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Synthesis of functionalized benzopyrans by sequential [3+3]-cyclization—Williamson reactions of 1,3-bis(trimethylsilyloxy)-7-chlorohepta-1,3-dienes

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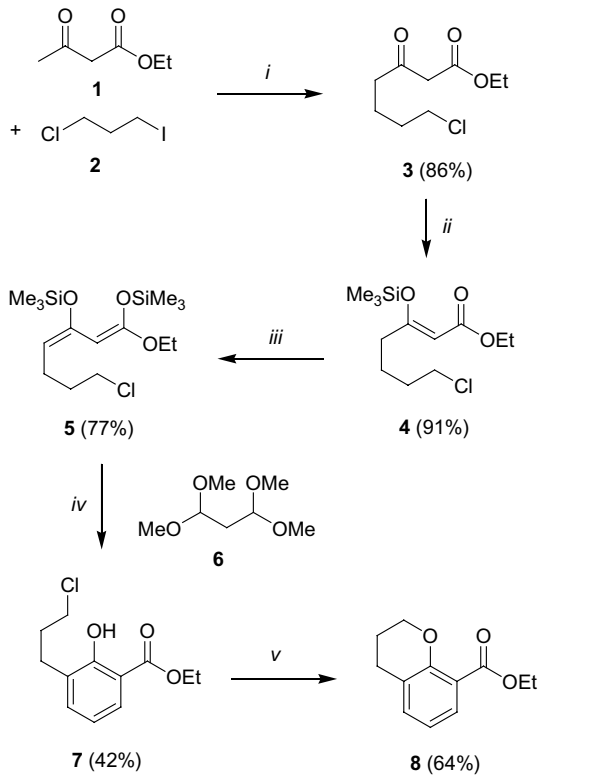
Abstract—Functionalized benzopyrans were regioselectively prepared by [3+3]-cyclization of 1,3-bis(trimethylsilyloxy)-7-chlorohepta-1,3-dienes with 3-silyloxy-2-eno-1-ones and subsequent intramolecular Williamson reactions of the salicylates thus formed.

1,3-Bis-silyl enol ethers—electroneutral equivalents of 1,3-dicarbonyl dianions—represent versatile synthetic building blocks in [3+2]-, [3+3]-, [4+2]- and [4+3]-cyclizations which provide a convenient access to a variety of pharmacologically relevant ring systems.[1–3] For example, Chan and co-workers reported an efficient one-pot synthesis of salicylates based on [3+3] cyclizations of 1,3-bis-silyl enol ethers with 3-silyloxyalk-2-en-1-ones or 1,1,3,3-tetramethoxypropane.[3,4] In all reactions reported to date, mainly nonfunctionalized 1,3-bis-silyl enol ethers have been employed. [5] Herein, we wish to report the synthesis and synthetic application of what are, to the best of our knowledge, the first halide-substituted 1,3-bis-silyl enol ethers.[6,7] The strategic placement of the latent chloride functionality allowed a convenient synthesis of functionalized benzopyrans by sequential [3+3]-cyclization—Williamson reactions.

The reaction of the dianion of ethyl acetoacetate (**1**) with 1-iodo-3-chloropropane (**2**) afforded, following a known procedure,[8] ethyl 7-chloro-3-oxoheptanoate (**3**). Treatment of the latter with Me_3SiCl/NEt_3 gave the silyl enol ether **4** (Scheme 1). Deprotonation of **4** with LDA and subsequent addition of Me_3SiCl afforded the novel 1,3-bis-silyl enol ether **5** in good yield. An intramolecular



Scheme 1. Synthesis of **8**. Reagents and conditions: i. (1) 2.3 LDA, THF, 0 °C, 1 h; (2) **2**, −78 → 20 °C; ii. Me_3SiCl, NEt_3, toluene, 20 °C, 24 h; iii. (1) LDA, THF, −78 °C, 1 h, (2) Me_3SiCl, 20 °C, −78 → 20 °C; iv. $TiCl_4$, CH_2Cl_2, −78 → 20 °C; v. NaH, TBAI, THF, 20 °C.

Keywords: Benzopyrans; Cyclizations; Ethers; Lewis acids; Silyl enol ethers.

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nucleophilic substitution of the chloride group or elimination of hydrogen chloride was not observed. The [3+3] cyclization of **5** with 1,1,3,3-tetramethoxypropane (**6**), following the conditions reported by Chan,[4] afforded the salicylate **7** with very good chemoselectivity. Treatment of a THF solution of **7** with sodium hydride (NaH) in the presence of tetrabutylammonium iodide (TBAI) afforded the benzopyran **8** in good yield.

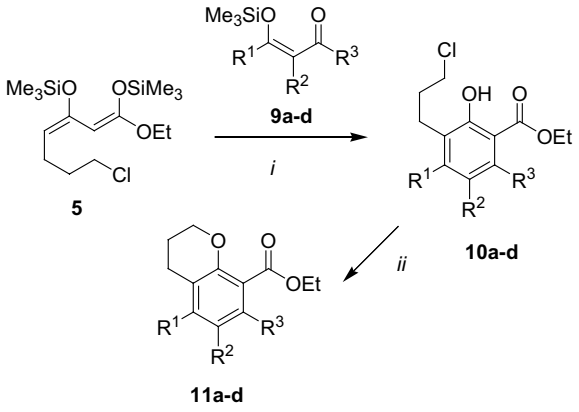
The [3+3] cyclization of 1,3-bis-silyl enol ether **5** with 3-silyloxyalk-2-en-1-ones **9** was next studied. The reaction of **5** with **9a**–**d**, following the conditions reported by Chan,[4] afforded the salicylates **10a**–**d** (Scheme 2). Salicylates **10a**–**d** were transformed into the benzopyrans **11a**–**d** in good yields (Table 1).[9,10]

The cyclization of 1,3-bis-silyl enol ether **5** with silyl enol ether **9e**, prepared from 2-(hydroxymethylidene)cyclohexan-1-one, gave the salicylate **10e** with very good regioselectivity (Scheme 3). Treatment of **10e** with NaH/TBAI afforded the tricyclic benzopyran **11e**.

The cyclization of **5** with **9f,** available by silylation of 2-acetylcyclohexanone, regioselectively afforded **10f** (Scheme 4). The latter was transformed into the tricyclic benzopyran **11f**.

The cyclization of **5** with **9g**, prepared from 2-acetyltetralone, regioselectively afforded **10g** which was transformed into the tetracyclic benzopyran **11g** (Scheme 5).

The $TiCl_4$-mediated cyclization of **5** with 1,1-diacetylcyclopropane (**12**), following our recently reported

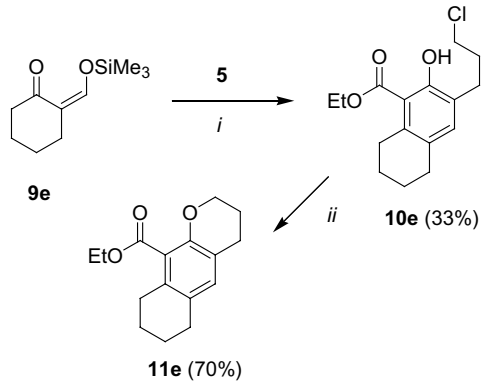


Scheme 2. Synthesis of benzopyrans **11a**–**d** Reagents and conditions: i. $TiCl_4$, CH_2Cl_2, −78 → 20 °C; ii NaH, TBAI, THF, 20 °C.

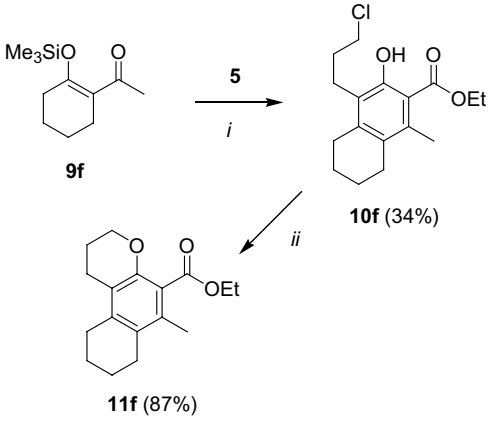
Table 1. Products and yields

10,**11**	R^1	R^2	R^3	% (**10**)[a]	% (**11**)[a]
a	Me	H	Me	46	70
b	Me	Me	Me	52	90
c	Me	Et	Me	43	82
d	Et	H	Et	42	65

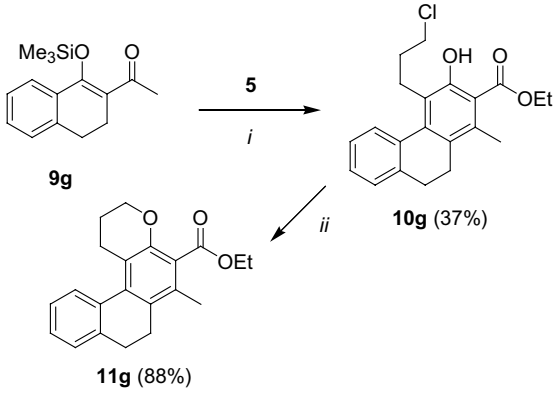
[a] Yields of isolated products.



Scheme 3. Synthesis of benzopyran **11e** Reagents and conditions: i. $TiCl_4$, CH_2Cl_2, −78 → 20 °C; ii. NaH, TBAI, THF, 20 °C.

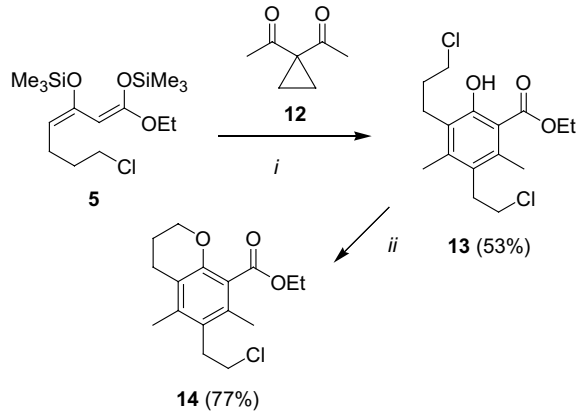


Scheme 4. Synthesis of benzopyran **11f** Reagents and conditions: i. $TiCl_4$, CH_2Cl_2, −78 → 20 °C; ii. NaH, TBAI, THF, 20 °C.



Scheme 5. Synthesis of benzopyran **11g** Reagents and conditions: i. $TiCl_4$, CH_2Cl_2, −78 → 20 °C; ii. NaH, TBAI, THF, 20 °C.

methodology,[11] regioselectively afforded the highly functionalized salicylate **13** by a domino '[3+3]-cyclization-homo-Michael' reaction (Scheme 6). Salicylate **13** was transformed into the chlorinated benzopyran **14**.



Scheme 6. Synthesis of benzopyran **14** Reagents and conditions: i. $TiCl_4$ (2 equiv), CH_2Cl_2, $-78 \rightarrow 20$ °C; ii. NaH, TBAI, THF, 20 °C.

Acknowledgments

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References and notes

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9. *General procedure*: to a CH_2Cl_2 solution of **5** and **9** was dropwise added $TiCl_4$ at -78 °C under argon atmosphere. The solution was stirred at -78 °C for 30 min and was subsequently warmed to 20 °C within 18 h. To the solution was added a saturated aqueous solution of $NaHCO_3$. The organic and the aqueous layer were separated and the latter was extracted with ether. The combined organic layers were dried (Na_2SO_4), filtered and the filtrate was concentrated in vacuo. The residue was purified by chromatography (silica gel, *n*-hexane–EtOAc 30/1). *Synthesis of* **10a**: starting with **5** (2.90 g, 8.2 mmol), **9a** (1.42 g, 8.2 mmol), $TiCl_4$ (1.55 g, 8.2 mmol) in CH_2Cl_2 (15 ml), **10a** was isolated as a colourless oil (1.02 g, 46%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.42 (t, 3H, CH_3CH_2O), 2.00 (m, 2 H, $CH_2CH_2CH_2Cl$), 2.25 (s, 3 H, CH_3), 2.49 (s, 3 H, CH_3), 2.78 (t, 2 H, $CH_2CH_2CH_2Cl$), 3.61 (t, 2 H, $CH_2CH_2CH_2Cl$), 4.42 (q, 2 H, CH_3CH_2O), 6.54 (s, 1 H, CH), 11.76 (s, 1 H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.2 (CH_3), 19.8 (CH_3), 23.6 (CH_2), 23.9 (CH_2), 31.8 (CH_2), 45.3 (CH_2), 61.4 (CH_2), 109.7 (C), 124.8 (CH), 125.2 (C), 138.4 (C), 143.1 (C), 161.1 (C), 172.2 (C). MS (EI, 70 eV): *m*/*z* = 272 (M^+, 6), 271 (M^+ + 1), 270 (M^+, 21), 224 (20), 189 (100), 162 (25), 161 (23), 91 (10). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2977 (s), 2937 (s), 1938 (w), 1653 (s), 1563 (m), 1447 (s), 1396 (s), 1376 (s), 1349 (s), 1311 (s), 1273 (s), 1232 (s), 1175 (s), 1037 (s), 848 (s). UV–vis (nm): λ_{max} (**1g** ε) = 215.8 (4.45), 253.4 (4.00), 315.7 (3.60). HRMS (FT-ICR): calcd for $C_{14}H_{20}O_3Cl$ ($[M+1]^+$): 271.11009; found: 271.10950. All new compounds gave satisfactory spectroscopic data and correct elemental analyses and/or high-resolution mass data.
10. *General procedure*: to a THF solution of **10** and of NaH was added TBAI. The reaction mixture was stirred at 20 °C for 20 h. The mixture was directly purified by column chromatography (silica gel, *n*-hexane–EtOAc 30/1 $\rightarrow$ 20/1). *Synthesis of* **11a**: starting with **10a** (59 mg, 0.22 mmol), NaH (8 mg, 0.33 mmol), *n*-Bu_4NI (144 mg, 0.44 mmol), **11a** was isolated as a colourless solid (36 mg, 70%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.36 (t, 3 H, CH_3CH_2O), 2.02 (m, 2 H, CH_2), 2.16 (s, 3 H, CH_3), 2.21 (s, 3 H, CH_3), 2.59 (t, 2 H, CH_2), 4.14 (t, 2 H, CH_2), 4.38 (q, 2 H, CH_3CH_2O), 6.75 (s, 1 H, CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.3 (CH_3), 18.9 (CH_3), 19.0 (CH_3), 22.0 (CH_2), 22.2 (CH_2), 60.9 (CH_2), 66.1 (CH_2), 118.6 (C), 120.9 (C), 123.1 (CH), 133.1 (C), 138.6 (C), 151.9 (C), 168.7 (C). MS (EI, 70 eV): *m*/*z* = 235 (M^++1, 12), 234 (M^+, 87), 189 (100), 161 (31), 132 (20), 102.8, 77 (12). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3414 (m), 2977 (s), 2938 (s), 1716 (s), 1612 (m), 1574 (m), 1457 (s), 1369 (m), 1303 (s), 1273 (s), 1151 (s), 1106 (s), 1056 (s), 959 (m). UV–vis (nm): λ_{max} (**1g** ε) = 206.7 (4.48), 284.5 (3.34).
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