Comprehensive Mass Analysis of Commercial Processes for L-Dopa Manufacture

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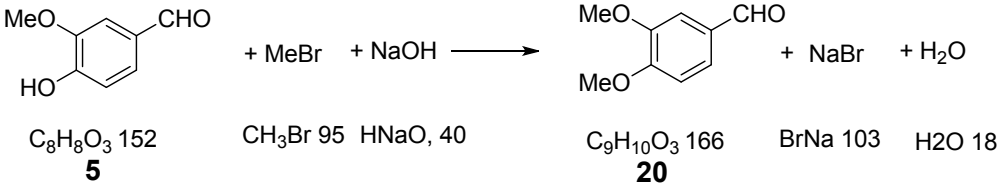
Supporting Information

The Sankyo Process

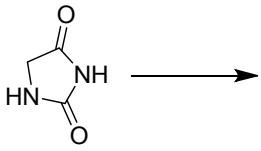
Reaction 1



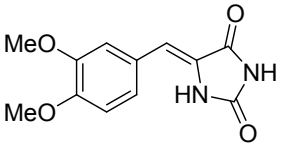
$C_8H_8O_3$ 152 **5** | CH_3Br 95 HNaO, 40 | $C_9H_{10}O_3$ 166 **20** | BrNa 103 | H2O 18

Input 287 Output 287

Reaction 2

20 + 

$C_3H_4N_2O_2$ 100 **21**



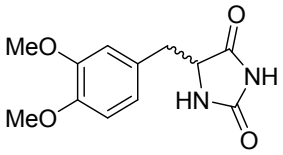
$C_{12}H_{12}N_2O_4$ 248 **22** | + H_2O H2O 18

Input 266 Output 266

Reaction 3

22 + H_2 Raney Ni

H_2 2



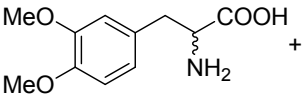
23 $C_{12}H_{14}N_2O_4$ 250

Input 250 Output 250

Reaction 4

23 + $2H_2O$

H2O 18

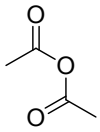


24, $C_{11}H_{15}NO_4$ 225 + CO_2, 44 + NH_3 H3N 17

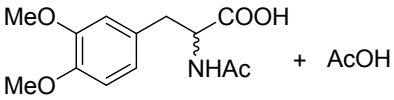
Input 286 Output 286

Reaction 5

24 +



$C_4H_6O_3$ 102



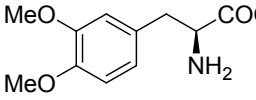
25, $C_{13}H_{17}NO_5$ 267 + AcOH $C_2H_4O_2$ 60

Input 327 Output 327

Reaction 6

25 + 0.5 H_2O Amidase

H2O 18



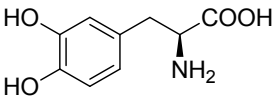
0.5 (*S*)-**24**, $C_{11}H_{15}NO_4$ 225 + 0.5 (*R*)-**25** 267 + 0.5 AcOH 60

Input 276 Output 276

Reaction 7

0.5 (S)-**24** + HBr

HBr 81



0.5 + MeBr

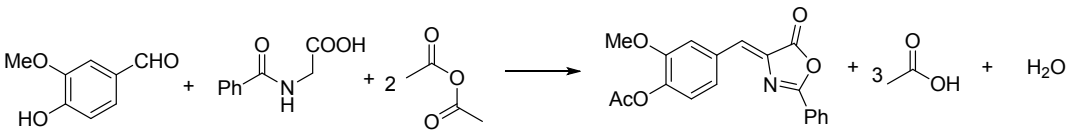
$C_9H_{11}NO_4$ 197 **1** L-Dopa | CH_3Br 95

Input 193.5 Output 193.5

Reaction	Input	Output	Mw	Equivalent	Mass
1	**5**		152	1	152
	MeBr		95	1	95
	NaOH		40	1	40
		20	166	1	
2	**21**		100	1	100
		22	248	1	
3	H_2		2	1	2
		23	250	1	
4	H_2O		18	2	36
		24	225	1	
5	Ac_2O		102	1	102
		25	267	1	
6	H_2O		18	0.5	9
		(*S*)-**24**	225	0.5	
7	HBr		81	1	162
		L-Dopa	197	0.5	**99**
Total input					698
Atom economy	0.141				

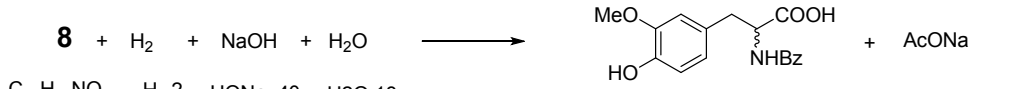
The Hoffman La-Roche Process

Reaction 1



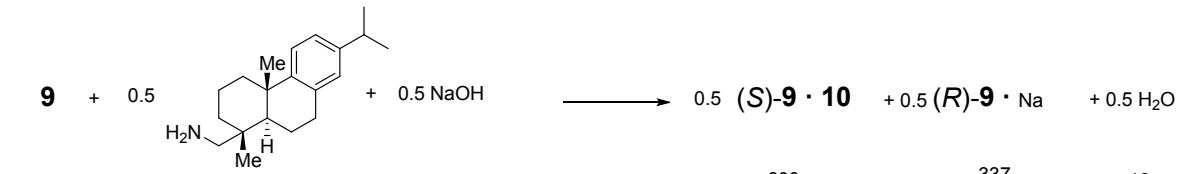
$C_8H_8O_3$ 152	$C_9H_9NO_3$ 179	$C_4H_6O_3$ 102	$C_{19}H_{15}NO_5$ 337.10	$C_2H_4O_2$ 60	H2O 18
5	**6**		**8**		
Total Mass	535		535		

Reaction 2



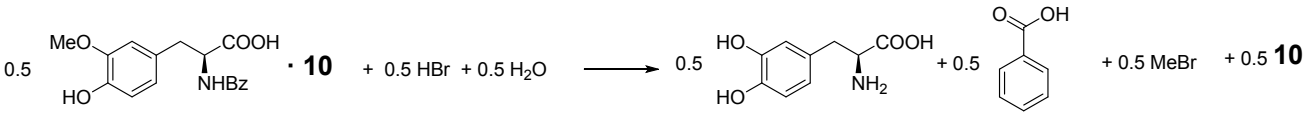
$C_{19}H_{15}NO_5$ 337.10	H_2 2	HONa, 40	H2O 18	$C_{17}H_{17}NO_5$, 315	$C_2H_3NaO_2$ 82.03
				9	
Total Mass	397			397	

Reaction 3



$C_{17}H_{17}NO_5$, 315	$C_{20}H_{31}N$ 285	HNaO, 40	600	337	18
	10				
Total Mass	478		478		

Reaction 4



600	HBr 81	18	$C_9H_{11}NO_4$ 197	$C_7H_6O_2$ 122	CH_3Br 95	285
(*S*)-**9**· **10**			**L-Dopa**			
Total Mass	350		350			

Atom economy

Reaction	Input	Output	Mw	Equivalent	Mass
1	**5**		152	1	152
	6		179	1	179
	Ac_2O		102	2	204
		8	337	1	
2	**H_2**		2	1	2
	NaOH		40	1	40
	H_2O		18	1	18
		9	315	1	
3	**10**		285	0.5	143
	NaOH		40	0.5	20
		(*S*)-**9** • **10**	600	0.5	
4	**HBr**		81	0.5	41
	H_2O		18	0.5	9
		L-Dopa	197	**0.5**	99
Total input					808
Atom economy	0.123				

Lab protocol for the Hofmann La-Roche Process[1]

Outline:

1. D,L-N-Benzoyl-3-(4)-(o-acetyl-vanillylidene)-2-oxazoline-5-one (**8**) is prepared by Erlenmeyer reaction with vanillin and hippuric acid.

2. The product is then reduced by hydrogenation under basic condition to give D,L-N-benzoyl-3-(4-hydroxy-3-methoxyphenyl)-alanine (**9**).

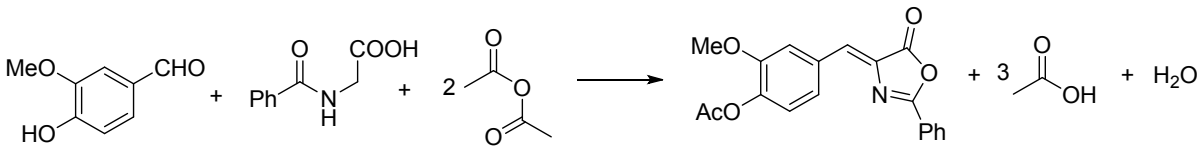
3. The D, L-N-benzoyl-3-(4-hydroxy-3-methoxyphenyl)-alanine is resolved by classical resolution by forming salt with dehydroabietylamine ((*S*)-**9** and **10**).

4. In the last step, the salt is decomposed and (*S*)-**9** is deprotected in aqueous HBr to give L-Dopa as the final product.

5. The D-enatiomer of N-benzoyl-3-(4-hydroxy-3-methoxyphenyl)-alanine can be recycled by racemization.

6. MeBr is decomposed by reacting with ethanolamine in a scrubber.

Step 1



$C_8H_8O_3$ 152 **5**

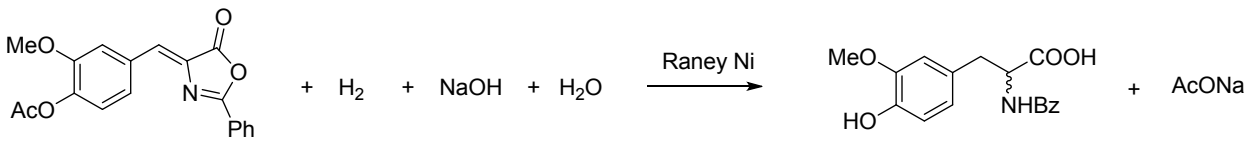
$C_9H_9NO_3$ 179 **6**

$C_{19}H_{15}NO_5$ 337.10 **8**

1. Mix 76 g of vanillin, 89.5 g of hippuric acid **6** and 75 g of sodium acetate with 150 ml of acetic anhydride and 25 ml of DMF. The mixture is heated to 100 °C for 30 min. When reaction completes, cool the mixture to ambient temperature, then add 700 ml of water over 15 min to crystallize the product. Chill the solution to 0 °C and continue the crystallization for 4 h. The product is isolated by filtration.
2. The solid is washed by 408 ml (3X of product) of water twice. After drying, 136 g of product **8** is isolated (80% yield).

Input								
Chemical	**Vol (ml)**	**Density (g/ml)**	**Weight (g)**	**Mw (g/mol)**	**mol**	**Role**	**X/ref 1 (g/g)**	**PMI**
Vanillin **5**			76	152	0.50	Reference 1	1.00	4.0
Hippuric acid **6**			89.5	179	0.50	reactant	1.18	4.8
Acetic anhydride	150	1.08	162	102	1.59	reactant	2.13	8.6
Sodium acetate			75	82	0.91	catalyst	0.99	4.0
DMF	25	0.944	23.6			Solvent	0.31	1.3
Total input			426.1				5.61	22.6
Theoretical Output								
Expected product								
Compound **8**			168.50	337	0.50	Product	2.22	
Acetic acid			90.00	60	1.50	by product	1.18	
Water			9.00	18	0.50	by product	0.12	
Solvent, excess								
Acetic anhydride		1.08	60.00	102	0.59	excess reactant	0.79	
Sodium acetate			75.00	82	0.91	catalyst	0.99	
DMF		0.944	23.6			solvent	0.31	
Total output			426.10				5.61	
Work up & isolation								
Water	700	1	700			Anti-solvent	9.21	37.1
water	816	1	816			Rinse	10.7	43.2
Total Mass			1516				19.9	80.3
Actual yield: 80%								
Compound **8**			136	337	0.40	Product	1.79	7.20
RF_1	0.5638			CRF_1	4.024			

Step 2



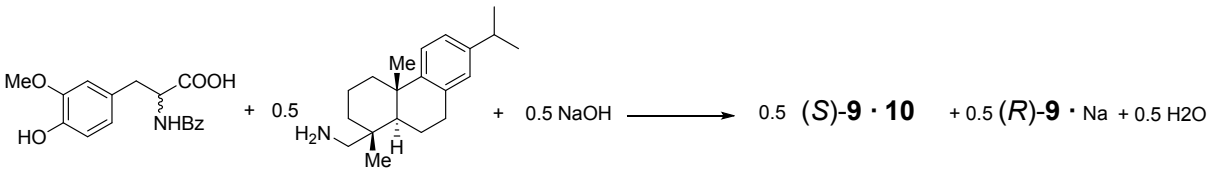
8 **9**

1. Mix 280 g of **8** with 6000 g water. Add 250 g of NaOH and then 70 g of Raney Nickel. Apply hydrogen to 100 atmosphere gauge pressure, and warm the mixture to 60 °C. Continue the reaction for 1 h to complete the hydrogenation.
2. After Nickel catalyst is removed by filtration, the pH of the aqueous solution is adjusted to 2 with 6 N HCl to crystallize the product. The acidified solution is allowed to stand at 0 °C for 16 h to complete the crystallization. The product is isolated by filtration and rinsed with 567 ml (3X final product) water.
3. To recrystallize the product, dissolve the crude product in 400 ml of methanol, and then add 800 ml of water as the anti-solvent. Keep the mixture at 0 °C for 16 h to finish the crystallization. Isolate the product by filtration and rinse with 567 ml water. After drying, 189 g of product **9** is obtained, corresponding to 72% yield.

Input								
Chemical	**Vol (ml)**	**Density (g/ml)**	**Weight (g)**	**Mw (g/mol)**	**mol**	**Role**	**X/ref 2 (g/g)**	**PMI**
Compound **8**			280	337	0.83	ref 2	1.00	(7.1)
water	6000	1.0	6000	18	333.33	Solvent	21.43	152.9
NaOH			250	40	6.25	reactant	0.89	6.4
Hydrogen*			1.66	2	0.83	reactant	0.01	0.04
Raney Ni			70			catalyst	0.25	1.8
Total input			6602				23.58	161.1
Theoretical Output								
Expected product								
rac- **9**			261.72	315	0.83	Product	0.93	
Sodium acetate			68.13	82	0.83	by product	0.24	
Solvent, excess reactant								
Water			5985.04			Solvent	21.38	
NaOH			216.77			Excess reactant	0.77	
Raney Ni			70.00			catalyst	0.25	
Total mass			6602				23.58	
Work up & isolation								
6N HCl	1041	1.11	1156				4.13	29.5
(HCl)			(228)	36.5	6.25	acidify	(0.81)	(5.8)
(Water)			(928)				(3.31)	(23.6)
Water			567			Rinse	2.03	14.5
MeOH	400	0.79	316			Solvent	1.13	8.1
water	800	1	800			Anti-solvent	2.86	20.4
water	567	1	567			Rinse	2.03	14.5
Total mass			2250				12.18	87.0
Actual yield: 72%								
rac- **9**			189	315	0.60		0.675	4.82
RF_2	1.486			CRF_2	7.137			

* Assuming only 1 equivalent of hydrogen is used.

Step 3



9 **10**

1. Prepare the half neutralized solution of **9** by mixing 31.5 g of **9** with 50 ml of 1 N NaOH and 80 ml of MeOH. Warm the solution to 50 °C to dissolve the solid. Add half

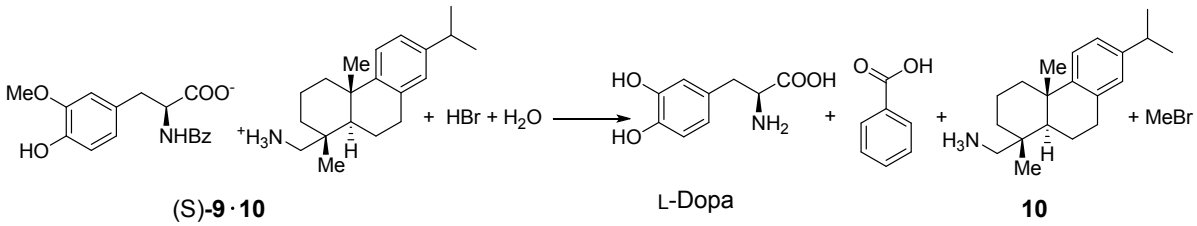
equivalent of resolution agent **10** as a methanol solution (14.2 g in 30 ml MeOH), followed by 10 ml MeOH rinse.

2. If needed, seed the solution to initiate crystallization. Continue crystallization at 50 °C for 1 h, then decrease the temperature to 25 °C over 3 h. Maintain the temperature at 25 °C for 16 to finish the crystallization.
3. Isolate the product by filtration. Rinse the crystalline solid with a cold (10 °C) mixture of MeOH and water (25 ml each). After drying, the amount of product (*S*)-**9 ·10** is 27 g, representing 45% yield (out of 50% theoretical yield).
4. Mother liquor of the resolution:

Chemical	**Mw**	**Wt**	Mol
(*R*)-**9** (82% ee)	315	17.3	0.055
Compound **10**	285	1.4	0.005
NaOH	40	2.0	0.05
MeOH (d 0.79)	32	114	
Water		75	

Input								
Chemical	**Vol (ml)**	**Density**	**Weight**	**Mw**	**mmol**	**Role**	**X/ref. 3**	**PMI**
rac-**9**			31.5	315	100	Reference 3	1.00	(4.80)
NaOH (1N)	50	1.04	52			Reactant	1.65	7.9
(NaOH)			(2)	40	50	Reactant	(0.06)	(0.3)
(water)			(50)			Solvent	(1.59)	(7.6)
Compound **10**			14.2	285	50	Reactant	0.45	2.2
MeOH	120	0.79	94.8			Solvent	3.01	14.5
Total			192.5				6.11	24.6
Theoretical Output								
Expected product								
(*S*)-**9·10**			29.89	600	50	**Product**	0.95	
(*R*)-**10**·Na			16.85	337	50	by product	0.53	
H_2O		1	0.90	18	50	by product	0.03	
Solvent, excess reactant								
Water			50			Solvent	1.59	
Methanol			94.8			Solvent	3.01	
Total mass			192.4				6.11	
Work up & isolation								
Water	25	1	25			Rinse	0.79	3.8
Methanol	25	0.79	19.75			Rinse	0.63	3.0
Total mass			44.75				1.42	6.8
Actual yield: 45%								
Salt (*S*)-**9 • 10**			27	600	0.045	product	0.86	4.13
RF_3	1.167			CRF_3	4.803			

Step 4



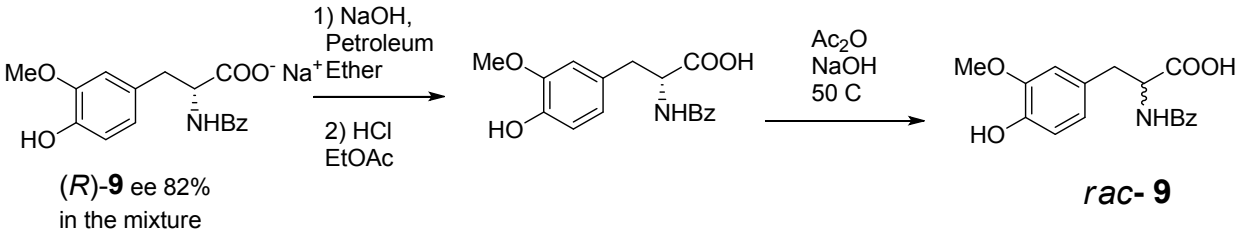
(S)-**9**·**10** L-Dopa **10**

1. Mix 30 g of the salt of (*S*)-**9** and **10** from Step 3 with 5 ml of water, 5 ml of toluene, and 38.4 ml (61.5 g) of 62% HBr. The solution is refluxed between 105-112 °C for 3 h.
2. After cooling, extract the solution with toluene (50 ml X2) to remove benzoic acid.
3. Reduced the solution volume by 80% by evaporation to remove water and HBr, and dilute the residual solution with 60 ml of water. The solution is treated with 1.5 g of activated charcoal for color removal.
4. The product is crystallized by pH adjustment with ammonia solution (10%). The final pH for crystallization is 5.5. Allow the solution to stand at 25 °C for 16 h. Filter to recover the crystalline solid. Dry under vacuum to give 7.3 g of the L-Dopa product (74% yield).

Input									
Chemical	**C (w/w %)**	**Vol (ml)**	**Density (g/ml)**	**Weight (g)**	**Mw (g/mol)**	**mmol**	**Role**	**X/ref. 4 (g/g)**	**PMI**
(*S*)-**9 ·10**				30.00	600	50.00	Ref. 4	1.00	(4.1)
Toluene		5	0.87	4.35			Solvent	0.145	0.60
HBr solution	62%	38.40	1.60	61.44			Reactant	2.05	8.4
(net HBr)				38.09	81	470.28	Reactant	(1.27)	(5.2)
(water)				23.35	18		Reactant	(0.78)	(3.2)
Water				5.00			Solvent	0.17	0.7
Total input				100.8				3.36	9.7
Theoretical Output									
L-Dopa				9.85	197	50	product	0.33	
Benzoic acid				6.10	122	50	by product	0.20	
dehydroabietylamine **10**				14.25	285	50	by product	0.48	
MeBr				4.75	94.9	50	by product	0.16	
Solvent, excess reactant									
Toluene		5	0.87	4.35			Solvent	0.145	
Water				27.45			Solvent	0.91	
HBr				34.04	81	420.28	Excess reactant	1.13	
Total output				100.8				3.36	
Work up & isolation									
Toluene		100	0.87	87			Solvent	2.9	11.9
NH_3 solution*	10%			57.16			Neutralize	1.91	7.9
(net NH_3)				(5.72)	17	336.23		(0.19)	(0.8)
(water)				(51.44)				(1.71)	(7.0)
NH_3 solution**	10%			14.29			Neutralize	0.48	2.0
(Net NH_3)				(1.43)	17	84.06		(0.05)	(0.2)
(water)				(12.86)				(0.43)	(1.8)
Water				60.00			Solvent	2.00	8.2
Active Carbon				1.5				0.05	0.2
Total isolation mass				220				7.34	30.1
Actual yield 74%									
L-Dopa				7.3	197	0.037	Product	0.2433	1.00
RF_4	4.116			CRF_4	4.116				

*NH_3 to neutralize the HBr in distillate ** NH_3 used in crystallization

Step 2-1 Racemization of D-enantiomer[2] (mother liquor of **Step 3**)



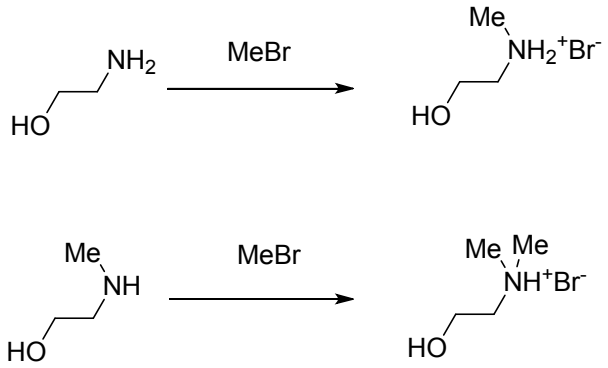
(*R*)-**9** ee 82%
in the mixture
from Reaction 3

rac- **9**

1. Add 50 ml of 2 N NaOH to the mother liquor of resolution in Step 3, and extract the aqueous mixture with 20 ml X2 petroleum ether.
2. Remove methanol from the aqueous phase by evaporation. The volume is reduced to 100 ml
3. Adjust the pH to <2 with 6 N HCl
4. Extract (*R*)-**9** with EtOAc (50 ml X 3 times)
5. Evaporate to remove EtOAc.
6. Mix the residue with 40 ml of 1 N NaOH, and 60 ml of acetic anhydride. Agitate the mixture at 50 °C for 4 h to complete the racemization.
7. Reduce the volume to 30 ml by evaporation.
8. Add 50 ml of water, and extract the mixture with EtOAc (50 ml X 2)
9. After solvent removal, 13 g of racemic **9** is isolated, representing 75% yield.

Input for (*R*)-9 cleaning (based on waste stream from **Step 3**)							
Chemical	**Vol (ml)**	**Density (g/ml)**	**Weight (g)**	**Mw (g/mol)**	**mol**	**Role**	**X/ref.3 (g/g)**
(*R*)-**9**			17.3	315	0.055	Waste from step3	(0.55)
Compound **10**			1.4	285	0.005	Waste from step3	(0.04)
NaOH			2.0	40	0.050	Waste from step3	(0.06)
MeOH	120	0.79	114.6			Waste from step3	(3.64)
Water	75		75.0			Waste from step3	(2.38)
2N NaOH	50.0	1.08	54.0			pH adjustment	1.71
(NaOH)			(4.0)	40.000	0.100		(0.13)
(Water)			(50.0)				(1.59)
Pet. Ether (d 0.64)	40.0	0.64	25.6			Solvent	0.81
6 N HCl	25.0	1.11	27.7			pH adjustment	0.88
(HCl)			(5.5)	36.500	0.150		(0.17)
(Water)			(22.3)				(0.71)
EtOAc	150.0	0.90	134.6			Solvent	4.76
Total input			452.1				14.35
Theoretical output							
Solvent, other chemicals							
Compound **10**			1.4				
MeOH			114.6				
Water			150.0	18			
Pet. Ether (d 0.64)			25.6				
NaCl			8.8	58.5	0.150		
EtOAc			134.6				
Cleaned (*R*)-9			17.3				
Total output			452.1				
Input for racemization							
1N NaOH	40.0	1.04	41.6				1.32
(NaOH)			(1.6)	40	0.04	Catalyst	(0.05)
(Water)			(40.0)	18	2.22	reactant	(1.27)
Ac_2O	60.0	1.082	64.93	102	0.64	Catalyst	2.06
Total input			123.9				3.93
Theoretical output							
rac-**9**			17.325	315	0.55	product	
Solvents, other chemicals							
Water			29.27	18	1.63		
Sodium acetate			3.28	82	0.04		
Acetic acid			73.99	60	1.23		
Total output			123.9				
Workup & isolation							
Water			50				1.59
EtOAc	100	0.897	90				2.84
Total			140				4.43
Step yield 75%							
rac-**9**			13	315	0.41		0.41

Step 4-1 Decomposition of MeBr in a scrubber[3]



Description[3]

1. The MeBr byproduct from Step 4 is introduced in to the scrubber containing aqueous solution of 17.5wt % Ethanolamine.
2. After Reaction 4 completes, the scrubbing reaction continues for additional 2 h while the residual MeBr in Reaction 4 is purged by nitrogen.
3. The removal efficiency is 99.9%.

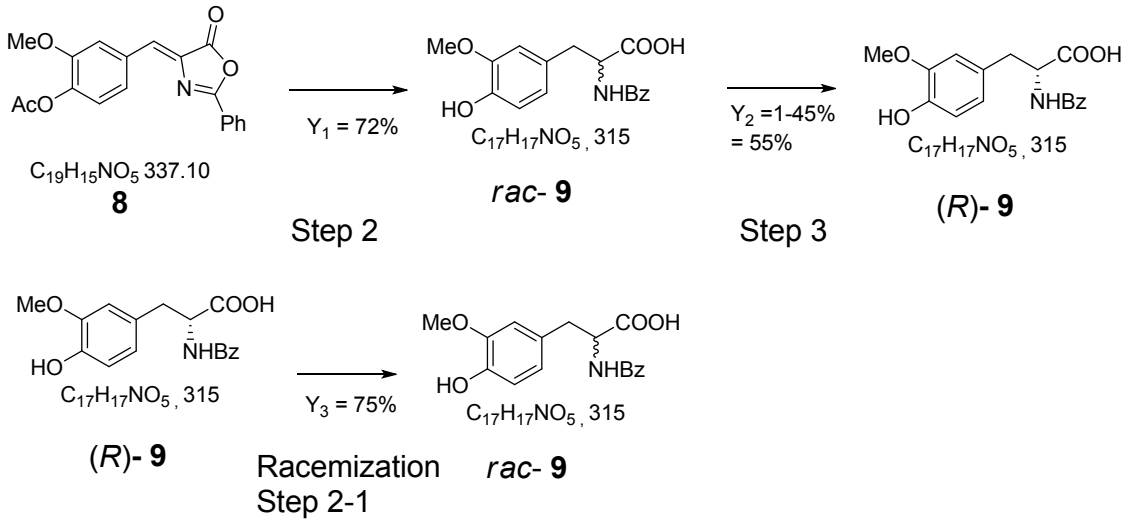
Input for MeBr scrubbing								
	Vol (ml)	**Density (g/ml)**	**Weight (g)**	**Mw (g/mol)**	**mol**	**Role**	**X/ref 4**	**PMI**
MeBr from Step 4			4.75	95	0.050	Step 4 by product	(0.16)	(0.66)
Ethanolamine		1.01	82.49	61.1	1.35	Reactant	2.75	11.3
Water			387.6			Solvent	12.92	53.2
Total input			474.8				15.83	64.5
Theoretical output								
$MeNH(CH_2)_2OH$ HBr			7.02	156.02	0.045		0.23	
$Me_2N(CH_2)_2OH$ HBr			0.85	170.05	0.005		0.03	
$NH_2(CH_2)_2OH$			79.43	61.1	1.300		2.65	
Water			387.6				12.92	
Total output			474.9				15.83	
$RF_{4\text{-}1}$	4.116			$CRF_{4\text{-}1}$	4.116			

Summary of mass efficiency for the process without racemization

Step	RF	CRF	Reactant	Catalyst	Solvent	Isolation	Total
1	0.56	4.02	17.3	4.0	1.3	80.3	102.9
2	1.49	7.13	6.4	1.8	152.9	87.0	248.1
3	1.17	4.8	10.1	0	14.5	6.8	31.4
4	4.12	4.12	8.4	0	1.3	30.1	39.8
4-1	4.12	4.12	11.3	0	53.2	0	64.5
Total			53.5	5.8	223.2	204.2	487

PMI evaluation for alternative process: racemization of (*R*)-**9** to give *rac*-**9**

Step 2-1 (*R*)-**9 isolation and racemization.**



- The racemization reaction (Step 2-1) is a parallel route to prepare *rac*-**9**. The total yield of *rac*-**9** is the sum of Step 2 and racemization (Step 2-1).

  Yield from racemization with Compound **8** as the base =
  $Y_1 Y_2 Y_3 = 72\% \times 55\% \times 75\% = 29.7\%$
  Total yield from both routes = 29.7% + 72% = 101.7%

- The *RF* for *rac*-**9**, with the additional racemization, is determined with the combined yield (effective yield):

$$RF_{2+rac} = \frac{1}{101.7\%} \frac{MW_{Compound\ 8}}{MW_{Compound\ 9}} = 1.052$$

Correspondingly,

$CRF_{2+rac} = RF_{2+rac} * CFR_3 = 1.052 * 4.803 = 5.053$

- The input for racemization uses *rac*-**9** from Step 2 (Ref 3) as the reference in the step protocol. For PMI evaluation, the reference should be adjusted to Compound **8** (Ref 2), the same reference as that in Step 2. The transformation factor is $1/RF_2$ (0.6729) since:

  Mass of Ref 3 $\cdot RF_2$ = Mass of Ref 2

Mass inventory for racemization (Step 2-1) with Compound **8** (ref. 2) as the reference

Input for (R)-**4** cleaning (based on waste stream from Reaction 3)									
Chemical	**Vol (ml)**	**Density (g/ml)**	**Weight (g)**	**Mw**	**mol**	**Role**	**X/ref.3 (g/g)**	**X/ref.2**	**PMI**
(*R*)-**9**			17.3	315	0.055	Waste from Step 3	0.55	0.370	(1.87)
Compound **10**			1.4	285	0.005	Waste from Step 3	0.04		(0.136)
NaOH			2.0	40	0.050	Waste from Step 3	0.06		(0.204)
MeOH	120	0.79	114.6			Waste from Step 3	3.64		(12.4)
Water	75		75.0			Waste from Step 3	2.38		(8.09)
2N NaOH	50.0	1.08	54.0			pH adjustment	1.71	1.15	5.8
(NaOH)			4.0	40.000	0.100		0.13		
(Water)			50.0				1.59	1.07	(5.41)
Pet. Ether (d 0.64)	40.0	0.64	25.6			Solvent	0.81	0.545	(2.8)
6 N HCl	25.0	1.11	27.7			pH adjustment	0.88	0.592	3.0
(HCl)			5.5	36.500	0.150		0.17		
(Water)			22.3				0.71	0.478	(2.42)
EtOAc	150.0	0.90	134.6			Solvent	4.76	3.20	16.2
Total input			452.1						**27.8**
Input for racemization									
1N NaOH	40.0	1.04	41.6				1.32	0.888	4.5
(NaOH)			1.6	40	0.04	Catalyst	0.05		
(Water)			40.0	18	2.22	reactant	1.27	0.855	(4.32)
Ac_2O	60.0	1.082	64.93	102	0.64	Catalyst	2.06	1.39	7.00
Total input			123.9						**11.5**
Workup & isolation									
Water			50				1.59	1.07	5.4
EtOAc	100	0.897	90				2.84	1.91	9.7
Total			140						**15.0**
Step yield 75%									
rac-**9**			13	315	0.41		0.41	0.276	1.39
RF_2		1.486	RF_{2+rac}		1.052		CRF_{2+rac}		5.053

Mass Inventory for Step 2 when racemization is included in the process

Input								
Chemical	**Vol (ml)**	**Density (g/ml)**	**Weight (g)**	**Mw**	**mol**	**Role**	**X/ref 2 (g/g)**	**PMI**
Compound **8**			280	337	0.83	ref 2	1.00	(5.05)
water	6000	1.0	6000	18	333	Solvent	21.43	108.3
NaOH			250	40	6.25	reactant	0.89	4.5
Hydrogen			1.66	2	0.83	reactant	0.01	0.04
Raney Ni			70			catalyst	0.25	1.3
Total input			6601.7				23.58	**114.1**
Work up & isolation								
6N HCl	1041	1.11	1156.3				4.13	20.9
(HCl)			228.1	36.5	6.25	acidify	0.81	
(Water)			928.1				3.31	(16.7)
Water			567			Rinse	2.03	10.3
MeOH	400	0.79	316			Solvent	1.13	5.7
Water	800	1	800			Anti-solvent	2.86	14.5
Water	567	1	567			Rinse	2.03	10.3
Total mass			2250				12.18	**61.5**
Actual yield: 72%								
rac- **9**			189	315	0.60		0.675	3.411
RF_2	1.486		RF_{2+rac}	1.052		CRF_{2+rac}	5.053	

The total PMI of *rac*-**9** from two routes = 1.39 + 3.411 = 4.801, which equals to the PMI of *rac*-**9** in Step 3.

For Step 1: the new $CRF_1 = RF_1 * CRF_{2+rac} = 0.5638 * 5.053 = 2.849$. The required PMI of Compound **8** from Step 1 is reduced from 7.20 to 5.05.

Mass Inventory for Step 1 when racemization is included in the process

Input								
Chemical	**Vol (ml)**	**Density (g/ml)**	**Weight (g)**	**Mw (g/mol)**	**mol**	**Role**	**X/ref 1 (g/g)**	**PMI**
Vanillin **5**			76	152	0.50	Reference 1	1.00	2.9
Hippuric acid **6**			89.5	179	0.50	reactant	1.18	3.4
Acetic anhydride	150	1.08	162	102	1.59	reactant	2.13	6.1
Sodium acetate			75	82	0.91	catalyst	0.99	2.8
DMF	25	0.944	23.6			Solvent	0.31	0.9
Total input			426.1				5.61	16.0
Theoretical Output								
Expected product								
Compound **8**			168.5	337	0.50	Product	2.22	
Acetic acid			90.0	60	1.50	by product	1.18	
Water			9.0	18	0.50	by product	0.12	
Solvent, excess								
Acetic anhydride		1.08	60.0	102	0.59	excess reactant	0.79	
Sodium acetate			75.0	82	0.91	catalyst	0.99	
DMF		0.944	23.6			solvent	0.31	
Total output			426.1				5.61	
Work up & isolation								
Water	700	1	700			Anti-solvent	9.21	26.2
water	816	1	816			Rinse	10.7	30.5
Total Mass			1516				19.9	56.7
Actual yield: 80%								
Compound **3**			136	337	0.40	Product	1.79	5.09
RF_1	0.5638			CRF_1	2.849			

Summary of material efficiency with racemization in the process

Contribution to global PMI by reaction steps

Step	RF	CRF	Reactant	Catalyst	Solvent	Isolation	Total
1	0.56	2.85	12.3	2.8	0.9	56.7	72.7
2	1.49	5.05	4.6	1.3	108.3	61.5	175.7
Rac.	1.05	5.05	0	11.5	0.00	42.8	54.3
3	1.17	4.8	10.1	0	14.5	6.8	31.4
4	4.12	4.12	8.4	0	1.3	30.1	39.8
4-1	4.12	4.12	11.3	0.00	53.2	0.00	64.5
Total			46.7	15.6	178.2	197.9	438

References

1. Jaffe, G. M., Rehl, W. R., Hoffman-La Roche, US 3714242, 1973
2. Kaiser, A. Scheer, M., Hausermann, W., Marti, L., Hoffman-La Roche, US3969397, 1976
3. K. Hettenback, D. J. am Ende, K. Leeman, E. Dias, N. Kasthurikrishnan, S. J. Brenek and P. Ahlijanian, *Org. Pro.Res. Dev.* 2002, **6**, 407-415

Flow diagram of Roche Process to manufacture 100 kg L-Dopa

		Roche Process Flow Diagram Step 1					Reaction Yield	0.8		
Input	Kg			**Stream**	**Waste (Kg)**	**Time (h)**	**Stream 1-1**	Weight (kg)	kMol	
Vanillin **5**	402.26	→	Erlenmeyer reaction				Acetic acid	476.4	7.94	From reaction
Hippuric acid **6**	473.7					20	NaOAc	398.2	4.86	
NaOAc	398.2						DMF	124.90		
Ac_2O	857.4		↓				(Ac_2O)	(318.5)	3.12	excess
DMF	124.9						HOAc	374.4	6.24	from Ac_2O
							Water	3696.4		
				1-1			Stream total	5070		
Water	3705	→	Crystallization, isolation	→	5036.55	4				
			↓				**Stream 1-2**			
							Water	4319		
			Rinse, dry	**1-2**			Organic	178.2		Un-isolated **8**
Water	4319	→		→	4439.30		Stream total	4497		
			↓							
Reaction input	2256									
Isolation input	8024		Compound **8**	**1-3**	**Est. Total waste**	**Total waste**				
Total input	10280		713		9567	9567				

		Roche Process Flow Diagram Step 2					Reaction Yield	0.72		
Input	Kg			**Stream**	**Waste (Kg)**	**Time (h)**	**Stream 2-1**	Weight (kg)	kMol	
Compound **8**	713	→	Hydrogenation, 100 atm, 60 °C	**2-1**			Raney Ni	178.4		
NaOH	637			→	178.37	1				
Water	15280						**Stream 2-2**			
Raney Ni	178.4		↓				NaOAc	173.7	2.12	
H_2	4.3						(NaOH)	552.3	13.8	
			↓				(HCl)	580.9	15.9	
			Crystallization 0 °C, isolation	**2-2**			NaCl	807.	13.8	
6N HCl	2945	→		→	20311.81	16	HCl	76.7	2.1	
Water	1447						Water	19301		
			↓				Stream total	20359		
			↓				**Stream 2-3**			
MeOH	806	→	Recrystallization 0 °C, isolation	**2-3**			MeOH	806		
Water	3487			→	4467.70	16	Water	3487		
							Organic	187		Un-isolated **9**
			↓				Stream total	4480		
Reaction input	16813		↓							
Isolation input	8685		*rac*-**9**	**2-4**	**Est. Total waste**	**Waste total**				
Total input	25498		480		25018	25018				

		Roche Process Flow Diagram Step 3					Reaction Yield	0.45	
Input	Kg			**Stream**	**Waste (Kg)**	**Time (h)**	**Stream 3-1**	**Weight (kg)**	kMol
rac - **9**	**480.2**	→	Diastereomer Crystallization, 25-50 °C				(*R*)-**9**	264.10	0.84
1 N NaOH	792.29					20	Compound **10**	20.58	0.072
Methanol	1441						NaOH	30.4	0.76
Compound **10**	216.1		↓				MeOH	1742.08	
							Water	1143.16	
MeOH	**301.6**	→	Isolation by filtration and drying	**3-1**			(*R*)-**9** in Stream 3-1 can be recycled by racemization		
Water	381.26			→	3200.30				
			↓						
Reaction input	2929								
Isolation input	682.81		Salt of (*S*)-**9**· **10**	**3-2**	**Est. total waste**	**Waste total**			
Total input	3612		412		3200	3200			

		Roche Process Flow Diagram Step 4					Reaction Yield	0.74		
Input	Kg			**Stream**	**Waste (Kg)**	**Time (h)**	**Stream 4-2**	**Wt (kg)**	kMol	
Salt of (*S*)-**9**· **10**	**411.6**	→	Deprotection Reflux at 110 °C	**4-1** →			Toluene	1244.62		
Toluene	59.27				65.10	3	Benzoic acid (122)	83.69	0.69	
62% HBr	843.7									
Water	68.61		↓							
							Stream 4-3			
			Remove benzoic acid by extraction with toluene	**4-2** →			NH_4Br (97.9)	452.71	4.62	
Toluene	1185	→			1328.30		Water	1009.01		
			↓				**Stream 4-4**			
			↓				Activated carbon	20.58		
NH_3 (10%)	786.1	→	Evaporation (80% reduction) to remove HBr, then neutralize distillate with NH_3	**4-3** →	1461.72					
						1	**Stream 4-5**			
							NH_4Br (97.9)	113.77	1.16	
			↓				Water	1076.34		
			↓				Compound **10**	195.50	0.69	
			Discoloration, filtration	**4-4** →			Organic	34.6		Unisolated **1**
Water	823.2	→			20.58					
Activated carbon	20.58									

Continue from the last page

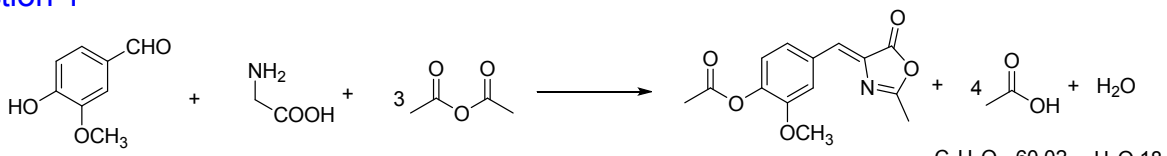
							Stream 4-1				
			Crystallization, Product isolation and drying	**4-5**			MeBr (94.9)	65.10	0.69	Gas
10% NH_3	197.6				1420.25						
Reaction input	2568.5		L-Dopa product (Kg)								
Isolation input	1827.4			**4-6**							
					Est. total waste	**Waste total**					
Step total	4396		**100**		4296	4296					

Roche Process Flow Diagram MeBr decomposition, Step 4-1

Input	Kg			**Stream**	**Waste (Kg)**	**Time (h)**			
MeBr (Stream 4-1)	65.10		Decompose MeBr with a scrubber	**4-7**			**Stream 4-7**		kMol
Ethanolamine	1133				6509.3		$MeNH(CH_2)_2OH$ HBr	96.80	0.62
Water	5312.0						$Me_2N(CH_2)_2OH$ HBr	11.07	0.07
							Water	5312	
							(HBr)		0.69
Total Input	6509.8						$NH_2(CH_2)_2OH$	1089.40	17.86
							Total Waste	6509.3	

The Monsanto Process

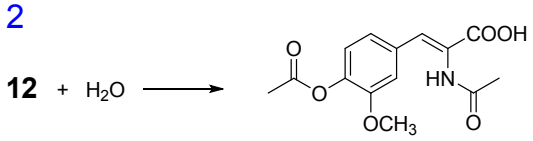
Reaction 1



$C_8H_8O_3$ 152 **5** + $C_2H_5NO_2$ 75 **11** + $C_4H_6O_3$ 102 → $C_{14}H_{13}NO_5$ 275 **12** + $C_2H_4O_2$ 60.02 + H_2O 18

Total Mass 533 533

Reaction 2

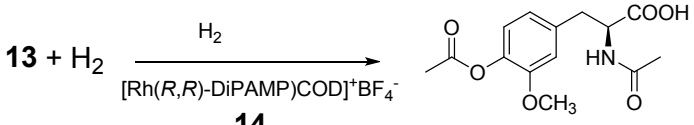


H_2O 18

$C_{14}H_{15}NO_6$ 293 **13**

Total Mass 293 293

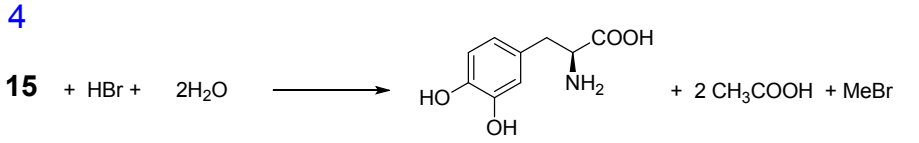
Reaction 3



H_2 2 **14** $C_{14}H_{17}NO_6$ 295 **15**

Total Mass 295 295

Reaction 4



HBr 81 H2O 18 $C_9H_{11}NO_4$ 197 **1** $C_2H_3O_2$ 60 CH_3Br 95

Total Mass 412 412

Atom economy

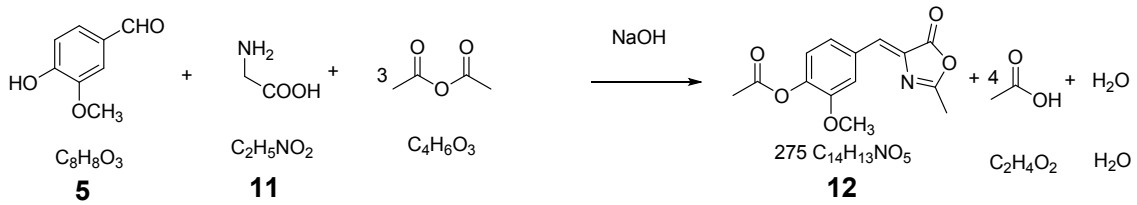
Reaction	Input	Output	Mw	Equivalent	Mass
1	**5**		152	1	152
	11		75	1	75
	Ac_2O		102	3	306
		12	275	1	
2	**H_2O**		18	1	18
		13	293	1	
3	**H_2**		2	1	2
		15	295	1	
4	**HBr**		81	1	81
	H_2O		18	2	36
		L-Dopa		1	**197**
Total input					670
Atom economy	0.294				

Lab Protocol of the Monsanto Process[1]

Outline:

1. Azlactone (*Z*)-2-methoxy-4-((2-methyl-5-oxooxazol-4(5H)-ylidene)methyl)phenyl acetate (**12**) is prepared by Erlenmeyer reaction from vanillin and glycine.
2. The azlactone **12** is then hydrolyzed to give the corresponding acetyl enamide **13**.
3. The enamide is reduced to the corresponding amide **15** by asymmetric hydrogenation with a [Rh(*R*,*R*)-DiPAMP]COD]$^+BF_4^-$ catalyst.
4. L-Dopa product is produced by de-protection of **15** with HBr.

Step 1



Description: [1,3]

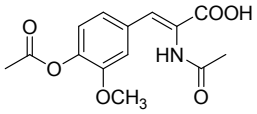
1. Mix 300 g of acetic anhydride, 10 g of NaOH, and 152 g vanillin (**5**), heat to 100 °C over 2 h.

2. Add 75 g glycine (**11**) and 102 g of acetic anhydride over 1 h. Hold the temperature for additional 2 h at 90-95 °C.
3. To start crystallization Cool to 50 °C over 2 h. and Decrease to 25 °C over 1 h and hold the temperature for 1 h to finish. Isolate the product **12** by filtration.
4. Wash the product with 200 g acetic acid under ambient temperature. The procedure gives 190 g of the azalactone product **12** (yield 69%)[2]

Input								
Chemical	**Vol (ml)**	**Density (g/ml)**	**Weight (g)**	**Mw**	**Mol**	**Role**	**X/ref. 1**	**PMI**
Vanillin **5**			152	152	1.00	Ref 1	1.00	1.63
Acetic anhydride		1.08	402	102	3.94	Reactant	2.64	4.32
NaOH			10	40	0.25	Catalyst	0.07	0.114
Glycine **11**			75	75	1.00	Reactant	0.49	0.801
Total input			639				4.20	6.87
Theoretical Output								
Expected Product								
Compound **12**			275	275	1	**Product**	1.81	
(Acetic acid)				60	4	by product		
(water)				18	1	by product		
(NaOH)				40	0.25	Catalyst		
(Acetic anhydride)				102	0.94	Excess reactant		
Acetic acid		1.05	337.9	60	5.63		2.22	
NaOAc			20.5	82	0.25		0.13	
Water		1	5.6	18	0.31		0.04	
Total			639				4.20	
Work up & isolation								
Acetic acid		1.05	200				1.32	2.158
Actual Yield 69%								
Compound **12**			190	275	0.69		1.25	2.04
RF_1	0.8011			CRF_1	1.635			

Step 2

12 + H_2O ⟶



(*Z*)-2-methoxy-4-((2-methyl-5-oxooxazol-4(5*H*)-ylidene)methyl)phenyl acetate

293 $C_{14}H_{15}NO_6$

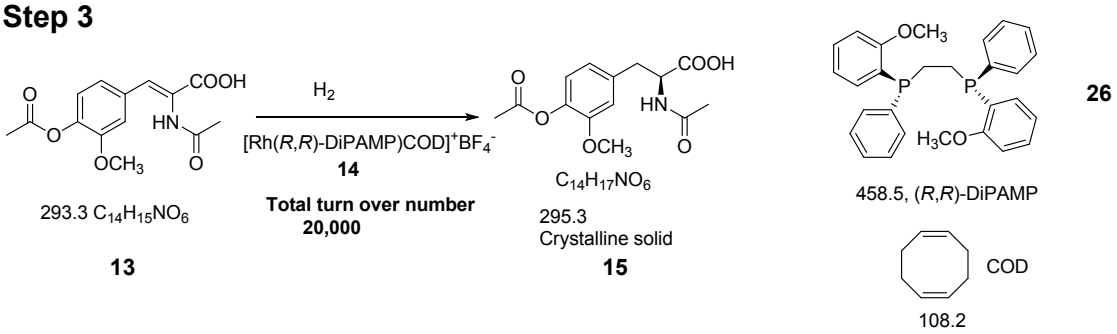
13

Description:

1. Hydrolysis: add 100 g **12** to 100 g water and 300 g of acetone (density = 0.79). Heat to reflux at 65 °C for 1 h and hold for 3 h.
2. Start to crystallize 13 by distilling off acetone (bp = 56 °C) over 4 h. Cool to room temperature over 2 h.
3. The liquid is removed by filtration to give 101.3 g of **13**, corresponding to 95% yield.

Input								
Chemical	**Vol (ml)**	**Density (g/ml)**	**Weight (g)**	**Mw**	**mol**	**Role**	**X/ref. 2**	**PMI**
Compound **12**			100	275	0.36	**Ref 2**	1.00	(2.04)
Acetone		0.79	300	58	5.17	solvent	3.00	6.12
Water			100	18	5.56	reactant	1.00	2.04
Total input			500				5.00	8.2
Theoretical Output								
Expected product								
Compound **13**			106.55	293	0.36	Product	1.07	
Solvents, excess reactants								
Acetone			300			Solvent	3.00	
Water			93.45	18	5.19	Excess reactant	0.93	
Total output			500				5.00	
Actual yield 95%								
Compound **13**			101.3	293	0.35		1.01	2.064
RF_2	0.988			CRF_2	2.041			

Step 3

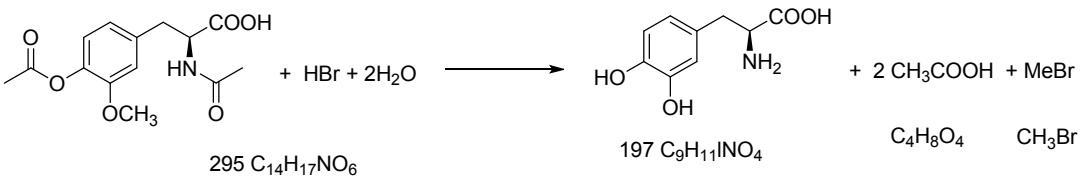


Description: [3]

1. Mix 100 g of **13** with 664 g iPrOH and 82.5 g Water, 37 g of 50% NaOH. The product is a slurry.
2. Purge the solution with nitrogen twice, followed by applying hydrogen at gauge pressure of 3.5 atm.
3. Raise the temperature to 50 °C over 1 h.
4. Add the solution of catalyst **14** (in 2 g of iPrOH), and continue the reaction for 1 h to complete. Cool the solution to 25 °C over 1 h.
5. Add 46 g of concentrated HCl (37%, d = 1.2, 436 g/L, 12 M) over 2 h to crystallize the product.
6. Distill (Azeotropic of iPrOH and water: bp = 80.3 °C, 12 wt % water,) to remove 600 ml of the solvent (d = 0.905) over 5 h, reducing the volume to about 400 ml.[4]
7. Cool the mixture to 25 °C over 3 h, followed by filtration to isolate the product **15**. The quantity is 90.6 g, corresponding to 90% yield. The *ee* is > 99%.

Input									
Chemical	**Concentration (w/w %)**	**Vol (ml)**	**Density**	**Weight (g)**	**Mw**	**mol**	**Role**	**X/ref. 3**	**PMI**
Compound **13**				100	293	0.34	Ref. 3	1.00	(2.07)
iPrOH			0.8	666			Solvent	6.66	13.76
Compound **14**				0.00129	756	1.71E-06	Catalyst	1.E-05	2.7.E-05
H_2				0.682	2	0.34	Reactant	0.01	0.014
Water				82.5			Solvent	0.83	1.715
NaOH solution	50%		1.52	37			Catalyst	0.37	0.764
(Water)				18.5				0.19	
(NaOH)				18.5	40	0.46		0.19	
Total input				886				8.86	16.2
Theoretical output									
Expected products									
Compound **15**				100.68	295	0.34	Product	1.01	
Compound **14**				0.00129			Catalyst	1.E-05	
NaOH				18.5			Catalyst	0.19	
Solvents excess reactants									
iPrOH				666			Solvent	6.66	
Water				101			Solvent	1.01	
Total output				886				8.86	
Work up & isolation									
HCl solution	37%		1.2	46				0.46	0.9504
(HCl)				17.02	36.5	0.47		(0.17)	
(Water)				28.98				(0.29)	
Total				46				0.46	0.95
Actual yield 90%									
Compound **15**				90.61	295	0.31	Product	0.91	1.88
RF_3	1.104			CRF_3	2.066				

Step 4



295 $C_{14}H_{17}NO_6$

15

197 $C_9H_{11}INO_4$

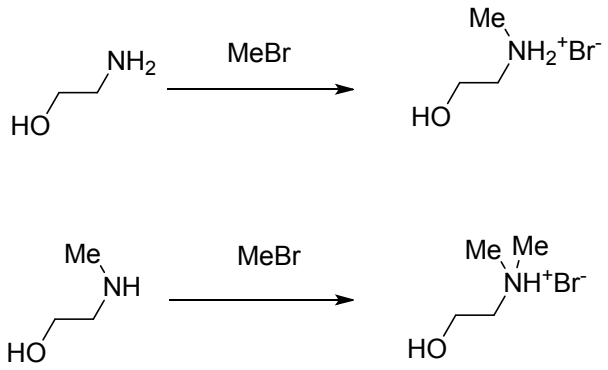
1

Description: [5]

1. Add 250 g HBr solution to 89 g of **15** (48%, d=1.49).
2. Heat to 105-110 °C over 2 h and reflux at the temperature for 3 h. Cool the solution to 25 °C over 3 h,
3. Neutralize the solution to pH 3 with NaOH (solution in 90 ml water) over 3 h.
4. Isolate crystalline L-Dopa product by filtration.
5. Re-slurry in water (90 ml) by heating to 90 °C over 1 h and hold at the temperature for 1 h, then cool the temperature to 25 °C over 2 h.
6. Recover the product by filtration.
7. Dry the product under vacuum to obtain 47.5 g final product **1** (0.24 mol, 80% yield).

Input									
Chemical	**Concentration**	**Vol (ml)**	**Density**	**Weight**	**Mw**	**mol**	**Role**	**X/Ref 4**	**PMI**
Compound **15**				89	295	0.30	**Ref 4**	1.00	(1.87)
HBr solution	48%		1.49	250				2.81	5.26
(HBr)				120	81	1.48	Reactant	(1.35)	(2.52)
(Water)				130	18	7.22	Reactant	(1.461)	(2.73)
Total input				339.00				3.81	5.26
Theoretical output									
Expected products									
L-Dopa **1**				59.43	197	0.30	Product	0.67	
Acetic acid				36.20	60	0.60	by product	0.41	
MeBr				28.66	95	0.30	by product	0.32	
Solvents, excess reactants									
HBr				95.56	81	1.18	Excess reactant	1.07	
Water				119.14	18	6.62	Excess reactant	1.34	
Total output				339.00				3.81	
Work up & isolation									
NaOH				48	40	1.2	neutralize	0.54	1.01
Water				180				2.02	3.78
total				228				2.56	4.79
Actual yield 80%									
L-Dopa **1**				47.55	197	0.24	Product	0.534	1.00
RF_4	1.872			CRF_4	1.872				

Step 4-1 Removal of MeBr by a scrubber



Description[6]

1. The MeBr byproduct from Step 4 is introduced in to the scrubber containing aqueous solution of 17.5wt % Ethanolamine.
2. After Reaction 4 completes, the scrubbing reaction continues for additional 2 h while the residual MeBr in Reaction 4 is purged by nitrogen.
3. The removal efficiency is 99.9%.

Input								
Chemical	**Vol (ml)**	**Density (g/ml)**	**Weight (g)**	**Mw**	**mol**	**Role**	**X/ref. 4**	**PMI**
MeBr from Step 4			28.66	95.00	0.30	Step 4 by product	0.32	(0.599)
Ethanolamine			497.71	61.10	8.15	Reactant	5.59	10.46
Water			2340.46	18.00		Solvent	26.30	49.23
Total input			2866.83				32.21	59.69
Theoretical output								
$MeNH(CH_2)_2OH$ HBr			42.36	156.00	0.27	product	0.48	
$Me_2N(CH_2)_2OH$ HBr			5.13	170.00	0.03	product	0.06	
$NH_2(CH_2)_2OH$			478.49	61.00	7.84	excess reactant	5.38	
Water			2340.46			Solvent	26.30	
Total output			2866.43				32.21	
$RF_{4\text{-}1} = RF_4$	1.872			$CRF_{4\text{-}1} = RF_4$ X1		1.872		

PMI summary

Step	RF	CRF	Reactant	Catalyst	Solvent	Isolation	Total
1	0.801	1.64	6.75	0.11	0.00	2.16	9.0
2	0.988	2.04	2.04	0.00	6.12	0.00	8.2
3	1.104	2.06	0.02	0.76	15.48	0.95	17.2
4	1.872	1.87	5.26	0.00	0.00	4.79	10.1
4-1	1.872	1.87	10.46	0.00	49.23	0.00	59.7
Total			24.53	0.88	70.83	7.90	104

Reference:

1. W. S. Knowles, M. L. Sabacky and B. D. Vineyard, Monsanto Co. GB1351911, 1974
2. K. N. F. Shaw, A. McMillan and M. D. Amstrong, *J. Am. Chem. Soc.* 1958 **23**, 27-32 (for yield correction from 45% to 69%)
3. W. S. Knowles, M. L. Sabacky, and B. D. Vineyard, Monsanto Co. US 4008281 1977,
4. L. H. Horseley, *Azeotropic data – III*, ed, R. F. Gould, American Chemical Society, Washington D. C.; **1973**; pp 18
5. Assuming deprotection yield 85%, and lose 5% after two washes. T. W. Green, and P. G. M. Wuts, in *Protective Groups in Organic Synthesis*, 2nd ed. Wiley, New York, **1991**, pp 146-148.
6. The amounts of chemicals are based on a pilot test results (Table 3, entry 4) of K. Hettenback, D. J. am Ende, K. Leeman, E. Dias, N. Kasthurikrishnan, S. J. Brenek and P. Ahlijanian, *Org. Process Res. Dev.* 2002, **6**, 407-415

Flow diagram of the Monsanto Process to manufacture 100 kg L-Dopa

		Monsanto Process Flow Diagram Step 1							
								Isolation yield	0.69
	Kg				**Waste (Kg)**	**Reaction time (h)**			
Compound 5	163		Erlenmeyer reaction 95 ˚C, filtration	**1-1**			**Stream 1-1**	Weight (kg)	kMol
Acetic anhydride	432	→		→	391	2	(NaOH)		0.27
Glycine	81						(AcOH)		4.30
NaOH	11		↓				(H_2O)		1.08
			↓				(Ac2O)		1.00
			Rinse, Dry	**1-2**			NaOAc	22	0.27
Acetic acid	215	→		→	307		Water	6	0.34
			↓				AcOH	363	6.04
			↓						
			↓				**Stream 1-2**		
Reaction input	686		**Compound 12**				AcOH	215	
Isolation input	215			**1-3**			Un-isolated **12**	92	0.33
					Estimated total waste	**Total Waste**			
Step total	901		204		697	697			

		Monsanto Process Flow Diagram Step 2						Isolation yield	0.95
	Kg				**Waste (Kg)**	**Reaction time (h)**			
Compound 12	204		Hydrolysis 65 °C, remove acetone by distillation	**2-1**			**Stream 2-1**	Weight (kg)	kMol
Acetone	612	→		→	612	4	Acetone	612	
Water	204								
			↓				**Stream 2-2**		
							Water	191	10.60
			Filtration	**2-2**			Un-isolated **13**	10	0.04
				→	201				
			↓						
			Compound 13						
Reaction input	1020			**2-3**					
					Estimated total waste	**Waste total**			
Step input	1020		207		814	813			

		Monsanto Process Flow Diagram Step 3						Isolation yield	0.9
	kg				**Waste (kg)**	**Reaction time (h)**			
Compound 13	207		Hydrogenation 50 °C				**Stream 3-1**	Wt (kg)	kmol
iPrOH	1376	→				1	iPrOH	987	
Water	171						Water	135	
50% NaOH	76		↓						
hydrogen	1.41						**Stream 3-2**		
Catalyst 14	0.0027						NaCl	55.89	0.96
							Catalyst **14**	0.0027	
			↓				Water	152.13	
			Neutralization Crystallization				iPrOH	389	
37% HCl	95.0	→					Un-isolated **15**	21	0.07
			↓						
			Distillation 85 °C	**3-1**					
				→	1122	5			

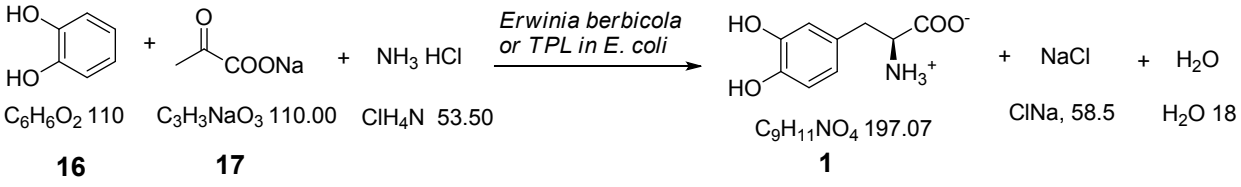
Continue from the last page

			↓						
			Filtration	3-2					
				→		618			
			↓						
Reaction input	1832								
Isolation input	95.0		**Compound 15**	**3-3**	**Estimated total waste**	**Waste total**			
Step total	1927		187.2	**kg**	1739	1739			

			Monsanto Process Flow Diagram Step 4					Yield	0.8
	kg				**Waste (Kg)**	**Reaction time**	**Stream 4-1**	Wt (kg)	**kmol**
Compound 15	187		Deprotection Reflux 110 °C	**4-1**			MeBr	60.28	0.63
48% HBr	526	→		→	60.28	3			
							Stream 4-2	Wt	**mol**
			↓				NaBr	256	2.48
NaOH	101	→	Neutralization Crystallization				AcOH	76	1.27
Water	189						Water	486	26.97
			↓				**Stream 4-3**	Wt	**mol**
			Filtration	**4-2**			Water	189	
				→	818		Un-isolated **1**	25	0.13
			↓						
			Reslurry at 90 °C						
Water	189	→				1			
			↓						
			Filtration	**4-3**					
				→	214				
Reaction input	713		↓						
Isolation input	480		**L-Dopa Product**						
				4-4	**Est. Total Waste**	**Waste total**			
Step Total	1193		100	**kg**	1093	1092			

		Step 4-1 MeBr Removal (from Step 4)					Removal	0.999	
	kg				**Waste (Kg)**	**Reaction time (h)**			
MeBr	60		Scrubbing				**Stream 4-5**	Weight(kg)	kMol
Ethanolamine	1046	→		→	**4-5**	3	$MeNH(CH_2)_2OH$ HBr	89	0.57
Water	4923						$Me_2N(CH_2)_2OH$ HBr	11	0.06
					Total Waste		Ethanolamine	1008	16.52
Total input	6030				6030		Water	4923	

The Ajinomoto Process



Total mass 274 274

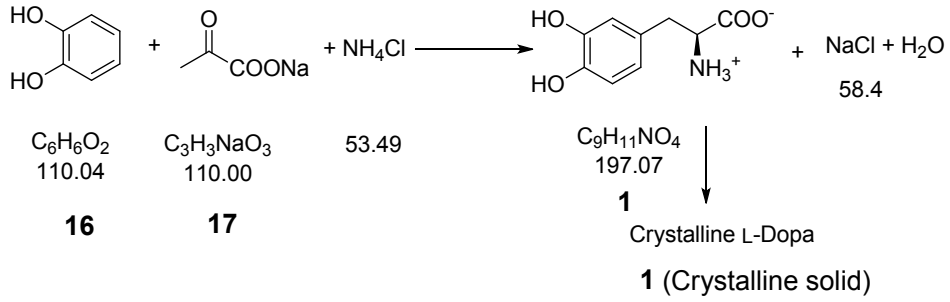
Reaction	Input	Output	Mw	Equivalent	Mass
1	**16**		110	1	110
	17		110	1	110
	NH_4Cl		54	1	54
Total input				1	274
		L-Dopa	197		**197**
Atom Economy	0.719				

Lab protocol for the Ajinomoto process

Outline:

1. Tyrosine Phenyl Lyase (TPL) is produced by high density fermentation of a strain of *E. coli* that over expresses TPL. The cells are isolated by Disk Stack Centrifuge after medium exchange with diafiltration.
2. The cleaned cells are used directly in the synthesis of L-Dopa from catechol, pyruvate, and ammonia.
3. Product L-Dopa is isolated from the mixture with centrifuge decanter.
4. Product is purified by re-crystallization under basic condition after discoloration with activated carbon.

Synthesis of L-Dopa[1-3]



Procedure

1. Dissolve Sodium pyruvate (12.43 kg) in water (739 kg), charge NH_4Cl (41.45 kg), $Na_2EDTA\ 2H_2O$ (2.49 kg), adjust the pH to 8.0. Cool the reaction mixture to 15 °C.
2. Start the reaction by adding the biocatalyst (75 kg wet cells), sodium bisulfite (1.66 kg), and catechol (8.29 kg) to the reaction mixture. Maintain the temperature at 15 °C, and pH at 8.0. Continue the agitation for 2 h.
3. Prepare the feed solution by dissolving sodium pyruvate (61.73 kg) and catechol (61.73 kg) in water (271 kg). Cool to 15 °C and adjust the pH to 8.0.
4. Add anhydrous L-dopa seed to the reaction mixture (7.65 kg), agitate for 1 h.
5. Add the feed solution (308 L) to the reaction mixture over 12 h. Continue agitation for 3 h to finish.
6. Product isolation: Separate the crystalline L-Dopa from cells and solution with decanter centrifuge after pH adjustment. Product: 171 kg wet cake, with 70% active (120 kg, yield at this point = 90%)
7. Product discoloration: Mix the wet cake with 418 kg water, adjust pH to 11.5 with 5 N sodium hydroxide (approx. 135 L) to dissolve L-Dopa. Add 6.4 kg of activated carbon to the solution, heat to 50 °C and agitate for 2 h. Filter to remove the insoluble.
8. Reactive crystallization: Cool the solution to 25 °C, Seed with 1 mol % (with catechol as reference) L-Dopa. Add 6N HCl (total about 113 L) at 25 °C over 6 h to crystallize L-Dopa product. The final pH is at 5.7.
9. Isolate the crystalline solid by filtration. Dry under vacuum to remove residual water. The product is 109 Kg (or 100 kg excluding seeds), representing 80% yield.[4]

Streams in reaction: [3]

Reactant stream	Volume Ratio	Chemical	Wt Concentration (g/L)	Mw	Molar concentration (mol/L)
Initial stream	1	Catechol	10	110	0.091
		Sodium pyruvate	15	110	0.136
		NH_4Cl	50	53.5	0.935
		$NaHSO_3$	2	104	0.019
		$Na_2EDTA\ 2H_2O$	3	372	0.008
		TPL	75		
Seed (added to initial stream)		L-Dopa	9.3	197	
Feed solution	0.372	Sodium pyruvate	200	110	1.818
		Catechol	200	110	1.818

Input								
Chemical	Vol (L)	Density g/ml	Weight (kg)	Mw	mol	Role	X/ref. 1	PMI
(Catechol, initial)			(8.29)	110	75.4	Reactant	(0.12)	(0.084)
(Na pyruvate initial)			(12.43)	110	113.0	Reactant	(0.18)	(0.126)
(Water)			(739)	18	41055.6	Solvent	(10.55)	(7.39)
NH_4Cl			41.45	53.5	774.8	Reactant	0.59	0.413
$Na_2EDTA\ 2H_2O$			2.49	372	6.7	chelation	0.04	0.027
TPL			75			Catalyst	(1.07)	(0.75)
$NaHSO_3$			1.66	104	16.0	Antioxidant	0.02	0.015
(Sodium pyruvate, feed)			(61.73)	110	561.2	Reactant	(0.88)	(0.616)
(Catechol, feed)			(61.73)	110	561.2	Reactant	(0.88)	(0.616)
(Water)			(271)	18	15055.6	Solvent	(3.87)	(2.71)
L-Dopa seed			7.65	197	38.8	Seed	0.11	0.077
Water, total			1010	18	56111.1	Solvent	14.42	10.1
Catechol, total			70.02	110	636.5	**Ref 1**	1.00	0.7
Sodium pyruvate total			74.16	110	674.2	reactant	1.06	0.742
Input total			1282				18.32	12.07
Theoretical output								
Expected product								
L-Dopa			133.0	197	675.4	Product	1.90	
Sodium chloride			37.2	58.5	636.5	by product	0.53	
Water			11.7	18	649.9	Solvent/by product	0.16	
Solvent, excess								
Water			1010.0	18	56111.1		14.42	
Na_2EDTA			2.2	336	6.7	Chelation	0.03	
TPL (wet cell)			75.0			Catalyst	1.07	
$NaHSO_3$			1.7	104	16.0	Antioxidant	0.02	
NH4Cl			7.4	53.5	138.2	Excess by product	0.11	
Sodium pyruvate			4.1	110	37.6	Excess by product	0.06	
Total			1282				18.32	
Work up & isolation								
Water			418				5.96	4.18
5 N NaOH solution	135	1.18	159				2.28	1.60
(NaOH)			27.0	40	675.4		0.39	(0.273)
(Water)			132				1.89	(1.32)
Activated Carbon			6.4				0.09	0.063
6 N HCl	112.5	1.09	122.69				1.75	1.23
(HCl)			24.65	36.5	675.4		0.35	(0.245)
(Water)			98.04				1.40	(0.98)
L-Dopa seed			1.25	197	6.4	mol/**ref 1** = 0.01	0.02	0.014
Total			707.27				10.10	7.09
Actual yield 79.75%								
L-Dopa			109	197	552.8		1.56	
Net (excluding seeding)			100	197	507.6		1.43	
RF_1	0.700			CRF_1	0.700			

Tyrosine phenol lyase preparation by high density fermentation[5]

1. Pick a single colony of the production strain from LB/antibiotic plate; inoculate to 50 ml (54 g) of semi-synthetic medium (SM-B) medium. Incubate at 37 °C for 16 h to reach $OD_{600} \geq 1.5$ (about 0.45 g dry cell weight or DCW /L or 1.5 X 10^9 cell/ml)
2. To prepare secondary seed, transplant the primary culture to 25 L (27 kg) SM-B, incubate at 37 °C for 16 h to reach $OD_{600} > 10$ (3 g DCW/L).
3. Transfer the secondary seed to 415 L (448 kg) of the main culture (SM-B medium, glucose 20 g/L), incubate at 37 °C for 8 h to reach $OD_{600} > 30$ (10 g DCW/L), or when growth slows down as indicated by the increase of pO_2
4. Start adding feed medium (FM) based on an exponential feeding strategy with growth rate $\mu = 0.15$,[4] OD_{600} is expected to reaches > 67 (20 g DCW/L) in 4 h, add IPTG (1 mol or 240 g, final concentration 2 mM) to induce the expression of TPL.
5. Continue adding FM for the rest of 8 Hours, over which the OD_{600} is expected to reach ~150, corresponding to cell weight of 50 g DCW/L. In total, 60 L (84.6 kg) of feed medium is added to the fermenter, giving the final volume to 500 L.[6,7]
6. Productivity: 50 g DCW (167 wet cell)/L, with 15% of the soluble protein is the desired enzyme. The total amount of wet cell is 83.5 kg.
7. Exchange the culture medium with 1500 L 5mM phosphate, pH 7 Buffer by diafiltration.[8]
8. Isolate cells by disc-stack centrifuge. The recovery of cells is > 90%.
9. Total catalyst: 83.5 x 0.9 = 75 kg wet cell (22.5 kg DCW), with 1.8 kg of desired TPL.

Input								
Chemical	Vol (L)	Density	Weight (kg)	Mw	mol	Role	X/ref. 2	PMI
(SM-B medium)	440	1.08	475.2			Starting medium	6.34	(4.76)
(Feed medium)	60	1.41	84.6			Feed medium	1.13	(0.848)
IPTG			0.24	238	1.0	Inducer	0.003	0.00225
29% NH_4OH	13.3	0.897	12		164	N source, base	0.16	0.12
Total media	513		572				7.46	5.60
Output								
TPL/wet cell			83.5			Biocatalyst	1.11	
(DCW)			25				0.33	
(water in wet cell)			58.5				0.78	
Fermentation waste			476				6.35	
Work up & isolation								
1500 L 10 mM phosphate pH 7								
(Water)			1500				20.00	15
1.25 g/L K_2HPO_4	136.1		1.875		14		0.025	0.019
0.05 g/L KH_2PO_4	174.2		0.075		0.4		0.001	0.00075
Total			1502				20.03	15.02
Actual yield								
Wet cell			75			**Ref 2**	1.00	0.75
RF_{11}	1.00			CRF_{11}	0.75			

Summary of PMI

Contributor	**PMI**
Reactants	1.9
Water, Other auxiliaries (EDTA, bisulfite)	10.2
Biocatalyst preparation	20.6
Product isolation	7.1
Total	39.7

References

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2. Reviews of Ajinomoto process: H. Enei and Y. Hideaki, *Prog. Ind. Microbiol*. 1986, **24**, 280-5.; T. Katayama and H. Kumagai, in *Encyclopedia of Industrial Biotechnology*, Vol. 3, ed. M. C, Flickinger, John Wiley & Sons, Inc. Hoboken, New Jersey, USA, 2010. pp 1937-1940
3. Ratio and volume of initial solution and feeding solution:

   Final concentration of L-Dopa = 110 g/L, corresponding to 0.56 mol L^{-1}.

   Total amount of L-Dopa product in solution:
   Catechol concentration of initial solution = 0.091 mol L^{-1}
   Catechol concentration in feeding solution = 1.82 mol L^{-1}

   $$\frac{0.091\ \times a + 1.82 \times b}{a + b} = 0.56,\ Therefore, b = 0.372\ a$$

   Where a is the volume of initial solution, and b is the volume of feeding solution.

4. Yield of L-Dopa product, and estimate the amount of reference reactant based on the expected amount of product.

   $R, moles\ of\ reference\ reactant$ (Catechol)
   $P, moles\ of\ final\ product$ (L-Dopa)
   $Q, moles\ of\ product\ excluding\ seed$
   $Y_1\ biocatalytic\ reaction\ yield$
   $Y_2\ Separation\ yield$
   $S_1\ molar\ ratio\ of\ seed\ vs\ R\ in\ biocatalytic\ reaction$
   $S_2\ molar\ ratio\ of\ seed\ vs\ R\ in\ recrystallization$

$$Theoretical\ moles\ of\ product = R + S_1R + S_2R$$

Actual yield of product

$$P = Y_2Y_1(R + S_1R) + Y_2S_2R = (Y_2Y_1 + Y_2Y_1S_1 + Y_2S_2)R$$

$$Overall\ Yield = \frac{Y_2Y_1(R + S_1R) + Y_2S_2R}{R + S_1R + S_2R} = \frac{Y_2Y_1(1 + S_1) + Y_2S_2}{1 + S_1 + S_2}$$

$$Q = P - S_1R - S_2R = Y_2Y_1(R + S_1R) + Y_2S_2R - S_1R - S_2R$$

Simplify $Q = (Y_2Y_1 + Y_2Y_1S_1 + Y_2S_2 - S_1 - S_2)R$

Therefore:

$$R = \frac{Q}{(Y_2Y_1 + Y_2Y_1S_1 + Y_2S_2 - S_1 - S_2)}$$

5. The protocol is based on fed-batch fermentation with semi-synthetic medium. X. Pei, Q. Wang, X. Qiu, L. Ying, J. Tao and T. Xie, T. *Appl. Biochem.* 2010, **162**, 1423-1434, *ibid*, 2011, **165**:416-425

6. Determine the volumes of initial and feed media

   - Determine glucose requirement based on concentration of dry cell weight (DCW/L)

   Final concentration X = 50 g DCW/L, Growth Yield with Glucose $Y_{X/S}$ = 0.55

   Final concentration of glucose in the medium S = 50/0.55 = 91 g/L

   - Determine the ratio of main culture medium vs feed medium:

   Glucose concentration: initial medium = 20 g/L, feed medium = 600 g/L

   In final fermentation mixture

   $a = \%\ Volume\ of\ main\ \ culture\ medium, b = \%\ of\ Volume\ of\ feed\ medium,$

   $600\ b + 20\ a = 91, \quad and \quad a = 1 - b.$

   $91 = (1 - b)20 + 600b,$ Solve the equation: $b = 0.122, \quad a = 0.878.\ Or\ a{:}b$ = 1: 0.139

- Determine the volumes of the media (Wet cell weight = DCW/0.3)

  Total volume =

$$\frac{Amount\ of\ catalyst\ (DCW)}{X} = \frac{Amount\ of\ wet\ cell}{X}\ \frac{10}{3}$$

  Volume of initial media = $0.878\ \times Total\ volume,$
  Volume of feed media = $0.122\ \times Total\ volume$

7. Summary of media

SM-B medium			
Material	CAS	Mw	Content (g/L)
Glucose	50-99-7	180.16	20
Yeast extract			32.3
K_2HPO_4	7778-77-0	136.1	15.3
KH_2PO_4	7758-11-4	174.2	9.7
$MgSO_4 7H_2O$	10034-99-8	246.47	2.63
$EDTANa_2\ 2H_2O$	139-33-3	372.2	0.018
Ampicillin	69-53-4	349.41	0.349
$CoCl_2\ 6H_2O$	7791-13-1	237.93	0.003172
$MnCl_2\ 2H_2O$	13446-34-9	161.87	0.015128
$CuCl_2\ 2H_2O$	10125-13-0	170.48	0.001464
H_3BO_3	10043-35-3	61.83	0.002928
$Na_2MoO_4\ 2H_2O$	10102-40-6	241.95	0.002684
$ZnOAc_2\ 2H_2O$	557-34-6	219.5	0.012688
Fe(III) Citrate	160105	244.95	0.098088
Water	7732-18-5	18	1000

Feed medium			
Material	CAS	Mw	Content(g/L)
Glucose	50-99-7	180.16	600
$MgSO_4\ 7H_2O$	10034-99-8	246.47	15.2
Ampicillin	69-53-4	349.41	0.34941
$COCl_2\ 6H_2O$	7791-13-1	237.93	0.09971
$MnCl_2\ 2H_2O$	13446-34-9	161.87	0.47554
$CuCl_2\ 2H_2O$	10125-13-0	170.48	0.04602
H_3BO_3	10043-35-3	61.83	0.09204

Na_2MoO_4 $2H_2O$	10102-40-6	241.95	0.08437
$ZnOAc_2$ $2H_2O$	557-34-6	219.5	0.39884
Fe(III)citrate	160105	244.95	3.08334
Water			793

Final media (91 g glucose/L final)				
Material	CAS	Mw	Weight (g/L)	kg /500 L
Glucose	50-99-7	180.16	90.8	45.38
Yeast extract			28.4	14.18
K_2HPO_4	7778-77-0	136.1	13.4	6.72
KH_2PO_4	7758-11-4	174.2	8.5	4.26
$MgSO_47H_2O$	10034-99-8	246.47	4.2	2.08
$EDTANa_2$ $2H_2O$	139-33-3	372.2	0.016	0.0079
Ampicillin	69-53-4	349.41	0.349	0.17
$CoCl_2$ $6H_2O$	7791-13-1	237.93	0.015	0.0075
$MnCl_2$ $2H_2O$	13446-34-9	161.87	0.071	0.036
$CuCl_2$ $2H_2O$	10125-13-0	170.48	0.0069	0.0034
H_3BO_3	10043-35-3	61.83	0.014	0.0069
Na_2MoO_4 $2H_2O$	10102-40-6	241.95	0.013	0.0063
$ZnOAc_2$ $2H_2O$	557-34-6	219.5	0.060	0.0299
Fe(III) Citrate	160105	244.95	0.462	0.23
Water	7732-18-5	18	975	487
IPTG	367-93-1	238.3	0.48	0.24
29% NH4OH solution (14.8 M)	1336-21-6	35	24	12
Total				573

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		Ajinomoto Process Step 1 TPL reaction and Purification					Reaction yield	0.9	Isolation yield	0.9
Input	**Kg**				**Waste (Kg)**	**Reaction time**	**Seeding S1**	0.061	**Seeding S2**	0.01
Sodium Pyruvate	12.5		Initial reaction at 15 ˚C, pH 8							
Water	739	→				2	**Stream 1-1**	Weight	mol	
NH_4Cl	41.4						NaCl	37.24	637	
Sodium EDTA	2.5		↓				Na_2EDTA	2.49		
TPL (Steam 1-7)	75.00						TPL (cell)	75.00		
$NaHSO_3$	1.68						$NaHSO_3$	1.68		
Catechol	8.30						NH_4Cl	7.40	138	
			↓				Sodium pyruvate	4.20	38	
			Initial reaction at 15 ˚C, pH 8				L-Dopa	12.54	64	
L-Dopa seed	7.65	→					(water by product)	11.47	637	
							(solvent water)	1010		
			↓				(Water in wet solid)	51.32		
			↓				total water	970		
sodium pyruvate	61.76		Initial reaction at 15 ˚C, pH 8				(L-Dopa active)	119.75	608	
catechol	61.76	→				15				
water	271									
			↓							
			↓							
			Centrifuge	~~1-1~~ →						
					1111					

Continue from the last page

							Stream 1-2			
							Activated carbon	6.37		
Water	418		Discolorization 50 ˚C	**1-2**						
5N NaOH	159	→		→	6.37	2				
Activated carbon	6.37						**Stream 1-3**			
							NaCl	39.5	675	
							(solvent water)	418		
			Reactive Crystallization 25 ˚C	**1-3**			(water from HCl)	98		
L-Dopa seed	1.26	→		→	763	6	(water from NaOH)	132		
6 N HCl	122.68						(reaction water)	12	675	
							(wet solid water)	51		
							Total water	712		
Reaction input	1282.58		**L-Dopa Product 4**				L-Dopa	12.10		
Isolation input	707									
			109	**1-4**						
			Net yield of L-Dopa (kg)	mol	**Estimated waste**	**Total waste**				
Total input	1990		100	507.6	1881.0	1880.2				
			Total catechol (mol)	637						
			Total catechol (kg)	70						

		Ajinomoto Process Step 1-1 Biocatalyst Production						yield	0.9
Input	**Kg**				**Waste (Kg)**	**Reaction time**			
			First stage seed, 37 ˚C						
SM-B	0.054	→					**Stream 1-5 +1-6**	Weight (kg)	
							Waste media	550	input - DCW
			↓				**buffer**	1449	
			Second stage seed, 37 ˚C				**Total**	1999	
SM-B	27	→							
			↓						
SM-B	448.5	→	High density fermentation, 37 ˚C						
Feed medium	84.6								
IPTG	0.024								
29% NH_4OH	12		↓						
Water	1500		Dia-filtration	**1-5** →					
Na_2HPO_4	1.87	→			Combined with 1-6				
NaH_2PO_4	0.075								
			↓						
			disc centrifuge	**1-6** →					
Fermentation input	572				Combined with 1-5				
Purification input	1501		↓						
			TPL in wet cell	**1-7**	Estimated waste				
Total input	2074		75		1999				

Waste stream inventory for L-Dopa manufacture processes

The waste streams are created in Process Flow Diagram. The mass of the components are expressed in E factor. Each stream is also characterized by its components in percentage.

The waste streams are evaluated in terms of quantity, composition, and hazardous concerns.

For waste streams, the management, treatment, and discharge are regulated by Clean Air Act (40CFR Part63, Subpart GGG)[2] and Clean Water Act (40CFR Part 439 Pharmaceutical Manufacture Point Source Category; 40CFR Part 122, National Pollutant Discharge Elimination System Permit Program; 40CFR Part 403, National Pretreatment Program).[3] Since hazardous wastes need to be managed and treated separately, the streams are examined for hazardous waste as defined and characterized by regulations in Resource Conservation and Recovery Act (RCRA).[1] Waste components with regulatory concerns are highlighted in the inventory.

Technical options for waste treatment, for specific streams are guided by the framework in the survey reports by US Environmental Protection Agency (EPA).[4,5]

Waste stream inventory

The Ajinomoto process

Ajinomoto 1-1	E	%	CAA	CWA	RCRA
NaCl	0.37	3.6			
Na_2EDTA	0.02	0.19			
TPL (cell)	(0.75)				
$NaHSO_3$	0.02	0.19			
NH_4Cl	0.07	0.67			
Sodium pyruvate	0.04	0.38			
L-Dopa	0.13	1.3			
total water	9.70	93.7			
Total	10.35	100			
Ajinomoto 1-2					
Activated carbon	0.06	100			
Ajinomoto 1-3					
NaCl	0.40	5.2			
water	7.12	93.2			
L-Dopa	0.12	1.6			
Total	7.63	100			
Ajinomoto 1-5+ 1-6					
Waste media	5.50	27.5			
5 mM phosphate	14.49	72.5			
Total	19.98	100.0			

The Monsanto Process

Monsanto 1-1	E	%	CAA	CWA	RCRA
NaOAc	0.22	5.66			
Water	0.06	1.57			
AcOH	3.63	92.77			
Total	3.91	100.00			
Monsanto 1-2					
AcOH	2.15	70.09			
Unisolated **12**	0.92	29.92			
Total	3.07	100.00			
Monsanto 2-1					
Acetone	6.12	100		√	√F003
Monsanto 2-2					
Water	1.91	94.92			
Un-isolated **13**	0.10	5.08			
Total	2.01	100.00			
Monsanto 3-1					
iPrOH	9.87	88.00		√	
Water	1.35	12.00			
Total	11.22	100.00			
Monsanto 3-2					
NaCl	0.56	9.05			
Catalyst **14**	0.00	0.00			
Water	1.52	24.64			
iPrOH	3.89	62.94		√	
Un-isolated **15**	0.21	3.37			
Total	6.18	100.00			
Monsanto 4-1					
MeBr	0.60	100	√		
Monsanto 4-2					
NaBr	2.56	31.26			
AcOH	0.76	9.33			
Water	4.86	59.41			
Total	8.18	100.00			
Monsanto 4-3					
Water	1.89	88.33			
Un-isolated **1**	0.25	11.67			
Total	2.14	100.00			
Monsanto 4-5				√*	
$MeNH(CH_2)_2OH$ HBr	0.89	1.48			
$Me_2N(CH_2)_2OH$ HBr	0.11	0.18			
Ethanolamine	10.08	16.71			
Water	49.23	81.63			
Total	60.30	100.00			

* Total ammonia as N regulated by CWA

The Roche Process

Roche 1-1	**E**	**%**	CAA	CWA	RCRA
Acetic acid	8.51	16.9			
Sodium acetate	3.98	7.9			
DMF	1.25	2.5			
Water	36.96	72.9			
Total	50.7	100.00			
Roche 1-2					
Water	43.2	96.0			
Un-isolated **8**	1.78	4.0			
Total	45.0	100			
Roche 2-1					
Raney Ni	1.8	100			
Roche 2-2					
NaOAc	1.74	0.9			
NaCl	8.07	4.0			
HCl	0.77	0.4			
Water	193	94.8			
Total	203.6	100			
Roche 2-3					
MeOH	8.1	18	√	√	
Water	34.9	77.8			
Un-isolated **9**	1.9	4.2			
Total	44.9	100			
Roche 3-1					
(*R*)-**9**	2.64	8.25			
Compound **10**	0.21	0.64			
NaOH	0.30	0.95			
MeOH	17.42	54.43	√	√	
Water	11.43	35.72			
Total	32.00	100.00			

Roche - continued

Roche 4-1	**E**	**%**	**CAA**	**CWA**	**RCRA**
MeBr	0.65	100	√		
Roche 4-2					
Toluene	12.45	93.70	√	√	√ F005
Benzoic acid	0.84	6.30			
Total	13.3	100.00			
Roche 4-3				√*	
NH_4Br	4.53	30.97			
Water	10.09	69.03			
Total	14.6	100.00			
Roche 4-4					
Activated carbon	0.2	100			
Roche 4-5				√*	
NH_4Br	1.14	8.01			
Water	10.76	75.79			
Compound **10**	1.96	13.77			
Un-isolated **1**	0.35	2.44			
Total	14.2	100.00			
Roche 4-7				√*	
$MeNH(CH_2)_2OH$ HBr	0.97	1.49			
$Me2N(CH_2)_2OH$ HBr	0.11	0.17			
Water	53.12	81.61			
$NH_2(CH_2)_2OH$	10.89	16.74			
Total Waste	65.1	100.00			

* Total ammonia as N regulated by CWA

Waste inventory summary

Process	**Ajinomoto**	**Monsanto**	**Roche**
Total E factor	39	103	485.4
Total number of waste streams	4	10	12
Gas waste stream	0	1	1
Solid waste stream	1	0	2
Solvent-free aqueous stream	3	2	3
Waste solvent or organic-laden stream	0	7	6
Hazardous waste based on RCRA	0	1	1
E factor of hazardous waste	0	6.1 (acetone)	12.5 (Toluene)
Hazardous Gas (MeBr)	0	1	1
E factor for MeBr	0	0.6	0.65

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