Palladium-Catalyzed Domino Carbopalladation/C–H Activation for the Synthesis of Tetrasubstituted Alkenes Bearing Five- and Seven-Membered Rings

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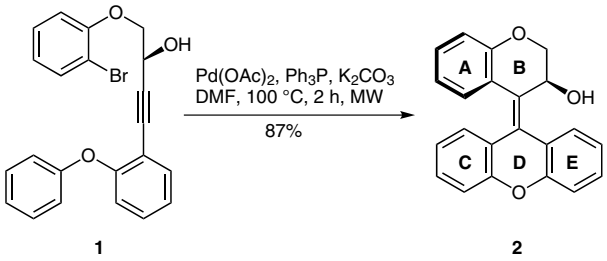
Abstract: A Pd-catalyzed domino carbopalladation/C–H-activation reaction of phenoxyphenyl-substituted propargylic alcohols was used for the synthesis of tetrasubstituted alkenes bearing either a dihydroindene or benzo[7]annulene motif. These compounds are of interest for the construction of molecular switches and motors.

Key words: palladium, domino reaction, C–H activation, tetrasubstituted alkenes, catalysis

Chemistry has reached a high level of performance and allows the preparation of complex molecular structures. Herein, transition-metal-mediated transformations and especially palladium-catalyzed cross-coupling reactions have emerged as powerful synthetic tools.[1] However, one major drawback is the prerequisite for prefunctionalization of one or both coupling partners. A more appropriate procedure in terms of economy and ecology is the direct C–H functionalization using readily available substrates.[2] Furthermore, combining the C–H activation with other Pd-catalyzed reactions in a domino mode would be even more appropriate and would allow the construction of complex structures with multiple bond formations in an economically and ecologically benign fashion.[3,4] Thus, the design of novel domino reactions employing palladium-catalyzed transformations of unfunctionalized aromatic scaffolds is a very promising approach especially for the preparation of new materials and natural products.[5]

Recently, we have developed domino carbopalladation–Stille and domino carbopalladation–Heck-type reactions for the synthesis of overcrowded tetrasubstituted helical alkenes.[6a,b] These compounds are of great interest as molecular switches and motors.[7] Though the approaches give good yields and are highly efficient, the use of stannanes is not very appropriate. To our delight, we were able to replace the ecologically less suitable Stille reaction by a direct C–H activation. Thus, the ecologically more friendly domino carbopalladation/C–H-activation reaction of alkyne **1** using 20 mol% of $Pd(OAc)_2$ gave the alkene **2** in 87% yield (Scheme 1).[6c]

Here we show that several other tetrasubstituted alkenes containing a five- and a seven-membered ring system **B** can be prepared using this method. Moreover, in the case

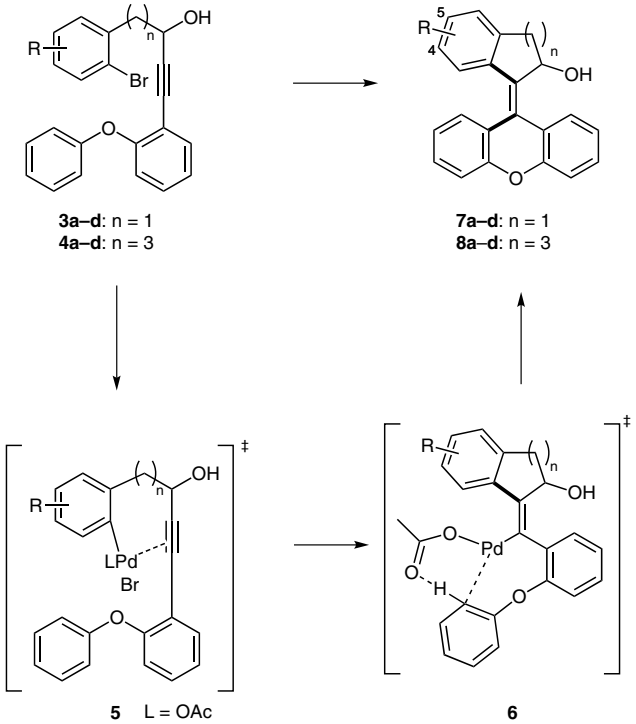


1 **2**

Scheme 1 Pd-catalyzed domino carbopalladation–C–H-activation reaction of alkyne **1** to give the tetrasubstituted alkene **2**

of the five-membered system the amount of palladium can be drastically reduced, and finally we have shown that instead of $Pd(OAc)_2$ also Pd on carbon can be used as catalyst. In this case, the use of acetate either as base or as ligand turned out to be essential.

Reaction of the propargylic alcohols **3** with a tether of n = 1 using $Pd(OAc)_2$ in the presence of triphenylphosphane and potassium carbonate led to the desired alkenes **7**, whereas reaction of the propargylic alcohols **4** with a



5 **6**

Scheme 2 Proposed mechanism for the domino transformation of propargylic alcohols **3** and **4** to give alkenes **7** and **8**

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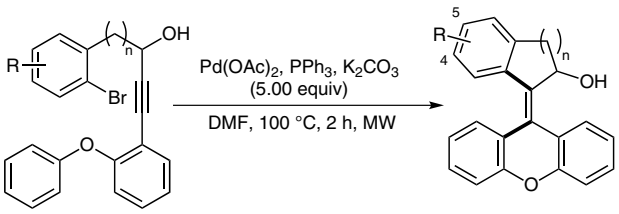
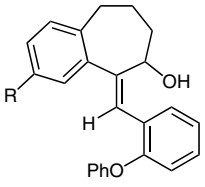
Table 1 Domino Reaction of **3a–d** and **4a–d** to Give the Dihydroindenes **7a–d** and the Benzo[7]annulenes **8a–d**



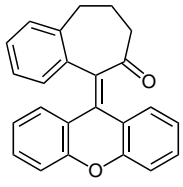
3a–d: n = 1
4a–d: n = 3

7a–d: n = 1
8a–d: n = 3

Entry	Substrate	R (n)	$Pd(OAc)_2$ (mol%)	Product	Yield (%)[a]
1	**3a**	H (1)	20	**7a**	76
2	**3a**	H (1)	10	**7a**	65
3	**3a**	H (1)	5	**7a**	60
4	**3b**	5-MeO (1)	20	**7b**	71
5	**3b**	5-MeO (1)	10	**7b**	76
6	**3b**	5-MeO (1)	5	**7b**	97
7	**3b**	5-MeO (1)	2	**7b**	88
8	**3b**	5-MeO (1)	10	**7b**	75[b]
9	**3c**	5-F (1)	20	**7c**	74[c]
10	**3c**	5-F (1)	10	**7c**	73
11	**3c**	5-F (1)	5	**7c**	70
12	**3d**	4,5-OCH_2O (1)	20	**7d**	99
13	**3d**	4,5-OCH_2O (1)	10	**7d**	99
14	**3d**	4,5-OCH_2O (1)	5	**7d**	83
15	**3d**	4,5-OCH_2O (1)	1.5	**7d**	63
16	**4a**	H (3)	20	**8a**	48[d]
17	**4b**	4-Me (3)	20	**8b**	65[c]
18	**4c**	4-F (3)	20	**8c**	20[c,e]
19	**4d**	4-F_3C (3)	20	**8d**	72[c]
20	**4d**	4-F_3C (3)	10	**8d**	46[c]



9a: R = H
9c: R = F



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[a] Yield of isolated products.
[b] Reaction conditions: Pd/C (10 mol%), LiOAc (4.0 equiv), *n*-Bu_4NOAc (3.0 equiv), MeCN–DMF–H_2O (5:5:1), 140 °C, 4 h, MW.
[c] dppp = 1,3-bis(diphenylphosphino)propane as ligand.
[d] Combined yield; inseparable mixture of **8a** and **9a** (30%); formation of **10** as byproduct (traces).
[e] Formation of **9c** (6%) as byproduct.

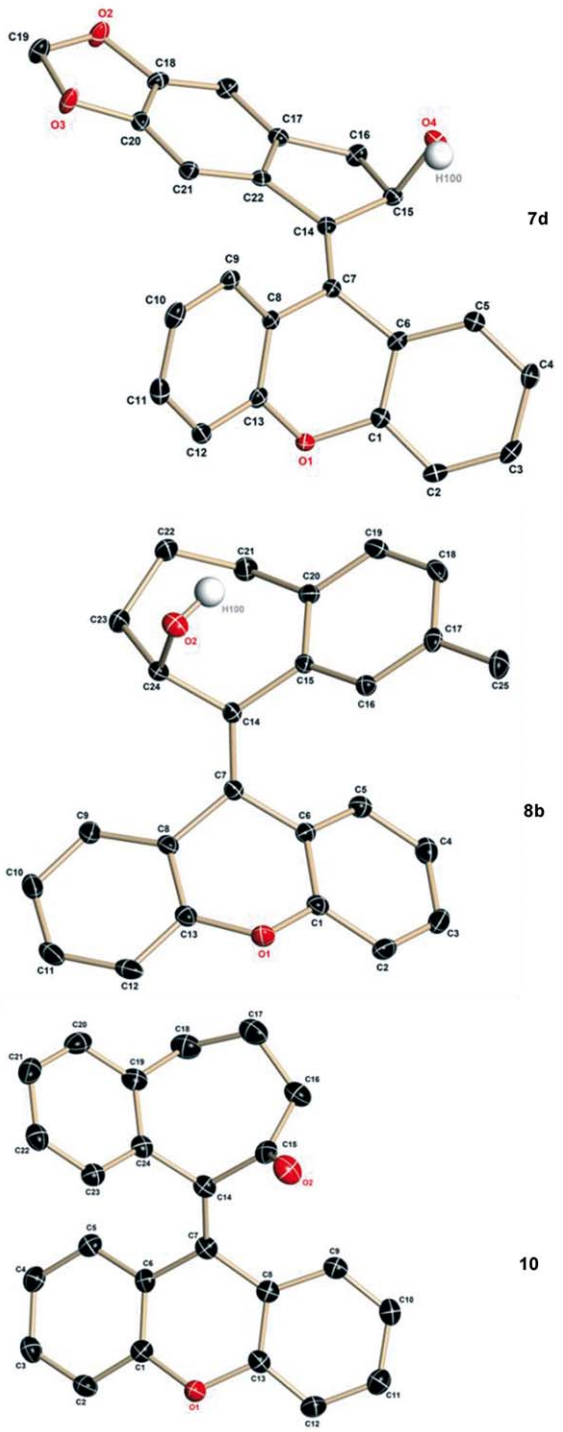


Figure 1 Crystal structure of dihydroindene **7d** (top), benzo[7]annulene derivative **8b** (middle), and ketone **10** (bottom); depicted are the corresponding anisotropic displacement parameters at the 50% probability level

tether of n = 3 gave the alkenes **8** (Scheme 2, Table 1). The reaction tolerates electron-donating as well as electron-withdrawing substituents in the substrates. We have also investigated the influence of the catalyst loading on the yields. For the substrates **3** usually the best results were obtained with 5–10 mol% of $Pd(OAc)_2$ with up to

99% yield, but as shown for **3b** and **3d** even 2 and 1.5 mol%, respectively, gave reasonable yields.

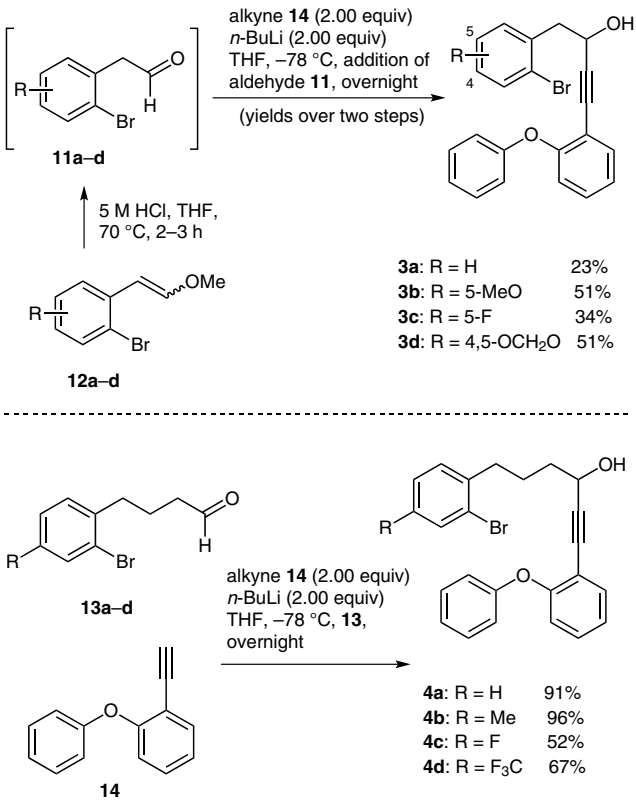
As already mentioned, the transformations of **3** as shown for **3b** can also be carried out using Pd/C (Table 1, entry 8).[8] The best yields were obtained in the presence of LiOAc (Table 2), but the use of *n*-Bu_4NOAc or KOAc also led to the product **7b** though in lower yields. However, using Li_2CO_3 or Cs_2CO_3 as a base a conversion did not take place. We therefore assume that after the oxidative addition and carbopalladation of **3** to give **5** an acetate-bridged complex **6** is formed as transition state within the C–H activation.[9]

Furthermore, the use of either $Pd(PPh_3)_4$ or $PdCl_2/Ph_3P$ in the presence of K_2CO_3 also led to alkene **7b** but only with moderate yields.

As expected, the formation of the seven-membered-ring compounds **8** from alkynes **4** occurred in lower yields as compared to the domino carbopalladation/C–H-activation reaction of **3** (Table 1); however, **8d** could still be obtained from **4d** in a good yield of 72% (Table 1, entry 19).

Here, however, 20 mol% of $Pd(OAc)_2$ had to be used to obtain reasonable results. The general lower yields in the formation of **8** can be explained by the unfavorable intermediate formation of an eight-membered palladacycle in **5**. This might also be the reason for the formation of significant amounts of the carbopalladation product **9a**, which was difficult to separate from the alkene **8a** and the ketone **10**. In the reaction of **4c** the alkene **9c** was also detected as byproduct but could be separated chromatographically.

The structure elucidation of the products was performed using NMR spectroscopy and mass spectrometry. Moreover, for **7d**, **8b**, and **10**, crystal structures were obtained (Figure 1).[10]



Scheme 3 Synthesis of propargylic alcohols **3a–d** and **4a–d** by alkynylation of the aldehydes **11a–d** and **13a–d** with **14**

The synthesis of the precursors **3a–d** and **4a–d** for the domino reactions was achieved by an alkynylation of the corresponding aldehydes **11a–d** and **13a–d**,[11] respectively, with the metalated alkyne **14** (Scheme 3). Due to their instability, the aldehydes **11** were not isolated but formed in situ by an acid-catalyzed hydrolysis of the corresponding enol ethers **12a–d**.[12]

Table 2 Domino Reaction of **3b** to Give **7b** Using Pd/C, $PdCl_2$, and $Pd(PPh_3)_4$

Entry	Catalyst	Base	Solvent	Yield (%)[a,b]
1	Pd/C	LiOAc, *n*-Bu_4NOAc	MeCN–DMF–H_2O[c]	75
2	Pd/C	LiOAc	DMF	62
3	Pd/C	*n*-Bu_4NOAc	DMF	62
4	Pd/C	KOAc	DMF	55
5	Pd/C	K_2CO_3	DMF	n.c.[d]
6	Pd/C	Li_2CO_3	DMF	n.c.[d]
7	Pd/C	Cs_2CO_3	DMF	decomp.
8	$Pd(PPh_3)_4$	K_2CO_3	DMF	45
9	$PdCl_2$[e]	K_2CO_3	DMF	34

[a] Yield of isolated products.
[b] Reaction conditions: catalyst (10 mol%), base (4.0 equiv), solvent, 140 °C, 4 h, MW.
[c] In a 5:5:1 mixture.
[d] n.c. = no conversion.
[e] Ph_3P (0.5 equiv) was added as ligand.

In summary, we have demonstrated that the domino carbopalladation/C–H-activation reaction is a suitable and highly efficient method for the synthesis of otherwise difficult to obtain tetrasubstituted alkenes **7a–d** and **8a–d** bearing a dihydroindene- and a benzo[7]annulene motif, respectively, in excellent to reasonable yields. The substrates **3a–d** and **4a–d** for the domino reaction could easily be obtained in a few steps starting from readily available building blocks.

General Procedure for the Palladium-Catalyzed Heck Reaction with Homoallylic Alcohols: Synthesis of 13c

A stirred solution of 2-bromo-4-fluoro-iodobenzene (1.23 g, 4.07 mmol, 1.00 equiv), 3-butenol (700 µL, 8.15 mmol, 2.00 equiv), $NaHCO_3$ (860 mg, 10.2 mmol, 2.50 equiv), and Et_3BnNCl (870 mg, 4.07 mmol, 1.00 equiv) in DMF (15 mL) was thoroughly degassed with argon for 15 min followed by addition of $Pd(OAc)_2$ (44.9 mg, 200 µmol, 5 mol%). The reaction mixture was heated to 40 °C for 26 h, and after cooling to r.t. and washing with a sat. aq NH_4Cl solution (100 mL) the aqueous layer was extracted with MTBE (3 × 50 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. Flash column chromatography (SiO_2, PE–MTBE = 5:1) yielded **13c** as a brown oil (520 mg, 52%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.94 (quin, *J* = 7.8 Hz, 2 H, 3-H_2), 2.49 (td, *J* = 7.2, 1.5 Hz, 2 H, 2-H_2), 2.74 (t, *J* = 7.4 Hz, 2 H, 4-H_2), 6.96 (td, *J* = 8.3, 2.8 Hz, 1 H, 5′-H), 7.17 (dd, *J* = 8.5, 6.0 Hz, 1 H, 6′-H), 7.28 (dd, *J* = 8.3, 2.8 Hz, 1 H, 3′-H), 9.78 (t, *J* = 1.5 Hz, 1 H, CHO) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.4 (C-3), 34.4 (C-4), 43.0 (C-2), 114.6 (C-5′), 120.0 (C-3′), 124.1 (C-2′), 130.9 (C-6′), 136.4 (C-1′), 161.8 (C-4′), 201.7 (C-1) ppm. ESI-MS (MeOH): *m/z* (%) = 243.0 (78) $[M - H]^-$. HRMS: *m/z* calcd for $C_{10}H_{10}BrFO$: 242.9826 $[M - H]^-$; found: 242.9826.

General Procedure for the Hydrolysis of Enol Ethers and Coupling with Alkynes: Synthesis of 3b

A solution of enol ether **12b** (500 mg, 2.06 mmol, 1.00 equiv) in THF (1.8 mL) was heated to 70 °C and treated with 5 M HCl (0.43 mL) for 3 h. The reaction was finished by addition of ice and a sat. aq $NaHCO_3$ solution (10 mL) immediately upon appearance of by-product indicated by TLC. The aqueous layer was extracted with EtOAc (100 mL). The combined organic extracts were then dried over Na_2SO_4 and concentrated in vacuo. The crude aldehyde was subsequently used for the next step.

A solution of alkyne **14** (783 mg, 4.11 mmol, 2.00 equiv) in THF (4.0 mL) was lithiated by dropwise addition of *n*-BuLi (1.62 mL, 2.5 M in *n*-hexane, 2.00 equiv) at –78 °C. The reaction mixture was stirred 15 min at –78 °C, warmed to r.t. over 30 min and was then slowly added to a solution of the crude aldehyde in THF (8.0 mL) at –78 °C. The reaction solution was stirred over night at –78 °C, warmed to r.t. over 1 h and finished by addition of a sat. aq NH_4Cl solution (40 mL). The aqueous layer was extracted with MTBE (3 × 100 mL), the combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. Flash column chromatography (SiO_2, PE–MTBE = 5:1) yielded **3b** [445 mg, 51% (over 2 steps)] as a yellow oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.83 (s, 1 H, OH), 3.05 (qd, *J* = 13.6, 6.8 Hz, 2 H, 1-H_2), 3.71 (s, 3 H, OCH_3), 4.75 (t, *J* = 6.8 Hz, 1 H, 2-H), 6.65 (dd, *J* = 8.8, 3.1 Hz, 1 H, 4′-H), 6.88 (d, *J* = 3.0 Hz, 1 H, 6′-H), 6.93 (d, *J* = 7.9 Hz, 1 H, 3″-H), 6.96–6.94 (m, 2 H, 2‴-H, 6‴-H), 7.07 (q, *J* = 7.4 Hz, 2 H, 5″-H, 4‴-H), 7.27 (td, *J* = 8.3, 1.7 Hz, 1 H, 4″-H), 7.33–7.29 (m, 2 H, 3‴-H, 5‴-H), 7.38 (d, *J* = 8.8 Hz, 1 H, 3′-H), 7.43 (dd, *J* = 7.7, 1.5 Hz, 1 H, 6″-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 44.1 (C-1), 55.4 (CH_3), 62.3 (C-2), 81.5 (C-4), 94.4 (C-3), 114.3 (C-4′), 114.9 (C-2′), 115.3 (C-1″), 117.6 (C-6′), 118.2 (C-2‴, C-6‴), 119.4 (C-3″), 122.9 (C-4‴), 123.4 (C-5″), 129.5 (C-3‴, C-5‴), 129.9 (C-4″), 133.1 (C-3′), 133.7 (C-6″), 137.1 (C-1′), 157.2 (C-2″), 157.3 (C-1‴), 158.6 (C-5′) ppm. ESI-MS (MeOH): *m/z* (%) = 447.1 (20) $[M + Na]^+$, 869.1 (100) $[2M + Na]^+$. HRMS: *m/z* calcd for $C_{23}H_{19}BrO_3$: 445.0393 $[M + Na]^+$, 447.0378 $[M + Na]^+$; found: 447.0379.

General Procedure for the Palladium-Catalyzed Domino Reactions: Synthesis of 7a

A solution of propargylic alcohol **3a** (30.0 mg, 76.3 µmol, 1.00 equiv), Ph_3P (20.0 mg, 76.3 µmol, 1.00 equiv), and K_2CO_3 (117 mg, 854 µmol, 11.2 equiv) in DMF (2.8 mL) was thoroughly degassed before $Pd(OAc)_2$ (3.80 mg, 15.0 µmol, 20 mol%) was added. The reaction mixture was heated to 100 °C for 2 h under microwave irradiation. After cooling to r.t. and quenching by addition of a sat. aq NH_4Cl solution (10 mL) the aqueous layer was extracted with MTBE (100 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by flash column chromatography (SiO_2, PE–MTBE = 5:1) to yield **7a** as a yellow solid (18.1 mg, 76%).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 2.01 (s, 1 H, OH), 2.99 (d, *J* = 17.1 Hz, 1 H, 3-H_a), 3.30 (dd, *J* = 17.1, 6.2 Hz, 1 H, 3-H_b), 5.41 (d, *J* = 6.0 Hz, 1 H, 2-H), 6.99 (t, *J* = 7.7 Hz, 1 H, 6-H), 7.15 (ddd, *J* = 7.6, 5.9, 1.2 Hz, 1 H, 2′-H), 7.19 (td, *J* = 7.4, 0.9 Hz, 1 H, 5-H), 7.27–7.20 (m, 3 H, 7′-H, 5′-H, 4-H), 7.31–7.27 (m, 2 H, 4′-H, 6′-H), 7.36 (ddd, *J* = 8.2, 7.3, 1.6 Hz, 1 H, 3′-H), 7.68 (d, *J* = 8.1 Hz, 1 H, 7-H), 7.80 (dd, *J* = 7.7, 1.4 Hz, 1 H, 1′-H), 8.10 (dd, *J* = 7.8, 1.5 Hz, 1 H, 8′-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 40.7 (C-3), 72.6 (C-2), 116.4 (C-5′), 117.0 (C-4′), 122.4 (C-2′), 123.6 (C-7′), 124.1 (C-7), 124.6 (C-1a′), 125.6 (C-4), 126.1 (C-8′), 126.3 (C-6), 126.4 (C-8a′), 126.5 (C-9′), 128.1 (C-6′), 128.6 (C-5), 129.1 (C-1′), 129.3 (C-3′), 137.9 (C-7a), 140.3 (C-1), 144.5 (C-3a), 153.3 (C-5a′), 154.2 (C-4a′) ppm. MS (EI, 70 eV): *m/z* (%) = 312.1 (18) $[M]^+$, 295.1 (18) $[M - OH]^+$, 181.1 (100) $[M - C_9H_8O]^+$. HRMS (EI): *m/z* calcd for $C_{22}H_{16}O_2$: 312.1150 $[M]^+$; found: 312.1158.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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