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Diastereoselective amidoallylation of glyoxylic acid with chiral *tert*-butanesulfinamide and allylboronic acid pinacol esters: efficient synthesis of optically active γ,δ-unsaturated α-amino acids

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This work is dedicated to Dr. Masanori Sakamoto, Professor Emeritus of Meiji Pharmaceutical University, on the occasion of his 77th birthday (KIJU)

ABSTRACT

A convenient synthesis of δ,γ-unsaturated amino acids has been developed. After a mixture of (*R*)-*tert*-butanesulfinamide and glyoxylic acid with molecular sieves in CH_2Cl_2 was stirred for 42 h at room temperature, allylboronic acid pinacol ester was added to the mixture to give (*R*)-2-((*R*)-*tert*-butanesulfinamido)pent-4-enoic acid with high diastereoselectivity. The corresponding reaction of (*Z*)-crotylboronic acid pinacol ester produced no product; however, that of (*E*)-crotylboronic acid pinacol ester produced (2*R*,3*S*)-2-((*R*)-*tert*-butylsulfinamido)-3-methylpent-4-enoic acid with excellent diastereoselectivity.

1. Introduction

δ,γ-Unsaturated amino acids are useful materials for medicinal and organic chemistry. Allylglycine is known to block glutamic acid decarboxylase[1] and to be a synthetic intermediate of piperazimycin A[2] and 2-amino-8-oxodecanoic acids, which are present in naturally occurring inhibitors of hystone deacetylase.[3] 2-Amino-3-methylpent-4-enoic acid derivatives have been used for the syntheses of isostatine (β-hydroxy-γ-amino acid),[4] 2-amino-3-cyclopropylbutanoic acid (a plant growth regulator),[5] (2*S*,3*S*)-*N*-methyl-δ-hydroxyisoleucine (a non-coded amino acid of halipeptin A),[6] and (2*S*,3*S*)-β-benzyloxyaspartic acid, (a potent non-transportable blocker activity to glutamate transporters).[7] 2-Amino-3-propylpent-4-enoic acid has been converted into bicyclic dipeptide mimetics for the cholecystokinin and opioid receptors.[8] 2-Amino-4-methylpent-4-enoic acid and its *tert*-butyl ester have been used for the synthesis of eponemycin[9] and manzacidin D,[10,11] respectively. Moreover, amino acids bearing the terminal double bonds have been used as potential precursors of homologous dehydroamino acids by means of olefin cross metathesis.[12–14]

The asymmetric synthesis of δ,γ-unsaturated amino acid derivatives has been well studied.[15] These derivatives have been obtained by fractional crystallization using (*S*)-α-methylbenzylamine[4] and kinetic resolution using acylases;[9,16,17] they have also been synthesized by asymmetric reactions. The [3,3]-sigmatropic rearrangement of optically active (*E*)- and (*Z*)-1-(*tert*-butyldimethylsilyl)-2-butenyl *N*-*tert*-butyloxycarbonylglycinates produced δ,γ-unsaturated amino acid derivatives.[18] The transfer of the Rh-catalyzed allylic alkylation with chirality from the allyl substrate to the attacking nucleophile was also investigated.[19] The asymmetric ester enolate Claisen rearrangement was developed using chelate-bridged enolates in the presence of chiral bidentate ligands.[20]

The use of allylic boron compounds for allylation has emerged as an important synthetic approach, providing a robust and chemoselective method for efficient and stereocontrolled access to various homoallylic amines.[21] For example, a chiral imino ester, which is obtained from α-methylbenzyl amine and butyl glyoxylate, reacts with allyl-9-BBN to afford an allylglycine derivative in 92% yield and 92% de.[22,23] In this case, the catalytic hydrogenation is needed to remove the α-methylbenzyl group, and the double bond in the side chain also converts into a single bond to give norvaline. Kobayashi et al. have developed the stereoselective synthesis of homoallylic primary amines using allylboronic acid pinacol esters.[24] A concise stereoselective synthesis of alloisoleucine has been achieved by using glyoxylic acid **1**, ammonia, and (*Z*)-crotylboronic acid pinacol ester **2b** via allylation following catalytic hydrogenation (Scheme 1, Eq. 1). Allylation of hydroxyglycine by allylboronic acid pinacol esters has also been developed.[25] Szabó et al. have developed an efficient one-pot synthesis of α-amino acids from allyl alcohols via the Petasis borono-Mannich reaction of allyl boronates generated in situ.[26] However, in these cases the products are mixtures of enantiomers.

On the other hand, *tert*-butanesulfinamide **4** is one of the best chiral auxiliaries in asymmetric synthesis by virtue of its excellent diastereocontrol.[27,28] The imines exhibit unique reactivity and stereoselectivity in various reactions, especially in the diastereoselective addition of *N*-(*tert*-butylsulfinyl)imines, which can be

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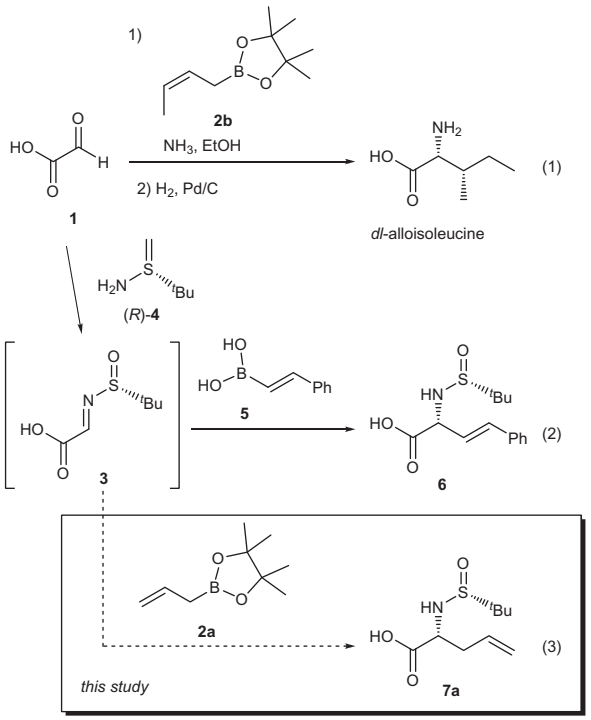


Scheme 1. Aminoallylation (Eq. 1) and Petasis borono–Mannich reaction (Eq. 2) in the reported studies and an amidoallylation (Eq. 3) used in this study.

prepared from aldehydes and ketones, while the *tert*-butylsulfinyl group cleaves easily under mild conditions. The addition of allylindium to *N*-(*tert*-butylsulfinyl)iminoacetic acid ester in saturated aqueous NaBr produced *N*-(*tert*-butylsulfinyl)allylglycine ethyl ester in excellent yield and with diastereoselectivity.[29] Recently, the diastereoselective Petasis borono-Mannich reaction[30–32] of (*R*)-*tert*-butanesulfinamide (*R*)-**4**, glyoxylic acid **1** and 2-phenylvinyl boronic acid **5** to give 2-phenylvinylglycine **6** was reported (Scheme 1, Eq. 2)[33] and the diastereoselectivity was then improved upon by adding Lewis acids.[34] Based on these reports, we considered that *N*-(*tert*-butylsulfinyl)iminoacetic acid **3** prepared from glyoxylic acid **1** and **4** (Scheme 1, Eq. 2) would also be a good substrate for allylation using allylboronic acid pinacol ester **2a** to give allylglycine **7a** diastereoselectively (Scheme 1, Eq. 3). Herein we report the amidoallylation of glyoxylic acid **1** with (*R*)-*tert*-butanesulfinamide (*R*)-**4** and 2-alkenyl boronic acid pinacol esters **2** to give optically active γ,δ-unsaturated amino acids **7**.

2. Results and discussion

2.1. Reaction conditions

Firstly, we investigated the reaction of (*R*)-*tert*-butanesulfinamide (*R*)-**4**, glyoxylic acid **1**[33,34] and allylboronic acid pinacol ester **2a**. The results are summarized in Table 1. After a mixture of (*R*)-**4** and **1** in $CDCl_3$ was stirred for 6.5 h (conditions 1), allylboronic acid pinacol ester **2a** was added to the reaction mixture (conditions 2). The desired allylglycine derivative **7a** was obtained, but in low yield (entry 1). We considered that the yield of **7a** would increase if the formation of the iminium intermediate **3** was enhanced, and removal of H_2O from the reaction system could provide this outcome. The effect of drying agents in the reaction mixture was thus studied, while molecular sieves (MS) 3 Å[35] were found to improve the yields at ambient temperature. The conversion of **2a** to **7a** in the presence of MS reached 38% and 46% with 0.33 g/mmol and 0.66 g/mmol of MS 3 Å, respectively (entries 2 and 3). A somewhat higher yield at a higher concentration (0.20 mol/L) was observed (entry 5); however, we selected the lower concentration (0.11 mol/L, entry 3) because of its good blending ability.

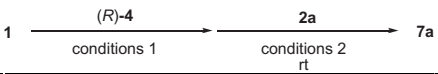
Next, we investigated the reaction times before and after adding allyl boronate pinacol ester **2a** (entries 6–8). A reaction time of 42 h before adding **2a** was the best time among entries 6–8, and the next allylation after adding **2a** needed 23 h to give **7a** in 88% yield (entry 7). Reactions in EtOH at room temperature and in 1,2-dichloroethane at refluxing temperature decreased the yields (entries 9 and 10).

A characteristic ^1H NMR signal in $CDCl_3$ at 8.02 ppm was observed from the mixture before adding allylboronic acid pinacol ester **2a** (Table 1). This signal was due to the imino proton of the *N*-(*tert*-butylsulfinyl)iminoacetic acid **3**. This allylation was also examined using ethyl *N*-(*tert*-butylsulfinyl)iminoacetate **8**,[35] which is a substrate for the Rh- and Pd-mediate additions of phenylboronic acid[36,37] and Zn-mediated cinnamylation of cinnamylzinc bromide.[38] A mixture of imine **8** and allylboronic acid pinacol ester **2a** in CH_2Cl_2 was stirred for 15 h at room temperature; however, the reaction did not proceed and **8** was recovered (Scheme 2).

2.2. Scope of the reaction

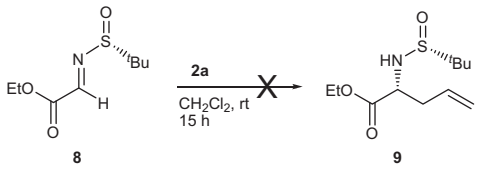
The reaction conditions in entry 7 (Table 1) were then applied to a variety of 2-alkenylboronic acid pinacol esters **2a–f** in order to determine the scope of the reactions (Table 2). Typically, after a mixture of (*R*)-*tert*-butanesulfinamide (*R*)-**4** and glyoxylic acid **1** was stirred for 42 h at room temperature, 2-alkenylboronic acid

Table 1
Diastereoselective amidoallylation of glyoxylic acid **1**



Entry	Conditions 1				Conditions 2	Yield of **7a**[a] (%)
	Solvent (mol/L)	Temp	MS 3 Å (g/mmol)	Time (h)	Time (h)	
1	$CDCl_3$ (0.11)	rt	—	6.5	15	12
2	$CDCl_3$ (0.11)	rt	0.33	6.5	15	38
3	$CDCl_3$ (0.11)	rt	0.66	6.5	15	46
4	$CDCl_3$ (0.20)	rt	—	6.5	15	19
5	$CDCl_3$ (0.20)	rt	0.66	6.5	15	49
6	CH_2Cl_2 (0.11)	rt	0.66	17	22	47
7	CH_2Cl_2 (0.11)	rt	0.66	42	23	88
8	CH_2Cl_2 (0.11)	rt	0.66	68	44	68
9	EtOH (0.11)	rt	0.66	47	20	70
10	$(ClCH_2)_2$ (0.11)	Reflux	0.66	4.5	19	38

[a] The yields of entries 1–5 were calibrated with the internal standard (Ph_3CH) by ^1H NMR integration, and yields of entries 6–10 were isolated yields.



Scheme 2.

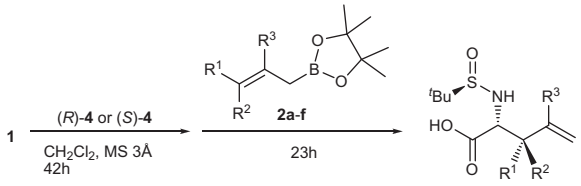
pinacol esters **2a–f** were added. The reactions were quenched after 23 h. The reaction of (*Z*)-crotylboronic acid pinacol ester **2b** gave no product (entry 2); however, that of (*E*)-crotylboronic acid pinacol ester **2c** gave *syn*-product **7c** (entry 3). (*E*)-Hex-2-en-1-ylboronic acid pinacol ester **2d**[39,40] also gave product **7d** (entry 5); however, the identical reaction of *trans*-cinnamylboronic acid pinacol ester **2e**[39,40] gave no product (entry 7). The reaction of 2-methyl-2-propenylboronic acid pinacol ester **2f**[40] gave isopropenylalanine derivative **7f** in 51% yield (entry 8).

syn-Products *ent*-**7c**, *ent*-**7d,** and *ent*-**7f**, which were the enantiomers of **7c**, **7d**, and **7f**, respectively, were also synthesized from (*S*)-**4** instead of (*R*)-**4** (entries 4, 6, and 9). The yields of **7** were not optimized and not identical to those of the corresponding enantiomers.

2.3. Removal of the *N-tert*-butylsulfinyl group

The optically active amino acids **7a**, **7c–f,** and *ent*-**7c–f** were treated with HCl aq (6 mol/L) at 90 °C to remove the *N-tert*-butylsulfinyl group[27,28] and then ion-exchanged with DOWEX 50 W × 4. Amino acids **10a**, **c**, and **d** were formed in 69%, 82%, and 90% yields,

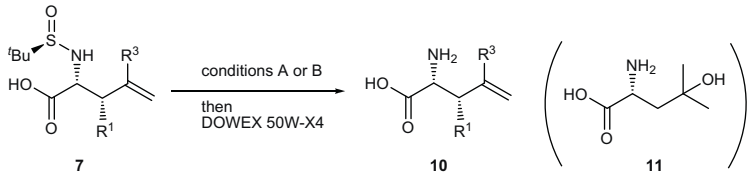
Table 2
Diastereoselective amidoallylation of glyoxylic acid **1**[a]



Entry	(*R*)- or (*S*)-**4**	Boronic acid pinacol ester **2**				Product **7**	
		No.	R^1	R^2	R^3	No.	Yield[b,c] (%)
1[d]	(*R*)	**2a**	H	H	H	**7a**	88
2	(*R*)	**2b**	H	Me	H	**7b**	0
3	(*R*)	**2c**	Me	H	H	**7c**	64
4	(*S*)	**2c**	Me	H	H	*ent*-**7c**	72
5	(*R*)	**2d**	^{n}Pr	H	H	**7d**	57
6	(*S*)	**2d**	^{n}Pr	H	H	*ent*-**7d**	65
7	(*R*)	**2e**	Ph	H	H	**7e**	0
8	(*R*)	**2f**	H	H	Me	**7f**	51
9	(*S*)	**2f**	H	H	Me	*ent*-**7f**	65

[a] See Section 4 for the general procedure.
[b] Isolated yields.
[c] Yields were not optimized.
[d] Identical data of entry 7 in Table 1.

Table 3
Removal of the *N-tert*-butylsulfinyl group from **7** and *ent*-**7**



Entry	Material **7**			Conditions[a]	Product **10**		
	No.	R^1	R^3		No.	Yield (%)	ee[b] (%)
1	**7a**	H	H	A	**10a**	69	94
2	**7c**	Me	H	A	**10c**	82[b]	>98
3	*ent*-**7c**	Me	H	A	*ent*-**10c**	84[b]	>98
4	**7d**	^{n}Pr	H	A	**10d**	90	>98
5	*ent*-**7d**	^{n}Pr	H	A	*ent*-**10d**	90	>98
6	**7f**	H	Me	A	**10f**	0 (**11**, 46)	(**11**, >98)
7	*ent*-**7f**	H	Me	A	*ent*-**10f**	0 (*ent*-**11**, 68)	(*ent*-**11**, >98)
8	**7f**	H	Me	B	**10f**	91	94
9	*ent*-**7f**	H	Me	B	*ent*-**10f**	93	94

[a] Condition A; HCl aq (6 mol/L), 90 °C, 4 h, condition B; HCl in dioxane (4 mol/L)/2-propanol (1:2), rt, 1 h.
[b] Estimated by HPLC analysis.

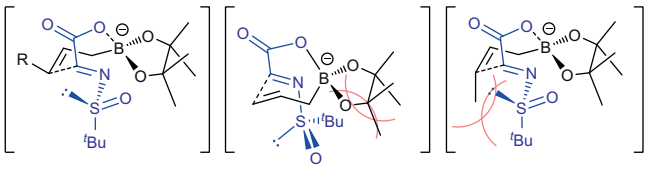


Figure 1. Mechanistic proposal for stereocontrol.

respectively (Table 3, entries 1, 2, and 4). In contrast, treatment of compound **7f** with HCl aq (6 mol/L) at 90 °C did not give amino acid **10f** but instead (*R*)-2-amino-4-hydroxy-4-methylpentanoic acid **11**[41,42] in 92% yield. Thus, the *N*-*tert*-butylsulfinyl group was removed smoothly; however, it was accompanied by conversion of the 2-methylprop-2-enyl group to a 2-hydoxy-2-methylpropyl group. In order to prevent the addition of water to the double bond of **7f**, we used a solution of HCl in dioxane (4 mol/L)/2-propanol (1:2) instead of HCl aq (6 mol/L), and **10f** and *ent*-**10f** were obtained from **7f** and *ent*-**7f** in 91% and 93% yields, respectively.

We determined their relative stereochemistry by comparison with reported ^{1}H and ^{13}C NMR spectroscopic data. The enantiomeric purities were determined with HPLC using a CROWNPAK CR(−) column. The enantiomeric excess (ee) of **10a**, **10f**, and *ent*-**10f** was 94% ee; and that of **10c–d**, **11**, and their corresponding enantiomers, *ent*-**10c–d** and *ent*-**11**, was more than 98% ee. The absolute stereochemistries of products **10a**, **c**, and **f** were determined by comparison of the specific rotations reported in the References (see Section 4). The absolute stereochemistry of **10d** was determined by its elution order in HPLC using CROWNPAK CR(−). Using this column, the L-amino acids were eluted prior to the D-amino acids.[43] The stereochemistry of **11** must be identical to that of **10f** because both amino acids **11** and **10f** were formed from **7f**. We also checked the final reaction conditions by HPLC analysis. A mixture of **10a** (94% ee) in HCl aq (6 mol/L) was stirred for 4 h at 90 °C; however, no racemization occurred.

2.4. Proposed transition states

Some transition states for the allylation of imines have been proposed. For example, in the allylation of some imines by allylboronic acid esters, six-membered transition states, including coordination of the boron and the lone pair of *N*-phenyl- and *N*-propylimines have been proposed.[44] In the Zn-mediated asymmetric cinnamylation to ethyl *N*-(*tert*-butylsulfinyl)iminoacetate **8**, a six-membered chair-like transition state with the zinc coordinated to the nitrogen of **8** and the oxygen of the *tert*-butylsulfinyl group have been proposed.[38] The nitrogen of the imines coordinated with the boron and zinc in these transition states; however, the nitrogen of the *tert*-butylsulfinyl group of **8** could not activate the boronic acid ester **2a** in our case. This would be a reason as to why the allylation of ethyl *N*-(*tert*-butylsulfinyl)iminoacetate **8** did not proceed (Scheme 2). On the other hand, reaction of boronates **2** and iminoacetic acid **3**, which would be formed from (*R*)-*tert*-butanesulfinamide (*R*)-**4** and glyoxylic acid **1**, proceeded smoothly at room temperature without the addition of activators (Table 1). Thus, boronates **2** need the carboxylic group for the activation of **2** in this reaction. This activation is similar to that of the Petasis borono–Mannich reaction (Scheme 1, Eq. 2); the carboxylic group of imine **3** activates the vinylboronic acids and then the vinyl group attacks the imino group.[32]

Based on the observed diastereofacial selectivity, the stereochemistry of the products can be explained with the stereochemical models shown in Figure 1. In transition states **TS-1** and **TS-2**, the carboxylic groups activate the allylboronic acid pinacol ester **2a**. The reaction may proceed via **TS-1** instead of **TS-3** because the large *tert*-butyl group can control the approach of the pinacol moiety of **2a**, and the *tert*-butyl group would interact with the pinacol group in **TS-2**. (*E*)-Crotylboronic acid pinacol ester **2c** was also reactive because the *trans*-methyl group was located outside of **TS-2**; however, steric repulsion between the *tert*-butyl group and *cis*-methyl group of (*Z*)-crotylboronic acid pinacol ester **2b**, which gave no product (Table 2, entry 2), may hinder the approach of the *tert*-butylsulfinylimine and crotyl group of **2b** (**TS-4**). A similar transition state including a fused five- and six-membered ring system has been proposed for a diastereoselective Pd/In mediated catalytic allylation of chiral *N*-sulfinyl-α-imino esters.[45]

3. Conclusion

In conclusion, we have developed a new diastereoselective amidoallylation of glyoxylic acid **1** with (*R*)-*tert*-butanesulfinamide (*R*)-**4** and 2-alkenylboronic acid pinacol esters **2** to give *N*-(*tert*-butylsulfinyl)-γ,δ-unsaturated amino acids **7**. The *N*-*tert*-butylsulfinyl group was removed by HCl in water or 2-propanol to afford the corresponding optically active γ,δ-unsaturated amino acids **10**. Considering the one-pot synthesis from glyoxylic acid **1** to allylglycine derivatives **7** (Table 2), this procedure is the shortest route to γ,δ-unsaturated amino acids **10** from commercially available starting materials without fractional crystallization[4,20] or enzymatic kinetic resolution.[9,16,17] These amino acids **10** have been used as starting materials as described in the Introduction.[2–14,17] In the amidoallylation, the carboxylic group of imine **3** could coordinate to the boron of the allylboronic acid esters (Fig. 1) likewise to the carboxylic group in the Petasis borono–Mannich reaction.[30–34] Since the aminoallylation (Scheme 1, Eq. 1) does not need a carboxylic group,[24] this is the first report of the reaction of imines and allylboronic acid esters activated by a carboxylic group.

4. Experimental

4.1. General

Melting points were measured with a Yanaco MP-3 apparatus and are uncorrected. Optical rotations were determined on a JASCO DIP-140 polarimeter. NMR spectra were obtained with a JEOL JNM-LA500 (^{1}H NMR: 500 MHz and ^{13}C NMR: 125 MHz) and a JEOL JNM-GSX400 (^{1}H NMR: 400 MHz and ^{13}C NMR: 100 MHz) spectrometers using tetramethylsilane as an internal standard or 3-(trimethylsilyl)propionic-2,2,3,3-d_4 acid sodium salt as an external standard. IR spectra were recorded on a JEOL FT/IR-4100 spectrophotometer. MS and high-resolution MS (HRMS) were taken on a JEOL JMS-DX302 spectrometer. Column chromatography was performed with silica gel 60 (spherical, 40–50 μm, Kanto Chemical). Analytical TLC was performed on plates pre-coated with 0.25 mm layer of silica gel 60 F_{254} (Merck). HPLC conditions: CROWNPAK CR(−) column eluted with pH 1.0 $HClO_4$ aq at 0 °C. Flow rate: 0.4 mL/min. Detection: UV detector at 200 nm.

4.2. General procedure for the amidoallylation of glyoxylic acid (Tables 1 and 2)

A mixture of (*R*)-*tert*-butanesulfinamide (*R*)-**4** (121 mg, 1.00 mmol), glyoxylic acid monohydrate **1** (92.0 mg, 1.00 mmol) and powdered molecular sieves 3 Å (648 mg) in CH_2Cl_2 (9.0 mL) was stirred for 42 h at room temperature. Allylboronic acid pinacol ester **2a** (168 mg, 1.00 mol) was added to the mixture, and the resulting mixture was stirred for 23 h at room temperature. The reaction mixture was filtered through a pad of Celite and the filtrate was concentrated in vacuo. The residue was purified by silica

gel column chromatography ($CHCl_3$/MeOH, 9:1) to afford allylglycine derivative **7a** (194 mg, 88%). Other amino acid derivatives **7c**, **d**, **f** and their enantiomers *ent*-**7c**, **d**, **f** were also synthesized on a 1.00 mmol scale. For the syntheses of *ent*-**7c**, **d,** and **f**, (*S*)-*tert*-butanesulfinamide (*S*)-**4** was used instead of (*R*)-*tert*-butanesulfinamide (*R*)-**4**.

4.2.1. (2*R*,R_S)-2-(*tert*-Butylsulfinamido)pent-4-enoic acid 7a

Pale yellow oil. $[\alpha]_D^{23} = -32.6$ (*c* 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.70–5.78 (1H, m, H_2C=C*H*), 5.13 (1H, d, *J* = 7.9 Hz, *H*HC=CH), 5.10 (1H, s, H*H*C=CH), 4.45 (1H, d, *J* = 7.6 Hz, NH, D_2O exchangeable), 3.98 (1H, dd, *J* = 12.8, 7.3 Hz, NCH), 2.72–2.57 (1H, m, C*H*H), 2.44–2.49 (1H, m, CH*H*), 1.24 (9H, s, ^{t}Bu). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 174.1 (C=O), 132.9 (*C*H=CH_2), 119.1 (CH=*C*H_2), 58.5 (NCH), 57.0 (C), 38.5 (CH_2), 23.0 (Me × 3). IR (film) cm^{-1}: 3274 (s), 2976 (s), 1734 (s), 1475 (s), 1372 (s), 1150 (s), 1011 (s). HRMS (positive FAB) *m*/*z*: 220.1002 $(M+1)^+$ (Calcd for $C_9H_{18}NO_3S$: 220.1008).

4.2.2. (2*R*,3*S*,R_S)-2-(*tert*-Butylsulfinamido)-3-methylpent-4-enoic acid 7c

Yellowish crystalline material, mp 127–129 °C. $[\alpha]_D^{24} = -78.5$ (*c* 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.73–5.80 (1H, m, C*H*=CH_2), 5.09 (1H, dd, *J* = 4.9, 0.9 Hz, CH=C*H*H), 5.06 (1H, d, *J* = 0.9 Hz, CH=CH*H*), 4.40 (1H, d, *J* = 8.2 Hz, NH), 3.88 (1H, dd, *J* = 8.2, 3.4 Hz, NCH), 2.61–2.68 (1H, m, MeC*H*), 1.29 (9H, s, ^{t}Bu), 1.03 (3H, d, *J* = 7.0 Hz, Me). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 172.9 (C=O), 139.3 (*C*H=CH_2), 116.0 (CH=*C*H_2), 62.9 (NCH), 57.1 (C), 41.5 (CH), 22.9 (Me × 3), 14.5 (Me). IR (KBr) cm^{-1}: 3268 (s), 2979 (s), 1721 (s), 1459 (m), 1384 (m), 1254 (m), 1024 (s). HRMS (positive FAB) *m*/*z*: 234.1160 $(M+1)^+$ (Calcd for $C_{10}H_{20}NO_3S$: 234.1165).

4.2.3. (2*S*,3*R*,S_S)-2-(*tert*-Butylsulfinamido)-3-methylpent-4-enoic acid *ent*-7c

$[\alpha]_D^{30} = +74.1$ (*c* 1.0, $CHCl_3$). ^{1}H NMR spectra were identical to those of **7c**. HRMS (positive FAB) *m*/*z*: 234.1166 $(M+1)^+$ (Calcd for $C_{10}H_{20}NO_3S$: 234.1165).

4.2.4. (2*R*,3*S*,R_S)-2-(*tert*-Butylsulfinamido)-3-propylpent-4-enoic acid 7d

Pale yellow oil. $[\alpha]_D^{29} = -37.9$ (*c* 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.60 (1H, dt, *J* = 17.1, 9.8 Hz, C*H*=CH_2), 5.11 (1H, d, *J* = 10.7 Hz, CH=C*H*H), 5.08 (1H, d, *J* = 17.4 Hz, CH=CH*H*), 4.36 (1H, d, *J* = 8.5 Hz, NH), 3.86 (1H, dd, *J* = 8.5, 5.2 Hz, CH), 2.37–2.43 (1H, m, NCH), 1.44–1.50 (1H, m, C*H*H), 1.20–1.49 (3H, m, CH*H* and CH_2), 1.29 (9H, s, ^{t}Bu). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 172.8 (C=O), 137.6 (*C*H=CH_2), 117.8 (CH=*C*H_2), 62.7 (NCH), 57.0 (C), 48.1 (CH), 31.8 (CH_2), 22.9 (Me × 3), 20.1, (CH_2), 13.9 (Me). IR ($CHCl_3$) cm^{-1}: 2956 (s), 1729 (s), 1456 (m), 1368 (m), 1039 (m). HRMS (positive FAB) *m*/*z*: 262.1482 $(M+1)^+$ (Calcd for $C_{12}H_{24}NO_3S$: 262.1478).

4.2.5. (2*S*,3*R*,S_S)-2-(*tert*-Butylsulfinamido)-3-propylpent-4-enoic acid *ent*-7d

$[\alpha]_D^{29} = +37.8$ (*c* 1.3, $CHCl_3$). ^{1}H NMR spectra were identical to those of **7d**. HRMS (positive FAB) *m*/*z*: 262.1482 $(M+1)^+$ (Calcd for $C_{12}H_{24}NO_3S$: 262.1478).

4.2.6. (2*R*,R_S)-2-(*tert*-Butylsulfinamido)-4-methylpent-4-enoic acid 7f

Pale yellow solid, mp 113–118 °C. $[\alpha]_D^{28} = -33.9$ (*c* 1.1, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.84 (1H, s, C=C*H*H), 4.77 (1H, s, C=CH*H*), 4.41 (1H, d, *J* = 8.5 Hz, NH), 4.03 (1H, dt, *J* = 8.9, 5.2 Hz, NCH), 2.53 (1H, dd, *J* = 14.0, 5.2 Hz, C*H*H), 2.33 (1H, dd, *J* = 14.0, 9.2 Hz, CH*H*), 1.74 (3H, s, Me), 1.26 (9H, s, ^{t}Bu). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 174.0 (C=O), 140.3 (*C*=CH_2), 114.6 (C=*C*H_2), 57.5 (NCH), 57.0 (C), 42.5 (CH_2), 23.0 (Me × 3), 22.0 (Me). IR (KBr) cm^{-1}: 3248 (s), 1717 (s), 1266 (s), 1017 (s). HRMS (positive FAB) *m*/*z*: 234.1163 $(M+1)^+$ (Calcd for $C_{10}H_{20}NO_3S$: 234.1165).

4.2.7. (2*S*,S_S)-2-(*tert*-Butylsulfinamido)-4-methylpent-4-enoic acid *ent*-7f

$[\alpha]_D^{30} = +32.2$ (*c* 1.0, $CHCl_3$). ^{1}H NMR spectra were identical to those of **7f**. HRMS (positive FAB) *m*/*z*: 234.1163 $(M+1)^+$ (Calcd for $C_{10}H_{20}NO_3S$: 234.1165).

4.3. General procedure to remove the *tert*-butylsulfinyl group (Table 3)

A mixture of **7a** (41.5 mg, 0.189 mmol) in aq HCl (6 mol/L, 1.9 mL) was stirred for 4 h at 90 °C. After the reaction mixture was concentrated in vacuo, the residue was purified over DOWEX 50 W × 4 (100–200 mesh, H^+ activated, 0.80 g). Next, H_2O followed by 2.8% NH_3 aq eluted **10a** (15.0 mg, 69%). For the synthesis of **10d**, *ent*-**10d**, **11,** and *ent*-**11**, the ion exchanged materials of them were chromatographed on silica gel (neutral) ($CHCl_3$/MeOH/28% NH_3 aq, 70:30:2).

4.3.1. (*R*)-2-Aminopent-4-enoic acid 10a

Colorless powder, mp 149 °C (dec). $[\alpha]_D^{25} = +23.7$ (*c* 0.11, H_2O) for 94% ee {Ref., $[\alpha]_D^{22} = +33.8$ (*c* 1.05, H_2O) for 95% ee[29]}. ^{1}H NMR (500 MHz, D_2O) δ: 5.75–5.83 (1H, m, C*H*=CH_2), 5.29 (1H, d, *J* = 17.1 Hz, CH=C*H*H), 5.27 (1H, d, *J* = 10.1 Hz, CH=CH*H*), 3.82 (1H, dd, *J* = 6.7, 5.2 Hz, NCH), 2.67 (1H, m, C*H*H), 2.63 (1H, m, CH*H*). ^{13}C NMR (D_2O, 125 MHz) δ: 177.0 (C=O), 134.2 (*C*H=CH_2), 123.3 (CH=*C*H_2), 56.8 (NCH), 37.7 (CH_2). NMR data were good agreement with those of the reported data.[29] IR (KBr) cm^{-1}: 2928 (s), 1578 (s). HRMS (positive FAB) *m*/*z*: 116.0709 $(M+1)^+$ (Calcd for $C_5H_{10}NO_2$: 116.0712). HPLC: t_S = 5.5 min and t_R = 7.0 min. (*RS*)-Allylglycine (Aldrich) was used as a (*RS*)-sample. **10a**:*ent*-**10a** = 97:3 (94% ee).

4.3.2. (2*R*,3*S*)-2-Amino-3-methylpent-4-enoic acid 10c

Product **10c** (31.9 mg, 82%) was obtained from **7c** (70.0 mg,) according to the procedure described in Section 4.3.1. Colorless powder, mp 205 °C (dec). $[\alpha]_D^{26} = -15.8$ (*c* 0.61, H_2O) {Ref., for (2*S*,3*R*)-isomer, $[\alpha]_D^{24} = +16.0$ (*c* 1.02, H_2O)[16]}. ^{1}H NMR (500 MHz, D_2O) δ: 5.86 (1H, ddd, *J* = 17.7, 10.5, 6.3 Hz, C*H*=CH_2), 5.27 (1H, d, *J* = 11.0 Hz, CH=C*H*H), 5.26 (1H, d, *J* = 16.8 Hz, CH=CH*H*), 3.78 (1H, d, *J* = 4.0 Hz, MeCH), 2.86–2.93 (1H, m, NCH), 1.11 (3H, d, *J* = 7.0 Hz, Me). ^{13}C NMR (D_2O, 125 MHz) δ: 174.0 (C=O), 138.3 (*C*H=CH_2), 118.2 (CH=*C*H_2), 59.1 (NCH), 38.4 (CH), 13.8 (Me). NMR data were good agreement with those of the reported data.[25] IR (KBr) cm^{-1}: 2944 (m), 1583 (s), 1508 (s), 1412 (m). HRMS (positive FAB) *m*/*z*: 130.0866 $(M+1)^+$ (Calcd for $C_6H_{12}NO_2$: 130.0869). HPLC: t_{2S} = 8.6 min and t_{2R} = 10.9 min. **10c**:*ent*-**10c** = >99:1 (>98% ee).

Useful characteristic NMR signals to distinguish **10c** from the corresponding *anti*-amino acid are as follows;[25] ^{1}H NMR (D_2O), *syn* 3.76 ppm (d, *J* = 4.1 Hz) and *anti* 3.61 ppm (d, *J* = 5.5 Hz). ^{13}C NMR (D_2O), *syn* 13.6 ppm and *anti* 16.0 ppm.

4.3.3. (2*S*,3*R*)-2-Amino-3-methylpent-4-enoic acid *ent*-10c

Product *ent*-**10c** (32.7 mg, 84%) was obtained from *ent*-**7c** (70.0 mg) according to the procedure described in Section 4.3.1. Mp 208 °C (dec). $[\alpha]_D^{26} = +16.9$ (*c* 0.61, H_2O) {Ref.[16] $[\alpha]_D^{24} = +16.0$ (*c* 1.02, H_2O)}. ^{1}H NMR spectra were identical to those of **10c**. HRMS (positive FAB) *m*/*z*: 130.0872 $(M+1)^+$ (Calcd for $C_6H_{12}NO_2$: 130.0869). HPLC: t_{2S} = 8.6 min and t_{2R} = 10.9 min. *ent*-**10c**:**10c** = >99:1 (>98% ee).

4.3.4. (2*R*,3*S*)-2-Amino-3-propylpent-4-enoic acid 10d

Product **10d** (26.8 mg, 90%) was obtained from **7d** (50.0 mg) according to the procedure described in Section 4.3.1. Colorless powder, mp 142–145 °C (dec). $[\alpha]_D^{23} = +2.2$ (*c* 0.54, MeOH). ^{1}H NMR (500 MHz, D_2O) δ: 5.62–5.74 (1H, m, *CH*=CH_2), 5.23 (1H, d, *J* = 11.7 Hz, *CH*=C*H*H), 5.22 (1H, d, *J* = 13.5 Hz, *CH*=CH*H*), 3.57 (1H, d, *J* = 3.6 Hz, NCH), 2.61 (1H, t, *J* = 4.2 Hz, CH), 1.28–1.53 (2H, m, CH_2), 1.41 (2H, q, *J* = 7.4 Hz, CH_2), 0.92 (3H, t, *J* = 7.2 Hz, CH_3). ^{13}C NMR (D_2O, 125 MHz) δ: 176.0 (C=O), 138.9 (*CH*=CH_2), 122.0 (CH=*C*H$_2$), 61.1 (NCH), 47.1 (CH), 34.2 (CH_2), 22.7 (CH_2), 15.8 (CH_3). IR (KBr) cm^{-1}: 2959 (s), 2936 (s), 1587 (s), 1405 (m). HRMS (positive FAB) *m*/*z*: 158.1179 $(M+1)^+$ (Calcd for $C_8H_{15}NO_2$: 157.1104). HPLC: t_{2R} = 63.2 min. **10d**:*ent*-**10d** = >99:1 (>98% ee).

4.3.5. (2*S*,3*R*)-2-Amino-3-propylpent-4-enoic acid *ent*-10d

Product *ent*-**10d** (27.0 mg, 90%) was obtained from *ent*-**7d** (50.0 mg) according to the procedure described in Section 4.3.1. Colorless powder, mp 143–147 °C (dec.). $[\alpha]_D^{25} = -3.2$ (*c* 0.62, MeOH). ^{1}H NMR spectra were identical to those of **11d**. HRMS (positive FAB) *m*/*z*: 158.1183 $(M+1)^+$ (Calcd for $C_8H_{15}NO_2$: 157.1104). HPLC: t_{2R} = 56.7 min. *ent*-**10d**:**10d** = >99:1 (>98% ee).

4.3.6. (*R*)-2-Amino-4-hydroxy-4-methylpentanoic acid 11

Product **11** (14.9 mg, 46%) was obtained from **7f** (51.3 mg) according to the procedure described in Section 4.3.1. Colorless solid. Mp 154 °C (dec). $[\alpha]_D^{31} = +9.80$ (*c* 0.33, MeOH). ^{1}H NMR (400 MHz, D_2O) δ: 3.94 (1H, dd, *J* = 9.6, 2.8 Hz, NCH), 2.11 (1H, dd, *J* = 15.2, 2.8 Hz, C*H*H), 1.92 (1H, dd, *J* = 15.6, 10.4 Hz, CH*H*), 1.34 (6H, s, Me × 2). ^{13}C NMR (D_2O, 100 MHz) δ: 175.6 (C=O), 71.6 (C), 53.2 (NCH), 42.6 (CH_2), 30.5 (Me), 27.2 (Me). NMR data were in good agreement with those of the reported data.[42] HRMS (positive FAB) *m*/*z*: 148.0969 $(M+1)^+$ (Calcd for $C_6H_{14}NO_3$: 148.0974). HPLC: t_R = 8.8 min and t_S = 5.9 min.

4.3.7. (*S*)-2-Amino-4-hydroxy-4-methylpentanoic acid *ent*-11

Product *ent*-**11** (21.8 mg, 68%) was obtained from *ent*-**7f** (50.6 mg) according to the procedure described in Section 4.3.1. $[\alpha]_D^{31} = -11.4$ (*c* 0.51, MeOH). ^{1}H NMR spectra were identical to those of **11**. HRMS (positive FAB) *m*/*z*: 148.0973 $(M+1)^+$ (Calcd for $C_6H_{14}NO_3$: 148.0974).

4.3.8. (*R*)-2-Amino-4-methylpent-4-enoic acid 10f

A mixture of **7f** (38.7 mg, 0.166 mmol) in HCl in dioxane (4 mol/L)/2-propanol (1:2, 5.0 mL) was stirred for 1 h at room temperature. After the reaction mixture was concentrated in vacuo, the residue was purified over DOWEX 50 W × 4 (100–200 mesh, H^+ activated, 0.78 g). H_2O followed by 2.8% NH_3 aq eluted **10f** (19.5 mg, 91%). Colorless powder, mp 200 °C (dec.). $[\alpha]_D^{18} = +40.7$ (*c* 0.39, H_2O) {Ref., for (*S*)-isomer, $[\alpha]_D^{20} = -30.9$ (*c* 1.04, H_2O)[9]}. ^{1}H NMR (400 MHz, D_2O) δ: 5.00 (1H, d, *J* = 1.2 Hz, C=C*H*H), 4.89 (1H, s, C=CH*H*), 3.84 (1H, dd, *J* = 8.0, 6.8 Hz, NC*H*), 2.68 (1H, dd, *J* = 14.7, 4.8 Hz, C*H*H), 2.50 (1H, dd, *J* = 14.4, 9.6 Hz, CH*H*), 1.77 (3H, s, CH_3). ^{13}C NMR (D_2O, 100 MHz) δ: 177.2 (C=O), 142.8 (C), 118 (C=*C*H$_2$), 55.3 (NCH), 41.7 (CH_2), 23.4 (CH_3). NMR data were in good agreement with those of the reported data.[9] IR (KBr) cm^{-1}: 2967 (s), 1555 (s), 1508 (m), 1405 (m). HRMS (positive FAB) *m*/*z*: 130.0872 $(M+1)^+$ (Calcd for $C_6H_{12}NO_2$: 130.0869). HPLC: t_R = 15.2 -min. **10f**:*ent*-**10f** = 97:3 (94% ee).

4.3.9. (*S*)-2-Amino-4-methylpent-4-enoic acid *ent*-10f

Product *ent*-**10f** (20.3 mg, 93%) was obtained from *ent*-**7f** (39.6 mg) according to the procedure described in Section 4.3.8. Colorless powder, mp 202 °C (dec). $[\alpha]_D^{20} = -36.3$ (*c* 0.45, H_2O) {Ref., $[\alpha]_D^{20} = -30.9$ (*c* 1.04, H_2O)[9]}. ^{1}H NMR spectra were identical to those of **10f**. HRMS (positive FAB) *m*/*z*: 130.0869 $(M+1)^+$ (Calcd for $C_6H_{12}NO_2$: 130.0869). HPLC: t_S = 9.5 min. *ent*-**10f**:**10f** = 97:3 (94% ee).

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