Ring Transformation of Glycidic Amides with *Ortho*-Metalated Phenols to Enantiopure 3-Hydroxychromanones

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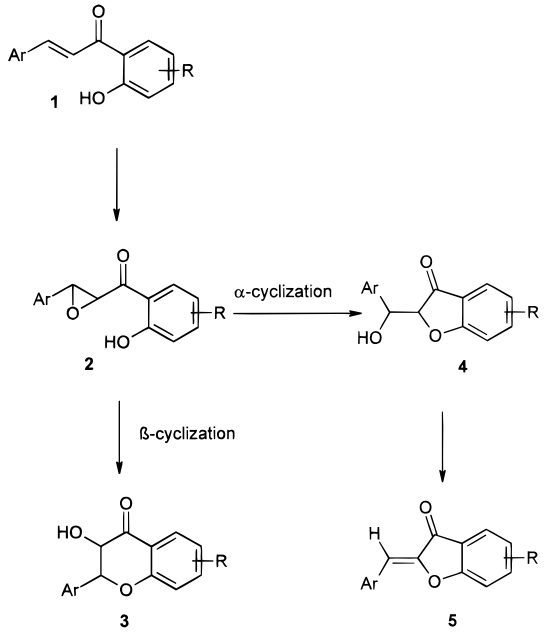
A novel access to hitherto unknown enantiopure 2-alkylchroman-4-ones **10** was found by a reaction of *ortho*-metalated O-MOM-protected phenols with Weinreb amides **8** of enantiopure *cis*- or *trans*-glycidic acids. Upon acidic hydrolysis, the resulting *o*-MOMO-benzoyloxiranes **9** undergo ring transformation to 2-alkylchroman-4-ones **10**. 2-Alkylidenecoumaran-3-ones **11** were formed as alternative products, depending on the configuration of the starting oxirane ring and on the type of phenol used as starting material.

Introduction

3-Hydroxyflavanones (*trans*-2,3-dihydro-2-aryl-3-hydroxy-4*H*-benzopyran-4-ones) and other 3-substituted chromanones are widely found in plants.[1,2] They are biologically important as intermediates in the biogenesis of naturally occurring flavanoid-type products. There are also pharmaceutically and other biologically active compounds found in this series.[3,4] Different routes have been developed to this class of products[5,6] such as stereoselective oxidation of flavanone derivatives by dimethyldioxirane, cyclization of 2′-hydroxychalcone dibromides or bromohydrins in the presence of a base, and oxidative ring closure of 2′-hydroxychalcones with alkaline hydrogen peroxide. In the last three cases, 2′-hydroxychalcone epoxides **2** have been postulated as intermediates that are ring-transformed by intramolecular nucleophilic attack of the phenolic OH-group at the *β*-position of the chalcone epoxide.[5] Such epoxides **2** can also be prepared by epoxidation of protected or unprotected 2′-hydroxychalcones **1** and transformed to 3-hydroxyflavones **3** in a separate step (Scheme 1).[5,6] As a side reaction, formation of 2-(α-hydroxybenzyl)-3-coumaranones **4**[5,8] by alternative attack of the phenolic OH-group at the α-position of the chalcone epoxide **2** and eventually their dehydration to products **5**[8] was observed.

Recently, optically active compounds were synthesized in the 3-hydroxychroman-4-one series with either 2-aryl substituents or 3-alkyl groups starting from optically active chalcone epoxides[6] or by asymmetric hydroxylation

Scheme 1



of chroman-4-ones,[7] respectively. 2-Alkyl-3-hydroxychroman-4-ones are scarce and not reported in optically active form. We report here a new access to 3-hydroxychroman-4-ones enabling the synthesis of enantiopure *cis*- or *trans*-products substituted by alkyl groups at position 2. This route is based on our general strategy to synthesize heterocycles by ring transformation of glycidic acid derivatives with binucleophiles that react at the carbonyl group and at one of the oxirane carbon atoms.[9] To achieve 3-hydroxychroman-4-ones we applied phenols **6** as binucleophiles and enantiopure Weinreb amides **8** of glycidic acids.

Results and Discussion

Although phenols **6** themselves are known as O−C−C binucleophilic building blocks, in our study both protection and activation were necessary. This could be conveniently attained by introducing a MOM-group to the oxygen atom. The O-MOM-moiety as an efficient *ortho*-

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Scheme 2

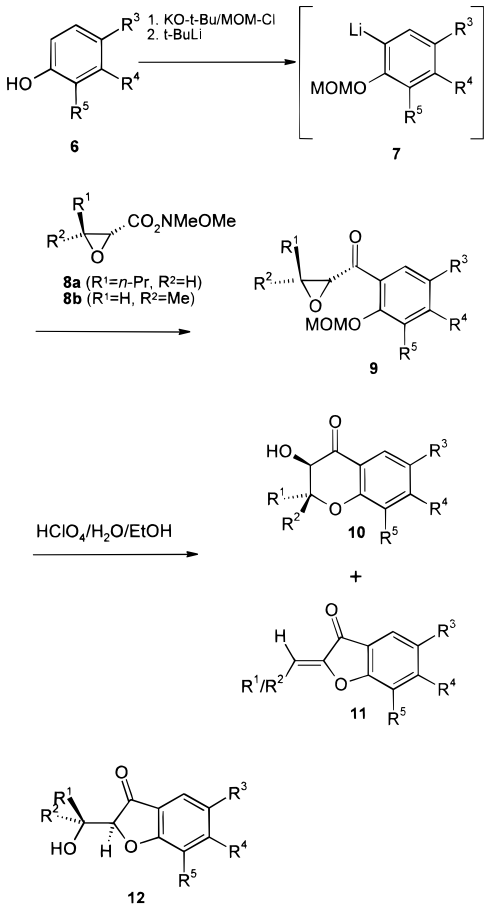

Table 1. Synthesis of Benzoyloxiranes 9, 3-Hydroxychroman-4-ones 10, and 2-Alkylidenecoumaranones 11

							yield (%)		
entry		R^1	R^2	R^3	R^4	R^5	**9**	**10**	**11**
1	**a**	*n*-Pr	H	H	H	H	95	89	
2	**b**	*n*-Pr	H	Me	H	H	61	76	
3	**c**	*n*-Pr	H	OMe	H	H	68	74	
4	**d**	*n*-Pr	H	H	CH=CHCH=CH		73		60
5	**e**	H	Me	H	H	H	83	62	13
6	**f**	H	Me	Me	H	H	63	64	10
7	**g**	H	Me	OMe	H	H	66	55	9
8	**h**	H	Me	H	CH=CHCH=CH		67		93
9	**i**	H	Me	CH=CHCH=CH		H	47	44	

directing group[10] allowed *ortho*-metalation with *t*-BuLi (formation of **7**) (Scheme 2). Subsequent reaction with enantiopure N-methoxy-*N*-methyloxirane carboxamides **8** formed the corresponding epoxides **9** in satisfactory to high yields (see Table 1). From several procedures reported for the ring transformation of *o*-hydroxybenzoyloxiranes to benzochromanones, acidic conditions[5,6] seemed advantageous over basic.[5,8] In our study, diluted HCl in water/EtOH[5] was not successful since either the MOM group survived or the oxirane moiety was cleaved to a corresponding chlorohydrin.[11] Refluxing of **9** in $HClO_4$/EtOH/water was appropriate, while TFA/EtOH/water gave lower yields. The *trans*-epoxides **9** required somewhat harsher reaction conditions (longer reaction times and higher concentration of acid), i.e., the tendency to the anticipated ring transformation turned out to be higher for the *cis*-epoxides **9**. In most cases the envisaged 2-alkyl-3-hydroxychroman-4-ones **10** were obtained in satisfactory yields in the *trans* as well as in the *cis* series depending on the configuration (*trans* or *cis*, respectively) of the starting glycidic amide **8**. Remarkably, the first members of *cis*-3-hydroxy-chroman-4-ones could just recently be synthesized but with 2-aryl substituents, i.e., of flavones.[6] As byproducts of **10**, 2-alkylidenecoumarones **11** (aurone analogues) were observed in some cases obviously formed from **9** by α-attack of the appearing phenolic OH group at the oxirane and subsequent dehydration. In a comparable ring transformation of a racemic 2-hydroxybenzoyloxirane reported in the literature[5] using HCl/water/EtOH at room temperature, α-attack predominated, too, leading to 2-(α-hydroxyalkyl)coumaranone **4**. The extent of α-attack at the benzoyloxiranes **9** (formation of **11**) seems to depend on the type of phenol **6** and on the configuration of **9** (see Table 1). Thus cases of exclusive formation of hydroxychromanones **10** were observed in the *trans* series (see Table 1, entries 1−3), while mixtures of **10** and 2-alkylidenecoumaranones **11** were formed in most cases of the *cis* series (see entries 5−7). It could be seen from a molecular model that the attack of the phenolic OH-group at the *β*-position by formation of **10** is somewhat sterically hindered in the *cis* series as compared with the *trans* series. 1-Naphthol derivatives **9d** and **9h** gave exclusive α-attack regardless of the relative configuration at the oxirane ring (entries 4 and 8). Since the OH-group of 1-naphthol is shielded by the *peri* H-atom, the cyclization obviously occurred at the sterically less hindered α-position of the oxirane ring affording **11**.[12]

Structure elucidation of products **10** and **11** was based on X-ray crystal analysis of the chromanone **10i**[13] and of benzofuranones **11**[14] and **11h**[15] and spectroscopic data (see Experimental Section). The ^3J (2-H, 3-H) coupling constants of **10** are in accordance with the relative configuration (∼6 Hz for *cis* and ∼12 Hz for *trans*, see Experimental Section) revealing bisaxial conformation of the protons at position 2 and 3 of the *trans* chromanones **10a**−**c**. No diastereomers of **8**−**10** could be observed in the crude products. Thus epimerization did not occur, and diastereomerically pure products **10** were formed. 3-Propyl-1-hydroxymethyloxirane[16] and methyl 3-methyloxirane-2-carboxylate[17] were used as starting materials for Weinreb amides **8** with ee = 94% and ee > 98%, respectively (check by chiral HPLC). Since racemization, i.e., inversion of configuration at both chiral ring atoms of the oxirane ring of **8**, was not possible in the reactions performed, products **8**−**10** have the same ee like the starting materials, i.e., 94 or 98%, respectively. The

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(14) Full details have been deposited at the Fachinformationzentrum Karlsruhe, 76344 Eggenstein-Leopoldshaven, Germany; this material can be obtained on quoting a full literature citation and the deposition number CSD-410341.
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2-alkylidenecoumaranones **11** were found to be *Z*[14,15] regardless if they are derived from *cis* or *trans* oxiranes **9**. Thus their formation can be interpreted by an E1-like β-elimination of water from intermediate 2-(α-hydroxyalkyl)coumaranone **12** affording the thermodynamically more stable (*Z*)-products.

In summary, a new route to 3-hydroxychroman-4-ones was developed, allowing the synthesis of enantiopure compounds in the *cis* or in the *trans* series with alkyl substituents in 2-position. Since all these compounds are new, an important gap in the flavanoid chemistry could be filled.

Experimental Section

General. Melting points were determined with a hot-stage apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ at 300 and 75.5 MHz, respectively, with TMS as internal standard. ^{13}C signal assignment is based on DEPT experiments, Optical rotation was determined with $c = 1$ in $CHCl_3$. Silica gel (0.04−0.063 mm, Merck) was used for preparative column chromatography. If not otherwise mentioned, chemicals were purchased from Merck. Starting materials **8** were prepared from known glycidic acids[16,17]and the resulting oxiranecarboxylic acids were reacted to the Weinreb amides **8**.[18]

Weinreb Amides 8. DCC (8.22 g, 40 mmol) was added to a solution of the oxirane carboxylic acid (R^1 = *n*-Pr, R^2 = H; 40 mmol) and Et_3N (5.53 mL, 40 mmol) or to a suspension of the K-salt (R^1 = H, R^2 = Me, 40 mmol) without Et_3N in 50 mL of dry THF (**8b**) or CH_2Cl_2 (**8a**) at 0 °C under argon atmosphere. *N*,*O*-Dimethylhydroxylamine hydrochloride (3.90 g, 40 mmol) was added, and the mixture was stirred at rt for 20 h. After filtration, the solution was evaporated and purified by column chromatography with CH_2Cl_2/acetone (95:5) to yield **8a** (R^1 = *n*-Pr, R^2 = H) in 82% or **8b** (R^1 = H, R^2 = Me) in 57% as a colorless oil.

8a: $[\alpha]^{20}_D = +2.1°$; ^{1}H NMR δ 0.92 (t, *J* = 7.2, 3 H), 1.43−1.59 (m, 4 H), 3.08 (m, 1 H), 3.17 (s, 3 H), 3.59 (d, *J* = 1.8, 1 H), 3.71 (s, 3 H); ^{13}C NMR δ 15.0 (CH_3), 20.6 (CH_2), 34.8 (CH_2), 33.7 (CH_3), 53.5 (CH_3), 59.2 (CH), 63.1 (CH), 169.8 (C). Anal. Calcd for $C_8H_{15}NO_3$ (173.24): C 55.46, H 8.75, N 8.09. Found: C 55.73, H 8.73, N 8.01.

8b: $[\alpha]^{20}_D = +82.5°$; ^{1}H NMR δ 1.24 (d, *J* = 5.4, 3 H), 3.14 (s, 3 H), 3.24 (m, 1 H), 3.64 (s, 3 C), 3.78 (d, *J* = 4.7, 1 H); ^{13}C NMR δ 13.6 (CH_3), 32.9 (CH_3), 53.8 (CH_3), 53.5 (CH), 62.1 (CH), 168.5 (C); HR-MS calcd: 145.0739, found: 145.0693.

General Procedure for the Preparation of (2-MOMObenzoyl)oxiranes 9. O-MOM-derivatives of phenols **6** were prepared in 70−90% yield, adopting a known procedure for MOM-protection of thiophenols.[19]

t-BuLi (0.99 mL, 1.58 mmol, 1.6 M in pentane) was added to a solution of the corresponding O-MOM-phenol (1.5 mmol) at 0 °C under argon atmosphere. The mixture was stirred at room temperature for 3 h. After being cooled to 0 °C, the Weinreb amide **8** (1.5 mmol) dissolved in dry diethyl ether (1 mL) was added, and the mixture was stirred at room temperature for 2 h. The mixture was quenched with diluted NH_4-Cl-solution (7 mL) and extracted with diethyl ether (2 × 7 mL). The combined organic phases were dried, evaporated, and purified by column chromatography with pentane/ether (1:1). The resulting colorless oils **9** were characterized just by ^{1}H and ^{13}C NMR spectra and were further converted to **10** and **11**.

9a: ^{1}H NMR δ 1.08 (t, *J* = 7.7, 3 H), 1.63−1.95 (m, 4 H), 3.22 (m, 1 H), 3.58 (s, 3 H), 4.15 (d, *J* = 2.0, 1 H), 5.37 (s, 2 H), 7.14−7.81 (m, 4 H); ^{13}C NMR δ 14.3 (CH_3), 19.6 (CH_2), 34.5 (CH_2), 56.9 (CH_3), 60.3 (CH), 60.8 (CH), 95.1 (CH_2), 115.1 (CH), 122.5 (CH), 130.8 (CH), 134.7 (CH), 127.5 (C), 157.2 (C), 197.4 (C).

9e: ^{1}H NMR δ 1.34 (d, *J* = 5.4, 3 H), 3.53 (m, 1 H), 3.56 (s, 3 H), 4.34 (d, *J* = 4.9, 1 H), 5.35 (dd, *J* = 7.8, 10.6, 2H), 7.12−7.86 (m, 4 H); ^{13}C NMR δ 13.5 (CH_3), 56.9 (CH_3), 55.4 (CH), 61.2 (CH), 94.9 (CH_2), 115.0 (CH), 122.4 (CH), 130.9 (CH), 135.0 (CH), 127.4 (C), 157.2 (C), 195.9 (C).

9h: ^{1}H NMR δ 1.30 (d, *J* = 5.3, 3 H), 3.45 (m, 1 H), 3.48 (s, 3 H), 4.42 (d, *J* = 4.7, 1 H), 5.12 (dd, *J* = 5.8, 8.6, 2 H), 7.19−8.22 (m, 6 H); ^{13}C NMR δ 13.1 (CH_3), 58.7 (CH_3), 56.0 (CH), 59.9 (CH), 102.4 (CH_2), 124.0 (CH), 125.1 (CH), 125.3 (CH), 127.4 (CH), 128.5 (CH), 129.1 (CH), 128.0 (C), 128.6 (C), 137.4 (C), 154.9 (C), 196.9 (C).

9i: ^{1}H NMR δ 1.26 (d, *J* = 5.4, 3 H), 3.43 (m, 1 H), 3.47 (s, 3 H), 4.27 (d, *J* = 4.9, 1 H), 5.30 (dd, *J* = 7.8, 8.0, 2 H), 7.29−8.19 (m, 6 H); ^{13}C NMR δ 13.5 (CH_3), 56.9 (CH_3), 55.6 (CH), 61.0 (CH), 95.2 (CH), 110.3 (CH), 125.5 (CH), 128.9 (CH), 129.7 (CH), 130.5 (CH), 132.4 (CH), 127.4 (C), 129.2 (C), 136.9 (C), 153.3 (C), 196.4 (C).

General Procedure for the Preparation of 3-Hydroxychroman-4-ones 10 and 2-Alkylidenecoumaranones 11. Aqueous $HClO_4$ (70%, 0.3 mmol for *cis*-epoxides, 0.4 mmol for *trans*-epoxides) was added to a solution of the benzoyloxirane **9** (1 mmol) in water/EtOH (2:3, 3 mL). The mixture was refluxed for 1 h (*cis*-epoxides **9)** or 1.5 h (*trans*-epoxides **9**) and was diluted with water (7 mL) after being cooled to room temperature. The mixture was extracted with CH_2Cl_2 (2 × 7 mL), and the combined organic phases were dried, evaporated, and purified by column chromatography with pentane/ether (1:1).

10a: colorless crystals, mp = 42−44 °C (after chromatography), R_f = 0.64, $[\alpha]^{20}_D = +79.4°$; ^{1}H NMR δ 0.94 (t, *J* = 7.4, 3 H), 1.43−1.97 (m, 4 H), 3.65 (s, 1 H), 4.07 (m, 1 H), 4.20 (d, *J* = 12.4, 1 H), 6.89−7.79 (m, 4 H); ^{13}C NMR δ 14.3 (CH_3), 18.2 (CH_2), 34.14 (CH_2), 73.2 (CH), 82.1 (CH), 118.2 (CH), 121.0 (CH), 127.6 (CH), 137.0 (CH), 118.9 (C), 162.3 (C), 195.3 (C). Anal. Calcd for $C_{12}H_{14}O_3$ (206.26): C, 69.87; H, 6.86. Found: C, 69.77; H, 6.91.

10e: colorless crystals, mp = 98 °C (hexane), R_f = 0.44, $[\alpha]^{20}_D = -158.5°$; ^{1}H NMR δ 1.21 (d, *J* = 6.7, 3 H), 3.63 (d, *J* = 2.2, 1 H), 4.69 (dd, *J* = 1.7, 6.1, 1 H), 4.84 (m, 1 H), 6.86−7.77 (m, 4 H); ^{13}C NMR δ 12.1 (CH_3), 72.7 (CH), 77.0 (CH), 118.9 (CH), 121.7 (CH), 127.0 (CH), 137.3 (CH), 119.2 (C), 180.0 (C), 194.3 (C). Anal. Calcd for $C_{10}H_{10}O_3$ (178.20): C, 67.40; H, 5.67. Found: C, 67.10; H, 5.68.

10i: light yellow crystals, mp = 153−155 °C (hexane), R_f = 0.49, $[\alpha]^{20}_D = -2.3°$; ^{1}H NMR δ 1.23 (d, *J* = 6.6, 3 H), 3.65 (d, *J* = 2.5, 1 H), 4.82 (dd, *J* = 2.4, 6.0, 1 H), 4.88 (m, 1 H), 7.25 (s, 1 H), 7.27−7.82 (m, 4 H), 8.38 (s, 1 H); ^{13}C NMR δ 12.3 (CH), 73.3 (CH), 76.5 (CH), 113.4 (CH), 124.9 (CH), 126.7 (CH), 128.8 (CH), 129.5 (CH), 129.7 (CH), 119.9 (C), 128.2 (C), 138.4 (C), 154.4 (C), 194.8 (C). Anal. Calcd for $C_{14}H_{12}O_3$ (228.26): C, 73.66; H, 5.31. Found: C, 73.35; H, 5.35.

11e: light yellow oil, R_f = 0.69, ^{1}H NMR δ 1.94 (d, *J* = 7.5, 3 H), 6.13 (q, *J* = 7.5, 1 H), 7.05−7.68 (m, 4 H); ^{13}C NMR δ 11.6 (CH_3), 112.7 (CH), 113.2 (CH), 123.3 (CH), 125.0 (CH), 137.3 (CH), 122.1 (C), 150.3 (C), 166.5 (C), 184.0 (C); MS *m*/*z* (%): 160 (M^+, 6), 121 (28), 92 (100), 65 (10).

11h: light yellow crystals, mp = 150−152 °C (hexane), R_f = 0.79; ^{1}H NMR δ 2.05 (d, *J* = 7.5, 3 H), 6.24 (q, *J* = 7.5, 1 H), 7.18−8.21 (m, 6 H); ^{13}C NMR δ 11.8 (CH_3), 113.4 (CH), 119.5 (CH), 122.3 (CH), 123.6 (CH), 127.3 (CH), 129.0 (CH), 130.7 (CH), 117.8 (C), 121.3 (C), 138.6 (C), 151.0 (C), 166.4 (C), 183.4 (C); MS *m*/*z* (%): 210 (M^+, 100), 170 (31), 114 (38), 126 (16) IR (KBr): 808 (C=*C*−*H*), 1629 (C=C), 1707 (C=O) Anal. Calcd for $C_{14}H_{10}O_2$ (210.24): C, 79.98; 4.80. Found: C, 80.05; H, 4.83.

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Supporting Information Available: X-ray crystal analyses of compounds **10i**, **11d**, and **11h**; ^{1}H and ^{13}C NMR spectra, mp, R_f, optical rotation, and elemental analyses of compounds **9b**, **9c**, **9d**, **9f**, **9g**, **10b**, **10c**, **10f**, **10g**, **11d**, **11f**, and **11g**. This material is available free of charge via the Internet at http://pubs.acs.org.

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