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AN IMPROVED SYNTHESIS OF A SALICYLATED DIVINYLCARBINOL DERIVATIVE AS A PART OF SALICYLIC MACROLIDES

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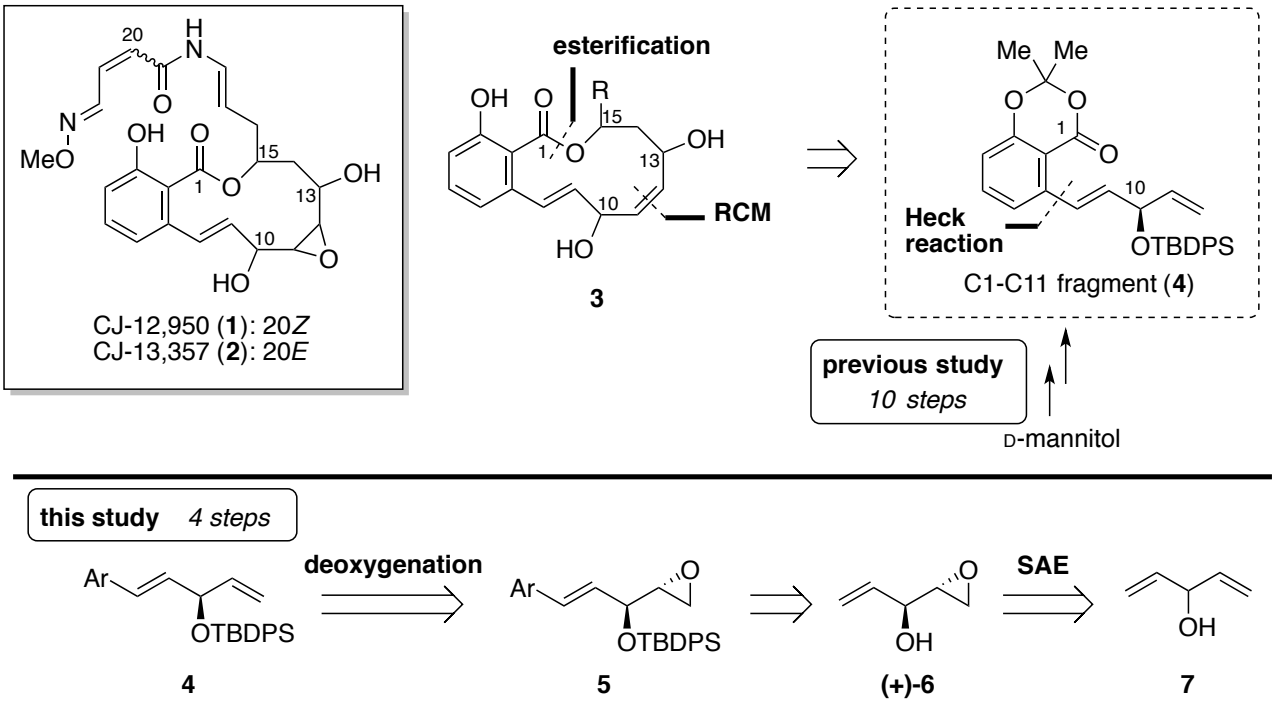
Abstract – An improved enantioselective synthesis of (*R*)-salicylated divinyl carbinol derivative (**4**), the key intermediate for the total synthesis of natural salicylic macrolides, has been achieved. Key steps of the synthesis involve the introduction of the chirality by reliable Sharpless asymmetric epoxidation, carbon-carbon bond formation via Heck reaction and the regeneration of a terminal alkene structure via deoxygenation. The efficient route shortened the reaction sequence and enabled the preparation of (*R*)-**4** in 4 steps in 28% overall yield from divinyl carbinol.

Natural salicylic macrolides with an unsaturated enamide side-chain have been found to exhibit various biological activities such as cytotoxicity and ATPase inhibitory activity.[1,2] Among them, CJ-12,950 and its geometrical isomer CJ-13,357 have a 12-membered lactone ring containing a 2,3-epoxy-1,4-diol structure.[3] Because these natural products enhance the low-density lipoprotein (LDL) receptor expression in human hepatocytes cells, they have been expected to be promising drug candidates for the treatment of hypercholesterolemia and hyperlipidemia. However, no total syntheses of CJ-12,950 and CJ-13,357 have been accomplished. In addition, the stereochemistries of C10, C13, and C15 in CJ-12,950 and CJ-13,357 have not yet been determined, while the planar structure of these natural products and stereochemistry of *cis*-epoxide at C11-C12 were elucidated. In our research projects on the synthesis of salicylic macrolides, we accomplished the formation of the 12-membered salicylate lactone ring by highly stereoselective ring-closing metathesis (RCM) in 2008.[4] Moreover, so as to improve the synthetic approach for natural salicylic macrolides, CJ-12,950 and CJ-13,357, pivotal chiral C1-C11 fragment **4** was designed and synthesized.[5] In this previous report, the synthesis commenced with inexpensive natural chiral pool, D-mannitol or L-ascorbic acid, to provide chiral intermediate (*R*)-**4** or (*S*)-**4**, respectively. The route

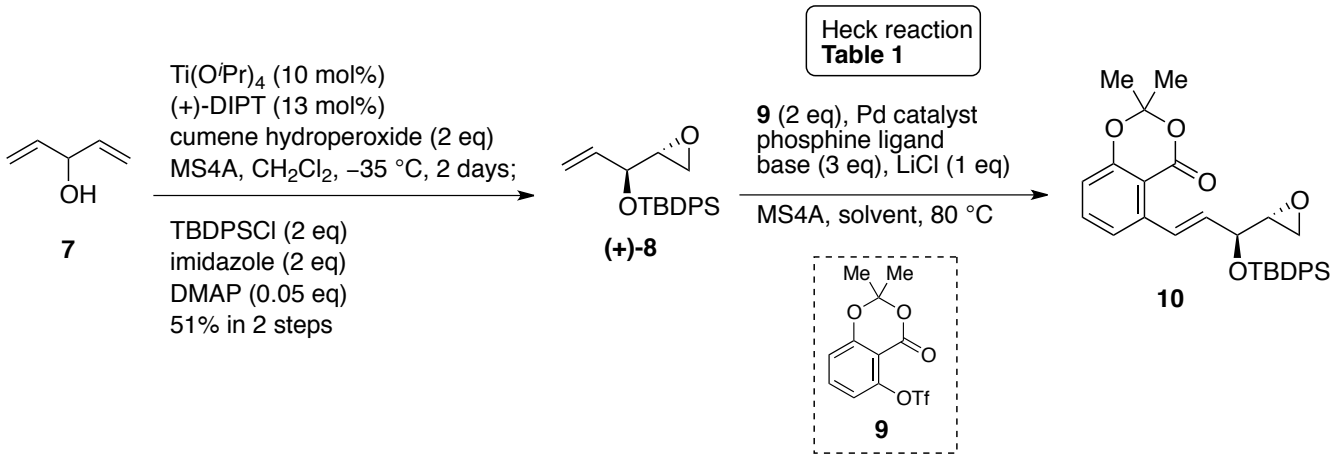
provided both enantiomers of **4** with high optical purity, fulfilling the requirement for the total synthesis of CJs and the determination of these stereochemistries. However, it needed overall 10 steps containing a redundant protection-deprotection sequence, as well as an undesired purification process involving a risk of epimerization. In this context, circumvention of such inefficient steps has been required to improve our intended synthetic route for the total synthesis of CJs. Herein, we report a short enantioselective synthesis of salicylated derivatives **4** as a part of salicylic macrolides by using Sharpless asymmetric expoxidation (SAE) (Scheme 1).



Scheme 1. Salicylic macrolide CJs and the synthetic plan of C1-C11 fragment **4**

Inspired by the previous successful synthetic studies utilizing **6** as a chiral building block,[6] we devised a new synthetic approach to **4** featuring reliable SAE of divinyl carbinol (**7**) and subsequent removal of epoxide by deoxygenation. Because the SAE is a secure reaction to provide both enantiomers by switching chiral sources, (+)- or (-)-diethyl tartrate, we presumed that both enantiomers of **4** could be synthesized via the above synthetic plan (Scheme 1). In this plan, late-stage deoxygenation was embedded to construct the terminal alkene moiety of the pivotal chiral fragment **4**.

The synthesis of **4** commenced with SAE of divinyl carbinol (**7**) to afford the known epoxide (+)-**6**. With the high volatility in mind, one-pot procedure for SAE and TBDPS protection was established, in which slightly excess amounts of reagents were required for the completion of silylation, to afford silyl ether (+)-**8** in 51% yield from **7** (Scheme 2). With chiral coupling partner (+)-**8** in hand, Heck coupling reaction of (+)-**8** with triflate **9**[7] to obtain coupling product **10** was thoroughly investigated (Scheme 2, Table 1).[8]



Scheme 2. Short-step preparation of **10** through SAE and Heck reaction

Table 1. Optimization of Heck coupling reaction of (+)-**8** and **9**

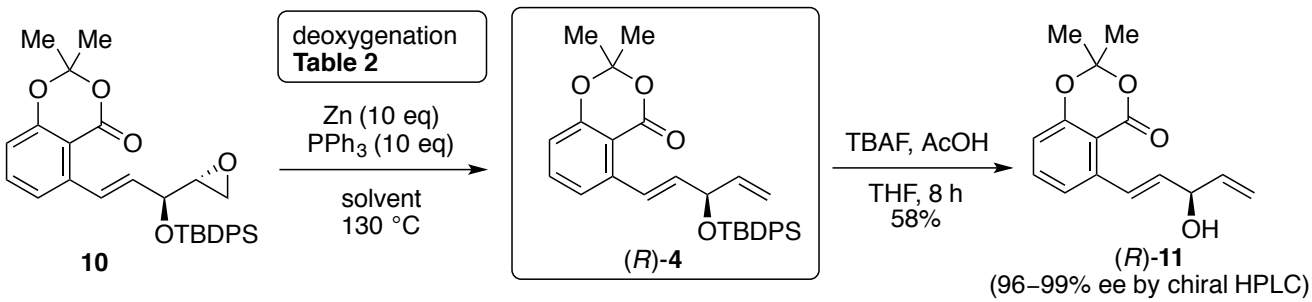
entry	Pd catalyst (mol%)	phosphine ligand (mol%)	base	solvent[a]	time (h)	yield of **10** (%)
1	Pd(OAc)$_2$ (20)	dppe (20)	Et$_3$N	MeCN	40	0
2	Pd(OAc)$_2$ (20)	dppf (20)	Et$_3$N	MeCN	40	0
3	Pd(OAc)$_2$ (20)	PPh$_3$ (40)	Et$_3$N	MeCN	42	31
4	Pd(OAc)$_2$ (20)	PCy$_3$ (40)	Et$_3$N	MeCN	42	30
5	Pd(OAc)$_2$ (20)	P(*o*-tolyl)$_3$ (40)	Et$_3$N	MeCN	45	37
6	Pd(P^{t}Bu$_3$)$_2$ (20)	—	Et$_3$N	MeCN	43	54
7	**Pd(OAc)$_2$ (20)**	**^{t}Bu-XPhos (40)**	**Et$_3$N**	**MeCN**	**13**	**70**
8	Pd(OAc)$_2$ (20)	^{t}Bu-XPhos (40)	Et$_3$N	toluene	40	16
9	Pd(OAc)$_2$ (20)	^{t}Bu-XPhos (40)	Et$_3$N	CPME	40	22
10	Pd(OAc)$_2$ (20)	^{t}Bu-XPhos (40)	Et$_3$N	DMF	40	6
11	Pd(OAc)$_2$ (20)	^{t}Bu-XPhos (40)	Et$_3$N	1,4-dioxane	40	21
12	Pd(OAc)$_2$ (20)	^{t}Bu-XPhos (40)	Cs$_2$CO$_3$	MeCN	41	15
13	Pd(OAc)$_2$ (20)	^{t}Bu-XPhos (40)	DIPEA	MeCN	41	52
14[b]	Pd(OAc)$_2$ (20)	^{t}Bu-XPhos (40)	Et$_3$N	MeCN	43	7
15	Pd(OAc)$_2$ (10)	^{t}Bu-XPhos (40)	Et$_3$N	MeCN	40	15
16[c]	Pd(OAc)$_2$ (20)	^{t}Bu-XPhos (40)	Et$_3$N	MeCN	18	56[d]
17[e]	**Pd(OAc)$_2$ (20)**	**^{t}Bu-XPhos (40)**	**Et$_3$N**	**MeCN**	**20**	**74**

a) 0.13 M substrate concentration (entries 1–13). 0.20-0.30 M substrate concentration (entry 14–17). b) LiCl was not used. c) As the large-scale experiment, 1.1 g of **(+)-8** was used. d) 61% brsm, e) LiCl (2 eq) was used.

Various combinations of a phosphine ligand and Pd(OAc)$_2$ were first surveyed in MeCN at 80 °C (entries 1−5). No coupling product was obtained by using bidentate phosphine ligands such as dppe and dppf

(entries 1 and 2), whereas the use of monodentate ligands such as PPh_3, PCy_3, and P(*o*-tolyl)$_3$ displayed a beneficial effect leading to the formation of **10** in 30-37% yields (entries 3−5). When Pd(P^tBu_3)$_2$ was used instead of a combination of a phosphine ligand and $Pd(OAc)_2$, the yield was increased to 54% (entry 6). This suggested that a bulky phosphine ligand might be more effective for the reaction, which stimulated us to use Buchwald ligands. As a result of the screening of some Buchwald ligands, ^{t}Bu-XPhos was found to be most effective for the reaction, affording **10** in 70% yield within shorter reaction time (entry 7). Then, although various solvents were screened, the other polar and nonpolar solvents diminished the reactivity (entries 8−11). Further optimization revealed that inorganic base lowered the yield and that the use of DIPEA was also ineffective albeit in moderate yield (entries 12 and 13). In the absence of LiCl, the reaction did not proceed efficiently (entry 14). Unfortunately, the decreased amount of Pd catalyst resulted in lowering the yield (entry 15). The condition on entry 7 was applicable for the gram-scale preparation of **10** in satisfactory yield (56%) (entry 16). Additional fine tuning of the reaction condition lead the optimized reaction condition: **8** (1 eq), **9** (2 eq), $Pd(OAc)_2$ (20 mol%), ^{t}Bu-XPhos (40 mol%), Et_3N (3 eq), LiCl (2 eq), MS4A in MeCN (0.2 M) at 80 °C for 20 hours (entry 17).

With the coupling product **10** in hand, we turned our attention to convert **10** to the target compound **4** through deoxygenation reaction (Scheme 3, Table 2).[9] Initially, epoxide **10** was treated with PPh_3 and Zn in toluene at 110 °C to give a trace amount of product **4** (data not shown). By changing the solvent to xylene and elevating temperature to 130 °C, **4** was obtained in 28% yield (entry 1). Pleasingly, the yield was improved to 81% by using *o*-dichlorobenzene as solvent (entry 2). Without Zn, no reaction occurred,



Scheme 3. Completion of the synthesis of the target compound **4**

Table 2. Deoxygenation of epoxide **10**

entry	solvent	Zn	time (h)	yield of **4** (%)
1	xylene	Zn	42	28
2[a]	***o*-DCB**	**Zn**	**1.5**	**81**
3	*o*-DCB	—	16	trace
4[b]	*o*-DCB	Zn	11	67

a) 54 mg of **10** was used. b) 835 mg of **10** was used.

showing that Zn is necessary for the reaction proceeding (entry 3). Under the optimal condition (entry 2), 835 mg of **10** could be converted to **4** in 67% yield with prolonged reaction time (entry 4).

Finally, after TBDPS ether of **4** was deprotected,[10] the optical purity of (*R*)-**11** was successfully determined to be sufficiently high (96−99% ee) by our previously established method using chiral HPLC.[5] In addition, (*S*)-**11** could be also synthesized with high optical purity (96−99% ee) via the established synthetic route. These results confirmed that new synthetic route described here is efficient for preparing both enantiomers of **4** with high optical purity.

In summary, we have developed and improved enantioselective synthetic route to the important intermediate **4** for the synthesis of salicylic macrolides, which is composed of Sharpless asymmetric epoxidation and subsequent deoxygenation. The synthesis proceeded in 4 steps and 28% overall yield, which was dramatically improved than our reported route in 10 steps and 4% overall yield. In addition, no epimerization occurred, and a chiral catalyst, (+)- or (−)- diisopropyl tartrate, provided (+)- and (−)-**4** respectively with high optical purity (96-99% ee). The improved method is now applied for synthetic studies of natural salicylate macrolides including CJs in our laboratory, which will be reported in due course.

EXPERIMENTAL

All reactions were carried out under argon atmosphere with dehydrated solvents under anhydrous conditions, unless otherwise noted. Dehydrated solvent was purchased from Kanto Chemical Co., Inc. Reagents were obtained from commercial suppliers and used without further purification, unless otherwise noted. Reactions were monitored by thinlayer chromatography (TLC) carried out on silica gel plates (Merck Kieselgel 60F254). Column chromatography was performed on Silica gel 60N (Kanto Chemical Co., Inc., spherical, neutral, 40-50 μm). Infrared spectra were obtained on a JASCO FT/IR-460Plus spectrometer. Only the strongest and/or structurally important absorption are reported as the IR data afforded in cm^{-1}.

^1H NMR and ^{13}C NMR spectra were recorded by using a JEOL ECX 400 or a JEOL ECX 500 spectrometer. The chemical shifts (δ) of ^1H NMR are given from TMS (0.00 ppm) in $CDCl_3$, as an internal reference. Coupling constant (*J*) is reported in hertz. Multiplicities are reported by using the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; br, broad. The chemical shifts (δ) of ^{13}C NMR are given from $CDCl_3$ (77.0 ppm) as an internal reference.

Mass spectra were recorded on a JEOL JMS-GCmate Ⅱ or a JEOL JMS-AX 505 HAD. The optical rotations were determined on a JASCO DIP-1000 instrument.

Epoxide (+)-8

To a suspension of activated MS4A (powder, 300 mg) in CH_2Cl_2 (9 mL) were added Ti(O*i*-Pr)$_4$ (0.27 mL,

0.93 mmol) and D-(+)-DIPT (0.24 mL, 1.2 mmol) at –20 °C. After the reaction mixture was stirred for 30 min at –20 °C, 1,4-pentadien-3-ol (0.90 mL, 9.3 mmol) and cumene hydroperoxide (2.7 mL, 19 mmol) were added to the solution. After the reaction mixture were stirred for 2 days at –20 °C, imidazole (1.26 g, 18.5 mmol), DMAP (56.2 mg, 0.460 mmol), and TBDPSCl (4.80 mL, 18.5 mmol) were added to the solution. After being stirred for 12 h at room temperature, the mixture was quenched with saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated. The resulting residue was purified by column chromatography (hexane/EtOAc = 95/5) to give epoxide **(+)-8** (1.94 g, 6.01 mmol, 65%) as a colorless oil.

(+)-8: $[\alpha]_D^{23}$ +0.336 (*c* 1.96, $CHCl_3$); ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.72-7.69 (2H, m), 7.67-7.64 (2H, m), 7.46-7.40 (2H, m), 7.40-7.34 (4H, m), 5.90 (1H, ddd, *J* = 17.2, 10.7, 5.9 Hz), 5.20 (1H, ddd *J* = 17.2, 1.5, 1.5 Hz), 5.13 (1H, ddd, *J* = 10.7, 1.5, 1.5 Hz), 3.96-3.93 (1H, m), 2.90 (1H, ddd, *J* = 5.2, 3.9, 2.5 Hz), 2.51 (1H, dd, *J* = 5.2, 3.9 Hz), 2.18 (1H, dd, *J* = 5.2, 2.5 Hz), 1.08 (9H, s); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 137.0, 135.9, 133.8, 133.5, 129.8, 129.7, 127.6, 127.5, 116.4, 74.2, 54.3, 45.5, 26.9, 19.4; IR (neat): 3071, 2931, 2858, 1472, 1428, 1248 cm^{-1}; MS (EI): *m/z* 281 (M-*t*-Bu$^+$); HRMS calcd for $C_{17}H_{17}O_2Si$: 281.0998 (M-*t*-Bu$^+$), found: 281.0959.

Alkene (+)-10 (Table 1, entry 14)

To a solution of **(+)-8** (220 mg, 0.656 mmol) in MeCN (3.3 mL) were added MS4A (powder, 744 mg), LiCl (55.2 mg, 1.31 mmol), triflate **9** (424 mg, 1.31 mmol), $Pd(OAc)_2$ (29.6 mg, 0.131 mmol), ^{t}Bu-XPhos (11 mg, 0.262 mmol), and NEt_3 (0.27 ml, 1.97 mmol). After degassed, the reaction mixture was stirred for 14 h at 80 °C. The mixture was cooled to room temperature and diluted with EtOAc. After the resulting solution was filtered through a pad of Celite, the filtrate was washed with H_2O and brine. The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography (hexane/Et_2O = 7/3) to give alkene **(+)-10** (251 mg, 0.487 mmol, 74%) as a colorless oil.

(+)-10: $[\alpha]_D^{24}$ +90.2 (*c* 0.405, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.80-7.67 (4H, m), 7.51 (1H, d, *J* = 15.9 Hz), 7.44-7.31 (7H, m), 7.08 (1H, d, *J* = 7.5 Hz), 6.84 (1H, d, *J* = 8.2 Hz), 5.96-5.85 (1H, m), 6.17 (1H, dd, *J* = 15.9, 6.0 Hz), 4.27 (1H, dd, *J* = 6.0, 5.4 Hz), 3.08-3.02 (1H, m), 2.58-2.52 (1H, m), 2.26 (1H, dd, *J* = 5.4, 3.0 Hz), 1.70 (6H, m), 1.10 (9H, s); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 160.0, 156.7, 141.3, 136.0, 135.9, 135.1, 133.5, 132.3, 130.1, 129.8, 129.7, 127.61, 127.60, 121.7, 116.4, 110.9, 105.2, 73.8, 54.6, 45.2, 27.0, 25.8, 25.5, 19.4; IR (neat): 2931, 1736, 1577, 1475, 1271 cm^{-1}; MS (EI): *m/z* 457 (M-*t*-Bu$^+$); HRMS calcd for $C_{27}H_{25}O_5Si$: 457.1471 (M-*t*-Bu$^+$), found: 457.1455.

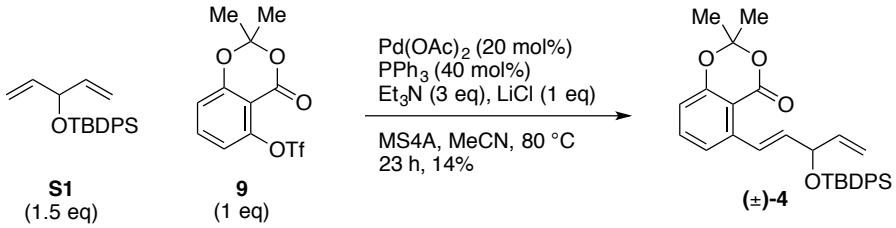
Diene (*R*)-4 (Table 2, entry 2)

To a solution of **(+)-10** (394 mg, 0.766 mmol) in *o*-dichlorobenzene (5.1 mL) were added Zn (washed

with 3 M aqueous HCl, 502 mg, 7.68 mmol) and PPh_3 (2.01 g, 7.68 mmol). After being stirred for 2 h at 130 °C, the reaction mixture was cooled to room temperature and diluted with CH_2Cl_2. After the resulting solution was filtered through a pad of Celite, the filtrate was washed with 10% aqueous $Na_2S_2O_3$ and the resulting aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography (hexane/Et_2O = 10/0 ~ 10/1 ~ 4/1) to give diene **(*R*)-4** (311 mg, 0.624 mmol, 81%) as a yellow oil.

Spectral data of diene **(*R*)-4** was identical with reported data.[5]

(±)-4



S1 (1.5 eq) **9** (1 eq) **(±)-4**

To a solution of diene **S1**[11] (74 mg, 0.23 mmol) in MeCN (1.1 mL) were added MS4A (powder, 181 mg), LiCl (6.5 mg, 0.15 mmol), triflate **9** (49 mg, 0.15 mmol), $Pd(OAc)_2$ (6.9 mg, 0.031 mmol), PPh_3 (16.1 mg, 0.0613 mmol), and NEt_3 (0.065 ml, 0.47 mmol). After being stirred for 23 h at 80 °C, the reaction mixture was cooled to room temperature and diluted with EtOAc. After the resulting solution was filtered through a pad of Celite, the filtrate was washed with H_2O and brine. The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography (hexane/Et_2O = 9/1) to give diene **(±)-4** (11 mg, 0.022 mmol, 14%) as a colorless oil.

Spectral data of diene **(±)-4** was identical with reported data.[5]

Silyl ether of diene **(*R*)-4** was deprotected according to the procedure we reported[5] to give alcohol **(*R*)-11.** Spectral data of alcohol **(*R*)-11** was identical with reported data.[5]

The optical purities of the alcohol **11** were determined as 96−99% ee by chiral HPLC analysis using CHIRALCEL OD-H. eluent: hexane/^{i}PrOH = 9 : 1, flow rate: 1 mL/min, temperature: 25 ºC, retention time: 13.5 min (*R*-isomer) and 15.6 min (*S*-isomer).

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REFERENCES AND NOTES

1. L. Yet, *Chem. Rev.*, 2003, **103**, 4283.
2. (a) D. L. Galinis, T. C. McKee, L. K. Pannell, J. H. Cardellina, and M. R. Boyd, *J. Org. Chem.*, 1997, **62**, 8968; (b) Y. Hayakawa, T. Tomikawa, K. Shin-Ya, N. Arao, K. Nagai, and K.-I. Suzuki, *J. Antibiot.*, 2003, **56**, 899; (c) Y. Hayakawa, T. Tomikawa, K. Shin-Ya, N. Arao, K. Nagai, K.-I. Suzuki, and K. Furihata, *J. Antibiot.*, 2003, **56**, 905.
3. K. A. Dekker, R. J. Aiello, H. Hirai, T. Inagaki, T. Sakakibara, Y. Suzuki, J. F. Thompson, Y. Yamauchi, and N. Kojima, *J. Antibiot.*, 1998, **51**, 14.
4. Y. Matsuya, S. Takayanagi, and H. Nemoto, *Chem. Eur. J.*, 2008, **14**, 5275.
5. Y. Oguma, N. Yamamoto, K. Sugimoto, and Y. Matsuya, *Heterocycles*, 2018, **97**, 283.
6. (a) S. Hatakeyama, K. Sakurai, and S. Takano, *J. Chem. Soc., Chem. Commun.*, 1985, 1759; (b) S. L. Schreiber, T. S. Schreiber, and D. B. Smith, *J. Am. Chem. Soc.*, 1987, **109**, 1525; (c) A. Romero and C.-H. Wong, *J. Org. Chem.*, 2000, **65**, 8264; (d) T. Yoshimitsu and K. Ogasawara, *J. Chem. Soc., Chem. Commun.*, 1994, 2197.
7. (a) A. Hadfield, H. Schweitzer, M. P. Trova, and K. Green, *Synth. Commun.*, 1994, **24**, 1025; (b) A. Fürstner and I. Konetzki, *Tetrahedron*, 1996, **52**, 15071.
8. I. P. Beletskaya and A. V. Cheprakov, *Chem. Rev.*, 2000, **100**, 3009.
9. N. Yamazaki and C. Kibayashi, *Tetrahedron Lett.*, 1988, **29**, 5767.
10. In this reaction, a side product was observed as a minor unidentified product on TLC, which caused the moderate yield of (*R*)-**11**.
11. A. Fawcett, D. Nitsch, M. Ali, J. M. Bateman, E. L. Myers, and V. K. Aggarwal, *Angew. Chem. Int. Ed.*, 2016, **55**, 14663.