equiv, 0.45 mmol) and HMPA (2 equiv, 0.6 mmol) in THF (1 mL), the reaction mixture was stirred at −78 °C for 45 min and then at rt for 3 h, followed by quenching with cold saturated $NaHCO_3$ solution. The aqueous phase was extracted with hexane. The combined organic layers were washed with brine and dried ($MgSO_4$). Removal of the solvent in vacuo gave crude silyl enol ether.

Ethyl 4-((*tert*-Butyldimethylsilyl)oxy)-6-oxobicyclo-[3.2.1]oct-2-ene-2-carboxylate (8). Following the general procedure for silylation of **5a** [(90 mg, 0.28 mmol); LDA (0.34 mmol); TBSCl (62 mg, 0.41 mmol); HMPA (0.56 mmol)], 107 mg (88%) of the crude silyl enol ether **7** was obtained after filtration through silica gel: ^1H NMR ($CDCl_3$) δ 6.28–6.30 (ca, 1 H), 5.19 (d, 1 H, J = 3.0 Hz), 4.49 (dd, 1 H, J = 5.2, 2.8 Hz), 4.19 (q, 2 H, J = 7.1 Hz), 3.07–3.10 (ca, 1 H), 2.67 (br ddd, 1 H, J = 5.2, 5.0, 1.4 Hz), 2.23 (ddd, 1 H, J = 10.0, 5.2, 5.0 Hz), 1.70 (d, 1 H, J = 10.0 Hz), 1.29 (t, 3 H, J = 7.1 Hz), 0.93 (s, 9 H), 0.92 (s, 9 H), 0.15 (s, 3 H), 0.13 (s, 6 H), 0.12 (s, 3 H).

To a stirred solution of **7** in THF (3 mL) was added 2 mL of 1 M HCl solution. After being stirred at rt for 1 h, the reaction mixture was quenched with saturated $NaHCO_3$ solution. The aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with brine and dried (Na_2SO_4). Removal of the solvent gave a crude product which was purified by flash column chromatography (silica gel, gradient elution, 5–20% EtOAc in hexane) to afford **8** (67 mg, 74%): R_f = 0.40 (hexane/EtOAc, 4:1); IR (film) ν_{max} 2956, 2931, 1746, 1716, 1642, 1258, 1107, 1063, 839 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.50 (dd, 1 H, J = 2.6, 1.2 Hz), 4.65 (dd, 1 H, J = 5.9, 2.6 Hz), 4.23 (q, 2 H, J = 7.2 Hz), 3.31–3.37 (ca, 1 H), 2.61 (br dd, 1 H, J = 5.9, 5.6 Hz), 2.37–2.45 (ddd, 1 H, J = 18.0, 6.0, 1.0 Hz), 2.23–2.32 (dd, 1 H, J = 18.0, 3.2 Hz), 2.08–2.15 (ddd, 1 H, J = 12.0, 5.6, 4.2 Hz), 1.96–2.03 (br dd, 1 H, J = 12.0, 3.2 Hz), 1.31 (t, 3 H, J = 7.2 Hz), 0.92 (s, 9 H), 0.09 (s, 3 H), 0.07 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 213.3, 165.8, 138.4, 137.9, 70.7, 60.9, 52.1, 48.8, 35.1, 32.1, 25.7, 18.2, 14.2, −4.7, −4.8; MS (EI, 70 eV) m/z (rel intensity) 324 (11, M^+), 309 (100), 193 (50), 75 (57); exact mass calcd for $C_{17}H_{28}O_4Si$ 324.1756, found 324.1748.

Ethyl 4-Hydroxy-6-oxobicyclo[3.2.2]non-2-ene-2-carboxylate (11b). Following the general procedure for silylation of **6a** [(100 mg, 0.30 mmol); LDA (0.36 mmol); TBSCl (70 mg, 0.45 mmol) and HMPA (0.6 mmol)], 115 mg (86%) of the silyl enol ether **10** was obtained after filtration through silica gel: ^1H NMR ($CDCl_3$) δ 6.45–6.48 (ca, 1 H), 5.34 (dd, 1 H, J = 8.1, 2.2 Hz), 4.19 (q, 2 H, J = 7.1 Hz), 4.11 (dd, 1 H, J = 4.4, 4.2 Hz), 3.48–3.53 (ca, 1 H), 2.60–2.64 (ca, 1 H), 1.86–1.98 (m, 1 H), 1.47–1.69 (m, 3 H), 1.29 (t, 3 H, J = 7.1 Hz), 0.92 (s, 9 H), 0.91 (s, 9 H), 0.12 (s, 12 H); exact mass calcd for $C_{24}H_{45}O_4Si_2$ 453.2856, found 453.2863.

A mixture of the silyl enol ether **10**, 1 M HCl solution (2 mL), and THF (4 mL) was stirred at rt for 4 h. The cooled reaction mixture was diluted with CH_2Cl_2 and poured into a saturated $NaHCO_3$ solution. The aqueous phase was extracted thoroughly with CH_2Cl_2. The combined organic layers were washed with brine and dried (Na_2SO_4). Removal of solvent gave a crude product, which was purified by flash column chromatography (silica gel, 10% deactivated with H_2O; hexane/EtOAc, 1:1) to yield **11b** (52 mg, 78%), as a white solid from ether: mp 91.5 °C (ether); R_f = 0.35 (hexane/EtOAc, 2:3); IR (KBr) ν_{max} 3388, 3002, 2948, 1716, 1690, 1654, 1255, 1185, 1050 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.86–6.88 (ca, 1 H), 4.50 (dd, 1 H, J = 4.0, 3.9 Hz), 4.22 (q, 2 H, J = 7.1 Hz), 3.52 (ca, 1 H), 2.82–2.86 (br dd, 1 H, J = 5.8, 4.4 Hz), 2.54 (d, 2 H, J = 3.7 Hz), 1.82–2.18 (m, 4 H), 1.31 (t, 3 H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 212.3, 153.2, 139.7, 139.3, 72.9, 61.3, 53.5, 47.2, 28.9, 25.3, 19.9, 14.1; MS (EI, 70 eV) m/z (rel intensity) 224 (M^+, 30), 195 (51), 178 (81), 136 (34), 107 (34), 91 (58), 79 (65), 55 (100). Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.20; H, 7.19.

Thermolysis of 9b. Following the general procedure for silylation of **5b** [(198 mg, 0.6 mmol); LDA (0.72 mmol); TBSCl (135 mg, 0.9 mmol); HMPA (0.6 mmol)], 230 mg (86%) of **9b** was obtained after filtration through silica gel: ^1H NMR ($CDCl_3$) δ 6.41 (d, 1 H, J = 12.1 Hz), 5.06 (d, 1 H, J = 12.1 Hz), 4.23 (br s, 1 H), 3.99–4.14 (m, 2 H), 2.48–2.54 (m, 2 H), 1.93–1.96 (m, 1 H), 1.75–1.80 (m, 1 H), 1.21 (t, 3 H, J = 7.1 Hz), 0.93 (s, 9 H), 0.90 (s, 9 H), 0.17 (s, 3 H), 0.16 (s, 3 H), 0.12 (s, 6 H).

A solution of **9b** (138 mg, 0.3 mmol) in dry benzene (5 mL) was placed in a pyrolysis tube and degassed. The tube was cooled with liquid nitrogen, sealed under vacuum, and then heated in a sand bath (150 °C) for 8 h. The tube was cooled to rt and unsealed. Removal of the solvent gave 132 mg (95%) of **7**.

Thermolysis of 12b. Following the general procedure for silylation of **6b** [(208 mg, 0.61 mmol); LDA (0.73 mmol); TBSCl (137 mg, 0.9 mmol); HMPA (1.2 mmol)], 241 mg (86%) of **12b** was obtained after filtration through silica gel: ^1H NMR ($CDCl_3$) δ 6.42 (d, 1 H, J = 12.0 Hz), 5.16 (d, 1 H, J = 12.0 Hz), 4.67 (dd, 1 H, J = 5.4, 2.7 Hz), 4.09 (q, 2 H, J = 7.1 Hz), 1.95–2.10 (m, 2 H), 1.67–1.79 (m, 2 H), 1.52–1.58 (m, 1 H), 1.45 (d, 1 H, J = 8.8 Hz), 1.23 (t, 3 H, J = 7.1 Hz), 0.93 (s, 9 H), 0.90 (s, 9 H), 0.19 (s, 3 H), 0.16 (s, 3 H), 0.12 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 170.3, 147.4, 143.8, 112.8, 101.0, 60.5, 34.9, 27.1, 26.3, 25.7, 21.2, 18.0, 16.9, 14.0, −4.4.

Silyl ether **12b** (97 mg) was subjected to the thermolysis following the same procedure as described above to give 86 mg (88%) of **10**.

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Registry No. 5a, 127179-60-6; **5b**, 127179-59-3; **6a**, 127085-76-1; **6b**, 127179-61-7; **7**, 138878-69-0; **8**, 138878-70-3; **9b**, 138878-71-4; **10**, 138878-72-5; **11b**, 138878-68-9; **12b**, 138878-67-8.

Supplementary Material Available: ^1H and ^{13}C NMR spectra for compounds **7**, **8**, **9b**, **10**, **11b**, and **12b** (9 pages). Ordering information is given on any current masthead page.

An Improved Procedure for the Introduction of the δ-Lactone Portion of HMG-CoA Reductase Inhibitors

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In 1985, Heathcock published the synthesis of the ketophosphonate **1** and demonstrated its use in the preparation of the hypocholesterolaemic HMG-CoA (3-hydroxy-3-methylglutaryl coenzyme A) reductase inhibitor compactin.[1] Subsequently, **1** has been used in the synthesis of other mevinic acids including dihydromevinolin,[2] as well as monocyclic[3] and heterocyclic[4] analogues of these compounds.

The coupling of **1** with aldehydes represents an attractive approach to the synthesis of this clinically important series of compounds since it introduces the crucial dihydroxy acid side chain as a single unit that can be easily

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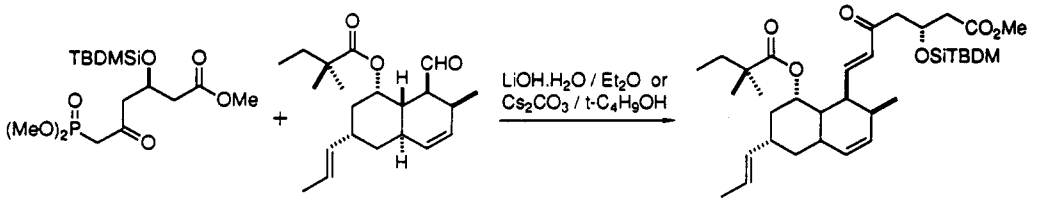
Scheme I



1 2 3

Table I. Conditions Used for Coupling Reaction[a]

base	solvent	% conversion[b]
DBU/LiCl	DMSO	40
LiHMDS	THF	40
LiHMDS	THF	20[c]
LiHMDS	Toluene	30
LiHMDS	MeCN	<10
LiHMDS	DMSO	<10
LiHMDS	Et_2O	75
$LiOH·H_2O$	THF	40
$LiOH·H_2O$	Et_2O	80
NaHMDS	THF	40[d]
NaHMDS	toluene	30[d]
NaH	THF	<10
KHMDS	THF	<10[d]
KOtBu	THF	45[d]
K_2CO_3	*i*-PrOH	25[d]
Cs_2CO_3	*i*-PrOH	60
$BaCO_3$	*i*-PrOH	<10
Cs_2CO_3	*t*-BuOH	50
Cs_2CO_3	*t*-BuOH	60[c]

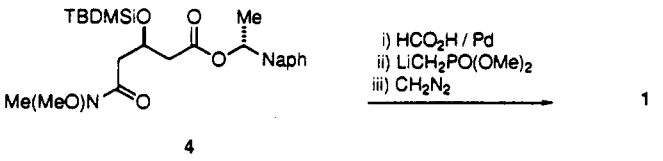
[a] All reactions were run at room temperature for 3–4 days with 1–1.2 equiv of ketophosphonate. Only reactions in which no β-elimination was seen are listed. [b] As estimated from the integrals of the aldehyde (δ 9.7), epimerized aldehyde (δ 9.8), and enone (δ 6.0 and 6.75) signals in the ^1H NMR spectrum of the crude reaction mixture. [c] With nonsilylated ketophosphonate. [d] No ketophosphonate 1 remaining.

and stereoselectively converted to the final products. However, this approach currently has three major drawbacks: (i) both the ketophosphonate 1 and product enones are base sensitive, and β-elimination of the silyloxy group is often observed (the coupling has to be monitored carefully and the reaction stopped after only 40–50% conversion); (ii) epimerization of the reacting aldehyde may take place; and (iii) the synthesis of 1 involves a difficult anion addition that is "extremely sensitive to the reaction conditions"[5] which makes large-scale syntheses problematic.

In this paper we describe conditions for the coupling reaction that can give yields in excess of 80% with no elimination or epimerization together with an improved synthesis of 1.

As part of our program on HMG-CoA reductase inhibitors we wished to couple the sterically congested aldehyde[6] 2 with the ketophosphonate 1 (Scheme I). In previous work the reaction between similar aldehydes and 1 has usually[1-4] been carried out using Roush–Masamune[7] conditions. Using such conditions we obtained only a 37% yield of enone 3 after 5 days, with recovery of most of the remaining aldehyde. We reasoned that by using 1 equiv of a strong base, the ketophosphonate anion would be formed irreversibly and the reaction would be speeded up. It was found that although lithium hexamethyldisilazide

Scheme II



4 → 1

in THF could be used to form the anion, the reaction proceeded at a similar rate and significant amounts of epimerized aldehyde were formed. An additional difficulty was that the yield of enone 3 decreased in larger (>1 g) scale preparations. Bases with other counterions were even less satisfactory. However, use of ether in place of THF gave higher, but still variable, yields (60–75%) together with some epimerized aldehyde (5–15%), a significant improvement over the original conditions. In trying to determine the reasons for the variability in yield we were surprised to find that lithium hydroxide (monohydrate) in ether gave an extremely clean reaction with yields of enone 3 in excess of 80% after 3 days and no detectable elimination or epimerization.[8] The unreacted aldehyde could be recovered and reused. We have carried out the reaction several times on a variety of scales (0.4–30 mmol) and obtained similar results in each preparation.

It would therefore appear that a strong base is not necessary to obtain good yields from this reaction. In support of this conclusion we have found that cesium carbonate can also be used as the base.[9] Again, the counterion is important since both barium and potassium carbonate give poor yields, and in this case the preferred solvent is 2-methyl-2-propanol. Using these conditions yields of enone 3 in excess of 50% have been obtained in 3–4 days, with no detectable side reactions. Similar yields have also been obtained with the unsilylated ketophosphonate.

The ketophosphonate 1 was prepared by a modification of the literature route[5] (Scheme II). In the previous synthesis it was obtained by addition of dimethyl (lithiomethyl)phosphonate to the amide ester 4, a reaction that is difficult to carry out and gives very variable mixtures of products, followed by an ester exchange. We have found that addition of the anion to the amide acid obtained by hydrogenolysis of 4 gives a clean reaction, and treatment of the crude product with diazomethane affords the ketophosphonate 1 in high yield. The entire synthesis of 1 from (*R*)-1-(1′-naphthyl)ethanol[10] can be carried out on a large scale (>100 g) with only one flash chromatography step required at the end to remove small amounts of impurities. We note that after this work was completed a similar modification was published.[11]

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In summary, we have revealed conditions for the efficient coupling of the sterically congested aldehyde 2 with the ketophosphonate 1 that are convenient to carry out, use cheap, readily available bases, and are suitable for large-scale syntheses. Furthermore, such conditions may also be applicable to the synthesis of other HMG-CoA reductase inhibitors and Wittig reactions where both the reagents and products are base sensitive.

Experimental Section

Organic solutions were dried over anhydrous magnesium sulfate. Ether refers to diethyl ether. NMR spectra were acquired at 250 MHz (proton) or 62.9 MHz (carbon) in deuteriochloroform. Coupling constants are given in Hertz.

Methyl (1*S*,2*S*,4a*R*,6*S*,8*S*,8a*S*,3′*R*)-7′-[1,2,4a,5,6,7,8,8a-Octahydro-2-methyl-8-[(2″,2″-dimethyl-1″-oxobutyl)oxy]-6-[(*E*)-prop-1-enyl]-1-naphthalenyl]-3′-[(*tert*-butyldimethylsilyl)oxy]-5′-oxohept-6′-enoate (3). Using Lithium Hydroxide. A mixture of ketophosphonate 1 (241 mg, 0.63 mmol) and lithium hydroxide monohydrate (26.5 mg, 0.63 mmol) in anhydrous ether (3 mL) was stirred at room temperature under argon for 35 min. The aldehyde 2 [(1*S*,2*S*,4a*R*,6*S*,8*S*,8a*S*)-1,2,4a,5,6,7,8,8a-octahydro-2-methyl-8-[(2″,2″-dimethyl-1″-oxobutyl)oxy]-6-[(*E*)-prop-1-enyl]naphthalene-1-carbaldehyde][6] (131 mg, 0.40 mmol) in ether (3 mL) was added and the resulting suspension stirred for 7 days. The suspension was then diluted with more ether (10 mL) and washed with ammonium chloride solution (3 mL) and brine (2 mL). Column chromatography eluting with hexane/ethyl acetate (12:1) gave the unreacted starting aldehyde (12 mg) followed by the required enone 3 (193 mg, 82%; 92% with respect to recovered aldehyde) which was recrystallized from ether/hexane: mp 93–94 °C; δ H 6.77 (1 H, dd, *J* = 17.5 and 10), 6.01 (1 H, d, *J* = 17.5), 5.75 (1 H, ddq, *J* = 15, 7.5 and 2.5), 5.65 (1 H, dq, *J* = 10.5 and 2.5), 5.5–5.3 (2 H, m), 4.95 (1 H, m), 4.62 (1 H, m), 3.68 (3 H, s), 2.83 (1 H, dd, *J* = 17.5 and 5), 2.74 (1 H, dd, *J* = 17.5 and 5), 2.65–2.2 (6 H, m), 2.05–1.2 (10 H, m), 1.14 (3 H, s), 1.12 (3 H, s), 0.95 (3 H, d, *J* = 7.5), 0.88–0.72 (12 H, m), 0.08 (3 H, s), 0.03 (3 H, s); δ C 195.77, 175.15, 170.05, 147.05, 134.46, 130.73, 130.54, 129.51, 121.68, 68.77, 64.55, 49.99, 46.09, 41.33, 41.23, 41.11, 41.01. 40.03, 35.70, 34.53, 34.44, 34.00, 31.56, 29.31, 24.30, 23.23, 23.05, 16.47, 15.03, 7.77, –6.13, –6.47; IR (KBr disc) 2970, 1740, 1720, 1698, 1630 cm^{-1}. Anal. Calcd for $C_{34}H_{56}O_6Si$: C, 69.34; H, 9.57. Found: C. 69.35; H, 9.58.

Using the above method with 7.0 g of aldehyde 2 (21 mmol), 11.29 g of ketophosphonate 1 (29.5 mmol), and 1.24 g of lithium hydroxide gave 0.92 g of recovered aldehyde and 9.45 g (76%; 88% with respect to recovered aldehyde) of enone 3.

Using Cesium Carbonate. 2-Methyl-2-propanol (14 mL) was added to a mixture of the ketophosphonate 1 (1.26 g, 3.30 mmol) and cesium carbonate (1.07 g, 3.28 mmol) and the resulting solution stirred at room temperature for 40 min under argon. A solution of the aldehyde[6] 2 (1.0 g, 3.01 mmol) in 2-methyl-2-propanol (6 mL) was added and the reaction stirred for 4 days. The resulting dark yellow solution was diluted with ether (40 mL) and washed with ammonium chloride solution (20 mL). The aqueous layer was extracted with more ether (2 × 20 mL), and the combined organic layers were washed with brine (2 × 15 mL), dried, and evaporated to give a dark yellow solid. Chromatography on silica eluting first with dichloromethane gave unreacted aldehyde (220 mg). Eluting with hexane/ethyl acetate (4:1) gave the desired enone as a pale yellow solid (930 mg, 53%; 68% with respect to recovered aldehyde).

Methyl (*R*)-3-[(*tert*-Butyldimethylsilyl)oxy]-6-(dimethoxyphosphinyl)-5-oxohexanoate (1). 10% Palladium on carbon (70 g) was carefully added to a solution of the amide[5] 4 (154 g, 0.33 mol) in ethanol (1.2 L) under an argon atmosphere. Formic acid (126 mL, 3.3 mol) was added slowly and the reaction stirred at room temperature overnight. The mixture was filtered through Celite, which was washed thoroughly with methanol, and the solution evaporated to give a greenish oil. The crude oil was cautiously taken up in potassium carbonate solution (1 M; 800 mL), which was then extracted with ether (3 × 200 mL). The aqueous layers were acidified with phosphoric acid (2 M) and extracted with ether (3 × 500 mL) which was dried and evaporated to give the acid as a pale yellow oil (85 g, 83% yield): δ H 0.06 (3 H, s), 0.09 (3 H, s), 0.85 (9 H, s), 2.5–2.88 (4 H, m), 3.18 (3 H, s), 3.68 (3 H, s), 4.62 (1 H, pentet, *J* = 4.8).

Dimethyl methylphosphonate (81 mL, 0.75 mol) in dry THF (400 mL) was added slowly to a solution of *n*-butyllithium (420 mL; 1.6 M in hexanes; 0.68 mol) at –78 °C under an argon atmosphere, and the resulting white suspension stirred for 30 min at –78 °C. A solution of the acid from the previous step (41.7 g, 0.137 mol) in dry THF (200 mL) was cooled to –78 °C and added slowly to the reaction vessel and the resulting yellow suspension stirred for 1 h. The cooling bath was removed and the reaction quenched with phosphoric acid (2 M, 400 mL). The mixture was partitioned between ether (500 mL) and phosphoric acid (2 M, 400 mL), the aqueous layer was extracted with ether (300 mL), and the combined organic layers were washed with brine (300 mL), dried, and evaporated to give the acid as a slightly yellow oil (55 g): δ H 0.06 (3 H, s), 0.09 (3 H, s), 0.83 (9 H, s), 2.54 (2 H, m), 2.88 (2 H, d, *J* = 5.5), 3.10 (2 H, d, *J* = 22.5), 3.76 (6 H, d, *J* = 11), 4.51 (1 H, pentet, *J* = 6.25).

The crude acid was dissolved in dichloromethane (600 mL) in an unblemished 1-L conical flask and cooled in an ice bath. Diazomethane[12] (0.180 mol) was bubbled into the reaction mixture until the bright yellow color persisted. Argon was bubbled through the solution to discharge excess diazomethane, and the solvent evaporated to give a yellow oil. Purification by chromatography on silica eluting with ethyl acetate gave the ketophosphonate 1 as a slightly yellow oil (40.2 g, 0.105 mol, 77% from the acid) with spectral data in accordance with the previously published description.[1]

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Temperature-Dependent Phototransposition Chemistry of 1,5-Dimethylpyrazole and 1,2-Dimethylimidazole

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Introduction

Permutation pattern analysis[1,2] of the pyrazole → imidazole phototransposition indicates that the isomerization occurs by three distinct permutation patterns (P_4, P_6, and P_7) and hence by three distinct transposition mechanisms. The mechanisms which have been proposed for the phototransposition of pyrazole and similar five-membered heterocycles[3-7] are the electrocyclic ring closure–nitrogen walk mechanism[8,9] and the ring contraction–ring expansion mechanism.[10] These mechanisms are illustrated in Scheme I. P_4, P_6, and P_7 in Scheme I refer to the per-

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