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MINI-REVIEW: THE CHEMISTRY OF VORAPAXAR – IS THERE ANY ROOM FOR IMPROVEMENT LEFT?

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This paper is dedicated to Professor Kaoru Fuji on the occasion of his 80th birthday.

Abstract – Based on the case of Vorapaxar, this review describes the key role of an early chemistry effort to enable rapid discovery of an optimal synthetic route to a commercially important product. The intramolecular Diels-Alder (IMDA) reaction developed by scientists from Schering to make natural product Himbacine in mid-'90s allowed formation of the Vorapaxar's backbone almost 10 years later. Since then this strategy has been followed by all companies. Additional improvements by Schering to the synthesis of Vorapaxar greatly limited the opportunities for generic manufacturers to secure new intellectual property. Most of the chemistry presented in this review comes from the patent applications and as such has not been subjected to rigorous peer review, but in our opinion this paper may serve as helpful information for readers in the area of drug discovery.

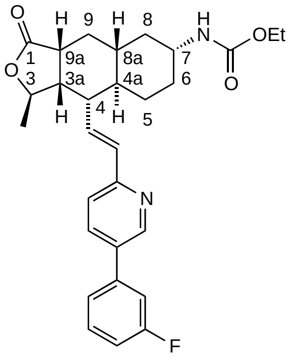
CONTENTS

1. INTRODUCTION

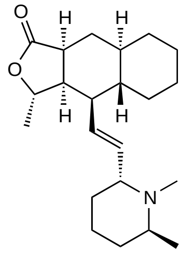
Typically, discovery of a new drug is accompanied by development of an original synthetic route, which is described in an early patent application devoted to the drug substance. Such route is usually gradually improved by the original inventors and later on by manufacturers of the generic drug form. An example where such improvements were truly significant has recently been described by us based on the case of tapentadol.[1] In this short review of the synthesis of Vorapaxar (**1**; SCH530348), we would like to present how the generic manufacturers have dealt with the issue of securing new intellectual property when the original inventors left little room for improvement. Vorapaxar (**1**) is the first thrombin receptor antagonist, which acts by reversible inhibition of protease-activated receptor-1 (PAR-1). Its structure is based on the natural product himbacine (**2**), although the scaffold configuration is inverted.

2. DISCUSSION OF SYNTHETIC STRATEGIES

Vorapaxar (**1**) was discovered by Schering-Plough and developed by Merck Sharp & Dohme for the treatment of acute coronary syndrome (ACS). In 2014 FDA approved Vorapaxar in the form of sulfate to reduce the risk of heart attacks and stroke in high-risk patients.[2] The EMA approval for the reduction of atherothrombotic events in adult patients with a history of myocardial infarction followed in 2015.[3] The marketing authorization in EU was later withdrawn for commercial reasons in 2017 at the request of Merck Sharp & Dohme.[4]

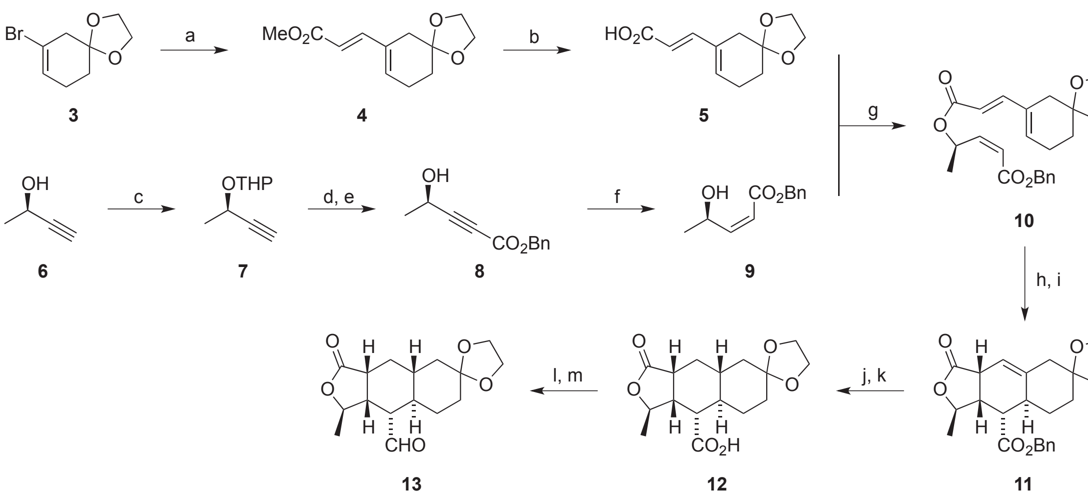


Vorapaxar (1)



Himbacine (2)

Synthetic strategy targeting **1** was built by scientists from Schering-Plough over a period of several years. The first steps leading to key aldehyde **13** (Scheme 1) were described in 2000 in their early patent application devoted to thrombin receptor antagonists.[5] The enantioselective intramolecular Diels-Alder reaction step (**10**→**11**) was adopted from the total synthesis of **2** developed earlier by Chackalamannil et al.[6]

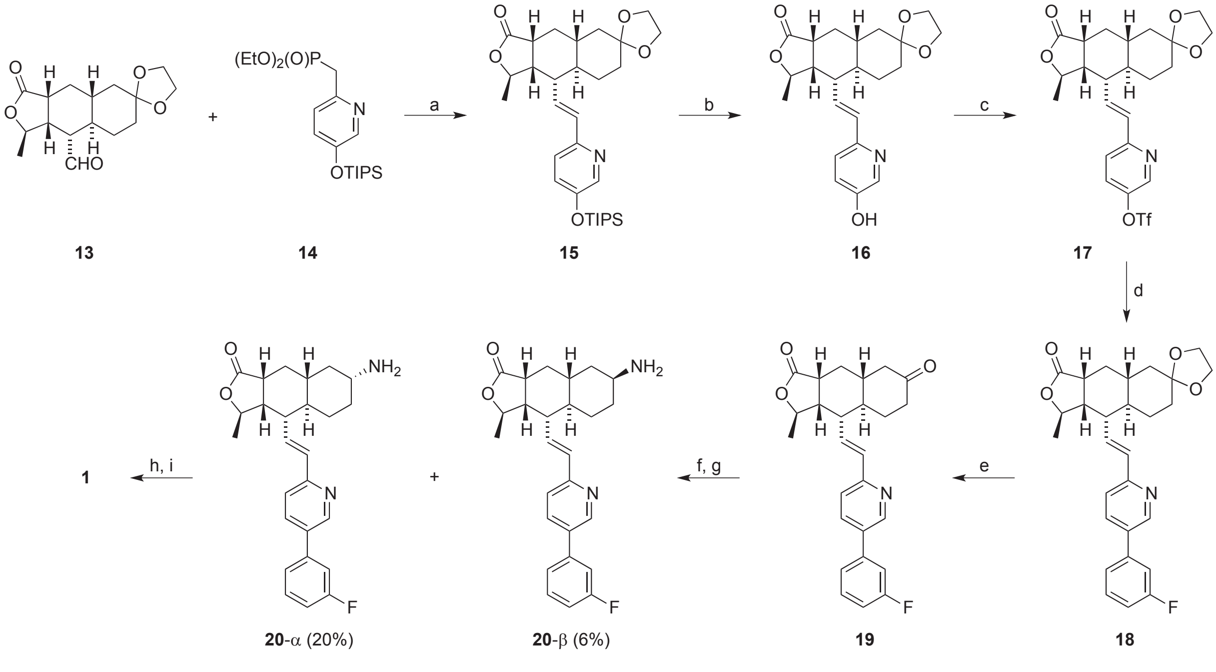


a) CH_2CHCO_2Me, $Pd(PPh_3)_2Cl_2$, Et_3N, DMF, 75 °C, 16 h; 71% b) 1.0 M NaOH, THF:MeOH=1:1 (v/v), rt, 4 h; 99% c) DHP, PTSA, 0 °C, 2 h; quant d) *n*-BuLi, THF, -78 °C, 20 min e) BnOC(O)Cl, THF, -78 °C, 2 h to rt; 71% f) H_2 (1 atm)/Lindlar, THF, 2.5 h, rt; 93% g) DCC, 4-pyrrolidinopyridine, DCM, 0 °C, 2 h to rt, 1 h; 79% h) xylene, 215 °C, 7 h i) DBU, THF, rt, 1 h; 48% j) H_2/10% Pd-C, AcOEt, rt k) H_2/PtO_2, AcOEt; 99% l) $SOCl_2$, toluene, 80 °C, 16 h m) Bu_3SnH, $Pd(PPh_3)_4$, toluene, 0 °C, 3 h; 48%

Scheme 1. Route of synthesis to the aldehyde **13** developed by Chackalamannil et al.[5]

The Lindlar reduction step (f) can also be performed after ester formation (g) and such strategy was used later on (cf Scheme 8).

Vorapaxar was first disclosed in patent application WO2003089428 where it was obtained from aldehyde **13** using the route shown in Scheme 2.[7]



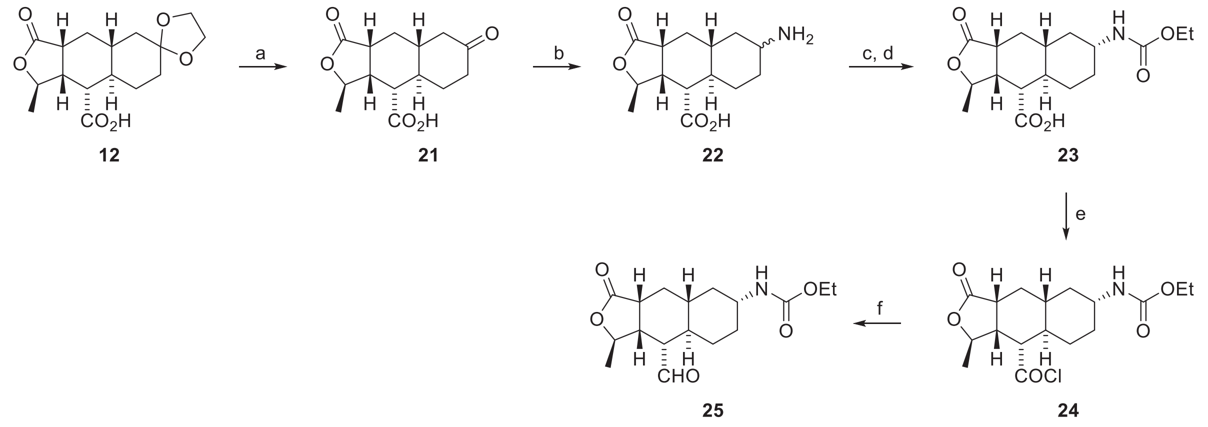
a) *n*-BuLi, THF, 0 °C, 30 min; yield not given b) TBAF, THF, 0 °C, 5 min; quant c) Tf_2O, pyridine, 0 °C, o/n; 80% d) *m*-$FC_6H_4B(OH)_2$, $Pd(PPh_3)_4$, K_2CO_3, PhMe, H_2O, EtOH, sealed tube, 100 °C, 2 h; 89% e) 1.0 N HCl, acetone, 50 °C, 1 h; 89% f) NH_3, $Ti(O$*i*$-Pr)_4$, 0 °C, 1 h then $TiCl_4$, 45 min g) $NaBH_3CN$, MeOH, rt, o/n h) separation of isomers by PTLC i) EtOC(O)Cl, Et_3N, DCM, 0 °C, 1 h; 86%

Scheme 2. Route of synthesis to Vorapaxar **1**[7]

The amino group was introduced through a two-step reductive amination of ketone **19**. A mixture of isomers **20**-α and **20**-β was formed in a low yield and had to be separated by means of chromatography. Pure 20-α was then converted into **1**.

Interestingly, the yield of reductive amination of other analogues of **19** was much higher (62% – 64% for *m*-CF_3 analogue),[8,9] which prompted some competitors to later search for improvements of this step. For instance Sandoz and Selvita developed a more efficient reductive amination of **19** using ammonium acetate and $NaBH_3CN$ to obtain 68% yield of the mixture of amine isomers **20**-α and **20**-β which could not be separated by column chromatography. In a quick salt and solvent screening with different *d*-tartaric acid derivatives and alcohol-water mixtures, the *d*-tartaric acid and *i*-PrOH-water mixture gave the best results regarding improvement of diastereomeric ratio. The mixture was then separated by repeated crystallization with *d*-tartaric acid to afford pure **20**-α in a final yield of 26.6%.[10]

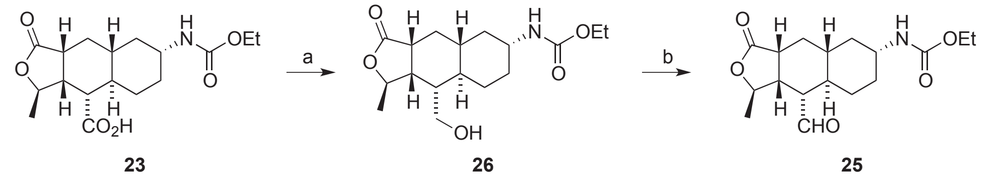
Scientists from Schering discovered that by bringing the reductive amination step much earlier in the reaction sequence and modifying the reaction conditions the yield of the relevant 7-NH_2 mixture **22** could be increased further to virtually 100% (Scheme 3).[11]



a) acetone, 1.0 N HCl, 50-60 °C, 1 h; 76% b) HCO_2NH_4, 10% Pd/C, H_2O, EtOH, 18-28 °C, 5 h; quant. c) EtOC(O)Cl, NaOH, EtOH, 20-30 °C, 30 min d) crystallization from AcOEt:heptane=1:1 (v/v); 50% e) $(COCl)_2$, DMF, 15-25 °C, 1 h f) H_2 (100 psi)/Pd-C, THF, lutidine, 20-25 °C, 16 h; 66%

Scheme 3. Modified synthesis of Vorapaxar intermediate **25**[11]

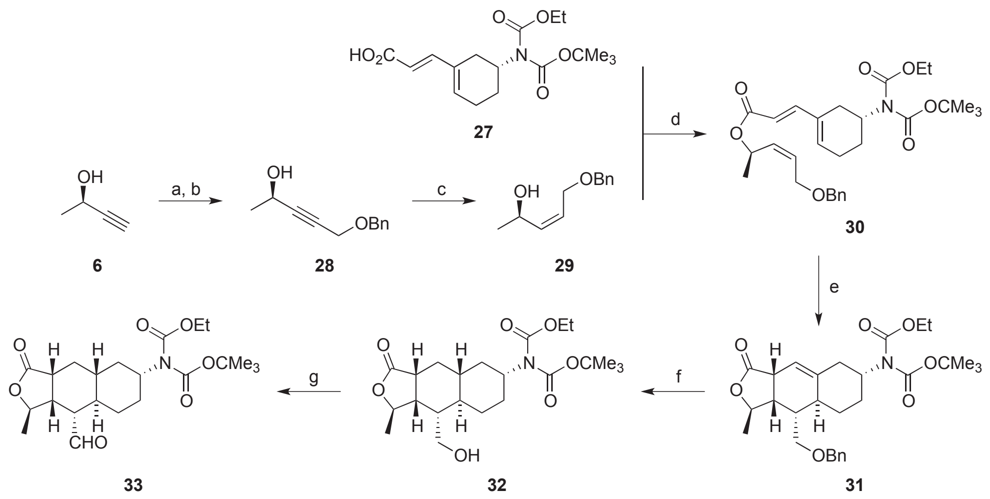
Separation of diastereoisomers was performed by crystallization at the stage of carbamates thus allowing the isolation of acid **23** in 50% yield. This acid was reduced to aldehyde **25** in 66% yield, although such a high yield has recently been questioned by scientists from Chemvon Biotechnology.[12] Trying to reproduce the H_2/Pd reduction protocol they could obtain only 10% of **25**. To circumvent the problem of low yield Chemvon proposed a two-step reduction-oxidation sequence with alcohol **26** as an intermediate (Scheme 4).



a) LiAlH(O*t*-Bu)$_3$, THF, <10 °C, 30 min; 93% b) PCC, silicagel, DCM, <30 °C, 30 min; 96% or Swern oxidation: (COCl)$_2$, DMSO, DCM, <-70 °C, 30 min then **26** in DCM, 1h <-60 °C followed by Et$_3$N, -60-0 °C; 97%

Scheme 4. Chemvon's approach to aldehyde **25**[12]

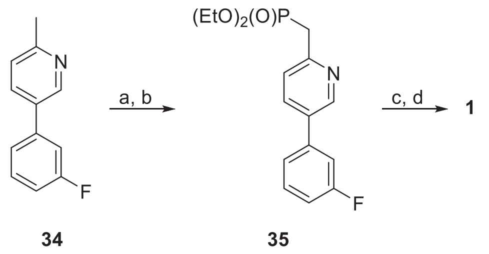
Another solution to the problem of aldehyde formation was proposed by BrightGene Bio-Medical Technology who constructed the core starting already from alcohol derivative **28** (Scheme 5) instead of ester **8**.[13]



a) *n*-BuLi, THF, -50 °C, 1 h b) BnOCH$_2$Cl, THF, -50 °C, 3 h; 89% c) H$_2$/Lindlar, AcOEt:H$_2$O=99:1 (v/v), 25 °C; 92% d) **27**, pivaloyl chloride, NMM, DMAP, toluene, 0 °C, 2 h then **29**, toluene-THF, 0 °C, 8-12 h; 120% (impure?) e) NMP, 150 °C, 4 h; 97% f) H$_2$ (4 atm)/10% Pd(OH)$_2$/C, THF:AcOH=50:1 (v/v), 60 °C, o/n; 108% g) PCC, silicagel, DCM, rt, 2 h; quant.

Scheme 5. BrightGene's approach to aldehyde **33**[13]

In the Schering's synthetic route aldehyde **25** served then as a direct precursor to **1** as shown in Scheme 6.[11]

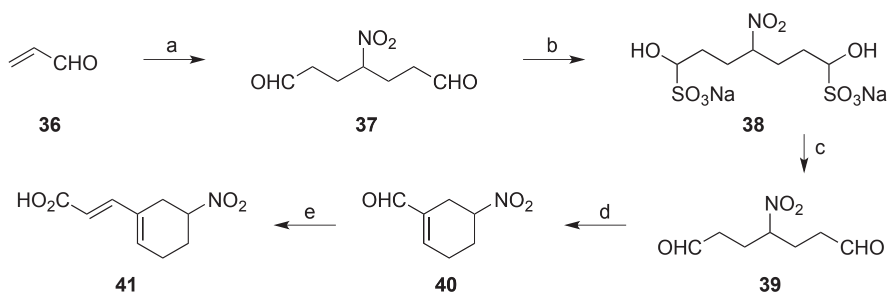


a) LDA, THF, -80 to -50 °C, 15 min b) (EtO)$_2$P(O)Cl, <-50 °C, 15 min; 85% c) LDA, THF, -20 °C, 1 h d) **25**, THF, <-20 °C, 1 h, 90%

Scheme 6. Synthesis of Vorapaxar **1** by Schering Plough[11]

Analogous Horner-Wadsworth-Emmons (HWE) reactions were used in all later Vorapaxar patent applications. In a patent application filed by Jiangsu Tasly Diyi Pharmaceutical the conditions for the HWE reaction were modified by using LHMDS/Ti(O*i*-Pr)$_4$ system at step c, Scheme 6, which allowed the reaction to be carried out closer to the room temperature (0 – 20 °C).[14] To create the *trans* double bond the same company explored also the Wittig reaction but the overall yield from **25** to **1** was below 16%.[14]

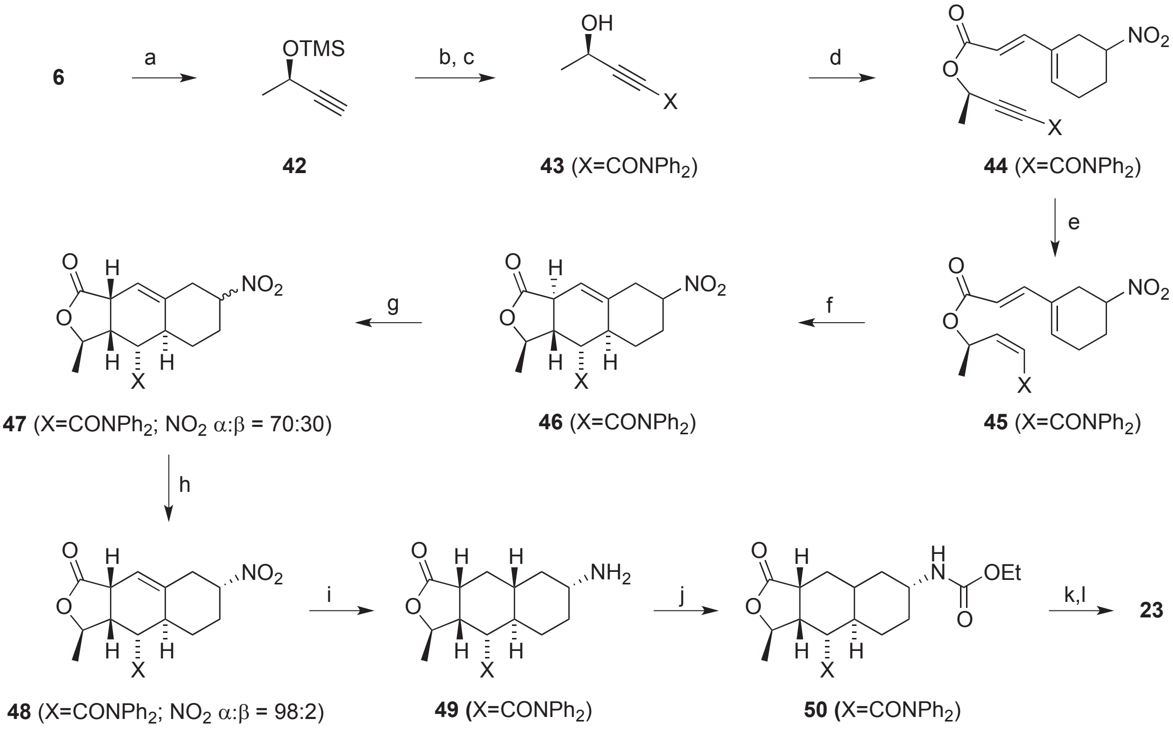
The most significant problem within the original synthetic route was how to stereoselectively install the C(7)-N bond. The reductive amination (cf the synthesis of **20** in Scheme 2 and **22** in Scheme 3) always led to mixtures of isomers, which were difficult to separate, particularly on a large scale. Scientists from Schering circumvented this issue in a brilliant way by utilizing the nitro group.[15] Synthesis of the key acid **41**, an analogue of **5**, is presented in Scheme 7.



a) MeNO$_2$, KOH, MeOH:*i*-PrOH=1:1 (v/v), <-20 °C, 4 h b) NaHSO$_3$ or Na$_2$S$_2$O$_5$, H$_2$O, 25 °C, 1 h then 1 h at 10 °C; 83% c) OHC-CO$_2$H, NaHCO$_3$, DCM:H$_2$O=44:56 (v/v), rt, 1 h; 86% d) pyrrolidine, benzoic acid, DCM, reflux, 15 h; 75% purity 80%) e) malonic acid, pyridine, 60 °C, 7 h; 60%

Scheme 7. Synthesis of acid **41** by Schering Plough[15]

This acid was coupled with the relevant homochiral alcohol **43** (X=CONPh$_2$), and the alkyne **44** (X=CONPh$_2$) was reduced to afford **45** (X=CONPh$_2$), the substrate for intramolecular Diels-Alder (IMDA) reaction (Scheme 8). For the reasons discussed by Chackalamannil et al.,[6] the major product of such enantioselective IMDA reaction would generate the *exo* adduct **46** (X=CONPh$_2$; with *trans* junction between C-3a and C-9a), which in the presence of DBU at room temperature undergoes isomerization to afford the *cis* lactone **47** (X=CONPh$_2$) as a mixture of α-NO$_2$ and β-NO$_2$ isomers in a ratio of around 70:30, respectively. The problem of their separation was solved by taking advantage of the acidity of the CH-NO$_2$ hydrogen in **46** (X=CONPh$_2$), which allowed isomerization to take place under the influence of DBU at 65 °C and dynamic crystallization[16] of the desired α-isomer from *i*-PrOH:EtOH=2:1 to afford **48** (X=CONPh$_2$) in 72% overall yield from **45** (X=CONPh$_2$). As the purity of **48** is critical at the further steps Schering scientists introduced later several modifications to the way the compound is isolated and purified.[17]



a) HMDS, H_2SO_4 (cat.), THF, reflux, 3-4 h b) HexLi, THF, -40 °C c) $Ph_2NC(O)$-Im, THF:toluene=71:29 (v/v), -40 °C; 84% d) **41**, $Me_3CC(O)Cl$, NMM, DMAP, toluene, <-5 °C then **43** (X=$CONPh_2$), toluene, <5 °C followed by DMAP (cat), THF, 0 °C, 12 h; 90-95% e) H_2 (100 psi)/Lindlar, toluene, 25-30 °C; 74% f) 1-methylpyrrolidone, 145 °C, 3.5 h g) DBU, rt, 1 h h) DBU, EtOH, 65 to 15 °C, 5 h; 72% from **45** i) HCO_2H, 10% Pd/C, THF:H_2O=6:4 (v/v), 45 to 55 °C, 4 h j) EtOC(O)Cl, Et_3N, THF, 5 to 20 °C, 30 min; 85% from **48** k) 5% $NaOH_{aq}$, THF, 40 °C, 4 h l) 2 N HCl_{aq}; 99%

Scheme 8. Synthesis of acid **23** by Schering Plough[15]

An analogous approach was also explored using the relevant benzyl ester **43** (X=CO_2Bn) instead of *N*,*N*-diphenylamide.[15]

The concept of utilizing the nitro derivative **41** (Scheme 8) survived the test of time as regardless of whether they decided to start from X=CO_2Bn, $CONPh_2$[18] or CH_2OBn[13,19], (e.g. **29**, Scheme 5), CH_2OMe[19], CH_2OAc[19] or $CH_2OTBDMS$[19] intermediates, the generic manufacturers in their later patent applications have followed the concept of using the nitro derivative to enable dynamic crystallization.[20] Some improvements have been introduced like the solvent (NMP replaced with anisole; this improves the conversion rate) [19] and base (DBU replaced with Et_3N to reduce the cost and increase the yield).[19]

To avoid creating any mixtures of α-C(7)-N and β-C(7)-N isomers one could potentially use a starting material where the requisite C-N bond is already present and the stereogenic carbon atom has the right configuration. Such an idea was realized in a patent application from BrightGene Bio-Medical Technology (Scheme 5) but the inventors did not disclose how they made the key starting material **27**.[13]

3. CONCLUSION

The original synthetic route to Vorapaxar took advantage of the prior research by Schering on the natural product Himbacine, particularly the intramolecular Diels-Alder (IMDA) reaction to form the drug backbone. The C(7)-N bond in Vorapaxar was initially introduced in a relatively non-selective manner but the company soon improved the process by using the key nitro group, which enabled isolation of a single diastereoisomer from the IMDA reaction mixture. Further improvements to the process, namely modification of a substituent at C(4), changing the isolation and purification protocols were disclosed soon thereafter. As a result the changes the generic manufacturers were able to introduce were limited to using alternative C(4) substituents, which removed the need to reduce the acid C(4)-CO_2H to the aldehyde. They were also able to optimize some steps by using different conditions, e.g. alternative reagents, solvent systems, temperature and concentrations. However, no fundamental alterations to the original route have been made, except for the use of a starting material where the C(7)-N bond is already present and the stereogenic carbon atom has the correct configuration. However, the inventors did not disclose how they prepared the key starting material.

It seems clear that by investing time and resources in proper researching the chemistry of the target drug a pharmaceutical company can leave very little room for improvement for generic manufacturers thus better securing intellectual property.

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Piotr Graczyk received his PhD degree from the Polish Academy of Sciences (PAS). He has over 10 years' academic work experience in Poland (PAS, Professor Mikolajczyk's lab) and abroad (Harvard University, Professor Kishi's lab) in the areas of natural product synthesis as well as organic and physical chemistry. While employed for 18 years by Eisai in the UK he acquired vast experience working in drug discovery, particularly by directing medicinal chemistry research for new drugs to treat neurodegenerative disorders such as multiple sclerosis, Parkinson's and Alzheimer's diseases. He has experience in leading multicultural and multidisciplinary teams in the areas of medicinal, analytical and physical chemistry as well as chemoinformatics, structure-based drug design and NMR spectroscopy. Since 2014 he has been working for Selvita where he currently holds a post of a Consulting Director. He is an author of or co-inventor on over 50 publications and patent applications. He is known for the introduction of Gini coefficient as a tool to measure selectivity of kinase inhibitors. He is a member of the Scientific Advisory Board of the *"Future Medicinal Chemistry"* and *"The Open Organic Chemistry Journal"*.