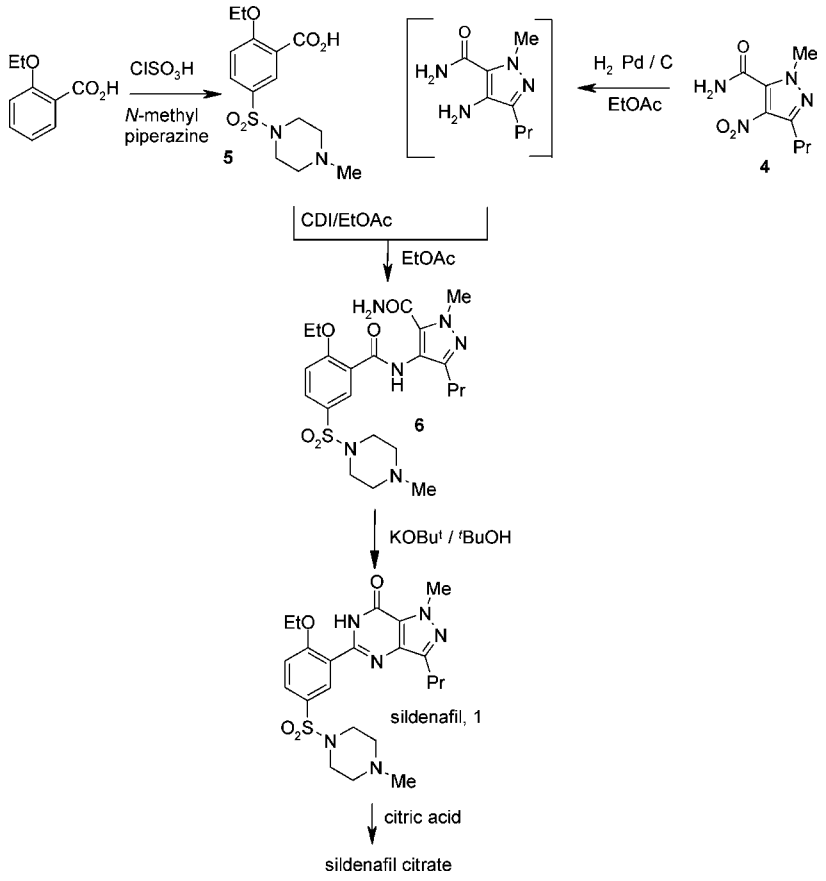
Scheme 1. **Commercial synthesis of sildenafil citrate**



single solvent (ethyl acetate) for the three telescoped steps (allowing easy solvent recovery without the need to fractionally separate different solvents) ensure that the environmental profile of the process is very clean.[5]

2.2. Convergent Syntheses of Sildenafil. The final steps for convergent syntheses of sildenafil which have been reported in the literature (including patents) are shown in Scheme 2. The condensation of the aldehyde **7** with the aminopyrazole **8** in boiling toluene yields dihydrosildenafil **9**. The yield can be improved from 52 to 95% by using an azeoptropic distillation to remove the water byproduct. Dihydrosildenafil **9** can be oxidised using Pd/C and a small quantity of trifluoroacetic acid at high temperatures or using sodium hydrogen sulphite to give sildenafil. This chemistry has been reported by Pfizer[6] and by Achmatowicz et al..[7] When sodium hydrogen sulphite is used as the oxidizing reagent, the overall yield from aminopyrazole **8** is 85%.

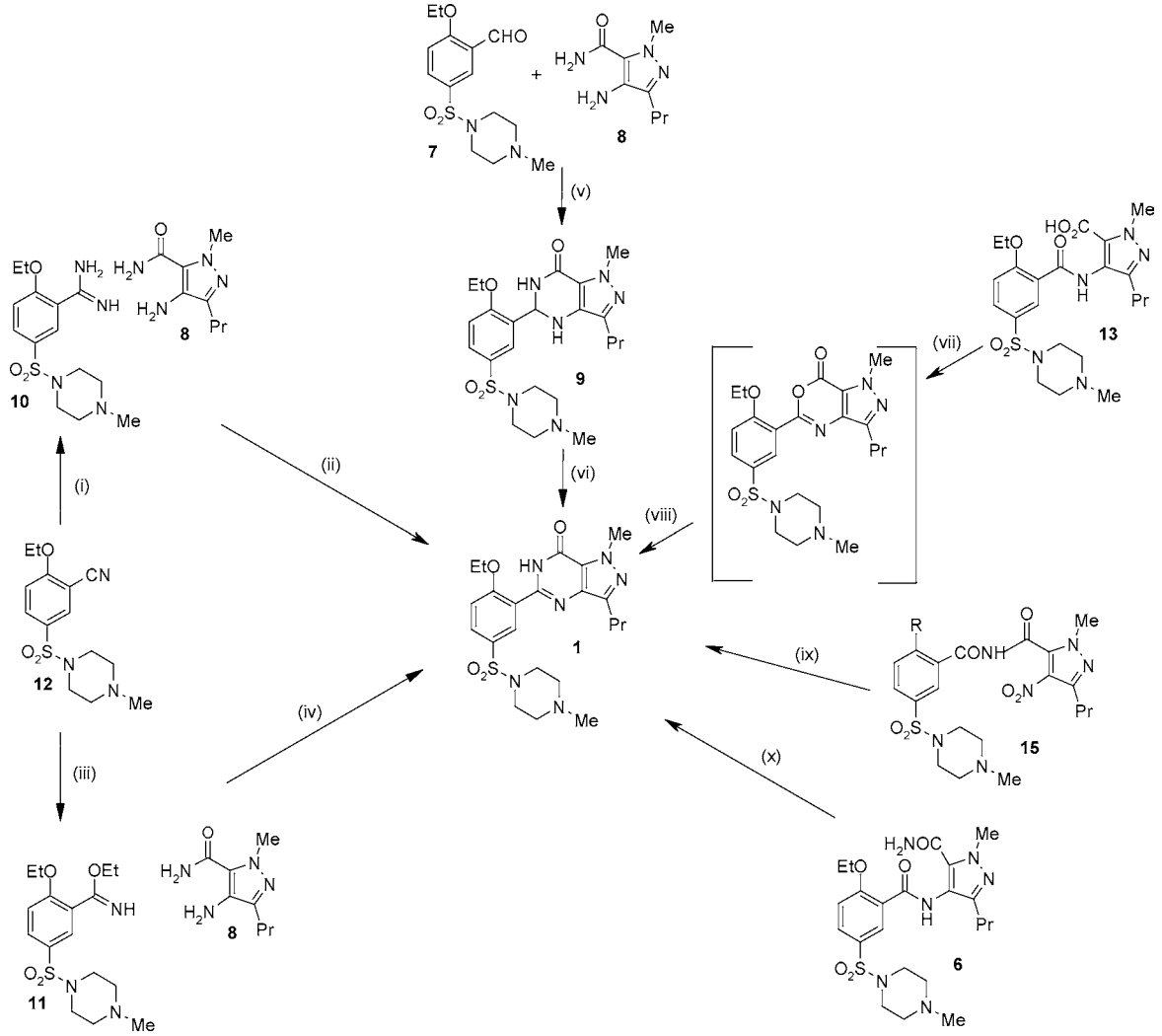
It is tempting to build the pyrimidine ring from either an amidine **10** or an iminoether **11**, and indeed both of these approaches have been reported by Pfizer.[8] The amidine can be made via reaction of the respective nitrile **12** with chloromethylaluminium amide (prepared from ammonium chloride and trimethyl aluminium). The iminoether **11** is made from the nitrile **12** by a Pinner reaction.[8]

Ring closure of the acid intermediate **13** using thionyl chloride to give the lactone which can be reacted with ammonia to give the pyrazolopyrimidinone would be a way of making sildenafil. This approach has not been used to prepare sildenafil itself, though the intermediate **14** (see Scheme 5) has been prepared in this way.[9] In addition, workers at Glaxo-Wellcome[10] have also shown that pyrimidines with PDE inhibitory activity can be prepared using this methodology. The nitrocompound (**15**, R = F) was prepared by workers at the Sanxiong company in China[11] by *N*-acylation of the amide group of pyrazole **4** with 2-fluorobenzoyl chloride (65% yield). This was followed by chlorosulphonation and sulphonamide formation (75%) to give (**15**, R = F). The nitrogroup is then reduced with tin-(II) chloride, and the resulting amine is cyclised. Finally the fluorine atom is displaced with the ethoxide group to give sildenafil.[11]

Ring closure from intermediate **6** is of course the commercial synthesis. However, two variants of this are to chlorosulphonate the intermediate **16** and convert to the sulphonamide **6** before the cyclisation[12] as shown in Scheme

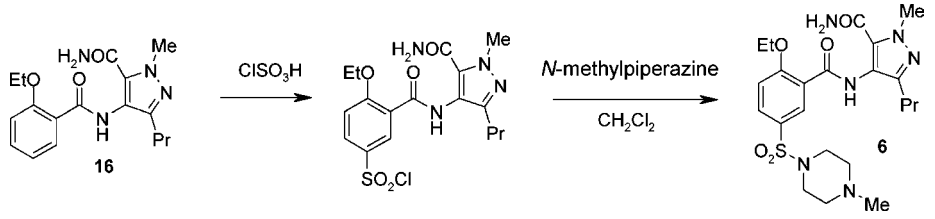
(5) Dunn, P. J.; Galvin, S.; Hettenbach, K. *Green Chemistry* **2004**, *6*, 43−48.
(6) Bunnage, M. E.; Levett, P. C.; Thomson, N. M. World Patent, WO 01/98303.
(7) Achmatowicz, O.; Balicki, R.; Chmielowiec, U.; Zaworska, A.; Szelejewki, W.; Magielka, S, Glowacka, A.; Wysoczynska, M.; Dzikowska, J.; Bober, L.; Landsberg, J.; Falkowski, C.; Roznerski, Z.; Marczak, B.; Kempa, A. World Patent, WO 01/22918.
(8) Dunn, P. J.; Dunne, C. World Patent, WO 01/98284.
(9) Dunn, P. J. Unpublished results.
(10) Dumaitre, B.; Dodic, N. *J. Med. Chem.* **1996**, *39*, 1635−1644.
(11) Yang, D.; Wang, H.; Shi, H. Chinese Patent CN 99-111153, 2001 (*Chem. Abs.* **2001**, *135*, 242238) and Yang, D.; Wang, H.; Shi, H. Chinese Patent CN-109345 (*Chem. Abs.* **2001**, *135*, 107334).
(12) Chaudhari, D. T.; Deshpande, P. B.; Khan, R. A. R. European Patent, EP 1 002 798.

Scheme 2. **Convergent Syntheses of Sildenafil with Final Pyrimidinone Ring Formation**[a]



[a] (i) Me_3Al (2 M in hexane), NH_4Cl, toluene, **12**, 5 °C then 80 °C (58%); (ii) **10**, **8** Δ xylene (7%); (iii) **12**, ethanol, HCl (g), 0 °C (48%); (iv) **11**, **8**, Δ xylene (85%); (v) **7**, **8** Δ toluene (52%) or **7**, **8** Δ toluene with azeotropic H_2O removal (95%); (vi) **9**, Pd/C, TFA, toluene 200 °C (84%) or **9**, $NaHSO_3$, Δ DMAc (90%); (vii) $SOCl_2$; (viii) NH_3, EtOH; (ix) $SnCl_2$, EtOH, 65 °C, 3 h (85%); (x) KOBu^t, Δ ^{t}BuOH, 6−8 h (95%).

Scheme 3. **Alternative synthesis of intermediate 6**

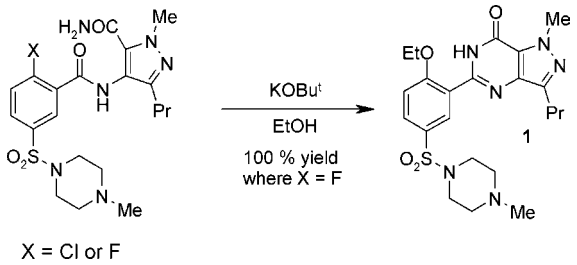


3. The second variant is to combine the cyclisation reaction with a nucleophilic displacement of a leaving group, such as chlorine or fluorine, preferably using ethanol as solvent and either ethoxide or a hindered alkoxide as base. This approach (shown in Scheme 4)[13] is interesting commercially, as 2-chlorobenzoic acid is cheaper than 2-ethoxybenzoic acid.

2.3. Nonconvergent Syntheses of Sildenafil. Not surprisingly there has been a lot of patent activity in producing nonconvergent syntheses of sildenafil. These approaches are summarised in Scheme 5.

Reduction of the carbamate **17** to sildenafil has been reported by workers at the Torcan company[14] in 61% yield,

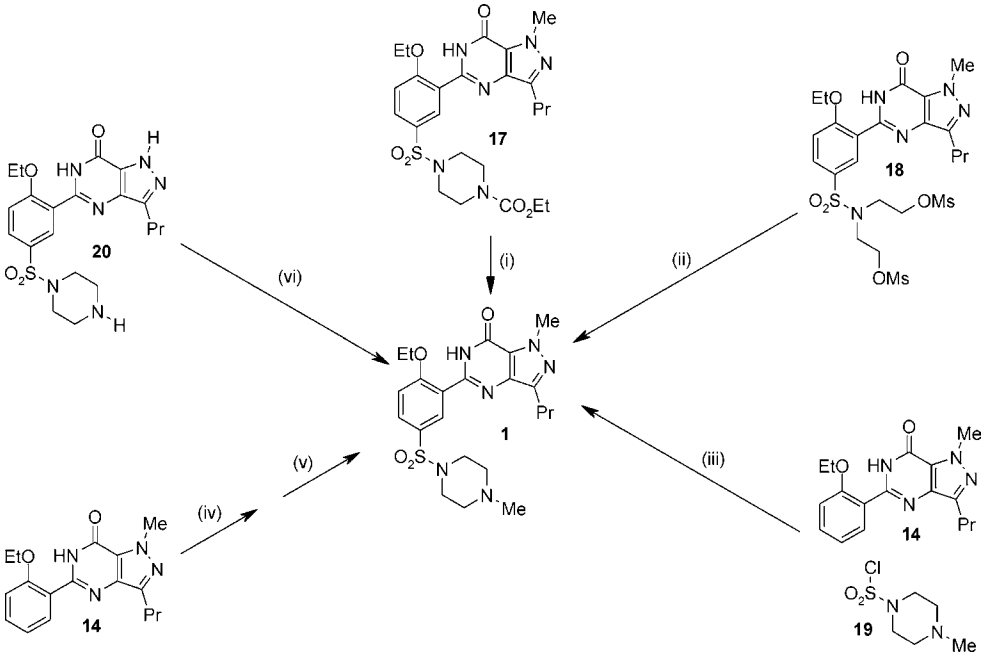
Scheme 4. **Cyclisation with simultaneous nucleophilic displacement**



though no information is given about the levels of formation of the secondary amine. The Torcan company have also

(13) Dunn, P. J.; Levett, P. C. European Patent, EP 0 994 115.

Scheme 5. **Nonconvergent syntheses of sildenafil**[a]



[a] (i) $LiAlH_4$, THF, 20−25 °C (61%); (ii) $MeNH_2$, EtOH, 25 °C (no yield given); (iii) **14**, **19**, $AlCl_3$, Δ CH_3NO_2 (45%); (iv) $ClSO_3H$, 25 °C; (v) *N*-methylpiperazine, toluene or methanol, 30 °C (73% over two steps); (vi) CH_2O (aq), HCO_2H, 50−60 °C (77%).

reported the synthesis of sildenafil by final step formation of the piperazine ring by reacting the dimesylate **18** with methylamine though no yields are given.[14] The synthesis of sildenafil using a Friedel−Crafts type reaction from pyrazolopyrimidinone **14** and the sulphamoyl chloride **19** (prepared from *N*-methylpiperazine and SO_2Cl_2[15]) has been reported by workers at the India Orchid company.[16] Chlorosulphonation of the pyrazolopyrimidinone **14** followed by sulphonamide formation was the original route of synthesis used by medicinal chemists at Pfizer.[17] Workers at the Cipla company have reported a synthesis of sildenafil which involves a double methylation of the intermediate **20** as the final step using formaldehyde and formic acid, though no information is given with respect to regioselectivity of the methylation on the pyrazole ring.[18]

2.4. Synthesis of Pyrazole 4. Pyrazole **4** is a key intermediate in the Pfizer commercial synthesis of sildenafil; it is the final isolated intermediate before the point of convergence in the commercial route. Not surprisingly, this compound has attracted the attention of a number of fine chemical companies leading to a number of patents and some excellent synthetic work.

Most published syntheses start from 2-pentanone, and the first stage is the condensation reaction with the diester of oxalic acid. A key point in this reaction is that the desired product is the thermodynamic product, so to obtain the best ratio it is necessary to age the reaction mixture as illustrated

Scheme 6. **Condensation of ketones with diethyl oxalate**

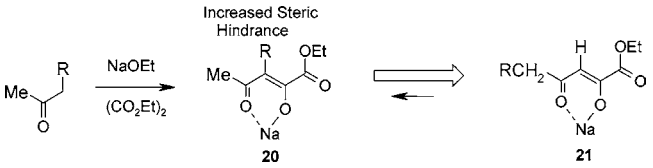
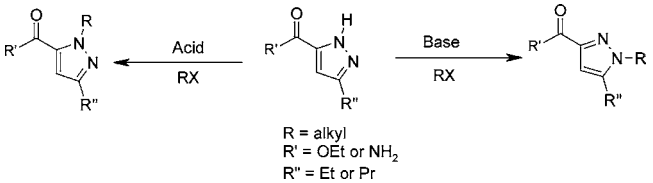


Table 1. **Initial and aged regiochemistry for the condensation of ketones and diethyl oxalate**

ketone	initial regiochemistry **21:20**	"aged" regiochemistry **21:20**
R = Me	1:1	8:1
R = Et	8:1	98:2
R = ^{i}Pr	98:2	>500:1

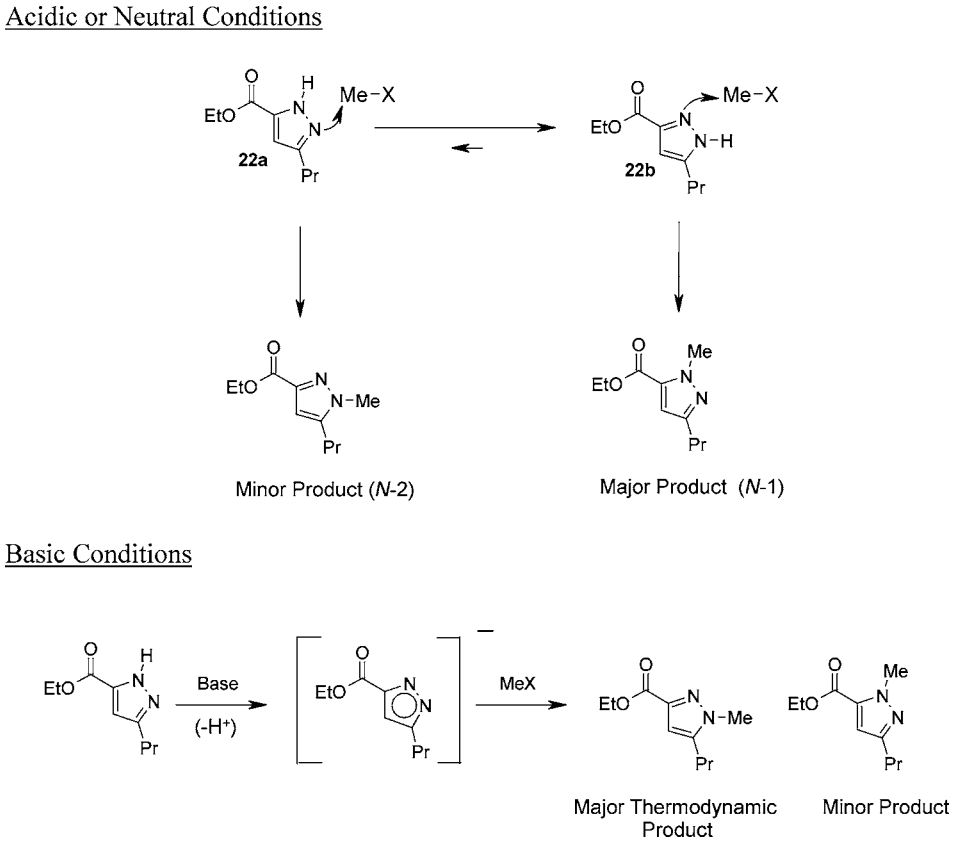
Scheme 7. **Alkylation of pyrazoles**



in Scheme 6 and Table 1.[19] The regiochemistry also improves as the steric hindrance of the R group increases (Me to Et to ^{i}Pr) and one plausible explanation for the observed effects is that the steric hindrance around the R group drives the reaction over to the thermodynamic product **21**. For sildenafil the desired product is shown in entry 2 in Table 1 (R = Et), with a 98:2 ratio of the desired product to the undesired regioisomer obtained after the reaction has been aged for several hours at 40 °C.

(14) Lu, Y.-F.; Antczak, C.; Tao, Y.; Oudenes, J. Canadian Patent 2 235 642.
(15) Matier, W. L.; Comer, W. T.; Deitchman, D. *J. Med. Chem.* **1972**, *15*, 538−541.
(16) Chaudhari, D. T.; Deshpande, P. B.; Khan, R. A. R. European Patent, EP 1 077 214.
(17) Bell, A. S.; Brown, A. S.; Terrett, N. K. European Patent, EP 0 463 756, 1991. Terrett, N. K.; Bell, A. S.; Brown, D.; Ellis, P. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1819−1824.
(18) Kankan, R. N. R.; Rao, D. R. World Patent, WO 01/19827.
(19) Dunn, P. J. Results presented at the Second Florida Heterocylic Chemistry Meeting 7th−9th March, 2001.

Scheme 8. **Ring methylation regioselectivity**



With the regiochemistry in the condensation reaction optimised, the next stage is to form the pyrazole. This can be done by reaction with hydrazine followed by methylation[17] or alternatively by reaction with methylhydrazine (see later). For the alkylation reaction there is a tendency to obtain the desired *N*-1 isomer under acidic or neutral conditions[17] and the undesired *N*-2 isomer under basic conditions[9] (Scheme 7).

There have been a number of theories put forward as to the reason for the observed regioselectivity,[20] but perhaps the most plausible explanation is that the *N*-2 isomer [such as pyrazole **22b**] is the most stable tautomer, so, under acidic or neutral conditions, the lone pair on the *N*-2 nitrogen is delocalised into the pyrazole ring and reaction takes place at the "pyridine-like" nitrogen to give the *N*-1 alkylated isomer as the major product. Under basic conditions there is formation of the anion which leads to the more stable *N*-2 isomer (Scheme 8). Supporting evidence for this hypothesis is that 5-alkylpyrazole-3-carboxylates have been shown to exist in the tautomer like **22b** in the solid state by X-ray crystallography.[21] In addition, NMR studies show that tautomers such as **22b** predominate over **22a** in solution.[21]

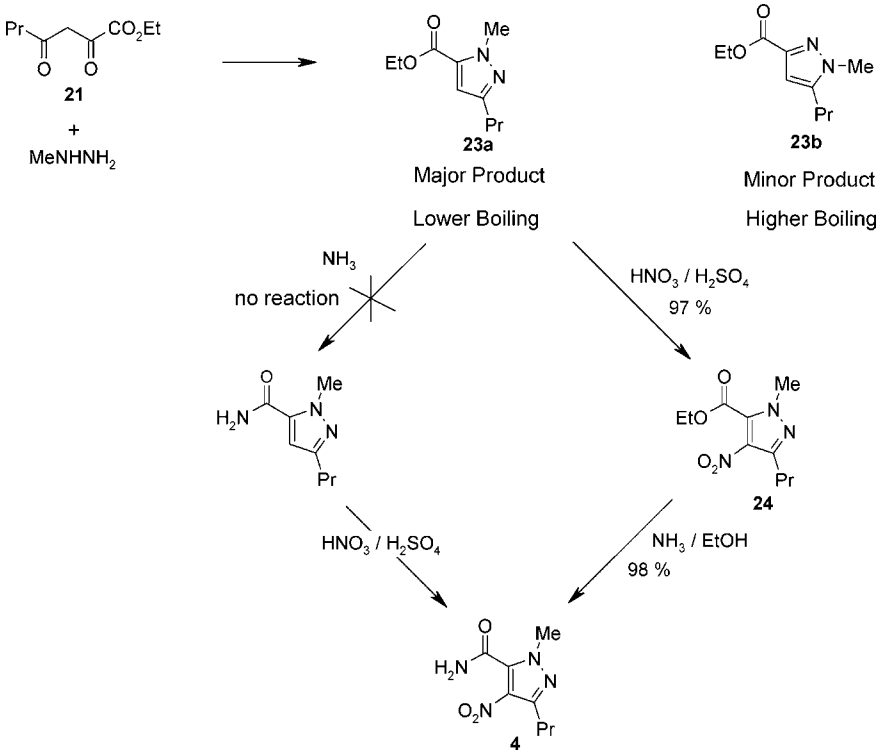
The *N*-1 isomer, formed under acidic or neutral conditions, can then be converted into pyrazole **4** by hydrolysis, nitration, and amide formation.[4,17]

Pyrazole **4** may also be prepared by reaction of **21** with methylhydrazine (Scheme 9). Under certain conditions this reaction can have a poor regioselectivity.[22] However some very interesting work reported in the patent literature[23] shows that if **21** is added to methylhydrazine in ethanol, then the desired pyrazole **23a** is formed as a 10:1 mixture with the minor regioisomer **23b**. If the addition is reversed and methylhydrazine is added to **21** in the same solvent (ethanol) and at the same temperature (5−10 °C), then the ratio of **23a** to **23b** is reversed to 4:5. The 10:1 mixture of regioisomers formed under the best conditions was readily separated by distillation with the desired isomer boiling at 125−128 °C/13 mm which is 40 °C lower than that of the undesired regioisomer.[23] This led to a 78.3% overall yield of pyrazole **23a** from methylhydrazine.[23,24]

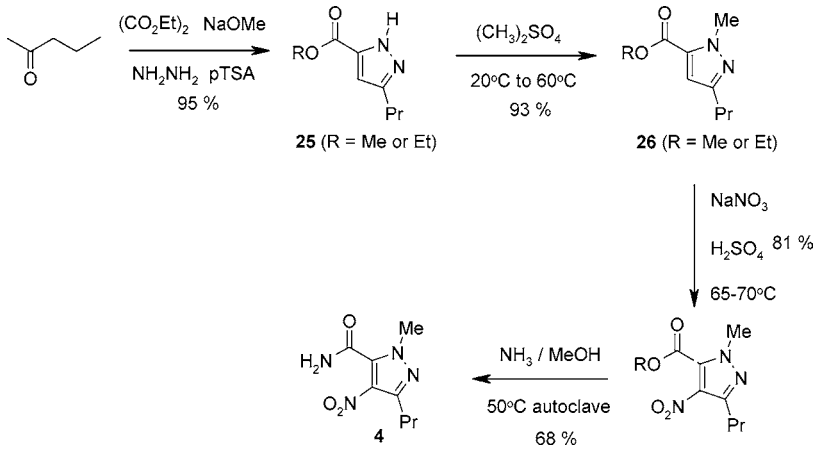
To complete the synthesis, a nitration reaction is required followed by an ammonolyis reaction. Workers at Bayer AG[25] have reported these transformations as highly efficient processes (Scheme 9). The pyrazole **23a** is nitrated with anhydrous nitric acid using anhydrous sulphuric acid as solvent. After quenching, extraction, and evaporation, the resulting nitroester is obtained, as an oil, in 97% yield. The nitro ester **24** is then converted through to the amide **4** using methanolic ammonia at 50 °C. The yield for the ammonolysis is 98%, and hence the overall yield from methylhydrazine to pyrazole **4** is 74.7% and the overall yield from methyl-

(20) Lednicer, D. In *The Organic Chemistry of Drug Synthesis*; Wiley-Interscience: New York; Vol. 6, p 180 [ISBN 0-471-24510-10 (v6)].
(21) Lourdes, I.; Concepcion, F.-F.; Rosa, M. C.; Concepcion, L.; Jagerovic, N.; Elguero, J. *Heterocycles* **1999**, *50*, 227−242.
(22) Kopp, M.; Lancelot, J.-C.; Dallemange, P.; Rault, S. *J. Heterocycl. Chem.* **2001**, *38*, 1045−1050.
(23) Muller, N.; Matzke, M. U.S. Patent 6,444,828 (note under certain conditions the regiochemistry for the methylhydrazine reaction can be 13:1).
(24) Muller, N.; Matzke, M. U.S. Patent 6,297,386.
(25) Heuer, L.; Muller, N.; Steffan, G. European Patent, EP 0 819 678, in German, same authors U.S. Patent 5,969,152, 1999 and U.S. Patent 6,025,499, in English.

Scheme 9. **Synthesis of pyrazole 4**



Scheme 10. **Alternative synthesis of pyrazole 4**



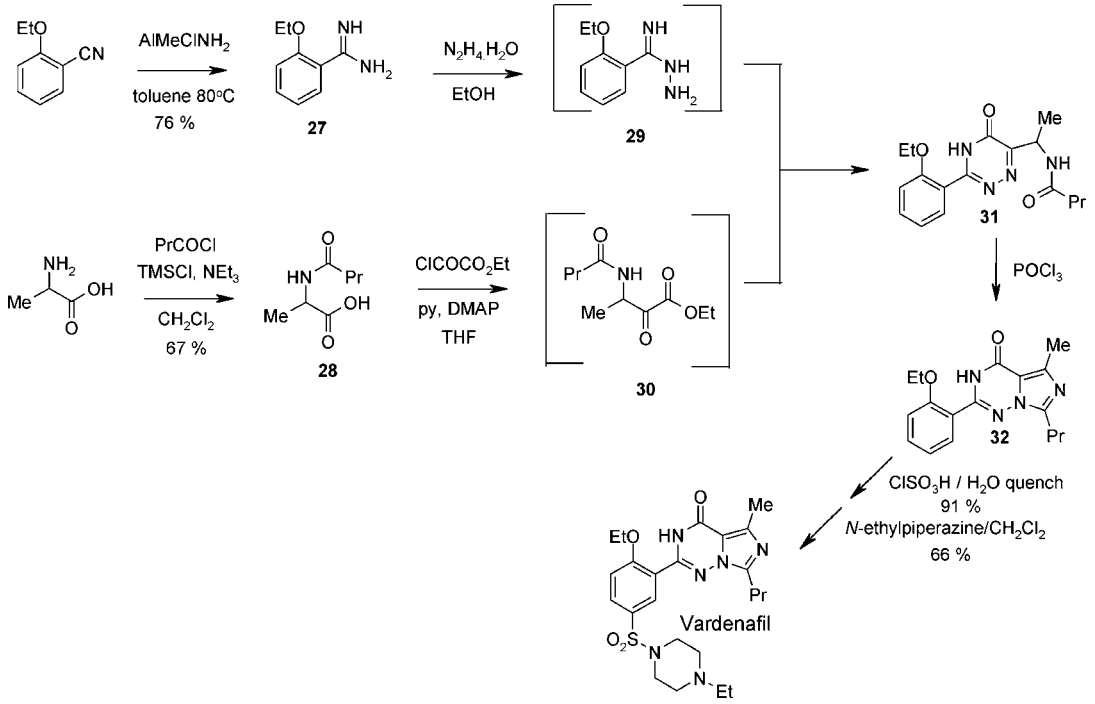
hydrazine to sildenafil citrate is 67%. The order in which the nitration and ammonolysis reactions are performed is crucial because it has been shown that ammonolysis of the unnitrated pyrazole **23a** does not occur at useful processing temperatures (Scheme 9).[9] The electron-withdrawing power of the nitro group, in conjugation with the carbonyl group, activates the ester to ammonolysis.

Another way of activating the ammonolysis reaction was published by Ley and Baxendale from Cambridge University.[26] The nitro group in the nitro ester **24** is first reduced to the amine, and then reaction with methanolic ammonia takes place at room temperature. It is interesting to speculate how the amino group activates the ammonolysis reaction. The Cambridge paper gives a synthesis of sildenafil using supported reagents at nearly every step. The late stage synthesis is based upon the synthetic strategy used by the Pfizer group.[4]

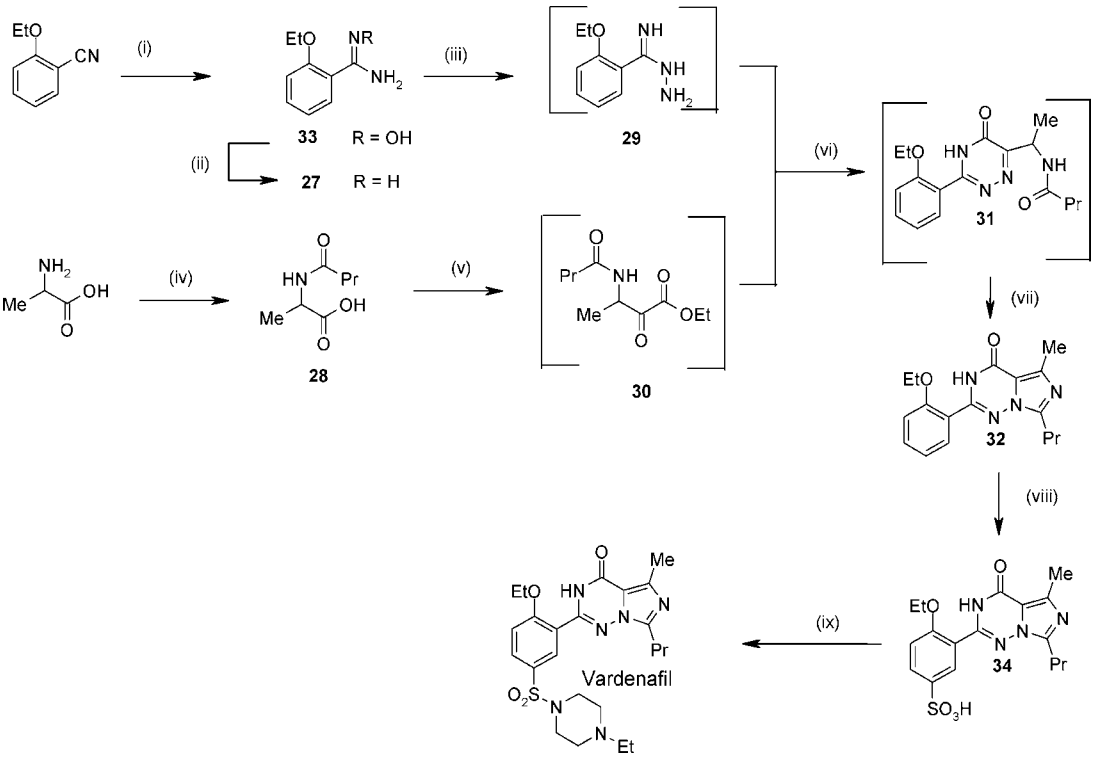
Workers at the India Orchid company[16] have shown that the condensation of 2-pentanone with diethyl oxalate may be catalysed by sodium methoxide which is cheaper than sodium ethoxide. After further condensation with hydrazine hydrate, the pyrazole **25** is obtained as a mixture of methyl and ethyl esters. Methylation with dimethyl sulphate is performed neat, as in the Pfizer medicinal chemistry synthesis.[17] This is a strongly exothermic process but gives excellent regioselectivity (better than when a cosolvent is used). The mixture of the methylated pyrazoles **26** is then nitrated and subjected to ammonolysis to give the desired pyrazole intermediate **4** (Scheme 10).

(26) Baxendale, I. R.; Ley, S. V. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1983−1986.

Scheme 11. **Medicinal chemistry synthesis of vardenafil**



Scheme 12. **Large-scale synthesis of vardenafil**[a]



[a] (i) $H_2NOH{\cdot}HCl$, NEt_3, Δ ^iPrOH, 68.2% yield on a 754 mol scale; (ii) H_2, Pd/C, HOAc, 50−60 °C; HCl, toluene; 90.7% yield on a 749 mol scale as HCl salt; (iii) $N_2H_4{\cdot}H_2O$, MeOH, 25 °C; (iv) PrCOCl, NaOH, H_2O, 68% on a 1122 mol scale; (v) $ClCOCO_2Et$, pyridine, DMAP (cat.) Δ THF; (vi) Δ MeOH; (vii) $POCl_3$, HOAc or AcCl, HOAc, 30 to 50.6% yield from **33** on a 957 mol scale; (viii) H_2SO_4, H_2O quench, 80.1% yield on a 621 mol scale; (ix) $SOCl_2$, DMF (cat.), xylene; *N*-ethylpiperazine, 93.2% yield on a 57.3 mol scale.

3. Vardenafil

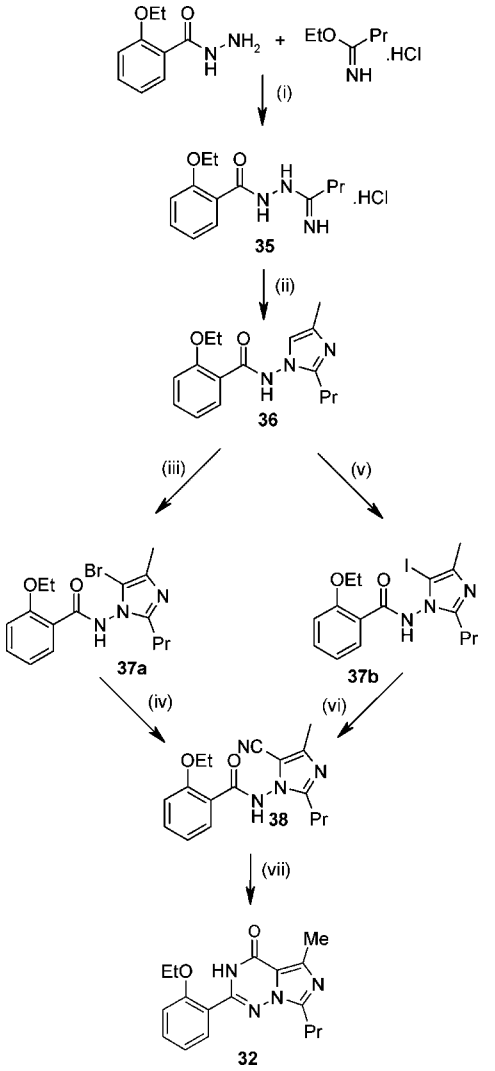
The medicinal chemistry synthesis of vardenafil (Levitra) is shown in Scheme 11.[27] The synthesis is based on a general route to imidazolotriazinones published by Hartley from Glaxo[28] and the chemical development and scale-up described by Marshall.[29] In the initial stages, 2-ethoxybenzonitrile is converted to the amidine **27** by reaction with $AlMeClNH_2$[30] (prepared from $AlMe_3$ and NH_4Cl).[31] Alanine is acylated to give **28** using in situ protection of the acid as the silyl ester. The next four reactions are then carried out without isolation. The amidine **27** is converted to the amidrazone **29** by reaction with hydrazine hydrate. The

acylated amino acid **28** is subjected to a Dakin−West reaction to give the intermediate **30** which reacts with the amidrazone to give **31**. In the general method to imidazolotriazinones, the Glaxo workers[28,29] used a high temperature cyclisation in polyphosphoric acid. For vardenafil, the dehydration/cyclisation reagent to give **32** was changed to $POCl_3$. The overall yield for the four nonisolated reactions is around 30% in the discovery paper. The imidazolotriazinone **32** is converted to vardenafil by chlorosulphonation and sulphonamide formation[27] in a sequence analogous to that in the medicinal chemistry synthesis of sildenafil.[17] Vardenafil is marketed as tablets made from the trihydrate of the hydrochloride salt.

A larger scale synthesis of vardenafil has also been reported,[32] and the reaction conditions and reported reaction scales are summarised in Scheme 12. The main changes are that the amidine **27** is now prepared via the amidoxime **33** which is hydrogenated over Pd/C in acetic acid and the resulting amidine **27** isolated as the hydrochloride salt. Acylation of racemic alanine to give **28** is performed using Schotten−Baumann conditions, and then the chemistry from **27** and **28** is again telescoped through four chemical reactions to give the imidazolotriazinone **32** with the yield improved to 50% under optimised conditions. In the medicinal chemistry route, chlorosulphonation of **32** was the next transformation; however there are difficulties in scaling up chlorosulphonation reactions (increased levels of hydrolysis during the increased quench times),[4] and in the large-scale synthesis, **32** is sulphonated to give the sulphonic acid **34** on a 195 kg scale.[32] The sulphonic acid **34** is reacted with thionyl chloride (catalysed by DMF) to give the sulphonyl chloride. Excess thionyl chloride is removed by distillation with xylene, and the resulting suspension is treated with *N*-ethylpiperazine to give vardenafil. Hence by using this method, quenching of the sulphonyl chloride on a large scale is avoided.

An alternative route to vardenafil intermediate **32** has been reported by Bayer[33] and is shown in Scheme 13. The amidrazone **35** is formed by reaction of an imidate and the acylhydrazine. The amidrazone **35** is then converted to the imidazole **36** by reaction with chloroacetone. The imidazole can then be electrophilically brominated or iodinated and either halide derivative converted to the nitrile by reaction with copper(I) cyanide. The nitrile **38** is hydrolyzed and cyclised to give the desired imidazolotriazinone **32** by heating in 48% sulphuric acid at 70 °C.

Scheme 13. **Alternative synthesis of vardenafil intermediate 32**[a]



[a] (i) Ethyl butanimidate hydrochloride, Et_3N (1 equiv), 2-ethoxybenzoylhydrazide (1 equiv), ^{i}PrOH, 25 °C, 48 h, 71.5% of **35** as the hydrochloride salt; (ii) **35** as HCl salt, K_2CO_3 (2 equiv), KI (0.7 equiv), chloroacetone (2 equiv), acetone, 15 °C, 20 h, 72%; (iii) **36**, HOAc, Br_2 (1.4 equiv), 25 °C, 3 h, 93%; (iv) **37a**, CuCN (2.9 equiv), pyridine, 100 °C, 6 h then further CuCN (0.47 equiv) added and the mixture heated for further 6 h at 100 °C, 80%; (v) **36**, Na_2CO_3 (3 equiv), I_2 (2.2 equiv), dioxan/water, 25 °C, 24 h, 81%; (vi) **37b**, CuCN (6.2 equiv), pyridine, 3 h, 100 °C, 80%; (vii) **38**, H_2SO_4, 2 h at 25 °C then 1 h at 70 °C, 50%.

4. Tadalafil

Tadalafil (Cialis) has a very different structure to sildenafil and vardenafil and is based upon a tetrahydro-β-carboline structure. Its synthesis is relatively straightforward and is based on the work of Anand[34] using four key building blocks namely, D-tryptophan methyl ester **39**, commercially available piperonal **40**, chloroacetyl chloride, and methylamine as shown in Scheme 14.

A useful summary of tadalafil (including a summary of synthesis) can be found in ref 35. The medicinal chemistry synthesis is shown in Scheme 15.[36,37]

In the medicinal chemistry synthesis (Scheme 15), (±)-tryptophan methyl ester **39** undegoes a Pictet−Spengler type

(27) Haning, H.; Niewohner, U.; Schenke, T.; Es-Sayed, M.; Schmidt, G.; Lampe, T.; Bischoff, E. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 865−868. Niewohner, U.; Es−Sayed, M.; Haning, H.; Schenke, T.; Schlemmer, K.-H.; Keldenich, J.; Bischoff, E.; Perzborn, E.; Dembowsky, K.; Serno, P.; Nowakowski, M. U.S. Patent 6,362,178 (see also Sorbera, L. A.; Martin, L.; Rabasseda, X.; Castaner, J. *Drugs Future* **2001**, *26*(2), 141−144).

(28) Isabel, C.; Latham, D. W. S.; Hartley, D.; Oxford, A. W.; Scopes, D. I. C. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1139−1146.

(29) Marshall, D. R. *Chem. Ind.* **1983**, 331−335.

(30) Garigipati, R. S. *Tetrahedron Lett.* **1990**, *31*, 1969−1972.

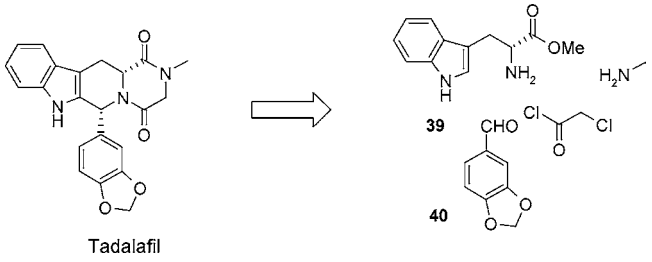
(31) Levin, J. I.; Turos, E.; Weinreb, S. M. *Synth. Commun.* **1982**, *12*(13), 989−993.

(32) Nowakowski, M.; Gehring, R.; Heilman, W.; Wahl, K.-H. World Patent, WO 02/50076.

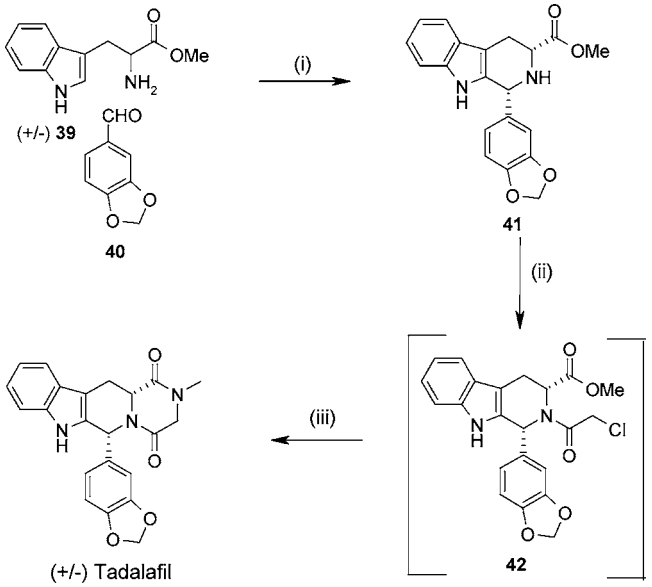
(33) Nowakowski, M.; Vetter, A. World Patent, WO 02/50075.

(34) Saxena, A. K.; Padam, C. J.; Anand, N.; Dua, R. R. *J. Med. Chem.* **1973**, *16*, 560−564 (see also Madrigal, A.; Grande, M.; Avendano, C. *J. Org. Chem.* **1998**, *63*, 2724−2727).

Scheme 14. **Building blocks for tadalafil**



Scheme 15. **Medicinal chemistry synthesis of tadalafil**[a]

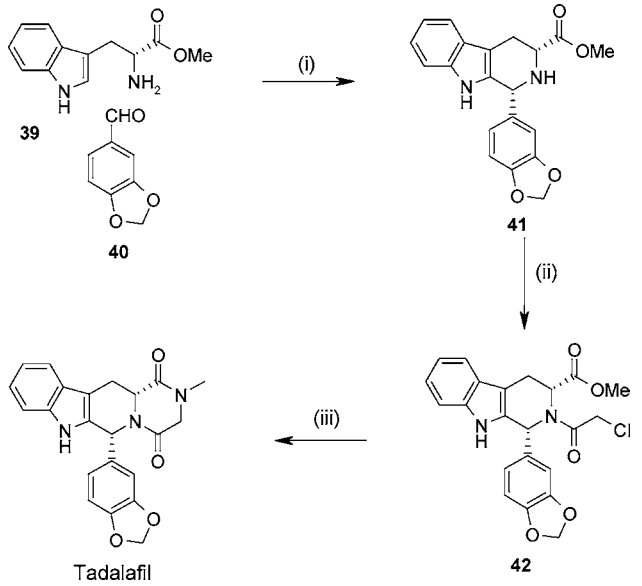


[a] (i) (±)-**39**, **40**, TFA, CH_2Cl_2, 0 to 25 °C, flash chrom. to separate cis (31%) from trans (31%); (ii) **41**, $ClCOCH_2Cl$, $NaHCO_3$, $CHCl_3$, 0 °C (82%); (iii) **42**, $MeNH_2$ (33% in EtOH), MeOH, 50 °C (61%).

reaction at ambient temperature. A mixture of the *trans*-isomer (31%) and the desired, lower melting *cis*-isomer **41** (31%) is obtained which can be separated by flash chromatography. Later patents indicate that the yield could be improved to 42% of the *cis*-isomer, with 28% of the *trans*-isomer for a reaction performed at 4 °C.[38] The *cis*-isomer **41** is acetylated with chloroacetyl chloride to give **42** which, following minimal purification, is reacted with methylamine to give (±)-tadalafil.

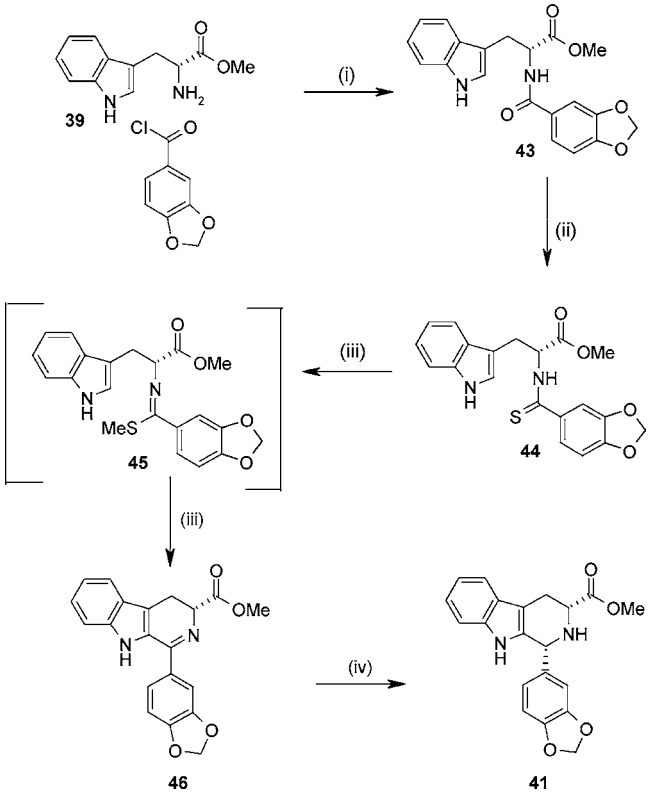
Subsequently, a large-scale chiral synthesis has been published in the patent literature;[39] the reaction conditions and reported reaction scales are shown in Scheme 16. The synthesis starts from the HCl salt of compound **39**. The use of the HCl salt eliminates the need to add TFA into the cyclisation reaction. In addition, the reaction solvent, 2-propanol, was found to solubilise the undesired *trans*-isomer, whereas the desired *cis*-isomer precipitates directly from the reaction. The isomers are in a dynamic equilibrium in solution; hence the insolubility of the *cis*-isomer drives the

Scheme 16. **Large-scale synthesis of tadalafil**[a]



[a] (i) D-Tryptophan methyl ester hydrochloride, **40** (1.1 equiv), ^{i}PrOH, 70−82 °C, 16−18 h; collect by filtration, 92% (196 mol scale); (ii) **41**, Et_3N (2.59 equiv), chloroacetyl chloride (1.39 equiv), 0−10 °C, THF, then stir for 2 h; concentrate, add ^{i}PrOH and H_2O; concentrate again and crystallise; cool to 20−25 °C and collect by filtration, 95% (216 mol scale); (iii) **42**, THF, $MeNH_2$ (5 equiv), 5−55 °C, 1 h; cool, add ^{i}PrOH and H_2O neutralise with 12 M HCl, concentrate, add IPA and H_2O, cool, crystallise, and collect by filtration, 95% (201 mol scale).

Scheme 17. **Alternative route to the tadalafil intermediate 41**[a]



[a] (i) D-Tryptophan methyl ester hydrochloride, piperonyloyl chloride (1.35 equiv), Et_3N (2.2 equiv), CH_2Cl_2, 0−25 °C, 2 h (100%); (ii) **43**, Lawesson's reagent (0.6 equiv), DME, 60 °C, 16 h (67%); (iii) **44**, MeI (6.8 equiv), CH_2Cl_2 at reflux (protected from light), 24 h; (iv) **46**, $NaBH_4$ (1.1 equiv), methanol, −78 °C, quench with acetone, 62% over two steps from compound **44**.

equilibrium over to the desired product. Hence a 92% yield of the *cis*-isomer is now obtained under the improved large-

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scale reaction conditions. Acylation of **41** is carried out using triethylamine as base. In the reported large-scale synthesis, the chloracetyl carboline **42** is isolated by crystallisation in 95% yield. Finally a condensation reaction between **42** and methylamine yields tadalafil. Hence the overall yield from D-tryptophan methyl ester was improved from 15%, in the medicinal chemistry synthesis, to 84% in the large-scale synthesis. The medicinal chemistry synthesis started from racemic **39** and therefore makes racemic tadalafil; however it was known in the literature[34] that the Pictet−Spengler reaction was stereospecific. The large-scale synthesis starts from D-tryptophan methyl ester hydrochloride and hence makes enantiomerically pure tadalafil.

An alternative route to tadalafil has also been published in the patent literature[40] and is shown in Scheme 17. D-Tryptophan methyl ester hydrochloride is acylated with piperonyloyl chloride to give the amide **43**. The amide is treated with Lawesson's reagent[41] to give the thioamide **44** which is alkylated with methyl iodide to give the thioimidate **45**. This compound undergoes cyclisation to give **46**. The dihydrocarboline **46** was reduced with sodium borohydride at −78 °C to give the desired *cis*-tetrahydrocarboline **41** in 62% yield from **44**. The tetrahydrocarboline **41** is then converted through to tadalafil using the methodology previously described in either Scheme 15 or 16. In the patent[40] several grams of tadalafil were prepared; however this route lacks the elegance and the atom efficiency[42] of the large-scale route described in Scheme 16.

5. Conclusions

This review demonstrates the innovation of process research and development chemists, in this case as applied to PDE5 inhibitors. The three pharmaceutical manufacturing companies have all developed greatly improved syntheses capable of producing large-scale batches. The innovation is not limited to the pharmaceutical manufacturing companies, and the syntheses of generic or fine chemical companies are also captured.

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