(EI): *m/e* 268 (m^+, 0), 250 (2), 156 (37), 139 (34), 135 (29), 57 (100), 43 (28), 41 (38). HRMS: calcd for $C_{16}H_{28}O_3$ (m + H) 269.2117, found 269.2047. $[\alpha]^{27}_{589} = -22.2°$, $c = 0.5$ ($CHCl_3$).

(1*R,2*S**,3*S**)-1-Acetoxy-2,3-epoxycyclohexane (7).** ^1H NMR (300 MHz, $CDCl_3$): δ 1.20–1.38 (m, 1 H), 1.78–1.82 (m, 2 H), 2.07 (s, 3 H), 3.26 (s, 2 H), 5.07–5.12 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.82, 70.80, 54.14, 52.73, 24.32, 22.43, 21.05, 19.26.

(1*R,2*R**,3*R**)-1-Acetoxy-2,3-epoxycyclohexane (8).** ^1H NMR (300 MHz, $CDCl_3$): δ 1.23–1.29 (m, 2 H), 1.41 (m, 1 H), 1.77–1.83 (m, 2 H), 1.95–2.00 (m, 1 H), 2.06 (s, 3 H), 3.03 (d, J = 3.9 Hz, 1 H), 3.19 (s, 1 H), 5.01 (t, J = 6.6 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.42, 21.05, 23.61, 25.72, 52.52, 53.30, 68.02, 170.18.

(1*R,2*S**,6*R**)-2-Acetoxy-6-butylcyclohexanol (7a).** ^1H NMR (300 MHz, $CDCl_3$): δ 0.83–0.89 (m, 6 H), 1.20–1.36 (m, 6 H), 1.44–1.47 (m, 3 H), 1.60–1.70 (m, 2 H), 2.07 (s, 3 H), 3.36 (dd, J = 8.9, 2.7 Hz, 1 H), 5.06 (t, J = 2.7 Hz, 1 H). ^{13}C NMR (74 MHz, $CDCl_3$): δ 14.03, 19.61, 22.58, 22.98, 28.43, 28.85, 31.26, 31.52, 39.29, 73.45, 74.28, 171.30. IR (neat): 3460, 2933, 2859, 1738, 1721, 1247 cm^{-1}. LRMS (EI): *m/e* 214 (m^+, 0), 154 (10), 11 (20), 137 (41), 136 (100), 43 (48).

(1*R,2*S**,3*R**)-2-Acetoxy-3-butylcyclohexanol (7b).** ^1H NMR (300 MHz, $CDCl_3$): δ 0.84 (t, J = 6.6 Hz, 3 H), 0.99–1.04 (m, 2 H), 1.17–1.32 (m, 7 H), 1.39–1.58 (m, 2 H), 1.78–1.86 (m, 3 H), 2.07 (s, 3 H), 3.98 (s, 1 H), 4.61 (dd, J = 10.1, 2.7 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.94, 18.85, 21.11, 22.81, 28.61, 30.78, 31.21, 31.51, 35.45, 68.00, 78.53, 170.65. IR (neat): 3460, 2934, 2860, 1729, 1721, 1244 cm^{-1}. LRMS (EI): *m/e* 214 (m^+, 0), 154 (14), 111 (27), 98 (60), 97 (100), 43 (46).

(1*R,2*R**,6*S**)-2-Acetoxy-6-butylcyclohexanol (8a).** ^1H NMR (300 MHz, $CDCl_3$): δ 0.83–0.89 (m, 3 H), 1.13–1.90 (m, 2 H), 1.23–1.26 (m, 6 H), 1.29–1.36 (m, 2 H), 1.66–1.81 (m, 3 H), 2.05 (s, 3 H), 2.08–2.09 (m, 1 H), 3.17 (dt, J = 9.3, 2.7 Hz, 1 H), 4.52–4.61 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.03, 22.59, 22.98, 28.69, 29.52, 30.21, 31.48, 31.53, 43.06, 76.75, 78.38, 171.46. IR (neat): 3418, 2934, 2861, 1736, 1721, 1458, 1244 cm^{-1}. LRMS (EI): *m/e* 214 (m^+, 0), 154 (6), 111 (13), 97 (100), 70 (18), 43 (35).

(1*R,2*R**,3*S**)-2-Acetoxy-3-butylcyclohexanol (8b).** ^1H NMR (300 MHz, $CDCl_3$): δ 0.82–0.86 (m, 3 H), 1.19–1.44 (m, 11 H), 1.64–1.90 (m, 3 H), 2.09 (s, 3 H), 3.41–3.49 (m, 1 H), 4.46 (dd, J = 9.8, 9.6 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.92, 21.08, 22.78, 23.06, 28.61, 29.71, 31.33, 33.85, 40.89, 73.78, 81.49, 172.33. IR (neat): 3459, 2933, 2859, 1738, 1721, 1376, 1246 cm^{-1}. LRMS (EI): *m/e* 214 (m^+, 0), 170 (15), 127 (25), 96 (100), 81 (35), 43 (50).

Acknowledgment. We thank the National Science Foundation for their generous support of this research.

Supplementary Material Available: ^1H and ^{13}C NMR spectra to indicate the purity of new compounds (32 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Selection of a Sommelet–Hauser or a Stevens Rearrangement Pathway of *N*,*N*-Dimethyl(substituted benzyl)ammonium *N*-Alkylides

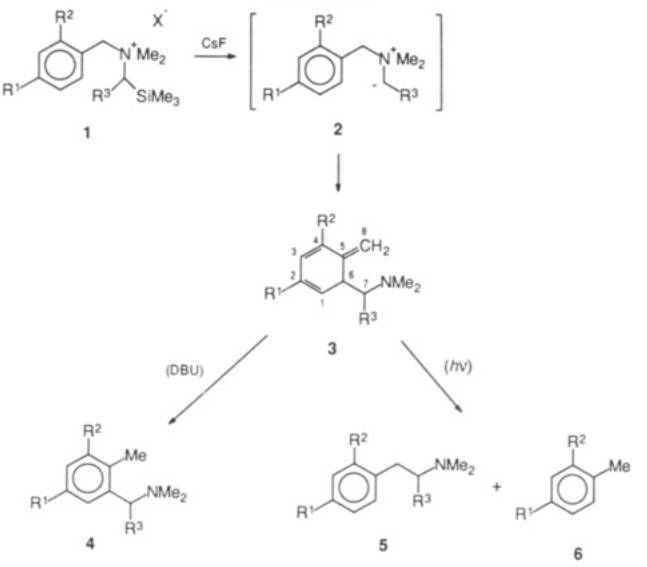
Tetsuya Tanaka, Naohiro Shirai, Junji Sugimori, and Yoshiro Sato*

Faculty of Pharmaceutical Sciences, Nagoya City University, Tanabe-dori, Mizuho-ku, Nagoya 467, Japan

Received April 16, 1992

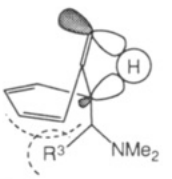
Benzylammonium *N*-ylides isomerize to a Sommelet–Hauser or a Stevens rearrangement product. The Sommelet–Hauser product is produced as a result of a [2,3] sigmatropic rearrangement of the ylide followed by proton migration to restore aromaticity, and the Stevens product has been regarded as a result of a [1,2] shift of the ylide through a caged radical pair intermediate.[1]

Scheme I



We revealed previously, in studies of fluoride ion induced desilylation reaction of *N*,*N*-dimethyl-*N*-[1-(trimethylsilyl)alkyl](substituted benzyl)ammonium halides (**1**), that the Sommelet–Hauser rearrangement products **4** are formed predominantly from the *N*-methylides (**2**, R^3 = H) with an electron-donating or a weak electron-releasing substituent (Hammett para-substituent constant, $\sigma_p < 0.23$), but the Stevens products **5** become predominant with increase of the Hammett σ_p constants ($\sigma_p > 0.6$).[2-4] The *N*-alkylides (**2**, R^3 = alkyl) were converted into **5** and toluenes (**6**), and both compounds were produced via radical-forming and -destroying pathways from 6-(1-aminoalkyl)-5-methylene-1,3-cyclohexadienes (**3**), which were initially formed by a [2,3] sigmatropic rearrangement of **2**.[5]

The conversion of **3** to **4** requires a [1,3] antarafacial migration of a hydrogen at the 6-position of **3** to the *exo*-methylene carbon (C-8) under thermal condition.



When R^3 of **3** is an alkyl group, its steric bulk interferes with the torsion of the molecule, thus allowing the [1,3] proton migration. Therefore, the carbon–carbon bond between C-6 and C-7 may be cleaved homolytically to a radical pair, radical recombination gives **5**, and hydrogen atom abstraction produces **6**.[5] Addition of a strongly basic amine to the reaction could aid the conversion of **3** to **4** by a proton-dissociation and -recombination pathway. Irradiation by UV light could assist the isomerization from **3** to **5** via the radical pathway or a suprafacial [1,3] migration of the aminoalkyl group to the C-8 carbon.[6]

(1) (a) Pine, S. H. *Org. React.* (*N.Y.*) **1970**, *18*, 403. (b) Lepley, A. R.; Giumanini, A. G. In *Mechanism of Molecular Migrations*; Thyagarajan, B. S., Ed.; Wiley-Interscience: New York, 1971; Vol. 3, p 297. (c) Zugrăvescu, I.; Petrovanu, M. *N-Ylid Chemistry*; McGraw-Hill: New York, 1976.
(2) Nakano, M.; Sato, Y. *J. Org. Chem.* **1987**, *52*, 1844.
(3) Shirai, N.; Sato, Y. *J. Org. Chem.* **1988**, *53*, 194.
(4) Shirai, N.; Watanabe, Y.; Sato, Y. *J. Org. Chem.* **1990**, *55*, 2767.
(5) Okazaki, S.; Shirai, N.; Sato, Y. *J. Org. Chem.* **1990**, *55*, 334.

0022-3263/92/1957-5034$03.00/0

Table I. Reaction of *N,N*-Dimethyl-*N*-[1-(trimethylsilyl)ethyl](4-substituted benzyl)ammonium Iodides (1a,b, R^3 = H, R^3 = Me) with CsF

	salt 1		reaction conditions[a]					
entry	no.	R^1	solvent	additive[c]	time (h)	amines 4 + 5 (%)	ratio[b] 4:5	toluenes 6 (%)
1	1a	H	HMPA		16	32[d,e]	8:88	50
2	1a	H	HMPA	DBU	24[f]	65	84:16	1
3	1a	H	HMPA	DABCO	22	28	45:55	12
4	1a	H	DMF		22	39[d,e]	4:92	32
5	1a	H	DMF	DBU	25	59	68:32	1
6	1b	MeO	HMPA		75	53[d]	<1:>99	37
7	1b	MeO	HMPA	DBU	88[f]	71	88:12	
8	1b	MeO	DMF		63	51[d]	1:99	13
9	1b	MeO	DMF	DBU	74[f]	58	30:70	

[a] Reaction was carried out at room temperature. [b] Determined by GLC analyses. [c] Five molar equiv were added. [d] Reference 5. [e] Contained small amounts of *N,N*-dimethyl-1-(4-methylphenyl)ethylamine.[5] [f] Stirred for 0.5 h at 10 °C and then at room temperature.

Table II. Reaction of *N,N*-Dimethyl-*N*-[(trimethylsilyl)methyl](substituted benzyl)ammonium Halides (1c–k, R^3 = H) with CsF in HMPA

	ammonium salt 1									
entry	no.	R^1	R^2	X	additive[a]	temp (°C)	time (h)	yield of 4 + 5 (%)	ratio[b] 4:5	ref
1	1c	MeO	H	I	none	rt	24	(3c, 66)		4
2	1c	MeO	H	I	DBU	rt	5	65	100:0	
3	1c	MeO	H	I	*hν*	rt	5	57	5:95	
4	1d	H	MeO	I	none	rt	25	76	100:0	2
5	1d	H	MeO	I	*hν*	10	5	58	12:88	
6	1e	Me	H	Br	none	rt	25	77	96:4	2
7	1e	Me	H	Br	*hν*	rt	5	80	24:76	
8	1e	Me	H	Br	*hν*	10	5	80	6:94	
9	1f	H	Me	Br	none	rt	25	84	96:4	2
10	1f	H	Me	Br	*hν*	10	5	76	47:53	
11	1g	H	H	Br	none	rt	15	84	97:3	2
12	1g	H	H	Br	*hν*	10	5	83	24:76	
13	1h	Cl	H	Cl	none	rt	23	84	>99:<1	2
14	1h	Cl	H	Br	*hν*	10	5	76	16:84	
15	1i	AcO	H	Br	none	rt	22	72	99:1	2
16	1i	AcO	H	Br	*hν*	10	5	77	12:88	
17	1j	CN	H	Br	none	rt	25	88	81:19	2
18	1j	CN	H	Br	DBU	rt	5	57	93:7	
19	1j	CN	H	Br	*hν*	10	5	77	77:23	
20	1k	NO_2	H	Br	none	rt	5	78	11:89	2
21	1k	NO_2	H	Br	DBU	10	5	75	29:71	

[a] DBU: 5 molar equiv were added. *hν*: Irradiated with a 100-W medium-pressure mercury lamp through the sidewall of a Pyrex flask. [b] Determined from the integrated values of GLC analysis (5% PEG-20M column).

The addition of DBU (5 molar equiv) in the reaction of *N,N*-dimethyl-*N*-[1-(trimethylsilyl)ethyl]benzylammonium iodide (**1a**) and the 4-methoxy-substituted analogue (**1b**) in HMPA apparently increased the yields of **4** with decrease of **6** (compare entry 1 with 2, and 6 with 7 in Table I). However, addition of DABCO in HMPA or DBU in DMF led to only a little improvement (entries 3–5, 8, and 9). No change in the product ratio was observed by the addition of triethylamine or diisopropylethylamine.

Although the reaction of *N,N*-dimethyl-*N*-[(trimethylsilyl)methyl]-4-methoxybenzylammonium iodide (**1c**) with CsF in HMPA gave only 6-[1-(dimethylamino)ethyl]-2-methoxy-5-methylene-1,3-cyclohexadiene[4] (**3c**) (entry 1 in Table II), the product changed to *N,N*-dimethyl-5-methoxy-2-methylbenzylamine (**4c**) in the presence of DBU (entry 2) and changed to *N,N*-dimethyl-2-(4-methoxyphenyl)ethylamine (**5c**) under irradiation with a 100-W medium-pressure mercury lamp (entry 3). In the reaction of a 4-methylbenzylammonium salt (**1e**), the ratio of **4e** to **5e** in HMPA was reversed under UV irradiation at 10 °C, but a mixture of both products was formed at room temperature (compare entries 6–8). UV irradiation at 10 °C of the other reactions caused an apparent increase of the Stevens product **5** (entries 5, 10, 12, 14, 16, and 19). The selectivity for Sommelet–Hauser products was increased by the addition of DBU to the reaction of a 4-cyanobenzylammonium salt (**1j**) (entry 18), but little effect was noted with the 4-nitrobenzyl salt (**1k**) (entry 21).

The stability of the intermediates **3** increases with increasing electron-donating effect of the substituents (R^1 or R^2), with a drop in the temperature, or by change of the solvent from DMF to HMPA.[4,5] The magnitude of the effect of the DBU addition or the UV irradiation was influenced by the stability of **3**.

Experimental Section

All reactions were carried out under a nitrogen atmosphere. HMPA was dried by distillation under reduced pressure from sodium. DMF was distilled under reduced pressure from barium oxide. Cesium fluoride was dried over P_2O_5 at 190 °C under reduced pressure. ^1H NMR spectra were recorded at 270 or 400 MHz. Distillation of the reaction products was performed by using a Büchi Kugelrohr distillation apparatus. All melting and boiling points are uncorrected.

Reaction of *N,N*-Dimethyl-*N*-[1-(trimethylsilyl)ethyl]-(4-substituted benzyl)ammonium Iodides (1a,b) with CsF. General Procedure. Ammonium halide (1, 2 mmol) was placed in a 50-mL flask equipped with a septum and a magnetic stirrer, and a test tube was connected to the flask by a short piece of rubber tubing. CsF (1.5 g, 10 mmol) was placed in the test tube. The apparatus was dried under reduced pressure and flushed with N_2. HMPA or DMF (10 mL) and then DBU (1.5 g, 10 mmol) or DABCO (1.1 g, 10 mmol) were added by syringe through the

(6) Morrison, R. T.; Boyd, R. N. *Organic Chemistry*, 5th ed.; Allyn and Bacon: Boston, 1987; p 1155.

septum. CsF was added from the test tube. The reaction mixture was stirred at room temperature for the time shown in Table I and was then poured into 1.5% $NaHCO_3$ and extracted with ether. The ethereal extract was washed with 1.5% $NaHCO_3$ and then extracted with 10% HCl. The acid extract was made alkaline with NaOH and extracted with ether. The ether layer was dried ($MgSO_4$) and concentrated under reduced pressure. Kugelrohr distillation of the residual oil gave a mixture of *N,N*-dimethyl-1-(2-methylphenyl)ethylamine[4] (**4a**) and *N,N*-dimethyl-1-benzylethylamine[4] (**5a**) or of *N,N*-dimethyl-1-(5-methoxy-2-methylphenyl)ethylamine (**4b**) and *N,N*-dimethyl-1-(4-methoxybenzyl)ethylamine[4] (**5b**). The product ratios were calculated on the basis of the integrated values of the GLC analyses (2-m, 5% PEG-20M column). The yields and ratios are shown in Table I.

The ether layers remaining after extraction with 10% HCl were analyzed by GLC (5% silicone SE-30) which indicated the presence of toluene (**6a**) or 4-methoxytoluene (**6b**). The yield of **6** is calculated by comparison of the integrated values of GLC with the internal standard (propylbenzene).

***N,N*-Dimethyl-1-(5-methoxy-2-methylphenyl)ethylamine (4b)**: bp 100 °C (5 Torr); ^1H NMR ($CDCl_3$) δ 1.29 (d, 3 H, J = 7 Hz), 2.22 (s, 6 H), 2.28 (s, 3 H), 3.34 (q, 1 H, J = 7 Hz), 3.78 (s, 3 H), 6.66 (dd, 1 H, J = 9, 2 Hz), 7.00 (m, 2 H). Anal. Calcd for $C_{12}H_{19}NO$: C, 74.57; H, 9.91; N, 7.25. Found: C, 74.52; H, 9.98; N, 7.25.

***N,N*-Dimethyl-*N*-[(trimethylsilyl)methyl]-2-methoxybenzylammonium Iodide (1d).** A solution of 2-methoxybenzoyl chloride (8.8 g, 52 mmol) in benzene (150 mL) was added to a stirred mixture of methyl[(trimethylsilyl)methyl]amine (6.1 g, 52 mmol) and 10% NaOH (60 mL) at room temperature, and stirring was continued for 30 min. The mixture was poured into water and extracted with ether. The ethereal extract was washed with water, dried ($MgSO_4$), concentrated, and distilled to give *N*-methyl-*N*-[(trimethylsilyl)methyl]-2-methoxybenzamide (10.9 g, 84%): bp 105–106 °C (0.09 Torr); IR (film) 1630 cm^{-1}; ^1H NMR ($CDCl_3$, 55 °C) δ 0.17 (s, 9 H), 2.84 (s, 3 H), 3.09 (bs, 2 H), 3.82 (s, 3 H), 6.89 (d, 1 H, J = 8.3 Hz), 6.97 (t, 1 H, J = 7.6 Hz), 7.22 (dd, 1 H, J = 7.6, 1.7 Hz), 7.32 (ddd, 1 H, J = 8.3, 7.6, 1.7 Hz). Anal. Calcd for $C_{13}H_{21}NO_2Si$: C, 62.11; H, 8.42; N, 5.57. Found: C, 62.05; H, 8.47; N, 5.35.

A mixture of *N*-methyl-*N*-[(trimethylsilyl)methyl]-2-methoxybenzamide (10.0 g, 40 mmol) and $LiAlH_4$ (1.5 g, 40 mmol) in ether (65 mL) was heated at reflux for 2 h. The mixture was quenched with AcOEt (60 mL), poured into 10% NaOH, and extracted with ether. The ethereal extract was dried ($MgSO_4$), concentrated, and distilled to give *N*-methyl-*N*-[(trimethylsilyl)methyl]-2-methoxybenzylamine (9.0 g, 81%): bp 128–129 °C (8 Torr); IR (film) 1245, 850 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.09 (s, 9 H), 1.98 (s, 2 H), 2.21 (s, 3 H), 3.47 (s, 2 H), 3.82 (s, 3 H), 6.85 (dd, 1 H, J = 7.6, 1.0 Hz), 6.93 (td, 1 H, J = 7.6, 1.0 Hz), 7.21 (td, 1 H, J = 7.6, 1.7 Hz), 7.36 (dd, 1 H, J = 7.6, 1.7 Hz). Anal. Calcd for $C_{13}H_{23}NOSi$: C, 65.77; H, 9.76; N, 5.90. Found: C, 65.74; H, 9.71; N, 5.68.

A solution of *N*-methyl-*N*-[(trimethylsilyl)methyl]-2-methoxybenzylamine (6.2 g, 26 mmol) and iodomethane (29.5 g, 208 mmol) in MeCN (80 mL) was heated at 60 °C for 1.5 h. The solvent was evaporated, and the residue was recrystallized from a mixture of AcOEt and MeOH to give **1d** (9.6 g, 97%): mp 158–159 °C; ^1H NMR ($CDCl_3$) δ 0.36 (s, 9 H), 3.28 (s, 6 H), 3.55 (s, 2 H), 3.91 (s, 3 H), 4.88 (s, 2 H), 7.00 (d, 1 H, J = 7.6 Hz), 7.07 (t, 1 H, J = 7.6 Hz), 7.49 (td, 1 H, J = 7.6, 1.3 Hz), 7.76 (dd, 1 H, J = 7.6, 1.3 Hz). Anal. Calcd for $C_{14}H_{26}NOSi$: C, 44.33; H, 6.91; N, 3.69. Found: C, 44.15; H, 7.21; N, 3.50.

***N,N*-Dimethyl-*N*-[(trimethylsilyl)methyl]-4-nitrobenzylammonium Bromide (1k).** A mixture of 4-nitrobenzyl bromide (1.06 g, 4.9 mmol), [(dimethylamino)methyl]trimethylsilane (0.67 g, 5.1 mmol), and acetone (10 mL) was heated at reflux for 2 h. The precipitated crystals were filtered, washed with ether, and dried to give **1k** (1.65 g, 97%): mp 196–198 °C; ^1H NMR ($CDCl_3$) δ 0.30 (s, 9 H), 3.34 (s, 2 H), 3.38 (s, 6 H), 5.46 (s, 2 H), 8.04 (d, 2 H, J = 8.7 Hz), 8.28 (d, 2 H, J = 8.7 Hz). Anal. Calcd for $C_{13}H_{23}N_2BrO_2Si$: C, 44.96; H, 6.67; N, 8.01. Found: C, 44.60; H, 6.49; N, 7.62.

Reaction of *N,N*-Dimethyl-*N*-[(trimethylsilyl)methyl]-(substituted benzyl)ammonium Halides (1c–k) with CsF. General Procedure. In a manner similar to that described for **1a,b**, an ammonium halide (2 mmol) and CsF (1.52 g, 10 mmol) were placed in a 30-mL Pyrex flask. HMPA (10 mL) was added into the flask. DBU (1.5 g, 10 mmol) was added or UV light was irradiated with a 100-W medium-pressure mercury lamp. CsF was added from the test tube, and the mixture was stirred under the conditions listed in Table II. The reaction mixture was poured into 1% $NaHCO_3$ (200 mL) and extracted with ether. The ethereal extract was washed with 1% $NaHCO_3$, dried ($MgSO_4$), and concentrated. Kugelrohr distillation of the residual oil gave a mixture of **4** and **5**. The ratio was determined from the GLC integrals.

Acknowledgment. This work was supported by a Grant-in-Aid for Scientific Research (No. 04671301) provided by the Ministry of Education, Science, and Culture, Japan.

Highly Practical, Enantiospecific Synthesis of the Cyclohexyl Fragment of the Immunosuppressant FK-506

Hiyoshizo Kotsuki,* Hideyuki Nishikawa, Yumi Mori, and Masamitsu Ochi

Department of Chemistry, Faculty of Science, Kochi University, Akebono-cho, Kochi 780, Japan

Received April 17, 1992

In light of the increasing importance of immunosuppressive agents in clinical transplantation, the well-known FK-506, isolated from *Streptomyces tsukubaensis* (No. 9993) by Fujisawa's group,[1] has received considerable attention from synthetic as well as medicinal chemists.[2] Although the total synthesis of FK-506 has been completed by groups at Merck and Harvard,[3] efforts to develop efficient strategies for the preparation of this remarkably bioactive compound and its segments continue.[4] The cyclohexyl C28–C34 fragment of FK-506 is also a component of the related immunosuppressant rapamycin (C39–C45 fragment),[5] and the essential role of this structural unit in biological actions has recently been explored.[6] Therefore, **10** and **11** as moderately-substituted synthons of this fragment have proven to be particularly attractive targets. Several approaches, including racemic and asymmetric syntheses, have been achieved to date.[7] In this

(1) Kino, T.; Hatanaka, H.; Hashimoto, M.; Nishiyama, M.; Goto, T.; Okuhara, M.; Kohsaka, M.; Aoki, H.; Imanaka, H. *J. Antibiot.* **1987**, *40*, 1249. Tanaka, H.; Kuroda, A.; Marusawa, H.; Hatanaka, H.; Kino, T.; Goto, T.; Hashimoto, M.; Taga, T. *J. Am. Chem. Soc.* **1987**, *109*, 5031.

(2) Schreiber, S. L. *Science* **1991**, *251*, 283. Kessler, H.; Mierke, D. F.; Donald, D.; Furber, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 954. Schreiber, S. L.; Liu, J.; Albers, M. W.; Rosen, M. K.; Standaert, R. F.; Wandless, T. J.; Somers, P. K. *Tetrahedron* **1992**, *48*, 2545. See also: Pranata, J.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1991**, *113*, 9483.

(3) Jones, T. K.; Mills, S. G.; Reamer, R. A.; Askin, D.; Desmond, R.; Volante, R. P.; Shinkai, I. *J. Am. Chem. Soc.* **1989**, *111*, 1157. Nakatsuka, M.; Ragan, J. A.; Sammakia, T.; Smith, D. B.; Uehling, D. E.; Schreiber, S. L. *Ibid.* **1990**, *112*, 5583.

(4) Maier, M. E.; Schöffling, B. *Tetrahedron Lett.* **1991**, *32*, 53 and references cited therein.

(5) Swindells, D. C. N.; White, P. S.; Findlay, J. A. *Can. J. Chem.* **1978**, *56*, 2491. Findlay, J. A.; Radics, L. *Ibid.* **1980**, *58*, 579. For the synthetic study on rapamycin, see: Chen, S.-H.; Horvath, R. F.; Joglar, J.; Fisher, M. J.; Danishefsky, S. J. *J. Org. Chem.* **1991**, *56*, 5834 and references cited therein.

(6) Somers, P. K.; Wandless, T. J.; Schreiber, S. L. *J. Am. Chem. Soc.* **1991**, *113*, 8045.

0022-3263/92/1957-5036$03.00/0