Organic Process Research & Development **2008,** *12,* 429–441

Route Scouting and Process Development of Lu AA26778

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Abstract:

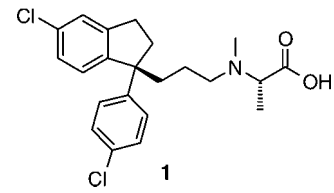
Route scouting and process development for the synthesis of (*S*)-2-({3-[(*S*)-5-chloro-1-(4-chloro-phenyl)indan-1-yl]propyl}methyl-amino)propionic acid, Lu AA26778, are described. The strategy is based on a short synthesis and SMB resolution of a key chiral intermediate for the introduction of one of the two stereocenters. The second stereocenter is introduced via a commercially available alanine ester, optionally bearing a *N*-methyl group. The main concern during scale-up of the synthesis was the safety of a step incorporating sodium dimsylate (the sodium salt of DMSO): this problem was solved using THF as a safety blanket in the large-scale process.

Introduction

When Lu AA26778 (**1**) (Chart 1) advanced into clinical development, we faced the task of synthesizing the compound in larger quantities. Unfortunately, the medicinal chemistry route was not suitable for the supply of even intermediate amounts of substance, and therefore, it was important to quickly identify a synthetic route suitable for immediate synthesis in the laboratory as well as rapid scale-up to kilogram quantities. Inspection of the target molecule reveals several synthetic challenges. Lu AA26778 (**1**) is an amino acid connected via a C3-linker to a functionalized indane core, and the molecule contains two stereogenic centers: one in the amino acid part of the skeleton, and a quaternary one in the indane. The major strategic challenges were the introduction of the quaternary stereocenter in the indane part of the molecule, and the expedient construction of the skeleton.

The medicinal chemistry synthesis, the first synthesis of stereochemically pure Lu AA26778, is depicted in Scheme 1. In this route, the desired stereochemistry at the carbon in the indane was obtained by chromatographic separation of the diastereomeric mixture of **5**. The absolute stereochemistry of **6** was unequivocally determined by X-ray crystallography, giving the absolute stereochemistry of Lu AA26778 (**1**), as the starting material **9** defines the other stereocenter. Unfortunately, this synthesis is rather lengthy because of two main factors: the resolution of the intermediate **4** involves two reactions, i.e. the formation of amide **5** and the subsequent hydrolysis of the diastereomerically pure amide **6**. Furthermore, the carbon skeleton is constructed in a laborious fashion: The intermediate **3** contains one carbon in excess, which is removed by decarboxylation; on the other hand, the side chain in **7** has to be elongated by one carbon, involving a total of five reactions. Finally, the overall yield of this synthesis is as low as approximately 1%, and therefore, this synthetic route is not suitable for the supply of even intermediate amounts of substance.

Chart 1



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Thus, we set out to devise a new synthesis, and after searching the literature, two fundamentally different strategies for the synthesis of 1-phenylindanes with a quaternary carbon atom emerged. The first strategy is based on the formation of the five-membered ring by cyclization of a suitably substituted linear alcohol[1,2] or ketone.[3] The second strategy involves the alkylation of a derivate of phenylindane already containing the five-membered ring, such as phenylindane,[4] a phenylindene,[4] or phenylindanon,[5] followed by functional group interconversion, if necessary. The latter principle appears to be the most attractive for the synthesis of **1**, since the starting material **2** in the medicinal chemistry route should give easy access to the 1-phenylindan or indene by reaction with 4-chlorophenylmagnesium bromide.[6] Stereoselective addition of carbonyl compounds to alkylindenyl anions has been reported,[7] but attempts to achieve stereoselective alkylations have been unsuccessful (ref 12 in ref 8). Furthermore, alkylation of anions of substituted indenes has been shown to suffer from the lack of regioselectivity,[4,8] whereas the alkylation of 1-phenylindane in the 1-position could be achieved in quantitative yield.[4] Apparently, the most expedient construction of the skeleton of **1** goes via the non-stereoselective alkylation of a 1-phenylindan derivative, whilst addressing the issue of introducing the desired stereochemistry separately.

On this basis, our general approach to the molecule is outlined via retrosynthetic analysis in Scheme 2: The amino

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(1) Angle, S. R.; Louie, M. S. *J. Org. Chem.* **1991**, *56*, 2853.
(2) El-Khawaga, A. M.; El-Zohry, M. F.; Abdel-Wahab, A. A.; Khalaf, A. A. *Bull. Soc. Chim. Fr.* **1987**, *6*, 1051.
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(4) Dykstra, S. J.; Berdahl, J. M.; Campbell, K. N.; Combs, C. M.; Lankin, D. G. *J. Med. Chem.* **1967**, *10*, 418.
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(6) de Paulis, T.; Betts, C. R.; Smith, H. E. *J. Med. Chem.* **1981**, *24*, 1021.
(7) Hoppe, D.; Hense, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2282.
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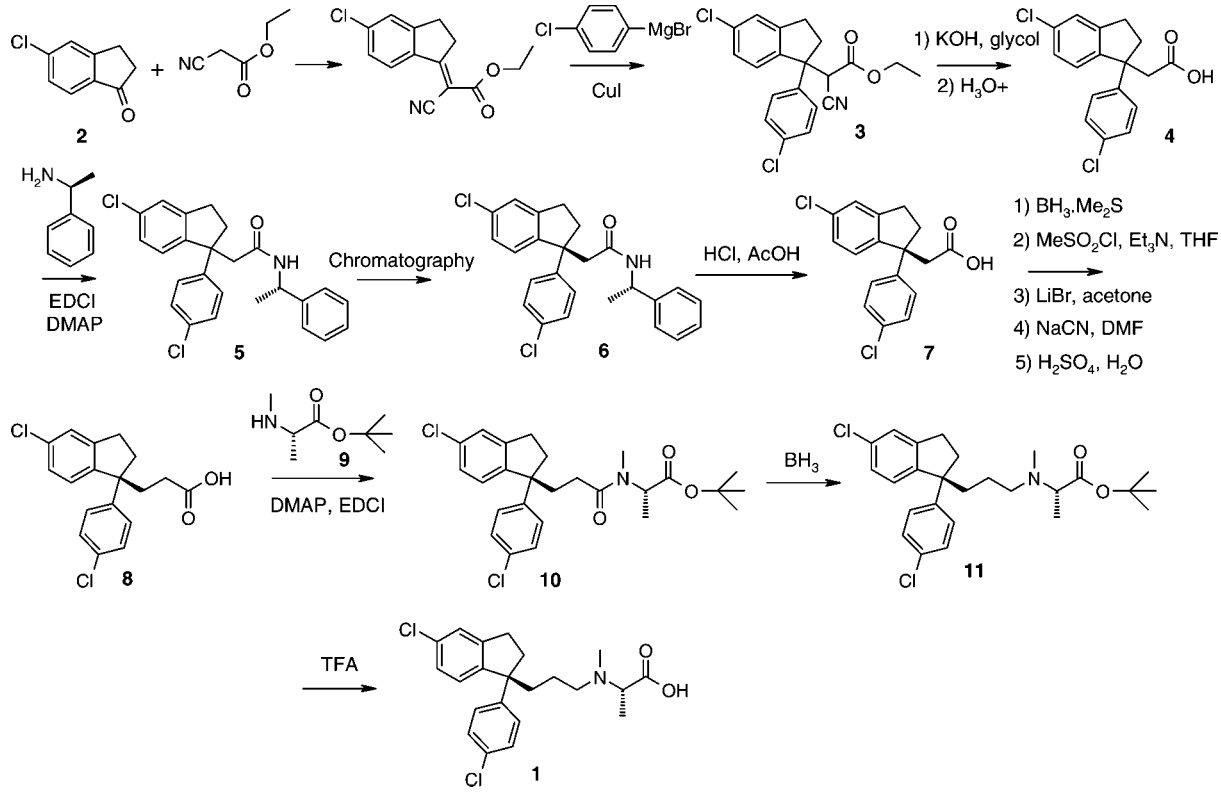
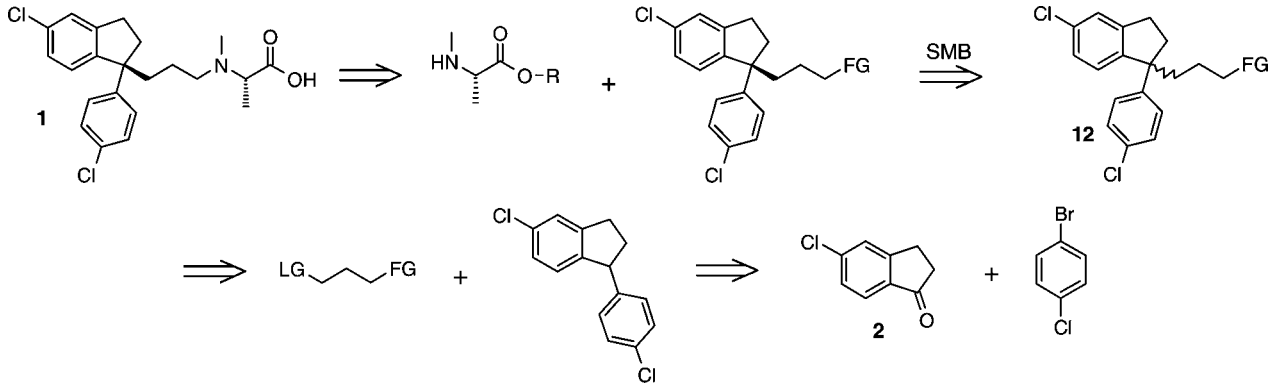
10.1021/op7002584 CCC: $40.75
Published on Web 05/16/2008

Scheme 1. **Medicinal chemistry route to Lu AA26778 (1)**



Scheme 2. **Retrosynthetic analysis of Lu AA26778 (1)**



acid could be introduced using an ester of *N*-methyl alanine or alanine. The other half of the molecule contains the phenyl indane skeleton with a C3 side chain, and we applied chiral liquid chromatography to obtain the desired stereochemical form, as this technique is reliable, fast to develop, and scaleable using simulated moving bed (SMB) chromatography.[9a] The side chain with the proper number of carbons could be introduced by an alkylation of the phenyl indane, which in turn could be synthesized from 5-chloro-1-indanone (**2**) and 1-bromo-4-chlorobenzene via a Grignard reaction. Now, the functional group (FG) in the key intermediate **12** has to fulfill two criteria; it should make the SMB separation feasible, and it should allow the further elaboration of the molecule.

Route scouting. Three molecules were synthesized and screened as candidates for resolution by SMB chiral chromatography (Chart 2). The purpose of the method development was to choose the best candidate for which the highest productivity could be obtained. The strategy involved the optimization of the main parameters having a direct impact on the productivity of the separation, i.e. those related to the intrinsic properties of the chiral stationary phase (CSP) and those conferred by the solvent. The CSP has to generate the highest selectivity and loading capacity. The solvent has to ensure the maximum solubility of the sample and the minimum viscosity to reach high flow rates.

All three candidates were screened on commercially available CSPs using analytical columns packed with material of 20 μm particle size. The screening strategy[9b] involved the use of CHIRALCEL OD, CHIRALCEL OJ, CHIRALPAK AD,

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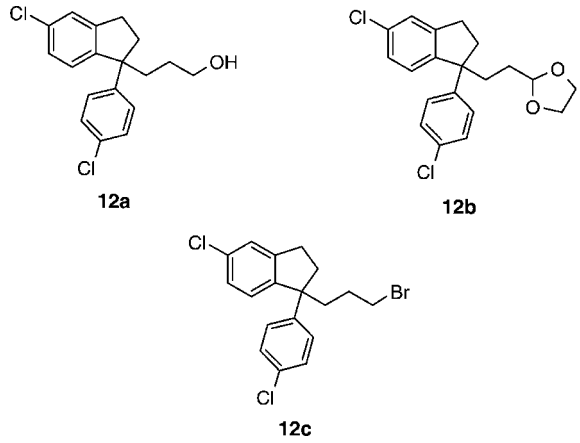
(10) Chen, C.-S.; Fujimoto, Y.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1982**, *104*, 7294.

Chart 2. **Candidates for the SMB separation**



and CHIRALPAK AS stationary phases in combination with mobile phases of pure acetonitrile, pure methanol, pure ethanol, and mixtures of heptane/2-propanol and heptane/ethanol.

The optimized results are reported in Table 1. Compound **12a** was separated on CHIRALCEL OD with selectivity greater than 2 in the five mobile phases. The compound solubility was found to be greater than 100 g/L in all these solvents with the exception of methanol, where it was 50 g/L. Compound **12b** was resolved with a selectivity of 1.6 on the same CSP, again with a very good solubility in the solvent (100 g/L), whereas compound **12c** was best separated on CHIRALCEL OJ (selectivity 2) with a solvent having a very low alcohol content (1% 2-propanol). Compound **12c** was eliminated since mobile phase composition with only 1% alcohol may be difficult to keep stable in practice.

The next step was to run loading studies for compounds **12a** and **12b** under each set of chromatographic conditions to determine the variation of the retention times with the injected sample quantity. The absolute values of the retention times together with the sample load values were entered into a computer-based simulation program, WinSMB,[9c] used to calculate the adsorption isotherm parameters. The simulation was then used to calculate the SMB operating parameters: the feed flow and the feed concentration, the switch time, the Raffinate and Extract flow and the Raffinate and Extract concentrations. The Raffinate refers to the first eluting enantiomer, and the Extract refers to the second eluting enantiomer. In Table 1, we report only the feed flow and its concentration obtained from the simulation as they were utilized to calculate the enantiomer productivity for data comparison.

The simulation results allowed the choice of the best candidate along with the most convenient and productive conditions for the preparative separation. For instance, compound **12a** gave a low productivity in methanol due to the low solubility in this solvent as well as a low productivity in ethanol due to the high solvent viscosity. The highest productivity was obtained in acetonitrile (1632 g en/kg/day); the choice of the single-solvent mobile phase was also motivated by an easier compound and solvent recovery compared with that from a mixture of solvents. As the predicted productivity of compound **12a** was appreciably higher than for **12b**, the former was chosen for further synthesis development. Details of the loading study and the experimental determination of the SMB production parameters are given in the Experimental Section.

As an alternative to the SMB resolution of **12a**, the possibility of performing an enzymatic resolution was studied. A series of 27 lipases and lipoprotein lipases, and five acylases, all commercially available, were screened for the ability of stereoselectively acylating the alcohol, see Scheme 3. *Pseudomonas fluorescens* lipase was found to be the most selective lipase for the reaction, acylating the undesired alcohol enantiomer with an E value[10] of 6–10, depending on the quality of the lipase used. *Aspergillus niger* was the second most selective lipase but had the opposite selectivity as compared to *P. fluorescens* lipase, acylating the desired alcohol with an E value of 4.0.

The reaction conditions were optimized with *P. fluorescens* lipase; the parameters studied included the nature of the acyl donor (four different vinyl esters, three different 2,2,2-trihalogenethyl esters, isopropenyl acetate, and valeric anhydride), the concentration of the substrate (10–100 mM), the equivalents of vinyl butyrate (0.5–2 equiv), the temperature (−5 to 65 °C), and the solvent (eight different solvents). The conclusion of these studies was that vinyl butyrate was the best acyl donor, the best solvents were toluene, 2-butanone, and 4-methyl-2-pentanone, and a temperature at or below room temperature gave the best selectivity. The concentration of the substrate and the equivalents of vinyl butyrate had no influence on the selectivity. Unfortunately, it was not possible to find conditions increasing the E value above the range of 6–10 found in the initial screening.

When performing the reaction on a 20 mg scale in toluene at room temperature, an enantiomeric purity of 98% or more of the desired alcohol enantiomer **13** could be obtained if the reaction was stopped at 74% conversion or more, see Table 2. At gram scale, the reaction was found to be appreciably faster than on mg scale. Performing the reaction starting with 4 and 19 g of **12a**, and running the reaction to 73% and 75% conversion, respectively, gave the desired enantiomer with 89% ee and 91% ee, respectively. The isolated yield was 20% and, unfortunately, the impurities in the racemate were concentrated in the desired product. Due to the large conversion needed to obtain a satisfactory enantiomeric purity of the product, the SMB process was obviously preferred for the resolution of **12a**.

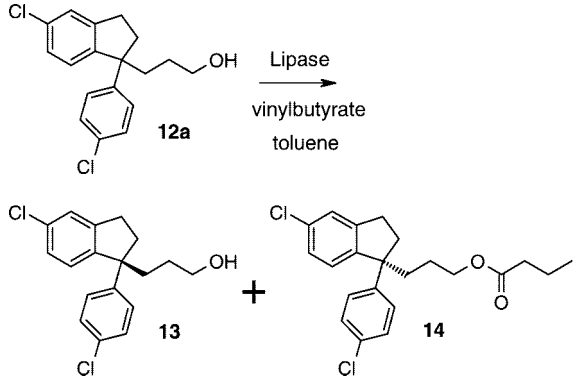
Having identified a proper candidate for the chiral chromatography, the synthesis shown in Scheme 4 could be elaborated in the laboratory: Compound **15** was synthesized by modifying the procedure used by de Paulis et al.[6] for the synthesis of similar compounds; after the reaction of 5-chloroindanone with 4-chlorophenylmagnesium bromide, the formed alkoxide was quenched and dehydrated by adding concentrated sulfuric acid to the reaction mixture. Thus, after workup, indene **15** could be isolated directly as a solid. Catalytic hydrogenation of **15** using Pd on charcoal provided indane **16.** Some dechlorination was observed in this step, but this could be limited to less than 3% by closely monitoring the reduction and stopping the reaction as soon as indene **15** was completely consumed (in our largest production batch, this gave less than 0.3% of the corresponding dechlorinated byproduct in the final product). The indane **16** was isolated as an oil in quantitative yield.

Table 1. **Optimization data for compounds 12a, b, c[a]**

entry	cmpd	CSP[b]	solvent	selectivity[c]	solubility g/L	feed flow mL/min	feed concn g/L	P^d g/kg/day
1	**12a**	OD	acetonitrile	2	~180	15.23	92	1632
2	**12a**	OD	methanol	2	~50	16.17	45	655
3	**12a**	OD	ethanol	3.3	~130	6.35	106	605
4	**12a**	OD	heptane/2-propanol, 85:15	2.2	~130	9	126	1022
5	**12a**	OD	heptane/ethanol, 90:10	2	~110	14.8	106	1415
6	**12b**	OD	heptane/2-propanol, 95:5	1.6	~110	10.09	110	998
7	**12c**	OJ	heptane/2-propanol, 99:1	2	~100	Not calculated		

[a] Columns 250 mm × 4.6 mm i.d., 20 μm, flow rate 1 mL/min, column temperature 30 °C. [b] Chiral Stationary phase; OD is CHIRALCEL OD, and OJ is CHIRALCEL OJ. [c] Selectivity is calculated as the ratio of the capacity factor of the second eluting and the first eluting enantiomer, k'_2/k'_1; the capacity factor is given as $k' = (t_r - t_0)/t_0$, where t_0 is the breakthrough time of the column and t_r is the retention time of the respective enantiomer. [d] Productivity calculated for a SMB unit with 8 mm × 50 mm i.d. columns and an operating pressure of 35 bar. In this system, the quantity of CSP was approximately 0.8 kg. The productivity was calculated with the following formula: P = Feed*[Feed]*60*24/(CSP*1000*2) where P is the productivity in g of enantiomer/kg CSP/day, Feed is the feed flow rate (mL/min), [Feed] is the feed concentration (g/L), and CSP is the quantity of CSP (kg).

Scheme 3. **The stereoselective enzymatic acylation of alcohol 12a**



Next, the alkylation of the phenylindane **16** was studied. Dyksta et al.[4] could alkylate the anion of 1-phenylindan formed using sodium amide in liquid ammonia with dialkylaminoalkyl halides. As we were not fond of scaling up a reaction involving liquid ammonia, we sought inspiration in the synthesis of citalopram, in which sodium hydride in DMSO[11] and LDA in THF[12] could be used in the alkylation of 1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (**21**, Chart 3). Therefore, a series of bases were tested in the alkylation step of **16**. These included *n*-butyllithium, LDA, sodium methoxide, sodium ethoxide, potassium *tert*-butoxide, KHMDS, and sodium hydride in DMSO; only the latter gave alkylation when the alkylchloride **17** was added. As mixtures of DMSO and bases are dangerous due to the possibility of a run away (discussed in more detail below), several possibilities of avoiding DMSO in the mixture were screened, including sodium hydride in NMP or THF, sodium hydride in DME with TMEDA or 18-crown-6 as solubilizer, or sodium hydride in THF with catalytic amounts of HMDS or diisopropylamine, all without success. Thus, the process development work was concentrated on diluting the DMSO with THF, working as a safety blanket; this is discussed in detail below.

The alkylation and the following deprotection in methanol with concentrated hydrochloric acid, gave the racemic alcohol **12a** in 50–85% yield over two steps. As this compound was an oil, the laboratory batches were purified by a rough chromatography on silica gel, but a more elegant procedure was developed for the pilot-plant production as described below. SMB separation of the racemic alcohol **12a** gave the enantiomer **13** with 99% ee in 45% yield. The stereochemistry was assigned by performing the rest of the synthesis with one of the enantiomers (incidentally the right one) and identifying the formed diastereoisomer by HPLC retention time using samples of **1** and its epimer, synthesized by the medicinal chemistry route, as reference standards.

The optically pure alcohol **13** was activated as the mesylate **19** and then coupled with *N*-methyl alanine *tert*-butyl ester (**9**); giving compound **20** in 41–55% yield over two steps in the laboratory procedure. The low yield could be correlated to a combination of residual solvent in **13** and the formation of the chloride corresponding to **19** formed from chloride anions stemming from the formation of the mesylate with methanesulfonyl chloride (this issue was solved in the plant by replacing THF with toluene and introducing an aqueous workup to remove chloride ions: see preparation of **19** in the Experimental Section). The resulting ester was purified by chromatography.

Finally, the *tert*-butyl ester **20** was deprotected with anhydrous hydrochloric acid in ether, and the hydrochloride of **1** could be isolated by evaporating the solvent. The hydrochloride was dissolved in aqueous potassium hydroxide, and pH was adjusted to 5–6, whereby the zwitterion of **1** precipitated. Recrystallization from ethyl acetate gave the desired crystal form of **1**, concluding the route scouting in a successful way. Approximately 200 g of (**1**) was synthesized in the laboratory using this synthesis; the overall yield was 7%, a 7-fold increase as compared to the medicinal chemistry route.

Process development. When considering the scale-up of the process, several issues had to be addressed: in the laboratory, the racemic alcohol **12a** was purified by a rough chromatography, and a more elegant procedure had to be found. Furthermore, finding a CRO, which could deliver the *N*-methyl alanine *tert*-butyl ester **9** in kilogram quantity in a timely manner turned out to be difficult; therefore, a process involving the use of an alanine ester, without the *N*-methyl group, was developed. However, the most important issue was the safety in the alkylation step involving sodium hydride in DMSO.

As reported in the literature, preparation of sodium dimsylate anion from NaH or Na in DMSO can be a quite treacherous undertaking: incidents ranging from laboratory- to production

(11) Bøgesø, K. P.; Toft, A. S. U.S. Patent 4,136,193, 1979.
(12) Petersen, H.; Bøgesø, K. P.; Sommer, M. B. PCT Int. Appl. WO 98/19511, 1998.

Table 2. **Representative experiments with the stereoselective enzymatic acylation of alcohol 12a**

Psedomonas fluorescens lipase							
specific activity U/mg	wt mg	**12a** wt g	time h	conversion %	ee ester **14** %	ee alcohol **13** %	yield %
309[a]	5	0.02	118	66	39	84	–
36[b]	5	0.02	118	74	33	98	–
1.9[c]	5	0.02	118	79	27	99.9	–
309[a]	15	4.5	52	73	–	89	20
309[a]	57	19	20	75	–	91	20

[a] Fluka cat. no. 28602. [b] Fluka cat. no. 95608. [c] Fluka cat. no. 71548.

Scheme 4. **Laboratory synthesis of Lu AA26778 (1)**

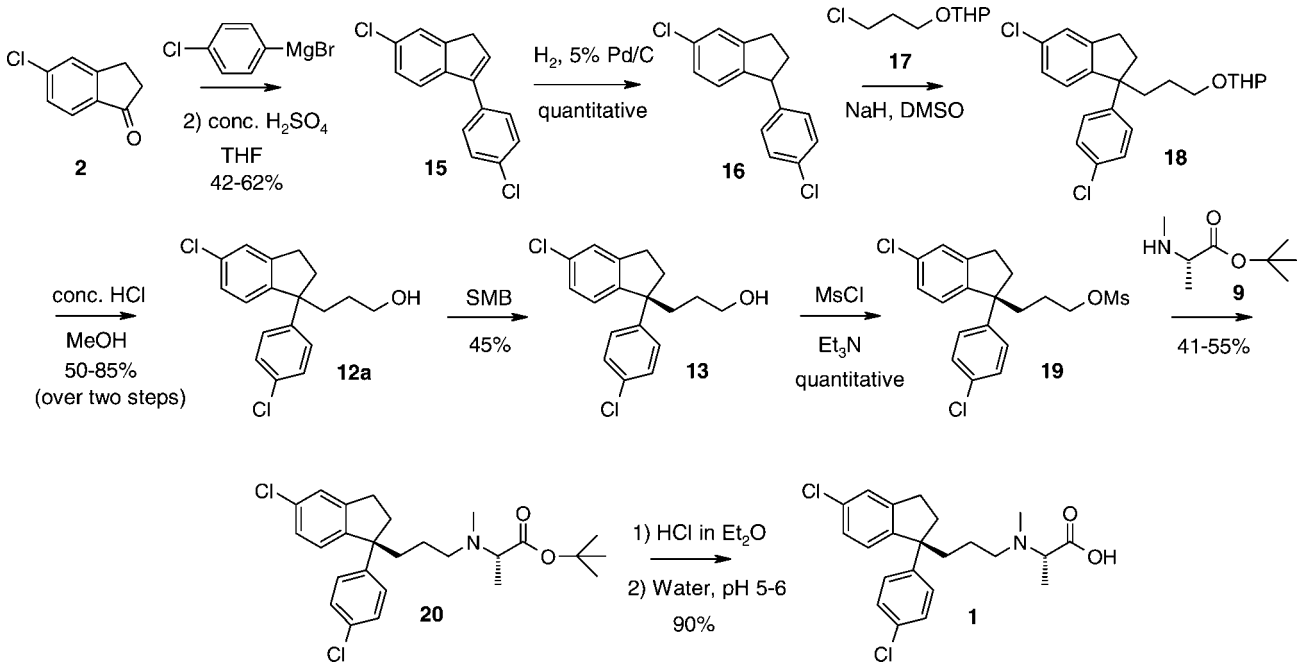
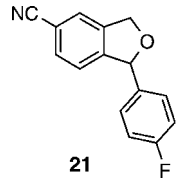


Chart 3



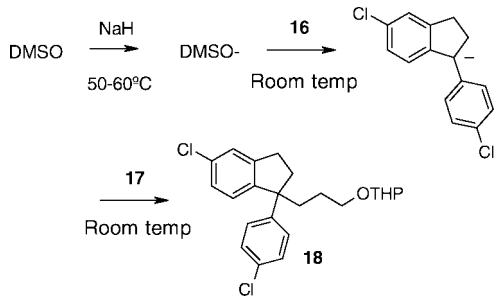
scale have been reported where runaway reactions and explosive behavior have occurred.[13–16] Several of these incidents have been investigated further; however, there is no conclusive evidence as to the cause of the accidents. The problems are due to the reactive nature of DMSO; pure DMSO begins to decompose at or slightly below its boiling point of 189 °C, producing heat and gas. The decomposition is self-accelerating, and traces of acid, base, or alkyl halides lower the onset temperature and hasten the process.[16] Pure DMSO decomposes with a heat release rate of 79 W/kg; in the presence of sodium hydroxide the heat release is 640 W/kg; and in the presence of chloroform, the decomposition is releasing heat even more rapidly at a rate of 2435 W/kg.[16] Furthermore, in investigations at Chilworth,[17] runaway behavior has been observed at 50–60 °C in the preparation of sodium dimsylate; therefore, making sodium dimsylate by simply heating a mixture of sodium hydride and DMSO to 60–70 °C[18] was clearly not an option.

The simplest solution would be to find a base other than sodium dimsylate, but as discussed above, all attempts to do so were unsuccessful; thus, we were forced to provide the safety by designing the process properly. The major problem with DMSO, apart from the fact, that it is a reactive solvent, is its high boiling point (189 °C), which hinders the dissipation of heat through vaporization: before accumulated heat can be dissipated by vaporization, a self-accelerating decomposition reaction has already been initiated. Therefore, we studied the possibility of diluting the DMSO with THF (boiling point 67 °C) or dimethoxyethane (DME, boiling point 82 °C), which could serve as a safety blanket.

The individual reactions in the process are shown in Scheme 5. First, sodium hydride reacts with DMSO at 50–60 °C to form the sodium dimsylate, then the indane **16** is added at room temperature to form the indane anion, which is alkylated at room

(13) French, F. A. *Chem. Eng. News* **1966**, *44*, 48.
(14) Olson, G. A. *Chem. Eng. News* **1966**, *44*, 7.
(15) Itoh, M.; Morisaki, S.; Muranaga, K.; Matsunaga, T.; Tohyama, K.; Tamura, M.; Yoshida, T. *Anzen Kogaku* **1984**, *23*, 269.
(16) Hall, J. *Loss Prev. Bull.* **1993**, *114*, 9.
(17) Rowe, S. Chilworth Technology Ltd., Southampton, United Kingdom. Private Communication to M.A.N., 2003.
(18) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1962**, *84*, 866.

Scheme 5. **Three consecutive reactions involved in the alkylation of 16**



temperature by addition of the alkyl chloride **17**. When this process was studied on a 1-g scale using different concentrations of DMSO in DME, the following three observations were made: (1) lowering the concentration of DMSO gave a longer lag time before evolution of hydrogen could be observed by the eye, (2) lowering the concentration of DMSO gave a lower degree of alkylation, and (3) lowering the concentration of DMSO gave a more vigorous evolution of hydrogen when the reaction mixture was quenched with ethanol. These observations indicated that a threshold concentration of DMSO had to be exceeded in order to ensure proper reaction between DMSO and sodium hydride; a ratio of DMSO:solvent of 1:6 appeared to be a proper choice as full alkylation was achieved, and no evolution of hydrogen was observed when the reaction mixture was quenched with ethanol. No significant difference in performance of THF and DME was observed. We verified on a 20-g scale, that the process worked well in THF, and then we turned to the study of the safety.

The results of our Reaction Calorimetry measurements are shown in Figure 1; when the reaction is performed in pure DMSO, the lowest reported decomposition temperature is 50 °C, and the heat evolved could give rise to a temperature increase of 500 K under adiabatic conditions, which is the major concern. The onset temperature for the formation of sodium dimsylate was 52 °C, slightly above the lowest observed decomposition temperature. The addition of the indane at room temperature could give rise to a temperature increase of 9 K under adiabatic conditions and is not of major concern. On the other hand, the alkylation reaction could give a temperature increase of 32 K under adiabatic conditions, which would raise the temperature above the onset temperature of the decomposition.

The situation changed significantly, when the reaction mixture was diluted with THF (Figure 1): Now, the lowest observed decomposition temperature was 100 °C, and the adiabatic temperature rise was 230 K. The formation of the dimsylate anion at 65 °C evolved enough heat to boil of 5–6% of the THF under adiabatic conditions. If also the addition of the indane **16** and the alkyl chloride **17** were carried out at reflux temperature, the complete heat evolution of the process would be able to boil off approximately 30% of the THF under adiabatic conditions—with no other consequence as a result. As this was the absolute worst-case scenario, the process was regarded as completely safe.

Now, being able to perform the synthesis in a safe manner, some practical issues had to be resolved; one being the purification of the racemic alcohol **12a**. This compound is the last of three consecutive oils in the synthesis, accumulating several impurities, as the two former oils, **16** and **18**, were not purified prior to use in the process. Furthermore, the compound was supposed to be used in the SMB process and therefore had to be purified in a convenient way; but merely scaling up the chromatography used in the laboratory would give a large workload and a huge amount of waste. Fortunately, we found that**12a** could be purified by liquid–liquid extraction using two organic solvents; when the raw product was dissolved in acetonitrile, the impurities, such as **16** and **18**, could be extracted using any of a variety of hydrocarbon solvents. The purity of an acetonitrile solution of **12a** could be increased from approximately 72% to approximately 95% by extraction with either hexanes, heptanes, or cyclohexane. This procedure was scaled up using heptanes, as it is the least problematic of the three solvents regarding HSE (Health, Safety and Environment); and Figure 2 illustrates the performance of the procedure during the purification of two batches in the pilot plant. After three washes with heptane, the purity of the alcohol in the acetonitrile phase had increased from 70−75% to approximately 94%. In this way it was possible to reduce the amount of waste from the purification by a factor of 3 as compared to the chromatography. As acetonitrile was used as eluent in the SMB process, **12a** was not isolated as an oil, but the solution was merely concentrated (to 171 g/L) before use in the SMB process.

During the SMB campaign, the parameters from the simulation (Table 1) were adjusted for the difference in feed concentration (92 g/L from the simulation compared to 171 g/L in production) and for the maximum pressure which could be reached in the system during the process, which was 30 bar instead of the 35 bar used in the simulation. The feed flow had to be decreased compared to that from the simulation to reach a raffinate purity of greater than the target value of 98% ee, although the extract purity could not be increased above 96% ee under these conditions. Calculation of the productivity of the process at 30 bar gave a value of 692 g enantiomer/kg/day, a value much lower than that obtained from the simulations. One hypothesis for the discrepancy between the predicted and the experimental results might be that the high level of impurity and the high sample concentration may have resulted in a deviation from the Langmuir adsorption isotherm used in the simulation, thus removing the model from reality. In our experience, this is often the case where compounds obtained by synthesis are directly used for chromatography without further purification; however, as described above, it was difficult to perform a more thorough purification, as **12a** is an oil. A total of 60 kg of **12a** was resolved during the SMB campaign, giving 27 kg of **13** (yield 45%) in 99% ee.

The last issue to be discussed regarding process development emerged as a consequence of the lack of availability of **9** in multikilogram quantities; the synthetic route had to be changed in order to substitute **9** with an ester of alanine. The methyl ester **22** (Scheme 6) was chosen, as it was readily available. When doing this, the *N*-methyl group had to be introduced after the coupling of the amine with the mesylate **19**, extending the synthesis by one step (Scheme 6). We selected the Eschweiler–Clarke method using a mixture of formic acid and formaldehyde, as this is known to give monomethylation of secondary amines, and has been used for methylation of free amino acids

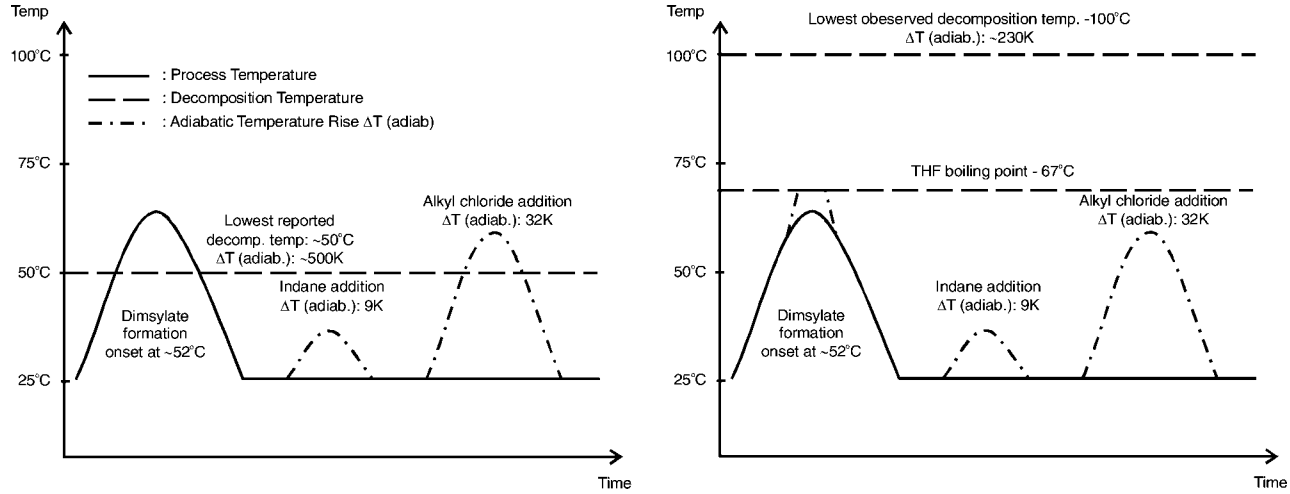


Figure 1. **Reaction calorimetric measurements of the steps involved in the alkylation of the indane 16. (Left) The situation in pure DMSO. (Right) The situation when the mixture is diluted with THF.**

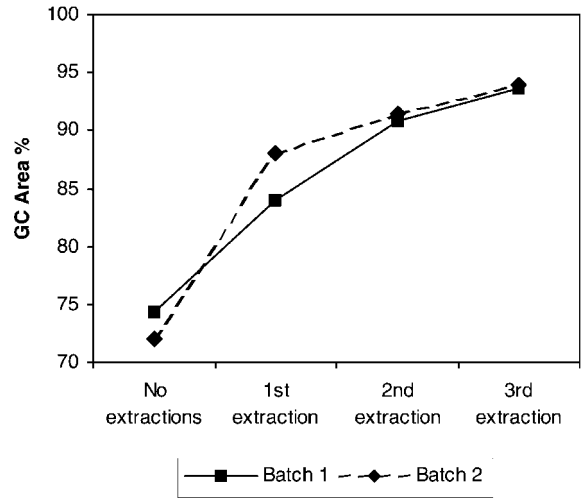


Figure 2. **Purification of the racemic alcohol 12a in the pilot plant by acetonitrile−heptane partitioning. The figure shows the purity of 12a in the acetonitrile phase after each extraction with heptanes.**

without compromising the optical activity.[19–22] Unfortunately, in the work described here, the reaction compromised the stereochemistry to a minor extent.

When the last part of the synthesis was performed using this route, some epimer of **1** (epimerized in the amino acid part) was detected in the product. Unfortunately, we were not able to analyse the diastereomeric purity of **23**, but **24** contained approximately 3% of its epimer even though alanine methyl ester used in the synthesis was stereochemically pure. After *N*-methylation, **1** contained 3–8% of its epimer, so some epimerization may occur in all the last three steps.

Several ways of mixing the reagents in the last step were tested in the laboratory in order to suppress the epimerization and to ensure that the process could be successfully scaled up. Figure 3 summarizes the results starting from **24** containing 2.8% of its epimer: Apparently, no particular measure could circumvent the epimerization, including using diethoxymethane as the formaldehyde source. On the other hand, in all the cases tested, recrystallization from ethyl acetate gave **1** containing less than 5% of the epimer, which was satisfactory according to the toxicologists. Finally, when comparing the dump-and-stir-with-rapid-heating strategy with the slow-heating strategy, it appears that the epimerization is reduced with slow heating, indicating that no problems would be encountered when scaling up the reaction.

In the kilo laboratory, diastereomeric ratios of 97:3 and 99:1 were found for two batches of **24**, and ratios in the range of 95:5 to 97:3 were observed for three batches of **1**. During the campaign, an analytical method for the determination of the diastereomeric ratio of **1** in the reaction mixture was developed, and it was possible to analyse one batch of the reaction mixture: a diastereomeric ratio for **1** of 90:10 in the reaction mixture was found, showing that the epimerization was noticeable in the kilo laboratory.

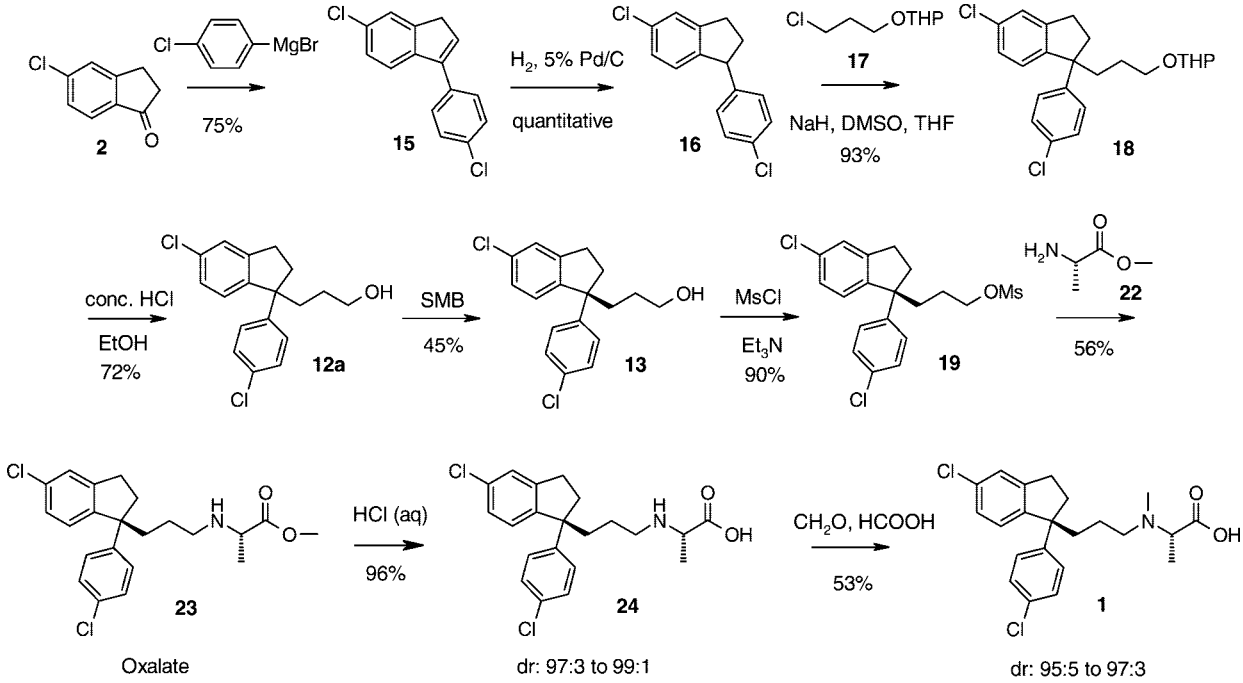
The yield in the kilo laboratory of the last step was approximately 53%, which is considerably lower than the yield of 85% in the laboratory. This was due to the formation of lipophilic impurities and polymers in the kilo laboratory, probably caused by the longer heating times. Apart from consuming some of the starting materials, the impurities also solubilized the product in the final precipitation: consecutive harvesting in the first run of the reaction raised the yield to a total of 58%, but the series of crops turned out to have decreasing diastereomeric purity. Therefore, only one crop was isolated from the two next batches.

The development work was concluded by the synthesis of 5 kg of **AA26778** (**1**), demonstrating the feasibility of the synthesis. The yields from the pilot-plant campaign are summarized in Scheme 6; the overall yield is approximately 5%, a 5-fold increase as compared to the medicinal chemistry route.

In order to circumvent the problems with the epimerisation in future production of our target molecule, the use of the methyl ester and the *tert*-butyl ester of *N*-methyl alanine in the coupling with the mesylate was studied and compared to the process used in the pilot plant (Scheme 7). Unfortunately, the diastereomeric purity could not be determined for the esters, only for the amino

(19) Quitt, P.; Hellerbach, J.; Vogler, K. *Helv. Chim. Acta* **1963**, *46*, 327.
(20) Kotake, H.; Saito, T.; Okubo, K. *Bull. Chem. Soc. Jpn.* **1969**, *42*, 1367.
(21) Narita, M.; Akiyama, M. *Bull. Chem. Soc. Jpn.* **1974**, *47*, 197.
(22) Morley, J. S.; Smith, J. M. *J. Chem. Soc. (C)* **1968**, 726.

Scheme 6. **Pilot plant and kilo lab synthesis of Lu AA26778 (1); the yields in the individual steps are given**



acids. As discussed above, the content of the epimer of **AA26778** in the reaction mixtures produced in the kilo laboratory campaign was up to 10%, which was mainly due to the epimerization in the final methylation step. The use of either the methyl ester or the *tert*-butyl ester of *N*-methyl alanine reduced the content of the epimer considerably; 1.4% or less of the epimer was found in the reaction mixture. No significant difference in the performance of the methyl ester and the *tert*-butyl ester was found. When the low yield in the final methylation step in the kilo laboratory is taken into consideration as well, the use of an ester of *N*-methyl alanine in future productions of **AA26778** would clearly be the choice.

Unfortunately, after having addressed several issues regarding large-scale production of **1**, the compound was rejected due to high toxicity, at the same time as the synthesis of 5 kg was concluded. That is the fate of the majority of compounds in the pharma industry—but then the knowledge and the fun are remembered.

Conclusion

A new process for the synthesis of **AA26778** (**1**) was developed consisting of 7–8 steps and a SMB separation of a racemic mixture, which represents a large simplification as compared to the medicinal chemistry route of 13 steps and a chromatography of a diastereomeric mixture. Thereby, the overall yield was increased from approximately 1% for the medicinal chemistry route to 5–7%. The chromatography of **12a**, performed in the laboratory synthesis, could be circumvented by purification of the oil by extraction using two organic solvents. Furthermore, the safety of the step incorporating DMSO and sodium hydride was ensured using THF as a safety blanket.

Experimental Section

General. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance AV-500 instrument or a Bruker Avance DPX-250 instrument; chloroform (99.8%D) or dimethyl sulfoxide (99.8%D) were used as solvents, and tetramethylsilane (TMS) was used as internal reference standard. Differential scanning calorimetry (DSC) was performed on a TA-Instruments DSC-2920 calibrated at 5 °C/min; about 2 mg of sample was heated 5 °C/min in a loosely closed pan under nitrogen flow. The elemental analyses were performed using a Vario El analysator from Elementar build to measure C, H, and N content; the value given is the mean of two determinations using approximately 4 mg each. The optical rotation was measured using a Perkin-Elmer model 241 polarimeter. Thermal Gravimetric Analysis (TGA) was performed on a TA-instruments TGA Q500, calibrated at 10 °C/min; about 5 mg of sample was heated 10 °C/min up to 300 °C in an open pan under nitrogen flow. The water determination was performed using a Metrohm 756 Karl Fischer Coulometer with 774 Oven Sample Processor; about 20 mg of sample was heated, and the released water was collected and determined coulometrically.

HPLC purity and concentration of **12a**, **16**, and **18** were determined using a Luna C8 column (Phenomenex), 100 mm × 4.6 mm i.d., 5 μm, at 40 °C; flow 1.0 mL/min of a gradient of (A) 25 mM phosphate buffer (pH 6):MeCN, 80:20 and (B) 25 mM phosphate buffer (pH 6):MeCN, 20:80; A:B, 25:75 for 4 min, then shift to 100% B during 6 min; detection was performed using a UV/DAD detector at 220 nm. Alternatively, the purity and concentration of **12a**, **16**, and **18** were determined by GC using an Rtx-5 Amine column (Restek), 30 m × 0.25 mm i.d., 0.50 μm, with the following parameters: carrier gas: He, 1.0 mL/min, injection temperature 250 °C, detection temperature 250 °C, column temperature 100 °C for 1.5 min, then 10 °C/min to 300 °C, which was held for 20 min, detection is performed using a FID detector. Purity and assay of **13**, **19**, **23**, and **24**, were determined by HPLC using a Luna C8 column, 100 × 4.6 mm i.d., 3 μm, at 40 °C; flow 1.0 mL/min of a gradient of (A) 12.5 mM phosphate buffer (pH 3):MeCN 80:20 and (B) water:MeCN 5:95; A:B 70:30 for 10 min, then shift

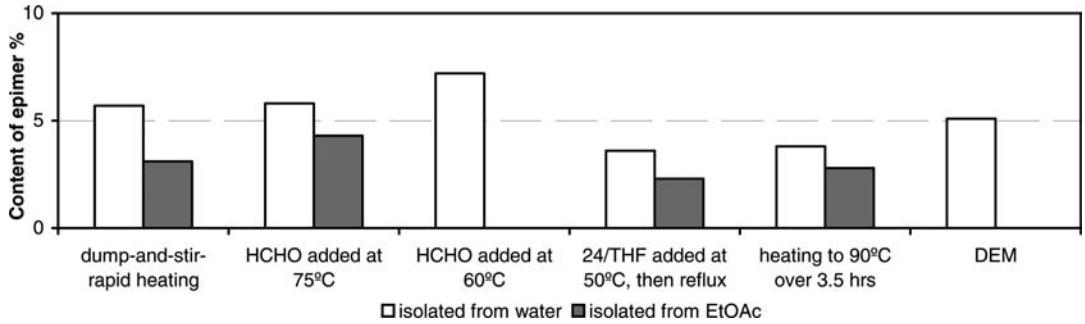
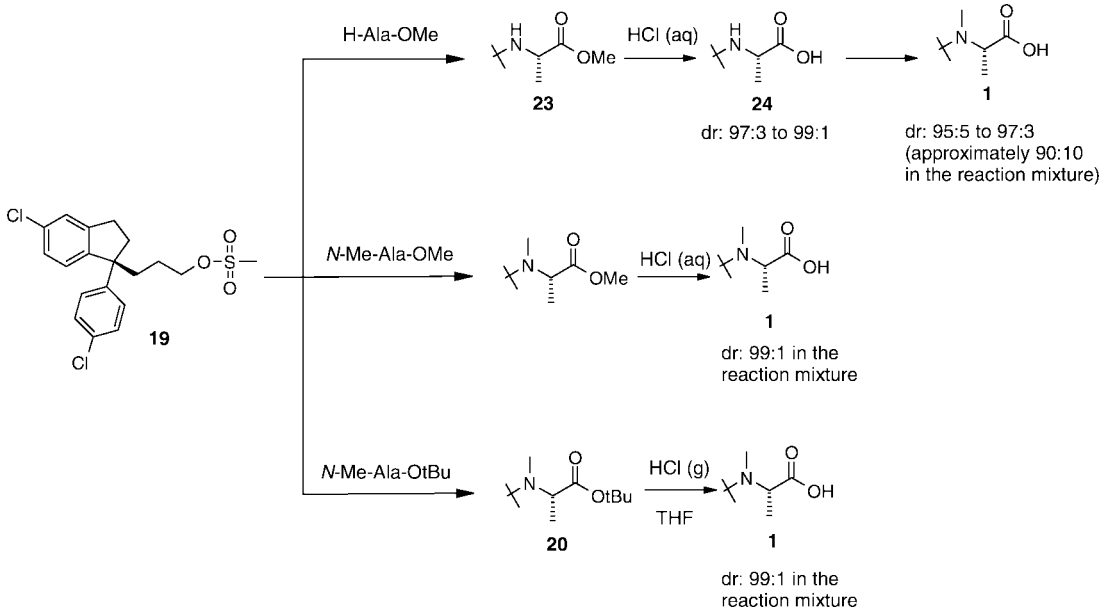


Figure 3. **Influence of order of addition of the reactants in the *N*-methylation step. The bars show the content of the epimer in the raw product isolated from water and the final product after recrystallization from ethyl acetate. The starting material 24 contained approximately 3% of its epimer.**

Scheme 7. **Diastereomeric ratio of 1 using different esters in the coupling reaction with the mesylate 19; the figures in the top are from the kilo lab campaign**



to 100% B during 15 min, which was held for 15 min; detection was performed using a UV/DAD detector at 220 nm. The concentration of alanine methyl ester in MeCN was determined by GC using a Rtx-5 Amine column (Restek), 30 m × 0.25 mm i.d., 0.50 μm, with the following parameters: carrier gas: He, 1.0 mL/min, injection temperature 175 °C, detection temperature 250 °C, column temperature 50 °C for 1.5 min, then 5 °C/min to 100 °C, which was held for 10 min; detection was performed using a FID detector. The purity of **1** was determined by HPLC using a Sunfire C18 column, 150 × 4.6 mm i.d., 3.5 μm, at 35 °C, flow 1.0 mL/min of a mixture of 10 mM ammonium formiate (pH 4.8):MeCN 55:45; detection was performed using a UV detector at 228 nm. The enantiomeric purity of **13** and its enantiomer was determined by chiral HPLC using a CHIRALCEL OD-H column (Daicel Chem. Ind.), 250 × 4.6 mm i.d., 5 μm, at 30 °C, flow 1.0 mL/min of a mixture of *n*-heptane:ethanol 90:10; detection was performed using a UV detector at 220 nm. The SMB in-process analytical method was performed on CHIRALCELOD-H column, 250 × 4.6 mm, using acetonitrile as mobile phase at a flow rate of 1 mL/min and a temperature of 25 °C. A DAD detector with a wavelength of 210 nm was used for detection. The selectivity for this separation was 1.6 ($k'_1 = 0.726$, $k'_2 = 1.165$). Determination of the content of the diastereoisomers (all four) in **1** was determined by chiral HPLC using a Chirobiotic V column, 250 mm × 4.6 mm i.d., 5 μm, at 20 °C, flow 1.0 mL/min of a mixture of 0.1% ammonium trifluoroacetate in MeOH:MeCN, 85:15; detection was performed using a UV detector at 228 nm. The diastereomeric purity of **24** was determined by fused silica capillary electrophoresis (CE) using the following conditions: Capillar: 50 μm i.d. × 48.5 cm, run buffer: 20 mM α cyclo dextrin in 25 mM sodium dihydrogen phosphate, pH 1.5, current: 70 μA, temperature: 22 °C, injection: 40 mbar for 4 s, detection 195 nm, sample concentration: 500 μg/mL. Relevant reference standards, including the diastereoisomers, were prepared by the general synthetic routes in this paper, and purified by crystallization or chromatography. All standards gave satisfactory elemental analysis and NMR spectra.

(*S*)-*N*-Methyl alanine *tert*-butyl ester hydrochloride and (*S*)-alanine methyl ester hydrochloride were delivered by Bachem AG, 5-chloro-1-indanone **2** was from Changzhou Synasia Pharmaceutical & Chemical Ltd., 4-bromochlorobenzene was from Sigma-Aldrich, 2-(3-chloropropoxy)tetrahydropyran was delivered by Fluka, and DMSO, containing less than 0.005% water, was from Sigma-Aldrich. Palladium on charcoal (5%, type 87L) was purchased from Johnson-Matthey. Other reagents

and solvents were obtained from commercial sources and used without further purification.

Methanesulfonic Acid 3-[(*S*)-5-chloro-1-(4-chlorophenyl)indan-1-yl]propyl Ester (19). A solution of alcohol **13** (195 g, 607 mmol) and triethyl amine (67.5 g, 667 mmol) in THF (2 L) was stirred on a cooling bath of ice and methanol. Methanesulphonyl chloride (76.4 g, 667 mmol) dissolved in THF (300 mL) was added at 0–5 °C. After stirring in the cooling bath for 2 h, more triethyl amine (2.45 g, 24 mmol) and methane sulfonyl chloride (2.78 g, 24 mmol) were added. The mixture was stirred for an hour in the cooling bath and filtered. The filtrate was evaporated on a rotary evaporator (50 °C in the water bath), giving 245 g (quantitative yield) of the title compound as an oil. ^{1}H NMR δ ($CDCl_3$) 7.28–7.23 (m, 3H), 7.21 (d, J = 8.0 Hz, 1H), 7.16 (d, J = 8.5 Hz, 2H), 7.06 (d, J = 8.0 Hz, 1H), 4.24–4.15 (m, 2H), 2.99 (s, 3H), 2.97–2.82 (m, 2H), 2.43–2.36 (m, 1H), 2.31–2.24 (m, 1H), 2.19–2.06 (m, 2H), 1.72–1.59 (m, 2H). ^{13}C NMR δ ($CDCl_3$) 146.54, 146.45, 145.36, 133.34, 128.88, 128.47, 127.08, 126.98, 126.22, 125.64, 70.50, 55.25, 41.35, 37.76, 35.83, 30.75, 25.55.

(*S*)-2-({3-[(*S*)-5-Chloro-1-(4-chlorophenyl)indan-1-yl]propyl}methylamino)propionic Acid *tert*-Butyl Ester (20). The mesylate **19** (189 g, 473 mmol) was dissolved in DMF (1.3 L), and (*S*)-2-methylaminopropionic acid *tert*-butyl ester **9** (188 g, 1.183 mol) (the free amine, obtained by extraction from an alkaline solution of the hydrochloride in water) was added. The mixture was stirred in an oil bath heated to 60 °C for three days. Water (2 L) was added, and pH was adjusted to approximately 2 with hydrochloric acid (4 M, 275 mL). The mixture was extracted with heptane (three times 1.0 L) (which removes some impurities) and ethyl acetate (three times 1.0 L). The combined ethyl acetate extracts were stirred with water (1.5 L), and the pH was adjusted to approximately 10.5 with sodium hydroxide (15%, 420 mL). The phases were separated, and the organic phase was washed with brine (1.2 L), dried with sodium sulfate, and evaporated to dryness on a rotary evaporator giving 140 g of oil. Chromatography of 75.5 g of the oil on silica gel 60 (0.06–0.2 mm, 1.20 kg) using a mixture of diethyl ether and heptane (gradient from 1:9 to 1:1) with 1% triethyl amine as eluent, gave 64.4 g of the title compound as an oil. ^{1}H NMR δ (DMSO-d_6) 7.34–7.20 (m, 7H), 3.16 (q, J = 7.1 Hz, 1H), 2.92–2.85 (m, 1H), 2.82–2.74 (m, 1H), 2.46–2.32 (m, 3H), 2.22–2.16 (m, 1H), 2.13 (s, 3H), 2.09–2.01 (m, 1H), 1.93–1.85 (m, 1H), 1.36 (s, 9H), 1.29–1.13 (m, 2H), 1.07 (d, J = 7.1 Hz, 3H). ^{13}C NMR δ (DMSO-d_6) 172.26, 147.93, 146.25, 145.98, 131.69, 130.89, 128.71, 128.44, 126.59, 126.33, 125.03, 80.15, 61.35, 55.01, 54.08, 39.82, 37.71, 37.38, 30.31, 28.19, 23.48, 15.11. The rest of the oil, 64.4 g, was purified in the same way, giving 55.4 g of the product. The combined yield was 120 g (55%). The excess of the amino acid ester **9** was recovered from the original acidic aqueous DMF phase, by making the solution alkaline, and extracting the free amine.

(*S*)-2-({3-[(*S*)-5-Chloro-1-(4-chlorophenyl)indan-1-yl]propyl}methylamino)propionic Acid (1). Anhydrous hydrochloric acid was bubbled through a solution of the *tert*-butyl ester **20** (120 g, 259 mmol) in diethyl ether (1.4 L). The mixture was stirred for two days at ambient temperature, and more hydrochloric acid was bubbled through occasionally. The mixture was evaporated on a rotary evaporator, giving 131 g of foam, which was stirred with water (1.4 L) and potassium hydroxide (57 g, 1.0 mol). After prolonged stirring and gentle heating, a highly alkaline solution with a little insoluble material was obtained. After filtration of the mixture, pH was lowered to 5–6 using hydrochloric acid (1 M, 540 mL) and a few pearls of potassium hydroxide, whereby the product precipitated. After stirring overnight, the product was harvested by filtration, filtered, washed with water (three times 200 mL), and dried in a vacuum oven at 50 °C. Yield 96 g (91%). As the product contained an impurity according to NMR, it was purified by dissolving it (91.5 g, 225 mmol) in a mixture of water (1.10 L) and potassium hydroxide (39.2 g, 697 mmol), and extracting the impurity with diethyl ether (two times 500 mL). Then, pH in the water phase was lowered to 6 by adding hydrochloric acid (1 M, approximately 600 mL), reprecipitating the product. After stirring overnight, the product was isolated by filtration, washed with water (three times 180 mL), and dried in the vacuum oven at 50 °C. Yield 84 g (80%). ^{1}H NMR δ (DMSO-d_6) 7.35–7.23 (m, 7H), 3.28 (q, J = 7.1 Hz, 1H), 2.94–2.86 (m, 1H), 2.83–2.75 (m, 1H), 2.74–2.63 (m, 2H), 2.44–2.37 (m, 1H), 2.37 (s, 3H), 2.24–2.17 (m, 1H), 2.14–2.05 (m, 1H), 1.93–1.84 (m, 1H), 1.41–1.32 (m, 2H), 1.17 (d, J = 7.1 Hz, 3H). ^{13}C NMR δ (DMSO-d_6) 171.1, 147.7, 146.3, 145.7, 131.8, 131.0, 128.7, 128.5, 126.7, 126.4, 125.1, 63.1, 54.9, 53.8, 39.7, 37.7, 36.8, 30.3, 21.9, 13.0. Purity (HPLC): 99.2%. Diastereomeric purity >99.5%. Water content (KF): 0.35%. Weight loss on heating (TGA): <0.1%. $[\alpha]_D^{20}$ 65.9° (c = 1, methanol). DSC: onset 89 °C, peak 100 °C. Anal. Calcd for $C_{22}H_{25}Cl_2NO_2$: C, 65.03; H, 6.20; N, 3.45. Found: C, 64.88; H, 6.32; N, 3.29.

***β*-Form of (*S*)-2-({3-[(*S*)-5-Chloro-1-(4-chlorophenyl)indan-1-yl]propyl}methylamino)propionic Acid (1).** The zwitterion of **1** (33 g), obtained as described above, was dissolved in ethyl acetate (660 mL) by heating. The mixture was stirred overnight, whereby the zwitterion precipitated. Filtration and drying in a vacuum oven gave 27 g of white solid. DSC: onset 149 °C, peak 155 °C. The solid (22.6 g) was heated to reflux for half an hour with ethyl acetate (650 mL), but this time, the zwitterion did not dissolve. After stirring at room temperature overnight, the solid was harvested by filtration and dried in a vacuum oven at 50 °C, giving 20 g of product. NMR was consistent with data given above. DSC: onset 157 °C, peak 160 °C. Weight loss on heating (TGA): <0.1%. Water content (KF): <0.1%. $[\alpha]_D^{20}$ 66.3° (c = 1, methanol). Anal. Calcd for $C_{22}H_{25}Cl_2NO_2$: C, 65.03; H, 6.20; N, 3.45. Found: C, 64.98; H, 6.25; N, 3.59.

6-Chloro-3-(4-chlorophenyl)-1H-indene (15). A 400-L stainless steel reactor was charged with magnesium turnings (7.0 kg, 288 mol), THF (25 L), and a solution of iodine in THF (0.01 mg/mL, 100 mL). The resulting suspension was heated to just below reflux (approximately 65 °C) under an atmosphere of nitrogen prior to initiation of the Grignard reaction. A small portion of a solution of 1-bromo-4-chlorobenzene (54.8 kg, 286 mol) in THF (160 L) was added, and a positive reaction start was detected by initiation of reflux. The remaining solution was then added over approximately 2 h, a rate which maintained reflux. Upon completion of the addition, reflux was maintained

by heating for approximately 1.5 h. The resulting Grignard reagent was cooled to 30–40 °C, rendered magnesium-free by filtration, and further cooled to 20–30 °C. A solution of 5-chloroindanone (31.5 kg, 189 mol) in THF (160 L) was then added at a rate to maintain <50 °C, and the mixture was allowed to stir for 60 min upon completion of the addition. The reaction mixture was then quenched and dehydrated by the addition of concentrated sulfuric acid (96%, 48.2 kg, 472 mol) at a rate to maintain <50 °C. Upon completion of the addition of acid, water (200 L) was added, and then THF was removed via distillation at atmospheric pressure. The aqueous phase was extracted twice with heptane (275 and 100 L), and the aqueous phase was then neutralized and discarded. The combined heptane phases were washed with two portions of water (150 L each) followed by a 15% aqueous sodium chloride solution (155 L). The heptane phase was then concentrated to 15% of its volume, at which point ethanol (400 L) was added. The remaining heptane was removed via azeotropic distillation, and a crystallization volume of 300 L was obtained. The solution was cooled to approximately 10 °C (seed crystals introduced at 50 °C) and aged overnight. After filtration and washing with ethanol (35 L), the beige powder was dried in a vacuum tray drier at 60 °C to give 36.5 kg (74%) of the title compound. ^{1}H NMR δ ($CDCl_3$) 7.54–7.50 (m, 3H), 7.47–7.43 (m, 3H), 7.33 (dd, $J = 2.0$ and 8.3 Hz, 1H), 6.60 (t, $J = 2.2$ Hz, 1H), 3.52 (d, $J = 2.2$ Hz, 2H) (main peaks; contains 10% impurity). ^{13}C NMR δ ($CDCl_3$) 146.8, 143.9, 142.5, 134.5, 134.0, 131.9, 131,6, 129.3 (two Cs), 126.9, 125.0, 121.3, 38.5. Mp 78–80 °C. Anal. Calcd for $C_{15}H_{10}Cl_2$: C, 68.99; H, 3.86. Found: C, 67.79; H, 3.90.

5-Chloro-1-(4-chlorophenyl)indane (16) in THF. A solution of **15** (35.0 kg, 134 mol) in THF (210 L) was blank filtered and transferred to a 400-L glass-lined vessel containing 5% Pd/C (2.0 kg). This slurry was transferred to a 600-L stainless steel autoclave heated to 25 °C and hydrogenated at 3 bar for 5.5 h. After purging of hydrogen, the slurry was transferred to a vessel containing anhydrous sodium sulfate (10 kg) for rough drying. The catalyst and drying agent were removed by recirculation over a pressure filter, and complete transfer was ensured by rinsing with THF (90 L). Subsequent concentration by distillation at atmospheric pressure to a final volume of 200 L afforded a yellowish solution of **16** that was used without further purification: 173 mg/mL GC assay (98% yield).

2-{3-[5-Chloro-1-(4-chlorophenyl)indan-1-yl]propoxy}tetrahydropyran (18) in Ethanol. A 100-L portion of **16** in THF was concentrated to approximately 0.6 kg/L by distillation at atmospheric pressure. Meanwhile, a scrupulously dried 900-L stainless steel vessel (whose ventilation was connected to an ethylene glycol scrubber followed by a chimney) was charged with a 60% dispersion of sodium hydride in mineral oil (4.1 kg, 103 mol), followed by THF (200 L) and finally DMSO (31.5 kg, 403 mol). **Caution: Order of addition is critical! NaH should not be mixed with pure DMSO.** The greyish suspension was then heated to 65 °C for 3 h (hydrogen evolution has visually ceased) and then cooled for storage at room temperature overnight. The yellowish solution was then cooled to 12 °C prior to the addition of the 0.6 kg/L solution (65.7 mol) of **16** in THF, which results in an immediate shift in color to dark red due to the formation of the indanyl anion. A solution of 2-(3-chloropropoxy)tetrahydro-2*H*-pyran (14.5 kg, 81.2 mol) in THF (15 L) was then added at a rate to maintain <40 °C during the addition. After a minimum of 30 min, ethanol (30 L) may be added to destroy any potential residual sodium hydride, and the system was then purged entirely of hydrogen. The reaction mixture was treated with water (289 L), and the THF was then removed by distillation at atmospheric pressure. After cooling to room temperature, the aqueous mixture was extracted with two portions of heptane (179 L each), and then the aqueous phase was discarded. The combined heptane phases were washed with 15% aqueous sodium chloride (350 L), and then the volume was reduced by one-half via distillation at atmospheric pressure. When a volume of 195 L was reached, the solution was cooled to allow the addition of ethanol (585 L). Azeotropic distillation was initiated, and the volume was reduced to 145 L; the concentration was adjusted by the addition of fresh ethanol (45 L) to give an ethanolic solution of the title compound that was used without further purification: concentration 119 mg/mL (dry weight), 85% yield.

3-[5-Chloro-1-(4-chlorophenyl)indan-1-yl]propan-1-ol (12a) in Acetonitrile. Approximately 400 L of an approximate 0.12 kg/L solution of **18** in ethanol (48 kg, 118 mol) and 37% hydrochloric acid (5.0 kg, 51 mol) was charged to an 800-L glass-lined vessel. This solution was stirred at room temperature for 24 h and then quenched by transfer to a vessel charged with anhydrous sodium carbonate (13.5 kg, 127 mol). Transfer was completed by a rinse of ethanol (15 L). Complete quench was ensured by pH check; pH 9 was recorded, and then the reaction mixture was concentrated (presence of sodium carbonate is critical, otherwise the reverse reaction is observed even in base-rinsed glassware) to 50% volume by distillation at atmospheric pressure. After cooling to <30 °C, acetonitrile (500 L) was added, and the volume was reduced to 125 L via azeotropic distillation. Acetonitrile (125 L) and heptane (199 L) were added, and the mixture was filtered through a pressure filter. Acetonitrile (15 L) was used to rinse the reactor and wash the filter cake. The phases were separated. The lower acetonitrile phase was removed, and the upper heptane phase was discarded. The acetonitrile phase was then washed with two portions of heptane (200 L each). The heptane phases were again discarded, and the acetonitrile phase of 255 L was concentrated by distillation to a volume of 175 L. In order to ensure a bp of 81 °C, acetonitrile (approximately 50 L) was added during the distillation. The solution of the racemic alcohol in acetonitrile was used without further purification: Purity 93 area%, assay 171 mg/mL (79% yield).

SMB Separation. The loading studies for compounds **12a**, **b** and **c** were run on columns of analytical dimensions (250 mm × 4.6 mm i.d.) packed with 20 μm preparative CSP. The flow rate for all experiments was 1 mL/min and a temperature of 30 °C was maintained. Sample concentrations were close to the maximum solubility in the given eluent. The results obtained for compound **12a** in three eluents, acetonitrile, methanol, and ethanol, on CHIRALCEL OD are reported in Table 3.

The SMB equipment used in production was a Licosep Laboratory unit with eight columns each 100 mm × 48 mm i.d. in size. The concentration of compound **12a** (total volume

Table 3. **Results from the loading studies with compound 12a**

acetonitrile				methanol				ethanol			
concn g/L	vol μL	Rt1 min	Rt2 min	concn g/L	vol μL	Rt1 min	Rt2 min	concn g/L	vol μL	Rt1 min	Rt2 min
94.50	10	4.85	6.19	45	50	4.32	5.36	127.47	10	3.76	5.36
94.50	25	4.85	6.00	45	100	4.29	5.17	127.47	25	3.76	5.09
94.50	50	4.85	5.79	45	150	4.29	5.04	127.47	50	3.76	4.80
94.50	70	4.83	5.65	45	200	4.27	4.93	127.47	100	3.73	4.48
94.50	80	4.83	5.60	–	–	–	–	127.47	150	3.71	4.24
94.50	100	4.83	5.52	–	–	–	–	–	–	–	–

360 L) was 171 g/L in acetonitrile. The simulation parameters were adjusted for the difference in feed concentration (92 g/L from the simulation compared to 171 g/L in production) and for the maximum pressure which could be reached in the system during the process, which was 30 bar instead of the 35 bar used in the simulation. The best experimental values of the operating parameters found for the process were: feed flow 4.50 mL/min and concentration 171 g/L, raffinate flow 33.36 mL/min and concentration 11.53 g/L, extract flow 99.24 mL/min and concentration 3.88 g/L, switch time 0.84 min., flow rate in zone I 355.97 mL/min, zone II 256.73 mL/min, zone III 261.23 mL/min, and zone IV 227.87 mL/min. The calculated productivity of the process at 30 bar is 692 g enantiomer/kg/day. A total of 27 kg **13** (yield 45%) was obtained with 99% ee. The raffinate was concentrated before use in the next step.

Methanesulfonic Acid 3-[(*S*)-5-Chloro-1-(4-chlorophenyl)indan-1-yl]propyl Ester (19) in Acetonitrile. Two solutions of **13** in acetonitrile were charged to a 300-L stainless steel reactor; 10.20 kg of a 34.0 wt % solution and 34.15 kg of a 21.4 wt % solution (10.8 kg, 33.6 mol). Toluene was added (160 kg). The solvent was changed to toluene via azeotropic distillation until a final distillate temperature of 112.6 °C was obtained. After cooling to room temperature, the volume was adjusted to 111 L with toluene, and then triethylamine (7.5 kg, 74 mol) was added. The resulting solution was cooled further to 12 °C, and a solution of methanesulfonyl chloride (6.5 kg, 57 mol) in toluene (28.0 kg) was added to the vessel at a rate to maintain a temperature <25 °C, followed by a rinse of toluene (5.0 kg). The reaction mixture was stirred at 20 °C for 30 min, where an in-process sample revealed <0.1% content of the starting material. The reaction mixture was quenched via the addition of a solution of sodium carbonate (7.2 kg) in water (70 L). Upon completion of the addition, the mixture was heated to 40–45 °C for 30 min, and the phases were then allowed to separate. The lower aqueous phase was removed, and the organic phase was concentrated by vacuum distillation, final volume 20 L. The residual oil was diluted with acetonitrile (167 L), and the residual toluene was removed by azeotropic distillation, final volume 25 L. Yield according to dry weight analysis: 12.4 kg (92%), purity: 93 area %.

(*S*)-2-{3-[(*S*)-5-Chloro-1-(4-chlorophenyl)indan-1-yl]propylamino}propionic Acid Methyl Ester (23) Oxalate. A mixture of L-alanine methyl ester hydrochloride (10.9 kg, 78.1 mol), potassium carbonate (21.8 kg, 158 mol), and acetonitrile (57 L) was stirred for 20 h at 22 °C and filtered. The filter cake was washed with acetonitrile, and the filtrates were combined; the volume was determined to 62 L. The concentration of alanine methyl ester in the combined filtrates was 87.9 g/L (GC-assay), giving a total of 5.45 kg (52.9 mol) in the solution. The solution of alanine methyl ester was added to the reactor containing the solution of **19** in acetonitrile above, and the mixture was heated to 65 °C for 22 h. Potassium carbonate (8.7 kg, 63 mol) and acetonitrile (17 L) were added, and stirring at 65 °C was continued for 45 h. The ratio of **19** to **23** was 1:9 (HPLC). The reaction mixture was cooled to room temperature and filtered, and the filter cake was washed with acetonitrile (40 L). The filtrates were combined; the volume was 105 L, and the concentration of **23** was 120.7 g/L (HPLC assay), giving a total 12.7 kg (31.3 mol) **23**. Oxalic acid dihydrate (4.2 kg, 47 mol) was added to a 200 L glass-lined reactor, and the solution of **23** in acetonitrile was added, followed by a rinse of water (13.9 kg). The mixture was stirred for 2 h at 15 °C and filtered. The filter cake was washed with acetonitrile (25 L) and ethyl acetate (50 L), and dried in a vacuum oven, giving 3.2 kg of **23** oxalate. A total of 10.5 kg of **23** oxalate was obtained, after harvesting two times more. The oxalate (10.5 kg) was stirred with water (107 L) for 1 h, filtered, and washed with water (21 L). This was repeated with the wet filter cake. After drying in a vacuum oven, 7.5 kg of the title compound was obtained (yield 49%). ^{1}H NMR δ (DMSO-d_6) 7.36–7.22 (m, 7H), 3.95 (q, J = 7.1 Hz, 1H), 3.72 (s, 3H), 2.95–2.87 (m, 1H), 2.86–2.76 (m, 3H), 2.42–2.36 (m, 1H), 2.25–2.18 (m, 1H), 2.18–2.10 (m, 1H), 1.97–1.90 (m, 1H), 1.47–1.38 (m, 2H), 1.37 (d, J = 7.1 Hz, 3H). ^{13}C NMR δ (DMSO-d_6) 171.0, 164.6, 147.4, 146.3, 145.7, 131.9, 131.1, 128.8, 128.6, 126.7, 126.4, 125.1, 54.9, 54.8, 53.1, 45.9, 39.7, 36.6, 30.3, 22.6, 15.3. Purity 94.3 area %, assay 93.7 w/w %. Weight loss on heating (TGA): 0.7%. DSC: onset 198 °C, peak 201 °C. Anal. Calcd for $C_{24}H_{27}Cl_2NO_6$: C, 58.07; H, 5.48; N, 2.82. Found: C, 58.38; H, 5.66; N, 2.71.

(*S*)-2-{3-[(*S*)-5-Chloro-1-(4-chlorophenyl)indan-1-yl]propylamino}propionic Acid (24). A 300-L glass-lined reactor was charged with **23** oxalate (7.5 kg, 15 mol), THF (70.0 kg), water (50.0 kg), and concentrated hydrochloric acid (25.0 kg). The mixture was heated to reflux for 22 h and cooled to 25 °C, less than 3% **23** remained in the mixture (HPLC). Sodium hydroxide (4 M, 60 L) was added in order to adjust pH to 6.4, and the mixture was stirred overnight. A small drop in pH to 5.2 was observed, and a small amount of sodium hydroxide was added to increase pH to 6.4. THF and methanol were removed by azoetropic distillation, final distillation temperature 100 °C and volume 130 L. Since pH had dropped to 1.5, THF (70 kg) was added again, and pH increased to 6.8 with sodium hydroxide (4 M, 6.3 L). THF was removed again by azeotropic distillation, final distillation temperature 100 °C. The mixture was cooled to 15 °C and stirred for 9 h, pH 6.2.

The product was isolated by filtration, washed with water (20 kg), and dried in a vacuum oven. Yield 7.3 kg (91%, when corrected for the w/w content). ^{1}H NMR δ (DMSO-d_6) 7.35–7.21 (m, 7H), 3.09 (q, J = 7.0 Hz, 1H), 2.93–2.85 (m, 1H), 2.84–2.73 (m, 2H), 2.72–2.65 (m, 1H), 2.42–2.35 (m, 1H), 2.23–2.09 (m, 2H), 1.95–1.87 (m, 1H), 1.46–1.35 (m 2H), 1.20 (d, J = 7.0 Hz, 3H). ^{13}C NMR δ (DMSO-d_6) 170.7, 147.5, 146.3, 145.6, 131.8, 131.0, 128.7, 128.5, 126.7, 126.4, 125.1, 57.6, 54.9, 46.1, 36.7, 30.3, 22.5, 16.2. Purity 89.8 area %, and assay 73.5 w/w %. Diastereomeric purity 99.4%. Weight loss on heating (TGA): 0.78%. Anal. Calcd for $C_{21}H_{23}Cl_2NO_2$: C, 64.29; H, 5.91; N, 3.57. Found: C, 58.77; H, 5.53; N, 3.10.

(*S*)-2-({3-[(*S*)-5-Chloro-1-(4-chlorophenyl)indan-1-yl]propyl}methylamino)propionic Acid (1). A 300-L glass-lined reactor was connected to a sodium hydroxide scrubber and charged with **24** (9.1 kg, 23 mol), formic acid (98%, 13.3 kg, 289 mol), and formaldehyde (37%, 12.8 kg, 158 mol). The mixture was heated to 90 °C—carefully, because vigorous foaming was expected—and at 60 °C the volume of the mixture was approximately 150 L. The mixture was stirred at approximately 90 °C for 2 h, and then cooled to room temperature; a process control showed less than 0.1% **24** (HPLC). The reaction mixture and sodium hydroxide (14%) were alternately added to water (111 kg) in small portions, keeping the pH at approximately 5. The addition of all the reaction mixture and 63 L of sodium hydroxide resulted in pH 6.2; pH was adjusted to pH 5.4 with concentrated hydrochloric acid (300 mL). The mixture was inoculated with **1**, heated to 40 °C, stirred at that temperature for two hours, and then cooled to 15 °C during 10 h. The raw product was isolated by filtration, washed with water (10 kg), and dried in a vacuum oven (40 °C). Yield 8.6 kg (91%). The raw product was recharged to the reactor, ethyl acetate (164 L) was added, and the mixture was heated to 60 °C, inoculated, stirred for 1 h at 60 °C, and then cooled to 15 °C during 10 h. The product was isolated by filtration, washed with ethyl acetate (30 L), and dried in a vacuum oven (50 °C). Yield 5.0 kg (54%). NMR was consistent with data given above. Purity 99.4 area %, assay 95.0 w/w % (both values are the sum of the values for all the diastereoisomers). Diastereomeric purity 95.3%. Water content (KF): <0.1%. Weight loss on heating (TGA): <0.3%. DSC: onset 155 °C, peak 159 °C. Anal. Calcd for $C_{22}H_{25}Cl_2NO_2$: C, 65.03; H, 6.20; N, 3.45. Found: C, 62.51; H, 6.04; N, 3.31.

Acknowledgment

We thank Peter Husted Madsen and Kenneth Rye Eiersted for invaluable discussions and their tireless efforts in Pilot Plant and Kilolab, Dr. Karl V. Vejrup and Henrik Nikolajsen for their analytical expertise, Dr. Garrick P. Smith for valuable discussion of the medicinal chemistry route, and Dr. Svend Treppendahl and Dr. Robert J. Dancer for helpful discussion on the chemistry.

Received for review November 12, 2007.

OP7002584