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Comparison of Large-Scale Routes to Manufacture Chiral *exo*-2-Norbornyl Thiourea

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Abstract:

Two routes aimed at the manufacture of chiral *exo*-2-norbornyl thiourea (1) on large scale are described. The first approach involves five chemical steps and hinges on a classical resolution via diastereomeric salt formation. The synthesis utilizes amine 2 as the resolution handle. The second approach includes two chemical steps and a chiral chromatography of (±)-1. Despite the larger initial investment necessary to acquire the chiral stationary phase used in the chromatographic approach, the shorter reaction sequence and efficiency of the chromatographic separation make the second route a more attractive option for long-term applications.

1. Introduction

The efficient preparation of chiral non-racemic building blocks continues to challenge synthetic chemists. Classical resolution of racemic mixtures has been a method of choice[1] to accomplish this goal. However, resolution by large-scale chiral chromatography has developed into an attractive alternative.[2] While resolution by diastereomeric salt formation has the benefit of implementation in simple reactors and equipment, large-scale chromatography can be scaled from a multi-kilogram to a multi-ton process. The criteria for deciding which approach is most attractive for large-scale applications lie in the overall synthetic strategy.

Thiourea **1** is a starting material[3] employed in the synthesis of AMG 221, an inhibitor of 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) discovered at Amgen (Scheme 1).[4] Inhibitors of 11β-HSD1 are potential therapeutic agents for the treatment of type 2 diabetes.[5] The preparation of **1** in racemic form has been reported.[6] However, the development of a route that could be utilized to prepare **1** in optically enriched form was desired. This contribution describes two strategies for the preparation of **1** with high optical purity. The first employs resolution by diastereomeric salt formation (classical resolution). The second achieves resolution by chiral chromatography. A comparison of these two methods reveals that the chromatographic approach is most effective due to the high efficiency of the separation, the relative ease of access to the racemate, and the fewer unit operations required. This report describes development activities around these two approaches and presents an evaluation of the two routes in terms of overall efficiency.

Retrosynthetic analyses of both approaches to **1** are shown in Scheme 1. In order to access a moiety which can form a chiral salt, the thiourea was envisioned as arising from *S*-(*exo*)-2-aminonorbornane (**2**). Conversion of the amino group of **2** can be achieved via a two-step process involving reaction with benzoyl isothiocyanate followed by hydrolysis of the benzoate moiety. Norbornyl amine **2** can be accessed from norbornene (**3**) via a Ritter reaction with CH_3CN, followed by hydrolysis of the resultant acetamide.[7]

During our development of a chiral assay for **1**, conditions developed on analytical scale suggested that preparative chiral chromatography may be a viable method for resolution of (±)-**1**. This raised the possibility of an alternative approach that would involve forming the thiourea directly via a Ritter reaction with isothiocyanate,[8] followed by ammonia addition and chromatographic separation of the enantiomeric mixture. While the chromatographic approach would require more specialized equipment to effect the resolution than a traditional crystallization, the relative ease of access to the racemic thiourea made it worth considering. A description of the strengths and drawbacks of these two approaches follows.

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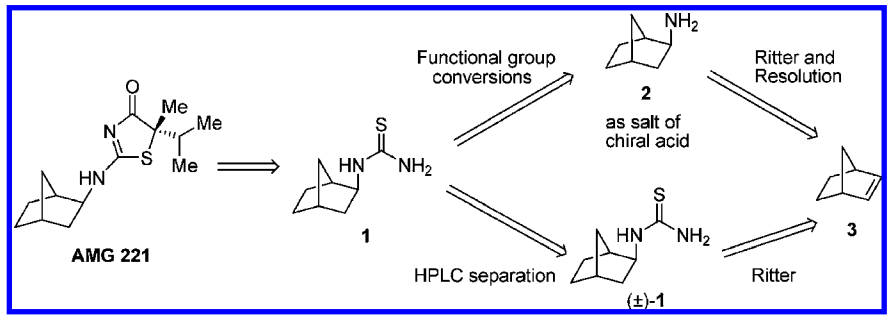
Scheme 1. **Approaches toward chiral norbornyl thiourea (1)**



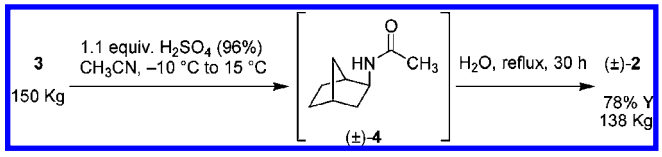
2. Results and Discussion

2.1. Classical Resolution Approach. *2.1.1. Synthesis of Amine 2 from Norbornene.* The amine racemate (±)-**2** was prepared in a two-step sequence via a Ritter reaction using CH_3CN and H_2SO_4 followed by hydrolysis of the resultant acetamide intermediate [(±)-**4**] (Scheme 2). The original literature procedure to conduct this transformation involved treatment of a relatively dilute (45 mL of CH_3CN per g of **3**) solution of norbornene with 4 equivalents of H_2SO_4.[7] Optimization of the experimental conditions revealed that the Ritter reaction could be carried out using a more concentrated CH_3CN solution (5 mL of CH_3CN per g of **3**) and 1.1 equivalents of H_2SO_4. In order to control the strong exotherm generated, H_2SO_4 was added over 2 h (scale of 0.5 kg of **3**) while maintaining the temperature between −10 and 15 °C. Following the addition, the mixture was warmed to 23 °C and stirred for an additional 2 h, resulting in complete consumption of **3**.

The acetamide group of (±)-**4** could be hydrolyzed directly without isolation. First, the excess CH_3CN was removed by distillation, water was added, and the dark mixture was refluxed. An extended age time at reflux (30 h) was found to be necessary to achieve complete hydrolysis of (±)-**4**. Following treatment with 10 M aqueous NaOH and extraction with MTBE, the crude residue was vacuum distilled to generate (±)-**2**. This procedure was demonstrated using 150 kg of **3**, affording (±)-**2** in 78% overall yield.

2.1.2. Classical Resolution of Amine ***2.*** A screen of 18 commercially available resolving agents was performed, and (*R*)-(+)-*N*-(1-phenylethyl)phthalamic acid (**5**) was identified as the most competent chiral acid for the classical resolution of (±)-**2**. The corresponding salts **6** (desired diastereomeric salt) and **7** (undesired diastereomeric salt, amorphous glassy solid with no defined melt) were prepared separately in >99.5/0.5 DR and their respective solubilities were measured in various solvents (Table 1). The differences in solubility between **6** and **7** in a number of solvents were large enough to expect that the resolution of (±)-**2** could be achieved via a single crystallization to generate salt **6** of high DR (>98/2) and >40% yield. Despite these solubility differences, resolution experiments carried out in these solvents did not yield salt **6** of >75/25 DR. These findings were attributed to the incorporation of **7** into the crystal lattice of salt **6** as a solid solution. X-ray powder diffraction (XRPD) spectra of salt **6** of various purity levels (>99.5/0.5 DR, 97.5/2.5 DR, and 90/10 DR) were measured and showed no noticeable differences. This single set of signals displayed in the XRPD spectra of salt **6** of various diastereomeric ratios suggests that the minor isomer (**7**) in this mixture is not present as a different polymorph and consequently supports the crystallization of the mixture as a solid solution.[9]

Scheme 2. **Synthesis of amine (±)-2 from 3 via a Ritter reaction**



It was determined experimentally that the use of mixtures of protic solvents (EtOH, IPA) and CH_3CN was superior to CH_3CN alone at achieving the desired resolution. Experimental conditions were surveyed to effect the resolution of (±)-**2** with **5** using mixtures of EtOH and CH_3CN (Table 2). Comparison of entries 1 and 2 with entry 3 (Table 2) reveals that the use of 0.5 or 0.75 equivalent of **5** in the resolution relative to the use of 1 equivalent of **5** did not offer an advantage with regard to the DR of resultant salt **6**. However, the yields of **6** were lower in the former instances than in the latter instance. All subsequent screening was thus conducted with 1 equivalent of **5**. Mixtures of CH_3CN and EtOH of various proportions were surveyed to carry out the resolution (entries 3−6). A 6/1 mixture of CH_3CN and EtOH was found to afford the maximum yield of salt **6** (43%, entry 5) without negatively affecting the DR (90/10). By comparison, the use of a 7/1 mixture of the two solvents (entry 6) afforded salt **6** of a lower DR (86/14). The conditions reported in entry 5 were selected to be applied on larger scale.

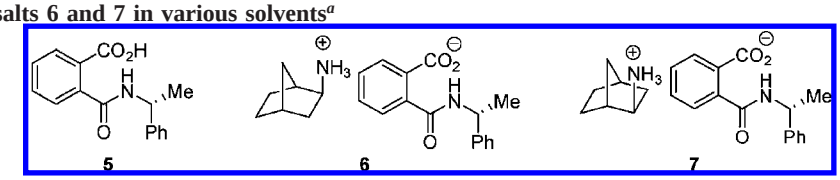
An overview of the resolution process to provide salt **6** of >99.5/0.5 DR is presented in Scheme 3. First, the resolution of (±)-**2** using **5** was conducted (Scheme 3). For this purpose, a solution of (±)-**2** in CH_3CN was added to **5** in EtOH at 60 °C, the mixture was seeded with **6** (>99.5/0.5 DR, 1.5 wt %), cooled to 50 °C, and aged for 12 h.[10] The slurry was cooled to 23 °C over 12 h. The total volume of solvents used was 24 L per kg of (±)-**2**. The yields ranged from 38% to 44%, and the diastereomeric ratios spanned from 88/12 to 91/9 for the resolution from (±)-**2**.

In order to obtain material of >99.5/0.5 DR, two recrystallizations of the initially generated salt (88/12 to 91/9 DR) were necessary (Scheme 3). The procedure for these recrystallizations involved dissolving **6** in EtOH at 60 °C, charging both CH_3CN (60 °C) and the seeds of **6** (>99.5/0.5 DR, 1.5 wt %), and cooling to 50 °C. The remainder of the procedure for the

(9) Kozma, D.; Tomor, K.; Novak, C.; Pokol, G.; Fogassy, E. *J. Therm. Anal.* **1996**, *46*, 1613–1623.

(10) The 12 h cycling time improved the DR of resultant salt **6** for the resolution and the subsequent recrystallizations.

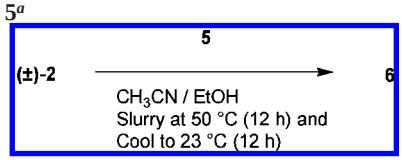
Table 1. **Solubility of salts 6 and 7 in various solvents**[a]



entry	solvent	solubility of **6** (mg/mL)	solubility of **7** (mg/mL)
1	IPA	24.7	>100
2	1-propanol	68.5	>100
3	CH_3CN	1.0	>100
4	IPAC	1.1	>100
5	THF	8.7	>100
6	1,2-DME	11.3	>100

[a] Solubilities measured at 23 °C.

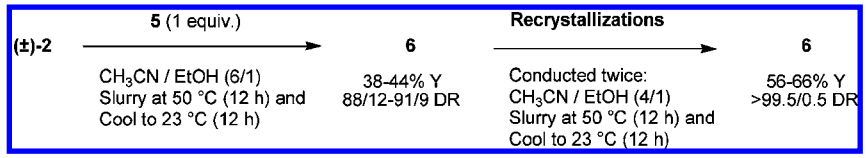
Table 2. **Resolution screen using chiral acid 5**[a]



entry	equivalents of **5**	CH_3CN/EtOH	total volume of solvents	**6** (%)	DR
1	0.5	4/1	25	21	90/10
2	0.75	4/1	25	27	92/8
3	1	4/1	25	36	90/10
4	1	5/1	24	40	91/9
5	1	6/1	24	43	90/10
6	1	7/1	24	46	86/14

[a] Reaction conditions: Total volume of solvents are reported in mL per g of (±)-**2** utilized. Isolated yields are reported. Scale of experiments span from 0.3 to 4 g of (±)-**2**.

Scheme 3. **Resolution and recrystallizations to provide salt 6 of >99.5/0.5 DR**



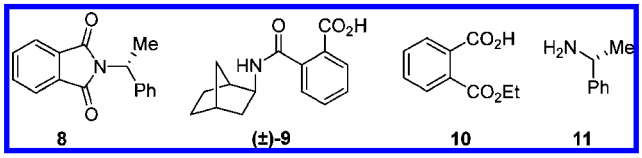
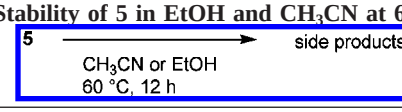


Figure 1. **Impurities generated in the resolution of (±)-2 with 5.**

Table 3. **Stability of 5 in EtOH and CH_3CN at 60 °C**[a]



entry	solvent	volume of solvent	**8** (%)	**10** (%)	**11** (%)
1	EtOH	1.4	7	37	40
2	CH_3CN	8.4	7	0	0

[a] Reaction conditions: Volumes of solvents are reported in mL per g of **5** utilized. Scale of experiments is 3 g of **5**. Percentages of side products are measured by ^{1}H NMR integration relative to **5**.

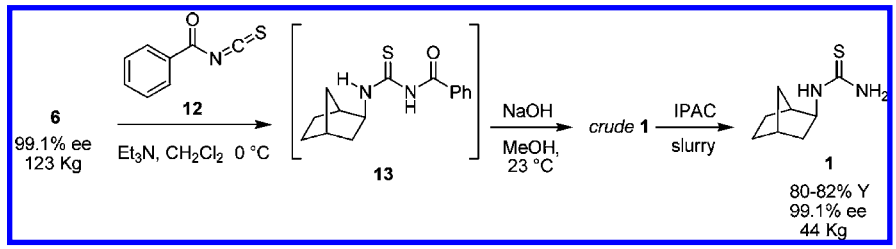
recrystallizations was identical to that used for the resolution process. The total volume of solvents employed was 12.5 L per kg of **6** in the first recrystallization and 10 L per kg of **6** in the second. The yields varied from 56% to 66% using salt **6** of 88/12 to 91/9 DR as starting material.

Four major impurities were formed in the resolution of (±)-**2** with **5** (Figure 1) and isolated from the reaction mixture. The identity of these compounds was determined by ^{1}H NMR comparison with independently synthesized[11] **8** and (±)-**9** and commercially available **10** and **11**. The level of these impurities relative to the total amount of both diastereomeric salts in a resolution experiment performed to afford 100 g of salt **6** (38% yield, 90.3/9.7 DR) was 5.5% of **8**, 2.1% of (±)-**9**, 13.0% of **10**, and 14.5% of **11**.

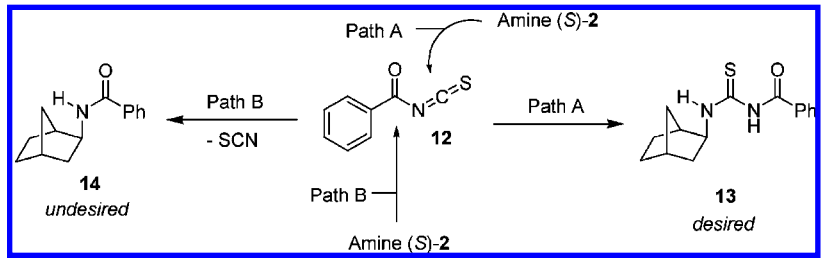
Impurities **8**, **10**, and **11** were potentially generated in significant amounts before addition of the CH_3CN solution of (±)-**2** to the EtOH solution of **5** at 60 °C. The preparation of this charging step involved warming a solution of **5** in EtOH to 60 °C. This took up to 1 h, and consequently the stability of **5** under these conditions had to be thoroughly understood. The stability of **5** in EtOH and CH_3CN at 60 °C was studied separately (Table 3). Stirring of **5** in EtOH for 12 h at 60 °C (entry 1) generated 37% of **10** and 40% of **11** relative to **5**,

(11) Compound (±)-**9** was prepared according to a reported procedure: Eddine, A. C.; Daich, A.; Jilale, A.; Decroix, B. *Heterocycles* **1999**, *51*, 2907–2915.

Scheme 4. **Synthesis of thiourea 1 from salt 6**



Scheme 5. **Proposed mechanism for formation of byproduct 14**



whereas the same experiment conducted in CH_3CN (entry 2) produced no **10** or **11**. Considering that **10** and **11** were the two principal impurities formed in the resolution experiment, the result may be improved by warming **5** in CH_3CN and (±)-**2** in EtOH instead of the opposite. This was first verified on small scale and subsequently demonstrated using 238 kg of (±)-**2** to afford 345 kg of **6** (42% yield, 90.1/9.9 DR). The levels of impurities relative to the total amount of both diastereomeric salts in this plant operation were 3.2% of **8**, 3.1% of (±)-**9**, 0.0% of **10**, and 3.7% of **11**. This protocol, providing a better isolated yield of **6** (42% vs 38%) and impurity profile relative to earlier results, represents our optimized procedure to carry out the resolution of (±)-**2**.

*2.1.3. Synthesis of Thiourea **1** from Salt **6**.* The synthesis of chiral building block **1** was completed by conversion of salt **6** into thiourea **1**. A two-step procedure was chosen whereby acylthiourea intermediate **13** was obtained from **6** by treatment with benzoyl isothiocyanate (**12**)[6] and subsequently solvolyzed to yield **1** (Scheme 4). To eliminate the need for a separate salt break step, chiral **6** was employed directly in this process. Suspension of **6** in CH_2Cl_2 was followed by addition of Et_3N and **12** to afford intermediate **13** in >95% purity. The main side product of the reaction was benzamide **14**, presumably arising from competitive attack of amine (*S*)-**2** at the carbonyl group rather than the isothiocyanate carbon of **12** (Scheme 5).[12] Benzamide **14** is not easily rejected in the subsequent processing steps. Consequently, its formation had to be minimized and controlled at this step. At ambient temperature the levels of **14** were of approximately 10%. Maintaining the reaction temperature below 0 °C minimized the formation of this impurity to less than 2%. A simple basic work up performed after the formation of **13** allowed the removal of chiral acid **5** and the crude process streams could be telescoped into the solvolysis by solvent exchange from CH_2Cl_2 to MeOH. Treatment of **13** with aqueous NaOH in MeOH afforded thiourea **1**, methyl benzoate and benzoic acid (presumably as sodium benzoate). Crude **1** precipitated from the reaction mixture and additional water was charged in order to minimize losses to the liquors (typically 2−3%). Benzamide **14** (0.5−1%) and methyl benzoate (8−10%) were the principal contaminates from the MeOH/water isolation. A suspension and slurry of crude **1** in IPAC effectively rejected these impurities with minimal losses of **1** (<5%). This protocol was demonstrated using 123 kg of **6** to afford 44 kg of **1** (82 wt % adjusted yield, 99.1% ee, Scheme 4).

2.2. Chromatographic Approach. *2.2.1. Preparation of (±)-**1**.* In order to facilitate the chromatographic separation of the enantiomers on production scale, a simple and efficient means to prepare (±)-**1** was required. The development of an inexpensive process to prepare the racemate would alleviate the need to obtain a near quantitative yield of resolved material and thus reduce the cost of the chromatographic resolution. Additionally, (±)-**1** had to be prepared in sufficiently high purity to prevent contamination of the chiral stationary phase.

The existing route to prepare (±)-**1** involved inexpensive starting material and reagents.[8] In the first step, norbornene was reacted with KNCS in the presence of H_2SO_4. Following aqueous work up, isothiocyanate intermediate **15** (Scheme 6) was purified and reacted with ammonia to afford crystalline **1**. Our goal was to improve the synthesis of (±)-**1** using a minimum number of unit operations and a simple purification of the racemate.

The existing procedure was developed into an efficient process with a few modifications. The isothiocyanate intermediate (**15**, Scheme 6) was formed by reaction of norbornene with NH_4NCS (in the presence of H_2SO_4) in a toluene/water mixture at 40 °C. Use of NH_4NCS instead of KNCS allowed for complete removal of the inorganic

(12) (a) Becher, J.; Frandsen, E. J. *Tetrahedron* **1977**, *33* (3), 341–343. (b) Zhang, Y.; Wei, T.; Lu, J. *Synth. Commun.* **1998**, *28* (17), 3243–3248.

Scheme 6. **Synthesis of (±)-1**

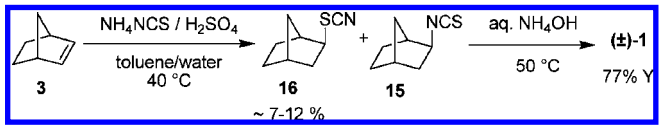


Table 4. **Solubility of (±)-1 in different solvents**[a]

entry	solvent	solubility of racemic **1** (mg/mL)
1	water	<1
2	MeOH	35
3	EtOH	21
4	IPA	12
5	CH_3CN	10
6	THF	38
7	EtOAc	5
8	CH_2Cl_2	3
9	Heptane	<1

[a] Measurements at 23 °C.

salts during the work up. Potassium salts were determined to be major impurities in the final product when KNCS was utilized in the process. Assay yields of 85% were obtained for the toluene solution and the major impurity present was thiocyanate **16**, as judged by ^{1}H NMR. This impurity reacted further in the subsequent step and the species thus generated was rejected in the final isolation. Isothiocyanate (±)-**15** was easily converted to (±)-**1** by treatment of the toluene solution with aqueous NH_4OH at 50 °C for 20 h. The process afforded (±)-**1** in 77% isolated yield over two steps.

2.2.2. Chiral Stationary Phase Screening and Physiochemical Data. Two parameters had to be settled upon in order to develop a scalable process for the chromatographic resolution of (±)-**1**. First, a solvent system in which the racemate had high solubility had to be identified. Second, a chiral stationary phase effecting an efficient enantiomeric separation (selectivity, α) of the mixture with a retention factor (k')[13] of between 2 and 5 had to be identified. Solubility studies using the racemate revealed that high (>20 mg/mL) solubility could be achieved in three common process solvents: MeOH, EtOH, and THF (Table 4).

A complete screen of chiral stationary phases (CSP) and solvent systems was carried out. During this study, a total of 78 CSPs and 330 chromatographic methods were evaluated. Of these, two method-stationary phase combinations showed promise: (1) Chiral Technologies T101, MeOH mobile phase and (2) Chiral Technologies CSP-2, MeOH mobile phase. The analytical separation using both conditions is shown in Figure 2. In order to select the optimal CSP for further optimization, loading studies were performed with the use of an analytical column (4.6 mm × 250 mm). These studies showed that while the separation was larger for CSP-2, T-101 exhibited superior loading capacity, resulting in an approximately 2-fold

(13) k' is defined as $k' = (r_t - t_0)/t_0$, where r_t is the retention time of *S*-**1** (time from injection to the peak maximum) and t_0 is the dead time of the column.

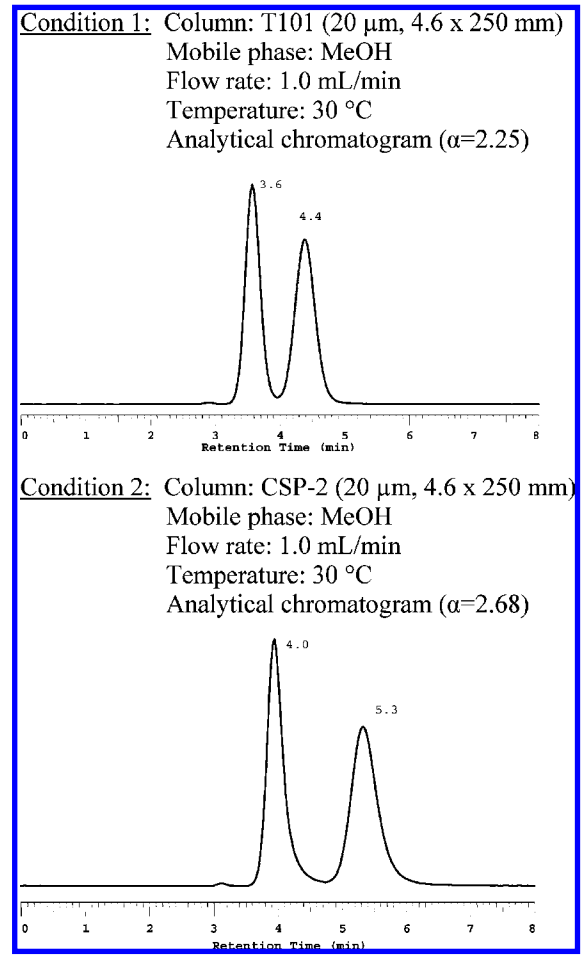


Figure 2. **Analytical separation of (±)-1.**

increase in productivity[14] (Figure 3). Further development of the method focused on the T101 CSP.

Additional screening of the resolution using T-101 CSP with alternative mobile phases on analytical scale revealed that the separation could be further optimized (Table 5). These experiments showed that the addition of 40% CH_3CN to the mobile phase increased selectivity[15] from 2.57 to 3.51 (entry 1 vs entry 6). Despite this increase in selectivity, an overall decrease in productivity was expected in such a case due to the reduced solubility of the racemate in CH_3CN/MeOH mixtures. This diminished solubility coupled with the increased complexity of recycling a binary solvent mixture led to the choice of pure MeOH as solvent system for the separation.

In order to model the separation, adsorption isotherm parameters were determined via a series of analytical and overloaded injections.[16] The adsorption isotherm shape used to fit the experimental data was based on a modified competitive Langmuir model. The parameters[17] for the adsorption isotherms are:

(14) The productivity is defined as the amount of desired enantiomer recovered from the column/amount of chiral stationary phase in the column/time from beginning of first peak to end of second peak. The units are normalized to kg of enantiomer/kg of CSP/24 h.
(15) Selectivity is defined as the ratio between the k' constant of the second peak and the k' constant of the first peak (k' second peak/k' first peak).
(16) Nicoud, R. M.; Seidel-Morgenstern, A. *Isol. Purif.* **1996**, *2*, 165.
(17) C_i is the concentration of the species in the liquid phase and $\bar{C}_i$ is the concentration of the species in the solid phase.

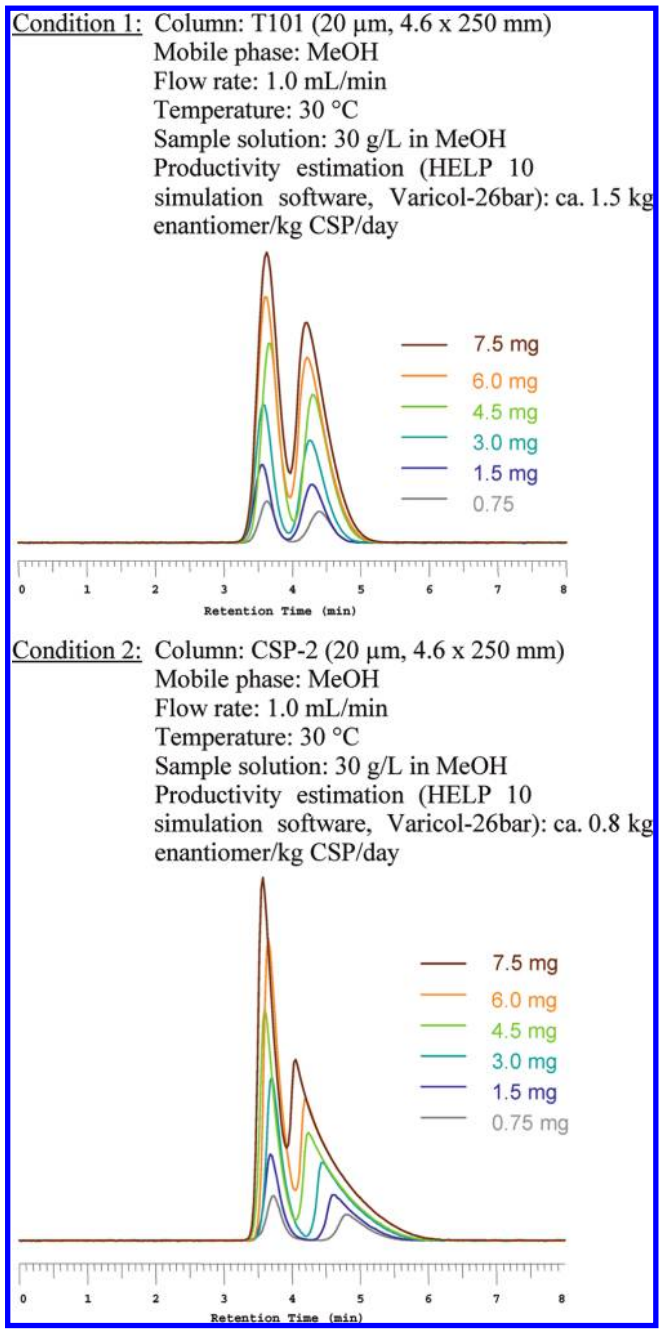


Figure 3. **Loading studies and estimation of productivity.**

$$\bar{c}_i = \lambda_i c_i + \frac{\bar{N}\tilde{K}_i c_i}{1+\sum_j \tilde{K}_j c_j}$$

	Lambda	Nbar*Ktilde	Nbarre
Component 1	0.39	0.40	30.61
Component 2	0.39	0.77	30.61

The pressure drop was measured in order to determine the Darcy law coefficient: $\Delta P/L$ (bar/cm) = 0.98 u (cm/s). The column efficiency was calculated by measuring the height equivalent to theoretical plate (HETP) at two flow rates. The following Van Deemter equation was obtained: HETP (cm) = 4.9dp (cm) + 0.41u (cm/sec). Using these parameters, modeling of the system was undertaken to establish the critical factors necessary to determine productivity on large scale.

2.2.3. Development of SMB/Varicol Process. The efficiency of a potential large-scale chromatographic resolution was evaluated using the HELP[18]-*CHROM* modeling software with the physiochemical data described for both a simulated moving bed (SMB) and a Varicol[19] process. For this study the SMB and Varicol processes were optimized for 99% purity and yield. Identical robustness margins were applied for the two options. Comparisons of some of the critical parameters for both processes are summarized in Table 6. The Varicol process resulted in a 15% increase in specific productivity as well as a reduction in eluent composition relative to a standard SMB process.

Table 5. **Optimization of eluent composition**

entry	solvent mixtures (v/v)	R_{t1} (min)	R_{t2} (min)	selectivity (α)
1	MeOH	3.63	4.61	2.57
2	MeOH/EtOH (4/1)	3.69	4.68	2.43
3	MeOH/1-propanol (4/1)	3.45	3.79	1.86
4	MeOH/IPA (4/1)	3.56	4.25	2.21
5	MeOH/CH_3CN (4/1)	3.36	4.14	3.17
6	MeOH/CH_3CN (3/2)	3.28	3.98	3.51
7	MeOH/CH_3CN (2/3)	3.37	4.08	3.00
8	MeOH/H_2O (4/1)	5.24	7.33	1.93

Table 6. **Comparison of SMB and Varicol processes**

parameter	SMB	varicol
column diameter (cm)	1	1
column length (cm)	13.8	15
number of columns	6	5
racemate concentration (g/L)	35	35
feed flow rate (mL/min)	1.32	1.60
daily production (g enantiomer/day)	33.25	35.5
specific productivity (g enantiomer/g CSP/day)	3.37	4.08
eluent composition (mL/g enantiomer)	5.24	7.33

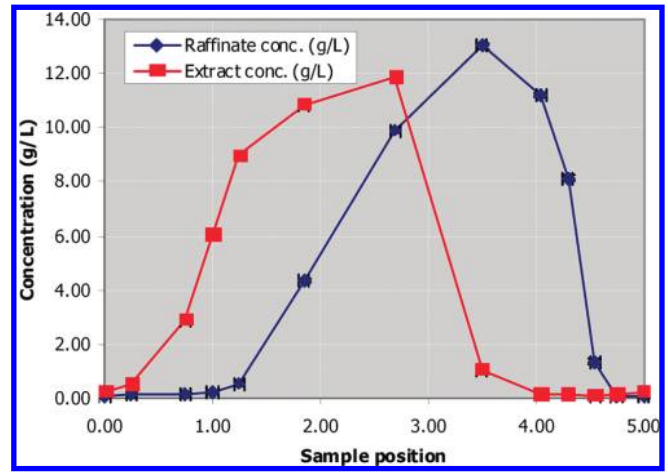


Figure 4. **Internal concentration profile.**

(18) HELP is a proprietary chromatographic modeling software developed by Novasep.
(19) Varicol is an advanced, multicolumn chromatographic process developed and patented by Novasep.

Table 7. **Operating conditions at manufacturing scale[a]**

entry	year production (metric ton of **1**/year))	column diameter (cm)	daily production (kg enantiomer/day)
1	5	20	15
2	10	30	35
3	20	45	78

[a] Column length: 15 cm. Number of columns: 5. Working days/year: 250−300. Eluent composition: 370 mL/g enantiomer.

A proof of concept study was performed utilizing 10 g of (±)-**1**. For this study specifications of >98% optical purity and >95% yield were set. Using 10 mm × 150 mm columns, 118 cycles were performed on a five-column μVaricol system.[20] The desired enantiomer (raffinate, *S*-**1**) was collected at 99% optical purity and 95% yield. The specific productivity was 0.90 kg of enantiomer/kg of CSP/day, consistent with values obtained in the modeling exercise (*vide supra*, Table 6). The internal concentration profile under these conditions is shown in Figure 4. The proof of concept study showed the Varicol process to be robust, meeting the purity and yield specifications.

The proof of concept study coupled with the modeling exercise allowed for the operating conditions at the proposed manufacturing scale to be determined. As can be seen in Table 7, large quantities of the optically pure material could easily be accessed using the Varicol process. Despite the large amount of eluent needed for the resolution, recycling of MeOH is straightforward. This allows the overall process to be practical from an operational and cost perspective.

3. Conclusion

The results obtained for these resolution routes allow for the two techniques to be compared in terms of efficiency of the resolution as well as overall synthetic approach. While both routes can deliver resolved **1** of high optical purity, they differ substantially with regards to the methods utilized. In the classical resolution approach (14.5% overall yield), **1** was prepared in five chemical steps from norbornene (**3**) via amine **2**, an intermediate that incorporates the necessary resolution handle. The resolution step required two recrystallizations of the phthalamic acid salt (**6**) initially generated in order to afford material of sufficiently high DR. This is most probably due to diastereomeric salts **6** and **7** crystallizing as a solid solution, since the thermodynamic solubility of the individual salts suggested the development of a considerably more efficient resolution to be possible. These two recrystallizations required a large number of unit operations and resulted in the isolation of salt **6** of >99.5/0.5 DR in relatively low overall yield (23%).

In contrast, in the chromatographic process (36.5% overall yield) (±)-**1** was prepared from **3** in two chemical steps and resolved with a high level of efficiency. The chiral stationary phase "resolving agent" is recyclable and has years of lifetime under the resolution conditions. Despite the large amount of solvent required to carry out the chromatographic resolution, recycling of the solvent on production scale would be highly efficient and straightforward due to the use of MeOH as a single solvent. These factors make the chromatographic approach a more attractive option for large-scale manufacture of **1**.

(20) The total pressure drop generated had an average value of 27 bar.

4. Experimental Section

GC and HPLC Methods. GC method for (±)-2: Agilent HP-5 (30 m × 0.32 mm × 0.25 μm), 1 μL injection, 1.5 mL/min, initial temperature 35 °C, temperature ramp 10 °C/min to 100 °C, FID detector, (±)-**2** at 11.73 min, **3** at 7.78 min. **Chiral GC method for 6** (analyzed as trifluoroacetamide derivative): Sample preparation is as follows. A sample of **6** (10 mg) was suspended in CH_2Cl_2 (1 mg/mL) and treated with aqueous 5 M NaOH (5 mL). The biphasic mixture was shaken and the layers were separated. The CH_2Cl_2 layer was treated with 50 μL of trifluoroacetic anhydride, the resultant solution was shaken and used for injection. Astec Beta TA (30 m × 0.25 mm × 0.25 μm), 1 μL injection, 4.0 mL/min, constant temperature 95 °C, FID detector, derivative of *R*-**2** at 12.1 min, derivative of *S*-**2** at 13.3 min. **HPLC method for (*S*)-1 or (±)-1**: XBridge C18 (100 mm × 3.0 mm × 3.5 μm), 3.0 μL injection, 0.7 mL/min, 30 °C, A: 0.1% $HClO_4$ in H_2O, B: CH_3CN, $t = 0$ min: 15% B, $t = 5$ min: 60% B, $t = 12$ min: 60% B, *S*-**1** or (±)-**1** at 4.12 min, (±)-**15** at 9.66 min. **Chiral HPLC method for (*S*)-1**: Chiralcel AD-H (250 mm × 4.6 mm × 5 μm), 10 μL injection, 1.0 mL/min, 25 °C, 90% hexane/10% EtOH, isocratic; *S*-**1** at 9.92 min, *R*-**1** at 12.45 min.

Amine (±)-2. A mechanically stirred solution of **3** (150 kg, 1596 mol) in CH_3CN (588 kg, 750 L) was kept under N_2 and cooled to −15 °C. H_2SO_4 (96% purity, 179 kg, 1755 mol, 1.1 equiv) was added over 2.5 h (batch temperature −5 to 15 °C). The solution was warmed to 23 °C and stirred for 1.5 h. The reaction mixture was concentrated under reduced pressure (20 mmHg) to remove the solvent. Water (265 L) was added and the resultant solution was refluxed for 30 h. The reaction mixture was cooled to 23 °C. Aqueous 10 M NaOH (665 kg, 500 L) was added (temperature ≤40 °C and pH of resultant mixture ∼13). The aqueous mixture was extracted with MTBE (1 × 270 kg and 2 × 135 kg). The organic phases were combined and washed with brine (50 kg). The organic phases were concentrated under reduced pressure to remove MTBE (500 mmHg, 50 °C). The residual material was fractionally distilled under reduced pressure (80 mmHg, boiling point 87−91 °C) to yield (±)-**2** as an oil (138 kg, 78%, 1245 mol, 98.9 wt %, 99.2 GCAP). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.73 (dd, J = 3.2, 7.6 Hz, 1H), 2.14 (br s, 1H), 1.84−1.88 (m, 1H), 1.56 (ddd, J = 4.0, 7.6, 12.8 Hz, 1H), 1.30−1.44 (m, 3H), 0.93−1.25 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 54.5, 44.9, 41.8, 35.5, 33.8, 27.8, 26.3; IR (neat): 3360, 2930, 2868, 1606, 1452, 1354, 1309, 1095, 943, 806 cm^{-1}; Exact Mass $[C_7H_{13}N + 1]^+$: calculated = 112.1121, measured = 112.1117.

Phthalamic Salt 6. (*R*)-(+)-*N*-(1-Phenylethyl)phthalamic acid (**5**) (578 kg, 2149 mol) was dissolved in CH_3CN (3827 kg, 4907 L) at 60 °C. Amine (±)-**2** (238 kg, 2144 mol) was dissolved in EtOH (645 kg, 816 L) at 60 °C and the resultant solution was added to the CH_3CN solution of **5** (60 °C) over 10 min. The mixture was seeded with **6** (12 kg, 99.7/0.3 DR) and cooled to 50 °C over

0.5 h. The heterogeneous mixture was stirred at 50 °C for 12 h and the following cooling ramp to 23 °C was applied: 50 to 40 °C (3 h), 40 °C (3 h), 40 to 30 °C (1.5 h), 30 °C (1.5 h), 30 to 23 °C (1.5 h), 23 °C (2 h). The mixture was filtered and the solid was rinsed with CH_3CN (400 kg, 513 L). Salt **6** was vacuum-dried at 30 °C for 12 h (345 kg, 41.7%, 908 mol, 100 LCAP, 90.1/9.9 DR). Salt **6** (345 kg, 908 mol, 90.1/9.8 DR) was dissolved in EtOH (688 kg, 871 L) at 60 °C. CH_3CN (2679 kg, 3434 L, 60 °C) was added over 0.3 h and the solution was seeded with **6** (5.1 kg, 99.7/0.3 DR). The mixture was cooled to 50 °C over 0.5 h. The heterogeneous mixture was stirred at 50 °C for 12 h and the following cooling ramp to 23 °C was applied: 50 to 40 °C (3 h), 40 °C (3 h), 40 to 30 °C (1 h), 30 °C (1 h), 30 to 23 °C (1 h), 23 °C (2 h). The mixture was filtered, and the solid was rinsed with CH_3CN (343 kg, 440 L). Salt **6** was vacuum-dried at 30 °C for 12 h (239 kg, 28.4%, 629 mol, 100 LCAP, 98.8/1.2 DR). Salt **6** (239 kg, 629 mol, 98.8/1.2 DR) was dissolved in EtOH (377 kg, 477 L) at 60 °C. CH_3CN (1486 kg, 1906 L, 60 °C) was added over 0.3 h and the solution was seeded with **6** (3.5 kg, 99.7/0.3 DR). The mixture was cooled to 50 °C over 0.5 h. The heterogeneous mixture was stirred at 50 °C for 12 h, and the following cooling ramp to 23 °C was applied: 50 to 40 °C (3 h), 40 °C (3 h), 40 to 30 °C (1 h), 30 °C (1 h), 30 to 23 °C (1 h), 23 °C (2 h). The mixture was filtered and the solid was rinsed with CH_3CN (178 kg, 230 L). Salt **6** was vacuum-dried at 30 °C for 12 h (198 kg, 23.2%, 521 mol, 100 LCAP, 99.8/0.2 DR). Mp 159−161 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 7.51−7.64 (m, 2H), 7.28−7.48 (m, 6H), 7.20−7.27 (m, 1H), 5.17 (q, J = 8.0 Hz, 1H), 3.00 (dd, J = 4.0, 8.0 Hz, 1H), 2.25−2.33 (m, 2H), 1.65−1.74 (m, 1H), 1.45−1.63 (m, 6H), 1.33−1.43 (m, 1H), 1.07−1.27 (m, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 176.6, 171.2, 145.5, 141.0, 135.3, 135.3, 131.1, 129.6, 129.4, 129.2, 128.0, 127.2, 54.9, 50.9, 41.9, 38.2, 37.4, 35.5, 28.7, 27.7, 23.0; IR (neat): 3277, 2967, 2937, 2627, 1638, 1544, 1510, 1380, 1329, 702 cm^{-1}. A single-crystal X-ray analysis of **6** was obtained, and the CIF for this analysis is included in the Supporting Information. Diastereomer **7** was synthesized from *R*-**2** and **5**. It is an amorphous glassy solid (no defined melt, XRPD available in Supporting Information). ^{1}H NMR (400 MHz, CD_3OD) δ 7.54−7.64 (m, 2H), 7.30−7.47 (m, 6H), 7.20−7.26 (m, 1H), 5.17 (q, J = 8.0 Hz, 1H), 3.03 (dd, J = 4.0, 8.0 Hz, 1H), 2.27−2.35 (m, 2H), 1.67−1.71 (m, 1H), 1.47−1.64 (m, 6H), 1.36−1.44 (m, 1H), 1.10−1.28 (m, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 176.8, 171.3, 145.6, 141.0, 135.6, 135.3, 131.1, 129.6, 129.4, 129.3, 128.0, 127.3, 55.0, 51.0, 42.0, 38.3, 37.5, 35.5, 28.7, 27.7, 23.0; IR (neat): 2958, 2873, 1630, 1545, 1448, 1371, 698 cm^{-1}.

Amide (±)-9. To a solution of phthalic anhydride (10 g, 0.067 mol) in IPA (40 mL) was added (±)-**2** (7.4 g, 0.067 mol) via syringe over 5 min. The mixture was stirred for 3 h and water was added (120 mL). The mixture was stirred for 2 h and filtered. The solid was rinsed with water (30 mL) and dried on filter to afford amide (±)-**9** (14.2 g, 82%). An analytically pure sample was obtained for characterization using chromatography (silica gel, 10% MeOH/CH_2Cl_2). Mp 148−152 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 7.91−7.97 (m, 1H), 7.54−7.61 (m, 1H), 7.47−7.54 (m, 1H), 7.37−7.42 (m, 1H), 3.78 (dd, J = 4.0, 8.0 Hz, 1H), 2.35−2.42 (m, 1H), 2.27 (br s, 1H), 1.70−1.80 (m, 1H), 1.44−1.62 (m, 4H), 1.14−1.35 (m, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 172.3, 169.7, 140.1, 133.0, 131.3, 131.2, 130.5, 129.1, 55.0, 43.2, 39.7, 37.1, 36.4, 29.6, 27.7; IR (neat): 3258, 2953, 1700, 1632, 1548, 1292 cm^{-1}; Exact Mass $[C_{15}H_{17}NO_3 + 1]^+$: calculated = 260.1826, measured = 260.1821.

Thiourea S-1. A solution of **6** (123.2 kg, 324.2 mol) and Et_3N (65.8 kg, 651.5 mol) in CH_2Cl_2 (1634 kg, 1241 L) under N_2 was cooled to −10 °C. Benzoyl isothiocyanate (**12**, 56 kg, 344 mol) was charged over 45 min (−10 and −5 °C). After an additional 15 min, reaction completion was measured (GC) and H_2O (618 kg, 618 L) was added. After separation of the layers, the organic phase was washed with aqueous NaOH (614 kg, 4% w/w) and aqueous HCl (615 kg, 7.3% w/w). The organic phase was filtered. Most of the CH_2Cl_2 was distilled under reduced pressure, MeOH (426 kg, 540 L) was charged, and the solvent exchange was completed by additional distillation of CH_2Cl_2. H_2O (60 kg, 60 L) was charged to the thick slurry. Aqueous NaOH (86 kg, 30% w/w) was charged over 20 min (27 °C). H_2O (1664 kg, 1664 L) was finally added over 1 h. The suspension was cooled to 14 °C, filtered, and the solids were washed twice with H_2O (2 × 30 L). The cake was dried at 45 °C under a N_2 sweep for 3 h. The cake was transferred back in the reactor and IPAC (177 kg, 203 L) was charged. The slurry was stirred for 3 h, cooled to 0 °C and filtered. The cake was rinsed with IPAC (3 × 5 L) and dried at 45 °C under a N_2 sweep for 3 h to afford *S*-**1** (44.1 kg, 80.0% yield, 259.4 mol, 99 wt %, 99.1 LCAP, 99.4% ee). Mp 180−182 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 3.97 (br s, 0.55H), 2.28 (s, 2H), 1.74−1.83 (m, 1H), 1.10−1.60 (m, 7H), ^{13}C NMR (100 MHz, $CDCl_3$, some signals doubled) δ 183.8, 180.3, 59.2, 58.0, 43.7, 43.0, 40.8, 40.3, 37.2, 36.4, 29.3, 27.5; IR (neat): 3225, 2954, 1613, 1558, 1453, 716 cm^{-1}; Exact Mass $[C_8H_{14}N_2S + H]^+$: calculated = 171.0956, measured = 171.0945.

Thiourea (±)-1. To a mixture of norbornene (188.3 g, 2 mol), toluene (942 mL), water (122 mL) and NH_4NCS (159.9 g, 2.1 mol) was added 12 M aqueous H_2SO_4 (165 mL, 2 mol) over 25 min. The reaction mixture was stirred at 40 °C for 3 h. The transformation was measured to be 96% complete (HPLC). IPA (188 mL) was charged and the mixture was cooled to 22 °C. The phases were separated and the organic layer was determined to contain 259 g of (±)-**15** (1.69 mol, 85% assay yield).

Aqueous NH_4OH (28−30%, 296 mL, 2.13 mol) was charged to this solution and the temperature was increased to 50 °C. After 20 h, the transformation was 99% complete (HPLC). The mixture was cooled to 22 °C, held for 1 h, and filtered through a M porosity sintered glass filter frit. The wet cake was washed with toluene (2 × 435 mL)

and H_2O (435 mL). The white solid was vacuum-dried at 45 °C (100 Torr) under a N_2 sweep for 72 h to afford (±)-**1** (261 g, 77% yield, 1.53 mol, 103 wt %, 100 LCAP).

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Supporting Information Available

Copies of ^{1}H and ^{13}C NMR spectra. XRPD analyses. Crystallographic information file (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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