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Synthesis of two possible diastereomers of reticulatain-1

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Abstract—A convergent synthesis of two possible diastereomers of reticulatain-1 (**1a** and **1b**) was accomplished. Comparison of the specific optical rotations of **1a** and **1b** did not allow for the strict determination of the absolute configuration. However, bis-(*R*)-MTPA esters of **1a** and **1b** showed a clear difference in chemical shifts in the ^{1}H NMR spectra. If the bis-(*R*)-MTPA ester of natural reticulatain-1 (**1**) is available, the absolute configuration of **1** will be determined. Inhibitory action of these compounds was examined with bovine heart mitochondrial complex I. Both compounds showed almost the same activity.

Annonaceous acetogenins, that have been isolated from a number of tropical or subtropical plants of the *Annonaceae*, have attracted much attention due to a wide variety of biological activities, for example, cytotoxic, antitumoral, antimalarial, antibiotic, antiparasitic, and antifeedant. So far, more than 350 compounds have been isolated.[1] Most of them possess one or more tetrahydrofuran (THF) rings, together with an α,β-unsaturated γ-lactone part on a C-35 or C-37 carbon chain. Reticulatain-1 (**1**) is a mono-THF acetogenin,[2] isolated from *Annona reticulata* in 1995.[3] A similar compound corresponding to the well-known reticulatacin (**2**)[4] was synthesized by Keinan[5] and us.[6] The absolute configuration of natural **1** has not been reported yet. However, because the *erythro-trans-threo* stereochemistry of the tetrahydrofuran ring of **1** has been determined by Figadère et al.,[3] and the (*S*) configuration of the secondary methyl group of the γ-lactone moiety is well known, it follows that the absolute stereochemistry of **1** is (17*R*,18*R*,21*R*,22*S*) or (17*S*,18*S*,21*S*,22*R*) (Fig. 1).

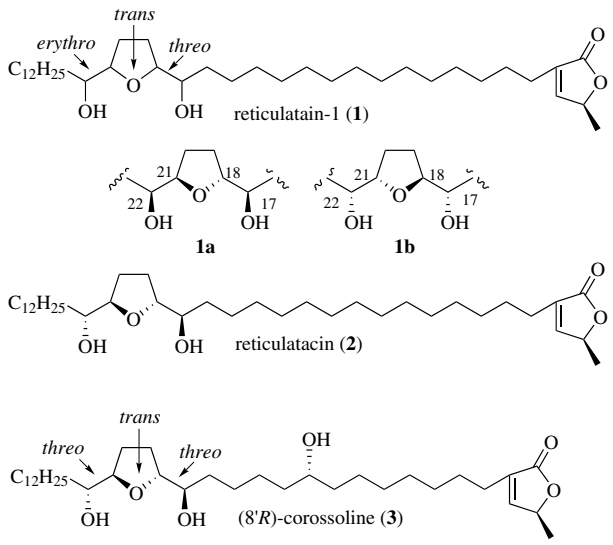

Figure 1. The structure of reticulatain-1.

The two possible structures, **1a** and **1b**, would be very difficult to differentiate by ^{1}H NMR or ^{13}C NMR spectroscopic data, because two stereogenic centers, that is, the THF ring part and the γ-lactone moiety are separated by a long carbon chain. In a previous paper, we prepared chiral building block **4** for synthesizing (8′*R*)-corossoline (**3**), mono-THF acetogenins, which possess the *threo-trans-threo* stereochemistry of the

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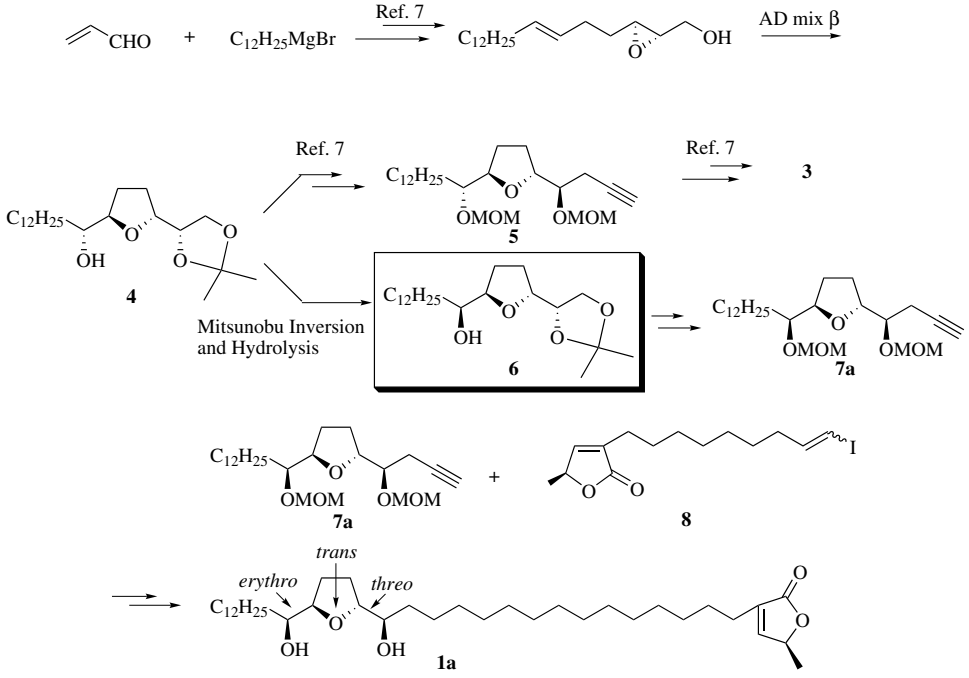
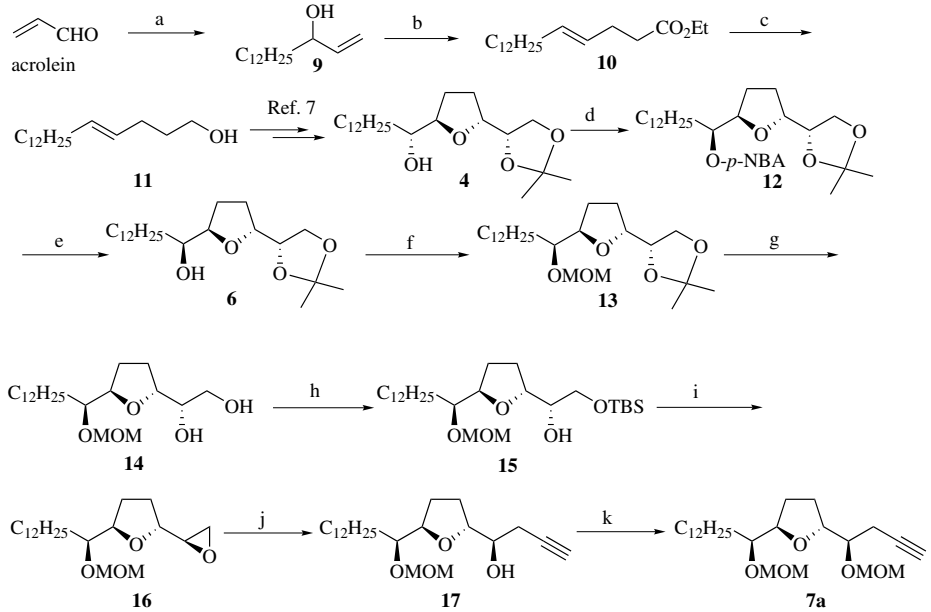


Scheme 1. Synthetic strategy of reticulatain-1.

tetrahydrofuran ring. In this paper, we prepared another chiral building block **6** for synthesizing mono-THF acetogenins, which possess *erythro-trans-threo* stereochemistry by using the Mitsunobu inversion from **4** (Scheme 1). To utilize this methodology, we planned to synthesize two candidates of reticulatain-1 (**1**), **1a** and **1b**.

As shown in Scheme 2, the THF part **15** of **1a** was constructed via a multi-step process starting from acrolein and laurylmagnesium bromide. Grignard reaction of acrolein with laurylmagnesium bromide gave allylic alcohol **9**. Johnson–Claisen rearrangement with 1,1,1-triethoxyethane and a catalytic amount of propionic acid gave ester **10**, which was then submitted to reduction with diisobutylaluminum hydride (DIBALH) to afford **11**. The conversion of compound **11** to **4** was performed using the Sharpless epoxidation and dihydroxylation according to our previously published method.[7]



Scheme 2. Synthesis of tetrahydrofuran part of **1a**. Reagents: (a) $C_{12}H_{25}MgBr$, Et_2O (95%); (b) $CH_3C(OEt)_3$, propionic acid (86%); (c) DIBALH, CH_2Cl_2 (95%); (d) *p*-nitrobenzoic acid, DEAD, THF (85%); (e) NaOH, MeOH (91%); (f) MOMCl, *i*-Pr_2NEt, CH_2Cl_2 (92%); (g) 60% AcOH, (96%); (h) TBSCl, Et_3N, DMAP, CH_2Cl_2 (100%); (i) 1) MsCl, Et_3N, CH_2Cl_2 2) TBAF, THF(96%); (j) lithium acetylide, ethylenediamine complex, DMSO (83%); (k) MOMCl, *i*-Pr_2NEt, CH_2Cl_2 (94%).

Table 1. Variation of the carboxylic acids in the Mitsunobu inversion of **4**[a]

Acid	pK_a	Yield (%)
Acetic acid	4.76	0
Benzoic acid	4.19	17
p-Nitrobenzoic acid	3.41	85

[a] The reaction was carried out in THF at room temperature for 12 h.

Compound **4** was then subjected to the Mitsunobu reaction.[8] In this reaction, the yields of products were highly dependent on the pK_a values of acids perhaps due to the steric hindrance of the acetonide group.[9] *p*-Nitrobezoate gave a good result. On the other hand, acetic acid or benzoic acid afforded the product in low yield (Table 1).

Hydrolysis of *p*-nitrobezoate **12** with methanolic NaOH gave building block **6**. The inverted secondary hydroxyl group of **12** was protected as the methoxymethyl (MOM) ether to afford **13**. Selective deprotection of the acetonide group of **13** with 60% AcOH gave diol **14**. Silylation of the primary hydroxyl group of **14** with *t*-butyldimethylchlorosilane (TBSCl), Et_3N, and 4-dimethylaminopyridine (DMAP) afforded **15**. Successive treatment with methanesulfonyl chloride (MsCl), tetrabutylammonium fluoride (TBAF) furnished terminal epoxide **16**. Alkynylation with lithium acetylide, an ethylene diamine complex, afforded alkyne **17**. Protection of the secondary hydroxyl group gave the THF moiety **7a**.

As shown in Scheme 3, γ-lactone **19** was constructed as we had reported earlier starting from **18**.[6] Oxidation with *m*CPBA followed by thermal elimination afforded the γ-lactone moiety **8**.

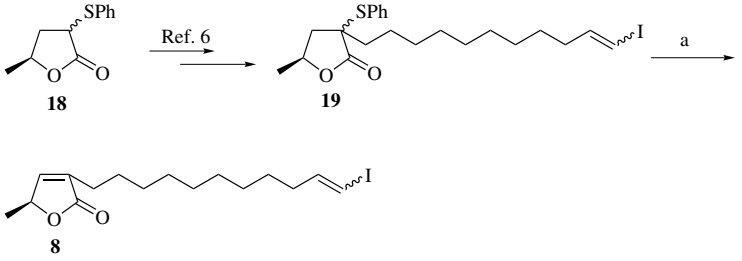
Both segments were coupled by the Sonogashira cross-coupling[10] reaction. The most effective catalyst system in this reaction is 5 mol% of $Cl_2Pd(PPh_3)_2$, 10 mol% of CuI in Et_3N to furnish cross-coupled product **20** in 85% yield. Diimide reduction[11] with *p*-$TsNHNH_2$ and NaOAc in ethylene glycol diethyl ether under reflux afforded saturated product **21**. When ethylene glycol dimethyl ether was used in this reaction, the reduction did not proceed smoothly. Finally, deprotection of MOM ethers with $BF_3{\cdot}Et_2O$ afforded candidate **1a**.[12] On the other hand, the other candidate **1b** was synthesized from **7b** using the same procedure as that employed for **1a** (Scheme 4).

The spectral data (^{1}H NMR, ^{13}C NMR, EIMS) of the synthetic **1a** and **1b** were in good agreement with those reported for natural **1**.[3] This indicates that the relative stereochemistry of natural **1** is *erythro-trans-threo* as reported by Figadère et al.[3] The two synthetic samples (**1a**, **1b**) could not be differentiated by the spectral data (^{1}H NMR, ^{13}C NMR, MS). On the other hand, their optical rotations showed different values. The specific rotation of synthetic **1a** ($[\alpha]_D^{30}$ +9.68°, *c* 1.00, $CHCl_3$) is lower than the reported value of natural occurring reticulatain −1[3] ($[\alpha]_D$ +22°, *c* 1, $CHCl_3$). On the other hand, that of **1b** ($[\alpha]_D^{27}$ +2.34°, *c* 1.00, $CHCl_3$) showed a very small value.[13] Judging from the specific optical rotations of **1a** and **1b**, it is difficult to determine the absolute configuration of natural reticulatain-1.[2e,14] We also prepared the corresponding bis-(*R*)-MTPA esters from synthetic **1a** and **1b**. The chemical shifts of H-17, H-18, H-21, and H-22 of both **1a** and **1b** showed a clear difference and they were in good agreement with those of the methine protons of Fujimoto's stereochemically defined model compounds (Fig. 2, Table 2).[15]

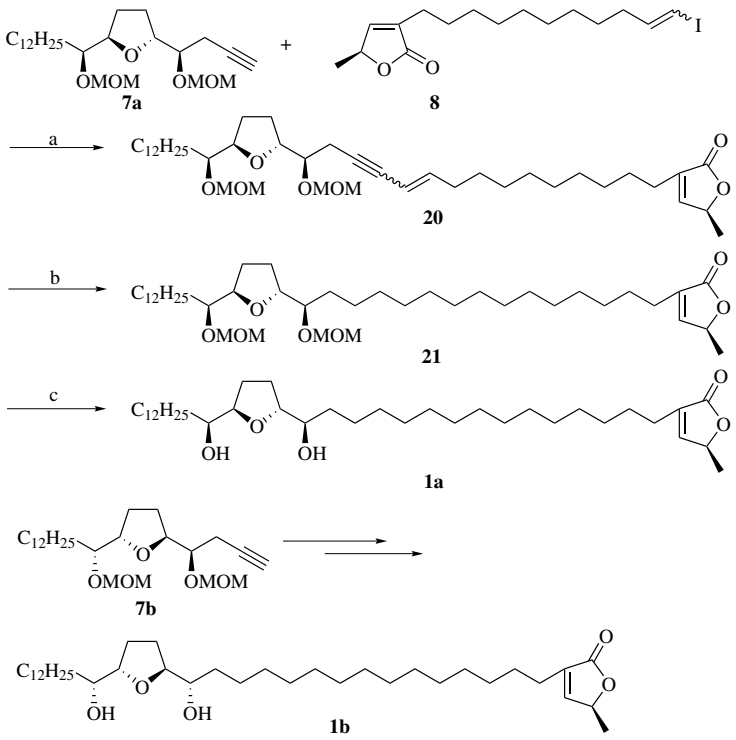
This indicates that if the bis-(*R*)-MTPA ester of natural **1** is available, the absolute configuration of reticulatain-1 will be definitely established.

Compounds **1a** and **1b** were tested as inhibitors of bovine-heart mitochondrial complex I. Both compounds exhibited almost the same activity (**1a**: $IC_{50} = 16$ nM, **1b**: $IC_{50} = 17$ nM). This observation is in agreement with the results reported by Miyoshi et al., who found that the stereochemistry around the THF rings was of minor importance.[16] Compared to the most potent acetogenin like bullatacin (IC_{50} 0.8 nM), the activity is much weaker. One reason is that the spacer moiety between the THF ring and the γ-lactone moiety (about 15 carbon atoms) is longer than the optimal length of the spacer (about 13 carbon atoms).[17] Another reason is the length of the tail that links the THF ring. Compounds **1a** and **1b** possess 13 carbon atoms while bullatacin has 11 carbon atoms. As Miyoshi et al. reported,[16] increase in hydrophobicity of the tail has a rather adverse effect on the activity due to some sort of trapping in the hydrophobic lipid bilayer of the mitochondria membrane. This would weaken the inhibition of mitochondrial complex I.

In conclusion, we have achieved total synthesis of two possible diastereomers of reticulatain-1 from building block **6**. On the basis of the present data, it is difficult to



Scheme 3. Synthesis of the γ-lactone part of **1a**. Reagents: (a) *m*CPBA, toluene, reflux (78%).



Scheme 4. Synthesis of **1a**. Reagents: (a) 5 mol% $Cl_2Pd(PPh_3)_2$, 10 mol% CuI, Et_3N (85%); (b) *p*-$TsNHNH_2$, NaOAc, ethylene glycol diethyl ether (61%); (c) $BF_3{\cdot}Et_2O$, DMS (87%).

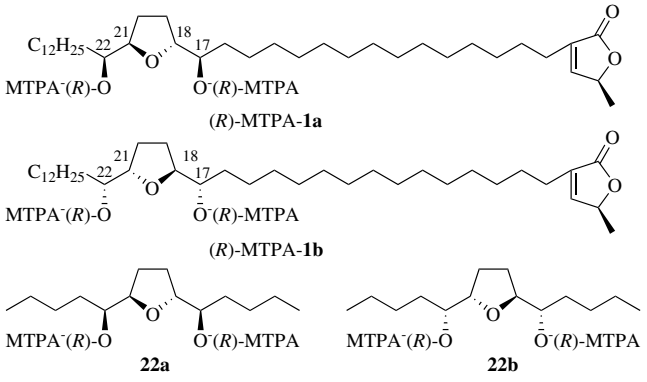


Figure 2. Bis-(*R*)-MTPA esters of **1a**, **1b**, and Fujimoto's model compounds **22a** and **22b**.

Table 2. ^1H NMR chemical shifts of the bis-(*R*)-MTPA esters of **1a** and **1b**

MTPA ester	17-H	18-H	21-H	22-H
(*R*)-MTPA-**1a**	4.98	3.76	3.98	5.26
22a	4.98	3.77	3.98	5.27
(*R*)-MTPA-**1b**	5.02	3.93	3.93	5.22
22b	5.03	3.94	3.94	5.22

determine the absolute configuration of natural reticulatain-1. The ^1H NMR chemical shifts of bis-(*R*)-MTPA esters of **1a** and **1b** showed a clear difference. This indicates that if the bis-(*R*)-MTPA ester of natural **1** is available, the absolute configuration of reticulatain-1 will be determined. Inhibitory action of these compounds was examined with bovine heart mitochondrial complex I. Both compounds showed almost the same activity.

Acknowledgements

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13. The data for **1b**: mp 87–90 °C, $[\alpha]_D^{28}$ +2.34° (*c* 1.00, $CHCl_3$). The IR, ^1H NMR, ^{13}C NMR, HREIMS data were identified with those of **1a**.
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