Tetrahedron: Asymmetry Vol. 2, No. 5, pp. 389-398, 1991
Printed in Great Britain

0957-4166/91 $3.00+.00
Pergamon Press plc

Asymmetric Conjugate Addition of Organometallic Reagents to Chiral α , β–Unsaturated Esters

Chenglin Fang, Tomoyuki Ogawa, Hiroshi Suemune, and Kiyoshi Sakai*

Faculty of Pharmaceutical Sciences, Kyushu University, Fukuoka 812, Japan

(*Received* 10 *April* 1991)

Abstract: Asymmetric conjugate addition to α,β-unsaturated ester was studied using four kinds of cyclic diols (**1c-4c**) as chiral auxiliaries. Among the tested substrates, (*R,R*)-cyclohexane-1,2-diol derivatives (**6a-c**) and (1*R*,2*S*)-2-hydroxymethylcyclopentanol derivative (**7a**) showed high and reverse diastereoselectivity in conjugate addition by organocuprates (R_2CuLi) and/or Grignard reagents in the presence of copper iodide (RMgBr + CuI), respectively.

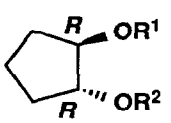
Introduction

Conjugate addition of organocopper reagents to *α,β*–unsaturated ketones or esters is a convenient procedure for carbon-carbon bond formation.[1] In particular, asymmetric conjugate addition to *α,β*–unsaturated carbonyl compounds is a valuable method for the synthesis of optically active *β*–substituted[2] or *α,β*–disubstituted carbonyl compounds.[3] Although there have been a number of reports on asymmetric conjugate addition, the development of powerful chiral auxiliaries is still an important and interesting subject of study for synthetic chemists.

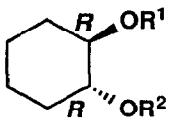
Recently, the potential of the chemo-enzymatic approach[4] in asymmetric synthesis has been demonstrated. Lipase-catalyzed hydrolysis of an ester or acetate is a convenient and useful method for the preparation of chiral building blocks and valuable auxiliaries.[5] The application of chiral cyclic alcohols obtained from *Pseudomonas fluorescens* lipase (PFL)-catalyzed enantioselective hydrolysis[6] to control the diastereoselective conjugate addition to their α,β-unsaturated esters is reported here.

Synthesis of Substrates

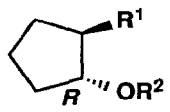
Four kinds of chiral cyclic diols (**1c-4c**)[6] were prepared by the chemo-enzymatic procedure as follows. PFL-catalyzed enantioselective hydrolyses of (*dl*)-*trans*-1,2-diacetoxy-cyclopentane ((*dl*)-**1a**) and -cyclohexane ((*dl*)-**2a**) gave the enantiomerically pure (1*R*,2*R*)-monoacetates (**1b**; 43%, **2b**; 42%, >99% e.e. each). Compounds **1b** and **2b** were converted to diols (**1c** and **2c**) by the usual solvolysis (K_2CO_3, MeOH) in quantitative yields. Similar kinetic resolution of ethyl (*dl*)-*trans* and/or *cis*-2-acetoxycyclopentanecarboxylate ((*dl*)-**3a** and -**4a**) using PFL afforded (1*R*,2*R*)-**3b** (31%, >99% e.e.) and (1*S*,2*R*)-**4b** (42%, >99% e.e.), respectively. Both chiral alcohols were converted to diols (**3c** and **4c**) by $LiAlH_4$ reduction. Substrates (**5**, **6a-c**, **7a** and **8a**) were obtained from the corresponding diols by the usual acylation with acid anhydride or acid chloride. Other substrates (**7b** and **8b**) acylated at the secondary hydroxy group were synthesized by a sequence of the following reactions in 32 and 35% overall yields, respectively: i) protection of the primary alcohol group in **3c** and **4c** as a *tert*-butyldiphenylsilyl ether; ii) acylation of secondary alcohol using crotonic anhydride; iii) deprotection of the *tert*-butyldiphenylsilyl ether.



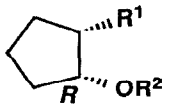
(*dl*)-1a: $R^1=R^2=Ac$
1b: $R^1=H$, $R^2=Ac$
1c: $R^1=R^2=H$



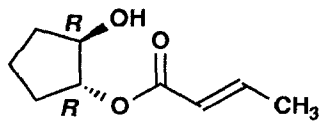
(*dl*)-2a: $R^1=R^2=Ac$
2b: $R^1=H$, $R^2=Ac$
2c: $R^1=R^2=H$



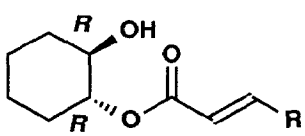
(*dl*)-3a: $R^1=COOEt$, $R^2=Ac$
3b: $R^1=COOEt$, $R^2=H$
3c: $R^1=CH_2OH$, $R^2=H$



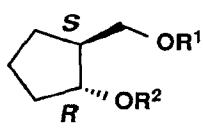
(*dl*)-4a: $R^1=COOEt$, $R^2=Ac$
4b: $R^1=COOEt$, $R^2=H$
4c: $R^1=CH_2OH$, $R^2=H$



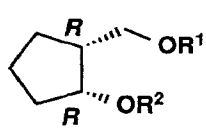
5



6a: R=CH_3
6b: R=Ph
6c: R=Et



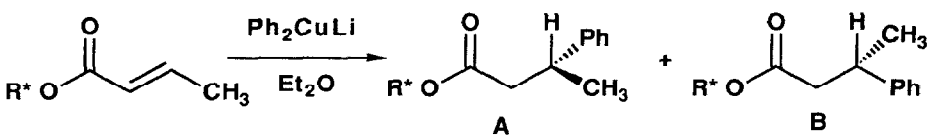
7a: R^1=crotonoyl, $R^2=H$
7b: $R^1=H$, R^2=crotonoyl



8a: R^1=crotonoyl, $R^2=H$
8b: $R^1=H$, R^2=crotonoyl

Conjugate addition of Ph_2CuLi to the homochiral crotonates (**5**, **6a**, **7a**,**b** and **8a**,**b**) was performed in ether under an Ar atmosphere. The results are summarized in Table 1.

Table 1



A B

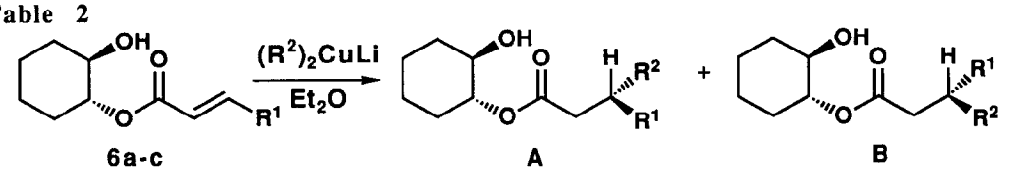
Entry	Substrate	Reac.Temp.(°C)	Product Yield (%)	Diast. Ratio (A:B)	Abs.Config.
1	**5**	-30	**9** (60)	64 : 36	*R*
2	**6a**	-30	**10** (66)	94 : 6	*R*
3	**7a**	-30	**11** (88)	8 : 92	*S*
4	**7b**	0*	**12** (87)	32 : 68	*S*
5	**8a**	-30	**13** (55)	67 : 33	*R*
6	**8b**	0*	**14** (23)	60 : 40	*R*

* Reaction of **7b** and **8b** did not take place at -30°C.

Among the substrates tested, compounds **6a** and **7a** afforded the best results in diastereomeric ratios of 94:6 (entry 2) and 8:92 (entry 3), respectively. Other substrates (**5**, **7b** and **8a,b**) resulted in low diastereomeric ratios of 40:60 to 33:67. The diastereomeric ratio was estimated by 270 MHz ^{1}H-NMR spectrum of 1,4-adducts. The absolute configuration of the newly generated asymmetric center of the 1,4-adducts (**9-14**) was determined by the sign of the specific rotation after conversion into 3-phenylbutyric acid.[7] In the cases of **5**, **6a** and **8a,b**, (*R*)-3-phenylbutyric acid was predominantly obtained, whereas the enantiomeric (*S*)-3-phenylbutyric acid was obtained in the cases of **7a,b**. These results could be understood through the concept that the approach of the reagent to the α,β-unsaturated carbonyl system of a substrate having a *zig-zag* conformation takes place from the site of the neighboring hydroxy group, however the case of **7b** was exceptional. Furthermore, it should be pointed out that from the absolute configuration of the newly generated chiral center in entry 2 and 3, attack of nucleophile to the α,β-unsaturated carbonyl system proceeded on the *re*-face of C3-sp2 carbon of **6a**, whereas it occurred on the *si*-face in the case of **7a**.

Chiral *trans*-cyclohexane-1,2-diol (**2c**) was found to be an effective auxiliary for conjugate addition. For studying the generality of this effect, conjugated addition of dialkyl (diaryl) copper lithium to **6a,b,c** was examined. The results are summarized in Table 2. In all cases, 1,4-adducts were obtained in good yields and high diastereoselectivity, and the products of type **A** were predominantly afforded. The diastereomeric ratio of **16** and **18** was determined by ^{1}H-NMR spectrum after conversion into (+)-α-methoxy-α-trifluoromethyl-phenylacetic acid esters (MTPA)[8] because of the difficulty of direct measurement. The absolute configuration and diastereomeric ratio of **15** were determined by the fact that $LiAlH_4$ reduction of **15** afforded (*S*)-(-)-3-methylpentanol[9] of 71% optical purity. Absolute configurations of **16** and **18** were assumed from comparison of ^{1}H-NMR spectra of the corresponding (+)-MTPA esters with that of **10**.

Table 2



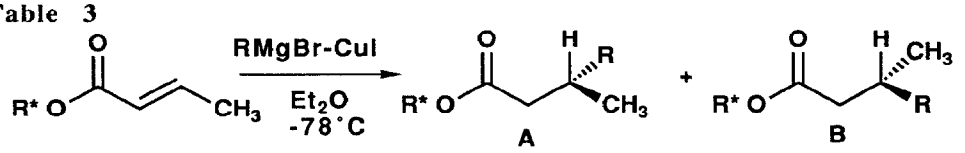
6a-c **A** **B**

Entry	Substrate	R^1	R^2	Product Yield(%)	Diast. Ratio (**A** : **B**)	Abs. Config.
1	**6a**	Me	Ph	**10** (66)	94 : 6	*R*
2	**6a**	Me	Bu	**15** (91)	86 : 14	*S*
3	**6b**	Ph	Bu	**16** (79)	91 : 9	*S*
4	**6b**	Ph	Me	**17** (71)	92 : 8	*S*
5	**6c**	Et	Ph	**18** (63)	86 : 14	*R*

Next, our attention was directed to the reactivity of other organometallic reagents for conjugated addition. After preliminary examination using $RCuBF_3$, RMgBr + CuI, and RLi, Grignard reagents in the presence of copper (I) iodide to **6a**, **7a**, **8a** and **8b** was selected for further study. The results shown in Table 3 suggest that the reagent of RMgBr + CuI was appropriate for the substrate **7a** to give high diastereoselectivity. The chemical yields in Table 3 were not satisfactory, but the diastereoselectivity of **7a** (entry 2,3 and 4) was as high as in the case of **6a,b,c** with R_2CuLi (Table 2). Reverse diastereoselectivity between **6a** and **7a** was also observed in

Table 3 similarly as in Table 1. The above findings show the high utility of the chiral diols (**2c** and **3c** (**7a** type)) as chiral auxiliaries.

Table 3



Entry	Substrate	R	Product Yield (%)	Diast. Ratio. (**A** : **B**)	Abs. Config.
1	**6a**	Ph	**10** (46)	78 : 22	*R*
2	**7a**	Ph	**11** (52)	7 : 93	*S*
3	**7a**	vinyl	**19** (42)	6 : 94	*S*
4	**7a**	Et	**20** (51)	11 : 89	*R*
5	**7b**	Ph	**12** (45)	49 : 51	-
6	**8a**	Ph	**13** (50)	52 : 48	-
7	**8b**	Ph	**14** (45)	53 : 47	-

In the two types of diastereoselective conjugate addition, that is, **6**-R_2CuLi and **7a**-RMgBr-CuI, the stereochemical course may be rationalized by assuming the transition states, Fig. 1 and 2, respectively. A free hydroxy group and an ester carbonyl of each substrate play an important role for the formation of a chelation complex with dialkylcuprate having a square-planar dimeric structure[1a,10] and/or with a mixed cuprate [RCuI]MgBr[11] formed by RMgBr and CuI. After formation of the copper(I)-alkene π-complex, a shift of R-substituent may occur from *re*-face in Fig. 1 and from *si*-face in Fig. 2 in a stereocontrolled manner. In Fig. 1 and 2, R-substituent might be located at a favorable position for conjugate addition to afford high diastereoselectivity in the contrast with other substrates (**5**, **7b** and **8a**,**b**).

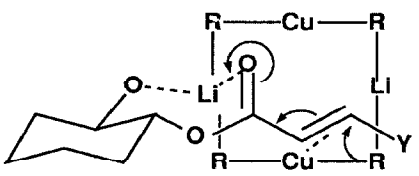


Figure 1

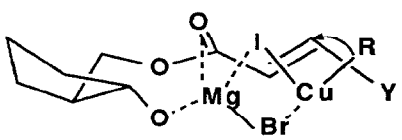


Figure 2

Experimental

IR spectra were measured with a JASCO A-202 spectrometer. ^{1}H-NMR and ^{13}C-NMR spectra were measured by a JEOL JNM-PX-100 or a JNM-GX 270 spectrometer using $CDCl_3$ as a solvent and tetramethylsilane (TMS) as an internal standard. Mass spectra were taken on a JEOL JMD-D-300 spectrometer. Optical rotation was measured on a JASCO DIP-360 polarimeter. Copper(I) bromide-dimethyl sulfide complex (Aldrich Chemical Company, Inc.) was purified according to ref. 12. Diethyl ether and tetrahydrofuran (THF) were dried and distilled from sodium-benzophenone ketyl under an Ar atmosphere prior to use. Each reaction was carried out under an Ar atmosphere. For column

chromatography, silica gel (Nakarai Tesque, Silica Gel 60, 230-400 mesh) was used. All organic solvent extracts were washed with brine and dried over anhydrous sodium sulfate.

***Pseudomonas fluorescens* lipase (PFL)-catalyzed enantioselective hydrolysis of (*dl*)-cyclic acetate** General procedure: *Pseudomonas fluorescens* lipase (Amano P) (5.0 g) was successively added to a stirred mixture of racemic substrate (10 g) in 0.1 M phosphate buffer (2 l, pH 7.0). After being stirred for 8 h at 30°C, the reaction mixture was extracted with ether (1 l x 2). The ether extract was washed and dried. The crude products were purified by column chromatography on silica gel. Enantiomeric excess of product was determined by ^{1}H-NMR after conversion into Mosher's ester.

(1*R*,2*R*)-1-Acetoxy-2-cyclopentanol (1b): A colorless oil, 43% yield, >99% ee. $[\alpha]_D^{25}$+29.3 (c=1.1, $CHCl_3$). IR (neat): 3400, 1720, 1445, 1220 cm^{-1}. ^{1}H NMR δ: 2.06 (3H, s, Ac), 3.17 (1H, br, OH), 4.09 (1H, m, 2-H), 4.80 (1H, m, 1-H). MS m/z: 144 (M^+), 101, 83.

(1*R*,2*R*)-1-Acetoxy-2-cyclohexanol (2b): A colorless oil, 42% yield, >99% ee. $[\alpha]_D^{24}$ -37.5 (c=1.1, $CHCl_3$). IR (neat): 3400, 1740, 1450, 1370, 1250 cm-1. ^{1}H NMR δ: 2.09 (3H, s, OAc), 3.55 (1H, m, 2-H), 4.57 (1H, m, 1-H).

Ethyl (1*R*,2*R*)-2-Hydroxycyclopentanecarboxylate (3b): A colorless oil, 31% yield, >99% ee. $[\alpha]_D^{21}$ -64.0 (c=1.2, MeOH). IR (neat): 3440, 1720, 1440, 1370, 1180 cm-1. ^{1}H-NMR δ: 1.26 (3H, t, J 7 Hz, $OCH_2\underline{CH_3}$), 2.65 (1H, m, 1-H), 4.14 (2H, q, J 7 Hz, $O\underline{CH_2}CH_3$), 4.36 (1H, m, 2-H). MS *m/z*: 158 (M^+), 140, 130.

Ethyl (1*S*,2*R*)-2-Hydroxycyclopentanecarboxylate (4b): A colorless oil, 42% yield, >99% ee. $[\alpha]_D^{19}$ -14.3 (c=1.05, $CHCl_3$). IR (neat): 3450, 1720, 1440, 1370, 1180 cm-1. ^{1}H NMR δ: 1.27 (3H, t, J 7 Hz, $OCH_2\underline{CH_3}$), 2.67 (1H, m, 1-H), 4.14 (2H, q, J 7 Hz, $O\underline{CH_2}CH_3$), 4.42 (1H, m, 2-H). MS *m/z*: 158 (M^+), 140, 130.

(*R*,*R*)-Cyclopentane-1,2-diol (1c) and (*R*,*R*)-cyclohexane-1,2-diol (2c) **1c** and **2c** were obtained by solvolysis in uaual manner (K_2CO_3-MeOH) from corresponding monoacetates (**1a** and **2a**) in quantitative yields. **1c**: A colorless oil, $[\alpha]_D^{20}$-15.0 (c=0.7, $CHCl_3$), IR (neat): 3350, 2950, 1070 cm^{-1}. ^{1}H NMR δ: 2.42 (2H, br, OHx2), 4.00 (2H, m, 1,2-H). **2c**: Colorless prisms, mp 110-111°C (AcOEt), $[\alpha]_D^{24}$ -36.5 (c=1.01, H_2O). IR (Nujol): 3350, 2960, 1075 cm^{-1}. ^{1}H-NMR δ: 2.40 (2H, br, OHx2), 3.38 (2H, m, 1,2-H).

(1*R*,2*S*)-2-Hydroxymethyl-1-cyclopentanol (3c) and its (1R,2R)-isomer (4c)

Compounds **3b** and **4b** were submitted to $LiAlH_4$ reduction in usual manner to afford **3c** and **4c** as a colorless oil in 80 and 85% yields, respectively. **3c**: $[\alpha]_D^{23}$ -13.7 (c=1.0, $CHCl_3$). IR (neat): 3440, 2950, 1060, 1020 cm^{-1}. ^{1}H NMR δ: 2.92 (2H, br, OHx2), 3.50 (1H, dd, J 10.5, 5.4 Hz, 2-CH), 3.73 (1H, dd, J 10.5, 8.1 Hz, 2-CH), 4.01(1H, m, 1-H). MS *m/z*: 98 (M^+-H_2O), 83, 80, 70, 54. High-MS for $C_6H_{10}O$ (M^+-H_2O): Calcd m/z 98.07316; Found 98.07257. **4c**: $[\alpha]_D^{22}$ -55.8 (c=1.0, $CHCl_3$). IR (neat): 3450, 2970, 1040, 1020 cm^{-1}. ^{1}H NMR: δ 2.81 (2H, br, OHx2), 3.76 (1H, dd, J 11.0, 7.1 Hz, 2-CH), 3.83 (1H, dd, J 11.0, 4.9 Hz, 2-CH), 4.38 (1H, m, 1-H). MS *m/z*: 98 (M^+-H_2O), 80, 70, 54. High-MS for $C_6H_{10}O$ (M^+-H_2O): Calcd *m/z* 98.07316; Found 98.07396.

Syntheses of substrates for conjugate addition General procedure for monocrotonates (**5, 6a, 7a, 8a**). To a solution of chiral diol (4 mmol) in CH_2Cl_2 (10 ml.) and dry pyridine (3 ml) was added crotonic anhydride (5.3 mmol) in the presence of the 4-dimethylaminopyridine (DMAP, 0.4 mmol). After being stirred overnight at room temperature, the reaction mixture was quenched with brine. The mixture was extracted with ethyl acetate (25 mlx3). After usual work-up, the crude product was purified by flash column chromatography (elution with hexane/EtOAc 5:1) to give monocrotonate as a colorless oil.

(1*R*,2*R*)-2-Hydroxycyclopentyl Crotonate (5): 46%, IR (neat): 3450, 2970, 1720, 1660, 1185 cm^{-1}. ^1H NMR δ: 1.90 (3H, dd, J 6.9, 1.7 Hz, 4-H), 4.09 (1H, m, 2'-H), 4.83 (1H, m, 1'-H), 5.84 (1H, dq, J 15.5, 1.7 Hz, 2-H), 7.0(1H, dq, J 15.5, 6.9Hz, 3-H). MS *m/z*: 170 (M^+), 152, 101, 69. High-MS for $C_9H_{14}O_3$ (M^+): Calcd *m/z* 170.02429; Found 170.02591.

(1*R*,2*R*)-2-Hydroxycyclohexyl Crotonate (6a): 56%, $[\alpha]_D^{20}$ -45.9 (c=1.05, $CHCl_3$). IR (neat): 3450, 2940, 1710, 1670, 1190 cm^{-1}. ^1H NMR: δ 1.90 (3H, dd, J 6.9, 1.7 Hz, 4-H), 3.59 (1H, m, 2'-H), 4.68 (1H, m, 1'-H), 5.87 (1H, dq, J 15.5, 1.7 Hz, 2-H), 7.01 (1H, dq, J 15.5, 6.9 Hz, 3-H). MS *m/z*: 184 (M^+), 166, 115, 98, 69. High-MS for $C_{10}H_{16}O_3$ (M^+): Calcd *m/z* 184.10994; Found 184.10874.

(1*R*,2*S*)-(1-Hydroxycyclopentan-2-yl)methyl Crotonate (7a): 58%, $[\alpha]_D^{22}$ -7.1 (c=1.01, $CHCl_3$). IR (neat): 3400, 2970, 1700, 1660, 1185 cm^{-1}. ^1H NMR: δ 1.89 (3H, dd, J 7.1, 1.7 Hz, 4-H), 4.04 (1H, dd, J 11.2, 6.8 Hz, 2'-CH), 4.13 (1H, m, 1'-H)), 4.20 (1H, dd, J 11.2, 5.8 Hz, 2'-CH), 5.85 (1H, dq, J 15.5, 1.7 Hz, 2-H), 7.03 (1H, dq, J 15.5, 7.1 Hz, 3-H). MS *m/z*: 166 (M^+-H_2O), 115, 98, 69. High-MS for $C_{10}H_{14}O_2$ (M^+-H_2O): Calcd *m/z* 166.09937; Found 166.09987.

(1*R*,2*R*)-(1-Hydroxycyclopentan-2-yl)methyl Crotonate (8a): 60%, $[\alpha]_D^{25}$+10.5 (c=1.15, $CHCl_3$). IR (neat): 3440, 2950, 1720, 1660, 1190 cm^{-1}. ^1H NMR: δ 1.89 (3H, dd, J 6.8, 1.7 Hz, 4-H), 4.07 (1H, dd, J 11.2, 4.9 Hz, 2'-CH), 4.12 (1H, m, 1'-H), 4.47 (1H, dd, J 11.2, 8.3 Hz, 2'-CH), 5.86 (1H, dq, J 15.6, 1.7 Hz, 2-H), 7.02 (1H, dq, J 15.6, 6.8 Hz, 3-H). MS *m/z*: 184 (M^+), 166, 153, 113. High-MS for $C_{10}H_{16}O_3$ (M^+): Calcd *m/z* 184.10994; Found 184.10902.

Compounds **6b** and **6c** were synthesized by similar monoesterification of **2c** with cinnamoyl chloride or *trans*-2-pentenoyl chloride, respectively.

(1*R*,2*R*)-2-Hydroxycyclohexyl (*E*)-Cinnamate (6b): 65%, $[\alpha]_D^{23}$ -38.4 (c=2.15, $CHCl_3$). IR (neat): 3450, 3060, 3040 1700, 1635, 1170 cm^{-1}. ^1H NMR: δ 3.15(1H, br, OH), 3.65 (1H, m, 2'-H), 4.73 (1H, m, 1'-H), 6.46 (1H, d, J 16.1 Hz, olefinic H), 7.41(5H, m), 7.71(1H, d, J 16.1 Hz, olefinic H)). MS *m/z*: 246 (M^+), 228, 183, 131, 98. High-MS for $C_{15}H_{16}O_3$ (M^+): Calcd *m/z* 246.12558; Found 246.12649.

(1*R*,2*R*)-2-Hydroxycyclohexyl (*E*)-2-Pentenoate (6c): 60%, $[\alpha]_D^{22}$ -26.4 (c=1.4, $CHCl_3$). IR (neat): 3450, 1710, 1655, 1185 cm^{-1}. ^1H NMR: δ 1.26 (3H, t, J 7.1 Hz, 5-H), 2.30 (2H, m, 4-H), 3.57 (1H, m, 2'-H), 4.61 (1H, m, 1'-H), 5.83 (1H, dt, J 15.7, 1.7 Hz, 2-H), 7.06 (1H, dt, J 15.7, 6.4 Hz, 3-H). MS *m/z*: 198 (M^+), 180, 151, 115, 83. High-MS for $C_{11}H_{18}O_3$ (M^+): Calcd *m/z* 198.12558; Found 198.12397.

Substrates **7b** and **8b** were synthesized from **3c** and **4c** by a sequence of reactions as silylation with t-$BuPh_2SiCl$, esterification with crotonic anhydride, and deprotection of silyl group with Bu_4NF in 32 and 35% over all yields, respectively.

(1*R*,2*S*)-2-Hydroxymethylcyclopentyl Crotonate (7b): A colorless oil, $[\alpha]_D^{24}$+36.2 (c=1.12, $CHCl_3$). IR (neat): 3450, 2960, 1720, 1660, 1185cm^{-1}. ^{1}H NMR: δ 1.88 (3H, dd, J 6.8, 1.7 Hz, 4-H), 3.54 (2H, m, 2'-CH2), 4.99 (1H, m, 1'-H), 5.82 (1H, dq, J 15.4, 1.7 Hz, 2-H), 6.99 (1H, dq, J 15.4, 6.8 Hz, 3-H). MS *m/z*: 184 (M^+), 166, 115, 98, 69. High-MS for $C_{10}H_{16}O_3$ (M^+): Calcd *m/z* 184.10994; Found 184.10932.

(1*R*,2*R*)-2-Hydroxymethylcyclopentyl Crotonate (8b): A colorless oil, $[\alpha]_D^{24}$ -3.75 (c=0.97, $CHCl_3$). IR(neat): 3490, 2850, 1720, 1660, 1180cm^{-1}. ^{1}H NMR: δ 1.90 (3H, dd, J 6.8, 1.7 Hz, 4-H), 2.75 (1H, br, OH), 3.25 (1H, dd, J 11.8, 9.0 Hz, 2'-CH), 3.60 (1H, dd, J 11.8, 5.1 Hz, 2'-CH), 5.33 (1H, m, 1'-H), 5.86 (1H, dq, J 15.6, 1.7 Hz, 2-H), 7.01 (1H, dq, J 15.6, 6.8 Hz, 3-H). MS *m/z*: 184 (M^+), 166, 153, 113, 69. High-MS for $C_{10}H_{16}O_3$ (M^+): Calcd *m/z* 184.10994; Found 184.10823.

General procedure for conjugate addition with organocuprate: Ph_2CuLi was prepared by addition of phenyl lithium (2.0 M in cyclohexane/diethyl ether, 4 mmol) to a suspention of CuBr-Me_2S (2 mmol) in Et_2O (10 ml) at 0°C and subsequent stirring for 10 min. Bu_2CuLi and Me_2CuLi were prepared in a similar manner using butyl lithium (1.6 M in hexane) and methyl lithium (1.11 M in ether) at -50°C and -25°C, respectively.

An substrate (0.4mmol) in Et_2O (1 ml) was added to a solution of R_2CuLi (2 mmol) at -30°C. After being stirred for 30 min, the reaction mixture was quenched with saturated aqueous NH_4Cl (10ml), and diluted with Et_2O (20ml). After stirred until the solid had been digested and aqueous layer turned deep blue, the etheral layer was separated, and aqueous layer was extracted with Et_2O (20mlx2). The combined solution was washed with brine, and then dried. After removal of solvent *in vacuo*, an oily residue was purified by flash column chromatograpgy on silica gel (15g.). The fraction eluted with 20% hexane/EtOAc(v/v) afforded 1, 4-adduct as a colorless oil.

(1'*R*,2'*R*,3*R*)-2'-Hydroxycyclopentyl 3-Phenylbutanoate (9) : 60% yield, 28% d.e. at C3, IR(neat): 3450, 3040, 1730, 1600, 1495, 1170 cm^{-1}. ^{1}H NMR for major isomer: δ 1.30 (3H, d, J 7.3 Hz, 4-H), 2.85 (2H, m, 2-H), 3.37 (1H, m, 3-H), 3.50 (1H, m, 2'-H), 4,44 (1H, m, 1'-H), 7.26 (5H, m, aromatic H); For minor isomer: δ 1.29 (d, J 6.9 Hz, 4-H). MS *m/z*: 248 (M^+), 164, 147, 119, 105, 84.

(1'*R*,2'*R*,3*R*)-2'-Hydroxycyclohexyl 3-Phenylbutanoate (10) : 66% yield, 88% d.e. at C3, $[\alpha]_D^{27}$ -60.2 (c=2.11, $CHCl_3$). IR (neat): 3450, 3035, 1730, 1600, 1495, 1165, 750, 695 cm^{-1}. ^{1}H NMR for major isomer: δ 1.32 (3H, d, J 6.9 Hz, 4-H), 2.58 (1H, dd, J 14.2, 7.5 Hz, 2-H), 2.64 (1H, dd, J 14.2, 8.1 Hz, 2-H), 3.27 (1H, m, 3-H), 3.36 (1H, m, 2'-H), 4.54 (1H, m, 1'-H), 7.29 (5H, m, aromatic H); For minor isomer: δ 1.30 (d, J 6.9 Hz, 4-H). ^{13}C NMR: δ 22.3 (q), 23.7 (t), 23.9 (t), 29.9 (t), 32.5 (t), 37.3 (d), 43.5 (t), 72.5 (d), 78.2 (d), 126.7 (d), 126.8 (dx2), 128.6 (dx2), 145.4 (s), 172.5 (s). MS m/z: 262 (M^+), 164, 118, 105, 98. High-MS for $C_{16}H_{22}O_3$ (M^+): Calcd *m/z* 262.15688; Found 262.15534. (+)-MTPA ester of **10** δ 3.42, 3.51 (total 3H, in ratio of 15 to 1, s, OMe)

(1'*R*,2'*S*,3*S*)-(1'-Hydroxycyclopentan-2'-yl)methyl 3-Phenylbutanoate (11) 88% yield, 84% d.e. at C3. $[\alpha]_D^{22}$ +1.97 (c=1.03, $CHCl_3$).IR (neat): 3420, 1730, 1600, 1500, 1185, 760, 700 cm^{-1}. ^1H NMR: δ 1.31(3H, d, J 7.3 Hz, 4-H), 2.57 (1H, dd, J 14.5, 7.3 Hz, 2-H), 2.65 (1H, dd, J 14.5, 6.9 Hz, 2-H), 3.26 (1H, m, 3-H), 3.78 (1H, m, 1'-H), 3.90 (1H, dd, J 10.9, 7.3 Hz, 2-CH), 4.06 (1H, dd, J 10.9, 6.6 Hz, 2-CH), 7.26 (5H, m); For minor isomer: δ 1.30 (d, J 7.3 Hz, 4-H). MS *m/z*: 262 (M^+), 244, 164, 118, 105, 80. High-MS for $C_{16}H_{22}O_3$ (M^+): Calcd *m/z* 262.15688; Found 262.15712.

(1'*R*,2'*S*,3*S*)-2'-Hydroxymethylcyclopentyl 3-Phenylbutanoate (12): 87% yield, 36% d.e. at C3. IR (neat): 3430, 3070, 1730, 1185, 760cm^{-1}. ^1H NMR for major isomer: δ 1.30 (3H, d, J 6.9 Hz, 4-H), 2.55 (1H, dd, J 14.8, 7.9Hz, 2-H), 2.62(1H, dd, J 14.8, 7.6Hz, 2-H), 3.26 (1H, m, 3-H), 3.44 (2H, m, 2'-CH_2), 4.84 (1H, m, 1'-H), 7.25 (5H, m, aromatic H); For minor isomer: δ 1.31 (d, J 6.9 Hz, 4-H). MS *m/z*: 262 (M^+), 244, 164, 118, 105, 98.

(1'*R*,2'*R*,3*R*)-(1'-Hydroxycyclopentan-2'-yl)methyl 3-Phenylbutanoate (13) 55% yield, 34% d.e. at C3. IR (neat): 3450, 1720, 1600, 1500, 1180, 760 cm^{-1}. ^1H NMR for major isomer: δ 1.31 (3H, d, J 7.3Hz, 4-H), 2.27 (1H, br, OH), 2.58 (1H, dd, J 14.9, 7.6 Hz, 2-H), 2.65 (1H, dd, J 14.9, 7.9 Hz, 2-H), 3.28 (1H, m, 3-H), 3.74 (1H, m, 1'-H), 3.94 (1H, dd, J 11.2, 4.9 Hz, 2'-CH), 4.31 (1H, dd, J 11.2, 9.9 Hz, 2'-CH), 7.26 (5H, m); For minor isomer: δ 1.30 (d, J 6.9 Hz, 4-H). MS *m/z*: 262 (M^+), 244, 164, 118, 105.

(1'*R*,2'*R*,3*R*)-2'-Hydroxymethylcyclopentyl 3-Phenylbutanoate (14): 23% yield, 20% d.e. at C3. IR (neat): 3450, 1730, 1600, 1495, 1185, 760 cm^{-1}. ^1H NMR for major isomer: δ 1.31(3H, d, J 7.3 Hz, 4-H), 2.30 (1H, br, OH), 2.61 (1H, dd, J 14.8, 8.9 Hz, 2-H), 2.67(1H, dd, J 14.8, 8.2 Hz, 2-H), 3.11 (1H, m, 3-H), 3.32 (2H, m, 2'-CH_2), 5.18 (1H, m, 1'-H), 7.26(5H, m); For minor isomer: δ 1.30 (d, J 6.9 Hz, 4-H). MS *m/z*: 262(M^+), 244, 164, 118, 105.

(1'*R*,2'*R*,3*S*)-2'-Hydroxycyclohexyl 3-Methylheptanoate (15): 91% yield, 72% d.e. at C3. IR (neat): 3480, 2980 1735, 1460, 1180 cm^{-1}. ^1H NMR: δ 0.89 (3H, t, J 6.3 Hz, 7-H), 0.94 (3H, d, J 6.6 Hz, 3-Me), 2.15 (1H, dd, J 14.4, 8.0 Hz, 2-H), 2.32 (1H, dd, J 14.4, 6.1Hz, 2-H), 3.55 (1H, m, 2'-H), 4.60 (1H, m, 1'-H). ^{13}H NMR: δ 14.1 (q), 19.7 (q), 22.8 (t), 23.8 (t), 23.9 (t), 29.1 (t), 30.1 (t), 30,5 (d), 33.1 (t), 36.4 (t), 42.2 (t), 72.9 (d), 78.0 (d), 170.7 (s). MS *m/z*: 242 (M^+), 224, 158, 127, 98, 57.

(1'*R*,2'*R*,3*S*)-2'-Hydroxycyclohexyl 3-Phenylheptanoate (16): 79% yield, 82% d.e. at C3. $[\alpha]_D^{22}$ -27.3 (c=2.0, $CHCl_3$). IR(neat): 3450, 3045, 1720, 1595, 1490, 1160, 750, 690 cm^{-1}. ^1H NMR: δ 0.83 (3H, t, J 6.9 Hz, 7-H), 2.64 (1H, dd, J 15.2, 9.3 Hz, 2-H), 2.70 (1H, dd, J 15.2, 6.3 Hz, 2-H), 3.08 (1H, m), 3.40 (1H, m, 2'-H), 4.42 (1H, m, 1'-H), 7.28 (5H, m). ^{13}C NMR: δ 13.9 (q), 22.6 (t), 23.7 (t), 23.8 (t), 29.5 (t), 29.7 (t), 32.6 (t), 36.3 (t), 41.8(t), 42.2 (d), 72.4(d), 78.1(d), 126.5 (d), 127.3 (dx2), 128.5 (dx2), 144.2 (s), 172.4(s). MS *m/z*: 304 (M^+), 206, 146, 98, 91. (+)-MTPA ester of **16** δ 3.42, 3.51 (total 3H, in ratio of 1 to 10.1, s, OMe).

(1'*R*,2'*R*,3*S*)-2'-Hydroxycyclohexyl 3-Phenylbutanoate (17=(3*S*)-10): 71% yield, 84% d.e. at C3. IR (neat): 3450, 3030, 1730, 1600, 1495, 1170, 760, 700cm^{-1}. ^1H NMR for major isomer: δ 1.30 (3H, d, J 6.9 Hz, 4-H), 2.62 (1H, dd, J 15.2, 7.6 Hz, 2-H), 2.69 (1H, dd, J 15.2, 7.9 Hz, 2-H), 3.27 (1H, m, 3-H), 3.43 (1H, m, 2'-H), 4.48 (1H, m, 1'-H), 7.29 (5H, m). ^{13}C NMR: δ 22.2 (q), 23.7 (t), 23.8 (t), 29.8(t), 32.7 (t), 36.6(d), 42.9 (t), 72.5 (d), 78.2 (d), 126.5 (d), 126.8 (dx2),

128.6 (dx2), 145.6 (s), 172.3 (s). MS *m/z*: 262 (M^+), 164, 118, 105, 98. See compound **10** for minor isomer. (+)-MTPA ester of **17** δ 3.42, 3.51 (total 3H, in ratio of 1 to 11, s, OMe).

(1'*R*,2'*R*,3*R*)-2'-Hydroxycyclohexyl 3-Phenylpentanoate (18): 63% yield, 72% d.e. at C3. IR (neat): 3450, 3030, 1730, 1600, 1500, 1170, 755, 700 cm^{-1}. ^{1}H-NMR: δ 0.80 (3H, t, J 7.3Hz, 5-H), 2.57 (1H, dd, J 13.9, 9.9 Hz, 2-H), 2.68(1H, dd, J 13.9, 5.9 Hz, 2-H), 2.98 (1H, m, 3-H), 3.31 (1H, m, 2'-H), 4.40 (1H, m, 1'-H), 7.30 (5H, m). ^{13}C NMR: δ 11.9 (q), 23.7 (t), 23.8 (t), 29.6 (t), 29.8 (t), 32.4 (t), 41.9 (t), 44.7 (d), 72.3 (d), 78.1 (d), 127.6 (d), 127.7 (dx2), 128.5 (dx2), 143.9 (s), 172.6 (s). MS *m/z*: 276 (M^+), 178, 132, 107, 119, 98, 91. (+)-MTPA ester of **18** δ 3.42, 3.51 (total 3H, in ratio of 1 to 5.3, s, OMe).

General procedure for conjugate addition with Grignard reagent

A solution of Grignard reagent (6.66 mmol) was added to a suspention of substrate (1.11 mmol) and CuI (1.27 g, 6.66 mmol) in dry ether (20 ml) at -78°C under an Ar atmosphere. The whole was stirred for 4 h at the same temperature. The reaction mixture was quenched with phosphate buffer (pH=7, 20 ml) at -30°C. The resulting insoluble materials were filtered off through Celite, and washed with ether. The organic layer was separated and aqueous layer was extracted with ether. The combined ether solution was dried and removed *in vacuo* to leave an oily residue, which was subjected to silica gel column chromatography to afford 1,4-adduct as a colorless oil.

(1'*R*,2'*S*,3*S*)-(1'-Hydroxycyclopentan-2'-yl)methyl 3-Methyl-4-pentenoate (19): 42% yield, 88% d.e. at C3. IR (neat): 3450, 1735, 1665, 1195 cm^{-1}. ^{1}H NMR for major isomer: δ 1.07 (3H, d, J 6.9 Hz, 3-Me), 2.29 (1H, dd, J 14.9, 7.3 Hz, 2-H), 2.38 (1H, dd, J 14.9, 7.2 Hz, 2-H), 2.68 (1H, m, 3-H), 3.99 (2H, m, 1'-H and 2'-CH), 4.13 (1H, dd, J 11.2, 5.9 Hz, 2'-CH), 4.97 (1H, ddd, J 9.2, 1.3, 1.3 Hz, 5-H), 5.06 (1H, ddd, J 17.2, 1.7, 1.3 Hz, 5-H), 5.79 (1H, ddd, J 17.2, 9.2, 6.9 Hz, 4-H); For minor isomer: δ 1.06 (d, J 6.6 Hz, 3-Me). MS *m/z*: 212 (M^+), 194, 114, 98, 80, 69.

(1'*R*,2'*S*,3*S*)-(1'-Hydroxycyclopentan-2'-yl)methyl 3-Methylpentanoate (20): 51% yield, 78% d.e. at C3. IR (neat): 3450, 2980, 1730, 1190cm^{-1}. ^{1}H NMR for major isomer: δ 0.89 (3H, t, J 7.1 Hz, 5-H), 0.94 (3H, d, J 6.9 Hz, 3-Me), 2.12 (1H, dd, J 14.5, 7.9 Hz, 2-H), 2.32 (1H, dd, J 14.5, 6.3 Hz, 2-H), 3.98 (1H, m, 1'-H), 4.02 (1H, dd, J 11.2, 7.3 Hz, 2'-CH), 4.14 (1H, dd, J 11.2, 6.3 Hz, 2'-CH); For minor isomer: δ 0.93 (d, J 7.3 Hz, 5-H). MS *m/z*: 215 (M^++1), 196, 158, 140, 116, 115, 98, 80.

Hydrolysis of 1,4-adducts: A typical example; A solution of **17** (75mg, 0.29mmol) and KOH (24mg, 0.43mmol) in EtOH (3ml) was refluxed for 4 h. After cooled to room temperature, 10% aqueous HCl (0.4ml) was added. The resulting precipitate was filtered off and the filtrate was concentrated under reduced pressure to leave an oily residue, which was purified by preparative TLC (n-hexane/EtOAc 1:1(v/v)) to afford (*S*)-3-phenylbutyric acid (*S*)-**21** (28mg, 59%), $[\alpha]_D^{26}$ +37.4 (c=2.5, benzene). IR (neat): 3350, 1705, 1600, 1495, 760, 700cm-1. ^{1}H NMR: δ 1.32 (3H, d, J 6.9 Hz, 4-H), 2.55 (1H, dd, J 15.5, 8.3 Hz, 2-H), 2.66 (1H, dd, J 15.5, 6.8 Hz, 2-H), 3.25 (1H, m, 3-H), 7.23 (5H, m). MS *m/z*: 164 (M^+), 118, 105, 77. In a similar manner, hydrolysis of **10** (Table 1) afforded (*R*)-**21**, ($[\alpha]_D^{23}$ -41.5 (c=0.9, benzene)) (lit. 7; for (*R*)-**21**, $[\alpha]_D$ -47.9 (benzene)).

$LiAlH_4$ reduction of 15: To a suspention of lithium aluminium hydride (33mg, 1mmol) in dry THF (3ml) was added a THF (1ml) solution of **15** (69mg) at 0°C. After being stirred for 2 h at room temperature, 5 drops of 10% aqueous HCl was added at 0°C, and dried over Na_2SO_4. The removal of solvent afforded the residue, which was subjected to preparative TCL (n-hexane/ EtOAc 1:1(v/v)) to afford the (*S*)-3-methyl-1-heptanol (33mg, 50%). $[\alpha]_D^{26}$ -2.18 (c=1.1, CH_2Cl_2) (lit. 9; $[\alpha]_D$ -3.07 (neat)). IR (neat): 3350, 2960, 1460, 1380, 1060cm^{-1}. ^{1}H NMR: δ 0.89 (3H, d, J 6.6Hz, overlapping 3H, distorted t, J 6.6Hz, two methyls), 1.38 (1H, m), 1.57 (2H, m), 3.67 (2H, m). MS *m/z*: 112 (M^+-H_2O), 84, 70, 55.[2b)]

References

1) (a) C. Ullenius and B. Christeson, *Pure & Appl.Chem.*, **60**, 57(1988); (b) R.J.K.Taylor, *Synthesis*, **1985**, 364; (c) R. S. Wilheim and J. A. Kozlowski, *Tetrahedron*, **40**, 5005 (1984).

2) (a) K. Tomioka and K. Koga, in " Asymmetric Synthesis" Vol 2, Ed. J.D.Morroson, Academic Press, **1983**, P.219. (b) P. Somfai, D. Tanner and T. Alsson, *Tetrahedron*, **41**, 5973 (1985); (c) S. Cardani, G. Poli, C. Scolastico, R. Villa, *Tetrahedron*, **44**, 5929 (1988). (d) A. Bermardi, S. Cardani, T. Pilati, G. Poli, C. Scolastico and R. Villa, *J. Org. Chem.*, **53**. 1600 (1988).

3) W. Oppolzer, A. J. Kingma and G. Poli, *Tetrahedron*, **45**, 479 (1989).

4) J. B. Jones, " Asymmetric Synthesis, Vol 5, Chiral Catalysts ", **1985**, P.309.

5) Y-F. Wang, C-S. Chen, G. Girdaukas and C. J. Sih, " Enzyme in Organic Synthesis ", **1985**, P.128, in Giba, Foundation Symposium **III**.

6) (a) Z-F. Xie, H. Suemune and K. Sakai, *J. Chem. Soc., Chem. Commun.*,**1987**, 838. (b) Z-F. Xie, I. Nakamura, H. Suemune and K. Sakai, *ibid*, **1988**, 966.

7) P. A. Levene and R. E. Marker, *J. Biol. Chem.*, **93**, 761 (1931).

8) J. A. Dale, H. S. Mosher, *J. Am. Chem. Soc.*, **95**, 512 (1973).

9) P. A. Levene and A. Rothen, *J. Org. Chem.*, **1**, 76 (1936).

10) S.H. Berts and R. A. J. Smith, *J. Am. Chem. Soc.*, **111**, 8276 (1989).

11) H. O. House, C-Y. Chu, J. M. Wilkins and M. J. Umen, *J. Org. Chem.*, **40**, 1460 (1975).