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Practical Synthesis of Chiral 2-Morpholine: (4-Benzylmorpholin-2-(*S*)-yl)-(tetrahydropyran-4-yl)methanone Mesylate, a Useful Pharmaceutical Intermediate

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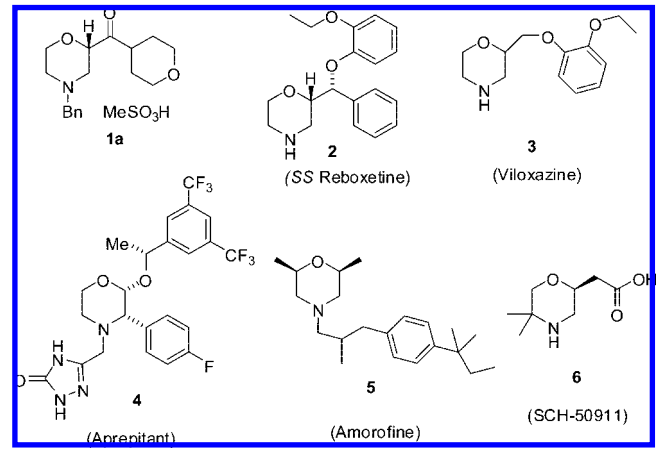
Abstract:

A commercial synthesis was developed for the production of (4-benzylmorpholin-2-(*S*)-yl)-(tetrahydropyran-4-yl)methanone mesylate, 1a, a key starting material for a phase 2, new investigational drug candidate at Eli Lilly and Company. The target compound was produced in the clinical pilot plant by the combination of two key steps: resolution of a morpholine amide intermediate to install the *S*-morpholino stereocenter in 35% yield and a high-yielding (89%) Grignard reaction to generate the title compound 1a, isolated as a mesylate salt. The Grignard reaction was found to proceed optimally when using a combination of I_2 and DIBAL-H for the initiation. In addition, the Grignard reagent formation was monitored by ReactMax calorimetry, and proof-of-concept studies were completed, demonstrating that the Grignard step could potentially be run as a continuous process with magnesium recycling.

Introduction

Selective norepinephrine reuptake inhibitors such as reboxetine[1] (**2**) and viloxazine[2] (**3**) which contain a common 2-morpholine backbone have been used for the treatment of depression (Scheme 1). While reboxetine is marketed as a racemic drug, the *2S,3S*-enantiomer (*S,S*-reboxetine) has greater affinity and selectivity toward the norepinephrine transporter.[3] In addition, the 2-morpholine structural skeleton is found in other pharmaceutically active compounds such as NK1-receptor antagonist aprepitant[4] (**4**), antifungal agent amorofine[5] (**5**), and selective GABA β-antagonist SCH-50911[6] (**6**). Despite the numerous examples of pharmaceutical compounds substituted at the 2-position of the morpholine ring, general synthetic methods are limited, and as in the case of *S,S*-reboxetine, the morpholine ring is typically formed in the late stages of the

Scheme 1. **Biologically active 2-substitututed morpholines**



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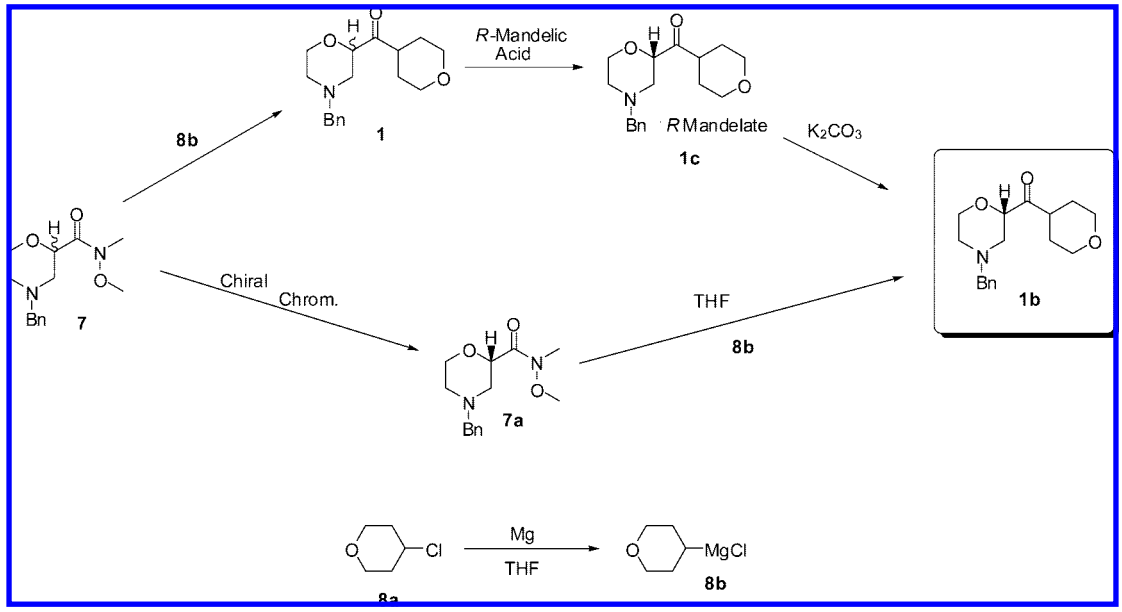
Scheme 2. **Early routes to 1b**[8]



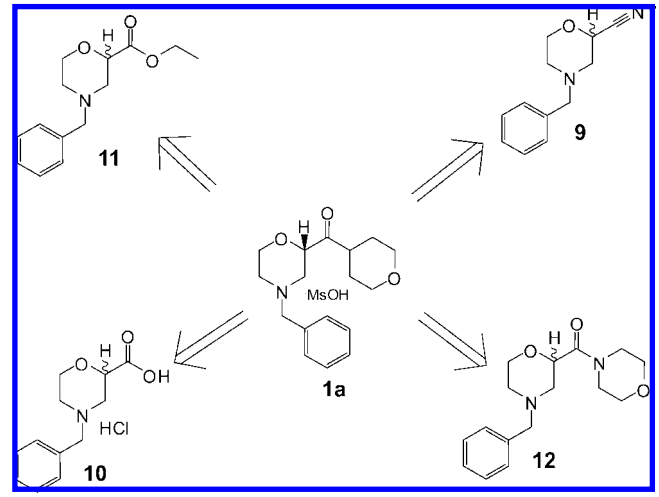
synthesis.[7] For these reasons, a potentially efficient entry into the reboxetine class of compounds is direct synthesis of the chiral 2-morpholine backbone. Herein we report a practical synthesis of (4-benzylmorpholin-2-(*S*)-yl)-(tetrahydropyran-4-yl)methanone mesylate (**1a**) which is structurally related to *S,S*-reboxetine (**2**) and is a key starting material for a phase 2 new investigational drug candidate at Eli Lilly and Company.

Results and Discussion

First-Generation Process (Scheme 2). The synthesis of the free base form of **1a** (4-benzylmorpholin-2-(*S*)-yl)-(tetrahydropyran-4-yl)methanone (**1b**), has previously been reported by Eli Lilly and Company.[8] The (1*S*)-morpholino chiral center was initially installed via chiral chromatography of a Weinreb amide precursor **7**, to produce *S*- **7a**, which was then converted to the **1b** *S*-isomer via a chemoselective reaction with the 4-chlorotetrahydropyran Grignard reagent, **8b** (Scheme 2). Alternatively, the racemic Weinreb amide intermediate **7** has been converted to racemic **1** via Grignard chemistry, where it was resolved as the *R*-mandelic acid salt, **1c** which is readily converted to optically pure *S*-isomer **1a** (>99% ee, Scheme 2). Key disadvantages to the aforementioned approaches include an overall low yield (~5%), the use of chiral chromatography, late-stage resolution, and lack of crystalline intermediates, a necessary feature for purity upgrade. In addition, little was known surrounding the Grignard reaction kinetics which was required prior to scale-up. Thus, we envisioned that development of more attractive routes to rapidly produce **1a** in multikilogram quantities could be realized using Grignard chemistry with potential precursors **9**,**10**, **11** or **12** (Scheme 3).

4-Benzyl-2-cyanomorpholine, **9** was prepared in 80% yield by reaction of commercially available N-benzyl-ethanolamine with 2-chloro acrylonitrile (2-CAN) followed by ring closure with 2*M* Potassium *tert*-butoxide/THF.[9] The synthesis of 4-benzylmorpholine-2-carboxylic acid, **10** was then accomplished via the direct hydrolysis of nitrile **9**. However, the high aqueous solubility of the acid (>200 mg/mL) made separation of the product from the resulting aqueous layer exceedingly difficult. Hydrolysis of nitrile **9** with 6 N HCl was found to be optimal and the hydrochloride salt, **10**, precipitated directly form the reaction mixture. Use of acetone as a wet cake rinse solvent was efficient at removing residual HCl and under these conditions the hydrochloride salt of **10** was rapidly prepared via a telescoped process on a multikilogram scale

Scheme 3. **Compound 1a retrosynthetic analysis**



(7) (a) Henegar, K. E.; Ball, C. T.; Horvath, C. M.; Maisto, K. D.; Mancini, S. E. *Org. Process Res. Dev.* **2007**, *11*, 346. (b) Henegar, K. E.; Cebula, M. *Org. Process Res. Dev.* **2007**, *11*, 354. (c) Cossy, J.; Pardo, D. G.; Metro, X. *J. Org. Chem.* **2008**, *73*, 707. (d) Melloni, P.; Della Torre, A.; Lazzari, E.; Mazzini, G.; Meroni, M. *Tetrahedron* **1985**, *41*, 1393.

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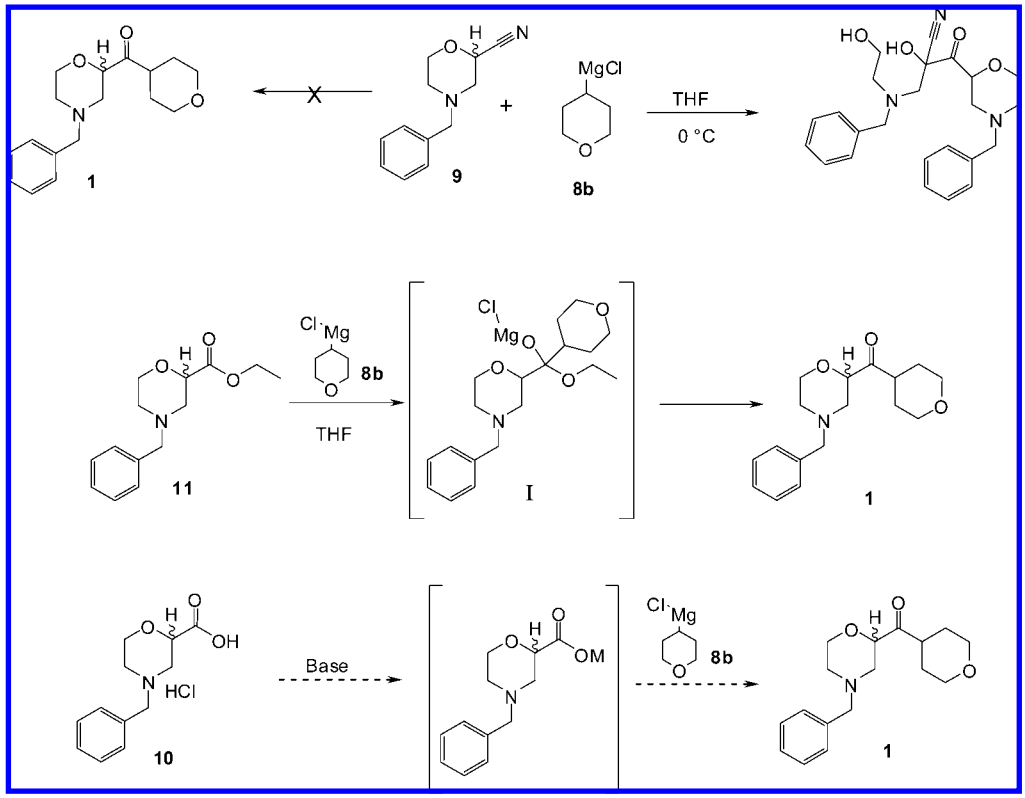
Scheme 4. **Synthesis of 1a from substrates 9, 10, and 11**



in 60−65% yield with >99% purity. In addition, treatment of nitrile **9** with concentrated sulfuric acid in ethanol results in an 87% yield of 4-benzylmorpholine-2-carboxylic acid ethyl ester, **11**.[8] With sufficient quantities of **9**, **10** and **11** on hand we sought to evaluate the direct preparation of **1** by the Grignard reaction of the 4-chlorotetrahydropyran Grignard reagent, **8b**, with each substrate.[10] The initial substrate evaluated was nitrile **9,** the Grignard reactions of which with aryl Grignard reagents have been shown to proceed with high chemoselectivity to produce aryl-2-morpholinones.[9b] Unfortunately, under the optimal conditions for aryl Grignard chemistry, Thorpe addition was the dominant pathway for the reaction of **8b** and nitrile **9** (Scheme 4).

In general, the main drawback of the Grignard reaction with esters is the formation of tertiary alcohol byproducts because intermediates of type **I** are not stable.[11] Nevertheless, in our case we wished to examine the impact of the morpholino oxygen on the stability of intermediate **I** and assess the extent of deprotonation alpha to the ester. It was found that under the best conditions (−20 °C and 1.5 equiv of Grignard reagent) an incomplete conversion resulted with 20−25% residual **11** and significant amounts (10−15%) of the tertiary alcohol byproduct. In order to test configurational stability of the α morpholino hydrogen, an aliquot of the reaction mixture was quenched with acetic-d_3-acid-*d*, and by mass spectroscopy and ^{1}H NMR we observed significant deuterium incorporation (45%). Based on these results, optimization of the ethyl ester approach was abandoned.

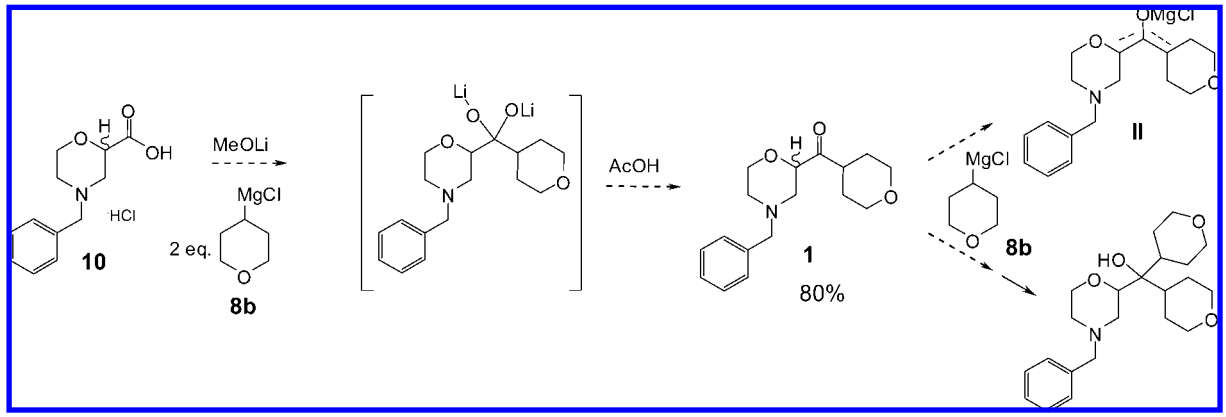
After observing that carboxylic acid **10** was very soluble in aqueous media, we were obliged to convert the acid to a salt using a hydride reagent or a base whose corresponding acid could easily be removed by distillation. Thus, we evaluated performance of the magnesium and lithium salts of **10** toward the **8b** Grignard reaction. Conversion of **10** to its magnesium salt with i-PrMgCl in THF is facile between −10 and 0 °C. However, we observed partial competitive nucleophilic addition to form the isopropyl ketone byproduct (5−12%). Initial attempts to prepare the lithium salt of **10** with butyllithium at −20 °C resulted in significant quantities of butyl ketone (30%) and dibutyl alcohol impurities (5%). Formation of the lithium salt was improved by the use of lithium hydroxide monohydrate in THF, but in this case it was difficult to remove water by using azeotropic distillation after salt formation, because the lithium carboxylate salt forms a gummy solid which entrains residual water. The best conditions for the formation of the lithium salt of **10** were achieved using 3.62 *M* MeOLi/THF, which proceeded rapidly without any detectable methyl ester byproduct. In this case the lithium carboxylate quickly precipitated to produce a thick mixture. For this reason the lithium salt was formed at 55 °C and the methanol byproduct was removed by atmospheric distillation. The lithium salt slurry was then cooled to room temperature prior to use in the Grignard reaction.

The magnesium and lithium salts of acid **10** were both evaluated toward the Grignard reaction with **8b**, and in side by

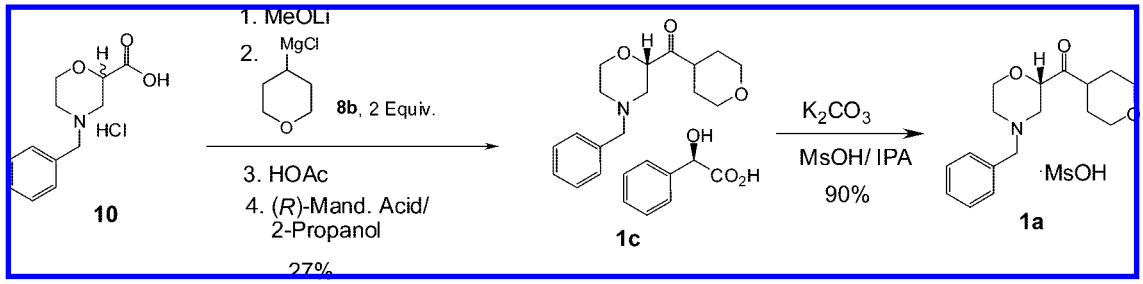
(10) (a) 4-Chlorotetrahydropyran is available in small quantities from Aldrich (CAS no. 1768-64-5) at $96.60/5 g. Larger quantities can be readily prepared via the following methods: Nikolic, N. A.; Gonda, E.; Longford, C. P.; Lane, N. T.; Thompson, D. W. *J. Org. Chem.* **1989**, *54*, 2748. (b) Bunnelle, W. H.; Seamon, D. W.; Mohler, D. L.; Ball, T. F.; Thompson, D. W. *Tetrahedron Lett.* **1984**, *25*, 2653.

(11) (a) Bachman, W. E., III; Hetzner, H. P. *Organic Syntheses*; John Wiley & Sons: New York, 1955; Collect. Vol. III, p 839. (b) Colonge, J.; Marey, R. *Organic Syntheses*; John Wiley & Sons: New York, 1963; Collect. Vol. IV, p 601.

Scheme 5. **Grignard reaction with acid 10**



Scheme 6. **First-generation process summary**



side experiments, the kinetics of the Grignard reaction strongly favored the Li over the Mg salt by nearly an order of magnitude. In addition, a key disadvantage for the magnesium salt was generation of the tertiary alcohol byproduct which could not be reduced. In the case where the lithium carboxylate was generated, we also formed 1 equiv of lithium chloride which could potentially have an impact on the Grignard reaction since the more nucleophilic ate complex species could have been formed.[12] However, spiking studies with lithium chloride resulted in no difference in the kinetic profile. The Grignard reaction with the lithium carboxylate was found to run best with 2 equiv of Grignard reagent between 20 and 25 °C; performing the Grignard chemistry with one equivalent of **8b** results in less than a 50% conversion. The kinetics were quite fast at early reaction times (90% conversion after 3 h) then slowed significantly (95% conversion after 21 h). The observation that full conversion was not achieved can be partially explained by deprotonation α to the carboxylate function. In fact, 30−40% of deuterated acid was observed by mass spectroscopy after quenching an aliquot of the reaction mixture in acetic-d_3-acid-*d*. In addition, the resulting magnesium intermediate **II** has the potential to be sufficiently basic to deprotonate the resulting product (Scheme 5). Thus, quenching conditions would need to be carefully considered for performing the analogous chemistry on a chiral substrate.

With an enabling route to produce racemic **1** in hand, a systematic screen of resolving agents was performed with the objective of obtaining the optically pure **1b** *S*-isomer. The best results were achieved with (*R*)-mandelic acid, and an efficient crystallization was developed where **1c** crystallized out of 2-propanol and was isolated in 27% yield with >99% ee (Scheme 6). The mandelate salt, **1c**, was then readily transformed to a methanesufonic acid salt **1a** in 90% yield.[13] The overall yield of the first-generation approach from acid **10** was 24% and was sufficiently enabling to produce the initial clinical quantities of **1a**.

Second-Generation Process. During the course of development we recognized that significant technical and environmental improvements were needed for the production of **1a** in order to make commercial-scale quantities.[14] Key potential improvements identified were: (1) resolve or introduce chirality at an earlier stage of the synthesis; (2) develop a strategy that employs an intermediate not prone to racemization; (3) reduce the usage of 4-chlorotetrahydropyran, **8a**, which is the most expensive reagent used in the synthesis; (4) develop a robust Grignard process that would operate safely with a variety of grades of magnesium. With these considerations in mind, we embarked on the synthesis of morpholine amide **12**, which we thought would offer advantages with regard to stability, economy, and purification.

Racemic Morpholine Amide 12 Synthesis. The initial strategy evaluated was conversion of acid **10** to amide **12** via an intermediate acid chloride using oxalyl chloride as the chlorinating agent. However, this approach was abandoned due to issues with the phosgene byproduct.[15] Rather, the acid

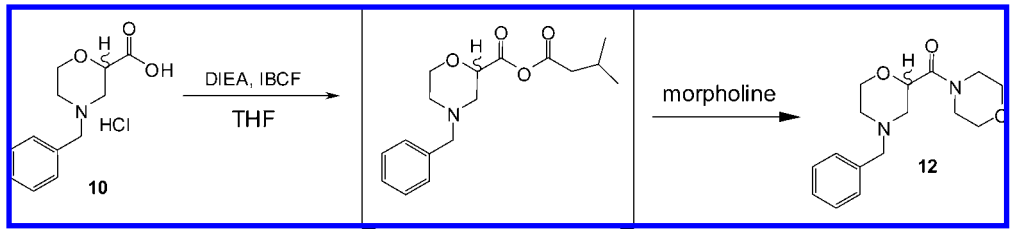
(12) (a) Knochel, P.; Krasovsky, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 3333. (b) Murso, A.; Lang, S.; Hawk, D. *Org. Process Res. Dev.* **2006**, *10*, 733.

(13) The mesylate salt **1a** is defined as a regulatory starting material. For 2-substituted morpholine systems, mesylate salts are common and generally deliver excellent impurity control. See ref 7a and Berg, S.; Larsson, L.-G.; Renyi, L.; Ross, S. B.; Thorbery, S.-O.; Thorell-Swantessen, G. *J. Med. Chem.* **1998**, *41*, 1934.

(14) The Weinreb amide **7**, described in reference 8, was chemically unresolvable, and the high cost of *N,O*-dimethylhydroxyamine hydrochloride would be untenable.

(15) Aldrich [79-37-8]; up to 1.0% phosgene content is listed for reagent grade material.

Scheme 7. **IBCF approach to amide 12 synthesis**



chloride intermediate was generated using thionyl chloride, but due to the low solubility of the resulting intermediate salts it was necessary to perform the chemistry in dichloromethane with 1 mol% DMF to assist with solubilization. The initial condition used CH_2Cl_2 (12 vol [L/ kg **10**]) as solvent, Hünig's base (2 equiv) to sequester HCl, DMF (0.08 equiv), and morpholine (2 equiv) as base and reactant. We quickly moved to evaluate replacement of suspected carcinogen dichloromethane with THF. When the THF conditions were run at 4-g scale it was discovered that the addition of $SOCl_2$ to a mixture of **10**, Hünig's base, and THF was very exothermic, but the reaction mixture did not become homogeneous at any time. Quenching a sample of the intermediate acid chloride mixture in MeOH for HPLC analysis showed that the conversion to acid chloride was incomplete, with 8% of acid **10** starting material remaining.

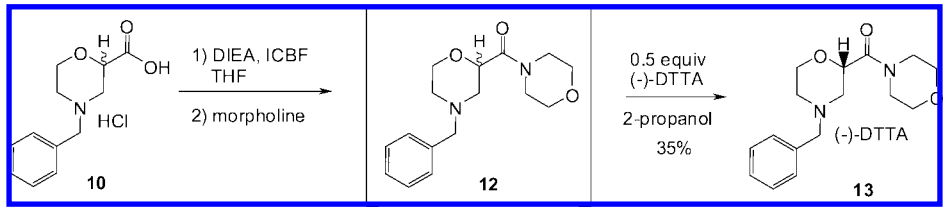
Optimization of the tandem chlorination/morpholine amide formation reaction was attempted within the following general design space: 10−12 volumes THF, 1.5−3.0 equiv of Hünig's base (DIEA), 1.5−3.0 equiv of morpholine, 1.05−1.15 equiv of $SOCl_2$, 0−0.5 volumes of DMF. Unfortunately, within these ranges improvements were not made to the conversion, and typically 8−16% residual starting material **10** remained. To better control the reaction conditions, a European-style jacketed flask was employed along with a heated-fluid circulator to maintain a constant temperature of 30 °C throughout the reaction. The amount of Hünig's base was increased slightly from 2 to 2.5 equiv, but the $SOCl_2$ used was decreased from 1.15 to 1.10 equiv. While the acid chloride formation left 14% residual acid **10**, by the end of the morpholine addition there was <1% of acid **10** remaining. The fact that the acid was eventually consumed intimated that the presence of the morpholine might help the conversion, either by changing the system's solubility characteristics or by providing an irreversible sink for the acid chloride. It was decided to test how the reaction would behave if the $SOCl_2$ was added to a mixture of all the other materials, again using the jacketed flask and heated fluid circulator to maintain temperature control. However, this reaction performed poorly, leaving 17% of the acid unreacted, and even after an additional 0.5 equiv of both morpholine and $SOCl_2$ were added in sequence the amount of remaining acid was 10%. One notable observation made during this experiment was that when the morpholine was added to the slurry of **10**, Hünig's base, DMF, and THF the slurry thickened, indicating the morpholine hydrochloride salt was less soluble than the DIEA·HCl salt. This was unfortunate because it indicated that the Hünig's base might not be a very efficient proton sponge in the presence of morpholine. Perhaps having a larger amount of DIEA present would increase the solubility of the morpholine hydrochloride thereby setting up a stronger equilibrium between the protonated morpholine and Hünig's base. To test this hypothesis an experiment was conducted where the DIEA was increased from 2.5 to 3 equiv, and the result was very surprising; the conversion to acid chloride was much poorer in the presence of increased DIEA, with 40% of **10** remaining. The deleterious effect of larger amounts of Hünig's base on the reaction was seen in later experiments as well when the reaction was performed at twice the dilution, and again when inverse addition was employed. These reactions never became homogeneous at any point, so there was a possibility that mass transfer mixing issues might be important. An inverse-addition experiment was set up employing addition of a slurry of Hünig's base, **10**, DMF, and THF to a solution of $SOCl_2$ and THF. The addition was performed in small aliquots at 24 °C, and a stir time was allowed between aliquots. At the end of the addition there was 8% acid **10** remaining, the same as the original conditions.

While the necessity of DMF in the reaction had not been firmly determined, there was some question as to whether a much larger amount could facilitate the reaction by increasing the solubility of intermediate salts. To this end, the inverse-addition reaction was repeated but with 0.5 vol of DMF rather than the 0.1 equiv previously used. The amount of acid left over rose to 10%, but that was still fairly close to the 8% unconverted when much smaller amounts of DMF were employed. Thus, it did not appear that DMF made much of an impact at low levels, and higher levels were not desired due to the difficulty of removing all of the DMF prior to resolution. Thus, due mainly to the incomplete conversions we decided that alternatives to $SOCl_2$ would be evaluated.

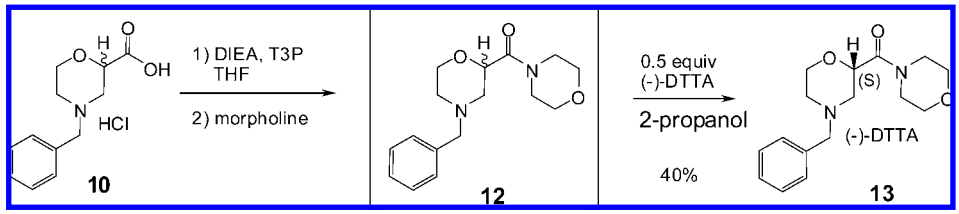
A rapid screen of peptide coupling reagents revealed that a mixed anhydride approach utilizing isobutyl chloroformate (IBCF) as a possible $SOCl_2$ replacement was feasible (Scheme 7).[16] Execution of the best prior conditions utilizing IBCF as a replacement for $SOCl_2$ using THF (10 vol), Hünig's base (2 equiv), IBCF (1.1 equiv), and morpholine (1.5 equiv) resulted in a stalled conversion with 9% **10** remaining, consistent with the thionyl chloride chemistry. The heterogeneous nature of the acid-to-mixed anhydride conversion was still a concern, and several attempts were made to overcome this issue. First, an increase from 2 equiv of Hünig's base to 3.1 equiv was carried out in order to complex all the acid possible and to see if the increased base content would impart more solubility to the intermediate salts. However, this reaction resulted in 10% of unconsumed **10**; not only was there no improvement but the extra DIEA would have to be removed via distillations so this avenue was not further pursued. Previous experience had shown

(16) (a) Prashad, M.; Har, D.; Ho, B.; Kim, H.; Girgis, M. J.; Chaudhary, A.; Repic, O.; Blacklock, T. J. *Org. Process Res. Dev.* **2004**, *8*, 330. (b) Prashad, M.; Prashad, K.; Repic, O.; Blacklock, T. J. *Org. Process Res. Dev.* **1999**, *3*, 409. (c) Shie, H. W.; Carlson, J. A.; Shore, M. G. *Tetrahedron Lett.* **1999**, *40*, 7167.

Scheme 8. **(−)-DTTA resolution**



Scheme 9. **T3P coupling/resolution process**



that the morpholine hydrochloride salt precipitated preferentially to that of Hünig's base, but it was unknown what effect it would have with the new coupling agent. Thus, a reaction was run in which IBCF was added to a mixture of all the other reagents at 22−35 °C, which resulted in the formation of 20% of a byproduct that was identified by LCMS as isobutylmorpholine carbamate. Due to timeline constraints the mixed anhydride IBCF chemistry was run in the pilot plant which replicated that laboratory model where reaction progress stalled at ∼10% residual acid **10** starting material. Ultimately, this was acceptable since the procedure contained an aqueous workup which rejected acid **10** to <1% of the crude amide product.

Morpholine Amide Resolution. A screening of pure racemic amide **12** with resolving agents revealed enrichment with the (*S*)-mandelate, quinate and (−)ditoluoyltartrate (−)-DTTA) salts. The initial crystallization with (−)-DTTA gave a very thick mixture, but in this case the mother liquor composition was 76% ee. This favorable eutectic prompted us to evaluate crystallization of the (−)-DTTA salt in a variety of solvents with varying stoichiometries. The optimal solvent was 2-propanol (20 volumes) with 0.5 equiv of resolving agent which allowed the (−)-DTTA salt to be formed in 40% yield with 100% ee from analytically pure **12**. With successful proof of concept established for the resolution, the next logical step was to telescope the resolution and morpholine amide synthesis steps. This was accomplished as several resolutions were successfully run which involved addition of the resolving agent either as a slurry or as a solution in 2-propanol. As discussed vide supra, the elimination of Hünig's base from the racemic **12** solution prior to resolution was critical in order to obtain a good yield. Many laboratory experiments were performed where one or more vacuum distillations removed the majority of the amine, and in those runs, samples were taken after each distillation and solvent add-back in order to evaluate the effectiveness of the distillations. A maximum level of residual DIEA was determined to be 3 mg/mL in order to achieve at least a 35% yield for the resolution step. Prior to this determination a pilot-plant resolution was performed with 10.7 mg/mL of residual DIEA in the crude mixture which resulted in only a 24% isolated yield. However, a second distillation was installed for the next two pilot-plant lots, which reduced the amount of residual DIEA to 1.5 and 1.4 mg/mL, respectively. For these lots, which were performed on a 45-kg scale, 33% and 38.4% yields of (−)-DTTA salt **13** were achieved with 98.8 and 97.5% ee, respectively (Scheme 8).

The use of 1-propanephosphonic acid cyclic anhydride (T3P) as a peptide coupling agent has significant precedent.[17] During the course of development, a screen revealed that T3P used under standard conditions (THF [10 vol], Hünig's base [2 equiv], T3P [1.2 equiv], and morpholine [1.5 equiv]) resulted in complete consumption of the starting acid after 3.5 h; it was the first experiment in which total consumption of intermediate **10** was observed. As a follow-up the T3P-mediated reaction was scaled up to 50 g and was telescoped with the resolution step. These experiments showed that the use of T3P provided resolved salt **13** in 40−41% yield, a 5% improvement relative to the IBCF process (Scheme 9).[18] While the T3P process was not adopted for the pilot-plant campaign due to timing constraints, it will potentially be implemented for future campaigns.

In order to perform the Grignard chemistry, it was necessary to develop an efficient free base procedure that would be amenable to facile water and (−)-DTTA counterion removal. In this regard, toluene would be the ideal extraction solvent because water could be removed azeotropically. However, an attempted free basing in a biphasic toluene/water system (9 vol of each) with 2.5 equiv of sodium carbonate failed to solubilize (−)-DTTA salt **13**, and the conversion failed. Fortunately, addition of 9 vol of THF to this mixture produced a complete solution after 15 min of stirring. HPLC analysis of both layers showed that the di-*p*-toluoyltartaric acid had partitioned almost exclusively into the aqueous layer (0.52% in the organic layer), although 3.4% of **13**

(17) (a) Boggs, S. D.; Cobb, J. D.; Gudmundsson, K. S.; Jones, L. A.; Matsuoka, R. T.; Millar, A.; Patterson, D. E.; Samano, V.; Trone, M. D.; Xie, S.; Zhou, X.-m. *Org. Process Res. Dev.* **2007**, *11*, 539. (b) Rzepecki, P.; Geib, N.; Cernovska, K.; Konig, B.; Schrader, J. *J. Org. Chem.* **2004**, *69*, 5169. (c) Liu, J. O.; Su, Z.; Dai, X. *Tetrahedron Lett.* **2000**, 44. (d) Wissman, H.; Hoescht, A. G. *Phosphorous Sulfur* **1987**, *30*, 643. (e) Wissman, H.; Kleiner, H. J.; Hoescht, A. G. *Angew. Chem.* **1980**, *92*, 129.

(18) T3P is purchased as a 50 wt % solution in ethyl acetate. While the cost is significantly higher than IBCF ($200/kg vs $20/kg), the 5% yield improvement would more than offset the extra reagent cost.

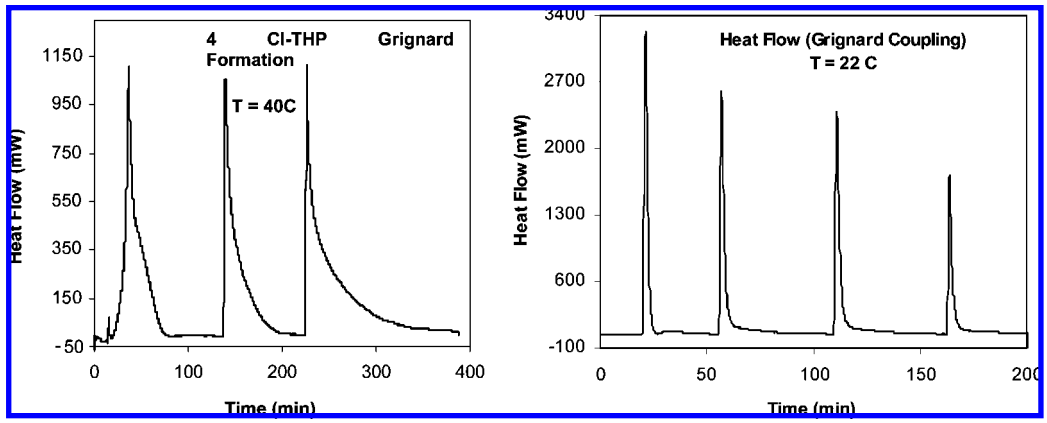


Figure 1. **Heat flow for Grignard formation and coupling reaction.**

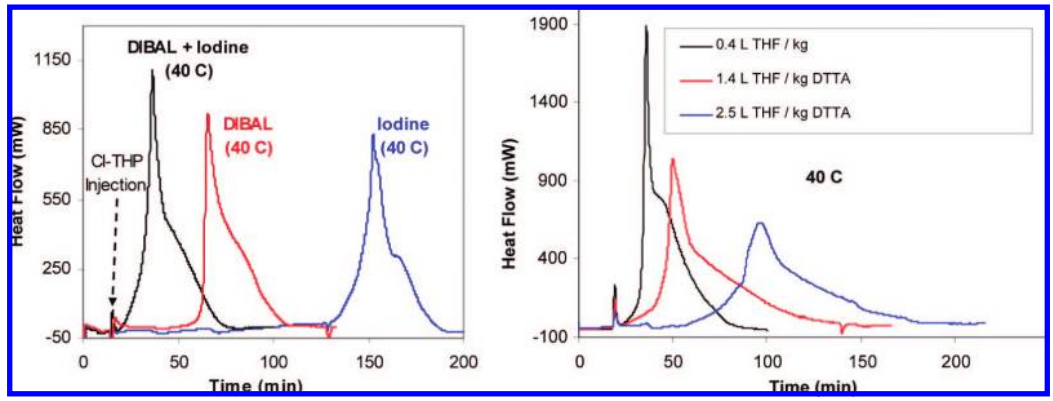


Figure 2. **Grignard initiator and dilution evaluation at 40 °C.**

remained in the aqueous as well.[19] There was some concern with possible racemization of the amide during the free base step, but the optical purity decreased only slightly from 97.0% in the starting material to 96.5% in the free base. In order to further streamline the process, an attempt was made to perform the free basing in THF/water (with no toluene), but the layers would not separate. Ultimately, the free base procedure was optimized with 6.5 vol (L/ kg **13**) of toluene, 6 vol of water, 3 vol of THF, and 3 equiv of sodium carbonate. These conditions were effectively implemented, and two pilot-plant lots were run with a 97% yield for the free base step.[20] Overall, the improved efficiency of this step strongly contributed to the reduced *E*-factor for the synthesis of **1a**.[21]

Grignard Chemistry. It is well-known that Grignard reactions are extremely moisture-sensitive. Consequently the organic solution of **12a** needed to be dried to a low level of water. After the free base procedure was implemented, solvent exchange under conventional conditions was performed to produce a 20−25 wt % solution of chiral amide **12a** with <300 ppm water. A method was developed to monitor the Grignard reaction initiation by ^{1}H NMR since the active Grignard reagent itself was not stable enough to analyze directly. An aliquot of the Grignard reaction mixture was quenched into CD_3OD, which would convert any active Grignard to THP. The extent of reaction could then be determined by comparing the integration of 4-chlorotetrahydropyran, **8a**, to tetrahydropyran (THP) ^{1}H NMR resonances. The 4-chlorotetrahydropyran multiplet at 4.2 ppm was a good indicator because this signal is far removed from other **8a** or any ^{1}H NMR resonances in THP. In addition, the multiplets in THP at 1.6 and 1.5 ppm were sufficiently resolved from the Cl-THP aliphatic resonances. Therefore, the extent of Grignard formation was calculated by comparison of the 4.2 ppm signal of Cl-THP with that of the 1.6 and 1.5 ppm signals of THP.

The Grignard reagent **8b** was initiated by addition of a small charge of **8a** to a THF suspension of magnesium (1.5 equiv) and iodine (cat.) and warmed to 60 °C; the initiation was generally accompanied by a 3−4 °C temperature rise. Once initiation was verified by ^{1}H NMR, then the remaining **8a** was fed at a rate such that a light reflux was not exceeded. After full conversion to active Grignard reagent was observed, the mixture was cooled to 23 °C, and then an amide **12a** toluene solution was fed over at least an hour. In a pure THF solvent system the Grignard reaction rate was dosing controlled. However, use of amide **12a** as a dilute toluene solution (<10 wt %) slows the reaction, and it can take up to 5 h to achieve reaction completion (<1% morpholine amide **12a**). Ultimately, the Grignard chemistry was found to be exceptionally sensitive to residual water, activator choice, and grades of magnesium. For these reasons, additional

(19) Extraction of the aqueous layer reduced this amount to 0.27%.
(20) In the aqueous process streams ~2−3% product was lost.
(21) (a) *E*-factor = total kg of all materials/per kg of active pharmaceutical ingredient (API). See: Sheldon, R. D. *Chem. Ind. (London).* **1992**, 93. (b) Sheldon, R. D. *CHEMTECH.* **1994**, *24*, 38.

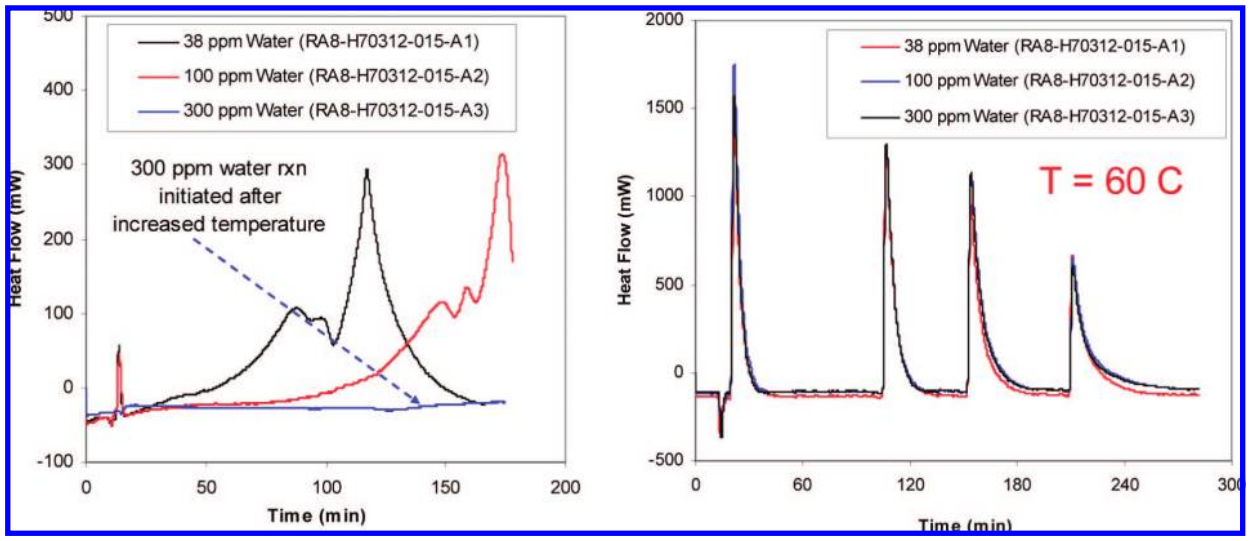


Figure 3. **Grignard reaction sensitivity to water at 40 and 60 °C.**

development was performed with reaction calorimetry using the ReactMax calorimeter on 5−10-mL-scale experiments. Such systems have been used industrially and academically for reaction kinetics and thermal characterization.[22] The measured heat flow was proportional to the measured reaction rate by the following relationship:

$$Q_{meas} = R_{rxn}\Delta H_{rxn} \quad (1)$$

where Q_{meas}, R_{rxn}, and ΔH_{rxn} are the measured heat flow (mW = mJ/s), instantaneous reaction rate (mol/s), and heat of reaction, respectively.[23] The heat flow profiles for the Grignard formation at 40 °C and subsequent reaction with morpholine amide **12a** at 22 °C were measured using standard conditions (Figure 1). The slow dissipation of heat during the Grignard formation is indicative of the reaction not being feed limited at 40 °C, with potential accumulation.[24] However, the heat load was proportional to the charge amount, indicating that the heat effects are uniformly distributed throughout the course of the Grignard formation. The subsequent reaction of the Grignard with amide **12a** administered as a 20 wt % solution in toluene was clearly feed limited; and the heat load was distributed uniformly throughout the course of the reaction.

Integration of the heat flow profiles yield a value of 54 kcal/mol and 37 kcal/mol for the Grignard formation and coupling reaction, respectively (Figure 1). The resulting adiabatic temperature rise can be calculated as follows:

$$\Delta T_{ad} = \frac{\text{Heat generated by reaction}}{\text{Heat sink from reaction mixture}} = \frac{N_{subs}\Delta H_{rxn}}{M_{rxn}C_p} \quad (2)$$

N_{subs}, ΔH_{rxn}, M_{rxn}, and C_p are the moles of reactant, heat of reaction, mass of the reaction mixture contents, and reaction mixture heat capacity, respectively. These measurements played a central role in determining safe pilot-plant operational procedure. For example, conducting the Grignard reaction with 0.4 L/kg THF results in an adiabatic heat rise of approximately 160 °C.[25] However, diluting the reaction mixture to 2.5 L/kg of **8b** results in a reduction of the adiabatic heat rise to 100 °C for the Grignard formation and coupling reactions, respectively. On pilot-plant scale, **8a** was charged to a mixture of THF, Mg, DIBAL-H,[26] and iodine in five equal portions. The resulting adiabatic heat rise for each injection would then be <20 °C which would result in a maximum pressure rise of <1 psig in a closed reactor.[27] In addition, samples were taken after each 20% addition of **8a** and analyzed by ^{1}H NMR to ensure consumption before proceeding to the coupling reaction.

As with any Grignard, one of the key drivers during development was to understand the factors that affected the initiation kinetics. There were early indications that the use of DIBAL-H along with iodine facilitated initiation kinetics compared to either one alone. The initiation kinetics (in the form of heat flow) using 0.4 L THF/kg of **12a** were measured in a parallel reaction calorimeter (Figure 2). In this experiment, **8a** was injected to all three reactors simultaneously, and while use of the DIBAL/iodine system initiated immediately, longer lag times were observed in cases where DIBAL-H and iodine were used separately. The apparent synergistic role of DIBAL-H and iodine is not completely understood; however, decreasing the

(22) (a) Dale, D. J. *Org. Process Res. Dev.* **2002**, *6*, 933. (b) Delhaye, L.; Stevens, C.; Merschaert, A.; Delbeke, P.; Briône, W.; Tilstam, U.; Borghese, A.; Geldoff, G.; Diker, K.; Dubois, A.; Barberis, M.; Casarubios, L. *Org. Process Res. Dev.* **2007**, *11*, 1104. (c) Stefanick, S.; Grim, J.; Liu, F.; Sorgi, K. L.; Maryanoff, C. A. *Org. Process Res. Dev.* **2003**, *7*, 1067. (d) Cajaiba da Silva, J. F.; Machado e Silva, C. F. P. *Org. Process Res. Dev.* **2002**, *6*, 829.

(23) Measurement of the instantaneous heat flow is a direct measurement of reaction rate which in turn allows calculation of conversion and reaction rate constants. Effective use requires correlation of the observed heat effect with other analytical techniques such as NMR or LC to ensure that other thermal events, i.e., side reactions, mixing, and crystallization are not confounding the results.

(24) Reactions near reflux were faster, but the kinetics were not feed-limited.

(25) Typical heat capacity value of 2 J/g/°C was used for calculation of the adiabatic heat rise.

(26) Tilstam, U.; Weinman, H. *Org Process Res. Dev.* **2002**, *6*, 905.

(27) Based on vapor pressure of THF at 80 °C since the reaction temperature in the pilot plant was 60 °C.

iodine charge from 4% to 0.8% suppressed the initiation kinetics. The synergistic effect of the DIBAL-H/iodine system was only present for Grignard initiation, and there was no such synergistic effect of reaction kinetics post initiation.

As with most Grignard reactions, the impact of water needs to be closely monitored and controlled. The initiation kinetics at 40 °C revealed that water levels needed to be controlled to around 100 ppm as higher levels (300 ppm) resulted in suppressed initiation at 40 °C (Figure 3). Upon completion of initiation at 40 °C, the reactor temperature was increased to 60 °C, and there was no impact of water on reaction kinetics post initiation. Significantly, increasing the Grignard formation temperature to 60 °C resulted in reduced sensitivity to the impact of water on initiation, as evidenced by an experiment at 465 ppm water that had a rapid initiation. However, water content beyond 465 ppm resulted in failure of the Grignard to initiate. In order to implement a safety margin, the water level was controlled to below 300 ppm for the initiation as well as for the coupling reaction with amide **12a**.[28] Most significantly, the initiation kinetics at 60 °C with water as high as 300 ppm showed dosing-controlled initiation. Thus, the decision was made to conduct the Grignard reaction in the pilot plant at 60 °C where the process was more robust and could be safely executed with dosing control.

Recently, there have been several reports of IR technology used to evaluate Grignard initiation and reaction chemistry.[29] Mid-IR and Raman spectroscopy were evaluated as online tools for monitoring the disappearance of **8a**, and early laboratory scale evaluation indicated that a weak band at 1150 cm^{-1} could be monitored for reaction progress. This peak was correlated with heat flow measurements, however, larger-scale experiments resulted in overlapping features that clouded this region. A weaker stretch at 830 cm^{-1} was measured, tracked, and correlated with heat flow and NMR data on laboratory scale. The mid-IR bands for the pyran stretches had weak intensity; and while they could be used to monitor initiation in the pilot plant, they could not be used to monitor the reaction progress after approximately 40−60% of **8a** had been converted. Grignard studies in the literature indicate that a band around 400−700 cm^{-1} might be present that could be ascribed to the C−Mg stretch; however, this stretch was not detected by mid-IR. In addition, Raman spectroscopy was also explored as a means to track the disappearance of **8b**, and future efforts for monitoring this reaction via Raman might be feasible with further development and calibration focused on the 337 cm^{-1} peak (Figure 4). Unfortunately, solids formed during the Grignard initiation that fouled monitoring by all IR approaches, thus we relied on temperature monitoring and ^1H NMR to verify that initiation had occurred.

Grignard Reaction Mixing Effects. The effect of mixing on coupling of the Grignard of **8a** with morpholine amide **12a** was conducted by examining the effect of charge time and addition mode on reaction performance. In one experiment, it

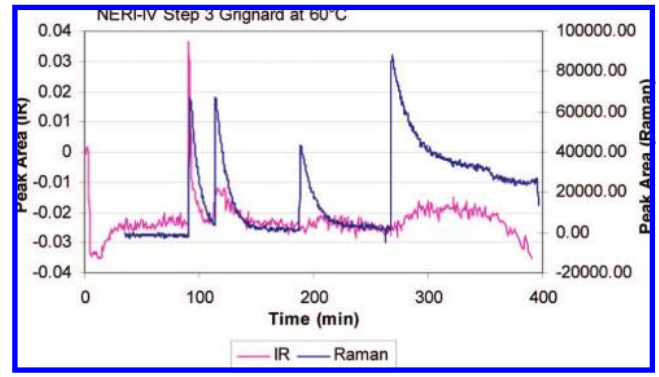


Figure 4. **Comparison of NIR and Raman spectra for initiation monitoring.**

Table 1. **Impact of reverse and normal addition mode for Grignard reaction**

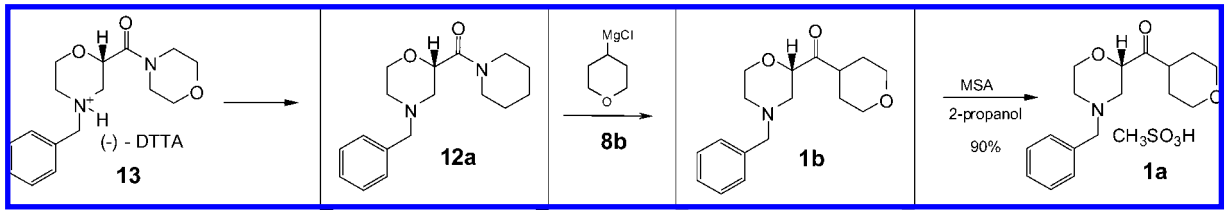
	entry 1	entry 2	entry 3
addition mode	reverse addition	normal addition	normal addition
feed rate	30 min.	1−2 min.	1−2 min.
reaction temperature	15 °C	15 °C	−10 °C
conversion	40%	68%	79%

was observed that the Grignard formation appeared to have proceeded normally, but only 20% of amide **12a** was converted to product. The only notable deviation from the standard procedure was that amide **12a** had been added over 10 min instead of the usual 1−2 h. In general, mixing effects are observed when the intrinsic reaction rate is faster than or equal to the mixing rate. To assess mixing effects, three experiments were conducted in parallel examining the effect of addition rate and mode at 15 °C: (1) Grignard addition to amide **12a** (inverse addition); (2) rapid addition of amide **12a** to the Grignard reagent at 23 °C, and; (3) rapid addition of amide **12a** to the Grignard reagent at −10 °C. The results show a trend consistent with adverse effect of poor mixing on reaction performance (Table 1). The reverse addition effectively mimics the extreme case of a poor mixing condition that would result from segregation of amide **12a** in the reaction mixture as a result of incomplete blending (Table 1, entry 1). The lower conversion with the reverse addition highlights the need to maintain low concentrations of amide **12a** during coupling with Grignard reagent **8b** in the toluene/THF solvent system. The apparent mixing sensitivity was partially reduced by lowering the reaction temperature, which in turn lowers the reaction rate while not affecting the mixing time scale. Nevertheless, these results underscored the need for a slow reaction feed and it is hypothesized that the active Grignard species is sufficiently basic to deprotonate amide **12a** when the latter is locally an excess reagent. Consequently, for pilot plant operations, the addition time of morpholine amide **12a** was increased to 5 h to suppress the mixing sensitivity and provide maximum performance. In addition, the temperature during the addition of amide **12a** was kept between 15 and 22 °C for two reasons: to control the exotherm and to minimize racemization of the product. Monitoring the coupling reaction is less complicated because introducing the amide **12a** moiety imparts a good chromophore that can be easily detected by HPLC analysis. The reaction is

(28) Since **8a** is added neat, a much higher water toleration is allowed for this substrate (1500 ppm).

(29) (a) Wiss, J.; Lanzlinger, M.; Wermuth, M. *Org. Process Res. Dev.* **2005**, *9*, 365. (b) Wiss, J.; Ermini, G. *Org. Process Res. Dev.* **2006**, *10*, 1282. (c) am Ende, D. J.; Clifford, P. J.; Deantonis, D. M.; Santamaria, C.; Brenek, S. J. *Org. Process Res. Dev.* **1999**, *3*, 319.

Scheme 10. **Synthesis of mesylate salt 1a**



typically done within two hours of completing the amide **12a** addition, though longer stir times are not harmful.

Grignard Reaction Workup. During initial development there was anecdotal evidence suggesting that performing the reaction quench by addition of the reaction mixture to acetic acid/water (inverse quench) rather than the typical addition of acetic acid/water directly to the reaction mixture (normal quench) was necessary to minimize stereochemical scrambling. We reasoned that the highly basic Grignard reagent, **8b**, could deprotonate product **1b**. However, because the inverse quench was less convenient, and would require the use of an additional tank when run in the pilot plant, we performed an experiment to assess the direct quench protocol. Whereas the typical crude **1b** enantiomeric excess is 96−98% by feeding the reaction mixture directly into acetic acid/water, the stereochemical purity was only 61.4% ee. Conversion of the crude to mesylate salt **1a** and crystallization/isolation in 7:3 2-propanol/toluene resulted in an ee upgrade only to 69%. In addition, the heat of reaction for the quench into acetic acid was measured at 67 kcal/mol which resulted in an adiabatic heat rise of 34 °C, of which 33% was attributed to the sensible heat effects associated with adding the reaction mixture at room temperature. For these reasons pilot plant operations for the quenching step were conducted by precooling the reaction mixture prior to direct addition to the cold acetic acid/water solution. This lowered the adiabatic heat rise to 23 °C and protected stereochemical integrity during the quenching process.

Mesylate Salt Formation and Crystallization. The initial procedure developed for crystallization of mesylate salt **1a** was successfully performed by heating a crude solution of free base **1b** in 10 vol. of 7:3 (v/v) 2-propanol/toluene, charging methanesulfonic acid at 60 °C, then the resulting slurry was heated to 70−75 °C in order to effect dissolution. The mesylate salt **1a** was then crystallized by slow cooling, and under these conditions thick mixtures result along with enrichment of undesired (*R*)-enantiomer. In addition, the resulting mesylate salt was found to retain high levels of residual toluene and 2-propanol (3−5%). In order to optimize the salt formation/crystallization sequence, three sets of experiments were run at 22 °C, 40 °C, and 60 °C. The primary rationale for evaluating multiple temperatures was to find a solvent ratio that would give good solubility of **1a** at higher temperatures and minimal solubility at room temperature where the isolation would take place. A secondary goal was to identify which solvent ratio had a solubility curve that was not as steep in the range where seeding (or initiation of crystallization) would take place. Each reactor well was charged with 2 g of **1a** and 20 mL of solvent were added at 2-propanol percentages of 0, 20, 50, 80, and 100% with respect to toluene. For the 40 and 60 °C experiments, the suspensions were heated to the prescribed temperature for 3 h and then whatever solid was still out of solution was filtered off and dried. For the 22 °C experiment, the mixtures were heated to 60 °C for 2 h, cooled to 22 °C, and then allowed to stir at that temperature overnight before filtering and drying. The filtrates were all concentrated and dried to constant weight and the filtrate mass was the number that was used to calculate solubility. The data are displayed as a function of solvent composition and temperature (Figure 5).

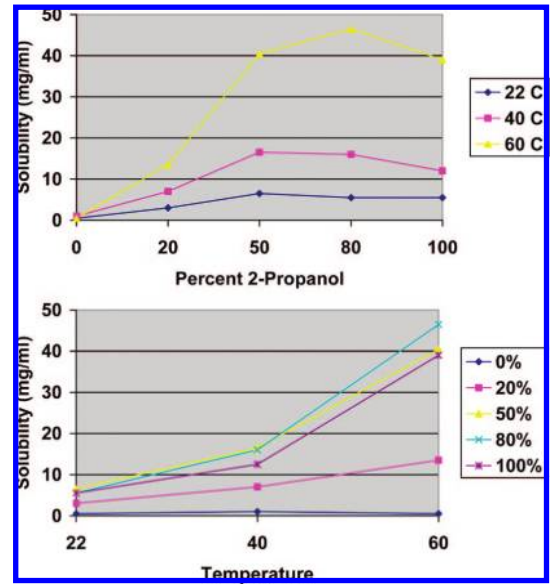


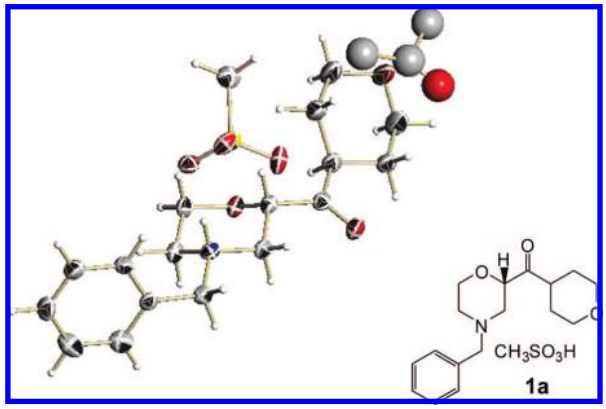
Figure 5. **1a solubility data.**

An analysis of Figure 5 demonstrates that using 20% or less of 2-propanol is not a practical option because **1a** is not soluble enough at 60 °C to prevent the salt from precipitating as soon as methanesulfonic acid is added. The best choices based upon solubility data at 22 °C are either 80% or 100% 2-propanol; both of these compositions also provide good solubility at 60 °C. Ultimately, the choice was made to switch the crystallization to 100% 2-propanol which was a simpler system and maximized yield.[30] Finally, eliminating toluene from the crystallization would alleviate the problem of high levels of toluene being retained in the isolated mesylate salt **1a**. The following protocol was devised for crystallization of the mesylate salt: crude **1b** was dissolved in 10 volumes (based on the theoretical amount of **1b** from the Grignard reaction) of 2-propanol, then heated to 70 °C. Methanesulfonic acid (1.0 equiv) was added in one portion and the solution was allowed to cool to 60 °C, which caused the salt to precipitate. After aging at 60 °C for an hour, the slurry was allowed to cool to 20−25 °C and was stirred for at least an hour. Filtration, washing with 2.5 volumes of

(30) Residual toluene <1% was readily achieved via solvent exchange due to the favorable azeotrope with 2-propanol/toluene.

2-propanol, and drying gave white crystalline **1a** in >98% enantiomeric purity in 90% yield (Scheme 10). In addition, the absolute stereochemistry of **1a** was confirmed by single X-Ray crystallography (Scheme 11).

Scheme 11. **ORTEP for 1a acetone solvate**



Impurity Removal. Efficient rejection of the undesired enantiomer in **1b** was of utmost importance to the crystallization. In addition, the crystallization would also be required to remove amide **12a** left unreacted from the Grignard reaction. Typically, amide **12a** taken into the three step process had a chiral purity ranging from 96−99%. Minor erosion of stereochemistry occurred during the Grignard reaction and quench so the crystallization of **1a** has been effected on crude **1b** lots ranging from 90−98% ee. Unless there were extenuating circumstances, the Grignard reaction generally proceeded to a low level of residual **12** (<0.5%). In order to test the robustness of the crystallization, a series of crude **1b** solutions with both typical and atypical levels of amide **12a** and (*R*)-enantiomer were evaluated under standard crystallization conditions (Table 2).

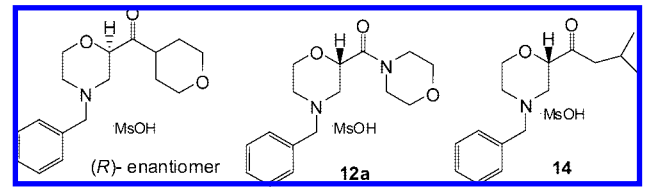
Table 2. **1a crystallization data**[a]

entry	crude % ee	**1a** % ee	isolated yield %	crude **12a** area %	final **12a** area %
1	94.7	99.9	90.7	0.11	ND
2	95.9	99.9	91.8	0.16	ND
3	96.2	99.9	91.6	0.10	ND
4	93.4	99.9	92.7	5.7	2.0
5	90.4	98.1	83.5	ND	ND
6	98.0	99.9	89.2	0.41	0.19
7	97.3	99.9	84.6	1.9	1.3

[a] All data reported for isolated solid **1a**.

The data clearly show that 2-propanol was effective at upgrading the chiral purity to acceptable levels from as low as 90% ee in the crude mixture. However, analysis of the filtrate revealed that the level of (*R*)-enantiomer was typically 2−3% higher than predicted by the crystallization so it was suspected that minor amounts of erosion was occurring during the mesylate salt formation and crystallization process. In order to test this hypothesis enantiomerically pure **1a** was heated to 60 °C in 2-propanol and the stereochemical purity was monitored. After 8 h the purity had dropped to 97.5% ee and after 24 h the stereochemical purity had dropped further to 80% ee. This set of data led us to keep careful control of the time the crystallization process was exposed to ≥60 °C temperatures during the pilot plant campaign.

Scheme 12. **Process impurities**



During the course of development a key impurity (*S*)-1-(4-benzylmorpholin-2-yl)-3-methylbutan-1-one, **14**, was identified by LCMS as a contaminant in some of the key **1a** lots (Scheme 12). The identity of this impurity was confirmed via independent synthesis by reaction of isobutylmagnesium chloride with amide **12a** followed by crystallization as its methane sulfonic acid salt. Initially, impurity **14** was thought to arise from small amounts of isobutyl chloride contaminating the **8a** feedstock, but GC analysis did not reveal any isobutyl chloride or potential precursors. An analysis of the historical lots of **1a** revealed a range of 0.00 −0.40% and the only tangible differences between these lots appeared to be the method of Grignard activation. It was noted that all lots produced with I_2 activation only resulted in no detectable **14** in the isolated product, whereas the lots that utilized DIBAL-H alone or in combination with iodine contained various levels of the impurity up to 0.40%. In order to test the idea that DIBAL-H was the source of the isobutyl ketone **14** impurity, a series of side by side Grignard reactions were performed with different activators, and the experimental data clearly supported this hypothesis (Table 3). During the course of this work, TMSCl appeared to be a promising surrogate for DIBAL-H, but initiation was very slow at 60 °C and only became reliable at reflux, which was outside the safe operating temperature. Unlike the (*R*)-enantiomer, which can be completely purged at levels 6−8% in the crude mixture, impurity **14** was only reduced by ~50% from levels present in the crude during the mesylate salt crystallization process. Under normal activation conditions, (Table 3, entry 1) up to 1% of impurity **14** could be produced in the crude, which translated to ~0.5% in the isolated product. However, since the next step in the synthetic sequence was found to effectively reduce the level of this impurity it was not necessary to alter the initiation conditions for long-term production.[31]

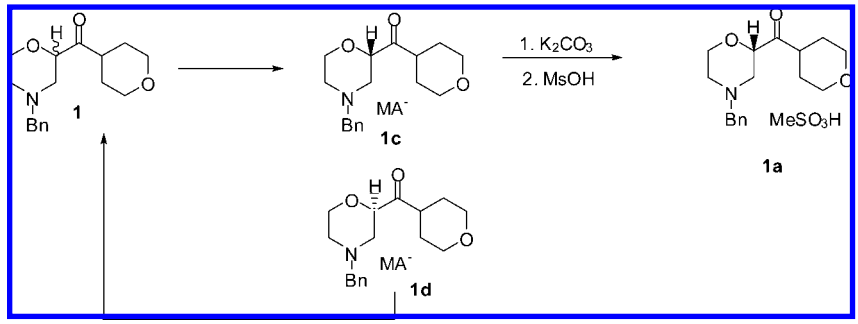
Table 3. **Grignard initiator screen**[a]

entry	activator	water (ppm)	initiation time (h)	**12a** area %	**14** area %	**1a** area %
1	4% DIBAL-H 3% I_2	120	2.5	1.28	1.01	97.7
2	11% TMSCl[b]	120	3.0	0.35	0.00	96.1
3	14% TMSCl	520	18	2.20	0.00	93.8
4	10% I_2	176	2.5	0.23	0.00	94.4
5	10% DIBAL-H 10% I_2	176	2.5	0.63	3.0	93.1
6	4% TMSCl	75	18	0.25	0.00	94.6
7	10% Vitride	75	2.5	34.6	0.00	57.1
8	20% DIBAL-H	75	2.5	34.5	0.31	59.2

[a] All data reported is in situ HPLC area % collected at 250 nm. [b] Grignard formation at reflux (67 °C); all others were completed at 60 °C.

(31) Specification of residual **14** contained in **1a** isolated solid for production lots was established at 0.50%. If necessary, recrystallization with 2-propanol reduces the level by ~50%.

Scheme 13. **Resolution recycle**



The optimized Grignard conditions were run in the clinical pilot plant to produce 55 kg of **1a** in two lots in high yield (89%) and purity (99.4% ee) (Table 4). Critical process parameters identified for the Grignard reaction included (1) <300 ppm water for initiation; (2) 60 °C operational temperature for Grignard; (3) amide **12a** feed rate of at least 1−2 h to active Grignard reagent on <50-g scale (5 h on pilot-plant scale); (4) quench by feeding reaction mixture to 2 equiv of acetic acid/water solution to preserve chiral integrity; (5) minimize time at ≥60 °C during mesylate salt crystallization.

Table 4. **1a pilot-plant campaign summary**[a]

entry	**13** (kg)	**13** ee (%)	**1a** (kg)	**1a** yield (%)	**1a** ee (%)
1	56	98.9	27.6	88.5	99.4
2	56	97.8	27.4	88.9	99.4
avg/total	112	98.3	55.0	88.7	99.4

[a] Data reported is HPLC area % at 250 nm for isolated solid, **1a**.

Recycling Resolution Studies. Based on the propensity of **1a** and **1b** to lose chiral integrity during the Grignard reaction, quench, and methanesulfonic acid salt crystallization processes, it was anticipated that development of a recycling process for the **1b** (*R*)-isomer should be possible (Scheme 13). In fact, the first-generation route to produce the desired **1a** (*S*)-isomer was accomplished via resolution of racemic **1b** with (*R*)-mandelic acid. We found that after isolation of (*R*)-mandelate **1c** (40.9 g, 31.4% yield) under typical process conditions, concentration of the filtrate (80% (*R*)-isomer), followed by dissolution in THF and treatment with 5 N NaOH at 55 °C resulted in complete racemization within 2 h. After aqueous workup and solvent exchange to 2-propanol, resolution with (*R*)-mandelic acid resulted in isolation of **1c** in 18.6% yield with 98.2% ee (Table 5). With successful proof of concept achieved, two additional recycles were performed to produce **1c** in 11.9% and 7.3% yields, respectively (Table 5). With three recycles included we were able to achieve a 69.2% yield of **1c** from racemic amide **12** hydrochloride salt.[8] It should be noted that for the third recycle, the enantiomeric excess had dropped to 97% and impurity **14** had enriched to double the amountobserved in the parent lot so further recycles were not pursued.

Table 5. **Batch recycle resolution data**[a]

entry	wt (g)	yield (%)	ee (%)	**14** (%)
main lot	40.9	31.3	99.7	0.34
recycle 1	24.2	18.6	98.2	0.50
recycle 2	15.5	11.9	99.4	0.45
recycle 3	9.5	7.3	97.0	0.71
overall	90.1	69.1	98.6	0.50

[a] Data reported is HPLC area % at 250 nm for isolated solid, **1c**.

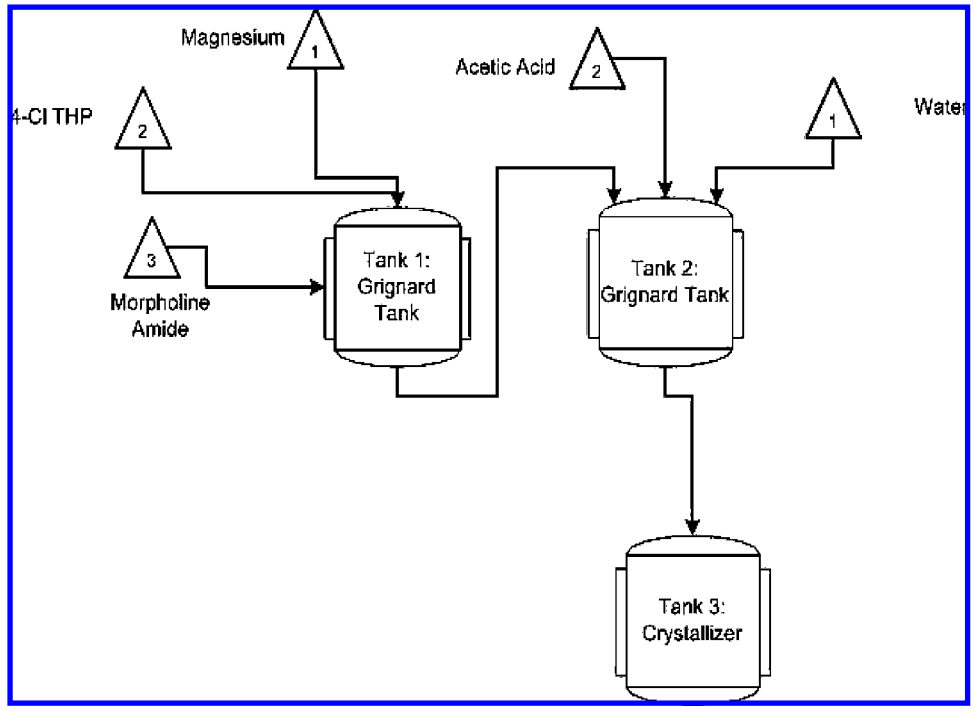
From acid **10**, an overall yield of 50% can be achieved for the **1c** mandelate salt epimerization/recycle process with three separate filtrate recycles which is a 14% yield improvement from the T3P process (Table 6, entries 3 and 5). From a process efficiency standpoint, the best processing sequence for recycling would be to run two separate resolutions, combine the filtrates, then execute the recycling process and this scenario was successfully developed to deliver a 54% yield of **1c** from racemic amide **12**. With a single filtrate recycle for every two lots produced of **1c**, efficiency is gained because roughly the same size **1c** lots are produced for both the main and recycled streams. However, in this case, the overall yield from acid **10** is only slightly improved relative to the T3P process (38 vs 36%) (Table 6, entries 3 and 4). A disadvantage to the mandelate recycle process relative to the DTTA resolution processes is a less favorable crystallization eutectic. Another disadvantage is that it is not possible to use amide **12** directly in the Grignard chemistry, rather it needs to be purified by conversion to an achiral salt form prior to use in the Grignard reaction, which reduces throughput. While a slight economic advantage could potentially be gained at present from the mandelate salt resolution with three recycles per lot, additional optimization is possible with the (−)-DTTA resolution. For example, a single epimerization/recycle of the amide **12** *R*-enantiomer in a modest 20% yield recovery would match the highest yielding mandelic acid recycle process. Thus, future development efforts will focus in this area.

Table 6. **1a process comparison**

entry	Scheme(s)	process	overall yield (%), **10** to **1a**
1	6	first-generation (Grignard reaction with acid **10**/mandelate salt resolution.	24
2	8−10	second-generation (ICBF/DTTA resolution/**1a** direct)	31
3	9−10	second-generation (T3P/DTTA resolution/**1a** direct)	36
4[a]	14	second-generation (mandelate salt/1 recycle per two lots)	38
5[b]	14	second-generation (mandelate salt/3 recycles per single lot)	50

[a] **10** → {79%} **12** HCl → {54%} **1c** → {90%} **1a**. [b] **10** → {79%} **12** HCl → {69%} **1c** → {90%} **1a**.

Scheme 14. **Magnesium recycle**



Magnesium Recycle. On small scale it is practical to quench the Grignard reagent and excess magnesium on a lot by lot basis. However, on pilot plant or commercial scale handling, of magnesium can be particularly hazardous. For high-volume processes it is often convenient to run Grignard reactions in continuous or near continuous fashion.[32] While the **8b** Grignard reagent is soluble in THF (~2 M), small amounts of fine metal particulates are difficult to avoid and may be particularly hazardous. We envisioned that a continuous process could be developed for production of **1a** as shown in Scheme 14. Key features include the use of dedicated vessels for the Grignard reaction, aqueous workup and crystallization. We anticipated that a large magnesium heel could be generated via a single activation process in the Grignard reactor that could be reused several times without addition of further magnesium or activation.[33] After the reaction was complete the crude reaction would be transferred through a filter directly into the quench tank containing excess acetic acid/water, which could also be potentially recycled. The crude **1b** solution would then be transferred to a crystallization vessel for production of mesylate salt **1a**.

In order to establish proof of concept for a continuous process, a Grignard reaction was run with 15 equiv of magnesium (based on amide **12a**) under otherwise standard conditions. After the Grignard reaction was verified to be complete (<1% amide **12a**), magnesium was removed by filtration, and the resulting filtrate was quenched by addition into acetic acid/water in the normal manner to produce crude **1b**. The process was then repeated an additional five times with the recycled magnesium (Table 7). A key observation was that

Table 7. **Magnesium recycling study**[a]

recycle	rxn ee (%)	quench ee (%)	**1b** (%)	**12a** (%)	**14** (%)
1	95.6	79.4	97.0	0.0	1.56
2	96.1	85.2	98.1	0.0	0.54
3	96.2	87.6	97.7	0.0	0.47
4	95.0	78.6	97.9	0.42	0.34
5	96.3	85.8	98.1	0.27	0.26
6	97.2	1.4	98.3	0.27	0.24
7	94.6	90.8	98.0	0.0	0.29

[a] In situ HPLC area % reported at 250 nm.

the reactions in each case performed as expected, with in situ ee of 95−97%. However, the stereochemical purities of the quenched mixtures were significantly lower than those observed in the reaction mixture. Since the isolation of excess magnesium was not accomplished in an airtight environment it was hypothesized that the decrease in ee was due to unwanted moisture. In fact, an extremely slow filtration was observed for the sixth recycle of magnesium which resulted in a complete scrambling of the stereochemistry where water condensation was possible (Table 7, entry 6). A separate recycle experiment where the magnesium and process stream were handled in an environment with reduced moisture resulted in an improved product ee (Table 7, entry 7).[34] In addition, performing the quench by addition of the reaction mixture into a large excess of acetic acid/water resulted in a high ee (98%). However, in this case higher than typical levels of **1b** were partitioned into the aqueous phase and required two toluene extractions to recover. Taken together, these data suggest that a continuous process with magnesium recycle is potentially feasible with further development.

(32) (a) Van Alsten, J. G.; Reeder, L. M.; Stanchina, C. L.; Knoechel, D. J. *Org. Process Res. Dev.* **2008**, *12*, 989. (b) Smith, A. A. *Org. Process Res. Dev.* **1997**, *1*, 165. (c) Harrington, P. J.; Lodewijk, E. *Org. Process Res. Dev.* **1997**, *1*, 75.

(33) Klokov, B. A. *Org. Process Res. Dev.* **2001**, *5*, 234.

(34) The results underscore the necessity to avoid moisture. This is less of a concern on a pilot plant or commercial scale where process streams can easily be fully inerted and dried.

Conclusions

A second-generation process to produce **1a** on pilot-plant scale in >98% ee and 31% overall yield from acid **10** was developed, an improvement of 30% from the first-generation approach. Key features include resolution of (−)-DTTA salt **13** and highly chemo- and stereoselective Grignard chemistry. We also demonstrated that the coupling/resolution step yield could be improved by 5% using T3P as a replacement for IBCF. Proof of concept studies were completed, demonstrating that it might be possible to run the Grignard process in continuous mode. In addition, feasibility of an alternate process to **1a** through a resolution/epimerization/recycle process with (*R*)-mandelic acid was demonstrated.

Experimental Section

Reaction solvents and reagents were used as purchased, and no special precautions were used to further dry them unless otherwise noted; reactions were carried out under a dry nitrogen atmosphere. Column chromatography, where necessary, was carried out with silica gel (230−400 mesh). ^{1}H NMR (300 or 400 MHz) and ^{13}C NMR (100 MHz) were recorded in $CDCl_3$ unless otherwise noted.

4-Benzylmorpholine-2-carboxylic Acid Hydrochloride (10). A 1-L flask was charged with 2-chloroacrylonitrile (2-CAN, 98% potency, 36.8 mL, 453 mmol, 1.01 equiv) and PhMe (105 mL). A solution of *N*-benzylethanolamine (66.0 mL, 95% potency, 440 mmol, 1 equiv) and PhMe (35 mL) was added to the flask, and the resulting solution was stirred overnight. Toluene (208 mL) was added, and the solution was cooled to <−5 °C with a brine/dry ice bath. In a separate 500-mL flask, KO-*t*-Bu (50.84 g, 98% potency, 444.0 mmol, 1.01 equiv) and THF (220 mL) were combined, and the resulting mixture was added to the cooled solution in the 1-L flask at a rate that kept the temperature <−1 °C. After 50 min, the mixture was quenched by adding water (175 mL), which raised the temperature to 3 °C. The organic layer was first rinsed with 10% (w/v) NaCl solution (75 mL), and then was concentrated to 235 g of solution. The solution was extracted with 6 *M* HCl, and the aqueous layer was transferred to a round-bottom flask where it was heated to reflux for 2.5 h. The heat was then turned off, and, when cooled, the solution was seeded with 4-benzylmorpholine-2-carboxylic acid hydrochloride (65.6 mg). Precipitation of the product created a thick slurry that was cooled to <10 °C for 45 min prior to filtration through polypropylene and paper on a Büchner funnel. The filter cake was rinsed with copious acetone (310 mL total), and was then dried in a 50 °C vacuum oven to provide 78.71 g of product **10** (98% potency, 68% yield) of a tan solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.61 (m, 2H), 7.42 (m, 3 H), 4.56 (d, J = 10.1 Hz, 1H), 4.33 (dd, J = 17.6, 13.2 Hz, 2H), 3.96 (m, 2H), 3.38 (d, J = 11.5 Hz, 1H), 3.16 (d, J = 11.9 Hz, 1H), 3.05 (m, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 168.8, 131.9, 130.0, 129.6, 129.2, 71.6, 63.2, 59.4, 51.4, 50.1; IR (KBr) 696, 750, 1101, 1147, 1284, 1413, 1444, 1753, 2604, 2867 cm^{-1}; MS (TOF) *m/z* 222.1122 (222.1125 calcd for $C_{12}H_{16}NO_3$, MH); Anal. Calcd for $C_{12}H_{16}ClNO_3$: C, 55.93; H, 6.26; Cl, 13.76; N, 5.43; O, 18.62. Found: C, 55.91; H, 6.16; N, 5.46; mp (DSC): 252 °C (dec).

(*S*)-(4-Benzylmorpholin-2-yl)(morpholino)methanone Di-*p*-toluoyl-L-(−)-tartrate (13). *Preparation I.* A 500-mL flask was charged with the acid salt **10** (19.99 g, 98% potency, 76.01 mmol, 1 equiv) and THF (180 mL). Diisopropylethylamine (27.0 mL, 153 mmol, 2.0 equiv) was added, and the mixture was heated to 30 °C. Isobutyl chloroformate (12.0 mL, 91.4 mmol, 1.2 equiv) was added via addition funnel at a rate that kept the temperature below 40 °C; the resultant slurry was stirred at 30 °C for 35 min. A solution of morpholine (10.0 mL, 115 mmol, 1.5 equiv) and THF (20 mL) was added via addition funnel at a rate that kept the temperature ≤40 °C. The solution was stirred for 1.5 h, and then PhMe and water were added (40 mL each). The pH of the mixture was adjusted to >8 with 5 M NaOH (29 mL); the layers were separated, and the aqueous layer was extracted with PhMe (40 mL). The combined organic layers were concentrated on a rotary evaporator to a volume of 100 mL, 2-propanol (200 mL) was added, and the solution was again concentrated to a volume of 150 mL. The mixture was polish filtered through a 0.45 μm PTFE membrane (with a 30-mL 2-propanol rinse) to remove the suspended salts from the workup. The filtrate was transferred to a 500-mL flask with a 2-propanol rinse (20 mL), and the solution was heated to 70 °C. Solid di-*p*-toluoyl-L-(−)-tartaric acid (13.81 g, 35.74 mmol, 0.5 equiv) was added, followed by a 2-propanol rinse (40 mL). The solution was seeded with the (*S*)-(4-benzylmorpholin-2-yl)(morpholino)methanone di-*p*-toluoyl-L-(−)-tartrate product (18.4 mg), and a thick slurry resulted. This slurry was heated to reflux and was maintained at that temperature for 2 h, after which the heat was shut off, and the mixture was allowed to cool slowly as it stirred overnight. The mixture was filtered through polypropylene backed with paper on a Büchner funnel, and the cake was rinsed with 2-propanol (50 mL) prior to drying in a 55 °C vacuum oven; 7.83 g (35%) of **13** was obtained as a white solid that was >99% ee by chiral HPLC analysis; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.86 (d, J = 8.4 Hz, 2H), 7.35 (d, J = 8.4 Hz, 2H), 7.32−7.22 (m, 5H), 5.76 (s, 2H), 4.26 (dd, J = 10.1, 2.2 Hz, 1H), 3.78 (m, 1H), 3.67−3.57 (m, 3H), 3.49−3.36 (m, 8H), 2.77 (d, J = 11.9 Hz, 1H), 2.70 (d, J = 11.5 Hz, 1H), 2.36−2.24 (m, 8H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 167.9, 166.8, 165.1, 144.8, 136.4, 129.9, 129.9, 129.8, 128.7, 127.9, 126.4, 72.3, 72.0, 66.7, 66.4, 66.0, 62.0, 53.8, 52.4, 46.0, 42.1, 21.7; IR (KBr) 1129, 1225, 1243, 1648, 1722 cm^{-1}; MS (TOF) *m/z* 291.1701 (291.1703 calcd for $C_{16}H_{23}N_2O_3$, MH); Anal. Calcd for $C_{36}H_{40}N_2O_{11}$: C, 63.90; H, 5.96; N, 4.14. Found: C, 63.83; H, 5.95; N, 4.29; $[\alpha]^{20}_{589}$ −62.2 (*c* 0.1, EtOH); mp (DSC): 175.2 °C.

Preparation II. A 1-L flask was charged with the acid salt **10** (49.99 g, 190.1 mmol, 98% potency, 1 equiv) and THF (450 mL). Diisopropylethylamine (68 mL, 380 mmol, 2.0 equiv) and 1-propanephosphonic acid cyclic anhydride (T3P, 50 wt % soln in EtOAc, 137 mL, 230 mmol, 1.2 equiv) were added sequentially, with the T3P addition being followed by a THF rinse (50 mL). Morpholine (25.0 mL, 287 mmol, 1.5 equiv) was added, and the temperature rose to 48 °C. After 1.25 h at 22 °C, the mixture was partitioned between water (200 mL) and PhMe (50 mL), and the pH was adjusted from 4 to 8 with 5 N NaOH (73 mL). The layers were separated, and the aqueous layer was rinsed with PhMe (2 × 100 mL); the combined

organic layers were concentrated to 175 mL of volume on a rotary evaporator. The concentrate was diluted with 2-propanol (500 mL) and reconcentrated to 175 mL of volume. This was diluted a second time with 2-propanol (500 mL), and the resulting mixture was filtered through a Celite pad on a glass-fritted filter; the cake was rinsed with 2-propanol (100 mL). The filtrate was charged to a1-L flask with a 2-propanol rinse (75 mL), and the solution was heated to reflux. In a 500-mL Erlenmeyer flask a mixture of di-*p*-toluoyl-L-(−)-tartaric acid (DTTA, 37.66 g, 98% potency, 95.52 mmol, 0.5 equiv) and 2-propanol (200 mL) was heated to 70 °C on a steam bath to obtain a solution. The DTTA solution was poured into the refluxing solution of racemic amide followed by a 2-propanol rinse (50 mL). After stirring the resulting solution at reflux for 30 min, the solution was seeded with the (*S*)-(4-benzylmorpholin-2-yl)(morpholino)methanone di-*p*-toluoyl-L-(−)-tartrate product (3.2 mg), and a thick slurry resulted. After 2 h at reflux the heat was turned off, and the mixture was allowed to cool as it was stirred overnight. The mixture was filtered through Polypro backed with paper on a Büchner funnel, and the filter cake was rinsed with 2-propanol (150 mL) prior to drying in a 55 °C vacuum oven; 51.31 g (40%) of **13** was obtained as a white solid that was >99% ee by chiral HPLC analysis.

(*S*)-(4-Benzylmorpholin-2-yl)(tetrahydro-2H-pyran-4-yl)-methanone Methanesulfonate (1a). *(S)-(4-Benzylmorpholin-2-yl)(morpholino)methanone (12a).* A 2-L flask was charged with (*S*)-(4-benzylmorpholin-2-yl)(morpholino)methanone di-*p*-toluoyl-L-(−)-tartrate (**13**, 60.03 g, 88.71 mmol, 1 equiv), PhMe (390 mL), water (360 mL), and THF (180 mL). Solid Na_2CO_3 (28.2 g, 266 mmol, 3 equiv) was added in one portion, and the mixture was stirred at 23 °C for 1 h, during which time all the solids dissolved. The layers were separated, and the aqueous layer was extracted with PhMe (250 mL). The combined organic layers were washed with water (300 mL), after which they were concentrated to a volume of 90 mL. The concentrated solution was diluted with PhMe (300 mL) and was again concentrated to 90 mL of volume; this dilution/concentration was repeated one additional time, and the concentrated solution was finally diluted with PhMe to a mass of 103 g with a water content of 173 ppm. This solution was used as-is in the Grignard reaction, with an assumed quantitative yield of *S*-free base **12a** (25.74 g).

Grignard Reaction and Mesylate Salt Formation. A 500-mL flask was charged with Mg (3.31 g, 136 mmol, 1.54 equiv) and THF (180 mL). Iodine (118.2 mg, 0.465 mmol, 0.005 equiv) and diisobutylaluminum hydride (3.6 mL, 1 M soln in PhMe, 3.6 mmol, 0.04 equiv) were added, and the mixture was heated to 60 °C. After 45 min, 4-chlorotetrahydropyran (**8a**, 16.52 g, 137.0 mmol, 1.54 equiv) was added in portions; the first portion was 20% of the total, and there was a 2-h stir at 60 °C after that addition. The remaining 80% of the material was added in four equal portions with 45 min of stirring between each addition. When all the **8b** was added, the mixture was stirred at 60 °C for 1.5 h. The mixture was allowed to cool to 22 °C and was then further cooled to 15 °C. The PhMe solution of amide **12a** (25 wt %) from above was added dropwise over 1 h, keeping the temperature between 15 and 22 °C. When the addition was complete, the mixture was allowed to stir at 22 °C overnight. The resulting solution was added dropwise to a solution of HOAc (13.8 mL, 241 mmol, 2.7 equiv) and water (75 mL) at 2 °C. The addition took 40 min, and the temperature was kept below 10 °C. When the addition was completed, the mixture was allowed to warm to 22 °C, at which point the layers were separated. The organic layer was rinsed sequentially with water (120 mL), a solution of Na_2CO_3 (9.44 g, 89.1 mmol, 1 equiv) in water (90 mL), and water (120 mL). The organic layer was concentrated to a volume of 60 mL on a rotary evaporator, and this concentrated solution was diluted with 2-propanol (250 mL) before being concentrated back to 60 mL of volume. The concentrated solution was diluted to a volume of 235 mL and, after being transferred to a 500-mL flask, was heated to 70 °C. Methanesulfonic acid (8.51 g, 88.6 mmol, 1 equiv) was added in one portion. The solution was allowed to cool to 60 °C, during which time the salt precipitated. The slurry was maintained at 60 °C for 1 h, after which it was allowed to cool to 22 °C. After a 4-h stir, the slurry was filtered, and the cake was rinsed with 2-propanol (80 mL) before being dried in a 45 °C vacuum oven to provide the product **1a** as a fluffy, white, crystalline solid (30.47 g, 89% from **13**). The solid was determined to be >99% ee by chiral HPLC; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.52 (m, 2H), 7.44 (m, 3H), 4.45 (m, 2H), 4.37 (s, 2H), 4.12 (dd, J = 12.8, 2.6 Hz, 1H), 3.82 (m, 3H), 3.44 (m, 2H), 3.28 (m, 3H), 3.05 (m, 3H); 2.38 (s, 3H); 1.66 (m, 2H), 1.41 (m, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 207.6, 131.8, 130.2, 129.4, 76.1, 66.6, 66.5, 64.0, 60.0, 51.2, 50.6, 43.1, 27.9, 27.6; IR (KBr) 528, 553, 697, 1126, 1164, 1210, 1222, 1715 cm^{-1}; MS (TOF) *m/z* 290.1748 (290.1751 calcd for $C_{17}H_{23}NO_3$, MH); Anal. Calcd for $C_{18}H_{27}NO_6S$: C, 56.08; H, 7.06; N, 3.63. Found: C, 55.77; H, 7.09; N, 3.73; $[\alpha]^{20}_{589}$ 2.0 (*c* 0.1, EtOH); mp (DSC): 178.9 °C.

(*S*)-(4-Benzylmorpholin-2-yl)(tetrahydro-2H-pyran-4-yl)-methanone (*R*)-Mandelate (1c). *Free-Basing of 13.* A 3-L flask was charged with (4-benzylmorpholin-2-yl)(morpholino)methanone hydrochloride (200.01 g, 611.98 mmol, 1 equiv), EtOAc (1 L), and water (750 mL), and the mixture was stirred vigorously while Na_2CO_3 (87 g, 820 mmol, 1.3 equiv) was added in several portions. The resulting mixture was stirred for 1 h, and then the layers were separated. The aqueous layer was extracted with EtOAc (500 mL), the combined organic layers were rinsed with water (750 mL), and the resulting organic solution was concentrated to an oil on a rotary evaporator. The oil was dissolved in PhMe (600 mL), and this solution was concentrated to an oil that was finally diluted with PhMe to a total mass of 891.94 g; the concentration of amide **12** was 19.95 wt %.

Grignard Reaction with 4-Chlorotetrahydropyran (8a). The Grignard reaction was the same as that employing (*S*)-(4-benzylmorpholin-2-yl)(morpholino)methanone **12a** described above; this experiment used 430.04 g (295.47 mmol) of the solution prepared above and resulted in a solution of racemic (4-benzylmorpholin-2-yl)(tetrahydro-2H-pyran-4-yl)methanone, **1b**, and 2-propanol with a total mass of 246 g, theoretically containing 85.49 g of free-base (34.7 wt %).

Resolution with (R)-Mandelic Acid. The **1b** crude solution (34.7 wt %) from the Grignard reaction was transferred to a 1-L flask with a 2-propanol rinse (72 mL), and the solution

was heated to 50 °C. A solution of (*R*)-mandelic acid (44.99 g, 295.7 mmol, 0.48 equiv) and 2-propanol (232 mL) was added dropwise over 50 min, maintaining a pot temperature of 50−55 °C. When the addition was completed, the heating mantle was removed, and the solution was allowed to cool to 22 °C, during which time the salt precipitated. The mixture stirred at 22 °C overnight. The slurry was filtered through paper on a Büchner funnel, and the cake was rinsed with 2-propanol (50 mL) prior to being dried in a 45 °C vacuum oven. Obtained was 40.9 g (92.6 mmol, 31% from the free-base) of **1c** as a crystalline white solid. Chiral HPLC analysis on the solid showed it to be >99% ee; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.42 (m 2H), 7.28 (m, 8H), 5.01 (s, 1H), 4.10 (dd, J = 9.7, 2.6 Hz, 1H), 3.88 (dt, J = 11.5, 2.6 Hz, 1H), 3.81 (m, 2H), 3.58 (dt, J = 11.0, 2.6 Hz, 1H), 3.50 (d, J = 1.8 Hz, 2H), 3.30 (dt, J = 11.5, 2.2 Hz, 2H), 3.01 (tt, J = 11.5, 3.5 Hz, 1H), 2.83 (m, 1H), 2.60 (dd, J = 11.5, 1.3 Hz, 1H), 2.13 (dt, J = 11.5, 3.5 Hz, 1H), 2.00 (dd, J = 10.1, 1.3 Hz, 1H), 1.62 (m, 2H), 1.41 (m, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 210.4, 174.5, 140.7, 137.8, 129.4, 128.6, 128.5, 128.0, 127.5, 127.0, 79.3, 72.8, 66.7, 66.6, 66.4, 62.5, 54.1, 52.8, 42.7, 28.1, 27.9; IR (KBr) 504, 697, 735, 1088, 1707 cm^{-1}; MS (TOF) *m*/*z* 290.1748 (290.1751 calcd for $C_{17}H_{23}NO_3$, MH); Anal. Calcd for $C_{25}H_{31}NO_6$: C, 68.01; H, 7.08; N, 3.17. Found: C, 68.10; H, 7.11; N, 3.33; $[\alpha]^{20}_{589}$ −42.3 (*c* 0.1, EtOH); mp (DSC): 101.5 °C.

(*S*)-1-(4-Benzylmorpholin-2-yl)-3-methylbutan-1-one Methanesulfonate (14). A 250-mL round-bottom flask (RBF) was charged with THF (47 mL) and isobutylmagnesium chloride (18.0 mL of a 2.0 *M* solution in THF, 36.0 mmol, 1.22 equiv). The solution was cooled to 3 °C and a solution of (*S*)-(4-benzylmorpholin-2-yl)(morpholino)methanone (**12a**, 8.58 g, 29.6 mmol, 1 equiv) and PhMe (40 mL) was added dropwise over 1 h, maintaining a pot temperature between 0 and 10 °C. When the addition was completed, the brown solution was allowed to warm to 22 °C. After 2 h the solution was cooled back down to <10 °C, and a solution of HOAc (4.6 mL, 80 mmol, 2.7 equiv) and water (60 mL) was added dropwise, keeping the temperature below 10 °C. The layers were allowed to separate, and the organic layer was washed with a solution of Na_2CO_3 (3.14 g, 29.6 mmol, 1 equiv) and water (60 mL), followed by an additional wash with water (60 mL). The organic layer was then concentrated to an oil that was chromatographed (20% EtOAc/hexanes) to provide the pure product as a colorless oil (7.01 g, 26.8 mmol, 91%).

The oil was dissolved in 2-propanol (70 mL) in a 250-mL RBF. The solution was heated to 73 °C, and methanesulfonic acid was added in one portion causing an exotherm to 75 °C. The solution was allowed to slowly cool to between 40 and 45 °C where precipitation of the salt occurred. The temperature was held in this range for 1 h, and then the mixture was allowed to cool to 22 °C as it stirred overnight. The slurry was filtered through paper on a Büchner funnel, and the cake was rinsed with 2-propanol (20 mL). A large quantity of precipitate formed in the filtrate as it cooled, so the filtrate was poured back onto the filter and was refiltered followed by a 2-propanol rinse (10 mL). The solid was dried in a 45 °C vacuum oven to provide **14** as a white solid (8.35 g, 87%) that was shown to be 98% ee by chiral HPLC; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.52 (m, 2H), 7.44 (m, 3H), 4.37 (s, 2H), 4.28 (m, 1H), 4.10 (dd, J = 12.8, 3.1 Hz, 1H), 3.80 (t, J = 12.3 Hz, 1H), 3.42 (d, J = 12.3 Hz, 1H), 3.25 (d, J = 12.3 Hz, 1H), 3.03 (m, 2H), 2.45 (d, J = 6.6 Hz, 2H), 2.38 (s, 3H), 1.98 (hep, J = 6.6 Hz, 1H), 0.82 (d, J = 6.6 Hz, 3H), 0.81 (d, J = 6.6 Hz, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 206.3, 131.8, 130.2, 129.3, 77.3, 63.9, 60.0, 51.1, 50.5, 47.1, 23.4, 22.7; IR (KBr) 528, 552, 697, 1153, 1221, 1461, 1715 cm^{-1}; MS (TOF) *m*/*z* 262.1800 (262.1802 calcd for $C_{16}H_{24}NO_2$, MH); Anal. Calcd for $C_{17}H_{27}NO_5S$: C, 57.12; H, 7.61; N, 3.92. Found: C, 57.44; H, 7.68; N, 4.08; $[\alpha]^{20}_{589}$ 60.0 (*c* 0.1, EtOH); mp (DSC): 163.0 °C.

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Supporting Information Available

^{1}H NMR, ^{13}C NMR, DSC, and mass spectrometry data for compounds **1a**, **1c**, **10**, **13** and **14**; X-ray crystallographic data for **1a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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