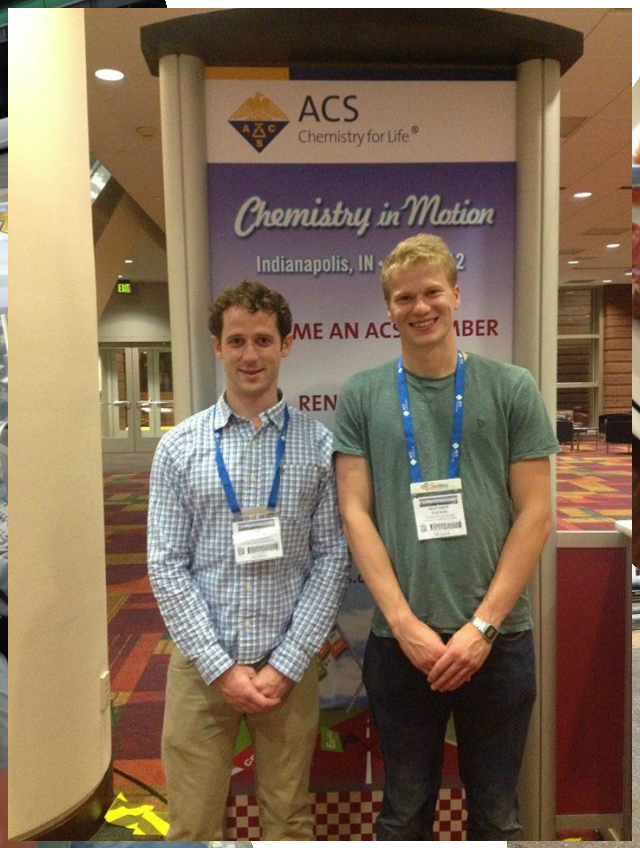
Literature Presentation

12/11/13

ACS 246th Fall Meeting, IND



Ryan A. Shenvi, Ph.D.

Bio

- Assistant Professor at the Scripps Research Institute
- Postdoc, with E.J. Corey (Harvard)
- Ph.D., P.S. Baran (Scripps)
- B.S., R.L. Funk (Penn State)

Awards

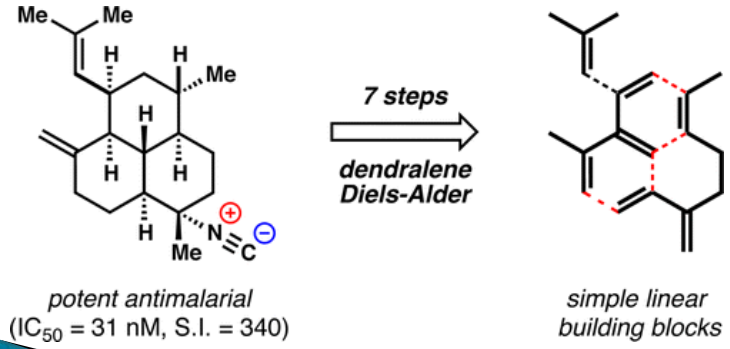
- Baxter foundation young investigator award
- Amgen Young Investigator Award

Research Interest

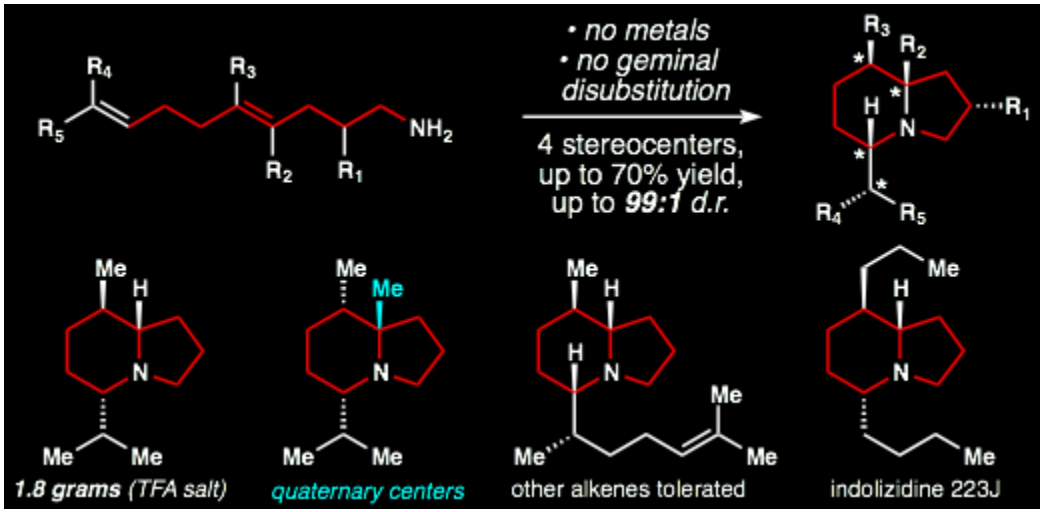
- Has three main areas of research all based around 'the design of short, high yielding, and economical routes of complex molecule cores':

- 1) Synthesis of terpeniod structures
- 2) Synthesis of pseudoalkolids
- 3) Exploration of natural scaffolds with specific applications in the treatment of Neglected Tropical Diseases.

"Synthesis of a Potent Antimalarial Amphilectene", J. Am. Chem. Soc. 2012, 134, 19604–19606.

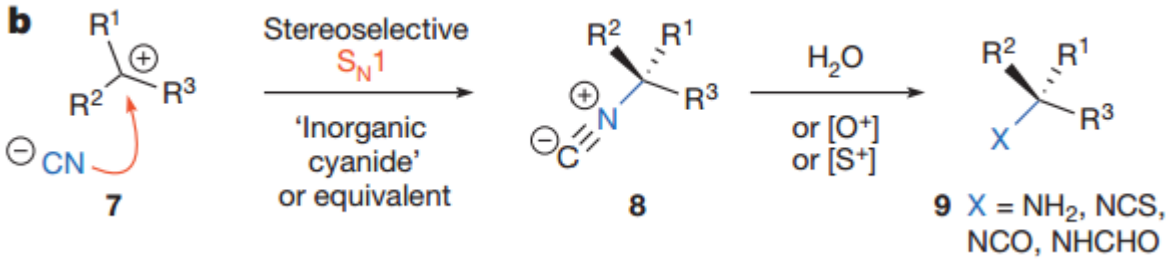


"A Stereoselective Hydroamination Transform to Access Polysubstituted Indolizidines", J. Am. Chem. Soc. 2012, 134, 2012–2015.



Stereoselective S_N1 reaction

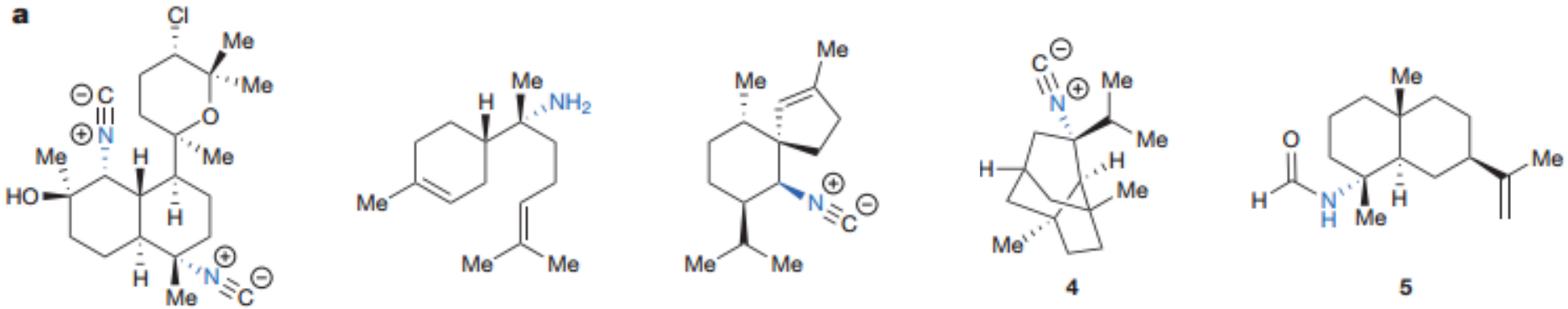
- The S_N2 reaction is well known to proceed with inversion of stereochemistry due to the backside attack of the electrophilic carbon by the nucleophile.
- Primary and secondary alcohols are viable precursor substrates however, tertiary alcohols and their derivatives either fail to react or give stereochemical mixtures.
- Shenvi reports the stereochemical inversion of chiral tertiary alcohols with a nitrogenous nucleophile facilitated by a Lewis-acid-catalysed solvolysis.



Nature, 2013, 501, 195–199.

Benefits

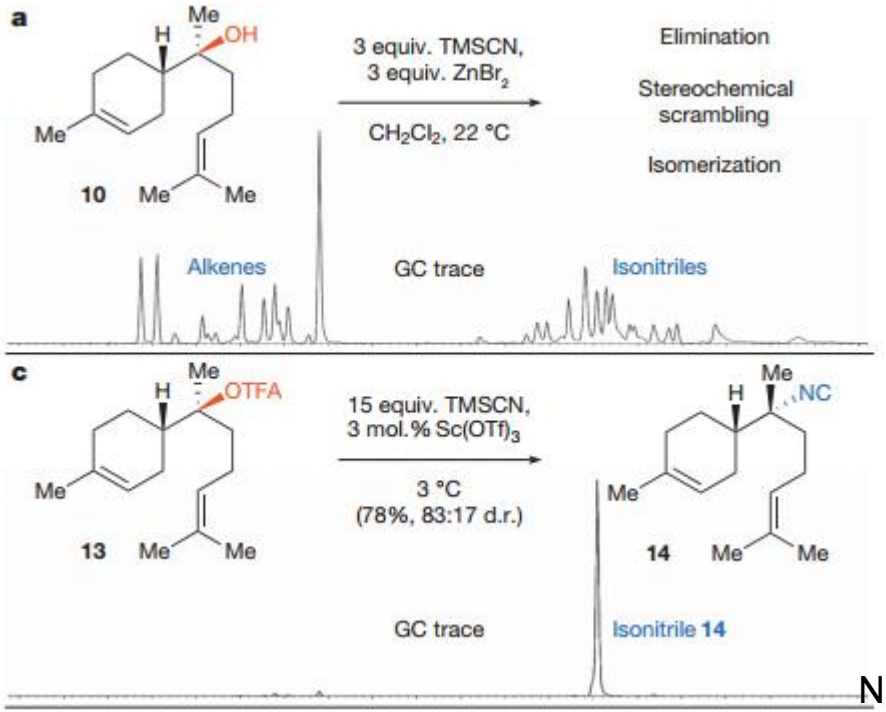
- Biosynthetic incorporation of nitrogen into secondary metabolites occurs almost exclusively through carbonyl chemistry (reductive amination, Mannich reactions, transamination). Mimicry of this has allowed simplified access to complex alkaloids.
- However many marine alkaloids (some potent biological activity) install nitrogen via the use of inorganic cyanide via a biosynthic pathway which is not well understood.
- Shenvi's new protocol gives access to these marine terpinods in a chemeo and stereoselective manner and also a general method for the inversion of tetiray alcohols.



Nature, 2013, 501, 195–199.

Current Methods

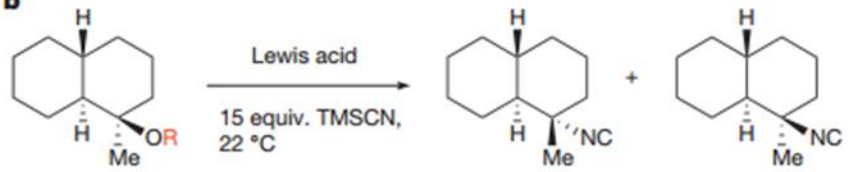
- Prior to this piece of methodology the isonitrile group was installed either through abiotic strategies or where nitriles attacking carbocations where the stereo outcome is defined by the cyclic scafford. This can be problematic however leading to isomeric mixtures or non-natural isomers.
- Some work developed the Lewis acid mediated ionisation of a tetiary leaving group in the presence of TMSCN, however the resulting isonitrile was a mixture of four steroisomers.



Nature, 2013, 501, 195–199.

Reaction Optimisation

b



11 **12-*eq*** **12-*ax***

Entry	Proportion (mol.%)	Lewis acid	R	Percentage **12**	d.r.
1	10	$ZnBr_2$	TFA	0	n/a
2	5	$Mg(OTf)_2$	TFA	0	n/a
3	5	$Bi(OTf)_3$	TFA	14	49:51
4	5	$Y(OTf)_3$	TFA	70	84:16
5	3	$Sc(OTf)_3$	TFA	86	88:12
6	3	$Sc(OTf)_3$	H	0	n/a
7	3	$Sc(OTf)_3$	Ac	75	76:24
8	3	$Sc(OTf)_3$	CHO	61	66:34
9	3	$Sc(OTf)_3$	$C(O)C_2F_5$	69	85:15
10	3	$Sc(OTf)_3$	$C(O)C_3F_7$	79	87:13

- Screened different leaving groups and Lewis acids, found TFA and $Sc(OTf)_3$ gave the best results.

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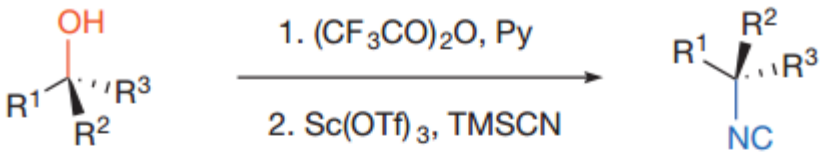
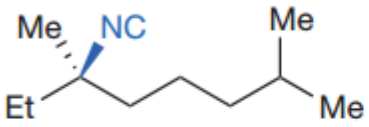
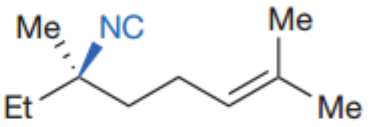
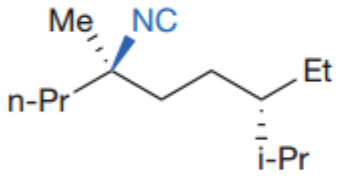




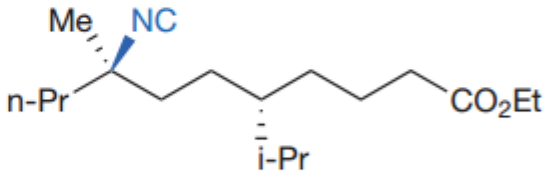
15: 78%, 90% inversion*
(84:16 from 7:93 e.r.)*



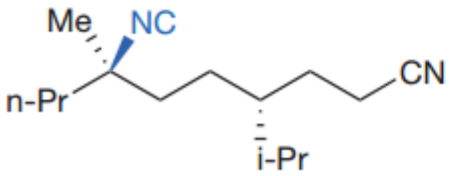
16: 79%, 88% inversion*
(83:17 from 7:93 e.r.)*



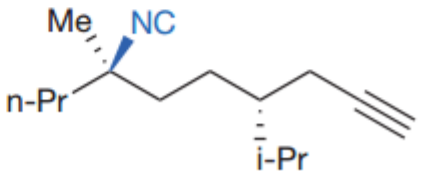
17: 71%, 88:12 d.r.



18: 68%, 89:11 d.r.



19: 67%, 86:14 d.r.



20: 74%, 88:12 d.r.

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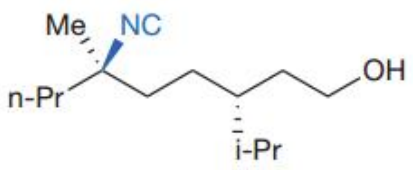
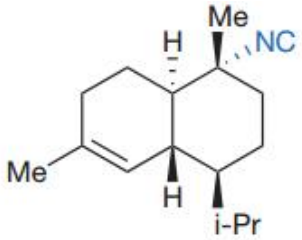
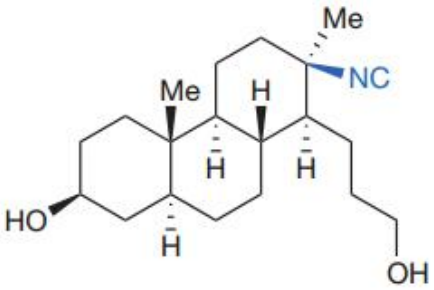


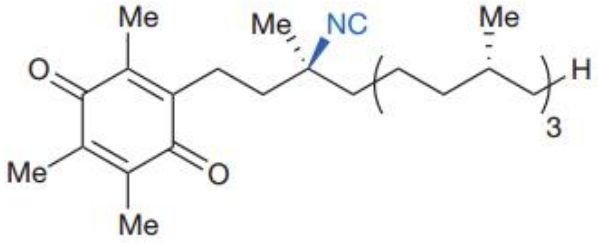
21: 71%, 90:10 d.r.†



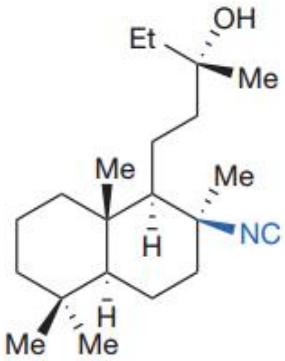
22: 59%, 91:9 d.r.



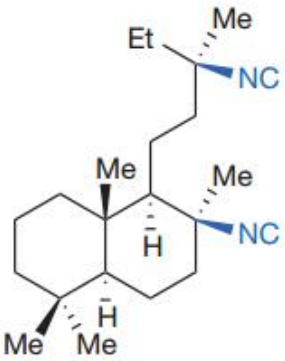
23: 69%, 91:9 d.r.†



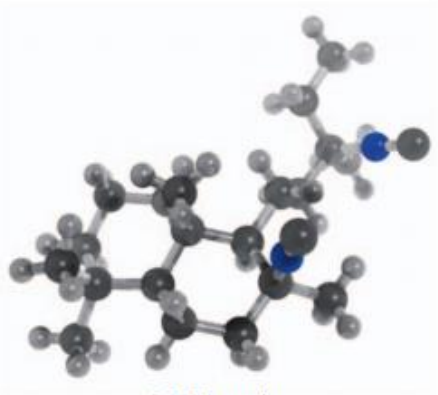
24: 62%, 90:10 d.r.†



25: 44%, 93:7 d.r.†



26: 34%, 88:12 d.r.



26 (X-ray)

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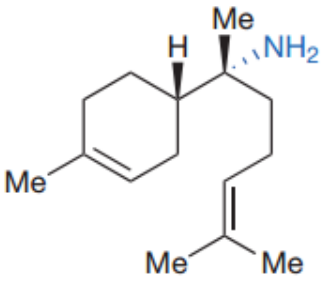
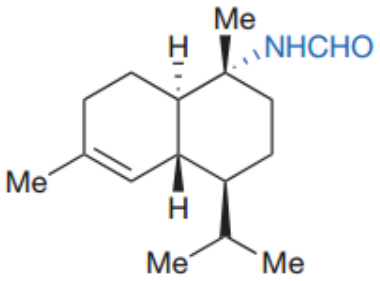
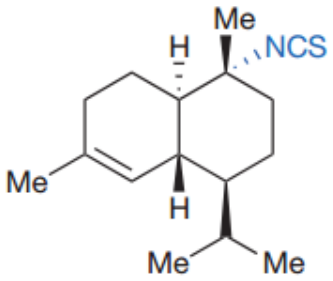
Functionalisation of insonitriles



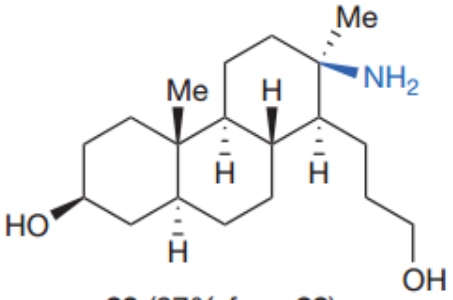
2 (94% from **10**)



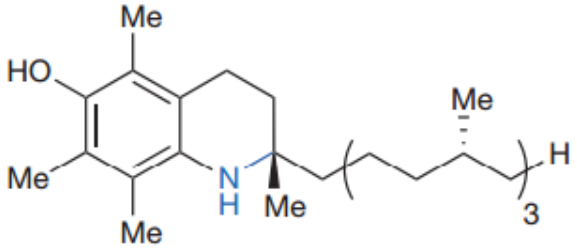
27 (72% from **22**)



28 (59% from **22**)



29 (97% from **23**)



30 (87% from **24**)

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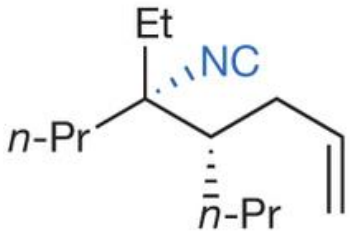
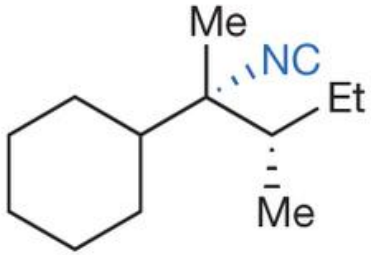
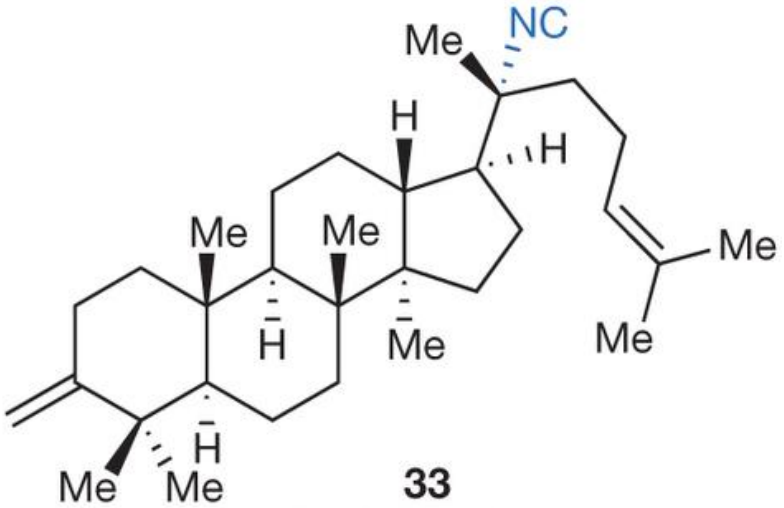
Limitations



31
58%, 70:30 d.r.



32
78%*, 63:37 d.r.



33
80%, 58:42 d.r.

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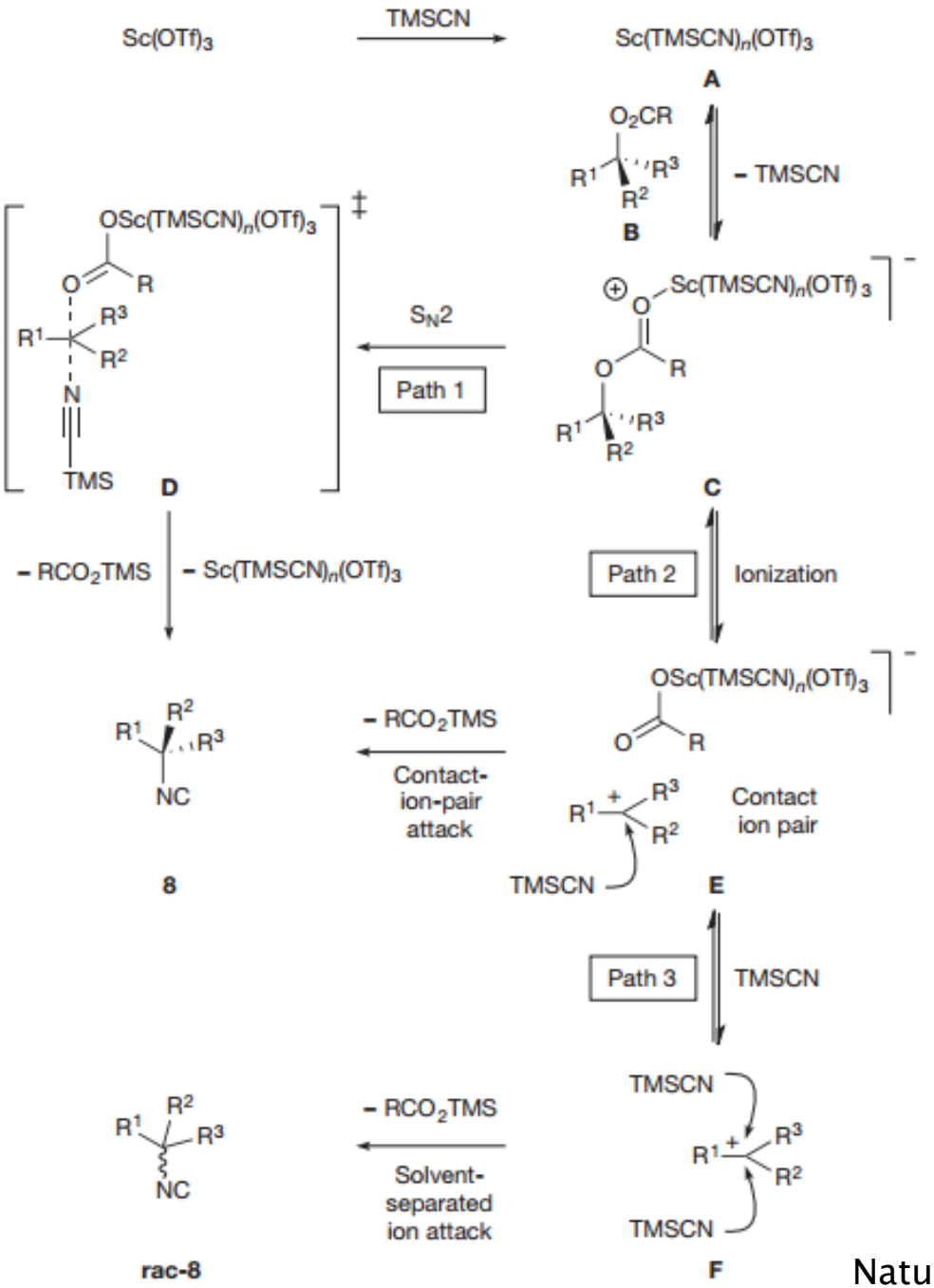

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Summary

- Have discussed the development of a stereoselective inversion of a tertiary activated alcohol.
- It is believed to take place by an S_N1 process where a tight ion pair negates attack from one face on the planar carbocation.
- Have discussed the scope and limitations of the methodology.
- Due to its mild conditions and complementary reactivity to current methodology this should find broad applications in the synthesis of natural products.