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Efficient Industrial Synthesis of the MDM2 Antagonist Idasanutlin *via* a Cu(I)-catalyzed [3+2] Asymmetric Cycloaddition§

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Sandmeyer Award 2017

Dedicated to Professor Elias J. Corey on the occasion of his 90th birthday.

Abstract: A concise asymmetric synthesis has been developed to prepare idasanutlin, a small molecule MDM2 antagonist. Idasanutlin is currently being investigated as a potential treatment for various solid tumors and hematologic malignancies. The highly congested pyrrolidine core, containing four contiguous stereocenters, was constructed *via* a Cu(I)/(*R*)-BINAP catalyzed [3+2]-cycloaddition reaction. This optimized copper(I)-catalyzed process has been used to produce more than 1500 kg of idasanutlin. The manufacturing process will be described, highlighting the exceptionally selective and consistent cycloaddition/isomerization/hydrolysis sequence. The excellent yields, short cycle times and reduction in waste streams result in a sustainable production process with low environmental impact.

Keywords: Asymmetric synthesis · Catalysis · Cycloaddition · Process chemistry

Dan Fishlock obtained his PhD in chemistry from the University of Waterloo (Canada) under the guidance of Prof. Eric Fillion in 2005, and conducted his post-doctoral research with Prof. Robert M. Williams at Colorado State University on the synthesis of the marine natural product ecteinascidin 743. In 2007 Dan joined the process research group at Roche in Palo Alto (CA), and subsequently moved to Roche in Nutley (NJ). In 2013 he joined the Process Chemistry & Catalysis department in Pharmaceutical Technical Development at F. Hoffmann-La Roche, Basel (CH) where he currently serves as lab head and chemical project leader. Dan has more than 25 publications and patents.

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Stefan Hildbrand studied organic chemistry at the University of Bern and gained his PhD under the supervision of Prof. Christian Leumann in 1996. After completing post-doctoral studies in the Trost group at Stanford University he moved as R&D scientist and Project Leader to the New Business Development Department at Lonza in Visp, Switzerland. In 2001 he joined the Chemical Development Department of F. Hoffmann-La Roche in Basel, where he started as a plant chemist. After a job rotation in a process research lab in 2003, he moved as lab head in the Process Development group. In 2010 he made a short-term job rotation

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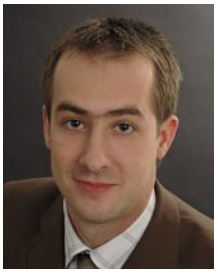
as Manager of Chemical Development to Florence (SC). From 2013 to 2016 he was a section head in Process Development and since October 2016 Stefan is the head of the Process Chemistry & Catalysis Department with 75 employees. Stefan has more than 50 publications (more than 30 patent applications). He is a member of the Swiss Chemical Society, a member of the Scientific Advisory Board for the ACS publication *Organic Process Research & Development* and a member the API Leadership Group of the 'International Consortium for Innovation & Quality (IQ) in Pharmaceutical Development'.



Christian Mössner studied chemistry at the Albert-Ludwigs University Freiburg and obtained his PhD in chemistry from the RWTH Aachen University, Germany, in 2005. He moved then to the Cambridge University (UK) to work with Ian Paterson on the marine macrolide spirastrellolide A as a DAAD postdoctoral fellow. In 2007, he joined Solvias AG (CH) as laboratory head in the department for chemical development & catalysis, where Christian was a recipient of the Sandmeyer Award in 2015. Since 2011, he works as a Principal Scientist in the department for Process Chemistry & Catalysis with F. Hoffmann-La Roche.

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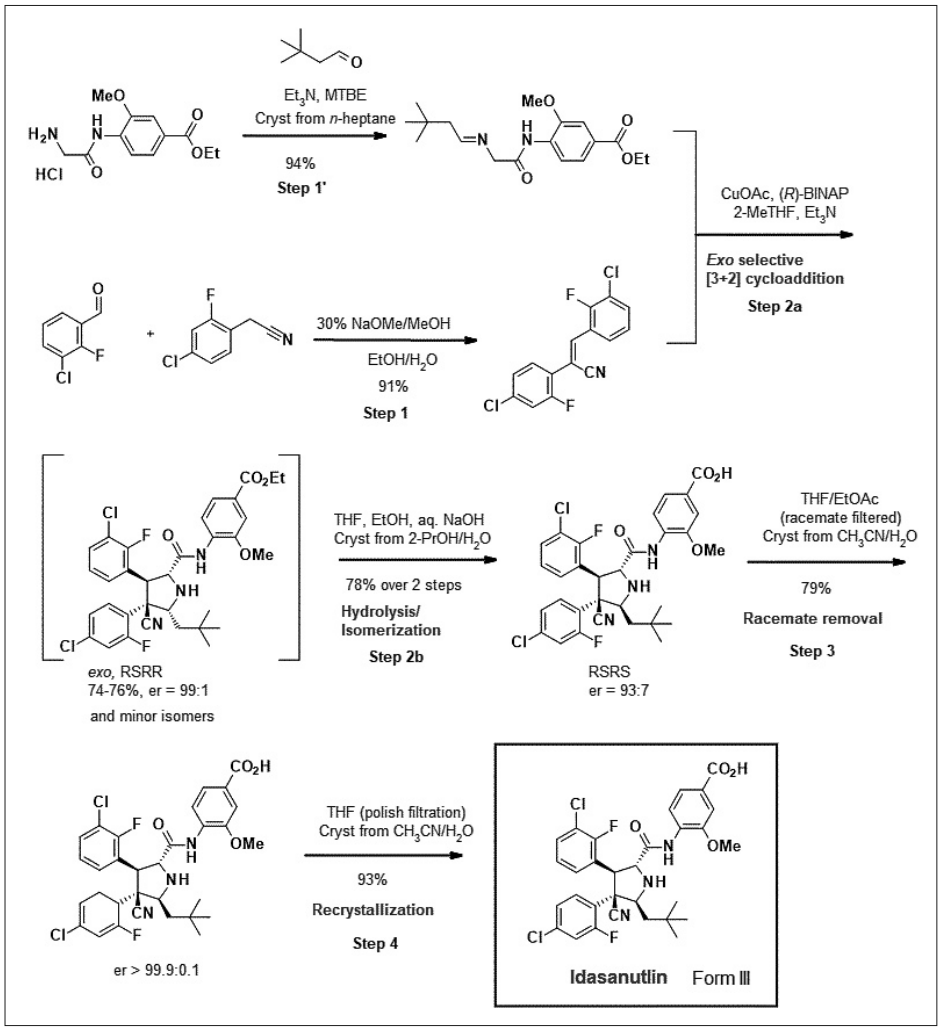
Markus Schantz received his degree in food chemistry and toxicology at the TU Kaiserslautern in Germany. He completed his PhD in the group of Prof. Dr. Richling

in 2011. After two years working for a smaller company he joined F. Hoffmann-La Roche in Basel in 2013 as analytical chemist. As lab head in the analytical development department he contributed to this project. Since 2016 he has taken over a position as group leader in analytical R&D diagnostics in Mannheim (DE).

1. Introduction

Idasanutlin (Scheme 1) is a potent small molecule inhibitor of the MDM2 (mouse double minute 2, also known as E3 ubiquitin-protein ligase MDM2) homolog protein antagonist discovered at F. Hoffmann-La Roche. MDM2 is an important negative regulator of the p53 tumor suppressor protein.[1] Inactivation of p53 is essential for the formation of the majority of human tumors.[2] Idasanutlin is designed to bind to MDM2 to potentially prevent the p53-MDM2 interaction, resulting in activation of p53. Idasanutlin shows efficacy in xenograft models and late-stage clinical trials are ongoing in patients suffering from acute myeloid leukemia (AML) and polycythemia vera.

The original medicinal chemistry route constructed the congested pyrrolidine carboxamide core *via* an azomethine ylide based [3+2]-cycloaddition reaction.[1a,3a] The medicinal chemistry synthesis employed stoichiometric silver fluoride in a racemic cycloaddition reaction to construct the pyrrolidine core for structure–activity relationship (SAR) studies and initial pre-clinical supplies. Process chemistry efforts toward a robust scalable process to support the clinical studies resulted in a catalytic asymmetric cycloaddition reaction using AgOAc with (*R*)-MeOBIPHEP as a chiral ligand. This second-generation route enabled good quality API synthesis on 100 kg-scale, and is described in a previous publication.[3a] However, a more efficient process was required to support the increasing API demand for clinical development and eventual commercial manufacturing. The Cu(I)OAc/(*R*)-BINAP-catalyzed asymmetric [3+2]-cycloaddition process, discussed herein, was ultimately developed and optimized for the manufacture of idasanutlin.[3b]



Scheme 1. The copper-catalyzed process for the manufacture of idasanutlin.

2. Copper-catalyzed [3+2]-cycloaddition

Idasanutlin contains a highly congested chiral pyrrolidine carboxamide core consisting of four contiguous stereocenters. Retrosynthetically, the pyrrolidine core can be constructed in a very concise and efficient manner using an azomethine ylide based [3+2]-cycloaddition reaction with an appropriately substituted electron-deficient olefin. The [3+2]-cycloaddition reactions between a dipole (azomethine ylide) and an appropriate dipolarophile (olefin) in presence of chiral Lewis acids are well established in the literature.[4] Indeed, the requisite reaction partners for idasanutlin offer both favorable electronics to facilitate the application of such methodology, and routes for their preparation are also relatively facile. The opportunity was clear to pursue a highly convergent synthesis route and a Cu(I)-catalyzed asymmetric [3+2]-cycloaddition was developed for this purpose.

The coupling partners for the [3+2]-cycloaddition reaction were readily accessed from non-complex starting materials (Scheme 1). The cycloaddition imine partner was prepared by condensation of 4-(2-amino-acetylamino)-3-methoxy-benzoic acid ethyl ester hydrochloride with 3,3-dimethyl butyraldehyde in the presence of triethylamine in methyl-*tert*-butyl ether (MTBE) at ambient temperature. After separation of precipitated $NEt_3 \cdot HCl$ by filtration, the imine was obtained by crystallization, following a solvent exchange to *n*-heptane, in a yield of 94% with excellent quality (99.9% area HPLC). The dipolarophile, a highly electron deficient stilbene, was prepared by Knoevenagel condensation of 3-chloro-2-fluoro-benzaldehyde and 2-(4-chloro-2-fluoro-phenyl) acetonitrile in ethanol/water in the presence of catalytic sodium methoxide. The desired product precipitated from the reaction mixture and was isolated by filtration. The only observed side product, with levels up to 6% in the reaction mixture, was the corresponding *E*-stilbene which does not precipitate from the reaction mixture and was completely removed to the mother liquor during solid-liquid separation. This optimized manufacturing process resulted in a yield of 91% with a GC purity of 99.9% area.

The [3+2]-cycloaddition was executed using only 0.50 mol% of the pre-catalyst CuOAc in combination with 0.53 mol% of the commercially available chiral phosphine, (*R*)-BINAP. The reaction was completed within 6 hours providing a constant ratio of diastereoisomeric products, with the *exo* cycloaddition product as the major isomer with approx. 75% area (HPLC) (*infra vide*). The selectivity of the cycloaddition reaction was found to be very robust, and within the temperature range of 0–40 °C minimal impact on enantioselectivity was observed. CuOAc is unable to catalyze the reaction in the absence of a phosphine ligand, and a pre-catalyst:ligand loading of 2:1 was equally effective with no impact on reaction rate or stereoselectivity. While the system does not require any premixing or aging of the metal–ligand complex, and solid addition of the pre-catalyst and the ligand to the reaction mixture is possible, the catalyst solution was premixed on scale-up.

The *exo* selective product contains all the structural features of idasanutlin, except the desired configuration at the C(5) tertiary carbon in the pyrrolidine core. Detailed investigations, both experimental as well as theoretical, of reaction products from the [3+2]-cycloaddition resulted in the identification of reaction conditions to epimerize the C(5) chiral center. The reaction conditions for epimerization were further optimized to concomitantly hydrolyze the ester functionality to the desired acid in idasanutlin. Taking advantage of the fact that idasanutlin is thermodynamically the most stable of all the potential diastereoisomers from the Cu(I)-catalyzed [3+2]-cycloaddition reaction, the hydrolysis/isomerization process was eventually developed to funnel all the minor diastereoisomers to enantioenriched idasanutlin. Telescoping of the [3+2]-cycloaddition reaction into the hydrolysis/isomerization step not only delivered enantioenriched idasanutlin with an enantiomeric ratio (er) of 93:7 and 78% yield for step 2, but also provided additional process efficiency. No impurity above 0.10% area HPLC is detected in the isolated product and this stage establishes the primary control of the impurity profile of idasanutlin.

In the following step, the undesired enantiomeric acid can be completely removed as a racemic mixture by exploiting the significant difference in solubilities of the racemic and the enantiopure acid in ethyl acetate:tetrahydrofuran (1:4 v/v) mixture. The solubility of the racemate is 0.52%w/w and the solubility of enantiopure idasanutlin is 11%w/w. The enantioenriched idasanutlin (er 93:7) was triturated in a 1:4 mixture of ethyl acetate:tetrahydrofuran (15 volumes) to quantitatively remove the insoluble racemate by filtration. From the filtrate so obtained, ethyl acetate/tetrahydrofuran was distilled off and exchanged

by acetonitrile for crystallization of the acetonitrile solvate of idasanutlin. During drying, the material desolvates to provide enantiopure product (er > 99.9:0.1) in 79% yield. Subsequent recrystallization from acetonitrile/water mixture provided the desired polymorph (Form III) of enantiopure idasanutlin (see Section 5 for a detailed discussion of the polymorph landscape).

The manufacturing process has an overall yield of 56% and is a significant improvement compared to the first-generation medicinal chemistry route (16% yield) and also the second-generation silver-catalyzed process (29% yield) (Fig. 1). The optimized process shows a much more favorable overall MI (mass intensity) factor, uses no undesired solvents, and an inexpensive, safe and sustainable catalyst system, and produces only one aqueous waste stream which is biodegradable.

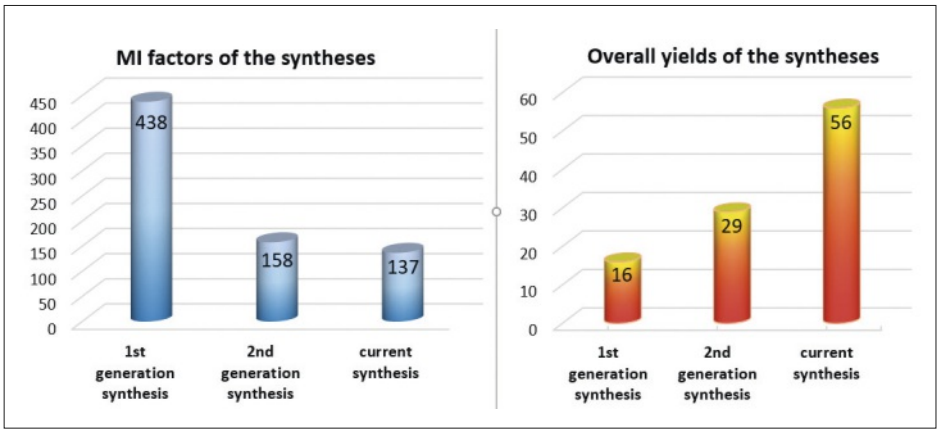


Fig. 1. Process research and development resulted in the current (commercial) convergent route using non-complex starting materials, encompassing the principles of Green Chemistry such as atom economy, minimization of isolations/waste, and avoidance of undesirable solvents, overall robustness and the high throughput in production. Mass intensity (MI) in kg/kg API, and % yield reported. The current synthesis yield shown excludes the final recrystallization step.

3. *Exo* Selectivity in the [3+2]-cycloaddition

Through the course of development, the stereoselectivity evolved from the non-selective first-generation medicinal chemistry silver-catalyzed process to the current copper-catalyzed process. The second-generation AgOAc/(*R*)-MeOBIPHEP catalyst system provided a mixture of diastereomeric ester intermediates, the desired *RSRS* stereochemistry (as in idasanutlin) was obtained in a modest er of 84:16 following isomerization. Subsequent transformations provided idasanutlin with only 44% overall yield from the stilbene starting material. It was clear that the best approach to improve the overall yield was to improve the diastereo- and enantioselectivity of the cycloaddition reaction. Other disadvantages of the Ag-catalyzed process, mainly related to precipitation of Ag salts, also needed improvement.

The Cu-catalyzed [3+2]-cycloaddition reactions of metallated azomethine ylides are proposed to predominately proceed *via* an *exo* transition state to deliver [3+2]-cycloaddition products containing 4,5-*trans* substituted pyrrolidines.[4] The major isomer obtained from our process has a *trans* relative stereochemistry between electron withdrawing group (–CN) at C(4) and the neopentyl group at C(5), supporting an *exo* transition state. Furthermore, as shown in Fig. 2, the Cu-based catalyst system produced significantly more of the *exo* isomer than the Ag-based catalyst system. Therefore, one of the two improvement criteria identified above was met by the Cu-based system.

Interestingly, the *exo* diastereoisomer in the Cu-catalyzed system was formed with the highest enantioselectivity of 99:1 (with *RSRR* as the major isomer). The

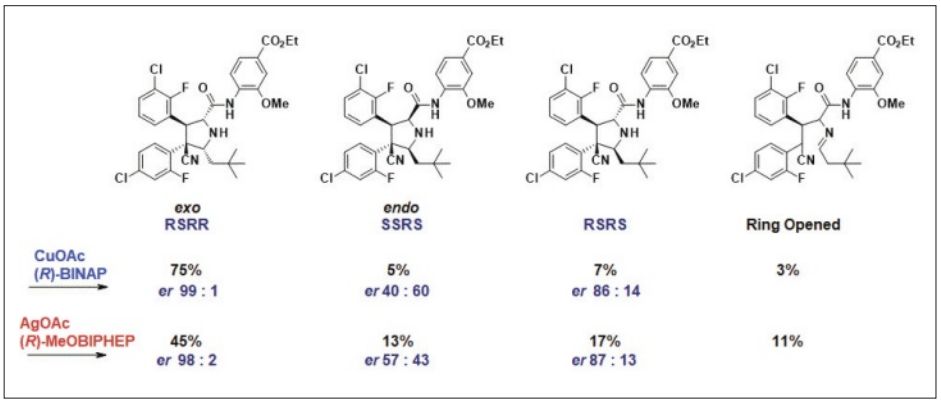


Fig. 2. The copper and silver catalyzed process provide a different distribution of *exo* and *endo* cycloaddition products. The highest enantioselectivity is observed for the major *exo* diastereoisomer.

[3+2]-cycloaddition reaction under these conditions can be presumed to proceed analogously as reported by Garner *et al.*,[4d] wherein the sterics around the metallated azoylidmethide complex is thought to direct the facial selectivity for the approach of the dipolarophile (stilbene) in the *exo* selective cycloaddition step. A model to rationalize the observed enantioselectivity for the *exo* cycloaddition product is presented in Fig. 3. As found in small molecule crystal structures of other Cu/(*R*)-BINAP complexes, coordination to the central Cu ion should be tetrahedral. Our binding model suggests that the Cu/(*R*)-BINAP complex aligns the *t*-butyl group in a downward orientation where it fills a small hydrophobic cavity. In this conformation, a bottom face approach of the dipolarophile with the Cu-coordinated azoylidmethide would be highly disfavored due to steric repulsion. Conversely, top face approach of the stilbene (dipolarophile), in the *exo* orientation, minimizes steric interactions with the substrate and chiral ligand and this produces the observed RSRR isomer of the cycloaddition step.

The isomer bearing the same configuration as idasanutlin was formed with only a moderate enantioselectivity of 86:14. This isomer could be an outcome of a step-wise mechanism (Michael addition followed by Mannich ring closure) *via* a zwitterionic intermediate as postulated by Garner *et al.*[4d] Although, the enantiomeric purity of the ring-opened product could not be determined at the ester stage, a ring-opened imine compound could be isolated and also converted to idasanutlin during hydrolysis/isomerization with an er > 99:1, indicating that the stereocenter at C(3) was formed with a high enantioselectivity.

4. Hydrolysis and Isomerization

During hydrolysis of the diastereomeric ester mixture, concomitant isomerization of *exo* and *endo* isomers occurs to produce the desired RSRS/SRSR acid isomers (Fig. 4).

This observation suggests that this relative stereochemistry is the thermodynamically most stable diastereomer of the

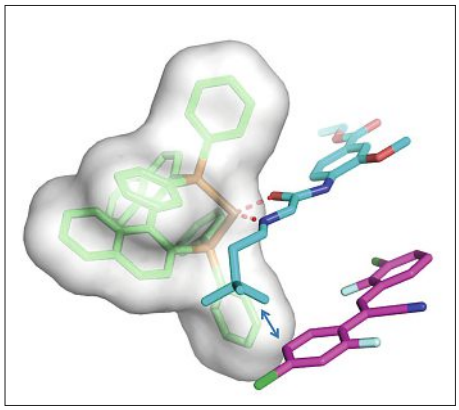


Fig. 3. Schematic argument for the enantioselectivity observed in the major (*exo* selective) product of the copper-catalyzed-cycloaddition. Tetrahedral coordination to the central Cu ion is shown by dashed lines. Approach of the dipolarophile (stilbene in magenta) from the bottom face is sterically hindered by the orientation of the *t*-butyl group and is therefore disfavored. Top face approach results in the *RSRR* ester product (er 99:1). Model was built with the program Moloc using the Cambridge Structural Database (CSD) small molecule crystal structure FIFHEH as template.

four possible diastereomers, and this is also confirmed by *ab initio* calculations.[3b] The relative internal energies (in gas phase) of the four theoretical diastereoisomers of a simplified pyrrolidine core (Ar = phenyl) were calculated quantum-mechanically and the results are presented in Fig. 5.

The relative energy differences of the diastreoisomeric pyrrolidine cores favor the formation of the *RSRS*/*SRSR* configuration under thermodynamic control. The fourth potential diastereoisomer, which would have the *SSRR*/*RRSS* stereochemistry, was never observed. Considering its high relative internal energy, it might be concluded that it is either not formed in the cycloaddition or, if formed, undergoes a rapid retro-Mannich ring opening reaction to give an intermediate such as the ring opened imine compound that was observed in the cycloaddition reaction mixture.

Under the hydrolysis/isomerization reaction conditions, it can be speculated that the diastereoisomers and other isomeric compounds in the cycloaddition reaction mixture are able to interconvert as illustrated in Fig. 6. The stereochemistry of the C(3) position is therefore critical for establishing the final stereochemical outcome.

The ring-opened imine has been experimentally demonstrated to rapidly undergo Mannich ring closure to form *RSRS*/*SRSR* isomer (62%) along with 22% of the *RSRR*/*SRSS* isomer, which further isomerizes to produce only the *RSRS*/*SRSR* product. Furthermore, epimerization at the C(5) position in the *exo* isomer to form *RSRS* with aqueous sodium hydroxide can be an outcome of retro-Mannich ring opening followed by Mannich ring closure cascade. The epimerization at the C(2) position in the *endo* isomer can be envisioned as deprotonation/protonation to the thermodynamically more stable diastereomer *RSRS*. Ester hydrolysis was relatively slow with 8 hours required for complete conversion of the *RSRS* ethyl ester to the corresponding acid (idasanutlin).

Fig. 7 presents the kinetics of the isomerization/hydrolysis step. The reaction profile correlates well with the relative energy calculations (Fig. 5). The major *exo* product (*RSRR*) of the cycloaddition very rapidly isomerizes to the desired *RSRS* ester or hydrolyzes to the corresponding *RSRR* acid, which also isomerizes to the desired *RSRS* acid. Based on these kinetic data, a simple in-process control was implemented to monitor residual *RSRS* ester to less than 0.20% area (HPLC) in this step, at which point all other isomeric esters and acids have been demonstrated to be consumed to less than 0.10%. The much higher relative energy *endo* ester (*SSRS*/*RRSR*) and its corresponding acid are almost instantly isomerized to the other diastereoisomeric populations.[5]

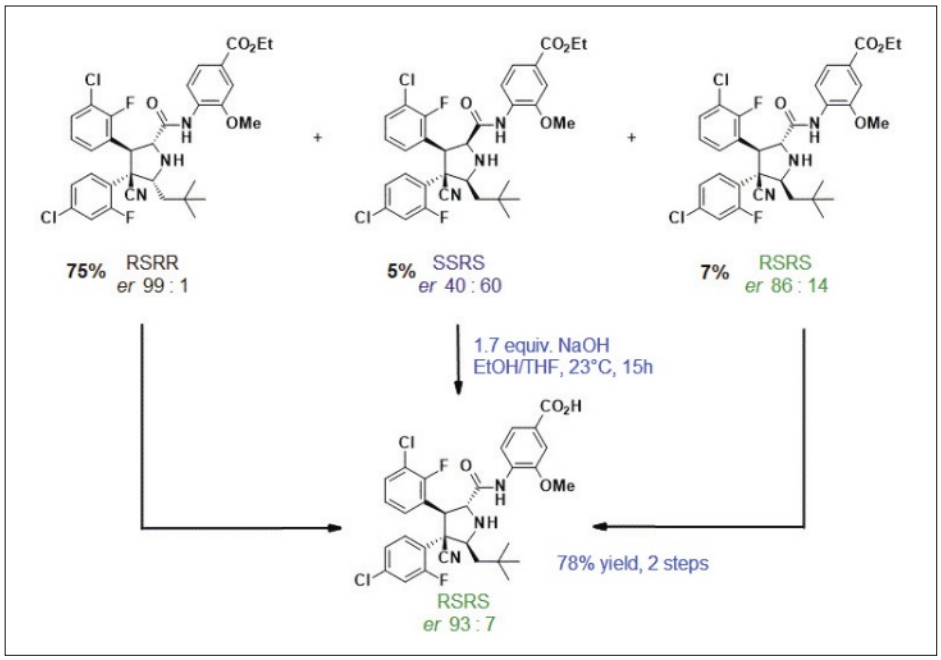


Fig. 4. All ester isomers from the cycloaddition mixture, including the 'ring-opened' imine form (Fig. 2) hydrolyze/isomerize under mild conditions to produce the major *RSRS*:*SRSR* acid with 93:7 er.

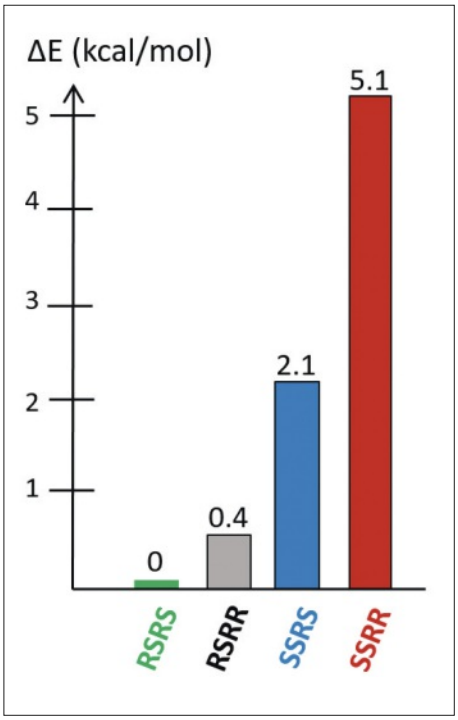


Fig. 5. Quantum-mechanically calculated relative stabilities of diastereoisomers: Relative internal energy differences of the four model diastereoisomers generated from the cycloaddition reaction of *Z*-Stilbene (conformational search: MOE/MMFF94x; QM optimization: B3LYP/cc-pVDZ).[3b] The enantiomeric pair *RSRS*/*SRSR*, ΔE = 0, possesses the relative stereochemistry required in idasanutlin.

Based on the stereoselectivity of the cycloaddition reaction, the anticipated amount of undesired enantiomeric *SRSR* acid after the hydrolysis/isomerization step is 5–8% and the results obtained on manufacturing scale were well in line with this theoretical value. The *RSRS* acid step product is consistently obtained with an er of 93:7 by crystallization from isopropanol/water. The largest impurities in the isolated step 2b product are the *exo* (*RSRR*/*SRSS*) acid isomer (typically 0.05% area HPLC) and (*R*)-BINAP (typically 0.6% w/w, measured as BINAP-O_2). The *SRSR* enantiomer and all other impurities are removed in the subsequent step 3, enan-

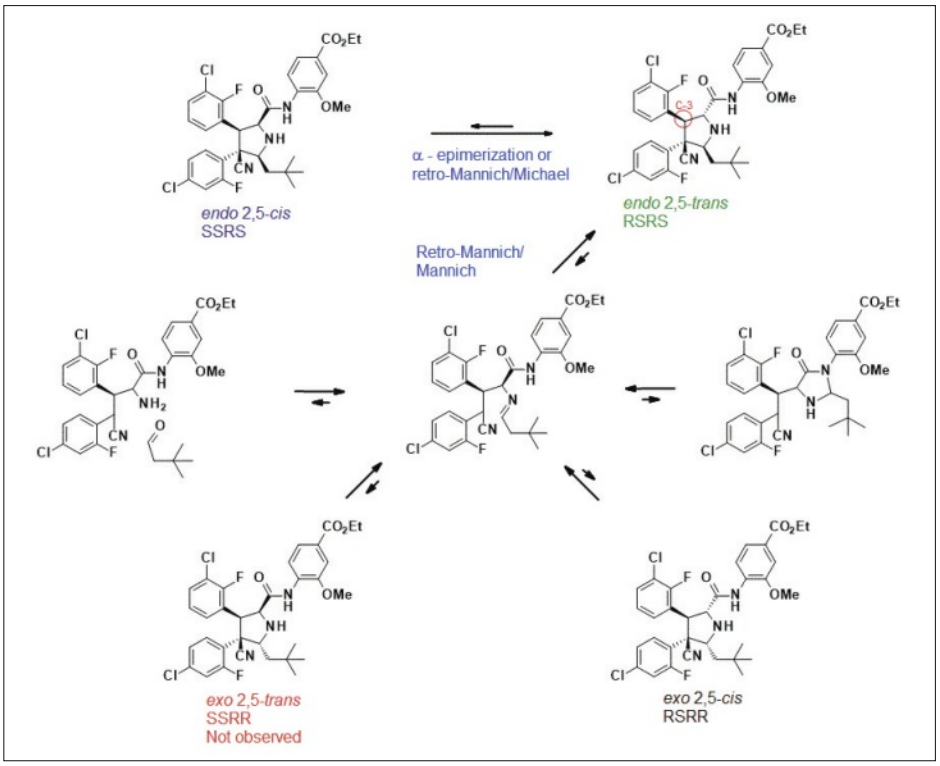


Fig. 6. Isomerization of ester (or acid) isomers can proceed *via* retro-Mannich/Mannich ring opening/closing and the thermodynamically favored *RSRS*(*SRSR*) isomer is formed, directed by the stereochemistry at C(3).

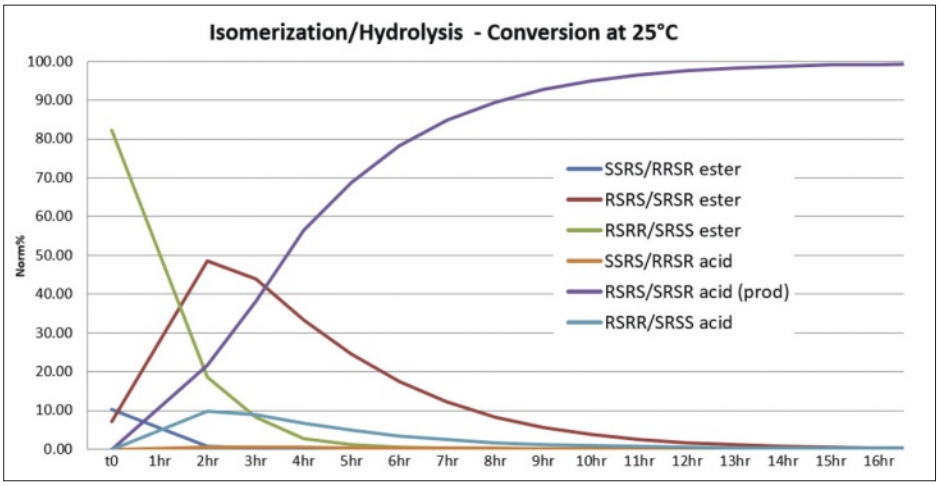


Fig. 7. The kinetics of the hydrolysis/isomerization step show that the major *exo* cycloaddition product (*RSRR*) is converted into the *RSRS* ester or acid over approx. 5 h (at 25 °C). The *endo* ester or acid isomers (*SSRS*/*RRSR*) are very rapidly consumed. Hydrolysis of the desired *RSRS* ester is the control criterion for this step.

tiopurity upgrade (*vide supra*, section 2), to provide enantiopure idasanutlin (er > 99.9:0.1).

5. Solid-state Landscape of Idasanutlin

Idasanutlin exhibits an extraordinarily high tendency to form different crystal forms, especially solvates. In the polymorph screen of idasanutlin, six polymorphs, an amorphous form, three hydrates, five solvate structure families (Form IX, Form X, Form XV, Form XVIII, and Form XXIII), and ten solvates were discovered. An overview and the relationship between the discovered solid forms is schematically depicted in Fig. 8.

5.1 *Solvates*

Idasanutlin exhibits a tendency to form multiple solvated crystal forms with the same solvent (*e.g.* with acetone: Form X, Form XV, Form XXI, Form XXIII, and Form XXIV). In addition to specific solvates (2-methyl THF hemi-solvate: Form VI, acetic acid sesqui-solvate: Form VII, dioxane solvates: Form XII and Form XXV, methanol solvates: Form XXII, toluene solvates: Form XIII and Form XIV, and acetone solvates: Form XXI and Form XXIV) multiple groups of isostructural solvated crystal forms (very similar XRPD pattern) were discovered (Form IX, Form X, Form XV, Form XVIII, and Form XXIII). In these structures, the solvent can be varied without significant change in the crystal lattice parameters. In this respect, it is worth noting that in the last step of the manufacturing idasanutlin is isolated as acetonitrile solvate (Form IX), converting into Form III after drying. The various solvates are summarized in Table 1.

5.2 *Hydrates*

Three hydrates of idasanutlin have been identified. An overview is given in Fig. 9. Hemi-hydrate Form V reversibly transforms into polymorph Form I upon de-hydration. Hemi-hydrate Form IV was only obtained *via* methanol solvate Form XXII by exchange of methanol against water. Long-term slurry equilibration of a mixture of Form I and Form III in water at 60 °C yielded the non-stoichiometric hydrate Form VIII. See Fig. 10 for a comparison of the XRPD patterns of hydrates Form IV, Form V, and Form VIII. During early development Form I was manufactured. To avoid the hygroscopicity of Form I and possible conversion to the hemi-hydrate Form V the crystallization process was redesigned to produce the non-hygroscopic Form III.

5.3 *Polymorphs*

To date, six polymorphic forms of idasanutlin have been discovered. The thermodynamic ranking of the polymorphs (Form I, Form III, Form XVI, Form XVII, Form XIX, and Form XX, see Fig. 11) was inconclusive. The longterm competing slurry experiments at different temperatures in a variety of solvents and solvent mixtures did not lead to a clear ranking of the known polymorphs with regard to their thermodynamic stability. Most of the experiments led to (new) solvated forms (see Fig. 12).

5.4 *Final Recrystallization of Idasanutlin*

The use of acetonitrile in the crystallization process results in the formation of a poorly soluble acetonitrile solvate. The acetonitrile in the solvate can easily be removed by drying, resulting in the solvate free Form III. The final process comprises crystallization from a water-acetonitrile mixture (1:2.5 w/w) and the isolated acetonitrile solvate (Form IX) is dried to easily remove the acetonitrile resulting in the solvate free Form III (93% yield).

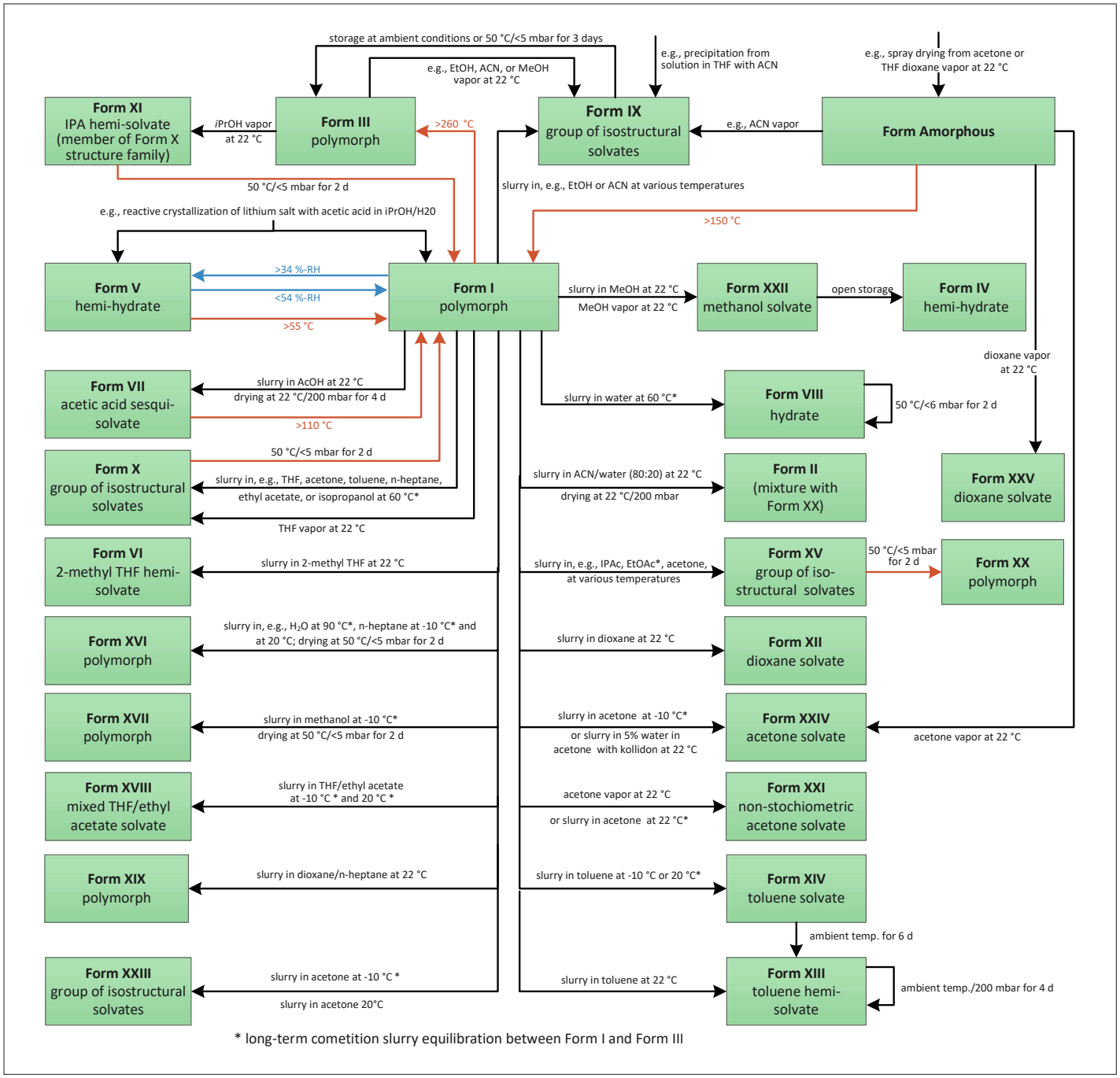


Fig. 8. Relationship diagram of the designated solid forms of idasanutlin. The process consistently produces Form III after drying.

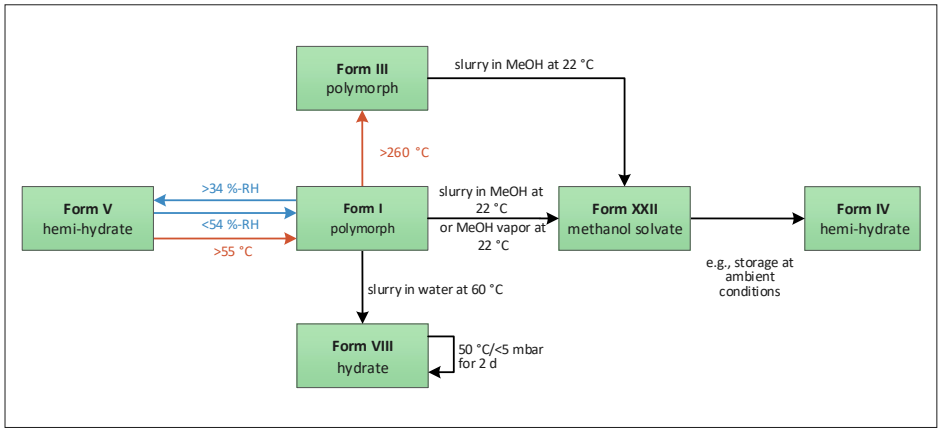


Fig. 9. Overview of the hydrates of idasanutlin (hemi-hydrate Form IV, hemi-hydrate Form V, and non-stoichiometric hydrate Form VIII).

6. Conclusion

A short and high-yielding manufacturing process for idasanutlin was developed. This convergent route uses readily accessible non-complex starting materials and encompasses the principles of Green Chemistry such as high atom economy, minimization of isolations and waste streams, and the avoidance of undesirable solvents. The exceptionally selective cycloaddition/isomerization/hydrolysis sequence uses an inexpensive chiral Cu(I) catalyst system. The process robustness and the high throughput have been demonstrated in the production of more than 1500 kg of idasanutlin to date to support ongo-

Table 1. Summary of solvates of idasanutlin.

Solid form	Nature of solid form	Remarks
Form VI	2-methyl THF hemi-solvate	conversion into Form I upon temperature induced de-solvation
Form VII	acetic acid sesqui-solvate	conversion into Form I upon temperature induced de-solvation
Form VIII	non-stoichiometric hydrate	hydrate obtained by long-term slurry equilibration of Form III/Form I in water at 60 °C
Form IX	solvate structure family	group of isostructural hemi-solvates, *e.g.* with acetonitrile, ethanol, methanol, *etc.*; transformation into Form III upon drying or storage at ambient conditions over time
Form X	solvate structure family	group of isostructural solvates; the representative is a THF hemi-solvate; comparable XRPD patterns were obtained with, *e.g.* acetone, toluene, n-heptane, ethyl acetate, isopropanol, etc.
Form XI	isopropanol hemi-solvate	Form XI is a member of the Form X solvate family
Form XII	dioxane solvate	undefined stoichiometry, wet state only
Form XIII	toluene hemi-solvate	specific solvate with toluene
Form XIV	toluene solvate	undefined stoichiometry, wet state only
Form XV	solvate structure family	group of isostructural solvates; comparable XRPD patterns were obtained with, *e.g.* acetone, ethyl acetate, isopropyl acetate, *etc.*; variable phenotypes of XRPD patterns depending on the solvent content
Form XVIII	family of isostructural mixed THF/ethyl acetate solvates	Family of solvated structures obtained after (competing) long-term slurry equilibration experiments in mixtures of THF and ethyl acetate at -10 °C and at 20 °C
Form XXI	acetone solvate	non-stoichiometric acetone solvate, obtained, *e.g.* by incubation of Form I with acetone vapor
Form XXII	methanol solvate	undefined stoichiometry (presumably methanol hemi-solvate) obtained, *e.g.* by incubation of Form I with methanol vapor; transformation into hemi-hydrate Form IV at ambient conditions
Form XXIII	solvate structure family	family of isostructural solvates, *e.g.* with acetone or methanol
Form XXIV	acetone solvate	undefined stoichiometry, wet state only, obtained, *e.g.* by incubation of Form Amorphous with acetone vapor
Form XXV	dioxane solvate	undefined stoichiometry, obtained, by incubation of Form Amorphous with dioxane vapor

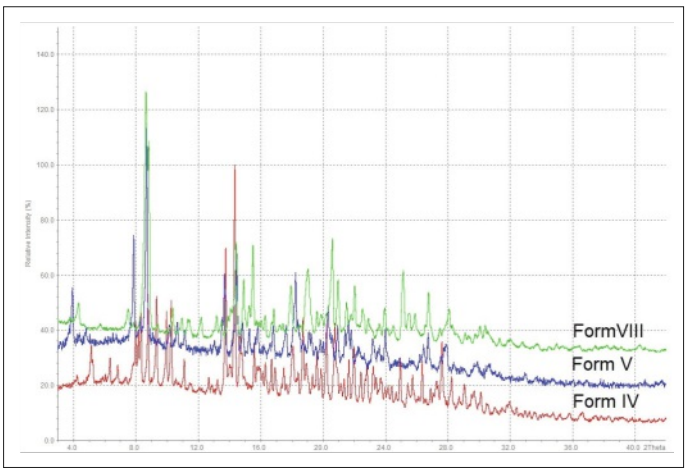


Fig. 10. Comparison of XRPD patterns of hydrated Forms (Form IV, Form V, and Form VIII) of idasanutlin.

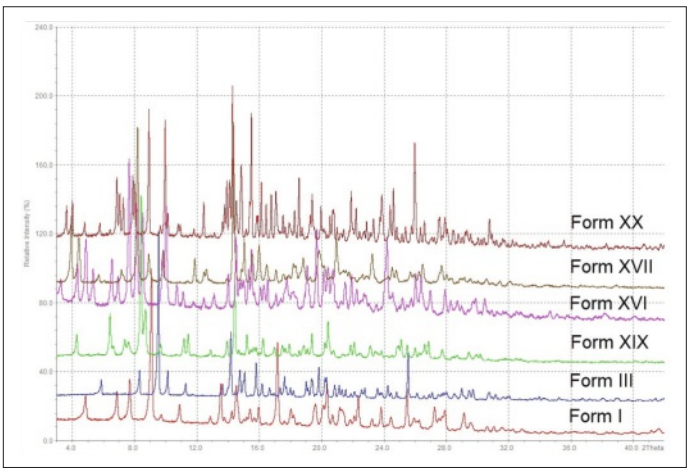


Fig. 11. Comparison of XRPD patterns of the known polymorphic Forms (Form I, Form III, Form XVI, Form XVII, Form XIX, and Form XX) of idasanutlin.

ing clinical studies, and currently used for manufacturing of future supplies.

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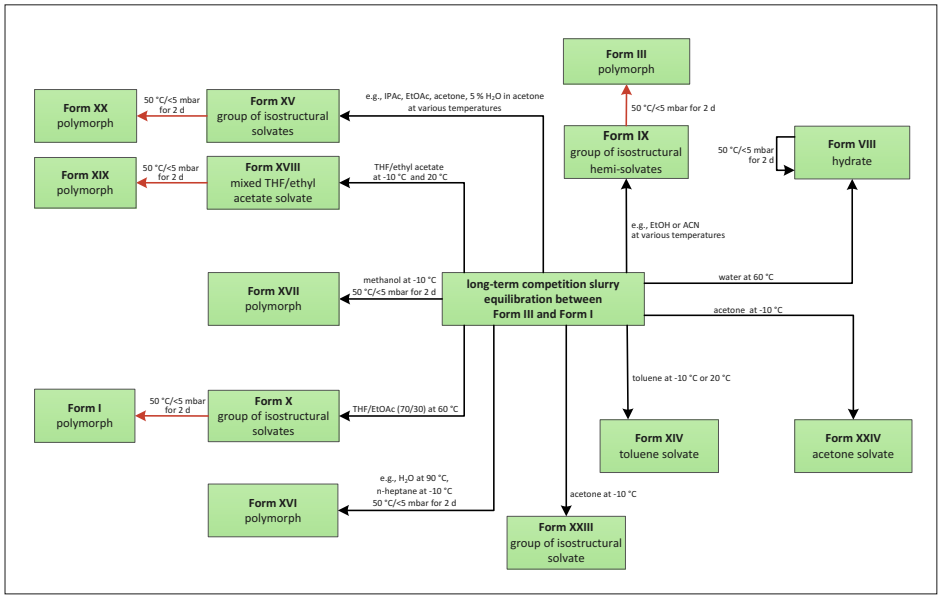

Fig. 12. Overview of crystal forms obtained as result of long-term competition slurry equilibration experiments started with mixtures of Form I and Form III of idasanutlin. The identified forms include the following crystal forms: polymorphs Form XVI, Form XVII, Form XIX (after drying), and Form XX (after drying); solvates Form IX (solvate family), Form X/XI (solvate family), Form XIV (toluene solvate), Form XV (solvate family), Form XVIII (mixed THF/ethyl acetate solvate), Form XXIII (solvate family), and Form XXIV (acetone solvate); hydrate Form VIII.

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[5] The isomerization process under basic conditions complicated the preparation of the reference compounds for the various acid isomers of idasanutlin. An enzymatic ester hydrolysis of each isolated ester using lipase OF was modestly successful, but suffered from a high enzyme loading and a need for chromatographic purification of the acids. More simply, replacing the ethyl ester with a benzyl ester enabled each acid to be obtained following more mild hydrogenolysis without significant isomerization.