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Development of a Scalable Synthetic Route towards a Thrombin Inhibitor, LB30057

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Abstract:

Described is a scalable synthetic route towards LB30057 (1) which is based upon a chiron approach using methyl tyrosinate hydrochloride as a starting material. In situ protection of methyl tyrosinate to its *N,O*-bis-trimethylsilyl derivative and subsequent *N*-selective introduction of naphthalenesulfonyl group provided methyl *N*-2-naphthalenesulfonyltyrosinate (9). After the phenol group of 9 was triflated to 10, nickel-catalyzed cyanation provided 11 in good yield. The acid chloride 11a was generated via hydrolysis of the ester group followed by the treatment with $SOCl_2$, and then coupled with cyclopentylmethylamine to give the amide 15. Imidate formation followed by amidrazone generation and final salt formation with maleic acid afforded 1.

Introduction

Thrombin is a trypsin-like serine protease playing a central role in both hemostasis and thrombosis.[1] Due to the implication of thrombosis in many cardiovascular diseases such as myocardial infarction, unstable angina, and deep vein thrombosis, a great deal of attention has been focused on the development of a small-molecule thrombin inhibitor as a therapeutic reagent.

In this context, we have been involved in the search for potent thrombin inhibitors having an amidrazone functionality, among which LB30057 (**1**, Figure 1) was chosen as a development candidate on the basis of its good potency, selectivity, and oral bioavailability profiles.[2] Herein, we present the development of a scalable synthetic route towards **1**.

Result and Discussions

Retrosynthetic analysis of **1** led us to recognize *p*-cyanophenylalanine as a key starting material. Earlier in the development, we prepared **1** starting from (*S*)-*p*-cyanophenylalanine by acylase-mediated enantioselective hydrolysis of racemic *N*-acetyl-*p*-cyanophenylalanine (Route b in Figure 1)[3] out of the other known synthetic methods, enantioselective catalytic hydrogenation[4] of *N*-acetyl-dehydro-*p*-cyanophenylalanine and diastereoselective alkylation[5] of bis-lactim ether with *p*-cyanobenzyl bromide. Although the recycling of the undesired enantiomer, as well as the enzyme, is well precedented, the high cost of *p*-cyanobenzyl bromide detracted our interest to a chiron approach (Route a in Figure 1) which is based upon functional group manipulation of the phenolic hydroxyl group of tyrosine to a cyano group.

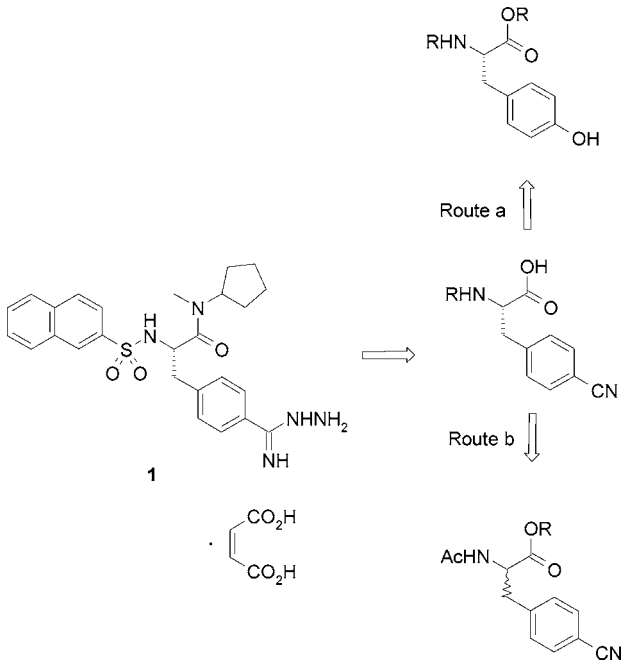

Figure 1.

In this regard, we have investigated the cyanation of the tyrosine triflate **4a** that is readily prepared from *N*-Boc tyrosine (**2**) (Scheme 1). Treatment of **2** with 2 equiv of *i*-butylchloroformate in the presence of 4-methylmorpholine (NMM) and subsequent addition of cyclopentylmethylamine afforded the amide carbonate **3** in 90% yield. Hydrolysis of

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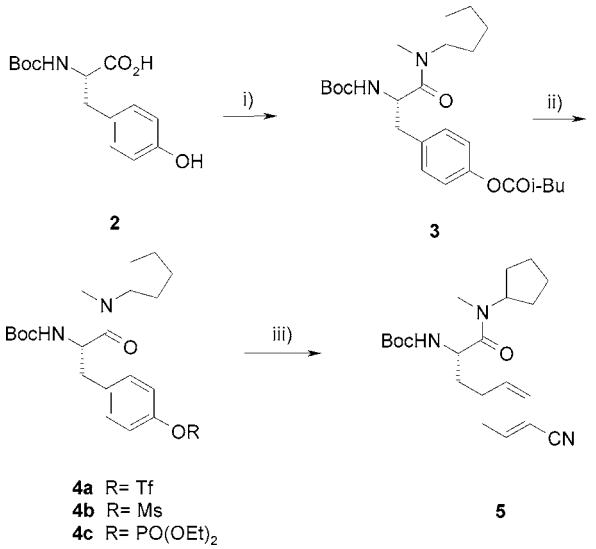
Scheme 1[a]



[a] Reagents and conditions: i) *i*-butylchloroformate, NMM, cyclopentylmethylamine; ii) (a) LiOH, MeOH, (b) Tf_2O, py, for **4a**, MsCl, py, for **4b**, $(EtO)_3PO$, I_2, py, for **4c**; iii) refer to Table 1.

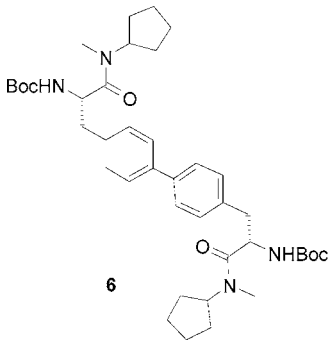
the phenolic carbonate group of **3** and triflation[6] of the generated hydroxyl group gave the triflate **4a** in overall 70% yield. Initial attempts of the transformation[7] of **4a** to **5** using potassium cyanide under palladium catalysis resulted in partial conversion and/or irreproducible outcomes. Since it is known that poisoning the palladium catalyst by high concentration of cyanide ion often leads to the breakdown of the catalytic cycle, we replaced potassium cyanide by zinc cyanide having much lower solubility in the reaction medium.[8] However, the combination of $Pd(PPh_3)_4$ and zinc cyanide afforded only 39% of **5** accompanied by recovered starting material in 39% (Table 1, entry 1). A better outcome was observed with the addition of 0.2 equiv of triphenylphosphine (entry 2) to lead to a moderate yield of 67%. Finally, addition of a catalytic amount of dppf [1,1′-bis-(diphenylphosphino)ferrocene][9] improved the conversion affording **5** in 91% yield. As a palladium source, $Pd(PPh_3)_4$ and $Pd_2(dba)_3$ (entries 3, 4, and 9) were the best, while $Pd(OAc)_2$ did not show any progress of the reaction. Change of solvent to acetonitrile (entry 5) or employment of other bidendate ligands such as dppe or dppp (entries 6 and 7) were found to be deleterious.

Table 1. **Cyanation of 4a using palladium catalyst**[a]

	catalyst	solvent	additive (mol %)	time (h)	yield (%) **5**	yield (%) **4a**
1	$Pd(PPh_3)_4$	DMF	−	24	39	39
2	$Pd(PPh_3)_4$	DMF	PPh_3 (20)	24	67	14
3	$Pd(PPh_3)_4$	DMF	dppf (4)	3	91	−
4	$Pd(PPh_3)_4$	NMP	dppf (4)	5	91	−
5	$Pd(PPh_3)_4$	CH_3CN	dppf (4)	24	23	77
6	$Pd(PPh_3)_4$	DMF	dppe (4)	24	14	86
7	$Pd(PPh_3)_4$	DMF	dppp (4)	24	23	77
8	$Pd(OAc)_2$	DMF	PPh_3 (20)	24	NR	
9	$Pd_2(dba)_3 \cdot CHCl_3$	DMF	dppf (4)	6	88	−

[a] All the reactions were performed with 0.6 equiv of zinc cyanide at 80 °C in the presence of 4 mol % of palladium catalyst.

Table 2. **Cyanation of 4a using nickel catalysts**[a]



	Ni(II) (mol %)	solvent	time (h)	temp (°C)	product **5**	product **6**	product **7**
1	$Ni(PPh_3)_2Cl_2$ (10)	CH_3CN	2	reflux	76	−	−
2	$Ni(PPh_3)_2Cl_2$ (5)	CH_3CN	2	reflux	72	−	−
3	$Ni(PPh_3)_2Cl_2$ (3)	CH_3CN	2	reflux	65	−	−
4	$Ni(PPh_3)_2Cl_2$ (1)	CH_3CN	5	reflux	NR	−	−
5	$Ni(PPh_3)_2Br_2$ (5)	CH_3CN	3	reflux	30	−	−
6	$Ni(PPh_3)_2Br_2$ (10)	CH_3CN	6	reflux	62	5	−
7	$Ni(PPh_3)_2Cl_2$ (5)	CH_3CN	3	50−60	70	−	−
8	$Ni(PPh_3)_2Cl_2$ (5)	DMF	3	75	85	2.3	2.9
9	$Ni(PPh_3)_2Cl_2$ (5)	NMP	3	75	85	2.3	1.0
10	$Ni(PPh_3)_2Cl_2$ (5)	NMP	3	50	84	−	−
11	$NiBr_2$ (10)	CH_3CN	2	reflux	65	−	−

[a] In general, 2 equiv of triphenylphosphine relative to Ni(II) catalysts, 1 equiv of zinc, and 1.5 equiv of KCN were used. With $NiBr_2$, 4 equiv of triphenylphosphine to $NiBr_2$ was used.

Having established the palladium-catalyzed cyanation protocol, we tested the nickel-catalyzed version of the same reaction to reduce catalyst cost. Under the conditions similar to those of Percec's procedure,[10] cyanation of **4a** proceeded as reported. As a nickel source, $Ni(PPh_3)_2Cl_2$ (Table 2, entries 1−4) showed slightly better yields than that of Ni $(PPh_3)_2$-Br_2 (entries 5−6); moreover, $NiBr_2$ in the presence of 4 equiv of triphenylphosphine also showed good conversion (entry 11). Under the same reaction conditions, the use of $NiCl_2$ failed to show any sign of the progress of the reaction. The cyanation reaction is slightly sensitive to the solvent. Aprotic polar solvents such as DMF or NMP showed the best yield (entries 8 and 9, 85% yield), while less polar solvent such as acetonitrile showed slightly lower, ∼70% yields (entries

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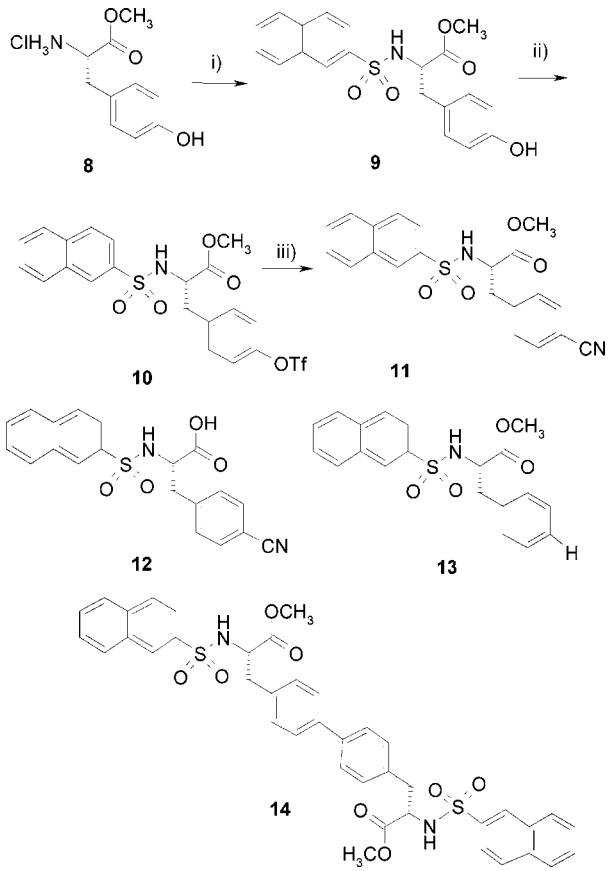
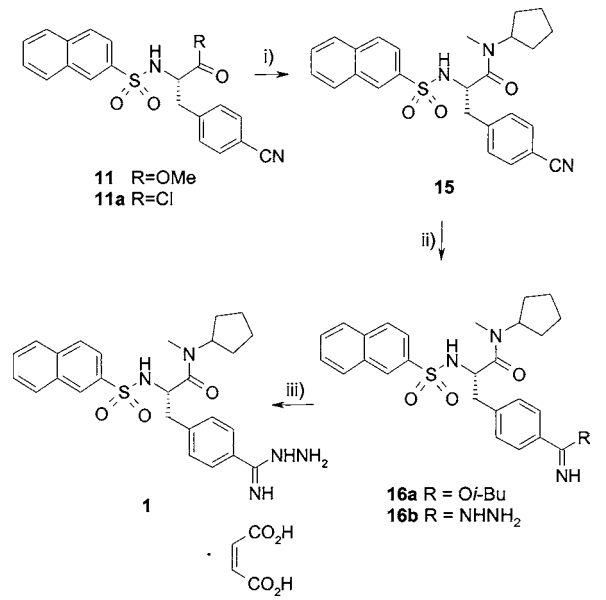
Scheme 2 [a]



[a] Reagents and conditions: i) TMSCl, py, then, naphthalenesulfonyl chloride, 3 N HCl; ii) Tf_2O, py; iii) see Tables 2 and 3.

Scheme 3 [a]



[a] Reagents and conditions: i) (a) **11**, LiOH, THF−H_2O, (b) $SOCl_2$, CH_2Cl_2, (c) *N*-cyclopentylmethylamine; ii) (a) AcCl, isobutyl alcohol−$CHCl_3$, (b) $NH_2NH_2 \cdot H_2O$; iii) maleic acid, EtOH.

Table 3. **Solvent influence on the impurity profile**[a]

	product (HPLC area %)			
solvent	**11**	**12**	**13**	**14**
CH_3CN	92	3	2	2
DMF	84	2	9	5
NMP	90	2	4	4

[a] All the reactions were performed with 0.1 equiv of $Ni(PPh_3)_2Cl_2$, 0.2 equiv of PPh_3, 1.2 equiv of KCN, and 0.1 equiv of Zn at the reaction temperature of 50−60 °C.

1, 2, and 3). Noteworthy was the formation of the small amount of homocoupled and protonated side products in polar aprotic solvents at 75 °C, which were absent in acetonitrile. Also, these side products were completely absent as the reaction temperature was lowered to 50 °C (entry 10).

In addition to the triflate group, less reactive methanesulfonate or diethylphosphonate groups were also tested in the nickel-catalyzed cyanation reaction. Contrary to the literature precedent,[11] only partial conversion (∼70%) of **4b** was observed when using a combination of zinc cyanide−$Ni(PPh_3)_2Cl_2$−zinc in acetonitrile. In contrast, the phosphonate **4c**[12] was only partially (∼30%) transformed to its cyanated product under a combination of potassium cyanide−$Ni(PPh_3)_2Cl_2$−zinc in DMF.

Although the established reaction route (Scheme 1) provided an efficient entry towards **5** via either palladium- or nickel-catalyzed cyanation reaction, we devised another route based upon the early introduction of the naphthalenesulfonyl group on the premise that it would not only eliminate the use of the Boc protecting group but also provide a high degree of crystallinity to all the intermediates, thus making the isolation more facile (Schemes 2 and 3). Reaction of methyl tyrosinate hydrochloride salt (**8**) with TMSCl in the presence of pyridine to give the *N*,O-bis-silylated product, which was treated with 2-naphthalenesulfonyl chloride to afford methyl *N*-2-naphthalenesulfonyl tyrosinate (**9**) after the removal of the tentatively protected *O*-TMS group during workup.[13] Triflation under the standard conditions afforded the triflate **10** as a white solid.

The cyanation of **10** was investigated in detail. Contrary to our concern about the possible detrimental interference of the acidic sulfonamide functionality of **10**, the cyanation reaction proceeded smoothly to give **11** under typical reaction conditions. However, the level of formation of the side products, namely the homocoupled compound **14**, the reduced compound **13**, and the hydrolyzed compound **12**, proved quite sensitive to the reaction conditions**,** particularly temperature and solvent (Tables 3 and 4). Cyanation at 50 °C, at 38 °C, and at 30 °C revealed that the reaction temperature is closely related to the formation of the hydrolyzed side product: 4−5% of **12** at 50 °C was reduced to less than 1% as the reaction temperature was lowered to 38 °C. Even at 30 °C, the reaction proceeded with a reaction profile similar to that done at 38 °C. However, the reproducibility of the reaction was poor at this temperature: the

(11) Contrary to the precedent described in ref 10, attempted repetition of the cyanation of phenol mesylate to benzonitrile using nickel catalyst provided phenol mesylate, phenol, and benzonitrile in the ratio of 1:1:3.

(12) Stowell, J. K.; Widlanski, T. S. *Tetrahedron Lett*. **1995**, *36*, 1825.

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Table 4. **Temperature effect on the impurity profile**[a]

	product (HPLC area %)			
temp (°C)	**11**	**12**	**13**	**14**
50	90	5	2	3
38	97	0.5	0.5	2
30	95	1	1	3

[a] All the reactions were performed with 0.1 equiv of $Ni(PPh_3)_2Cl_2$, 0.2 equiv of PPh_3, 1.2 equiv of KCN, and 0.1 equiv of Zn in CH_3CN.

progress of the reaction stalled occasionally after only partial conversion. The impurity profile was also dependent on solvent choice: 1−2% of **13** in acetonitrile or NMP increased to 6−7% in DMF. Concentration in the range of 1−4 mL of acetonitrile/g of **10** showed no significant difference. An interesting observation was that the order of addition of the reactants was very critical. Addition of the starting material **10** to a stirred mixture of nickel (II) species, triphenylphosphine, zinc, and KCN was found to be best, whereas when the last added material was either the Ni(II) species or zinc, no progress of the reaction was observed.

An unexpected bonus of introducing the naphthalenesulfonyl group at an early stage of the synthesis was that the use of an acid chloride intermediate in the amide coupling reaction became feasible to provide **15** in good yield (Scheme 3). Moreover, the acid chloride intermediate **11a** was easily isolated as a stable and storable solid to lead to an easy diversification platform for medicinal chemical purposes. Conversion of the cyano moiety of **15** to the imidate group of **16a** was accomplished in isobutyl alcohol/hydrochloric acid solution. The subsequent formation of the amidrazone functionality afforded **16** as a crystalline compound. Final salt formation with maleic acid afforded LB30057 (**1**).Due to the hindered rotation through the amide bond of **1**, the proton NMR spectrum at ambient temperature showed a mixture of two rotamers that was coalesced at 80 °C and became indiscernible at 140 °C (Figure 2).

Conclusion

In conclusion, we have devised a scalable synthetic route towards LB30057 (**1**) using a nickel-catalyzed cyanation reaction as a key step. In the course of the study, we examined and verified the functional group tolerance of the key reaction and also delineated the influence of the solvent and the reaction temperature on the formation of the side products. Moreover, the strategic introduction of the naphthalenesulfonyl group at an early stage has not only eliminated the redundant use of a protecting group but has also caused the entire intermediate crystalline solid to render the isolation and purification very efficient.

Experimental Section

Solvents and reagents were obtained from commercial sources and used without further purification. NMR spectra were obtained on a Bruker 400 MHz and a JEOL 500 MHz spectrometer. HPLC analyses were carried out on a Hewlett-Packard 1100 system and a Waters 490E detector and 616 pump system. Mass spectra were collected using a Finnegan

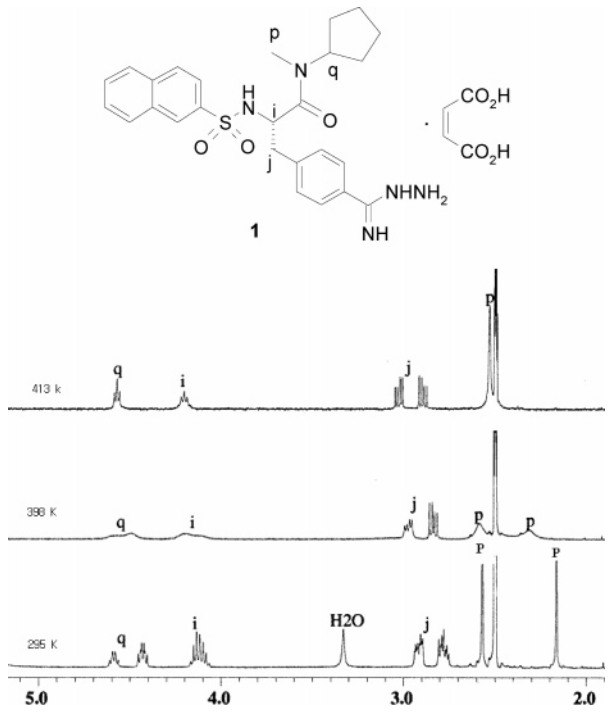

Figure 2.

LCQ mass spectrometer system and a JEOL JMX-700 mass spectrometer.

(2*S*)-2-(*N*-*tert*-Butoxycarbonyl)-amino-*N*-cyclopentyl-3-(4-cyanophenyl)-*N*-methylpropanamide (5). To a stirred mixture of $Pd[(PPh)_3]_4$ (7.01 g, 0.03 equiv), dppf (3.36 g, 0.03 equiv), zinc cyanide (14.25 g, 0.6 equiv), and **4a** (100 g, 0.202 mol) was added DMF (500 mL) under nitrogen atmosphere. The mixture was heated at 80 °C for 4 h. The mixture was cooled to room temperature, and ethyl acetate (800 mL) and saturated sodium bicarbonate (500 mL) solution were added. After vigorous stirring for 30 min, the organic layer was separated, and the aqueous layer was extracted with ethyl acetate (300 mL). The combined organic layer was washed with brine and concentrated in vacuo. Column chromatography (hexane/ethyl acetate = 7:3) afforded **5** (68.2 g, 91%) as a viscous oil. ^1H NMR ($CDCl_3$, 300 MHz, mixture of two rotamers) δ 7.61 (m, 2H), 7.32 (m, 2H), 5.47 (br t, 1H, NH), 5.01−4.86 (m, 2H), 4.12 (m, 1H), 3.10−2.94 (m, 2H), 2.75, 2.62 (2s, 3H), 1.40 (s, 9H), 1.90−1.20 (m, 8H); IR (neat) 3412, 3296, 2973, 2872, 2228, 1763, 1709, 1635, 1503, 1489, 1451, 1416, 1367, 1282, 1248, 1169, 1050, 1021, 889, 826, 563 cm^{-1}; MS (FAB, *m*/*z*): 372 ($M^+ + 1$); Anal. Calcd for $C_{21}H_{29}N_3O_3$: C, 67.90; H, 7.87; N, 11.31. Found C, 67.7; H, 8.1; N, 11.2. The optical purity of **5** was determined by chiral HPLC (Chiralpak AS, hexane/ethanol, 80/20 (v/v), 1.0 mL/min, 230 nm, 38 °C) to show 98% ee. The retention times for (*S*)- and (*R*)-isomers are 7.55 and 20.78 min, respectively.

Methyl (2*S*)-3-(4-Hydroxyphenyl)-2-[(2-naphthylsulfonyl)amino]propanoate (9). To a stirred solution of methyl tyrosinate hydrochloride salt (42 g, 0.18 mol) and pyridine (57.4 g, 0.72 mol) in CH_2Cl_2 (120 mL) was added dropwise TMSCl (47.2 g, 0.44 mol) at room temperature. After 1 h, the mixture became a clear solution, to which naphthalenesulfonyl chloride (42.0 g, 0.185 mol) was added. After

keeping the mixture overnight, 3 N HCl was added, and the mixture was stirred vigorously for 1 h. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was concentrated in vacuo. The residue was recrystallized in toluene to give 54.5 g (78%) of **9** as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.33 (s, 1H), 7.91 (m, 3H), 7.68 (m, 3H), 6.90 (d, J = 8.4 Hz, 2H), 6.62 (d, J = 8.4 Hz, 2H), 5.18 (d, J = 9.1 Hz, 1H), 4.92 (br s, 1H), 4.21 (dt, J = 15, 6.0 Hz, 1H), 3.37 (s, 3H), 3.00 (dd, J = 13.5, 5.7 Hz, 1H), 2.93 (dd, J = 13.5, 6.5 Hz, 1H); IR ($CHCl_3$) 3082 (s), 3060 (s), 3026 (s), 2924 (w), 2850 (s), 1601 (s), 1493 (s), 1452 (s) cm^{-1}; $[\alpha]^{28.7}_D$ −13.06° (*c* 1.00, CH_3CN); MS (FAB, *m*/*z*): 386 (M^+ + 1); Anal. Calcd for $C_{20}H_{19}NO_5S$: C, 62.3; H, 5.0; N, 3.6. Found: C, 62.3; H, 4.9; N, 3.7.

Methyl (2*S*)- 3-(4-{[(Trifluoromethyl)sulfonyl]oxy}-phenyl)-2-[(2-naphthylsulfonyl)amino]propanoate (10). To a stirred solution of **9** (32 g, 83 mmol) and pyridine (7.9 g, 99.6 mmol) in of CH_2Cl_2 (200 mL) was added triflic anhydride (25.8 g, 91 mmol) at 0 °C. After 3 h, the mixture was quenched with 1 N HCl solution, and the separated organic layer was washed with saturated $NaHCO_3$ solution and concentrated. The residue was recrystallized in 10% aqueous ethanol to give 36.9 g (86%) of **10** as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.35 (s, 1H), 7.92 (m, 3H), 7.68 (m, 3H), 7.16 (d, J = 8.7 Hz, 2H), 7.08 (d, J = 8.7 Hz, 2H), 5.29 (d, J = 8.7 Hz, 1H), 4.25 (dt, J = 8.7, 6.2 Hz, 1H), 3.40 (s, 3H), 3.12 (dd, J = 14.5, 5.7 Hz, 1H), 3.02 (dd, J = 14.5, 8.1 Hz, 1H); IR ($CHCl_3$) 3262 (m), 1747 (w), 1501 (s), 1424 (s), 1213 (s), 1136 (s) cm^{-1}; $[\alpha]^{28.8}$ −3.72° (*c* 0.50, $CHCl_3$); MS (FAB, *m*/*z*): 518 (M^+ + 1); Anal. Calcd for $C_{21}H_{18}NO_7S_2F_3$: C, 48.7; H, 3.5; N, 2.7. Found: C, 48.9; H, 3.5; N, 2.8.

Methyl (2*S*)-3-(4-Cyanophenyl)-2-[(2-naphthylsulfonyl)amino]propanoate (11). To a stirred mixture of Ni-$(PPh_3)_2Cl_2$ (10 mol %, 10.14 g, 15.5 mmol), PPh_3 (8.13 g, 30.1 mmol), KCN (12.11 g, 182 mmol), and Zn (1.01 g, 15.5 mmol) in acetonitrile (210 mL) was added **10** (80 g, 155 mmol) at room temperature under nitrogen atmosphere, and the mixture was heated at 35−40 °C. After 2.5 h, the mixture was cooled to room temperature, and 3 N HCl (600 mL) solution and ethyl acetate (600 mL) were added. After vigorous stirring for 1 h, the organic layer was separated, washed with water, and concentrated to ca. half volume. Hexane (300 mL) was added, and the formed solid was filtered to give 55 g (90%) of **11** as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.31 (s, 1H), 7.89 (m, 3H), 7.67 (m, 3H), 7.39 (d, J = 6.5 Hz, 2H), 7.17 (d, J = 6.5 Hz, 2H), 5.57 (d, J = 8.9 Hz, 1H), 4.27 (m, 1H), 3.45 (s, 3H), 3.15 (dd, J = 13.8, 4.3 Hz, 1H), 3.00 (dd, J = 13.8, 6.1 Hz, 1H); IR ($CHCl_3$) 3250 (m), 2222 (s), 1743 (m), 1345 (w), 1158 (s) cm^{-1}; $[\alpha]^{26.6}_D$ +6.60° (*c* 0.10, $CHCl_3$); MS (FAB, *m*/*z*): 395 (M^+ + 1); Anal. Calcd for $C_{21}H_{18}N_2O_4S$: C, 63.9; H, 4.6; N, 7.1. Found: C, 63.6; H, 4.6; N, 6.9.

(2*S*)-3-(4-Cyanophenyl)-2-[(2-naphthylsulfonyl)amino]-propanoic Acid (12). To a stirred solution of **11** (50.0 g, 126.8 mmol) in THF (150 mL) and H_2O (150 mL) was added lithium hydroxide monohydrate (12.1 g, 287 mmol) at 0 °C. After 4 h, the mixture was quenched with 6 N HCl solution, and THF was evaporated in vacuo. The resulting solution was extracted with methylene chloride (150 mL), and toluene was added to the separated organic layer. Slow removal of methylene chloride led to the formation of a solid, which was filtered, washed with toluene, and dried with nitrogen purge to give 44.3 g (92%) of **12** as a white solid. ^{1}H NMR (CD_3OD, 500 MHz) δ 8.19 (s, 1H), 7.93 (m, 2H), 7.83 (d, J = 8.7 Hz, 1H), 7.61 (m, 3H), 7.27 (d, J = 7.8 Hz, 2H), 7.21 (d, J = 8.3 Hz, 2H), 4.14 (dd, J = 10.1, 4.6 Hz, 1H), 3.13 (dd, J = 13.8, 4.6 Hz, 1H), 2.85 (dd, J = 13.8, 3.7 Hz, 1H); MS (FAB, *m*/*z*): 381 (M^+ + 1).

(2*S*)-3-(4-Cyanophenyl)-2-[(2-naphthylsulfonyl)amino]-propanoyl Chloride (11a). A mixture of **12** (10.1 g, 26.6 mmol), and thionyl chloride (14.1 g, 118.5 mmol) in methylene chloride (50 mL) was refluxed for 12 h. The mixture was cooled to room temperature, and toluene (100 mL) was added. After evaporation of most of methylene chloride, the formed solid was filtered, washed with toluene, and dried with nitrogen purge to give 8.7 g (82.1%) of **11a** as a yellowish solid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.27 (s, 1H), 6.89 (m, 3H), 6.79 (m, 2H), 6.57 (m, 1H), 6.32 (m, 2H), 6.24 (m, 2H), 4.70 (d, J = 9.2 Hz, 1H), 3.53 (m, 1H), 2.30 (m, 1H), 2.05 (m, 1H); MS (FAB, *m*/*z*): 399 (M^+ + 1).

(2*S*)-3-(4-Cyanophenyl)-*N*-cyclopentyl-*N*-methyl-2-[(2-naphthylsulfonyl)amino] Propanamide (15). To a stirred solution cyclopentylmethylamine (4.5 g, 45.4 mmol) in methylene chloride (50 mL) was added dropwise **11a** (8.5 g, 21.3 mmol) at 0 °C. After the reaction was completed, ethanol was added, and most of the methylene chloride was removed by evaporation in vacuo. The formed solid was filtered, washed with toluene, and dried with nitrogen purge to give 9.1 g (93%) of **15** as a white solid. The optical purity of **15** was determined by chiral HPLC (Chiralpak AS, hexane/ethanol = 85/15 (v/v), 1.0 mL/min, 230 nm, 38 °C) to show 97% ee. The retention time for (*R*)- and (*S*)-isomers are 18.4 and 21.2 min, respectively. One time recrystallization of the product in ethanol enhanced the ee value to ≥99.9%; mp 158−162 °C; ^{1}H NMR (DMSO-d_6, 400 MHz, recorded at 393 K) δ 8.30 (s, 1H), 8.05 (d, J = 8.8 Hz, 1H), 7.97 (d, J = 8.8 Hz, 2H), 7.71 (d, J = 8.8 Hz, 1H), 7.70−7.60 (m, 2H), 7.52 (d, J = 8.4 Hz, 2H), 7.45 (br s, 1H), 7.32 (d, J = 8.4 Hz, 1H), 4.54 (t, J = 7 Hz, 1H), 4.22 (quintet, J = 7.8 Hz, 1H), 2.99 (dd, J = 13.6, 6.4 Hz, 1H), 2.87 (dd, J = 13.6, 7.6 Hz, 1H), 2.53 (s, 3H), 1.1−1.55 (m, 8H); ^{13}C NMR (DMSO-d_6, 100 MHz, recorded at 393 K) δ 168.8, 141.9, 137.7, 133.6, 131.1, 130.9, 129.6, 128.1, 128.0, 127.7, 126.9, 126.5, 126.3, 121.5, 117.6, 109.1, 55.5, 53.0, 38.2, 27.3, 23.0; $[\alpha]^{27.4}_D$ −87.93° (*c* 1.00, $CHCl_3$); MS(FAB, *m*/*z*): 462 (M^+ + 1); Anal. Calcd for $C_{26}H_{27}N_3O_3S$: C, 67.65; H, 5.90; N, 9.10. Found: C, 67.7; H, 5.8; N, 8.8.

Isobutyl 4-{(2*S*)-3-(*N*-Cyclopropyl-*N*-methylamino)-2-[(2-naphthylsulfonyl)amino]-3-oxopropyl}benzene-carboximidoate Hydrochloride (HCl Salt of 16a). Compound **15** (57.8 g, 125 mmol) was stirred in isobutyl alcohol/chloroform (1:1 v/v, 500 mL). To the solution was added acetyl chloride (80 g, 1.02 mol) at room-temperature,

maintaining the reaction temperature below 20 °C. After the completion of the reaction, excess hydrogen chloride was removed by nitrogen bubbling. The solution was concentrated to ca. 1/3 volume. The residue was triturated with *tert*-butylmethyl ether and the formed solid was filtered to give 67.5 g (95%) of HCl salt of **16a** as a white solid. ^{1}H NMR (DMSO-d_6, 413 K) δ 8.33 (s, 1H), 7.97 (m, 3H), 7.70 (m, 5H), 7.19 (d, J = 8.0 Hz, 2H), 6.87 (br. 1H), 4.55 (m, 1H), 4.19 (m, 1H), 3.47 (d, J = 6 Hz, 2H), 3.00 (dd, J = 13.6, 6.8 Hz, 1H), 2.87 (dd, J = 13.6, 7.2 Hz, 1H), 2.54 (s, 3H), 1.91 (m, 1H), 1.64−1.10 (m, 8H), 1.00 (d, J = 6.8 Hz, 6H); ^{13}C NMR (DMSO-d_6, 413 K) δ 170.7, 168.7, 140.9, 139.4, 135.3, 134.1, 132.8, 130.4, 130.0, 129.9, 129.8, 129.7, 129.3, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 123.3, 71.3, 70.7, 69.0, 57.2, 54.9, 40.0, 29.3, 29.0, 28.8, 24.6, 19.7, 19.6, 19.5.

(2*S*)-*N*-Cyclopentyl-3-{4-[hydrazino(imino)methyl]phenyl}-*N*-methyl-2-[(2-naphthylsulfonyl)amino]propanamide (16b). HCl salt of **16a** (30 g, 52.5 mmol) was dissolved in acetonitrile (375 mL) at room temperature. To the solution was added 5 g of hydrazine hydrate (1.85 equiv). The resulting suspension was stirred at room temperature for 12 h. To the mixture was added 0.1 N NaOH to adjust the pH of the reaction mixture to ca. 11. The organic phase was separated and concentrated to give 22.5 g (87%) of **16b** as a brown solid. ^{1}H NMR (DMSO-d_6, 413 K) δ 8.35 (s, 1H), 8.00 (m, 3H), 7.76 (d, J = 6.8 Hz, 1H), 7.67 (m, 2H), 7.54 (d, J = 8.4 Hz, 2H), 7.11 (d, J = 8 Hz, 2H), 4.54 (m, 1H), 4.19 (m, 1H), 2.68 (dd, J = 13.6, 7.2 Hz, 1H), 2.84 (dd, J = 13.0, 7.2 Hz, 1H), 2.50 (s, 3H), 1.52−1.15 (m, 8H); ^{13}C NMR (DMSO-d_6, 413 K) δ 169.7, 138.3, 134.1, 131.6, 129.2, 128.6, 128.5, 128.1, 128.0, 127.3, 126.9, 125.7, 122.1, 56.0, 53.8, 38.9, 28.1, 27.8, 27.6, 23.4; MS (FAB, *m*/*z*): 494 (M^+ + 1), 987 ($2M^+$ + 1).

LB30057 (1). Compound **16b** (22.48 g, 45.56 mmol) was suspended in ethanol (240 mL). To the suspension was added a solution of maleic acid in ethanol (6.48 g, 55.8 mmol in 25 mL of ethanol) at room temperature. The mixture became a homogeneous solution immediately after the completion of the addition of maleic acid solution. In few minutes, crystalline **1** began to precipitate. After 4 h, the precipitates were collected, and the filter cake was washed with ethanol (80 mL × 2). The cake was dried by nitrogen purge to give 25.48 g (90%) of **1** as a beige solid; mp 180−181 °C dec; ^{1}H NMR (DMSO-d_6, 413 K) δ 8.34 (s, 1H), 8.03 (d, J = 7.9 Hz, 1H), 8.01 (d, J = 8.5 Hz, 1H), 7.99 (d, J = 9.8 Hz, 1H), 7.74 (dd, J = 8.6, 1.8 Hz, 1H), 7.66 (m, 2H), 7.60 (d, J = 8.0 Hz, 2H), 7.36 (d, J = 8.5 Hz, 2H), 6.01 (s, 2H), 4.57 (t, J = 6.7 Hz, 1H), 4.20 (d, J = 8.7 Hz, 1H), 3.02 (dd, J = 13.5, 6.1 Hz, 1H), 2.90 (dd, J = 13.5, 8.0 Hz, 1H), 2.53 (3H, s), 1.52−1.24 (8H, m); MS (CI, *m*/*z*): 494 (M^+ + 1), 117 ($C_4H_4O_4$+H, maleic acid); The optical purity of **1** (t_R = 12 min for **1** and 9 min for its enantiomer) showed better than 99% ee by HPLC analysis (analytical conditions: Chiralpak AD column-250 × 4.6 mm, 10 μm particle size; column temp: 35 °C; mobile phase: hexane: a solution of 75:25 of ethanol−methanol:trifluoroacetic acid = 82:18:0.1; 1.0 mL/min; 235 nm; injection volume 10 μL).

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