of TMEDA a mixture of 2.6 g (0.02 M) of ethyl acetoacetate and 3.75 g (0.025 M) of ethyl benzoate in 50 mL of ether was added dropwise at room temperature (under N_2). Initially the color of the reaction mixture was reddish brown. Then it turned pale yellow at the end of the addition. The reaction mixture was stirred at room temperature for 16–18 h. Acetic acid workup, as above, gave an oil, which upon flash chromatography on a silica gel column (>200 mesh without binder), with *n*-hexane for the eluting solvent gave 0.350 g (10% recovery) of ethyl benzoate. Further elution with *n*-hexane–ethyl acetate (3:1) gave 4.5 g (85%; 87% on the basis of recovery) of ethyl 5-phenyl-3,5-dioxopentanoate (**7b**) as a pale yellow oil, identical with the earlier sample.

5-Phenyl-3,5-dioxopentanoic Acid (7a). To a solution of potassium hydroxide (0.560 g) in 5 mL of absolute alcohol was added 0.4 g of ethyl 5-phenyl-3,5-dioxopentanoate (**7b**) dissolved in 2 mL of absolute alcohol at room temperature. The reaction mixture was stirred for 15 min, decomposed with crushed ice, and acidified with ice-cold 3 N HCl. The precipitated acid was filtered, washed with 20 mL of ice-cold water, and dried. The acid was crystallized from ether–petroleum ether (1:2) to give 0.350 g (80%) of 5-phenyl-3,5-dioxopentanoic acid (**7a**): mp 94–95 °C (lit.[5] 94–96 °C); IR (Nujol) 3300–3000, 1740, 1625, 1575, 1200, 1140, and 1050 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.55 (s, 2 H), 3.72 (br s, 1 H, D_2O exchangeable), 6.30 (s, 1 H, D_2O exchangeable), 7.45 (m, 3 H, phenyl protons at the 3, 4, and 5 positions), 7.85 (m, 2 H, phenyl protons at the 2 and 6 positions), 12.00 (br s, 1 H, D_2O exchangeable).

Anal. Calcd for $C_{11}H_{10}O_4$: C, 64.07; H, 4.89. Found: C, 64.32; H, 4.93.

6-Phenyl-4-hydroxy-α-pyrone (8a). Ester **7b** (0.5 g) was heated slowly under vacuum (3 mmHg) to 150 °C (ca. 45 min), kept at this temperature for an additional 5 min, and slowly cooled to room temperature. A pale yellow solid was obtained, which was crystallized from ethyl methyl ketone, mp 254–255 °C (lit.[5] 258–259 °C dec); IR (Nujol) 3650–3200, 1650, 1620, 1550, 1250, and 1070 cm^{-1}; ^1H NMR ($CDCl_3$, Me_2SO-d_6) δ 3–5 (br s, 1 H, exchanges with D_2O), 5.41 (d, 1 H, J = 2.8 Hz, exchanges with D_2O), 6.65 (d, 1 H, J = 2.5 Hz), 7.5 (m, 3 H, phenyl protons at the 3, 4, and 5 positions), 7.8 (m, 2 H, phenyl protons at the 2 and 6 positions).

Anal. Calcd for $C_{11}H_8O_3$: C, 70.21; H, 4.29. Found: C, 70.11; H, 4.31.

Anibine (1). To a solution of LDA (prepared from 5 g (0.05 M) of diisopropylamine and *n*-butyllithium (0.05 M) at 0 °C in ether) containing 2 mL (0.02 M) of TMEDA a mixture of 2.6 g (0.02 M) of ethyl acetoacetate and 3.4 g (0.025 M) of ethyl nicotinate in 50 mL of ether was added dropwise at room temperature (under N_2). Initially the reaction mixture was reddish brown, and it turned to yellow or reddish yellow. The reaction mixture was stirred at room temperature for 16–18 h. Workup, as above, gave a red oil which upon flash chromatography on a silica gel column (>200 mesh without binder) with hexane–ethyl acetoacetate (9:1) for the eluting solvent gave 1.5 g (44% recovery) ethyl nicotinate. Further elution with hexane–ethyl acetate (1:1) yielded 2.6 g (47%; 83% on the basis of recovery) of ethyl 5-(3′-pyridyl)-3,5-dioxopentanoate (**7d**): IR (neat) 3600–3200, 1750, 1700, 1610, 1300, 1035, and 950 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.1–1.5 (t and m, 3 H, OCH_2CH_3 of the enol isomers), 3.4, 3.9 (s, 2 H, $COCH_2C{=}C$ of the enol isomers), 4–4.5 (m, 2 H, OCH_2CH_3 of the enol isomers), 6.35 and 6.87 (two singlets, 1 H, olefinic protons of the enol isomers), 7.3–8.9 (m, 4 H, pyridyl protons of the enol isomers).

As in the case of **7b**, 0.5 g of ester **7d** on cyclization gave a light brown solid, which was crystallized from dioxane–hexane (1:1) to give 0.360 g (90%) of 4-hydroxy-6-(3′-pyridyl)-α-pyrone (**8b**): mp 207–209 °C (lit.[4] 212 °C dec); IR (Nujol) 3650–3200, 1730, 1720, 1600, 1250, and 1225 cm^{-1}; ^1H NMR ($CDCl_3$, Me_2SO-d_6) δ 3–4 (br s, 1 H, exchanges with D_2O), 5.45 (d, 1 H, J = 2.5 Hz, exchanges with D_2O, H_3), 6.60 (d, 1 H, J = 2.5 Hz, H_5), 7.35 (dd, 1 H, $J_{5',6'}$ = 5 Hz, $J_{5',4'}$ = 8 Hz, $H_{5'}$), 8.10 (m, 1 H, $H_{4'}$), 8.67 (dd, 1 H, $J_{6',5'}$ = 5 Hz, $J_{6',4'}$ = 1.5 Hz, $H_{6'}$), 8.9 (d, 1 H, $J_{2',4'}$ = 2.5 Hz, $H_{2'}$). A satisfactory analytical sample could not be obtained for the compound.

α-Pyrone **8b** (0.280 g) was treated with an ethereal solution of diazomethane at room temperature. The reaction mixture was left at room temperature for 2 h. Removal of the solvent and crystallization of the residue from 95% ethanol gave 0.180 g (66%) of anibine (**1**): mp 176–177 °C (lit.[1] 177–178 °C); IR (Nujol) 3150, 1730, 1645, and 1570 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.0 (s, 3 H, OCH_3), 5.5 (d, 1 H, J = 2.5 Hz, H_3), 6.5 (d, 1 H, J = 2.5 Hz, H_5), 7.35 (dd, 1 H, $J_{5',6'}$ = 5 Hz, $J_{5',4'}$ = 8 Hz, $H_{5'}$), 8.10 (m, 1 H, $H_{4'}$), 8.67 (dd, 1 H, $J_{6',5'}$ = 5 Hz, $J_{6',4'}$ = 1.5 Hz, $H_{6'}$), 9.0 (d, 1 H, $J_{2',4'}$ = 2.5 Hz, $H_{2'}$).

Anal. Calcd for $C_{11}H_9O_3N$: C, 65.02; H, 4.43. Found: C, 65.00; H, 4.50.

Registry No. 1, 643-91-4; **7a**, 5526-43-2; **7b**, 86969-12-2; **7d**, 86969-13-3; **8a**, 5526-38-5; **8b**, 80601-69-0; **12b**, 86969-14-4; ethyl acetoacetate, 141-97-9; ethyl benzoate, 93-89-0; ethyl nicotinate, 614-18-6; TMEDA, 110-18-9.

Synthesis of the Major Pheromonal Component of the Monarch Butterfly (*Danaus plexippus*) via Palladium-Catalyzed 1,4-Functionalization of Isoprene

Jan-E. Nyström and Jan-E. Bäckvall*

Department of Organic Chemistry, Royal Institute of Technology, S-100 44 Stockholm, Sweden

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4-Chloroprenyl acetate (**2**), regioselectively prepared by palladium(II)-catalyzed 1,4-acetoxychlorination of isoprene, was selectively functionalized in the 1- and 4-positions to afford **6**, which is readily transformed to the dimethyl ester of the pheromone (*E,E*)-3,7-dimethyldeca-2,6-diene-1,10-dioic acid (**1a**) of the Monarch butterfly. The allylic chloro group in **2** was chemoselectively substituted with sodium dimethyl malonate (classically or with palladium(0) catalysis) without affecting the allylic acetoxy group, which subsequently was replaced with sodium methyl acetoacetate using palladium(0) catalysis to give **5**. The configuration of the double bond in **5** is >95% *E* when triphenylphosphine is used as ligand. A double alkylation of **2** to **5** can also be performed as a one-pot sequence. Selective double decarboxylation of **5** gave methyl (*E*)-4-methyl-8-oxo-4-nonenoate (**6**) in 35% overall yield from isoprene. Transformation of **6** to the dimethyl ester of **1** has been described elsewhere.

Pheromones of certain butterflies contain a degraded sesquiterpenoid skeleton. For example, Meinwald and co-workers were able to isolate **1a** (major) and **1b** (minor) from the hairpencils of males of the Monarch butterfly

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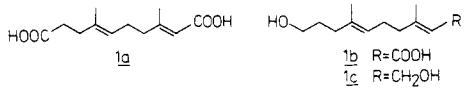
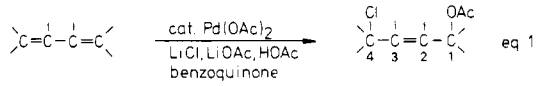
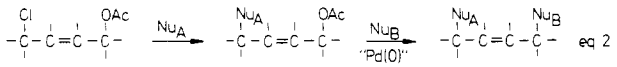


(*Danaus plexippus*)[1] and the diol **1c** from the male queen butterfly (*Danaus gilippus berenice*).[2] Previous syntheses of Monarch butterfly pheromones **1a** and **1b** have been described from ethyl geranate[3] and geraniol,[4] as well as from simpler starting materials such as acrolein dimethyl acetal,[5] methyl vinyl ketone epoxide,[6] 2-bromoethanol,[7] and isoprene monoepoxide.[8]

We recently reported that conjugated dienes can be selectively oxidized to 1-acetoxy-4-chloro-2-alkenes in acetic acid (eq 1).[9,10] The 1,4-acetoxychlorination is highly



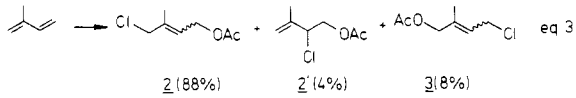
stereoselective (overall cis addition), as demonstrated by oxidation of cyclic 1,3-dienes, and in some cases a good regioselectivity can be realized. It was also demonstrated that the chloroacetates can be selectively functionalized in the allylic positions (eq 2).[9,10] The chloro group can



be substituted by either a classical or a palladium(0)-catalyzed nucleophilic substitution reaction (Nu_A) without affecting the acetoxy group. In a subsequent palladium(0)-catalyzed step the acetoxy group can then be displaced by a second nucleophile (Nu_B). The nucleophiles examined, amines or stabilized carbanions, can be added to either position, and it should be emphasized that the chloro group is always displaced first. Herein we apply the principle shown in eq 2 to the synthesis of the major pheromonal component **1a** of the Monarch butterfly, using 1-acetoxy-4-chloro-3-methyl-2-butene (**2**), the chloroacetate of isoprene, as the key intermediate in the synthesis.

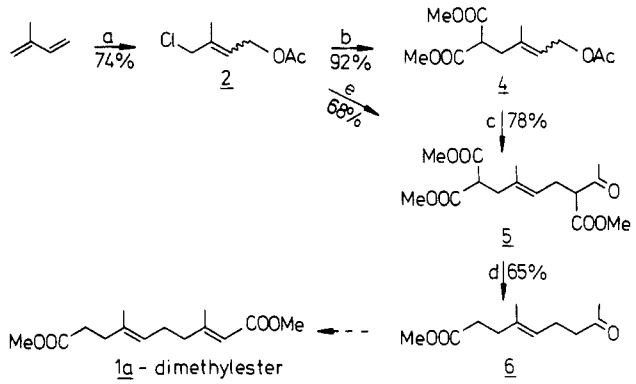
Results and Discussion

The synthesis of the dimethyl ester of **1a** from isoprene is outlined in Scheme I. Palladium-catalyzed acetoxychlorination of isoprene at ambient temperature gave a product in 74% isolated yield, consisting of **2** (88%, *E*:*Z* = 3.6:1), **2′** (4%), and **3** (8%).[11] In order to avoid com-



peting Diels–Alder addition between the oxidant (benzoquinone) and the diene, the latter was added slowly (16 h) to the reaction mixture. Acetoxychlorination of isoprene in acetic acid with *tert*-butyl hypochlorite has been reported, but the method is less selective and gives only moderate yields of **2**.[12]

Scheme I[a]



[a] a, $Pd(OAc)_2$ catalyst, HOAc, benzoquinone, LiCl, LiOAc, 30 °C; b, $Pd(OAc)_2$-PPh_3 catalyst, NaCH(COOMe)$_2$, THF, 20 °C; c, $Pd(OAc)_2$-PPh_3 catalyst, NaCH(COMe)(COOMe), THF, 55 °C; d, H_2O, LiCl, Me_2SO, 170 °C; e, $Pd(OAc)_2$-PPh_3 catalyst, THF, NaCH(COOMe)$_2$, 20 °C, then NaCH(COMe)(COOMe), 55 °C.

The chloride in **2** was smoothly displaced by sodium dimethyl malonate in refluxing acetonitrile, yielding the monoalkylated product **4** (76%). As an alternative procedure for the transformation of **2** to **4** the chloroacetate **2** was allowed to react with sodium dimethyl malonate at 16 °C in THF in the presence of a palladium catalyst ($Pd(OAc)_2/PPh_3$).[13] The latter procedure is rapid (98% conversion after 5 min according to GLC) and results in a higher isolated yield (92%). The *E*/*Z* ratio was slightly changed during the palladium-catalyzed transformation of **2** to **4** and was increased to 4.3/1 in **4** (GLC, ^1H NMR). The (*E*)-**2** isomer reacts ca. two times faster than the (*Z*)-**2** isomer in the palladium-catalyzed substitution, which is consistent with the less steric hindrance for the palladium catalyst in the activation of (*E*)-**2**.

Palladium-catalyzed alkylation of **4** with sodium methyl acetoacetate gave **5** in 78% isolated yield. The rate and the stereochemical outcome of this reaction depend on the phosphine ligand used. Thus, triphenylphosphine as ligand afforded >95% of the *E* isomer, whereas 1,2-bis(diphenylphosphino)ethane as ligand gave an *E*/*Z* ratio of 85/15. The latter reaction was found to be approximately 40–50 times faster than the former. A double selective decarbomethoxylation was performed by heating **5** in wet dimethyl sulfoxide in the presence of LiCl to give **6** in 65% yield.[14] The *E*/*Z* ratio of **5** and **6** was established by ^1H NMR spectroscopy. Comparison with the reported[6] ^1H NMR spectra of the *E* and *Z* isomer of **6** showed that **6** was of *E* configuration. The transformation of the ester **6** to the dimethyl ester of the pheromone **1a** and subsequent transformations to **1b** and **1c** have been reported.[5,6] The sequence outlined in Scheme I thus formally constitutes a short route to the pheromonal components **1**.

The synthesis can be made more efficient by making the two alkylations in one pot, since the palladium-catalyzed substitution of the chloro group takes place chemoselectively without affecting the acetoxy group.[9,10] Thus, re-

(1) (a) Meinwald, J.; Chalmers, A. M.; Pliske, T. E.; Eisner, T. *Tetrahedron Lett.* **1968**, 4893. (b) Meinwald, J.; Chalmers, A. M.; Pliske, T. E.; Eisner, T. *J. Chem. Soc., Chem. Commun.* **1969**, 86.

(2) Meinwald, J.; Meinwald, Y. C.; Mazzocchi, P. H. *Science (Washington, D.C.)* **1967**, *164*, 1174.

(3) Trost, B. M.: Weber, L. *J. Org. Chem.* **1975**, *40*, 3617.

(4) (a) Katzenellenbogen, J. A.; Christy, K. I. *J. Org. Chem.* **1974**, *39*, 3315. (b) Mazaki, Y.; Sakura, K.; Kaji, K. *Chem. Lett.* **1980**, 1061.

(5) Miles, D. H.; Lowey, D.; Johnson, W. S. *Tetrahedron Lett.* **1972**, 3019.

(6) Trost, B. M.; Bogdanowics, M. J.; Frazee, W. J.; Saltzman, T. M. *J. Am. Chem. Soc.* **1978**, *100*, 5512.

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(10) Byström, S.; Bäckvall, J-E.; Nordberg, R.; Nyström, J.-E. Swedish Patent Appl. 1982, 8 201 911-8.

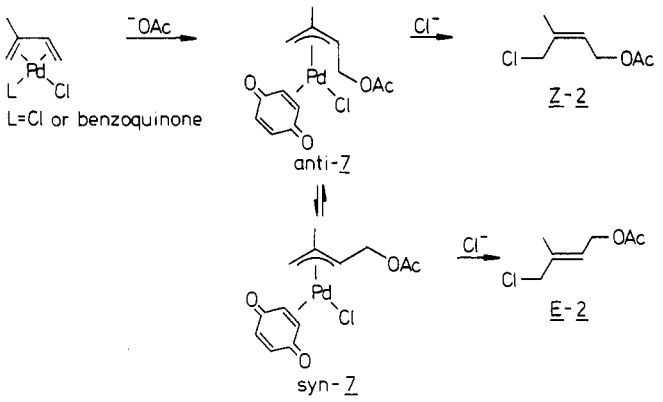
(11) The *E* configuration of the major isomer, which had been enriched relative to the minor one by preparative GLC, was established by NOE measurements. Thus, irradiation of the CH_2Cl group in **2** gave a 31% enhancement of the olefin proton, whereas irradiation of the CH_3 group gave only a 4% enhancement.

(12) Oroshnik, W.; Mallory, R. A. *J. Am. Chem. Soc.* **1950**, *72*, 4608.

(13) The catalyst used in all reactions was $Pd(OAc)_2$ associated with either 4 equiv of PPh_3 or 2 equiv of $Ph_2PCH_2CH_2PPh_2$.

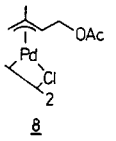
(14) Krapcho, A. P.; Weimaster, J. F.; Eldridge, J. M.; Jahngren, Jr., E. G. E.; Lovey, A. J.; Stephenes, W. P. *J. Org. Chem.* **1978**, *43*, 138.

Scheme II



action of **2** with 2.0 equiv of sodium dimethyl malonate in tetrahydrofuran at ambient temperature in the presence of 2% of palladium catalyst[13] produced **4** within 20 min. Sequential addition of 2 equiv of methyl acetoacetate (to quench the excess dimethyl malonate anion) and 4 equiv of sodium methyl acetoacetate and then warming the mixture at 55 °C for 23 h afforded **5** in 68% overall isolated yield from **2**.

The configuration of the double bond in 4-chloroprenyl acetate (**2**) most likely reflects the geometry in the intermediate π-allyl complex **7** (Scheme II). The anti complex (*anti*-**7**) would give (*Z*)-**2** and the syn complex (*syn*-**7**) would give (*E*)-**2**. It is known that reaction of isoprene with $PdCl_2$ in acetic acid gives only the dimeric syn complex **8**, related to *syn*-**7**, as the thermodynamic product.[15]



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A likely explanation for the *E*/*Z* mixture of **2** is that the initial acetate attack in fact takes place on a very reactive cisoid (η^4-diene)palladium complex. The complex *anti*-**7** thus formed would then undergo a syn–anti isomerization, but the chloride attack would be fast enough to trap some of the anti isomer.[16]

The palladium-catalyzed alkylation of **4** to **5** in which the olefin geometry of the minor isomer (*Z*)-**4** is changed from *Z* to *E* needs some comment. It has previously been observed that 3,3-disubstituted allylic acetates undergo palladium-catalyzed nucleophilic substitutions with the olefin geometry retained.[17,18] The present results show that the olefin stereochemistry in the reaction of 3,3-disubstituted allylic acetate depends on both the substrate and the ligand. We conclude that the previously observed retention of the geometry around a trisubstituted double bond in palladium-catalyzed allylic alkylations is not a general phenomenon.

Concluding Remarks

4-Chloroprenyl acetate (**2**) is a bifunctional electrophilic prenylating agent which can be selectively functionalized in the 1- and 4-positions. The chloroacetate (*E*)-**2** has previously been used in the syntheses of vitamins A[19] and K,[20] although it was prepared by less conveniant methods. Despite the isomeric *E*/*Z* mixture of chloroacetate **2** (*E*/*Z* = 3.6/1), it has now been shown to be useful for the stereospecific synthesis of trisubstituted double bonds of the *E* configuration by using palladium(0)-catalyzed substitution reactions. In light of this work and the fact that other metals (Fe, Cu, Ni, Mo) can also promote nucleophilic substitution of an allylic acetoxy group,[20,21] the acetoxychlorination method[9] used herein opens new ways of using isoprene more directly in terpenoid syntheses.[22]

Experimental Section

Infrared spectra were recorded on a Perkin-Elmer 420 spectrophotometer. NMR spectra were obtained with a Bruker WP 200 MHz FT spectrometer. ^{13}C NMR multiplicities were obtained by proton off-resonance decoupling at 1650 Hz. The slow diene additions were performed with a Sage Instruments (Division of Orion Research Inc.) Model 355 syring pump. Bulb-to-bulb distillations were performed with a Büchi kugelröhr apparatus. Tetrahydrofuran (THF) was distilled from a deep blue solution of potassium/benzophenone. Acetonitrile, analytical grade, was dried with 4 Å molecular sieves. Dimethylsulfoxide (Me_2SO) was distilled from calcium hydride and stored over 4 Å molecular sieves. Dimethyl malonate and methyl acetoacetate were distilled and then stored over 4 Å molecular sieves. Sodium dimethyl malonate was generated with sodium hydride and dimethyl malonate in THF. The THF was removed in vacuo and replaced with CH_3CN when required. Palladium acetate was purchased from Engelhardt Industries. 1,2-Bis(diphenylphosphino)ethane (biphos) was purchased from Aldrich. Microanalyses were performed by "Centrala Analyslaboratoriet Kemikum" Uppsala, Sweden. GLC analyses were performed on 2.4 m × 6 mm glass column packed with 5% SE on Chromosorb W.

1-Acetoxy-4-chloro-3-methyl-2-butene (2). To a stirred solution of palladium acetate (90 mg, 0.4 mmol), benzoquinone (950 mg, 8.8 mmol), $LiOAc{\cdot}2H_2O$ (856 mg, 8.4 mmol), and LiCl (386 mg, 9.2 mmol) in 20 mL of acetic acid at 30 °C was slowly added isoprene (272 mg, 4.0 mmol) via a syringe (using a syringe pump) during 16 h. The reaction mixture was allowed to stir for another 10 h and was quenched with 10 mL of brine and extracted with pentane (5 × 20 mL). The yellow organic phase was washed twice with 5 mL of H_2O, twice with 5 mL of saturated aqueous Na_2CO_3, and twice with 5 mL of 2 M NaOH, and dried ($MgSO_4$). After filtration the solvent was evaporated and the residue was bulb-to-bulb distilled (100 °C/1 torr), yielding 480 mg (74%) of a yellow liquid, which consisted of (*E*)-**2** (69%), (*Z*)-**2** (19%), **2′** (4%), and **3** (8%): IR (neat) 2950, 1740, 1440, 1380, 1240, 1030 cm^{-1}. Anal. Calcd for $C_7H_{11}ClO_2$: C, 51.70; H, 6.82; Cl, 21.80. Found: C, 51.80; H, 6.70; Cl, 21.73.

(*E*)-**2**: ^1H NMR ($CDCl_3$) δ 5.70 (br t, J = 6.78 Hz, 1 H, CH=C), 4.63 (dt, J = 6.76 Hz, J = 0.6 Hz, 2 H, CH_2OAc), 4.02 (d, J = 0.6 Hz, 2 H, CH_2Cl), 2.07 (s, 3 H, AcO), 1.83 (d, J = 0.6 Hz, 3 H, CH_3C=C); ^{13}C NMR ($CDCl_3$) δ 170.80 (CH_3COO), 137.00 (CH_3C=CH), 123.80 CH_3C=CH, 60.78 (CH_2OAc), 50.81 (CH_2Cl), 20.91 (CH_3COO), 14.61 (CH_3C=C).

(*Z*)-**2**: ^1H NMR ($CDCl_3$) δ 5.56 (br t, J = 7 Hz, 1 H, *CH*=C), 4.63 (d, J = 7 Hz, 2 H, CH_2OAc), 4.10 (s, 2 H, CH_2Cl), 2.06 (s, 3 H, AcO), 1.90 (d, J = 0.3 Hz, 3 H, CH_3C=C).

(15) (a) Rowe, J. M.; White, D. A. *J. Chem. Soc. A* **1967**, 1451. (b) Alkylation of **8** was the key step in a vitamin A synthesis: Manchand, P. S. Wong, H. S.; Blunt, J. F. *J. Org. Chem.* **1978**, *43*, 4769.

(16) Acetoxychlorination of 1,3-butadiene gave (*E*)- and (*Z*)-1-acetoxy-4-chloro-2-butene in a ratio of ca. 95:5: Nyström, J.-E.; Bäckvall, J.-E., unpublished results.

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(21) (a) Magid, R. M. *Tetrahedron* **1980**, *36*, 1901. (b) Yamamoto, Y.; Yamamoto, S.; Ytagi, H.; Muramaya, K. *J. Am. Chem. Soc.* **1980**, *102*, 2318. (c) Roustan, J. L.; Marour, I. Y.; Houlihan, F. *Tetrahedron Lett.* **1979**, 3721. (d) Yamamoto, T.; Ishizu, J.; Yamamoto, A. *J. Am. Chem. Soc.* **1981**, *103*, 6863. (e) Trost, B. M.; Lautens, M. *Ibid.* **1982**, *104*, 5543.

(22) (a) Sequential palladium-catalyzed alkylation of 2-cyclopentene-1,4-diol dicarboxylates was recently studied,[22b] and a discrete two-step alkylation has been used to construct vinylcyclopropanes from 2-alkene-1,4-diol derivatives.[22c] For related sequential nucleophilic substitutions see also ref 22d. (b) Valpey, R. S.; Miller, D. J.; Esters, J. M.; Godleski, S. A. *J. Org. Chem.* **1982**, *47*, 4717. (c) Genet, J. P.; Piau, F. *Ibid.* **1981**, *46*, 2414. (d) Tanigawa, Y.; Nishimura, K.; Kawasaki, A.; Murahashi, S. I. *Tetrahedron Lett.* **1982**, 23, 5549.

2′: ^{1}H NMR ($CDCl_3$) δ 5.11 (br s, 1 H, one of C=CH_2), 5.02 (br s, 1 H, one of C=CH_2), 4.54 (t, J = 7 Hz, 1 H, CH—Cl), 4.30 (d, J = 7 Hz, 2 H, CH_2OAc), 2.08 (s, 3 H, AcO), 1.83 (s, 3 H, CH_3C=C).

3 (distinguishible peaks in mixture with **2**): ^{1}H NMR ($CDCl_3$) δ 4.15 (d, J = 8 Hz, 2 H, CH_2Cl).

Methyl 6-Acetoxy-2-carbomethoxy-4-methyl-4-hexenoate (4) Using Classical Nucleophilic Substitution. To a solution of sodium dimethyl malonate (2.2 mmol) in 20 mL of CH_3CN was added 326 mg (1.94 mmol) of **2**. The reaction mixture was stirred for 4 h at 80 °C and then allowed to cool to room temperature. Sodium bicarbonate (0.5 g) was added and after stirring for another 30 min the precipitate (NaCl) was filtered off. The mother liquor was concentrated to 496 mg of a brown oil. The excess dimethyl malonate was removed by bulb-to-bulb distillation at 100 °C (1 torr), and distillation of the residue (200 °C (1 torr)) gave 380 mg (76%) of **4** as a colorless oil. The E/Z ratio (3.5/1) was established by both GLC and ^{1}H NMR (vide infra).

4 via Palladium(0)-Catalyzed Nucleophilic Substitution. To a stirred solution of 324 mg (2 mmol) of **2**, 9 mg (0.04 mmol) of palladium acetate, and 42 mg (0.16 mmol) of triphenylphosphine in 2 mL of THF was added 20 mL of 0.4 M sodium dimethyl malonate (8 mmol) in THF under nitrogen atmosphere at 16 °C. A brownish homogeneous solution was formed immediately and turned pale in a few seconds on precipitation of sodium chloride. After 20 min, the reaction mixture was cooled to about −10 °C, and 3 mL of 1 M H_2SO_4 was added. After extraction with ether (5 × 15 mL) the combined organic phase was washed with 5 mL of water and 5 mL of brine and finally dried ($MgSO_4$). After filtration the solvent was evaporated and the residue was eluated through a 0.5 × 10 cm silica gel column with 15 mL of pentane and then 30 mL of ether. The ethereal fraction was concentrated and the excess dimethyl malonate was removed by bulb-to-bulb distillation (100 °C (1 torr)). Distillation of the residue (487 mg) (200 °C (1 torr)) gave 472 mg (92%) of product **4** as a colorless liquid. The E/Z ratio (4.3/1) was established by both GLC and ^{1}H NMR. IR (neat): 2960, 1740, 1440, 1240, 1160, 1025 cm^{-1}. Anal. Calcd for $C_{12}H_{18}O_6$: C, 55.81; H, 7.02. Found: C, 55.60; H, 7.05.

(*E*)-**4**: ^{1}H NMR ($CDCl_3$) δ (br t, J = 7.0 Hz, 1 H, CH=C), 4.55 (d, J = 7.0 Hz, 2 H, CH_2OAc), 3.73 (s, 6 H, CH_3O), 3.60 (t, J = 7.8 Hz, 1 H, $CH(COOMe)_2$), 2.65 (d, J = 7.8 Hz, 2 H, $CH_2CH(COOMe)_2$), 2.04 (s, 3 H, OAc), 1.72 (s, 3 H, CH_3C=C); ^{13}C NMR ($CDCl_3$) 170.8 (s, CO in AcO), 169.2 (s, CO in CO_2Me), 137.6 (s, C=CH), 121,4 (d, C=CH), 60.9 (t, CH_2OAc), 52.5 (q, CH_3O), 50.3 (d, $CH(COOMe)_2$), 38.3 (t, $CH_2CH(COOCH_3)_2$), 20.9 (q, CH_3 in AcO), 16.2 (q, CH_3C=C).

(*Z*)-**4**: ^{1}H NMR ($CDCl_3$) δ 5.35 (br t, J = 7 Hz, 1 H, CH=C), 4.58 (d, J = 7 Hz, 2 H, CH_2OAc), 3.73 (s, 6 H, CH_3O), 3.58 (t, J = 8.0 Hz, 1 H, $CH(COOMe)_2$), 2.72 (d, J = 8 Hz, 2 H, $CH_2CH(COOMe)_2$), 2.05 (s, 3 H, AcO), 1.76 (s, 3 H, CH_3C=C).

Methyl (*E*)-2,7-Dicarbomethoxy-4-methyl-8-oxo-4-nonenoate (5). A solution of 7.2 mmol of sodium methyl acetoacetate, prepared from 940 mg (8 mmol) of methyl acetoacetate and 24 mg (712 mmol) of sodium hydride (90%), in 15 mL of THF was added to a stirred solution of 453 mg (1.76 mmol) of **4**, 9.7 mg (0.043 mmol) of palladium acetate, and 41.5 mg (0.16 mmol) of triphenylphosphine in 2 mL of THF at room temperature under nitrogen atmosphere. After the homogeneous yellow solution was stirred at 55 °C for 24 h (98% conversion after 21 h (GLC)), the reaction mixture was cooled to ambient temperature and then 2.5 mL of 1 M H_2SO_4 and 20 mL of saturated $NaHCO_3$ was added. After extraction with ether (5 × 15 mL) the combined organic phase was washed with 5 mL of saturated $NaHCO_3$ and 5 mL of brine and dried ($MgSO_4$). After filtration the solvent was evaporated and the residue (1.1 g) was eluated through a 0.5 × 10 cm column of silica gel with 15 mL of pentane, 15 mL of pentane/ether (4/1), and finally 40 mL of ether. The ether fraction was concentrated and the excess methyl acetoacetate was removed by bulb-to-bulb distillation (100 °C (1 torr)). Distillation of the residue (460 mg) at 250 °C (1 mm) gave 432 mg (78%) of **5** as a colorless oil (>95% *E*): ^{1}H NMR($CDCl_3$) δ 5.11 (br t, J = 7.3 Hz, 1 H, CH=C), 3.73 (s, 3 H, MeCOCHCOOCH_3), 3.72 (s, 6 H, $CH(COOCH_3)_2$), 3.54 (t, J = 7.9 Hz, 1 H, $CH(COOCH_3)_2$), 3.44 (t, J = 7.5 Hz, 1 H, $CH_3COCHCOOCH_3$), 2.6–2.5 (m, 4 H, $CH_2C(CH_3)$=$CHCH_2$), 2.22 (s, 3 H, $CH_3COCHCOOMe$), 1.65 (s, 3 H, CH_3C=C); ^{13}C NMR ($CDCl_3$) δ 202.5 (s, $CH_3COCHCOOCH3$), 169.8 (s, $CH_3COCHCOOCH_3$), 169.4 (s, $CH(COOCH_3)_2$, 134.3 (s, C=CH), 124.2 (d, C=CH), 59.3 (d, $CH_3COCHCOOCH_3$), 52.5 (q, $COOCH_3$), 52.4 (d, $CH(COOCH_3)_2$), 38.5 (t, $CH_2CH(COOCH_3)$, 29.2 (q, $CH_3COCHCOOCH_3$), 26.9 (t, $CH_2CH(COCH_3)COOCH_3$), 15.9 (q, CH_3C=C); IR (neat) 2960, 1740, 1440, 1250 br, 1160 cm^{-1}. Anal. Calcd for $C_{15}H_{22}O_7$: C, 57.31; H, 7.05. Found: C, 57.61; H, 6.97. The *Z* isomer of **5** is distinguishible in an E/Z mixture by ^{1}H NMR ($CDCl_3$) δ 2.24 (s, CH_3CO).

When the same reaction was performed with 1,2-bis(diphenylphosphino)ethane (32 mg, 0.08 mmol) as ligand, **5** was obtained in 76% isolated yield within 1 h in an E/Z ratio of 85/15.

One-Pot Synthesis of 5 from 2. A. PPh_3 as Ligand. To a stirred solution of 324 mg (2 mmol) of **2**, 9.6 mg (0.04 mmol) of palladium acetate, and 41 mg (0.16 mmol) of triphenylphosphine in 4 mL of THF under nitrogen atmosphere at room temperature was added 10 mL of 0.4 M sodium dimethyl malonate (4.0 mmol) in THF. The conversion was monitored by GLC and after 20 min all of **2** had been consumed. Methyl acetoacetate (464 mg, 4.0 mmol) and 20 mL of 0.4 M sodium methyl acetacetate (8 mmol) in THF was added and the temperature was raised to 55 °C. After 23 h, the reaction was worked up as described above for **5**. The excess dimethyl malonate and methyl acetoacetate was removed by bulb-to-bulb distillation (110 °C (1 torr)). Distillation of the residue (574 mg) at 250 °C (1 torr) gave 427 mg (68%) of **5** (>95% *E*).

B. $Ph_2PCH_2CH_2PPh_2$ as Ligand. The same procedure was used but triphenylphosphine was replaced with 1,2-bis(diphenylphosphino)ethane (32 mg, 0.08 mmol) and the reaction time of the second step was only 1 h; yield 357 mg (58%) of **5** (E/Z = 85/15).

Methyl (*E*)-4-Methyl-8-oxo-4-nonenoate (6). A solution of 393 mg (1.25 mmol) of **5**, 215 mg (5.1 mmol) of LiCl, and 45 mg (2.5 mmol) of H_2O was heated in 3 mL of Me_2SO to 173 °C. The homogeneous yellow solution turned opalescent in a few minutes with evolution of gas. After 45 min (97% conversion after 25 min) the reaction mixture was poured on ice (~7 g) and extracted with pentane (5 × 5 mL) and ether (10 mL). The combined organic layer was washed with H_2O (5 mL) and brine (5 mL) and dried ($MgSO_4$). The solvent was evaporated and the Me_2SO was removed by bulb-to-bulb distillation (80 °C (1 torr)). Distillation of the residue (220 mg) gave 160 mg (65%) of **6** (>95% *E*) as a colorless liquid.[6] The E/Z ratio can be established by ^{1}H NMR.

(*E*)-**6**: ^{1}H NMR ($CDCl_3$) 5.11 (br t, J = 6.2 Hz, 1 H, HC=C), 3.66 (s, 3 H, CH_3O), 2.5–2.2 (m, 4 H, $CH_2C(CH_3)$=$CHCH_2$), 2.13 (s, 3 H, CH_3CO), 1.73 (s, 3 H, CH_3C=C); ^{1}H NMR ($CCl_4/CDCl_3$ = 8/1) δ 5.08 (br t, J = 6.5 Hz, 1 H, 3.63 (s, 3 H, CH_3OOC), 2.5–2.2 (m, 4 H, $CH_2C(CH_3)$=CCH_2), 2.09 (s, 3 H CH_3CO), 1.63 (s, 3 H, CH_3C=C); ^{13}C NMR ($CDCl_3$) 208.41 (s, CH_3COCH_2), 173.71 (s, CH_3OOC), 136.67 (s, CH=CCH_3), 123.49 (d, CH=CCH_3), 51.48 (q, CH_3OOC), 45.53 (t), 34.58 (t), 31.91 (t), 29.91 (q, CH_3COCH_2), 22.37 (t), 15.87 (q, CH=CCH_3); IR (neat) 2960, 1740, 1720, 1440, 1260, 1160 cm^{-1}. The *Z* isomer of **6** is distinguishible in an E/Z mixture by ^{1}H NMR ($CDCl_3$) δ 1.68 (s, CH_3C=C).

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Registry No. (*E*)-**2**, 24529-80-4; (*Z*)-**2**, 24529-81-5; **2′**, 38872-51-4; **3**, 58511-44-7; (*E*)-**4**, 87040-02-6; (*Z*)-**4**, 87040-03-7; (*E*)-**5**, 87040-04-8; (*E*)-**6**, 67884-61-1; PPh_3, 603-35-0; $Ph_2PCH_2CH_2PPh_2$, 1663-45-2; $NaCH(COOMe)_2$, 18424-76-5; NaCH(COMe)(COOMe), 34284-28-1; isoprene, 78-79-5; 1,3-butadiene, 106-99-0; (*E*)-1-acetoxy-4-chloro-2-butene, 34414-28-3; (*Z*)-1-acetoxy-4-chloro-2-butene, 55613-61-1.