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Palladium-catalyzed preparation of *exo*-aryl derivatives of the norbornane skeleton

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Abstract

Norbornene and norbornadiene derivatives have been shown to react with aryl and vinyl halides in the presence of a palladium catalyst, formic acid, and tributylamine or piperidine to give hydroarylated and hydrovinylated derivatives in good to high yield. Extension of the reaction to the hindered α,β -unsaturated aldehydic system of myrtenal produced a monocyclic derivative through a palladium-catalyzed ring opening.

Introduction

We recently required a series of various substituted *exo*-aryl derivatives of the norbornane skeleton (**6**). These compounds are usually prepared through electrophilic [1] or homolytic [2] aromatic substitution reactions; these methods give good results when a phenyl group is to be attached to the norbornyl structure, but cannot be easily extended to the synthesis of functionalized aryl derivatives. For example, lack of selectivity in carbon–carbon bond formation is to be expected, as well as limitations on the types of functionalities that can be tolerated, when substituted benzenes are concerned.

Attempts to overcome these difficulties by carrying out an electrophilic aromatic substitution on a preformed *exo*-phenyl norbornene derivative generally result in a more complex multistep process.

Since hindered olefins are known [3] to add organopalladium species to give σ -alkylpalladium intermediates, which cannot undergo a *syn*- β -hydridopalladium elimination, we attempted the synthesis of **6** by extending our palladium-catalyzed hydroarylation reaction [4,5] to norbornene and norbornadiene systems. Hereafter we report the results of this study.

Results and discussion

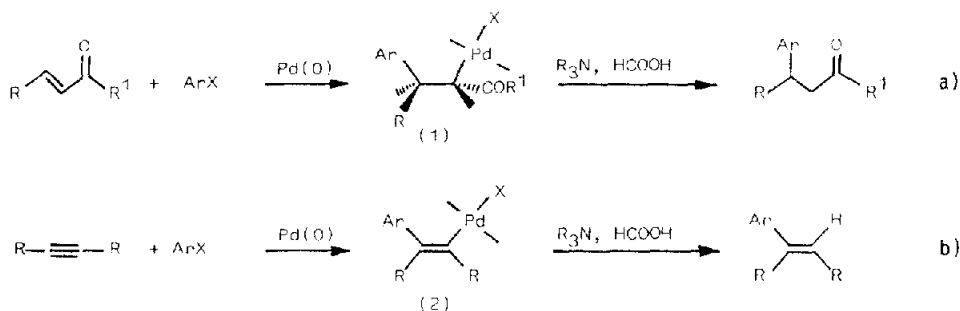
The key step of the hydroarylation reaction is the conversion of the carbon-palladium bond of σ -alkyl (**1**) [4] and σ -alkenylpalladium (**2**) [5] intermediates into the carbon-hydrogen bond, the hydrogen donor being the trialkylammonium formate salt (Scheme 1).

With acyclic α,β -enones and -enals (Scheme 1a) the success of this step depends on the influence of steric, electronic and medium factors [6] on the balance between (i) rotation around the $C_\alpha-C_\beta$ bond of **1** followed by *syn*- β -elimination of HPdX (vinyllic substitution path) and (ii) formate-induced introduction of a $C_\alpha-H$ bond in place of the $C_\alpha-Pd$ bond (conjugate addition-type path). The reaction of **2** (Scheme 1b) is more straightforward (since the rotation/elimination process cannot take place) and we thought it likely that σ -alkylpalladium intermediates (**5**) derived from the Pd-catalyzed reaction of norbornene systems (**3**) and aryl halides (**4**) (Scheme 2) would behave similarly.

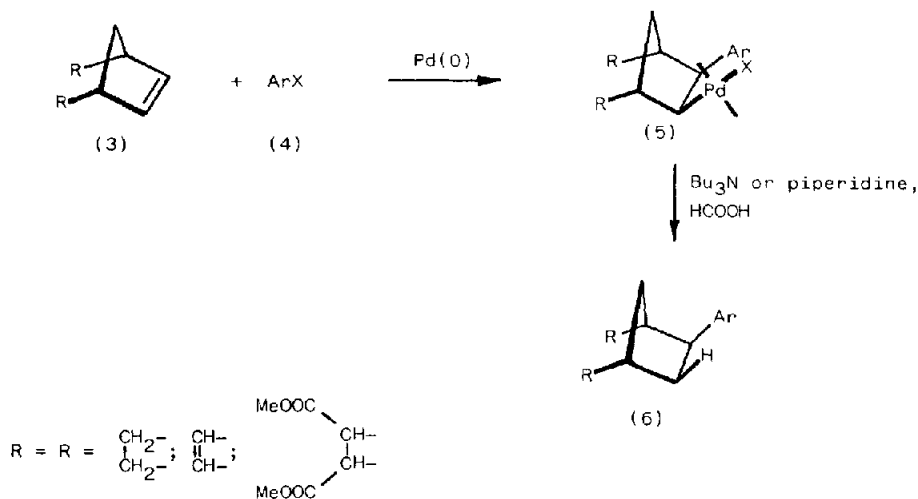
We have found that the reactions of norbornene derivatives with aryl iodides in the presence of $Pd(OAc)_2(PPh_3)_2$, tributylamine or piperidine, and formic acid do, in fact, provide a simple high yield, general synthesis of *exo*-aryl derivatives (**6**).

The results (Table 1) show that this hydroarylation reaction can provide a direct and convenient entry into this class of compounds. While we have generally employed an excess of the aryl iodide in the reaction of norbornene and 4,5-dicarbomethoxy-1,2-norbornene, depending on the nature of the aryl iodide it is possible to use smaller amounts with satisfactory results (Table 1, entry e, note b). Alternatively, a slight excess of norbornene may be used (Table 1, entry b).

With norbornadiene it seems that an excess of the hindered olefin is necessary to obtain 4-*exo*-aryl norbornenes in good yield (Table 1, entries g, h). These compounds may be useful synthetic intermediates for the preparation of *trans*-4-aryl-*cis*-1,3-cyclopentanedicarboxylic acids [7]. A wide range of the aryl iodides can be used.



Scheme 1.

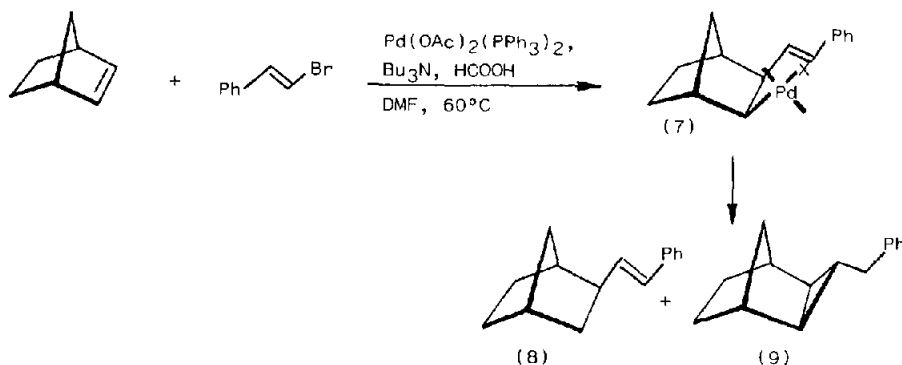


Scheme 2.

The hydroxyl group of 4-hydroxyphenyl iodide did not interfere in the reaction whereas with 4-aminophenyl iodide better results were obtained after protection of the amino group.

The depicted configuration of the hydroarylated products was expected on the basis of the stereochemical outcome of related palladium catalyzed reactions of norbornenes [3], and was confirmed from the ^1H NMR spectra by the absence of any discernible vicinal coupling between the bridgehead protons and those on the carbon bearing the aromatic ring [8]. Furthermore the ^1H NMR spectrum of **6a** was superimposable on that of an independently-prepared sample [1].

We also attempted the hydrovinylation of norbornene using bromostyrene [9*]. Under our usual conditions the styryl derivative (**8**) and the cyclopropane derivative (**9**) were obtained in 59 and 10% yield, respectively, showing the higher tendency for the relevant σ -alkylpalladium intermediate (**7**) to undergo formate reduction to **8**

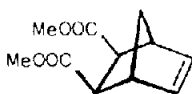


Scheme 3.

* Reference numbers with asterisks indicate notes in the list of references.

Table 1

Palladium-catalyzed hydroarylation of norbornene derivatives

Entry ^c	Hindered olefin (3)	Aryl iodide (4)	3/4 molar ratio	Reaction time (h)	<i>exo</i> -Aryl derivative 6 (x) (% yield) ^a
a		PhI	1/2.4	8	83
b		4-MeCONHC ₆ H ₄ I	1.1/1	4	90 ^c
c		4-H ₂ NC ₆ H ₄ I	1/2.4	6	29
d		3-MeC ₆ H ₄ I	1/2.4	8	72
e		4-HOC ₆ H ₄ I	1/2.4 ^b	6	65
f		2-HOCH ₂ C ₆ H ₄ I	1/2.4	8	70
g		4-MeOC ₆ H ₄ I	3/1	6	84 ^c
h		4-MeOC ₆ H ₄ I	1/1.1	6	30 ^d
i		4-MeOCOC ₆ H ₄ I	3/1	8	85 ^c
l		PhI	1/2.4	3	85
m		2-MeOC ₆ H ₄ I	1/2.4	8	83
n		4-ClC ₆ H ₄ I	1/2.4	8	73

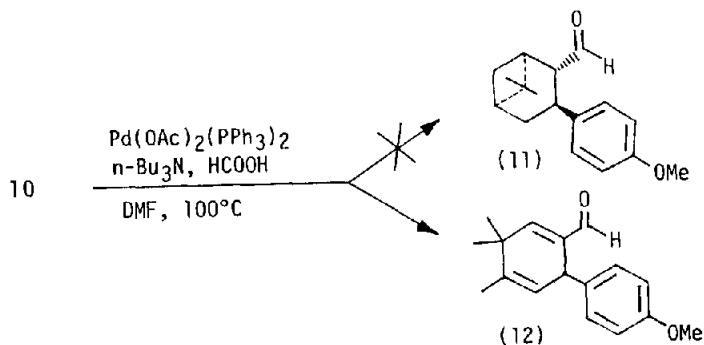
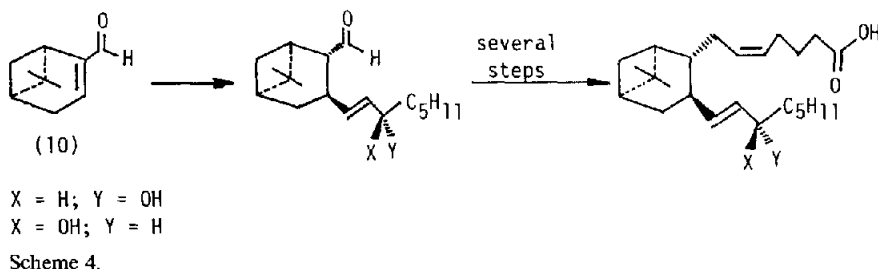
^a Yields are from single non-optimized runs, are based on the amount of the starting hindered olefin **3** introduced and refer to pure isolated products. ^b When the 3/4 molar ratio was 1/1, compound **6e** was isolated in 52% yield (reaction time 6 h). ^c Based on the amount of aryl iodide initially present. ^d Under these conditions, a 18% yield of the bis(4-methoxyphenyl) derivative, whose regiochemistry has not been investigated, was isolated: m.p. 75–78 °C; IR (KBr): 1600, 1240, 820 cm⁻¹; ¹H NMR (CDCl₃): δ 1.45–1.94 (m, 6H), 2.43 (m, 2H), 2.78 (dd, 1H, *J* 8.8, 5.9 Hz), 2.88 (dd, 1H, *J* 8.8, 5.1 Hz), 3.76 (s, 3H), 3.77 (s, 3H), 6.82 (d, 2H, *J* 8.5 Hz), 6.83 (d, 2H, *J* 8.5 Hz), 7.15 (d, 2H, *J* 8.5 Hz), 7.16 (d, 2H, *J* 8.5 Hz).

^e Also denotes x in **6(x)**.

than intramolecular cyclopropanation to **9** (Scheme 3). Under conditions reported by Chiusoli et al. [10] (NH₄⁺ HCOO⁻, Pd(PPh₃)₄, and anisole as the solvent) the **8/9** ratio ranges from 1.7 at room temperature to 0.3 at 110 °C. The higher ratio we found (5.9) can probably be ascribed to the higher efficiency of our reducing system.

In the light of these results, we examined the extension of the reaction to the hindered α,β-unsaturated aldehydic system of myrtenal (**10**). Myrtenal has been reported to be a useful reagent for the preparation of pinane analogues of thromboxane A₂ (Scheme 4) [11].

A key step in this synthesis is the conjugate addition of a functionalized vinyl cuprate to **10**, and it thus seemed to us of interest to examine the feasibility of a palladium-catalyzed addition to **10** to provide a new route to pinane analogues of



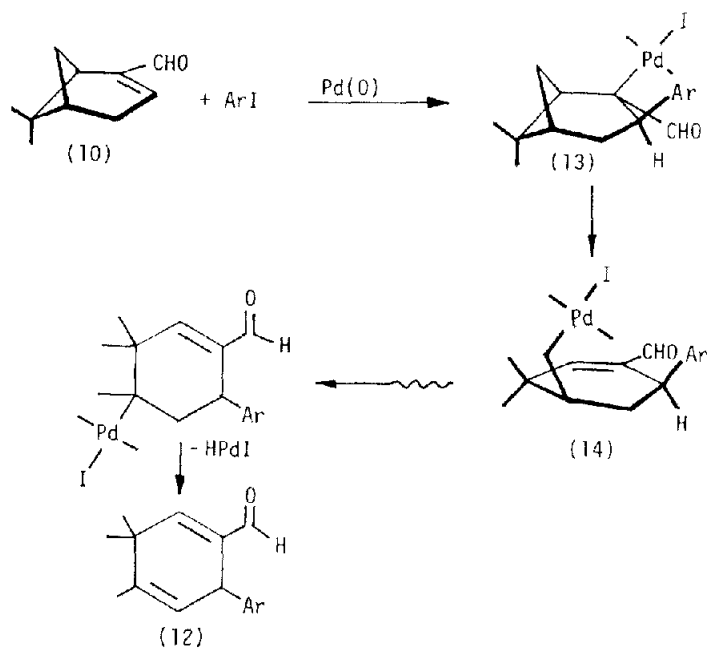
Scheme 5.

thromboxane- A_2 . Bromostyrene was selected as the model halide. Unfortunately, the reaction of **10** with bromostyrene under the usual conditions led to only a small degree of conversion of the myrtenal (all the bromostyrene had disappeared from the reaction mixture when 80% of myrtenal was still present), and formation of a complex mixture of products that we did not study further. Cleaner results were obtained when **10** was brought into reaction with 4-methoxyphenyl iodide, but the reaction did not produce any detectable amount of the expected addition product **11** but instead gave the monocyclic derivative **12** (31% yield; starting material recovered in 40% yield) (Scheme 5).

The structure of **12** has been assigned on the basis of its NMR spectra. The 1H -NMR spectrum of **12** revealed the presence, inter alia, of a vinyl methyl group undergoing allylic interaction with an olefinic proton and a second olefinic proton as a broad singlet. The presence of two trisubstituted double bonds was confirmed by ^{13}C NMR and attached proton test (APT) spectroscopy; the non-aromatic portion of the molecule appeared to contain three methyl, three methine, and three quaternary carbon atoms, in addition to the aldehydic one.

Formation of **12** can be rationalized in terms of *syn*-addition of arylpalladium species formed in situ to the α,β -unsaturated system to give the σ -alkylpalladium intermediate **13**, followed by rearrangement of **13** to **14** [12], and β -elimination/readdition/ β -elimination of $HPdX$ (Scheme 6).

The stereochemistry of addition of σ -arylpladium species to the carbon-carbon double bond is expected on the basis of steric considerations as well as on the reported structure of π -allylpalladium complexes derived from hindered olefins closely related to myrtenal, such as dehydro- β -pinene [13] and β -pinene [14].



Ar = 4-MeO-C₆H₄

Scheme 6.

Under our reducing conditions, trapping of **13** with formate should favour formation of the addition product **11**. However, rearrangement of **13** to **14** proved to be faster, and only the monocyclic derivative **12** was isolated. Accordingly, reaction of **10** with 4-methoxyphenyl iodide, Pd(OAc)₂(PPh₃)₂, and *n*-Bu₃N without formic acid gave **12** in 33% yield (starting material recovered in 32% yield). Similar results (35% yield of **12**) were obtained by using Pd(OAc)₂[P(*o*-tol)₂]₂ formed in situ as the catalyst.

Experimental

Melting points were determined with a Büchi 510 apparatus and are uncorrected. All starting materials, catalysts, and solvent were obtained commercially and used without further purification. 4-Acetylamidophenyl iodide and 4-carbomethoxyphenyl iodide were prepared from commercially available 4-aminophenyl iodide and 4-iodobenzoic acid by standard methods. Reactions were carried out on a 1.5–5.0 mmol scale. The products were purified by flash chromatography (silica gel 40–63 μ , Merck) or preparative HPLC (Chromatospac Prep 10 from Jobin Yvon equipped with a Prep LC/system 500A, solvent delivery system and refractive index detector, from Waters Associates) on axially compressed columns packed with silica gel 20–45 μ (Amicon Co.), with *n*-hexane/AcOEt mixtures as eluants.

NMR spectra and ATP spectra (Table 2) were recorded with a Varian XL-300 spectrometer. IR spectra were recorded on a Nicolet 5DX FT/IR spectrometer. All the isolated products gave satisfactory microanalyses.

Table 2
Characterization of compounds **6**^a

Compound	M.p. (°C)	IR ν (cm ⁻¹)	¹ H NMR δ (CDCl ₃) (ppm) ^b
6a	oil (lit. [1] b.p. 76 °C/0.8 mmHg)	1600, 750, 700 ^c	1.14–1.38 (m, 3H), 1.51–1.79 (m, 5H), 2.33 (m, 2H), 2.73 (dd, 1H, <i>J</i> 8.3, 5.8 Hz), 7.10–7.28 (m, 5H)
6b	152–154	1650, 810 ^d	1.13–1.37 (m, 3H), 1.48–1.79 (m, 5H); 2.13 (s, 3H), 2.31 (m, 2H), 2.68 (dd, 1H, <i>J</i> 8.7, 5.7 Hz), 7.15 (d, 2H, <i>J</i> 8.5 Hz), 7.40 (d, 2H, <i>J</i> 8.5 Hz), 7.82 (brs, 1H)
6c	29–31	3440, 3360, 820 ^d	1.11–1.35 (m, 3H), 1.48–1.74 (m, 5H), 2.29 (m, 2H), 2.63 (dd, 1H, <i>J</i> 8.3, 5.9 Hz), 3.37 (brs, 2H), 6.62 (d, 2H, <i>J</i> 8.9 Hz), 7.00 (d, 2H, <i>J</i> 8.9 Hz)
6d	oil	1620, 780, 700 ^c	1.07–1.29 (m, 3H), 1.45–1.70 (m, 5H), 2.24 (s and m superimposed, 5H), 2.62 (dd, 1H, <i>J</i> 8.3, 5.6 Hz), 6.86–7.13 (m, 4H).
6e	122–123	3240, 820 ^d	1.04–1.27 (m, 3H); 1.38–1.67 (m, 5H), 2.21 (m, 2H), 2.57 (dd, 1H, <i>J</i> 8.6, 5.6 Hz), 5.40 (brs, 1H), 6.75 (d, 2H, <i>J</i> 8.4 Hz), 6.99 (d, 2H, <i>J</i> 8.4 Hz).
6f	oil	3300, 750 ^c	1.22–1.40 (m, 3H), 1.51–1.63 (m, 4H), 1.75–1.82 (m, 1H), 1.94 (s, 1H), 2.36 (brs, 2H), 2.89 (dd, 1H, <i>J</i> 8.7, 5.6 Hz), 4.67 and 4.73 (ABq, 2H, <i>J</i> 12.2 Hz); 7.15–7.39 (m, 4H)
6g	28–29	1610, 1250, 830 ^c	1.38–1.41 (m, 1H), 1.53–1.71 (m, 3H), 2.64 (dd, 1H, <i>J</i> 8.6, 4.7 Hz), 2.82 (brs, 1H), 2.92 (brs, 1H), 3.74 (s, 3H), 6.13 (m, 1H), 6.22 (m, 1H), 6.81 (d, 2H, <i>J</i> 8.5 Hz), 7.17 (d, 2H, <i>J</i> 8.5 Hz)
6i	oil	1720, 810 ^c	1.02–1.76 (m, 4H), 2.74 (dd, 1H, <i>J</i> 8.6, 5.0 Hz), 2.95 (m, 2H), 3.88 (s, 3H), 6.17 (m, 1H), 6.25 (m, 1H), 7.32 (d, 2H, <i>J</i> 8.7 Hz), 7.96 (d, 2H, <i>J</i> 8.7 Hz)
6l	76–77	1720, 760, 705 ^d	1.37 (d, 1H, <i>J</i> 10.0 Hz), 1.66–1.77 (m, 2H), 2.14 (ddd, 1H, <i>J</i> 12.7, 9.0, 2.7 Hz), 2.65 (m, 1H), 2.70 (m, 1H), 2.98 (dd, 1H, <i>J</i> 11.8, 3.6 Hz), 3.15 (ddd, 1H, <i>J</i> 11.8, 4.5, 1.8 Hz), 3.52 (t, 1H, <i>J</i> 7.5 Hz), 3.70 (s, 6H), 7.14–7.31 (m, 5H)
6m	110–111	1730–770 ^d	1.35 (d, 1H, <i>J</i> 10.2 Hz), 1.57 (dtd, 1H, <i>J</i> 13.3, 5.3, 1.8 Hz), 1.75 (t, 1H, <i>J</i> 8.9 Hz), 2.45 (ddd, 1H, <i>J</i> 13.3, 8.9, 2.2 Hz), 2.63 (m, 1H), 2.71 (m, 1H), 2.98 (ddd, 1H, <i>J</i> 11.5, 4.0, 1.8 Hz), 3.17 (dd, 1H, <i>J</i> 11.5, 4.0 Hz), 3.48 (dd, 1H, <i>J</i> 8.9, 5.3 Hz), 3.69 (s, 3H), 3.70 (s, 3H), 3.81 (s, 3H), 6.82–7.20 (m, 4H)
6n	49–51	1720, 810 ^d	1.38 (d, 1H, <i>J</i> 10.0 Hz), 1.59–1.71 (m, 2H), 2.09 (ddd, 1H, <i>J</i> 12.8, 9.1, 2.7 Hz), 2.59 (m, 1H), 2.71 (m, 1H), 2.96 (dd, 1H, <i>J</i> 11.7, 3.9 Hz), 3.17 (ddd, 1H, <i>J</i> 11.7, 4.7, 1.6 Hz), 3.53 (t, 1H, 7.8 Hz), 3.69 (s, 6H), 7.20–7.28 (m, 4H)

^a Mass spectra in agreement with the proposed structures and satisfactory microanalyses were obtained.

^b Recorded with a Varian XL 300 WB spectrometer. ^c Liquid film. ^d KBr.

General procedure of reaction of norbornene and norbornadiene systems with aryl and vinyl halides. This is exemplified for the preparation of *exo*-2-(4'-acetamidophenyl)norbornene (Table 1, entry b). To a stirred solution of norbornene (0.46 g, 4.88 mmol), 4-acetamidophenyl iodide (1.159 g, 4.44 mmol), piperidine (1.285 g, 15.1 mmol), and $\text{Pd}(\text{OAc})_2(\text{PPh}_3)_2$ (0.166 g, 0.22 mmol) in DMF (2 ml), HCOOH (0.539 g, 11.72 mmol) was added all at once. The mixture was stirred at 60 °C for 4 h under nitrogen. Then AcOEt and water were added, the organic layer was separated, dried (Na_2SO_4), and evaporated. Flash chromatography of the residue on silica gel (n-hexane/ AcOEt 60/40 as eluant) gave **6b** (0.92 g, 90% yield).

Reaction of myrtenal with 4-methoxyphenyl iodide. To a stirred solution of myrtenal (0.250 g, 1.67 mmol), 4-methoxyphenyl iodide (0.938 g, 4.01 mmol), and $\text{n-Bu}_3\text{N}$ (1.051 g, 5.68 mmol) in DMF (0.5 ml), was added a solution of $\text{Pd}(\text{OAc})_2(\text{PPh}_3)_2$ (0.0622 g, 0.083 mmol) in DMF (0.5 ml). The mixture was purged with nitrogen and stirred at 100 °C under nitrogen for 1 h. Then Et_2O and 0.2 *N* HCl were added, the organic layer was separated, washed with water, dried (Na_2SO_4), and evaporated. The residue was purified by preparative HPLC, with elution with a 95/5 n-hexane/ AcOEt mixture, to give compound **12** (0.107 g, 33% yield): m.p. 134–135 °C (as the 2,4-dinitrophenylhydrazone); IR (neat): 1688, 835 cm^{-1} ; ^1H NMR (CDCl_3): δ 1.28 (s, 3H), 1.38 (s, 3H), 1.78 (s, 3H), 3.76 (s, 3H), 4.24 (bs, 1H), 5.43 (bs, 1H), 6.59 (s, 1H), 6.98 (AA'BB' system, 4H), 9.41 (s, 1H); ^{13}C NMR (CDCl_3): 18.169, 27.770, 27.864, 37.211, 40.002, 55.185, 113.780, 124.063, 129.204, 135.012, 135.907, 138.818, 157.647, 158.127, 193.434 ppm; MS (*m/e*): 256 (M^+).

Acknowledgements

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