STUDIES ON THE STEREOCHEMISTRY OF THEONEZOLIDES A-C[1]: ELUCIDATION OF THE RELATIVE CONFIGURATIONS OF 1,3-DIOL MOIETIES OF THE C-4 ~ C-17 FRAGMENT

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Abstract- Four model compounds having *syn* and *anti* 1,3-diol type moieties corresponding to C-8/C-10 and C-14/C-16 positions contained in the C-4 ~ C-17 fragment of theonezolides A-C were prepared. Comparison of their spectral data suggested that the 1,3-diol at C-8/C-10 and the OH/OMe groups at C-14/C-16 positions of theonezolides A-C were both *syn*.

Theonezolides A (**1**), B (**2**), and C (**3**) are novel cytotoxic 37-membered macrolides consisting of two principal fatty acid chains isolated from the Okinawan marine sponge *Theonella* sp.,[1,2] which have been revealed to possess unique bioactivity of induction of rabbit platelet shape change and aggregation.[3] Theonezolides A ~ C (**1** ~ **3**) contain 23 chiral centers, among which the absolute configuration of one chiral center at the terminal position bearing a primary amine and secondary methyl groups (C-75, C-73, and C-77 of **1** ~ **3**, respectively) was determined as all *R* on the basis of synthesis of their ozonolysis products.[1] Here we describe our study on the stereochemistry of the theonezolides as to the C-4 ~ C-17 fragment (**4**),[4] which was commonly obtained by ozonolysis of the three macrolides, theonezolides A ~ C (**1** ~ **3**).[1,2] This fragment (**4**) contains 4 chiral centers which comprise two 1,3-diol type moieties (14-OAc/16-OMe and 8-OAc/10-OAc). Their relative configurations were investigated by preparation of four model compounds (**5**/**6** and **7**/**8**) corresponding to *syn* and *anti* diastereomers for the 14-OAc/16-OMe and 8-OAc/10-OAc moieties, respectively. As a result, the two 1,3-diol type moieties were both suggested as *syn* as described below.

Synthesis of the four model compounds (*syn*: **5** and **7**; *anti*: **6** and **8**) began with the diastereoisomeric homoallyl alcohols [**9** (*syn*) and **10** (*anti*)], respectively, which were both prepared from (-)-(*S*)-malic acid by literature procedures.[5] Preparation of the diastereomer (**5**) was outlined in Scheme 1. The secondary hydroxyl group of the *syn* homoallyl alcohol (**9**) was protected as a benzyl ether, and the

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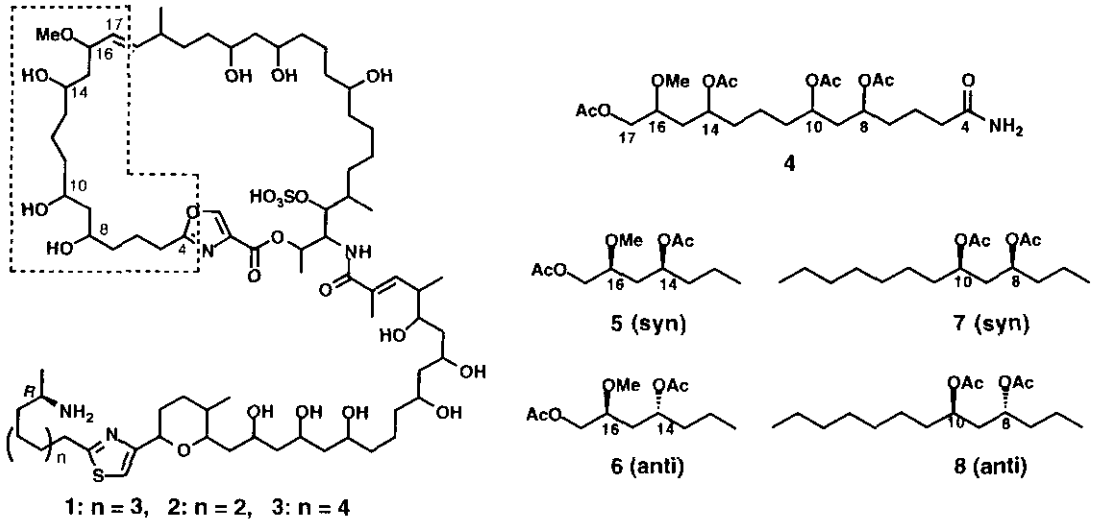
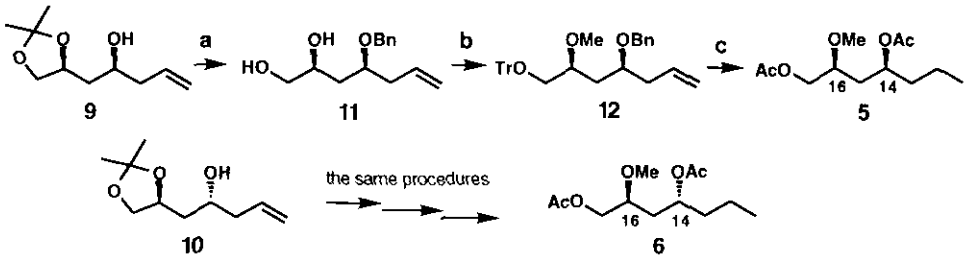
†Dedicated to Dr. Bernhard Witkop on the occasion of his 80th birthday



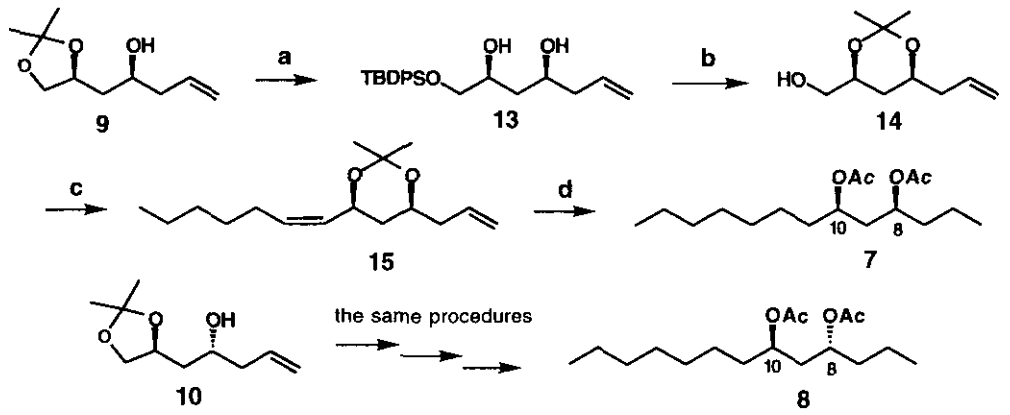
acetonide group was deprotected to give the 1,2-diol (**11**). The primary hydroxyl group of **11** was protected as triphenylmethyl (Tr) group, and the remaining hydroxyl group was then methylated to furnish the methyl ether (**12**). Hydrogenolysis of both benzyl and trityl groups of **12** followed by acetylation afforded the *syn* diastereomer (**5**).[6] The *anti* diastereomer (**6**)[6] was obtained by the same procedures for **5** (Scheme 1), starting from the *anti* homoallyl alcohol (**10**).

The *syn* diacetate (**7**) was prepared as shown in Scheme 2. After removal of the acetonide group of the *syn* homoallyl alcohol (**9**), the primary hydroxyl group was selectively protected as *t*-butyldiphenylsilyl (TBDPS) group to give the 1,3-diol (**13**). Protection of the 1,3-diol group of **13** as isopropylidene ketal followed by desilylation afforded the acetonide (**14**), which was oxidized with pyridinium chlorochromate and the resulting aldehyde was subjected to Wittig reaction with *n*-hexyltriphenylphosphonium bromide to give the *Z*-olefin (**15**) predominantly. Hydrogenation of **15** followed by hydrolysis of the acetonide and acetylation furnished the *syn* diastereomer (**7**).[6] Starting from the *anti* homoallyl alcohol (**10**), the *anti* diacetate (**8**)[6] was also prepared by the same methods as shown in Scheme 2.

Comparisons of the ^{1}H and ^{13}C NMR data of synthetic *syn* and *anti* diastereomers (**5**/**6** and **7**/**8**) with



Scheme 1. (a) 1) BnBr, NaH, *n*-Bu4N^{+}I^{-}, DMF (79%); 2) 3N HCl, THF (99%). (b) 1) Ph3CCl, DMAP, pyridine (64%); 2) MeI, KH, THF (92%). (c) 1) H_2, 20% Pd(OH)2/C, EtOH (66%); 2) Ac_2O, pyridine (85%).



Scheme 2. (a) 1) 3N HCl, THF (80%); 2) *t*-$BuPh_2SiCl$, imidazole, CH_2Cl_2 (53%). (b) 1) $(Me)_2C(OMe)_2$, PPTS, CH_2Cl_2 (72%); 2) 2N NaOH, EtOH (50%). (c) 1) PCC, MS 3Å, CH_2Cl_2 (72%); 2) *n*-BuLi, $Me(CH_2)_5P^+Ph_3Br^-$, THF (32%, 2 steps). (d) 1) H_2, Pd/C (10%), EtOH (84%); 2) 3N HCl, THF (99%); 3) Ac_2O, pyridine (65%).

those of the C-4 ~ C-17 fragment (**4**) derived from the natural specimens were outlined in Tables 1 and 2, which apparently showed that the ^1H and ^{13}C chemical shifts of *syn* diastereomers (**5** and **7**) corresponded to those of **4** quite better than those of *anti* diastereomers (**6** and **8**), as to both of the C-14 ~ C-17 positions and the C-8 ~ C-10 positions, respectively. Particularly, the ^1H NMR signals for

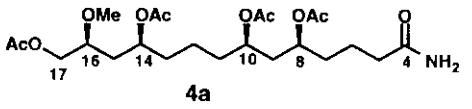
Table 1. Comparison of the ^1H and ^{13}C NMR Data of **4** (natural), **5** (synthetic, *syn*), and **6** (synthetic, *anti*)[4]

position	4	5	6	position	4	5	6
		δ_C				δ_H	
14	70.9	71.0	70.7	14	5.24 m	5.21 m	5.40 m
15	36.4	36.5	37.6	15	1.90 m	1.89 m	1.60 (2H) m
					1.64 m	1.66 m	
16	76.5	76.6	76.0	16	3.40 m	3.38 m	3.34 m
17	64.8	64.8	65.5	17	4.24 dd	4.25 dd	4.17 m
					J = 4.1, 11.8	*J* = 4.0, 11.7	
					4.08 dd	4.07 dd	3.99 m
					J = 5.0, 11.8	*J* = 4.1, 11.5	
OMe	56.8	56.8	57.9	OMe	3.20 s	3.17 s	3.28 s

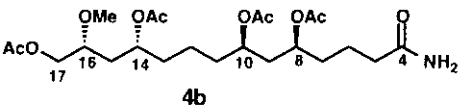
Table 2. Comparison of the ^1H and ^{13}C NMR Data of **4** (natural), **7** (synthetic, *syn*), and **8** (synthetic, *anti*)[4]

position	4	7	8	position	4	7	8
		δ_C				δ_H	
8,10	70.8,70.4	71.2,70.9	69.8,69.5	8,10	5.13 m	5.22 m	5.24 m
9	39.3	39.3	39.1	9	1.90 m	1.90 m	1.80 (2H) m
					1.64 m	1.65 m	

methylene protons located between the two oxymethines were characteristic: the two methylene protons of *syn* diastereomers (**5**) (H_2-15) and (**7**) (H_2-9) were magnetically non-equivalent, while those of *anti* diastereomers (**6**) (H_2-15) and (**8**) (H_2-9) resonated equivalently.[7] The methylene proton signals of **4** (H_2-15 and H_2-9) were both magnetically non-equivalent. Thus, the two 1,3-diol type systems of the C-4 ~ C-17 fragment (**4**), the 14-OAc/16-OMe and 8-OAc/10-OAc moieties, were both suggested as *syn*. Consequently, out of sixteen possibilities, four feasible structures (**4a** and **4b** and their enantiomers) now remain for the C-4 ~ C-17 fragment (**4**) of theonezolides A ~ C (**1** ~ **3**). Further investigation to establish the absolute stereochemistry of **4** is currently in progress by us on the basis of synthesis of **4a** and **4b**.



4a



4b

ACKNOWLEDGMENT.

This work was partly supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports, and Culture of Japan.

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2. J. Kobayashi, K. Kondo, M. Ishibashi, M. R. Wälchli, and T. Nakamura, *J. Am. Chem. Soc.*, 1993, **115**, 6661.
3. M.-C. Rho, Y.-H. Park, M. Sasaki, M. Ishibashi, K. Kondo, J. Kobayashi, and Y. Ohizumi, *Can. J. Physiol. Pharmacol.*, 1996, **74**, 193.
4. The numberings of the carbons of compound (**4**) and other compounds described here corresponded to those of the parent natural product, theonezolide A (**1**).[2]
5. S. Hanessian, A. Ugolini, and M. Therien, *J. Org. Chem.*, 1983, **48**, 4427; P. J. Kocienski, S. D. A. Street, C. Yeates, and S. F. Cambell, *J. Chem. Soc., Perkin Trans. 1*, 1987, 2189.
6. **5**: $[\alpha]_D^{31}$ -12.8° (*c* 1.3, $CHCl_3$); IR (neat) ν_{max} 1740, 1360, and 1240 cm^{-1}; EIMS *m/z* 247 $(M+H)^+$, 215 $(M-OMe)^+$, 187 $(M-CH_3CO_2)^+$, and 173 $(M-CH_3CO_2CH_2)^+$. **6**: $[\alpha]_D^{31}$ -2.9° (*c* 2.0, $CHCl_3$); IR (neat) ν_{max} 1740, 1380, and 1240 cm^{-1}; EIMS *m/z* 247 $(M+H)^+$, 215 $(M-OMe)^+$, 187 $(M-CH_3CO_2)^+$, and 173 $(M-CH_3CO_2CH_2)^+$. **7**: $[\alpha]_D^{27}$ -5.1° (*c* 2.3, $CHCl_3$); IR (neat) ν_{max} 1740, 1370, and 1240 cm^{-1}; FABMS (positive, matrix: 3-nitrobenzyl alcohol) *m/z* 301 $(M+H)^+$. **8**: $[\alpha]_D^{27}$ -4.7° (*c* 3.4, $CHCl_3$); IR (neat) ν_{max} 1740, 1370, and 1240 cm^{-1}; FABMS (positive, matrix: 3-nitrobenzyl alcohol) *m/z* 301 $(M+H)^+$.
7. For related arguments, see: J. S. Mynderse and R. E. Moore, *Phytochemistry*, 1979, **18**, 1181.

Received, 26th December, 1997