SUPPORTING INFORMATION

Selective Epimerization of Rapamycin Via a Retroaldol/Aldol Mechanism Mediated by Titanium Tetraisopropoxide

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Compound Synthesis.

General Methods. All reagents and solvents were analytical grade and used as purchased without further purification. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker ARX-300 or DRX-600 instrument. Chemical shifts are reported in ppm downfield from tetramethylsilane. In cases where a mixture of rotamers is present, only the chemical shifts of the major rotamer are reported. Low resolution mass spectra (LRMS) were obtained on a Micromass Platform II quadrupole mass spectrometer operating in electrospray mode. Flash chromatography was performed on silica gel (Merck, 230-400 mesh). Analytical TLC was performed on silica gel 60 F_{254} plates (Merck). Rapamycin related reactions were monitored by both normal phase and reverse phase analytical HPLC at 280 nm wavelength. The normal phase HPLC uses Kromasil silica column (4.6 mm x 25 cm) with 4.0/42.5/50/200 : MeOH/EtOAc/Hexanes/CH_2Cl_2 as the eluent at 1.0 mL/min flow rate at room temperature. The reverse phase HPLC uses Kromasil C18 column (4.6 mm x 25 cm) with 80/20 : MeOH/H_2O as the eluent at 1.0 mL/min flow rate at 50˚C. Preparative HPLC separations were carried out on a Kromasil silica column (21.4 mm x 25 cm) at 20 mL/min flow rate.

General procedure for epimerization of rapamycin. To a solution of rapamycin (510 mg, 0.56 mmol) in CH_2Cl_2 (35.2 mL), $Ti(OiPr)_4$ (494 μL, 1.67 mmol) was added dropwise at room temperature. The reaction mixture turned pale yellow. After 30 min, the solution was poured into a separatory funnel containing a heterogeneous mixture of 1N HCl and EtOAc. The organic layer was sequentially washed with saturated aqueous $NaHCO_3$, H_2O, brine, dried over Na_2SO_4, filtered and concentrated under vacuum. The retention time for all the products are listed below.

Compound	*Normal Phase*	*Reverse Phase*
	retention time (min)	retention time (min)
28-secorapamycin (**5**)	15.89	13.80
28,29-bisepirapamycin (**4**)	24.51	14.24
29-epirapamycin (**3**)	25.88	13.11
rapamycin (**1**)	30.95	11.60
28-epirapamycin (**2**)	33.21	13.80
rapamycin tautomer	39.68	14.79
28-epirapamycin tautomer	43.26	14.54

28-Epirapamycin (2). The crude mixture was purified using silica gel flash chromatography (2/1 hexanes/acetone) to give **2** as a white solid (61%): ^{1}H NMR (DMSO-d_6, 600 MHz, 6:1 mixtures of trans:cis rotamers; data for the *trans*-rotamer) 6.43 (s, 1H, OH-13), 6.40 (dd, *J* = 14.5, 11.4 Hz, 1H, H-4), 6.24 (dd, *J* = 14.0, 11.0 Hz, 1H, H-3), 6.17 (dd, *J* = 14.5, 10.1 Hz, 1H, H-2), 6.11 (d, *J* = 11.0 Hz, 1H, H-5), 5.44 (dd, *J* = 14.5, 10.1 Hz, 1H, H-1), 5.02 (m, 1H, H-22), 4.93 (d, *J* = 7.9 Hz, 1H, H-20), 4.93 (s, 1H, H-26), 4.01 (d, *J* = 6.6 Hz, 1H, H-29), 4.01 (m, 1H, H-9), 3.84 (d, *J* = 6.6 Hz, 1H, H-28), 3.61 (d, *J* = 13.2 Hz, 1H, H-7), 3.44 (d, *J* = 14.0 Hz, 1H, H-16e), 3.30 (s, 3H, H-46), 3.21 (q, *J* = 8.3 Hz, 1H, H-25), 3.19 (m, 1H, H-43), 3.16 (s, 3H, H-50), 3.06 (d, *J* = 13.6 Hz, 1H, H-16a), 3.03 (s, 3H, H-36), 2.80 (m, 1H, H-42), 2.72 (dd, *J* = 17.1, 3.5 Hz, 1H, H-23R), 2.39 (dd, *J* = 17.5, 8.3 Hz, 1H, H-23S), 2.34 (m, 1H, H-31), 2.25 (m, 1H, H-33), 2.13 (d, *J* = 12.7 Hz, 1H, H-19e), 2.01 (m, 1H, H-12), 1.91 (d, *J* = 10.5 Hz, 1H, H-41e), 1.85 (t, *J* = 10.1 Hz, 1H, H-8), 1.81 (d, *J* = 13.6 Hz, 1H, H-10e), 1.74 (m, 1H, H-44e), 1.69 (s, 3H, H-49), 1.65 (m, 1H, H-18e), 1.64 (m, 1H, H-38), 1.63 (m, 1H, H-32), 1.61 (m, 1H, H-19a), 1.60 (s, 3H, H-35), 1.56 (m, 1H, H-17e), 1.52 (m, 2H, H-11e, H-45e), 1.34 (m, 1H, H-18a), 1.27 (m, 2H, H-17a, H-40), 1.17 (m, 1H, H-44a), 1.16 (m, 1H, H-10a), 1.10 (m, 1H, H-32S), 1.02 (m, 1H, H-39), 1.00 (d, *J* = 6.1 Hz, 3H, H-34), 0.94 (m, 1H, H-39), 0.84 (m, 1H, H-11a), 0.84 (d, *J* = 4.8 Hz, 3H, H-48), 0.83 (d, *J* = 5.7 Hz, 3H, H-51), 0.77 (d, *J* = 6.6 Hz, 3H, H-47), 0.73 (d, *J* = 6.6 Hz, 3H, H-37), 0.56 (q, *J* = 11.8 Hz, 1H, H-41); ^{13}C NMR (DMSO-d_6, 125 MHz) 210.7 (C-30), 207.9 (C-24), 199.4 (C-14), 169.4 (C-15), 166.6 (C-21), 139.4 (C-1), 138.0 (C-6,C-27), 132.5 (C-3), 130.6 (C-2), 127.5 (C-5), 127.1 (C-4), 125.4 (C-26), 98.9 (C-13), 84.8 (C-29), 83.8 (C-42), 82.2 (C-7), 76.2 (C-28), 74.0

(C-22), 73.2 (C-43), 66.2 (C-9), 57.4 (C-50), 56.8 (C-46), 55.5 (C-36), 50.8 (C-20), 45.4 (C-25), 43.6 (C-16), 40.4 (C-23), 40.2 (C-31), 39.9 (C-8), 39.1 (C-32), 38.5 (C-39), 35.8 (C-33), 35.4 (C-41), 34.8 (C-12), 33.3 (C-38), 32.8 (C-44), 32.6 (C-40), 31.1 (C-11), 29.5 (C-10), 26.3 (C-19), 26.2 (C-45), 24.4 (C-17), 21.6 (C-34), 20.4 (C-18), 15.6 (C-37), 15.5 (C-48), 15.2 (C-47), 13.7 (C-51), 12.8 (C-49), 10.3 (C-35); LRMS (ES+): $(M+Na)^+$ 936.64; (ES-): $(M-H)^-$ 912.08.

28-Epirapamycin tautomer: ^{1}H NMR (DMSO-d_6, 600 MHz, 2:1 mixture of *trans*:*cis* rotamers; data for the *trans*-rotamer): 7.36 (s, 1H), 6.46 (t, *J* = 13.9 Hz, 1H), 6.29-6.20 (m, 2H), 6.10 (t, *J* = 13.2, 1H), 5.39 (dd, *J* = 11.0, 14.3 Hz, 1H), 5.21 (brd, *J* = 9.2 Hz, 1H), 5.01 (d, *J* = 9.7 Hz, 1H), 4.95 (d, *J* = 4.7 Hz, 1H), 4.61 (d, *J* =12.4 Hz, 1H), 4.06 (brs, 1H),), 4.01 (d, *J* = 4.9 Hz, 1H), 3.76-3.68 (m, 2H), 3.32 (s, 3H), 3.18 (s, 3H), 3.07 (s, 3H), 2.85-2.79 (m, 1H), 2.73-2.66 (m, 2H), 2.52-2.40 (m, 2H), 2.32-2.22 (m, 1H); LRMS (ES+): $(M+Na)^+$ 936.43; (ES-): $(M-H)^-$ 912.25.

Benzaldehyde adduct 6. Rapamycin (648 mg, 0.71 mmol) was dissolved in CH_2Cl_2 (35.4 mL) and stirred at room temperature. Benzaldehyde (360 μL, 3.54 mmol) and $Ti(OiPr)_4$ (580 μL, 2.13 mmol) were added simultaneously producing a pale yellow solution. After 72 min, the solution was added to a separatory funnel containing a heterogeneous solution of 1N HCl and EtOAc. The organic layer was washed with saturated aqueous $NaHCO_3$, H_2O and brine, dried over $NaSO_4$, filtered and concentrated under vacuum. Flash chromatographic purification (silica gel, 25% EtOAc/hexanes) yielded four diastereomers as two mixtures of two diastereomers each, **6a** and **6b** as a white solids (combined 625 mg, 86%). **6a** (a mixture of two diastereomers, 1:1 ratio of rotamers for each diastereomer, data of characteristic peaks for trans rotamer are listed): ^{1}H NMR ($CDCl_3$, 600 MHz) of diastereomer one: 9.45 (s, 1H, H-28), 4.83 (s, 1H, H-13), 4.83 (brs, 1H, benzylic proton), 3.98 (d, *J* =6.1 Hz, 1H, H-29). Data for diastereomer two: 9.46 (s, 1H, H-28), 4.03 (s, 1H, H-13), 4.77 (brs, 1H, benzylic proton), 3.95 (d, *J* = 5.0 Hz, 1H, H-29); LRMS (ES+): $(M+Na)^+$ 1042.87; (ES-): $(M-H)^-$ 1018.27. **6b** (a mixture of two diastereomers, 1:1 ratio of rotamers for each diastereomer, data of characteristic peaks for trans rotamer are listed): ^{1}H NMR ($CDCl_3$, 600 MHz) for diastereomer one: 9.45 (s, 1H, H-28), 4.90 (brd, *J* = 5.5 Hz, 1H, benzylic proton), 4.79 (s, 1H, H-13), 3.86 (d, *J* =6.2 Hz, 1H, H-29). Data for diastereomer two: 9.44 (s, 1H, H-28), 4.93 (brd, *J* = 4.2 Hz, 1H, benzylic proton), 4.04 (s, 1H, H-13), 3.84 (d, *J* = 6.5 Hz, 1H, H-29); LRMS (ES+): $(M+Na)^+$ 1042.86; (ES-): $(M-H)^-$ 1019.38.

Macrocyclization of 6b to rapamycin diastereomers 2-4. To a solution of **6b** (173 mg, 0.17 mmol) in CH_2Cl_2 (85 mL) was added $Ti(OiPr)_4$ (150 μL, 0.51 mmol) at room temperature. The reaction mixture turned to a pale yellow solution. After 1.5 hour, the reaction was quenched by addition of 1N HCl. The organic layer was washed with saturated aqueous $NaHCO_3$, H_2O and brine, dried over $NaSO_4$, filtered and concentrated under vacuum. Individual diastereomers were not isolated, rather the chemical yield for combined rapamycin diastereomers was determined to be 63% by HPLC weight-based analysis of the product mixture. Uncyclized benzaldehyde adducts (**6b** and **6a** combined) were also recovered in the product mixture to the extent of 29% (determined by weight-based HPLC analysis).

Compound 8. To a solution of lithium bis(trimethylsilyl)amide (1M, 5 mL in THF) at -78 ^{0}C was added propiophenone (665 μL, 5.0 mmol). After 1 hr, 2,3-(methylenedioxy)benzaldehyde (750 mg, 5.0 mmol) in THF (5 mL) was added. The resulting solution was stirred for 40 min before saturated NH_4Cl was added. The reaction mixture was warmed to room temperature and diluted with ether, washed with 1N HCl, aqueous $NaHCO_3$, brine and dried over $MgSO_4$. Flash chromatographic purification (silica gel, 15% to 20% EtOAc/hexanes) afforded 0.9 g (63%) of **8** as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) (5.4:1 mixture of syn/anti diastereomers, data for syn diastereomer) 7.88 (t, *J* = 7.3 Hz, 2H), 7.51 (t, *J* = 7.3 Hz, 1H), 7.41 (d, *J* = 6.8 Hz, 2H), 6.92 (d, *J* = 7.9 Hz, 1H), 6.75 (t, *J* = 7.9 Hz, 1H), 6.67 (d, *J* = 7.8 Hz, 1H), 5.93 (d, *J* = 1.1 Hz, 1H), 5.83 (d, *J* = 1.1 Hz, 1H), 5.21 (dd, *J* = 13.1, 3.1 Hz, 1H), 3.85 (m, 1H), 3.27 (d, *J* = 3.1 Hz, 1H) 1.09 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 205.6, 147.5, 143.7, 136.2, 133.9, 129.1, 128.9, 124.3, 122.0, 120.5, 108.1, 101.3, 69.8, 45.2, 11.9; LRMS (ES+): $(M+Na)^+$ 307.09.

Compound 9. To a solution of **8** (66 mg, 0.23 mmol) in CH_2Cl_2 (4.6 mL) was added $Ti(OiPr)_4$ (68.5 μL, 0.23 mmol) followed by addition of phenyl acetaldehyde (109 μL, 0.93 mmol). After 40 min, the reaction mixture was diluted with ether, washed with 1N HCl, aqueous $NaHCO_3$, brine and dried over $MgSO_4$. Flash chromatographic purification (silica gel, 15% to 20% EtOAc/hexanes) afforded 36 mg (61%) of **9** as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) (only syn diastereomer) 7.84 (d, *J* = 7.6 Hz, 2H), 7.56 (t, *J* = 7.2 Hz, 1H), 7.45 (d, *J* = 7.7 Hz, 2H), 7.40-7.18 (m, 5H), 4.29 (brs, 1H), 3.52-3.46 (m, 1H), 2.94 (brs, 1H), 2.92-2.75 (m, 2H), 1.33 (d, *J* = 7.1 Hz, 3H); LRMS (ES+): $(M+Na)^+$ 277.08.

X-Ray Crystallographic Structure Determination of 28-Epirapamycin (2).

Data Collection

A clear crystal of $C_{51}H_{79}NO_{13}$ having approximate dimensions of 0.2 x 0.2 x 0.4 mm was mounted on a glass fiber. All measurements were made on a Rigaku AFC7R diffractometer with graphite monochromated Cu-Kα radiation and a 12kW rotating anode generator.

Cell constants and an orientation matrix for data collection, obtained from a least-squares refinement using the setting angles of 25 carefully centered reflections in the range $20.32 < 2\theta < 34.66°$ corresponded to a primitive orthorhombic cell with dimensions:

$$a = 20.69(1)\ \text{Å}$$
$$b = 22.56(1)\ \text{Å}$$
$$c = 11.22(2)\ \text{Å}$$
$$V = 5238(8)\ \text{Å}^3$$

For Z = 4 and F.W. = 914.18, the calculated density is 1.16 g/cm^3. The systematic absences of:

$$h00: h \neq 2n$$
$$0k0: k \neq 2n$$
$$001: 1 \neq 2n$$

uniquely determine the space group to be:

$$P2_12_12_1\ (\#19)$$

The data were collected at a temperature of 20 ± 1°C using the ω-2θ scan technique to a maximum 2θ value of 110.1°. Omega scans of several intense reflections, made prior to data collection, had an average width at half-height of 0.20° with a take-off angle of 6.0°. Scans of (0.84 + 0.35 tan θ)° were made at a speed of 0.0°/min (in omega). The weak reflections ($I < 15.0\sigma(I)$) were rescanned (maximum of 4 rescans) and the counts were accumulated to ensure good counting statistics. Stationary background counts were recorded on each side of the reflection. The ratio of peak counting time to background counting time was 2:1. The diameter of the incident beam collimator was 0.5 mm and the crystal to detector distance was 400 mm.

Data Reduction

A total of 3724 reflections was collected. The intensities of three representative reflection were measured after every 50 reflections. No decay correction was applied.

The linear absorption coefficient, μ, for Cu-Kα radiation is 6.3 cm^{-1}. Azimuthal scans of several reflections indicated no need for an absorption correction. The data were corrected for Lorentz and polarization effects.

Structure Solution and Refinement

The structure was solved by and expanded using Fourier techniques[1]. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included but not refined. The final cycle of full-matrix least squares refinement[2] was based on 1643 observed reflections ($I > 3.00\sigma(I)$) and 586 variable parameters and converged (largest parameter was 3.23 times its esd) with unweighted and weighted agreement factors of:

$$R = \Sigma||Fo| - |Fc||/\Sigma|Fo| = 0.056$$
$$R_w = \sqrt{(\Sigma\omega(|Fo| - |Fc|)^2/\Sigma\omega Fo^2)}] = 0.062$$

The standard deviation of an observation of unit weight[3] was 2.42. The weighting scheme was based on counting statistics and included a factor (p = 0.002) to downweight the intense reflections. Plots of $\Sigma\omega(|Fo|-|Fc|)^2$ versus $|Fo|$, reflection order in data collection, $\sin\theta/\lambda$ and various classes of indices showed no unusual trends. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.16 and -0.17 $e^-/Å^3$, respectively.

Neutral atom scattering factors were taken from Cromer and Wabers.[4] Anomalous dispersion effects were included in Fcalc[5]; the values for Δf' and Δf'' were those of Creagh and McAuley[6]. The values for the mass attenuation coefficients are those of Creagh and Hubbel[7]. All calculations were performed using the teXsan[8] crystallographic software package of Molecular Structure Corporation.

References

1. DIRDIF92: Beurskens, P.T., Admiraal, G., Beurskens, G., Bosman, W.P., Garcia-Granda, S., Gould, R.O., Smits, J.M.M. and Smykalla, C. (1992). The DIRDIF program system, Technical Report of the Crystallography Laboratory, University of Nijmegen, The Netherlands.

2. Least-Squares:
   Function minimized: $\Sigma\omega(|Fo| - |Fc|)^2$
   where $w = 1/\sigma^2(Fo) = 4Fo2/\sigma^2(Fo^2)$
   $\sigma^2(Fo^2) = s^2(C+R^2B)+(pFo^2)^2/Lp^2$
   S = Scan rate
   C = Total Integrated Peak Count
   R = Ratio of Scan Time to background counting time
   B = Total Background Count
   Lp = Lorentz-polarization factor
   p = p-factor

3. Standard deviation of an observation of unit weight:
   $\sqrt{(\Sigma\omega(|Fo| - |Fc|)^2/(No - Nv)}$
   where: No = number of observations
   Nv = number of variables

4. Cromer, D. T. & Waber, J. T.; "International Tables for X-ray Crystallography", Vol. IV, The Kynoch Press, Birmingham, England, Table 2.2 A (1974).

5. Ibers, J. A. & llamilton, W. C.; Acta Crystallogr., 17, 781 (1964).

6. Creagh, D. C. & McAuley, W.J .; "International Tables for Crystallography", Vol C, (A.J.C. Wilson, ed.), Kluwer Academic Publishers, Boston, Table 4.2.6.8, pages 219-222 (1992).

7. Creagh, D. C. & Hubbell, J.H.; "International Tables for Crystallography", Vol C, (A.J.C. Wilson, ed.), Kluwer Academic Publishers, Boston, Table 4.2.4.3, pages 200-206 (1992).

8. teXsan: Crystal Structure Analysis Package, Molecular Structure Corporation (1985 & 1992).

Experimental Details

A. Crystal Data

Empirical Formula	$C_{51}H_{79}NO_{13}$
Formula Weight	914.18
Crystal Color, Habit	clear

Crystal Dimensions	0.2 x 0.2 x 0.4 mm
Crystal System	orthorhombic
Lattice Type	P
No. of Reflections Used for Unit Cell Determination (2θ range)	25 (20.3 - 34.7°)
Omega Scan Peak Width at Half-height	0.20°
Lattice Parameters	a = 20.69(1) Å b = 22.56(1) Å c = 11.22(2) Å V = 5238(8) Å^3
Space Group	$P2_12_12_1$ (#19)
Z value	4
D_{calc}	1.159 g/cm^3
F_{000}	1984.00
μ(MoKα)	6.35 cm^{-1}

B. Intensity Measurements

Diffractometer	Rigaku AFC7R
Radiation	CuKα (N = 1.54178 Å) graphite monochromated
Attenuator	Ni foil (factors = 1.00, 8.90, 8.90, 8.90)
Take-off Angle	6.0°
Detector Aperture	6.0 mm horizontal; 6.0 mm vertical
Crystal to Detector Distance	40 cm
Temperature	20.0°C
Scan Type	ω-2θ
Scan Rate	0.0°/min (in omega) (4 rescans)
Scan Width	(0.84 + 0.35 tanθ)°
$2\theta_{max}$	110.1°
No. of Reflections Measured	Total: 3724
Corrections	Lorentz-polarization

C. Structure Solution and Refinement

Structure Solution	Direct Methods
Refinement	Full-matrix least-squares
Function Minimized	$\Sigma\omega(\|Fo\| - \|Fc\|)^2$
Least Squares Weights	$1/\sigma^2(Fo) = 4Fo2/\sigma^2(Fo^2)$
p-factor	0.00
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (I>3.00σ(I))	1643
No. Variables	586
Reflection/Parameter Ratio	2.80
Residuals: R; Rw	0.056; 0.062
Goodness of Fit Indicator	2.42
Max Shift/Error in Final Cycle	3.23
Maximum peak in Final Diff. Map	0.16 e$^-$/Å^3
Minimum peak in Final Diff. Map	-0.17 e$^-$/Å^3

Figure 1. Molecular structure and atomic numbering of 28-epirapamycin (**2**).

Table 1. Atomic coordinates and B_{iso}/B_{eq}

atom	x	y	z	Beq
0(1)	0.0677(4)	0.3550(4)	0.5491(8)	5.1(2)
0(2)	0.0742(4)	0.4176(4)	0.3057(9)	6.2(3)
0(3)	0.2013(4)	0.4230(4)	0.2734(8)	5.1(2)
0(4)	0.3040(5)	0.2571(4)	0.0366(10)	7.5(3)
0(6)	0.1748(4)	0.0436(4)	0.605(1)	7.0(3)
0(8)	0.0961(4)	0.2066(3)	0.5188(8)	4.4(2)
0(10)	0.1650(4)	0.4467(4)	1.0366(8)	6.2(3)
0(11)	0.2381(4)	0.4274(4)	0.8421(8)	5.4(3)
0(12)	0.0065(4)	0.1679(4)	0.5981(9)	6.7(3)
0(14)	0.4130(5)	-0.1178(4)	0.732(1)	9.6(4)
0(15)	0.1874(3)	0.3216(3)	0.3006(7)	3.6(2)
0(16)	0.4035(6)	0.0560(6)	0.878(1)	11.1(4)
0(17)	0.4693(5)	0.0424(6)	0.881(1)	9 9(4)
N(1)	0 0397(5)	0.2914(4)	0.3997(9)	4.0(3)
C(071)	0.1376(7)	0.1686(6)	0.588(1)	5.1(4)
C(073)	0.1033(6)	0.3808(5)	0.357(1)	4.2(4)
C(075)	0.2539(5)	0.2467(5)	0.225(1)	4 5(3)
C(080)	0.3112(7)	0.0342(6)	0.627(1)	5 0(4)
C(082)	0.2784(7)	0.0645(6)	0.524(1)	5.8(4)
C(083)	0.1784(5)	0.3792(6)	0.350(1)	3 9(4)
C(085)	0.2113(6)	0.3859(6)	0.472(1)	4.6(4)
C(088)	0.0331(7)	0.2038(6)	0.537(1)	5.2(4)
C(089)	0.0698(5)	0.3394(5)	0.445(1)	3.8(3)
C(090)	0.2545(6)	0.3097(6)	0.274(1)	4.8(4)
C(093)	0.4584(6)	0.0671(7)	0.260(1)	6.1(4)
C(095)	0.3164(6)	0.2329(6)	0.154(1)	5.1(4)
C(096)	0.0001(6)	0.2555(6)	0.478(1)	4.5(3)
C(097)	0.3322(6)	0.1671(6)	0.144(1)	5 0(4)
C(106)	0.2825(6)	0.3743(7)	0.448(1)	6.1(4)
C(111)	0.2244(7)	0.1747(6)	0.755(1)	7 3(5)
C(119)	0.2018(7)	0.4460(6)	0.525(1)	6.5(5)
C(128)	0.2930(7)	0.3150(6)	0.388(1)	6.4(5)
C(129)	0.0546(6)	0.2658(5)	0.279(1)	4 4(4)
C(130)	0.0064(6)	0.2468(6)	0.216(1)	5.4(4)
C(131)	0.0436(8)	0.2032(7)	0.295(2)	8.0(5)
C(132)	-0.0620(6)	0.2339(6)	0.413(1)	5 7(4)
C(133)	0.3544(9)	0.2528(7)	-0.040(2)	10.4(6)
C(134)	0.2797(7)	0.1267(6)	0.088(1)	5.9(4)
C(137)	0.2041(6)	0.3777(6)	0.893(1)	4.2(4)
C(138)	0.1484(7)	0.4032(6)	0.950(1)	5 4(4)
C(139)	0.1045(7)	0.3563(6)	1.009(1)	7.1(5)
C(140)	0.0859(6)	0.3103(6)	0.920(1)	5.2(4)
C(141)	0.1467(7)	0.2824(6)	0.855(1)	5.1(4)
C(142)	0.1843(6)	0.3308(6)	0.798(1)	4.9(4)
C(143)	0.2078(7)	0.0798(6)	0.548(1)	5.8(4)
C(144)	0.1810(7)	0.1361(5)	0.501(1)	5 4(4)
C(145)	0.1203(6)	0.2380(6)	0.761(1)	5 3(4)
C(146)	0.1708(6)	0.2080(6)	0.681(1)	4 5(4)
C(147)	0.3880(6)	0.1472(6)	0.190(1)	5.1(4)

Table 1. Atomic coordinates and B_{iso}/B_{eq} (continued)

atom	x	y	z	Beq
C(148)	0.4071(6)	0.0852(6)	0.201(1)	4 9(4)
C(149)	0.5196(6)	-0.0099(5)	0.356(1)	5.1(4)
C(150)	0.5301(7)	-0.0743(7)	0.391(1)	6.2(5)
C(151)	0.6003(8)	-0.0884(7)	0.366(1)	8.3(5)
C(152)	0.5151(7)	-0.0821(6)	0.525(1)	6.2(4)
C(153)	0 4454(7)	-0.0654(6)	0.553(1)	5 5(4)
C(154)	0 4759(7)	0.0062(5)	0.278(1)	5.4(4)
C(155)	0 3995(7)	-0.1060(7)	0.484(2)	8.4(5)
C(156)	0.4359(6)	-0.0751(7)	0.686(1)	6.6(5)
C(157)	0.4089(6)	0.0964(6)	0.629(2)	8.8(5)
C(159)	0.3043(8)	0.4162(7)	0.814(1)	7.3(5)
C(160)	0.4525(7)	-0.0218(7)	0.765(1)	6.7(5)
C(164)	0.5305(8)	-0.0393(7)	0.910(2)	8.5(5)
C(165)	0.3919(7)	0.0148(7)	0.783(1)	7.1(5)
C(167)	0.3676(6)	0.0470(6)	0.674(1)	4.8(4)
C(168)	0.2824(8)	0.0255(8)	0.410(1)	8.6(6)
H(1)	0.1711	0.4426	0.2331	3.0000
H(2)	0.3968	0.0936	0.8479	3.0000
H(4)	0.2760	0.0065	0.6518	3.0000
H(5)	0.3008	0.1042	0.4881	3.0000
H(7)	0.1948	0.3439	0.5414	3.0000
H(8)	0.4906	0.0924	0.2846	3.0000
H(9)	0.2991	0.4051	0.3947	3.0000
H(10)	0.2059	0.1494	0.8118	3.0000
H(11)	0.1580	0.4501	0.5541	3.0000
H(12)	0.3383	0.3095	0.3717	3.0000
H(13)	0.0760	0.2954	0.2319	3.0000
H(14)	-0.0845	0.2059	0.4631	3.0000
El(15)	0.2596	0.1482	0.0255	3.0000
El(16)	0 0777	0.2738	0.9599	3.0000
H(17)	0.1657	0.2636	0.9080	3.0000
H(18)	0.2321	0.3201	0.7652	3.0000
H(19)	0.1715	0.3515	0.7341	3 0000
H(20)	0.1581	0.1284	0.4300	3.0000
H(21)	0.0908	0.2583	0.7106	3.0000
El(22)	0.1914	0.2363	0.6363	3.0000
H(23)	0.4051	0.1710	0.2479	3.0000
H(24)	0.4958	-0.1068	0.3461	3.0000
H(25)	0.6140	-0.1235	0.4027	3.0000
H(26)	0.5152	-0.1211	0.5251	3.0000
H(27)	0.5432	-0.0478	0.5857	3.0000
H(28)	0 4444	-0.0135	0.5340	3.0000
H(29)	0.4404	-0.0288	0.2243	3.0000
H(30)	0.4092	-0.1462	0.5033	3 0000
H(31)	0.4022	0.1310	0.6727	3.0000
H(32)	0.3245	0.4491	0.7759	3.0000
H(33)	0.3089	0.3822	0.7618	3.0000
H(34)	0.3525	-0.0093	0.8087	3.0000
H(35)	0.2835	-0.0158	0.4336	3.0000
H(36)	0.2505	0.2190	0.2904	3.0000

Table 1. Atomic coordinates and B_{iso}/B_{eq} (continued)

atom	x	y	z	Beq
H(37)	0.3634	0.2123	-0.0578	3.0000
H(38)	0 3475	0.2741	-0.1106	3.0000
H(39)	0.0642	0.3195	0.8601	3.0000
H(40)	0.3872	0.0482	0.1510	3.0000
H(41)	0.6098	-0.0888	0.2835	3.0000
H(42)	0.3560	-0.0979	0.5096	3.0000
H(43)	0.5465	0.0199	0.3911	12.4158
H(45)	0.0328	0.2800	0.1999	6.8710
H(46)	0.0046	0.2279	0.1419	6.8710
H(49)	0.2486	0.1163	0.1463	7.3217
H(50)	0.3001	0.0926	0.0579	8.3326
H(51)	-0.0905	0.2664	0.3984	5.7366
H(52)	0.0828	0.2328	0.2877	5.8235
H(53)	-0.0142	0.2815	0.5400	5.8235
H(56)	0.2501	0.1504	0.7001	9.1848
H(57)	0.2527	0.2021	0.7912	7.2724
H(58)	0.0978	0.2075	0.8029	7.3217
H(60)	0.0666	0.3758	1.0403	7.3217
H(61)	0.1232	0.4223	0.8895	7.3217
H(62)	0.2300	0.3593	0.9515	5.8235
H(63)	0.3292	0.4071	0.8851	8.4163
H(65)	0.1481	0.4441	1.1152	8.0803
H(67)	0.2439	0.0312	0.3638	11.0960
H(68)	0.3188	0.0345	0.3652	5.8235
H(69)	0 4539	0.0852	0.6327	10.4626
H(70)	0.3987	0.1033	0.5462	8.4163
H(73)	0.5462	0.0015	0.9066	10.1388
H(74)	0.4033	-0.0995	0.4024	9.3652
H(75)	0.6279	-0.0559	0.4003	5.9629
H(76)	0.3524	0.2527	0.1889	6.0404
H(77)	0.2173	0.2414	0.1748	6.0404
H(78)	0.2711	0.3367	0.2160	9.1848
H(80)	0 3070	0.3766	0.5198	9.1848
H(81)	0.2305	0.4528	0.5892	8.6030
H(82)	0.2082	0.4761	0.4657	7.6051
H(84)	0.1121	0.1395	0.6292	7.9236
H(85)	0.2800	0.2845	0 4426	6.6113
H(86)	-0.0808	0.1907	0.2514	9.8834
H(87)	0.0164	0.1698	0.3081	11.5212
H(88)	0 3933	0.2688	-0.0017	6.6552
H(89)	0.1271	0.3391	1.0749	6.5927
H(90)	0.2174	0.1616	0.4823	9.5090
H(91)	0.5383	-0.0532	0.9891	10.4522
H(92)	0.5573	-0.0617	0.8564	9.5090
H(93)	0.4879	0 0026	0.7301	7.6051
H(95)	0.3114	0.1614	0.2226	10.9306

$$B_{eq} = 8/3\ \pi^2(U_{11}(aa^*)^2 + U_{22}(bb^*)^2 + U_{33}(bb^*)^2 + 2U_{12}aa^*bb^*\cos\gamma + 2U_{13}aa^*cc^*\cos\beta + 2U_{23}bb^*cc^*\cos\alpha)$$

Table 2. Anisotropic Displacement Parameters

atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
0(1)	0.055(6)	0.083(7)	0.055(6)	-0.003(6)	0.006(6)	-0.022(6)
0(2)	0.047(5)	0 073(7)	0.115(9)	0.009(6)	0.008(6)	0.022(7)
0(3)	0 058(6)	0.070(6)	0.065(7)	0.007(6)	0.000(6)	0.018(6)
0(4)	0.108(8)	0.095(7)	0.081(8)	0.031(7)	0.033(8)	0.025(7)
0(6)	0.059(6)	0.068(7)	0.14(1)	0.006(6)	0.009(7)	0.032(7)
0(8)	0.041(5)	0.066(6)	0.058(6)	0.007(5)	-0.010(5)	0.017(6)
0(10)	0.107(7)	0.072(7)	0 057(7)	-0.008(6)	0.022(6)	-0.009(6)
0(11)	0.068(6)	0.073(6)	0.065(7)	-0.004(6)	0.002(6)	-0.004(6)
0(12)	0.056(6)	0.095(7)	0.103(8)	-0.020(6)	0.007(7)	0.046(7)
0(14)	0.121(9)	0.088(8)	0.16(1)	-0.010(8)	0.049(9)	0.054(8)
0(15)	0 035(5)	0.041(5)	0.062(6)	0.003(5)	0.003(5)	-0.004(5)
0(16)	0.125(9)	0.19(1)	0.107(10)	0.036(9)	-0.011(9)	0.052(10)
0(17)	0.068(7)	0.21(1)	0.098(10)	-0.003(8)	-0.008(7)	0 058(9)
N(1)	0.052(7)	0.067(7)	0.034(7)	0.006(6)	0.007(6)	0.012(7)
C(071)	0.087(10)	0.055(9)	0.054(10)	-0.019(9)	-0.014(9)	-0.003(9)
C(073)	0.08(1)	0.025(8)	0.060(10)	-0.009(8)	0 009(9)	0.014(8)
C(075)	0.034(7)	0.056(9)	0.08(1)	0.017(7)	0.010(8)	0.002(9)
C(080)	0.07(1)	0.064(10)	0.06(1)	-0.014(9)	0.006(10)	0.004(9)
C(082)	0.08(1)	0.073(10)	0.07(1)	-0.021(9)	0.00(1)	0.02(1)
C(083)	0.025(7)	0.072(10)	0.051(10)	-0.005(8)	0.001(8)	0.016(9)
C(085)	0.049(9)	0.08(1)	0.045(9)	0.010(8)	0.002(9)	-0 003(9)
C(088)	0.08(1)	0.07(1)	0.05(1)	-0.006(10)	-0.01(1)	-0.005(10)
C(089)	0.024(7)	0.041(8)	0.08(1)	-0.005(7)	-0.013(8)	-0.002(9)
C(090)	0.041(8)	0.07(1)	0.067(10)	-0.001(8)	-0.006(9)	-0.003(9)
C(093)	0.054(9)	0.11(1)	0.07(1)	-0.003(10)	-0.012(9)	-0.01(1)
C(095)	0.061(10)	0.05(1)	0.08(1)	0 007(9)	0.005(10)	0.010(9)
C(096)	0.035(8)	0.062(9)	0.07(1)	0.003(8)	0.007(9)	0.006(9)
C(097)	0.058(9)	0.061(9)	0.07(1)	-0.013(8)	0.028(9)	0.015(9)
C(106)	0.067(10)	0.12(1)	0.048(10)	-0.01(1)	0 000(9)	-0.02(1)
C(111)	0.12(1)	0.08(1)	0.08(1)	0.00(1)	-0.02(1)	-0.02(1)
C(119)	0.09(1)	0.07(1)	0.09(1)	-0.011(10)	0.01(1)	-0.02(1)
C(128)	0.08(1)	0.09(1)	0.07(1)	0.033(9)	0.02(1)	0.00(1)
C(129)	0.071(9)	0.051(9)	0.046(9)	-0.005(7)	0.010(8)	-0.009(8)
C(130)	0.059(8)	0.07(1)	0.08(1)	-0.009(9)	-0.017(10)	0.007(10)
C(131)	0.10(1)	0.13(1)	0.08(1)	-0.06(1)	0.00(1)	0.00(1)
C(132)	0 047(9)	0.07(1)	0.09(1)	-0.020(9)	0.01(1)	0.022(10)
C(133)	0.21(2)	0.09(1)	0.09(1)	0.03(1)	0.07(1)	0.03(1)
C(134)	0.08(1)	0.08(1)	0.07(1)	0.013(10)	0.025(10)	-0.017(10)
C(137)	0.060(9)	0.061(9)	0.039(8)	0.007(8)	0.005(9)	0 008(8)
C(138)	0.10(1)	0.055(10)	0.05(1)	-0.008(10)	-0.01(1)	-0.025(9)
C(139)	0.10(1)	0.09(1)	0.07(1)	-0.040(10)	0.01(1)	0.03(1)
C(140)	0.07(1)	0.07(1)	0.06(1)	-0.008(9)	0.013(9)	0.008(9)
C(141)	0.07(1)	0.09(1)	0.036(9)	-0.004(10)	-0.016(9)	0.012(9)
C(142)	0 055(9)	0.08(1)	0.054(9)	-0.005(9)	0.005(8)	0.021(10)
C(143)	0.068(10)	0.08(1)	0.07(1)	-0.010(9)	0.006(10)	-0.01(1)
C(144)	0.10(1)	0.049(9)	0.06(1)	0.017(9)	0.011(10)	-0.011(9)
C(145)	0.09(1)	0.050(9)	0.06(1)	0.000(9)	-0.019(10)	0.013(9)
C(146)	0.065(10)	0.066(9)	0.04(1)	0.005(9)	0.012(9)	0.006(9)
C(147)	0.051(9)	0.09(1)	0.055(10)	-0.001(9)	-0 003(9)	-0.012(9)
C(148)	0.059(9)	0.051(9)	0.08(1)	-0.004(9)	0.002(10)	-0.004(9)

Table 2. Anisotropic Displacement Parameters (continued)

atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
C(149)	0.069(10)	0.063(9)	0.06(1)	0.040(8)	0.006(9)	0.021(8)
C(150)	0.057(9)	0.08(1)	0.09(1)	0.028(9)	0.02(1)	0.00(1)
C(151)	0.16(2)	0.09(1)	0.06(1)	0.02(1)	0.02(1)	0.04(1)
C(152)	0.08(1)	0.07(1)	0.09(1)	0.018(9)	0.02(1)	0.00(1)
C(153)	0.08(1)	0.07(1)	0.06(1)	-0.005(9)	0.003(9)	0.003(9)
C(154)	0.09(1)	0 043(9)	0.07(1)	0.025(8)	-0.01(1)	0 005(9)
C(155)	0.09(1)	0.10(1)	0.12(2)	-0.01(1)	0.01(1)	-0.02(1)
C(156)	0.052(10)	0.10(1)	0.10(1)	0.024(10)	0.02(1)	0.02(1)
C(157)	0.048(9)	0.06(1)	0.23(2)	-0.012(8)	-0.04(1)	0.02(1)
C(159)	0.10(1)	0.11(1)	0.08(1)	0.00(1)	0.00(1)	-0.01(1)
C(160)	0.07(1)	0.13(1)	0.06(1)	0.04(1)	0.006(10)	0.03(1)
C(164)	0.10(1)	0.11(1)	0.11(1)	-0.01(1)	-0.06(1)	0.01(1)
C(165)	0.10(1)	0.10(1)	0.06(1)	-0.02(1)	-0.03(1)	-0.03(1)
C(167)	0.060(9)	0.048(9)	0.08(1)	-0.013(8)	0.00(1)	-0.002(9)
C(168)	0.12(1)	0.13(1)	0.08(1)	0.05(1)	0.01(1)	0.04(1)

The general temperature factor expression:

$$\exp(-2\pi^2(a^{*2}U_{11}h^2 + b^{*2}U_{22}k^2 + c^{*2}U_{33}l^2 + 2a^*b^*U_{12}hk + 2a^*c^*U_{13}hl + 2b^*c^*U_{23}kl))$$

NMR Structure Determination of 28-Epirapamycin (2), 29-Epirapamycin (3), and 28,29-Bisepirapamycin (4).

Two dimensional NMR homonuclear (^{1}H-^{1}H) experiments (COSY, ROESY, TOCSY and NOESY) of a 10 mM DMSO-d_6 solution of rapamycin and compounds **2-4** were acquired on a Bruker DRX600 spectrometer using standard methods.[1] The direct one bond ^{13}C-^{1}H (HETCOR) and multiple bond ^{13}C-^{1}H (HMBC) correlations were obtained using gradient NMR methods.[2,3] The ^{13}C and ^{1}H NMR assignment of rapamycin agrees well with that reported earlier.[4]

The NMR basis for the assignment of the stereochemistry at positions 28 and 29 for compounds **2-4** is illustrated by describing the process for compound **2** (28-epirapamycin). Table 1 compares a subset of assignments for rapamycin and compound **2**.

Table 1: Assignment of ^{13}C and ^{1}H NMR Chemical shifts in DMSO-d_6 at 300°K.

Atoms	Rapamycin		Compound **2**	
	δ(^{1}H)	δ(^{13}C)	δ(^{1}H)	δ(^{13}C)
CH(26)	5.08	125.0	4.94	125.4
C(27)	-	137.0	-	138.0
CH(28)	4.01	75.7	3.84	76.2
CH(29)	3.95	85.5	4.01	84.8
C(30)	-	210.7	-	212.6
CH_3(49)	1.74	13.4	1.70	12.8
CH_3(50)	3.15	57.0	3.17	57.4

In the X-ray structure of rapamycin, the methyl(49) group and the CH(28) proton lie in a gauche orientation. In the HMBC spectrum of rapamycin, no long-range correlation peak was observed between the two groups due to the small value of $^3J_{C\text{-}H}$, consistent with the gauche orientation of the groups. However, in the corresponding spectrum of compound **2**, the peak between the carbon of the methyl(49) group and the CH(28) proton appeared clearly indicating the $^3J_{C\text{-}H}$ has increased consistent with the premise that positions of H(28) and OH(28) are swapped-i.e. that an epimerization has occurred at the C(28) carbon. Moreover, based on the same X-ray structure, the methyl(49) group is equidistant from the CH(28) and CH(29) protons. As expected, in the NOESY spectrum of rapamycin, two peaks of almost equivalent intensity were observed. In the NOESY spectrum of compound **2**, the peak between the methyl(49) group protons and the CH(28) proton has reduced intensity compared to the peak between the methyl(49) group protons and the CH(29) proton, indicating that the distance between the methyl group protons and the CH(28) proton has increased, consistent with an epimerization at C(28) carbon. Therefore, both through bond (HMBC) and through space (NOESY) experiments indicate that an epimerization has occurred at the C(28) carbon position. This analysis was confirmed by X-ray crystallographic analysis.

Compounds **3** and **4** were analyzed in similar fashion. The chemical shift assignments for compounds **2**, **3** and **4** are shown in Table 2 below.

Table 2: Assignment of ^{13}C and ^{1}H NMR Chemical shifts in DMSO-d_6 at 300°K of compounds **2-4**.

Atom(s)	Compound **2**		Compound **3**		Compound **4**	
	$\delta(^1H)$	$\delta(^{13}C)$	$\delta(^1H)$	$\delta(^{13}C)$	$\delta(^1H)$	$\delta(^{13}C)$
CH(1)	5.46	139.4	5.33	140.5	5.36	140.2
CH(2)	6.13	130.6	6.14	129.8	6.17	129.5
CH(3)	6.16	132.5	6.14	132.8	6.13	133.2
CH(4)	6.41	127.1	6.39	126.9	6.38	126.5
CH(5)	6.11	127.2	6.02	127.5	6.05	127.5
C(6)	-	138.0	-	137.6	-	137.4
CH(7)	3.62	82.2	3.58	82.5	3.62	82.5
CH_2(8)	1.15($H_{pro\text{-}R}$), 1.85($H_{pro\text{-}S}$)	39.9	1.29($H_{pro\text{-}R}$), 1.83($H_{pro\text{-}S}$)	40.1	1.34($H_{pro\text{-}R}$), 1.85($H_{pro\text{-}S}$)	39.9
CH(9)	4.00	66.2	3.96	66.3	3.91	66.3
CH_2(10)	1.16(H_{ax}), 1.82(H_{eq})	29.5	1.16(H_{ax}), 1.78(H_{eq})	29.8	1.17(H_{ax}), 1.78(H_{eq})	30.0
CH_2(11)	0.84(H_{ax}), 1.52(H_{eq})	31.1	0.86(H_{ax}), 1.52(H_{eq})	31.14	0.87(H_{ax}), 1.53(H_{eq})	31.3
CH(12)	2.02	34.8	1.98	35.1	2.01	34.8
C(13)	-	98.9	-	98.9	-	99.0
C(14)	-	199.4	-	-	-	199.2
C(15)	-	169.4	-	169.4	-	169.0
CH_2(16)	3.05(H_{ax}), 3.43(H_{eq})	43.6	3.11(H_{ax}), 3.44(H_{eq})	43.5	3.07(H_{ax}), 3.45(H_{eq})	43.5
CH_2(17)	1.27(H_{ax}), 1.57(H_{eq})	24.4	1.31(H_{ax}), 1.57(H_{eq})	24.4	1.30(H_{ax}), 1.57(H_{eq})	24.5
CH_2(18)	1.40(H_{ax}), 1.66(H_{eq})	20.43	1.30(H_{ax}), 1.67(H_{eq})	20.4	1.31(H_{ax}), 1.68(H_{eq})	20.6
CH_2(19)	1.60(H_{ax}), 2.09(H_{eq})	26.3	1.58(H_{ax}), 2.07(H_{eq})	26.4	1.59(H_{ax}), 2.11(H_{eq})	26.3
CH(20)	4.94	50.8	4.92	50.9	4.95	50.9
C(21)	-	166.6	-	167.4	-	166.7
CH(22)	5.03	74.0	5.07	73.8	5.08	74.0
CH_2(23)	2.37($H_{pro\text{-}S}$), 2.74($H_{pro\text{-}R}$)	40.4	2.55($H_{pro\text{-}S}$), 2.65($H_{pro\text{-}R}$)	40.7	2.57($H_{pro\text{-}S}$), 2.79($H_{pro\text{-}R}$)	40.2
C(24)	-	207.9	-	208.2	-	207.9
CH(25)	3.21	45.4	3.35	45.1	5.18	45.4
CH(26)	4.94	125.4	5.24	124.4	3.29	124.8
C(27)	-	138.0	-	138.7	-	139.2
CH(28)	3.84	76.2	4.08	74.3	3.95	76.0
CH(29)	4.01	84.8	3.68	88.8	3.75	87.5
C(30)	-	212.6	-	213.2	-	212.7
CH(31)	2.41	40.2	2.63	39.8	2.55	40.7
CH_2(32)	1.10($H_{pro\text{-}S}$), 1.63($H_{pro\text{-}R}$)	39.1	1.25($H_{pro\text{-}S}$), 1.55($H_{pro\text{-}R}$)	39.2	1.22($H_{pro\text{-}S}$), 1.45($H_{pro\text{-}R}$)	38.7
CH(33)	2.26	35.8	2.20	35.8	2.21	35.1
CH_3(34)	0.98	21.6	0.97	21.9	0.96	22.2
CH_3(35)	1.60	10.32	1.62	10.61	1.62	10.5
CH_3(36)	3.05	55.5	3.03	55.5	3.04	55.5
CH_3(37)	0.72	15.6	0.73	15.6	0.73	15.5
CH(38)	1.67	33.3	1.71	33.4	1.71	33.6
CH_2(39)	0.94, 1.02[a]	38.48	0.95, 1.08[a]	38.3	0.97, 1.10[a]	38.2
CH(40)	1.21	32.6	1.26	32.6	1.24	32.6
CH_2(41)	0.58(H_{ax}), 1.89(H_{eq})	35.4	0.58(H_{ax}), 1.91(H_{eq})	35.2	0.60(H_{ax}), 1.91(H_{eq})	35.1
CH(42)	2.83	83.8	2.81	83.8	2.83	83.9
CH(43)	3.17	73.2	3.16	73.2	3.17	73.2
CH_2(44)	1.17(H_{ax}), 1.74(H_{eq})	32.8	1.17(H_{ax}), 1.75(H_{eq})	32.8	1.17(H_{ax}), 1.74(H_{eq})	32.9
CH_2(45)	1.52[b]	26.2	1.52[b]	26.3	1.51[b]	26.3
CH_3(46)	3.32	56.8	3.3	56.7	3.30	56.7
CH_3(47)	0.77	15.2	0.78	15.2	0.79	15.0
CH_3(48)	0.84	15.5	0.95	15.9	0.97	15.6
CH_3(49)	1.70	12.8	1.58	14.0	1.58	12.8
CH_3(50)	3.17	57.4	3.23	58.7	3.17	57.8
CH_3(51)	0.83	13.7	0.94	14.8	0.85	13.8

a. The diastereotopic assignment of the two CH(39) protons could not be accomplished.
b. Signals are nearly identical.

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