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Asymmetric Allylic Alkylation Catalyzed by Palladium-Sparteine Complexes

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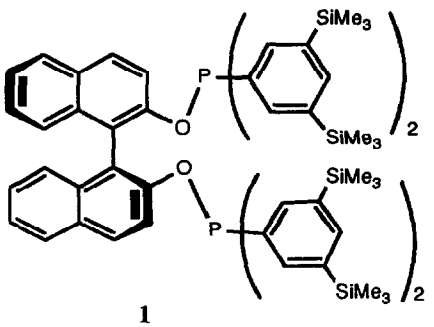
Abstract. The cationic complex [Pd(η^3-C_3H_5)(sparteine)]PF_6 (**6**) was found to be a suitable catalyst precursor for the asymmetric alkylation of allylic acetates with Na[CH(COOMe)$_2$] as the nucleophile. This constitutes one of the first and still rare examples of a phosphine-free system for this type of Pd-catalyzed reaction. Using 5 mol % of **6**, alkylation products were obtained in up to 90 % isolated yield and 85 % enantiomeric excess. The alkylation reaction was shown to occur with overall retention of configuration, indicating an analogous mechanism to the one previously proposed for phosphine-containing catalysts. The reactivity of allylic acetates is strongly dependent upon the nature of the substituents, open-chain aliphatic substrates being unreactive.

1. Introduction. - The use of chiral transition-metal complexes as catalysts for stereoselective C-C bond forming reactions has developed in recent years to a topic of fundamental importance .[1] The so-called allylic alkylation is one of the best known among this type of reactions.[2] It allows the Pd-catalyzed substitution of a suitable leaving group (typically acetate) in allylic position by a soft nucleophile (typically malonate anions). Owing to the well documented occurence of Pd(0)-species during the catalytic cycle, the use of ancillary ligands has been so far restricted to phosphines and phosphites[3] which are able to stabilize low oxidation states.[4] Several chiral chelating diphosphines have been used in the asymmetric allylic alkylation. High degrees of enantioselection were achieved by applying different approaches. *Trost*[5] designed ligand **1** (see Chart 1.) in order to create a chiral pocket around the metal. The introduction of the bulky TMS-groups on the phenyl substituents of the phosphorus ligands and the enlargement of the chelating ring allows to expand the chiral environement toward the region where the nucleophilic attack is going to take place. *Bosnich*[6] emphasized the importance of the 1,1-diaryl substitution pattern in the allylic substrate in order to obtain high rates of interconversion between diastereomeric complexes (*Curtin-Hammett* kinetics[7]) and a high degree of regio- and enantioselection in the Pd(*S,S*-chiraphos)-catalyzed reaction. *Hayashi*[8] conceived a functionalized chiral ferrocenylphosphine (**3**) in which the incorporated hydroxyl groups interact with the incoming nucleophile and direct its attack preferentially onto one of the diastereotopic sites of 1,3-disubstituted allyl ligands. Examples of products and selectivities obtained by applying these successful concepts are given in Chart 1.

Chart 1.



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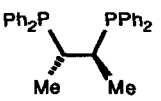

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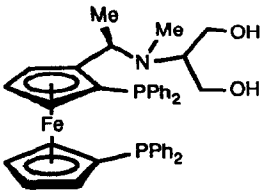

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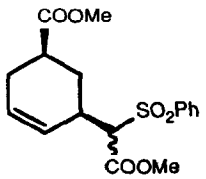
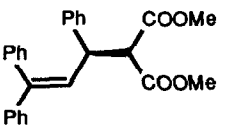
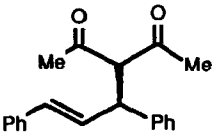


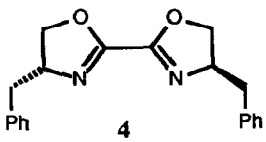
69 % e.e.
(B. M. Trost et al., 1985)



84 % e.e.
(B. Bosnich et al., 1985)



90 % e.e.
(T. Hayashi et al., 1986)



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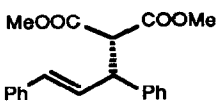


77 % e.e.

(A. Pfaltz et al., 1991)

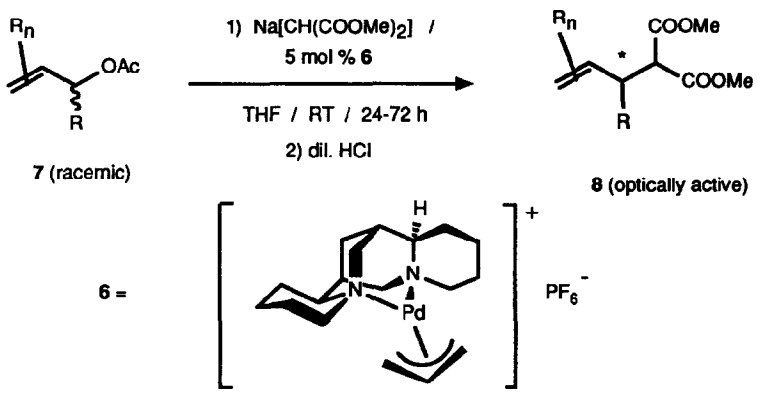
To our knowledge so far the only catalytic palladium system for the asymmetric allylic alkylation, not containing phosphines, has been very recently reported by *Pfaltz*.[9] In analogy to his semicorrinato ligands,[10] *Pfaltz* prepared 4,4',5,5'-tetrahydrobis(oxazoles) (bisoxazolines) of type **4**, and found these ligands to ensure a quite high enantioselectivity in the allylic alkylation of 1,3-diphenyl-allyl acetate. Meanwhile, similar ligands have been shown by other research groups to impart very high stereoselectivities to several types of transition-metal catalyzed reactions.[11]

The readily available, naturally occuring alkaloid (-)-sparteine has been described as an effective chiral ligand among others for e.g. asymmetric *Reformatzky* reactions,[12] as well as for *Grignard*-induced anionic polymerizations.[13] Our approach was therefore to test the ability of sparteine to act as an ancillary ligand in Pd(II)-allyl complexes, susceptible to nucleophilic attack by stabilized anions such as $Na[CH(COOMe)_2]$ (**5**), and which could be employed as catalyst precursors. In addition we speculated that the rather rigid and bulky sparteine would be able to significantly induce differentiation between the two diastereotopic sites of a 1,3-disubstituted allyl ligand, thus leading to enantioselection upon nucleophilic attack. *Trost*[14] showed in an

early report on the stoichiometric allylic alkylation of $[Pd(\eta^3\text{-MeCHCHCHMe})Cl]_2$ with **5** in the presence of various chiral ligands that sparteine would compete, among others, with e.g. (+)-DIOP for asymmetric induction (up to 25 % e.e.). To our knowledge this is the only report on the use of this alkaloid in the allylic alkylation. We have already communicated the synthesis, 2D NMR studies, and X-ray structural characterization of cationic $Pd(\eta^3\text{-allyl})$(sparteine) complexes.[15] Here, we report the observation of the catalytic activity of the parent complex $[Pd(\eta^3\text{-}C_3H_5)(sparteine)]PF_6$ (**6**) in the alkylation of variuos allylic acetates by $Na[CH(COOMe)_2]$ (**5**).

2. Results and Discussion. - 5 mol % of complex **6** in THF at room-temperature catalyze the substitution reaction of acetate in substrates of type **7** by sodium dimethylmalonate giving products **8** (see Scheme 1.). It is important to note that the catalytic activity of the present system is qualitatively *ca.* one to two orders of magnitude lower than that observed for phosphine-containing catalysts. Thus, complete conversion of the allylic acetate and/or deactivation of the catalyst by formation of Pd-black takes in general 48 to 72 h. A selection of the results obtained are summarized in Table 1.

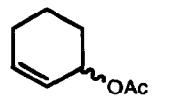
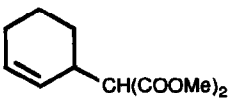
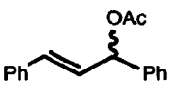
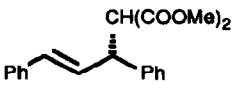
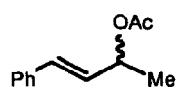
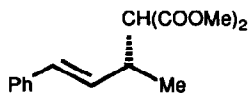
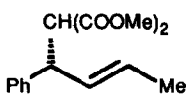
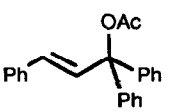
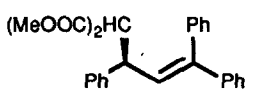
Scheme 1.



Starting from either racemic or achiral allylic acetates, the optically active alkylated products obtained show enantiomeric excesses (e.e.) of up to 85 % for **8d** and **8e** (the e.e.'s were determined by NMR, see Exp. Section). Such a selectivity favorably compares with that observed for catalysts containing chiral chelating diphosphines. Thus **8e** was formed in 84 % e.e. using the Chiraphos-system described by *Bosnich*.[6] On the other hand, it is interesting to note that the same catalyst gives **8b** in only 22 % e.e. compared with 75 % e.e. for the present Pd-sparteine system. This latter result nicely parallels the selectivity observed by *Pfaltz* (77 % e.e.),[9] but is significantly lower than the e.e.'s reported by *Hayashi* for structurally related products.[8]

Substrate **7c** illustrates the general problem of the regioselectivity in the allylic alkylation of unsymmetrically substituted allylic substrates. As it is found for most Pd-catalyzed substitution reactions,[16] the Pd-sparteine catalyst at hand preferentially directs the nucleophilic attack at the less hindered terminus of the allyl fragment. A product ratio **8c/8d** of 83/17 was thus observed. It is interesting to note that the e.e. of the minor product **8d** is much higher than that of its counterpart **8c** (85 vs. 21 % e.e., respectively).

Table 1. Allylic alkylation with $Na[CH(COOMe)_2]$ catalyzed by complex **6**.

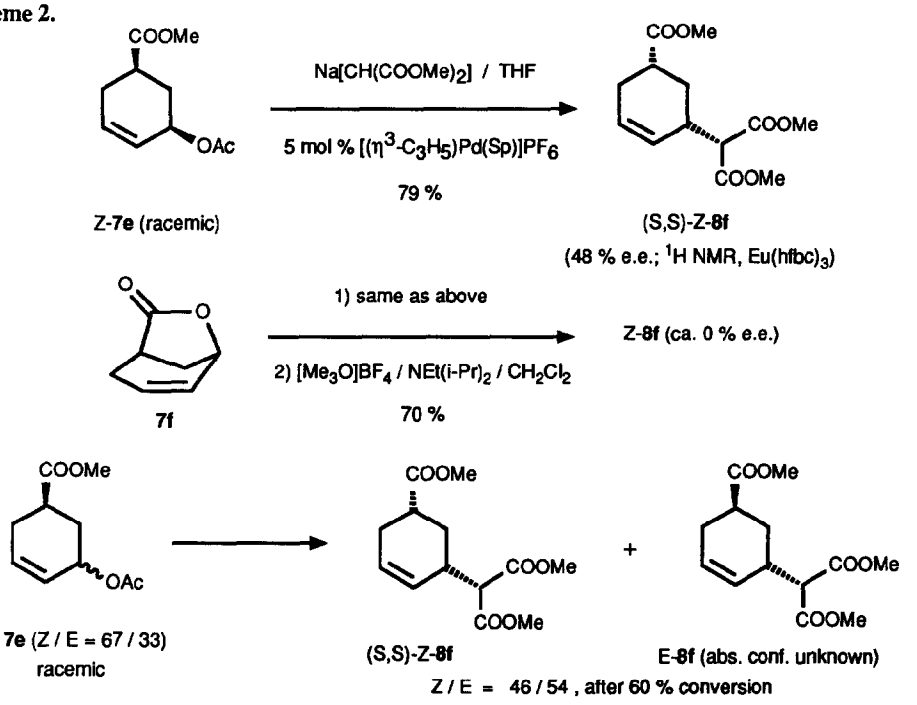
Substrate	Product	Yield (%)[a]	e.e. (%)	abs. conf.
 **7a**	 **8a**	82	50[b]	(-)-?
 **7b**	 **8b**	77	75[c]	(+)-R
 **7c**	 **8c**	62	21[c]	(+)-R
	 **8d**	13	85[c]	(-)-S
 **7d**	 **8e**	61	85[c]	(-)-R

[a] Isolated yields, after distillation or chromatography; [b] Determined by NMR using the paramagnetic shift reagent $Eu(hfbc)_3$; [c] Determined by NMR using the diamagnetic shift reagent (S)-(+)-TAE.[19]

It is well accepted that Pd-catalyzed allylic alkylation reactions using soft nucleophiles and phosphines as ancillary ligands occur with overall retention of configuration at the alkylated carbon atom.[17] Due to the different electronic properties of the Pd-sparteine complexes at hand compared to those of corresponding chelating aryl diphosphine compounds (e.g. no possibility of π-backbonding, more basic ligand), it was of interest to ascertain whether or not the present catalytic reaction follows a similar pathway. Starting from the substrates *Z*-**7e** and **7f**, developed by *Trost* as mechanistic probes,[18] the only alkylation product formed under Pd/sparteine catalytic conditions was *Z*-**8f**. This demonstrates that the reaction indeed occurs with overall retention of configuration, thus allowing the assumption of the same mechanistic features previously reported for phosphine containing catalysts. The results are shown in Scheme 2. It is intriguing to observe that the

product *Z*-**8f** was formed in optically active form (48 % e.e.) only from substrate **7e**, the alternative bicyclic starting material **7f** giving racemic *Z*-**8f**. Furthermore, when a 2 to 1 mixture of *Z*- and *E*-**7e** was reacted with **5**, and the reaction quenched after ca. 60 % conversion, the product mixture consisted of 46 % of *Z*-**8f** and 54 % of *E*-**8f**. This indicates that the rate of the oxidative addition of the *E*-configurated substrate (axially arranged acetoxy group) is about twice that of *Z*-**7e**.

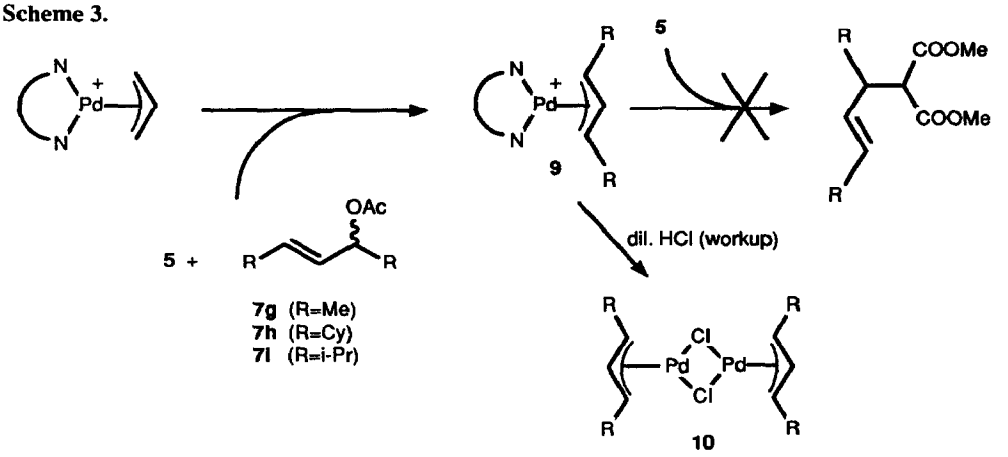
Scheme 2.



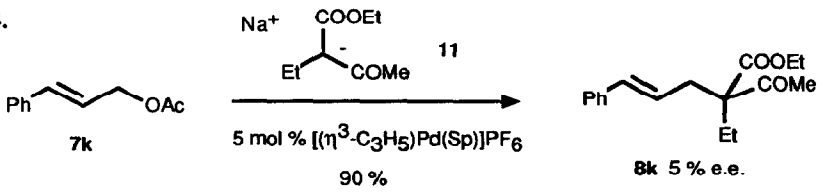
When open-chain 1,3-dialkyl allylic acetates were reacted with **5** in the presence of 5 mol % of **6**, no alkyation product was formed in detectable amounts. The palladium used as catalyst could be recovered after conventional workup in form of complexes of type **10** in up to 80% yield, as illustrated in Scheme 3. This observation indicates that the generation of a Pd(0)-species and the oxidative addition of the substrates did occur, but that the nucleophilic attack of **5** on the intermediates **9** (for the present system probably the rate determining step) does not take place at any reasonable rate. The only reactive allyl complexes bearing alkyl substituents are those derived from the *cyclic* substrates **7a**, **7e**, and **7f**, where the 1,3-substituents display an *anti* arrangment. The dramatic lack of reactivity of allyl complexes **9**, which are very likely to be *syn,syn* configurated, could be due to steric reasons. This furthermore points to the higher reactivity (electrophilicity) of the corresponding aryl substituted complexes, able to circumvent similar steric effects.

In an attempt to achieve induction at the homoallylic position, the prochiral nucleophile **11** (derived from ethyl 2-acetyl-butanoate) was reacted with cinnamyl acetate, **7k** (see Scheme 4.). The product **8k** was formed in high chemical yield, but in only 5 % e.e. This is not too surprising in view of the increased distance between the resident chirality in the catalyst and the forming stereogenic center in the transition state.

Scheme 3.



Scheme 4.



3. Conclusions. - We have shown that the cationic allyl palladium(II)-sparteine complex **6** catalyzes the allylic alkylation reaction, and is able to induce in some cases high degrees of enantioselection (up to 85 % e.e.). These are comparable to those of some of the most efficient catalysts containing chiral chelating phosphine ligands, thus adding a new entry to the already large arsenal of catalysts for the title reaction. More importantly, this demonstrates that chelating nitrogen compounds can indeed be suitable ligands for a catalytic system in which Pd(0)-species are generally invoked as reaction intermediates. Whereas Pd(0)-complexes stabilized by phosphine ligands are well known, a corresponding sparteine species still remains elusive . The applicability of our system seems to be restricted to either cyclic substrates or such bearing aryl substituents, a limitation which does not apply to the more common catalysts known from the literature. A further limitation of **6** is the rather low activity, as reflected by the turnover number of ca. 0.5/h.

4. Experimental Section. - *General.* All reactions with air- or moisture sensitive materials were carried out under an atmosphere of argon using standard *Schlenk*-techniques. Freshly distilled solvents (CH_2Cl_2 from powdered CaH_2, Et_2O and THF from Na/benzophenone ketyl and MeOH from NaOMe) were used throughout. Sparteine (*Sigma*) was distilled under reduced pressure and stored under argon. Optical rotations were measured on a *Perkin-Elmer* 241 polarimeter using 10 cm cells. ^1H NMR spectra were run on Bruker AC 250 or AM 300 instruments. Elemental analyses were performed by Analytical Research Services, CIBA-GEIGY AG. Allylic acetates were prepared following conventional methodologies. Spectroscopical and analytical data of individual alkylation products described in this work (**8c**,[17] **8d**,[17] **8e**,[6a] and **8f**[18a]), have already been reported in the literature, and will not be detailed here.

The synthesis of *[Pd(η^3-C_3H_5)(sparteine)]PF_6 (6)* has been already reported,[15] but is reproduced here for convenience. 1 ml (4.25 mmol) of sparteine was added to a solution of 707 mg (1.93 mmol) of [Pd(η^3-C_3H_5)Cl]$_2$ in 30 ml CH_2Cl_2. A solution of 977 mg (3.86 mmol) $AgPF_6$ in 10 ml MeOH was added and the mixture was stirred in the dark for 1 h. The finely divided precipitate of AgCl was filtered off on a *Celite*-plug. Slow addition of 50 ml Et_2O to the filtrate induced crystallization of the product which was collected by filtration, washed with Et_2O and pentane, and dried *in vacuo*. Yield: 1.88 g (92 %). $[\alpha]_D^{22}$=-67 (*c*=1.035, CH_2Cl_2), m.p. 215-218° (dec.). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.17-3.82 (complex *m*, 28H); 4.00 (br. *d*, *J*=12.5, 1H); 4.25 (br. *d*, *J*=11.5, 1H); 5.82-6.03 (*m*, 1H). Anal. calcd. for $C_{18}H_{31}F_6N_2PPd$: C 41.04, H 5.93, N 5.32, F 21.64, P 5.88; found: C 41.11, H 5.93, N 5.33, F 21.60, P 5.85.

Catalytic Allylic Alkylation. General Procedure. The reaction of 2-cyclohexenyl acetate (**7a**) is illustrative of the general method for all catalytic reactions described in this study. A filtered solution of ca. 42 mmol of Na[CH(COOCH$_3$)$_2$], **5**, generated from 5.65 g (42.8 mmol) of dimethyl malonate and 1.008 g (42 mmol) of NaH in 100 mL of THF, was added dropwise to a 100 mL THF mixture containing 564 mg (1.07 mmol) of **6**, 3.0 g (21.4 mmol) of **7a**, and 0.5 mL (ca. 2 mmol) of sparteine. The initially partly suspended **6** dissolved within 1 h, whereupon the yellowish and slightly milky reaction mixture turned to brown-yellow. After stirring it at r.t. for 3 days, 50 mL of 1 N HCl were added. The mixture was extracted with Et_2O, the organic phase was dried over $MgSO_4$, and evaporated. Distillation of the oily residue *in vacuo* afforded 3.72 g (82 %) of **8a**. Sbp.: 70°C (1 mbar); $[\alpha]^{22}_D$=-15.6 (c=2.6, $CHCl_3$), the absolute configuration of the major enantiomer was not determined; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.31-1.43 (m, 1H), 1.50-1.63 (m, 1H), 1.66-1.83 (m, 2H), 1.95-2.04 (m, 2H), 2.85-2.93 (m, 1H), 3.29 (d, J=9, C*H*(COOCH$_3$)$_2$), 3.74 (s, COOC*H*$_3$), 3.75 (s, COOC*H*$_3$), 5.48-5.51 (m, *H*C=CH), 5.73-5.82 (m, HC=C*H*). Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 61.75; H, 7.56. The e.e. was determined by NMR using the paramagnetic shift reagent Eu(hfbc)$_3$ by integration of the signals of the diastereotopic ester methyl groups and of the methyne proton signal of the malonate moiety: 50 % e.e. The error margin of this determination is estimated to be up to ±5 %. Alternatively, for other alkylation products (see Table 1.), the diamagnetic chiral shift reagent (+)-(*S*)-2,2,2-trifluoro-1-(9-anthryl)ethyl alcohol ((+)-(*S*)-TAE) could also be successfully used for the e.e. determination.[19]

Methyl 2-carbomethoxy-3,5-diphenylpent-4-enoate (8b). $[\alpha]^{22}_D$=+16.0 (c=3.2, EtOH); 75 % e.e. by NMR, (+)-(*S*)-TAE: integration of the methyne signal of the malonate moiety at δ 3.95. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.53 (s, COOC*H*$_3$), 3.70 (s, COOC*H*$_3$), 3.95 (d, J=11, C*H*E$_2$), 4.27 (dd, J=11, 8, PhC*H*CE$_2$), 6.32 (dd, J=15, 8, *H*C=CHPh), 6.48 (d, J=15, HC=C*H*Ph), 7.15-7.44 (m, 10 Ph-H). MS *m/z* 324 (M^+), 292, 260, 232, 205, 193, 192, 178, 115. Anal. Calcd for $C_{20}H_{20}O_4$: C, 74.06; H, 6.22. Found: C, 74.11; H, 6.26.

Ethyl 2-acetyl-2-ethyl-5-phenylpent-4-enoate (8k). Sdp.: 118-119°C (0.2 mbar); $[\alpha]^{22}_D$=+1.8 (c=2.275, $CHCl_3$); ca. 5% e.e. by NMR, (+)-(*S*)-TAE: integration of the methyl group signal at δ 0.82). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.82 (t, J=7.5, 3H), 1.26 (t, J=7.5, 3H), 1.97 (m, 2H), 2.16 (s, 3H), 2.74 (m, 2H), 4.21 (q, J=7.5, 2H),5.97 (dt, J=15, 7.5, 1H), 6.42 (dt, J=15, 1, 1H), 7.15-7.33 (m, 5H). MS *m/z* 274 (M^+), 245, 231, 201, 200, 185, 171,157, 129, 117. Anal. Calcd for $C_{17}H_{22}O_3$: C, 74.42; H, 8.08. Found: C, 74.22; H, 8.12.

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