JOC The Journal of Organic Chemistry

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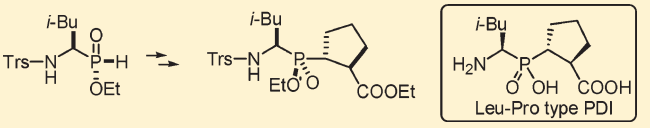
Diastereoselective Synthesis of the Leu-Pro Type Phosphinyl Dipeptide Isostere

Takehiro Yamagishi,† Naoko Tashiro, and Tsutomu Yokomatsu*

School of Pharmacy, Tokyo University of Pharmacy and Life Sciences, 1432-1 Horinouchi, Hachioji, Tokyo 192-0392, Japan

Supporting Information

ABSTRACT: A diastereoselective synthesis of the Leu-Pro type phosphinyl dipeptide isostere in its protected form was achieved from stereodefined α-amino-*H*-phosphinate. The methodology involved a cross-coupling reaction with alkenyl triflate and subsequent diastereoselective hydrogenation of the alkene moiety, which capitalized on the phosphorus chirality.



Phosphinyl dipeptide isosteres (PDIs) have been utilized as important compounds for the development of potent and selective inhibitors of various aspartic proteases and Zn metalloproteases.[1] PDIs contain the chemically stable phosphinic moiety, $-P(O)OHCH_2-$, which mimics the tetrahedral transition state of a scissile peptide bond in enzymatic hydrolysis. The stereochemistry of PDIs has been shown to affect their biological activities.[2−4]

Several groups have investigated the preparation of PDIs owing to their utility in medicinal chemistry,[5−8] with the exception of the amino acid−proline mimetics (Xaa-Pro type PDIs), which have been rarely studied. The reported access to Xaa-Pro type PDIs involves Michael addition of α-amino-*H*-phosphinic acids to *c*-pentenyl carboxylates[9] or S_N2' reactions to *c*-pentenyl acetates and subsequent olefin reduction.[10] However, high diastereoselectivity has not been achieved in these reactions. It might be difficult to prepare Xaa-Pro type PDIs because they possess a chiral center at the α′ position compared to other PDIs. Our interest in diastereoselective synthesis of Leu-Pro type PDI **1** and its diastereomer **2** (Figure 1) roots from the expected usefulness in the development of inhibitors against human T-cell leukemia virus type I (HTLV-1) protease, which is the aspartic protease that cleaves Leu-Pro bonds selectively and is responsible for HTLV-1.[11]

We have recently succeeded in preparing PDIs in their protected forms based on the concept of asymmetric induction from the chiral phosphorus atom of the phosphinate moiety to the neighboring carbon atom. The methodology involves Michael addition of α-amino-*H*-phosphinates[12,13] having defined relative configuration to an acrylate, followed by alkylation of the corresponding lithium enolates. The reaction sequence featured high diastereoselectivity controlled by the phosphorus chirality.[14] However, attempts to prepare the Leu-Pro type PDI by this methodology were unsuccessful since the analogous Michael addition to *c*-pentenyl carboxylates proceeded sluggishly, resulting in a quite low yield of the desired adduct.

Aiming at concise and stereocontrolled synthesis of one isomer of target compound **1**, we envisioned a new methodology

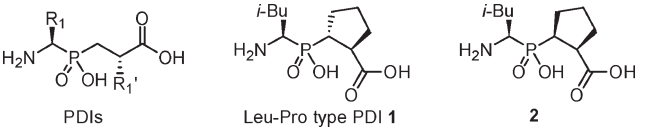
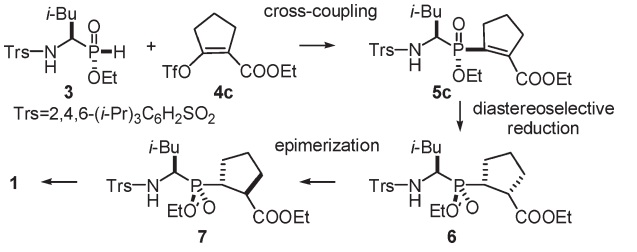


Figure 1. Structures of PDI derivatives.

Scheme 1. Strategies for Stereoselective Synthesis of 1 in Its Protected Form

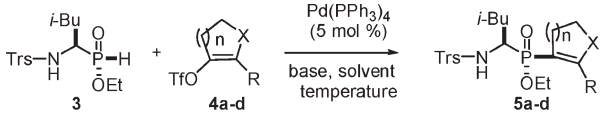


according to the above-mentioned concept. Our methodology relied upon cross-coupling of Leu type α-amino-*H*-phosphinates **3**[12,13] with alkenyl triflate **4c**, followed by diastereoselective hydrogenation of the resulting alkene **5c**, wherein selectivity would be controlled by the phosphorus chirality (Scheme 1). To reconcile the relative stereochemistry of the *c*-pentane moiety of **6** with that of **1**, epimerization to **7** is required. Herein we report the development of diastereocontrolled synthesis of racemic **1** in its protected form.

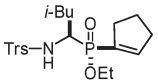
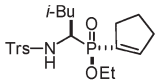
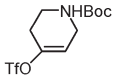
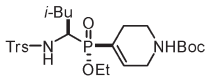
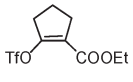
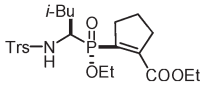
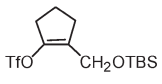
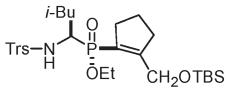
Montchamp and co-workers have demonstrated that Pd-catalyzed cross-coupling reactions of alkenyl halides and their related compounds with *H*-phosphinic acids are valuable means for synthesizing phosphinic acid derivatives through C−P bond formation.[15−17] The corresponding reactions using *H*-phosphinates

Received: April 5, 2011
Published: May 25, 2011

Table 1. Pd-Catalyzed Coupling Reactions of 3 and 4a−d



R=H, COOEt; CH_2OTBS; X=CH_2, NHBoc; n=1,2

Entry	4	5	conditions[a]	time (h)	yield (%)
1	 **4a**	 **5a**	A	7	58
2	**4a**	**5a**  **5a'**	B	7	25[b]
3	**4a**	**5a**	C	22	82
4	 **4b**	 **5b**	C	28	81
5	 **4c**	 **5c**	C	6	0
6	 **4d**	 **5d**	C	6	0

[a] Condition A: Et_3N, toluene, 80 °C. Condition B: Cs_2CO_3, toluene, 80 °C. Condition C: DABCO, CH_3CN, rt. [b] Combined yield of a mixture of diastereomers.

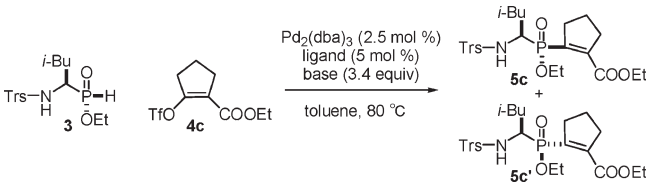
bearing a chiral center at the phosphorus atom have been reported in limited cases with retention of the phosphorus configuration.[18,19] We thus speculated that cross-coupling reactions of α-amino-*H*-phosphinate **3** with alkenyl triflate would be achieved without losing the phosphorus chirality.

To test the possibility of this methodology, a cross-coupling reaction of racemic **3** with alkenyl triflate **4a** as a model substrate was first investigated (Table 1). When **3** was treated with **4a** in the presence of $Pd(PPh_3)_4$ (5 mol %) and Et_3N (3.4 equiv) as a base in toluene at 80 °C (condition A), the desired reaction occurred to give product **5a** in 58% yield as a single diastereomer (entry 1). On the other hand, a similar reaction employing Cs_2CO_3 in place of Et_3N (condition B) proceeded sluggishly to give the product in lower yield (entry 2). Unfortunately, formation of **5a** and its diastereomer **5a′** arising from the phosphorus chirality was observed in a ratio of 9.1:1 by ^{31}P NMR analysis of the crude products. This result might be associated with the existence of a phosphorus(III) tautomer of *H*-phosphinate **3**.[20] A survey of several conditions (base, solvent, and temperature) revealed that the reaction using DABCO in CH_3CN at room temperature (condition C) was optimum to afford **5a** in 82% yield, preventing formation of **5a′** (entry 3).[21] The reaction of **3** with **4b**,[22] derived from *N*-Boc piperidone, under condition C gave product **5b** in good yield as a single diastereomer (entry 4). The relative configuration of **5b** was confirmed by X-ray crystallography, which proved the present reaction proceeded with retention of phosphorus configuration. However, when **4c** bearing a conjugated ester moiety was subjected to coupling condition C for eventual access to **1**, no reaction was observed (entry 5). Employing silyl ether **4d** instead of **4c** also resulted in no reaction (entry 6), which suggested that the poor reactivity of **4c** might be due to steric factors and not the electron-withdrawing nature of the ester moiety on the double bond.

It has been reported that related Pd-catalyzed cross-coupling reactions with *H*-phosphonate nucleophiles could be promoted by employing large bite angle phosphine ligands, which accelerate rate-determining reductive elimination from metallophosphonate complexes.[23−25] On the basis of these reports, we next screened bidentate ligands in coupling reactions of **3** and **4c** (Table 2). Using catalyst $Pd_2(dba)_3$ (2.5 mol %) with dppp (5 mol %) as a

dx.doi.org/10.1021/jo200669r |J. Org. Chem. 2011, 76, 5472–5476

Table 2. Pd-Catalyzed Coupling Reactions of 3 and 4c

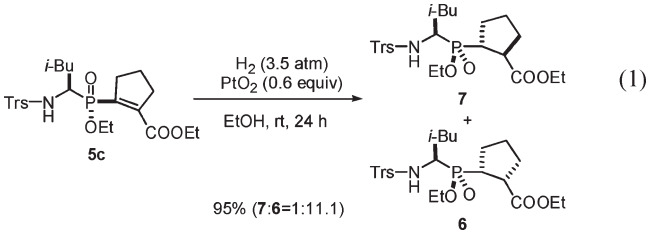


entry[a]	ligand	base	time (h)	yield (%)[b]	dr (**5c**:**5c′**)[c]
1	dppp	DABCO	18	11	4.9:1
2	*rac*-BINAP	DABCO	29	10	4.8:1
3	Xantphos	DABCO	27	44	3.9:1
4	dppf	DABCO	5.5	64	23:1
5	DPEphos	DABCO	2.5	55	15:1
6	DPEphos	K_2CO_3	2.5	63	>99:1
7[d]	DPEphos	K_2CO_3	2.5	84	>99:1

[a] Carried out with 1 equiv of **3** and 0.9 equiv of **4c** except for entry 7. [b] Combined yield of **5c** and **5c′**. [c] Determined by ^{31}P NMR analysis of crude products. [d] Carried out with 2.0 equiv of **4c**.

ligand in the presence of DABCO (3 equiv) in toluene at 80 °C, the coupling reaction proceeded sluggishly, giving products in quite low yield (entry 1). The formation of **5c** and its diastereomer **5c′** was observed in a ratio of 4.9:1. Although racemic BINAP was also inefficient (entry 2), employing Xantphos, which has a relatively large bite angle, led to increased chemical yield up to 44% (entry 3). Further increases in chemical yield were obtained by employing dppf and DPEphos, giving **5c** in 64% and 55% yields, respectively (entries 4 and 5). However, slight formation of **5c′** was detected in each reaction. We found that by employing K_2CO_3 instead of DABCO in the reaction with DPEphos the production of **5c′** was suppressed (entry 6). To our delight, increasing the amount of **4c** from 0.9 equiv to 2.0 equiv improved the chemical yield up to 84% (entry 7).

Having established the cross-coupling reaction of α-amino-*H*-phosphinate with alkenyl triflate, we focused our attention on the diastereoselective reduction of the olefin moiety of the product **5c** [eq 1].[26] A survey of catalysts [$RhCl(PPh_3)_3$, $Ir(COD)(Py)(PCy_3)PF_6$, 10% Pd–C, PtO_2] in the hydrogenation of **5c** found optimal conditions with PtO_2 (0.6 equiv) under 3.5 atm of H_2, providing the desired *trans*-cyclopentane product **7** and the undesired *cis*-cyclopentane **6** in a ratio of 1:11.1 in good yield (95%).[27] Isolation of **6** was readily achieved by recrystallization (hexane–EtOAc) or preparative TLC. Formation of minor diastereomer **7** was associated with epimerization of the product **6** but was not due to diastereofacial selection in the hydrogenation of **5c**. The relative configuration of **6** was verified by X-ray crystallography. The stereochemistry of **7** was confirmed by performing two-dimensional ^{31}P and ^{1}H heteronuclear NOE (HOESY)[28] experiments. In the HOESY spectrum of **7**, the



(1)

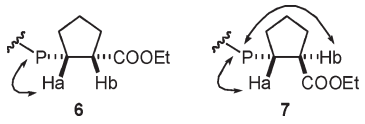


Figure 2. Selected HOESY correlations of **6** and **7**.

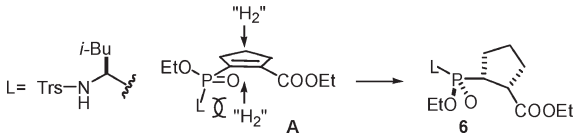
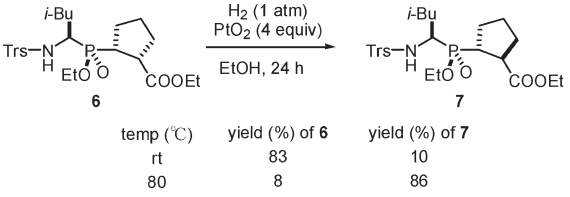


Figure 3. Proposed model for diastereoselectivity in hydrogenation of **5c**.

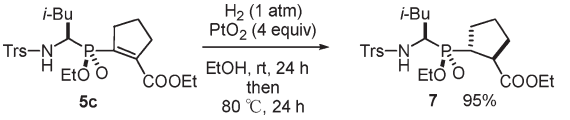
phosphorus atom and proton Hb were correlated, but no correlation was observed in **6** (Figure 2).

Selective formation of **6** in the above-mentioned reaction could be accounted for by **5c** adopting conformation **A**, wherein the oxygen atom of the phosphinyl moiety was in the inside position to minimize $A^{(1,3)}$-strain (Figure 3). The approach of the reducing reagent toward the olefin moiety might occur from the less hindered upper face, opposite to the bulky group L, leading to **6**.

To reconcile the relative stereochemistry of **6** with the target compound **1**, epimerization was next investigated [eq 2]. Although epimerization of **6** with base (DABCO, Et_3N) was examined, the desired products were not obtained. On the basis of the results of eq 1, when **6** was treated with 4 equiv of PtO_2 under a hydrogen atmosphere (1 atm) at room temperature, epimerization occurred to give **7**, albeit in only 10% yield. Increasing the temperature to 80 °C improved the chemical yield up to 86%. No reaction was observed when an amount of PtO_2 was decreased from 4 equiv to 1 equiv. One-pot synthesis of **7** was also possible, exposing **5c** to PtO_2 under hydrogenation conditions and then warming from room temperature to 80 °C. Compound **7** was obtained selectively in 95% yield [eq 3].



(2)



(3)

In conclusion, we have developed a method for the stereocontrolled synthesis of Leu-Pro PDI as its protected form. This methodology featured stereoretentive Pd-catalyzed cross-coupling of α-amino-*H*-phosphinate with alkenyl triflate and highlydiastereoselective hydrogenation of the olefin moiety controlled by the phosphorus chirality. Since optically active α-amino-*H*-phosphinate is now available,[13] studies to extend this methodology to optically active variants are in progress.

dx.doi.org/10.1021/jo200669r |*J. Org. Chem.* 2011, 76, 5472–5476

EXPERIMENTAL SECTION

2-({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)cyclopent-1-en-1-yl Trifluoromethanesulfonate (4d). To a stirred solution of 2-(hydroxymethyl)cyclopent-1-en-1-yl trifluoromethanesulfonate[29] (343 mg, 1.39 mmol) in DMF (2.8 mL) solution was added a solution of imidazole (199 mg, 2.93 mmol) in DMF (1.5 mL) and a solution of TBSCl (231 mg, 1.53 mmol) in DMF (1.5 mL) at 0 °C. After stirring for 4 h at room temperature, the mixture was poured into H_2O and extracted with Et_2O. The combined extracts were washed with brine and dried over $MgSO_4$. Removal of the solvent gave a residue, which was purified by column chromatography (hexane:EtOAc = 1:0 to 10:1) to give **4d** (434 mg, 86%). Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.25 (2H, s), 2.64 (2H, t, J = 7.3 Hz), 2.48 (2H, t, J = 7.2 Hz), 1.98 (2H, dt, J = 7.9, 7.9 Hz), 0.89 (9H, s), 0.071 (6H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 142.3, 132.0, 120.6, 116.3, 57.2, 31.1, 29.2, 25.8, 19.3, 18.3, −5.6. IR (neat) 1335 cm^{-1}. MS m/z 361 (MH^+). HRMS calcd for $C_{13}H_{24}O_4SiSF_3$: 361.1117 (MH^+). Found: 361.1124.

(1*R,R_p*)-Ethyl Cyclopent-1-en-1-yl(3-methyl-1-{[(2,4,6-triisopropylphenyl)sulfonyl]amino}butyl)phosphinate (5a).** To a stirred solution of **3** (50.0 mg, 0.11 mmol)[12,13] in CH_3CN (0.5 mL) was successively added a solution of **4a** (22.1 mg, 0.10 mmol)[30] in CH_3CN (1.3 mL), DABCO (38.9 mg, 0.35 mmol), and $Pd(PPh_3)_4$ (5.9 mg, 0.0051 mmol) at room temperature. After stirring for 22 h at the same temperature, the mixture was poured into aqueous saturated NH_4Cl solution and extracted with EtOAc. The combined extracts were washed with brine and dried over $MgSO_4$. Removal of the solvent gave a residue, which was purified by column chromatography (hexane:EtOAc = 2.1 to 0:1) to give **5a** (43.0 mg, 82%). White crystals. Mp 137−138 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.11 (2H, s), 6.74 (1H, ddd, J = 1.7, 1.7, 10.0 Hz), 4.88 (1H, br.d, J = 9.3 Hz), 4.07−3.96 (3H, m), 3.94−3.85 (1H, m), 3.77−3.68 (1H, m), 2.87 (1H, dq, J = 6.9, 6.9 Hz), 2.63−2.54 (1H, m), 2.49−2.35 (3H, m), 1.98−1.85 (2H, m), 1.61−1.52 (1H, m), 1.42−1.21 (23H, m), 0.71 (3H, d, J = 6.9 Hz), 0.69 (3H, d, J = 7.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 152.5, 151.8 (d, J_{CP} = 11.1 Hz), 149.1, 135.2 (d, J_{CP} = 1.6 Hz), 133.1 (d, J_{CP} = 123.9 Hz), 123.4, 61.0 (d, J_{CP} = 6.9 Hz), 49.8 (d, J_{CP} = 112.8 Hz), 38.9, 34.4 (d, J_{CP} = 17.6 Hz), 34.1, 33.3 (d, J_{CP} = 12.7 Hz), 29.9, 24.79, 24.77, 24.3 (d, J_{CP} = 8.8 Hz), 24.0 (d, J_{CP} = 10.1 Hz), 23.60, 23.59, 22.8, 21.6, 16.4 (d, J_{CP} = 6.0 Hz). ^{31}P NMR (121 MHz, $CDCl_3$) δ: 38.98. IR (KBr) 3092, 1327, 1157, 1038 cm^{-1}. MS m/z 512 (MH^+); HRMS calcd for $C_{27}H_{47}NO_4PS$: 512.2963 (MH^+). Found: 512.2974.

(1*R,R_p*)-*tert*-Butyl 4-[Ethoxy(3-methyl-1-{[(2,4,6-triisopropylphenyl)sulfonyl]amino}butyl)phosphoryl]-3,6-dihydropyridine-1(2*H*)-carboxylate (5b).** This compound was prepared from **3** (50.0 mg, 0.11 mmol), **4b** (33.8 mg, 0.10 mmol),[22] DABCO (38.9 mg, 0.35 mmol), and $Pd(PPh_3)_4$ (5.9 mg, 0.0051 mmol) in an analogous manner to that of **5a**. Purification of the residue by column chromatography (hexane:EtOAc = 2:1 to 0:1) gave **5b** (52.0 mg, 81%). White crystals. Mp 72−75 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.12 (2H, s), 6.79 (1H, br.d, J = 18.6 Hz), 4.76 (1H, br.d, J = 7.1 Hz), 4.23−4.16 (1H, m), 4.09−4.03 (1H, m), 4.01−3.87 (4H, m), 3.76 (2H, br.d, J = 6.7 Hz), 3.31 (1H, br.s), 2.89 (1H, dq, J = 6.9, 6.9 Hz), 2.36−2.31 (1H, br.m), 2.24−2.19 (1H, br.m), 1.55−1.48 (10H, m), 1.39−1.10 (23H, m), 0.68 (3H, d, J = 6.7 Hz), 0.63 (3H, d, J = 6.1 Hz). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 154.7, 152.7, 149.1, 143.0 (d, J_{CP} = 6.8 Hz), 135.0, 126.5 (d, J_{CP} = 119.8 Hz), 123.5, 80.0, 61.3 (d, J_{CP} = 6.8 Hz), 48.6 (d, J_{CP} = 121.4 Hz), 44.8, 40.3, 38.5, 34.2, 30.0, 28.4, 24.81, 24.79, 24.3, 24.2, 23.7, 23.6, 22.8, 21.5, 16.5 (d, J_{CP} = 5.7 Hz), 14.1. ^{31}P NMR (121 MHz, $CDCl_3$) δ: 40.84. IR (KBr) 3116, 1700, 1333, 1163, 1034 cm^{-1}. MS m/z 627 (MH^+). HRMS calcd for $C_{32}H_{56}N_2O_6PS$: 627.3597 (MH^+). Found: 627.3618.

(1*R,R_p*)- and (1*R**,S_p*)-Ethyl 2-[Ethoxy(3-methyl-1-{[(2,4,6-triisopropylphenyl)sulfonyl]amino}butyl)phosphoryl]cyclopent-1-ene-1-carboxylate (5c and 5c′).** To a stirred solution of $Pd_2(dba)_3$ (2.6 mg, 0.0025 mmol) in toluene (0.5 mL) was added Xantphos (3.0 mg, 0.0051 mmol), and the mixture was stirred for 30 min at room temperature under a nitrogen atmosphere. To the mixture was successively added a solution of **4c** (29.4 mg, 0.102 mmol)[31,32] in toluene (1.3 mL), **3** (50 mg, 0.11 mmol), and DABCO (38.9 mg, 0.35 mmol), and the mixture was stirred for 27 h at 80 °C. The mixture was poured into aqueous saturated NH_4Cl and extracted with EtOAc. The combined extracts were washed with brine and dried over $MgSO_4$. Removal of the solvent gave a residue, which was chromatographed on silica gel (hexane:EtOAc = 2:1 to 1:1) to give a mixture of **5c** and **5c′** (26 mg, 44%, ratio = 3.9:1). Each diastereomer was separated by preparative TLC (EtOAc).

5c. White crystals. Mp 59−62 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.12 (2H, s), 5.85 (1H, dd, J = 5.6, 9.6 Hz), 4.27 (2H, ddd, 7.2, 7.2, 7.2 Hz), 4.15−3.90 (5H, m), 2.96−2.67 (5H, m), 2.08−1.87 (2H, m), 1.55−1.46 (1H, m), 1.43−1.14 (26H, m), 0.70 (3H, d, J = 6.4 Hz), 0.64 (3H, d, J = 6.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.8 (d, J_{CP} = 3.6 Hz), 152.4, 149.4 (d, J_{CP} = 7.9 Hz), 149.3, 140.9 (d, J_{CP} = 115.5 Hz), 135.2 (d, J_{CP} = 1.6 Hz), 123.4, 61.5 (d, J_{CP} = 7.2 Hz), 61.3, 50.9 (d, J_{CP} = 110.8 Hz), 38.6 (d, J_{CP} = 2.0 Hz), 37.7 (d, J_{CP} = 9.5 Hz), 36.6 (d, J_{CP} = 14.3 Hz), 34.2, 29.8, 24.83, 24.78, 24.2 (d, J_{CP} = 9.7 Hz), 23.6, 22.92, 22.87 (d, J_{CP} = 9.5 Hz), 21.4, 16.4 (d, J_{CP} = 5.8 Hz), 14.0. ^{31}P NMR (121 MHz, $CDCl_3$) δ: 38.69. IR (KBr) 3103, 1721, 1329, 1160, 1034 cm^{-1}. MS m/z 584 (MH^+). HRMS calcd for $C_{30}H_{51}NO_6PS$: 584.3175 (MH^+). Found: 584.3179.

5c′. White crystals. Mp 123−126 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.13 (2H, s), 5.30 (1H, dd, J = 5.2, 9.6 Hz), 4.31−4.19 (3H, m), 4.12−4.01 (2H, m), 3.88−3.70 (2H, m), 2.94−2.78 (5H, m), 1.95 (2H, dt, J = 7.6, 7.6 Hz), 1.51−1.14 (27H, m), 0.74 (3H, d, J = 6.4 Hz), 0.70 (3H, d, J = 6.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.2 (d, J_{CP} = 3.8 Hz), 152.4, 149.2, 148.9 (d, J_{CP} = 8.9 Hz), 141.4 (d, J_{CP} = 115.0 Hz), 135.3, 123.4, 61.3, 51.1 (d, J_{CP} = 107.5 Hz), 38.9 (d, J_{CP} = 4.3 Hz), 37.9 (d, J_{CP} = 9.1 Hz), 36.3 (d, J_{CP} = 14.3 Hz), 34.2, 30.0, 24.8, 24.0 (d, J_{CP} = 2.6 Hz), 23.6 (d, J_{CP} = 2.6 Hz), 23.2, 22.8 (d, J_{CP} = 9.4 Hz), 21.1, 16.3 (d, J_{CP} = 5.4 Hz), 14.1. ^{31}P NMR (121 MHz, $CDCl_3$) δ: 39.11. IR (KBr) 3124, 1729, 1328, 1157, 1025 cm^{-1}. MS m/z 584 (MH^+). HRMS calcd for $C_{30}H_{51}NO_6PS$: 584.3175 (MH^+). Found: 584.3156.

(1*R,R_p*,2*R**,3*S**)-Ethyl 2-[Ethoxy(3-methyl-1-{[(2,4,6-triisopropylphenyl)sulfonyl]amino}butyl)phosphoryl]cyclopentanecarboxylate (6).** To a solution of **5c** (50.0 mg, 0.086 mmol) in EtOH (4 mL) was added PtO_2 (11.7 mg, 0.051 mmol), and the mixture was stirred for 24 h at room temperature under hydrogen atmosphere (3.5 atm). The catalyst was removed by filtration through a pad of Celite, and the filtrate was evaporated to give a residue. Purification of the residue by silica gel column chromatography (hexane:EtOAc = 1:1) gave a mixture of **7** and **6** (48 mg, 95%, ratio = 1:11.1). One isomer **6** was isolated by recrystallization from hexane−EtOAc. White crystals. Mp 170−171 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.14 (2H, s), 5.32 (1H, dd, J = 2.8, 9.8 Hz), 4.25−3.89 (7H, m), 3.11−3.06 (1H, m), 2.89 (1H, dq, J = 6.8, 6.8 Hz), 2.52−2.43 (1H, m), 2.03−1.90 (4H, m), 1.72−1.54 (2H, m), 1.43−1.36 (2H, m), 1.30−1.21 (25H, m), 0.71 (3H, d, J = 6.8 Hz), 0.69 (3H, d, J = 6.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 174.6 (d, J_{CP} = 4.8 Hz), 152.7, 149.3, 135.1, 123.6, 62.4 (d, J_{CP} = 7.2 Hz), 50.7 (d, J_{CP} = 101.0 Hz), 44.3, 40.8 (d, J_{CP} = 91.1 Hz), 38.3, 34.2, 30.0, 29.9 (d, J_{CP} = 12.4 Hz), 25.1 (d, J_{CP} = 2.0 Hz), 24.9, 24.8, 24.1 (d, J_{CP} = 9.0 Hz), 23.9 (d, J_{CP} = 13.4 Hz), 23.6, 23.1, 21.5, 16.5 (d, J_{CP} = 4.8 Hz), 14.1. ^{31}P NMR (121 MHz, $CDCl_3$) δ: 52.17. IR (KBr) 3109, 1731, 1329, 1157, 1038 cm^{-1}. MS m/z 586 (MH^+). HRMS calcd for $C_{30}H_{53}NO_6PS$: 586.3331(MH^+). Found: 586.3337.

(1*R,R_p*,2*R**,3*R**)-Ethyl 2-[Ethoxy(3-methyl-1-{[(2,4,6-triisopropylphenyl)sulfonyl]amino}butyl)phosphoryl]cyclopentanecarboxylate (7).** To a solution of **6** (30.0 mg, 0.051 mmol) in EtOH (2.4 mL) was added PtO_2 (46.5 mg, 0.20 mmol), and the mixture was stirred for 24 h at 80 °C under a hydrogen atmosphere (1 atm). The catalyst was removed by filtration through a pad of Celite, and the filtrate was evaporated

dx.doi.org/10.1021/jo200669r |*J. Org. Chem.* 2011, 76, 5472–5476

to give a residue. Purification of the residue by preparative TLC ($CHCl_3$:MeOH = 300:1) gave **7** (26.0 mg, 86%). White crystals. Mp 49−50 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.13 (2H, s), 5.48 (1H, dd, J = 2.5, 9.2 Hz), 4.22−3.99 (6H, m), 3.83−3.76 (1H, m), 3.26−3.20 (1H, m), 2.91 (1H, dq, J = 6.9, 6.9 Hz), 2.71−2.65 (1H, m), 2.09−1.92 (3H, m), 1.89−1.84 (1H, m), 1.76−1.63 (2H, m), 1.56−1.51 (1H, m), 1.41−1.12 (26H, m), 0.68 (3H, d, J = 6.7 Hz), 0.64 (3H, d, J = 6.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 176.0 (d, J_{CP} = 4.6 Hz), 152.6, 149.3, 135.0 (d, J_{CP} = 2.2 Hz), 123.5, 61.5 (d, J_{CP} = 6.9 Hz), 61.1, 50.5 (d, J_{CP} = 96.8 Hz), 45.4 (d, J_{CP} = 2.4 Hz), 39.8 (d, J_{CP} = 3.7 Hz), 38.6 (d, J_{CP} = 92.4 Hz), 34.2, 31.8 (d, J_{CP} = 7.6 Hz), 29.9, 27.5 (d, J_{CP} = 1.9 Hz), 26.5 (d, J_{CP} = 8.3 Hz), 24.9, 24.8, 24.3 (d, J_{CP} = 9.2 Hz), 23.6, 22.8, 21.5, 16.5 (d, J_{CP} = 5.5 Hz), 14.1. ^{31}P NMR (121 MHz, $CDCl_3$) δ: 53.49. IR (neat) 3115, 1734, 1156, 1329, 1036 cm^{-1}. MS m/z 586 (MH^+). HRMS calcd for $C_{30}H_{53}NO_6PS$: 586.3331(MH^+). Found: 586.3356.

Procedure for the One-Pot Synthesis of 7. To a stirred solution of **5c** (30 mg, 0.051 mmol) in EtOH (2.4 mL) was added PtO_2 (46.7 mg, 0.21 mmol). After stirring for 24 h at room temperature under a hydrogen atmosphere, the mixture was warmed to 80 °C and stirred for 24 h at the same temperature. The catalyst was removed by filtration through a pad of Celite, and the filtrate was concentrated to give a residue. This residue was purified by preparative TLC ($CHCl_3$:MeOH = 300:1) to give **7** (28.4 mg, 95%). The ^{1}H NMR spectrum was identical with that of **7**.

■ ASSOCIATED CONTENT

Supporting Information. Spectral data of new compounds and crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: yokomatu@toyaku.ac.jp.

Present Addresses

†School of Pharmacy, Ohu University, 31-1 Tomita-machi, Misumidou, Kooriyama-city, Fukushima 963-8611, Japan.

■ ACKNOWLEDGMENT

This work was supported in part by a Grant-in-Aid for Scientific Research (C) from the Ministry of Education, Culture, Sports, Science and Technology of Japan. We also thank the Promotion and Mutual Aid Corporation for Private Schools of Japan for supporting this work. We wish to thank Mr. Haruhiko Fukaya and Mrs. Chiseko Sakuma (the analytical center of this university) for their help performing the X-ray crystallographic analysis and HOESY experiments.

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