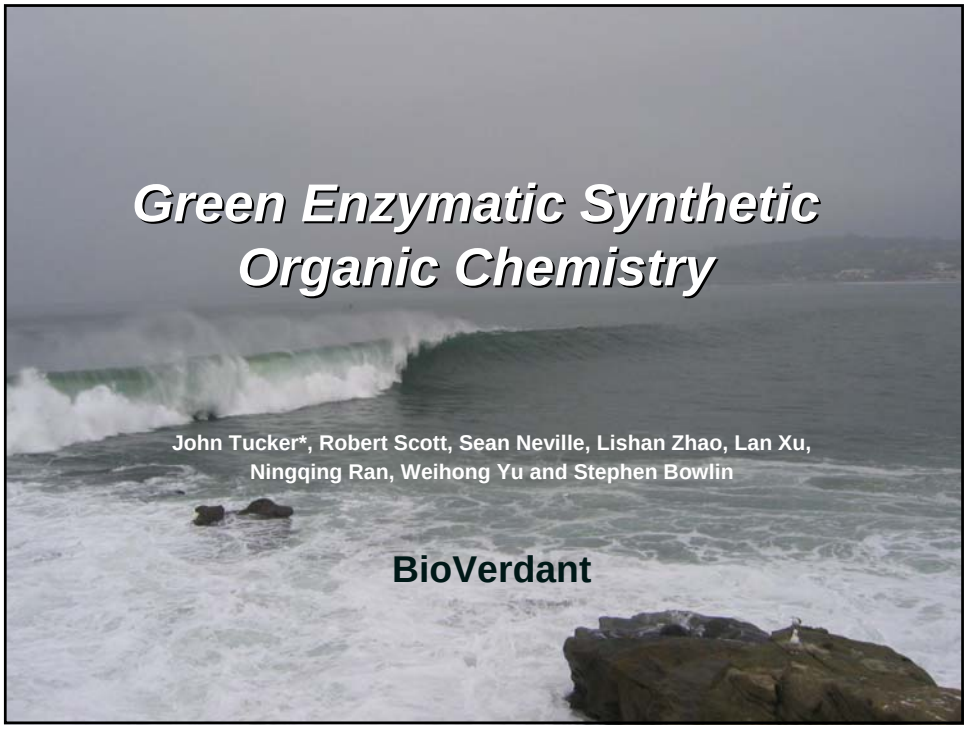

Green Chemistry is Cost Efficient

	Environmentally Thinking	Economically Thinking
Atom Economy	Minimal by-product formation, ***reduced environmental burden***	More from less – incorporate total value of materials **reduced cost**
Solvent Reduction	Less solvent waste, ***reduced environmental burden***	Higher throughput, less energy, **reduced cost**
Reagent Optimization	Catalytic, low stoichiometry, recyclable reagents minimize usage, ***reduced environmental burden***	Higher efficiency - higher selectivities **reduced cost**
Convergency	***Reduced environmental burden*** due to increased process efficiency	Higher efficiency – fewer operations **reduced cost**
Energy Reduction	***Reduced environmental burden*** from power generation, transport, and use	Reduced energy reflects increased efficiency, shorter process, mild conditions **reduced cost**
In-situ Analysis	Reduced possibility for exposure or release to the environment	Real-time data increases throughput and process efficiency, fewer reworks **reduced cost**
Safety	Non-hazardous materials reduce risk of exposure, release, explosions and fires	***Worker safety*** and reduced down time, Reduced time on special control measures. **reduced cost**

Org. Proc. Res. Dev.*, **2006,*10*, 315

Pharmaceutical Green Chemistry*…

- …**begins with *intent***
  - *Green Chemistry is not just good chemistry; it is the highest efficiency potential that exists for every chemical process, serving as both an inspiration for and a measure of the best chemistry*
    - *Green Chemistry should be a priority driver, not a by-product of achieved goals*

Org. Proc. Res. Dev.*, **2006,*10*, 315

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Pharmaceutical Green Chemistry…

- …**evolves through awareness and application of the 12 principles of Green Chemistry**

"Problems cannot be solved at the same level of awareness that created them" *-Albert Einstein*

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Broad and General Exemplification of Technical Green Chemistry

- **Commitment to a new mindset**
  - Routinely applying the priorities of the12 principles and accepting new expectations of difficulty and creativity
  - *Within the context of current capabilities*
    - Relies upon established precedent
    - Analyzing cause and effect
  - *Changing the way you think and the priorities you set…not your technical solutions*

Targeted Green Chemistry

- **Using Green Chemistry principles to guide new technology or methodology development**
  - Where does current technology fail?
    - Solvent, selectivity, reaction conditions…
  - How can we overcome this deficiency?
    - Ionic liquids, supercritical fluids, reactors on a chip or a cell, continuous flow, sonication, microwave chemistry, biotransformation
- *Changing your technical approach to achieve goals that are <u>unreachable</u> using current methodology*

Carpe Diem?

- Human nature demands immediate Green Chemistry solutions
  - Toolbox has many empty drawers
- A long-term shift in behavior based upon the 12 principles is needed
  - Broad and General
  - Targeted
- ***Its planting time…not harvest time***

Biotransformation

- Highly specific and chemically efficient
  - High regio/stereo selectivity
- Renewable Catalysts
  - Recyclable, innocuous
- Aqueous Environment
  - Reduced solvent waste
- Low Energy Requirement
  - Near ambient processing
- Enables new and unique synthetic pathways
  - Complementary to traditional synthetic chemistry

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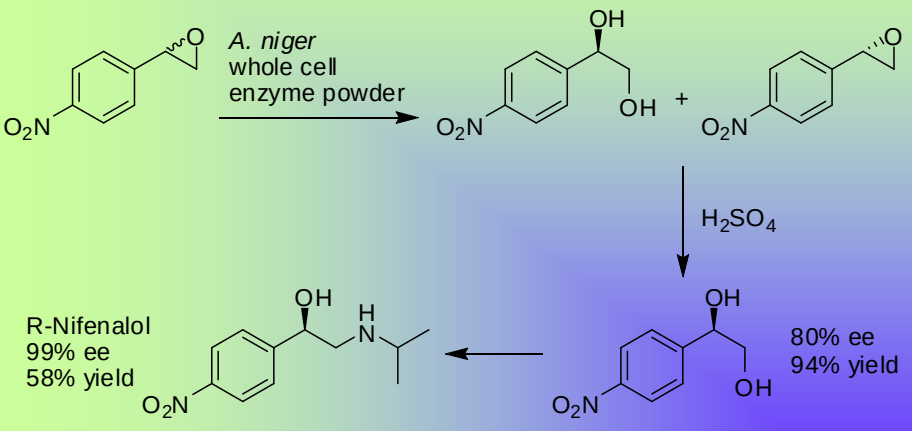
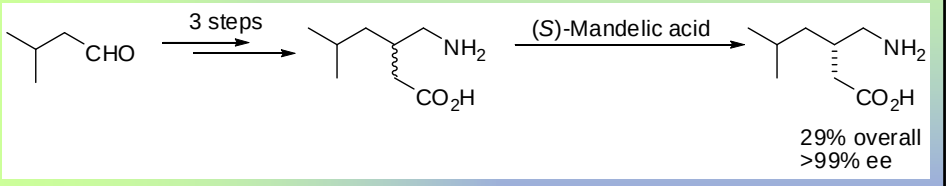
Enantioconvergent Synthesis of Nifenalol



Faber *et al*, *Tetrahedron*, 1997, 9707

Pregabalin (Lyrica®)

Initial Synthesis

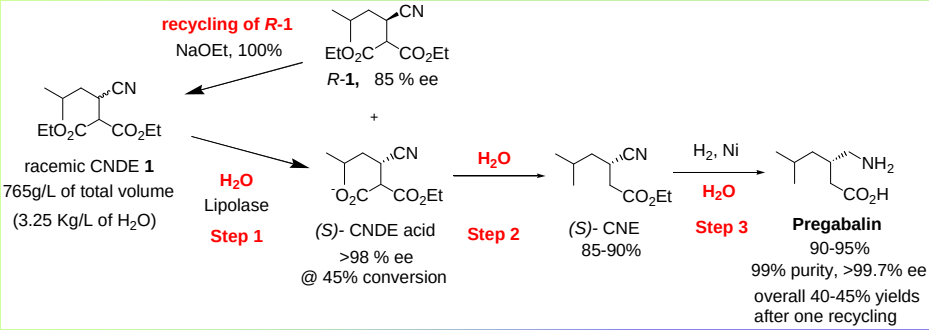


- Classical resolution
  - *Requires stoichiometric mandelic acid*
- Undesired enantiomer difficult to recycle
  - *75% of everything becomes waste*
- Overall low yield, low throughput, and high cost make this undesirable

Org. Proc. Res. Dev., **1997**,*1*, 26

Pregabalin

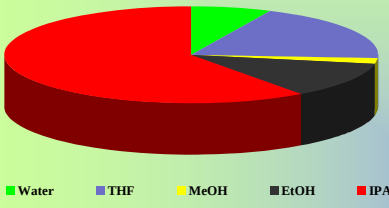
Improved Synthesis



- Biocatalysis replaces classical resolution
  - *All reactions performed exclusively in water!*
  - *Organic solvent used for drying and cleaning only*
  - *Higher yield, less waste*

Enzymatic Pregabalin Synthesis: An Aqueous Process

1st Generation Route Solvent Use



Enzymatic Route Solvent Use

- Solvent Eliminated
  - *11 million gallons each year!*
- Raw Material Reduction
  - *>800 metric tons of CNDE*
  - *1600 metric tons of (S)-mandelic acid*
  - *500 metric tons of nickel (>98%)*

Winner of the 2006 IChemE Award in Green Chemistry and Engineering

So, is Enzymatic Synthesis Aladdin's Lamp of Green Chemistry?

Green Chemistry is outside of techniques used but rather resides within the intent and the result of technical application

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Typical Scenario

- Segregation of scientific disciplines
  - Process Chemistry team invents a synthetic route…

Small achiral building block

⇩

Large achiral intermediate

Chiral Organic Chemistry ⇩ Biochemistry team asked to provide an enzyme to perform the identical transformation

Large chiral intermediate

⇩

Large chiral pharmaceutical

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A Cooperative Retrosynthetic Approach is Better…

- Strategic blend of disciplines key to efficient and ***general*** enzyme application
- By choosing intermediates that favor enzyme strengths and minimize challenges, higher relative rates of success can be realized
  - Known/well-understood transformations
    - Beware co-factors, secondary enzymes
  - Early intermediates
    - Solubility, functionality, stability
  - You can invent new specific enzyme technology…but why not apply available technology strategically?

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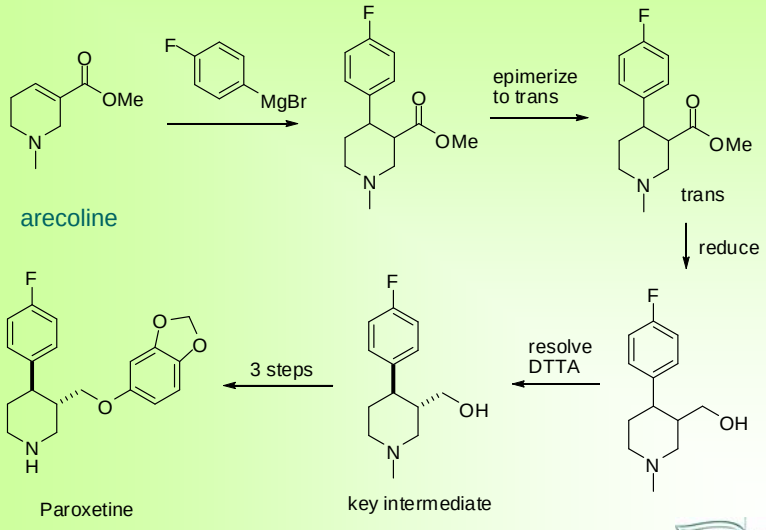
Current Paroxetine Synthesis



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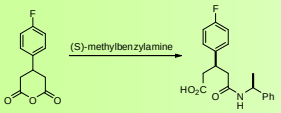
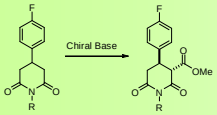
Alternate Routes

DESYMMETRIZATION

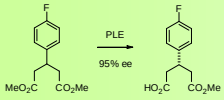


Tetrahedron Asymmetry, **2001** (12) 419-426

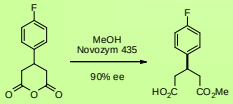


Synlett, **2002**, 12, 2074-6

Tetrahedron, **2003**, 59, 9213-9230



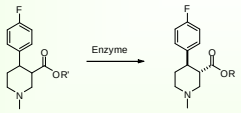
Tetrahedron Lett., **2000**, 41, 5647-51



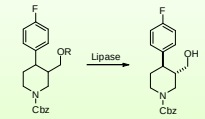
Tetrahedron: Asymmetry, **2003** , 16, 2475-85

OR

RESOLUTION

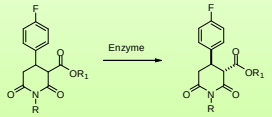


WO200102932

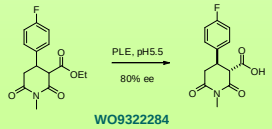


R = H (acylation rxn), Ac (hydrolysis rxn)

J. Org. Chem., **2001**, 66, 8947-8953

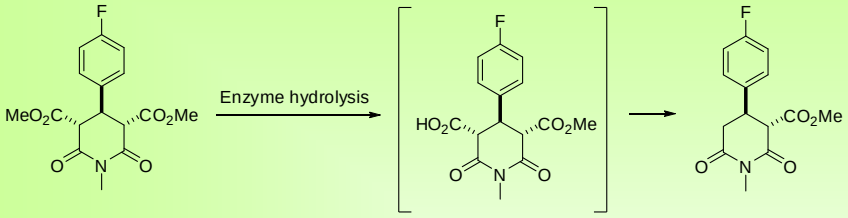


US5258517



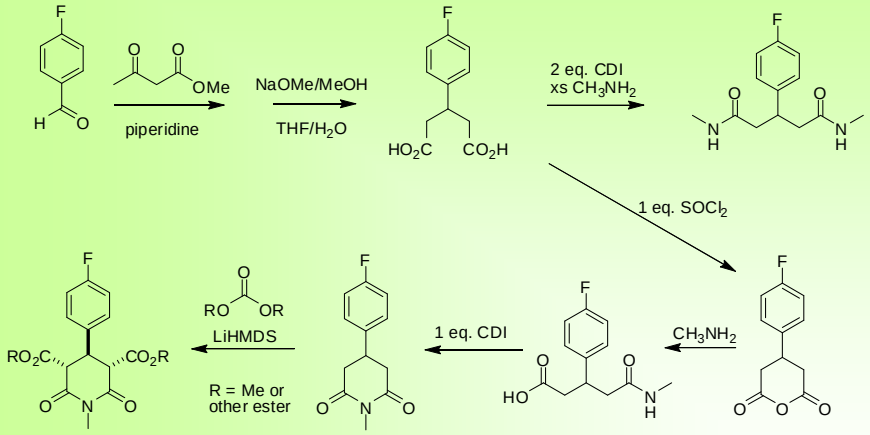
WO9322284

More is Better



- Novel desymmetrization of imide with two ester functionalities
- Produces chiral imide-monoester previously demonstrated (*via* resolution) to produce paroxetine
- ***Theoretical 100% transformation***

Enzyme Substrate Synthesis



*Catalytic KCN provides access to transesterification

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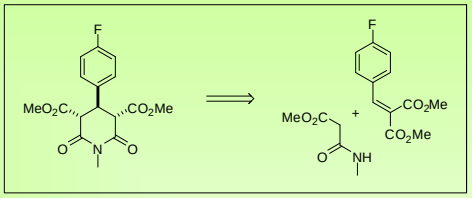
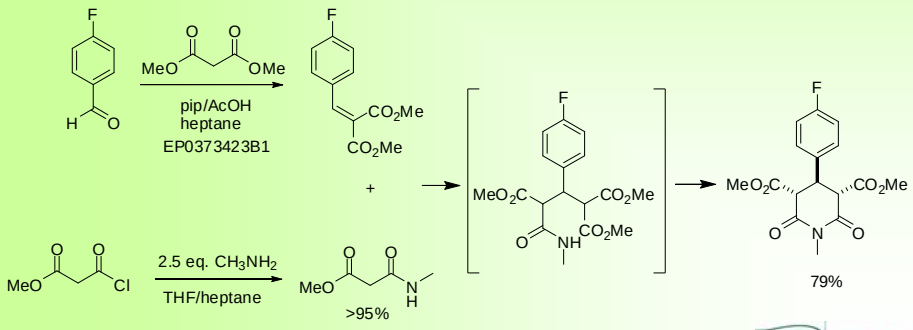
2nd Generation Synthesis





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Enzyme Screening

Table 1. Hits identified from screening

enzyme	yield %										
	1a	1b	1c	1d	1e	1f	1g	2a	2b	3a	3b
1	-	-	-	-	12	13	15	-	14	-	5
2	*29*	***100***	**-**	**-**	***47***	**-**	**-**	***19***	**-**	***10***	**-**
3	*100*	***100***	**-**	**-**	***54***	***17***	***19***	**-**	**-**	***15***	**-**
4	3	-	-	-	18	19	-	-	-	-	-
5	-	-	-	-	15	14	-	-	-	-	-
6	***33***	***4***	**-**	**-**	***48***	***65***	***64***	***4***	***8***	**-**	**-**
7	3	6	-	-	23	30	28	-	-	-	-
8	18	3	-	-	29	**66**	*a*	-	-	-	-
9	16	2	-	-	28	**73**	*a*	-	-	-	-
10	10	-	-	-	-	29	**44**	-	-	-	-
11	50	5	-	-	**62**	**78**	**73**	-	14	-	-
12	36	15	-	-	**51**	**64**	**66**	-	14	-	-
13	46	18	-	-	**57**	**75**	**77**	-	14	-	-

#6 provides 95:5 desired selectivity

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Optimization

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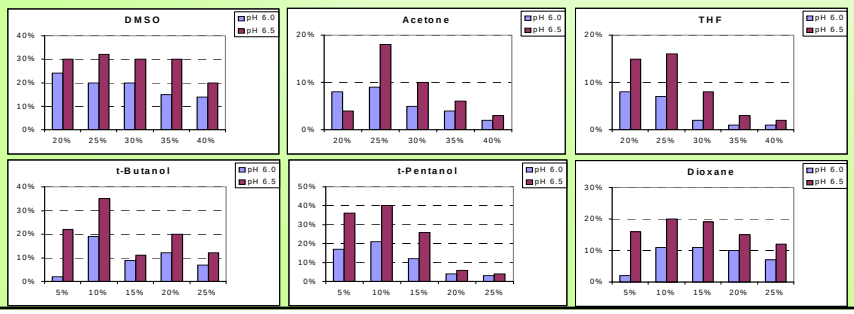
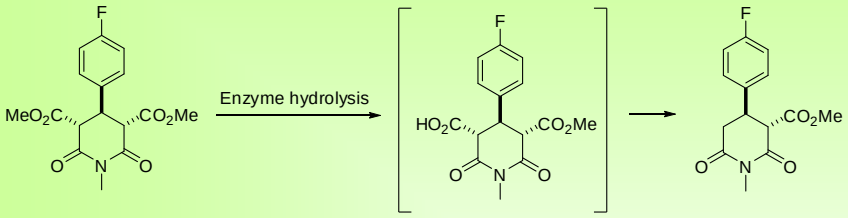
- Solvent
  - Acetone, DMSO, t-BuOH, t-Pentanol, Dioxane, MTBE, THF, Etc.
- Temperature
  - Faster at higher temperature
- pH
  - a balance between enzyme activity and background hydrolysis



Greener Chemistry?



- 71% isolated yield
  - A better process demonstrated!
  - Multigram scale
  - 90% ee
- Altered paradigm works
  - Cooperative retrosynthesis favoring enzyme strengths

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To Be Taken Home…

- *Pharmaceutical Green Chemistry*
  - Begins with intent and evolves through awareness
    - Not just "good chemistry" but the inspiration and measure of the best chemistry
  - May be "broad and general" Green Chemistry
    - New priorities
    - Uses currently available technologies
  - May also be "targeted" Green Chemistry
    - Technology driven
    - Ultimately destined for general Green Chemistry toolbox
- *Green Enzymatic Synthetic Organic Chemistry*
  - Enhanced by an amalgam of disciplines
    - Cooperative retrosynthetic approach with biochemists and synthetic organic chemists working together

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Thank You

- *Walter Schoepf*
- *Kim Albizati and Alex Tao*
- *Berkeley W. Cue*

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Biocatalysis is our technology…
...People are our strength

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