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Asymmetric Synthesis of (+)-Phosphinothricin and Related Compounds by the Michael Addition of Glycine Schiff Bases to Vinyl Compounds

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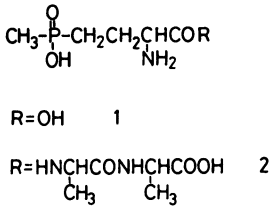
(*S*)-(+)-Phosphinothricin was prepared in good optical yield by the Michael addition of chiral glycine Schiff base derived from (*S*)-2-hydroxy-3-pinanone to vinyl phosphorus compound. (*R*)-(−)-Phosphinothricin, an enantiomeric isomer, can also be prepared from the same chiral glycine Schiff base by choosing suitable reaction temperature.

The stereochemistry of an amino carbon is a biologically important factor in naturally occurring phosphorus analogues of glutamic acid, such as phosphinothricin ((*S*)-(+)-(**1**)),[1] its alanylalanine derivative **2**,[1] and (+)-2-amino-4-phosphonobutyric acid ((*S*)-(+)-(**3**)),[2] which have been paid a special attention for their herbicidal[3] and antiviral activities.

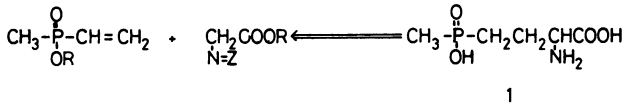


Scheme 1.

Although several methods for the racemic synthesis were already known[4], there have been reported a few example for the asymmetric synthesis.[5] In our preliminary communications,[4g,5] we reported a practical synthesis of (±)-**1** and an effective asymmetric synthesis of (*S*)-(+)-**1**, (*S*)-(+)-**3**, and their enantiomers by the Michael addition of glycine Schiff base to vinyl phosphorus compounds. In the latter, the S- and R-configuration were induced from two glycine Schiff bases bearing different chiral auxiliaries derived from (*S*)-2-hydroxy-3-pinanone ((−)-(**9**)) and its (R)-isomer (+)-**9**, respectively. In the course of our study on the asymmetric Michael addition, it has been found that the stereochemistry of the Michael adducts is reversed depending on reaction temperature to yield the *S*-enantiomer at −78 °C and *R*-enantiomer at an elevated temperature. Thus, both enantiomers can be easily prepared from a single chiral glycine Schiff base (−)-**10** by choosing suitable reaction temperature. In this paper, we would like to report the features of the Michael addition of glycine Schiff bases to several kinds of vinyl compounds in detail.

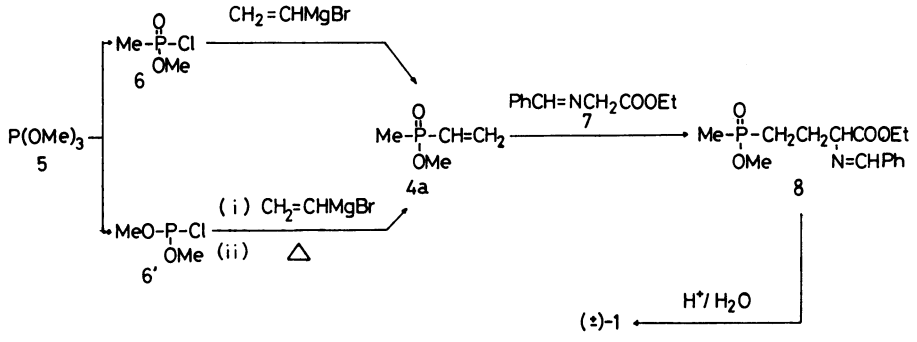
Results and Dicussion

Our basic strategy for the synthesis of glutamic acid analogues involves the Michael addition of glycine Schiff base to appropriate vinyl compounds; The retrosynthetic analysis of **1** is illustrated in Scheme 2.



Scheme 2.

Racemic Synthesis of Phosphinothricin 1. Racemic (±)-**1** was synthesized according to the procedures shown in Scheme 3. Methyl vinylmethylphosphinate (**4a**), a Michael acceptor, was conveniently prepared by the following two methods: Trimethyl phosphite (**5**) was converted to methylphosphonochloridate **6** by the Arbusov rearrangement followed by chlorination. Coupling of a vinyl group with phosphorus atom was

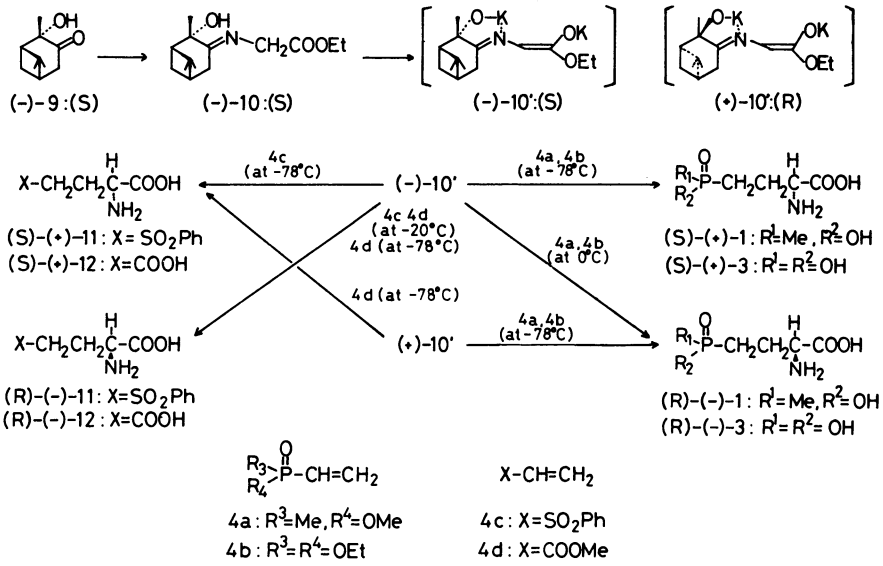


Scheme 3.

accomplished by the addition of vinylmagnesium bromide to **6** in tetrahydrofuran (THF) to give the desired phosphinate **4a** in 61% yield. As a vinyl group could be directly introduced into various phosphonochoridate, this procedure provides a general and facile method for the preparation of vinylalkylphosphinates. According to an alternative method, phosphorochloridite **6'**, prepared by treating **5** with phosphorous trichloride, was subjected to alkylative coupling with vinylmagnesium bromide in THF and the resulting vinylphosphonite was heated to afford **4a**. The α-amino acid part could be successfully introduced into the vinyl group of **4a** by utilizing Schiff base **7** of glycine ethyl ester as a Michael donor. Treatment of the Schiff base with **4a** in the presence of 0.2 equiv of base afforded the adduct **8**, which was successively refluxed with 6M-hydrochloric acid (1 M=1 mol dm^{-3}) for 24 h to give racemic phosphinothricin (±)-**1** as shown in Table 1 after purification (Dowex 50×2). Although the use of either sodium ethoxide or potassium hydroxide in ethanol gave the (±)-**1** in good yield, the latter base was preferable in practice because the reaction is carried out at room temperature (Entries 1—4). The use of the other bases, DBN and Triton B, could not improve the yield of (±)-**1**. (Entries 6, 7).

Asymmetric Synthesis of (*S*)-(+)-1 and (*R*)-(−)-1. A successful Michael addition of the achiral glycine Schiff base **7** suggested that the desired S-configuration of **1** would be prepared by a similar procedure utilizing a chiral Schiff base **7**. Attempted experiment to perform the asymmetric addition of **7** to **4a** in the presence of a chiral base, quinine, was unsuccessful, while the addition of a chiral Schiff base to **4a** provided optically active adduct **1**. Although a number of asymmetric reactions with chiral acceptors has been known,[6] there have been reported a few examples of using chiral Michael donors.[7]

The asymmetric Michael addition was shown in Scheme 4. Chiral Schiff bases (−)-**10** and (+)-**10** having chiral auxiliaries were readily prepared by the condensation of glycine ethyl ester with (*S*)-2-hydroxy-3-pinanone (−)-(**9**) and its (R)-isomer (+)-(**9**) obtained by oxidation of natural (+)-α-pinene and (−)-α-pinene, respectively.[8] The results of the Michael addition of these chiral Schiff base to



Scheme 4.

Table 1. The Michael Addition of **7** to **4a**

Entry	Base	Ratio[a]	Solvent	Temperature/°C (Time/h)	Yield/% (±)-**1**
1	EtONa	1 : 1.5 : 0.25	EtOH	−10 (5)	64
2	EtONa	1 : 1 : 0.25	EtOH	−10 (4)	50
3	EtONa	1 : 1 : 0.25	EtOH	5 (7)	36
4	KOH	1 : 1.5 : 0.2	EtOH	r.t. (2)	65
5	KOH	1 : 1.5 : 0.2	PhH	r.t. (4)	30
6	DBN	1 : 1.5 : 0.2	$PhCH_3$	r.t. (6)	11
7	Triton B	1 : 1.5 : 0.2	EtOH	r.t. (2)	26

a) Molar ratio of **4a** : **7** : base.

vinylphosphinate **4a** investigated under various conditions at −78 °C are summarized in Table 2. (Entries 1—10) Metalation of the chiral Schiff base (−)-**10** with two equivalents of potassium *t*-butoxide (*t*-BuOK) in THF followed by conjugate addition of the dianion **10′** to an equimolar amount of vinylphosphinate **4a** at −78 °C gave the Michael adduct, which was further converted into the desired phosphinothricin (S)-(+)-**1** with 79% optical purity in 66% yield (Entry 1). The results of the effects of concentration and molar ratio of the reactants, reverse addition of the reactants, and solvent are summarized in Entries 2—9. Particularly, reverse addition of the reactants reduced enantiomeric excess extremely from 79 to 2%. In addition, similar treatment after metalation of (−)-**10** with other base, sodium hydride or lithium diisopropylamide, gave no desired product. Judging from extreme decrease of the optical purities shown in the effects of the reverse addition and change of the molar ratio, a proceeding metalation of (−)-**10** with *t*-BuOK seemed to be important for this asymmetric synthesis. Similar asymmetric addition of the other glycine Schiff base (+)-**10** to **4a** gave unnatural phosphinothricin (*R*)-(−)-(**1**) with 73% optical purity in a similar yield as (*S*)-(+)-**1**. (Entry 10).

The stereoselectivity is not influenced by the kind of the solvents, such as toluene, Et_2O, and THF. (Entries 1, 8, and 9) However, addition of hexamethylphosphoric triamide (HMPA) or dicyclohexano-18-

Table 2. The Asymmetric Michael Addition of (−)-**10** and (+)-**10** to Vinyl Compounds **4a**, **4b**, **4c**, and **4d** in the Presence of *t*-BuOK

Entry	Michael		Condition				Amino acid			
	Acceptor	Donor	Ratio[a]	Additive	Solvent (Concn)[b]	Temperature °C	Compd No.	Total yield/%	$[\alpha]_D^{25}$ deg	Optical purity/% (Confign.)
1	**4a**	(−)-**10**	1 : 1 : 2		THF (16)	−78	**1**	66	+13.4[c]	79[d] (S)
2	**4a**	(−)-**10**	1 : 1 : 2		THF (4)	−78	**1**	63	+8.2[c]	48[d] (S)
3	**4a**	(−)-**10**	1 : 1 : 2		THF (8)	−78	**1**	49	+10.6[c]	62[d] (S)
4	**4a**	(−)-**10**	1 : 1 : 2		THF (79)	−78	**1**	45	+6.0[c]	35[d] (S)
5	**4a**	(−)-**10**	1 : 2 : 2		THF (16)	−78	**1**	59	+12.7[c]	75[d] (S)
6	**4a**	(−)-**10**	2 : 1 : 2		THF (16)	−78	**1**	39	+5.6[c]	33[d] (S)
7	**4a**	(−)-**10**[e]	1 : 1 : 2		THF (16)	−78	**1**	62	+0.3[c]	2[d] (S)
8	**4a**	(−)-**10**	1 : 1 : 2		Et_2O (16)	−78	**1**	65	+13.3[c]	78[d] (S)
9	**4a**	(−)-**10**	1 : 1 : 2		$PhCH_3$ (16)	−78	**1**	56	+10.1[c]	59[d] (S)
10	**4a**	(+)-**10**	1 : 1 : 2		THF (16)	−78	**1**	64	−12.4[c]	73[d] (R)
11	**4b**	(−)-**10**	1 : 1 : 2		THF (16)	−78	**1**	68	+14.6[f]	50[g] (S)
12	**4b**	(+)-**10**	1 : 1 : 2		THF (16)	−78	**3**	65	−13.0[f]	45[g] (R)
13	**4d**	(−)-**10**	1 : 1 : 2		THF (16)	−78	**12**	57	−17.7[f]	56[h] (R)
14	**4d**	(+)-**10**	1 : 1 : 2		THF (16)	−78	**12**	55	+14.9[f]	47[h] (S)
15	**4a**	(−)-**10**	1 : 1 : 2		THF (16)	−60	**1**	49	−4.8[c]	28[d] (R)
16	**4a**	(−)-**10**	1 : 1 : 2		THF (16)	−50	**1**	46	−6.8[c]	40[d] (R)
17	**4a**	(−)-**10**	1 : 1 : 2		THF (16)	−35	**1**	66	−8.0[c]	47[d] (R)
18	**4a**	(−)-**10**	1 : 1 : 2		THF (16)	−20	**1**	43	−11.5[c]	68[d] (R)
19	**4a**	(−)-**10**	1 : 1 : 2		THF (16)	−10	**1**	31	−8.6[c]	51[d] (R)
20	**4a**	(−)-**10**	1 : 1 : 2		THF (16)	0	**1**	24	−11.7[c]	69[d] (R)
21	**4a**	(−)-**10**	1 : 1 : 2		THF (16)	10	**1**	23	−11.8[c]	69[d] (R)
22	**4a**	(−)-**10**	1 : 1 : 2		THF (16)	20	**1**	15	−10.0[c]	59[d] (R)
23	**4a**	(−)-**10**	1 : 1 : 2		THF (16)	−78→0	**1**	57	−6.2[c]	43[d] (R)
24	**4a**	(−)-**10**	1 : 1 : 2	HMPA[i]	THF (16)	−78	**1**	42	+7.6[c]	45[d] (S)
25	**4a**	(−)-**10**	1 : 1 : 2	8-crown[i]	THF (16)	−78	**1**	51	+6.8[c]	40[d] (S)
26	**4b**	(−)-**10**	1 : 1 : 2		THF (16)	−60	**3**	41	−3.57[f]	12[g] (R)
27	**4b**	(−)-**10**	1 : 1 : 2		THF (16)	−40	**3**	30	−20.7[f]	71[g] (R)
28	**4b**	(−)-**10**	1 : 1 : 2		THF (16)	−20	**3**	44	−20.9[f]	72[g] (R)
29	**4b**	(−)-**10**	1 : 1 : 2		THF (16)	0	**3**	35	−19.6[f]	68[g] (R)
30	**4d**	(−)-**10**	1 : 1 : 2		THF (16)	−20	**12**	39	−21.6[f]	69[h] (R)
31	**4c**	(−)-**10**	1 : 1 : 2		THF (16)	−78	**11**	45	+7.23[f]	
32	**4c**	(−)-**10**	1 : 1 : 2		THF (16)	−20	**11**	22	−25.1[f]	

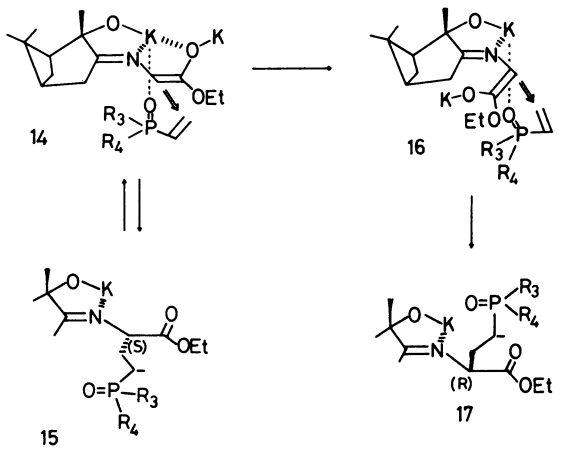
a) Molar ratio of **4** : **10** : base. b) Molar concentration/%. c) *c* 1.0 in H_2O. d) Based on $[\alpha]_D^{25}$ +17° (*c* 1.0, H_2O) in Ref. 14. e) Reverse addition ((−)-**10** was added to **4a**). f) *c* 1.0 in 6M HCl. g) Based on $[\alpha]_D$ +29° (6M HCl) in Ref. 2. h) Based on $[\alpha]_D$ +31.4° of (+)-glutamic acid. i) Five equivalents of the additive was used.

crown-6 (18-crown-6) which has strong ability to solvate cations,[9] at −78 °C, reduced optical purity of the product (Entries 24 and 25). It is assumed that the chelate structure existed in transition state plays an important role in controlling the stereochemistry and a strong coordination of solvent depressed stereoselectivity by interfering the chelation.[10]

Thus, the metalation of (−)-**10** with base resulted in the formation of five-membered rigid chelate structure and next phosphorus oxygen of vinyl phosphorus compound would coordinate to the potassium cation of potassium alkoxide. Consequently, the Michael addition would take place preferentially from the botton face as shown in **14**.

The Asymmetric Michael Addition of 10 to Other Vinyl Compounds. Similar additioin of **10** at −78 °C to three vinyl acceptors, diethyl vinylphosphonate (**4b**), phenyl vinyl sulfone (**4c**), and methyl acrylate (**4d**), was further investigated as shown in Scheme 4. Asymmetric addition of (−)-**10** and (+)-**10** to **4b** smoothly proceeded in a similar way to afford biologically interesting phosphonic acid (*S*)-(+)-**3**,[2] and its isomer (*R*)-(−)-**3** in good optical yields, respectively (Entries 11 and 12). Although addition of (−)-**10** to **4c** also took place smoothly, the data of the optical rotation and high-performance liquid chromatography (HPLC) analysis suggested that the expected chiral sulfone (+)-**11** had less enantiomeric excess than those of phosphorus compound (*S*)-(+)-**1** and (*S*)-(+)-**3** (Entry 31). Interestingly, addition of (−)-**10** and (+)-**10** to **4d** gave (−)-glutamic acid (*S*)-(−)-**12** and and its isomer (*R*)-(+)-**12** in fairly good yields, respectively (Entries 13 and 14). That is, the result of these reactions at −78 °C indicated that the stereochemical course of the addition of (−)-**10** and (+)-**10** to methyl acrylate **4d** was the same as that of alkylation and opposite to that of addition to vinyl phosphorus compounds **4a** and **4b**. However, study of the effect of reaction temperature in these reaction revealed another information about the stereochemistry as described in the following.

Effect of Reaction Temperature. It was found that the reaction temperature is strongly influential on the diastereoface selectivity of the addition as summarized in Table 2 (Entries 15—32). For example, addition product **1** prepared from (−)-**10** with **4a** at 0 °C had negative optical rotation (Entry 20). When the reaction temperature is elevated from −78 up to 20 °C, increase of enantiomeric excess of (*R*)-(−)-**1** was observed. Furthermore, treatment of (−)-**10** with **4a** at −78 °C for 1 h and then at 0 °C for 0.5 h before quenching also afforded (*R*)-(−)-**1** (Entry 23), which was assumed to be produced by isomerization of (*S*)-(+)-**1** formed at −78 °C. These results suggested that (*R*)-(−)-**1** obtained from (−)-**10** with **4a** at 0 °C appeared to be a thermodynamic product.[11] It is assumed that, at low temperature, the reaction



Scheme 5.

proceeds via a double chelated intermediate and the addition takes place from the α face to produce **15** as shown in **14**, **15**, whereas at elevated temperature, the potassium enolate adopts the cisoid conformation shown as the increased molecular mobility leads to the potassium-oxygen interaction being broken. The addition then occurs from the α face as for **14** to produce, this time, **17** as shown in **16**, **17**.

Almost the same results were observed in addition of (−)-**10** to phosphonate **4b** (Entries 11 and 26—29). In the reaction of phenyl vinyl sulfone **4c**, similar change of the stereochemistry was observed by changing reaction temperature from −78 to −20 °C (Entries 31 and 32). Although the change of the configuration was not observed in the reaction of (−)-**10** with **4d**, enantiomeric excess of addition product (*R*)-(−)-**12** at elevated temperature was increased compared with that at −78 °C (Entries 13 and 30). Therefore, in this Michael addition of (−)-**10** to four vinyl acceptors, increase of the product with R-configuration was observed by an elevation of the reaction temperature. From these results, it is assumed that the geometry of the imine and potassium enolate in **10'** at the reaction temperature play an important role in this asymmetric Michael addition. Addition of intermediate **14** or **16** to the acceptor always takes place from the face opposite to the β-methyl in pinanone, resulting in **15** or **17**, respectively.

As the addition products of (−)-**10** to **4a** and **4b** were obtained in good optical yields either −78 or 0 °C, this asymmetric Michael addition was useful for preparation of S- and R-enantiomers of **1** and **3** from (−)-**10** and vinyl phosphorus compounds by just changing reaction temperature.

The herbicidal activity of synthesized (*S*)-(+)-**1** was nearly equal to natural (*S*)-(+)-**1** in foliage treatment. However, synthesized (*R*)-(−)-**1**, unnatural form, had almost no herbicidal activity.

Experimental

The IR spectra were recorded on a JASCO IR-G spectrometer and mass spectra on a JEOL-OISG spectrometer. The ^1H and ^{13}C NMR spectra were taken on a Varian FT-80A spectrometer using TMS or DSS as an internal standared.

Methyl Methylphosphonochloridate (6): The chloride **6** was prepared from trimethyl phosphite and phosphorus pentachloride according to the procedure in Ref. 12; bp 59—61 °C (11 mmHg) (1 mmHg=133.322 Pa) (lit,[12] 64 °C (15 mmHg)).

Dimethyl Phosphorochloridite (6′): The chloride 6′ was prepared from trimethyl phosphite and phosphorus trichloride by the procedure in Ref. 13; bp 40 °C (40 mmHg).

Methyl Methylvinylphosphinate (4a): Method A: A solution of 1.00 M vinylmagnesium bromide in THF (18.7 ml, 18.7 mmol) was added dropwise to a solution of methyl methylphosphonochloridate (2.00 g, 15.6 mmol) in THF (5 ml) under argon at −20 °C, and the mixture was stirred at the same temperature for 1 h, 2M ammonium chloride (10 ml) was added to the reaction mixture. The solution was extracted with chloroform (15 ml×3) and dried over magnesium sulfate. The solvent was removed in vacuo, and the residue was distilled to give **4a** (1.14 g, 61%) as a colorless oil; bp 74—76 °C (14 mmHg); IR (neat) 1610 (C=C), 1300 (P=O), 1210 (P=O), and 1030 (P-O-CH_3) cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.51 (3H, d, J=15 Hz), 3.65 (3H, d, J=11 Hz), 5.80—6.50 (3H, m).

Method (B); To a stirred solution of the chloride **6′** (2.00 g, 15.6 mmol) in THF (10 ml) was added 1.00 M vinylmagnesium bromide (1.72 ml, 1.72 mmol) in THF dropwise with cooling to maintain the reaction temperature at −10 °C. The mixture was stirred for 3 h at 0 to 25 °C. After distillation (bp 40—45 °C (30 mmHg)), the colorless oil was heated at 60 °C for 9 h. The solution was distilled to give **4a** (1.42 g, 76%) as a colorless oil; bp, IR, and NMR data were identical with those of **4a** in Method (A).

(±)-Phosphinothricin (±)-(1): Entry 4 in Table 1; To a stirred solution of the Schiff base **7** (1.19 g, 6.24 mmol) and 95% KOH (47 mg, 0.838 mmol) in EtOH (5 ml) was added a solution of vinylphosphinate **4a** (500 mg, 4.16 mmol) in EtOH (5 ml) at room temperature. After the reaction mixture was stirred for 2 h at room temperature, the solvent was removed. To the residue was added 6M HCl (20 ml) and the solution was refluxed for 24 h. After concentration of the resulting solution followed by washing with benzene, the residue was dissolved in EtOH-H_2O (1:1, 12 ml) and a large excess amount of propylene oxide was added. The resulting solution was concentrated and purified by ion-exchange resin (Dowex 50×2). Elution with water and subsequent removal of water gave (±)-**1** as a colorless crystals (490 mg, 69%); mp 211—213 °C (lit, [14] (mp 214 °C); ^1H NMR (D_2O) δ=1.45 (3H, d, J=14 Hz), 1.5—2.6 (4H, m), 4.04 (1H, t, J=6 Hz); ^{13}C NMR (D_2O) δ=14.81 (d, J=92.8), 23.96 (d, J=2.4 Hz), 26.58 (d, J=92.2 Hz), 54.43 (d, J=16.2 Hz), 172.9 (s).

Entry 1 in Table 1; to a stirred solution of sodium (19.2 mg, 0.833 mmol) in EtOH (5 ml) was added a solution of the Schiff base **7** (956 mg, 5.00 mmol) in EtOH (1 ml) at −10°C, followed by addition of a vinylphosphinate **4a** (400 mg, 3.33 mmol) in EtOH (1 ml) at −10 °C. After the same workup and purification, (±)-**1** was obtained as a colorless crystals, (387 mg, 64%); mp 212—214 °C.

(−)- and (+)-2-Hydroxy-3-pinanone (−)-9 and (+)-(9): The ketol (−)-**9** was prepared from (1*R*,5*R*)-(+)-α-pinene ($[\alpha]_D^{22}$ +47.1° (neat)) by the procedure in Ref. 8; bp 115—117 °C (15 mmHg) (lit,[8] 118—119 °C (15 mmHg); $[\alpha]_D^{25}$ −37.0° (*c* 2.60, $CHCl_3$) (lit,[8] $[\alpha]_D^{25}$ −38.9° (*c* 2.64, $CHCl_3$)); IR (neat) 3450 (OH) and 1720 (C=O) cm^{-1}; NMR ($CDCl_3$) δ=0.89 (3H, s), 1.37 (3H, s), 1.38 (3H, s), 1.6—2.6 (6H, m); the optical purity of the ketol (−)-**9** may be estimated to be at least 92.5%.

According to the same procedure, (+)-**9** was prepared from (1*S*,5*S*)-(+)-α-pinene ($[\alpha]_D^{22}$ −42.0° (neat)); $[\alpha]_D^{25}$ +33.0° (*c* 2.60, $CHCl_3$).

The Chiral Schiff Base (−)-(10) and (+)-(10): A solution of glycine ethyl ester hydrochloride (2.99 g, 21.4 mmol), the ketol (−)-**9** (3.00 g, 17.8 mmol), and triethylamine (2.17 g, 21.4 mmol) in benzene (50 ml) containing boron trifluoride etherate (0.1 g) was refluxed for 6 h using a Dean-Stark apparatus under nitrogen. After filtration followed by evaporation, the reasidue was distilled to give (−)-**10** (3.52 g, 78%) as a slight yellow oil; bp 106—108 °C (0.3 mmHg); $[\alpha]_D^{25}$ −7.6° (*c* 3.00, $CHCl_3$); IR (neat) 3250 (OH), 1760 (COOEt), and 1660 (C=N) cm^{-1}; NMR ($CDCl_3$) δ=0.88 (3H, s), 1.29 (3H, t, J=7 Hz), 1.34 (3H, s), 1.52 (3H, s), 1.6—2.6 (6H, m), 2.60 (1H, s), 4.15 (2H, s), 4.20 (2H, q, J=7 Hz); FD MS *m/z* 254 (M+1). According to the same procedure, (+)-**10** was prepared from (+)-**9**; $[\alpha]_D^{25}$ +6.8° (*c* 3.00, $CHCl_3$).

General Procedure for Reaction of the Chiral Schiff Base (10) with Michael Acceptors:. To a stirred solution of potassium *t*-butoxide (1.58 mmol) in THF (3 ml) was added a solution of the chiral Schiff base **10** (0.789 mmol) in THF (1 ml) at −78°C, followed by addition of a solution of vinyl compound (0.789 mmol) in THF (1 ml) at −78 °C under argon. After stirred for 1 h at −78 °C, 1M HCl (3 ml) was added to the resulting yellow solution and the solvent was removed. To the residue was added 6M HCl (4 ml) and the solution was refluxed for 24 h. After concentration of the resulting solution followed by washing with benzene, the residue was dissolved in EtOH-H_2O (4 ml) and a large excess amount of propylene oxide was added. The resulting solution was concentrated and purified by ion-exchange resin (Dowex 50×2). Elution with water and subsequent removal of water gave the amino acid.

(−)-and (+)-Phosphinothricin (−)- and (+)-(1): Entry 1 in Table 2; (S)-(+)-**1** was obtained from vinylphosphinate **4a** as a colorless crystals according to the general procedure; mp 214—216 °C (decomp); ^1H NMR (D_2O) δ=1.45 (3H, d, J=14 Hz), 1.5—2.6 (4H, m), 4.04 (1H, t, J=6 Hz); FD MS *m/z* 182 (M+1).

Entry 23 in Table 2; After the addition reaction according to the general procedure, the reaction mixture was stirred for 1 h at −78 °C and then warmed at 0 °C for 0.5 h.

Entries 24 and 25 in Table 2; To a stirred solution of *t*-BuOK (1.58 mmol) and additive (3.95 mmol) in THF (4 ml) was added a solution of the chiral Schiff base (−)-**10** (0.789 mmol) in THF (1 ml) at −78 °C, followed by addition of a solution of vinylphosphinate **4a** (0.789 mmol) in THF (1 ml) at −78 °C under argon. The reaction mixture was stirred for 1 h at −78 °C.

Entry 18 in Table 2; to a stirred solution of *t*-BuOK

(1.58 mmol) in THF (3 ml) was added a solution of the chiral Schiff base (−)-**10** (0.789 mmol) in THF (1 ml) at −20 °C, followed by addition of a solution of vinylphosphinate **4a** (0.789 mmol) in THF (1 ml) at −20 °C under argon. The reaction mixure was stirred for 1 h at −20 °C.

Recovery of the Ketol (−)-(9): After the reaction according to the general procedure, the workup and purification was carried out as follows. To the reaction mixture was added satd. aq NH_4Cl (3 ml) and the solution was extracted with ethyl acetate (8 ml×2). After the extract was washed with satd. aq NaCl, the solvent was removed in vacuo. The residue was added 1 M aq HCl (2 ml) and the solution was heated at 45 °C for 24 h. The reaction mixture was extracted with benzene (2 ml×2). After the solvent was removed in vacuo, the residue was purified by column chromatography (silica gel, benzene) to give (−)-**9** (95 mg, 72%) as a colorless oil; $[\alpha]_D^{25}$ −34.7° (*c* 2.50, $CHCl_3$).

2-Amino-4-phosphonobutyric acid (3): Entry 28 in Table 2; (R)-(−)-**3** was obtained from the chiral Schiff base (−)-**10** and vinylphosphonate **4b** as colorless crystals according to the procedure in Entry 18 as described above; FD MS *m/z* 184 (M+1); mp 226 °C (decomp); NMR (D_2O) δ=1.5—2.6 (4H, m), 4.03 (1H, t, *J*= 6Hz).

2-Amino-4-phenylsulfonylbutyric Acid (11): Entry 32 in Table 2; (R)-(−)-**11** was obtained from the chiral Schiff base (−)-**10** and phenyl sulfone **4c** as a colorless crystals according to the procedure in Entry 18 as described above; FD MS *m/z* 244 (M+1); mp 216 °C (decomp); ^1H NMR (D_2O) δ=2.1—2.6 (2H, m), 3.5—3.8 (2H, m), 3.92 (1H, t, *J*=6Hz), 7.7—8.2 (5H, m). For elemental analysis, methyl 2-acethylamino-4-phenylsulfonylbutyrate was derived from **11**. Found: C, 51.87; H, 5.95; N, 4.72; S, 10.61%. Calcd for $C_{13}H_{17}NO_5S$: C, 52.16; H, 5.72; N, 4.68; S, 10.71%.

Glutamic Acid (12): Entry 30 in Table 2; (R)-(−)-**12** was obtained from the chiral Schiff base (−)-**10** and methyl acrylate **4c** as colorless crystals according to the procedure in Entry 18 as described above; FD MS *m/z* 148 (M+1); mp 198 °C (decomp).

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