New Syntheses of the Benzoquinone Primin and its Water-Soluble Analog Primin Acid via Heck Reactions

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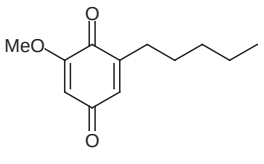
Received 23 December 1998; revised 11 February 1999

Dedicated to the memory of Professor Claude Benezra

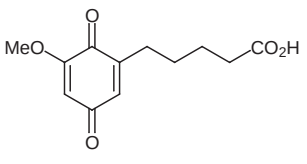
Abstract: The syntheses of primin, 2-methoxy-6-pentylbenzoquinone (**1**), a major allergen of *Primula obconica*, and its water-soluble acid analog primin acid (**2**) are reported. The key steps were *ortho*-lithiation reactions of protected hydroquinones, palladium coupling (Heck) reactions, and salcomine-catalyzed oxidations of phenols to quinones.

Key words: primin, quinone, *ortho*-lithiation, palladium coupling, salcomine

Primin, 2-methoxy-6-pentylbenzoquinone (**1**), has been isolated from a variety of plants, including *Primula obconica* (primrose)[1,2] and *Miconia sp*.[3,4] In addition to its antimicrobial[5] and insect feeding [4] activities, this benzoquinone is also known for its allergenic properties. Primin is indeed a strong sensitizer and has long been recognized to induce contact dermatitis.[6,7] Synthetic primin has been included for some time in the European standard patch testing series, which is used to identify plant sources in people subject to contact dermatitis.[8–11] The immune response is believed to be mediated by the formation of antigenic adducts resulting from the Michael addition of the nucleophilic protein residues to the quinone.[12] In order to investigate in more detail the type of amino acids involved in this process, the position of nucleophilic addition, and the structures of the adducts, the synthesis of primin was of interest to us. Although some information can be assessed by chemical reactions run in organic solvents, biologically relevant *in vitro* experiments are best performed in aqueous medium. A fundamental requirement, however, to run *in vitro* tests is to have molecules that are soluble in the aqueous cell culture media.[13] The limited solubility of primin (LogP 2.99) in aqueous media prompted us to design a more water-soluble analog. Primin acid (**2**) (LogP 0.96, i.e. about 100 times more hydrophilic) was selected. The carboxylic functionality at the terminal position of the alkyl chain is away from the reactive center of the molecule and is not expected to modify the reactivity of the quinone moiety.

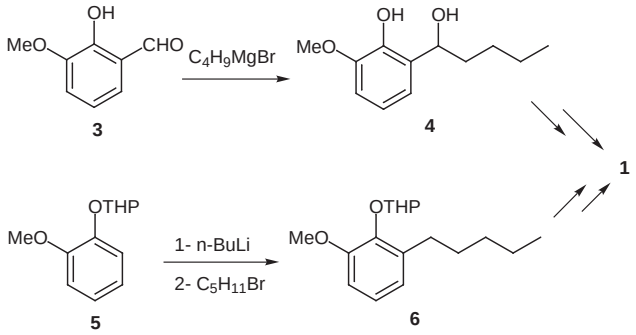


Primin (**1**)



Primin acid (**2**)

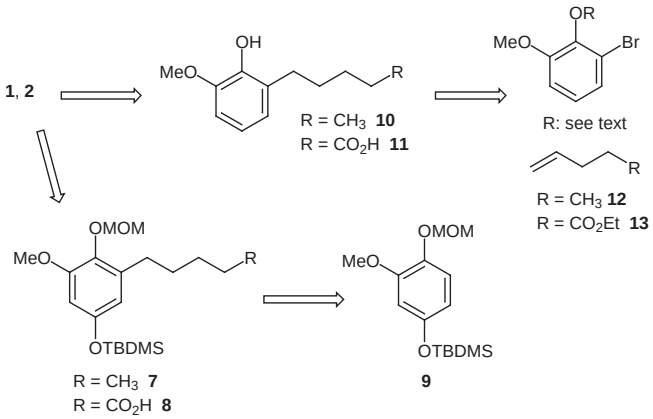
The synthesis of primin **(1)** was first reported by Schildknecht et al. in 1967[1] and later by de Lima *et al*.[5] Primin **(1)** and some of its homologous alkyl analogs were subsequently prepared for structure-biological activity relationships.[14–16] Key steps in recent syntheses (Scheme 1) involved the addition of an alkyl Grignard to 2-hydroxy-3-methoxybenzaldehyde (**3**) to form the benzyl alcohol **4**,[5,14] and *ortho*-lithiation of tetrahydropyranyl guaiacol (**5**) yielding **6** (ca. 60% overall yield to **1**).[16]



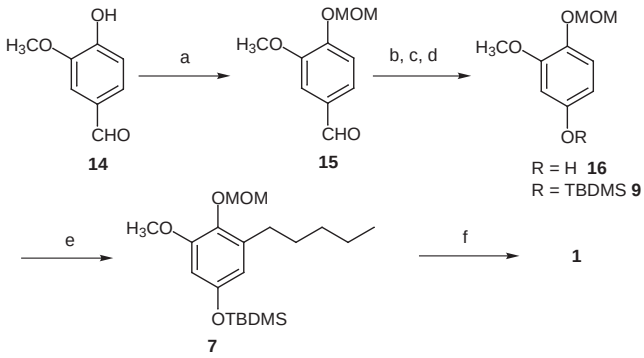
Scheme 1

p-Benzoquinones can be efficiently prepared by oxidation of either protected hydroquinone or phenol derivatives. Methods for the oxidation of *p*-dimethoxybenzene with nitric acid,[18] silver oxide in acidic medium,[18] and CAN[19] have been reported. More recently, CAN in combination with pyridine dicarboxylic acid derivatives was shown to be a very mild and efficient method of oxidation.[20] We first focused our effort on the synthesis of **1** and **2** via the protected hydroquinones **7** and **8**, which could be prepared using an *ortho*-lithiation/alkylation sequence from the correctly protected methoxyhydroquinone **9** (Scheme 2). This efficient route to primin **(1)** was unsuccessful, however, in preparing the analog primin acid **(2)**, as detailed below. This prompted us to develop an alternative synthetic pathway via phenols **10** and **11**, emphasizing a palladium-catalyzed coupling reaction between a bromoaromatic and an alkene. Phenols can be efficiently oxidized to benzoquinones in a homogenous phase reaction

using the cobalt(II) complex salcomine under an oxygen atmosphere.[21,22] Primin **(1)** and primin acid **(2)** were both prepared via this methodology, using alkenes **12** or **13**.



Scheme 2



Reagents and conditions: a) NaH/MOMCl/DMF, 91%; b) *m*-CPBA/CH_2Cl_2, 94%; c) KOH/EtOH/H_2O, 78%; d) TBDMSCl/imidazole/DMF, 90%; e) i. TMEDA/*s*-BuLi/THF, –78°C, ii. $MgBr_2/Et_2O$, iii. $C_5H_{11}Br$, 73%; f) CAN/2,6-pyridinedicarboxylic acid/MeCN/H_2O, 90%

Scheme 3

1. *ortho*-Lithiation Directed Reactions

ortho-Directing groups have been widely used in aromatic chemistry to introduce substituents regioselectively.[23–26] The methoxymethoxy (MOM) protecting group was selected based on the high yields of introduction and removal as well as its good *ortho*-directing properties.[27–29] The MOM group was quantitatively introduced by the reaction of vanillin (**14**) with MOMCl (Scheme 3). The vanillin derivative **15** was further reacted in a Dakin reaction,[30,31] followed by base hydrolysis of the intermediate formate ester to phenol **16**. The protection of the resulting hydroxy group was achieved using *tert*-butyldimethylsilyl chloride (TBDMSCl) and yielded **9**.

Alkylation of the lithium salt of **9** did not proceed in good yields (*s*-BuLi/THF, 33%; BuLi/TMEDA/Et_2O, 18%; BuLi/THF/TMEDA, 26%). The conversion of the lithium salt to an intermediate Grignard using $MgBr_2$, followed by alkylation,[32] however, afforded the alkylated product **7** in 72% yield. Both the methoxy and the methoxymethylene groups are effective *ortho*-directing groups. The MOM group is expected, however, to be more efficient because the lithium cation is more tightly complexed to the oxygen in a six member ring. *ortho*-Lithiation was therefore expected at the position *ortho* to the MOM group. No regioisomer was isolated. NMR data, however, were not conclusive for the structure of **7**, because the two aromatic protons coincidentally had the same chemical shift (δ = 6.25, s) and showed no coupling constant. The conversion of **7** to primin **(1)**, which is a known compound, by oxidation with CAN in combination with 2,6-pyridine dicarboxylic acid (90% yield) [20] can be argued as proof of the regioselective *ortho*-lithiation.

Attempts to prepare the analog primin acid **(2)** via a similar sequence of *ortho* lithiation/alkylation were unsuccessful. The alkylation of the Grignard or lithium salt of **9** with methyl 5-bromovalerate failed, as well as attempts of alkylation via cuprate derivatives[33] generated from the lithium salt using CuBr•Me_2S or CuCN. This synthetic pathway was abandoned and efforts were pursued to prepare primin acid **(2)** via a palladium-catalyzed coupling reaction.

2. Heck Reactions

Palladium-mediated carbon-carbon coupling reactions have found an extremely wide use in organic chemistry and many methods and conditions are now available.[34–40] The early reactions developed by Heck allow the coupling between a bromo- or iodo-aromatic and an alkene, resulting in *trans*-styrenyl systems, with the *exo* double bond isomers as byproducts.[34,41,42] A large variety of groups is tolerated on the aromatic moiety, although terminal alkenes are more reactive than internal alkenes due to steric interactions in the intermediate palladium complexes. The catalyst Pd(0) is generated in situ from $Pd(OAc)_2$ and triphenylphosphine or an analogous phosphine, affording a homogenous catalytic reaction. The Heck reaction between ethyl pent-4-enoate (**13**) and 6-bromoguaiacol (**18**), prepared in 65% yield by Pearson bromination of guaiacol (**17**) (Scheme 4),[43] gave low yields of coupling (Table). This result was consistent with literature precedents, and

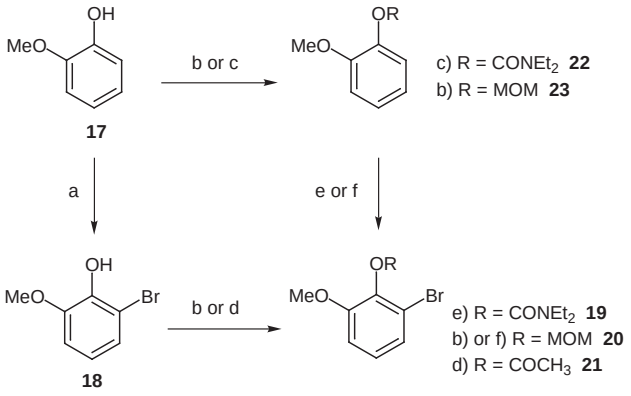
Table Heck Reactions with Ester **13**

Substrate	R	Product	Yield (%)	*endo*/*exo* (%)
18	H	**29**	10	not determined
27[b]	Me	**28a**/**28b**	90	75:25[b]
20	CH_2OMe	**24a**/**24b**	93	80:20
21	COMe	**25a**/**25b**	92	86:14
19	$CONEt_2$	**26**	85	100: 0

[a] Yields after purification by chromatography on silica gel.
[b] Experimental results and structures not given in this paper. Please see Ref. 45.

the lack of reaction is presumably due to the competitive quaternarization of the phosphorus ligands.[41]

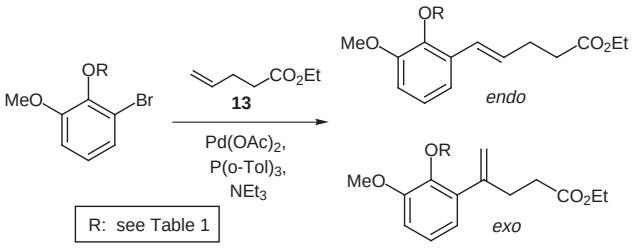
Three protected bromophenols, **19–21**, were prepared using various functional groups, namely a carbamate, a methoxymethyl, and an acetyl (Scheme 4). The bromocarbamate derivative **19** was easily prepared by reaction of **17** with diethylcarbamyl chloride followed by *ortho*-directed bromination of the aromatic **22**.[44] A similar pathway was attempted to prepare the 3-bromo-1-methoxy-2-methoxymethoxybenzene (**20**), but the bromination of **23** did not proceed in good yield. Several conditions were tried, including varying the temperature of formation of the anion, the base (BuLi or *s*-BuLi), the solvent (THF or Et_2O), and the brominating agent (Br_2 or BrCN), but the best yield obtained was only 38%. Moreover, the reaction yield dropped to 20% when the reaction was run on a scale larger than 4 mmoles. Introduction of the bromine atom first, leading to 6-bromoguaiacol (**18**), followed by protection of the phenol group revealed, however, a much easier route to **20**. The 2-acetoxy-3-bromo-1-methoxybenzene (**21**) was easily obtained by acetylation of **18**.



Reagents and conditions: a) i. *t*-$BuNH_2$/toluene, ii. Br_2, 65%; b) i. NaH/Et_2O, ii. MOMBr, 97%; c) i. NaH/Et_2O, ii. $ClCONEt_2$, 93%; d) MeCOCl/pyridine/DMAP (cat.)/CH_2Cl_2, 99%; e) i. *s*-BuLi/TMEDA/Et_2O, ii. Br_2, 87%; f) i. BuLi/TMEDA/Et_2O, ii. Br_2, 38%

Scheme 4

Heck reactions with all three protected phenols **19–21** (Scheme 5) proceeded in high yields (85–93% after purification, Table). The ratio of *endo* (a mixture of *endo* isomers is actually obtained, as discussed below, but only the main isomer is shown in Scheme 5) to *exo* double bond was dependent on the bulkiness of the protecting group (Table). While the MOM derivative **20** yielded an 80:20 mixture of benzylic alkenes **24a**/**24b** (*endo/exo*), the acetyl derivative **21** afforded a 86:14 ratio of alkenes **25a**/**25b**, and the diethylcarbamate **19** gave the *endo* isomer **26** only. Independent results obtained with 3-bromo-1,2-dimethoxybenzene (**27**) showed a 75:25 ratio of alkenes **28a** and **28b**.[45] The *endo*/*exo* selectivity can be rationalized by looking at the transition state of formation of the complex between the alkene and the aromatic-palladium compound (Figure). Large groups on the aromatic ring induce a higher steric hindrance in the formation of the intermediate palladium complex, favoring the approach of the alkene with the methylene group toward the aromatic ring and the R chain away.



Scheme 5

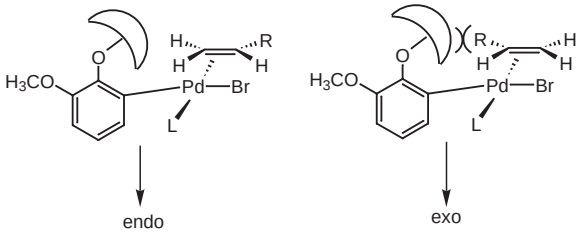
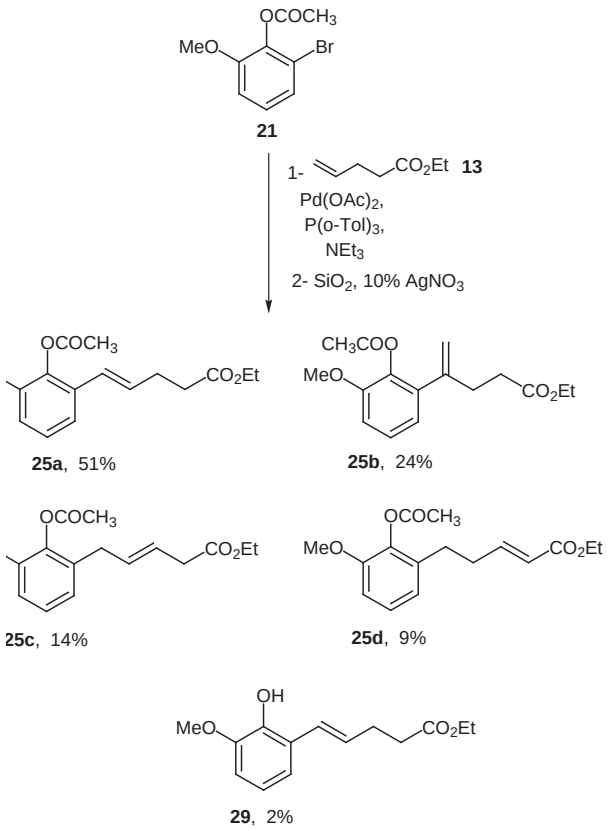


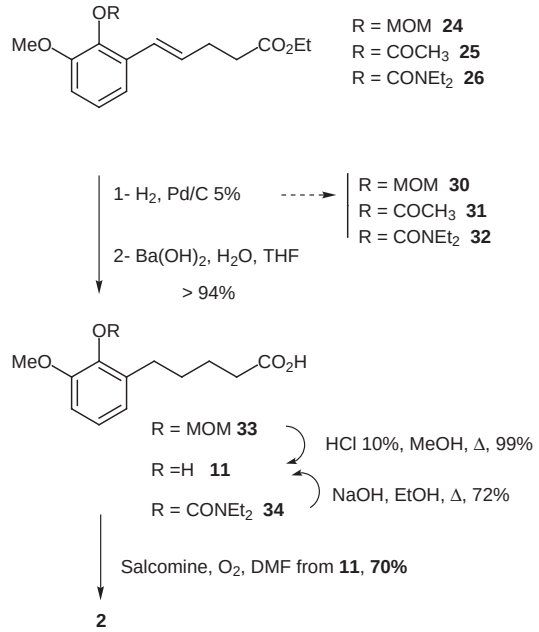
Figure. Formation of the intermediate palladium complex

What was defined above as the *endo* isomer was actually a mixture of three different alkenes, resulting from the migration of the double bond along the alkyl chain. Using the acetyl protected derivatives **25**, we were able to isolate, quantify, and identify by ^1H NMR the various isomers (Scheme 6) obtained in a typical Heck reaction (100°C, 28 h). The separation of each isomer was achieved by chromatography on silica gel pre-treated with aqueous 10% $AgNO_3$ solution. The ratio of *exo* **25b** and three *endo* isomeric alkenes **25a**, **25c**, and **25d** are shown in Scheme 6. As expected the major isomer was the alkene **25a** resulting directly from the coupling. The two other *endo* isomers **25c**, and **25d** were observed in significant amounts (24 and 9% respectively). The deprotected phenol **29** was also isolated as a byproduct (ca. 2% yield). Similar migration of the double bond was observed by ^1H NMR with the carbamate and MOM analogs **26** and **24a**, although no attempt was made to separate the various isomers. The next step of our synthesis consisted in the reduction of the alkene, so the position of the double bond was therefore of relatively minor importance.

After catalytic hydrogenation of the double bond, the esters **30–32** were converted to the corresponding acids **33**, **34**, and **11**, by deprotection with $Ba(OH)_2$ in a water/THF mixture (Scheme 7).[46] The acetyl protective group from **31** was removed simultaneously. The MOM protective group was quantitatively removed from 33 using a methanolic solution of 10% HCl[47] and the carbamate group was removed from 34 in 70% yield using ethanolic NaOH.[48] The phenol 11 was then oxidized to the benzo-



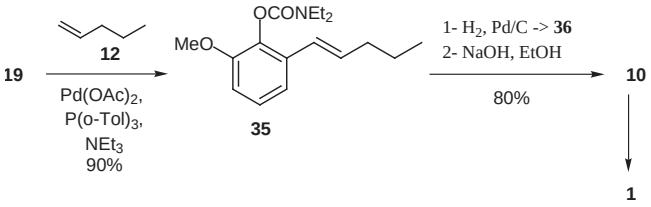
Scheme 6



Scheme 7

quinone **2** in 70% yield using salcomine in DMF under an atmosphere of oxygen.

Primin **(1)** also was synthesized via a Heck reaction (Scheme 8) by reaction of bromocarbamate **19** with pent-1-ene (**12**). Pent-1-ene was volatile under the conditions of the reaction and 5 equivalents were necessary to achieve the reaction. Catalytic hydrogenation of alkene **35** to the corresponding *n*-alkyl **36** followed by deprotection of the carbamate with ethanolic NaOH afforded the phenol **10**, which was oxidized to primin **(1)** with salcomine.



Scheme 8

In conclusion, two new syntheses of primin (**1**) from guaiacol (52% overall yield) and vanillin (40% overall yield) are described. Although the overall yield of synthesis via the Heck reaction is lower than the overall yield of the synthesis proceeding via *ortho*-lithiation reaction from guaiacol (60%),[16] it allows more flexibility regarding the groups than can be introduced. The hydrophilic analog primin acid (**2**) was prepared via a Heck reaction. The best pathway proceeds via the acetyl derivative for it allows the simplest and most reproducible deprotection reactions. Biological tests are currently in progress to evaluate the fate and behavior of primin acid **(2)** in *in vitro* testing.

CAUTION! Primin **(1)** is a strong sensitizer and should be handled with care, avoiding skin contact.

Reagents and starting materials were obtained from commercial suppliers and were used without further purification. THF and Et_2O were distilled over sodium/benzophenone ketyl. Toluene and CH_2Cl_2 were distilled under nitrogen from P_2O_5. All reactions were conducted using flame dried glassware under an atmosphere of dry N_2. Chromatography refers to flash column chromatography on silica gel unless otherwise noted. ^1H and ^{13}C NMR spectra were recorded on a Bruker WP 200-MHz SY spectrometer. Chemical shifts δ are expressed in ppm downfield from internal TMS. Coupling constant values (*J*) are given in Hertz (Hz). IR spectra were recorded on a Perkin-Elmer 1600 FT-IR. Melting points were obtained using a Büchi-Tottoli 510 apparatus and are uncorrected. Elemental analyses were performed by Centre de Recherche des Macromolécules de Strasbourg. LogP calculations were obtained using ACD LogP software (ACD/Labs). Silica gel chromatography were done using Kieselgel Merck (040–0.063 mm) and with unpurified solvents unless otherwise indicated. The following compounds are known compounds: **1**,[1] **10**,[1] **23**,[29] **18**,[49] **21**,[50] **22**,[50] **27**.[51]

Methoxymethoxyvanillin (15)

Under anhydrous conditions and an atmosphere of argon, NaH (7.2 g, 300 mmol) was added portionwise at 0°C to a solution of vanillin (**14**; 38.0 g, 250 mmol) in anhyd DMF (350 mL). After stirring for 15 min at 0°C, chloromethyl methyl ether (28.5 mL, 375 mmol) was added and the mixture was stirred for 14 h at 25°C. H_2O (100 mL) was then added and the solution was extracted with CH_2Cl_2 (3 × 150 mL). The combined organic phases were washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure. The crude was

recrystallized from EtOAc/hexane to give **15** (45 g, 92%) as white crystals; mp 39°C.

^{1}H NMR ($CDCl_3$): δ = 3.45 (s, 3 H), 3.85 (s, 3 H), 5.25 (s, 2 H), 7.32 (m, 3 H), 9.80 (s, 1 H).

IR ($CHCl_3$): ν = 1688 cm^{-1} (C=O).

Anal. Calcd for $C_{10}H_{12}O_4$: C, 61.22, H, 6.16. Found C, 60.99, H, 5.96.

3-Methoxy-4-methoxymethoxyphenol (16)
Under anhydrous conditions, *m*-CPBA (recrystallized, 45.0 g, 262 mmol) was added portionwise at 0°C to a solution of aldehyde **15** (21.3 g, 128 mmol) in anhyd CH_2Cl_2 (250 mL). After stirring for 5 h at 25°C, the mixture was filtered and the filtrate was washed with an aq solution of $NaHCO_3$ and then with brine. The organic phase was dried ($MgSO_4$) and evaporated under reduced pressure to give an intermediate formate (25.5 g, 94%, colorless oil), that was used as such. This intermediate was hydrolyzed using a solution of 10% KOH (120 mL) and EtOH (60 mL) at 50°C for 10 min. The mixture was washed with Et_2O (100 mL) and the aqueous phase was acidified with 1 N HCl and extracted with Et_2O (2 × 100 mL). The combined organic phase was washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure. The crude mixture was recrystallized (EtOAc/hexane) to give **16** (17.24 g, 78%) as white crystals; mp 69°C.

^{1}H NMR ($CDCl_3$): δ = 3.53 (s, 3 H), 3.80 (s, 3 H), 5.12 (s, 2 H), 5.49 (s, 1 H), 6.29 (dd, 1 H, *J* = 2.8, 8.6 Hz), 6.45 (d, 1 H, *J* = 2.8 Hz), 6.96 (d, 1 H, *J* = 8.6 Hz).

IR ($CHCl_3$): ν = 3580 cm^{-1} (OH).

Anal. Calcd for $C_9H_{12}O_4$: C, 58.69, H, 6.56. Found C, 58.63, H, 6.39.

4-*tert*-Butyldimethylsilyloxy-2-methoxy-1-methoxymethoxybenzene (9)
Under anhydrous conditions, imidazole (6.1 g, 89.6 mmol) followed by TBDMSCl (13.5 g, 89.6 mmol) were added to a solution of **16** (11 g, 60 mmol) in anhyd DMF (100 mL). The reaction was over in 7 h and the precipitate formed during the reaction was filtered. The DMF was evaporated under reduced pressure and the precipitate was dissolved in Et_2O. The organic phase was washed with brine, dried ($MgSO_4$) and evaporated to give a crude mixture that was purified by silica gel chromatography (hexane/EtOAc, 8:2) to give **9** (16 g, 90%) as a colorless liquid.

^{1}H NMR ($CDCl_3$): δ = 0.18 (s, 6 H), 0.97 (s, 9 H), 3.52 (s, 3 H), 3.83 (s, 3 H), 5.14 (s, 2 H), 6.34 (dd, 1 H, *J* = 8.6, 2.7 Hz), 6.43 (d, 1 H, *J* = 2.7 Hz), 6.98 (d, 1 H, *J* = 8.6 Hz).

IR ($CHCl_3$): ν = 980 cm^{-1}(Si–O).

Anal. Calcd for $C_{15}H_{26}O_4Si$: No good elemental analysis could be obtained despite many attempts.

4-*tert*-Butyldimethylsilyloxy-2-methoxy-1-methoxymethoxy-6-pentylbenzene (7)
Under anhydrous conditions, TMEDA (0.28 mL, 1.84 mmol) and *sec*-BuLi (1.3 mL, 1.84 mmol) were dissolved in THF (50 mL) and the mixture was cooled down to –78°C. A solution of **9** (0.50 g, 1.67 mmol) in THF (6 mL) was added dropwise. After 30 min, $MgBr_2$ (1.3 g, 5.02 mmol) was added. After 15 min, the mixture was warmed up to 25°C until a clear solution was obtained and the mixture was then cooled down to –78°C for 40 min, during which bromopentane (0.42 mL, 3.35 mmol) was added. The mixture was allowed to warm up to 25°C and was then heated to reflux for 4 h. After cooling down, the reaction was hydrolyzed by addition of an aq solution of 10% NH_4Cl and extracted with Et_2O (3 × 50 mL). The combined organic phase was washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure. The crude product was purified by silica gel chromatography (hexane/Et_2O, 9:1) to give **7** (0.45 g, 73%) as a colorless liquid.

^{1}H NMR ($CDCl_3$): δ = 0.19 (s, 6 H), 0.86 (t, 3 H, *J* = 6.8 Hz), 0.98 (s, 9 H), 1.30 (m, 6 H), 2.60 (t, 2 H, *J* = 7.7 Hz), 3.68 (s, 3 H), 3.78 (s, 3 H), 4.99 (s, 2 H), 6.25 (s, 2 H).

IR ($CHCl_3$): ν = 982 cm^{-1} (Si–O).

Anal. Calcd for $C_9H_{12}O_4$: C, 65.17, H, 9.84. Found C, 65.37, H, 10.06.

3-Bromo-1-methoxy-2-methoxymethoxybenzene (20)
NaH (264 mg, 11 mmol) was added portionwise to a solution of bromoguaiacol **18** (2.0 g, 10 mmol) in anhyd THF (60 mL) at 0°C. After stirring the mixture for 30 min a 25°C, MOMBr (1.0 mL, 12 mmol) was added at 0°C. The mixture was stirred for 16 h at 25°C, neutralized using a satd aq solution of NH_4Cl, and extracted with Et_2O (3 × 30 mL). The combined organic phases were washed with brine and dried ($MgSO_4$). After evaporation of the solvent, the crude material was purified by silica gel chromatography (hexane/EtOAc, 85:15) to yield **20** (2.4 g, 96%) as a colorless oil.

^{1}H NMR ($CDCl_3$): δ = 3.65 (s, 3 H), 3.83 (s, 3 H), 5.16 (s, 2 H), 6.84 (dd, 1 H, *J* = 8.4 Hz), 6.92 (t, 1 H), 7.14 (dd, 1 H, *J* = 8.0, 1.6 Hz).

^{13}C NMR ($CDCl_3$): δ = 56.0, 57.9, 98.6, 111.8, 117.8, 125.0, 125.2, 143.2, 153.6.

IR ($CHCl_3$): ν = 1481 (O–CH_2–O), 1218 (C–O), 758 cm^{-1} (C–Br).

Anal. Calcd for $C_9H_{11}BrO_3$: C, 43.75, H, 4.48, Br, 32.34. Found C, 43.67, H, 4.48, Br, 32.43.

2-Acetoxy-3-bromo-1-methoxybenzene (21)
Phenol **18** (2.0 g, 10 mmol) was dissolved in anhyd CH_2Cl_2 (30 mL). Pyridine (3.0 mL, 30 mmol) was then added at 0°C, followed by addition of a catalytic amount of DMAP and acetyl chloride (1.5 mL, 15 mmol), and the mixture was stirred for 2.5 h at 25°C. After filtration, the organic phase was washed with a solution of 2 N HCl (3 × 25 mL) and dried ($MgSO_4$). The crude mixture was purified by silica gel chromatography (hexane/EtOAc, 85:15) to yield **21** (2.43 g, 99%) as white crystals; mp 39°C.

^{1}H NMR ($CDCl_3$): δ = 2.36 (s, 3 H), 3.82 (s, 3 H), 6.90 (dd, 1 H, *J* = 8.0, 1.4 Hz), 7.07 (t, 1 H), 7.18 (dd, 1 H, *J* = 8.2, 1.4 Hz).

^{13}C NMR ($CDCl_3$): δ = 20.5, 56.3, 111.5, 117.3, 124.5, 127.4, 138.0, 152.7, 167.9.

IR ($CHCl_3$): ν = 1769 (C=O), 1271, 1201 (C-O), 1039 (C-O (Ac)), 759 cm^{-1} (C-Br).

Anal. Calcd for $C_9H_9BrO_3$: C, 44.11, H, 3.70, Br, 32.60. Found C, 44.19, H, 3.63, Br, 32.81.

Heck Coupling Reactions of Bromoaromatics 18–21, 27 with the Alkene 13 (Table); General Procedure
In a one-neck flask closed using a septum and tighted up with a hose connector clamp, the appropriate bromoaromatic (1 equiv), $Pd(OAc)_2$ (0.02 equiv), tri-*o*-tolylphosphine (0.08 equiv) and the alkene **13** (2.5 equiv) were stirred until dissolved. Et_3N (minimum 2.5 equiv) was then added. The mixture was then heated up to 100°C for 12 to 36 h. After cooling down, the mixture was diluted with Et_2O and filtered over Celite. The solvent was evaporated and the crude material was purified by silica gel chromatography.

In most cases only ^{1}H NMR spectra are reported because a mixture of isomeric alkenes was obtained. The purity of the reduced compounds, however, supports the proposed structures.

Ethyl 5-(2'-Methoxymethoxy-3'-methoxyphenyl)pent-4-enoate (24, mixture of isomers, major one described)
Colorless oil.

^{1}H NMR ($CDCl_3$): δ = 1.22 (t, 3 H), 2.48 (m, 4 H), 3.57 (s, 3 H), 3.83 (s, 3 H), 4.12 (q, 2 H, *J* = 7.2 Hz), 5.14 (s, 2 H), 6.22 (dt, 1 H, *J* = 16.0, 7.0 Hz), 6.80 (m, 3 H), 7.00 (t, 1 H, *J* = 7.8 Hz).

IR ($CHCl_3$): ν = 1734 (C=O), 1254, 1168 cm^{-1} (C–O).

Ethyl 5-(2'-Acetoxy-3'-methoxyphenyl)pent-4-enoate (25a)
Colorless oil.

^{1}H NMR ($CDCl_3$): δ = 1.22 (t, 3 H), 2.34 (s, 3 H), 2.48 (m, 4 H), 3.80 (s, 3 H), 4.10 (q, 2 H, *J* = 7.2 Hz), 6.21 (m, 1 H), 6.44 (d, 1 H, *J* = 16.0 Hz), 6.81 (dd, 1 H, *J* = 7.2, 2.4 Hz), 7.13 (m, 2 H).

IR ($CHCl_3$): ν = 1762, 1732 (C=O), 1470, 1274, 1170 cm^{-1} (C–O).

Ethyl 4-(2'-Acetoxy-3'-methoxyphenyl)pent-4-enoate (25b)
Colorless oil.

^{1}H NMR ($CDCl_3$): δ = 1.22 (t, 3 H), 2.26 (s, 3 H), 2.36 (t, 2 H), 2.69 (td, 2 H, *J* = 7.0 Hz), 3.81 (s, 3 H), 4.09 (q, 2 H, *J* = 7.2 Hz), 5.02 (m, 1 H), 5.18 (m, 1 H, *J* = 1.2 Hz), 6.80 (dd, 1 H, *J* = 8.0 Hz), 6.87 (dd, 1 H, *J* = 8.2, 1.2 Hz), 7.15 (t, 1 H).

IR ($CHCl_3$): ν = 1760, 1730 (C=O), 1476, 1280, 1172 cm^{-1} (C–O).

Ethyl 5-(2'-Acetoxy-3'-methoxyphenyl)pent-3-enoate (25c)
Colorless oil.

^{1}H NMR ($CDCl_3$): δ = 1.25 (t, 3 H), 2.34 (s, 3 H), 3.02 (m, 2 H), 3.27 (m, 2 H), 3.82 (s, 3 H), 4.14 (q, 2 H, *J* = 7.2 Hz), 5.65 (m, 2 H), 6.85 (m, 2 H), 7.13 (t, 1 H, *J* = 7.6 Hz).

IR ($CHCl_3$): ν = 1760, 1728 (C=O), 1471, 1276, 1170 cm^{-1} (C–O).

Ethyl 5-(2'-Acetoxy-3'-methoxyphenyl)pent-2-enoate (25d)
Colorless oil.

^{1}H NMR ($CDCl_3$): δ = 1.25 (t, 3 H), 2.32 (s, 3 H), 2.47 (m, 2 H), 2.66 (m, 2 H), 3.80 (s, 3 H), 4.16 (q, 2 H, *J* = 7.2 Hz), 5.63 (m, 1 H), 5.83 (dt, 1 H, *J* = 15.6, 1.4 Hz), 6.82 (m, 2 H), 7.12 (t, 1 H, *J* = 7.6 Hz).

IR ($CHCl_3$): ν = 1756, 1712 (C=O), 1476, 1280, 1172 cm^{-1} (C–O).

Ethyl 5-(2'-*N*,*N*-Diethylcarbamato-3'-methoxyphenyl)pent-4-enoate (26, mixture of isomers, major one described)
Colorless oil.

^{1}H NMR ($CDCl_3$): ν = 1.08 (br m, 6 H), 1.25 (t, 3 H), 2.48 (m, 4 H), 3.45 (m, 4 H), 3.80 (s, 3 H), 4.14 (q, 2 H, *J* = 7.1 Hz), 6.32 (d, 1 H, *J* = 0.8 Hz), 6.52 (dt, 1 H, *J* = 16.0, 6.5 Hz), 6.90 (m, 3 H).

IR ($CHCl_3$): ν = 1732, 1720 (C=O), 1264, 1160 cm^{-1} (C-O).

Ethyl 5-(2'-Hydroxy-3'-methoxyphenyl)pent-4-enoate (29, mixture of isomers, major one described)
Colorless oil.

^{1}H NMR ($CDCl_3$): δ = 1.22 (t, 3 H), 2.48 (m, 4 H), 3.86 (s, 3 H), 4.11 (q, 2 H, *J* = 7.2 Hz), 5.70 (m, 1 H), 5.84 (s, 1 H), 6.20 (m, 1 H), 6.76 (m, 2 H), 6.97 (dd, 1 H, *J* = 8.2, 1.2 Hz).

IR ($CHCl_3$): ν = 3320 (OH), 1730 (C=O), 1258, 1164 cm^{-1} (C–O).

Catalytic Hydrogenation of Alkenes 24-26; General Procedure
The mixture of alkenes obtained as above from the Heck coupling reaction was dissolved in EtOAc together with 5% Pd/C and the heterogeneous solution was stirred vigorously for 2 h under an atmosphere of H_2. After one equivalent of gas was consumed, the mixture was filtered over Celite and the reaction was rerun with less catalyst for 1 h. After filtration and evaporation of the solvent, the reduced product was obtained quantitatively in pure form.

Ethyl 5-(2'-Methoxymethoxy-3'-methoxyphenyl)pentanoate (30)
Colorless oil.

^{1}H NMR ($CDCl_3$): δ = 1.24 (t, 3 H), 1.65 (m, 4 H), 2.28 (t, 2 H), 2.60 (m, 2 H), 3.55 (s, 3 H), 3.80 (s, 3 H), 4.11 (q, 2 H, *J* = 7.2 Hz), 5.03 (s, 2 H), 6.70 (dd, 1 H, *J* = 7.2, 1.6 Hz), 6.74 (dd, 1 H, *J* = 7.0, 1.6 Hz), 6.97 (t, 1 H).

Anal. Calcd for $C_{16}H_{24}O_5$: C, 64.84, H, 8.16. Found C, 65.17, H, 8.32.

Ethyl 5-(2'-acetoxy-3'-methoxyphenyl)pentanoate (31)
Colorless oil.

^{1}H NMR ($CDCl_3$): δ = 1.22 (t, 3 H), 1.60 (m, 4 H), 2.34 (s, 3 H), 2.51 (m, 4 H), 3.80 (s, 3 H), 4.10 (q, 2 H, *J* = 7.2 Hz), 6.80 (m, 2 H), 7.10 (t, 1 H, *J* = 8.0 Hz).

^{13}C NMR ($CDCl_3$): δ = 14.3, 20.5, 24.8, 29.5, 29.8, 34.1, 55.9, 60.2, 110.0, 121.6, 126.3, 135.3, 138.2, 151.2, 168.8, 173.4.

IR ($CHCl_3$): ν = 3022, 2939 (CH), 1765, 1729 (C=O), 1478, 1275, 1174 cm^{-1} (C–O).

Anal. Calcd for $C_{16}H_{22}O_5$: C, 65.29; H, 7.53. Found C, 65.05, H, 7.69.

Ethyl 5-(2'-*N*,*N*-Diethylcarbamato-3'-methoxyphenyl)pentanoate (32)
Colorless oil.

^{1}H NMR ($CDCl_3$): δ = 1.20 (t, 9 H), 1.65 (m, 4 H), 2.30 (t, 2 H), 2.58 (m, 4 H), 3.40 (m, 4 H), 3.80 (s, 3 H), 4.14 (q, 2 H, *J* = 7.2 Hz), 6.78 (m, 2 H), 7.06 (t, 1 H, *J* = 8.0 Hz).

^{13}C NMR ($CDCl_3$): δ = 13.4, 14.2, 24.8, 29.6, 29.9, 34.2, 42.2, 55.9, 60.1, 110.1, 121.5, 125.5, 135.8, 139.0, 152.0, 153.8, 173.5.

IR ($CHCl_3$): ν = 2977, 2937 (CH), 1732, 1721 (C=O), 1276, 1087 cm^{-1} (C–O).

Anal. Calcd for $C_{19}H_{29}NO_5$: C, 64.93, H, 7.95, N, 3.98. Found C, 65.11, H, 8.11, N, 3.92.

5-(2'-Methoxymethoxy-3'-methoxyphenyl)pentanoic Acid (33)
The ester **30** (3 mmol) was dissolved in THF (20 mL) and a satd solution of $Ba(OH)_2$ (40 mL) was added. The reaction was complete in about 4 h and 1 N HCl was then added dropwise until pH 2. The aqueous phase was extracted with EtOAc (5 × 50 mL) and the combined organic phases were washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure. The crude material was purified by silica gel chromatography to give the acid in yields over 90%.

Colorless oil.

^{1}H NMR ($CDCl_3$): δ = 1.58 (qn, 2 H), 1.69 (qn, 2 H), 2.32 (t, 2 H), 2.76 (t, 2 H), 3.44 (m, 4 H), 3.83 (s, 3 H), 5.07 (s, 2 H), 7.02, (m, 3 H).

5-(2'-Hydroxy-3'-methoxyphenyl)pentanoic Acid (11)
To a solution of the carbamate **34** (4.45 mmol) in EtOH (50 mL) was added NaOH (1.78 g, 44.5 mmol) in large excess. The mixture was refluxed for 12 h. The excess of NaOH was neutralized at 0°C using a solution of 1 N HCl, and the aqueous solution was extracted with EtOAc (3 × 100 mL). The combined organic phase was washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure. The crude was purified by silica gel chromatography to give the deprotected product (80%) as white crystals; mp 123–124°C (Lit.[52] mp 125–126°C).

^{1}H NMR (acetone-d_6): δ = 1.63 (m, 4 H), 2.30 (t, 2 H, *J* = 7.0 Hz), 2.62 (t, 2 H, *J* = 7.0 Hz), 6.60 (m, 3 H), 7.00 (s, 1 H), 8.18 (s, 1 H).

^{13}C NMR ($CDCl_3$): δ = 24.5, 29.2, 29.3, 34.0, 56.1, 108.5, 119.3, 128.0, 143.6, 146.6, 180.3.

IR ($CHCl_3$): ν = 3540, 3200–2950 (OH), 1756, 1711 cm^{-1} (C=O).

5-(3'-Methoxy-*p*-benzoquinone)pentanoic Acid (2)
Salcomine Oxidation: In dry glassware purged with oxygen, phenol **11** (1.0 mmol) was dissolved in anhyd DMF (5 mL) and salcomine was added (0.1 mmol). The mixture was vigorously stirred and the

reaction was followed by TLC. After consumption of the starting material (6 h), DMF was evaporated under vacuum and the crude mixture was purified by chromatography, using degassed silica gel and solvents (hexane/EtOAc, 5:5), and using N_2 pressure to flash the solvent. The quinone **2** was obtained as yellow crystals in 70% yield; mp 98°C.

^{1}H NMR ($CDCl_3$): δ = 1.67 (m, 4 H), 2.40 (m, 4 H), 3.84 (s, 3 H), 5.85 (d, 1 H), 6.50 (d, 1 H, *J* = 2.4 Hz).

^{13}C NMR ($CDCl_3$): δ = 25.1, 30.8, 34.0, 37.3, 56.0, 107.1, 132.7, 145.2, 158.5, 179.7, 182.0, 187.5.

IR ($CHCl_3$): ν = 3400-2700 (OH), 1734, 1680, 1604 (C=O), 1436, 1252 cm^{-1} (C–O).

Anal. Calcd for $C_{12}H_{14}O_5$: C, 60.50, H, 5.92. Found: C, 60.78, H, 6.14.

Oxidation with CAN: The protected hydroquinone **7** (1.6 mmol) and 2,6-pyridinedicarboxylic acid (0.67 g, 4 mmol) were dissolved in MeCN/H_2O (10 mL, 7:3), and a solution of CAN (2.19 g, 4 mmol) in MeCN/H_2O (10 mL, 1:1) was added dropwise at 0°C. The mixture was stirred 40 min at 0°C and 10 min at 25°C. H_2O (10 mL) was then added and the mixture was extracted using CH_2Cl_2 (3 × 30 mL). The combined organic phases were washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure, to yield a crude mixture that was purified by silica gel chromatography (EtAOc/hexane, 1:1). The solvent and the silica gel were degassed prior to the chromatography. The quinone **2** was recovered in 62% yield.

***N,N*-Diethylcarbamato-2-methoxy-6-(pent-1'-enyl)benzene (35, mixture of isomers)**

General procedure described for Heck coupling was adopted for **19** with 5 equiv of the alkene **12** instead of 2.5 equiv; Colorless liquid.

^{1}H NMR ($CDCl_3$): δ = 0.94 (t, 3 H, *J* = 7.2 Hz), 1.21 (m, 6 H), 2.00 (m, 4 H), 3.47 (m, 4 H), 3.81 (s, 3 H), 6.21 (d, 1 H, *J* = 15.9 Hz), 6.46 (dd, 1 H, *J* = 15.9, 6.6 Hz), 6.90 (m, 3 H).

IR ($CHCl_3$): ν = 1722 cm^{-1} (C=O).

***N,N*-Diethylcarbamato-2-methoxy-6-pentylbenzene (36)**

Hydrogenation of **35** following the general procedure gave **36**; colorless liquid.

^{1}H NMR ($CDCl_3$): δ = 0.89 (t, 3 H), 1.25 (m, 6 H), 1.59 (m, 6 H), 2.54 (t, 2 H, *J* = 7.1 Hz), 3.47 (m, 4 H), 3.81 (s, 3 H), 6.75 (m, 3 H).

IR ($CHCl_3$): ν = 1714 cm^{-1} (C=O).

Anal. Calcd for $C_{17}H_{27}NO_3$: C, 69.59, H, 9.26, N, 4.77. Found C, 69.75, H, 9.20, N, 4.70.

6-Pentylguaiacol (10)

Same hydrolysis procedure as described for **11** from the diethylcarbamate **34** was used; Colorless liquid.

^{1}H NMR ($CDCl_3$): δ = 0.92 (t, 3 H), 1.38 (m, 4 H), 1.65 (m, 2 H), 2.65 (t, 2 H), 3.89 (s, 3 H), 5.71 (s, 1 H), 6.75 (m, 3 H).

^{13}C NMR ($CDCl_3$): δ = 14.2, 22.8, 29.7, 29.8, 32.0, 56.0, 108.3, 119.3, 122.5, 128.9, 143.7, 146.5.

IR ($CHCl_3$): ν = 3432 (OH), 3010, 2931, 2866 (CH), 1264, 1077 cm^{-1} (C–O).

Acknowledgement

LV and SM were both financially supported by MRE fellowships from the French Government.

References

(1) Schildknecht, H.; Schmidt, H. *Z. Naturforsch.* **1967**, *22b*, 287.
(2) Bloch, B.; Karrer, P. *Vjschr. naturforsch. Ges., Zurich*, **1927**, *72*, 1; *Chem. Abstr.* **1928**, *22*, 2784.
(3) Marini-Bettolo, G. B.; Monache, F. D.; da Lima, O. G.; Coelho, S. B. *Gazz. Chim. Ital.* **1971**, *101*, 41.
(4) Bernays, E.; Lupi, A.; Bettolo, R. M.; Mastrofrancesco, C.; Tagliatesta, P. *Experentia* **1984**, *40*, 1010.
(5) de Lima, O. G.; Marini-Bettolo, G. B.; Delle Monache, F.; Coelho, J. S.; d'Albuquerque, L. I.; Maciel, G. M.; Lacerda, A.; Martins, D. G. *Rev. Inst. Antibiot.* **1970**, *10*, 29; *Chem Abstr*. **1970**, *77*, 29622.
(6) Fregert, S.; Hjorth, N. *Contact Dermatitis* **1977**, *3*, 172.
(7) Schulz, K. H.; Garbe, I.; Hausen, B. M.; Simatupang, M. H. *Arch. Dermatol. Res.* **1979**, *264*, 275.
(8) Ducombs, G. *Allerg. Immunol*. **1990**, *22*, 280.
(9) Fregert, S.; Hjorth, N.; Schulz, K. H. *Arch. Dermatol.* **1968**, *98*, 144.
(10) Ingber, A.; Menne, T. *Contact Dermatitis* **1990**, *23*, 15.
(11) Tabar, A. I.; Quirce, S.; Garcia, B. E.; Rodriguez, A.; Olaguibel, J. M. *Contact Dermatitis* **1994**, *30*, 47.
(12) Dupuis, G.; Benezra, C. *Allergic Contact Dermatitis to Simple Chemicals: A Molecular Approach*; M. Deckert: New York, 1982.
(13) In *Meeting report and highlights*; Williams, D. C. M., L., Ed.; Commission of the European Commnunities, Bruxelle: Dublin, 1992.
(14) König, W. A.; Faasch, H.; Heitsch, H.; Colberg, C.; Hausen, B. M. *Z. Naturforsch. B.* **1993**, *48*, 387.
(15) Hausen, B. M.; Heitsch, H.; Borrmann, B.; Koch, D.; Rathmann, R.; Richter, B.; König, W. A. *Contact Dermatitis* **1995**, *33*, 12.
(16) Bieber, L. W.; De Andrade Chiapetta, A.; De Moraes e Souza, M. A.; Generino, R. M. *J. Nat. Prod*. **1990**, 53, 706.
(17) Snyder, C. D.; Rapoport, H. *J. Am.. Chem. Soc.* **1974**, *96*, 8046.
(18) Rao, D. V.; Ulrich, H.; Sayigh, A. A. R. *J. Org. Chem.* **1975**, *40*, 2548.
(19) Jacob, P.; Callery, P. S.; Shulgin, A. T.; Castagnoli, N. Jr. *J. Org. Chem.* **1976**, *41*, 3627.
(20) Syper, L.; Kloc, K.; Miochowski, J.; Szulc, Z. *Synthesis* **1979**, 521.
(21) Van Dort, H. M.; Geursen, H. J. *Recl. Trav. Chim. Pays Bas* **1967**, *86*, 520.
(22) De Jonge, C. R. H. I.; Hageman, H. J.; Hoentjen, G.; Mijs, W. J. *Org. Synth.* **1977**, *57*, 78.
(23) Gilman, H. *Org. React.* **1954**, *8*, 258.
(24) Snieckus, V. *Bull. Soc. Chim.* **1988**, *1*, 67.
(25) Saa, J. M.; Martorell, G.; Frontera, A. *J. Org. Chem.* **1996**, *61*, 5194.
(26) Bauer, W.; von Ragué Schleyer, P. *J. Am. Chem. Soc.* **1989**, *111*, 7191.
(27) Townsend, C. A.; Bloom, L. M. *Tetrahedron Lett.* **1981**, *22*, 3923.
(28) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*; 2nd ed.; Wiley: New York, 1991.
(29) Ronald, R. C.; Winkle, M. R. *Tetrahedron* **1982**, *39*, 2031.
(30) Dakin, H. D. *Am. Chem. J.* **1909**, *42*, 477.
(31) Baker, W.; Bondy, H. F.; Gumb, J.; Miles, D. *J. Chem. Soc.* **1953**, 1615.
(32) Sibi, P.; Jahil Miah, R. A.; Snieckus, V. *J. Org. Chem.* **1984**, *49*, 737.
(33) Keinan, E.; Eren, D. *J. Org. Chem.* **1987**, *52*, 3872.
(34) Heck, R. F. *Pure Applied Chem.* **1978**, *50*, 691.
(35) Collum, D. B. *Tet. Lett.* **1995**, *36*, 3111.
(36) Larock, R. C.; Tu, C. *Tetrahedron* **1995**, *51*, 6635.
(37) Cabri, W.; Candiani, I. *Acc. Chem. Res.* **1995**, *28*, 2.

(38) Moreno-Manas, M.; Perez, M.; Pleixats, R. *J. Org. Chem.* **1996**, *61*, 2346.
(39) Badone, D.; Baroni, M.; Cardamone, R.; Ielmini, A.; Guzzi, U. *J. Org. Chem.* **1997**, *62*, 7170.
(40) Jutand, A.; Molesh, A. *J. Org. Chem.* **1997**, *62*, 261.
(41) Heck, R. F. *Org. React.* **1982**, 345.
(42) Ziegler, C. B.; Heck, R. F. *J. Org. Chem.* **1978**, *43*, 2941.
(43) Pearson, D. E.; Wysong, R. D.; Breder, C. V. *J. Org. Chem.* **1967**, *32*, 2358.
(44) Sibi, M. P.; Chattopadhyay, S.; Dankwardt, J. W.; Snieckus, V. *J. Am.Chem. Soc.* **1985**, *107*, 6312.
(45) Mabic, S.; Paré, M.; Stampf, J.-L.; Benezra, C.; Lepoittevin, J.-P. *Chem. Res. Toxicol.* **1998**, In press.
(46) Inoue, K.; Sakai, K. *Tetrahedron Lett.* **1977**, *18*, 4063.
(47) Auerbach, J.; Weinreb, S. M. *J. Chem. Soc., Chem. Commun.* **1974**, 298.
(48) Jäger, G.; Geiger, R.; Siedel, W. *Chem. Ber.* **1968**, *101*, 2762.
(49) Drake, N. L.; Harris, H. C.; Bjaeder, C. *Am. Soc.* **1948**, *70*, 168.
(50) Sibi, P.; Snieckus, V. *J. Org. Chem.* **1983**, *48*, 3923.
(51) Stevens, R. V.; Bisacchi, G. S. *J. Org. Chem.* **1982**, *47*, 2393.
(52) Carpenter, P. D.; Humphreys, D. J.; Proctor, G. R.; Rees, L. G. *J. Chem. Soc. Perkin Trans. I* **1974**, 1527.

Article Identifier:
1437-210X,E;1999,0,07,1127,1134,ftx,en;C07498SS.pdf