was added through the rubber septum by using a hypodermic syringe. Carbon dioxide gas evolution was monitored by GLC analysis of a gaseous sample taken out through the rubber septum with a hypodermic syringe. After the quantitative carbon dioxide gas evolution was observed, a GLC internal standard was added. GLC analysis (a silicone DC 550 column or a PEG 20M column) of the reaction mixture gave the GLC yield of the allylic alkylation or isomerization product.

The allylic alkylation products **9**–**16** and the isomerization products **17**–**19** were isolated by GLC and were identified by the spectroscopic data in Table II. The allylic alkylation product **9** (2.22 g, 13.2 mmol, 88%), which was produced by the palladium-catalyzed reaction of 1-oxocyclohexane-2-carboxylic acid (2.13 g, 15.0 mmol) and **2** (1.21 mL, 15.0 mmol) in 120 mL of THF, was isolated by column chromatography on silica gel using ether as eluent.

Acknowledgment. This work was supported in part by Grant-in Aid for Scientific Research 60550588 from the Ministry of Education, Science, and Culture of Japan.

Registry No. **1**, 614-20-0; **2**, 930-22-3; **3**, 7437-61-8; **4**, 69429-05-6; **5**, 6812-25-5; **6**, 34485-82-0; **7**, 13295-59-5; **8**, 6705-51-7; (*E*)-**9**, 105182-95-4; (*Z*)-**9**, 33739-85-4; (*E*)-**10**, 105182-96-5; (*Z*)-**10**, 105183-01-5; **11**, 105182-97-6; **12**, 105182-98-7; **13**, 105182-99-8; (*E*)-**14**, 27267-99-8; (*Z*)-**14**, 27267-38-5; (*E*)-**15**, 33739-83-2; (*Z*)-**15**, 33739-82-1; **16**, 105183-00-4; **17**, 26431-13-0; **18**, 75082-96-1; **19**, 4096-34-8; $Pd(PPh_3)_4$, 14221-01-3; 2-oxocyclohexanecarboxylic acid, 18709-01-8; 3-methyl-2-oxocyclohexanecarboxylic acid, 52456-87-8; 3-oxoglutaric acid, 542-05-2.

Organopalladium Approaches to Prostaglandins. 5.[1] Synthesis of Bicyclic and Tricyclic Prostanoic Acids and Thiophene-Containing Prostaglandin Endoperoxide Analogues via Thienylpalladation of Bicyclic Alkenes[2]

R. C. Larock,* D. R. Leach, and S. M. Bjorge

Department of Chemistry, Iowa State University, Ames, Iowa 50011

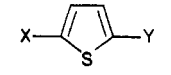
Received July 15, 1986

Thiophene-containing prostaglandin endoperoxide analogues **18**–**20** are readily available by addition of thienylpalladium species to norbornene and norbornadiene and subsequent reaction with the appropriate alkynyllithium reagent. Elaboration of the bicyclic palladium intermediate using alkenyltin or -copper reagents, or a carbonylation approach, affords endoperoxide analogue **25**. Hydrogenation and subsequent saponification of thiophenes **16** and **17** afford the first bicyclic (**31**) and tricyclic (**32**) prostanoic acids.

There has been considerable interest in introducing the thiophene and tetrahydrothiophene rings into prostaglandins.[3-10] While these sulfur-containing rings have been introduced into a variety of positions in the primary prostaglandins, there appear to be no examples of such analogues in the prostaglandin endoperoxide series. Our recent interest[1,2,11,12] in employing palladium chemistry in the synthesis of prostaglandin endoperoxide analogues encouraged us to examine possible methods for introducing the thiophene ring into the carboxylic acid side chain of such analogues. Unlike all previous work in this area, we desired to introduce the thiophene ring into the C_4–C_7 positions of the analogues, since that should mimic the normal olefinic C_5–C_6 cis stereochemistry common to most prostaglandins. Besides the obvious interest in exploring the biological activity of such thiophene-containing analogues, we also anticipated that hydrogenation of the thiophene ring might provide an easy entry into the first bicyclic and tricyclic prostanoic acids. At this time we report the details of our efforts in this area.

Results and Discussion

Our basic approach to the thiophene-containing endoperoxide analogues required the preparation of thienylmercurials **3** and **5**. Methyl (*E*)-3-(2-thienyl)acrylate (**2**)



1: X = H; Y = (*E*)-CH=CHCO$_2$H
2: X = H; Y = (*E*)-CH=CHCO$_2$CH$_3$
3: X = ClHg; Y = (*E*)-CH=CHCO$_2$CH$_3$
4: X = H; Y = CH$_2$CH$_2$CO$_2$CH$_3$
5: X = ClHg; Y = CH$_2$CH$_2$CO$_2$CH$_3$

was prepared from the commercially available acid **1**, by acid-catalyzed esterification, in 88% yield. Methyl 3-(2-thienyl)propanoate (**4**) was prepared by hydrogenation[13] of the unsaturated acid **1**, followed by esterification, in 79% overall yield. These heterocycles were then mercurated by a modification of Volhard's procedure,[14] involving 2 equiv of $HgCl_2$ and 10 equiv of NaOAc in aqueous ethanol, to afford thienylmercurials **3** and **5** in 86% and 83% yields, respectively.

While the addition of π-allyl, aryl, benzylic, and vinylic palladium species to bicyclic alkenes is well-known,[15] there have been no examples of the addition of heterocyclic

(1) Part 4: Larock, R. C.; Babu, S. *Tetrahedron Lett.* **1985**, *26*, 2763.
(2) For a preliminary communication of this work see: Larock, R. C.; Leach, D. R.; Bjorge, S. M. *Tetrahedron Lett.* **1982**, *23*, 715.
(3) Teulon, J.-M. U.S. Patent 4 122 091, 1978.
(4) Vlattas, I. U.S. Patent 3 970 670, 1976.
(5) Vlattas, I. U.S. Patent 4 041 047, 1977.
(6) Vlattas, I. U.S. Patent 3 881 017, 1975.
(7) Vlattas, I. U.S. Patent 4 077 979, 1978.
(8) Bartmann, W.; Beck, G.; Reuschling, D.-B.; Seeger, K.; Teufel, H. U.S. Patent 4 258 053, 1981.
(9) Schaaf, T. K.; Bindra, J. S. U.S. Patent 4 065 472, 1977.
(10) Patterson, J. W.; Fried, J. H. U.S. Patent 3 922 289, 1975.
(11) Larock, R. C.; Burkhart, J. P.; Oertle, K. *Tetrahedron Lett.* **1982**, *23*, 1071.
(12) Larock, R. C.; Leach, D. R. *J. Org. Chem.* **1984**, *49*, 2144.
(13) Sam, J.; Thompson, A. *J. Pharm. Sci.* **1963**, *52*, 898.
(14) Volhard, J. *Justus Liebig Ann. Chem.* **1892**, *267*, 172.
(15) Larock, R. C.; Hershberger, S. S.; Takagi, K.; Mitchell, M. A. *J. Org. Chem.* **1986**, *51*, 2450 and references therein.

0022-3263/86/1951-5221$01.50/0

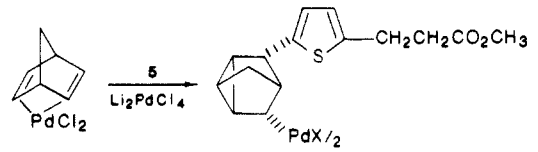
palladium species to such alkenes. We have observed that the reaction of mercurials **3** or **5**, Li_2PdCl_4, and norbornene in acetonitrile affords the corresponding stable, cis-exo organopalladium adducts **6** and **8** in 67% and 78% isolated yields, respectively (eq 1). Attempts to prepare analogous

(1)

6: X = Cl; Y = (*E*)-CH=CHCO$_2$CH$_3$
7: X = Hfacac; Y = (*E*)-CH=CHCO$_2$CH$_3$
8: X = Cl; Y = CH$_2$CH$_2$CO$_2$CH$_3$
9: X = Hfacac; Y = CH$_2$CH$_2$CO$_2$CH$_3$

furan-containing organopalladium compounds did not result in stable adducts, and all attempts to synthesize furan-containing prostaglandin endoperoxide analogues were abandoned. It appears that the sulfur atom in these adducts is critical to their stability.

Organomercurial **5** has also been reacted with (norbornadiene)palladium dichloride to give a stable nortricyclyl adduct **10** in 74% isolated yield (eq 2). The



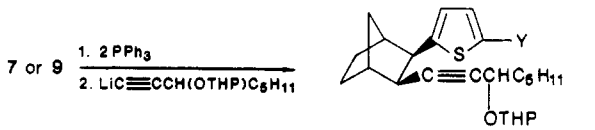
(2)

10: X = Cl
11: X = Hfacac

structure of this compound has been assigned on the basis of the lack of olefinic resonances in the ^{1}H NMR spectrum and the presence of a strong band at 810 cm^{-1} in the infrared spectrum, which is characteristic of nortricyclene ring systems.[16] Analogous nortricyclyl adducts have been observed upon reaction of diphenylmercury[17,18] (followed by pyridine) and vinylic mercuric chlorides[15] with (norbornadiene)palladium dichloride.

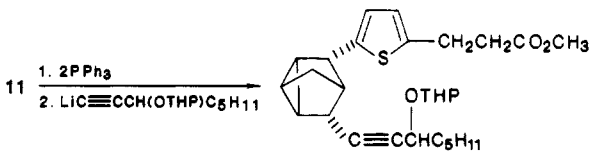
Several methods have been explored for introducing the unsaturated alcohol side chain common to prostaglandins into these palladium intermediates. We have previously had considerable success in displacing palladium in such compounds by alkynyllithium reagents.[11,15] Previous work[11] has shown that reactions of bicyclic organopalladium compounds with alkynyllithium reagents proceed more cleanly and in higher yield when the chloride anion on palladium is exchanged for the (hexafluoroacetyl)acetonate group. This was accomplished in yields of 98%, 100%, and 96%, respectively, by treating palladium complexes **6**, **8**, and **10** with 1 equiv of AgOAc in chloroform followed by 1.5–2.0 equiv of (hexafluoroacetyl)acetone. The resulting palladium compounds **7**, **9**, and **11** were not characterized but were subsequently treated with 2 equiv of PPh_3, followed by 1.05 equiv of 1-lithio-3-[(2-tetrahydropyranyl)oxy]-1-octyne at −78 °C for approximately 1 h, and then slowly warmed to room temperature. The cross-coupled alkynes **12**–**14** were obtained as an inseparable mixture of diastereomers in yields of 77%, 68%, and 75%, respectively (eq 3 and 4), and carried on as diastereomeric mixtures.

Removal of the tetrahydropyranyl ether group using catalytic amounts of *p*-TsOH in methanol afforded hydroxy esters **15**–**17** in yields of 83%, 85%, and 83%, respectively.



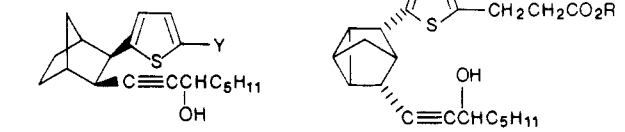
(3)

12: Y = (*E*)-CH=CHCO$_2$CH$_3$
13: Y = CH$_2$CH$_2$CO$_2$CH$_3$



(4)

14



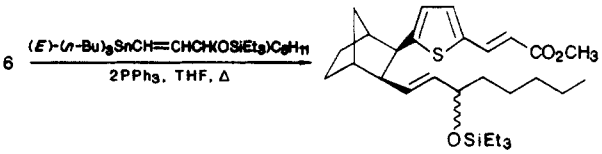
15: Y = (*E*)-CH=CHCO$_2$CH$_3$
16: Y = CH$_2$CH$_2$CO$_2$CH$_3$
18: Y = (*E*)-CH=CHCO$_2$H
19: Y = CH$_2$CH$_2$CO$_2$H

17: R = CH$_3$
20: R = H

Hydrolysis of the methyl esters to afford the corresponding carboxylic acids **18**–**20** in yields of 96%, 82%, and 86%, respectively, was effected by refluxing for 30 min with 2 N KOH in aqueous methanol.

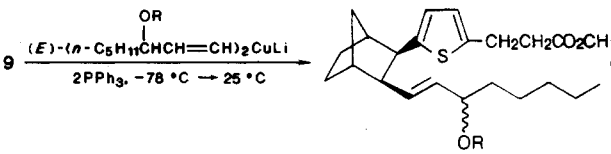
While we have observed in a number of cases that acetylenic alcohols show greater biological activity than the corresponding allylic alcohols, it was deemed desireable to have an efficient route to the corresponding *E* allylic alcohols. Heck olefination[19] of our palladium intermediates by enones appeared promising, but complex **6** failed to react with 8 equiv of methyl vinyl ketone and 5 equiv of diisopropylethylamine in 1 day at room temperature. Reaction of our palladium intermediates with 2 equiv of PPh_3 followed by alkenyllithium or -zinc or mercury reagents afforded no more than traces of the desired cross-coupled product. The major product from the lithium and zinc reactions involved substitution of the palladium moiety by hydrogen.

Alkenylstannanes and cuprates were more promising, but the yields remained low (eq 5 and 6). Cleavage of the



(5)

21 (34%)



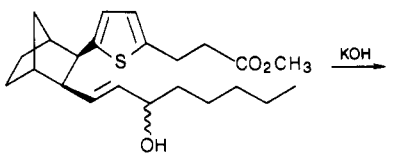
(6)

22: R = SiMe$_2$(*t*-Bu) (31%)
23: R = THP (55%)

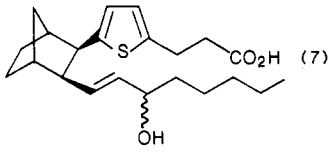
t-BuMe$_2$Si group in compound **22** with 3:1:1 acetic acid/water/THF proceeded in 77% yield, while THP removal in compound **23** afforded the desired alcohol **24** in 60% yield. Methyl ester **24** was saponified with 2 N KOH in aqueous methanol to provide prostaglandin analogue **25** in 77% yield (eq 7).

Since the overall yield of allylic alcohol **25** by the alkenylmetallic approaches was low, a more efficient method

(16) Vedejs, E.; Weeks, P. D. *Tetrahedron Lett.* **1974**, 3207.
(17) Segnitz, A.; Bailey, P. M.; Maitlis, P. M. *J. Chem. Soc., Chem. Commun.* **1973**, 698.
(18) Segnitz, A.; Kelly, E.; Taylor, S. H.; Maitlis, P. M. *J. Organomet. Chem.* **1977**, *124*, 113.
(19) Heck, R. F. *Org. React.* **1982**, *27*, 345.

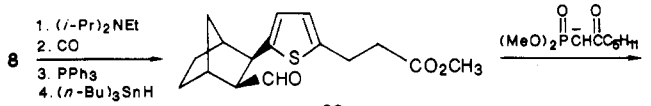


24

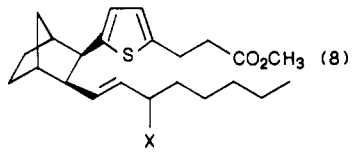


25 (7)

to accomplish this transformation was sought. Sequential treatment of palladium compound 8 with diisopropylethylamine, carbon monoxide, PPh_3, and tri-*n*-butyltin hydride afforded aldehyde **26** in 100% yield, which underwent phosphonate coupling to afford the desired enone **27** in 86% yield, alongside 10% of the cis isomer (eq 8).



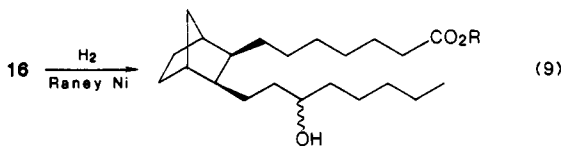
26



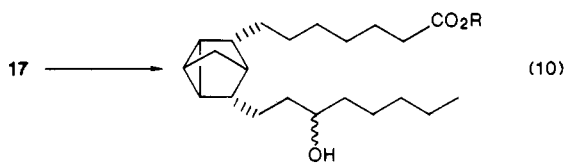
27: X = =O
24: X = —OH (8)

Reduction of enone **27** to allylic alcohol **24** was accomplished in 95% yield using 9-BBN[20] in THF at 0 °C. The overall yield of alcohol **24** from palladium intermediate **8** was 82%, a significant improvement over the vinylcuprate or -stannane approaches.

The ease with which we have been able to prepare the thiophene-containing endoperoxide analogues encouraged us to examine the hydrogenation of these compounds as an efficient route to the first bicyclic and tricyclic prostanoic acids. The reductive desulfurization of substituted thiophenes to alkanes is a well-known reaction.[21] Hydrogenation of esters **16** and **17** over Raney nickel W-7 in ethanol afforded the fully saturated prostanoids **29** and **30** in 82% and 83% yields, respectively (eq 9 and 10).



29: R = CH_3
31: R = H (9)



30: R = CH_3
32: R = H (10)

Hydrogenation of the methyl esters, instead of the acids, was preferred due to the ease of their subsequent purification by chromatography. Hydrolysis of the methyl esters to the corresponding acids **31** and **32** was accomplished by refluxing with 2 N KOH in aqueous methanol in yields of 86% and 95%, respectively.

The biological activity of these new prostaglandin analogues has been examined by Bristol Laboratories of Syracuse, NY. The compounds were evaluated for in vitro inhibition of arachidonic acid induced platelet aggregation in rabbit platelet rich plasma. The effective concentrations necessary to reduce the induced blood platelet aggregation by 50% (EC_{50}) (ng/mL) follow: **15** (970), **16** (1500), **17** (1300), **18** (29000), **19** (15000), **20** (24000), **24** (10800), **25** (40000), **30** (>256000), **31** (6100), **32** (76000). For comparison, the EC_{50} values for PGE_1 and PGI_2 were determined to be 18 and 4 ng/mL, respectively. While these compounds are significantly less active than other compounds prepared in our laboratories[11] or the natural prostaglandins, it is noteworthy that the acetylenic alcohols **16** and **19** are more active than their olefinic counterparts **24** and **25**, a pattern we have observed earlier.

Experimental Section

Equipment. Proton NMR spectra were recorded on either a Varian EM-360 or HA-100 spectrometer. ^{13}C NMR spectra were recorded on a JEOL-FX90Q spectrometer. Infrared spectra were recorded on a Beckman IR-4250 infrared spectrometer. Mass spectra were obtained on an AEI MS-902 high-resolution mass spectrometer, while GC–mass spectra were recorded on a Finnegan 4023 GC–MS data system.

Reagents. All chemicals were used directly as obtained commercially unless otherwise noted. THF and diethyl ether were distilled from calcium hydride. Dimethoxyethane (DME) was distilled from lithium aluminum hydride. *n*-Butyllithium and *tert*-butyllithium were obtained from Alfa and titrated before use with 2,5-dimethoxybenzyl alcohol.[22] Copper(I) iodide was obtained from Alfa and purified by a literature procedure.[23] Diisopropylethylamine was distilled from calcium hydride.

(*E*)-3-[(*tert*-butyldimethylsilyl)oxy]-1-iodo-1-octene,[24] (*E*)-1-(tri-*n*-butylstannyl)-3-[(triethylsilyl)oxy]-1-octene,[25] (norbornadiene)palladium dichloride,[26] and3-[(2-tetrahydropyranyl)oxy]-1-octyne[27] were prepared by literature procedures. Raney nickel W-7 was prepared by a literature procedure using Raney nickel–aluminum alloy from W. R. Grace.[28]

Syntheses of Thiophenes 2 and 4. Methyl (*E*)-3-(2-Thienyl)acrylate (2). (*E*)-3-(2-Thienyl)acrylic acid (1; K and K Labs; 10.0 g, 65 mmol) was refluxed in 100 mL of methanol with 3 drops of concentrated H_2SO_4 for 8 h. The mixture was then diluted with ether, washed twice with 10% $NaHCO_3$, and dried over anhydrous sodium sulfate. Removal of the solvent in vacuo and recrystallization from hexane gave 9.35 g [55.6 mmol (86%)] of methyl (*E*)-3-(2-thienyl)acrylate (**2**), mp 42 °C (lit.[29] mp 40–42.2 °C).

Methyl 3-(2-Thienyl)propionate (4). 3-(2-Thienyl)propanoic acid (2.30 g, 14.7 mmol), prepared by hydrogenation of 3-(2-thienyl)acrylic acid according to a literature procedure,[13] was treated as above to afford 2.35 g (95%) of methyl 3-(2-thienyl)-propionate (**4**): ^1H NMR ($CDCl_3$) δ 2.4–2.8 (2 H, m, CH_2CO), 2.9–3.35 (2 H, m, thienyl-CH_2), 3.60 (3 H, s, OCH_3), 6.5–7.2 (3 H, m, thienyl).

Syntheses of Organomercurials 3 and 5. The synthesis of methyl 3-[5-(chloromercurio)-2-thienyl]propionate (**5**) is representative. Methyl 3-(2-thienyl)propionate (**4**; 2.0 g, 11.8 mmol)

(20) Krishnamurthy, S.; Brown, H. C. *J. Org. Chem.* **1977**, *42*, 1197.
(21) Petit, G. R.; Van Tamelen, E. E. *Organic Reactions*; Wiley: New York, 1962; pp 393–398.
(22) Winkle, M. R.; Lansinger, J. M.; Ronald, R. C. *J. Chem. Soc., Chem. Commun.* **1980**, 87.
(23) Kauffman, G. B.; Teter, L. A. *Inorg. Synth.* **1963**, *7*, 9.
(24) Corey, E. J.; Beames, D. *J. Am. Chem. Soc.* **1972**, *94*, 7210.
(25) Chen, S.; Schaub, R.; Grudzinskas, C. *J. Org. Chem.* **1978**, *43*, 3450.
(26) Drew, D.; Doyle, J. R. *Inorg. Synth.* **1972**, *13*, 52.
(27) Crundwell, E.; Pinnegan, M. A.; Templeton, W. *J. Med. Chem.* **1969**, *8*, 41.
(28) Billica, H. R.; Adkins, H. *Organic Syntheses*; Horning, E. C., Ed.; Wiley: New York, 1955; Collect. Vol. III, p 176.
(29) Heck, R. F. *J. Am. Chem. Soc.* **1968**, *90*, 5518.

in 5 mL of ethanol was added to a solution of 6.4 g (23.6 mmol) of $HgCl_2$ and 6.7 g of NaOAc in 35 mL of 30% ethanol. This was allowed to stand for 2 days after which time the product was isolated by filtration and recrystallized to give 3.77 g (83%) of methyl 3-[5-(chloromercurio)-2-thienyl]propionate (**5**): mp 155–157 °C; ^1H NMR (Me_2SO-d_6) δ 2.68 (2 H, d, J = 6 Hz, CH_2CO), 3.04 (2 H, d, J = 6 Hz, thienyl-CH_2), 3.59 (3 H, s, OCH_3), 6.8–7.1 (2 H, m, thienyl). Anal. Calcd for $C_8H_9O_2SHgCl$: C, 23.71; H, 2.24; O, 7.90; S, 7.91. Found: C, 23.65; H, 2.31; O, 8.02; S, 8.06.

Methyl 3-[5-(chloromercurio)-2-thienyl]acrylate (3): 86% yield; mp 243–245 °C; ^1H NMR (acetone-d_6) δ 3.75 (3 H, s, OCH_3), 6.24 (1 H, d, J = 16 Hz, =CHCO), 7.18 (2 H, d, J = 4 Hz, thienyl), 7.73 (1 H, d, J = 16 Hz, CH=CCO). Anal. Calcd for $C_8H_7O_2SHgCl$: C, 23.83; H, 1.75; O, 7.94; S, 7.95. Found: C, 23.87; H, 1.63; O, 7.76; S, 7.61.

Synthesis of Compounds 6 and 8. The synthesis of compound **8** is representative. Norbornene (Aldrich; 1.88 g, 20.0 mmol), 0.35 g of palladium chloride (2.0 mmol), and 0.18 g of lithium chloride (4.1 mmol) were dissolved in 15 mL of acetonitrile and the resultant mixture cooled to 0 °C. To this was added 0.81 g (2.0 mmol) of methyl 3-[5-(chloromercurio)-2-thienyl]propionate (**5**) while back-flushing with nitrogen. The reaction was then allowed to warm slowly to room temperature and stirred for 24 h. The reaction was then cooled to 0 °C and filtered. The green solid obtained was dissolved in CH_2Cl_2, filtered through Celite to remove palladium metal, washed with saturated NH_4Cl, and dried over anhydrous magnesium sulfate. Removal of the solvent in vacuo afforded 1.58 g (78%) of **8**: mp 155–157 °C dec; ^1H NMR ($CDCl_3$) δ 0.8–1.8 (6 H, m), 2.35–3.2 (8 H, m), 3.68 (3 H, s, OCH_3), 6.62 (1 H, d, J = 3.5 Hz, thienyl), 6.98 (1 H, d, J = 3.5 Hz, thienyl); IR (KBr) 1740 (C=O), 1170 (CO) cm^{-1}. Anal. Calcd for $C_{15}H_{19}O_2SPdCl$: C, 44.46; H, 4.73; O, 7.90; S, 7.91. Found: C, 44.65; H, 4.82; O, 8.15; S, 8.04.

Compound 6: 67% yield; mp 165 °C dec; ^1H NMR ($CDCl_3$) δ 1.1–1.6 (6 H, m), 1.9–2.15 (1 H, m), 2.6 (2 H, m), 3.05 (1 H, d, J = 8 Hz), 3.75 (3 H, s, OCH_3), 6.25 (1 H, d, J = 16 Hz, =CHCO), 6.75 (1 H, d, J = 7 Hz, thienyl), 7.2 (1 H, d, J = 7 Hz, thienyl), 7.6 (1 H, d, J = 16 Hz, HC=CCO); IR (KBr) 1720 (C=O), 1160 (CO), 980 [(*E*)-C=C] cm^{-1}. Anal. Calcd for $C_{15}H_{17}O_2SPdCl$: C, 44.68; H, 4.25; O, 7.96; S, 7.94. Found: C, 44.90; H, 4.32; O, 8.02; S, 8.03.

Synthesis of Compound 10. (Norbornadiene)palladium dichloride (1.51 g, 5.61 mmol) was stirred in 40 mL of acetonitrile and the resultant mixture cooled to 0 °C under nitrogen. Methyl 3-[5-(chloromercurio)-2-thienyl]propionate (**5**; 2.27 g, 5.60 mmol) was added while back-flushing with nitrogen. The reaction was allowed to slowly warm to room temperature and stirred for 8 h. The reaction was then cooled to 0 °C and filtered. The green solid was dissolved in methylene chloride, treated with charcoal, filtered through Celite, and evaporated in vacuo to afford 1.67 g (74%) of **10**: mp 181–182 °C dec; ^1H NMR ($CDCl_3$) δ 1.45 (2 H, br s), 1.6–1.9 (2 H, m), 1.9–2.1 (2 H, m), 2.2–2.5 (2 H, m), 2.5–3.2 (4 H, m, CH_2CH_2), 3.72 (3 H, s, OCH_3), 6.73 (2 H, s, thienyl): IR (KBr) 1740 (C=O), 1170 (CO), 810 (nortricyclene ring system) cm^{-1}. Anal. Calcd for $C_{15}H_{17}O_2SPdCl$: C, 44.69; H, 4.25. Found: C, 44.56; H, 4.53.

Synthesis of Compounds 7, 9, and 11. The synthesis of compound **7** is representative. Compound **6** (406 mg, 1.008 mmol) and 176 mg of silver acetate (1.06 mmol) were stirred for 1 h in 10 mL of chloroform. The suspension was then filtered through Celite to remove AgCl. (Hexafluoroacetyl)acetone (0.27 g, 1.3 mmol) was added, and the yellow solution was stirred for 30 min. The solvent was then removed in vacuo to afford 568 mg (98%) of compound **7** as a yellow brown oil.

Reaction of Compounds 7, 9, and 11 with 1-Lithio-3-[(2-tetrahydropyranyl)oxy]-1-octyne. The reaction of compound **7** is representative. 3-[(2-Tetrahydropyranyl)oxy]-1-octyne (196.6 mg, 0.935 mmol) was dissolved in 5 mL of THF and the resultant mixture cooled to −78 °C under nitrogen. The acetylene was deprotonated by adding 0.40 mL (0.908 mmol) of 2.27 N *n*-butyllithium and stirring for 1 h at −78 °C. Compound **7** (499 mg, 0.868 mmol) and 456 mg (1.74 mmol) of triphenylphosphine were stirred for 30 min in 8 mL of THF at room temperature under nitrogen and then cooled to −78 °C. The solution of the lithium acetylide was then transferred via stainless-steel cannula to the cold solution of the palladium complex. This was stirred at −78 °C for 1 h and then allowed to slowly warm to room temperature overnight. The reaction was then quenched with 1 mL of CH_3OH. The solvent was then removed in vacuo and the residue extracted with three 25-mL portions of hexanes. The extract was filtered through Celite, concentrated, and purified by chromatography on silica gel using 29:1 benzene/ethyl acetate as eluent to afford 311 mg (77%) of compound **12**: R_f 0.29; ^1H NMR ($CDCl_3$) δ 0.8–2.2 (23 H, m), 2.3–3.6 (6 H, m), 3.72 (3 H, s, OCH_3), 4.08 (1 H, m, C≡CCHOR), 4.51 (1 H, br s, OCHO), 6.04 (1 H, d, J = 16 Hz, (*E*)-C=CHCO), 6.69 (1 H, d, J = 3.5 Hz, thienyl), 7.00 (1 H, d, J = 3.5 Hz, thienyl), 7.65 (1 H, d, J = 16 Hz, (*E*)-CH=CCO).

Compound 13: 68% yield; R_f 0.51, 9:1 benzene/ethyl acetate; ^1H NMR ($CDCl_3$) δ 0.7–2.3 (23 H, m), 2.35–3.6 (8 H, m), 3.68 (3 H, s, OCH_3), 4.0 (1 H, m, C≡CCHOR), 4.55 (1 H, m, OCHO), 6.51 (2 H, s, thienyl).

Compound 14: 75% yield; R_f 0.28; 7:1 hexanes/ethyl acetate; ^1H NMR ($CDCl_3$) δ 0.6–1.7 (25 H, m), 2.1–2.8 (4 H, m), 2.9–3.15 (2 H, m), 3.68 (3 H, s, OCH_3), 3.75–4.0 (1 H, m, C≡CCHOR), 4.6–4.7 (1 H, m, OCHO), 6.45–6.75 (2 H, m, thienyl).

Synthesis of Compounds 15–17. The synthesis of compound **15** is representative. Compound **12** (230 mg, 0.489 mmol) and 5 mg of *p*-TsOH were stirred in 10 mL of CH_3OH for 6 h. The solution was diluted with benzene, washed with 2 N $KHCO_3$ and water, and dried over sodium sulfate. Chromatography on silica gel using 9:1 benzene/ethyl acetate as eluent afforded compound **15**: 148 mg (83%); R_f 0.27; ^1H NMR ($CDCl_3$) δ 0.7–2.2 (16 H, m), 2.45 (2 H, br s), 2.75 (1 H, dt, J = 2 and 8 Hz), 3.12 (1 H, d, J = 9 Hz), 3.73 (3 H, s, OCH_3), 4.00 (1 H, br s, C≡CCHO), 6.00 (1 H, d, J = 16 Hz, (*E*)-C=CHCO), 6.66 (1 H, d, J = 4 Hz, thienyl), 6.97 (1 H, d, J = 4 Hz), 7.60 (1 H, d, J = 16 Hz, (*E*)-CH=CCO); IR ($CHCl_3$) 3600 (OH), 1710 (C=O), 1620 (C=C), 1160 (CO) cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 167.32, 151.46, 137.54, 136.96, 130.65, 125.77, 115.04, 85.50, 62.43, 51.50, 48.06, 44.35, 43.38, 42.21, 37.78, 36.09, 31.54, 30.30, 27.90, 24.65, 22.57, 19.98; MS for $C_{23}H_{30}O_3S$, m/z calcd 386.19157, found 386.19013.

Compound 16: 85% yield; R_f 0.34 (9:1 benzene/ethyl acetate); ^1H NMR ($CDCl_3$) δ 0.7–2.2 (18 H, m), 2.3–3.5 (8 H, m), 3.68 (3 H, s, OCH_3), 4.05 (1 H, m, C≡CCHO), 6.55 (2 H, s, thienyl); IR ($CHCl_3$) 3600 (OH), 2240 (C≡C), 1740 (C=O), 1175 (CO) cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 172.72, 145.41, 140.21, 123.95, 123.36, 85.97, 85.45, 62.23, 51.57, 47.73, 44.29, 43.38, 42.21, 37.72, 35.90, 31.48, 30.30, 27.90, 25.30, 24.71, 22.57, 13.98; MS for $C_{23}H_{32}O_3S$, m/z calcd 388.20722, found 388.20905.

Compound 17: 83% yield; R_f 0.32 (3.4:1 hexanes/ethyl acetate); ^1H NMR ($CDCl_3$) δ 0.9–1.02 (3 H, t, J = 4 Hz, CH_3), 1.1–1.8 (17 H, m), 2.25–2.8 (4 H, m), 3.0–3.25 (3 H, m), 3.70 (3 H, s, OCH_3), 3.9 (1 H, br s, C≡CCHO), 6.62 (1 H, d, J = 4 Hz, thienyl), 6.73 (1 H, dd, J = 1 and 4 Hz, thienyl); IR ($CHCl_3$) 1730 (C=O) cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 172.72, 145.08, 141.44, 124.34, 123.43, 84.34, 62.10, 51.63, 45.52, 41.68, 41.55, 37.59, 35.77, 34.66, 34.53, 31.54, 25.43, 24.91, 22.63, 16.06, 14.83, 14.05, 11.58; MS for $C_{23}H_{30}O_3S$, m/z, calcd 386.19157, found 386.19258.

Synthesis of Compounds 18–20. The procedure for compound **18** is representative. Hydroxy ester **15** (112 mg, 0.290 mmol) was stirred for 2 h in 5 mL of methanol and 1 mL of 2 N KOH and then refluxed for 30 min. Upon cooling, the reaction was diluted with ether, washed with 2 N H_2SO_4 and water, and dried over sodium sulfate. After evaporation of the solvent in vacuo, the residue was chromatographed on silica gel [1:1 hexanes/ethyl acetate, R_f 0.26] to afford 104 mg (96%) of compound **18**: ^1H NMR ($CDCl_3$) δ 0.8–2.2 (19 H, m), 2.3–2.66 (2 H, br s), 2.8 (1 H, d, J = 9 Hz), 3.2 (1 H, d, J = 9 Hz), 4.08 (1 H, m, C≡CCHO), 6.07 (1 H, d, J = 16 Hz, (*E*)-C=CHCO), 6.6–7.2 (4 H, m, thienyl, OH), 7.75 (1 H, d, J = 16 Hz, CH=CCO); IR ($CHCl_3$) 1670 (C=O), 1615 (C=C), 1205 (CO) cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 172.06, 152.39, 139.50, 136.79, 131.37, 126.01, 114.63, 85.65, 62.52, 48.11, 44.42, 43.45, 42.26, 37.76, 36.13, 31.53, 30.28, 27.90, 24.70, 22.59, 14.03; MS for $C_{22}H_{28}O_3S$, m/z calcd 372.17593, found 372.17406.

Compound 19: 82% yield; R_f 0.26 (1:1 hexanes/ethyl acetate); ^1H NMR ($CDCl_3$) δ 0.85 (3 H, t, J = 4 Hz, CH_3), 1.05–2.2 (14 H, m), 2.3–3.5 (8 H, m), 4.10 (1 H, m, C≡CCHO), 6.38 (2 H, s, OH), 6.60 (2 H, s, thienyl); IR ($CHCl_3$) 3580 (OH), 1720 (C=O), 1120 (CO) cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 177.27, 145.41, 140.14, 124.01, 123.49, 86.43, 84.93, 62.49, 47.73, 44.35, 43.44, 42.27, 37.59, 36.03, 35.83, 31.48, 30.30, 27.96, 25.10, 24.71, 22.57, 13.98; MS for C_{22}-

$H_{30}O_3S$, m/z calcd 374.19157, found 374.19307.

Compound 20: 86% yield; R_f 0.37 (1:1 hexanes/ethyl acetate); ^1H NMR ($CDCl_3$) δ 0.9 (3 H, t, J = 4 Hz, CH_3), 1.1–1.9 (14 H, m), 2.2–3.1 (6 H, m), 3.9 (1 H, m, C≡CCHO), 6.5–6.8 (4 H, m, thienyl, OH); IR (neat) 3400 (br) (OH), 2240 (C≡C), 1740 (C=O) cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 177.40, 145.02, 141.18, 124.34, 123.49, 96.18, 84.54, 62.23, 45.52, 41.62, 41.49, 37.46, 35.64, 34.73, 34.53, 31.54, 25.17, 24.84, 22.63, 16.06, 14.83, 14.05, 11.51; MS for $C_{22}H_{26}O_2S$ ($M^{\cdot+} - H_2O$), m/z calcd 354.16535, found 354.16579.

Synthesis of Compound 21. Compound **6** (143.3 mg, 0.356 mmol) was stirred under nitrogen with 191 mg (0.727 mmol) of triphenylphosphine in 6 mL of THF for 30 min. To this was added a solution of 199.8 mg (0.376 mmol) of (*E*)-1-(tri-*n*-butylstannyl)-3-[(triethylsilyl)oxy]-1-octene in 1 mL of THF. After 24 h at room temperature there had been essentially no change in the reaction, as determined by TLC analysis, so the reaction was refluxed for 24 h. Upon cooling, the reaction was diluted with ether, washed with saturated NH_4Cl, and concentrated on a rotary evaporator. Chromatography afforded 58 mg (34%) of compound **21** as a mixture of disastereomers, which are not readily separable: R_f 0.32 and 0.27 (benzene); ^1H NMR ($CDCl_3$) δ 0.8–2.5 (48 H, m), 3.80 (3 H, s, OCH_3), 4.05 [1 H, m, $CH(OSiEt_3)$], 5.5–7.1 (3 H, m, vinyl, =CHCO), 7.35 (2 H, s, thienyl), 7.7 (1 H, d, J = 16 Hz, CH=CCO).

Synthesis of Compound 22. (*E*)-1-Lithio-3-[(*tert*-butyldimethylsilyl)oxy]-1-octene was prepared from the iodide by Corey's method.[24] Copper(I) iodide (108.2 mg, 0.569 g) was suspended in 5 mL of THF under nitrogen and the resultant mixture cooled to −78 °C whereupon 1.13 mmol of the organolithium compound at −78 °C was added via cannula. The resulting solution was stirred for 1 h at −78 °C. Compound **9** (293 mg, 0.508 mmol) and 135 mg (0.513 mmol) of triphenylphosphine were stirred under nitrogen in 10 mL of THF. After 3 min the solution containing the palladium complex was cooled to −78 °C, and the −78 °C solution of the cuprate was added via cannula. The reaction was then allowed to slowly warm to room temperature overnight. The reaction was then quenched with 1 mL of methanol and the solvent removed in vacuo. The black residue that remained was extracted with three 25-mL portions of hexanes. The extracts were then filtered through Celite and concentrated to give 270 mg of a yellow oil. Purification by flash chromatography using 14:1 hexanes/ethyl acetate as eluent afforded 80.0 mg (31%) of compound **22** and 78.0 mg (51%) of reduction product, R_f 0.27. Compound **22**: R_f 0.37; ^1H NMR ($CDCl_3$) δ 0.12 (6 H, s, $SiCH_3$), 0.8–2.0 (27 H, m), 2.1–3.4 (8 H, m), 3.80 (3 H, s, OCH_3), 3.90 (1 H, m, CHOSi), 5.1–5.25 (2 H, m, vinyl), 6.6 (2 H, br s, thienyl).

Synthesis of Compound 24 from Compound 22. Compound **22** (152 mg, 0.30 mmol) was stirred for 12 h in 5 mL of a 3:1:1 mixture of acetic acid/THF/water. The reaction was then diluted with ether, washed with saturated $NaHCO_3$ and brine, and dried over $MgSO_4$. After being concentrated, the residue was purified by flash chromatography using 3.4:1 hexanes/ethyl acetate as the eluent to afford 91 mg (77%) of compound **24**: R_f 0.35; ^1H NMR ($CDCl_3$) δ 0.8–2.2 (18 H, m), 2.3–3.2 (8 H, m), 3.67 (3 H, s, OCH_3), 3.7–3.85 (1 H, m, CHO), 5.1–5.3 (2 H, m, vinyl), 6.4–6.6 (2 H, m, thienyl); IR ($CHCl_3$) 1730 (C=O), 1190 (CO) cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 172.70, 145.28, 140.14, 133.19, 132.86, 123.62, 72.77, 51.76, 51.57, 48.71, 43.70, 43.38, 42.73, 37.00, 36.74, 35.96, 35.31, 31.80, 30.37, 28.81, 28.68, 25.30, 25.04, 24.84, 22.50, 13.98; MS for $C_{23}H_{34}O_3S$, m/z calcd 390.22288, found 390.22283.

Synthesis of (*E*)-3-[(2-Tetrahydropyranyl)oxy]-1-iodo-1-octene. Dihydropyran (1.30 g, 19.1 mmol) and 4.70 g (18.5 mmol) of (*E*)-1-iodo-1-octen-3-ol were stirred for 20 h with 2 drops of concentrated HCl. The reaction was then diluted with ether, washed twice with saturated $NaHCO_3$, and dried over $MgSO_4$. Purification by flash chromatography with 14:1 hexanes/ethyl acetate afforded 3.95 g (63%) of (*E*)-3-[(2-tetrahydropyranyl)-oxy]-1-iodo-1-octene: R_f 0.42; ^1H NMR ($CDCl_3$) δ 0.8–1.8 (17 H, m), 3.2–4.1 (4 H, m), 4.6 (1 H, br s, OCHO), 6.2–6.5 (2 H, m, vinyl).

Synthesis of Compound 23. (*E*)-3-[(2-Tetrahydropyranyl)-oxy]-1-iodo-1-octene (1.57 g, 4.65 mmol) was lithiated with 9.03 mmol of *tert*-butyllithium in 18 mL of ether at −78 °C for 3 h. This solution was added to a −78 °C suspension of copper(I) iodide (419 mg, 2.20 mmol) in 20 mL of THF and stirred for 1 h to form the cuprate. Compound **9** (1.165 g, 2.02 mmol) and 1.05 g (4.01 mmol) of triphenylphosphine were stirred in 20 mL of THF for 30 min and the resultant mixture then cooled to −78 °C. The solution of the cuprate was then added and the mixture allowed to slowly warm to room temperature overnight. After the mixture was quenched with 1 mL of methanol, the THF was removed in vacuo and the product extracted with three 25-mL portions of hexanes. The hexane extract was filtered and concentrated to afford 1.26 g of residue. This was purified by chromatography to give 440 mg (55%) of compound **23**: R_f 0.28 (8:1 hexanes/ethyl acetate); ^1H NMR ($CDCl_3$) δ 0.9 (3 H, t, J = 5 Hz, CH_3), 1.0–2.2 (22 H, m), 2.3–2.7 (3 H, m), 2.8–3.2 (3 H, m), 3.3–3.6 (2 H, m, CH_2O), 3.65 [4 H, s, OCH_3 and CH(OTHP)], 4.5–4.7 (1 H, br m, OCHO), 5.0–5.3 (2 H, m, vinyl), 6.3–6.5 (2 H, m, thienyl).

Synthesis of Compound 24 from Compound 23. Compound **23** (304 mg, 0.640 mmol) and 5 mg of *p*-TsOH were stirred in 10 mL of methanol for 14 h. The mixture was then diluted with ether, washed with brine, and dried over $MgSO_4$. The residue was purified by flash chromatography to give 151 mg (61%) of compound **24**.

Synthesis of Compound 25. Compound **24** (105 mg, 0.268 mmol) was refluxed for 30 min in 8 mL of methanol and 2 mL of 2 N KOH. Upon cooling, the reaction was diluted with ether, acidified with 50 mL of 2 N H_2SO_4, washed with brine, and dried over $MgSO_4$. Purification by chromatography with 30:15:1 hexanes/ethyl acetate/glacial acetic acid afforded 78 mg (77%) of compound **25**: R_f 0.31 (30:15:1 hexanes/ethyl acetate/acetic acid); ^1H NMR ($CDCl_3$) δ 0.9 (3 H, t, J = 5 Hz, CH_3), 1.1–2.3 (19 H, m), 2.3–2.85 (2 H, m), 3.05 (2 H, t, J = 9 Hz, CH_2CO), 3.7–3.9 (1 H, m, CHOH), 5.1–5.3 (2 H, m, vinyl), 6.4–6.8 (4 H, m, aryl, OH, CO_2H); IR (neat) 1720 (C=O), 965 (C=C) cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 176.88, 145.28, 140.08, 133.77, 133.12, 132.60, 132.21, 123.69, 72.96, 51.83, 48.64, 43.83, 43.25, 43.12, 42.60, 36.87, 36.68, 36.03, 35.38, 34.73, 31.80, 30.43, 28.88, 25.17, 24.84, 22.57, 14.11; MS for $C_{23}H_{32}O_3S$, m/z calcd 376.20722, found 376.20584.

Synthesis of Compound 26. Compound **8** (1.28 g, 3.16 mmol) and 0.83 g (6.4 mmol) of diisopropylethylamine were dissolved in 30 mL of THF and the resultant mixture stirred under nitrogen for 10 min. The flask was then flushed with CO and stirred for 40 min. Triphenylphosphine (1.66 g, 6.33 mmol) was added, and the reaction was stirred for 30 min. Tri-*n*-butyltin hydride (1.10 g, 3.78 mmol) was then added, and the reaction was stirred for 1 h. THF was removed in vacuo, and the product was extracted with 200 mL of hexanes. Filtration through Celite and removal of the solvent on a rotary evaporator gave 1.9 g of residue that was purified by flash chromatography to afford 0.97 g (100%) of compound **26**: R_f 0.30 (4:1 hexanes/ethyl acetate); ^1H NMR ($CDCl_3$) δ 0.8–2.0 (7 H, m), 2.2–2.6 (4 H, m), 2.7–3.35 (3 H, m), 3.65 (3 H, s, OCH_3), 6.53 (2 H, s, thienyl), 9.13 (1 H, d, J = 3 Hz, CHO); IR (neat) 2710 (CHO), 1740 (CO_2CH_3), 1720 (CHO) cm^{-1}; MS for $C_{16}H_{20}O_3S$, m/z calcd 292.11320, found 292.11362.

Synthesis of Compound 27. Sodium hydride (170 mg, 4.77 mmol; 67% dispersion in mineral oil) was washed with three 5-mL portions of hexanes under nitrogen and then suspended in 45 mL of DME. Dimethyl (2-oxoheptyl)phosphonate (1.15 g, 5.18 mmol) in 5 mL of DME was added via syringe and the resultant mixture stirred for 1 h. Compound **26** (924 mg, 3.16 mmol) in 5 mL of DME was added, and the reaction was stirred for 3 h at room temperature. After quenching with 0.5 mL of acetic acid, the solvent was removed in vacuo. The product was extracted with 100 mL of hexanes and filtered through Celite. Flash chromatography of the residue gave 1.05 g (86%) of compound **27**: R_f 0.29 (6:1 hexanes/ethyl acetate); ^1H NMR ($CDCl_3$) δ 0.83 (3 H, t, J = 5 Hz, CH_3), 1.0–1.9 (12 H, m), 1.9–2.8 (7 H, m), 2.8–3.3 (3 H, m), 3.60 (3 H, s, OCH_3), 5.67 (1 H, d, J = 16 Hz, (*E*)-C=CHC=O), 6.18 (1 H, dd, J = 7 and 16 Hz, (*E*)-CH=CC=O), 6.37 (2 H, s, thienyl); IR (neat) 1740 (CO_2CH_3), 1680 (C=O), 1630 (*trans*-C=C), 980 (*trans*-C=C) cm^{-1}.

Reduction of Enone 27 to Compound 24. Compound **27** (190 mg, 0.90 mmol) was dissolved in 10 mL of THF under nitrogen and the resultant mixture cooled to 0 °C. 9-BBN (65.0 mg, 0.533 mmol; Aldrich) was added, and the reaction was stirred for 3 h at 0 °C. Methanol (0.5 mL) was added to hydrolyze excess hydride, and the solvent was removed in vacuo. The residue was taken up in 25 mL of pentane and treated with 34 mg (0.56 mmol) of ethanolamine to complex the boron. After filtration, the solution was then washed with three 25-mL portions of water and three 25-mL portions of brine. Purification by flash chroma-

tography afforded 182 mg (95%) of allylic alcohol **24**, identical in all respects with that prepared previously.

Synthesis of Compounds 29 and 30 by Raney Nickel Hydrogenation. The procedure for the synthesis of compound **30** is representative. Compound **17** (180 mg, 0.466 mmol) and Raney nickel W-7 prepared from 2.5 g of alloy[28] were shaken in 40 mL of absolute ethanol in a Parr shaker under 60 psi of hydrogen for 48 h. The mixture was then diluted with ether, filtered, washed twice with brine, and dried over $MgSO_4$. Flash chromatography afforded 141 mg (83%) of compound **30**: R_f 0.35 (4:1 hexanes/ethyl acetate); ^1H NMR ($CDCl_3$) δ 0.88 (3 H, t, J = 5 Hz, CH_3), 1.2–1.9 (31 H, m), 2.3 (2 H, t, J = 7 Hz, CH_2CO), 3.7 (4 H, s, overlapping peaks, OCH_3, C*H*OH); IR (neat) 3430 (OH), 1740 (C=O) cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 174.14, 72.02, 71.06, 51.27, 46.34, 37.68, 36.81, 36.21, 33.99, 31.88, 30.69, 29.60, 29.33, 29.06, 26.73, 26.62, 25.27, 24.84, 22.56, 15.30, 13.95, 11.40; MS for $C_{23}H_{40}O_3$, m/z calcd 364.29775, found 364.29664.

Compound 29: 82% yield; R_f 0.37 (4:1 hexanes/ethyl acetate); ^1H NMR ($CDCl_3$) δ 0.9 (3 H, t, J = 6 Hz, CH_3), 1.1–1.9 (30 H, m), 1.9–2.1 (3 H, br s), 2.3 (2 H, t, J = 7 Hz, CH_2CO), 3.7 (4 H, s, overlapping peaks, OCH_3, C*H*OH); IR (neat) 3420 (OH), 1740 (C=O) cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 174.22, 72.38, 72.05, 51.31, 46.82, 46.56, 40.77, 37.78, 37.52, 37.39, 34.01, 32.65, 31.86, 29.91, 29.52, 29.13, 25.75, 25.56, 25.30, 24.91, 22.57, 13.98; MS for $C_{23}H_{42}O_3$, m/z calcd 366.31340, found 366.31398.

Synthesis of Compounds 31 and 32. The synthesis of compound **31** is representative. Compound **29** (125 mg, 0.342 mmol) was refluxed for 30 min in 10 mL of a 4:1 mixture of methanol and 2 N KOH. Upon cooling, the reaction was diluted with ether, acidified with 10 drops of concentrated HCl, washed with brine, and dried over $MgSO_4$. Purification by chromatography afforded 104 mg (86%) of compound **31**: R_f 0.43 (1:1 hexanes/ethyl acetate); ^1H NMR ($CDCl_3$) δ 0.95 (3 H, t, J = 7 Hz, CH_3), 1.2–1.8 (30 H, m), 2.0 (2 H, br s), 2.37 (2 H, t, J = 7 Hz, CH_2CO), 3.7 (1 H, m, C*H*OH), 6.35 (2 H, br s, OH, CO_2H); IR (neat) 3410 (OH), 1720 (C=O) cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 179.16, 72.77, 72.38, 46.95, 46.63, 40.90, 37.78, 37.46, 34.08, 32.78, 31.93, 30.04, 29.52, 29.00, 25.95, 25.56, 25.36, 24.71, 22.70, 14.05; MS for $C_{22}H_{38}O_2$ ($M^{\cdot+} - H_2O$), m/z calcd 334.28718, found 334.28753.

Compound 32: 95% yield; R_f 0.39 (1:1 hexanes/ethyl acetate); ^1H NMR ($CDCl_3$) δ 0.8–1.1 (3 H, t, J = 7 Hz, CH_3), 1.2–2.1 (30 H, m), 2.3 (2 H, t, J = 6 Hz, CH_2CO), 3.5–3.7 (1 H, m, C*H*OH), 6.5 (2 H, br s, OH, CO_2H); IR (neat) 3400 (OH), 1730 (C=O) cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 178.90, 72.31, 46.50, 37.59, 37.33, 37.07, 36.35, 34.08, 32.00, 30.63, 29.59, 29.26, 28.81, 26.79, 25.36, 24.65, 22.70, 15.41, 15.22, 14.05, 11.51; MS for $C_{22}H_{36}O_2$ ($M^{\cdot+} - H_2O$), m/z calcd 332.27153, found 332.27232.

Acknowledgment. We gratefully acknowledge the National Institutes of Health and the American Heart Association, Iowa Affiliate, for financial support; Proctor and Gamble for fellowship support for D.R.L.; Johnson Matthey Inc. and Engelhard Industries for generous loans of palladium salts; and Bristol Laboratories of Syracuse, NY, for carrying out the biological testing.

Synthesis of Optically Pure Enantiomers of Grandisol

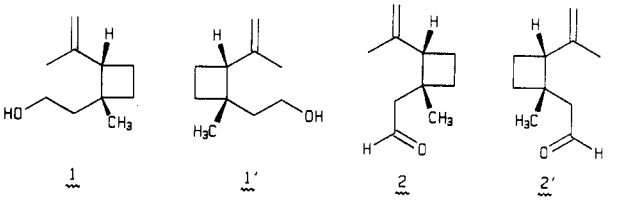
Francis X. Webster and Robert M. Silverstein*

State University of New York, College of Environmental Science and Forestry, Syracuse, New York 13210

Received July 30, 1986

The synthesis of both enantiomers of grandisol (**1** and **1'**) of greater than 99% optical purity is described. The key step is the separation of diastereomeric amides **11** and **12** and subsequent cleavage to give optically pure acids **8** and **8'**. Since **8** and **8'** contain a quaternary chiral center, the optical purity of derived grandisol **1** and **1'** is ensured.

Work in our laboratories has been directed at determining the composition of aggregating pheromones for several bark weevils of the genus *Pissodes* Germar. *P. strobi*, the white pine weevil, is notorious among forest insects for its deformation of pines and spruces throughout North America.[1] The northern pine weevil, *P. approximatus*, is not as economically important as *P. strobi*, although larvae may kill stressed trees and intense feeding by adults may be injurious to small trees.[2] The first evidence of an aggregation pheromone was reported by Booth and Lanier.[3] Subsequently, the suspected pheromone components for both species have been isolated and identified.[4] These components are the same for both species, namely, grandisol (*cis*-2-isopropenyl-1-methylcyclobutaneethanol) (**1** and **1'**) and grandisal (the corresponding aldehyde) (**2** and **2'**). Grandisol (**1** and **1'**) is well-known as one of the components of the aggregation pheromone of the cotton boll weevil (*Anthonomus grandis*).[5] In field tests, synthetic, racemic grandisol and



1 **1'** **2** **2'**

grandisal, along with suitable host material (red pine bolt), attracted beetles in numbers statistically identical with those of caged males (natural source of pheromone) for *P. approximatus*.[4] *P. strobi*, however, did not respond to the synthetic racemic compounds. Since the importance of optically pure semiochemicals has been well established,[6] we considered the possibility that *P. strobi* produces and responds to a single enantiomer or a specific blend of enantiomers.

Since chromatographic and spectrometric methods of determining the enantiomeric composition of grandisol by

(1) (a) MacAloney, H. J. *N. Y. State Coll. For. Syracuse Univ., Tech. Publ.* **1930**, *3*, 1. (b) Taylor, R. L. *Entomol. Am.* **1930**, *9*, 167.
(2) Finnegan, R. J. *Can. Entomol.* **1958**, *90*, 348.
(3) Booth, D. C.; Lanier, G. N. *Ann. Entomol. Soc. Am.* **1974**, *67*, 992.
(4) Booth, D. C.; Phillips, T. W.; Claesson, A.; Silverstein, R. M.; Lanier, G. N.; West, J. R. *J. Chem. Ecol.* **1983**, *9*, 1.
(5) Tumlinson, J. H.; Hardee, D. D.; Gueldner, R. C.; Thompson, A. C.; Hedin, P. A.; Minyard, J. P. *Science (Washington, D.C.)* **1969**, *166*, 1010.
(6) Silverstein, R. M. In *Chemical Ecology: Odour Communication in Animals*; Ritter, F. F. Ed.; Elsevier/North Holland: Amsterdam, 1979; pp 133–158.

0022-3263/86/1951-5226$01.50/0