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SYNTHESIS OF (*S*)- AND (*R*)-SPOROCHNOL BY USING THE ALLYLIC SUBSTITUTION OF THE SECONDARY ALLYLIC PICOLINATE†

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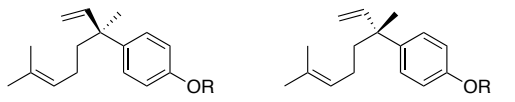
Abstract – The allylic substitution of secondary allylic picolinates and copper reagents for the construction of a quaternary carbon was applied to synthesis of sporochnol. The enantiomerically enriched allylic picolinate (*R*)-**5** was synthesized through the asymmetric hydrogen transfer of acetylene ketone **11** and the Pd-catalyzed methylation of the iodoallylic alcohol **16a**. The key allylic substitution of the allylic picolinate (*R*)-**5** with 4-$MeOC_6H_4MgBr$/$Cu(acac)_2$ (2:1) proceeded with 95% chirality transfer with 98% regioselectivity to afford anti S_N2' product **6** in 89% yield, which was converted to the methyl ether of unnatural (*R*)-sporochnol. Similarly, the methyl ether of (*S*)-sporochnol (the natural form) was synthesized.

(*S*)-Sporochnol, isolated from the Caribbean marine alga *Sporochnus bolleanus*, is an effective chemical defense against marine herbivores.[1] However, the defense mechanism including the structure-activity relationship is not clarified. Up to date, several constructions of a quaternary carbon have been applied to synthesis of (*S*)- as well as (*R*)-sporochnol (Figure 1).[2] The asymmetric copper-assisted allylic substitution of the primary allylic alcohol derivatives reported by the two groups[2q,r] is among the most convenient strategies. This allylic substitution proceeds with high regioselectivity at the γ position (S_N2'), but suffers from the somewhat low asymmetric induction of 82% ee and 57% ee. In contrast, use of secondary allylic esters in the allylic substitution have benefit of attaining high enantiopurity as delineated in Scheme 1, in which the picolinoxy leaving group on allylic picolinates **3** and the copper reagents derived from ArMgBr and $Cu(acac)_2$ are responsible for the observed high stereo- and regioselection.[3,4] Herein, we present synthesis of sporochnol using this method. We first studied synthesis

† This paper is dedicated to Professor Dr. Lutz F. Tietze on the occasion of his 75th birthday.

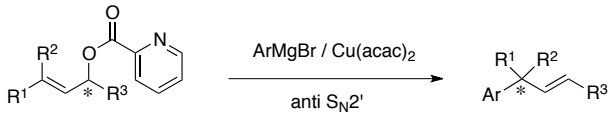
of allylic picolinate (*R*)-**5** to discuss efficiency with the previous method[3] and (*R*)-**5** was then transformed to (*R*)-**1** (Scheme 2). With the established method in hand synthesis of (*S*)-**1** was also accomplished.



natural form (*S*)-**1** (R = H)
methyl ether (*S*)-**2** (R = Me)

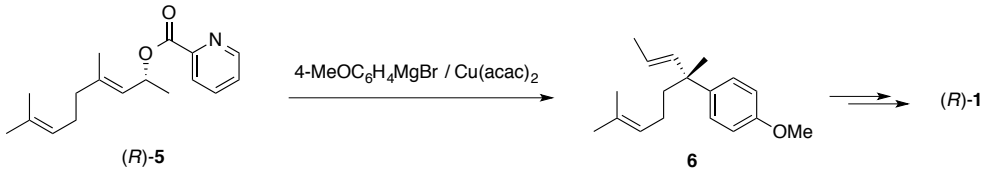
unnatural form (*R*)-**1** (R = H)
methyl ether (*R*)-**2** (R = Me)

Figure 1. Sporochnol and its methyl ether



3 **4**

Scheme 1. Construction of a quaternary carbon by the allylic substitution



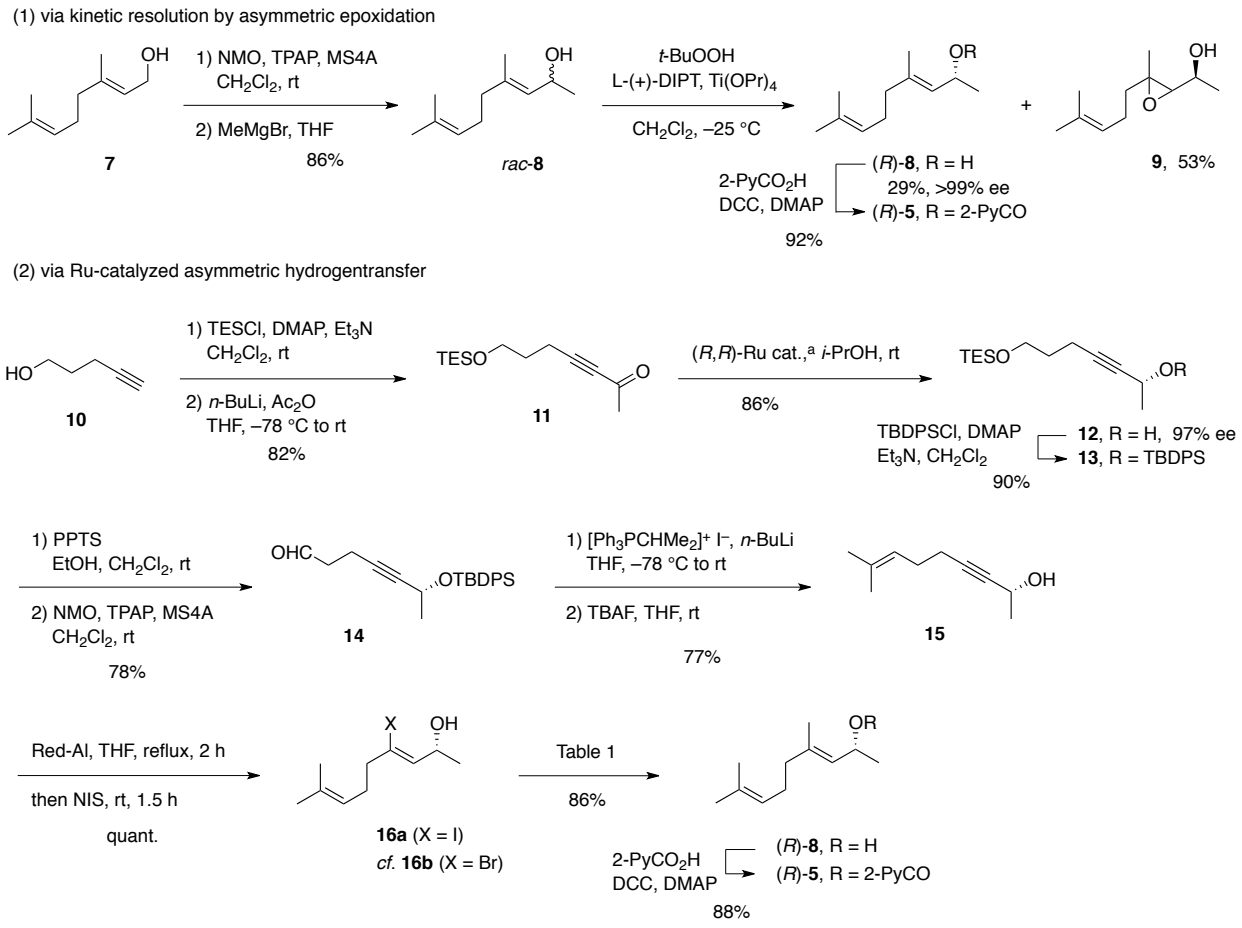
(*R*)-**5** **6**

Scheme 2. A strategy for synthesis of (*R*)-sporochnol

In our previous construction of quaternary carbons, alcohol (*R*)-**8**, the precursor of picolinate (*R*)-**5**, was synthesized with 82% ee starting from geraniol (**7**) via Corey–Bakshi–Shibata reduction[5] (CBS reduction) of the corresponding ketone with (*S*)-MeCBS. In the present study the kinetic resolution of racemic alcohol *rac*-**8** was examined according to the literature procedure[6] using the Sharpless asymmetric epoxidation[7] (the upper equation of Scheme 3), producing (*R*)-**8** (>99% ee by chiral HPLC) and epoxide **9** in 29% and 53% yields, respectively, after chromatography on silica gel. This yield of (*R*)-**8** was among the level similar to that reported,[6] and epoxide **9** was a roughly 1:1 mixture of the diastereomers by ^{1}H and ^{13}C–APT NMR spectroscopy,[8] though the single diastereomer for the epoxide is drawn in the reported supporting information.[6] Since the yield of (*R*)-**8** with high % ee was low, epoxidation of the Et and *i*-Pr homologues (derived from **7** with EtMgBr and *i*-PrMgBr) was also attempted. However, the allylic alcohols were isolated in 21% and 28% yields with 90 and 77% ee, respectively. Finally, alcohol (*R*)-**8** was converted to picolinate (*R*)-**5** in 92% yield by the standard method.

As an alternative synthesis of (*R*)-**5**, a sequence of reactions shown in the lower part of Scheme 3 was envisioned. Among the steps involved in, slow methylation of **16**(**a**,**b**) was anticipated because of the cis stereochemistry regarding to the halogen atom (X) and the CH(OH)Me group on the olefin moiety. Thus,

the 1,3-allylic strain on the olefin was expected to place the Me and OH groups out of the allylic plane, blocking the methylation. Probably, because of this steric reason, the previous methylation of a similar vinyl iodide was achieved with Me_2Zn and $Pd(t\text{-}Bu_3P)_2$.[9] To avoid the use of such an unstable catalyst, the methylation of **16**(**a**,**b**) was studied as described below.

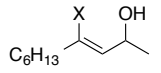
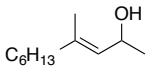
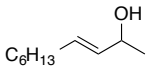
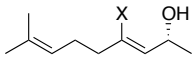
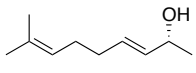


Scheme 3. Synthesis of the allylic picolinate by two methods

[a] Ru[(1*R*,2*R*)-TsDPEN](*p*-cymene).

Acetylene **10** was first converted to ynone **11** in two steps. The asymmetric hydrogen transfer reaction of **11** with Ru[(1*R*,2*R*)-TsDPEN](*p*-cymene)[10] produced alcohol **12** in 86% yield with 97% ee (as determined by chiral HPLC analysis of the derived benzoate), and the alcohol was converted to the TBDPS ether **13** in 90% yield. The TES group was removed and the resulting alcohol was oxidized to afford aldehyde **14** in 78% yield. Wittig reaction of **14** with the ylide prepared from $[Ph_3PCHMe_2]^+ I^-$ and *n*-BuLi followed by deprotection of the TBDPS group produced alcohol **15** in 77% yield. Hydroalumination with Red-Al and subsequent reaction with NIS gave vinyl iodide **16a** quantitatively. Similarly, bromide **16b** was synthesized by adding NBS after the Red-Al reaction. Both of the halides **16a**,**b** were used for the next methylation.

Table 1. Methylation of the model and the real vinyl halides

Entry	Sub-strate	Me–M (equiv)	Cat. (equiv)	Additive (equiv)	Temp.	Time (h)	Product[a] Me : H : SC	Yield[b] (%)
	 **17a**, X = I **17b**, X = Br	Me–M, cat., additive THF, temp., time	 **18** (Me product) +  **19** (H product) + starting compound (SC) **17a** or **17b**					
1	**17b**	MeMgBr (4)	$Ni(acac)_2$ (0.2)	–	rt	13	81 : 10 : 9	nd
2	**17a**	MeMgBr (4)	$Ni(acac)_2$ (0.2)	–	rt	13	70 : 30 : <1	nd
3	**17a**	MeMgBr (6)	$Fe(acac)_3$ (0.5)	NMP (9)	0 °C	0.5	16 : 16 : 68	nd
4	**17a**	MeMgBr (6)	$Fe(acac)_3$ (0.5)	NMP (9)	rt	2	57 : 43 : <1	nd
5	**17a**	MeMgCl (6)	$Fe(acac)_3$ (0.5)	NMP (9)	0 °C	2	27 : 20 : 53	nd
6	**17a**	MeLi (3), $ZnCl_2$ (3)	$Pd_2(dba)_3{\cdot}CHCl_3$ (0.1)	dppf (0.1)	rt	21	92 : 8 : <1	nd
7	**17a**	MeMgBr (3), $ZnCl_2$ (3)	$Pd_2(dba)_3{\cdot}CHCl_3$ (0.1)	dppf (0.1)	rt	21	90 : 6 : 4	nd
8	**17a**	MeLi (3), ZnI_2 (3)	$Pd_2(dba)_3{\cdot}CHCl_3$ (0.1)	dppf (0.1)	rt	20	94 : 3 : 3	nd
9	**17b**	MeLi (3), $ZnCl_2$ (3)	$Pd_2(dba)_3{\cdot}CHCl_3$ (0.1)	dppf (0.1)	rt	22	8 : 2 : 90	nd
	 **16a**, X = I **16b**, X = Br	Me–M, cat., additive THF, temp., time	(*R*)-**8** (Me product) +  **20** (H product) + starting compound (SC) **16a** or **16b**					
10	**16a**	MeLi (3), ZnI_2 (3)	$Pd_2(dba)_3{\cdot}CHCl_3$ (0.1)	dppf (0.1)	rt	25	86 : 9 : 5	nd
11	**16a**	MeLi (3), ZnI_2 (3)	$Pd_2(dba)_3{\cdot}CHCl_3$ (0.15)	dppf (0.15)	rt	37	93 : 7 : <1	86
12	**16b**	MeMgBr (6)	$Ni(acac)_2$ (0.2)	–	50[c]	13	86 : 11 : 3	55

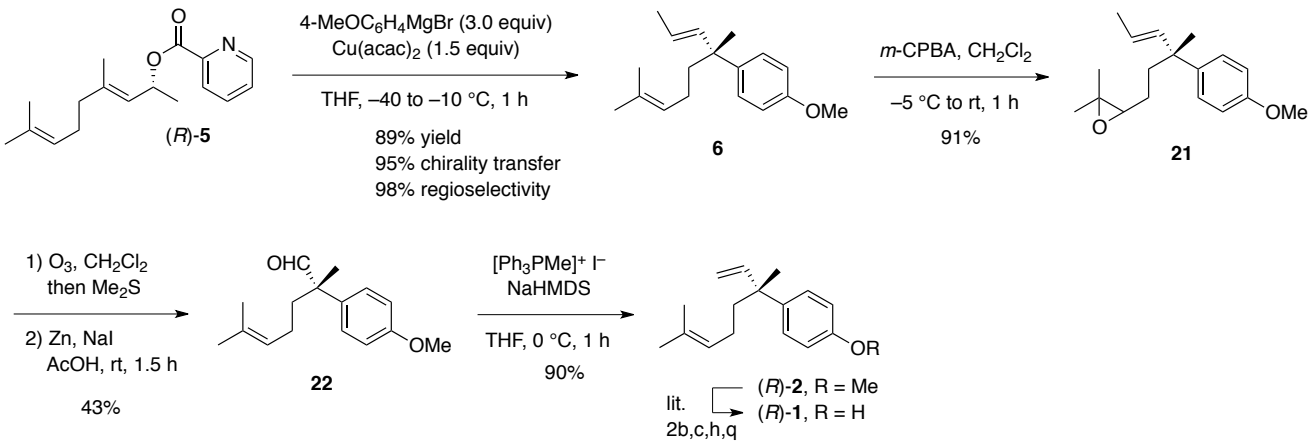
[a] Determine by ^{1}H NMR using the following absorbance for one proton (δ): **17a**, 5.59 (d, J = 7.2 Hz); **17b**, 5.74 (d, J = 7.5 Hz); **18**, 5.20 (d, J = 8.4 Hz); **19**, 5.50 (dd, J = 15.3 Hz, 6.3 Hz); **16a**, 5.59 (d, J = 7.2 Hz); **16b**, 5.74 (d, J = 7.5 Hz); (*R*)-**8**, 5.22 (d, J = 8.4 Hz); **20**, 5.53 (dd, J = 15.3 Hz, 6.6 Hz). [b] nd: Not determined because of the model study (entries 1–9) or the low product selectivity (entry 10). [c] Reaction at rt for 14 h gave a 74 : 6 : 20 mixture.

On the basis of the previous study on the Ni-catalyzed arylation of the cis bromo-allylic alcohol derivatives with arylborates,[11] methylation of a model bromide **17b** with MeMgBr was first attempted in the presence of $Ni(acac)_2$ to produce a 81:10:9 mixture of **18**, the deiodinated compound **19**, and the starting compound (abbreviated as Me, H, and SC in Table 1) (entry 1). Iodide **17a** was more reactive than the bromide, but less product selective (70%) (entry 2). Based on the observed reactivity, iodide **17a** was used for further study. Fe-Catalyzed methylation with MeMgX (X = Br, Cl) was attempted in the presence of NMP (*N*-methyl-2-pyrrolidone) according to the literature procedure for alkylation of alkenyl and aryl halides.[12] However, product selectivity under the conditions of entries 3–5 was quite low. We then investigated Pd-catalyzed reaction under the Negishi conditions.[13] As shown in entry 6, methylation of iodide **17a** with MeZnCl·LiCl (3 equiv) in the presence of $Pd_2(dba)_3{\cdot}CHCl_3$ (0.1 equiv) and dppf (0.1 equiv) gave **18** with 92% product-selectivity over **19** and **17a**. A similar ratio was observed with MeMgBr-based zinc reagent (entry 7). Further investigation found an excellent product-selectivity with

ZnI_2 (entry 8, cf. entry 6). The excellent conditions of entry 6 was applied to bromide **17b**, which showed little reactivity (entry 9).

The procedure used in entry 8 was applied to the real iodide **16a** to obtain a somewhat lower ratio of 86:9:5 for (*R*)-**8**, **20**, and **16a** (abbreviated as Me, H, and/or SC as well) (entry 10). Fortunately, the use of the slightly larger quantity of the Pd catalyst resulted in 93% product-selectivity of (*R*)-**8**, which was isolated in 86% yield after chromatography (entry 11). The Ni-catalyzed methylation with MeMgBr under the conditions of entry 1 was also attempted to give (*R*)-**8** in 55% yield with 86% product-selectivity (entry 12). Finally, alcohol (*R*)-**8** was converted to picolinate (*R*)-**5**.

Overall yield of (*R*)-**5** from acetylene alcohol **10** was 29% in 11 steps, whereas that of the former from geraniol (**7**) was 23% in 4 steps. Taking the overall yields, the total steps, and almost equal ease of access to the (*S*)-isomer into consideration, the former synthesis would be suitable for synthesis of natural sporochnol (*S*)-**5** and the enantiomer (*R*)-**5**, while the latter would be useful for synthesis of analogues of sporochnol.

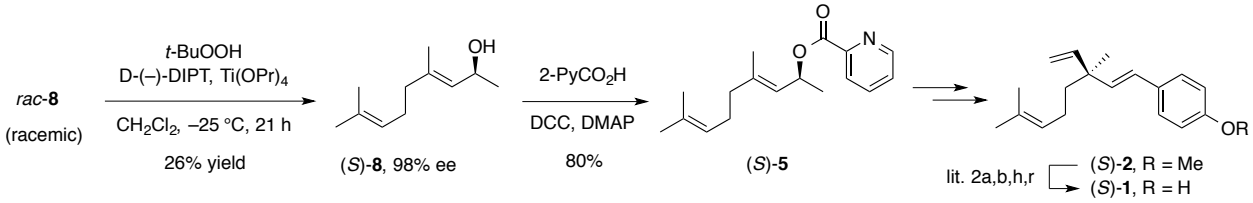


Scheme 4. Synthesis of (*R*)-sporochnol

The last part of the synthesis is delineated in Scheme 4. The required copper reagent (1.5 equiv), prepared from 4-$MeOC_6H_4MgBr$ and $Cu(acac)_2$ in the 2:1 ratio, was subjected to the allylic substitution of (*R*)-**5** (>99% ee, 1 equiv). The reaction proceeded smoothly to afford **6** in 89% yield with 95% chirality transfer (CT) and 98% regioselectivity. The absolute configuration of the product was assigned later by comparing the optical rotations of (*R*)-**2** synthesized herein and reported in the literature. Epoxidation of **6** with *m*-CPBA proceeded regioselectively to afford **21** (1:1 mixture of the diastereomers) in 91% yield. The olefin part of **21** was cleaved by ozonolysis, and the epoxide moiety was reduced with Zn, NaI, and AcOH according to the literature procedure[14] to furnish aldehyde **22** in 43% yield. Finally, Wittig reaction of the aldehyde with $Ph_3P{=}CH_2$ gave the known methyl ether (*R*)-**2** in 90% yield: 95% ee by chiral HPLC

analysis; $[\alpha]_D^{19}$ –3.0 (*c* 0.35, $CHCl_3$); cf. reported[2c] $[\alpha]_D^{20}$ –3.7 (*c* 1, $CHCl_3$). The methyl ether can be converted to (*R*)-sporochnol ((*R*)-**1**) as described in the literature.[2b,c,h,q]

In a similar way, (*S*)-**5** (98% ee) was synthesized via the Sharpless asymmetric epoxidation of *rac*-**8** with (D)-(–)-DIPT (Scheme 5). Allylic substitution of (*S*)-**5** proceeded with 95% CT as well and the further transformation afforded (*S*)-**2**: 93% ee by chiral HPLC; $[\alpha]_D^{20}$ +2.7 (*c* 0.12, $CHCl_3$); cf. reported[2r] $[\alpha]_D^{20}$ +3.0 (*c* 1.1, $CHCl_3$).



Scheme 5. Synthesis of (*S*)-sporochnol

In summary, we established a new method for synthesis of sporochnol with high ee. The preparation of the allylic picolinate **5** through the Sharpless asymmetric epoxidation is straightforward for synthesis of sporochnol as such, whereas the method starting from acetylene **10** (the second method in Scheme 3) would be flexible for study of the structure-activity relationship of sporochnol.

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8. Epoxide **9** (diastereomeric mixture): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.23 and 1.35 (2 d, J = 6.5 and 6.5 Hz, 3 H), 1.29 and 1.37 (2 s, 3 H), 1.62 (s, 3 H), 1.69 (s, 3 H), 1.22–1.79 (m, 3 H), 2.03–2.19 (m, 2 H), 2.63 and 2.70 (2 d, J = 8.0 and 8.0 Hz, 1 H), 3.59–3.78 (m, 1 H), 5.01–5.15 (m, 1 H); ^{13}C–APT NMR (75 MHz, $CDCl_3$) δ 16.6 and 17.0 (+), 17.8 and 19.2 (+), 20.8 (+), 23.9 (–), 25.76 and 25.79 (+), 38.6 and 38.8 (–), 61.6 and 61.8 (–), 66.2 and 66.4 (+), 67.1 and 67.9 (+), 123.4 and 123.5 (+), 132.2 and 132.3 (–).
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