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Stereospecific Pd(O)-Catalyzed Malonate Additions to Allylic Hydroxy Phosphonate Derivatives: A Formal Synthesis of (−)-Enterolactone

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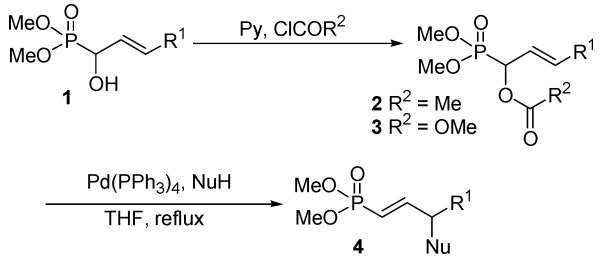
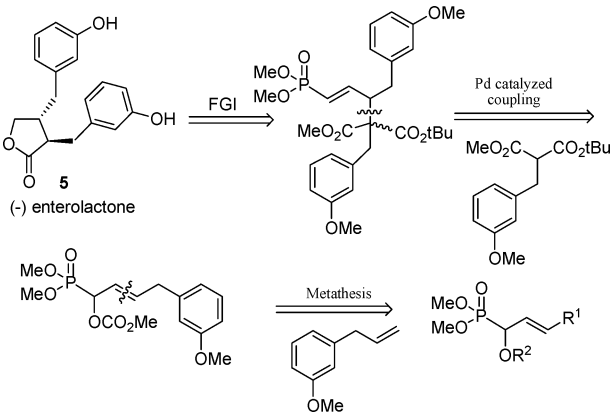
Abstract: A combination of cross-metathesis and malonate addition was applied to a formal synthesis of the mammalian lignan enterolactone **5**. The cross-metathesis of alkene **6** and phosphonate **3a** gave the substituted allylic phosphonate **3d**. The palladium-catalyzed addition of malonate **10d** to the allylic phosphonate **3d** was stereospecific and highly regioselective and yielded the vinyl phosphonate **11d**. The vinyl phosphonate **11d** was converted in two steps into the lactone **14**, a known intermediate in the synthesis of enterolactone **5**.

Recent advances in catalytic asymmetric phosphonylation of unsaturated aldehydes[1] and other methods[2,3] have resulted in the availability of allylic hydroxy phosphonates in high enantiomeric excess. These nonracemic hydroxy phosphonates display some of the rich chemistry associated with allylic alcohols and consequently should prove to be useful as building blocks for asymmetric synthesis. It has been shown that allylic hydroxy phosphonates can serve as useful intermediates in the synthesis of γ-substituted phosphonates by 1,3-transposition of functionality and that the steric and electronic influence of the phosphorus moiety can enhance the stereochemical and regiochemical outcome of the reactions.[4,5] In a nice illustration of the effect of the phosphonate on regioselectivity, Zhu and Lu demonstrated that the palladium-catalyzed addition of nucleophiles (amine and malonate) to the acetate derivatives **2** of racemic allylic hydroxy phosphonates **1** (Scheme 1) takes place exclusively at the 3-position to give the γ-substituted vinyl phosphonates **4** in high yield.[5] Palladium-catalyzed additions of nitrogen and carbon nucleophiles to racemic allylic phosphonates were later employed in the successful synthesis of fosfomycin and ω-phosphono amino acids.[5c−f] Having demonstrated that the palladium (0)-catalyzed intermolecular addition of amines to nonracemic allylic hydroxy phosphonate derivatives proceeds with complete chirality transfer,[6] we turned our attention to the exploration of reactions with carbon-based nucleophiles.[7,8]

SCHEME 1. Palladium(0)-Catalyzed Reactions of Allylic Hydroxy Phosphonate Derivatives



SCHEME 2. Retrosynthetic Analysis for Enterolactone



Lignans are widely distributed plant natural products with diverse biological activity.[9] However, enterolactone **5** (Scheme 2) was the first lignan isolated from a mammalian source.[10] Enterolactone **5** and structurally related

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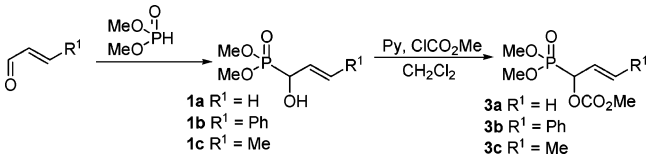
lactones display some interesting biological activities[11] and consequently have been the targets of several successful racemic and enantioselective syntheses.[12,13]

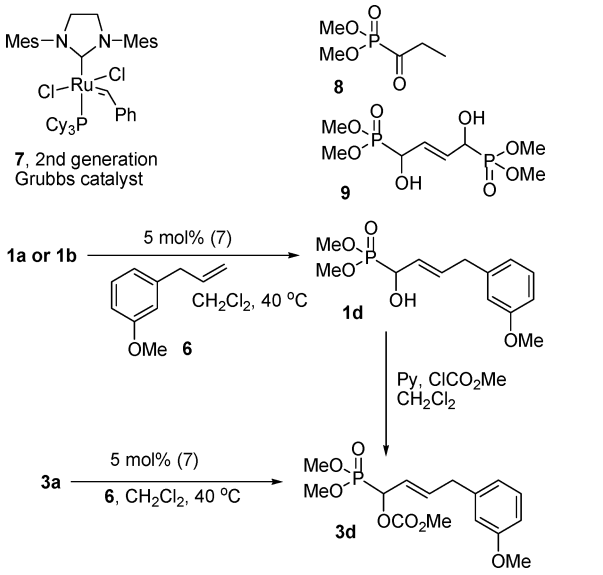
We proposed a highly convergent route to enterolactone **5**, in which the benzyl side chains are derived from an alkene and a substituted malonate (Scheme 2). It was planned to couple an alkene to a simple, nonracemic acrolein-derived phosphonate via an alkene cross-metathesis reaction. Palladium-catalyzed addition of a substituted malonate would then give a fully functionalized vinyl phosphonate. Further functional group manipulation on the vinyl phosphonate would yield enterolactone **5**.

The cross-metathesis reaction has become a powerful tool for alkene synthesis,[14] and examples of both cross-metathesis (CM) and ring-closing metathesis (RCM) involving vinyl and allyl phosphonates have been reported.[15,16] However, metathesis reactions involving interconversion of allylic hydroxy phosphonates remain to be explored. Cross-metathesis of a simple acrolein-derived hydroxy phosphonate with an alkene potentially provides an efficient way to synthesize structurally more complex substituted allylic hydroxy phosphonates with the advantage of utilizing a single nonracemic precursor.[17]

SCHEME 3. Synthesis of Allylic Phosphonates



SCHEME 4. Cross-Metathesis Reactions of Allylic Phosphonates



The racemic hydroxy phosphonates **1a**−**c** were prepared (Scheme 3) by the Et_3N-catalyzed addition of dimethyl phosphite to the corresponding aldehyde.[18] The nonracemic (*R*)-phosphonates were prepared by catalytic asymmetric phosphonylation using L-dimethyl tartrate and titanium isopropoxide as a catalyst.[1a] The hydroxy phosphonates **1a**−**c** were reacted with methyl chloroformate in pyridine to give the corresponding carbonates **3a**−**c**.

Attempted cross-metathesis of hydroxy phosphonate **1a** and alkene **6** in $CHCl_3$ (5 mol % second-generation Grubbs catalyst) yielded the phosphonate **1d** in a low 26% isolated yield (Scheme 4). The formation of **1d** was complicated by a competing alkene migration reaction leading to acyl phosphonate **8** and homodimerization to give the diphosphonate **9**. Reactions performed in CH_2Cl_2 led almost exclusively to the diphosphonate **9**, which precipitates from solution.[17] Since the carbonates **3** are ultimately required for the palladium-catalyzed additions, the cross-metathesis between phosphonate **3a** and alkene **6** was examined. Reaction of phosphonate **3a** with alkene **6** in CH_2Cl_2 (5 mol % second-generation Grubbs catalyst) gave the hetero-cross-metathesis product **3d** in a 68% isolated yield. The homodimer of alkene **6** was also formed; however, no homodimerization of the phosphonate was observed. Fortunately, the dimer of alkene **6**

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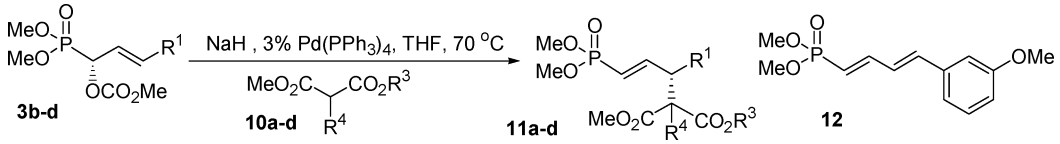
TABLE 1. Palladium-Catalyzed Malonate Addition to Allylic Phosphonates



phosphonate			malonate			product		
compd	R^1	ee	compd	R^3	R^4	compd	yield	ee
3b	Ph	95%	**10a**	Me	H	**11a**	75%(E)[a] 13% (Z) + $Ph_3P(O)$[a]	95%[c]
3b	Ph	88%	**10b**	Me	3-$MeOC_6H_4CH_2$	**11b**	45%[a]	>80%[d]
3d	3-$MeOC_6H_4CH_2$	(±)	**10c**	*t*-Bu	3-$MeOC_6H_4CH_2$	**12**	38%[a]	
3c	Me	(±)	**10c**	*t*-Bu	3-$MeOC_6H_4CH_2$	**11c**	24%[a](68%)[b]	(±)
3d	3-$MeOC_6H_4CH_2$	70%	**10d**	*t*-Bu	H	**11d**	85%[a]	70%[e]
		95%					85%[a]	92%[e]

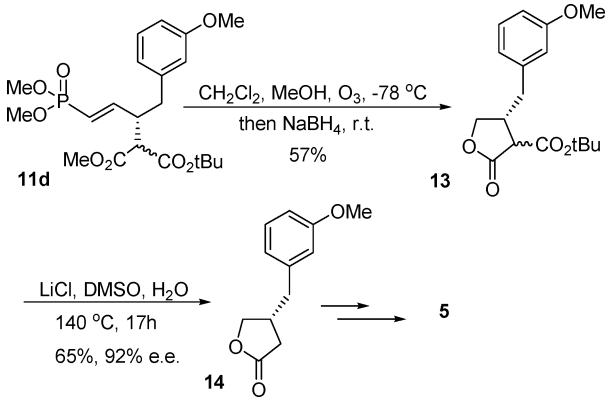
[a] Isolated yield. [b] Conversion based on ^{31}P NMR spectrum of the crude product. [c] Determined by HPLC on a ChiralPak AD column. [d] Determined by HPLC on a Whelk-O column. [e] Determined by HPLC of lactone **14** on a Chirobiotic-T column.

also entered into the metathesis reaction with phosphonate **3a**; therefore, its formation had little consequence on the reaction outcome. Furthermore, nonracemic **3a** (70% ee) gave nonracemic **3d** with no erosion of the enantiomeric excess.

Hydroxy phosphonate **1b** can be recrystallized to >95% ee and therefore appeared to be a promising precursor for the synthesis of other hydroxy phosphonates of high enantiomeric excess. Cross-metathesis reaction of phosphonate **1b** with alkene **6** stopped at approximately 50% conversion (Scheme 4). Unfortunately, phosphonates **1b** and **1d** were inseparable. However, cycling the isolated product mixture (**1b** + **1d**) through the metathesis reaction four times afforded **1d** (95% ee, 36% yield) with sufficient purity to proceed. The hydroxy phosphonate **1d** was converted to the corresponding carbonate **3d** by reaction with methyl chloroformate in pyridine (95% yield) with no loss of enantiomeric excess.

Zhu and Lu reported the addition of malonate anion to the acrolein-derived acetoxy allylic phosphonate **2**.[5a,b] However, the effect of substitution on the malonate or phosphonate and the stereochemical course of the reaction were not described. Therefore, several malonate addition reactions were carried out to examine these parameters (Table 1). Addition of dimethyl malonate **10a** to the nonracemic cinnamyl phosphonate **3b** (95% ee) proceeded smoothly to give predominantly the (*E*)-vinyl phosphonate **11a(*E*)** (75% yield, 95% ee) with complete chirality transfer. In addition, a small amount of the (*Z*)-vinyl phosphonate was observed and isolated as a comixture with triphenyl phosphine oxide. The P−H couplings of the vinyl protons in the ^1H NMR spectra easily distinguish the (*E*)- and (*Z*)-isomers **11a**. In particular, H-2 of the (*Z*)-vinyl phosphonate **11a(*Z*)** exhibits a trans P−H coupling constant of 49 Hz, whereas H-2 of the (*E*)-vinyl phosphonate **11a(*E*)** shows a cis P−H coupling constant of 25 Hz. The benzyl-substituted malonate **10b** also added to phosphonate **3b** with high chirality transfer, albeit in a lower yield for a similar reaction time. Unfortunately, the addition of the benzyl-substituted malonate **10c** to phosphonate **3d**, required for the proposed synthesis of enterolactone, resulted in formation of the diene **12** as the major isolable product. However, the addition of **10c** to the crotanyl phosphonate **3c** was successful and no elimination product (diene) was observed. Although a variety of conditions and palladium catalysts were examined for the addition of the benzyl-substituted malonate **10c** to phosphonate **3d**, none were successful. Fortunately, the less bulky *tert*-butyl methyl malonate **10d** underwent clean addition to phosphonate **3d** with almost complete chirality transfer.

SCHEME 5. Formal Synthesis of (−)-Enterolactone



Given the results shown in Table 1, the planned synthesis of enterolactone was revised (Scheme 5). (1*R*)-Phosphonate **3d**, prepared in 95% ee, was reacted with *tert*-butyl methyl malonate **10d** to give the adduct **11d** as a mixture of diastereomers in 85% yield (Table 1). Ozonolysis of the vinyl phosphonate **11d** and in situ reduction of the oxidation products with sodium borohydride in methanol gave the lactone **13** (57%) (Scheme 5). The *tert*-butyl ester was cleaved and decarboxylated by treatment with LiCl in DMSO at 140 °C to give the lactone **14** in 65% yield. The lactone had an enantiomeric excess of 92% measured by HPLC. The optical rotation {$[\alpha]_D$ +6.7 (*c* 1.1, $CHCl_3$)} of the lactone **14** confirmed the absolute configuration (4*R*), and the magnitude of the rotation was consistent with enantiomeric excess determined by HPLC.[13] Sibi et al. reported the conversion of lactone **14** to enterolactone **5**.[13c] Thus, synthesis of lactone **14** represents a formal synthesis of enterolactone **5**.

The observed lactone stereochemistry is consistent with the expected reaction mechanism[20,21] for malonate addition to a carbonate involving inversion of configuration during π-allyl formation and inversion during nu-

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cleophilic attack (i.e., overall retention). It is believed that the diene **12** is formed from the π-allyl intermediate via a base-induced elimination,[21] a process that is known to compete with addition.[22] The substituted malonate **10c** is probably too bulky and acts as a base rather than a nucleophile. Furthermore, the conjugation of the aromatic ring to the diene makes elimination favorable.

In summary, the palladium-catalyzed addition of *tert*-butyl methyl malonate **10d** to (1*R*)-phosphono allylic carbonate **3d** results in the formation of the vinyl phosphonate **11d**. The vinyl phosphonate **11d**, formed with retention of configuration, was converted to the known (−)-enterolactone precursor (4*R*)-4-[(3-methoxyphenyl)methyl]dihydro-2-(3*H*)-furnanone.

Experimental Section

(±)- or (*R*)-(2*E*)-Dimethyl [1-(Methoxycarbonyloxy)-4-(3-methoxyphenyl)-2-butenyl]phosphonate 3d. Second-generation Grubbs catalyst (0.284 g, 0.335 mmol) was dissolved in CH_2Cl_2 (10 mL). Phosphonate **3a** (1.5 g, 6.7 mmol) and 3-(3-methoxyphenyl)propene **6** (1.49 g, 10.0 mmol) were added, and the reaction flask was placed in a preheated oil bath and heated at 40 °C for 12 h. The reaction mixture was allowed to cool, and then the solvent was evaporated in vacuo. The crude product was purified by chromatography (SiO_2, CH_2Cl_2/EtOAc 20:80) to give dimethyl [1-(methoxycarbonyloxy)-4-(3-methoxyphenyl)-2-butenyl]phosphonate **3d** as a pale yellow oil (1.56 g, 68%): IR (neat, NaCl) 1755 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.20 (1H, t, J = 7.8 Hz), 6.74 (3H, m), 6.07 (1H, m), 5.65 (1H, m), 5.49 (1H, dd, J_{HH} = 7.9 Hz, J_{HP} = 13 Hz), 3.81 (3H, s), 3.79 (6H, d, J_{HP} = 11 Hz), 3.78 (3H, s), 3.42 (2H, m); ^{13}C NMR ($CDCl_3$) δ 160.0, 154.9 (d, J_{CP} = 9.5 Hz), 140.7 (d, J_{CP} = 2.3 Hz), 136.4 (d, J_{CP} = 12.3 Hz), 129.7, 122.1 (d, J_{CP} = 3.9 Hz), 121.1, 114.4, 112.0, 72.9 (d, J_{CP} = 169 Hz), 55.6, 55.3, 55.1 (d, J_{CP} = 7.1 Hz), 53.9 (d, J_{CP} = 6.5 Hz), 38.8 (d, J_{CP} = 1.3 Hz); ^{31}P NMR ($CDCl_3$) δ 20.7; HRMS (EI, M^+) calcd for $C_{15}H_{21}O_7P$ 344.1025, found 344.1027.

General Procedure for the Addition of Malonates to Allylic Carbonates 3b−d. NaH (3.47 mmol) was suspended in anhydrous THF (16 mL), and then the malonate (3.47 mmol) in THF (1 mL) was added. The mixture was stirred at room temperature for 3−4 min. The phosphonate (2.9 mmol) was added, followed by $Pd(PPh_3)_4$ (0.09 mmol, 3 mol %). The reaction flask was placed in a preheated oil bath and heated at 70 °C for 1 h. The reaction mixture was allowed to cool, and then it was partitioned between brine and Et_2O. After separation, the aqueous layer was re-extracted with Et_2O and the combined organic layers were dried over anhydrous Na_2SO_4. The solvent was evaporated in vacuo to give the crude product.

Addition of *tert*-Butyl Methyl Malonate 10d to Dimethyl [1-(Methoxycarbonyloxy)-4-(3-methoxyphenyl)-2-butenyl]-phosphonate 3d. NaH (0.139 g, 3.48 mmol) in THF (16 mL), malonate **10d** (0.61 mL, 3.48 mmol) in THF (1 mL), phosphonate **3d** (0.99 g, 2.9 mmol), and $Pd(PPh_3)_4$ (0.101 g, 0.09 mmol). The crude product was purified by chromatography (SiO_2, hexane/acetone 50:50) to give a diastereoisomeric (50:50) mixture of malonate adducts **11d** as a pale yellow oil (1.08 g, 84%): IR (neat) 1728 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.18 (1H, t, J_{HH} = 8.0 Hz), 6.72 (3H, m), 6.63 (1H, m), 5.48 (1H, m), 3.78 (3H, s), 3.75 (1.5H, s), 3.72 (1.5H, s), 3.63 (1.5H, d, J_{HP} = 11 Hz), 3.62 (1.5H, d, J_{HP} = 11 Hz), 3.53 (3H, d, J_{HP} = 11 Hz), 3.41 (1H, app t, J_{HH} = 7.6 Hz), 3.20 (1H, m), 2.92 (1H, m), 2.65 (1H, m), 1.47 (4.5H, s), 1.46 (4.5H, s); ^{13}C NMR ($CDCl_3$) 168.9, 168.5 167.9, 166.7, 159.9, 152.5 (d, J_{CP} = 4.9 Hz), 139.9, 129.7, 121.8 (d, J_{CP} = 3.8 Hz), 118.8 (d, J_{CP} = 183 Hz), 115.1 (d, J_{CP} = 3.5 Hz), 112.3, 82.9 (x2), 56.1, 55.9, 55.3, 52.7, 52.5 (d, J_{CP} = 5 Hz), 52.4 (d, J_{CP} = 5 Hz), 46.1 (d, J_{CP} = 11 Hz), 45.8 (d, J_{CP} = 11 Hz),38.3, 28.1(x2); ^{31}P NMR ($CDCl_3$) δ 20.6; HRMS (FAB, NBA/CsI, $[M + Cs]^+$) calcd for $C_{21}H_{31}O_8PCs$ 575.0810, found 575.0820.

3-(*tert*-Butoxycarbonyl)-4-[(3-methoxyphenyl)methyl]-dihydro-2(3*H*)-furanone 13. The vinyl phosphonate **11d** (0.873 g, 1.97 mmol) was dissolved in anhydrous MeOH (16 mL) and CH_2Cl_2 (20 mL), and the resulting solution was cooled to −78 °C. O_3 was bubbled into the solution until the starting material had been consumed (TLC). The reaction flask and solution were flushed with argon to remove residual O_3, and then $NaBH_4$ (0.448 g, 11.8 mmol) was added. The mixture was allowed to warm to room temperature, and stirring was continued overnight. The reaction mixture was washed twice with H_2O, and the aqueous layer was re-extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4, and the solution was concentrated in vacuo. The crude product was purified by chromatography (SiO_2, EtOAc/hexanes 1:1) to give the lactone **13** (0.34 g, 57%): IR (neat) 1780, 1729 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.21 (1H, t, J = 7.9 Hz), 6.73 (3H, m), 4.38 (1H m), 3.93 (1H, m), 3.77 (3H, s), 3.20 (2H, m), 2.76 (2H, m), 1.38 (9H, s); ^{13}C NMR ($CDCl_3$) δ 171.3, 166.4, 159.9, 138.9, 129.9, 121.2, 114.7, 112.3, 82.7, 71.2, 55.2, 53.0, 41.5, 37.9, 27.8; HRMS (EI, M^+) calcd for $C_{17}H_{22}O_5$ 306.1467, found 306.1469.

4-[(3-Methoxyphenyl)methyl]dihydro-2(3*H*)-furanone 14. The lactone **13** (0.032 g, 0.11 mmol) was dissolved in DMSO (2 mL) and H_2O (1 drop), and then LiCl (0.0089 g, 0.21 mmol) was added. The reaction mixture was heated at 140 °C for 17 h. The reaction mixture was cooled, diluted with H_2O, and extracted with EtOAc (3×). The combined EtOAc extracts were washed with 1 N HCl, saturated $NaHCO_3$, and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified by chromatography (SiO_2, EtOAc/hexanes 50:50) to give the lactone **14** (0.014 g, 65%): IR (neat) 1778 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.24 (1H, t, J = 7.9 Hz), 6.8 (3H, m), 4.34 (1H, dd, J = 6.9, 9.1 Hz), 4.03 (1H, dd, J = 6.0, 9.1 Hz), 3.80 (3H, s), 2.84 (1H, m), 2.76 (2H, m), 2.61 (1H, dd, J = 7.9, 17 Hz), 2.29 (1H, dd, J = 6.9, 17 Hz), ^{13}C NMR ($CDCl_3$) δ 177.0, 160.1, 140.0, 130.0, 121.1, 114.8, 112.0, 72.8, 55.4, 39.1, 37.2, 34.4; HRMS (EI, M^+) calcd for $C_{12}H_{14}O_3$ 206.0943, found 206.0944. The lactone had 92% ee determined by HPLC, $[\alpha]_D$ +6.7 (1.1, $CHCl_3$) (lit.[3c] **(4*R*)-4-[(3-methoxyphenyl)methyl]-dihydro-2(3*H*)-furanone** $[\alpha]_D$ +6.7 (1.66, $CHCl_3$).

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Supporting Information Available: Experimental and characterization data for compounds **1a**, **(*R*)1a**, **(*R*)1b**, **3a**, **3b**, **(*R*)3d**, **6**, **11a−c**, and **12**, spectra for compounds **1a**, **1b**, **3a**, **3b**, **3d**, **6**, **11a−d**, and **12−14**, and HPLC data for compounds **1b**, **3b**, **11a**, **3d**, and **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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