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Stereo-controlled synthesis of analogs of peumusolide A, NES non-antagonistic inhibitor for nuclear export of MEK

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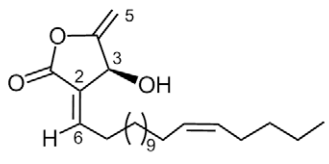
ABSTRACT

Stereo-controlled construction of the core structure of peumusolide A (**1**), α-alkylidene-β-hydroxy-γ-methylenebutyrolactone, was developed by a combination of regio- and stereo-selective hydroiodination of 2-yn-1-ol and asymmetric reduction of 1-yn-4-en-3-one as the key reactions. By using this protocol, all the four stereoisomers of the analog of **1** were synthesized from the common starting material.

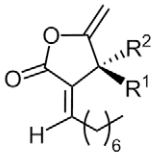
Export of MAPK/ERK kinase (MEK) from the nucleus to the cytoplasm was found to be essential process for cell proliferation in many kinds of MEK-activated tumor cells.[1] Thus, inhibitors for nuclear export of MEK have been anticipated to be highly attractive seed principles toward new anti-tumor agents. In this context, we have been engaged in search for nuclear export inhibitors of MEK to disclose peumusolide A (**1**) as the first MEK-export inhibitor with NES non-antagonistic mode. In addition, peumusolide A (**1**) was found to be a promising anti-tumor scaffold with the novel mechanism of action by demonstrating selective growth inhibition for the MEK-activated tumor cells by **1**.[2] Besides peumusolide A (**1**), several congenic polyketides with interesting biological activities have been revealed very recently.[3,4] Despite such attractive biological properties, the asymmetric synthesis of the core structure in these polyketides, α-alkylidene-β-hydroxy-γ-methylenebutyrolactone, was only achieved by using the sulfoxide as a chiral auxiliary.[5] However, the synthetic route involved strict geometrical limitation giving only (2*E*)-isomers.

In the structural elucidation of **1**, we synthesized a pair of enantiomers of **2** with 2*E*-configuration according to the reported procedure to establish the configuration at C-3. To elucidate participation of the stereochemistry of the C_2–C_6 double bond in the biological activity of peumusolide A (**1**), we embarked on the development of stereo-selective construction procedure providing (2*Z*)-isomers as well as (2*E*)-isomers of α-alkylidene-β-hydroxy-γ-methylenebutyrolactones. This letter describes the synthesis of the four stereoisomers of the analog of peumusolide A (**1**) (Fig. 1).

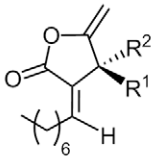
Our retrosynthetic approach to (*S*)-**3**, illustrated in Figure 2, includes regio- and stereo-selective hydroiodination of 2-yn-1-ol and enantioselective reduction of 4-en-1-yn-3-one as the key reactions. In brief, construction of the lactone framework would be conducted by alkyne-lactonization of 4-carboxy-1-yn-3-ol **i** at the last stage. The carboxylic acid **i** was planned to be prepared from optically active secondary alcohol **ii**, which would be provided by asymmetric reduction of 4-en-1-yn-3-one **iii**. The ketone **iii** was envisioned to be obtained by coupling of iodoalkene **5a** and protected 2-yn-1-al **iv**. The (*E*)-iodoalkene **5a** is accessible from decyn-1-ol (**4**) by cis-selective hydroiodination. In addition, (*Z*)-iodoalkene **5b** is afforded by trans-selective hydroiodination of the common starting material **4**. Application of the same synthetic procedure of (*S*)-**3** to **5b** enables to facilely provide the (*E*)-isomer, (*S*)-**2**. Obviously, both (*R*)-enantiomers of (*S*)-**2** and (*S*)-**3** will be readily furnished by alternation of the chirality of a reagent for asymmetric reduction.



peumusolide A (**1**)



(*S*)-**2** (R^1=OH, R^2=H)
(*R*)-**2** (R^1=H, R^2=OH)



(*S*)-**3** (R^1=OH, R^2=H)
(*R*)-**3** (R^1=H, R^2=OH)

Figure 1. Chemical structures of peumusolide A (**1**) and targeted analogs.

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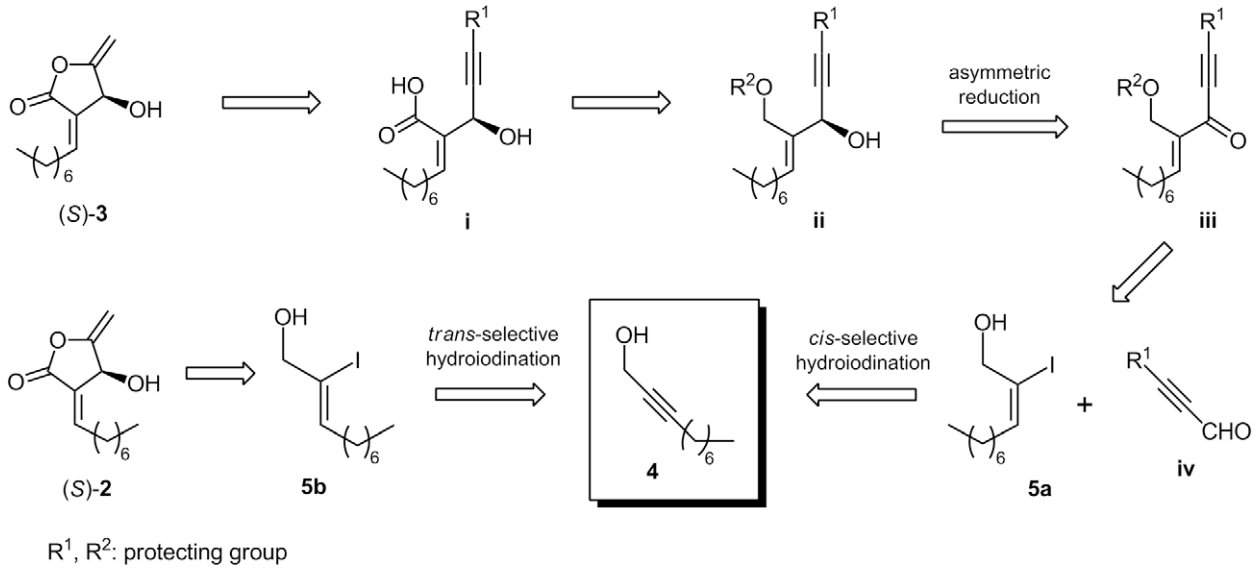
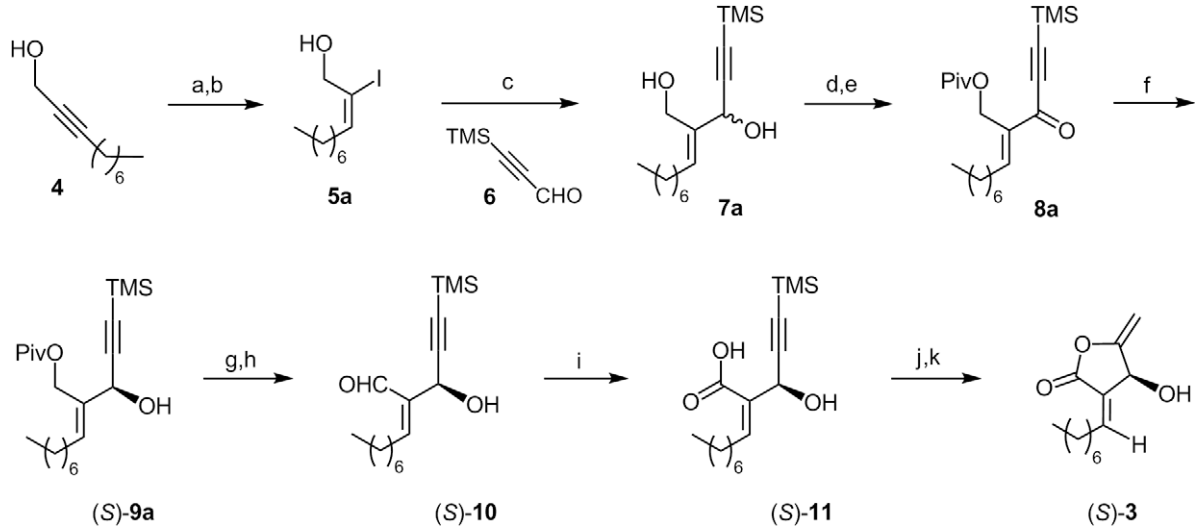


Figure 2. Retrosynthetic analysis of targeted analogs.

The synthesis of (*S*)-**3** was executed as shown in Scheme 1. Palladium (0)-catalyzed hydrostannylation of 2-decyn-1-ol (**4**) by $(Ph_3P)_4Pd$ and *n*-Bu_3SnH followed by direct iododestannylation regio- and stereo-selectively proceeded to afford (*E*)-2-iodo-2-decen-1-ol (**5a**).[6] Coupling of the iodoalkene **5a** and 3-trimethylsilyl-2-propyn-1-al (**6**) using MeLi and *t*-BuLi gave en-yne-diol **7a**. After protection of the primary hydroxyl group in **7a** as pivaloyl ester, the resulting ester was converted to conjugated ketone **8a** by MnO_2 oxidation. Asymmetric reduction of the ketone **8a** with the complex of (*S*)-2-methyl-CBS-oxazaborolidine and BH_3 [(*S*)-CBS catalyst][7] provided the optically active secondary alcohol (*S*)-**9a** in 83% yield with 93% ee. Because of the absence of precedented reduction of 4-substituted 4-en-1-yn-3-one by the CBS catalyst, the absolute configuration of (*S*)-**9a** was determined by modified Mosher's method.[8] As depicted in Figure 3, distributions of $\Delta\delta$ values from the corresponding (*S*)- and (*R*)-MTPA esters (**9b** and **9c**) revealed (*S*)-**9a** to bear the predicted *S*-configuration.

Sequential reductive cleavage of the pivaloyl group with $LiBH_4$ and selective oxidation of the primary hydroxyl group with MnO_2 provided aldehyde (*S*)-**10**, which was further oxidized with $NaClO_2$ to give alkynyl carboxylic acid (*S*)-**11**. Removal of the trimethylsilyl group with K_2CO_3 in MeOH followed by Ag (I)-mediated alkyne-lactonization furnished the desired γ-lactone. After chiral HPLC separation of the lactone, the absolute configuration at C-3 of (*S*)-**3**[9] was unambiguously confirmed by the CD spectra described in our previous report.[2]

Next, we examined the synthesis of (*S*)-**2**, the geometrical isomer of (*S*)-**3**, by application of the above-mentioned protocol (Scheme 2). Successive treatment of **4** with *n*-BuLi, *i*-Bu_2AlH (DIBAL), and iodine induced trans-selective hydroiodination to provide (*Z*)-iodoalkene **5b**. The iodoalkene **5b** was transformed to the optically active alcohol (*S*)-**9b** in the same manner for the preparation of (*S*)-**9a**. In contrast to the synthesis of (*S*)-**10**, MnO_2 oxidation of diol, prepared by removal of the pivaloyl group in (*S*)-



Scheme 1. Synthesis of (*Z*)-analog, (*S*)-**3** and (*R*)-**3**. Reagents and conditions: (a) Bu_3SnH, $(Ph_3P)_4Pd$, benzene, rt; (b) I_2, CH_2Cl_2, rt, 75% (two steps); (c) MeLi, *t*-BuLi, **6**, Et_2O, −30 °C to −78 °C, 75%; (d) PivCl, pyridine, $(CH_2Cl)_2$, reflux, 67%; (e) MnO_2, CH_2Cl_2, rt, 82%; (f) (*S*)- or (*R*)-2-methyl-CBS-oxazaborolidine, BH_3·THF, THF, −40 °C, 85% (93% ee) for (*S*)-**9a**, 84% (92% ee) for (*R*)-**9a**; (g) $LiBH_4$, THF, 0 °C, 76% for *S*-isomer, 74% for *R*-isomer; (h) MnO_2, CH_2Cl_2, rt, quant. for (*S*)- and (*R*)-**10**; (i) $NaClO_2$, 2-methyl-2-butene, NaH_2PO_4, *t*-BuOH–H_2O, rt, 60% for (*S*)-**11**, 61% for (*R*)-**11**; (j) K_2CO_3, MeOH–THF, rt, 93% for *S*-isomer, 92% for *R*-isomer; (k) Ag_2CO_3, C_6H_6, 80 °C, 89% for (*S*)-**3**, 88% for (*R*)-**3**.

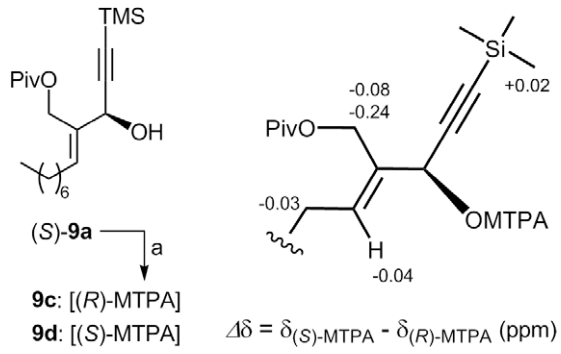
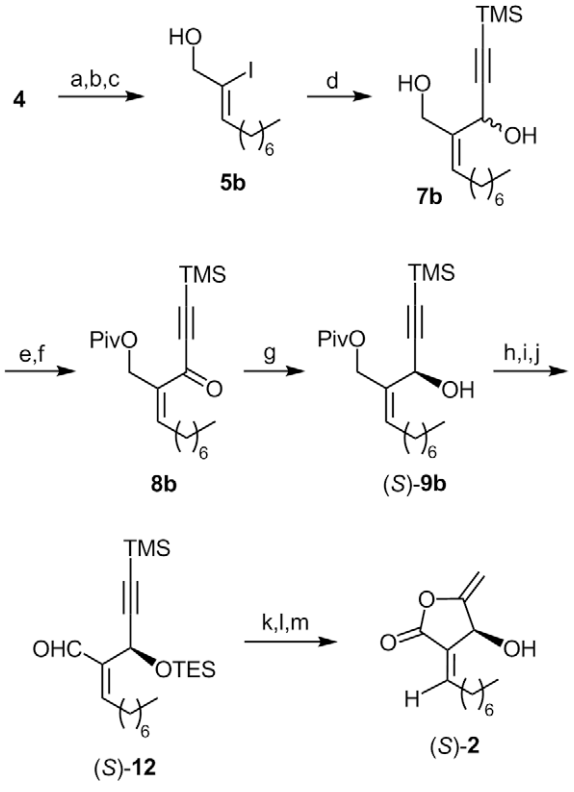


Figure 3. Establishment of stereochemistry in (*S*)-**9a**. Reagents and conditions: (a) (*R*)- or (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetic acid, EDCI·HCl, DMPA, CH_2Cl_2, rt, 59% for **9c**, 58% for **9d**.

9b, afforded the corresponding ketoalcohol as a sole product, therefore the protection of the secondary hydroxyl group in (*S*)-**9b** was revealed to be necessary. Introduction of the triethylsilyl (TES) group followed by removal of the pivaloyl protection afforded primary alcohol, which was oxidized with MnO_2 to give aldehyde (*S*)-**12**. After $NaClO_2$ oxidation of (*S*)-**12** concomitant with removal of the TES group, the resulting hydroxycarboxylic acid was converted to (*S*)-**2** by the same procedure to (*S*)-**3**.[10] The C-3 configuration of (*S*)-**2** was confirmed by the CD spectra after chiral



Scheme 2. Synthesis of (*E*)-analog, (*S*)-**2** and (*R*)-**2**. Reagents and conditions: (a) *n*-BuLi, Et_2O, −20 °C; (b) DIBAL, Et_2O, 35 °C; (c) I_2, Et_2O, rt, 71% (three steps); (d) MeLi, *t*-BuLi, **6**, Et_2O, −30 °C to −78 °C, 76%; (e) PivCl, pyridine, $(CH_2Cl)_2$, reflux; (f) MnO_2, CH_2Cl_2, rt, 53% (two steps); (g) (*S*)- or (*R*)-2-methyl-CBS-oxazaborolidine, BH_3·THF, THF, −40 °C, 82% (83% ee) for (*S*)-**9b**, 83% (82% ee) for (*R*)-**9b**; (h) TESCl, pyridine, CH_2Cl_2, rt; (i) $LiBH_4$, THF, rt; (j) MnO_2, CH_2Cl_2, reflux, 97% for (*S*)-**12**, 98% for (*R*)-**12** (three steps); (k) $NaClO_2$, 2-methyl-2-butene, NaH_2PO_4, *t*-BuOH–H_2O, 40 °C, 90% for *S*-isomer, 86% for *R*-isomer; (l) K_2CO_3, MeOH–THF, rt; (m) Ag_2CO_3, C_6H_6, 80 °C, 87% for (*S*)-**2**, 88% for (*R*)-**2** (two steps).

Table 1
Inhibitory activity for MEK export of peumusolide A (**1**) and four analogs

	Configuration of C_3	Geometry of C_2–C_6	IC_{50} (μM)
(*S*)-**1**	*S*	*E*	3.7
(*R*)-**1**	*R*	*E*	17.4
(*S*)-**2**	*S*	*E*	3.5
(*R*)-**2**	*R*	*E*	16.2
(*S*)-**3**	*S*	*Z*	3.8
(*R*)-**3**	*R*	*Z*	18.7

HPLC separation. By utilization of (*R*)-CBS catalyst, both 3*R* enantiomers [(*R*)-**2** and (*R*)-**3**[9]] were also synthesized in the same manner.

Finally, we evaluated inhibitory effect of peumusolide A (**1**) and the synthesized four analogs for nuclear export of MEK in HeLa cells by an indirect fluorescent antibody technique.[2] Table 1 summarizes IC_{50} values of all compounds for nuclear export of MEK. Comparison of the biological activity in the three pairs of enantiomers indicated that the configuration at C-3 is crucial for the inhibitory activity for MEK export. On the other hand, the geometry of the C_2–C_6 double bond was found to have little influence on the biological potency.

In conclusion, we developed the stereo-controlled construction of the optically active α-alkylidene-β-hydroxy-γ-methylenebutyrolactone, the core structure of peumusolide A (**1**) with MEK-export inhibitory activity. This protocol comprises both regio- and stereo-selective hydroiodination of 2-yn-1-ol and enantioselective reduction of 1-yn-4-en-3-one as the key reactions to furnish all types of stereoisomers. Evaluation of MEK-export activity of the synthesized analogs clarified 3*R* configuration to be curial for the biological efficacy of the congers of peumusolide A (**1**), while the geometry of the C_2–C_6 double bond was shown to have little influence of inhibition for nuclear export of MEK. It is noteworthy that the present study opens an avenue to the synthesis of (2*Z*)-α-alkylidene-β-hydroxy-γ-methylenebutyrolactones coexisting with the *E*-congeners in the nature.[11,12] Our synthetic protocol enables to assemble peumusolide A (**1**) analogs, thereby exploration of more potent analogs than **1** is currently underway in our group.

Acknowledgments

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9. (*S*)-**3**: colorless oil, $[\alpha]_D^{24}$ −32.5 (*c* 0.90, MeOH), CD λ^{MeOH} (Δε): 226 nm (−3.5), IR ν_{max} (KBr) cm^{-1}: 3442, 1768, 1670, ^1H NMR (500 MHz, $CDCl_3$) δ: 6.69 (1H, td, *J* = 7.9, 2.0 Hz, 6-H), 5.12 (1H, br s, 3-H), 4.89 (1H, dd, *J* = 2.4, 2.4 Hz, 5-Ha), 4.67 (1H, br s, 5-Hb), 2.77 (2H, m, 7-H), 1.49 (2H, m, 8-H), 1.25–1.30 (8H, m, 9, 10, 11, 12-H), 0.88 (3H, t, *J* = 6.6 Hz, 13-H), FAB-MS (*m*/*z*): 225 $[M+H]^+$, HR FAB-MS (*m*/*z*): calcd for $C_{13}H_{20}O_3$+H; 225.1491, found; 225.1496. (*R*)-**3**: colorless oil,

$[\alpha]_D^{24}$ +32.2 (*c* 0.90, MeOH), CD λ^{MeOH} ($\Delta\varepsilon$): 226 nm (+3.5), FAB-MS (*m*/*z*): 225 $[M+H]^+$, HR FAB-MS (*m*/*z*): calcd for $C_{13}H_{20}O_3$+H; 225.1491, found; 225.1493. The IR and ^{1}H NMR spectra were superimposable on those of (*S*)-**3**.

10. In the synthesis of (*S*)-**3**, MnO_2 oxidation to the *Z*-isomer of (*S*)-**12** was unsuccessful because of extreme lability of the reactants. Therefore, the *Z*-analog (*S*)-**3** was synthesized without protecting the secondary hydroxyl group in (*S*)-**9a**.
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