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A "Bottom-Up" Approach to Process Development: Application of Physicochemical Properties of Reaction Products toward the Development of Direct-Drop Processes

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Abstract:

The "bottom-up" approach to development of direct-drop processes is a powerful, yet simple, strategy that every process chemist should consider for the development of efficient, cost-effective, and environmentally friendly processes. This approach is aided by a "parallel crystallization" technique, which allows for rapid identification of multiple solvent systems for the crystallization of the desired product using a minimal amount of material and solvent. This "bottom-up" approach is illustrated by several examples where the desired product is crystallized directly from the reaction mixture.

Introduction

Traditionally, a synthetic organic chemist thinks about a chemical step in a linear sequence from reaction to work-up (isolation) to purification. The chemist tends to focus more on "how to conduct the reaction" than on "how to work-up and isolate the product", because the chemical reactions are often performed on relatively small scales where after work-up, the product is typically purified by distillation or chromatography. In an industrial setting, however, since a significant portion of the cost of drug substance stems from the costs of capital, labor, and waste disposal, it is important to develop not only safe and robust reaction conditions, but also efficient and environmentally friendly work-up and isolation procedures.[1]

We describe herein a strategy, termed the "bottom-up" approach, which addresses these process development issues by focusing on the reaction, work-up, and isolation as an integrated whole. This approach relies on first gathering information on the physicochemical properties of reaction product(s), such as solubility and crystallization characteristics of the reaction product and by-products, and then using this information to define reaction, work-up, and purification conditions. The approach often leads to one-pot processes where the product is isolated by crystallization directly from the reaction mixture (direct-drop processes). This "bottom-up" approach offers several advantages: (1) reduction in the number of unit operations, (2) reduction in cycle-time, (3) reduction in solvent usage, (4) reduction in organic and aqueous waste, and (5) reduction in cost. We recommend using this approach soon after route selection and well in advance of any scale-up operations.

The "Bottom-up" Strategy

Figure 1 outlines the steps of this strategy. A few grams of the desired product are prepared by any available method. Purified starting materials and product are used to generate linearity curves (concentration vs area counts) by HPLC or GC. The solubility of the starting materials, product, and by-products are determined. Attempts are made to identify several crystallization solvent systems for the product. The reaction solvent(s) and solvents for work-up and isolation are then chosen on the basis of the solubility data of the starting material, product, by-products, and the crystallization data of the product. The solvent (or solvent system) of choice is generally the one in which the starting materials, reagents, and by-products are very soluble, but the product is not. Finally, the protocol is tested and fine-tuned by an iterative process until it is optimized.

Since the "bottom-up" strategy relies on finding suitable solvent systems for the crystallization of the product, a systematic approach to rapid screening of crystallization systems is necessary. This can be achieved by a "parallel crystallization" technique. This technique allows for the identification of multiple solvent systems for crystallization, using a minimal amount of material with minimal effort.

The "Parallel Crystallization" Technique

There are two types of nucleation, which generally precede crystallization.[2] Primary nucleation occurs with formation of clusters of molecules at the submicrometer level. When the concentration exceeds saturation (supersaturation), the clusters become nuclei. Secondary nucleation is caused by particles resulting from primary nucleation (or seeds) which helps to initiate crystallization.

There are many strategies to achieve supersaturation leading to crystallization, including cooling, evaporation, and addition of an anti-solvent (nonsolvent). On a small scale, it is difficult to control the rate of cooling or the rate of evaporation, but the addition of an anti-solvent in combination with seeding can be done easily to achieve supersaturation and then to initiate crystallization. Since these experiments can be done in parallel on a test-tube scale, one

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(1) Anderson, N. G. *Practical Process Research & Development*; Academic Press: San Diego, California, 2000.

(2) Mohan, R.; Boateng, K. A.; Myerson, A. S. *J. Cryst. Growth* **2000**, *212*, 489 and references therein.

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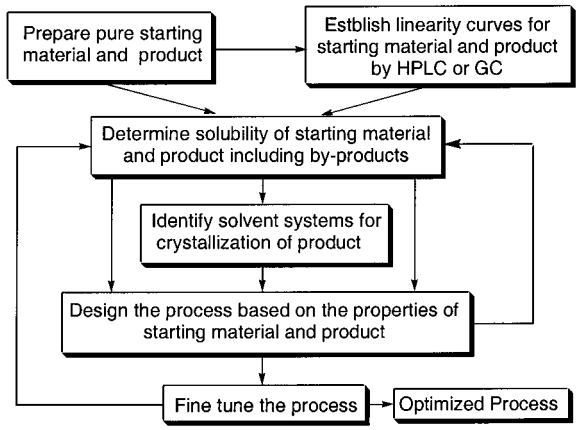


Figure 1. **The "bottom-up" process development strategy.**

can rapidly identify multiple crystallization systems. This anti-solvent addition strategy is termed the "parallel crystallization" technique.

Since impurities can interfere with crystallization, the first step in applying this technique is to prepare a sufficient amount of high quality product (ca. 400 mg). Salts of a product having an acid or amine functionality are best prepared by dissolving the pure product and the counter base (or acid) separately in appropriate solvents, mixing the two solutions in equimolar ratio and then removing solvents under vacuum to afford a solid. This method of preparation of the salts has two distinct advantages. First, the composition of the substrate remains the same during various crystallization attempts, and second, this portion of the work can be automated with the use of liquid handling systems.

The second step of this technique is to determine the solubility of the product (or its salts) in different solvents. Those solvents, which could potentially react with the substrate, are eliminated from the test. The solubility can be determined qualitatively by dissolving a known amount (ca. 10 mg) of material in a minimum amount of solvent. Or, if a well characterized product standard is available, then the absolute solubility can be determined by making a saturated solution of the material in a known volume of solvent and then determining the concentration by comparing against the product standard curve (concentration vs HPLC or GC area counts).

The third step of this technique is to identify solvent system(s) for crystallization of a given product (or its salts). It is best illustrated by the following generic example. The circles in Figure 2 represent various test tubes and the letters within these circles represent the following:

I = insoluble, S = soluble, Δ = heat (ca. 50 °C), CR = crystals, PPT = precipitate, OIL = oiling, Open Circles = no solid observed or not attempted.

In this example, the first row contains results of the solubility test. The substrate is insoluble in water, methyl *tert*-butyl ether (MTBE), and heptane. It is soluble in MeOH, EtOH, acetone, and tetrahydrofuran (THF) and dissolves in 2-propanol (IPA) and ethyl acetate (EtOAc) upon heating. The second row shows that upon cooling and seeding, the product crystallized out from IPA and EtOAc. This row provides information on crystallization from unitary systems.

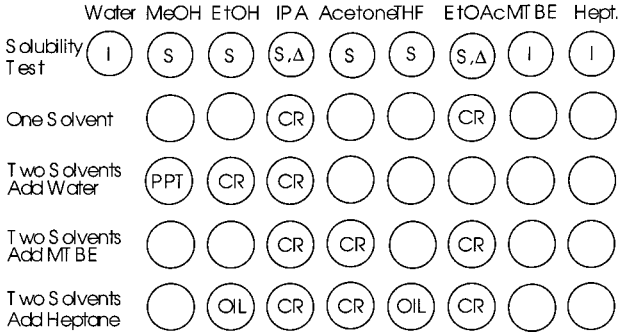


Figure 2. **Parallel crystallization pallet.**

The third row indicates that upon addition of the anti-solvent water to the test tubes containing water-miscible solvents, precipitation occurred in one case, and crystallization occurred in two cases. This row offers two aqueous binary solvent systems for crystallization. The fourth row contains results from the addition of the anti-solvent MTBE to the test tubes containing MTBE miscible solvents. Crystallization is observed in three cases. Similarly, when heptane is added (fifth row), crystallization is observed in three cases and oiling occurred in two cases.[3]

The above generic example serves to illustrate the fact that by using the "parallel crystallization" technique; one can identify several solvent systems for crystallization of the product very quickly and then use this information in the "bottom-up" strategy to develop direct-drop processes. If applied to the final step, this "parallel crystallization" technique can provide understanding of the polymorphic nature of the final drug substance and help identify solvent systems to control the formation of the desired polymorph. It can also provide very useful information on the shape and size of the crystals, which can be used to improve the filtration characteristics of the crystal slurry.

There is another crystallization technique, which can be used when isolation of a very water-soluble compound in its salt form is required from aqueous reaction mixtures. This technique takes advantage of the common-ion effect and is based on the Le Chatelier's principle.[4] Thus, in aqueous solutions, the solubility of the compound in salt form can be decreased by adding large amounts of a common-ion which is more soluble than the salt of the compound.

Application

The following examples serve to illustrate the "bottom-up" strategy and the two types of crystallization techniques.

Example 1. *Change of Reaction Solvent.* In this example, the preparation of amide **3** via coupling of the arylamine **2** with acyl chloride **1** was initially done in *N*,*N*-dimethylacetamide (DMA) (Scheme 1). After the reaction was complete, the mixture was quenched into water to precipitate

(3) Oiling or heavy precipitation may be prevented by either working at slightly lower product concentration or by identifying three-solvent systems for crystallization. The third solvent is selected on the basis of the dielectric constant and solubility characteristics of the substrate in the third solvent.

(4) Le Chatelier's principle states that, "if, to a system in equilibrium, a stress is applied, the system will react so as to relieve the stress". (a) Thomsen, V. E. *J. Chem. Educ.* **2000**, *77*, 173. (b) Raviolo, A. *J. Chem. Educ.* **2001** *78* 629.

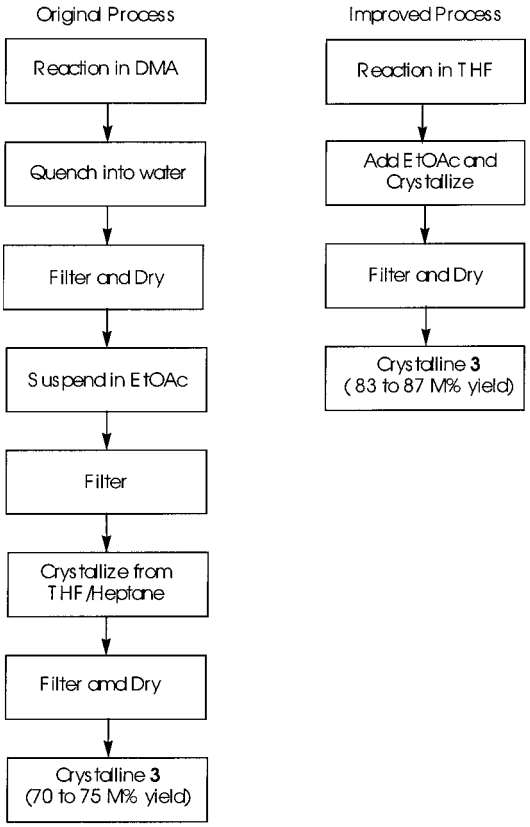
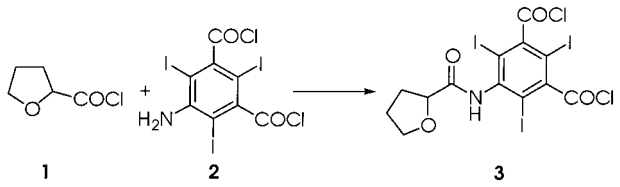


Figure 3. **Original and improved processes for the preparation of 3.**

Scheme 1



the product. The product was filtered, washed, and dried. It was suspended in EtOAc and filtered to remove residual DMA and some impurities. This material was then crystallized from THF/heptane to give pure **3** in 70−75% yields. This process was lengthy and inefficient, used four solvents and three filtrations (two were extremely slow), and generated large amounts of organic and aqueous waste.[5]

On the basis of the "bottom-up" strategy, the solubilities of the starting material **2** (**1** is a liquid) and the product **3** in various solvents and solvent combinations were determined. Using the "parallel crystallization" technique, solvent systems for the crystallization of product were studied. The best crystallization solvent systems were THF/heptane and THF/EtOAc. On the basis of the solubility and crystallization data, THF was chosen as the solvent for the coupling reaction. For the crystallization of the product, EtOAc, instead of heptane (used in the original process), was employed. The one-pot process (Figure 3) required only one filtration, reduced waste streams by more than 80%, shortened the

(5) Merinelli, E.; Arunachalam, T.; Diamantidis, G.; Emswiller, J.; Fan, H.; Neubeck, R.; Pillai, K.; Wagler, T.; Chen, C.-K.; Natalie, K.; Soundararajan, N.; Ranganathan, R. *Tetrahedron* **1996**, *52*, 34, 11177.

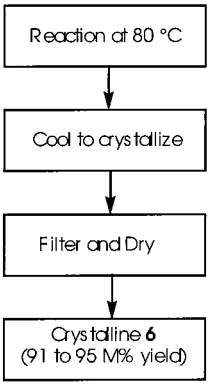
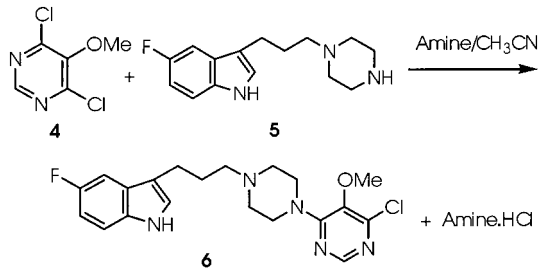


Figure 4. **One-pot process for the preparation of 6.**

Scheme 2



processing time by more than 50%, and afforded product in higher yields (83−87%). This process was implemented in the pilot plant to make several hundred kilos of **3**.

Example 2. *Selection of Appropriate Reaction Solvent and Amine.* On the basis of the solubility of the starting materials and crystallization characteristics of the product, acetonitrile was chosen as the solvent for the coupling reaction of **4** with **5** and for the crystallization of **6** (Scheme 2).[6] Since the coupling reaction could be done in the presence of any amine base, it was necessary to identify a base whose corresponding hydrochloride salt would be soluble in acetonitrile to enable development of a direct-drop process. Several amine hydrochloride salts were made, and their solubility in acetonitrile was determined. Diisopropylethylamine hydrochloride (DIPEA·HCl) salt was found to be very soluble in acetonitrile. Therefore, DIPEA was chosen as the base for the reaction. This process (Figure 4) afforded product in 91−95% yield with an HPLC area percent of >99.[7]

Example 3. *Selection of Mixed Solvents for the Reaction and Crystallization.* This simple hydrolysis of methyl ester **7** and isolation of the drug substance ifetroban sodium **8** (Scheme 3) originally required extensive work as shown in Figure 5 (Process A).[8]

In the second generation of this process (Process B, Figure 5) the intermediate isolation of the free acid **9** was eliminated. The dichloromethane solution of free acid was exchanged

(6) Although acetonitrile is not a preferred solvent from environmental and cost points of view, it was selected in this example because it offered unique opportunities to simplify the overall process.

(7) Anderson, N. G.; Ary, T.; Berg, J.; Bernot, P.; Chan, Y.; Chen, C.-K.; Davies, M.; DiMarco, J.; Dennis, R.; Deshpande, R.; Do, H.; Droghini, R.; Early, W.; Gougoutas, J.; Grosso, J.; Harris, J.; Haas, O.; LaJeunesse, J.; Lust, D.; Madding, G.; Modi, S.; Moniot, J.; Nguyen, A.; Palaniswamy, V.; Phillipson, D.; Simpson, J.; Thoraval, D.; Thurston, D.; Tse, K.; Polomski, R.; Wedding, D.; Winter, W. *Org. Process Res. Dev.* **1997**, *1*, 300.

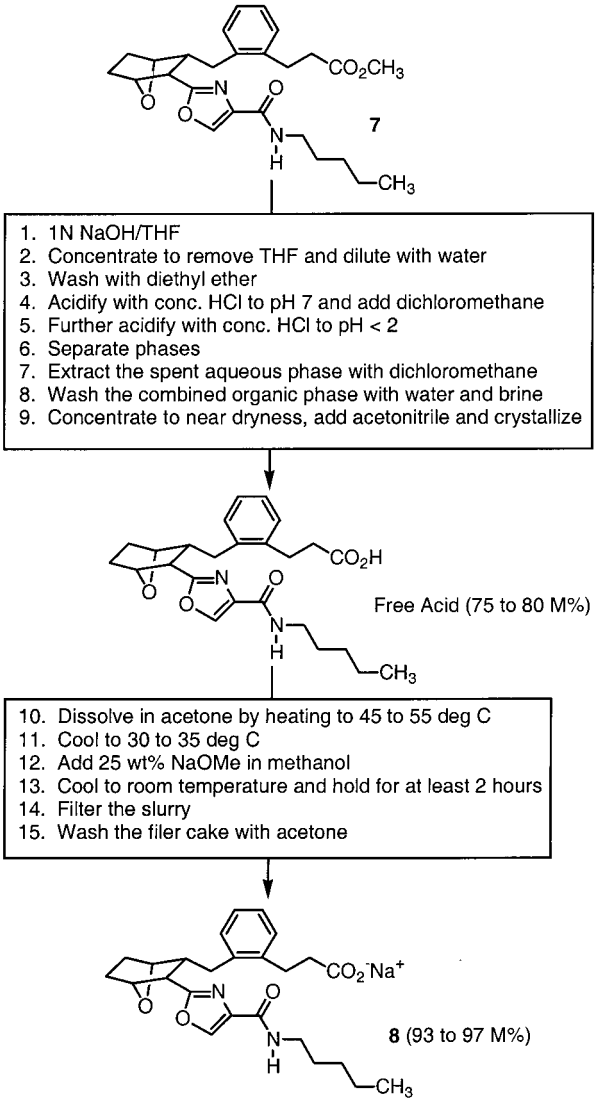
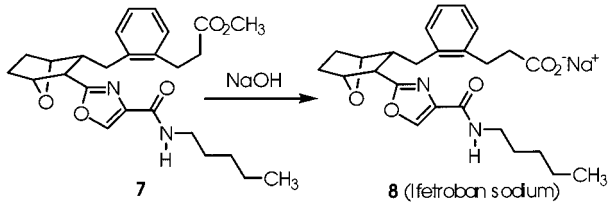


Figure 5. **Process A for the preparation of 8. In Process B, steps 3 and 9 were eliminated.**

Scheme 3



into acetone, and the rest of the processing remained the same as Process A. Processes A and B did not incorporate the "direct-drop" approach to isolate the product. To make this process a true one-pot (direct-drop) process, we needed to crystallize **8** directly from the hydrolysis reaction mixture. The major obstacles were the limited solubility of NaOH in the reaction solvent and the amount of water required for the hydrolysis reaction to go to completion.

(8) (a) Mueller, R. M. A Practical Synthesis of Ifetroban Sodium. In *Process Chemistry in the Pharmaceutical Industry*; Gadamasetti, K. G., Ed.; Marcel Dekker: New York, 1999; p 37. (b) Mueller, R. H.; Wang, S.; Pansegrau, P.; Jannotti, J.; Poss, M.; Thottathil, J.; Singh, J.; Humora, M.; Kissick, T.; Boyhan, B. *Org. Process Res. Dev.* **1997**, *1*. 14. (c) Swaminathan, S.; Singh, A. K.; Li, W.-S.; Venit, J.; Natalie, K., Jr., Simpson, J.; Weaver, R.; Silverberg, L. *Tetrahedron Lett.* **1998**, *39*, 4769.

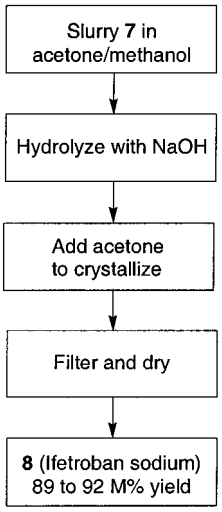


Figure 6. **Process C: One-pot process for the preparation of 8.**

Table 1. **Comparison of Processes A, B, and C for the preparation of 8**

process	A	B	C
total time	>7 days	4 days	40 h
overall yield	76−83 mol %	86−94 mol %	89−92 mol %
HPLC purity	98.3−99.5	97.8−99.7	98.5−99.4
heating or cooling	yes	yes	no
distillation	yes	yes	no
phase splits	6	5	0
solvents used	MeOH, acetone, THF, EtOEt, CH_3CN, CH_2Cl_2	MeOH, acetone, THF, MTBE, CH_2Cl_2	MeOH, acetone
aqueous waste	39 L/kg	19 L/kg	none
organic waste	>100 L/kg	>100 L/kg	37 L/kg

Using the "parallel crystallization" technique, several one and two-solvent systems were identified for the crystallization of **8**. Attempted reaction and crystallization from single-solvent systems in the presence of varying amounts of water did not lead to success. Either the hydrolysis reaction did not go to completion, or, the isolated product was contaminated with NaOH. Binary solvent systems showed more promising results. The hydrolysis reaction went well when conducted in acetone/methanol (12:1) with 10 wt % NaOH in water/methanol (1:2). The product was simply crystallized by addition of more acetone. This direct-drop approach (Figure 6, Process C) afforded product of high quality in 89−92% yields. The advantage of this new process is elucidated in the comparison Table 1.

The following examples 4 and 5 illustrate the "bottom-up" approach by applying the principle of "common-ion effect" in crystallizing water soluble product directly from the aqueous reaction mixture (salting-out).

Example 4. *Change of Reaction Solvent to Water and Adjustment of pH to Induce Crystallization.* The disodium salt **11**, which was found to be extremely water soluble, was chosen as the final crystal form.[9] Initial reaction, work-up, and isolation conditions are shown in Figure 7.

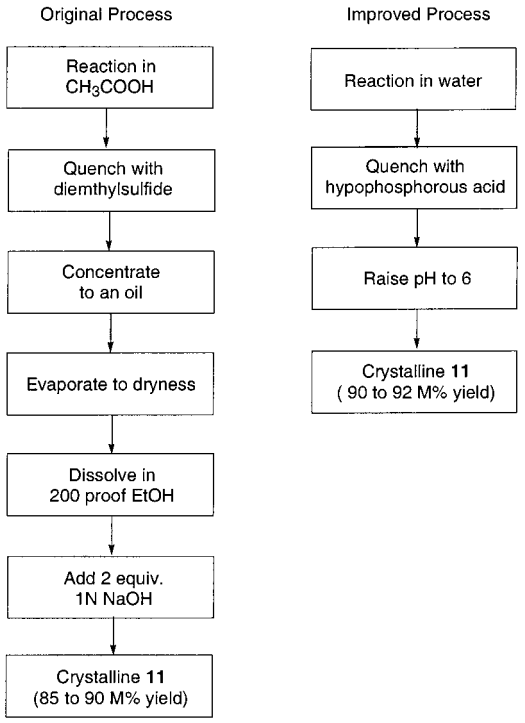
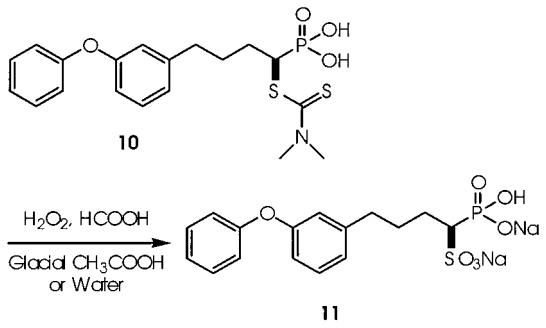


Figure 7. **Original and improved processes for the preparation of 11.**

Scheme 4



To develop a direct-drop process using the principle of "common-ion effect", it was necessary to know the pK_a of the mono-, di- and trisodium salts. These were determined by potentiometric titration. The pK_a of the disodium salt was 6 and that of the mono- and trisodium salts were <3 and 10, respectively. Since the salting out protocol for crystallization works most effectively in aqueous systems (the presence of organic solvents reduces the solubility of the salt), water was evaluated as a potential solvent for the oxidation reaction. The oxidation reaction worked well in water, and glacial acetic acid was replaced with water (Scheme 4). The use of dimethyl sulfide to quench the excess hydrogen peroxide generated DMSO, which interfered with the crystallization of product. Other reducing agents were evaluated, and dimethyl sulfide was effectively substituted with 50% aqueous hypophosphorous acid. With the new reaction solvent and quench, the product was crystallized directly from the reaction mixture simply by adjusting the pH. To optimize

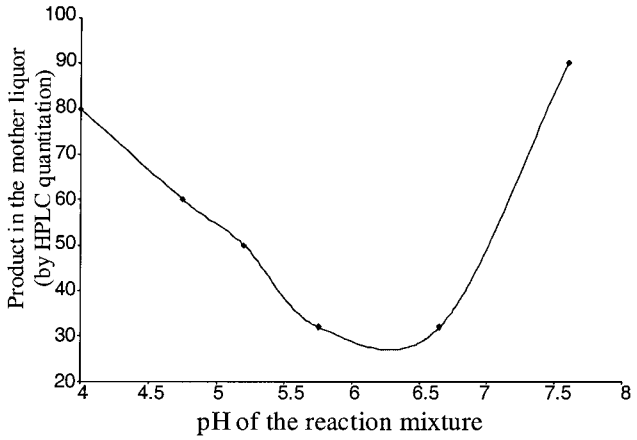
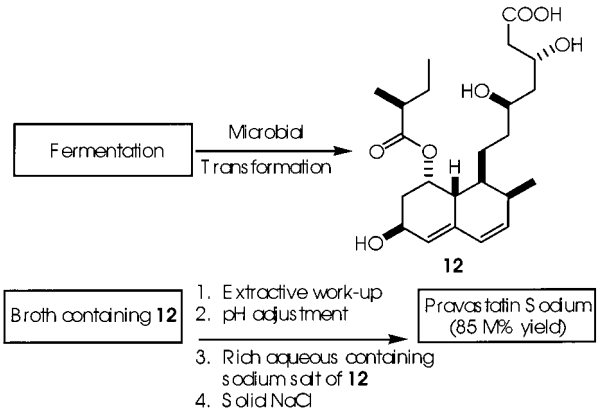


Figure 8. **Effect of pH on the mother liquor loss of 11.**

Scheme 5



the yield of product from this direct-drop process, the effect of pH on the yield of product was studied (Figure 8). The disodium salt began to crystallize out at as low pH as 4; however, the mother liquor loss at pH 4 was very high. The loss was minimal between pH 6.05 and 6.25. Beyond pH 6.25, the mother liquor loss began to increase again due to formation of the trisodium salt, which was more soluble than the disodium salt. Between pH 6.05 and 6.25, the sodium salts of formic, hypophosphorus, and phosphoric acids were present in high enough concentration to help lower the solubility of **11**. The modified process is shown in Figure 7.

Example 5. *Isolation from Fermentation Broth: Use of NaCl to Induce Crystallization.* The cholesterol-lowering drug, Pravachol (pravastatin sodium) is produced by microbial transformation.[10] The sodium salt of **12** was extracted into water from the fermentation broth through a series of extractions and pH adjustments. Due to the extremely high solubility of pravastatin sodium in water, it could not be extracted from water using common organic solvents. However, by employing the common-ion effect principle, the sodium salt could be easily crystallized from water. To accomplish this, the pH of the aqueous solution was adjusted to the desired pH, and the aqueous solution was cooled. The solution was saturated with NaCl and stirred for several hours

(9) Lawrence, M. R.; Biller, S. A.; Dickson, J. K., Jr.; Logan, J.; Magnin, D.; Sulsky, R.; DiMarco, J.; Gougoutas, J.; Beyer, B.; Taylor, S.; Lan, S.-J.; Ciosek, C., Jr.; Harrity, T.; Jolibois, K.; Kunselman, L.; Slusarchyk, D. *J. Am. Chem. Soc.* **1996**, *118*, 11668.

(10) (a) Jekkel, A.;Konya, A.; Barta, I.; Ilkoy, E.; Somogye, G.; Ambrus, G.; Horvath, G.; Albrecht, K.; Szabo, I.; Mozes, J.; Salat, J.; Andor, A.; Birincsik, L.; Boros, S.; Lang, I.; Bidlo, M. PCT Int. Appl. WO0046175, 2000. (b) Takano, Y.; Hasegawa, M.; Mori, H.; Ando, K.; Ochiai, K.; Motoyama, H.; Ozaki, A. PCT Int. Appl. WO9907872, 1999.

to crystallize pravastatin sodium. Recrystallization from an appropriate solvent system afforded the product in the desired crystal form (Scheme 5).

Conclusions

The usefulness of the bottom-up approach to development of direct-drop processes is illustrated by five examples. This approach, in conjunction with the "parallel crystallization" technique, can help define efficient, rugged, and environmentally friendly direct-drop processes.

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