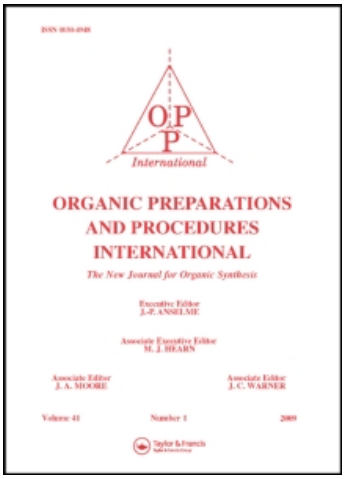



**Organic Preparations and Procedures International**
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

# IMPROVED SYNTHESIS OF TADALAFIL

Yunlong Zhang[a]; Qian He[a]; Huasheng Ding[a]; Xihan Wu[a]; Yuyuan Xie[a]
[a] State Key Laboratory of Drug Research, Institute of Materia Medica, Shanghai Institutes for Biological Sciences, Shanghai, PR CHINA

**To cite this Article** Zhang, Yunlong , He, Qian , Ding, Huasheng , Wu, Xihan and Xie, Yuyuan(2005) 'IMPROVED SYNTHESIS OF TADALAFIL', Organic Preparations and Procedures International, 37: 1, 99 — 102
**To link to this Article: DOI:** 10.1080/00304940509355408
**URL:** http://dx.doi.org/10.1080/00304940509355408

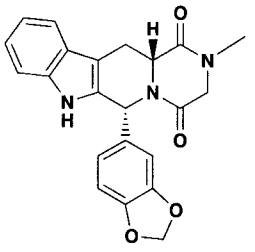
# IMPROVED SYNTHESIS OF TADALAFIL

*Submitted by* Yunlong Zhang, Qian He, Huasheng Ding, Xihan Wu* and Yuyuan Xie
(10/21/04)

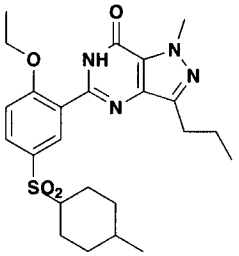
*State Key Laboratory of Drug Research, Institute of Materia Medica*
*Shanghai Institutes for Biological Sciences*
*Shanghai, 201203, P. R. CHINA*
*e-mail: xhwu@mail.shcnc.ac.cn*



Tadalafil (*Fig. 1*, *Cialis*™, Icos/Lilly),[1,2] which was approved in 2003 by the FDA for the treatment of male erectile dysfunction (MED), has elicited a great deal of interest in its analogues because of its decreased side-effects and significantly longer duration of action compared to Sildenafil (*Viagra*™, Pfizer).[3,4,5]



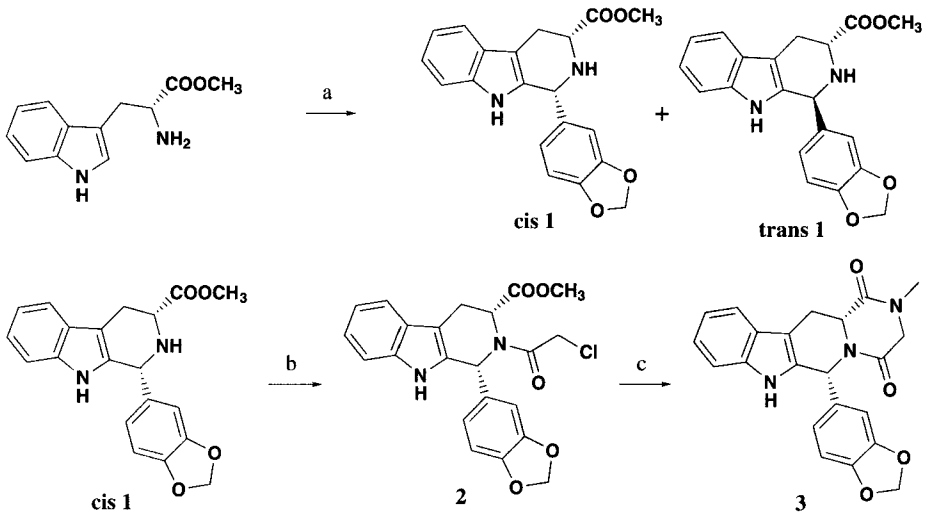
tadalafil



sildenafil

**Fig. 1**

The reported synthesis of tadalafil[1] is not without problematic steps. The *Icos* route (*Scheme 1*) which utilizes trifluoroacetic acid (TFA) to catalyze the Pictet-Spengler reaction not



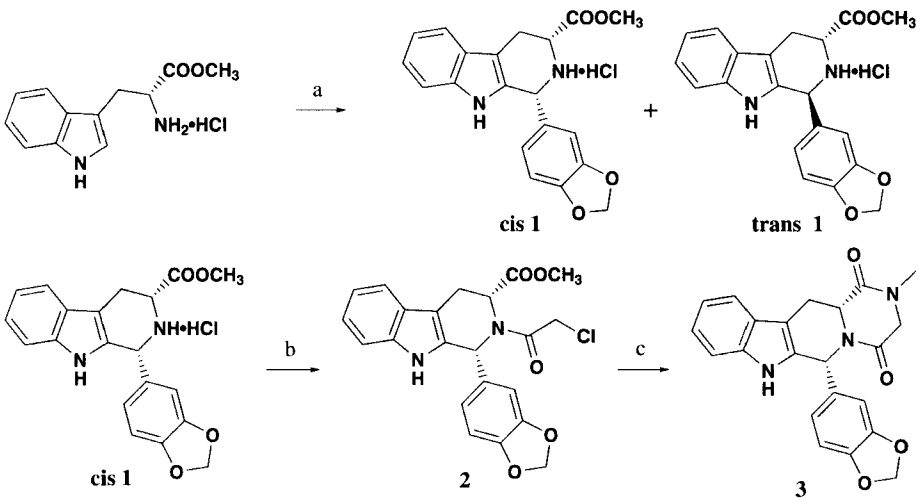
a) Piperonal (1.04 equiv), TFA (2 equiv), $CH_2Cl_2$, +4°C, 5 d (41%, 1.5:1 cis:trans); b) $ClCOCH_2Cl$ (2.4 equiv), $NaHCO_3$ (1.2 equiv), $CHCl_3$ (62%); c) $MeNH_2$ (3.8 equiv), MeOH, 50°C, 16 h (70%)

**Scheme 1**

only involves the use of low temperature (4°C) and long reaction times (5 days) but only gives moderate yields (41%) of the desired *cis*-diastereomer.

Some modifications have been suggested to overcome the drawbacks of the original sequence. Jefferson *et al.*[6] reported a method in which chloroacetyl chloride was used as the acylating reagent to promote the Pictet-Spengler of the N-acyliminium salt to **1** in *step a*. Although this modification has the advantage of eliminating the subsequent acylation step (*step b*), even lower reaction temperatures (–25°C) were required and produced the desired isomer in only modest yield (44%) and in poor diastereoselectivity (1.3:1 *cis*:*trans*). Orme *et al.*[7] proposed that the diastereoselectivity could be improved if D-tryptophan methyl ester hydrochloride was refluxed with piperonal in isopropyl alcohol. However, the relatively expensive isopropyl alcohol must be anhydrous and free from acetone.

In our effort to obtain tadalafil analogs, we found that 0.25 equiv of conc. hydrochloric acid can be used instead of TFA (2 equiv) for the traditional Pictet-Spengler reaction (*step a*) with a significantly higher yield (86%) of the desired *cis*-diastereomer (*Scheme 2*). Thus, D-tryptophan methyl ester hydrochloride was refluxed with piperonal for 36 h under the catalysis of




a) Piperonal (1.09 equiv), conc. HCl (0.25 equiv), methanol, reflux, 36 h, monitored by HPLC (85%, 10:1 cis:trans); b) $ClCOCH_2Cl$ (2.1 equiv), $NaHCO_3$ (2.4 equiv), $H_2O/CH_2Cl_2$ (78%); c) $MeNH_2$ (2.8 equiv), $CHCl_3$, reflux, 7 h (88%)

**Scheme 2**

methanolic hydrochloric acid (0.16 mol/L) and the *cis*-isomer precipitated as its hydrochloride salt while the *trans*-salt remained in solution. Presumably, under these conditions, the methanolic hydrochloric acid effects the epimerization at the indole C-1 by scission of the carbon-nitrogen bond,[12] and the different solubility in methanol between the isomer salts favors a more complete conversion to *cis*-isomer. In the second step, addition of a solution of chloroacetyl chloride in dichloromethane to an aqueous solution of *cis*-1 gave the desired product which could be isolated easily and did not require further purification. The product thus obtained was reacted with methylamine in refluxing chloroform to afford tadalafil in a good yield (88%) (*step c*).

In summary, we report a facile and diastereoselective route for the synthesis of tadalafil. This procedure has the advantages of higher yields and greater diastereoselectivity, easier work-up, and shortened reaction times.

## EXPERIMENTAL SECTION

Melting points were determined using a Büchi 510 melting point apparatus, and were not corrected. $^1$H NMR spectra were recorded on Varian Mercury Plus 400 MHz spectrometer. Microanalyses were carried out on a Leco CHN-200 elemental analyzer.

**Synthesis of *cis*-Tetrahydro-β-carboline Hydrochloride (*cis*-1).**- D-Tryptophan methyl ester hydrochloride (100 g, 0.39 mol) and piperonal (64 g, 0.43 mol, 1.09 equiv) were dissolved in methanol (600 mL), and conc. hydrochloric acid (8 mL, 0.25 equiv) was added. The progress of the reaction was monitored by HPLC. After refluxing for 36 hr with mechanical stirring, the mixture was stored in the refrigerator overnight. The solid which preciptated was collected and washed with ether (2 x 100 mL), and dried to afford the *cis*-tetrahydro-β-carboline hydrochloride (130 g, 85%) as a white solid, mp. 208-210°C, *lit.*[1] 209-212°C. EIMS: 350 ($M^+$, 36%), 307, 149, 70 (100%). $^1$H NMR ($CDCl_3$): δ 7.52 (d, 1H, $J$ = 7.4), 7.50 (s, 1H), 7.21 (d, 1H, $J$ = 7.7), 7.12 (m, 2H), 6.87 (d, 1H, $J$ = 7.9), 6.79 (m, 2H), 5.94 (s, 2H), 5.15 (s, 1H), 3.94 (dd, 1H, $J_1$ = 4.2, $J_2$ = 11.1), 3.80 (s, 3H), 3.20 (dd, 1H, $J_1$ = 4.2, $J_2$ = 15.1), 2.97 (dd, 1H, $J_1$ = 11.3, $J_2$ = 15.1).
HPLC details: Column: ZORBAX Elipse XDB-C 18, 4 x 150 mm; MeCN/$H_2O$ gradient: MeCN 0 min 15%, 20 min 85%; temperature: 25°C; flow rate: 0.6 mL/min; UV Det.: 285 nm; injection volume: 3 μL; retention Time: 17.5 min.

**Synthesis of N-Chloroacetylcarboline (2).**- The *cis*-isomer obtained above (116 g, 0.30 mol) and $NaHCO_3$ (60 g, 0.71 mol) were added into a mixture of 650 mL of water and 700 mL of $CH_2Cl_2$. After stirring for 2 h, a solution of 29 mL of chloroacetyl chloride (0.63 mol) in 50 mL $CH_2Cl_2$ was added dropwise over 2 h with ice-bath cooling and agitation; stirring was continued overnight without temperature control. The precipitate was collected and dried to give 100 g (78%) of colorless solid, mp. 227-230°C, *lit.*[1] 233°C. $^1$H NMR ($CDCl_3$): δ 7.75 (s, 1H), 7.60 (d, 1H, $J$ = 7.4), 7.38 (d, 1H, $J$ = 7.7), 7.19 (m, 2H), 6.90 (s, 1H), 6.84 (s, 1H), 5.66 (m, 2H), 5.92 (s, 2H), 4.94 (s, 1H), 4.35 (d, 1H, $J$ = 12.1), 4.22 (d, 1H, $J$ = 12.4), 3.67 (d, 1H, $J$ = 16.1), 3.18 (s, 3H), 3.18 (d, 1H, $J$ = 20.6).

**Synthesis of Tadalafil (3).**- Intermediate **2** (100 g, 0.23 mol) was suspended in 1500 mL of $CHCl_3$ and 80 mL of an ethanolic methylamine solution (0.65 mol, 33% in ethanol) was added. The mixture was refluxed for 7 h, the solvent was removed, and the residue washed with aqueous ethanol (water-ethanol 1:1), and dried under vacuum to afford 80 g (88%) of white solid, mp. 301-302°C, *lit.*[1] 302-303°C. $[\alpha]_D^{20}$ = +71 (c = 1.05, $CHCl_3$), *lit.*[1] $[\alpha]_D^{20}$ = + 71 (c = 1.00, $CHCl_3$). EIMS: 389 (M, 100%), 390, 262, 204. $^1$H NMR ($CDCl_3$): δ 7.80 (s, 1H), 7.61 (d, 1H, $J$ = 6.7), 7.28 (d, 1H, $J$ = 6.4), 7.17 (m, 2H), 6.87 (d, 1H, $J$ = 7.9), 6.71 (m, 2H), 6.16 (s, 1H),

5.58 (d, 2H, $J$ = 9.6), 5.30 (s, 1H), 4.32 (dd, 1H, $J_1$ = 11.9, $J_2$ = 5.0), 4.03 (m, 2H), 3.79 (dd, 1H, $J_1$ = 16.3 $J_2$ = 4.9), 3.21 (dd, 1H, $J_1$ = 15.9 $J_2$=11.6), 3.10 (s, 3H).

*Anal.* Calcd for $C_{22}H_{19}N_3O_4$: C, 67.86; H, 4.92; N, 10.79. Found: C, 67.84; H, 4.66; N, 10.81

## REFERENCES


1. A. C. Daugan, PCT Int. WO 9519978; *Chem. Abstr.*, **124**, p55977h (1996).

2. A. C. Daugan, P. Grondin, C. Ruauld, A.-N. Le Monnier de Gouville, H. Coste, J. M. Linget, J. Kirilovsky, F. Hyafil, and R. Labaudinière, *J. Med. Chem.*, **46**, 4533 (2003).

3. M. N. Graham, A. M. N. Charlotte, G. Eugene and Million A.William., *Bioorg. Med. Chem. Lett.*, **13**, 1425 (2003).

4. W. Jiang, Z. Sui, M. J. Macielag, S. P. Walsh, J. J. Fiordeliso, J. C. Lanter, J. Guan, Y. Qiu, P. Kraft, S. Bhattacharjee, E. Craig, D. Haynes-Johnson, T. M. John, and J. Clancy, *J. Med. Chem.*, **46**, 441 (2003).

5. L. A. Sorbera, L. Martin, P. A. Leeson and J. Castañer, *Drugs of the Future*, **26**, 15 (2001)

6. R. D. Revell, N. Srinivasan and A. Ganesan, *Synlett*, 1428 (**2004**).

7. M. W. Orme, M. J. Martinelli, C. W. Doecke and J. M. Pawlak, PCT Int. WO2004011463, *Chem. Abstr.*, **140**, 146170m (2004).

8. P. D. Bailey, M. H. Moore, K. M. Morgan, D. I. Smith and J. M. Vernon, *Tetrahedron Lett.*, **35**, 3587 (1994).

9. P. D Bailey, S. P. Hollinshead and N. R. McLay, *Tetrahedron Lett.*, **28**, 5177 (1987).

10. P. Zhang and J. M. Cook, *Tetrahedron Lett.*, **36**, 6999 (1995).

11. H. Yamada, T. Kawate, M. Matsumizu, A. Nishida, K. Yamaguchi, and M. Nakagawa, *J. Org. Chem.*, **63**, 6348 (1998).

12. E. D. Cox and J. M. Cook, *Chem. Rev.*, **95**, 1797 (1995).