DOI: 10.1002/adsc.200800339

Straightforward Synthesis of Perhydrofuro[2,3-*b*]furans through a Wacker-Type Reaction

Francisco Alonso,[a,*] Daniel Sánchez,[a] Tatiana Soler,[b] and Miguel Yus[a,*]

[a] Departamento de Química Orgánica, Facultad de Ciencias, and Instituto de Síntesis Orgánica (ISO), Universidad de Alicante, Apdo. 99, 03080 Alicante, Spain
Fax: (+34)-9-6590-3549; e-mail: falonso@ua.esyus@ua.es

[b] Unidad de Cristalografía de Rayos X, Servicios Técnicos de Investigación, Facultad de Ciencias, Universidad de Alicante, Apdo. 99, 03080 Alicante, Spain

Received: June 2, 2008; Revised: July 10, 2008; Published online: August 13, 2008

Abstract: An efficient synthesis of substituted perhydrofuro[2,3-*b*]furans has been accomplished from readily accesible 3-methylidene-1,5-diols based on an intramolecular acetalisation under Wacker-type reaction conditions.

Keywords: intramolecular acetalisation; palladium catalysis; perhydrofuro[2,3-*b*]furans; Wacker reaction

Introduction

The perhydrofuro[2,3-*b*]furan unit is present in many natural products with important biological activities. Members of the clerodane family, such as lupuline A (**I**), contain this fragment and show potential insect antifeedant as well as antibacterial activity (Figure 1).[1] The mentioned dioxabicyclic moiety is also present in communiol D (**II**), isolated from the fungus *Podospora communis*.[2] Aflatoxin B_2[3] (**III**) and asteltoxin[4] (**IV**) are important mycotoxins with very potent toxicity and carcinogenecity,[5] whereas TMC-114[6] (**V**) is a HIV-protease inhibitor, which has been recently approved by the FDA for AIDS treatment under the name Darunavir (Figure 1).

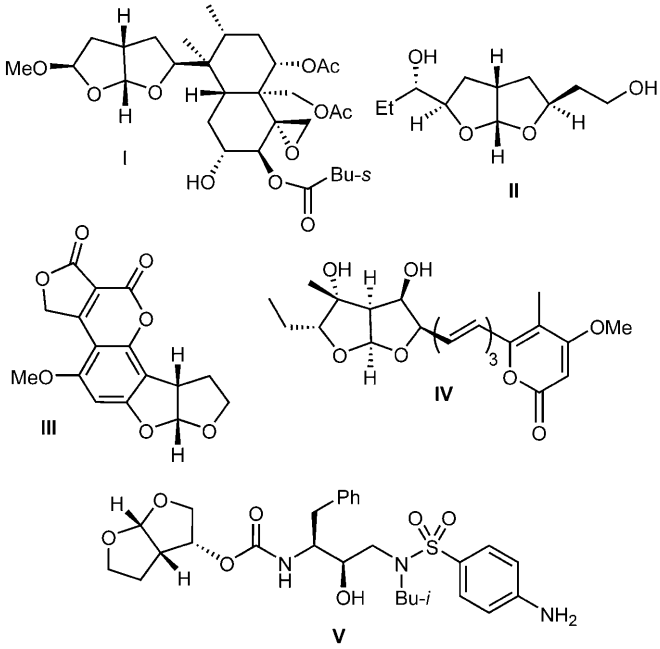
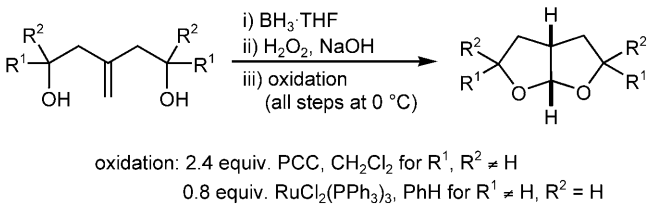


Figure 1. Examples of perhydrofuro[2,3-*b*]furans.

In recent years, much attention has been focused on the development of efficient methodologies for the construction of perhydrofuro[2,3-*b*]furans because of their structural attractiveness and synthetic challenge. Most of the methodologies to synthesise the 2,8-dioxabicyclo[3.3.0]octane moiety use an inter- or intramolecular cyclisation on a pre-formed tetrahydrofuran ring through lactol formation,[7] radical cyclisation,[8] haloetherification,[9] cycloaddition,[10] or intramolecular carbozincation.[11] Double intramolecular cyclisations from an acyclic precursor are, however, much less common.[12] Due to our interest in the synthesis of fused bicyclic[13] and spirocyclic[14] polyether skeletons, we reported the synthesis of differently substituted 3-methylidene-1,5-diols from new trimethylenemethane dianion synthons, which subsequently could be transformed into the corresponding perhydrofuro[2,3-*b*]furans.[13a,b,d] This transformation involved three steps: hydroboration, alkaline hydrogen peroxide oxidation, and final oxidation of the hydroxymethyl moiety in the resulting triol. The latter oxidation had to be performed with PCC in dichloromethane (for the hydromethylated tertiary 1,5-diols) or with $RuCl_2(PPh_3)_3$ in benzene (for the hydroxymethylated secondary 1,5-diols) (Scheme 1). The whole process, however, cannot be considered very efficient since: (a) three synthetic steps were needed with low atom economy, (b) consequently, the process was time-consuming and the product yields were rather



Scheme 1. Three-step synthesis of perhydrofuro[2,3-*b*]furans from 3-methylidene-1,5-diols.

moderate (36–75%), (c) the reactions were performed in non-green media, and (d) the rather toxic reagents were used in stoichiometric amounts.

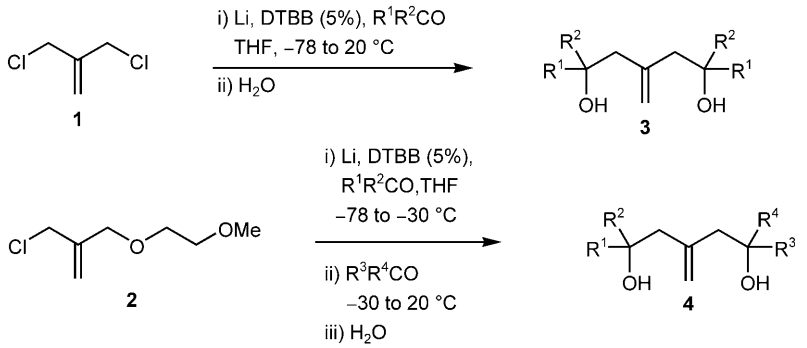
On the other hand, the palladium-catalysed intramolecular Wacker-type reaction is a versatile method for the synthesis of oxygen-containing heterocycles.[15] Thus, starting from a dihydroxyalkene, interesting dioxabicyclic structures can be obtained, including bicyclic acetals.[15,16] For the cyclisation to occur, however, the alkene must be terminal. The palladium-catalysed acetalisation of alkenes has also been carried out with hydroxyalkenes and an alcohol (intramolecular-intermolecular oxypalladation),[15] or with activated substrates (α,β-unsaturated carbonyl compounds) and an alcohol or diol (intermolecular oxypalladation).[17] In every case, the presence of a terminal alkene is mandatory. Geminal disubstituted alkenes are less reactive in this reaction due to ineffective coordination of Pd(II) to the alkene. To the best of our knowledge, the only examples reported so far involve methacryloyl derivatives and methanol,[15,17a] whereas the intramolecular acetalisation of a dihydroxy-substituted geminal alkene has never been reported.

We want to report herein the first intramolecular acetalisation of a geminal alkene moiety, which is present in a 3-methylidene-1,5-diol, and under Wacker-type reaction conditions, leads to perhydrofuro[2,3-*b*]furans in a straightforward and efficient manner.

Results and Discussion

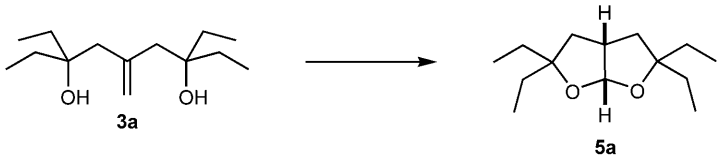
The starting symmetrically-substituted methylidene-1,5-diols **3** were prepared from commercially available 3-chloro-2-(chloromethyl)propene (**1**) by reaction with lithium and a catalytic amount of DTBB (4,4′-di-*tert*-butylbiphenyl) in the presence of different carbonyl compounds (Scheme 2).[13d] The reagent 2-chloromethyl-3-(2-methoxyethoxy)propene (**2**), derived from **1**, allowed the reaction with a first carbonyl compound through a selective chloro-lithium exchange at −78 to −30 °C, and with a second carbonyl compound at −30 °C to room temperature, through an allylic carbon-oxygen bond reductive cleavage, leading to the corresponding unsymmetrically substituted methylidene-1,5-diols **4** (Scheme 2).[13d]

The palladium-catalysed cyclisation reaction under Wacker-type reaction conditions was optimised using 3,7-diethyl-5-methylidenenonane-3,7-diol (**3a**) as the model substrate and the results are shown in Table 1. Initial cyclisation attempts were carried out under standard reaction conditions with the $PdCl_2$ (10 mol%)-$CuCl_2$ catalytic system in different solvents and atmospheres. Low to modest conversions were achieved in HOAc (Table 1, entries 1–3),[16] the presence of oxygen at reflux providing the best result. The results obtained in the most commonly used mixture of solvents for Wacker processes,[18] DMF-H_2O, were also disappointing (Table 1, entries 4 and 5). In contrast, much better conversions were reached when the reactions were performed in alcoholic solvents (Table 1, entries 6–8). Up to 82% yield was obtained in MeOH under an oxygen atmosphere at 50 °C for 24 h (Table 1, entry 6). In an attempt to shorten the reaction times, we also studied the $Pd(OAc)_2$ (10 mol%)-H_2O_2 catalytic system.[19] In this case, HOAc led to moderate conversions (Table 1, entries 9–11), whereas MeOH proved to be an inappropriate solvent (Table 1, entry 12). We were very pleased, however, upon observing a 70% yield in only 4 h when the reaction was carried out using 10 mol% $PdCl_2$ in H_2O_2-MeOH at 70 °C (Table 1, entry 13). This yield could be even improved by the combined oxidating action



Scheme 2. Synthesis of the starting 3-methylidene-1,5-diols.

Table 1. Optimisation of the reaction conditions for the cyclisation of **3a** to **5a**.



Entry	Catalyst [mol%]	Oxidant [mol%]	Solvent–atmosphere	Temperature [°C]	Time [h]	Yield [%][a]
1	$PdCl_2$ (10)	$CuCl_2$ (300)	HOAc/NaOAc–Ar	r.t.	24	14
2	$PdCl_2$ (10)	$CuCl_2$ (500)	HOAc/NaOAc–air	50	41	28
3	$PdCl_2$ (10)	$CuCl_2$ (500)	HOAc–O_2	reflux	10	45
4	$PdCl_2$ (10)	$CuCl_2$ (500)	DMF/H_2O 7:1–air	r.t.	24	10
5	$PdCl_2$ (10)	$CuCl_2$ (300)	DMF/H_2O 7:1–O_2	r.t.–50	24	0
6	$PdCl_2$ (10)	$CuCl_2$ (500)	MeOH–O_2	50	24	82
7	$PdCl_2$ (10)	$CuCl_2$ (500)	MeOH–air	50	24	34
8	$PdCl_2$ (10)	$CuCl_2$ (500)	EtOH–O_2	65	19	70
9	$Pd(OAc)_2$ (10)	H_2O_2 (500)	HOAc–Ar	r.t.	17	51
10	$Pd(OAc)_2$ (10)	H_2O_2 (500)	HOAc–Ar	80	6	45
11	$Pd(OAc)_2$ (10)	H_2O_2 (500)	HOAc–Ar	80	15	57
12	$Pd(OAc)_2$ (10)	H_2O_2 (500)	MeOH–Ar	50	6	trace
13	$PdCl_2$ (10)	H_2O_2 (1000)	MeOH	70	4	70
14	$PdCl_2$ (10)	$CuCl_2$ (100)-H_2O_2 (500)	MeOH	70	3	85
15	$PdCl_2$ (1)	$CuCl_2$ (10)-H_2O_2 (500)	MeOH	70	8	3
16	$PdCl_2$ (5)	$CuCl_2$ (5)-H_2O_2 (500)	MeOH	70	8	20
17	$PdCl_2$ (5)	$CuCl_2$ (20)-H_2O_2 (500)	MeOH	70	5	88
18	$PdCl_2$ (5)	$CuCl_2$ (50)-H_2O_2 (500)	MeOH	70	8	96
19	$PdCl_2$ (5)	$CuCl_2$ (100)-H_2O_2 (500)	MeOH	70	8	86

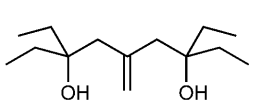
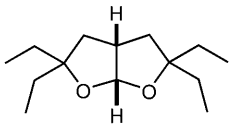
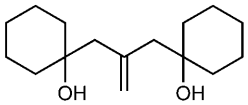
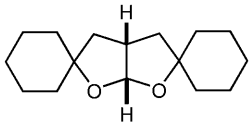
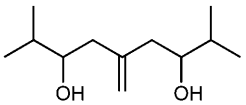
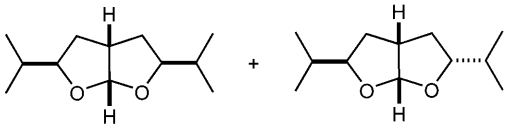
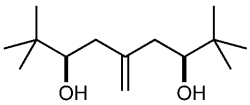
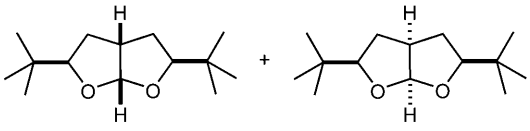
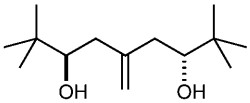
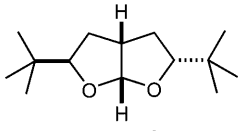
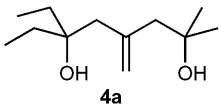
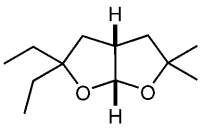
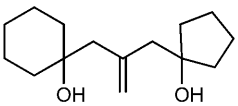
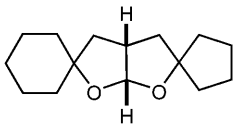
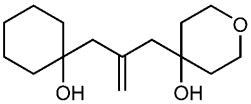
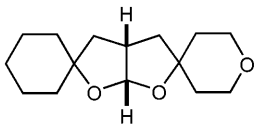
[a] Determined by GLC. The data obtained are very close to the corresponding conversion values with variations $\leq 2\%$.

of $CuCl_2$ and H_2O_2 (Table 1, entry 14). Further optimisation of the amounts of catalyst and oxidants in the latter system (Table 1, entries 15–19) led to a final catalytic system composed of $PdCl_2$ (5 mol%)-$CuCl_2$ (50 mol%)-H_2O_2 (500 mol%)-MeOH, with which up to 96% yield was achieved at 70 °C for 8 h (Table 1, entry 18).

With the optimised reaction conditions in hand, we studied the palladium-catalysed intramolecular acetalisation of different methylidenic diols (Table 2). The symmetrically-substituted diols **3a**–**d** (Table 2, entries 1–5) were prepared from the trimethylenemethane dianion synthon **1** as shown in Scheme 2. Diols **3a** and **3b**, derived from pentan-3-one and cyclohexanone, respectively, were cyclised in high isolated yields (Table 2, entries 1 and 2). Diol **3c**, derived from isobutyraldehyde, was obtained as a 1:1 mixture of diastereoisomers, its cyclisation leading to a 1:1 mixture of compounds β-*cis*-**5c** and *trans*-**5c** (Table 2, entry 3). From these results it can be inferred that the cyclisation of *meso*-**3c** was highly diastereoselective, since the corresponding product α-*cis*-**5c**, in which both isopropyl groups and the hydrogen atoms at the ring fusion are located on opposite sides of the bicyclic structure, was not obtained. Diols **3d** derived from pivalaldehyde were also obtained as a 1:1 diastereomeric mixture. In this case, however, they could be separated by column chromatography and independently subjected to the palladium-catalysed intramolecular cyclisation (Table 2, entries 4 and 5). The cyclisation of *meso*-**3d** also proved to be diastereoselective, leading to a 94:6 mixture of the perhydrofuro[2,3-*b*]furans β-*cis*-**5d** and α-*cis*-**5d** in high yield. It is noteworthy that under the formerly reported cyclisation conditions (see Scheme 1) a *ca.* 1:1 mixture of the above mentioned perhydrofuro[2,3-*b*]furans was obtained.[13d] On the other hand, diol *dl*-**3d** led to the expected perhydrofuro[2,3-*b*]furan *trans*-**5d** in good yield.

We next studied the palladium-catalysed cyclisation of various unsymmetrically-substituted methylidenic diols **4**, prepared from the trimethylenemethane dianion synthon **2** and two different ketones (Table 2, entries 6–8). The effectivity in the cyclisation of diol **4a**, derived from pentan-3-one and acetone, was below the average due to a loss of mass in the work-up procedure. In contrast, diols **4b** and **4c**, derived from cyclohexanone and cyclopentanone, and cyclohexanone and tetrahydro-4*H*-pyran-4-one, respectively, furnished the corresponding tetracyclic products **6b** and **6c** in good to high yields (Table 2, entries 7 and 8). The structure and stereochemistry of compounds **5** and **6** was unequivocally assigned by comparison of their physical and spectroscopic data with those previously reported by us. It is worthy of note that this one-step Wacker-type cyclisation of diols **3** and **4** was,

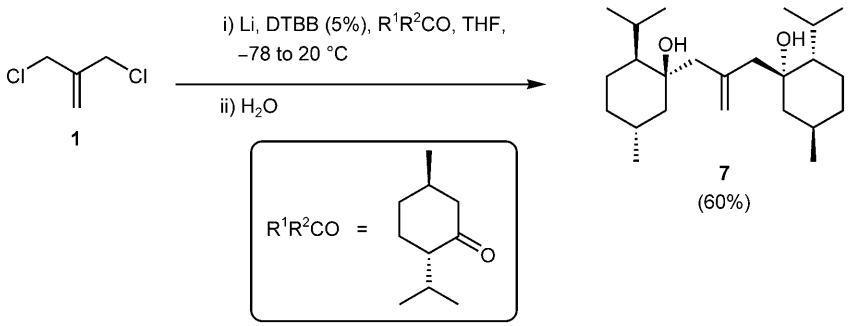
Table 2. Obtention of perhydrofuro[2,3-*b*]furans **5** and **6**.

Entry	Starting diol	Product[b]	Yield [%][c]
1	 **3a**	 **5a**	94
2	 **3b**	 **5b**	92
3	 (*meso* + *dl*)-**3c**	 β-*cis*-**5c** 1:1 *trans*-**5c**	86
4	 *meso*-**3d**	 β-*cis*-**5d** 94:6 α-*cis*-**5d**	86
5	 *dl*-**3d**	 *trans*-**5d**	78
6	 **4a**	 **6a**	55[d]
7	 **4b**	 **6b**	92
8	 **4c**	 **6c**	71[d]

[a] 5 mol% $PdCl_2$, 50 mol% $CuCl_2$, 5 equiv H_2O_2, MeOH, 70 °C, 8 h.
[b] All isolated products were ≥ 95% pure (GLC). Diastereomeric ratio determined by ^1H NMR.
[c] Crude yield unless otherwise stated.
[d] GLC yield.

in every case, higher yielding than the former three-step procedure.

We also devised the possibility of synthesising chiral non-racemic perhydrofuro[2,3-*b*]furans. For this purpose, 3-chloro-2-(chloromethyl)propene (**1**) was submitted to DTBB-catalysed lithiation in the presence of (−)-menthone. The major methylidenic diol obtained [commercially available (−)-menthone is 90% pure and contains isomenthone] was purified by column chromatography and assigned to the C_2-sym-



Scheme 3. Preparation of methylidenic diol **7** derived from (−)-menthone.

metrical diol **7** (Scheme 3). The new stereogenic centres arise from the attack of the organolithium intermediate to the less hindered carbonyl face, rendering the corresponding diaxial diol. This assignement was unequivocally confirmed by X-ray crystallography (Figure 2). It is worthy of note that, in contrast with the behaviour observed for some 4-methylidene-1,7-diols previously reported by us,[14 g] neither intramolecular nor intermolecular hydrogen bonding was observed for the 3-methylidene-1,5-diol **7** (Figure 3).

Methylidenic diol **7** proved to be reluctant towards intramolecular acetalisation under the above optimised reaction conditions, being cyclised in low yield after 8 h. By using a double amount of the components of the catalytic system, however, the reaction reached total conversion after 24 h. The expected product **8** was isolated in moderate yield after column chromatography as an enantiomerically pure perhydrofuro[2,3-*b*]furan (Scheme 4).

On the basis of related Wacker-type oxidations,[15,18] a catalytic cycle (Scheme 5) was proposed for this new palladium-catalysed intramolecular acetalisation involving: (a) olefin activation by formation of the π-complex **VI**, (b) intramolecular oxypalladation to give the σ-palladium intermediate **VII**, (c) dehydropalladation leading to the π-palladium hydride complex **VIII**, (d) second intramolecular oxypalladation to furnish the σ-palladium hydride complex **IX**, and (e) reductive elimination. Due to the presence of MeOH as a

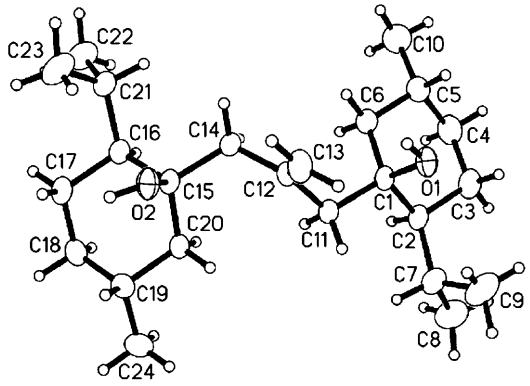


Figure 2. Plot showing the X-ray structure and atomic numbering for compound **7**.

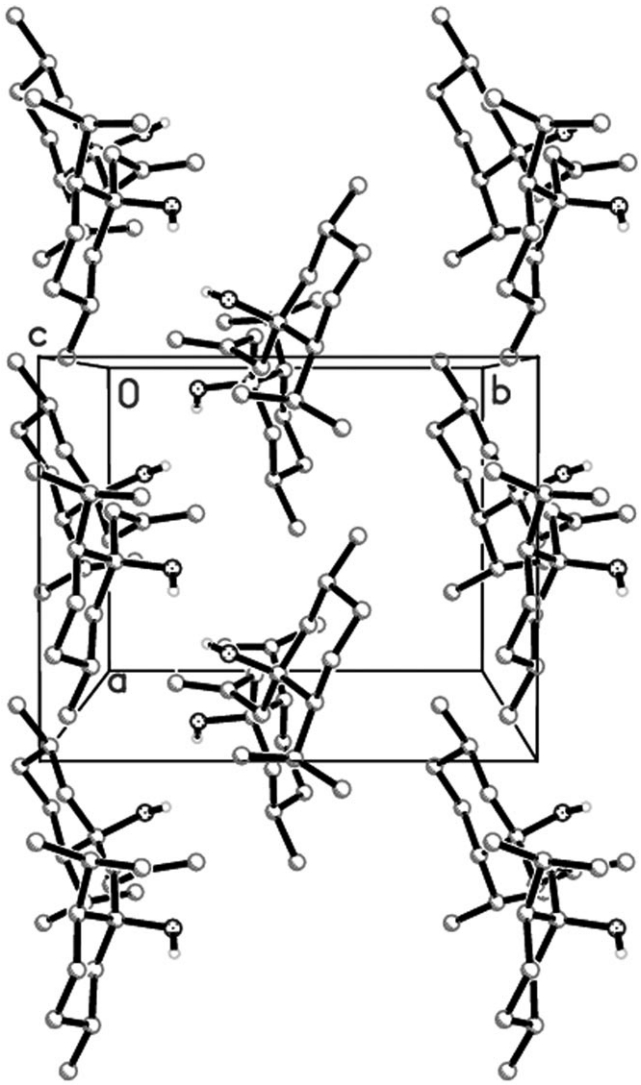
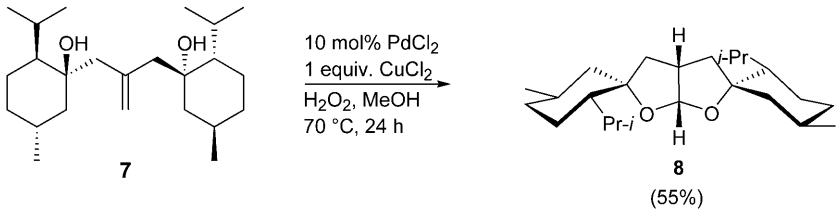
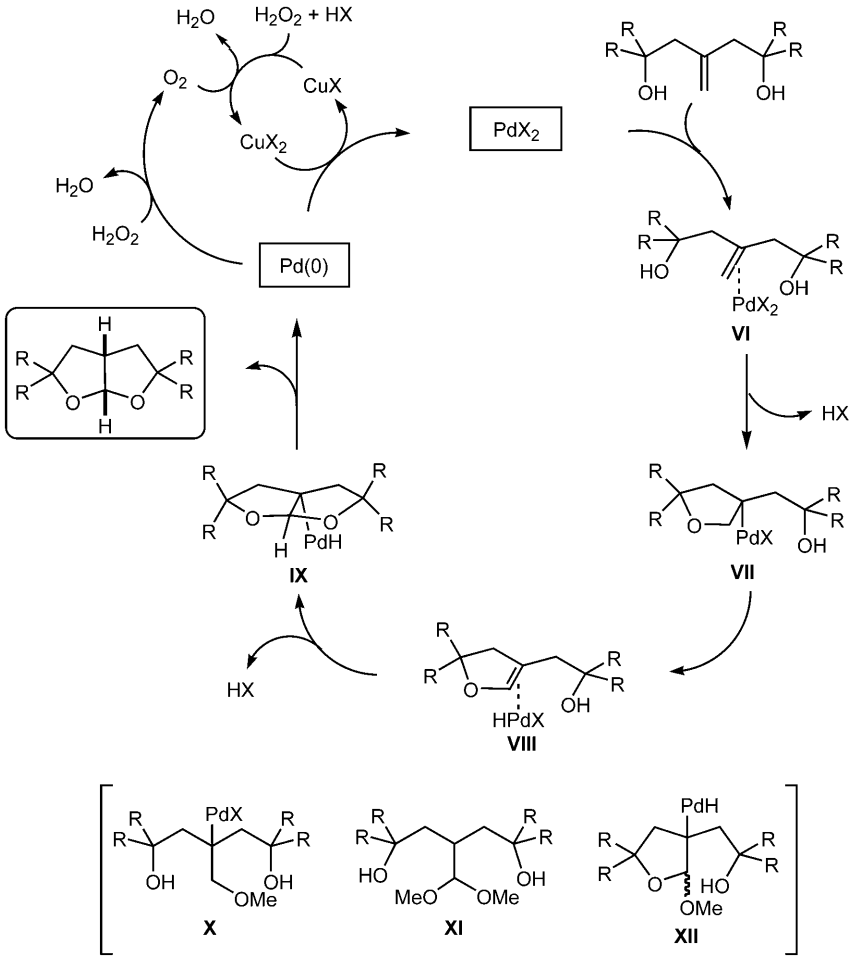


Figure 3. Unit cell plot of **7** in the crystal. The hydrogen atoms, except the hydroxy group hydrogen atoms, have been omitted for clarity.



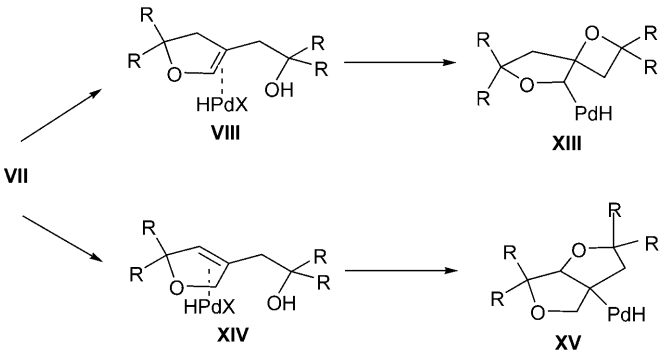
Scheme 4. Cyclisation of methylidenic diol **7** derived from (−)-menthone.



Scheme 5. Proposed catatytic cycle for the Wacker-type intramolecular acetalisation of methylidenic diols **3**, **4**, and **7**.

solvent in the reaction medium, intermolecular oxypalladations leading to species of the type **X**-**XII** cannot be ruled out. In this case, intermediates **XI** and **XII** could further undergo intramolecular transacetalisation reactions to afford the perhydrofuro[2,3-*b*]furans. The catalytic cycle is closed by the re-oxidation of Pd(0) with $CuCl_2$ and the re-oxidation of Cu(I) by the action of O_2 and/or H_2O_2. It is known that H_2O_2 can directly oxidise Cu(I) to Cu(II),[20] an additional Cu(I) oxidation by the O_2 evolved from the palladium-catalysed H_2O_2 decomposition,[21] however, cannot be disregarded. Formation of small amounts of Pd(0) has been observed in some experiments where the re-oxidation step was not completely effective. This result is in agreement with a Pd(0)/Pd(II) mechanism operating in this reaction instead of the alternative Pd(II)/Pd(IV) mechanism.

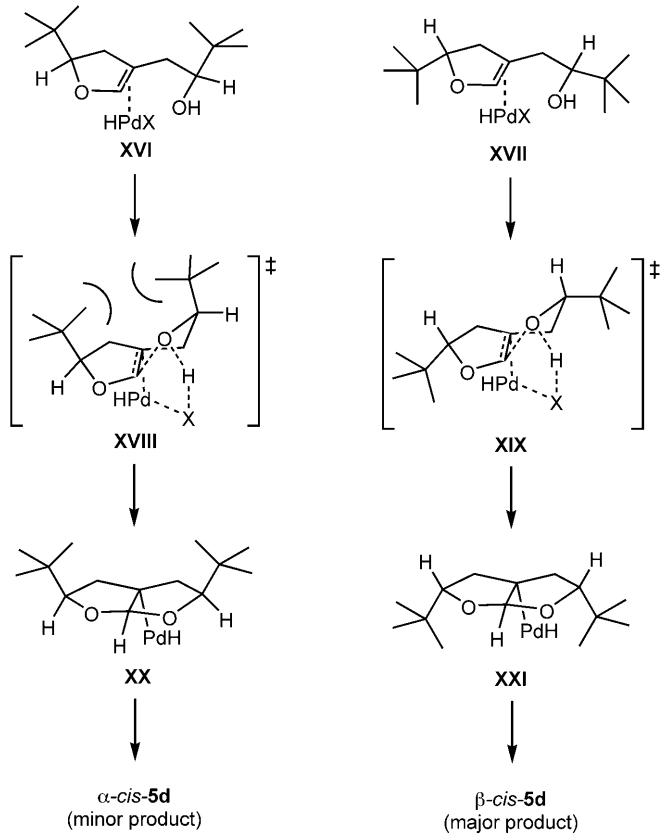
It is worthy of note that the above cyclisations proved to be highly regioselective as products derived from the alternative intramolecular oxypalladations, through intermediates **VIII** and **XIV** to **XIII** and **XV**, respectively, were never observed (Scheme 6). 1,6-Dioxaspiro[3.4]octanes, the products that would arise from the reductive elimination of **XIII**, were previously obtained, however, by intramolecular iodoetherification of diols **3**.[14a] On the other hand, products de-



Scheme 6.

rived from **XV** are not formed, very probably, because the dehydropalladation of **VII** to **VIII**, involving the OC–H bond, prevails over that of **VII** to **XIV**.

We also tried to rationalise the high stereoselectivity observed in the cyclisation of *meso*-**3c** and *meso*-**3d**, which is exemplified for the *tert*-butyl derivative *meso*-**3d** in Scheme 7. Starting from the two plausible π-palladium hydride complexes **XVI** and **XVII**, resulting from a first cyclisation, the corresponding and hypothetical transition states **XVIII** and **XIX** have been proposed for the second cyclisation. Transition state **XVIII** shows a clear and unfavourable steric interaction involving the two *tert*-butyl groups. This interaction is, however, minimised in transition state **XIX**, which through intermediate **XXI** would lead to β-*cis*-**5d** as the major product.



Scheme 7.

Conclusions

We have reported, for the first time, the palladium-catalysed intramolecular acetalisation of a dihydroxy-substituted geminal alkene. The cyclisation is carried out under optimised Wacker-type conditions, involving catalytic palladium(II), substoichiometric copper(II), and hydrogen peroxide in methanol. The process is regiospecific and has been applied to a variety of substrates affording the corresponding perhydrofuro[2,3-*b*]furans in moderate to high yields. A high stereoselectivity was achieved in the cyclisation reaction of *meso* compounds. Moreover, an enantiomerically pure perhydrofuro[2,3-*b*]furan has also been successfully synthesized in a straightforward manner from (−)-menthone. The methodology described herein represents a notable improvement with respect to that previously reported by us since (a) the whole transformation is carried out in one pot (one *vs.* three synthetic steps) with higher atom economy, (b) the process is faster, (c) the product yields are higher, (d) the reaction is performed in a greener medium, and (e) catalytic amounts of less toxic reagents are used.

Experimental Section

General Remarks

Melting points were obtained with a Reichert Thermovar apparatus. Optical rotations were measured with a Perkin–Elmer 341 polarimeter with a thermally jacketted 5 cm cell at approximately 20 °C. Concentrations (*c*) are given in g/100 mL and [α] values are given in units of 10^{-1} deg cm^2 g^{-1}. NMR spectra were recorded on a Bruker Avance 300 and Bruker Avance 400 (300 and 400 MHz for ^{1}H NMR, and 75 and 100 MHz for ^{13}C NMR, respectively). Mass spectra (EI) were obtained at 70 eV on an Agilent 5973 spectrometer. HR-MS analyses were carried out on a Finnigan MAT95S spectrometer. The purity of volatile compounds and the chromatographic analyses (GLC) were determined with a Hewlett Packard HP-6890 instrument equipped with a flame ionisation detector and a 30 m capillary column (0.32 mm diameter, 0.25 μm film thickness), using nitrogen (2 mL min^{-1}) as carrier gas, $T_{injector}$ = 275 °C, T_{column} = 60 °C (3 min) and 60–270 °C (15 °C min^{-1}). Flash column chromatography was performed using silica gel 60 of 40–60 microns. $PdCl_2$ (Merck), $CuCl_2$ (Aldrich), H_2O_2 (Acros), and MeOH (Panreac) were commercially available.

The starting methylidenic diols **3**, **4**, and **7** were prepared following previously reported procedures.[13d] Compounds **3** and **4** were characterised by comparison of their physical

and spectroscopic data with those previously reported.[13d] Data for new compound **7** are given below.

(1*S*,2*S*,5*R*)-1-(2-{[(1*S*,2*S*,5*R*)-1-Hydroxy-2-isopropyl-5-methylcyclohexyl]methyl}prop-2-enyl)-2-isopropyl-5-methylcyclohexan-1-ol (7): Colourless solid; $t_r = 18.68$; $R_f = 0.49$ (hexane-EtOAc 96:4); mp 105 °C (hexane); $[\alpha]_D^{20}$: +12.0 (*c* 1.0, CH_2Cl_2); IR (KBr): $\nu = 3541$ (O–H), 3066, 1625, 891 (HC=C) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.76$–1.02, 1.31–1.77 (2 m, 34 H, 6 × CH_3, 6 × CH_2, 4 × CH), 1.91, 3.12 (2 d, $J = 14.0$ Hz, 4 H, 2 × CH_2C=CH_2), 2.14–2.23 (m, 2 H, 2 × CH), 2.57 (s, 2 H, 2 × OH), 4.80 (s, 2 H, H_2C=C); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 18.1$, 22.6, 23.8, 25.5, 28.0, 51.6 (6 × CH_3, 6 × CH), 20.8, 35.0, 46.6, 47.2 (8 × CH_2), 74.7 (2 × CO), 117.3 (H_2C=C), 144.8 (C=CH_2); MS (EI): *m/z* (%) = 364 (M^+, <1), 346 ($M^+ - H_2O$, 2), 192 (10), 177 (26), 155 (63), 149 (25), 138 (10), 137 (100), 136 (17), 112 (10), 95 (30), 83 (11), 81 (55), 69 (44), 55 (31); HR-MS: *m/z* = 346.3221, calcd. for $C_{24}H_{44}O_2$: 364.3341 [$M^+ - H_2O$]: 346.3236.

Palladium-Catalysed Cyclisation of the Methylidenic Diols 3, 4, and 7; General Procedure

A solution of $PdCl_2$ (8.9 mg, 0.05 mmol), $CuCl_2$ (67.2 mg), MeOH (10 mL), and the corresponding diol (1 mmol) was prepared in a screw top tube, followed by the addition of a 35% H_2O_2 solution (0.43 mL). The top was airtight on the reaction tube which was heated at 70 °C for 8 h. Then, hexane (20 mL) and saturated NaCl solution (10 mL) were added to the resulting mixture. The aqueous phase was extracted with hexane (6 × 20 mL) and the organic phase was dried with anhydrous Na_2SO_4 followed by filtration through celite. The filtrate was evaporated (15 Torr), giving the corresponding perhydrofuro[2,3-*b*]furan as an oil, that in the case of compound **8** was purified by column chromatography (silica gel, hexane/ether).

The perhydrofuro[2,3-*b*]furans **5** and **6** were characterised by comparison of their physical and spectroscopic data with those previously reported.[13d] Data for the new compound **8** are given below.

Dispiro[(1*S*,2*S*,4*R*)-1-isopropyl-4-methylcyclohexane-2,2′-*cis*-tetrahydrofurano[2,3-*b*]furan-5′,2″-{(1*S*,2*S*,4*R*)-1-isopropyl-4-methylcyclohexane}] (8): Colourless oil; $t_r = 18.51$; $R_f = 0.61$ (hexane-ether, 96:4); $[\alpha]_D^{20}$: −12.5 (*c* 0.7, CH_2Cl_2); IR (neat): $\nu = 1383$, 1364 cm^{-1} (CH, *i*-Pr); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 0.73$–0.96 (6d, $J = 6.8$ Hz, 18 H, 6 × CH_3), 0.97–1.04, 1.39–1.51, 1.56–1.82, 1.87–1.93, 2.06–2.13 [5 m, 21 H, 8 × CH_2, 5 × CH), 2.19–2.25 [dd, $J = 13.2$, 10.4 Hz, 1 H, CH], 2.77–2.87 (m, 1 H, C*H*CHCO), 5.52 (d, $J = 5.7$ Hz, 1 H, OCHO); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 17.9$, 18.7, 22.4, 24.1, 26.1, 26.5 (6 × CH_3), 22.1, 22.5, 35.0, 35.3, 41.5, 42.9 (2 × CH_2CH-*i*-Pr, 2 × CH_2CH_2CH-*i*-Pr, 2 × CCH_2CHCH$_3$), 27.9, 29.0, 42.8, 47.5, 50.4 [6 × CHCH$_3$, CHCHO, 2 × CH-*i*-Pr], 47.6, 51.2 (OCCH_2CHCH_2CO), 87.8, 90.5 [2 × CH_2CO], 109.4 (OCHO); MS (EI): *m/z* (%) = 362 (M^+, 18), 344 (17), 277 (48), 189 (12), 176 (16), 175 (100), 174 (24), 151 (13), 149 (18), 137 (15), 135 (12), 109 (15), 95 (30), 93 (10), 83 (12), 81 (25), 69 (39), 67 (13), 55 (27); HR-MS: *m/z* = 362.3186, calcd. for $C_{24}H_{42}O_2$: 362.3185.

X-Ray Crystallography

Compound **7** was recrystallised from diethyl ether. Data collection was performed on a Bruker Smart CCD diffractometer, based on three ω-scan runs (starting ω = −34°) at the values of ø = 0°, 120°, 240° with the detector at 2θ = −32°. For each of these runs, 606 frames were collected at 0.3° intervals. An additional run at ø = 0° of 100 frames was collected to improve redundancy. The diffraction frames were integrated using the SAINT[22] programme and the integrated intensities were corrected for Lorentz polarisation effects with SADABS.[23]

X-ray data for 7:[24] $C_{24}H_{44}O_2$, $M = 364.59$; orthorhombic, $a = 8.5673(10)$ Å, $b = 10.5340(12)$ Å, $c = 25.875(3)$ Å; $V = 2335.2(5)$ Å^3; space group $P2_12_12_1$; $Z = 4$; $\rho_{cald} = 1.037$ Mg m^{-3}; $\lambda = 0.71073$ Å; $\mu = 0.063$ mm^{-1}; $F(000) = 816$; $T = 23 \pm 1$ °C. The structure was solved by direct methods[25] and refined to all 2371 unique F^2_o by full matrix least squares (SHELX97).[26] All the hydrogen atoms were placed at idealised positions and refined as rigid atoms. Final $wR2 = 0.1324$ for all data and 243 parameters; $R_1 = 0.0502$ for 1797 $F_o > 4\sigma(F_o)$.

Acknowledgements

This work was generously supported by the Spanish Ministerio de Educación y Ciencia(MEC; grant no. CTQ2004-01261 and CTQ2007-65218; Consolider Ingenio 2010-CSD2007-00006) and the Generalitat Valenciana (GV; grant no. GRUPOS03/135). D. S. thanks the Vicerrectorado de Investigación, Desarrollo e Innovación of the University of Alicante for a predoctoral grant.

References

[1] a) F. Camps, J. Coll, *Phytochemistry* **1993**, *32*, 1361–1370; b) H. Chen, R. X. Tan, Z. L. Liu, Y. Zhang, *J. Nat. Prod.* **1996**, *59*, 668–670.

[2] a) Y. Che, J. B. Gloer, J. A. Scott, D. Malloch, *Tetrahedron Lett.* **2004**, *45*, 6891–6894; b) M. Enomoto, T. Nakahata, S. Kuwahara, *Tetrahedron* **2006**, *62*, 1102–1109.

[3] For reviews, see: a) R. E. Minto, C. A. Townsed, *Chem. Rev.* **1997**, *97*, 2537–2555; b) C. A. Townsed, R. E. Minto, in: *Comprehensive Natural Products Chemistry*, Vol. 1, (Eds.: D. Barton, K. Nakanishi, D. Meth-Cohn, V. Sankawa), Elsevier, Oxford, **1999**, chapter 1.17.

[4] See, for instance: a) J. Mulzer, J.-T. Mohr, *J. Org. Chem.* **1994**, *59*, 1160–1165; b) J. V. Raman, H. K. Lee, R. Vleggaar, J. K. Cha, *Tetrahedron Lett.* **1995**, *36*, 3095–3098.

[5] W. F. Busby Jr., G. N. Wogan, in: *Chemical Carcinogens*, 2nd edn., Vol. 182, (Ed.: C. Searle), American Chemical Society, Washington DC, **1984**, pp 945–1136.

[6] a) A. K. Ghosh, D. W. Shin, L. Swanson, K. Krishnan, H. Cho, K. A. Hussain, D. E. Walters, L. Holland, J. Buthod, *Il Farm.* **2001**, *56*, 29–32; b) A. K. Ghosh, B. D. Chapsal, J. T. Weber, H. Mitsuya, *Acc. Chem. Res.* **2008**, *41*, 78–86.

[7] a) M. Kulkarni, R. Rasne, *J. Chem. Soc. Perkin Trans. 1* **1998**, 2479–2480; b) T. L. Graybill, E. G. Casillas, K. Pal, C. A. Townsend, *J. Am. Chem. Soc.* **1999**, *121*, 7729–7746.

[8] a) S. Mayer, J. Praudi, T. Bamhaoud, S. Bakkras, O. Guillom, *Tetrahedron* **1998**, *54*, 8753–8770; b) M. Uchiyama, M. Hirai, M. Nagata, R. Katoh, R. Ogawa, A. Ohta, *Tetrahedron Lett.* **2001**, *42*, 4653–4656.
[9] a) M. Jalali, G. Boussac, J.-Y. Lallemand, *Tetrahedron Lett.* **1983**, *24*, 4307–4310; b) S. A. Eastham, S. P. Ingham, M. R. Hallett, J. Herbert, P. Quayle, J. Raftery, *Tetrahedron Lett.* **2006**, *47*, 2299–2304.
[10] a) M. C. Pirrung, Y. R. Lee, *J. Am. Chem. Soc.* **1995**, *117*, 4814–4821; b) S. C. Roy, P. K. Mandal, *Tetrahedron* **1996**, *52*, 12495–12498; c) Y. R. Lee, B. S. Kim, H. C. Wang, *Tetrahedron* **1998**, *54*, 12215–12222; d) F.-E. Chen, H. Fu, G. Meng, Y. Cheng, Y.-L. Hu, *Synthesis* **2000**, 1091–1094; e) P. Müller, S. Chappellet, *Helv. Chim. Acta* **2005**, *88*, 1010–1021.
[11] A. Vaupel, P. Knochel, *J. Org. Chem.* **1996**, *61*, 5743–5753.
[12] a) E. A. Gebbinck, C. T. Bouwman, M. Bourgois, B. J. M. Jansen, A. de Groot, *Tetrahedron* **1999**, *55*, 11051–11076; b) R. Roggenbuck, A. Schmidt, P. Eilbracht, *Org. Lett.* **2002**, *4*, 289–291; c) M. Tiecco, L. Testaferri, L. Bagnoli, C. Scarponi, V. Purgatorio, A. Temperini, F. Marini, C. Santi, *Tetrahedron: Asymmetry* **2005**, *16*, 2429–2435; d) A. K. Ghosh, J. Li, R. S. Perali, *Synthesis* **2006**, 3015–3018; e) B. Linclau, M. J. Jeffery, S. Josse, C. Tomassi, *Org. Lett.* **2006**, *8*, 5821–5824.
[13] a) F. Alonso, E. Lorenzo, M. Yus, *Tetrahedron Lett.* **1997**, *38*, 2187–2190; b) F. Alonso, E. Lorenzo, M. Yus, *Tetrahedron Lett.* **1998**, *39*, 3303–3306; c) E. Lorenzo, F. Alonso, M. Yus, *Tetrahedron Lett.* **2000**, *41*, 1661–1665; d) E. Lorenzo, F. Alonso, M. Yus, *Tetrahedron* **2000**, *56*, 1745–1757; e) F. Alonso, E. Lorenzo, J. Meléndez, M. Yus, *Tetrahedron* **2003**, *59*, 5199–5208; f) F. Alonso, J. Meléndez, M. Yus, *Russ. Chem. Bull.* **2003**, *52*, 2628–2656; g) F. Alonso, J. Meléndez, M. Yus, *Tetrahedron Lett.* **2005**, *46*, 6519–6524; h) F. Alonso, J. Meléndez, M. Yus, *Tetrahedron* **2006**, *62*, 4814–4822.
[14] a) F. Alonso, L. R. Falvello, P. E. Fanwick, E. Lorenzo, M. Yus, *Synthesis* **2000**, 949–952; b) F. Alonso, J. Meléndez, M. Yus, *Helv. Chim. Acta* **2002**, *85*, 3262–3271; c) F. Alonso, J. Meléndez, M. Yus, *Tetrahedron Lett.* **2004**, *45*, 1717–1720; d) F. Alonso, B. Dacunha, J. Meléndez, M. Yus, *Tetrahedron* **2005**, *61*, 3437–3450; e) B. Dacunha, F. Alonso, J. Meléndez, M. Yus, *Acta Crystallogr.* **2005**, *A61*, C157; f) J. Meléndez, F. Alonso, M. Yus, *Tetrahedron Lett.* **2006**, *47*, 1187–1191; g) F. Alonso, J. Meléndez, T. Soler, M. Yus, *Tetrahedron* **2006**, *62*, 2264–2277.
[15] For a review, see: T. Hosokawa, S.-I. Murahashi, in: *Handbook of Organopalladium Chemistry for Organic Synthesis* Vol. 2, (Ed.: E. Negishi), Wiley-Interscience, Hoboken, USA, **2002**, pp 2169–2192.
[16] For a recent example, see: M. Babjak, L. Remeň, P. Szolcsányi, P. Zálupský, D. Mikloš, T. Gracza, *J. Organomet. Chem.* **2006**, *691*, 928–940.
[17] a) T. Hosokawa, S.-I. Murahashi, in: *Handbook of Organopalladium Chemistry for Organic Synthesis* Vol. 2, (Ed.: E. Negishi), Wiley-Interscience, Hoboken, USA, **2002**, pp. 2141–2159; b) A. Kishi, S. Sakaguchi, Y. Ishii, *Org. Lett.* **2000**, *2*, 523–525; c) Z.-Y. Wang, H.-F. Jiang, X. Y. Ouyang, C.-R. Qi, S.-R. Yang, *Tetrahedron* **2006**, *62*, 9846–9854.
[18] a) J. Tsuji, *Synthesis* **1984**, 369–384; b) J. Tsuji, in: *Handbook of Organopalladium Chemistry for Organic Synthesis* Vol. 1, (Ed.: E. Negishi), Wiley-Interscience, Hoboken, USA, **2002**, pp 449–468.
[19] M. Roussel, H. Mimoun, *J. Org. Chem.* **1980**, *45*, 5387–5390.
[20] See, for instance: a) D. W. Colcleugh, W. F. Graydon, *Can. J. Chem.* **1962**, *40*, 1497–1509; b) K. V. Ponganis, M. A. de Araujo, H. L. Hodges, *Inorg. Chem.* **1980**, *19*, 2704–2709.
[21] See, for instance: a) V. R. Choudhary, A. G. Gaikwad, *React. Kinet. Catal. Lett.* **2003**, *80*, 27–32; b) V. R. Choudhary, C. Samanta, P. Jana, *Appl. Catal. A: Gen.* **2007**, *332*, 70–78.
[22] *SAINT* version 6.28 A: *Area Detector Integration Software*; Siemens Industrial Automation Inc.: Madison, WI, **1995**.
[23] G. M. Sheldrick, *SADABS*: *Area Detector Absorption Correction*; Göttingen University: Göttingen, Germany, **1996**.
[24] CCDC 687887 contains the supplementary crystallographic data for this paper (compound **7**). These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif. Copies can also be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44–1223–336033; email: deposit@ccdc.cam.ac.uk.
[25] *SIR92*, A. Altomare, G. Cascarano, G. Giacovazzo, A. Gualiardi, *J. Appl. Crystallogr.* **1993**, 26, 343–350.
[26] G. M. Sheldrick, *Acta Crystallogr.* **2008**, *A64*, 112–122.

