Pergamon

Tetrahedron Letters, Vol. 38, No. 26, pp. 4627-4630, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00992-1

Enantioselective Synthesis of (3*R*,6*S*,7*R*,18*R*,19*S*)-, (3*R*,6*S*,7*R*,18*R*,19*R*)-, and (3*R*,6*S*,7*R*,18*S*,19*R*)-Quassiols A. A Comment on the Stereochemistry of Natural Quassiol A

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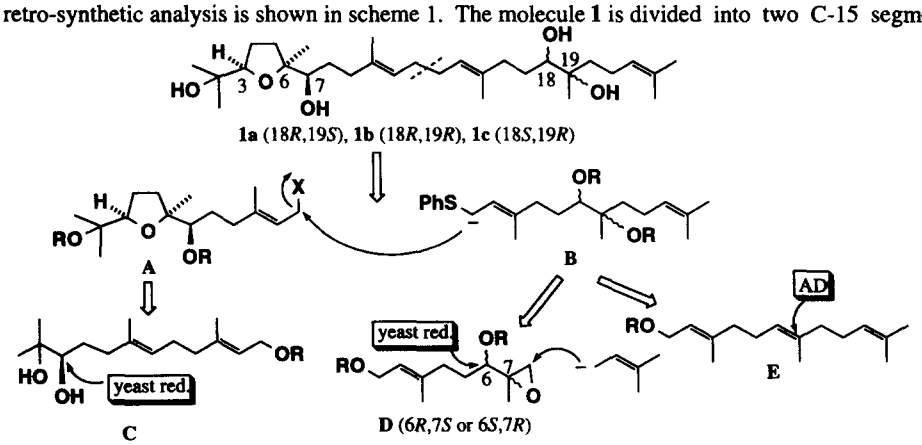
Abstract: (3*R*,6*S*,7*R*,18*R*,19*S*)-, (3*R*,6*S*,7*R*,18*R*,19*R*)-, and (3*R*,6*S*,7*R*,18*S*,19*R*)-Quassiols A were synthesized enantioselectively by using baker's yeast reduction and asymmetric dihydroxylation, but their optical properties were not identical to that of natural quassiol A. Stereostructure of natural quassiol A was proposed.

Quassiol A (**1**) is a triterpene ether isolated together with its 18-monoacetate, quassiol B (**2**), from *Quassia multiflora*.[1] Although the plane structure has been determined on the basis of spectroscopic analyses, its stereostructure including absolute stereochemistry has not yet been clarified except for the relative configuration at C-3, C-6, and C-7 as shown. In order to determine the absolute stereostructure, we synthesized (3*R*,6*S*,7*R*,18*R*,19*S*)-**1a**, (3*R*,6*S*,7*R*,18*R*,19*R*)-**1b**, and (3*R*,6*S*,7*R*,18*S*,19*R*)-**1c**, enantioselectively. Although their optical properties were not consistent with those of natural product, we would like to propose the enantiomer of **1a** for the stereostructure of natural quassiol A.

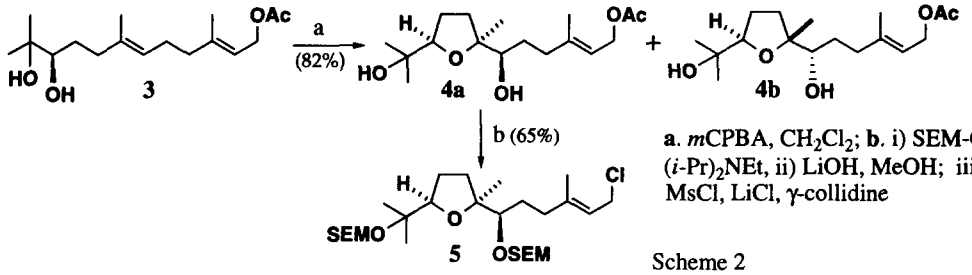
The retro-synthetic analysis is shown in scheme 1. The molecule **1** is divided into two C-15 segments **A**



Scheme 1

and **B** which would be derived from farnesol or geraniol derivatives -**C**, **D**, **E**- in enantioselective manner using baker's yeast reduction[2] and asymmetric dihydroxylation (AD)[3] as the chirality induction method .

The synthesis of left-half segment **A** is illustrated in scheme 2. (10*R*)-10,11-Dihydroxyfarnesyl acetate (**3**) derived from farnesol in high enantiomeric purity[2] was treated with *m*-chloroperbenzoic acid to yield two diastereomeric tetrahydrofuran derivatives **4a** and **4b** in ca. 1 : 1 ratio. The stereochemistry was determined by applying modified Mosher's method[4,5] unequivocally. The less polar (3*R*,6*S*,7*R*)-diol **4a** was then converted in three steps into a chloride **5**.



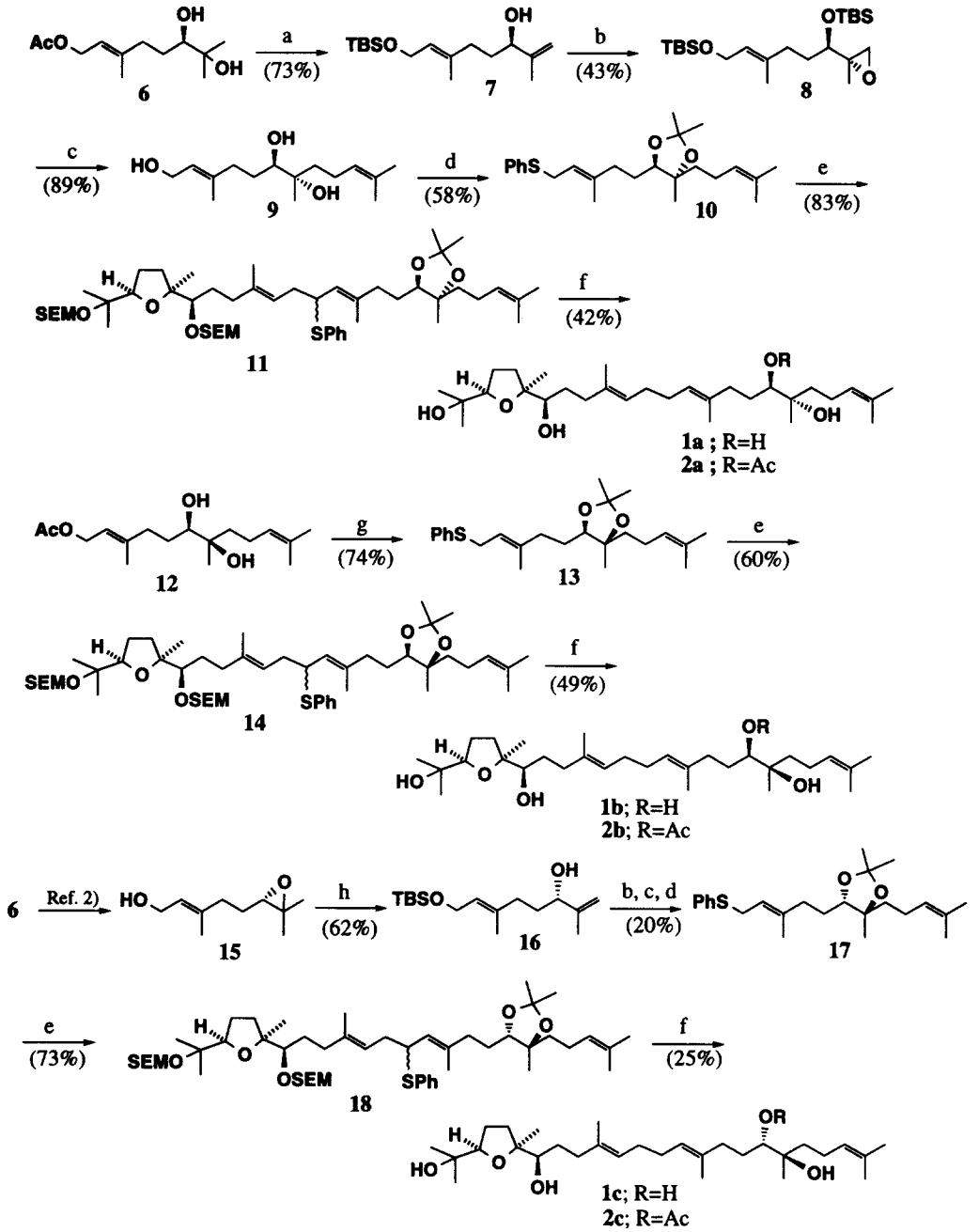
Scheme 2

The right-half segment (6*R*,7*S*)-**B** was synthesized through **D** as follows. The known (*R*)-diol **6**[2] was transformed into the allylic alcohol **7** by acetylation, dehydration, hydrolysis, and selective silylation of primary alcohol. Epoxidation of **7** using Sharpless' method[6] took place stereoselectively to give (*S*)-epoxide **8** as the major product. Thus obtained **8** was reacted with prenyl Grignard reagent in the presence of cuprous iodide to afford the triol **9** in high yield after desilylation. The 1,2-diol part of **9** was protected as an acetonide and the terminal hydroxyl group was converted into phenyl sulfide giving **10**.

Reaction of lithio-anion of **10** with **5** afforded the coupling product **11** in high yield. Desulfurization followed by the purification with $AgNO_3$-impregnated silica-gel chromatography and the hydrolysis of SEM and acetonide protecting groups furnished (3*R*,6*S*,7*R*,18*R*,19*S*)-quassiol A (**1a**) whose ^1H and ^{13}C NMR spectra were indistinguishable from those of natural quassiol A. The optical rotation of **1a** ($[\alpha]_D$ +8.3°) was very close to that of natural quassiol A ($[\alpha]_D$ -9.8°)[1] with opposite sign. However, comparison of the optical rotation of 18-monoacetate disclosed that synthetic **2a** ($[\alpha]_D$ +8.4°) and natural **2** ($[\alpha]_D$ +4.9°)[1] are not enantiomeric each other.

In order to clarify the relative configuration at C-18 and C-19, (6*R*,7*R*)-**13** was prepared from the known diol **12**[7] and reacted with the chloride **5** as described above. Similar desulfurization and deprotection of the coupling product **14** afforded (3*R*,6*S*,7*R*,18*R*,19*R*)-quassiol A (**1b**). The ^1H and ^{13}C NMR spectra of **1b** were apparently different from those of natural quassiol A,[8] which revealed that quassiol A has *anti* 1,2-diol moiety at C-18 and C-19.

Finally, we challenged to the synthesis of (3*R*,6*S*,7*R*,18*S*,19*R*)-quassiol A (**1c**). The (*S*)-epoxide **15**, readily available from **6** was converted to an allylic alcohol **16**, which was then transformed into the sulfide **17** by the same procedure described above. Coupling of **17** with the chloride **5** followed by the similar desulfurization and deprotection gave rise to **1c**. Although the ^1H and ^{13}C NMR spectra of **1c** was again identical to those of natural product, the optical rotations of **1c** ($[\alpha]_D$ +0.9°) and its 18-acetate **2c** ($[\alpha]_D$ +1.1°) were completely



a. i) Ac_2O, Py, ii) $POCl_3$, Py, iii) LiOH, MeOH, iv) TBS-Cl, imidazole; **b**. i) $VO(acac)_2$, *t*-BuOOH, ii) TBS-Cl, imidazole; **c**. i) $Me_2C{=}CHCH_2MgCl$, CuI, ii) *n*-Bu_4NF; **d**. i) DMP, PPTS, ii) MsCl, LiCl, γ-collidine, iii) PhSNa; **e**. *n*-BuLi, DABCO, **5**; **f**. i) Na, *t*-BuOH, ii) SiO_2-5%$AgNO_3$ chromat. iii) TsOH; **g**. i) DMP, PPTS, ii) LiOH, MeOH, iii) MsCl, LiCl, γ-collidine, iv) PhSNa; **h**. i) TBS-Cl, imidazole, ii) Al(*i*-PrO)$_3$, Tol.

Scheme 3

different from those of natural products, **1** and **2**.

Thus, we have synthesized three stereoisomers corresponding to quassiol A and propose the enantiomer of **1a** as the most probable stereostructure of natural quassiol A on the basis of the facts that ^{1}H and ^{13}C NMR spectral data of **1a** as well as the specific rotation are well consistent with those of natural product.[9)]

We are grateful to Prof. W. F. Tinto, University of the West Indies, for various data of quassiol A. This work was supported by a Grant-in-Aid for a Scientific Research (No. 08680642) from the Ministry of Education, Science and Culture of Japan.

References and Notes

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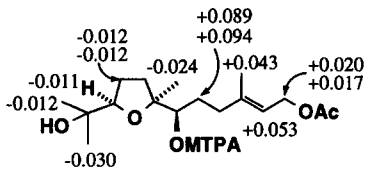
5) $\triangle\delta$ ($=\delta_S - \delta_R$) values of MTPA ester of **4a**:



As the following NMR data reveal, quassiol A has (3*R**,6*S**,7*R**)-configuration.

	1, 25		2	3		4	5	6	7		26	
	^{13}C	^{1}H	^{13}C	^{13}C	^{1}H	^{13}C	^{13}C	^{13}C	^{13}C	^{1}H	^{13}C	^{1}H
4a	25.96	1.11	72.64	85.98	3.80	27.53	33.53	87.17	77.35	3.43	23.01	1.14
	27.01	1.20										
4b	25.21	1.12	72.14	86.65	3.75	27.72	34.88	88.02	76.98	3.38	22.79	1.13
	27.72	1.16										
1	25.93	1.10	72.62	85.87	3.79	27.54	33.29	87.24	77.44	3.44	23.25	1.12
	27.04	1.19										
7-epi **1a**	25.90	1.10	72.68	86.33	3.82	27.55	35.83	86.91	77.83	3.35	25.41	1.11
	27.01	1.20										

6) Rossiter, B. E.; Verhoeven, T. R.; Sharpless, K. B. *Tetrahedron Lett.* **1979**, 4733-4736.

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8) ^{1}H and ^{13}C NMR data of **1**, **1a**, and **1b** around the diol part (in CD_3OD):

	17	18		19	20	29	
	^{13}C	^{13}C	^{1}H	^{13}C	^{13}C	^{13}C	^{1}H
1	30.52	78.13	3.27	75.35	39.37	22.01	1.09
1b	30.75	77.93	3.32	75.58	39.16	22.27	1.10
1a	30.61	78.20	3.28	75.42	39.44	22.05	1.10

9) In the private communication, Prof. Tinto, who has isolated quassiols A and B, agreed with the opinion that the stereostructure of quassiol A is the enantiomer of **1a** after our results have been presented. The reason for the inconsistency of optical rotation between **2** and **2a** is not clear.

(*Received in Japan* 28 *April* 1997; *revised* 14 *May* 1997; *accepted* 16 *May* 1997)