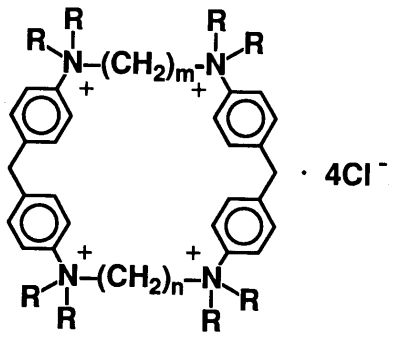
MOLECULAR RECOGNITION AND DISCRIMINATION OF HYDROPHOBIC GUESTS IN WATER BY QUATERNARY AMMONIUM CYCLOPHANES HAVING DIARYLMETHANE UNITS

Kazunori ODASHIMA,[1a] Hajime KAWAKAMI, Atsushi MIWA, Isabelle SASAKI,[1b] and Kenji KOGA*
Faculty of Pharmaceutical Sciences, University of Tokyo, Hongo, Bunkyo-Ku, Tokyo 113, Japan

A series of quaternary ammonium cyclophanes, **2b~e** and **4a~d**, having well-defined hydrophobic cavities rationally designed with diphenylmethane and naphthylphenylmethane units, respectively, were synthesized and fully characterized. A systematic study on the molecular recognition and discrimination properties of these hosts in neutral water was carried out. Whereas host **2** having diphenylmethane units formed inclusion complexes selectively with aromatic guests, host **4** having naphthylphenylmethane units were proved to form inclusion complexes with bulky aliphatic guests that were not complexed by host **2**.

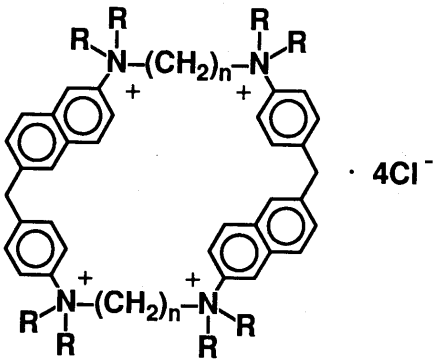
KEYWORDS macrocycle; cyclophane; hydrophobic cavity; host-guest complex; inclusion compound; molecular recognition; structure discrimination; hydrophobic guest

Water-soluble cyclophanes constitute a promising class of totally synthetic hosts having hydrophobic cavities to capture organic guests in water.[2] We have previously reported a series of water-soluble cyclophanes, CPmn (**1a~c,f~i**), having diphenylmethane units as structural components for hydrophobic cavities.[3] The hosts having C_4 or longer bridges (**1b,c,g~i**) showed guest inclusion properties in acidic water with marked selectivity toward aromatic guests.[3c,d,f] Such aromatic selectivity can be rationally explained by the inclusion geometry shown schematically in Fig. 1, based on firm evidence by X-ray crystallography[3a,e] and detailed NMR study.[3b] We have also reported the synthesis of a related host having naphthylphenylmethane units (**3b**) and its quaternary ammonium derivative (**4b**, soluble in water at all pHs), as well as some preliminary results on the guest binding.[3g] In this communication we wish to describe a systematic study on the guest discrimination properties of a series of quaternary ammonium cyclophanes having diphenylmethane or naphthylphenylmethane units with connecting bridges of various lengths (**2b~e**,[4] **4a~d**). The rational design of well-defined hydrophobic cavities by the use of these diarylmethane units has resulted in unique guest discrimination in water.



1 ·4HCl : R = H (CPmn·4HCl)
2 : R = CH_3 (QCPmn)

a: m=n=3 **f: m=3, n=5**
b: m=n=4 **g: m=4, n=5**
c: m=n=5 **h: m=5, n=6**
d: m=n=6 **i: m=5, n=8**
e: m=n=7



3 ·4HCl : R = H
4 : R = CH_3

a: n=3
b: n=4
c: n=5
d: n=6

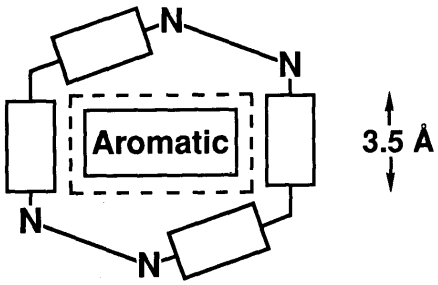


Fig. 1. Schematic Representation of the Hydrophobic Cavity for Aromatic Guests Formed by Host **1** (Protonated Form) Having Diphenylmethane Units (Based on X-Ray Crystallography[3a,e] and NMR Studies[3b])

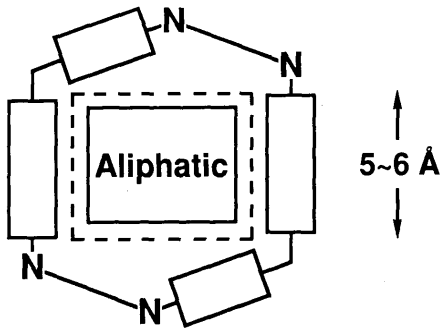


Fig. 2. Design of a Host for Aliphatic Guests by Rigid Extension of the Hydrophobic Cavity with Naphthylphenylmethane Units [3f]

Compounds **2b~e** and **4a~d** were synthesized by *N*-quaternization[5] of the corresponding tetraamines (**1b~e**, **3a~d**),[6] followed by ion exchange ($I^- \rightarrow Cl^-$) and purification by repeated reprecipitation from MeOH/acetone or MeOH/Et_2O. The purity of the quaternized compounds was carefully checked by HPLC.[7] Satisfactory IR and ^1H NMR spectra, and elemental analyses (C, H, N, Cl) were obtained for the air-dried samples[8] that were proved to be pure by HPLC.[7] The chlorides of the quaternary ammonium cyclophanes are highly soluble in water, whereas the corresponding iodides and perchlorates are much less soluble. Complexation in water with hydrophobic guests (**5~10**) by hosts **2** and **4** was examined by ^1H NMR.[9] Host-induced upfield shifts of the guest proton signals were used as probes of the guest inclusion.[3a,b] Stability constants (K_S) of the 1:1 host-guest complexes are listed in TABLE I.[10] The following results show interesting aspects of guest discrimination in water by these hosts.[11]

(1) The formation of inclusion complexes with hydrophobic guests was observed for all of the hosts having C_4 or longer bridges (**2b~e**, **4b~d**), as shown by the large upfield shifts of the guest proton signals (> 1 ppm) expected upon inclusion within the cavities of cyclophanes.[3a,b] On the other hand, inclusion complex formation was negligible for host **4a** having C_3 bridges.[12]

(2) Hosts **2b~e** (QCP44~77) having diphenylmethane units showed marked selectivity toward aromatic guests (**5~7**), whereas inclusion complex formation with aliphatic guests (**8~10**) was negligible.[12] The stability constants of the host-guest complexes by hosts **2b** and **2d** are listed in TABLE I. Thus, the aromatic selectivity, the most important property of host **1**,[3d] was proved to be retained in the corresponding quaternary ammonium hosts.

(3) Among the aromatic guests, host **2b** (QCP44) having the smaller cavity preferred **5** and **6**, whereas **2d** (QCP66) having the larger cavity preferred **7**. This can be explained on the basis of the steric fit between the host and guest. Thus these hosts are capable of discriminating aromatic guests having different structures, as observed for host **1**.[3d]

(4) Hosts **4b~d** (n=4~6), having naphthylphenylmethane units, formed inclusion complexes with bulky aliphatic guests (**8**, **9**) that were not complexed by host **2**. On the other hand, inclusion complex formation with cyclohexanesulfonate (**10**), a smaller aliphatic guest, was negligible for all of the hosts.[12] Furthermore, complexation with aromatic guests by host **4** was generally weaker than that by host **2**. Thus, the inclusion ability for bulky aliphatic guests as well as the inclination toward aliphatic selectivity was observed for the hosts designed to have rigidly extended hydrophobic cavities by the use of naphthylphenylmethane units (Fig. 2).

(5) Of the aliphatic guests, the adamantane derivative (**8**) was most strongly complexed by host **4b** (n = 4) and the camphor derivative (**9**) by host **4c** (n = 5). The observed discrimination of the aliphatic guests can be ascribed to the structural fit between the hydrophobic cavity of the host and the adamantane or camphor moiety of the guest.

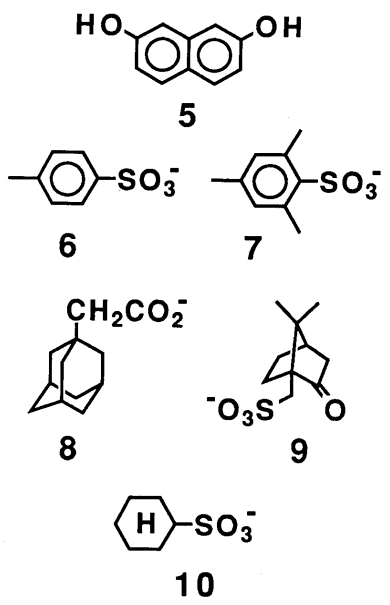
The systematic study described above clearly shows that the inclusion and discrimination of hydrophobic guests in water by quaternary ammonium cyclophanes **2** and **4** are controlled mainly by the proper fit between the hydrophobic cavity of the host and the hydrophobic moiety (aromatic or aliphatic) of the guest. Thus such a mode of molecular recognition, so far studied systematically only with host **1** in acidic water,[3d] has now been firmly extended to neutral pH region by a series of quaternary ammonium hosts **2** and **4**. Consequently, the present study confirmed the effectiveness and versatility of diarylmethane units for rational design and synthesis of hydrophobic cavities of well-defined structure.

TABLE I. Stability Constants of the Host-Guest Complexes with Aromatic and Aliphatic Guests [a]

Guest	**2b** (QCP44)	**2d** (QCP66)	**4b** (n=4)	**4c** (n=5)	**4d** (n=6)
5	1.5×10^3	9.0×10^2	3.3×10^2	2.5×10^2	3.1×10^2
6	3.3×10^3	1.1×10^3	4.7×10^2	1.4×10^3	1.0×10^3
7	9.0×10^2	1.9×10^3	3.3×10^2	2.0×10^3	9.0×10^2
8	*b*)	*b*)	6.0×10^2	4.0×10^2	1.9×10^2
9	*b*)	*b*)	7.5×10^1	3.5×10^2	2.4×10^2

a) K_S [M^{-1}] of the 1:1 complexes in water (D_2O) determined by ^1H NMR at 28 ± 2°C.[11] For guests **6**~**10** sodium salts were used. Although the pD of the sample solutions was not controlled, the guests are estimated to be mainly in the monoanionic form.

b) Negligible formation of inclusion complex.[12]



REFERENCES AND NOTES

1) *a*) Present address: Department of Chemistry, Faculty of Science, Hokkaido University, Sapporo 060, Japan; *b*) JSPS postdoctoral fellow (1987-1988).

2) For reviews, see: *a*) I. Tabushi and K. Yamamura, *Top. Curr. Chem.*, 113, 145 (1983); *b*) Y. Murakami, *ibid.*, 115, 107 (1983); *c*) K. Odashima and K. Koga, "Cyclophanes," Vol. 2, ed. by P. M. Keehn and S. M. Rosenfeld, Academic Press, New York, 1983, Chapter 11; *d*) J. Franke and F. Vögtle, *Top. Curr. Chem.*, 132, 135 (1986); *e*) F. Diederich, *Angew. Chem., Int. Ed. Engl.*, 27, 362 (1988).

3) *a*) K. Odashima, A. Itai, Y. Iitaka, and K. Koga, *J. Am. Chem. Soc.*, 102, 2504 (1980); *idem*, *J. Org. Chem.*, 50, 4478 (1985); *b*) K. Odashima, A. Itai, Y. Iitaka, Y. Arata, and K. Koga, *Tetrahedron Lett.*, 21, 4347 (1980); *c*) T. Soga, K. Odashima, and K. Koga, *ibid.*, 21, 4351 (1980); *d*) K. Odashima, T. Soga, and K. Koga, *ibid.*, 22, 5311(1981); *e*) K. Mori, K. Odashima, A. Itai, Y. Iitaka, and K. Koga, Abstracts of Papers, The 9th International Congress of Heterocyclic Chemistry, Tokyo, Japan, August 1983, p. 130; *idem*, *Heterocycles*, 21, 388 (1984); *f*) I. Takahashi, K. Odashima, and K. Koga, *Tetrahedron Lett.*, 25, 973 (1984); *g*) H. Kawakami, O. Yoshino, K. Odashima, and K. Koga, *Chem. Pharm. Bull.*, 33, 5610 (1985).

4) Although some of these compounds were also reported by others, systematic studies on their molecular recognition and discrimination properties in water have not been examined. See: *a*) J. Winkler, E. Coutouli-Argyropoulou, R. Leppkes, and R. Breslow, *J. Am. Chem. Soc.*, 105, 7198 (1983); *b*) H. J. Schneider and K. Philippi, *Chem. Ber.*, 117, 3056 (1984).

5) Exhaustive *N*-methylation by $CH_3I/(n\text{-}Bu)_3N$ in DMF or DMF-H_2O employing the reported procedure: H. Z. Sommer, H. I. Lipp, and L. L. Jackson, *J. Org. Chem.*, 36, 824 (1971).

6) The tetraamines **1b,c** and **3b** have been reported.[3a,c,g] Tetraamines **1d,e** and **3a,c,d** were synthesized similarly as described for **1b**[3a] and **3b**,[3g] respectively, and fully characterized by IR, ^1H NMR, mass spectra, and elemental analyses (C, H, N). **1d** (CP66), mp 160-162°C (dec.) ($CHCl_3$/MeOH); **1e** (CP77), mp 157-158°C (dec.) (benzene);† **3d**, mp 150-152°C (dec.) (measured in a capillary sealed under argon). Compounds **3a, 3b** and **3c** did not show clear melting points. † The authors are indebted to Mr. Kazuhiko Mori for the synthesis of this compound.

7) On cation exchange column (Radial-Pak SCX (Waters Ltd.)) with 0.6-0.8 M aq Et_3N·HBr containing 45% CH_3CN (v/v) (apparent pH adjusted to 7). Detected at 254 nm.

8) Analytical samples: **2b**(QCP44)·$7H_2O$, mp 177-179°C (dec.); **2c**(QCP55)·$13.5H_2O$, mp 206-207.5°C (dec.); **2d**(QCP66)·$9.5H_2O$, mp 180-181.5°C (dec.); **2e**(QCP77)·$11H_2O$, mp 174-176°C (dec.); **4a**·$5H_2O$, mp 176-178°C (dec.); **4b**·$5H_2O$, mp 165-170°C (dec.); **4c**·$7.5H_2O$, mp 167-169°C (dec.); **4d**·$6H_2O$, mp 164-166°C (dec.). Drying these samples *in vacuo* for a long time caused some decomposition as detected by HPLC.[7] The air-dried samples are nonhygroscopic and hence suited to accurate weighing for the complexation experiments.

9) The complexation experiments were carried out below the critical micelle concentrations (CMC) of the hosts. The CMC values in H_2O (or D_2O) determined by the ring method (surface tension measurement) or the ^1H NMR method are as follows: **2**, $> 1 \times 10^{-1}$ M; **4a**, 1.1×10^{-2} M; **4b**, 1.4×10^{-1} M; **4c**, 1.1×10^{-2} M; **4d**, 3.5×10^{-2} M. The values determined by the both methods were in good agreement.

10) The stability constants were calculated from the host-induced upfield shifts of the guest proton signals (TMS was used as an external standard).[3a,b] The non-linear curve fitting procedure with the least-squares method was applied with the program (DELTA) devised by Dr. Akiko Itai, Faculty of Pharmaceutical Sciences, University of Tokyo.

11) Since some participation of electrostatic interaction was observed in the complexation by host **1**,[3d] comparison of the complex stabilities in the present study was made among the complexes with monoanionic guests (except for guest **5**).

12) Host-induced upfield shifts below the CMC of the host were much smaller (< 0.2 ppm) than expected for the formation of an inclusion complex of moderate stability ($K_S > 50$ M^{-1}).

(Received November 1, 1988)

SYNTHESIS OF (11S)-(+)- AND (11R)-(-)-JALAPINOLIC ACIDS. A REVISION OF CHEMICAL STRUCTURES OF MERREMOSIDES B AND D

Hirotaka SHIBUYA, Keiko KAWASHIMA, Nam In BAEK, Norihiko NARITA, Masayuki YOSHIKAWA, and Isao KITAGAWA*

Faculty of Pharmaceutical Sciences, Osaka University, 1-6, Yamada-oka, Suita, Osaka 565, Japan

(11S)-(+)-Jalapinolic acid (11a) and (11R)-(-)-jalapinolic acid (13a) have been synthesized from cyclododecanone (2) via Sharpless asymmetric epoxidation of an allylic alcohol (6). Since synthetic (11S)-(+)-jalapinolic acid (11a) and natural jalapinolic acid (1) derived from merremosides were found identical in all respects including their specific rotations, the previously proposed chemical structures of merremosides b and d, two resin-glycosides isolated from Merremia mammosa Choisy. (Convolvulaceae), have been revised to 14 and 15 respectively.

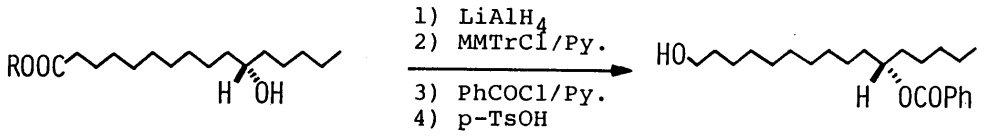
KEYWORDS jalapinolic acid; methyl jalapinolate; Merremia mammosa; Convolvulaceae; resin-glycoside; Sharpless epoxidation; Horeau's method; HPLC optically active; merremoside

Resin-glycosides, which are oligoglycosides of hydroxy-fatty acids, are of current interest in regard to their chemical and biochemical characteristics. Recently, we reported the isolation and chemical structures of two resin-glycosides named merremosides b and d from the tuber of an Indonesian medicinal plant Merremia mammosa Choisy. (Convolvulaceae).[1] In those proposed structures, the absolute configuration at C-11 of jalapinolic acid, the common hydroxy-fatty acid aglycone, appeared to be R according to Horeau's method.[2,3] Since the optical yields in Horeau's esterification were low and the 11R configuration of jalapinolic acid lacked definite proof, we have attempted to determine the C-11 configuration by synthesis. Here we present the synthesis of (11S)-(+)- and (11R)-(-)-jalapinolic acid (11a and 13a) using Sharpless asymmetric epoxidation[4] as the key reaction, and their comparison with natural jalapinolic acid (1) which was obtained by hydrolysis of merremosides b and d.[1]

Baeyer-Villiger oxidation of cyclododecanone (2) followed by methanolysis and subsequent ethoxyethylation (in CH_2Cl_2) afforded an ω-hydroxydodecanoic acid derivative (4) in satisfactory yield. Phenylselenation (in THF) of 4 followed by oxidative elimination (30% H_2O_2, 0°→30°) gave an α,β-unsaturated ester (5) in 63% yield, which was then converted in good yield by reduction with diisobutylaluminum hydride to an allylic alcohol (6).

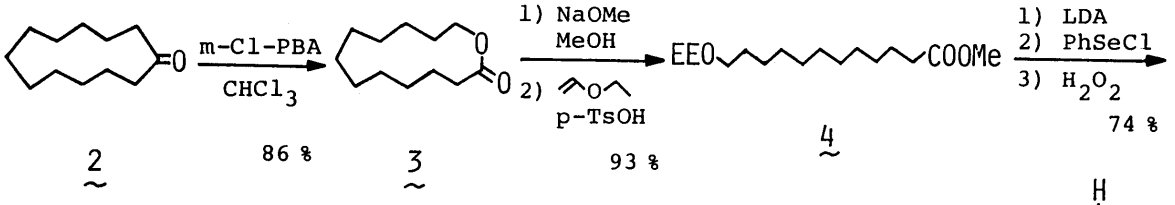
Sharpless epoxidation[4] using diethyl L-(+)-tartrate of the allylic alcohol (6) provided (10S,11S)-epoxide [7a, $[\alpha]_D^{29}$ -18° (c=3.1, $CHCl_3$), e.e. 92%],[5] whereas the epoxidation of 6 using diethyl D-(-)-tartrate gave (10R,11R)-epoxide [8a, $[\alpha]_D^{27}$ +17° (c=2.1, $CHCl_3$), e.e. 92%], in 83% and 82% yields respectively. The enantiomeric excess (e.e.) in each asymmetric epoxidation was determined by ^1H NMR analysis (500 MHz in $CDCl_3$) of the respective acetates (7b and 8b) in the presence of tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium (III).[5]

Among two epoxides, (10S,11S)-epoxide (7a) was converted in 63% yield to (11R)-terminal epoxide (9) by successive treatment with diisobutylaluminum hydride, p-tosyl chloride-pyridine, and alkali (10% NaOMe-MeOH). Grignard reaction of 9 (in THF) followed by benzoylation and acidic hydrolysis (in 95% EtOH) afforded (11S)-diol 11-monobenzoate [10, $[\alpha]_D^{26}$ +1.3° (c=0.8, $CHCl_3$)] in 40% yield. Chromic acid oxidation of 10 followed by diazomethane methylation and methanolysis provided methyl (11S)-(+)-jalapinolate [11b, $[\alpha]_D^{30}$ +0.9° (c=0.7, $CHCl_3$)], which was further converted by treatment with aqueous potassium hydroxide to (11S)-(+)-jalapinolic acid [11a, $[\alpha]_D^{27}$ +0.7° (c=0.9, $CHCl_3$)] in moderate yield.

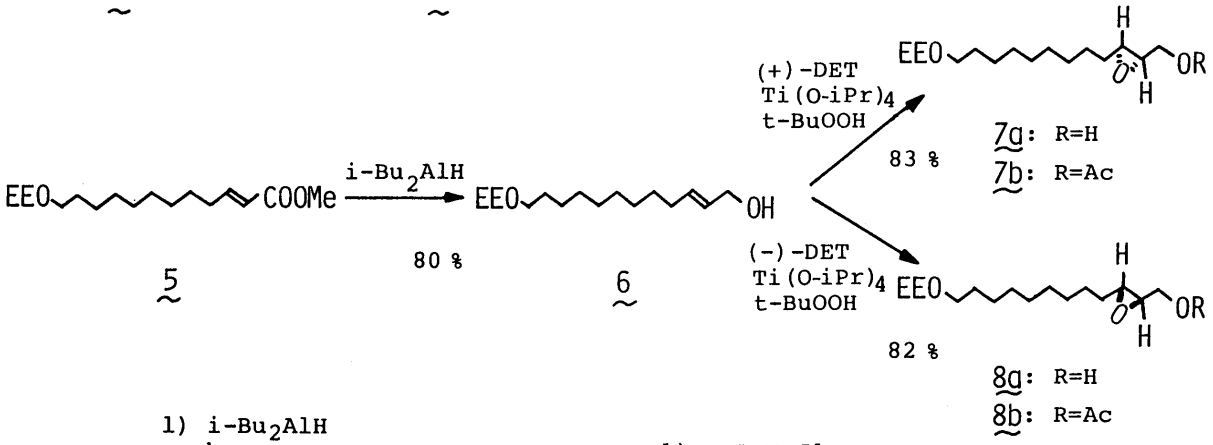


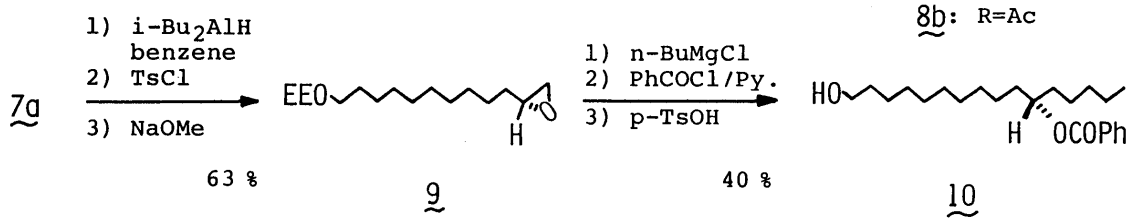
1 : R=H (jalapinolic acid)
1g: R=CH_3

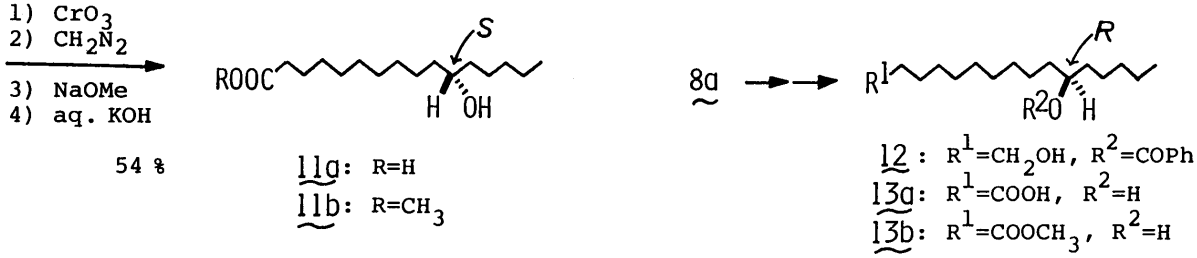
1b

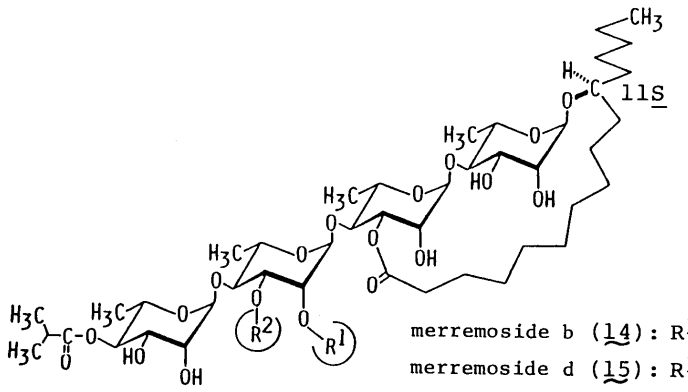


2 — 86 % → 3 — 93 % → 4 — 74 %









merremoside b (14): R^1=$COCH(CH_3)_2$, R^2=H
merremoside d (15): R^1=H, R^2=$COCH(CH_3)_2$

By a similar procedure, (10R,11R)-epoxide (8a) was converted to (11R)-(-)-jalapinolic acid [13a, $[\alpha]_D^{27}$ -0.8° (c=0.9, $CHCl_3$)] via (11R)-diol 11-monobenzoate [12, $[\alpha]_D^{27}$ -1.4° (c=2.5, $CHCl_3$)] and methyl (11R)-(-)-jalapinolate [13b, $[\alpha]_D^{27}$ -0.9° (c=1.7, $CHCl_3$)] in comparably good yields.

Synthetic (11S)-(+)-jalapinolic acid (11a) and natural jalapinolic acid (1) derived from merremosides by hydrolysis were found to be identical with each other by comparison of their physicochemical properties including their specific rotations. In addition, methyl jalapinolate (1a) and diol 11-monobenzoate (1b), which were prepared from natural jalapinolic acid (1), were also found to be identical with synthetic 11b and 10, respectively. Thus, the absolute configuration at C-11 of jalapinolic acid (1) has been defined as S.

Next, we applied Horeau's method to two synthetic methyl esters (11b, 13b) and natural methyl jalapinolate (1a). When the sample was 11b or 1a, the resulting 2-phenylbutanoic acid exhibited a plus sign of specific rotation: $[\alpha]_D^{26}$ +0.13° (c=3.1, benzene) for 11b or $[\alpha]_D^{26}$ +0.18° (c=5.1, benzene) for 1a. In contrast, when 13b was submitted to Horeau's method, the sign of specific rotation of the resulting 2-phenylbutanoic acid was minus: $[\alpha]_D^{26}$ -0.19° (c=3.3, benzene). These results would suggest opposite assignment to the above defined C-11 configuration. But, here again, the optical yield in each esterification was low.

Furthermore, we have found that the 3,5-dinitrophenylcarbamates of methyl (11S)-(+)- and (11R)-(-)-jalapinolates (1a or 11b, and 13b) can be separated by HPLC using chiral adsorbent (SUMIPAX OA-2100, eluting with n-hexane:1,2-dichloroethane:EtOH=100:20:1).

Consequently, the chemical structures of merremosides b and d now should be depicted as 14 and 15, respectively, possessing (11S)-(+)-jalapinolic acid moiety as their aglycone.

Recently, we have elucidated the chemical structures of other merremosides, a, c, e, f, g, h_1, h_2, and their analogous resin-glycosides, named mammosides A, B, H_1, and H_2, which were also isolated from the same plant.[6] The evidence for these structure elucidations will be reported in our forthcoming paper.

REFERENCES AND NOTES

1) I. Kitagawa, H. Shibuya, Y. Yokokawa, N. I. Baek, K. Ohashi, M. Yoshikawa, A. Nitta, and H. Wiriadinata, Chem. Pharm. Bull., 36, 1618 (1988).
2) a) A. Horeau, Tetrahedron Lett., 1961, 506; b) A. Horeau, ibid., 1962, 965.
3) a) Prior to our previous work,[1] the absolute configuration of jalapinolic acid was reported also to be R by application of the Horeau's method.[3b]; b) N. Noda, M. Ono, K. Miyahara, T. Kawasaki, and M. Okabe, Tetrahedron, 43, 3889 (1987).
4) T. Katsuki and K. B. Sharpless, J. Am. Chem. Soc., 102, 5974 (1980).
5) Y. Gao, R. M. Hanson, J. M. Klunder, S. Y. Ko, H. Masamune, and K. B. Sharpless, J. Am. Chem. Soc., 109, 5765 (1987).
6) I. Kitagawa, N. I. Baek, K. Kawashima, K. Ohashi, Y. Yokokawa, H. Shibuya, and M. Yoshikawa, presented at the 30th Symposium on the Chemistry of Natural Products. (Fukuoka, Oct. 1988), Symposium Papers, p. 252.

(Received November 17, 1988)