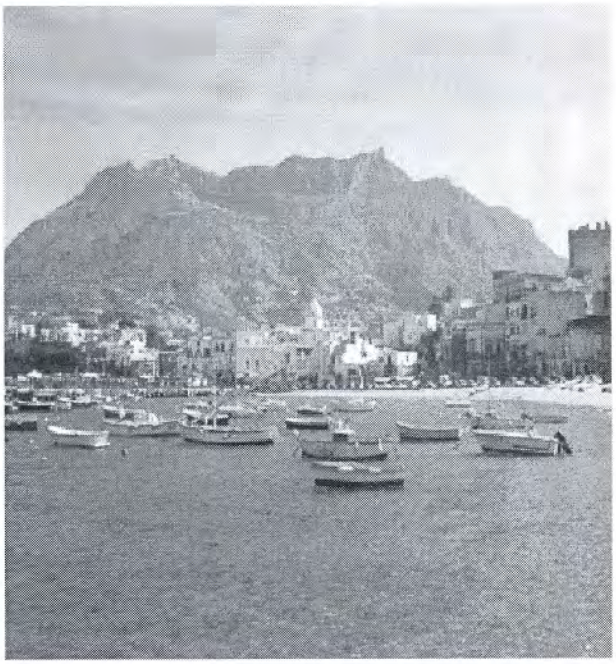
PRACTICAL SYNTHESIS OF NEW INVESTIGATIONAL THERAPEUTICS

Development of a scalable synthesis of BILN 2061, a novel HCV Protease inhibitor

Dept. of Chemical Development, Boehringer Ingelheim, Ridgefield CT



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Therapeutic Need

- Over 170 million people are infected with hepatitis C virus (HCV) worldwide (WHO 1997).
- > 70% of infected individuals will develop chronic hepatitis C. Chronic hepatitis C is a progressive condition leading to end-stage liver disease (cirrhosis and hepatocellular carcinoma).
- Available interferon-containing therapies have limited efficacy and have significant side effects.

Hepatitis C - Standard Therapy

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- Interferon α or β (subcutaneous administration).
- Rebetron: Intron A + oral ribavirin, launched in 1998 (USA).
  - New standard therapy: 50% sustained response rate (genotype I virus).
  - Treatment cost: ~ $17,000/year ($1,440/month) per patient.

Hepatitis C Virus Particle and Genome

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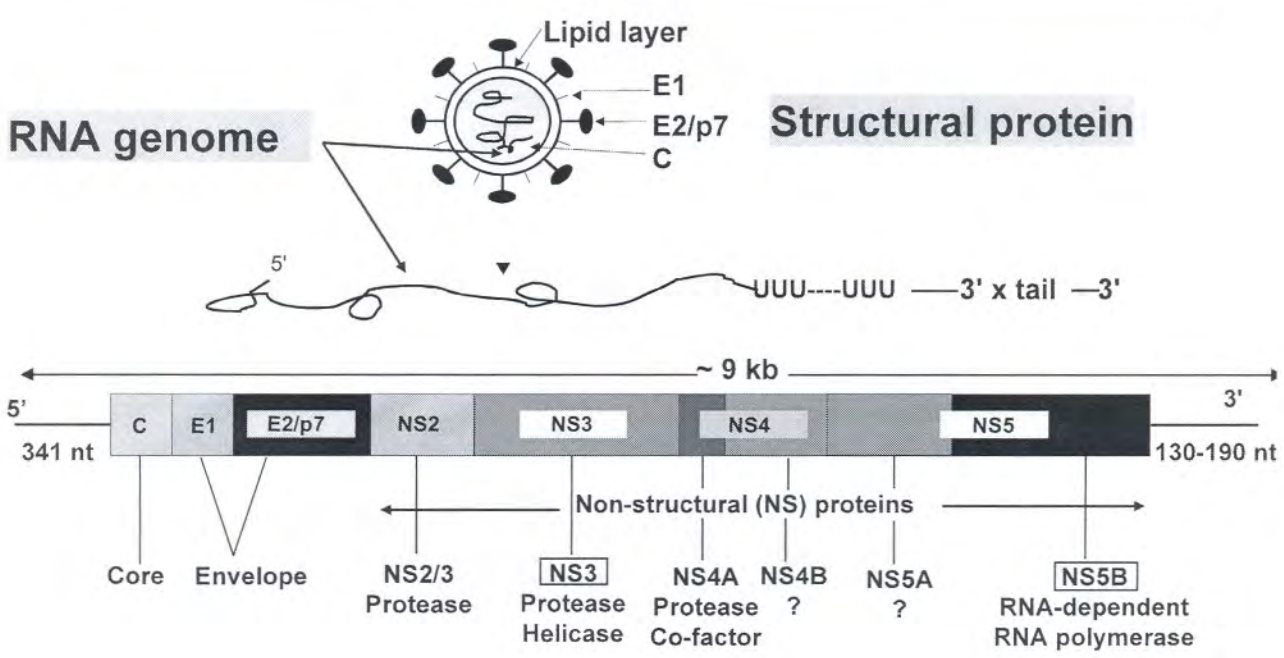

Hepatitis C Virus NS3 Protease

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- Cleaves at NS3/4A; NS4A/4B; NS4B/5A and NS5A/5B. Good medicinal target.

- In *in vitro* assays, it was found that protease is inhibited by a hexapeptide (N-terminal) produced by cleavage of substrate from NS5A/5B [DDIVPC].

- This can be the basis for rational drug design.

- Rapid peptide screening shows:

  DDIVPC IC_{50} = 71μM

  DdIVPC IC_{50} = 4 μM (replaced L-Asp with D-Asp)

M. Llinàs-Brunet *et al. Bioorg. Med. Chem. Lett.* **1998**, *8*, 1713

Initial SAR Work

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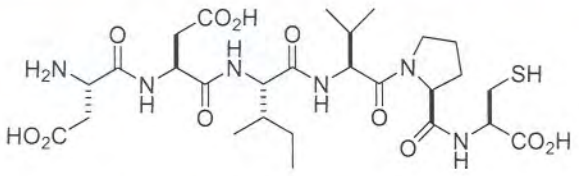
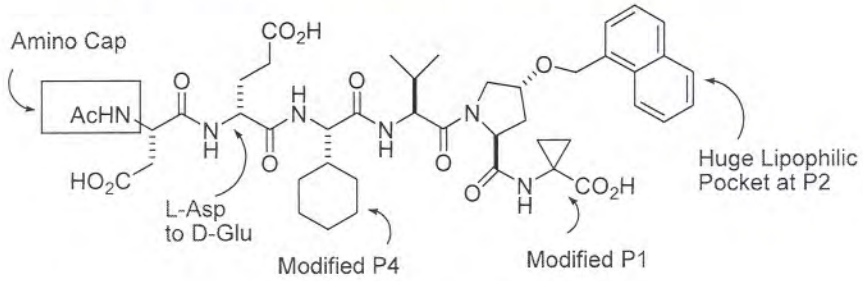


PEPTIDE LEAD / DDIVPC / IC_{50}= 71 μM



MODIFIED PEPTIDE IC_{50} = 0.013 μM

M. Llinàs-Brunet *et al. Bioorg. Med. Chem. Lett.* **2000**, *10*, 2267

From Peptides to Peptidomimetics

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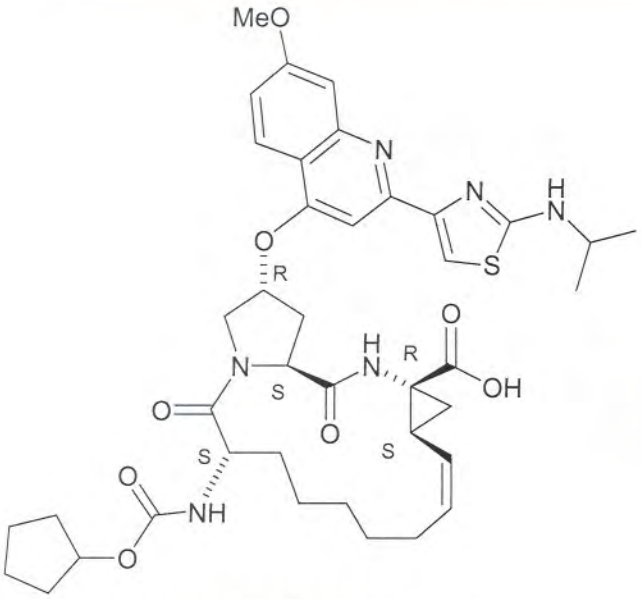

BILN 2061
Clinical Candidate

Reversible inhibitor of HCV genotype Ia and Ib, K_i = 0.3-0.66 nM.
Good PK, metabolic stability.

Structure-Activity Relationships:
Angew. Chem. Int. Ed. Engl. **2003**, *42*, 1356
J. Med. Chem. **2004**, *47*, 123
J. Med. Chem. **2004**, *47*, 1605
J. Med. Chem. **2004**, *47*, 2511
Nature **2003**, *426*, 186

Discovery Synthesis:
Org. Lett. **2004**, *4*, 2901.

BILN 2061: Clinical Proof of Principle

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- Administered in solution (Water, PEG 400, EtOH) at 200 mg bid, for 2 days.
- Viral titer dropped from an average of 10^6 copies/mL to <1,500 (LOD) in most patients.
- Viral titer rebounded in 6-13 days after treatment was discontinued (as expected).

H. Hinrichsen *et al. Gastroenterology, in press.*

BILN 2061: Retrosynthetic Analysis

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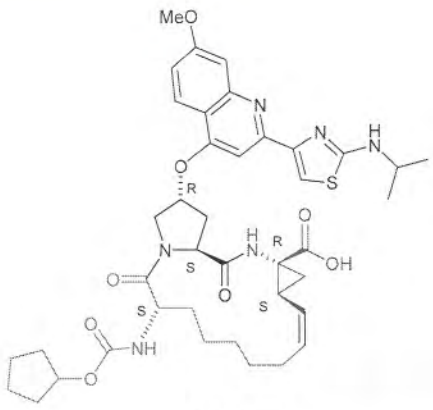
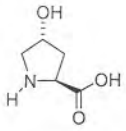


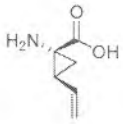
BILN 2061

$C_{40}H_{50}N_6O_8S$
MW 774.95
5 Asymmetric Centers
(Z) -Alkene
15-Membered Ring

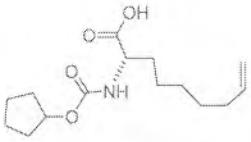
Amenable to convergent assembly



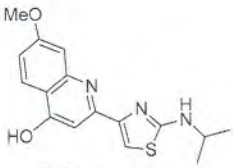
INRF1 (P2)



INRF3 (P1)



INRF15 (P3)



INRF13

Program Goals

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• Develop "**Expedient Route**" in order to supply early batches for toxicology and phase Ia studies (0.5 - 1.0 Kg).

• Develop cost-effective **"Practical Route"** and develop it into a process that can form the basis for commercial manufacturing:

- Highly Reproducible.
- No chromatographies.
- Control of all organic impurities > 0.1 %.
- Control of all residual organic volatiles (ICH guidelines).
- Control or inorganic impurities (Ru?).
- Control of solid-state properties of Active Pharmaceutical Ingredients (API) (polymorph, crystal habit, particle size).

N.G. Anderson "*Practical Process Research and Development*", Academic Press, San Diego, **2000**.

Estimating Capacity Costs: Throughput

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- VTR = Volume/Time Requirement in m^3 x h / tons
  (the lower the better)
- V = Utilizable volume of reactor (m^3)
- T_S = Standard time needed on **bottleneck** reactor or operation (h)
- O_S = Output per batch (tons)
- T_C = Product change time
- F = Operating factor (≤1); covers deviations from 24 h 7/7 work routine, lack of materials, operators, equipment downtime, *etc.*

$$VTR = \frac{V}{O_S}\left(\frac{T_S}{F} + T_C\right)$$

The BILN 2061 Chemistry Team

Boehringer Ingelheim

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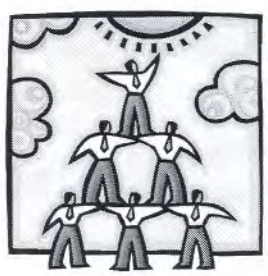

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Synthesis of Racemic P1 Unit

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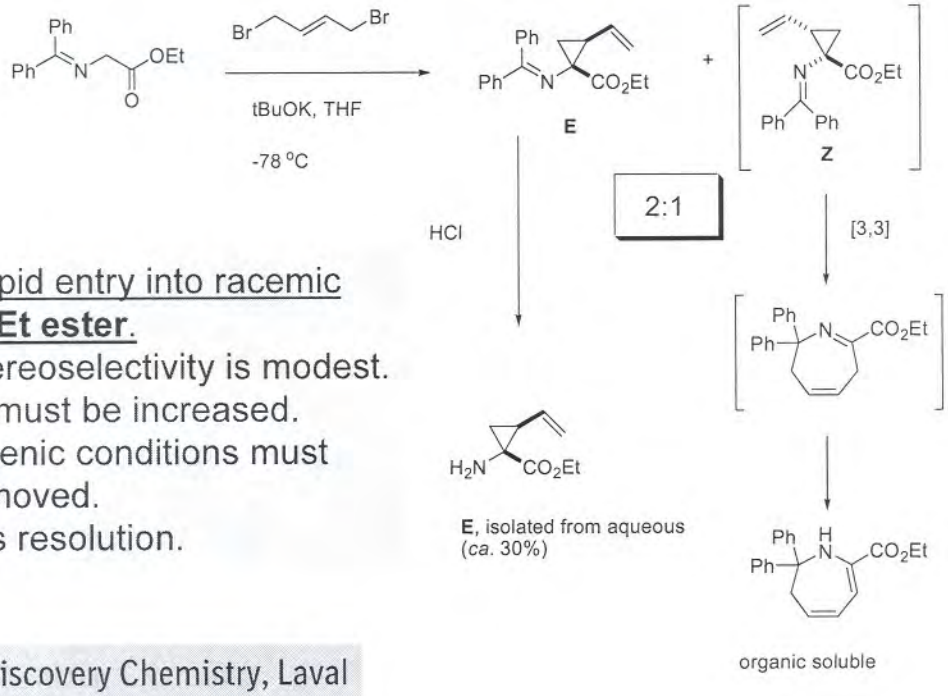

Very rapid entry into racemic **INRF3 Et ester**.

- Diastereoselectivity is modest.
- Yield must be increased.
- Cryogenic conditions must be removed.
- Needs resolution.

Discovery Chemistry, Laval

Route to P1: Optimization

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Imine: Benzaldehyde best (selected).

Counterion effect (tBuO base) on diastereoselectivity: Li > Na > K (d.e.=20:1 with Li, 10:1 with Na, 2:1 with K).

Solvents: Non-polar solvents (PhMe) give best yields.

Esters: *Et* best, *Me* 5-8% lower yield.

Concentration: No difference in yield over practicable range (0.28-0.7 M).

Temperature: No difference in range **20-45 °C** . No improvements at lower temperature, just prolonged reaction times.

P1:Scalable Process

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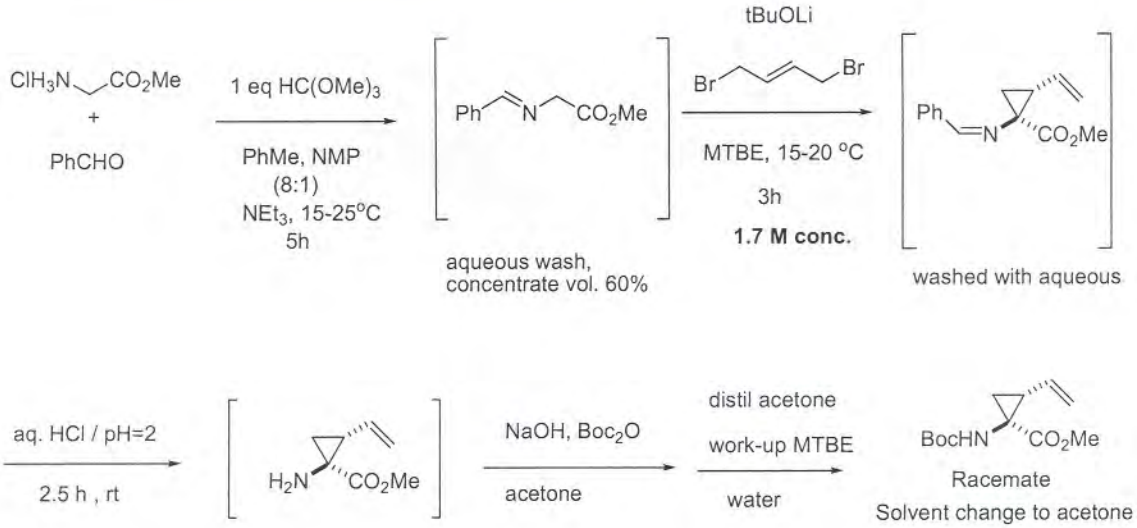

Process Chemistry, Ridgefield and BIKG Biberach

P1: Scalable Process

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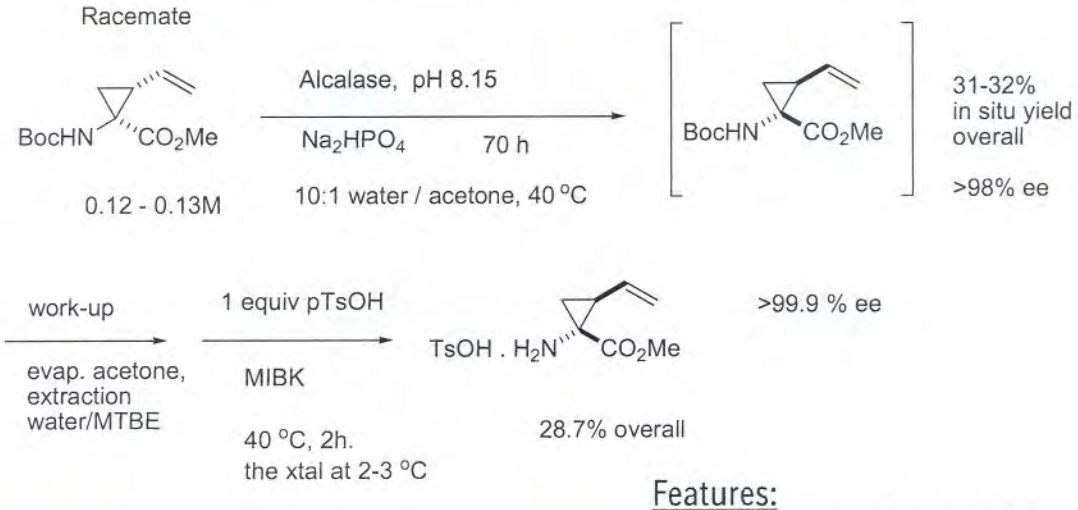


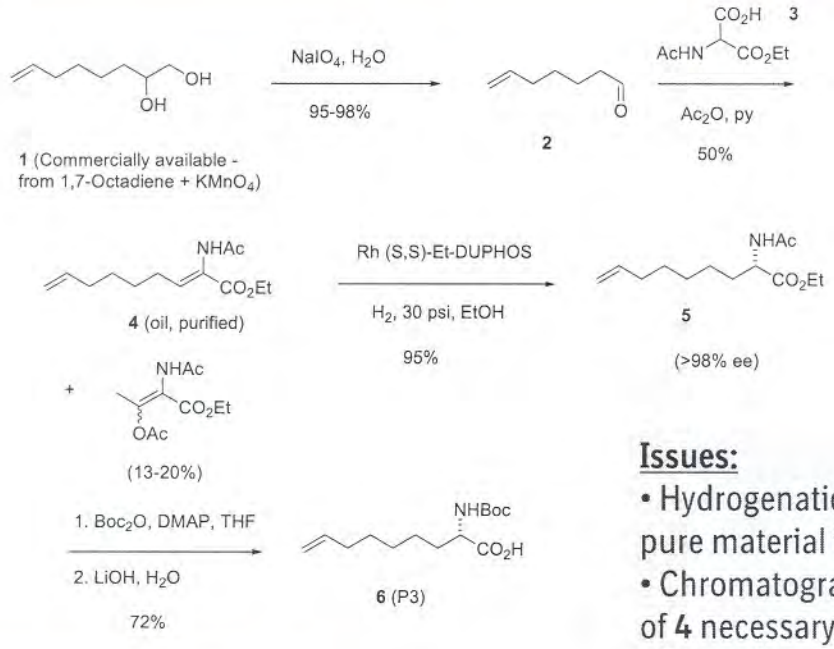
Process Chemistry, Ridgefield and Biberach

Features:

- No isolations till the end.
- Use of NMP in first step to increase solubility and throughput (>10 fold).
- Scalable to >100 Kg
- Tosylate aids isolation.

P3 Unit: Discovery Synthesis

Boehringer Ingelheim



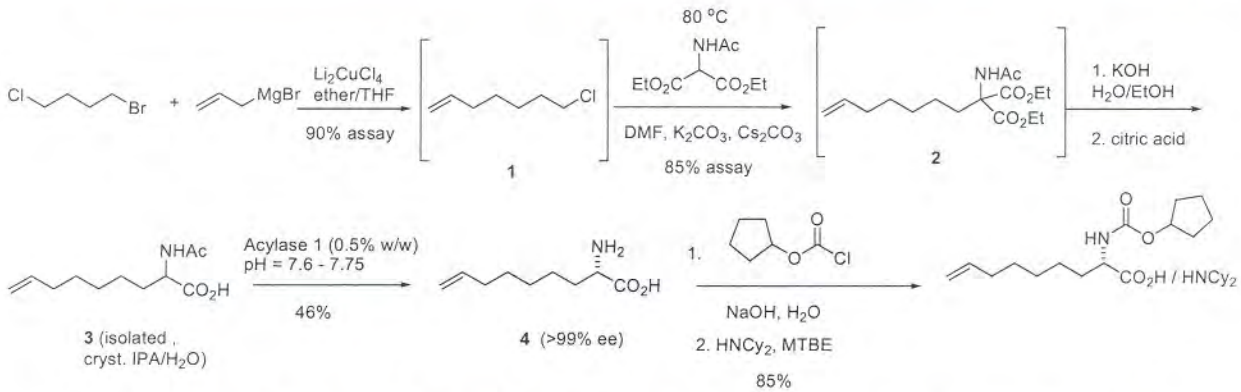
Issues:

- Hydrogenation requires pure material for high ee.
- Chromatography or distillation of **4** necessary.
- Protecting groups used

Discovery Chemistry, Laval

P3 Unit: Scalable Synthesis

Boehringer Ingelheim



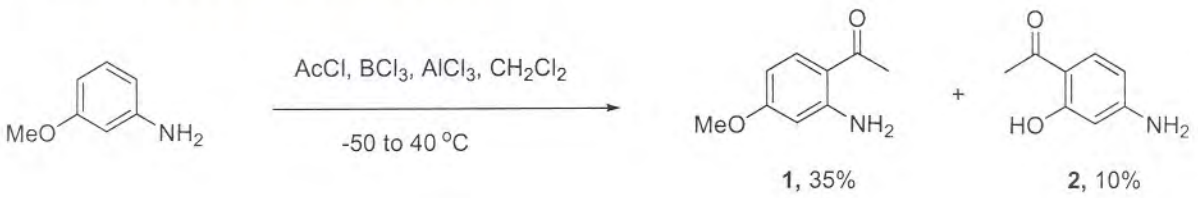
- Preparation of **2** using 1,4-dibromobutane gives lower yield in Grignard coupling.
- Recycle of **(R)-3** possible by racemization with Ac_2O at reflux followed by resolution as above (71% total yield after one recycle).
- DCHA salt used for crystallinity. Process smoothly scalable to >100 Kg.

Process Chemistry, Ridgefield

Synthesis of Quinolone Unit

Boehringer Ingelheim

Step 1: Friedel-Crafts Reaction



1, 35% **2**, 10%

- Literature procedure: *J. Org. Chem.* **1979**, *44*, 578; *J. Am. Chem. Soc.* **1978**, *100*, 4842.
- Reported yield: 40%. Obtained on 300g scale: 35%.
- Difficulty in scale-up due to further reaction (decomposition) of **1** and emulsions during work-up.
- *m*-Anisidine is a very attractive starting material.

Discovery Chemistry, Laval, and Process Chemistry, Ridgefield

An Alternative: Sugasawa Reaction

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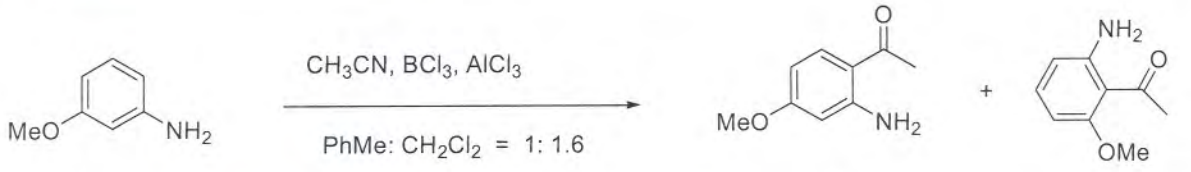


1 **2**

Highlight of solvent effects:

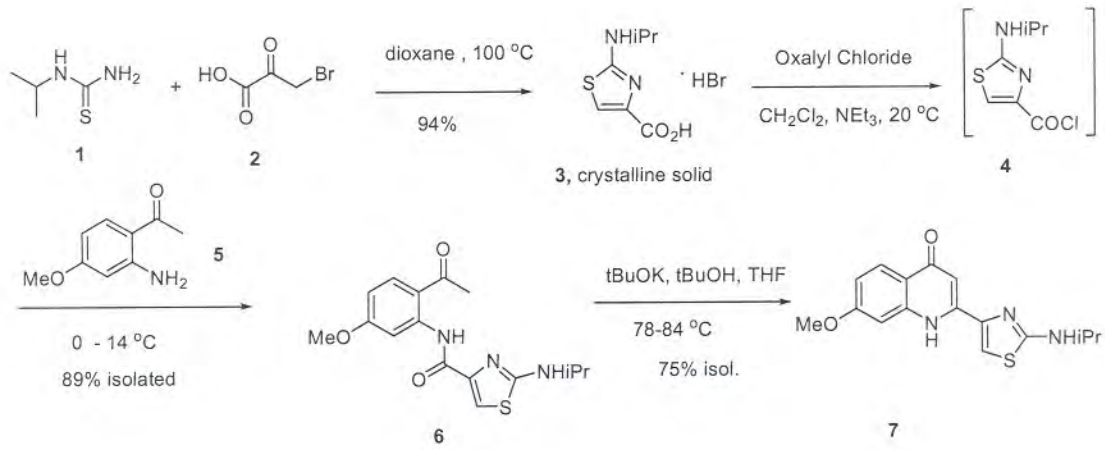
Solvent	Ratio 1/2
CH_2Cl_2	1.4 : 1
PhMe	6 : 1

- Order of addition important: preform anisidine/BCl_3 complex, then CH_3CN, then $AlCl_3$
- Optimum temperature: 40 °C. Optimum pH for work-up: 3.0
- Purified by MTBE slurry at reflux.
- Typical isolated yields: 42-47% on multikilo scale.

Discovery Chemistry, Laval, and Process Chemistry, Ridgefield

Synthesis of Quinolone Unit (cont.)

Boehringer Ingelheim



1 2 3 4 5 6 7

Discovery Chemistry, Laval, and Process Chemistry, Ridgefield

Scale-up Problems

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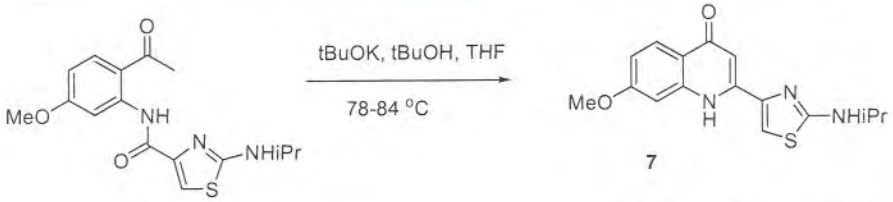
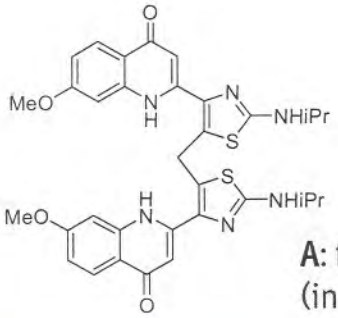


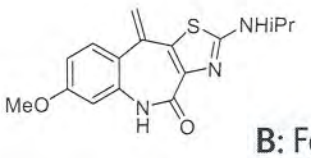
6 7

Early lots had only 64-78% purity (HPLC)

Major impurities Isolated:



A: formed from CH_2Cl_2 (incomplete removal)



B: Formed at lower temperatures.
Ratio (Product/B) is solvent dependent

Process Chemistry, Ridgefield

Solution to Scale-up Problems

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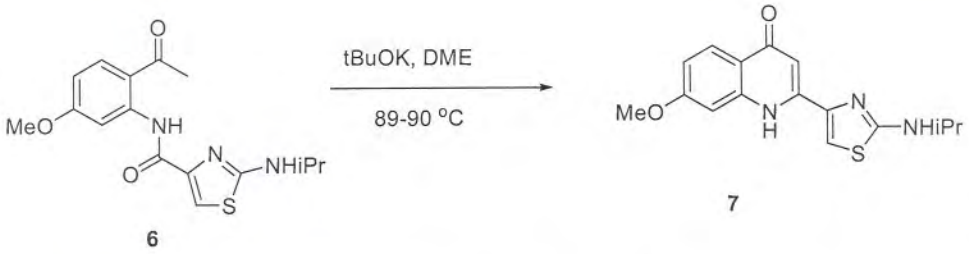

6 7

- DME best solvent to minimize formation of **B** (probably minimizes deprotonation of NH-*i*Pr group).
- Dichloromethane "chased" with DME prior to cyclization.
- Crude product is purified by slurry in DME / water.
- HPLC Assay yield 82%, isolated 77% .
- Reproduced on multikilo scale.

Process Chemistry, Ridgefield

ASSEMBLING THE PUZZLE

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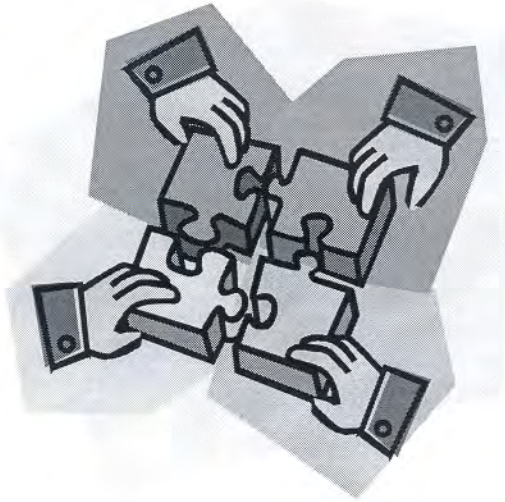
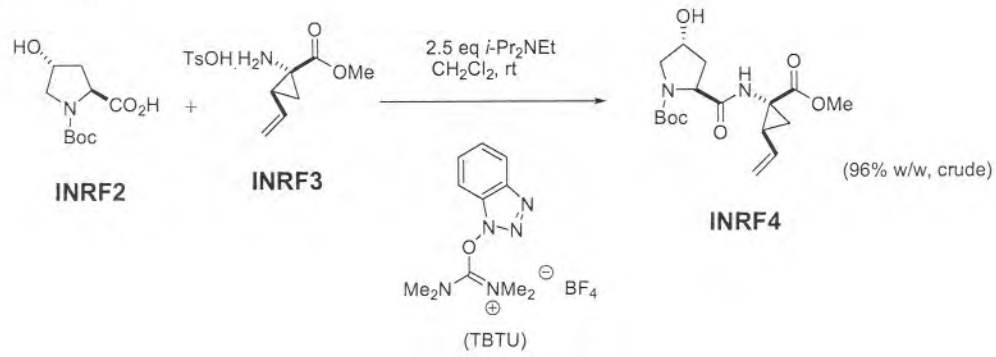


1. Assemble quickly.
2. Find the assembly that minimizes number of "moves" and total cost.

"Expedient Assembly" of BILN 2061

Boehringer Ingelheim

Step 1:



- **INRF 4** used as crude solid, after HCl and $NaHCO_3$ washes (EtOAc).
- Issues to address: high cost and safety problems with TBTU.

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"Expedient Assembly" of BILN 2061

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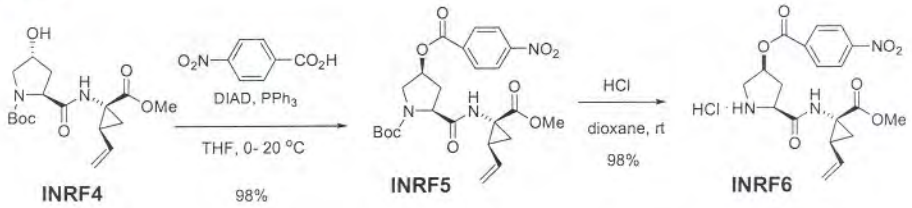
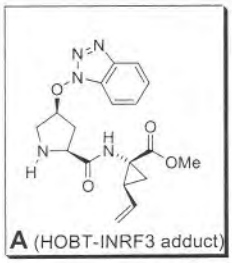
Steps 2-3:





- Problem on scale-up: formation of imp. **A** if HOBT is not completely removed after TBTU coupling.
- Extra $NaHCO_3$ washings were added and overall yield of **INRF6** (after EtAOc/MTBE slurry) was >95%.
- Issues: Mitsunobu step has poor **Reaction Mass Efficiency** (RME = Kg product/ Σ [mass inputs])

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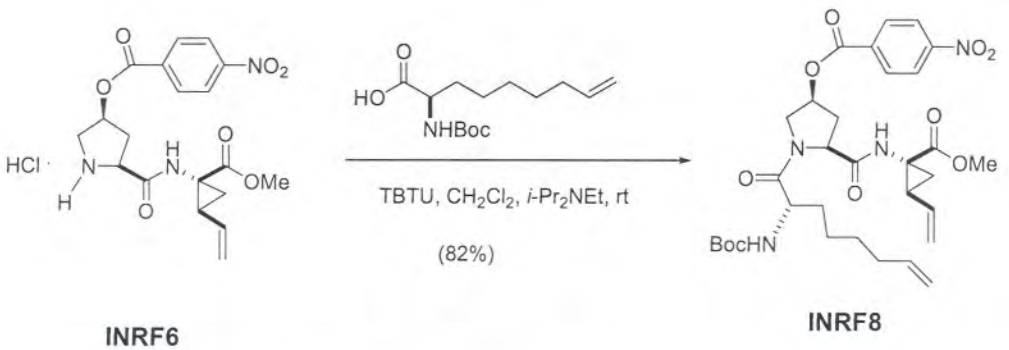
"Expedient Assembly" of BILN 2061

Boehringer Ingelheim

Step 4:



INRF6 **INRF8**

- Issues: use of TBTU.
- HOBT interferes in next step and washes must be extensive [$NaHCO_3$/ PhMe-MTBE (1:2 v/v)]. **INRF8** used as a crude product.

Discovery Chemistry, Laval, and Process Chemistry, Ridgefield

"Expedient Assembly" of BILN 2061

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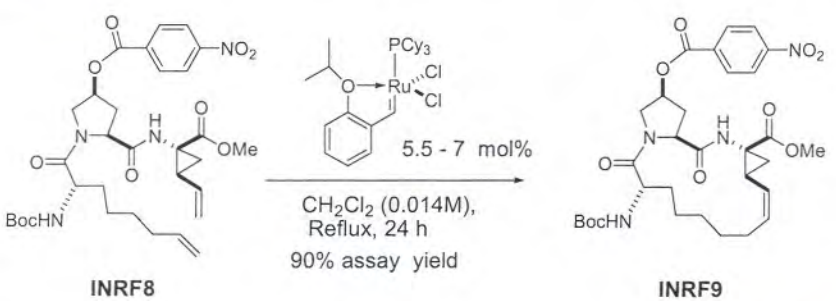
Step 5:



INRF8 **INRF9**

INRF8 forms dimers and oligomers at higher concentrations.

Concentr. INRF8	Yield of INRF9
0.01 M	90%
0.03 M	64%
0.05 M	60%
0.10 M	45%

Discovery Chemistry, Laval, and Process Chemistry, Ridgefield

"Expedient Assembly" of BILN 2061: Metathesis Work-up

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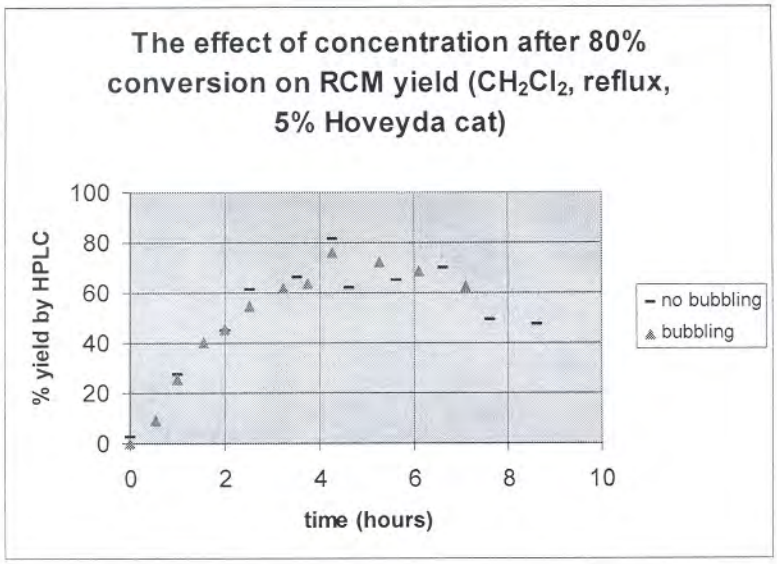
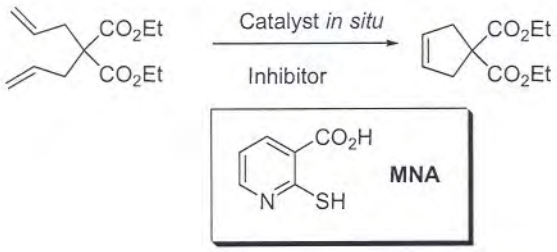


Metathesis product in some runs decomposes upon concentration! Sweeping off ethene has no effect.

"Expedient Assembly" of BILN 2061: Metathesis Work-up

Boehringer Ingelheim



- Catalyst is still partially active after reaction completion (test with diallyl diethyl malonate).
- Screen set up searching for catalyst inhibitor.
- MNA effective and easily removed into $NaHCO_3$.
- 5 equiv MNA at 30 °C for 6h destroys catalyst.
- 2-3 Bicarbonate washes and charcoal/celite filtration afford 85% yield (97% purity) INRF9.

"Expedient Assembly" of BILN 2061

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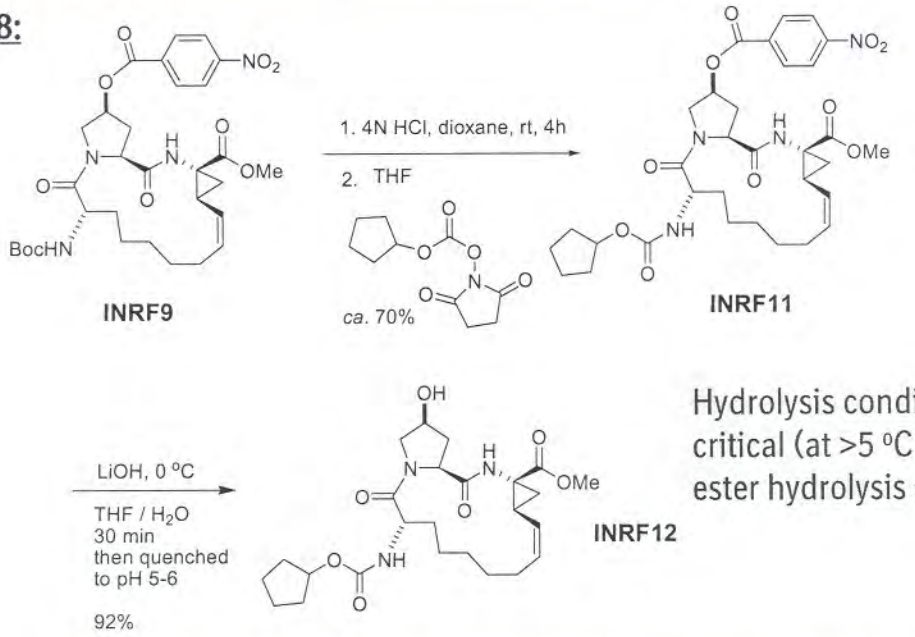
Step 6-8:



Hydrolysis conditions critical (at >5 °C Me ester hydrolysis ensues)

Discovery Chemistry, Laval, and Process Chemistry, Ridgefield

"Expedient Assembly" of BILN 2061

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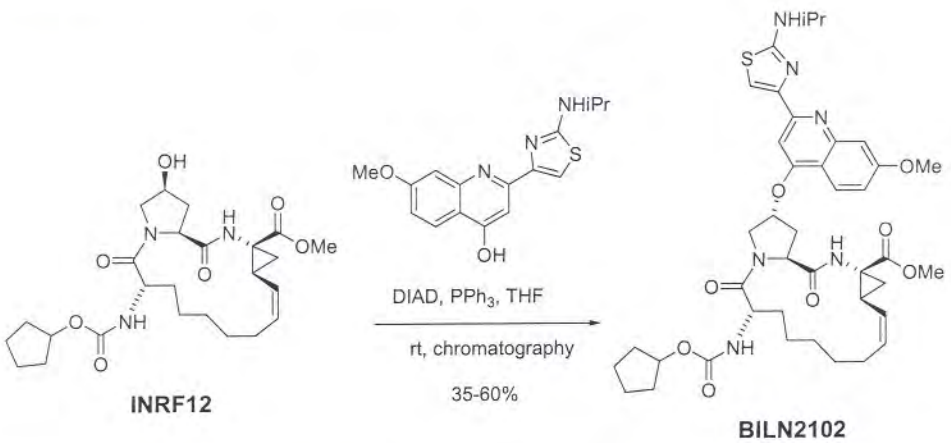
Step 9-10



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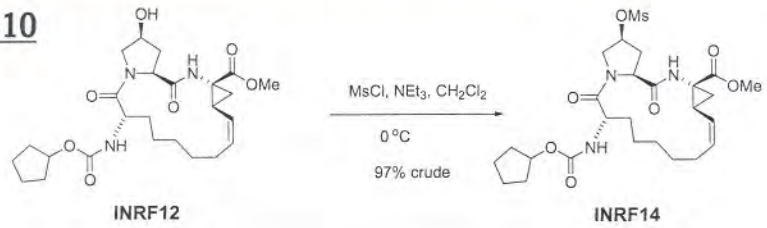
Second Mitsunobu has also low RME, generating side-products one step before API. Yield is erratic. Chromatography needed.

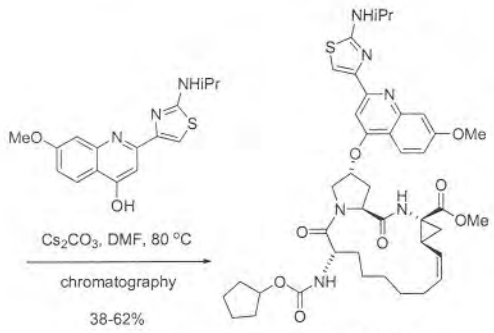
"Expedient Assembly" of BILN 2061: Improved Etherification

Boehringer Ingelheim

Step 9-10



INRF12 → INRF14



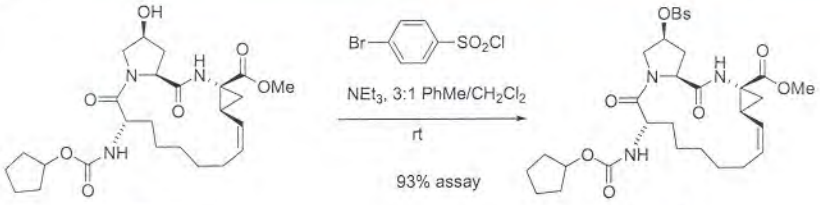
BILN2102

Procedure scaled to 650g; Yield is erratic and again chromatography is necessary. Mesylate is unstable, elimination products obtained.

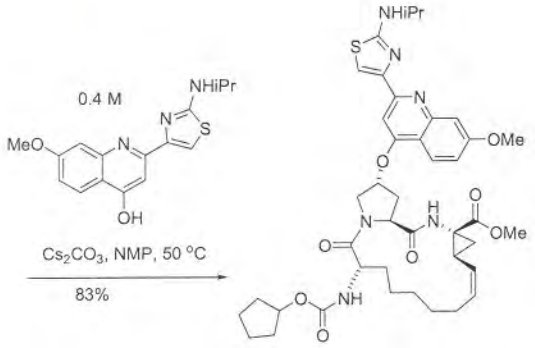
Discovery Chemistry, Laval, and Process Chemistry, Ridgefield

End-game solution

Boehringer Ingelheim



INRF12 → INRF14



BILN2102

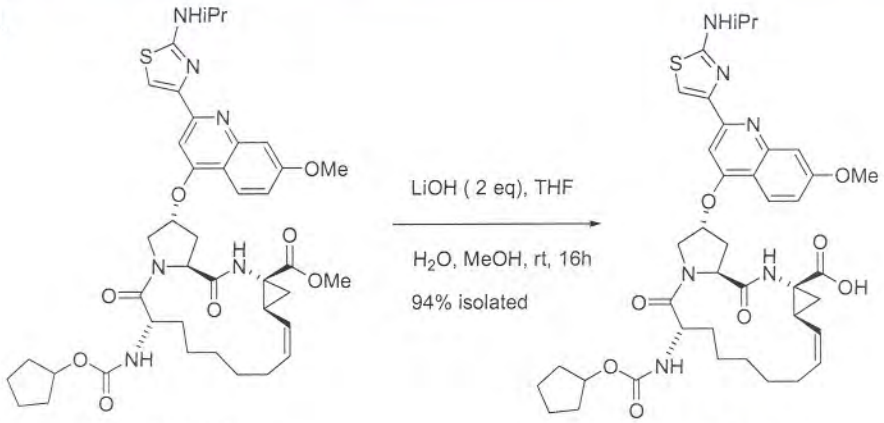
- Several sulfonates tested for $t_{1/2}$ in DMF at 80 °C (with Cs_2CO_3).
- Brosylate $t_{1/2}$= 21h (longest).
- Temperature lowered.
- Concentration doubled (at 0.2 M, 76% yield).
- No chromatography.

Process Chemistry, Ridgefield

"Expedient Assembly" of BILN 2061

Boehringer Ingelheim

Step 11



BILN2102

BILN2061
98.6 % pure

BILN 2061 can be used as such or recrystallized (EtOH/H_2O) for formation of desired polymorph.

Discovery Chemistry, Laval, and Process Chemistry, Ridgefield

"Expedient Assembly": Summary

Boehringer Ingelheim

Total: 11 Steps (Overall: 26)

Only 4 building steps (affixations):
2 amide couplings
1 ether formation
1 olefin RCM

Extra steps (refunctionalizations):
4 deprotections
2 O-activations
1 amine capping

Costly Process! Synthetic Efficiency needs improvement!

Too many cooks.....

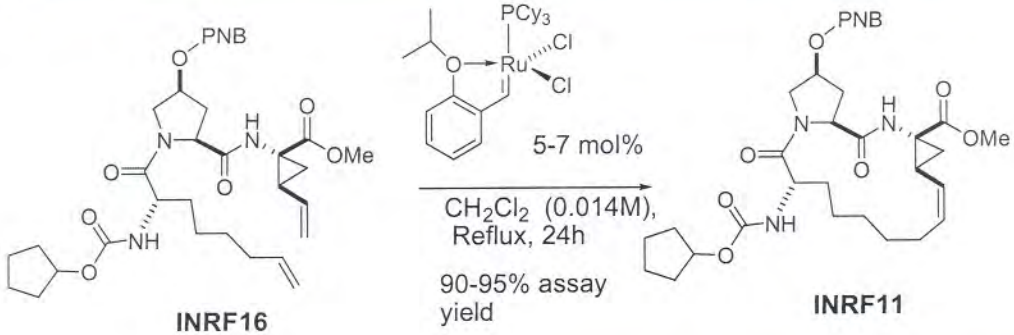
Boehringer Ingelheim

Verderben den Brei...

Guastan la cucina...

Issues with Current RCM Conditions

Boehringer Ingelheim

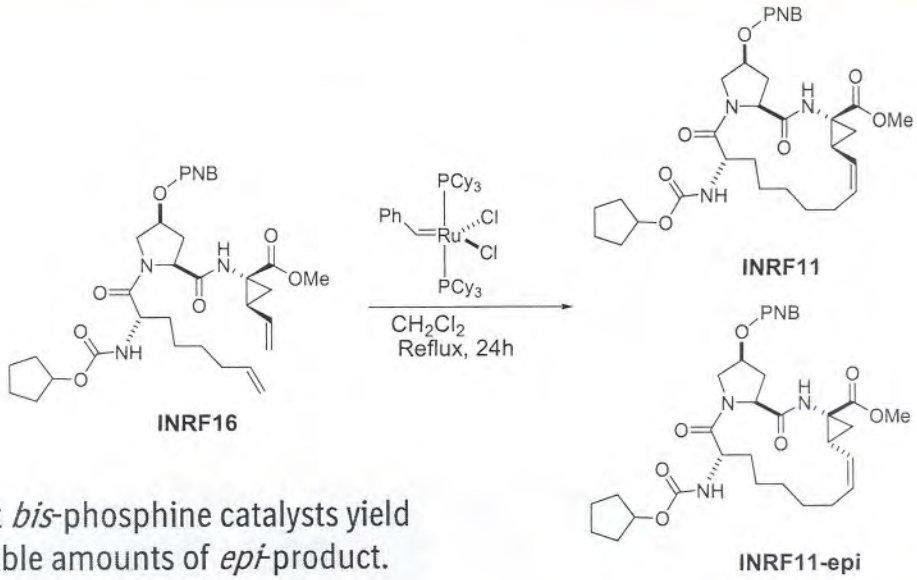


Issues:
-High Catalyst Load
-Dilute Reaction
-Long Reaction Time
-Laborious work-up.
-Catalyst load depends on purity of **INRF16**.

Purity INRF16	Catal. Load for >98% conv.
Crude	5-7%
After charcoal/silica	2-3%
Silica chrom.	0.5-1.0%

Background to Current RCM Conditions

Boehringer Ingelheim

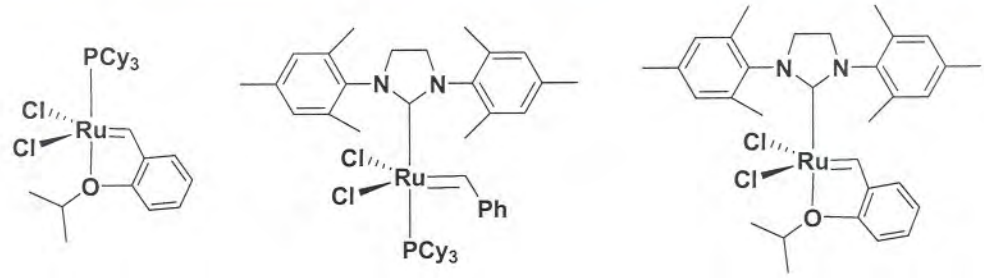


Most *bis*-phosphine catalysts yield variable amounts of *epi*-product.

Discovery Chemistry, Laval

Currently Available RCM Catalysts

Boehringer Ingelheim



1st Hoveyda (1H) **2nd Grubbs (2G)** **2nd Hoveyda (2H)**

Imidazolium-substituted catalysts are much more stable than 1st generation catalysts.

They also react more readily due to more favorable association with olefins.

R.H. Grubbs, "*Handbook of Metathesis*"; Wiley-VCH, Weinheim, **2003**.

RCM of INRF16 With Different Catalysts

Boehringer Ingelheim

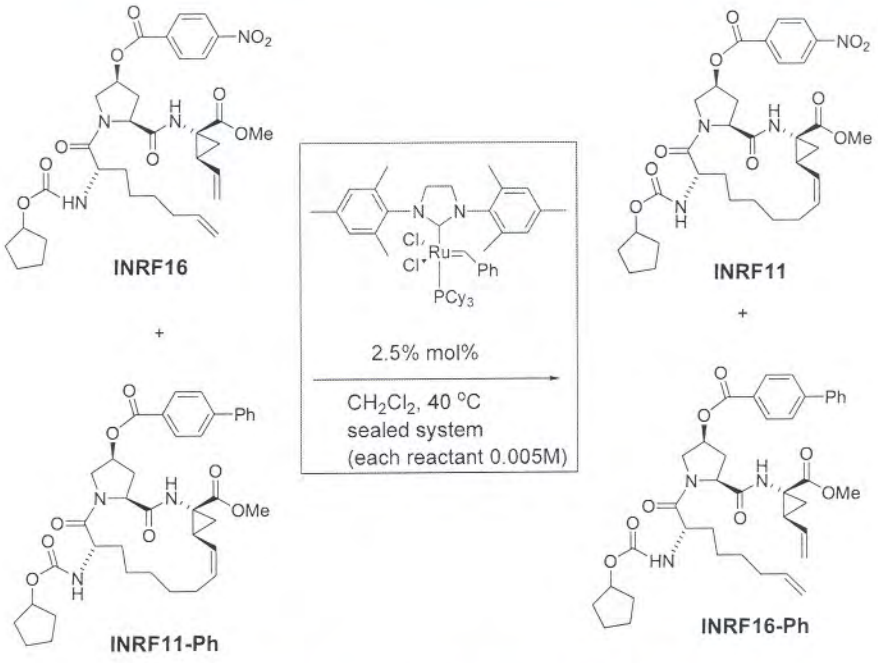
Entry	Catalyst (mol %)	Solvent	Temp. (°C)	Reaction Time	Yield INRF11 (assay)	Area % Dimers (LC-MS)
1	5% 1H	CH_2Cl_2	40	24h	90%	N.D.
2	3% 1H*	PhMe	60	20h	96%	<0.5%
3	1% 2H	PhMe	55	1h	85%	9-11%
4	1% 2G	PhMe	60	1h	87%	8%

* INRF16 purified by charcoal/silica filtration

Process Chemistry, Ridgefield

Reversibility Test

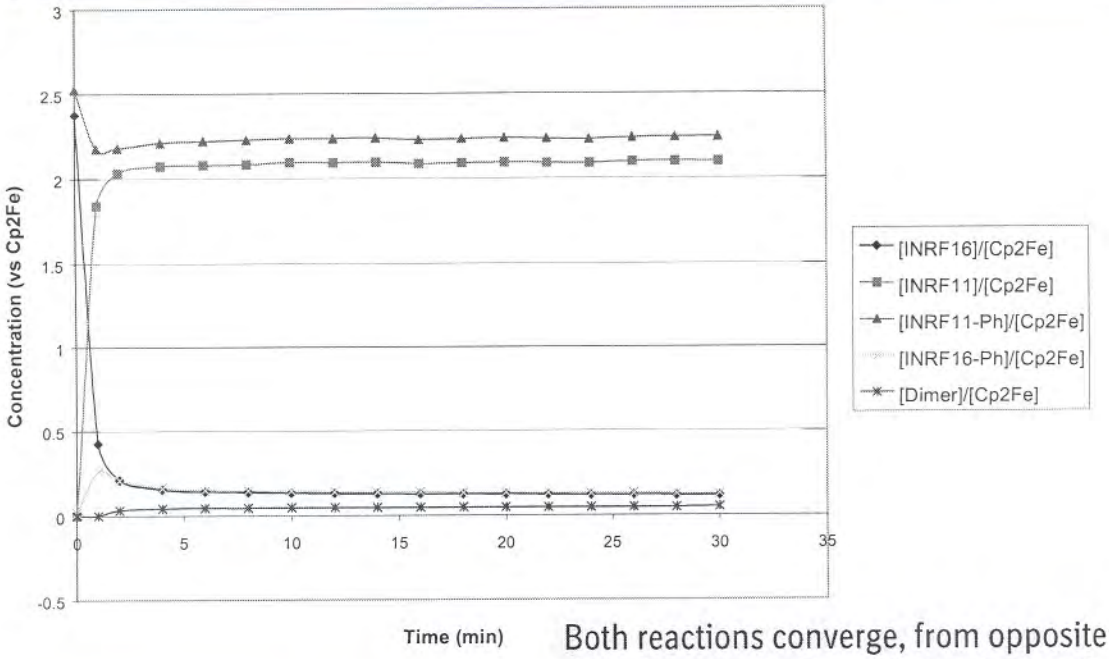
Boehringer Ingelheim



Process Chemistry, Ridgefield

Reversibility Test: Results

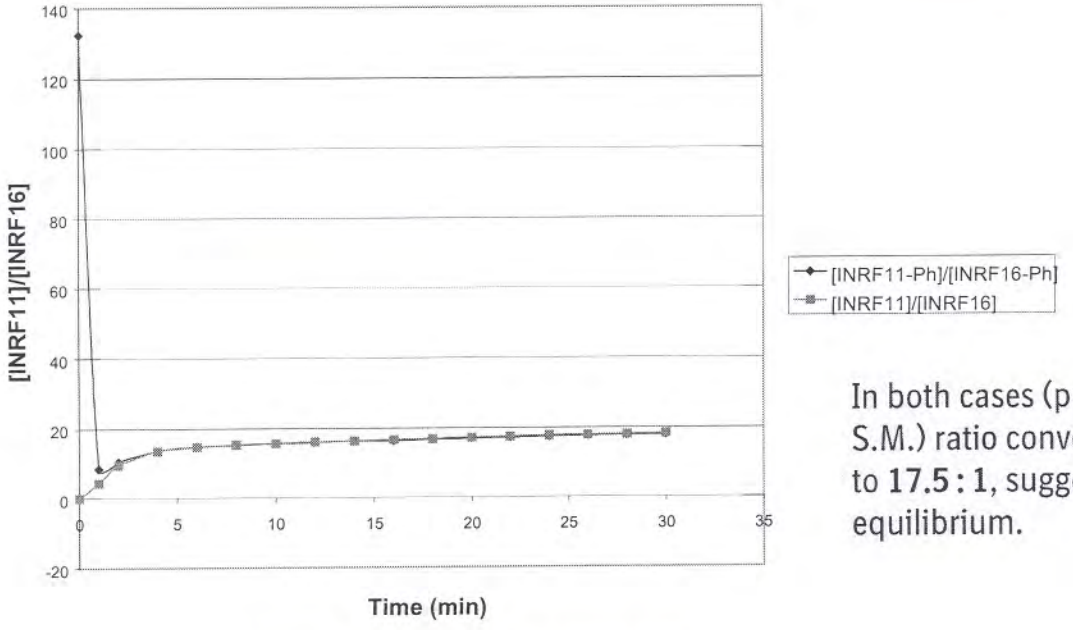
Boehringer Ingelheim



Both reactions converge, from opposite directions, to: 88% prod., 5% S.M., 7% dimer(s).

Reversibility Test: Results

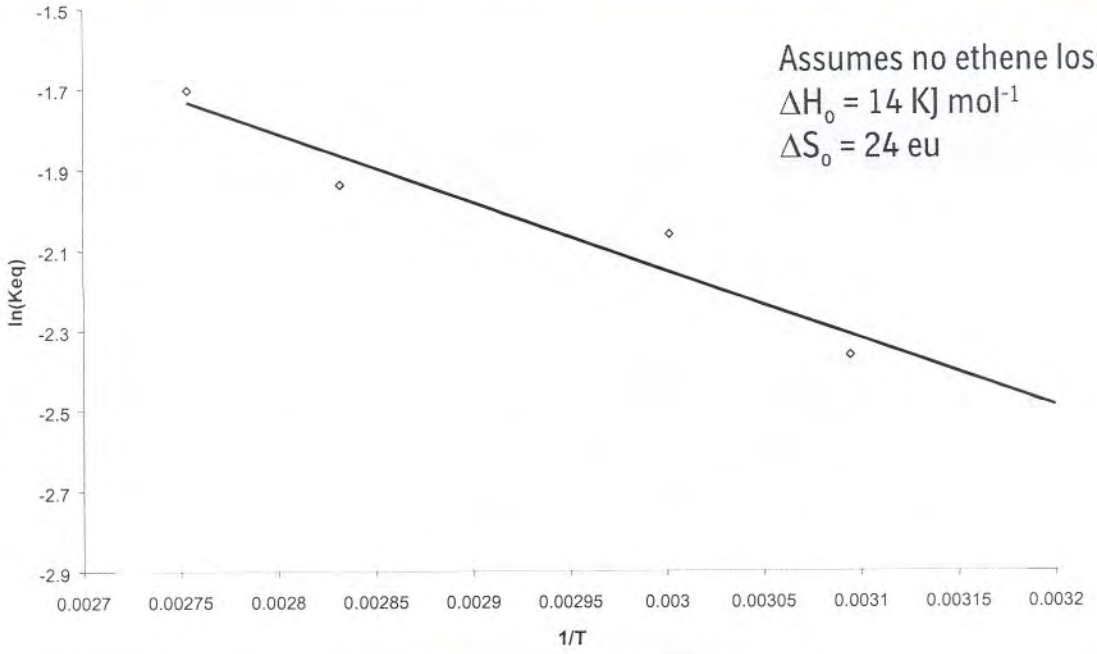
Boehringer Ingelheim



In both cases (product: S.M.) ratio converge to **17.5 : 1**, suggesting equilibrium.

Van't Hoff Plot: Equilibration of INRF16 and INRF11

Boehringer Ingelheim



Process Chemistry, Ridgefield

Tentative Conclusions

Boehringer Ingelheim

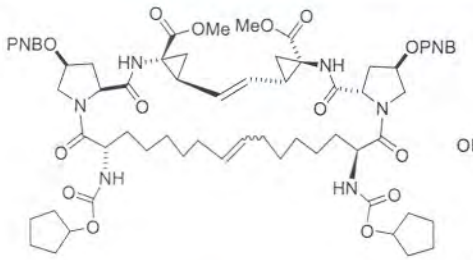
- With 1H catalyst, $t_{1/2}$ = *ca.* 720 min. Ethene evaporation is faster than reaction, driving equilibrium to >95% INRF11. Catalyst not active enough to form dimer(s) under the conditions used.

- With 2G catalyst, $t_{1/2}$ = *ca.* 0.5 min. Ethene evaporation slower. Fast equilibrium appears to ensue, accompanied by *ca.* 7% dimers.

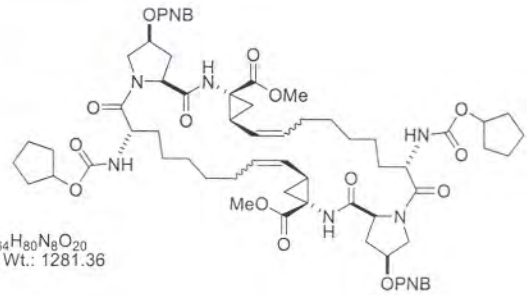
- Higher TON and TOF of new-generation catalysts must be balanced against lower yield and purification problems.

Isolation of INRF11 Cyclic Dimers

Boehringer Ingelheim



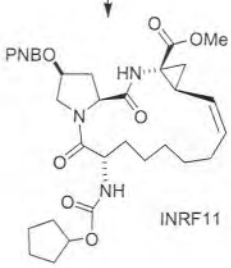
OR



$C_{64}H_{80}N_8O_{20}$
Mol. Wt.: 1281.36

Major dimer (purified)

2G Cat.
Ethylene
Tol. 55°C



INRF11

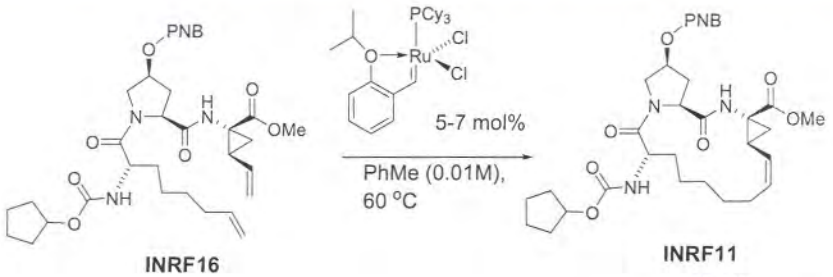
>6 Cyclic Dimers Detected by HPLC (head-to-head and head-to -tail).

Formation of **INRF11** in ca. 70% conversion confirms reversibility.

Process Chemistry, Ridgefield

Unanticipated Problem: Epimerization in a Front Run!

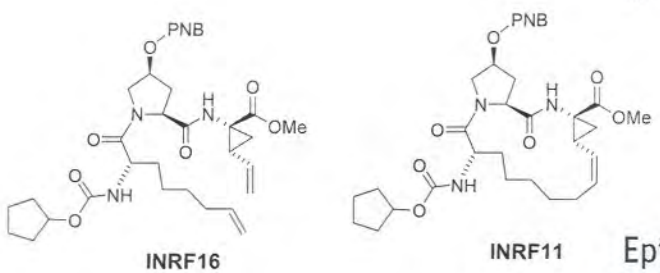
Boehringer Ingelheim



INRF16

5-7 mol%
PhMe (0.01M),
60 °C

INRF11
30-40%



INRF16 **INRF11**

(50% total epimerization)

Epimerization never before observed with 1H catalyst. Investigation necessary.

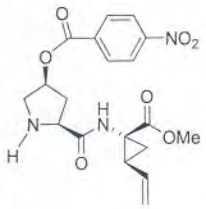
Process Chemistry, Ridgefield

Epimerization Problem: Control Experiments (PhMe at 60 °C)

Boehringer Ingelheim

Catalyst	Promoter	Time (h)	INRF16 Left (*)	INRF11 prod.	Epi-INRF16	Epi-INRF11
4%1H	none	24h	-	100%	-	-
4%1H	5%INRF6	15h	2%	78%	**2%**	**17%**
6%1H	12% pyrrolidine	48h	65%	3%	**26%**	**6%**
4%1H	12% N-Me pyrrolidine	17h	2%	82%	**2%**	**14%**
2%1H	5% PPh_3	1.5 h	8%	74%	**5%**	**13%**
5%1H	5% PCy_3	2h	5.7%	54%	**13.3%**	**27%**
2%2H	5% INRF6	6h	-	100%	-	-

(*) Quantities are relative amounts by HPLC



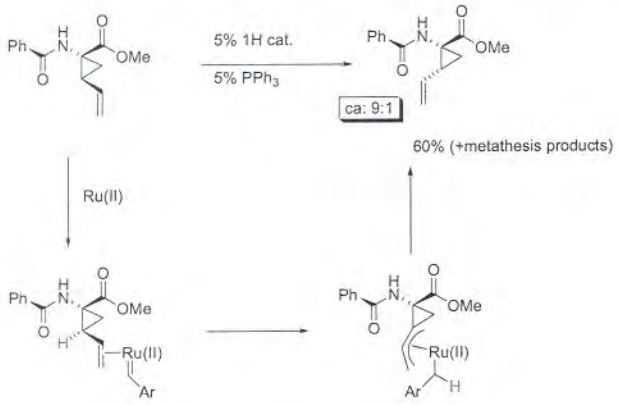
INRF6 (2-4%) found in crude **INRF16** used in metathesis.

Process Chemistry, Ridgefield

Epimerization Problem: Preliminary Conclusions

Boehringer Ingelheim

Possible Mechanism (must be investigated)

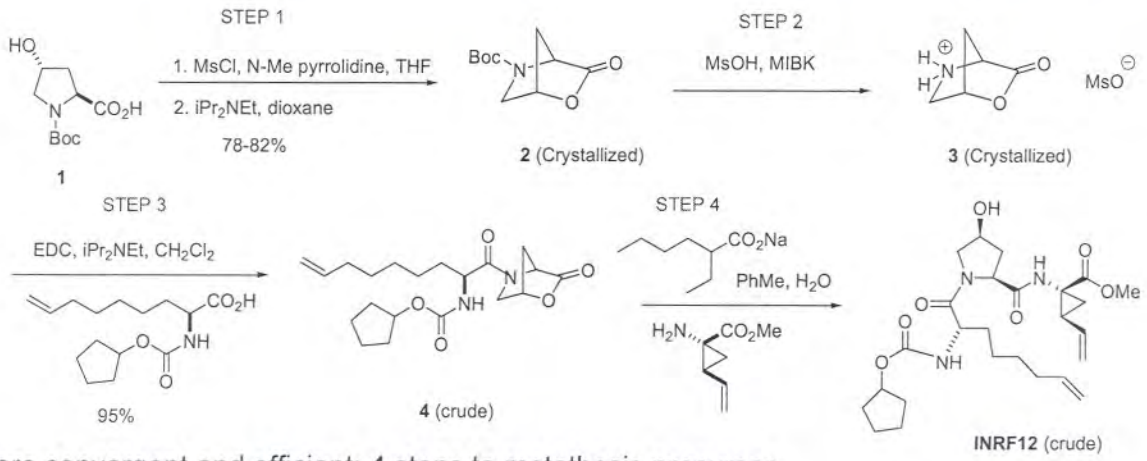


- **INRF16** must be assayed for **INRF6** content (acid wash), and phosphines.
- This may explain why 1G catalyst leads to epimerization (high lability of coordinated phosphine).
- Ru-H addition/elimination also possible

Discussion of olefin isomerization mechanisms:
Schmidt, B. *Eur. J. Org. Chem.* **2004**, 1865-80.
Also: S. Nolan *et al. J. Organomet. Chem.* **2002**, *643-4*, 247.

Practical Synthesis: New Assembly

Boehringer Ingelheim

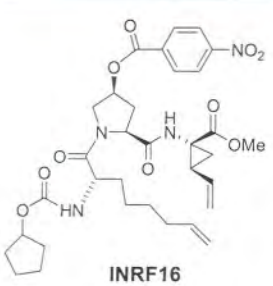


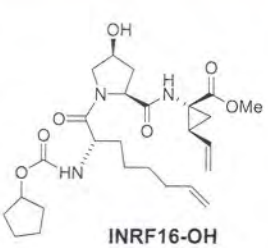
- More convergent and efficient: 4 steps to metathesis precursor.
- Metathesis, OH activation, etherification, ester hydrolysis remaining (4 steps).
- No Mitsunobu reactions. Two protecting groups eliminated.
- Caveat: metathesis on **INRF 12** is unknown.
- **MURPHY'S LAW #5: If nothing can possibly go wrong, something will anyway!**

Process Chemistry, BIKG Ingelheim

RCM of INRF12

Boehringer Ingelheim


INRF16

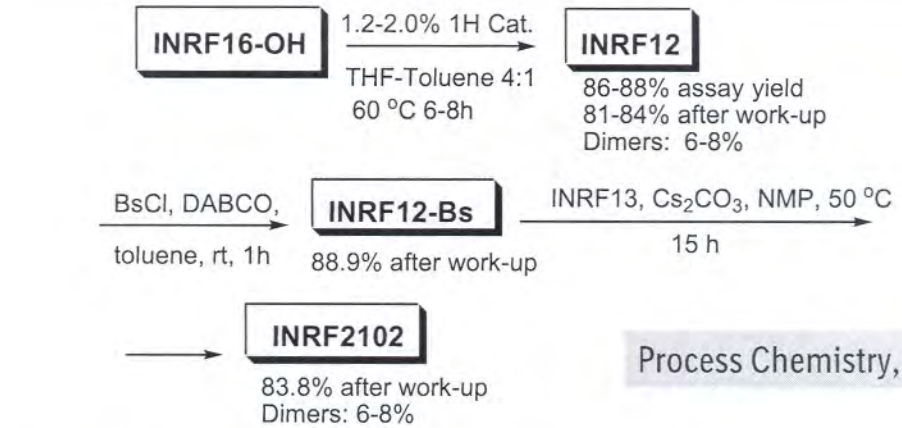

INRF16-OH

RCM of **INRF16OH** produces more dimers compared to **INRF16** (Process Chemistry, Ridgefield).

Starting Material	Catalyst	Solvent	Temp °C	Time (h)	Yield (assay)	Total dimers
INRF16	1H,5%	CH_2Cl_2	40	20	89%	<1%
INRF16OH	1H,2-5%	CH_2Cl_2	40	20	75-82%	13%
INRF16OH	2G, 2%	CH_2Cl_2	40	20	78%	13%
INRF16OH	2G, 2%	PhMe	60	0.1-18	72%	15-20%
INRF16OH	2H, 1%	PhMe	55	1	65%	9-11%
INRF16OH	2H,1.2%	1:4 PhMe/THF	60	8	88%	6%

RCM of INRF16-OH on 45g Scale

Boehringer Ingelheim



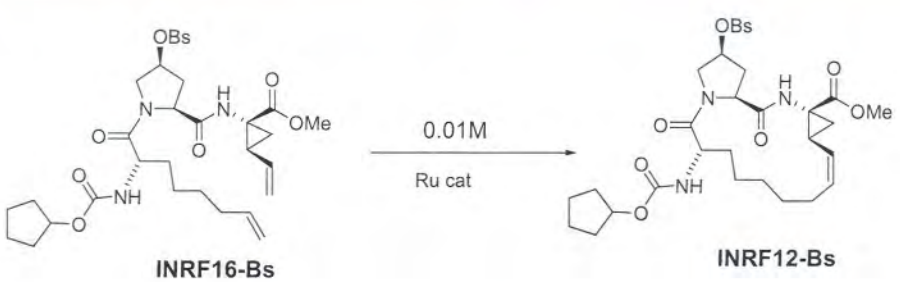
Process Chemistry, Ridgefield

Removal of Dimers by Recrystallization of BILN2102.

	Dimers	Vol EtOAc	EtOAc/ MCH	Cryst. temp	Final temp	ML loss	Dimer remaining
1	6-8%	10	1 : 1.5	80	rt	14%	0.4%
2	0.4%	7	1 : 1.5	80	rt	5%	0.09%

Metathesis on INRF16-Bs

Boehringer Ingelheim



INRF16-Bs

INRF12-Bs

Catalyst	Solvent	Temperature	RCM Yield	Total Dimers
1H, 4%	CH_2Cl_2	40 °C	83%	4-5%
1H, 4%	PhMe	80°C	85%	4-5%
1H, 2-3.5%	PhMe	60 °C	87%	5-6%
2H, 2%	PhMe	60 °C	72%	14-15%
2G, 2%	PhMe	60 °C	69%	16-17%

Process Chemistry, Ridgefield

Scaling up RCM of INRF16-Bs in PhMe

Boehringer Ingelheim

- **INRF16-Bs** was purified by treatment with Charcoal and Silica in toluene then submitted to RCM in toluene with **1H catalyst** (60 °C)

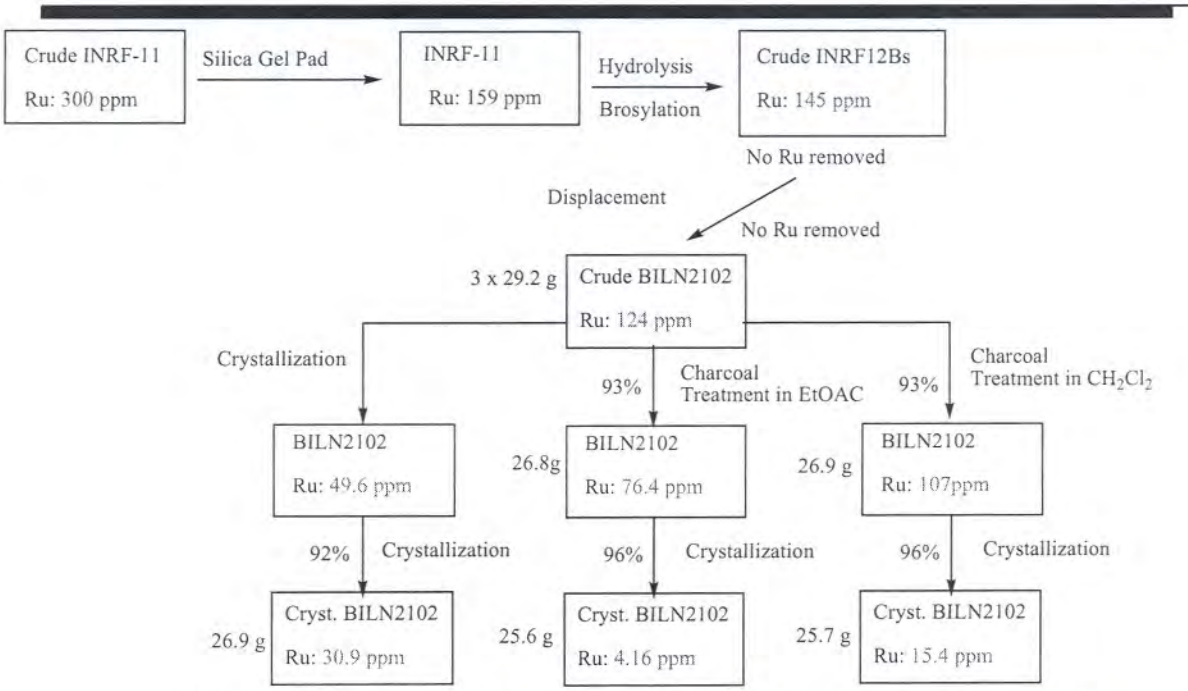
Batch	Conditions	Conversion	Assay Yield	Isolated Yield	% Dimers
305g	2 mol%, 14h +1 mol%, +10h	90% >98%	86% 95%	85%	5.1%
361g	3 mol%, 14h +1.2 mol%, +10h	96% >98%	91% 92%	86%	5.9%
445g	2 mol%, 14h +1 mol%, +10h	93% >98%	88% 94%	87%	4.9%

Crystallization leads to satisfactory purity in >90% recovery.

Process Chemistry, Ridgefield

Ru Removal with 2-Mercaptonicotinic acid

Boehringer Ingelheim



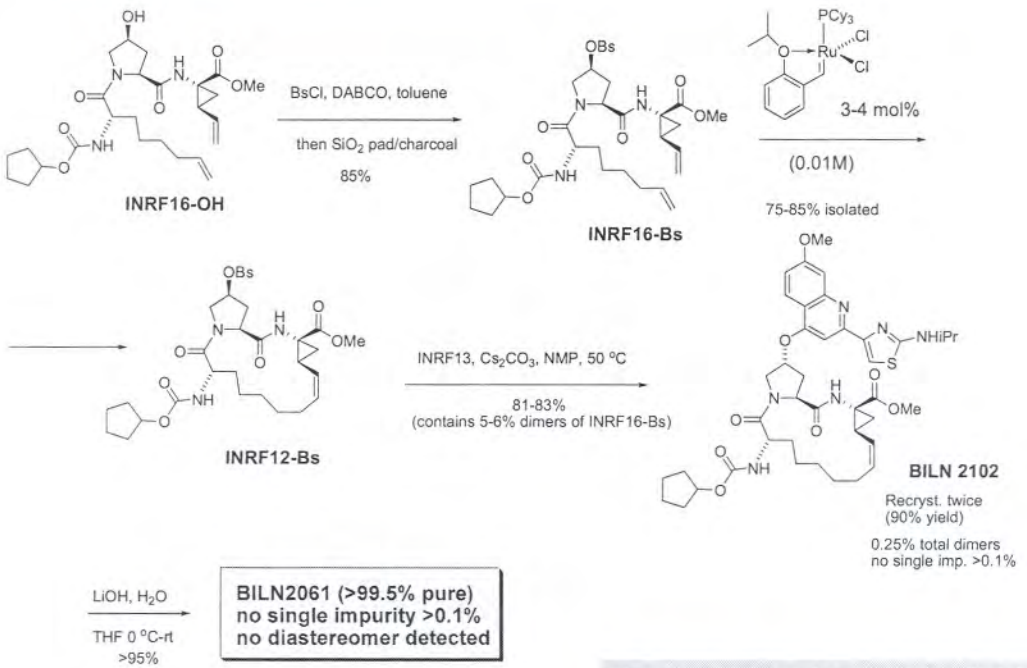
Charcoal treatment is necessary

Charcoal treatment and crystallization are needed

Charcoal treatment in EtOAc is more efficient

Completion of the Assembly

Boehringer Ingelheim



Process Chemistry, Ridgefield

Progress Report

Boehringer Ingelheim

Two scalable routes to BILN 2061 were identified.

Areas for improvements (ongoing):

-More efficient synthesis of building blocks.

-Reduced RCM reaction time and higher TON catalyst.

-More efficient end-game strategy.

-Stay tuned.

Boehringer Ingelheim R&D, Ridgefield, Connecticut

Boehringer Ingelheim

Thank you....

Boehringer Ingelheim

GRAZIE DELL'ATTENZIONE!