

**STUDIES ON THE STEREOCHEMISTRY OF THEONEZOLIDES
A-C¹: ELUCIDATION OF THE RELATIVE CONFIGURATIONS
OF 1,3-DIOL MOIETIES OF THE C-4 ~ C-17 FRAGMENT**

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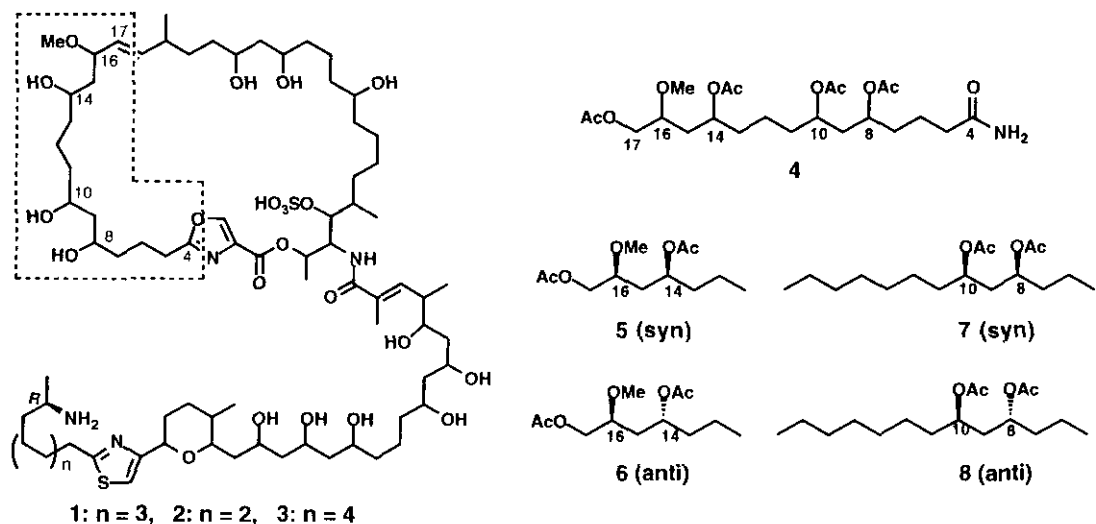
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Abstract- Four model compounds having *syn* and *anti* 1,3-diol type moieties corresponding to C-8/C-10 and C-14/C-16 positions contained in the C-4 ~ C-17 fragment of theonezolidines A-C were prepared. Comparison of their spectral data suggested that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

Theonezolidines 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 Theonezolidines 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 theonezolidines as to the C-4 ~ C-17 fragment (**4**),⁴ which was commonly obtained by ozonolysis of the three macrolides, theonezolidines 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

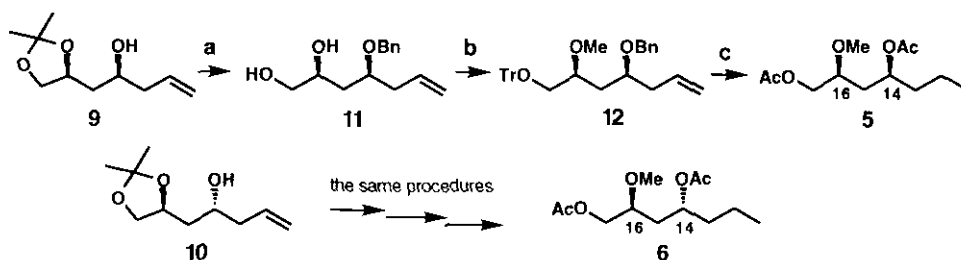
[†]Dedicated to Dr. Bernhard Witkop on the occasion of his 80th birthday



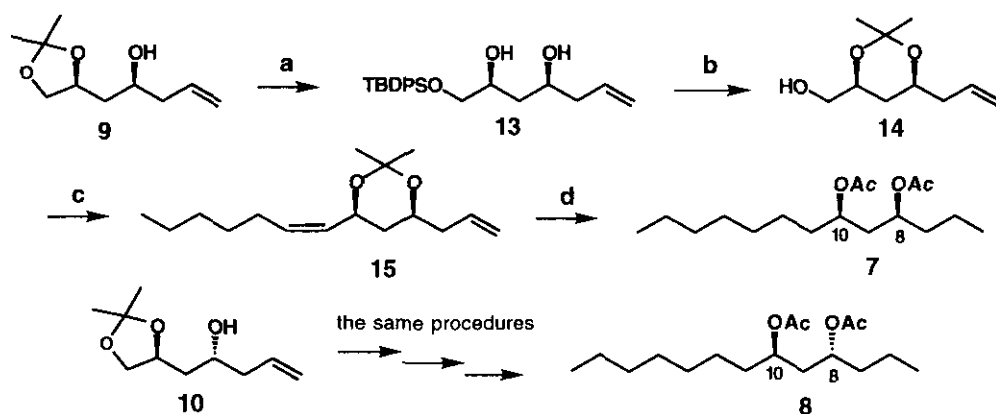
acetone group was deprotected to give the 1,2-diol (**11**). The primary hydroxyl group of **11** was protected as triphenylmethyl (Tr) group, and the remaining hydroxyl group was then methylated to furnish the methyl ether (**12**). Hydrogenolysis of both benzyl and trityl groups of **12** followed 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 acetone 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 acetone (**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 acetone 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 ¹H and ¹³C 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) H₂, 20% Pd(OH)₂/C, EtOH (66%); 2) Ac₂O, pyridine (85%).



Scheme 2. (a) 1) 3N HCl, THF (80%); 2) *t*-BuPh₂SiCl, imidazole, CH₂Cl₂ (53%). (b) 1) (Me)₂C(OMe)₂, PPTS, CH₂Cl₂ (72%); 2) 2N NaOH, EtOH (50%). (c) 1) PCC, MS 3Å, CH₂Cl₂ (72%); 2) *n*-BuLi, Me(CH₂)₅P⁺Ph₃Br⁻, THF (32%, 2 steps). (d) 1) H₂, Pd/C (10%), EtOH (84%); 2) 3N HCl, THF (99%); 3) Ac₂O, 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 ¹³C 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

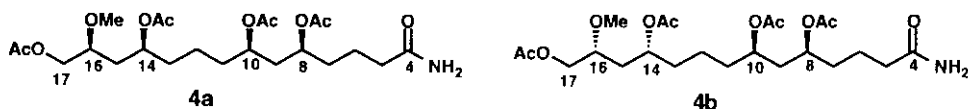
Table 1. Comparison of the ¹H and ¹³C NMR Data of 4 (natural), 5 (synthetic, *syn*), and 6 (synthetic, *anti*)⁴

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
					<i>J</i> = 4.1, 11.8	<i>J</i> = 4.0, 11.7	
					4.08 dd	4.07 dd	3.99 m
					<i>J</i> = 5.0, 11.8	<i>J</i> = 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 ¹³C 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**) (H₂-15) and (**7**) (H₂-9) were magnetically non-equivalent, while those of *anti* diastereomers (**6**) (H₂-15) and (**8**) (H₂-9) resonated equivalently.⁷ The methylene proton signals of **4** (H₂-15 and H₂-9) 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 theonezolidines 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**.



ACKNOWLEDGMENT.

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REFERENCES AND NOTES

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4. The numberings of the carbons of compound (**4**) and other compounds described here corresponded to those of the parent natural product, theonezolidine A (**1**).²
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6. **5**: $[\alpha]_D^{31} -12.8^\circ$ (*c* 1.3, CHCl₃); IR (neat) ν_{\max} 1740, 1360, and 1240 cm⁻¹; EIMS *m/z* 247 (M+H)⁺, 215 (M-OMe)⁺, 187 (M-CH₃CO₂)⁺, and 173 (M-CH₃CO₂CH₂)⁺. **6**: $[\alpha]_D^{31} -2.9^\circ$ (*c* 2.0, CHCl₃); IR (neat) ν_{\max} 1740, 1380, and 1240 cm⁻¹; EIMS *m/z* 247 (M+H)⁺, 215 (M-OMe)⁺, 187 (M-CH₃CO₂)⁺, and 173 (M-CH₃CO₂CH₂)⁺. **7**: $[\alpha]_D^{27} -5.1^\circ$ (*c* 2.3, CHCl₃); IR (neat) ν_{\max} 1740, 1370, and 1240 cm⁻¹; FABMS (positive, matrix: 3-nitrobenzyl alcohol) *m/z* 301 (M+H)⁺. **8**: $[\alpha]_D^{27} -4.7^\circ$ (*c* 3.4, CHCl₃); 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.

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