Rapid Synthesis of Novel 2-Deoxy-*C*-Glycoside Amino Acids

MASTER DEGREE IN CHEMISTRY

Academic Year 2019-2020

Supervising Profs.:
Prof. Dr. P. R. Schreiner
Prof. Dr. T. Carofiglio

Candidate:
Antonio Pulcinella

Supervisor:
Dr. R. C. Wende

C-Glycosides and Sugar Amino Acids (SAAs)

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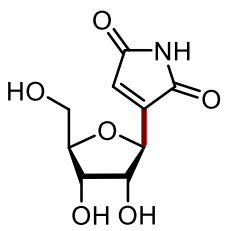
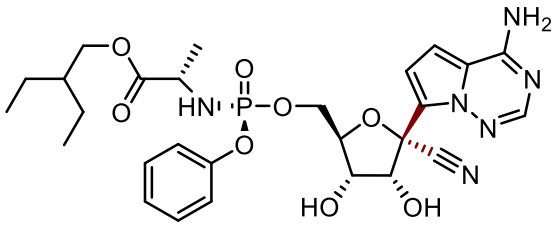
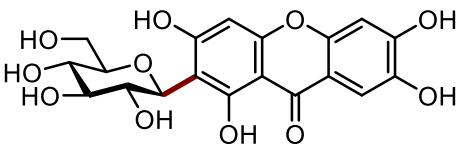


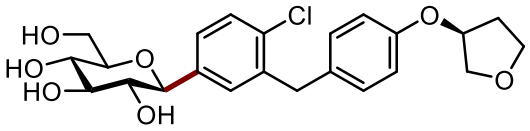
Showdomycin



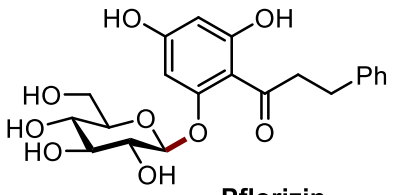
Remdesivir



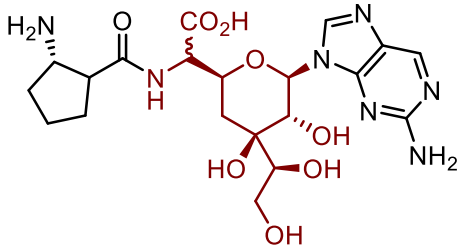
Mangiferin



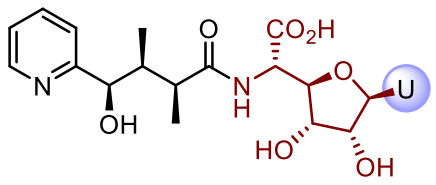
Empagliflorizin



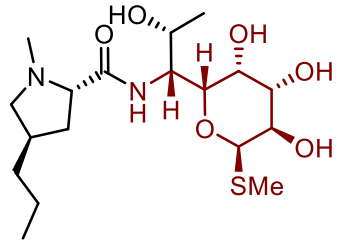
Pflorizin



Amipurimycin



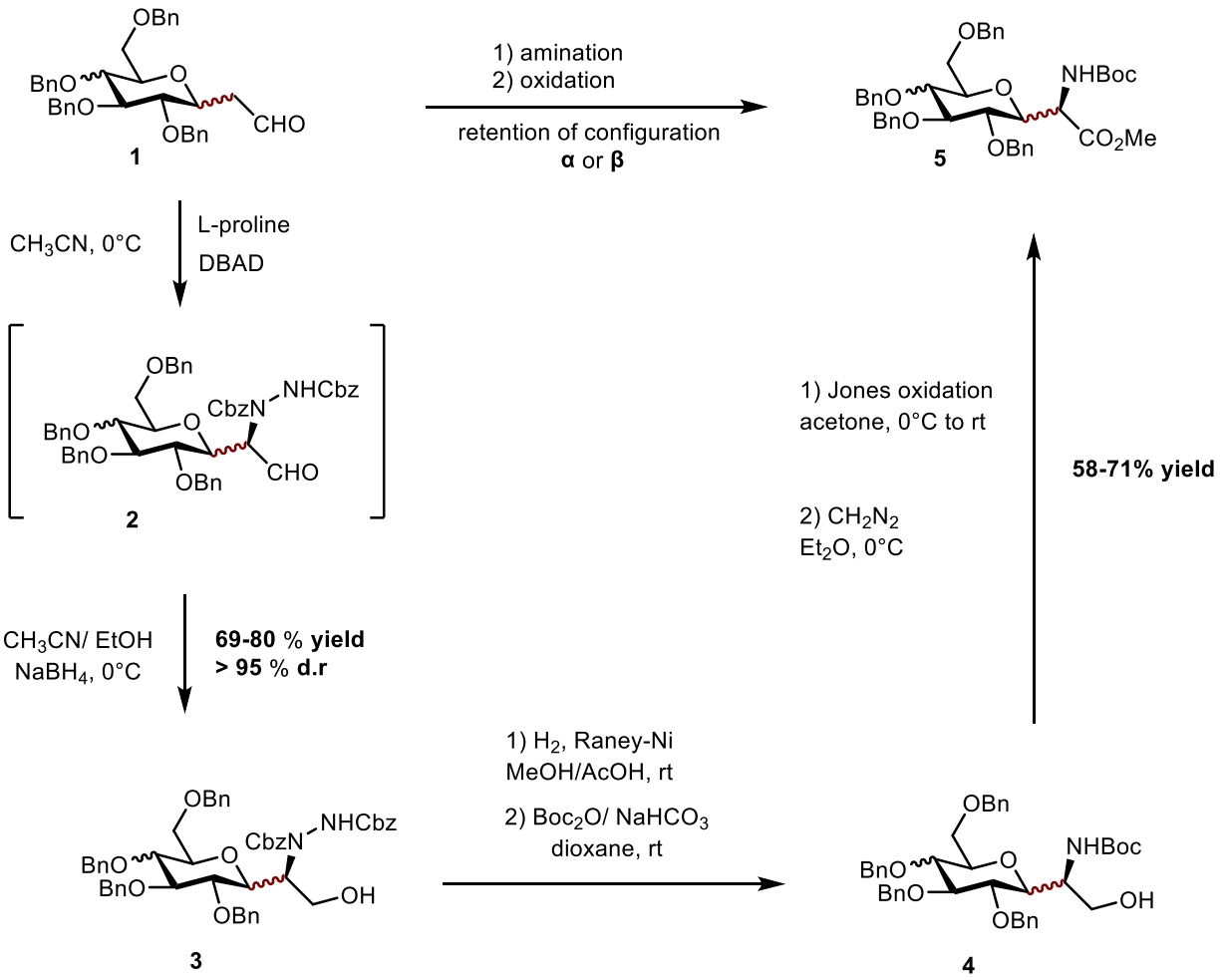
Nikkomycin
U= Uracil



Lincomycin

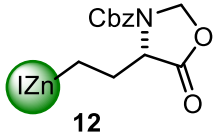
Y. Yang, B. Yu, *Chem. Rev*. **2017**, *117*, 12281; C. S. Stauffer, A. Datta, *J. Org. Chem*. **2008**, 73, 4166; T. von Keutz, J. D. Williams, C. O. Kappe, *Org. Process Res. Dev.* **2020**.

State of the Art: *C*-Glycosyl Glycine



A. Nuzzi, A. Massi, A. Dondoni, *Org. Lett.* **2008**, *10*, 4485

State of the Art: *C*-Analogues of Glycosyl Serine



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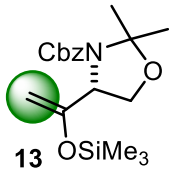

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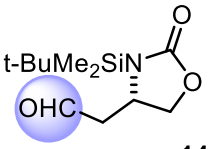
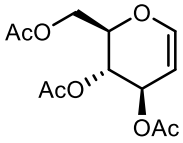


14

12, 13 nucleophilic synthons

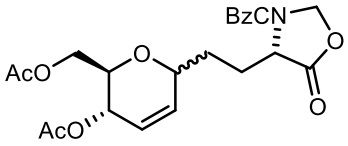
14 electrophilic and radical synthon



15

12, $BF_3{\cdot}Et_2O$

50% yield

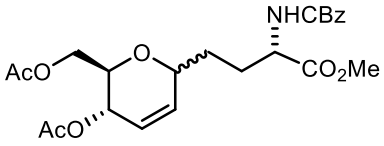


16

9:1 **α** to **β**

1) MeONa
2)Ac_2O

quantitative



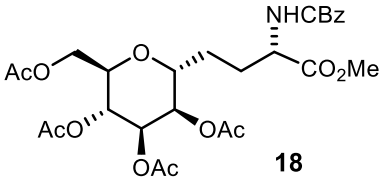
17

Diaster. Separation

17 α

1) OsO_4
2) Ac_2O, Py

68% yield



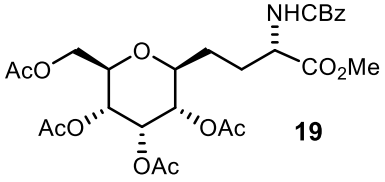
18

C-mannose analogue

17 β

1) OsO_4
2) Ac_2O, Py

68% yield



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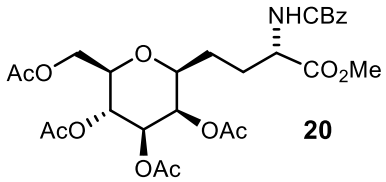

20

1:1 mixture of **19**, **20**

B. J. Dorgan, R. F. W. Jackson, *Synlett.* **1996**, 859.

Aim of the Project

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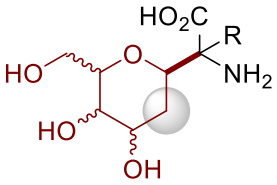
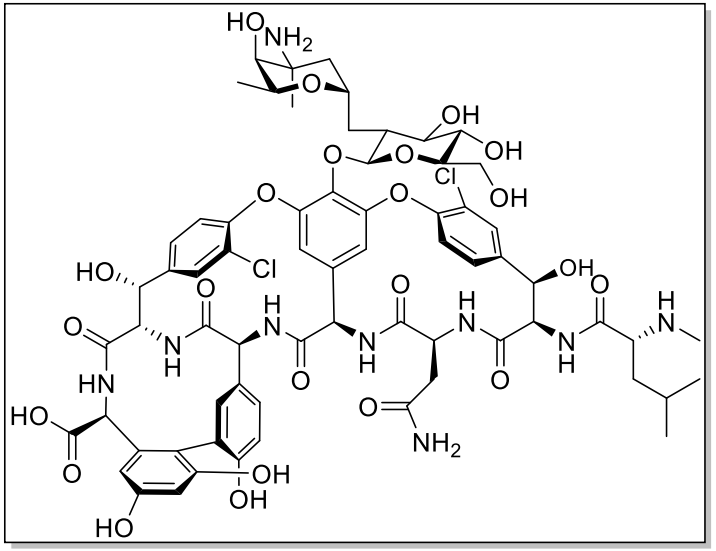
Contribute



Building Block for Complex Bio-Inspired Structures

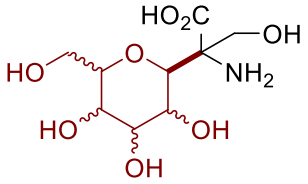
Never Synthesized to Date (2-Deoxy)

Synthetically Challenging

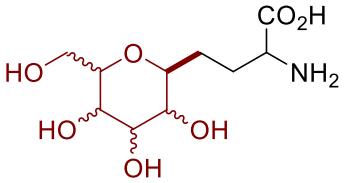


Vancomycin

...Fill the Gap

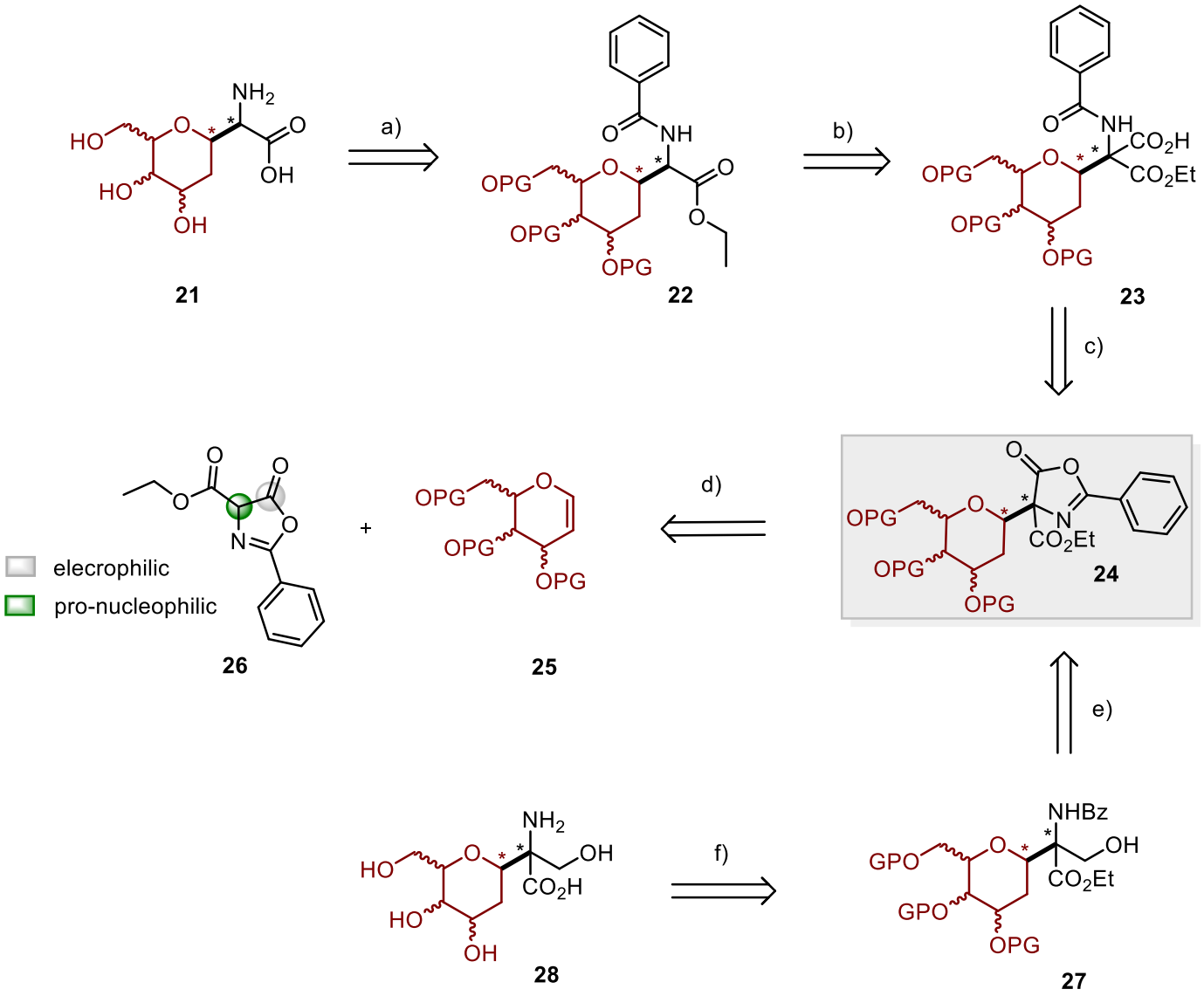


- Formal *C*-serine analogue
- Synthetic challenge, elusive to date

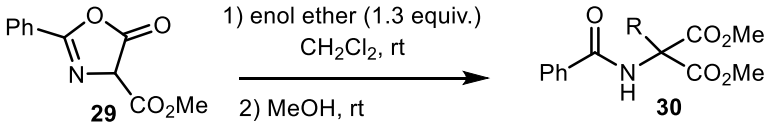


-Glycine analogue with an aliphatic "spacer"
-Many reported protocols

Retrosynthetic Strategy



Intermolecular Ene Reaction



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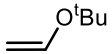
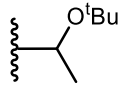
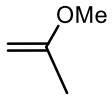
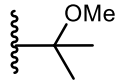
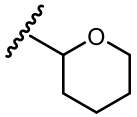
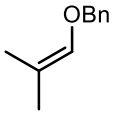
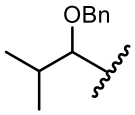
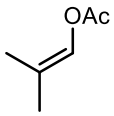
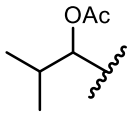
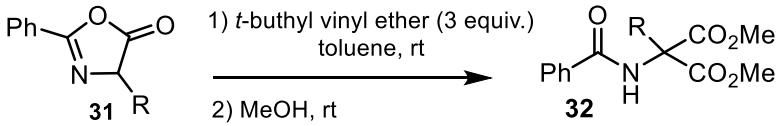
1			99
2			95
3			99
4			68[b]
5			0[c]

Reaction conditions: 2-phenyl-4-carbomethoxy-5-oxazolone (0.5 mmol), enol ether (0.7 mmol), diphenyl phosphate (10 mol%), benzene (20 mL), rt. [b] Reaction refluxed for 24 h and 3.0 equiv of the enol ether used

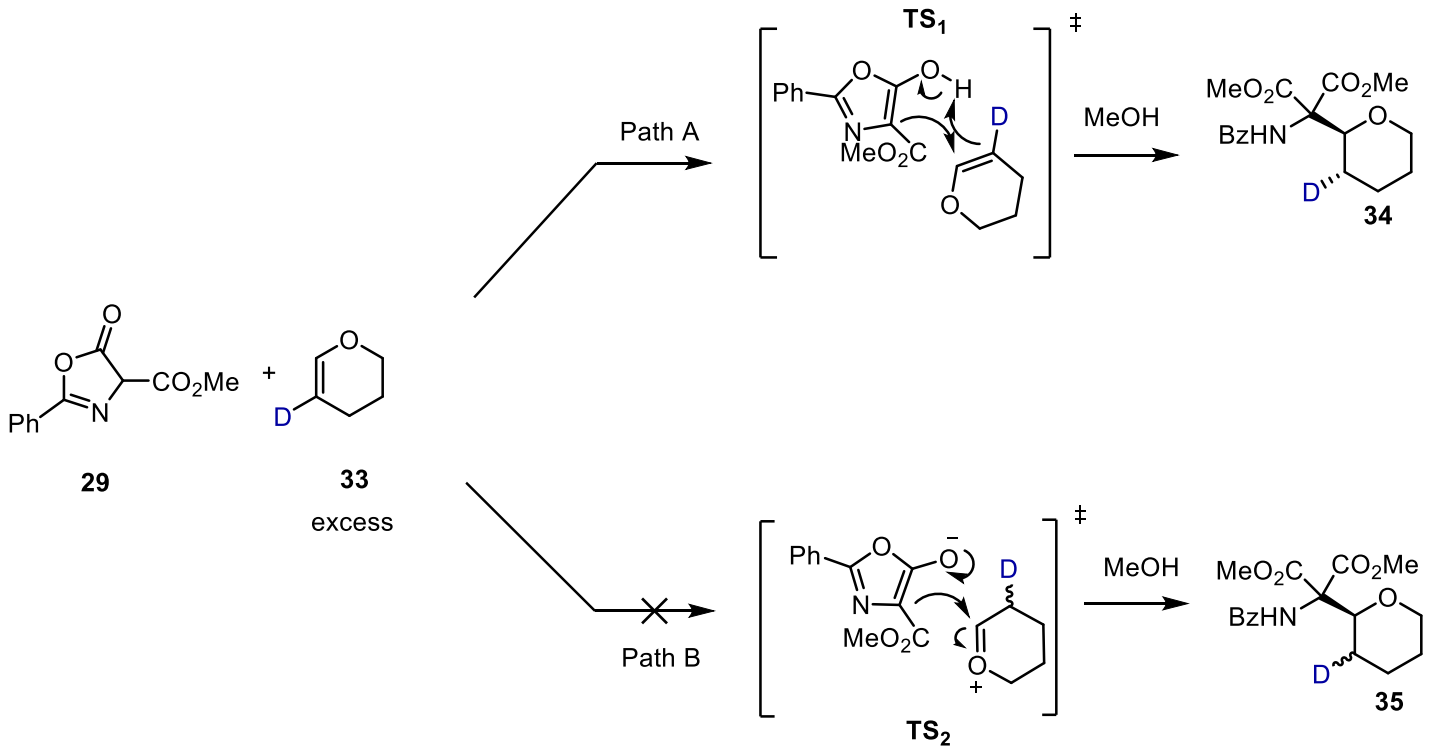


entry	R	temp. (°C)	time	Yield (%)
1	CO_2Me	rt	20 min.	99
2	Ph	110	8 h	95[a]
3	Me	110	24 h	0[b]

[a] yield based on the oxazole intermediate, [b] reaction resulted in recovery of the starting materials

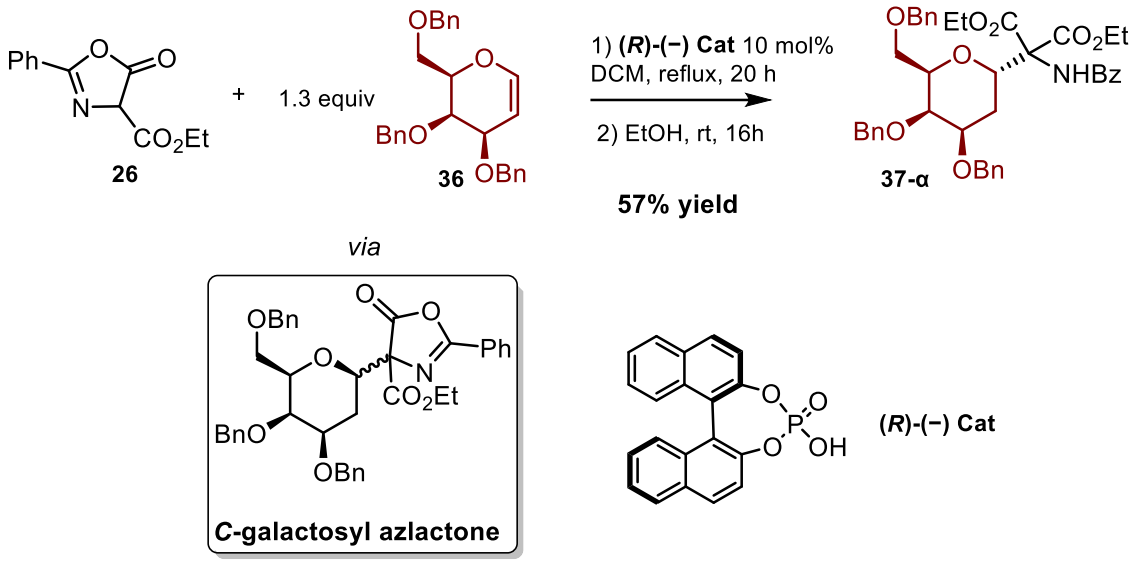
J. S. Fisk, J. J. Tepe, *J. Am. Chem. Soc.* **2007**, *129*, 3058.

Mechanistic Insight

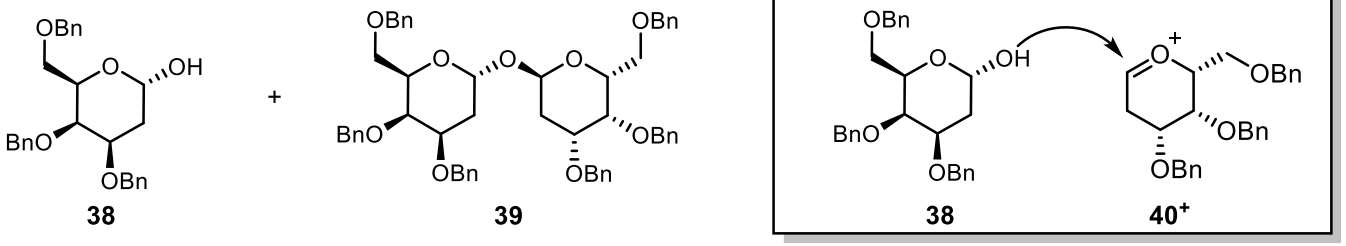


J. S. Fisk, J. J. Tepe, *J. Am. Chem. Soc.* **2007**, *129*, 3058.

Preliminary Results

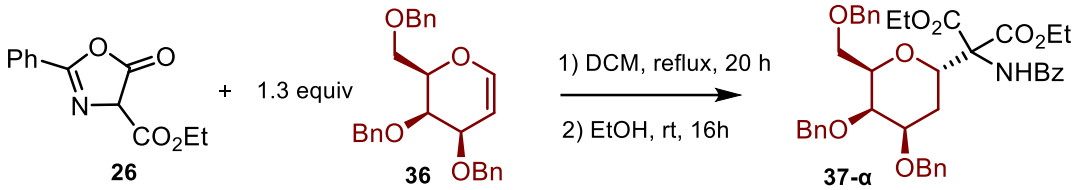


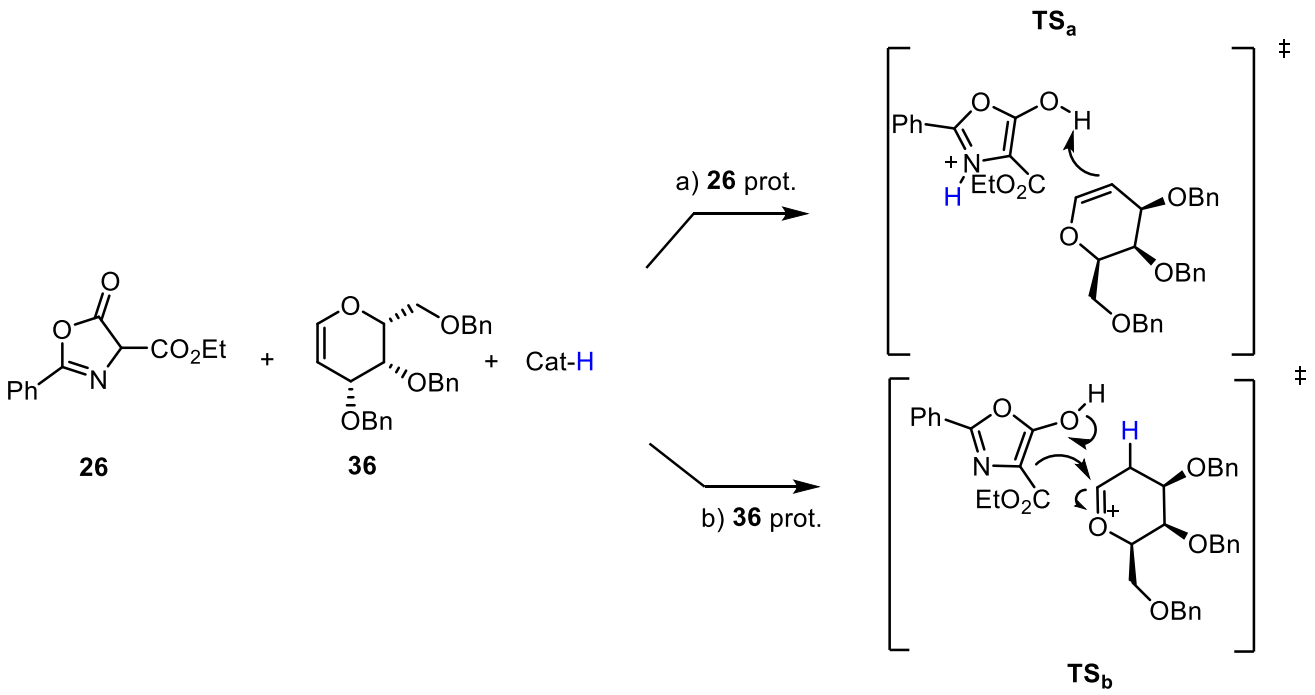
Rapid Hydrolysis of **36** Precluding Full Conversion



Shift in the Mechanism?

Catalyst Free (Ene reaction)





K. Kanomata, Y. Nagasawa, Y. Shibata, M. Yamanaka, F. Egawa, J. Kikuchi, M. Terada, *Chemistry* **2020**, *26*, 3364.

Optimization of Anomeric C-C Bond Formation

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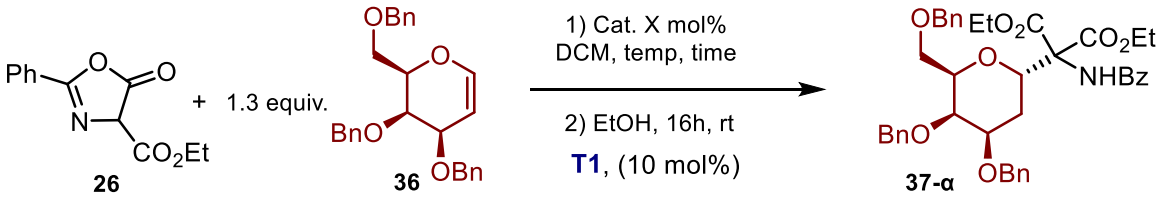
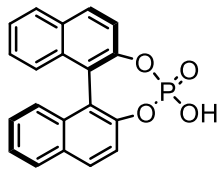
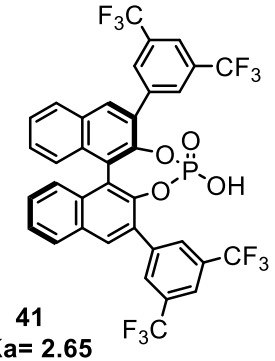


entry	Cat.	temp (°C)	time (h)	yield (%)[b]
1	**(R)-(−) Cat**[a]	20	16	27
2	**(R)-(−) Cat-T1**[a]	20	16	56
3	**41-T1**[a]	20	16	65
4	**PTSA**[b]	20	1	86

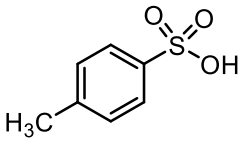
All reaction carried out on a 0.2 mmol scale.[a] 10 mol% used, [b] 5 mol% used. (reaction reproduced and yields verified via ^{1}H NMR analysis). Unoptimized reaction times



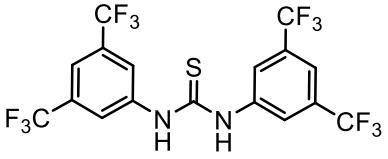
(R)-(−) Cat
pKa= 3.60



41
pKa= 2.65



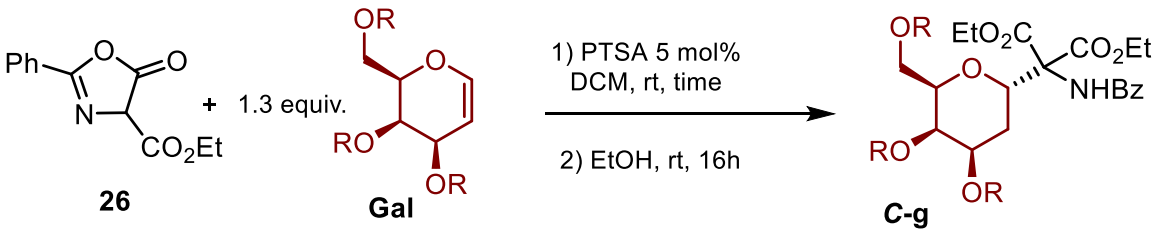
PTSA
pKa= -2.00



T1
Thiourea

C. Yang, X.-S. Xue, X. Li, J.-P. Cheng, *J. Org. Chem.* **2014**, *79*, 4340; C. Palo-Nieto, A. Sau, R. Williams, M. C. Galan, *J. Org. Chem.* **2017**, *82*, 407.

Effect of the Protecting Group

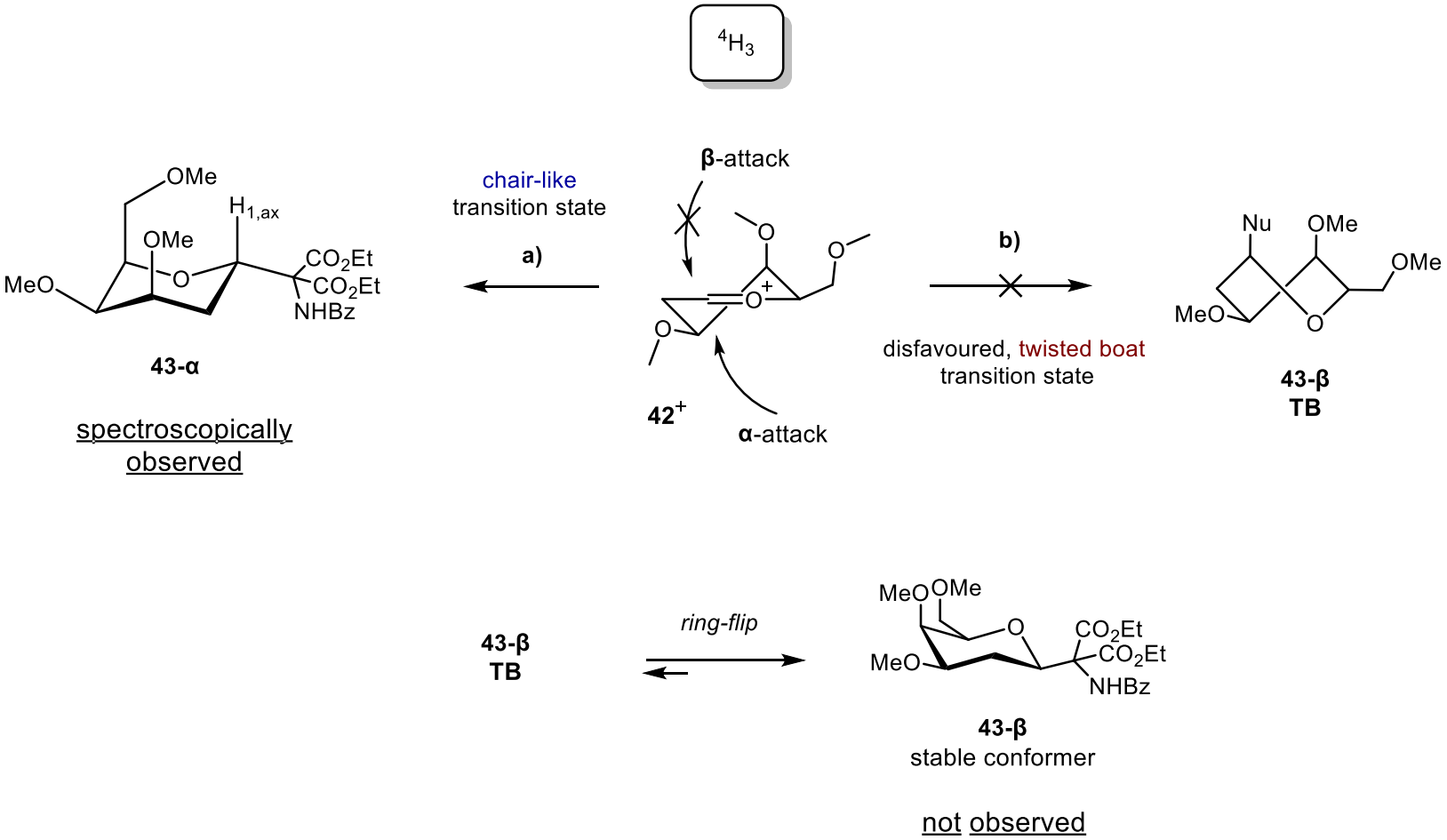


entry	R	time (h)	α:β[a]	%Yield[b]
1	Bn	1	α	86
2	Ac	24	-	0
3	Me	0.25	α	80

All reaction carried out in a 0.2 mmol scale. [a]Diasteromeric ratio determined by ^{1}HNMR.[b]yield after column chromatography.

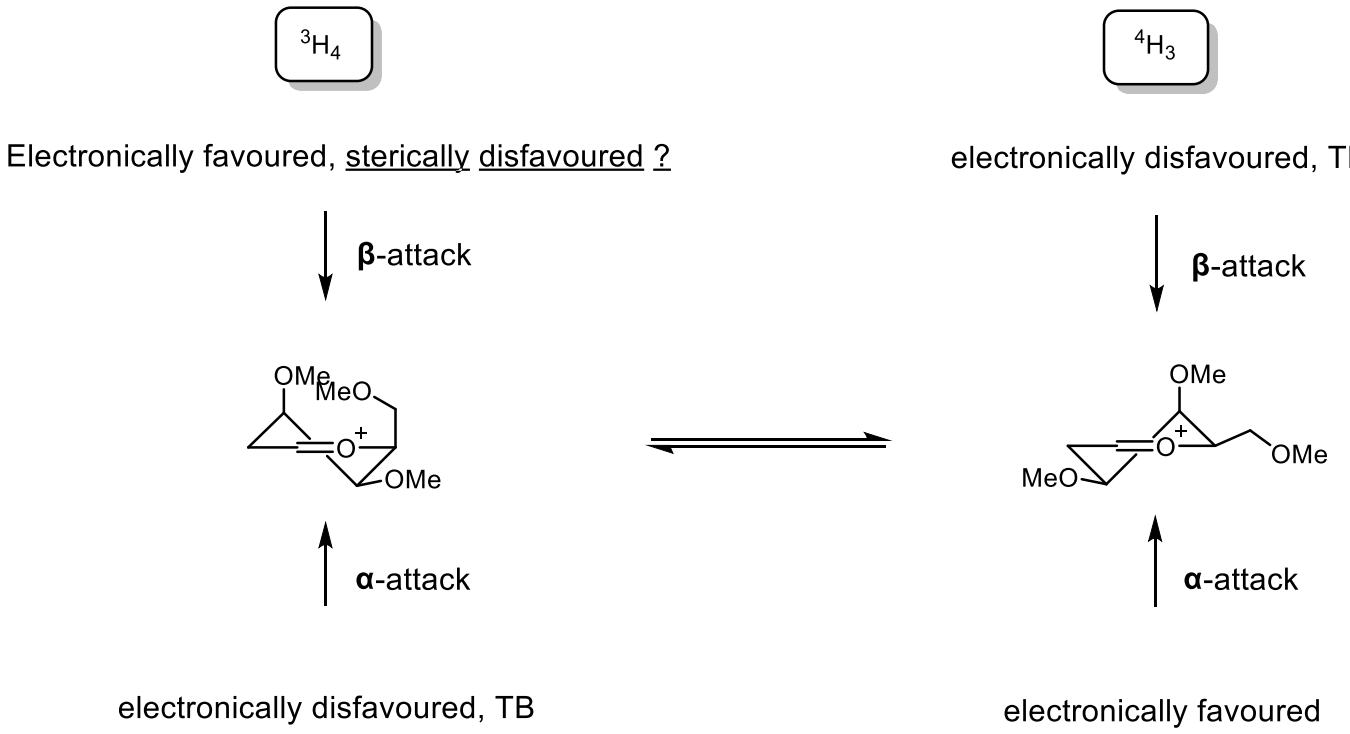
- Also with MeO (entry 3), <u>α only</u>
- Only steric hindrance?

Origin of Stereoselectivity

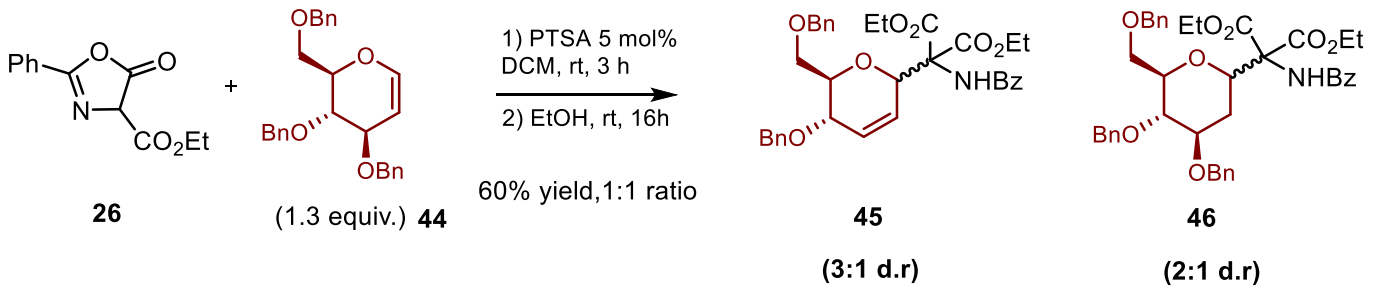


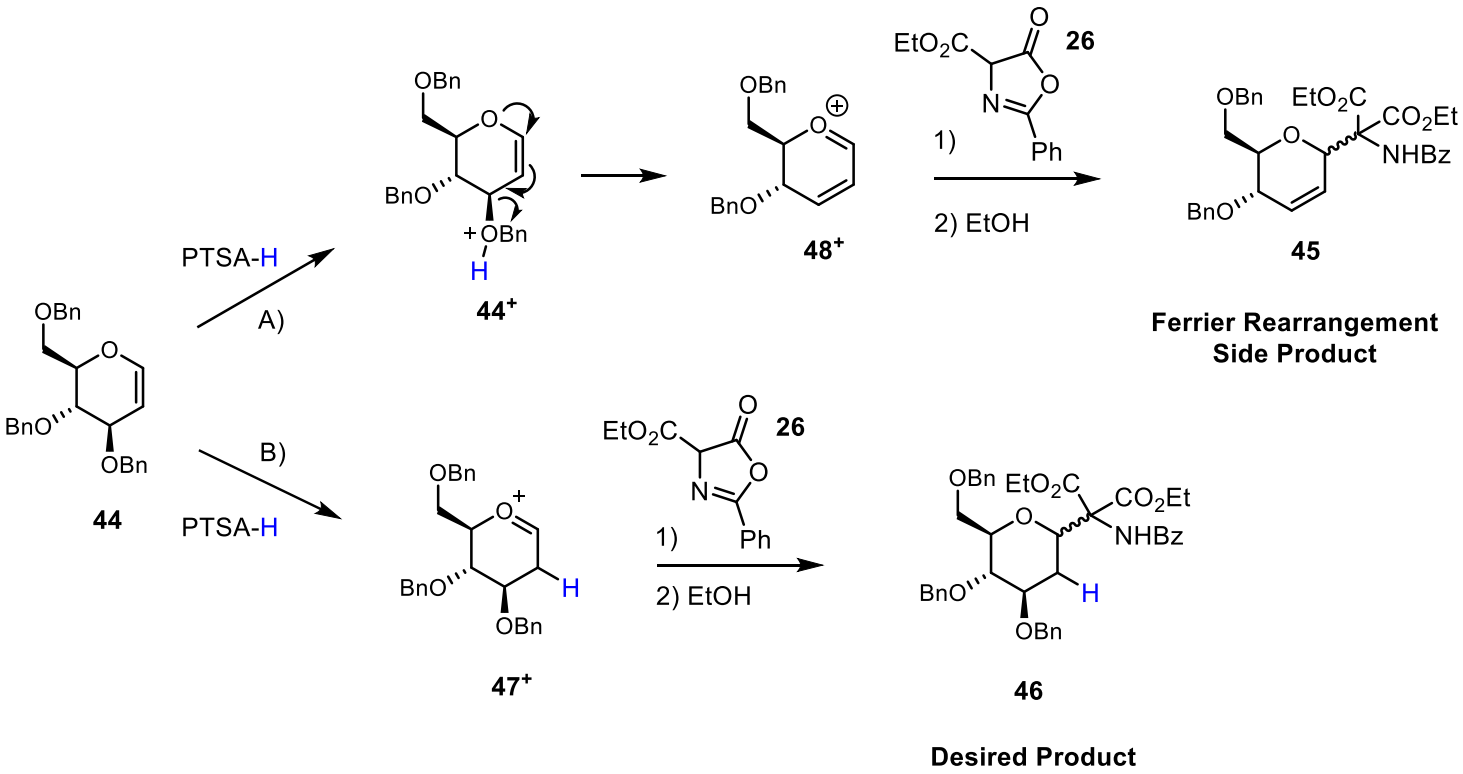
L. Ayala, C. G. Lucero, J. A. C. Romero, S. A. Tabacco, K. A. Woerpel, *J. Am. Chem. Soc.* **2003**, *125*, 15521.,
E. I. Balmond, D. M. Coe, M. C. Galan, E. M. McGarrigle, *Angew. Chem. Int. Ed.* **2012**, *51*, 9152

Origin of Stereoselectivity

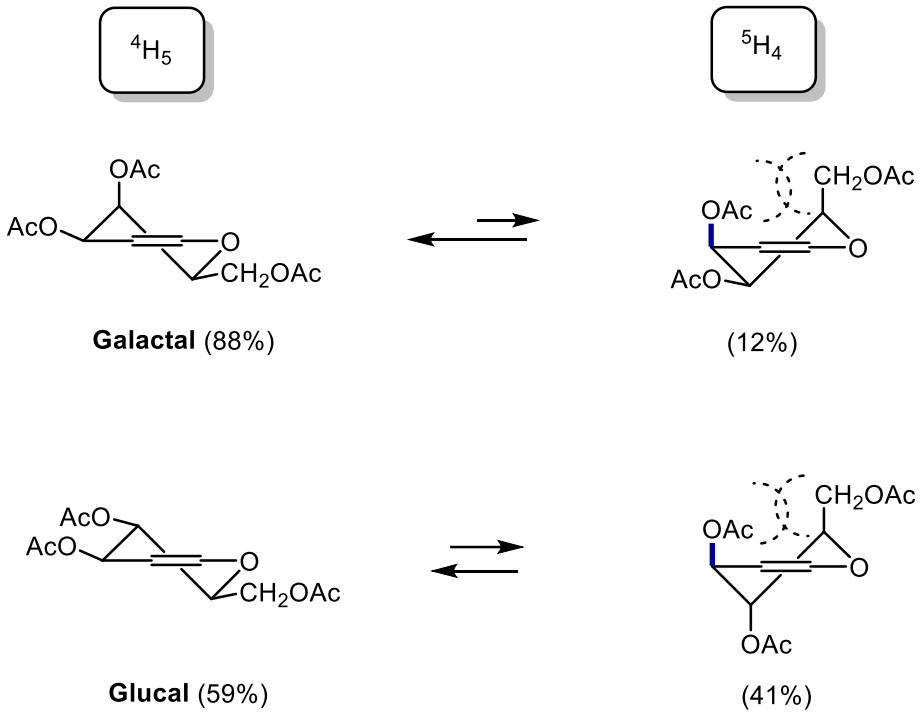


Glycal Scope





Different Reactivity Pathway

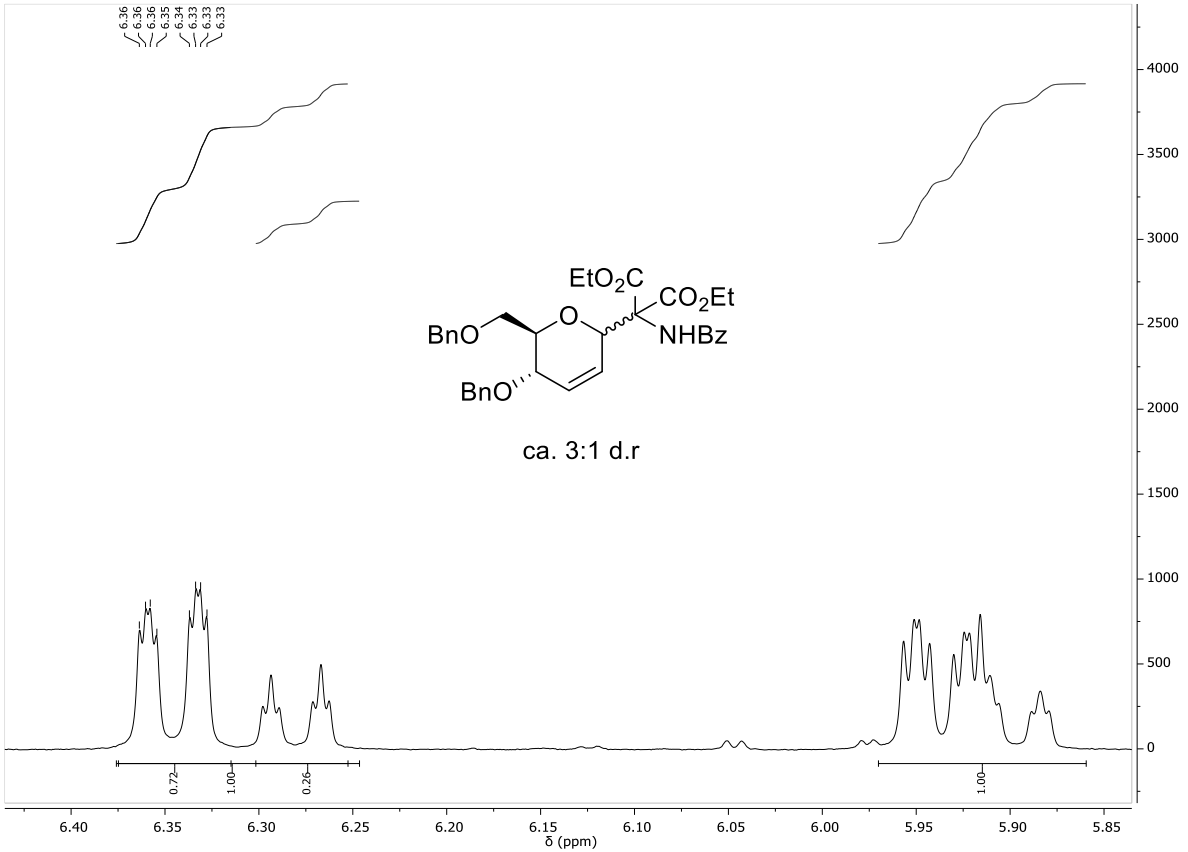


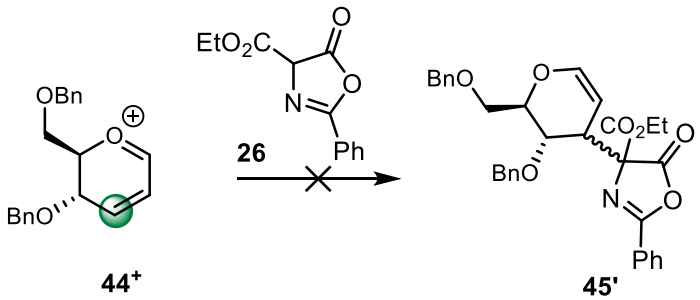
1-3 diaxial strain favours $^4H_5$

VAE (vinylogous anomeric effect) favours $^5H_4$

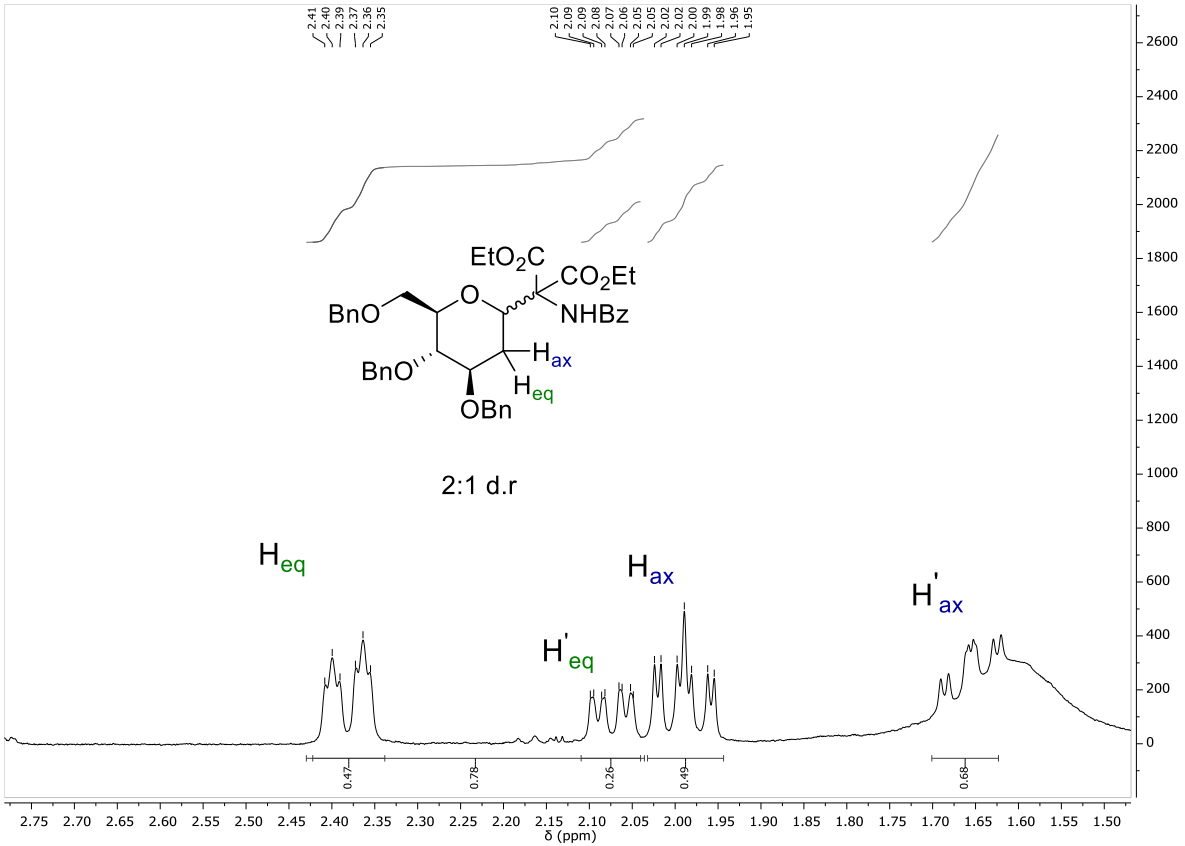
M. Gómez, F. Lobo, C. Uriel, J. C. López, *Eur. J. Org. Chem.* **2013**, 7221.,
R. J. Ferrier, W. G. Overend, A. E. Ryan, *J. Chem. Soc.* **1962**, 3667.

Assignment of 45

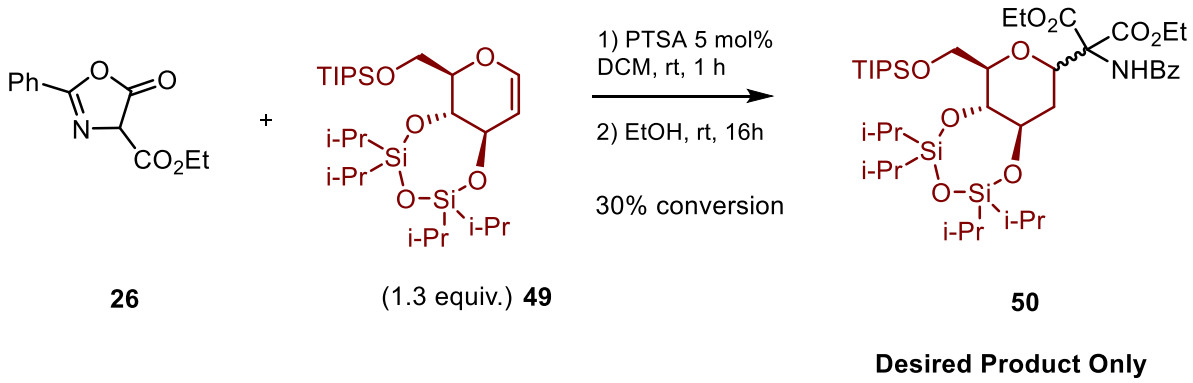




Assignment of 46

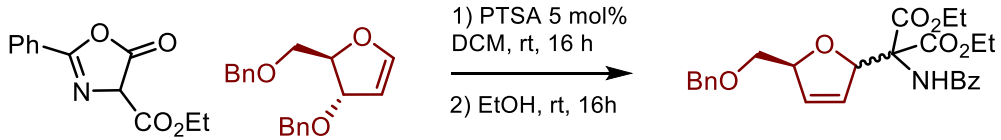


Glycal Scope



26 (1.3 equiv.) **49** **50**

Desired Product Only

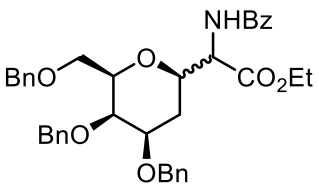


26 **51** **52**

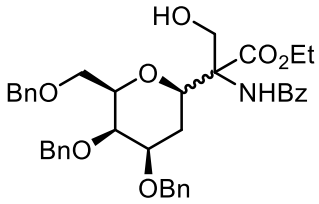
ESI-MS detected

E. I. Balmond, D. Alifonso, D. M. Coe, R. W. Alder, E. M. McGarrigle, M. C. Galan, *Angew. Chem. Int. Ed.* **2014**, *53*, 8190.

Design of the Divergent Synthetic Strategy

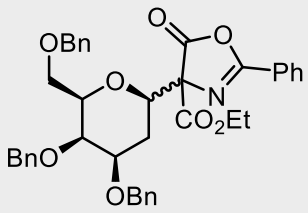


Glycine analogue



Serine analogue

Decarboxylation



***C*-galactosyl azlactone**

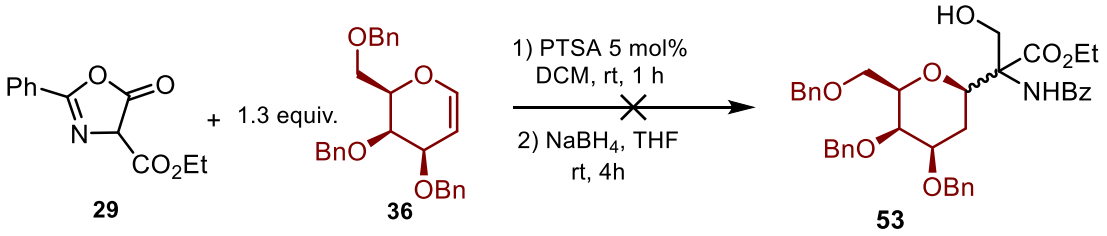
Reduction

high atom-economy

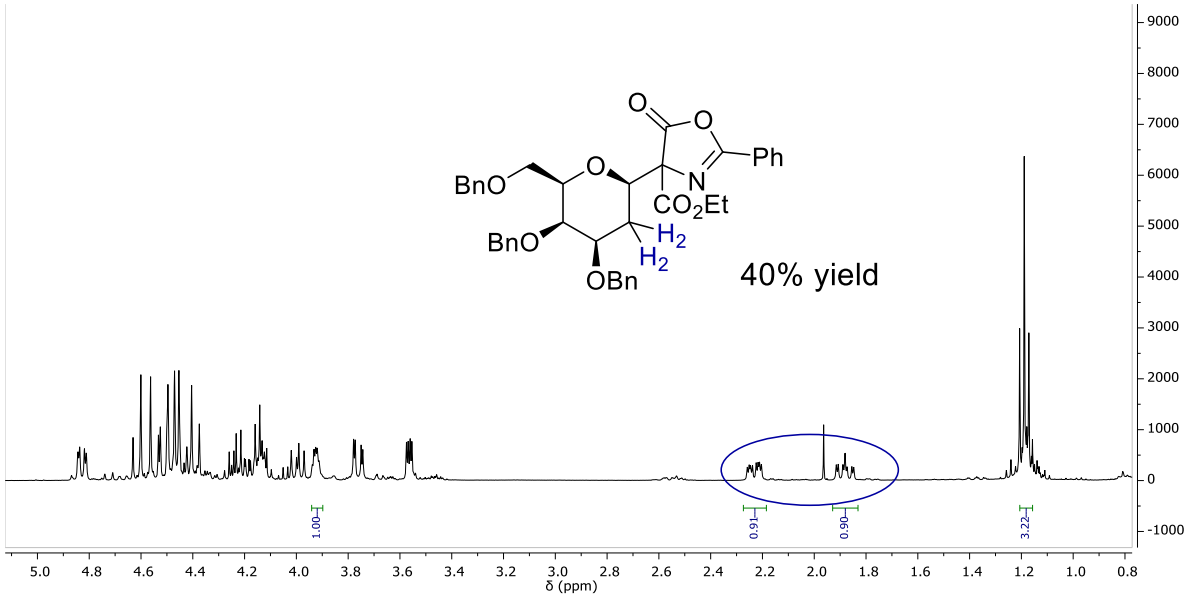
facile further functionalization

rapid approach

Synthesis of 2-Deoxy-*C*-Galactosyl Serine

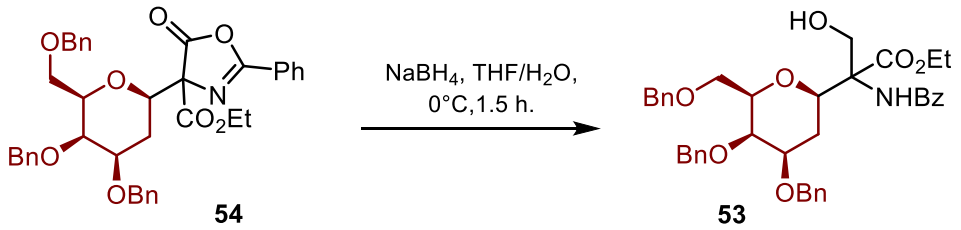


Isolation of the Intermediate



R. A. Mosey, J. S. Fisk, T. L. Friebe, J. J. Tepe, *Org. Lett.* **2008**, *10*, 825

Synthesis of 2-Deoxy-*C*-Galactosyl Serine

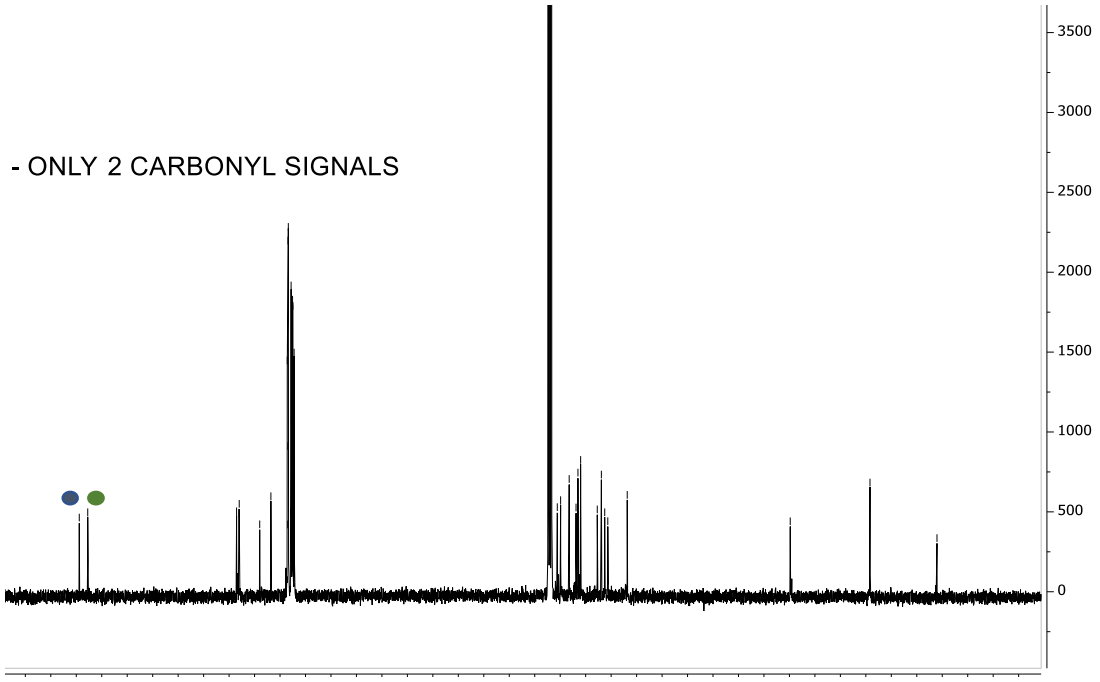


C-galactosyl azlactone

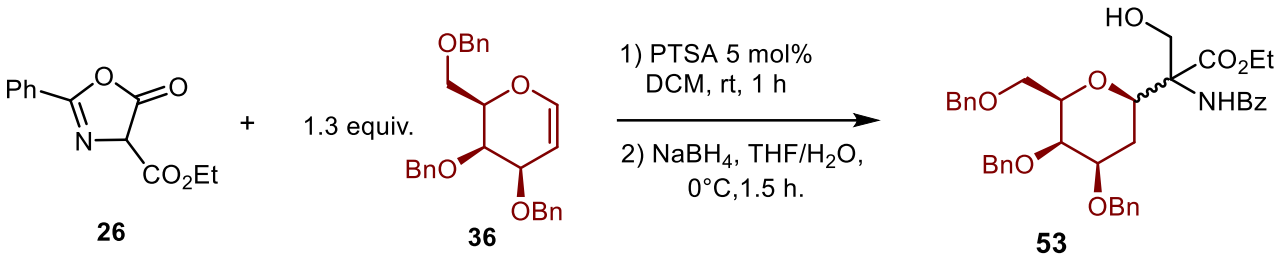
ONE DIASTEREOISOMER

20% yield, **α only**

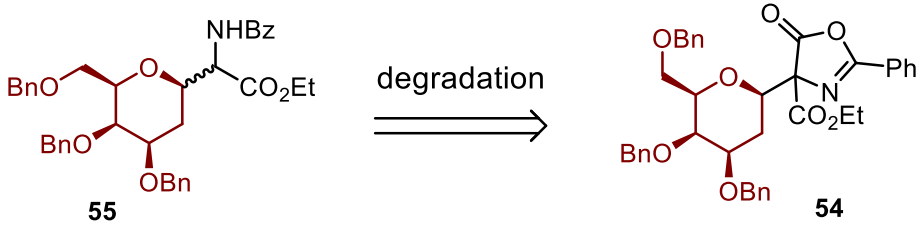
ONE DIASTEREOISOMER



Synthesis of 2-Deoxy-*C*-Galactosyl Serine



52% yield, **α only**, 1:1 d.r



10% yield, 1:1 d.r

C-galactosyl azlactone

Synthesis of 2-Deoxy-*C*-Galactosyl Glycine

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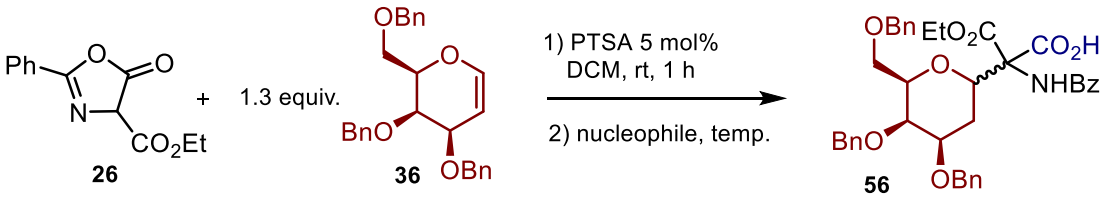
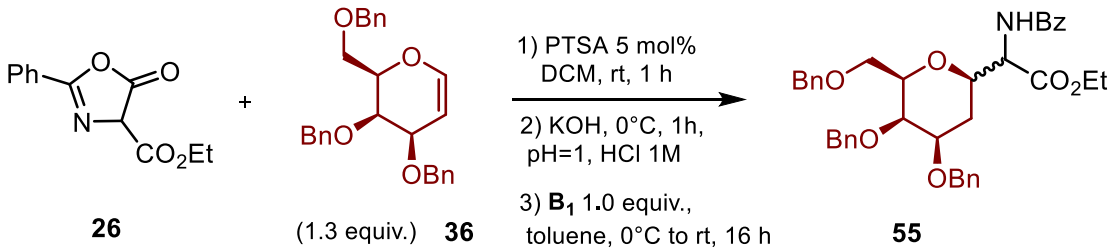


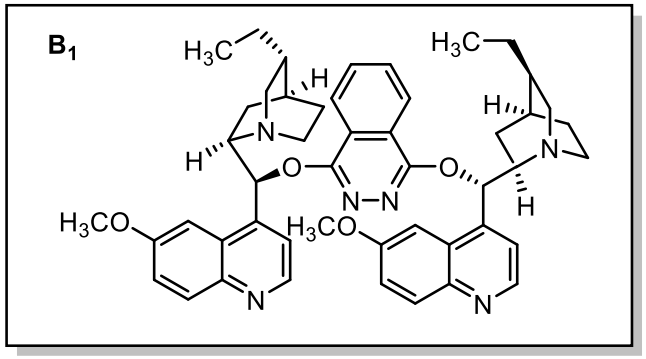
entry	nu	solvent	time (h)	temp (C°)	outcome
1	H_2O	DCM	16	20	low conv.
2	H_2O	THF	16	20	complex mix.
3	KOH[a]	THF/H_2O	1	0	clean reaction

All reaction were carried out on a 0.2 mmols scale. (nucleophile = nu). [a] 1.0 equiv. of KOH.
Reaction progress monitored by TLC and ESI-MS

Not Possible to Isolate

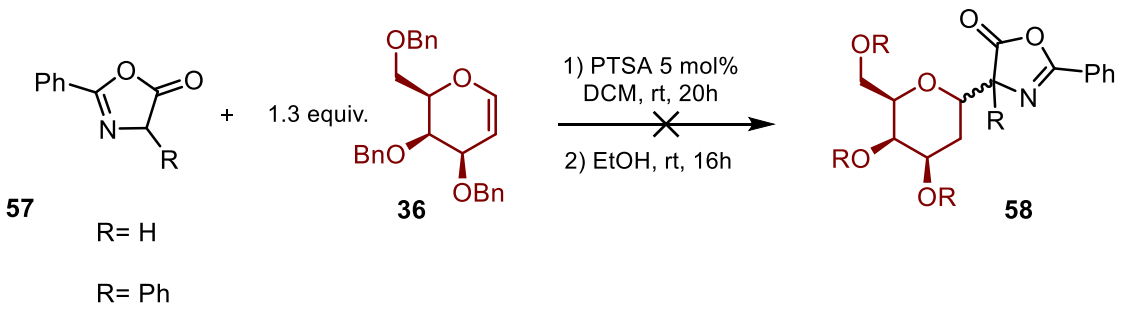
Synthesis of 2-Deoxy-*C*-Galactosyl Glycine



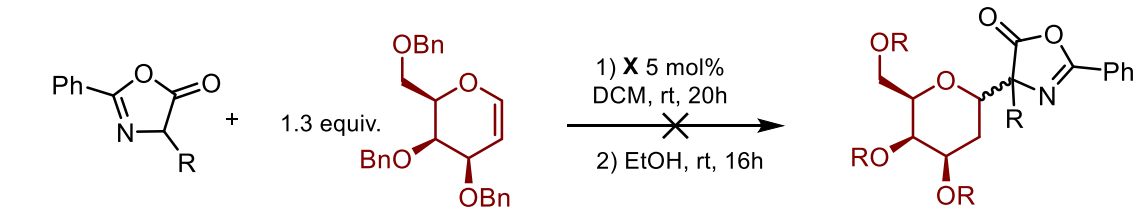


- 2:1 d.r, proof of concept
- With NEt_3 as base 1:1 d.r obtained

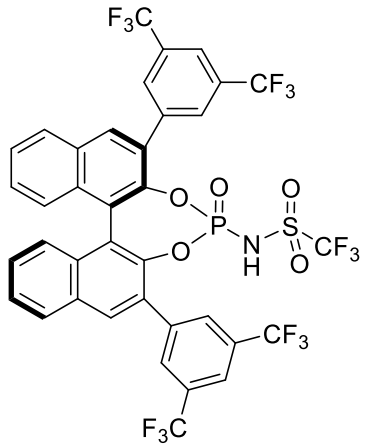
Oxazolone Scope



57 R= H; R= Ph **36** **58**



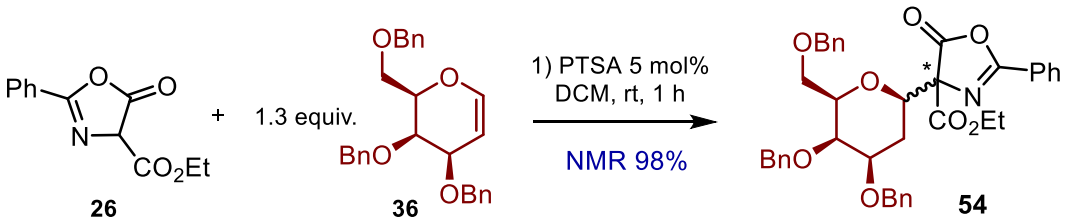
57 R= H; R= Ph; R= CO_2Et **36** **58**

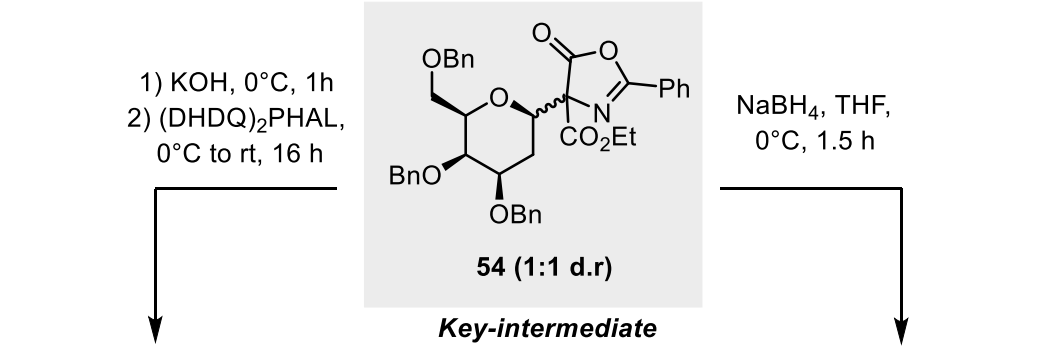


59
pKa =-3.88

J. Kikuchi, Y. Aizawa, M. Terada, *Org. Chem. Front.* **2020**, *7*, 1383

Conclusions





75% yield, **α only**, 2:1 d.r

52% yield, **α only**, 1:1 d.r

never synthesized to date (2-deoxy)

rapid approach

formal C-glycosyl serine (elusive to date)

Conclusions

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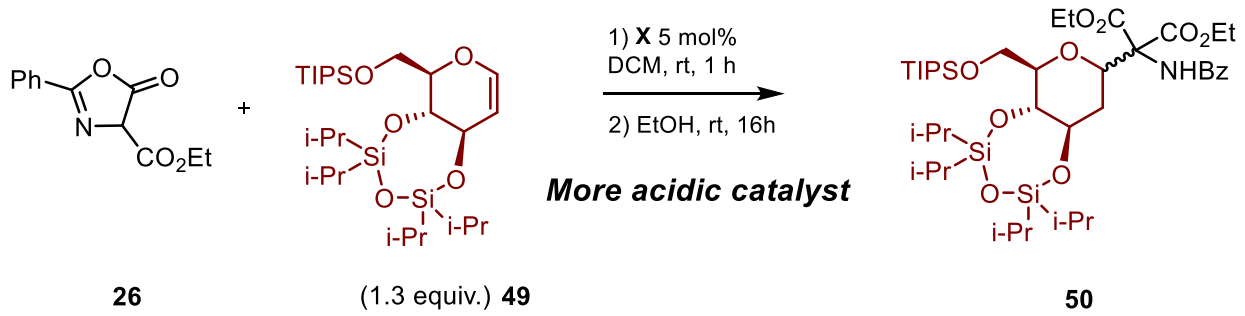
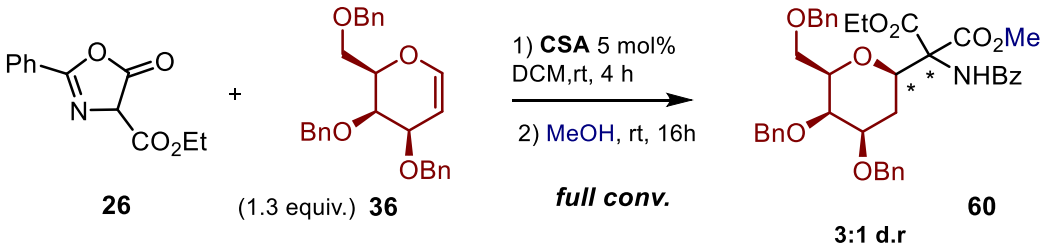
- Lower yield for glucal
- Not applicable fto other oxazolones
- Only Ferrier product for ribal
- No diastereoselectivity on the quaternary carbon

Outlook



26 (1.3 equiv.) **49** **50**

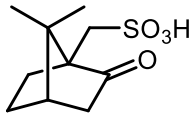
catalyst acidity only relevant for glycal activation



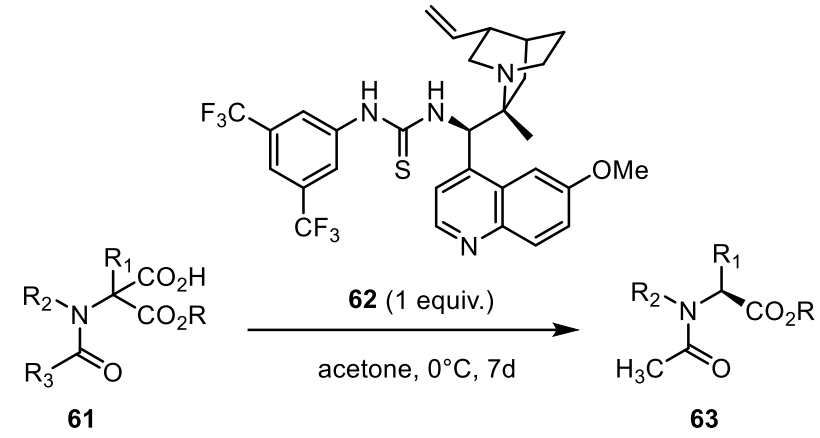
26 (1.3 equiv.) **36** **60**

3:1 d.r

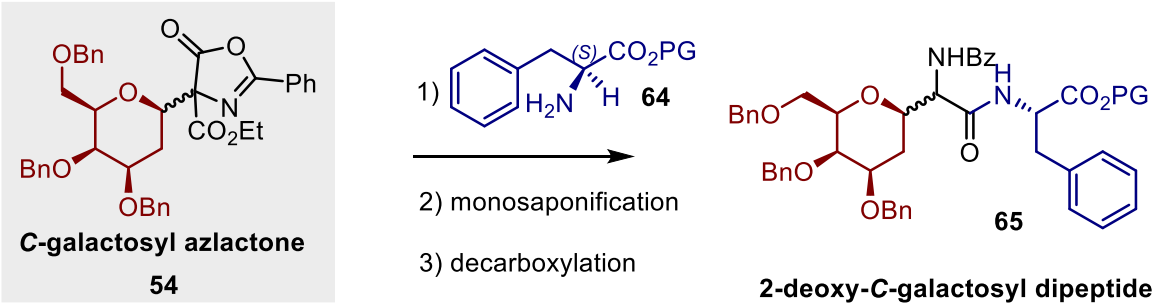
(1S)-(+)-10-Camphorsulfonic acid
CSA



Outlook



M. Amere, M.-C. Lasne, J. Rouden, *Org. Lett.* **2007**, *9*, 2621.



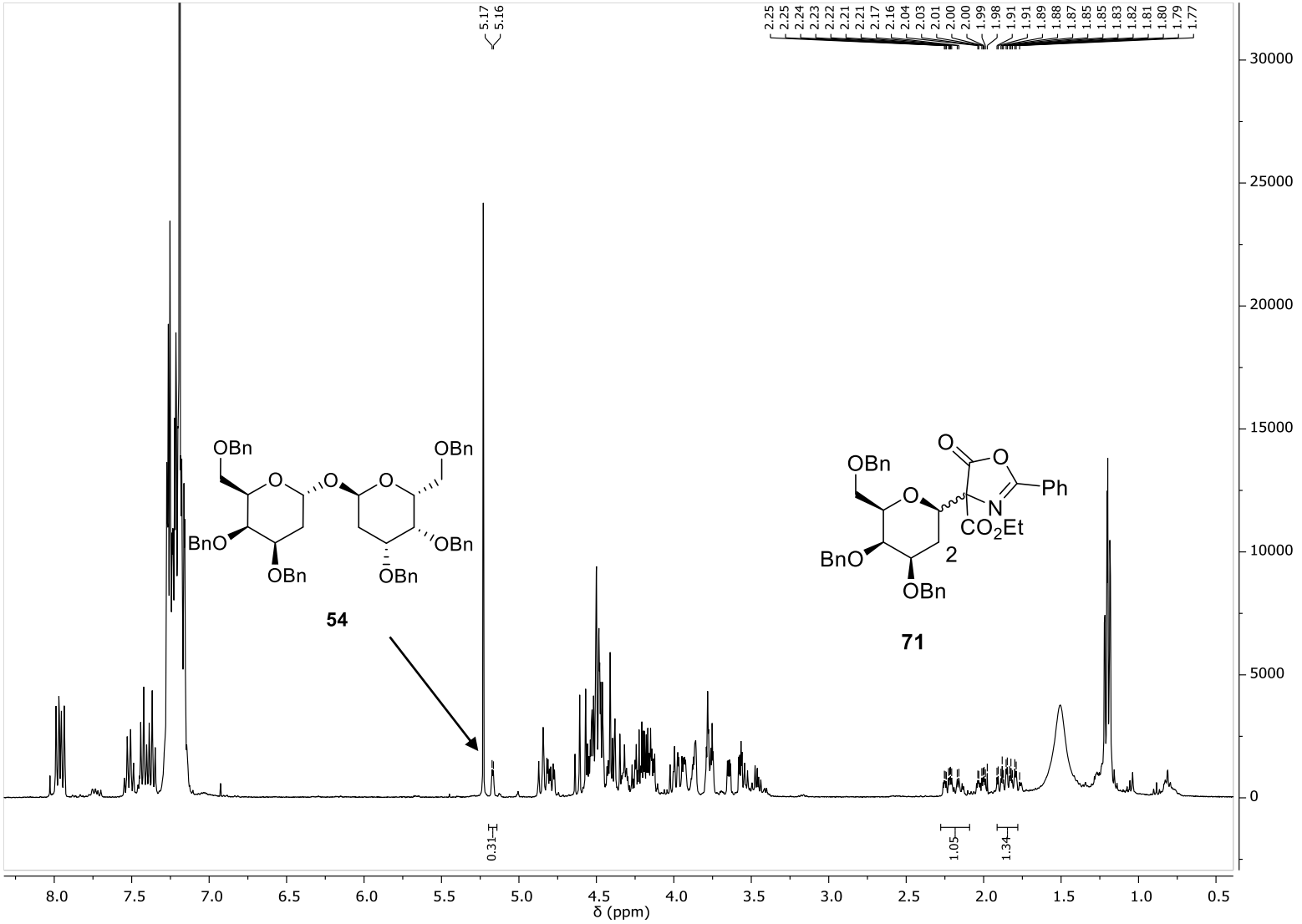
Acknowledgements

- Prof. Dr. Schreiner
- Dr. Wende
- Prof. Dr. Carofiglio
- All PRS group members
- Special thanks to organocatalysis subgroup

THANK YOU FOR YOUR ATTENTION !

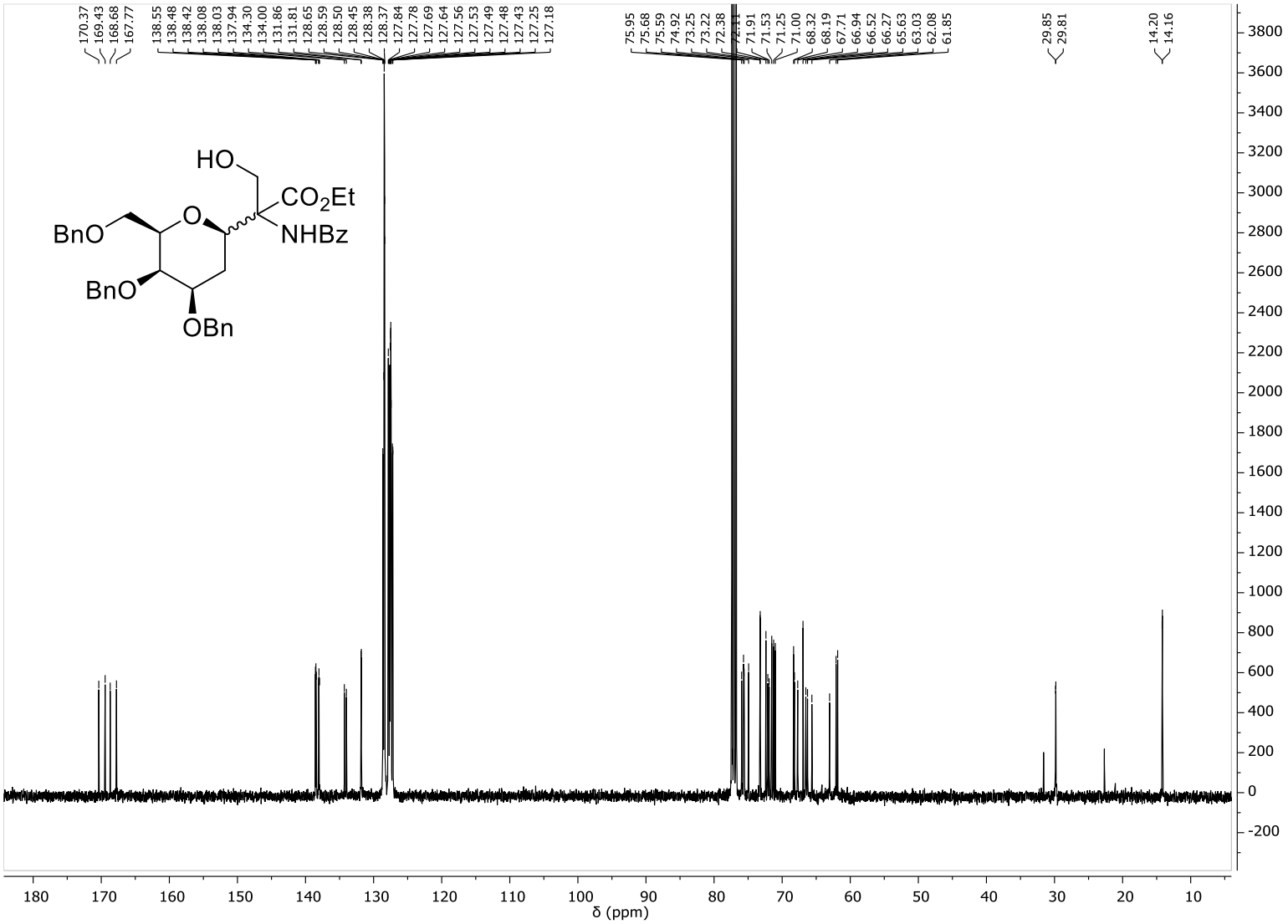
Supportin Info. 1

JUSTUS-LIEBIG-UNIVERSITÄT GIESSEN

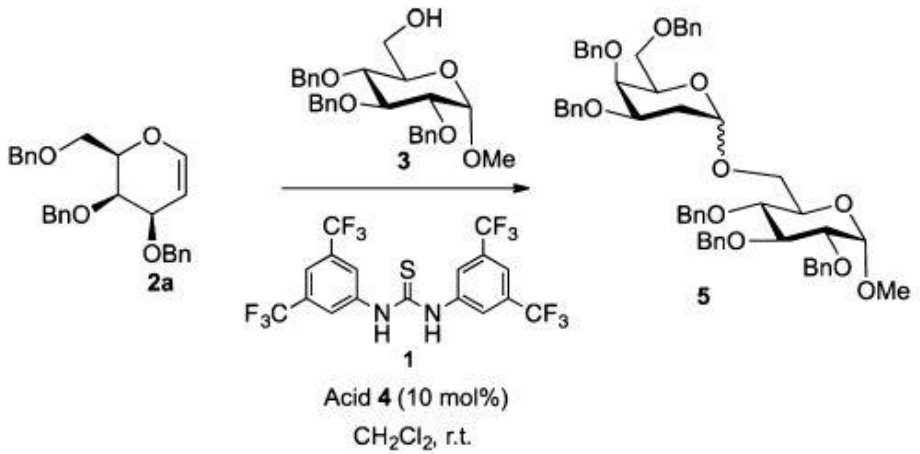


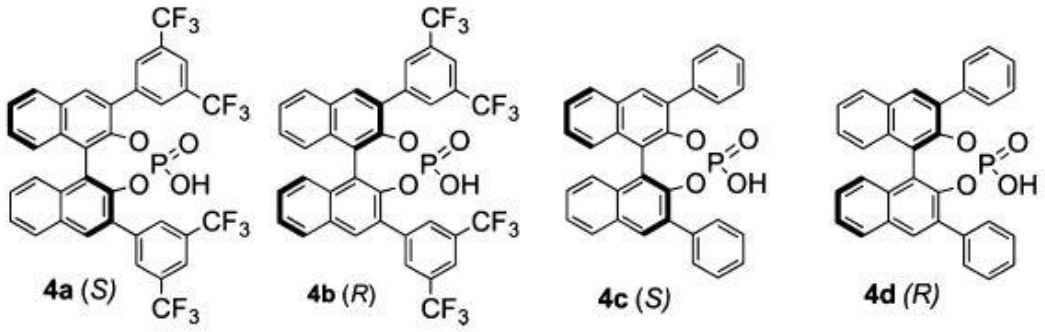
Supportin Info. 2

JUSTUS-LIEBIG-UNIVERSITÄT GIESSEN



Supportin Info. 3





entry		acid	time (h)	yield (%)[c]	α:β[c]
1	–		24	0	N/A
2	4a[a]		20	55	9:1
3	4a		3	82	7:1
4	4b[a]		20	70	>30:1
5	4b		3	89	>30:1