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Synthesis of an immunomodulator (+)-conagenin and its analogs

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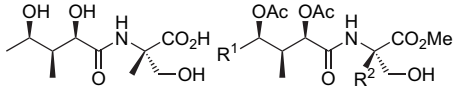
Abstract—Stereoselective synthesis of an immunomodulator (+)-conagenin was achieved. Both amine and carboxylic acid moieties were prepared from commercially available optically active methyl 3-hydroxy-2-methylpropanoate using dirhodium(II)-catalyzed C–H amination and chelation-controlled reductions as key steps. In addition, demethyl analogs of conagenin were synthesized using similar procedures.

1. Introduction

Ishizuka and co-workers isolated (+)-conagenin (Fig. 1, **1**) from fermentation broths of *Streptomyces roseosporus* MI696-AF3 in 1991 as a low molecular weight immunomodulator[1] after screening for substances that modulate immune response in conjunction with T-cell functions. Although most immunomodulators primarily cause activation of macrophages to enhance inflammatory responses, which frequently down regulates diseases, conagenin stimulates activated T cells to produce lymphokines and generate antitumor effector cells in vitro and in vivo.[1–3] In tumor bearing mice, conagenin administration inhibited tumor growth, and NK activity remained at normal level,[4] and **1** prevents myelosuppression induced by antitumor agents such as 5-fluorouracil, mitomycin C.[5,6] In addition, conagenin incubation enhanced phagocytic function of alveolar macrophages.[7,8]

Because of these biological activities and its unique highly functionalized structure, **1** has attracted much attention from researchers in the field of synthetic chemistry. To date, five total syntheses,[9–13] including ours[12] and a formal synthesis[14] of (+)-**1**, have been reported, in addition to syntheses of its analogs[15] and a partial synthesis.[16] We have recently reported the stereoselective total synthesis of (+)-**1**.[12]



(+)-conagenin (**1**) **2** : R^1 = H, R^2 = Me; **3** : R^1 = Me, R^2 = H

Figure 1.

Keywords: Conagenin; Immunomodulator; Dirhodium(II)-catalyzed C–H amination; Chelation-controlled reduction.
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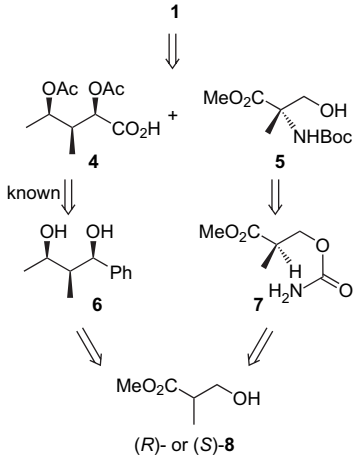
This report provides a full account of our total synthesis of **1** and synthesis of its demethyl analogs **2** and **3** (Fig. 1).

2. Results and discussion

Our strategy for total synthesis of **1** was outlined in Scheme 1. Both amine **5** and carboxylic acid **4** moieties were synthesized starting from commercially available methyl 3-hydroxy-2-methylpropanoate (**8**) because **8** is widely used in natural product synthesis as a starting material[17] and both of its enantiomers are commercially available. Synthesis of α-methylserine moiety **5** should be achieved quickly from **7** based on stereospecific dirhodium(II)-catalyzed C–H amination reaction[18–21] as a key step. Carboxylic acid moiety **4** has been already prepared effectively from diol **6** by the Hatakeyama[9] and the Ichikawa[11] groups. Therefore, we envisioned the use of **6** as a precursor of **4**. The diol **6** should

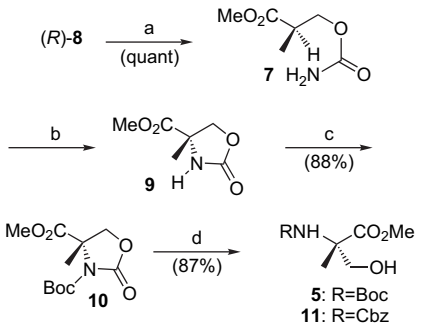


Scheme 1.

be prepared by stereoselective introductions of methyl and phenyl groups to **8**.

2.1. Synthesis of α-methylserine moiety

We first investigated the utility of C–H amination for short synthesis of α-methylserine (Scheme 2). Reaction of (*R*)-**8** with trichloroacetyl isocyanate in dichloromethane at room temperature gave the corresponding trichloroacetyl carbamate, which was treated with neutral alumina[22] without purification to afford carbamate **7** in quantitative yield. Then we examined dirhodium(II)-catalyzed C–H amination of **7** under Du Bois' conditions.[18] Therefore, treatment of **7** with 5 mol % of dirhodium(II) tetraacetate, 1.4 equiv of phenyliodine(III) diacetate, and 2.3 equiv of magnesium oxide in dichloromethane under reflux for 17 h gave the corresponding C–H amination product **9** in only 9% yield along with 83% of recovered **7** (53% yield based on the consumed **7**). The NH group of oxazolidinone **9** was protected with *tert*-butoxycarbonyl (Boc) group in the usual manner to afford **10** in 88% yield. The oxazolidinone ring of **10** was opened by treatment with cesium carbonate in methanol[23] to give optically pure *N*-Boc-α-methylserine methyl ester **5**, $[\alpha]_D^{28}$ +2.23 (*c* 1.33, $CHCl_3$) {lit.[24] $[\alpha]_D^{18}$ +1.9 (*c* 0.54, $CHCl_3$)}, in 87% yield. Optical purity of the synthesized α-methylserine was determined to be 96.8% ee by chiral HPLC analysis of its *N*-benzyloxycarbonyl (Cbz) derivative **11**,[11] which was prepared from **9** by protection of NH group with Cbz group and following oxazolidinone ring opening, using Daicel Chiralpak AD-H (hexane/^{i}PrOH, 90:10, 0.5 mL min^{-1}). This result reveals that the dirhodium(II)-catalyzed C–H amination of **7** proceeded with retention of configuration, as Espino and Du Bois reported.[18]



Scheme 2. Reagents and conditions: (a) $CCl_3CON{=}C{=}O$, CH_2Cl_2, rt, 1 h then neutral Al_2O_3; (b) see Table 1; (c) $(Boc)_2O$, Et_3N, DMAP, THF, rt, 2 h; and (d) Cs_2CO_3, MeOH, rt, 2.5 h.

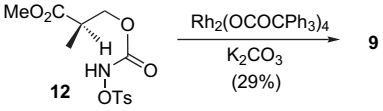
This method became a convenient procedure for the synthesis of α-methylserine. However, the key C–H amination reaction is not satisfactory. Therefore, we next examined other reaction conditions (Table 1). When 10 mol % of $Rh_2(OAc)_4$, 4.2 equiv of $PhI(OAc)_2$, and 6.9 equiv of MgO were used, the reaction was accelerated and the yield was increased to 24% (Entry 1). Both longer reaction time and further larger amounts of reagents were not effective (Entries 2 and 3). Influences of other solvents, dirhodium catalysts, and hypervalent iodine reagents were investigated (Entries 4–11). Among them, the highest yield was obtained using the reaction with dirhodium(II) bis(α,α,α′,α′-tetramethyl-1,3-benzenedipropanoate) $[Rh_2(esp)_2]$,[25] in which 44% of isolated **9** along with 35% of recovered **7** (68% yield based on the consumed **7**) were provided (Entry 10).

Table 1. C–H animation reaction of **7**[a]

Entry	Rh(II)	Solvent	Temperature	Yield of **9** (%)	Recovery of **7** (%)	Yield based on consumed **7** (%)
1	$Rh_2(OAc)_4$	CH_2Cl_2	Reflux	24	64	67
2[b]	$Rh_2(OAc)_4$	CH_2Cl_2	Reflux	30	53	64
3[c]	$Rh_2(OAc)_4$	CH_2Cl_2	Reflux	28	41	47
4	$Rh_2(OAc)_4$	$CHCl_3$	Reflux	8	9	9
5	$Rh_2(OAc)_4$	$(ClCH_2)_2$	Reflux	25	16	30
6	$Rh_2(OAc)_4$	Benzene	Reflux	24	15	29
7	$Rh_2(OAc)_4$	CH_3CN	50 °C	25	59	63
8	$Rh_2(OAc)_4$	THF	50 °C	0	0	0
9	$Rh_2(oct)_4$	CH_2Cl_2	Reflux	22	65	63
10	$Rh_2(esp)_2$	CH_2Cl_2	Reflux	44	35	68
11[d]	$Rh_2(OAc)_4$	CH_2Cl_2	Reflux	0	67	0

[a] The reaction was carried out using 10 mol % of Rh(II) catalyst, 4.2 equiv of $PhI(OAc)_2$, and 6.9 equiv of MgO for 17 h.
[b] The reaction was heated for 40 h.
[c] Rh(II) catalyst of 30 mol %, 12.6 equiv of $PhI(OAc)_2$, and 20.7 equiv of MgO were used.
[d] $PhI(OCOCF_3)_2$ was used instead of $PhI(OAc)_2$.

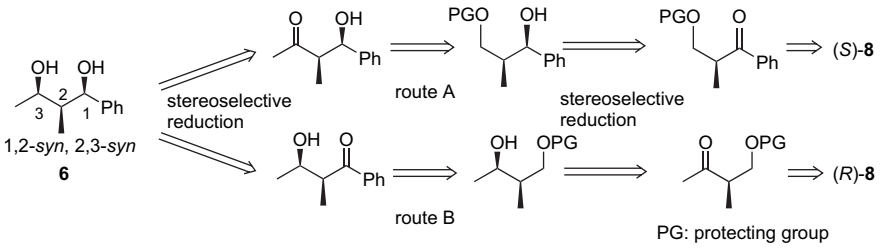
Alternatively, we attempted C–H amination of *N*-tosyloxycarbamate **12** using Lebel's procedure.[26] According to the reported protocol, (*R*)-**8** was treated with 1,1′-carbonyldiimidazole, followed by *N*-hydroxylamine hydrochloride to give the corresponding *N*-hydroxycarbamate, which was tosylated with tosyl chloride and triethylamine to afford **12**. Unfortunately, treatment of **12** and potassium carbonate in the presence of dirhodium(II) tetrakis(triphenylacetate) in dichloromethane at room temperature gave the oxazolidinone **9** in 29% yield without any recovery of **12** (Eq. 1).



(1)

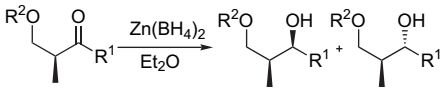
2.2. Synthesis of carboxylic acid moiety 4

The next subject is the stereoselective synthesis of diol **6** and its conversion into carboxylic acid moiety **4**. From the perspective of applicability to syntheses of a wide range of analogs, we chose a stepwise procedure for **6** from the same starting material, methyl 3-hydroxy-2-methylpropanoate (**8**). Stereoselective construction of three continuing stereocenters of **6** is expected to occur by stepwise chelation-controlled reductions of the corresponding ketones (Scheme 3) from studies related to the chemistry of methyl 3-hydroxy-2-methylpropanoate.[17,27] Then we investigated routes A and B using stereoselective chelation-controlled reductions. Because it is known that racemic β-hydroxy phenyl ketone **13a** is stereoselectively reduced with zinc borohydride to give *syn* diol **14a** with high level,[28] we first examined route A. According to reported protocol, treatment of β-hydroxy phenyl ketones **13a** with zinc borohydride in diethyl ether at 0 °C for 30 min gave rise to *syn* alcohol **14a** stereoselectively in high yield (Table 2, Entry 1). In addition, *p*-methoxybenzyl (PMB) ether **13b** was reduced stereoselectively to afford **14b** under identical conditions (Table 2, Entry 2).



Scheme 3.

Table 2. Stereoselective reduction of α-methyl-β-alkoxy-ketones

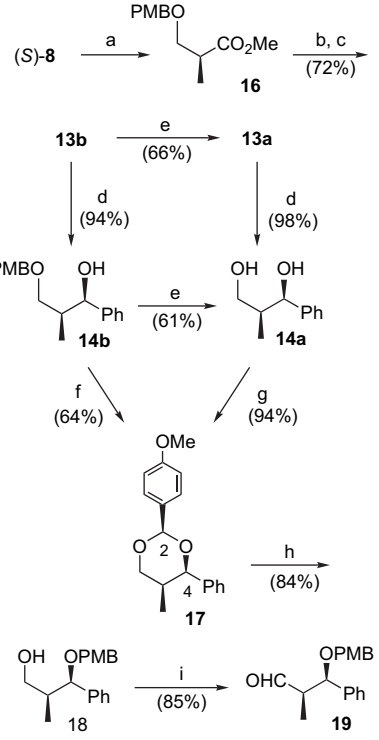


Entry	**13**	R^1	R^2	Yield (%)	**14**:**15**[a]
1	**a**	Ph	H	98	17:1
2	**b**	Ph	PMB	94	19:1
3	**c**	Me	H	Low	1.1:1[b]
4	**d**	Me	PMB	92	1.4:1[b]

[a] Determined by ^{1}H NMR.
[b] The stereochemistry of neither diastereomer was determined.

Because α-methylserine moiety **5** was successfully prepared from (*R*)-**8**, we expected route B, starting from the same (*R*)-**8**, should be a more convenient procedure than route A, starting from (*S*)-**8**. Reductions of methyl ketones **13c** and **13d** were investigated with the hope of obtaining high stereoselectivity (Table 2, Entries 3 and 4). Unfortunately, reductions of **13c** and **13d** with zinc borohydride afforded a non-selective mixture of **14** and **15**, respectively. Therefore, we envisioned to prepare **6** according to route A. A similar difference of stereoselectivity in between the reduction of phenyl ketone and that of methyl ketone was observed in a similar $TiCl_4$ mediated reduction.[29]

Route A proved to be the most suitable for synthesis of **6**. Therefore, we started stereoselective introduction of phenyl group according to route A (Scheme 4). The hydroxy group of starting (*S*)-**8** was protected as PMB ether with 2-PMBoxy-3-nitropyridine using the Mukaiyama protocol[30] to give known **16**. Hydrolysis of **16** with lithium hydroxide, followed by treatment with 2 equiv of phenyl lithium afforded phenyl ketone **13b**. As described above, chelation-controlled reduction of PMBoxy-ketone **13b** was accomplished using zinc borohydride to afford *syn*-alcohol **14b** in 94% yield as a major isomer. The ratio of *syn*-isomer and *anti*-isomer was estimated as 19:1 by integration of the respective intensities of the peak heights of the signals due to the methyl protons at 2-position that appeared at δ 0.85 (d) and 0.75 (d), in the ^{1}H NMR spectrum of the mixture. Treatment of **14b** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in the presence of molecular sieves 3 Å (MS 3A) in anhydrous dichloromethane gave benzylideneacetal **17** in 64% yield as a single diastereomer. The stereochemistry of **17** was determined by a coupling constant in the ^{1}H NMR spectrum of **17** and nuclear Overhauser effect (NOE) experiments to be thermodynamically stable 2,4-*syn*-4,5-*syn*-isomer; $J_{4,5}$ was 2.7 Hz and positive NOEs were observed between H-2 and H-4 protons and H-4 and H-5 protons (Fig. 2). These results suggested the 1,2-*syn* relationship of **14b**. Alternatively, deprotection of **13b** with DDQ gave hydroxyl ketone **13a**, which was reduced with zinc borohydride to afford the optically active **14a** (*syn*:*anti*= 17:1) stereoselectively. The stereochemistry of **14a** was determined through the comparison of spectroscopic data to those of the known authentic sample.[28,31,32] Also, de(*p*-methoxy)benzylation of **14b** with DDQ gave **14a**. The resulting diol **14a** was successfully converted into **17** by treatment with *p*-anisaldehyde dimethyl acetal in the presence of camphorsulfonic acid (CSA) in 94% yield.



Scheme 4. Reagents and conditions: (a) Ref. 30; (b) LiOH, H_2O–MeOH, rt, 4 h; (c) PhLi, Et_2O, rt, 30 min; (d) $Zn(BH_4)_2$, Et_2O, 0 °C, 30 min; (e) DDQ, CH_2Cl_2–MeOH, rt, 2 h; (f) DDQ, MS 3A, CH_2Cl_2, rt, 1.5 h; (g) *p*-anisaldehyde dimethylacetal, CSA, CH_2Cl_2, rt, 12 h, (h) DIBAL-H, CH_2Cl_2, −80 °C to 0 °C, 1 h; and (i) Dess–Martin periodinane, CH_2Cl_2, rt, 30 min.

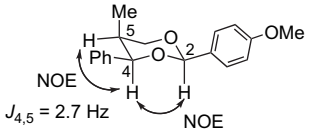
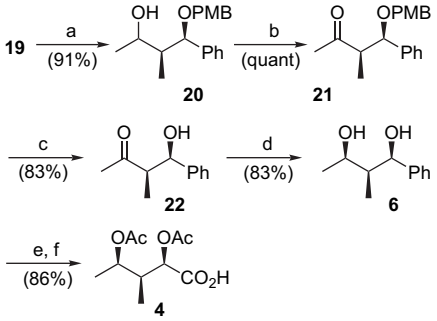


Figure 2.

Subsequent diisobutylaluminum hydride (DIBAL-H) reduction of **17** gave rise to the primary alcohol **18** in 84% yield. Dess–Martin periodinane oxidation of **18** produced **19** in 85% yield.

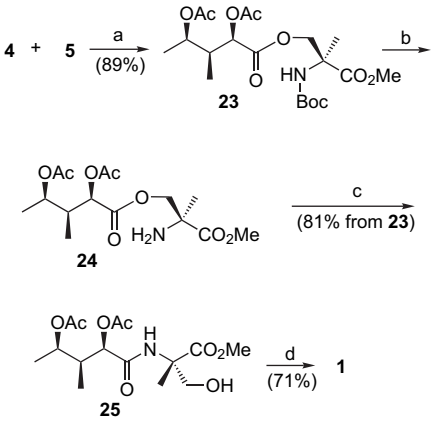
Next, the stereoselective construction of another chiral center was investigated (Scheme 5). Methylation of **19** with methyllithium in diethyl ether afforded a 4:1 mixture of two diastereomers[33] of secondary alcohol **20** in 91% yield. The mixture was oxidized with Dess–Martin periodinane to provide methyl ketone **21**. Then stereoselective reduction of **21** was examined. In contrast to the reduction of **13b**, unfortunately, reduction of PMBoxy-ketone **21** with zinc borohydride in diethyl ether occurred with a low level of diastereoselectivity (2:1)[33] to give **20**, which might be caused by the difficulty of formation of chelation of ether oxygen with zinc atom because of the steric hindrance of large substituents, such as phenyl and PMB groups, around the ether oxygen (Fig. 3, **A**). To form the more rigid chelated complex **B** (Fig. 3), PMB group was removed: compound **21** was reacted with DDQ in dichloromethane to give β-hydroxyketone **22** in 83% yield. The desired stereoselective reduction of **22** was accomplished by treatment with zinc borohydride, in diethyl ether at 0 °C to afford the known diol **6** (>50:1), $[\alpha]_D^{27}$ +35.4 (*c* 1.06, $CHCl_3$) {lit.[9] $[\alpha]_D^{24}$ +35.5 (*c* 0.46, $CHCl_3$), lit.[11] $[\alpha]_D^{18}$ +41.0 (*c* 1.05, $CHCl_3$)}, in 83% yield. According to the reported procedure,[9,11] protection of both hydroxy groups as acetates and oxidation of phenyl group with ruthenium tetraoxide afforded the carboxylic acid moiety **4** (86%).



Scheme 5. Reagents and conditions: (a) MeLi, Et_2O, −80 °C to 0 °C, 1 h; (b) Dess–Martin periodinane, CH_2Cl_2, rt, 30 min; (c) DDQ, CH_2Cl_2–MeOH, rt, 2 h; (d) $Zn(BH_4)_2$, Et_2O, 0 °C, 30 min; (e) Ac_2O, pyridine, DMAP, rt, 30 min; and (f) cat. $RuCl_3$, H_5IO_6, CH_3CN–CCl_4–H_2O, rt, 18 h.

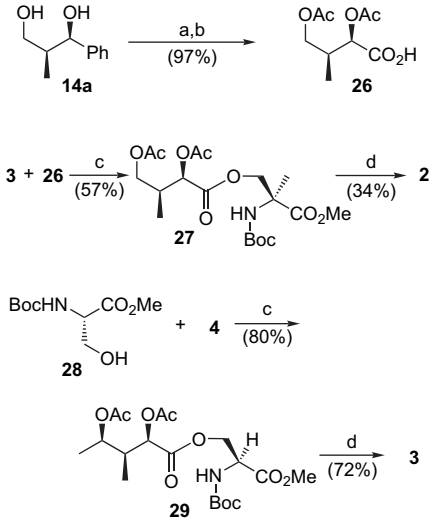
2.3. Completion of synthesis of conagenin and application to preparation of demethyl analogs

Finally, conversion to (+)-conagenin (**1**) was accomplished using a modified Ichikawa's procedure[11] (Scheme 6). Thereby, condensation of **4** and **5** proceeded using 1,3-dicyclohexylcarbodiimide (DCC) in the presence of 1-hydroxybenzotriazole (HOBt) in dichloromethane to give ester **23** in 89% yield. The resultant **23** was deprotected by treatment with trifluoroacetic acid to produce amine **24**, which was converted into **25** by *O*–*N* intramolecular acyl migration using sodium bicarbonate to afford diacetylconagenin methyl ester **25** in 81% yield from **23**. Deprotection was carried out under basic conditions to provide (+)-conagenin (**1**), mp 154–157 °C, $[\alpha]_D^{28}$ +56.6 (*c* 0.20, MeOH) {lit.[1] mp 159–161 °C, $[\alpha]_D^{27}$ +55.4, lit.[11] mp 153–155 °C, $[\alpha]_D^{20}$ +56.8 (*c* 0.44, MeOH)}, in 71% yield. Spectroscopic data of **1** were identical to those of the reported sample.[9,11]



Scheme 6. Reagents and conditions: (a) DCC, HOBt, DMAP, CH_2Cl_2, rt, 1.5 h; (b) CF_3CO_2H, CH_2Cl_2, rt, 4 h; (c) saturated $NaHCO_3$, THF, rt, 10 h; and (d) 1 M K_2CO_3–MeOH (1:3), rt, 2 h.

The total synthesis of (+)-conagenin was accomplished. Therefore, we applied our methodology to the synthesis of its analogs by using the synthetic intermediates (Scheme 7). The diol **14a** was acetylated (97%) and then its phenyl group was oxidized to afford **26**, which was used as the carboxylic acid moiety lost one carbon. Amido formation of **26** with methylserine **5** was accomplished via ester **27** according to the same procedure of conagenin synthesis to give



Scheme 7. Reagents and conditions: (a) Ac_2O, pyridine, DMAP, rt; (b) cat. $RuCl_3$, H_5IO_6, CH_3CN–CCl_4–H_2O, rt; (c) DCC, HOBt, DMAP, CH_2Cl_2, rt; (d) CF_3CO_2H, CH_2Cl_2, rt then saturated $NaHCO_3$, THF, rt.

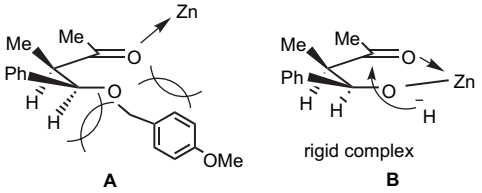


Figure 3.

demethyl derivative **2**. It is known that the α-alkyl α-amino acids increase conformational restrictions in peptides and thereby change their biological activity and stability.[34] Therefore, it is very interesting to investigate the difference of conformations and activities of between conagenin and its serine derivative that has no methyl group at α-position of amino acid moiety. Coupling of pentanoic acid **4** with *N*-Boc-serine methyl ester **28**[35] gave ester **29** (72%), which was converted into **3** by deprotection of Boc group and *O*–*N* acyl migration as a single diastereomer in 80% yield.

3. Conclusion

The convergent total synthesis of (+)-**1** was accomplished starting from commercially available methyl 3-hydroxy-2-methylpropanoate **8**. Amine moiety **5** was synthesized using C–H amination reaction as a key step. Carboxylic acid moiety **4** was prepared based on chelation-controlled reductions with zinc borohydride. As applications of this methodology, demethyl derivatives **2** and **3** were synthesized. Conversion of **2** and **3** to their free acids and investigation of their conformations and biological activities are now underway in our laboratory.

4. Experimental

4.1. General

Melting points are uncorrected. IR spectra were recorded using JASCO FT/IR-460 Plus spectrophotometer. ^{1}H NMR spectra were determined with Varian Unity plus 500 (500 MHz), Varian Gemini 300 (300 MHz), and JEOL JNM-FX270 (270 MHz) spectrometers, tetramethylsilane as an internal standard. ^{13}C NMR spectra were determined with Varian Unity plus 500 (125 MHz), Varian Gemini 300 (75 MHz), and JEOL JNM-FX270 (67.5 MHz) spectrometers. All ^{13}C NMR spectra were determined with complete proton decoupling. High resolution MS were determined with JEOL JMS-GCmate and JEOL JMS-AX505HAD instruments. Optical rotations were measured with JASCO DIP-1000 polarimeter. Column chromatography was performed on Silica Gel 60 PF_{254} (Nacalai Tesque) under pressure. Methyl (*R*)-3-hydroxy-2-methylpropanoate [(*R*)-**8**] was purchased from Aldrich and methyl (*S*)-3-hydroxy-2-methylpropanoate [(*S*)-**8**] was gifted by Mitsubishi Rayon Co. Ltd.

4.1.1. Methyl (*R*)-3-carbamoyloxy-2-methylpropanoate (7). Trichloroacetyl isocyanate (1.75 g, 9.31 mmol) was added to a solution of (*R*)-**8** (1.0 g, 8.47 mmol) in CH_2Cl_2 (50 mL) at room temperature under a nitrogen atmosphere and the mixture was stirred for 1 h. Then a mixture was passed through a short neutral Al_2O_3 column with ethyl acetate and the mixture was concentrated. The residue was chromatographed on silica gel (40% EtOAc in hexane) to give **7** (1.39 g, quant) as colorless crystals: mp 55–57 °C (EtOAc–hexane); $[\alpha]_D^{28}$ −109.0 (*c* 1.18, $CHCl_3$); IR (KBr) cm^{-1}: 3445, 3353, 3301, 3208, 1740, 1716; ^{1}H NMR (300 MHz, $CDCl_3$) *δ*: 1.20 (3H, d, *J*=7.1 Hz), 2.81 (1H, quintet d, *J*=7.1, 5.8), 3.71 (3H, s), 4.17 (1H, dd, *J*=10.7, 5.8 Hz), 4.23 (1H, dd, *J*=10.7, 7.4 Hz), 4.74 (2H, br s); ^{13}C NMR (75 MHz, $CDCl_3$) *δ*: 13.6, 39.2, 51.8, 66.0, 156.7, 174.4; Anal. Calcd for $C_6H_{11}NO_4$: C, 44.72; H, 6.88; N, 8.69. Found: C, 45.09; H, 6.85, N, 8.53.

4.1.2. Methyl (*S*)-4-methyl-2-oxooxazolidine-4-carboxylate (9). A suspension of **7** (98 mg, 0.61 mmol), $PhI(OAc)_2$ (823 mg, 2.55 mmol), MgO (169 mg, 4.19 mmol), and $Rh_2(esp)_2$ (46 mg, 0.06 mmol) in CH_2Cl_2 (3.0 mL) was refluxed for 17 h. After the mixture was cooled to room temperature, it was passed through a short Celite pad and the filtrate was concentrated. The residue was chromatographed on silica gel (50% EtOAc in hexane) to give **9** (43 mg, 44%) and starting **7** (34 mg, 35%). The compound **9** was obtained as colorless crystals: mp 45–47 °C (EtOAc–hexane); $[\alpha]_D^{28}$ −11.5 (*c* 1.06, $CHCl_3$); IR (KBr) cm^{-1}: 3230, 3125, 1793, 1743, 1730; ^{1}H NMR (270 MHz, $CDCl_3$) *δ*: 1.59 (3H, s), 3.81 (3H, s), 4.15 (1H, d, *J*=8.9 Hz), 4.70 (1H, d, *J*=8.9 Hz), 6.30 (1H, br s); ^{13}C NMR (67.5 MHz, $CDCl_3$) *δ*: 24.3, 53.2, 60.8, 73.0, 158.1, 172.6; HRMS *m*/*z* calcd for $C_6H_9NO_4$ (M^+) 159.0532, found 159.0536.

4.1.3. 3-*tert*-Butyl 4-methyl (*S*)-4-methyl-2-oxooxazolidine-3,4-dicarboxylate (10). A mixture of **9** (147 mg, 0.92 mmol), $(Boc)_2O$ (403 mg, 1.85 mmol), Et_3N (327 mg, 3.23 mmol), and DMAP (23 mg, 0.18 mmol) in THF (9 mL) was stirred at room temperature under a nitrogen atmosphere for 2 h. The mixture was diluted with Et_2O. The solution was washed with saturated aqueous NH_4Cl, water, and brine, dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel (25% EtOAc in hexane) to give **10** (263 mg, 88%) as a colorless oil: $[\alpha]_D^{27}$ −0.34 (*c* 1.43, $CHCl_3$); IR (neat) cm^{-1}: 1823, 1752, 1730; ^{1}H NMR (300 MHz, $CDCl_3$) *δ*: 1.52 (9H, s), 1.75 (3H, s), 3.81 (3H, s), 4.05 (1H, d, *J*=8.8 Hz), 4.32 (1H, d, *J*=8.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) *δ*: 22.1, 28.1 (3), 53.4, 63.4, 71.0, 84.8, 148.5, 151.6, 170.8; HRMS *m*/*z* calcd for $C_{11}H_{17}NO_6$ (M^+) 259.1056, found 259.1073.

4.1.4. Methyl (*S*)-2-*tert*-butoxycarbonylamino-3-hydroxy-2-methylpropanoate (5). A mixture of **10** (263 mg, 1.01 mmol) and Cs_2CO_3 (66 mg, 0.2 mmol) in MeOH (10 mL) was stirred at room temperature for 2.5 h. The mixture was diluted with Et_2O. The solution was washed with saturated aqueous NH_4Cl, water, and brine, dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel (40% EtOAc in hexane) to give **5** (206 mg, 87%) as a colorless oil: $[\alpha]_D^{28}$ +2.23 (*c* 1.34, $CHCl_3$) {lit.[23] $[\alpha]_D^{18}$ +1.9 (*c* 0.54, $CHCl_3$)}; IR (neat) cm^{-1}: 3600–3200, 1717, 1696; ^{1}H NMR (300 MHz, $CDCl_3$) *δ*: 1.44 (9H, s), 1.47 (3H, s), 3.78 (3H, s), 3.78 (1H, d, *J*=11.0 Hz), 3.96 (1H, d, *J*=11.3 Hz), 5.35 (1H, br s); ^{13}C NMR (75 MHz, $CDCl_3$) *δ*: 21.1, 28.5 (3), 52.9, 61.2, 67.1, 80.5, 155.4, 173.9; HRMS *m*/*z* calcd for $C_{10}H_{19}NO_5$ (M^+) 233.1263, found 233.1237.

4.1.5. 3-Benzyl 4-methyl (*S*)-4-methyl-2-oxooxazolidine-3,4-dicarboxylate. A mixture of **9** (18 mg, 0.11 mmol), $(Cbz)_2O$ (65 mg, 0.22 mmol), Et_3N (63 mg, 0.6 mmol), and DMAP (3 mg, 0.02 mmol) in THF (1.5 mL) was stirred at room temperature under a nitrogen atmosphere for 48 h. The mixture was diluted with Et_2O. The solution was washed with saturated aqueous NH_4Cl, water, and brine, dried ($MgSO_4$) and concentrated. The residue was

chromatographed on silica gel (30% EtOAc in hexane) to give the titled compound (21 mg, 64%) as a colorless oil: $[\alpha]_D^{27}$ −18.8 (*c* 1.00, $CHCl_3$); IR (neat) cm^{-1}: 1826, 1808, 1751; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.75 (3H, s), 3.64 (3H, s), 4.07 (1H, d, *J*=9.1 Hz), 4.34 (1H, d, *J*=9.1 Hz), 5.26 (1H, A of ABq, *J*=12.4 Hz), 5.35 (1H, B of ABq, *J*=12.4 Hz), 7.26–7.43 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.7, 53.3, 63.4, 68.9, 71.2, 128.1 (2), 128.5 (3), 134.5, 150.2, 151.0, 170.3; HRMS *m/z* calcd for $C_{14}H_{15}NO_6$ (M^+) 293.0899, found 293.0887.

4.1.6. Methyl (*S*)-2-benzyloxycarbonylamino-3-hydroxy-2-methylpropanoate (11). A mixture of 3-benzyl 4-methyl (*S*)-4-methyl-2-oxooxazolidine-3,4-dicarboxylate (20 mg, 0.06 mmol) and Cs_2CO_3 (5 mg, 0.01 mmol) in MeOH (1 mL) was stirred at room temperature for 2 h. The mixture was diluted with Et_2O. The solution was washed with saturated aqueous NH_4Cl, water, and brine, dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel (40% EtOAc in hexane) to give **11** (12 mg, 67%) as a colorless oil: $[\alpha]_D^{27}$ +5.36 (*c* 0.50, $CHCl_3$) {lit.[11] $[\alpha]_D^{21}$ +3.9 (*c* 0.31, $CHCl_3$)}; IR (neat) cm^{-1}: 3600–3200, 1724, 1514; ^1H NMR (270 MHz, $CDCl_3$) δ: 1.51 (3H, s), 2.93 (1H, br s), 3.77 (3H, s), 3.81 (1H, dd, *J*=11.2, 6.9 Hz), 4.02 (1H, dd, *J*=11.2, 5.28 Hz), 5.10 (2H, s), 5.66 (1H, br s), 7.30–7.41 (5H, m); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ: 20.5, 52.9, 61.4, 66.6, 67.0, 128.1 (2), 128.2, 128.6 (2), 136.1, 155.5, 173.6; HRMS *m/z* calcd for $C_{13}H_{17}NO_5$ (M^+) 267.1107, found 267.1114. HPLC (Daicel Chiralpak AD-H (0.46× 25 mm); hexane/^{i}PrOH, 9:1; flow rate 0.5 mL min^{-1}; UV 254 nm): (*R*)-**11**: t_R 33.8 min (1.6%); (*S*)-**11**, t_R 51.8 min (98.4%).

4.1.7. (*S*)-3-(4-Methoxybenzyloxy)-2-methyl-1-phenylpropan-1-one (13b). An aqueous solution of LiOH (1.5 N, 2.5 mL, 3.78 mmol) was added to a solution of **16** (300 mg, 1.26 mmol) in MeOH (6 mL) and the mixture was stirred at room temperature for 4 h. After the reaction mixture was acidified by adding 10% HCl solution the mixture was extracted with EtOAc, washed with water, and brine, dried ($MgSO_4$) and concentrated to give crude acid (282 mg, quant), which was used without purification. A solution of PhLi in Et_2O (1.5 mol L^{-1}, 0.32 mL, 0.47 mmol) was added to a solution of the crude acid (52 mg, 0.23 mmol) in Et_2O (3 mL) at 0 °C under a nitrogen atmosphere. The mixture was stirred at room temperature for 30 min. The mixture was diluted with Et_2O. The solution was washed with saturated aqueous NH_4Cl, water, and brine, dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel (10% EtOAc in hexane) to give **13b** (48 mg, 72%) as a colorless oil: $[\alpha]_D^{27}$ +27.4 (*c* 2.70, $CHCl_3$); IR (neat) cm^{-1}: 1681, 1612; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.21 (3H, d, *J*=6.9 Hz), 3.47–3.56 (1H, m), 3.73–3.86 (2H, m), 3.78 (3H, s), 4.40 (1H, d, *J*=11.5 Hz), 4.46 (1H, d, *J*=11.5 Hz), 6.83 (2H, d, *J*=8.8 Hz), 7.18 (2H, d, *J*=8.8 Hz), 7.42–7.48 (2H, m), 7.51–7.58 (1H, m), 7.91–7.98 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 15.0, 41.5, 55.2, 72.2, 73.0, 113.6 (2), 128.2 (2), 128.4 (2), 129.0 (2), 130.2, 132.8, 136.5, 158.9, 202.6; HRMS *m/z* calcd for $C_{18}H_{20}O_3$ (M^+) 284.1413, found 284.1405.

4.1.8. (1*R*,2*S*)-3-(4-Methoxybenzyloxy)-2-methyl-1-phenylpropan-1-ol (14b). A solution of $Zn(BH_4)_2$ in Et_2O (ca. 0.15 mol L^{-1}, 2.4 mL, 0.36 mmol), prepared from $NaBH_4$ and $ZnCl_2$ according to the reported procedure, was added to a solution of **13b** (93 mg, 0.33 mmol) in Et_2O (5 mL) at 0 °C under a nitrogen atmosphere. The mixture was stirred at the same temperature for 30 min. The mixture was poured into 10% HCl, and extracted with EtOAc. The extract was washed with saturated aqueous $NaHCO_3$, water, and brine, dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel (10% EtOAc in hexane) to give a 19:1 mixture of **14b** and its *anti*-isomer (88 mg, 94%) as a colorless oil: IR (neat) cm^{-1}: 3600–3200, 1612, 1586, 1513, 1248; ^1H NMR for the major isomer (500 MHz, $CDCl_3$) δ: 0.85 (3H, d, *J*=7.3 Hz), 2.12–2.22 (1H, m), 3.22 (1H, s), 3.45 (1H, dd, *J*=9.2, 6.3 Hz), 3.50 (1H, dd, *J*=9.2, 4.3 Hz), 3.82 (3H, s), 4.46 (2H, s), 4.91 (1H, d, *J*=3.3 Hz), 6.90 (2H, d, *J*=6.6 Hz), 7.22–7.32 (7H, m); selected signals for the minor isomer δ: 0.75 (3H, d, *J*=7.3 Hz); ^{13}C NMR for the major isomer (125 MHz, $CDCl_3$) δ: 11.2, 40.1, 55.3, 73.1, 73.7, 76.3, 113.8 (2), 126.1 (2), 126.9, 127.9 (2), 129.3 (2), 130.1, 142.9, 159.3; HRMS *m/z* calcd for $C_{18}H_{22}O_3$ (M^+) 286.1569, found 286.1541. The ratio of **14b** and its *anti*-isomer was estimated to be 19:1 by integration of the intensities of the peak height of the signals due to the methyl protons at 2-position, which appeared at δ 0.85 (d) and 0.75 (d), respectively.

4.1.9. (2*R*,4*R*,5*S*)-2-(4-Methoxyphenyl)-5-methyl-4-phenyl[1,3]dioxane (17). After a suspension of **14b** (31 mg, 0.11 mmol) and MS 3A (40 mg) in CH_2Cl_2 (2 mL) was stirred at room temperature for 30 min under a nitrogen atmosphere, DDQ (20 mg, 0.12 mmol) was added to the mixture and stirred at the same temperature for further 1.5 h. The mixture was diluted with Et_2O, washed with saturated aqueous $NaHCO_3$, water, and brine, dried ($MgSO_4$) and concentrated. The purification of the residue by chromatography on silica gel (10% EtOAc in hexane) and recrystallization from EtOAc–hexane gave **17** (20 mg, 64%) with >99% purity determined by ^1H NMR as colorless crystals: mp 52–53 °C; $[\alpha]_D^{28}$ +51.7 (*c* 1.74, $CHCl_3$); IR (KBr) cm^{-1}: 1616, 1588, 1518, 1498; ^1H NMR (300 MHz, $CDCl_3$) δ: 0.96 (3H, d, *J*=6.9 Hz), 1.92 (1H, qtd, *J*=6.9, 2.6, 1.4 Hz, 5-H), 3.82 (3H, s), 4.12 (1H, dd, *J*=11.3, 1.4 Hz, 6-H_{eq}), 4.30 (1H, dd, *J*=11.3, 2.5 Hz, 6-H_{ax}), 5.14 (1H, d, *J*=2.7 Hz, 4-H), 5.67 (1H, s, 2-H), 6.93 (2H, d, *J*=8.8 Hz), 7.20–7.30 (1H, m), 7.30–7.4 (4H, m), 7.53 (2H, d, *J*=8.5 Hz), positive NOEs were observed between protons appearing at δ 1.92 and 4.30, δ 1.92 and 5.14, δ 4.30 and 5.14, δ 4.30 and 5.67, and δ 5.14 and 5.67; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 11.6, 34.3, 55.5, 73.5, 80.9, 102.0, 113.7 (2), 125.4 (2), 127.0, 127.6 (2), 128.2 (2), 131.5, 140.6, 160.0; Anal. Calcd for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09. Found: C, 76.15; H, 7.16; HRMS *m/z* calcd for $C_{18}H_{20}O_3$ (M^+) 284.1413, found 284.1403.

4.1.10. (*S*)-3-Hydroxy-2-methyl-1-phenylpropan-1-one (13a). A mixture of **13b** (77 mg, 0.272 mmol) and DDQ (65 mg, 0.285 mmol) in CH_2Cl_2–MeOH (10:1, 5 mL) was stirred at room temperature for 2 h. The mixture was diluted with CH_2Cl_2. The solution was washed with saturated aqueous $NaHCO_3$, water, and brine, dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel (20% EtOAc in hexane) to give **13a** (29 mg, 66%) as a colorless oil: $[\alpha]_D^{29}$ +45.2 (*c* 0.95, EtOH) {lit.[36] (*R*)-isomer: $[\alpha]_D^{24}$

−42.1 (*c* 0.28, EtOH)}; IR (neat) cm^{-1}: 3600–3200, 1678; ^1H NMR (270 MHz, $CDCl_3$) δ: 1.24 (3H, d, *J*=6.9 Hz), 2.41 (1H, br s), 3.68 (1H, quintet d, *J*=6.9, 4.3 Hz), 3.80 (1H, dd, *J*=11.2, 4.3 Hz), 3.94 (1H, dd, *J*=11.2, 6.9 Hz), 7.48 (2H, t, *J*=7.3 Hz), 7.58 (1H, t, *J*=7.3 Hz), 7.97 (2H, d, *J*=7.3 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ: 14.5, 42.9, 64.5, 128.4 (2), 128.7 (2), 133.3, 136.1, 204.4; HRMS *m*/*z* calcd for $C_{10}H_{12}O_2$ (M^+) 164.0837, found 164.0853.

4.1.11. (1*R*,2*S*)-2-Methyl-1-phenylpropane-1,3-diol (14a).

(i) From **13a**. A solution of $Zn(BH_4)_2$ in Et_2O (ca. 0.15 mol L^{-1}, 9.3 mL, 1.4 mmol) was added to a solution of **13a** (209 mg, 1.27 mmol) in Et_2O (12 mL) at 0 °C under a nitrogen atmosphere. The mixture was stirred at the same temperature for 30 min. The mixture was poured into 10% HCl, and extracted with EtOAc. The extract was washed with saturated aqueous $NaHCO_3$, water, and brine, dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel (50% EtOAc in hexane) to give **14a** (208 mg, 98%) as colorless crystals: mp 73–75 °C (EtOAc–hexane); $[\alpha]_D^{27}$ +56.1 (*c* 0.75, $CHCl_3$) {lit.[31] $[\alpha]_D^{20}$ +57.8 (*c* 0.45, $CHCl_3$), lit.[32] $[\alpha]_D^{20}$ +52.6 (*c* 0.57, $CHCl_3$)}; IR (KBr) cm^{-1}: 3600–3200, 1603, 1493, 1452. ^1H NMR (270 MHz, $CDCl_3$) δ: 0.82 (3H, d, *J*=7.3 Hz), 2.00–2.10 (1H, m), 2.87 (2H, s), 3.64 (2H, d, *J*=4.9 Hz), 4.92 (1H, d, *J*=4.0 Hz), 7.23–7.42 (5H, m); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ: 10.7, 41.3, 66.4, 76.5, 126.1 (2), 127.2, 128.1 (2), 142.6; Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 71.99; H, 8.40.
(ii) From **14b**. A mixture of **14b** (6 mg, 0.02 mmol) and DDQ (5 mg, 0.02 mmol) in CH_2Cl_2–MeOH (10:1, 1 mL) was stirred at room temperature for 2 h. The mixture was diluted with CH_2Cl_2. The solution was washed with saturated aqueous $NaHCO_3$, water, and brine, dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel (50% EtOAc in hexane) to give **14a** (6 mg, 61%), whose spectroscopic data were identical with those of the samples prepared from **13a**.

4.1.12. (2*R*,4*R*,5*S*)-2-(4-Methoxyphenyl)-5-methyl-4-phenyl[1,3]dioxane (17) from 14a. A mixture of **14a** (50 mg, 0.18 mmol), CSA (4 mg, 0.018 mmol), and *p*-anisaldehyde dimethyl acetal (39 mg, 0.21 mmol) in CH_2Cl_2 (2 mL) was stirred at room temperature for 12 h under a nitrogen atmosphere. The mixture was diluted with EtOAc. The solution was washed with saturated aqueous $NaHCO_3$, water, and brine, dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel (10% EtOAc in hexane) to give **17** (47 mg, 94%), whose melting point and spectroscopic data were identical with those of the samples prepared from **14b**.

4.1.13. (2*S*,3*R*)-3-(4-Methoxybenzyloxy)-2-methyl-3-phenylpropan-1-ol (18). A toluene solution of DIBAL-H (1 M, 0.11 mL, 0.11 mmol) was added to a solution of **17** (19 mg, 0.07 mmol) in CH_2Cl_2 (2 mL) at −80 °C under a nitrogen atmosphere and then stirred at the same temperature for 1 h. The reaction mixture was allowed to warm to 0 °C and acetone (1 mL), MeOH (1 mL), and saturated aqueous NH_4Cl (1 mL) were added to the mixture. The whole mixture was diluted with Et_2O and dried ($MgSO_4$). After filtration using Celite, the filtrate was concentrated. The residue was chromatographed on silica gel (20% EtOAc in hexane) to give **18** (16 mg, 84%) as a colorless oil: $[\alpha]_D^{29}$ +97.5 (*c* 1.44, $CHCl_3$); IR (neat) cm^{-1}: 3600–3200, 1613, 1586, 1514, 1249; ^1H NMR (300 MHz, $CDCl_3$) δ: 0.86 (3H, d, *J*=7.1 Hz), 2.00–2.10 (1H, m), 2.24 (1H, br), 3.47 (1H, dd, *J*=10.7, 4.4 Hz), 3.57 (1H, dd, *J*=10.7, 7.1 Hz), 3.81 (3H, s), 4.18 (1H, A of ABq, *J*=11.5 Hz), 4.47 (1H, B of ABq, *J*=11.5 Hz), 4.51 (1H, d, *J*=4.9 Hz), 6.88 (2H, d, *J*=8.8 Hz), 7.22 (2H, d, *J*=8.8 Hz), 7.30–7.39 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 11.8, 41.6, 55.3, 65.8, 70.4, 83.2, 113.8 (2), 127.3 (2), 127.5, 128.3 (2), 129.4 (2), 130.2, 139.8, 159.2; HRMS *m*/*z* calcd for $C_{18}H_{22}O_3$ (M^+) 286.1569, found 286.1544.

4.1.14. (2*R*,3*R*)-3-(4-Methoxybenzyloxy)-2-methyl-3-phenylpropan-1-al (19). A mixture of **18** (57 mg, 0.2 mmol) and Dess–Martin periodinane (127 mg, 0.30 mmol) in CH_2Cl_2 (3 mL) was stirred at room temperature for 30 min. The mixture was diluted with Et_2O, the whole was washed with saturated aqueous $Na_2S_2O_3$, saturated aqueous $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (10% EtOAc in hexane) to give **19** (48 mg, 85%) as a colorless oil: $[\alpha]_D^{29}$ +60.9 (*c* 1.40, $CHCl_3$); IR (neat) cm^{-1}: 1725, 1612, 1513, 1249; ^1H NMR (270 MHz, $CDCl_3$) δ: 1.08 (3H, d, *J*=6.9 Hz), 2.66 (1H, br quintet, *J*=6.5 Hz), 3.81 (3H, s), 4.21 (1H, A of ABq, *J*=11.5 Hz), 4.48 (1H, B of ABq, *J*=11.5 Hz), 4.77 (1H, d, *J*=4.9 Hz), 6.87 (2H, d, *J*=8.6 Hz), 7.19 (2H, d, *J*=8.6 Hz), 7.27–7.42 (5H, m), 9.66 (1H, s); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ: 8.6, 53.1, 55.3, 70.2, 79.7, 113.8 (2), 127.1, 127.9 (2), 128.6 (2), 129.4 (2), 130.0, 139.1, 159.3, 203.6; HRMS *m*/*z* calcd for $C_{18}H_{20}O_3$ (M^+) 284.1413, found 284.1411.

4.1.15. (2*R*,3*S*,4*R*)- and (2*S*,3*S*,4*R*)-4-(4-Methoxybenzyloxy)-3-methyl-4-phenylbutan-2-ol (20). An ether solution of MeLi (2 M, 0.13 mL, 0.26 mmol) was added to a solution of **19** (48 mg, 0.17 mmol) in Et_2O (2 mL) at −80 °C under a nitrogen atmosphere and stirred at the same temperature for 1 h. After the reaction was allowed to warm to 0 °C, the mixture was poured into saturated aqueous NH_4Cl and extracted with Et_2O. The extract was washed with brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (20% EtOAc in hexane) to give a 4:1 mixture of diastereomers of **20** (46 mg, 91%), which was used quickly in the next step. The diastereomeric mixture of **20** was obtained as a colorless oil: IR (neat) cm^{-1}: 3600–3300, 1613, 1514, 1250; ^1H NMR (300 MHz, $CDCl_3$) δ: 0.78 (3/5H, d, *J*=7.1 Hz), 0.87 (12/5H, d, *J*=7.1 Hz), 1.13 (12/5H, d, *J*=6.6 Hz), 1.14 (3/5H, d, *J*=6.6 Hz), 1.64 (4/5H, qdd, *J*=7.1, 3.8, 1.9 Hz), 1.81 (1/5H, quintet d, *J*=7.0, 3.6 Hz), 3.00 (4/5H, br s), 3.20 (1/5H, br s), 3.70 (1/5H, quintet, *J*=6.6 Hz), 3.81 (3H, s), 4.00 (4/5H, qd, *J*=6.6, 1.9 Hz), 4.20 (1/5H, A of ABq, *J*=11.3 Hz), 4.22 (4/5H, A of ABq, *J*=11.3 Hz), 4.49 (4/5H, B of ABq, *J*=11.3 Hz), 4.50 (1/5H, B of ABq, *J*=11.3 Hz), 4.61 (4/5H, d, *J*=3.8 Hz), 4.69 (1/5H, d, *J*=3.6 Hz), 6.88 (2H, d, *J*=8.6 Hz), 7.22 (2H, d, *J*=8.6 Hz), 7.27–7.42 (5H, m); HRMS *m*/*z* calcd for $C_{19}H_{24}O_3$ (M^+) 300.1726, found 300.1711.

4.1.16. (3*R*,4*R*)-4-(4-Methoxybenzyloxy)-3-methyl-4-phenylbutan-2-one (21). A mixture of **20** (46 mg,

0.15 mmol) and Dess–Martin periodinane (111 mg, 0.26 mmol) in CH_2Cl_2 (3 mL) was stirred at room temperature for 30 min. The mixture was diluted with Et_2O, the whole was washed with saturated aqueous $Na_2S_2O_3$, saturated aqueous $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (20% EtOAc in hexane) to give **21** (46 mg, quant) as a colorless oil: $[\alpha]_D^{29}$ +55.8 (*c* 1.06, $CHCl_3$); IR (neat) cm^{-1}: 1712, 1514, 1249; ^1H NMR (270 MHz, $CDCl_3$) δ: 1.18 (3H, d, *J*=6.6 Hz), 1.87 (3H, s), 2.89 (1H, quintet, *J*=6.9 Hz), 3.80 (3H, s), 4.16 (1H, A of ABq, *J*=11.2 Hz), 4.40 (1H, B of ABq, *J*=11.2 Hz), 4.53 (1H, d, *J*=7.3 Hz), 6.86 (2H, d, *J*=8.7 Hz), 7.19 (2H, d, *J*=8.7 Hz), 7.27–7.40 (5H, m); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ: 12.6, 30.0, 54.3, 55.2, 70.2, 81.4, 113.7 (2), 127.3 (2), 127.8, 128.4 (2), 129.4 (2), 130.2, 140.1, 159.2, 210.8; HRMS *m/z* calcd for $C_{19}H_{22}O_3$ (M^+) 298.1569, found 298.1570.

4.1.17. (3*R*,4*R*)-4-Hydroxy-3-methyl-4-phenylbutan-2-one (22). A mixture of **21** (112 mg, 0.40 mmol) and DDQ (95 mg, 0.42 mmol) in CH_2Cl_2–MeOH (10:1, 5 mL) was stirred at room temperature for 2 h. The mixture was diluted with CH_2Cl_2, washed with saturated aqueous $NaHCO_3$, water, and brine, dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel (20% EtOAc in hexane) to give **22** (54 mg, 83%) as a colorless oil: $[\alpha]_D^{27}$ +51.0 (*c* 0.95, $CHCl_3$); IR (neat) cm^{-1}: 3600–3300, 1703, 1453, 1357; ^1H NMR (270 MHz, $CDCl_3$) δ: 1.09 (3H, d, *J*=7.3 Hz), 2.15 (3H, s), 2.84 (1H, qd, *J*=7.3, 3.6 Hz), 3.05 (1H, s), 5.11 (1H, d, *J*=3.6 Hz), 7.26–7.35 (5H, m); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ: 10.1, 29.3, 53.1, 73.0, 125.9 (2), 127.4, 128.3 (2), 141.7, 213.5; HRMS *m/z* calcd for $C_{11}H_{14}O_2$ (M^+) 178.0994, found 178.0990.

4.1.18. (1*R*,2*S*,3*R*)-2-Methyl-1-phenylbutane-1,3-diol (6). A solution of $Zn(BH_4)_2$ in Et_2O (ca. 0.15 mol L^{-1}, 1.1 mL, 0.17 mmol) was added to a solution of **22** (24 mg, 0.13 mmol) in Et_2O (2 mL) at 0 °C under a nitrogen atmosphere. The mixture was stirred at the same temperature for 30 min. The mixture was poured into 10% HCl, and extracted with EtOAc. The extract was washed with saturated aqueous $NaHCO_3$, water, and brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (30% EtOAc in hexane) to give **6** (20 mg, 83%) as a colorless oil: $[\alpha]_D^{27}$ +35.4 (*c* 1.06, $CHCl_3$) {lit.[9] $[\alpha]_D^{24}$ +35.5 (*c* 0.46, $CHCl_3$), lit.[11] $[\alpha]_D^{18}$ +41.0 (*c* 1.05, $CHCl_3$)}; IR (neat) cm^{-1}: 3600–3200, 1451; ^1H NMR (500 MHz, $CDCl_3$) δ: 0.83 (3H, d, *J*=6.5 Hz), 1.23 (3H, d, *J*=6.5 Hz), 1.72 (1H, qt, *J*=7.3, 2.5 Hz), 4.24 (1H, qd, *J*=6.5, 2.0 Hz), 5.04 (1H, d, *J*=3.0 Hz), 7.26–7.35 (5H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 4.1, 21.6, 45.1, 72.1, 78.5, 125.6 (2), 127.0, 128.1 (2), 143.4; HRMS *m/z* calcd for $C_{11}H_{16}O_2$ (M^+) 180.1150, found 180.1137.

4.1.19. (1*R*,2*S*,3*R*)-1,3-Diacetoxy-2-methyl-1-phenylbutane. A mixture of **6** (46 mg, 0.254 mmol), pyridine (0.5 mL), Ac_2O (0.5 mL), and DMAP (1 mg) was stirred at room temperature for 30 min. The mixture was concentrated and the residue was chromatographed on silica gel (10% EtOAc in hexane) to give (1*R*,2*S*,3*R*)-1,3-diacetoxy-2-methyl-1-phenylbutane (58 mg, 86%) as a colorless oil: $[\alpha]_D^{28}$ +68.4 (*c* 1.52, $CHCl_3$); IR (neat) cm^{-1}: 1739, 1454, 1373, 1237, 1020; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.04 (3H, d, *J*=6.9 Hz), 1.20 (3H, d, *J*=6.3 Hz), 1.98 (3H, s), 2.09 (3H, s), 2.00–2.10 (1H, m), 4.67 (1H, qd, *J*=6.3, 4.1 Hz), 5.72 (1H, d, *J*=6.9 Hz), 7.20–7.35 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 10.2, 17.9, 21.3 (2), 43.6, 70.8, 76.9, 126.4 (2), 127.8, 128.3 (2), 139.2, 179.9, 170.1; HRMS *m/z* calcd for $C_{15}H_{20}O_4$ (M^+) 264.1362, found 264.1350.

4.1.20. (2*R*,3*S*,4*R*)-2,4-Diacetoxy-3-methylpentanoic acid (4). A mixture of (1*R*,2*S*,3*R*)-1,3-diacetoxy-2-methyl-1-phenylbutane (58 mg, 0.219 mmol), $RuCl_3 \cdot nH_2O$ (9 mg, 0.044 mmol), and periodic acid (998 mg, 4.38 mmol) in CCl_4–CH_3CN–H_2O (2:2:3, 2 mL) was vigorously stirred at room temperature for 18 h. 2-Propanol (2.4 mL) was added to the resultant mixture and the whole was stirred at the same temperature for further 30 min. The reaction was poured into water and extracted with CH_2Cl_2. The extract was washed with brine, dried ($MgSO_4$), and concentrated to give **4** (110 mg), which was used without purification: ^1H NMR (300 MHz, $CDCl_3$) δ: 1.08 (3H, d, *J*=7.3 Hz), 1.24 (3H, d, *J*=6.8 Hz), 2.05 (3H, s), 2.15 (3H, s), 2.21–2.32 (1H, m), 4.95–5.01 (1H, m), 5.15 (1H, d, *J*=3.5 Hz).

4.1.21. (*R*)-2-*tert*-Butoxycarbonylamino-2-methoxycarbonylpropyl (2*R*,3*S*,4*R*)-2,4-diacetoxy-3-methylpentanoate (23). DCC (20 mg, 0.09 mmol) was added to a solution of α-methylserine **5** (14 mg, 0.06 mmol), crude pentanoic acid **4** (17 mg, 0.073 mmol), and HOBt (13 mg, 0.096 mmol) in CH_2Cl_2 (0.7 mL) at room temperature. After the mixture was stirred for 30 min, DMAP (9 mg, 0.072 mmol) was added in one portion. After being stirred at room temperature for 1.5 h, the reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was chromatographed on silica gel (30% EtOAc in hexane) to give **23** (24 mg, 89%) as a colorless oil: $[\alpha]_D^{27}$ +22.5 (*c* 0.91, $CHCl_3$); IR (neat) cm^{-1}: 1743, 1719, 1507, 1455, 1371, 1240; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.00 (3H, d, *J*=6.9 Hz), 1.22 (3H, d, *J*=6.6 Hz), 1.43 (9H, s), 1.52 (3H, s), 2.05 (3H, s), 2.13 (3H, s), 2.21 (1H, quintet d, *J*=6.0, 3.8 Hz), 3.77 (3H, s), 4.43–4.64 (2H, m), 4.93 (1H, quintet, *J*=6.3 Hz), 5.07 (1H, d, *J*=3.8 Hz), 5.38 (1H, br s); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 10.6, 17.4, 20.6, 21.3, 28.3 (3), 39.5, 52.9, 58.7, 66.2, 71.1, 72.8, 153.9, 168.7, 170.1, 170.2, 172.3; HRMS *m/z* calcd for $C_{18}H_{30}NO_8$ ($M^+-OCOCH_3$) 388.1971, found 388.1965.

4.1.22. Methyl (*S*)-2-((2*R*,3*S*,4*R*)-2,4-diacetoxy-3-methylpentanoylamino)-3-hydroxy-2-methylpropanoate (25). Trifluoroacetic acid (0.12 mL) was added to a solution of **23** (56 mg, 0.125 mmol) in CH_2Cl_2 (1.2 mL) and the reaction mixture was stirred at room temperature for 4 h. The mixture was concentrated to give crude **24** (91 mg), which was dissolved in THF (2.5 mL). Saturated aqueous $NaHCO_3$ (2.5 mL) was added at 0 °C and the mixture was stirred at room temperature for 10 h. The resultant mixture was concentrated and the residue was chromatographed on silica gel (75% EtOAc in hexane) to give **25** (35 mg, 81% from **23**) as a colorless oil: $[\alpha]_D^{28}$ +32.1 (*c* 1.285, $CHCl_3$) {lit.[11] $[\alpha]_D^{21}$ +32.9 (*c* 0.35, $CHCl_3$)}; IR (neat) cm^{-1}: 3700–3200, 1739, 1523, 1452, 1375, 1243; ^1H NMR (270 MHz, $CDCl_3$) δ:1.02 (3H, d, *J*=7.1 Hz), 1.26 (3H, d, *J*=6.3 Hz), 1.55 (3H, s), 2.07 (3H, s), 2.18 (3H, s), 2.28 (1H, qt, *J*=7.1, 5.2 Hz), 3.28 (1H, br s), 3.80 (3H, s), 3.82 (1H, d,

J=11.8 Hz), 4.14 (1H, d, J=11.8 Hz), 4.94–5.06 (1H, m), 5.02 (1H, d, J=5.5 Hz), 7.14 (1H, s); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ: 9.8, 18.1, 19.7, 19.9, 21.3, 39.7, 53.1, 62.5, 65.4, 71.0, 75.2, 168.7, 170.3, 170.8, 173.3; HRMS m/z calcd for $C_{15}H_{26}NO_8$ (M^++H) 348.1658, found 348.1628.

4.1.23. (+)-Conagenin (1). Aqueous K_2CO_3 (1.0 M, 0.1 mL) was added to a solution of **25** (10 mg, 0.0287 mmol) in MeOH (0.3 mL) at 0 °C and the mixture was stirred at room temperature for 2 h. The reaction mixture was neutralized with aqueous $KHSO_4$ (1.0 M, 0.29 mL). The reaction mixture was concentrated and the residue was purified by ODS column chromatography (Cosmosil 75 C18-OPN, H_2O followed by 19:1 H_2O–MeCN as an eluent) to give **1** (5 mg, 71%) as colorless crystals: mp 154–157 °C (lit.[1] mp 159–161 °C, lit.[11] mp 153–155 °C); $[\alpha]_D^{28}$ +56.6 (c 0.2, MeOH) {lit.[1] $[\alpha]_D^{27}$ +55.4, lit.[11] $[\alpha]_D^{20}$ +56.8 (c 0.44, MeOH)}; IR (KBr) cm^{-1}: 3488, 3369, 3327, 3058, 1702, 1636, 1529, 1457, 1253; ^{1}H NMR (300 MHz, CD_3OD) δ: 0.94 (3H, d, J=7.1 Hz), 1.22 (3H, d, J=6.3 Hz), 1.52 (3H, s), 1.89 (1H, qdd, J=6.9, 5.5, 2.5 Hz), 3.82 (1H, d, J=11.0 Hz), 3.85 (1H, quintet, J=6.0 Hz), 4.01 (1H, d, J=11.0 Hz), 4.16 (1H, d, J=2.7 Hz), 8.05 (1H, s, exchanged with CD_3OD); ^{13}C NMR (75 MHz, CD_3OD) δ: 8.2, 19.9, 21.2, 43.7, 62.4, 66.0, 71.2, 75.3, 175.8, 176.1; FABHRMS m/z calcd for $C_{10}H_{20}NO_6$ (M^++H) 250.1291, found 250.1294.

4.1.24. (1*R*,2*S*)-1,3-Diacetoxy-2-methyl-1-phenylpropane. According to the procedure described for the preparation of (1*R*,2*S*,3*R*)-1,3-diacetoxy-2-methyl-1-phenylbutane, the tiltled compound (191 mg, 97%) was prepared from **14a** (131 mg, 0.79 mmol), pyridine (1.5 mL), Ac_2O (1.5 mL), and DMAP (3 mg) as a colorless oil: $[\alpha]_D^{27}$ +38.7 (c 1.50, $CHCl_3$); IR (neat) cm^{-1}: 1737, 1376; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.98 (3H, d, J=6.9 Hz), 2.04 (3H, s), 2.11 (3H, s), 2.29 (1H, septet, J=6.6 Hz), 3.79 (1H, dd, J=11.0, 5.8 Hz), 4.02 (1H, dd, J=11.0, 6.6 Hz), 5.79 (1H, d, J=6.0 Hz), 7.25–7.37 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 12.6, 21.1, 21.4, 38.6, 66.0, 76.2, 126.5 (2), 128.0, 128.5 (2), 139.0, 170.1, 171.0; HRMS m/z calcd for $C_{14}H_{18}O_4$ (M^+) 250.1205, found 250.1163.

4.1.25. (2*R*,3*S*,4*R*)-2,4-Diacetoxy-3-methylpentanoic acid (26). According to the procedure described for the preparation of **4**, crude **26** (146 mg) was prepared from (1*R*,2*S*)-1,3-diacetoxy-2-methyl-1-phenylpropane (97 mg, 0.39 mmol), $RuCl_3\cdot nH_2O$ (24 mg, 0.11 mmol), and periodic acid (1.77 g, 7.75 mmol) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.03 (3H, d, J=7.1 Hz), 2.07 (3H, s), 2.16 (3H, s), 2.51–2.54 (1H, m), 3.94–4.09 (2H, m), 5.21 (1H, d, J=3.0 Hz).

4.1.26. (*R*)-2-*tert*-Butoxycarbonylamino-2-methoxycarbonylpropyl (2*R*,3*S*)-2,4-diacetoxy-3-methylbutanoate (27). According to the procedure described for the preparation of **23**, **27** (81 mg, 57%) was prepared from **3** (76 mg, 0.32 mmol), crude **26** (85 mg, 39 mmol), DCC (108 mg, 0.52 mmol), HOBt (71 mg, 0.52 mmol), and DMAP (48 mg, 0.39 mmol) as a colorless oil, which was used without purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.96 (3H, d, J=7.1 Hz), 1.44 (9H, s), 1.53 (3H, s), 2.07 (3H, s), 2.14 (3H, s), 2.38–2.50 (1H, m), 3.77 (3H, s), 3.96 (1H, dd, J=11.0, 8.8 Hz), 4.02 (1H, dd, J=11.0, 6.0 Hz), 4.50–4.70 (3H, m), 5.12 (1H, d, J=3.3 Hz).

4.1.27. Methyl (*S*)-2-((2*R*,3*S*)-2,4-diacetoxy-3-methylbutanoylamino)-3-hydroxy-2-methylpropanoate (2). According to the procedure described for the preparation of **25**, **2** (21 mg, 34%) was prepared from **27** (81 mg, 0186 mmol), CF_3CO_2H (0.14 mL), and saturated aqueous $NaHCO_3$ (1.6 mL) as a colorless oil: $[\alpha]_D^{27}$ +34.6 (c=1.01, $CHCl_3$); IR (neat) cm^{-1}: 3600–3200, 1741, 1674, 1523, 1457, 1373, 1231; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.00 (3H, d, J=7.1 Hz), 1.56 (3H, s), 2.07 (3H, s), 2.21 (3H, s), 2.52 (1H, qd, J=6.9, 3.6 Hz), 3.18 (1H, br s), 3.81 (3H, s), 3.82 (1H, d, J=11.8 Hz), 4.00 (2H, d, J=7.1 Hz), 4.15 (1H, d, J=11.8 Hz), 5.21 (1H, d, J=3.6 Hz), 7.10 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 11.4, 19.9, 21.0, 21.1, 35.0, 53.4, 62.5, 65.0, 65.7, 73.9, 168.9, 170.2, 171.0, 173.5; HRMS m/z calcd for $C_{14}H_{23}NO_8$ (M^+) 333.1424, found 333.1470.

4.1.28. (*R*)-2-*tert*-Butoxycarbonylamino-2-methoxycarbonylethyl (2*R*,3*S*,4*R*)-2,4-diacetoxy-3-methylpentanoate (29). According to the procedure described for the preparation of **23**, **29** (145 mg, 80%) was prepared from *N*-Boc-L-serine methyl ester (**28**)[34] (92 mg, 0.42 mmol), crude **4** (117 mg, 0.5 mmol), DCC (139 mg, 0.67 mmol), HOBt (91 mg, 0.67 mmol), and DMAP (62 mg, 0.5 mmol) as a colorless oil, which was used without purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.01 (3H, d, J=7.1 Hz), 1.22 (3H, d, J=6.3 Hz), 1.46 (9H, s), 2.04 (3H, s), 2.14 (3H, s), 2.12–2.24 (1H, m), 3.77 (3H, s), 4.40 (1H, dd, J=11.3, 3.0 Hz), 4.53 (1H, dd, J=11.3, 3.3 Hz), 4.55–4.62 (1H, m), 4.92 (1H, quintet, J=6.0 Hz), 5.05 (1H, d, J=3.8 Hz), 5.38 (1H, br d, J=8.0 Hz).

4.1.29. Methyl (*S*)-2-((2*R*,3*S*,4*R*)-2,4-diacetoxy-3-methylpentanoylamino)-3-hydroxypropanoate (3). According to the procedure described for the preparation of **25**, **3** (82 mg, 72%) was prepared from **29** (145 mg, 0.33 mmol), CF_3CO_2H (0.25 mL), and saturated aqueous $NaHCO_3$ (4.3 mL) as a colorless oil: $[\alpha]_D^{27}$ +45.8 (c 1.42, $CHCl_3$); IR (neat) cm^{-1}: 3600–3200, 1741, 1672, 1532, 1440, 1375, 1241; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.04 (3H, d, J=7.1 Hz), 1.25 (3H, d, J=6.3 Hz), 2.07 (3H, s), 2.17 (3H, s), 2.26–2.40 (1H, m), 3.05 (1H, br s), 3.81 (3H, s), 3.84–4.05 (2H, m), 4.64 (1H, dt, J=6.9, 3.3 Hz), 4.90–5.00 (1H, m), 5.08 (1H, d, J=6.0 Hz), 6.88 (1H, d, J=7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 9.6, 18.1, 20.9, 21.4, 39.8, 52.9, 54.7, 62.7, 70.9, 75.1, 168.8, 170.1, 170.3, 171.0; HRMS m/z calcd for $C_{14}H_{24}NO_8$ (M^++H) 334.1502, found 334.1501.

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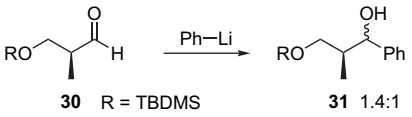
27. Indeed, addition of phenyl lithium to aldehyde **30**, which should be a suitable substrate for Felkin–Anh controlled nucleophilic attack leading to *syn* product, gave a non-stereoselective mixture of the corresponding alcohol **31** (Eq. 2).



30 R = TBDMS **31** 1.4:1 (2)

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