Palladium-Catalyzed Intramolecular Allylic Alkylation Reaction in Marine Natural Product Synthesis: Enantioselective Synthesis of (+)-Methyl Pederate, a Key Intermediate in Syntheses of Mycalamides

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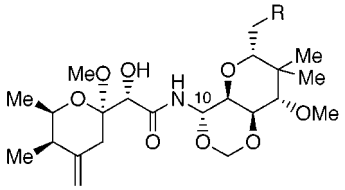
A novel preparation of (+)-methyl pederate (**4**), a key intermediate in syntheses of mycalamides (**1**), marine natural products from a New Zealand sponge of the genus *Mycale*, is described. The key step involves palladium-catalyzed intramolecular allylic alkylation of the carbonate **21**, derived from (+)-(4*R*,5*R*,*E*)-5-(*tert*-butyldimethylsiloxy)-4-methyl-2-hexenol (**13**), yielding lactones **5** in 87% yield. Demethoxycarbonylation of the cyclization products **5** and further functional group transformations led to (+)-methyl pederate (**4**).

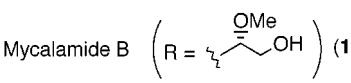
Introduction

Mycalamides A (**1a**)[1] and B (**1b**)[2] are strong antiviral and antitumor compounds isolated from a New Zealand marine sponge *Mycale* species. Furthermore, mycalamides (**1**) are recently reported to exhibit immunosuppressive activity via inhibition of T cell activation.[3] Each contains a trioxabicyclo[4.4.0]decane ring system and *N*-acyl aminal unit at C10. Because of their unique structures and pharmacological activities, mycalamides (**1**) and their relatives [theopederins A−E (**2**)[4] and onnamide A (**3**)[5]] are attractive candidates for total syntheses.[6]

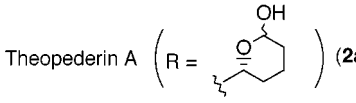
In our first contribution to this area, we herein describe an enantioselective preparation of (+)-methyl pederate (**4**), a possible key intermediate to mycalamides (**1**), based upon a palladium-catalyzed intramolecular allylic alkylation reaction.[7]



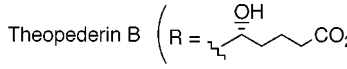
Mycalamide A (R =) (**1a**)



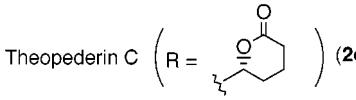
Mycalamide B (R =) (**1b**)



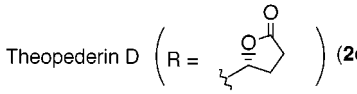
Theopederin A (R =) (**2a**)



Theopederin B (R =) (**2b**)



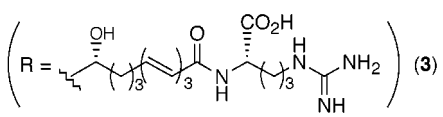
Theopederin C (R =) (**2c**)



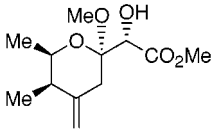
Theopederin D (R =) (**2d**)

Theopederin E (R = OH) (**2e**)

Onnamide A



(R =) (**3**)



Methyl pederate (**4**)

(1) Perry, N. B.; Blunt, J. W.; Munro, M. H. G. *J. Am. Chem. Soc.* **1988**, *110*, 4850−4851.
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(6) Total syntheses of mycalamides A and B and onnamide A: (a) Hong, C. Y.; Kishi, Y. *J. Org. Chem.* **1990**, *55*, 4242−4245. (b) *Idem J. Am. Chem. Soc.* **1991**, *113*, 9693−9694. (c) Nakata, T.; Matsukura, H.; Jian, D.; Nagashima, H. *Tetrahedron Lett.* **1994**, *35*, 8229−8232. Related synthetic studies: (d) Tsuzuki, K.; Watanabe, T.; Yanagiya, M.; Matsumoto, T. *Tetrahedron Lett.* **1976**, 4745−4748. (e) Adams, M. A.; Duggan, A. J.; Smolanoff, J.; Meinwald, J. *J. Am. Chem. Soc.* **1979**, *101*, 5364−5370. (f) Nakata, T.; Nagao, S.; Mori, N.; Oishi, T. *Tetrahedron Lett.* **1985**, *26*, 6461−6464. (g) Nakata, T.; Nagao, S.; Oishi, T. *Ibid.* **1985**, *26*, 6465−6468. (h) Matsuda, F.; Tomiyoshi, N.; Yanagiya, M.; Mastumoto, T. *Tetrahedron* **1988**, *44*, 7063−7080. (i) Kocienski, P.; Jarowicki, K.; Marczak, S. *Synthesis* **1991**, 1191−1200. (j) Roush, W. R.; Marron, T. G. *Tetrahedron Lett.* **1993**, *34*, 5421−5424. (k) Hoffmann, R. W.; Schlapbach, A. *Ibid.* **1993**, *34*, 7903−7906. (l) Marron, T. G.; Roush, W. R. *Ibid.* **1995**, *36*, 1581−1584. (m) Hoffmann, R. W.; Breitfelder, S.; Schlapbach, A. *Helv. Chim. Acta* **1996**, *79*, 346−352. (n) Kocienski, P.; Raubo, P.; Davis, J. K.; Boyle, F. T.; Davies, D. E.; Richter, A. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1797−1808. (o) Roush, W. R.; Marron, T. G.; Pfeifer, L. A. *J. Org. Chem.* **1997**, *62*, 474−478.

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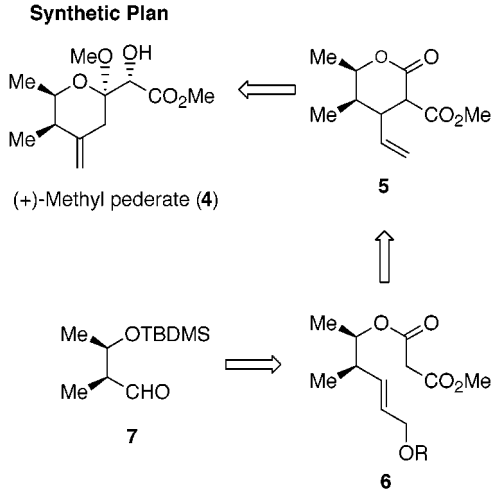
Scheme 1

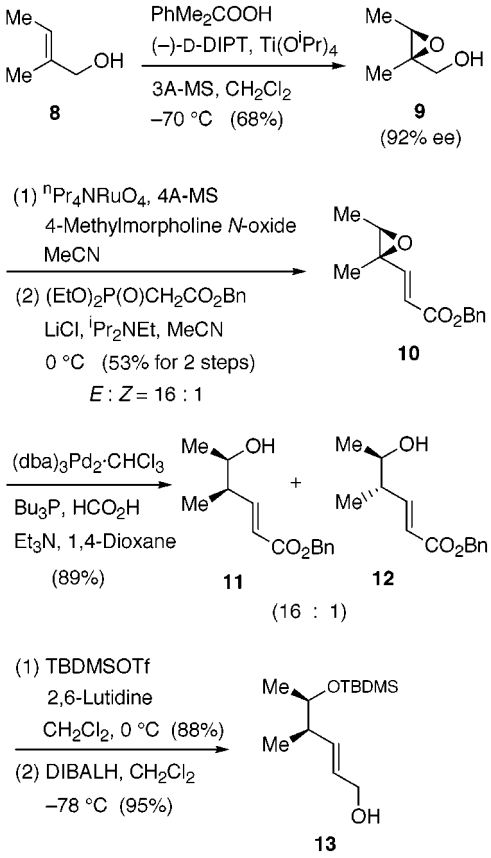


Synthetic Plan. For synthesizing (+)-methyl pederate (**4**) in an enantioselective manner, the novel synthetic strategy depicted in Scheme 1 was designed, employing a palladium-catalyzed intramolecular allylic alkylation. Namely, when the regioselective (*6-exo-trig*) cyclization of the allylic alcohol derivative **6** obtained from the chiral aldehyde **7** occurs, the vinyl δ-lactones **5** can be produced. Demethoxycarbonylation, followed by coupling reaction with a glycolic acid derivative, would furnish the methyl pederate skeleton, transformable into **4**.

Results and Discussion

Preparation of (4*R*,5*R*,*E*)-5-(*tert*-butyldimethylsiloxy)-4-methyl-2-hexenol (13). (A) Route via Palladium-Catalyzed Hydrogenolysis. To synthesize the requisite carbonate **21** for the key step (**21** → **5**), a palladium-catalyzed regio- and stereoselective hydrogenolysis[8] route was first adopted (Scheme 2). Tiglic alcohol (**8**)[9b] was subjected to the Sharpless asymmetric epoxidation[9] (cumene hydroperoxide, (−)-diisopropyl tartrate, titanium(IV) isopropoxide, 3 Å molecular sieves, CH_2Cl_2, −70 °C) to afford the 2,3-epoxy alcohol **9** with 92% ee, determined by using the Mosher ester analysis.[10] After oxidation of **9** with tetrapropylammonium perruthenate in the presence of 4-methylmorpholine *N*-oxide,[11] the efficient construction of the (*E*)-olefin **10** (*E*:*Z* = 16:1) was achieved by utilization of the Masamune−Roush procedure.[12] Palladium-catalyzed hydrogenolysis[8] of the resulting (*E*)-alkenyloxirane **10** was conducted with the tris(dibenzylideneacetone)dipalladium(0)−chloroform adduct [$(dba)_3Pd_2{\cdot}CHCl_3$] in the presence of $Bu_3P-HCO_2H-Et_3N$ in 1,4-dioxane to provide the alcohol **11** as the major isomer in a 16:1 mixture. Although separation of the stereoisomers **11** and **12** was difficult at this stage, it was found that the desired major isomer was easily separated as the corresponding allylic alcohol **13** after DIBALH reduction. Therefore, the mixture of homoallylic alcohols **11** and **12** was subjected to protection (*tert*-butyldimethylsilyl trifluoromethanesulfonate, 2,6-lutidine, CH_2Cl_2, 0 °C) followed by DIBALH reduction (95%). A route that could provide material suitable for the subsequent key step was now available.

Scheme 2



(B) Route via Aldol Reaction. It was considered that the requisite allylic alcohol **13** could be formed in a more efficient manner via chemoselective reduction of the thiol ester **17** (Scheme 3). Two stereogenic centers on **15** were constructed through a diastereoselective aldol addition of the boron enolate derived from the (4*S*,5*R*)-norephedrine-based chiral carboximide **14**[13] with acetaldehyde (>98% de by ^{1}H NMR analysis). For excising the imide auxiliary of **15**, several procedures were surveyed, including transamination[14] to the *N*-methoxy-*N*-methylamide, transesterification[13] with lithium benzyloxide, and $LiAlH_4$ reduction.[13] Typically, these reactions were capricious and less selective when performed on a large scale. To alleviate this bottleneck, an alternative solution was sought. Removal of the oxazolidinone auxiliary was readily achieved (99%) by using Damon's reported lithio mercaptide procedure.[15] Following protection of **16**, the resulting thiol ester **17** was efficiently reduced to the

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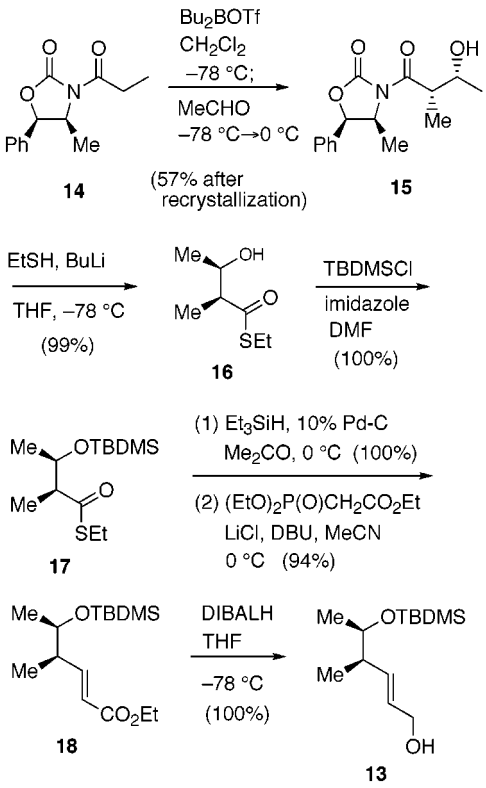
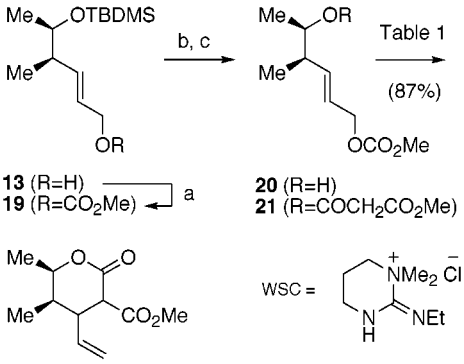
Scheme 3



aldehyde **7** by Fukuyama's hydrosilylation method[16] using 10% palladium−charcoal. When **7** was subjected to the standard conditions for Masamune−Roush olefination,[12] the only obtainable product was **18**. It should be noted that the (*Z*)-olefin was not detected by ^{1}H NMR analysis. After reduction of **18** with DIBALH, the alcohol **13** was obtained in quantitative yield.

Palladium-Catalyzed Intramolecular Allylic Alkylation Reactions Leading to *δ*-Lactones. With a route to multigram quantities of **13** firmly in hand, our synthetic elaboration was next focused on the *δ*-lactone formation of the allyl ether **21**. Attempts to control the ring size of the products in palladium-catalyzed intramolecular allylic alkylation processes have been reported.[17] However, the lack of examples[18] of their applications to the synthesis of complex natural products may, in part, be due to the relatively low product yields. We have carried out extensive studies on the palladium-catalyzed intramolecular lactonization of the allylic alcohol derivative **21**. Conversion of the alcohol **13** to the carbonate **21** was achieved via the reaction sequence summarized in Scheme 4. Namely, carbonate formation (98%) of **13** followed by deprotection of the TBDMS group of **19** with Bu_4NF provided the alcohol **20**, which was subjected to esterification with malonic acid monomethyl ester in the presence of DMAP and [1-(3-(dimethylamino)propyl)]-3-ethylcarbodiimide hydrochloride (WSC) to give **21**. The representative results, summarized in Table 1, show that the outcome of the lactonization reaction can be altered

Scheme 4



a: $ClCO_2Me$, Pyridine, CH_2Cl_2, 0 °C (98%), b: Bu_4NF, THF (79%), c: $MeO_2CCH_2CO_2H$, DMAP, WSC, CH_2Cl_2 (88%)

Table 1. Conditions and Yields of Pd-Catalyzed Cyclization Reaction of Compound 21

entry	catalyst	ligand	solvent	temp (°C)	time (h)	yield (%)
1[a]	$Pd(Ph_3P)_4$	dppe	THF	reflux	3	19
2[a]	$(dba)_3Pd_2{\cdot}CHCl_3$	dppe	THF	reflux	7	low
3	$(dba)_3Pd_2{\cdot}CHCl_3$	Ph_3P	THF	reflux	0.5	25
4	$Pd(OAc)_2$[b]	Bu_3P	MeCN	reflux	1	33
5	$Pd(OAc)_2$[b]	Ph_3P	MeCN	reflux	6.5	48
6	$Pd(OAc)_2$[b]	Ph_3P	DMSO	90	5	70
7	$Pd(OAc)_2$[b]	Ph_3P	DMF	45	7.5	66
8[c]	$Pd(OAc)_2$[b]	Ph_3P	DMF	90	6.5	87

[a] NaH (1 equiv) was added. [b] All reactions were carried out by using $Pd(OAc)_2$ (10 mol %) and PPh_3 (40 mol %). [c] The reaction was conducted in a sealed tube.

dramatically by varying the reaction conditions. In the first set of reactions Pd(0) was utilized as a catalyst. In contrast to entry 1, $(dba)_3Pd_2{\cdot}CHCl_3$ did not effect the cyclization (entry 2). The yield of this lactonization improved upon using a catalytic amount of $Pd(OAc)_2$ with phosphine ligand (entries 4 and 5). For evaluation of the effect of solvent, we performed the same reaction by employing DMSO, in which the cyclized products **5** were obtained in 70% yield (entry 6). At higher temperatures, this reaction proceeds smoothly, providing the desired compounds **5** (entries 7 and 8). From these results, we could conclude that the selective *δ*-lactone formation has been governed by the several factors including solvent and palladium catalyst. In addition, the yield is highly dependent upon the polarity of the solvent.

Synthesis of (+)-Methyl Pederate. Having found conditions for the preparation of **5**, the stage was now set for the completion of the synthesis. After demethoxycarbonylation (76%) of **5**, the corresponding lactone was generated as a 3:1 mixture of diastereomers. The nonstereoselectivity of the cyclization was of little consequence, since both of the diastereomers could be converted efficiently to the bicyclic lactone **22** using Nakata's procedure.[6g] Namely, the above lactone was subjected to ozonolysis (O_3, MeOH, −78 °C; Me_2S), followed by acidic treatment (concd HCl, CH_2Cl_2), to afford **22** in 97% yield for two steps. After transformation of **22** into the thioacetal **23**, coupling reaction[6e] of *O*-(2-methoxy-2-propyl)glycolate with **23** in the presence of LDA, carried out between −78 °C and −15 °C, produced the coupled products, which were allowed to react in succession with trimethyl orthoformate and MeOH in the presence of 10-camphorsulfonic acid, and benzoyl chloride to furnish the

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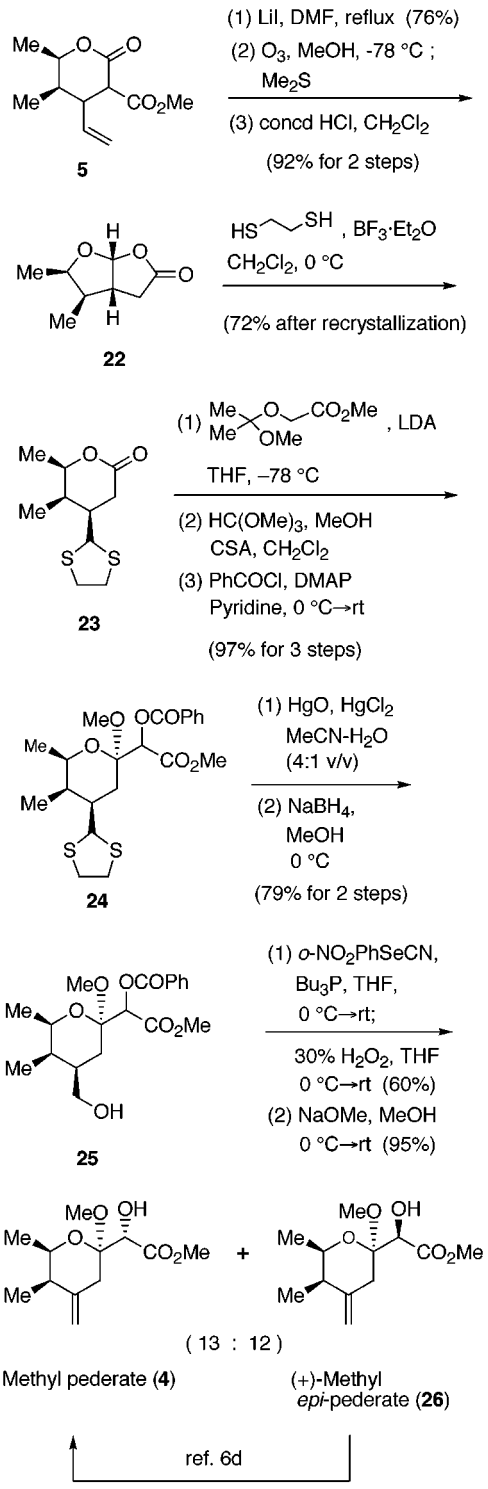
Scheme 5



benzoate **24** as a 1:1 mixture of epimers. Subsequent conversion to **25** was accomplished in 79% overall yield through dethioacetalization and reduction with $NaBH_4$ (Scheme 5).

Application of Grieco's *o*-nitrophenylselenenylation method[19] to **25** produced the selenide, which was treated with 30% hydrogen peroxide to give the corresponding *exo*-olefin. Finally, hydrolysis of the benzoate moiety with NaOMe yielded an easily separable 13:12 mixture of (+)-methyl pederate (**4**) and (+)-methyl *epi*-pederate (**26**). The latter could be recycled to a mixture of **4** and **26** (5:1, respectively) by Collins oxidation and reduction with $NaBH_4$.[6d] The spectral properties (^{1}H NMR, IR) of synthetic (+)-methyl pederate (**4**), $[\alpha]^{22}_D$ +131.16 (CH_2Cl_2) [lit.[6o] $[\alpha]^{23}_D$ +115 (CH_2Cl_2)], were identical in all respects to those provided by Dr. Nakata.

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Experimental Section

General. Unless otherwise noted, all reactions were performed in oven-dried glassware, sealed with a rubber septum under an atmosphere of argon. Anhydrous tetrahydrofuran (THF) and dichloromethane (CH_2Cl_2) were purchased from Kanto Chemical Co., Inc. Pyridine, toluene, triethylsilane (Et_3SiH), diisopropylamine (i-Pr_2NH), boron trifluoride diethyl etherate ($BF_3{\cdot}Et_2O$), 1,4-dioxane, and triethylamine (Et_3N) were distilled from CaH_2. Hexamethylphosphoramide (HMPA) and dimethyl sulfoxide (DMSO) were distilled from CaH_2 under reduced pressure. *N*,*N*-Dimethylformamide (DMF) was distilled under argon from $CaSO_4$. Acetone (Me_2CO) and methanol (MeOH) were distilled under argon immediately prior to use. Unless otherwise mentioned, materials were obtained from commercial suppliers and used without further purification. Organic extracts were dried by being stirred over anhydrous $MgSO_4$, filtered through Celite, and concentrated under reduced pressure with the aid of a rotary evaporator. Flash chromatography was carried out using Merck 60 (230–400 mesh) or Cica 60 (spherical/40–100 μm) silica gel. Reactions and chromatography fractions were analyzed employing precoated silica gel 60 F_{254} plates (Merck). Compounds were visualized using a ultraviolet lamp (254 nm) and/or by staining with *p*-anisaldehyde (in EtOH), phosphomolybdic acid (in EtOH), or ammonium molybdate (in 10% H_2SO_4). IR spectra were recorded as films on NaCl plates unless otherwise noted. ^{1}H NMR spectra were measured as $CDCl_3$ solutions at 300 MHz. Chemical shifts are expressed in ppm downfield from internal tetramethylsilane or relative internal $CHCl_3$. *J* values are in hertz.

(+)-(2*R*,3*R*)-2,3-Epoxy-2-methyl-1-butenol (9). To a stirred solution of (*E*)-2-methyl-2-butenol (**8**)[9b] (1.00 g, 11.6 mmol) and diisopropyl D-tartrate (342 mg, 1.46 mmol) in CH_2Cl_2 (60 mL) at −25 °C was added 3 Å molecular sieves (9.32 g, powdered), and then the mixture was again stirred at −25 °C for 0.5 h. After slow addition of Ti(Oi-Pr)$_4$ (0.310 mL, 1.22 mmol) at −25 °C, the resulting mixture was stirred at the same temperature for 0.5 h, and cumene hydroperoxide (4.10 mL, 80%, 22.0 mmol) was added dropwise at −78 °C. The mixture was again stirred at −70 °C for 13 h. The mixture was quenched by addition of a solution of Bu_3P (2.40 mL, 9.76 mmol) and citric acid (170 mg, 0.810 mmol) in a 1:9 mixture of Me_2CO and Et_2O (20 mL) at −78 °C and then allowed to warm to room temperature. After 20 min of stirring at room temperature, the solution was filtered through Celite. The filtrate was concentrated to leave an oil, which was chromatographed. Elution with a 1:2 mixture of hexanes–EtOAc gave **9** (802 mg, 68%) as a colorless oil. $[\alpha]^{22}_D$ +17.4 (*c* 0.690, CH_2Cl_2). IR 3450 cm^{-1}. ^{1}H NMR δ 1.28 (3H, s), 1.32 (3H, d, J = 5.5), 2.00 (1H, dd, J = 8.2 and 4.7), 3.17 (1H, q, J = 5.5), 3.57 (1H, dd, J = 12.4 and 8.2) and 3.70 (1H, dd, J = 12.4 and 4.7). ^{13}C NMR (75.4 MHz) δ 13.4, 13.8, 55.9, 61.1 and 65.4.

(−)-Benzyl (4*R*,5*R*,*E*)-4,5-Epoxy-4-methyl-2-hexenoate (10). To a stirred solution of **9** (115 mg, 1.13 mmol) in MeCN (5 mL) were added 4 Å molecular sieves (565 mg, powdered), 4-methylmorpholine *N*-oxide (198 mg, 1.70 mmol), and Pr_4NRuO_4 (19.8 mg, 97%, 56.4 μmol) at room temperature, and then the resulting suspension was again stirred at room temperature for 1 h. After filtration through Celite, the filtrate was concentrated to afford the aldehyde, which was immediately used in subsequent Masamune–Roush olefination without further purification.

To a slurry of LiCl (57.5 mg, 1.36 mmol) in MeCN (2 mL) were added dropwise a solution of diethyl [(benzyloxycarbonyl)-methyl]phosphonate (389 mg, 1.36 mmol) at room tempera-

ture, followed after 5 min by a solution of the above aldehyde in MeCN (5 mL) at 0 °C. After 1 h of stirring at 0 °C, the solvent was removed by reduced pressure to furnish the residue, which was diluted with Et_2O. The ethereal layer was washed with H_2O and saturated NaCl, dried, filtered, and evaporated to leave an oil, which was chromatographed. Elution with an 8:1 mixture of hexanes−EtOAc afforded a 16:1 mixture of (*E*)- and (*Z*)-**10** (139 mg, 53% for two steps) as a colorless oil. $[\alpha]^{22}_D$ −28.5 (*c* 0.108, $CHCl_3$). IR 1720 cm^{-1}. ^1H NMR δ 1.35 (2.82H, d, J = 5.0), 1.36 (0.18H, d, J = 5.0), 1.42 (2.82H, s), 1.43 (0.18H, s), 5.86 (0.06H, d, J = 11.0), 6.05 (0.94H, d, J = 15.0), 6.41 (0.06H, d, J = 11.0) and 6.80 (0.94H, d, J = 15.0). HRMS calcd for $C_{14}H_{16}O_2$ (M^+ − 16) 216.1149, found 216.1152.

(+)-Benzyl (4*R*,5*R*,*E*)-5-Hydroxy-4-methyl-2-hexenoate (11). To a stirred solution of $(dba)_3Pd_2{\cdot}CHCl_3$ (7.4 mg, 7.2 μmol) in 1,4-dioxane (1 mL) was added Bu_3P (1.8 μL, 7.2 μmol) at room temperature. After being stirred at room temperature for 5 min, Et_3N (67 μL, 0.48 mmol) and a solution of HCO_2H (45 μL, 1.2 mmol) in 1,4-dioxane (2 mL) were added at room temperature, and then the resulting mixture was stirred at the same temperature for 5 min. To this was slowly added a solution of **10** (55.5 mg, 0.239 mmol) in 1,4-dioxane (2 mL) at room temperature, and the mixture was continued to stir at room temperature for 9.5 h. The reaction mixture was subjected to short column chromatography, and the solvent was removed to yield an oil, which was chromatographed. Elution with a 1:1 mixture of hexanes−EtOAc furnished a 16:1 mixture of **11** and **12** (49.8 mg, 89%) as a colorless oil. $[\alpha]^{22}_D$ +21.6 (*c* 0.098, $CHCl_3$). IR 3450 and 1715 cm^{-1}. ^1H NMR δ 1.07 (0.18H, d, J = 6.5), 1.11 (2.82H, d, J = 6.5), 1.16 (2.82H, d, J = 6.0), 1.18 (0.18H, d, J = 6.0), 5.87 (0.06H, dd, J = 15.0 and 1.0), 5.92 (0.94H, dd, J = 15.0 and 1.0), 6.99 (0.06H, dd, J = 15.0 and 7.5) and 7.00 (0.94H, dd, J = 15.0 and 7.5). HRMS calcd for $C_{14}H_{18}O_3$ (M^+) 234.1255, found 234.1195.

(−)-(4*S*,5*R*)-4-Methyl-5-phenyl-3-propanoyl-1,3-oxazolidin-2-one (14). To a stirred solution of (4*S*,5*R*)-norephedrine-2-oxazolidinone[13] (16.9 g, 95.2 mmol) in THF (100 mL) at −78 °C was added dropwise BuLi (63.8 mL, 10 wt % in hexane, 99.6 mmol), and then the resulting solution was stirred at −78 °C for 1 h. After slow addition of propionyl chloride (9.97 mL, 112 mmol) at −78 °C, the mixture was allowed to warm to 0 °C and maintained at the same temperature for an additional 1.5 h. The mixture was quenched with 1 M K_2CO_3 (100 mL) at 0 °C and diluted with EtOAc. The organic layer was washed with saturated NaCl, dried, filtered, and evaporated to leave an oil, which was chromatographed. Elution with a 2:1 mixture of hexanes−EtOAc yielded **14** (22.1 g, 100%) as a colorless oil. Kügelrohr distillation (110 °C/0.1 mmHg) gave the pure **14**. $[\alpha]^{25}_D$ −51.8 (*c* 0.690, $CHCl_3$). IR 1700 cm^{-1}; ^1H NMR δ 0.89 (3H, d, J = 6.8), 1.22 (3H, t, J = 7.5), 2.92 (2H, q, J = 7.5), 4.78 (1H, dq, J = 7.8 and 6.8), 5.68 (1H, d, J = 7.2) and 7.34 (5H, s). Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 66.70; H, 6.57; N, 5.95.

(−)-(4*S*,5*R*,2′*S*,3′*R*)-3-(3-Hydroxy-2-methylbutanoyl)-4-methyl-5-phenyl-1,3-oxazolidin-2-one (15). To a stirred solution of **14** (3.43 g, 14.7 mmol) in CH_2Cl_2 (20 mL) at −78 °C was slowly added Bu_2BOTf (16.9 mL, 1 M in CH_2Cl_2, 16.9 mmol), followed after 10 min by Et_3N (2.67 mL, 19.2 mmol). The resulting mixture was stirred at −78 °C for 0.5 h and at 0 °C for 1 h. Upon cooling to −78 °C, freshly distilled acetaldehyde (1.51 mL, 29.4 mmol) was slowly added at −78 °C, and the mixture was stirred for 0.5 h at the same temperature and then warmed to 0 °C for 0.5 h. The reaction was quenched by addition of 0.25 M KH_2PO_4 (25 mL) and then allowed to warm to room temperature. To this were slowly added MeOH (50 mL) and 30% H_2O_2 (22.5 mL) in MeOH (67.5 mL) at room temperature, and the resulting solution was again stirred at the same temperature for 45 min. After removal of the solvent, 10% $NaHCO_3$ (70 mL) was added, and then the solution was extracted with EtOAc. The organic layer was washed with saturated NaCl, dried, filtered, and evaporated to furnish an oil, which was chromatographed. Elution with a 1:2 mixture of hexanes−EtOAc gave rise to **15** (3.27 g, 80%) as a colorless powder. The solid thus obtained was recrystallized from Et_2O−hexane to provide **15** (2.34 g, 57%) as colorless prisms, mp 116−118 °C, judged by ^1H NMR spectroscopy to consist of >98% one diastereomer: $[\alpha]^{24}_D$ −30.0 (*c* 0.151, $CHCl_3$). IR 3350, 1780, and 1680 cm^{-1}; ^1H NMR δ 0.90 (3H, d, J = 7.0), 1.22 (3H, d, J = 6.6), 1.25 (3H, d, J = 7.0), 2.93 (1H, br d, J = 3.0), 3.76 (1H, dq, J = 6.6 and 3.0), 4.15−4.25 (1H, m), 4.81 (1H, dq, J = 7.2 and 6.6), 5.69 (1H, d, J = 7.2), and 7.20−7.45 (5H, m). Anal. Calcd for $C_{15}H_{19}NO_4$: C, 64.96; H, 6.90; N, 5.05. Found: C, 64.87; H, 6.83; N, 5.04.

(+)-*S*-Ethyl (2*S*,3*R*)-3-Hydroxy-2-methylbutanethioate (16). To a −78 °C solution of ethanethiol (53 μL, 0.720 mmol) in THF (5 mL) was added dropwise BuLi (0.347 mL, 10 wt % in hexane, 0.542 mmol), and then the solution was stirred at the same temperature for 10 min. To this was slowly added a solution of **15** (100 mg, 0.361 mmol) at −78 °C, and the mixture was again stirred at the same temperature for 0.5 h. The mixture was quenched with saturated NH_4Cl at 0 °C, and then the resulting mixture was extracted with EtOAc. The organic layer was washed in succession with saturated $CuSO_4$, H_2O, saturated $NaHCO_3$, H_2O, and saturated NaCl, dried, filtered, and evaporated to leave an oil, which was chromatographed. Elution with a 2:1 mixture of hexanes−EtOAc furnished the thiol ester **16** (58.0 mg, 99%) as a colorless oil, together with (4*S*,5*R*)-norephedrine-2-oxazolidinone (53.0 mg, 100%). **16**: $[\alpha]^{26}_D$ + 14.5 (*c* 0.123, $CHCl_3$). IR 3400 and 1680 cm^{-1}; ^1H NMR δ 1.18 (3H, d, J = 6.2), 1.22 (3H, d, J = 4.4), 1.26 (3H, t, J = 7.3), 2.39 (1H, d, J = 3.6), 2.63 (1H, dt, J = 4.4 and 3.7), 2.89 (2H, q, J = 7.3) and 4.09 (1H, ddq, J = 6.2, 3.7 and 3.6). Anal. Calcd for $C_7H_{14}O_2S$: C, 51.82; H, 8.70; S, 19.76. Found: C, 52.03; H, 8.59; S, 19.80.

(+)-*S*-Ethyl (2*S*,3*R*)-3-(*tert*-Butyldimethylsiloxy)-2-methylbutanethioate (17). To a stirred solution of **16** (13.9 mg, 85.8 μmol) in DMF (2 mL) were added TBDMSCl (15.6 mg, 0.103 mmol) and imidazole (11.6 mg, 0.172 mmol) at room temperature, and then the mixture was stirred at the same temperature for 10 h. The mixture was diluted with Et_2O, and the ethereal layer was washed with H_2O, saturated NaCl, dried, filtered, and evaporated to provide an oil, which was chromatographed. Elution with a 5:1 mixture of hexanes−EtOAc afforded **17** (23.8 mg, 100%) as a colorless oil. $[\alpha]^{25}_D$ +2.25 (*c* 0.203, $CHCl_3$). IR 1680 cm^{-1}; ^1H NMR δ 0.04 (3H, s), 0.05 (3H, s), 0.85 (9H, s), 1.15 (3H, d, J = 6.2), 1.18 (3H, d, J = 7.0), 1.23 (3H, t, J = 7.3), 2.58 (1H, dt, J = 7.0 and 7.0), 2.84 (2H, q, J = 7.3), and 4.02 (1H, dq, J = 7.0, 6.2). Anal. Calcd for $C_{13}H_{28}O_2SSi$: C, 56.47; H, 10.21; S, 11.59. Found: C, 56.63; H, 10.14; S, 11.62.

(+)-Ethyl (4*R*,5*R*,*E*)-5-(*tert*-Butyldimethylsiloxy)-4-methyl-2-hexenoate (18). To a stirred solution of **17** (2.00 g, 7.25 mmol) in Me_2CO (20 mL) was added 10% Pd−C (44 mg). After being stirred for 10 min, Et_3SiH (3.47 mL, 21.7 mmol) was slowly added at 0 °C, and the reaction solution was again stirred for 5 min at 0 °C and for 10 min at room temperature. The catalyst was filtered off and washed with Me_2CO. Concentration of the combined filtrate and washings gave an oil, which was chromatographed. Elution with a 20:1 mixture of hexanes−EtOAc afforded the aldehyde **7** (1.57 g, 100%) as a colorless oil. IR 2850 and 1730 cm^{-1}; ^1H NMR δ 0.03 (3H, s), 0.05 (3H, s), 0.85 (9H, s), 1.05 (3H, d, J = 7.1), 1.16 (3H, d, J = 6.7), 2.36 (1H, ddq, J = 7.1, 4.9 and 1.1), 4.24 (1H, dq, J = 6.7 and 4.9), and 9.74 (1H, q, J = 1.1).

To a slurry of LiCl (873 mg, 20.6 mmol) in MeCN (4 mL) were slowly added diethyl [(ethoxycarbonyl)methyl]phosphonate (4.09 mL, 20.6 mmol) and DBU (1.98 mL, 13.3 mmol) at room temperature and then a solution of the above aldehyde in MeCN (12 mL) at 0 °C. After being stirred at 0 °C for 1 h, the mixture was allowed to warm to room temperature and diluted with Et_2O. The ethereal layer was washed with H_2O, saturated NaCl, dried, filtered, and evaporated to afford **18** (1.60 g, 94%) as a colorless oil. $[\alpha]^{26}_D$ +13.2 (*c* 0.207, $CHCl_3$). IR 1710 and 1650 cm^{-1}; ^1H NMR δ 0.04 (3H, s), 0.05 (3H, s), 0.89 (9H, s), 1.04 (3H, d, J = 6.6), 1.09 (3H, d, J = 6.2), 1.29 (3H, t, J = 7.1), 2.25−2.37 (1H, m), 3.74 (1H, dq, J = 6.2 and 6.0), 4.12 (2H, q, J = 7.1), 5.80 (1H, dd, J = 15.8 and 1.1), and 6.96 (1H, dd, J = 15.8 and 7.9). Anal. Calcd for $C_{15}H_{30}O_3Si$: C, 62.89; H, 10.55. Found: C, 62.68; H, 10.53.

(+)-(4*R*,5*R*,*E*)-5-(*tert*-Butyldimethylsiloxy)-4-methyl-2-hexenol (13). (A): To a stirred solution of the mixture **11** and **12** (68.0 mg, 0.291 mmol) in CH_2Cl_2 (2 mL) were added dropwise 2,6-lutidine (68.0 μL, 0.580 mmol) and TBDMSOTf (80.0 μL, 0.350 mmol) at 0 °C, and then the mixture was stirred at 0 °C for 3 h. The mixture was quenched by additions of saturated $NaHCO_3$ and saturated $KHSO_4$, and the resulting solution was extracted with Et_2O. The ethereal layer was dried, filtered, and evaporated to give an oil, which was chromatographed. Elution with a 20:1 mixture of hexanes−EtOAc provided the TBDMS ethers (89.0 mg, 88%) as a colorless oil. $[\alpha]^{22}_D$ +15.0 (*c* 0.415, $CHCl_3$). IR 1720 cm^{-1}. ^1H NMR δ 0.03 (3H, s), 0.04 (3H, s), 0.88 (9H, s), 1.03 (3H, d, J = 6.9), 1.08 (3H, d, J = 6.3), 5.85 (0.06H, dd, J = 15.0 and 1.0), 5.86 (0.94H, dd, J = 15.0 and 1.0), 6.99 (0.06H, dd, J = 15.0 and 7.5), and 7.03 (0.94H, dd, J = 15.0 and 7.5). HRMS calcd for $C_{16}H_{23}O_3Si$ (M^+ − 57) 291.1415, found 291.1404.

To a −78 °C solution of the above material (89.0 mg, 0.256 mmol) in CH_2Cl_2 (3 mL) was slowly added DIBALH (0.57 mL, 0.96 M in hexane, 0.547 mmol), and the mixture was again stirred at −78 °C for 1 h. The mixture was quenched by addition of MeOH (0.3 mL) and 0.5 M sodium potassium tartrate (3 mL), and then the resulting solution was stirred at room temperature for 12 h. The mixture was extracted with CH_2Cl_2, and the organic layer was dried, filtered, and evaporated to afford an oil, which was chromatographed. Elution with a 4:1 mixture of hexanes−EtOAc gave rise to **13** (59.7 mg, 95%) as a colorless oil: $[\alpha]^{26}_D$ +11.6 (*c* 0.20, $CHCl_3$). IR 3350 and 1650 cm^{-1}; ^1H NMR δ 0.01 (3H, s), 0.02 (3H, s), 0.86 (9H, s), 0.96 (3H, d, J = 7.0), 1.04 (3H, d, J = 6.2), 1.56 (1H, br t, J = 4.4), 2.19 (1H, dq, J = 7.0 and 6.5), 3.62 (1H, dq, J = 6.5 and 6.2), 4.11 (2H, br t, J = 4.4), and 5.58−5.65 (2H, m). Anal. Calcd for $C_{13}H_{28}O_2Si$: C, 63.88; H, 11.54. Found: C, 63.83; H, 11.52.

(B): To a −78 °C solution of **18** (4.70 g, 16.4 mmol) in THF (60 mL) was added dropwise DIBALH (36.3 mL, 0.95 M in hexane, 34.5 mmol), and then the solution was stirred at the same temperature for 1 h. To this were added H_2O (36 mL), Et_2O (50 mL) and hexanes (50 mL) at −78 °C, and the resulting mixture was allowed to warm to room temperature. After 9 h of stirring at room temperature, Celite and $MgSO_4$ were added at 0 °C. The insoluble solid was filtered off and washed with Et_2O. Concentration of the combined filtrates and washings left an oil, which was chromatographed. Elution with a 6:1 mixture of hexanes−EtOAc provided **13** (4.07 g, 100%) as a colorless oil. Characteristics are identical to those synthesized previously.

(+)-(4*R*,5*R*,*E*)-5-(*tert*-Butyldimethylsiloxy)-4-methyl-2-hexenyl Methyl Carbonate (19). To a stirred solution of **13** (4.00 g, 16.3 mmol) in CH_2Cl_2 (150 mL) were added slowly methyl chloroformate (1.64 mL, 21.2 mmol) and pyridine (1.58 mL, 19.5 mmol) at 0 °C, and the mixture was again stirred at the same temperature for 1 h. The mixture was quenched by addition of H_2O, and the resulting solution was extracted with Et_2O. The ethereal layer was dried, filtered, and evaporated to yield an oil, which was chromatographed. Elution with a 15:1 mixture of hexanes−EtOAc furnished the carbonate **19** (4.84 g, 98%) as a colorless oil. Kügelrohr distillation (86 °C/4 mmHg) provided the pure **19**. $[\alpha]^{24}_D$ +13.2 (*c* 0.155, $CHCl_3$). IR 1750 cm^{-1}; ^1H NMR δ 0.01 (3H, s), 0.02 (3H, s), 0.86 (9H, s), 0.96 (3H, d, J = 6.5), 1.03 (3H, d, J = 6.5), 2.18 (1H, ddq, J = 7.0, 7.0 and 6.5), 3.62 (1H, dq, J = 7.0 and 6.5), 3.75 (3H, s), 4.56 (2H, br t, J = 6.0), 5.55 (1H, ddt, J = 15.0, 6.6 and 0.7), and 5.77 (1H, ddt, J = 15.0, 7.0 and 1.0). HRMS calcd for $C_{13}H_{27}OSi$ (M^+ − 75) 227.1832, found 227.1866. Anal. Calcd for $C_{15}H_{30}O_4Si$: C, 59.56; H, 10.00. Found: C, 59.42; H, 10.20.

(+)-(4*R*,5*R*,*E*)-5-Hydroxy-4-methyl-2-hexenyl Methyl Carbonate (20). To a stirred solution of **19** (251 mg, 0.831 mmol) in THF (5 mL) was slowly added Bu_4NF (0.481 mL, 1 M in THF, 1.66 mmol) at room temperature, and the mixture was stirred at room temperature for 20 h and then at 30 °C for 1 h. After removal of the solvent, the residue was chromatographed. Elution with a 2:1 mixture of hexanes−EtOAc gave rise to **20** (123 mg, 79%) as a colorless oil. Kügelrohr distillation (103 °C/6 mmHg) furnished the pure **20**. $[\alpha]^{25}_D$ +27.3 (*c* 0.107, $CHCl_3$). IR 3400 and 1750 cm^{-1}; ^1H NMR δ 1.04 (3H, d, J = 7.0), 1.14 (3H, d, J = 6.6), 1.65 (1H, br s), 2.27 (1H, br dq, J = 7.0 and 6.2), 3.70 (1H, dq, 6.6 and 6.2), 3.79 (3H, s), 4.61 (2H, d, J = 6.3), 5.64 (1H, ddt, J = 15.6, 6.3 and 0.7), and 5.79 (1H, br dd, J = 15.6 and 7.5). HRMS calcd for $C_7H_{12}O$ (M^+ − 76) 112.0888, found 112.0866. Anal. Calcd for $C_9H_{16}O_4$: C, 57.44; H, 8.57. Found: C, 57.21; H, 8.58.

(+)-(4*R*,5*R*,*E*)-5-(Methoxymalonyl)-4-methyl-2-hexenyl Methyl Carbonate (21). To a solution of **20** (489 mg, 2.60 mmol), monomethyl malonate (430 mg, 3.64 mmol), and DMAP (444 mg, 3.64 mmol) in CH_2Cl_2 (20 mL) was added dropwise a solution of WSC (697 mg, 3.64 mmol) in CH_2Cl_2 (20 mL) at 0 °C, and then the resulting solution, after 10 min, was allowed to warm to room temperature. The mixture was again stirred at the same temperature for 24 h. After removal of the solvent, the residue was diluted with Et_2O. The ethereal layer was washed with H_2O, saturated NaCl, dried, filtered, and evaporated to give an oil, which was chromatographed. Elution with a 3:1 mixture of hexanes−EtOAc provided **21** (659 mg, 88%), together with the starting material (47.1 mg). Kügelrohr distillation (108 °C/4 mmHg) gave the pure **21**. $[\alpha]^{25}_D$ +23.9 (*c* 0.129, $CHCl_3$). IR 1750, 1740, and 1730 cm^{-1}; ^1H NMR δ 1.03 (3H, d, J = 7.0), 1.18 (3H, d, J = 6.6), 2.46 (1H, dq, J = 7.0 and 6.4), 3.38 (2H, s), 3.75 (3H, s), 3.79 (3H, s), 4.60 (2H, d, J = 5.5), 4.87 (1H, dq, J = 6.6 and 6.4) and 5.59−5.77 (2H, m). HRMS calcd for $C_{11}H_{17}O_4$ (M^+ − 75) 213.1126, found 213.1109. Anal. Calcd for $C_{13}H_{20}O_7$: C, 54.16; H, 6.99. Found: C, 53.99; H, 6.77.

(+)-(4*R*,5*R*)-4,5-Dimethyl-2-(methoxycarbonyl)-3-vinylpentanolide (5). Entry 1: To a slurry of NaH (3.8 mg, 60%, 95 μmol, washed three times with hexanes) in THF (0.5 mL) was slowly added a solution of **21** (27.1 mg, 94.1 μmol) in THF (0.5 mL) at 0 °C, and the resulting mixture was stirred at 0 °C for 15 min and then at room temperature for 0.5 h. This solution was slowly added via cannula to a solution of $Pd(Ph_3P)_4$ (5.4 mg, 4.7 μmol) and bis(diphenylphosphino)-ethane (dppe) (3.7 mg, 9.4 μmol) in THF (1 mL) under reflux, and then the mixture was again heated under reflux for 3 h, cooled to room temperature, and diluted with Et_2O. The organic layer was washed with H_2O, saturated NaCl, dried, filtered, and evaporated to leave an oil, which was chromatographed. Elution with a 3:1 mixture of hexanes−EtOAc gave **5** (3.70 mg, 19%) as a colorless oil. Kügelrohr distillation (140 °C/5 mmHg) afforded **5** as a mixture of four diastereomers. $[\alpha]^{22}_D$ + 50.6 (*c* 0.119, $CHCl_3$). IR 1750, 1745, and 1720 cm^{-1}; ^1H NMR δ 0.85 (0.27H, d, J = 7.0), 0.90 (1.96H, d, J = 7.0), 0.98 (0.21H, d, J = 7.0), 0.99 (0.56H, d, J = 7.0), 1.31, 1.34, 1.36, and 1.37 (totally 3H, each d, each J = 6.6), 1.91−2.05 (1H, m), 3.08−3.18 (1H, m), 3.40 (0.33H, d, J = 11.0), 3.48 (0.67H, d, J = 11.0), 3.77 (3H, s), 4.58 (0.33H, dq, J = 6.6 and 2.2), 4.71 (0.67H, dq, J = 6.6 and 2.2), 5.10−5.22 (2H, m), and 5.76 (1H, ddd, J = 16.0, 10.0 and 6.8). HRMS calcd for $C_{11}H_{16}O_4$ (M^+) 212.1048, found 212.1039. Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.28; H, 7.60.

Entry 2: To a stirred suspension of NaH (5.2 mg, 60%, 0.130 mmol, washed three times with hexanes) in THF (0.3 mL) was added dropwise a solution of **21** (34.0 mg, 0.118 mmol) in THF (0.5 mL) at room temperature, and then the mixture was stirred for 40 min. To a stirred solution of dppe (9.4 mg, 24 μmol) in THF (0.3 mL) was added $(dba)_3Pd_2{\cdot}CHCl_3$ (6.1 mg, 5.9 μmol) at room temperature, and the resulting mixture was again stirred for 20 min. To this was slowly added at room temperature the carbanion solution described above, and then the mixture was stirred at room temperature for 7 h. TLC analysis showed that **5** were generated along with numerous byproducts.

Entry 3: To a stirred solution of Ph_3P (2.0 mg, 7.6 μmol) in THF (0.5 mL) was added $(dba)_3Pd_2{\cdot}CHCl_3$ (1.0 mg, 0.97 μmol) at room temperature, and then the mixture was stirred at room temperature for 10 min. After slow addition of a solution of **21** (27.1 mg, 94.1 μmol) in THF (0.5 mL) at room temperature, the resulting solution was again stirred at the same temperature for 3.5 h, and then heated under reflux for 0.5 h. After removal of a precipitate through Celite, the filtrate

was concentrated to provide an oil. Purification in the same way furnished **5** (4.9 mg, 25%).

Entry 4: To a solution of **21** (34.3 mg, 0.119 mmol) in MeCN (2 mL) were added $Pd(OAc)_2$ (2.70 mg, 11.0 mmol) and Bu_3P (11.9 μL, 48.0 μmol) at room temperature, and then the mixture was heated under reflux for 1 h. Workup in the same way gave rise to **5** (8.40 mg, 33%).

Entry 5: To a solution of **21** (33.6 mg, 0.117 mmol) in MeCN (2 mL) were added $Pd(OAc)_2$ (2.60 mg, 11.0 μmol) and Ph_3P (11.5 mg, 43.9 μmol) at room temperature, and the mixture was heated under reflux for 6.5 h. Workup in the usual way provided **5** (11.8 mg, 48%).

Entry 6: To a solution of **21** (772 mg, 2.68 mmol) in DMSO (1 mL) were added $Pd(OAc)_2$ (65.4 mg, 0.268 mmol) and Ph_3P (280 mg, 1.07 mmol) at room temperature, and then the mixture was heated at 90 °C for 5 h. The mixture was cooled to room temperature and then diluted with Et_2O. The ethereal layer was washed with H_2O and saturated NaCl, dried, filtered, and evaporated to leave an oil. Purification in the same way furnished **5** (395 mg, 70%).

Entry 7: To a solution of **21** (20.6 mg, 71.5 μmol) in DMSO (1 mL) were added $Pd(OAc)_2$ (1.70 mg, 6.97 μmol) and Ph_3P (7.50 mg, 28.6 μmol) at room temperature, and the mixture was heated at 45 °C for 7.5 h. Workup in the same way gave **5** (10.1 mg, 66%).

Entry 8: A mixture of **21** (29.7 mg, 0.103 mmol), $Pd(OAc)_2$ (2.50 mg, 10.3 μmol), and Ph_3P (10.7 mg, 4.12 μmol) in DMF (1 mL) was heated at 90 °C in a sealed tube for 6.5 h. Workup in the same way provided **5** (18.9 mg, 87%).

(−)-(1*R*,2*R*,6*R*,7*R*)-6,7-Dimethyl-3-oxo-2,8-dioxabicyclo-[3.3.0]octane (22). To a solution of **5** (390 mg, 1.84 mmol) in DMF (20 mL) was added LiI (493 mg, 3.68 mmol) at room temperature, and the solution was heated under reflux for 5 h. The reaction was cooled to room temperature and then quenched by addition of H_2O. The resulting mixture was extracted with Et_2O. The ethereal layer was dried, filtered, and evaporated to yield an oil, which was chromatographed. Elution with a 4:1 mixture of hexanes−EtOAc gave a 3:1 mixture of the corresponding lactones (215 mg, 76%) as a colorless oil. $[\alpha]^{22}_D$ +48.07 (*c* 0.03, $CHCl_3$). IR 1740, 1640 cm^{-1}; ^1H NMR δ 0.85 (2H, d, J = 7.1), 0.99 (1H, d, J = 7.1), 1.31 (1H, d, J = 6.6), 1.34 (2H, d, J = 6.6), 1.80−1.98 (1H, m), 2.36−2.48 (1.2H, m), 2.56−2.68 (1H, m), 2.72−2.83 (0.8H, m), 4.52−4.62 (1H, m), 5.03−5.19 (2H, m), 5.73 (0.33H, ddd, J = 16.8, 10.1 and 5.6), and 5.80 (0.67H, ddd, J = 16.8, 10.1 and 5.6). HRMS calcd for $C_9H_{14}O_2$ (M^+) 154.0933, found 154.0989.

Through a stirred solution of the above material (181 mg, 1.17 mmol) in MeOH (10 mL) at −78 °C was passed a stream of O_3. When the reaction mixture maintained a blue color for 15 min, the stream of ozone was replaced by nitrogen and the solution was stirred until the color dissipated. To the resulting clear reaction mixture was added Me_2S (0.40 mL, 5.86 mmol) at −78 °C, and the solution was allowed to warm to room temperature. After being stirred for 1 h at room temperature, the solvent was removed under reduced pressure to leave a residue (ca. 250 mg), which was taken up in CH_2Cl_2 (15 mL). To this was slowly added concd HCl (2 mL) at room temperature, and the mixture was again stirred at the same temperature for 15 h. The mixture was neutralized with saturated $NaHCO_3$ at 0 °C, and then the resulting solution was extracted with Et_2O. The ethereal layer was washed with saturated NaCl, dried, filtered, and evaporated to afford a solid, which was chromatographed. Elution with a 1:1 mixture of hexanes−EtOAc gave **22** (168 mg, 92% for two steps) as a powder. Recrystallization from Et_2O furnished **22** as prisms, mp 58−59 °C. $[\alpha]^{19}_D$ −10.5 (*c* 0.05, $CHCl_3$). IR 1780 cm^{-1}; ^1H NMR δ 0.97 (3H, d, J = 7.0), 1.23 (3H, d, J = 6.2), 2.10 (1H, ddt, J = 7.0, 5.0 and 2.0), 2.45 (1H, dd, J = 17.6 and 3.3), 2.75−2.83 (1H, m), 2.88 (1H, dd, J = 17.6 and 10.5), 4.33 (1H, dq, J = 6.2 and 5.0), and 6.06 (1H, d, J = 5.1). HRMS calcd for $C_8H_{13}O_3$ ($M^+ + 1$) 157.0864, found 157.0877. Anal. Calcd for $C_8H_{12}O_3$: C, 61.52; H, 7.74. Found: C, 61.52; H, 7.71.

(−)-(3*R*,4*R*,5*R*)-4,5-Dimethyl-3-(1,3-dithiolan-2-yl)pentanolide (23). To a solution of **22** (161 mg, 1.03 mmol) in CH_2Cl_2 (10 mL) were added dropwise 1,2-ethanedithiol (0.104 mL, 1.24 mmol) and $BF_3{\cdot}Et_2O$ (0.15 mL, 1.03 mmol) at 0 °C, and then the mixture was stirred at the same temperature for 0.5 h. After removal of a portion of the solvent, the residue was chromatographed. Elution with a 2:1 mixture provided **23** (241 mg, 100%) as a colorless powder. Recrystallization of the above material from Et_2O−heptane furnished **23** (171 mg, 72%) as colorless prisms, mp 150−151 °C. $[\alpha]^{22}_D$ −18.3 (*c* 0.77, $CHCl_3$). IR 1710 cm^{-1}; ^1H NMR δ 0.89 (3H, d, J = 7.1), 1.35 (3H, d, J = 6.6), 2.12−2.21 (2H, m), 2.26 (1H, dd, J = 17.6 and 12.0), 2.91 (1H, ddd, J = 17.6, 6.3 and 0.8), 3.18−3.28 (4H, m), 4.34 (1H, d, J = 9.9) and 4.48 (1H, dq, J = 6.6 and 2.2). HRMS calcd for $C_{10}H_{16}O_2S_2$ (M^+) 232.0591, found 232.0564. Anal. Calcd for $C_{10}H_{16}O_2S_2$: C, 51.69; H, 6.94; S, 27.60. Found: C, 51.63; H, 6.99; S, 27.72.

(+)-Methyl (2*R*,4*R*,5*R*,6*R*)-[5,6-Dimethyl-4-(1,3-dithiolan-2-yl)-2-methoxytetrahydropyranyl]-2-*O*-benzoylglycolate (24). To a −78 °C solution of LDA, prepared from *i*-Pr_2NH (0.109 mL, 0.776 mmol) and BuLi (0.497 mL, 10 wt % in hexanes, 0.776 mmol), in THF (5 mL) was slowly added a solution of methyl *O*-(2-methoxy-2-propyl)glycolate[6a] (125 mg, 0.776 mmol) in THF (5 mL), and the mixture was stirred at −78 °C for 10 min and then at 0 °C for 15 min. To this was slowly added a solution of **23** (100 mg, 0.431 mmol) in THF (5 mL) at −78 °C, and the resulting solution was again stirred at −78 °C for 2 h and at 0 °C for 0.5 h. The mixture was quenched by dropwise addition of EtOH (0.5 mL) at 0 °C and allowed to warm to room temperature. The resulting solution was diluted with Et_2O and H_2O and separated. The aqueous layer was extracted with Et_2O, and the combined ethereal layers were washed with H_2O, saturated NaCl, dried over K_2CO_3, filtered, and evaporated to leave a residue (273 mg), which without purification was used in the subsequent step. To a solution of the above compound in CH_2Cl_2 (1 mL) were added MeOH (1 mL), trimethyl orthoformate (0.5 mL, 4.57 mmol), and 10-camphorsulfonic acid (48 mg, 0.216 mmol), and the resulting solution was stirred at room temperature for 1 h. After addition of $NaHCO_3$, the mixture was extracted with Et_2O. The organic layer was washed with saturated NaCl, dried (K_2CO_3), filtered, and evaporated to an oil, which was used in the next step without purification. $[\alpha]^{23}_D$ +43.3 (*c* 0.09, $CHCl_3$). IR 3340 and 1740 cm^{-1}; ^1H NMR δ 0.71 (1.5H, d, J = 7.0), 0.88 (1.5H, d, J = 7.0), 1.16 (1.5H, d, J = 6.8), 1.18 (1.5H, d, J = 6.8), 1.54−1.62 (1H, m), 1.73 (1H, dd, J = 12.0 and 11.9), 1.83−2.14 (2H, m), 3.29 (1.5H, s), 3.33 (1.5H, s), 3.82 (3H, s), 3.83−3.91 (1H, m), 4.27 (0.5H, d, J = 10.2), 4.30 (0.5H, d, J = 10.2), 4.32 (0.5H, d, J = 6.4) and 4.38 (0.5H, d, J = 4.5). HRMS calcd for $C_{14}H_{24}O_5S_2$ ($M^+ - 32$) 304.0802, found 304.0815.

To a solution of the above alcohol (231 mg) and DMAP (0.5 mg, 4.10 μmol) in pyridine (1 mL) was slowly added benzoyl chloride (75.2 μL, 647 μmol) at 0 °C, and the solution was stirred at 0 °C for 15 min and at room temperature for 8 h. The mixture was quenched by addition of saturated $KHSO_4$ at 0 °C, and the mixture was extracted with Et_2O. The ethereal layer was washed with saturated NaCl, dried, filtered, and evaporated to give an oil, which was chromatographed. Elution with a 6:1 mixture of hexanes−EtOAc provided a 1:1 mixture of **24** (185 mg, 97% for three steps) as a colorless oil. $[\alpha]^{24}_D$ +34.2 (*c* 0.07, $CHCl_3$). IR 1760 and 1730 cm^{-1}; ^1H NMR δ 0.75 (1.5H, d, J = 7.5), 0.90 (1.5H, d, J = 7.5), 1.15 (1.5H, d, J = 7.5), 1.20 (1.5H, d, J = 7.5), 1.80−2.22 (3H, m), 2.40−2.60 (1H, m), 3.18−3.22 (4H, m), 3.23 (1.5H, s), 3.40 (1.5H, s), 3.78 (1.5H, s), 3.82 (1.5H, s), 3.82−3.90 (1H, m), 4.32 (0.5H, d, J = 7.5), 4.38 (0.5H, d, J = 7.5), 5.30 (0.5H, s), 5.39 (0.5H, s), 7.40−7.48 (2H, m), 7.50−7.64 (1H, m), 8.00−8.12 (2H, m). HRMS calcd for $C_{21}H_{28}O_6S_2$ ($M^+ - 32$) 408.1064, found 408.1081.

(+)-Methyl (2*R*,4*R*,5*R*,6*R*)-[5,6-Dimethyl-4-(hydroxymethyl)-2-methoxytetrahydropyranyl]-2-*O*-benzoylglycolate (25). A mixture of **24** (50.8 mg, 0.115 mmol), HgO (37.6 mg, 0.173 mmol), and $HgCl_2$ (62.6 mg, 0.230 mmol) in a mixture of MeCN (0.8 mL) and H_2O (0.2 mL) was heated at 62 °C for 3 h. The mixture was cooled to room temperature and then diluted with Et_2O. The resulting mixture was filtered through Celite. The filtrate was separated, and the

organic layer was washed in succession with 5 M NH_4OAc, H_2O, saturated $NaHCO_3$, H_2O, and saturated NaCl, dried, filtered, and evaporated to yield the aldehyde (63.2 mg), which was immediately used in the subsequent reaction without purification. IR 2725, 1760, 1740, and 1730 cm^{-1}; ^1H NMR δ 0.75 (1.5H, d, J = 7.0), 0.89 (1.5H, d, J = 7.0), 1.11 (1.5H, d, J = 7.0), 1.16 (1.5H, d, J = 6.8), 1.76−2.24 (3H, m), 2.50−2.68 (1H, m), 3.29 (1.5H, s), 3.44 (1.5H, s), 3.80 (1.5H, s), 3.81 (1.5H, s), 3.92−4.08 (1H, m), 5.38 (0.5H, s), 5.43 (0.5H, s), 7.40−7.48 (2H, m), 7.56−7.64 (1H, m), 7.98−8.12 (2H, m) and 9.69 (1H, s).

To a 0 °C solution of the above aldehyde in MeOH (1 mL) was added $NaBH_4$ (4.30 mg, 0.115 mmol) in several portions, and then the mixture was again stirred at 0 °C for 0.5 h. To this was added saturated NH_4Cl (4 mL) at 0 °C, and the solvent was removed under reduced pressure. The resulting solution was extracted with Et_2O, and the ethereal layer was washed with H_2O and saturated NaCl, dried, filtered, and evaporated to afford an oil, which was chromatographed. Elution with a 1:1 mixture of hexanes−EtOAc furnished **25** as a 1:1 mixture (33.4 mg, 79% for two steps) as a colorless oil. $[\alpha]^{25}_D$ +63.4 (*c* 0.31, $CHCl_3$). IR 3500, 1750, and 1730 cm^{-1}; ^1H NMR δ 0.71 (1.5H, d, J = 7.0), 0.88 (1.5H, d, J = 7.0), 1.14 (1.5H, d, J = 5.5), 1.16 (1.5H, d, J = 5.5), 1.34−1.48 (1H, m), 1.72−1.82 (2.5H, m), 1.92 (0.5H, dd, J = 3.5 and 3.5), 2.21−2.34 (1H, m), 3.28 (1.5H, s), 3.42 (1.5H, s), 3.56 (2H, dd, J = 7.0 and 7.0), 3.79 (1.5H, s), 3.79 (1.5H, s), 3.86−3.96 (1H, m), 5.32 (0.5H, s), 5.38 (0.5H, s), 7.44−7.50 (2H, m), 7.56−7.63 (1H, m) and 8.04−8.10 (2H, m). HRMS calcd for $C_{18}H_{23}O_6$ (M^+ − 31) 355.1493, found 355.1499.

(+)-Methyl Pederate (4). To a stirred solution of **25** (18.2 mg, 0.130 mmol) and 2-nitrophenyl selenocyanate (44.8 mg, 0.200 mmol) in THF (2 mL) at 0 °C was slowly added Bu_3P (49.0 μL, 0.200 mmol), and the mixture was again stirred at 0 °C for 10 min and then at room temperature for 8 h. The mixture was subjected to column chromatography on Florisil. Elution with a 5:1 mixture of hexanes−EtOAc produced the selenide (229 mg), a colorless oil, together with a small portion of inseparable impurities. IR 1750 and 1730 cm^{-1}; ^1H NMR δ 0.76 (1.5H, d, J = 7.0), 0.94 (1.5H, d, J = 6.6), 1.16 (1.5H, d, J = 6.6), 1.17 (1.5H, d, J = 6.6), 1.75−2.16 (3H, m), 2.36−2.50 (1H, m), 2.80−3.00 (2H, m), 3.26 (1.5H, s), 3.40 (1.5H, s), 3.80 (1.5H, s), 3.81 (1.5H, s), 3.84−3.92 (1H, m), 5.33 (0.5H, s), 5.38 (0.5H, s), 7.28−7.62 (6H, m), 7.86−8.08 (2H, m) and 8.24−8.40 (1H, m). HRMS calcd for $C_{25}H_{29}NO_8Se$ 551.1057, found 551.1099.

To a 0 °C solution of the above selenide in THF (2 mL) was added dropwise 30% H_2O_2 (0.170 mL, 1.50 mmol), and the resulting mixture was again stirred at 0 °C for 1 h and then at room temperature for 10 min. After addition of H_2O and Et_2O, the organic layer was washed with 10% Na_2CO_3 and H_2O, dried, filtered, and evaporated to give an oil, which was chromatographed. Elution with a 6:1:0.07 mixture of hexanes−EtOAc−Et_3N afforded a 1:1 mixture of the olefin (26.9 mg, 60% for two steps) as a colorless oil. $[\alpha]^{25}_D$ +73.4 (*c* 0.27, $CHCl_3$). IR 1760 and 1740 cm^{-1}; ^1H NMR δ 0.95 (1.5H, d, J = 7.0), 1.11 (1.5H, d, J = 7.7), 1.14 (1.5H, d, J = 6.2), 1.16 (1.5H, d, J = 7.0), 2.14 (0.5H, d, J = 13.9), 2.18−2.29 (1H, m), 2.46 (0.5H, d, J = 14.7), 2.91 (0.5H, ddd, J = 14.6, 2.5 and 1.6), 3.05 (0.5H, ddd, J = 13.9, 3.3 and 1.7), 3.27 (1.5H, s), 3.40 (1.5H, s), 3.81 (3H, s), 3.86−3.96 (1H, m), 4.74 (0.5H, dd, J = 2.2 and 2.2), 4.80 (0.5H, dd, J = 2.2, 2.2), 4.87 (1H, br s), 5.36 (0.5H, s), 5.43 (0.5H, s), 7.38−7.50 (2H, m), 7.52−7.64 (1H, m), 8.00−8.12 (2H, m). HRMS calcd for $C_{11}H_{15}O_3$ (M^+ − 153) 195.1020, found 195.1017.

To a 0 °C solution of the above benzoate (26.9 mg, 77.0 μmol) in MeOH (4 mL) was slowly added a solution of NaOMe (8.4 mg, 155 μmol) in MeOH (1 mL), and the mixture was again stirred at 0 °C for 10 min, and then at room temperature for 1 h. After removal of the solvent, the residue was diluted with Et_2O. The ethereal layer was washed with H_2O, dried, filtered, and evaporated to afford an oil, which was chromatographed. Elution with a 6:1:0.07 mixture of hexanes−EtOAc−Et_3N provided (+)-methyl pederate (**4**) (9.3 mg, 50%) as a colorless oil. $[\alpha]^{22}_D$ + 131.16 (*c* 0.09, CH_2Cl_2) [lit.[6o] $[\alpha]^{23}_D$ +115 (*c* 0.30, CH_2Cl_2)]. IR 3400 and 1740 cm^{-1}; ^1H NMR δ 0.94 (3H, d, J = 7.0), 1.16 (3H, d, J = 6.2), 2.22 (1H, br dq, J = 7.0 and 2.7), 2.31 (1H, dt, J = 14.0 and 2.0), 2.37 (1H, d, J = 14.0), 2.90 (1H, d, J = 5.6), 3.30 (3H, s), 3.84 (3H, s), 3.92 (1H, dq, J = 6.2 and 2.7), 4.36 (1H, d, J = 5.5), 4.73 (1H, dd, J = 2.0 and 1.1) and 4.83 (1H, dd, J = 2.0 and 0.8). HRMS calcd for $C_{11}H_{15}O_3$ (M^+ − 49) 195.1020, found 195.1013. Further elution gave (+)-methyl *epi*-pederate (**26**) (8.5 mg, 45%). Recrystallization from Et_2O of **26** gave rise to prisms, mp 68−69 °C. $[\alpha]^{24}_D$ +87.15 (*c* 0.070, $CHCl_3$). IR 3400 and 1740 cm^{-1}; ^1H NMR δ 1.02 (3H, d, J = 7.0), 1.17 (3H, d, J = 6.6), 1.92 (1H, d, J = 14.3), 2.21 (1H, br dq, J = 7.0 and 2.5), 2.78−2.80 (2H, m), 3.34 (3H, s), 3.82 (3H, s), 3.92 (1H, dq, J = 6.6 and 2.5), 4.43 (1H, d, J = 4.4), 4.70 (1H, dd, J = 2.2 and 2.1) and 4.84 (1H, t, J = 2.0). HRMS calcd for $C_{10}H_{16}O_4$ (M^+ − 44) 200.1048, found 200.1034. Anal. Calcd for $C_{12}H_{20}O_5$: C, 59.00; H, 8.25. Found: C, 59.38; H, 8.05.

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Supporting Information Available: ^1H NMR spectra (300 MHz) for compounds **9**, **10**, **11**, **24**, **25**, and **4** (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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