testing other ligands in order to fully evaluate the potential for any enantiomeric selectivity under the above reaction conditions.

Experimental Section

General Comments. Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. ^1H NMR spectra were obtained in deuterium oxide with 3-(trimethylsilyl)propionic acid sodium salt as a reference on a Varian EM-390, a Chemagnetics A-200, or a General Electric GN-300 spectrometer. Chemical ionization mass spectra (CIMS) were recorded with isobutane by use of a Finnigan MAT Model 8430 spectrometer. Elemental analyses were determined by M-H-W Laboratories, Phoenix, AZ. Aqueous titanium(III) chloride solutions (13%, Fluka) were titrated with cerium(IV) sulfate.[21] Chiral high-pressure liquid chromatography was conducted on a Beckmann/Altex Model 332 chromatograph using a Pirkle covalent D-naphthylalanine column (25 cm, Regis Chemical Co.).[22] TLC was performed on aluminum-backed silica gel 60 F-24, 0.2-mm plates purchased from MCB Reagents. Solvents were dried and purified by standard methods.

α-Keto Esters. Ethyl 2-oxobutylate and ethyl 3,3-dimethyl-2-oxobutyrate were prepared by a literature procedure.[19]

Oximes. Ethyl 2-(hydroxyimino)butyrate and ethyl 2-(hydroxyimino)-3,3-dimethylbutyrate were prepared in 87% and 92% yield, respectively, from the α-keto esters and hydroxylamine hydrochloride. Dimethyl 2-(hydroxyimino)glutarate was prepared in quantitative yield from the corresponding diacid via addition of thionyl chloride to a methanolic solution at −78 °C. The 2-(hydroxyimino)glutaric acid was prepared from 2-oxoglutaric acid and hydroxylamine hydrochloride in 35% yield.

General Procedure for Oxime Reduction. To a solution of 9.24 g (61.6 mmol) of L-tartaric acid and 5.90 g (0.148 mol) of sodium hydroxide in 30 mL of water was added 7.0 mL (6.3 mmol) of 0.9 M aqueous titanium trichloride. The pH of the resulting green solution was adjusted to 7.0 (NaOH/HCl). To the mixture was added 210 mg (5.55 mmol) of solid sodium borohydride, followed quickly by 2.0 mmol of oxime in 5 mL of methanol. The mixture became lighter in color and was stirred for 20 min under nitrogen and then for 17 h in air. The pH of the final white mixture was exactly 7.0 and was adjusted to 8.5 with saturated aqueous dipotassium hydrogen phosphate. The mixture was extracted with dichloromethane (200 mL). The combined extracts were dried ($MgSO_4$), filtered, and concentrated to 10 mL. To the solution was added 3.0 mL of 1.0 M ethereal hydrogen chloride, and the mixture was concentrated in vacuo. The residual solid was rinsed with ether (2 × 10 mL), and residual ether was evaporated to afford the amine hydrochloride as a pale yellow solid. Recrystallization gave pure material as a white solid.

Methyl 2-aminopropionate hydrochloride (2a) (73%, ether/methanol): mp 105–110 °C; ^1H NMR (200 MHz, D_2O) δ 1.55 (d, J = 7, 3 H, CH_3), 3.84 (s, 3 H, CO_2Me), 4.20 (q, J = 7, 1 H, CHN); CIMS (relative intensity) m/e 104 (free amine + 1, 100).

Ethyl 2-aminobutyrate hydrochloride (2b) (63%, ether/ethanol): mp 136–138 °C; ^1H NMR (200 Hz, D_2O) δ 1.01 (t, J = 6, 3 H, CH_2CH_3), 1.30 (t, J = 6, 3 H, $CO_2CH_2CH_3$), 1.99 (m, 2 H, $CHCH_2$), 4.09 (t, J = 6, 1 H, $CHCH_2$), 4.32 (q, J = 6, 2 H, CO_2CH_2); CIMS (relative intensity) m/e 132 (free amine + 1, 100). Anal. Calcd for $C_6H_{14}ClNO_2$: C, 42.99; H, 8.42; N, 8.36. Found: C, 42.79; H, 8.32; N, 8.31.

Ethyl 2-amino-3,3-dimethylbutyrate hydrochloride (2c) (68%, ethyl acetate/hexane): mp 108–110 °C; ^1H NMR (200 MHz, D_2O) δ 1.09 (s, 9 H, tBu), 1.32 (t, J = 6, 3 H, CH_2CH_3), 3.80 (s, 1 H NCHCO$_2$), 4.31 (q, J = 6, 2 H, CH_2CH_3); CIMS (relative intensity) m/e 160 (free amine + 1, 100). Anal. Calcd for $C_8H_{18}ClNO_2$: C, 49.10; H, 9.27; N, 7.16. Found: C, 48.79; H, 9.30; N, 7.14.

Methyl 2-amino-2-phenylacetate hydrochloride (2d) (82%, ether/methanol): mp 197–199 °C; ^1H NMR (200 MHz D_2O) δ 3.85 (s, 3 H, CO_2CH_3), 5.30 (s, 1 H, NCHCO$_2$), 7.50 (m, 5 H, Ph); CIMS (relative intensity) m/e 166 (free amine + 1, 100).

Dimethyl glutamate hydrochloride (2e) (64%, ether/methanol): mp 148–150 °C; ^1H NMR (300 MHz, D_2O) δ 2.10–2.30 (m, 2 H, CH_2CHN), 2.40–280 (m, 2 H, CH_2CO_2), 3.65 (s, 3 H, CO_2CH_3), 3.80 (s, 3 H, NCHCO$_2CH_3$), 4.20 (t, J = 6, 1 H, NCHCO$_2$); CIMS (relative intensity) m/e 176 (free amine + 1, 100).

Derivatives. To further characterize the above amines and in order to determine accurately the percent ee, if any, the 3,5-dinitrobenzoyl derivatives were prepared and analyzed by chiral HPLC.[23] However, no enantiomeric excess was found.

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Registry No. **1a**, 5634-53-7; **1b**, 5339-83-3; **1c**, 120927-14-2; **1d**, 24607-22-5; **1e**, 120927-15-3; **2a**, 13515-97-4; **2b**, 55410-21-4; **2c**, 120927-16-4; **2d**, 15028-40-7; **2e**, 13515-99-6; $H_3CCH_2COCOOEt$, 15933-07-0; $(H_3C)_3CCOCOOEt$, 5333-74-4; NON=C(COOH)CH_2CH_2COOH, 2211-15-6; $HOOCCOCH_2CH_2COOH$, 328-50-7; $NaBH_4$, 16940-66-2; $TiCl_3$, 7705-07-9.

(21) Citterio, A.; Cominelli, A.; Bonavoglia, F. *Synthesis* **1986**, 308.
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Reaction of 1,*exo*-5-Dimethyl-3-oxo-*exo*-6-carbomethoxytricyclo[5.2.1.0^{2,6}]dec-8-ene with Ethanedithiol in the Presence of Boron Trifluoride Etherate. A Novel Fragmentation Process

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Introduction

Substituted *endo*-tricyclo[5.2.1.0^{2,6}]dec-8-en-3-ones are of intense current interest as intermediates in the synthesis of polyquinane natural products.[1-4] In this connection,[3,4] reaction of the title compound, **1**, with ethanedithiol in the presence of boron trifluoride etherate catalyst has been investigated. Although this reaction was intended simply to convert the ketone functionality in **1** into the corresponding dithioethylene ketal, it readily became apparent that the reaction had taken a different course. Detailed analysis of the proton and carbon-13 NMR spectra of the reaction product indicates that this material possesses the structure **2** shown in Scheme I.

Results and Discussion

The reaction of **1** with ethanedithiol–$F_3B{\cdot}OEt_2$, performed in methylene chloride solution at −78 °C, afforded **2** (80% yield) as a viscous oil. A control experiment established that no reaction occurred when **1** was mixed with $F_3B{\cdot}OEt_2$ under these conditions in the absence of ethanedithiol.

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(2) Ghosh, S. K.; Satapathi, K.; Subba Rao, P. S. V.; Sarkar, T. *Synth. Commun.* **1988**, *18*, 1883.
(3) Marchand, A. P.; Suri, S. C. *Abstracts of Papers*, 188th National Meeting of the American Chemical Society, Philadelphia, PA, August, 1984; American Chemical Society: Washington, DC, 1984; ORGN 55.
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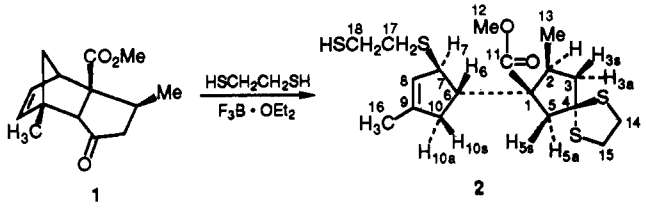
0022-3263/89/1954-3751$01.50/0

Scheme I



Atom numberings in the following NMR spectral analysis correspond with those given for **2** in Scheme I. The stereochemistries at C(6) and C(7) and the assignments of protons on C(3), C(5), and C(10) in **2** were arrived at via analysis of (i) the magnitudes of proton–proton scalar couplings and application of the Karplus relationship, (ii) the results of proton–proton NOE experiments, and (iii) analysis of COSY and relay COSY[5,6] spectra. Thus, the trans nature of H(6)–H(7) and of H(6)–H(10a) is suggested by the magnitudes of their respective coupling constants (i.e., 4.9 Hz gleaned via analysis of the resonance at δ 2.62). Analysis of the resonance at δ 1.75 reveals that the coupling constant, J, between H(6) and H(10s) amounts to 10 Hz; this result suggests that H(6) and H(10s) are mutually cis. No NOE enhancement was observed between H(6) and H(7), a result which is consistent with the earlier conclusion that these protons are mutually trans.

Irradiation of H(2) results in NOE enhancement of H(3a) (δ 2.2) and of the methyl protons at C(13). However, no corresponding NOE enhancement is observed for H(3s) (δ 1.7). These observations suggest that H(2) and H(3a) are mutually cis, whereas H(2) and H(3s) are mutually trans. Two additional NMR experiments were performed that reinforce this conclusion. First, selective irradiation of the methyl H(13) protons (δ 0.95) results in NOE enhancement for the resonance at δ 1.7 [i.e., H(3s)] but not for the signal at δ 2.2 [i.e., H(3a)]. Second, a relay COSY spectrum[5,6] obtained for **2** indicates a correlation between H(13) and H(3a) that is absent in the corresponding normal COSY spectrum.

Assignment of H(5s) and H(5a) in **2** (δ 3.05 and 2.3, respectively) is facilitated by the observation that irradiation of H(2) produces sharpening of the resonance at δ 2.3 but has no effect upon the appearance of the resonance at δ 3.05. Long-range (four-bond) coupling via a "zigzag" pathway is anticipated between H(2) and H(5a) but not between H(2) and H(5s). Irradiation of either H(12) or H(13) produced no detectable change in the signals that correspond to either H(5s) or H(5a); hence, we were unable to confirm the assignments of H(5s) and H(5a) via an NOE experiment.

The COSY spectrum of **2** shows a correlation between H(2) and the resonance at δ 2.3 [i.e., H(5a)] but not between H(2) and the signal at δ 3.05 [i.e., H(5s)]. However, the corresponding relay COSY spectrum[5,6] does contain a correlation between H(2) and H(5s). All other correlations in the relay COSY spectrum are consistent with the spectral assignments given above.

Proton and ^{13}C NMR chemical shift assignments along with observed ^{13}C spin–lattice relaxation times (T_1^{obsd}), NOE values, and dipole–dipole relaxation times (T_1^{DD}) are summarized in Table I. Assignments of ^{13}C signals that appear in the table are consistent with the observed spin–lattice relaxation times. In particular, the four quaternary carbons C(1), C(4), C(9), and C(11) all display relatively long T_1's due to their much longer T_1^{DD} values. All of the methine carbons, i.e., C(2), C(6), C(7), and C(8), display spin–lattice relaxation times on the order of ca. 1.2 s, while ring methylene carbons C(3), C(5), and C(10) all display considerably shorter T_1 values (ca. 0.7 s, which is roughly half of that for the methine carbons). The similarity of the T_1^{DD} values between the methine carbon C(2) on the cyclopentane ring and the methine carbons C(6) and C(7) on the cyclopentene ring suggest that similar rotational correlation times are operative for the two rings.

T_1 values for the methylene carbons, C(14) and C(15), in the dithioketal ring are considerably longer than are the corresponding T_1 values for C(3), C(5), and C(10). Comparison of the T_1^{DD} values indicates less efficient dipole–dipole relaxation for the carbons in the thioketal ring relative to the other methylene carbons. Apparently, C(14) and C(15) undergo additional internal motion relative to the methylene carbons in the cyclopentene and cyclopentane ring in **2**.

Methyl carbon C(16) displays a T_1^{DD} that is roughly three times that of methine carbons C(2), C(6), and C(8); this result suggests that this methyl group is a free rotor. By way of contrast, T_1^{DD} for methyl carbon C(13) is approximately equal to that of the methine carbons. The C(13) methyl group is not completely rigid relative to the ring (a result that would require its T_1^{DD} to be one-third of that of the methine ring carbon atoms). Nevertheless, rotation of the C(13) methyl group clearly is restricted.

Some comments concerning the mechanism of formation of **2** in this unusual reaction are warranted. The occurrence of BF_3-promoted ring cleavages in appropriately substituted polycyclic ketones is well documented.[7,8] Either of two mechanisms might be operative: (i) Initial 5-*exo*-*trig*[9] ring opening might occur to afford an intermediate carbocation, **3**. This process could be followed by nucleophilic trapping of **3** by ethanedithiol (path a). (ii) Alternatively, concerted fragmentation of **1** might occur, i.e., nucleophilic attack by ethanedithiol at C(8) might be concomitant with cleavage of the C(1)–C(2) σ-bond in the substrate (path b, Scheme II).[7,8]

Recently, we reported[8] that BF_3-promoted fragmentation of **1**, when performed in the *absence* of ethanedithiol, proceeds smoothly at −10 °C to afford the corresponding cyclopentenone in 95% yield after 6 h. The corresponding reaction, when performed in the *presence* of ethanedithiol at −78 °C, is complete in less than 5 min and does not proceed completely to the cyclopentenone stage. As noted above, no reaction occurs at −78 °C in the absence of ethanedithiol. On the basis of these observations, we conclude either (i) that the stepwise process (path a) operates with rate-determining nucleophilic capture of **3** or (ii) that the concerted mechanism (path b) is operative. We favor the latter option for two reasons. (i) By analogy to an S_N1 reaction, it seems more likely that the stepwise process (path a), if operative, would proceed with rate-determining cleavage of the C(1)–C(2) σ-bond in the substrate. (ii) We observe that formation of the carbon–sulfur bond at C(8) occurs stereospecifically from the *exo* face of the carbon–carbon double bond in the substrate, a

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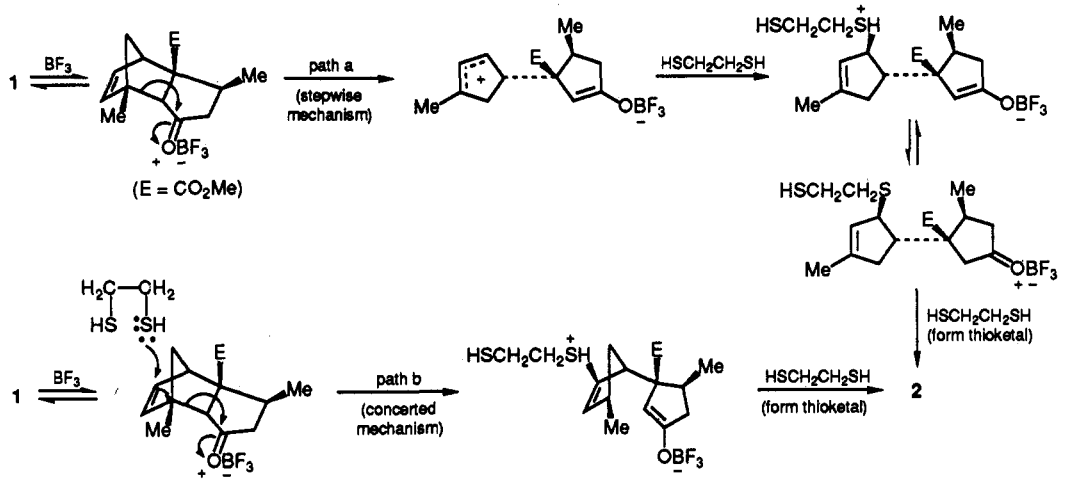
Table I. Proton and Carbon-13 Chemical Shift Assignments in 2

proton chemical shift assignments in 2			carbon-13 chemical shift assignments in 2				
proton	δ, ppm	remarks	carbon atom	δ, ppm	NOE, η^a	T_1^{obsd}, s	$T_1^{DD,c}$ s
2	2.55	J(2–13) = 6.7 Hz	1 (or 4)	67.7	1.20	13.0 ± 1.3	21.6
3a	2.2		2	41.2	1.83	1.18 ± 0.03	1.3
3s	1.7		3	52.9	1.82	0.67 ± 0.02	0.7
5a	2.3	unresolved ^4J(2–5a)	4 (or 1)	61.2	0.84	11.7 ± 0.6	27.7
5s	3.05	J(5a–5s) = 15.5 Hz	5	47.7	1.62	0.69 ± 0.03	0.8
6	2.90	J(6–10s) = 10 Hz, J(6–10a) = 4.9 Hz, J(6–7) = 4.9 Hz	6	47.2	1.87	1.16 ± 0.06	1.2
			7	52.2	2.00	1.12 ± 0.04	1.1
			8	125.7	1.37	1.24 ± 0.04	1.8
7	3.82		9	142.0	0.89	10.8 ± 2	24.1
8	5.32	broad singlet	10	42.4	1.37	0.67 ± 0.02	1.0
10a	2.62		11	175.6	1.11[b]	21.7 ± 6	38.9
10s	1.75		12	51.5	1.43	3.7 ± 0.2	5.1
12	3.65		13	14.4	1.32	0.89 ± 0.04	1.3
13	0.95		14 (or 15)	39.8	1.57	1.47 ± 0.07	1.9
14, 15	3.30	multiplet	15 (or 14)	40.1	1.77	1.60 ± 0.07	1.8
16	1.7	broad singlet	16	16.5	1.41	2.5 ± 0.2	3.5
17, 18	2.8	multiplet	17 (or 18)	34.5	2.04	1.96 ± 0.05	2.0
			18 (or 17)	25.2	2.08	2.22 ± 0.07	2.2

[a] Average of two experiments, based upon integration. [b] Value from one experiment. [c] Wehrli, F. W. In *Topics in Carbon-13 NMR Spectroscopy*; Levy, G. C., Ed.; Wiley: New York, 1976; Vol. 2, p 353.

Scheme II



process that is difficult to rationalize if a "free" carbocation such as **3** were to intervene prior to nucleophilic attack by ethanediol.

Experimental Section

Melting points are uncorrected. High-resolution mass spectra were obtained by the Midwest Center for Mass Spectrometry at the University of Nebraska, Lincoln, NE 68588-0362.

Reaction of 1 with Ethanedithiol–F_3B·OEt_2. A solution of 1[3] (468 mg, 2.00 mmol) in methylene chloride (10 mL) was cooled to −78 °C by application of an external ice bath. To this cold solution was added sequentially with stirring ethanedithiol (470 mg, 5.00 mmol) and boron triflouride etherate (705 mg, 5.00 mmol). After 5 min, thin-layer chromatographic analysis of the reaction mixture indicated the absence of 1. The cold bath was removed, and the reaction mixture was allowed to warm to ca. 0 °C and then was quenched by addition of 10% aqueous sodium bicarbonate solution (15 mL) with vigorous stirring. The reaction mixture was allowed to warm slowly to ambient temperature and then was extracted with methylene chloride (3 × 15 mL). The combined extracts were washed sequentially with water (10 mL) and with brine (10 mL). The organic layer was dried (anhydrous magnesium sulfate) and filtered, and the filtrate was concentrated in vacuo. The residue was purified via column chromatography on silica gel (5% ethyl acetate–hexane mixed solvent as eluent). Pure **2** (650 mg, 80%) was thereby obtained as a colorless viscous oil: IR (neat) 2575 (w), 1730 (s), 1655 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 0.95 (d, J = 6.7 Hz, 3 H), 1.60 (br s, 1 H), 1.70 (br s, 3 H), 1.70–1.80 (m, 2 H), 2.23 (d, J = 9 Hz, 1 H), 2.30 (d, J = 15.5 Hz, 1 H), 2.50–2.68 (m, 2 H), 2.70–2.85 (m, 4 H), 2.90 (q, J = 6.7 Hz, 1 H), 3.05 (d, J = 15.5 Hz, 1 H), 3.25–3.40 (m, 4 H), 3.69 (s, 3 H), 3.83 (br s, 1 H), 5.30 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.41 (q), 16.51 (q), 25.26 (t), 34.52 (t), 39.79 (t), 40.12 (t), 41.19 (d), 42.46 (t), 47.08 (d), 47.69 (t), 51.59 (q), 52.12 (d), 52.91 (t), 61.20 (s), 67.68 (s), 125.67 (d), 142.03 (s), 175.73 (s).

Anal. Calcd for $C_{18}H_{28}O_2S_4$: M_r 404.0972. Found (high-resolution mass spectroscopy): M_r 404.0957.

NMR Experiments. Proton and carbon-13 NMR spectra were obtained at 300 and 75 MHz, respectively. Proton NMR experiments were performed at 4000-Hz spectral width, 32K transform, no delay between acquisitions. Carbon-13 NMR experiments were run with Waltz proton decoupling and typically were performed at 17 500-Hz spectral width, 32K transform, no delay between acquistions. Proton–proton NOE experiments were usually one transient with a continuous wave decoupling field with γH_2 = 112 Hz. Carbon-13 T_1 values were obtained by using the standard inversion-recovery pulse sequence with a 120 s delay time between acquisitions. Data were analyzed by using the manufacturer's standard three-parameter fitting routine. $^{13}C\{^1H\}$ NOE values were found from the ratio of the integration of peaks in ^{13}C NMR spectra run with and without NOE. A repetition delay time of 130 s was used. The NOE values listed in the table are the average of two determinations. COSY and relay COSY experiments were acquired with 1K data points × 128 increments (zero-filled to 1K). The mixing period used for the relay COSY experiment was 0.1 s.

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Synthesis of (±)-*threo*-3-[(Benzyloxycarbonyl)oxy]-2-fluorotetradecanoic Acid

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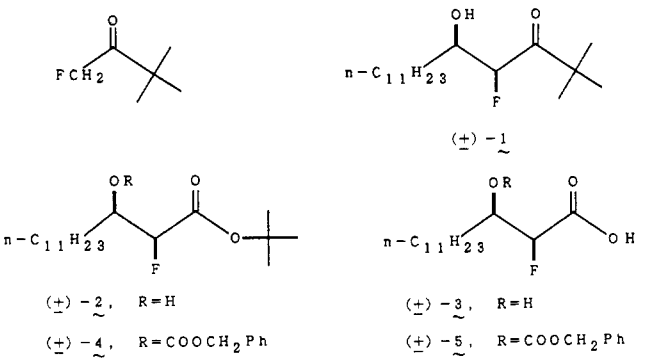
Endotoxic lipopolysaccharide (LPS) is a component of the outer membrane of Gram-negative bacteria, and most of its biological activity depends on its lipid A part.[1] Lipid A has two (*R*)-3-hydroxytetradecanoyl groups at the 2- and 3-positions of glucosamine, and also (*R*)-3-acyloxytetradecanoyl groups at the 2′- and 3′-positions of another glucosamine moiety (Figure 1). We are interested in the biological activity of lipid A analogues containing a fluorinated hydroxytetradecanoyl group at the 2-, 3-, 2′-, or 3′-position of two glucosamines. Therefore, we attempted to synthesize *threo*-3-[(benzyloxycarbonyl)oxy]-2-fluorotetradecanoic acid to obtain the fluorinated lipid A analogue.[2]

The synthesis of *threo*-2-fluoro-3-hydroxyalkanoic acids by the aldol reactions of the lithium enolate of ethyl fluoroacetate with various aldehydes has been reported by Welch et al.,[3] although the *threo*/*erythro* diastereoselectivity was moderate (ca. 1:3 to 1:1.2). It has also been reported that in aldol reactions of the lithium enolate of 1-fluoro-3,3-dimethyl-2-butanone with various aldehydes, a relatively high *threo* selectivity (ca. 16:1 to 49:1) was observed.[4] Therefore, we applied Welch's procedure to dodecanal. The result was excellent *threo* selectivity. Baeyer–Villiger reaction with various oxidizing agents of the resulting *threo*-2,2-dimethyl-4-fluoro-5-hydroxy-3-hexadecanone (1) gave the *tert*-butyl ester of (±)-*threo*-2-fluoro-3-hydroxytetradecanoic acid. The results are reported herein.

Treatment of the lithium enolate of 1-fluoro-3,3-dimethyl-2-butanone[4] with dodecanal[5] at −78 °C gave (±)-*threo*-2,2-dimethyl-4-fluoro-5-hydroxy-3-hexadecanone (1) in 78% yield as a crystalline solid (mp 35 °C) after chromatographic purification. In a gauche relationship, $J_{H4,H5}$ is predicted to be less than 5 Hz, in agreement with the observed value $J_{H4,H5}$ of 2.5 Hz.[4] The *erythro* isomer was not detected by ^1H and ^{13}C NMR analyses. Baeyer–Villiger oxidation of the ketone 1 with *m*-chloroperbenzoic acid, peracetic acid, trifluoroperacetic acid, or monoperoxyphthalic acid was carried out under various conditions.



However, the results were poor, due to formation of many byproducts. On the other hand, oxidation of 1 with 5 equiv of magnesium monoperphthalate hexahydrate in ethanol at 50 °C for 18 h gave (±)-*tert*-butyl *threo*-2-fluoro-3-hydroxytetradecanoate (2) in 57% yield accompanied by the starting ketone 1 (26%) after chromatographic separation. Treatment of 2 with trifluoroacetic acid yielded compound 3 quantitatively. In addition, compound 2 easily gave the benzyloxycarbonyl-protected compound 4 in the usual way, because the carboxylic acid was protected as its *tert*-butyl ester. Then, treatment of 4 with trifluoroacetic acid produced the corresponding acid 5 as a crystalline solid (mp 78 °C).

Thus the O-protected *threo*-2-fluoro-3-hydroxytetradecanoic acid was obtained in four steps from 1-fluoro-3,3-dimethyl-2-butanone.

Experimental Section

Melting points were uncorrected. ^1H NMR and ^{13}C NMR spectra were recorded at 60 and 67.8 MHz, respectively, using tetramethylsilane as an internal standard. Column chromatography was carried out on columns packed with Merck silica gel 60 (230–400 mesh ASTM) using slightly increased pressure (1.2 atm) for elution.

(±)-*threo*-2,2-Dimethyl-4-fluoro-5-hydroxy-3-hexadecanone (1). To a solution of hexamethyldisilazane (106.4 g, 0.66 mol) in THF (440 mL) was added a solution of butyllithium (1.6 M in hexane, 412 mL) at 0–10 °C under nitrogen with magnetic stirring. To the resulting solution was added a solution of 1-fluoro-3,3-dimethyl-2-butanone (74.4 g, 0.63 mol) in THF (300 mL) at −78 °C with stirring. After 5 min, dodecanal (115.8 g, 0.63 mol) was added with stirring at −78 °C. After 20 min of stirring the reaction mixture was quenched with a solution of acetic acid (40 g) in THF (200 mL), concentrated in vacuo, and diluted with EtOAc (2.5 L). The solution was washed with aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and concentrated to give an oily residue that was chromatographed on a silica gel (1.2 kg) column. Elution with cyclohexane–EtOAc (19:1) gave 148 g of 1 (78% yield) as a crystalline solid: mp 34–35 °C (needles from hexane); ^1H NMR (60 MHz) ($CDCl_3$) δ 0.8–1.0 (3 H, m), 1.2–2.0 (29 H, m), 2.17 (1 H, d, J = 7 Hz, OH), 4.96 (1 H, dd, J = 2.5 Hz, $J_{H,F}$ = 48 Hz, C_4-H), 4.0 (1 H, m, $J_{H,F}$ = 24 Hz, C_5-H); ^{13}C NMR ($CDCl_3$) δ 14.1, 22.7, 25.6, 25.7 (2 C), 29.3, 29.5, 29.57 (2 C), 29.63 (2 C), 31.9, 32.57, 32.6, 44.3, 71.7 (d, $J_{C,F}$ = 21.5 Hz, C-5), 95.7 (d, $J_{C,F}$ = 189.7 Hz, C-4), 212.5 (d, $J_{F,C}$ = 19.6 Hz, C-3); IR ν_{max} (Nujol) 3500, 1703 cm^{-1}; MS m/z 303 (M^+ + 1). Anal. Calcd for $C_{18}H_{35}O_2F$: C, 71.48; H, 11.66; F, 6.28. Found: C, 71.08; H, 11.96; F, 6.20.

(±)-*tert*-Butyl *threo*-2-Fluoro-3-hydroxytetradecanoate (2). A mixture of 1 (112.8 g) and magnesium monoperphthalate hexahydrate (923 g, 5 equiv) in ethanol (2.3 L) was stirred at 50 °C for 18 h. The reaction mixture was concentrated in vacuo, diluted with EtOAc (6 L), washed with brine, and filtered. The filtrate was dried over $MgSO_4$, filtered, and concentrated to give an oily mixture, which was chromatographed on a silica gel (5.4 kg) column. Elution with cyclohexane–EtOAc (19:1) gave 67.6 g of 2 (57% yield) and 29.6 g of 1 (26%): ^1H NMR ($CDCl_3$) δ 0.85–1.05 (3 H, m), 1.1–1.8 (29 H, m), 2.2 (1 H, broad, OH), 3.94 (1 H, m, $J_{H,F}$ = 25 Hz, C_3-H), 4.67 (1 H, dd, J = 3 Hz, $J_{H,F}$ = 49

(1) (a) Sidorezyk, Z.; Zähringer, U.; Rietchel, E. T. *Eur. J. Biochem.* **1983**, *173*, 15. (b) Imoto, M.; Kusumoto, S.; Shiba, T.; Naoki, H.; Iwashita, T.; Rietschel, E. T.; Wollenweber, H. W.; Galanos, C.; Luderitz, O. *Tetrahedron Lett.* **1983**, *24*, 4017.

(2) The protection of the 3-hydroxy group of 3 is necessary for further conversion to the lipid A analogues.

(3) (a) Welch, J. T.; Eswarakrishnan, S. *J. Chem. Soc., Chem. Commun.* **1985**, 186. (b) Welch, J. T.; Seper, K.; Eswarakrishnan, S.; Samartino, J. *J. Org. Chem.* **1984**, *49*, 4720.

(4) Welch, J. T.; Seper, K. W. *Tetrahedron Lett.* **1984**, *25*, 5247.

(5) When we use a solidified reagent stored for a long time, the yield becomes less than 10%.

(6) Compound 5 showed 41.4% inhibition of aldose reductase at 4 μg/mL in dimethyl sulfoxide.

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