SUPPORTING INFORMATION

Identification and Structure-Activity Relationships of Chromene-Derived Selective Estrogen Receptor Modulators for Treatment of Postmenopausal Symptoms

Nareshkumar Jain, Jiayi Xu, Ramesh M. Kanojia, Fuyong Du, Guo Jian-Zhong, Emmanuel Pacia, Muh-Tsann Lai, Amy Musto, George Allan, Michael Reuman, Xun Li, DoWon Hahn, Martin Cousineau, Sean Peng, David Ritchie, Ronald Russell, Scott Lundeen, and Zhihua Sui*

Johnson & Johnson Pharmaceutical Research & Development LLC,

665 Stockton Drive, Exton, PA19341

e-mail address: drnfjain@gmail.com;

Table of Content: **Page**

General Information. Optical Rotations were measured on a Perkin Elmer model 341 polarimeter. ^{1}H and ^{13}C spectra were measured on either a Bruker 300 MHz, 400 MHz or 500 MHz instrument. In the case of ^{13}C spectra, these measurements were taken with full proton decoupling. Data for proton spectra were reported as follows: chemical shifts are reported in ppm, utilizing the residual solvent as an internal standard, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, nd = narrow doublet), coupling constants (Hz). Analytical high performance liquid chromatography (HPLC) coupled with MS and UV diodray detectors, was performed on an Agilent 1100 series instrument at 280 nM (UV detector) and mass ranging from 300-1000 (MS detector) using the following conditions: (a) Phenonmenex, luna 5µ, phrnyl-hexyl 150x4.60 mm, Solvent A: H_2O (0.1% TFA), Solvent B: CH_3CN (0.1% TFA), gradient 20-90% of solvent A to B, flow rate: 1ml/min, total run time: 15 min. (b) Phenonmenex, luna 5µ 150x4.60 mm, Solvent A: H_2O (0.1% TFA), Solvent B: CH_3CN (0.1% TFA), gradient 20-90% of solvent A to B, flow rate: 1ml/min, total run time: 15 min. (c) YMC diol 120 100 x 4.6 mm (achiral, normal phase) column, Solvent system 50% IPA in hexanes, Isocratic solvent sytem, flow rate: 1 min / mL, run time: 20 min. and (d) a Diacel ChiralPak AD 250 x 4.6 mm (chiral) column using an isocratic solvent mixture 50:50 IPA/Hexanes, at a flow rate of 1 mL/min.

For thin layer chromatography (TLC) analysis throughout this work, Analtech Uniplate precoated plates were used in conjunction with a variety of developing reagents including phosphomolybdic acid (PMA) and para-anisaldehyde (PAA) in addition to UV light. Purification

of materials was carried out using an ISCO chromatography system with pre-packed silica gel columns. High-resolution mass spectrometry (HRMS) was performed by M-Scan, Inc. and elemental analyses by QTI Technologies. All reagents and solvents were used as received from commercial source.

Following compounds were prepared using Scheme 2

Synthesis of Compound **8a:**

[2-(4-iodo-phenoxy)-ethyl]-piperidine (1.5 g , 4.5 mmol) was dissolved in 10 ml THF and cooled to –78 ^{o}C. To the solution was added dropwise 1.8 ml n-butyllithium (2.5 M in hexane). The solution was stirred at –78 ^{o}C for 30 min before the addition of 0.82g (1.5 mmol) lactal 14 g (X2=X1=OTBS, n=3)[8] in 5 ml THF, stirred for another 30 min after the addition and quenched with aqueous ammonium chloride, extracted with ethyl acetate, and the organic layer was combined and dried over sodium sulfate.

After removal of the solvent, the crude product was dissolved into 15 ml toluene and was cooled to 0 ^{o}C HCl (36.5%, 0.5 ml) was added dropwise. The reaction mixture was stirred at 0 ^{o}C for 1 hour. Diluted with ethyl acetate and washed with 5% $NaHCO_3$, then brine. The organic layer was dried over sodium sulfate and concentrated. The crude product was dissolved into 15 ml THF and was added 3.75 ml 1.0 M TBAF in THF. The reaction mixture was stirred for 1 hour, diluted with ethyl acetate and washed with aqueous ammonium chloride then brine. The organic layer was combined and dried over sodium sulfate. After removal of the solvent, the crude product was purified on HPLC. Purity: 97% by HPLC; LC-MS: R_f =3.791 min, m/z: 500 (M + 1), 522 (M + 23). ^{1}H NMR (CD_3OD) δ 1.49 (broad s, 2H), 1.69 (broad s, 4H), 1.91 (broad m, 2H), 2.08 (broad m, 2H), 2.71 (broad m, 4H), 2.92 (broad m, 2H), 3.74 (broad s, 1H), 4.12 (broad m, 2H), 4.56 (broad s, 1H), 5.95 (s, 1H), 6.08 ~ 7.65 (m, 10H). HRMS, m/z calcd for C31H34NO5 ($M+H^+$) 500.2437, found 500.2439; Anal Calcd for C31H35NO6 ($M+H_2O$) C, 71.93; H, 6.82; N, 2.71; O, 18.55; found C, 71.92; H, 6.79; N, 2.69;

Preparation of 5-[4-(2-Dimethylamino-ethoxy)-phenyl]-11,12-dihydro-5H-6,13-dioxa-benzo[3,4]cyclohepta[1,2-a]naphthalene-2,8-diol (**1b**):To a solution of 4.64 g 1-[2-(4-iodo-phenoxy)-ethyl]-dimethylamine (15.95 mmol) in 40 ml THF at –78 ^{o}C was added dropwise 6.38 ml n-butyllithium (2.5 M in hexane). The solution was stirred at –78 ^{o}C for 30 min before the solution of lactal (**14a)** (2.8g , 5.32 mmol) in 10 ml THF was added slowly, stirred for another 30 min after the addition and quenched with aqueous ammonium chlorideandextracted with ethyl acetate. The organic layer was combined and dried over sodium sulfate. After removal of the solvent the crude product was dissolved into 200 ml toluene and 1.64 ml of TFA was added. The solution was stirred for 1 hour and neutralized with 5% $NaHCO_3$and extracted with ethyl acetate. The organic layer was combined and dried over sodium sulfate. The crude product was dissolved into 50 ml acetonitrile and was added 5 ml 70% HF in pyridine at room temperature. The reaction mixture was stirred overnight and diluted with ethyl acetate and washed with 5% $NaHCO_3$, then brine. The organic layer was dried over sodium sulfate and concentrated. The crude product was purified with flash column chromatography eluted with 5% methanol in dichloromethane. Purity, 97% by HPLC, LC-MS: Rf= 1.98, MS: m/z, 446 (M + 1), 468 (M + 23); ^{1}HNMR (CD_3OD, 400 MHz) δ (ppm) 7.4 (d, J = 8.4 Hz, 2H), 7.15 (d, J = 8.4 Hz, 1H), 7.02 (d, J = 8.4 Hz, 1H), 6.85 (d, J = 8.4 Hz, 2H), 6.5 (m, 2H), 6.35 (dd, ^{1}J = 8.4 Hz, ^{2}J = 2 Hz, 1H), 6.15 (d, J = 2 Hz, 1H), 6.05 (s, 1H), 4.6 (m, 2H), 4.25 (t, J = 4 Hz, 2H), 3.5 (t, J = 4 Hz, 2H), 3.3 (m, 2H), 2.9 (s, 6H). HRMS, m/z calcd for $C_{27}H_{27}NO_5$ (M+) 445.5070, found 445.5997

The racemic compound **1b** was loaded onto a ChiralPak AD chiral HPLC column (5 cm I.D. x 50 cm L) and eluted with 80% IPA and 20% Hexanes at the 150 mL/min flow rate. The two peaks were collected to yield the tow enantiomers as follows: **1b**-*(R*) as peak Peak 1; [α] = + 66 °, (c = 0.402, MeOH) and **1b**-*(S)* as peak 2; [α] = - 65 °, (c = 0.5, MeOH)

Preparation of 5-[4-(2-Diisopropylamino-ethoxy)-phenyl]-11,12-dihydro-5H-6,13-dioxa-benzo[3,4]cyclohepta[1,2-a]naphthalene-2,8-diol (**1c**): Following the procedure described for **1b**, lactal **14a** (1.5 g, 2.85 mmol) was reacted in sequence with [2-(4-iodo-phenoxy)-ethyl]-diisopropyl-amine HCl and then *HF.Py* to yield 1.1g of the title compound as a pink solid.

Purity 97%, LC-MS: Rf=2.4, MS (m/z): MH^+ (502), MH^- (500). ^1H NMR ($CDOD_3$) δ 1.28 (d, 12H, J = 5.3 Hz), 2.78 (m, 2H), 3.25 (m, 2H), 3.52 (m, 2H), 4.05 (m, 2H), 4.56 (m, 2H), 6.05 ~ 7.35 (m, 11H). HRMS, m/z calcd for $C_{31}H_{35}NO_5(M^+)$ 501.2515, found 501.2515, Anal Calcd for C, 74.23; H, 7.03; N, 2.79; O, 15.95, found C, 74.19; H, 7.04; N, 2.78;

The racemic 5-[4-(2-Diisopropylamino-ethoxy)-phenyl]-11,12-dihydro-5H-6,13-dioxa-benzo[3,4]cyclohepta[1,2-a]naphthalene-2,8-diol compound (1.4 g) was loaded onto a ChiralPak AD chiral HPLC column (5 cm I.D. x 50 cm L) and eluted with 80% IPA and 20% Hexanes at the 150 mL/min flow rate. The two peaks were rcollected to yield the two enantiomers as follows: Peak 1: 5R-(+)-[4-(2-Diisopropylamino-ethoxy)-phenyl]-11,12-dihydro-5H-6,13-dioxa-benzo[3,4]cyclohepta[1,2-a]naphthalene-2,8-diol, **1c**-(*R*); $[\alpha]_D$= +43(c=0.112, MeOH), MS (m/z): MH^+ (502), MH^- (500) Peak 2: 5S-(-)-[4-(2-Diisopropylamino-ethoxy)-phenyl]-11,12-dihydro-5H-6,13-dioxa-benzo[3,4]cyclohepta[1,2-a]naphthalene-2,8-diol, **1c**-(*S*) $[\alpha]_D$= -69(c=0.812, MeOH), MS (m/z): MH^+ (502), MH^- (500)

Preparation of 5-[4-(2-Azepan-1-yl-ethoxy)-phenyl]-11,12-dihydro-5H-6,13-dioxa-benzo[3,4]cyclohepta[1,2-a]naphthalene-2,8-diol (**1d**): Following the procedure as described for **1b**, lactal **14a** (1.5 g,2.85 mmol) was reacted in sequence with 1-[2-(4-iodo-phenoxy)-ethyl]-azepane, HCl and then *HF.Py* to yield the title 1.1 g of compound (1d) as a light yellow solid. Purity: 95% by LCMS: Rf 2.13, MS (m/z): MH^+ (500), MH^- (498); ^1H NMR ($CDOD_3$) δ 1.65 (m, 4H), 1.84 (m, 4H), 2.78 (m, 2H), 3.35 (m, 4H), 3.48 (m, 2H), 4.18 (m, 2H), 4.61 (m, 2H), 6.02 (s, 1H), 6.18 ~ 7.35 (m, 10 H) HRMS, m/z calcd for $C_{31}H_{34}NO_5(M+H^+)$ Exact Mass: 500.2437, found 500.2444.

The racemic compound 5-[4-(2-Azepan-1-yl-ethoxy)-phenyl]-11,12-dihydro-5H-6,13-dioxa-benzo[3,4]cyclohepta[1,2-a]naphthalene-2,8-diol (**1d**) (1.1 g) was loaded onto a ChiralPak AD chiral HPLC column (5 cm I.D. x 50 cm L) and eluted with 50% IPA and 50% Hexanes at the 200 mL/min flow rate. The two peaks were recollected to yield the two enantiomers as follows: Peak 1: **1d**-(*R*): $[\alpha]_D$ = + 33(c=0.11, MeOH), MS (m/z): MH^+ (500), MH^- (498) and Peak 2: 5S-

(-)-[4-(2-Azepan-1-yl-ethoxy)-phenyl]-11,12-dihydro-5H-6,13-dioxa-benzo[3,4]cyclohepta[1,2-a]naphthalene-2,8-diol **1d**-(*S*). $[\alpha]_D$ = - 39(c=0.51, MeOH)MS (m/z): MH^+ (500), MH^- (498)

Preparation of [4-(2-Piperidin-1-yl-ethoxy)-phenyl]-11,12-dihydro-5H-6,13-dioxa-benzo[3,4]cyclohepta[1,2-a]na phthalene-2,8-diol, **1a**: Following the procedure as described for **1b**, lactal **14a** (1.5 g,2.85 mmol) was reacted in sequence with 1-[2-(4-iodo-phenoxy)-ethyl]-azepane, HCl and then *HF.Py* to yield the title 1.2 g of compound **1a**(96% pure by HPLC). The racemic compound **1a** (1.1 g) was loaded onto a ChiralPak AD chiral HPLC column (5 cm I.D. x 50 cm L) and eluted with 80% IPA and 20% Hexanes at the 150 mL/min flow rate. The two peaks were collected to yield the tow enantiomers as follows: Peak 1: 5R-(+)-[4-(2-Piperidin-1-yl-ethoxy)-phenyl]-11,12-dihydro-5H-6,13-dioxa-benzo[3,4]cyclohepta[1,2-a]naphthalene-2,8-diol **1a**-(*R*): ^{1}H NMR (CD3OD) δ 1.46 (m, 2H), 1.59 (m, 4H), 2.55 (m, 4H), 2.72 (M, 2H), 2.81 (m, 2H), 4.02 (t, 2H, J = 5.4 Hz). 4.60 (m, 2H), 6.05 (s, 1H), 6.14 ~ 7.34 (m, 10H). m.p. 147 ~149 °C [α] = + 57 °, (c = 0.302, MeOH). Anal. cacld. for C30H31NO5.0.95 H2O, C, 71.68; H, 6.60; N, 2.79; Found: C, 71.67; H, 6.52; N, 2.57. MS (m/z): MH+ (486). Peak 2: 5S-(-)-[4-(2-Piperidin-1-yl-ethoxy)-phenyl]-11,12-dihydro-5H-6,13-dioxa-benzo[3,4]cyclohepta[1,2-a]naphthalene-2,8-diol **1a**-(*S*): [α] = - 59 °, (c = 0.41, MeOH). MS (m/z): MH+ (486). HRMS, m/z calcd for C30H32NO5 ($M+H^+$) 486.5788, found 486.5783; Anal Calcd for C31H35NO6 (M+MeOH) C, 71.93; H, 6.82; N, 2.71; O, 18.55, found C, 71.92; H, 6.81; N, 2.72

Preparation of 5-[4-(2-Morpholin-4-yl-ethoxy)-phenyl]-11,12-dihydro-5H-6,13-dioxa-benzo[3,4]cyclohepta[1,2-a]naphthalene-2,8-diol **1f**: To a solution of 2.0 g 1-[2-(4-iodo-phenoxy)-ethyl]-piperidine (6.1 mmol) in 20 ml THF at –78 ^{o}C was added dropwise 2.5 ml n-butyllithium (2.5 M in hexane). The solution was stirred at –78 ^{o}C for 30 min before the solution of 1.05 g lactal **14a** (2.0 mmol) in 5 ml THF was added slowly, stirred for another 30 min after the addition, quenched with aqueous ammonium chloride and extracted with ethyl acetate. The

organic layer was combined and dried over sodium sulfate. After removal of the solvent, the crude product was dissolved in 100 ml toluene and 0.67 ml of 36.5% HCl was added. The solution was stirred for 1 hour and neutralized with 5% $NaHCO_3$ and extracted with ethyl acetate. The organic layer was combined and dried over sodium sulfate. after concentration, the crude product was dissolved in 20 ml acetonitrile and was added 1 ml 70% HF in pyridine at room temperature. The reaction mixture was stirred overnight and diluted with ethyl acetate and washed with 5% $NaHCO_3$, then brine. The organic layer was dried over sodium sulfate and concentrated. The crude product was purified with flash column chromatography eluted with 5% methanol in dichloromethane. Aslight yellow solid was yielded (0.90 g , 92%).Purity: 97% by LCMS: R_f=2.682 min, m/z: 488 (M + 1); ^{1}HNMR (DMSO-d_6, 400 MHz) δ (ppm) 9.7 (bs, 1H), 9.55 (bs, 1H), 7.3 (d, *J* = 8.4 Hz, 2H), 7.2 (d, *J* = 8.4 Hz, 1H), 7.05 (d, *J* = 8.4 Hz, 1H), 6.8 (d, *J* = 8.4 Hz, 2H), 6.45 (m, 2H), 6.3 (d, ^1J = 8.4 Hz, ^2J = 2 Hz, 1H), 6.12 (d, *J* = 2 Hz, 1H), 6.1 (s, 1H), 4.55 (m, 2H), 4.0 (t, *J* = 8.4 Hz, 2H), 2.9 (m, 8H), 2.7 (m, 2H), 2.6 (t, *J* = 8.4 Hz, 2H). HRMS, m/z calcd for $C_{29}H_{30}NO_6$ ($M+H^+$) 488.2073, found 488.2079 The racemic compound **1f** (0.9 g) was loaded onto a ChiralPak AD chiral HPLC column (5 cm I.D. x 50 cm L) and eluted with 80% IPA and 20% Hexanes at the 150 mL/min flow rate. The two peaks were collected to yield the two enantiomers as follows: **1f-**(*R*) as peak one [α] = + 27 °, (c = 0.304, MeOH) and **1f-**(*S*) as peak two [α] = - 28 °, (c = 0.41, MeOH)

Preparation of 5-[4-(2-Pyrrolidin-1-yl-ethoxy)-phenyl]-11,12-dihydro-5H-6,13-dioxa-benzo[3,4]cyclohepta[1,2-a]naphthalene-2,8-diol, **1e**: To a solution of 1.9 g 1-[2-(4-iodo-phenoxy)-ethyl]- pyrrolidine(6.0 mmol) in 20 ml THF at –78 ^oC was added dropwise 2.5 ml n-butyllithium (2.5 M in hexane). The solution was stirred at –78 ^oC for 30 min before the solution of 1.05 g lactal **14a** (2.0 mmol) in 5 ml THF was added slowly. The reactin mixture was stirred for another 30 min after the addition and then quenched with aqueous ammonium chloride and extracted with ethyl acetate. The organic layer was combined and dried over sodium sulfate. After removal of the solvent the crude product was dissolved into 100 ml toluene and 0.67 ml of 36.5% HCl was added. The solution was stirred for 1 hour and neutralized with 5% $NaHCO_3$ and extracted with ethyl acetate. The organic layer was dried over sodium sulfate. after removal of

the solvent, the crude product was dissolved in 20 ml acetonitrile and was added 1 ml of 70% HF in pyridine at room temperature. The reaction mixture was stirred overnight and diluted with ethyl acetate and washed with 5% $NaHCO_3$, then brine. The organic layer was dried over sodium sulfate and concentrated. The crude product was purified with flash column chromatography eluted with 5% Methanol in dichloromethane. 0.90 g slight yellow solid was yielded (95% Pure). LCMS: Rf = 2.701 min, >97%, m/z: 472 (M + 1); ^{1}H NMR (CD_3OD) δ 1.46 (m, 2H), 1.54 (m, 2H), 2.55 (m, 4H), 2.72 (M, 2H), 2.79 (m, 2H), 4.04 (t, 2H, J = 5.4 Hz). 4.60 (m, 2H), 6.15 (s, 1H), 6.14 ~ 7.34 (m, 10H). HRMS, m/z calcd for $C_{29}H_{30}NO_5$ 472.2124, found 472.2119. The racemic compound **1e** (0.9 g) was loaded onto a ChiralPak AD chiral HPLC column (5 cm I.D. x 50 cm L) and eluted with 80% IPA and 20% Hexanes at the 150 mL/min flow rate. The two peaks were collected to yield the tow enantiomers as follows: **1e-**(*R*) as peak one [α] = + 29 °, (c = 0.41, MeOH) and **1e-**(*S*) as peak one [α] = - 31 °, (c = 0.21, MeOH)

Preparation of 5-[4-(2-Piperidin-1-yl-ethoxy)-phenyl]-11,12-dihydro-5H-6,13-dioxa-benzo[3,4]cyclohepta[1,2-a]naphthalen-2-ol, **3d**: Following the procedure described for **2b**, Lactal **14b** was reacted with 1-[2-(4-iodo-phenoxy)-ethyl]-piperidine **(**Scheme 2, X_2=H, Y_2=OTBS, NR_2= -NC_5H_{10}[c]) to yield 2-(8-(tert-Butyl-dimethyl-silanyloxy)-5-{hydroxy-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-methyl}-2,3-dihydro-benzo[b]oxepin-4-yl)-phenol **16d,** which was then treated with HCl (12N, 4 eq., 0.67 mL) in toluene (100 mL) to yield 1-(2-{4-[2-(tert-Butyl-dimethyl-silanyloxy)-11,12-dihydro-5H-6,13-dioxa-benzo[3,4]cyclohepta[1,2-a]naphthalen-5-yl]-phenoxy}-ethyl)-piperidine as a crude oil. The crude unsubstituted piperidine was then treated with *HF•Pyridine* (70% HF, 30% Py, 0.5 mL) in CH_3CN (20 mL) at room temperature for 30 min. The reaction mixture was diluted with ethyl acetate:THF (1:1) and then washed with 5% $NaHCO_3$ and brine. The reaction mixture was dried, concentrated and purified by flash chromatograph eluted with 5% MeOH in DCM to yield the title compound as a slightly yellow solid. Purity 95% by LC-MS: Rf=2.1, MS (m/z): MH^+ (470). ^{1}H NMR (Acetone-d_6) δ 1.35 (m, 2H), 1.49 (m, 4H), 2.42 (br s, 4H), 2.64 (m, 2H), 2.71 ~ 2.98 (m, 3H), 3.91 (m, 2H),

4.59 ~ 4.74 (m, 2H), 6.21 (s, 1H), 6.55 ~ 7.45 (m, 11H), ^{1}H NMR (DMSO-d6) δ 1.36 (m, 6H), 2.28 ~ 2.59 (m, 6H), 2.65 (m, 1H), 2.89 (m, 1H), 3.91 (t, 2H, J = 6.6 Hz), 4.59 (m, 2H), 6.16 ~ 7.38 (m, 12H), 9.65 (s, 1H) HRMS, m/z calcd for $C_{30}H_{31}NO_4$ 469.2253, found 469.2249.

The racemic 5-[4-(2-Piperidin-1-yl-ethoxy)-phenyl]-11,12-dihydro-5H-6,13-dioxa-benzo[3,4]cyclohepta[1,2-a]naphthalen-2-ol **3d** compound (800 mg) was loaded was loaded onto a ChiralPak AD chiral HPLC column (5 cm I.D. x 50 cm L) and eluted with 100% IPA at the 150 mL/min flow rate. The two peaks were collected to yield the enantiomers as follows: Peak 1: 5R-[4-(2-Piperidin-1-yl-ethoxy)-phenyl]-11,12-dihydro-5H-6,13-dioxa-benzo[3,4]cyclohepta[1,2-a]naphthalen-2-ol as **3d**-(R): MS (m/z): MH^+ (470); [α]D = +39 (c = 0.23, MeOH) and Peak 2: 5S-(+)-[4-(2-Piperidin-1-yl-ethoxy)-phenyl]-11,12-dihydro-5H-6,13-dioxa-benzo[3,4]cyclohepta[1,2-a]naphthalen-2-ol, **3d**-(S): MS (m/z): MH^+ (470); [α]D = -37 (c = 0.43, MeOH)

Preparation of 5-[4-(2-Azepan-1-yl-ethoxy)-phenyl]-11,12-dihydro-5H-6,13-dioxa-benzo[3,4]cyclohepta[1,2-a]naphthalen-2-ol, **3c**: Following the procedure described for **1b**, the lactal **14 (**1.89 g, 2.0 mmol) was reacted with 1-[2-(4-Iodo-phenoxy)-ethyl]-azepane to yield the 950 mg of title compound **3c** as a yellow solid, Purity 97% by LC-MS, Rf= 3.1, MS (m/z): MH^+ (484) ^{1}H NMR (Acetone-d_6) δ1.54 (m, 8H), 2.58 ~2.95 (m, 8H), 3.95 (m, 2H), 4.59 ~ 4.74 (m, 2H), 6.21 (s, 1H), 6.51 ~ 7.45 (m, 11H); ^{1}H NMR (DMSO-d_6) δ 1.51 (broad s, 8H), 2.45 (broad m, 4H), 2.70 (broad m, 2H), 3.22 (broad s, 2H), 3.91 (t, 2H, J = 6.6 Hz), 4.56 (m, 2H), 6.15 (s, 1H), 6.39 ~ 7.36 (m, 11H), 9.67 (s, 1H) HRMS m/z calcd for $C_{31}H_{33}NO_4$(M+) 483.2410, found 483.2415. The racemic 5-[4-(2-Azepan-1-yl-ethoxy)-phenyl]-11,12-dihydro-5H-6,13-dioxa-benzo[3,4]cyclohepta[1,2-a]naphthalen-2-ol compound (950 mg) was loaded was loaded onto a ChiralPak AD chiral HPLC column (5 cm I.D. x 50 cm L) and eluted with 100% IPA at the 150 mL/min flow rate. The two peaks were collected to yield the enantiomers as follows: Peak 2: 5S-(-)-[4-(2-Azepan-1-yl-ethoxy)-phenyl]-11,12-dihydro-5H-6,13-dioxa-benzo[3,4]cyclohepta[1,2-a]naphthalen-2-ol **3c**-(*S*) $[\alpha]_D$= -28(c=0.12, MeOH); MS (m/z): MH^+

(484) and Peak 1: 5R-(+)-[4-(2-Azepan-1-yl-ethoxy)-phenyl]-11,12-dihydro-5H-6,13-dioxa-benzo[3,4]cyclohepta[1,2-a]naphthalen-2-ol, **3c**-(*R*), $[\alpha]_D$= +38 (c=0.25, MeOH). MH^+ (484).

Preparation of 5-[4-(2-Dimethylamino-ethoxy)-phenyl]-11,12-dihydro-5H-6,13-dioxa-benzo[3,4]cyclohepta[1,2-a]naphthalen-2-ol, **3a:** Following the procedure described for **1b**, lactal **14b** was reacted in sequence with [2-(4-iodo-phenoxy)-ethyl]-dimethyl-amine HCl and then *HF.Py* to yield the title compound as a yellow solid. Purity 96% by LC-MS, Rf= 2.93, MS (m/z): MH^+ (430); ^1H NMR ($CDCl_3$) δ 2.28 (s, 6H), 2.72 (m, 2H), 2.82 (m, 2H), 3.95 (m, 2H), 4.59 (m, 2H), 6.02 (s, 1H), 6.41 ~ 7.29 (m, 11H); ^1H NMR (DMSO-d6) δ 2.13 (s, 6H), 2.43 ~ 2.92 (m, 4H), 3.95 (t, 2H, J = 6.6 Hz), 4.59 (m, 2H), 6.15 (s, 1H), 6.38 ~ 7.39 (m, 11H), 9.69 (s, 1H). HRMS m/z calcd for $C_{27}H_{28}NO_4$ ($M+H^+$) 430.2018, found 430.1998

The racemic 5-[4-(2-Dimethylamino-ethoxy)-phenyl]-11,12-dihydro-5H-6,13-dioxa-benzo[3,4]cyclohepta[1,2-a]naphthalen-2-ol compound (890 mg) was loaded onto a ChiralPak AD chiral HPLC column (5 cm I.D. x 50 cm L) and eluted with 20% MeOH and 80% IPA at the 150 mL/min flow rate. The two peaks were collected to yield the enantiomers as follows: Peak 1: 5R-(+)-[4-(2-Dimethylamino-ethoxy)-phenyl]-11,12-dihydro-5H-6,13-dioxa-benzo[3,4]cyclohepta[1,2-a]naphthalen-2-ol, **3a**-(*R*): $[\alpha]_D$ = +38(C=0.3, MeOH) MS (m/z): MH^+ (430) and Peak 2 as 5S-(-)-[4-(2-Dimethylamino-ethoxy)-phenyl]-11,12-dihydro-5H-6,13-dioxa-benzo[3,4]cyclohepta[1,2-a]naphthalen-2-ol, **3a**-(*S*): $[\alpha]_D$ = -36(C=0.32, MeOH) MS (m/z): MH^+ (430)

Preparation of 5-[4-(2-Diethylamino-ethoxy)-phenyl]-11,12-dihydro-5H-6,13-dioxa-benzo[3,4]cyclohepta[1,2-a]naphthalene-2,8-diol, **3b:** Following the procedure described for **1b**, lactal **14b** was reacted in sequence with [2-(4-iodo-phenoxy)-ethyl]-diethyl-amine HCl and then *HF.Py* to yield the title compound as a yellow solid. Purity: 96% by LC-MS: Rf 2.41, MS (m/z): MH^+ (458). ^1H NMR ($CDCl_3$) δ 1.1(m, 6H) 2.71 (m, 4H), 2.72 (m, 2H), 2.82 (m, 2H), 3.95 (m, 2H), 4.59 (m, 2H), 6.02 (s, 1H), 6.41 ~ 7.29 (m, 11H).; HRMS m/z calcd for $C_{29}H_{32}NO_4$

458.2331, found 458.2336. The racemic 5-[4-(2-Diethylamino-ethoxy)-phenyl]-11,12-dihydro-5H-6,13-dioxa-benzo[3,4]cyclohepta[1,2-a]naphthalen-2-ol compound (1.1 g) was loaded onto a ChiralPak AD chiral HPLC column (5 cm I.D. x 50 cm L) and eluted with 20% MeOH and 80% IPA at the 150 mL/min flow rate. The two peaks were collected to yield the enantiomers as follows: Peak 1: 5R-(+)-[4-(2-Diethylamino-ethoxy)-phenyl]-11,12-dihydro-5H-6,13-dioxa-benzo[3,4]cyclohepta[1,2-a]naphthalen-2-ol, **3b**-(*R*): $[\alpha]_D$ = +42 (C=0.3, MeOH) MS (m/z): MH^+ (458) and Peak 2 as 5S-(-)-[4-(2-Diethylamino-ethoxy)-phenyl]-11,12-dihydro-5H-6,13-dioxa-benzo[3,4]cyclohepta[1,2-a]naphthalen-2-ol, **3b**-(*S*): $[\alpha]_D$ = -41 (C=0.31, MeOH) MS (m/z): MH^+ (458)

Preparation of 5-[4-(2-Azepan-1-yl-ethoxy)-phenyl]-8-fluoro-11,12-dihydro-5H-6,13-dioxa-benzo[3,4]cyclohepta[1,2-a]naphthalen-2-ol, **3f**: The title compound was prepared according to the procedure described for **1b** starting from lactal **14**d (1.1 g). Purity 97% by LC-MS MS (m/z): M+H= 501; ^{1}H NMR ($CDCl_3$) δ 1.61 (m, 8H), 2.71 ~ 2.99 (m, 8H), 3.92 (t, 2H, J = 6.6 Hz), 4.66 (m, 2H), 6.08 (s, 1H), 6.46 ~ 7.36 (m, 10H) HRMS m/z calcd for $C_{31}H_{32}FNO_4$ 501.2315 found 501.2326. The racemic 5-[4-(2-Azepan-1-yl-ethoxy)-phenyl]-8-fluoro-11,12-dihydro-5H-6,13-dioxa-benzo[3,4]cyclohepta[1,2-a]naphthalen-2-ol compound **3f** (700 mg) was loaded onto a ChiralPak AD chiral HPLC column (5 cm I.D. x 50 cm L) and eluted with 80% IPA and 20% Hexanes at the 150 mL/min flow rate. The two peaks were collected to yield the two enantiomers as follows: Peak 1: 5R-(+)-[4-(2-Azepan-1-yl-ethoxy)-phenyl]-8-fluoro-11,12-dihydro-5H-6,13-dioxa-benzo[3,4]cyclohepta[1,2-a]naphthalen-2-ol, 3f-(R): [α]D= +24.2(c=0.305, MeOH) MS (m/z): M+H=501 and Peak 2: 5S-(-)-[4-(2-Azepan-1-yl-ethoxy)-phenyl]-8-fluoro-11,12-dihydro-5H-6,13-dioxa-benzo[3,4]cyclohepta[1,2-a]naphthalen-2-ol, **3f**-(*S*): [α]D= -28.2(c=0.5, MeOH), MS (m/z): M+H=501.

Preparation of 5-[4-(2-Dimethylamino-ethoxy)-phenyl]-11,12-dihydro-5H-6,13-dioxa-benzo[3,4]cyclohepta[1,2-a]naphthalen-8-ol, **4a**:

Following the same three-step sequence described for preparation of **1b**, lactal **14c** was reacted in sequence with [2-(4-Iodo-phenoxy)-ethyl]-dimethyl-amine HCl and then *HF.Py* to yield the title compound as a **4a** as brown solid, Purity 97%, MS (m/z): MH^+ (430) ^{1}H NMR (DMSO-d6) δ 2.12 (s, 6H), 2.49 ~ 2.90 (m, 4H), 3.95 (t, 2H, J = 6.6 Hz), 4.61 (m, 2H), 6.09 ~ 7.23 (m, 11H), 9.54 (s, 1H) HRMS m/z calcd for $C_{27}H_{28}NO_4$ ($M+H^+$) 430.2018, found 430.1998

The racemic 5-[4-(2-Dimethylamino-ethoxy)-phenyl]-11,12-dihydro-5H-6,13-dioxa-benzo[3,4]cyclohepta[1,2-a]naphthalen-8-ol, **4a**, compound (800 mg) was loaded onto a ChiralPak AD chiral HPLC column (5 cm I.D. x 50 cm L) and eluted with 100% IPA at the 150 mL/min flow rate. The two peaks were collected to yield the two enantiomers as follows:

Peak 1: 5R-(+)-[4-(2-Dimethylamino-ethoxy)-phenyl]-11,12-dihydro-5H-6,13-dioxa benzo[3,4]cyclohepta[1,2-a]naphthalen-8-ol, **4a**-(R): $[\alpha]_D$= +42(c= 0.34, MeOH). MS (m/z): MH^+ (430) and Peak 2: 5S-(-)-[4-(2-Dimethylamino-ethoxy)-phenyl]-11,12-dihydro-5H-6,13-dioxa benzo[3,4]cyclohepta[1,2-a]naphthalen-8-ol, **4a**-(S): $[\alpha]_D$= - 42(c= 0.34, MeOH), MS (m/z): MH^+ (430)

5-[4-(2-Azepan-1-yl-ethoxy)-phenyl]-11,12-dihydro-5H-6,13-dioxa-benzo[3,4]cyclohepta[1,2-a]naphthalen-8-ol, **4b**:

Following the same three-step sequence described for preparation of **1b**, lactal **14c** was reacted in sequence with 1-[2-(4-iodo-phenoxy)-ethyl]-azepane, HCl and then *HF.Py* to yield the title compound **4b** as a yellow solid. Purity: 95% by LC-MS: Rf= 2.9, MS (m/z) =483.[1] H NMR (Acetone-d_6) δ δ1.54 (m, 8H), 2.68 ~2.95 (m, 8H), 3.98 (m, 2H), 4.74 (m, 2H), 6.18 (s, 1H), 6.21 ~ 7.39 (m, 11H). ^{1}H NMR (DMSO-d6) δ 1.55 (broad s, 8H), 2.68 ~ 2.92 (m, 8H), 3.92 (t, 2H, J = 6.6 Hz), 4.61 (m, 2H), 6.14 ~ 7.38 (m, 12H). 9.56 (s, 1H) HRMS m/z calcd for $C_{31}H_{33}NO_4$(M+) 483.2410, found 483.2421.

The racemic 5-[4-(2-Azepan-1-yl-ethoxy)-phenyl]-11,12-dihydro-5H-6,13-dioxa-benzo[3,4]cyclohepta[1,2-a]naphthalen-8-ol, **4b**, compound (840 mg) was loaded onto a ChiralPak AD chiral HPLC column (5 cm I.D. x 50 cm L) and eluted with 40% MeOH and 60% IPA at the 100 mL/min flow rate. The two peaks were collected to yield the two enantiomers: Peak 1: 5R-(+)-[4-(2-Azepan-1-yl-ethoxy)-phenyl]-11,12-dihydro-5H-6,13-dioxa-benzo[3,4]cyclohepta[1,2-a]naphthalen-8-ol, **4b**-(*R*) [α]D= +37(c=0.11, MeOH) MS (m/z): MH^+ (483) and Peak 2: 5S-(-)-[4-(2-Azepan-1-yl-ethoxy)-phenyl]-11,12-dihydro-5H-6,13-dioxa-benzo[3,4]cyclohepta[1,2-a]naphthalen-8-ol, **4b**-(*S*). [α]D= -39(c=0.51, MeOH). MS (m/z): MH^+ (483)

5-[4-(3-Hydroxy-propoxy)-phenyl]-11,12-dihydro-5H-6,13-dioxa-benzo[3,4]cyclohepta[1,2-a]naphthal ene-2,8-diol, **1l**: 1.28 g tert-Butyl-[3-(4-iodo-phenoxy)-propoxy]-dimethyl-silane (3.26 mmol) was dissolved into 10 ml THF and cooled to –78 ^oC before the slow addition of 1.2 ml 2.5 M *n*-butyllithium in hexane (3 mmol). After 1 hour the lactol, **14a** (400 mg) in 5 ml THF was added slowly into the solution. The reaction mixture was stirred for another 30 min ,quenched with aqueous ammonium chloride, extracted with ethyl acetate and dried over sodium sulfate. The crude material was dissolved into 40 ml toluene and cooled to 0 ^oC, 0.15 ml TFA (2 mmol) was added and the reaction was kept at 0 ^oC for 1 hour. The reaction mixture was transferred into a separation funnel and washed with 5% aqueous sodium bicarbonate and brine in sequence. The organic layer was dried over sodium sulfate and concentrated. The crude material was dissolved in 10 ml THF and 4 ml 1.0 M tetrabutyl ammonium fluoride in THF (4 mmol) was added slowly. The solution was stirred at room temperature for 1 hour and worked up by washing with brine. The organic layer was dried over sodium sulfate and concentrated. Flash column chromatography yield a slight orange solid 260 mg, 60% of **1l**. ^{1}HNMR (CD_3OD, 300 MHz) δ (ppm) 7.3 (d, J = 9 Hz, 2H), 7.15 (d, J = 9 Hz, 1H), 7.0 (d, J = 9 Hz, 1H), 6.75 (d, J = 9 Hz, 2H), 6.5 (m, 2H), 6.35 (dd, ^1J = 9 Hz, ^2J = 2 Hz, 1H), 6.2 (d, J = 2 Hz, 1H), 6.0 (s, 1H), 4.6 (m, 2H), 3.95 (t, J = 6 Hz, 2H), 3.7 (t, J = 6 Hz, 2H), 2.8 (m, 2H), HPLC (Luna, 5 μ C18 (2), Acetonitrile-water with 0.05% TFA) RT = 5.749, over 97% pure. HRMS m/z calcd for C26H24O6 432.1573, found 432.1567

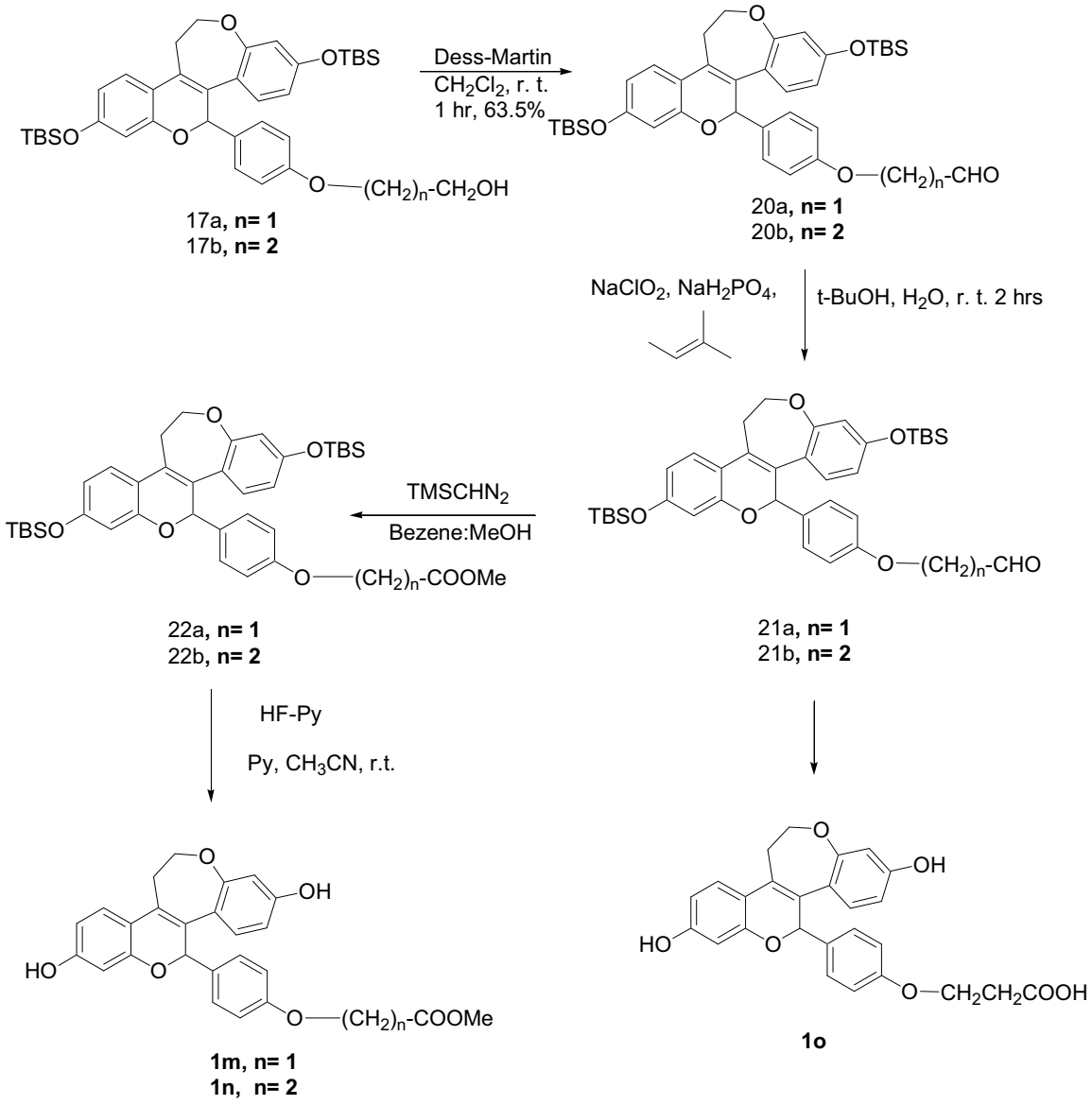
Preparation of 5-[4-(2-Hydroxy-ethoxy)-phenyl]-11,12-dihydro-5H-6,13-dioxa-benzo[3,4]cyclohepta[1,2-a]naphthalene-2,8-diol, **1k**: tert-Butyl-[3-(4-iodo-phenoxy)-ethanoxy]-dimethyl-silane (10.87 g, 30 mmol) was dissolved in 100 ml THF and cooled to –78 ^{o}C before the slow addition of 12 ml 2.5 M *n*-butyllithium in hexane (30 mmol). After 1 hour the lactol in 20 ml THF was added slowly into the solution, stirred for another 30 min, quenched with aqueous ammonium chloride, extracted with ethyl acetate and dried over sodium sulfateafter removal of the solvent, the crude material was dissolved in 200 ml toluene and cooled to 0 ^{o}C, 0.77 ml TFA (30 mmol) was added. The reaction mixture was kept at 0 ^{o}C for 1 hour and transferred into a separation funnel and washed with 5% aqueous sodium bicarbonate and brine in sequence. The organic layer was dried over sodium sulfate and concentrated. The crude material was dissolved into 100 ml THF and 30 ml 1.0 M tetrabutyl ammonium fluoride in THF (30 mmol) was added slowly. The solution was stirred at room temperature for 1 hour and worked up by washing with brine. The organic layer was dried over sodium sulfate and concentrated. Flash column chromatography yield slight pink crystals 2.3 mg, 55%. ^{1}HNMR (DMSO-d_6, 400 MHz) δ (ppm) 9.6 (s, 1H), 9.45 (s, 1H), 7.3 (d, J = 9 Hz, 2H), 7.2 (d, J = 9 Hz, 1H), 7.05 (d, J = 9 Hz, 1H), 6.8 (d, J = 9 Hz, 2H), 6.45 (m, 2H), 6.3 (dd, ^{1}J = 9 Hz, ^{2}J = 2 Hz, 1H), 6.1 (m, 2H), 4.8 (t, J = 6 Hz, 1H), 4.45 (m, 2H), 3.9 (t, J = 6 Hz, 2H), 3.7 (m, 2H), 2.8 (m, 2H), MS: 783.3 (M + 23), 761.3 (M + 1). HPLC (Luna, 5 μ C18 (2), Acetonitrile-water with 0.05% TFA) RT = 5.749, over 97% pure. HRMS m/z calcd for $C_{25}H_{22}O_6$ 418.1416 found 418.1434.

2-{4-[2,8-Bis-(tert-butyl-dimethyl-silanyloxy)-11,12-dihydro-5H-6,13-dioxa-benzo[3,4]cyclohepta[1,2-a]naphthalen-5-yl]-phenoxy}-ethanol **17a**: 2-(4-Iodo-phenoxy)-ethanol (20 g , 75.8 mmol) was dissolved into 200 ml THF at –10 ^{o}C before the slowly addition of 152 ml 1 M *iso*-propylmagnesium bromide in THF (152 mmol). The reaction was allowed to warm to room temperature. After 30 minutes 8 g (15.2 mmol) of lactol **14a** in 20 ml THF was added slowly into the solution. After stirring for another 30 min the reaction was quenched with aqueous ammonium chloride, extracted with ethyl acetate, dried over sodium sulfate and concentrated. The crude material was dissolved in 300 ml toluene and cooled to 0 ^{o}C. TFA (1.17

ml , 15.2 mmol) was added and the reaction was kept at 0 ^{o}C for 1 hour. The reaction mixture was transferred into a separation funnel and washed with 5% aqueous sodium bicarbonate and brine in sequence. The organic layer was dried over sodium sulfate and concentrated. Flash column chromatography yielded white crystals 5.61 mg (57%) of **17a**. Chiral separation on preparation HPLC yielded eluted with 10% iso-propanol in hexane 2.4 g and 2.2 g of each enantiomers as pink crystals.

^{1}HNMR ($CDCl_3$, 300 MHz) δ (ppm) 7.38 (d, *J* = 9 Hz, 2H), 7.1 (d, *J* = 9 Hz, 1H), 7.0 (d, *J* = 9 Hz, 1H), 6.9 (d, *J* = 9 Hz, 2H), 6.6 (d, *J* = 2 Hz, 1H), 6.5 (dd, ^{1}J = 9 Hz, ^{2}J = 2 Hz, 1H), 6.4 (dd, ^{1}J = 9 Hz, ^{2}J = 2 Hz, 1H), 6.3 (d, *J* = 2 Hz, 1H), 6.0 (s, 1H), 4.7 (t, *J* = 6 Hz, 2H), 4.0 (t, *J* = 6 Hz, 2H), 3.9 (m, 2H), 2.85 (t, *J* = 6 Hz, 2H), 1.96 (t *J* = 6 Hz, 1H), 0.97 (s, 9H), 0.94 (s, 9H), 0.2 (s, 6H), 0.16 (s, 6H); MS: 669 (M + 23), 647 (M + 1); HPLC: RT = 5.101, >99% pure; Anal Calcd for $C_{37}H_{50}O_6Si_2$: C, 68.69; H, 7.79, Si: 8.68. Found: C: 68.47, H: 7.67, Si: 9.32; Peak 1 as **17-(R)**: $[\alpha]_D$ ($CHCl_3$, c = 0.30) = + 33.5^{o} and Peak 2 as **17a**-(S): $[\alpha]_D$ ($CHCl_3$, c = 0.36) = - 33.5^{o};

Scheme 4a



Preparation of {4-[2,8-Bis-(tert-butyl-dimethyl-silanyloxy)-11,12-dihydro-5H-6,13-dioxa-benzo[3,4]cyclohepta[1,2-a]naphthalen-5-yl]-phenoxy} acetaldehyde, **20a**: The alcohol **17a** (158 mg , 0.244 mmol) and Dess-Martin reagent (114 mg , 0.268 mmol) were dissolved in 3 ml of dichloromethane. The solution was stirred at room temperature for one hour, and then worked up by washing continuously with 5% sodium bicarbonate and brine. The organic layer was dried over anhydrous sodium sulfate and concentrated. Flash column chromatography on silica gel eluted with 30% ethyl acetate in hexane yield a slight yellow solid 100 mg (63.5%) of **20a**.

^{1}HNMR ($CDCl_3$, 300 MHz) δ (ppm) 9.8 (s, 1H), 7.4 (d, *J* = 9 Hz, 2H), 7.1 (d, *J* = 9 Hz, 1H), 7.0 (d, *J* = 9 Hz, 1H), 6.75 (d, *J* = 9 Hz, 2H), 6.6 (d, *J* = 2 Hz, 1H), 6.55 (dd, ^1J = 9 Hz, ^2J = 2 Hz, 1H), 6.4 (dd, ^1J = 9 Hz, ^2J = 2 Hz, 2H), 6.3 (d, *J* = 2 Hz, 1H), 6.05 (s, 1H), 4.65 (t, *J* = 6 Hz, 2H), 4.5 (s, 2H), 2.95 (t, *J* = 6 Hz, 2H), 1.0 (s, 9H), 0.95 (s, 9H), 0.25 (s, 6H), 0.15 (s, 6H). MS: 645 (M + 1), 677 (M + 23). HRMS m/z calcd for $C_{37}H_{48}O_6Si_2$ 644.2989 found 644.2911

{4-[2,8-Bis-(tert-butyl-dimethyl-silanyloxy)-11,12-dihydro-5H-6,13-dioxa-benzo[3,4]cyclohepta[1, 2-a]naphthalen-5-yl]-phenoxy}-acetic acid: **21a**: To a solution of sodium dihydrogen phosphate (680 mg , 5.67 mmol) in 6.8 ml water was added 16.7 ml of *t*-butyl alcohol and 5.2 ml of 2-methyl-2-butene. Aldehyde **20a** (524 mg , 0.81 mmol) was dissolved in the solution and sodium chlorite (670 mg , 7.4 mmol) was added slowly. The mixture was stirred at room temperature for 2 hours, worked up by washing with aqueous sodium hydrogensulfite, 0.1 N HCl, and brine in sequence. The organic layer was dried over anhydrous sodium sulfate and concentrated. The crude product was used for the next step without purification. MS: 661.2 (M + 1).

Preparation of {4-[2,8-Bis-(tert-butyl-dimethyl-silanyloxy)-11,12-dihydro-5H-6,13-dioxa-benzo[3,4]cyclohepta[1,2-a]naphthalen-5-yl]-phenoxy}-acetic acid methyl ester, **22a**: The crude acid, **21a,** was dissolved into a mixture of 7 ml of benzene and 2 ml of methanol at room temperature followed by the addition of 1 ml of 2 M $TMSCHN_2$ in hexane. after concentration of the solvent flash column chromatography yielded 371 mg **22a** as a colorless oil (68% for two steps). ^{1}HNMR ($CDCl_3$, 300 MHz) δ (ppm) 7.4 (d, *J* = 9 Hz, 2H), 7.1 (d, *J* = 9 Hz, 1H), 7.0 (d, *J* = 9 Hz, 1H), 6.75 (d, *J* = 9 Hz, 2H), 6.6 (d, *J* = 2 Hz, 1H), 6.55 (dd, ^1J = 9 Hz, ^2J = 2 Hz, 1H), 6.4 (dd, ^1J = 9 Hz, ^2J = 2 Hz, 2H), 6.3 (d, *J* = 2 Hz, 1H), 6.05 (s, 1H), 4.65 (t, *J* = 6 Hz, 2H), 4.5 (s, 2H), 3.75 (s, 3H), 2.95 (t, *J* = 6 Hz, 2H), 1.0 (s, 9H), 0.95 (s, 9H), 0.25 (s, 6H), 0.15 (s, 6H). MS: 697 (M + 23), 675 (M + 1). HPLC: Rf = 5.182, >99% HRMS m/z calcd for $C_{38}H_{50}O_7Si_2$ 674.3095 found: 674.29998

Preparation of [4-(2,8-Dihydroxy-11,12-dihydro-5H-6,13-dioxa-benzo[3,4]cyclohepta[1,2-a]naphthalen-5-yl)-phenoxy]-acetic acid methyl ester **1m**: di-TBS methyl ester **22a** (371 mg , 0.55 mmol) was dissolved into a mixture of 1 ml pyridine and 5 ml of acetonitrile at room

temperature. 0.5 ml of 70% hydrogen fluoride in pyridine was added and stirred overnight. The reaction mixture was diluted with ethyl acetate and washed with 5% aqueous sodium bicarbonate and brine. The organic layer was dried over anhydrous sodium sulfate and concentrated. Flash column chromatography on silica gel eluted with 50 to 100% ethyl acetate in hexane yielded **1m** asa solid (223 mg , 91%). ^{1}HNMR (DMSO-d_6, 300 MHz) δ (ppm) 9.5 (s, 1H), 9.36 (s, 1H), 7.2 (d, J = 9 Hz, 2H), 7.07 (d, J = 9 Hz, 1H), 6.95 (d, J = 9 Hz, 1H), 6.67 (d, J = 9 Hz, 2H), 6.35 (m, 2H), 6.2 (dd, ^1J = 9 Hz, ^2J = 2 Hz, 1H), 6.0 (d, J = 2 Hz, 2H), 4.6 (s, 2H), 4.4 (m, 2H), 3.55 (s, 3H), 2.6 (m, 2H). MS: 469 (M + 23). HPLC: RT = 3.039, >97% pure HRMS m/z calcd for $C_{26}H_{22}O_7$ ($M+H^+$) 446.1366, found: 446.1368

3-{4-[2,8-Bis-(tert-butyl-dimethyl-silanyloxy)-11,12-dihydro-5H-6,13-dioxa-benzo[3,4]cyclohepta[1,2-a]naphthalen-5-yl]-phenoxy}-propan-1-ol, **17b**: 3-(4-Iodo-phenoxy)-propanol (2.78 g , 10 mmol) was dissolved into 20 ml THF at room temperature before the slow addition of 20 ml 1 M *iso*-propylmagnesium bromide in THF (20 mmol). After 30 min the lactol (1.05 g , 2 mmol) in 5 ml THF was added slowly into the solution. The mixture was stirred for another 30 min the reaction was quenched with aqueous ammonium chloride, extracted with ethyl acetate, dried over sodium sulfate and concentrated. The crude material was dissolved into 40 ml toluene and cooled to 0 ^{o}C. 0.15 ml TFA (2 mmol) was added and the reaction was kept at 0 ^{o}C for 1 hour. The reaction mixture was transferred into a separation funnel and washed with 5% aqueous sodium bicarbonate and brine in sequence. The organic layer was dried over sodium sulfate and concentrated. Flash column chromatography yield white crystals 610 mg, (46% for two steps). Chiral separation on preparation HPLC eluted with 10% iso-propanol in hexane gave each enantiomers 17b-(R) as peak 1 and 17b-(S) as peak 2. ^{1}HNMR ($CDCl_3$, 300 MHz) δ (ppm) 7.38 (d, J = 9 Hz, 2H), 7.1 (d, J = 9 Hz, 1H), 7.0 (d, J = 9 Hz, 1H), 6.9 (d, J = 9 Hz, 2H), 6.6 (d, J = 2 Hz, 1H), 6.5 (dd, ^1J = 9 Hz, ^2J = 2 Hz, 1H), 6.4 (dd, ^1J = 9 Hz, ^2J = 2 Hz, 1H), 6.3 (d, J = 2 Hz, 1H), 6.0 (s, 1H), 4.66 (t, J = 6 Hz, 2H), 4.05 (t, J = 6 Hz, 2H), 3.8 (m, 2H), 2.87 (t, J = 6 Hz, 2H), 2.0 (m, 2H), 1.7 (t, J = 6 Hz, 1H), 0.97 (s, 9H), 0.94 (s, 9H), 0.2 (s, 6H), 0.16 (s, 6H);

MS: 683 (M + 23), 661 (M + 1); HPLC: RT = 5.101, >97% pure Anal Calcd for $C_{38}H_{52}O_6Si_2$: C, 69.05; H, 7.93, Si: 8.50. Found: C: 68.68, H: 8.00; Si: 8.90; Peak 1 $[\alpha]_D$ ($CHCl_3$, c = 0.36) = + 29.5^o; Peak 2 $[\alpha]_D$ ($CHCl_3$, c = 0.36) = - 29.5^o

Preparation of 3-{4-[2,8-Bis-(tert-butyl-dimethyl-silanyloxy)-11,12-dihydro-5H-6,13-dioxa-benzo[3,4]cyclohepta[1,2-a]naphthalen-5-yl]-phenoxy}-propionaldehyde, **20b**: To the flask with 560 mg of the starting alcohol **17b** (0.847 mmol), 539 mg Dess-Martin reagent (1.27 mmol) and 142 mg sodium bicarbonate (1.69 mmol) were added 10 ml of dichloromethane. The solution was stirred at room temperature for one hour, and then worked up by washing continuously with 5% sodium bicarbonate and brine. The organic layer was dried over anhydrous sodium sulfate and concentrated. Flash column chromatography on silica gel eluted with 30% ethyl acetate in hexane yield slight yellow solid 384 mg (69%) of **20b**. ^{1}HNMR ($CDCl_3$, 300 MHz) δ (ppm) 9.8 (s, 1H), 7.4 (d, J = 9 Hz, 2H), 7.1 (d, J = 9 Hz, 1H), 7.0 (d, J = 9 Hz, 1H), 6.75 (d, J = 9 Hz, 2H), 6.6 (d, J = 2 Hz, 1H), 6.55 (dd, ^1J = 9 Hz, ^2J = 2 Hz, 1H), 6.4 (dd, ^1J = 9 Hz, ^2J = 2 Hz, 2H), 6.3 (d, J = 2 Hz, 1H), 6.05 (s, 1H), 4.65 (t, J = 6 Hz, 2H), 4.2 (t, J = 6 Hz, 2H), 2.8 (m, 4H), 0.97 (s, 9H), 0.92 (s, 9H), 0.20 (s, 6H), 0.10 (s, 6H).

Preparation of 3-{4-[2,8-Bis-(tert-butyl-dimethyl-silanyloxy)-11,12-dihydro-5H-6,13-dioxa-benzo[3,4]cyclohepta[1,2-a]naphthalen-5-yl]-phenoxy}-propionic acid, **21b**: To a solution of 487 mg sodium dihydrogen phosphate (4.06 mmol) in 4.8 ml water was added 12 ml *t*-butyl alcohol and 4 ml 2-methyl-2-butene. Aldehyde **20b** (384 mg , 0.58 mmol) was dissolved in the solution and 477 mg sodium chlorite (5.2 mmol) was added slowly. The mixture was stirred at room temperature for 2 hoursand worked up by washing with aqueous sodium hydrogensulfite, 0.1 N HCl, and brine in sequence. The organic layer was dried over anhydrous sodium sulfate and concentrated. Flash column chromatography on silica gel eluted with 20-80% ethyl acetate in hexane yielded 359 mg slight pink solid (92%) of **21b**. ^{1}HNMR (DMSO-d_6, 300 MHz) δ (ppm) 12.3(s, 1H), 7.3 (m, 3H), 7.1 (d, J = 9 Hz, 1H), 6.8 (d, J = 9 Hz, 2H), 6.6 (dd, ^1J = 9 Hz, ^2J = 2 Hz, 1H), 6.55(d, J = 2 Hz, 1H), 6.4 (dd, ^1J = 9 Hz, ^2J = 2 Hz, 1H), 6.2 (d, J = 2 Hz, 2H), 4.57 (m, 2H), 4.07 (t, J = 6 Hz, 2H), 2.9-2.7 (m, 2H), 2.6 (t, J = 6 Hz, 2H), 0.93 (s, 9H), 0.90 (s, 9H), 0.18 (s, 6H), 0.14 (s, 6H); HPLC: 4.987 min, >95% pure; MS: 675 (M + 1); Anal Calcd for

$C_{38}H_{50}O_7Si_2$: C, 67.62; H, 7.47; Si, 8.32. Found: C: 67.05, H: 7.49; Si: 8.29; HRMS m/z calcd for $C_{38}H_{50}O_7Si_2$ 674.3095, found 674.3112

Preparation of 3-{4-[2,8-Bis-(tert-butyl-dimethyl-silanyloxy)-11,12-dihydro-5H-6,13-dioxa-benzo[3,4]cyclohepta[1,2-a]naphthalen-5-yl]-phenoxy}-propionic acid methyl ester, **22b**: 187 mg of the acid (0.277 mmol) was dissolved into a mixture of 3.5 ml of benzene and 1 ml of methanol at room temperature followed by the addition of 0.21 ml of 2 M $TMSCHN_2$ in hexane. Concentrated and purified by flash column chromatography. ^{1}HNMR ($CDCl_3$, 300 MHz) δ (ppm) 7.4 (d, J = 9 Hz, 2H), 7.1 (d, J = 9 Hz, 1H), 7.0 (d, J = 9 Hz, 1H), 6.75 (d, J = 9 Hz, 2H), 6.6 (d, J = 2 Hz, 1H), 6.55 (dd, ^1J = 9 Hz, ^2J = 2 Hz, 1H), 6.4 (dd, ^1J = 9 Hz, ^2J = 2 Hz, 2H), 6.3 (d, J = 2 Hz, 1H), 6.05 (s, 1H), 4.65 (t, J = 6 Hz, 2H), 4.17 (t, J = 6 Hz, 2H), 3.69 (s, 3H), 2.86 (t, J = 6 Hz, 2H), 2.75 (t, J = 6 Hz, 2H), 0.97 (s, 9H), 0.93 (s, 9H), 0.20 (s, 6H), 0.16 (s, 6H); MS: 711 (M + 23), 689 (M + 1); HPLC: RT = 5.280, >97% pure. HRMS m/z calcd for C39H53O7Si2: 689.3330 found 689.3328.

3-[4-(2,8-Dihydroxy-11,12-dihydro-5H-6,13-dioxa-benzo[3,4]cyclohepta[1,2-a]naphthalen-5-yl)-phenoxy]-propionic acid, **1o**: 90 mg of the starting di-TBS acid (0.13 mmol) was dissolved into a mixture of 0.4 ml pyridine and 2 ml of acetonitrile at room temperature. 0.2 ml of 70% hydrogen fluoride in pyridine was added and stirred overnight. Diluted with ethyl acetate-THF (1:1) and washed with 5% aqueous sodium bicarbonate and brine. The organic layer was dried over anhydrous sodium sulfate and concentrate. Flash column chromatography on silica gel eluted with 10% methanol in dichloromethane yielded 57 mg of slight pink solid (98%). ^{1}HNMR (Acetone-d_6, 300 MHz) δ (ppm) 9 (bs, 1H), 7.4 (d, J = 9 Hz, 2H), 7.25 (d, J = 9 Hz, 1H), 7.1 (d, J = 9 Hz, 1H), 6.86 (d, J = 9 Hz, 2H), 6.58 (m, 2H), 6.4 (dd, ^1J = 9 Hz, ^2J = 2 Hz, 1H), 6.27 (d, J = 2 Hz, 1H), 6.1 (s, 1H), 4.65 (m, 2H), 4.2 (t, J = 6 Hz, 2H), 2.9 (m, 2H), 2.75 (t, J = 6 Hz, 2H); MS: 469 (M + 23), 447 (M + 1); HPLC: RT = 2.891, >97% pure. HRMS m/z calcd for C26H23O7: 447.1444, found 447.14443.

1-(2-{4-[2,8-Bis-(tert-butyl-dimethyl-silanyloxy)-11,12-dihydro-5H-6,13-dioxa-benzo[3,4]cyclohepta[1,2-a]naphthalen-5-yl]-phenoxy}-ethyl)-pyrrolidine-2,5-dione, **19i**: In a flask 49.5 mg succinimide (0.5 mmol) and 131.2 mg triphenylphosphine (0.5 mmol) were dissolved into 5 ml THF. The starting alcohol **17b-(S)** (323 mg, 0.5 mmol) in 1 ml THF and 0.079 ml DEAD in 1 ml THF were added into the flask at the same rate by syringes. The reaction was stirred overnight at room temperature. After concentration of the solvent, flash column chromatography gave a white powder of **19i**-(*S*) (0.28 g ,77%). ^{1}HNMR ($CDCl_3$, 400 MHz) δ (ppm) 7.3 (d, *J* = 9 Hz, 2H), 7.1 (d, *J* = 9 Hz, 1H), 7.0 (d, *J* = 9 Hz, 1H), 6.9 (d, *J* = 9 Hz, 2H), 6.6 (d, *J* = 2 Hz, 1H), 6.5 (dd, ^1J = 9 Hz, ^2J = 2 Hz, 1H), 6.4 (dd, ^1J = 9 Hz, ^2J = 2 Hz, 1H), 6.3 (d, *J* = 2 Hz, 1H), 6.0 (s, 1H), 4.64 (t, *J* = 6 Hz, 2H), 4.1 (t, *J* = 6 Hz, 2H), 3.5 (m, 2H), 2.85 (t, *J* = 6 Hz, 2H), 2.43 (m, 4H), 0.96 (s, 9H), 0.93 (s, 9H), 0.19 (s, 6H), 0.15 (s, 6H); MS: 727 (M + 23); $[\alpha]_D$ ($CHCl_3$, c = 0.32) = -35.5^o; HRMS m/z calcd $C_{41}H_{54}NO_7Si_2$ ($M+H^+$): 728.3439 found: 728.3440

1-{2-[4-(2,8-Dihydroxy-11,12-dihydro-5H-6,13-dioxa-benzo[3,4]cyclohepta[1,2-a]naphthalen-5-yl)-phenoxy]-ethyl}-pyrrolidine-2,5-dione, **1i-(S)**, 220 mg of the **19i-(S)** (0.30 mmol) was dissolved into a mixture of 1 ml pyridine and 10 ml of acetonitrile at room temperature, 0.5 ml of 70% hydrogen fluoride in pyridine was added and stirred overnight. The reaction mixture was diluted with ethyl acetate-THF (1:1) and washed with 5% aqueous sodium bicarbonate and brine. The organic layer was dried over anhydrous sodium sulfate and concentrated. Flash column chromatography on silica gel eluted with 20-100% ethyl acetate in hexane yielded 145 mg of slight pink solid (97%) of **1i**. ^{1}HNMR (DMSO-d_6, 400 MHz) δ (ppm) 9.6 (s, 1H), 9.48 (s, 1H), 7.3 (d, *J* = 9 Hz, 2H), 7.2 (d, *J* = 9 Hz, 1H), 7.05 (d, *J* = 9 Hz, 1H), 6.75 (d, *J* = 9 Hz, 2H), 6.6 (m, 2H), 6.3 (dd, ^1J = 9 Hz, ^2J = 2 Hz, 1H), 6.1 (m, 2H), 4.55 (m, 2H), 4.05 (m, 2H), 3.68 (t, *J* = 6 Hz, 2H), 2.86 (m, 1H), 2.7 (m, 1H) 2.5 (m, 4H); HPLC: RT = 8.861 >95%; HPLC: RT = 3.158 >95%; $[\alpha]_D$ ($CHCl_3$, c = 0.22) = -35.5^o; HRMS m/z calcd $C_{29}H_{26}NO_7$ ($M+H^+$): 500.1709, found: 500.1712

Preparation of 1-{2-[4-(2,8-Dihydroxy-11,12-dihydro-5H-6,13-dioxa-benzo[3,4]cyclohepta[1,2-a]naphthalen-5-yl)-phenoxy]-ethyl}-pyrrolidine-2,5-dione, **1i**-(*R*): Same procedure as of for 1i-(S) and starting from alcohol **17a**-(R). $[\alpha]_D$ ($CHCl_3$, c = 0.31) = +35.5^o

1-{3-[4-(2,8-Dihydroxy-11,12-dihydro-5H-6,13-dioxa-benzo[3,4]cyclohepta[1,2-a]naphthalen-5-yl)-phenoxy]-propyl}-pyrrolidine-2,5-dione, **1j**-(*R*): The title compound was prepared according to the procedure described for **1i** starting from alchohol **17b**-(*R*): ^{1}HNMR (DMSO-d_6, 400 MHz) δ (ppm) 9.6 (s, 1H), 9.48 (s, 1H), 7.3 (d, *J* = 9 Hz, 2H), 7.2 (d, *J* = 9 Hz, 1H), 7.05 (d, *J* = 9 Hz, 1H), 6.75 (d, *J* = 9 Hz, 2H), 6.6 (m, 2H), 6.3 (dd, ^1J = 9 Hz, ^2J = 2 Hz, 1H), 6.1 (m, 2H), 4.55 (m, 2H), 4.05 (m, 2H), 3.68 (t, *J* = 6 Hz, 2H), 2.86 (m, 1H), 2.7 (m, 1H) 2.5 (s, 4H); HPLC: RT = 2.905 >97%; HRMS m/z calcd C30H30NO8 (M+H+): 532.1971, found: 532.1973, $[\alpha]_D$ ($CHCl_3$, c = 0.61) = +25.3^o

1-{3-[4-(2,8-Dihydroxy-11,12-dihydro-5H-6,13-dioxa-benzo[3,4]cyclohepta[1,2-a]naphthalen-5-yl)-phenoxy]-propyl}-pyrrolidine-2,5-dione, **1j**-(*S*): The title compound was prepared according to the procedure described for **1i** starting from alchohol **17b**-(*S*): ^{1}HNMR (DMSO-d_6, 400 MHz) δ (ppm) 9.6 (s, 1H), 9.48 (s, 1H), 7.3 (d, *J* = 9 Hz, 2H), 7.2 (d, *J* = 9 Hz, 1H), 7.05 (d, *J* = 9 Hz, 1H), 6.75 (d, *J* = 9 Hz, 2H), 6.6 (m, 2H), 6.3 (dd, ^1J = 9 Hz, ^2J = 2 Hz, 1H), 6.1 (m, 2H), 4.55 (m, 2H), 3.87 (t, *J* = 6 Hz, 2H), 3.47 (t, *J* = 6 Hz, 2H), 2.86 (m, 1H), 2.7 (m, 1H) 2.56 (s, 4H), 1.85 (m, 2H); HPLC: RT = 3.232 >99%; HRMS m/z calcd $C_{30}H_{30}NO_8$ (M+H+): 532.1971, found: 532.1969, ($CHCl_3$, c = 1) = -29.3^o.

Preparation of (S)-2,8-Bis-(tert-butyl-dimethyl-silanyloxy)-5-[4-(3-iodo-propoxy)-phenyl]-11,12-dihydro-5H-6,13-dioxa-benzo[3,4]cyclohepta[1,2-a]naphthalene **18b**-(*S*): To the solution of the starting alchol **17b**-(*S*) (370 mg, 0.572 mmol) in 5 ml DMF was added 517 mg (1.14 mmol) of methyltriphenoxyphosphonium iodide at ambient temperature and stirred for 30 minutes, diluted with ethyl acetate and washed with water, and then brine. The organic layer was dried over sodium sulfate and concentrated. 400 mg of white solid was yielded after purification on silica gel eluted with 10% ethyl acetate in hexane (94%). ^{1}HNMR ($CDCl_3$, 300 MHz) δ (ppm) 7.38 (d, *J* = 9 Hz, 2H), 7.1 (d, *J* = 9 Hz, 1H), 7.0 (d, *J* = 9 Hz, 1H), 6.9 (d, *J* = 9 Hz, 2H), 6.6 (d, *J* = 2 Hz, 1H), 6.5 (dd, ^1J = 9 Hz, ^2J = 2 Hz, 1H), 6.4 (dd, ^1J = 9 Hz, ^2J = 2 Hz, 1H), 6.3 (d, *J* = 2 Hz, 1H), 6.0 (s, 1H), 4.66 (t, *J* = 6 Hz, 2H), 3.96 (t, *J* = 6 Hz, 2H), 3.33 (t, *J* = 6.6 Hz, 2H), 2.85 (m, 2H), 2.2 (m, 2H), 0.98 (s, 9H), 0.95 (s, 9H), 0.21 (s, 6H), 0.17 (s, 6H); MS: 793 (M

+ 23); 771 (M + 1); HPLC: RT = 5.620, >98% pure, Anal Calcd for $C_{38}H_{51}IO_5Si_2$: C: 59.21, H: 6.67; I: 16.46. Found: C: 59.17, H: 6.67; I: 17.13; $[\alpha]_D$ ($CHCl_3$, c = 0.36) = +28.7°;

Preparation of (S)-2,8-Bis-(tert-butyl-dimethyl-silanyloxy)-5-[4-(3-iodo-propoxy)-phenyl]-11,12-dihydro-5H-6,13-dioxa-benzo[3,4]cyclohepta[1,2-a]naphthalene **18b**-(*R*): The title compound was prepared according to the procedure described for **18**-(S) sarting from alchohol **17b**-(*R*): $[\alpha]_D$ ($CHCl_3$, c = 0.39) = -29°;

Preparation of 5-[4-(3-Piperidin-1-yl-propoxy)-phenyl]-11,12-dihydro-5H-6,13-dioxa-benzo[3,4]cyclohepta[1,2-a]naphthalene-2,8-diol, **1p**-(*S*):

Step 1: To a flask was added the starting iodide **18b**-(*S*) (220 mg ,0.285 mmol), potassium bicarbonate (42.8 mg , 0.428 mmol), 42.3 µl piperidine (0.428 mmol) and 3 ml of acetonitrile. The reaction was kept at 60 °C overnight, diluted with 100 ml ethyl acetate and washed with brine twice, the organic layer was dried over sodium sulfate and concentrated. Flash column chromatography yielded 172 mg white powder (83%). **19p-(S)**: ^{1}HNMR ($CDCl_3$, 300 MHz) δ (ppm) 7.38 (d, *J* = 9 Hz, 2H), 7.1 (d, *J* = 9 Hz, 1H), 7.0 (d, *J* = 9 Hz, 1H), 6.9 (d, *J* = 9 Hz, 2H), 6.6 (d, *J* = 2 Hz, 1H), 6.5 (dd, ^1J = 9 Hz, ^2J = 2 Hz, 1H), 6.4 (dd, ^1J = 9 Hz, ^2J = 2 Hz, 1H), 6.3 (d, *J* = 2 Hz, 1H), 6.0 (s, 1H), 4.66 (t, *J* = 6 Hz, 2H), 3.96 (t, *J* = 6 Hz, 2H), 2.85 (m, 2H), 2.4 (m, 6H), 1.9 (m, 2H), 1.55 (m, 4H), 1.42 (m, 2H), 0.97 (s, 9H), 0.94 (s, 9H), 0.20 (s, 6H), 0.16 (s, 6H); MS: 728 (M + 1); HPLC: RT = 4.609, >99% pure Anal Calcd for $C_{43}H_{61}NO_5Si_2$: C, 70.93; H, 8.44; N, 1.92. Found: C: 70.62, H: 8.68; N: 1.82; $[\alpha]_D$ ($CHCl_3$, c = 0.30) = - 24°;

Step 2: The starting material (150 mg , 0.21 mmol) was dissolved into a mixture of 1 ml pyridine and 3 ml of acetonitrile at room temperature, 0.5 ml of 70% hydrogen fluoride in pyridine was added and stirred overnight, diluted with ethyl acetate-THF (1:1) and washed with 5% aqueous sodium bicarbonate and brine. The organic layer was dried over anhydrous sodium sulfate and concentrated. Flash column chromatography on silica gel eluted with 0-5% methanol in dichloromethane yielded slight pink solid of **1p**-(*S*).

^{1}HNMR (CD_3OD, 300 MHz) δ (ppm) 7.38 (d, *J* = 9 Hz, 2H), 7.1 (d, *J* = 9 Hz, 1H), 7.0 (d, *J* = 9 Hz, 1H), 6.9 (d, *J* = 9 Hz, 2H), 6.6 (d, *J* = 2 Hz, 1H), 6.5 (dd, ^1J = 9 Hz, ^2J = 2 Hz, 1H), 6.4 (dd, ^1J = 9 Hz, ^2J = 2 Hz, 1H), 6.3 (d, *J* = 2 Hz, 1H), 6.0 (s, 1H), 4.6 (m, 2H), 3.96 (t, *J* = 6 Hz, 2H), 2.8 (m, 8H), 2.0 (m, 2H), 1.67 (m, 4H), 1.53 (m, 2H); MS: 500 (M + 1); HPLC: RT = 5.226, >97% pure ; HRMS m/z calcd $C_{30}H_{30}NO_8$ (M+H+): C31H34NO5 (M+H+): 500.2437, found: 500.2539 Anal Calcd for C, 74.53; H, 6.66; N, 2.80; O, 16.01 found C, 74.48; H, 6.85; N, 2.78. $[\alpha]_D$ (MeOH, c = 0.20) = - 14^o

Preparation of 5-[4-(3-Piperidin-1-yl-propoxy)-phenyl]-11,12-dihydro-5H-6,13-dioxa-benzo[3,4]cyclohepta[1,2-a]naphthalene-2,8-diol, **1p**-(*S*): The title compound was prepared according to the procedure described for **1p**-(S) starting from iodide **18b**-(*R*): $[\alpha]_D$ (MeoH, c = 0.24) = + 17^o;

Preparation of (R)- 5-[4-(2-Thiomorpholin-4-yl-ethoxy)-phenyl]-11,12-dihydro-5H-6,13-dioxa-benzo[3,4]cyclohepta[1,2-a]naphthalene-2,8-diol, **1g**-(*R*): The title compound was prepared according to the procedure described for **1p**-(S) starting from iodide **18a**-(*R*): : ^{1}HNMR (DMSO-d_6, 400 MHz) δ (ppm) 9.65 (bs, 1H), 9.53(bs, 1H), 7.25-7.1 (m, 3H), 6.85 (m, 2H), 6.70 (dd, ^1J = 9 Hz, ^2J = 2 Hz, 1H), 6.60 (dd, ^1J = 9 Hz, ^2J = 2 Hz, 1H), 6.45-6.32 (m, 2H), 6.15 (m, 2H), 4.65 (m, 2H), 3.95 (t, *J* = 6 Hz, 2H), 2.75 (m, 1H), 2.76 (m, 5H), 2.65 (t, *J* = 6 Hz, 2H), 2.57 (m, 4H). LCMS: 2.819 min, >97%, m/z: 504 (M + 1); HRMS m/z calcd C29H30NO5S: 504.1845, found 504.1865; Anal Calcd for C, 69.16; H, 5.80; N, 2.78; O, 15.88; S, 6.37 found C, 69.28; H, 5.79; N, 2.79; $[\alpha]_D$ (MeOH, c = 0.24) = + 66^o

Preparation of (S)- 5-[4-(2-Thiomorpholin-4-yl-ethoxy)-phenyl]-11,12-dihydro-5H-6,13-dioxa-benzo[3,4]cyclohepta[1,2-a]naphthalene-2,8-diol, **1g**-(*S*): The title compound was prepared according to the procedure described for **1p**-(S) starting from iodide **18a**-(*S*): $[\alpha]_D$ ($CHCl_3$, c = 1.1) = - 50.5^o

Preparation of *R*-5-{4-[2-(4-Methyl-piperazin-1-yl)-ethoxy]-phenyl}-11,12-dihydro-5H-6,13-dioxa-benzo[3,4]cyclohepta [1,2-a]naphthalene-2,8-diol, **1h-(R)**: The title compound was prepared according to the procedure described for **1p**-(S) starting from iodide **18a**-(*R*) and

^{1}HNMR (DMSO-d_6, 300 MHz) δ (ppm) 9.95 (bs, 1H), 9.83(bs, 1H), 7.65-7.18 (m, 3H), 6.95 (m, 2H), 6.80 (dd, ^1J = 9 Hz, ^2J = 2 Hz, 1H), 6.80 (m, 2H), 6.32 (dd, ^1J = 9 Hz, ^2J = 2 Hz, 1H), 6.15 (m, 2H), 4.55 (m, 2H), 3.95 (t, J = 6 Hz, 2H), 2.85 (m, 1H), 2.70 (m, 1H), 2.60 (t, J = 6 Hz, 2H), 2.40 (m, 4H), 2.40 (m, 4H)2.15 (s, 3H). LCMS: 2.514 min, >97%, m/z: 501 (M + 1); : $[\alpha]_D$ (MeOH, c = 0.21) = + 66^o LCMS: R_f= 2.819 min, >97% pure, , m/z: 501 (M + 1); HRMS m/z calcd for $C_{30}H_{33}N_2O_5$(M+H+) 501.2389 found : 501.2411.

Preparation of *R*-5-{4-[2-(4-Methyl-piperazin-1-yl)-ethoxy]-phenyl}-11,12-dihydro-5H-6,13-dioxa-benzo[3,4]cyclohepta [1,2-a]naphthalene-2,8-diol, **1h**-(*S*): $[\alpha]_D$ (MeOH, c = 0.61) = - 59^o

2-{3-[2,8-Bis-(tert-butyl-dimethyl-silanyloxy)-11,12-dihydro-5H-6,13-dioxa-benzo[3,4]cyclohepta[1,2-a]naphthalen-5-yl]-phenoxy}-ethanol, **23**: 3-(3-Iodo-phenoxy)-propanol (6 g , 22.7 mmol) was dissolved into 100 ml THF at room temperature before the slow addition of 45 ml 1 M *iso*-propylmagnesium bromide in THF (20 mmol). After 30 min lactol **14a** (2.37 g, 4.5 mmol) in 30 ml THF was added slowly into the solution. After stirring for another 30 min the reaction was quenched with aqueous ammonium chloride, extracted with ethyl acetate, dried over sodium sulfate and concentrated. The crude material was dissolved into 200 ml toluene and cooled to 0 ^{o}C. TFA (0.4 ml , 4.5 mmol) was added and the reaction was kept at 0 ^{o}C for 1 hour. The reaction mixture was transferred into a separation funnel and washed with 5% aqueous sodium bicarbonate and brine in sequence. The organic layer was dried over sodium sulfate and concentrated. Flash column chromatography yield white crystals 1.13 g, (77% for two steps) of **23**.

^{1}HNMR ($CDCl_3$, 300 MHz) δ (ppm) 7.17-7.0 (m, 5H), 6.75 (dd, ^1J = 9 Hz, ^2J = 2 Hz, 1H), 6.6 (d, J = 2 Hz, 1H), 6.55 (dd, ^1J = 9 Hz, ^2J = 2 Hz, 1H), 6.4 (dd, ^1J = 9 Hz, ^2J = 2 Hz, 1H), 6.35 (d,

J = 2 Hz, 1H), 6.05 (s, 1H), 4.66 (t, *J* = 6 Hz, 2H), 4.0 (t, *J* = 6 Hz, 2H), 3.85 (m, 2H), 2.87 (m, 2H), 2.0 (t, *J* = 6 Hz, 1H), 0.97 (s, 9H), 0.94 (s, 9H), 0.2 (s, 6H), 0.16 (s, 6H); MS: 647 (M + 1), 669 (M + 23); HPLC: RT = 10.740, Purity > 97% pure, HRMS cacld for $C_{37}H_{51}O_6Si_2$: 647.3224 found 647.3290.

Chiral separation on preparation HPLC eluted with 10% iso-propanol in hexane gave each enantiomers as crystals. Peak 1 as 23-(R) : $[\alpha]_D$ ($CHCl_3$, c = 0.30) = + 51°; and Peak 2 as 23-(S); $[\alpha]_D$ ($CHCl_3$, c = 0.31) = - 51°;

(R)-2,8-Bis-(tert-butyl-dimethyl-silanyloxy)-5-[3-(2-iodo-ethoxy)-phenyl]-11,12-dihydro-5H-6,13-dioxa-benzo[3,4]cyclohepta[1,2-a]naphthalene, **24**-(R): To a solution of the starting material **23**-(*R*) (370 mg, 0.572 mmol) in 5 ml DMF was added (517 mg, 1.14 mmol) of methyltriphenoxyphosphonium iodide at ambient temperature and stirred for 30 minutes, diluted with ethyl acetate and washed with water, and then brine. The organic layer was dried over sodium sulfate and concentrated. Awhite solid was yielded after purification on silica gel eluted with 10% ethyl acetate in hexane (380 mg, 89%). ^{1}HNMR ($CDCl_3$, 400 MHz) δ (ppm) 7.15-7.0 (m, 5H), 6.75 (dd, ^1J = 9 Hz, ^2J = 2 Hz, 1H), 6.6 (d, *J* = 2 Hz, 1H), 6.53 (dd, ^1J = 9 Hz, ^2J = 2 Hz, 1H), 6.4 (dd, ^1J = 9 Hz, ^2J = 2 Hz, 1H), 6.3 (d, *J* = 2 Hz, 1H), 6.05 (s, 1H), 4.6 (m, 2H), 4.15 (t, *J* = 6 Hz, 2H), 3.3 (m, 2H), 2.85 (m, 2H), 0.97 (s, 9H), 0.94 (s, 9H), 0.2 (s, 6H), 0.16 (s, 6H); $[\alpha]_D$ ($CHCl_3$, c = 0.33) = + 53°. HRMS cacld for $C_{37}H_{50}IO_5Si_2(M+H^+)$: 757.2242, found 757.2199.

(S)-2,8-Bis-(tert-butyl-dimethyl-silanyloxy)-5-[3-(2-iodo-ethoxy)-phenyl]-11,12-dihydro-5H-6,13-dioxa-benzo[3,4]cyclohepta[1,2-a]naphthalene, **24**-(S): $[\alpha]_D$ ($CHCl_3$, c = 0.31) = -53.5°.

5R-[3-(2-Piperidin-1-yl-ethoxy)-phenyl]-11,12-dihydro-5H-6,13-dioxa-benzo[3,4]cyclohepta[1,2-a]na

phthalene-2,8-diol, **2a-(*R*)**: The title compound was prepared according to the procedure described for **1p**-(S) starting from iodide **24**-(*R*) and piperidine: ^{1}HNMR (DMSO-d_6, 400 MHz) δ (ppm) 9.63(s, 1H), 9.5 (s, 1H), 7.25-7.1 (m, 3H), 6.95 (m, 2H), 6.8 (dd, ^1J = 9 Hz, ^2J = 2 Hz, 1H), 6.5(dd, ^1J = 9 Hz, ^2J = 2 Hz, 1H), 6.45 (d, J = 2 Hz, 1H), 6.3 (dd, ^1J = 9 Hz, ^2J = 2 Hz, 1H), 6.2 (m, 2H), 4.55 (m, 2H), 4.0 (m, 2H), 2.8 (m, 2H), 2.7 (m, 2H), 2.4 (m, 4H), 1.5 (m, 4H), 1.4 (m, 2H); LCMS: 2.705 min, >97%, m/z: 486 (M + 1). $[\alpha]_D$ (MeOH, c = 0.4) = + 44.8^o). HRMS, m/z calcd for C30H32NO5 (M+H$^+$) 486.5788, found 486.5793; Anal Calcd for C31H35NO6 (M+MeOH) C, 71.93; H, 6.82; N, 2.71; O, 18.55, found C, 71.96; H, 6.86; N, 2.77

5S-[3-(2-Piperidin-1-yl-ethoxy)-phenyl]-11,12-dihydro-5H-6,13-dioxa-benzo[3,4]cyclohepta[1,2-a]na

phthalene-2,8-diol, **2a-(*S*)**: The title compound was prepared according to the procedure described for **1p**-(S) starting from iodide **24**-(*S*) and piperidine: $[\alpha]_D$ (MeOH, c = 0.31) = - 46^o

5R-[3-(2-Thiomorpholin-4-yl-ethoxy)-phenyl]-11,12-dihydro-5H-6,13-dioxa-benzo[3,4]cyclohepta[1,2-]naphthalene-2,8-diol, **2c**-(*R*): The title compound was prepared according to the procedure described for **1p**-(S) starting from iodide **24**-(*R*) and thiomorpholine: ^{1}HNMR (DMSO-d_6, 400 MHz) δ (ppm) 9.65 (bs, 1H), 9.53(bs, 1H), 7.25-7.1 (m, 3H), 6.95 (m, 2H), 6.80 (dd, ^1J = 9 Hz, ^2J = 2 Hz, 1H), 6.50 (dd, ^1J = 9 Hz, ^2J = 2 Hz, 1H), 6.45 (d, J = 2 Hz, 1H), 6.32 (dd, ^1J = 9 Hz, ^2J = 2 Hz, 1H), 6.15 (m, 2H), 4.65 (m, 2H), 3.95 (t, J = 6 Hz, 2H), 2.85 (m, 1H), 2.70 (m, 5H), 2.65 (t, J = 6 Hz, 2H), 2.57 (m, 4H). LCMS: 2.719 min, Purity >97%, m/z: 504 (M + 1); HRMS m/z calcd C29H30NO5S: 504.1845, found 504.1865; Anal Calcd for C, 69.16; H, 5.80; N, 2.78; O, 15.88; S, 6.37 found C, 69.31; H, 5.77; N, 2.77; $[\alpha]_D$ (MeOH, c = 0.24) = + 56^o

Preparation of 5S-[3-(2-Thiomorpholin-4-yl-ethoxy)-phenyl]-11,12-dihydro-5H-6,13-dioxa-benzo[3,4]cyclohepta[1,2-a]naphthalene-2,8-diol, **2c**-(*S*): The title compound was prepared according to the procedure described for **1p**-(S) starting from iodide **24**-(*S*) and thiomorpholine: $[\alpha]_D$ (MeOH, c = 0.43) = - 56^o

Preparation of 5R-{3-[2-(4-Methyl-piperazin-1-yl)-ethoxy]-phenyl}-11,12-dihydro-5H-6,13-dioxa-benzo[3,4]cyclohepta[1,2-a]naphthalene-2,8-diol, **2b**-(*R*): The title compound was prepared according to the procedure described for **1p**-(S) starting from iodide **24**-(*R*) and 1-methyl-piperazine: ^{1}HNMR (DMSO-d_6, 300 MHz) δ (ppm) 9.65 (bs, 1H), 9.53(bs, 1H), 7.25-7.1 (m, 3H), 6.95 (m, 2H), 6.80 (dd, ^1J = 9 Hz, ^2J = 2 Hz, 1H), 6.50 (m, 2H), 6.32 (dd, ^1J = 9 Hz, ^2J = 2 Hz, 1H), 6.15 (m, 2H), 4.55 (m, 2H), 3.95 (t, J = 6 Hz, 2H), 2.85 (m, 1H), 2.70 (m, 1H), 2.60 (t, J = 6 Hz, 2H), 2.40 (m, 4H), 2.30 (m, 4H)2.15 (s, 3H). LCMS: 2.514 min, >97%, m/z: 501 (M + 1); :); HRMS m/z calcd for $C_{30}H_{33}N_2O_5$(M+H+) 501.2389 found : 501.2459. $[\alpha]_D$ (MeOH, c = 0.21) = + 56^o

Preparation of 5S-{3-[2-(4-Methyl-piperazin-1-yl)-ethoxy]-phenyl}-11,12-dihydro-5H-6,13-dioxa-benzo[3,4]cyclohepta 1,2-a]naphthalene-2,8-diol, **2b**-(*S*): The title compound was prepared according to the procedure described for **1p**-(S) starting from iodide **24**-(*S*) and 1-Methyl-piperazine: $[\alpha]_D$ (MeOH, c = 0.31) = - 53^o

Preparation of 5S-(-)-1-{2-[4-(2,8-Dimethoxy-11,12-dihydro-5H-6,13-dioxa-benzo[3,4]cyclohepta[1,2-a]naphthalen-5-yl)-phenoxy]-ethyl}-piperidine **7**-(*S*): 5S-(-)-[4-(2-Piperidin-1-yl-ethoxy)-phenyl]-11,12-dihydro-5H-6,13-dioxa-benzo[3,4]cyclohepta[1,2-a]naphthalene-2,8-diol, **1a**-(*S*) (1 g) was dissolved in CH_3CN/MeOH (3:1) (28 mL). $TMSCH_2N_2$ (2M in hexane, 10 mL, excess) and was stirred overnight. The reaction mixture was concentrated to dryness and purified on SiO_2 using 5% MeOH in CH_2Cl_2 to yield the title compound as a yellow solid ^{1}H NMR ($CDCl_3$) δ 1.40 (m, 2H), 1.59 (m, 4H), 2.49 (broad s, 4H), 2.72 (m, 2H), 2.91 (m, 2H), 3.71 (s, 3H), 3.78 (s, #H), 4.05 (m, 2H), 4.69 (m, 2H), 6.05 (s, 1H),

6.36 ~ 7.39 (m, 10H); 97 % Pure by LC-MS: Rf 4.1 MS (m/z): MH+ (514). HRMS: m/z cacld for $C_{32}H_{36}NO_5$ (M+H+) 514.2593, found 514.2603. [α] = -7.9 (c = 0.6 g/100 mL, $CHCl_3$, 25 °C)

Preparation of 5R-(-)-1-{2-[4-(2,8-Dimethoxy-11,12-dihydro-5H-6,13-dioxa-benzo[3,4]cyclohepta[1,2-a]naphthalen-5-yl)-phenoxy]-ethyl}-piperidine **7**-(*R*): 5S-(-)-[4-(2-Piperidin-1-yl-ethoxy)-phenyl]-11,12-dihydro-5H-6,13-dioxa-benzo[3,4]cyclohepta[1,2-a]naphthalene-2,8-diol, **1a**-(*R*) (1.1 g) was dissolved in CH_3CN/MeOH (3:1) (30 mL). $TMSCH_2N_2$ (2M in hexane, 11.3 mL, excess) and was stirred overnight. The reaction mixture was concentrated to dryness and purified on SiO_2 using 5% MeOH in CH_2Cl_2 to yield the title compound as a yellow solid ^{1}H NMR ($CDCl_3$) δ 1.40 (m, 2H), 1.59 (m, 4H), 2.49 (broad s, 4H), 2.72 (m, 2H), 2.91 (m, 2H), 3.71 (s, 3H), 3.78 (s, #H), 4.05 (m, 2H), 4.69 (m, 2H), 6.05 (s, 1H), 6.36 ~ 7.39 (m, 10H), MS (m/z): MH+ (514). ^{13}C NMR (400 MHz, DMSO-d6): 160.08, 159.35, 158.6, 157.3, 152.32, 130.68, 129.33, 128.85, 128.17, 125.36, 124.14, 123.19, 128.85, 128.17, 125.36, 124.14, 123.19, 117.00, 114.18, 109.67, 107.37, 106.04, 102.27, 77.84, 76.58, 65.38, 57.29, 55.18, 55.29, 54.19, 27.95, 25.5, 23.88. Anal calcd C, 74.68; H, 7.05; N, 2.72; O, 15.54; found C, 74.71; H, 7.09; N, 2.69; % Purity: >98% by LC-M:, Rf=4.4, MS (m/z): MH+ (514) ; [α] = +7.2 (c = 0.38 g/100 mL, $CHCl_3$, 25 ^{o}C)

Preparation of 2-Methoxy-5S-(-)-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-11,12-dihydro-5H-6,13-dioxa-benzo[3,4]cyclohepta[1,2-a]naphthalen-8-ol, **6**-(*S*) and 8-Methoxy-5S-(-)-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-11,12-dihydro-5H-6,13-dioxa-benzo[3,4]cyclohepta[1,2-a]naphthalen-2-ol, **5**-(S): 5S-(-)-[4-(2-Piperidin-1-yl-ethoxy)-phenyl]-11,12-dihydro-5H-6,13-dioxa-benzo[3,4]cyclohepta[1,2-a]naphthalene-2,8-diol (10 g) **1a**-(*S*) was dissolved in CH_3CN/MeOH (3:1) (280 mL) and 1.1 equivalent of $TMSCH_2N_2$ (2M in hexane 10.2 mL) and was stirred overnight. The reaction mixture was concentrated to dryness and purified on SiO_2 using 5-10% MeOH in CH_2Cl_2. to yield a mixture of the title compounds as yellow foam. The mixture of compounds (2.9g) was loaded onto a ChiralPak AD chiral HPLC column 5 cm I.D. x 50 cm L)

and eluted with 100% IPA at the 150 mL/min flow rate. The two peaks were collected to yield the two title compounds as follows:

Peak 1: 2-Methoxy-5S-(-)-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-11,12-dihydro-5H-6,13-dioxa-benzo[3,4]cyclohepta[1,2-a]naphthalen-8-ol, **6**-(*S*): ^{1}H NMR (DMSO-d6) δ 1.42 (s, 2H), 1.61 (s, 4H), 2.41 ~ 3.14 (m, 8H), 3.67 (s, 3H), 4.24 (s, 2H), 4.59 (m, 2H), 6.14 ~ 7.28 (m, 11H). Purity: >97 by LC-MS: R_f= 2.9, MS (m/z): MH+ (500) HRMS calcd for C31H34NO5 (M+H+) 500.2437 found 500.1987 Anal calcd for C, 74.38; H, 6.85; N, 2.80; O, 15.98; found C, 74.41; H, 6.91; N, 2.77

Peak 2 as 8-Methoxy-5S-(-)-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-11,12-dihydro-5H-6,13-dioxa-benzo[3,4]cyclohepta[1,2-a]naphthalen-2-ol, **5-**(S) ^{1}H NMR (CD_3OD) δ 1.41 (broad s, 2H), 1.59 (broad s, 4H), 2.50 (broad s, 4H0, 2.68 (m, 2H), 2.81 (m, 2H), 3.78 (m, 2H), 4.61 (t, 2H, J = 6.0 Hz), 6.02 (s, 1H), 6.22 ~ 7.29 (m, 10H). MS (m/z): MH+ (500). HRMS calcd for C31H34NO5 (M+H+) 500.2437 found 500.1687; Purity: >96 by LC-MS: R_f= 2.88, MS (m/z): MH+ (500)

Preparation of 2-Methoxy-5R-(-)-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-11,12-dihydro-5H-6,13-dioxa-benzo[3,4]cyclohepta[1,2-a]naphthalen-8-ol, **7**-(*R*) And 8-Methoxy-5R-(-)-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-11,12-dihydro-5H-6,13-dioxa-benzo[3,4]cyclohepta[1,2-a]naphthalen-2-ol, **6**-(R): 5R-(-)-[4-(2-Piperidin-1-yl-ethoxy)-phenyl]-11,12-dihydro-5H-6,13-dioxa-benzo[3,4]cyclohepta[1,2-a]naphthalene-2,8-diol **1a**-(*R*) (5 g) was dissolved in CH_3CN/MeOH (3:1) (150 mL) and 1.1 equivalent of $TMSCH_2N_2$ (2M in hexane, 5 mL) and was stirred overnight. The reaction mixture was concentrated to dryness and purified on SiO_2 using 5-10% MeOH in CH_2Cl_2 to yield a mixture of the title compounds as yellow foam. The mixture of compounds (1.4g) was loaded onto a ChiralPak AD chiral HPLC column 5 cm I.D. x 50 cm L) and eluted with 100% IPA at the 150 mL/min flow rate. The two peaks were collected to yield the two title compounds as follows: Peak 1: 2-Methoxy-5R-(-)-[4-(2-piperidin-1-yl-ethoxy)-

phenyl]-11,12-dihydro-5H-6,13-dioxa-benzo[3,4]cyclohepta[1,2-a]naphthalen-8-ol, **6**-(*R*): ^{1}H NMR (DMSO-d6) δ 1.42 (s, 2H), 1.61 (s, 4H), 2.41 ~ 3.14 (m, 8H), 3.67 (s, 3H), 4.24 (s, 2H), 4.59 (m, 2H), 6.14 ~ 7.28 (m, 11H). ^{1}3C NMR(DMSO, 400 MHz): 159.92, 158.18, 157.78, 157.42, 152.29, 130.75, 129.35, 128.14, 125.66, 123.97, 121.67, 117.18, 111,15, 110.95, 108.75, 106.87, 102.27, 77.58, 76.53, 65.37, 57.29, 55.09, 54.29, 29.00, 25.50, 23.88 (m, 10H). Purity: >96% by LC-MS: R_f= 2.9, MS (m/z): MH+ (500); HRMS calcd for $C_{31}H_{34}NO_5$ (M+H+) 500.2437 found 500.1987; Anal calcd for C, 74.38; H, 6.85; N, 2.80; O, 15.98; found: C, 74.46; H, 6.97; N, 2.79; [α] = +78.2 (c = 0.88 g/100 mL, MeOH, 25 ^{o}C).

and Peak 2 as 8-Methoxy-5R-(-)-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-11,12-dihydro-5H-6,13-dioxa-benzo[3,4]cyclohepta[1,2-a]naphthalen-2-ol,

6-(*R*) ^{1}H NMR (CD_3OD) δ 1.41 (broad s, 2H), 1.59 (broad s, 4H), 2.50 (broad s, 4H0, 2.68 (m, 2H), 2.81 (m, 2H), 3.78 (m, 2H), 4.61 (t, 2H, J = 6.0 Hz), 6.02 (s, 1H), 6.22 ~ 7.29 (m, 11H). ^{13}C-NMR (DMSO, 400 MHz) 159.21, 158.45, 158.41, 157.39, 152.29, 130.37, 129.29, 129.10, 128.9, 124.39, 124.131, 123.36, 116.69, 111.73, 109.11, 108.55, 107.30, 103.64, 77.74, 76.40, 65.37, 57.30, 55.17, 54.30, 28.00, 25.51, 23.88.); HRMS calcd for $C_{31}H_{34}NO_5$ (M+H+) 500.2437 found 500.2217; Anal calcd for C, 74.38; H, 6.85; N, 2.80; O, 15.98; found: C, 74.56; H, 6.88; N, 2.91; [α] = +36 (c = 0.38 g/100 mL, MeOH, 25 ^{o}C).

Alkaline Phosphatase Assay in Human Endometrial Ishikawa Cells

This assay was run according to the procedure described by Albert et a., *Cancer Res*, **(9910)**, 50(11), 330-6-10, with minor modification.

Ishikawa cells (from ATCC) were maintained in DMEM/F12 (1:1) phenol red free medium (Gibco) supplemented with 10% calf serum (Hyclone). 24 hours prior to testing, the medium was changed to DMEM/F12 (1:1) phenol red free containing 2% calf serum.

Compounds to be tested in the agonist mode were added to the culture media at varying concentrations. Compounds to be treated in the antagonist mode were prepared similarly, and 10 nM 17β-estradiol was also added to the culture media. The cells were then incubated at 37^{o}C for 3 days. On the fourth day, the media was remove, 1 volume of 1X Dilution Buffer (Clontech) was added to the well followed by addition of 1 volume of Assay Buffer (Clontech). The cells were then incubated at room temperature for 5 minutes. 1 volume of freshly prepared Chemiluminescence Buffer (1 volume of chemiluminescent substrate (CSPD) in 19 volume Chemiluminescent Enhancer with final concentration of CSPD at 1.25 mM; Sigma Chemical Co.) was added. The cells were incubated at room temperature for 10 minutes and then quantified on a luminometer. The increase of chemiluminescence over vehicle control was used to calculate the increase in alkaline phosphatase activity.

MCF-7 Cell Proliferation Assay

This assay was run according to the procedure described by Welshons, et al., (*Breast Cancer Res. Treat.,* **1987**, 10(2), 169-75), with minor modification. Briefly, MCF-7 cells (from Dr. C. Jordan, Northwestern University) were maintained in RPMI 1640 phenol red free medium (Gibco) in 10% FBS (Hyclone), supplemented with bovine insulin and non-essential amino acid (Sigma). The cells were initially treated with 4-hydoxyltamoxifen (10^{-8} M) and let stand at 37^{o}C for 24 hours. Following this incubation with tamoxifen, the cells were treated with compounds at various concentrations. Compounds to be tested in the agonist mode were added to the culture media at varying concentrations. Compounds to be treated in the antagonist mode were prepared similarly, and 10 nM 17β-estradiol was also added to the culture media. The cells were incubated

for 24 hours at 37°C. Following this incubation, 0.1 Ci of ^{14}C-thymidine (56mCi/mmol, Amersham) was added to the culture media and the cells were incubated for an additional 24 hours at 37°C. The cells were then washed twice with Hank's buffered salt solution (HBSS) (Gibco) and counted with a scintillation counter. The increase in the ^{14}C-thymidine in the compound treated cells relative to the vehicle control cells were reported as percent increase in cell proliferation.

Estrogen Receptor β Fluorescence Polarization Assay

This assay monitors binding of a fluorescent analog of estrogen (Fluormone ES2, Panvera) to the estrogen receptor. Plates are read in a fluorometer that can be set to polarization mode. A decrease in fluorescence relative to vehicle control is an indication of binding of a compound to the receptor.

It is crucial to avoid introduction of air bubbles into the reaction in each well of the 96 well plate throughout this procedure. (Bubbles on the surface of the reaction disrupt light flow, affecting the polarization reading.) However, it is also crucial to effectively mix the reaction components upon addition to the well.

On ice, a 2X standard mixture of Assay Buffer (Panvera), 10 nM DTT and 40 nM ES2 was prepared. On ice, a 2X reaction mixture of Assay Buffer (Panvera), and 20 nM hER-β (Panvera) and 40 nM ES2 was also prepared.

Dilutions of test compound were prepared in 30% (v/v) dimethyl sulfoxide/50 mM HEPES, pH 7.5. At this point, the dilutions were 40X the final required concentration.

The standard mixture at 50 μL was then added to each well. The reaction mixture at 48 μL was added to all wells. The compound dilution at 2.5 μL was added to the appropriate wells. The reaction mixtures were mixed using a manual pipette, a roll of aluminum foil adhesive cover was placed on the plate and the plate incubated at room temperature for 1 hour.

Each well on the plate was then read in an LjL Analyst with an excitation wavelength of 265 nm and an emission wavelength of 538.

Estrogen Receptor α Flash Plate Assay

This assay monitors binding of radiolabeled estrogen to the estrogen receptor. It is performed on a BioMek 2000 (Beckman). Plates are read in a scintillation counter (Packard TopCount), with decreased counts an indication of binding of a compound to the receptor. The assay was run according to the procedure described by Allan, et al., *Anal. Biochem.* **(1999)**, 275(2), 243-247.

On day one, 100 L of Estrogen Screening Buffer (ESB, Panvera) containing 5mM dithiothreitol (DTT, Panvera), 0.5 μg mouse anti-estrogen receptor monoclonal antibody (SRA-1010, Stressgen) and 50 ng purified human estrogen receptor α (Panvera) were added to each well of a 96 well FlashPlate Plus plate crosslinked with goat anti-mouse antibodies (NEN Life Sciences). The plate was sealed and incubated at 4°C overnight.

On day two, each well was washed three times with 200 μL PBS, pH 7.2, at room temperature. To each well was then added 98 μL radiolabeled estrogen (0.5 nM, which equals 6 Ci for a 120 Ci/mmol batch, Amersham), diluted in ESB and 5mM dithiothreitol (DTT). To individual wells were then added 2.5 μL test compound diluted in 30% (v/v) dimethyl sulfoxide/50 mM HEPES, pH 7.5. The wells were mixed three times by aspiration, the plate sealed and incubated at room temperature for one hour. The wells were then counted for 1 min in a TopCount scintillation counter (Packard)

Protocol for immature rat uterotropic study

Introduction

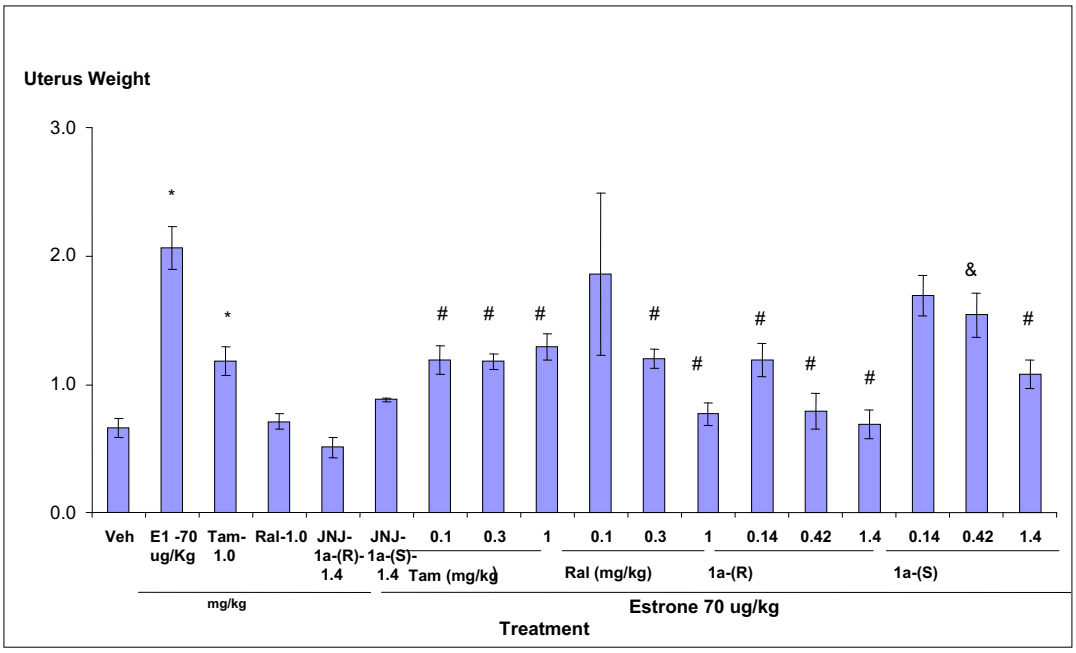
Selective Estrogen Receptor Modulators (SERM) act as estrogen agonist or antagonist on uterus. It is well established that estrogens are known for their uterotropic activities to stimulate uterine

growth. The immature rat uterotropic model (Reference 1-3) is used to get a rapid and accurate assessment of the activity of a compound in the uterus. This can be used in either the agonist mode (compound alone) or antagonist mode (compound + estrogen). Because the animals have not matured sexually, there is minimal endogenous estrogen to complicate the evaluation. Immature rats which are unexposed to estrogen, are administered with an estrogen, Estrone for three days. The uteri grow rapidly, and the weight of uterus increases sharply in three days. Co-treatment with estrogen antagonist could block the stimulation, whiles estrogen agonist synergistically enhances the stimulation. The difference between the weight of uterus from vehicle control animals and that from treated animals is a sensitive indicator of estrogen agonist or antagonist activity. This model has been used as a classical measure to evaluate activities of estrogen agonists and antagonists including SERMs. The affects of these compounds in this model have been predictive of the clinical responses in reported women.

Materials and methods

Eighteen Nineteen days old immature rats (45-55 gm) are obtained from Charles River Laboratories (Wilmington, MA). They are housed in groups of three in wire-mesh cages at an ambient temperature of 21 to 23 °C with an automated 12/12 hour light/dark cycle and access to water and a commercial rodent food ad libitum. The rats are treated daily for three consecutive days with Estrone (Sigma, St. Louise, MO), at 70 μg/kg/day (in 0.1 ml of sesame oil, s.c..) alone or along with testing compounds with oral administration by gavaging. There are three animals per group. The rats are euthanized 24 hours after the final dose, and their uteri are were excised, cleaned of surrounding fat and connective tissue, incised slightly to release luminal fluid, blotted on filter paper, and weighed. The ratio of uterine weight and body weight is expressed as an indicator of uterotropic activity.

Effect of **1a**-*(R)* and **1a**-*(S)* on Uterine Weight in Immature



Note: *: significant difference compared to Veh control (p<0.001);

#: significant difference compared to E1-70 ug/kg (p<0.001);

&: significant difference compared to E1-70 ug/kg (p<0.05);

Tam: Tamoxifen; Ral: Raloxifene; E1: Estrone

1. REFERENCES

1. Lerner, Leonard J.; Hilf, Russell; Turkheimer, A. Robert; Michel, Inge; Engel, Stanford L. Effects of hormone antagonists on morphological and biochemical changes induced by hormonal steroids in the immature rat uterus. Endocrinology 1966: 78, 111-24.

2. Gabbard, R. Bruce; Hamer, Leslie F.; Segaloff, Albert. Structure-activity relationships of four 11-hydroxyestrones isomeric at the C-9 and C-11 positions. Steroids 1981: 37, 243-55.

3. McKim, James M., Jr.; Wilga, Paul C.; Breslin, William J.; Plotzke, Kathy P.; Gallavan, Robert H.; Meeks, Robert G. Potential estrogenic and antiestrogenic activity of the cyclic siloxane octamethylcyclotetrasiloxane (D4) and the linear siloxane hexamethyldisiloxane (HMDS) in immature rats using the uterotrophic assay. Toxicological Sciences 2001: 63, 37-46.

4. Ashby, J.; Odum, J.; Foster, J. R. Activity of raloxifene in immature and ovariectomized rat uterotrophic assays. Regulatory Toxicology and Pharmacology 1997: 25, 226-231.

5. (a) Ke, H. Z.; Brown, T. A.; Thompson, D. D. Lasofoxifene (CP-336,156), a novel selective estrogen receptor modulator, in preclinical studies. Journal of the American Aging Association 2002: 25, 87-99 (b) Riggs, Lawrence; Hartmann, Lynn C. Selective estrogen-receptor modulators - mechanisms of action and application to clinical practice. New England Journal of Medicine 2003: 348, 618-629.

Pharmacokinetics and Drug Metabolism

Pharmacokinetics

The pharmacokinetic properties of JNJ-19398990 = **7**-R were evaluated in both female rats and monkeys. The primary metabolites, JNJ26529126 = **5**-(*R*) JNJ-26529152 as **6**-(*R*) and JNJ-17148066 as **1a-**(*R*) were also measured in these animals.

Methods of Analysis

Blood samples (0.5 ml) were collected into heparinized tubes post dose via orbital sinus puncture. Blood samples were centrifuged for cell removal, and precisely 200 μL of

plasma supernatant is then transferred to a clean vial, placed on dry ice, and subsequently stored in a -70^{o}C freezer prior to analysis.

Plasma samples were prepared as follows. Four hundred microliters of acetonitrile containing internal standard is added to 200 uL of plasma to precipitate proteins. Samples were centrifuged at 5000 x G for 3 minutes and supernatant removed for analysis by LC-MS-MS. Calibration standards were prepared by adding appropriate volumes of stock solution directly into plasma and treated identically to collected plasma samples. Calibration standards are typically prepared in the range of 0.1 to 10 μM for quantitation. LC-MS-MS analysis is performed using either multiple reaction or selected ion monitoring for detection of characteristic ions for each drug candidate and internal standard used was Propranolol. Results were calculated by WinNonlin Pro version 3.1.

Single dose pharmacokinetics in rats

Plasma concentrations of JNJ-19398990 and its metabolites, JNJ-26529126, JNJ-26529152, and JNJ-17148066 were determined following a single administration of JNJ-19398990 (i.v. 2 mg/kg, p.o. 10 mg/kg) to adult female rats. The compound was formulated for both IV and oral dosing as a solution in a vehicle of 20% w/v cyclodextrin in 0.1 N citric acid.

The parent compound, JNJ-19398990, and the metabolites reached detectable blood levels following both oral and intravenous administrations (Table 8, Figure 115). The parent and the pooled monomethoxy intermediates reached blood levels that were approximately equivalent and the dihydroxy metabolite (JNJ-17148066) was present at very low levels (Figure 16). The bioavailability of JNJ-19398990 was determined to be 30.8%.

Glucuronidation and sulfation of the three metabolites were also examined. Sulfation products of JNJ-26529126 (or JNJ-26529152) and JNJ-17148066 were detected at very low levels. No glucuronidation products were found.

Table 8. Pharmacokinetic parameters of JNJ-19398990 and JNJ-26529126[a], JNJ-26529152 [a], and JNJ-17148066 [a] in female rats.

Compound	Formulation	Route	Dose (mg/kg)	C_{max} (ng/mL)	t_{max} (hr)	$t_{1/2}$ (hr)	AUC (ng·hr/mL)	F (%)
JNJ-19398990	20% cyclodextrin in 0.1N citric acid	i.v.	2	1035	0.08	5.82	1392	-
	0.5% methocel	p.o.	10	168	5.0	7.2	2268	30.8
JNJ-26529126		i.v.	-	15.2	8.0	-	-	-
		p.o.	-	91.4	8.0	-	-	-
JNJ-26529152		i.v.	-	7.6	8.0	-	-	-
		p.o.	-	33.3	8.0	-	-	-
JNJ-17148066		i.v.	-	1.6	8.0	-	-	-
		p.o.	-	3.9	6.0	-	-	-

[a]Concentrations determined in animals dosed with JNJ-19398990.

Figure 15. Plasma concentrations of JNJ-19398990 following a single dose administration in female rats

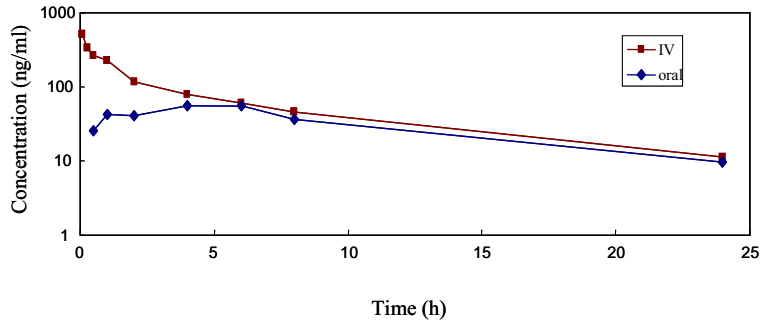
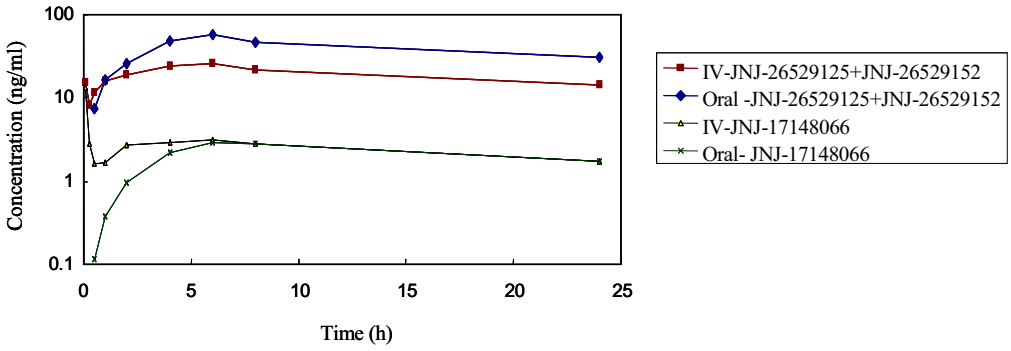


Figure 16. Plasma concentrations of JNJ-26529126, JNJ-26529152, and JNJ-17148066 following a single dose administration of JNJ-19398990 in female rats



Protocol for in vivo ovariectomized rat model

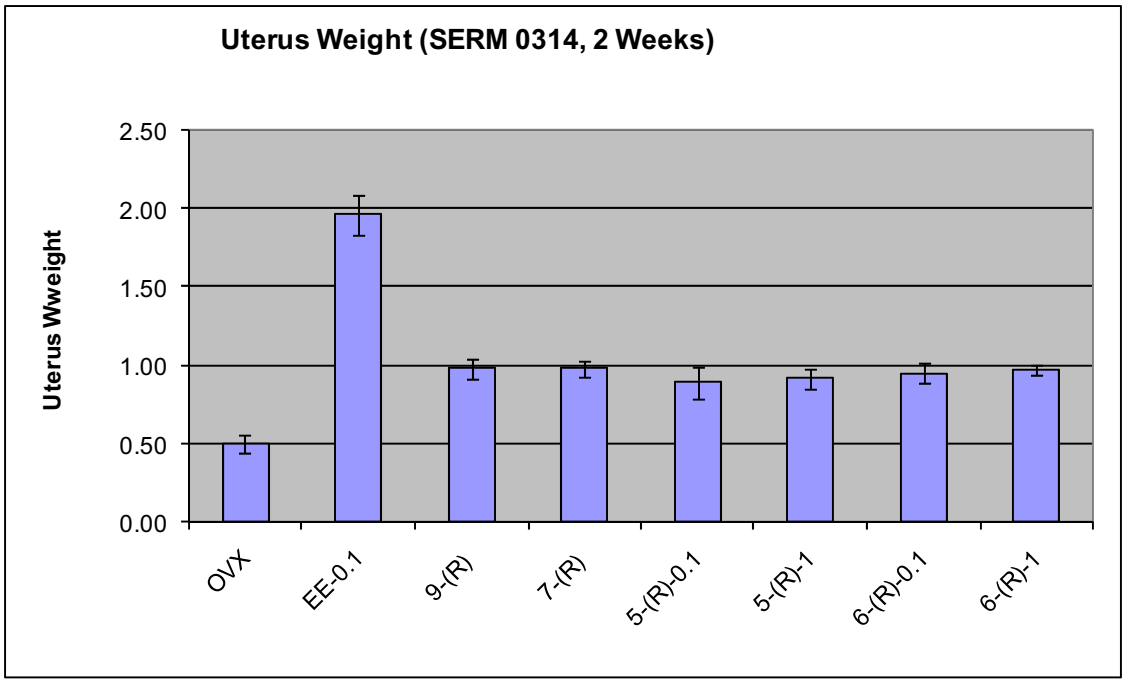
Introduction:

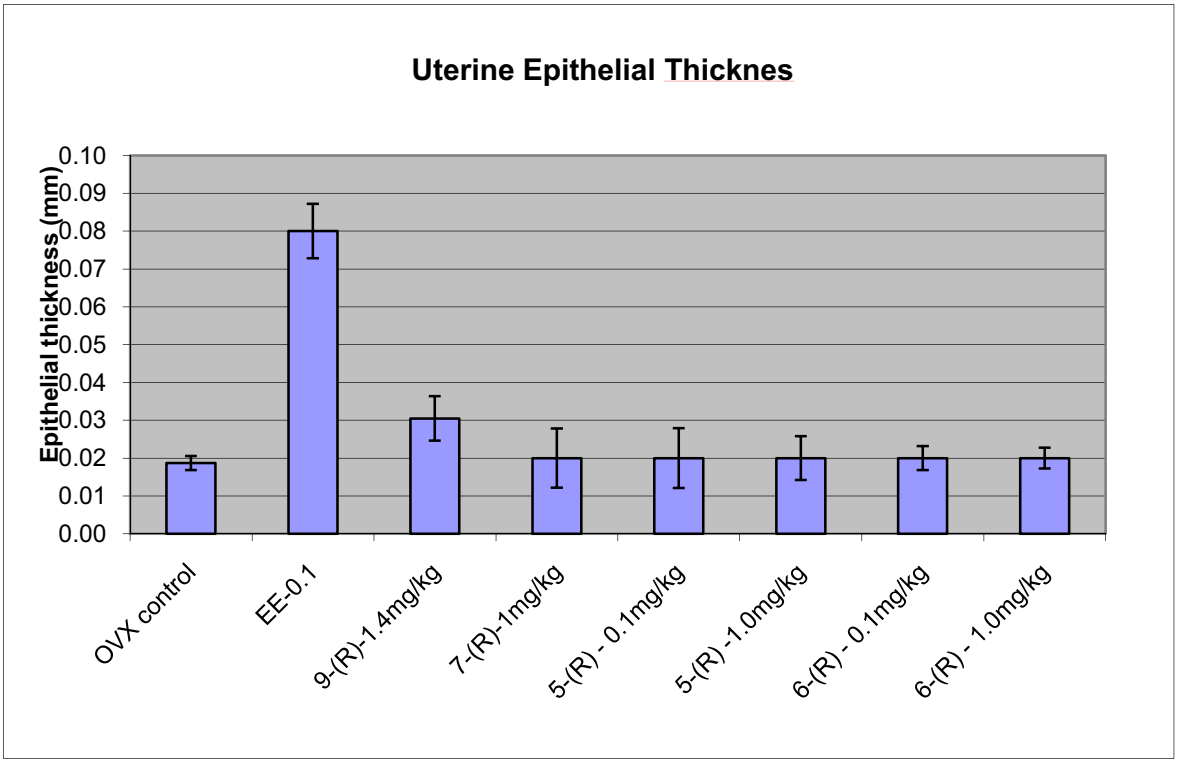
The adult ovariectomized estrogen-deficiency rat model is applied to evaluate the tissue selective effects of Selective Estrogen Receptor Modulators (SERM). The model is useful because the responses in several tissues can be used to evaluate the tissue selective properties of SERM compounds. It provides information on ovariectomy-induced bone loss, and plasma lipids, uterine and vaginal effects, as well as other pathological changes in cardiovascular system, and reproductive system. This model has been used to characterize many estrogen agonist and antagonist activities of SERMs (1). The treatment of testing compounds can be adjusted for 2 weeks or 6 weeks. Bone density measurement on isolated bones is conducted in the 6-weeks animal model. The affects of these compounds in this model have been in line with the clinical responses in reported women (2).

Materials and methods

Adult female animals (> 6 months old, Charles River Laboratories, Wilmington, MA) are used. The rats are housed individualy in wire-mesh cages at an ambient temperature of 21 to 23 °C with an automated 12/12 hour light/dark cycle and access to water and a commercial rodent food ad libitum. Each treatment group consisted of 6-14 animals. The animals are ovariectomized under sterile condition and anesthesia. Twenty four hours after the surgery, testing compounds are administered daily by gavaging for 6 weeks. Other reference treatment groups include sham-

operated control, and ovariectomized control, ethanylestradiol (EE, 5 mg/kg/day), and raloxifene (1 mg/kg/day). 0.5% Methocel is used as the vehicle for all compounds.





1.1.1. Measurement of serum total cholesterol levels

Blood samples are collected orbitally, after 2 weeks of treatment and or at the end of study. Serum samples are shipped to LarCorp LabCorp (Burlington, NC) and analyzed with a Roche Hitachi 717 Chemistry Analyzer. All reagents are obtained from Roche Diagnostics.

1.1.2. Vaginal cytology

Vaginal smear is taken by flushing the vagina with water using a pipette. The water containing vaginal epithelial cells is put on to a slide followed by examination of cytology of the epithelial cells under microscope to determine the cycling stage of the animal.

Measurement of uterine weight

Animals are euthanatized at the end of study with CO_2. The uteri are excised, cleaned of surrounding fat and connective tissue, incised slightly to release luminal fluid, blotted on filter paper, and weighed.

1.1.3. Measurement of uterine epithelial thickness

1. Immunohistochemistry

Immunohistochemistry is performed as described in Reference 5. All incubations are performed at room temperature. After microwaving the slides in Target (Dako, Carpenturia, CA), the slides are placed in PBS, then 3% H2O2, rinsed in PBS and then appropriate blocking serum was added for 10 minutes. Subsequently, the primary antibodies (cocktail: pan-cytokeratin (1:25, Sigma, St. Louis, MO) and smooth muscle actin (1:100, Dako) are applied to the slides for 30 minutes. Proper species isotype antibody (Vector Labs, Burlingham, CA) is substituted as the primary antibody for the negative control. After several PBS washes, a biotinylated secondary antibody (Vector Labs) is placed on the slides for 30 minutes. Subsequently, the slides are washed in PBS and then the avidin-biotin complex (ABC, Vector Labs) was applied to the cells for 30 minutes.

The presence of the primary antibodies is detected by adding DAB (3'-diaminobenzidine HCl; Biomeda, Foster City, CA) for 2 times 5 minutes. Slides are briefly exposed to Mayer's hematoxylin for 1 minute, dehydrated and coverslipped.

2. Image analysis methods

Image analysis is applied to count the thickness of the epithelium, which is easily identified by the antibody labeling. The image analysis is performed using an Olympus BX50 light microscope, Sony 3CCD digital camera interfaced with a IBM 350PC using Image Pro (v 3.0) analysis software (Phase 3 Imaging Systems, Glen Mills, PA). A special tool is used to draw a line at the base of the epithelial cells of the uterus, while another line is draw along the apical, luminal surface of the epithelial cells. The computer calculates average distance between the two traced lines.

1.1.4. Measurement of bone mineral density

After euthanatization, the left tibia is removed from the animal, and is defleshed and fixed in 10% of Formalin. Ex-Vivo pQCT is conducted at Dr. Jee's laboratory at the Radiobiology Division, University of Utah, Salt Lake City, UT. The trabecular and cortical BMD and BMC measurements are carried out using a XCT 960A peripheral quantitative computerized tomography system (pQCT, Norland Medical Systems, Fort Atkinson, WI) on the proximal tibial metaphysis at 5 mm and 6 mm distal to the knee joint. A voxel size of 0.148 mm is used and a threshold of 0.600cm 1 for cancellous bone is used.

References

1. Frolik C A; Bryant H U; Black E C; Magee D E; Chandrasekhar S Time-dependent changes in biochemical bone markers and serum cholesterol in ovariectomized rats: effects of raloxifene HCl, tamoxifen, estrogen, and alendronate. BONE 1996: 18, 621-7.

2. Ma, Yanfei L.; Bryant, Henry U.; Zeng, Qingqiang; Palkowitz, Alan; Jee, Webster S. S.; Turner, Charles H.; Sato, Masahiko. Long-term dosing of arzoxifene lowers cholesterol, reduces bone turnover, and preserves bone quality in ovariectomized rats. Journal of Bone and Mineral Research. 2002: 17, 2256-2264.

3. Ke, H. Z.; Brown, T. A.; Thompson, D. D. Lasofoxifene (CP-336,156), a novel selective estrogen receptor modulator, in preclinical studies. Journal of the American Aging Association. 2002: 25, 87-99.

4. Walsh BW, Kuller LH, Wild RA, Paul S, Farmer M, Lawrence JB, Shah AS, Anderson PW. Effects of raloxifene on serum lipids and coagulation factors in healthy postmenopausal women. JAMA 1998: 279, 1445-1451.

5. D'Andrea MR, Derian CK, Leturcq D, Baker SM, Brunmark A, Ling P, Darrow AL, Santulli RJ, Brass LF, Andrade-Gordon P. Characterization of protease activated receptor (PAR-2) immunoreactivity in normal human tissues. J Histochem Cytochem 1998: 46, 157-164.

1.1.4.1.1. Protocol for ovariectomized rat hot flush model

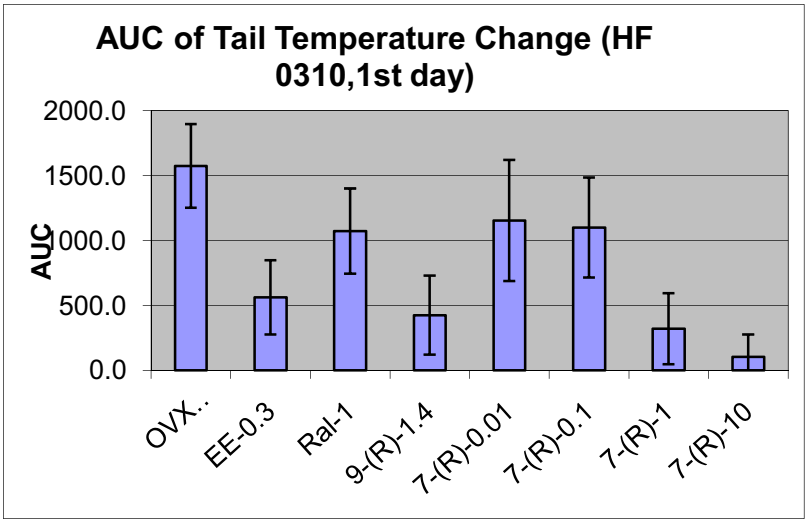
Introduction

Selective estrogen receptor modulators (SERM) have divergent activities depending on the tissue it is acting upon. That is it has agonist properties in some tissues and antagonist properties in another. One of the important activities of SERM compounds is the ability to increase or reduce the incidence and severity of the hot flush, a symptom that frequently occurs in postmenopausal women (Reference 1). This activity is rtested in a rodent model for hot flush.

In the ovariectomized rat hot flush model, morphine-addicted rats undergo morphine withdrawal, after which they experience a “hot flush” that can be measured by their tail skin temperature. Estrogens have been shown to block this hot flush (2-6). This model has been used to characterize several SERMs including raloxifene and bazedoxifene (6). The affects of these compounds in this model have been predictive of the clinical responses in reported women (2, 7-9).

Materials and methods

Adult female Sprague-Dawley rats (3 months old, Charles River Laboratories, Wilmington, MA) are used. Each treatment group consisted of 8 to 25 animals. They are housed individually in wire-mesh cages at an ambient temperature of 21 to 23 °C with an automated 12/12 hour light/dark cycle and access to water and a commercial rodent food ad libitum. The rats are ovariectomized under anesthesia. Six days after ovariectomy, treatment of the rats is initiated. All compounds are administered either testing compounds or vehicle (sesame oil), ethinyl estradiol (EE), and raloxifene orally by gavage. The rats are injected (s.c.) with a suspension containing 75 mg and 150 mg of morphine (freebase) on day 3 and day 5 of treatment, respectively. On the last day of treatment, the animals are lightly anesthetized with ketamine (80 mg/kg, i.m.). Following the anesthesia, a thermistor (YSI 400 series, YSI Precision Temperature Group, Dayton, OH), connected to a data acquisition system (Acquisition interface Model ACQ-10, Gould 6600 Amplifier, Gould Instrument System Inc. Valley view, OH), is placed on the tail of the animals. Following the measurement of the baseline tail skin temperature for about 20 minutes, naloxone (2.0 mg/kg, s.c. Sigma, St. Louis, MO) is administered to induce the morphine withdrawal. Tail skin temperature is then measured for an additional 60 minutes. Multiple comparisons among the treatment groups at each time point are used for analysis. The values of maximal temperature change (ΔT) are reported. Statistical analysis (t-test) is conducted by Preclinical Biostatistics, JJPRD with an analysis program of Wilcoxon Ranl Sum Test from Statxact (Version 4, Statistical Solutions, Saugus, MA).



OVX vs EE-0.3: p=0.025 ; OVX vs **9**-(*R*)-1.4: p=0.015

References

1. Berendsen H H; Weekers A H; Kloosterboer H J, Effect of tibolone and raloxifene on the tail temperature of oestrogen-deficient rats. European Journal of Pharmacology 2001, 419, p47-54.

2. Merchenthaler I, Funkhouser JM, Carver JM, Lundeen SG, Ghosh K, Winneker RC. The effect of estrogens and antiestrogens in a rat model for hot flush. Maturitas 1998: 30, 307-316.

3. Kobayashi T, Tamura M, Hayashi M, Katsuura Y, Tanabe H, Ohta T, Komoriya K. Elevation of tail skin temperature in ovariectomized rats in relation to menopausal hot flushes. Am. J. Physiol. 2000: 278(4, Pt. 2), R863-R869.

4. Berendsen HHG, Weekers AHJ, Kloosterboer HJ. Effect of tibolone and raloxifene on the tail temperature of oestrogen-deficient rats. Eur. J. Pharmacol. 2001, 419: 47-54.

5. Hosono T, Chen X-M, Miyatsuji A, Yoda T, Yoshida K, Yanase-Fujiwara M, Kanosue K. Effects of estrogen on thermoregulatory tail vasomotion and heat-escape behavior in freely moving female rats. Am. J. Physiol. 2001: 280(5, Pt. 2), R1341-R1347.

6. Komm BS, Lyttle CR. Developing a SERM: stringent preclinical selection criteria leading to an acceptable candidate (WAY-140424) for clinical evaluation. NY Acad. Science. 2001: 949:317-326.

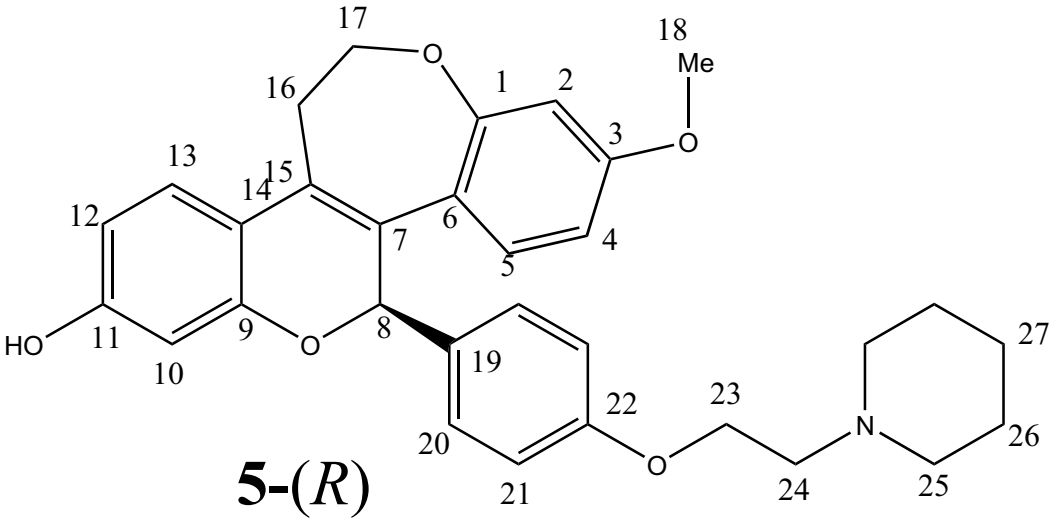
7. Katovich MJ and O'Meara J, Effect of chronic estrogen on the skin temperature response to naloxone in morphine-dependent rats. Can J Physiol Pharmacol, 1987, 65, p563–567.

8. Simpkins, JW , Katovich, MJ and Song, Similarities between morphine withdrawal in the rat and the menopausal hot flush. Life Sciences, 1983, 32, p1957–1966.

9. MJ Katovich, JW Simpkins, LA Berglund and J. O'Meara, I-C, Regional skin temperature changes in a rat model for the menopausal hot flush. Maturitas, 1986, 8, p67–76.

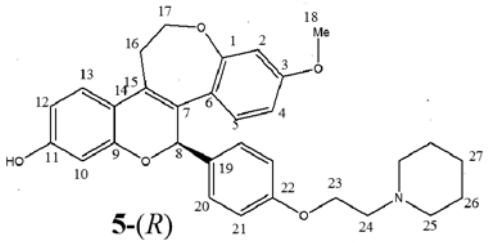
Structure Determination of **5**-(R)

(Peak2)



5-(*R*)

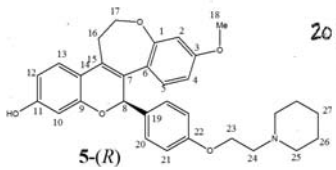
809-monomethoxy Peak 2



BRUKER

```
Current Data Parameters
NAME                  NJ809pk2
EXPNO                        1
PROCNO                       1

F2 - Acquisition Parameters
Date_                 20030607
Time                     16.56
INSTRUM                  spect
PROBHD       5 mm Multinu
PULPROG                    zg
TD                       32768
SOLVENT                  DMSO
NS                         16
DS                          2
SWH                   4803.074 Hz
FIDRES                0.146578 Hz
AQ                    3.4111989 sec
RG                         256
DW                     104.100 usec
DE                     178.29 usec
TE                       300.0 K
D1                  1.00000000 sec

============ CHANNEL f1 ===========
NUC1                        1H
P1                       7.75 usec
PL1                      1.00 dB
SFO1                400.1320807 MHz

F2 - Processing parameters
SI                       16384
SF                  400.1300064 MHz
WDW                         EM
SSB                          0
LB                       0.30 Hz
GB                           0
PC                        1.00
```

809-monomethoxy Peak 2

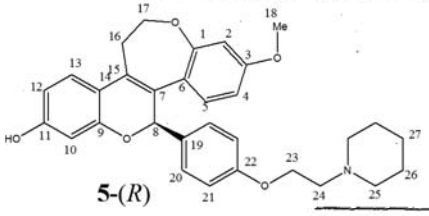


5-(*R*)

BRUKER

```
Current Data Parameters
NAME                  NJ809pk2
EXPNO                        2
PROCNO                       1

F2 - Acquisition Parameters
Date_                 20030607
Time                     17.02
INSTRUM                  spect
PROBHD       5 mm Multinu
PULPROG                cosygs
TD                         2048
SOLVENT                   DMSO
NS                           1
DS                           8
SWH                   4816.956 Hz
FIDRES                2.352029 Hz
AQ                    0.2126324 sec
RG                        574.7
DW                      103.800 usec
DE                        6.50 usec
TE                       300.0 K
d0                    0.00000300 sec
D1                    1.00000000 sec
d13                   0.00000300 sec
D16                   0.00015000 sec
IN0                   0.00020760 sec

============ CHANNEL f1 =============
NUC1                         1H
P0                        7.75 usec
P1                        7.75 usec
PL1                       1.00 dB
SFO1                400.1320807 MHz

============ GRADIENT CHANNEL ========
P16                    1000.00 usec

F1 - Acquisition parameters
ND0                          1
TD                         128
SFO1                 400.1321 MHz
FIDRES              37.632465 Hz
SW                     12.038 ppm
FnMODE               undefined

F2 - Processing parameters
SI                        1024
SF                  400.1300064 MHz
WDW                       SINE
SSB                          0
LB                        0.00 Hz
GB                           0
PC                        1.40

F1 - Processing parameters
SI                        1024
MC2                         QF
SF                  400.1300064 MHz
WDW                       SINE
SSB                          0
LB                        0.00 Hz
GB                           0
```

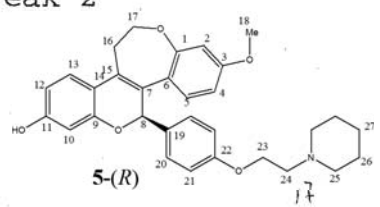
809-monomethoxy Peak 2



BRUKER

```
Current Data Parameters
NAME                  NJ809pk2
EXPNO                        2
PROCNO                       1

F2 - Acquisition Parameters
Date_                 20030607
Time                     17.02
INSTRUM                  spect
PROBHD       5 mm Multinu
PULPROG                 cosygs
TD                         2048
SOLVENT                   DMSO
NS                           1
DS                           8
SWH                   4816.956 Hz
FIDRES                2.352029 Hz
AQ                    0.2126324 sec
RG                        574.7
DW                      103.800 usec
DE                        6.50 usec
TE                       300.0 K
d0                    0.00000300 sec
D1                    1.00000000 sec
d13                   0.00000300 sec
D16                   0.00015000 sec
IN0                   0.00020760 sec

============ CHANNEL f1 =============
NUC1                         1H
P0                        7.75 usec
P1                        7.75 usec
PL1                       1.00 dB
SFO1                400.1320807 MHz

============ GRADIENT CHANNEL ========
P16                    1000.00 usec

F1 - Acquisition parameters
ND0                          1
TD                         128
SFO1                 400.1321 MHz
FIDRES              37.632465 Hz
SW                     12.038 ppm
FnMODE              undefined

F2 - Processing parameters
SI                        1024
SP                 400.1300064 MHz
WDW                       SINE
SSB                          0
LB                        0.00 Hz
GB                           0
PC                        1.40

F1 - Processing parameters
SI                        1024
MC2                         QF
SF                 400.1300064 MHz
WDW                       SINE
SSB                          0
LB                        0.00 Hz
GB                           0

2D NMR plot parameters
CX2                      20.00 cm
CX1                      20.00 cm
F2PLO                     7.594 ppm
F2LO                   3038.59 Hz
F2PHI                     5.854 ppm
F2HI                   2342.39 Hz
F1PLO                     7.570 ppm
F1LO                   3029.18 Hz
F1PHI                     5.925 ppm
F1HI                   2370.61 Hz
F2PPMCM                0.08700 ppm/cm
F2HZCM                34.81003 Hz/cm
F1PPMCM                0.08229 ppm/cm
F1HZCM                32.92841 Hz/cm
```

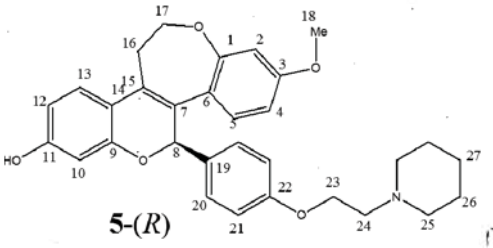
809-monomethoxy Peak 2



BRUKER

```
Current Data Parameters
NAME                  NJ809pk2
EXPNO                        3
PROCNO                       1

F2 - Acquisition Parameters
Date_                 20030607
Time                     17.08
INSTRUM                  spect
PROBHD     5 mm Multinu
PULPROG                inv4gs
TD                       2048
SOLVENT                  DMSO
NS                         96
DS                          8
SWH                4816.956 Hz
FIDRES             2.352029 Hz
AQ                 0.2126324 sec
RG                       13004
DW                   103.800 usec
DE                     6.50 usec
TE                     300.0 K
CNST2              145.0000000
d0                 0.00000300 sec
D1                 1.50000000 sec
d2                 0.00344828 sec
d12                0.00002000 sec
d13                0.00000300 sec
D16                0.00015000 sec
d20                0.00242528 sec
IN0                0.00002259 sec

============ CHANNEL f1 =============
NUC1                       1H
P1                       7.75 usec
p2                      15.50 usec
PL1                      1.00 dB
SFO1               400.1320807 MHz

============ CHANNEL f2 =============
CPDPRG2                 garp
NUC2                     13C
P3                      12.75 usec
PCPD2                   75.00 usec
PL2                      0.00 dB
PL12                    17.40 dB
SFO2               100.6227903 MHz

============ GRADIENT CHANNEL ========
P16                   1000.00 usec

F1 - Acquisition parameters
ND0                          2
TD                         128
SFO1               100.6228 MHz
FIDRES             172.938568 Hz
SW                 219.991 ppm
FnMODE                undefined

F2 - Processing parameters
SI                        2048
SF                 400.1300064 MHz
WDW                         no
SSB                          0
LB                    0.00 Hz
GB                           0
PC                        1.40

F1 - Processing parameters
SI                        1024
MC2                         QF
SF                 100.6127466 MHz
WDW                         no
SSB                          0
LB                    0.00 Hz
GB                           0
```

809-monomethoxy Peak 2

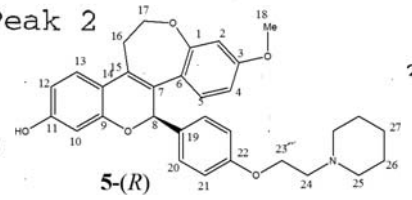


5-(*R*)

BRUKER

```
Current Data Parameters
NAME                  NJ809pk2
EXPNO                        4
PROCNO                       1

P2 - Acquisition Parameters
Date_                 20030607
Time                     23.02
INSTRUM                  spect
PROBHD       5 mm Multinu
PULPROG      inv4gslplrnd
TD                        2048
SOLVENT                   DMSO
NS                          96
DS                          16
SWH                 4816.956 Hz
FIDRES              2.352029 Hz
AQ                  0.2126324 sec
RG                    11585.2
DW                    103.800 usec
DE                      6.50 usec
TE                     300.0 K
CNST2               145.0000000
d0                  0.00000300 sec
D1                  1.50000000 sec
d2                  0.00344828 sec
D6                  0.06500000 sec
d13                 0.00000300 sec
D16                 0.00015000 sec
IN0                 0.00002259 sec

============ CHANNEL f1 =============
NUC1                        1H
P1                        7.75 usec
p2                       15.50 usec
PL1                       1.00 dB
SFO1                400.1320807 MHz

============ CHANNEL f2 =============
NUC2                       13C
P3                       12.75 usec
PL2                       0.00 dB
SFO2                100.6227903 MHz

============ GRADIENT CHANNEL ========
P16                   1000.00 usec

F1 - Acquisition parameters
ND0                          2
TD                         128
SFO1                100.6228 MHz
FIDRES              172.938568 Hz
SW                  219.991 ppm
FnMODE                undefined

F2 - Processing parameters
SI                        2048
SF                  400.1300064 MHz
WDW                       SINE
SSB                          0
LB                        0.00 Hz
GB                           0
PC                        1.40

F1 - Processing parameters
SI                        1024
MC2                         QF
SF                  100.6127466 MHz
WDW                       SINE
SSB                          0
LB                        0.00 Hz
GB                           0
```

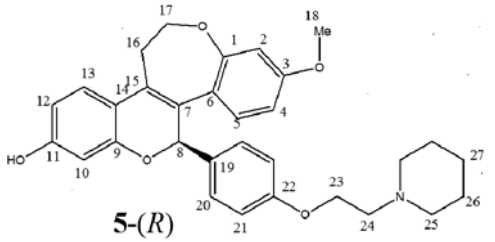
809-monomethoxy Peak 2



BRUKER

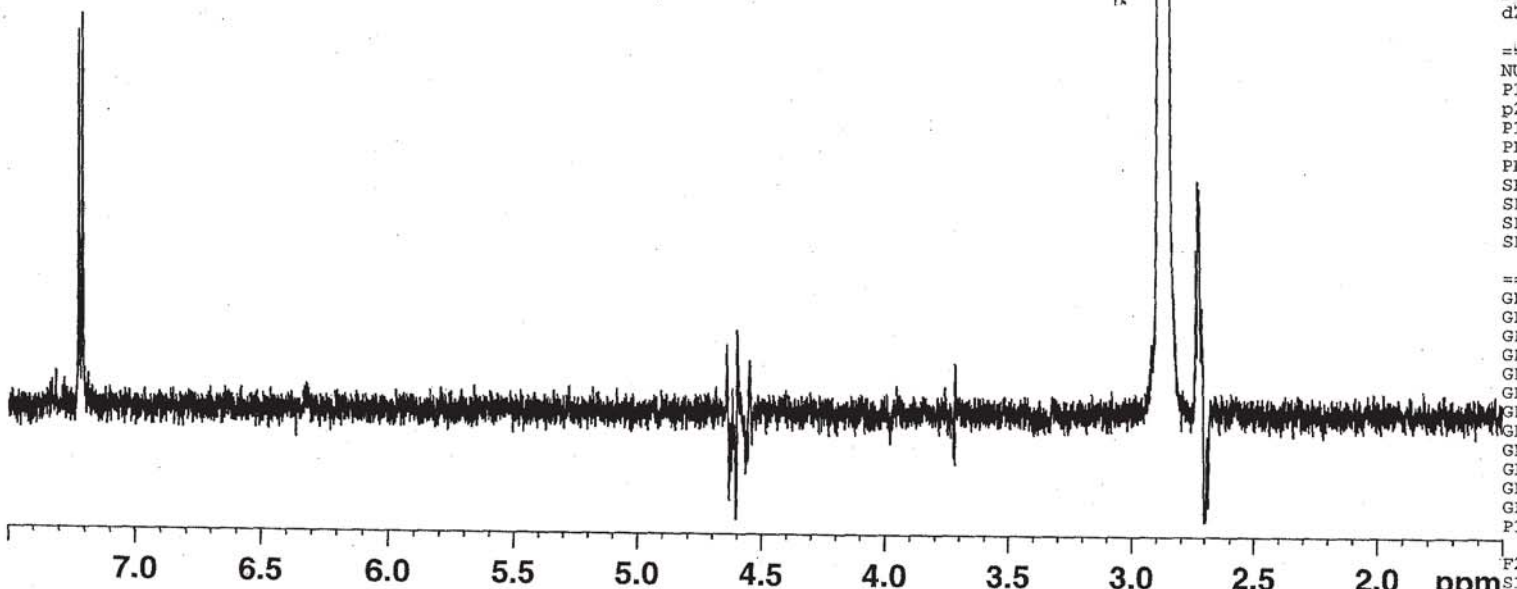
```
Current Data Parameters
NAME                  NJ809pk2
EXPNO                        4
PROCNO                       1

F2 - Acquisition Parameters
Date_                 20030607
Time                     23.02
INSTRUM                  spect
PROBHD     5 mm Multinu
PULPROG    inv4gslplrnd
TD                       2048
SOLVENT                  DMSO
NS                         96
DS                         16
SWH                4816.956 Hz
FIDRES             2.352029 Hz
AQ                 0.2126324 sec
RG                   11585.2
DW                   103.800 usec
DE                     6.50 usec
TE                    300.0 K
CNST2              145.0000000
d0                 0.00000300 sec
D1                 1.50000000 sec
d2                 0.00344828 sec
D6                 0.06500000 sec
d13                0.00000300 sec
D16                0.00015000 sec
IN0                0.00002259 sec

============ CHANNEL f1 =============
NUC1                      1H
P1                     7.75 usec
p2                    15.50 usec
PL1                    1.00 dB
SFO1               400.1320807 MHz

============ CHANNEL f2 =============
NUC2                     13C
P3                    12.75 usec
PL2                    0.00 dB
SFO2               100.6227903 MHz

============ GRADIENT CHANNEL ========
P16                 1000.00 usec

F1 - Acquisition parameters
ND0                        2
TD                       128
SFO1               100.6228 MHz
FIDRES             172.938568 Hz
SW                 219.991 ppm
FnMODE               undefined

F2 - Processing parameters
SI                       2048
SP                 400.1300064 MHz
WDW                      SINE
SSB                         0
LB                       0.00 Hz
GB                          0
PC                       1.40

F1 - Processing parameters
SI                       1024
MC2                        QF
SF                 100.6127466 MHz
WDW                      SINE
SSB                         0
LB                       0.00 Hz
GB                          0
```

NJ 809 - monomethoxy - peak 2
1-D NOESY



5-(*R*)

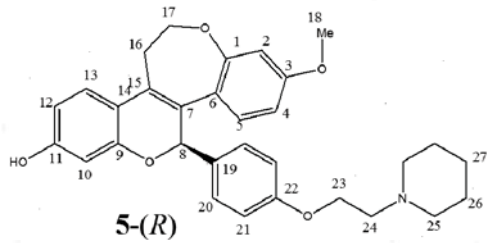
NOE
16 - 13



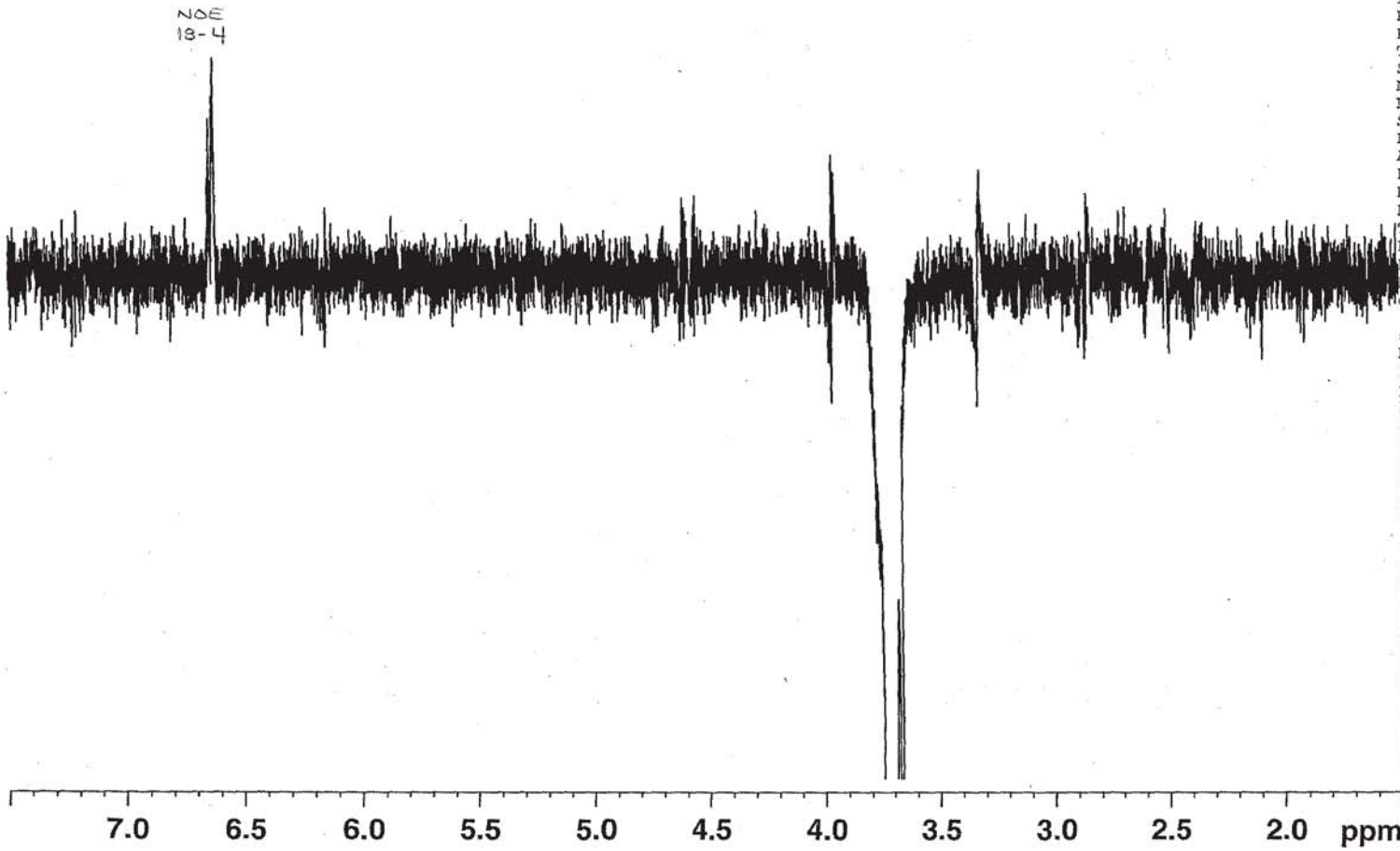
BRUKER

```
Current Data Parameters
NAME          nj809pk2_noe
EXPNO                    3
PROCNO                   1

F2 - Acquisition Parameters
Date_             20030630
Time                 17.23
INSTRUM              spect
PROBHD   5 mm BBI 1H-BB
PULPROG          selnogp.2
TD                   65536
SOLVENT                DMSO
NS                       128
DS                         4
SWH               5733.945 Hz
FIDRES            0.087493 Hz
AQ                5.7147894 sec
RG                       512
DW                  87.200 usec
DE                   6.00 usec
TE                   300.0 K
D1              2.00000000 sec
D8              0.50000000 sec
D16             0.00005000 sec
d20             0.24895000 sec

======== CHANNEL f1 ========
NUC1                     1H
P1                    7.70 usec
p2                   15.40 usec
P12                40000.00 usec
PL0                  120.00 dB
PL1                   -1.00 dB
SFO1          600.1332107 MHz
SP2                  59.58 dB
SPNAM2          Gaus1.1000
SPOFF2           -1488.73 Hz

====== GRADIENT CHANNEL =====
GPNAM1             sine.100
GPNAM2             sine.100
GPNAM3             sine.100
GPX1                  0.00 %
GPX2                  0.00 %
GPX3                  0.00 %
GPY1                  0.00 %
GPY2                  0.00 %
GPY3                  0.00 %
GPZ1                 15.00 %
GPZ2                 40.00 %
GPZ3                -40.00 %
P16                1000.00 usec

F2 - Processing parameters
SI                    32768
SF            600.1300000 MHz
WDW                      EM
SSB                       0
LB                     0.30 Hz
GB                        0
PC                     1.00
```

NJ 809 - monomethoxy peak 2
1-D NOESY



5-(*R*)



BRUKER

Current Data Parameters
NAME nj809pk2_noe
EXPNO 2
PROCNO 1

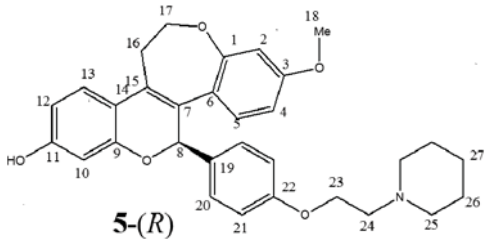
F2 - Acquisition Parameters
Date_ 20030630
Time 17.04
INSTRUM spect
PROBHD 5 mm BBI 1H-BB
PULPROG selnogp.2
TD 65536
SOLVENT DMSO
NS 96
DS 4
SWH 5733.945 Hz
FIDRES 0.087493 Hz
AQ 5.7147894 sec
RG 512
DW 87.200 usec
DE 6.00 usec
TE 300.0 K
D1 2.00000000 sec
D8 0.50000000 sec
D16 0.00005000 sec
d20 0.24895000 sec

======== CHANNEL f1 ========
NUC1 1H
P1 7.70 usec
p2 15.40 usec
P12 40000.00 usec
PL0 120.00 dB
PL1 -1.00 dB
SFO1 600.1332107 MHz
SP2 59.58 dB
SPNAM2 Gaus1.1000
SPOFF2 -979.87 Hz

====== GRADIENT CHANNEL =====
GPNAM1 sine.100
GPNAM2 sine.100
GPNAM3 sine.100
GPX1 0.00 %
GPX2 0.00 %
GPX3 0.00 %
GPY1 0.00 %
GPY2 0.00 %
GPY3 0.00 %
GPZ1 15.00 %
GPZ2 40.00 %
GPZ3 -40.00 %
P16 1000.00 usec

F2 - Processing parameters
SI 32768
SF 600.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

No title



5-(*R*)

Current Data Parameters

NAME	23046-x003
EXPNO	11
PROCNO	1

F2 - Acquisition Parameters

Date_	20080329
Time	22.05
INSTRUM	spect
PROBHD	5 mm QNP 1H/13
PULPROG	zgpg30
TD	65536
SOLVENT	DMSO
NS	256
DS	2
SWH	23980.814 Hz
FIDRES	0.365918 Hz
AQ	1.3664756 sec
RG	2298.8
DW	20.850 usec
DE	7.00 usec
TE	298.2 K
D1	1.00000000 sec
d11	0.03000000 sec
DELTA	0.89999998 sec
MCREST	0.00000000 sec
MCWRK	0.01500000 sec

======== CHANNEL f1 ========

NUC1	13C
P1	9.75 usec
PL1	3.00 dB
SFO1	100.6228298 MHz

======== CHANNEL f2 ========

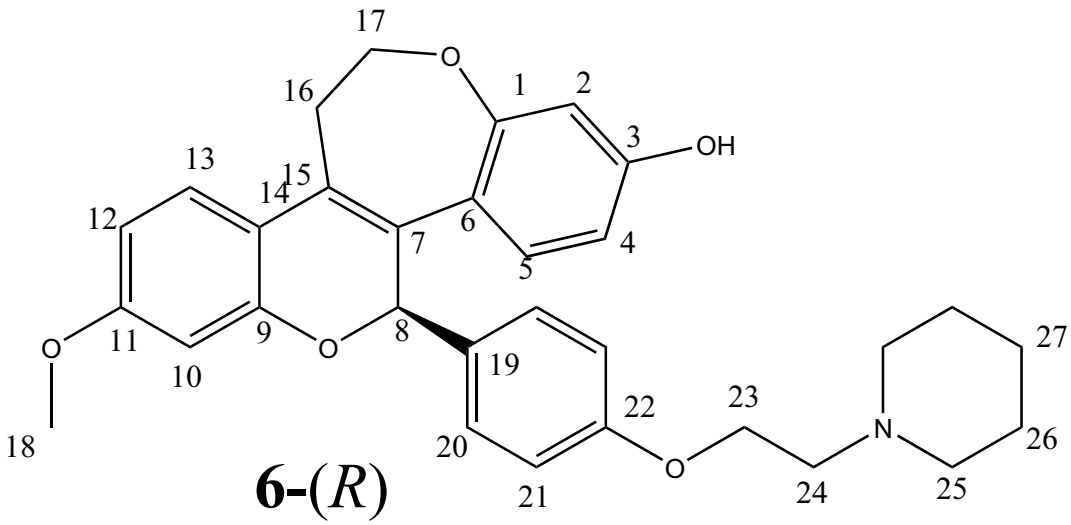
CPDPRG2	waltz16
NUC2	1H
PCPD2	81.00 usec
PL2	3.60 dB
PL12	22.93 dB
PL13	25.00 dB
SFO2	400.1316005 MHz

F2 - Processing parameters

SI	32768
SF	100.6128193 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

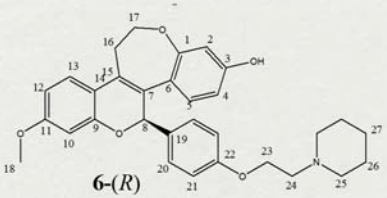
Structure Determination of **6**-(R)

(Peak 1)



6-(*R*)

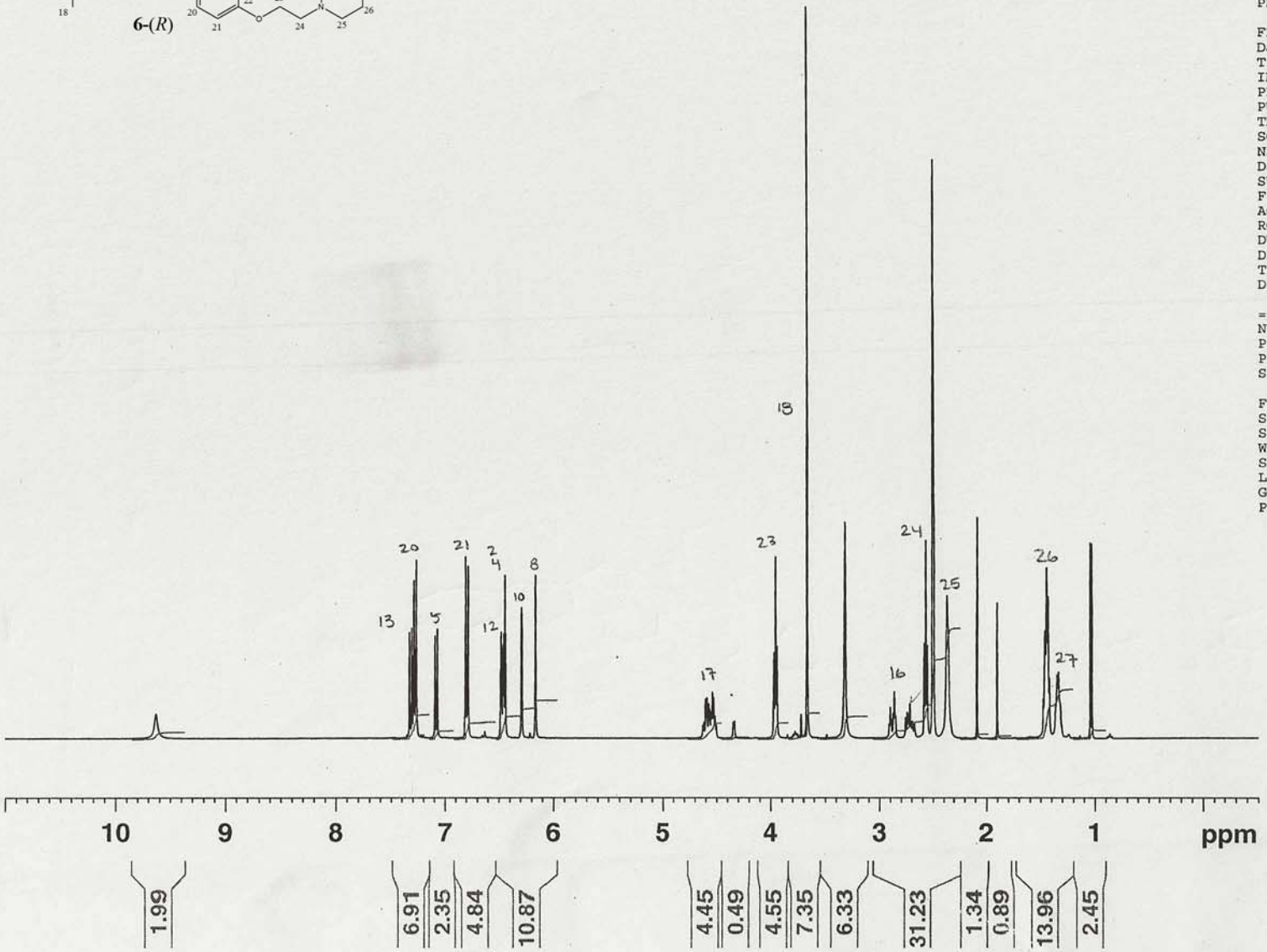
809-monomethoxy Peak 1



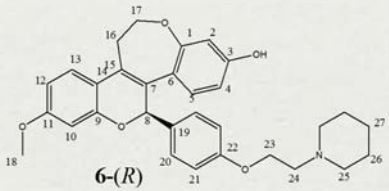
6-(*R*)

BRUKER

```
Current Data Parameters
NAME                  NJ809pk1
EXPNO                        1
PROCNO                       1

F2 - Acquisition Parameters
Date_              20030606
Time                 18.12
INSTRUM              spect
PROBHD     5 mm Multinu
PULPROG                zg
TD                  32768
SOLVENT              DMSO
NS                      16
DS                       2
SWH               4803.074 Hz
FIDRES               0.146578 Hz
AQ                3.4111989 sec
RG                     256
DW                 104.100 usec
DE                 178.29 usec
TE                   300.0 K
D1              1.00000000 sec

============ CHANNEL f1 ============
NUC1                    1H
P1                   7.75 usec
PL1                  1.00 dB
SFO1          400.1320807 MHz

F2 - Processing parameters
SI                   16384
SF            400.1300030 MHz
WDW                     EM
SSB                      0
LB                    0.30 Hz
GB                       0
PC                    1.00
```



NJ 809 peak 1
1-D NOESY



BRUKER

Current Data Parameters
NAME nj809pk1_noe
EXPNO 3
PROCNO 1

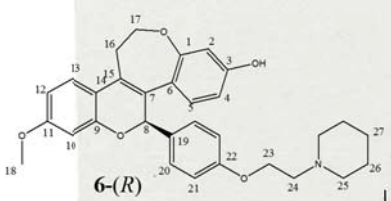
F2 - Acquisition Parameters
Date_ 20030625
Time 14.28
INSTRUM spect
PROBHD 5 mm BBI 1H-BB
PULPROG selnogp.2
TD 65536
SOLVENT DMSO
NS 128
DS 4
SWH 5733.945 Hz
FIDRES 0.087493 Hz
AQ 5.7147894 sec
RG 256
DW 87.200 usec
DE 6.00 usec
TE 300.0 K
D1 2.00000000 sec
D8 0.50000000 sec
D16 0.00005000 sec
d20 0.24895000 sec

======== CHANNEL f1 ========
NUC1 1H
P1 7.70 usec
p2 15.40 usec
P12 40000.00 usec
PL0 120.00 dB
PL1 -1.00 dB
SFO1 600.1332107 MHz
SP2 59.58 dB
SPNAM2 Gaus1.1000
SPOFF2 -1484.72 Hz

====== GRADIENT CHANNEL =====
GPNAM1 sine.100
GPNAM2 sine.100
GPNAM3 sine.100
GPX1 0.00 %
GPX2 0.00 %
GPX3 0.00 %
GPY1 0.00 %
GPY2 0.00 %
GPY3 0.00 %
GPZ1 15.00 %
GPZ2 40.00 %
GPZ3 -40.00 %
P16 1000.00 usec

F2 - Processing parameters
SI 32768
SF 600.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

809-monomethoxy Peak 1

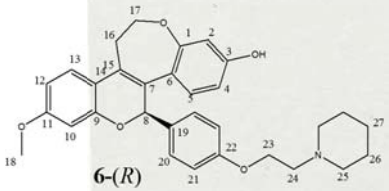


6-(*R*)

BRUKER

```
Current Data Parameters
NAME                  NJ809pk1
EXPNO                        2
PROCNO                       1

F2 - Acquisition Parameters
Date_                 20030606
Time                     18.21
INSTRUM                  spect
PROBHD       5 mm Multinu
PULPROG                cosygs
TD                       2048
SOLVENT                  DMSO
NS                          1
DS                          8
SWH                  4816.956 Hz
FIDRES               2.352029 Hz
AQ                   0.2126324 sec
RG                      1149.4
DW                     103.800 usec
DE                       6.50 usec
TE                      300.0 K
d0                   0.00000300 sec
D1                   1.00000000 sec
d13                  0.00000300 sec
D16                  0.00015000 sec
IN0                  0.00020760 sec

============ CHANNEL f1 =============
NUC1                        1H
P0                        7.75 usec
P1                        7.75 usec
PL1                       1.00 dB
SFO1                400.1320807 MHz

============ GRADIENT CHANNEL ========
P16                    1000.00 usec

F1 - Acquisition parameters
ND0                         1
TD                        128
SFO1                400.1321 MHz
FIDRES               37.632465 Hz
SW                      12.038 ppm
FnMODE                undefined

F2 - Processing parameters
SI                       1024
SF                  400.1300030 MHz
WDW                      SINE
SSB                         0
LB                       0.00 Hz
GB                          0
PC                       1.40

F1 - Processing parameters
SI                       1024
MC2                        QF
SF                  400.1300030 MHz
WDW                      SINE
SSB                         0
LB                       0.00 Hz
GB                          0

2D NMR plot parameters
CX2                     15.00 cm
CX1                     15.00 cm
F2PLO                    7.603 ppm
F2LO                  3042.01 Hz
F2PHI                    0.807 ppm
F2HI                   323.06 Hz
F1PLO                    7.579 ppm
F1LO                  3032.60 Hz
F1PHI                    0.784 ppm
F1HI                   313.65 Hz
F2PPMCM               0.45301 ppm/cm
F2HZCM              181.26305 Hz/cm
F1PPMCM               0.45301 ppm/cm
F1HZCM              181.26305 Hz/cm
```

809-monomethoxy Peak 1

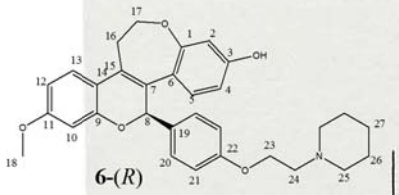


6-(*R*)

BRUKER

```
Current Data Parameters
NAME                NJ809pk1
EXPNO                      2
PROCNO                     1

F2 - Acquisition Parameters
Date_              20030606
Time                 18.21
INSTRUM              spect
PROBHD     5 mm Multinu
PULPROG             cosygs
TD                   2048
SOLVENT               DMSO
NS                       1
DS                       8
SWH               4816.956 Hz
FIDRES            2.352029 Hz
AQ                0.2126324 sec
RG                   1149.4
DW                 103.800 usec
DE                   6.50 usec
TE                  300.0 K
d0                0.00000300 sec
D1                1.00000000 sec
d13               0.00000300 sec
D16               0.00015000 sec
IN0               0.00020760 sec

============ CHANNEL f1 ============
NUC1                    1H
P0                    7.75 usec
P1                    7.75 usec
PL1                   1.00 dB
SFO1          400.1320807 MHz

============ GRADIENT CHANNEL ========
P16                1000.00 usec

F1 - Acquisition parameters
ND0                      1
TD                     128
SFO1            400.1321 MHz
FIDRES         37.632465 Hz
SW                12.038 ppm
FnMODE         undefined

F2 - Processing parameters
SI                    1024
SF            400.1300030 MHz
WDW                   SINE
SSB                      0
LB                    0.00 Hz
GB                       0
PC                    1.40

F1 - Processing parameters
SI                    1024
MC2                     QF
SF            400.1300030 MHz
WDW                   SINE
SSB                      0
LB                    0.00 Hz
GB                       0

2D NMR plot parameters
CX2                  15.00 cm
CX1                  15.00 cm
F2PLO                7.603 ppm
F2LO              3042.01 Hz
F2PHI                0.807 ppm
F2HI               323.06 Hz
F1PLO                7.579 ppm
F1LO              3032.60 Hz
F1PHI                0.784 ppm
F1HI               313.65 Hz
F2PPMCM           0.45301 ppm/cm
F2HZCM          181.26305 Hz/cm
F1PPMCM           0.45301 ppm/cm
F1HZCM          181.26305 Hz/cm
```

809-monomethoxy Peak 1

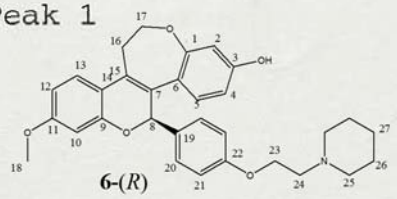


6-(*R*)

BRUKER

```
Current Data Parameters
NAME                  NJ809pk1
EXPNO                        2
PROCNO                       1

F2 - Acquisition Parameters
Date_                 20030606
Time                     18.21
INSTRUM                  spect
PROBHD       5 mm Multinu
PULPROG                cosygs
TD                       2048
SOLVENT                   DMSO
NS                          1
DS                          8
SWH                  4816.956 Hz
FIDRES               2.352029 Hz
AQ                   0.2126324 sec
RG                      1149.4
DW                     103.800 usec
DE                       6.50 usec
TE                      300.0 K
d0                   0.00000300 sec
D1                   1.00000000 sec
d13                  0.00000300 sec
D16                  0.00015000 sec
IN0                  0.00020760 sec

============ CHANNEL f1 =============
NUC1                        1H
P0                       7.75 usec
P1                       7.75 usec
PL1                      1.00 dB
SFO1                400.1320807 MHz

============ GRADIENT CHANNEL ========
P16                   1000.00 usec

F1 - Acquisition parameters
ND0                         1
TD                        128
SFO1                400.1321 MHz
FIDRES               37.632465 Hz
SW                      12.038 ppm
FnMODE                undefined

F2 - Processing parameters
SI                       1024
SF                  400.1300030 MHz
WDW                      SINE
SSB                         0
LB                       0.00 Hz
GB                          0
PC                       1.40

F1 - Processing parameters
SI                       1024
MC2                        QF
SF                  400.1300030 MHz
WDW                      SINE
SSB                         0
LB                       0.00 Hz
GB                          0

2D NMR plot parameters
CX2                     15.00 cm
CX1                     15.00 cm
F2PLO                    7.603 ppm
F2LO                  3042.01 Hz
F2PHI                    0.807 ppm
F2HI                   323.06 Hz
F1PLO                    7.579 ppm
F1LO                  3032.60 Hz
F1PHI                    0.784 ppm
F1HI                   313.65 Hz
F2PPMCM                0.45301 ppm/cm
F2HZCM               181.26305 Hz/cm
F1PPMCM                0.45301 ppm/cm
F1HZCM               181.26305 Hz/cm
```

809-monomethoxy Peak 1



BRUKER

Current Data Parameters
NAME NJ809pk1
EXPNO 3
PROCNO 1

F2 - Acquisition Parameters
Date_ 20030606
Time 18.27
INSTRUM spect
PROBHD 5 mm Multinu
PULPROG inv4gs
TD 2048
SOLVENT DMSO
NS 96
DS 8
SWH 4816.956 Hz
FIDRES 2.352029 Hz
AQ 0.2126324 sec
RG 13004
DW 103.800 usec
DE 6.50 usec
TE 300.0 K
CNST2 145.0000000
d0 0.00000300 sec
D1 1.50000000 sec
d2 0.00344828 sec
d12 0.00002000 sec
d13 0.00000300 sec
D16 0.00015000 sec
d20 0.00242528 sec
IN0 0.00002259 sec

========== CHANNEL f1 ==========
NUC1 1H
P1 7.75 usec
p2 15.50 usec
PL1 1.00 dB
SFO1 400.1320807 MHz

========== CHANNEL f2 ==========
CPDPRG2 garp
NUC2 13C
P3 12.75 usec
PCPD2 75.00 usec
PL2 0.00 dB
PL12 17.40 dB
SFO2 100.6227903 MHz

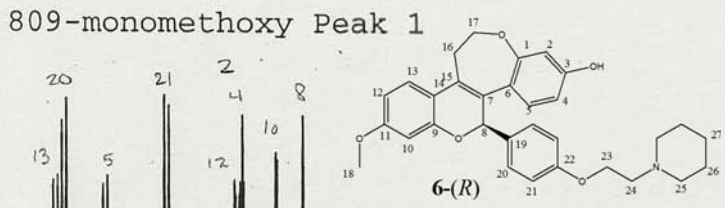
========== GRADIENT CHANNEL ========
P16 1000.00 usec

F1 - Acquisition parameters
ND0 2
TD 128
SFO1 100.6228 MHz
FIDRES 172.938568 Hz
SW 219.991 ppm
FnMODE undefined

F2 - Processing parameters
SI 2048
SF 400.1300030 MHz
WDW SINE
SSB 0
LB 0.00 Hz
GB 0
PC 1.40

F1 - Processing parameters
SI 1024
MC2 QF
SF 100.6127685 MHz
WDW SINE
SSB 0
LB 0.00 Hz
GB 0

809-monomethoxy Peak 1

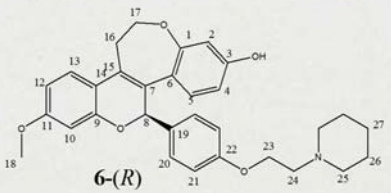


BRUKER

```
Current Data Parameters
NAME                  NJ809pk1
EXPNO                        4
PROCNO                       1

F2 - Acquisition Parameters
Date_                 20030607
Time                      0.22
INSTRUM                  spect
PROBHD       5 mm Multinu
PULPROG      inv4gslplrnd
TD                        2048
SOLVENT                   DMSO
NS                          96
DS                          16
SWH                 4816.956 Hz
FIDRES              2.352029 Hz
AQ                  0.2126324 sec
RG                    11585.2
DW                    103.800 usec
DE                      6.50 usec
TE                     300.0 K
CNST2               145.0000000
d0                  0.00000300 sec
D1                  1.50000000 sec
d2                  0.00344828 sec
D6                  0.06500000 sec
d13                 0.00000300 sec
D16                 0.00015000 sec
IN0                 0.00002259 sec

============ CHANNEL f1 =============
NUC1                        1H
P1                       7.75 usec
p2                      15.50 usec
PL1                      1.00 dB
SFO1                400.1320807 MHz

============ CHANNEL f2 =============
NUC2                       13C
P3                      12.75 usec
PL2                      0.00 dB
SFO2                100.6227903 MHz

============ GRADIENT CHANNEL ========
P16                   1000.00 usec

F1 - Acquisition parameters
ND0                         2
TD                        128
SFO1                100.6228 MHz
FIDRES              172.938568 Hz
SW                  219.991 ppm
FnMODE                undefined

F2 - Processing parameters
SI                        2048
SF                  400.1300030 MHz
WDW                       SINE
SSB                          0
LB                        0.00 Hz
GB                           0
PC                        1.40

F1 - Processing parameters
SI                        1024
MC2                         QF
SF                  100.6127685 MHz
WDW                       SINE
SSB                          0
LB                        0.00 Hz
GB                           0
```

peak 1

No title



Current Data Parameters
NAME 23046-x004
EXPNO 11
PROCNO 1

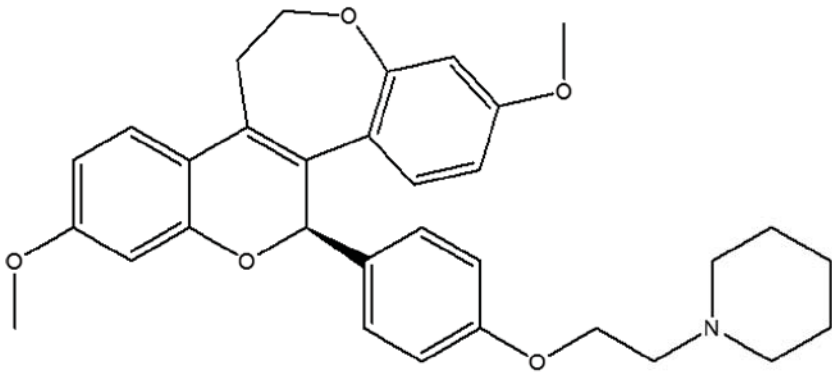
F2 - Acquisition Parameters
Date_ 20080329
Time 22.23
INSTRUM spect
PROBHD 5 mm QNP 1H/13
PULPROG zgpg30
TD 65536
SOLVENT DMSO
NS 256
DS 2
SWH 23980.814 Hz
FIDRES 0.365918 Hz
AQ 1.3664756 sec
RG 13004
DW 20.850 usec
DE 7.00 usec
TE 298.2 K
D1 1.00000000 sec
d11 0.03000000 sec
DELTA 0.89999998 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec

======== CHANNEL f1 ========
NUC1 13C
P1 9.75 usec
PL1 3.00 dB
SFO1 100.6228298 MHz

======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 81.00 usec
PL2 3.60 dB
PL12 22.93 dB
PL13 25.00 dB
SFO2 400.1316005 MHz

F2 - Processing parameters
SI 32768
SF 100.6128193 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

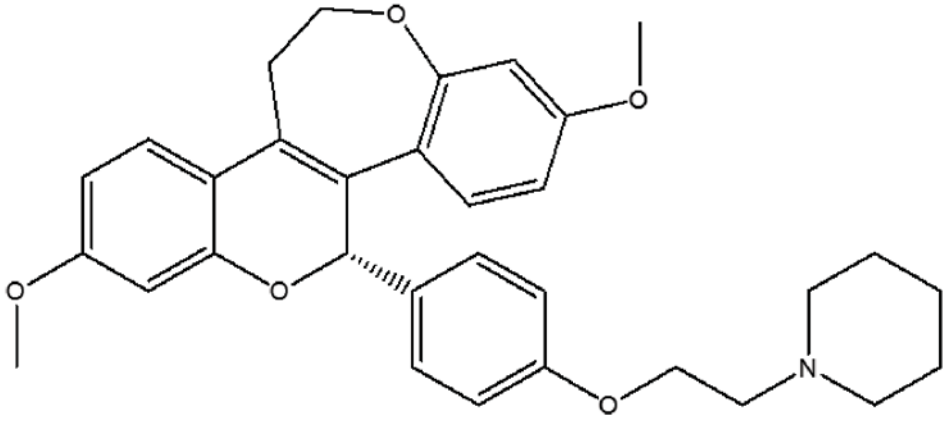
^{1}H NMR and ^{13}NMR of **7**-(R)



7-(R)

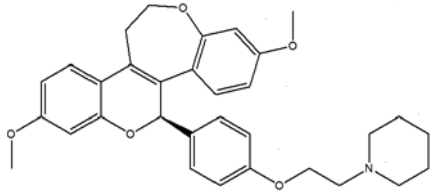
&

Crystal Structre analysis Report for **7**-(*S*)



7-(S)

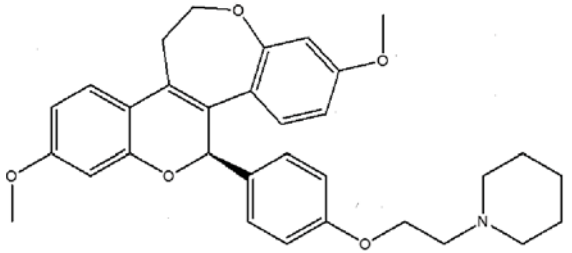
No title



7-(R)


```
Current Data Parameters
NAME          23046-x001
EXPNO                 10
PROCNO                 1

F2 - Acquisition Parameters
Date_           20080329
Time              21.27
INSTRUM            spect
PROBHD   5 mm QNP 1H/13
PULPROG             zg30
TD                 65536
SOLVENT             DMSO
NS                    16
DS                     2
SWH           8278.146 Hz
FIDRES        0.126314 Hz
AQ            3.9584243 sec
RG                   128
DW              60.400 usec
DE               7.00 usec
TE               297.2 K
D1            1.00000000 sec
MCREST        0.00000000 sec
MCWRK         0.01500000 sec

======== CHANNEL f1 ========
NUC1                  1H
P1                 8.50 usec
PL1                3.60 dB
SFO1        400.1324710 MHz

F2 - Processing parameters
SI                 32768
SF          400.1300000 MHz
WDW                   EM
SSB                    0
LB                0.30 Hz
GB                     0
PC                 1.00
```

No title



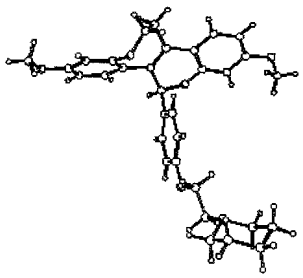
7-(R)


```
Current Data Parameters
NAME          23046-x001
EXPNO                 11
PROCNO                 1

F2 - Acquisition Parameters
Date_           20080329
Time              21.25
INSTRUM            spect
PROBHD   5 mm QNP 1H/13
PULPROG          zgpg30
TD                65536
SOLVENT             DMSO
NS                    256
DS                      2
SWH           23980.814 Hz
FIDRES         0.365918 Hz
AQ             1.3664756 sec
RG                 3251
DW               20.850 usec
DE                7.00 usec
TE                297.2 K
D1            1.00000000 sec
d11           0.03000000 sec
DELTA         0.89999998 sec
MCREST        0.00000000 sec
MCWRK         0.01500000 sec

======== CHANNEL f1 ========
NUC1                 13C
P1                 9.75 usec
PL1                3.00 dB
SFO1        100.6228298 MHz

======== CHANNEL f2 ========
CPDPRG2         waltz16
NUC2                1H
PCPD2            81.00 usec
PL2               3.60 dB
PL12             22.93 dB
PL13             25.00 dB
SFO2        400.1316005 MHz

F2 - Processing parameters
SI                 32768
SF          100.6128193 MHz
WDW                   EM
SSB                    0
LB                  1.00 Hz
GB                     0
PC                  1.40
```

BRIEF EXPERIMENTAL DESCRIPTION TO BE INCLUDED IN TEXT OR AS A FOOTNOTE AT TIME OF PUBLICATION

Single crystals of (**S**-$C_{32}H_{35}NO_5$) are, at -80±2°C,monoclinic, space group $P2_1$ - C_2^2 (No. 4) with **a** = 11.166(1) Å, **b** = 10.690(1) Å, **c** = 11.523(1) Å, ß = 94.147(2)°, V = 1371.8(3) $Å^3$ and Z = 2 molecules {d_{calcd} = 1.243 gcm^{-3}; μ_a(MoK $\bar{\alpha}$) = 0.083 mm^{-1}}. A full hemisphere of diffracted intensities (1868 10-second frames with an omega scan width of 0.30°)was measured using graphite-monochromated MoKα radiation on a Bruker SMART APEX CCD Single Crystal Diffraction System. X-rays were provided by a fine-focus sealed x-ray tube operated at 50kV and 35mA. Lattice constants were determined with the Bruker SAINT software package using peak centers for 4360 reflections. A total of 14506 integrated reflection intensities having 2θ(MoK $\bar{\alpha}$) < 61.01°were produced using the Bruker program SAINT; 7450 of these were unique and gave R_{int} = 0.053. The Bruker SHELXTL-PC software package was used to solve the structure using "direct methods" techniques. All stages of weighted full-matrix least-squares refinement were conducted using F_o^2 data with the SHELXTL-PC Version 5 software package. Final agreement factors at convergence are: R_1(unweighted, based on F) = 0.057 for 6165 independent reflections having 2θ(MoK$\bar{\alpha}$) < 61.01° and I>2σ(I); R_1(unweighted, based on F) = 0.066 and wR_2 (weighted, based on F^2) = 0.126 for all 7450 independent reflections having 2θ(MoK$\bar{\alpha}$) < 61.01°. Since there were no atoms present which were heavier than oxygen, the absolute configuration could not be determined experimentally using anomalous dispersion of the x-rays; the "Flack" absolute structure parameter refined to a final value of 1.1(8).

The structural model incorporated anisotropic thermal parameters for all nonhydrogen atoms and isotropic thermal parameters for all hydrogen atoms. The two methyl groups (C_{21}, C_{23} and their hydrogens) were included in the structural model as rigid groups (assuming idealized sp^3- hybridization of the carbon atom and a C-H bond length of 0.98 Å) which were allowed to rotate about their O-C bonds in least-squares refinement cycles. All additional hydrogen atoms were included in the structure factor calculations as idealized atoms (assuming sp^2- or sp^3-hybridization of the carbon atoms and C-H bond lengths of 0.95 - 1.00 Å) "riding" on their respective carbon atoms. The isotropic thermal parameter of each hydrogen atom was fixed at a value 1.2 (nonmethyl) or 1.5 (methyl) times the equivalent isotropic thermal parameter of the carbon atom to which it is covalently bonded.



Crystalytics Company
Crystal Structure Analysis Report

Compound Formula: (S-$C_{32}H_{35}NO_5$) Reference Code: CGS9-0704

Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
Sample JNJ-19399003-AAA-23182817

Dr. Alexandra Shedlow

Description of Single-Crystal Sample and Mounting Used for Data Collection:

1) Color: Colorless
2) Shape: Rectangular parallelepiped
3) Dimensions: 0.14 mm. x 0.34 mm. x 0.38 mm.
4) Indices of Faces:
5) Crystal Mount: Crystal was frozen in Paratone N oil and suspended inside a nylon cryoloop.
6) Crystal Orientation: Crystal had a random orientation.
7) Comments:

Space Group and Cell Data:

1) Crystal System: Monoclinic Space Group and Number[1]: $P2_1$ - C_2^2 (No. 4)
2) Number of Computer-Centered Reflections Used in the Least-Squares Refinement of the Cell Dimensions: 4360 having $7.63° < 2\theta(MoK_{\overline{\alpha}}) < 60.00°$ and measured at -80±2 °C
3) Lattice Constants with esd's:

a = 11.166(1) Å	α = 90.000°	V = 1371.8(3) Å^3
b = 10.690(1) Å	β = 94.147(2)°	Z = 2 molecules
c = 11.523(1) Å	γ = 90.000°	λ = 0.71073 Å

4) Molecular Weight: 513.61 amu Calculated Density: 1.243 g·cm^{-3}
5) Linear Absorption Coefficient[2a]: 0.083 mm^{-1} F(000) = 548.
6) Comments: Crystals were grown from a saturated ethanol solution.

Description of Data Collection[3]:

1) Instrument: Bruker SMART APEX CCD Single Crystal Diffraction System
2) X-ray Source: Sealed fine focus X-ray tube
3) Radiation: MoK$\bar{\alpha}$ Power: 50 kV 35 mA
4) X Monochromator: X Graphite ___Other (Specify:)
   ___Filter: ___Nickel ___Niobium ___Other (Specify:)
5) Incident Beam Collimator Diameter: 0.5 mm Temperature: -80±2°C
6) Scan Axis: X Omega or ___ Phi
7) Scan Width: 0.30° 2θ Range of Data : 7.62°- 61.01°
8) Sample to Detector Distance: 6.000 cm
9) Portion of Ewald Sphere Collected: Hemisphere
10) Number of frames collected: 1868 Seconds/frame: 10
11) Total Number of Reflections Collected: 14506
12) Number of Independent Reflections Collected: 7450
13) Data Collected: $-15 \le h \le 15$; $-14 \le k \le 14$; $-16 \le l \le 16$ R_{int}[4] = 0.053

Data Reduction[3]:

1) Lorentz and Polarization Corrections? Yes
2) Absorption Correction: None Range of relative transmission factors:
   ____ Empirical Correction using Measurements for Equivalent Reflections
   (____ Reflections used)
   ____ Face-Indexed Gaussian Grid Correction
3) Comments:

Structure Solution[5]:

1) Method(s) Used in Structure Solution
   ___Heavy-atom Patterson Techniques
   XX Direct Methods
      a) XX SHELXTL/PC
      b) ___Other
   ___Other Techniques
2) Hydrogen Atom Positions Located? Yes
   After Refinement Cycle # 2 by XX Difference Fourier
   XX Calculated
3) Comments:

Structure Refinement[5]: (see next page for summary of refinement cycles)

1) Final Scale Factor: 0.669(1)

2) Extinction Parameter[6] Refined? No Final Value:
Form: $k[1+0.001(x)(F_c^2)(\lambda^3)/\sin(2\theta)]^{-1/4}$

3) Anomalous Dispersion Corrections[2b] for Which Atoms: O, N, C

4) Variable Occupancies for Which Atoms? None

Atom	Final Occupancy	Atomic Form Factor[2c] Used

5) Refinement Constraints/Restraints: The two methyl groups (C_{21}, C_{23} and their hydrogens) were included in the structural model as rigid groups (assuming idealized sp^3- hybridization of the carbon atom and a C-H bond length of 0.98 Å) which were allowed to rotate about their O-C bonds in least-squares refinement cycles. All additional hydrogen atoms were included in the structure factor calculations as idealized atoms (assuming sp^2- or sp^3-hybridization of the carbon atoms and C-H bond lengths of 0.95 - 1.00 Å) "riding" on their respective carbon atoms. The isotropic thermal parameter of each hydrogen atom was fixed at a value 1.2 (nonmethyl) or 1.5 (methyl) times the equivalent isotropic thermal parameter of the carbon atom to which it is covalently bonded.

6) Shift/Error Analysis for Final Least-Squares Cycle[7]:
Maximum Shift for all Parameters: 0.000 σ_p Mean Shift for all Parameters: 0.000 σ_p

7) Peaks found in Final Difference Fourier Map: There were no peaks present in the final difference Fourier map above the background level (0.24 $e^-/Å^3$). The minimum and mean electron density in the final difference Fourier were -0.28 and 0.00 $e^-/Å^3$, respectively. The rms deviation from the mean electron density was 0.05 $e^-/Å^3$.

References and Notes

1. "International Tables for X-Ray Crystallography", Vol. A, Kluwer Academic Publishers, Dordrecht, 1995.

2. "International Tables for X-Ray Crystallography", Vol. C, Kluwer Academic Publishers, Dordrecht, 1992; a) Tables 4.2.4.2pp. 193-199; b) Tables 4.2.6.8pp 219-222; c) Tables 6.1.1.4 pp 500-502.

3. Data acquisition and reduction was accomplished using standard versions of Bruker software for the diffraction system.

4. $R_{int} = \Sigma | F_o^2 - F_o^2(mean) | \ / \ \Sigma[F_o]^2$

5. All structure determination and refinement calculations were performed on an IBM compatible 586 personal computer using the Bruker SHELXTL Version 5.0 PC interactive software package.

6. A. C. Larson in "Crystallographic Computing", **1970**, Ed. F. R. Ahmed, Munksgaard, Copenhagen, pp 291-294.

7. σ_p is the estimated standard deviation of the parameter in question.

8. Refinement on F^2 for all reflections. Weighted R-factors wR_2 and all goodnesses of fit S are based on F^2, conventional R-factors R_1 are based on F, with F set to zero for negative F^2. The observed criterion of $F^2 > 2sigma(F^2)$ is used only for calculating "R-factor obs" etc. and is not relevant to the choice of reflections for refinement. R-factors based on F^2 are statistically about twice as large as those based on F, and R-factors based on all data will be even larger.

9. The anisotropic thermal parameter is of the form:
$exp[-2\pi^2(U_{11}h^2a^{*2} + U_{22}k^2b^{*2} + U_{33}l^2c^{*2} + 2U_{12}hka^*b^* + 2U_{13}hla^*c^* + 2U_{23}klb^*c^*)]$.

10. The weighting scheme used is defined as: $w = 1 / [\sigma^2(F_o^2) + (a^*P)^2 + b^*P + d + e^*\sin(\theta)]$ where $P = [F_o^2 + 2F_c^2]/3$. In this case, a= 0.0603, b= 0, d = 0 and e = 0.

11. $\underline{R}_1 = \Sigma | \ |F_o| - |F_c| \ | / \Sigma |F_o|$

12. $w\underline{R}_2 = [\Sigma[w(F_o^2 - F_c^2)^2] / \Sigma[w(F_o^2)^2]]^{1/2}$

13. GooF = S = $[\Sigma[w(F_o^2 - F_c^2)^2]/(n-p)]^{1/2}$ where n is the total number of reflections and p is the number of parameters refined.

14. The value of the "Flack absolute structure parameter", x, should be 0.00 for the correct enantiomorphic description and 1.00 for the inverted description: a) H. D. Flack, *Acta Cryst.*, **1983**, *A39*, 876-881; b) G. Bernardinelli and H. D. Flack, *Acta Cryst.*, **1985**, *A41*, 500-511.

Table 1. (continued)

Atom Type[b]	Fractional Coordinates 10^4x	10^4y	10^4z	Equivalent Isotropic Thermal Parameter, U, $Å^2 \times 10^3$ [c]
C_{28}	2613(2)	1604(2)	410(2)	38(1)
C_{29}	1740(2)	2407(2)	-79(2)	34(1)
O_{30}	4581(1)	1374(1)	1448(1)	43(1)
C_{31}	4317(2)	88(2)	1664(2)	38(1)
C_{32}	5307(2)	-429(2)	2454(2)	55(1)
N_{33}	5029(2)	-1720(2)	2759(2)	40(1)
C_{34}	4894(2)	-1875(3)	3987(2)	70(1)
C_{35}	4511(3)	-3210(5)	4232(4)	110(2)
C_{36}	5359(3)	-4148(4)	3796(4)	118(2)
C_{37}	5554(3)	-3901(3)	2556(4)	93(1)
C_{38}	5938(2)	-2566(2)	2378(2)	55(1)

[a] The numbers in parentheses are the estimated standard deviations in the last significant digit.
[b] Atoms are labeled in agreement with Figure 1.
[c] This is one-third of the trace of the orthogonalized U_{ij} tensor.

Table 1. Atomic Coordinates for Nonhydrogen Atoms in Crystalline (**S**-$C_{32}H_{35}NO_5$) [a]

Atom Type[b]	Fractional Coordinates 10^4x	10^4y	10^4z	Equivalent Isotropic Thermal Parameter, U, $Å^2 \times 10^3$ [c]
C_1	-2023(2)	3480(2)	2108(2)	34(1)
C_2	-1036(2)	4181(2)	1831(2)	32(1)
C_3	-706(1)	4171(2)	699(2)	28(1)
C_4	-1335(2)	3488(2)	-184(2)	27(1)
C_5	-2328(2)	2806(2)	125(2)	33(1)
C_6	-2670(2)	2783(2)	1254(2)	37(1)
O_7	220(1)	4949(1)	452(1)	31(1)
C_8	927(2)	4581(2)	-508(2)	27(1)
C_9	146(2)	4078(2)	-1521(2)	27(1)
C_{10}	-927(2)	3569(2)	-1362(2)	28(1)
C_{11}	650(2)	4068(2)	-2673(2)	32(1)
C_{12}	555(2)	2995(2)	-3365(2)	34(1)
O_{13}	93(1)	1897(1)	-2955(1)	37(1)
C_{14}	-1181(2)	1839(2)	-2831(2)	38(1)
C_{15}	-1681(2)	3066(2)	-2398(2)	33(1)
C_{16}	1252(2)	5092(2)	-3116(2)	39(1)
C_{17}	1716(2)	5058(2)	-4189(2)	49(1)
C_{18}	1597(2)	3996(3)	-4859(2)	49(1)
C_{19}	1016(2)	2954(2)	-4452(2)	41(1)
O_{20}	-2426(1)	3415(2)	3201(1)	48(1)
C_{21}	-1810(2)	4146(3)	4084(2)	65(1)
O_{22}	2080(2)	4044(2)	-5923(1)	71(1)
C_{23}	1960(3)	2967(4)	-6644(2)	86(1)
C_{24}	1910(1)	3690(2)	-65(1)	26(1)
C_{25}	3001(2)	4154(2)	415(2)	31(1)
C_{26}	3881(2)	3364(2)	899(2)	34(1)
C_{27}	3679(2)	2087(2)	918(2)	31(1)

Table 2. Anisotropic Thermal Parameters for Nonhydrogen Atoms in Crystalline (**S**-$C_{32}H_{35}NO_5$) [a,b]

Atom Type[c]	Anisotropic Thermal Parameters ($Å^2 \times 10^3$) U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C_1	32(1)	33(1)	39(1)	6(1)	7(1)	9(1)
C_2	30(1)	31(1)	33(1)	-2(1)	0(1)	5(1)
C_3	24(1)	23(1)	36(1)	2(1)	2(1)	5(1)
C_4	26(1)	20(1)	35(1)	1(1)	-1(1)	5(1)
C_5	29(1)	25(1)	45(1)	-4(1)	1(1)	1(1)
C_6	30(1)	31(1)	52(1)	5(1)	9(1)	1(1)
O_7	31(1)	27(1)	34(1)	-5(1)	4(1)	-3(1)
C_8	27(1)	24(1)	30(1)	1(1)	2(1)	-3(1)
C_9	29(1)	23(1)	30(1)	1(1)	0(1)	4(1)
C_{10}	30(1)	22(1)	32(1)	-2(1)	-1(1)	3(1)
C_{11}	29(1)	36(1)	30(1)	5(1)	-1(1)	5(1)
C_{12}	32(1)	38(1)	30(1)	4(1)	-1(1)	9(1)
O_{13}	39(1)	32(1)	41(1)	-2(1)	3(1)	7(1)
C_{14}	38(1)	38(1)	38(1)	-10(1)	-2(1)	-1(1)
C_{15}	27(1)	37(1)	34(1)	-4(1)	-4(1)	3(1)
C_{16}	39(1)	41(1)	37(1)	10(1)	-1(1)	1(1)
C_{17}	48(1)	57(1)	43(1)	20(1)	4(1)	-3(1)
C_{18}	48(1)	68(2)	32(1)	14(1)	8(1)	17(1)
C_{19}	44(1)	49(1)	31(1)	2(1)	1(1)	17(1)
O_{20}	48(1)	58(1)	41(1)	7(1)	15(1)	4(1)
C_{21}	44(1)	118(2)	34(1)	6(1)	4(1)	6(1)
O_{22}	88(1)	87(1)	41(1)	18(1)	27(1)	17(1)
C_{23}	110(3)	109(3)	42(1)	3(2)	34(2)	33(2)
C_{24}	27(1)	26(1)	25(1)	1(1)	2(1)	-3(1)
C_{25}	30(1)	21(1)	42(1)	1(1)	1(1)	-3(1)
C_{26}	25(1)	29(1)	46(1)	0(1)	-4(1)	-6(1)
C_{27}	27(1)	27(1)	38(1)	4(1)	0(1)	-2(1)
C_{28}	36(1)	20(1)	57(1)	3(1)	-8(1)	-7(1)

Table 2. (continued)

Atom Type[c]	Anisotropic Thermal Parameters ($Å^2 \times 10^3$) U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C_{29}	31(1)	27(1)	43(1)	4(1)	-9(1)	-6(1)
O_{30}	31(1)	27(1)	69(1)	10(1)	-12(1)	-4(1)
C_{31}	36(1)	26(1)	52(1)	8(1)	-4(1)	-2(1)
C_{32}	51(1)	33(1)	76(2)	9(1)	-23(1)	-3(1)
N_{33}	40(1)	33(1)	46(1)	9(1)	-7(1)	1(1)
C_{34}	53(2)	97(2)	60(2)	12(2)	14(1)	18(2)
C_{35}	59(2)	153(4)	118(3)	89(3)	10(2)	-12(2)
C_{36}	76(2)	77(2)	195(4)	91(3)	-32(3)	-12(2)
C_{37}	98(3)	34(1)	142(3)	-8(2)	-27(2)	14(2)
C_{38}	66(2)	49(1)	51(1)	-3(1)	8(1)	5(1)

[a] The numbers in parentheses are the estimated standard deviations in the last significant digit.
[b] The form of the anisotropic thermal parameter is: $\exp[-2\pi^2(U_{11}h^2a^{*2} + U_{22}k^2b^{*2} + U_{33}l^2c^{*2} + 2U_{12}hka^*b^* + 2U_{13}hla^*c^* + 2U_{23}klb^*c^*)]$.
[c] Atoms are labeled in agreement with Figure 1.

Table 3. Atomic Coordinates for Hydrogen Atoms in Crystalline (S-$C_{32}H_{35}NO_5$) [a]

Atom Type[b]	Fractional Coordinates 10^4x	10^4y	10^4z
H_2	-596	4660	2410
H_5	-2783	2345	-457
H_6	-3340	2296	1446
H_8	1327	5352	-783
H_{14a}	-1347	1163	-2277
H_{14b}	-1599	1626	-3592
H_{15a}	-1708	3691	-3034
H_{15b}	-2513	2932	-2179
H_{16}	1343	5832	-2662
H_{17}	2118	5769	-4467
H_{19}	935	2218	-4914
H_{21a}	-2206	4056	4811
H_{21b}	-1822	5026	3847
H_{21c}	-977	3858	4202
H_{23a}	2317	3133	-7381
H_{23b}	1106	2767	-6798
H_{23c}	2372	2260	-6250
H_{25}	3143	5030	410
H_{26}	4622	3697	1217
H_{28}	2480	726	398
H_{29}	1014	2071	-430
H_{31a}	4250	-385	924
H_{31b}	3545	19	2031
H_{32a}	6068	-405	2064
H_{32b}	5408	85	3168
H_{34a}	4283	-1282	4238
H_{34b}	5665	-1690	4432
H_{35a}	4469	-3320	5082

Summary of Full Matrix Least-Squares Refinement[8] Cycles

Cycle Number	sin θ/ λ Minimum	sin θ/ λ Maximum	Anisotropic[9] Atoms Number and Type	Isotropic Atoms Number and Type	Isotropic Atoms Positions Refined	Isotropic Atoms Thermal Parameters	# Refined Parameters	R_1 (unweighted, based on F) R_1[11]	# Observed Reflections	$F_o / \sigma(F_o)$ Cutoff	R_2 (weighted, based on F^2)[10] R_2[12]	Total # Independent Reflections	'Goodness-of-fit' (Goof)[13]	Extinction Correction
1	0.00	0.71		5 O, 1 N 32 C	X	X	153	0.127	6165	4.0	0.299	7450	2.390	
2	0.00	0.71	5 O, 1 N 32 C				343	0.081	6165	4.0	0.196	7450	1.569	
3	0.00	0.71	5 O, 1 N 32 C	*35 H			345	0.057	6165	4.0	0.126	7450	0.996	

* See Item 5 on page 3 regarding the treatment of the hydrogen atoms.

Final Statistics from Cycle #3 for All of the Reflection Data: R_1 = 0.066; wR_2 = 0.126; GOOF = 0.996 for 7450 reflections

The absolute configuration could not be determined experimentally since the "Flack" absolute structure parameter[14] refined to a final value of 1.1(8).

Table 3. (continued)

Atom Type[b]	Fractional Coordinates 10^4x	10^4y	10^4z
H_{35b}	3698	-3357	3856
H_{36a}	6135	-4104	4267
H_{36b}	5027	-5000	3877
H_{37a}	4802	-4068	2073
H_{37b}	6180	-4475	2301
H_{38a}	6712	-2406	2828
H_{38b}	6052	-2421	1545

[a] The two methyl groups (C_{21}, C_{23} and their hydrogens) were refined as rigid rotors (using idealized sp^3-hybridized geometry and a C-H bond length of 0.98 Å) which were allowed to rotate about their O-C bonds in the least-squares refinement cycles. All of the remaining hydrogen atoms were included in the final structure factor calculations as idealized atoms (assuming sp^2- or sp^3-hybridization of the carbon atoms and C-H bond lengths of 0.95 -1.00 Å) "riding" on their respective carbon atoms. The isotropic thermal parameters of all hydrogen atoms were fixed at values 1.2 (nonmethyl) or 1.5 (methyl) times the (equivalent) equivalent isotropic thermal parameter of the carbon atom to which they are covalently bonded.

[b] Hydrogen atoms are labeled with the same numerical subscripts as the carbon atoms atoms to which they are covalently bonded; they also carry an additional literal subscript (a, b or c), where necessary, to distinguish between hydrogens bonded to the same carbon.

Table 4. Bond Lengths in Crystalline (S-$C_{32}H_{35}NO_5$) [a]

Type[b]	Length, Å	Type[b]	Length, Å
C_3-O_7	1.373(2)	C_{32}-N_{33}	1.463(3)
C_{12}-O_{13}	1.379(2)	N_{33}-C_{34}	1.443(3)
C_1-O_{20}	1.370(2)	N_{33}-C_{38}	1.450(3)
C_{18}-O_{22}	1.376(3)		
C_{27}-O_{30}	1.371(2)	C_1-C_2	1.389(3)
		C_1-C_6	1.394(3)
O_7-C_8	1.459(2)	C_2-C_3	1.380(2)
O_{13}-C_{14}	1.442(2)	C_3-C_4	1.399(2)
O_{20}-C_{21}	1.420(3)	C_4-C_5	1.394(2)
O_{22}-C_{23}	1.420(4)	C_5-C_6	1.382(3)
O_{30}-C_{31}	1.432(2)	C_{11}-C_{12}	1.397(3)
		C_{11}-C_{16}	1.400(3)
C_4-C_{10}	1.466(2)	C_{12}-C_{19}	1.389(3)
C_8-C_9	1.506(2)	C_{16}-C_{17}	1.374(3)
C_8-C_{24}	1.513(2)	C_{17}-C_{18}	1.374(4)
C_9-C_{11}	1.479(2)	C_{18}-C_{19}	1.388(3)
C_{10}-C_{15}	1.509(2)	C_{24}-C_{25}	1.392(2)
		C_{24}-C_{29}	1.385(2)
C_{14}-C_{15}	1.524(3)	C_{25}-C_{26}	1.382(3)
C_{31}-C_{32}	1.486(3)	C_{26}-C_{27}	1.384(3)
C_{34}-C_{35}	1.522(5)	C_{27}-C_{28}	1.387(2)
C_{35}-C_{36}	1.492(6)	C_{28}-C_{29}	1.387(3)
C_{36}-C_{37}	1.485(6)		
C_{37}-C_{38}	1.509(4)	C_9-C_{10}	1.340(2)

[a] The numbers in parentheses are the estimated standard deviations in the last significant digit.

[b] Atoms are labeled in agreement with Figure 1.

Table 5. Bond Angles in Crystalline (**S**-$C_{32}H_{35}NO_5$) [a]

Type[b]	Angle, (deg)	Type[b]	Angle, (deg)
$C_3O_7C_8$	116.9(1)	$O_{13}C_{12}C_{11}$	121.3(2)
$C_{12}O_{13}C_{14}$	117.8(1)	$O_{13}C_{12}C_{19}$	117.0(2)
$C_1O_{20}C_{21}$	117.1(2)	$C_{19}C_{12}C_{11}$	121.5(2)
$C_{18}O_{22}C_{23}$	117.7(2)	$C_{17}C_{16}C_{11}$	122.0(2)
$C_{27}O_{30}C_{31}$	117.2(1)	$C_{18}C_{17}C_{16}$	120.0(2)
		$C_{17}C_{18}O_{22}$	116.3(2)
$C_{34}N_{33}C_{38}$	110.5(2)	$O_{22}C_{18}C_{19}$	123.6(2)
$C_{34}N_{33}C_{32}$	112.5(2)	$C_{17}C_{18}C_{19}$	120.1(2)
$C_{38}N_{33}C_{32}$	110.5(2)	$C_{18}C_{19}C_{12}$	119.5(2)
		$C_{25}C_{24}C_8$	120.1(2)
$O_{20}C_1C_2$	123.9(2)	$C_{29}C_{24}C_8$	121.6(2)
$O_{20}C_1C_6$	115.7(2)	$C_{29}C_{24}C_{25}$	118.2(2)
$C_2C_1C_6$	120.4(2)	$C_{26}C_{25}C_{24}$	121.3(2)
$C_3C_2C_1$	118.9(2)	$C_{25}C_{26}C_{27}$	119.8(2)
$O_7C_3C_2$	116.6(2)	$O_{30}C_{27}C_{26}$	116.1(2)
$O_7C_3C_4$	120.7(2)	$O_{30}C_{27}C_{28}$	124.1(2)
$C_2C_3C_4$	122.5(2)	$C_{26}C_{27}C_{28}$	119.8(2)
$C_5C_4C_3$	117.0(2)	$C_{29}C_{28}C_{27}$	119.8(2)
$C_3C_4C_{10}$	118.0(2)	$C_{24}C_{29}C_{28}$	121.2(2)
$C_5C_4C_{10}$	125.0(2)		
$C_6C_5C_4$	121.9(2)	$O_7C_8C_9$	111.7(1)
$C_5C_6C_1$	119.4(2)	$O_7C_8C_{24}$	109.4(1)
$C_{10}C_9C_8$	120.9(2)	$C_9C_8C_{24}$	113.7(1)
$C_{11}C_9C_8$	117.5(1)	$O_{13}C_{14}C_{15}$	112.5(2)
$C_{10}C_9C_{11}$	121.5(2)	$C_{10}C_{15}C_{14}$	111.6(2)
$C_9C_{10}C_4$	119.4(2)	$O_{30}C_{31}C_{32}$	108.1(2)
$C_4C_{10}C_{15}$	121.3(2)	$N_{33}C_{32}C_{31}$	109.7(2)
$C_9C_{10}C_{15}$	119.3(2)	$N_{33}C_{34}C_{35}$	109.9(3)
$C_{12}C_{11}C_9$	120.0(2)	$C_{36}C_{35}C_{34}$	111.9(2)

Table 5. (continued)

Type[b]	Angle, (deg)	Type[b]	Angle, (deg)
$C_{16}C_{11}C_9$	123.1(2)	$C_{37}C_{36}C_{35}$	110.2(3)
$C_{12}C_{11}C_{16}$	116.9(2)	$C_{36}C_{37}C_{38}$	111.2(3)
$N_{33}C_{38}C_{37}$	109.7(2)		

[a] The numbers in parentheses are the estimated standard deviations in the last significant digit.

[b] Atoms are labeled in agreement with Figure 1.

Table 6. Torsion Angles in Crystalline (**S**-$C_{32}H_{35}NO_5$) [a]

Type[b]	Angle, (deg)	Type[b]	Angle, (deg)
O_{20}-C_1-C_2-C_3	179.7(2)	O_{13}-C_{14}-C_{15}-C_{10}	-47.8(2)
C_6-C_1-C_2-C_3	-0.3(3)	C_{12}-C_{11}-C_{16}-C_{17}	0.9(3)
C_1-C_2-C_3-O_7	175.5(2)	C_9-C_{11}-C_{16}-C_{17}	179.9(2)
C_1-C_2-C_3-C_4	0.5(3)	C_{11}-C_{16}-C_{17}-C_{18}	-0.2(3)
O_7-C_3-C_4-C_5	-174.6(2)	C_{16}-C_{17}-C_{18}-O_{22}	179.7(2)
C_2-C_3-C_4-C_5	0.2(2)	C_{16}-C_{17}-C_{18}-C_{19}	-0.4(3)
O_7-C_3-C_4-C_{10}	3.7(2)	C_{17}-C_{18}-C_{19}-C_{12}	0.1(3)
C_2-C_3-C_4-C_{10}	178.4(2)	O_{22}-C_{18}-C_{19}-C_{12}	-179.9(2)
C_3-C_4-C_5-C_6	-1.2(2)	O_{13}-C_{12}-C_{19}-C_{18}	-173.8(2)
C_{10}-C_4-C_5-C_6	-179.3(2)	C_{11}-C_{12}-C_{19}-C_{18}	0.7(3)
C_4-C_5-C_6-C_1	1.4(3)	C_2-C_1-O_{20}-C_{21}	2.0(3)
O_{20}-C_1-C_6-C_5	179.4(2)	C_6-C_1-O_{20}-C_{21}	-178.0(2)
C_2-C_1-C_6-C_5	-0.6(3)	C_{17}-C_{18}-O_{22}-C_{23}	-179.2(2)
C_2-C_3-O_7-C_8	153.2(1)	C_{19}-C_{18}-O_{22}-C_{23}	0.9(3)
C_4-C_3-O_7-C_8	-31.7(2)	O_7-C_8-C_{24}-C_{29}	91.5(2)
C_3-O_7-C_8-C_9	41.1(1)	C_9-C_8-C_{24}-C_{29}	-34.2(2)
C_3-O_7-C_8-C_{24}	-85.8(2)	O_7-C_8-C_{24}-C_{25}	-85.9(2)
O_7-C_8-C_9-C_{10}	-25.3(2)	C_9-C_8-C_{24}-C_{25}	148.5(2)
C_{24}-C_8-C_9-C_{10}	99.2(2)	C_{29}-C_{24}-C_{25}-C_{26}	-2.0(3)
O_7-C_8-C_9-C_{11}	159.9(1)	C_8-C_{24}-C_{25}-C_{26}	175.5(2)
C_{24}-C_8-C_9-C_{11}	-75.7(2)	C_{24}-C_{25}-C_{26}-C_{27}	-0.5(3)
C_{11}-C_9-C_{10}-C_4	173.8(2)	C_{25}-C_{26}-C_{27}-O_{30}	-177.9(2)
C_8-C_9-C_{10}-C_4	-0.8(2)	C_{25}-C_{26}-C_{27}-C_{28}	2.5(3)
C_{11}-C_9-C_{10}-C_{15}	-5.0(3)	O_{30}-C_{27}-C_{28}-C_{29}	178.4(2)
C_8-C_9-C_{10}-C_{15}	-179.6(2)	C_{26}-C_{27}-C_{28}-C_{29}	-2.1(3)
C_5-C_4-C_{10}-C_9	-169.0(2)	C_{25}-C_{24}-C_{29}-C_{28}	2.4(3)
C_3-C_4-C_{10}-C_9	12.9(2)	C_8-C_{24}-C_{29}-C_{28}	-175.0(2)
C_5-C_4-C_{10}-C_{15}	9.8(3)	C_{27}-C_{28}-C_{29}-C_{24}	-0.4(3)
C_3-C_4-C_{10}-C_{15}	-168.3(2)	C_{26}-C_{27}-O_{30}-C_{31}	169.2(2)

Table 6. (continued)

Type[b]	Angle, (deg)	Type[b]	Angle, (deg)
C_{10}-C_9-C_{11}-C_{12}	-42.0(2)	C_{28}-C_{27}-O_{30}-C_{31}	-11.2(3)
C_8-C_9-C_{11}-C_{12}	132.7(2)	C_{27}-O_{30}-C_{31}-C_{32}	-168.2(2)
C_{10}-C_9-C_{11}-C_{16}	139.1(2)	O_{30}-C_{31}-C_{32}-N_{33}	176.2(2)
C_8-C_9-C_{11}-C_{16}	-46.2(2)	C_{31}-C_{32}-N_{33}-C_{34}	-116.5(2)
C_{16}-C_{11}-C_{12}-O_{13}	173.0(2)	C_{31}-C_{32}-N_{33}-C_{38}	119.5(2)
C_9-C_{11}-C_{12}-O_{13}	-5.9(3)	C_{38}-N_{33}-C_{34}-C_{35}	-60.4(3)
C_{16}-C_{11}-C_{12}-C_{19}	-1.2(3)	C_{32}-N_{33}-C_{34}-C_{35}	175.6(2)
C_9-C_{11}-C_{12}-C_{19}	179.8(2)	N_{33}-C_{34}-C_{35}-C_{36}	55.5(4)
C_{19}-C_{12}-O_{13}-C_{14}	-113.1(2)	C_{34}-C_{35}-C_{36}-C_{37}	-51.8(4)
C_{11}-C_{12}-O_{13}-C_{14}	72.4(2)	C_{35}-C_{36}-C_{37}-C_{38}	53.4(4)
C_{12}-O_{13}-C_{14}-C_{15}	-37.9(2)	C_{34}-N_{33}-C_{38}-C_{37}	62.3(3)
C_9-C_{10}-C_{15}-C_{14}	73.7(2)	C_{32}-N_{33}-C_{38}-C_{37}	-172.6(2)
C_4-C_{10}-C_{15}-C_{14}	-105.1(2)	C_{36}-C_{37}-C_{38}-N_{33}	-58.6(3)

[a] The numbers in parentheses are the estimated standard deviations in the last significant digit.

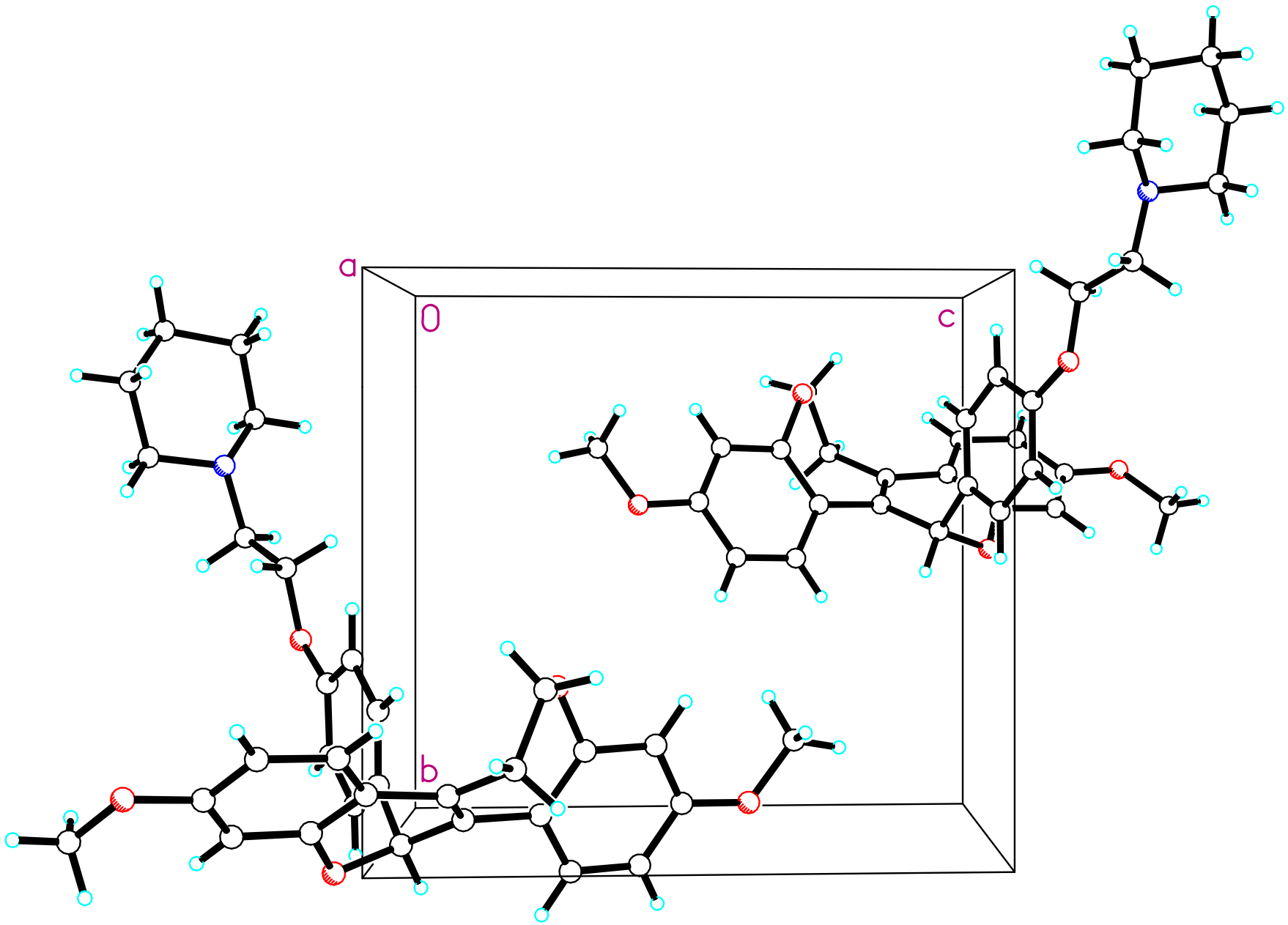
[b] Atoms are labeled in agreement with Figure 1.

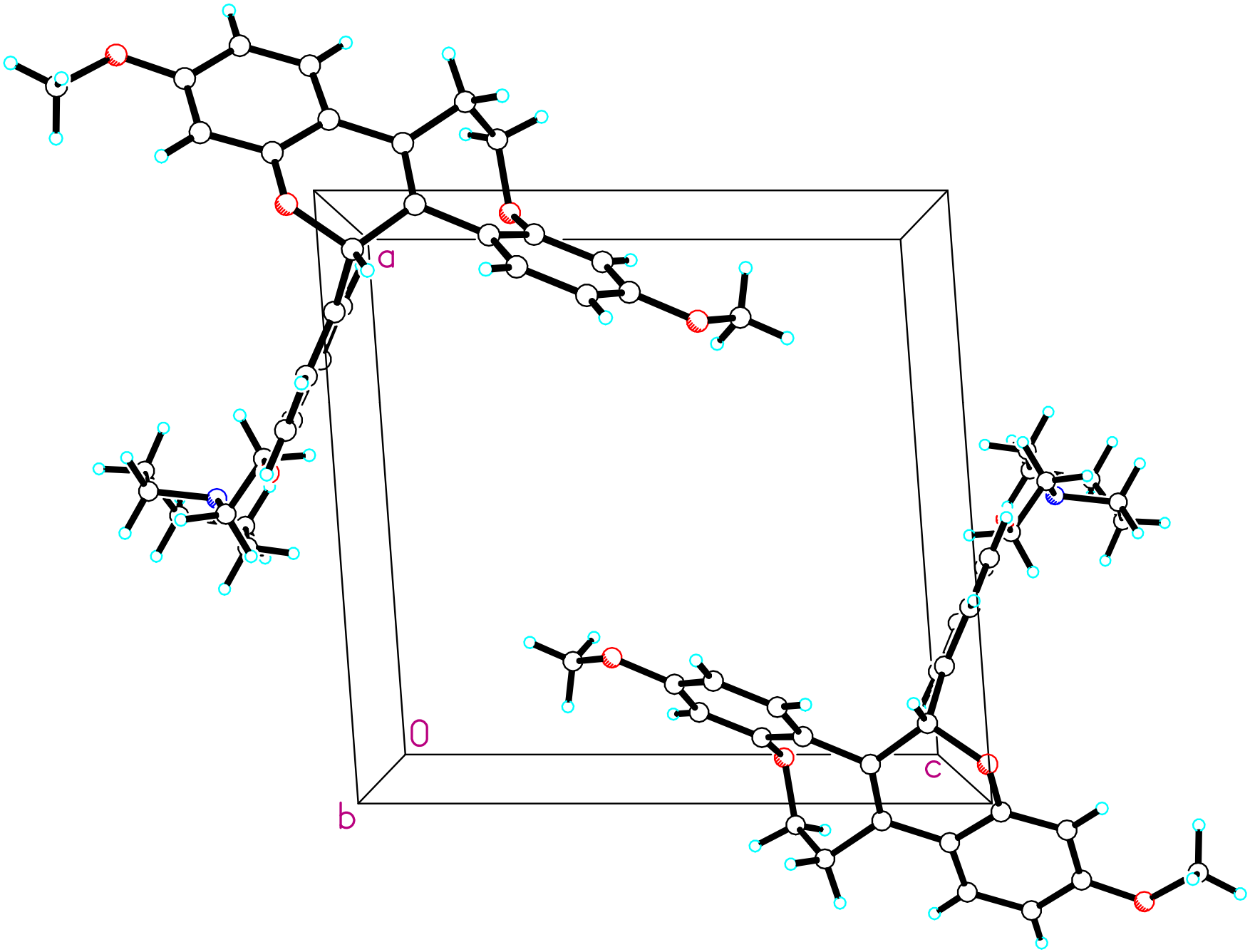
FIGURE CAPTIONS

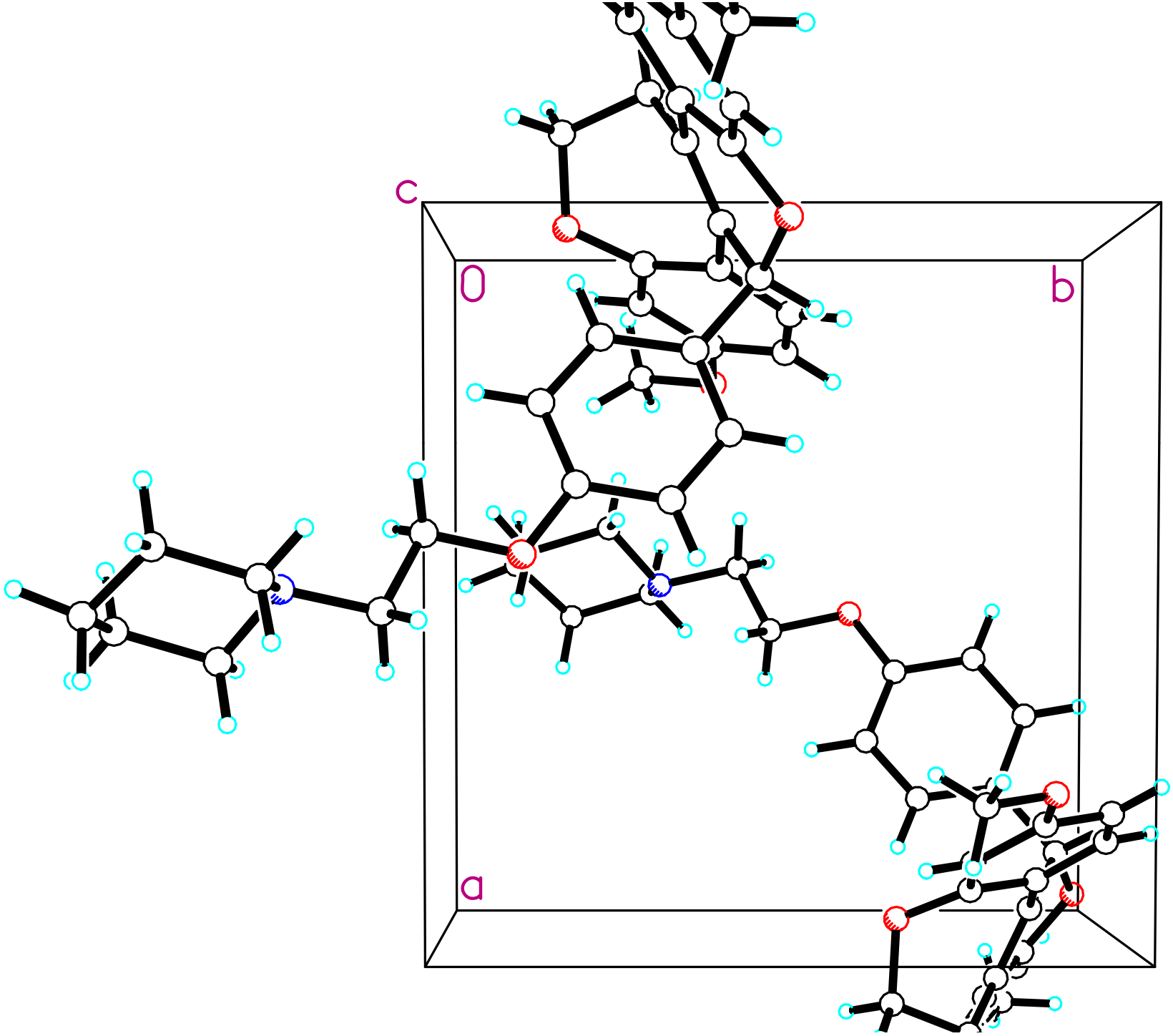
Figure 1a. shows a perspective drawing of the solid-state structure for the (**S**-$C_{32}H_{35}NO_5$) molecule. Nonhydrogen atoms are represented by 50% probability thermal vibration ellipsoids and hydrogen atoms are represented by arbitrarily-small spheres which are in no way representative of their true thermal motion.

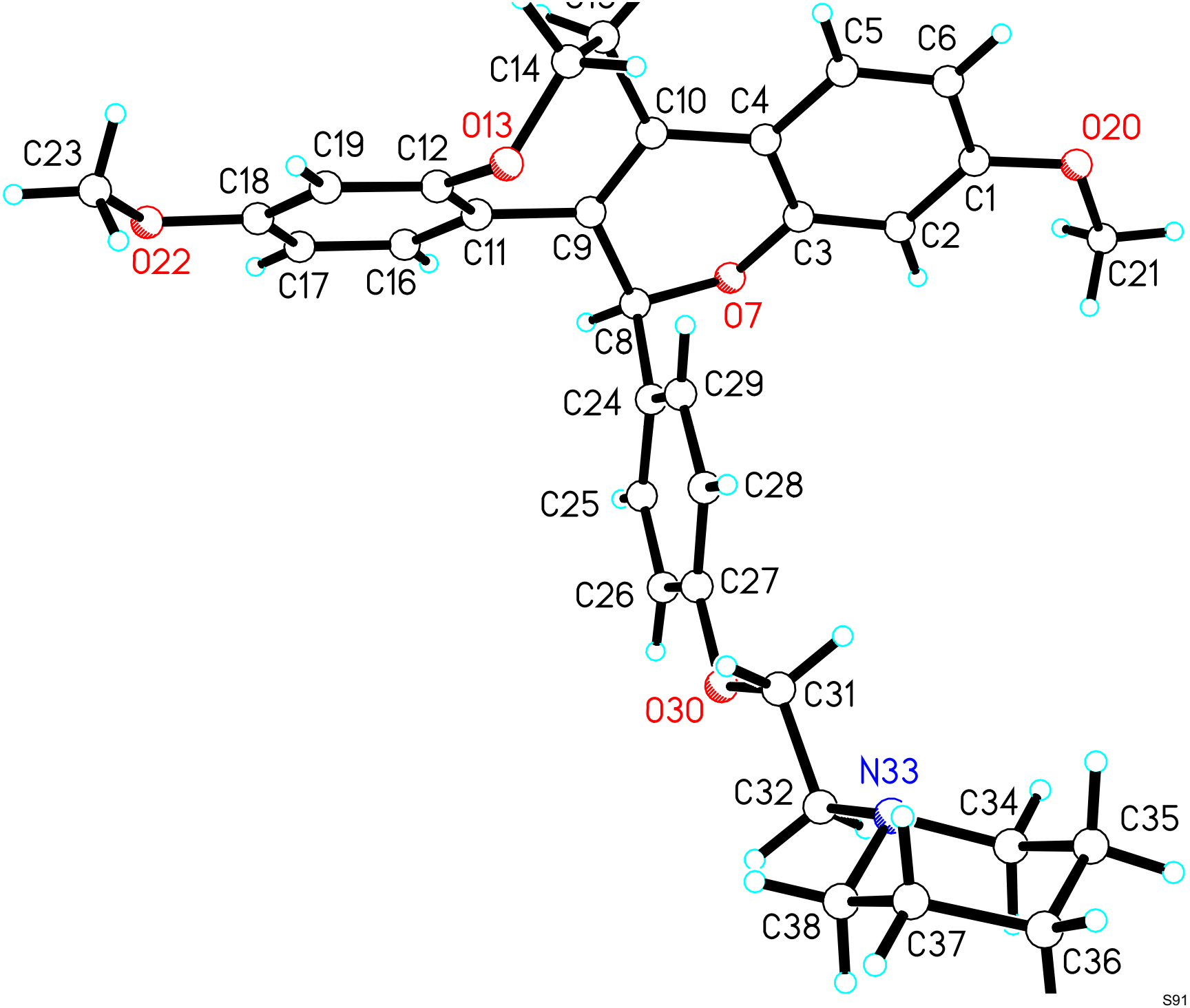
Figure 1b. shows a perspective drawing of the solid-state structure for the (**S**-$C_{32}H_{35}NO_5$) molecule. The view is the same as in Figure 1a but atoms are now represented by: oxygen and nitrogen, medium-sized shaded spheres; carbon, medium-sized open spheres; and hydrogen, small open spheres, respectively.

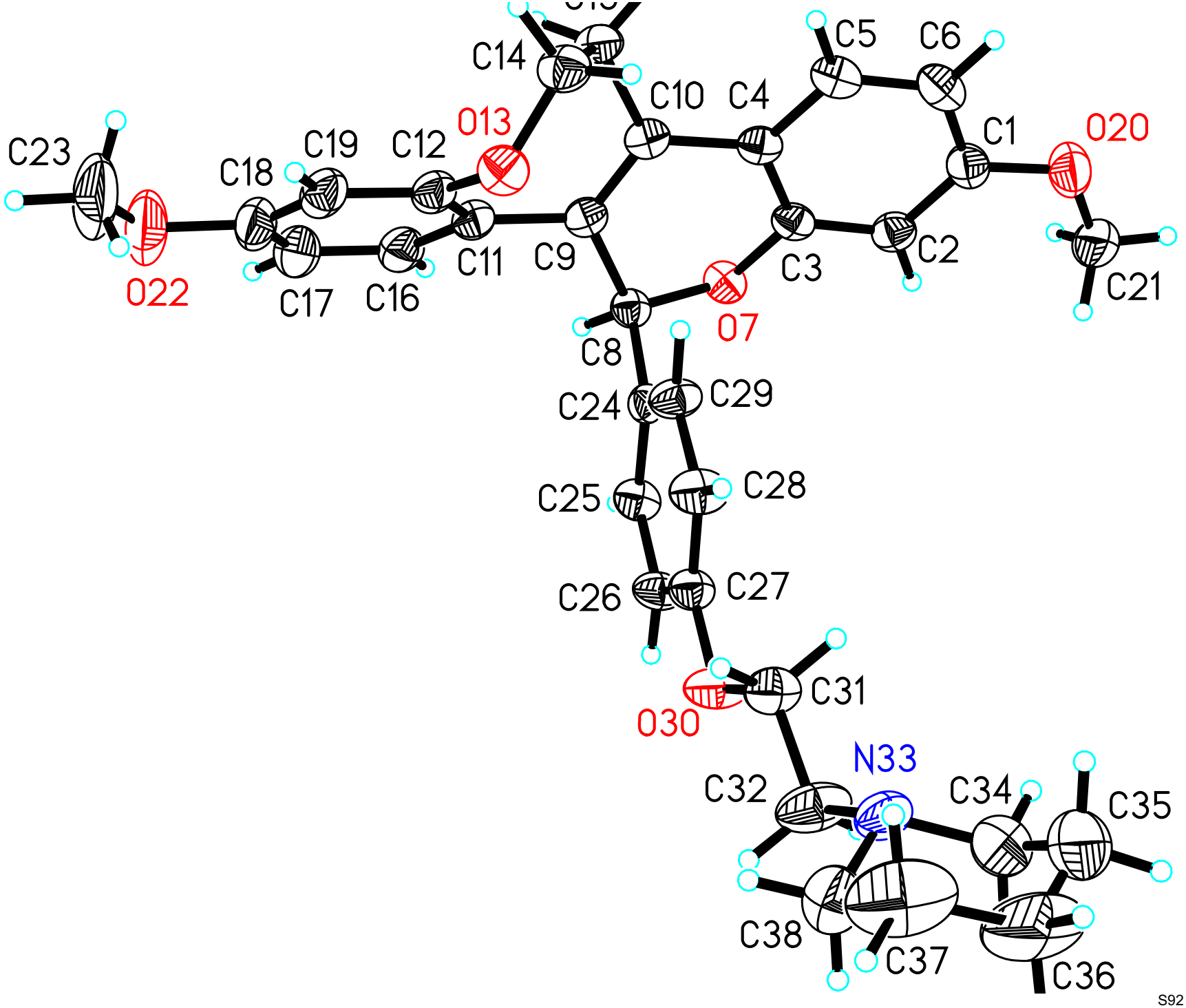
Figure 1c. shows a space-filling drawing of the solid-state structure for the (**S**-$C_{32}H_{35}NO_5$) molecule. The view is the same as in Figure 1a.

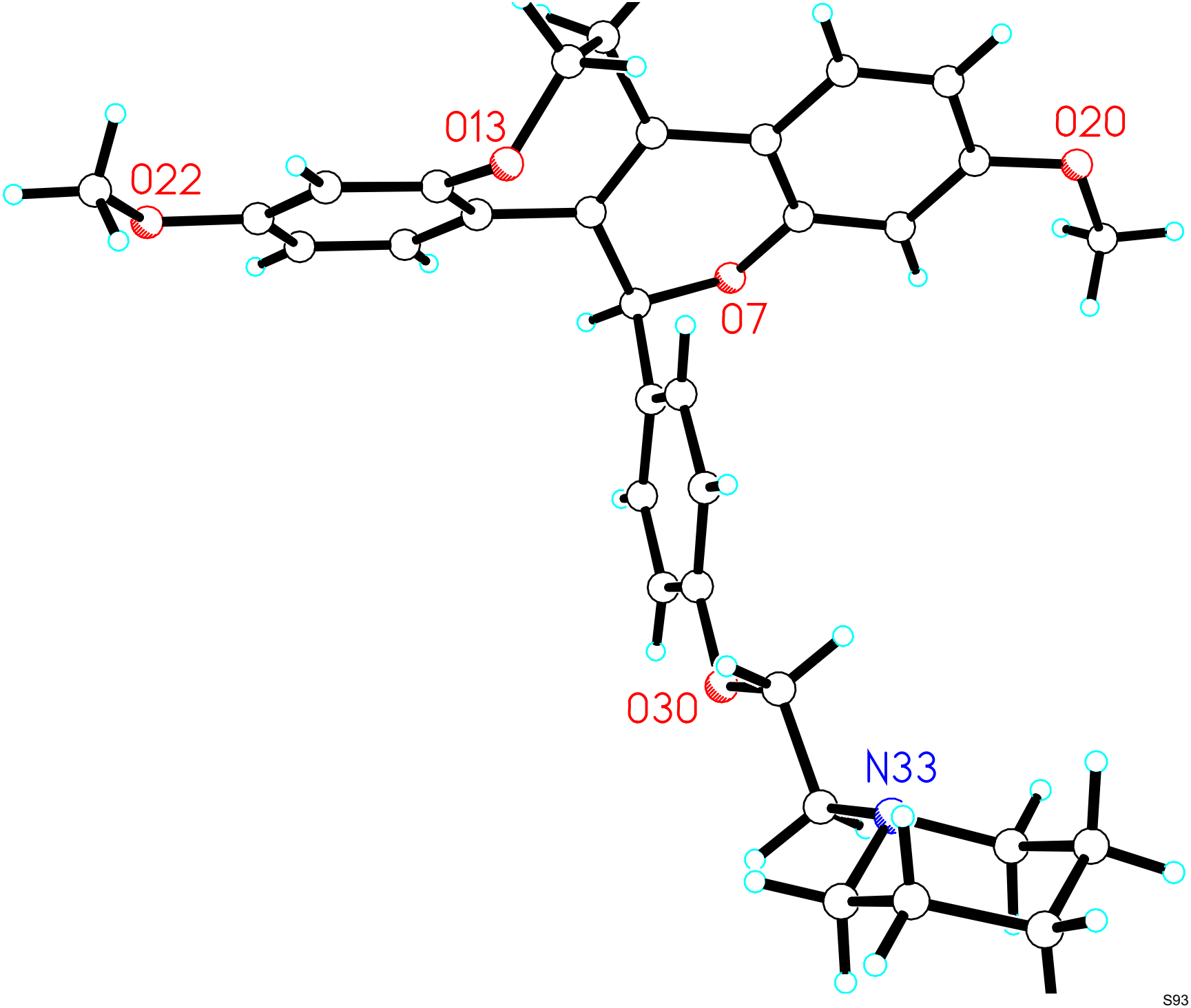

a
0
c
b

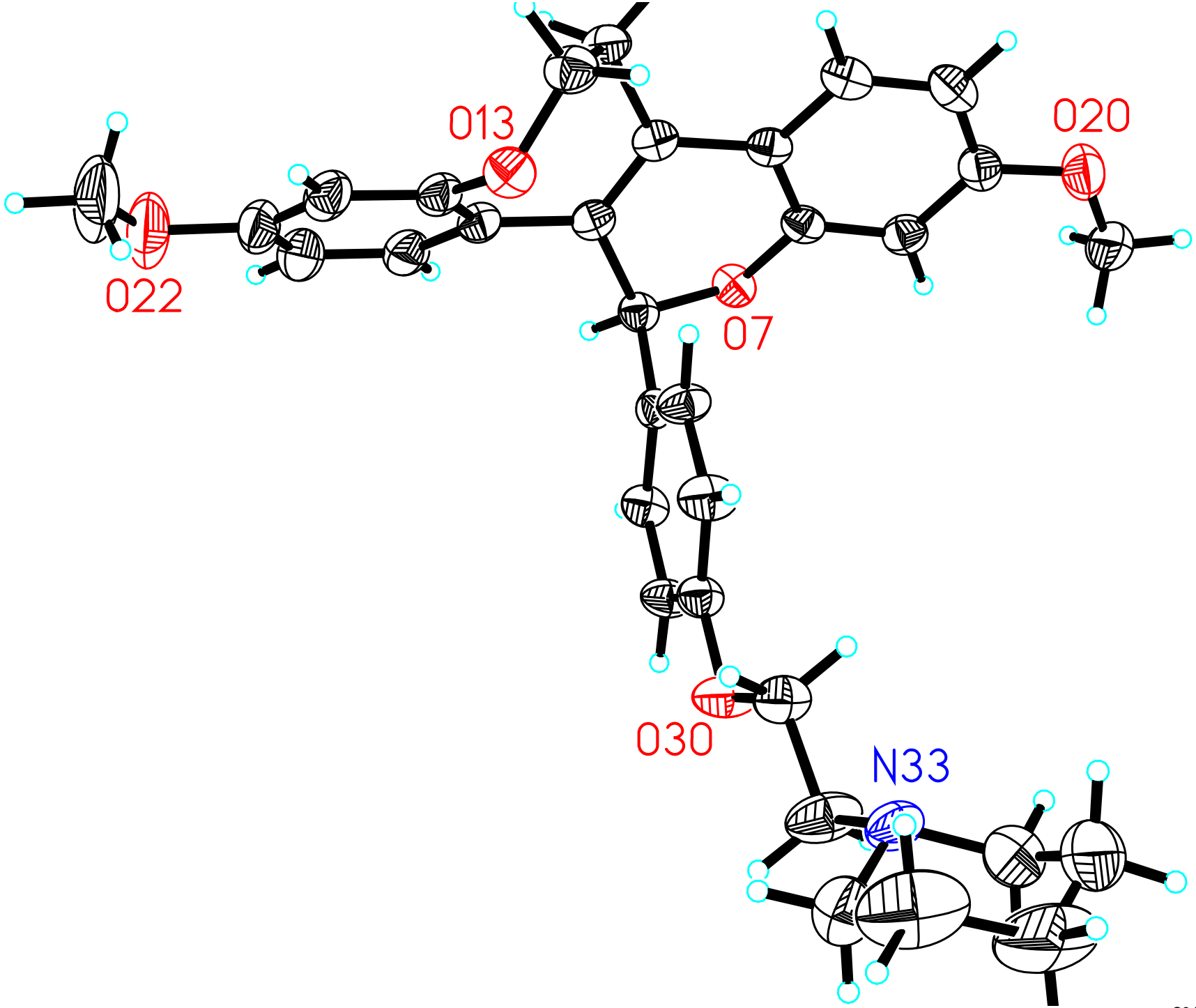

a
0
b
c

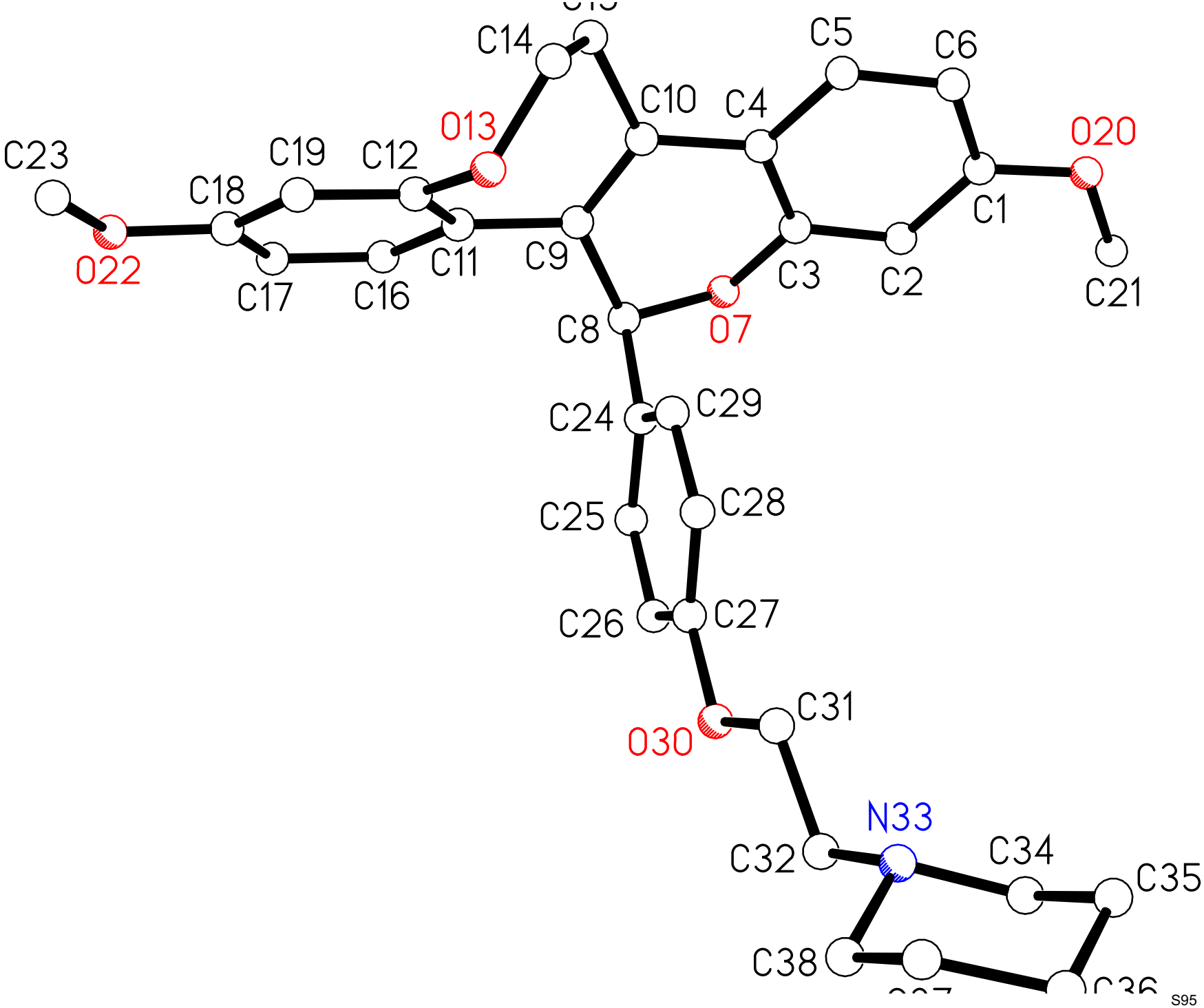

c
0
b
a

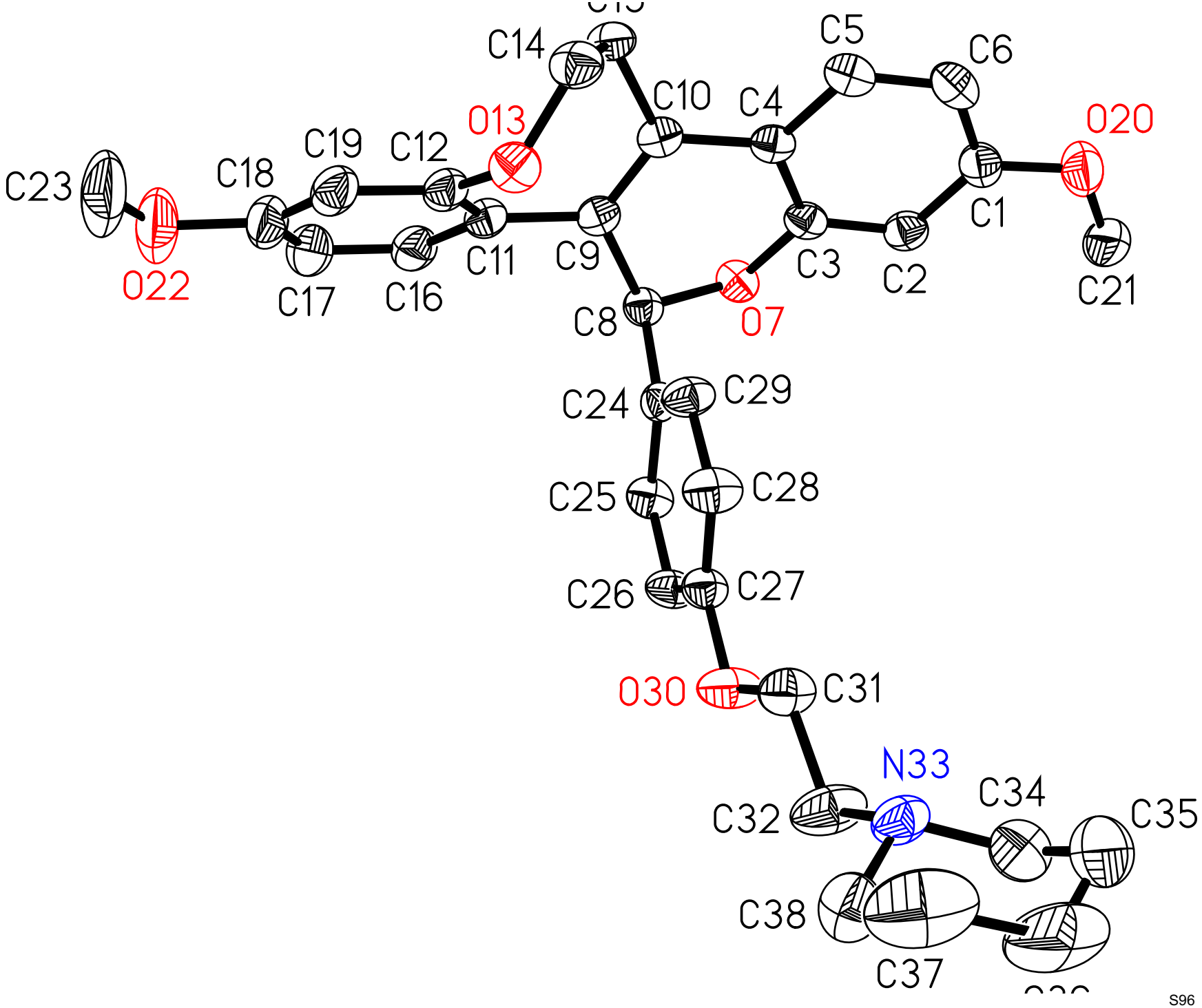

C14
C5
C6
C10
C4
O13
C23
C19
C12
O20
C18
C1
C11
C9
C3
C2
O22
C17
C16
O7
C21
C8
C29
C24
C28
C25
C27
C26
O30
C31
N33
C32
C34
C35
C38
C37
C36

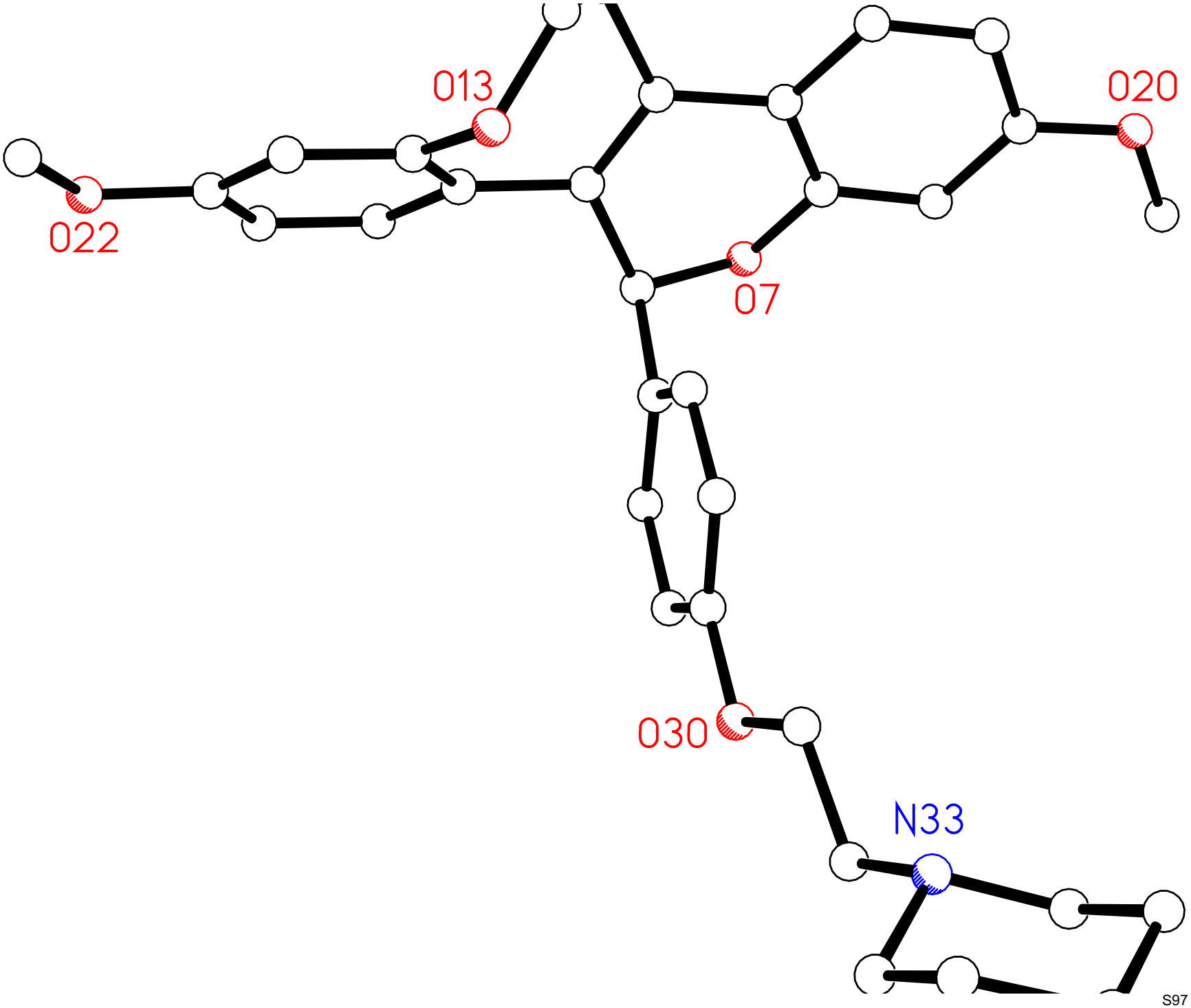

C14
C5
C6
C10
C4
O13
C1
O20
C23
C19
C12
C18
C2
C21
O22
C17
C16
C11
C9
C3
O7
C8
C24
C29
C25
C28
C26
C27
O30
C31
N33
C32
C34
C35
C38
C37
C36

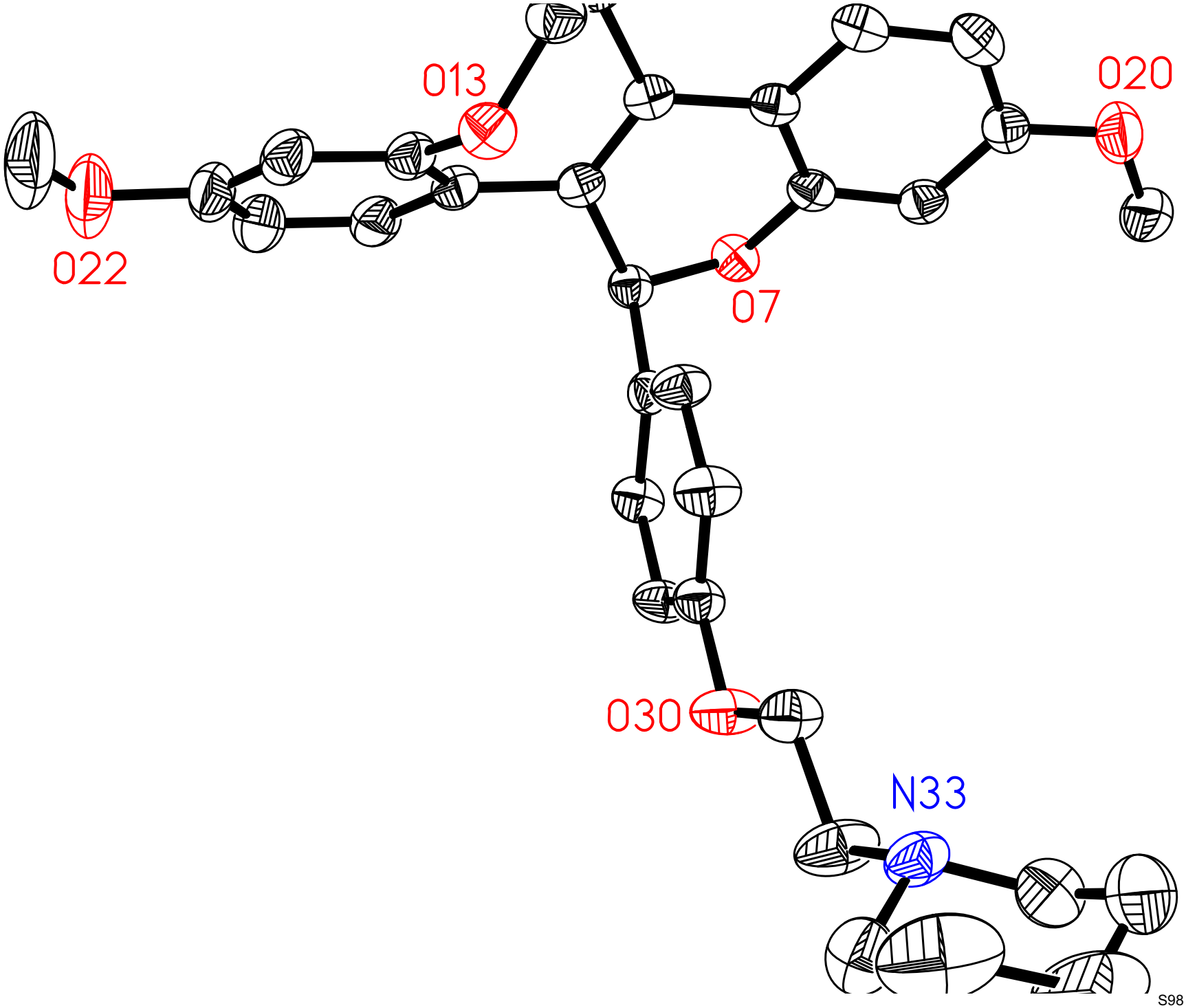

O13
O22
O20
O7
O30
N33

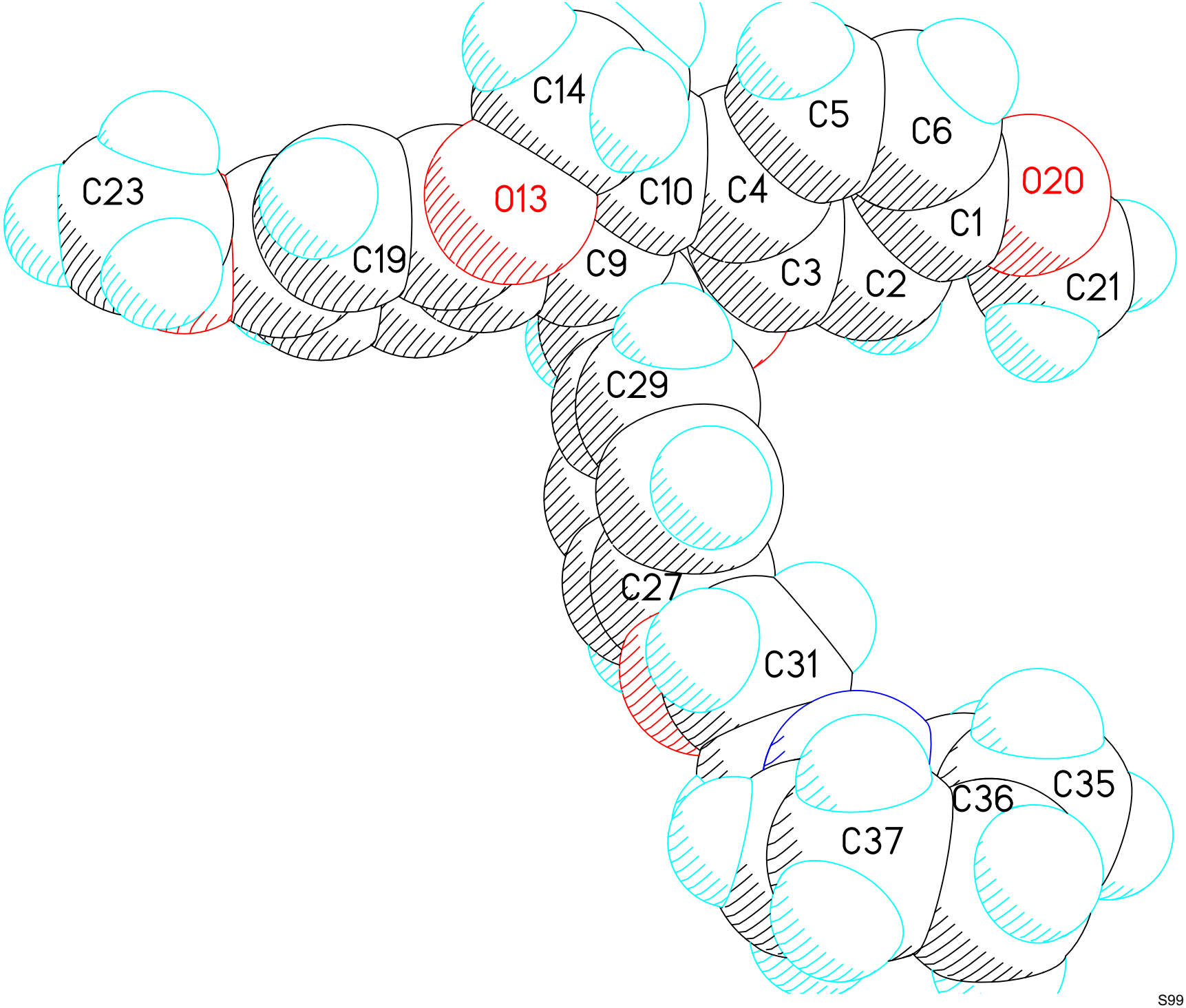

O13
O20
O22
O7
O30
N33


C14
C5
C6
C10
C4
O13
O20
C23
C19
C12
C18
C1
C11
C9
C3
C2
O22
C17
C16
C21
O7
C8
C24
C29
C25
C28
C26
C27
C31
O30
N33
C32
C34
C35
C38
C36


C14
C5
C6
C10
C4
O13
O20
C19
C12
C18
C23
C1
C11
C9
C3
C2
O22
C17
C16
O7
C21
C8
C24
C29
C25
C28
C26
C27
O30
C31
N33
C32
C34
C35
C38
C37


O13
O20
O22
O7
O30
N33
S97


O13
O20
O22
O7
O30
N33


C14
C5
C6
C23
013
C10
C4
020
C1
C19
C9
C3
C2
C21
C29
C27
C31
C35
C36
C37

S99