JOC Article
pubs.acs.org/joc

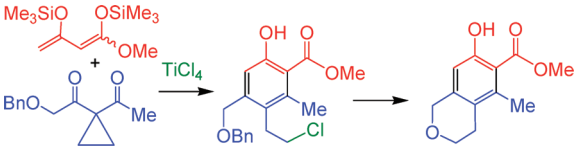
Chelation Control in the [3 + 3] Annulation Reaction of Alkoxy-Substituted 1,1-Diacylcyclopropanes with 1,3-Bis(trimethylsilyloxy)-1,3-butadienes. Diversity-Oriented Synthesis of Isochromanes

Vahuni Karapetyan,[†] Satenik Mkrtchyan,[†] Jennifer Hefner,[†] Christine Fischer,[‡] and Peter Langer*[,†,‡]

[†]*Institut für Chemie der Universität Rostock, Albert-Einstein-Strasse 3a, D-18059 Rostock, Germany and* [‡]*Leibniz Institut für Katalyse e.V. an der Universität Rostock, Albert-Einstein-Strasse 29a, D-18059 Rostock, Germany*

peter.langer@uni-rostock.de

Received November 1, 2009



Functionalized arenes were prepared by chelation-controlled [3 + 3] cyclization/cyclopropane opening reactions of 1-trimethylsilyloxy-1,3-butadienes with benzyloxy- or methoxy-substituted 1,1-diacylcyclopropanes. A number of benzyloxy-substituted derivatives were transformed into isochromanes by deprotection and subsequent cyclization. Mixed chromanes−isochromanes were prepared starting with 1,3-bis(silyloxy)-1,3-butadienes containing a remote chloride group.

Introduction

3,4-Dihydro-2*H*-chromenes (chromanes) represent pharmacologically relevant heterocycles which occur in a variety of natural products (Scheme 1).[1,2] For example, bavachromanol has been isolated from leaves of *Maclura tinctoria L.* (Venezuela).[2a] The chromanol moiety of vitamin E (α-tocopherol) exhibits antiandrogen properties.[3] Natural products containing an isochromane substructure are also of pharmacological relevance. For example, the natural product pseudodeflectusine, which has been isolated from *Aspergillus pseudodeflectus*, exhibits selective cytotoxic activity against several human cancer cell lines.[4] The isochromane derivatives pseudoanguillosporines A and B, which have been isolated first time by Kock et al. from *Pseudoanguillospora*, show antibacterial and antifungal activity.[5]

Finn et al. have prepared chromanes from salicylic aldehydes and vinylboronic acids in the presence of catalytic amounts of dibenzylamine.[6] Jones et al. reported the synthesis of chromanes by Diels−Alder reactions of *o*-quinone methides, which were generated from salicylic aldehydes and alcohols.[7] We have reported the synthesis of 6-(2-hydroxybenzoyl)-3,4-dihydro-2*H*-chromenes based on sequential [3+3]-cyclization/Williamson reactions of 1,3-bis(trimethylsilyloxy)-7-chlorohepta-1,3-dienes with 3-silyloxy 2-en-1-ones and 3-formylchromones.[8]

Recently, we have reported[9] the synthesis of functionalized phenols by $TiCl_4$-mediated [3 + 3] cyclization[10] of 1,3-bis(trimethylsilyloxy)-1,3-butadienes[11] with 1,1-diacylcyclopropanes.

*To whom correspondence should be addressed. Fax: +49-381-498-6411.

(1) Hepworth, J. *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., eds.; Elsevier Science: Oxford, 1984; Vol. 3, p 737.

(2) (a) Bavachromanol: Sohly, H. N.; Joshi, A. S.; Nimrod, A. C.; Walker, L. A.; Clark, A. M. *Planta Med.* **2001**, *67*, 87. (b) Calyxin L: Tezuka, Y.; Gewali, M. B.; Ali, M. S.; Banskota, A. H.; Kadota, S. *J. Nat. Prod.* **2001**, *64*, 208.

(3) *Römpp-Lexikon Naturstoffe*; Fugmann, B., Ed.; Georg Thieme Verlag: Stuttgart, 1997.

(4) (a) Vismiaguianone E: Seo, E.-K.; Wani, M. C.; Wall, M. E.; Navarro, H.; Mukherjee, R.; Farnsworth, N. R.; Kinghorn, A. D. *Phytochemistry* **2000**, *55*, 35. (b) Grandinal: Singh, I. P.; Hayakawa, R.; Etoh, H.; Takasaki, M.; Konoshima, T. *Biosci. Biotechnol. Biochem.* **1997**, *61*, 921. (c) Calomelanol A: Asai, F.; Iinuma, M.; Tanaka, T.; Mizuno, M. *Phytochemistry* **1991**, *30*, 3091. (d) Iryantherin E: Conserva, L. M.; Yoshida, M.; Gottlieb, O. R.; Martinez V., J. C.; Gottlieb, H. E. *Phytochemistry* **1990**, *29*, 3911.

(5) Kock, I.; Draeger, S.; Schulz, B.; Elsässer, B.; Kurtan, T.; Kenez, A.; Antus, S.; Pescitelli, G.; Salvadori, P.; Speakman, J.-B.; Rheinheimer, J.; Krohn, K. *Eur. J. Org. Chem.* **2009**, 1427.

(6) Wang, Q.; Finn, M. G. *Org. Lett.* **2000**, *2*, 4063.

(7) Jones, R. M.; Selenski, C.; Pettus, T. R. R. *J. Org. Chem.* **2002**, *67*, 6915.

(8) Nguyen, V. T. H.; Appel, B.; Langer, P. *Tetrahedron* **2006**, *62*, 7674.

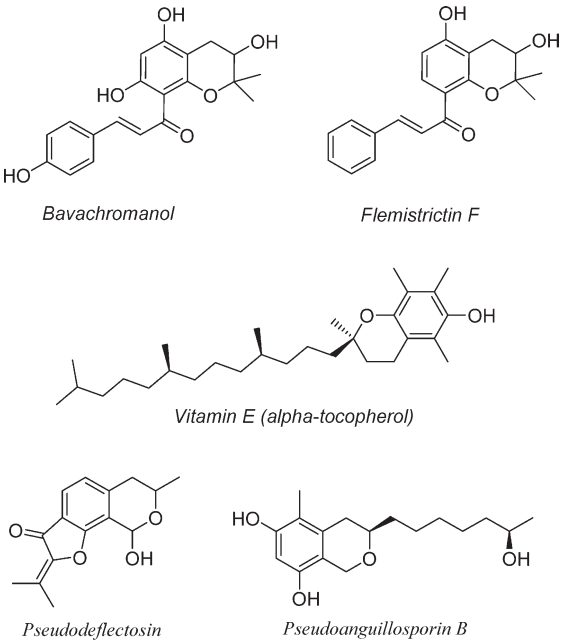
(9) (a) Langer, P.; Bose, G. *Angew. Chem., Int. Ed.* **2003**, *42*, 4033. (b) Bose, G.; Nguyen, V. T. H.; Ullah, E.; Lahiri, S.; Görls, H.; Langer, P. *J. Org. Chem.* **2004**, *69*, 9128.

(10) For a review of [3+3] cyclizations, see: Feist, H.; Langer, P. *Synthesis* **2007**, 327.

(11) For a review of 1,3-bis(silyl enol ethers), see: Langer, P. *Synthesis* **2002**, 441.

DOI: 10.1021/jo902334q Published on Web 01/11/2010

SCHEME 1. Structures of Bavachromanol, Flemistrictin F, Vitamin E, Pseudodeflectusine, and Pseudoanguillosporine B



Although symmetrical cyclopropanes were employed in most cases, some unsymmetrical substrates have also been studied. The cyclization of 1,3-bis(silyloxy)-1,3-butadienes with 1-acetyl-1-formylcyclopropane and with 1-acetyl-1-benzoylcyclopropane proceeded by regioselective attack of the terminal carbon atom of the diene onto the more reactive carbonyl group (i.e., the formyl and the acetyl group, respectively). Recently, we have reported preliminary results related to the regiodirecting effect of chelating[12,13] alkoxy groups present in 1,1-diacylcyclopropane.[14] Herein, we report full details and a comprehensive study of the scope of our methodology. In addition, we report its application to the synthesis of various functionalized chromanes and isochromanes.

Results and Discussion

1-Methoxypentane-2,4-dione,[15] 1-benzyloxypentane-2,4-dione,[16] and 4-methoxy-1-phenylbutane-1,3-dione[17] are known compounds which were prepared according to the literature. Hitherto unknown 4-benzyloxy-1-phenylbutane-1,3-dione was prepared, in analogy to the synthesis of 1-benzyloxypentane-2,4-dione, by Claisen condensation of benzyl 2-(benzyloxy)acetate with acetophenone in 50% yield. The potassium carbonate-mediated reaction of the four 1,3-diketones with 1,2-dibromoethane in DMSO afforded the cyclopropanes **2a**−**d** in moderate yields (Scheme 2, Table 1).

SCHEME 2. Synthesis of 2a−d

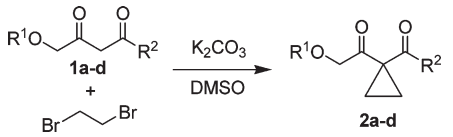
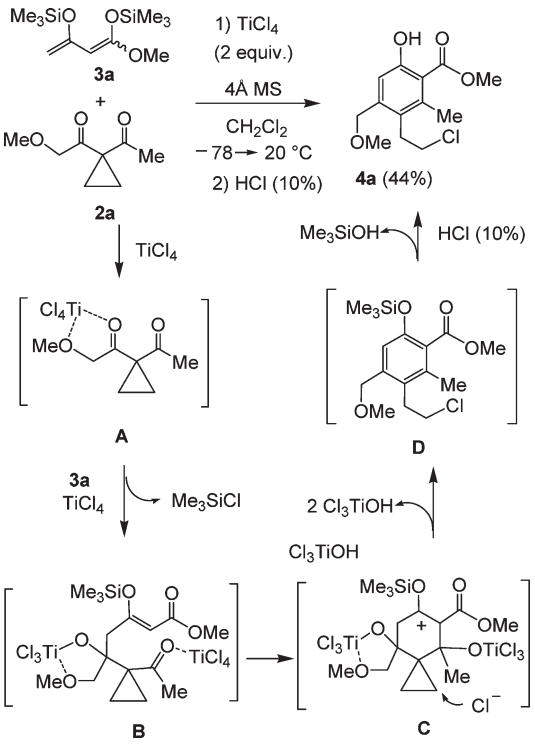


TABLE 1. Synthesis of 2a−d

1, 2	R^1	R^2	% (2)[a]
a	Me	Me	40
b	Me	Ph	40
c	Bn	Me	42
d	Bn	Ph	40

[a]Yields of isolated products.

SCHEME 3. Possible Mechanism of the Formation of 4a



The $TiCl_4$-mediated cyclization of **2a** with 1,3-bis(trimethylsilyloxy)-1,3-butadiene **3a**, readily available in two steps from methyl acetoacetate,[18] afforded the 5-chloroethyl-4-(methoxymethyl)salicylate **4a** (Scheme 3). The moderate yield of **4a** can be explained by practical problems during the chromatographic purification. The best yields of **4a** were obtained when 1.0 equiv of **2a**, 1.5 equiv of **3a**, and 2.0 equiv of $TiCl_4$ were employed. The low concentration (c(**2a**) = 0.01 M) and the presence of molecular sieves (4 Å) (for the removal of water) also played an important role.

The regioselectivity can be explained by the Lewis acid-directing effect of the methoxy group of the substrate. The chelation of $TiCl_4$ by the methoxy and the neighboring carbonyl group of **2a** results in the formation of intermediate **A**. The $TiCl_4$-mediated attack of the terminal carbon atom of **3a** onto **2a** gives rise to the formation of intermediate **B** which

(12) For reviews of chelation control in Lewis acid-mediated reactions, see: (a) Yamamoto, H. *Lewis Acid Chemistry: A Practical Approach*; Oxford University Press: Oxford, 1999. (b) Mahrwald, R. *Chem. Rev.* **1999**, *99*, 1095. (c) Santelli, M.; Pons, J. M. *Lewis Acids and Selectivity in Organic Synthesis*; CRC Press: Boca Raton, 1996. (d) Shambayati, S.; Schreiber, S. L. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 1, pp 283−324.

(13) Chelation control has been reported for the [4 + 3] annulation reaction of benzyloxy-substituted 1,4-dicarbonyl compounds with bis(silyl enol ethers): Molander, G. A.; Eastwood, P. R. *J. Org. Chem.* **1996**, *61*, 1910.

(14) Hefner, J.; Langer, P. *Tetrahedron Lett.* **2008**, *49*, 4470.

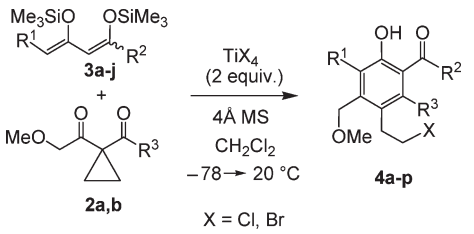
(15) Bruce, W. F.; Coover, H. W. *J. Am. Chem. Soc.* **1944**, *66*, 2092.

(16) Wenner, W.; Plati, J. T. *J. Org. Chem.* **1946**, *11*, 751.

(17) Gault, H.; Viout, A. *Bull. Soc. Chim. Fr.* **1951**, 713.

(18) (a) Chan, T.-H.; Brownbridge, P. *J. Am. Chem. Soc.* **1980**, *102*, 3534. (b) Brownbridge, P.; Chan, T.-H.; Brook, M. A.; Kang, G. J. *Can. J. Chem.* **1983**, *61*, 688.

SCHEME 4. Synthesis of 4a−p



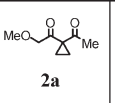
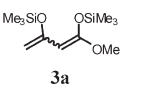
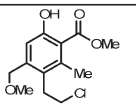
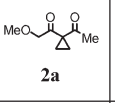
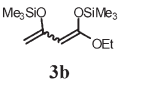
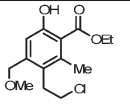
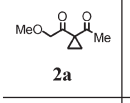
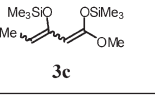
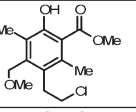
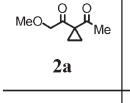
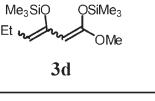
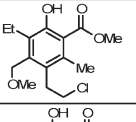
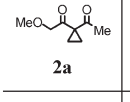
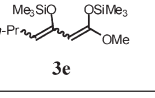
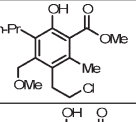
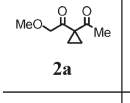
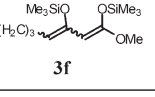
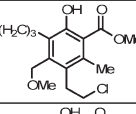
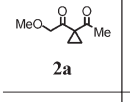
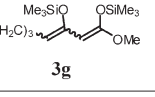
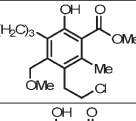
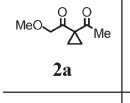
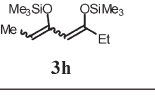
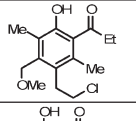
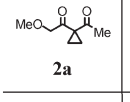
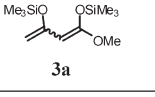
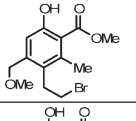
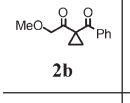
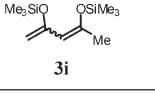
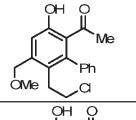
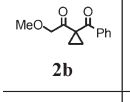
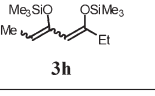
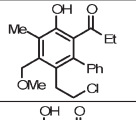
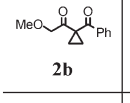
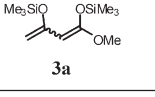
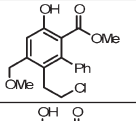
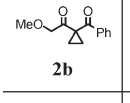
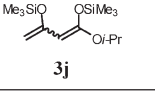
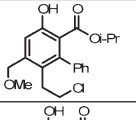
undergoes a cyclization via the central carbon atom of the 1,3-dicarbonyl unit (intermediate **C**). The product is subsequently formed by Lewis acid-assisted cleavage of the spirocyclopropane moiety and aromatization by attack of a chloride ion onto the cyclopropane (intermediate **D**) and hydrolysis upon aqueous workup. The process can be regarded as a domino [3+3] cyclization/cyclopropane opening reaction.[18]

The $TiCl_4$- or $TiBr_4$-mediated cyclization of **2a** and **2b** with 1,3-bis(trimethylsilyloxy)-1,3-butadienes **3a−j**, prepared from the corresponding 1,3-dicarbonyl compounds in two steps,[18] afforded the 4-chloroethyl- and 4-bromoethyl-3-(methoxymethyl)phenols **4a−p** in 30−73% yields (Scheme 4, Table 2). The employment of $TiCl_4$ or $TiBr_4$ is equally efficient in terms of yield. All reactions proceeded with very good regioselectivity. Although some products were isolated in only moderate yields, only one regioisomer could be isolated in all reactions. Only hydrolyzed 1,3-bis(silyl enol ether) could be isolated as a side product (which is understandable because the diene was used in a slight excess, 1.5 equiv). The low yields are a result of practical problems during the chromatographic purification. The yields of the products derived from **2b** were in many cases better than those of the products derived from **2a**. Relatively low yields were obtained for products **4h**,**j**,**k** derived from dienes **3h** and **3j**. These dienes, which have been prepared from 1,3-diketones, are less reactive than the other dienes which have been prepared from β-ketoesters.

Depending on the position of the attack of the 1,3-bis(silyl enol ether) onto the 1,1-diacylcyclopropane the formation of two regioisomers is possible. Substituent R^1 can be located ortho or para to R^3. The two possible regioisomers of product **4a** are depicted in Scheme 5. The structures of the products were established by 2D NMR experiments (^{1}H,^{1}H-NOESY, ^{1}H,^{13}C-HMBC). A NOESY experiment shows an interaction between the methylene group CH_2OMe (δ = 4.43 ppm) and the aromatic proton (δ = 6.90 ppm), which proves the presence of isomer **A**. An HMBC experiment exhibits a $^3J_{C,H}$-coupling between the methylene group CH_2OMe (^{1}H: δ = 4.43 ppm; ^{13}C: δ = 73.8 ppm) and the aromatic CH-group (^{1}H: δ = 6.90 ppm; ^{13}C: δ = 116.8 ppm). In contrast, an NOE interaction between the methyl group (δ = 2.50 ppm) and the aromatic proton (δ = 6.90 ppm), which would be diagnostic for isomer **B**, was not observed. The low-field shift of the hydroxyl proton shows that the latter is involved in solution in an intramolecular hydrogen bond to the neighbored ester carbonyl group.

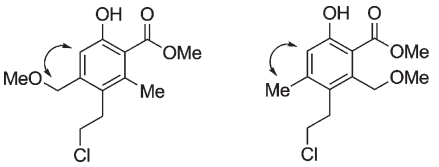
The novel benzyloxy-substituted 1,1-diacylcyclopropanes **2c** and **2d** were prepared by cyclopropanation of 1-benzyloxypentane-2,4-dione and 4-benzyloxy-1-phenylbutane-1,3-dione, respectively. The cyclization of **2c**,**d** with 1,3-bis(trimethylsilyloxy)-1,3-butadienes **3a−m** in the presence of $TiCl_4$ or $TiBr_4$

TABLE 2. Synthesis of Salicylates 4a−p

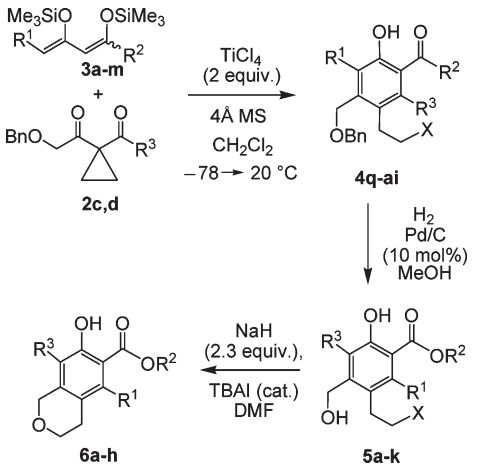
2	3	4		% (4)[a]
 **2a**	 **3a**		**a**	44
 **2a**	 **3b**		**b**	38
 **2a**	 **3c**		**c**	32
 **2a**	 **3d**		**d**	52
 **2a**	 **3e**		**e**	58
 **2a**	 **3f**		**f**	30
 **2a**	 **3g**		**g**	35
 **2a**	 **3h**		**h**	30
 **2a**	 **3a**		**i**	46
 **2b**	 **3i**		**j**	33
 **2b**	 **3h**		**k**	36
 **2b**	 **3a**		**l**	62
 **2b**	 **3j**		**m**	73
2b	**3c**		**n**	48
2b	**3d**		**o**	59
2b	**3a**		**p**	49

[a]Yields of isolated products.

SCHEME 5. Possible Regioisomers of 4a



SCHEME 6. Synthesis of Isochromanes 6a−h



afforded the functionalized phenols **4q−ai** (Scheme 6, Table 3). All products were again formed with very good regioselectivity by attack of the terminal carbon atom of the diene onto the carbonyl group located next to the benzyloxy group. The debenzylation of **4q−ai** afforded the alcohols **5a−k**, which were transformed by Williamson reaction into the isochromanes **6a−h** (Scheme 6, Table 3).

Treatment of salicylates **4g**, **4y**, and **4ah**, which contain two chloride groups, with NaH/TBAI afforded chromanes **7a−c** (Scheme 7, Table 4). The benzyloxy-substituted derivatives **7b**,**c** were hydrogenated to give the free alcohols **8a**,**b**. The base-mediated cyclization of **8a**,**b** afforded heterocycles **9a**,**b** containing a chromane and an isochromane moiety.

In conclusion, we have reported the first chelation-controlled domino [3 + 3] cyclization/cyclopropane opening reactions of 1,3-bis(trimethylsilyloxy)-1,3-butadienes with 1,1-diacylcyclopropanes. These reactions provide a convenient approach to highly functionalized phenols which are not readily available by other methods. The regioselectivity can be explained by the Lewis acid-directing effect of the alkoxy groups of the substrates.

Experimental Section

General Methods. Chemical shifts of the ^{1}H and ^{13}C NMR are reported in parts per million using the solvent internal standard (chloroform, 7.26 and 77.0 ppm, respectively). Infrared spectra were recorded on an FTIR spectrometer. Mass spectrometric data (MS) were obtained by electron ionization (EI, 70 eV), chemical ionization (CI, isobutane), or electrospray ionization (ESI). Melting points are uncorrected. The solvent CH_2Cl_2 (anhydrous, 99.8%) was purchased directly from ACROS and used without further purification, and $TiCl_4$ was purchased from Aldrich and freshly destilled prior to use. Analytical thin-layer chromatography was performed on 0.20 mm 60 A

TABLE 3. Synthesis of Salicylates 4q−ai, 5a−k, and Isochromanes 6a−h

2	3	% (4)[a]		% (5)[a]		% (6)[a]	
2c	3a		q 46		a 61		a 62
2c	3j		r 53		b 75		b 52
2c	3k		s 48		c 87		c 54
2c	3l		t 62				
2c	3c		u 68		d 87		d 67
2c	3d		v 41		e 80		
2c	3e		w 58				
2c	3m		x 35		f 85		e 44
2c	3g		y 47		g 79		
2c	3a		z 79				
2d	3h		aa 32				
2d	3a		ab 37		h 96		f 72
2d	3b		ac 35				
2d	3j		ad 62				
2d	3k		ae 58		i 78		g 50
2d	3d		af 64		j 56		
2d	3m		ag 46		k 68		h 57
2d	3g		ah 63				
2d	3a		ai 52				

[a]Yields of isolated products.

silica gel plates. Column chromatography was performed using 60A silica gel (60−200 mesh). All cyclization reactions were carried out in Schlenk tubes under an argon atmosphere. 1-Methoxypentane-2,4-dione, 1-benzyloxypentane-2,4-dione, 4-methoxy-1-phenylbutane-1,3-dione, and 4-benzyloxy-1-phenylbutane-1,3-dione were prepared according to the literature.[15−17]

4-Benzyloxy-1-phenylbutane-1,3-dione (1d). This compound was prepared according to the literature.[16,17] Starting with benzyl 2-(benzyloxy)acetate (10.25 g, 40.0 mmol), acetophenone (6.01 g, 50.0 mmol), and sodium ethoxide (3.40 g, 50.0 mmol) in diethyl ether (40 mL), 4-benzyloxy-1-phenylbutane-1,3-dione was obtained as a pale yellow oil (5.37 g, 50%), R_f = 0.58 (heptane/EtOAc = 1:1). The product was purified by chromatography (heptane/EtOAc = 100:1 → 15:1). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 4.19 (s, 2H), 4.66 (s, 2H), 6.56 (s, 1H), 7.28−7.57 (m, 8H), 7.89−7.94 (m, 2H), 15.92 (s, 1H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 71.7, 73.4, 93.5, 127.1, 127.9, 128.0, 128.5, 128.6, 132.5, 134.4, 137.2, 183.1, 194.6. IR (ATR, cm^{-1}): ν = 3467 (w), 3030 (w), 2863 (w), 1682 (s), 1451 (m), 1264 (s), 1103 (s), 688 (s). MS (EI, 70 eV): m/z = 162 (86), 161 (19), 147 (100), 105 (67), 91 (87). HRMS (ESI+): calcd for $C_{17}H_{16}NaO_3$ ([M + Na]$^+$) 291.09917, found 291.09902.

Synthesis of Cyclopropanes 2a−d. To a DMSO solution (2.5 mL per 1 mmol of 1,3-diketone) of the 1,3-diketone **1** was added powdered K_2CO_3 (3.0 equiv) under argon atmosphere. 1,2-Dibromomethane (1.3 equiv) was dropwise added with stirring. The reaction mixture was stirred at 20 °C for approximately 18 h, and subsequently water (300 mL) was added. The organic and the aqueous layers were separated, and the latter was extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with water (3 × 30 mL) and brine. The aqueous and the organic layers were separated, the latter was dried (Na_2SO_4) and filtered, and the filtrate was concentrated in vacuo. The residue was purified by vacuum distillation or by chromatography (heptanes/EtOAc = 100:1 → 5:1).

1-Acetyl-1-(methoxymethyl)carbonylcyclopropane (2a). Starting with 1-methoxypentane-2,4-dione **1a** (5.011 g, 38.50 mmol), 1,2-dibromoethane (9.402 g, 50.0 mmol), and K_2CO_3 (15.96 g, 115.50 mmol) in DMSO (100 mL), **2a** was obtained as a pale yellow oil (2.41 g, 40%). Bp = 46 °C (p = 0.15 Torr). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.43−1.46 (m, 2H), 1.50−1.52 (m, 2H), 2.10 (s, 3H), 3.38 (s, 3H), 4.31 (s, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 17.4, 26.3, 41.0, 59.1, 77.1, 202.9, 203.6. IR (ATR, cm^{-1}): ν = 2827 (w), 1687 (s), 1195 (m), 1125 (s). MS (GC, 70 eV): m/z = 111 (100), 69 (85), 45 (81), 43 (94). HRMS (ESI+): calcd for $C_8H_{12}NaO_3$ ([M + Na]$^+$) 179.06787, found 179.06790.

General Procedure for the Synthesis of Salicylates 4a−ai. To a CH_2Cl_2 solution (100 mL) of **2** (1.0 mmol) and 1,3-bis(silyl enol ether) **3** (1.5 mmol) in the presence of molecular sieves (4 Å, 1.00 g) was dropwise added $TiCl_4$ (0.22 mL, 2.0 mmol) at −78 °C under argon atmosphere. The solution was allowed to warm to 20 °C within 18 h with stirring and subsequently filtered. The filtrate was poured into hydrochloric acid (10%, 100 mL), the organic and the aqueous layers were separated, and the latter was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried (Na_2SO_4) and filtered, and the filtrate was concentrated in vacuo. The residue was purified by chromatography (silica gel, heptanes/EtOAc = 15:1 → 7:1).

5-(2-Chloroethyl)-4-methoxymethyl-6-methylsalicylic Acid Methyl Ester (4a). Starting with **2a** (0.156 g, 1.00 mmol), **3a** (0.391 g, 1.50 mmol), and $TiCl_4$ (0.22 mL, 2.00 mmol) in CH_2Cl_2 (100 mL), **4a** was obtained as a pale yellow solid (0.120 g, 44%). Mp = 77−78 °C. R_f = 0.38 (heptane/EtOAc = 3:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.50 (s, 3H), 3.06−3.12 (m, 2H), 3.42 (s, 3H), 3.52−3.57 (m, 2H), 3.97 (s, 3H), 4.43 (s, 2H), 6.90 (s, 1H), 10.61 (s, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 14.5, 32.9, 43.3, 52.7, 59.9, 73.8, 113.9, 116.8, 127.3, 140.0, 143.8, 160.7, 172.0. IR (KBr, cm^{-1}): ν = 3025 (m), 2892 (w), 1660 (s), 1445 (s), 1198 (m), 1100 (s), 710 (m). MS (EI, 70 eV): m/z = 274 (M$^+$, ^{37}Cl, 16), 272 (M$^+$, ^{35}Cl, 46), 240 (100), 133 (96). HRMS (EI): calcd for $C_{13}H_{17}ClO_4$ ([M]$^+$, ^{35}Cl) 272.08099, found 272.08061.

SCHEME 7. Synthesis of Heterocycles 9a,b

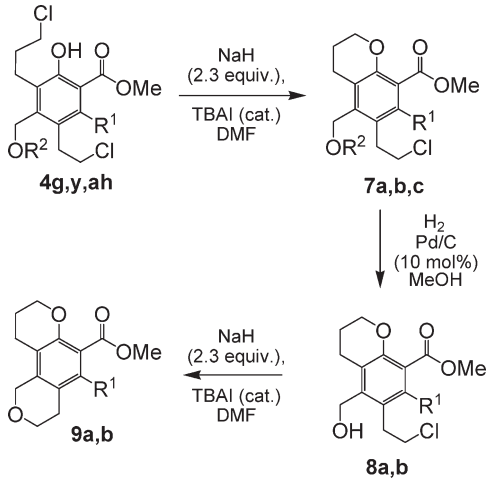
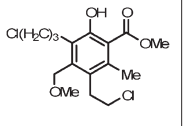
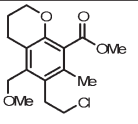
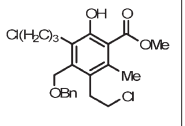
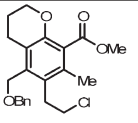
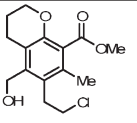
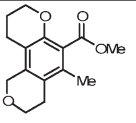
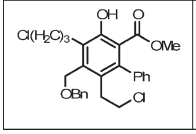
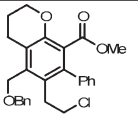
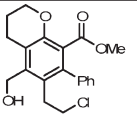
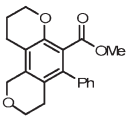


TABLE 4. Synthesis of Chromanes 7a−c, 8a,b, and 9a,b

4g,y,ah	% (7)[a]		% (8)[a]		% (9)[a]	
		a 69				
		b 73		a 96		a 47
		c 63		b 61		b 80

[a]Yields of isolated products.

Anal. Calcd for $C_{13}H_{17}ClO_4$ (272.72): C, 57.25; H, 6.28. Found: C, 57.24; H, 6.39.

4-Benzyloxymethyl-5-(2-chloroethyl)-6-methylsalicylic Acid Methyl Ester (4q). Starting with **2c** (0.232 g, 1.00 mmol), **3a** (0.391 g, 1.50 mmol), and $TiCl_4$ (0.22 mL, 2.00 mmol) in CH_2Cl_2 (100 mL), **4q** was obtained as a pale yellow solid (0.162 g, 46%). Mp = 90−93 °C. R_f = 0.54 (heptane/EtOAc = 1:1). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.50 (s, 3H), 3.07−3.14 (m, 2H), 3.50−3.57 (m, 2H), 3.97 (s, 3H), 4.52 (s, 2H), 4.60 (s, 2H), 6.95 (s, 1H), 7.31−7.34 (m, 5H), 10.63 (s, 1H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 18.3, 32.6, 42.9, 52.3, 70.9, 72.8, 113.5, 116.6, 127.0, 127.9, 128.0, 128.5, 137.6, 139.6, 143.4, 160.3, 171.6. IR (ATR, cm^{-1}): ν = 3030 (w), 2834 (w), 1651 (s), 1435 (s), 1197 (m), 1111 (m), 737 (m). MS (EI, 70 eV): m/z = 348 (M^+, ^{35}Cl, 4), 242 (43), 210 (100), 161 (34), 91, (99). HRMS (EI): calcd for $C_{19}H_{21}ClO_4$ ($[M]^+$, ^{35}Cl) 348.11229, found 348.11328. Anal. Calcd for $C_{19}H_{21}ClO_4$ (348.82): C, 65.42; H, 6.07. Found: C, 64.56; H, 5.97.

General Procedure for the Synthesis of Products 5 and 8. To a EtOAc solution (10 mL) of **4** or **7** (1.0 mmol) was added Pd/C (10 wt % Pd, 10 mol %) at 20 °C under argon atmosphere. The flask was evacuated and filled with hydrogen (3×), and the mixture was stirred under hydrogen atmosphere for 48 h. The mixture was filtered (Celite) and washed with EtOAc (300 mL), and the aqueous and the organic layers were separated. The latter was dried (Na_2SO_4) and filtered, and the filtrate was concentrated in vacuo. The residue was purified by chromatography (silica gel, heptanes/EtOAc = 10:1→5:1).

5-(2-Chloroethyl)-4-hydroxymethyl-6-methylsalicylic Acid Methyl Ester (5a). Starting with **4q** (0.091 g, 0.26 mmol) and Pd/C (0.028 g, 0.026 mmol Pd) in ethyl acetate (3 mL), **5a** was obtained as a colorless solid (0.041 g, 61%). Mp = 86−88 °C. R_f = 0.20 (heptane/EtOAc = 1:1). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.92 (s, 1H), 2.49 (s, 3H), 3.08−3.14 (m, 2H), 3.52−3.59 (m, 2H), 3.97 (s, 3H), 4.71 (s, 2H), 6.94 (s, 1H), 10.67 (s, 1H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 18.3, 32.2, 42.9, 52.3, 63.6, 113.3, 115.0, 126.2, 139.6, 145.9, 160.5, 171.6. IR (ATR, cm^{-1}): ν = 3374 (m), 3020 (w), 2918 (w), 1661 (s), 1445 (m), 1383 (w), 1182 (m), 1138 (m), 699 (m), 599 (w). MS (GC, 70 eV): m/z = 260 (M^+, ^{37}Cl, 7), 258 (M^+, ^{35}Cl, 22), 226 (64), 177 (100). HRMS (EI): calcd for $C_{12}H_{15}ClO_4$ ($[M]^+$, ^{35}Cl) 258.06534, found 258.06482.

General Procedure for the Synthesis of Products 6, 7, and 9. To a DMF solution (20 mL) of **4**, **5**, or **8** (1.0 mmol) was added TBAI (2.0 mmol) under argon atmosphere, and the reaction mixture was cooled to −78 °C. The cooling bath was replaced by an ice/NaCl mixture (−23 °C), and NaH (2.3 mmol) was added. After the mixture was stirred for 14−20 h, EtOAc (5 mL) and ice/water (5 mL) were added, and the solution was neutralized with hydrochloric acid (10%). The organic and the aqueous layers were separated, and the latter was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried (Na_2SO_4) and filtered, and the filtrate was concentrated in vacuum. The residue was purified by chromatography (silica gel, heptanes/EtOAc = 10:1→3:1).

6-(2-Chloroethyl)-5-methoxymethyl-7-methylchromane-8-carboxylic Acid Methyl Ester (7a). Starting with **4g** (0.050 g, 0.14 mmol), TBAI (0.106 g, 0.29 mmol), and NaH (0.009 g, 0.22 mmol NaH) in DMF (2 mL), **7a** was obtained as a colorless solid (0.031 g, 69%). Mp = 92−93 °C. R_f = 0.36 (heptane/EtOAc = 1:1). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.96−2.06 (m, 2H), 2.21 (s, 3H), 2.82 (t, ^3J = 6.5 Hz, 2H), 3.09−3.16 (m, 2H), 3.43 (s, 3H), 3.50−3.56 (m, 2H), 3.89 (s, 3H), 4.11−4.15 (m, 2H), 4.40 (s, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 16.4, 22.0, 22.1, 32.9, 43.3, 52.3, 58.6, 66.1, 68.1, 120.7, 124.5, 128.2, 132.1, 136.5, 150.5, 169.2. IR (ATR, cm^{-1}): ν = 2989 (w), 2918 (w), 1725 (s), 1446 (m), 1283 (s), 1201 (m), 1118 (m), 1079 (s), 792 (m), 728 (m). MS (EI, 70 eV): m/z = 314 (M^+, ^{37}Cl, 14), 312 (M^+, ^{35}Cl, 47), 280 (100), 245 (97), 233 (90), 213 (71), 201 (54). HRMS (EI): calcd for $C_{16}H_{21}ClO_4$ ($[M]^+$, ^{35}Cl) 312.11229, found 312.11187. Anal. Calcd for $C_{16}H_{21}ClO_4$ (312.79): C, 61.44; H, 6.77. Found: C, 61.34; H, 6.82.

6-(2-Chloroethyl)-5-hydroxymethyl-7-methylchromane-8-carboxylic Acid Methyl Ester (8a). Starting with **7b** (0.114 g, 0.29 mmol) and Pd/C (0.031 g, 0.029 mmol Pd) in ethyl acetate (3 mL), **8a** was obtained as a colorless solid (0.083 g, 96%). R_f = 0.09 (heptane/EtOAc = 1:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.65 (s, 1H), 1.98−2.06 (m, 2H), 2.21 (s, 3H), 2.88 (t, ^3J = 6.6 Hz, 2H), 3.14−3.20 (m, 2H), 3.54−3.60 (m, 2H), 3.90 (s, 3H), 4.13−4.16 (m, 2H), 4.69 (s, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 16.4, 22.0, 22.1, 32.5, 43.5, 52.3, 58.5, 66.1, 120.3, 124.6, 127.7, 132.3, 138.7, 150.7, 169.2. IR (ATR, cm^{-1}): ν = 3435 (br, w), 2950 (w), 1727 (s), 1440 (m), 1197 (m), 1114 (s), 804 (m), 724 (m). MS (EI, 70 eV): m/z = 300 (M^+, ^{37}Cl, 16), 298 (M^+, ^{35}Cl, 60), 280 (53), 267 (37), 249 (100). HRMS (EI): calcd for $C_{15}H_{19}ClO_4$ ($[M]^+$, ^{35}Cl) 298.09664, found 298.09631. Anal. Calcd for $C_{15}H_{19}ClO_4$ (298.76): C, 60.30; H, 6.41. Found: C, 60.71; H, 6.39.

7-Hydroxy-5-methylisochromane-6-carboxylic Acid Methyl Ester (6a). Starting with **5a** (0.100 g, 0.39 mmol), TBAI (0.288 g, 0.78 mmol), and NaH (0.036 g, 0.90 mmol NaH) in DMF (10 mL), **6a** was obtained as a colorless solid (0.054 g, 62%). Mp = 89−90 °C. R_f = 0.36 (heptane/EtOAc = 1:1). An alternative synthesis of **5a** is based on the use of Me_3SiOTf rather than $TiCl_4$ in 10 mL of CH_2Cl_2. Starting with **1a** (0.156 g, 1.00 mmol), **2a** (0.391 g, 1.50 mmol), and Me_3SiOTf (0.36 mL, 2.00 mmol) in CH_2Cl_2 (10 mL), **5a** was obtained as a colorless solid (0.045 g, 20%). R_f = 0.45 (heptane/EtOAc = 3:1). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.40 (s, 3H), 2.67 (t, ^3J = 5.8 Hz, 2H), 3.96 (s, 3H), 3.97 (t, ^3J = 5.8 Hz, 2H), 4.70 (s, 2H), 6.50 (s, 1H), 10.65 (s, 1H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 17.6, 26.3, 52.2, 65.7, 68.3, 110.6, 112.2, 123.9, 139.4, 141.8, 159.4, 171.8. IR (ATR, cm^{-1}): ν = 3014 (w), 2849 (w), 1662 (s), 1445 (m), 1201 (m), 1120 (s), 804 (m). MS (GC, 70 eV): m/z = 222 (M^+, 39), 190 (100), 160 (31), 104 (25). HRMS (EI): calcd for $C_{12}H_{14}O_4$ ($[M]^+$) 222.08866, found 222.08853.

1,3,4,8,9,10-Hexahydropyrano[3,4-*f*]chromene-6-carboxylic Acid Methyl Ester (9a). Starting with **8a** (0.060 g, 0.20 mmol), TBAI (0.155 g, 0.42 mmol), and NaH (0.012 g, 0.30 mmol NaH) in DMF (3 mL), **9a** was obtained as a colorless solid (0.025 g, 47%). Mp = 145−147 °C. R_f = 0.07 (heptane/EtOAc = 1:1). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.96−2.06 (m, 2H), 2.10 (s, 3H), 2.46 (t, ^3J = 6.6 Hz, 2H), 2.62 (t, ^3J = 5.7 Hz, 2H), 3.90 (s, 3H), 3.92 (t, ^3J = 5.7 Hz, 2H), 4.11−4.15 (m, 2H), 4.61 (s, 2H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 15.4, 20.3, 21.7, 25.8, 52.2, 64.9, 66.1, 66.1, 115.5, 121.9, 123.8, 131.6, 134.8, 149.3, 169.3. IR (ATR, cm^{-1}): ν = 2963 (w), 2849 (w), 1721 (s), 1453 (m), 1284 (s), 1203 (m), 1102 (s), 866 (m), 734 (w). MS (GC, 70 eV): m/z = 262 (M^+, 100), 247 (22), 232 (50), 203 (22). HRMS (EI): calcd for $C_{15}H_{18}O_4$ ($[M]^+$) 262.11996, found 262.11980. Anal. Calcd for $C_{15}H_{18}O_4$ (262.30): C, 68.68; H, 6.92. Found: C, 68.44; H, 7.02.

Acknowledgment. Financial support by the State of Mecklenburg-Vorpommern (scholarships for V.K. and S.M.) is gratefully acknowledged.

Supporting Information Available: Experimental procedures, compound characterization, and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.