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Process Development and Scale-Up of the PPAR Agonist NNC 61-4655

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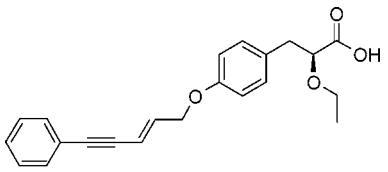
Abstract:

A scalable synthetic route of the nonselective but PPARα-preferring potent PPAR agonist NNC 61-4655 aimed for treatment of type 2 diabetes was developed. The synthetic pathway comprises the convergent synthesis and coupling of the two key intermediates *E*-5-(chloropent-3-en-1-ynyl)benzene 8 (prepared in a five-step synthesis in 18% overall yield) and (*S*)-2-ethoxy-3-(4-hydroxyphenyl)propanoic acid isopropyl ester 9. The 2-aminoethanol salt of NNC 61-4655 was selected in a preclinical salt selection program as the appropriate salt form for further development. More than 900 g of NNC 61-4655, 2-aminoethanol was finally synthesized under GMP in 98.7% purity. In comparison to the original medicinal chemistry route, starting from phenylpropargyl aldehyde 1, the overall yield towards NNC 61-4655 could be enhanced from 24 to 37%. An improved scalable two-step synthesis for 8 was developed on a laboratory scale (≥33−35% overall yield) shortly after the GMP batch.

Introduction

Type 2 diabetes is a polygenic and progressive metabolic disorder characterized by insulin resistance, hyperglycaemia, hypertriglyceridaemia, and low plasma HDL-cholesterol. Untreated type 2 diabetes leads to several chronic diseases such as retinopathy, nephropathy, neuropathy, and cardiovascular diseases such as atherosclerosis, the latter leading to increased mortality.[1] Due to the forecasted epidemic in type 2 diabetes, the increasing financial and social costs, and the complicated pathology of the disease, new therapies are needed which address both the insulin resistance and dyslipidemic components of the disease.[2−4]

Peroxisome proliferator-activated receptors (PPARs) are transcription factors that belong to the nuclear hormone receptor superfamily. PPAR has three isoforms designated PPARα, PPARγ, and PPARδ, which differ in ligand selectivity and biological action.[5] A number of PPAR agonists exhibiting different receptor subtype profiles, such as rosiglitazon (PPARγ),[6] pioglitazone (PPARγ),[7] fenofibrate (PPARα),[8] and clofibrate (PPARα),[8] have been shown to have beneficial effects on the described characteristics of type 2 diabetes.[9] However, neither the fibrates nor the glitazones both lower triglycerides and increase HDL-c as well as lower blood glucose and improve insulin sensitivity. To achieve this biological response both dual-acting PPARα,γ agonists[10] and triple-acting PPARα,γ,δ agonists[11] have been designed. Several dual-acting PPARα,γ agonists (e.g., ragaglitazar/NNC 61-0029,[12] tesaglitazar/AZ242,[13] and LY465608[14]) are currently being investigated in preclinical and clinical trials.



NNC 61-4655

Figure 1. **Structure of the PPAR-agonist NNC 61-4655.**

NNC 61-4655 belongs to the class of nonselective but PPARα-preferring potent PPAR agonists (α:EC_{50} = 0.0067 μM; γ:EC_{50} = 1.13 μM; δ:EC_{50} = 6.90 μM). **NNC 61-4655** has excellent pharmacokinetic properties and was shown to have more efficacious in vivo effects in male db/db mice than seen with both rosiglitazone and pioglitazone.[15] Due to the unique PPAR receptor subtype profile together with the impressive pharmacological properties, **NNC 61-4655** was chosen as a promising antidiabetic drug candidate (see Figure 1).

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(1) Porte, D., Jr.; Schwartz, M. W. *Science* **1996**, *27*, 699−700.
(2) Cobb, J.; Dukes, I. *Ann. Rep. Med. Chem.* **1998**, *33*, 213−221.
(3) Grover, S. A.; Coupal, L.; Zowall, H.; Dorais, M. *Circulation* **2000**, *102*, 722−727.
(4) Bailey, C. J. *TiPS* **2000**, *21*, 259−265
(5) Guan, G.; Zhang, Y.; Breyer, M. D. *Drug News Perspect.* **2002**, 15(3), 147−154.
(6) Chilcott, J.; Tappenden, P.; Jones, M. L.; Wright, J. P. *Clin. Ther.* **2001**, *23*, 1792−1823.
(7) Boyle, P. J.; King, A. B.; Olansky, L.; Marchetti, A.; Lau, H.; Magar, R.; Martin, J. *Clin. Ther.* **2002**, *24*, 378−396.
(8) Staels, B.; Dallongeville, J.; Auwerx, J.; Schoonjans, K.; Leitersdorf, E.; Fruchart, J.-C. *Circulation* **1998**, *98*, 2088−2093.
(9) Willson, T. M.; Brown, P. J.; Sternbach, D. D.; Henke, B. R. *J. Med. Chem.* **2000**, *43*, 527−550.
(10) Sauerberg, P.; Pettersson, I.; Jeppesen, L.; Bury, P. S.; Mogensen, J. P.; Wassermann, K.; Brand, C. L.; Sturis, J.; Wöldike, H. F.; Fleckner, J.; Andersen, A.-S. T.; Mortensen, S. B.; Svensson, L. A.; Rasmussen, H. B.; Lehmann, S. V.; Polivka, Z.; Sindelar, K.; Panajotova, V.; Ynddal, L.; Wulff, E. M. *J. Med. Chem.* **2002**, *45*, 789−804.
(11) Mogensen, J. P.; Jeppesen, L.; Bury, P. S.; Pettersson, I.; Fleckner, J.; Nehlin, J.; Frederiksen, K. S.; Albrektsen, T.; Din, N.; Mortensen, S. B.; Svensson, L. A.; Wassermann, K.; Wulff, E. M.; Ynddal, L.; Sauerberg, P. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 257−260.
(12) Ebdrup, S.; Pettersson, I.; Rasmussen, H. B.; Deussen, H.-J.; Jensen, A. F.; Mortensen, S. B.; Fleckner, J.; Pridal, L.; Nygaard, L.; Sauerberg, P. *J. Med. Chem.* **2003**, *46*, 1306−1317.
(13) Cronet, P.; Petersen, J. F. W.; Folmer, R.; Blomberg, N.; Sjöblom, K.; Karlsson, U.; Lindstedt, E.-L.; Bamberg, K. *Structure* **2001**, *9*, 699−706.

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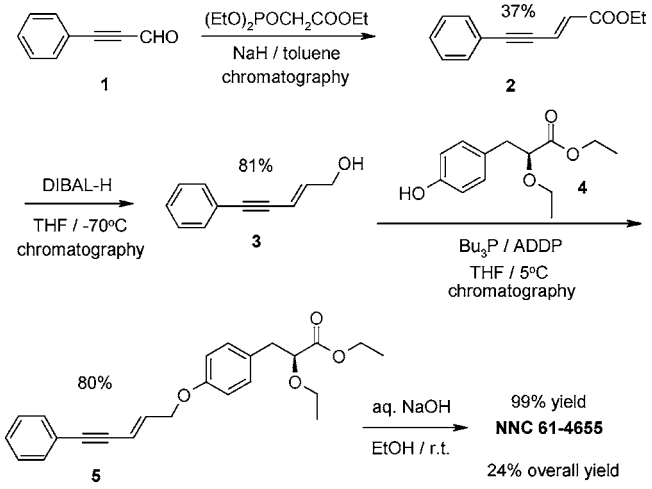
Scheme 1. **Medicinal chemistry synthesis of the PPAR-agonist NNC 61-4655**



Thus, **NNC 61-4655** was needed in amounts of several hundred grams for preclinical development. A GMP batch, preferably as a pharmaceutical acceptable salt, to be used as first human dose material in phase I studies, had to be produced on a multi-100-g scale.[16] It therefore became necessary to develop a scalable synthesis that would provide the quantities needed for further development and to identify a pharmaceutically acceptable salt of **NNC 61-4655**.

Results and Discussion

The Medicinal Chemistry Synthesis. The original medicinal chemistry route is depicted in Scheme 1. Commercially available phenylpropargyl aldehyde **1** (Aldrich) was reacted with triethyl phosphonoacetate in a Horner−Emmons reaction to give the α,β-unsaturated ester **2**. Following a general procedure for Wittig−Horner olefinations, the conditions used were slightly different from those of the procedure earlier described by Krause (e.g. THF was replaced by toluene).[17] The isolated yield was significantly lower than that reported earlier,[18] apparently due to significant losses during the chromatography purification step. Reduction of the ester **2** with a two molar excess of diisobutyl aluminum hydride (DIBAL-H) at −70 °C gave the allylic alcohol **3**[19] in 81% yield after chromatography.[20] Alkylation of ethyl (*S*)-2-ethoxy-3-(4-hydroxyphenyl)propanoate **4**,[12,21] which was on hand from another development project, with **3** under Mitsunobu[22] conditions with tri-*n*-butylphosphine/1,1′-(azodicarbonyl)dipiperidine (ADDP), followed by chromatography, gave the ester **5** in 80% yield. Hydrolysis of **5** to the carboxylic acid gave the desired product **NNC 61-4655** in 24% overall yield[23] starting from phenylpropargyl aldehyde **1**.

The existing route had a number of obstacles that had to be solved before scaling. The starting phenylpropargyl aldehyde **1** was not commercially available in larger quantities and therefore had to be synthesized. At some stage in the Wittig−Horner reaction, foaming was observed during the addition of **1** to the deprotonated triethyl phosphonoacetate. Running the DIBAL-H reduction of **2** at such a low temperature as −70 °C was not possible with our regular equipment. The *exothermic* quenching of the DIBAL-H reaction mixture by addition of water would be a safety issue on large scale. The Mitsunobu coupling of **3** and **4** uses expensive reagents and requires the cumbersome removal of tri-*n*-butylphosphine oxide and the reduced ADDP from the product. All reactions were run rather diluted, which would lead to unacceptable large reaction volumes on large scale. Furthermore, the numerous chromatographic steps were unsuitable for scaling.

The Scaled GMP-Kilo-Laboratory Synthesis. To provide material for phase I studies as rapidly as possible,[24] we decided to retain and to optimize the synthetic procedures provided by Medicinal Chemistry for scaling, except for the Mitsunobu coupling, which was judged to be nonscalable.

The acetylenic compounds were considered to be a potential *safety risk* during scale-up, particularly as some are being distilled.[25,26] Therefore, before scaling the synthesis in the GMP-kilo laboratory, we investigated the thermal properties of intermediates by DSC to identify our safety window towards exotherms which were found to be in the range of 95−127 kJ/mol.[27]

The synthesis of **1** in a two-step synthesis from commercially available phenylacetylene **6** had been described in the literature.[28,29] The intermediate phenylpropargyl aldehyde diethyl acetal **7** was then prepared, closely following the original literature procedure (Scheme 2).[28] The subsequent procedure for the preparation of **1**[29] had to be optimized prior to scaling. The acetal cleavage was run more concentrated, and the formed ethanol was removed from the reaction mixture by distillation to shift the equilibrium of the reaction towards **1**. It was important to control the distillation of ethanol accurately as otherwise we observed losses of product **1** that was removed azeotropically together with the ethanol during distillation. The diethyl ether used in the literature synthesis was replaced by MTBE for extraction. **1** (2.1 kg, 93% pure) was finally synthesized in 46% overall yield.[30]

(14) Etgen, G. J.; Oldham, B. A.; Johnson, W. T.; Broderick, C. L.; Montrose, C. R.; Brozinick, J. T.; Misener, E. A.; Bean, J. S.; Bensch, W. R.; Broks, D. A.; Shuker, A. J.; Rito, C. A.; McCarthy, J. R.; Ardecky, R. A.; Tyhonas, J. S.; Dana, S. L.; Bilakovics, J. M.; Paterniti, Jr., J. R.; Ogilvie, K. M.; Liu, S.; Kauffman, R. F. A. *Diabetes* **2002**, *51*, 1083−1087.

(15) Sauerberg, P.; Bury, P. S.; Mogensen, J. P.; Deussen, H.-J.; Pettersson, I.; Fleckner, J.; Nehlin, J.; Frederiksen, K. S.; Albrektsen, T.; Din, N.; Svensson, L. A.; Ynddal, L.; Wulff, E. M.; Jeppesen, L. *J. Med. Chem.* **2003**, *46*, 4883−4894.

(16) A GMP-batch synthesized immediately after drug candidate selection will be used for preclinical pharmacology and toxicicology studies and thereby at the same time qualify for first human dose.

(17) Krause, N. *Chem. Ber.* **1990**, *123*, 2173−2180.

(18) An isolated yield of surprising 91% (analytically pure) after chromatography followed by Kugelrohr distillation was claimed in ref 17 on a 60 mM scale.

(19) Takeuichi, R.; Tanabe, K.; Tanaka, S. *J. Org. Chem.* **2000**, *65*, 1558−1561.

(20) Yoon, N. M.; Gyoung, Y. S. *Org. Chem.* **1985**, *50*, 2443−2450.

(21) Ebdrup, S.; Deussen, H.-J.; Zundel, PCT-Appl. WO 01/11072.

(22) Hughes, D. L. *Org. Prepr. Proced. Int.* **1996**, *28*, 127−164.

(23) The medicinal chemistry yields are not corrected for purity.

(24) The aim is to produce this batch speedily to obtain an evaluation of the project value as quickly as possible, rather than to develop a perfect production route.

(25) Silver, L. *Chem. Eng. Progr.* **1967**, *63*, 43−49.

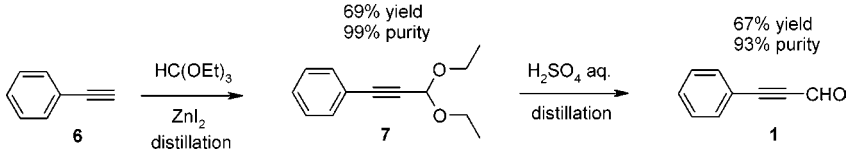
(26) Whiting, M. C. *Chem. Eng. News* **1972**, *50*, 86−87.

(27) As impurities, even traces, often effect the *safety* windows for acetylenic compounds, a comprehensive *safety* evaluation should be conducted before scaling to pilot plant.

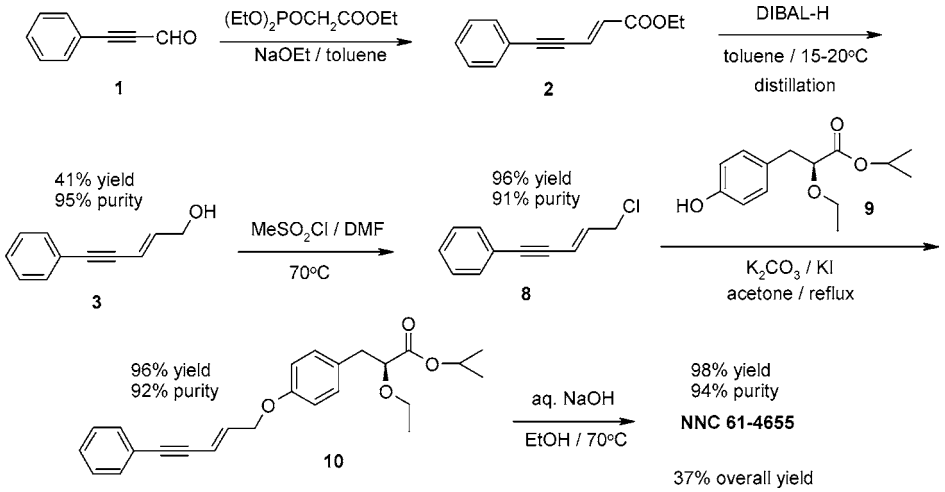
(28) Howk, B. W.; Sauer, J. C. *Organic Syntheses*; John Wiley & Sons: New York, 1963; Collect. Vol. IV, pp 801−803.

(29) Allen, C. F. H.; Edens, C. O., Jr. *Organic Syntheses*; John Wiley & Sons: New York, 1955; Collect. Vol. III, pp 731−733.

Scheme 2. **Scaled GMP-kilo-laboratory synthesis of phenylpropargyl aldehyde 1**



Scheme 3. **Scaled GMP-kilo-laboratory synthesis of the PPAR-agonist NNC 61-4655**



For the synthesis of **2** (Scheme 3) we replaced NaH by NaOEt as this reagent was safer to handle on large scale and foaming was avoided during deprotonation. Other bases, such as KOtBu, NaOH, KOH, K_2CO_3, and Et_3N were tested in THF, MTBE, and toluene with the aim to improve yield and purity of the product. In-process HPLC analyses indicated an average of 18% side products with KOtBu and 28% with NaOEt in toluene. Although KOtBu was most promising with respect to the purity of the product, this base was discarded due to gel formation of the reaction mixture in toluene.[31] The total *cis*-isomer of **2** formed, as detected by ^{1}H NMR, was always less than 3%, independent of the reaction conditions. Attempts to purify crude **2** by distillation resulted in unacceptable losses, presumably due to decomposition. To improve the overall yield, **2** was consequently used without purification in the next step.

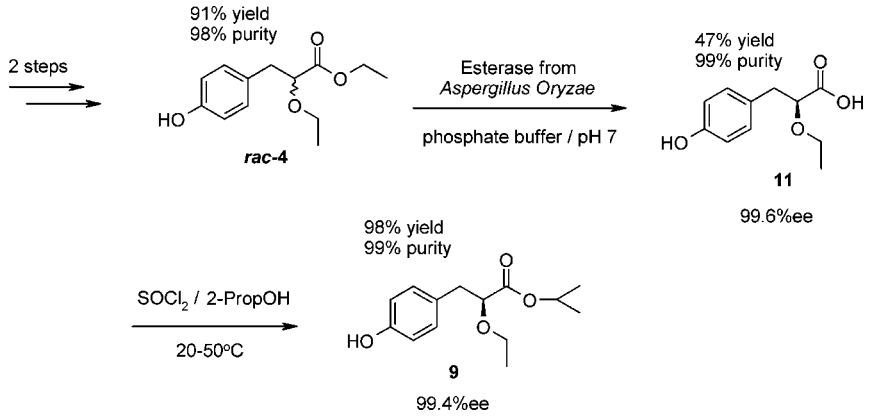
The procedure for the DIBAL-H reduction of **2** was changed significantly in comparison to the medicinal chemistry procedure, leading to a much safer process.[32] The excess of DIBAL-H was reduced from one molar to 10%. THF was replaced by toluene, and the volume was reduced 100 times. The reduction was carried out between 15 and 20 °C (allowing a better control of the *exothermic* reaction as the added DIBAL-H reacted instantaneously). Quenching of the reaction mixture was done by reversed sequence of addition (again to gain improved control). However, unpurified **2** contained phosphoric organic impurities, which were reduced to phosphine. Therefore, the reaction should only be carried out in a well-ventilated fume hood. The aqueous/organic solvent ratio during workup was optimized to achieve satisfactory phase separation. We knew from small-scale experiments starting with pure **2** that the DIBAL-H reduction was a very clean reaction, and we never detected any *cis*−*trans* isomerization. Neither an excess of DIBAL-H nor prolonged reaction time led to over-reduction or more byproduct formation. The yield over both steps {**1** →**2** →**3**} was 41%, mainly due to losses during the distillation of **3**.[33]

The most straightforward solution to avoid the Mitsunobu-coupling was to replace the hydroxyl group in **3** by a leaving group to allow C−O bond formation by nucleophilic attack of the phenolate anion of **4**. The conversion of allylic alcohols to allylic chlorides without allylic rearrangement, by using a mixture of methanesulfonyl chloride, lithium chloride, and collidine in DMF, had been described in the literature.[34] Our process research revealed that lithium chloride and collidine were not necessary for the reaction. We assume that the transformation proceeded via the iminium salt generated in situ from methanesulfonyl chloride and DMF in contrast to the mechanism described by Collington and Meyers in ref 34.[35]

The reaction during the addition of methanesulfonyl chloride to a solution of **3** in DMF was *exothermic*. The inner temperature of the reaction mixture immediately rose gradually upon addition of methanesulfonyl chloride but could be easily kept at around 70 °C by controlling the addition rate. The mixture was stirred at 70 °C for 1−5 h followed by the addition of water and extraction of the product into toluene to give **8** in 96% yield and 91% purity. The purity obtained for **8** solely depended on the purity of the starting material

(30) To obtain higher yields, the distillation steps might be omitted during future campaigns without significantly compromising the purities.
(31) Due to the time pressure of the project, we were not able to carry out more experiments with KOtBu to avoid gel formation, e.g. to test that base with other solvents on a multigram scale.
(32) Experiments to replace DIBALH with $LiALH_4$ and Red-Al only resulted in degradation of **2**.
(33) A maximum of 63% yield had been obtained earlier on a 250-g scale.
(34) Collington, E. W.; Meyers, A. I. *J. Org. Chem.* **1971**, *36*, 3044−3045.
(35) Taylor, E. C., Ed. *Advances in Organic Chemistry: Methods and Results*; Iminium Salts in Organic Chemistry. Böhme, H., Viehe, H. G., Eds.; Vol. 9, Parts 1 and 2; John Wiley & Sons: New York, 1979.

Scheme 4. **Pilot-plant synthesis of (*S*)-2-ethoxy-3-(4-hydroxyphenyl)propanoic acid isopropyl ester 9[21,36,37]**



3 (additional *cis*−*trans* isomerization was usually ≤1%) and did not change with minor variations of reaction parameters. As short-path distillation of **8** did not improve its purity, the compound was used without purification in the next step.

The key intermediate phenol **9** was readily available in kilogram quantities from a pilot-plant campaign of our ragaglitazar development project.[12,21] Therefore, and not due to chemical reasons, the isopropyl ester **9** was used for scaling instead of the ethyl ester **4** used in the original medicinal chemistry synthesis. The pilot-plant process on a 40−50-kg scale towards r***ac*-4**, starting from 4-benzyloxybenzaldehyde, and the enzymatic hydrolysis to **11** has been published before (Scheme 4).[21,36,37] The key intermediate **9** was prepared by acid-catalyzed esterification of **11** in excess 2-propanol.[12] This procedure had been further optimized for pilot-plant scale and was run on a 42-kg scale to yield **9** in 99% chemical and 99.4% optical purity.

Alkylation of the phenol **9**[12,21] with the allylic chloride **8** in acetone, with a catalytic amount of potassium iodide, using potassium carbonate as a base, readily gave the ester **10** in 96% yield and 92% purity as an oil, which was used without purification in the next step. **NNC 61-4655** was then obtained from **10** by simple saponification with aqueous sodium hydroxide in 98% yield and 94% purity. The amount of solvents used during saponification was significantly (ca. 6×) reduced in comparison to the original medicinal chemistry procedure. To achieve practical solubility and phase separation at these high concentrations, the hydrolysis had to be carried out at 70 °C along with the workup at 55−60 °C. **NNC 61-4655** was a low-melting wax (mp ≥ 71 °C), which could not be crystallized and was therefore used directly in the following salt formation. No *cis*−*trans* isomerization and less than 1% racemization was observed under the reaction conditions during the transformation {**8** + **9** →**10** → **NNC 61-4655**}.

Salt Assessment and Preparation. A suitable salt of **NNC 61-4655** was highly desirable at this stage of the project. First, a salt of **NNC 61-4655** might give the possibility of purifying the final product by crystallization, second a salt would be preferred for pharmaceutical development.[38,39]

To identify a suitable salt of **NNC 61-4655** for pharmaceutical development, various bases, which are commonly used in pharmaceutical products, were screened for salt formation with the carboxylic acid **NNC 61-4655** (pK_a = 3.6) in a range of solvents. Precipitates of **NNC 61-4655** on milligram scale were obtained with potassium hydroxide, sodium hydroxide, L-arginine, L-lysine, 2-aminoethanol, ethylenediamine, benethamine, and benzathine. The precipitates were tested by differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), powder X-ray diffraction (XRD), and dynamic vapor sorption (DVS) to elucidate their melting points, thermal properties, crystallinities, and hygroscopicities, respectively. Additionally the following properties were calculated by semi-emperical calculations: intrinsic solubility, pH solubility profile, and ionisable properties (pK_a values). Four crystalline salts (L-arginine, 2-aminoethanol, benethamine, and benzathine) were then selected as first-round salt candidates on the basis of crystal and thermodynamic properties, hygroscopicity, and aqueous solubilities (see Table 1).

During the progression of the project, more data relevant for salt selection were generated in parallel, and the final salt candidate was elected: The results of a four-week stability study[40] revealed a possible instability of the benethamine salt, which was excluded as a candidate. The otherwise overall favorable L-arginine was not chosen due to its degradation susceptibility towards light exposure. The benzathine salt was discarded due to its low melting point and its unfavorable acid ratio. The 2-aminoethanol salt of **NNC 61-4655** (Scheme 5) was chosen as the preferred candidate for further development. Its high melting point together with a demonstrated integrity of the crystal form, a good chemical stability, and its non-hygroscopicity made it appropriate for tablet formulation.[41] Furthermore, this salt had the highest acid ratio and sufficient solubility of 3.0 mg/mL (pH 7) to

(36) Deussen, H.-J.; Zundel, M.; Valdois, M.; Lehman S. V.; Weil, V.; Hjort, C., M.; Østergaard, P. R.; Marcussen, E.; Ebdrup, S. *Org. Process Res. Dev.* **2003**, *7*, 82−88.

(37) Rahbek Østergaard, P.; Mailand Hjort, C.; Deussen, H.-J.; Zundel, M., Ebdrup, S.; Christensen, S.; Patkar, S. PCT-Appl. WO 02/12472.

(38) Stahl, H. W.; Wermuth, C. G. *Handbook of Pharmaceutical Salts, Properites, Selection, and Use*; Wiley-VCH: Weinheim, 2002.

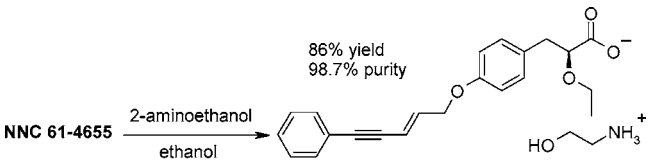
(39) Bastin, R. J.; Bowker, M. J.; Slater, B. J. *Org. Process Res. Dev.* **2000**, *5*, 427−435.

(40) Performed at three different conditions, 40 °C/75% relative humidity, 60 °C/ambient humidity, ambient humidity and temperature/ light exposure, and analyzed with the following methods: XRD, Karl Fischer, HPLC purity and assay, DSC, and TGA.

Table 1. **Comparison of first-round NNC 61-4655 salt candidates**

test	**NNC 61-4655** L-arginine	**NNC 61-4655** aminoethanol	**NNC 61-4655** benethamine	**NNC 61-4655** benzathine
appearance of powder	white	yellow	pale yellow	white
melting point DSC onset (°C)	208.5	147.9	120.2	109.2
preliminary polymorphism study	no other form detected	no other form detected	no other form detected	no other form detected
other thermal behavior	nothing detected	nothing detected	nothing detected	nothing detected
aqueous solubility (mg/mL)	2.0	3.0	0.06	0.1
hygroscopicity	non-hygroscopic	non-hygroscopic	non-hygroscopic	non-hygroscopic
acid ratio	67%	85%	62%	59%
four-week stability study[40]	light-sensitive 13% decrease	stable	4−6% decrease at 40 and 60 °C	stable

Scheme 5. **Scaled GMP-kilo-laboratory synthesis of the salt NNC 61-4655, 2-aminoethanol**



NNC 61-4655, 2-aminoethanol

satisfy standard dissolution requirements. Another advantage was that it was easiest to crystallize and the obtained crystals had the best filtration properties on large scale.

Ten solvents (EtOAc, EtOH, acetone, CH_3CN, iPrOAc, THF, iPrOH, tBuOAc, 1-PrOH, MTBE) were tested to find the optimum solvent for the preparation and crystallization of **NNC 61-4655**, **2-aminoethanol**, first on a milligram- and then on a multigram scale. The same crystal form was always found, independent of the crystallization conditions and the solvent. We finally choose ethanol as the solvent of choice, which allowed a good control of the crystallization process, yielded filterable crystals, enhanced the relative purity of the salt by 4−5% in comparison to the crude acid, and gave a reasonable isolated yield (≥86%) of **NNC 61-4655**, **2-aminoethanol** on scaling of the crystallization procedure.[42] Thus, the crude **NNC 61-4655** from the GMP-kilo-synthesis was transformed into its 2-aminoethanol salt **NNC 61-4655**, **2-aminoethanol** in 86% yield and 98.7% HPLC purity.[43] This allowed us to explore the final salt form of the future drug as early as in preclinical development and for the first human dose.

Conclusions from the Scaled GMP-Kilo-Laboratory Synthesis. A scalable synthetic route was developed for the synthesis of the title compound on the basis of a modified medicinal chemistry route. More than 900 g of **NNC 61-4655**, **2-aminoethanol** was finally synthesized in 32% overall yield starting from phenylpropargyl aldehyde **1** under GMP conditions only three months after this compound had been selected as a drug candidate for pharmaceutical development. The overall yield towards **NNC 61-4655** was enhanced in comparison to that from the original medicinal chemistry route from 24% yield[23] to 37%. The quantity and quality of the batch was adequate to allow complete preclinical and phase I clinical studies with the same batch. A pharmaceutically acceptable salt with excellent properties was identified early in the development process, and this should facilitate the whole future development program.

However, the current synthesis has some drawbacks with regard to a future production on a commercial scale. The synthesis of the allylic chloride **8** requires five steps and only gives **8** in 18% overall yield. Although this yield might be improvable by more optimization work (e.g. by omitting distillation steps), we decided to search for a new synthetic route towards **8** due to the following reasons: (a) The current synthesis for the intermediate **3** requires DIBAL-H, which is pyrophoric and rather expensive. A literature search and our initial investigations indicated that DIBAL-H might not be exchangeable with another reducing reagent.[32] (b) The existing procedure for the ester **2** would have to be significantly improved with regard to the current process and workup. The formation of phosphine during the reduction of **2** would be a safety issue on a commercial production scale. Conversely, it was obvious to retain the sequence {**8** + **9** → **10**} due to the availability of the key intermediate **9**.[36] Therefore, we continued with our development program just after the preparation of the first GMP batch to find a shorter route towards the second key intermediate **8**, which will be described in the following section.

Development Work after the GMP-Kilo-Laboratory Synthesis and Final Conclusions. The synthesis of 5-phenylpent-1-en-4-yn-3-ol **12** (Scheme 6) from phenylacetylene **1** and acrolein has been described in the literature although without giving experimental details.[44] Chou et al.[45] have recently illustrated that **12** can be transformed into **8** by different halogenating agents in varying yields and *E*/*Z*-ratios. By improving the described methods and adapting the procedures to become applicable for large-scale production we developed a straightforward two-step synthesis for the key intermediate **8** on a laboratory scale (44 g). The allylic alcohol **12** was obtained by addition of deprotonated phenylacetylene to acrolein in 86−93% yield as a raw product of 65−70% purity. The major obstacle of this reaction was undesired polymerization of acrolein, which

(41) A mechanical grinding stability experiment and an eight-week stability study under accelerated storage conditions (60 °C/ambient humidity) performed after the preparation of the GMP-batch confirmed the selection of the **NNC 61-4655, 2-aminoethanol** salt as development candidate.

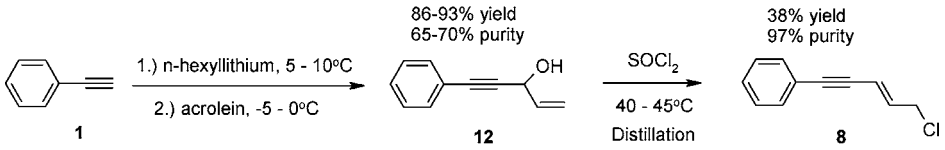
(42) No polymorphism was observed for any of the batches produced.

(43) HPLC: 0.31% ***cis*-NNC 61-4655**; two major impurities of unknown structure (0.10% + 0.77%); CE: ≤1.7% ***R*-NNC 61-4655**; KF water: 0.07%; 0.14% solvent residue (EtOH).

(44) Mahrwald, R.; Quint, S. *Tetrahedron Lett.* **2000**, *56*, 7463−7468.

(45) Chou, S.-Y.; Tseng, C.-L.; Chen, S.-F. *Tetrahedron Lett.* **2000**, *41*, 3895−3898.

Scheme 6. **Improved two-step synthesis of the key-intermediate 8**



could be suppressed by optimizing the reaction conditions, mainly by keeping the reaction temperature below 0 °C. The crude compound **12** was then chlorinated with thionyl chloride to give a 5/1 *E*/*Z*-mixture of **8**. By two subsequent distillation steps the *trans*-isomer **8** could be obtained in 38% isolated yield and 97% purity containing less than 3% of the *cis*-isomer. It is expected that this yield will be improved by up to 15% on further scaling due to residual *trans*-isomer **8** in the distillation remainder, which could not be transferred in our equipment on our employed scale. Thus, a scalable two-step synthesis for **8** was developed (≥33−35% overall yield) on a laboratory scale, which could substitute the five-step (18% overall yield) synthesis, used for the first scaling, during the following campaigns and in future production (*Important note*: A *safety* investigation should be carried out for this reaction sequence before further scale up!).

With respect to the coupling step of **8** and **9** and the following steps, further optimization of the process might be achievable. If coupling would be possible with the acid **11** instead of the ester **9**, the esterification step from **11** → **9** could be omitted. The coupling reaction might be carried out in the same solvent in which **8** or **9**/**11** are obtained to avoid an additional solvent-stripping step. More generally, the overall procedure from the coupling of **8** and **9** towards **NNC 61-4655**, **2-aminoethanol** might be further improved.

Despite the promising results, the synthetic route described in this article was no longer an option for future campaigns due to patent application by a competitor claiming compound **9**.[46] Future laboratory activities were initiated to find a novel proprietary scalable route which does not employ **9** for the synthesis of **NNC 61-4655**, **2-aminoethanol** to be used in future campaigns (including production of phase II material).

Experimental Section

General Procedures. Experimental details are described on the largest scale carried out. To produce sufficient amounts of the title compound, some reactions were run multiple times. Batches were then pooled before proceeding with the next reaction step, whenever appropriate. All chemicals, unless otherwise stated, were from Aldrich. ^{1}H NMR spectra were recorded at either 200 MHz on a Bruker Avance DPX 200 or at 400 MHz on a Bruker Avance DRX 400 instrument. Mass spectra were recorded on a Finnigan LCQ quadrupole ion-trap mass spectrometer with an electrospray ion source. The sample in the form of an MeCN: water (1:1) solution (121 mg/L) was introduced using a syringe pump inlet (flow: 3 μL/min). Source voltage: 3.3 kV. Capillary voltage: 8.56 V. Capillary temp: 200 °C. Collision energy: 36%. Elemental analyses were performed on a Fisons instrument EA 1108 elemental analyzer. The capillary electrophoresis (CE) analysis was performed on a HP3DCE instrument (Agilent, Waldborn, Germany) equipped with an auto sampler, a capillary cartridge, a high-voltage power supply, a diode array detector, electrodes, and a hydrostatic injection system. The electrophoretic data system was the HP Chemstation software, and the data were collected with a frequency of 10 Hz. The CE separations were carried out with untreated fused-silica capillaries from Agilent with the following dimensions: 80.5 cm total length with 72.0 cm effective length, 50 μm inner diameter, and extended light path with an inner diameter of 150 μm at the detector window. The electrolyte was prepared by dissolving 3.0% (w/v) sulfobutyl ether-β-cyclodextrin (Advasep 4, Cydex, Inc., Overland Park, KS) and 0.50% (w/v) dimethyl-β-cyclodextrin (Agilent, Waldborn, Germany) both in 50 mM borate buffer pH 9.3 (Agilent) followed by filtering through a 0.45 μm polypropylene filter. To this solution was added 5% (v/v) MeCN to give the final electrolyte. The electrophoresis was carried out in normal polarity mode. The electrophoretic conditions were as follows: voltage, 21 kV; current, 50 μA; capillary temperature controlled at 25 °C; injection was 50 mbar for 4.0 s; detection, UV at 205 nm with reference of 380 nm. The sample concentration was 0.05 mg/mL in 1/5 acetonitrile/5 mM borate buffer pH 9.3. The capillary was conditioned with 0.1 N NaOH for 20 min daily and flushed with 0.1 N NaOH (3 min), water (2 min), and electrolyte (3 min) between each run. HPLC: (a) detection: 273 nm; flow: 1.0 mL/ min; column: Water Symmetri C18, 5 μm, 3 mm × 150 mm; 35 °C, gradient (15−65%): MeCN, 0.25 M phosphate buffer pH 7; (b) detection: 250 nm; flow: 1.0 mL/ min; column: Merck LiChrospher RP-18, 5 μm, 4 mm × 250 mm; 35 °C; gradient (20−80%): MeCN/water (20:80, v:v) + 0.1% H_3PO_4, MeCN + 0.1% H_3PO_4. (c) detection: 220 nm; flow: 1.0 mL/ min; column: Merck LiChrospher RP-18, 5 μm, 4 mm × 250 mm; 35 °C, isocratic MeCN/water (26:74, v:v) + 0.1% H_3PO_4. Powder X-ray diffraction patterns were recorded on a Bruker D8 Advance diffractometer equipped with a multilayer mirror that selects the Cu Kα radiation (λ = 1.5418 Å). Samples were mounted in flat plate reflection geometry, and the diffracted intensities were detected with a scintillation counter. Scan ranges were 2−30° in diffraction angle 2θ with steps of 0.03° and a speed of 6 s/step. All the aforementioned salts were crystalline. Differential scanning analysis (DSC) for melting-point determination was executed on a MDSC 2920, TA Instruments. Samples (approximately 2−5 mg) were heated in pinhole-crimped aluminium pans from 25 to 280 °C at a rate of 5 °C/min. The DSC measuring chamber was continuously purged with dry nitrogen during the runs, and the instrument was routinely calibrated with

(46) Andersson, K. PCT-Appl. WO 99/62872.

indium and tin. DSC for safety evaluation was executed from 25 to 500 °C at a rate of 10 °C/min without nitrogen purging under air. Thermogravimetric analysis (TGA) experiments were executed on a Thermo Gravimetric Analyser, model 2959, TA Instruments. Samples (approximately 5 mg) were heated in an open platinum pan from 25 to 250 °C at a rate of 10 °C/min. The TGA measuring chamber was continuously purged with dry nitrogen during the runs, and the instrument was routinely calibrated with indium and aluminium. The hygroscopicity properties were investigated by using a dynamic vapor sorption instrument as approximately 15 mg of sample was placed on the sample pan of the instrument. A full cycle of isotherms (sorption and desorption at 25 °C) with equilibrating stations at 10, 20, 30, 40, 50, 60, 70, 80, 90, and 98% relative humidity (RH) was performed. Prior to analysis, the apparatus was calibrated using a built-in calibration program and a certified 100-mg weight. The pH solubility profile of the free acid of **NNC 61-4655** and of the various counterions and the corresponding pK_a values were calculated by use of the ACD Solubility and pK_a program modules, both version 4.0.[47] Gas chromatograms of compound **12** and **8** were recorded on a Hewlett-Packard HP6890 equipped with an FID detector. A temperature ramp (60 to 290 °C at 15 °C/min) was applied. Gas flow: 1.4 mL (He)/min. Column: Optima 5 (Macherey & Nagel), 25 m, 320 μm, film thickness 0.25 μm. Samples were diluted with dichloromethane (to approximately 1%), and 1 μL portions thereof were analyzed using a 20:1 split mode.

Phenylpropargylaldehyde Diethyl Acetal (7). Into a reaction flask equipped with a thermometer and a 25-cm fractionating column (Raschig ring filled) were charged 2.90 kg (28.4 mol) of phenylacetylene **6** (*exothermic* DSC-onset: 189 °C) (98%), 4.21 kg (28.4 mol) of triethyl orthoformate (99%), and 170.5 g (0.53 mol) of zinc iodide (>98%). Ethanol was slowly distilled from the reaction mixture, which was heated to about 117 °C inner temperature before refluxing in the still-head was begun. A total of 1.9 L of distillate (bp 76−80 °C) was collected over a period of 5 h as the inner temperature of the reaction mixture gradually rose to 196 °C (due to external heating). The reaction mixture was cooled to room temperature and filtered through a pad of Celite. The filtrate was then distilled under reduced pressure at 3.5 mbar. A total of 700 g of fore-run was discarded until a boiling point of 111 °C was reached. The remaining main fraction was then distilled at 112−130 °C inner temperature (bp: 102−104 °C/2.0 mbar) to give 4.00 kg (69% yield, HPLC-purity: 99%) of **6** (*exothermic* DSC-onset: 293 °C) as a colorless oil. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.40 (m, 2H), 7.48 (m, 1H), 7.59 (m, 2H), 9.39 (s, 1H).

Phenylpropargylaldehyde (1). Into a reaction flask equipped with a nitrogen inlet, a thermometer, and a variable takeoff splitter distillation head fitted with a 27-cm fractionating column (Raschig ring filled) was charged 4.676 kg (22.9 mol) of phenylpropargylaldehyde diethyl acetal **7** (99%). Sulfuric acid (4 N, 4.8 L) was added, and the reaction mixture was slowly heated with stirring. The ethanol formed was distilled off at such a reflux rate that the still-head temperature was kept between 79 and 85 °C (inner temperature to 86−96 °C). A total of 2750 mL of distillate was collected over a period of about 5 h. The reaction mixture was cooled to room temperature and extracted twice with 3.4 L of MTBE. The combined MTBE phases were washed with 2.7 L of water, and the MTBE was removed in vacuo. The obtained oil was then distilled (short path) at 84−106 °C inner temperature (bp: 78−80 °C/4.0 mbar) to give 2.117 kg (67% yield based on 93% HPLC-purity) of **1** (*exothermic* DSC-onset: 175 °C) as a colorless oil containing 4% (HPLC) of **7**. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.28 (t, 6H), 3.74 (m, 4H), 5.49 (s, 1H), 7.31 (m, 3H), 7.48 (m, 2H).

***E*-5-Phenyl-pent-2-en-4-ynoic Acid Ethyl Ester (2).** NaOEt (96%) (699 g, 9.86 mol) was suspended in 7.25 L of dry toluene under a nitrogen atmosphere. Triethyl phosphonoacetate (Fluka 99%) (2.112 kg, 9.42 mol) dissolved in 1.2 L of dry toluene was added dropwise to the stirred suspension, keeping the inner temperature between 21 and 24 °C. The mixture was stirred for an additional 30 min at that temperature after complete addition. Phenylpropargylaldehyde **1** (93%) (1.115 kg, 8.22 mol) dissolved in 2.0 L of dry toluene was added dropwise over 1.5 h to the stirred mixture, keeping the inner temperature between at 20−25 °C. The mixture was stirred for an additional 60 min at that temperature after complete addition. Sulfuric acid (4 N, 6.6 L) was then added cautiously, keeping the inner temperature between 0 and 25 °C. The organic phase was separated and washed twice with 4.4 and 2.2 L of aqueous $NaHCO_3$ (10%). The toluene was then removed in vacuo to give 2.013 kg (100% = 1.645 kg) of crude **2** as brown oil,[48] which was used in the next step without purification. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.31 (t, 3H), 4.24 (q, 2H), 6.29 (d, 1H, J = 15 Hz), 6.98 (d, 1H, J = 15 Hz), 7.3 (m, 3H), 7.48 (m, 2H).

***E*-4-Phenylbut-1-en-3-yn-1-ol (3).** *Caution*: This step should only be carried out in a well-ventilated fume hood due to the formation of phosphine originating from phosphor-containing impurities! Raw *E*-5-phenyl-pent-2-en-4-ynoic acid ethyl ester **2** (1.266 kg, ~5.17 mol) dissolved in 540 mL of dry toluene was added dropwise over 1.5 h to 6.48 kg (11.39 mol) of diisobutylaluminium hydride (DIBAL-H 25 wt % solution in toluene), keeping the inner temperature between 15 and 20 °C under a nitrogen atmosphere (*gas evolution*!). The reaction mixture was stirred at 15−20 °C inner temperature for another 30 min after complete addition. The reaction mixture was then added *cautiously* over 2.5 h to 9.8 L of hydrochloric acid (4 N) with stirring, keeping the inner temperature between 15 and 25 °C (*exothermic*!). The organic phase was separated and washed with 4.0 L of water. The toluene was removed in vacuo to give 903 g of an oil, which was distilled (short path) at 134−170 °C oil bath temperature (bp: 114−118 °C/1.5−3.0 mbar) to give 356 g (41% yield based on 95% HPLC-purity over two steps: {**1**→**2**→**3**} of **3** (*exothermic* DSC-onset: 253 °C) as a colorless oil. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.88 (br s,

(47) Advance Chemistry Development Inc., 90 Adelaide Street West, Toronto, Ontario M5H 3V9, Canada.

(48) *Exothermic* DSC-onset of pure **2** (after distillation): 248 °C.

1H), 4.25 (dd, 2H), 5.96 (dd, 1H), 6.34 (dd, 1H), 7.27 (m, 3H), 7.42 (m, 2H).

***E*-5-(Chloropent-3-en-1-ynyl)benzene (8) from Phenylbut-1-en-3-yn-1-ol 3.** *E*-4-Phenylbut-1-en-3-yn-1-ol **3** (95%) (678.3 g, 4.07 mol) was dissolved in 1.9 L of DMF. Methanesulphonyl chloride (540.0 g, 4.71 mol) was added dropwise with stirring, and the inner temperature rose to 70 °C (ice-bath cooling is necessary). The reaction mixture was further stirred at that temperature for 1.5 h. The reaction mixture was cooled to room temperature, and 1.9 L of water was added within 30 min (temperature rose to 33 °C). The mixture was extracted twice with 1.3 L of toluene. The combined organic phases were washed twice with 1.3 L of water. The toluene was removed in vacuo to give 755.0 g of raw **9** (*exothermic* DSC-onset: 219 °C) (96% yield based on 91% HPLC-purity) as an oil (containing <4% *cis*-isomer and ≤3% **3**), which was used in the next step without purification. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 4.12 (dd, 2H), 5.98 (dd, 1H), 6.28 (dd, 1H), 7.30 (m, 3H), 7.42 (m, 2H).

(*S*)-*E*-2-Ethoxy-3-[4-(5-phenylpent-2-en-4-ynyloxy)phenyl]propanoic Acid Isopropyl Ester (10). (*S*)-2-Ethoxy-3-(4-hydroxyphenyl)propanoic acid isopropyl ester **9** (99%, containing 0.3% *R*-isomer) (1.042 kg, 4.09 mol) and 700.0 g (3.60 mol) of *E*-5-(chloropent-3-en-1-ynyl)benzene **8** (91%) were dissolved in 2.4 L of acetone followed by the addition of 821.0 g (5.94 mol) of potassium carbonate and 66.0 g (0.396 mol) of potassium iodide. The mixture was refluxed for 5 h and then allowed to cool to room temperature. MTBE (1.35 L), and 4.6 L of water were added to the mixture. The organic phase was separated and washed twice with 1.2 L of aqueous NaOH (1 N) and with 1.2 L of saturated NaCl solution. The solvents were removed in vacuo to give 1.468 kg of **10** (96% yield based on 92% HPLC purity) as an oil, which was used in the next step without purification. ^{1}H NMR 400 MHz ($CDCl_3$) δ 1.15 (3H, d, J = 7 Hz), 1.16 (3H, t, J = 7 Hz), 1.22 (3H, d, J = 7 Hz), 2.94 (2H, d, J = 6.6 Hz), 3.35 (1H, m), 3.59 (1H, m), 3.94 (1H, t, J = 6.6 Hz), 4.59 (2H, dd, J = 5.3 Hz, 1.8 Hz), 4.98−5.07 (*1H*, m), 6.05 (1H, dt, J = 15.8 Hz, 1.8 Hz), 6.36 (1H, dt, J = 15.8 Hz, 5.3 Hz), 6.82 (2H, d, J = 9 Hz), 7.16 (2H, d, J = 9 Hz), 7.28−7.30 (3H, m), 7.41−7.43 (2H, m). ^{13}C NMR 100 MHz ($CDCl_3$) δ 15.51, 22.23, 38.83, 66.48, 68.05, 68.75, 80.81, 87.55, 91.01, 112.66, 114.92, 123.54, 128.73, 130.12, 130.92, 131.93, 138.17, 157.50, 172.52.

(*S*)-*E*-2-Ethoxy-3-[4-(5-phenylpent-2-en-4-ynyloxy)phenyl]propanoic Acid (NNC 61-4655). A mixture of 1.466 kg (3.44 mol) of (*S*)-*E*-2-ethoxy-3-[4-(5-phenylpent-2-en-4-ynyloxy)phenyl]propanoic acid isopropyl ester **10** (92%), 4.9 L of ethanol (96%), and 5.6 L of aqueous NaOH (1 N) solution was heated for 3 h at 70 °C inner temperature with stirring. The ethanol was distilled off under reduced pressure, and 20.6 L of saturated NaCl solution was added to the reaction mixture, which was kept at 60 °C to obtain a clear solution. The basic water phase was then washed 3× with 2.0 L of MTBE at 55 °C. MTBE (2.0 L) was added to the mixture, and the water phase was acidified to pH 2 with concentrated hydrochloric acid. The organic phase was separated, and the water phase was extracted with 2.0 L of MTBE. The MTBE of the combined organic phases was removed in vacuo to give 1.257 kg of **NNC 61-4655** (98% yield based on 94% HPLC-purity) as an oil, which solidified on standing to give a brown wax. **NNC 61-4655** was used in the following crystallization without purification. ^{1}H NMR 400 MHz (acetone-d_6) δ 1.10 (3H, t, J = 7 Hz), 2.90 (1H, dd, J = 14 Hz, 8 Hz), 3.01 (1H, dd, J = 14 Hz, 4 Hz), 3.38 (1H, dq, J = 7 Hz, 9 Hz), 3.63 (1H, dq, J = 7 Hz, 9 Hz), 4.04 (1H, dd, J = 8 Hz, 4 Hz), 4.69 (2H, dd, J = 5.3 Hz, 1.8 Hz), 6.14 (1H, dt, J = 16 Hz, 1.8 Hz), 6.43 (1H, dt, J = 16 Hz, 5.3 Hz), 6.90 (2H, d, J = 8.5 Hz), 7.21 (2H, d, J = 8.5 Hz), 7.36−7.40 (3H, m), 7.43−7.47 (2H, m). ^{13}C NMR 100 MHz (acetone-d_6) δ 15.41, 38.77, 66.37, 68.09, 80.53, 88.03, 90.89, 112.38, 115.19, 124.01, 129.30, 129.39, 130.96, 131.32, 132.20, 139.66, 158.04, 173.38.

(*S*)-*E*-2-Ethoxy-3-[4-(5-phenylpent-2-en-4-ynyloxy)phenyl]propanoic Acid, 2-Aminoethanol (NNC 61-4655, 2-Aminoethanol). (*S*)-*E*-2-Ethoxy-3-[4-(5-phenylpent-2-en-4-ynyloxy)phenyl]propanoic acid **NNC 61-4655** (94%) (977.0 g, 2.62 mol) was dissolved in 4.6 L of ethanol (96%). The solution was heated to reflux, and 178.7 g (2.90 mol) of 2-aminoethanol (99%) dissolved in 280 mL of ethanol (96%) was added dropwise to the boiling mixture. The mixture was slowly allowed to cool to ambient temperature overnight with stirring (crystallization starts at 70 °C). The formed crystals were filtered off and washed 3× with 500 mL of ethanol (96%). The crystals were dried at 30 °C in vacuo overnight and sieved (1.0 mm) to give 935.8 g of **NNC 61-4655, 2-aminoethanol** (86% yield based on 98.7% HPLC-purity) as light-yellow crystals (DSC onset: 152.5 °C, DSC melting: 155.1 °C) (containing 0.31% *cis*-isomer and ≤1.7% *R*-isomer). Anal. Calcd for C, H, N [corrected for 0.07% water (Karl Fischer)]: C, 70.00; H, 7.11; N, 3.40. Found: C, 70.04; H, 7.34; N, 3.36. ESI-MS: 351 (MH^+). ^{1}H NMR 400 MHz (DMSO-d_6) δ 1.00 (3H, t), 2.64−2.70 (1H, m), 2.79 (2H, t), 2.84−2.88 (1H, m), 3.13−3.21 (1H, m), 3.52−3.58 (3H, m), 3.63−3.67 (1H, m), 4.65 (2H, d), 6.14 (1H, d), 6.41 (1H, dt), 6.84 (2H, d), 7.14 (2H, d), 7.37−7.41 (3H, m), 7.43−7.48 (2H, m).

5-Phenylpent-1-en-4-yn-3-ol (12). Phenylaetylene **6** (98%) (128.7 g, 1.23 mol) was added dropwise over 1 h to 350.0 g (1.2 mol) of *n*-hexyllithium in *n*-hexane (2.4 N) under an inert atmosphere, keeping the inner temperature between 5 and 10 °C. MTBE (148 g) was added to the suspension, which was stirred for 2 h at room temperature. The mixture was cooled to −5−0 °C, and a solution of 56.1 g (0.95 mol) of acrolein (95%) in 222 g of MTBE was added over 1 h at that temperature. The suspension slowly became a homogeneous mixture after it slowly (30 min) had been heated to room temperature. This mixture was slowly added to a slurry of 79 g of acetic acid (98%) and 290 g of ice, keeping the inner temperature below 30 °C. The organic phase was separated, and the water phase was extracted with 55 g of MTBE. The combined organic phases were washed with 100 mL water, and the solvent was removed in vacuo to give 198.9 g of **12** (86−93% yield based on 65−70% GC purity) as orange oil, which was used in the next step without purification (*Important note*: A thorough *safety* investigation

should be carried out for this reaction before further scale up). ^{1}H NMR 200 MHz ($CDCl_3$) δ 3.1 (1H, s br), 5.14 (1H, d, J = 5 Hz), 5.26 (1H, d, J = 10 Hz), 5.52 (1H, d, J = 16 Hz), 6.09 (1H, ddd, J = 5/10/16 Hz), 7.23−7.36 (3H, m), 7.40−7.52 (2H, m).

***E*-5-(Chloropent-3-en-1-ynyl)benzene (8) from 5-Phenylpent-1-en-4-yn-3-ol (12).** Thionyl chloride (112.5 g, 0.96 mol) was added dropwise over 1 h to a solution of 145.3 g (0.63 mol) of crude 5-phenylpent-1-en-4-yn-3-ol **(12)** (69%) dissolved in 155 g of toluene, keeping the inner temperature between 40 and 45 °C (*gas evolution*: SO_2, HCl!). The mixture was then stirred for a further 12 h at that temperature and then slowly added (remainders were transferred with an additional 50 g of toluene) to a slurry of 139.8 g of potassium carbonate in 50 g of water and 250 g of ice with vigorous stirring (inner temperature ≤ 40 °C). If necessary, the pH was adjusted to 7, and the organic phase was separated. The organic phase was then washed with 100 mL of water at 35−40 °C, and the solvent was removed in vacuo to give 151.7 g of an oil (containing 59% **8** and 12% *cis*-isomer), which was distilled (short path) at ≤120 °C inner temperature (bp: 96−103 °C/0.6−0.8 mbar) to give 92 g of crude **8**. The crude **8** was fractionally redistilled with a Sulzer column (20 theoretical plates) at ≤130 °C inner temperature (bp: 82−85 °C/0.7−1.0 mbar) to give 44.0 g of **8** (38% yield based on 97% HPLC-purity) as an oil (containing ≤3% *cis*-isomer).

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