Palladium(II)-Catalyzed Asymmetric Acetalization of Alkenes

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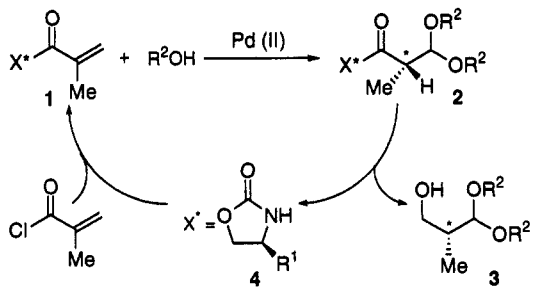
The terminal olefinic carbon of *N*-methacryloyl-2-oxazolidinones is smoothly acetalized by alcohols in the presence of $PdCl_2$ catalyst. The use of 4(*S*)-isopropyl-, phenyl-, and *tert*-butyl-2-oxazolidinones as the chiral auxiliary resulted in the formation of the corresponding (2′*S*)-acetals in 61, 80, and 95% de, respectively. Reductive removal of the auxiliary with $LiAlH_4$ followed by deacetalization produced (*R*)-3-hydroxy-2-methylpropanal. The enantiomer of this compound, derived from 4(*R*)-substituted oxazolidinones, served as a building block for synthesizing a 1β-methylcarbapenem precursor in high enantiomeric excess. In the acetalization of 3′,3′-dideuteriated methacryloyl-4-isopropyloxazolidinone with MeOH, one D-atom on the terminal olefinic carbon stereoselectively migrated to the chiral center in the product acetal. On the basis of this 1,2-hydride migration and the conformational preference of the methacryloyl moiety, the reaction pathway and the mechanism of the diastereoselection are discussed.

Acetalization of alkenes under palladium catalysis, which has developed into an industrial process,[1] has a great deal of potential utility in synthetic chemistry. Development of an asymmetric version of this reaction would undoubtedly expand such possibilities.[2] While monosubstituted alkenes with electron-withdrawing groups such as COOR and COR are smoothly acetalized by alcohols or diols,[3] geminal disubstituted alkenes are less reactive because of ineffective coordination of Pd(II) to the alkenes due to steric hindrance. For example, methacrylic esters undergo only ~30% reaction under the same conditions in which acrylic esters are acetalized in more than 90% yield. If the reactivity of the methacryloyl moiety in **1** (Scheme 1) is enhanced by incorporating chiral oxazolidinone **4**, diastereoselective acetalization of the prochiral alkenes becomes more accessible. Since reductive removal of the oxazolidinone auxiliary (X*) from acetal **2** proceeds nearly quantitatively,[4] realization of asymmetric acetalization provides an entry into optically active hydroxy acetals such as **3** which can serve as useful chiral building blocks. Pd(II)-assisted asymmetric alkylation/carbonylation of monosubstituted alkenes using chiral oxazolidinones, as recently reported by Hegedus et al.,[5] provides unique methodology for the synthesis of various natural products. The versatility of the oxazolidinone auxiliary developed by Evans[6] is undoubtedly advanced by establishment of the reaction sequence depicted in Scheme 1.

Apart from synthetic utility, realization of asymmetric acetalization offers profitable information on the mechanistic aspects of palladium chemistry.[7] The acetalization of alkenes proceeds via nucleophilic attack of ROH on the alkene coordinated to Pd(II), followed by Pd–H elimination.[3a,8] The pathways are quite fundamental for these types of reactions, such as the ketonization of alkenes with H_2O.[9] Details of the mechanistic process will be revealed by the stereochemical outcome of the present acetalizations.[10] Herein, we describe mechanistic details of the highly diastereoselective acetalization of methacryloyl derivatives **1** with alcohols, as well as the synthetic application of this new methodology.

Scheme 1



Results and Discussion

General Survey. In order to survey the general features of the reaction, (4*S*)-*N*-methacryloyl-4-isopro-

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(7) (a) Trost, B. M.; Verhoeven, T. R. *Comprehensive Organometallic Chemistry*; Wilkinson, G., Ed.; Oxford University Press: New York, 1982; Vol. 8, pp 854–983. (b) Henry P. M. *Palladium Catalyzed Oxidation of Hydrocarbon*; Reidel: Dordrecht, 1980; pp 41–84.

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Table 1. Acetalization of 1 (R^1 = *i*-Pr) with Various Alcohols[a]

entry	R^2 (equiv)	temp, °C	time, h	acetal **2**	yield,[b] %	de,[c] %
1	Me (10)	50	24	**2a**	72	43
2	Et (10)	50	24	**2b**	76	43
3	*n*-Pr (10)	50	24	**2c**	75[d]	48
4	Me (25)	25	96	**2a**	66	61
5	Me (50)	25	29	**2a**	54[d]	64

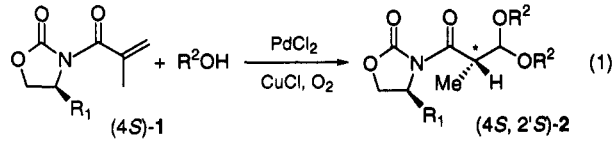
[a] The reaction was performed by using $PdCl_2$ (10 mmol), CuCl (1 equiv), and alcohols in DME. [b] Isolated yield unless otherwise noted. [c] Diastereomer excesses were determined by GLC and/or 270 MHz ^{1}H NMR. [d] Determined by 270 MHz ^{1}H NMR.

Table 2. Substituent Effect of R^1 on % de

entry	substrate	product R^1		time, h	yield, %	de, %
1	**1a**	*i*-Pr	**2a**	96	66	61
2	**1b**	Me	**2d**	96	61	23
3	**1c**	$PhCH_2$	**2e**	96	30	32
4	**1d**	Ph[a]	**2f**	24	92	71
5	**1d**	Ph[b]	**2f**	96	88	80
6	**1e**	*t*-Bu	**2g**	80	89	95

[a] Reaction was performed at 50 °C. [b] CH_2Cl_2 was used as solvent.

pyloxazolidinone (**1a**) was first acetalized (eq 1) with various alcohols under the conditions shown in Table 1.



(1)

1	R^1
a	*i*-Pr
b	Me
c	$PhCH_2$
d	Ph
e	*t*-Bu

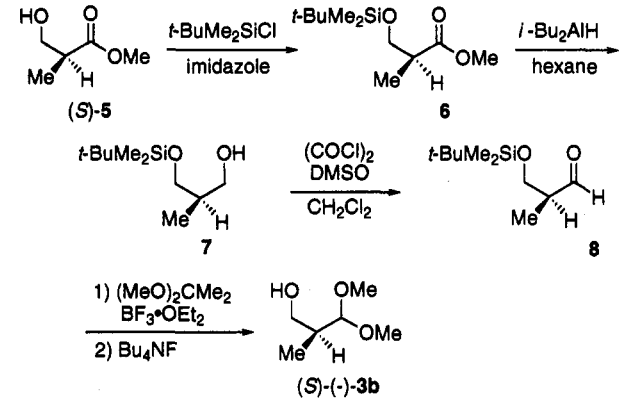
2	R^1	R^2
a	*i*-Pr	Me
b	*i*-Pr	Et
c	*i*-Pr	*n*-Pr
d	Me	Me
e	$PhCH_2$	Me
f	Ph	Me
g	*t*-Bu	Me

As expected, the reaction proceeded smoothly to give acetals **2a–c** in good yields. The diastereomeric excesses of the acetals were determined by GLC analysis using a capillary column and/or from ^{1}H NMR peak areas of the doublet signals due to the C′-2 methyl protons.

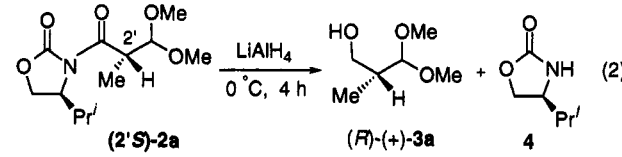
As can be seen in Table 1, virtually no difference in selectivity and reactivity was observed with alcohol substituents R = Me, Et, and *n*-Pr (entries 1–3). The reaction rate and selectivity depended only on the reaction temperature. Decreasing the temperature from 50 °C to 25 °C greatly retarded the reaction, but use of excess amounts of MeOH (25 equiv) at 25 °C allowed the acetalization to proceed to completion in 96 h (entry 4). Under these conditions, the selectivity increased from 43% de to 61% de (entries 1 and 4). When MeOH was used as solvent (entry 5), the reaction was accelerated but resulted in accompanying side reactions such as deacylation of the methacryloyl moiety from the oxazolidinone. Thus, we decided to use 25 equiv of MeOH at 25 °C in DME solvent as standard conditions.

Table 2 shows that the diastereoselectivity is dependent on the steric bulkiness of the substituents (R) at the 4-position of the oxazolidinone, and the % de follows the order of R = Me < CH_2Ph < *i*-Pr < Ph < *t*-Bu. The electronic nature of the substituent[6d,e] does not appear to be associated with the selectivity. The highest selectivity was attained with R= *t*-Bu (95% de) (entry 6). When the substituent R was an aryl group, as in **1d** (R = Ph), no appreciable reaction took place, presumably because of the substrate's low solubility in DME solvent. When **1d** was dissolved in DME at a higher temperature (50 °C) (entry 4), the reaction proceeded well to afford a 92% yield of acetal **2f** with moderate selectivity (71% de). When **1d** was acetalized in CH_2Cl_2 at a lower temperature (25 °C), the selectivity increased to 80% de. Thus, either DME or CH_2Cl_2 can be used as the solvent, although the reaction of **1a** (R = *i*-Pr) with MeOH in CH_2Cl_2 rather than DME (25 °C) showed no improvement in diastereoselectivity.

Scheme 2



The newly created chiral center in product **2a** was determined to be the 2′*S* configuration by the following method. The acetal **2a** (50% de) was converted into hydroxy acetal **3a** upon treatment with $LiAlH_4$ (eq 2), and (4*S*)-isopropyloxazolidinone (**4**) was quantitatively recovered. The $[\alpha]_D$ value of the **3a** obtained was +23.0°



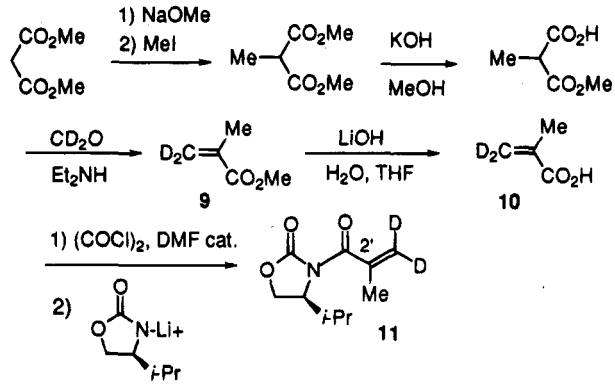
(2)

(*c* 0.92, $CHCl_3$). According to Scheme 2, the authentic, optically active **3b** was prepared from methyl (*S*)-(+)-3-hydroxy-2-methylpropanate (**5**). Protection of the OH group of **5** with *tert*-butyldimethylsilyl chloride, followed by reduction with diisobutylaluminium hydride (DIBALH) and subsequent Swern oxidation, afforded aldehyde **8**. Acetalization of **8** with 2,2-dimethoxypropane followed by desilylation gave hydroxy acetal **3b** with $[\alpha]^{25}_D$ −26.2° (*c* 1.02, $CHCl_3$) (~57% ee) (Experimental Section).

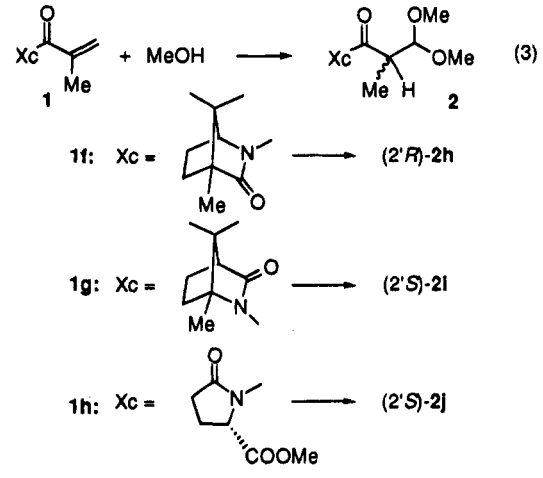
Comparison of the $[\alpha]_D$ values of **3a** and **3b** allowed us to assign the absolute configuration of the product acetal. Namely, the use of (4*S*)-oxazolidinones as chiral auxiliaries, derived from natural L-amino acids, results in the formation of (2′*S*)-acetals **2**, which lead to (*R*)-(+)-hydroxy acetal **3a**. Of course, when (4*R*)-oxazolidinones are employed, acetals of the opposite configuration are produced (*vide infra*). For the preparation of optically active hydroxy acetal (*R*)-(+)-**3a**, the use of **1d** (R = Ph) or **1e** (R = *t*-Bu) is optimal, since the product acetal **2f** (R = Ph) or **2g** (R = *t*-Bu) is readily purified to its single diastereomer upon one recrystallization.

Camphor lactam skeletons such as **1f** and **1g** (eq 3) have recently been demonstrated to be effective chiral

Scheme 3



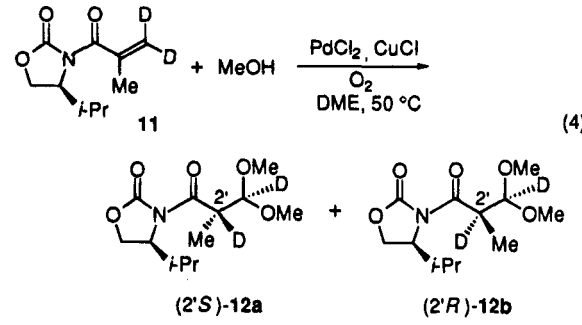
auxiliaries.[11,12] Their applicability to the present reaction was thus examined. The acetalization of methacryloyl-



camphor lactam **1f** with MeOH gave (2′*R*)-acetal **2h** in 68% de (78% yield), whereas (2′*S*)-acetal **2i** was obtained from **1g** in 50% de (40% isolated yield). $LiAlH_4$ reduction of **2h** or **2i** afforded (−)-**3b** or (+)-**3a**, respectively. Although the stereoselectivity was not high in either case, it is noteworthy that the opposite stereochemical outcome was produced by the two camphor lactam regioisomers. When (2*S*)-carbomethoxypyrrolidone was used as the chiral auxiliary, no higher stereoselectivity (40% de) was attained (**1h** → **2j**).

Mechanistic Study. The present acetalization creates the chiral center via incorporation of a hydrogen atom onto the prochiral sp^2 carbon of the methacryloyl moiety of **1**. In order to determine the origin of the H atom, the acetalization of **1a** (R = *i*-Pr) was performed with CH_3OD (10 equiv) (DME, 50 °C, 24 h). However, virtually no D-atom incorporation was observed in product **2a** (80% yield, 50% de) by NMR spectroscopy. This means that simple addition of MeOH to the methacryloyl moiety does not take place. An alternative possibility for creation of the chiral center is intramolecular H atom migration from the terminal olefinic proton to the prochiral C-2′ carbon. To investigate this possibility, dideuteriated alkene **11** was prepared from 1,1-dideuteriated methyl methacrylate **9**[13] (Scheme 3) obtained from Mannich-type condensation of CD_2O with 2-methylmalonic acid monomethyl ester. Hydrolysis of **9** followed by treatment with oxalyl chloride gave the corresponding acid chloride which was then reacted with (4*S*)-isopropyloxazolidinone lithium salt to give dideuteriated substrate **11**.

The acetalization of **11** with MeOH (DME, 50 °C, 76 h) gave a 3:1 mixture (50% de) of (2′*S*)-**12a** and (2′*R*)-**12b** in 82% yield (eq 4). In the ^1H NMR spectrum of this



mixture, the methyl protons at C-2′ appeared essentially as two sets of singlet peaks, indicating that the D atom is incorporated at this position. Thus, the stereoselective 1,2-migration of an H(D) atom onto the terminal olefinic carbon creates the chiral center. In order to evaluate the extent of D-atom incorporation, each of the diastereomers **12a** and **12b** was isolated and subjected to ^1H NMR analysis. The methyl signal of the major diastereomer (2′*S*)-**12a** consisted of a single peak at δ 1.24 and a small doublet (δ 1.16, J = 6.7 Hz). Similarly, the methyl signal of the minor diastereomer (2′*R*)-**12b** appeared as a singlet at δ 1.16 and a doublet at δ 1.17 (J = 6.7 Hz). A quartet due to the proton incorporated at C-2′ was observed at δ 4.39. Irradiation of the C-2′ proton changed the doublet signal at δ 1.17 to a singlet, indicating that the doublet at δ 1.17 can certainly be ascribed to the C-2′ methyl signal. The extent of D-atom incorporation was determined by comparing peak areas of the singlet and doublet signal and was found to be 92% for (2′*S*)-**12a** and 79% for (2′*R*)-**12b**. Factoring in the ratio of (2′*S*)-**12a** to (2′*R*)-**12b** formed, it was found that the extent of D-atom incorporation was 89%. Analysis of D-atom content by mass spectrometry also showed a 90% D atom incorporation in acetal **12**. Namely, *ca.* 10% of the D atoms were lost during the reaction, and the H atom of MeOH was incorporated into the product to the extent of ~10%. This result is different from that obtained when MeOD was used, where no D-atom incorporation took place.

The proposed reaction pathway leading to (2′*S*)-acetal is shown in Scheme 4 where a (4*R*)-oxazolidinone serves as the chiral auxiliary. Among the various conformations of substrate **1**, the *s-trans* conformer shown in Scheme 4 is more stable than the *s-cis* isomer, because of steric interference between the methyl group on the olefin and the substituent R on the oxazolidinone. An MM2 calculation using the Tektronix CAChe system[14] supports this view. $PdCl_2$ approaches the *s-trans* olefin from its *re* face where no bulky substituent R is present. Subsequent nucleophilic attack of MeOH on the olefin in a trans fashion produces σ-bonded Pd(II) intermediate **14** from which β-Pd−H elimination takes place. Readdition of Pd−H to the resulting vinyl ether **15** from the same face (*re*) creates the chiral center in **16**. Thus, stereose-

(11) Boeckman, R. K., Jr.; Nelson, S. G.; Gaul, M. D. *J. Am. Chem. Soc.* **1992**, *114*, 2258. We are grateful to Prof. R. K. Boeckman, Jr., for informing us of the procedures for the preparation of **1f** and **1g**.

(12) Boeckman, R. K., Jr.; Johnson, A. T.; Musselman, R. A. *Tetrahedron Lett.* **1994**, *35*, 8521.

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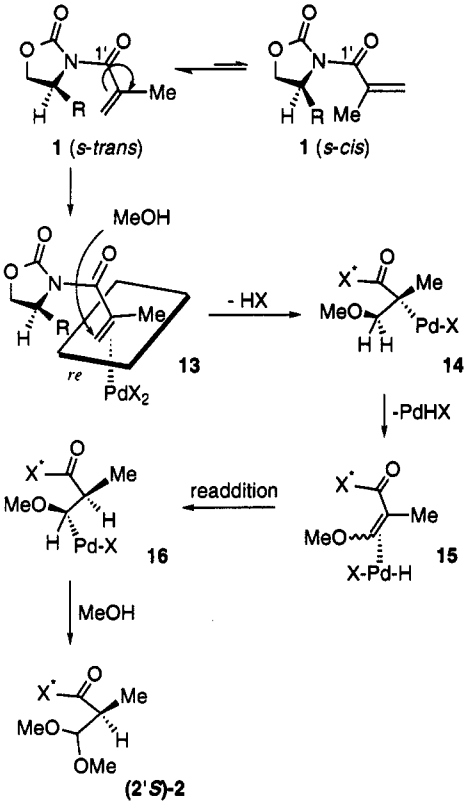
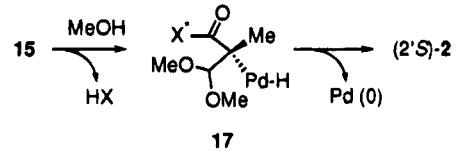
(14) We are indebted to SONY Tektronix for the MM 2 caluculation of this compound.

Scheme 4



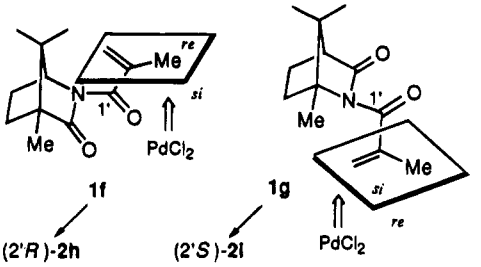
Scheme 5



lective 1,2-H(D) migration results. The C−Pd bond in **16** is then displaced by MeOH to give the product acetal (2′*S*)-**2**.[15] In the case of 1,1-dideuteriated alkene **11**, vinyl ether complex **15** bearing XPd−D is formed. Compared to XPd−H, readdition of XPd−D is retarded by the isotope effect, and thus vinyl ether is liberated from the palladium to some extent. Therefore, Michael addition of MeOH to the vinyl ether[3] gives rise to D-atom loss in the product.

Scheme 5 shows an alternative pathway leading to acetal (2′*S*)-**2**, in which nucleophilic attack of MeOH on vinyl ether complex **15** with loss of HX produces **17**, from which reductive elimination leads to acetal **2** along with Pd(0). Although this mechanism cannot be rigorously excluded from the present results, it seems unlikely because Pd(0) was not observed in the present acetalization as reported previously.[16] In addition, the pathway shown in Scheme 4 has the following support. The readdition process of Pd−H to coordinated alkenes such as **15** → **16**, which occurs fast, is very common in palladium chemistry,[17] and the Wacker oxidation of ethylene to acetaldehyde involves readdition of Pd−H to a vinyl alcohol intermediate.[7b] The displacement of a

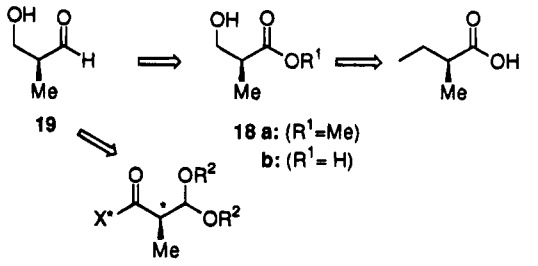
Scheme 6



σ-C−Pd bond by MeOH to form a C−OMe bond has been documented in the literature.[18] This process results in the formation of an HPdX species which reacts with O_2 to give PdOOH as the catalytically active species. A catalytic cycle involving this species is also reasonable with respect to our previous results.[3a,16]

The conformational preference of the methacryloyl moiety is an important factor controlling the stereoselectivity. As is common in oxazolidinone chemistry, the rotation about the C-1′−N bond must be fixed via chelation of the carbonyl groups to the metal salts present.[19] This is also applicable to the case of camphor lactam **1f**. The conformational preference about the C-1′−N bond as well as that of the methacryloyl moiety in **1f**[11] as shown in Scheme 6 allows palladium to approach the *si* face of the olefin, resulting in the formation of (2′*R*)-acetal **2h**. In the case of **1g**, a similar model accounts for the formation of (2′*S*)-acetal **2i**.

Synthetic Application. Enantiomerically pure aldehyde **19** bearing an α-methyl substituent, as shown below, serves as a useful synthetic building block for intriguing natural products.[20] The aldehyde is obtainable from hydroxy ester **18a**. The preparation of this ester is



at present dependent on the fermentation of isobutyric acid by *Psudomonas putida* to give (2*S*)-3-hydroxy-2-methylpropanoic acid (**18b**).[21] However, the yield is not high (48%). While aldehyde **19** is prepared from **18a**, as shown in Scheme 2 (*vide supra*), via reduction of **6** followed by Swern oxidation, the present, asymmetric acetalization provides an alternative route to the aldehyde synthon, starting from methacryloyl chloride (Scheme 1).[22] Since the oxazolidinone moiety in **2** can be transformed into an ester or carboxylic acid,[6f,h] the present

(15) (a) Lee, H.-B.; Henry, P. M. *Can. J. Chem.* **1976**, *54*, 1726. (b) Uemura, S.; Zushi, K.; Okano, M. *J. Chem. Soc., Chem. Commun.* **1972**, 234.

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(17) (a) Reference 7b, pp 84−133. (b) Portnoy, M.; Milstein, D. *Organometallics* **1994**, *13*, 600.

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(19) (a) Castellino, S. *J. Org. Chem.* **1990**, *55*, 5197. (b) Castellino, S.; Dwight, W. J. *J. Am. Chem. Soc.* **1993**, *115*, 2986.

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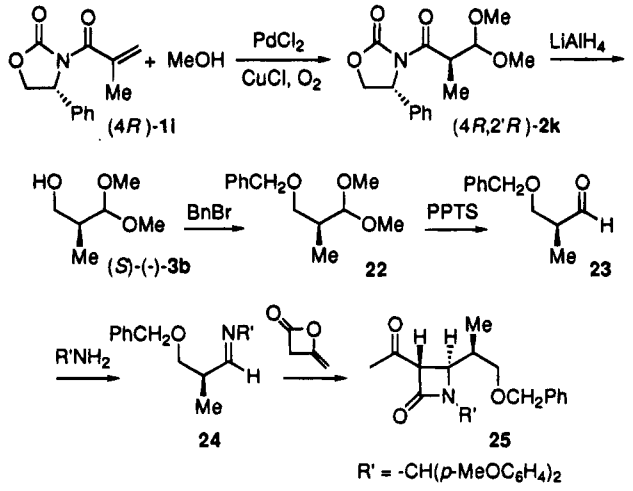
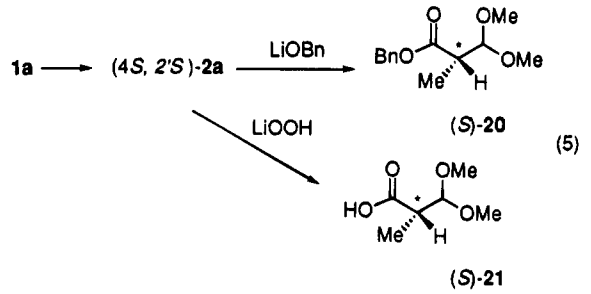
(21) Goodhue, C. T.; Schaeffer, J. R. *Biotechnol. Bioeng.* **1971**, *13*, 203.

Scheme 7

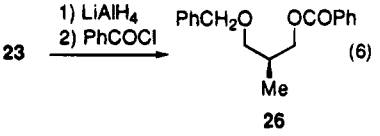


method also offers a route to β-functionalized α-methyl substituted acetals such as **20** and **21** in optically active forms (eq 5).



Using this methodology, we synthesized optically active azetidinone **25** in high enantiomeric excess as shown in Scheme 7. The azetidinone **25** is a precursor of the antibiotic 1β-methylcarbapenem and has the (1'*S*)-configuration on the chiral center of the side chain.[23] An acetalization using a (4*R*)-substituted oxazolidinone would give (4*R*,2*R*')-acetal **2** which could give rise to (2*S*)-aldehyde **23** leading to (1'*S*)-**25**. Methacryloyl (4*R*)-oxazolidinone **1i** (R = Ph), prepared from D-phenylglycine, was thus acetalized with MeOH (50 °C, CH_2Cl_2) on a gram scale to afford an 80% de of acetal **2k** as a colorless crystal in 88% yield. As mentioned earlier, the single diastereomer of (4*R* 2'*R*)-**2k** was readily obtained after one recrystallization from hexane–diisopropyl ether [60% yield from (4*R*)-**1i**]. Reduction of pure **2k** with $LiAlH_4$ gave hydroxy acetal (*S*)-(−)-**3b** (60% after purification). Protection of the OH group in (*S*)-(−)-**3b** with benzyl bromide afforded **22** (58%).

In the subsequent deacetalization, suppression of racemization was crucial for the synthesis of **23**. The use of Amberlyst-15 as a catalyst[24] in aqueous acetone at 25 °C gave aldehyde **23** quantitatively, but 35% racemization took place. When pyridinium tosylate (PPTS)[25] was used as a catalyst, a 98% ee of aldehyde **23** was obtained in 99% yield. The optical purity of aldehyde **23** was determined by HPLC analysis using a chiral column (CHIRAPAK OJ), after **23** was converted into benzoyl ester **26** by $LiAlH_4$ reduction followed by esterification (eq 6). The aldehyde **23** was then reacted with di-*p*-anisylmethylamine to give imine **24**. According to the procedure of Terashima el al.,[23] the reaction of imine **24** with diketene (toluene, −20 °C) gave azetidinone **25** and a small amount of its diastereomer (8:1) (41% yield from **23**).



In summary, the present acetalization of methacryloyl derivatives offers a route for synthesizing (*R*)- or (*S*)-3-hydroxy-2-methylpropanal dimethyl acetal, a useful building block in organic synthesis. In addition, a mechanistic study of the acetalization revealed that the chiral center of the product acetal is created by *trans*-oxypalladation and 1,2-stereoselective hydride migration, if the conformational preference of the substrate **1** is valid.

Experimental Section

Materials. L-Valine, L-alanine, L-*tert*-leucine, L-phenylglycine, and D-phenylglycine were commercially available. (4*R*)-Benzyl-2-oxazolidinone and methyl (*S*)-(+)-3-hydroxy-2-methylpropionate were also commercially available. $PdCl_2$ was obtained from nakalai tesque. Commercially available CuCl was purified by literature procedure.[26] Formaldehyde-d_2 (30% in D_2O, stabilized with CD_3OD) was obtained from Merck Chemical Co., Ltd. Tetrahydrofuran (THF) and benzene were distilled from benzophenone ketyl under argon atmosphere. Dimethoxyethane (DME), dichloromethane, dimethylformamide (DMF), diisopropylamine, triethylamine, and dimethyl sulfoxide (DMSO) were distilled over calcium hydride under argon atmosphere. Methanol and ethanol were distilled over magnesium alkoxide.

Optically pure 4(*S*)-isopropyl-2-oxazolidinone was prepared by the literature procedure[27] which involves esterification of L-valine and protection of the amino group by benzyl chloroformate followed by cyclization with sodium hydroxide. Other oxazolidinones were prepared by reduction of amino acids with diborane followed by condensation of diethylcarbonate.[6g]

Typical Procedure for the Preparation of *N*-Methacryloyloxazolidinones: Preparation of (4*S*)-*N*-Methacryloyl-4-phenyl-2-oxazolidinone (1d). Into a soultion of (*S*)-4-phenyloxazolidinone (20.0 g, 123 mmol) in dry THF (180 mL) was added slowly a solution of *n*-BuLi (1.1 equiv, 135 mmol) in hexane (1.60 M, 85.0 mL) at −78 °C under argon atmosphere, and the solution was stirred at −50 °C for 60 min. Methacryloyl chloride (13.8 mL, 141 mmol) was added slowly to the above solution, and the flask was warmed to room temperature. After the mixture was stirred for 1 h, hexane (200 mL), ethyl acetate (120 mL), water (120 mL), K_2CO_3 (3.0 g), and glycine (750 mg) were successively added, and the mixture was stirred for 30 min at room temperature. The aqueous layer was extracted with ethyl acetate (200 mL × 3). The organic layers were combined, washed with brine (100 mL × 2), and dried over $MgSO_4$. Removal of the solvent followed by recrystallization from hexane–ethyl acetate gave (4*S*)-(−)-3-(methacryloyl)-4-phenyl-2-oxazolidinone **1d** (R = Ph) in 94% yield. Spectral and analytical data of methacryloyloxazolidinones **1a-d** are as follows.

1a (R = *i*-Pr): 99%; mp 68–69 °C; IR (KBr) 3005, 1790, 1685, 1225 cm^{-1}; ^1H NMR δ 0.91 (d, *J* = 6.1 Hz, 3H), 0.94 (d, *J* = 6.8 Hz, 3H), 2.04 (dd, *J* = 1.5, 1.0 Hz, 3H), 2.39 (dqq, *J* = 4.2, 6.8, 7.1 Hz, 1H), 4.20 (dd, *J* = 9.0, 4.6 Hz, 1H), 4.33 (dd,

(22) The aldehyde synthon is also obtainable from the reaction of titanium enolate of (4*S*)-*N*-propionyl-4-benzyl-2-oxazolidinone with orthoformate; see ref 6j.

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J = 9.0, 8.5Hz, 1H), 4.50 (ddd, J = 8.5, 4.5, 4.2 Hz, 1H), 5.40–5.43 (m, 2H); ^{13}C NMR δ 14.9, 17.8, 19.2, 28.3, 58.2, 63.6, 129.5, 139.9, 153.4, 171.1; $[\alpha]^{24}_D$ +98.3° (*c* 1.11, $CHCl_3$). Anal. Calcd for $C_{10}H_{15}NO_3$: C, 60.90; H, 7.67; N, 7.10. Found: C, 61.10; H, 7.64; N, 7.07.

1b (R = Me): 65%; mp 48–49.5 °C; IR (KBr) 1780, 1690, 1385, 1340, 1225, 1130 cm^{-1}; ^{1}H NMR δ 1.33 (d, J = 5.9 Hz, 3H), 2.02 (dd, J = 1.7, 1.0 Hz, 3H), 3.98 (dd, J = 8.2, 5.0 Hz, 1H), 4.48 (t, J = 8.2 Hz, 1H), 4.55 (m, 1H), 5.42 (dq, J = 1.7, 0.7 Hz, 1H), 5.43 (dq, J = 0.7, 0.7 Hz, 1H); ^{13}C NMR δ 18.5, 18.9, 50.7, 69.1, 120.7, 139.8, 153.1, 171.1; $[\alpha]^{24}_D$ +96.4° (*c* 1.17, $CHCl_3$). Anal. Calcd for $C_8H_{11}NO_3$: C, 56.80; H, 6.55; N, 8.28. Found: C, 56.88; H, 6.58; N, 8.20.

1c (R = CH_2Ph): 73%; mp 69–70 °C; IR (KBr) 1790, 1685, 1395, 1355, 1220, 760, 700 cm^{-1}; ^{1}H NMR δ 2.04 (dd, J = 1.7, 1.0 Hz, 3H), 2.85 (dd, J = 13.4, 9.0 Hz, 1H), 3.34 (dd, J = 13.4, 3.4 Hz, 1H), 4.17 (dd, J = 9.0, 4.9 Hz, 1H), 4.25 (dq, J = 9.0, 7.6 Hz, 1H), 4.71 (dddd, J = 9.0, 7.6, 4.9, 3.4 Hz, 1H), 5.43 (m, 2H), 7.20–7.37 (m, 5H); ^{13}C NMR δ 19.0, 37.5, 55.2, 66.4, 120.6, 127.3, 128.9, 129.4, 135.0, 139.6, 152.8, 171.0; $[\alpha]^{24}_D$ +73.3° (*c* 0.58, $CHCl_3$). Anal. Calcd for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.16; N, 5.71. Found: C, 68.62; H, 6.22; N, 5.67.

1d (R = Ph): mp 162–165 °C; IR (KBr) 1790, 1690, 1390, 1330, 1235, 1210, 1065, 740, 700 cm^{-1}; ^{1}H NMR δ 2.02 (dd, J = 1.6, 1.1 Hz, 3H), 4.25 (dd, J = 8.9, 6.5 Hz, 1H), 4.71 (t, J = 8.9 Hz, 1H), 5.47 (dd, J = 8.9, 6.5 Hz, 1H), 5.49 (m, 2H), 7.26–7.39 (m, 5H); ^{13}C NMR δ 18.7, 58.1, 69.9, 121.9, 126.1, 128.9, 129.2, 138.0, 139.3, 153.2, 170.3; $[\alpha]^{24}_D$ +71.6° (*c* 0.82, $CHCl_3$). Anal. Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.28; H, 5.72; N, 5.98.

1e (R = *t*-Bu): 94%; mp 61–64 °C; IR (KBr) 3030, 1780, 1685, 1325, 1185, 1110, 910, 760 cm^{-1}; ^{1}H NMR δ 0.95 (s, 9H), 2.07 (dd, J = 1.5, 1.0 Hz, 3H), 4.29 (d, J = 5.4 Hz, 1H), 4.29 (d, J = 5.4, 1H), 4.54 (t, J = 5.4 Hz, 1H), 5.50–5.53 (m, 2H); ^{13}C NMR δ 19.1, 25.4, 35.8, 60.3, 64.9, 121.8, 139.6, 153.8, 171.4; $[\alpha]^{24}_D$ +65.1° (*c* 1.26, $CHCl_3$). Anal. Calcd for $C_{11}H_{17}NO_3$: C, 62.54; H, 8.11; N, 6.63. Found: C, 62.15; H, 8.03; N, 6.61.

(1*R*,4*S*)-3-Methacryloyl-1,7,7-trimethyl-3-azabicyclo-[2.2.1]heptan-3-one (1f). A solution of (1*R*,4*S*)-1,7,7-trimethyl-3-azabicyclo[2.2.1]heptan-2-one[11] (769 mg, 3.16 mmol) in 2 mL of THF was added slowly to a suspension of NaH (60% dispersion in oil) (1.2 equiv, 3.79 mmol, 152 mg) in 5 mL of THF at 0 °C. Once addition was complete, the mixture was warmed to room temperature and stirred for 10 h. Methacryloyl chloride (1.2 equiv, 396 mg) was then added to the above solution at 0 °C, and the mixture was stirred for 10 min and for 3 h at room temperature. Saturated NH_4Cl solution (0.5 mL) was added, and the volatiles were evaporated *in vacuo*. The residue was dissolved in a minimum amount of saturated $NaHCO_3$ solution and extracted with ether (50 mL × 3). The combined organic extracts were washed with brine and dried over $MgSO_4$. Filteration, concentration *in vacuo*, and SiO_2 column chromatography (16 g, 1.5 × 20 cm, hexane/ether = 3/1) gave **1f** as a colorless oil (198 mg, 28%): IR (neat) 2970, 1750, 1670, 1340 cm^{-1}; ^{1}H NMR δ 0.95 (s, 3H), 0.99 (s, 3H), 1.06 (s, 3H), 1.54–1.88 (m, 4H), 1.99 (dd, J = 1.7, 1.0 Hz, 3H), 4.20 (d, J = 2.4 Hz, 1H), 5.31 (dq, J = 1.0, 1.0 Hz, 1H), 5.36 (dq, J = 1.7, 1.0 Hz, 1H); ^{13}C NMR δ 9.4, 17.6, 18.5, 18.9, 26.6, 30.6, 47.4, 56.2, 64.5, 119.4, 141.1, 170.2, 177.4.

(1*R*,4*S*)-2-Methacryloyl-1,7,7-trimethyl-2-azabicyclo-[2.2.1]heptan-3-one (1g). Compound **1g** was prepared from (1*R*,4*S*)-1,7,7-trimethyl-2-azabicyclo [2.2.1]heptan-3-one[11] by the same procedure as above. **1g**: 18%; mp 85–87 °C; ^{1}H NMR δ 0.94 (s, 3H), 1.09 (s, 3H), 1.43 (s, 3H), 1.63 (m, 1H), 1.83 (m, 1H), 1.99 (dd, J = 1.2, 1.2 Hz, 3H), 2.01–2.21 (m, 2H), 2.38 (d, J = 4.4 Hz, 1H), 5.46–5.48 (m, 1H), 5.50–5.51 (m, 1H); ^{13}C NMR δ 12.6, 17.6, 18.6, 18.7, 24.2, 31.9, 47.8, 55.5, 72.7, 122.4, 142.2, 172.4, 177.3; $[\alpha]^{28}_D$ +10.70° (*c* 1.24, $CHCl_3$); HRMS calcd for $C_{13}H_{23}NO_5$ 221.1416, found 221.1395 (M^+).

Methyl (5*S*)-*N*-(Methacryloyl)-2-pyrrolidone-5-carboxylate (1h). Compound **1h** was similarly prepared from methyl (*S*)-2-pyrrolidone-5-carboxylate obtained by esterification of (*S*)-(−)-2-pyrrolidone-5-carboxylic acid (Aldrich). **1h:** 75%; colorless oil; IR (neat) 2959, 1748 1682, 1638, 1439, 1373, 1325, 1281 , 1215, 1150, 1080, 1042, 993; ^{1}H NMR δ 2.02 (dd, J = 1.0, 1.5 Hz, 3H), 2.11 (dddd, J = 13.9, 4.5, 3.6 Hz, 1H), 2.40 (ddd, J = 18.0, 13.0, 9.0 Hz, 1H), 2.58 (dd, J = 4.5, 9.0 Hz, 1H), 2.69 (dd, J = 18.0, 9.0 Hz, 1H), 3.79 (s, 3 H), 4.77 (dd, J = 3.7, 9.0 Hz, 1H), 5.43–5.40 (m, 2H); ^{13}C NMR δ 18.7, 21.8, 31.5, 52.6, 57.9, 120.5, 140.3, 171.3, 171.4, 173.2. Anal. Calcd for $C_{10}H_{13}NO_4$: C, 56.87; H, 6.20; N; 6.63. Found: C, 56.57; H, 6.05; N, 6.62.

General Procedure for Pd(II)-Catalyzed Acetalization of 1 with Alcohols. In a 25 mL round-bottomed flask equipped with rubber balloon filled with oxygen and a magnetic stirring bar were placed $PdCl_2$ (9 mg, 0.05 mmol), CuCl (50 mg, 0.5 mmol), and **1** (0.5 mmol). To the flask was added dry DME (1.0 mL) and an alcohol (25 equiv) via syringe. The resulting mixture was stirred at room temperature (25 °C), and the progress of reaction was monitored by GLC. When the reaction was completed (24–96 h), the resulting mixture was filtered through a pad of Florisil (2.0 g, 1.2 × 2.5 cm, ether, 150 mL). Removal of the solvent followed by SiO_2 column chromatography (hexane/AcOEt = 8/2) gave pure acetal **2**. Results of the acetalization of **1a** (R = *i*-Pr) with various alcohols are given in Table 1. Chemical yields and diastereomeric excesses of **2a–g** are shown in Table 2, and those of **2h–j** are shown below. Spectral and analytical data of major diastereomers of **2a–j** are listed below.

2a: bp 160–180 °C (1 mmHg); IR (neat) 2900, 1789, 1700, 1385, 1300, 1240, 1205, 1115, 710 cm^{-1}; ^{1}H NMR δ 0.88 (d, J = 7.0 Hz, 3H), 0.92 (d, J = 7.0 Hz, 3H), 1.22 (d, J = 7.0 Hz, 3H), 2.35 (m, 1H), 3.33 (s, 3H), 3.35 (s, 3H), 4.19 (dd, J = 7.0 Hz, 1H), 4.27 (dd, J = 7.0 Hz, 1H), 4.41–4.47 (m, 1H), 4.60 (d, J = 8.0 Hz, 1H); ^{13}C NMR δ 13.5, 14.7, 17.8, 28.5, 40.2, 51.6, 55.4, 58.5, 63.3, 105.2, 153.6, 174.0. Anal. Calcd for $C_{12}H_{21}NO_5$: C, 55.58; H, 8.16; N, 5.40. Found: C, 55.81; H, 8.01; N, 5.51.

2b: bp 200 °C (1 mmHg); IR (neat) 2940, 1780, 1700, 1460, 1305, 1300, 1200, 1120, 710 cm^{-1}; ^{1}H NMR δ 0.88 (d, J = 7.1 Hz, 3H), 0.92 (d, J = 7.1 Hz, 3H), 1.14 (t, J = 7.1 Hz, 3H), 1.20 (t, J = 7.1 Hz, 3H), 1.22 (d, J = 7.1 Hz, 3H), 2.34 (dqq, J = 4.2, 7.1, 7.1 Hz, 1H), 3.49 (dq, J = 9.8, 7.1 Hz, 1H), 3.56 (q, J = 7.1 Hz, 1H), 3.60 (q, J = 7.1 Hz, 1H), 3.69 (dq, J = 9.8, 7.1 Hz, 1H), 4.06–4.32 (m, 3H), 4.42 (ddd, J = 7.5, 4.2, 3.4 Hz, 1H), 4.68 (d, J = 8.1 Hz, 1H); ^{13}C NMR δ 13.6, 14.7, 14.9, 15.1, 17.9, 28.8, 40.9, 58.7, 60.1, 63.1, 63.4, 103.7, 153.8, 174.3. Anal. Calcd for $C_{14}H_{25}NO_5$: C, 58.52; H, 8.77; N, 4.87. Found: C, 58.55; H, 8.73; N, 4.90.

2c: colorless oil; IR (neat) 2880, 1786, 1703, 1462, 1385, 1300, 1235, 12904, 1142, 1119, 1167, 991, 955, 775, 710 cm^{-1}; ^{1}H NMR δ 0.87 (t, J = 7.1 Hz, 3H), 0.88 (t, J = 7.1 Hz, 3H), 0.92 (t, J = 7.1 Hz, 3H), 0.94 (t, J = 7.1 Hz, 3H), 1.22 (d, J = 6.8 Hz, 3H), 1.52 (tq, J = 7.1, 7.1 Hz, 2H), 1.59 (tq, J = 7.1, 7.1 Hz, 2H), 2.35 (dqq, J = 4.2, 7.1, 7.1 Hz, 1H), 3.36 (dt, J = 9.3, 6.6 Hz, 1H), 3.48 (dt, J = 6.6, 6.6 Hz, 1H), 3.49 (dt, J = 6.6, 6.6 Hz, 1H), 3.61 (dt, J = 9.3, 6.6 Hz, 1H), 4.20 (d, J = 7.1 Hz, 1H), 4.21 (d, J = 7.1 Hz, 1H), 4.29 (dq, J = 8.1, 6.8 Hz, 1H), 4.40 (ddd, J = 7.1, 4.2, 4.2 Hz, 1H), 4.67 (d, J = 8.1 Hz, 1H); ^{13}C NMR δ 10.5, 10.7, 13.5, 14.9, 17.9, 22.9, 23.1, 28.8, 40.7, 58.7, 63.4, 66.0, 69.7, 103.9, 153.8, 174.4; MS (EI) 256 (M^+ − OPr^n); MS (CI) 316 (M + 1), 256 (M^+ − OPr^n).

2d: bp 180–190 °C (1 mmHg); IR (neat) 2990, 1780, 1700, 1460, 1390, 1345, 990, 950, 765, 695 cm^{-1}; ^{1}H NMR δ 1.19 (d, J = 7.1 Hz, 3H), 1.40 (d, J = 6.4 Hz, 3H), 3.33 (s, 3H), 3.35 (s, 3H), 3.97 (dd, J = 8.6, 2.7 Hz, 1H), 4.18 (dd, J = 8.1, 7.1 Hz, 1H), 4.43 (dd, J = 8.6, 5.4 Hz, 1H), 4.50–4.64 (m, 1H), 4.59 (d, J = 8.1 Hz, 1H); ^{13}C NMR δ 13.2, 19.1, 40.3, 50.6, 51.8, 55.4, 68.9, 105.3, 174.0, 174.3. Anal. Calcd for $C_{12}H_{21}NO_5$: C, 51.94; H, 7.41; N, 6.06. Found: C, 51.87; H, 7.21; N, 6.08.

2e: IR (neat) 1780, 1700, 1455, 1385, 760, 705 cm^{-1}; ^{1}H NMR δ 1.24 (d, J = 6.8 Hz, 3H), 2.78 (dd, J = 13.4, 9.5 Hz, 1H), 3.25 (dd, J = 13.4, 3.4 Hz, 1H), 3.33 (s, 3H), 3.36 (s, 3H), 4.10–4.26 (m, 3H), 4.62 (d, J = 7.0 Hz, 1H), 4.68 (ddt, J = 9.5, 3.4, 7.1 Hz, 1H), 7.19–7.36 (m, 5H); ^{13}C NMR δ 13.2, 37.9, 40.3, 51.7, 55.3, 55.4, 66.0, 105.3, 127.3, 128.9, 129.4, 135.2, 153.0, 174.1; HRMS calcd for $C_{16}H_{21}NO_5$ 307.1420, found 307.1411.

2f: mp 118.0–120.0 °C; IR (KBr) 2980, 1790, 1710, 1475, 1380, 1240, 1120, 1060, 770 cm^{-1}; ^{1}H NMR δ 1.12 (d, J = 7.1 Hz, 3H), 3.33 (s, 3H), 3.37 (s, 3H), 4.25 (dd, J = 8.8, 3.2 Hz,

Table 3. Experimental Details for $LiAlH_4$ Reduction of 2a and 2h–j[a]

acetal (mg, mmol)	% de[c]	$LiAlH_4$ (mg, mmol)	product	yield of 3[b] (mg, %)	$[\alpha]_D$ (c, $CHCl_3$)
2a (232, 0.89)	50	114, 3.00	(+)-**3a**	69, 58	+23.0° (0.92)[d]
2h (80, 0.28)	68	33, 0.87	(−)-**3b**	37, 98[e]	*f*
2i (300, 1.06)	nd	121, 3.18	(+)-**3a**	84, 59	+3.29° (0.30)
2j (530, 1.94)	nd	243, 6.42	(−)-**3b**	71, 27	−18.8° (0.79)

[a] In the case of **2a**, 4 mL of THF was used as the solvent. [b] Isolated yield as the pure compound unless otherwise noted. [c] The % de of acetal used in this experiment. [d] The ^1H NMR spectrum of **3a** upon addition of $Eu(tfc)_3$ (**3a**/Eu* = 15 mg/6 mg) showed 50% de. [e] Estimated from a mixture of **3b** and chiral auxiliary by ^1H NMR. [f] The configuration of (−)-**3b** was determined by ^1H NMR spectrum upon addition of $Eu(tfc)_3$ (**3b**/Eu* = 20 mg/10 mg).

1H), 4.25 (dq, J = 7.1, 8.1 Hz, 1H), 4.55 (d, J = 8.1 Hz, 1H), 4.67 (dd, J = 8.8, 8.6 Hz, 1H), 5.43 (dd, J = 8.6, 3.2 Hz, 1H), 7.25–7.41 (m, 5H); ^{13}C NMR δ 13.2, 40.4, 51.7, 55.5, 57.7, 69.8, 105.2, 125.6, 128.6, 129.2, 139.2, 153.3, 173.5; $[\alpha]^{25}_D$ +112.0° (*c* 1.07, $CHCl_3$). Anal. Calcd for $C_{15}H_{19}NO_5$: C, 61.42; H, 6.53; N, 4.78. Found: C, 61.32; H, 6.40; N, 4.81.

2g: IR (KBr) 2970, 1765, 1710, 1380, 1320, 1230, 1185, 1115, 1045, 970, 705 cm^{-1}; ^1H NMR δ 0.93 (s, 9H), 1.25 (d, J = 7.1 Hz, 3H), 3.32 (s, 3H), 3.34 (s, 3H), 4.17–4.33 (m, 3H), 4.43 (dd, J = 7.2, 1.8 Hz, 1H), 4.57 (d, J = 8.3 Hz, 1H); ^{13}C NMR δ 14.0, 25.7, 35.7, 40.0, 5.13, 55.6, 61.1, 65.2, 105.4, 154.4, 174.2; MS (EI) 273 (M^+), 242 (M^+ − OMe), 131, 99, 75. Anal. Calcd for $C_{13}H_{23}NO_5$: C, 57.13; H, 8.48; N, 5.12. Found: C, 56.93; H, 8.30; N, 5.08.

2h: 78% (96 h), 68% de; ^1H NMR δ 0.92 (s, 6H), 1.05 (s, 3H), 1.16 (d, J = 6.8 Hz, 3H), 1.50–2.05 (m, 4H), 3.32 (s, 6H), 4.23 (dq, J = 6.8, 8.1 Hz, 1H), 4.31 (d, J = 2.7 Hz, 1H), 4.56 (d, J = 8.1 Hz, 1H); ^{13}C NMR δ 9.5, 13.0, 17.7, 18.4, 26.7, 30.1, 41.4, 46.9, 51.5, 55.2, 56.4, 63.6, 105.8, 173.7, 178.5.

2i; 52% (96 h), 66% de; ^1H NMR δ 0.91 (s, 3H), 1.01 (s, 3H), 1.15 (d, J = 6.8 Hz, 3H), 1.50 (s, 3H), 1.65 (m, 1H), 1.84 (m, 1H), 2.00 (m, 2H), 2.34, (d, J = 6.8 Hz, 1H), 3.32 (s, 3H), 3.33 (s, 3H), 4.23 (dq, J = 6.8, 7.8 Hz, 1H), 4.54 (d, J = 7.8 Hz, 1H); ^{13}C NMR δ 13.7, 13.9, 17.6, 18.6, 23.2, 32.0, 42.5, 47.2, 51.7, 55.2, 55.4, 73.3, 105.8, 175.9, 178.3.

2j: 67% yield (48 h); 52% de; ^1H NMR δ 1.19 (d, J = 7.0 Hz, 3H), 2.80–2.00 (m, 4H), 3.34 (s, 3H), 3.35 (s, 3H), 3.76 (s, 3H), 4.19 (dq, J = 7.0, 8.0 Hz, 1H) 4.61 (d, J = 8.0 Hz, 1H), 4.78 (dd, J = 2.5, 9.5 Hz, 1H); ^{13}C NMR δ 12.9, 21.1, 32.1, 41.7, 51.9, 52.6, 55.0, 58.0, 105.3, 171.6, 174.0, 174.9; MS (EI) 272 (M^+ − 1), 242 (M^+ − OMe).

$LiAlH_4$ Reduction of Acetals 2a and 2h–j: General Procedure. To a solution of acetal **2** in dry THF was slowly added $LiAlH_4$ at 0 °C. The solution was stirred at room temperature for 20 h, and then water was slowly added. After the solution was dried over $MgSO_4$, the reaction mixture was filtered off and washed with ether. Removal of the solvent gave a mixture of **3a** (or **b**) and chiral auxiliary. Kugelrohr distillation (80–100 °C/10 mmHg) followed by preparative GLC gave pure **3a** (or **b**): ^1H NMR δ 0.90 (d, J = 6.8 Hz, 3H), 2.04 (dddq, J = 6.6, 6.8, 4.9, 6.8 Hz, 1 H), 2.68 (br, 1 H), 3.37 (s, 3H), 3.43 (s, 3H), 3.55 (d, J = 6.8 Hz, 1H), 3.56 (d, J = 6.8 Hz, 1H), 4.22 (d, J = 6.6 Hz, 1H); ^{13}C NMR δ 12.2, 37.7, 53.0, 55.3, 65.2, 109.1. SiO_2 chromatography of the distillation residure (CH_2Cl_2/AcOEt = 1/1) gave the chiral auxiliary. The experimental details for **2a** and **2h–j** are summarized in Table 3.

Preparation of Authentic (*S*)-3-(*tert*-Butyldimethylsiloxy)-2-methylpropanal Dimethyl Acetal (3b). To a stirred solution of methyl (*S*)-(+)-3-hydroxy-2-methylpropionate (4.73 g, 40 mmol, commercially available) in dry DMF (25 mL) were added *tert*-butyldimethylsilyl chloride (7.24 g, 48 mmol) and imidazole (4.09 mg, 60 mmol) at 0 °C under argon atmosphere. After the solution was stirred for 5 h at room temperature, the mixture was successively diluted with hexane (100 mL), water (10 mL × 5), and brine (10 mL). The organic layer was dried over $MgSO_4$ and evaporated *in vacuo*. Distillation (86–89 °C/7 mmHg) gave compound **6** (7.52 g, 86%): IR (neat) 2955, 1745, 1260, 835, 775 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 0.01 (s, 6H), 0.88 (s, 9H), 1.14 (d, J = 7.1 Hz, 3H), 2.65 (ddq, J = 6.8, 6.1, 7.1 Hz, 1H), 3.65 (dd, J = 9.8, 6.1 Hz, 1H), 3.68 (s, 3H), 3.78 (dd, J = 9.8, 6.8 Hz, 1H); ^{13}C NMR δ −5.5, 13.4, 18.2, 25.7, 42.5, 51.4, 65.3, 175.4. To a solution of **6** (6.97 g, 30 mmol) in dry toluene (25 mL) was added a solution of DIBALH (1.50 M solution in toluene, 42.0 mL) under argon atmosphere while the temperature was kept under −60 °C. After the solution was stirred for 30 min at −60 °C and for 30 min at −30 °C, the mixture was poured into cold water (50 mL). After filtration, the organic layer was separated, washed with brine, and dried over $MgSO_4$. Concentration followed by distillation (95 °C/8 mmHg) gave (*S*)-3-(*tert*-butyldimethylsiloxy)-2-methylpropanol (**7**) (3.09 g, 50%): IR (neat) 3320, 2955, 1255, 1090, 835, 755 cm^{-1}; ^1H NMR δ 0.10 (s, 6H), 0.86 (d, J = 6.8, 7.8 Hz, 3H), 0.92 (s, 9H), 1.86–2.03 (m, 1H), 2.85 (br, 1H), 3.56 (dd, J = 9.8, 7.8 Hz, 1H), 3.60 (br, 2H), 3.74 (dd, J = 9.8, 4.6 Hz, 1H); ^{13}C NMR δ −5.5, −5.6, 13.1, 18.2, 25.7, 37.1, 68.2 68.7. To a stirred solution of oxalyl chloride (1.4 mL, 16.2 mmol) in dichloromethane (35 mL) at −60 °C was slowly added DMSO (32 mmol, 2.3 mL) dropwise at constant temperature.[28] After the mixture was stirred for 20 min, a solution of compound **7** (2.8 g, 14.7 mmol) in dichloromethane (7.0 mL) was added dropwise to the above mixture. After the mixture was stirred for 15 min, triethylamine (10 mL) was added dropwise. The mixture was further stirred for 30 min at the same temperature and allowed to warm to room temperature. The reaction was then quenched with water, and the aqueous layer was extracted twice with ethyl acetate. The combined organic layers were washed with water and brine, dried over $MgSO_4$, and evaporated. Distillation (97–101 °C/28 mmHg) gave compound **8** (1.72 g, 58%): IR (neat) 2960, 1475, 1380, 1360, 1255, 835, 775 cm^{-1}; ^1H NMR δ 0.05 (s, 6H), 0.87 (s, 9H), 1.08 (d, J = 7.1 Hz, 3H), 2.52 (m, 1H), 3.79 (dd, J = 10.0, 6.1 Hz, 1H), 3.85 (dd, J = 10.0, 5.1 Hz, 1H), 9.72 (d, J = 1.5 Hz, 1H); ^{13}C NMR δ −5.6, −5.5, 10.3, 18.2, 25.8, 48.8, 63.4, 204.5; $[a]^{27}_D$ +25.5° (*c* 2.23, $CHCl_3$). To a solution of 2,2-dimethoxypropane (0.92 mL, 7.5 mmol) in dry acetone (5.0 mL) were added BF_3·OEt_2 (10 μL) and compound **8** (500 mg, 2.5 mmol). After the solution was stirred at room temperature for 3 h, triethylamine (50 μL) was added to the mixture. Volatiles were evaporated, and dichloromathane (100 mL) was added to the residue. The solution was washed with saturated $NaHCO_3$ (10 mL) and brine (10 mL × 2) and dried over $MgSO_4$. Evaporation followed by a short column chromatography (SiO_2, 3.0 g, hexane/AcOEt/triethylamine = 19/1/0.1) gave (*S*)-1-(*tert*-butyldimethylsiloxy)-2-methylpropanal dimethyl acetal (414 mg, 67%): IR (neat) 2960, 1575, 1380, 1360, 1255, 835, 775 cm^{-1}; ^1H NMR δ 0.04 (s, 6H), 0.90 (s, 9H), 0.93 (d, J = 6.8 Hz, 3H), 1.91 (m, 1H), 3.36 (s, 3H), 3.37 (s, 3H), 3.53 (dd, J = 9.6, 5.7 Hz, 1H), 3.59 (dd, J = 9.6, 5.0 Hz, 1H), 4.23 (d, J = 6.4 Hz, 1H); ^{13}C NMR δ −5.5, 11.6, 18.3, 25.9, 38.7, 53.9, 54.7, 64.4, 106.5; $[\alpha]^{28}_D$ +5.55° (*c* 0.79, $CHCl_3$). Into a solution of this acetal (360 mg, 1.45 mmol) in dry THF (1.0 mL) were added Bu_4NF (1.0 M in THF, 3.0 mL, 3.0 mmol) at 0 °C. The solution was stirred at room temperature for 1 h. After evaporation of solvent, dichloromathane (100 mL) was added to the residue. The solution was washed with brine (20 mL × 3) and dried over anhydrous $MgSO_4$. Evaporation followed by a short column chromatography (SiO_2, 8.0 g, hexane/AcOEt = 6/4) gave acetal (*S*)-**3b** (240 mg, quantitative yield) which was purified by preparative GLC: ^1H NMR δ 0.91 (d, J = 7.0 Hz, 3H), 2.04 (dddq, J = 6.8, 6.6, 4.9, 6.8 Hz, 1H), 2.68 (br, 1H), 3.37 (s, 3H), 3.43 (s, 3H), 3.56 (d, J= 6.8 Hz, 1H), 3.56 (d, J = 6.0 Hz, 2H), 4.22 (d, J = 4.9 Hz, 1H); ^{13}C NMR δ 12.1, 37.7, 53.0, 55.3, 65.0, 109.0; $[\alpha]^{30}_D$ −26.2° (c 1.02, $CHCl_3$). The optical purity of this compound was decreased down to ~57%, because the aldehyde **8** is sensitive toward racemization.

Pd(II)-Catalyzed Acetalization of 1a with Methanol-d_1 (MeOD). According to the general procedure, the acetalization was performed by using 0.2 mL of methanol-d_1 (0.2 mL, nakalai tesque). When the reaction was completed after 24 h, the reaction mixture was filtered through a pad of Florisil (2.0 g, 1.2 × 2.5 cm, ether, 150 mL). Removal of the solvent

(28) Tidwell, T. T. *Synthesis* **1990**, 857.

gave crude acetal **2a** (108 mg, 83%), the D-atom content of which was analyzed by 270 MHz ^{1}H NMR.

Preparation of 1,2-Dideuteruated Methyl Methacrylate (10). The compound **10** was prepared from dimethyl 2-methylmalonate as shown in Scheme 3.[13] Into a solution of sodium methoxide (200 mmol) in methanol was added methyl malonate (26.4 g, 200 mmol) at 0 °C. After the solution was heated to 50 °C, methyl iodide (18.1 mL, 290 mmol) was added dropwise over 30 min. The reaction mixture was heated at 55 °C for 2.5 h and then neutralized with glacial acetic acid. After evaporation of methanol *in vacuo*, the resulting sodium iodide was dissolved in water (70 mL) containing concd HCl (1.0 mL). The organic layer was separated, and the aqueous layer was extracted with ether (100 mL × 2). The organic layers were combined, dried by shaking quickly with $CaCl_2$, and filtered immediately. The organic layer was washed with water (30 mL) containing NaOH (10 g) and then 2 N HCl (30 mL) and dried over $MgSO_4$. The solvent was evaporated *in vacuo* to give dimethyl 2-methylmalonate (22.0 g, 75%): ^{1}H NMR δ 1.43 (d, J = 7.3 Hz, 3H), 3.46 (q, J = 7.3 Hz, 1H), 3.74 (s, 6H). A solution of dimethyl 2-methylmalonate (19.4 g, 134 mmol) in methanol (135 mL) containing KOH (8.9 g, 134 mmol) was stirred at room temperature for 24 h. Methanol was evaporated *in vacuo*, and the residue was diluted with H_2O (100 mL) and extracted with CH_2Cl_2 (50 mL × 1). The aqueous layer was acidified to pH ~2 with concd HCl and extracted with CH_2Cl_2 (100 mL × 3) and ether (100 mL × 2). The extracts were combined, dried over $MgSO_4$, and evaporated *in vacuo* to give crude oil. Distillation (125–127 °C/12 mmHg) gave 2-(methoxycarbonyl)propanoic acid (15.4 g, 88%): IR (neat) 1720, 1035, 879 cm^{-1}; ^{1}H NMR δ 1.46 (d, J = 7.3 Hz, 3H), 3.51 (q, J = 7.3 Hz, 1H), 3.77 (s, 3H) 9.70–10.1 (br, 1H); ^{13}C NMR δ 13.5, 45.8, 52.6, 170.3, 175.6. 2-(Methoxycarbonyl)-propanoic acid (7.47 g, 56.6 mmol) and diethylamine (3.92 g, 53.6 mmol) were added to 30% CD_3O in D_2O (Merck, 5.0 mL, 50.6 mmol) at 0 °C, and the mixture was stirred at room temperature for 40 h. The organic layer was separated, and the aqueous layer was saturated with K_2CO_3 and extracted with ether (50 mL × 2). The organic layers were combined, washed with 2 N HCl (30 mL) and brine (30 mL), and dried over $MgSO_4$. Evaporation of ether gave **9** (3.27 g, 63%): ^{1}H NMR δ 1.94 (s, 3H), 3.75 (s, 3H); ^{13}C NMR δ 18.0, 51.6, 136.0. A solution of **9** (3.27 g, 32 mmol) in THF (180 mL) and water (90 mL) containing LiOH·H_2O (13.4 g, 320 mmol) was stirred at room temperature for 24 h. THF was evaporated *in vacuo*, and the residue was extracted with ether (50 mL × 1). The aqueous layer was acidified to pH ~2 with concd HCl and extracted with ether (100 mL × 4). The extracts were combined, dried over $MgSO_4$, and evaporated *in vacuo* to give a crude oil. Kugelrohr distillation (80–90 °C/10 mmHg) gave **10** (1.49 g, 53%): ^{1}H NMR δ 1.95 (s, 3H), 8.0–10.3 (br, 1H); ^{13}C NMR δ 17.7, 127.5, 135.6, 172.9. The D-atom content of **10** was ~100% by ^{1}H NMR.

Preparation of Oxazolidinone 11. Into a solution of **10** (160 mg, 1.57 mmol) and a catalytic amount of DMF (10 μL) in dry methylene chloride (1.0 mL) was slowly added oxalyl chloride (273 μL, 3.13 mmol) at 0 °C, and the mixture was stirred at room temperature for 2 h. Solvent and excess oxalyl chloride were evaporated *in vacuo* to give 1,1-dideuteriated methacryloyl chloride. In a 25 mL round-bottomed flask equipped a magnetic stirring bar were placed (*S*)-4-isopropyl-oxazolidinone (710 mg, 5.50 mmol) and dry THF (5 mL) under argon, and the solution was stirred at −78 °C. To the flask was slowly added a solution of *n*-BuLi in hexane (1.53 M, 3.95 mL, 6.04 mmol), and the solution was stirred at −50 °C for 40 min. To this solution was slowly added a THF (10 mL) solution of 1,1-dideuteriated methacryloyl chloride prepared above, and the mixture was warmed to room temperature. Into the resulting mixture was successively added hexane (6 mL), ethyl acetate (4 mL), and water (4 mL), and the mixture was stirred for 30 min at room temperature. The aqueous layer was extracted with ethyl acetate (30 mL × 3). The organic layers were combined, washed with brine (30 mL × 2), and dried over $MgSO_4$. Removal of the solvent followed by SiO_2 column chromatography (20 g, hexane/AcOEt = 85/15) gave 3′,3′-dideuteriated (4*S*)-*N*-methacryloyl-4-isopropyl-2-oxazolidinone (**11**) (166 mg, 54%): IR (KBr) 3000, 1790, 1685, 1370, 1300, 1215, 1120, 1060, 1015, 750 cm^{-1}; ^{1}H NMR δ 0.84 (d, J = 6.8 Hz, 3H), 0.86 (d, J = 6.8 Hz, 3H), 1.96 (s, 3H), 2.42 (dqq, J = 4.2, 6.8, 6.8 Hz, 1H), 4.13 (dd, J = 4.9, 9.0 Hz, 1H), 4.25 (dd, J = 8.6, 9.0 Hz, 1H), 4.13 (ddd, J = 4.2, 4.9, 8.6 Hz, 1H); ^{13}C NMR δ 14.8, 17.7, 19.0, 28.2, 58.2, 63.5, 139.6, 119.5 (m), 153.3, 171.0; HRMS calcd for $C_{10}H_{14}D_2NO_3$ 199.1175, found 199.1164.

Pd(II)-Catalyzed Acetalization of Oxazolidinone 11. In a 25 mL round-bottomed flask equipped with rubber balloon filled with oxygen and a magnetic stirring bar were placed $PdCl_2$ (5.3 mg, 0.03 mmol), CuCl (30 mg, 0.3 mmol), and **11** (60 mg, 0.3 mmol). To the flask were added dry DME (0.6 mL) and methanol (0.12 mL), and the mixture was stirred at 50 °C. The progress of reaction was monitored by GLC analysis. When the reaction was completed after 36 h, the resulting mixture was filtered through a pad of Florisil (2.0 g, 1.2 × 2.5 cm, ether, 150 mL). Removal of the solvent gave a crude oil from which a mixture of **12a** and **12b** (64 mg, 82%, **12a/12b** = 3.0/1.0; 50% de by ^{1}H NMR) was isolated by preparative TLC (hexane/AcOEt = 7/3, R_f 0.5): HRMS calcd for $C_{12}H_{19}D_2NO_5$ 261.1545, found 261.1561. Each of **12a** and **12b** was isolated by flash column chromatography (hexane/AcOEt). The D-atom content of **12a** or **12b** was, respectively, estimated by 270 MHz ^{1}H NMR and EI mass spectrum. No D-atom loss was observed during the workup process.

12a (major diastereomer): ^{1}H NMR δ 0.88 (d, J = 6.8 Hz, 3H), 0.92 (d, J = 7.1 Hz, 3H), 1.21 (s, 2.76H, $CDCH_3$), 1.22 (d, 0.24H, $-CHCH_3$), 2.34 (dqq, J = 4.0, 7.1, 6.8 Hz, 1H), 3.32 (s, 3H), 3.35 (s, 3H), 4.20 (dd, J = 9.0, 3.1 Hz, 1H), 4.27 (dd, J = 9.0, 7.9 Hz, 1H), 4.45 (ddd, J = 7.9, 7.1, 3.1 Hz, 1H); ^{13}C NMR δ 13.5, 14.7, 17.9, 28.7, 51.3, 55.4, 58.5, 63.3, 153.7, 174.2; MS(EI) 261 (M^+, 0.57), 246 (M^+ − Me, 18.81), 230 (M^+ − OMe, 100), 229 (32.23).

12b (minor diastereomer): ^{1}H NMR δ 0.90 (d, J = 7.0 Hz, 3H), 0.91 (d, J = 7.0 Hz, 3H), 1.21 (s, 2.40H, $CDCH_3$), 1.22 (d, J = 6.8 Hz, 0.60H, $-CHCH_3$), 2.34 (dqq, J = 4.0, 7.0, 7.0 Hz, 1H), 3.34 (s, 3H), 3.34 (s, 3H), 4.18 (dd, J = 9.0, 3.8 Hz, 1H), 4.26 (dd, J = 9.0, 8.3 Hz, 1H), 4.36 (q, J = 6.8 Hz, 0.20H, $-CHCH_3$), 4.48 (ddd, J = 8.3, 4.0, 3.8 Hz, 1H, NCH); ^{13}C NMR δ 12.4, 14.5, 17.8, 28.3, 51.8, 55.0, 63.0, 153.8, 174.3; MS(EI) 261 (M^+, 1.38), 246 (M^+ − Me, 14.95), 230 (M^+ − OMe, 100), 229 (14.47).

Transformation of (4*S*,2′*S*)-2a into Benzyl (*S*)-3,3-Dimethoxy-2-methylpropanonate (20). To a magnetically stirred, cooled (−10 °C) solution of lithium benzoxide,[6f] prepared from benzyl alcohol (433 mg, 4.0 mmol) in THF (5.0 mL) and *n*-BuLi (1.52 M in hexane, 3.0 mmol), was added a solution of **2a** (518 mg, 2.0 mmol) in THF (2.5 mL) over 0.5 h period. The reaction mixture was warmed to 0 °C, stirred for 1.5 h, and then quenched by addition of saturated aqueous ammonium chloride. Volatiles were removed *in vacuo*, and the product was extracted with dichloromethane (50 mL × 3). The combined organic extracts were successively washed with water and brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo* to give a yellow oil (920 mg). SiO_2 column chromatography (20 g, 1.5 × 20 cm, hexane/AcOEt = 10/1, 8/2, 0/10) afforded **20** (335 mg, 70%, 50% ee) as a colorless liquid. Further elution with ethyl acetate gave 4-isopropyl-2-oxazolidinone (234 mg, 91%). The % ee of **20** was determined by 270 MHz ^{1}H NMR using the shift reagent of Eu(tfc)$_3$ to be 50% ee. **20**: bp 165 °C/1 mmHg; ^{1}H NMR δ 1.19 (d, J = 7.1 Hz, 3H), 2.83 (dq, J = 7.8, 7.1 Hz, 1H), 3.33 (s, 3H), 3.34 (s, 3H), 4.52 (d, J = 7.8 Hz, 1H), 5.15 (s, 2H), 7.30–7.37 (m, 5H); ^{13}C NMR δ 12.5, 43.4, 53.2, 54.7, 66.2, 105.4, 128.0, 128.1, 128.5, 136.1, 173.3; $[\alpha]^{25}_D$ +6.34° (*c* 1.07, $CHCl_3$) (50% ee). Anal. Calcd for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61. Found: C, 65.36; H, 7.53.

Transformation of (2*S*, 2′*S*)-2a into 3,3-Dimethoxy-2-methylpropanoic Acid (21). Into a solution of **2a** (130 mg, 0.5 mmol) in THF (7.5 mL) and H_2O (2.1 mL) was added 30% H_2O_2 (0.40 mL, 4.0 mmol, 8.0 equiv) and then LiOH·H_2O (42 mg, 1.0 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 15 h, cooled to 0 °C, and treated with a solution of Na_2SO_3 (0.56 g, 4.4 mmol) in H_2O (3.0 mL) and then 0.5 N $NaHCO_3$ (5 mL). THF was evaporated *in vacuo*,

and the aqueous residue was diluted to 50 mL with H_2O and extracted with dichloromethane (50 mL × 4). The extracts were combined, dried over Na_2SO_4, and evaporated *in vacuo* to give 4-isopropyl-2-oxazolidinone (61 mg, 95%). The aqueous phase was acidified to pH ~2 with 6 N HCl and extracted with ethyl acetate (75 mL × 4). The extracts were combined and dried over Na_2SO_4. Evaporation *in vacuo* gave **21** (70 mg, 95%): IR (neat) 3050, 1710, 1460, 1110, 970, 735 cm^{-1}; ^1H NMR δ 1.22 (d, J = 7.1 Hz, 3H), 2.80 (dq, J = 7.3, 7.1 Hz, 1H), 3.38 (s, 3H), 3.41 (s, 3H), 4.52 (d, J = 7.3 Hz, 1H), 8.80–9.80 (br, 1H); ^{13}C NMR δ 12.3, 43.2, 53.5, 55.0, 105.2, 179.0.

Pure diastereomer of (4*S*,2′*S*)-acetal **2g** (R = *t*-Bu) was similarly transformed into (*S*)-**21**. Treatment of this compound with CH_2N_2 gave the optically pure methyl ester of (*S*)-(+)-**21**: 65%; IR (neat) 1740, 1460 cm^{-1}; ^1H NMR δ 1.17 (d, J = 7.1 Hz, 3H), 2.79 (dq, J = 7.8, 7.1 Hz, 1H), 3.35 (s, 3H), 3.38 (s, 3H), 3.70 (s, 3H), 4.50 (d, J = 7.8 Hz, 1H); ^{13}C NMR δ 12.5, 43.2, 51.7, 53.2, 54.8, 105.5, 174.0; $[\alpha]^{29}_D$ +13.4° (*c* 0.484, $CHCl_3$).

Large Scale Preparation of Acetal 2k (R = Ph). In a 300 mL round-bottomed flask equipped with rubber balloon filled by oxygen and a magnetic stirring bar were placed $PdCl_2$ (709 mg, 4.0 mmol), CuCl (792 mg, 8.0 mmol), and (4*R*)-*N*-methacryloyl-4-phenyl-2-oxazolidinone (**1i**) [9.28 g, 40 mmol, $[\alpha]^{25}_D$ −76.7° (*c* 0.55, $CHCl_3$)] under an oxygen atmosphere. To the flask were added DME (160 mL) and methanol (16 mL, 400 mmol). After being stirred at 50 °C for 40 h, the resulting mixture was cooled to room temperature, ether (150 mL) was added, and the mixture was filtered through a short column of Florisil (50 g, 3.0 × 15 cm, ether, 150 mL) to remove catalysts. Evaporation of the solvent gave colorless crystal **2k** (10.5 g, 88%) which was recrystallized from hexane–diisopropyl ether to give **2k** as a single diastereomer (7.16 g, 60%): mp 118.0–120.0 °C; IR (KBr) 2980, 1790, 1710, 1475, 1380, 1240, 1120, 1060, 770 cm^{-1}; ^1H NMR δ 1.12 (d, J = 7.1 Hz, 3H), 3.33 (s, 3H), 3.37 (s, 3H), 4.25 (dd, J = 8.5, 3.2 Hz, 1H), 4.25 (dq, J = 7.1, 8.1 Hz, 1H), 4.55 (d, J = 8.1 Hz, 1H), 4.67 (dd, J = 8.8, 8.6 Hz, 1H), 5.43 (dd, J = 8.6, 3.2 Hz, 1H), 7.25–7.41 (m, 5H); ^{13}C NMR δ 13.2, 40.4, 51.7, 55.5, 57.7, 69.8, 105.2, 125.6, 128.6, 129.2, 139.2, 153.3, 173.5; $[\alpha]^{25}_D$ −116.3° (*c* 0.873, $CHCl_3$). Anal. Calcd for $C_{15}H_{19}NO_5$: C, 61.42; H, 6.53; N, 4.78. Found: C, 61.32; H, 6.40; N, 4.81.

(*S*)-1-(Benzyloxy)-3,3-dimethoxy-2-methylpropane (22). The compound (*R*)-(−)-**2k** (2.34 g, 8.0 mmol) was treated with $LiAlH_4$ (910 mg, 24.0 mmol) in THF (80 mL), as montioned above, to give (*S*)-(−)-**3b** (711 mg, 66%, bp 120–125 °C). Into a THF solution (11 mL) of (*S*)-(−)-**3b** (698 mg, 5.21 mmol) was added potassium *tert*-butoxide (680 mg, 6.06 mmol) at 0 °C, and the mixture was stirred at 0 °C for 1 h. Benzyl bromide (1.08 g, 6.86 mmol) was then added, and the mixture was stirred at room temperature for 60 h. The reaction mixture was poured into H_2O (50 mL), extracted with ether (25 mL × 4), and dried over $MgSO_4$. Concentration *in vacuo* followed by SiO_2 column chromatography (35 g, 2.4 × 15 cm, hexane/AcOEt = 19/1) gave **22** (680 mg, 58%): IR (neat) 2880, 1495, 1455, 1072, 740, 700 cm^{-1}; ^1H NMR δ 0.99 (d, J = 6.8 Hz, 3H), 2.08 (m, 1H), 3.35 (s, 3H), 3.36 (s, 3H), 3.37 (dd, J = 9.2, 6.2 Hz, 1H), 3.49 (dd, J = 9.2, 5.2 Hz, 1H) 4.25 (d, J = 6.1 Hz, 1H), 4.49 (s, 2H), 7.23–7.34 (m, 5H); ^{13}C NMR δ 12.1, 36.9, 54.4, 54.6, 72.0, 73.1, 106.6, 127.4, 127.5, 128.3, 138.7.

(*S*)-3-(Benzyloxy)-2-methylpropanal (23). To a solution of the acetal **22** (157 mg, 0.7 mmol) in acetone (7.0 mL) containing water (130 μL) was added pyridinium tosylate (53 mg, 0.3 equiv, 0.21 mmol). The mixture was stirred at 60 °C for 4 h and cooled to room temperature. The product was extracted with ether (50 mL), washed with water (25 mL × 3), and dried over $MgSO_4$. Filtration followed by evaporation gave essentially pure (*S*)-(**23**) (125 mg, 100%): IR (neat) 2930, 1725, 1455, 1360, 1100, 740, 700 cm^{-1}; ^1H NMR δ 1.14 (d, J = 7.1 Hz, 3H), 2.66 (m, 1H), 3.63 (dd, J = 9.3, 5.4 Hz, 1H), 3.69 (dd, J = 9.3, 6.5 Hz, 1H), 4.52 (s, 2H), 7.23–7.34 (m, 5H), 9.73 (d, J = 1.7 Hz, 1H); ^{13}C NMR δ 10.7, 46.8, 70.2, 73.3, 127.6, 127.7, 128.4, 138.0, 203.7.

(3*S*,4*R*)-1-(Di-*p*-anisylmethyl)-3-acetyl-4-[(*R*)-1-(benzyloxymethyl)ethyl]-2-azetidinone (25). The imine **24** was prepared from di-*p*-anisylmethylamine[29] (170 mg, 0.70 mmol) and **23** (125 mg, 0.70 mmol). According to the procedure of Terashima,[23] the imine **24** was reacted with diketene (295 mg, 3.5 mmol) at −20 °C. Usual workup gave a diastereomer mixture of **25** (136 mg, 41% yield, diastereomer ratio = 8/1) which was subjected to medium pressure chromatography (SiO_2 50 g; 0.5 kg/cm; hexane/2-propanol = 97/3). The fraction (40 mL), obtained after 200 mL elution was passed, gave (3*S*,4*R*,1′*R*)-azetidinone **25**. From the ^1H NMR (270 MHz, $CDCl_3$) spectrum of this compound using $Eu(tfc)_3$, the optical purity was determined to be 92% ee. **25**: IR (neat) 2855, 1755, 1710, 1610, 1510, 1250, 1175 cm^{-1}; ^1H NMR δ 0.88 (d, J = 7.1 Hz, 3H), 1.80–1.95 (m, 1H), 2.19 (s, 3H) , 3.21 (dd, J = 9.3, 4.9 Hz, 1H), 3.30 (dd, J = 9.3, 4.9 Hz, 1H), 3.77 (s, 3H), 3.79 (s, 3H), 4.12 (dd, J = 5.6, 2.4 Hz, 1H), 4.20 (d, J = 2.4 Hz, 1H) 4.35 (d, J = 11.8 Hz, 1 H), 4.41 (d, J = 11.8 Hz, 1H), 6.8–7.4 (m, 13H); ^{13}C NMR δ 14.1, 30.0, 34.9, 55.2, 57.8, 62.1, 65.2, 71.9, 73.5, 113.9, 113.9, 127.7, 127.8, 128.4, 129.2, 129.3, 131.2, 138.0, 159.0, 159.1, 163.4, 200.7; HRMS calcd for $C_{30}H_{34}NO_5$ (M + H^+) 488.2437, found 488.2442. A sample from the following elution (30 mL) showed $[\alpha]^{22}_D$ −49.3° (*c* 0.609, $CHCl_3$). The decrease in % ee in the present experiment, compared to that (95% ee) of the literature,[23] is probably due to the use of higher temperature (−20 °C).

Determination of % ee of 23. Into a suspension of $LiAlH_4$ (7.0 mg, 0.18 mmol) in dry THF (2.0 mL) were added a solution of (*S*)-(**23**) (62 mg, 0.35 mmol) in dry THF (3.0 mL) over 15 min under argon, and the solution was stirred at room temperature for 1 h. To this was added slowly saturated ammonium chloride (0.1 mL) and ether (50 mL), and the mixture was dried over $MgSO_4$ and filtered. Evaporation of solvent gave pure (*R*)-3-(benzyloxy)-2-methyl-1-propanol (56 mg, 89%): IR (neat) 3430, 2955, 1095, 1040, 735, 700 cm^{-1}; ^1H NMR δ 0.89 (d, J = 7.1 Hz, 3H), 1.98–2.14 (m, 1H), 2.2–2.6 (br, 1H), 3.42 (dd, J = 9.0, 7.8 Hz, 1H), 3.54 (dd, J = 9.0, 4.6 Hz, 1H), 3.61 (m, 2H), 4.52 (s, 2H), 7.2–7.4 (m, 5H); $[\alpha]^{22}_D$ +17.0° (*c* 0.271, $CHCl_3$) (lit. $[\alpha]^{25}_D$ +13.0°[19]). A solution of (*R*)-3-(benzyloxy)-2-methyl-1-propanol (36 mg, 0.20 mmol) in dry CH_2Cl_2 (2.0 mL) were added 4-(*N*,*N*-dimethylamino)pyridine (DMAP) (49 mg, 0.4 mmol) and benzoyl chloride (26 μL, 0.22 mmol) under argon. The solution was stirred at room temperature for 2 h. To this was added glycine (15 mg), K_2CO_3 (27 mg), and water (4.0 mL) to remove unreacted benzoyl chloride. After being stirred for 1 h, the mixture was extracted with dichloromethane (50 mL). The extract was washed with 2 N HCl (20 mL), saturated $NaHCO_3$ (20 mL), and brine (50 mL) and dried over $MgSO_4$. Evaporation of solvents followed by SiO_2 short column chromatography (1.0 g, 1 × 3 cm, hexane/AcOEt = 1/1) gave pure benzoate **26** (49 mg, 88%). Enantiomeric excess determined by HPLC (CHIRALPAK OJ, 1.0% 2-propanol in hexane) was >98% ee: IR (neat) 1720, 1605, 1450, 1275, 1110, 1025, 735, 710 cm^{-1}; ^1H NMR δ 1.07 (d, J = 7.1 Hz, 3H), 2.28 (m, 1H), 3.45 (dd, J = 9.3, 5.9 Hz, 1H), 3.50 (dd, J = 9.3, 6.4 Hz, 1H), 4.27 (dd, J = 10.7, 6.1 Hz, 1H), 4.34 (dd, J = 10.7, 6.1 Hz, 1H), 4.52 (s, 2H), 7.2–8.2 (m, 10H); ^{13}C NMR δ 14.2, 33.6, 66.9, 72.2, 73.1, 127.5, 127.5, 128.3, 129.5, 130.5, 132.8, 138.4, 166.5; $[\alpha]^{22}_D$ +3.00° (*c* 1.20, $CHCl_3$); HRMS calcd for $C_{18}H_{20}O_3$ (M^+) 284.1412, found 284.1418.

Supporting Information Available: ^1H and ^{13}C NMR spectra of compounds for which no elemental analysis was obtained (36 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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