Tetrahedron xxx (2014) 1–8

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis of a chiral phosphonium salt for the preparation of α-substituted alaninol derivatives

Takashi Tsuji [a,*], Keisuke Suzuki [a], Tsuyoshi Nakamura [a], Takahide Nishi [b]

[a] Medicinal Chemistry Research Laboratories, Daiichi Sankyo Co, Ltd, 1-2-58 Hiromachi, Shinagawa-ku, Tokyo 140-8710, Japan
[b] Daiichi Sankyo India Pharma Pvt. Ltd, Village Sarhaul, Sector 18, Udyog Vihar Industrial Area, Gurgaon 122015, Haryana, India

ARTICLE INFO

Article history:
Received 6 March 2014
Received in revised form 21 May 2014
Accepted 22 May 2014
Available online xxx

Keywords:
Wittig reaction
Chiral
α,α-Disubstituted α-amino alcohol
$S1P_1$ receptor agonist
TAAR agonist

ABSTRACT

We herein report the synthesis of a chiral phosphonium salt, {[(4*S*)-4-methyl-2-oxo-1,3-oxazolidin-4-yl]methyl}(triphenyl)phosphonium iodide **13** to provide a new Wittig reagent for the general method of synthesizing α-substituted alaninol derivatives. Our method described here is widely applicable to reactions with various types of aldehyde to afford olefin products with high *E*-selectivity, enabling us to provide a new approach to the synthesis of chiral $S1P_1$ agonists including our key intermediates, and of the trace amine-associated receptor 1 (TAAR1) agonist.

1. Introduction

In recent years, a great deal of attention has been paid to the synthesis of α,α-disubstituted α-amino acids or alcohols not only due to the ubiquitous existence of their structures among natural products, but also with a view to the design and synthesis of biologically active compounds. In the area of natural products, myriocin (**1**),[1] sphingofungin E and F (**2**, **3**)[2] are known as representative compounds possessing a α,α-disubstituted α-amino acid part as their structural feature (Fig. 1). On the other hand, for instance in the area of medicinal chemistry, α,α-disubstituted α-amino alcohol or carboxylic acid has been recognized as one of the common structural motifs of $S1P_1$ agonists, which is a novel mechanism of action to be able to afford promising medical treatment for various autoimmune diseases. Indeed, many amphipathic lipid-like molecules containing α,α-disubstituted α-amino alcohol or carboxylic acid units, such as compound **4**–**7** have been reported as potent $S1P_1$ agonists by several groups.[3–5] In particular, fingolimod (FTY720, **4**) has been launched in 2010 as an effective therapeutic agent for multiple sclerosis.[6] In addition, a research group of Roche disclosed a patent concerning the trace amine-associated receptor 1 (TAAR1) agonist[7] represented by **8** possessing a chiral 4,5-dihydro-1,3-oxazol-2-ylamine structure, which is supposed to be a novel mechanism of action for the treatment of schizophrenia. Although considerable efforts have already been implemented into developing the synthetic method for α,α-disubstituted α-amino acids and alcohols,[8] the recent emersion of medicinal chemistry interest toward these classes of compounds still requires establishing a new efficient method of constructing these structures.

Meanwhile, our group has conducted a series of research programs to explore efficacious and safer $S1P_1$ agonists that led us to find a promising clinical candidate CS-0777 (**7**)[5] and its analogues, possessing a chiral 2-methyl-2-aminoethanol structure. Preliminary studies indicated that the stereochemistry of the quaternary carbon center is closely associated with biological activity, and the (*R*)-configuration of the amino alcohol moiety was critically needed to show the $S1P_1$ agonistic activity. Therefore, our research campaign on $S1P_1$ receptor agonists focused on the synthesis of a chiral α,α-disubstituted α-amino alcohol structure having various heteroaromatic rings, such as pyrrole, thiophene, or furan rings adjacent to the chiral center. Our general synthetic approach is described in Scheme 1 in a retrosynthetic manner. We had consistently set compound **9** as a key intermediate throughout our derivatization campaign. In the previous method (shown as 'route a' in Scheme 1), compound **9** was synthesized from chiral aldehyde **10**, and aryl phosphonium salt **11**. Compound **10** was obtained via either enzymatic desymmetrization or Seebach's diastereoselective alkylation methods,[9] and aryl phosphonium salt **11** could be prepared from the corresponding arylmethyl halide **12**. However, due to the instability of electron-rich arylmethyl halide **12**, at times we

* Corresponding author. Tel.: +81 3 3492 3131; fax: +81 3 5436 8563; e-mail addresses: tsuji.takashi.y3@daiichisankyo.co.jp, t-taka4@i.softbank.jp (T. Tsuji).

0040-4020/$ – see front matter © 2014 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tet.2014.05.086

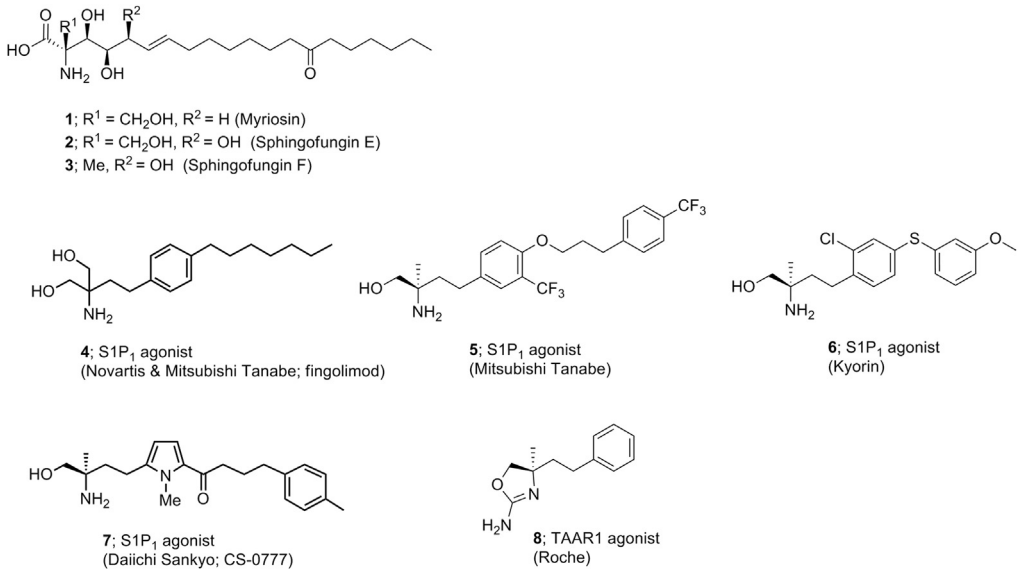
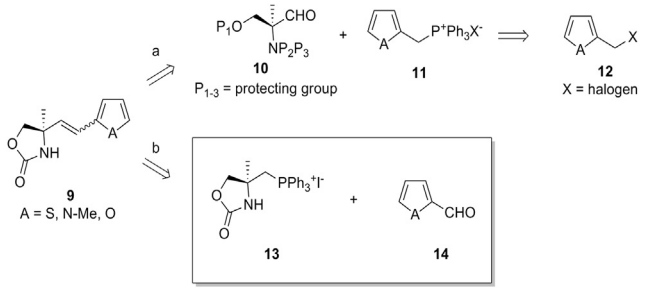


Fig. 1. Biological active compounds, possessing the α,α-disubstituted α-amino alcohol unit.



Scheme 1. Retrosynthesis of key intermediates **9** of $S1P_1$ modulator (a; previous route, b; new route).

had to modify the synthetic route of phosphonium salt to detour unstable intermediates, such as 2-bromomethyl pyrrole, which easily decomposed at ambient temperature. In the process of our effort to improve the synthetic route of **9**, we focused on an alternative method using novel chiral phosphonium salt **13** (shown as 'route b' in Scheme 1). This umpolung strategy allowed us to synthesize a broad structure variation in the part of the aromatic ring of **9** by directly using commercially available aldehydes **14** without step-demanding synthesis of each heteroaromatic phosphonium salt **11**.

Regarding the phosphonium salt containing amino alcohol moiety, Itaya et al.[10] and Sibi et al.[11] previously reported the Wittig reaction using **15** and **16**, respectively (Fig. 2). They reported the preparation and the reactions of **15** and **16** with various aldehydes that provided the coupling products in good yields, and utilized them as the precursors of unnatural amino acids. However, to the best of our knowledge, no reports have been published about the phosphonium salt bearing the quaternary carbon along with 2-aminoalcohol functional groups, which would be a useful Wittig reagent to construct a α,α-disubstituted α-amino alcohol structure. In this manuscript, we report the synthesis of a novel chiral phosphonium salt, {[(4*S*)-4-methyl-2-oxo-1,3-oxazolidin-4-yl]methyl}(triphenyl)phosphonium iodide **13** and the results of the reactions of **13** with various aldehydes.

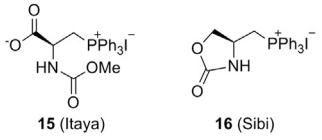
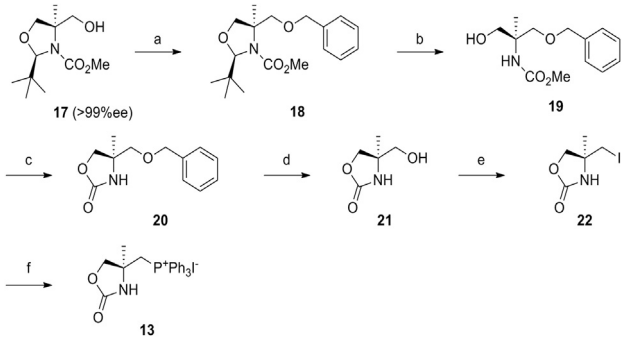


Fig. 2. Wittig reagents bearing the tertiary carbon center at α-position of the amino acid unit.

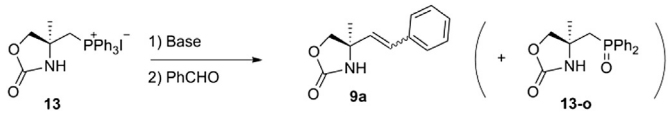
2. Results & discussion

The synthetic route of the {[(4*S*)-4-methyl-2-oxo-1,3-oxazolidin-4-yl]methyl}(triphenyl)phosphonium iodide **13** from **17** is shown in Scheme 2. Chiral alcohol **17** was synthesized by our previously reported method using commercially available L-serine as a starting material.[9c] The protection of the primary alcohol **17** with benzyl bromide proceeded smoothly in the presence of NaH in DMF to provide **18** in good yield. After the deprotection of the *t*-butylmethylidene group of **18**, successive treatment with *t*-BuOK in THF gave oxazolidinone **20** in good yield. The deprotection of the benzyl group was achieved by hydrogenation using Pd–C in EtOH to give alcohol **21** in 91% yield (two steps). Alcohol **21** was treated with *p*-TsCl in pyridine, and the resulting tosylate was successively converted to iodide **22** with NaI in acetone under a reflux condition. A reaction of **22** with triphenylphosphine in DMF provided the desired phosphonium salt **13** in moderate yield as a stable white crystalline solid.



Scheme 2. Reagents and conditions: (a) $PhCH_2Br$, NaH, DMF, 88%; (b) *p*-TsOH monohydrate, MeOH; (c) *t*-BuOK, THF, 95% (two steps); (d) H_2, Pd–C, K_2CO_3, EtOH (91%); (e) *p*-TsCl, pyridine, and then NaI, acetone, 78%; (f) PPh_3, DMF, 57%.

Table 1
Wittig reactions with phosphonium salt **13** and benzaldehyde



Entry	Conditions	Phosphonium salt **13** (equiv)	Base (equiv)	Yield (%)	*E*/*Z*[a]	ee (%)[b]
1	*n*-BuLi, −78 °C, 0.5 h, then rt, 2 h	1.2	2.3	46	>99/1	N.T.[c]
2	*n*-BuLi, −78 °C, 0.5 h, then rt, 2 h	1.2	1.2	Trace	N.T.	N.T.
3	*n*-BuLi, −78 °C, 0.5 h, then rt, 2 h	1.5	2.9	83	>99/1	N.T.
4	*n*-BuLi, −78 °C, 0.5 h, then rt, 2 h	2.0[e]	3.9	99	>99/1	98.6
5	*n*-BuLi, 0 °C, 0.5 h, then rt, 2 h	2.0	3.9	N.R.[d]	—	N.T.
6	LiHMDS, −78 °C, 0.5 h, then rt, 2 h	2.0	3.9	80	>99/1	N.T.
7	NaHMDS, −78 °C, 0.5 h, then rt, 2 h	2.0	3.9	76	>99/1	N.T.

[a] Established by ^{1}H NMR.
[b] Estimated by chiral HPLC compared with the corresponding racemic compound.
[c] N.T.=not tested.
[d] Benzaldehyde was 90% recovered (N.R.=no reaction).
[e] Redundant phosphonium salt **13** was recovered as phosphine oxide **13-o** in 99% yield (based on the theoretical amount of non-reacted phosphonium salt **13**) after a regular work-up manipulation.

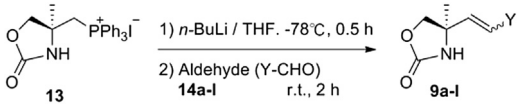
Having established the preparation method for phosphonium salt **13**, we first conducted the optimization of the reaction condition toward aldehydes in several parameters, such as the equivalent of phosphonium salt, a base for deprotonation, and the reaction temperature by using benzaldehyde as a counter substrate. The results of the evaluation of those factors are summarized in Table 1.

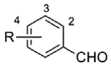
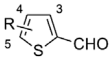
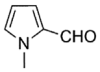
The reaction between benzaldehyde and 1.2 equiv of ylide prepared from phosphonium salt **13** by treatment with 2.3 equiv of *n*-BuLi afforded the desired coupling product in 46% yield along with high *E*-selectivity (entry 1). Concerning the deprotonation of phosphonium salt **13**, 2.0 equiv of the base was essentially needed to prepare dianionic ylide (entry 1, 2). The product yield was improved by increasing the amount of phosphonium salt and culminating with 2.0 equiv of phosphonium salt to benzaldehyde (entry 3, 4), and the enantiomeric excess of product was confirmed to be maintained (entry 4). The redundant phosphonium salt **13** was recovered not as itself, but as phosphine oxide **13-o** quantitatively instead.[12] No other byproducts, such as the one formed via β-elimination of the nitrogen atom of phosphonium salt **13**, were observed as long as the reaction mixture was kept at −78 °C, while raising the temperature to 0 °C at the deprotonation step impaired the reaction (entry 5). We assume that an anion on the oxazolone ring, formed via deprotonation on a nitrogen atom, effectively prevented the β-elimination reaction of a nitrogen atom during the reaction process at low temperatures. The selection of the base did not affect the reaction drastically, but using LiHMDS or NaHMDS slightly deteriorated the yield of **9a** (entry 6, 7). Throughout Table 1, the geometry of product **9a** was consistently regulated to an *E* isomer completely, which was identical to the previous results reported by Sibi et al.[11a] Use of NaHMDS as the base (lithium-free condition) did not influence the predominant *E*-selectivity, although removal of the lithium ion was generally known to decrease the *E*-selectivity in the Wittig reaction. In fact, Sibi et al. previously reported the drastic deterioration of *E*-selectivity under the lithium-free condition, where the *E*/*Z*-selectivity deteriorated from >99:1 to 3.2:1. The difference between Sibi's and our results was thought to be due to the bulkiness of our phosphonium salt, which destabilized the transition state for the *cis* isomer, resulting in the high *E*-selectivity.

With an optimized condition (Table 1, entry 4) in hand, scope and limitation regarding the substrate of this reaction was then explored with various aromatic and aliphatic aldehydes as shown in Table 2.

The reactions between phosphonium salt **13** and various aromatic aldehydes proceeded smoothly to afford each alkene with high *E*-selectivity. It is noteworthy that *ortho*-substituted compounds, such as 2,4-Me_2 (**14b**) and 2-CO_2Me (**14c**), which are thought to be less reactive, nevertheless gave the corresponding products (**9b**, **9c**) in 72% and 75% yields, respectively (entry 2, 3). Furthermore, highly electron rich aldehyde, such as 2,4,6-$(OMe)_3$ (**14d**) and 4-NMe_2 (**14e**), also afforded the corresponding alkenes **9d** and **9e** in acceptable yields (entry 4, 5). As the instability of benzyl halide possessing electron donating groups, such as the alkoxy- or alkylamino group at a *para* or *ortho* position generally complicates the preparation of their phosphonium salt, our

Table 2
The reactions of aromatic and aliphatic aldehydes with Wittig reagent **13**



Entry	Aldehyde (Y–CHO, **14a**–**l**)		Product (**9a**–**l**)	Yield (%)	*E*/*Z*[a]
1	R=H	**14a**	**9a**	99	>99/1
2	 2,4-Me_2	**14b**	**9b**	72	>99/1
3	2-CO_2Me	**14c**	**9c**	75	>99/1
4	2,4,6-$(OMe)_3$	**14d**	**9d**	89	>99/1
5	4-NMe_2	**14e**	**9e**	63	>99/1
6	R=H	**14f**	**9f**	75	>99/1
7	 3-Me	**14g**	**9g**	99	>99/1
8	3-Br	**14h**	**9h**	66	>99/1
9		**14i**	**9i**	83	>99/1
10		**14j**	**9j**	82	>99/1
11	*n*-$C_6H_{13}CHO$	**14k**	**9k**	62	71/29
12		**14l**	**9l**	62	88/12

[a] Established by ^{1}H NMR.

umpolung strategy could provide a complementary method to synthesize α-substituted alaninol derivatives having electron rich aromatic groups. Hetero aromatic aldehydes, such as 2-formylthiophene (**14f**), 2-formyl-1-methylpyrrole (**14i**) or 2-formylfuran (**14j**), gave the corresponding olefin compounds in good yields (entry 6, 9, 10). Substituted heteroaryl aldehydes, such as 3-Me (**14g**) and 3-Br (**14h**), also gave the olefin compounds (**9g**, **9h**), although the yield of **9h** was slightly deteriorated (66%) compared to **9g** (99%). The geometrical selectivity of the products was not influenced by the fashion of aromatic rings to solely give *E* alkenes as a major isomer. In terms of the reaction with aliphatic aldehydes, the yields of the products tended to be inferior to aromatic aldehydes, probably because those aldehydes were partly inactivated by conversion to the corresponding enolates in the basic condition (entry 11, 12). Furthermore, the *E*-selectivity was also deteriorated, which had the same tendency as the results reported by Sibi et al.[11a]

As we could obtain basic information regarding the reaction condition and scope of substrate of the Wittig reaction using phosphonium salt **13**, we then turned our focus to the application of **13**. Several examples using phosphonium salt **13** for the synthesis of biological active compounds are depicted in Scheme 3. As for the synthesis of our $S1P_1$ agonist intermediates, a wide variety of heterocyclic key intermediates were able to be synthesized from the corresponding commercially available aldehydes in only a two-step manipulation, which allowed us to enhance the efficiency of synthesizing a broad structural variation (Scheme 3, Eq. 1). Namely, the Wittig reaction using phosphonium salt **13** with 2-formylthiophene (**14f**), 2-formyl-1-methylpyrrole (**14i**) or 2-formylfuran (**14j**) afforded olefin products (**9f**, **9i**, and **9j**), respectively in good yields (Table 2), and they were reduced with 10% Pd–C in MeOH under a hydrogen atmosphere to respectively give key compounds[9b] **23a**, **23b**, and **23c** in good yields. This new approach could be applicable to a short step synthesis of the chiral analogue of FTY720 (**25**),[13] which is an invaluable tool for the elucidation of the mechanism of action of FTY720 (Scheme 3, Eq. 2). Commercially available aldehyde **24** was reacted with the ylide prepared from our phosphonium salt **13** to afford an olefin compound in 77% yield. The olefin moiety was reduced by hydrogenation with Pd–C, and successive alkaline hydrolysis of the oxazolidinone part gave the chiral analogue of FTY720 (**25**) in 90% yield for two steps. The synthesis of another $S1P_1$ agonist (**6**) was also achieved by using aldehyde **26**[14] and the same transformations as compound **25** (Scheme 3, Eq. 3). Furthermore, TAAR1 agonist **8** was able to be synthesized by this manner (Scheme 3, Eq. 4). Starting from **9a**, the corresponding amino alcohol was obtained by the same procedure (hydrogenation and hydrolysis), and then the 1-aminooxazoline structure of **8** was successively constructed by treatment with cyanogen bromide in the presence of potassium carbonate in THF (69% yield in three steps).

3. Conclusion

In conclusion, we have established the method for preparation of optically active phosphonium salt **13**, bearing the quaternary carbon along with 2-aminoalcohol functional groups. The ylide prepared from phosphonium salt **13** was revealed to react with various aromatic and aliphatic aldehydes in moderate to good yields, providing not only a practical synthetic method for the $S1P_1$ receptor modulators and their key intermediates represented by **23a**–**c**, **25**, and **6**, but also a short synthetic route for a chiral TAAR1 agonist **8**. These results manifest a wide applicability of phosphonium salt **13** for the synthesis of biologically active compounds. It is synthetically noteworthy that the Wittig reaction using **13** with various aldehydes afforded corresponding alkenes with high *E*-selectivity, which would be a good flag for stereoselective installation of further functionalities. Further applications of phosphate **13** will be reported in due course.

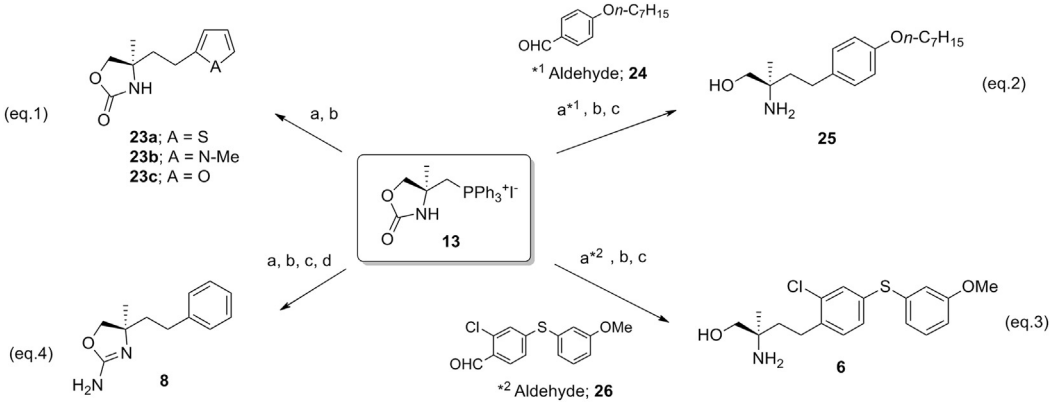
4. Experimental section

4.1. General

Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. ^1H and ^{13}C NMR spectra were recorded on Unity Mercury Plus 400 or 500 spectrometer (Varian) and chemical shifts are given in parts per million from tetramethylsilane (TMS) as an internal standard. Optical rotations were measured on a JASCO P-1030, HORIBA SEPA-300 or an Autopol V plus digital polarimeter. IR absorption spectra were recorded on a Jasco FT/IR-610 spectrophotometer. The mass spectra (Low- or High-resolution mass) spectroscopy was carried out with a JEOL GCmate or JEOL JMS-AX505H. Elemental analyses and melting point calculations were performed by the analytical department of Daiichi Sankyo RD Novare Co., Ltd. Thin-layer chromatography (TLC) was performed on Merck precoated TLC glass sheets with silica gel $60F_{254}$. Separation of the compounds by column chromatography was carried out with silica gel 60 (Merck, 230–400 mesh ASTM).

4.2. Synthesis of compounds

*4.2.1. Methyl (2R,4R)-4-[(benzyloxy)methyl]-2-tert-butyl-4-methyl-1,3-oxazolidine-3-carboxylate (**18**).* Sodium hydride (60%, 2.2 g, 58 mmol) was added to a solution of methyl (2*R*,4*R*)-2-*tert*-butyl-4-(hydroxymethyl)-4-methyl-oxazolidine-3-carboxylate (**17**) (11 g,



Scheme 3. Reagents and conditions: (a) Aldehyde, *n*-BuLi, THF, 77–99%; (b) H_2, Pd–C, MeOH; (c) KOH, MeOH, H_2O, 71–90% (two steps); (d) cyanogen bromide, K_2CO_3, THF, 69%.

Please cite this article in press as: Tsuji, T.; et al., Tetrahedron (2014), http://dx.doi.org/10.1016/j.tet.2014.05.086

48 mmol) in DMF (100 mL) at 0 °C. After stirring for 10 min, benzylbromide (10.7 g, 62 mmol) was added to the reaction mixture at 0 °C. The solution was warmed to ambient temperature and stirred for 2 h. After quenching with saturated aq NH_4Cl (100 mL), the resulting biphasic mixture was extracted with AcOEt (200 mL×2). The combined organic layer was washed with water (100 mL) and brine (100 mL), dried over Na_2SO_4, filtered, and evaporated. Purification by silica gel column chromatography (hexane:AcOEt=5:1 to 3:1) provided **18** (13.6 g, 88%) as a pale yellow oil. $[\alpha]_D^{20}$ −13.6 (*c* 1.0, CH_3OH); ^1H NMR (500 MHz, $CDCl_3$) δ ppm; 0.89 (s, 9H), 1.39 (s, 3H), 3.63 (m, 1H), 3.64 (s, 3H), 3.86 (br s, 1H), 3.72 (d, 1H, *J*=8.8 Hz), 4.13 (d, 1H, *J*=8.8 Hz), 4.51 (q, 2H, *J*=11.7 Hz), 5.11 (br s, 1H), 7.24–7.35 (m, 5H); ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm; 20.6, 26.5, 38.6, 52.0, 63.4, 73.5, 74.7, IR (KBr) cm^{-1}: 2954, 1707, 1441, 1338, 1311, 1174, 1111, 1063, 1028, 958, 737, 698; MS (FAB) *m*/*z*: 322 $(M+H)^+$; HRMS (ESI): calcd for $C_{18}H_{28}NO_4$ $[M+H]^+$ 322.2022; found 322.2018.

*4.2.2. Methyl [(2S)-1-(benzyloxy)-3-hydroxy-2-methylpropan-2-yl] carbamate (**19**).* To a solution of methyl (2*R*,4*R*)-4-[(benzyloxy) methyl]-2-*tert*-butyl-4-methyl-1,3-oxazolidine-3-carboxylate (**18**) (9.9 g, 25 mmol) in MeOH (120 mL) was added *p*-TsOH monohydrate (1.5 g, 8.5 mmol), and then the solution was refluxed for 1 h. The reaction mixture was evaporated in vacuo, giving the crude **19** (13.6 g) as a pale yellow oil. The crude **19** was carried on to the next step without further purification. MS (FAB) *m*/*z*: 254 $(M+H)^+$.

*4.2.3. (4R)-4-[(Benzyloxy)methyl]-4-methyl-1,3-oxazolidin-2-one (**20**).* To a solution of the crude methyl [(2*S*)-1-(benzyloxy)-3-hydroxy-2-methylpropan-2-yl]carbamate (**19**) (13.6 g) in THF (200 mL) was added *t*-BuOK (7.7 g, 68 mmol) at ambient temperature, and then the solution was stirred for 3 h. After quenching with aq 1 N HCl (100 mL), the resulting biphasic mixture was extracted with AcOEt (100 mL×2). The combined organic layer was washed with water (100 mL) and brine (100 mL), dried over Na_2SO_4, filtered, and evaporated. Purification by silica gel column chromatography (hexane:AcOEt=3:1 to 1:2) provided **20** (8.8 g, 95% for two steps) as a colorless oil. $[\alpha]_D^{20}$ 7.3 (*c* 1.0, CH_3OH); ^1H NMR (500 MHz, $CDCl_3$) δ ppm; 1.35 (s, 3H), 3.35 (d, 2H, *J*=4.4 Hz), 4.00 (d, 1H, *J*=8.8 Hz), 4.19 (d, 1H, *J*=8.8 Hz), 4.53 (d, 2H, *J*=2.4 Hz), 5.26 (s, 1H), 7.27–7.36 (m, 5H); ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm; 23.0, 57.3, 73.4, 73.6, 75.1, 127.7, 128.0, 128.5, 137.5, 159.2; IR (KBr) cm^{-1}: 3271, 1738, 1383, 1254, 1194, 1097, 1039, 933, 737, 698; MS (FAB) *m*/*z*: 222 $(M+H)^+$; HRMS (ESI): calcd for $C_{12}H_{16}NO_3$ $[M+H]^+$ 222.1130; found 222.1121.

*4.2.4. (4R)-4-(Hydroxymethyl)-4-methyl-1,3-oxazolidin-2-one (**21**).* To a solution of (4*R*)-4-[(benzyloxy)methyl]-4-methyl-1,3-oxazolidin-2-one (**20**) (2.6 g, 11.8 mmol) in EtOH (150 mL) was added potassium carbonate (6.0 g, 43 mmol) and 10% Pd–C (50% wet, 4.0 g), and then the suspension was stirred for 3 h under a hydrogen atmosphere. The reaction mixture was filtered through a Celite pad and evaporated in vacuo, giving **21** (2.6 g, 91%) as a white solid. The crude **21** was of high purity and carried on to the next step without further purification. ^1H NMR (500 MHz, CD_3OD) δ ppm: 1.22 (s, 3H), 3.37 (d, 1H, *J*=11.2 Hz), 3.43 (d, 1H, *J*=11.2 Hz), 3.98 (d, 1H, *J*=8.6 Hz), 4.29 (d, 1H, *J*=8.6 Hz); MS (FAB) *m*/*z*: 132 $(M+H)^+$.

*4.2.5. (4S)-4-(Iodomethyl)-4-methyl-1,3-oxazolidin-2-one (**22**).* To a solution of (4*R*)-4-(hydroxymethyl)-4-methyl-1,3-oxazolidin-2-one (**21**) (4.2 g, 31 mmol) in pyridine (40 mL) was added *p*-TsCl (8.9 g, 46 mmol), and then the solution was stirred for 3 h at ambient temperature. After an addition of aq 1 N HCl (100 mL), the resulting biphasic mixture was extracted with CH_2Cl_2 (100 mL×2). The combined organic layers were washed with aq 2 N HCl (50 mL) and brine (50 mL), dried over Na_2SO_4 filtered, and evaporated, giving a crude tosylate. To a solution of the obtained crude tosylate in acetone (120 mL) was added NaI (18 g, 117 mmol), and then the suspension was refluxed for 12 h. The reaction mixture was filtrated and evaporated in vacuo. The residue was diluted with AcOEt (150 mL) and the organic layer was washed with saturated aq Na_2SO_3 (50 mL) and brine (50 mL), dried over Na_2SO_4, filtered, and evaporated. Purification by silica gel column chromatography (hexane:AcOEt=2:1 to 1:2) provided **22** (5.8 g, 78% for two steps) as a colorless oil. $[\alpha]_D^{20}$ −14.9 (*c* 1.0, CH_3OH); ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 1.58 (s, 3H), 3.31 (d, 2H, *J*=4.9 Hz), 4.15 (d, 1H, *J*=8.8 Hz), 4.28 (d, 1H, *J*=8.8 Hz), 5.68 (br s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm; 15.1, 25.4, 57.2, 74.9, 158.5; IR (KBr) cm^{-1}: 3248, 1776, 1401, 1289, 1214, 1140, 1051, 956, 762; MS (FAB) *m*/*z*: 242 $(M+H)^+$; HRMS (ESI): calcd for $C_5H_9NO_2I$ $[M+H]^+$ 241.9678; found 241.9687.

*4.2.6. {[(4S)-4-Methyl-2-oxo-1,3-oxazolidin-4-yl]methyl}(triphenyl) phosphonium iodide (**13**).* To a solution of (4*S*)-4-(iodomethyl)-4-methyl-1,3-oxazolidin-2-one (**22**) (4.2 g, 17 mmol) in DMF (20 mL) was added PPh_3 (46 g, 174 mmol), and then the solution was stirred for 3 h at 110 °C. The reaction mixture was diluted with MeOH/AcOEt (20 mL/50 mL), and then left at ambient temperature for 1 day. After the removal of supernatant liquid by decantation, the residue was evaporated in vacuo, giving a crude phosphonium compound (**13**) (7 g). Recrystallization from MeOH/AcOEt (20 mL/200 mL) provided **13** (5.0 g, 57%) as a white solid. Mp: 106.0 °C; $[\alpha]_D^{20}$ −37.3 (*c* 1.6, CH_3OH); ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 1.73 (s, 3H), 3.81–3.87 (m, 2H), 4.40 (dd, 1H, *J*=3.2, 12.8 Hz), 4.76 (dd, 1H, *J*=3.2, 12.8 Hz), 6.52 (s, 1H), 7.71–7.75 (m, 6H), 7.80–7.84 (m, 3H), 7.97–8.01 (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm; 30.3 (d, *J*=8.0 Hz), 32.2 (d, *J*=49.1 Hz), 57.0 (d, *J*=4.6 Hz), 74.8, 118.0 (d, *J*=85.9 Hz), 130.7 (d, *J*=12.7 Hz), 134.0 (d, *J*=10.3 Hz), 135.3 (d, *J*=3.0 Hz), 157.2; IR (KBr) cm^{-1}: 3394, 3225, 2854, 1741, 1438, 1108, 1052, 747, 690; HRMS (ESI): calcd for $C_{23}H_{23}INO_2P$ $[M-I]^+$ 376.1466; found 376.1461.

*4.2.7. (4R)-4-Methyl-4-[(E)-2-phenylethenyl]-1,3-oxazolidin-2-one (**9a**) and (4S)-4-(diphenylphosphorylmethyl)-4-methyl-oxazolidin-2-one (**13**–**o**).* Typical procedure of a Wittig reaction: To a suspension of the phosphonium salt (**13**) (500 mg, 1.0 mmol, 2.0 equiv) in THF (5 mL) was added *n*-butyllithium (1.9 M in hexane, 1.0 mL, 1.95 mmol, 3.9 equiv) at −78 °C and then the solution was stirred for 30 min at the same temperature. After the addition of benzaldehyde (54 mg, 0.5 mmol, 1.0 equiv) at −78 °C, the reaction mixture was gradually warmed to ambient temperature and stirred for 2 h. After quenching with saturated aq NH_4Cl (10 mL), the resulting biphasic mixture was extracted with AcOEt (10 mL×2). The combined organic layer was washed with water (10 mL) and brine (10 mL), dried over Na_2SO_4, filtered, and evaporated. Purification by silica gel column chromatography (hexane:AcOEt=3:1 to 1:1) provided **9a** (101 mg, 99% yield, 98.6% ee) as a white solid, and **13-o** (156 mg, 99% yield) as a white solid. The enantiomeric excess of **9a** was determined by HPLC analysis by using the following condition. DAICEL CHIRALCEL IA column (4.6ϕ×150 mm), hexane:EtOH=95:5 (0 min)—50:50 (8.0 min), flow rate: 2.0 ml/min, temperature: 25.0 °C. The retention times of (*S*)-**9a** and (*R*)-**9a** were 4.6 min and 5.3 min, respectively. (Compound **9a**) mp: 155.6 °C; $[\alpha]_D^{20}$ −61.0 (*c* 0.27, CH_3OH); ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 1.53 (s, 3H), 4.17 (d, 1H, *J*=8.3 Hz), 4.23 (d, 1H, *J*=8.3 Hz), 5.09 (s, 1H), 6.21 (d, 1H, *J*=16.1 Hz), 6.59 (d, 1H, *J*=16.1 Hz), 7.26–7.36 (m, 5H); ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm; 25.6, 58.5, 76.5, 126.7, 128.3, 128.7, 130.1, 131.2, 135.7, 159.0; IR (KBr) cm^{-1}: 3293, 1756, 1710, 1393, 1288, 1171, 1042, 967, 751, 659; MS (ESI) *m*/*z*: 203 $(M)^+$; Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.45; N, 6.89. Found: C, 70.80; H, 6.49; N, 6.83. (Compound **13-o**) mp: 181.4 °C; $[\alpha]_D^{20}$ +9.1 (*c* 0.41, CH_3OH); ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 1.34 (s, 3H), 4.09 (d, 1H, *J*=8.8 Hz),

Please cite this article in press as: Tsuji, T.; et al., Tetrahedron (2014), http://dx.doi.org/10.1016/j.tet.2014.05.086

2.60–2.78 (m, 2H), 4.21 (d, 1H, *J*=8.8 Hz), 6.44 (br s, 1H), 7.46–7.57 (m, 5H), 7.67–7.71 (m, 2H), 7.78–7.82 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm; 26.7, 39.9 (d, *J*=69.1 Hz), 57.3 (d, *J*=4.8 Hz), 77.4 (d, *J*=12.5 Hz), 128.9 (d, *J*=3.6 Hz), 129.0 (d, *J*=3.6 Hz), 130.3 (d, *J*=9.5 Hz), 130.6 (d, *J*=9.5 Hz), 132.2, 132.3, 132.8 (d, *J*=90.6 Hz), 133.6 (d, *J*=93.0 Hz), 157.7; IR (KBr) cm^{-1}: 3308, 1758, 1439, 1255, 1175, 1034, 930, 752, 699; HRMS (ESI): calcd for $C_{17}H_{19}NO_3P$ $[M+H]^+$ 316.1103; found 316.1105.

*4.2.8. (4R)-4-[(E)-2-(2,4-Dimethylphenyl)ethenyl]-4-methyl-1,3-oxazolidin-2-one (**9b**).* Pale yellow solid. Mp: 115.5 °C; $[\alpha]_D^{20}$ −42.5 (*c* 0.19, CH_3OH); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 1.56 (s, 3H), 2.28 (s, 6H), 4.17 (d, 1H, *J*=8.3 Hz), 4.23 (d, 1H, *J*=8.3 Hz), 5.03 (br s, 1H), 6.05 (d, 1H, *J*=15.6 Hz), 6.77 (d, 1H, *J*=15.6 Hz), 6.96 (s, 1H), 6.97 (d, 1H, *J*=8.3 Hz), 7.27 (d, 1H, *J*=8.3 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm; 19.7, 21.1, 25.7, 58.7, 76.6, 125.6, 127.0, 127.8, 131.2, 131.6, 132.0, 135.6, 138.0, 158.9; IR (KBr) cm^{-1}: 3206, 3112, 2970, 2871, 1782, 1736, 1403, 1291, 1037, 984; HRMS (ESI): calcd for $C_{14}H_{18}NO_2$ $[M+H]^+$ 232.1338; found 232.1337.

*4.2.9. Methyl 2-{(E)-2-[(4R)-4-methyl-2-oxo-1,3-oxazolidin-4-yl] ethenyl}benzoate (**9c**).* Pale yellow solid. Mp: 90.5 °C; $[\alpha]_D^{20}$ −18.0 (*c* 0.17, CH_3OH); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 1.59 (s, 3H), 3.88 (s, 3H), 4.18 (d, 1H, *J*=8.3 Hz), 4.26 (d, 1H, *J*=8.3 Hz), 5.20 (br s, 1H), 6.06 (d, 1H, *J*=16.1 Hz), 7.34 (m, 1H), 7.42 (d, 1H, *J*=16.1 Hz), 7.45–7.50 (m, 2H), 7.92 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm; 25.3, 52.2, 58.7, 76.3, 127.6, 127.8, 128.6, 129.8, 130.7, 132.3, 133.7, 138.0, 158.9, 167.5; IR (KBr) cm^{-1}: 3206, 3112, 2970, 2871, 1782, 1736, 1403, 1291, 1037, 984; HRMS (ESI): calcd for $C_{14}H_{16}NO_4$ $[M+H]^+$ 262.1079; found 262.1077.

*4.2.10. (4R)-4-[(E)-2-(2,4,6-Trimethoxylphenyl)ethenyl]-4-methyl-1,3-oxazolidin-2-one (**9d**).* Off-white solid. Mp: 119.7 °C; $[\alpha]_D^{20}$ −27.1 (*c* 0.22, CH_3OH); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 1.59 (s, 3H), 3.85 (s, 3H), 3.86 (s, 6H), 4.20 (d, 1H, *J*=10.5 Hz), 4.28 (d, 1H, *J*=10.5 Hz), 5.26 (br s, 1H), 6.16 (s, 2H), 6.60 (d, 1H, *J*=20.5 Hz), 6.86 (d, 1H, *J*=20.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm; 25.7, 55.3, 55.7, 59.3, 77.1, 90.5, 106.0, 120.3, 131.7, 158.8, 159.4, 160.6; IR (KBr) cm^{-1}: 3313, 2941, 1764, 1732, 1605, 1460, 1230, 1124, 1039, 817; HRMS (ESI): calcd for $C_{15}H_{20}NO_5$ $[M+H]^+$ 294.1341; found 294.1358.

*4.2.11. (4R)-4-[(E)-2-(4-Dimethylaminophenyl)ethenyl]-4-methyl-1,3-oxazolidin-2-one (**9e**).* White solid. Mp: 137.5 °C; $[\alpha]_D^{20}$ −76.5 (*c* 0.090, CH_3OH); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 1.56 (s, 3H), 2.97 (s, 6H), 4.16 (d, 1H, *J*=8.5 Hz), 4.23 (d, 1H, *J*=8.5 Hz), 5.25 (br s, 1H), 6.02 (d, 1H, *J*=15.9 Hz), 6.51 (d, 1H, *J*=15.9 Hz), 6.69 (d, 2H, *J*=8.0 Hz), 7.26 (d, 2H, *J*=8.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm; 25.5, 40.5, 58.5, 76.8, 112.5, 126.5, 127.6, 130.1, 150.1, 158.7; IR (KBr) cm^{-1}: 3372, 3253, 2904, 1768, 1720, 1608, 1522, 1355, 1188, 1035, 966, 806, 770; HRMS (ESI): calcd for $C_{14}H_{19}N_2O_2$ $[M+H]^+$ 247.1447; found 247.1439.

*4.2.12. (4R)-4-Methyl-4-[(E)-2-(thiophen-2-yl)ethenyl]-1,3-oxazolidin-2-one (**9f**).* Yellow oil. $[\alpha]_D^{20}$ −62.7 (*c* 0.38, CH_3OH); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 1.49 (s, 3H), 4.16 (d, 1H, *J*=8.5 Hz), 4.22 (d, 1H, *J*=8.5 Hz), 5.03 (s, 1H), 6.04 (d, 1H, *J*=16.1 Hz), 6.71 (d, 1H, *J*=16.1 Hz), 6.94–6.98 (m, 2H), 7.18 (d, 1H, *J*=5.4 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm; 25.2, 58.5, 76.5, 123.5, 125.1, 127.0, 127.6, 130.5, 140.7, 159.1; IR (KBr) cm^{-1}: 3264, 1735, 1388, 1280, 1034, 956, 697; HRMS (ESI): calcd for $C_{10}H_{11}NO_2S$ $[M+H]^+$ 210.0589; found 210.0594.

*4.2.13. (4R)-4-Methyl-4-[(E)-2-(3-methylthiophen-2-yl)ethenyl]-1,3-oxazolidin-2-one (**9g**).* Pale yellow oil. $[\alpha]_D^{20}$ −36.4 (*c* 0.62, CH_3OH); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 1.54 (s, 3H), 2.22 (s, 3H), 4.16 (d, 1H, *J*=8.3 Hz), 4.22 (d, 1H, *J*=8.3 Hz), 5.01 (br s, 1H), 5.97 (d, 1H, *J*=15.6 Hz), 6.72 (d, 1H, *J*=15.6 Hz), 6.78 (d, 1H, *J*=4.9 Hz), 7.07 (d, 1H, *J*=4.9 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm; 50.7, 58.7, 76.6, 121.8, 123.6, 129.8, 130.8, 134.2, 136.4, 159.1; IR (KBr) cm^{-1}: 3218, 1730, 1401, 1286, 1173, 1036, 957, 724; HRMS (ESI): calcd for $C_{11}H_{14}NO_2S$ $[M+H]^+$ 224.0745; found 224.0746.

*4.2.14. (4R)-4-[(E)-2-(3-Bromothiophen-2-yl)ethenyl]-4-methyl-1,3-oxazolidin-2-one (**9h**).* Pale yellow oil. $[\alpha]_D^{20}$ −41.2 (*c* 1.0, CH_3OH); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 1.57 (s, 3H), 4.17 (d, 1H, *J*=8.3 Hz), 4.23 (d, 1H, *J*=8.3 Hz), 5.08 (br s, 1H), 6.12 (d, 1H, *J*=16.1 Hz), 6.77 (d, 1H, *J*=16.1 Hz), 6.93 (d, 1H, *J*=5.9 Hz), 7.17 (d, 1H, *J*=5.9 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm; 25.4, 58.5, 76.2, 111.73, 122.0, 124.9, 130.9, 132.6, 135.0, 158.7; IR (KBr) cm^{-1}: 3220, 3107, 1744, 1727, 1402, 1295, 1036, 961, 870, 727; HRMS (ESI): calcd for $C_{10}H_{11}NO_2SBr$ $[M+H]^+$ 287.9694; found 287.9691.

*4.2.15. (4R)-4-Methyl-4-[(E)-2-(1-methyl-1H-pyrrol-2-yl)ethenyl]-1,3-oxazolidin-2-one (**9i**).* Pale yellow oil. $[\alpha]_D^{20}$ −30.8 (*c* 0.23, CH_3OH); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 1.52 (s, 3H), 3.60 (s, 3H), 4.15 (d, 1H, *J*=8.3 Hz), 4.19 (d, 1H, *J*=8.3 Hz), 5.00 (s, 1H), 5.95 (d, 1H, *J*=15.6 Hz), 6.08 (d, 1H, *J*=3.2 Hz), 6.33 (dd, 1H, *J*=2.0, 3.2 Hz), 6.46 (d, 1H, *J*=15.6 Hz), 6.59 (d, 1H, *J*=2.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm; 25.8, 34.1, 58.6, 76.8, 107.0, 108.2, 118.7, 123.8, 127.9, 129.8, 158.9; IR (KBr) cm^{-1}: 3278, 1734, 1478, 1375, 1033, 957, 712; MS(FAB) *m*/*z*: 207 $(M+H)^+$; HRMS (ESI): calcd for $C_{11}H_{14}N_2O_2$ $[M+H]^+$ 207.1134; found 207.1127.

*4.2.16. (4R)-4-[(E)-2-(Furan-2-yl)ethenyl]-4-methyl-1,3-oxazolidin-2-one (**9j**).* Pale yellow oil. $[\alpha]_D^{20}$ −44.1 (*c* 0.20, CH_3OH); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 1.52 (s, 3H), 4.12 (d, 1H, *J*=8.3 Hz), 4.24 (d, 1H, *J*=8.3 Hz), 4.96 (s, 1H), 6.16 (d, 1H, *J*=16.1 Hz), 6.28 (d, 1H, *J*=3.4 Hz), 6.37 (dd, 1H, *J*=1.7, 3.4 Hz), 6.40 (d, 1H, *J*=16.1 Hz), 7.34 (d, 1H, *J*=1.7 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm; 25.5, 58.5, 76.6, 109.6, 111.6, 118.5, 129.4, 142.6, 151.4, 159.0; IR (KBr) cm^{-1}: 3276, 1749, 1391, 1039, 739; HRMS (ESI): calcd for $C_{10}H_{11}NO_3$ $[M+H]^+$ 194.0817; found 194.0813.

*4.2.17. (4R)-4-Methyl-4-(oct-1-en-1-yl)-1,3-oxazolidin-2-one (**9k**).* Colorless oil. $[\alpha]_D^{20}$ −30.4 (*c* 0.98, CH_3OH); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 0.86 (t, 3H, *J*=7.6 Hz), 1.19–1.38 (m, 8H), 1.41 (s, 2.1H), 1.46 (s, 0.9H), 1.99–2.07 (m, 2H), 4.06 (d, 0.7H, *J*=8.3 Hz), 4.10 (d, 0.7H, *J*=8.3 Hz), 4.21 (d, 0.3H, *J*=8.3 Hz), 4.28 (d, 0.3H, *J*=8.3 Hz), 5.00 (s, 0.7H), 5.15 (s, 0.3H), 5.41–5.50 (m, 1.4H), 5.64–5.70 (m, 0.6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm; 14.1, 22.6, 25.5, 28.8, 29.0, 31.6, 32.1, 58.2, 76.7, 131.6, 131.9, 132.0, 133.8, 159.1; IR (KBr) cm^{-1}: 3261, 2925, 1746, 1387, 1281, 1038, 969, 770; HRMS (ESI): calcd for $C_{12}H_{21}NO_2$ $[M+H]^+$ 212.1651; found 212.1654.

*4.2.18. (4R)-4-(2-Cyclohexylethenyl)-4-methyl-1,3-oxazolidin-2-one (**9l**).* Colorless oil. $[\alpha]_D^{20}$ −23.6 (*c* 0.44, CH_3OH); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 0.99–1.33 (m, 6H), 1.41 (s, 2.7H), 1.41 (s, 0.3H), 1.62–1.74 (m, 4H), 1.92–1.98 (m, 0.9H), 2.07–2.17 (s, 0.1H), 4.07 (d, 1H, *J*=8.3 Hz), 4.10 (d, 1H, *J*=8.3 Hz), 4.90 (br s, 0.9H), 5.10 (br s, 0.1H), 5.36–5.25 (m, 0.2H), 5.44 (d, 0.9H, *J*=15.6 Hz), 5.62 (dd, 0.9H, *J*=6.8, 15.6 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm; 25.6, 25.9, 26.1, 32.7, 40.2, 58.2, 76.7, 129.6, 137.1, 159.0; IR (KBr) cm^{-1}: 3210, 2922, 2849, 1742, 1397, 1286, 1038, 968, 771, 701; HRMS (ESI): calcd for $C_{12}H_{19}NO_2$ $[M+H]^+$ 210.1494; found 210.1496.

*4.2.19. (4R)-4-Methyl-4-[2-(thiophen-2-yl)ethyl]-1,3-oxazolidin-2-one (**23a**).* To a solution of (4*R*)-4-methyl-4-[(*E*)-2-(thiophen-2-yl) ethenyl]-1,3-oxazolidin-2-one (**9f**) (200 mg, 0.95 mmol) in methanol (10 mL) was added 10% Pd–C (50% wet, 20 mg), and then the suspension was stirred for 2 h under a hydrogen atmosphere at ambient temperature. The reaction mixture was filtered through

Please cite this article in press as: Tsuji, T.; et al., Tetrahedron (2014), http://dx.doi.org/10.1016/j.tet.2014.05.086

a Celite pad and evaporated in vacuo. Purification by silica gel column chromatography (hexane:AcOEt=3:1 to 1:2) provided **23a** (184 mg, 92% yield, 99% ee) as a pale yellow solid. The enantiomeric excess of (4*R*)-methyl-4-[2-(thiophen-2-yl)ethyl]oxazolidin-2-one (**23a**) was determined by HPLC analysis by using the following condition. DAICEL CHIRALCEL OD-H (4.6ϕ×250 mm), hexane:2-propanol=60:40, flow rate: 0.5 ml/min, temperature: 25.0 °C. The retention times of (*S*)-**23a** and (*R*)-**23a** were 16.8 min and 17.6 min, respectively. Mp: 83.5 °C; $[\alpha]_D^{20}$ +7.8 (*c* 2.0, $CHCl_3$), +1.9 (*c* 0.10, CH_3OH); ^1H NMR (400 MHz, $CDCl_3$) δ : 1.42 (s, 3H), 2.08–1.92 (m, 2H), 3.00–2.84 (m, 2H), 4.08 (d, 1H, *J*=8.4 Hz), 4.19 (d, 1H, *J*=8.4 Hz), 5.39 (br s, 1H), 6.81 (d, 1H, *J*=3.6 Hz), 6.93 (dd, 1H, *J*=5.2, 3.6 Hz), 7.15 (d, 1H, *J*=5.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm; 24.6, 25.9, 42.3, 57.5, 75.5, 123.6, 124.6, 127.0, 147.6, 159.5; IR (KBr) cm^{-1}: 3283, 1770, 1399, 1244, 1043, 941, 846, 775, 706, 691; HRMS (ESI): calcd for $C_{10}H_{14}NO_2S$ $[M+H]^+$ 212.0275; found 212.0741.

*4.2.20. (4R)-4-Methyl-4-[2-(1-methyl-1H-pyrrol-2-yl)ethyl]-1,3-oxazolidin-2-one (**23b**).* Compound **23b** was obtained as a yellow oil from **9i** by using the procedure described for **23a** in 88% yield (99% ee). The enantiomeric excess of (4*R*)-4-methyl-4-[2-(1-methylpyrrol-2-yl)ethyl]oxazolidin-2-one (**23b**) was determined by HPLC analysis by using the following condition. DAICEL CHIRALCEL OJ (4.6ϕ×250 mm), hexane:2-propanol=70:30, flow rate: 1.0 ml/min, temperature: 25.0 °C. The retention times of (*S*)-**23b** and (*R*)-**23b** were 12.5 min and 15.5 min, respectively. $[\alpha]_D^{20}$ +1.2 (*c* 0.30, CH_3OH); ^1H NMR (400 MHz, $CDCl_3$) δ : 1.42 (s, 3H), 2.00–1.87 (m, 2H), 2.70–2.58 (m, 2H), 4.07 (d, 1H, *J*=8.3 Hz), 4.14 (d, 1H, *J*=8.3 Hz), 5.15 (br s, 1H), 5.88 (d, 1H, *J*=3.2 Hz), 6.05 (dd, 1H, *J*=3.2 Hz, 2.4 Hz), 6.58 (t, 1H, *J*=2.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm; 20.8, 25.8, 33.6, 38.9, 57.5, 75.7, 105.7, 106.8, 121.9, 131.0, 158.8; IR (KBr) cm^{-1}: 3289, 3103, 2977, 2938, 1759, 1713, 1495, 1397, 1381, 1309, 1281, 1231, 1032, 945, 928, 776, 718, 706, 656; HRMS (ESI): calcd for $C_{11}H_{17}N_2O_2$ $[M+H]^+$ 209.1290; found 209.1291.

*4.2.21. (4R)-4-[2-(Furan-2-yl)ethyl]-4-methyl-1,3-oxazolidin-2-one (**23c**).* Compound **23c** was obtained as a pale yellow oil from **9j** by using the procedure described for **23a** in 78% yield (99% ee). The enantiomeric excess of (4*R*)-methyl-4-[2-(furan-2-yl)ethyl]-1,3-oxazolidin-2-one (**23c**) was determined by HPLC analysis by using the following condition. DAICEL CHIRALCEL AD (4.6ϕ×250 mm), hexane:2-propanol=85:15, flow rate: 1.0 ml/min, temperature: 25.0 °C. The retention times of (*S*)-**23c** and (*R*)-**23c** were 13.1 min and 15.4 min, respectively. $[\alpha]_D^{20}$ +2.2 (*c* 0.11, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ : 1.38 (s, 3H), 1.68–1.61 (m, 2H), 1.98–1.94 (m, 2H), 2.72 (t, 2H, *J*=8.0 Hz), 4.04 (d, 1H, *J*=8.4 Hz), 4.11 (d, 1H, *J*=8.4 Hz), 5.92 (br s, 1H), 6.03 (d, 1H, *J*=2.6 Hz), 6.29 (d, 1H, *J*=2.6 Hz), 7.31 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm; 22.8, 25.6, 38.4, 57.4, 75.5, 105.5, 110.4, 141.3, 154.0, 159.0; IR (KBr) cm^{-1}: 3450, 2975, 2928, 2250, 1755, 1599, 1508, 1400, 1381, 1147, 1045, 1010; HRMS (ESI): calcd for $C_{10}H_{14}NO_3$ $[M+H]^+$ 196.0974; found 196.0967.

*4.2.22. (4R)-4-{(E)-2-[4-(Heptyloxy)phenyl]vinyl}-4-methyl-1,3-oxazolidin-2-one (**25a**).* To a suspension of the phosphonium salt (**13**) (200 mg, 0.4 mmol) in THF (5 mL) was added *n*-butyllithium (2.7 M in hexane, 0.29 mL, 0.77 mmol) at −78 °C and then the solution was stirred for 30 min at the same temperature. After the addition of 4-heptoxybenzaldehyde (**24**) (44 mg, 0.2 mmol) at −78 °C, the reaction mixture was gradually warmed to ambient temperature and then stirred for 2 h. After quenching with a saturated aq NH_4Cl (10 mL), the resulting biphasic mixture was extracted with AcOEt (10 mL×2). The combined organic layer was washed with water (10 mL) and brine (10 mL), dried over Na_2SO_4, filtered, and evaporated. Purification by silica gel column chromatography (hexane:AcOEt=3:1 to 1:2) provided **25a** (49 mg, 77%) as a pale yellow solid. Mp: 70.7 °C; $[\alpha]_D^{20}$ −44.5 (*c* 0.14, CH_3OH); ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 0.87 (t, 3H, *J*=7.8 Hz), 1.23–1.36 (m, 6H), 1.39–1.45 (m, 2H), 1.54 (s, 3H), 1.72–1.79 (m, 2H), 3.93 (t, 2H, *J*=6.6 Hz), 4.15 (d, 1H, *J*=8.8 Hz), 4.21 (d, 1H, *J*=8.8 Hz), 5.02 (br s, 1H), 6.06 (d, 1H, *J*=16.1 Hz), 6.52 (d, 1H, *J*=16.1 Hz), 6.83 (d, 2H, *J*=6.8 Hz), 7.27 (d, 2H, *J*=6.8 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm; 14.1, 22.6, 25.6, 26.0, 29.1, 29.3, 31.8, 58.6, 68.1, 76.7, 114.7, 127.9, 128.2, 128.7, 129.7, 159.1, 159.4; IR (KBr) cm^{-1}: 3268, 2929, 2857, 1776, 1607, 1513, 1252, 1175, 1044; HRMS (ESI): calcd for $C_{19}H_{28}NO_3$ $[M+H]^+$ 318.2069; found 318.2068.

*4.2.23. (2R)-2-Amino-4-[4-(heptyloxy)phenyl]-2-methylbutan-1-ol (**25**).* To a solution of (4*R*)-4-{(*E*)-2-[4-(heptyloxy)phenyl]vinyl}-4-methyl-1,3-oxazolidin-2-one (**25a**) (30 mg, 0.1 mmol) in methanol (5 mL) was added 10% Pd–C (50% wet, 10 mg), and then the suspension was stirred for 2 h under a hydrogen atmosphere at ambient temperature. The reaction mixture was filtered through a Celite pad and evaporated in vacuo. The residue was diluted with THF (2 mL) and methanol (1 mL). Aq 5 N potassium hydroxide (1 mL) was added to the solution, which was then refluxed for 18 h. After cooling to room temperature, water (10 mL) was added to the reaction mixture and the resulting biphasic mixture was extracted with CH_2Cl_2 (10 mL×2). The combined organic layer was washed with water (10 mL) and brine (10 mL), dried over Na_2SO_4, filtered, and evaporated, providing **25** (25 mg, 90%) as a colorless oil. $[\alpha]_D^{20}$ −2.4 (*c* 0.92, CH_3OH); ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 0.86 (t, 3H, *J*=6.8 Hz), 1.10 (s, 3H), 1.22–1.77 (m, 12H), 2.56 (t, 2H, *J*=8.5 Hz), 3.29 (d, 1H, *J*=10.3 Hz), 3.34 (d, 1H, *J*=10.3 Hz), 3.90 (t, 2H, *J*=6.6 Hz), 6.80 (d, 2H, *J*=6.6 Hz), 7.07 (d, 1H, *J*=6.6 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm; 14.1, 22.6, 24.5, 26.0, 29.1, 29.3, 29.4, 31.8, 42.2, 53.0, 68.1, 70.3, 114.6, 129.1, 134.1, 157.4; IR (KBr) cm^{-1}: 3147, 2923, 2855, 2737, 1740, 1613, 1513, 1276, 1244, 1060, 825; MS(ESI) *m*/*z*: 294 $(M+H)^+$; Anal. Calcd for $C_{18}H_{31}NO_2$: C, 73.67; H, 10.65; N, 4.77. Found: C, 73.37; H, 10.60; N, 4.64.

*4.2.24. 2-Chloro-4-[(3-methoxyphenyl)sulfanyl]benzaldehyde (**26**).* To a solution of 3-methoxybenzenethiol (1.4 g, 10 mmol) and 2-chloro-4-fluorobenzaldehyde (1.6 g, 10 mmol) in DMF (10 mL) was added potassium carbonate (2.1 g, 15 mmol) at ambient temperature, and then the suspension was stirred for 30 min at 45 °C. After cooling at 0 °C, water (25 mL) was added to the reaction mixture. The resulting biphasic mixture was extracted with AcOEt (30 mL×2). The combined organic layer was washed with water (30 mL) and brine (30 mL), dried over Na_2SO_4, filtered, and evaporated. Purification by silica gel column chromatography (hexane:AcOEt=5:1 to 1:1) provided **26** (2.5 g, 91%) as a white solid. Mp: 84.3 °C; ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 3.80 (s, 3H), 6.97 (m, 1H), 7.10–7.02 (m, 4H), 7.34 (t, 1H, *J*=8.1 Hz), 7.74 (d, 1H, *J*=8.1 Hz), 10.33 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm; 55.5, 115.7, 119.7, 125.3, 126.8, 127.6, 129.4, 129.6, 130.8, 131.1, 138.5, 148.6, 160.5, 188.8; IR (KBr) cm^{-1}: 3076, 2874, 1677, 1579, 1481, 1381, 1250, 1212, 1043, 853, 797, 691; HRMS (ESI): calcd for $C_{14}H_{12}O_2SCl$ $[M+H]^+$ 279.0247; found 279.0251; Anal. Calcd for $C_{14}H_{11}ClO_2S$: C, 60.32; H, 3.98; Cl, 12.72; S, 11.50. Found: C, 60.19; H, 4.12; Cl, 12.55; S, 11.54.

*4.2.25. (4R)-4-[(E)-2-{2-Chloro-4-[(3-methoxyphenyl)sulfanyl]phenyl}ethenyl]-4-methyl-1,3-oxazolidin-2-one (**6a**).* To a suspension of the phosphonium salt (**13**) (500 mg, 1.0 mmol) in THF (5 mL) was added *n*-butyllithium (1.9 M in hexane, 1.0 mL, 1.95 mmol) at −78 °C, and then the solution was stirred for 30 min at the same temperature. After the addition of 2-chloro-4-[(3-methoxyphenyl) sulfanyl]benzaldehyde (**26**) (139 mg, 0.5 mmol) at −78 °C, the reaction mixture was gradually warmed to ambient temperature and stirred for 2 h. After quenching with a saturated aq NH_4Cl (10 mL), the resulting biphasic mixture was extracted with AcOEt (10 mL×2). The combined organic layer was washed with water

Please cite this article in press as: Tsuji, T.; et al., Tetrahedron (2014), http://dx.doi.org/10.1016/j.tet.2014.05.086

(10 mL) and brine (10 mL), dried over Na_2SO_4, filtered, and evaporated. Purification by silica gel column chromatography (hexane:AcOEt=4:1 to 1:2) provided **6a** (300 mg, 80%) as a pale yellow oil. $[\alpha]_D^{20}$ −39.1 (*c* 0.45, CH_3OH); ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 1.58 (s, 3H), 3.37 (s, 3H), 4.18 (d, 1H, *J*=8.3 Hz), 4.23 (d, 1H, *J*=8.3 Hz), 5.03 (s, 1H), 6.17 (d, 1H, *J*=16.1 Hz), 6.85 (m, 1H), 6.92–6.90 (m, 2H), 6.92 (d, 1H, *J*=16.1 Hz), 7.11 (m, 1H), 7.236–7.23 (m, 2H), 7.37 (d, 1H, *J*=7.8 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm; 25.4, 55.4, 58.7, 76.3, 114.0, 117.4, 124.5, 126.1, 127.3, 128.3, 130.3, 130.4, 132.2, 133.9, 134.0, 134.8, 138.3, 158.8, 160.3; IR (KBr) cm^{-1}: 3258, 1744, 1586, 1471, 1376, 1282, 1246, 1037, 969, 858, 770, 688; HRMS (ESI): calcd for $C_{19}H_{19}NO_3SCl$ $[M+H]^+$ 376.0774; found 376.0769.

*4.2.26. (4R)-4-(2-{2-Chloro-4-[(3-methoxyphenyl)sulfanyl]phenyl} ethyl)-4-methyl-1,3-oxazolidin-2-one (**6b**).* To a solution of (4*R*)-4-[(*E*)-2-{2-chloro-4-[(3-methoxyphenyl)sulfanyl]phenyl}ethenyl]-4-methyl-1,3-oxazolidin-2-one (**6a**) (100 mg, 0.26 mmol) in AcOEt (10 mL) was added 10% Pd–C (50% wet, 100 mg), and then the suspension was stirred for 6 h under a hydrogen atmosphere at ambient temperature. The reaction mixture was filtered through a Celite pad and evaporated in vacuo. Purification by silica gel column chromatography (hexane:AcOEt=3:1 to 1:2) provided **6b** (79 mg, 80%) as a pale yellow oil. $[\alpha]_D^{20}$ +1.5 (*c* 0.76, CH_3OH); ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 1.40 (s, 3H), 1.86–1.80 (m, 2H), 2.77–2.65 (m, 2H), 3.76 (s, 3H), 4.09 (d, 1H, *J*=7.1 Hz), 4.25 (d, 1H, *J*=7.1 Hz), 5.05 (s, 1H), 6.80 (m, 1H), 6.86 (m, 1H), 6.91 (m, 1H), 7.13–7.09 (m, 2H), 7.21 (m, 1H), 7.28 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm; 26.0, 28.1, 40.4, 55.4, 57.7, 75.4, 113.4, 116.8, 124.0, 129.4, 130.2, 130.8, 131.3, 134.3, 135.7, 135.8, 137.1, 159.0, 160.2; IR (KBr) cm^{-1}: 3262, 1747, 1589, 1475, 1283, 1230, 1040, 772; HRMS (ESI): calcd for $C_{19}H_{21}NO_3SCl$ $[M+H]^+$ 378.0931; found 378.0926.

*4.2.27. (2R)-2-Amino-4-{2-chloro-4-[(3-methoxyphenyl)sulfanyl] phenyl}-2-methyl-butan-1-ol (**6**).* To a solution of (4*R*)-4-(2-{2-chloro-4-[(3-methoxyphenyl)sulfanyl]phenyl}ethyl)-4-methyl-1,3-oxazolidin-2-one (**6b**) (20 mg, 0.06 mmol) in THF (1 mL) and methanol (1 mL) was added aq 5 N potassium hydroxide (0.5 mL), and then the solution was refluxed for 12 h. After cooling to room temperature, water (10 mL) was added to the reaction mixture and the resulting biphasic mixture was extracted with CH_2Cl_2 (10 mL×2). The combined organic layer was washed with water (10 mL) and brine (10 mL), dried over Na_2SO_4, filtered, and evaporated, providing **6** (16 mg, 91%) as a colorless oil. $[\alpha]_D^{20}$ −2.0 (*c* 0.53, $CHCl_3$), −3.5 (*c* 0.19, CH_3OH); ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 1.12 (s, 3H), 1.67–1.54 (m, 2H), 2.76–2.66 (m, 2H), 3.32 (d, 1H, *J*=10.3 Hz), 3.37 (d, 1H, *J*=10.3 Hz), 3.75 (s, 3H), 6.78 (d, 1H, *J*=8.3 Hz), 6.85 (m, 1H), 6.88 (m, 1H), 7.15–7.13 (m, 2H), 7.20 (t, 1H, *J*=8.3 Hz), 7.30 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm; 24.3, 27.9, 40.1, 53.0, 55.3, 70.3, 113.2, 116.4, 123.4, 129.7, 130.8, 131.6, 134.4, 134.7, 136.3, 139.0, 160.1; IR (KBr) cm^{-1}: 2931, 1747, 1587, 1473, 1246, 1229, 1039, 853, 772, 686; HRMS (ESI): calcd for $C_{18}H_{23}NO_2SCl$ $[M+H]^+$ 352.1138; found 352.1148.

*4.2.28. (4R)-4-Methyl-4-(2-phenylethyl)-4,5-dihydro-1,3-oxazol-2-amine (**8**).* To a solution of (4*R*)-4-methyl-4-[(*E*)-2-phenylethenyl]-1,3-oxazolidin-2-one (**9a**) (100 mg, 0.26 mmol) in AcOEt (10 mL) was added 10% Pd–C (50% wet, 100 mg), and then the suspension was stirred for 6 h under a hydrogen atmosphere at ambient temperature. The reaction mixture was filtered through a Celite pad and evaporated in vacuo. The residue was diluted by THF (1 mL) and methanol (1 mL). Aq 5 N potassium hydroxide (0.5 mL) was added to the solution, which was then refluxed for 12 h. After cooling to room temperature, water (10 mL) was added to the reaction mixture and the resulting biphasic mixture was extracted with CH_2Cl_2 (10 mL×2). The combined organic layer was washed with water (10 mL) and brine (10 mL), dried over Na_2SO_4, filtered, and evaporated, providing pale yellow oil. To a solution of the obtained residue in THF (8 mL) was added potassium carbonate (62 mg, 0.46 mmol) and cyanogen bromide (54 mg, 0.51 mmol) at 0 °C under a N_2 atmosphere. After stirring for 6 h at ambient temperature, water (10 mL) was added to the reaction mixture and the resulting biphasic mixture was extracted with AcOEt (10 mL×2). The combined organic layer was washed with water (10 mL) and brine (10 mL), dried over Na_2SO_4, filtered, and evaporated. Purification by silica gel column chromatography (AcOEt:MeOH=1:0 to 5:1) provided **8** (69 mg, 69%) as a pale yellow solid. Mp: 103.8 °C; $[\alpha]_D^{20}$ +6.5 (*c* 0.74, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 1.30 (s, 3H), 1.90–1.75 (m, 2H), 2.69–2.58 (m, 2H), 3.28 (br s, 2H), 3.94 (d, 1H, *J*=8.3 Hz), 4.09 (d, 1H, *J*=8.3 Hz), 7.28–7.25 (m, 5H); ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm; 27.3, 30.7, 43.6, 67.8, 78.1, 125.8, 128.3, 128.4, 142.4, 159.3; IR (KBr) cm^{-1}: 3432, 2968, 2211, 1702, 1671, 1410, 1218, 1006, 756, 705, 501; HRMS (ESI): calcd for $C_{12}H_{17}N_2O$ $[M+H]^+$ 205.1341; found 205.1348.

References and notes

1. (a) Bagli, J. F.; Kluepfel, D.; St-Jacques, M. *J. Org. Chem.* **1973**, *38*, 1253; (b) Miyake, Y.; Kozutsumi, Y.; Nakamura, S.; Fujita, T.; Kawasaki, T. *Biochem. Biophys. Res. Commun.* **1995**, *211*, 396; (c) Chen, J. K.; Lane, W. S.; Schreiber, S. L. *Chem. Biol.* **1999**, *6*, 221.
2. (a) Horn, W. S.; Smith, J. L.; Bills, G. F.; Raghoobar, S. L.; Helmes, G. L.; Kurta, M. B.; Marrina, J. A.; Frommer, B. R.; Thornton, R. A.; Mandala, S. M. *J. Antibiot.* **1992**, *45*, 1692; (b) Ikeuchi, K.; Hayashi, M.; Yamamoto, T.; Inai, M.; Asakawa, T.; Hamashima, Y.; Kan, T. *Eur. J. Org. Chem.* **2013**, *30*, 6789.
3. For compound **5**, see: Kiuchi, M.; Tashiro, K.; Hamada, M.; Sugahara, K. EP Patent 2,168,944, 2010.
4. For compound **6**, see: Yamamuro, N.; Nakamaru, K.; Yasue, T. U.S. Patent 324,057, 2010.
5. For compound **7**, see: Nishi, T.; Miyazaki, S.; Takemoto, T.; Suzuki, K.; Iio, Y.; Nakajima, K.; Ohnuki, T.; Kawase, Y.; Nara, F.; Inaba, S.; Izumi, T.; Yuita, H.; Ohshima, K.; Doi, H.; Inoue, R.; Tomisato, W.; Kagari, T.; Shimozato, T. *ACS Med. Chem. Lett.* **2011**, *2*, 368.
6. (a) Forrest, M.; Sun, S.-Y.; Hajdu, R.; Bergstrom, J.; Card, D.; Doherty, G.; Hale, J.; Keohane, C.; Meyers, C.; Milligan, J.; Mills, S.; Nomura, N.; Rosen, H.; Rosenbach, M.; Shei, G.-J.; Singer, I. I.; Tian, M.; West, S.; White, V.; Xie, J.; Proia, R. L.; Mandala, S. *J. Pharmacol. Exp. Ther.* **2004**, *309*, 758; (b) Sanna, M. G.; Liao, J.; Jo, E.; Alfonso, C.; Ahn, M.-Y.; Peterson, M. S.; Webb, B.; Lefebvre, S.; Chun, J.; Gray, N.; Rosen, H. *J. Biol. Chem.* **2004**, *279*, 13839; (c) Adachi, K.; Kohara, T.; Nakao, N.; Arita, M.; Chiba, K.; Mishina, T.; Sasaki, S.; Fujita, T. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 853.
7. (a) Galley, G.; Groebke, Z. K.; Norcross, R.; Atalder, H. WO Patent 2008/092785 A1, 2008. (b) Sotnikova, D. T.; Caron, G. M.; Gainetdinov, R. R. *Mol. Pharmacol.* **2009**, *76*, 229.
8. For reviews, see, e.g.: (a) Ohfune, Y.; Shinada, T. *Eur. J. Org. Chem.* **2005**, 5127; (b) Tanaka, M. *Chem. Pharm. Bull.* **2007**, *55*, 349; (c) Vogt, H.; Bräse, S. *Org. Biomol. Chem.* **2007**, *5*, 406; (d) Soengas, R. G.; Estévez, A. M.; Estévez, J. C.; Estévez, R. J. *Tetrahedron: Asymmetry* **2012**, *23*, 1238; (e) Buyck, T.; Wang, Q.; Zhu, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 12714.
9. (a) Tsuji, T.; Iio, Y.; Takemoto, T.; Nishi, T. *Tetrahedron: Asymmetry* **2005**, *16*, 3139; (b) Nakamura, T.; Tsuji, T.; Iio, Y.; Miyazaki, S.; Takemoto, T.; Nishi, T. *Tetrahedron: Asymmetry* **2006**, *17*, 2781; (c) Iio, Y.; Yamaoka, M.; Jin, M.; Nakamura, Y.; Nishi, T. *Tetrahedron: Asymmetry* **2011**, *22*, 323.
10. (a) Itaya, T.; Shimomichi, M.; Ozawa, M. *Tetrahedron Lett.* **1988**, *29*, 4129; (b) Itaya, T.; Iida, T.; Shimizu, S.; Mizutani, A.; Morisue, M.; Sugimoto, Y.; Tachinaka, M. *Chem. Pharm. Bull. Jpn.* **1993**, *41*, 252; (c) Itaya, T.; Kanai, T.; Iida, T. *Tetrahedron Lett.* **1997**, *38*, 1979.
11. (a) Sibi, M. P.; Rutherford, D.; Renhowe, P. A.; Li, B. *J. Am. Chem. Soc.* **1999**, *121*, 7509; (b) Sibi, M. P.; Christensen, J. W. *J. Org. Chem.* **1999**, *64*, 6434.
12. We tried to reuse **13-o** for the Wittig reaction by using the following procedure. To a solution of **13-o** (10 mg, 1 equiv) and LiBr (3 mg, 1 equiv) in THF (3 mL) was added *n*-butyllithium (1.9 M in hexane, 35 μL, 2 equiv) at −30 °C, and then the solution was stirred for 30 min. After cooling to −78 °C, aldehyde 26 (9 mg, 1 equiv) was added. The solution was gradually warmed to ambient temperature and stirred for 2 h. The reaction mixture was analyzed by LC–MS to detect no desired alkenes or coupling product but intact phosphine oxide **13-o**. For the reference, see: (a) Cavalla, D.; Cruse, W. B.; Warren, S. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1883; (b) Cavalla, D.; Warren, S. *Tetrahedron Lett.* **1983**, *24*, 295.
13. (a) Hinterding, K.; Albert, R.; Cottens, S. *Tetrahedron Lett.* **2002**, *43*, 8095; (b) Hinterding, K.; Cottens, S.; Albert, R.; Zecri, F.; Buehlmayer, P.; Spanka, C.; Brinkmann, V.; Nussbaumer, P.; Ettmayer, P.; Hoegenauer, K.; Gray, N.; Pan, S. *Synthesis* **2003**, 1667.
14. Aldehyde **26** was synthesized from commercially available reagents by following a procedure described in Ref. 4. The details are also shown in our Experimental section.

Please cite this article in press as: Tsuji, T.; et al., Tetrahedron (2014), http://dx.doi.org/10.1016/j.tet.2014.05.086