Synthetic Studies of Venturicidins. Synthesis of the C1–C14 Segment of Venturicidins

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The C1–C14 segment of venturicidins, (2*R*,6*R*)-3,6-dihydro-6-[(*E*)-7-(dimethoxyphosphinyl)-1-methyl-6-oxo-1-heptenyl]-2-methoxy-5-methyl-2*H*-pyran-2-acetic acid (**1**), has been synthesized. The C8–C13 segment of venturicidins, (*E*)-2-bromo-7-(4,4′-dimethoxytriphenylmethoxy)-2-heptene (**2**), was lithiated with *t*-butyllithium and the resulting vinyllithium compound was coupled with the C1–C7 segment, (2*Z*,7*S*)-7-(*t*-butyldimethylsilyloxy)-8-(*t*-butyldiphenylsilyloxy)-2-methyl-5,5-(trimethylenedithio)-2-octenal (**4**), to afford the alcohol. A subsequent seven-step conversion of this alcohol furnished the synthesis of the C1–C13 segment, (2*R*,6*R*)-3,6-dihydro-6-[(*E*)-6-hydroxy-1-methyl-1-hexenyl]-2-methoxy-5-methyl-2*H*-pyran-2-acetate (**9**). Finally, the known four-step transformation led **9** to the target compound **1**.

The 20-membered macrolide antibiotics venturicidins, A and B, were isolated from several *Streptomyces*[1] and their structures were elucidated by chemical degradations, spectroscopic investigations, and an X-ray crystallographic analysis.[2] Venturicidins exhibit strong activity against a number of plant pathogenic fungi[1] and mitochondorial ATPase.[3] Recently, the aglycone of venturicidins has been synthesized in the optically active form by Akita, Oishi, and their co-workers.[4] Their synthesis consists of the preparation of the C1–C14 and the C15–C27 segments (Fig. 1) and a subsequent condensation of both segments followed by intramolecular Wittig–Horner coupling. In the preparation of the C1–C14 segment **1**, they used the Evans asymmetric aldol reaction in order to secure the C7-stereogenic center[5] and regioselective dehydration under the Mitsunobu conditions to construct the C5–C6 double bond.[4a,6] During the course of our synthetic studies of venturicidins,[7] we succeeded in synthesizing the optically active **1** by using a conceptually different synthetic route, which we describe in this account.

Results and Discussion

Synthetic Plan. The C1–C14 segment **1** includes two chiral centers at the C3 and the C7 positions. Since it could be assumed that the C3-stereogenic center would be established under acidic equilibrium conditions,[4a,6] we aimed at creating the C7-stereogenic center. Since all attempts to assign the chirality of the starting material to the C7-stereogenic center were unsuccessfull, we next planned to establish the C7 center by coupling of the vinyllithium or the vinylchromium reagent generated from **2** or **3**, respectively, with α,β-unsaturated aldehyde **4**, which possesses one chiral center at a remote position (Scheme 1). Aldehyde **4** was obtained by connecting the dithiane derivative **16**, which was derived from (*R*)-glycidol, and the allyl chloride derivative **20** (vide infra). It was anticipated that the chirality in aldehyde **4** might influence the stereoselectivity of the coupling between **4** and **2** (or **3**). When the opposite stereochemical outcome is necessary, we can select (*S*)-glycidol as a starting material. We succeeded in realizing a lithio coupling between **2** and **4** and a $NiCl_2/CrCl_2$-mediated[8] coupling between **3** and **4** as well as a further transformation of each adduct to dihydropyrans **5** and **6**, respectively. Although dimethoxyphosphinyl-substituted aldehyde **7** and/or methoxycarbonyl-substituted carboxylic acid **8** could be obtained from **6** or from **5** (via **6**), their final conversion to the target compound **1** was unsuccessfull because of the instability of **7** and/or **8** under each of the reaction conditions (oxidation and phosphonate introduction, respectively). Therefore, we next planned to synthesize hydroxy ester **9**, which had already been transformed to the target compound **1** via aldehyde **10** by Akita, Oishi, and their co-workers.[4a]

Synthesis of the C8–C13 Segment. The dianion of 5-hexyn-1-ol was silylated with trimethylsilyl chloride (TMSCl) to give **11**, which was subjected to stereospecific reductive alkylation[9] by successive hydroalumination and methylation to afford a trisubstituted olefin **12** (Scheme 2). The *Z*-configuration of **12** was confirmed by a 6.7% NOE enhancement of the olefinic hydrogen at 5.95 ppm by irradiation of the olefinic methyl quartet at 1.74 ppm. Bromination of **12** with bromine in CH_2Cl_2 at −78 °C and subsequent debromosilylation[10] with NaOMe afforded vinyl bromide **13** as a sole product in 71% overall yield from 5-hexyn-1-ol. Irradiation of the olefinic hydrogen at 5.83 ppm caused no NOE enhancement of the olefinic methyl group at 2.21 ppm. This was protected as its 4,4′-dimethoxytriphenylmethyl (DMTr) ether to afford **2** in 97% yield. On the other hand, **13** was oxidized with pyridinium chlorochromate (PCC) in CH_2Cl_2 to afford

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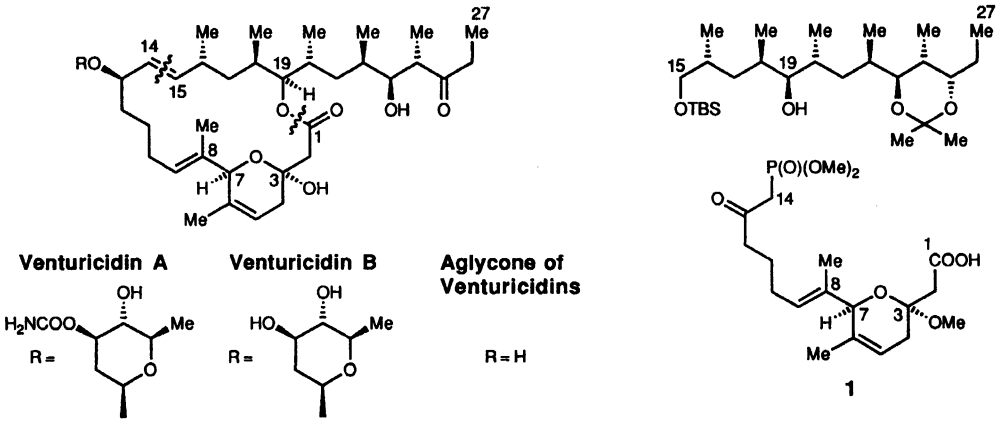
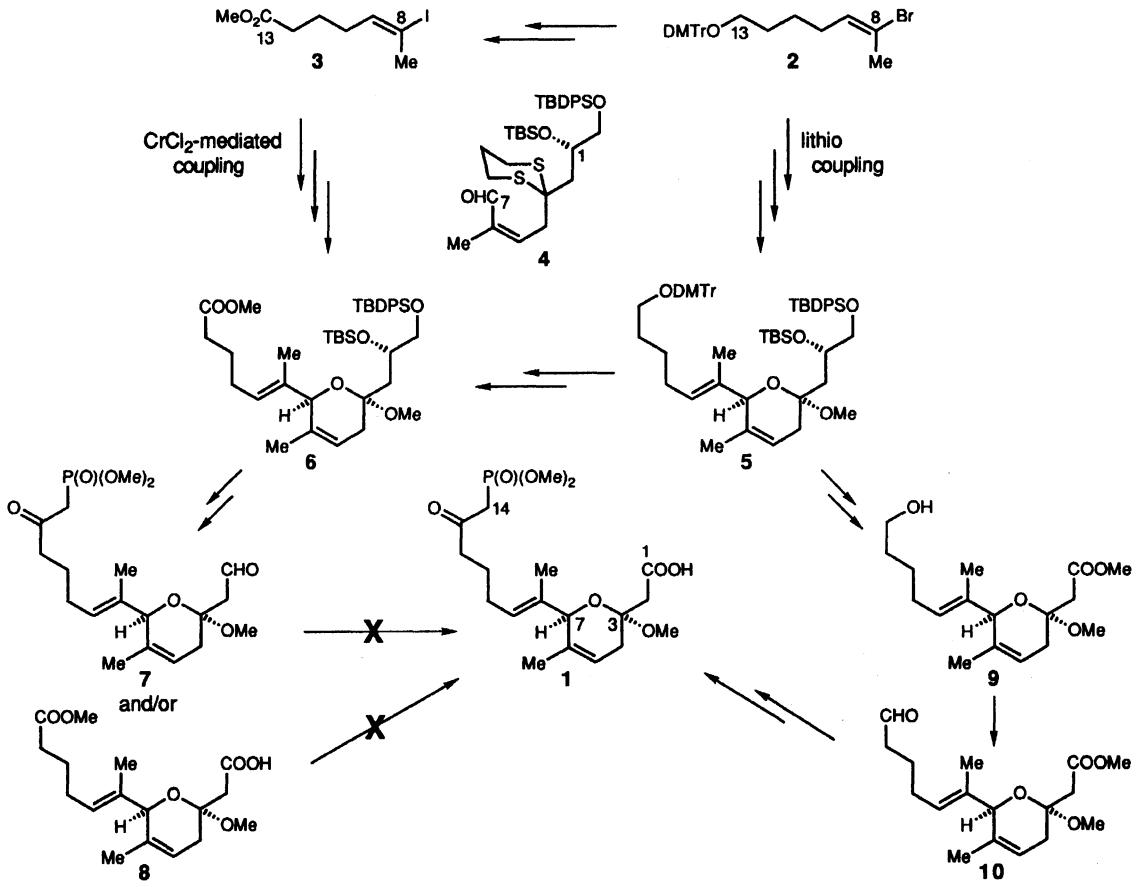


Fig. 1.

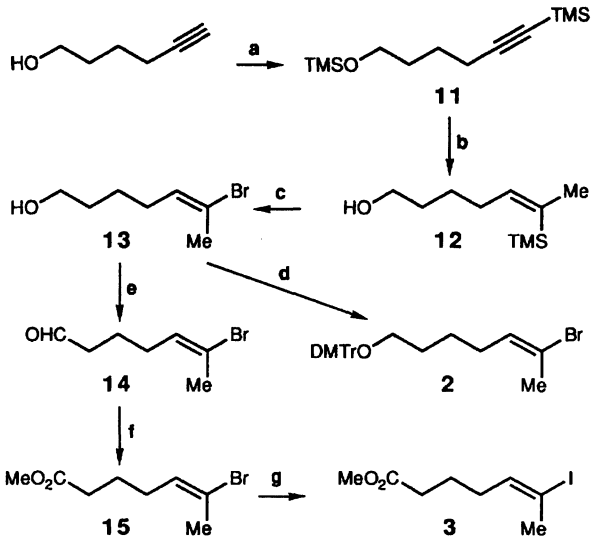


Scheme 1.

aldehyde **14**, which was further oxidized with sulfamic acid–sodium chlorite in aqueous dioxane;[11] the resulting carboxylic acid was protected as its methyl ester to afford vinyl bromide **15** in 68% yield from **13**. Finally, vinyl bromide **15** was treated with potassium iodide and copper(I) iodide in hexamthylphosphoric triamide (HMPA)[12] at 140 °C to provide vinyl iodide **3**. However, the conversion was incomplete and the R_f-values of **3** and **15** on TLC were very close. Therefore, **3** contaminated with ca. 25% of **15** was used without further purification. The stereochemical assignment of **3** was determined by NOE measurements (no NOE between the olefinic hydrogen and the olefinic methyl group).

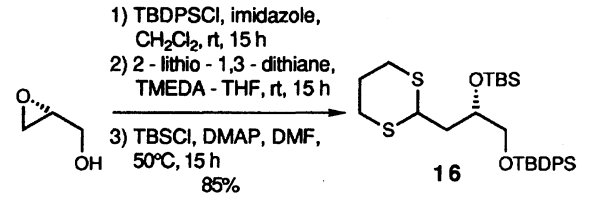
Synthesis of the C1–C3 Segment. (*R*)-Glycidol was silylated with *t*-butylchlorodiphenylsilane (TBDPSCl) and imidazole; the resulting silyl ether[13] was added to a solution of 2-lithio-1,3-dithiane to give the adduct, the secondary alcohol of which was silylated with *t*-butylchlorodimethylsilane (TBSCl) and 4-dimethylaminopyridine (DMAP) to afford the C1–C3 segment **16** in 85% overall yield (Scheme 3).

Synthesis of the C4–C7 Segment. 2-Propyn-

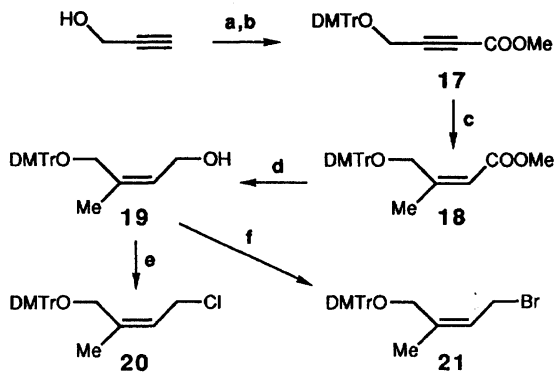


(a) *n* - BuLi, TMEDA, THF, - 50°C, 45 min, then TMSCl, - 50 to - 10°C, 2 h; (b) (i) DIBAL, hexane - ether, rt, 20 h, (ii) MeLi, 0°C, 1.5 h, (iii) MeI, rt, 15 h; (c) (i) Br_2, CH_2Cl_2, - 78°C, 1 h, (ii) NaOMe, CH_2Cl_2 - MeOH, 0°C, 1 h, rt, 1.5 h, 71% for 4 steps; (d) DMTrCl, Et_3N, DMF, rt, 2 h, 97%; (e) PCC, MS 3AP, CH_2Cl_2, rt, 0.5 h; (f) (i) H_2NSO_3H, $NaClO_2$, 7 : 3 dioxane - H_2O, rt, 10 min, (ii) CH_2N_2, ether, rt, 0.5 h, 68% from **13**; (g) CuI, KI, HMPA, 140°C, 10 min.

Scheme 2.

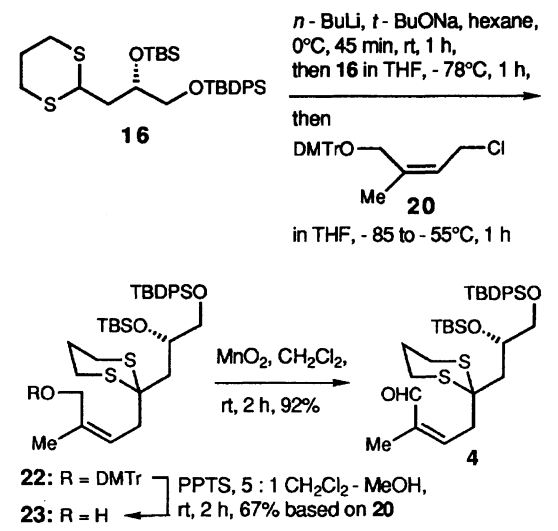


Scheme 3.



(a) DMTrCl, Et_3N, CH_2Cl_2, rt, 2 h, 69%; (b) *n* - BuLi, THF, - 60°C, 1 h, then ClCOOMe, - 60 to 0°C, 2 h; (c) Me_2CuLi, ether, - 100 ~ - 85°C, 3 h; (d) DIBAL, toluene, - 78 to - 35°C, 3 h, 92% for 3 steps; (e) MsCl, LiCl, collidine, MeCN, 0°C, 4 h, 69%; (f) MsCl, LiBr, collidine, MeCN, 0°C, 2.5 h, 66%.

Scheme 4.



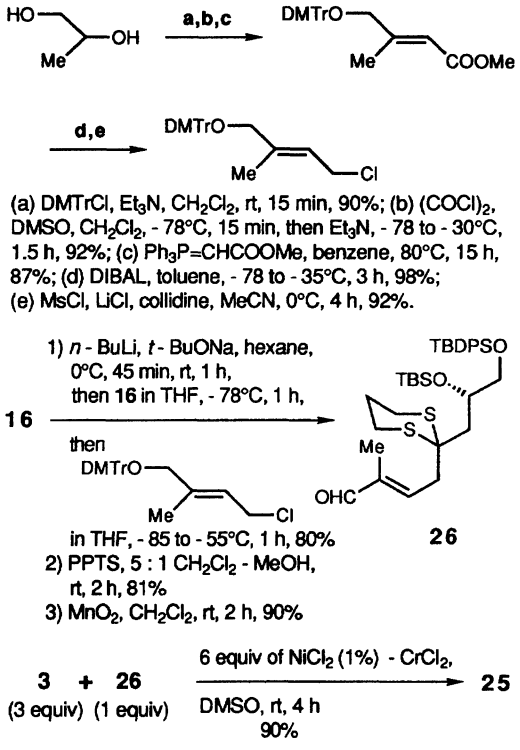
Scheme 5.

1-ol was protected with 4,4′-dimethoxytriphenylmethyl chloride (DMTrCl)-triethylamine (69% yield); the resulting ether was subjected to methoxycarbonylation to afford **17** (Scheme 4). The conjugate addition of lithium dimethylcuprate(I)[14] to **17** in ether at −100——−85 °C provided **18** as a sole product. Irradiation of the olefinic methyl doublet at 2.09 ppm produced a 14.2% NOE enhancement of the olefinic hydrogen at 5.62 ppm. This implies that the olefin geometry of **18** is *Z*. The reduction of **18** with diisobutylaluminum hydride (DIBAL) afforded **19** in 92% yield (three steps). Standard bromination or chlorination of **19** furnished chloride **20** (69%) or bromide **21** (66%).

Assemblage of the C1–C7 Segment. With all the segments now in hand, the assemblage of the C1–C7 segment was examined next (Scheme 5). Dithiane **16** was treated with *n*-BuLi/*t*-BuONa in hexane (Lipshutz procedure);[15] to this was added vinyl chloride **20** to afford **22**, which was deprotected with pyridinium *p*-toluenesulfonate (PPTS) in 5 : 1 CH_2Cl_2–MeOH to provide alcohol **23** in 67% yield based on **20**. On the other hand, the coupling of the same anion of **16** with vinyl bromide **21** gave the desired compound **22** and the S_N2' product as an 1 : 1 mixture. The alcohol **23** was oxidized with MnO_2 in CH_2Cl_2 to give (*Z*)-aldehyde **4** in 92% yield. Irradiation of the broad singlet at 1.81 ppm (vinylic methyl group) caused a 9.4% NOE enhancement of the vinylic hydrogen at 6.76 ppm, which implies that **4** possesses the *Z*-configuration.

Coupling of the C1–C7 and the C8–C13 Segments. We first examined the coupling of the C1–C7 segment **4** and the C8–C13 segment **3** and/or **15** by using a $NiCl_2/CrCl_2$-mediated reaction. The $NiCl_2/CrCl_2$-mediated coupling reacton of iodo olefins with aldehydes or alkenyl trifluoromethanesulfonates with aldehydes has been extensively examined by Kishi and his co-workers[8a] or Takai and his co-workers,[8b] respectively. We examined a number of conditions to achieve this coupling; the relevant data are summarized in Table 1. In the case of the coupling of vinyl bromide

15 with aldehyde **4**, DMF was the best solvent, albeit in low yield (Entries 1—3). It is worth mentioning that the product was **25** having an *E*-configuration on the C5—C6 double bond, and that **25** consisted of only one diastereomer,[16] the C7-configuration of which has not been determined. In the case of the coupling of vinyl iodide **3**, contaminate with ca. 25% of **15** (vide supra), with aldehyde **4**, DMSO was the best solvent (Entries 4 and 5), providing **25** in 92% yield as the sole product. When a mixture of **4** and $CrCl_2$ (and/or $CrCl_2$ containing 1 wt% of $NiCl_2$) in DMSO was stirred at room temperature for 3 h, almost complete isomerization of (*Z*)-aldehyde **4** to (*E*)-aldehyde **26** occurred. In order to further confirm the stereochemical assignment of **25** and **26**, **26** was prepared by the definite route shown in Scheme 6, and was subjected to the $NiCl_2/CrCl_2$-mediated coupling reaction with **3** to provide **25**, identical by a comparison of its ^{1}H NMR spectrum and TLC mobilities with that obtained from the coupling of **3** (and/or **15**) with **4** under conditions A in Table 1. To overcome this unpleasant isomerization, after vinyl iodide **3** was pre-mixed with $NiCl_2/CrCl_2$ in DMSO at room temperature, aldehyde **4** was added to this mixture (Entries 6—9). Under the best conditions of Entry 9 in Table 1, the desired coupling product **24** was obtained in 94% yield as ca. a 1.7:1 mixture of the C7-epimers. As mentioned in the synthetic plan, this compound **24** could be transformed to **7** and/or **8** via **6**; the final conversion of them to **1** was unsuccessfull because of an instability of **7** and/or **8** under the each reaction condition (oxidation and phosphonate introduction, respectively). Therefore, we next undertook a synthesis of hydroxy ester **9**, which had already been transformed to the target compound **1** by Akita, Oishi, and their coworkers.[4a]



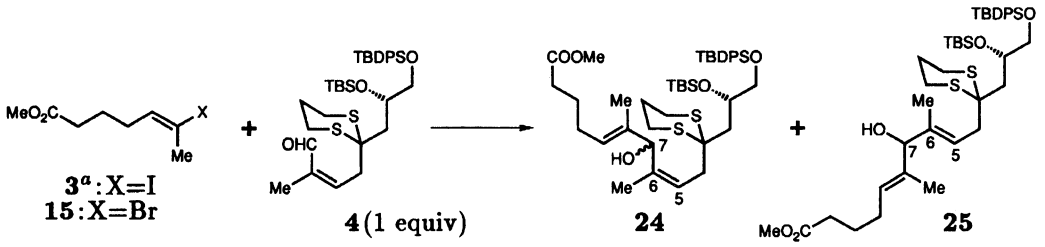
Scheme 6.

Final Stage. Vinyl bromide **2** was lithiated with *t*-butyllithium in THF at −90——80 °C for 0.5 h; to this was added aldehyde **4**, providing the coupling product **27** and its C7-epimer in 58 and 34% yields, respectively (Scheme 7). The C7-configuration of these products could not be determined at this stage. Therefore, the major product was used for the next transformation.[17] The major product **27** was treated with $HgCl_2$–$CaCO_3$ in aqueous acetone under the Corey's conditions[18] to afford a cyclic product, which was methylated[4a,6] with PPTS-trimethyl orthoformate in 4:1 MeOH–CH_2Cl_2 to give alcohol **28** in 91% yield. The relative stereochemistry of the dihydropyran moiety in **28** was established by the NOE experiments. Namely, irradiation of H-7 at 4.26 ppm produced a 7.4% NOE enhancement of the 3-OMe singlet at 3.29 ppm, indicating a *syn* relationship of the dihydropyran side chains. Reprotection of **28** with DMTrCl-triethylamine in CH_2Cl_2 provided **5** in 94% yield. Further elaboration of **5** into methyl ester **29** was accomplished in 76% overall yield by desilylation [$(n$-Bu)$_4$NF], oxidative cleavage of the diol function [$Pb(OAc)_4$], oxidation to carboxylic acid ($NaClO_2$),[11,19] and esterification (CH_2N_2). The methyl ester **29** was treated with PPTS in 5:1 CH_2Cl_2–MeOH to provide alcohol **9** in 79% yield. This alcohol had already been transformed to the desired final compound **1** by Akita, Oishi, and their co-workers.[4a] We reallized the same transformation of **9** to **1**. The data (^{1}H NMR, IR, optical rotation) of the synthetic sample of **1** were identical with that kindly provided by Professor Akita. This implies that the major coupling product **27** had the desired configuration, as depicted in Scheme 7. Since the appropriately protected C15–C27 segment of venturicidins has already been synthesized,[7] total synthetic studies of the aglycone of venturicidins are now in progress.

Experimental

The melting points were determined on a micro hot-stage Yanaco MP-S3 and were uncorrected. Optical rotations were measured on a JASCO DIP-360 photoelectric polarimeter in chloroform unless otherwise noted. IR spectra were recorded on either a BIO RAD DIGILAB FTS-65 or a JASCO IR-810 spectrometer and ^{1}H NMR spectra were on either a JEOL GSX270 or a JEOL GSX400 spectometer in $CDCl_3$ using TMS as internal standard unless otherwise noted. Silicagel TLC and column chromatography were performed on a Merck TLC 60F-254 and a Merck Kieselgel 60 or a Fuji-Davison BW-820MH, respectively. Air-and/or moisture-sensitive reactions were carried out under an atmosphere of argon with oven-dried glassware. In general, the organic solvents were purified and dried by appropriate procedures, and evaporation and concentration were carried out under reduced pressure below 30 °C, unless otherwise noted.

Table 1. $NiCl_2/CrCl_2$-Mediated Coupling of Vinyl Halide **3** (and/or **15**) with Aldehyde **4**

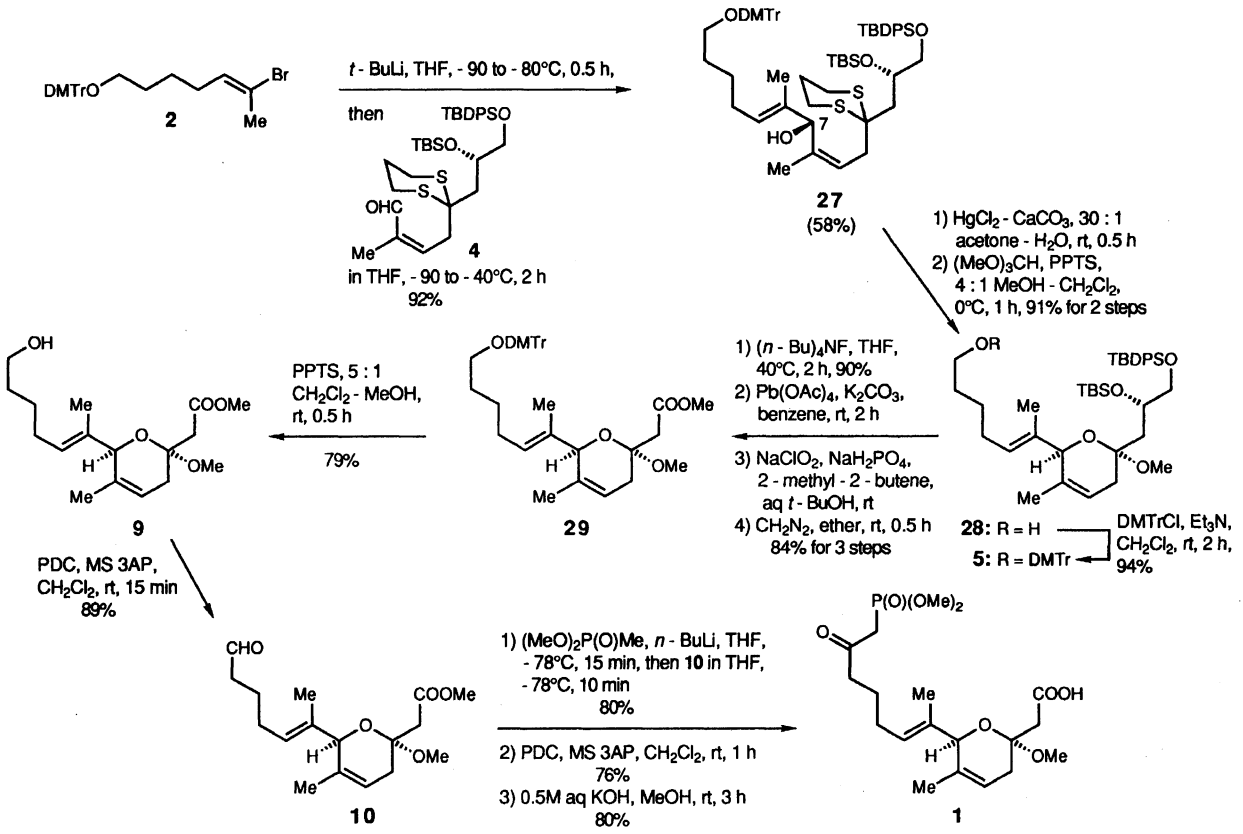


Entry	Vinyl halide	Equiv of vinyl halide	Equiv of $NiCl_2$(1%)-$CrCl_2$	Solvent	Conditions[b]	**24**/**25** ratio	Isolated (**24**+**25**) yield (%)
1	**15**	2	4	THF	A	—	Nr[c]
2	**15**	2	4	DMSO	A	—	Nr
3	**15**	2	4	DMF	A	0/100	32
4	**3**	2	4	DMF	A	—	Nr
5	**3**	2	4	DMSO	A	0/100	92
6	**3**	1.5	3	DMSO	B	100/0	42
7	**3**	2	4	DMSO	B	94/4	68
8	**3**	3	6	DMSO	B	87/13	94
9	**3**	3	6	DMSO	C	100/0	94

a) **3** used in these reactions was contaminated with ca. 25% of **15**. b) Conditons A: To a solution of **3** (or **15**) and **4** in solvent was added $NiCl_2$ (1%)–$CrCl_2$ and the mixture was stirred at r.t. for 4 h. Conditions B: A mixture of $NiCl_2$(1%)–$CrCl_2$ and solvent was stirred at r.t. for 0.5 h. To this was added a solution of **3** (or **15**) in solvent and the mixture was stirred for 10 min. To this was added a solution of **4** in solvent and the mixture was stirred at r.t. for 4 h. Conditions C: A mixture of $NiCl_2$(1%)–$CrCl_2$ and solvent was stirred at r.t. for 0.5 h. To this was added a solution of **3** (or **15**) in solvent and the mixture was stirred for 1 h. To this was added a solution of **4** in solvent and the mixture was stirred at r.t. for 4 h. c) No reaction.

(*E*)-6-Bromo-5-hepten-1-ol (13). To a stirred solution of 5-hexyn-1-ol (4.50 ml, 40.8 mmol) and *N,N,N′,N′*-tetramethylethylenediamine (TMEDA; 24.6 ml, 163 mmol) in dry THF (120 ml) was added at −50 °C 1.64 M *n*-BuLi (1 M=1 mol dm^{-3}) in hexane (54.7 ml, 89.7 mmol). After 45 min at −50 °C, TMSCl (11.4 ml, 89.8 mmol) was added and the mixture was gradually warmed to −10 °C during 2 h. The reaction mixture was poured into saturated aqueous NH_4Cl and the new mixture was extracted with hexane. The extracts were washed with saturated aqueous NH_4Cl, saturated aqueous NaCl, dried, and concentrated below 10 °C to afford **11** as a colorless syrup: 9.80 g after azeotropic concentration with benzene (two times); R_f=0.75 (4:1 hexane–ethyl acetate); ^{1}H NMR (270 MHz, $CHCl_3$=7.26) δ=0.11 and 0.14 (each 9H, eash s, 2×$SiMe_3$), 1.50—1.70 (4H, m, 2×H-2 and 2×H-3), 2.24 (2H, t, $J_{3,4}$=7.0 Hz, 2×H-4), and 3.60 (2H, t, $J_{1,2}$=6.3 Hz, 2×H-1). To a solution of 1.0 M DIBAL in hexane (89.0 ml, 89.0 mmol) and dry ether (45 ml) was added at room temperature a solution of the above **11** (9.80 g) in dry hexane (30 ml); the mixture was stirred at room temperature for 20 h. To this was added at 0 °C 1.19 M MeLi in ether (74.7 ml, 88.9 mmol); the mixture was stirred at 0 °C for 1.5 h. To this was added at 0 °C MeI (12.6 ml, 202 mmol) and the new mixture was stirred at room temperature for 15 h. Water was carefully added to the cooled (0 °C) reaction mixture, the insoluble materials were filtered with Celite and the filter cake was washed with ether. The combined filtrate and washings were wahsed with saturated aqueous NaCl, dried, and concentrated to afford **12** as a colorless syrup: 7.20 g after azeotropic concentration with benzene (two times); R_f=0.45 (4:1 hexane–ethyl acetate); ^{1}H NMR (270 MHz, $CHCl_3$=7.26) δ=0.12 (9H, s, $SiMe_3$), 1.34—1.64 (5H, m, 2×H-2, 2×H-3, and OH), 1.74 (3H, q, $J_{5,7}$=1.6 Hz, 3×H-7), 2.04—2.17 (2H, m, 2×H-4), 3.64 (2H, t, $J_{1,2}$=6.5 Hz, 2×H-1), and 5.95 (1H, tq, $J_{4,5}$=7.4 Hz and $J_{5,7}$=1.6 Hz, H-5) (Irradiation at 1.74 ppm produced a 6.7% NOE enhancement at 5.95 ppm). To a stirred solution of the above **12** (7.20 g) in dry CH_2Cl_2 (72 ml) was added at −78 °C a 3 M solution of bromine in dry CH_2Cl_2 (14.2 ml, 42.6 mmol). After 1 h at −78 °C, saturated aqueous $Na_2S_2O_3$ was added and the mixture was extracted with ether. The extracts were washed with saturated aqueous $Na_2S_2O_3$, saturated aqueous NaCl, dried, and concentrated. The residue was dissolved in dry CH_2Cl_2 (134 ml) and dry MeOH (53 ml); to this was added at 0 °C 4.9 M NaOMe in MeOH (11.8 ml, 57.8 mmol). After 1 h at 0 °C and 1.5 h at room temperature, water was added and the mixture was extracted with 1:1 hexane–ether, the extracts were then washed with saturated aqueous $Na_2S_2O_3$, saturated aqueous NaCl, dried, and concentrated. The residue was chromatographed on silica gel (500 g) with 7:2 hexane–ethyl acetate to afford **13** (5.59 g, 71% from 5-hexyn-1-ol) as a colorless syrup: R_f=0.3 (7:2 hexane–ethyl acetate); IR ($CHCl_3$) 1651, 1433, 1381, 1228, 1062, and 1038 cm^{-1}; ^{1}H NMR (270 MHz) δ=1.33 (1H, br, OH), 1.38—1.67 (4H, m, 2×H-2 and 2×H-3), 1.99—2.10 (2H, m, 2×H-4), 2.21 (3H, br q, $J_{5,7}$=1.8 Hz, 3×H-7), 3.64 (2H, t, $J_{1,2}$=6.5 Hz, H-1), and 5.83 (1H, tq, $J_{4,5}$=7.6 Hz and $J_{5,7}$=1.8 Hz, H-5) (Irradiation at 5.83 ppm produced no NOE enhancement at 2.21 ppm). Found: C, 43.80; H, 7.03%. Calcd for $C_7H_{13}BrO$: C, 43.55; H, 6.79%.

(*E*)- 2- Bromo- 7- (4, 4′- dimethoxytriphenylmethoxy)-2-heptene (2). To a stirred solution of **13** (7.10 g,



Scheme 7.

36.8 mmol) in dry DMF (142 ml) were added at room temperature triethylamine (8.20 ml, 58.8 mmol) and DMTrCl (16.2 g, 47.8 mmol). After 2 h at room temperature, water was added and the mixture was extracted with ether; the extracts were then washed with saturated aqueous NaCl, dried, and concentrated. The residue was chromatographed on silica gel (900 g) with 10 : 1 hexane–ethyl acetate to afford **2** (17.6 g, 97%) as a colorless syrup: R_f=0.33 (10 : 1 hexane–ethyl acetate); IR ($CHCl_3$) 1609, 1509, 1250, 1177, 1036, and 831 cm^{-1}; ^1H NMR (270 MHz) δ=1.40—1.675 (4H, m, 2×H-5 and 2×H-6), 1.98 (2H, br q, $J_{3,4}=J_{4,5}$=7.5 Hz, 2×H-4), 2.16 (3H, br d, $J_{1,3}$=1.0 Hz, 3×H-1), 3.04 (2H, t, $J_{6,7}$=6.3 Hz, 2×H-7), 3.79 (6H, s, 2×OMe), 5.81 (1H, br tq, $J_{1,3}$=1.0 Hz and $J_{3,4}$=7.5 Hz, H-3), 6.78—6.86 and 7.15—7.46 (total 13H, each m, aromatic protons). Found: C, 67.82; H, 6.45%. Calcd for $C_{28}H_{31}BrO_3$: C, 67.88; H, 6.31%.

Methyl (*E*)-6-Bromo-5-heptenoate (15). To a stirred solution of **13** (2.00 g, 10.4 mmol) in dry CH_2Cl_2 (40.0 ml) were added at room temperature molecular sieves 3A powder (MS 3AP)(10 g) and PCC (4.00 g, 18.6 mmol). After 0.5 h at room temperature, the reaction mixture was diluted with ether and the resulting suspension was transferred to a column filled with silica gel (80 g). The column was eluted with ether and the eluant was concentrated to afford aldehyde **14** as a colorless syrup: 1.90 g; R_f=0.54 (4 : 1 hexane–ethyl acetate). This (1.90 g, 9.94 mmol) was dissolved in 7 : 3 dioxane–water (95 ml); to this were added at 0 °C sulfamic acid (2.90 g, 29.9 mmol) and $NaClO_2$ [2.70 g, 25.7 mmol (86%)]. After 10 min at room temperature, saturated aqueous NaCl was added and the mixture was extracted with ether. The extracts were dried and concentrated. The residue was dissolved in etherial diazomethane. After 0.5 h at room temperature, the reaction mixture was concentrated and the residue was chromatographed on silica gel (110 g) with 10 : 1 hexane–ethyl acetate to afford **15** (1.56 g, 68% from **13**) as a colorless syrup: R_f=0.35 (10 : 1 hexane–ethyl acetate); IR ($CHCl_3$) 1732, 1438, 1228, 1164, and 1102 cm^{-1}; ^1H NMR (270 MHz) δ=1.72 (2H, quint, $J_{2,3}=J_{3,4}$=7.2 Hz, 2×H-3), 2.06 (2H, br q, $J_{3,4}=J_{4,5}$=7.2 Hz, 2×H-4), 2.21 (3H, br s, 3×H-7), 2.32 (2H, t, $J_{2,3}$=7.2 Hz, 2×H-2), 3.68 (3H, s, OMe), and 5.81 (1H, br tq, $J_{5,7}$=1.0 Hz and $J_{4,5}$=7.2 Hz, H-5). Found: C, 43.85; H, 6.08%. Calcd for $C_8H_{13}BrO_2$: C, 43.46; H, 5.93%.

Methyl (*E*)-6-Iodo-5-heptenoate (3). To a stirred solution of **15** (1.50 g, 6.78 mmol) in dry HMPA (7.5 ml) were added at room temperature CuI (1.90 g, 9.98 mmol) and KI (1.70 g, 10.2 mmol); the mixture was heated at 140 °C for 10 min. After cooling to ambient temperature, water was added and the mixture was extracted with ether. The extracts were washed with saturated aqueous NaCl, dried, and concentrated. The residue was chromatographed on silica gel (55 g) with 10 : 1 hexane–ethyl acetate to afford **3** (1.74 g) as a colorless syrup. This sample was contaminate with ca. 25% of **15**: R_f=0.33 (10 : 1 hexane–ethyl acetate); IR ($CHCl_3$) 1732, 1438, 1228, 1162, 1099, 875, and 830 cm^{-1}; ^1H NMR (270 MHz) δ=1.72 (2H, quint, $J_{2,3}=J_{3,4}$=7.2 Hz, 2×H-3), 2.06 (2H, br q, $J_{3,4}=J_{4,5}$=7.2 Hz, 2×H-4), 2.32 (2H, t, $J_{2,3}$=7.2 Hz, 2×H-2), 2.36 (3H, br s, 3×H-7), 3.68 (3H, s, OMe), and 6.13 (1H, br tq, $J_{5,7}$=1.0

Hz and $J_{4,5}$=7.2, H-5) (Irradiation at 2.36 ppm produced no NOE enhancement at 6.13 ppm). An analytical sample of **3** was obtained by carefull silica-gel column chromatography. Found: C, 36.03; H, 4.94%. Calcd for $C_8H_{13}IO_2$: C, 35.84; H, 4.89%.

(*S*)-2-(*t*-Butyldimethylsilyloxy)-1-(*t*-butydiphenylsilyloxy)-4,4-(trimethylenedithio)butane (16). To a stirred solution of (*R*)-glycidol (2.85 g, 38.5 mmol) and imidazole (3.40 g, 49.9 mmol) in dry CH_2Cl_2 (51 ml) was added at 0 °C TBDPSCl (10.3 ml, 39.6 mmol). After 15 h at room temperature, the reaction mixture was poured into saturated aqueous NaCl and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with 0.4 M aqueous HCl, saturated aqueous $NaHCO_3$, saturated aqueous NaCl, dried, and concentrated. The residue [12 g; R_f=0.54 (25:1 toluene–ethyl acetate)] was azeotropically concentrated with toluene (two times) and used without any purification. To a stirred solution of 1,3-dithiane (8.86 g, 73.7 mmol) and TMEDA (52.2 ml, 346 mmol) in dry THF (160 ml) was added at −35 °C 1.66M *n*-BuLi in hexane (41.7 ml, 69.2 mmol). After 1.5 h at −30 °C, a solution of the above-mentioned sample (12 g) in dry THF (80 ml) was added at −30 °C and the mixture was stirred at room temperature for 15 h. The reaction mixture was poured into saturated aqueous NaCl; this mixture was extracted with ether. The extracts were washed with 1 M aqueous HCl, saturated aqueous $NaHCO_3$, saturated aqueous NaCl, dried, and concentrated. The residue was chromatographed on silica gel (500 g) with 5:1 hexane–ethyl acetate to afford dithiane derivative [15.4 g, 92% from (*R*)-glycidol] as a colorless syrup [R_f=0.32 (5:1 hexane–ethyl acetate)]. To a stirred solution of this syrup (8.00 g, 18.5 mmol) in dry DMF (80 ml) were added at room temperature DMAP (3.40 g, 27.8 mmol) and TBSCl (3.60 g, 23.9 mmol). After 15 h at 50 °C, water was added and the mixture was extracted with 10:1 hexane–ether. The extracts were washed with saturated aqueous NaCl, dried, and concentrated. The residue was chromatographed on silica gel (450 g) with 20:1 hexane–ethyl acetate to afford **16** [9.30 g, 85% overall yield from (*R*)-glycidol] as a colorless syrup: R_f=0.38 (20:1 hexane–ethyl acetate); $[\alpha]_D^{24}$ −15.8° (*c* 4.26); IR ($CHCl_3$) 1472, 1428, 1256, 1112, 1082, 837, and 807 cm^{-1}; ^1H NMR (270 MHz, $CHCl_3$=7.26) δ=−0.11 and 0.03 (each 3H, each s, $SiMe_2$), 0.83 and 1.05 (each 9H, each s, 2×t-Bu), 1.77—2.25 (4H, m, 2×H-3 and $SCH_2CH_2CH_2S$), 2.74—2.90 (4H, m, $SCH_2CH_2CH_2S$), 3.46 (1H, dd, $J_{1,2}$=7.0 Hz and J_{gem}=10.0 Hz, H-1), 3.59 (1H, dd, $J_{1',2}$=4.4 Hz and J_{gem}=10.0 Hz, H-1′), 3.98 (1H, m, H-2), and 4.13 (1H, dd, $J_{3,4}$=9.8 Hz and $J_{3',4}$=5.0 Hz, H-4). Found: C, 63.86; H, 8.11%. Calcd for $C_{29}H_{46}O_2Si_2S_2$: C, 63.68; H, 8.48%.

(*Z*)-4-(4,4′-Dimethoxytriphenylmethoxy)-3-methyl-2-buten-1-ol (19). To a stirred solution of DMTrCl (50.0 g, 148 mmol) in dry CH_2Cl_2 (210 ml) were added at 0 °C triethylamine (30.9 ml, 222 mmol) and 2-propyn-1-ol (8.60 ml, 148 mmol). After 2 h at room temperature, water was added and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were washed with saturated aqueous NaCl, dried, and concentrated. The residue was chromatographed on silica gel (1 kg) with 15:1 and then 12:1 hexane–ethyl acetate to afford colorless crystals [36.2 g, 69%; R_f=0.65 (3:1 hexane–ethyl acetate)]. To a stirred solution of these crystals (36.2 g, 101 mmol) in dry THF (360 ml) was added at −78 °C 1.62 M *n*-BuLi in hexane (74.8 ml, 121 mmol) and the mixture was stirred at −60 °C for 1 h. To this was added at −60 °C methyl chloroformate (12.5 ml, 162 mmol); the mixture was gradually warmed to 0 °C for 2 h. The reaction mixture was poured into saturated aqueous $NaHCO_3$; this mixture was then extracted with ether. The extracts were washed with saturated aqueous NaCl, dried, and concentrated. The residue **17** was azeotropically concentrated with toluene (two times) and used without any purification: 42.1 g, 100%; R_f=0.38 (5:1 hexane–ethyl acetate); ^1H NMR (270 MHz) δ=3.76 and 3.78 (3H and 6H, 3×OMe), 3.91 (2H, s, 2×H-4), 6.80—6.86 and 7.19—7.47 (4H and 9H, each m, aromatic protons). To a suspension of CuI (11.1 g, 58.3 mmol) in dry ether (960 ml) was added at 0 °C 1.06 M MeLi in ether (110 ml, 117 mmol) and the mixture was stirred at 0 °C for 45 min. To this was added at −100 °C a precooled (−90 °C) solution of **17** (20.2 g) in dry ether (160 ml); the mixture was stirred at −90—−85 °C for 3 h. Saturated aqueous NH_4Cl was added and the organic layer was separated. The aqueous layer was extracted with ether and the combined organic layers were washed with saturated aqueous NH_4Cl, saturated aqueous NaCl, dried, and concentrated. The residue **18** was used without any purifications: 21.0 g, 100%; R_f=0.53 (5:1 hexane–ethyl acetae); ^1H NMR (270 MHz) δ=2.09 (3H, br d, $J_{2,Me}$=1.5 Hz, 3-Me), 3.56 (3H, s, OMe), 3.78 (6H, s, 2×OMe), 4.32 (2H, br, 2×H-4), 5.62 (1H, br q, $J_{2,Me}$=1.5 Hz, H-2), 6.77—6.86 and 7.15—7.46 (4H and 9H, each m, aromatic protons) (irradiation at 2.09 ppm produced a 14.2% NOE enhancement at 5.62 ppm). To a stirred solution of **18** (21.0 g) in dry toluene (400 ml) was added at −78 °C 1.02 M DIBAL in toluene (119 ml, 121 mmol). The reaction mixture was gradually warmed to −35 °C during 3 h. MeOH (8.75 ml) and water (14.6 ml) were added and the mixture was stirred at room temperature for 1 h. The insoluble materials were filtered with Celite and the filter cake was washed with CH_2Cl_2. The combined filtrate and washings were concentraed and the residue was chromatographed on silica gel (600 g) with 5:2 and then 2:1 hexane–ethyl acetate to afford **19** (18.8 g, 92% for three steps) as a colorless syrup: R_f=0.29 (5:2 hexane–ethyl acetate); IR ($CHCl_3$) 1608, 1509, 1251, 1177, 1035, and 832 cm^{-1}; ^1H NMR (270 MHz) δ=1.42 (1H, br t, $J_{1,OH}$=5.8 Hz, OH), 1.87 (3H, br s, 3-Me), 3.62 (2H, br s, 2×H-4), 3.79 (6H, s, 2×OMe), 3.95 (2H, br t, $J_{1,2}$=7.0 Hz and $J_{1,OH}$=5.8 Hz, 2×H-1), 5.55 (1H, br tq, $J_{1,2}$=7.0 Hz and $J_{2,Me}$=1.5 Hz, H-2), 6.78—6.86 and 7.15—7.49 (4H and 9H, each m, aromatic protons). Found: C, 77.67; H, 7.28%. Calcd for $C_{26}H_{28}O_4$: C, 77.20; H, 6.98%.

(*Z*)-1-Chloro-4-(4,4′-dimethoxythriphenylmethoxy)-3-methyl-2-butene (20). To a stirred solution of **19** (2.56 g, 6.36 mmol) in dry acetonitrile (60 ml) were added at room temperature LiCl (1.58 g, 37.3 mmol) and 2,4,6-trimethylpyridine (2.50 ml, 18.9 mmol). To this was added at 0 °C methanesulfonyl chloride (1.44 ml, 18.6 mmol); this mixture was then stirred at 0 °C for 4 h. The reaction mixture was poured into water; this mixture was extracted with hexane, and the extracts were washed with saturated aqueous NaCl, dried, and concentrated. The residue was chromatographed on silica gel (80 g) with 15:1 and then 12:1 hexane–ethyl acetate to afford **20** (1.86 g, 69%) as a colorless syrup: R_f=0.35 (12:1 hexane–ethyl acetate); IR ($CHCl_3$)

1609, 1509, 1251, 1177, 1036, and 832 cm^{-1}; ^1H NMR (270 MHz) δ=1.88 (3H, br s, 3-Me), 3.63 (2H, br s, 2×H-4), 3.79 (6H, s, 2×OMe), 3.94 (2H, br d, $J_{1,2}$=7.8 Hz, 2×H-1), 5.52 (1H, br t, $J_{1,2}$=7.8 Hz, H-2), 6.79—6.88, 7.16—7.38, and 7.40—7.49 (total 13H, m, aromatic protons). Found: C, 74.38; H, 6.63%. Calcd for $C_{26}H_{27}ClO_3$: C, 73.84; H, 6.43%.

(*Z*)-1-Bromo-4-(4,4′-dimethoxytriphenylmethoxy)-3-methyl-2-butene (21). Compound **21** was obtained from **19** (38.2 mg, 0.0949 mmol), MsCl (0.0184 ml, 0.238 mmol), LiBr (33.0 mg, 0.380 mmol), 2,4,6-collidine (0.0326 ml, 0.247 mmol), and dry acetonitrile (1 ml) by the same procedure as described above for the preparation of **20** from **19**: 29.0 mg, 66%; R_f=0.50 (15:1 hexane–ethyl acetate); ^1H NMR (270 MHz) δ=1.88 (3H, br s, 3-Me), 3.65 (2H, s, 2×H-4), 3.79 (6H, s, 2×OMe), 3.85 (2H, d, $J_{1,2}$=7.8 Hz, 2×H-1), 5.60 (1H, br t, $J_{1,2}$=7.8 Hz, H-2), 6.78—6.89, 7.16—7.38, and 7.42—7.50 (total 13H, m, aromatic protons).

(2*Z*,7*S*)-7-(*t*-Butyldimethylsilyloxy)-8-(*t*-butyldiphenylsilyloxy)-2-methyl-5,5-(trimethylenedithio)-2-octen-1-ol (23). To a stirred solution of *t*-BuONa (2.17 g, 22.6 mmol) in dry hexane (54 ml) was added at 0 °C 1.66 M *n*-BuLi in hexane (12.8 ml, 21.2 mmol). After 45 min at 0 °C and 1 h at room temperature, a solution of **16** (11.6 g, 21.2 mmol) in dry THF (50 ml) was added at −78 °C to this mixture. After 1 h at −78 °C, the reaction mixture was cooled to −85 °C, and to this was added a solution of **20** (6.89 g, 16.3 mmol) in dry THF (40 ml); the new mixture was gradually warmed to −55 °C for 1 h. Water was added and the mixture was extracted with 1:1 hexane–ether; the extracts were then washed with saturated aqueous NaCl, dried, and concentrated. The residue **22** [18.1 g; R_f=0.38 (6:1 hexane–ethyl acetate)] was dissolved in dry CH_2Cl_2 (100 ml) and dry MeOH (20 ml); after adding PPTS (151 mg, 0.601 mmol) the mixture was stirred at room temperature for 2 h. The reaction mixture was poured into saturated aqueous $NaHCO_3$ and the new mixture was extracted with $CHCl_3$. The extracts were washed with saturated aqueous NaCl, dried, and concentrated. The residue was chromatographed on silica gel (500 g) with 10:1 and then 6:1 hexane–ethyl acetate to afford **23** (6.87 g, 67% based on **20**) as a colorless syrup: R_f=0.22 (6:1 hexane–ethyl acetate); $[\alpha]_D^{26}$ −5.5° (*c* 4.15); $[\alpha]_{365}^{26}$ −20.8° (*c* 4.15); IR ($CHCl_3$) 1472, 1428, 1256, 1111, 1000, 837, and 808 cm^{-1}; ^1H NMR (270 MHz, $CHCl_3$=7.26) δ=−0.12 and 0.04 (each 3H, each s, $SiMe_2$), 0.78 and 1.07 (each 9H, each s, 2×*t*-Bu), 1.26 (1H, t, $J_{1,OH}$=7.0 Hz, OH),1.84 (3H, br s, 2-Me), 1.89—2.05 and 2.56—3.00 (3H and 7H, each m, 2×H-4, 2×H-6, and $SCH_2CH_2CH_2S$), 3.44 (1H, dd, J_{gem}=9.8 Hz and $J_{7,8}$=8.0 Hz, H-8), 3.61 (1H, dd, J_{gem}=9.8 Hz and $J_{7,8'}$=4.2 Hz, H-8′), 4.02—4.22 (3H, m, 2×H-1 and H-7), 5.02 (1H, br t, $J_{3,4}$=7.6 Hz, H-3), 7.35—7.50 and 7.65—7.75 (6H and 4H, m, 2×Ph). Found: C, 64.85; H, 8.43%. Calcd for $C_{34}H_{54}O_3Si_2S_2$: C, 64.71; H, 8.62%.

(2*Z*,7*S*)-7-(*t*-Butyldimethylsilyloxy)-8-(*t*-butyldiphenylsilyloxy)-2-methyl-5,5-(trimethylenedithio)-2-octenal (4). A mixture of **23** (6.87 g, 10.9 mmol), MnO_2 (38.4 g, 442 mmol), and dry CH_2Cl_2 (140 ml) was stirred at room temperature for 2 h. The reaction mixture was filtered with Celite and the filter cake was washed with CH_2Cl_2. The combined filtrate and washings were concentrated and the residue was chromatographed on silica gel (300 g) with 60:1 toluene–ethyl acetate to afford **4** (6.27 g, 92%) as a colorless syrup: R_f=0.36 (60:1 toluene–ethyl acetate); $[\alpha]_D^{28}$ −3.1° (*c* 2.73); $[\alpha]_{435}^{28}$ −5.0° (*c* 2.73); IR ($CHCl_3$) 1674, 1472, 1428, 1257, 1110, 837, and 807 cm^{-1}; ^1H NMR (270 MHz, $CHCl_3$=7.26) δ=−0.13 and 0.02 (each 3H, each s, $SiMe_2$), 0.78 and 1.07 (each 9H, each s, 2×*t*-Bu), 1.81 (3H, br s, 2-Me), 1.85—2.05 and 2.59—3.02 (3H and 5H, each m, 2×H-6 and $SCH_2CH_2CH_2S$), 3.09 (1H, br dd, J_{gem}=15.0 Hz and $J_{3,4}$=7.2 Hz, H-4), 3.30 (1H, br dd, J_{gem}=15.0 Hz and $J_{3,4'}$=8.0 Hz, H-4′), 3.43 (1H, dd, J_{gem}=9.7 Hz and $J_{7,8}$=8.0 Hz, H-8), 3.63 (1H, dd, J_{gem}=9.7 Hz and $J_{7,8'}$=4.4 Hz, H-8′), 4.14 (1H, m, H-7), 6.76 (1H, br t, $J_{3,4}$=7.2 Hz and $J_{3,4'}$=8.0 Hz, H-3), 7.35—7.50 and 7.64—7.70 (4H and 6H, each m, aromatic protons), and 10.14 (1H, s, H-1) (Irradiation at 1.81 ppm produced a 9.4% NOE enhancement at 6.76 ppm). Found: C, 65.10, H, 8.14%. Calcd for $C_{34}H_{52}O_3Si_2S_2$: C, 64.92, H, 8.33%.

$NiCl_2$/$CrCl_2$-Mediated Coupling. Entry 5 in Table 1: To a stirred solution of **3** (85.0 mg, 0.317 mmol) and **4** (100 mg, 0.159 mmol) in dry DMSO (2.0 ml) was added at room temperature $NiCl_2$ (1%)–$CrCl_2$ [0.8 mg (0.006 mmol) of $NiCl_2$ and 78.0 mg (0.635 mmol) of $CrCl_2$]. After 4 h at room temperature, water was added and the mixture was extracted with ether. The extracts were washed with saturated aqueous NaCl, dried, and concentrated. The residue was chromatographed on silica gel (10 g) with 4:1 hexane–ethyl acetate to afford **25** (113 mg, 92%) as a colorless syrup: R_f=0.24 (5:1 hexane–ethyl acetate); ^1H NMR (270 MHz, $CHCl_3$=7.26) δ=−0.14 and 0.04 (each 3H, each s, $SiMe_2$), 0.79 and 1.08 (each 9H, each s, 2×*t*-Bu), 1.49 and 1.52 (each 3H, each br s, 6- and 8-Me), 1.72 (2H, quint, $J_{2,3}$=$J_{3,4}$=8.0 Hz, 2×H-3), 1.80—2.05 (3H, m, H-12 and $SCH_2CH_2CH_2S$), 2.09 (2H, br q, $J_{3,4}$=$J_{4,5}$=8.0 Hz, 2×H-4), 2.32 (2H, t, $J_{2,3}$=8.0 Hz, 2×H-2), 2.55—3.00 (7H, m, 2×H-10, H-12′, and $SCH_2CH_2CH_2S$), 3.46 (1H, dd, $J_{13,14}$=J_{gem}=10.0 Hz, H-14), 3.62 (1H, dd, $J_{13,14'}$=4.2 Hz and J_{gem}=10.0 Hz, H-14′), 3.66 (3H, s, OMe), 4.14 (1H, m, H-13), 4.38 (1H, br s, H-7), 5.50 (1H, br t, $J_{4,5}$=8.0 Hz, H-5), 5.76 (1H, br t, $J_{9,10}$=7.0 Hz, H-9), 7.33—7.48 and 7.64—7.73 (6H and 4H, m, aromatic protons).

Entry 9 in Table 1: $NiCl_2$(1%)–$CrCl_2$ [2.2 mg (0.017 mmol) of $NiCl_2$ and 218 mg (1.77 mmol) of $CrCl_2$] was added to dry DMSO (4.5 ml) and the mixture was stirred at room temperature for 0.5 h. To this was added at room temperature a solution of **3** (243 mg, 0.906 mmol) in dry DMSO (1.2 ml). After 1 h at room temperature, a solution of **4** (210 mg, 0.334 mmol) in dry DMSO (1.0 ml) was added at room temperature. After 4 h at room temperature, water was added and the mixture was extracted with ethyl acetate. The extracts were washed with saturated aqueous NaCl, dried, and concentrated. The residue was chromatographed on silica gel (25 g) with 5:1 hexane–ethyl acetate to afford **24** (242 mg, 94%) as a colorless syrup: R_f=0.33 (5:1 hexane–ethyl acetate); ^1H NMR (270 MHz, $CHCl_3$=7.26) for **24-major**: δ=−0.13 and 0.03 (each 3H, each s, $SiMe_2$), 0.78 and 1.08 (each 9H, each s, 2×*t*-Bu), 1.47 and 1.61 (each 3H, each br s, 6- and 8-Me), 1.72 (2H, quint, $J_{2,3}$=$J_{3,4}$=7,8 Hz, 2×H-3), 1.78—2.05 (4H, m, H-12, OH, and $SCH_2CH_2CH_2S$), 2.11 (2H, q, $J_{3,4}$=$J_{4,5}$=7.8 Hz, 2×H-4), 2.32 (2H, t, $J_{2,3}$=7.8 Hz, 2×H-2), 2.55—3.00 (7H, m, H-12′, 2×H-10, and $SCH_2CH_2CH_2S$), 3.44 (1H, dd, J_{gem}=$J_{13,14}$=9.0 Hz, H-14), 3.62 (1H, dd, J_{gem}=9.0 Hz and

$J_{13,14'}$=4.0 Hz, H-14'), 3.67 (3H, s, OMe), 4.13 (1H, m, H-13), 4.94 (1H, br s, H-7), 5.50—5.65 (2H, m, H-5 and 9), 7.32—7.48 and 7.62—7.72 (6H and 4H, each m, aromatic protons) [for **24-minor**: δ=−0.11 and 0.04 (each 3H, each s, $SiMe_2$), 1.49 (3H, br s, 5- or 8-OMe), and 4.89 (1H, br s, H-7)].

Isomerization of 4 to 26. To a stirred solution of **4** (100 mg, 0.159 mmol) in dry DMSO (2.5 ml) was added at room temperature $CrCl_2$ (78 mg, 0.635 mmol). After 3 h at room temperature, water was added and the mixture was extracted with ether. The extracts were washed with saturated aqueous NaCl, dried, and concentrated. The residue was chromatographed on silica gel (5 g) with 60:1 toluene–ethyl acetate to afford **26** (92 mg, 92%) as a colorless syrup: R_f=0.36 (60:1 toluene–ethyl acetate); ^{1}H NMR (270 MHz, $CHCl_3$=7.26) δ=−0.13 and 0.02 (each 3H, each s, $SiMe_2$), 0.77 and 1.08 (each 9H, each s, 2×*t*-Bu), 1.76 (3H, br s, 2-Me), 1.80—2.05 and 2.60—3.10 (3H and 7H, each m, 2×H-4, 2×H-6, and $SCH_2CH_2CH_2S$), 3.43 (1H, dd, J_{gem}=9.8 Hz and $J_{7,8}$=8.0 Hz, H-8), 3.63 (1H, dd, J_{gem}=9.8 Hz and $J_{7,8'}$=4.2 Hz, H-8'), 4.09—4.20 (1H, m, H-7), 6.80 (1H, br t, $J_{3,4}=J_{3,4'}$=7.0 Hz, H-3), 7.35—7.95 and 7.63—7.70 (6H and 4H, m, aromatic protons), and 9.44 (1H, s, H-1).

(5*E*,7*R*,8*Z*,13*S*)-13-(*t*-Butyldimethylsilyloxy)-14-(*t*-butyldiphenylsilyloxy)-1-(4,4'-dimethoxytriphenylmethoxy)-6,8-dimethyl-11,11-(trimethylenedithio)-5,8-tetradecadien-7-ol (27) and Its C7-Epimer. To a stirred solution of **2** (1.07 g, 2.16 mmol) in dry THF (22 ml) was added at −90 °C 1.41 M *t*-BuLi in pentane (3.00 ml, 4.23 mmol) and the mixture was warmed to −80 °C during 0.5 h and then re-cooled to −90 °C. To this was added a solution of **4** (0.970 g, 1.54 mmol) in dry THF (5 ml) and the mixture was warmed to −40 °C during 2 h. Saturated aqueous NH_4Cl was added and the mixture was extracted with ether. The extracts were washed with saturated aqueous NaCl, dried, and concentrated. The residue was chromatographed on silica gel (150 g) with 6:1 hexane–ethyl acetate and then rechromatographed on silica gel (150 g) with 30:1 benzene–ether to afford **27** (932 mg, 58%) and its C7-epimer (548 mg, 34%) as colorless syrups.

27: R_f=0.35 (30:1 benzene–ether); $[\alpha]_D^{26}$ +17.9° (*c* 3.29); IR ($CHCl_3$) 1608, 1509, 1466, 1251, 1177, 1111, 1036, and 834 cm^{-1}; ^{1}H NMR (270 MHz, $CHCl_3$=7.26) δ=−0.11 and 0.05 (each 3H, each s, $SiMe_2$), 0.80 and 1.09 (each 9H, each s, 2×*t*-Bu), 1.45 and 1.62 (each 3H, each br s, 6- and 8-Me), 1.40—1.70 (4H, m, 2×H-2 and 2×H-3), 1.77—2.10 (6H, m, 2×H-4, H-12, OH, and $SCH_2CH_2CH_2S$), 2.56—3.00 (7H, m, $SCH_2CH_2CH_2S$, 2×H-10, and H-12'), 3.05 (2H, t, $J_{1,2}$=6.0 Hz, 2×H-1), 3.46 (1H, dd, J_{gem}=9.8 Hz and $J_{13,14}$=8.0 Hz, H-14), 3.64 (1H, dd, J_{gem}=9.8 Hz and $J_{13,14'}$=4.2 Hz, H-14'), 3.79 (6H, s, 2×OMe), 4.16 (1H, m, H-13), 4.95 (1H, br s, H-7), 5.48—5.66 (2H, m, H-5 and H-9), 6.80—6.87, 7.15—7.47, and 7.65—7.73 (23H, m, aromatic protons). Found: C, 71.46; H, 8.06%. Calcd for $C_{62}H_{84}O_6Si_2S_2$: C, 71.22; H, 8.10%.

C7-epimer of 27: R_f=0.39 (30:1 benzene–ether); $[\alpha]_D^{27}$ −19.7° (*c* 3.19); IR ($CHCl_3$) 1608, 1509, 1466, 1251, 1177, 1111, 1036, and 834 cm^{-1}; ^{1}H NMR (270 MHz, $CHCl_3$=7.26) δ=−0.01 and 0.06 (each 3H, each s, $SiMe_2$), 0.79 and 1.08 (each 9H, each s, 2×*t*-Bu), 1.48 and 1.62 (each 3H, each br s, 6- and 8-Me), 1.40—1.70 (4H, m, 2×H-2 and 2×H-3), 1.75—2.12 (6H, m, 2×H-4, H-12, OH, and $SCH_2CH_2CH_2S$), 2.58—3.00 (7H, m, 2×H-10, H-12', and $SCH_2CH_2CH_2S$), 3.05 (2H, t, $J_{1,2}$=6.0 Hz, 2×H-1), 3.47 (1H, dd, J_{gem}=9.8 Hz and $J_{13,14}$=8.0 Hz, H-14), 3.63 (1H, dd, J_{gem}=9.8 Hz and $J_{13,14'}$=4.2 Hz, H-14'), 3.79 (6H, s, 2×OMe), 4.13 (1H, m, H-13), 4.90 (1H, br s, H-7), 5.51—5.64 (2H, m, H-5 and H-9), 6.80—6.87, 7.15—7.47, and 7.65—7.73 (23H, m, aromatic protons). Found: C, 71.60; H, 8.09%. Calcd for $C_{62}H_{84}O_6Si_2S_2$: C, 71.22; H, 8.10%.

(*E*)-2-[(2*R*,6*R*)-6-[(*S*)-2-(*t*-Butydimethylsilyloxy)-3-(*t*-butyldiphenylsilyloxy)propyl]-5,6-dihydro-6-methoxy-3-methyl-2*H*-pyran-2-yl]-7-(4,4'-dimethoxytriphenylmethoxy)-2-heptene (5). To a stirred solution of **27** (2.96 g, 2.83 mmol) in 30:1 acetone–water (90 ml) were added at room temperature $CaCO_3$ (3.96 g, 36.9 mmol) and $HgCl_2$ (4.61 g, 17.0 mmol). After 1.5 h at room temperature, *N*-ethyldiisopropylamine (4.44 ml, 25.5 mmol) was added and the mixture was stirred at room temperature for 0.5 h. After concentration of acetone, ethyl acetate (45 ml), water (30 ml), and $Na_2S{\cdot}9H_2O$ (12.2 g, 50.8 mmol) were added and the mixture was stirred at room temperature for 2 h. The insoluble materials were filtered with Celite and the filter cake was washed with ethyl acetate. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with saturated aqueous NaCl, dried, and concentrated. The residue was dissolved in 4:1 MeOH–CH_2Cl_2 (90 ml) and to this was added trimethyl orthoformate (1.86 ml, 17.0 mmol). To this was added at 0 °C PPTS (576 mg, 2.29 mmol) and the mixture was stirred at 0 °C for 1 h. The reaction mixture was neutralized with Amberlite IRA-400(OH) ion-exchange resin and the resin was filtered. The filtrate was concentrated and the residue was chromatographed on silica gel (50 g) with 10:1 toluene–ethyl acetate to afford **28** (1.71 g, 91% for two steps) as a colorless foam: R_f=0.28 (4:1 hexane–ethyl acetate); ^{1}H NMR (270 MHz, $CHCl_3$=7.26) δ=−0.16 and 0.01 (each 3H, each s, $SiMe_2$), 0.80 and 1.04 (each 9H, each s, 2×*t*-Bu), 1.40—1.70 (4H, m, 2×H-2 and 2×H-3), 1.50 and 1.52 (each 3H, each br s, 2×olefinic Me), 2.03—2.38 (5H, m), 2.52 (1H, dd, *J*=15.0 Hz and 3.4 Hz), 3.29 (3H, s, OMe), 3.42 (1H, dd, J_{gem}=9.6 Hz and *J*=7.7 Hz), 3.56 (1H, dd, J_{gem}=9.6 Hz and *J*=4.4 Hz), 3.65 (2H, t, $J_{1,2}$=6.3 Hz), 3.88 (1H, m), 4.26 (1H, br s), 5.43—5.56 (2H, m, olefinic hydrogens), 7.30—7.47, and 7.60—7.73 (6H and 4H, m, 2×Ph) (irradiation at 4.26 ppm produced a 7.4% NOE enhancement at 3.29 ppm). To a stirred solution of **28** (1.71 g, 2.56 mmol) in dry CH_2Cl_2 (34 ml) were added at 0 °C triethylamine (1.07 ml, 7.68 mmol) and DMTrCl (1.13 g, 3.34 mmol). After 2 h at room temperature, water was added and the mixture was extracted with ethyl acetate. The extracts were washed with saturated aqueous NaCl, dried, and concentrated. The residue was chromatographed on silica gel (100 g) with 11:1 hexane–ethyl acetate to afford **5** (2.33 g, 94%) as a colorless foam: R_f=0.56 (4:1 hexane–ethyl acetate); $[\alpha]_D^{29}$ −3.7° (*c* 3.23); $[\alpha]_{435}^{29}$ −10.8° (*c* 3.23); IR ($CHCl_3$) 1608, 1510, 1250, 1177, 1113, 1035, and 830 cm^{-1}; ^{1}H NMR (270 MHz, $CHCl_3$=7.26) δ=−0.15, and 0.00 (each 3H, each s, $SiMe_2$), 0.79 and 1.04 (each 9H, each s, 2×*t*-Bu), 1.35—1.70 (10H, m), 1.95—2.40 (5H, m), 2.52 (1H, dd, *J*=15.0 Hz and 3.2 Hz), 3.04 (2H, t, $J_{6,7}$=6.0 Hz, 2×H-7), 3.28 (3H, s, OMe), 3.42 (1H, dd, J_{gem}=10.0 Hz and *J*=7.8 Hz), 3.55 (1H, dd,

J_{gem}=10.0 Hz and J=4.2 Hz), 3.79 (6H, s, 2×OMe), 3.87 (1H, m), 4.25 (1H, br s), 5.41—5.53 (2H, m, olefinic hydrogens), 6.80—6.85, 7.30—7.47, and 7.64—7.70 (total 23H, m, aromatic protons). Found: C, 74.40; H, 8.33%. Calcd for $C_{60}H_{80}O_7Si_2$: C, 74.34; H, 8.32 %.

(2*R*,6*R*)-3,6-Dihydro-6-[(*E*)-6-(4,4′-dimethoxytriphenylmethoxy)-1-methyl-1-hexenyl]-2-methoxy-5-methyl-2*H*-pyran-2-acetate (29). To a stirred solution of **5** (1.93 g, 1.99 mmol) in dry THF (100 ml) was added at 0 °C 1.0 M (n-Bu)$_4$NF in THF (12.0 ml, 12.0 mmol). After 2 h at 40 °C, the reaction mixture was concentrated and the residue was chromatographed on silica gel (100 g) with 6:1 $CHCl_3$–acetone to afford diol (1.10 g, 90%) as a colorless syrup. To this (1.10 g, 1.78 mmol) in dry benzene (55 ml) were added at room temperature K_2CO_3 (840 mg, 6.08 mmol) and $Pb(OAc)_4$ (1.92 g, 4.33 mmol). After 2 h at room temperature, the reaction mixture was filtered with Celite and the filter cake was washed with benzene. The combined filtrate and washings were concentrated. The residue was dissolved in t-BuOH (10.0 ml) and to this were added successively 2-methyl-2-butene (5 ml) and aqueous (3 ml) solution of $NaClO_2$ (387 mg, 4.28 mmol) and NaH_2PO_4 (518 mg, 4.32 mmol). After the addition was completed, the reaction mixture was immediately extracted with ether. The extracts were washed with saturated aqueous NaCl, dried, and concentrated. The residue was dissolved in etherial diazomethane. After 0.5 h at room temperature, the mixture was concentrate and the residue was chromatographed on silica gel (50 g) with 5:1 hexane–ethyl acetate to afford **29** (925 mg, 84% for three steps) as a colorless syrup: R_f= 0.27 (5:1 hexane–ethyl acetate); $[\alpha]_D^{28}$ +1.8° (c 3.46); $[\alpha]_{546}^{28}$ +1.7° (c 3.46); IR ($CHCl_3$) 1735, 1608, 1509, 1442, 1302, 1249, 1177, 1069, 1035, and 832 cm^{-1}; ^{1}H NMR (270 MHz) δ=1.44 and 1.49 (each 3H, each s, 2×olefinic Me), 1.40—1.70 (4H, m), 2.04 (2H, br dt, J=7.4 and 7.4 Hz), 2.24, (1H, br dd, J=16.0 and 5.0 Hz), 2.58 (1H, br dd, J=16.0 and 1.5 Hz), 2.69 and 2.81 (each 1H, ABq, J_{gem}=14.0 Hz), 3.04 (2H, t, J=6.2 Hz), 3.35, 3.68, and 3.79 (3H, 3H, and 6H, each s, 4×OMe), 4.27 (1H, br s), 5.41—5.54 (2H, m, olefinic hydrogens), 6.78—6.86, 7.15—7.35, and 7.40—7.46 (total 13H, m, aromatic protons). Found: C, 74.01; H, 7.99%. Calcd for $C_{38}H_{46}O_7$: C, 74.24; H, 7.54 %.

(2*R*,6*R*)-3,6-Dihydro-6-[(*E*)-7-(dimethoxyphosphinyl)-1-methyl-6-oxo-1-heptenyl]-2-methoxy-5-methyl-2*H*-pyran-2-acetic Acid (1). To a stirred solution of **29** (460 mg, 0.748 mmol) in dry CH_2Cl_2 (12 ml) and dry MeOH (2.3 ml) was added at room temperature PPTS (17.0 mg, 0.0676 mmol). After 0.5 h at room temperature, saturated aqueous $NaHCO_3$ was added and the mixture was extracted with $CHCl_3$. The extracts were washed with saturated aqueous NaCl, dried, and concentrated. The residue was chromatographed on silica gel (12 g) with 2:1 hexane–ethyl acetate to afford **9** (186 mg, 79%) as a colorless syrup: R_f=0.20 (3:1 hexane–ethyl acetate). To a stirred solution of **9** (186 mg, 0.595 mmol) in dry CH_2Cl_2 (5.6 ml) were added at room temperature MS 3AP (600 mg) and PDC (403 mg, 1.07 mmol). After 15 min at room temperature, ether was added and the mixture was filtered with Celite. The filter cake was washed with ether and the combined filtrate and washings were concentrated and the residue was chromatographed on silica gel (15 g) with 3:1 hexane–ethyl acetate to afford **10** (164 mg, 89%) as a colorless syrup: R_f=0.31 (3:1 hexane–ethyl acetate). To a stirred solution of dimethyl methylphosphonate (0.0687 ml, 0.634 mmol) in dry THF (1.2 ml) was added at −78 °C 1.64 M n-BuLi in hexane (0.354 ml, 0.581 mmol). After 15 min at −78 °C, this solution was added at −78 °C to a solution of **10** (164 mg, 0.528 mmol) in dry THF (7.0 ml) with double-ended needle. After 10 min at −78 °C, saturated aqueous NH_4Cl was added and the mixture was extracted with ethyl acetate. The extracts were washed with saturated aqueous NaCl, dried, and concentrated. The residue was chromatographed on silica gel (12 g) with 5:1 and then 2:1 ethyl acetate–THF to afford a colorless syrup [184 mg, 80%; R_f=0.31 (7:3 ethyl acetate–THF)]. This (170 mg, 0.391 mmol) was dissolved in dry CH_2Cl_2 (7.0 ml) and to this were added at room temperature MS 3AP (390 mg) and PDC (295 mg, 0.784 mmol). After 1 h at room temperature, ether was added and the mixture was filtered with Celite. The filter cake was washed with ether and the combined filtrate and washings were concentrated; the residue was then chromatographed on silica gel (10 g) with 1:2 hexane–ethyl acetate to afford a colorless syrup [129 mg, 76%; R_f=0.19 (1:10 hexane–ethyl acetate)]. This (129 mg, 0.298 mmol) was dissolved in MeOH (1.7 ml) and to this was added 0.5 M aqueous KOH (2.1 ml); the mixture was stirred at room temperature for 3 h. The reaction mixture was diluted with ethyl acetate and this was washed with 10% aqueous cooled (0 °C) citric acid. The aqueous layer was extracted with ethyl acetate and the combined organic layers were washed with saturated aqueous NaCl, dried, and concentrated. The residue was chromatographed on silica gel (6 g) with 8:1 $CHCl_3$–MeOH to affor **1** (100 mg, 80%) as a colorless syrup: R_f=0.49 (8:1 $CHCl_3$–MeOH); $[\alpha]_D^{28}$ −11.3° (c 1.80, benzene) [lit,[4a] $[\alpha]_D^{20}$ −12.4° (c 1.74, benzene)]; IR (neat) 2950, 2850, 1720, 1440, 1400, 1360, 1250, 1180, 1120, 1030, 860, and 820 cm^{-1}; ^{1}H NMR (400 MHz, benzene-d_6, TMS=0) δ=1.28—1.60 (2H, m), 1.47 and 1.61 (each 3H, each br s, 2×olefinic Me), 1.68—1.80, 1.88—1.99, 2.02—2.14, and 2.26—2.38 (each 1H, each m), 2.41 (1H, ddd, J=18.2, 7.2, and 6.0 Hz), 2.50 (1H, ddd, J=18.2, 7.2, and 7.2 Hz), 2.59 (1H, d, J=13.4 Hz), 2.88 (1H, d, J=13.4 Hz), 2.90 (1H, dd, J=22.8 and 13.8 Hz), 2.98 (1H, dd, J=22.8 amd 13.8 Hz), 3.26 (3H, s, OMe), 3.36 and 3.41 (each 3H, each d, J=11.2 Hz, 2×OMe), 4.39 (1H, br s), 5.35 (1H, br t, J=7.6 Hz), and 5.44 (1H, br d, J=4.2 Hz).

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17) Compound **27** could be also obtained by the $NiCl_2/CrCl_2$-mediated coupling between the vinyl iodide derivative, which was prepared from vinyl bromide **2** as described for the preparation of **3** from **15** (Scheme 2), and aldehyde **4** under the conditons C in Table 1, and the ratio of **27** and its C7-epimer was ca. 1.7 : 1.

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