JOC Notes

Highly Regio- and Stereoselective Synthesis of Polysubstituted Cyclopropane Compounds via the Pd(0)-Catalyzed Coupling−Cyclization Reaction of 2-(2′,3′-Allenyl)malonates with Organic Halides

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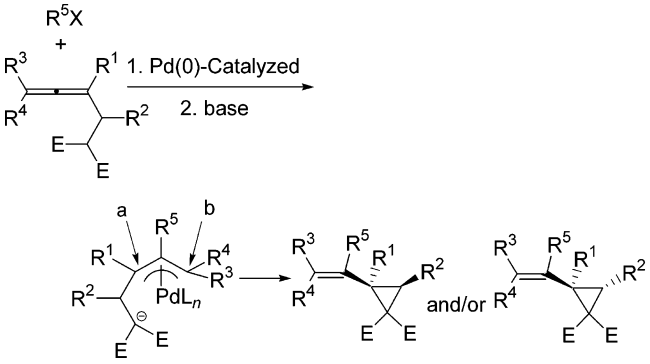
Abstract: A new method for highly regio- and stereoselective synthesis of polysubstituted cyclopropane compounds via the Pd(0)-catalyzed coupling−cyclization reaction of 2-(2′,3′-allenyl)malonates with organic halides is described. In these reactions, the starting materials are easily available and the operation is convenient. The ratios of *trans*-isomer/*cis*-vinylic cyclopropanes are up to 98:2.

The cyclopropyl group has been playing a prominent role in organic chemistry.[1] This smallest cycloalkane is found as a basic structural element in a wide range of naturally occurring compounds[2] and has also been used as a versatile synthetic intermediate in organic synthesis.[3−5] Thus, it still is of current interest to develop efficient methods for the stereoselective synthesis of polysubstituted functionalized cyclopropanes.

Recently, palladium-catalyzed reactions of allenes have been most extensively investigated to achieve numerous transformations.[6,7] On the basis of our previous work,[8,9] a Pd(0)-catalyzed coupling−cyclization reaction of 2-(2′,3′-allenyl)malonates with organic halides was developed for the regioselective synthesis of cyclopropane or cyclopentene derivatives via a π-allyl palladium intermediate.[10] It is a challenge to control both the regio- and stereoselectivity of the reactions if there is a substitutent R^2 at the 2′-position of the allenic compounds (Scheme 1). Here, we wish to report our recent observation on the highly regio- and stereoselective synthesis of polysubstituted cyclopropane derivatives.

SCHEME 1



Synthesis of 2-(2′,3′-alkadienyl)malonates 2. Compounds **2a**−**e** were prepared from the $Pd(PPh_3)_4$-catalyzed alkylation reaction of malonates in $ClCH_2CH_2Cl$ with the corresponding 2,3-alkadienyl acetates **1a**−**e**, which, in turn, were prepared from the corresponding 2,3-allenols[11] and acetic anhydride (Scheme 2).[12]

Cyclization Reaction of 2-(2′,3′-Allenyl)malonates with Organic Halides. When the reaction of dimethyl

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(1) For some reviews, see: (a) Special thematic issue on cyclopropanes and related rings: de Meijere, A. *Chem. Rev.* **2003**, *103*, 931−1648. (b) Taylor, R. E.; Engelhardt, F. C.; Schmitt, M. J. *Tetrahedron* **2003**, *59*, 5623. (c) de Meijere, A.; Kozhushkov, S. I.; Fokin, A. A.; Emme, I.; Redlich, S.; Rchreiner, P. R. *Pure Appl. Chem.* **2003**, *75*, 549. (d) Donaldson, W. A. *Tetrahedron* **2001**, *57*, 8589.

(2) (a) Faust, R. *Angew. Chem. Int. Ed.* **2001**, *40*, 2251. (b) Salaün, J. *Top. Curr. Chem.* **2000**, *207*, 1. (c) Salaün, J. *Curr. Med. Chem.* **1995**, *2*, 511. (d) Djerassi, C.; Doss, G. A. *New J. Chem.* **1990**, *14*, 713.

(3) For reviews on the divinylcyclopropane rearrangements leading to more functionalized alkanes, see: (a) Davies, H. M. L. *Tetrahedron* **1993**, *49*, 5203. (b) Hudlicky, T.; Fan, R.; Reed, J.; Gadamasetti, K. G. *Org. React.* **1992**, *41*, 1. (c) Piers, E. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, UK, 1991; Vol. 5, p 971. (d) Mann, J. *Tetrahedron* **1986**, *42*, 4611.

(4) For reviews on the vinylcyclopropane rearrangements leading to functionalized alkanes, see: (a) Hudlicky, T.; Reed, J. W. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, UK, 1991; Vol. 5, p 899. (b) Goldschmidt, Z.; Crammer, B. *Chem. Soc. Rev.* **1988**, *17*, 229. (c) Hudlicky, T.; Kutchan, T. M.; Naqvi, S. M. *Org. React.* **1985**, *33*, 247.

(5) For reviews on ring-opening reactions of cyclopropane leading to acylic compounds, see: (a) Nonhebel, D. C. *Chem. Soc. Rev.* **1993**, *22*, 347. (b) Wong, H. N. C.; Hon, M. Y.; Tse, C. W.; Yip, Y. C.; Tanko, J.; Hudlicky, T. *Chem. Rev.* **1989**, *89*, 165. (c) Salaün, J. R. Y. *Top. Curr. Chem.* **1988**, *144*, 1. (d) Reissig, H. U. *Top. Curr. Chem.* **1988**, *144*, 73.

(6) (a) For a review on the palladium-catalyzed chemistry of allenes, see: Zimmer, R.; Dinesh, C. U.; Nandanan, E.; Khan, F. A. *Chem. Rev.* **2000**, *100*, 3067. (b) For a recent highlight, see: Hashmi, A. S. K. *Angew. Chem. Int. Ed.* **2000**, *39*, 3590. (c) Ma, S. *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-i., Ed.; John Wiley & Sons: Hoboken, NJ, 2002; Vol. 1, pp 1491−1521. (d) Ma, S. *Acc. Chem. Res.* **2003**, *36*, 701.

(7) (a) Ohno, H.; Toda, A.; Miwa, Y.; Taga, T.; Osawa, E.; Yamaoka, Y.; Fujii, N.; Ibuka, T. *J. Org. Chem.* **1999**, *64*, 2992. (b) Jeong, I.-Y.; Nagao, Y. *Tetrahedron Lett.* **1998**, *39*, 8677. (c) Nemoto, H.; Yoshida, M.; Fukumoto, K. *J. Org. Chem.* **1997**, *62*, 6450. (d) Oppolzer, W.; Pimm, A.; Stammen, B.; Hume, W. E. *Helv. Chim. Acta* **1997**, *80*, 623. (e) Okuro, K.; Alper, H. *J. Org. Chem.* **1997**, *62*, 1566. (f) Grigg, R.; Xu, L. *Tetrahedron Lett.* **1996**, *37*, 4251. (g) Grigg, R.; Rasul, R.; Redpath, J.; Wilson, D. *Tetrahedron Lett.* **1996**, *37*, 4609. (h) Larock, R. C.; Zenner, J. M. *J. Org. Chem.* **1995**, *60*, 482. (i) Ma, S.; Negishi, E. *J. Org. Chem.* **1994**, *59*, 4730. (j) Walkup, R. D.; Guan, L.; Mosher, M. D.; Kim, S. W.; Kim, Y. S. *Synlett* **1993**, 88. (k) Larock, R. C.; Berrios-Pena, N. G.; Fried, C. A. *J. Org. Chem.* **1991**, *56*, 2615.

(8) (a) Ma, S.; Zhao, S. *Org. Lett.* **2000**, *2*, 2495. (b) Ma, S.; Jiao, N.; Zhao, S.; Hou, H. *J. Org. Chem.* **2002**, *67*, 2837.

(9) (a) Ahmar, M.; Cazes, B.; Gore, J. *Tetrahedron Lett.* **1985**, *26*, 3795. (b) Ahmar, M.; Cazes, B.; Gore, J. *Tetrahedron* **1987**, *43*, 3453. (c) Cazes, B. *Pure Appl. Chem.* **1990**, *62*, 1867. (d) Besson, L.; Bazin, J.; Gore, J.; Cazes. B. *Tetrahedron Lett.* **1994**, *35*, 2881. (e) Gamez, P.; Ariente, C.; Gore, J.; Cazes, B. *Tetrahedron* **1998**, *54*, 14835. (f) Yamamoto, Y.; Almasum, M.; Fujiwara, N. *Chem. Commun.* **1996**, 381. (g) Oh, C. H.; Rhim, C. Y.; Song, C. H.; Ryu, J. H. *Chem. Lett.* **2002**, 1140.

(10) (a) Shimizu, I.; Tsuji, J. *Chem. Lett.* **1984**, 233. (b) Ahmar, M.; Cazes, B.; Gore, J. *Tetrahedron Lett.* **1984**, *25*, 4505.

(11) Xu, D.; Li, Z.; Ma, S. *Chem. Eur. J.* **2002**, *8*, 5012.

(12) Fleming, I.; Higgins, D.; Lawrence, N. I.; Thomas, A. P. *J. Chem. Soc., Perkin Trans. 1* **1992**, *24*, 3331.

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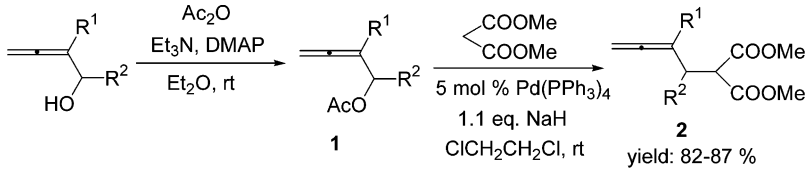
SCHEME 2



1a: R^1 = *n*-C_4H_9; R^2 = CH_3 **2a**: R^1 = *n*-C_4H_9; R^2 = CH_3

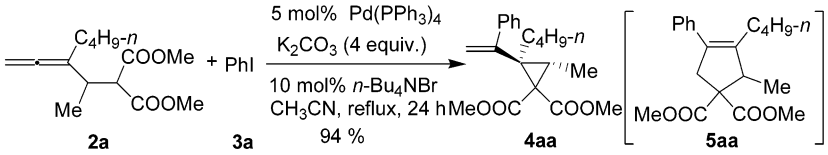
1b: R^1 = *n*-C_6H_{13}; R^2 = CH_3 **2b**: R^1 = *n*-C_6H_{13}; R^2 = CH_3

1c: R^1 = *n*-C_6H_{13}; R^2 = Ph **2c**: R^1 = *n*-C_6H_{13}; R^2 = Ph

1d: R^1 = CH_3; R^2 = CH_3 **2d**: R^1 = CH_3; R^2 = CH_3

1e: R^1 = Bn; R^2 = CH_3 **2e**: R^1 = Bn; R^2 = CH_3

SCHEME 3

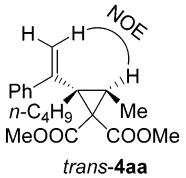


trans-**4aa**:*cis*-**4aa** = 96:4

2-(1′-methyl-2′-butyl-2′,3′-butadienyl)malonate (**2a**) and PhI (**3a**) was carried out in the presence of 5 mol % of $Pd(PPh_3)_4$, 10 mol % of *n*-Bu_4NBr as the phase transfer catalyst, and 4.0 equiv of K_2CO_3 in the CH_3CN under reflux, it was very interesting to find that the cyclopropane derivative **4aa** was formed as the sole product in 94% yield with the ratio of *trans*-**4aa**/*cis*-**4aa** as high as 96:4 (Scheme 3). The stereochemistry of **4aa** was determined by the $^1H-^1H$ NOESY spectra (Figure 1). The formation of the cyclopentene derivative **5aa** was not observed.

The $Pd(PPh_3)_4$-catalyzed coupling−cyclization reaction of dimethyl 2-(1′-methyl-2′-hexyl-2′,3′-butadienyl)malonate (**2b**) and PhI in different solvents was studied (Table 1). The reaction in CH_3CN gave **4ba** in 86% yield (*trans*-**4ba**:*cis*-**4ba** = 95:5) (entry 1, Table 1). When the reaction was carried out in DMSO, low yield and stereoselectivity of **4ba** were observed (entry 3, Table 1). The reactions in DMF and toluene gave similar results; however, they were slower (entries 4 and 5, Table 1). Therefore, we defined Conditions A (5 mol % of $Pd(PPh_3)_4$, 10 mol % of *n*-Bu_4NBr, 4.0 equiv of K_2CO_3, CH_3CN, reflux) for the highly regio- and stereoselective preparation of cyclopropane derivative **4ba**. If the reaction was conducted in the absence of *n*-Bu_4NBr (Conditions B: 5 mol % of $Pd(PPh_3)_4$, K_2CO_3 (4.0 equiv), CH_3CN, reflux) the ratio of *trans*-**4ba**/*cis*-**4ba** decreased slightly while the yield was higher (compare entry 2 with entry 1, Table 1).

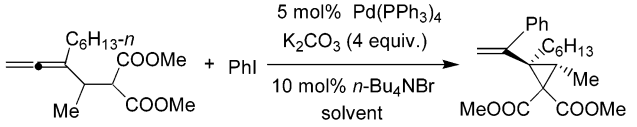
On the basis of these preliminary results, we extended this reaction to different 2-(2, 3-allenyl)malonates. The results of these reactions leading to cyclopropane derivatives **4** as the sole products are summarized in Table 2.



trans-**4aa**

FIGURE 1.

TABLE 1. The $Pd(PPh_3)_4$-Catalyzed Coupling−Cyclization Reaction of Dimethyl 2-(1′-Methyl-2′-hexyl-2′,3′-butadienyl)malonate (2b) with PhI in Different Solvents[a]



entry	solvent	time (h)	yield of **4ba** (%)	cis:trans
1	CH_3CN	17	86	5:95
2[c]	CH_3CN	16	93	6:94
3	DMSO	16	81	8:92
4	DMF	34	85	6:94
5	toluene	60	85	6:94

[a] PhI (1.2 equiv) was used. [b] The first letter refers to the allene while the second letter refers to the halide. [c] The reaction was carried out in the absence of Bu_4NBr.

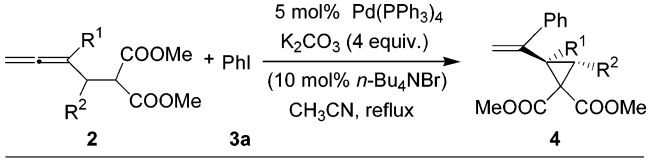
The results of the $Pd(PPh_3)_4$-catalyzed coupling−cyclization reactions of **2b** and **2c** with different organic halides under Conditions A and B were summarized in Table 3. It should be noted that the configuration of the C=C bond in 1-alkenyl iodide remained unchanged during the reaction (entries 2, 4, and 6, Table 3).

In summary, we have developed a new protocol for the highly regio- and stereoselective synthesis of polysubstituted cyclopropane compounds. Further studies in this area are being pursued in our laboratory.

Experimental Section

Starting Materials. (1) Synthesis of (3-*n*-Butyl)penta-3,4-dien-2-yl Acetate (1a). Typical procedure A: Acetic anhydride (1.1 mL, 11.2 mmol) was added to the mixture of (3-*n*-butyl)penta-3,4-dien-2-ol (1.12 g, 8 mmol), Et_3N (1.52 mL, 11 mmol), and DMAP (97 mg, 0.8 mmol) in Et_2O (25 mL). The solution was stirred at room temperature for 1 h as monitored by TLC. Evaporation and purification via flash chromatography

TABLE 2. The Pd(PPh$_3$)$_4$-Catalyzed Coupling−Cyclization Reactions of 2 with PhI in CH$_3$CN[a]



2 3a 4

entry	2 R^1/R^2/(**2**)	time (h)[b]	**4**[c]	yield (*c*/*t*)[d] Cond. A	Cond. B
1	*n*-C$_6$H$_{13}$/Me/(**2b**)	17 (10)	**4ba**	86 (5:95)	93 (6:94)
2	*n*-C$_6$H$_{13}$/Ph/(**2c**)	36 (13)	**4ca**	86 (4:96)	91 (4:96)
3	Me/Me/(**2d**)	21 (25)	**4da**	93 (6:94)	72 (5:95)
4	Bn/Me(**2e**)	42 (25)	**4ea**	88 (20:80)	80 (13:87)

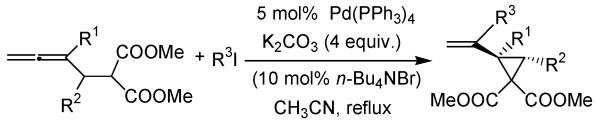
[a] PhI (1.2 equiv) was used. [b] The reaction time for Conditions A. The reaction time for Conditions B is given in parentheses. [c] The first letter refers to the allene while the second letter refers to the halide. [d] *c*/*t* = cis/trans.

on silica gel (eluent: petroleum ether:ethyl acetate = 20:1) afforded 1.455 g (100%) of **1a.**[11] The analytical data are the same as what were reported by us in ref 11.

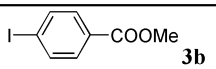
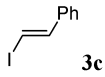
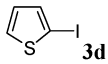
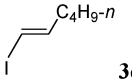
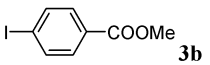
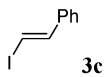
(2) Synthesis of Dimethyl 2-(1′-methyl-2′-butyl-2′,3′-butadienyl)malonate (2a). Typical procedure B: To a mixture of NaH (60% dispersion in mineral oil, 11 mg, 1.1 equiv) and Pd(PPh$_3$)$_4$ (14.5 mg, 5 mol %) in dry ClCH$_2$CH$_2$Cl (2.0 mL) was added subsequently dimethyl malonate (0.09 mL, 3.0 equiv) and (3-*n*-butyl)penta-3,4- dien-2-yl acetate **1a**[11] (46 mg, 0.25 mmol) under nitrogen. The resulting mixture was stirred at room temperature for 24 h as monitored by TLC. Then the solution was quenched with an aqueous solution of saturated NaCl (2 mL) and extracted with ether (20 mL). The organic layer was washed with brine (3 × 8 mL) and dried over anhydrous sodium sulfate. After evaporation, the residue was purified by flash chromatography on silica gel (eluent: petroleum ether:ethyl acetate = 20:1) to afford 53 mg (83%) of **2a**; liquid; IR (neat) 2956, 1955, 1760, 1739, 1435 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 4.63−4.78 (m, 2 H), 3.73 (s, 3 H), 3.70 (s, 3 H), 3.48 (d, J = 10.4 Hz, 1 H), 2.62−2.77 (m, 1 H), 1.92−2.02 (m, 2 H), 1.24−1.45 (m, 4 H), 1.07 (d, J = 6.60 Hz, 3 H), 0.89 (t, J = 7.15 Hz, 3 H); ^{13}C NMR (75.4 MHz, CDCl$_3$) δ 204.7, 169.2, 168.9, 106.8, 78.5, 57.2, 52.6, 52.5, 36.4, 30.8, 29.8, 22.5, 17.9, 14.1; MS *m*/*z* (%) 254 (M$^+$, 12.20), 93 (100); HRMS *m*/*z* (EI) calcd for C$_{14}$H$_{22}$O$_4$ 254.15181, found 254.15498.

Pd(0)-Catalyzed Coupling−Cyclization Reaction of Allenylmalonates with Organic Halides. Conditions A: Preparation of 1,1-Bis(methoxycarbonyl)-2-butyl-2-(1′-phenyl-ethenyl)-3-methylcyclopropane (4aa). Typical procedure: To a mixture of potassium carbonate (112 mg, 0.8 mmol), *n*-Bu$_4$NBr (6.4 mg, 10 mol %), and Pd(PPh$_3$)$_4$ (12 mg, 5 mol %) in CH$_3$CN (2 mL) was added dimethyl 2-(1′-methyl-2′-butyl-2′,3′-butadienyl) malonate **2a** (51 mg, 0.2 mmol) and iodobenzene (49 mg, 1.2 equiv, 0.24 mmol) subsequently under nitrogen. The resulting mixture was refluxed for 24 h as monitored by TLC. After filtration, washing with ether, and evaporation, the residue was purified by flash chromatography on silica gel (eluent: petroleum ether:ethyl acetate = 20:1) to afford 62 mg (94%) of **4aa** (*cis*-**4aa**:*trans*-**4aa** = 4:96); liquid; IR (neat) 2955, 1733, 1626, 1576, 1435, 1229 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) *trans*-**4aa**, δ 7.51 (d, J = 8.80 Hz, 2 H), 7.11−7.26 (m, 3 H), 5.62 (s, 1 H), 5.12 (s, 1 H), 3.73 (s, 3 H), 3.36 (s, 3 H), 2.21 (q, J = 6.80 Hz, 1 H), 1.82−1.96 (m, 1 H), 1.01−1.32 (m, 8 H), 0.71 (t, J = 7.05 Hz, 3 H); ^{13}C NMR (75.4 MHz, CDCl$_3$) δ 168.7, 167.9, 145.5, 138.5, 128.4, 127.7, 126.5, 116.5, 52.6, 52.5, 43.9, 43.5, 30.2, 29.8, 29.1, 23.1, 14.3, 10.6; the following data were discernible for the cis isomer, *cis*-**4aa**, 7.62 (d, J = 8.60 Hz, 2 H), 5.80 (s, 1 H), 4.98 (s, 1 H), 3.77 (s, 3 H), 3.29 (s, 3 H),

TABLE 3. The Pd(PPh$_3$)$_4$-Catalyzed Coupling−Cyclization Reactions of 2 with Organic Halides in CH$_3$CN[a]



2 3 4

entry	R^1/R^2/**2**	R^{3}I (**3**)	time (h)[b]	**4**[c]	Cond. A yield (*c*/*t*)[d]	Cond. B yield (*c*/*t*)[d]
1	*n*-C$_6$H$_{13}$/Me/**2b**	 **3b**	9(35)	(**4bb**)	77(6:94)	49(6:94)
2	*n*-C$_6$H$_{13}$/Me/**2b**	 **3c**	20(13)	(**4bc**)	98(11:89)	72(7:93)
3	*n*-C$_6$H$_{13}$/Me/**2b**	 **3d**	21(13)	(**4bd**)	83(8:92)	61(7:93)
4	*n*-C$_6$H$_{13}$/Me/**2b**	 **3e**	21(24)	(**4be**)	88(6:94)	60(5:95)
5	*n*-C$_6$H$_{13}$/Ph/**2c**	 **3b**	99(72)	(**4cb**)	76(5:95)	60(7:93)
6	*n*-C$_6$H$_{13}$/Ph/**2c**	 **3c**	20(13)	(**4cc**)	86(6:94)	88(6:94)

[a] RI (1.2 equiv) was used. [b] The reaction time for Conditions A. The reaction time for Conditions B is given in parentheses. [c] The first letter refers to the allene while the second letter refers to the halide. [d] *c*/*t* = cis/trans.

0.82 (t, J = 6.96 Hz, 3 H); MS m/z (%) 330 (M^+, 3.35), 270 (100). Anal. Calcd for $C_{20}H_{26}O_4$: C 72.73, H 7.88. Found: C 72.70, H 7.71.

Conditions B: Preparation of 1,1-Bis(methoxycarbonyl)-2-hexyl-2-(1′-phenylethenyl)-3-methylcyclopropane (4ba). Typical procedure: To a mixture of potassium carbonate (140 mg, 1.0 mmol) and $Pd(PPh_3)_4$ (15 mg, 5 mol %) in CH_3CN (2 mL) was added dimethyl 2-(1′-methyl-2′-hexyl-2′,3′-butadienyl)malonate **2b** (70 mg, 0.25 mmol) and iodobenzene (61 mg, 1.2 equiv, 0.3 mmol) subsequently under nitrogen. The resulting mixture was refluxed for 16 h as monitored by TLC. After filtration, washing with ether, and evaporation, the residue was purified by flash chromatography on silica gel (eluent: petroleum ether:ethyl acetate = 20:1) to afford 83 mg (93%) of **4ba** (*trans*-**4ba**:*cis*-**4ba** = 94:6). **4ba** viscous liquid; IR (neat) 2954, 1736, 1623, 1575, 1435, 1222 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) *trans*-**4ba**, δ 7.52 (d, J = 9.70 Hz, 2 H), 7.15−7.28 (m, 3 H), 5.64 (s, 1 H), 5.13 (s, 1 H), 3.75 (s, 3 H), 3.36 (s, 3 H), 2.17−2.27 (m, 1 H), 1.83−1.98 (m, 1 H), 1.20 (d, J = 6.75 Hz, 3 H), 1.02−1.29 (m, 9 H), 0.74 (t, J = 7.03 Hz, 3 H); the following data were discernible for the cis isomer, *cis*-**4ba**, δ 7.64 (d, J = 9.0 Hz, 2 H), 7.28−7.17 (m, 3 H), 5.81 (s, 1 H), 4.98 (s, 1 H), 3.78 (s, 3 H), 3.31 (s, 3 H); MS m/z (%) 358 (M^+, 7.03), 298 (100). Anal. Calcd for $C_{22}H_{30}O_4$: C 73.74, H 8.38. Found: C 73.43, H 8.23.

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Supporting Information Available: Typical experimental procedures, analytical data for compounds not listed in the text, ^1H NMR and ^{13}C NMR spectra of those compounds, and the NOSEY spectra of **4aa**. This material is available free of charge via the Internet at http://pubs.acs.org.

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