Separation Science and Technology
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713708471

Compound Separation by Cyclic, Selective Dissolution. Isolation of Diastereomeric, 1β-Methylcarbapenem Key Intermediates

Dean R. Bender[a]; Anthony M. Demarco[a]; James A. McCauley[a]
[a] DEPARTMENT OF PROCESS RESEARCH AND DEPARTMENT OF ANALYTICAL RESEARCH MERCK RESEARCH, LABORATORIES DIVISION OF MERCK & CO., INC., RAHWAY, NEW JERSEY

To cite this Article Bender, Dean R. , Demarco, Anthony M. and McCauley, James A.(1993) 'Compound Separation by Cyclic, Selective Dissolution. Isolation of Diastereomeric, 1β-Methylcarbapenem Key Intermediates', Separation Science and Technology, 28: 5, 1169 — 1176

To link to this Article: DOI: 10.1080/01496399308018027

URL: http://dx.doi.org/10.1080/01496399308018027

SEPARATION SCIENCE AND TECHNOLOGY, 28(5), pp. 1169–1176, 1993

Compound Separation by Cyclic, Selective Dissolution. Isolation of Diastereomeric, 1β-Methylcarbapenem Key Intermediates

DEAN R. BENDER,* ANTHONY M. DEMARCO,*
and JAMES A. MCCAULEY

DEPARTMENT OF PROCESS RESEARCH AND DEPARTMENT OF ANALYTICAL RESEARCH
MERCK RESEARCH LABORATORIES
DIVISION OF MERCK & CO., INC.
P.O. BOX 2000, RAHWAY, NEW JERSEY 07065

Abstract

A practical method for separation of the methyl esters of two diastereomeric, α-methylated, 2-azetidinon-4-ylacetic acid derivatives by selective dissolution using two solvents in which their relative solubilities are distinctly different is described. The less soluble diastereomer was first isolated from isopropanol in which the solubility of the more soluble diastereomer is 1.65 times that of the less soluble diastereomer. The more soluble diastereomer was then isolated from the mother liquor after a solvent switch to toluene in which the solubility of the more soluble diastereomer is only 1.15 times that of the less soluble diastereomer. The isolation cycle was then repeated to separate more of the diastereomers. This method is particularly useful for isolation of the *more* soluble component. A proposed explanation of the solubility differences suggests that the approach may be widely applicable to the separation of other structurally similar compounds.

INTRODUCTION

High yield separation of structurally similar compounds to produce each component in high purity is frequently accomplished by chromatography (*1*), fractional crystallization (*2*), and direct crystallization (*3*). While these methods can be practical on a large scale, development and/or equipment requirements often make them unattractive for the more routine, "medium-scale" separation problems frequently encountered during product and synthesis development.

---

*To whom correspondence should be addressed.

We report a practical separation which exploits differences in relative solubilities of two compounds in different solvents and which requires only normal batch processing equipment (*4*). While this approach is sometimes used to separate structurally *dissimilar* compounds, its potential for practical separation of structurally *similar* compounds does not seem to be widely appreciated. Indeed, for diastereomeric salts it has been said "that the nature of the solvent has only a small effect on the *ratio* of solubilities of the two diastereomers, except in the case of differential solvation" (*5*). We show in this article that changing the nature of the solvent can change the ratio of diastereomer solubilities to an extent large enough to be useful. A process of the type described here would in some cases be an attractive alternative to a schematically similar process, extractive crystallization (*6*), which employs crystallization from a melt to isolate one component of a mixture and crystallization from solvent to isolate the other. There are only a few commercial applications of extractive crystallization (*6b*). In practice, multiple purification stages are often required (*6b*). The process would not be practical for high melting compounds, and it also would not be suitable for compounds which are unstable at their melting points.

Our motivation for devising this approach stemmed from the need to produce quantities of the β-methyl compound **2** (Fig. 1), a key intermediate for synthesis of the pharmaceutically important 1β-methylcarbapenems **4** (Fig. 1) (*7*). Early methods for methylation of **1** and epimerization of **3** allowed large-scale production of mixtures of β-methyl **2** and the α-methyl diastereomer **3** with isolated isomer ratios [**2**(β)/**3**(α)] ranging from 1/2 (methylation) to 3/2 (epimerization) (*8*). However, separation of these

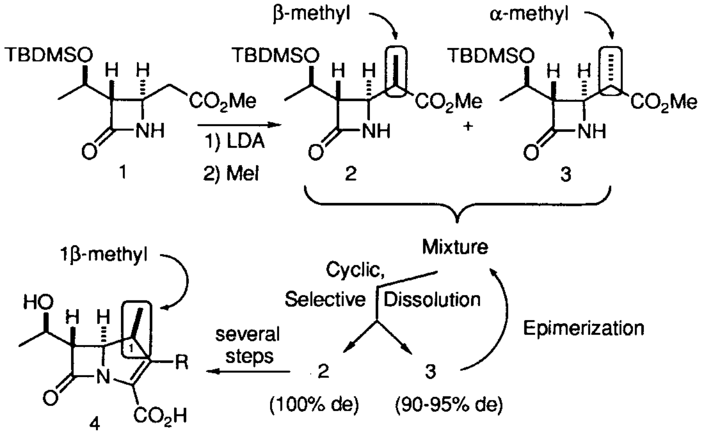

FIG. 1. Synthetic sequence for 1β-methylcarbapenems.

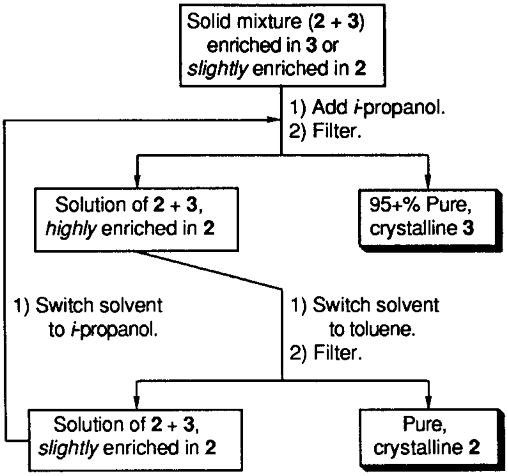

FIG. 2. Illustration of cyclic, selective dissolution.

compounds by chromatography was not practical. Thus, the approach described below was developed. Figure 1 illustrates the role of this separation method in the overall synthetic sequence, while Fig. 2 illustrates the method. We later developed a stereoselective synthesis of **2** suitable for large scale (*9*).

EXPERIMENTAL

General

Mixtures of **2** and **3** were prepared as described in Section D of Reference *9*. Reagent-grade solvents from commercial suppliers were used as is. HPLC assays for **2** and **3** are described in Reference *9*. X-ray powder diffraction was carried out with a Phillips system (APD 3200). Slurries were mechanically stirred under N_2. Batch temperatures were maintained within 0.5°C of the given temperatures with a controlled temperature circulating bath. Solvent evaporations and exchanges ("flushes") were carried out *in vacuo*.

Solubility measurements were carried out by mechanically shaking mixtures of solid and solvent in glass ampules in a constant temperature bath. The solids were allowed to settle; then the mother liquor was drawn off through a cotton plug, weighed, and evaporated. Amounts of **2** and **3** in the weighed residue were determined by HPLC assay against external standards.

Cyclic, Selective Dissolution

A solid mixture (9.21 kg), resulting from methylation (*8*) of **1** and containing 6.04 kg of α-methyl **3** and 3.02 kg of β-methyl **2** (by HPLC assay), was mixed with isopropanol [IPA, 14.35 L (4.75 mL/g of **2**)]. The resulting slurry was stirred and heated at 40°C for 1 h, cooled over 3 h to 20°C, held at 20°C for 14 h, and then filtered. The solid was washed with IPA/water (3/2, v/v, 3 × 1.5 L), suction-air dried (1 h), then dried in an air-flow oven at 45–50°C, yielding 4.32 kg of **3** having an isomer composition (**3**/**2**) of 96/4 (HPLC assay).

The mother liquor and the first two washes (the third wash was rich in **3** and saved for a later isolation of **3**) were combined, evaporated to a thick slurry, flushed with toluene (5 × 2 L), then weighed and assayed to determine the amounts of **2** (2.67 kg), **3** (1.68 kg), and residual toluene [gross weight minus (**2** + **3**)]. The toluene slurry was diluted with additional toluene [10.43 L (6.20 mL/g of **3**) minus residual in slurry] while keeping the batch temperature below 25°C. The slurry was stirred at 25°C for 14 h and then filtered. The solid was washed with hexane/toluene (80/20, v/v, 3 × 300 mL) followed by hexane (300 mL) and then dried as described for isolation of **3** to yield 587 g of **2** with a wt% purity of 99+% (HPLC assay).

The mother liquor and the first two washes (the last two washes were rich in **2** and saved for a later isolation of **2**) were evaporated to a thick slurry, flushed with IPA (5 × 2 L), weighed and assayed to determine the amounts of **2** (1.91 kg), **3** (1.62 kg), and residual IPA. The slurry was diluted as described above [IPA added equals 9.07 L (4.75 mL/g of **2**) minus residual IPA in slurry] while keeping the batch temperature below 20°C. To this slurry was added more of the original mixture (2.775 kg of **3**; 1.387 kg of **2**) followed by more IPA (6.59 L). This slurry was treated as described before for the isolation of **3** to yield 2.47 kg of **3**, again with an isomer composition (**3**/**2**) of ~96/4. Additional **2** was isolated from the filtrate and washes in the same manner as described for the first isolation of **2**.

In this series of isolations, the slurries were filtered without determining whether optimum distribution of **2** and **3** had been achieved. To "fine tune" yield and purity for each half cycle, a small aliquot (e.g., 10 mL) of slurry can be removed using a wide-bore pipette and filtered as described for the main batch (except that the mother liquor is kept separate from the washes). HPLC assay of the washed solid and the mother liquor will indicate the solid purity and isomer ratio in the mother liquor. Product distribution between the solid and liquid phases can then be adjusted by slightly raising or lowering the temperature of the slurry.

RESULTS AND DISCUSSION

The isolation sequence (Fig. 2) begins with selective dissolution of all of β-methyl **2** and some of α-methyl **3** from a solid mixture (enriched in **3** or slightly enriched in **2**) into isopropanol (IPA), in which the solubility of β-methyl **2** is 1.65 times that of the α-methyl diastereomer **3**. After filtration of the undissolved portion of **3**, the solvent of the resulting mother liquor is removed and replaced with toluene. Now, with the solubility of **2** only 1.15 times that of **3**, the amount of toluene is adjusted to the minimum required to dissolve the low levels of α-methyl **3**. With **3** and 70% of **2** dissolved in toluene, the undissolved portion of β-methyl **2** can be isolated by filtration. At this point the resulting mother liquor is slightly enriched in **2** ($\beta/\alpha \approx 1.15$). After solvent exchange back to IPA, another isolation cycle can be carried out to produce additional but obviously reduced amounts of **2** and **3**. Alternatively, more solid mixture can be added to maintain a constant batch size. An excellent toluene/IPA azeotrope facilitates the solvent exchanges and allows the isolation cycles to be conveniently carried out without ever having to evaporate mother liquors to dryness. We have used this cyclic, selective dissolution process, coupled with epimerization of isolated α-methyl **3**, to produce multikilogram quantities of pure β-methyl **2** for use in making the pharmaceutically important 1β-methylcarbapenems **4** (7).

Isolation yield depends on solubility ratios according to Eq. (1) [α = α-methyl **3**, β = β-methyl **2**, and S = solubility]:

$$Y_n = 1 - R^n \tag{1}$$

where Y = yield of available β ($Y = 1$ corresponds to 100% yield)
n = number of cycles where one cycle is two isolations (α from isopropanol; β from toluene)
$R = \dfrac{(S_\beta/S_\alpha)\text{ in toluene}}{(S_\beta/S_\alpha)\text{ in isopropanol}}$

From this equation it is clear that only two cycles are necessary to separate ~50% of the mixture. The number of cycles required to give a specific yield is described by Eq. (2). These equations clearly hold only if additional mixture is not added. Adding more mixture would start a new cycle count.

$$n = \frac{\log(1 - Y_n)}{\log R} \tag{2}$$

The discovery of this method began with conventional considerations. We first confirmed that the desired β-methyl **2** was, unfortunately, more soluble than **3** in solvents then considered suitable for isolation by crystallization (e.g., hexanes). Also, pure **2** could not be crystallized from mother liquors enriched in **2**. *Relative* solubilities of the pure isomers in cyclohexane were then found to change as a function of temperature—i.e., S_β/S_α was 1.5 at 50°C, 1.35 at 25°C, and 1.17 at 5°C. This suggested the possibility of isolating **3** at the higher temperature, then **2** at the lower temperature. But when this possibility was tested on mixtures of the isomers, the temperature dependence was reduced to an extent which made the approach unusable. When solubilities of each diastereomer were measured in cyclohexane in the presence of the other, the solubility of each isomer not surprisingly increased, and the solubility ratio (S_β/S_α) decreased. As other solvents were surveyed, two significant trends were then noted. The magnitude of the solubility increase for the isomers in a mixture versus pure was highly solvent-dependent—e.g., the sum of the solubilities for each isomer in a mixture versus pure doubled in cyclohexane, but increased only 17% in IPA. More importantly, the magnitude of the decrease in S_β/S_α on going from pure isomers to mixed isomers paralleled the change in total solubility. For example, S_β/S_α dropped from 1.32 to 1.16 in cyclohexane while in IPA the ratio dropped to a lesser extent (1.72 to 1.65). This effect increased the *difference* in relative solubility to an amount which was large enough to be considered useful.

More solvents were then surveyed with the goals of reducing even further the value of R in Eq. (1) and finding a pair of solvents which provided solubilities of **2** and **3** in a range convenient for large-scale isolations. Solubilities in cyclohexane at 20–25°C were much too low, but toluene provided a 10-fold increase and a slightly improved solubility ratio (S_β/S_α = 1.15). Acetonitrile, dimethoxyethane, and ethyl acetate/hexanes gave ratios of 1.21, 1.16 and 1.25, respectively, but the branched ether, methyl *tert*-butylether, gave a higher ratio (1.4). Alcohols provided the highest ratios, but, of those tried, none were better than the branched alcohol, IPA (S_β/S_α for 95% ethanol, *n*-propanol, and IPA were 1.55, 1.52, and 1.65, respectively). We thus settled on toluene and IPA as the solvents of choice. As mentioned earlier, the toluene/IPA azeotrope was excellent (close to 50/50 at atmospheric pressure), and total solubilities in these two solvents were close enough to each other to allow the same size equipment to be used for both "halves" of the isolation cycle.

Several operational details were critical for consistent performance. For both halves of the cycle, equilibrium was reached more quickly from excess solid (i.e., by selective dissolution) than by crystallizing. Thus, after solvent displacement, excess solid was crystallized by constituting the batch at less than target temperature and at 60–80% of target volume (6.20 mL toluene/g α-methyl **3** or 4.75 mL IPA/g β-methyl **2**). Then the remainder of the solvent was added. For isolation of **2** from toluene, the slurry was simply stirred overnight at 25°C (use of 25% more solvent and stirring at 20°C sometimes led to supersaturation with **2**, thus reducing the yield). For isolation of **3** from IPA, the slurry was first stirred at 35–40°C for 1–2 hours, then at 20°C overnight.

A recent discussion of solute–solvent interaction (*10*) suggests an explanation of the solubility differences described in this article and lays the groundwork for potential extension of this cyclic, selective dissolution method to the separation of other structurally similar compounds. Alcohols can be expected to participate in hydrogen bonding interactions with the diastereomers **2** and **3** involving "well-defined stoichiometries and structures." The stabilities of these complexes would be influenced by steric differences between **2** and **3** as well as by steric demands of the solvent. This could explain why alcohols provided the largest solubility ratios for **2** and **3** and why the branched solvent IPA was the best of those tried. On the other hand, the aromatic solvent toluene and other hydrocarbon solvents are capable only of "largely nonspecific" Debye and London dispersion interactions with polar solute molecules. These interactions are "usually much less influenced by steric requirements." This could explain the lower solubility ratios in hydrocarbon solvents as well as the large solubility increase in these solvents for the isomers in a mixture versus pure. In hydrocarbon solvents, hydrogen bonding interactions can involve only the solute molecules **2** and **3**, and the strength of these interactions can be expected to change significantly depending on whether identical or different molecules are involved.

This point of view suggests that the best approach to determining the feasibility of applying this cyclic, selective dissolution method to other separations of structurally similar compounds is to focus, on the one hand, on solvent classes capable of an interaction with solute which would recognize differences between the molecules to be separated, and, on the other hand, on solvents whose interactions with solute would be nonspecific. One must then do only two types of measurements: 1) determine solubilities in an appropriate variety of solvents using a *mixture* of the compounds to be separated, and 2) monitor the physical state of the undissolved solids (e.g., by x-ray powder diffraction or differential thermal analysis) to make certain that a solid phase different from that of each of the components does not form.

ABBREVIATIONS

de	diastereomeric excess
HPLC	high-performance liquid chromatography
IPA	isopropanol

LDA	lithium diisopropylamide
MeI	methyl iodide
TBDMS	*tert*-butyldimethylsilyl

REFERENCES

1. For a recent discussion of large-scale chromatography, see P. C. Wankat, in *Handbook of Separation Process Technology* (R. W. Rousseau, Ed.), Wiley, New York, 1987, Chap. 14.
2. Recent discussions of fractional crystallization: (*a*) S. J. Jancic, in *Industrial Crystallization 87* (J. Nyvlt and S. Zacek, Eds.), Elsevier, New York, 1989, p. 57. (*b*) J. W. Mullin, *Crystallization*, 2nd ed., Butterworths, London, 1972, Chaps. 7 and 8.
3. Review: J. Jacques, A. Collet, and S. H. Wilen, *Enantiomers, Racemates, and Resolutions*, Wiley, New York, 1981.
4. Some of these results have been disclosed: D. R. Bender, I. Shinkai, A. M. DeMarco, and J. A. McCauley, U.S. Patent 4,816,577 (March 28, 1989).
5. Ref. *3*, p. 383.
6. For recent discussions of extractive crystallization, see (*a*) J. P. Tare and M. R. Chivate, in *Analysis and Design of Crystallization Processes* (AIChE Symposium Series No. 153, Vol. 72; R. W. Rousseau and M. A. Larson, Eds.), American Institute of Chemical Engineers, 1976, p. 95. (*b*) G. H. Dale, *Encycl. Chem. Process Des., 13,* 456 (1981). (*c*) S. Rajagopal, K. M. Ng, and J. M. Douglas, *AIChE J., 37,* 437 (1991).
7. (*a*) D. H. Shih, F. Baker, L. Cama, and B. G. Christensen, *Heterocycles, 21,* 29 (1984). Recent examples and leading references: (*b*) Meropenem (SM-7338): M. Sunagawa, H. Matsumura, T. Inoue, M. Fukasawa, and M. Kato, *J. Antibiot., 43,* 519 (1990); H. C. Neu, A. Novelli, and N.-X. Chin, *Antimicrob. Agents Chemother., 33,* 1009 (1989). (*c*) LJC10,627: K. Ubukata, M. Hikida, M. Yoshida, K. Nishiki, Y. Furukawa, K. Tashiro, M. Konno, and M. Mitsuhashi, *Antimicrob. Agents Chemother., 34,* 994 (1990). (*d*) C. U. Kim, B. Y. Luh, P. F. Misco, and M. J. M. Hitchcock, *J. Med. Chem., 32,* 601 (1989).
8. Section D of Ref. *9*.
9. D. R. Bender, A. M. DeMarco, D. G. Melillo, S. M. Riseman, and I. Shinkai, *J. Org. Chem., 57,* 2411 (1992).
10. D. J. W. Grant and T. Higuchi, *Solubility Behavior of Organic Compounds* (Techniques of Chemistry, 21), Wiley, New York, 1990, Chap. 5.7.1.

Received by editor March 30, 1992
Revised July 13, 1992