Articles

Efficient Degradation of FK-506 to a Versatile Synthetic Intermediate

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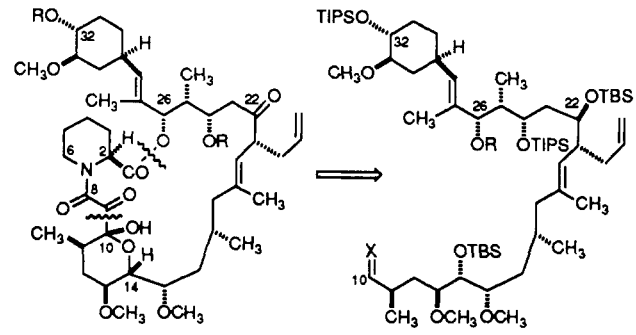
An 11-step degradation of natural FK-506 (1) to selectively protected C_{10}–C_{34} synthetic intermediate **2** has been accomplished in 14% overall yield. The key steps include: (a) lead tetraacetate mediated C_9–C_{10} bond cleavage of 24,32-bis(triisopropylsilyl)-FK-506 (**3**), (b) simultaneous C_{10} ester, C_{22} ketone reduction/C_{26} oxygen deacylation, and (c) selective bis(triethylsilylation) of the resulting triols **7a,b**. The degradate **2** is ready for reacylation at the C_{26} hydroxyl terminus; hydrolysis of the dimethyl acetal moiety then provides an aldehyde ready for homologation at the C_{10} terminus.

The macrolide antibiotic FK-506 (1)[1] has stimulated a great deal of interest in the synthetic community owing to its remarkable immunosuppressive activity and challenging molecular architecture. Following the successful total synthesis of 1,[2,3] interest has focussed on the search for analogues of 1 with increased activity and lower toxicity. Semisynthetic modifications of 1 that change, add, or remove specific functional groups provide such analogues for biological evaluation. However, analogues involving *substitution* of the amino acid moiety (pipecolinic acid, C_1–N_7) with other amino acids while leaving the remainder of functionality about the macrocyclic array unperturbed are more suited for attack from synthetic intermediates.[2,3] Unfortunately, the limited quantities of late intermediates available by multistep total synthesis presents an obvious drawback in the later scenerio. Thus, rapid access to a late synthetic intermediate would greatly aid in the preparation of FK-506 homologues.

Coleman and Danishefsky have reported the successful excision of the C_1–C_9 tricarbonyl/amino acid moiety (Scheme I, wavy lines) of FK-506.[4] However, the subsequent selective manipulation of the hydroxyl functionalities of the resulting C_{10}–C_{34} tetrol has not been reported. Thus, a unified route from FK-506 to a late synthetic precursor is desired. Herein we wish to report the efficient, 11-step degradation of natural FK-506 to the selectively protected C_{10}–C_{34} intermediate **2**. This semisynthetic degradate played a key role in supplementing material supplies for the development of end game chemistry in the first total synthesis of 1[2] and for the synthesis of ^{13}C-(C_9)-FK-506.[5] In the preceding communication,[6] we detail the utility of **2** in the synthesis of amino acid homologues of FK-506.

Scheme I



1 R = H (FK-506)
3 R = TIPS

2 R = H, X = $(OCH_3)_2$
12 R = TES, X = O
13 R = *(S)-N*-(Boc)-pipecolate, X = $(OCH_3)_2$
14 R = *(S)-N*-(Boc)-pipecolate, X = O

In order to excise the pipecolinic acid moiety of FK-506, we opted to cleave the C_9–C_{10} bond prior to deacylation of the C_{26} oxygen and intersect our synthetic route at the point immediately prior to amino acid introduction. This decision was based on the known work[4] as well as our findings concerning the instability of the FK-506 tricarbonyl system toward benzilic acid rearrangement[7] with hydroxide ion.

Lead tetraacetate mediated cleavage of the C_9–C_{10} linkage of 24,32-bis(triisopropylsilyl)-FK-506 (**3**) in methanolic benzene afforded a mixture of the hydroxy ester **4** (Scheme II) and the corresponding δ-lactone, the later as the major component. Subjection of the crude mixture to methanolic potassium carbonate gave a 70% overall yield of **4** from **3** after chromatography. Silylation of the se-

(1) (a) Tanaka, H.; Kuroda, A.; Marusawa, H.; Hatanaka, H.; Kino, T.; Goto, T.; Hashimoto, M.; Taga, T. *J. Am. Chem. Soc.* **1987**, *109*, 5031–5033. (b) Kino, T.; Hatanaka, H.; Hashimoto, M.; Nishiyama, M.; Goto, T.; Okuhara, M.; Kohsaka, M.; Aoki, H.; Imanaka, H. *J. Antibiot.* **1987**, *40*, 1249–1255. (c) Taga, T.; Tanaka, H.; Goto, T.; Tada, S. *Acta Crystallogr.* **1987**, *C43*, 751–753.

(2) (a) Jones, T. K.; Mills, S. G.; Reamer, R. A.; Askin, D.; Desmond, R.; Volante, R. P.; Shinkai, I. *J. Am. Chem. Soc.* **1989**, *111*, 1157–1159. (b) End game experimental procedures: Jones, T. K.; Reamer, R. A.; Desmond, R.; Mills, S. G. *J. Am. Chem. Soc.* **1990**, *112*, 2998–3017.

(3) (a) Nakatsuka, M.; Ragan, J. A.; Sammakia, T.; Smith, D. B.; Uehling, D. E.; Schreiber, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 5583–5601. See ref 19 in this paper for other synthetic approaches to FK-506 and fragments. (b) For a formal total synthesis of FK-506, see: Jones, A. B.; Villalobos, A.; Linde, R. G., II; Danishefsky, S. J. *J. Org. Chem.* **1990**, *55*, 2786–2797.

(4) (a) Coleman, R. S.; Danishefsky, S. J. *Heterocycles* **1989**, *28*, 157–161. (b) See also: Egbertson, M.; Danishefsky, S. J. *J. Org. Chem.* **1989**, *54*, 11–12.

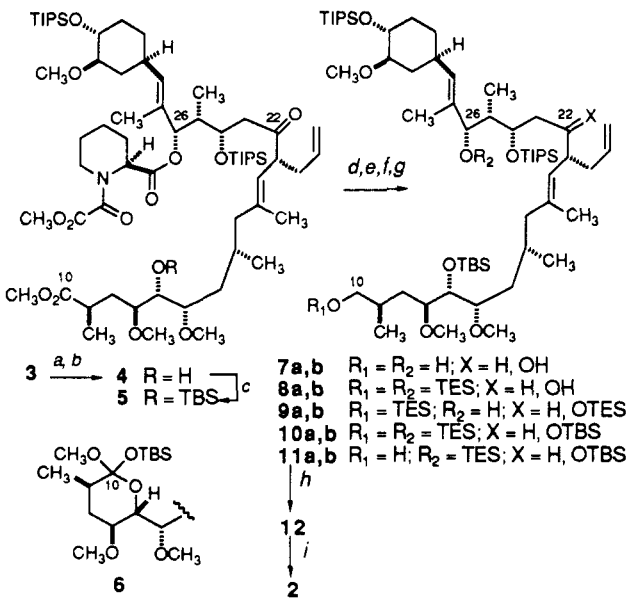
(5) Askin, D.; Reamer, R. A.; Joe, D.; Volante, R. P.; Shinkai, I. *Tetrahedron Lett.* **1989**, *30*, 6121–6124.

(6) Askin, D.; Reamer, R. A.; Joe, D.; Volante, R. P.; Shinkai, I. *J. Org. Chem.*, preceding communication in this issue.

(7) Askin, D.; Reamer, R. A.; Jones, T. K.; Volante, R. P.; Shinkai, I. *Tetrahedron Lett.* **1989**, *30*, 671–674.

0022-3263/90/1955-5451$02.50/0

Scheme II[a]



[a] Reagents and conditions: (a) $Pb(OAc)_4$, benzene/CH_3OH, 25 °C; (b) K_2CO_3, CH_3OH, 25 °C; (c) TBSOTf, lutidine, CH_2Cl_2, 0 °C; (d) $LiAlH_4$, THF, 0 °C; (e) TESCl, pyridine, −10 °C; (f) TBSOTf, lutidine, CH_2Cl_2, 0 °C; (g) HOAc, H_2O/THF, 50 °C, separate epimers; (h) oxalyl chloride, DMSO, Et_3N, CH_2Cl_2, −78 °C to −50 °C; or CrO_3-(pyr)$_2$, CH_2Cl_2, 25 °C; (i) $CH(OCH_3)_3$, pyridinium *p*-toluenesulfonate, CH_3OH/THF, 25 °C.

lectively exposed C_{14}-hydroxyl group with *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) gave the TBS ether **5** in 78% yield. Surprisingly, the ortho-lactone **6** was produced as a byproduct in this step (10%). An attempt to suppress the formation of **6** by substitution of the milder silylating agent *tert*-butyldimethylsilyl chloride led only to recovery of starting material.

Exhaustive reduction of **5** with lithium aluminum hydride effected simultaneous deacylation of the C_{26} pipecolinic ester and reduction of the ketone and methyl ester functionalities to afford the inseparable triols **7a** and **7b** as a 2.5 to 1 mixture (66%). The reduction of the C_{22} ketone proceeded to afford predominantly the same (*R*) stereochemistry as produced in the aldol condensation in the totally synthetic route[8] (vide infra). The pivotal bis-triethylsilylation of the triol mixture **7a,b** with triethylsilyl chloride (TESCl) in pyridine[9] gave the bis(TES-ethers) **8a,b**, contaminated with 5–10% of the isomeric bis(TES-ethers) **9a,b**. Silylation of the extremely hindered C_{22}-hydroxyl group of **8a,b** with TBSOTf then gave the persilylated compounds **10a,b**. Treatment of **10a,b** with aqueous acetic acid in THF effected selective C_{10} ether desilylation in the presence of the labile C_{26}-TES ether to give the epimers **11a** and **11b** (49% and 16% overall, respectively) after chromatography. Although only the epimer **11a** was utilized for further study, it is likely that the epimer **11b** would also be synthetically useful.

Swern oxidation of alcohol **11a** gave the corresponding aldehyde **12**[10] (96%). Acetalization of **12** with pyridinium *p*-toluenesulfonate and trimethyl orthoformate in methanolic THF proceeded with concomitant desilylation at C_{26} to afford the desired intermediate **2** (84%). Acylation of alcohol **2** with (*S*)-*N*-Boc-pipecolinic acid gave the *N*-Boc-pipecolinic ester derivative **13** (97%), which was subjected to acidic hydrolysis to afford the aldehyde **14** (94%). The identity of **14** with material prepared by total synthesis was confirmed by ^1H NMR, thin layer chromatography, and reconversion to FK-506.[2]

Experimental Section

General. Silica gel chromatography was carried out on E. M. Science silica (0.040–0.063 mm particle size) under a positive pressure of nitrogen. Analytical thin-layer chromatography was carried out on E. Merck Reagents 0.25 mm 60-F_{254} plates; visualization of compounds was effected by dipping in aqueous ammonium molybdate/cerric sulfate solution followed by heating or with UV light. Solvents for extraction and chromatography were reagent grade and used as received. Tetrahydrofuran (THF), CH_2Cl_2, pyridine, methanol, 2,6-lutidine, benzene, dimethyl sulfoxide, and triethylamine were dried with 3-Å molecular sieves. Water content was determined by Karl Fischer titration. Reactions were performed under an inert atmosphere of dry nitrogen in oven-dried glassware (110 °C). Brine refers to a saturated aqueous solution of sodium chloride. Infrared spectra were recorded in $CHCl_3$ solution (sh = shoulder). Only carbonyl stretching absorptions are reported.

FK-506 24,32-Bis(triisopropylsilyl ether) (3). To a 0 °C solution of FK-506 (1) (10.2 g, 12.7 mmol) in 125 mL of CH_2Cl_2 were added 2,6-lutidine (7.4 mL, 63 mmol) and triisopropylsilyl trifluoromethanesulfonate (TIPSOTf, 14.3 mL, 53.2 mmol). After stirring at 0 °C for 1.5 h, the yellow tinted solution was warmed to 25 °C and aged for 16 h. The mixture was then cooled to 0 °C, methanol (1.55 mL, 38.2 mmol) was added dropwise, and the resulting solution was aged for 15 min at 0 °C. The mixture was partitioned with saturated aqueous $NaHCO_3$ (500 mL) and CH_2Cl_2 (200 mL) and the layers were separated. The aqueous phase was re-extracted with CH_2Cl_2 (2 × 200 mL). The combined CH_2Cl_2 phase was washed with water (200 mL), dried ($MgSO_4$), and concentrated in vacuo to afford 20 g of a yellow viscous oil. Chromatography on silica gel (325 g) with hexanes/ethyl acetate (5:1) as the eluent afforded 14.04 g (99%) as **3** as a colorless foam: ^{13}C NMR (62.9 MHz, $CDCl_3$, major amide rotamer) 208.8, 196.5, 168.9, 164.5, 138.5, 135.6, 132.4, 131.3, 123.3, 116.4, 97.7, 84.4, 75.5, 75.0, 73.7, 73.6, 69.5, 57.4, 57.2, 56.3, 53.7, 49.4, 40.7, 39.0, 36.0, 35.6, 34.9, 34.2, 32.6, 35.0, 34.8, 30.4, 28.0, 25.3, 24.2, 20.5, 19.3, 18.3, 18.1, 16.0, 15.5, 12.8, 12.7, 11.3; IR 1745, 1735, 1705, 1650. Anal. Calcd for $C_{62}H_{109}NO_{12}Si_2$: C, 66.69; H, 9.84; N, 1.25. Found: C, 66.88; H, 9.71; N, 1.25.

Methyl Ester 4. To a 25 °C solution of triisopropylsilyl ether **3** (23.1 g, 20.7 mmol) in 300 mL of benzene and 100 mL of methanol was added $Pb(OAc)_4$ (9.67 g, 21.8 mmol), and the resulting mixture was aged at 25 °C for 4 h. The mixture was then quenched into saturated aqueous $NaHCO_3$ (800 mL) and extracted with ethyl acetate (3 × 350 mL). The combined ethyl acetate extracts were washed with water (350 mL), dried ($MgSO_4$), and concentrated in vacuo to afford 22.9 g of a white gummy foam. The foam was dissolved in methanol (300 mL) at 25 °C and concentrated in vacuo to remove any residual ethyl acetate. The foam was then redissolved in methanol (350 mL) at 25 °C and anhydrous K_2CO_3 (145 mg) was added. After 2 h additional K_2CO_3 (43 mg) was added. After 5 h total reaction time at 25 °C the solution was decanted away from the solid K_2CO_3 and was concentrated in vacuo to afford 23.4 g of a yellow tinted gum. Chromatography on silica gel (1150 g) with CH_2Cl_2/acetone (20:1) as the eluent followed by CH_2Cl_2/acetone (15:1) afforded 16.8 g (70%) of the desired methyl ester **4** as a colorless foam and 2.52 g (10%) of the corresponding valerolactone as a colorless foam. The ester **4** was immediately carried on to the next step and was not stored to avoid relactonization: ^1H NMR (300.1 MHz, $CDCl_3$) 5.37 (br d, J = 8.8, 1 H), 5.27 (d, J = 9.3, 1 H), 5.19 (br d, J = 5, 1 H), 3.87 (s, 3 H, major amide rotamer), 3.82 (s, 3 H, minor amide rotamer), 3.67 (s, 3 H), 3.42, 3.37, 3.34 (3 × s, 3 × 3 H), 2.74 (m, 1 H), 1.70 (br d, J = 1.0, 3 H), 1.66 (br d, J = 1.0, 3 H), 1.20 (d, J = 6.8, 3 H), 0.82 (d, J = 6.5, 3 H), 0.84 (d, J = 6.5, 3 H).

(8) Mills, S.; Desmond, R.; Reamer, R. A.; Volante, R. P.; Shinkai, I. *Tetrahedron Lett.* **1988**, *29*, 281–284.

(9) Hart, T. W.; Metcalfe, D. A.; Scheinmann, F. *J. Chem. Soc., Chem. Commun.* **1979**, 156–157.

(10) On multigram runs, the oxidation of **11a** to **12** was carried out by using Collins' reagent: Ratcliffe, R.; Rodehorst, R. *J. Org. Chem.* **1970**, *35*, 4000–4002.

C_{14}-TBS Ether 5. To a 0 °C solution of the hydroxy ester 4 (16.8 g, 14.2 mmol) in 210 mL of CH_2Cl_2 was added 2,6-lutidine (3.3 mL, 28 mmol) and then TBS-OTf (4.9 mL, 21 mmol), and the solution was stirred at 0 °C for 2 h and then allowed to warm to 25 °C. After 1 h at 25 °C additional TBS-OTf (0.35 mL, 1.5 mmol) was added to the 25 °C solution. After an additional 1.5 h, the solution was cooled to 0 °C and methanol (0.58 mL, 14 mmol) was added, and the mixture was aged at 0 °C for 15 min. The mixture was partitioned with saturated aqueous $NaHCO_3$ (1000 mL) and extracted with CH_2Cl_2 (3 × 300 mL). The combined CH_2Cl_2 layer was washed with water (1 × 300 mL), dried ($MgSO_4$), and concentrated in vacuo to afford 21.4 g of a tan oil that was purified by chromatography of silica gel (1070 g) with hexanes/ethyl acetate (5:1) as the eluent. TBS ether **5** (14.4 g, 78%) was isolated as a white gummy foam: ^1H NMR (300.1 MHz, $CDCl_3$) 5.37 (d, J = 8.8, 1 H), 5.27 (d, J = 9.3, 1 H), 5.18 (br d, J = 5, 1 H), 4.26 (m, 1 H), 3.86 (s, 3 H), 3.65 (s, 3 H), 3.42, 3.36, 3.27 (3 × s, 3 × 3 H), 2.71 (m, 1 H), 1.68 (br s, 3 H), 1.66 (br s, 3 H), 1.16 (d, J = 6.8, 3 H), 0.83, 0.81 (overlapping d's, 6 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) (major amide rotamer) 208.7, 177.2, 168.8, 163.1, 161.3, 139.0, 136.0, 135.5, 131.2, 123.4, 116.6, 84.3, 82.5, 81.0, 80.1, 74.9, 73.4, 67.6, 58.7, 57.4, 57.3, 52.6, 52.5, 51.6, 51.4, 46.6, 46.5, 44.2, 38.8, 38.4, 36.0, 35.9, 35.5, 35.0, 34.9, 34.1, 30.4, 27.3, 26.6, 25.9, 25.1, 20.8, 20.0, 18.3_2, 18.2_8, 18.2_2, 18.0_8, 18.0_5, 16.5, 12.9, 12.6, 11.7, 8.8, -4.6, -4.7; IR 1735, 1715 (sh), 1660. Anal. Calcd for $C_{70}H_{129}NO_{14}Si_3$: C, 65.02, H, 10.05; N, 1.08. Found: C, 65.18; H, 10.06; N, 1.09. For **6**: ^1H NMR (300.1 MHz, $CDCl_3$) 5.37 (br d, J = 8.8, 1 H), 5.28 (d, J = 9.3, 1 H), 5.20 (br d, J = 5, 1 H), 3.87 (s, 3 H), 3.41, 3.37, 3.36 (3 × s, 3 × 3 H), 3.16 (s, 3 H), 1.67 (br s, 6 H), 0.98 (d, J = 6.8, 3 H), 0.90 (s, 9 H), 0.19 (s, 3 H), 0.16 (s, 3 H).

Triols 7a,b. To a solution of methyl ester **5** (13.3 g, 10.3 mmol) in THF (375 mL) was added $LiAlH_4$ (1.18 g, 31.1 mmol) in several portions, and the gray suspension was aged at 0 °C for 3 h. Diethyl ether (300 mL) was added and then water was cautiously added dropwise until bubbling had stopped (several mL). The mixture was then partitioned with saturated aqueous Na_2SO_4 (400 mL) and extracted with ethyl acetate (3 × 400 mL). The combined ethyl acetate layer was washed with brine (400 mL), dried ($MgSO_4$), and concentrated in vacuo to afford 11.8 g of a brownish gummy foam. The crude foam was purified by chromatography on silica gel (580 g), eluting with hexanes/ethyl acetate (3:1) to afford 5.9 g (66%) of the triols **7a,b** as a 2.5 to 1 mixture of C_{22}-R/S epimers, respectively, as a colorless foam. For **7a**: ^1H NMR (300.1 MHz, $CDCl_3$) 5.37 (br d, J = 9.3, 1 H), 4.89 (br d, J = 9.8, 1 H), 4.34 (br dd, J = 10.3, 3.9, 1 H), 4.20 (br d, J = 2.9, 1 H), 3.94 (dd, J = 5.9, 1.5, 1 H), 3.45, 3.40, 3.34 (3 × s, 3 × 3 H), 2.61 (dd, J = 7.8, 4.9, 1 H), 1.62 (br s, 3 H), 1.59 (br s, 3 H), 0.83 (d, J = 6.4, 3 H), 0.80 (d, J = 6.8, 3 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) 137.3, 136.7, 134.1, 129.7, 125.8, 116.1, 84.6, 81.1, 79.6, 79.2, 75.1_0, 75.0_6, 73.0, 72.0, 67.2, 58.6, 57.5, 56.5, 47.0, 45.2, 39.0, 38.5, 36.9, 36.5, 36.3, 35.0, 34.3, 33.3, 32.6, 30.8, 27.4, 25.9, 20.0, 18.3, 18.2, 18.0_9, 18.0_7, 17.1, 16.6, 13.7, 13.3, 13.2, 12.6, 4.9, -4.5, -4.7. Anal. Calcd for $C_{60}H_{120}Si_3O_9$: C, 67.36; H, 11.30. Found: C, 67.39; H, 11.38.

C_{22}-Alcohols 8a,b. To a -10 °C solution of triols **7a,b** (2.33 g, 2.18 mmol) in pyridine (33 mL) was added TESCl (740 μL, 4.40 mmol) over a 5-min period. After a 1.8-h age at -10 °C, additional TESCl (92 μL, 0.55 mmol) was added. After an additional 1-h age, methanol (88 μL, 2.2 mmol) was added and the mixture was aged at -10 °C for 15 min. The mixture was partitioned with saturated aqueous $NaHCO_3$ (100 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The combined CH_2Cl_2 layer was washed with saturated aqueous $NaHCO_3$ (100 mL), dried ($MgSO_4$), and concentrated in vacuo to afford 3.7 g of a tan viscous oil. The crude mixture was purified by chromatography on silica gel (175 g) with hexanes/ethyl acetate (18:1 to 15:1) as the eluent to afford 2.73 g (96%) of the C_{22} alcohols **8a,b** as a colorless foam. For **8a**: ^1H NMR (300.1 MHz, $CDCl_3$) 5.16 (br d, J = 8.8, 1 H), 4.87 (br d, J = 9.8, 1 H), 4.00 (d, J = 9.8, 1 H), 3.86 (dd, J = 5.9, 1.5, 1 H), 3.50 (dd, J = 9.8, 5.4, 1 H), 3.44, 3.40, 3.31 (3 × s, 3 × 3 H), 3.39 (dd, J = 9.8, 6.4, 1 H), 3.27 (br dt, J = 9.3, 2.0, 1 H), 3.15 (m, 1 H), 2.46 (m, 1 H), 1.60 (br s, 3 H), 1.59 (br s, 3 H), 0.82 (d, J = 6.4, 3 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) 137.2, 136.8, 136.1, 132.6, 125.9, 115.9, 84.5, 81.1, 80.9, 80.7, 75.1, 73.7, 72.1, 69.5, 67.8, 58.8, 57.4, 57.0, 46.9, 45.2, 39.5, 39.4, 38.8, 36.4, 36.0, 35.0, 34.5, 34.3, 33.2, 30.6, 27.3, 25.9, 20.0, 18.5, 18.4, 18.2, 18.1_0, 18.0_8, 16.6, 13.2, 12.6, 10.9, 8.7, 6.9, 6.8, 5.0, 4.4, -4.5, -4.7. Anal. Calcd for $C_{72}H_{148}O_9Si_5$: C, 66.61; H, 11.49. Found: C, 66.82, H, 11.77.

C_{22}-TBS Ethers 10a,b. To a 0 °C solution of C_{22} alcohols **8a,b** (4.55 g, 3.50 mmol) in 100 mL of CH_2Cl_2 were added 2,6-lutidine (1.20 mL, 10.3 mmol) and then TBS-OTf (1.60 mL, 6.97 mmol). After 30 min, the mixture was brought to 26 °C and aged for 14 h. The mixture was cooled to 0 °C, methanol (215 μL, 5.30 mmol) was added, and the mixture was aged for 30 min. The mixture was partitioned with 3% aqueous $NaHCO_3$ (125 mL) and extracted with CH_2Cl_2 (3 × 125 mL). The combined CH_2Cl_2 layer was washed with water (125 mL), dried ($MgSO_4$), and concentrated in vacuo to afford 5.3 g of a tan oil. The crude mixture was purified by chromatography on silica gel (260 g), eluting with hexanes/ethyl acetate (15:1) to afford 4.86 g (98%) of the C_{22}-TBS ethers **10a,b** as a gummy white foam. For **10a**: ^1H NMR (300.1 MHz, $CDCl_3$) 5.19 (br d, J = 8.8, 1 H), 4.06 (d, J = 9.3, 1 H), 3.87 (dd, J = 5.4, 1.5, 1 H), 3.51 (dd, J = 9.8, 5.4, 1 H), 3.45, 3.40, 3.32 (3 × s, 3 × 3 H), 3.39 (dd, J = 9.8, 6.8, 1 H), 3.29 (br dt, J = 9.3, 2.0, 1 H), 3.17 (m, 1 H), 1.61 (br s, 3 H), 1.55 (br s, 3 H), 0.82 (d, J = 6.4, 3 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) 137.7, 135.8, 134.9, 132.4, 127.9, 115.4, 84.6, 81.2, 80.9, 80.3, 75.0, 73.6, 72.9, 70.0, 67.9, 58.7, 57.3, 57.0, 47.2, 45.1, 41.2, 40.3, 38.8, 35.6, 35.1, 34.6, 34.3, 33.2, 30.7, 27.3, 26.0, 20.0, 18.7, 18.6, 18.2_5, 18.1_3, 18.1_0, 16.6, 13.3, 12.6, 11.6, 9.0, 7.0, 6.9, 5.0, 4.4, -3.6, -4.4, -4.5, -4.7. Anal. Calcd for $C_{78}H_{162}O_9Si_6$: C, 66.32; H, 11.56. Found: C, 65.93; H, 11.77.

(22*R*)-C_{10}-Primary Alcohol 11a. To a solution of bis-TES ethers **10a,b** (4.85 g, 3.43 mmol) in 155 mL of THF were added 15.5 mL of water and 30 mL of acetic acid over 10 min. The mixture was warmed to 40 °C and aged for 12 h and then warmed to 50 °C and aged for 2.5 h. The mixture was cooled to 0 °C and poured slowly into a suspension of 72 g of $NaHCO_3$ in 450 mL of water. The mixture was then extracted with ethyl acetate (3 × 450 mL) and the combined ethyl acetate layer was washed with saturated aqueous $NaHCO_3$ (115 mL) and brine (115 mL) and dried ($MgSO_4$). The volatiles were removed in vacuo to afford 5.01 g of a tan gum that was purified by silica gel chromatography (675 g). Gradient elution with hexanes/ethyl acetate (8:1 to 2:1) afforded 742 mg (17%) of pure less polar (22*S*)-C_{10}-primary alcohol **11b**, 305 mg (7%) of mixed fractions, and 2.32 g (52%) of the (22*R*)-C_{10}-primary alcohol **11a** as a colorless foam. For **11a**: ^1H NMR (300.1 MHz, $CDCl_3$) 5.19 (br d, J = 8.8, 1 H), 4.06 (d, J = 9.3, 1 H), 3.94 (dd, J = 5.9, 1.5, 1 H), 3.85 (br dd, J = 10.5, 3.5, 1 H), 3.46, 3.39, 3.34 (3 × s, 3 × 3 H), 2.63 (dd, J = 7.3, 4.9, 1 H), 1.61 (br s, 3 H), 1.54 (br s, 3 H), 0.82 (d, J = 6.4, 3 H), 0.10 (s, 6 H), 0.03 (s, 3 H), 0.00_4 (s, 3 H). Anal. Calcd for $C_{72}H_{148}O_9Si_5$: C, 66.61; H, 11.49. Found: C, 66.47, H, 11.73.

Aldehyde 12 (Swern Procedure). To a -78 °C solution of oxalyl chloride (148 μL, 1.70 mmol) in 10 mL of CH_2Cl_2 was added a solution of dimethyl sulfoxide (200 μL, 2.82 mmol) in 4 mL of CH_2Cl_2 over 5 min and the resulting mixture was aged at -78 °C for 30 min. A solution of the primary alcohol **11a** (1.06 g, 0.816 mmol) in 10 mL of CH_2Cl_2 was added to the -78 °C chlorosulfonium salt solution followed by a 5-mL CH_2Cl_2 flush. The resulting white slurry was aged at -78 °C for 1.5 h, then triethylamine (983 μL, 7.05 mmol) was added, and the solution was warmed to -40 °C and aged for 1 h. Aqueous $NaHSO_4$ (0.5 M, 75 mL) was added at -40 °C and the mixture was extracted with hexanes (4 × 100 mL). The combined hexane layer was washed with water (1 × 50 mL), dried ($MgSO_4$), and concentrated in vacuo to afford 1.05 g of crude material that was chromatographed on silica gel (90 g). Elution with hexanes/ethyl acetate (15:1) gave 977 mg (96%) of the aldehyde **12** as a colorless foam: ^1H NMR (300.1 MHz, $CDCl_3$) 9.60 (d, J = 1.0, 1 H), 5.19 (br d, J = 8.8, 1 H), 4.06 (d, J = 9.3, 1 H), 3.97 (dd, J = 5.4, 1.5, 1 H), 3.85 (br dd, J = 10.7, 3.9, 1 H), 3.43, 3.39, 3.19 (3 × s, 3 × 3 H), 2.53 (m, 1 H), 1.61 (br d, J = 1.0, 3 H), 1.55 (br s, 3 H), 1.10 (d, J = 6.4, 3 H), 0.83 (d, J = 6.4, 3 H); IR 1720. Anal. Calcd for $C_{72}H_{146}O_9Si_5$: C, 66.71; H, 11.35. Found: C, 66.89, H, 11.49.

12 (Collins' Procedure). To a 25 °C solution of pyridine (730 μL, 9.04 mmol) in CH_2Cl_2 (16 mL) was added CrO_3 (453 mg, 453 mmol), and the resulting burgandy solution was aged for 20 min. A solution of alcohol **11a** (984 mg, 0.758 mmol) in 3 mL of CH_2Cl_2 was added via cannula, followed by (2 × 1 mL) rinses of CH_2Cl_2. After aging the mixture at 25 °C for 1.5 h, the solution was decanted away from the tar-like residue and the flask was rinsed with CH_2Cl_2 to give a total organic phase of 125 mL. The CH_2Cl_2

layer was washed with saturated aqueous $NaHCO_3$ (25 mL), dried ($MgSO_4$), and concentrated in vacuo to afford 1.04 g of a brown foam that was purified by silica gel chromatography (80 g). Elution with hexane/ethyl acetate (20:1) gave 820 mg (84%) of the aldehyde **12** as a colorless foam.

Dimethyl Acetal 2. To a solution of aldehyde **12** (2.07 g, 1.60 mmol) at 0 °C in 105 mL of THF was added methanol (155 mL), trimethyl orthoformate (3.13 mL, 28.6 mmol), and pyridinium *p*-toluenesulfonate (PPTS, 555 mg, 2.21 mmol) and the mixture was warmed to 18 °C. After 2 h, 444 mg of PPTS was added, and the mixture was warmed to 25 °C. After 3 h at 25 °C, pyridine (4.9 mL, 60 mmol) was added with ice bath cooling and the mixture was poured into 250 mL of saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3 × 200 mL). The combined CH_2Cl_2 layer was washed with 3% aqueous $NaHCO_3$ (120 mL), dried ($MgSO_4$), and concentrated in vacuo. The resulting crude oil was chromatographed on 200 g of silica gel, eluting with hexanes/ethyl acetate ((15:1), 1.6 L; (8:1), 850 mL; (3:1), flush) to afford 1.64 g (84%) of the dimethyl acetal **2** as a colorless oil: ^1H NMR (300.1 MHz, $CDCl_3$) 5.42 (br d, J = 8.8, 1 H), 4.36 (m, 1 H), 4.24 (br s, 1 H), 4.06 (d, J = 5.9, 1 H), 3.90 (br s, 1 H), 3.86 (dd, J = 5.9, 1.0, 1 H), 3.45, 3.40, 3.35, 3.34, 3.31 (5 × s, 5 × 3 H), 2.43 (m, 1 H), 1.59 (br s, 3 H), 1.57 (br s, 3 H), 0.94 (d, J = 6.8, 3 H), 0.82 (d, J = 6.4, 3 H), 0.76 (d, J = 6.8, 3 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) 137.3, 135.6, 133.3, 128.9, 126.8, 115.7, 109.3, 84.7, 81.1, 81.0, 79.3, 76.3, 75.2, 73.7, 72.5, 58.9, 57.5, 56.9, 54.9, 53.5, 47.1, 45.2, 39.5, 38.9, 36.6, 36.5, 36.4, 35.1, 34.4, 33.2, 32.6, 30.9, 27.2, 26.0, 20.1, 18.2, 18.1_1, 18.0_8, 16.6, 16.3, 14.4, 13.4, 12.6, 3.7, -3.5, -4.1, -4.6, -4.7. Anal. Calcd for $C_{68}H_{138}O_{10}Si_4$: C, 66.50; H, 11.32. Found: C, 66.43; H, 11.68.

***N*-Boc-pipecolate 13.** To a -20 °C solution of alcohol **2** (308 mg, 0.251 mmol) in 4.4 mL of CH_2Cl_2 was added solid (*S*)-*N*-Boc-pipecolinic acid (231 mg, 1.00 mmol), dicyclohexylcarbodiimide (208 mg, 1.00 mmol) and 4-(dimethylamino)pyridine (6.0 mg, 0.050 mmol). The initially homogeneous solution was aged at -20 °C for 21 h and then filtered and the filter cake washed with hexane/ethyl acetate solution (12:1). The combined organic phase was concentrated in vacuo and the residue chromatographed on 95 g of silica gel. Elution with hexanes/ethyl acetate (3:1) gave 436 mg (97%) of the pipecolinic ester **13** as a colorless foam: ^{13}C NMR (75.5 MHz, $CDCl_3$, many resonances are broadened (br) or doubled (dbl) due to 1/1 carbamate rotamers; these doubled resonances precede (dbl)) 170.6 (br), 155.4 (br), 137.5 (br), 136.6, 136.2 (dbl), 135.1, 135.0 (dbl), 130.9, 130.8 (dbl), 127.5, 127.4 (dbl), 115.6 (br), 109.3, 84.4, 82.3, 82.1 (dbl), 81.1, 81.0, 79.7, 79.6 (dbl), 74.7, 73.8, 72.8, 69.7, 69.3 (dbl), 58.9, 57.1, 56.9, 54.9, 53.5, 47.1, 44.5, 44.3 (dbl), 42.0, 41.0 (dbl), 40.4 (br), 38.9, 38.4, 38.1 (dbl), 35.9, 35.7 (dbl), 35.6, 35.1, 34.1, 33.1, 32.6, 30.3, 28.3, 27.1, 27.0, 26.8 (dbl), 25.9_5, 25.9_1, 25.0, 24.7 (dbl), 20.8, 20.4 (dbl), 20.1, 18.6, 18.5, 18.2, 18.0_9, 18.0_6, 16.6, 16.3, 13.3, 12.6, 12.1 (br), 9.3, 9.2 (dbl), -3.7, -4.4, -4.5, -4.7; IR 1740, 1700. Anal. Calcd for $C_{79}H_{155}Si_4O_{13}N$: C, 65.92; H, 10.85; N, 0.97. Found:[11] C, 65.86; H, 10.72; N, 1.01.

Aldehyde 14. To a solution of dimethyl acetal **13** (348 mg, 0.242 mmol) in 11 mL of CH_2Cl_2 at 25 °C were added glyoxylic acid monohydrate (225 mg, 2.44 mmol) and acetic acid (140 μL). The resulting suspension was heated to 40 °C and aged for 2 h. The suspension was cooled to 0 °C, diluted with CH_2Cl_2 (100 mL), and washed with saturated aqueous $NaHCO_3$ (3 × 50 mL). The solution was dried ($MgSO_4$) and concentrated in vacuo to afford 330 mg of crude product that was chromatographed on 29 g of silica gel. Elution with hexanes/ethyl acetate (12:1) gave 318 mg (94%) of the aldehyde **14** as a colorless oil. For spectral data, see ref 2b. Anal. Calcd for $C_{77}H_{149}Si_4O_{12}N$: C, 66.38; H, 10.78; N, 1.01. Found:[11] C, 66.32; H, 10.69; N, 1.09.

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Supplementary Material Available: Copies of ^1H and/or ^{13}C NMR spectra for compounds **2**, **4**, **5**, **7a,b**, **8a,b**, **10a,b**, **11a**, **12**, and **13** (15 pages). Ordering information is given on any current masthead page.

(11) The combustion analyses for these compounds in a prior paper[2b] by one of us (R.R.) was that obtained from this naturally derived material.

Rearrangement of Rigid Cyclopropylcarbinyl Radicals: Investigation of a Reporter System for the Detection of Very Short Lived Radicals

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The ring-opening rearrangements of the spiro[cyclopropane-1,1′-indan]-2′-yl radicals **1** and **2**, the dispiro-[cyclopropane-1,1′-indan-3′,1″-cyclopropane]-2′-yl radical **3**, and the 3′,4′-dihydrospiro[cyclopropane-1,1′-(2′*H*)-naphthalen]-2′-yl radicals **4** and **5** were investigated by the tin hydride method. At 75 °C, the following unimolecular rate constants (k_r) were obtained: 2.1×10^9 s^{-1} (**1**), 8.6×10^9 s^{-1} (**2**), 5.3×10^8 s^{-1} (**3**), 3.0×10^9 s^{-1} (**4**), and 3.6×10^9 s^{-1} (**5**). The rate of ring opening of the 3′,3′-dimethylspiro[cyclopropane-1,1′-indan]-2′-yl radical **2** is comparable to that of the bicyclo[2.1.0]pent-2-yl radical and is one of the fastest cyclopropylcarbinyl radical rearrangements currently known.

Introduction

A central issue for a number of reactions that can be formulated either as two sequential inner-sphere single-electron transfers or as a one-step two-electron process is how these conceptually different pathways can be distinguished experimentally.[1,2] The difficulty of this distinction is well recognized; an in-cage process of two sequential single-electron transfers in which the second electron transfer is more rapid than molecular reorientation will not differ from a concerted two-electron-transfer process with presently available mechanistic probes. Because of our interest in halogen–lithium interchange, a reaction for which this mechanistic dichotomy exists, we initiated a

(1) For summaries, see: (a) Andrieux, C. P.; Gelis, L.; Saveant, J.-M. *J. Am. Chem. Soc.* **1990**, *112*, 786. (b) Lehmann, R. E.; Bockman, T. M.; Kochi, J. K. *Ibid.* **1990**, *112*, 458. (c) Pross, A. *Acc. Chem. Res.* **1985**, *18*, 212. (d) Eberson, L. *Adv. Phys. Org. Chem.* **1982**, *18*, 79.

(2) For discussion of a representative case, see: (a) Newcomb, M.; Curran, D. P. *Acc. Chem. Res.* **1988**, *21*, 206. (b) Ashby, E. C. *Ibid.* **1988**, *21*, 414.

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