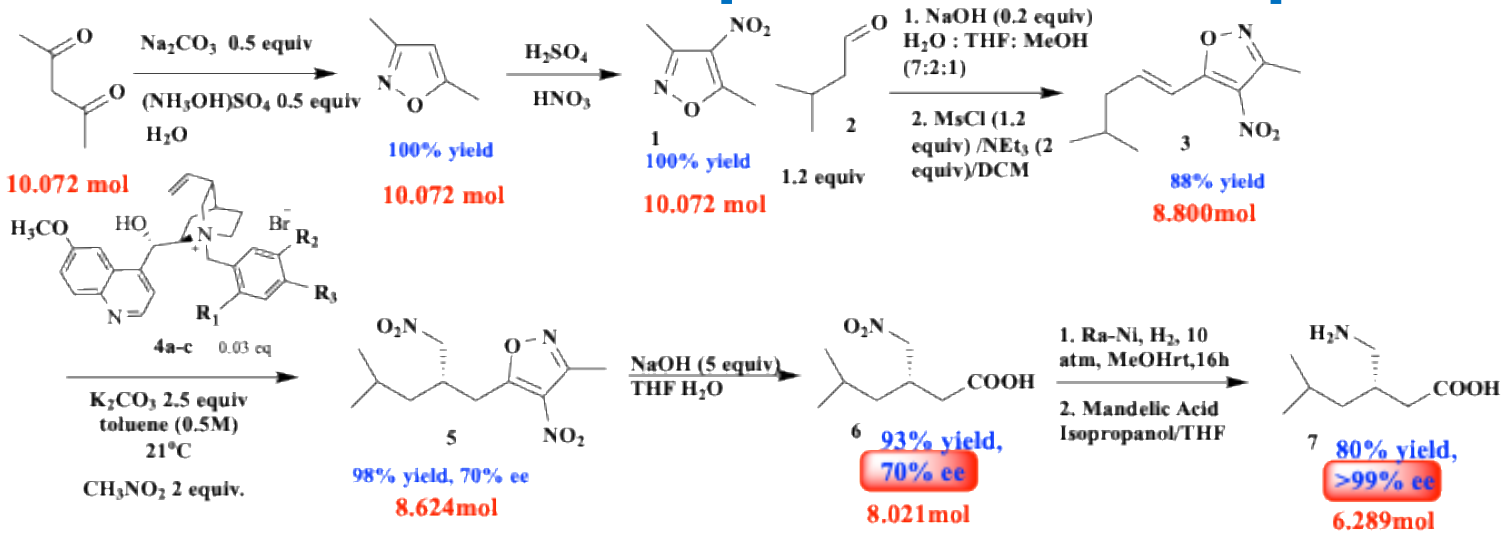
Green Chemistry for a Circular Economy

Horizon Tranpharm Public Symposium
Helsinki, Finland | 11 September 2026
Orion Pharma, Orionintie 1A, 02200 Espoo

Prof. Mauro F A Adamo

KelAda Pharmachem
Targeting Better Processes

Lessons from the process development of (S)-Pregabalin



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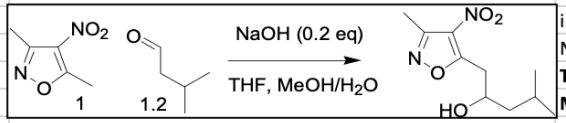
M.F.A. Adamo *Angew. Chem., Int. Ed. 48* (**2009**) 9342–9345

M.F.A. Adamo, *Org. Process Res. Dev. 19* (**2015**) 1274–1281

Step 3



isovaleraldehyde	$4,100	Ton	1.033	$4,235	0	4,235
NaOH	$300	Ton	0.080	$24	0	24
THF	**$2,000**	**1,000 Litres**	**0.900**	**$1,800**	0	1,800
MeOH	**$200**	**1,000 Litres**	**1.440**	**$288**	0	288
DCM	**$200**	**1,000 Litres**	**7.738**	**$1,548**	0	1,548

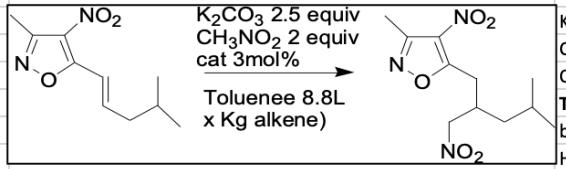
Reagent Cost: 4,259$; **Reagent Mass: 1,113 kg**
Solvent Cost: 3,636$; **Solvent Mass: 8,878 kg**

Step 4

MsCl	$1,350	Ton	1.253	$1,692	0	1,692
NEt3	$800	Ton	1.850	$1,480	0	1,480
DCM	**$200**	**1,000 Litres**	**18.490**	**$3,698**	0%	3,698

Reagent Cost: 3,172$; **Reagent Mass: 3,103 kg**
Solvent Cost: 3,698$; **Solvent Mass: 18,490 kg**

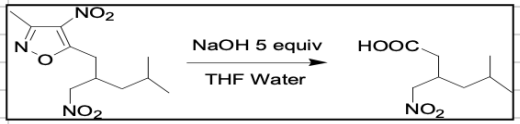
Step 5



K2CO3	$500	Ton	3.034	$1,517	0	1,517
CH3NO2	$1,600	Ton	1.072	$1,715	0	1,715
Quinidine	$30	kg	0.000	$0	0	0
Toluene	**$750**	**1,000 Litres**	**14.093**	**$10,570**	70%	3,171
bromide	$70	kg	0.000	$0	0	0
HCl	$100	Ton	0.002	$0	0	0

Reagent Cost: 3,232$; **Reagent Mass: 4,104 kg**
Solvent Cost: 10,570$; **Solvent Mass: 14,093 kg**

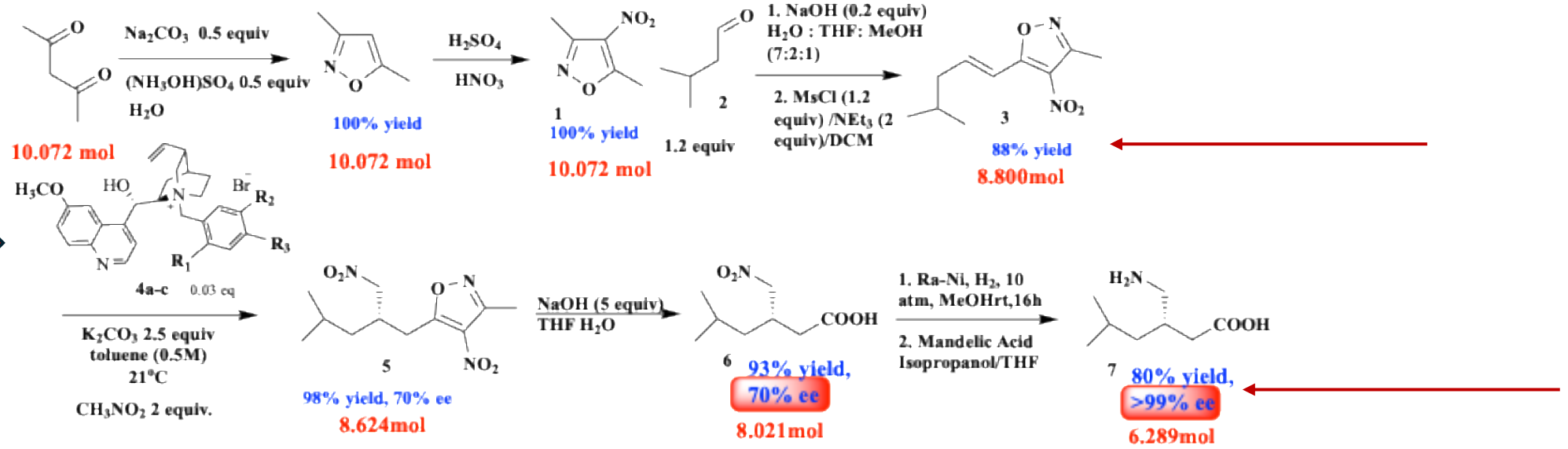
Step 6



						0
NaOH	$300	Ton	1.720	$516	0	516
THF	**$2,000**	**1,000 Litres**	**1.147**	**$2,294**	70%	688
HCl	$100	Ton	0.005	$1	0	1

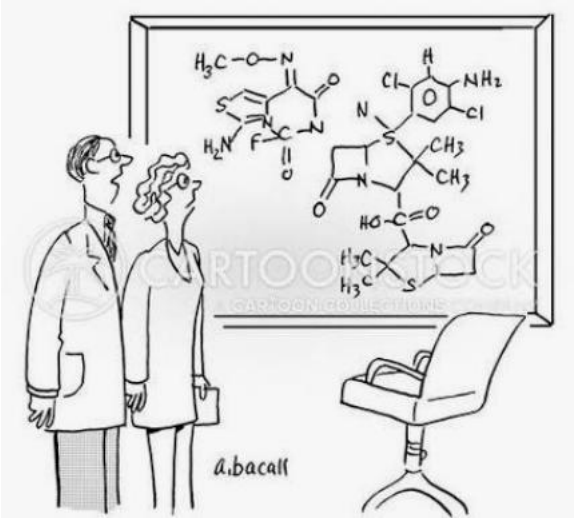
Reagent Cost: 5162$; **Reagent Mass: 1,702 kg**
Solvent Cost: 2,294$; **Solvent Mass: 1,147 kg**

Lessons from the process development of (S)-Pregabalin



Derived from Quinidine, the bitter flavor in tonic water

What the Synthetic Chemist sees



(i) Number of Steps
(ii) Yield per step
(iii) Mildness of conditions

M.F.A. Adamo, *Org. Process Res. Dev. 19* (**2015**) 1274–1281

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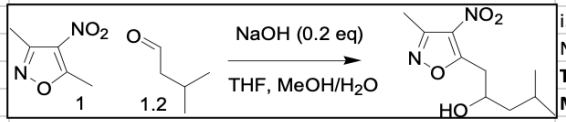
What the Business man sees

Estimated RMC's per kg of *Pregablin* **33.507** (vs 65$/Kg)

Step 3		isovaleraldehyde	$4,100	Ton	1.0	$4,235	0	4,235
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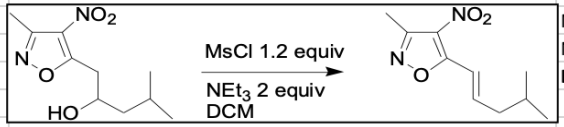
Step 4		MsCl	$1,350	Ton	1.253	$1,692	0	1,692
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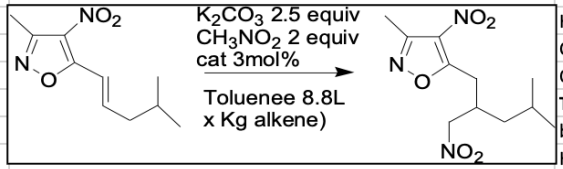
Step 5		K2CO3	$500	Ton	3.034	$1,517	0	1,517
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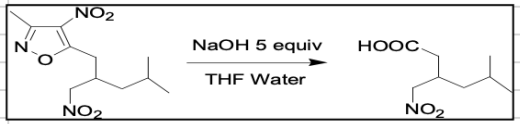
Step 6								0
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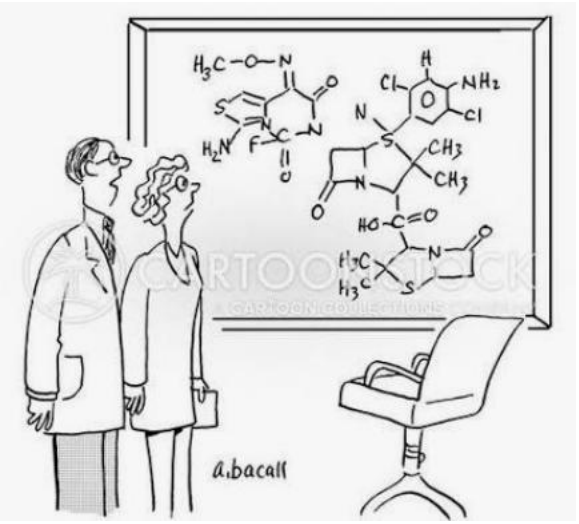
What ALL should see: traditional step-wise (batch) approach is neither cost-efficient nor sparing resources => need for better syntheses



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Methods to reduce the mass used for synthesis

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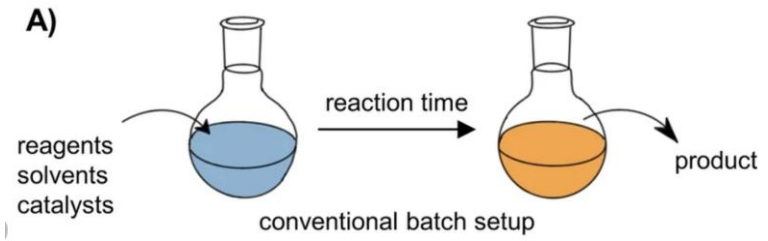
1. **Combining reactions**: i.e. multicomponent reactions (*Transpharm* synthesis of Atomoxetine)
2. **Adopting engineering solutions that decrease % of solvent** (in-flow and mechanochemistry)

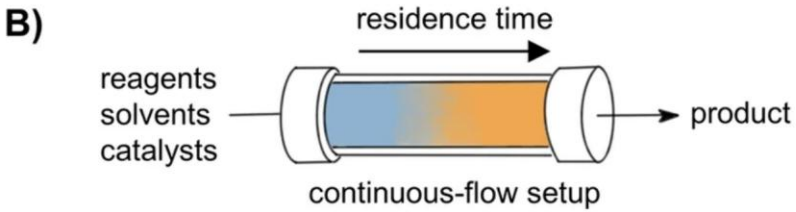
General Mapping: Molarity vs. Percentage

The sweet spot for most lab-scale flow synthesis sits between **0.1 M and 1.0 M**. For an average organic molecule (molecular weight of 150 to 250 g/mol), this translates to:

Molarity Range	Approximate Percentage Range	Context in Flow Synthesis
0.05 M – 0.2 M	**~1% – 4%**	Highly dilute. Used for high-throughput screening, photochemistry, or highly exothermic steps to control heat.
0.2 M – 0.5 M	**~4% – 10%**	The standard "starting point" for most lab-scale flow protocols.
0.5 M – 1.0 M	**~10% – 20%**	Moderately concentrated. Ideal for improving throughput if solubility permits.
1.0 M – 3.0 M+	**~20% – 40%+**	Highly concentrated or "neat" reagents. Used in industrial scale-up to minimize solvent waste and maximize output.



Batch conditions



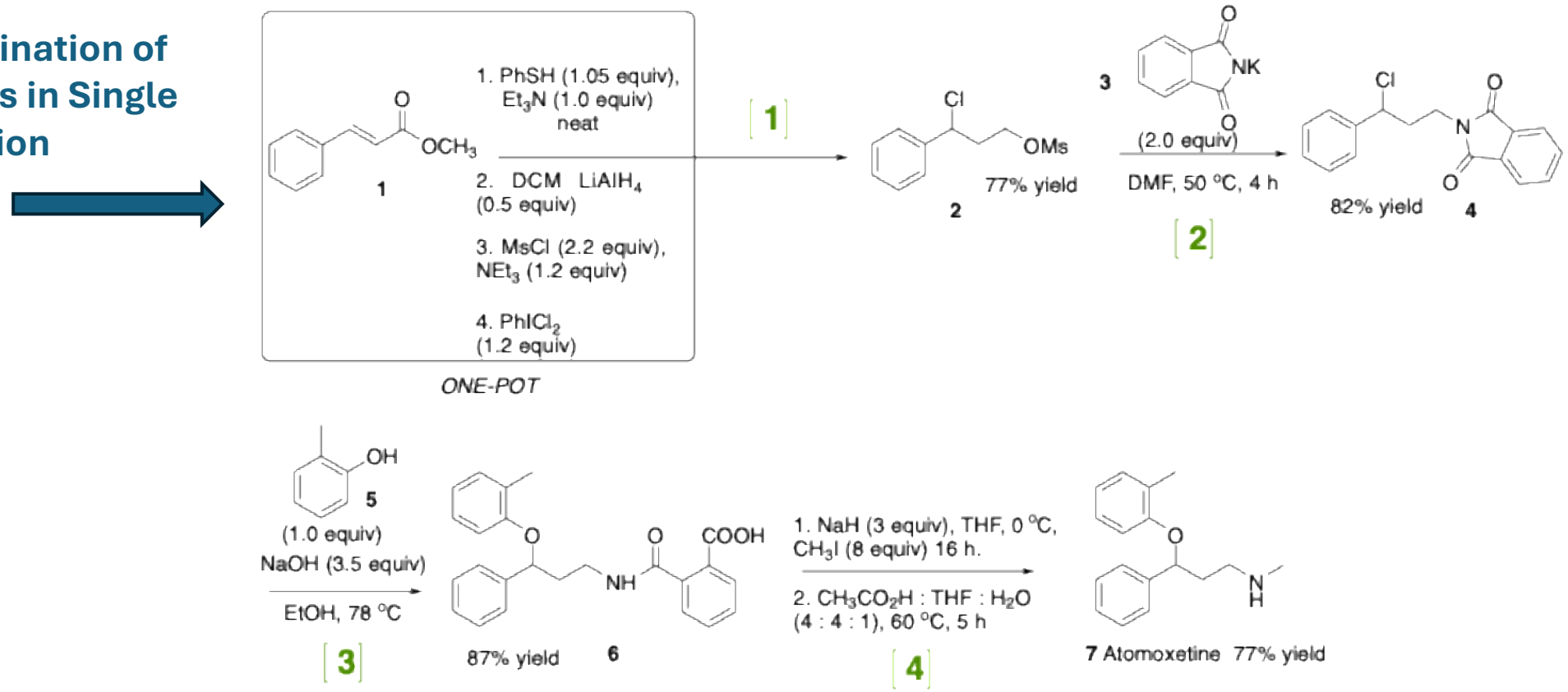
In-Flow Conditions

3. Device of new methodology to "reclaim" C (and O) from biomass

Preparation of Atomoxetine : developed a shorter procedure

Originator (Eli-Lilly) process run in six steps; developed synthesis run in 4 steps.

Combination of 4 steps in Single Reaction



Adamo MFA *Tetrahedron Letters 171–172* (**2025**) *155800*

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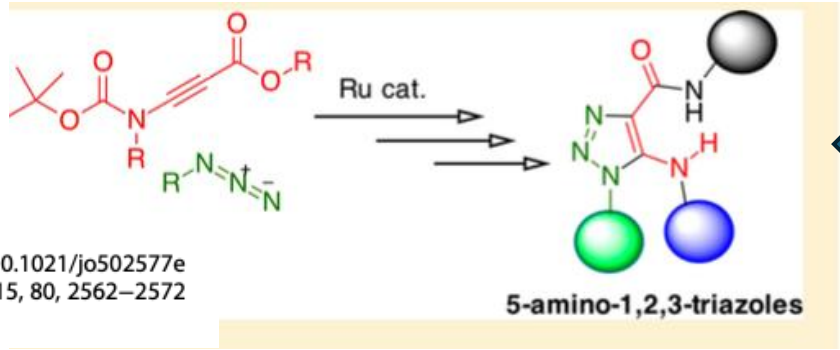
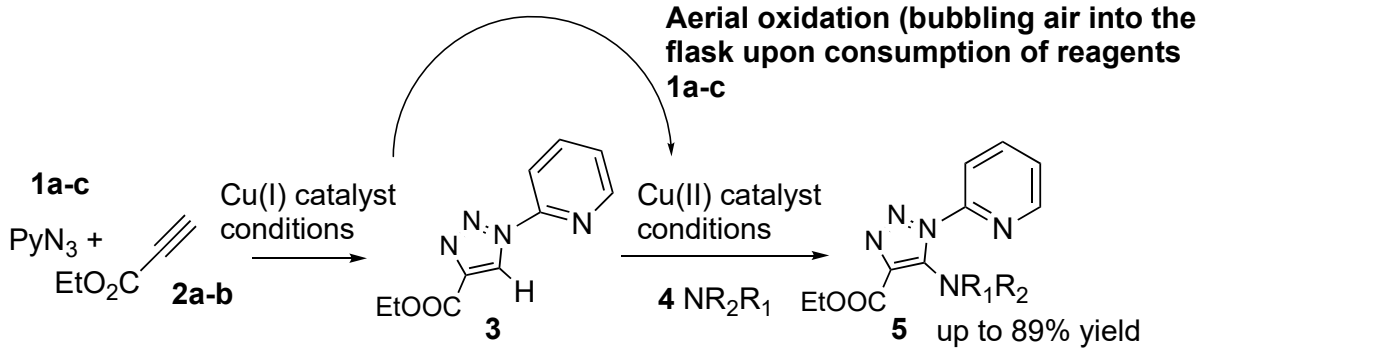
Preparation of peptidomimetics (α,β-carbetoxy-aminotriazoles) via 3-MCR tandem Cu(I) dipolar cycloaddition-Cu(II) C-H activation.

The triazoles amino acids were employed for the preparation of dipeptides having the structural motives typical of β-turn inducers.



DOI: 10.1021/jo502577e
J. Org. Chem. 2015, 80, 2562–2572

Preparation of these compounds requires **7 steps**



Huisgen Cycloaddition: run under catalytic Cu(I)

C-H activation: run under catalytic Cu(II)

Transpharm procedure obtained the same product in **a single step**

Achieved in a single step, by using the same metal species in two different oxidation states and using aerial oxygen for their interconversion

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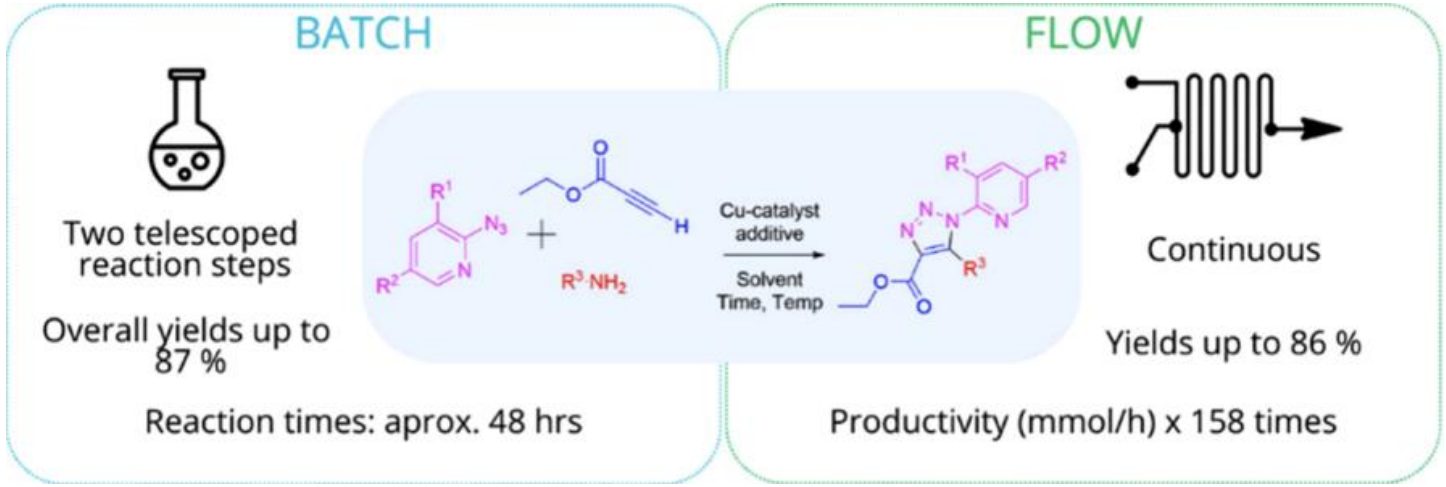
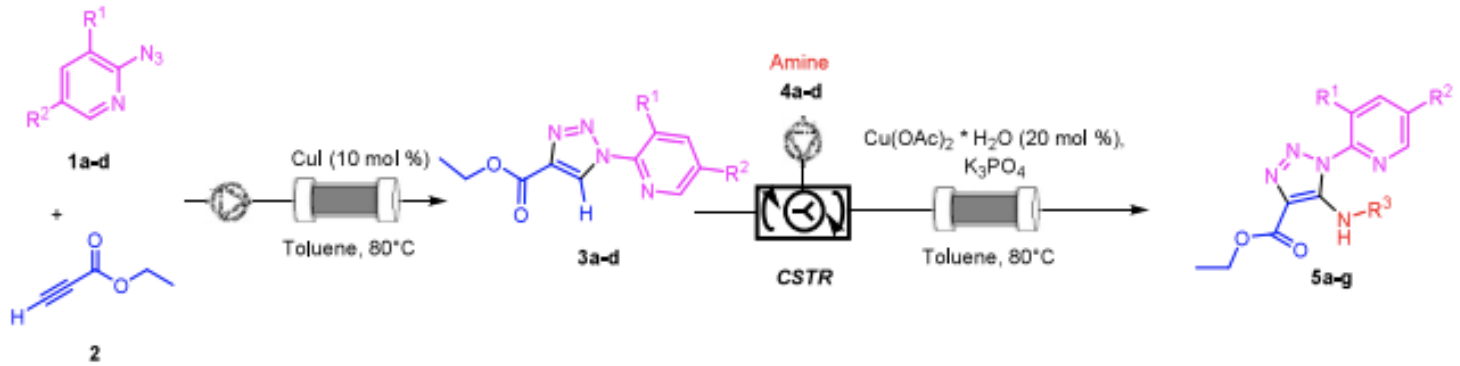
Preparation of peptidomimetics (α,β-carbetoxy-aminotriazoles) via 3-MCR tandem Cu(I) dipolar cycloaddition-Cu(II) C-H activation





Emanuela Donato, Martha C. Mayorquín-Torres, Alessandra Puglisi, Maurizio Benaglia, Mauro F. A. Adamo, and Christian V. Stevens*

Cite This: *Org. Lett.* 2025, 27, 4423–4427

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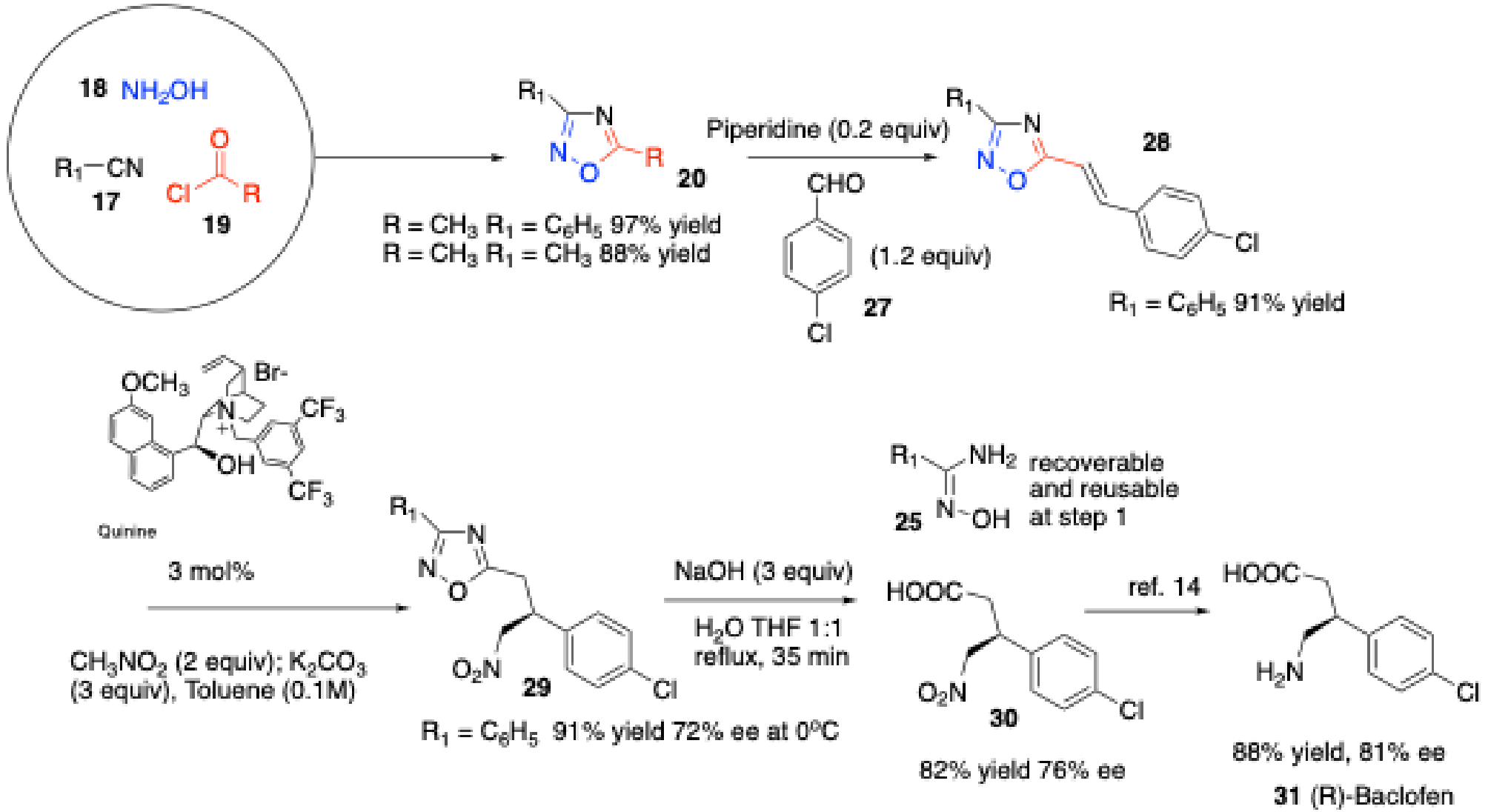
Transpharm preparation of (*R*)-Baclophen



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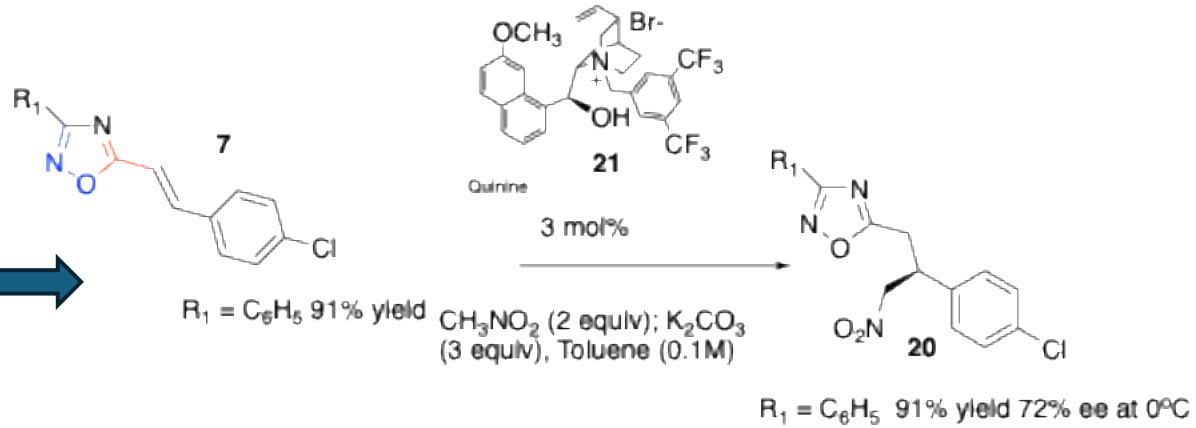
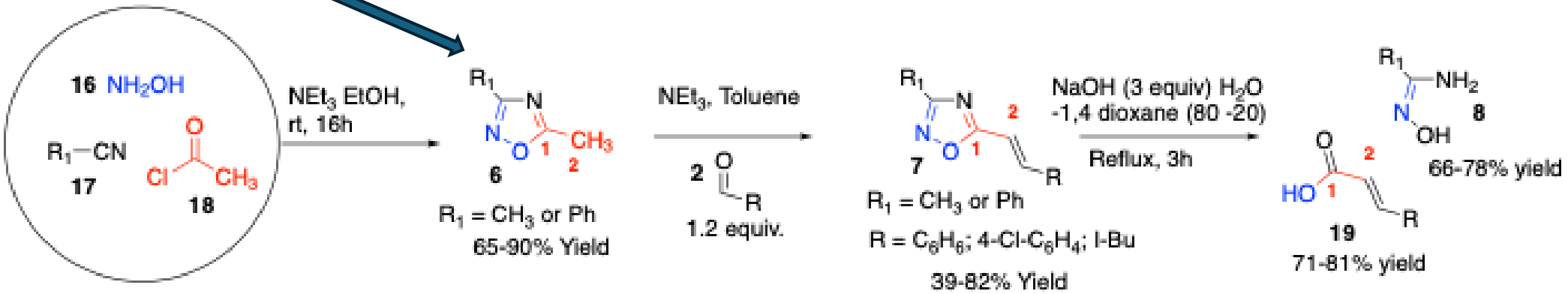
Preparation of (*R*)-Baclophen

Two new reagents were designed and created

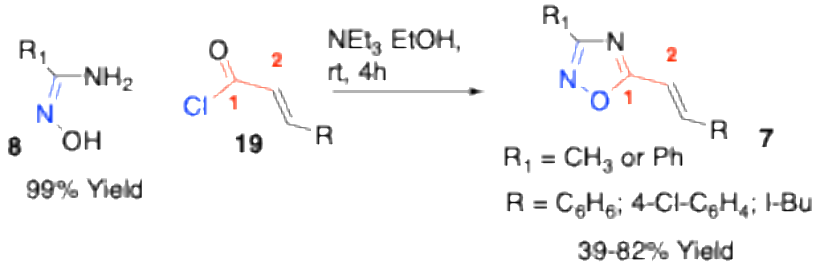


Scheme 7: PTC Enantioselective reaction of **7** and CH_3NO_2

Side product obtained at the end of process can be recycled



Scheme 5: Preparation of 1,2,4-oxadiazoles **6** and their synthetic application



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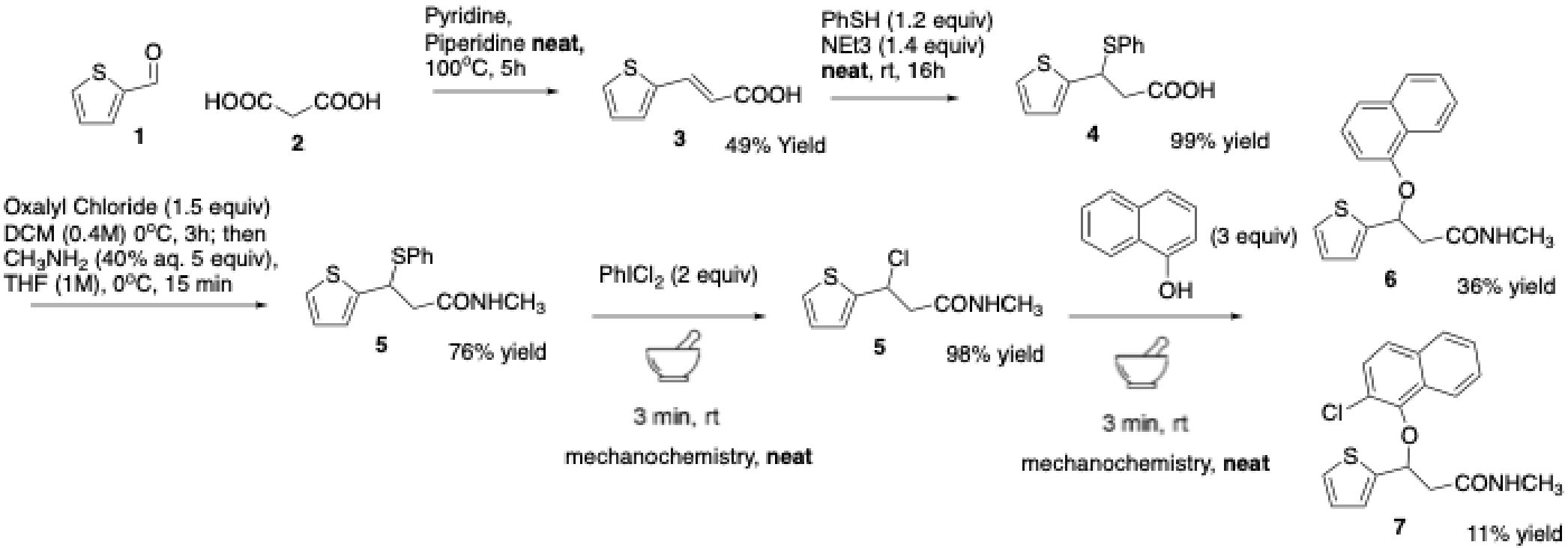
Preparation of Duloxetine : developed a “solventless” procedure



On route to Duloxetine

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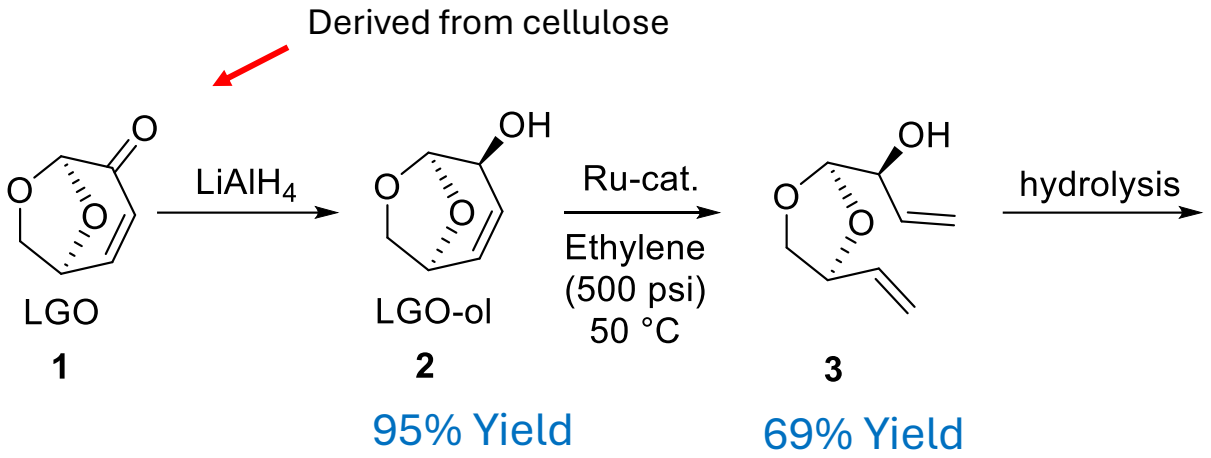
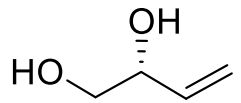
From Levoglusenone to Advanced intermediates for APIs

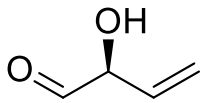


Chiral building blocks



(*R*)-but-3-ene-1,2-diol

and



(*S*)-2-hydroxybut-3-enal

4 82% Yield **5**

Scope of the research: convert the molecule LGO (**1**) to the chiral building blocks **4** and **5**. The desired building blocks will be used in the preparation of API (e.g. statins)

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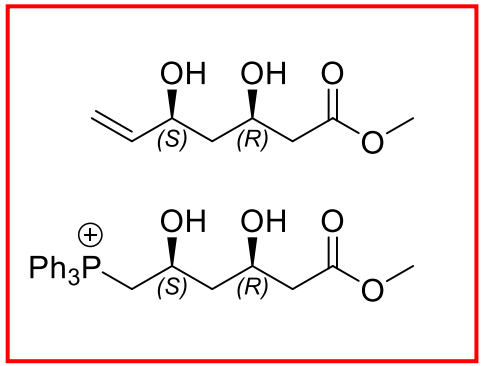
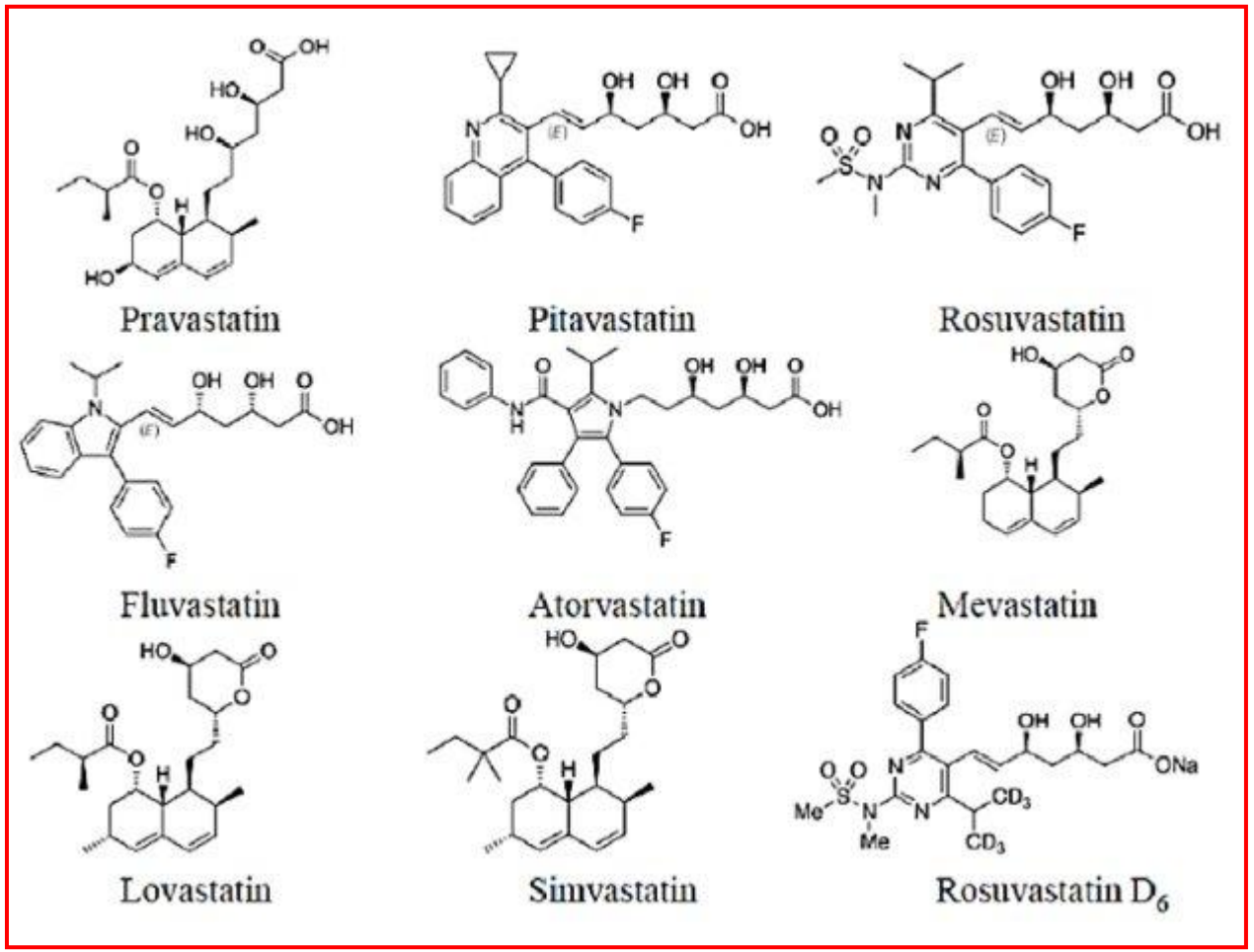
From Levoglusenone to Advanced intermediates for APIs

Statin fragments



Statin family



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In Conclusion:

- Advances have been made towards “better” syntheses that: (i) use less materials; (ii) are shorter; (iii) avoid polluting metals; are economically advantageous.

- This was possible via the adoption of (i) new designer reagents: (new methodology and engineering concepts (in flow, mechanochemistry, Multicomponent Reactions); (iii) exploitation of neglected resources (*i.e.* cellulose).

.....*TO BE CONTINUED*

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