munition of capacity or the liberation of disagreeable odors. The minimum capacity of **2a** was determined to be 0.86 mmol/g as determined by its use in N-trifluoroacetylation reactions with benzylamine (see method 1).

**Polymer-Bound Benzyl Trifluoroacetate (2b).** In a manner similar to that described for **2a**, 30 g of polymer-bound benzyl alcohol (**1b**) gave 31 g of **2b**. The infrared spectrum of **2b** exhibited characteristic absorptions at 1700 $cm^{-1}$. The minimum capacity of **2b** was determined to be 0.75 mmol/g as determined by its use in N-trifluoroacetylation reactions with benzylamine (method 1). Resin **2b** did show some dimunition in capacity after storage for several months.

**Preparation of N-Substituted Trifluoroacetamides 4a-e (Method 1).** In a typical procedure, to a suspension of 3.0 g (2.7 mmol) of polymer **2a** in 25 mL of dry dioxane was added 0.75 g (7 mmol) of benzylamine (**3b**). The mixture was refluxed under an argon atmosphere for 3 h, cooled to room temperature and filtered. The recovered polymer **1a** was washed twice with 10 mL of dioxane, three times with 10 mL of ethanol, four times each with 10-15 mL of dichloromethane and ether and finally dried. The IR spectrum of recovered **1a** exhibited a weak absorbance at 2560 $cm^{-1}$ (SH), and the carbonyl absorbance, characteristic of **2a**, had disappeared. The filtrate was evaporated to dryness. The crude product was dissolved in methylene chloride, ether, or ethyl acetate, washed with cool 5% HCl and cool brine, and dried over magnesium sulfate. Evaporation of the solvent gave 0.6 g of crude *N*-benzyl-2,2,2-trifluoroacetamide (**4b**). Flash chromatography[18] of the residue using methylene chloride as eluant gave in 86% yield 0.54 g of pure **4b**: mp 75-76 °C (lit.[4] mp 75-76 °C). From the yield of **4b**, it was calculated that polymer **2a** had a loading capacity of 0.86 mmol of *S*-benzyl 2,2,2-trifluorothioacetate groups per gram of polymer.

Similarly, 3-amino-1-propanol (**3e**) and **2a** gave as an oil in 90% yield pure *N*-(3-hydroxypropyl)-2,2,2-trifluoroacetamide (**4e**): IR (film) 3330, 3100, 2980-2890, 1720, 1570, 1180, 1060, 730 $cm^{-1}$; $^1H$ NMR $\delta$ 1.85 (q, 2), 3.3-3.8 (t of t overlapping, 4), 2.3-2.6 (m, br, 2); MS; *m/z* (relative intensity) 171 (7) ($M^+$), 126 (100), 114 (20), 102 (20), 84 (40), 69 (56), 41 (27).

**Preparation of N-Substituted Trifluoroacetamides 4a-c,f-i (Method 2).** In a typical reaction, 6 g (a two times excess, 5.3 mmol) of polymer **2a** or **2b** and 0.24 g (3 mmol) of (*S*)-2-amino-1-propanol (**3f**) was refluxed under argon for 3 h and worked up with ethyl acetate as described above for method 1 to give in 90% yield (from **2a**) after distillation 0.45 g of *N*-(*S*)-(2-hydroxy-1-methylethyl)-2,2,2-trifluoroacetamide (**4f**): bp 100-102 °C (1.2 mm); mp 80-81 °C; $[\alpha]^{22}_D$ -15.3° (*c* 4.5, EtOH); IR (Nujol) 3340, 3160, 1695, 1250, 1220, 1180, 1050, 730 $cm^{-1}$; $^1H$ NMR [$(CD_3)_2CO$] $\delta$ 1.18 (d, 3, $J$ = 6 Hz), 2.8 (m, br, 1), 3.38 (m, 2), 3.88 (t, 2, $J$ = 8 Hz); MS; *m/z* (relative intensity) 171 (4) ($M^+$), 156 (40), 140 (100), 92 (15), 69 (60), 45 (15).

**Preparation of *N*-Trifluoroacetyl Amino Acids 4g,h.** With method 1 described above, polymer **2a** was stirred with equivalent amounts of L-valine (**3h**) and triethylamine in anhydrous methanol for 72 h at room temperature. The resin was filtered and washed as described above and the filtrate worked-up as previously described[11] to give pure **4h**: mp 87-88 °C (lit. mp 88-89 °C).

Similarly, but with method 2 described above, polymer **2a** or **2b** was stirred with equivalent amounts of L-alanine (**3g**) and gave pure **4g**: mp 70-71 °C [after sublimation, 110-115 °C (0.01 mm)] (lit.[11] mp 70-71 °C).

**Preparation of 4i,j and Salts 5 and 6.** With method 1 or 2 as described above, *tert*-butylamine (**3i**) or diisopropylamine (**3j**) reacted with polymer **2a** to give *tert*-butylammonium 2,2,2-trifluoroacetate (**5**) and diisopropylammonium 2,2,2-trifluoroacetate (**6**) (Table I).

With method 2 and polymer **2b**, **3j** gave only salt **6**, but **3i** yielded a 1:3 mixture of **4i**: mp 45 °C (lit.[4] mp 44-45 °C) and **5** (Table I).

With a previously described method,[4] amine **3j** reacted with trifluoroacetic anhydride to give **4j**: mp 53 °C (lit.[4] mp 52-53 °C).

**Acknowledgment.** This investigation has been supported by a grant from Schering-Plough Corp.

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# Organopalladium Approaches to Prostaglandins. 8.[1] Ethyl (Acetoxymercurio)acetate Approach to Prostaglandin Endoperoxide Analogues

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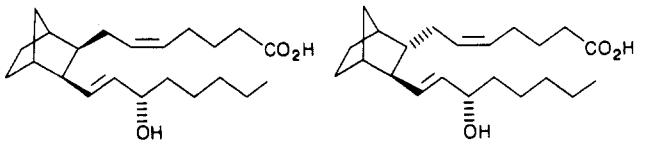
The synthesis of stable analogues of the prostaglandin endoperoxides ($PGG_2$ and $PGH_2$) has received considerable attention from organic chemists in recent years.[2,3] We have recently reported organopalladium approaches to these compounds employing $\pi$-allylic,[4] benzylic,[5,6] thienyl,[7,8] and vinylic[1] palladium intermediates. The latter approach affords easy entry to endoperoxide analogues **1** and **2**, which are effective inhibitors of blood platelet aggregation.[1]




**1** **2**

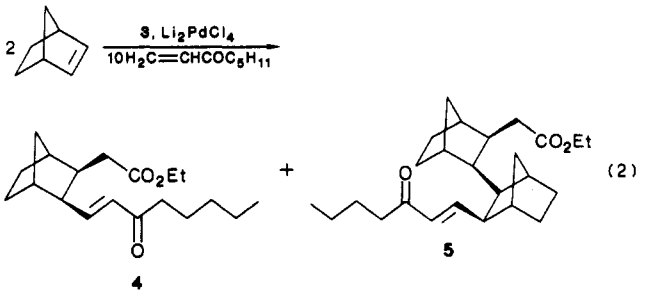
Recently, we have discovered an even more efficient synthesis of exo-exo analogues of compound **1** using an organopalladium intermediate derived from ethyl (acetoxymercurio)acetate (**3**) which we wish to report on at this time.

## Results and Discussion

Ethyl (acetoxymercurio)acetate (**3**) is readily available in high yield in one step from commercially available 1,1-difluoroethylene (eq 1).[9] Reaction of compound **3** with

$$Hg(OAc)_2 + H_2C{=}CF_2 + EtOH \rightarrow \underset{\mathbf{3}}{AcOHgCH_2CO_2Et} \quad (1)$$

$Li_2PdCl_4$, 2 equiv of norbornene, and 10 equiv of 1-octen-3-one for 4 days resulted in an ~4:1 ratio of the desired keto ester **4** and the double insertion product **5** in 70% overall yield (eq 2). Keto ester **4** is a diastereomeric




**4** **5** (2)

(1) For "Organopalladium Approaches to Prostaglandins. 7. Synthesis of Prostaglandin Endoperoxide Analogs by Vinylpalladation of Norbornene", see: Larock, R. C.; Hsu, M. H.; Narayanan, K., manuscript in preparation.

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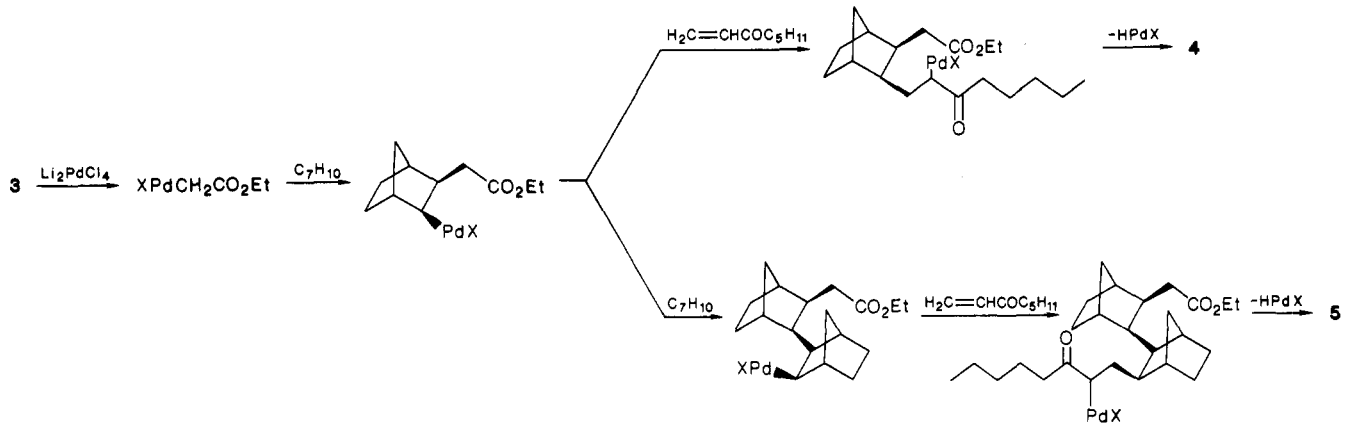
**Scheme I**




mixture of products resulting from addition of the keto and ester side chains to opposite ends of the norbornene double bond. The diastereomeric mixture of **4** can be separated from compound **5** by column chromatography in 40% unoptimized yield. The assignment of structure for compound **5** is based solely on mass spectral analysis and mechanistic arguments.

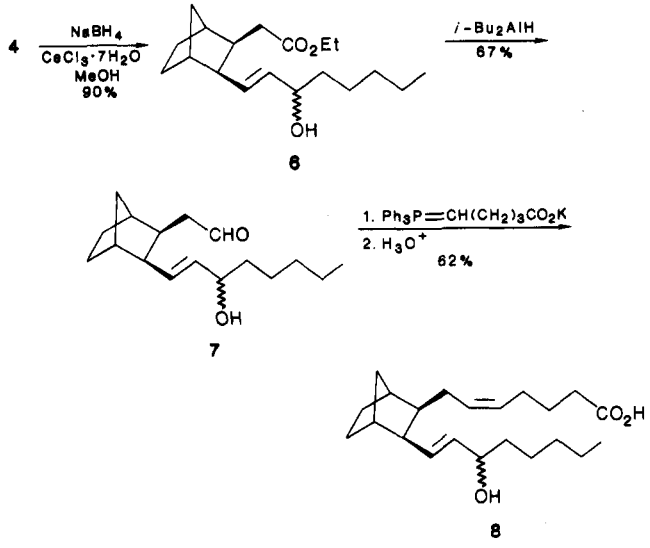
Compounds **4** and **5** in eq 2 presumably arise as shown in Scheme I. Clearly norbornene inserts more readily into the carbon–palladium bond of the organopalladium intermediates than 1-octen-3-one. We have never observed any products of direct coupling of the initial organopalladium compound $XPdCH_2CO_2Et$ with 1-octen-3-one even though five times as much enone as norbornene is present at the start of the reaction.

The facile construction of keto ester **4** in one step from readily available starting materials makes it a particularly valuable intermediate for the synthesis of exo–exo prostaglandin endoperoxide analogues. For example, keto ester **4** is readily elaborated to endoperoxide analogue **8** by a sequence involving (1) $NaBH_4$–$CeCl_3$ reduction to hydroxy ester **6**, (2) *i*-$Bu_2AlH$ reduction to hydroxy aldehyde **7**, and (3) Wittig olefination (Scheme II). This three-step synthesis of an effective inhibitor of blood platelet aggregation proceeds in 37% unoptimized, overall yield from readily available keto ester **4**. The direct reduction of keto ester **4** to hydroxy aldehyde **7** by *i*-$Bu_2AlH$ did not proceed as cleanly as the above two-step sequence.

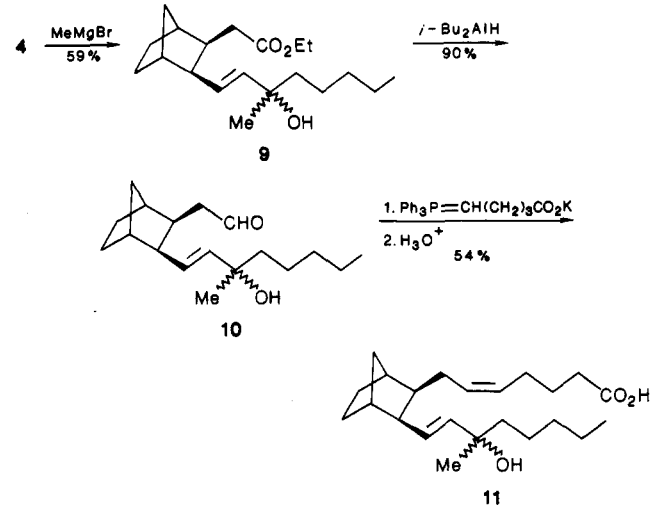
The introduction of substituents at C-15 is also readily effected by using intermediate **4**. For example, low-temperature Grignard addition to keto ester **4** and subsequent elaboration as described above provides the methyl alcohol **11** in good yield (Scheme III).

The C-15 (*S*) epimer of alcohol **8** has previously been reported to be an effective inhibitor of arachidonic acid and ADP induced blood platelet aggregation.[1] Compounds **8** and **11** are presently undergoing biological testing.

**Scheme II**




**Scheme III**




## Experimental Section

**Equipment.** Proton NMR spectra were recorded on either a Varian EM-360 or a Nicolet NT-300 spectrometer. Carbon-13 NMR spectra were recorded on either a JEOL FX-90Q or a Nicolet NT-300. Infrared spectra were recorded on either a Beckmann IR-4250 or a Beckmann Accu-lab spectrometer. High-resolution mass spectra were obtained on either an AEI-MS-902 or a Kratos MS-50. Thin-layer chromatography was preformed on Merck 60f-254 silica gel plates from American Scientific Products. Merck Kieselgel 60 (230–400 mesh) for flash column chromatography was purchased from American Scientific Products.

**Reagents.** All chemicals were used directly as obtained commercially unless otherwise noted. THF was distilled from calcium hydride. Palladium chloride was generously supplied by Jonnson Matthey, Inc., and Englehard Industries. Methylmagnesium bromide in diethyl ether, *i*-$Bu_2AlH$ in dichloromethane, 1-octen-3-ol, norbornene, (4-carboxybutyl)triphenylphosphonium bromide, and $CeCl_3·7H_2O$ were obtained commercially from Aldrich Chemical Company. 1,1-Difluoroethylene was purchased from SCM Specialty Chemicals in Gainesville, FL. 1-Octen-3-one was obtained by oxidation of 1-octen-3-ol with pyridinium chlorochromate using a standard procedure.[10] Ethyl (acetoxy-

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mercurio)acetate (3) was prepared according to the literature procedure.[9]

**Synthesis of Compounds 4 and 5.** Palladium chloride (0.89 g, 5 mmol) and lithium chloride (0.42 g, 10 mmol) were dissolved in 50 mL of dry THF. The solution was cooled to 0 °C, and ethyl (acetoxymercurio)acetate (3) (1.73 g, 5 mmol), norbornene (0.94 g, 10 mmol), and 1-octen-3-one (6.3 g, 50 mmol) were added. The reaction was stirred at 0 °C for 1 h and was then allowed to warm up to room temperature. After being stirred for 4 days, the reaction mixture was diluted with ether, filtered, washed with saturated ammonium chloride solution, and dried over $Na_2SO_4$. After removal of the solvent, the excess 1-octen-3-one was distilled under reduced pressure. Gas chromatographic–mass spectral analysis of the reaction mixture showed that the desired product 4 was obtained along with compound 5 in a ratio of ~4:1 in a total yield of 70%. The mixture was separated by column chromatography using 4:1 hexane/ethyl acetate as the eluant.

The desired product 4 was isolated in 40% yield: $^1$H NMR ($CDCl_3$) $\delta$ 0.91 (3 H, t, $J$ = 7 Hz, $CH_3$), 1.16–2.52 (23 H, m), 4.06 (q) and 4.07 (q) (2 H, $J$ = 7.2 Hz, $OCH_2$, diastereomeric ester hydrogens), 6.05 (1 H, d, $J$ = 14.5 Hz, C=CHC=O), 6.59 (1 H, dd, $J$ = 10.7 and 14 Hz, CH=CC=O); $^{13}$C NMR ($CDCl_3$) $\delta$ 200.1, 172.8, 146.8, 130.5, 60.2, 49.1, 43.4, 42.7, 41.6, 40.3, 36.5, 33.5, 31.4, 29.5, 28.7, 23.9, 22.4, 14.1, 13.8; IR (neat) 2960 (CH), 1745 (ester C=O), 1680 (enone C=O), 1610 (C=C) cm$^{-1}$; MS (70 eV), $m/z$ 306 ($M^+$), 278 ($M^+ - CH_2{=}CH_2$), 261 ($M^+ - OCH_2CH_3$), 260 ($M^+ - CH_3CH_2OH$), 207 ($M^+ - COC_5H_{11}$), 162 (207 - $OCH_2CH_3$); MS, $m/z$ 306.22065 (calcd for $C_{19}H_{30}O_3$, 306.21950).

Compound 5: MS (70 eV), $m/z$ 400 ($M^+$), 372, 344, 327, 286, 215, 205, 147, 133, 119, 99, 91, 79, 67, 54, 43.

**Synthesis of Compounds 6 and 7.** A general literature procedure was employed.[11] The enone 4 (0.27 g, 0.89 mmol) and $CeCl_3{\cdot}7H_2O$ (0.33 g, 0.89 mmol) were dissolved in methanol (2.25 mL). Sodium borohydride (0.034 g, 0.89 mmol) was added, and the reaction mixture was stirred for 5 min. It was then diluted with ether and water, and the ether layer was separated. The aqueous layer was extracted with ether, dried over $Na_2SO_4$, and evaporated to give 0.247 g (90% yield) of crude hydroxy ester 6, which was immediately reduced further.

The hydroxy ester 6 was reduced to hydroxy aldehyde 7 by using $i$-$Bu_2AlH$ and a procedure identical with that described later for the synthesis of compound 10: 60% overall yield from compound 4; $^1$H NMR ($CDCl_3$) $\delta$ 0.81–2.4 (24 H, m), 3.90 (1 H, m, C*H*OH), 5.2–5.4 (2 H, m, vinyl), 9.57 (1 H, s, CHO); $^{13}$C NMR ($CDCl_3$) $\delta$ 202.5, 138.5, 128.4, 68.4, 49.2, 46.4, 43.2, 42.7, 41.7, 41.3, 41.2, 33.4, 32.4, 29.6, 28.2, 27.9, 23.8, 23.7, 22.5, 14.0 (extra peaks due to diastereomers); IR (neat) 3400–3200 (OH), 2960 (CH), 1720 (C=O) cm$^{-1}$; MS, $m/z$ 246.19826 [calcd for $C_{17}H_{26}O$ ($M^+$ - 18), 246.1983].

**Synthesis of Compound 8.** Hydroxy aldehyde 7 was subjected to the Wittig reaction as described later for the synthesis of compound 11, and the desired acid 8 was obtained in 62% yield: $^1$H NMR ($CDCl_3$) $\delta$ 0.89–2.42 (31 H, m), 3.7–3.8 (1 H, m, C*H*OH), 5.20–5.52 (4 H, m, vinyl); $^{13}$C NMR ($CDCl_3$) $\delta$ 177.5, 133.2, 131.9, 128.3, 127.6, 73.2, 49.8, 49.2, 47.3, 47.2, 43.3, 42.6, 39.8, 37.3, 33.1, 31.9, 29.8, 29.3, 25.3, 24.4, 22.7, 14.1; IR (neat) 3500–2700 ($CO_2H$, OH), 1710 (C=O) cm$^{-1}$; MS, $m/z$ 330.25643 [calcd for $C_{22}H_{34}O_2$ ($M^+$ - 18), 330.25588].

**Synthesis of Hydroxy Ester 9.** A general literature procedure was followed.[12] Compound 4 (0.22 g, 0.72 mmol) was taken up in 37 mL of dry THF and cooled to -78 °C. To this was added 3.77 mL (15.75 equiv) of 3.0 M MeMgBr in diethyl ether. The reaction as stirred at -78 °C for 4 h. The reaction was then quenched with 10 mL of saturated ammonium chloride solution and allowed to warm up to room temperature. After an additional 25 mL of saturated ammonium chloride solution was added, the reaction mixture was extracted with ether. The ether layer was washed with saturated sodium chloride solution and dried over $Na_2SO_4$ and the solvent removed under vacuum. Column chromatography of the resulting residue using 1:1 hexane/ethyl acetate as the eluant yielded 137 mg (59% yield) of compound 9: $^1$H NMR ($CDCl_3$) $\delta$ 0.79–2.4 (28 H, m), 4.05 (2 H, q, $J$ = 7 Hz, $OCH_2$), 5.3–5.4 (2 H, m, vinyl); $^{13}$C NMR ($CDCl_3$) $\delta$ 173.7, 138.0, 128.2, 72.7, 60.2, 49.2, 43.3, 43.3, 42.8, 42.8, 37.0, 33.4, 32.4, 29.8, 29.0, 28.2, 27.6, 23.9, 23.7, 22.7, 14.3, 14.1 (extra peaks due to diastereomers); IR (neat) 3800–3150 (OH), 2880 (C=CH), 1730 (C=O), 1640 (C=C) cm$^{-1}$; MS, $m/z$ 304.23916 [calcd for $C_{20}H_{30}O_2$ ($M^+$ - $H_2O$), 304.2402].

**Synthesis of Hydroxy Aldehyde 10.** Ester 9 (137 mg, 0.425 mmol) was taken up in 28 mL of methylene chloride and cooled to -78 °C. This solution was treated with 1.4 mL of 1 M $i$-$Bu_2AlH$ in methylene chloride (3.3 equiv) and stirred for 3 h at -78 °C. The reaction mixture was then quenched with 1 mL of methanol and treated with 3 mL of saturated ammonium chloride solution. The reaction mixture was then warmed to room temperature, diluted with ether, washed with saturated ammonium chloride solution, and dried over $Na_2SO_4$ and the solvent removed under vacuum. Flash column chromatography of the resulting residue yielded 106 mg (90% yield) of the desired hydroxy aldehyde 10: $^1$H NMR ($CDCl_3$) $\delta$ 0.75–2.4 (26 H, m), 5.32–5.34 (2 H, m, vinyl), 9.57 (1 H, m, CHO); $^{13}$C NMR ($CDCl_3$) $\delta$ 202.8, 138.4, 128.4, 72.7, 49.2, 49.1, 46.4, 43.2, 42.9, 41.7, 41.3, 41.2, 33.4, 32.3, 29.7, 29.0, 28.2, 27.8, 23.7, 22.6, 14.0 (extra peaks due to diastereomers); IR (neat) 3500–3300 (OH), 2960 (CH), 1720 (C=O) cm$^{-1}$; MS, $m/z$ 260.2142 [calcd for $C_{18}H_{28}O$ ($M^+$ - 18), 260.2140].

**Synthesis of Compound 11.** A general literature procedure for this Wittig reaction was employed.[13] (4-Carboxybutyl)triphenylphosphonium bromide (0.70 g, 1.58 mmol) was suspended in 6 mL of THF under a nitrogen atmosphere. Potassium *tert*-butoxide (0.36 g, 3.2 mmol) was added, and the orange-colored mixture was stirred for 15 min at room temperature. Then hydroxy aldehyde 10 (0.11 g, 0.395 mmol) in 3.8 mL of THF was added, and the reaction mixture was stirred at room temperature for 3 h. Sulfuric acid (40 mL of 2 N) and water were added, and the product was extracted with ether, washed with 2 N sulfuric acid and water, and dried over $MgSO_4$. The residue obtained after evaporation of the solvent was chromatographed by using 1:1 hexane/ethyl acetate plus a few drops of acetic acid to yield 77 mg (54% yield) of compound 11: $^1$H NMR ($CDCl_3$) $\delta$ 0.80–2.24 (34 H, m), 5.2–5.4 (4 H, m, vinyl); $^{13}$C NMR ($CDCl_3$) $\delta$ 178.2, 133.0, 131.6, 128.5, 127.6, 76.6, 49.7, 47.6, 43.5, 40.1, 35.5, 33.5, 33.1, 32.4, 31.9, 30.0, 29.8, 29.3, 26.8, 26.6, 24.9, 24.7, 22.7, 14.1 (extra peaks due to diastereomers); IR (neat) 3500–3200 (OH, $CO_2H$), 1720 (C=O) cm$^{-1}$; MS, $m/z$ 344.27101 [calcd for $C_{23}H_{36}O_2$ ($M^+$ - 18), 344.27154].

**Acknowledgment.** We gratefully acknowledge the National Institutes of Health and the American Heart Association, Iowa Affiliate, for financial support, and Johnson Matthey Inc. and Englehard Industries for generous loans of palladium chloride.

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## Synthesis of 4-Phenyl-5*H*-pyrido[3,4-*b*][1,4]benzothiazin-3-(2*H*)-ones (4-Phenylazaphenothiazines) via Activated Dimethylformamide Reagents

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We previously reported on the synthesis and biological activity of a series of oxopyridobenzothiazine-4-carbonitriles (azaphenothiazines).[1] These compounds were synthesized by a novel $\alpha$-pyridone annulation reaction,

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