Stereo- and Regioselective Palladium-Catalysed Hydroarylation and Hydrovinylation of Functionalised Alkynes: a Route to Substituted *Z*-2-Cinnamyl Esters, 3-Chromen-2-ols, and Coumarins

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Abstract. The palladium-catalysed hydroarylation and hydrovinylation of methyl 3-phenylpropynoate and 3,3-diethoxy-1-(*o*-tetrahydropyranyloxy)phenyl-1-propyne with aryl and vinyl halides or triflates in the presence of $Pd(OAc)_2$ and KOOCH has been studied. The reaction affords stereoselectively *syn* addition products. The regiochemical outcome appears to be controlled by steric effects and the new carbon-carbon bond is generated preferentially on the carbon far from the aromatic ring ligated to the acetylenic carbon. The reaction can be applied to the synthesis of 3-substituted-3-chromen-2-ols and 3-substituted coumarins.

As part of our ongoing interest in the development of new synthetic procedures based on the palladium-catalysed hydroarylation and hydrovinylation of carbon-carbon multiple bonds,[1] we have undertaken a study aimed at exploring the extension of this methodology to alkynes conjugated to an ester functionality. The impetus for this research came from the idea of providing an approach to the unusual class of functionalised *Z*-cinnamyl esters [this configuration is expected on the basis of the established *syn* stereochemistry of hydroarylation(hydrovinylation) reactions of alkynes][2] and, in the presence of nucleophiles close to the acetylenic moiety, a route to cyclic derivatives through a sequential hydroarylation (hydrovinylation)/cyclization process.[3,4]

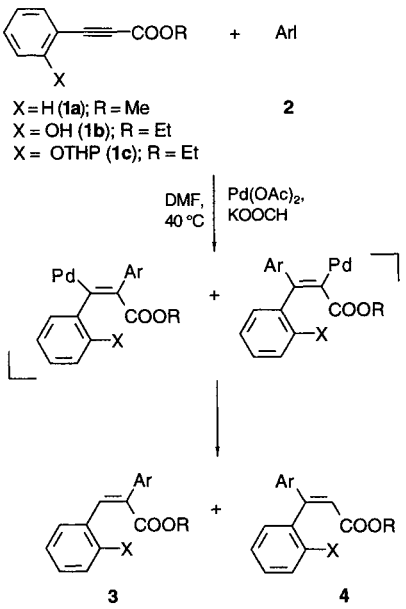
Methyl 3-phenylpropynoate **1a**, prepared in 73% isolated yield through a one-pot two-step reaction from phenyl iodide and propynoic acid,[5] was used as model. Its reaction with a variety of aryl iodides **2** in the presence of potassium formate and $Pd(OAc)_2$ at 40 °C in DMF[6] (Scheme 1) afforded stereoselectively methyl *Z*-2-arylcinnamates **3**[7] in satisfactory yield, together with minor amounts of the regioisomeric derivatives **4** (Table 1). The regiochemistry of the reaction seems to depend on a balance between steric and electronic factors controlling the carbopalladation step:[4] steric factors, related to the aromatic ring ligated to the acetylenic carbon and providing the strongest directing effect, act in such a way that the added aryl unit ends up close to the carbonyl function, and electronic factors, related to the ester group, favour the formation of **4**. The present result is in agreement with the regiochemistry of related palladium-catalysed additions of "σ-arylpalladium halides" to alkyl phenylpropynoates[8,9] and alkynes containing carbon-carbon triple bonds conjugated to electron-withdrawing groups such as 4-phenyl-3-butyn-2-one[4,9] and 3-phenylpropynal.[9]

We next extended our study to include alkyl 3-phenylpropynoates bearing a nucleophilic centre on the aromatic ring, so as to generate hydroarylation derivatives prone to undergo cyclization reactions. To this end, and with an eye to developing a route to 3-substituted coumarins complementing our synthesis of 4-substituted coumarins based on the palladium-catalysed vinylic substitution/cyclization sequence,[10] **1b** (containing a free *o*-hydroxy group) and its tetrahydropyranyl derivative **1c** were selected as potential building blocks.[11] The hydroarylation of **1b** with *p*-iodoanisole under the above conditions provided a straight route to the coumarin derivative **10a**, but it was isolated in a sparing 19% yield, along with numerous other products that we have not further investigated. Compound **1c**, which afforded a more tractable mixture, produced **3c** in 59% yield and also the regioisomer **4c** in 10% yield.

Table 1. Palladium-Catalysed Hydroarylation of Methyl 3-Phenylpropynoate **1a** (Scheme 1)[a,b,c]

entry	2	yield (%) of 3	yield (%) of 4
1	*p*-MeO-C_6H_4-I (**2a**)	52 (**3aa**)	9 (**4aa**)
2	*p*-Me-C_6H_4-I (**2b**)	53 (**3ab**)	3 (**4ab**)
3	*p*-MeOC-C_6H_4-I (**2c**)	57 (**3ac**)	6 (**4ac**)
4	*m*-F-C_6H_4-I (**2d**)	52 (**3ad**)	8 (**4ad**)
5	*m*-CF_3-C_6H_4-I (**2e**)	56 (**3ae**)	10 (**4ae**)
6	*p*-MeCONH-C_6H_4-I (**2f**)	66 (**3af**)	10 (**4af**)

[a] Reactions were carried out on a 0.2 g scale, at 40 °C in DMF under an argon atmosphere, using the following molar ratios: **1a**:**2**:KOOCH:$Pd(OAc)_2$ = 1:2.4:2.4:0.05. [b] Yields refer to single runs and are given for isolated products. [c] **3** and **4** were isolated as regioisomeric mixtures. Yields were calculated by NMR analysis



Scheme 1

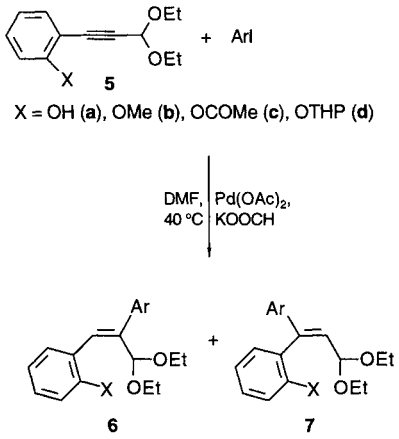
We surmised that the substitution of the ester functionality with a group exerting minor electronic effects on the carbon-carbon triple bond might shift even further the carbopalladation step towards a sterically biased reaction and, ultimately, favour the formation of hydroarylation products with the added aryl unit far from the aromatic ring ligated to the acetylenic carbon. Consequently, we explored the utilization of alkynes bearing a masked carbonyl centre on the propargyl carbon. On the basis of our previous studies on the hydroarylation(hydrovinylation) of acetylenic acetals and ketals, which showed that an increase in the steric bulk of the propargyl carbon may limit the directing effect of the aryl group in the carbopalladation step,[4] 3,3-diethoxy-1-aryl-1-

propynes, accommodating oxygen (pro) nucleophiles in the *ortho* position, were selected as substrates (Scheme 2). These compounds are readily available through the palladium-catalysed coupling of aryl iodides with the commercially available 3,3-diethoxy-1-propyne.[13] Our results are summarized in Table 2.

Table 2. Palladium-Catalysed Hydroarylation of 3,3-Diethoxy-1-Aryl-1-propynes **5** containing Oxygen (Pro)nucleophiles in the *ortho* Position with *p*-iodoanisole (Scheme 2) **2a** [a]

entry	5[b] X	reaction time (h)	yield (%) of 6[c]	yield (%) of 7
1	OH (**5a**; 2 h, 83%)	4	36 (**6aa**)	-
2	OMe (**5b**; 1.5 h, 76%)	24	60 (**6ba**)	-
3	OCOMe (**5c**; 2.0 h, 83%)	6[d]	45 (**6ca**)	8 (**7ca**)
4	OTHP (**5d**; 2.0 h, 86%)	4	66 (**6da**)	-

[a] Reactions were carried out on a 0.2 g scale, at 40 °C in DMF under an argon atmosphere, using the following molar ratios: **5**:**2a**:KOOCH:Pd(OAc)$_2$ = 1:2.4:2.4:0.05. [b] Figures in parentheses refer to reaction times and yields of **5**. [c] Yields refer to single runs and are given for isolated products. [d] **6ca** and **7ca** were isolated as regioisomeric mixtures. Yields were calculated by NMR analysis



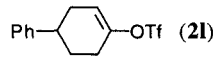
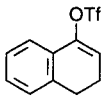
Scheme 2

The most effective approach to regioselective hydroarylation derivatives involved 3,3-diethoxy-1-(*o*-tetrahydropyranyloxy)phenyl-1-propyne **5d**:[14,15] **6da** was isolated in 66% yield[16] and no regioisomeric **7da** was discernible in the reaction mixture (Table 2, entry 4). Therefore, this alkyne has been adopted as standard building block and subjected to hydroarylation conditions with a variety of aryl iodides and vinyl halides or triflates. The corresponding compounds **6** were isolated in satisfactory yield (Table 3) and the reaction was found to tolerate a wide range of substituents amenable of further functionalization.

Of course, the utilization as starting alkyne of a masked aldehyde means that an oxidation step is needed in case the reaction is employed to develop a synthesis of coumarins. On the other hand, the utilization of an aldehyde equivalent in the hydroarylation (hydrovinylation) step can provide additional synthetic opportunities and widen the scope of the methodology. For example, even 3-chromen-2-ols might be accessible besides coumarins.

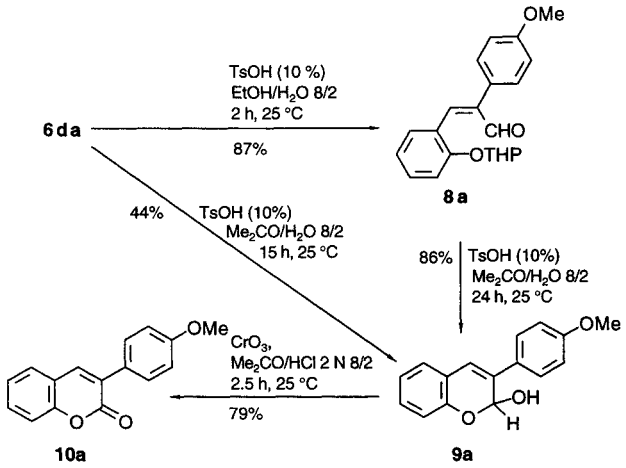
As a probe of this protocol for the synthesis of oxygen-containing heterocycles, the cyclization of **6da** was examined. The corresponding 3-chromen-2-ol derivative **9a**[17] was isolated in about 75% overall yield (49% overall yield, calculated on the starting alkyne **5d**) through a stepwise acid-catalysed procedure that involves the isolation of the

Table 3. Palladium-Catalysed Hydroarylation and Hydrovinylation of **5d** [a]

entry	2	reaction time (h)	yield (%) of 6[b]
1	*p*-Me-C$_6$H$_4$-I (**2b**)	24	65 (**6db**)
2	*p*-MeCO-C$_6$H$_4$-I (**2c**)	29	43 (**6dc**)
3	*m*-CF$_3$-C$_6$H$_4$-I (**2e**)	24	47 (**6de**)
4	*p*-MeCONH-C$_6$H$_4$-I (**2f**)	24	58 (**6df**)
5	PhI (**2g**)	20	71 (**6dg**)
7	*m*-MeO-C$_6$H$_4$-I (**2h**)	25	51 (**6dh**)
8	*p*-F-C$_6$H$_4$-I (**2i**)	25	43 (**6di**)
9	*m*-EtOOC-C$_6$H$_4$-I (**2j**)	24	37 (**6dj**)
10	PhCH=CHBr (**2k**)[c]	24	57 (**6dk**)
11	 (**2l**)	24	51 (**6dl**)
12	 (**2m**)	4	35 (**6dm**)

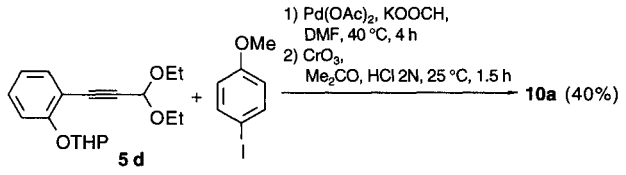
[a] Reactions were carried out on a 0.2 g scale, at 40 °C in DMF under an argon atmosphere, using the following molar ratios: **5d**:**2**:KOOCH:Pd(OAc)$_2$ = 1:2.4:2.4:0.05. [b] Yields refer to single runs and are given for pure, isolated products. All compounds had satisfactory elemental analysis and spectral data were consistent with postulated structures. [c] As an *E/Z* mixture. However, only the styryl derivative from the *E* isomer was isolated

aldehyde derivative **8a**[18] (Scheme 3). The direct conversion of **6da** into **9a** (Scheme 3) proved to be less efficient. The oxidation of **9a** with CrO_3 produced the coumarin **10a** in 79% yield.[19]



Scheme 3

Finally, the reaction sequence leading to the formation of the coumarin product from **5d** can even be conducted as a one-pot operation that omits the isolation of hydroarylation and chromenol intermediates.[20] Compound **10a** was in this case isolated in a satisfactory 40% overall yield (it represents the overall yield for five steps in the reaction sequence) (Scheme 4).



Scheme 4

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5 Synthesis of methyl 3-phenylpropynoate **1a**: to a stirred solution of propynoic acid (0.35 mL, 5.71 mmol) and phenyl iodide kept at 0 °C under argon atmosphere (0.64 mL, 5.711 mmol) in DMF (2.0 mL), were added $Pd(OAc)_2(PPh_3)_2$ (0.087 g, 0.11 mmol), CuI (0.043 g, 0.23 mmol) and *i*-Pr_2NH (2.0 mL). Then, the reaction mixture was warmed up to room temperature and stirred for 5 h. Ethyl acetate was added and the resulting solution was washed with 2N HCl, saturated NaCl solution, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was diluted in DMF (2.0 mL) and K_2CO_3 (2.37 g, 17.13 mmol) and methyl iodide (1.1 mL, 5.71 mmol) were added. The reaction mixture was stirred at room temperature for 3 h. Ethyl acetate was added and the resulting solution was washed with 2N HCl, saturated NaCl solution, dried (Na_2SO_4), concentrated under reduced pressure, and purified by chromatography (silica gel, 40 g; *n*-hexane/ethyl acetate 99/1 v/v) to give **1a** (0.67 g, 73% yield); mp: oil; IR (liquid film) 2212, 1716, 1203, 760, 690 cm^{-1}; ^1H NMR δ 7.58 (d, J = 8.0 Hz, 2H), 7.46-7.35 (m, 3H), 3.84 (s, 3H); ^{13}C NMR δ 154.50, 133.01, 130.71, 128.60, 119.52, 86.52, 80.35, 52.83; MS *m/e* (relative intensity) 161 (M^+ +1, 100), 129 (11); Anal. Calcd for $C_{10}H_8O_2$: C, 74.98; H, 5.54. Found C, 74.88; H, 5.56.
6. For the hydroarylation of **1a**, see the typical procedure for the hydroaylation of **5d** (ref. 15).
7. The regiochemistry of **3** was assigned on the basis of standard ^1H-^{13}C HETCOR studies. Their stereochemistry was assigned on the basis of NOE studies.
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11. Compound **1b** was isolated in 30% yield on treatment of *o*-hydroxyphenyl iodide with ethyl propynoate in the presence of Cu_2O according to the conditions described in ref. 12. Under the same conditions, *o*-(tetrahydropyranyloxy)phenyl iodide gave a mixture of **1b** and **1c**. Compound **1c** was prepared in 60% yield through the reaction of **1b** with dihydropyran according to standard procedures.
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13. Compounds **5** were prepared according to the conditions described in: Sakamoto, T.; Shiga, F.; Yasuhara, A.; Uchiyama, D.; Kondo, Y.; Yamanaka, H. *Synthesis* **1992**, 746.
14. 3,3-Diethoxy-1-(*o*-tetrahydropyranyloxy)phenyl-1-propyne **5d**: mp: oil; IR (liquid film) 2230, 752 cm^{-1}; ^1H NMR δ 7.42 (d, J = 7.7 Hz, 2H), 7.27 (t, J = 6.9 Hz, 1H), 7.11 (d, J = 6.9 Hz, 1H), 6.93 (t, J = 7.7 Hz, 1H), 5.54 (s, 2H), 4.05-3.55 (m, 6H), 2.25-1.50 (m, 6H) 1.17 (t, J = 7.0 Hz, 6H); ^{13}C NMR δ 158.09, 133.63, 130.27, 121.48, 115.45, 112.55, 96.58, 92.14, 88.26, 82.13, 61.83, 60.99, 30.37, 25.41, 18.38, 15.30; MS *m/e* (relative intensity) 304 (M^+, 2), 174 (100), 146 (46); Anal. Calcd for $C_{18}H_{24}O_4$: C, 71.01; H, 7.95. Found C, 71.12; H, 7.97.
15. General procedure for the palladium-catalysed hydroarylation or hydrovinylation of 3,3-diethoxy-1-(*o*-tetrahydropyranyloxy)-phenyl-1-propyne **5d**: to a solution of 3,3-diethoxy-1-(*o*-tetrahydropyranyloxy)phenyl-1-propyne (0.200 g, 0.66 mmol), *p*-iodoanisole (0.370 g, 1.58 mmol) and potassium formate (0.133 g, 1.58 mmol) in DMF (2 mL) was added palladium diacetate (0.007 g, 0.033 mmol) under argon. The mixture was warmed at 40 °C and stirred for 4 h. After cooling, the reaction mixture was diluted with ethyl acetate, washed with water, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by chromatography (silica gel, 40 g; *n*-hexane/ethyl acetate 98/2 v/v) to give **6da** (0.180 g, 66%); mp: oil; IR (liquid film) 2943, 1605, 1515, 826, 752 cm^{-1}; ^1H NMR δ 7.68 (d, J = 8.4 Hz, 2H), 7.40-6.80 (m, 7H), 5.47 (s, 1H), 5.25 (s, 1H), 3.80 (s, 3H), 3.93-3.75 (m, 2H), 3.65-3.31 (m, 4H) 2.18-1.50 (m, 6H), 1.05-1.12 (m, 6H); ^{13}C NMR δ 158.71, 154.64, 138.81, 131.68, 130.54, 129.09, 128.63, 127.70, 126.44, 120.97, 114.66, 113.19, 101.49, 96.08, 62.47, 62.40, 61.73, 55.07, 30.31, 25.16, 18.64, 15.10; MS *m/e* (relative intensity) 412 (M^+, 3), 282 (29), 237 (100); Anal. Calcd for $C_{25}H_{32}O_5$: C, 72.78; H, 7.82. Found C, 72.63; H, 7.80.
16. The regio- and stereochemistry of **6** (Table 3) was usually assigned on the basis of NOE studies. In cases where clean NOE studies were prevented by the chemical shifts of the vinylic and aromatic protons, the stereochemistry was assumed to be *Z* on the basis of the likely structural analogy with the other products in the series and with the results obtained in related reactions.[4]
17. Acid-catalysed hydrolysis of **6da** to **8a**: a solution of **6da** (0.150 g, 0.36 mmol) and *p*-toluenesulfonic acid (0.007 g, 0.036 mmol) in $EtOH/H_2O$ 80/20 (2 mL) was stirred at room temperature for 2 h. The reaction mixture was diluted with ethyl acetate, washed with water, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by chromatography (silica gel, 40 g; *n*-hexane/ethyl acetate 90/10 v/v) to give **8a** (0.106 g, 87%); mp: 142-144 °C; IR 2946, 2835, 1678, 1608, 824, 774 cm^{-1}; ^1H NMR δ 9.94 (s, 1H), 7.85 (s, 1H), 7.43-6.81 (m, 8H), 5.41 (s, 1H), 4.95-3.45(m, 2H), 3.74 (s, 3H), 1.90-1.45 (m, 6H); 13C NMR δ 192.84, 159.68, 155.31, 142.43, 140.01, 132.46, 131.14, 130.04, 128.83, 123.92, 121.13, 114.85, 113.78, 96.59, 62.22, 55.31, 30.26, 25.05, 18.77; MS *m/e* (relative intensity) 338 (M^+, 10), 254 (94), 237 (100); Anal. Calcd for $C_{21}H_{22}O_4$: C, 74.52; H, 6.56. Found C, 74.44; H, 6.58. Hydrolysis of **8a** to 3-(*p*-methoxyphenyl)-3-chromen-2-ol **9a**: a solution of (*Z*)-2-(*p*-methoxyphenyl)-3-(*o*-tetrahydropyranyloxy) phenyl)-2-propenal **8a** (0.082 g, 0.24 mmol) and *p*-toluenesulfonic acid (0.005 g, 0.024 mmol) in Me_2CO/H_2O 80-20 v/v (2 mL) was stirred at room temperature for 15 h. The reaction mixture was diluted with ethyl acetate, washed with water, dried over Na_2SO_4 and concentrated under reduced

pressure. The residue was purified by chromatography (silica gel, 40 g; *n*-hexane/ethyl acetate 90/10 v/v) to give **9a** (0.053 g, 86%); mp: 220 (dec); IR 3263, 2927, 1606, 1516, 827, 752 cm^{-1}; ^1H NMR δ 7.57 (d, J = 8.8 Hz, 2H), 7.24 (m, 2H), 7.09-6.87 (m, 5H), 6.26 (bd, J = 7.4 Hz, 1H), 3.86 (s, 3H), 3.37 (bd, J = 7.4 Hz, 1H); ^{13}C NMR δ 159.69, 149.45, 131.72, 129.22, 128.83, 127.18, 127.09, 122.09, 121.17, 119.31, 116.92, 114.32, 91.66, 55.43; MS *m/e* (relative intensity) 254 (M^+, 27), 237 (100); Anal. Calcd for $C_{16}H_{14}O_3$: C, 75.56; H, 5.55. Found C, 75.64; H, 5.57.

18. The regio- and stereochemistry of **8a** was assigned on the basis of NOE studies.

19. Oxidation of 3-(*p*-methoxyphenyl)-3-chromen-2-ol **9a** to 3-(*p*-methoxyphenyl)coumarin **10a**: a solution of 3-(*p*-methoxy phenyl)-3-chromen-2-ol (0.100 g, 0.39 mmol) and CrO_3 (0.079 g, 0.079 mmol) in Me_2CO/2N HCl 80/20 v/v (3 mL) was stirred at room temperature for 2.5 h. The reaction mixture was diluted with ethyl acetate, washed with saturated $NaHCO_3$, water, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by chromatography (silica gel, 40 g; *n*-hexane/ethyl acetate 90/10 v/v) to give **10a** (0.078 g, 79% yield); mp: 129-131 °C; IR: 1720, 1605, 834, 760 cm^{-1}; ^1H NMR δ 7.75 (s, 1H), 7.67 (d, J = 7.0 Hz, 2H), 7.56-7.48 (m, 2H), 7.41-7.28 (m, 2H), 6.96 (d, J = 7.0 Hz, 2H), 3.84 (s, 3H); 13C NMR δ 160.93, 160.16, 153.27, 138.61, 131.07, 129.86, 127.76, 127.06, 124.50, 123.50, 119.86, 116.39, 113.93, 55.40; MS *m/e* (relative intensity) 252 (M^+, 100), 209 (52), 181 (25); Anal. Calcd for $C_{16}H_{12}O_3$: C, 76.17; H, 4.80. Found C, 76.25; H, 4.79.

20. One-pot preparation of 3-(*p*-methoxyphenyl)-coumarin **10a** from 3,3-diethoxy-1-(*o*-tetrahydropyranyloxy)phenyl-1-propyne **5d**: to a solution of 3,3-diethoxy-1-(*o*-tetrahydropyranyloxy)phenyl-1-propyne (0.200 g, 0.66 mmol), *p*-iodoanisole (0.370 g, 1.58 mmol) and potassium formate (0.133 g, 1.58 mmol) in DMF (2 mL) was added palladium diacetate (0.007 g, 0.033 mmol) under argon. The mixture was warmed at 40 °C and stirred for 4 h. After cooling, the reaction mixture was diluted with ethyl acetate, washed with water, dried over Na_2SO_4 and concentrated under reduced pressure. The crude mixture was dissolved in Me_2CO/ 2N HCl 80/20 v/v (3 mL) and CrO_3 (0.132 g, 0.133 mmol) was added. The solution was stirred for 1 h at room temperature. The reaction mixture was diluted with ethyl acetate, washed with saturated NaHCO3, water, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by chromatography (silica gel, 40 g; *n*-hexane/ethyl acetate 90/10 v/ v) to give **10a** (0.066 g, 40% yield).