DOI: 10.1002/adsc.200700516

Palladium-Catalyzed Cyclization of Enediynes to Benzopyranones

Wei-Ren Chang,[a] Yu-Hsiang Lo,[a] Chia-Ying Lee,[a] and Ming-Jung Wu[a,*]

[a] Faculty of Medicinal and Applied Chemistry, Kaohsiung Medical University, Kaohsiung, Taiwan, R.O.C.
Fax: (+886)-7-312-5339; e-mail: mijuwu@kmu.edu.tw

Received: October 30, 2007; Revised: April 1, 2008; Published online: May 16, 2008

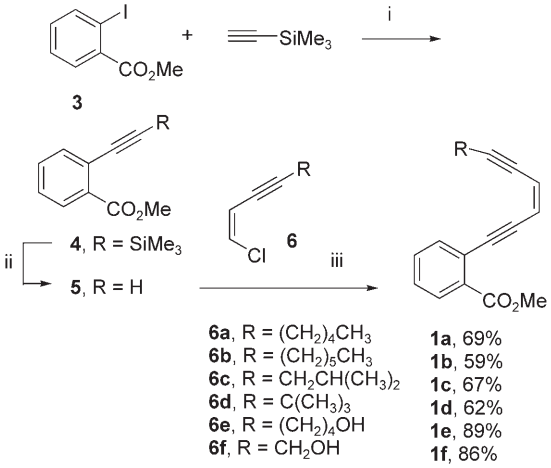
Supporting information for this article is available on the WWW under http://asc.wiley-vch.de/home/.

Abstract: Treatment of methyl 2-[6-substituted-3(*Z*)-hexen-1,5-diynyl]benzoates (**1**) with five mol% of palladium chloride and three equivalents of cupric chloride in refluxing acetonitrile gave dibenzo[*b*,*d*]pyran-6-ones (**2**) in modest to good yields.

Keywords: alkynes; cyclization; dibenzo-[*b*,*d*]pyranones; enediynes; heterocycles; palladium

Many biologically active natural products and pharmaceutically important compounds contain a dibenzo-[*b*,*d*]pyran-6-one skeleton. Thus, the development of syntheses of functionalized dibenzo[*b*,*d*]pyran-6-ones has attracted much attention from organic chemists.[1] Palladium-catalyzed cyclization reactions are very powerful methods for the construction of heterocyclic compounds.[2] Ma reported the use of a catalytic amount of $PdCl_2$ and equivalents of $CuCl_2$ for the carbonylation of propargyl alcohols and amines to give β-lactones[3] and β-lactams,[4] respectively. Similar reaction conditions have been applied to the carbonylation of terminal alkynes[5] and the synthesis of 3-halobenzo[*b*]furans by Li.[6] Recently, we found that treatment of 1,2-dialkynylbenzenes with five mol% of $PdCl_2$ and two equivalents of $CuCl_2$ gave benzofulvenes in good chemical yields.[7] Our continued interest in the cyclization reactions of enediynes for the synthesis of heterocycles[8] encouraged us to investigate the cyclization reaction of methyl 2-[6-substituted-3(*Z*)-hexen-1,5-diynyl]benzoates (**1**) in the presence of catalytic amount of $PdCl_2$ and three equivalents of $CuCl_2$ to give functionalized dibenzo-[*b*,*d*]pyran-6-ones (**2**).

The synthesis of methyl 2-[6-alkyl-3(*Z*)-hexen-1,5-diynyl]benzoates (**1a–f**) starting from methyl 2-iodobenzoate (**3**) is outlined in Scheme 1. A Sonogashira coupling reaction of **3** with trimethylsilylacetylene using $Pd(PPh_3)_4$ as the catalyst gave compound **4** in 91% yield. The silyl group was removed by treatment



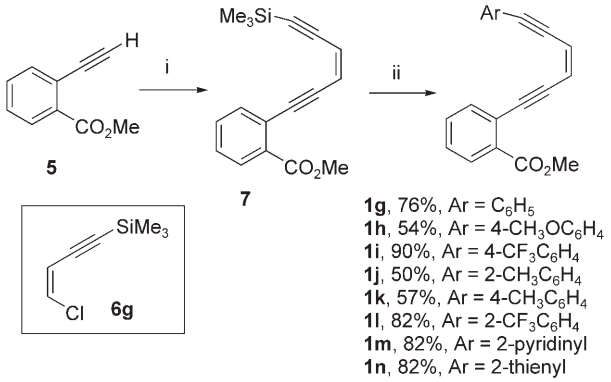
Reagents and conditions: (i) $Pd(PPh_3)_4$, CuI, *n*-$BuNH_2$, Et_2O, r.t., 6 h, 78% (ii) K_2CO_3, MeOH, 86% (iii) **6**, $Pd(PPh_3)_4$, CuI, *n*-$BuNH_2$, Et_2O, r.t., 6 h, 69%.

Scheme 1. Preparation of **1a–f**.

of **4** with methanol in the presence of potassium carbonate to give **5** in 85% yield. Compound **5** was then coupled with various vinyl chlorides **6a–f** under the Sonogashira coupling reaction conditions to give the desired products **1a–f** in 59–89% yields, respectively. The synthesis of methyl 2-[6-aryl-3(*Z*)-hexen-1,5-diynyl]benzoates (**1g–n**) is outlined in Scheme 2. Compound **5** was coupled with vinyl chloride **6g** using $Pd(PPh_3)_4$ as the catalyst to give enediyne **7** in 76% yield. Compound **7** was then treated with various aryl iodides in the presence of a catalytic amount of $Pd(PPh_3)_4$ in methanol to give **1g–n** in 50–90% yields.

Treatment of compound **1a** with five mol% of $PdCl_2$ and three equivalents of $CuCl_2$ in various organic solvents gave cyclization adduct **2a** in 3–65% yields. It was found that compound **2a** could be obtained in the highest yield (65%) in refluxing acetonitrile. The results are summarized in Table 1 and the structure of compound **2a** was unambiguously determined by X-ray crystallography[9] (Figure 1).

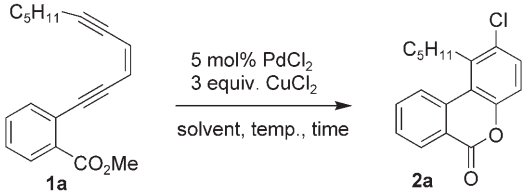
Other methyl 2-[6-substituted-3(*Z*)-hexen-1,5-diynyl]benzoates **1b–i** bearing different substituents on the



Reagents and conditions: (i) **6g**, $Pd(PPh_3)_4$, CuI, *n*-$BuNH_2$, Et_2O, r.t., 6 h, 76% (ii) ArI, $Pd(PPh_3)_4$, CuI, K_2CO_3, MeOH, r.t., 4 h.

Scheme 2. Preparation of **1g–n**.

Table 1. Solvent effects on the cyclization reactions.



Solvent	Temp [°C]	Time [h]	Yield [%]
CH_3CN	reflux	1	65
THF	reflux	1	45
Et_2O	reflux	12	30
Toluene	80	24	24
DMF	80	24	23
Benzene	reflux	24	22
DMSO	80	24	9
CH_2Cl_2	reflux	24	9
CH_3OH	reflux	24	3

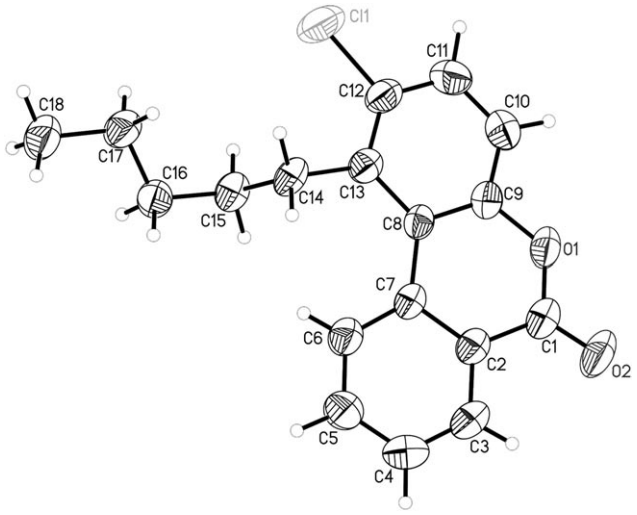
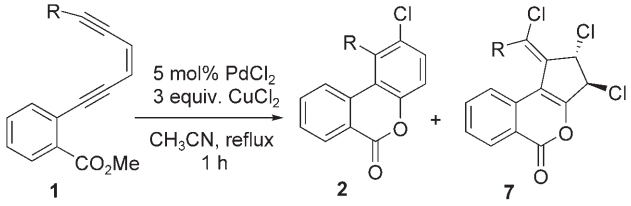


Figure 1. ORTEP plot of the X-ray crystal structure of **2a.**

Table 2. Synthesis of various dibenzo[*b*,*d*]pyran-6-ones.



Compounds	R	Products (Yield [%])	
1a	$(CH_2)_4CH_3$	**2a** (65)	
1b	$(CH_2)_5CH_3$	**2b** (63)	
1c	$CH_2CH(CH_3)_2$	**2c** (40)	**7c** (8)
1d	$C(CH_3)_3$	**2d** (11)	**7d** (15)
1e	$(CH_2)_4OH$	**2e** (47)	
1f	CH_2OH	**2f** (76)	
1g	C_6H_5	**2g** (65)	**7g** (11)
1h	4-$CH_3OC_6H_4$	**2h** (47)	**7h** (13)
1i	4-$CF_3C_6H_4$	**2i** (50)	
1j	2-$CH_3C_6H_4$	**2j** (32)	**7j** (8)
1k	4-$CH_3C_6H_4$	**2k** (39)	**7k** (10)
1l	2-$CF_3C_6H_4$	**2l** (35)	
1m	2-pyridinyl	**2m** (42)	
1n	2-thienyl	**2n** (28)	**7n** (trace)

terminal alkynes have also been subjected to the cyclization reaction under the optimal reaction conditions. The results are summarized in Table 2. With the exception of compound **1d**, these reactions gave the dibenzo[*b*,*d*]pyran-6-ones in modest to good yields. The low yield of dibenzo[*b*,*d*]pyran-6-one **2d** obtained by cyclization of **1d** could be due to steric hinderance caused by the *tert*-butyl group, which adversely affects the cyclization reaction. It was also found that if a bulky substituent, such as isobutyl, is present at the 6-position a small amount (8%) of an undesired product (**7c**) was obtained. The structure of **7c** was unambiguously determined by X-ray crystallography[9] (Figure 2). Similar results were observed in the reactions of **1d**, **1g** and **1h**. Compounds **2d**, **2g** and **2h** were obtained in 11%, 65% and 45% yields along with **7d**, **7g** and **7h** in 15%, 11% and 13% yields, respectively. Reaction of **1i** under the same reaction conditions gave cyclization adduct **2i** in 50% yield, however no five-membered ring adduct of the type **7** was observed. Compounds **1g**, **1h** and **1i** all have an aryl group at the alkyne terminus, but only **1i** bearing an electron-withdrawing group at the *para* position of the aryl ring did not give the five-membered ring adduct **7**. This observation led us to explore substituent effects upon this cyclization reaction. Accordingly, compounds **1j–n** were prepared and subjected to the cyclization reaction conditions. The results show that compounds bearing an electron-donating group on the aryl ring, such as **1j** and **1k**, gave dibenzo-[*b*,*d*]pyran-6-ones **2j** and **2k** as the major products along with the minor adducts **7j** and **7k** in 8% and

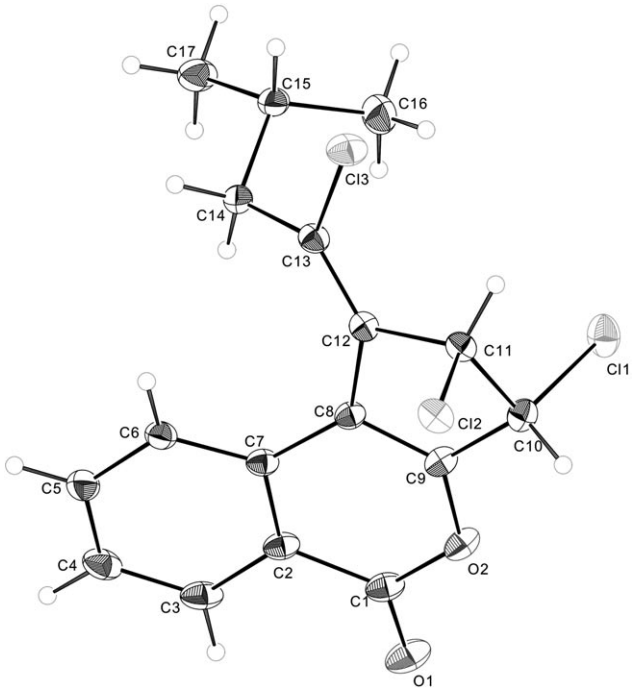
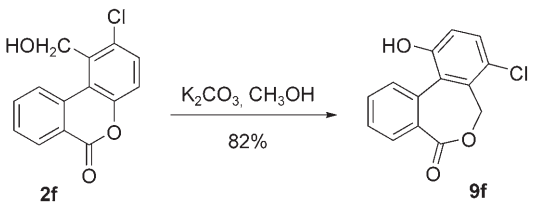


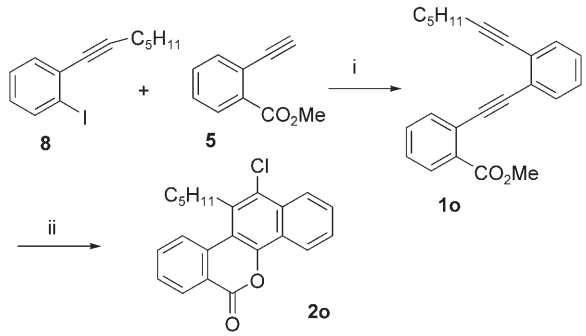
Figure 2. ORTEP plot of the X-ray crystal structure of **7c**.

10% yields, respectively. Compound **1l** bearing a trifluoromethyl group at the 2-position of the phenyl ring gave only the dibenzo[*b*,*d*]pyran-6-one **2l** albeit in lower yield (35%). The low yield of this reaction could be due to steric hinderance caused by the *ortho* substituent. The electron-deficient pyridinyl ring has also been employed in this cyclization reaction. Cyclization of compound **1m** gave compound **2m** as the only product. Compound **1n** containing a more electron-rich thienyl group gave **2n** in 28% yield and a trace amount of the five-membered ring adduct **7** could be observed in the ^{1}H NMR spectrum of the crude reaction mixture.

Compound **1o** has also been prepared by the palladium-catalyzed coupling reaction of **5** with 2-(1-heptynyl)-1-iodobenzene (**8**). Treatment of **1o** with five mol% of $PdCl_2$ and three equivalents of $CuCl_2$ under optimal reaction conditions gave the 6*H*-benzo[*d*]naphthol[1,2-*b*]pyran-6-one product **2o** in 63% yield. (Scheme 3) Finally, compound **2f** was converted to the seven-membered ring lactone **9f** in 82% yield by treatment with methanol in the presence of potassium carbonate [Eq. (1)].



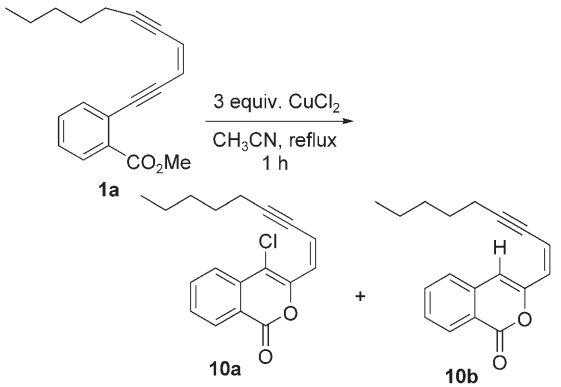
(1)



Reagents and conditions: (i) $Pd(PPh_3)_4$, CuI, *n*-$BuNH_2$, Et_2O, r.t., 6 h, 78% (ii) $PdCl_2$, $CuCl_2$, CH_3CN, reflux, 1 h, 63%.

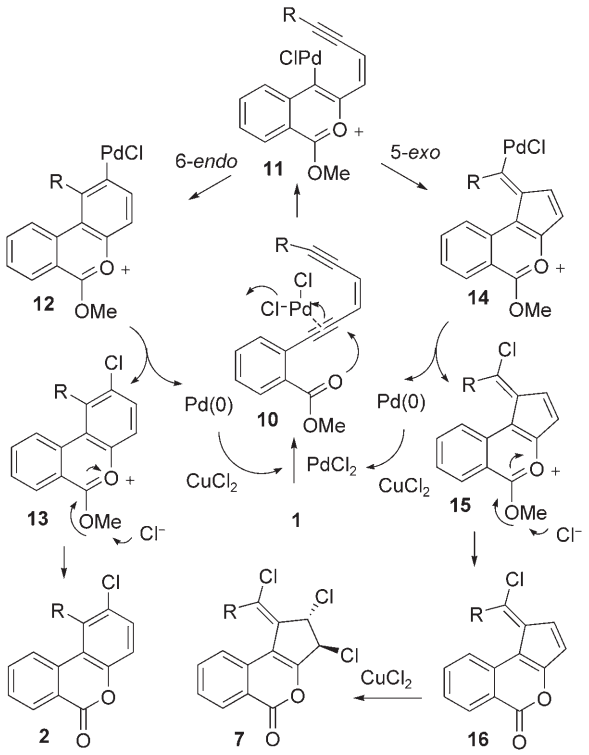
Scheme 3. Synthesis of compound **2o**.

We have also carried out control experiments by simply treating **1a** with three equivalents of $CuCl_2$ in the absence of $PdCl_2$ in refluxing CH_3CN for 1 h. The monocyclized product **10a** was obtained in 64% yield along with **10b** in 32% yield [Eq. (2)]. However,



(2)

treatment of **1a** with one equivalent of $PdCl_2$ under the same reaction conditions, gave compound **2a** in 61% yield as the only product. As a result of these control experiments, we find that $PdCl_2$ is required for the formation of the dibenzo[*b*,*d*]pyran-6-ones. The proposed mechanism for the formation of products **2** and **7** is outlined in Scheme 4. Initially, palladium(II) coordinates with the triple bond of the substrate (**1**) to form complex **10**. The carbonyl oxygen of the ester functionality then attacks C-2 of the alkyne to form oxonium ion **11**. This vinyl palladium intermediate may then undergo either 6-*endo* or 5-*exo* cyclization to form intermediate **12** or **14**, respectively. In the presence of $CuCl_2$, the C–Pd bond would be cleaved to form a C–Cl bond to provide intermediate **13**. Finally, the methyl group of **13** is then removed by nucleophilic attack of chloride to give compounds **2**. On the other hand, cleavage of the C–Pd bond of intermediate **14** by $CuCl_2$, followed by removing the methyl group of **15** by nucleophilic attack



Scheme 4. The proposed mechanism for the formation of compounds **2** and **7**.

of chloride would give fulvene **16**. Compound **16** may react with $CuCl_2$ to give trichloro products **7**. Basically, the second cyclization step favors the 6-*endo* pathway to provide the aromatized product. However, when the substituent on the terminal alkyne is a more sterically hindered alkyl group or a more electron-rich aryl ring, the 5-*exo* adducts are obtained as minor products.

In conclusion, we have developed an efficient synthetic method for the construction of the dibenzo-[*b*,*d*]pyran-6-one ring system. This method involves a one-step palladium-catalyzed tandem cyclization reaction of enediynes. Yields are from modest to good. We have also observed substituent effects on this cyclization reaction. The application of this methodology to the synthesis of natural products is currently under investigation.

Experimental Section

Coupling Reaction of Methyl 2-Ethynylbenzoate (5) with Vinyl Chloride (6) (Method A)

To a stirred solution of vinyl chloride (7.5 mmol) in anhydrous ether (20 mL) in the presence of $Pd(PPh_3)_4$ (5 mol%) was added a solution of methyl 2-ethynylbenzoate (1.2 g, 7.5 mmol) , CuI (5 mol%) and *n*-butylamine (0.5 mL) in anhydrous ether (20 mL). The resulting solution was stirred at room temperature for 6 h, quenched with saturated NH_4Cl solution and extracted with EtOAc (60 mL × 3). The combined organic extracts were washed with saturated Na_2CO_3 solution and dried over anhydrous $MgSO_4$. After filtration and removal of solvent, the residue was purified by column chromatography (silica gel 400 mesh, 1:30 EtOAc:hexane as eluent) to give the products.

Cyclization of Methyl 2-[6-Substituted-3(*Z*)-hexen-1,5-diynyl]benzoate (Method B)

The reaction mixture of methyl 2-[6-substituted 3(*Z*)-hexen-1,5-diynyl]benzoate (0.36 mmol), $PdCl_2$ (3.16 mg, 5 mol%) and $CuCl_2$ (145 mg, 1.08 mmol) in CH_3CN (5 mL) was heated to reflux and stirred at this temperature for 1 h. After cooling to room temperature, the reaction mixture was quenched with saturated NH_4Cl solution and extracted with EtOAc (30 mL × 2). The combined organic extracts were dried over anhydrous $MgSO_4$. After filtration and removal of solvent, the residue was purified by column chromatography (silica gel 400 mesh, 1:30 EtOAc:hexane as eluent) to give the products.

Acknowledgements

We thank the National Science Counci of the Republic of Chinal for financial support.

References

[1] a) J. M. Schmidt, G. B. Tremblay, M. Page, J. Mercure, M. Feher, R. Dunn-Dufault, M. G. Peter, P. R. Redden, *J. Med. Chem.* **2003**, *46*, 1289; b) X. Wang, K. F. Bastow, C. M. Su, Y. L. Lin, H. J. Yu, M. D. Don, T. S. Wu, S. Nakamura, K. H. Lee, *J. Med. Chem.* **2004**, *47*, 5816; c) X. Wang, K. Nakagawa-Goto, K. F. Bastow, M. D. Don, T. S. Wu, K. H. Lee, *J. Med. Chem.* **2006**, *49*, 5631; d) T. Kawasaki, Y. Yamamoto, *J. Org. Chem.* **2002**, *67*, 5138; e) L. D. Via, E. Uriarte, E. Ouezada, A. Dolmella, M. G. Ferlin, O. Gia, *J. Med. Chem.* **2003**, *46*, 3800; f) Q. J. Zhou, K. Worm, R. E. Dolle, *J. Org. Chem.* **2004**, *69*, 5147; g) V. T. H. Nguyen, P. Langer, *Tetrahedron Lett.* **2005**, *46*, 1013; h) H. Abe, K. Nishioka, S. Takeda, M. Arai, Y. Takeuchi, T. Harayama, *Tetrahedron Lett.* **2005**, *46*, 3197; i) R. Girotti, A. Marracchi, L. Minuti, O. Piermatti, F. Pizzo, L. Vaccaro, *J. Org. Chem.* **2006**, *71*, 70; j) S. Madan, C. H. Cheng, *J. Org. Chem.* **2006**, *71*, 8312.

[2] a) J. J. Li, G. W. Gribble, *Palladium in Heterocyclic Chemistry: A Guide for the Synthetic Chemist*, Elsevier Science Ltd., Oxford, **2000**; b) J. Tsuji, *Palladium Reagents and Catalyst: Innovations in Organic Synthesis*, John Wiley & Sons, New York, **1995**; c) R. F. Heck, *Palladium Reagents in Organic Synthesis*, Academic Press, New York, **1985**.

[3] S. Ma, B. Wu, X. Jiang, S. Zhao, *J. Org. Chem.* **2005**, *70*, 2568.

[4] S. Ma, B. Wu, X. Jiang, *J. Org. Chem.* **2005**, *70*, 2588.

[5] J. H. Li, S. Tang, Y. X. Xie, *J. Org. Chem.* **2005**, *70*, 477–479.

[6] Y. Ling, S. Tang, X. D. Zhang, L. Q. Mao, Y. X. Xie, J. H. Li, *Org. Lett.* **200**6, 8, 3017.

[7] C. Y. Lee, M. J. Wu, *Eur. J. Org. Chem.* **2007**, 3463.
[8] a) M. J. Wu, C. F. Lin, S. H. Chen, *Org. Lett.* **1999**, *1*, 767; b) M. J. Wu, C. Y. Lee, C. F. Lin, *Angew. Chem.* **2002**, *114*, 4251; *Angew. Chem. Int. Ed.* **2002**, *41*, 4077; c) M. J. Wu, C. F. Lin, W. D. Lu, *J. Org. Chem.* **2002**, *67*, 5907; d) C. Y. Lee, C. F. Lin, J. L. Lee, C. C. Chiu, W. D. Lu, M. J. Wu, *J. Org. Chem.* **2004**, *69*, 2106; e) Z. Y. Chen, M. J. Wu, *Org. Lett.* **2005**, *7*, 475.
[9] Crystal data for **2a**: $C_{18}H_{17}ClO_2$, unit cell parameters: $a=10.790$ (3), $b=12.210$ (4), $c=13.502$ (4), $\alpha=71.731$ (5), $\beta=67.179$ (5), $\gamma=68.035$ (5), space group *P*-1. Crystal data for **7c**: $C_{17}H_{15}Cl_3O_2$, unit cell parameters: $a=7.21130$ (10), $b=9.01260$ (10), $c=14.2796$ (3), $\alpha=105.4050$ (10), $\beta=90.5200$ (10), $\gamma=112.8580$ (10), space group *P*-1. CCDC 683257 (**2a**) and CCDC 683176 (**7c**) contain 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 or CCDC, 12 Union Road, Cambridge CB2 1ED, UK [fax:+44-(1223)-336-033; e-mail deposit@ccdc.cam.ac.uk.

