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Articles

Practical and Large-Scale Synthesis of *rac*-(3*S*,4a*R*,10a*R*)-6-Methoxy-1-propyl-1,2,3,4,4a,5,10,10a-octahydrobenzo[*g*]quinoline-3-carboxylic Acid Methyl Ester

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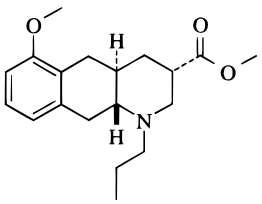
Abstract:

3- Substituted octahydrobenzo[*g*]quinolines are important intermediates for pharmaceutically active compounds. A short, efficient synthesis, which is feasible for large-scale manufacturing of *rac*-(3*S*,4a*R*,10a*R*)-6-methoxy-1-propyl-1,2,3,4,4a,5,10,10a-octahydrobenzo[*g*]quinoline-3-carboxylic acid methyl ester is presented. As starting materials the cheap and readily available 1,6-dimethoxynaphthalene and ethoxymethylenecyanoacetic acid ethyl ester were chosen. All atoms of the skeleton were introduced in the first step, by the reaction of 7-lithiated 1,6-dimethoxynaphthalene with ethoxymethylenecyanoacetic acid ethyl ester. Subsequent hydrogenation, followed by Birch reduction and acidic cyclization gave the 6-methoxy-2,3,4,4a,5,-10-hexahydrobenzo[*g*]quinoline-3-carboxylic acid·hydrochloride in high yield. The trans fusion of the two six-membered rings was established after $NaBH_4$ reduction. After esterification, *n*-propylation, and kinetic protonation of an intermittantly formed trimethylsilylketene acetal, the desired product was isolated in high yield and excellent purity.

Introduction

Ergot alkaloids and their synthetic derivatives show a wide spectrum of physiological activities.[1] Octahydrobenzo[*g*]-quinolines, synthetic analogues of the ergot family structure, are potent dopamine agonists.[2]

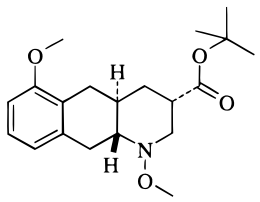
The synthesis of the **racemic** intermediate **1**[3] has been of interest in our development activities and under investigation for several years.



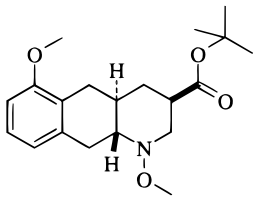
1

The research synthesis[2] (Scheme 1) started from 5-methoxy-2-tetralone **2**.[4] The methylene group at C1 had to be protected reversibly as the diphenyldithioketal **3** with the use of *S*-phenyl benzenethiosulfonate.[5] The lithium enolate of **3** was generated at low temperature and alkylated with *tert*-butyl 2-(bromomethyl)acrylate[6] to yield **4**. The dithioketal function was reductively removed with aluminium amalgam to give the ketone **5**. After transforming to the oxime **6**, this intermediate **6** was reduced by sodium cyanoborohydride to a mixture of diastereomers, which cyclized at room temperature to the four diastereomers **7**. These diastereomers were separated by column chromatography over silica gel.

The trans fused diastereomers **7a** and **7b** were isolated in 24.5 and 0.5% yield, respectively.



7a



7b

The two cis fused diastereomers were isolated in 38% yield. Intermediate **7a** was converted to the corresponding methyl ester and reduced to the amine with Zn in acetic acid. Finally, catalytic hydrogenation over Pd/C in the presence of propionaldehyde yielded compound **1**.

This synthesis had several scale-up problems: that is, safety problems in the manufacturing of *S*-phenyl benzenethiosulfonate, and problems with the use of 2-bromomethylacrylic acid *tert*-butylester, the use of aluminum amalgam, the use of sodium cyanoborohydride, and the need for chromatographic separation of **7a** (poor yield). This research synthesis was designated as not suitable for scale-up! We had to eliminate first the most critical issues for a development synthesis.

(1) Berde, B.; Stürmer, E. In *Ergot Alkaloids and Related Compounds*; Schield, H. B., Ed.; Springer Press: Berlin/Heidelberg/New York, 1978. Schardt, F.; Miskra, R. B. *Ther. Ggw.* **1982**, *121*, 26.
(2) Nordmann, R.; Petcher, T. J. *J. Med. Chem.* **1985**, *28*, 367.
(3) All compounds drawn with stereobonds are racemic!
(4) Cornforth, J. W.; Robinson, R. *J. Chem. Soc.* **1949**, 1855.
(5) Trost, B. M.; Massiot, G. S. *J. Am. Chem. Soc.* **1977**, *99*, 4405.
(6) Holm, A.; Scheuer, P. J. *Tetrahedron Lett.* **1980**, *21*, 1125. Lattrell, R.; Lohaus, G. *Liebigs Ann. Chem.* **1974**, 870.

 10.1021/op0000531 CCC: $19.00
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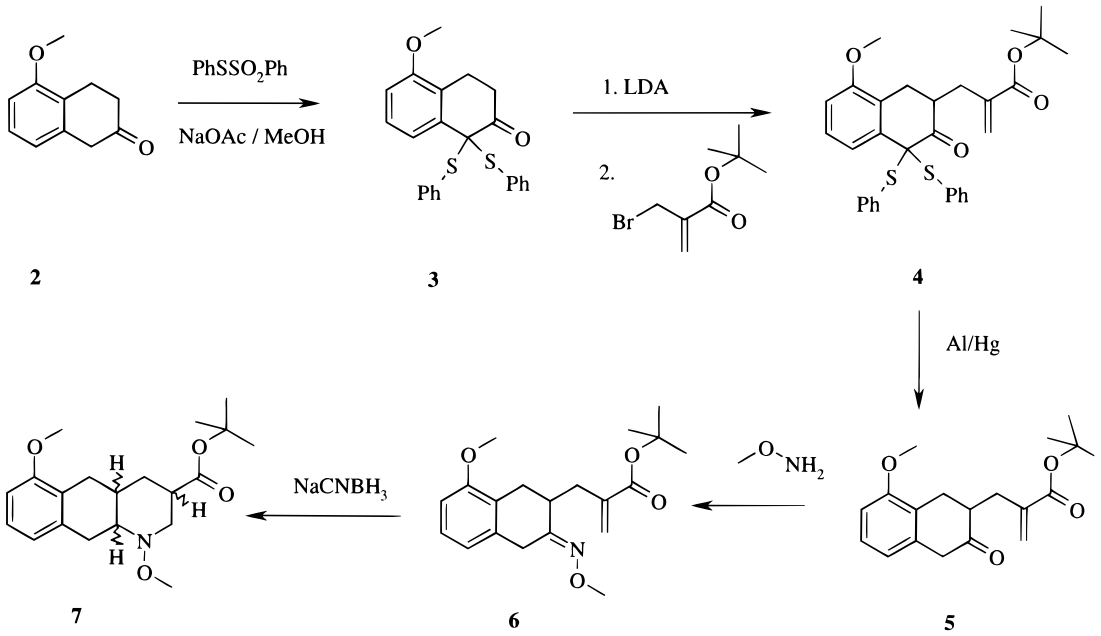
Scheme 1



Results and Discussion

Due to severe time pressure, we basically wanted to follow the original route, namely to start from 5-methoxy-2-tetralone **(2)**, which was manufactured from 1,6-dimethoxynaphthalene **(15)** in 66% yield by reacting **15** with sodium in boiling *n*-butanol. Product **2** was then treated with preformed magnesium methyl carbonate[7] in DMF at 140 °C. The carboxy group was selectively introduced at the 3-position. This is probably due to the steric bulk of the magnesium enolate carboxy complex, causing an unfavourable steric interaction with the peri hydrogen at C-8, thus blocking carboxylation at the 1-position.[8] The β-ketoacid thus formed was esterified to the ester **8** and isolated in 56% yield, based on **2**. The ester **8** was treated with ammonia in the presence of acetic acid, and the resulting imine directly reduced with $NaBH_4$ to give the amine **9** as a diastereomeric mixture (83% yield based on **8**)**.** Intermediate **9** is reacted with methyl acrylate to yield **10** in 96% yield. After Dieckmann condensation in the presence of sodium methoxide in toluene at 90 °C, the trans fusion of the two six-membered rings was generated, and the product **11** precipitated as the acetate salt in 79% yield, whereby the configuration at C-3 (acidic hydrogen) is labile. The nitrogen was protected with the Z-group, the ketoester reduced, followed by removal of the Z-group to give intermediate **12** in 83% yield (based on **11)** as a mixture of diastereomers. N-Propylation and elimination of the OH group yielded product **13** in 79% based on **12**. Intermediate **13** was hydrogenated to product **14** in 85% yield. The stereochemistry of C3 was inverted by a known method[9] to give intermediate **1** in 85% yield (Scheme 2).

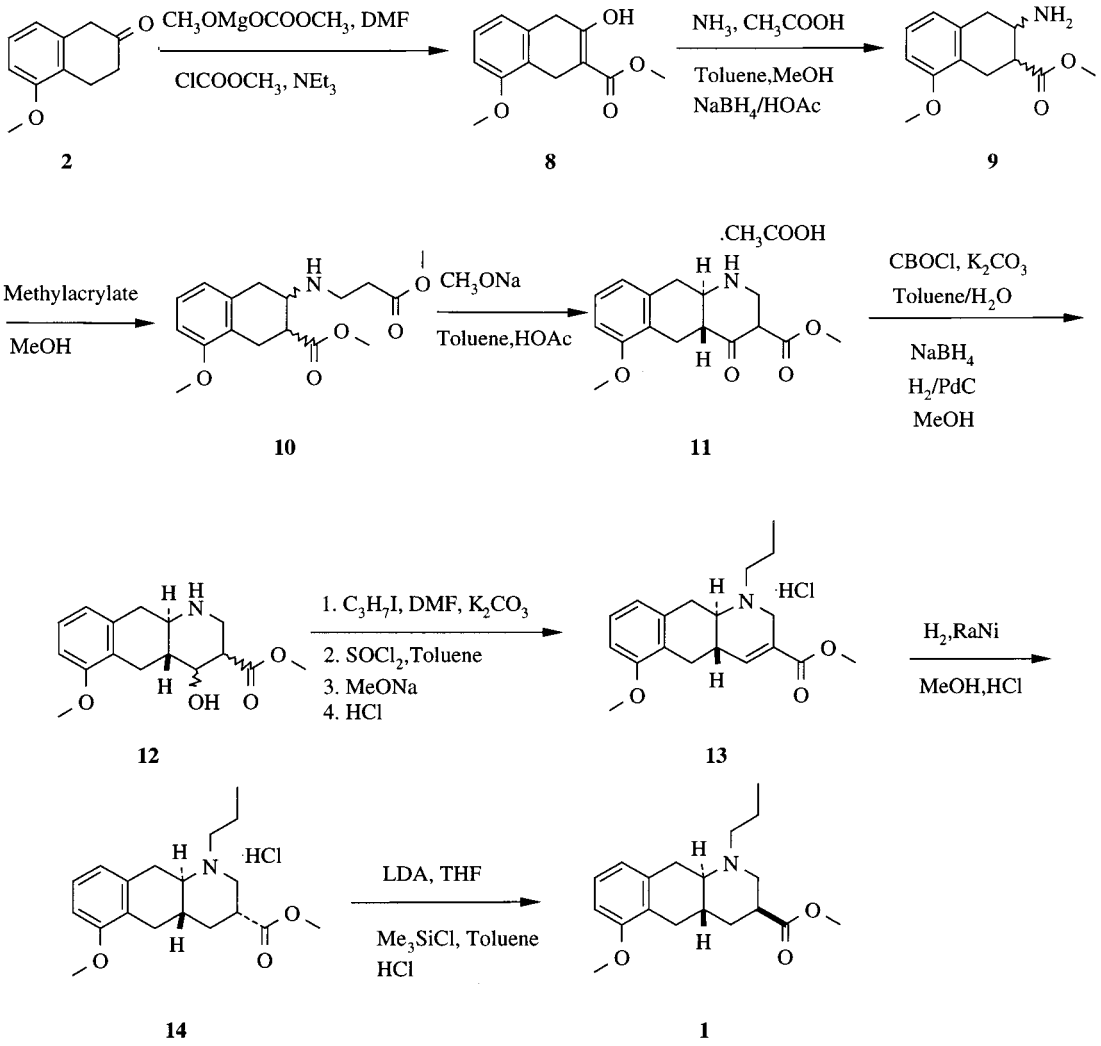
This first development synthesis eliminated most of the critical issues and produced no major problems in the pilot plant, but the synthesis is still very long. In particular the preparation of intermediate **8** from **2** was a bottleneck in the pilot plant during scale-up, because the reactions had to be run under very dilute conditions and the initially formed β-ketoacid, which was initially formed, was not stable and could not be stored. Thus, for further development activities there was an urgent need to obtain a shorter and more efficient synthesis.

Among several approaches investigated, one was chosen and optimized, and the compound was manufactured on multi-kilogram scale. The chosen strategy was similar to the former approaches, namely to start from a naphthalene ring system and build up the heterocyclic ring. We basically wished to follow the concept designed for the synthesis of octahydrobenzo[*g*]quinolines by the group of Hacksell.[10] The key steps were the preparation of the cyclic iminium hydrochloride, which was accessible after Birch reduction of a corresponding 3-cyanoethyl- 2-methoxynaphthalene derivative, followed by the stereoselective trans reduction of the iminum hydrochloride (Scheme 3).

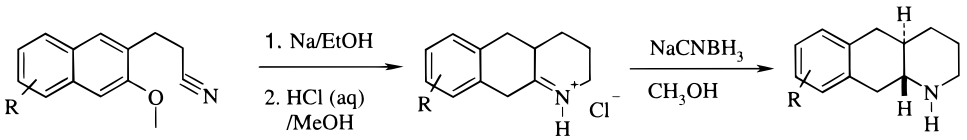
The starting material for this strategy (Scheme 4) was 1,6-dimethoxynaphthalene (**15**), which could be selectively ortho lithiated at the C-7 position[11] with hexyllithium in THF. This lithium compound was treated at −70 °C with a THF solution of ethoxymethylene cyanoacetic acid ethylester (**16**) to give the intermediate **17**. The isolation of **17** was simple, as it precipitated from the reaction mixture after acidification with aqueous sulfuric acid and could be directly filtered. After recrystallization from toluene, **17** could be isolated in

(7) Stiles, M. *J. Am. Chem. Soc.* **1959**, *81*, 2598. Finkbeiner, H. L.; Stiles, M. *J. Am. Chem. Soc.* **1963**, *85*, 616.
(8) Pelletier, S. W.; Chappell, R. L.; Parthasarathy, P. C.; Lewin, N. *J. Org. Chem*. **1966**, *31*, 1747−1752. S. W. Pelletier, P. C. Parthasarathy, *Tetrahedron Lett.* **1964**, *2*, 103.
(9) Baenziger, M.; Mak, C.-P.; Muehle, H.; Nobs, F.; Prikoszovich, W.; Reber, J.-L.; Sunay, U. *Org. Process Res. Dev.* **1997**, *1*, 395−406.
(10) Mellin, C.; Hacksell, U. *Tetrahedron* **1987**, *43*, 5443.
(11) Johansson, A. M.; Mellin, C.; Hacksell, U. *J. Org. Chem.* **1986**, *51*, 5252. Barnes, R. A.; Bush, W. M. *J. Am. Chem. Soc.* **1959**, *81*, 4705. Wilson, J. M.; Cram, D. J. *J. Org. Chem.* **1984**, *49*, 4930.
(12) For hydrogenation of similar systems see: Lee, J.; Gauthier, D.; Rivero, R. A. *J. Org. Chem.* **1999**, *64*, 3060. Pollack, M. A. *J. Am.Chem. Soc.* **1943**, *65*, 1335.

Scheme 2

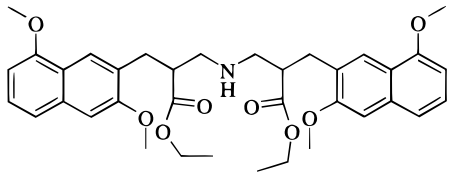


Scheme 3

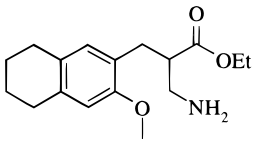


55% yield (>97% purity by GC) as a single isomer. The (E) double bond geometry was proved by NMR experiments. The other regioisomers, which were formed, were removed almost entirely by the two crystallization steps. Although this yield is not as high as we would like, we could establish, in one step, all of the atoms which are required for the octahydroquinoline system. We investigated several other conditions in order to improve the yield (addition of the lithium intermediate to the THF solution of **16**; different reaction temperatures, varying the ratios of the reagents), but the yield never exceeded 60%. From intermediate **17** to the octahydrobenzo[*g*]quinoline system several reduction steps have to follow. The next step was the hydrogenation[12] of the unsaturated nitrile system in **17** to the aminoester function of **18**. A catalyst screening was performed, and Pt/C (5%) in the presence of a mineral acid (HCl or H_2SO_4) showed the best results. Two byproducts **19** and **20** were isolated.

19 is a self-condensation product of the desired hydrogenation product **18** with an imine intermediate. The amount of **19** formed is dependent on the hydrogen pressure, the reaction temperature, and the strength of acid. The higher



19



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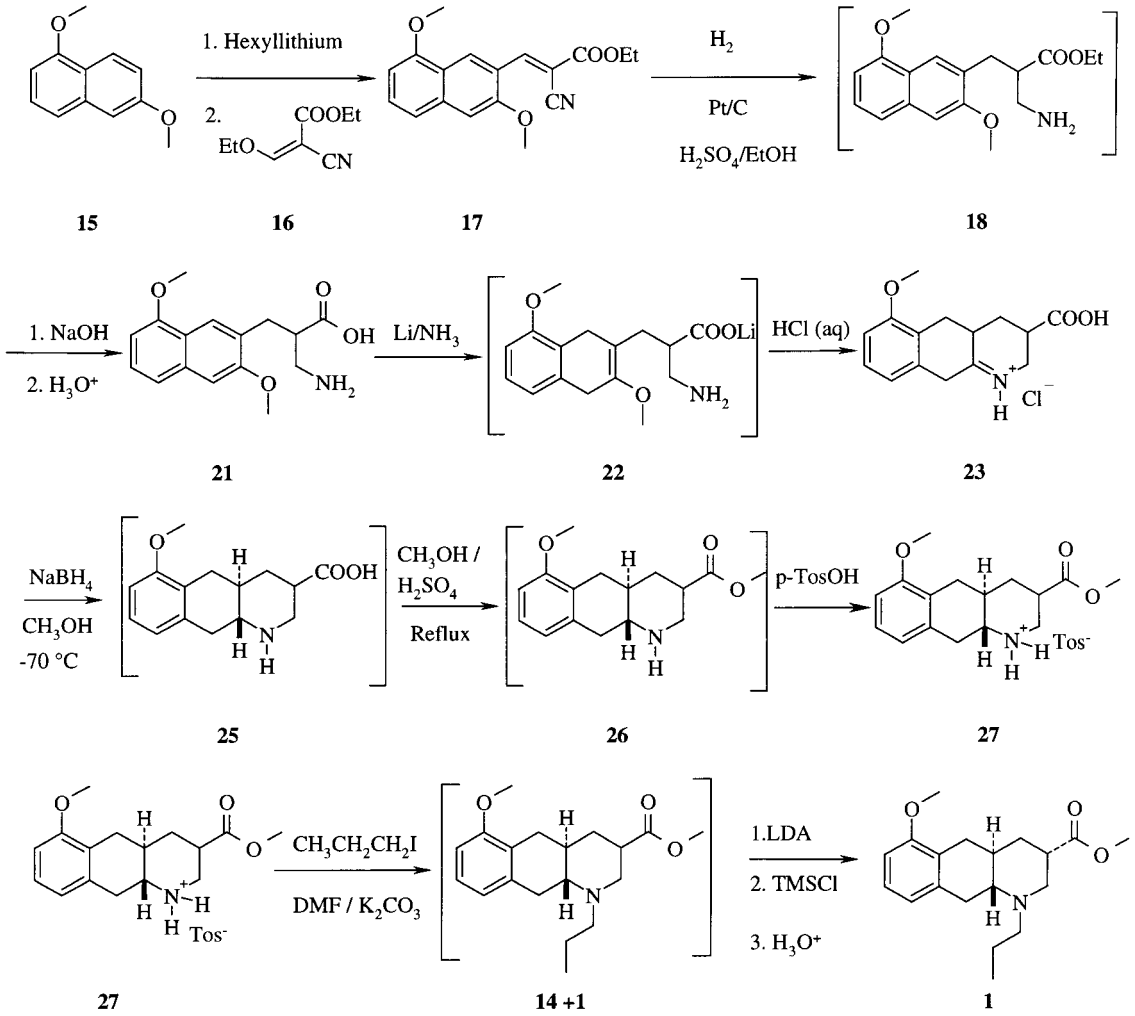
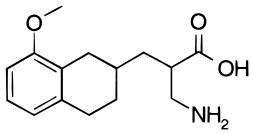
Scheme 4



the pressure in the hydrogenation, the less **19** was formed. With increasing reaction temperature the amount of **19** was also higher. In the presence of a weaker acid such as acetic acid almost 50% of **19** was formed. Since the starting material was very insoluble in ethanol at room temperature we had to run the hydrogenation at elevated temperature (10 bar; 50 °C). The amount of **19** formed was in the range of 5−10% relative to the desired product **18**. Fortunately it can be removed almost completely after hydrolysis to the amino acid **21**. The hydrogenation almost stops after theoretical hydrogen consumption, and the amount of the over-reduced byproduct **20** never exceeded 2%. The hydrogenation product **18** is not isolated but is directly hydrolysed to the amino acid **21**, which was isolated after precipitation at pH 8. This intermediate was recrystallized via the intermediate lithium salt. The yield of **21**, based on **17**, was 83%, and with a purity higher than 99% (HPLC area). Up to 6% water in **21** is tolerated in the subsequent Birch reduction to **22**.

The Birch reduction of the amino acid **21** was performed in liquid ammonia[13] and THF with 2.4 equiv of lithium and 2 equiv of *tert*-butyl alcohol.[14] These conditions were found after extensive study of the reaction. By using THF as a cosolvent the amount of ammonia could be reduced significantly. The use of *tert*-butyl alcohol as the proton source in addition to the proton of the carboxylic acid and the presence of an excess of available proton sources with respect to lithium was crucial. Under these conditions the amount of the over-reduced byproduct **24** never exceeded 3% (area HPLC) and was unproblematic in this amount.



24

Specifically a suspension of **21** in THF *tert*-butyl alcohol and liquid ammonia was treated with lithium granules at −70 °C. During the addition the starting material dissolved, and a blue-coloured solution appeared. When the reaction was complete, the intermediate **22** started to precipitate. The ammonia was then evaporated, water added, and the THF

(13) The ammonia was distilled from steel cylinders, also in plant scale, to prevent the introduction of iron impurities, which can catalyze the decomposition reaction of lithium with ammonia or *tert*-butyl alcohol; Harvey, R. G. *J. Org. Chem.* **1967**, *32*, 238; Harvey, R. G.; Urberg, K. *J. Org. Chem.* **1968**, *33*, 2570; Harvey, R. G. *Synthesis* **1970**, 161.

(14) For Birch reduction in similar solvent systems, see: Dryden, H. L.; Webber, G. M.; Burtner, R. R.; Cella, J. A. *J. Org. Chem.* **1961**, *26*, 3237; Donaldson, R. E.; Fuchs, P. L. *J. Org. Chem.* **1977**, *42*, 2032.

removed by distillation. The aqueous solution of **22** was then added to hydrochloric acid. The desired, cyclised product **23** precipitated and was filtered. The yield of **23** was in the range of 92−97% based on **21**. Intermediate **23** was stored under argon. In solid form it is stable at least over 3 months, in solution **23** decomposes rapidly, probably due to aromatization. The distilled ammonia is directly neutralized in aqueous sulfuric acid (also on plant scale) and disposed. In a further scale-up the ammonia could be reused, by condensing it in a second low-temperature reactor.

Hacksell[10] used sodium cyanoborohydride for the reduction of his imminium hydrochloride system. It was obvious that we had to find another reducing agent, to get a feasible and scaleable process. We found that sodium borohydride in methanol is suitable for this reduction. The iminium hydrochloride **23** is dissolved in methanol and cooled to −70 °C, and then 1.5 equiv of $NaBH_4$ is added portionwise. We found that the reaction can also be run at 0 °C, but the yield of isolated **27** was about 5% lower than if the reaction was performed at −70 °C. We decided to run the $NaBH_4$ reduction at −70 °C. The excess of $NaBH_4$ was decomposed 2 h after the addition. In this $NaBH_4$ reduction <5% of the cis diastereomers were formed. Then the reaction mixture of intermediate **25** is added to a solution of sulfuric acid in methanol, whereby **25** is transformed to the methylester **26** at reflux temperature. After evaporation of methanol and an aqueous workup the two diastereomers were isolated as their *p*-toluenesulfonic acid salts in 78% yield based on **23**. This crystallization step effectively removed impurities such as the cis diastereomers, and the corresponding methylester of **21** and **24.** The two diastereomers of **27** (ratio almost 1:1) show an HPLC purity of >98%. Intermediate **27** is alkylated with *n*-propyliodide in DMF in the presence of K_2CO_3 to give an almost 1:1 diastereomeric mixture of the products **1** and **14**. The undesired isomer **14** (methylester is equatorial) could be converted via kinetic protonation of the corresponding trimethylsilylketene acetal to intermediate **1** (methylester is axial) by a known method.[9] The crude product **1** was filtered over silica gel to remove polar byproducts and finally crystallized from methanol. Product **1** was isolated in 85% yield based on **27** in an HPLC purity of >99%.

By this new elaborated process product **1** was manufactured from 1,6-dimethoxynaphthalene **(15)** in only five isolated steps and an overall yield of 27−29% based on 1,6-dimethoxynaphthalene. This was a significant improvement as compared to the former development process, which consists of nine isolated steps starting from **15** and an overall yield of 13% to product **1**. The synthesis of intermediate **1** was performed on multi-kilogram scale reproducibly and without any problems.

Experimental Section

Experimental work is described only for the final process, which was developed and manufactured, on multi-kilogram scale. The conditions were optimized and checked by our internal risk analysis process (DERA).[15] Intermediates **17**, **18**, **21**, **23**, **25**, **26**, and **27** were not previously reported in the literature. The starting materials, solvents, and reagents were of technical grade, available in bulk, and had the same quality as used in the pilot plant. All reactions were carried out under an atmosphere of nitrogen except the Birch reduction (conversion of **21** to **22**), which was performed under argon atmosphere (also on plant scale), due to the possible formation of lithiumnitride.[16] The NMR spectras were measured on a Brucker Avance 400 spectrometer and the chemical shifts are given in δ (ppm).

2-Cyano-3-(3,8-dimethoxynaphthalene-2-yl)acrylic Acid Ethyl Ester (17). 1,6-Dimethoxynaphthalene (**15**) (60.24 g, 320 mmol) was dissolved in 464 mL THF and cooled to −20 °C. Then 107 g hexyllithium (33% solution in hexane, 383 mmol) was added, and the mixture was stirred at 0 °C for 3 h. This reaction mixture was then cooled to −70 °C, and then a solution of ethoxmethylenecyanoacetate **(16)** (62.24 g, 368 mmol) in 310 mL THF was added, at such a rate that the temperature did not rise above −65 °C. After the addition was complete the reaction mixture was stirred for an additional hour at −65 °C, then warmed to −20 °C within 1 h, and finally 1 M sulfuric acid (220 mL) was added and the temperature raised to 0 °C. During the addition the product started to precipitate. The mixture was stirred for 30 min at 0 °C, then the product was filtered and dried in vacuo for 18 h at 60 °C.

This crude product was recrystallized from toluene (160 mL) to yield 54.6 g (175 mmol, 55%) of intermediate **17** after drying in vacuo for 20 h at 60 °C: mp 159 °C −161 °C; ^{1}H NMR ($CDCl_3$ 400 MHz): 1.46 (t, J = 7.1, 3H), 4.02 (s, 3H, OCH_3), 4.05 (s, 3H, OCH_3), 4.44 (q, J = 7.1, 2 H), 6.74 (d, J = 7.6, 1H, H−C7), 7.13 (s, 1H, H−C4), 7.31 (d, J = 7.7, 1H, H−C5), 7.47 (m, 1H, H−C6), 8.86 (s, 1H, H−C3), 9.28 (s, 1H, H−C1). Anal. Calcd for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50; N, 4.50. Found: C, 69.13; H, 5.57; N, 4.44.

2-Aminomethyl-3-(3,8-dimethoxynaphthalene-2-yl)-propionic Acid (21). A suspension of 2-cyano-3-(3,8-dimethoxynaphthalene-2-yl)acrylic acid ethylester (**17**) (60 g, 193 mmol) in 900 mL ethanol was hydrogenated in the presence of 12 g Pt/C (5%) and sulfuric acid (30 g) at 50 °C and 10 bar. After the theoretical amount of hydrogen had been consumed (∼4 h) the hydrogenation was stopped. The catalyst was removed by filtration, washed with ethanol, and concentrated to a volume of 540 mL. Then 540 mL of water was added, followed by lithium hydroxide monohydrate (34.85 g, 831 mmol). This mixture was heated to reflux for 3 h, and then the pH was adjusted to pH 8−8.5 by addition of acetic acid (30.4 g) whereupon the product precipitated. The mixture was cooled to 20 °C, and the product was filtered. The wet filtercake was suspended in water (540 mL) and ethanol (540 mL), dissolved as the lithium salt, by

(15) Spaar, R.; Suter, G. A simplified Hazard Analysis Scheme for Use in Process Development. Presented at the 7th International Symposium on Loss Prevention and Safety Production in the Process Industry, Taorimina, Italy, May 4−8, 1992.

(16) Rabideau, P. W. *Tetrahedron* **1989**, *45*, 1579; Recommendation of CHEMETALL in their brochure "Lithium Metal Properties and Applications" to work under argon, when using lithium metal.

addition of lithium hydroxide monohydrate (8.92 g, 213 mmol), and heated to 60 °C, and then the pH was adjusted to pH 8.0−8.5 by addition of acetic acid (12.8 g, 213 mmol). The product precipitated, and the suspension was cooled to 20 °C, filtered, washed with ethanol/water, and dried in vacuo at 80 °C for 24 h to yield 46.1 g (159 mmol, 83%) of **21**: mp 243 °C −246 °C; ^{1}H NMR (CD_3OD/NaOD 400 MHz): 2.65−3.14 (m, 5H), 3.94 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 6.71−6.74 (m, 1H, H−C7), 7.15 (s, 1H, H−C4), 7.26−7.32 (m, 2H, H−C5 and H−C6), 8.00 (s, 1H, H−C1). MS: 290 (MH^+), 243; 201.

Analytical Data of Compound 19: 3-(3,8-Dimethoxy-naphthalen-2-yl)-2-{[3-(3,8-dimethoxy-naphthalen-2-yl)-2-ethoxycarbonyl-propylamino]-methyl}-propionic Acid Ethyl Ester (19). ^{1}H NMR (DMSO 400 MHz): 1.02 (t, J = 7.0, 6H, OCH_2CH_3), 1.95 (br. s, 1H, NH), 2.60−3.05 (m, 10H), 3.85−3.97 (m, 10H, 2× OCH_3; OCH_2CH_3), 6.75−6.81 (m, 2H, H−C7), 7.23 (s, 2H, H−C4), 7.28−7.38 (m, 4H, H−C5, H−C6), 7.85 (s, 2H, H−C1). MS: 617 (M^+), 416, 330, 202.

Analytical Data of the Corresponding Methyl Ester of Compound 20: 2-Aminomethyl-3-(3-methoxy-5,6,7,8-tetrahydro-naphthalen-2-yl)-propionic Acid Methyl Ester. ^{1}H NMR (DMSO 400 MHz): 1.37 (br. s, 2H, NH_2), 1.62−1.74 (m, 4H, H−C6, H−C7), 2.52−2.72 (m, 9H), 3.54 (s, 3H), 3.70 (s, 3H), 6.58 (s, 1H, H−C4), 6.72 (s, 1H, H−C1). MS: 278 (MH^+), 246, 217, 175.

6-Methoxy-2,3,4,4a,5,10-hexahydrobenzo[*g*]quinoline-3-carboxylic Acid · Hydrochloride (23). 2-Aminomethyl-3-(3,8-dimethoxynaphthalene-2-yl)propionic acid (**21**) (40 g, 138.2 mmol) was suspended in THF (400 mL) and *tert*-butyl alcohol (20.48 g, 276.3 mmol). This suspension was cooled to −70 °C, and ammonia (150 g) was condensed into the mixture, followed by the portionwise addition of lithium metal (2.3 g, 331.4 mmol). After 1.5 h the cooling bath was removed, and ammonia was evaporated and neutralised in 35% aqueous sulfuric acid (the amount of *tert*-butyl alcohol in the distilled ammonia is <1% of the total *tert*-butyl alcohol put into the reaction). To the suspension water (270 mL) was added, and the THF and *tert*-butyl alcohol were distilled off at 50 °C in vacuo. This aqueous solution of **22** was then poured into concentrated hydrochloric acid (116 g), at a temperature below 10 °C. The desired product **23** precipitated, the mixture was stirred for 4 h in the ice bath, and then the product was filtered and washed with 2 M hydrochloric acid (72 mL), followed by ethyl acetate (100 mL) and dried in vacuo at 40 °C for 48 h to yield 39.7 g (134 mmol, 97%) of product **23**: mp 248 °C −251 °C; ^{1}H NMR (DMSO-d_6 400 MHz): 1.60−1.75 and 1.90−2.00 and 2.15−2.25 and 2.35−2.42 (m, 2H, H−C4), 2.45−2.57 and 2.62−2.72 and 3.38−3.41 (m, 2H, H−C5), 2.96−3.18 (m, 2H, H−C3, H−C4a), 3.42−3.92 (m, 2H, H−C2), 3.80 (s,-3H, OCH_3), 4.09−4.30 (m, 2H, H−C10), 6.79−6.86 (m, 1H, H−C7), 6.87−6.95 (m, 1H, H−C9), 7.20−7.28 (m, 1H, H−C8).

***rac*- (3*R*,4a*R*,10a*R*)- and *rac*-(3*S*,4a*R*,10a*R*)-6-Methoxy-1,2,3,4,4a,5,10,10a-octahydro-benzo[*g*]quinoline-3-carboxylic Acid Methyl Ester *p*-Toluenesulfonic Acid Salt (27).** 6-Methoxy-2,3,4,4a,5,10-hexahydrobenzo[*g*]quinoline-3-carboxylic acid · hydrochloride (**23**) (29.6 g, 100 mmol) was dissolved in methanol (592 mL) and cooled to −70 °C. Then $NaBH_4$ (5.68 g, 150 mmol) was added portionwise, so that the temperature did not rise above −65 °C and the hydrogen evolution was under control. After the addition was complete, the mixture was stirred for an additional 2 h, then warmed to −30 °C, and poured on a solution of sulfuric acid (32.3 g) in methanol (125 mL). The reaction mixture was heated to reflux for 3.5 h. Then the methanol was evaporated, and from the residue an aqueous workup was done (ethyl acetate/water/NaOH/Na_2CO_3; pH > 9). The ethyl acetate was evaporated, the residue of **26** was dissolved again in ethyl acetate, and the two diastereomers were precipitated at 70 °C as their *p*-toluenesulfonic acid salts, by adding a solution of *p*-toluenesulfonic acid (17.1 g, 90 mmol) in ethyl acetate (150 mL). The suspension was seeded with the product mixture, cooled in the ice bath, filtered, and washed with cold ethyl acetate. The product was dried in vacuo for 20 h at 60 °C to yield 35.1 g (78.4%) of **27**. HPLC: about 1:1 diastereomeric mixture (99.4% area), assay (titration: 99.0%). Anal. Calcd for $C_{23}H_{29}NO_6S$: C, 61.73; H, 6.53; N, 3.13. Found: C, 61.30; H, 6.58; N, 3.23.^{1}H NMR ($CDCl_3$ 400 MHz): *rac*-(3*R*,4a*R*,10a*R*) isomer: free base: 1.34−1.53 (m, 2H, 4ax and 4a), 1.68 (br s, 1H, NH), 2.12−2.26 (m, 2H, 4 eq, 5ax), 2.52−2.64 (m, 3H, 3ax, 10ax, 10a), 2.77−2.83 (m, 1H, 2ax), 2.87−2.98 (m, 2H, 5eq, 10 eq), 3.33−3.38 (m, 1H, 2 eq), 3.68 (s, 3H, $COOCH_3$), 3.79 (s, 3H, OCH_3), 6.64−6.70 (m, 2H, H7,H9), 7.06−7.10 (m,1H, H8). *rac*-(3*S*,4a*R*,10a*R*) isomer: free base: 1.47−1.61 (m, 2H, 4ax, 4a), 1.97 (br s, 1H, NH), 2.07−2.14 (m, 1H, 5ax), 2.38−2.41 (m, 1H, 4 eq), 2.54−2.69 (m, 3H, 3eq, 10ax, 10a), 2.88−2.99 (m, 3H, 2ax, 5eq, 10 eq), 3.52−3.57 (m, 1H, 2eq), 3.73 (s, 3H, $COOCH_3$), 3.81 (s, 3H, OCH_3), 6.65−6.72 (m, 2H, H7,H9), 7.07−7.11 (m, 1H, H8).

***rac*-(3*S*,4a*R*,10a*R*)-6-Methoxy-1-propyl-1,2,3,4,4a,5,10,-10a-octahydrobenzo[*g*]quinoline-3-carboxylic Acid Methyl Ester (1).** *rac*-(3*R*,4a*R*,10a*R*) and *rac*-(3*S*,4a*R*,10a*R*)-6-Methoxy-1,2,3,4,4a,5,10,10a-octahydrobenzo[*g*]quinoline-3-carboxylic acid methyl ester *p*-toluenesulfonic acid salt (**27**) (168 g; 375.4 mmol) was suspended in DMF (1680 mL). Then pulverized K_2CO_3 (79.8 g; 577 mmol) was added, and the reaction mixture was heated to 50 °C. Within 20 min *n*-propyliodide (153.6 g; 904 mmol) was added, and the reaction mixture was stirred for an additional 2.5 h at 50 °C. Then toluene (2700 mL) was added, and the reaction mixture was cooled to 10 °C, followed by the addition of 1320 mL water. The phases were separated, and the aqueous phase was extracted three times with toluene (3 × 480 mL), and finally the combined organic phases were washed three times with water (3 × 390 mL). The toluene was evaporated to dryness and dried in vacuo to yield a mixture of **1** and **14** (124 g).

To a solution of diisopropylamine (76.2 g; 753 mmol) in THF (144 mL) 33% hexyllithium in hexane (201 g; 720 mmol) was added at −40 °C. After 30 min a solution of the above residue of **1** and **14** in THF (960 mL) was added at −40 °C within 1 h. After another 0.5 h trimethylchlorosilane

(62.4 g; 574.4 mmol) was added at −40 °C within 20 min. After stirring for another 30 min at −40 °C this reaction mixture was poured on 1200 mL 15% HCl (aq), at such a rate that the temperature was between 5 and 10 °C (2 h). After the addition was complete the pH was brought to 9−9.5 by addition of 30% NaOH (685 g; to get to pH 7), followed by the addition of 15% Na_2CO_3 solution (175 g), and the phases were separated. The water phase was extracted twice with toluene (2 × 600 mL), and the combined organic phases were washed with brine (3 × 350 mL). The solvent was evaporated, and the residue was filtered over silica gel (200 g) with toluene:ethyl acetate (9:1). The desired product fractions were evaporated to dryness, and the product was crystallized from methanol (468 mL) to yield 102.3 g of **1** (85%) after drying at 60 °C in vacuo for 20 h: mp 97.5−98.5 °C; Anal. Calcd for $C_{19}H_{27}NO_3$: C, 71.89; H, 8.57; N, 4.41. Found: C, 71.95; H, 8.71; N, 4.43. ^{1}H NMR ($CDCl_3$ 400 MHz): 0.86 (t, J = 7.3; 3H, CH_3), 1.22−1.29 (m, 1H, 4ax), 1.41−1.50 (m, 2H, $C\underline{H}_2CH_3$), 1.80−1.88 (m, 1H, 4a), 2.05−2.17 (m, 2H, 5ax, 10a), 2.28−2.75 (m, 6H), 2.94 (dd, J = 17.3; 4.9; 1H, 5 eq), 3.09 (dd, J = 16.1; 4.9; 1H, 10 eq), 3.41−3.44 (m, 1H, 2eq), 3.68 (s, 3H, $COOCH_3$), 3.79 (s, 3H, OCH_3), 6.62 (d, J = 8.1, 1H, H9), 6.68 (d, J = 7.7, 1H, H7), 7.04−7.08 (m, 1H, H8).

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