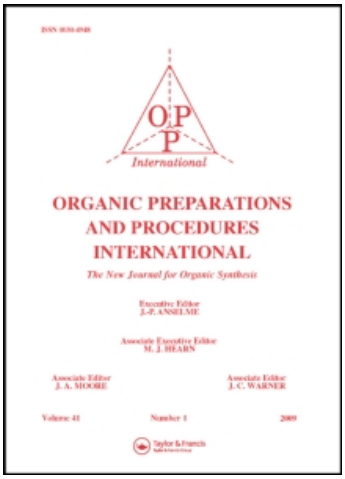


Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

SYNTHESIS OF (+)-9-O-DESMETHYL-α-DIHYDROTETRABENAZINE, PRECURSOR FOR THE HIGH AFFINITY VMAT2 IMAGING PET RADIOLIGAND [^{11}C]-(+)-α-DIHYDROTETRABENAZINE

Karl G. Boldt[a]; George A. Brine[a]; Ken Rehder[a]
[a] Center for Organic and Medicinal Chemistry RTI International, Research Triangle Park, NC

To cite this Article Boldt, Karl G. , Brine, George A. and Rehder, Ken(2008) 'SYNTHESIS OF (+)-9-O-DESMETHYL-α-DIHYDROTETRABENAZINE, PRECURSOR FOR THE HIGH AFFINITY VMAT2 IMAGING PET RADIOLIGAND [^{11}C]-(+)-α-DIHYDROTETRABENAZINE', Organic Preparations and Procedures International, 40: 4, 379 — 384
To link to this Article: DOI: 10.1080/00304940809458097
URL: http://dx.doi.org/10.1080/00304940809458097

ORGANIC PREPARATIONS AND PROCEDURES INT., 40 (4), 379-410 (2008)

OPPI BRIEFS

SYNTHESIS OF (+)-9-O-DESMETHYL-α-DIHYDROTETRABENAZINE, PRECURSOR FOR THE HIGH AFFINITY VMAT2 IMAGING PET RADIOLIGAND [^{11}C]-(+)-α-DIHYDROTETRABENAZINE

Submitted by (10/18/07)

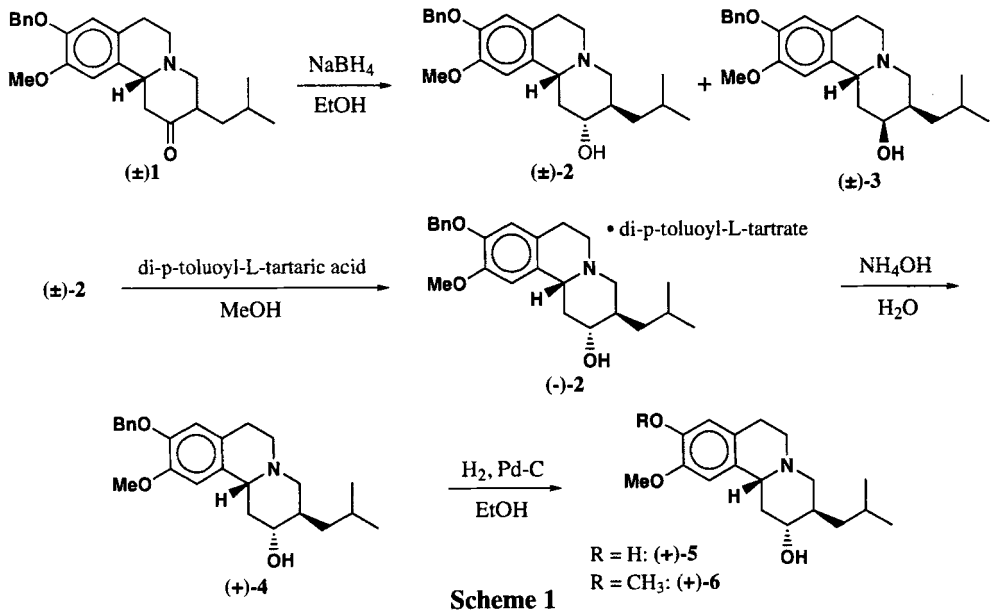
Karl G. Boldt, George A. Brine and Ken Rehder*

Center for Organic and Medicinal Chemistry
RTI International, Research Triangle Park, NC 27709
e-mail: krehder@rti.org

The vesicular monoamine transporter (VMAT) has two pharmacologically distinct isoforms, VMAT1 and VMAT2.[1] In contrast to VMAT1, VMAT2 is primarily found in the central nervous system of rodents and humans, and is involved in the transport of monoamine neurotransmitters. VMAT2 has been postulated as a potential target for psychostimulant abuse pharmacotherapies[1], and as a probe to monitor and diagnose neurodegenerative disorders such as Parkinson's and Huntington's disease.[2] More recently, VMAT2 has been found expressed in human islet beta cells in the pancreas,[3] and its use as a surrogate marker for beta cell mass loss and progression of diabetes has been suggested.[4] As a result, imaging of VMAT2, particularly with high affinity positron emitting tomography (PET) ligands, is an area of ongoing research interest.[1,2]

(+)-α-Dihydrotetrabenazine ((+)-DTBZ, (+)-**6**) (*Scheme 1*) is a high affinity VMAT2 ligand.[3] This material was previously obtained *via* separation of the enantiomers of the racemic compound by chiral HPLC and its absolute stereochemistry was determined.[5] Preparation of a suitable VMAT2 PET imaging precursor, (+)–9-O-desmethyl-α-dihydrotetrabenazine ((+)-**5**) was also described, and involved selective O-demethylation of (±)-DTBZ with sodium hydride/N-methylaniline/HMPA, followed by enantiomeric separation by chiral HPLC. Conversion of (+)-**5** to [^{11}C]-(+)-DTBZ (labeled in the 9-OMe position) yields a suitable, high affinity VMAT2 PET imaging ligand.[6] During the course of an ongoing research gram quantities of (+)-**5** were required, but the previous method[5] was deemed unsuitable for that scale. An alternative approach was therefore implemented, the results of which are reported herein.

Synthesis of key intermediate (±)-2-oxo-3-isobutyl-9-benzyloxy-10-methoxy-1,2,3,4,6,7-hexahydro-11bH-benzo[a]quinolizine ((±)-**1**) was performed as previously reported.[7,8] Initial attempts to enantiomerically resolve (±)-**1** *via* diastereomeric salt formation



Scheme 1

were unsuccessful. In the hope of better success with the attempted resolution, (±)-**1** was reduced with $NaBH_4$ in EtOH to give a 4:1 mixture of (±)-**2** and (±)-**3** by HPLC analysis of the crude reaction mixture. Assignment of the *trans* stereoisomer was based on analogy ^1H and ^{13}C NMR data obtained on reduction of the structurally related tetrabenazine.[9] This diastereomeric mixture was subsequently separated by fractional recrystallization in methanol to give (±)-**2** in 67% yield.[8]

Enantiomeric resolution of (±)-**2** was achieved *via* reaction with one equivalent of di-*p*-toluoyl-L-tartartic acid and recrystallization of the resulting salt to give pure (-)-**2** di-*p*-toluoyl-L-tartrate in 88% yield. Conversion of (-)-**2** di-*p*-toluoyl-L-tartrate to its free base was performed by treatment with concentrated NH_4OH followed by extraction, producing (+)-**4** in 98% yield. The enantiomeric purity was determined by chiral HPLC analysis and (+)-**4** was determined to be >99% ee.[5] Deprotection of the benzyl group of (+)-**4** *via* hydrogenolysis gave (+)-**5** in 74% yield after recrystallization. The overall yield from (±)-**1** was 43%.

The synthesis described herein provides the preparation of gram quantities of (+)-**5** without tedious separation of isomers by preparative chiral HPLC.

EXPERIMENTAL SECTION

Mps were obtained on a Thomas Hoover capillary apparatus and are corrected. ^1H and ^{13}C nuclear magnetic resonance (NMR) spectra were determined on either a Bruker Avance 300 MHz NMR spectrometer or a Varian AMX-500 NMR spectrometer. Mass spectra (MS) were obtained on a Perkin-Elmer Sciex API 150 EX mass spectrometer outfitted with APCI (atmospheric pressure chemical ionization) or ESI (turbospray) sources. MS samples were introduced

by means of an Agilent 1100 Series liquid chromatography system. Optical rotations were measured using an Autopol IV automatic polarimeter (Rudolph Research Analytical Corporation) and a glass cell (1.5 mL volume; 100 mm pathlength). TLC analyses were carried out on commercial precoated analytical silica gel 60 F254 glass plates (E. Merck, 5 x 10 cm) using the solvent systems indicated. Spot visualization was achieved by inspection under UV light and then by staining with iodine or with a combination of 5% phosphomolybdic acid in ethanol and 10% ceric sulfate in 10% sulfuric acid followed by heating on a hot plate.

Chiral HPLC analyses were obtained on a system composed of a Waters 1525 binary pump system, a Waters 717 auto sampler, a Waters 2487 dual wavelength absorbance detector, and Waters Empower software for system operation and data handling. Regular HPLC analyses were performed on a Rainin HPLC dual pump system using two Rainin solvent pumps (25 mL pump heads), a Rainin solvent mixer, a Rheodyne injector, a Varian dual wavelength detector, and Rainin Dynamax software (run on a Power Macintosh 7200) for both gradient control and data handling. The columns and solvent systems are provided below. Column chromatography was carried out on E. Merck silica gel 60, 230-400 mesh. In-house nitrogen gas (produced from liquid nitrogen) was employed to provide an inert atmosphere. Elemental analyses were carried out by Atlantic Microlab Inc., Norcross, GA.

***trans*-2-Hydroxy-3-isobutyl-9-benzyloxy-10-methoxy-1,2,3,4,6,7-hexahydro-11bHbenzo[a]quinolizine [(±)-2].**- Compound (±)-**1** (18.3 g, 0.046 mole) was dissolved in ethanol (1.20 L) with heating. The resulting solution was cooled to room temperature, treated with $NaBH_4$ (6.20 g, 0.16 mole) and stirred at room temperature for 21 h. The reaction mixture was evaporated *in vacuo* to give a white solid which was partitioned between CH_2Cl_2 (500 mL) and H_2O (500 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 400 mL). The CH_2Cl_2 layers were combined, dried (Na_2SO_4, overnight), filtered and evaporated *in vacuo* to give 18.3 g (99%) of a white solid. The crude product was analyzed by HPLC: major peak (82.6%), t_R 14.3 min, and minor peak (17.4%), t_R 16.8 min, on a Waters XTerra C_{18} column (3.5 μ) (4.6 x 150 mm) using a gradient (25% B to 65% B over 30 min) at 1.0 mL/min with UV detection at 220 nm, with solvent A being 0.1% TFA/H_2O and solvent B being 0.1% TFA/CH_3CN. The reaction was repeated starting with 20.5 g (0.052 mole) of (±)-**1** to give an additional 20.4 g (99%) of white solid. The combined solids (38.7 g) were dissolved in MeOH (600 mL) by heating on the steam bath. The solution was concentrated to 300 mL and the solution was cooled to room temperature followed by cooling in the refrigerator for 2 h. The solid was collected and dried *in vacuo* to give 26.1 g (67%) of (±)-**3** as white crystals, mp. 175-178°C, (*lit.*[8] mp. 175-177°C); TLC single spot, R_f 0.79, [silica gel, EtOAc]; chiral HPLC peak (51%), t_R 18.1 min, and peak (49%), t_R 20.8 min on a Phenomenex Chirex (S)-Val and (R)-NEA (4.6 x 250 mm) using isocratic 97.5% A: 2.5% B at 1.0 mL/min with UV detection at 254 nm with solvent A being hexane/1,2-dichloroethane (5:1) and solvent B being 0.1% TFA/EtOH.

^1H NMR ($CDCl_3$): δ 0.93 (d, 3H, J = 6.5 Hz), 0.91 (d, 3H, J = 6.5 Hz), 1.06 (ddd, 1H, J = 13.9, 9.7, 4.3 Hz), 1.48 (dd, 1H, J = 23.1, 11.8 Hz), 1.55-1.60 (m, 2H), 1.66-1.76 (m, 2H), 1.96 (dd, 1H, J = 11.8 Hz), 2.42 (m, 1H), 2.55 (m, 1H), 2.96 (m, 1H), 2.99-3.08 (m, 2H), 3.11 (d, 1H, J = 11.3 Hz), 3.39 (m, 1H), 3.85 (s, 3H), 5.11 (s, 2H), 6.61 (s, 1H), 6.70 (s, 1H), 7.29 (dd, 1H, J =

7.2, 7.2 Hz), 7.35 (dd, 1H, J = 7.7, 7.2 Hz), 7.42 (d, 1H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$): δ 21.9, 24.4, 25.5, 29.3, 39.9, 40.7, 41.8, 52.1, 56.3, 60.2, 61.1, 71.1, 74.8, 108.8, 114.4, 126.6, 127.5, 128.0, 128.7, 130.2, 137.4, 146.9, 148.1; MS (ESI) (positive ion): *m/z* 396.6 (M+H).

Anal. Calcd. for $C_{25}H_{33}NO_3$: C, 75.91; H, 8.41; N, 3.54. Found: C, 76.09; H, 8.48; N, 3.54.

The filtrate from above was evaporated *in vacuo* and the solid obtained was rinsed with hexanes (200 mL) to give 12.0 g (31%) of crude mixture of (±)-**3** and (±)-**2**, HPLC major peak (70%) of (±)-**3**, t_R 16.1 min, and a minor peak (27.4%) of (±)-**2**, t_R 14.1 min, on a Waters XTerra C_{18} column (3.5 μ) (4.6 x 150 mm) using a gradient (25% B to 65% B over 30 min) at 1.0 mL/min with UV detection at 220 nm, with solvent A being 0.1% TFA/H_2O and solvent B being 0.1% TFA/CH_3CN.

(-)-*trans*-2-Hydroxy-3-isobutyl-9-benzyloxy-10-methoxy-1,2,3,4,6,7-hexahydro-11bHbenzo[a]quinolizine salt [(-)-2 di-*p*-toluoyl-L-tartrate].- Compound (±)-**2** (25.9 g, 0.066 mole) was dissolved in MeOH (1000 mL) with heating and treated with di-*p*-toluoyl-L-tartaric acid (25.3 g, 0.066 mole) and warmed 5 min to give a solution. The solution was cooled to room temperature and then evaporated *in vacuo* to give a solid (51.7 g). The solid was dissolved in acetone (650 mL) and the solution was concentrated to 400 mL and cooled to room temperature. The solution was seeded with crystals from a previous resolution. After standing for 5 days the crystals were collected and rinsed with acetone (100 mL) to give a solid. The solid was dried *in vacuo* at room temperature to give a white solid (26.6 g). The white solid (26.6 g) was suspended in boiling acetone (700 mL) and MeOH (700 mL) was added to give a solution. The volume was 1.40 L and the solution was concentrated with heating to 700 mL. The solution was diluted to 1.40 L with acetone and concentrated to 700 mL. The dilution was repeated and the solution was concentrated to 400 mL, seeded with a crystal from a previous resolution, and then cooled to room temperature. After standing 4 days the crystals were collected and rinsed with acetone (100 mL) and dried *in vacuo* at room temperature to give 19.2 g (38%) of (-)-**2** di-*p*-toluoyl-L-tartrate as a white solid. A second crop of crystals (3.1 g, 6%) was recovered from the filtrate, for a total of 22.4 g (44%) of (-)-**2** di-*p*-toluoyl-L-tartrate suitable for use in the next reaction: mp. 143-144°C foaming; TLC single spot, R_f 0.85, [silica gel, $CHCl_3$:MeOH:concentrated NH_4OH (90:9:1)]; chiral HPLC (free base) single peak (100%), t_R 21.0 min, on a Phenomenex Chirex (S)-Val and (R)-NEA (250 x 4.6 mm) using isocratic 97.5% A: 2.5% B at 1.0 mL/min with UV detection at 254 nm with solvent A being hexane/1,2-dichloroethane (5:1) and solvent B being 0.1% TFA/EtOH, (The other enantiomer has a t_R 18.1 min and was not observed in the analysis.) ^{1}H NMR (CD_3OD): δ 0.90 (d, 3H, J = 5.8 Hz), 0.94 (d, 3H, J = 5.8 Hz), 1.07 (m, 1H), 1.60-1.76 (m, 3H), 1.84-1.94 (m, 1H), 2.39 (s, 6H), 2.77-2.89 (m, 3H), 3.10-3.29 (m, 2H), 3.49-3.67 (m, 3H), 3.82 (s, 3H), 4.30 (d, 1H, J = 12.1 Hz), 5.06 (s, 2H), 5.83 (s, 2H), 6.73 (s, 1H), 6.82 (s, 1H), 7.26-7.43 (m, 9H) 7.99 (d, 4H J = 7.9 Hz); OR $[\alpha]_D^{21}$ -45.1° (c 1.061, MeOH).

Anal. Calcd. for $C_{45}H_{51}NO_{11}$: C, 69.13; H, 6.57; N, 1.79. Found: C, 68.83; H, 6.49; N, 1.85.

(+)-*trans*-2-Hydroxy-3-isobutyl-9-benzyloxy-10-methoxy-1,2,3,4,6,7-hexahydro-11bHbenzo[a]quinolizine [(+)-4].- (-)-**2** di-*p*-toluoyl-L-tartrate (22.4 g, 28.6 mmole) was suspended in H_2O (400 mL) and concentrated NH_4OH (10.0 mL) was added. The pH was 10 by pH paper. The mixture was extracted by CH_2Cl_2 (3 x 400 mL) and the combined extracts were dried (Na_2SO_4), filtered and evaporated *in vacuo* to give 11.1 g (98%) of (+)-**4** as an off white solid: mp. 138-140°C; TLC single spot, R_f 0.79, [silica gel, $CHCl_3$:MeOH: concentrated NH_4OH (90:9:1)]; chiral HPLC single peak (100%), t_R 24.9 min, on a Phenomenex Chirex (S)-Val and (R)-NEA (250 x 4.6 mm) using isocratic 97.5% A: 2.5% B at 1.0 mL/min with UV detection at 254 nm with solvent A being hexane/1,2-dichloroethane (5:1) and solvent B being 0.1% TFA/EtOH, (The other enantiomer has a t_R 18.1 min and was not observed in the analysis.)

^1H NMR ($CDCl_3$): δ 0.91 (d, 3H, J = 6.4 Hz), 0.93 (d, 3H, J = 6.4 Hz), 1.06 (ddd, 1H, J = 13.8, 10.3, 4.4 Hz), 1.48 (dd, 1H, J = 23.0, 11.2 Hz), 1.54-1.62 (m, 2H), 1.64-1.76 (m, 2H), 1.96 (apparent dd, 1H, J = 11.2 Hz), 2.42 (m, 1H), 2.55 (m, 2H), 2.96 (m, 1H), 2.99-3.08 (m, 2H), 3.11 (d, 1H, J = 11.2 Hz), 3.39 (m, 1H), 3.85 (s, 3H), 5.11 (s, 2H), 6.61 (s, 1H), 6.70 (s, 1H), 7.29 (apparent dd, 1H, J = 7.3, 7.3 Hz), 7.35 (apparent dd, 2H, J = 7.3, 7.3 Hz), 7.42 (d, 1H, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$): δ 21.7, 24.1, 25.3, 29.0, 39.6, 40.5, 41.6, 51.8, 56.1, 59.9, 60.8, 70.9, 74.5, 108.4, 114.0, 126.2, 127.1, 127.6, 128.3, 129.8, 137.0, 146.5, 147.6; MS (ESI) (positive ion): *m/z* 396.6 (M+H); OR $[\alpha]_D^{22}$ +68.1° (c 1.016, $CHCl_3$). The ^1H NMR showed the sample was solvated with CH_2Cl_2.

Anal. Calcd. for $C_{25}H_{33}NO_3 \cdot 0.1\ CH_2Cl_2$: C, 74.62; H, 8.28; N, 3.47. Found: C, 74.83, 74.76; H, 8.39, 8.33; N, 3.49, 3.48 (duplicate analysis).

(+)-(2R,3R,11bR)-9-O-Desmethyl-α-dihydrotetrabenazine [(+)-5].- A 500 mL Parr bottle flushed with N_2 was added a solution of (+)-**4** (11.0 g 27.8 mmole) in EtOH (200 mL) then 10 wt % Palladium on carbon (0.50 g) was added and the mixture was hydrogenated at 40 psi H_2 for 6 h. TLC analysis [silica gel, $CHCl_3$:MeOH: concentrated NH_4OH (90:9:1)] showed no starting material remained in the reaction mixture. The reaction mixture was warmed on a steam bath to dissolve some of the product which had precipitated from the reaction mixture and filtered to remove the catalyst. The catalyst was rinsed with hot EtOH (3 x 100 mL) and the filtrates were evaporated *in vacuo* to give a yellow orange solid (8.36 g). The solid was recrystallized from MeOH/EtOAc to give 6.29 g (74%) of (+)-**5** as yellow orange crystals: mp. 206-208°C dec; TLC single spot, R_f 0.42, [silica gel, $CHCl_3$:MeOH:concentrated NH_4OH (90:9:1)]; Chiral HPLC single peak (100%), t_R 18.3 min, on a Phenomenex Chirex (S)-Val and (R)-NEA (250 x 4.6 mm) using isocratic 90% A: 10% B at 1.0 mL/min with UV detection at 254 nm with solvent A being hexane/1,2-dichloroethane (5:1) and solvent B being 0.5% TFA/EtOH; HPLC major peak (98.6%), t_R 7.1 min, on a Dynamax C_{18} column (5 μ) (4.6 x 250 mm) using a gradient (25% B to 65% B over 30 min) at 1.0 mL/min with UV detection at 220 nm, with solvent A being 0.1% TFA/H_2O and solvent B being 0.1% TFA/CHCN.

^{1}H NMR (CD_3OD, 500 mHz): δ 0.95 (d, 3H, J = 6.3 Hz), 0.97 (d, 3H, J = 6.3 Hz), 1.00-1.07 (m, 1H), 1.46 (dd, 1H, J = 23.9, 11.7 Hz,), 1.64-1.78 (m, 3H), 2.02 (apparent dd, 1H, J = 11.7 Hz), 2.43-2.52 (m, 1H), 2.56-2.66 (m, 1H), 2.97-3.06 (m, 4H), 3.18 (d, 1H, J = 11.2 Hz), 3.83 (s, 1H), 6.55 (s, 1H), 6.76 (s, 1H); ^{13}C NMR (CD_3OD): δ 23.2, 25.8, 27.6, 30.5, 41.8, 42.0, 43.0, 54.1, 57.6, 62.0, 63.5, 75.8, 110.5, 117.1, 128.6, 130.3, 147.3, 148.5; MS (ESI) (positive ion): *m/z* 306.4 (M+H); MS (ESI) (negative ion): *m/z* 304.7 (M-H); OR $[\alpha]_D^{22}$ +76.1° (c 1.052, MeOH). *Anal.* Calcd for $C_{18}H_{27}NO_3$: C, 70.79; H, 8.91; N, 4.59. Found: C, 70.64; H, 8.86; N, 4.55.

Acknowledgement.- This work was supported by the National Institute of Mental Health under Contract N01-MH-32005.

REFERENCES

1. G. Zheng, L. P. Dwoskin and P. A. Crooks, *The AAPS Journal*, **8**, E682 (2006).

2. R. Goswami, D. E. Ponde, M.-P. Kung, C. Hou, M. R. Kilbourn and H. F. Kung, *Nuclear Medicine and Biology*, **33**, 685 (2006).

3. M. Anlauf, R. Eissele, M. K.-H. Schafer, L. E. Eiden, R. Arnold, U. Pauser, Gunter Kloppel and E. Weihe, *J. Histochemistry & Cytochemistry*, **51**, 1027 (2003).

4. F. Souza, N. Simpson, A. Raffo, C. Saxena, A. Maffei, M. Hardy, M. Kilbourn, R. Goland, R. Leibel, J. J. Mann, R. Van Heertum and P. E. Harris, *J. Clin. Invest.*, **116**, 1506 (2006).

5. M. R. Kilbourn, L. C. Lee, M. J. Heeg and D. M. Jewett, *Chirality*, **9**, 59 (1997).

6. M. Kilbourn, *Med. Chem. Res.*, **5**, 113 (1995).

7. N. Whittaker, *J. Chem. Soc. (C)*, 85 (**1969**).

8. D. E. Schwartz, H. Bruderer, J. Rieder and A. Brossi, *Biochemical Pharmacology*, **15**, 645 (1966).

9. L. C. Lee, T. V. Borght, P. S. Sherman, Kirk A. Frey and M. R. Kilbourn, *J. Med. Chem.*, **39**, 191 (1996).

****