Synthesis of Homophthalates by [3 + 3] Cyclocondensation Reactions of 1,3-Bis(silyloxy)-1,3-butadienes with Silylated Methyl 3,5-Dioxohexanoate

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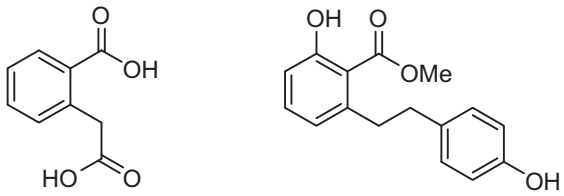
Homophthalates were prepared by formal [3 + 3] cyclocondensation of 1,3-bis(silyl enol ethers) with silylated methyl 3,5-dioxohexanoate.

Key words: Homophthalates, Cyclizations, Silyl Enol Ethers, Regioselectivity

Introduction

Homophthalates (Fig. 1) are of considerable relevance to the synthesis of natural products [1]. Lunularic acid (6-(4-hydroxyphenethyl)salicylic acid; Fig. 1) plays an important role in the regulation of the growth of plants [2]. Homophthalates also represent versatile synthetic building blocks. For example, Arai *et al.* reported the condensation of 3-methoxyhomophthalic acid with anisol to give an isocumarine which was transformed by catalytic hydrogenation and reaction with boron tribromide into lunularic acid [3]. Another example is the synthesis of sclerin from methyl 3-oxopentanoate *via* a dimethyl homophthalate [4]. Sclerin is a natural product isolated from the fungus *Sclerotinia libertiana* and is known to act as a phytohormon [5]. Homophthalates were earlier prepared by cyclization of 1,3-bis(silyl enol ethers) [6 – 9] with trimethylorthoacetate, acetyl chloride or acetic anhydride [4 – 10]. The reaction follows a 2 : 1 stoichiometry and proceeds by condensation to give an open-chain adduct and by subsequent formal [3 + 3] cyclocondensation. Homophthalates are also available by [4 + 2] cycloaddition of 1,3-bis(silyl enol ethers) with dimethyl allene-1,3-dicarboxylate [11]. Herein, we report a stepwise synthesis of homophthalates by formal [3 + 3] cyclocondensation of 1,3-bis(silyl enol ethers) with silylated 3,5-dioxoesters.

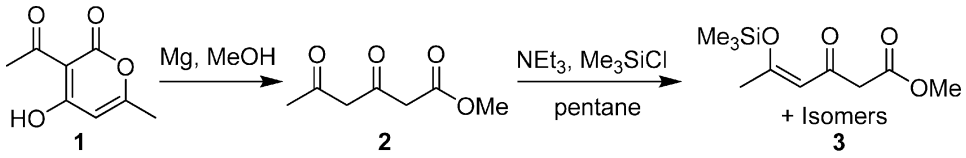


Homophthalic acid **Lunularic acid**

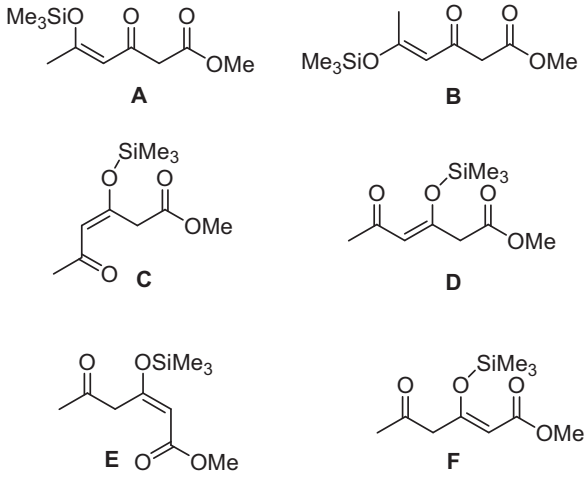
Fig. 1. Homophthalic acid and lunularic acid.

Results and Discussion

Methyl 3,5-dioxohexanoate (**2**) was prepared by reaction of dehydracetic acid (**1**) with magnesium methanolate in 89 % yield (Scheme 1) [12]. Silylation of **2** resulted in the formation of silyl enol ether **3** (77 % yield) which exists as a mixture of three isomers which were not structurally assigned. The 6 theoretically possible regioisomers and E/Z-isomers are depicted in Scheme 2. 1,3-Diketones are more readily enolized than β-ketoesters. Therefore, we believe that isomers **E** and **F** are not present, although we do not have an experimental proof. Detailed NMR experiments were not possible, due to the unstable nature of the product. However, the exact structure of the isomers is presumably not relevant for the subsequent cyclization reaction, because it is known that the silyl groups and double bond configurations can be interconverted un-



Scheme 1. Synthesis of **3**.



Scheme 2. Possible isomers of **3**.

der the conditions of $TiCl_4$-mediated [3+3] cyclization reactions with 1,3-bis(silyl enol ethers) [10].

The $TiCl_4$-mediated formal [3 + 3] cyclization of **3** with 1,3-bis(silyl enol ether) **4a**, prepared from methyl acetoacetate, resulted in the formation of homophthalate **5a** in 45 % yield (Scheme 3, Table 1). The best yield was obtained when 1.0 equiv. of **3**, 1.5 equiv. of **4a** and 1.1 equiv. of $TiCl_4$ were employed, and when the reaction was carried out in a highly concentrated solution (c(**3**) = 0.4 mol L^{-1}). The reaction proceeded with excellent regioselectivity. Only the regioisomer containing a homophthalate structure with both ester groups located *ortho* to each other was obtained. The

Table 1. Synthesis of **5a**–**c** and *iso*-**5a**–**c**.

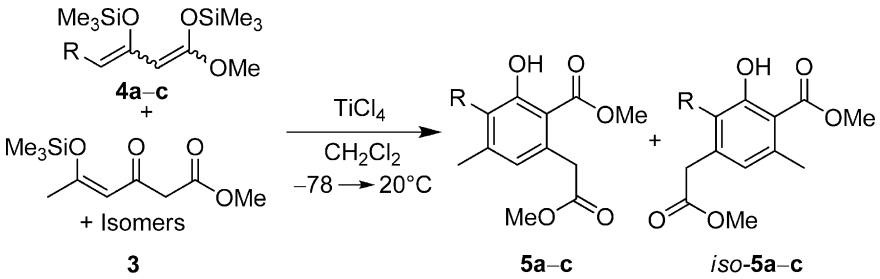
4, **5**	R	**5** (%) [a]	*iso*-**5** (%) [a]
a	H	45	0
b	Me	20	10
c	Et	41	0

[a] Yields of isolated products.

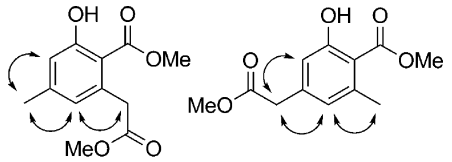
other isomer, containing the ester groups located *para* to each other was not observed. The structure of **5a** (isomer **A**) was established by a ^{1}H,^{1}H-NOESY experiment (Scheme 4). A ^{1}H,^{1}H-NOESY correlation was observed between the methyl group (δ = 2.30 ppm) and the aromatic protons (δ = 6.54 ppm and δ = 6.77 ppm). The methylene group (δ = 3.84 ppm) only showed a correlation with the aromatic proton resonating at δ = 6.54 ppm. The NOE correlations expected for isomer **B** were not observed.

The structure was independently confirmed by an X-ray crystal structure analysis (Fig. 2). Both intra- and intermolecular hydrogen bonds are observed. The intramolecular distances are d(O(3)–H···O(1) = 1.79(2) Å and d(O(3)···O(1)) = 2.565(1) Å. The intermolecular distances are d(O(3)–H···O(3)* = 2.853 Å and d(O(3)···O(3)*) = 3.022 Å (* = neighboring molecule). Between the benzene rings π-stacking interactions are observed with d_{min}(center) = 3.690 Å.

The cyclization of 1,3-bis(silyl enol ether) **4b** with **3** afforded a separable mixture of the regioisomers **5b** (20 %) and *iso*-**5b** (10 %). The structures were established by ^{1}H,^{1}H-NOESY und ^{1}H,^{13}C-HMBC experi-



Scheme 3. Synthesis of **5a**–**c** and *iso*-**5a**–**c**.



Isomer A **Isomer B**

Scheme 4. Observed NOESY correlations of **5a** (isomer **A**) and expected correlations of *iso*-**5a** (isomer **B**).

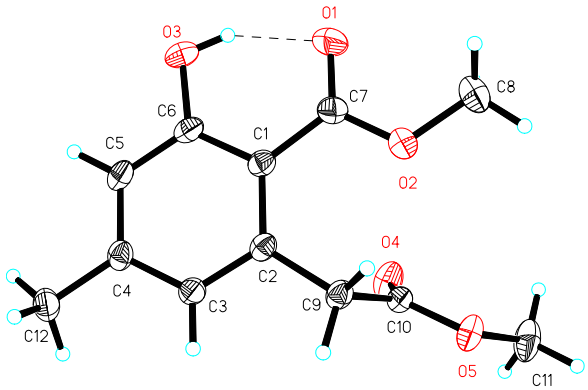
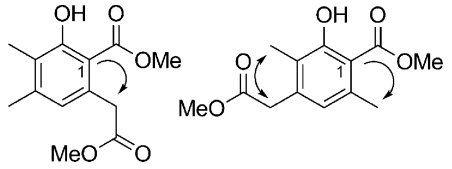


Fig. 2. ORTEP plot of **5a** (displacement ellipsoids at the 50 % probability level; H atoms as spheres with arbitrary radii).



Scheme 5. Diagnostic NOESY correlations (double headed arrow) and HMBC correlations (single headed arrow) of **5b** (left) and *iso*-**5b** (right).

ments (Scheme 5). A diagnostic ^{1}H,^{1}H-NOESY correlation is observed for **5b** between the methyl group located at carbon C-3 and the methylene group. For **5b**, a ^{1}H,^{13}C-HMBC correlation was observed between carbon atom C-1 (^{13}C: $\delta = 109.0$ ppm) and the methylene group (^{1}H: $\delta = 3.81$ ppm). For *iso*-**5b**, a ^{1}H,^{13}C-HMBC correlation was observed between carbon atom C-1 (^{13}C: $\delta = 110.6$ ppm) and the methyl group located at carbon C-6 (^{1}H: $\delta = 2.48$ ppm).

The cyclization of diene **4c** with **3** afforded homophthalate **5c** in 41 % yield. The structure of the product was established based on the comparison of the ^{1}H NMR chemical shifts of the methylene protons of **5a**, **5b**, **5c** and *iso*-**5b**. This comparison suggests that the methylene protons of the homophthalates, containing the methylene group *ortho* to the methoxycarbonyl group, are shifted downfield by 0.2 ppm as compared to the regioisomer in which the methylene group is located *para* to the methoxycarbonyl group.

The regioselective formation of homophthalates **5a**–**c** can be explained by the assumption that the more nucleophilic terminal carbon atom of the diene undertakes an attack onto the sterically less hindered lateral keto group of **3** (and not onto the more hindered central keto group). In addition, a chelation control (interaction of the Lewis acid $TiCl_4$ with the ester groups of both substrates) may also play a role.

Experimental Section

*Synthesis of **3***

Compound **2** (1.0 equiv.) was dissolved in pentane (2 mL per mmol), and triethylamine (1.3 equiv.) was added under argon atmosphere. After stirring for 30 min, trimethylsilyl chloride (1.5 equiv.) was dropwise added. The mixture was stirred for 3 days at room temperature. The mixture was filtered under argon atmosphere, and the filtrate was concentrated *in vacuo*. Starting with **2** (2.372 g, 15.0 mmol), triethylamine (1.973 g, 19.5 mmol) and Me_3SiCl (2.444 g, 22.5 mmol) in pentane (30 mL), **3** was isolated as an orange oil (2.67 g, 77 %). The compound exists as a mixture of three isomers (see Scheme 2) which were not structurally assigned. The exact configuration is irrelevant for the cyclization reaction. Therefore, the ^{1}H NMR signals are given with the overall integration. The compound is unstable and has to be used directly after its preparation. – ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 0.28$, 0.28, 0.29 (3 × s, 9H, $Si(CH_3)_3$), 2.14, 2.28, 2.20 (3 × s, 3H, CH_3), 3.34, 3.39 (3 × s, 2H, CH_2, partial signal overlap), 3.65, 3.72, 3.74 (3 × s, 3H, OCH_3), 5.25 (3 × s, 1H, CH, signal overlap).

*General procedure for the synthesis of homophthalates **5a–c***

To a CH_2Cl_2 solution of **3** was added **4** and, subsequently, $TiCl_4$ at −78 °C. The temperature of the solution was allowed to warm to 20 °C during 14 h with stirring. To the solution was added hydrochloric acid (10 %, 20 mL), and the organic and the aqueous layer were separated. The latter was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and the filtrate was concentrated *in vacuo*. The residue was purifed by chromatography (silica gel, *n*-heptane, EtOAc).

*Methyl 6-(2-methoxy-2-oxoethyl)-4-methyl-salicylate (**5a**)*

Starting with **3** (0.230 g, 1.00 mmol), **4a** (0.391 g, 1.50 mmol) and $TiCl_4$ (0.12 mL, 1.10 mmol) in CH_2Cl_2 (2.5 mL), **5a** was isolated as a colorless solid (0.164 g, 45 %);

m. p. 79 – 81 °C. – $R_f = 0.39$ (heptane-EtOAc 1 : 1). – ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.30$ (s, 3H, CH_3), 3.69 (s, 3H, CH_2COOCH_3), 3.84 (s, 2H, CH_2), 3.87 (s, 3H, OCH_3) 6.54 (s, 1H, H-5), 6.77 (s, 1H, H-3), 11.22 (s, 1H, OH). – ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 21.5$ (CH_3), 42.5 (CH_2), 51.8 (OCH_3), 109.4 (C-1), 117.7, 125.3 (CH_{Ar}), 136.0 (C-6), 145.7 (C-4), 163.1 ($C_{Ar}OH$), 171.0 (CH_2COOCH_3), 172.0 ($COOCH_3$). – IR (ATR, cm^{-1}): $\tilde{\nu} = 3100$ (w), 2951 (w), 1737 (s), 1657 (s), 1437 (s), 1164 (m), 733 (m). – MS (GC, 70 eV): m/z (%) = 238 (42) $[M]^+$, 206 (52), 178 (86), 174 (43), 163 (100), 119 (42). – HRMS (EI, 70 eV): m/z (%) = 238.08419 (calcd. 238.08358 for $C_{12}H_{14}O_5$, $[M]^+$). – Anal. for $C_{12}H_{14}O_5$(238.24): calcd. C 60.50, H 5.92; found C 61.13, H 5.96.

*Methyl 6-(2-methoxy-2-oxoethyl)-3,4-dimethyl-salicylate (**5b**)*

Starting with **3** (0.230 g, 1.00 mmol), **4b** (0.433 g, 1.50 mmol) and $TiCl_4$ (0.12 mL, 1.10 mmol) in CH_2Cl_2 (2.5 mL), **5b** (0.051 g, 20 %) and *iso*-**5b** (0.035 g, 10 %) were isolated as colorless solids; m. p. 100 – 102 °C. – $R_f =$ 0.37 (heptane-EtOAc 1 : 1). – ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 2.16$ (s, 3H, C3-CH_3), 2.27 (s, 3H, C4-CH_3), 3.68 (s, 3H, CH_2COOCH_3), 3.81 (s, 2H, CH_2), 3.87 (s, 3H, OCH_3), 6.54 (s, 1H, Ar), 11.60 (s, 1H, OH). – ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 11.5$ (C3-CH_3), 20.4 (C4-CH_3), 42.5 (CH_2), 51.8, 51.8 (OCH_3), 109.0 (C-1), 124.6 (C-3), 125.4 (CH_{Ar}), 132.6 (C-6), 143.8 (C-4), 161.2 ($C_{Ar}OH$), 171.6 (CH_2COOCH_3), 172.3 ($COOCH_3$). – IR (ATR, cm^{-1}): $\tilde{\nu} = 3024$ (w), 2943 (w), 1731 (s), 1654 (m), 1429 (m), 1135 (m), 771 (m). – MS (GC, 70 eV): m/z (%) = 252 (46) $[M]^+$, 220 (100), 192 (55), 160 (49), 133 (26). – HRMS (EI, 70 eV): m/z (%) = 252.09970 (calcd. 252.09923 for $C_{13}H_{16}O_5$, $[M]^+$). – Anal. for $C_{13}H_{16}O_5$(252.26): calcd. C 61.90, H 6.39; found C 61.40, H 6.38.

*Methyl 4-(2-methoxy-2-oxoethyl)-3,6-dimethyl-salicylate (**iso-5b**)*

$R_f = 0.43$ (heptane-EtOAc 1 : 1). – ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 2.17$ (s, 3H, C3-CH_3), 2.48 (s, 3H, C6-CH_3), 3.61 (s, 2H, CH_2), 3.69 (s, 3H, CH_2COOCH_3), 3.94 (s, 3H, OCH_3), 6.58 (s, 1H, Ar), 11.70 (s, 1H, OH). – ^{13}C NMR (125.8 MHz, $CDCl_3$): $\delta = 11.5$, 23.8 (CH_3), 39.3 (CH_2), 52.0, 52.1 (OCH_3), 110.6 (C-1), 123.2 (C-3), 124.4 (CH_{Ar}), 137.9, 138.8 (C_{Ar}), 161.2 ($C_{Ar}OH$), 171.2 (CH_2COOCH_3), 172.5 ($COOCH_3$).

*Methyl 3-ethyl-6-(2-methoxy-2-oxoethyl)-4-methyl-salicylate (**5c**)*

Starting with **3** (0.230 g, 1.00 mmol), **4c** (0.433 g, 1.50 mmol) and $TiCl_4$ (0.12 mL, 1.10 mmol) in CH_2Cl_2 (2.5 mL), **5c** was isolated as a colorless solid (0.108 g, 41 %); m. p. 101 – 103 °C. – $R_f = 0.38$ (heptane-EtOAc 1 : 1). – ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 1.11$ (t, $^3J = 7.5$ Hz, 3H, CH_2CH_3), 2.30 (s, 3H, CH_3), 2.68 (q, $^3J = 7.1$ Hz, 2H, CH_2CH_3), 3.68 (s, 3H, CH_2COOCH_3), 3.80 (s, 2H, CH_2), 3.86 (s, 3H, OCH_3), 6.52 (s, 1H, Ar), 11.56 (s, 1H, OH). – ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 12.9$, 19.4 (CH_3), 19.5 (CH_2CH_3), 42.5 (CH_2), 51.8, 51.8 (OCH_3), 109.2 (C_{Ar}), 125.8 (CH_{Ar}), 130.5, 132.8, 143.1 (C_{Ar}), 161.1 ($C_{Ar}OH$), 171.6, 172.3 (COO). – IR (ATR, cm^{-1}): $\tilde{\nu} = 2959$ (m), 1739 (s), 1648 (m), 1436 (s), 1168 (m), 759 (m). – MS (GC, 70 eV): m/z (%) = 266 (44) $[M]^+$, 234 (60), 206 (28), 174 (100), 146 (27). – HRMS (EI, 70 eV): m/z (%) = 266.11480 (calcd. 266.11488 for $C_{14}H_{18}O_5$, $[M]^+$).

*Crystal structure determination of **5a***

Suitable single crystals of **5a** were obtained from dichloromethane. Intensity data were collected on a Bruker X8Apex Diffractometer with CCD camera (graphite-monochromatized Mo K_α radiation, $\lambda = 0.71073$ Å). *Crystal data*: Monoclinic space group $P2_1/c$, $a = 7.5776(2)$, $b = 20.1852(5)$, $c = 8.1722(2)$ Å, $\beta = 112.8560(10)°$, $Z =$ 4; $wR2 = 0.1069$ for 161 refined parameters and 3326 unique data; largest diff. peak/hole: 0.38/−0.21 e Å^{-3}. *Programs used*: Data analysis and space group determination: XPREP [13]; structure solution and refinement: SHELXS/L-97 [14, 15].

CCDC 929422 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

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