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Stereoselective catalytic hydrogenation and conjugate reduction of 4-methyl itaconate derivatives bearing chiral auxiliary

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Abstract—The catalytic hydrogenation of 4-methyl itaconate derivatives bearing chiral auxiliary and their conjugate reduction with *n*-Bu_3SnH in the presence of Lewis acid were examined to reveal their diastereoselectivity. The homogeneous catalytic hydrogenation of 4-methyl itaconyl (1*S*)-(-)-2,10-camphorsultam with the Crabtree's catalyst $[Ir(COD)(PCy_3)(py)]PF_6$ in CH_2Cl_2-MeOH (2:1 v/v) gave less polar (1*S*,2'*S*)-diastereomer in 84% yield, while the conjugate reduction of the α-methylene amide with *n*-Bu_3SnH (2 equiv) using MgI_2 (7 equiv) as an additive in CH_2Cl_2 gave more polar (1*S*,2'*R*)-diastereomer in 70% yield.

Keywords: Itaconyl camphorsultam, Crabtree's catalyst, Conjugate reduction, Tributyltin hydride, Lewis acid, Solvent effect

1. Introduction

The 1,5-dimethylalkyl motif is ubiquitous in many natural products such as several insect pheromones, vitamins E and K_1, and membrane lipids of archaebacteria.[1] C5 Chiral unit **A** bearing two different functional groups, such as X=CH_2OH,[2] CO_2H,[3] or CONRR',[4-6] Y=CO_2Me (Fig.1) is a versatile intermediate for the synthesis of these natural products. Enantio- and diastereoselective syntheses of C5 chiral unit **A** have been investigated extensively. Asymmetric hydrogenation of 4-methyl itaconate (**1**) using chiral rhodium catalyst is an efficient and direct method to obtain C5 chiral unit **A**.[3] Base-mediated alkylations of *N*-propanoyl oxazolidinones derived from L-valinol or (1*S*,2*R*)-(+) norephedrine,[4] and *N*-propanoyl camphorsultam[5] using alkyl bromoacetate

as electrophile is highly diastetreoselective. Regio- and stereocontrolled conjugate radical addition to fumarate bearing chiral auxiliary is also an efficient method providing chiral C5 unit **A**.[6]

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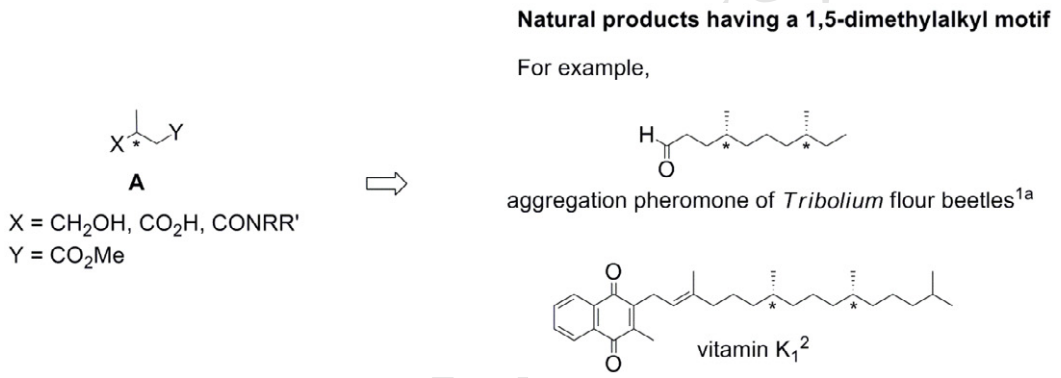
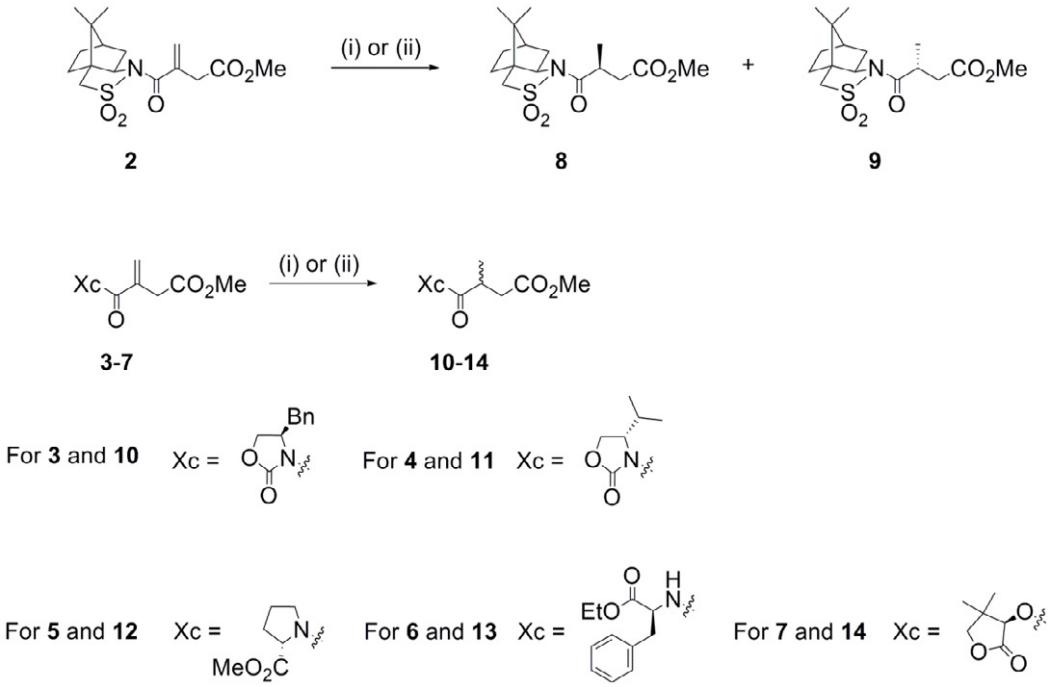


Fig.1.

In our previous work we reported the diastereoselective heterogeneous catalytic hydrogenation of α,β-unsaturated esters in the presence of $MgBr_2$[7] and the diastereoselective conjugate reduction of α,β-unsaturated esters and amides using *n*-Bu_3SnH and Lewis acid $MgBr_2{\cdot}OEt_2$,[8] both with high diastereoselectivity, i.e., 1,3-stereoinduction controlled by the seven-membered chelate formation.

We now report the catalytic hydrogenation of 4-methyl itaconate derivatives bearing chiral auxiliary **2-7** by the use of Pd/C or the Crabtree's catalyst, (1,5-cyclooctadiene)(pyridine)(tricyclohexylphosphine)iridium(I) hexafluorophosphate, and the conjugate reduction of **2**, **3**, **5** and **6** with *n*-Bu_3SnH in the presence of Lewis acid (Scheme 1). The products **8-14** of these diastereoselective reactions will be versatile intermediate **A** (X = CONRR', CO_2R, Y = CO_2Me) for the synthesis of the natural products bearing 1,5-dimethylalkyl motif.

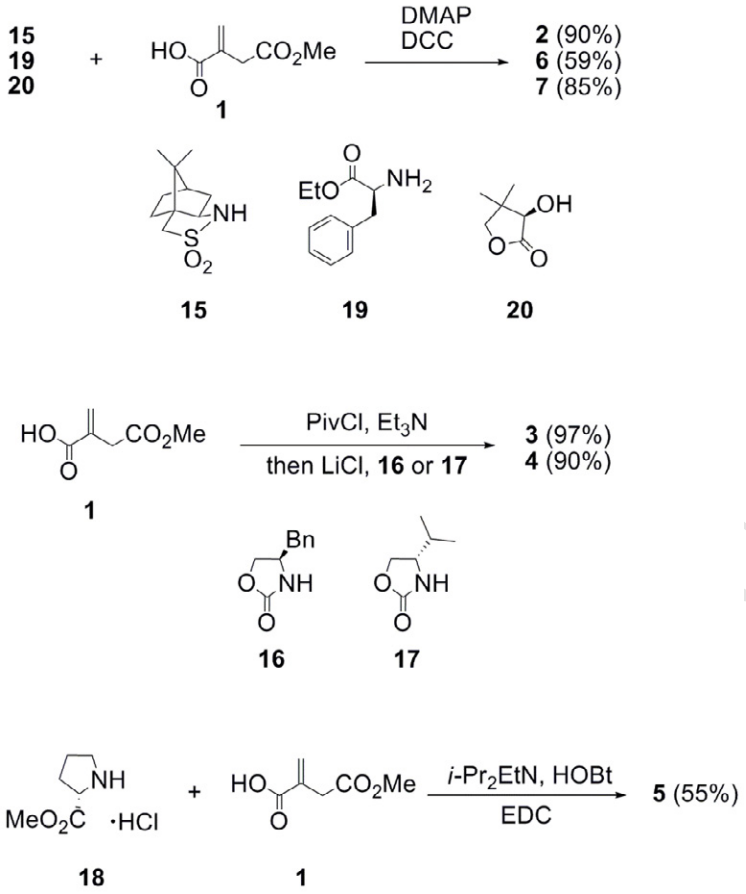


Scheme 1. (i) Catalytic hydrogenation. (ii) Conjugate reduction with *n*-Bu_3SnH in the presence of Lewis acid.

2. Results and discussion

2.1 Catalytic hydrogenation of compounds 2-7

Compounds **2-7** were prepared from 4-methyl itaconate (**1**) using chiral auxiliaries, (*S*)-(-)-2,10-camphorsultam (**15**), (*R*)-4-benzyl-2-oxazolidinone (**16**), (*S*)-4-isopropyl-2-oxazolidinone (**17**), L-proline methyl ester hydrochloride (**18**), L-phenylalanine ethyl ester (**19**) and pantolactone (racemic) (**20**), respectively (Scheme 2).[9]



Scheme 2. Preparation of substrates **2**-**7** and their yields.

We first performed the catalytic hydrogenation of camphorsultam derivative **2** (Table 1).[7,10] The catalytic hydrogenation of **2** on Pd/C (10%) in THF at room temperature gave a mixture of diastereomers **8** and **9** in a ratio of 2.7:1 in high yield (entry 1). The diastereomer ratio was ameliorated by lowering the reaction temperature to -20 ^{o}C (entry 2), but the reaction did not proceed in the presence of $MgBr_2 \cdot OEt_2$ as an additive.[7] The hydrogenation using the Crabtree's catalyst, $[Ir(COD)(PCy_3)(py)]PF_6$, in CH_2Cl_2 at room temperature showed a similar diastereoselectivity (entry 3) and at -20 ^{o}C increased the selectivity (entry 4). The diastereomer ratio depended significantly on solvent. The hydrogenation with the homogeneous catalyst in THF gave **8** and **9** in a ratio of 8.7:1, but in poor yield (entry 5). Activation of the reaction of **2** in THF by adding I_2 (2 equiv) or KI (2equiv) was attempted,[11] but the reaction did not proceed at all. In a mixed-solvent of CH_2Cl_2-THF (2:1 v/v) the homogeneous hydrogenation proceeded in high yield and with good diastereoselectivity (entry 6). A higher

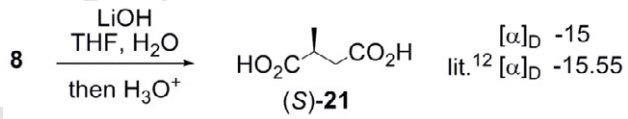
diastereoselectivity (**8**/**9** = 6.4:1) was achieved by using CH_2Cl_2-MeOH (2:1 v/v) as solvent (entry 7). The reaction using [Ir(1,5-cyclooctadiene)$(PMePh_2)_2$]PF_6 was attempted, but did not proceed.

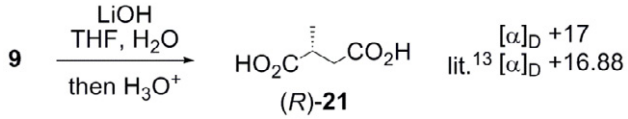
Table 1
Diastereoselective catalytic hydrogenation of sulfonamide **2**

Entry	Catalyst (mol%)	Solvent	Temp (^oC)	Yield (%)	Diastereomer ratio[a] **8** : **9**
1	Pd/C (30)	THF	rt	96	2.7 : 1
2		THF	-20	97	3.6 : 1
3	Crabree's (10)[b]	CH_2Cl_2	rt	80	3.5 : 1
4	(20)	CH_2Cl_2	-20	quant	5.6 : 1
5	(10)	THF	rt	36	8.7 : 1
6	(5)	CH_2Cl_2-THF (2:1)	rt	99	5.2 : 1
7	(5.8)	CH_2Cl_2-MeOH (2:1)	rt	97	6.4 : 1

[a] Diastereomer ratio was determined by ^{1}H NMR integration of C*H*Me.
[b] [Ir(COD)(PCy_3)(py)]PF_6.

The stereochemistry of **8** and **9** was determined as follows. The diastereomers were separated using silica gel column chromatography and their respective hydrolysis with lithium hydroxide, followed by acidification, afforded (*S*)-methylsuccnic acid (*S*)-**21** {$[\alpha]_D^{23}$ -15 (*c* 0.50, EtOH); lit.[12] $[\alpha]_D^{25}$ -15.55 (*c* 2.16, EtOH)} and (*R*)-methylsuccnic acid (*R*)-**21** {$[\alpha]_D^{25}$ +17 (*c* 0.47, EtOH); lit.[13] $[\alpha]_D^{20}$ +16.88 (*c* 2.16, EtOH)} (Scheme 3).





Scheme 3. Determination of the absolute configuration of **8** and **9**.

Subsequently, we examined the diastereoselective hydrogenation of **3**-**7** (Table 2). The catalytic hydrogenation of **3** and **5** using the Crabtree's catalyst $[Ir(COD)(PCy_3)(py)]PF_6$ in CH_2Cl_2 gave **10** and **12**, respectively, but in poor yields and with low diastereoselectivities. The hydrogenation of **3**-**7** on Pd/C without Lewis acid showed poor diastereoselectivities. We therefore examined the reaction using various catalysts (Pd/C, Pt/C, PtO_2), Lewis acids ($MgBr_2$, $MgBr_2{\cdot}OEt_2$, $Yb(OTf)_3$), solvents, and temperatures.[7] The catalytic hydrogenation of oxazolidinones **3** and **4** on Pd/C in the presence of $MgBr_2$ (3 equiv) gave diastereomeric mixtures **10** (88% yield; dr 3.8:1) and **11** (96% yield; dr 4.0:1), respectively (entries 1 and 2). The reaction of amides **5** and **6** on Pd/C in the presence of $MgBr_2$ (1.5 equiv) gave diastereomeric mixtures **12** (97% yield; dr 3.8:1) and **13** (quantitative yield; dr 2.8:1), respectively (entries 3 and 4). The hydrogenation of ester **7** on Pd/C in the presence of $MgBr_2{\cdot}OEt_2$ (1.5 equiv) gave **14** (81% yield) (entry 5) with a lower diastereoselectivity (dr 1.8:1) compared to those of **10**-**13**. Thus the addition of $MgBr_2$ increased the diastereoselectivity in the hydrogenation of **3**-**6** on Pd/C, although the diastereoselectivity in the hydrogenation of ester **7** was not affected. However, the reactions of **3**-**6** were inferior in diastereoselectivity compared to that of **2** using the Crabtree's catalyst (Table 1, entry 7), and furthermore, it was difficult to separate the diastereomers **10**, **12**, **13** and **14** using silica gel column chromatography except for oxazolidinone **11**. The stereochemistry of the hydrogenation products **10**-**14** was not assigned. Thus the combination of appropriate chiral auxiliary, camphorsultam, and the Crabtree's catalyst realized the preparation of a C5 chiral unit **8** with high diastereoselectivity and high yield.

Table 2

Diastereoselective catalytic hydrogenation of **3**-**7** on 10% Pd/C at room temperature[a]

Entry	Substrate	Additive (equiv)	Solvent	Yield (%)	Diastereomer ratio
1	**3**	$MgBr_2$ (3)	CH_2Cl_2	88	3.8 : 1
2	**4**	$MgBr_2$ (3)	CH_2Cl_2	96	4.0 : 1
3	**5**	$MgBr_2$ (1.5)	CH_2Cl_2	97	3.8 : 1
4	**6**	$MgBr_2$ (1.5)	CH_3CN	quant	2.8 : 1
5	**7**	$MgBr_2{\cdot}OEt_2$ (1.5)	THF	81	1.8 : 1

[a] 25 mol% Pd/C was used.

2.2 Conjugate reduction of compounds 2, 3, 5 and 6

We next carried out the conjugate reduction of **2, 3, 5** and **6** using *n*-Bu_3SnH (2 equiv) or (*n*-$C_8H_{17})_3SnH$ (2 equiv) in the presence of Lewis acid to reveal their diastereoselectivity. First, the conjugate reduction of sulfonamide **2** was performed (Table 3). As reported before,[8] the reduction did not achieve without Lewis acid (entry 1). When the reduction was performed in the presence of $MgBr_2$ (3 equiv) and LiI (0.1 equiv) at 0 ^oC in CH_2Cl_2 under N_2 atmosphere, diastereomer **9** was yielded predominantly (entry 2). Entry 3 shows that the reduction using MgI_2 (3 equiv) as an additive gave a mixture of **8** and **9** quantitatively, but the diastereoselectivity was lower. The use of 7 equiv of MgI_2 as an additive gave **9** with higher diastereoselectivity and in high yield (entry 4).[14] When the reduction performed at -78 ^oC, both the yield and diastereoselectivity were lowered (entry 5). The conjugate reduction of **2** using (*n*-$C_8H_{17})_3SnH$ (2 equiv) and MgI_2 (7 equiv) at 0 ^oC showed lower selectivity (**8**/**9** = 1:2.4) (entry 6). Thus, as shown in entry 4, the reduction of **2** with *n*-Bu_3SnH in the presence of MgI_2 (7 equiv) gave compound **9** predominantly in contrast to the catalytic hydrogenation of **2** yielding compound **8** predominantly (Table 1, entry 7).

Table 3

Diastereoselective conjugate reduction of sulfonamide **2** with Bu_3SnH or $(n\text{-}C_8H_{17})_3SnH$ in CH_2Cl_2

Entry[a]	Lewis acid (equiv)	Temp (^oC)	Yield (%)	Diastereomer ratio[b] **8** : **9**
1	–	0	nr	–
2	$MgBr_2$ (3)[c]	0	76	1 : 3.1
3	MgI_2 (3)	0	quant	1 : 2.5
4	MgI_2 (7)	0	86	1 : 4.4
5	MgI_2 (7)	-78	43	1 : 3.2
6	MgI_2 (7)	0	62	1 : 2.4

[a] *n*-Bu_3SnH (2 equiv) was used for entries 1-5 and $(n\text{-}C_8H_{17})_3SnH$ (2 equiv) was used for entry 6. [b] Diastereomer ratio was determined by ^1H NMR integration of C*H*Me. [c] LiI (0.1 equiv) was added.

The conjugate reduction of **3** and **6** with *n*-Bu_3SnH in the presence of MgI_2 proceeded in high yield, but with poor diastereoselectivity (dr 1.6:1 for **10** and dr 1:1.6 for **13**). The conjugate reduction of amide **5** did not proceed even in the presence of Lewis acid.

We confirmed subsequently the chelate ring formation of **2** by the complexation experiment with MgI_2 in $CDCl_3$.[1a,8b,15] The large difference of chemical shift increments $\Delta\delta$ values [δ_H (substrate **2** + MgI_2) - δ_H (substrate **2**)] suggests the chelate ring formation, which lowered the LUMO energy of **2** and consequently accelerated the conjugate reduction (Fig. 2). The reactivity and the diastereoselectivity may be enhanced by the seven membered chelate ring formation through the coordination of Mg^{2+} to the amide carbonyl oxygen and ester carbonyl oxygen atoms as well as by the six membered chelate ring formation through the coordination of Mg^{2+} to the amide carbonyl oxygen and sulfone oxygen atoms.[15]

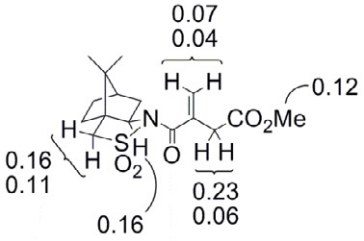


Fig. 2. Δδ values: Δδ (ppm) = [δ_H (substrate **2** + 3 equiv of MgI_2) - δ_H (substrate **2**)]. The δ_H (substrate **2** + 3 equiv of MgI_2) values were obtained after sonication of **2** with MgI_2 (7 equiv) in $CDCl_3$.

The origin of diastereoselectivity in the catalytic hydrogenation and the conjugate reduction of **2** can be rationalized as below (Fig.3).

(1) The catalytic hydrogenation of **2** proceeds probably through the conformation which minimizes the unfavorable dipole-dipole interaction by adopting *anti* (S-N-C=O) conformation and the steric repulsion by adopting twisted conformation close to *s-cis* (CH_2-C-C=O).[16] The attack of hydrogen atom to the prochiral α-carbon preferentially from the less hindered *Re*-face (opposite the sulfonamide oxygen) gives diastereomer **8**.

(2) In the conjugate reduction of **2** with *n*-Bu_3SnH in the presence of MgI_2, the formation of six and seven membered chelate rings was suggested by the complexation experiment mentioned above. The β-attack of hydride ion gives the (*Z*)-enolate intermediate.[8b] Subsequently, the protonation to the prochiral α-carbon occurs preferentially from the less hindered *Si*-face to give diastereomer **9**. In the catalytic hydrogenation of **3**-**5** (Table 2, entries 1-3) chelate ring formation plays an important role as well,[7] because of the poor diastereoselectivity in the hydrogenation without Lewis acid. The catalytic hydrogenation of oxazolidinone **22** on Pd/C in the presence of $MgBr_2$ gave **23** (73% yield, dr = 1:2.3) together with isomerized product **24** (7% yield) (Scheme 4). The lower diastereoselective hydrogenation of **23** lacking methoxycarbonyl group suggests the contribution of seven membered chelate ring to enhance the diastereoselectivity in the reaction of **3**.

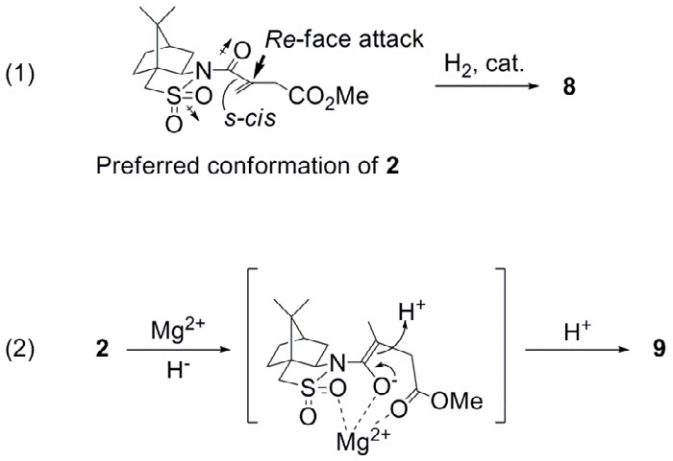
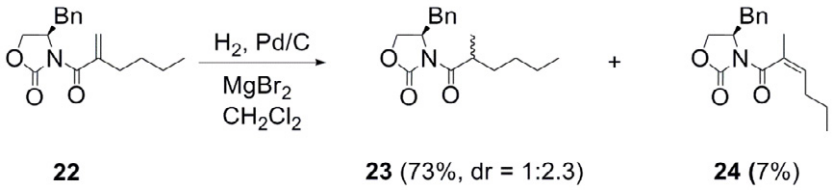


Fig. 3 Diastereoselective reaction pathways of **2**.



Scheme 4. Catalytic hydrogenation of **22**.

3. Conclusion

The homogeneous catalytic hydrogenation of 4-methyl itaconyl (1*S*)-(-)-2,10-camphorsultam (**2**) with the Crabtree's catalyst [Ir(COD)(PCy_3)(py)]PF_6 in CH_2Cl_2-MeOH (2:1 v/v) gave less polar (1*S*,2'*S*)-diastereomer **8** in 84% yield, while the conjugate reduction of the α-methylene amide **2** with *n*-Bu_3SnH (2 equiv) using MgI_2 (7 equiv) as an additive in CH_2Cl_2 gave more polar (1*S*,2'*R*)-diastereomer **9** in 70% yield. These complementary reactions will be efficient and direct methods to obtain C5 chiral units useful for the synthesis of natural products possessing 1,5-dimethylalkyl motif.

4. Experimental

4.1 General

Melting points were determined with Yanaco micro melting point apparatus. Optical rotations were measured on a JASCO P-2200 polarimeter. ^{1}H NMR spectra were recorded on a JEOL JNM-AL 400 (400 MHz) spectrometer or Bruker DRX600 (600 MHz) with $CDCl_3$ as a solvent and tetramethylsilane as an internal standard. ^{13}C NMR spectra were recorded on the instruments operating at 100 MHz or 150 MHz with $CDCl_3$ as a solvent and an internal standard (δ 77.0). Mass spectra (EI^+) were obtained on a JEOL JMS-700 mass spectrometer. Mass spectra (ESI) and high resolution mass spectra (ESI) were obtained on a JMS-T100TD (AccuTOF TLC) mass spectrometer. IR spectra were taken on a Perkin-Elmer 2000 spectrometer. For thin layer chromatography (TLC) analysis, Merck precoated plates (silica gel 60 F_{254}) were used. Visualization was accomplished by UV light and potassium permanganate or phosphomolybdic acid. Products were purified by column chromatography using Kanto silica gel 60 (spherical neutral).

4.2 Preparation of substrates 2-7 and 22.

4.2.1 Methyl 3-{(1*S*,5*R*,7*R*)-10,10-dimethyl-3,3-dioxo-3λ^6-thia-4-azatricyclo [5.2.1.0^{1,5}]decane-4-carbonyl)}but-3-enate (2)

To a stirred solution of 4-methyl itaconate (**1**) (864 mg, 6.0 mmol) in dry CH_2Cl_2 (23 ml) were added 4-(dimethylamino)pyridine (161 mg, 1.3 mmol) and (*S*)-(-)-2,10-camphorsultam (**15**) (431 mg, 2.0 mmol). The mixture was cooled to 0 ^{o}C and *N*,*N*'-dicyclohexylcarbodiimide (1.36 g, 6.6 mmol) was added. The mixture was stirred at 0 ^{o}C for 1 h under N_2 atmosphere. The solution was warmed to room temperature and further stirred overnight. The resulting precipitates of *N*,*N*'-dicyclohexylurea were filtered off and the filtrate was washed successively with 5% aqueous $NaHCO_3$, water, 1 N HCl, water and brine. The organic layer was dried over anhydrous Na_2SO_4 and evaporated in vacuo. The residue was purified by column chromatography on silica gel [SiO_2 51 g; hexane-EtOAc (5:1 then 3:1 v/v)] to afford amide **2** (612 mg, 90%) as a colorless solid. Mp 86.2 ^{o}C (from diethyl ether); $[\alpha]_D^{22}$ -82.9 (*c* 1.95, $CHCl_3$); IR (KBr) 3119, 1738, 1674, 1633, 1436, 1328, 1175, 1132, 1114, 1063, 979, 764 cm^{-1}; ^{1}H-NMR (600 MHz) δ 6.05 (1H, d, *J* = 1.0 Hz, =C*H*H), 5.88 (1H, d, *J* = 1.0 Hz, =CH*H*), 4.06 (1H, dd, *J* = 7.5, 4.9 Hz, NCH), 3.69 (3H, s, OMe), 3.52 (1H, d, *J* = 13.7 Hz, C*H*HSO$_2$), 3.47 (1H, d, *J* = 16.1 Hz, C*H*HCO$_2$Me), 3.45(1H, d, *J* =

13.7 Hz, CH*H*SO_2), 3.25 (1H, d, *J* = 16.1 Hz, CH*H*CO_2Me), 2.05-2.00 (2H, m, CH_2), 2.00-1.85 (3H, m, CH, CH_2), 1.49-1.29 (2H, m, CH_2), 1.22 (3H, s, Me), 1.00 (3H, s, Me); ^{13}C-NMR (100 MHz) δ 169.9, 169.0, 135.6, 127.7, 65.4, 53.2, 51.8, 47.8, 47.5, 44.9, 38.0, 32.9, 26.2, 20.9, 19.7; MS (EI^+) (*m*/*z*) 341 (M^+, 1%), 310 (15), 277 (16), 218 (19), 127 (100), 99 (72), 69 (32), 59 (25); HRMS calcd for $C_{16}H_{24}NO_5S$ (MH^+) 342.1375, found 342.1396.

4.2.2 Methyl 3-[(4*R*)-4-benzyl-2-oxooxazolidine-3-carbonyl]but-3-enoate (3)

To a solution of 4-methyl itaconate (**1**) (432 mg, 3.00 mmol) in dry THF (8 ml) at -25 ^{o}C under N_2 atmosphere was added triethylamine (800 µl, 5.78 mmol). Pivaloyl chloride (720 µl, 5.94 mmol) was added and the mixture was stirred for 2 h. The solution was warmed to -20 ^{o}C. Lithium chloride (218 mg, 5.18 mmol) and (*R*)-4-benzyl-2-oxazolidinone (**16**) (356 mg, 2.01 mmol) were added and the mixture was stirred for 1.5 h. 0.2 N HCl and water were added and the product was extracted with EtOAc. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine (twice). The organic layer was dried over anhydrous Na_2SO_4 and evaporated in vacuo. The residue was purified by silica gel column chromatography [SiO_2 30 g; hexane-EtOAc (3:1 v/v)] to afford **3** (594 mg, 97%) as an oil. $[\alpha]_D^{26}$ -46.9 (*c* 2.83, $CHCl_3$); IR (neat) 3063, 3029, 3003, 2954, 1784, 1733, 1682, 1640, 1584, 1495, 1354, 1331, 1210, 1109, 921, 796, 760, 705 cm^{-1}; ^{1}H-NMR (400 MHz) δ 7.36-7.22 (5H, m, Ph), 5.69 (1H, s, =C*H*H), 5.65 (1H, s, =CH*H*), 4.75 (1H, m, NCH), 4.26 (1H, t, *J* = 8.8 Hz, OC*H*H), 4.18 (1H, dd, *J* = 8.8, 4.8 Hz, OCH*H*), 3.70 (3H, s, OMe), 3.62 (1H, d, *J* = 16.8 Hz, C*H*HCO_2Me), 3.48 (1H, d, *J* = 16.8 Hz, CH*H*CO_2Me), 3.44 (1H, dd, *J* = 13.2, 3.2 Hz, C*H*HPh), 2.80 (1H, dd, *J* = 13.2, 9.8 Hz, CH*H*Ph); ^{13}C-NMR (100 MHz) δ 170.3, 168.9, 152.6, 136.0, 135.0, 129.1, 128.5, 126.9, 124.2, 66.2, 55.1, 51.7, 38.5, 37.1; MS (ESI^+) (*m*/*z*) 304 (MH^+); HRMS calcd for $C_{16}H_{18}NO_5$ (MH^+) 304.1185, found 304.1178.

4.2.3 Methyl 3-[(4*S*)-4-isopropyl-2-oxooxazolidine-3-carbonyl]but-3-enoate (4)

To a solution of 4-methyl itaconate (**1**) (432 mg, 3.0 mmol) in dry THF (8 ml) was added triethylamine (800 µl, 5.8 mmol) at -25 ^{o}C under N_2 atmosphere. Pivaloyl chloride (720 µl, 5.9 mmol) was added and the mixture was stirred for 2 h. The solution was warmed to -20 ^{o}C. Lithium chloride (219 mg, 5.2 mmol) and (*S*)-4-isopropyl-2-oxazolidinone (**17**) (260 mg, 2.0 mmol) were added and the mixture was stirred for 1.5 h. Treatment of the reaction mixture as described for the preparation of **3** and subsequent silica gel column chromatography [SiO_2 30 g; hexane-EtOAc (2:1

then 1:1 v/v)] gave **4** (452 mg, 90%) as an oil. $[\alpha]_D^{26}$ +53.5 (*c* 2.98, $CHCl_3$); IR (neat) 2965, 1781, 1735, 1685, 1636, 1330, 1302, 1202, 1016, 927, 796 cm^{-1}; ^{1}H-NMR (400 MHz) δ 5.67 (1H, s, =C*H*H), 5.63 (1H, s, =CH*H*), 4.56 (1H, dt, *J* = 8.8, 4.4 Hz, NCH), 4.34 (1H, t, *J* = 8.8 Hz, OC*H*H), 4.23 (1H, dd, *J* = 8.8, 4.3 Hz, OCH*H*), 3.68 (3H, s, OMe), 3.62 (1H, d, *J* = 16.8 Hz, C*H*HCO_2Me), 3.42 (1H, d, *J* = 16.8 Hz, CH*H*CO_2Me), 2.42 (1H, m, C*H*Me_2), 0.93 (6H, t, *J* = 6.7 Hz, Me×2); ^{13}C-NMR (100 MHz) δ 170.0, 168.7, 152.9, 136.1, 123.5, 63.1, 57.9, 51.5, 38.3, 27.9, 17.3, 14.3; MS (ESI^+) (*m*/*z*) 256 (MH^+); HRMS calcd for $C_{12}H_{18}NO_5$ (MH^+) 256.1185, found 256.1191.

4.2.4 Methyl (2*S*)-1-(2-Methoxycarbonylmethylpropenoyl)pyrrolidine-2-carboxylate (5)

To a stirred solution of L-proline methyl ester hydrochloride (**18**) (166 mg, 1.00 mmol) in dry CH_2Cl_2 (3 ml) at 0 °C were added diisopropylethylamine (180 μl), 1-hydroxybenzotriazole hydrate (34.1 mg, 0.25 mmol) and 4-methyl itaconate (**1**) (132 mg, 0.92 mmol). 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide (192 mg, 1.00 mmol) was added and the mixture was stirred at room temperature under N_2 atmosphere overnight. 3 N HCl was added and the organic layer was washed successively with saturated aqueous $NaHCO_3$ and brine. The organic layer was dried over anhydrous Na_2SO_4 and evaporated in vacuo. The residue was purified by silica gel column chromatography [SiO_2 5 g; hexane-EtOAc (7:1 to 1:1 v/v)] to afford **5** (128 mg, 55%; rotational isomers ratio 4.2:1) as an oil. $[\alpha]_D^{23}$ -37 (*c* 0.38, $CHCl_3$); IR (neat) 3091, 1741, 1653, 1620, 1441, 1199, 1174, 1016, 949, 797 cm^{-1}; ^{1}H-NMR (600 MHz) *major rotational isomer*: δ 5.51 (1H, s, =C*H*H), 5.49 (1H, s, =CH*H*), 4.54 (1H, t, *J* = 7.3 Hz, NCH), 3.88 (1H, m, NC*H*H), 3.71 (1H, m, NCH*H*), 3.73 (3H, s, CO_2Me), 3.68 (3H, s, CO_2Me), 3.60 (1H, d, *J* = 17.1 Hz, C*H*HCO_2Me), 3.27 (1H, d, *J* = 17.1 Hz, CH*H*CO_2Me), 2.30 (1H, m, C*H*H), 2.08-1.89 (3H, m, CH*H*, CH_2); *minor rotational isomer*: δ 5.31 (1H, s, =C*H*H), 5.23 (1H, s, =CH*H*), 4.86 (1H, d, *J* = 8.2 Hz, CH), 3.74 (1H, m, NC*H*H), 3.68 (1H, m, NCH*H*), 3.73 (3H, s, CO_2Me), 3.68 (3H, s, CO_2Me), 3.57 (1H, d, *J* = 17.1 Hz, C*H*HCO_2Me), 3.14 (1H, d, *J* = 17.1 Hz, CH*H*CO_2Me), 2.25-2.17 (1H, m, CH), 2.11 (1H, m, CH), 2.08-1.89 (2H, m, CH_2); ^{13}C-NMR (100 MHz) *major rotational isomer*: δ 172.3, 171.0, 168.8, 137.5, 120.0, 58.6, 51.9, 51.7, 49.5, 38.8, 29.3, 25.2; *minor rotational isomer*: δ173.1, 170.7, 169.6, 138.3, 118.6, 61.3, 52.1, 51.7, 45.8, 39.0, 30.9, 22.4; MS (EI^+) (*m*/*z*) 255 (M^+, 10%), 224 (16), 196 (49), 127 (100), 99 (29), 70 (65), 69 (21), 59 (14); HRMS calcd for $C_{12}H_{18}NO_5$ (MH^+) 256.1185, found 256.1188.

4.2.5 Methyl 3-{[(1*S*)-1-ethoxycarbonyl-2-phenylethyl]carbamoyl}but-3-enoate (6)

To a solution of L-phenylalanine (331 mg, 2.00 mmol) in dry ethanol (6 ml) was added thionyl chloride (300 μl). The reaction mixture was stirred at 100 ^{o}C overnight under N_2 atmosphere. The solution was evaporated in vacuo. The residue was dissolved in ethanol and the solution was evaporated in vacuo again. The residue was dissolved in 10% aqueous NaOH. The product was extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4 and evaporated in vacuo. The residue afforded L-phenylalanine ethyl ester (**19**) (289 mg, 75%) as an oil. ^{1}H-NMR (400 MHz) δ 7.33-7.19 (5H, m, Ph), 4.17 (2H, q, *J* = 7.2 Hz, C*H*$_2$Me), 3.71 (1H, dd, *J* = 7.8, 5.4 Hz, CH), 3.09 (1H, dd, *J* = 13.5, 5.4 Hz, C*H*HPh), 2.87 (1H, dd, *J* = 13.5, 7.8 Hz, CH*H*Ph), 1.49 (2H, brs, NH_2), 1.24 (3H, t, *J* = 7.2 Hz, Me).

To a stirred solution of 4-methyl itaconate (**1**) (211 mg, 1.46 mmol) in dry CH_2Cl_2 (2 ml) were added 4-(dimethylamino)pyridine (16.2 mg, 0.133 mmol) and L-phenylalanine ethyl ester (**19**) (257 mg, 1.33 mmol). The mixture was cooled to 0 ^{o}C and *N*,*N*'-dicyclohexylcarbodiimide (301 mg, 1.46 mmol) was added. The mixture was stirred at 0 ^{o}C for 1 h under N_2 atmosphere. The solution was warmed to room temperature and further stirred overnight. The resulting precipitates of *N*,*N*'-dicyclohexylurea were filtered off and the filtrate was washed successively with 5% aqueous $NaHCO_3$, water, 1 N HCl, water and brine. The organic layer was dried over anhydrous Na_2SO_4 and evaporated in vacuo. The residue was purified by silica gel column chromatography [SiO_2 11 g; hexane-EtOAc (5:1 to 3:1 v/v)] to afford L-phenylalanine ethyl ester amide (**6**) (250 mg, 59%) as an oil. $[\alpha]_D^{23}$ +51.5 (*c* 1.40, $CHCl_3$); IR (neat) 3393, 1745, 1715, 1669, 1632, 1536, 1447, 1298, 1283, 1229, 1211, 1190, 1020, 942, 756, 709 cm^{-1}; ^{1}H-NMR (400 MHz) δ 7.32-7.12 (5H, m, Ph), 6.56 (1H, brd, *J* = 7.3 Hz, NH), 5.72 (1H, s, =C*H*H), 5.49 (1H, s, =CH*H*), 4.89 (1H, dt, *J* = 7.8, 5.9 Hz, OCH), 4.18 (2H, q, *J* = 7.3 Hz, C*H*$_2$Me), 3.68 (3H, s, CO_2Me), 3.36 (2H, s, C*H*$_2$$CO_2$Me), 3.17 (1H, dd, *J* = 13.6, 5.9 Hz, C*H*HPh), 3.16 (1H, dd, *J* = 13.6, 5.4 Hz, CH*H*Ph), 1.25 (3H, t, *J* = 7.3 Hz, CH_2*Me*); ^{13}C-NMR (100 MHz) δ 171.0, 170.8, 166.5, 137.6, 135.7, 129.0, 128.1, 126.7, 121.6, 61.2, 53.2, 51.8, 37.6, 37.5, 13.9; MS (EI^{+}) (*m*/*z*) 319 (M^{+}, 7%), 288 (5), 246 (8), 214 (6), 176 (74), 148 (15), 127 (100), 120 (13), 99 (31), 91 (20), 69 (14), 58 (19); HRMS calcd for $C_{17}H_{22}NO_5$ (MH^{+}) 320.1498, found 320.1507.

4.2.6 4-Methyl 1-(4,4-dimethyl-2-oxotetrahydrofuran-3-yl)-2-methylenesuccinate (7)

To a stirred solution of 4-methyl itaconate (**1**) (476 mg, 3.30 mmol) in dry CH_2Cl_2 (6 ml) were added 4-(dimethylamino)pyridine (37.0 mg, 0.303 mmol) and pantolactone (**20**) (390 mg, 3.00 mmol). The mixture was cooled to 0 ^oC and *N*,*N'*-dicyclohexylcarbodiimide (742 mg, 3.59 mmol) was added. The mixture was stirred at room temperature overnight under N_2 atmosphere. Ethyl acetate was added and the solution was stirred for 1 h and the resulting mixture was filtered and the filtrate was evaporated in vacuo. The residue was purified by silica gel column chromatography [SiO_2 28 g; hexane-EtOAc (10:1 to 3:1 v/v)] to afford pantolactone ester **7** (649 mg, 85%) as an oil. IR (neat) 3113, 1796, 1739, 1643, 1438, 1200, 1145, 1033, 1014, 998, 944, 812 cm^{-1}; ^{1}H-NMR (400 MHz) δ 6.47 (1H, s, =CH*H*), 5.84 (1H, s, =C*H*H), 5.43 (1H, s, OCH), 4.08 (1H, d, *J* = 8.8 Hz, OC*H*H), 4.04 (1H, d, *J* = 8.8 Hz, OCH*H*), 3.71 (3H, s, OMe), 3.43 (1H, d, *J* = 17.1 Hz, CH*H*CO_2Me), 3.39 (1H, d, *J* = 17.1 Hz, C*H*HCO_2Me), 1.23 (3H, s, Me), 1.13 (3H, s, Me); ^{13}C-NMR (100 MHz) δ 171.2, 169.8, 164.0, 132.2, 129.4, 75.3, 74.9, 51.1, 39.6, 36.6, 21.8, 19.0; MS (EI^+) (*m*/*z*) 225 (M^+ - OMe, 6%), 143 (23), 127 (100), 113 (11), 99 (28), 69 (25), 59 (14); HRMS calcd for $C_{12}H_{17}O_6$ (MH^+) 257.1025, found 257.1025.

4.2.7 (4*R*)-4-Benzyl-3-(2-butylpropenoyl)oxazolidin-2-one (22)

To a solution of 2-butylpropenoic acid (293 mg, 2.3 mmol)[17] in dry THF (10 ml) at -30 ^oC was added triethylamine (620 μl, 4.5 mmol) under N_2 atmosphere. Pivaloyl chloride (540 μl, 4.5 mmol) was carefully added and the mixture was stirred for 2 h. The solution was warmed to -20 ^oC. Lithium chloride (163 mg, 3.9 mmol) and (*R*)-4-benzyl-2-oxazolidinone (266 mg, 1.5 mmol) were added and the mixture was stirred for 2 h. The product was extracted with ethyl acetate. The organic layer was washed with saturated aqueous NH_4Cl, 1N aqueous NaOH and brine. The organic layer was dried over anhydrous Na_2SO_4 and the solution was evaporated in vacuo. The residue was purified by column chromatography on silica gel [ehexane-EtOAc (7:1)] to afford **22** (388 mg, 90%) as a colorless solid. Mp 47.6 ^oC (from diethyl ether); IR (neat) 1786, 1682, 1393, 1353, 1312, 1220, 1056, 1043, 1006, 757, 703 cm^{-1}; ^{1}H-NMR (400 MHz) δ 7.36-7.19 (5H, m, Ph), 5.41 (1H, s, =C*H*H), 5.39 (1H, s, =CH*H*), 4.71 (1H, m, NCH), 4.24 (1H, t, *J* = 9.2 Hz, OC*H*H), 4.16 (1H, dd, *J* = 9.2, 4.6 Hz, OCH*H*), 3.35 (1H, dd, *J* = 13.5, 3.5, C*H*HPh), 2.83 (1H, dd, *J* = 13.5, 9.4, CH*H*Ph), 2.42-2.37 (2H, m, CH_2), 1.53-1.44 (2H, m, CH_2), 1.43-1.33 (2H, m, CH_2), 0.92 (3H, t, *J* = 7.3 Hz, CH_3); ^{13}C-NMR (100 MHz) δ 170.4, 152.3, 143.9, 134.8, 129.0, 128.3, 126.8, 118.2, 65.9, 54.6, 37.0, 32.2, 29.4, 21.7, 13.4; MS (ESI^+) *m/z* 288 (MH^+); HRMS calcd for $C_{17}H_{22}NO_3$ (MH^+) 288.1600, found 288.1619.

4.3 Catalytic hydrogenation

4.3.1 Catalytic hydrogenation of 2 using Crabtree's catalyst.

To a solution of amide **2** (34 mg, 0.10 mmol) in CH_2Cl_2-MeOH (2:1 v/v) (3 ml) was added [Ir(1,5-cyclooctadiene)(pyridine)(tricyclohexylphosphine)]PF_6 (4.7 mg, 5.8 mol%) and the mixture was stirred under H_2 atmosphere at room temperature for 5 h. After filtration through a pad of Celite and Florisil, the solvent was evaporated in vacuo. The residue was purified by silica gel column chromatography [SiO_2 3 g; hexane-EtOAc (9:1 to 5:1 v/v)] to afford a mixture of **8** and **9** (33 mg, 97% yield; dr 6.4:1).

4.3.2 Isolation of compounds **8** and **9**

A mixture of the hydrogenated products **8** and **9** (272 mg) was submitted to silica gel column chromatography [SiO_2 8 g; hexane-EtOAc (8:1 then 4:1 v/v)] to give **8** (210 mg) and **9** (53 mg).

*Methyl (3S)-4-{(1S,5R,7R)-10,10-dimethyl-3,3-dioxo-3λ^6-thia-4-azatricyclo [5.2.1.0^{1,5}]dec-4-yl}-3-methyl-4-oxobutanoate (**8**)*

Less polar diastereomer [R_f 0.57 (hexane-EtOAc 1:1 v/v)]; mp 112.9 ^oC (from diethyl ether); $[\alpha]_D^{25}$ -56.5 (*c* 1.02, $CHCl_3$); IR (KBr) 1733, 1682, 1333, 1166, 1137 cm^{-1}; ^{1}H-NMR (400 MHz) δ 3.90 (1H, dd, *J* = 7.8, 4.8 Hz, NCH), 3.64 (3H, s, OMe), 3.50(1H, d, *J* = 13.7 Hz, C*H*HSO_2), 3.46 (1H, d, *J* = 13.7 Hz, CH*H*SO_2), 3.45 (1H, m, C*H*Me), 2.84 (1H, dd, *J* = 16.1, 9.3 Hz, C*H*HCO_2Me), 2.47 (1H, dd, *J* = 16.1, 9.3 Hz, CH*H*CO_2Me), 2.16 (1H, m, CH), 2.03 (1H, dd, *J* = 13.7, 7.6 Hz, CH), 1.95-1.84 (3H, m, CH_2, CH), 1.45-1.32 (2H, m, CH_2), 1.24 (3H, s, Me), 1.23 (3H. d, *J* = 6.8 Hz, CH*Me*), 0.98 (3H, s, Me); ^{13}C-NMR (100 MHz) δ 174.4, 171.4, 65.3, 53.0, 51.6, 48.4, 47.7, 44.6, 38.9, 38.1, 36.1, 32.8, 26.5, 20.6, 20.0, 17.0; MS (EI^+) (*m*/*z*) 343 (M^+, 0.5%), 312 (13), 279 (19), 129 (100), 101 (22), 93 (9), 69 (9), 59 (51); HRMS calcd for $C_{16}H_{26}NO_5S$ (MH^+) 344.1531, found 344.1573.

*(3R)-4-{(1S,5R,7R)-10,10-dimethyl-3,3-dioxo-3λ^6-thia-4-azatricyclo[5.2.1.0^{1,5}]dec-4-y} -3-methyl-4-oxobutanoate (**9**)*

More polar diastereomer [R_f 0.49 (hexane-EtOAc 1:1 v/v)]; mp 134.8-135.0 ^oC (from diethyl ether); $[\alpha]_D^{25}$ -74.6 (*c* 0.765, $CHCl_3$); IR (KBr) 1732, 1682, 1339, 1227, 1138 cm^{-1}; ^{1}H-NMR (400 MHz) δ 3.92 (1H, t, *J* = 6.4 Hz, NCH), 3.66 (3H, s, OMe), 3.50(1H, d, *J* = 13.7 Hz, C*H*HSO_2), 3.46(1H, d, *J* = 13.7 Hz, CH*H*SO_2), 3.51 (1H, m, C*H*Me), 2.86 (1H, dd, *J* = 16.6, 8.8 Hz, C*H*HCO_2Me), 2.40 (1H, dd, *J* = 16.6, 9.3 Hz, CH*H*CO_2Me), 2.10-2.07 (2H, m, CH_2), 1.95-1.83 (3H, m, CH_2, CH), 1.45-1.30 (2H, m,

CH_2), 1.26 (3H, d, *J* = 7.3 Hz, CH*Me*), 1.16 (3H, s, Me), 0.97 (3H, s, Me); ^{13}C-NMR (100 MHz) δ 174.5, 171.7, 65.0, 53.0, 51.7, 48.4, 47.7, 44.6, 38.4, 36.7, 36.6, 32.8, 26.4, 20.8, 19.9, 18.3; MS (EI^+) (*m*/*z*) 343 (M^+, 1%), 312 (16), 279 (14), 129 (100), 101 (34), 93 (11), 69 (11), 59 (61); HRMS calcd for $C_{16}H_{26}NO_5S$ (MH^+) 344.1531, found 344.1557.

4.3.3 Hydrolysis of 8

To a solution of sulfonamide **8** (30 mg, 0.09 mmol) in THF (1 ml) and water (1 ml) was added lithium hydroxide monohydrate (11 mg, 0.27 mmol). The mixture was stirred at room temperature for 5 h and evaporated in vacuo to remove THF. The aqueous layer was acidified with HCl (pH 1) and then washed with CH_2Cl_2. To the aqueous layer was added anhydrous Na_2SO_4, and the resulting solid was put on a silica gel column and eluted successively with hexane-EtOAc (4:1 v/v; 100 ml) and EtOAc (20 ml). Ethyl acetate fraction was evaporated in vacuo to afford (*S*)-methylsuccinic acid (*S*)-(**21)** (5.0 mg, 42% yield) as a colorless solid. $[\alpha]_D^{23}$ -15 (*c* 0.50, EtOH); ^{1}H-NMR (400 MHz) δ 2.93 (1H, m, CH), 2.71 (1H, dd, *J* = 17.2, 8.8 Hz, C*H*H), 2.59 (1H, dd, *J* = 17.2, 4.7 Hz, CH*H*), 1.29 (3H, d, *J* = 6.8 Hz, Me).

4.3.4 Hydrolysis of 9

Sulfonamide **9** (31 mg, 0.09 mmol) was hydrolyzed with lithium hydroxide monohydrate (11 mg, 0.27 mmol) in THF (1 ml)-H_2O (1 ml) as described above to give (*R*)-methylsuccnic acid (*R*)-(**21**) (4.7 mg, 40% yield). $[\alpha]_D^{23}$ +17 (*c* 0.47, EtOH).

4.3.5 Catalytic hydrogenation of 3 on Pd/C in the presence of $MgBr_2$

To a solution of **3** (25 mg, 0.082 mmol) in CH_2Cl_2 (3 ml) was added $MgBr_2$ (47 mg, 0.25 mmol) and the mixture was stirred at room temperature for 15 min. 10% Pd/C (22 mg, 25 mol%) was added and the mixture was stirred for 20 h under H_2 atmosphere. After filtration through a pad of Celite and Florisil, the solvent was evaporated in vacuo and the residue was purified by silica gel column chromatography [SiO_2 3 g; hexane-EtOAc (5:1 v/v)] to afford **10** (22 mg, 88% yield; dr 3.8:1).

*Methyl (3RS))-4-[(4R)-4-benzyl-2-oxooxazolidin-3-yl]-3-methyl-4- oxobutanoate (**10**)*

IR (neat) 1783, 1733, 1700, 1559, 1506, 1353, 1197, 1106 cm^{-1}; ^{1}H-NMR (400 MHz) *major diastereomer*: δ 7.36-7.16 (5H, m, Ph), 4.67 (1H, m, NCH), 4.22-4.14 (3H, m, OCH_2, C*H*Me), 3.67 (3H, s, OMe), 3.33 (1H, dd, *J* = 13.7, 3.2 Hz, C*H*HPh), 2.95 (1H, dd, *J* = 17.0, 10.0 Hz, CH*H*CO_2Me), 2.76 (1H, dd, *J* = 13.7, 10.0 Hz, C*H*HPh), 2.47 (1H, dd, *J* = 17.0, 4.6 Hz, CH*H*CO_2Me), 1.23 (3H, d, *J* = 7.3 Hz, CH*Me*); *minor*

diastereomer: δ 7.30-7.12 (5H, m, Ph), 4.62 (1H, m, NCH), 4.14-4.06 (3H, m, OCH_2, C*H*Me), 3.59 (3H, s, OMe), 3.24 (1H, dd, *J* = 13.3, 3.2 Hz, C*H*HPh), 2.93 1H, dd, *J* = 17.0, 10.0 Hz, CH*H*CO_2Me), 2.77 (1H, dd, *J* = 13.7, 10.0 Hz, C*H*HPh), 2.43 (1H, dd, *J* = 17.0, 4.6 Hz, CH*H*CO_2Me), 1.27 (3H, dd, *J* = 7.3, 1.4 Hz, CH*Me*); ^{13}C-NMR (100 MHz) *major diastereomer*: δ 175.8, 172.06, 152.78, 135.3, 129.28, 128.7, 127.1, 65.8, 55.1, 51.5, 37.30, 37.26, 34.24, 17.0; *minor diastereomer*: δ 172.3, 170.08, 152.80, 135.0, 129.25, 128.7, 127.0, 66.0, 54.9, 51.5, 37.7, 36.8, 34.19, 17.2; MS (ESI^+) (*m*/*z*) 306 (MH^+); HRMS calcd for $C_{16}H_{20}NO_5$ (MH^+) 306.1341, found 306.1357.

4.3.6 Catalytic hydrogenation of 4 on Pd/C in the presence of $MgBr_2$

To a solution of **4** (46 mg, 0.18 mmol) in CH_2Cl_2 (4 ml) was added $MgBr_2$ (101 mg, 0.54 mmol) and the mixture was stirred at room temperature for 15 min. 10% Pd/C (53 mg, 27 mol%) was added and the mixture was stirred for 20 h under H_2 atmosphere. After filtration through a pad of Celite and Florisil, the solvent was evaporated in vacuo and the residue was purified by silica gel column chromatography [SiO_2 2 g; hexane-EtOAc (2:1 v/v)] to afford **11** (45 mg, 96% yield; dr 4.0:1).

*Methyl (3RS)-4-[(4S)-4-isopropyl-2-oxooxazolidin-3-y])-3-methyl-4-oxobutanoate (**11**)*

IR (neat) 1783, 1733, 1699, 1360, 1301, 1197, 1016 cm^{-1}; ^{1}H-NMR (400 MHz) less polar [R_f 0.60 (hexane-EtOAc (1:1 v/v)], *major diastereomer*: δ 4.44 (1H, dt, *J* = 8.2, 3.5 Hz, NCH), 4.30-4.20 (2H, m, OCH_2), 4.15 (1H, m, C*H*Me), 3.65 (3H, s, OMe), 2.92 (1H, dd, *J* = 16.9, 10.1 Hz, C*H*HCO_2Me), 2.43 (1H, dd, *J* = 16.9, 4.6 Hz, CH*H*CO_2Me), 2.38 (1H, m, C*H*Me_2), 1.20 (3H, d, *J* = 6.9 Hz, CH*Me*), 0.93 (6H, t, *J* = 6.9 Hz, CH*Me_2*); more polar [R_f 0.51 (hexane-EtOAc (1:1 v/v)], *minor diastereomer*: δ 4.47 (1H, dd, *J* = 8.2, 3.7 Hz, NCH), 4.32 (1H, t, *J* = 8.7 Hz, OC*H*H), 4.21 (1H, dd, *J* = 9.2, 2.7 Hz, OC*H*H), 4.14 (1H, m, C*H*Me), 3.66 (3H, s, OMe), 2.89 (1H, dd, *J* = 16.9, 10.5 Hz, C*H*HCO_2Me), 2.40 (1H, dd, *J* = 16.9, 4.1 Hz, CH*H*CO_2Me), 2.33 (1H, m, C*H*Me_2), 1.26 (3H, d, *J* = 7.3 Hz, CH*Me*), 0.91 (3H, d, *J* = 7.3 Hz, CH*Me*Me), 0.88 (3H, d, *J* = 6.9 Hz, CHMe*Me*); ^{13}C-NMR (100 MHz) *major diastereomer*: δ 175.7, 171.9, 153.42, 62.96, 58.4, 51.48, 37.4, 34.2, 28.0, 17.73, 17.0, 14.2; *minor diastereomer* δ 175.9, 172.4, 153.46, 63.37, 58.2, 51.51, 36.7, 34.2, 28.4, 17.67, 17.5, 14.6; MS (ESI^+) (*m*/*z*) 258 (MH^+); HRMS calcd for $C_{12}H_{20}NO_5$ (MH^+) 258.1341, found 258.1338.

4.3.7 Catalytic hydrogenation of 5 on Pd/C in the presence of $MgBr_2$

To a solution of **5** (31 mg, 0.12 mmol) in CH_2Cl_2 (3 ml) was added $MgBr_2$ (34 mg, 0.18 mmol) and the mixture was stirred at room temperature for 15 min. 10% Pd/C (32 mg. 25 mol%) was added and the mixture was stirred under H_2 atmosphere for 3.5 h. After

filtration through a pad of Celite and Florisil, the solvent was evaporated in vacuo to afford **12** (30 mg, 97% yield; dr 3.8:1).

*Methyl (2S)-1-[(2RS)-3-methoxycarbonyl-2-methylpropanoyl]pyrrolidine-2-carbonate (**12**)*

IR (neat) 1746, 1733, 1652, 1436, 1360, 1197, 1173 cm^{-1}; ^{1}H-NMR (400 MHz) *major diastereomer*: δ 4.52, (1H, dd, *J* = 8.3, 4.4 Hz, NCH), 3.78-3.63 (2H, m, NCH_2), 3.72 (3H, s, CO_2Me), 3.65 (3H, s, CO_2Me), 3.06 (1H, m, C*H*Me), 2.89 (1H, dd, *J* = 16.6, 9.6 Hz, C*H*HCO_2Me), 2.38 (1H, m, CH*H*CO_2Me), 2.24 (1H, m, C*H*HCH), 2.13-1.96 (3H, m, CH*H*CH, C$H_2$$CH_2$N), 1.20, (3H, d, *J* = 6.8 Hz, CH*Me*); *minor diastereomer*: δ 4.47 (1H, dd, *J* = 8.3, 4.4 Hz, NCH), 3.78-3.63 (2H, m, NCH_2), 3.72 (3H, s, CO_2Me), 3.65 (3H, s, CO_2Me), 3.06 (1H, m, C*H*Me), 2.81 (1H, dd, *J* = 16.6, 7.8 Hz, C*H*HCO_2Me), 2.38 (1H, m, CH*H*CO_2Me), 2.24 (1H, m, C*H*HCH), 2.13-1.96 (3H, m, CH*H*CH, C$H_2$$CH_2$N), 1.16 (3H, d, *J* = 6.8 Hz, CH*Me*); ^{13}C-NMR (100 MHz) *major rotational isomer of the major diastereomer*: δ 174.2, 173.1, 172.59, 58.6, 52.12, 51.6, 46.85, 37.4, 34.1, 29.10, 24.9, 16.9; *minor rotational isomer of the major diastereomer*: δ 175.0, 173.1, 172.56, 59.4, 52.43, 51.6, 46.6, 38.6, 34.2, 31.4, 22.8, 17.7; *major rotational isomer of the minor diastereomer*: δ 174.0, 172.9, 172.62, 58.8, 52.1, 51.7, 46.88, 37.8, 34.3, 29.18, 24.8, 17.0; *minor rotational isomer of the minor diastereomer*: δ (three carbonyl carbon signals were not observed or overlapped with those of diastereomers mentioned above), 59.2, 52.64, 51.6, 46.4, 37.6, 34.6, 29.1, 22.5, 17.6; MS (ESI^+) (*m/z*) 258 (MH^+); HRMS calcd for $C_{12}H_{20}NO_5$ (MH^+) 258.1341, found 258.1341.

4.3.8 Catalytic hydrogenation of 6 on Pd/C in the presence of $MgBr_2$

To a solution of **6** (25 mg, 0.078 mmol) in dry CH_3CN (3 ml) was added $MgBr_2$ (22 mg, 0.12 mmol) and the mixture was stirred at room temperature for 15 min. 10% Pd/C (20 mg, 24 mol%) was added and the mixture was stirred for 2 h under H_2 atmosphere. After filtration through a pad of Celite and Florisil, the solvent was evaporated in vacuo to afford **13** (25 mg, 100% yield; dr 2.8:1).

*Methyl (3RS)-N-[(1S)-1-ethoxycarbonyl-2-phenylethyl]-3-methylsuccinamate (**13**)*

IR (KBr) 3329, 1738, 1657, 1535, 1439, 1263, 1200, 1032, 702 cm^{-1}; ^{1}H-NMR (600 MHz) *major diastereomer*: δ 7.30-7.10 (5H, m, Ph), 6.15 (1H, brd, *J* = 7.2 Hz, NH), 4.83 (1H, dt, *J* = 7.6, 6.0 Hz, NCH), 4.18, (2H, q, *J* = 7.1 Hz, OCH_2Me), 3.648, (3H, s, OMe), 3.14 (1H, dd, *J* = 13.7, 5.8 Hz, C*H*HPh), 3.12 (1H, dd, *J* = 13.7, 8.0 Hz, CH*H*Ph), 2.78-2.68 (2H, m, C$H_2$$CO_2$Me), 2.34 (1H, m, C*H*Me), 1.25 (3H, t, *J* = 7.3 Hz, CH_2*Me*); *minor diastereomer* δ 7.30-7.10 (5H, m, Ph), 6.15 (1H, brd, *J* = 7.2 Hz, NH),

4.86 (1H, dt, *J* = 7.9, 6.0 Hz, NCH), 4.16 (2H, q, *J* = 7.1 Hz, OC*H*$_2$Me), 3.653, (3H, s, OMe), 3.11 (1H, dd, *J* = 13.7, 8.0 Hz, C*H*HPh), 3.10 (1H, dd, *J* = 13.7, 8.0 Hz, CH*H*Ph), 2.78-2.68 (2H, m, C*H*$_2$CO$_2$Me), 2.34 (1H, m, C*H*Me), 1.23 (3H, t, *J* = 7.1 Hz, CH$_2$*Me*), 1.16 (3H, d, *J* = 6.8 Hz, CH*Me*); ^{13}C-NMR (100 MHz) *major diastereomer*: δ 174.19, 172.44, 171.32, 135.79, 129.22, 128.32, 126.86, 61.36, 53.0, 51.64, 38.0, 37.64, 36.86, 17.7, 14.1; *minor diastereomer*: δ 174.21, 173.42, 171.27, 135.82, 129.21, 128.30, 126.88, 60.31, 51.66, 37.85, 37.66, 36.82, 21.0, 14.2; MS (EI$^+$) (*m*/*z*) 321 (M$^+$, 6%), 290 (8), 248 (10), 216 (10), 176 (83), 148 (18), 129 (100), 120 (24), 101 (20), 91 (25), 69 (11), 59 (32); HRMS calcd for $C_{17}H_{24}NO_5$ (MH$^+$) 322.1654, found 322.1688.

4.3.9 Catalytic hydrogenation of 7 on Pd/C in the presence of $MgBr_2$·OEt_2

To a solution of **7** (50 mg, 0.19 mmol) in dry THF (3 ml) was added $MgBr_2$·OEt_2 (77 mg, 0.30 mmol) and the mixture was stirred at room temperature for 15 min. 10% Pd/C (54 mg, 27 mol%) was added and the mixture was stirred for 3.3 h under H_2 atmosphere. After filtration through a pad of Celite and Florisil, the solvent was evaporated in vacuo and the residue was purified by silica gel column chromatography [SiO_2 2 g, hexane-EtOAc (10:1 to 4:1 v/v)] to afford **14** (40 mg, 81% yield; dr 1.8:1).

*4-Methyl 1-(4,4-dimethyl-2-oxotetrahydrofuran-3-yl)-2-methylsuccinate (**14**)*

IR (neat) 1795, 1743, 1159, 1096, 1071 cm^{-1}; ^{1}H-NMR (400 MHz) *major diastereomer*: δ 5.37 (1H, s, OCH), 4.04 (2H, dd, *J* = 15.6, 9.3 Hz, CH$_2$O), 3.70 (3H, s, OMe), 3.09 (1H, m, C*H*Me), 2.81 (1H, dd, *J* = 16.6, 7.3 Hz, CH*H*CO$_2$Me), 2.52 (1H, dd, *J* = 16.6, 6.3 Hz, C*H*HCO$_2$Me), 1.32 (3H, d, *J* = 7.3 Hz, CH*Me*), 1.21 (3H, s, Me), 1.11 (3H, s, Me); *minor diastereomer* δ 5.38 (1H, s, OCH), 4.04 (2H, dd, *J* = 15.6, 9.3 Hz, OCH$_2$), 3.69 (3H, s, OMe), 3.04 (1H, m, C*H*Me), 2.79 (1H, dd, *J* = 17.0, 8.3 Hz, CH*H*CO$_2$Me), 2.51 (1H, dd, *J* = 17.0, 5.4 Hz, C*H*HCO$_2$Me), 1.31 (3H, d, *J* = 7.3 Hz, CH*Me*), 1.22 (3H, s, Me), 1.14 (3H, s, Me); ^{13}C-NMR (100 MHz) *major diastereomer*: δ 173.7, 171.9, 171.6, 76.07, 74.99, 51.77, 40.25, 37.23, 35.8, 22.97, 19.8, 16.9; *minor diastereomer*δ 174.4, 172.1, 171.8, 76.11, 74.96, 51.73, 40.31, 37.2, 35.6, 22.89, 21.0, 17.0; MS (EI$^+$) (*m*/*z*) 227 (M$^+$ - OMe, 16%), 129 (100), 113 (39), 101 (50), 69 (16), 59 (79), 55 (6); HRMS calcd for $C_{12}H_{19}O_6$ (MH$^+$) 259.1181, found 259.1200.

4.3.10 Catalytic hydrogenation of 22 on Pd/C in the presence of $MgBr_2$

To a solution of **22** (49 mg, 0.17 mmol) in dry CH_2Cl_2 (3 ml) was added $MgBr_2$ (96 mg, 0.51 mmol) and the mixture was stirred at room temperature for 15 min. 10% Pd/C (43 mg, 24 mol%) was added and the mixture was stirred overnight under H_2 atmosphere.

After filtration through a pad of Celite and Florisil, the solvent was evaporated in vacuo and the residue was purified by silica gel column chromatography [SiO_2 2 g, hexane-EtOAc (10:1 v/v)] to afford a mixture of **23** (less polar diastereomer /more polar diastereomer =1.9:1) and **24** (42 mg). Separation of the mixture was performed using silica gel column chromatography [SiO_2 10 g, hexane-EtOAc (30:1 to 15:1 v/v)] to afford less polar diastereomer of **23** (11 mg, 22% yield), more polar diastereomer of **23** (25 mg, 51% yield) and **24** (3.4 mg, 7% yield).

(4R)-4-Benzyl-3-[(2RS)-2-methylhexanoyl]oxazolidin-2-one **(23)** MS (ESI^+) *m/z* 290 (MH^+); HRMS calcd for $C_{17}H_{24}NO_3$ (MH^+) 290.1756, found 290.1789.

*Less polar minor diastereomer of **23***

IR (neat) 1784, 1699, 1386, 1349, 1208, 1099, 762, 703 cm^{-1}; ^{1}H-NMR (400 MHz) δ 7.35-7.21 (5H, m, Ph), 4.68 (1H, ddt, *J* = 9.6, 6.4, 3.2 Hz, NCH), 4.23-4.15 (2H, m, OCH_2), 3.71 (1H, sextet, *J* = 6.9 Hz, COCH), 3.27 (1H, dd, *J* = 13.5, 3.5, C*H*HPh), 2.77 (1H, dd, *J* = 13.5, 9.6, CH*H*Ph), 1.75 (1H, m, COCHC*H*H), 1.43 (1H, m, COCHCH*H*), 1.35-1.28 (4H, m, CH_2×2), 1.22 (3H, d, *J* = 6.9 Hz, CH*Me*), 0.89 (3H, t, *J* = 7.1 Hz, CH_2*Me*); ^{13}C-NMR (100 MHz) δ 177.4, 153.1, 135.3, 129.4, 128.9, 127.3, 66.0, 55.3, 37.9, 37.7, 33.1, 29.4, 22.7, 17.4, 14.0.

*More polar, major diastereomer of **23***

IR (neat) 1784, 1699, 1386, 1349, 1208, 1098, 762, 703 cm^{-1}; ^{1}H-NMR (400 MHz) δ 7.35-7.21 (5H, m, Ph), 4.69 (1H, ddt, *J* = 11.1, 7.4, 3.7 Hz, NCH), 4.21-4.11 (2H, m, OCH_2), 3.75 (1H, sextet, *J* = 6.9 Hz, COCH), 3.30 (1H, dd, *J* = 13.3, 3.7, C*H*HPh), 2.74 (1H, dd, *J* = 13.3, 9.6, CH*H*Ph), 1.79 (1H, m, COCHC*H*H), 1.45 (1H, m, COCHCH*H*), 1.35-1.34 (4H, m, CH_2×2), 1.18 (3H, d, *J* = 6.9 Hz, CH*Me*), 0.91 (3H, t, *J* = 6.9 Hz, CH_2*Me*); ^{13}C-NMR (100 MHz) δ177.4, 153.1, 135.4, 129.4, 128.9, 127.3, 65.9, 55.3, 38.0, 37.4, 33.5, 29.2, 22.7, 16.7, 14.0.

*(4R)-4-Benzyl-3-[(Z)-2-methylhex-2-enoyl]oxazolidin-2-one (**24**)*

^{1}H-NMR (400 MHz) δ 7.35-7.19 (5H, m, Ph), 6.10 (1H, td, *J* = 7.3, 1.4 Hz, =CH), 4.72 (1H, m, NCH), 4.25 (1H, t, *J* = 8.8 Hz, OC*H*H), 4.15 (1H, dd, *J* = 8.8, 5.7 Hz, OCH*H*), 3.36 (1H, dd, *J* = 13.3, 3.2, C*H*HPh), 2.83 (1H, dd, *J* = 13.3, 9.2, CH*H*Ph) , 2.18 (2H, q, *J* = 7.3 Hz, =CHCH_2), 1.91 (3H, s, =CMe), 1.49 (2H, sextet, *J* = 7.3 Hz, CH_2Me), 0.96 (3H, t, *J* = 7.3 Hz, CH_2*Me*); ^{13}C-NMR (100 MHz) δ 172.0, 153.2, 140.1, 135.2, 130.7, 129.5, 128.9, 127.3, 66.3, 55.5, 37.5, 30.4, 21.7, 13.9, 13.5; MS (ESI^+) *m/z* 288 (MH^+).

4.4 Conjugate reduction.

Following the procedures described in the literature[8], **2, 3, 5** and **6** were reduced using *n*-Bu_3SnH in the presence of Lewis acid.

4.4.1 Conjugate reduction of 2 with *n*-Bu_3SnH in the presence of MgI_2

To a solution of **2** (30 mg, 0.087 mmol) in CH_2Cl_2 (3 ml) was added MgI_2 (178 mg, 0.64 mmol) and the mixture was stirred at room temperature for 15 min. To the mixture cooled to 0 ^oC was added *n*-Bu_3SnH (50 µl, 0.19 mmol) and the reaction mixture was stirred at the temperature for 16 h. KF and water were added and the mixture was stirred at room temperature overnight. After filtration and evaporation, the residue was purified by silica gel column chromatography [SiO_2 3 g; hexane-EtOAc (15:1 v/v) then hexane-EtOAc (9:1 v/v)] to give a mixture of **8** and **9** (26 mg, 86% yield; **8**/**9** = 1:4.4).

4.4.2 Conjugate reduction of 3 with *n*-Bu_3SnH in the presence of MgI_2

To a solution of **3** (49 mg, 0.16 mmol) in CH_2Cl_2 (3 ml) was added MgI_2 (123 mg, 0.43 mmol) and the mixture was stirred at room temperature for 15 min. To the mixture cooled to 0 ^oC was added *n*-Bu_3SnH (80 µl, 0.30 mmol) and the reaction mixture was stirred at the temperature for 15 h. KF and water were added and the mixture was stirred at room temperature overnight. After filtration and evaporation, the residue was purified by silica gel column chromatography [SiO_2 3 g; hexane-EtOAc (20:1 v/v) then hexane-EtOAc (5:1 v/v)] to give an inseparable mixture of **10** (50mg, 100% yield; dr 1.6:1).

4.4.3 Conjugate reduction of 6 with *n*-Bu_3SnH in the presence of MgI_2

To a solution of **6** (26 mg, 0.081 mmol) in CH_2Cl_2 (3 ml) was added MgI_2 (69 mg, 0.25 mmol) and the mixture was stirred at room temperature for 15 min. To the mixture cooled to 0 ^oC was added *n*-Bu_3SnH (30 µl, 0.16 mmol) and the reaction mixture was stirred at the temperature for 17 h. KF and water were added and the mixture was stirred at room temperature overnight. After filtration and evaporation, the residue was purified by silica gel column chromatography [SiO_2 3 g; hexane-EtOAc (5:1 v/v) then hexane-EtOAc (3:1 v/v)] to give an inseparable mixture of **13** and the starting material **6** (23mg, 86% yield; **13**/**6** = 6.4:1; dr 1:1.6 for **13**).

References

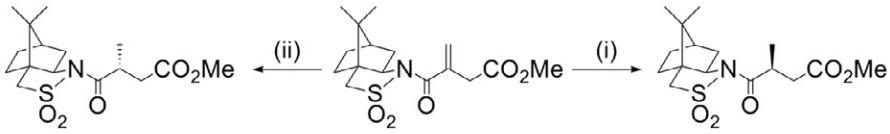
1. (a) Kameda, Y.; Nagano, H. *Tetrahedron* **2006**, *62*, 9751-9757; (b) Nagano H.; Kuwahara, R.; Yokoyama. F. *Tetrahedron* **2007**, *63*, 8810-8814.
2. Schmida, R.; Antoulas, S.; Rüttimann, A.; Schmid, M.; Vecchi, M.; Weiserb, H.

Helv. Chim. Acta **1990**, *73*, 1276-1299.

3. (a) Hekking, K. F. W.; Lefort, L.; Vries, A. H. M.; Delft, F. L.; Schoemaker, H. E.; Vries, J. G.; Rutjes, F. P. J. T. *Adv. Synth. Catal.* **2008**, *350*, 85-94; (b) Ostermeier, M.; Brunner, B.; Korff, C.; Helmchen, G. *Eur. J. Org. Chem.* **2003**, 3453-3459; (c) Minnaard, A. J.; Feringa, B. L.; Lefort, L.; de Vries, J. G. *Acc. Chem. Res.* **2007**, *40*, 1267-1277; (d) Ager, D. J.; de Vries, A. H. M.; de Vries, J. G. *Chem. Soc. Rev.* **2012**, **41**, 3340-3380.
4. Fadel, A.; Salaün, J. *Tetrahedron Lett.* **1988**, *29*, 6257-6260.
5. Oppolzer, W.; Moretti, R.; Thomi, S. *Tetrahedron Lett.* **1989**, *30*, 5603-5606.
6. (a) Stack, J. G.; Curran, D. P.; Rebek Jr., J.; Ballester, P. *J. Am. Chem. Soc.* **1991**, *113*, 5918-5920; (b) Sibi, M. P.; Ji, J. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 274-276; (c) Sibi, M. P.; Jasperse, C. P.; Ji, J. *J. Am. Chem. Soc.* **1995**, *117*, 10779-10780.
7. Nagano, H.; Yokota, M.; Iwazaki, Y. *Tetrahedron Lett.* **2004**, *45*, 3035-3037.
8. (a) Hirasawa, S.; Nagano, H.; Kameda, Y. *Tetrahedron Lett.* **2004**, *45*, 2207-2209; (b) Hirasawa, S.; Tajima, Y.; Kameda, Y.; Nagano, H. *Tetrahedron* **2007**, *63*, 10930-10938.
9. (a) Vandewalle, M.; van der Eycken, J.; Oppolzer,W.; Vullioud, C. *Tetrahedron* **1986**, *42*, 4035-4043; (b) Thom, C.; Kocieński, P. *Synthesis* **1992**, 582-586; (c) Clark, W. M.; Bender, C. *J. Org. Chem.* **1998**, *63*, 6732-6734; (d) Oppolzer, W.; Poli, G.; Kingma, A. J.; Starkemann, C.; Bernardinelli, G. *Helv. Chim. Acta* **1987**, *70*, 2201-2214; (e) Nelson, T. D.; LeBlond, C. R.; Frantz, D. E.; Matty, L.; Mitten, J. V.; Weaver, D. G.; Moore, J. C.; Kim, J. M.; Boyd, R.; Kim, P.-Y.; Gbewonyo, K.; Brower, M.; Sturr, M.; McLaughlin, K.; McMasters, D. R.; Kress, M. H.; McNamara, J. M.; Dolling, U. H. *J. Org. Chem.* **2004**, *69*, 3620-3627.
10. Jawaid, S.; Farrugia, L. J.; Robins, D. J. *Tetrahedron: Asymmetry* **2004**, *15*, 3979-3988.
11. Qiu, L.; Kwong, F. Y.; Wu, J.; Lam, W. H.; Chan, S.; Yu, W.-Y.; Li, Y.-M.; Guo, R.; Zhou, Z.; Chan, A. S. C. *J. Am. Chem. Soc.* **2006**, *128*, 5955-5965.
12. Gramatica, P.; Manitto, P.; Monti, D.; Speranza, G. *Tetrahedron* **1988**, *44*, 1299-1304.
13. Morimoto, T.; Yamazaki, A.; Achiwa, K. *Chem. Pharm. Bull.* **2004**, *52*, 1367-1371.
14. Fürmeier, S.; Griep-Raming, J.; Hayen, A.; Metzger, J. O. *Chem. Eur. J.* **2005**, *11*, 5545-5554.
15. Nagano, H.; Toi, S.; Matsuda, M.; Hirasawa, T.; Hirasawa, S.; Yajima, T. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2525-2538.

16. (a) Garner, P.; Dogan, Ö.; Youngs, W. J.; Kennedy, V. O.; Protasiewicz, J.; Zaniewski, R. *Tetrahedron* **2001**, *57*, 71-85; (b) Kim, B. H.; Curran, D. P. *Tetrahedron*, **1993**, *49*, 293-318.
17. Stetter, H.; Kuhlmann, H. *Synthesis* **1979**, 29-30.

Graphical Abstract



70% yield 84% yield

(i) H_2, cat. $[Ir(COD)(PCy_3)(py)]PF_6$, CH_2Cl_2-MeOH (2:1), rt
(ii) *n*-Bu_3SnH, MgI_2, CH_2Cl_2, 0 °C

Fig. 1. C5 Chiral unit **A** for the synthesis of natural products having 1,5-dimethylalkyl motif.