# Synthesis of 2,3-Bis(acetoxymethyl)bicyclo[2.2.1]hepta-2,5-diene and Its Use in Palladium-Catalyzed Elimination

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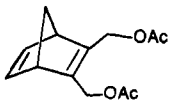
The synthesis of a novel polyfunctional bicyclic compound, 2,3-bis(acetoxymethyl)bicyclo[2.2.1]hepta-2,5-diene (**1**), is reported. The obtained prochiral synthon may be considered as a useful substrate on the route toward natural products and compounds of pharmaceutical interest. Submission of **1** to palladium-catalyzed elimination affords vinylic acetate **3**, 2-methylene-3-(acetoxyvinyl)bicyclo-[2.2.1]hept-5-ene, in excellent yields.

Although the palladium-catalyzed nucleophilic reactions of allylic acetates have been the subject of numerous and important studies over the past 30 years,[1] to our knowledge, bicyclic substrates featuring an "ene" diacetate moiety have never been reported in this kind of reactions. Since the use of such compounds may also provide useful synthons for natural products syntheses, as new mechanistic insights, we decided to set up for the synthesis of 2,3-bis(acetoxymethyl)bicyclo[2.2.1]hepta-2,5-diene (**1**) and its subsequent submission to palladium-promoted elimination.

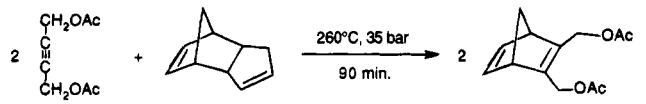



**1**

Initially, we planned the synthesis of **1** *via* the Diels–Alder reaction between cyclopentadiene and dimethyl acetylenedicarboxylate,[2] followed by reduction of the adduct and final diacetylation of the resulting diol. However, the use of various reducing agents such as lithium aluminum hydride, sodium borohydride, or diisobutyl aluminum hydride (DIBAL) led to the formation of unseparable mixtures of several partly reduced products. Similar difficulties have been encountered by Hart *et al.*, who proposed a novel method based on the use of DIBAL and *n*-butyllithium.[3] This "ate" reagent reduced some unsaturated bicyclic diesters to the corresponding enediols with good to excellent yields. In our case, the desired diol from **1** could only be obtained in low yield (25–30%) together with other products, similar to the previously obtained mixtures.

Luh *et al.* reported in 1982 a method for the obtention of the desired diol issued from **1**, reducing the [2.2.1]-nickelocene adduct with lithium aluminum hydride (52% chemical yield).[4] The complexation of **1** with iron pentacarbonyl and subsequent reduction was considered as well.[5] Yet, both approaches have been abandoned, being too time consuming and not feasible for upscaling. Thus, we decided to explore the direct Diels–Alder reaction between cyclopentadiene and 1,4-diacetoxy-2-butyne (**2**), the latter being prepared by diacetylation of commercially available 2-butyne-1,4-diol in the absence of base (Scheme 1).

**Scheme 1**




**2** **1**

**Table 1. Optimized Synthesis of *1* from *2* and Cyclopentadiene or Dicyclopentadiene**

| entry | *t* (min) | *T* (°C) | *p* (bar) | **1**[d] (%) | **2**[d] (%) | byproduct[d] | yield **1**[e] (%) |
|---|---|---|---|---|---|---|---|
| 1[a] | 135 | 130 | 1 | 8 | 68 | 24 | |
| 2[a] | 155 | 200 | 1 | 34 | 53 | 13 | 22 |
| 3[a] | 165 | 220 | 1 | 52 | 41 | 7 | 37 |
| 4[b] | 150 | 220 | 1 | 53 | 25 | 22 | 36 |
| 5[b] | 70 | 200 | 30 | 38 | 37 | 25 | 18 |
| 6[b] | 60 | 210 | 40 | 43 | 35 | 22 | 21 |
| 7[c] | 60 | 210 | 60 | 42 | 22 | 36 | 22 |
| 8[c] | 75 | 220 | 30 | 63 | | 37 | 44 |
| 9[c] | 80 | 220 | 30 | 68 | 10 | 22 | 45 |
| 10[c] | 90 | 220 | 35 | 65 | | 35 | 42 |
| 11[c] | 90 | 240 | 35 | 72 | | 28 | 54 |
| 12[c] | 90 | 260 | 35 | 85 | | 15 | 65 |

[a] A 1:1 molar ratio of cyclopentadiene and **2** was used. [b] A 3:10 molar ratio of dicyclopentadiene and **2** was used. [c] A 5:8 molar ratio of dicyclopentadiene and **2** was used. [d] Determined by GC analysis on the reaction mixture. [e] Chemical yield after two successive distillations (see Experimental Section).

The yield of this uncatalyzed cycloaddition reaction could only be improved when moderately increased temperature and pressure were applied (Table 1); the use of Lewis acid catalysts lead to unidentifiable polymeric products.

As can be seen, the use of dicyclopentadiene is appropriate, the dimer being cracked at temperatures superior to 170 °C.[6] Among the selected examples, entry 12 represents the optimal reaction conditions. Thus, pure **1** was obtained in 65% yield when heating a mixture

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(1) (a) Tsuji, J.; Minami, I. *Acc. Chem. Res.* **1987**, *20*, 140. (b) Trost, B. M. *Angew. Chem.* **1989**, *101*, 1199. (c) Trost, B. M.; Verhoeven, T. R. In *Comprehensive Organometallic Chemistry*; Pergamon Press: Oxford, 1982; Vol. 8, p 799. (d) Frost, C. G.; Howarth, J.; Williams, J. M. J. *Tetrahedron: Asymmetry* **1992**, *3*, 1089.

(2) (a) Grieger, R. A.; Eckert, C. A. *J. Am. Chem. Soc.* **1970**, *92*, 7149. (b) Grieger, R. A.; Eckert, C. A. *Ind. Eng. Chem. Fundam.* **1971**, *10*, 369.

(3) Anantanaryan, A.; Hart, G. *J. Org. Chem.* **1991**, *56*, 991.

(4) Luh, T. Y.; Lung, C. L. *J. Chem. Soc., Chem. Commun.* **1982**, 57.

(5) (a) Davies, S. G. *Organotransitionmetal Chemistry*; Pergamon Press: Oxford, 1982; pp 9–13, 91. (b) McQuillen, F. J.; Parker, D. G.; Stephenson, G. R. *Transitionmetal Organometallics for Organic Synthesis*; Cambridge University Press; Cambridge 1991; p 173. (c) Grée, R. *Synthesis* **1989**, 341 and references cited therein.

(6) Magnusson, G. *J. Org. Chem.* **1985**, *50*, 1998.

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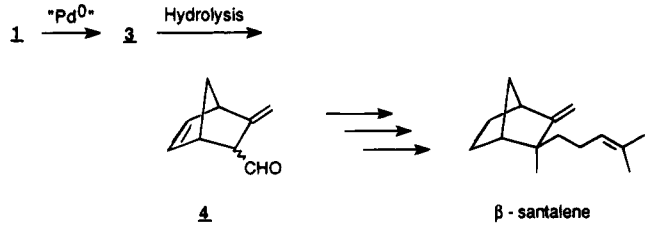
**Scheme 2**



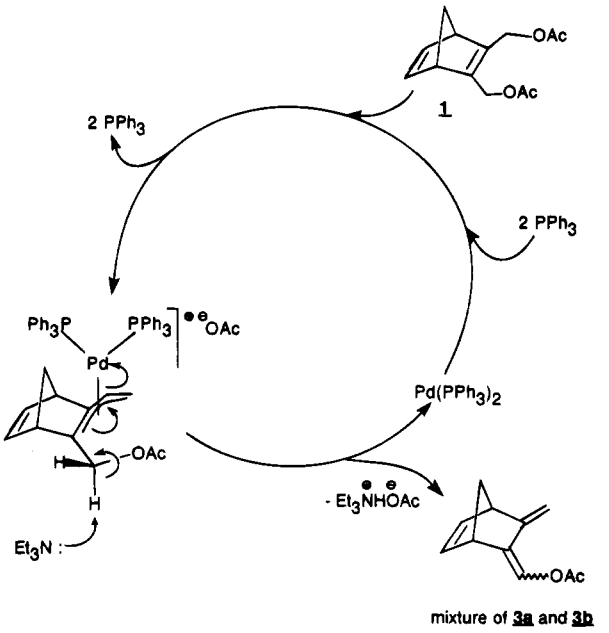

of dicyclopentadiene and **2** (5:8 molar ratio) to 260 °C for 1.5 h under 35 bar nitrogen pressure in a stainless steel autoclave, followed by two successive distillations. Unreacted starting material may be recovered at this stage for recycling.

Our aim was to use **1** as substrate in palladium-catalyzed elimination in order to obtain the corresponding vinylic acetate **3**. Hydrolysis of **3** should then provide the bicyclic aldehyde **4**, potential precursor for bicyclic natural products, i.e., β-santalene[7] (Scheme 2). The title compound may also be considered as starting material leading to synthons toward prostaglandins of the PGF series.[11]

The palladium-catalyzed elimination on allylic acetates using organophosphorus ligands has been widely studied, and it found application in organic synthesis.[12] This reaction proceeds *via* a π-allyl complex under the influence of heat and/or an organic base. Chiral ligands, such as the ferrocenyl phosphine introduced by Hayashi *et al.*, led to optically enriched products (up to 81% ee) using 4-*tert*-butyl-1-vinylcyclohexyl acetoacetate as substrate.[13] Thus, **1** being prochiral with respect to the elimination reaction, its use could lead to interesting results in enantioselective synthesis.

In the presence of 3 mol % of $Pd(PPh_3)_4$ and 1.5 equiv of triethylamine in refluxing THF, **1** yields quantitatively within 2 h compound **3**. In our case, the base is not necessary, though longer reaction times are required for complete conversion. Palladium salts give satisfactory yields as well; thus, it seems likely that the substrate itself reduces the metal in the course of the reaction, in order to maintain the catalytic cycle.[14] Table 2 displays the results for the reaction with triphenylphosphine as ligand under different conditions.

**Scheme 3**




mixture of **3a** and **3b**

**Table 2. Elimination Reaction on 1 with Different Sources of Pd (3 Mole% of Catalyst, Ligand $PPh_3$, Refluxing THF)**

| Pd source | ligand (equiv) | reaction time (h) | conversn (% by GC) |
|---|---|---|---|
| $Pd(PPh_3)_4$ | 4 | 4 | 83 |
| $Pd(dba)_2$ | 2 | 3 | 95 |
| $Pd(acac)_2$ | 2 | 3 | 100 |
| $Pd(OAc)_2$ | 2 | 2 | 7 |
| $Pd(OAc)_2$ | 4 | 3 | 79 |
| $Pd(OAc)_2$ | 8 | 3 | 100 |
| $Pd(OAc)_2$ | 10 | 2 | 95 |

A similar mechanism as described by Hayashi *et al.*, implying an intermediate π-allyl complex, can be envisaged[13] (Scheme 3).

Vinylic acetate **3** was obtained in excellent yields as a 90:10 mixture of isomers **3a** and **3b**, using palladium tetrakis(triphenylphosphine) as catalyst in THF solution. On changing the solvent to dioxane, a 70:30 mixture of the isomers resulted. The structures of **3a** and **3b** were elucidated by careful analysis of the $^1H$ NMR spectra, and further structural information was made available *via* the COSY spectra of the above mixtures (see Experimental Section).

Though we could not demonstrate the stereochemistry of the intermediate π-allyl complex, we propose, coherent with several examples of structures of related complexes, that the palladium lies in the *exo* position.[15] From this complex, the base may induce β-proton elimination to produce **3** under regeneration of the catalyst. Noting the absence of 2,3-dimethylenebicyclo[2.2.1]hept-5-ene, a possible product issued from double elimination of the acetate group when conducting the reaction in absence of the acceptor base, we may presume that the π-allyl intermediate may also act as a nucleophile rather than an electrophile. In fact, Trost *et al.* showed that the nucleophilic character of the π-palladium complex de-

(7) (a) Apsimon, J. *The Total Synthesis of Natural Products*; John Wiley; New York, 1983; Vol. 5, p 249. (b) Attempts to hydrolyze **3** using standard methods such as acidic or basic conditions failed to produce aldehyde **4**. However, the action of methyllithium on **3** at −78 °C leads to **4** in 51% chemical yield (not optimized). The results of the attempted hydrolysis reactions will be discussed in a future paper. Aldehyde **4** is inaccessible by the classical Diels–Alder reaction between cyclopentadiene and unstable butadienal **5**. The latter cannot be prepared by oxidation of butadienol[8] or by photolysis of furan.[9] However, butadienal has been isolated at low temperature by flash vacuum thermolysis of the corresponding anthracenic Diels–Alder adduct.[10]

(8) Bertrand, M.; Gil, G.; Viala, J. *Tetrahedron Lett.* **1979**, *18*, 1595.

(9) Rendall, W. A.; Torres, M.; Strausz, O. P. *J. Org. Chem.* **1985**, *50*, 3034.

(10) (a) Hakiki, A.; Rippol, J. L.; Thuillier, A. *Tetrahedron Lett.* **1984**, *25*, 3459. (b) Hakiki, A.; Rippol, J. L.; Thuillier, A. *Bull. Soc. Chim. Fr.* **1985**, *5*, 911.

(11) (a) Mitra, A. *The Synthesis of Prostaglandins*; John Wiley: New York, 1977. (b) Roberts, S. M.; Scheinmann, F. *New Synthetic Routes to Prostaglandins and Thromboxanes*; Academic Press: London, 1982.

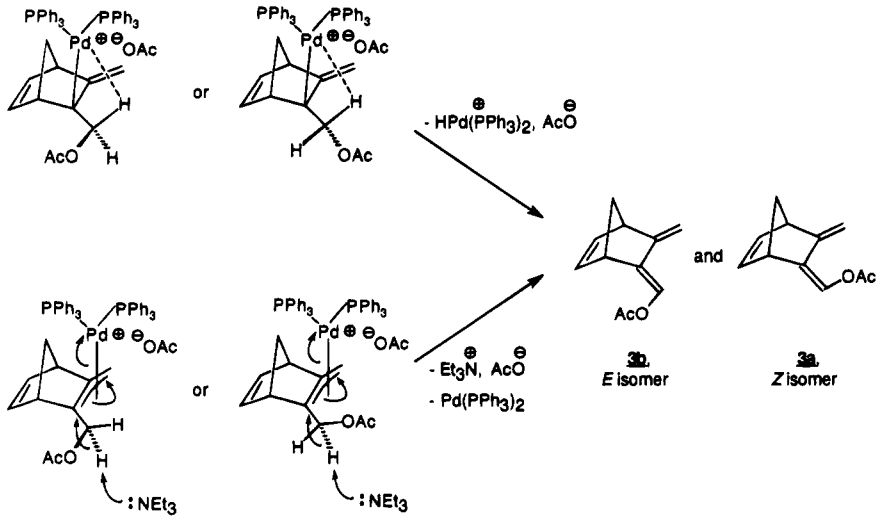
(12) (a) Tsuji, J.; Yamakawa, T.; Kaito, M.; Mandai, T. *Tetrahedron Lett.* **1978**, *19*, 2075. (b) Hauser, F. M.; Tommasi, R.; Hewawasam, P.; Rho, Y. S. *J. Org. Chem.* **1988**, *53*, 4886. (c) Harrison, J. T.; Kimura, G.; Bohme, E.; Fridge, J. H. *Tetrahedron Lett.* **1969**, *10*, 1589. (d) Suzuki, M.; Oda, Y.; Noyori, R. *J. Am. Chem. Soc.* **1979**, *101*, 1623. (e) Trost, B. M.; Verhoeven, T. R.; Fortunak, J. M. *Tetrahedron Lett.* **1979**, *20*, 2301. (f) Bäckvall, J. E.; Anderson, P. G.; Stone, G. B.; Gogoll, A. *J. Org. Chem.* **1991**, *56*, 2988.

(13) Hayashi, T.; Kishi, K.; Uozumi, Y.; Ito, Y. *Tetrahedron: Asymmetry* **1991**, *2*, 195.

(14) In fact, aminophosphines such as $P(NMe_2)_3$, $PhP(NMe_2)_2$, $Ph_2PNMe_2$, and some alkyl arylphosphites such as $P(OEt)_3$, $PhP(OEt)_2$, and $Ph_2POEt$ proved to be inactive ligands.

(15) (a) Godleski, S. A.; Gundlach, K. B.; Ho, H. Y.; Keinan, E.; Frolow, F. *Organometallics* **1984**, *3*, 21. (b) Castanet, Y.; Petit, F. *J. Mol. Catal.* **1986**, *35*, 143.

**Scheme 4**




pends on the nature of the leaving group: it seems that the acetate is not nucleophilic enough to inverse the polarity of the intermediate complex (Umpolung)[16] (Scheme 4).

The two hypothetical pathways, base-induced $\beta$-proton elimination and *syn* $\beta$-elimination of HPdOAc, originate, respectively, from an intermediate $\pi$-allyl or a Pd–C $\sigma$-complex, bearing the acetate group in an anti position with respect to the allylic system.[17] Thus, the observed ratio of isomers **3a** and **3b** can be rationalized, since the eliminated proton is likely to be in an antiperiplanar position with respect to the metal.

In conclusion, we can state that the thermal Diels–Alder reaction between cyclopentadiene and 1,4-diacetoxy-2-butyne (**2**) allows the preparation of the title compound **1** in about 65 g per batch from cheap starting materials. The interest of bicyclic **1** as substrate in palladium-catalyzed reactions lies in its prochiral nature toward enantioselective reactions. The chemical differentiation of two enantiotopic groups in prochiral substrates remains one of the major challenges in asymmetric synthesis.[18] Such reactions should produce useful synthons, exemplified here by the discussed elimination reaction, providing enol acetate **3**, a precursor to bicyclic aldehyde **4**.[19] Actually, we investigate a versatile route for the obtention of $\beta$-santalene with **4** as the main intermediate. The use of **1** in other palladium-catalyzed reactions, such as alkylation, amination, and hydrogenolysis, is currently being studied in our laboratory.

## Experimental Section

Dichloromethane was distilled over calcium hydride and THF from potassium benzophenone ketyl. Acetyl chloride, 2-butyne-1,4-diol, and dicyclopentadiene were purchased from Fluka and were used as such. All reactions involving the use of palladium catalysts were run under dry nitrogen, and the solvents were thoroughly degassed by bubbling with nitrogen.

$^1$H and $^{13}$C NMR spectra were recorded in $C_6D_6$ or $CDCl_3$ solution as indicated, at 100.00 and 25.18 MHz, respectively (the usual abbreviations are used: s = singlet, d = doublet, t = triplet, q = quadruplet, m = multiplet). The positive chemical shift values are given in ppm and the coupling constants in Hz. Infrared spectra were recorded as thin films for liquids and as KBr disks for solids (the usual abreviations are used: s = strong, m = medium, l = large, sh = sharp). Gas chromatography was run on a BP 20 capillary column 25 m × 0.32 mm; gas vector He, 1.0 bar. Elemental analyses were performed by the Service de Microanalyse de la Faculté de St Jérôme.

**Preparation of 1,4-Diacetoxy-2-butyne (2).** A solution of 2-butyne-1,4-diol (129.0 g; 1.50 mol) in dry dichloromethane was placed in a two-necked flask equipped with a dropping funnel and a condenser which was connected to a gas-trap filled with a 20% sodium hydroxide solution. A solution of acetyl chloride (251.2 g; 3.20 mol) in dichloromethane (200 mL) was added dropwise with stirring while HCl evolution started. The mixture was then stirred overnight at room temperature and then brought to reflux for 2 h. After being cooled to room temperature, the mixture was washed quickly with 10% $NaHCO_3$ (150 mL) and dried over $MgSO_4$. Removal of the solvent *in vacuo* left an oily residue which was distilled to afford 242.5 g (95% yield) of **2** as a colorless liquid (bp 96 °C/0.2 Torr) which crystallised slowly upon storage at room temperature: mp 34–36 °C; $^1$H NMR ($C_6D_6$) $\delta$ 2.86 (s, 6H), 4.69 (s, 4H); $^{13}$C NMR ($C_6D_6$) $\delta$ 19.9, 51.4, 80.3, 169.4; IR (cm$^{-1}$) 2945 (w), 1750 (s), 1432 (m), 1222 (s), 1027 (m). Anal. Calcd for $C_8H_{10}O_4$: C, 56.47; H, 5.92. Found: C, 56.35; H, 6.05.

**Preparation of 2,3-Bis(acetoxymethyl)bicyclo[2.2.1]-hepta-2,5-diene (1).** A mixture of **2** (68.0 g; 0.40 mol) and dicyclopentadiene (26.4 g; 0.20 mol) was placed in a 100 mL stainless steel autoclave which was heated to 260 °C under nitrogen pressure (35 bar) with vigorous shaking for 1.5 h. After being cooled to room temperature, the mixture was distilled through a short Vigreux column to separate unreacted starting material from **1**. Redistillation through a packed column (30 cm long, stainless steel turnings 2 mm) afforded 61.3 g (65% yield) of **1** as a colorless liquid: bp 105 °C/0.2 Torr; $^1$H NMR ($C_6D_6$) $\delta$ 1.99 (m, 2H), 2.07 (s, 6H), 3.52 (t, J = 1.8 Hz, 2H), 4.74 (d, J = 4.8 Hz, 4H), 6.78 (t, J = 1.9 Hz, 2H); $^{13}$C NMR ($C_6D_6$) $\delta$ 20.8, 52.6, 60.3, 71.7, 142.4, 147.9, 170.8; IR (cm$^{-1}$) 3080 (w), 2975 (m), 2940 (m), 1742 (s), 1225 (sh), 1122 (m). Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83. Found: C, 66.33; H, 6.92.

**Preparation of 2-Methylene-3-(acetoxyvinyl)bicyclo-[2.2.1]hept-5-ene (3).** To a stirred solution of $Pd(PPh_3)_4$ (0.70 g; 0.6 mmol) in THF (10 mL) was added triethylamine (3.0 g; 30 mmol) followed by a solution of **1** (4.72 g; 20.0 mmol) in 5 mL of dry THF under a nitrogen atmosphere. The mixture was heated to reflux, and the reaction was monitored by GC. After 2 h, the reaction mixture was cooled to room temperature and filtered over a short silica column eluting with ether. The eluate was washed with 5% HCl solution (2 × 10 mL) and dried over $MgSO_4$. The solvents were removed *in vacuo*, and the

(16) (a) Trost, B. M.; Tometzki, G. B. *Synthesis* **1991**, 1235. (b) Trost, B. M.; Tometzki, G. B. *J. Org. Chem.* **1988**, *53*, 915.
(17) Cacchi, S. *Pure Appl. Chem.* **1990**, *62*, 713.
(18) (a) Trost, B. M.; Van Vranken, D. L.; Bingel, C. *J. Am. Chem. Soc.* **1992**, *114*, 9327. (b) Trost, B. M. *Pure Appl. Chem.* **1992**, *64*, 315.
(19) (a) Bertrand, M.; Monti, H.; Huong, K. C. *Tetrahedron Lett.* **1974**, *15*, 15. (b) Oppolzer, W.; Chapuis, C. *Tetrahedron Lett.* **1983**, *24*, 4665.

residue was purified by Kugelrohr distillation. **3** was obtained as a 90:10 mixture of **3a** and **3b** isomers (colorless oil, 3.32 g; 95% yield): bp 70 °C/0.2 Torr. Dioxane at reflux temperature as the solvent gave a 70:30 mixture of the isomers after 8 h in 27% chemical yield.

Assignment of signals in the proton NMR spectra was carried out *via* analysis of its COSY spectra for the two mixtures of **3a** and **3b** in 90:10 and 70:30 ratios, respectively. Off-diagonal responses in the COSY spectrum of the 70:30 mixture correlate the innermost proton of the exocyclic double bond with the vinylic proton, the latter resonates at 7.40 ppm. This signal is weakened for the spectrum of the 90:10 mixture. Further, absence of the off-diagonal correlation for the acetyl protons (1.61 ppm) with the proton of the exocyclic double bond in the 70:30 mixture's spectrum and its presence in the 90:10 mixture's spectrum clearly indicates that the major isomer has the configuration *E*: $^1$H NMR ($C_6D_6$) *Z* isomer **3a** $\delta$ 1.61 (m, 2H), 1.65 (s, 3H), 3.00 (s, 1H), 3.13 (s, 1H), 5.27 (s, 1H), 5.61 (s, 1H), 6.09 (m, 2H), 7.39 (s, 1H); $^{13}$C NMR ($C_6D_6$) $\delta$ 20.0, 47.5, 51.4, 51.6, 108.7, 125.1, 129.1, 136.9, 137.0, 147.7, 167.1;$^1$H NMR ($C_6D_6$) *E* isomer **3b** $\delta$ 1.54 (m, 2H), 1.57 (s, 3H), 3.00 (s, 1H), 3.13 (s, 1H), 4.87 (s, 1H), 5.03 (s, 1H), 6.07 (m, 2H), 7.63 (s, 1H); $^{13}$C NMR ($C_6D_6$) $\delta$ 19.9, 45.1, 51.4, 53.0, 108.6, 125.0, 129.2, 136.9, 137.0, 147.8, 167.1; IR ($cm^{-1}$) 3080 (w), 2982 (m), 1756 (s), 1211 (s), 1080 (m). Anal. Calcd for $C_{16}H_{20}O_6$: C, 74.98; H, 6.86. Found: C, 74.87; H, 6.75.

**Supplementary Material Available:** $^1$H and $^{13}$C NMR spectra of **1** and the correlations XHCORR and COSY of the 90:10 and 70:30 mixture of **3a** and **3b** (10 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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