 131.4, 155.0.

HRMS-ESI: *m*/*z* $[M + MeOH + Na]^+$ calcd for $C_{18}H_{25}O_2$: 273.1855; found: 273.1853.

4,4′-Oxidobis[(2*R*,3*S*,3a*S*,4*R*,9b*R*)-2-cyclohexyl-3-methyl-2,3,3a,9b-tetrahydro-4*H*-furo[3,2-*c*]chromene] (15ca)
Colorless liquid; yield: 0.011 g (13%); R_f = 0.66 (Et_2O–pentane, 1:5).

^1H NMR (300 MHz): δ = 0.80–1.94 (m, 24 H), 1.04 (d, *J* = 6.7 Hz, 6 H), 2.12 (m, 2 H), 3.27 (dd, *J* = 7.5, 6.6 Hz, 2 H), 4.84 (d, *J* = 6.5 Hz, 2 H), 5.32 (d, *J* = 6.5 Hz, 2 H), 6.84 (d, *J* = 8.2 Hz, 2 H), 6.97 (t, 2 H), 7.20 (t, 2 H), 7.39 (d, *J* = 7.6 Hz, 2 H).

^{13}C NMR (100 MHz): δ = 18.3, 25.8, 26.0, 26.3, 28.9, 29.1, 37.6, 41.9, 49.6, 72.1, 90.3, 95.9, 116.7, 121.6, 122.8, 129.0, 130.1, 151.1.

(2*R*,3*S*,3a*R*,9b*R*)-2-Benzyl-3-methyl-2,3,3a,9b-tetrahydro-4*H*-furo[3,2-*c*]chromene (14da)
Colorless oil; yield: 0.044 g (63%) from 0.25 mmol of **12da**; R_f = 0.56 (Et_2O–pentane, 1:5); $[\alpha]_D^{20}$ +12.1 (*c* 1.04, $CHCl_3$); er 92:8.

IR (film): 3029, 2922, 1490, 1453, 1222, 1010, 758 cm^{-1}.

^1H NMR (400 MHz): δ = 0.96 (d, *J* = 6.8 Hz, 3 H), 1.71 (m, 1 H), 2.11 (m, 1 H), 2.75 (dd, *J* = 13.8, 5.9 Hz, 1 H), 2.93 (dd, *J* = 13.8, 6.6 Hz, 1 H), 3.68 (dd, *J* = 11.1, 9.4 Hz, 1 H), 3.76 (m, 1 H), 4.10 (dd, *J* = 11.1, 4.6 Hz, 1 H), 4.75 (d, *J* = 6.1 Hz, 1 H), 6.85 (dd, *J* = 8.2, 1.2 Hz, 1 H), 6.96 (dt, *J* = 7.6, 1.2 Hz, 1 H), 7.16–7.29 (m, 6 H), 7.41 (dd, *J* = 7.6, 1.7 Hz, 1 H).

^{13}C NMR (100 MHz): δ = 17.3, 40.6, 41.2, 44.9, 65.6, 72.2, 86.6, 116.8, 121.1, 122.2, 126.3, 128.2, 129.2, 129.4, 131.1, 138.3, 154.9.

Anal. Calcd for $C_{19}H_{20}O_2$ (280.36): C, 81.40; H, 7.19. Found: C, 81.08; H, 7.24.

4,4′-Oxidobis[(2*R*,3*S*,3a*S*,4*R*,9b*R*)-2-benzyl-3-methyl-2,3,3a,9b-tetrahydro-4*H*-furo[3,2-*c*]chromene] (15da)
Colorless liquid; yield: 0.022 g (31%) from 0.25 mmol of **12da**; R_f = 0.34 (Et_2O–pentane, 1:5).

^1H NMR (300 MHz): δ = 0.83 (d, *J* = 6.7 Hz, 6 H), 1.73 (q, *J* = 7.0 Hz, 2 H), 2.17 (m, 2 H), 2.60 (dd, *J* = 13.6, 5.1 Hz, 2 H), 2.76 (dd, *J* = 13.6, 6.9 Hz, 2 H), 3.69 (m, 2 H), 4.90 (d, *J* = 7.2 Hz, 2 H), 5.39 (d, *J* = 5.5 Hz, 2 H), 6.83–7.50 (m, 18 H).

^{13}C NMR (100 MHz): δ = 16.5, 41.0, 41.2, 49.5, 72.3, 86.7, 95.7, 117.1, 122.2, 123.6, 126.2, 128.2, 129.3, 129.3, 130.2, 138.4, 150.7.

(2*S*,3*S*,3a*R*,9b*R*)-3-Methyl-2-phenyl-2,3,3a,9b-tetrahydro-4*H*-furo[3,2-*c*]chromene (14ea)
Colorless oil; yield: 0.052 g (65%); R_f = 0.48 (Et_2O–pentane, 1:5); $[\alpha]_D^{20}$ –105.9 (*c* 1.20, $CHCl_3$); er 92:8.

IR (film): 2960, 1487, 1454, 1222, 1088, 1023, 759 cm^{-1}.

^1H NMR (400 MHz): δ = 1.20 (d, *J* = 6.7 Hz, 3 H), 1.93 (m, 1 H), 2.31 (m, 1 H), 3.91 (dd, *J* = 11.1, 8.1 Hz, 1 H), 4.19 (dd, *J* = 11.1, 4.3 Hz, 1 H), 4.50 (d, *J* = 8.4 Hz, 1 H), 5.01 (d, *J* = 6.8 Hz, 1 H), 6.90 (dd, *J* = 8.3, 1.1 Hz, 1 H), 7.00 (dt, *J* = 7.6, 1.1 Hz, 1 H), 7.19–7.30 (m, 6 H), 7.47 (dd, *J* = 7.6, 1.7 Hz, 1 H).

^{13}C NMR (100 MHz): δ = 16.1, 44.4, 45.3, 65.5, 73.0, 88.4, 116.9, 121.3, 122.8, 126.3, 127.7, 128.3, 129.2, 131.2, 141.0, 154.8.

Anal. Calcd for $C_{18}H_{18}O_2$ (266.33): C, 81.17; H, 6.81. Found: C, 80.82; H, 7.09.

4,4′-Oxidobis[(2*S*,3*S*,3a*S*,4*R*,9b*R*)-3-methyl-2-phenyl-2,3,3a,9b-tetrahydro-4*H*-furo[3,2-*c*]chromene] (15ea)
White solid; yield: 0.026 g (32%); R_f = 0.24 (Et_2O–pentane, 1:5); mp 176 °C.

^{1}H NMR (400 MHz): δ = 0.99 (d, *J* = 6.7 Hz, 6 H), 1.86 (m, 2 H), 2.34 (m, 2 H), 4.41 (d, *J* = 9.3 Hz, 2 H), 5.10 (d, *J* = 7.7 Hz, 2 H), 5.49 (d, *J* = 5.1 Hz, 2 H), 6.79 (dd, *J* = 8.2, 1.2 Hz, 2 H), 6.99 (dt, *J* = 7.7, 1.2 Hz, 2 H), 7.08–7.28 (m, 12 H), 7.43 (dd, *J* = 7.7, 1.7 Hz, 2 H).

^{13}C NMR (100 MHz): δ = 15.1, 44.5, 49.4, 72.8, 88.4, 95.7, 117.2, 122.3, 123.4, 126.6, 127.7, 128.3, 129.3, 130.2, 140.4, 150.3.

X-ray crystal structure analysis for rac-**15ea***:* formula $C_{36}H_{34}O_5$, *M* = 546.63, colorless crystal 0.35 × 0.30 × 0.20 mm, *a* = 9.127(1), *b* = 24.957(1), *c* = 12.965(1) Å, β = 101.75(1)°, *V* = 2891.3(4) Å^3, ρ_{calc} = 1.256 g cm^{-3}, μ = 0.661 mm^{-1}, empirical absorption correction (0.802 ≤ *T* ≤ 0.879), *Z* = 4, monoclinic, space group $P2_1/c$ (No. 14), λ = 1.54178 Å, *T* = 223 K, ω and φ scans, 28341 reflections collected (±*h*, ±*k*, ±*l*), [(sinθ)/λ] = 0.58 Å^{-1}, 4632 independent (R_{int} = 0.060) and 4186 observed reflections [$I \geq 2\,\sigma(I)$], 372 refined parameters, R = 0.046, wR^2 = 0.121, max. residual electron density 0.20 (–0.21) e Å^{-3}, hydrogen atoms calculated and refined as riding atoms.

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References

(1) Responsible for X-ray crystal structure data.
(2) Morimoto, Y.; Nishikawa, Y.; Tanaka, T. *Angew. Chem. Int. Ed.* **2006**, *45*, 810.
(3) Marston, A.; Zagorski, M. G.; Horstettmann, K. *Helv. Chim. Acta* **1988**, *71*, 1210.
(4) Selvam, C.; Jachak, S. M.; Gnana Oli, R.; Thilagavathi, R.; Chakraborti, A. K.; Bhutani, K. K. *Tetrahedron Lett.* **2004**, *45*, 4311.
(5) (a) Hoppe, D.; Krämer, T.; Freire Erdbrügger, C.; Egert, E. *Tetrahedron Lett.* **1989**, *30*, 1233. (b) Ünaldi, S.; Özlügedik, M.; Fröhlich, R.; Hoppe, D. *Adv. Synth. Catal.* **2005**, *347*, 1621.
(6) (a) Hoppe, D.; Zschage, O. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 69. (b) Paulsen, H.; Graeve, C.; Hoppe, D. *Synthesis* **1996**, 141.
(7) For reviews, see: (a) Hoppe, D.; Hense, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2282. (b) Hoppe, D.; Marr, F.; Brüggemann, M. *Top. Organomet. Chem.* **2003**, *5*, 61. (c) Christoph, G.; Hoppe, D. In *The Chemistry of Organolithium Compounds*; Rappoport, Z.; Marek, I., Eds.; Wiley: Chichester, **2004**, 1055.
(8) Reviews: (a) Reetz, M. T. *Organotitanium Reagents in Organic Synthesis*; Springer: Berlin, **1986**. (b) Weidmann, B.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 32. (c) Reetz, M. T. In *Organometallics in Synthesis*, 2nd ed.; Schlosser, M., Ed.; Wiley: Chichester, **2002**, 817.
(9) Risatti, C. A.; Taylor, R. E. *Angew. Chem. Int. Ed.* **2004**, *43*, 6671.
(10) (a) Mukaiyama, T.; Kobayashi, S. *Org. React.* **1994**, *46*, 1. (b) Mukaiyama, T. *Tetrahedron* **1999**, *55*, 8609. (c) Mukaiyama, T. *Angew. Chem. Int. Ed.* **2004**, *43*, 5590.
(11) For mechanistically related syntheses, see: (a) Hoffmann, R. W.; Giesen, V.; Fuest, M. *Liebigs Ann. Chem.* **1993**, 629. (b) Hanaki, N.; Link, J. T.; McMillan, D. W. C.; Overman, L. E.; Trankle, W. G.; Wurster, J. A. *Org. Lett.* **2000**, *2*, 223.
(12) The chromenols **12** were isolated as mixtures of anomers in ratios between 61:29 and 91:9 (measured by ^{1}H NMR in $CDCl_3$). The configuration at the anomeric carbon atom was not determined.
(13) Review: Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841.
(14) Review: Ley, S.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639.
(15) Data sets were collected with Enraf Nonius CAD4 and Nonius KappaCCD diffractometers, programs used: (a) Data collection EXPRESS: Nonius B.V., 1994. (b) Data collection COLLECT: Nonius B.V., 1998. (c) Data reduction MolEN: Fair K., Enraf-Nonius B.V., 1990. (d) Data reduction Denzo-SMN: Otwinowski, Z.; Minor, W. *Meth. Enzymol* **1997**, *276*, 307. (e) Absorption correction data for CCD data Denzo: Otwinowski, Z.; Borek, D.; Majewski, W.; Minor, W. *Acta Cryst., Sect. A* **2003**, *59*, 228. (f) Structure solution SHELXS-97: Sheldrick, G. M. *Acta Cryst., Sect. A* **1990**, *46*, 467. (g) Structure refinement SHELXL-97: Sheldrick G. M., Universität Göttingen, 1997. (h) Graphics SCHAKAL: Keller E., Universität Freiburg, 1997. CCDC 602901 – 602903 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.htm [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(1223)336033, E-mail: deposit@ccdc.cam.ac.uk].
(16) Review: Kursanov, D. N.; Parnes, Z. N.; Loim, N. M. *Synthesis* **1974**, 633.
(17) Racemic material of compounds **12**–**15** were obtained starting with racemic homoaldol adducts **6** prepared by analogous TMEDA mediated deprotonation–substitution.
(18) The starting 2-hydroxy-3-phenylbenzaldehyde was synthesized by a new directed *ortho*-lithiation-formylation protocol: (a) Kauch, M.; Hoppe, D. *Synthesis* **2006**, 1575. (b) Kauch, M.; Snieckus, V.; Hoppe, D. *J. Org. Chem.* **2005**, *70*, 7149.
(19) NMR data are given for the major anomer of chromenol **12**; see ref. 12.