

**Asymmetric Syntheses for the Large Scale Preparation of the
Collagenase Selective Inhibitor Ro 32-3555 (Trocade™)**

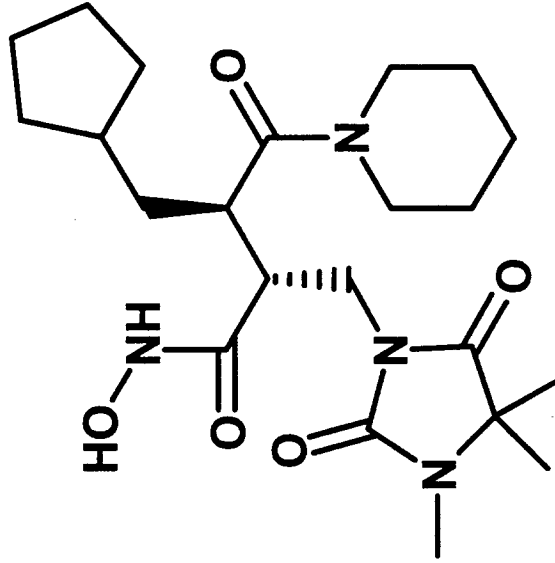
Dr. H. Hilpert, Pharmaceuticals Division, Process Research,

F. Hoffmann - La Roche Ltd., CH-4070, Basel, Switzerland

Cartilage Protective Agent

Trocade™

P.A. Brown,
Roche Welwyn
Research Center



IC₅₀: ca. 5 nm
oral bioavailability: 43% (man)
clinical phase II trials for
rheumatoid arthritis

Ro 32-3555

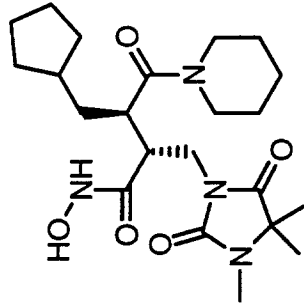
Pharmaceuticals



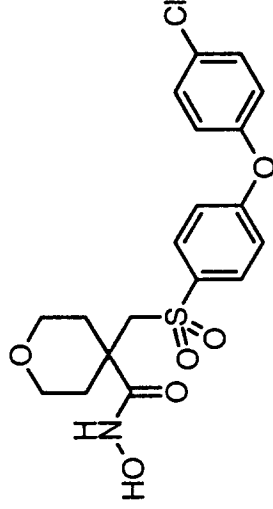


Matrix Metalloproteinase Inhibitors in Clinical Trials

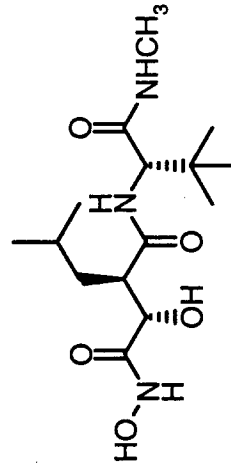
2



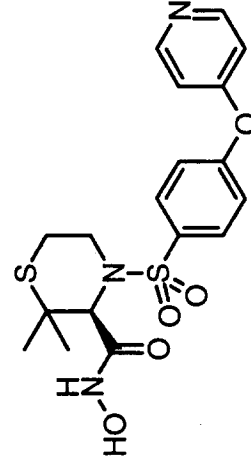
Roche, Ro 32-3555
Trocade™



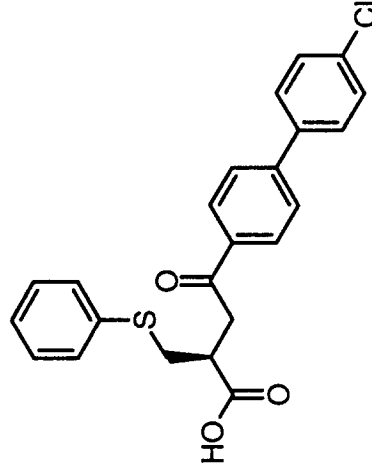
Roche Bioscience, RS 113-0830



British Biotech, BB-2516
Marimastat



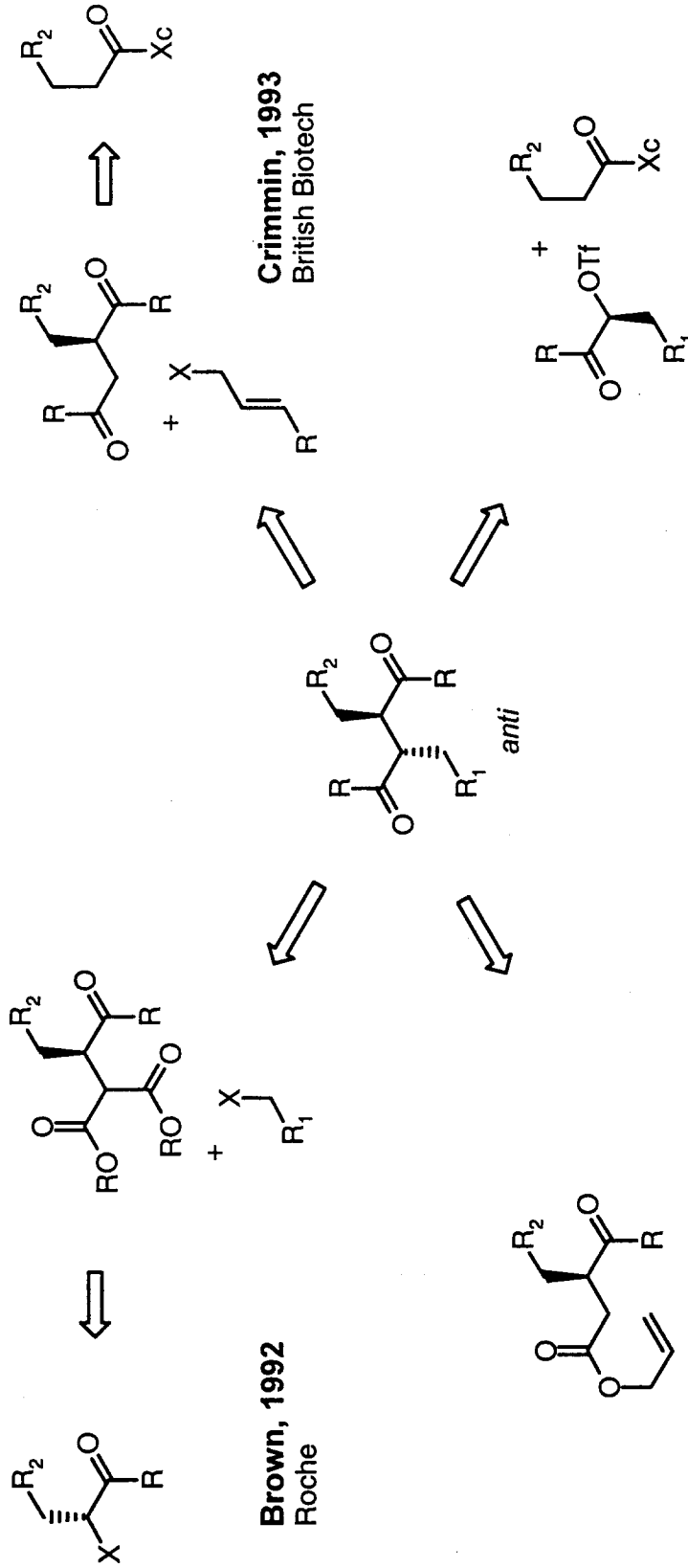
Agouron, AG 3340



Bayer, BAY 12-9566

Methods to Prepare 2,3-Substituted Succinates

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Brown, 1992
Roche

Crimmin, 1993
British Biotech

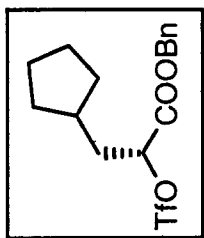
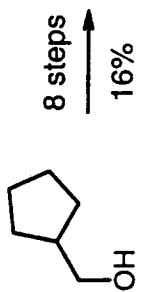
Martin, 1998
British Biotech

Decicco, 1995
Dupont Merck



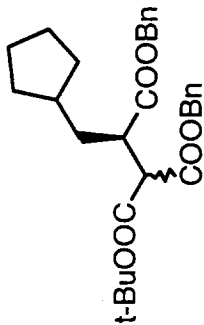
Drug Discovery Route: Overview

4

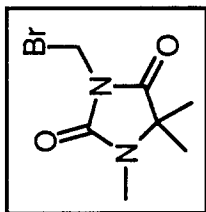
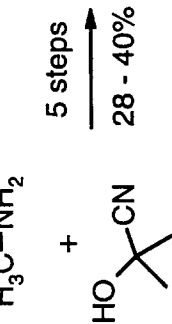


Triflate

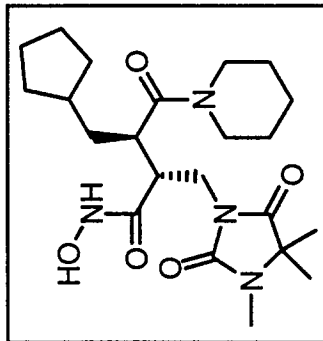
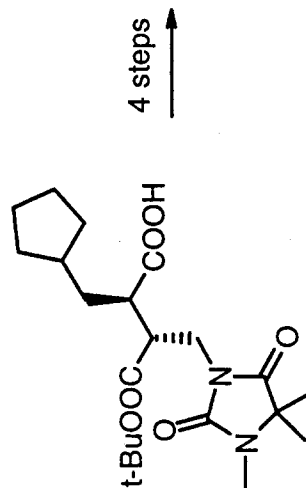
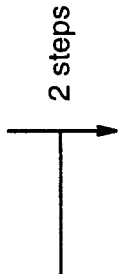
1 step



20 steps
overall yield: 2.8%



Hydantoin

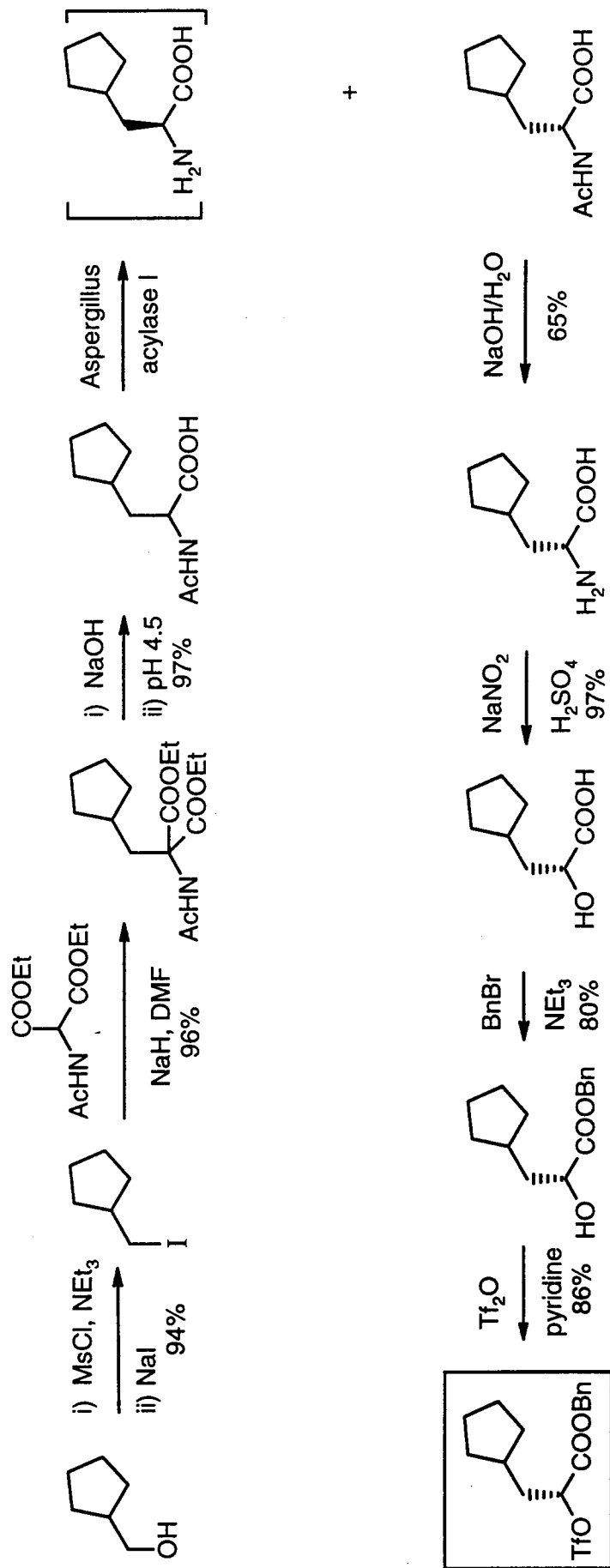


Ro 32-3555



Drug Discovery Route: Synthesis of the Triflate

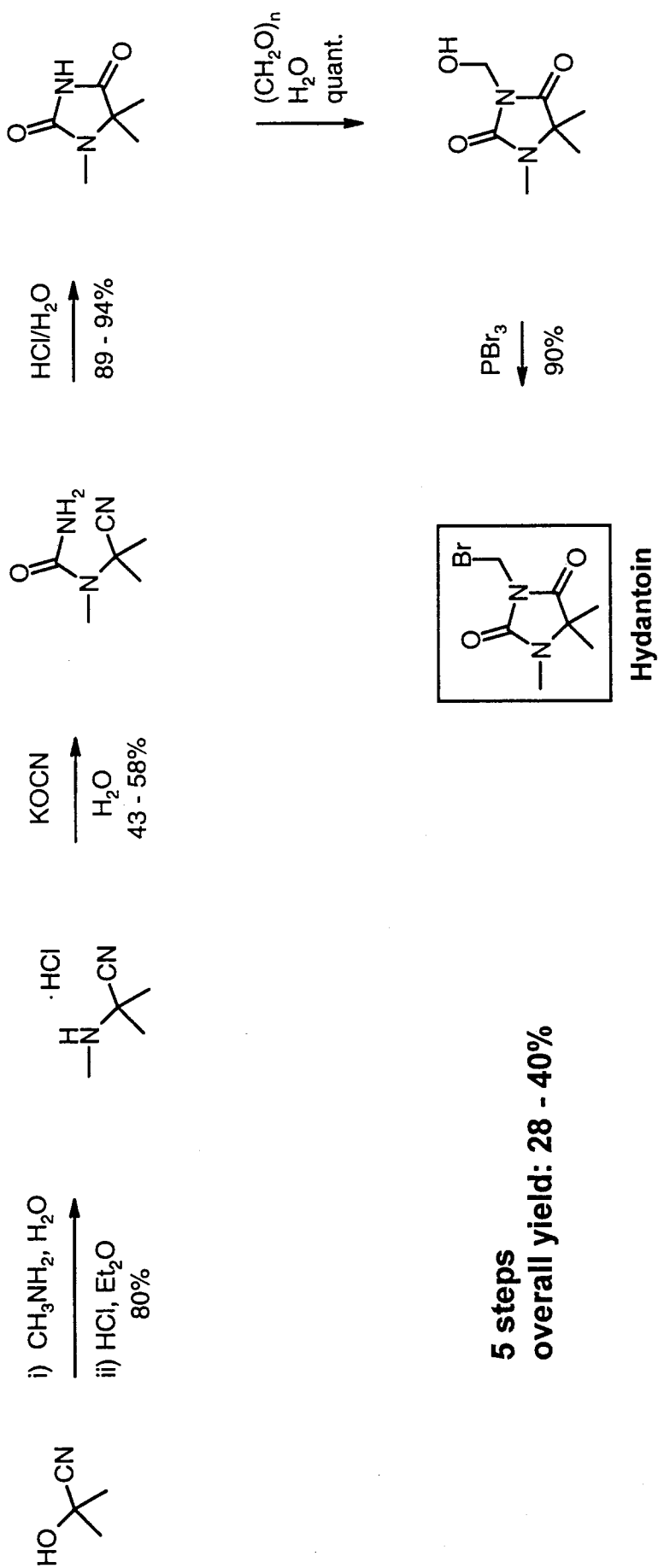
5



8 steps
overall yield: 16%



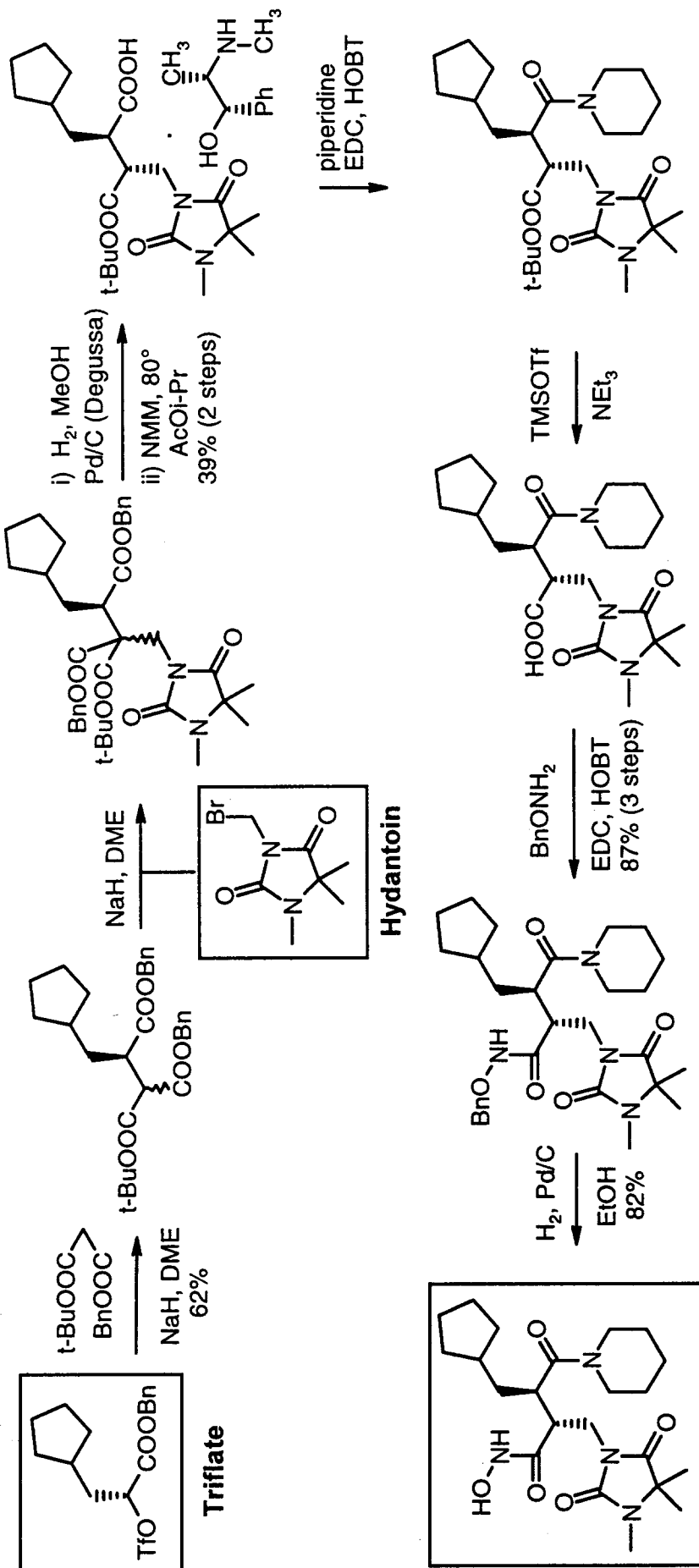
Drug Discovery Route: Synthesis of the Hydantoin **6**





Drug Discovery Route: Assembly of the Building Blocks

7



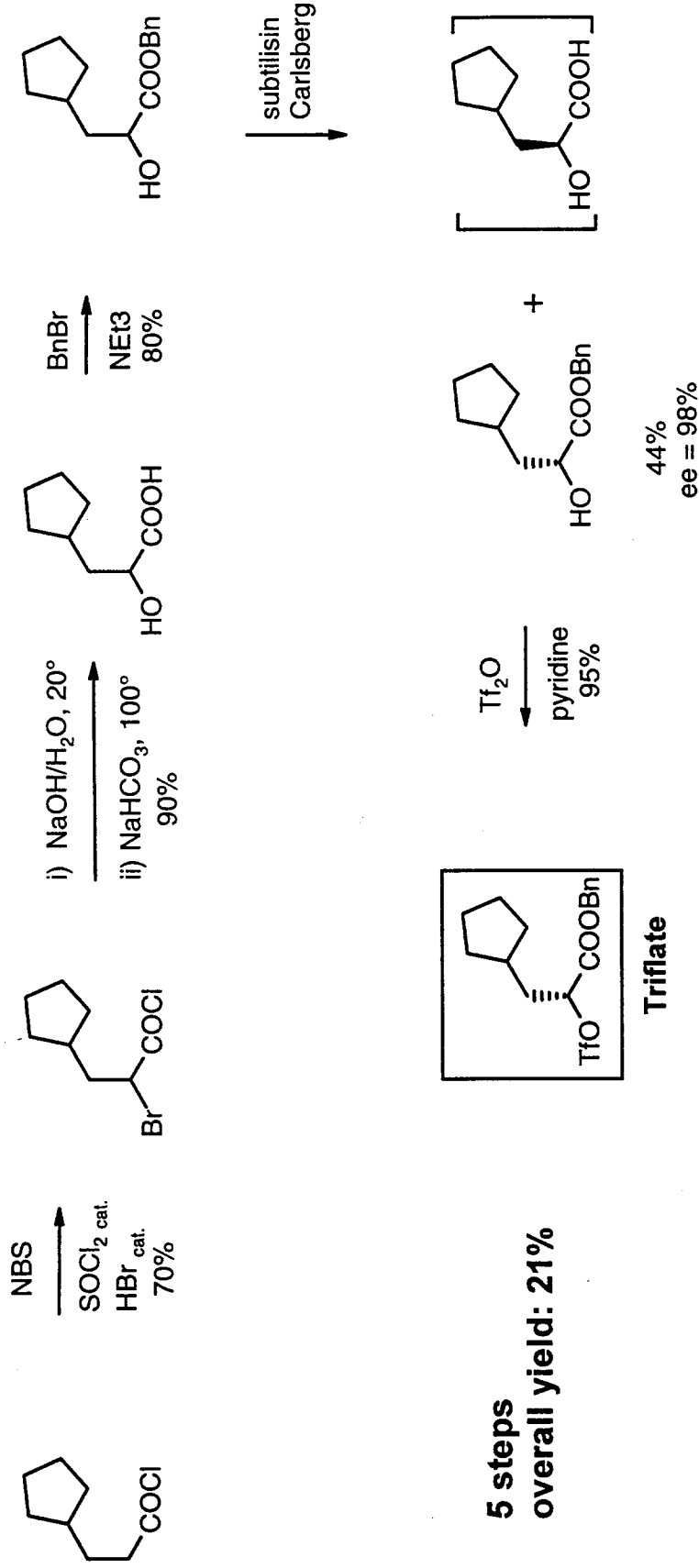
20 steps
overall yield: 2.8%

Ro 32-3555

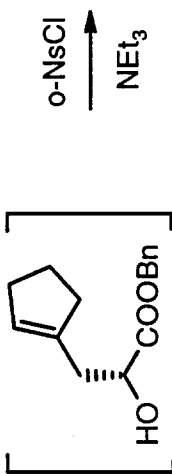
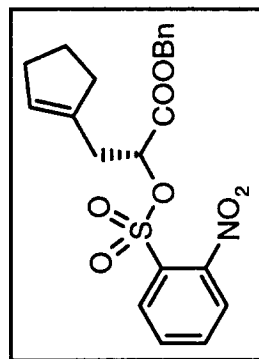


'Trouble Shooting': Alternative Route to the Triflate

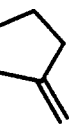
8



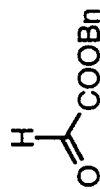
'Trouble Shooting': A Short Access to the Nosylate Building Block 9



1.5 mole% catalyst
 $\xrightarrow{\text{CH}_2\text{Cl}_2/\text{toluene}, 22^\circ}$
 molecular sieve



+



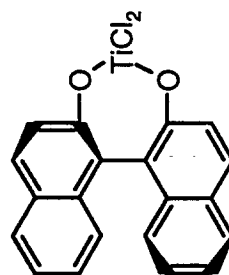
$\xrightarrow[\text{NEt}_3]{\text{o-NsCl}}$

ee = 95%

Nosylate

99.0% (chem. purity)
 99.9% (ee)

catalyst:

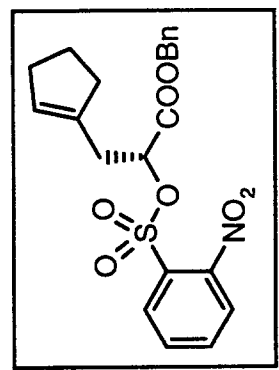


molecular sieve: content water ee

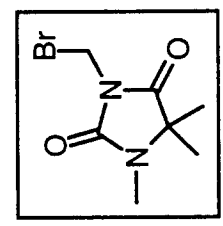
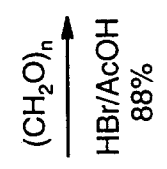
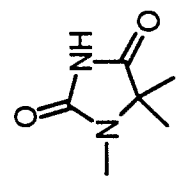
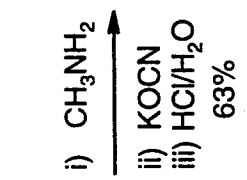
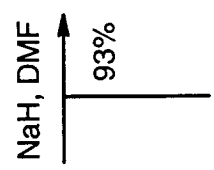
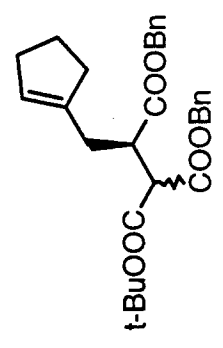
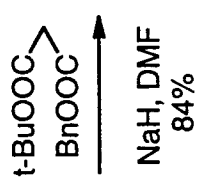
	3%	25%
	6-10%	95%

2 steps
overall yield: 67%

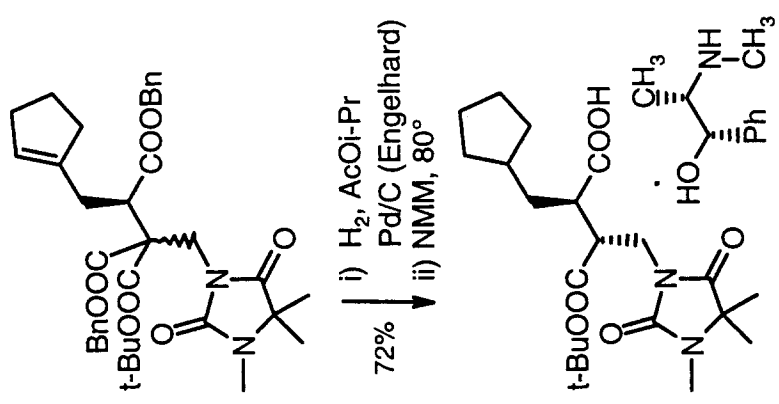
'Trouble Shooting': Assembly of the Building Blocks



Nosylate



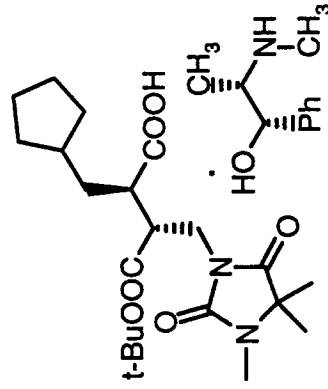
Hydantoin



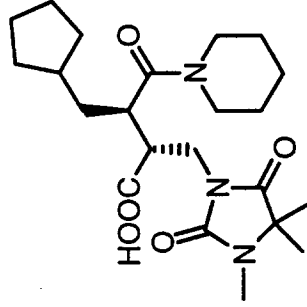


'Trouble Shooting': Final Steps

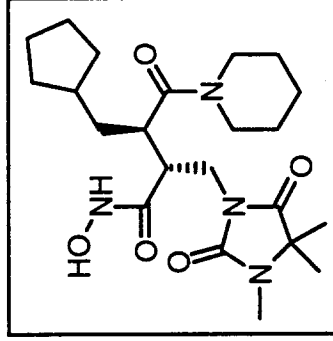
11



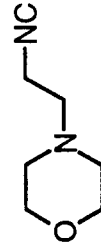
i) piperidine, DCC
HOPO_{cat.} →
ii) HBr/AcOH
82%



i) MEI, HOPO
TMSO-NH₂ →
ii) H₂O
80 - 85%



Ro 32-3555

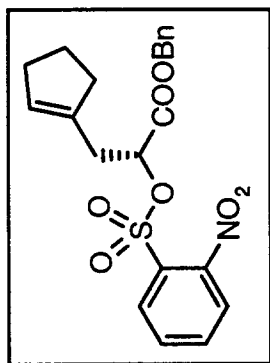


MEI:

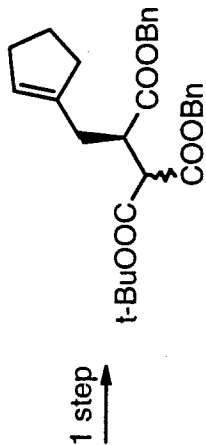
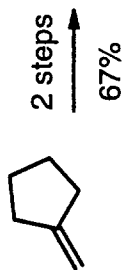


The 'Trouble Shouted' Synthesis: Overview

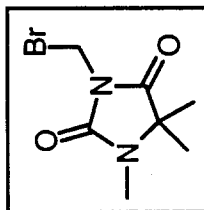
12



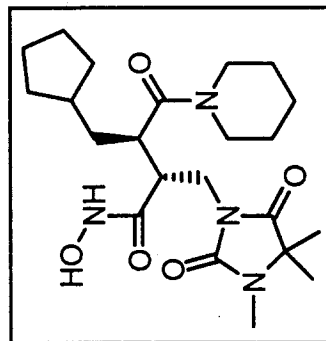
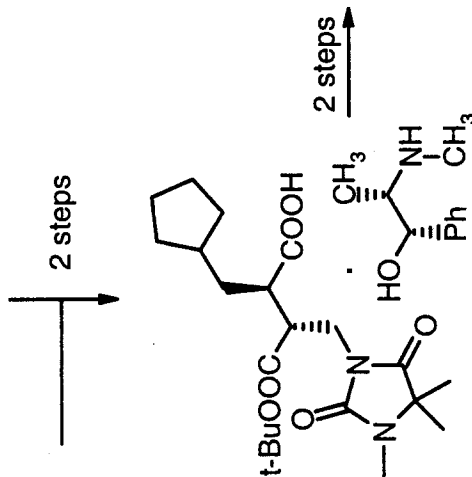
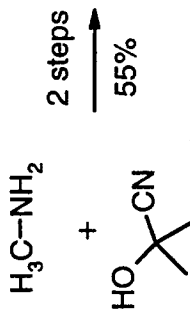
Nosylate



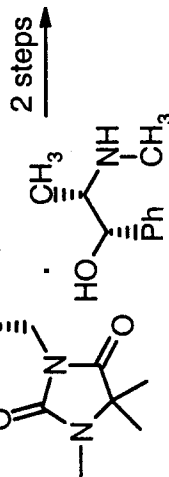
9 steps
overall yield: 24%



Hydantoin



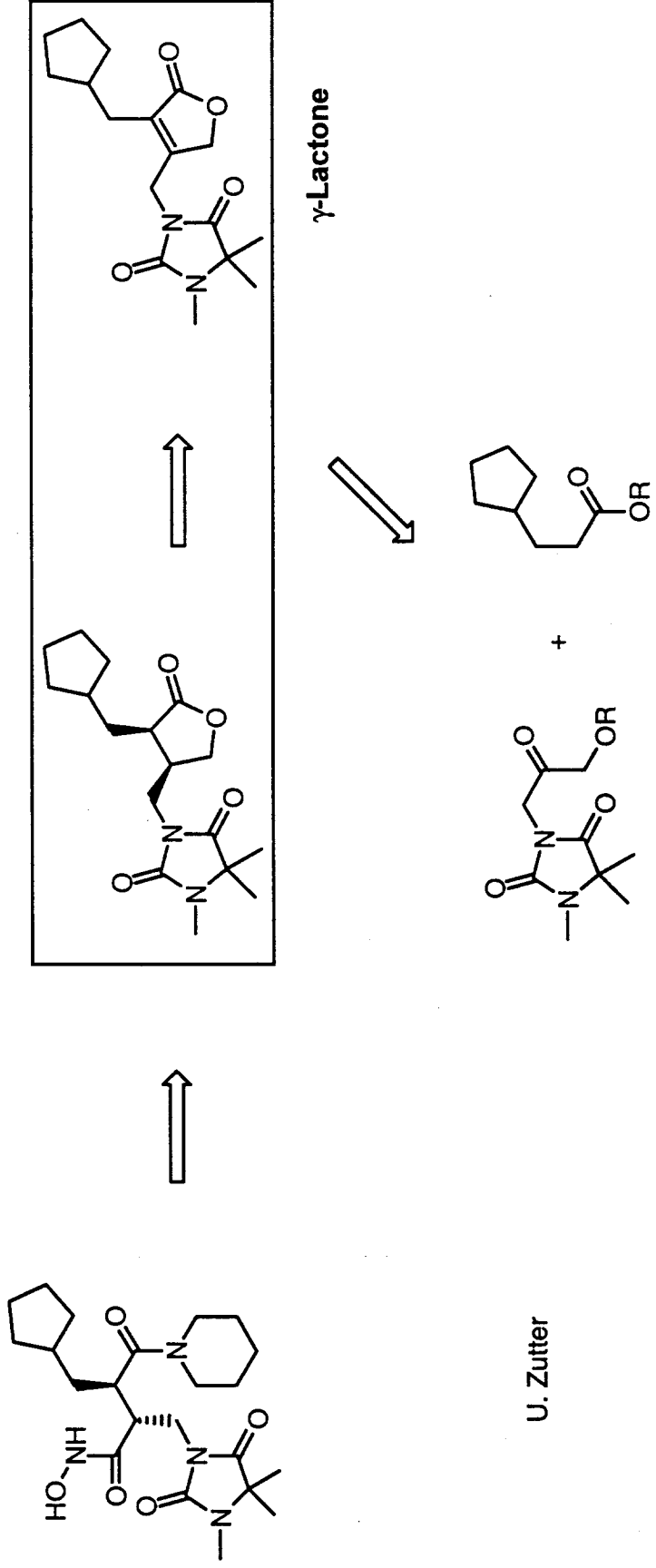
Ro 32-3555





New γ -Lactone Route: Retrosynthesis

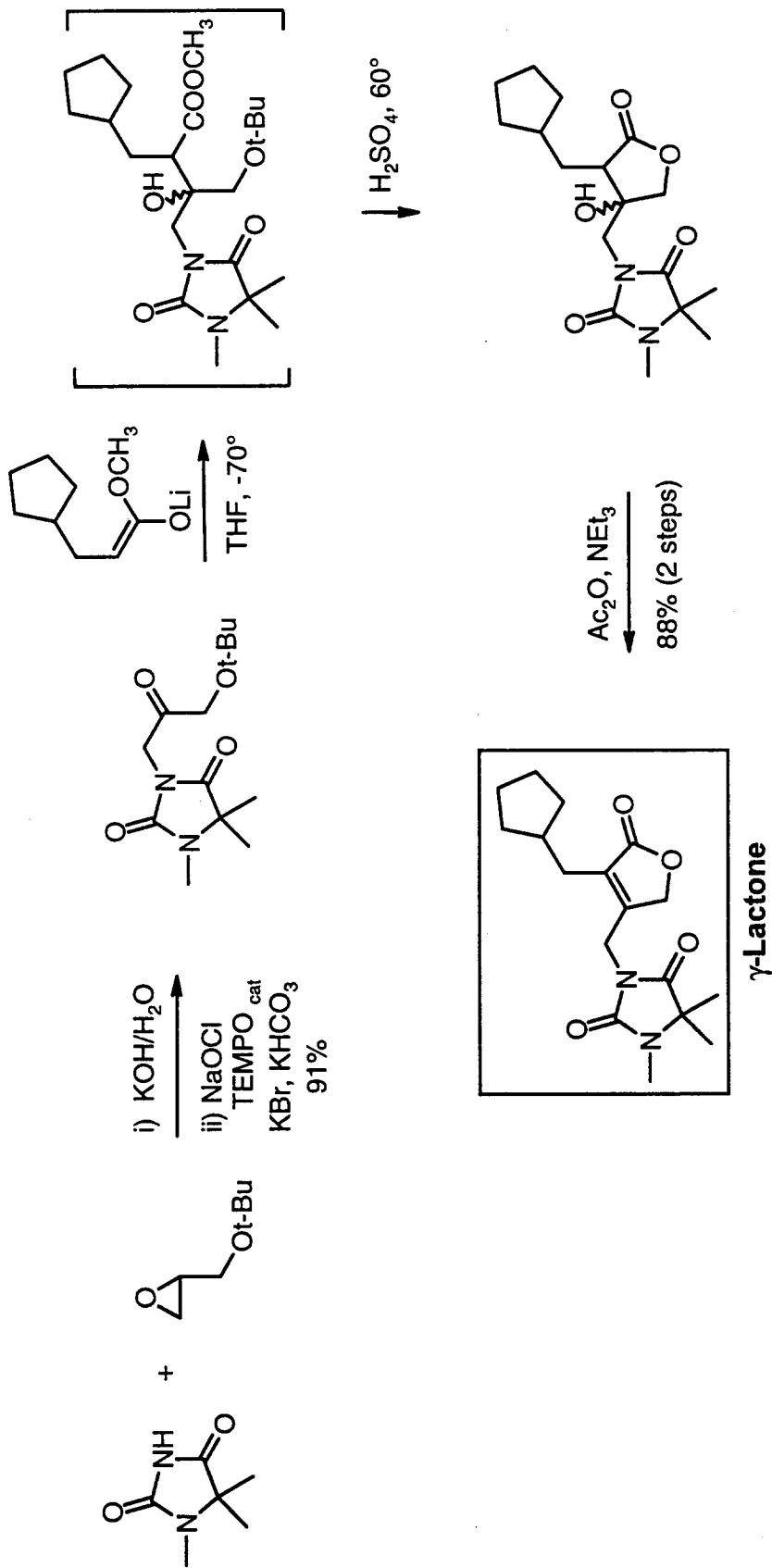
13





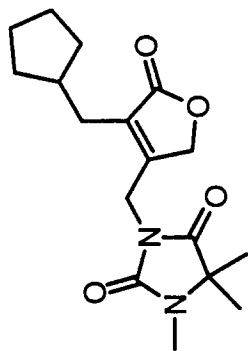
New γ -Lactone Route: Synthesis of the Substrate

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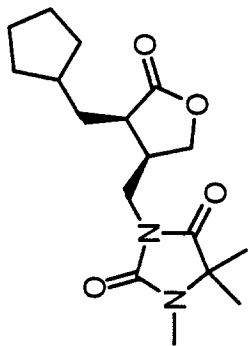




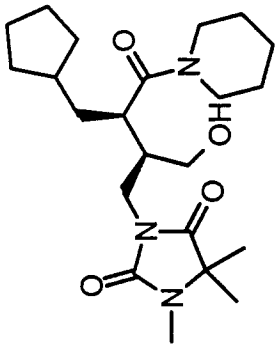
New γ -Lactone Route: Asymmetric Hydrogenation and Final Steps 15



H_2 , catalyst
 $s/c = 1000$
 100 bar
 80° (71h)
 $ee > 98\%$
 $de > 98\%$
 yield: quant.

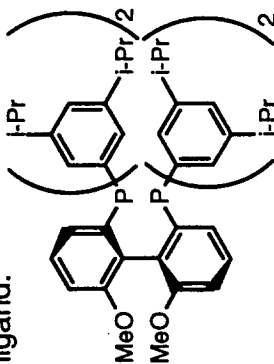


piperidine
 $\xrightarrow{AlCl_3}$
 86%



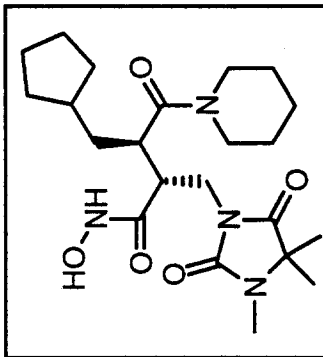
catalyst: $[Rh(\text{ligand})(COD)]^+ SbF_6^-$

ligand:



(R)-3,5-di-Pr-MeOBIPHEP

83%
 \xrightarrow{NaOCl}
 TEMPO cat.
 $KBr, NaHCO_3$



Ro 32-3555

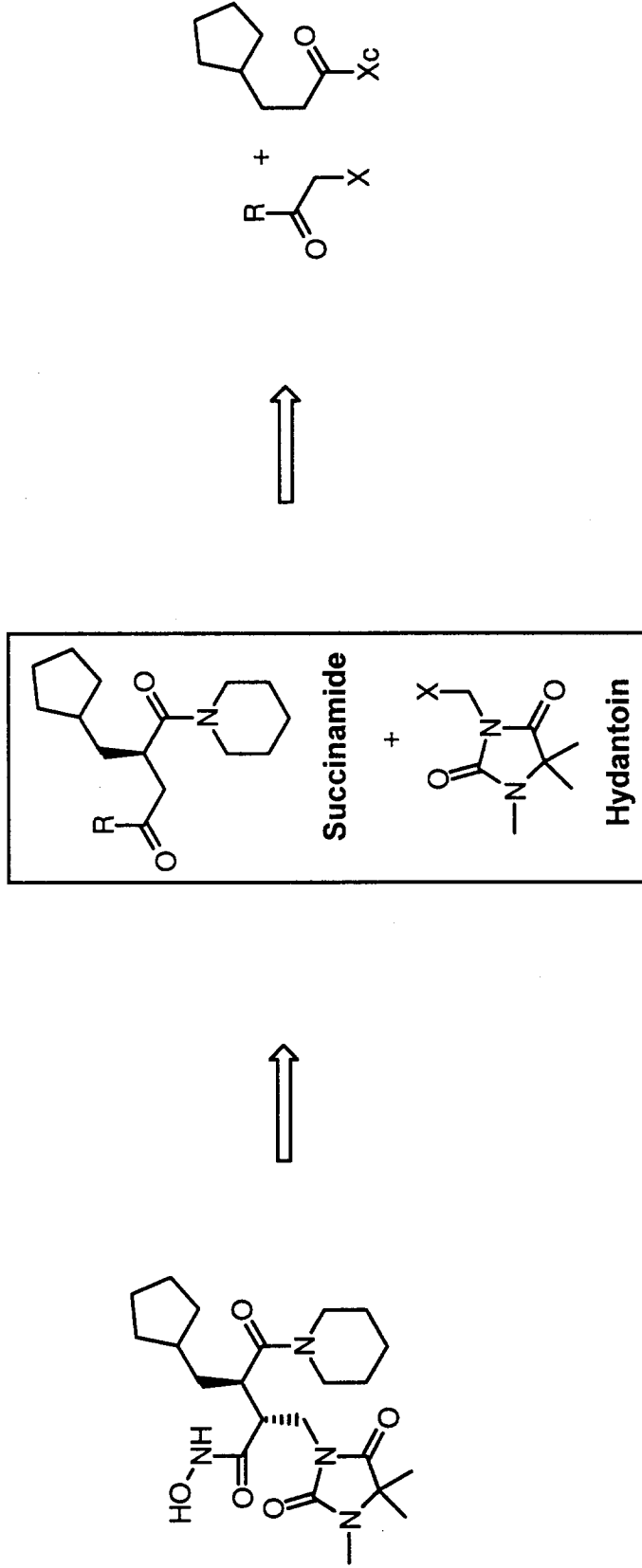
$\xrightarrow{TMSO-NH_2}$
 80 - 85%

7 steps, overall yield: 49%

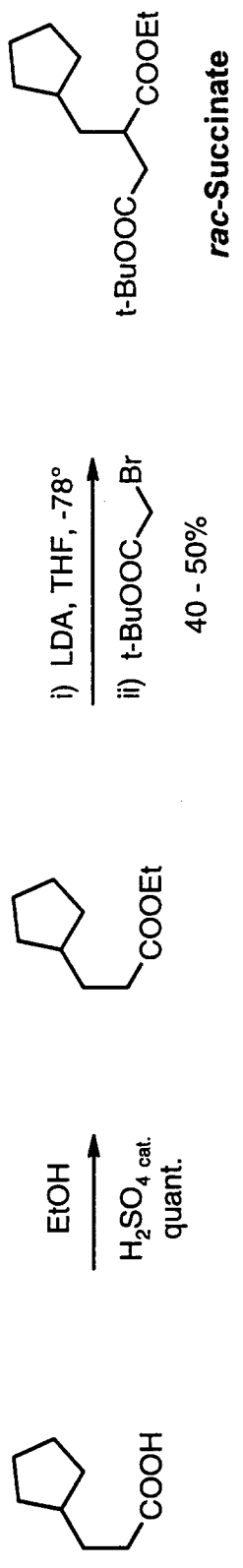


New Succinamide Route: Retrosynthesis

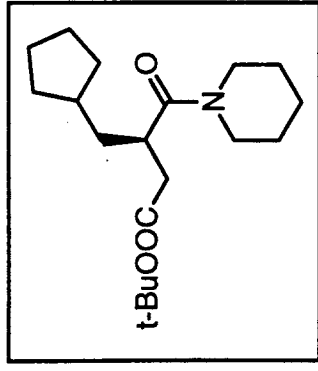
16



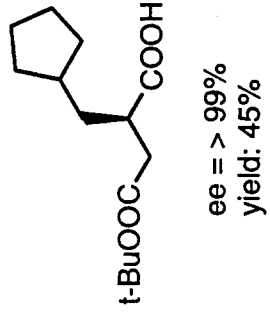
New Succinamide Route: Enzymatic Approach to the Succinamide 17



5 steps
overall yield: 31%

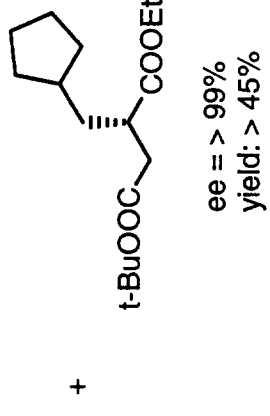


piperidine
DCC
quant.



Succinamide

subtilisin
Carlsberg



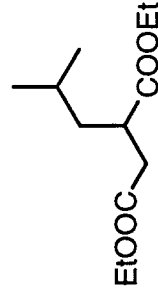
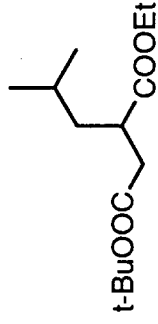
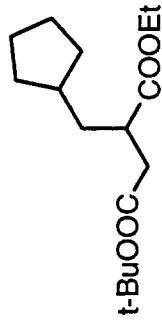
(R)-Succinic acid

(S)-Succinate



Substrate Specificity of Subtilisin Carlsberg

18

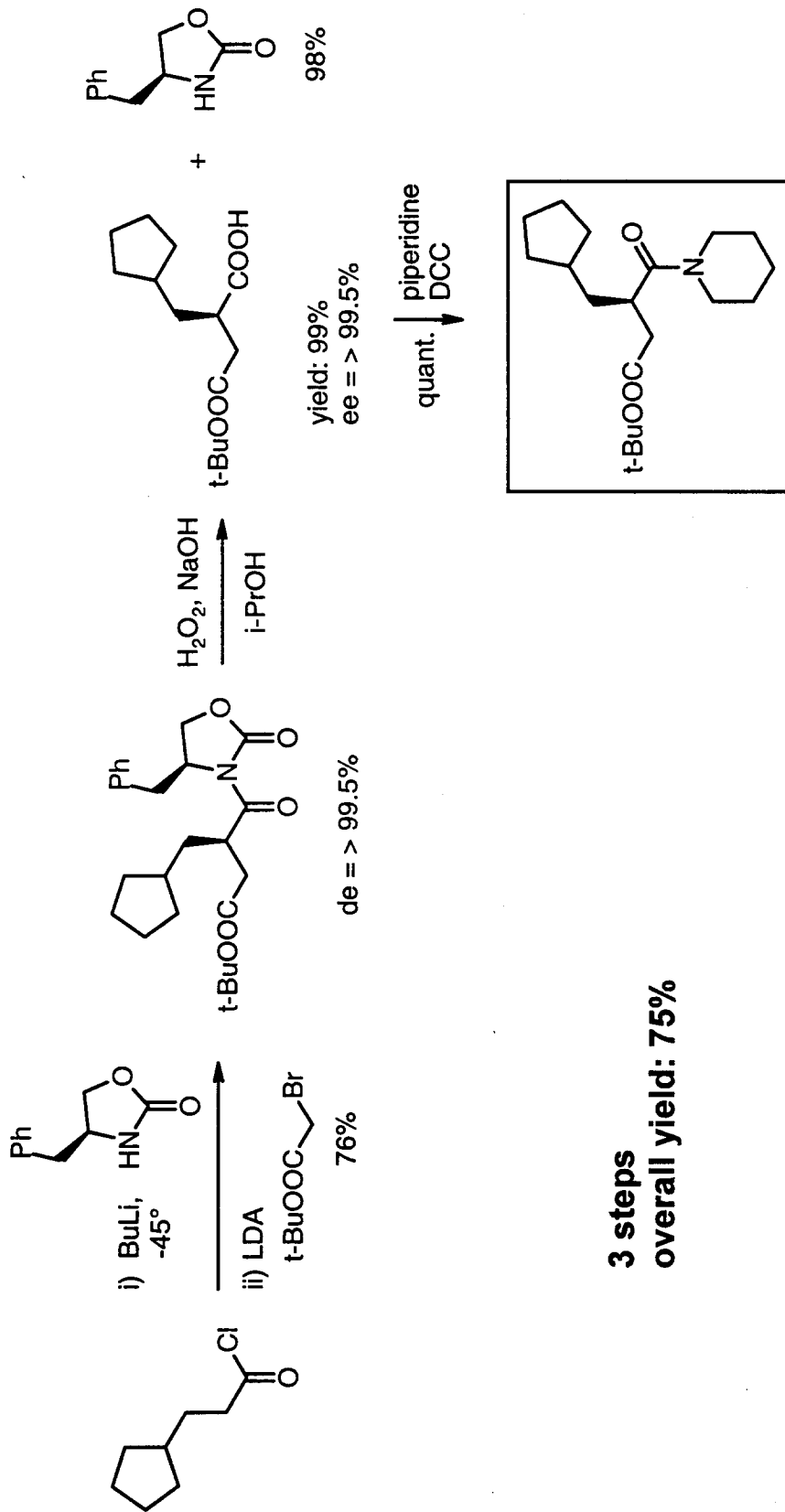


optimized conditions

(yield: 40 - 45%, ee = >98%)

s/e (g/ml)	1	2	10
conc.	2%	18%	20%
time	43 h	27 h	48 h

New Succinamide Route: A Short Access to the Succinamide 19

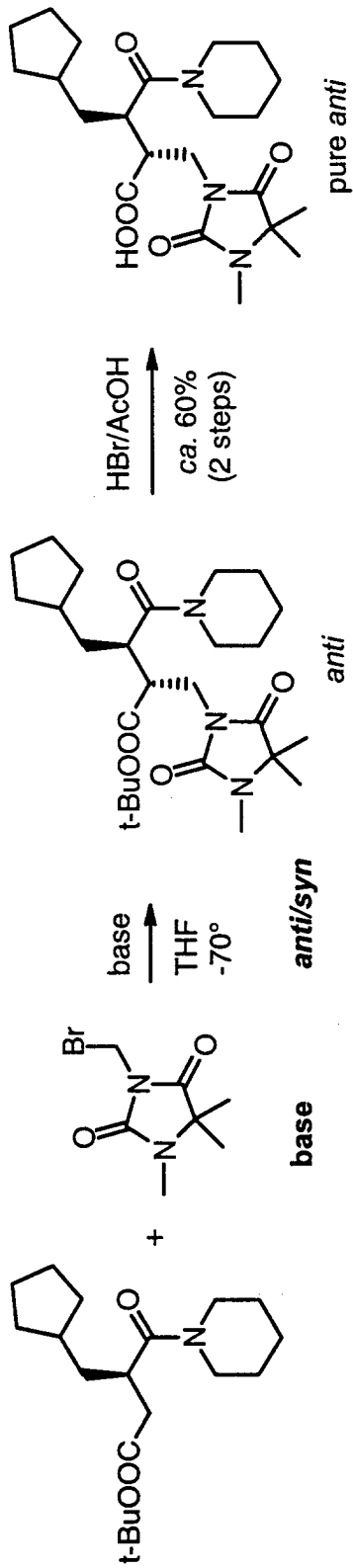


3 steps
overall yield: 75%



New Succinamide Route: Stereoselective Alkylation

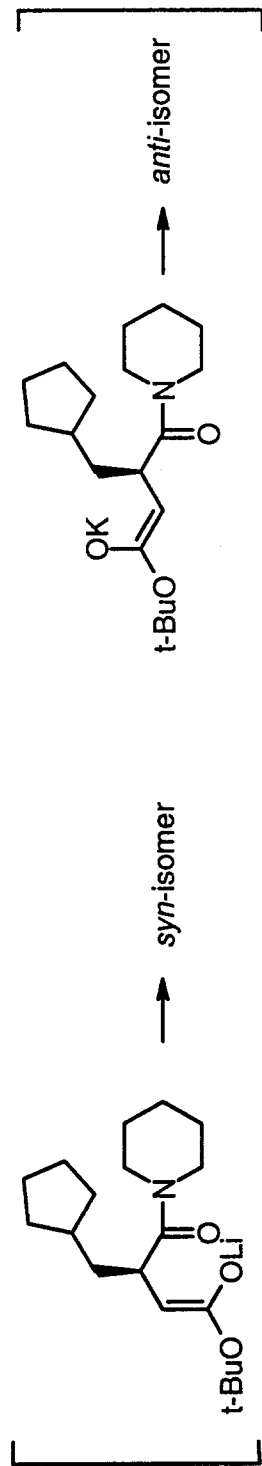
20



base
THF
-70°

base **anti/syn**

LDA 15 : 85
 NaN(TMS)₂ 50 : 50
 KN(TMS)₂ 86 : 14

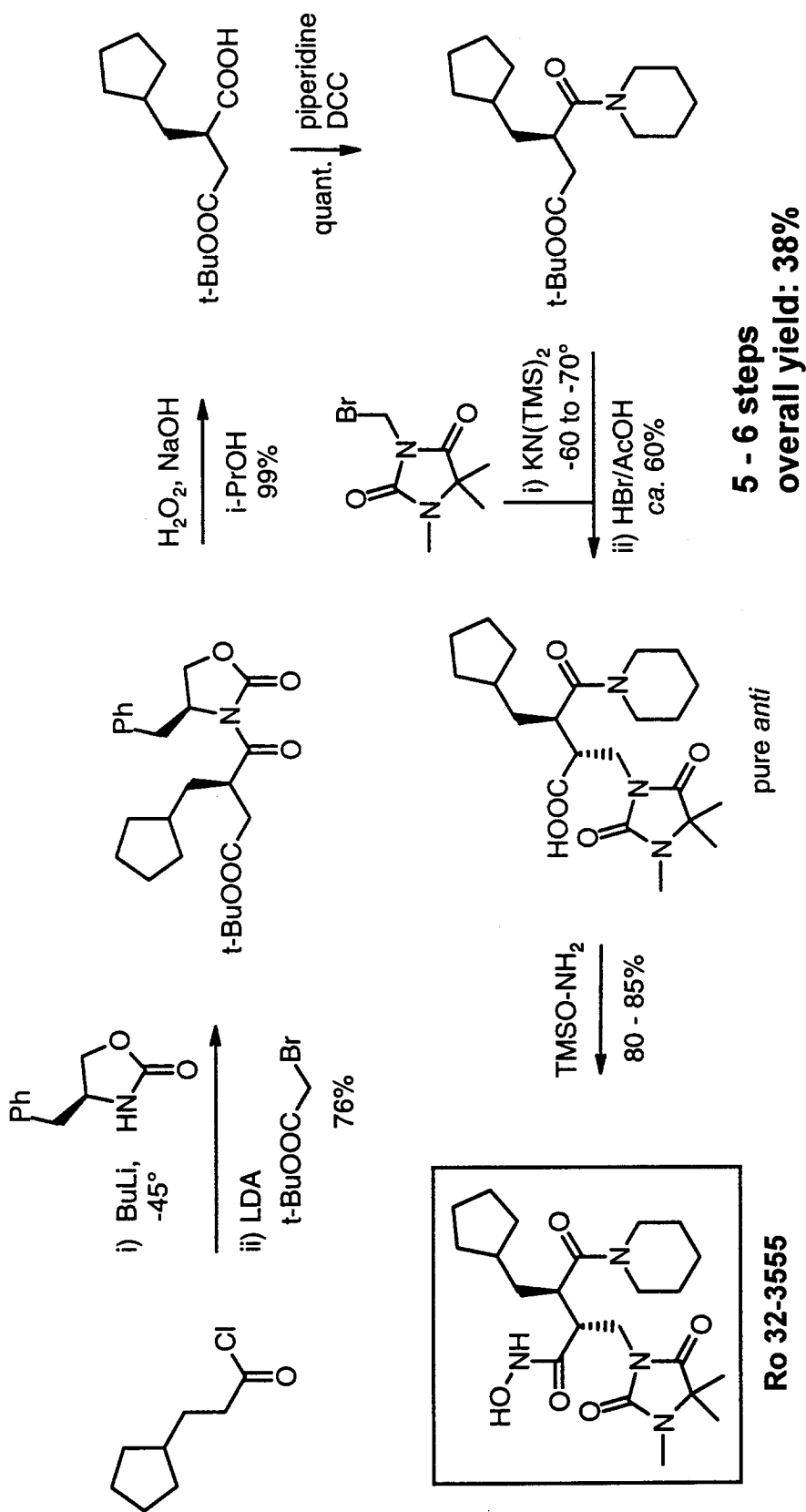


base

base

New Succinamide Route: Achievements

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The Team

22

Drug Discovery

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Dr. U. Zutter
Mr. K. Bolliger

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Dr. F. Stäbler
Mr. W. Schemmer

Analytics

Mr. V. Meduna
Mr. J.-C. Jordan
Dr. J. Schmidt
Mr. F. Vix

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