Regioselective Synthesis of 5-(2-Methoxyethyl)biphenyls by Formal [3+3] Cyclocondensations of 1,3-Bis(trimethylsilyloxy)-1,3-butadienes

Franziska Bendrath[a,b], Verena Specowius[a,b], Zharylkasyn A. Abilov[c], Ashot. S. Saghyan[d,e], Christine Fischer[b], and Peter Langer[a,b]

[a] Institut für Chemie, Universität Rostock, Albert-Einstein-Straße 3a, 18059 Rostock, Germany
[b] Leibniz Institut für Katalyse an der Universität Rostock e. V., Albert-Einstein-Straße 29a, 18059 Rostock, Germany
[c] Al-Farabi Kazakh National University, Al-Farabi ave. 71, 050040 Almaty, Kazakhstan
[d] Faculty of Chemistry, Yerevan State University, Alex Manoogian 1, 0025 Yerevan, Armenia
[e] Scientific and Production Center "Armbiotechnology" of NAS RA, Gyurjyan str. 14, 0056 Yerevan, Armenia

Reprint requests to Prof. Dr. Peter Langer. Fax: +49-381-498-6412.
E-mail: peter.langer@uni-rostock.de

Z. Naturforsch. **2013**, *68b*, 378 – 382 / DOI: 10.5560/ZNB.2013-2298
Received November 21, 2012; in revised form December 19, 2012

5-(2-Methoxyethyl)biphenyls have been prepared by regioselective formal [3+3] cyclocondensations of 1,3-bis(trimethylsilyloxy)-1,3-butadienes.

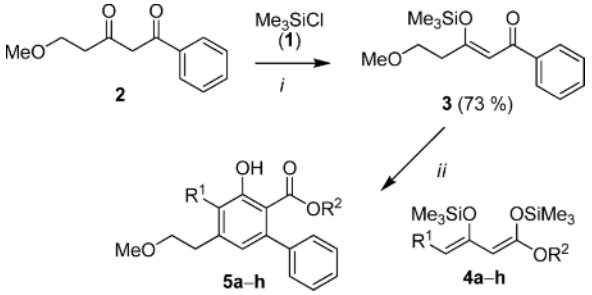
Key words: Arenes, Cyclizations, Silyl Enol Ethers, Regioselectivity

Introduction

2-Phenylethanols and their methyl ethers are present in a variety of natural products. Parent 2-phenylethanol represents an ingredient of many etheric oils which are extracted from various flowers, such as roses. Their ethers and esters are extensively used in the parfum, cosmetics and food industries [1 – 5]. Related hydroxylated natural products include hydroxytyrosol or the secoiridoidglycoside oleuropein which are extracted from the leaves and fruits of olive trees. They exhibit antioxidative, antiviral, antimicrobial, anti-inflammatory, antiproliferative and pro-apoptotic properties and are used as pharmaceuticals and as ingredients of food and cosmetics [6 – 12]. It has been shown that hydroxytyrosol is available by an industrially applicable fermentative process using genetically modified microorganisms [13]. Hydroxylated biaryls also represent pharmacologically important core structures. The cynandiones A–C [14 – 17], isolated from many plant sources, show a broad spectrum of pharmacological activities. Likewise, structurally related flavones are of considerable pharmacological relevance [18 – 24]. Biaryls are synthetically available by palladium(0)-catalyzed cross-coupling reactions [25, 26]. A limitation of this approach lies in the synthesis of the required starting materials. In fact, highly functionalized or substituted aryl halides or triflates are not readily available. An alternative strategy relies on the application of a building block strategy. In recent years, we have broadly studied the synthesis of arenes and biaryls by formal [3+3] cyclization reactions of 1,3-bis(trimethylsilyloxy)-1,3-butadienes with suitable 1,3-dielectrophiles [27 – 29]. Herein, we report a new convenient and regioselective synthesis of 5-(2-methoxyethyl)biphenyls by application of this methodology.

Results and Discussion

The reaction of commercially available 5-methoxy-1-phenylpentane-1,3-dione (**2**) with chlorotrimethylsilane (**1**) gave silyl enol ether **3** (Scheme 1). The reaction of **3** with 1,3-bis(trimethylsilyloxy)-1,3-butadienes **4a–h** [30 – 32] (1.5 – 2.0 equiv.) in the presence of $TiCl_4$ (1.1 equiv.) afforded the 5-(2-methoxyethyl)biphenyls **5a–h** in 32 % – 79 % yields (Table 1). It proved to be important to carry out the



Scheme 1. Synthesis of **5a**–**h**; *i*: NEt_3, TMSCl, *n*-pentane, 20 °C, 72 h; *ii*: 1) $TiCl_4$, CH_2Cl_2, −78 to 20 °C, 12 – 14 h; 2) 10 % aqueous HCl.

Table 1. Synthesis of **5a**–**h**.

4, **5**	R^1	R^2	Yield[a] (%) of **5**
a	H	Me	52
b	Me	Me	43
c	Et	Me	41
d	*n*Pr	Me	79
e	H	*i*Pr	32
f	H	Bn	44
g	*n*Oct	Me	40
h	*n*Dec	Me	44

[a] Yields of isolated products.

reaction in a highly concentrated solution in CH_2Cl_2 (2 mL mmol^{-1}) at −78 °C.

The products containing the phenyl group located *ortho* to the ester group were formed with excellent regioselectivity. The formation of the opposite regioisomers, containing the phenyl group located *para* to the ester group, was not observed. The moderate yields can be explained by hydrolysis or oxidative dimerization [33, 34] of the dienes. Besides the steric hindrance, the purity of each individual diene also plays an important role. The structure of **5e** was confirmed by ^{1}H,^{1}H-NOESY experiments (Fig. 1). Diagnostic correlations were observed between the protons of the phenyl group with the *iso*-propoxy group and between the CH_2 groups of the 2-methoxyethyl chain with the aromatic protons of the salicylate moiety. Comparison of the spectroscopic data of **5e** with those of the other derivatives suggest that all products are formed with the same pattern of regioselectivity.

In conclusion, we succeeded in the synthesis of 5-(2-methoxyethyl)biphenyls by formal [3+3] cyclocondensations of 1,3-bis(trimethylsilyloxy)-1,3-butadienes from readily available starting materials. The cyclizations proceeded with excellent regioselectivity. The regioselectivity may be explained by chelation of $TiCl_4$ by the methoxy and the silyloxy group which results in predominant activation of the carbon atom attached to the silyloxy group (instead of the carbonyl carbon atom).

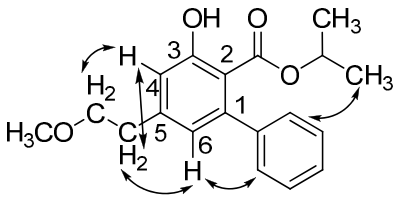


Fig. 1. ^{1}H,^{1}H-NOESY correlations of **5e**.

Experimental Section

*Synthesis of **3***

To a solution of 5-methoxy-1-phenylpentane-1,3-dione (**2**) (4.18 g, 20.29 mmol) in pentane (1 mL·mmol^{-1}) and CH_2Cl_2 (1 mL·mmol^{-1}) was added triethylamine (3.80 mL, 27.0 mmol) at 20 °C, and the solution was stirred for 30 min. Subsequently, chlorotrimethylsilane (4.15 mL, 30.50 mmol) was added, and the solution was stirred for 74 h at 20 °C. The solvent was removed *in vacuo*, and to the residue was added pentane (50 mL). The mixture was filtered, and the filtrate was concentrated *in vacuo*. The residue was again washed with pentane (50 mL), the suspension was filtered and the filtrate concentrated *in vacuo* to give **3** (73 %) as a red oil. Due to the unstable nature of the product, it was directly used after its preparation for further transformations.

*General procedure for the synthesis of 5-(2-methoxyethyl)-2-hydroxybiphenyl-carboxylates **5a**–**h***

To a solution of **3** (1.0 mmol) and of **4a**–**h** (1.5 – 2.0 mmol) in dry CH_2Cl_2 (2 mL mmol^{-1} **3**) was added $TiCl_4$ (1.1 mmol) at –78 °C. The solution was allowed to warm to 20 °C within 6 h and was stirred for 6 – 8 h at 20 °C. To the solution was added aqueous hydrochloric acid (10 %, 10 mL mmol^{-1}), and the mixture was extracted with CH_2Cl_2 (3 × 50 mL). 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).

*Methyl 2-hydroxy-4-(2-methoxyethyl)-6-phenylbenzoate (**5a**)*

Starting with **3** (557 mg, 2.0 mmol), **4a** (521 g, 2.0 mmol) and $TiCl_4$ (0.22 mL, 2.0 mmol) in CH_2Cl_2 (4 mL), **5a** was isolated by chromatography (silica gel, *n*-heptane-EtOAc = 50 : 1 to 10 : 1) (296 mg, 52 %) as a yellow oil.

– ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 2.86$ (t, $^3J = 6.8$ Hz, 2H, CH_2), 3.34 (s, 3H, OCH_3), 3.46 (s, 3H, OCH_3), 3.62 (t, $^3J = 6.8$ Hz, 2H, CH_2), 6.66 (d, $^4J = 1.5$ Hz, 1H, $C_{Ar}H$), 6.88 (d, $^4J = 1.5$ Hz, 1H, $C_{Ar}H$), 7.20 – 7.23 (m, 2H, $C_{Ar}H$), 7.30 – 7.38 (m, 3H, $C_{Ar}H$), 10.72 (s, 1H, OH). – ^{13}C NMR ($CDCl_3$, 63 MHz): δ = 36.1 (CH_2), 51.6 (OCH_3), 58.7 (OCH_3), 72.5 (CH_2OCH_3), 110.6 (C), 116.6 ($C_{Ar}H$), 123.6 ($C_{Ar}H$), 126.8 ($C_{Ar}H$), 127.5 ($C_{Ar}H$), 128.1 ($C_{Ar}H$), 142.8 (C), 144.8 (C), 145.8 (C), 161.6 (C-OH), 171.3 (C=O). – IR (ATR, cm^{-1}): $\nu = 3056$ (w), 3027 (w), 2982 (w), 1660 (s), 1611 (m), 1567 (m), 1501 (w), 1482 (w), 1437 (m), 1417 (m), 1266 (s), 1209 (s), 1162 (w), 1141 (w), 1111 (w), 1003 (w). – MS (EI, 70 eV): m/z (%) = 286 (47) $[M]^+$, 255 (20), 254 (100), 225 (10), 224 (41), 181 (30), 165 (17). 152 (40). – HRMS (EI, 70 eV): m/z = 286.119768 (calcd. 286.11996 for $C_{17}H_{18}O_4$, $[M]^+$). – Anal. for $C_{17}H_{18}O_4$ (286.32): calcd. C 71.31, H 6.34; found C 71.390, H 6.397.

*Methyl 2-hydroxy-4-(2-methoxyethyl)-3-methyl-6-phenylbenzoate (**5b**)*

Starting with **3** (557 mg, 2.0 mmol), **4b** (549 g, 2.0 mmol) and $TiCl_4$ (0.22 mL, 2.0 mmol) in CH_2Cl_2 (4 mL), **5b** was isolated by chromatography (silica gel, *n*-heptane-EtOAc = 50 : 1 to 10 : 1) (256 mg, 43 %) as a colorless oil. – ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 2.27$ (s, 3H, CH_3), 2.93 (t, $^3J = 7.4$ Hz, 2H, CH_2), 3.35 (s, 3H, OCH_3), 3.46 (s, 3H, OCH_3), 3.57 (t, $^3J = 7.4$ Hz, 2H, CH_2), 6.65 (s, 1H, $C_{Ar}H$), 7.19 – 7.22 (m, 2H, $C_{Ar}H$), 7.29 – 7.37 (m, 3H, $C_{Ar}H$), 11.06 (s, 1H, OH). – ^{13}C NMR ($CDCl_3$, 63 MHz): $\delta = 11.3$ (CH_3), 34.1 (CH_2), 51.5 (OCH_3), 58.7 (OCH_3), 72.1 (CH_2OCH_3), 109.5 (C), 123.6 ($C_{Ar}H$), 124.0 (C), 126.6 ($C_{Ar}H$), 127.5 ($C_{Ar}H$), 128.2 ($C_{Ar}H$), 141.6 (C), 143.0 (C), 143.1 (C), 159.8 (C-OH), 171.9 (C=O). – IR (ATR, cm^{-1}): $\nu = 3056$ (w), 3025 (w), 1657 (s), 1608 (w), 1601 (w), 1563 (w), 1499 (w), 1480 (w), 1436 (s), 1396 (m), 1298 (w), 1266 (s), 1236 (w), 1211 (w), 1196 (w), 1171 (s), 1140 (w), 1111 (w), 1095 (w), 1049 (w), 1030 (w), 1010 (m). – MS (EI, 70 eV): m/z (%) = 300 (52) $[M]^+$, 269 (21), 268 (100), 254 (14), 253 (77), 237 (26), 235 (11), 209 (17), 195 (19), 152 (27). – HRMS (EI, 70 eV): m/z = 300.136154 (calcd. 300.13561 for $C_{18}H_{20}O_4$, $[M]^+$). – Anal. for $C_{18}H_{20}O_4$ (300.35): calcd. C 71.98, H 6.71; found C 71.965, H 6.741.

*Methyl 3-ethyl-2-hydroxy-4-(2-methoxyethyl)-6-phenylbenzoate (**5c**)*

Starting with **3** (557 mg, 2.0 mmol), **4c** (577 g, 2.0 mmol) and $TiCl_4$ (0.22 mL, 2.0 mmol) in CH_2Cl_2 (4 mL), **5c** was isolated by chromatography (silica gel, *n*-heptane-EtOAc = 50 : 1 to 10 : 1) (256 mg, 41 %) as a colorless oil. – ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta = 1.19$ (t, $^3J = 7.4$ Hz, 3H, CH_3), 2.76 (q, $^3J = 7.4$ Hz, 2H, CH_2), 2.93 (t, $^3J = 7.4$ Hz, 2H, CH_2), 3.35 (s, 3H, OCH_3), 3.46 (s, 3H, OCH_3), 3.58 (t, $^3J = 7.4$ Hz, 2H, CH_2), 6.65 (s, 1H, $C_{Ar}H$), 7.19 – 7.23 (m, 2H, $C_{Ar}H$), 7.28 – 7.38 (m, 3H, $C_{Ar}H$), 10.99 (s, 1H, OH). – ^{13}C NMR ($CDCl_3$, 63 MHz): $\delta = 13.9$ (CH_3), 19.3 (CH_2), 33.3 (CH_2), 51.5 (OCH_3), 58.7 (OCH_3), 72.8 (CH_2OCH_3), 109.7 (C), 123.7 ($C_{Ar}H$), 126.5 ($C_{Ar}H$), 127.5 ($C_{Ar}H$), 128.2 ($C_{Ar}H$), 130.1 (C), 141.6 (C), 142.5 (C), 143.0 (C), 159.7 (C-OH), 171.9 (C=O). – IR (ATR, cm^{-1}): $\tilde{\nu} = 3057$ (w), 3025 (w), 1658 (s), 1601 (m), 1559 (m), 1502 (w), 1482 (w), 1436 (m), 1396 (m), 1358 (w), 1318 (w), 1280 (s), 1171 (m), 1140 (m), 1112 (w), 1102 (w), 1074 (w), 1063 (w), 1032 (w), 1000 (w). – MS (EI, 70 eV): m/z (%) = 314 (85) $[M]^+$, 283 (23), 282 (100), 267 (72), 251 (91), 235 (28), 232 (34). 223 (41), 178 (26), 165 (61). – HRMS (EI, 70 eV): m/z = 314.151550 (calcd. 314.15126 for $C_{19}H_{22}O_4$, $[M]^+$).

*Methyl 2-hydroxy-4-(2-methoxyethyl)-6-phenyl-3-propylbenzoate (**5d**)*

Starting with **3** (557 mg, 2.0 mmol), **4d** (604 g, 2.0 mmol) and $TiCl_4$ (0.22 mL, 2.0 mmol) in CH_2Cl_2 (4 mL), **5d** was isolated by chromatography (silica gel, *n*-heptane-EtOAc = 50 : 1 to 10 : 1) (516 mg, 79 %) as a yellow oil. – ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 1.03$ (t, $^3J = 7.4$ Hz, 3H, CH_3), 1.54 – 1.66 (m, 2H, CH_2), 1.68 – 1.73 (m, 2H, CH_2), 2.93 (t, $^3J = 7.4$ Hz, 2H, CH_2), 3.35 (s, 3H, OCH_3), 3.45 (s, 3H, OCH_3), 3.57 (t, $^3J = 7.4$ Hz, 2H, CH_2), 6.65 (s, 1H, $C_{Ar}H$), 7.19 – 7.23 (m, 2H, $C_{Ar}H$), 7.39 – 7.37 (m, 3H, $C_{Ar}H$), 10.99 (s, 1H, OH). – ^{13}C NMR ($CDCl_3$, 63 MHz): $\delta = 14.5$ (CH_3), 22.8 (CH_2), 28.1 (CH_2), 33.4 (CH_2), 51.5 (OCH_3), 58.7 (OCH_3), 72.8 (CH_2OCH_3), 109.6 (C), 123.6 ($C_{Ar}H$), 126.5 ($C_{Ar}H$), 127.5 ($C_{Ar}H$), 128.2 ($C_{Ar}H$), 128.8 (C), 141.6 (C), 142.8 (C), 143.0 (C), 159.8 (C-OH), 171.9 (C=O). –IR (ATR, cm^{-1}): $\tilde{\nu} = 3057$ (w), 3026 (w), 1658 (s), 1601 (m), 1559 (m), 1501 (w), 1483 (w), 1437 (s), 1396 (m), 1358 (w), 1318 (w), 1296 (w), 1269 (s), 1211 (w), 1196 (w), 1171 (m), 1140 (w), 1107 (br, s), 1075 (w), 1039 (w), 1030 (w), 1000 (w). – MS (EI, 70 eV): m/z (%) = 328 (98) $[M]^+$, 297 (23), 296 (97), 281 (57), 265 (100), 246 (36), 237 (75). 236 (23). – HRMS (EI, 70 eV): m/z = 328.167053 (calcd. 328.16691 for $C_{20}H_{24}O_4$, $[M]^+$). – Anal. for $C_{20}H_{24}O_4$ (328.40): calcd. C 73.15, H 7.37; found C 73.015, H 7.330.

*iso-Propyl 2-hydroxy-4-(2-methoxyethyl)-6-phenylbenzoate (**5e**)*

Starting with **3** (2.00 mmol, 557 mg), **4a** (2.20 mmol, 600 mg) and $TiCl_4$ (2.20 mmol, 0.24 mL) in 4 mL CH_2Cl_2, **5e** was isolated by chromatography (silica gel, heptane-EtOAc = 100 : 1 to 20 : 1) (198 mg, 32 %) as a slightly yellow oil. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.83 (d, 6H, $^3J_{H,H} = 6.23$ Hz, $CH[CH_3]_2$), 2.86 (t, 2H, $^3J_{H,H} = 6.99$ Hz, $CH_2CH_2OCH_3$), 3.25 (s, 3H, OCH_3), 3.63 (t, 2H, $^3J_{H,H}$ = 6.99 Hz, $CH_2CH_2OCH_3$), 4.92 (sept, 1H, $^3J_{H,H} = 6.23$ Hz, $CH[CH_3]_2$), 6.64 (d, 1H, $^4J_{H,H} = 1.89$ Hz, Ar), 6.88 (d, 1H,

$^4J_{H,H}$ = 1.89 Hz, Ar), 7.19 – 7.23 (m, 2H, Ph), 7.31 – 7.34 (m, 3H, Ph), 11.02 (s, 1H, OH). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.9 (OCH[CH_3]), 36.1 (OCH_2CH_2), 58.7 (OCH_3), 68.9 (OCH[CH_3]), 72.6 (OCH_2CH_2), 110.6 (C_q), 116.6, 123.4 (CH_{Ar}), 126.6, 127.5, 128.3 (CH_{Ph}), 143.3, 145.0, 145.4 (C_q), 161.8 (COH), 170.4 (CO). – IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3057 (w), 3027 (w), 1653 (s), 1616 (s), 1568 (m), 1501 (w). – MS (EI, 70 eV): m/z = 314 (37) $[M]^+$, 254 (100), 224 (31), 181 (16), 152 (18), 45 (11). – HRMS (EI, 70 eV): m/z = 314.15140 (calcd. 314.15126 for $C_{19}H_{22}O_4$, $[M]^+$).

*Benzyl 2-hydroxy-4-(2-methoxyethyl)-6-phenylbenzoate (**5f**)*

Starting with **3** (0.87 mmol, 242 mg), **4b** (1.00 mmol, 340 mg) and $TiCl_4$ (1.00 mmol, 0.12 mL) in 3 mL of CH_2Cl_2, **5f** was isolated by chromatography (silica gel, heptane-EtOAc = 100 : 1 to 20 : 1) (139 mg, 44 %) as a colorless oil. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.94 (t, $^3J_{H,H}$ = 6.80 Hz, 2H, $CH_2CH_2OCH_3$), 3.42 (s, 3H, OCH_3), 3.70 (t, $^3J_{H,H}$ = 6.80 Hz, 2H, $CH_2CH_2OCH_3$), 5.06 (s, 2H, CH_2), 6.72 (d, $^4J_{H,H}$ = 1.70 Hz, 1H, Ar), 6.86 (dd, 2H, Ph), 6.96 (d, $^4J_{H,H}$ = 1.70 Hz, 1H, Ar), 7.27 – 7.33 (m, 8H, Ph), 10.87 (s, 1H, OH). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 36.7 (OCH_2CH_2), 58.7 (OCH_3), 66.9 (OCH_2CH_2), 72.5 (CH_2Ph), 110.0 (C_q), 116.7, 123.7 (CH_{Ar}), 126.8, 127.7, 128.0, 128.1, 128.2, 128.2 (CH_{Ph}), 134.4, 142.8, 144.9, 145.8 (C_q), 161.8 (COH), 170.8 (CO). – IR (ATR, cm^{-1}): = 3060 (w), 3032 (w), 1656 (s), 1610 (s), 1568 (s), 1497 (m). – MS (EI, 70 eV): m/z = 362 (18) $[M]^+$, 254 (47), 152 (11), 91 (10), 65 (11), 45 (19). – HRMS (EI, 70 eV): m/z = 362.15051 (calcd. 362.15126 for $C_{23}H_{22}O_4$, $[M]^+$).

*Methyl 2-hydroxy-4-(2-methoxyethyl)-3-(n-octyl)-6-phenylbenzoate (**5g**)*

Starting with **3** (1.50 mmol, 418 mg), 4 c (1.70 mmol, 634 mg) and $TiCl_4$ (1.70 mmol, 0.19 mL) in 3 mL of CH_2Cl_2, **5g** was isolated by chromatography (silica gel, heptane-EtOAc = 100 : 1 to 20 : 1) (238 mg, 40 %) as a colorless oil. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.87 – 0.91 (m, 3H, CH_3), 1.26 – 1.59 (m, 12H, CH_2), 2.69 – 2.74 (m, 2H, $CH_3[CH_2]_6CH_2$), 2.94 (t, 2H, $^3J_{H,H}$ = 7.37 Hz, $CH_2CH_2OCH_3$), 3.36 (s, 3H, OCH_3), 3.46 (s, 3H, OCH_3), 3.58 (t, 2H, $^3J_{H,H}$ = 7.37 Hz, $CH_2CH_2OCH_3$), 6.65 (s, 1H, Ar), 7.20 – 7.23 (m, 2H, Ph), 7.29 – 7.38 (m, 3H, Ph), 10.99 (s, 1H, OH). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (CH_3), 22.7, 26.2, 29.3, 29.5, 29.7, 30.1, 31.9, 33.3 (CH_2), 51.5, 58.7 (OCH_3), 72.8 (CH_2), 109.6 (C_q), 123.6 (CH_{Ar}), 126.5, 127.5, 128.2 (CH_{Ph}), 129.0, 141.6, 142.6, 143.1 (C_q), 159.8 (COH), 171.9 (CO). – IR (ATR, cm^{-1}): = 3058 (w), 3026 (w), 1660 (s), 1601 (m), 1560 (m). – MS (EI, 70 eV): m/z = 398 (51) $[M]^+$, 349 (17), 307 (100), 253 (35), 237 (19), 45 (23). – HRMS (ESI, 70 eV): m/z = 421.23544 (calcd. 421.23493 for $C_{25}H_{34}NaO_4$, $[M+Na]^+$). – Anal. for $C_{25}H_{34}O_4$ (398.535): calcd. C 75.34; H 8.60; found C 75.10; H 8.77.

*Ethyl 3-(n-decyl)-2-hydroxy-4-(2-methoxyethyl)-6-phenylbenzoate (**5h**)*

Starting with **3** (1.50 mmol, 418 mg), **4d** (1.70 mmol, 634 mg) and $TiCl_4$ (1.70 mmol, 0.19 mL) in 3 mL of CH_2Cl_2, **5h** was isolated by chromatography (silica gel, heptane-EtOAc = 100 : 1 to 20 : 1) (291 mg, 44 %) as a colorless oil. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.73 (t, 3H, $^3J_{H,H}$ = 7.25 Hz, OCH_2CH_3), 0.86 – 0.91 (m, 3H, CH_3), 1.25 – 1.56 (m, 16H, CH_2), 2.68 – 2.74 (m, 2H, $CH_3[CH_2]_8CH_2$), 2.93 (t, 2H, $^3J_{H,H}$ = 7.57 Hz, $CH_2CH_2OCH_3$), 3.36 (s, 3H, OCH_3), 3.58 (t, 2H, $^3J_{H,H}$ = 7.57 Hz, $CH_2CH_2OCH_3$), 3.96 (q, 2H, $^3J_{H,H}$ = 7.25 Hz, OCH_2CH_3), 6.63 (s, 1H, Ar), 7.7.19 – 7.23 (m, 2H, Ph), 7.31 – 7.34 (m, 3H, Ph), 1.14 (s, 1H, OH). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.9, 14.1 (CH_3), 22.7, 26.1, 26.3, 29.6, 29.6, 29.7, 30.1, 31.9, 33.3 (CH_2), 58.7 (OCH_3), 60.8 (OCH_2), 72.8 (CH_2), 109.8 (C_q), 123.4 (CH_{Ar}), 126.4, 127.5, 128.2 (CH_{Ph}), 129.0, 141.7, 142.4, 143.4 (C_q), 159.9 (COH), 171.4 (CO). – IR (ATR, cm^{-1}): = 3059 (w), 3025 (w), 1656 (s), 1698 (w), 1691 (m), 1561 (m). – MS (EI, 70 eV): m/z = 440 (33) $[M]^+$, 377 (13), 336 (30), 335 (100), 268 (13), 237 (14), 45 (19). – HRMS (ESI): m/z = 463.28249 (calcd. 463.28188 for $C_{28}H_{41}NaO_4$, $[M+Na]^+$).

[1] S. Hayashi, L. Yagi, T. Ishikawa, M. Kawasaki, T. Asai, J. Picone, C. Turnbull, J. Hiratake, K. Sakata, M. Takada, K. Ogawa, N. Watanabe, *Tetrahedron* **2004**, *60*, 7005.

[2] N. Oka, H. Ohishi, T. Hatano, M. Hornberger, K. Sakata, N. Watanabe, *Z. Naturforsch.* **1999**, *54c*, 889.

[3] J.-P. Savina, D. Kohler, P. Brunerie, *USP 5965780*, **1999**.

[4] M. Etschmann, W. Bluemke, D. Sell, J. Schrader, *Appl. Microbiol. Biotechnol.* **2002**, *59*, 1.

[5] K. D. Pering, J. M. Behan, J. N. Ness, J. H. Duprey, D. C. Hooper, D. A. McNulty, PCT Int. Appl. WO2005103214 (A2), **2005**.

[6] N. Vasallo, *Polyphenols and Health: New and Recent Advances*, 1st ed. Nova Science Publishers, **2008**, pp. 31.

[7] S. Gomez-Alonso, M. D. Salvador, G. Fregpane, *J. Agric. Food Chem.* **2002**, *50*, 6812.
[8] B. Le Tutour, D. Guedon, *Phytochemistry* **1992**, *31*, 1173.
[9] M. del Carmen Recio, R. M. Giner, S. Manez, J. L. Rios, *Planta Med* **1994**, *60*, 232.
[10] G. Bisignana, A. Tomaino, R. Lo Cascio, G. Crisafi, N. Uccella, A. Saija, *J. Pharm. Pharmacol.* **1999**, *51*, 971.
[11] S. K. Gupta, Bioderm Research, US20050048008 (A1), **2005**.
[12] M. Rouanet, J. J. Potherat, H. Cousse, Fabre Piere Sante, FR2772235 (A1), **1999**.
[13] J. Achkar, A. Ferrandez, DE112007002823T5, **2009**.
[14] Y.-L. Lin, Y.-M. Wu, Y.-H. Kuo, *Phytochemistry* **1997**, *45*, 1057.
[15] P.-L. Huang, S.-J. Won, S.-H. Day, C.-N. Lin, *Helv. Chim. Acta* **1999**, *82*, 1716.
[16] Y.-L. Lin, T.-C. Lin, Y.-H. Kuo, *J. Nat. Prod.* **1997**, *60*, 368.
[17] M. S. Buchanan, M. Gill, J. Yu, *J. Chem. Soc., Perkin Trans. 1* **1997**, 919.
[18] B. Das, G. Mahender, Y. K. Rao, A. Prabhakar, B. Jagadeesh, *Chem. Pharm. Bull.* **2005**, *53*, 135.
[19] A. Basile, S. Sorbo, J. A. Lopez-Saez, R. C. Cobianchi, *Phytochemistry* **2003**, *62*, 1145.
[20] J.-J. Chen, C.-Y. Duh, J.-F. Chen, *Planta Med.* **2005**, *71*, 659.
[21] E. M. Anam, O. D. Ekpa, P. V. Gariboldi, F. N. I. Morah, M. I. Dosunmu, *Indian J. Chem., Sect. B* **1993**, *32*, 1051.
[22] B. Dasgupta, B. A. Burke, K. L. Stuart, *Phytochemistry* **1981**, *20*, 153.
[23] G.-Z. Zeng, N.-H. Tan, X.-J. Hao, Q.-Z. Mu, R.-T. Li, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 6178.
[24] G.-Z. Zeng, X.-L. Pan, N.-H. Tan, J. Xiong, Y.-M. Zhang, *Eur. J. Med. Chem.* **2006**, *41*, 1247.
[25] A. de Meijere, F. Diederich (Eds.), *Metal-Catalyzed Cross-Coupling Reactions*, Wiley-VCH, Weinheim **2004**.
[26] For a review of stereoselective syntheses of functionalized biaryls, see: G. Bringmann, A. J. M. Mortimer, P. A. Keller, M. J. Gresser, J. Garner, M. Breuning, *Angew. Chem. Int. Ed.* **2005**, *44*, 5384.
[27] For a review of 1, 3-bis(trimethylsilyloxy)-1,3-dienes in general, see: P. Langer, *Synthesis* **2002**, 441.
[28] For reviews of [3+3]cyclizations, see: H. Feist, P. Langer, *Synthesis* **2007**, 327.
[29] G. Karapetyan, T. T. Dang, M. Sher, T. V. Ghochikyan, A. Saghyan, P. Langer, *Curr. Org. Chem.* **2012**, *16*, 557.
[30] T. H. Chan, P. Brownbridge, *J. Am. Chem. Soc.* **1980**, *102*, 3534.
[31] G. A. Molander, K. O. Cameron, *J. Am. Chem. Soc.* **1993**, *115*, 830.
[32] V. T. H. Nguyen, E. Bellur, B. Appel, *Synthesis* **2006**, 2865.
[33] P. Brownbridge, T. H. Chan, M. A. Brook, G. J. Kang, *Can. J. Chem.* **1983**, *61*, 688.
[34] K. Hirai, I. Ojima, *Tetrahedron Lett.* **1983**, *24*, 785.