Three-component, one-pot tandem Sonogashira/Suzuki–Miyaura coupling reactions and derivatization for the synthesis of a library of ceramide-transport protein inhibitors that were designed *in silico*

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Abstract: We have developed a one-pot, tandem Sonogashira/Suzuki–Miyaura coupling reaction, which is unknown synthetically, and applied it for the synthesis of a library of potential natural ligand nonmimetic inhibitors of the lipid-transfer protein, ceramide-transport protein (CERT). The characteristic feature of this reaction is that the two-step coupling reaction proceeds smoothly with only 5 mol% of palladium catalyst. Furthermore, the location of the formed carbon–carbon bond would be strictly defined because of the difference in reactivity. Therefore, many derivatives could be synthesized in high yields without the formation of regioisomeric byproducts by the same procedure. We also performed a semi-gram scale synthesis of several derivatives to provide the bioactive assey. After synthesizing as many as 113 derivatives, we identified a nonnatural mimetic inhibitor with activity comparable to that of the known inhibitor (1*R*,3*S*)-HPA-12.

Introduction

Lipids are the principal constituents of all cell membranes and play important roles in its function and organelle structure. Lipid-transfer proteins mediate interorganelle transport of membrane lipids at organelle contact sites in cells, playing fundamental roles in the lipidome and membrane biogenesis in eukaryotes.[1] The ceramide-transport protein (CERT) carries ceramide from the endoplasmic reticulum to the Golgi apparatus, converting it into the phosphosphingolipid, sphingomyelin.[2] CERT was demonstrated to be a key player in the homeostasis of the ceramide–sphingomyelin axis of the cellular lipidome and has several advantages as a model lipid-transfer protein for the development of novel inhibitors with a rational strategy.[3]
We previously developed a ceramide-mimetic compound, (1*R*,3*S*)-HPA-12, as a potent inhibitor of CERT.[4,5] (1*R*,3*S*)-HPA-12 binds to a ceramide-binding pocket in CERT, thereby acting as a competitive antagonist, whereas it does not affect the ceramide-metabolizing enzymes.[6] Nevertheless, natural ligand-mimetic compounds may directly bind not only to the desired target, but also to various undesired targets sharing the same natural ligand. Therefore, we started the development of a series of small chemicals with no apparent ceramide mimicry, but with potent inhibitory activity of the function of CERT in human cultured cells. Cocrystallographic structures of the ceramide-binding of CERT with multiple types of ceramide species have been solved.[7] After an *in silico* virtual screening of ca. 3×10^6 compounds for protein–chemical compound docking (calculations were performed by Daiich Sankyo RD Novare Co. Ltd., Tokyo, Japan), we identified one candidate, hereafter referred to as seed compound **1** (SC1), which has no obvious ceramide-like structure (Figure 1).[8]

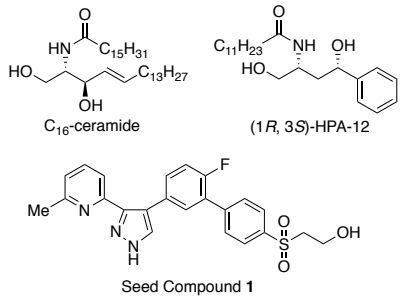


Figure 1. The structure of C_{16}-ceramide, (1*R*,3*S*)-HPA-12, and seed compound **1**.

A surface plasmon resonance (SPR) assay, which is a quantitative assay system that can be used to determine the physical affinity of low-molecular-weight chemicals for CERT, revealed that that the binding constant of SC1 was approximately 400 times weaker than that of (1*R*,3*S*)-HPA-12.[8] Moreover, X-ray crystallographic analysis confirmed the

predicted hydrogen-bonding network between SC1 and the ceramide-binding pocket in the cocrystal complex. Based on these results, we considered that SC1 was a promising initial compound for the development of a natural ligand-nonmimetic inhibitor of CERT.

Synthetic strategy

For the systematic expansion of SC1 derivatives, the structural backbone of the target compound needed to be simple but amenable to modification through combinatorial synthesis. Judging from the cocrystal complex of SC1 with the CERT protein,[8] the terminal hydroxyethanesulfonyl group of SC1 was expected to be crucial for the formation of a hydrogen-bonding network to several amino acids of the ceramide-binding pocket in the CERT protein in a similar mode to the natural ligand ceramide. However, although the pyrazole unit has no hydrogen-bonding interaction to the CERT protein, it may work as a "hinge" for the structure of SC1. The 2-pyridyl group, another terminal group of SC1, did not participate in any clear interaction at this stage. For ease of synthesis, we next attempted to find more simplified compounds before constructing diverse sets of SC-derivatives. For this purpose, we replaced the pyrazole moiety with a simple hydrocarbon so that it we could focus on the role of the "hinge" in the new CERT inhibitors. To allow hydrogen bonding between the CERT inhibitor at two different locations of the amino acids of the CERT protein, the "hinge" is required to separate the rigid parts of the structure by an appropriate distance and with optimal conformation. Therefore, we set the hydrocarbon derivatives C≡C (**2**), C−C (**3**), *trans* C=C (**4**), *cis* C=C (**5**), or cyclopropyl (**6** for *cis* and **7** for *trans*) groups as the "hinge" structure (Figure 2).

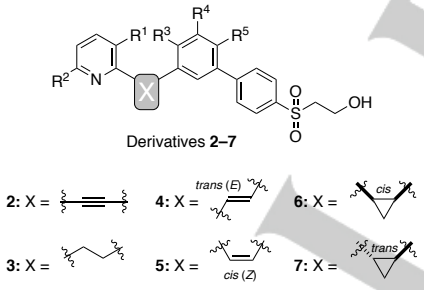
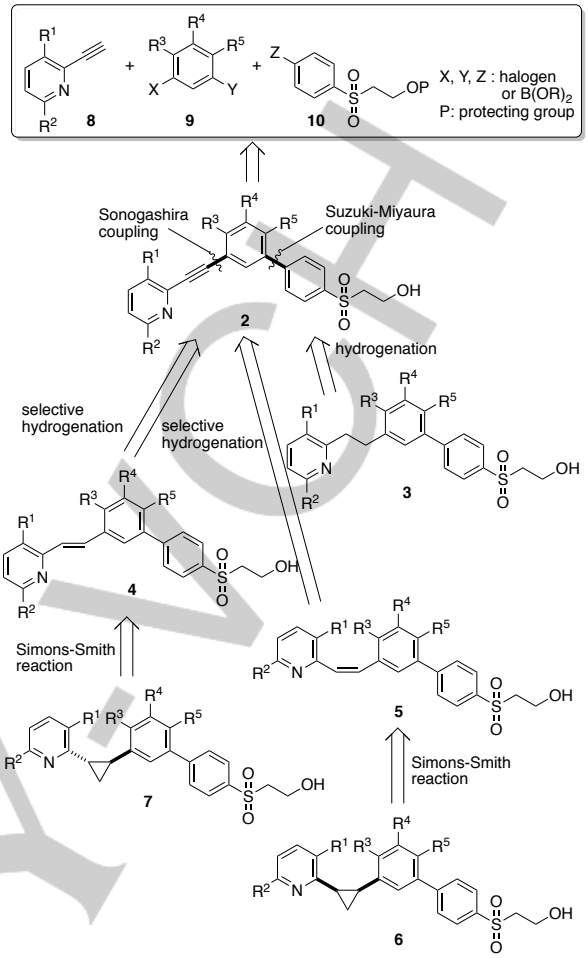


Figure 2. The structure of the target compounds **2**–**7**.

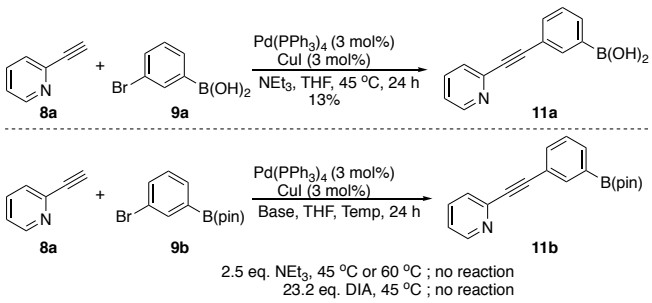
Since it was expected that compounds **3**–**7** could be easily derived from the corresponding precursor **2** in either one or two steps, it was desirable to synthesize the series of compounds **2** on a gram scale and to convert them into the target compounds **3**–**7** (Scheme 1). The **2** series would be converted into the **3** series by catalytic hydrogenative reduction by using our developed palladium catalyst.[9] However, the **4** or **5** series would be synthesized by *E*/*Z* selective partial reduction from the **2** series with a palladium catalyst.[10] The **7** or **6** series would be converted through the cyclopropanation of the **4** or **5** series, respectively, through an improved modification of the Simons–Smith reaction.[11]



Scheme 1. The target CERT inhibitor candidates **2**–**7** and their retrosynthetic strategy.

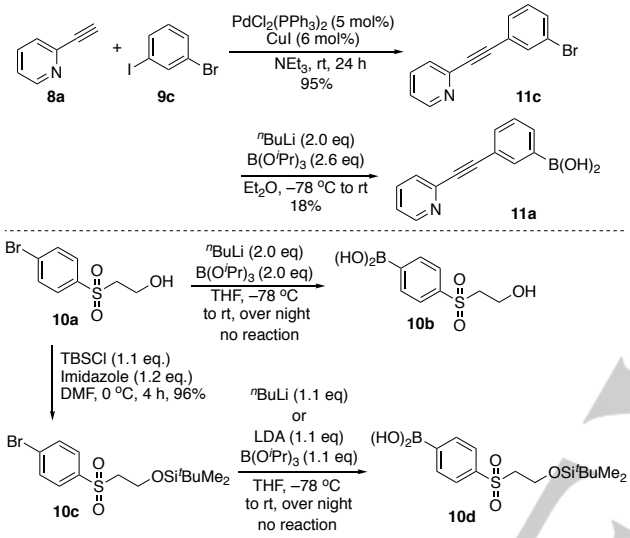
Results and Discussion

It was envisioned that the compound **2** series could be synthesized by connecting the units in stages by using Sonogashira[12,13] and Suzuki–Miyaura coupling.[14] First, we examined the Sonogashira coupling reaction, which tends to proceed under milder conditions than the Suzuki–Miyaura coupling. The combination of commercially available **8a** and **9a** gave the corresponding target product **11a** in only 13% yield (Scheme 2, top). No improvement was found when pinacol ester **9b** was used instead of **9a** (Scheme 2, bottom).



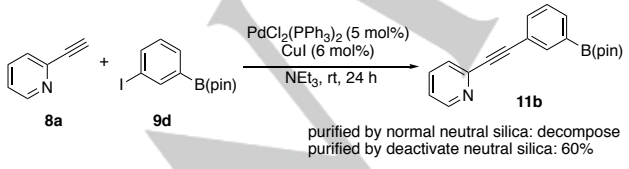
Scheme 2. The initial trials of Sonogashira coupling reaction.

When the reaction was carried out with **9c**[12b,c] in an effort to improve the reactivity, the reaction proceeded smoothly even at room temperature, and the corresponding compound **11c** was obtained in high yield (95%).[12b] To conduct the Suzuki–Miyaura coupling reaction of **11c** with "right-side" unit **10a**[15] for the next step, we tried to synthesize **11a** by boration of **11c**; however, the yield was extremely low (Scheme 3, top). Although the boration of the "right-side" unit **10a** was examined so that coupling with **11c** could be performed, the desired reaction did not proceed. Several nucleophilic reactions of ^{n}BuLi to **10a** might proceed to give a complex mixture. The same tendency was observed in the case of boration of **10c**, which was silyl-protected 10a. In this case, contained the silicon rearranged complex compounds were also seem like formed (Scheme 3, bottom).



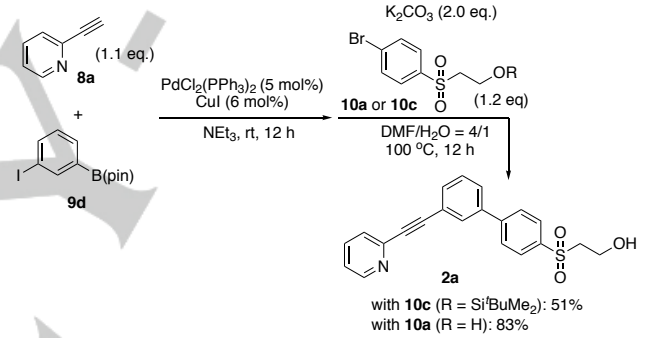
Scheme 3. Attempted derivatization of each unit for the Suzuki–Miyaura coupling.

Based on the finding that the Sonogashira coupling reaction using aryl iodide proceeded smoothly, and that the borylation of **10a**, **10c**, and **11c** failed, we conducted the Sonogashira coupling reaction with **9d**, which has higher reactivity than **9a** or **9b** as a substrate. The reaction itself proceeded successfully; however, the target compound **11b** was difficult to isolate. Finally, **11b** was isolated in 60% yield by using water-containing deactivated neutral silica gel (Scheme 4).



Scheme 4. The optimized Sonogashira coupling.

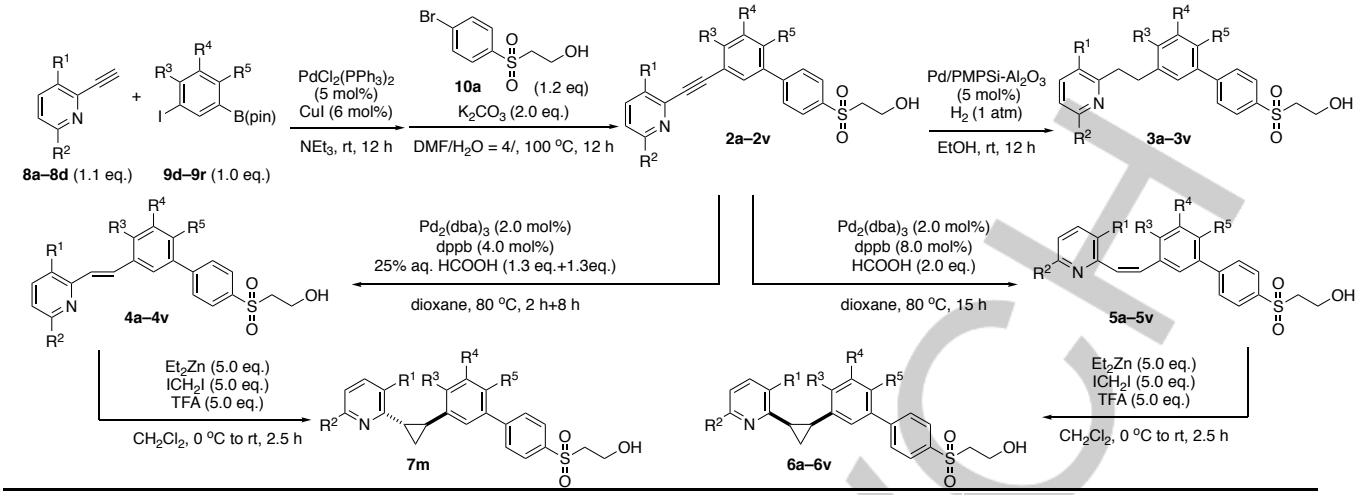
Given that both the Sonogashira and Suzuki–Miyaura coupling reactions use a palladium catalyst, we envisioned that a one-pot tandem reaction may proceed in which the palladium catalyst would be used for both coupling reactions, which is also effective in green chemistry. To our knowledge, there are only two examples of such one-pot tandem Sonogashira/Suzuki–Miyaura coupling reactions[16] to provide biaryl acetylene compounds,[17] such as **2**, without addition of any palladium catalyst at the second-step coupling reaction.[18] Indeed, after the Sonogashira coupling reaction under the conditions already described in Scheme 4, we added the "right-side" unit **10c** with base and additional solvents continuously, and then the mixture was heated. Interestingly, the TBDMS group of primary alcohol could not withstand under the reaction conditions (100 ˚C in aqueous DMF with potassium carbonate) and desilylated desired three-component coupling compound **2a** was obtained in 51% yield as the main product. Compare with the **11b** as an intermediate in the reaction mixture, compound **2a** was stable and could be purified easily using conventional neutral silica gel. The three-component coupling reaction could also be conducted with unprotected **10a** to give **2a** directly in 83% yield (Scheme 5).



Scheme 5. Developed one-pot tandem Sonogashira/Suzuki–Miyaura coupling reactions for the synthesis of **2a**.

With these optimized conditions in hand, **2a**–**v** were synthesized by combinations of various "left-side" units **8a**–**d**, central units **9d**–**r** and **10a**, and further derivatizations were performed to synthesize **3a**–**v**, **4a**–**v**, **5a**–**v**, **6a**–**v**, and **7m**, respectively (Table 1).[8] As noted previously, the characteristic feature of this three-component, one-pot tandem coupling reaction is that the two-step coupling reaction proceeds smoothly with only 5 mol% of palladium catalyst. Furthermore, the location of the formed carbon–carbon bond would be strictly defined because of the difference in reactivity: i.e., one is the terminal acetylene–aryl iodine and the other is aryl boron–aryl bromine. Therefore, even compounds such as **2m**–**v** could be synthesized in high yields without the formation of regioisomeric byproducts, which would be expected to be difficult to separate by column chromatography.

Table 1. The synthesis of derivatives as CERT inhibitors[a].



	Coupling Yield to **2** (%)	Yield of **2** to **3** (%)	Yield of **2** to **4** (%)	Yield of **2** to **5** (%)	Yield of **5** to **6** (%)	Yield of **4** to **7** (%)
a	83	quant.	34 (**2a** 60)	15 (**2a** 79)	10 (**5a** 57)	-
b (R^5 = F)	77	94	89	80	27 (**5b** 15)	-
c (R^2 = Me)	77	94	51 (**3c** 26)	81	25 (**5c** 62)	-
d (R^2 = Me, R^5 = F)	83	94	65	89	29 (**5d** 40)	-
e (R^4 = ^{t}Bu)	78	44 (**2e** 43)	80 (**2e** 2)	79	30 (**5e** 33)	-
f (R^4 = Me)	84	62 (**2f** 32)	90	39 (**2f** 32)	79	-
g (R^4 = CF_3)	68	88 (**2g** 2)	69	61 (**3g** 4)	NR	-
h (R^3 = Me)	68	81	70 (**2h** 10)	47 (**3h** 30)	56 (**5h** 19)	-
i (R^1 = Me)	89	80	29 (**2i** 69)	56	11 (**5i** 70)	-
j (R^2 = R^3 = Me)	64	89	67 (**3j** 13)	60 (**2j** 23, **3j** 5)	70	-
k (R^1 = R^3 = Me)	73	76	58 (**2k** 41)	35 (**2k** 38, **3k** 6)	32 (**5k** 30)	-
l (R^5 = Me)	66	76 (**2l** 23)	97	70	56	-
m (R^3 = ^{n}Pr)	57	93	59	22	69	8 (**4m** 61)
n (R^3 = ^{n}C_5H_{11})	65	77 (**2n** 11)	48 (**2n** 25)	77 (**2n** 4)	62 (**5n** 20)	-
o (R^3 = ^{i}Pr)	39	33 (**2o** 36)	53	70 (**2o** 24)	8 (**5o** 68)	-
p (R^3 = ^{i}Bu)	52	38 (**2p** 50)	50	64 (**2p** 30)	NR	-
q (R^1 = Me, R^3 = ^{n}Pr)	70	89	49 (**2q** 47)	14 (**4q** 77)	4 (**5q** 79)	-
r (R^1 = ^{n}C_5H_{11}, R^3 = ^{n}Pr)	76	quant.	38 (**2r** 59)	7 (**2r** 20, **4r** 73)	10 (**5r** 78)	-
s (R^3 = ^{n}C_7H_{15})	71	96	57	29 (**4s** 67)	72	-
t (R^3 = ^{n}C_8H_{17})	78	89	55	62 (**4t** 37)	41	-
u (R^3 = ^{c}C_6H_{11})	44	82	71	82 (**4u** 15)	73 (**5u** 17)	-
v (R^3 = ^{c}C_5H_9)	69	81	59	70 (**4v** 18)	74 (**5v** 16)	-

[a] For all compounds, R^1 = R^2 = R^3 = R^4 = R^5 = H unless otherwise specified. The yields of recovered starting materials or isolated by-products are shown in parentheses.

The coupling reactions generally proceeded smoothly with high yields, except for **2o**, **2p**, and **2u**, which have bulky substituents at R^3. Alkynes **2** were easily converted into alkanes **3** by hydrogenation. For the synthesis of *trans*-alkenes **4** and *cis*-alkenes **5**, the reactions were relatively clean with some recovery of the starting materials. Furthermore, even under *cis*-selective conditions, thermodynamically stable *trans*-alkenes **4q** or **4r** were obtained predominantly when **5q** or **5r** were used as substrates. Although not examined in detail, neither **6g** nor **6p** could be synthesized under conventional Simons–Smith reaction

conditions. When the same cyclopropanation conditions used for *cis* derivatives were applied for the synthesis of *trans*-cyclopropane **7m** from **4m**, the yield of the desired product was only 8%, with 61% recovered starting material. In fact, given that the SPR activity of **7m** was lower than that of **6m**, we did not optimize the reaction conditions for the synthesis of other derivatives of the **7** series.

The SPR activity of the 113 derivatives thus synthesized was examined,[19] and it was found that **6n** was a potent inhibitor. We then conducted a 0.5 to 1.0 g scale synthesis of **6n** (see Experimental section). Although **6n** was synthesized as a racemate, we conducted optical resolution by chiral HPLC column chromatography, and it was revealed that the (1*S*,2*R*)-isomer had almost the same binding constant with CERT protein as that of (1*R*,3*S*)-HPA-12 based on the SPR assay. X-ray crystallographic analysis of a cocrystal of (1*S*,2*R*)-**6n** and CERT revealed that the cyclopropane ring of **6n** played the expected role of a "hinge." As we also anticipated, the 2-pyridyl group of **6n** participated in hydrogen bonding with an amino acid within the CERT protein. This new hydrogen bond, which did not exist in the case of SC1, might strongly assist the ability of **6n** to function as an antagonist of CERT. Moreover, the *n*-pentyl group in the central unit of **6n** seems to have a suitable hydrophobic interaction that enables it to fit the hydrophobic pocket of the CERT protein.

Conclusions

We have developed a one-pot, tandem Sonogashira/Suzuki–Miyaura coupling reaction, which is unknown synthetically, and applied it for the synthesis of a library of potential natural ligand nonmimetic inhibitors of a lipid-transfer protein, CERT. The characteristic feature of this three-component, one-pot tandem coupling reaction is that the two-step coupling reaction proceeds smoothly with only 5 mol% palladium catalyst. After synthesizing as many as 113 derivatives, a non-natural mimetic inhibitor was identified that had an activity comparable to that of the known inhibitor (1*R*,3*S*)-HPA-12.

Experimental Section

Details of the synthetic procedures used to obtain the compounds listed in Table 1, and the starting materials, together with ^{1}H and ^{13}C NMR spectra of synthesized compounds, are available from the generalist repository figshare (DOI: 10.6084/m9.figshare.7398533). Here, we will describe the gram-scale synthesis of compound **2n** and its derivatization to **3n**–**6n** as a typical experimental procedure. We also present the characterization data for compounds **10c** and **11b**, which were not previously reported as intermediates under investigation or in routes not achieved.

Gram-scale synthesis of 2n: A 50 mL single-necked round-bottom flask equipped with stirring bar and reflux condenser was flame-dried under vacuum, and then charged with Ar. To this flask, copper iodide (6.0 mol%, 46.7 mg, 0.240 mmol), 3-iodo-4-pentylbenzeneboronic acid pinacol ester (**9m**) (1.60 g, 4.00 mmol), and bis(triphenylphosphine)palladium(II) dichloride (5.0 mol%, 141 mg, 0.200 mmol), triethylamine (11.2 mL), and 2-ethynylpyridine (**8a**) (1.1 eq., 0.436 mL, 4.40 mmol) were added successively. After stirring at room temperature for 12 hours, DMF (16.0 mL), water (4.00 mL), 4-hydroxyethylsulfonylbromobenzene (**10a**) (1.2 eq., 1.17 g, 4.80 mmol), and potassium carbonate (2.0 eq., 1.15 g, 8.00 mmol) were added successively and the resulting reaction mixture was stirred and heated at 100 °C for 12 hours. After cooling, the mixture was diluted with water (10 mL) and ethyl acetate (10 mL) filtered over a Celite® pad, and the organic phase was separated. The aqueous layer was extracted with ethyl acetate (3 × 20 mL) and the combined organic layer was washed with water (2 × 50 mL) and brine (2 × 50 mL), and dried over anhydrous Na_2SO_4. The solvent was evaporated *in vacuo* and the residue was purified by silica gel column chromatography (hexane/ethyl acetate, 1:1, v/v), to give 4'-(2-hydroxyethanesulfonyl)-4-pentyl-3-(pyridin-2-ylethynyl)-1,1'-biphenyl **(2n)** (1.13 g, 65%). ^{1}H-NMR ($CDCl_3$) δ: 8.65 (1H, d, *J* = 4.1 Hz), 7.99 (2H, d, *J* = 8.7 Hz), 7.86 (1H, d, *J* = 1.8 Hz), 7.79 (2H, d, *J* = 8.2 Hz), 7.71 (1H, td, *J* = 7.8, 1.8 Hz), 7.54 (2H, td, *J* = 5.3, 2.7 Hz), 7.37 (1H, d, *J* = 7.8 Hz), 7.27 (1H, ddd, *J* = 7.7, 4.9, 1.3 Hz), 4.05 (2H, dd, *J* = 11.0, 6.4 Hz), 3.40 (2H, dd, *J* = 7.1, 3.9 Hz), 2.94 (2H, t, *J* = 7.8 Hz), 2.89 (1H, t, *J* = 6.4 Hz), 1.75 (2H, dd, *J* = 15.1, 7.3 Hz), 1.43–1.38 (4H, m), 0.90 (3H, t, *J* = 7.1 Hz). ^{13}C-NMR ($CDCl_3$) δ: 14.0, 22.5, 30.3, 31.6, 34.3, 56.4, 58.4, 87.5, 92.5, 122.6, 122.9, 127.2, 127.8, 127.8, 128.6, 129.7, 131.6, 136.2, 136.4, 137.5, 143.4, 145.9, 146.2, 150.2; HRMS (*m*/*z*): $[M+H]^+$ calcd. for $C_{26}H_{28}NO_3S$: 434.17899; found: 434.17957.

Derivatization from 2n to 3n:[9] Pd/PMPSi-Al_2O_3 (5.0 mol%, 74.1 mg, Pd 0.099 mmol g^{-1}), 2n (63.6 mg, 0.1467 mmol) and ethanol (2.0 mL) were added to a 30 mL pear-shaped single-necked flask with stirring bar. H_2 gas (balloon) was introduced into the reaction vessel and the contents of the flask was stirred for 12 h. The reaction mixture was filtered through a Celite® pad then washed with ethyl acetate (10 mL). The solvent was evaporated *in vacuo* and the residue was purified by preparative PTLC (hexane/ethyl acetate, 1:2, v/v, twice), to give 4'-(2-hydroxyethanesulfonyl)-4-pentyl-3-(pyridin-2-ylethyl)-1,1'-biphenyl (3n) (49.5 mg, 77%) together with recovered starting material (7.1 mg, 11%). ^{1}H NMR ($CDCl_3$) δ: 8.58 (1H, t, *J* = 2.5 Hz), 7.95 (2H, t, *J* = 4.1 Hz), 7.70 (2H, t, *J* = 4.4 Hz), 7.59 (1H, td, *J* = 7.6, 1.8 Hz), 7.39 (2H, t, *J* = 4.8 Hz), 7.27 (1H, t, *J* = 3.7 Hz), 7.15 (1H, td, *J* = 6.2, 1.1 Hz), 7.09 (1H, d, *J* = 7.8 Hz), 4.04 (2H, s), 3.40 (2H, dd, *J* = 6.9, 4.1 Hz), 3.29 (1H, s), 3.12 (4H, ddd, *J* = 14.4, 8.0, 4.4 Hz), 2.67 (2H, t, *J* = 7.8 Hz), 1.61 (2H, dd, *J* = 15.6, 7.3 Hz), 1.38 (4H, dd, *J* = 7.1, 3.4 Hz), 0.91 (3H, t, *J* = 7.1 Hz). ^{13}C NMR ($CDCl_3$) δ: 14.0, 22.5, 30.8, 31.8, 32.3, 32.8, 39.7, 56.3, 58.4, 121.3, 123.0, 125.0, 127.7, 128.3, 130.0, 136.3, 136.4, 136.9, 140.0, 141.7, 147.0, 149.3, 161.0. HRMS (*m*/*z*): $[M+H]^+$ calcd. for $C_{26}H_{32}NO_3S$: 438.21029; found: 438.20928.

Derivatization from 2n to 4n:[10] An oven-dried 10 mL glass tube containing a stirring bar was charged with $Pd_2(dba)_3{\cdot}CHCl_3$ (2.0 mol%, 4.3 mg, 4.15 μmol), dppb (4.0 mol %, 3.7 mg, 8.70 μmol) and (**2n**) (86.3 mg, 0.199 mmol). The tube was sealed and then evacuated and backfilled with Ar. Dioxane (0.6 mL) was subsequently injected and, after stirring the mixture at room temperature for 15 min, aqueous HCO_2H (25%; 48 μL, 1.3 eq., 0.26 mmol) was added. The reaction was heated to 80 °C for 2 h, then further aqueous HCO_2H (25%; 48 μL, 1.3 eq., 0.26 mmol) was added. The mixture was heated at 80 °C for another 8 h, then filtered through a Celite® pad, and washed with ethyl acetate (10 mL). The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (hexane/ethyl acetate, 1:2, v/v), to give (*E*)-4'-(2-hydroxyethanesulfonyl)-4-pentyl-3-(pyridin-2-yl-2vinyl)-1,1'-biphenyl (**4n**) (41.8 mg, 48%) together with recovered starting material (21.5 mg, 25%). ^{1}H NMR ($CDCl_3$) δ: 8.62 (1H, d, *J* = 4.1 Hz), 7.99 (2H, d, *J* = 8.7 Hz), 7.93 (1H, d, *J* = 15.6 Hz), 7.88 (1H, d, *J* = 1.8 Hz), 7.81 (2H, d, *J* = 8.7 Hz), 7.69 (1H, td, *J* = 7.8, 1.8 Hz), 7.48 (1H, dd, *J* = 7.8, 1.8 Hz), 7.43 (1H, d, *J* = 8.2 Hz), 7.31 (1H, d, *J* = 8.2 Hz), 7.16 (2H, dd, *J* = 13.7, 9.2 Hz), 4.04 (2H, d, *J* = 5.5 Hz), 3.41 (2H, t, *J* = 5.5 Hz), 3.18 (1H, s), 2.84 (2H, t, *J* = 7.8 Hz), 1.65 (2H, dd, *J* = 15.1, 7.3 Hz), 1.38 (4H, t, *J* = 3.7 Hz), 0.90 (3H, t, *J* = 7.1 Hz). ^{13}C NMR ($CDCl_3$) δ: 14.0, 22.4, 30.7, 31.6, 33.0, 56.3, 58.4, 122.0, 122.2, 125.0, 126.9, 127.8, 128.5, 129.9, 130.2, 130.5, 136.1, 136.6, 136.8, 137.2, 142.1, 146.8, 149.7, 155.5. HRMS (*m*/*z*): $[M+H]^+$ calcd. for $C_{26}H_{30}NO_3S$: 436.19464; found: 436.19137.

Gram-scale synthesis of 5n from 2n:[10] An oven-dried 10 mL glass tube containing a stirring bar was charged with $Pd_2(dba)_3{\cdot}CHCl_3$ (2.0 mol%, 49.7 mg, 48.0 μmol), dppb (8.0 mol%, 82.0 mg, 192 μmol) and **2n** (1045.4 mg, 2.41 mmol). The tube was sealed and then evacuated and backfilled with Ar, then dioxane (2.4 mL) was subsequently injected. After stirring the mixture at room temperature for 15 min, HCO_2H (98%; 189 μL, 2.0 eq. 4.80 mmol) was added. The mixture was heated at 80 °C for 15 h, then filtered through a Celite® pad, and washed with ethyl acetate (20 mL). The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (hexane/ethyl acetate, 1:1 to 1:2, v/v), to give (*Z*)-4'-(2-hydroxyethanesulfonyl)-4-pentyl-3-(pyridin-2-yl-2-vinyl)-1,1'-biphenyl (**4n**) (805.3 mg, 77%) together with recovered starting material (46.4 mg, 4%). ^{1}H NMR ($CDCl_3$) δ: 8.57 (1H, d, *J* = 4.1 Hz), 7.88 (2H, d, *J* = 8.7 Hz), 7.52 (2H, d, *J* = 8.7 Hz), 7.46 (1H, dd, *J* = 8.0, 2.1 Hz), 7.36 (3H, td, *J* = 9.8, 4.0 Hz), 7.07 (1H, t, *J* = 6.2 Hz), 6.99 (2H, dd, *J* = 14.7, 10.1 Hz), 6.84 (1H, d, *J* = 12.4 Hz), 4.00 (2H, t, *J* = 5.7 Hz), 3.36 (3H, t, *J* = 5.5 Hz), 2.69 (2H, t, *J* = 7.8 Hz), 1.63 (2H, t, *J* = 7.6 Hz), 1.35 (4H, dd, *J* = 7.3, 3.7 Hz), 0.89 (3H, t, *J* = 7.1 Hz). ^{13}C NMR ($CDCl_3$) δ: 13.9, 22.4, 30.1, 31.6, 33.3, 56.2, 58.3, 121.8, 123.6, 126.5, 127.5, 128.3, 128.4, 130.2, 131.7, 132.1, 135.6, 136.2, 136.5, 137.1, 142.0, 146.4, 149.4, 155.9. HRMS (*m*/*z*): $[M+H]^+$ calcd. for $C_{26}H_{30}NO_3S$: 436.19464; found: 436.19450.

Semi-gram-scale synthesis of 6n from 5n:[11] Anhydrous CH_2Cl_2 (9.2 mL) was added to a solution of diethylzinc (1.1 M in hexanes, 5.0 eq., 8.4 mL, 9.24 mmol) under Ar atmosphere. The solution was cooled in an ice bath and a solution of trifluoroacetic acid (5.0 eq., 708 μL, 9.24 mmol) in anhydrous CH_2Cl_2 (4.6 mL) was then added dropwise *very slowly* into the reaction mixture by using a syringe. After stirring for 15 min, a solution of CH_2I_2 (5.0 eq., 744 μL, 9.24 mmol) in anhydrous CH_2Cl_2 (4.6 mL) was added. After an additional 20 min of stirring, a solution of **5n** (805.3 mg, 1.85 mmol) in anhydrous CH_2Cl_2 (4.6 mL) was added. After stirring for 1 h at 0 °C, the ice bath was removed, and the mixture was stirred until the reaction was complete. The reaction was quenched with saturated aqueous NH_4Cl and CH_2Cl_2 (10 mL), and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL), and the combined organic layers were washed with saturated $NaHCO_3$ (50 mL), and brine (50 mL), and then dried over Na_2SO_4, filtered, concentrated *in vacuo*, and purified by column chromatography (hexane/ethyl acetate, 1:1, v/v), to give *cis*-4'-(2-hydroxyethanesulfonyl)-4-pentyl-3-(2-(pyridin-2-yl) cyclopropyl)-1,1'-biphenyl (**6n**) (515.4 mg, 62%) together with recovered starting material (163.8 mg, 20%). ^{1}H NMR ($CDCl_3$) δ: 8.28 (1H, dq, *J* = 5.0, 0.9 Hz), 7.94 (2H, dt, *J* = 8.5, 2.0 Hz), 7.65 (2H, dt, *J* = 8.8, 1.9 Hz), 7.35 (1H, d, *J* = 1.9 Hz), 7.29 (2H, tt, *J* = 10.3, 3.4 Hz), 7.08 (1H, t, *J* = 4.0 Hz), 6.89 (1H, ddd, *J* = 7.3, 4.9, 1.0 Hz), 6.74 (1H, t, *J* = 4.0 Hz), 4.04-4.02 (2H, m), 3.39 (2H, td, *J* = 4.1, 2.3 Hz), 3.25 (1H, br s), 2.80-2.69 (2H, m), 2.63 (1H, dd, *J* = 16.0, 8.8 Hz), 2.55-2.48 (1H, m), 1.92-1.88 (1H, m), 1.63-1.51 (2H, m), 1.45-1.27 (5H, m), 0.90 (3H, dd, *J* = 9.0, 5.1 Hz). ^{13}C NMR ($CDCl_3$) δ: 11.4, 14.0, 22.5, 24.4, 25.8, 29.7, 31.8, 32.2, 56.3, 58.4, 120.5, 121.9, 125.0, 127.6, 128.3, 128.6, 128.9, 135.2, 135.3, 135.8, 136.9, 144.0, 147.1, 148.3,158.4. HRMS (*m*/*z*): $[M+H]^+$ calcd. for $C_{27}H_{32}NO_3S$: 450.21029; found: 450.20989.

Preparation of 10c: A 10 mL two-necked round-bottom flask equipped with a stirring bar was flame-dried under vacuum and then charged with Ar. To this flask, **10a** (1.3336 g, 5.0 mmol) and imidazole (0.4085 g, 6.0 mmol), and then dry DMF (5.0 mL) were added successively. After stirring at room temperature to dissolved all materials, then the reaction mixture was cool to at 0 ˚C. ^{t}Butyldimethylsilyl chloride (0.829 g, 5.5 mmol) dissolved in 5.0 mL of dry DMF was added via syringe then stirring for 4 hours. The reaction mixture was quenched with water (20 mL) and ethyl acetate (20 mL), and the layers were separated. The aqueous layer was extracted with ethyl acetate (2 × 10 mL), and the combined organic layers were washed with water (30 mL), and brine (30 mL), and then dried over Na_2SO_4, filtered, concentrated *in vacuo*, and purified by column chromatography (hexane/ethyl acetate, 9:1, v/v), to give **10c** (1.8244 g, 96%). ^{1}H NMR ($CDCl_3$) δ: 7.77 (2H, dd, *J* = 8.5, 2.3 Hz), 7.68 (2H, dd, *J* = 8.5, 2.3 Hz), 4.01–3.98 (2H, m), 3.34–3.33 (2H, m), 0.76 (9H, s), –0.05 (6H, s). ^{13}C NMR ($CDCl_3$) δ: 139.2, 132.4, 129.7, 128.9, 59.0, 57.1, 25.6, 18.0, –5.7.

Preparation of 11b: A 10 mL two-necked round-bottom flask equipped with a stirring bar was flame-dried under vacuum and then charged with Ar. To this flask, copper iodide (6.0 mol%, 4.6 mg, 0.024 mmol), 3-iodobenzeneboronic acid pinacol ester (**9d**) (132.1 mg, 0.40 mmol), and bis(triphenylphosphine)palladium(II) dichloride (5.0 mol%, 14.0 mg, 0.020 mmol), triethylamine (1.13 mL), and 2-ethynylpyridine (**8a**) (1.1 eq., 0.0444 mL, 0.44 mmol) were added successively. After stirring at room temperature for 24 hours, diluted with diethyl ether (5 mL), then filtered over a Celite® pad with diethyl ether (20 mL). The filtrate was washed with water (2 × 20 mL) and brine (1 × 20 mL), and then dried over anhydrous Na_2SO_4. The solvent was evaporated *in vacuo* and the residue was purified by deactivated silica gel (prepared by addition of 10 mL of water to 20 g of dry neutral silica-gel then stir until smooth) column chromatography (hexane/ethyl acetate, 4:1, v/v), to give **11b** (43.1 mg, 60%). ^{1}H NMR ($CDCl_3$) δ: 8.62 (1H, d, *J* = 4.0 Hz), 8.09 (1H, s), 7.80 (1H, dd, *J* = 7.4, 1.1 Hz), 7.68 (2H, td, *J* = 6.4, 4.5 Hz), 7.51 (1H, d, *J* = 7.4 Hz), 7.38 (1H, t, *J* = 7.7 Hz), 7.28–7.22 (1H, m), 1.35 (12H, s). ^{13}C NMR ($CDCl_3$) δ: 150.0, 143.4, 138.6, 136.1,135.0, 134.4, 127.7, 127.1, 122.7, 121.7, 89.3, 88.6, 84.0, 24.8.

Chiral Separation of 6n: An experimental condition for the resolution of **6n** by chiral HPLC has been reported in Supplemental METHOD of ref.8. Both enantiomers of **6n** were separated by CHIRALPAK® IA-3 (Daicel Corporation, 4.6 mm id. x 250 mm length) as a chiral column. The absolute configuration of each enantiomer was determined by X-ray co-crystallography of CERT protein with each compound (see Fig. 5 in ref. 8). After separation, we measured the optical rotation of each samples.

(+)-(1*S*,2*R*)-6n: HPLC (hexane:*i*PrOH, 6:4, v/v, flow rate = 1.0 ml min^{-1}, UV detection at 254 nm) t_R = 6.7 min.; $[\alpha]_D^{33.3}$ = +109.0 (c 1.32, $CHCl_3$)

(–)-(1*R*,2*S*)-6n: HPLC (hexane:*i*PrOH, 6:4, v/v, flow rate = 1.0 ml min^{-1}, UV detection at 254 nm) t_R = 9.5 min.; $[\alpha]_D^{33.8}$ = –106.5 (c 1.26, $CHCl_3$)

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: one-pot •tandem • C–C coupling • Green chemistry • palladium

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[18] For examples of the addition of further palladium catalyst at the second step coupling stage, even in the one-pot tandem three-component coupling, see: a) K. M. Saini, R. K. Saunthwal, A. K. Verma, *Org. Biomol. Chem.*, **2017**, *15*, 10289–10298; b) A. K. Danodia, R. K. Saunthwal, M. Patel, R. K. Tiwari, A. K. Verma, *Org. Biomol. Chem.*, **2016**, *14*, 6487–6496; c) S. Cacchi, G. Fabrizi, A. Goggiamani, A. Iazzetti, R. Verdigione, *Tetrahedron*, **2015**, *71*, 9346–9356.

[19] In this report, we synthesized 109 derivatives. The other four compounds were prepared by using another method. Details are given

in the generalist repository figshare (DOI: 10.6084/m9.figshare.7398533).

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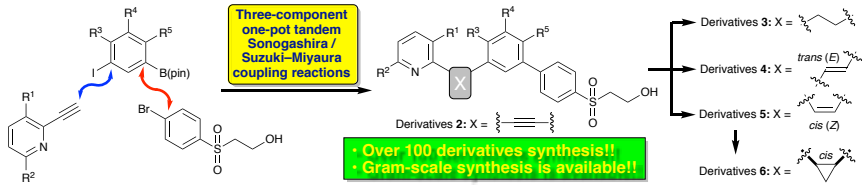

We have developed a one-pot, tandem Sonogashira/Suzuki–Miyaura coupling reaction, which is unknown synthetically, and applied it for the synthesis of a library of potential natural ligand nonmimetic inhibitors of the lipid-transfer protein, ceramide-transport protein (CERT). After synthesizing as many as 113 derivatives, we identified a nonnatural mimetic inhibitor with activity comparable to that of the known inhibitor (1*R*,3*S*)-HPA-12.