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Dilevalol via Resin-Mediated Epimerization: A Case Study. Reaction Mechanism to Reactor Design to a Viable Process

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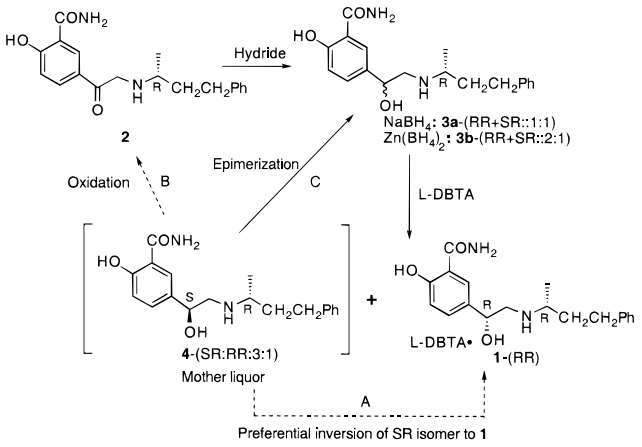
Abstract:

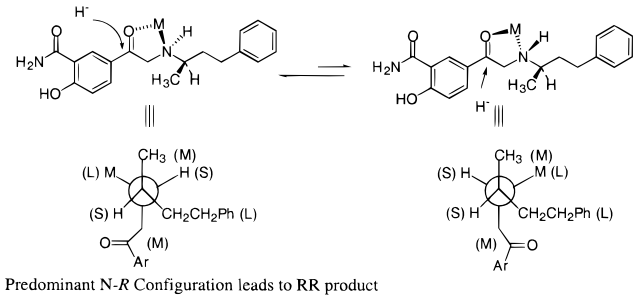
A case study on a novel commercial process for the preparation of dilevalol, 5-[1-hydroxy-2-[(1-methyl-3-phenylpropyl)-amino]-ethyl]salicylamide, (*R*,*R*)-1, from crude (*S*,*R*)-1, is described. This covers all of the work from the initial laboratory observation of an acid-induced racemization of the benzylic carbinol (epimerization) of pure (*R*,*R*)-1, to the identification and optimization of an acidic resin that facilitated the epimerization of the core-process-generated crude (*S*,*R*)-1 on a solid support, and the subsequent reactor modification culminating in a cost-efficient, industrial-scale, semi-continuous batch process for the preparation of dilevalol.

Dilevalol (*R*,*R*)-**1**·HCl, the eutomer of labetalol [racemic-**1**] with β_1-receptor blockade and significantly reduced α-receptor blockade activity, is a potent bronchodilator.[1,2] Work towards a nonproprietary, commercial synthesis is depicted in Scheme 1. This involved the reduction of ketone **2** to the alcohol **3a** with $NaBH_4$ or to **3b** via $Zn(BH_4)_2$. In either case the *R*,*R*-isomer was crystallized via the use of dibenzoyl-L-tartaric acid (L-DBTA). To enhance the utility of the chiral amine moiety after isolation of **1**, the conversion of the *S*,*R*-isomer in the process mother liquors to the desired *R*,*R*-isomer was of interest. This paper describes an efficient process for such a conversion. This emerged from the initial incidental laboratory observation which, after rigorous laboratory optimization, followed by engineering equipment design was converted into an industrially feasible process.

Scheme 1



Scheme 2



Predominant N-*R* Configuration leads to RR product

Asymmetric Induction. Hartley[3] had shown that reductions of aminoketone **2** (or its *N*-methyl derivative) with $NaBH_4$ proceed with little, if any (0−8% de), 1,4-asymmetric induction from the existing chiral center incipient in the *R*-amine moiety. However, he found for the *N*-benzyl derivative of **2** that de's as high as 52% could be obtained using $NaBH_4$ and with a bulky reducing reagent such as L-Selectride the de increased to 64%.[2] To account for these results, Hartley proposed that the reduction of *N*-benzyl aminoketone-**2** proceeded through a nonchelated transition state and the observed selectivity "is mainly a consequence of steric approach control to a molecule in which rotation is restricted by the *N*-benzyl group."

Encouraged by these results for the reduction of *N*-benzyl aminoketone-**2**, a program was undertaken to determine if a suitable reducing reagent/complex could be found that would allow for high de for the reduction of aminoketone **2**, since we wished to avoid the added number of steps, and more importantly, the additional costs required for introducing and removing the *N*-benzyl group. Although Hartley reported only a modest de (8%) for the reduction of **2** using $NaBH_4$, it was thought that either the use of a more bulky reducing reagent or the addition of a reagent that would allow for formation of a transient metal complex might be able to mimic the effect of the *N*-benzyl group. For the latter case, the newly formed *N*-chiral center can adopt either the *R*- or *S*-configuration, as illustrated by the two Newman projections depicted in Scheme 2. However, the *R*-isomer is thermodynamically more favored since the large M group is situated between the small H and medium methyl group. This, in turn, should direct the hydride attack from the backside, leading to the *R*,*R*-isomer.

A number of nonchiral reducing reagents were screened and these results are listed in Table 1. In all cases the de's were determined by GC.[4] The bulky reducing reagents did not show much improvement, as the best result was with

(1) Walker, D. In Dilevalol Hydrochloride. Development of a Commercial process. *Process Chemistry in the Pharmaceutial Industry*; Gadamasetti, K. G.. Ed.; Mercell Decker, NY, 1999; p 125.
(2) Gold, E. J.; Chang, W.; Cohen, M.; Baum, T.; Ehrreich, S.; Johnson, G.; Prioli, N.; Sybertz, E. J. *J. Med. Chem.* **1982**, *25*, 1363.
(3) Hartley, D. *Chem. Ind.* **1981**, 551.

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Table 1. **Asymmetric reduction via 1,4-induction, non-chiral reducing reagents[a,b]**

number	reagent	solvent	temperature	*RR*:*SR*
1	$NaBH_4 \cdot Ni(OAc)_2$	MeOH	0 °C → rt	51:49
2	$NaBH_4 \cdot Cu(OAc)_2$	MeOH	0 °C → rt	51:49
3	$NaBH_4 \cdot CuCl_2$	MeOH	0 °C → rt	54:46
4	$NaBH_4 \cdot CeCl_3$	$EtOH/H_2O$	−15 °C → rt	52:48
5	$NaBH_4 \cdot CoCl_2$	DME[3]	rt	55:45
6	$NaBH_4 \cdot Al_2O_3$	THF	rt	54:46
7	$NaBH_4 \cdot AlEt_2Cl$	THF	−78 °C → rt	50:50
8	$NaBH_4 \cdot SnCl_2 \cdot 2H_2O$	MeOH	0 °C → rt	55:45
9	$NaBH_4 \cdot ZnCl_2$	MeOH	0 °C → rt	53:47
10	$NaBH_4 \cdot Zn(OPiv)_2$	DME	rt	58:42
11	$NaBH_4/Ti(O\text{-}i\text{-}Pr)_4$	THF	−78 °C → rt	40:60
12	$NaBH_4/Ti(O\text{-}i\text{-}Pr)_4$	MeOH	0 °C → rt	52:48
13	$NaCNBH_3 \cdot ZnCl_2$	Et_2O	rt	54:46
14	$BaBH_4 \cdot Cu(OAc)_2 \cdot H_2O$	THF	rt	53:47
15	$Zn(BH_4)_2$	THF	0 °C	59:41
16	$Zn(BH_4)_2$	THF	−10 °C	63:37
17	$Zn(BH_4)_2$	DME	−10 °C	61:39
18	$Zn(BH_4)_2 \cdot 1.5DMF$	CH_3CN	rt	53:47
19	$Zn(BH_4)_2 \cdot 1.5DMF$	THF	−10 °C	60:40
20	K-Selectride	THF	−40 °C → rt	54:46
21	KS-Selectride	THF	0 °C	50:50
22	L-Selectride	THF	−78 °C → rt	58:42
23	LS-Selectride	THF	−78 °C → rt	60:40
24	$LiEt_3BH$	THF	−78 °C → rt	56:44
25	$Al(O\text{-}i\text{-}Pr)_3$	*i*-PrOH	reflux	53:47
26	$(i\text{-}Pr)_2NH \cdot BH_3$	CH_2Cl_2	−78 °C → rt	54:46
27	$(i\text{-}Pr)_2NH \cdot BH_3$	THF	0 °C	55:45
28	$(i\text{-}Pr)_2NH \cdot BH_3/Mg(OCOCF_3)_2$	CH_2Cl_2	0 °C	55:45
29	$(i\text{-}Pr)_2NH \cdot BH_3/Mg(OCOCF_3)_2$	CH_2Cl_2	−40 °C	42:58
30	$(i\text{-}Pr)_2NH \cdot BH_3/Mg(OCOCF_3)_2$	CH_2Cl_2	−78 °C	29:71
31	$(i\text{-}Pr)_2NH \cdot BH_3/Mg(OCOCF_3)_2$	toluene	−78 °C	46:54
31	$(i\text{-}Pr)_2NH \cdot BH_3/Mg(OCOCF_3)_2$	Et_2O	0 °C	46:54
32	$(i\text{-}Pr)_2NH \cdot BH_3/Li(OCOCF_3)_2$	CH_2Cl_2	−78 °C → rt	52:48
33	$(i\text{-}Pr)_2NH \cdot BH_3/CF_3CO_2H$	CH_2Cl_2	−78 °C → rt	51:49
34	$(i\text{-}Pr)_2NH \cdot BH_3/MgCl_2$	CH_2Cl_2	−78 °C → rt	50:50
35	$(i\text{-}Pr)_2NH \cdot BH_3/Cu(OAc)_2 \cdot H_2O$	THF	−78 °C → rt	52:48
36	$(i\text{-}Pr)_2NH \cdot BH_3/CoCl_2 \cdot 6H_2O$	THF	−78 °C	51:49
37	$(i\text{-}Pr)_2NEt \cdot BH_3/Mg(OCOCF_3)_2$	CH_2Cl_2	−78 °C	52:48
38	$t\text{-}BuNH_2 \cdot BH_3/BF_3 \cdot Et_2O$	Et_2O	−78 °C → rt	51:49
39	$t\text{-}BuNH_2 \cdot BH_3/Mg(OCOCF_3)_2$	THF	−78 °C → rt	48:52
40	$t\text{-}BuNH_2 \cdot BH_3/Mg(OCOCF_3)_2$	CH_2Cl_2	−78 °C → rt	45:55
41	$t\text{-}BuNH_2 \cdot BH_3/Ti(O\text{-}i\text{-}Pr)_4$	CH_2Cl_2	−78 °C → rt	45:55

[a] In general, the reductions were carried out by dissolving **2** in the specified solvent and temperatures and adding 1−3 molar equiv of the reducing reagent, depending on whether the free base or the HCl salt of **2** was used. The reactions samples were quenched with MeOH and the diastereomeric ratio was determined by capillary GC.[4] [b] $Zn(BH_4)_2$ was prepared *in situ* by mixing $NaBH_4$ and $ZnCl_2$ in 1:0.5 molar ratios in THF and the final concentration of $Zn(BH_4)_2$ was ∼0.7 M. [c] DME = 1,2-dimethoxyethane.

LS-Selectride, in which case the de increased to 20%. Similarly, Valery−Meerwein−Pondorf conditions or Li and Ba borohydrides also did not show any significant improvement (6−8% de). In general, for the sodium borohydride·metal complexes the reduction did not occur with any significant enhancement, as typically the de's ranged from 0 to 16%. However, for the $Ti(O\text{-}i\text{-}Pr)_4$ complex a reversal in selectivity was observed (entry 11), as it showed a preference for the *S*,*R*-diastereomer using THF as the solvent. Noteworthy is the fact that the selectivity shifts back to the normal slight preference for the *R*,*R*-diastereomer when MeOH was used as a solvent (entry 12). The best results were obtained using $Zn(BH_4)_2$, as de's as high as 26% were obtained for the *R*,*R*-diastereomer (entry 16).

Turning away from the metal borohydrides, a number of amine boranes or their complexes were also investigated. Interestingly, for $(i\text{-}Pr)_2NH \cdot BH_3$ itself, the typical results were obtained, with a slight preference for the *R*,*R*-diastereomer. Although addition of additives such as $CoCl_2$ and $Cu(OAc)_2$ did not have any appreciable effect, the addition of $Mg(OCOCF_3)_2$ did have a pronounced effect on the reduction, as de's as high as 42% were obtained, but for the *S*,*R*-diastereomer (Entry 30). That the effect was due to the specific combination of the $(i\text{-}Pr)_2NH \cdot BH_3/Mg(OCOCF_3)_2$

(4) GC: (a) Fused silica capillary column (4 m × 0.25 mm) coated with SP-2250 with film thickness of 0.2 μm, FID detector. Injector and detector ports at 250 °C, column oven at 240 °C. Helium as a carrier gas with 20−30 cm/sec/linear velocity. Inject 1 μL. Run time of 10 min. Sample prepared by derivatization with methylboronic acid (GLC grade) in pyridine and allowed to stand at room temperature for 20 min; or (b) in an alternative GC method the column used was 10% OV-17 on 100/120 mesh Gas Chrom Q packed in a 6 ft × 1/4 in glass column, or equivalent. The carrier gas was helium at a flow rate of 30 mL/min. Both injector and detector temperature were about 340 °C. The oven temperature was about 300 °C. Detection was with flame ionization. Derivatization of the amino alcohols were made with 1-butaneboronic acid in dry pyridine (over 4 Å molecular sieves) before injection on the column.

Table 2. **Asymmetric reduction via 1,4-induction, chiral reducing reagents[a,b]**

number	reagent	solvent	temperature	*RR*:*SR*
1	$NaBH_4$·(L)-penicillamine	THF	rt	69:31
2	$NaBH_4$·(D)-penicillamine	THF	rt	38:62
3	$NaBH_4$·(D)-mandelic acid	THF	rt	55:45
4	$NaBH_4$·(D)-leucine	THF	rt	60:40
5	$NaBH_4$·(D)-*tert*-leucine	THF	rt	72:28
6	$NaBH_4$·(L)-isoleucine	THF	rt	41:59
7	$NaBH_4$·(D)-phenylalanine	THF	rt	62:38
8	$NaBH_4$·(L)-proline	THF	rt	51:49
9	$NaBH_4$·(D)-proline	THF	rt	49:51
10	$NaBH_4$·(D)-tryptophan	THF	rt	59:41
11	$NaBH_4$·(D)-tyrosine	THF	rt	55:45
12	$NaBH_4$·(L)-threonine	THF	rt	60:40
13	$NaBH_4$·(L)-cysteine	THF	rt	51:49
14	$NaBH_4$·(L)-cystine	THF	rt	56:44
15	$NaBH_4$·(L)-lactic acid	THF	rt	56:44
16	$NaBH_4$·(L)-aspartic acid	THF	rt	59:41
17	$NaBH_4$·(L)-tartaric acid	THF	rt	55:45
18	$NaBH_4$·(L)-valine	THF	rt	37:73
19	$NaBH_4$·(D)-valine	THF	rt	70:30
20	$NaBH_4$·(L)-valine· $Mg(OCOCF_3)_2$	THF	rt	63:37
21	$NaBH_4$·(D)-valine· $Mg(OCOCF_3)_2$	THF	rt	40:60
22	$NaBH_4$·(D)-valinol	THF	rt	57:43
23	Diisopinocampheylborane	THF	−78 °C → rt	54:46
26	$LiAlH_4$·(*R*)-BINOL· 2 eq EtOH	THF	−78 °C	15:85
27	$LiAlH_4$·(*S*)-BINOL· 2 eq EtOH	THF	−78 °C	81:19
28	$LiAlH_4$·Chirald	Et_2O	−78 °C	20:80
29	$LiAlH_4$·(*S*)-2-anilinomethyl)pyrrolidine	Et_2O	−78 °C → rt	66:34
30	$LiAlH_4$·(*l*)-menthol	Et_2O	0 °C → rt	48:52
31	*t*-$BuNH_2$·BH_3/Mg−(+)-tartrate	MeOH	0 °C → rt	52:48
32	L-selectride/Mg−(+)-tartrate	THF	−78 °C → rt	55:45
	Hydrogenation Conditions:[c]			
33	(*R*)−(*S*)-BPPFOH·$[Rh(COD)Cl]_2$, 1 eq TEA	EtOH	rt	73:27
34	(*S*,*S*)-BPPM·$[Rh(COD)Cl]_2$, 1 eq TEA	EtOH	rt	69:31
35	(−)-DIOP·$[Rh(COD)Cl]_2$	EtOH	rt	60:40
36	(*S*)-BINAP·$[Rh(COD)Cl]_2$	EtOH	rt	60:40
37	(*R*)−(+)-PROPHOS·$[Rh(COD)Cl]_2$	EtOH	rt	61:39

[a] In general, the reductions were carried out by dissolving **2** in the specified solvent and temperatures and adding 1−3 molar equiv of the reducing reagent, depending on whether the free base or the HCl salt of **2** was used. [b] The reactions samples were quenched with MeOH, and the diastereomeric ratio was determined by capillary GC.[4] [c] All hydrogenations were carried out at 50 psi H_2 with substrate:catalyst ratio of 50:1. Hydrogenation times were 1−6 days.

complex was clearly demonstrated by the fact that Li-$(OCOCF_3)_2$, $MgCl_2$, CF_3CO_2H or the substitution of (*i*-$Pr)_2NEt$·BH_3 for (*i*-$Pr)_2NH$·BH_3, under identical reaction conditions, gave the normal selectivity (0−4% de) for the R, R-diastereomer. A similar, but smaller selectivity for the *S*,*R*-diastereomer was also observed for the *t*-$BuNH_2$·BH_3 complexes with $Mg(OCOCF_3)_2$ and Ti(O-*i*-$Pr)_4$.

A possible explanation for the unexpected reversal of selectivity for these cases, as well as the previously mentioned example with $NaBH_4$/Ti(O-*i*-$Pr)_4$ in THF, may be that the reduction occurs from the same face ("front-side") attack as the metal in the *N*-*R*-configuration five-membered transition state depicted in Scheme 2 (assuming the chelated transition state). Use of more polar solvents, such as MeOH or higher temperatures, which presumably breaks up the complex, would then account for the selectivity favoring the *R*,*R*-diastereomer. In the cases with $NaBH_4$, $Zn(BH_4)_2$ and the bulky Selectride reducing reagents, the reduction may be proceeding via a nonchelated transition state as proposed by Hartley.[3] The possibility remains that competitive reduction mechanisms at different rates could be occurring in all cases, leading to the above results.

Since the nonchiral reducing reagents did not give appreciable selectivity for the desired *R*,*R*-diastereomer, a number of chiral reducing reagents were also investigated and these results are listed in Table 2. Itoh et al.[5] had reported that complexes formed from amino acids such as (D)-proline and $NaBH_4$ were effective for asymmetric reduction of amino ketones. A number of these types of complexes were examined (entries 1−21) and the best results were obtained using either the $NaBH_4$·(D)-valine or the $NaBH_4$·(D)-*tert*-leucine complexes in which case de's of 40−44% were obtained. Interestingly, the addition of $Mg(OCOCF_3)_2$ had a similar effect as when added to the achiral reducing reagents. As before, the selectivity was reversed (Compare entries 19 and 21).

Several other chiral reducing reagents, such as Brown's[6] chiral isopinocampheylchloroborane reagent, as well as the chiral $LiAlH_4$ complexes formed from BINOL,[7] Chirald,[8]

(5) Umino, N.; Iwakuma, T.; Itoh, N. *Chem. Pharm. Bull.* **1979**, *27*, 1479.
(6) Chandrasekharan, J.; Ramachandran, P. V.; Brown, H. C. *J. Org. Chem.* **1985**, *50*, 5446.
(7) BINOL is 1,1′-bi-2-naphthol. See Noyori, R.; Tomino, I.; Tanimoto, Y.; Nishizawa, M. *J. Am. Chem. Soc.* **1984**, *106*, 6709.

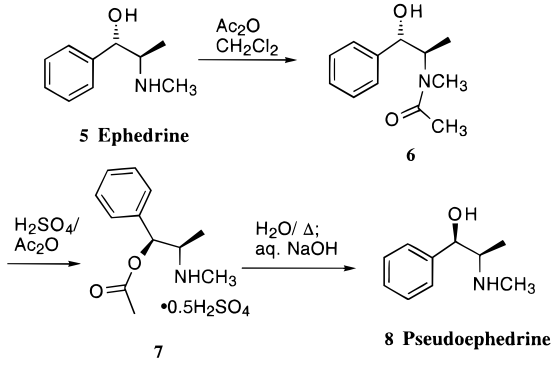
(*l*)-menthol[9] and (*S*)-2-(anilinomethyl)pyrrolidine[10] were tried (entries 23−32). Although both the Chirald and (*l*)-menthol complexes showed selectivity for the undesired *S*,*R*-diastereomer, the remaining reagents showed selectivity for the desired *R*,*R*-diastereomer, with the (*S*)-BINOL·$LiAlH_4$ complex affording the best result yet observed for the reduction of amino ketone **2**, with a de of 62%.

Hiyashi et al.[11] reported that catalytic hydrogenation of a secondary amino ketone (similar to **2**) proceeded in excellent yield with 95% ee using the (*R*)-(*S*)-BPPFOH·Rh chiral complex. This ligand, as well as a number of other chiral hydrogenation catalysts were also tried, including (*S*,*S*)-BPPM,[10] (−)-DIOP,[11] (*S*)-BINAP,[12] and (*R*)-(+)-PROPHOS,[13] and these results are also depicted in Table 2 (entries 33−37). The best results were obtained using the BPPF−OH ligand, in which case a 46% de was observed.

Although the selectivity for reduction of aminoketone **2** was as high as 63:37 with the achiral reducing reagents and as high as 81:19 with the chiral reducing reagents, the fact remained that recrystallization of **1** with L-DBTA in aqueous butanol or ethanol was necessary to improve the enantiomeric and chemical purities leading to acceptable quality **1**. However, under the best crystallization conditions the recovery of the desired product was partial, and it left **4** (with ∼1:3 mixture of *R*,*R*- to *S*,*R*-isomer) in the mother liquor. To make this process more economical by utilizing the chiral amine moiety more efficiently, a route for obtaining additional **1** from the mother liquors was desirable. For this purpose three options were considered: (A) A preferential conversion of the *S*,*R*-isomer to the *R*,*R*-isomer; (B) the oxidation of the benzylic alcohols of **4** to the preexisting penultimate intermediate **2** which could then be reduced; or (C) a nonselective, complete racemization of the benzylic carbinol, that is, epimerization, of **4** (1:3 mixture of *RR*:SR isomers) to **3a** (1:1 mixture of *RR*:SR). Although less efficient than the first alternative, the last two allow for a convenient recycling via the existing process.

An additional approach involving a Mitsunobu type inversion[16] which could invert both alcohols of **4** to a mixture of 3:1::*RR*:SR isomers, was ruled out for the following reasons. The cost of Mitsunobu reagents and the removal of the byproducts resulting from the use of Mitsunobu reagents as well as the one resulting from the participation of the amine or the phenolic group during the inversion reaction

Scheme 3



were anticipated to introduce economic burden and create complications[17] in the isolation of acceptable quality **1**, especially when tight specifications for the final product were already set.

For option A the previously known ephedrine to ψ-ephedrine conversion[18] was appealing since if it could selectively invert one of the two isomers (ideally inversion of the *S* center of the *S*,*R*-isomer), it could lead to the most desirable process. As a control, this inversion was applied to (*R*,*R*)-**1**. At the end of the reaction sequence (Scheme 3, shown for ephedrine), instead of recovering either unchanged (*R*,*R*)-**1** (a desirable outcome) or the inverted product (*S*,*R*)-**1** (an undesirable outcome), compound **3a** (1:1 mixture of *RR*:*SR*) was obtained! Thus, this approach, where the epimerization of the benzylic alcohol had taken place, was undesirable for a one-step conversion of **4** to **1**.

For option B, in control experiments, the oxidation of **1**, a β-amino alcohol, to the corresponding aminoketone **2** was investigated. This oxidation proved difficult. Under a variety of oxidation conditions[19−32] significant discoloration along

(8) Chirald is (2*S*,3*R*)-(+)-4-(dimethylamino)-1,2-diphenyl-3-methyl-2-butanol. See Yamaguchi, S.; Mosher, H. S. *J. Org. Chem.* **1973**, *38*, 1870.
(9) Andisano, R.; Angeloni, A. S.; Marzocchi, S. *Tetrahedron* **1973**, *29*, 913.
(10) Mukaiyama, T.; Asami, M.; Hanna, J.-i.; Kobayashi, S. *Chem. Lett.* **1977**, 783.
(11) (*R*)-(*S*)-BPPF−OH is (*R*)-α-[(*S*)-2-bis(diphenylphosphine)ferrocenyl]ethanol. See Hayashi, T.; Katsumura, A.; Kinishi, M.; Kumada, M. *Tetrahedron Lett.* **1979**, *20*, 425.
(12) (*S*,*S*)-BPPM is (2*S*,4*S*)-(−)-1-*tert*-butoxycarbonyl-4-(diphenylphosphino)-2-(diphenylphosphinomethyl)pyrrolidine. See Achiwa, K.; Kagure, T.; Ojima, I. *Tetrahedron Lett.* **1977**, *18*, 4431.
(13) (−)-DIOP is (2*R*,3*R*)-(−)-2,3-O-*iso*propylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane. See Kagan, H. B.; Dang, T.-P. *J. Am. Chem.. Soc.* **1972**, *94*, 6429.
(14) (*S*)-BINAP is (*S*)-(−)-2, 2′-bis(diphenylphosphino)-1, 1′-binaphthyl. See Takaya, H.; Noyori, R. et al. *J. Org. Chem.* **1986**, *51*, 629.
(15) (*R*)-PROPHOS is (2*R*)-(+)-bis(1,2-diphenylphosphino)propane. See Fryzuk, M. D.; Bosnich, B. *J. Am. Chem. Soc.* **1978**, *100*, 5491.
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(17) Protection of the phenolic OH, and the amine nitrogen could have overcome some of these problems and the ones perceived for the oxidations. However, from a commercial point of view this need for extra protection/deprotection was unattractive.
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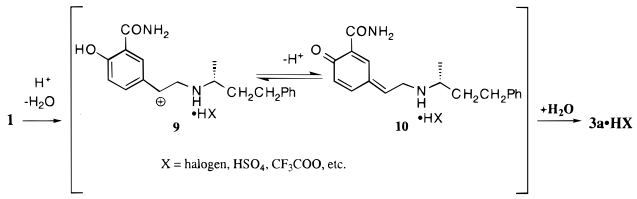
Scheme 4



with a mixture of products resulted. Although the aminoketone was present in most of these reactions, its isolation without chromatographic purification was difficult.[17] The inability of this process to produce the desired product which could be readily isolated forced a reinvestigation of the epimerization observed above.

As for option C, observations were made earlier in the process[33] that the formation of hydrochloride salt of the (*R,R*)-**1** under nonambient conditions with aqeous HCl had led to a lowering of de's by a partial epimerization of the alcohol center. This fact, coupled with the epimerization observed under option A, indicated that it was probably the aqueous acidic conditions (a step common to both procedures) that caused the epimerization of the alcohol center through the intermediacy of the quinonemethide species**10** and its tautomer **9**, **(**Scheme 4) with or without the involvement of the aziridine species **11**.[34]

This prompted the development of option C, a complete epimerization of the amino alcohol **4** in the mother liquor to **3a**. To develop the above observation into a process, the efforts were divided in two parts. These were (i) the identification of ideal parameters for epimerization of **1**, and (ii) the application of these parameters to the crude mixture of the isomers in the core process mother liquor (which contained excess L-DBTA and butanol) for the conversion of **4** to **1** via **3a**.

Epimerization Parameters. To establish the parameters for acid-induced epimerization, initial small-scale laboratory control experiments were conducted on pure **1**, and the results are summarized in Table 3.

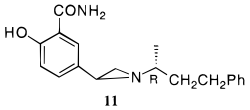
It was clear from the above experiments that aqueous conditions, lower pH, and moderately high temperature were necessary for an efficient epimerization. This is in agreement with the proposed quinonemethide-based mechanism.

Application of Epimerization for the Preparation of 1 from 4. Although a preferential conversion of the *S,R*-isomer to *R,R*-isomer was not possible, theoretically a kinetic resolution of **4** to **1** as depicted in Scheme 5 was possible. Since a crystallization of **1** from **3a** with L-DBTA can be accomplished in aqueous butanol (or ethanol), additional L-DBTA was added to the mother liquor containing **4** prior to acid-catalyzed epimerization (entries 1,2 of Table 4). In these cases only a trace of solid was visible at the end of the reaction. HPLC[35] and GC[4] analysis of the reaction mixtures showed epimerization along with a large number of new products. Some of these new compounds were the result of decomposition of L-DBTA under the experimental conditions as determined by entry 2. The other decomposition products were subsequently identified as shown in entries 3,4 below. Realizing that the instability of L-DBTA to aqueous mineral acids would not allow for a practical kinetic resolution or epimerization, removal of L-DBTA was deemed necessary for the conversion of **4** to **1**. Thus, after the removal of L-DBTA as a Na salt, crude **4** in water/alcohol was subjected to acidic epimerization (Table 4, entries 3,4). In both cases up to 20% of *n*-butyl ethers **13a** formed which cocrystallized with **1**·L-DBTA at the end. A confirmation (MS, NMR) of these structures was made via the synthesis of these compounds in alcohol as a solvent as shown below in Scheme 6.[36] The use of milder acids, such as pTSA or CF_3COOH in place of H_2SO_4 also led to the formation of these ethers. The use of EtOH in place of *n*-butanol resulted in the ethyl ethers **13b**. Thus, the removal of alcohols *and* L-DBTA from the mother liquors, that is, formation of free base **4**, became necessary for the epimerization to generate good quality product.

With free base **4** as the substrate, essentially all of the successful conditions listed in Table 3 became a viable option. Although HCl led to a faster epimerization under the conditions evaluated, the use of HCl was less desirable than H_2SO_4 as it would restrict the type of equipment that could be used in the plant, and furthermore, the recovery of the product was somewhat low as it generated **12** (HCl-induced amide hydrolysis is well-documented in the literature). On the basis of the purity profile of the epimerized mixture, the rate, and the cost of reagents, it was determined that sulfuric acid was the acid of preference at this stage, and the subsequent optimization work was done with it. In experiments 22−24 (Table 3) the addition of 1% glacial acetic acid helped solubilize the substrate without affecting the rate or the recovery, whereas the addition of 1 mol equiv of 2.5 N HCl improved the rate of epimerization while typically lowering the recovery of **3** by ∼3−5%. Further optimization work revealed that with aqueous H_2SO_4 the reaction concentration of 5−25% (some suspension) had no significant effect on the rate of epimerization of pure **1** or on the recovery of **3a**. Naturally, higher reaction concentrations meant more throughput and less neutralization at the end of the reaction, and hence it was preferred. These conditions were evaluated for the epimerization of free base **4** (Table 4, entries 5−7). Since crude, free base **4** was more

(33) Personal communication with Dr. Esther Babad. The author (D.G.) greatly appreciates many stimulating discussions with Dr. Babad on this project.

(34) It is possible that this process may be favored by protonation of the amine under the acidic conditions which could enhance the proton transfer to the benzylic hydroxy group, accelerating the quinonemethide formation.



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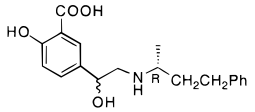
(35) HPLC: (a) μ-Bondapak C-18 or equivalent, (30 cm × 4 mm), Methanol: 0.07 M KH_2PO_4 (55:45) adjusted to pH 7.5 with 1 N aqueous NaOH, flow rate 1 mL/min, 254 nm detection. Internal standard: *o*-phenylphenol; or (b) Waters phenyl column 25 cm × 4 mm; 40% acetonitrile/water containing 0.01% sodium decanesulfonic acid; flow rate 1 mL/min; 254 nm.

(36) HPLC: Under the system described in ref 35 above, the butyl ethers (resolved) had an average RRt of 3.95, whereas the ethyl ethers (a broad hump) had a RRt of 1.8 (compared to **1** with Rr of 1.0). GC: Under the system described in ref 4a, the butyl ethers had a RRt of 1.28, whereas the ethyl ethers had RRt of 0.84 (compared to **1** with Rr of 1.0).

Table 3. **Epimerization of pure 1**

no.	substrate	conditions[a]	*RR*:*SR* ratio[b]	comments
1	**1**·HCl	EtOH/H_2O, reflux, 3 days	<5% epimerization	
2	**1**·HCl	*i*-PrOH/H_2O, reflux, 3 days	<5% epimerization	
3	**1**·HCl	*n*-BuOH, reflux, 3 h	<5% epimerization	
4	**1**·HCl	cat. pTSA, EtOAc, reflux, 3 h	<5% epimerization	
5	**1**·HCl	cat. pTSA, ^{i}PrOH, reflux, 3 h	<5% epimerization	
6	**1**·HCl	gl. CH_3COOH, 85°, 8 h	<5% epimerization	
7	**1**·HCl	50% aq. CH_3COOH, 90°, 2 days	1:1	
8	**1**·HCl	50% aq. CH_3COOH, 110°, 50 psi, 21 h	6:4	
9	**1**·HCl	50% aq. CH_3COOH, 130°, 65 psi, 15 h	1:1	dec
10	**1**·HCl	CF_3COOH, 55 °C, 8 h	53:47	trc. dec
11	**1**·HCl	50% aq. CF_3COOH, 90 °C, 1 day	1:1	80% yield
12	**1**·HCl	50% aq. HCOOH, reflux, 32 h	1:1	
13	**1**·HCl	90% HCOOH, reflux, 18 h	1:1	40% yield
14	**1**·HCl	50% aq. CF_3COOH, 85°, 8 h	55:45	87% yield
15	**1**·HCl	50% (20N) aq. H_2SO_4, 45°, 3 h	1:1	89% yield
16	**1**·HCl	25% (10N) aq. H_2SO_4, 50°, 3 h	1:1	89% yield
17	**1**·HCl	10 N(83%) aq. HCl, 50°, 3 h	1:1	82% yield[c]
18	**1**	10 N (83% aq.) HCl, 60°, 5 h	1:1	78% yield[c]
19	**1**	6 N (50% aq.) HCl, 60°, 5 h	53:47	83% yield
20	**1**	20 N (50%) aq. H_2SO_4, 40°, 8 h	1:1	98% yield
21	**1**	20 N (50%) aq. H_2SO_4, 50°, 6 h	1:1	95% yield
22	**1**	10 N (25%) aq. H_2SO_4, 55°, 3 h	1:1	92% yield
23	**1**	5 N (12%) aq. H_2SO_4, 55°, 2 h	9:1	
24	**1**	2.5 N (6%) aq. H_2SO_4, 50°, 6 h	95:5	
25	**1**	40% aq. HNO_3, 40°, 3 h	56:44	58% yield
26	**1**	concentrated HNO_3, rt, 1 h	60:40	67% yield
27	**1**	50% aq. H_3PO_4, 40°, 26 h	73:27	92% yield
28	**1**	10 N (25%) aq. H_2SO_4, 65°, 2.5 h	1:1	88% yield
29	**1**	10 N (25%) aq. H_2SO_4, 70°, 2 h	1:1	75% yield
30	**1**	10 N (25%) aq. H_2SO_4, 100°, 1 h	1:1	44% yield

[a] Screening experiments were done at 2−5% reaction concentration under the conditions described above. Scale up of the H_2SO_4 epimerization were done at up to 25% reaction concentration which is described in the text. Where applicable, the *RR*:*SR* ratios were determined with GC,[4] and quantitations performed with HPLC.[35] [b] Ideally a complete epimerization within a period of 4−5 h was desirable. Thus, recovery and yield determination was conducted only for selected experiments. [c] 5−10% of compound **12** formed in these reactions.



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Scheme 5

soluble than pure **1**, no additional reagents were needed for its solubilization.

The outcome for the acid-induced epimerization of **4** paralleled the results obtained when pure **1** was used as a substrate for epimerization. After epimerization and workup, **1**·L-DBTA was isolated, leaving second generation **4** in the mother liquors. This second generation **4**, after removal of L-DBTA and *n*-butanol was subjected to a second epimerization with > 80% overall recovery of **3a** for the second cycle. This established the much desired recyclability of the process.

In principle, on the basis of the quality of isolated **1** and the mass balance during epimerization, the above process appeared attractive. However, the need for the removal of L-DBTA and *n*-butanol from the mother liquors, the neutralization of H_2SO_4 after epimerization followed by extraction of **3a**, and finally isolation of the desired product by a *partial* crystallization of **1** as a L-DBTA salt made this process labor intensive as well as volumetrically inefficient overall. Hence, a more practical alternative was sought.

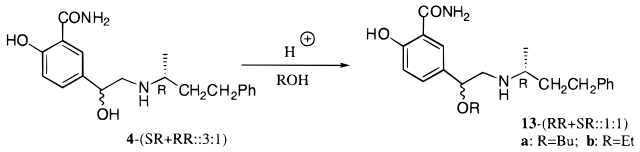
It appeared that, if the substrate, a secondary base, could be retained on a sulfonic acid resin, it would allow for a thorough washing of the resin with *n*-butanol followed by water for the removal of L-DBTA and *n*-BuOH, respectively (both of which could be recovered and recycled as detailed later). Additionally **4** could be epimerized on the resin by heating with steam/hot water (to attain 50−60 °C). A pH adjustment of the resin with a minimum amount of base could elute the epimerized product from the resin which could then be regenerated, effectively serving as a catalyst. Thus, the use of resin could lead to an elegant, environmentally friendly, economical epimerization process. To evaluate this possibility the following control experiments were conducted. When an aqueous solution of **1** was treated with Amberlite IR-120 resin, none of the substrate remained in the aqueous layer as judged by HPLC. Naturally, the same was true for the aqeous *n*-BuOH containing substrate. Encouraged by these results we designed a systematic program to convert this observation into a viable process. Salient features of this work are described below.

Table 4. **Epimerization[a] of the material 4 from core process mother liquors: (*SR*:*RR*::~75:25)**

no.	substrate	conditions	*RR*:*SR*	comments
1	**4**·L-DBTA, *n*-BuOH	aq. TFA, 90°, 8 h	1:1	dec
2	**4**·L-DBTA	aq. TFA, 70°, 6 h	1:1	dec
3	**4** aq. *n*-BuOH[b]	10 N (25% aq.) H_2SO_4, 40°, 2 h	1:2[d]	
4	**4** aq. *n*-BuOH	10 N (25% aq.) H_2SO_4, 40°, 4 h	1:1[d]	63% yield
5	free base **4**[c]	10 N (25% aq.) H_2SO_4, 55°, 2 h	1:1	87% yield
6	free base **4**	5 N (12% aq.) H_2SO_4, 55°, 6 h	1:1	83% yield
7	free base **4**	10 N (87% aq.) HCl, 55°, 3 h	1:1[e]	70% yield

[a] Epimerizations conditions were similar to the ones described under Table 3. [b] Aqueous *n*-BuOH solution were prepared as follows: The mother liquors from core process (*n*-BuOH saturated with water) were treated with sat. aq. Na_2CO_3 to pH 8−9. The resultant layers were separated, the aq. layer was extracted with EtOAc and combined with the organic layer. The combined organic layer was concentrated to remove EtOAc and the remaining *n*-BuOH solution of **3a** was used for epimerization. [c] Free base **4** was prepared as follows: The *n*-BuOH mother liquors were concentrated to a semisolid under vacuum at 35 °C. To this was added EtOAc followed by sat. aq. Na_2CO_3 such that the pH of the aq. layer remained at 8−9. The EtOAc layer was separated and dried under vacuum to a light tan solid which was the used for epimerization. [d] *n*-Butyl ethers **13a** formed. [e] Amide hydrolysis to the carboxylic acid **12** accounted for the mass balance.

Scheme 6



Resin Studies. To minimize the large number of experiments needed to determine the optimum resin, as well as the parameters that could be used with the selected resin(s) for the desired process, some practical assumptions were made up front. It was decided that although the core process was still being optimized, the typical mother liquors to be used were essentially of similar composition (within ±8% variation in the numbers described here, i.e., consisting of 85% *n*-butanol/water with the *R*,*R*-amino alcohol, the *S*,*R*-amino alcohol, and the L-DBTA components in approximately 12, 38, and 55 g/L amounts, respectively) to the one that would be eventually used. Only the commercially (bulk) available[37] sulfonic acid resins would be screened for this study. For these resins, the following interdependent properties, available from the manufacturer of the resins, were considered likely to influence the epimerization process. In general, the resin capacity, degree of cross linkage, particle size, the size of the cavities (resulting from the cross-linkage of the polymer in the resin bed; in wet resins the hydrated sulfonate groups swell, whereas the presence of alcohols depletes the water in the cavities, resulting in shrinkage of the resin) all influence the mass transport as well as adsorption of amino alcohol **4** on the resin. Furthermore, the parameters controlled in the laboratory, for example, temperature, the rate of addition of mother liquors to the resin, the rate of agitation of the resin, can also influence the mass transport and hence the degree as well as the rates of adsorption and epimerization. All except the rates of agitation (kept at minimum to allow for a column process mode, and to minimize physical degradation of the resin) were studied.

(37) The IR resins were obtained from Rohm and Haas Co, Philadelphia, Pa. The rest of the resins were obtained from the Dow Chemical Co, Larkin Laboratory, Midland, Michigan.

Table 5. **Loading capacities of various sulfonic acid resins**

resin type[a]	% cross linkage	amino alcohol loaded g/L[b]	H^+ capacity eq/L of wet resin	saturation capacity g/L of wet resin (g)
IR 120	8.0	100	1.9	624
IR 118	8.0	100	1.3	427
IR 200	8.0	114	1.7	558
XF8 43280	6.0	165	2.1	690
XUR 0525-L87-109-1	4.5	162	1.1	361
Ionac 241-T	4.0	206	1.1	361
XFS 43279	3.5	220	1.1	361
XFS	2	170	0.5	165

[a] Resins were stirred with excess of amino alcohol **4** (FW 328.4) for ~18 h at room temperature. [b] The concentration of amino alcohol was determined by HPLC.[35b]

The data indicated that the extent of the amino alcohol loading on the resin was primarily influenced by the degree of cross-linkage, whereas the H^+ capacity of the resin played a minor role. The resins with 6−8% cross linkage resulted in inefficient loading. On the other hand XFS appeared attractive from the loading perspective, but with all of its acidic sites occupied it would not allow for epimerization without exogenous acid. Additionally, mass balance determination in this case indicated adsorption of *n*-BuOH on the resin as well, which could be detrimental as it could form the butyl ethers. Thus, XFS 43279, Ionac 241-T, and the XUR resins were chosen for further optimization. After some additional work on these resins (similar to the one described below for XFS 43279) and commercial considerations, XFS 43279 was chosen as the resin of choice. The rest of this manuscript details the use of this resin for the development of the epimerization process.

The Resin Loading Capacity As a Function Of Cross Linkage and H^+ Capacity. The resin loading capacity was determined by gently stirring the commercially available wet resins with a large excess of typical core process mother liquor at room temperature for an overnight period. The total amino alcohol in solution before and after resin treatment was determined with HPLC. The results of this study are shown in Table 5.

Rate of Amino Alcohol Loading on the Resin. Experiments were undertaken to determine the optimum loading parameters for Dowex XFS 43279(H+). Here the resin was gently agitated with a large amount of mother liquor containing excess amino alcohol **4** at 23°, 30°, 50°, 60°, 70°, 80°, and 90 °C in a batch mode. This study indicated that the loading was temperature-dependent with optimum loading attained at 40 °C. Further increase in loading temperature either decreased the loading, or at 70 °C and above led to ethers formation. The relevant results from this study are summarized in Table 6 and additional information is provided

Table 6. **Temperature effect on amino alcohol loading (g/L) for XFS 43279[a]**

time (h)	23 °C	30 °C	40 °C	50 °C	60 °C
0	0	0	0	0	0
1.0	105	139	150	167	158
1.25	111	148	155	170	154
1.5	127	149	162	171	154
2	124	153	170	172	151
2.5	133	160	171	170	151
3	140	162	173	171	149
3.5	144	166	180	170	150
4.0	148	167	179	168	151
5	154	174	181	167	150
6	160	178	182	164	150
7	163	177	180	160	149
8	160	179	181	160	151

[a] The results were obtained using the analytical procedures described under Table 5.

in Figure 1. From these experiments, an optimum loading period of 3.5 h at a temperature of 40 °C was selected for ~50% resin saturation (which would allow for epimerization without additional acid).

Recovery Of Amino Alcohol Loaded on the Resin. Although the resin loading was determined by measuring the decrease in the amino alcohol content of the mother liquor after resin treatment, it was also important to know the quality and the ease of recovery of the amino alcohol from the resin. A systematic study was undertaken to optimize the recovery of the absorbed compound from the resin. The results of this work are summarized in Table 7.

The total recovery as a function of NaOH molarity and bed-volumes is shown in Figure 2 below. Note that the first bed-volume of 3 M NaOH recovered slightly more amino alcohol than 2 M NaOH. Between 2 and 3 M NaOH, (both of which led to excellent recovery of the amino alcohol), 2 M NaOH was desirable as it meant less shock to the resin, and less acid use for the subsequent pH adjustment. This eventually resulted in a better crystallization of **1**·L-DBTA (discussed later) compared to 3 M NaOH.

The Rates Of Epimerization. Having identified the optimized loading and recovery parameters, the rate of epimerization on the loaded column was next investigated. Here two possibilities were explored. Epimerization without additional acid was the first choice as it could be better suited for resin stability, and also minimize unit operations. On the other hand, epimerization with additional acid would improve the throughput.

Epimerization Without Additional Acid. On the basis of the observations made with sulfuric acid, it was clear that temperature would significantly influence the rate of epimerization of the amino alcohol loaded on the Dowex XFS 43279 resin. Hence the rate of epimerization as a function of temperature was studied. The results are summarized in Table 8 and depicted in Figure 3.

This study indicated that at 60 °C the epimerization was incomplete even after prolonged heating (Figure 3), whereas at 70, 80, and 90 °C, a complete epimerization was accomplished in 9, 4, and 1 h, respectively. In separate side-by-side comparisons it was determined that extended heating at 90 °C for 2 h resulted in lower (84%) recovery of **3** compared to 95% recovery of **3** after 1 h at 90 °C. Thus, with the resin loaded at ~50% of the capacity, a temperature of 85−90 °C for a period of about 1 h was considered optimum for epimerization.

Resin Loading vs Epimerization. During the above resin loading recovery study it became clear that the resin not only allowed for the removal of *n*-BuOH as well as the expensive L-DBTA, by selectively absorbing the amino alcohols, but it also allowed for the removal of the remainder of the impurities formed during the preceding portion of synthesis of **3a**. In reality it was also observed that XFS 43279 allowed for the above even when it was loaded near its saturation point with respect to its H^+ capacity. Thus, in the next set of experiments, the entire process of loading, epimerization, and recovery was evaluated on the above resin using under-loaded to over-loaded resin. As shown in Table 9, over-loaded resin led to a very slow epimerization upon heating of the resin. Prolonged heating of 90% loaded resin did not drive the epimerization to completion. It was obvious at this stage that the addition of (sulfuric) acid could enhance the rate of epimerization. The commercial feasibility of such a process was also seriously evaluated, and the results of this work are discussed below.

These experiments also demonstrated that the remainder of the mass balance under prolonged or over-heated conditions in the resin-induced epimerization of the amino alcohol was accounted for by the formation of **12**, a compound not seen during aqueous H_2SO_4 epimerization. Compound **12** is not readily absorbed on the resin and does not crystallize as a L-DBTA salt under the conditions in which **1**·L-DBTA is crystallized. Thus, although its formation during this process lowers the yield, it did not interfere with isolation of acceptable quality **1**.

High-Loading Exogenous Acid Epimerization. It appeared that 90% loading offered an opportunity to increase the throughput only if epimerization could be completed. With 90% of the acidic sites occupied with the amino alcohol, the remaining 10% acidic sites afforded limited opportunity for epimerization. The addition of a limited amount of an exogenous acid such as H_2SO_4 (or less preferably, HCl), could lead to complete epimerization through synergism. In control experiments, introduction of either HCl or H_2SO_4 resulted in complete epimerization.

For the use of H_2SO_4 three variables were examined: temperature, acid concentration, and reaction time. The results of this study are summarized in Table 10. Note that for these experiments the plots of the log of enantiomeric excess vs time were linear. Such plots led to the determination of epimerization half-life which is listed in the table. The linearity of reaction rates to acid strength further supports a simple acid-catalyzed quinonemethide mechanism for the epimerization reaction.

From these data, epimerization conditions of 1.2 N H_2SO_4/80 °C/2.5 h and 0.6 N H_2SO_4/90 °C/1.5 h were considered to be reasonable conditions for large-scale work and were chosen for yield determination. At 90% capacity loading, epimerization at 90 °C with 0.6 N H_2SO_4 gave 82%

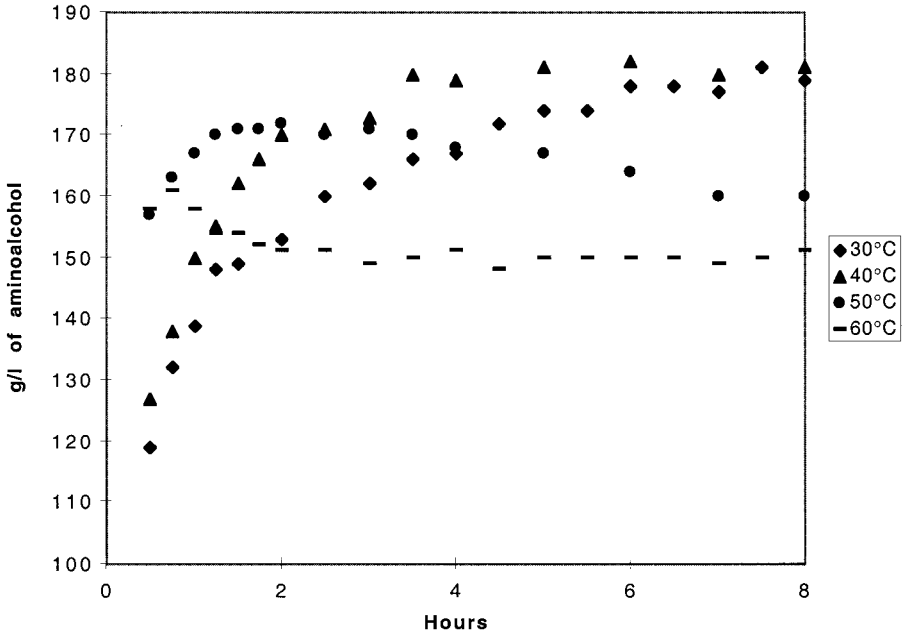


Figure 1. **Temperature effect on loading.**

Table 7. **Per cent recovery of free base vs molarity of sodium hydroxide in *n*-butanol[a]**

cycle	layer	1 M	2 M	3 M	4 M	5 M
1	*n*-butanol	51% (1 b.v[b])	86%(1 b.v)	87.6%(1 b.v)	86.3% (1 b.v)	81.6%(1 b.v)
	aqueous	0.8% (1 b.v)	1.1%(1 b.v)	0.4%(1 b.v)	0.2%(1 b.v)	0%(1 b.v)
2	*n*-butanol	38%(1 b.v)	7.4%(1 b.v)	4.8%(0.5 b.v)	4.9%(0.5b.v)	4.3%(0.5 b.v)
	aqueous	0.5%(1 b.v)	1.0%(1 b.v)	0%(1 b.v)	0%(0.5 b.v)	0%(0.5 b.v)
3	*n*-butanol	3.7%(1 b.v)	4.9%(1 b.v)	1.6%(0.5 b.v)	1.3%(0.5 b.v)	1.0%(0.5 b.v)
	aqueous	0.2%(1 b.v)	0%(1 b.v)	0%(0.5 b.v)	0%(0.5 b.v)	0%(0.5 b.v)
4	*n*-butanol	0%(0.5 b.v)	0%(0.5 b.v)	0.9%(0.5 b.v)	0.7%(0.5 b.v)	0.6%(0.5 b.v)
	aqueous	0%(0.5 b.v)	0%(0.5 b.v)	0%(0.5 b.v)	0%(0.5 b.v)	0%(0.5 b.v)
5	*n*-butanol	0%(0.5 b.v)	0%(0.5 b.v)	0.3%(0.5 b.v)	0.2%(0.5 b.v)	0%(0.5 b.v)
	aqueous	0%(0.5 b.v)	0%(0.5 b.v)	0%(0.5 b.v)	0%(0.5 b.v)	0%(0.5 b.v)
total recovered		93.8%	100%	95.3%	93.6%	87.5%

[a] For these experiments, saturated *n*-butanol solutions mixed with aqueous sodium hydroxide solutions of known strength were used to elute the resins in batch process mode with minimum agitation under nitrogen atmosphere at room temperature for 45 min. The resin was filtered. The pH of the filtrate was adjusted to 8.3 with 6 N H_2SO_4. The layers were split and analyzed separately by the HPLC procedure listed under Table 5. This cycle was repeated as necessary. [b] b.v. represents bed volume.

recovery yield, compared with an 86% yield at 80 °C with 1.2 N acid. While these yields are comparable to that obtained with 60% loading and no added acid epimerization, the throughput was increased by approximately by 1.5 times. In either case, **1**·L-DBTA could be crystallized[38] from **3a** obtained at any one of the above resin loadings.

Transferring the Process to the Plant. The experimental data was used as a foundation to conduct a series of pilot plant trials to further define the manufacturing process for the recovery of dilevalol·L-DBTA. The primary objectives of the trials were to demonstrate, under plant conditions, the loading, epimerization, and elution characteristics of the process; to determine the lifetime of the ion-exchange resin; and to study the crystallization and filtration characteristics of the dilevalol·L-DBTA isolated via the recovery process. The development effort was primarily focused on implementing the process in a multi-purpose bulk pharmaceutical chemical facility, utilizing as much existing process equipment as possible to minimize the capital investment. Initially the pilot plant-scale epimerizations of mother liquors were conducted using a 12 in diameter × 10 ft ion-exchange column, with the intention of scaling up to an existing 36 in diameter column, both of which were available at the time (Figure 4).

Mother liquors from the core process containing 25 ± 5% of the *R*,*R*-isomer were used for this work. The mother liquors were loaded on the resin at ambient temperature (15−25 °C)[39] at a flow rate of about 2 L/min. The resin was loaded to approximately 160 g/L during the pilot trials (less than 50% loading), with leakage during loading minimized (0−3%) by reducing the flow rate to the column when the pH

(38) In a typical crystallization, 1.1 mol of L-DBTA and the amino alcohol in 15−20 volumes of *n*-BuOH saturated with water was heated at 50 °C (pH of solution was 3.4−3.6). The mixture was cooled to 25 °C with agitation and filtered. Typically the crystallized product (33−37% yield) contained >97: 3 ratio of the isomers as determined by GC.

(39) Laboratory optimum of 40 °C would necessitate capital investment, which was ruled out from commercial point of view. The necessary loading was achieved by controlling the rate of loading.

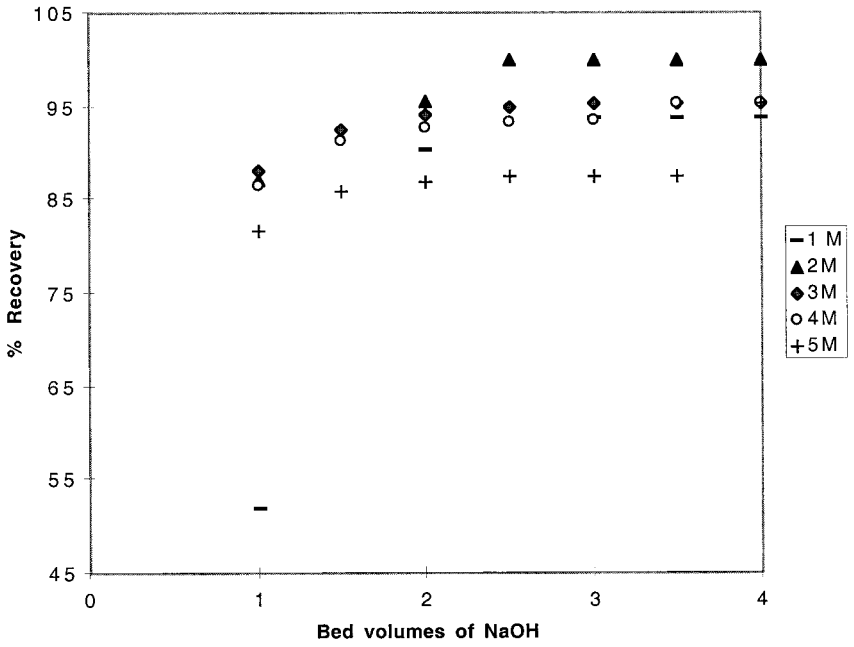


Figure 2. **Recovery of amino alcohol vs NaOH.**

Table 8. **Rates of epimerization of amino alcohol loaded on Dowex XFS-43279 (%*RR*)[a,b]**

time (h)	60 °C	70 °C	80 °C	90 °C
0	33.0	33.0	33.0	33.0
1	35.0	35.5	46.0	49.6
2	36.0	38.9	47.9	50.0
3	36.7	41.9	49.0	50.0
4	38.9	44.4	48.9	50.0
5	40.0	46.9	50.0	50.0
6	40.9	48.0	50.0	50.0
7	41.5	48.9	50.0	50.0
8	42.0	49.0	50.0	50.0
9	42.6	49.3	50.0	50.0
10	42.9	49.5	50.0	50.0
11	43.3	49.7	50.0	50.0
12	43.6	49.7	50.0	50.0

[a] In a batch operation mode, the resin loaded with amino alcohol was filtered. (The filtrates were saved for the recovery of L-DBTA and *n*-butanol, which is described later in this manuscript). The resin was washed with *n*-BuOH and water to remove the residual amounts of L-DBTA and *n*-butanol, respectively. Additional water was added, and the resin was heated under nitrogen at the indicated temperatures in the graphs. At the time points, resins were removed and treated as described under the recovery section to elute the amino alcohol. GC procedure[4b] was used to determine *RR*:*SR* ratios. [b] The need of nitrogen atmosphere for the epimerization process was known from the following experiments which had been conducted prior to the above study. A resin sample loaded with amino alcohol was split into two equal portions. One-half was epimerized under air and the other under nitrogen at 80 °C for 5 h. The yield of amino alcohol recovered from the resin under nitrogen was 98% compared to 78% under air. The presence of air results in the amino alcohol degradation.

of the spent mother liquors began to rise, indicative of increasing concentration of the amino alcohol in solution. The typical leakage of amino alcohol during mother liquor loading is shown in Figure 5.

After the resin was washed with *n*-BuOH and water (to remove L-DBTA and *n*-BuOH, respectively), epimerization was achieved by passing heated deionized water through the resin column at temperatures between 80 °C to 90 °C. When the isomer ratio of the product reached 50 ± 3% *RR*, the heating was stopped as at this stage epimerization was considered to be complete. After allowing the column to cool to ~45 °C, elution was conducted by pumping 2 N sodium hydroxide saturated with 12% v/v *n*-butanol through the column at a flow rate of about 2 L/min. The first one or two bed-volumes of the column effluent contained no product. When the pH increased to above 8 the eluate was collected for product recovery. The next two bed-volumes of the eluate contained about 60% of the epimerized amino alcohols. However, an additional four or five bed-volumes were necessary to increase the recovery to above 80%. Typical elution profiles from the pilot trials are shown in Figure 6 for epimerizations at both 80 °C and 90 °C.

One of the difficulties in the column elution was the precipitation and oiling of the product in the column effluent, presumably due to high localized concentrations of amino alcohol in the resin bed. Additional *n*-butanol during elution did not significantly increase product solubility and recovery from the column process. A further complication in the column scale-up effort was the variability of the process yield with respect to the epimerization temperature. In the column operation, the yield for epimerization at 80 °C was 88−100%, whereas at 90 °C it was 73−92%. Some of this was due to the formation of **12**, as seen in the laboratory batches, where as the rest appeared to be resulting from inefficiencies in eliminating oxygen and *n*-butanol from the system, causing degradation of the product on the column.

After adding *n*-butanol to the combined eluants to ensure the proper amino alcohol concentration for crystallization of the dilevalol·L-DBTA, the pH of the eluate was adjusted from a pH ≥ 12 to pH 8.5 ± 0.1 using sulfuric acid, and the product was extracted into the *n*-butanol layer for crystallization. After the addition of L-DBTA, the dilevalol·L-DBTA that crystallized from the epimerization process was more difficult to filter than that from the core process. Investigation of this difficulty revealed that since large volumes of eluates were generated from the column, they required correspond-

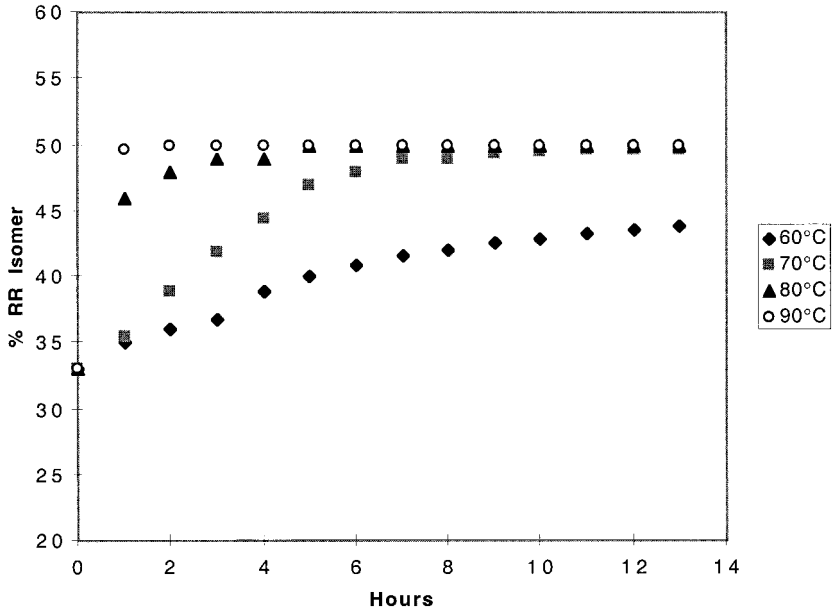


Figure 3. **Temperature effect on rates of Epimerization.**

Table 9. **Resin loading vs epimerization**[a]

loading	under-loading	normal loading	over-loading
% of H^+ capacity	30%	60%	90%
elution yield	70%	81%	92%
SR:*RR*	54:46	51:49	38:62

[a] Epimerization was conducted at 80−90 °C for 2.5 h to allow for maximum epimerization at higher loading. Mass balance indicated formation of **12** in 19, 9, and 2% amounts for 30, 60, and 90% loading, respectively. Thus, prolonged heating past epimerization under the "normal", i.e., 50% loading, is undesirable.

Table 10. **Overloaded resin exogenous acid-catalyzed epimerization rate study**[a]

H_2SO_4 concd temperature time, ratio	4.0 N 60 °C *RR*:*SR*	0.3 N 80 °C *RR*:*SR*	0.6 N 80 °C *RR*:*SR*	1.2 N 80 °C *RR*:*SR*	0.6 N 90 °C *RR*:*SR*
0	23:77	27:73	28:72	24:76	25:75
0.5	24:76	30:70	-	37:63	38:62
1.0	-	31:69	30:70	42:58	46:54
1.5	-	34:66	38:61	-	50:50
2.0	-	37:63	43:57	46:54	-
2.5	29:71	39:61	-	49:51	-
3.0	31:69	-	48:52	-	-
4.0	-	44:56	52:48	-	-
5.0	36:64	45:55	50:50	-	-
6.0	37:63	46:54	-	-	-
t1/2	322	136	74	36	24

[a] Resin aliquots were removed from the epimerization slurries with time as described above. These samples were assayed by GC for *RR*:*SR* ratio as described earlier.

ingly larger amounts of sulfuric acid to neutralize the sodium hydroxide present. As a result, the dilevalol·L-DBTA crystallization slurries filtered poorly due to the presence and coprecipitation of sodium sulfate, occasionally resulting in a two-phase crystallization and filtration in the plant. Regardless of these difficulties, these slurries were successfully filtered using either a rotary pressure filter or centrifuge.

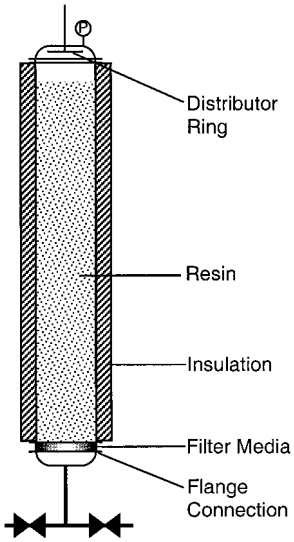


Figure 4. **Resin column.**

The resin was initially regenerated to its hydrogen form using 20% w/w sulfuric acid. The concentration of the sulfuric acid used for regeneration was later decreased to 7% w/w to minimize precipitation of calcium sulfate in the resin bed; the calcium being present as a result of the resin deionizing the city water content of the core process mother liquors during the loading process. The resin was successfully regenerated to 96−100% of its original capacity for seven consecutive trials. However, after the seventh column trial the adsorbed amino alcohols could not be epimerized without first reactivating the resin by either an acidic wash or conducting the epimerization in 5% w/w sulfuric acid. In this case an additional loss of product (14%) was noticed during epimerization in the presence of sulfuric acid at 80 °C.

In addition to some difficulties described above, several additional factors contributed to the decision to proceed with the batch operation recovery process for full-scale production. Whereas the batch process cycle times were primarily mass-

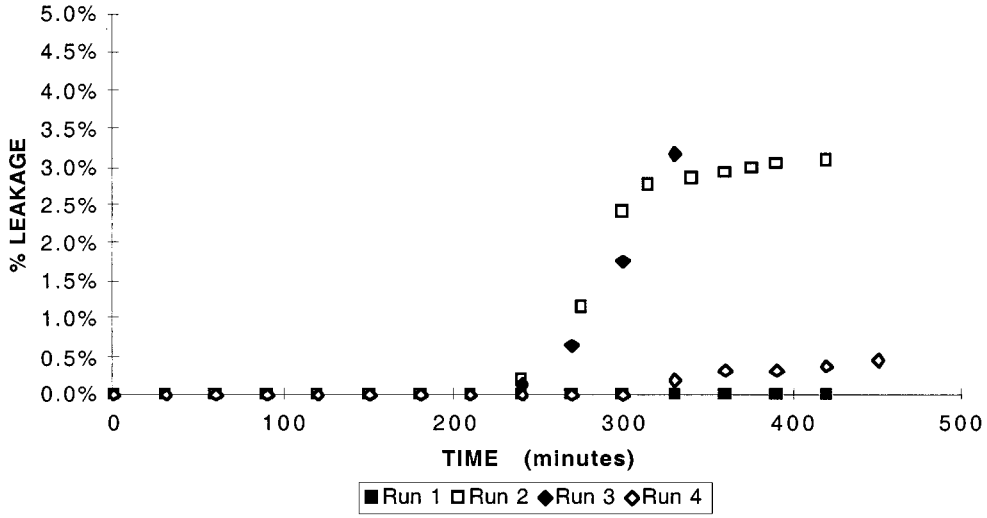


Figure 5. **Leakage during loading.**

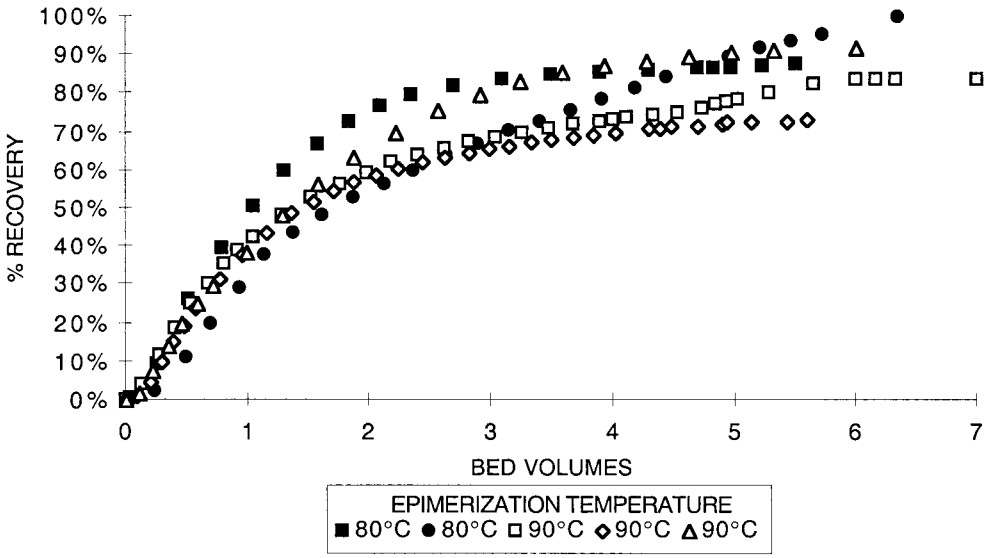


Figure 6. **Elution recovery.**

transfer dependent, the processing times associated with the column operation were determined by the fluid mechanics of the system. The column cycle time was significantly extended since only very low flow rates could be achieved even with a large pressure drop across the column. This physical limitation was exacerbated by significant particle attrition occurring within the resin bed over the course of the column trials. It also became difficult to ensure complete epimerization after several runs: this was the result of an "overloading" condition observed at the top of the column as well as the affinity for the resin to deionize the 15% city water present in the mother liquors. Both factors resulted in fewer acid sites being available on the resin to achieve complete epimerization. Finally, the largest contributing factor was the elution profile of the product from the column. Between six and seven bed-volumes were required for complete elution of the product from the column.

Scale-up of the batch process was more straightforward compared to utilizing the existing plant columns. For the batch process only four bed-volumes of the eluants were necessary for product recovery. This significant reduction in the eluate volume not only improved the reproducibility of the product crystallization, but also increased the throughput of the process in the existing plant equipment. The main challenge was isolating the solutions from the ion-exchange resin. Initial attempts involved filtering the resin between the loading, epimerization, and elution cycles; however, in full-scale production this method would increase the potential for personnel exposure and require additional labor and equipment for the process. To better conduct pilot plant trials of the batch process, 316 L stainless steel filter cylinders were purchased and installed on a dip pipe in the resin reactor to filter the process solutions from the resin. Since the reactor had a large diameter with a relatively small overall height of resin, the pressure drop when filtering through the resin was much less severe than that in the 10 ft column, affording much quicker removal of the process solutions for further processing and causing a smaller amount of particle attrition.

As reported previously, the mother liquor loading operation for the batch process was temperature-dependent, so that this was conducted between 40 and 60 °C to maintain leakage at $\leq$4%. In this temperature range, a desired resin loading

Table 11. **Representative batch process plant results**

resin	1000 L
dilevalol M/L	176.8 kg
loaded on resin	169.0 kg
spent	6.3 kg (3.6%)
loss to *n*-butanol wash	1.2 kg
loss to water wash	0.27 kg
total leakage	7.9 kg (4.4%)
eluate 1	124.6 kg
eluate 2	23.5 kg
n-butanol wash	6.1 kg
total eluate	154.2 kg
loss to water washes	2.0 kg
acid from hydrolysis	12.5 kg
total mass balance	175 kg (99%)

of between 175 g/L and 200 g/L for the batch process was realized. After filtering the spent mother liquor, the resin was washed with *n*-butanol and deionized water prior to epimerization. Difficulties similar to the column process in achieving complete epimerization were experienced during the batch trials; therefore, a 5% w/w sulfuric acid wash was added to ensure a reproducible process. Epimerization of the amino alcohol was accomplished by agitating the resin in deionized water for 2 to 3 h at 90 °C. An inert atmosphere was maintained in the reactor during epimerization by sparging nitrogen through the filter cylinders. Recovery of the epimerized product was accomplished in two two-bed-volume elutions with 2 N sodium hydroxide saturated with 12% v/v *n*-butanol at temperatures below 50 °C. Temperatures above 50 °C caused degradation of the product in the eluates. One hour for each elution was necessary to maximize recovery of the epimerized product from the resin. The eluates were transferred to other vessels for pH adjustment and phase separation, while the resin was regenerated with dilute sulfuric acid for its next cycle.

Over the course of the first 50 batches, a slow particle attrition of the resin was observed. Initially, the majority of the resin was in the 150−350 μm range, but by the 50th batch almost half was smaller than 150 μm. Titration of the regenerated resin to determine its activity was based on its volume, and on this basis no loss in resin activity was observed. The particle attrition resulted in a reduction in the overall volume of resin in the reactor, due to a reduction in the void volume per liter of resin and due to some physical losses of resin as well. To make up for these losses, approximately 15% additional resin was necessary to bring the volume of resin in the reactor back to the initial volume.

The recovered dilevalol·L-DBTA was crystallized independently in a batch operation, with the product collected and washed on a centrifuge. Due to the smaller eluate volumes, the sodium sulfate burden was significantly reduced in the dilevalol·L-DBTA crystallizations from the batch epimerization process, significantly improving the filterability of the slurries. The mother liquors from the recovered dilevalol·L-DBTA crystallization were combined with those from the core process for further epimerization. Typical plant results are shown in Table 11.

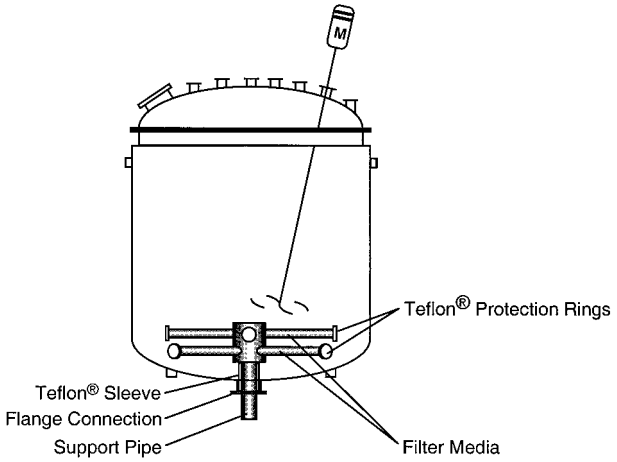


Figure 7. **Resin reactor.**

Resin Reactor Design For a Semicontinuous Commercial Batch Process. Having proven the cost-effectiveness of the reproducible resin process in generating good quality **1**, we focused our efforts on scaling up this process on production scale. Vendors with expertise in fabricating the filtration assemblies for large water deionizing systems were contacted to assist in the design of the resin reactor. Use of filter cylinders installed in the bottom of the reactor was necessary to remove the liquid streams from the resin as shown in Figure 7. The full-scale manufacturing process required the purchase and installation of a 2000-gallon glass-lined reactor to accommodate the resin. Rather than the standard curved-blade impeller, a glass-lined pitched-blade turbine agitator was installed in the reactor to improve the mixing of the resin. A hub assembly with two radially oriented tiers of four 1 in × 12 in filter cylinders was fabricated for the production reactor. The filtration assembly was supported from the bottom outlet of the reactor. A Teflon[40] annular sleeve and Teflon protection rings for the ends of the filter cylinders were necessary to protect the glass lining against scratches. The filtration assembly and media were constructed in 316 L stainless steel for the start-up of the manufacturing process.

The Manufacturing process. The plant design for the final process includes the recovery of L-DBTA and *n*-butanol as well, as shown in Figure 7. Flow rates and processing times were balanced to maximize the throughput of both the dilevalol and L-DBTA recovery processes. In the final process, water was added to the spent mother liquors and their pH adjusted to between 7 and 8 to partition the L-DBTA into the aqueous layer for its recovery. Residual *n*-butanol was removed from this aqueous stream by vacuum distillation, and the L-DBTA was recovered as a solid upon the addition of dilute sulfuric acid. The crystallization of the recovered L-DBTA was almost instantaneous, affording the opportunity to operate the L-DBTA crystallizer in a semicontinuous mode while collecting the product on a centrifuge. The amino alcohols in *n*-BuOH were loaded on the column for epimerization. The remaining *n*-butanol streams from the

(40) Teflon is a registered trademark of E. I. du Pont de Nemours and Company.

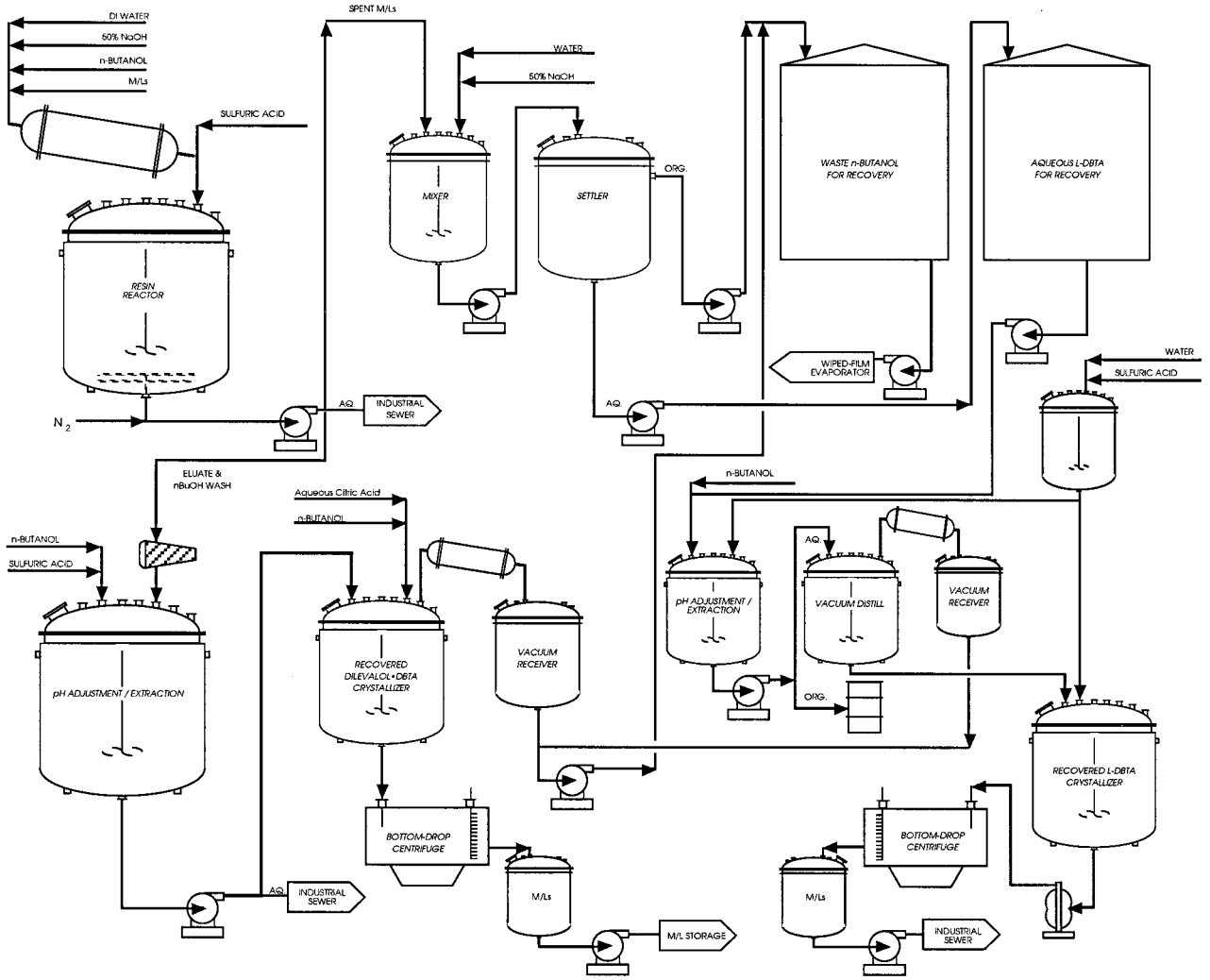


Figure 8. **Plant design for dilevalol recovery processes.**

spent mother liquors, as well as various *n*-butanol washes from the process, were collected for solvent recovery using a wiped-film evaporator.

The batch process was successfully demonstrated on a manufacturing scale approximately 70 times, recovering several tonnes of dilevalol·L-DBTA which was converted to good quality (meeting or exceeding analytical specifications set for the material obtained from the core process) dilevalol hydrochloride salt.[41] The average recovery of the epimerized amino alcohols was 83% for the loading, epimerization, elution, and pH adjustment steps. The recovered dilevalol·L-DBTA crystallization step yield was ~33%, resulting in an overall yield of ~25%. Additionally, 83% of the L-DBTA (expensive reagent at this stage of this product life) present in the original mother liquors was recovered as part of the process and recycled into the crystallization of dilevalol·L-DBTA. The overall plant design for the dilevalol recovery process is shown in Figure 8.

Improved Throughput Commercial Process Plans. Anticipating increased demand for the product and encouraged by the stability of the resin to dilute acid-catalyzed epimerization, we sought to increase the throughput of this process. The experiment described earlier in this manuscript, where higher (90%) resin-loaded amino alcohol was epimerized with the help of additional acid (sulfuric acid in that case) was successfully scaled up in the pilot plant on a 100 kg scale. Thus, with proper equipment resistant to acid corrosion, this process could lead to enhanced throughput, meeting the increased demands. For further improvement in the commercial process, specifications for an alternate filtration assembly constructed in Hastelloy C-276 were generated. This was done to allow for implementing the proposed process, which involved the potential use of dilute sulfuric acid with or without the help of a controlled amount of hydrochloric acid in the process (to take advantage of the better solubility of sodium chloride versus sodium sulfate, and faster epimerization). These changes were not put into practice as a commercial decision was made not to continue with this product.

(41) Dilevalol hydrochloride was prepared from the L-DBTA salt as follows: To a slurry of dilevalol dibenzoyl-L-tartrate in methyl-isobutyl ketone (MIBK) and water was added aqueous NaOH to a pH of 8.4−9.8. The MIBK layer containing the free base was combined with fresh water and then treated with concentrated HCl to pH ≤ 1, maintaining a temperature of 50−60 °C. The resultant slurry was cooled to about 20 °C, filtered, washed with MIBK and water, and dried at 75 °C. The yield was 85−95%. Typical purity of this material was >97%, producing quality material that passed a battery of tests.

In summary, through a combination of understanding the reaction mechanism, an optimization of reagent, (a sulfonic acid resin in this case), and appropriate modifications to the reactor, a novel, fully reproducible, commercial epimerization process for the preparation of dilevalol, from what would otherwise have been an expensive waste, was developed. This process was scaled up to prepare several tonnes of dilevalol.

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