Chemical shift values are referenced to internal $CHCl_3$. Pig liver esterase (PLE EC 3.1.1.1 of type I) and crude porcine pancreatic lipase (PPL EC 3.1.1.2 of type II) were obtained from Sigma Chemical Co. and used without further purification.

General Preparation of (±)-2 and 3. To a dry THF (50 mL) solution of LDA, prepared from diisopropylamine (3.4 g, 30 mmol) and *n*-butyllithium (hexane 2.5 M solution, 12.6 mL, 31.5 mmol) was added a THF solution (8 mL) of methyl acetoacetate (1.74 g, 15 mmol) at about −78 °C under a nitrogen atmosphere. After the solution became dark red (15 min), a THF solution (6 mL) of the corresponding aldehyde (15 mmol) was added. The solution was then stirred for 20 min at −78 °C and, after TLC monitoring, quenched with a 2 N HCl solution. The mixture was then extracted with CH_2Cl_2, and the organic layer was dried over Na_2SO_4. Concentration of the solvents in vacuo afforded the crude aldols of type B (see Scheme I), which were purified by flash chromatography on silica gel.

The aldols of type B were then subjected to the diastereoselective reduction according to ref 7b.

To a THF (10 mL) solution of the aldol B (1 mmol) at about −80 °C and under a nitrogen atmosphere, $Ti(Oi\text{-}Pr)_4$ (1.1 mmol) was added, the solution was stirred for 30 min, and then an excess of $NaBH_4$ (5 mmol) was added. The reaction was completed in 1.5 h (TLC monitoring), and the mixture was then quenched with saturated NH_4Cl solution. All the organic solvents were then removed in vacuo, and the residue was extracted with AcOEt (four times). The organic layers were dried over Na_2SO_4 and concentrated in vacuo affording crude mixture of syn–anti diols (95:5), which were separated by flash chromatography. The overall yield of the two reactions was of 61% for compound **2** and of 57% for compound **3**.

Compound 2: white solid; mp 32–34 °C; ^1H NMR 1.4–1.6 (m, 2 H), 1.6–1.8 (m, 2 H), 2.38 (dd, CH_2CO, 2 H), 2.5–2.8 (m, CH_2Ph), 3.56 (s, OCH_3, 3 H), 3.73 (m, CHOH, 1 H), 4.18 (m, CHOH, 1 H), 4.4 (bs, OH, 2 H), 7.0–7.2 ppm (m, 5 H); IR (OH) 3500, (C=O) 1728 cm^{-1}. Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.63; H, 7.99. Found: C, 66.49; H, 8.03.

Compound 3: white gum; ^1H NMR 0.8–0.95 (m, 2 H), 1.0–1.4 (m, 6 H), 1.5–2.0 (m, 10 H), 2.5–2.6 (m, CH_2CO, 2 H), 3.2 (bs, OH, 1 H), 3.68 (s, OCH_3, 3 H), 3.82 (m, CHOH, 1 H), 4.26 ppm (m, CHOH, 1 H); IR (OH) 3500, (C=O) 1725 cm^{-1}. Anal. Calcd for $C_{14}H_{26}O_4$: C, 65.07; H, 10.15. Found: C, 65.01; H, 10.19.

General Procedure for Enzymatic Lactonization of Racemic 2 and 3 with Condition A (PLE). To the 3,5-dihydroxy esters **2** and **3** (0.54 mmol), suspended in a 10 mL of a 0.1 M phosphate buffer solution at pH 7.3, 30 μL of a PLE suspension in 3.2 M $(NH_4)_2SO_4$ solution were added. The addition of 1 M NaOH solution, monitored by a pH-stat (AMEL 234), proceeded until 0.4 equiv of base had been consumed (40% of conversion). The mixture was carefully acidified with 1 M HCl (pH 3–4) and immediately extracted with AcOEt (four times).

The organic layers were washed with brine until neutrality and then dried over Na_2SO_4 and concentrated in vacuo. The crude mixture was then purified by flash chromatography (hexanes/AcOEt, 1:1, as eluent), affording the starting dihydroxy esters **2–3** (R_f = 0.6, 51%) and the lactones **4–5** (R_f = 0.5, 40%) as white solids.

Compound 4 (3*S*,5*S*): white solid; mp 74–76 °C; ^1H NMR 1.8–2.2 (m, 4 H), 2.5–3.0 (m, 4 H), 1.0–1.5 (bs, OH, 1 H), 4.36 (bs, CHOH, 1 H), 4.68 (m, CHOR, 1 H), 7.1–7.3 ppm (m, 5 H); IR 1730 cm^{-1} (C=O lactone); $[\alpha]_D$ = −15.3° *c* = 3 g/100 mL).

Compound 5 (3*S*,5*S*): white solid; mp 70–71 °C [lit. mp 69–70.5 °C (ref 4)]; ^1H NMR 0.8–1.0 (m, 2 H), 1.0–1.5 (m, 6 H), 1.5–2.0 (m, 9 H), 2.5–2.7 (m, CH_2CO, 2 H), 3.0 (bs, OH, 1 H), 4.3 (m, CHOH, 1 H), 4.62 ppm (m, CHOR, 1 H); IR 1725 cm^{-1} (C=O lactone); $[\alpha]_D$ = −11.7° (*c* = 1.45 g/100 mL).

General Procedure for the Enzymatic Lactonization of Racemic 2–3 with Condition B (PPL). PPL (200 mg) was added to a solution of the racemic compounds **2–3** (0.8 mmol) in dry ether (10 mL), and the suspension was vigorously shaken at 100 rpm at room temperature in a tightly stoppered conical flask. The reaction progress was monitored both by HPLC and ^1H NMR measurements. After 96 h (40% of the conversion) the reaction was stopped by filtering off the enzyme and washing with AcOEt. The organic solvents were then removed in vacuo, and the crude mixture was then chromatographed (hexanes/AcOEt, 1:1, as eluent), affording the starting dihydroxy esters **2–3** (48%) and the resulting lactones **6–7** (35%), which have the same ^1H NMR and IR data of compounds **4** and **5**.

Compound 6: white solid; mp 74–76 °C; $[\alpha]_D$ = +51.3° (*c* = 0.73 g/100 mL) [lit. values $[\alpha]_D$ = +45.6° (ref 12b), $[\alpha]_D$ = +68.8° (ref 12c), $[\alpha]_D$ = +46.11° (ref 12d)].

Compound 7: white solid; mp 69–70 °C; $[\alpha]_D$ = +34.1° (*c* = 0.85 g/100 mL) [lit. value $[\alpha]_D$ = +29° (ref 12f)].

Determination of the Enantiomeric Excess for Lactones 4–7: Procedure for Compounds 6 and 7. To a solution of lactone (**6** or **7**) (15 mg, 0.065 mmol) in dry pyridine (2 mL) (−)-camphanic acid chloride (0.07 mmol) was added at −10 °C. The reaction, monitored by TLC, was stopped after 4 h, diluting the mixture in ether. The organic layer was washed with 2 N HCl and then with brine until neutrality. The reaction mixtures were analyzed by ^1H NMR and HPLC before and after being purified by silica gel chromatography, showing no difference in the diastereomeric ratio. Compounds **8a** and **8b** were then purified by flash chromatography (hexanes/AcOEt, 8:2, as eluent, R_f = 0.6) and analyzed by HPLC chromatography (Merck column RP 18, with CH_3CN/H_2O, 7:3, as eluent), showing a single peak. ^1H NMR values for **8a**: 0.92 and 1.03 ppm as the only geminal methyl signals detectable (ee >98%). ^1H NMR values for **8b**: 0.86 and 0.96 ppm as the only geminal methyl signals detectable (ee >98%).

The same (−)-camphanic derivatives **8a–b** were obtained in the described condition starting from racemic lactones **6** and **7** (easily prepared by standard conditions from **2** and **3**). ^1H NMR values for the (1:1) diastereomeric mixture of **8a**: 0.90, 0.92, 1.01, and 1.03 ppm for geminal methyl signals as singlets. ^1H NMR values for the (1:1) diastereomeric mixture of **8b** 0.85, 0.86, 0.94, and 0.96 ppm for geminal methyl signals as singlets.

Acknowledgment. This work was supported by MURST, progetto "Sintesi e reattività organica"; we also thank CNR, Centro per lo Studio della Chimica delle Sostanze Organiche Naturali, Università "La Sapienza" Roma, for financial and technical assistance.

A New, Versatile Method for the Modification of Synthetic Pyrethroids: Regio- and Stereoselective Monoarylation and Heteroarylation of (2,2-Dihaloethenyl)cyclopropanecarboxylates Catalyzed by Palladium–Phosphine Complexes[1]

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The esters of (2,2-dihaloethenyl)cyclopropanecarboxylic acid (**1**) represented by permethrin (**1a**),[2] cypermethrin,[3] and deltamethrin (**1b**)[4] make up the most important part of the present household and agricultural insecticides. In the modification[5] of these synthetic pyrethroids, effort has chiefly been directed toward alcoholic parts while the acidic part, especially the dihaloethenyl moiety, has remained relatively unexplored.

Nevertheless, flumethrin (**2**),[6] a representative of pyrethroids having a partially modified ethenyl moiety,

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(3) Elliott, M.; Farnham, A. W.; Janes, N. F.; Needham, P. H.; Pulman, D. A. *Pestic. Sci.* **1975**, *6*, 537.

(4) Elliott, M.; Farnham, A. W.; Janes, N. F.; Needham, P. H.; Pulman, D. A. *Nature (London)* **1974**, *248*, 710.

(5) Elliott, M.; Janes, N. F. *Chem. Soc. Rev.* **1978**, *7*, 473.

(6) Fuchs, R. A.; Hammann, I.; Stendel, W. Ger. Offen. 2, 730, 515; *Chem. Abstr.* **1979**, *90*, 151658e.

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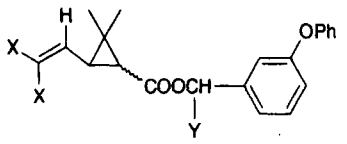
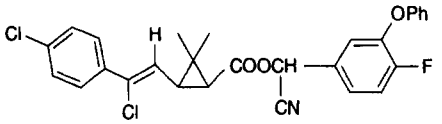


X = Cl or Br, Y = H or CN

1

1a; X = Cl, Y = H (racemic mixture)

1b; X = Br, Y = CN(1R,(1α)-S)

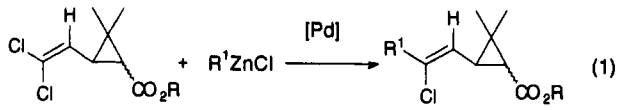


2

(Z)-R(Cl)C=CH—,[7] instead of Cl_2C=CH—, has already been commercialized. Recently, cyhalothrin[7a,b] and bifenthrin,[7c] which contain a (Z)-CF_3(Cl)C=CH— group, have also been found to exhibit more potent activity than the parent pyrethroids. They have been prepared mainly by traditional methods[8] used for permethric acid synthesis, e.g., Wittig–Horner olefination[9] of 3-formyl-2,2-dimethylcyclopropanecarboxylates, cyclopropanation of substituted dienes with diazoacetate,[7a,10] and ring closure reaction of 4-chloro-[11] or 4-alkenyl-3,3-dimethylalkanoic acid esters.[12] Unfortunately, all the previous methods require multistep operations and suffer from poor stereocontrol of the double bond[13] and/or of the cyclopropane ring.

We anticipated that a *direct* modification of the dihaloethenyl part of commercial pyrethroids should provide a shortcut to partially modified pyrethroids, but such an approach has not appeared so far.

Described herein is a new and versatile method for the *direct* and *stereoselective* conversion of (2,2-dihaloethenyl)dimethylcyclopropanecarboxylate into [(Z)-2-substituted-2-haloethenyl]dimethylcyclopropanecarboxylate by a palladium–phosphine complex catalyzed monocoupling reaction (eq 1).[14]



(1)

The representative results are shown in Table I. Typically, when ethyl *trans*-3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropanecarboxylate (3) was allowed to react with 1.1 equiv of phenylzinc chloride[16] at ambient temperature for 5 h in the presence of 1 mol % of [$PdCl_2$(dppb)], dppb = $Ph_2P(CH_2)_4PPh_2$, regio- and stereoselective monocoupling occurred to give ethyl *trans*-3-[(Z)-2-chloro-2-phenylethenyl]-2,2-dimethylcyclopropanecarboxylate (7)[17] in 91% yield (entry 1). The cyclopropane stereoisomer 11[17] was obtained similarly starting from the cis counterpart 4 (entry 5). Thus, the stereochemistry about the cyclopropane ring was retained completely during the reaction. The geometries of the double bond in products 7 and 11 were assigned by NOE measurement.[18] A variety of aryl- and heteroarylzinc reagents similarly coupled with (dichloroethenyl)cyclopropanecarboxylates having various alcoholic parts (1a, 3–5) to give the corresponding monocoupling products stereoselectively in good yields (entries 2, 3, and 5–8). High-yield preparation of the acidic component of flumethrin (2; entry 2) and direct heteroarylation of *trans*-permethrin (1a) demonstrate the usefulness of the reaction (entry 8).

The resultant monocoupling products were quite resistant toward further metal-assisted arylation. Thus, with (dichloroethenyl)cyclopropanecarboxylates, diarylation products were scarcely obtained even when excess amounts of arylzinc reagents were used. In contrast, 1-hexynylzinc chloride[16] (2.5-fold) gave dicoupling product 10 preferentially (entry 4). The reason is not clear yet, but the alkynyl group first introduced may increase the reactivity of the monocoupling product owing to the electron-withdrawing nature, facilitating the second alkynylation.

With a dibromo analogue, methyl *cis*-3-(2,2-dibromoethenyl)-2,2-dimethylcyclopropanecarboxylate (6),[20] readily available from 5, either monocoupling or dicoupling could be achieved selectively according to the stoichiometry of organozinc reagents: an equimolar amount (1.1 equiv) of arylzinc reagent gave monocoupling product (entry 9) and an excess amount (2.8 equiv) of organozinc reagent afforded dicoupling product (entry 10), respectively.

The subsequent treatment of monocoupling product 15 with another organozinc reagent led to unsymmetrically disubstituted (ethenyl)cyclopropane derivative 17 stereoselectively (entry 11).

In summary, we report a novel and highly efficient method for the structural modification of commercial

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(12) Japan Kokai Tokkyo Koho Jp 82 21, 347; *Chem. Abstr.* **1982**, *97*, 5852s.

(13) A useful method for the stereoselective synthesis of the acidic parts of CF_3-containing pyrethroids has recently been reported, Z/E = 86–93/14–7: Fujita, M.; Hiyama, T.; Kondo, K. *Tetrahedron Lett.* **1986**, *27*, 2139.

(14) The higher reactivity of the E halogen atom in 1,1-dihalo-1-alkenes and in (E)- and (Z)-1-bromo-1-alkenes has been demonstrated by us and others.[15] Detailed mechanism of the palladium-catalyzed stereoselective monocoupling reaction of 1,1-dichloro-1-alkenes will be reported in due course.

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(17) A mixture of Z and E isomers was described in ref 11a.

(18) Irradiation of the olefinic proton in 7 and 11 led to 5.7% and 6.1% NOE of the aromatic ortho protons, respectively. Geometries of other monocoupling products were established similarly by NOE experiments; intensities of NOEs were 3.7–8.3% ($CDCl_3$ solution, 23 °C). Though a small NOE (1.2%) was observed with product 14, its stereochemistry was further assigned by comparing the two bonded CH coupling value ($^2J_{CH}$ = 7 Hz) between the vinylic quaternary carbon and the vinylic proton in 14 with that ($^2J_{CH}$ = 7 Hz) in 7, since there is a significant difference in the $^2J_{CH}$ value between (E)- and (Z)-chloroethenes.[19]

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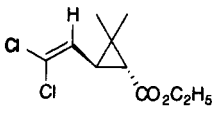
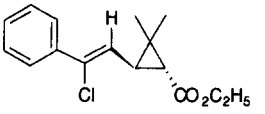
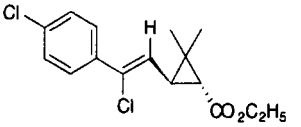
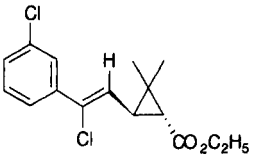
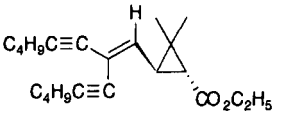
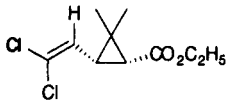
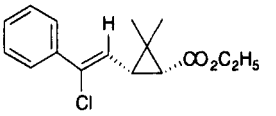
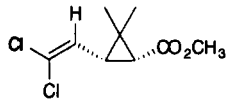
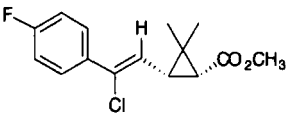
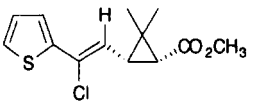
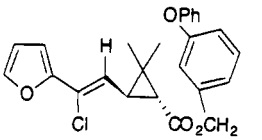
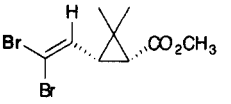
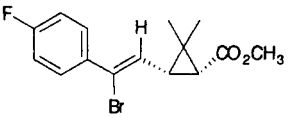
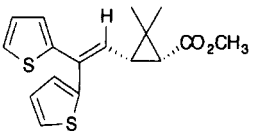
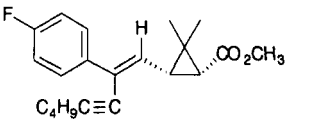
Table I. Coupling of Dihaloethenyl Cyclopropanecarboxylates with Organozinc Reagents Catalyzed by Palladium Complexes[a]

entry	halide	R_1ZnCl[b]	product[c]	yield, %[b]
1	 (3)	A	 (7)	86 (91)
2	(3)	B	 (8)	81
3	(3)	C	 (9)	81
4	(3)	D[e,f]	 (10)	80
5	 (4)	A[g]	 (11)	100
6	 (5)	E	 (12)	89
7	(5)	F	 (13)	61
8	*trans*-1a	G[g]	 (14)	87
9	 (6)	E	 (15)	(72)
10	(6)	F[e,g]	 (16)	57
11	(15)	D[f]	 (17)	96

[a] Unless otherwise mentioned, all reactions were carried out at room temperature for 5–8 h. Halide/R_1ZnCl/[$PdCl_2$(dppb)] = 1/1–1.2/0.02. [b] A = PhZnCl; B = 4-ClC_6H_4ZnCl; C = 3-ClC_6H_4ZnCl; D = 1-hexynyl-ZnCl; E = 4-FC_6H_4ZnCl; F = 2-thienyl-ZnCl; G = 2-furyl-ZnCl. [c] All products were fully characterized by spectroscopic analysis (IR, NMR, MS) and gave satisfactory elemental and/or HRMS data. [d] Yield after isolation by silica gel PTLC. Yield in parentheses was determined by GLC. [e] Excess (2.5–3.0-fold) of organozinc reagents was used. [f] 50 °C (bath temperature), 14–16 h. [g] 15–18 h.

pyrethroids having a dihaloethenyl group based on the palladium-catalyzed monocoupling reaction. This has made the direct modification of the acidic parts of permethrin and deltamethrin possible for the first time. The highly stereoselective conversion of readily available stereodefined permethric and deltamethric acid esters make the present method more attractive than previous ones.

Experimental Section

All experiments were carried out under an argon atmosphere. THF was distilled from $LiAlH_4$. A stock THF solution of $ZnCl_2$ was prepared by dissolving $ZnCl_2$ (dried 8 h at 80 °C (2 mmHg)) in THF.[21] PTLC was performed on Merck Kieselgel 60 PF_{254} (Art. 7747). [$PdCl_2$(dppb)][22] was prepared according to the literature procedure. A mixture of ethyl *trans*- (3),[23] and *cis*-(2,2-dichloroethenyl)cyclopropanecarboxylate (4)[23] and methyl *cis*-(2,2-dibromoethenyl)cyclopropanecarboxylate (6)[20] were prepared by published procedures. The two stereoisomers (3 and 4) were separated by preparative HPLC. Other starting dihalides (5 and *trans*-1a) were kind gifts from Sumitomo Chemical Co., Ltd.

Melting points were taken on a Yanaco Model MP500D instrument and are uncorrected. ^1H NMR (300 MHz), ^{13}C NMR (75.4 MHz), and ^{19}F NMR (282.3 MHz) were recorded on a Varian XL-300 spectrometer in $CDCl_3$ with tetramethylsilane as an internal standard. Mass spectra were obtained on a Hitachi M-80 mass spectrometer at 20 eV. IR spectra were recorded on a Shimadzu IR-435 spectrophotometer. Gas chromatography was performed by using a Shimadzu GC-4C PT instrument with a 3 mm × 3 m column packed with 30% QF-1 on Celite 545. Preparative HPLC was done by using a Waters Model 302 with a reversed-phase 19 mm × 15 cm column (μ-Bondasphere C 18, eluant, MeOH:H_2O = 80:20). The purity of all products was over 95% by ^1H NMR and GC analyses.

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(22) Sugi, Y.; Bando, K. *Chem. Lett.* **1976**, 727.
(23) Nakada, Y.; Endo, R.; Muramatsu, S.; Ide, J.; Yura, Y. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1511.

Ethyl *trans*-3-[(*Z*)-2-Chloro-2-(4-chlorophenyl)ethenyl]-2,2-dimethylcyclopropanecarboxylate (8). A Typical Procedure for the Synthesis of Monosubstituted (Chloroethenyl)cyclopropanecarboxylates. Preparation of the title compound (entry 2) is exemplary of the procedure used for the preparation of other monocoupling products (entries 1, 3, 5–9). A solution of 4-ClC_6H_4ZnCl was prepared by mixing a THF solution of $ZnCl_2$ (5 mL, 1.5 mmol) and 4-ClC_6H_4MgBr (1.5 mL, 1.24 mmol) followed by stirring at room temperature for 1.5 h. To a THF solution (3 mL) of **3** (238 mg, 1.00 mmol) and [$PdCl_2$(dppb)] (8.5 mg, 0.014 mmol) was added the 4-ClC_6H_4ZnCl solution at 0 °C under argon atmosphere. The mixture was stirred at room temperature for 6 h and hydrolyzed with H_2O. Extraction with Et_2O, drying ($MgSO_4$), and concentration, followed by purification by PTLC (silica gel, EtOAc/hexane = 1/50), gave 273 mg of product (0.81 mmol, 81%): ^1H NMR δ 1.24 (s, 3 H), 1.29 (t-like, J = 7.0 Hz, 3 H), 1.36 (s, 3 H), 1.68 (d, J = 5.4 Hz, 1 H), 2.53 (dd, J = 5.4 and 8.3 Hz, 1 H), 4.08–4.25 (dq, 2 H), 5.84 (d, J = 8.3 Hz, 1 H), 7.31 (m, 2 H), 7.47 (m, 2 H); ^{13}C NMR δ 14.4, 20.3, 22.8, 29.4, 33.5, 35.5, 60.6, 125.5, 127.5, 128.5, 133.8, 134.3, 136.4, 171.4; IR (neat) 1722 cm^{-1}; mass spectrum m/e (relative intensity) 314 (10.0), 313 (3.1), 312 (M^+, 14.6), 239 (100), 203 (19.0); exact mass calcd for $C_{16}H_{18}Cl_2O_2$ 312.0683, found 312.0707.

Ethyl *trans*-3-[(*Z*)-2-Chloro-2-phenylethenyl]-2,2-dimethylcyclopropanecarboxylate (7). Isolated as an oil by PTLC (benzene/hexane = 1/1): ^1H NMR δ 1.24 (s, 3 H), 1.29 (t-like, J = 7.2 Hz, 3 H), 1.36 (s, 3 H), 1.67 (d, J = 5.6 Hz, 1 H), 2.54 (dd, J = 5.6 and 8.4 Hz, 1 H), 4.09–4.25 (two dq, 2 H), 5.86 (d, J = 8.4 Hz, 1 H), 7.27–7.38 (m, 3 H), 7.52–7.57 (m, 2 H); ^{13}C NMR δ 14.4, 20.3, 22.7, 29.3, 33.5, 35.4, 60.5, 124.9, 126.2, 128.3, 128.5, 135.0, 137.9, 171.5; IR (neat) 1723 cm^{-1}; mass spectrum m/e (relative intensity) 280 (5.0), 278 (M^+, 15.5), 243 (45.9), 205 (100.0), 169 (29.2); exact mass calcd for $C_{16}H_{19}ClO_2$ 278.1072, found 278.1059.

Ethyl *cis*-3-[(*Z*)-2-Chloro-2-phenylethenyl]-2,2-dimethylcyclopropanecarboxylate (11). Isolated as an oil by PTLC (EtOAc/hexane = 1/15): ^1H NMR δ 1.27 (t, J = 7.15 Hz, 3 H), 1.31 (s, 3 H), 1.33 (s, 3 H), 1.90 (d, J = 8.6 Hz, 1 H), 2.37 (dd, J = 8.6 and 8.8 Hz, 1 H), 4.12 (q, J = 7.15 Hz, 2 H), 6.60 (d, J = 8.8 Hz, 1 H), 7.27–7.37 (m, 3 H), 7.57–7.61 (m, 2 H); ^{13}C NMR δ 14.3, 15.0, 27.8, 28.6, 32.4, 33.1, 60.2, 122.7, 126.3, 128.3, 128.3, 133.9, 138.2, 171.0; IR (neat) 1721 cm^{-1}; mass spectrum m/e (relative intensity) 280 (6.2), 279 (3.4), 278 (M^+, 18.6), 243 (57.7), 205 (100), 169 (30.2); exact mass calcd for $C_{16}H_{19}ClO_2$ 278.1072, found 278.1055.

Ethyl *trans*-3-[(*Z*)-2-Chloro-2-(3-chlorophenyl)ethenyl]-2,2-dimethylcyclopropanecarboxylate (9). Isolated as an oil by PTLC (EtOAc/hexane = 1/15): ^1H NMR δ 1.25 (s, 3 H), 1.29 (t-like, J = 7.15 Hz, 3 H), 1.36 (s, 3 H), 1.69 (d, J = 5.4 Hz, 1 H), 2.53 (dd, J = 5.4 and 8.3 Hz, 1 H), 4.09–4.25 (two dq, 2 H), 5.88 (d, J = 8.3 Hz, 1 H), 7.26–7.30 (m, 2 H), 7.39–7.46 (m, 1 H), 7.51–7.53 (m, 1 H); ^{13}C NMR δ 14.4, 20.3, 22.8, 29.5, 33.5, 35.6, 60.6, 124.3, 126.3, 126.3, 128.4, 129.6, 133.4, 134.4, 139.7, 171.3; IR (neat) 1723 cm^{-1}; mass spectrum m/e (relative intensity) 314 (7.5), 313 (2.1), 312 (M^+, 10.8), 277 (43.3), 239 (100); exact mass calcd for $C_{16}H_{18}Cl_2O_2$ 312.0682, found 312.0653.

Methyl *cis*-3-[(*Z*)-2-Chloro-2-(4-fluorophenyl)ethenyl]-2,2-dimethylcyclopropanecarboxylate (12). Isolated by PTLC (EtOAc/hexane = 1/50): mp 56.7–57.2 °C (MeOH); ^1H NMR δ 1.30 (s, 3 H), 1.32 (s, 3 H), 1.91 (d, J = 8.5 Hz, 1 H), 2.35 (dd, J = 8.5 and 8.8 Hz, 1 H), 3.67 (s, 3 H), 6.52 (d, J = 8.8 Hz, 1 H), 7.02 (dm, J_{HF} = 8.5 Hz, 2 H), 7.55 (dm, J_{HF} = 5.3 Hz, 2 H); ^{13}C NMR δ 15.0, 27.9, 28.5, 32.1, 33.2, 51.4, 115.0, 115.3, 122.5, 128.1, 128.2, 132.9, 134.4, 134.5, 161.1, 164.4, 171.4; IR (KBr) 1713 cm^{-1}; mass spectrum m/e (relative intensity) 284 (6.7), 282 (M^+, 17.0), 247 (100), 223 (69.3); exact mass calcd for $C_{15}H_{16}ClFO_2$ 282.0821, found 282.0820. Anal. Calcd for $C_{15}H_{16}ClFO_2$: C, 63.72; H, 5.70. Found: C, 63.59; H, 5.61.

Methyl *cis*-3-[(*Z*)-2-Chloro-2-(2-thienyl)ethenyl]-2,2-dimethylcyclopropanecarboxylate (13). Isolated as an oil by PTLC (EtOAc/hexane = 1/50): ^1H NMR δ 1.29 (s, 3 H), 1.32 (s, 3 H), 1.90 (d, J = 8.5 Hz, 1 H), 2.32 (dd, J = 8.5 and 8.9 Hz, 1 H), 3.67 (s, 3 H), 6.58 (d, J = 8.9 Hz, 1 H), 6.96 (dd, J = 5.2 and 3.7 Hz, 1 H), 7.19 (dd, J = 5.2 and 1.3 Hz, 1 H), 7.22 (dd, J = 3.7 and 1.3 Hz, 1 H); ^{13}C NMR δ 15.1, 28.1, 28.5, 32.3, 32.9, 51.5, 121.2, 125.0, 125.1, 127.2, 127.4, 142.3, 171.2; IR (neat) 1727 cm^{-1}; mass spectrum m/e (relative intensity) 272 (10.1), 271 (4.2), 270 (M^+, 24.8), 235 (100), 211 (63.3); exact mass calcd for $C_{13}H_{15}ClO_2S$ 270.0480, found 270.0497.

Methyl *cis*-3-[(*Z*)-2-Bromo-2-(4-fluorophenyl)ethenyl]-2,2-dimethylcyclopropanecarboxylate (15). After silica gel chromatography (EtOAc/hexane = 1/15), the product was purified by HPLC: mp 51.7–52.1 °C (MeOH); ^1H NMR δ 1.31 (s, 3 H), 1.32 (s, 3 H), 1.91 (d, J = 8.4 Hz, 1 H), 2.29 (dd, J = 8.4 and 8.4 Hz, 1 H), 3.67 (s, 3 H), 6.59 (d, J = 8.4 Hz, 1 H), 7.01 (dm, J_{HF} = 8.5 Hz, 2 H), 7.52 (dm, J_{HF} = 5.3 Hz, 2 H); ^{13}C NMR δ 15.1, 28.0, 28.5, 32.1, 35.8, 51.5, 114.9, 115.2, 125.4, 126.4, 129.2, 129.3, 136.1, 136.1, 161.0, 164.3, 171.3; IR (KBr) 1713 cm^{-1}; mass spectrum m/e (relative intensity) 328 (11.2), 326 (M^+, 11.1), 269 (30.5), 267 (31.3), 247 (100); exact mass calcd for $C_{15}H_{16}BrFO_2$ 326.0316, found 326.0293. Anal. Calcd for $C_{15}H_{16}BrFO_2$: C, 55.06; H, 4.93. Found: C, 55.02; H, 4.91.

3-Phenoxybenzyl *trans*-3-[(*Z*)-2-Chloro-2-(2-furyl)ethenyl]-2,2-dimethylcyclopropanecarboxylate (14). Isolated as an oil by PTLC (EtOAc/hexane = 1/10): ^1H NMR δ 1.23 (s, 3 H), 1.33 (s, 3 H), 1.74 (d, J = 5.3 Hz, 1 H), 2.52 (dd, J = 5.3 and 8.8 Hz, 1 H), 5.11 (s, 2 H), 6.00 (d, J = 8.8 Hz, 1 H), 6.38 (dd, J = 3.4 and 1.8 Hz, 1 H), 6.47 (d, J = 3.4 Hz, 1 H), 6.92–7.13 (m, 6 H), 7.27–7.37 (m, 4 H); ^{13}C NMR δ 20.2, 22.6, 29.8, 33.0, 35.4, 65.8, 108.3, 111.5, 118.2, 118.3, 119.0, 121.9, 122.7, 123.4, 124.0, 129.8, 129.9, 138.1, 142.7, 150.8, 156.9, 157.5, 171.1; IR (neat) 1724 cm^{-1}; mass spectrum m/e (relative intensity) 424 (7.7), 423 (5.6), 422 (M^+, 22.1), 195 (100.0), 183 (85.1); exact mass calcd for $C_{25}H_{23}ClO_4$ 422.1283, found 422.1262.

General Procedure for the Synthesis of Dialkylation Products. The following compounds were prepared by essentially the same method as the general procedure described previously for the monocoupling except that an excess amount of organozinc reagent (see Table I) was employed.

Ethyl *trans*-3-[2,2-Di(1-hexynyl)ethenyl]-2,2-dimethylcyclopropanecarboxylate (10). To a solution of 487 mg (2.1 mmol) of **3** and 49 mg (0.082 mmol) of [$PdCl_2$(dppb)] in 5 mL of dry THF was added a THF solution (36 mL) of 1-hexynylzinc chloride (4.8 mmol) at 0 °C under argon atmosphere. The mixture was stirred at 50 °C (bath temperature) for 14 h. The reaction mixture was hydrolyzed, extracted with Et_2O, and dried over $MgSO_4$, and the solvent was removed. PTLC (EtOAc/hexane = 1/10) of the residue gave the product as an oil in 80% yield. An analytical sample was obtained by preparative GLC: ^1H NMR δ 0.91 (t, J = 7.2 Hz, 3 H), 0.93 (t, J = 7.2 Hz, 3 H), 1.19 (s, 3 H), 1.26 (t-like, J = 7.2 Hz, 3 H), 1.30 (s, 3 H), 1.33–1.61 (m, 8 H), 1.63 (d, J = 5.3 Hz, 1 H), 2.30 (t, J = 6.9 Hz, 2 H), 2.37 (t, J = 6.8 Hz, 2 H), 2.55 (dd, J = 5.3 and 9.8 Hz, 1 H), 4.05–4.21 (two dq, 2 H), 5.81 (d, J = 9.8 Hz, 1 H); ^{13}C NMR δ 13.6, 13.6, 14.3, 19.0, 19.2, 20.4, 21.9, 22.0, 22.6, 29.9, 30.6, 30.7, 34.9, 36.1, 60.4, 76.7, 79.0, 88.1, 94.2, 107.2, 143.0, 171.4; IR (neat) 2224, 1725 cm^{-1}; mass spectrum m/e (relative intensity) 328 (M^+, 15.8), 299 (42.7), 271 (78.2), 117 (100); exact mass calcd for $C_{22}H_{32}O_2$ 328.2401, found 328.2424.

Methyl *cis*-3-[2,2-Di(2-thienyl)ethenyl]-2,2-dimethylcyclopropanecarboxylate (16). Isolated by PTLC (EtOAc/hexane = 1/50): mp 86.6–86.9 °C (MeOH); ^1H NMR δ 1.18 (s, 3 H), 1.36 (s, 3 H), 1.76 (d, J = 8.5 Hz, 1 H), 2.04 (dd, J = 8.5 and 9.4 Hz, 1 H), 3.69 (s, 3 H), 6.56 (d, J = 9.4 Hz, 1 H), 6.87 (dd, J = 1.3 and 3.6 Hz, 1 H), 6.92 (dd, J = 3.6 and 5.0 Hz, 1 H), 7.06 (m, 1 H), 7.07 (m, 1 H), 7.14 (dd, J = 1.3 and 5.0 Hz, 1 H), 7.36 (m, 1 H); ^{13}C NMR δ 15.1, 28.2, 28.5, 32.8, 33.9, 51.4, 124.1, 124.9, 125.6, 125.8, 126.7, 127.1, 128.1, 130.1, 140.2, 146.7, 171.3; IR (KBr) 1711 cm^{-1}; mass spectrum m/e (relative intensity) 320 (7.3), 319 (13.4), 318 (M^+, 67.5), 259 (100); exact mass calcd for $C_{17}H_{18}O_2S_2$ 318.0747, found 318.0751. Anal. Calcd for $C_{17}H_{18}O_2S_2$: C, 64.12; H, 5.69. Found: C, 63.91; H, 5.73.

Methyl *cis*-3-[(*E*)-2-(4-Fluorophenyl)-2-(1-hexynyl)ethenyl]-2,2-dimethylcyclopropanecarboxylate (17). To a solution of 169 mg (0.52 mmol) of **15** and 29 mg (0.049 mmol) of [$PdCl_2$(dppb)] in dry THF (3 mL) was added a THF solution of 1-hexynylzinc chloride (1.05 mmol) at 0 °C. The mixture was stirred at 50 °C (bath temperature) for 16 h. After usual workup, the product was isolated as an oil by PTLC (EtOAc/hexane = 1/10): ^1H NMR δ 0.95 (t, J = 7.3 Hz, 3 H), 1.29 (s, 3 H), 1.35 (s, 3 H), 1.43–1.66 (m, 4 H), 1.91 (d, J = 8.5 Hz, 1 H), 2.47 (t, J = 6.9 Hz, 2 H), 2.55 (dd, J = 8.5 and 9.8 Hz, 1 H), 3.66 (s, 3 H),

6.69 (d, J = 9.8 Hz, 1 H), 6.99 (dm, J_{HF} = 8.6 Hz, 2 H), 7.56 (dm, J_{HF} = 5.4 Hz, 2 H); ^{13}C NMR δ 13.6, 15.0, 19.3, 22.0, 28.5, 28.8, 30.9, 32.9, 35.2, 51.4, 78.0, 96.4, 114.9, 115.1, 123.7, 127.5, 127.6, 131.1, 134.8, 134.9, 160.6, 163.9, 171.5; IR (neat) 2232, 1726 cm^{-1}; mass spectrum m/e (relative intensity) 328 (M^+, 36.5), 269 (61.2), 213 (100), 198 (50.2); exact mass calcd for $C_{21}H_{25}FO_2$ 328.1838, found 328.1849.

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Registry No. *trans*-**1a**, 52341-32-9; **1a** (Y = CN), 52315-07-8; **1b**, 52918-63-5; **3**, 63142-57-4; **4**, 63142-56-3; **5**, 61976-30-5; **6**, 113830-50-5; **7**, 133575-08-3; **8**, 78479-01-3; **9**, 133472-19-2; **10**, 133472-20-5; 11, 133575-09-4; **12**, 133575-10-7; **13**, 133472-21-6; **14**, 133472-22-7; **15**, 133472-23-8; **16**, 133472-24-9; **17**, 133472-25-0; A, 28557-00-8; B, 89523-62-6; C, 133472-26-1; D, 65960-05-6; E, 133472-27-2; F, 81745-84-8; G, 81745-86-0; $PdCl_2$(dppb), 29964-62-3.

Supplementary Material Available: ^{1}H NMR and ^{13}C NMR spectra for all new compounds (18 pages). Ordering information is given on any current masthead page.

Synthesis of 2,3-*O*-Isopropylidene-D-glyceraldehyde in High Chemical and Optical Purity: Observations on the Development of a Practical Bulk Process

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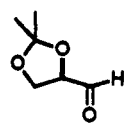
We recently required an expedient, practical synthesis for 2,3-*O*-isopropylidene-D-glyceraldehyde (**1**) that would be readily adaptable to a multiple-kilogram scale. The frequent appearance[1] of this compound in the literature testifies to its importance as a chiral pool material, while the number of reported procedures[2,3] for obtaining this material bear witness to the generally unsatisfactory nature of existing technology for its synthesis. Our involvement with this compound as a starting material in a linear synthesis route required examination and modification of existing chemistries to enable a practical bulk synthesis of this compound. We report here our findings, which represent improvements on existing literature procedures and provide access to **1** of high quality in an efficient and reliable manner.



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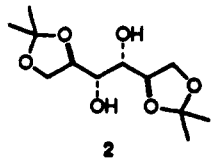
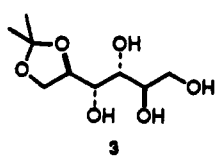


2

The majority of procedures for obtaining **1** have employed variants of the classic Baer and Fisher preparation dating from the 1930's.[3a] Thus, D-mannitol has been ketalized using a variety of methods[2,3] to provide 1,2:5,6-diisopropylidene-D-mannitol (**2**). The 3,4 glycol linkage of this material was then cleaved, generally with either lead tetraacetate[3a,b] or sodium periodate[3c-j] to provide **1**. Other modifications of this general approach have appeared,[4] as have syntheses of **1** from other source materials;[5] these require additional steps which render them unattractive as candidates for a large-scale process.

Opting for a two-step process from D-mannitol as the most expeditious route to **1**, we examined several of the methods for the synthesis of diacetonide **2**.[2d] We selected the procedure reported by Chittenden, which used catalytic stannous chloride ($SnCl_2$) and 2,2-dimethoxypropane to ketalize D-mannitol in 54–58% recrystallized yield.[2b] The procedure was chosen for its combination of high throughput, low catalyst loads, simple processing, and reproducibility.

Our initial examination of this procedure foreboded several problems for large-scale processing. Attempted recrystallization of the crude **2** from dibutyl ether as per the Chittenden procedure gave gelatinous material requiring large volumes of solvent to enable stirring, thus effectively limiting throughput. Use of other solvents gave similar results. Moreover, the recrystallized material varied in quality and was eventually found to be contaminated with 5–10% of 1,2-monoacetonide **3**,[2c] as determined by ^{1}H NMR (DMSO-d_6). Since the cleavage of **3** would require 3 molar equiv of oxidant to afford **1**, its presence was undesirable. It was found that a simple slurry of the crude reaction material in dichloromethane (CH_2Cl_2), followed by filtration, effectively removed any traces of **3** from the product solution. The other major byproduct, triacetonide **4** (15–20%),[6] did not interfere in the subsequent step and therefore did not require removal.



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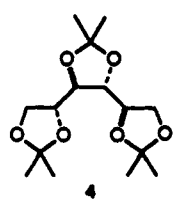

4

In initial experiments, the reaction sometimes failed to go to completion, remaining heterogeneous. It was found that commercial supplies of 1,2-dimethoxyethane (glyme) contained low levels of diphenylamine and isoquinoline, both potentially detrimental to the tin catalyst. Control experiments demonstrated an inhibiting effect for isoquinoline; diphenylamine-spiked reactions showed no aberration. Simple distillation of solvent prior to use,

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