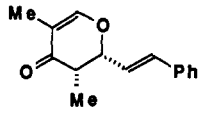
Table I. Asymmetric Hetero-Diels-Alder Reaction of the Diene 2 and Benzaldehyde[a]

entry	chiral ketone[b] (equiv)	(±)-1 (equiv)	% yield[c]	% ee[d,e] (confign)
1	*d*-camphor (0.15)	0.3	80 (17)	22 (2*S*,3*S*)
2	*d*-3-bromocamphor (0.15)	0.3	66 (32)	70 (2*S*,3*S*)
3	(2)	2	62 (19)	61 (2*S*,3*S*)
4	(0.3)	0.3	72 (24)	80 (2*S*,3*S*)
5	(0.6)	0.3	60 (31)	75 (2*S*,3*S*)
6	(0.3)	0.3	84 (12)[f]	68 (2*S*,3*S*)
7	(0.2)	0.2	78 (20)	79 (2*S*,3*S*)
8	(0.1)	0.1	78 (19)	82 (>98)[h] (2*S*,3*S*)
9	*l*-3-bromocamphor (0.1)	0.1	75 (18)[g]	82 (2*R*,3*R*)
10	*d*-3-iodocamphor (0.15)	0.3	70 (28)	13 (2*S*,3*S*)
11	*d*-camphorquinone (0.15)	0.3	75 (21)	22 (2*S*,3*S*)
12	*d*-fenchone (0.15)	0.3	62 (28)	2 (2*S*,3*S*)
13	(−)-pinocamphone (0.15)	0.3	67 (25)	2 (2*S*,3*S*)
14	*l*-menthone (0.15)	0.3	70 (27)[g]	5 (2*R*,3*R*)
15	*l*-*cis*-carvone tribromide (0.15)	0.3	53 (45)	19 (2*S*,3*S*)

[a] Unless otherwise specified, the reaction was carried out in degassed CH_2Cl_2 using 1.05 equiv of the diene 2 per benzaldehyde at −78 °C for 3 h. [b] For the preparation of *d*-3-iodocamphor, *d*-camphorquinone, (−)-pinocamphone, and *l*-*cis*-carvone tribromide, see ref 4-7. Other chiral ketones are commercially available. [c] Isolated yield of the cis adduct 3. The values in parentheses refer to the yields of the trans isomer 4. [d] Optical yield of the major cis isomer 3. [e] Determined by HPLC analysis of the (*R*)-(+)-MTPA ester of the alcohol, which was derived from the cis adduct 3 by 1,4-reduction with L-Selectride followed by reduction of the resulting saturated ketone with $NaBH_4$. [f] Use of toluene as solvent. [g] The enantiomers of 3 and 4 were produced. [h] Optical purity was upgraded by recrystallization from hexane.

Similarly, the hetero-Diels-Alder reaction of *trans*-cinnamaldehyde and the diene 2 with 0.2 equiv each of (±)-1 and *d*-3-bromocamphor in CH_2Cl_2 at −78 °C gave rise to the cis adduct 5 in 72% yield (74% ee; 92% ee after one recrystallization from hexane with 30-40% recovery).[9,10]



5

The present approach represents the uniqueness and synthetic utility of the highly oxygenophilic organoaluminum reagents in asymmetric reactions. Here a chiral ketone plays the role of chemical antagonist toward one enantiomer of racemic organoaluminums. Finally, the concept and execution of the work described herein demonstrates a potential for broader applicability of the in situ generated catalyst via diastereoselective complexation in asymmetric synthesis.

(1) Maruoka, K.; Itoh, T.; Shirasaka, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1988**, *110*, 310.
(2) Maruoka, K.; Hoshino, Y.; Shirasaka, T.; Yamamoto, H. *Tetrahedron Lett.* **1988**, *29*, 3967.
(3) Maruoka, K.; Araki, Y.; Yamamoto, H. *J. Am. Chem. Soc.* **1988**, *110*, 2650.
(4) *d*-3-Iodocamphor: Bruhl, J. W. *Ber.* **1904**, *37*, 2163.
(5) *d*-Camphorquinone: Riley, H. A.; Gray, A. R. *Organic Synthesis*; Wiley: New York, 1943; Collect. Vol. II, p 509.
(6) *l*-*cis*-Carvone tribromide: Wolinsky, J.; Hamsher, J. J.; Hutchins, R. O. *J. Org. Chem.* **1970**, *35*, 207.
(7) (−)-Pinocamphone: Brown, H. C.; Garg, C. P. *J. Am. Chem. Soc.* **1961**, *83*, 2952.
(8) In the recrystallization from hexane, the racemic 3 separated out first as colorless crystals, and concentration of the remaining mother liquor yielded the essentially pure 3 (>98% ee) as colorless solids.
(9) With the optically pure 1 the cis adduct 5 was produced in 90% ee.
(10) The trans isomer of 5 was obtained in 22% yield.

Total Synthesis of Boromycin

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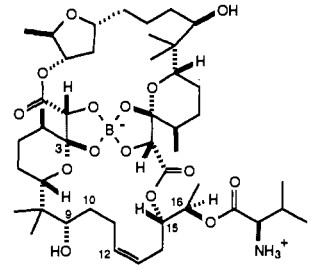
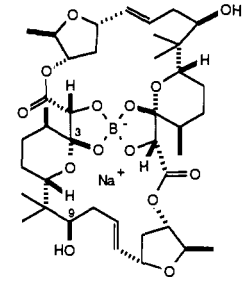
The molecular architecture of boromycin (**1**),[2] with its borate core embedded in a densely functionalized superstructure of oxygen substituents, presents a synthetic challenge that demands careful strategic analysis. Exquisitely designed for its role of encapsulation and transport of alkali metal cations, the structure of **1** differs from that of the symmetrical diolide aplasmomycin (**2**)[3] in two important respects. These are (a) reversal of hydroxyl configuration at C(9) and (b) an open quadrant in the lower right segment [C(12)-C(16)] of **1** that provides a locus for attachment of a D-valinyl ester whose protonated amino group occupies the orifice of the natural cryptand. A progression of synthetic and related studies has laid valuable groundwork for our approach to **1**[4-10]



1



2

and has also culminated in a recent total synthesis of **2**,[11] but significant revision of earlier plans has been necessary to conclude these efforts. We now report the first total synthesis of **1** employing a strategy that elaborates and couples in head-to-tail fashion protected versions of the upper and lower half structures to produce a 34-membered macrocycle. The finale to this sequence is a ring contraction ("double Chan" reaction) based on the rearrangement of an α-acyloxyacetate to an α,β-enediolate[12] and previously exemplified in our synthesis of **2**.[11]

Ortholactone **3**, available from (*R*)-(+)-pulegone,[9] provided the C(3)-C(10) segment common to the two halves of **1** and was

(1) Fellow of the John Simon Guggenheim Memorial Foundation, 1988-1989.
(2) (a) Hütter, R.; Keller-Schierlein, W.; Knusel, F.; Prelog, V.; Rodgers, G. C., Jr.; Suter, P.; Vogel, G.; Voser, W.; Zahner, H. *Helv. Chim. Acta* **1967**, *50*, 1533. (b) Dunitz, J. D.; Hawley, D. M.; Miklos, D.; White, D. N. J.; Berlin, Y.; Marušič, R.; Prelog, V. *Helv. Chim. Acta* **1971**, *54*, 1709. (c) Marsh, W.; Dunitz, J. D.; White, D. N. J. *Helv. Chim. Acta* **1974**, *57*, 10.
(3) (a) Okazaki, T.; Kitahara, T.; Okami, Y. *J. Antibiot.* **1975**, *28*, 176. (b) Okami, Y.; Okazaki, T.; Kitahara, T.; Umezawa, H. *J. Antibiot.* **1976**, *29*, 1019. (c) Nakamura, H.; Iitaka, Y.; Kitahara, T.; Okazaki, T.; Okami, Y. *J. Antibiot.* **1977**, *30*, 714. (d) Sato, K.; Okazaki, T.; Maeda, K.; Okami, Y. *J. Antibiot.* **1978**, *31*, 632.
(4) Avery, M. A.; White, J. D.; Arison, B. H. *Tetrahedron Lett.* **1981**, *22*, 3123.
(5) White, J. D.; Avery, M. A.; Choudhry, S. C.; Dhingra, O. P.; Kang, M.-c.; Whittle, A. J. *J. Am. Chem. Soc.* **1983**, *105*, 6517.
(6) White, J. D.; Kang, M.-c.; Sheldon, B. G. *Tetrahedron Lett.* **1983**, *24*, 4539.
(7) White, J. D.; Choudhry, S. C.; Kang, M.-c. *Tetrahedron Lett.* **1984**, *25*, 3671.
(8) Somers, T. C.; White, J. D.; Lee, J. J.; Keller, P. J.; Chang, C.-j.; Floss, H. G. *J. Org. Chem.* **1986**, *51*, 464.
(9) White, J. D.; Kuo, S.-c.; Vedananda, T. R. *Tetrahedron Lett.* **1987**, *28*, 3061.
(10) For an approach to 1 based on a different strategy, see: (a) Hanessian, S.; Delorme, D.; Tyler, P. C.; Demailly, G.; Chapleur, Y. In *Current Trends in Organic Synthesis*; Nozaki, H., Ed.; Pergamon: New York, 1983; p 205 and references cited therein. (b) Hanessian, S.; Delorme, D.; Tyler, P. C.; Demailly, G.; Chapleur, Y. *Can. J. Chem.* **1983**, *61*, 634.

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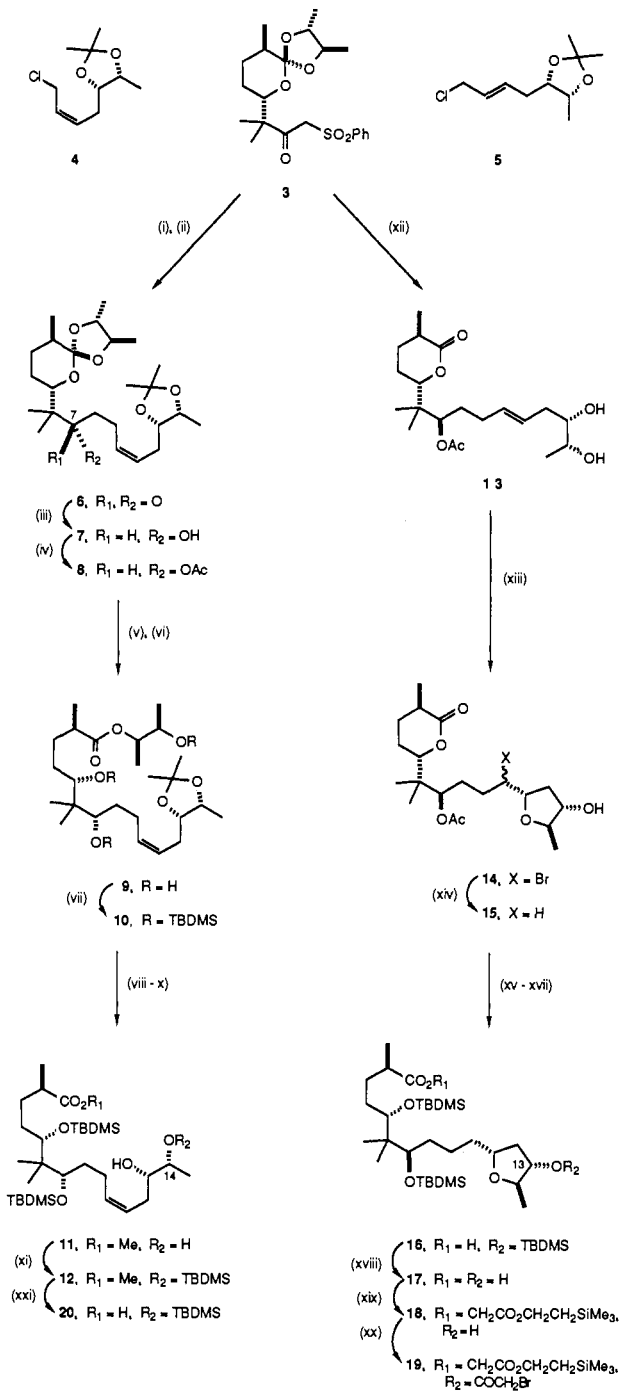
Scheme I[a]

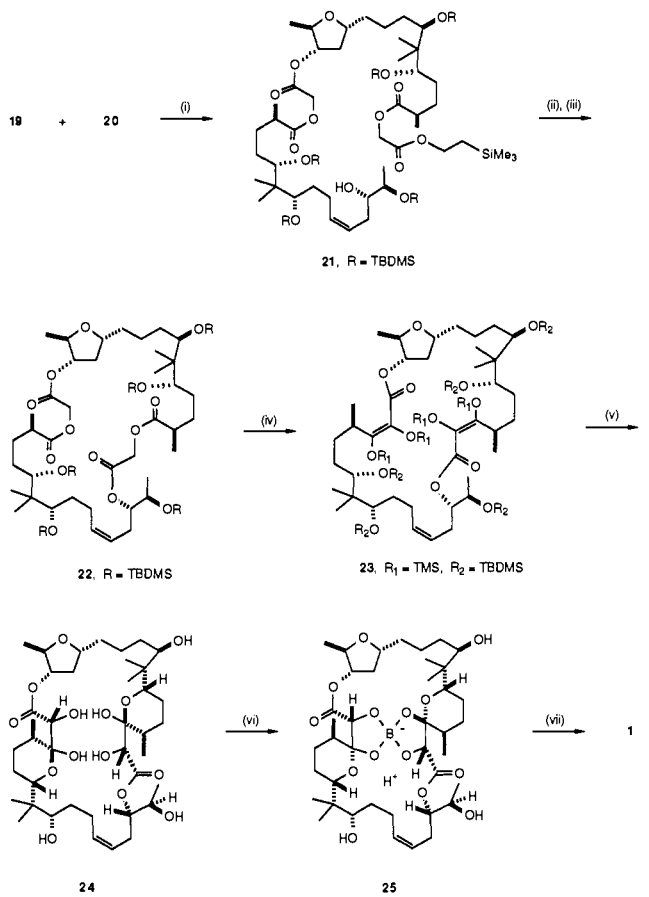


[a] (i) *n*-BuLi, KI, **4**, THF–DMSO, 40 °C, 24 h (97%); (ii) Al/Hg, THF–H_2O (10:1), 75 °C, 1 h (98%); (iii) $LiB[CH(CH_3)C_2H_5]_3H$, THF, 0 °C, 3 h (97%, 7*S*:7*R* 3.5:1); (iv) Ac_2O, Pyr–DMAP–CH_2Cl_2, room temperature, 18 h (96%); (v) $LiAlH_4$, THF, 0 °C, 2 h; (vi) *p*-TsOH, THF–H_2O (4:1), room temperature, 18 h (93% from **7**); (viii) 3 N NaOH, MeOH–THF (1:2), reflux, 18 h; (ix) CH_2N_2, Et_2O, 0 °C, 2 h (80% from **10**); (x) pyridinium *p*-toluenesulfonate, MeOH, reflux, 5 h; (xi) *t*-$BuMe_2SiOTf$, 2,6-lutidine, CH_2Cl_2, −78 °C, 1 h (71%); (xii) ref 11; (xiii) *N*-bromosuccinimide, Et_2O–MeCN (5:1), −110 °C, 4 h (52%); (xiv) *n*-Bu_3SnH, AIBN, C_6H_6, reflux, 2 h (99%); (xv) 10% NaOH, MeOH, room temperature, 24 h; (xvi) *t*-$BuMe_2SiOTf$, 2,6-lutidine, CH_2Cl_2, 0 °C, 3 h; (xvii) *p*-TsOH, hexane–EtOAc (3:1), room temperature, 18 h (78% from **15**); (xviii) *n*Bu_4NF (1 M), THF, room temperature, 3 h (93%); (xix) $BrCH_2CO_2CH_2CH_2SiMe_3$, K_2CO_3, Me_2CO, reflux, 3 h (85%); (xx) $BrCH_2COBr$, Pyr–DMAP, CH_2Cl_2, 0 °C, 0.5 h (97%); (xxi) 3 N NaOH, THF–MeOH (2:1), reflux, 1.5 h (98%).

alkylated in one case with (*Z*)-allylic chloride **4**[6] and in the other with *E* isomer **5**.[7] Although the keto group of **6** was reduced previously with $NaBH_4$ to afford a 2:1 mixture of *R* and *S* alcohols,[7] it was discovered that this ratio could be reversed in favor of the *S* alcohol **7** (3.5:1) when L-Selectride was the reductant.[13] The derived acetate **8** was separated from the unwanted 7*R* epimer, and the latter was returned to **6** for recycling by straightforward reduction ($LiAlH_4$, THF) and oxidation (PCC, CH_2Cl_2). After reduction of **8**, **7** was hydrolyzed to **9**, and this triol was protected as its tris(*tert*-butyldimethylsilyl) ether **10**. Saponification of **10**, followed by acidic hydrolysis of the acetonide and treatment with diazomethane, produced **11** which underwent selective silylation at the more accessible, C(14) hydroxyl substituent. Confirmation of the structure of **12** was obtained by oxidation (PCC, CH_2Cl_2) to a ketone in which the C(14) proton appeared as a quartet (δ 4.17) in the ^1H NMR spectrum.

The upper half structure of **1** was prepared from **13**, available from **3** and **5** by a route that affords the 7*R* acetate with high stereochemical efficiency.[11] Treatment of **13** with *N*-bromosuccinimide effected cyclization[14] to a pair of easily separated

Scheme II[a]



[a] (i) K_2CO_3, Me_2CO, reflux, 2 h (83%); (ii) *n*-Bu_4NF (1 M), THF, −23 °C for 0.5 h, then 0 °C for 20 min; (iii) 2-chloropyridinium methiodide, DMAP, MeCN, room temperature, 45 min (42% from **21**); (iv) $(Me_3Si)_2NLi$, THF, 0 °C, 40 min, then Me_3SiOTf, 0 °C, 20 min; (v) *n*-Bu_4NF, THF, room temperature, 18 h, then 1 N HCl, room temperature, 0.5 h (36% from **22**); (vi) $(MeO)_3B$, MeOH, reflux, 14 h (64%); (vii) ref 5.

(11) White, J. D.; Vedananda, T. R.; Kang, M.-c.; Choudhry, S. C. *J. Am. Chem. Soc.* **1986**, *108*, 8105. For an earlier synthesis of **2**, see: (a) Corey, E. J.; Pan, B.-C.; Hua, D. H.; Deardorff, D. R. *J. Am. Chem. Soc.* **1982**, *104*, 6816. (b) Corey, E. J.; Hua, D. H.; Pan, B.-C.; Seitz, S. P. *J. Am. Chem. Soc.* **1982**, *104*, 6818.

(12) Lee, S. D.; Chan, T. H.; Kwon, K. S. *Tetrahedron Lett.* **1984**, *25*, 3399.

(13) A plausible rationale for this result can be found in complexation of Li^+ with carbonyl and pyran oxygens, so that approach to the si face of the ketone by the sterically demanding reductant is obstructed by the overhanging ortholactone.

(14) Demole, E.; Enggist, P. *Helv. Chim. Acta* **1971**, *54*, 456.

bromo tetrahydrofurans, and the major isomer **14** was reduced with tri-*n*-butylstannane[15] to **15**. Saponification of **15**, followed by exhaustive silylation, furnished **16** which, upon brief exposure to tetra-*n*-butylammonium fluoride, was selectively deblocked at the C(13) silyl ether to yield **17**. Activation of **17** in a form (**19**) suitable for coupling with the lower half of **1** was accomplished by reaction with 2-(trimethylsilyl)ethyl α-bromoacetate,[16] which afforded **18**, and then with α-bromoacetyl bromide. The potassium carboxylate **20** from saponification of **12** condensed smoothly with **19** to produce **21**. Treatment of the latter with fluoride furnished a monohydroxy acid which underwent lactonization[17] to yield the macrocycle **22**.

Contraction of **22** was effected with 2 equiv of base, and entrapment of the intermediate ene diolates with trimethylsilyl triflate afforded in good yield the unstable dilactone **23** (mixture of *E* and *Z* isomers) as a material exhibiting conspicuous fluorescence on TLC. Exhaustive desilylation of **23** with tetra-*n*-butylammonium fluoride, followed by brief exposure to mineral acid, furnished a highly nonpolar heptaol **24** that was found to be identical in spectroscopic properties and chromatographic behavior with material previously obtained by degradation of boromycin.[2c,18] Finally, **24**, upon treatment with anhydrous trimethyl borate in methanol at reflux, afforded **25** ($[\alpha]^{20}_D$ + 88.8°), identical by comparison of ^{1}H and ^{13}C NMR spectra, IR spectra, and optical rotation with a sample of desvalinylboromycin ($[\alpha]^{20}_D$ + 93.9°) obtained (sodium-free) from natural **1**. Since **25** has already been converted to **1** by esterification with BOC-D-val, followed by treatment with trifluoroacetic acid,[4] this sequence constitutes a synthesis of boromycin.

Acknowledgments. We thank Dr. John Hannah, Merck and Co., Rahway, NJ, for generous supplies of boromycin and Thomas Scanlan and Jeffrey Fitzner for experimental assistance. Financial support was provided by the National Institutes of Health (AI 10964). The multinuclear Bruker AM 400 NMR spectrometer was purchased in part through grants from the National Science Foundation (CHE-8216190) and from the M. J. Murdock Charitable Trust to Oregon State University.

Supplementary Material Available: $[\alpha]_D$, IR, ^{1}H NMR, ^{13}C NMR, and analytical data for compounds **6**, **8**, **10**, **12**, **13**, **15**, **16**, **18**, **19**, **21**, **22**, **24**, and **25** (4 pages). Ordering information is given on any current masthead page.

(15) Kuivila, H. G. *Synthesis* **1970**, 499.
(16) Prepared from 2-(trimethylsilyl)ethanol and α-bromoacetyl bromide.
(17) Mukaiyama, T.; Usui, M.; Saigo, K. *Chem. Lett.* **1976**, 49.
(18) Two more polar isomers of **24** were present in minor quantities and are presumed to be C(2) epimers; these also afforded **25** upon treatment with trimethyl borate.

Does the Mechanism of Symmetric Methyl Transfer to Water from Water Differ from That for Transfer to Water from Other Leaving Groups?

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We have measured the rates of acid-catalyzed ^{18}O exchange between L_2O and CH_3OL in H_2O and D_2O (eq 1, L = H or D).

$$L_2O + CH_3{}^{18}OL \xrightarrow[L^+]{k_{ex}^L} L_2{}^{18}O + CH_3OL \qquad (1)$$

The value of k_{ex}^H/k_{ex}^D (1.63 at 140 °C when $[H^+] = [D^+] = 1$ M) is larger than the values of k^H/k^D observed for other S_N2 reactions of L_2O (≲1.3 at much lower temperatures)[1] and could result either from a dynamic solvent effect or from acid/base catalysis.

Table I. Observed Rate Constants and Isotope Effects of 140 °C[a]

$[H^+]^b$	$[MeOH]^b$	$10^5 k_{ex}^{H\,c}$	$[D^+]^b$	$[MeOD]^b$	$(k^H/k^D)/(K_a^H/K_a^D)$
1.024	1.01	6.19	1.021	1.01	1.64
1.050	0.50	6.25	1.013	0.50	1.62
0.503[d]	0.50	3.01	0.499[d]	0.50	1.63

[a] All values in each line are for one pair of reactions (H and D) that were run concurrently. [b] M at ca. 20 °C. At 140 °C, thermal expansion and solvent vaporization combine to reduce these values by ca. 7%. [c] From eq 2; units are s^{-1}. Standard deviations of all k_{ex}^H and k_{ex}^D values, as estimated from the scatter of observed δ values, were ≲1%. [d] $LiClO_4$ added to maintain ionic strength = 1.0 M.

Reactions were run in concurrent pairs (one in H_2O, one in D_2O) in sealed ampoules immersed in an oil bath at 140.0 ± 0.3 °C. The ampoules contained aliquots of solutions of $CH_3{}^{18}OL$ (0.67 atom % ^{18}O)[2] in $H_2O/HClO_4$ and in $D_2O/DClO_4$. Six H_2O and six D_2O ampoules were withdrawn from each pair of reactions during the course of 3 half-times. The CH_3OL in each ampoule was isolated by distillation followed by GC and pyrolyzed to CO,[3,4] and the δ value[5] was measured with a Micromass 602E isotope ratio mass spectrometer. Each k_{ex} was evaluated by least-squares fit of those δs to eq 2, where δ_∞, $(\delta_0 - \delta_\infty)$ and k_{ex} are the fitted parameters.

$$\delta_t - \delta_\infty = (\delta_0 - \delta_\infty)e^{-k_{ex}t} \qquad (2)$$

If the mechanism of this exchange is as usually assumed,[6] prior equilibrium hydron transfer to CH_3OL followed by bimolecular attack by L_2O (eq 3 and 4),

$$L_3O^+ + CH_3OL \overset{(K_a^L)^{-1}}{\rightleftharpoons} L_2O + CH_3OL_2^+ \qquad (3)$$

$$L_2O + CH_3OL_2^+ \xrightarrow{k^L} L_2OCH_3^+ + OL_2 \qquad (4)$$

application of the McKay derivation[7] shows that k_{ex}^L is related to the rate and equilibrium constants in that mechanism by eq 5. The parenthetical sum in eq 5 cancels when the H/D isotope

$$k^L/K_a^L = k_{ex}^L/\{[L^+]([L_2O] + [CH_3OL])\} \qquad (5)$$

effect (IE) on k^L/K_a^L is evaluated from a pair of runs in which $[CH_3OD] = [CH_3OH]$ and $[DClO_4] \approx [HClO_4]$, since the molar volumes of H_2O and D_2O differ by less than 0.1% at 140 °C[8] (eq 6). Observed values of k_{ex}^H and $(k^H/k^D)/(K_a^H/K_a^D)$ are given in Table I.

$$\frac{k^H/k^D}{K_a^H/K_a^D} = \frac{k_{ex}^H[D^+]}{k_{ex}^D[H^+]} \qquad (6)$$

The value of K_a^H/K_a^D is known[9] to be 0.95 ± 0.02 at 25 °C. Assuming its temperature dependence to be purely exponential ($K_a^H/K_a^D = e^{-\delta\Delta H^\circ/RT}$) predicts a value of 0.96$_4$ at 140 °C. Thus the mean of the $(k^H/k^D)/(K_a^H/K_a^D)$ values in Table I (1.63 ± 0.01) corresponds to $k^H/k^D \approx 1.57$ at 140 °C for the rate-determining displacement step (eq 4).

(1) Laughton, P. M.; Robertson, R. E. In *Solute–Solvent Interactions*; Coetzee, J. F., Ritchie, C. D., Eds.; Marcel Dekker: New York, 1969; pp 399–538.
(2) Prepared from $CH_3OSO_2CH_3$ and $H_2{}^{18}O$ (1.5 atom % ^{18}O), dried with Mg, distilled, and diluted with natural abundance CH_3OH.
(3) (a) O'Leary, M. H.; Marlier, J. F. *J. Am. Chem. Soc.* **1979**, *101*, 3300–3306. (b) Marlier, J. F. Ph.D. Thesis, University of Wisconsin-Madison, May 1978.
(4) Borowitz, J. L.; Raviv, A.; Rona, P.; Sadeh, D.; Samuel, D.; Klein, F. S. *J. Labelled Compd.* **1965**, *1*, 259–265.
(5) $\delta = 1000(R/R_{std} - 1)$, where R and R_{std} are the observed $^{12}C^{18}O/(^{12}C^{16}O + {}^{13}C^{16}O)$ ratios in sample and standard.
(6) Dostrovsky, I.; Kleln, F. S. *J. Chem. Soc.* **1955**, 4401–4406.
(7) (a) McKay, H. A. C. *J. Am. Chem. Soc.* **1943**, *65*, 702–706. (b) Espenson, J. H. *Chemical Kinetics and Reaction Mechanisms*; McGraw-Hill: New York, 1981; pp 50–55.

0002-7863/89/1511-0792$01.50/0