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A New Practical Route for the Manufacture of (4aR,10aR)-9-Methoxy-1-methyl-6-trimethylsilanyl-1,2,3,4,4a,5,10,10a-octahydrobenzo[*g*]quinoline

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Abstract:

Different synthetic routes to the enantiomerically pure octahydrobenzo[*g*]quinoline derivative JNZ092 were evaluated for their suitability to rapidly prepare a first clinical batch on a kilogram scale. On the basis of the experience of previous octahydrobenzo[*g*]quinoline projects a new linear synthesis of JNZ092 was established and scaled up successfully. The overall yield was increased by a factor 10 and the preparation time shortened significantly as compared to those of the medicinal chemistry route. As the key strategy all atoms of the octahydrobenzo[*g*]quinoline skeleton were introduced early by the reaction of the 6-lithiated 1,7-dimethoxynaphthalene with ethyl-2-cyano-3-ethoxyacrylate. As a valuable technological refinement the practicability of a chromatographic technique with repetitive feed injection for the problematic separation of the enantiomers was demonstrated.

Introduction

Synthetic analogues of ergot alkaloids are of interest in the pharmaceutical and agrochemical industry, because they exhibit a wide spectrum of physiological activities.[1] The enantiomerically pure JNZ092 (**1**;[2] Figure 1) belongs to the new octahydrobenzo[*g*]quinoline class of the ergot analogue structure family,[3,4] which centrally interacts with serotoninergic and α-1-adrenergic receptors without having re-uptake inhibitory activities for other neurotransmitters. It was chosen for clinical development because of its potential to act as an antidepressant and attention-enhancing drug without triggering behavioral or cardiovascular side effects.

In this contribution we describe our experiences with the successful scale-up of a new synthesis for JNZ092 (**1**) established during the early development phase. With the focus on the short-term delivery of the drug substance and an uncompromised process safety, we succeeded in welding several synthetic concepts used before in related projects, such as **2**[4] and **3**[5] (Figure 1), into an improved new synthesis which could satisfy the immediate demands for kg amounts.

Syntheses Evaluation

The medicinal chemistry route for JNZ092 (**1**),[2] comprising 11 chemical steps as outlined in Scheme 1, was deemed unsuitable for large-scale manufacture because of several scale-up difficulties encountered already in bench-scale experiments during the preparation of clinical supplies for **2**, which shared the same intermediate **8** with JNZ092.

Starting from 1,7-dimethoxy naphthalene (**4**) a Birch reduction afforded the 8-methoxy-2-tetralone (**5**), which was regioselectively carboxylated with magnesium methylate and carbon dioxide according to Pelletier et al.,[6] and the resulting acid was esterified with methyl chloroformate in the presence of triethylamine to give the air-sensitive β-ketoester **6**. The Michael addition of the sodium anion of **6** to acrylonitrile, followed by carbodemethoxylation to yield the ketonitrile **7**, proved to be particularly cumbersome on scale-up, because it combined a low and unreliable yield with product solutions which were sensitive to air, temperature, and light. Piperidine ring closure by hydrogenation over platinium oxide in an ethanol/chloroform mixture and direct reductive methylation of the cyclization product with formaldehyde/formic acid gave a 1:2-ratio of the cis/trans diastereomers, from which the *trans*-octahydrobenzo[*g*]quinoline **8** was separated by chromatography. The further transformations to the drug substance **1** employed the resolution of the enantiomers, bromination, and silylation. The major disadvantage of this linear synthesis was the low overall yield (<1%) and a huge waste stream per kilogram of product. Particular weak points besides the mentioned Michael reaction were the low regioselectivity of the piperidine ring annellation, the late resolution of the optical antipodes, and the need for at least five chromatographic purifications.

In the course of our development activities towards another ergot project we had established a new large-scale

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(5) Bänziger, M.; Cercus, J.; Stampfer, W.; Sunay, U. *Org. Process Res. Dev.* **2000**, *4*, 460.

(6) Pelletier, S. W.; Chappell, R. L.; Parthasarathy, P. C.; Lewin, N. *J. Org. Chem.* **1966**, 31, 1747.

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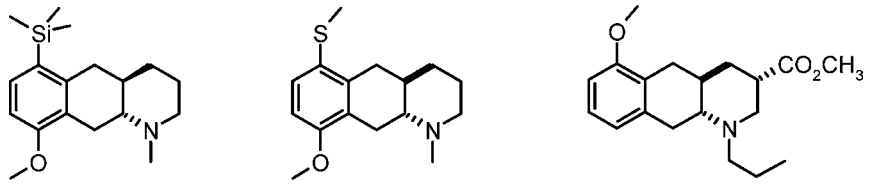
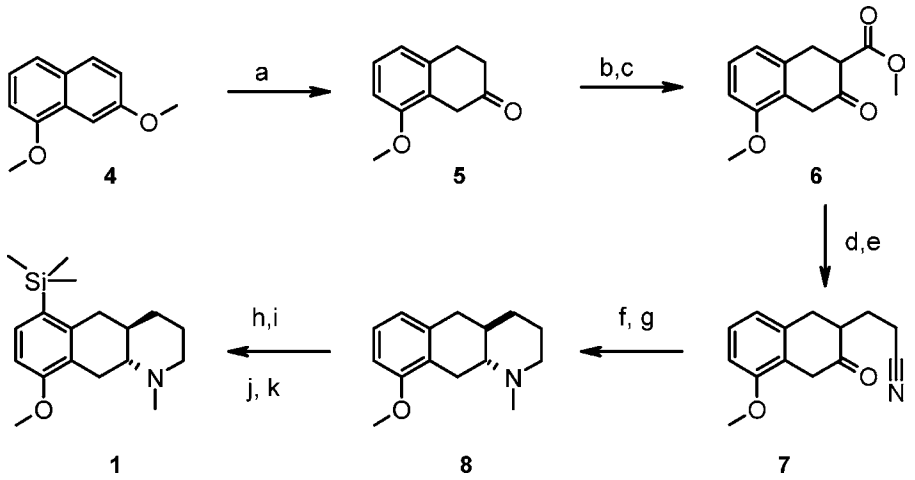


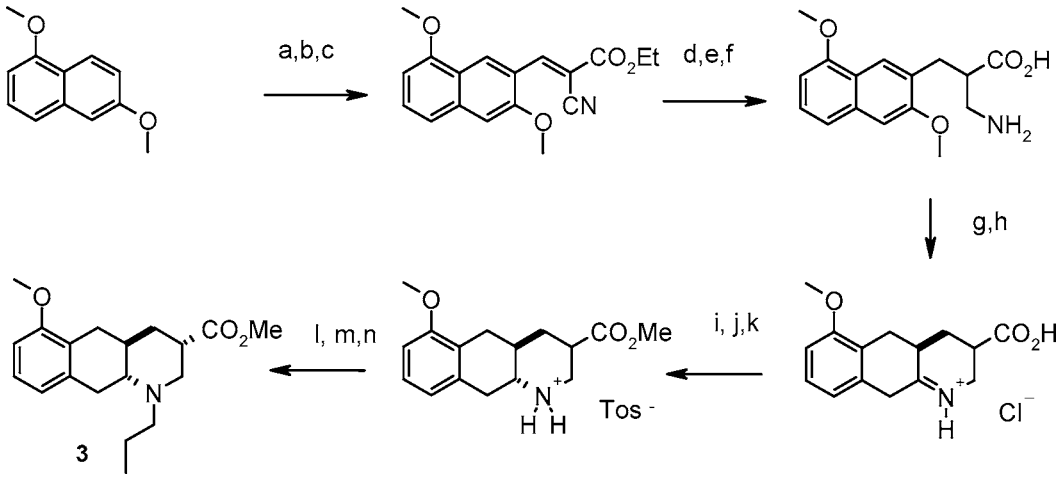
Figure 1. **Octahydrobenzo[*g*]quinolines 1−3.**

Scheme 1. **Research synthesis of JNZ092 (1)[a]**



[a] Reagents and solvents (yield): a) Na, EtOH, H^+ (85%); b) Mg, CO_2, MeOH (73%); c) $ClCO_2Me$, NEt3, CH_2Cl_2 (82%); d) CH_2═CHCN, toluene, MeOH (40%); e) LiCl, tetramethylurea (70%); f) PtO_2, H_2, EtOH, $CHCl_3$; g) HCHO, HCOOH; separation of cis/trans diastereomers (63%); h) (−)-*o*,*o*-ditoluolyl-L-tartaric acid, acetone, diethyl ether (21%); i) Br_2, CH_2Cl_2, CCl_4 (95%); j) *n*-BuLi, TMSCl, THF (60%); k) maleic acid, acetone, diethyl ether (85%).

Scheme 2. **Octahydrobenzo[*g*]quinoline synthesis from ortho-lithiated 1,6-dimethoxynaphthalene[a]**



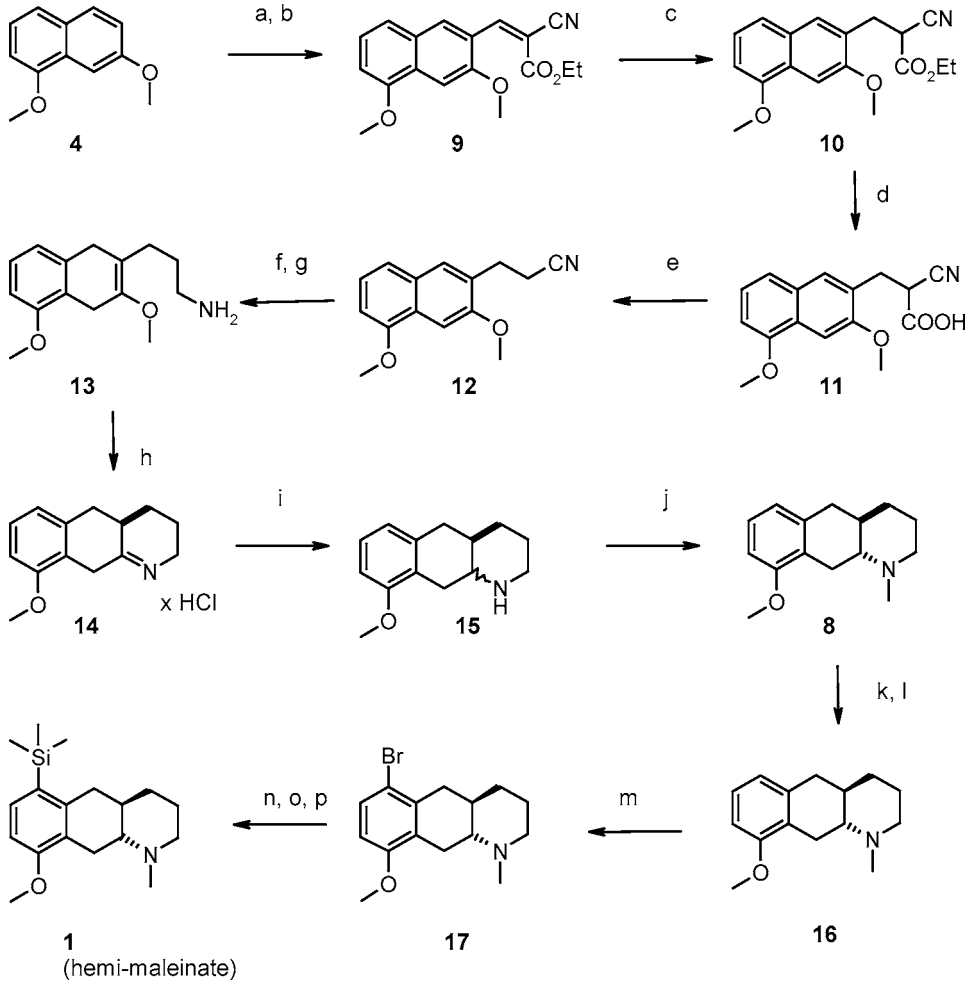
[a] Reagents and solvents: a) hexyllithium; b) ethyl-2-cyano-3-ethoxyacrylate; c) 1 M H_2SO_4; d) H_2; Pt/C; e) LiOH; f) HOAc; g) Li /NH_3/THF; h) HCl (aq); i) $NaBH_4$/MeOH; j) MeOH/H_2SO_4; k) *p*-TosOH; l) *n*-propyliodide/K_2CO_3; m) LDA /TMSCl; n) H_3O^+.

process to the structurally similar octahydrobenzo[*g*]quinoline **3**.[5] As outlined in Scheme 2, the strategy had been to react an ortho-lithiated 1,6-dimethoxynaphthalene with ethyl-2-cyano-3-ethoxyacrylate, followed by catalytic hydrogenation and Birch reduction. This approach was a versatile extension of a generally applicable concept for the construction of octahydrobenzo[*g*]quinolines, initially designed by Hacksell et al.[7] who utilized palladium-catalyzed Heck-reactions of 7-iodo-1,6-dimethoxynaphthalenes and acrylates as the key assembly step.

We reasoned that an analogous strategy could also be exploited for the assembly of the octahydrobenzo[*g*]quinoline skeleton of **1** starting from 1,7-dimethoxynaphthalene (**4**), as outlined in Scheme 3. Careful catalytic hydrogenation of the adduct **9** to avoid the concurrent reduction of the nitrile moiety,[5] subsequent ester cleavage and decarboxylation should lead to the stable propionitrile intermediate **12** already described by the Hacksell group.[7] Also the next steps, the

(7) Mellin, C.; Hacksell, U. *Tetrahedron* **1987**, *43*, 5443.

Scheme 3. **New synthesis of JNZ092 (1)**[a]



[a] Reagents and solvents: a) *n*-BuLi, THF; b) ethyl-2-cyano-3-ethoxyacrylate; c) H_2, Pt−C; d) NaOH; H_2SO_4; e) NaCl, dimethylacetamide; f) Na, butanol; h) aq HCl; i) $NaBH_4$, butanol, acetic acid, water; j) HCO_2H, HCHO; k) separation of cis/trans diastereomers; l) (−)-*o*,*o*-ditoluolyl-L-tartaric acid; m) NaOH/TBME; n) aq HBr 48%; $NaBrO_3$, water, acetic acid; o) *n*-BuLi, THF, TBME, cyclohexane; p) TMSCl; q) maleic acid.

Birch reduction, acidic cyclization, and trans diastereoselective reduction to intermediate **15** had literature precedence.[7]

Thus, the experimental work toward **15** could be dedicated to optimize the reaction conditions and simplify the workup procedures. Because of the project's time constraints it was planned to follow the medicinal chemistry route for the last steps towards the drug substance **1** and to postpone the exploration of stereoselective annelation strategies to a later development stage.

Assembly of the Octahydrobenzo[*g*]quinoline Skeleton. *Intermediate 8.* We expected the ortho-directed metalation of 1,7-dimethoxynaphthalene (**4**) to show a better regioselectivity in the reaction with ethyl-2-cyano-3-ethoxyacrylate than that of the 1,6-dimethoxynaphthalene, since several literature examples with structurally related mono- and dimethoxynaphthalene derivatives suggested an equilibrium between C6- and C8 lithiation,[8] from which preferentially the adduct **9** should be formed with the bulky Michael acceptor (Scheme 4).

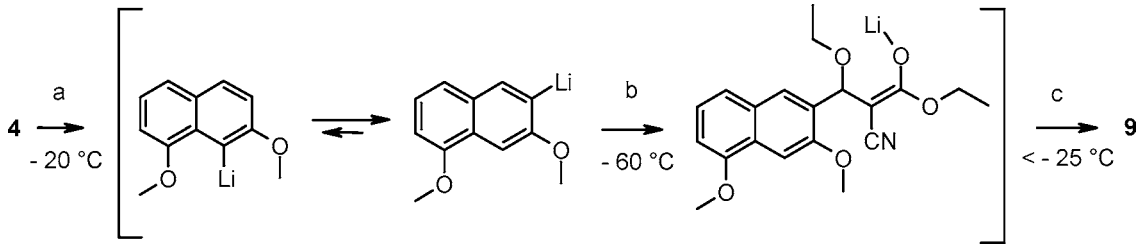
The yields of **9** from the first experiments, however, were disappointingly low. One reason was that the ortho-lithiation of 1,7-dimethoxynaphthalene (**4**) was incomplete even with an excess of butyllithium after several hours at −20 °C. Another crucial variable was the addition of the ethyl-2-cyano-3-ethoxyacrylate for which a low temperature below −60 °C was shown to be preferable. The main factor influencing the yield and quality of the product **9**, however, was found to be the temperature during the addition of the sulfuric acid for workup. The temperature should be kept below −25 °C to avoid unproductive side reactions, presumably occurring from the proposed ester enolate anion intermediate (Scheme 4). In this way the desired adduct **9** could be isolated in up to 83% total yield, which was in comparison to the same reaction with the 1,6-dimethoxynaphthalene[5] a yield increase of more than 20%.

The hydrogenation of **9** was done with a 5% platinum on carbon catalyst at normal pressure.[9] The product **10** could

(8) (a) Barnes, R. A.; Bush, W. M. *J. Am. Chem. Soc.* **1959**, *81*, 4705. (b) Shirley, D. A.; Harmon, T. E.; Cheng, C. F. *J. Organomet. Chem.* **1974**, *69*, 327. (c) Narasimhan, N. S.; Mali, R. S. *Tetrahedron* 1**975**, *31*, 1005. (d) Wilson, J. M.; Cram J. D. *J. Org. Chem.* **1984**, *49*, 4930. (e) Johansson, A. M., Mellin, C.; Hacksell, U. *J. Org. Chem.* **1986**, *51*, 5252.

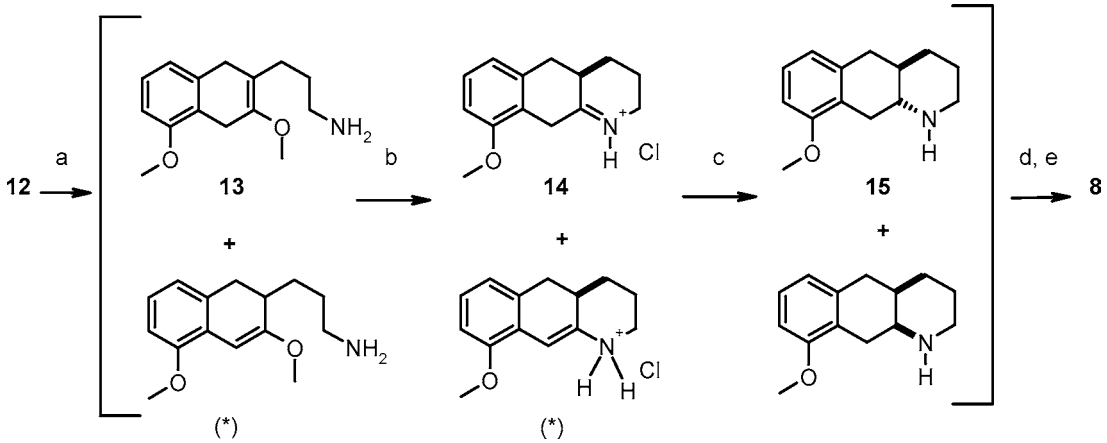
(9) For hydrogenation of similar systems see: (a) Lee, J.; Gauthier, D.; Rivero, R. A. *J. Org. Chem.* **1999**, *64*, 3060. (b) Pollack, M. A. *J. Am. Chem. Soc.* **1943**, *65*, 1335.

Scheme 4. **Proposed mechanistic model for the formation of intermediate 9**[a]



[a] Reagents and conditions: a) *n*-BuLi, THF, TBME, cyclohexane; b) ethyl-2-cyano-3-ethoxyacrylate; c) 1 M H_2SO_4.

Scheme 5. **"Telescoping" the reaction sequence 12 [→ 13 → 14 → 15] → 8 to avoid material loss**[a]



[a] Reagents and conditions: a) sodium, butanol; ca. 95 °C; b) HCl aq, butanol; c) $NaBH_4$, butanol, ethanol, water, acetic acid; d) HCHO 40% aq, HCOOH; e) separation of diastereomers. (*) Tentative structure assignment for byproducts (^{1}H NMR).

be isolated in 79% yield after crystallization. The only drawback was the high dilution of the reaction, since the starting material had a rather low solubility in the organic solvents used usually in hydrogenation reactions. The carbodeethoxylation was performed in two steps. In the first step the ester **10** was hydrolyzed to the acid **11**, which was isolated in 93% yield. We found that the subsequent decarboxylation step worked best in the presence of water and sodium chloride in dimethylacetamide at approximately 130−150 °C, under conditions similar to those recommended by Krapcho for carbodealkylation reactions,[10] to yield the literature-known propionitrile **12**[7] in 85% yield.

The next key step, the simultaneous reduction of the methoxynaphthalene moiety and the nitrile function, was done by carefully adding sodium metal pieces into the butanol solution of **12** at 90−100 °C. These conditions were preferred over the protocol by Hacksell,[7] who used ethanol as the solvent and consequently needed a huge excess of sodium (42 equiv in comparison to 7.5). The reason for this dramatic improvement simply was the slow rate of sodium butoxide formation in butanol as compared to fast sodium ethoxide formation in refluxing ethanol. On larger scale, to minimize the handling hazards associated with the addition of reactive sodium at elevated temperatures to a hydrogen-emitting flammable fluid, the pre-cut sodium cubes were added in small portions through a nitrogen-inertized double air-lock system into the reactor. The reaction temperature of 90−100 °C was found to be particularly important, because the added sodium pieces immediately melted and thus were consumed rapidly in the product-forming reduction steps. At lower temperatures (80−85 °C) the conversion to **13** was hampered, presumably because of the lower surface of the unmolten metal cubes from which now paradoxically sodium butoxide formation occurred predominantly. As a side product, particularly at temperatures above 100 °C, the 1,3-rearranged enol ether was formed (tentative structure assignment, see Scheme 5), which in the acidic hydrolysis also led to the cyclic iminium salt **14**.

Thus, the use of butanol had a further advantage because in the hydrolytic workup the oxidation-sensitive enol ether mixture **13** could be separated with the butanol layer, and converted directly to the cyclic iminium salt **14** by treatment with 15% aqueous HCl. When the water and excess of hydrochloric acid were removed by azeotropic distillation, it was possible to crystallize the iminium hydrochloride **14** in approximately 65% yield. However, we decided against this isolation option and subjected the butanol suspension of **14** (which contained other reducible impurities, tentatively assigned as "enamines" generated from **14** by 1,3 H-shifts, see Scheme 5) directly to the sodium borohydride reduction.[11,12] The rational for this was that the cis/trans regioselectivity was not significantly affected, but the yield of **15** increased because the proposed enamine impurities also produced **15** to some extent. Butanol alone proved not to be a suitable solvent for the sodium borohydride reduction. We found that, besides additional acetic acid to enhance the reduction power of sodium borohydride and to avoid reagent accumulation, the presence of water and ethanol (or methanol) as solubility mediators was necessary in order to have

(10) (a) Review: Krapcho, A. P. *Synthesis* **1982**, 805. (b) Krapcho, A. P. *Synthesis* **1982**, 893. (c) Martin, L. J.; Rawson, D. J.; Williams, J. M. J. *Tetrahedron: Asymmetry* **1998**, *9*, 3723.

an acceptable conversion rate and selectivity in the reduction to the diastereomeric mixture **15**. Cis/trans ratios from 1:4 up to 1:9 were achieved, dependent on the amount of water or ethanol added, which points to the possible involvement of different borohydride species in the reduction. Again, no purification was done at this stage and the semisolid **15** after the hydrolytic workup was directly converted to the corresponding *N*-methylated cis/trans-mixture **8** following an optimized protocol for the reductive Leuckart−Wallach methylation.[13] The desired *N*-methylated trans diastereomer **8** was isolated after a chromatographic purification in 63% yield (based on **12**) and excellent diastereomeric purity (>98%). This means, that the average yield for these five "telescoped"[14] process steps was >90%. Usually such telescoping of reaction sequences by circumventing product isolation or purification is paid for with less robust and less flexible processes since (a) the probability for unknown parameter combinations increases with the variability of the impurity profile entering the subsequent reaction step and (b) the organizational strain on the pilot plant and analytical personal increases with the process complexity. In our example this was justified because selective reactions were involved, and the problems indeed arose from equilibrating products hampering the isolation operations.

Resolution of Enantiomers. The resolution of racemic **8** into the enantiomers was done by diastereomeric salt formation with (−)-*o*,*o*-ditoluoyl-L-tartaric acid in ethanol or acetone, based on the research method. Ditoluoyl-L-tartaric acid in a 1:1 ratio was the superior resolving agent,[15] for which yields of up to 39% of the free base **16** had been repeatedly obtained on a multi-ten-gram scale. The first technical scale-up batch of this method, however, did not work well because the conditions for the isolation for the pure diastereomeric salt proved not to be robust at all. Investigations into the problem revealed that the crystallization of the (−)-1:1-ditoluoyl-L-tartrate salt of **16** was kinetically favored in any suitable solvent (such as acetone, methanol, ethanol, 2-propanol, and their mixtures with ethers), but then gradually the (+)-diasteromeric salt cocrystallized to give a (±)-salt conglomerate. The tendency for this detrimental cocrystallization was delayed by the presence of water and, ironically, also the residual cis impurity (<1%) in the very pure trans compound **16**. The most important factor, however, was found to be the temperature for the isolation of the diastereomeric salt. At a temperature of 37 °C, with stringent observation of the course of the crystallization with HPLC analysis, finally the enantiopure (−)-ditoluoyl tartrate salt could be isolated also on a larger scale and converted to the free base **16** in yields up to 34% (average 29%).

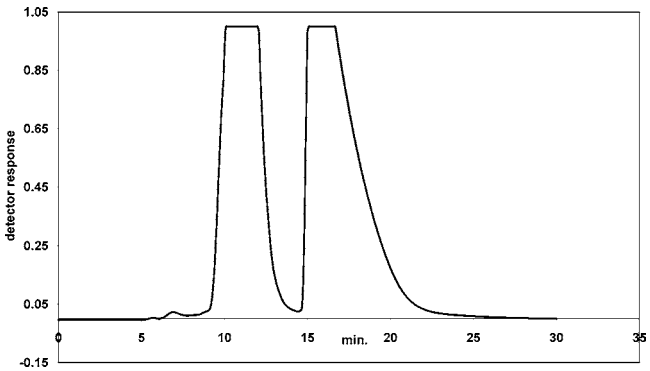


Figure 2. **Chromatographic enantioseparation of 8 on Chiralpak-AD. Chromatographic conditions (injection: 10 g of 8 dissolved in 200 mL of mobile phase; mobile phase: hexane/2-propanol = 98/2 (v/v); flow rate: 400 [mL/min]; ambient temp.; UV-detection: 220 nm; CSP: 2 kg; column diameter: 12 cm i.d.; back pressure: 22 bar).**

As a fall-back position a second method for the enantiomeric resolution was evaluated in our labs using chromatographic separation on Chiralpak AD and demonstrated to have a considerable potential for future batches. The moderate solubility of **8** in the mobile phase (hexane with only 2% 2-propanol), in combination with a large separation factor (α) and a good capacity for the above-mentioned chiral stationary phase (CSP), allowed the easy separation of **8** into its enantiomers with batch elution chromatography. In a typical chromatographic run, as shown in Figure 2, 10 g of **8** was separated quantitatively (yield: ~49%) within 15 min on a column containing 2 kg of CSP.

To enhance the productivity, the loadability was increased further using an automated feed injection technique, which in principle employs the concerted loading of the next sample while the preceding sample is still separating on the column. Thus, the rapid separation of 20-g samples had been realized on lab scale, with only a small decrease of yield. If the fraction between the collected enantiomers was rechromatographed, the yield was again practically quantitative. Considering a pilot-plant column with such a repetitive injection device and a continuous 24-h process, production rates of 0.8 kg of **8**/kg of CSP within 1 day should be feasible. According to our experiences a further increase in productivity can be achieved, if the process is performed under simulated moving bed (SMB) conditions. Productivity would increase by a factor of 2, whereas the real savings will then arise from the reduced amount of mobile phase, which is

(11) Iminium ions are the proposed intermediates in the reductive amination of carbonyl compounds (Review: Baxter, E. W.; Reitz, A. B. In *Organic Reactions*; Overman, L. E., Ed.; Wiley: New York, 2002; Vol. 59, p 1) for which reducing reagents such as sodium cyanoborohydride (Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2897), sodium triacetoxyborohydride (Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996**, *61*, 3849), or sodium borohydride have been recommended (e.g., Schellenberg, K. A. *J. Org. Chem.* **1963**, *28*, 3259). Trans-selective reductions of cylic imines have been reported also with sodium /ethanol (Vierhapper, F. W.; Eliel, E. L. *J. Org. Chem.* **1975**, *40*, 2734).

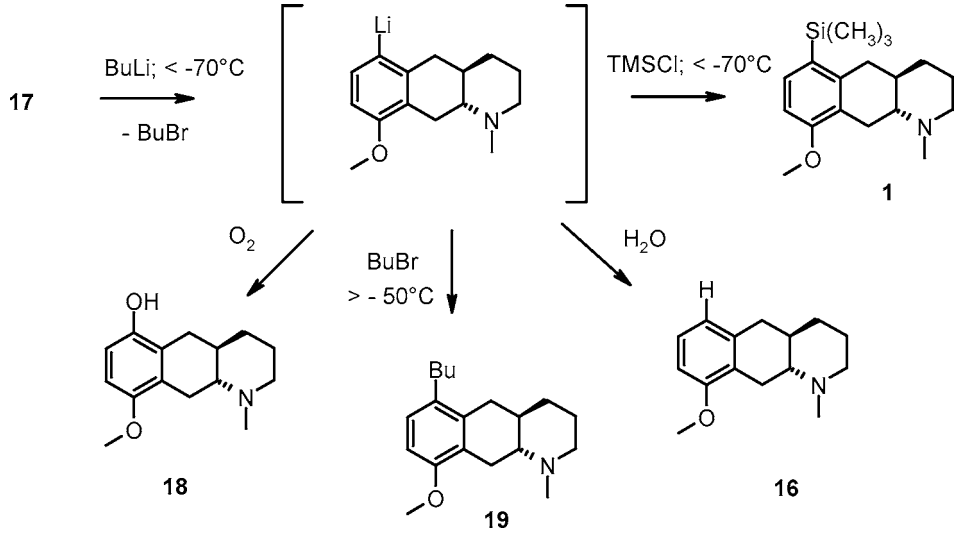
(12) Hydrogenation over platinum on carbon, palladium on carbon and platinum oxide was also tested but resulted in an increased amount of the cis diastereomer, as precedented (e.g., refs 4 and 7).

(13) (a) Li, X.; Schenkel, L. B.; Kozlowski, M. C. *Org. Lett.* **2000**, *2*, 875. (b) Kardos, J.; Blandl, T.; Luyen, N. D.; Doernyei, G.; Gács-Baitz, E.; Simony, M.; Cash, D. J.; Blaskó, G.; Szántay, C. *Eur. J. Med. Chem.* **1996**, *31*, 761. (c) Kitamura, M.; Lee, D.; Hayashi, S.; Tanaka, S.; Yoshimura, M. *J. Org. Chem.* **2002**, *67*, 8685.

(14) The term "telescoping" has been used before to describe sequential multistep/multipot processes with shortened or omitted isolation procedures for the involved intermediates; see, e.g.: Dale, D. J.; Draper, J.; Dunn, P. J.; Hughes, M. L.; Hussain, F.; Levett, P. C.; Ward, G. B.; Wood, A. S. *Org. Process Res. Dev.* **2002**, *6*, 767.

(15) Other resolving reagents, such as e.g., L-tartaric acid, dibenzoyl-L-tartaric acid, L-malic acid, (S)-mandelic acid, (1S)-10-camphorsulfonic acid, had been tested for **8**. The results with regard to optical purity, yield, and crystallization behavior were rated as less favorable as compared to the diastereomeric salt formation with *o*,*o*-ditoluoyl-L-tartaric acid.

Scheme 6. **Reactivity of lithiated 17 towards electrophiles actually or potentially present in the reaction mixture**



typically in the order of 10 compared with batch elution chromatography.

Bromination and Silylation to 1. The bromination had been done in the medicinal chemistry route via the slow addition of an excess of bromine to a solution of the starting material **16** in a dichloromethane/tetrachloromethane solution at 0 °C, followed by a reductive workup with aqueous sodium sulfite and a chromatographic purification.[2] Two equivalents of bromine were necessary because the product precipitated from the reaction mixture as the insoluble and rather corrosive hydroperbromide salt (**17**·HBr_3) which did not participate in the reaction as a brominating agent. The objective of our experimental efforts was to replace this wasteful protocol by the bromide/bromate method in an acidic aqueous medium,[16] in which bromine is generated in situ ($5\ Br^- + BrO_3^- + H^+ \rightarrow 3\ Br_2 + 3\ H_2O$), presumably via a hypobromous acid transient which also is a strong brominating reagent.[17] Indeed the suspension of **16** in aqueous hydrobromic acid could be "titrated" by gradually adding the aqueous sodium bromate solution at 40 °C until a persistent yellow color of bromine indicated the end of the reaction. Addition of the bromate solution was preferred, because alkali bromates generally are strong oxidizing reagents in acidic medium due to the oxygen-generating disproportion reaction to hypobromous acid ($BrO_3^- + H^+ \rightarrow [HBrO_3] \rightarrow O_2 + [HOBr]$)[17] and are able to oxidatively degrade ethers (such as **17**) in autocatalytic reactions.[18] With the inverse bromide/bromate method it was possible to avoid the bromine excess as well as overbromination and isolate the crystalline pure hydrobromide salt of **17** simply by filtration from the reaction mixture. However, it was necessary to add acetic acid to the reaction suspension to achieve complete conversion, presumably because the low solubility of the hydrobromide of **17** caused gradual occlusion of the starting material **16**. The reaction can be performed similarly also in hydrogen bromide/acetic acid solution which enhances solubility and reactivity. The aqueous bromide/bromate procedure was scaled up without problems, and the product base **17** was isolated in up to 92% yield and an excellent purity (>99%), after treatment of the hydrobromide with sodium hydroxide and a crystallization.

The final silylation step to **1** was done via rapid bromo−lithium exchange at temperatures below −70 °C, by addition of butyllithium in cyclohexane to the THF/TBME solution of the intermediate **17**, followed by quenching the anion with TMSCl as outlined in Scheme 6.

The lithium anion of **17** was found to be quite stable in the temperature range between −90 to −50 °C in the solvent mixture, even when the time until addition of the quench solution was delayed by several hours. The alkylation reaction with butyl bromide, generated in the halogen−lithium exchange reaction, was not of significance under the reaction conditions, and **19** (Scheme 6) was only formed slowly if the temperature was raised above −50 °C. The lithium anion of **17**, however, was rather sensitive to humidity and oxidation. Thus, on large scale the inertization of the reactor, and particular the careful inertization of the premixed solution of TMSCl in THF prior to the addition, was of some importance to avoid the oxidation to **18** as a side reaction. If **18** was present in the reaction mixture above 1%, an additional chromatographic purification step was necessary because the final salt formation was hampered by a strong tendency for crust formation, initiated by the salt of **18** precipitating on the reactor walls. With the silylated product free of **18**, the hemi-maleinate salt of **1** was isolated reliably in 78 to 84% yield based on **17**.

Conclusions

The work presented here may be seen as an example of how the continuous refinement of mechanistic concepts for the involved reactions can be used to define and optimize the unit operations of the technical processes. The overall

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yield of the developed synthesis could be improved by a factor of 10 in comparison to that of the former research synthesis. Although not yet exploited for its potential of stereoselective annelation strategies, this synthesis should be applicable also to other chiral quinoline systems which, given a current trend in organic catalysis, could be useful in chiral catalysis.[19]

Experimental Section

Experimental work is described only for the process, which was developed and manufactured on multikilogram scale. The procedures are not fully optimized and reflect the early development stage of the project. The conditions were checked for potential hazards by our internal risk analysis process (DERA)[20] and fulfilled the criteria for safe manufacture on the scale given.

The starting materials, solvents, and reagents were of technical grade, available in bulk. Butyllithium-cyclohexane solutions were obtained from Chemetall. Chiralpak-AD used for the chromatographic separation of the enantiomers consists of amylose tris(3,5-dimethylphenylcarbamate) coated on silica gel (20 μm) and has been purchased from Daicel (Japan). All reactions were carried out under an atmosphere of nitrogen. The NMR spectra were measured on a Bruker Avance 400 spectrometer. The chemical shifts are given in δ (ppm). HPLC purity is given as area normalization.

1,7-Dimethoxynaphthalene (4). To a mixture of 1,7-dihydroxynaphthalene (9.5 kg, 59.3 mol) and NaOH (5.7 kg, 142.5 mol) in 57.6 kg of water at 20 °C was added dimethyl sulfate (22.4 kg, 178 mol) within 1.5 h at a rate to maintain the temperature. This mixture was stirred for another 2 h, heated to 80 °C for 0.5 h, cooled, and left overnight (16 h) at 20 °C. Toluene (95 L) and Filteraid (1.5 kg) were added, and the two-phase system was filtered. After an aqueous workup (toluene/H_2O; NaOH) the toluene layer was evaporated and the crude product **4** distilled by short-path distillation at 134 °C under reduced pressure of 0.5 mbar, to yield 8.83 kg (79% yield) of 1,7-dimethoxynaphthalene, **4**. ^{1}H NMR ($CDCl_3$, 400 MHz): 3.87 (s, 3H), 3.93 (s, 3H), 6.74 (d, J = 7, 1H), 7.08 (dd; J = 2, 9; 1H), 7.18 (t, J = 8, 1H), 7.29 (d, J = 8, 1H), 7.46 (d, J = 2, 1H), 7.62 (d, J = 9, 1H). MS: 188. (M^+): 173, 145, 115.

2-Cyano-3-(3,5-dimethoxynaphthalene-2-yl)acrylic Acid Ethylester (9). To a solution of 1,7-dimethoxynaphthalene (**4**, 19.3 kg, 103 mol) in THF (226 L) at −20 °C was added *n*-BuLi (20% solution in cyclohexane, 40.4 kg, 126 mol) within 1 h. The reaction mixture was stirred at 0 °C for another 3 h and cooled to −70 °C; during 1.25 h a solution of ethyl-2-cyano-3-ethoxyacrylate (20.1 kg, 119 mol) in THF (111 L) was added at such a rate that the temperature did not rise above −65 °C. The reaction mixture was stirred for an additional hour at −65 °C and then warmed to −30 °C; within 0.5 h sulfuric acid (1 M aqueous solution, 64.3 kg) was added, keeping the temperature below −25 °C. During the addition the product started to precipitate. The temperature of the reaction mixture was raised to 0 °C and kept for an additional 30 min. The solids were collected by filtration, washed with ethyl acetate/hexane, and dried under reduced pressure at 50 °C to yield intermediate **9** (21.7 kg, 68%). By extracting the mother liquor with toluene and recrystallization a second crop of **9** (4.8 kg, 15%) was obtained. ^{1}H NMR ($CDCl_3$, 400 MHz): 1.35 (t, J = 7, 3H), 3.94 (s, 3H), 3.95 (s, 3H), 4.35 (q, J = 7, 2H), 6.82 (d, J = 7, 1H), 7.22 (t, J = 8, 1H), 7.41 (d, J = 8, 1H), 7.49 (s, 1H), 8.66 (s, 1H), 8.79 (s, 1H). MS: 311. (M^+): 296, 268, 241, 208, 180.

2-Cyano-3-(3,5-dimethoxynaphthalen-2-yl)propionic Acid Ethylester (10). Intermediate **9** (21.63 kg, 69 mol) was hydrogenated in a mixture of ethanol (202 L) and THF (216 L) over 5% Pt/C (3.26 kg) under normal pressure at 20−30 °C. After the theoretical uptake of 1 equiv of hydrogen (8.5 h) the hydrogenation was stopped, the catalyst was filtered and washed with ethanol, and the solvent was evaporated under reduced pressure to a volume of ca. 45 L. This suspension was gradually cooled to 0 °C, and the solids were filtered, washed with ethanol (5 L) and hexane (8 L), and dried under reduced pressure at 45 °C to yield **10** (17.16 kg, 79%). HPLC purity: >99%. ^{1}H NMR ($CDCl_3$, 400 MHz): 1.28 (t, J = 7, 3H), 3.31 (dd; J = 13, 9; 1H), 3.49 (dd; J = 13, 7; 1H), 3.96 (s, 3H); 4.01 (s, 3H), 3.96−4.05 (m, 1H). 4.16−4.32 (m, 2H), 6.79 (dd, J = 8, 1H), 7.26 (t, J = 8, 1H), 7.32 (d, J = 9, 1H), 7.52 (s, 1H), 7.62 (s, 1H). MS: 313. (M^+): 298, 201, 173.

2-Cyano-3-(3,5-dimethoxynaphthalene-2-yl)propionic Acid (11). To a solution of **10** (11.32 kg, 36 mol) in ethanol (112 L) was added a solution of NaOH (1.74 kg, 43.5 mol) in H_2O (42 L) within 15 min. This mixture was heated to reflux for 3.5 h, stirred overnight at 25 °C, and concentrated at approximately 40 °C under reduced pressure to remove ethanol. The residue was dissolved in an ethyl acetate (50 L)/toluene (70 L) mixture, and sulfuric acid (50% aqueous solution, 16 L) was added. The layers were separated, and the organic phase was concentrated under reduced pressure to a volume of ca. 45 L. Solids were isolated by filtration after cooling to 0 °C, washed with ethyl acetate and hexane, and dried under reduced pressure to give **11** (6.88 kg, 67%. HPLC purity: >95%). From the mother liquor an additional crop of **11** (2.1 kg, 20%. HPLC purity: >97%) was obtained. ^{1}H NMR ($CDCl_3$, 400 MHz): 3.27 (dd; J = 14, 8; 1H), 3.53 (dd, J = 13; 7, 1H), 3.93 (s, 3H), 3.99 (s, 3H), 4.11 (dd, J = 6; 9; 1H), 6.80 (d, J = 7, 1H), 7.25 (t, J = 7, 1H), 7.34 (d, J = 8, 1H), 7.53 (s, 1H), 7.64 (s, 1H), 9.20−9.80 (br s, 1H). MS: 285. (M^+): 270, 241, 201, 173, 158.

3-(3,5-Dimethoxynaphthalene-2-yl)propionitrile (12). Intermediate **11** (12.57 kg, 44.1 mol) and NaCl (7.46 kg) were suspended in *N*,*N*-dimethylacetamide (25 L) and H_2O (2.75 L). This mixture was slowly heated to 125 °C, where CO_2 evolution started, and was kept at this temperature for another 2.5 h. [Caution: To avoid a rapid pressure rise the

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temperature should be raised carefully to the onset of decarboxylation.] After reaction was complete, the mixture was cooled to 20 °C and distributed between ethyl acetate and H_2O. The ethyl acetate layer was evaporated under reduced pressure to a volume of ca. 5 L and cooled to 0 °C. The solids were collected by filtration, washed with a mixture of ethyl acetate/hexane (1:1 v/v, 4 L), and dried under reduced pressure at 40 °C to yield product **12** (8.24 kg, 77%). From the mother liquor, concentrated to a volume of ca. 1 L, a second crop of **12** (1.5 kg, 14%) was isolated. ^{1}H NMR ($CDCl_3$, 400 MHz): 2.69 (t, $J = 8$, 2H), 3.09 (t, $J = 7$, 2H), 3.94 (s, 3H), 3.98 (s, 3H), 6.79 (dd; $J = 7$, 1; 1H), 7.24 (t, $J = 8$, 1H), 7.32 (d, $J = 9$, 1H), 7.51 (s, 1H), 7.58 (s, 1H). MS: 241. (M^+): 226, 201, 173, 158.

rac*-(4aR,10aR)-9-Methoxy-1-methyl-1,2,3,4,4a,5,10,-10a-octahydrobenzo[*g*]quinoline (16).** (a) *Birch/Bouveault Blanc Reduction of **12. To a solution of **12** (8.2 kg, 34 mol) in *n*-butanol (165 L) were carefully added through an nitrogen-inertized double air-lock system pieces of Na metal (5.8 kg, 252 mol) at a temperature of 90−95 °C, within approximately 7 h at such a rate that the preceding portion had dissolved before a new one was added. [Note: Sodium bars were pre-cut with adequate precaution into cubes of ca. 2 cm × 2 cm × 2 cm and kept under mineral oil until use. No efforts were made to remove the mineral oil film before entering the cubes (3−10 pieces, maximum) into the reaction]. After addition was completed, the mixture was stirred for an additional 1 h at 95 °C and cooled to 20 °C. H_2O (90 L) was slowly added at a rate to maintain the temperature. The layers were separated. The organic layer was washed with H_2O (35 L), and the combined aqueous phases were extracted with *n*-butanol (30 L).

(b) *Cleavage of Enol Ether **13** and in Situ Cyclization.* HCl (18% aqueous solution, 14.9 L) was added to the combined butanol solution of **13**, prepared in (a), at such a rate that the temperature was maintained below 10 °C. The reaction mixture was stirred for another 2 h at 20 °C, and then water and residual hydrochloric acid were removed by refluxing the reaction mixture at a temperature of ca. 50 °C under reduced pressure at a water trap. At the end of the distillation the hydrochloride **14** started to crystallize.

(c) *Reduction of Cyclic Iminium Hydrochloride **14***. To the suspension of **14** in butanol, prepared in (b), H_2O (1.7 L), ethanol (20.7 L), and acetic acid (3.7 L) were added. Then at 0 °C $NaBH_4$ (2.49 kg, 65.7 mol) was carefully added within 3.5 h in small portions through a double air-lock system. [*Caution*: initial hydrogen evolution is strong.] The reaction mixture was warmed to 20 °C over an additional hour, and H_2O (48 L) was added at such a rate that the temperature could be maintained below 20 °C. After stirring for another 1 h, HCl (18% aqueous solution, 12.4 L) was added to destroy residual $NaBH_4$ and cleave alkali-persistent boronic acid adducts of the product amine **15**. Then the mixture was basified again by adding NaOH (30% aqueous solution, 19.9 L), and the mixture was left overnight. After an aqueous workup (butanol/H_2O), the butanol layer was evaporated under reduced pressure at 50 °C to give an oily residue.

(d) *Leukart−Wallach N-Methylation.* To the evaporation residue containing **15**, prepared in (c), formic acid (5.14 L) was added. The mixture was heated to 60 °C, and formaldehyde (36% aqueous solution, 4.31 L) was added during 1 h. After another 2 h at 75 °C the reaction mixture was cooled to 10 °C, diluted with H_2O (10 L) and 30% NaOH (10 L) and ethyl acetate. The ethyl acetate layer was separated and evaporated under reduced pressure to yield a semicrystalline residue containing a cis/trans diastereomeric mixture of **8**.

(e) Chromatographic Separation Of Cis/Trans Diastereomers. The evaporation residue, prepared in (d), was purified on silica gel (50 kg) with an eluent mixture EtOAc/ MeOH/ NH_4OH (1000:10:1 v/v/v), to yield **8** (4.44 kg, HPLC purity: ≥95%). From another chromatography run on silica gel (3.85 kg), separating several contaminated fractions, a second crop of **8** (0.55 kg) was obtained. The total yield of **8** was 4.99 kg (63% based on **12**). ^{1}H NMR ($CDCl_3$, 400 MHz): 1.04−1.22 (m, 1H), 1.66−2.06 (m, 5H), 2.16−2.32 (m, 1H), 2.36−2.58 (m, 5H), 2.76 (dd; $J = 16$, 5; 1H), 2.96−3.08 (m, 1H), 3.27 (dd; $J = 17$, 5; 1H), 3.80 (s, 3H), 6.60−6.70 (m, 2H), 7.04−7.12 (m, 1H). MS: 231. (M^+): 216, 115, 110.

(4aR,10aR)-9-Methoxy-1-methyl-1,2,3,4,4a,5,10,10a-octahydrobenzo[*g*]quinoline (16). (a) To a solution of intermediate **8** (1.48 kg, 6.4 mol) in EtOH 90% (13.5 L) a solution of (−)-di-*o*,*o*-*p*-toluoyl tartaric acid in EtOH 90% (64 L) was added and the mixture heated to 70 °C to obtain a clear solution. The temperature was lowered to 45 °C, and the mixture was seeded. Over 60 min the temperature was further lowered to 37 °C and kept for another 2 h to complete crystallization. Samples of the solids were taken and checked by HPLC for enantiopurity. The solids were collected by filtration via a heated filter (37 °C), washed with ethanol 95% (3 L) of 25 °C, and dried under reduced pressure at 45 °C to yield the ditoluoyl salt of **16** (1.4 kg, 35%) as colorless crystals. HPLC purity: 98.6%.

(b) To a suspension of the ditoluoyl salt of **16** (3.59 kg, 5.8 mol) in TBME (25 L) and water (23 L) at 25 °C an aqueous sodium hydroxide solution (30%, 1.6 L) was slowly added to adjust to pH 12−13. The layers were separated. The water layer was extracted with TBME (total 30 L), and the combined organic layers were washed with water (16 L). The solvent was removed under reduced pressure at 50 °C to yield **16** (1.34 kg, 99%) as a colorless crystalline residue. (HPLC chemical purity: >98%, enantiomeric purity: >98%).

(4aR,10aR)-6-Bromo-9-methoxy-1-methyl-1,2,3,4,4a,5,-10,10a-octahydrobenzo[*g*]quinoline (17). To a solution of **16** (1.34 kg, 5.79 mol) in H_2O (13.4 L) and acetic acid (10 L) was added HBr (48% aqueous solution, 1.7 L, 15.1 mol). At 40 °C a solution of sodium bromate (0.37 kg, 2.4 mol) in H_2O (7.0 L) was added within 50 min at a rate to maintain the temperature. The reaction suspension was stirred for another 1 h at 40 °C, diluted with H_2O (9.7 L), and cooled to 25 °C. A solution of sodium thiosulfate (135 g) in H_2O (2.7 L) was added to destroy the excess of brominating reagent. The suspension was cooled to 0 °C, and the solids (hydrobromide of **17**) were collected by filtration and washed

with H_2O (6 L). In the aqueous workup (TBME (20 L)/H_2O (12 L)/NaOH (30% aqueous solution, 1.8 L) the free base **17** was liberated at a pH 13−14. The organic layer was separated and concentrated to 1 L and after adding hexane (0.6 L) was gradually cooled to 0 °C. The solids were collected by filtration, washed with hexane (1 L), and dried at 45 °C under reduced pressure to yield 1.64 kg of product **17** (92%; HPLC chemical purity: >99%, enantiomeric purity: >99%). ^{1}H NMR ($CDCl_3$, 400 MHz): 1.03−1.16 (m, 1H), 1.60−1.95 (m, 5H), 2.16−2.28 (m, 1H), 2.32−2.44 (m, 4H), 2.86−3.02 (m, 2H), 3.22 (dd; J = 17, *5*; 1H), 6.50 (d, J = 9, 1H), 7.27 (d, J = 9, 1H). MS: 311. (M^+): 309. (M^+): 296, 294, 230, 173, 158.

(4aR,10aR)-9-Methoxy-1-methyl-6-trimethylsilanyl-1,2,3,4,4a,5,10,10a-octahydrobenzo[*g*]quinoline Hemimaleinate (1). *(a) Silylation.* To the solution of intermediate **17** (1.3 kg, 4.2 mol) in THF (13 L) and TBME (13 L) at −75 °C was added *n*-BuLi (20% solution in cyclohexane, 2.04 kg, 6.4 mol) at a rate such that the temperature did not rise above −70 °C. After rinsing with TBME (0.5−1 L) and stirring for another 15 min, TMSCl (0.96 kg, 8.8 mol) was added within 20 min at a rate such that the temperature did not rise above −70 °C. After the addition was complete, the reaction mixture was warmed to 0 °C, and NaOH (2 M aqueous solution, 1.3 L) was added at a temperature below 10 °C, followed by H_2O (45 L). The mixture was warmed to ambient temperature, and the layers were separated. The aqueous layer was extracted with TBME, and the combined organic layers were washed with water. The organic phase was concentrated by distillation under reduced pressure at 40 °C to give crude **1** (1.13 kg, 89%; MS: 304 (M + H)) as a slightly red-colored solid.

(b) Chromatography. The batch described under (a) contained oxidation product **18** in an amount higher than 1% (HPLC) and therefore was dissolved in 1.4 L hexanes for chromatography. The hexane solution was filtered at approximately 50 bar over a pad of silica gel (25 kg, preconditioned with hexane/ triethylamine (20:1 w/w)), and the product was eluted with hexane/TBME mixtures (3:1 and 2:1 v/v; detection UV 254 nm). The product fractions containing pure **1** were concentrated under reduced pressure at 40 °C to give **1** (0.96 kg, 85% recovery) as a colorless solid evaporation residue.

(4aR,10aR)-6-Hydroxy-9-methoxy-1-methyl-1,2,3,4,-4a,5,10,10a-octahydrobenzo[*g*]quinoline (18): ^{1}H NMR $CDCl_3$, 400 MHz: 1.16 (m, 1H), 1.60−2.00 (series of m, 5H), 2.15−2.28 (m, 2H), 2.35 (dd, 1H), 2.43 (s, 3H), 2.90 (dd, 1H), 3.00 (br d, 1 H), 3.32 (dd, 1H), 3.78 (s, 3H), 6.59 (AB, 2H). MS: 247. (M^+): 232, 150, 97, 82, 77.)

(c) Hemi-maleinate formation. Crude **1** (0.87 g, 2.87 mol) was dissolved in TBME (total 23.5 L), treated with activated carbon (0.1 kg), and filtered at 36 °C to a solution of maleic acid (0.35 kg, 3.0 mol) in acetone (1.34 kg). After seeding, the product **1** started gradually to crystallize as the hemi-maleinate salt. The suspension was cooled to 0 °C over a period of 7 h and kept for another 1 h at this temperature. The solids were collected by filtration, washed with TBME (2 L), and dried at 50 °C to yield **1** as the hemi-maleinate salt (1.0 kg, 83%. HPLC chemical purity: >99.5%, enantiomeric purity: >99.9%). ^{1}H NMR ($CDCl_3$, 400 MHz): 0.21 (s, 9H), 1.20 −1.36 (m, 1H), 1.80−1.90 (m, 1H), 1.98−2.07 (m, 1H), 2.16−2.28 (m, 2H), 2.46−2.56 (m, 1H), 2.72−2.90 (m, 6H), 3.02 (dd; J = 17, 5; 1H), 3.28−3.38 (m, 1H), 3.56−3.68 (m, 1H), 3.74 (s, 3H), 6.22 (s, 2H), 6.62 (d, J = 8, 1H), 7.26 (d, J = 8, 1H), 12.14 (br s, 1H).

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