Total Syntheses of Lyconadins A–C

Takuya Nishimura, Aditya K. Unni, Satoshi Yokoshima, and
Tohru Fukuyama

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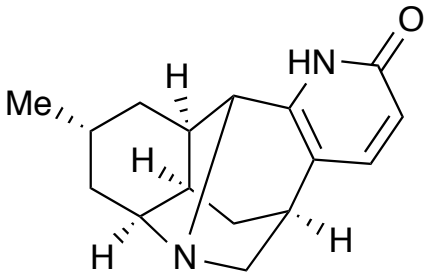
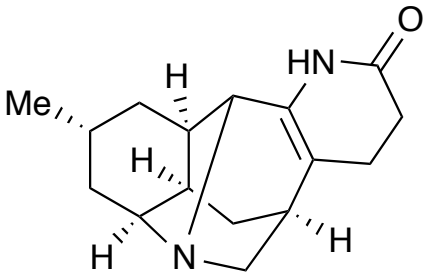
Kyu Ok Jeon
Wipf Group – Current Literature
Feb-23-2013

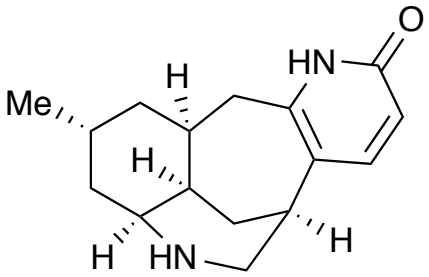
Structure of lyconadins A–C



lyconadin A (**1**)



lyconadin B (**2**)



lyconadin C (**3**)

Lyconadin A was isolated from *Lycopodium complanatum* in 2001 by Kobayashi et al.

The first total synthesis of (+)-lyconadin A was accomplished by Beshore and Smith in 2007.

Sarpong and coworkers reported the total syntheses of (±)- and (+)-lyconadin A.

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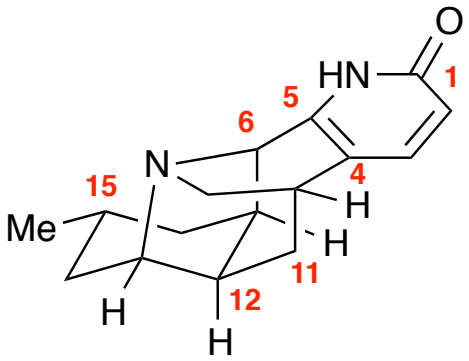
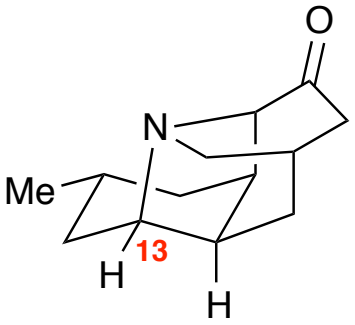
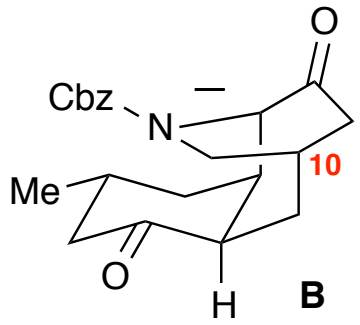
Retrosynthetic Analysis: Smith's Work



lyconadin A

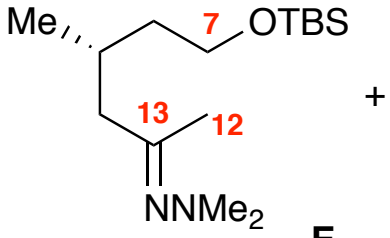


A



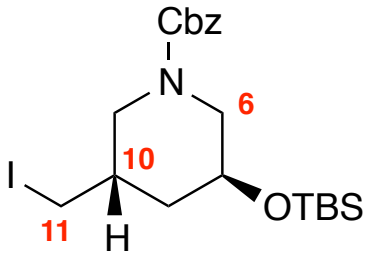
B

intramolecular conjugate addition

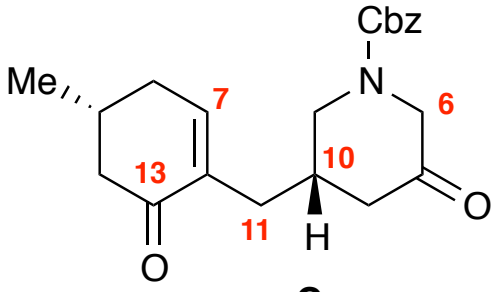


E

+

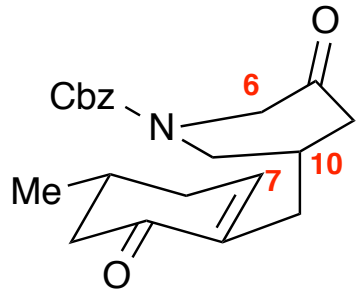


D



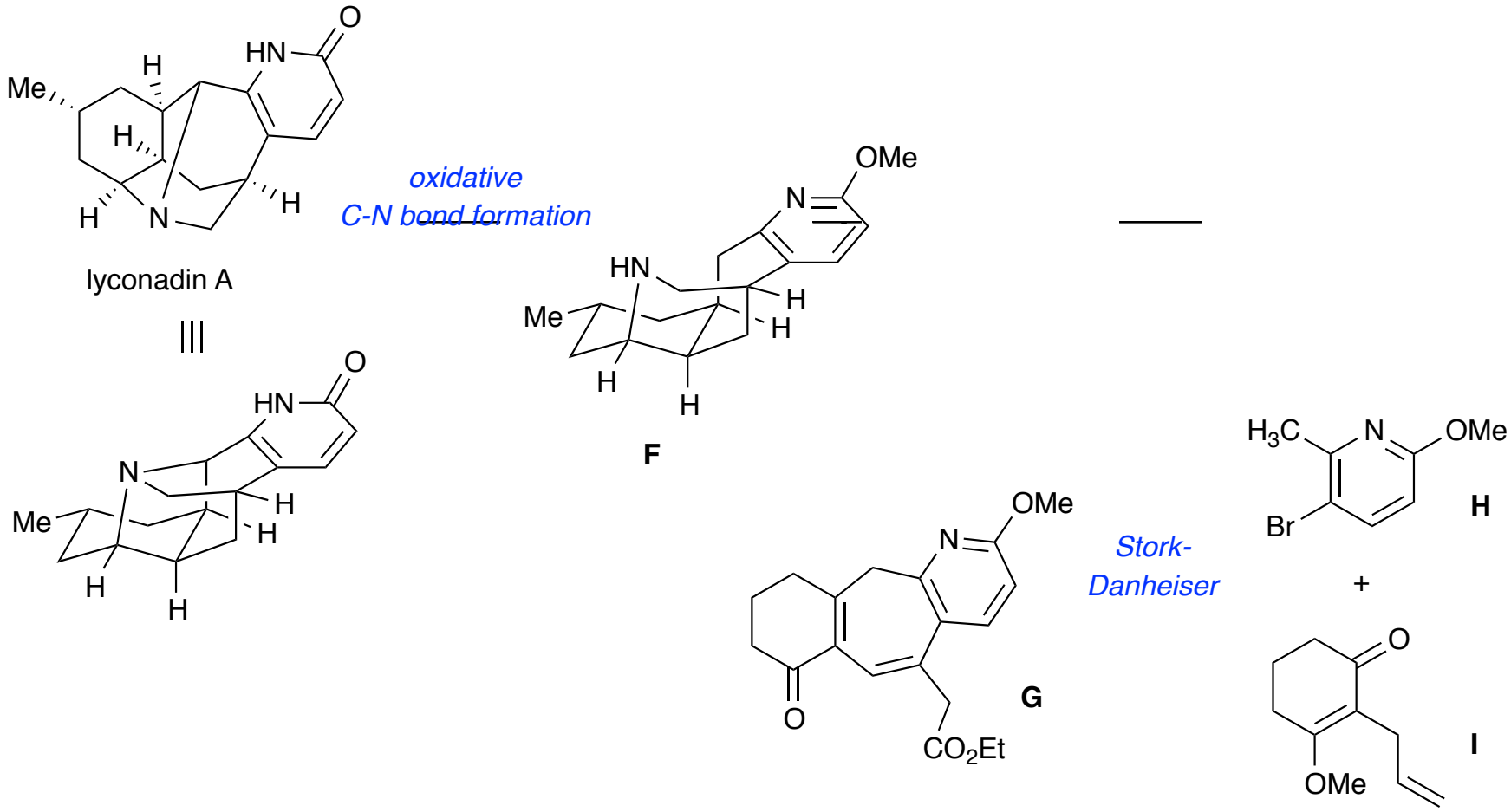
C

≡



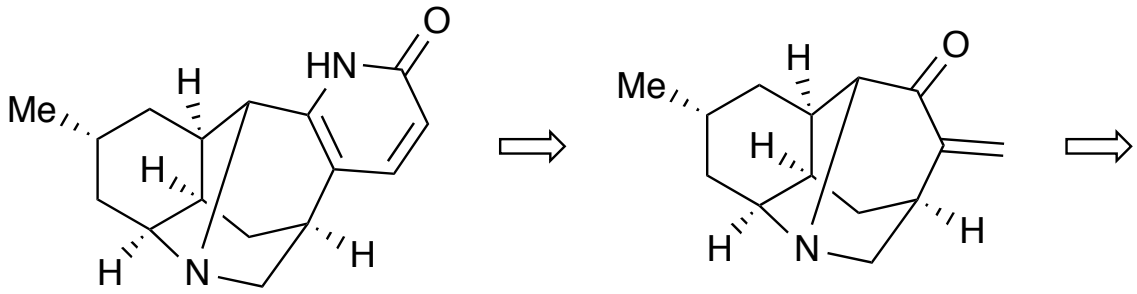
Beshore, D. C.; Smith, A. B., III. *J. Am. Chem. Soc.* **2007**, *129*, 4148–4149.
Beshore, D. C.; Smith, A. B., III. *J. Am. Chem. Soc.* **2008**, *130*, 13778–13789.

Retrosynthetic Analysis: Sarpong's Work

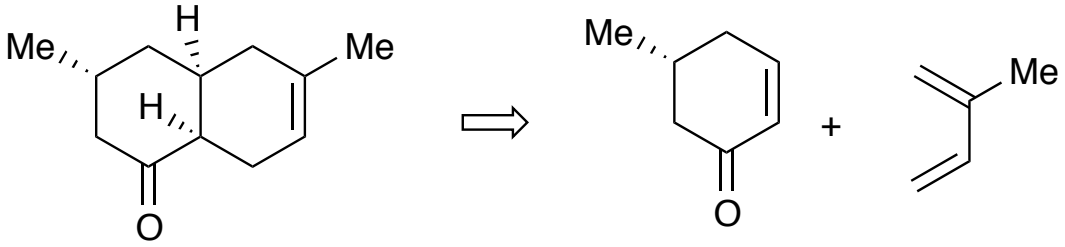


Bisai, A.; West, S.; Sarpong, R. *J. Am. Chem. Soc.* **2008**, *130*, 7222–7223.
West, S.; Bisai, A.; Lim, A. D.; Narayan, R. R.; Sarpong, R. *J. Am. Chem. Soc.* **2009**, *131*, 11187–11194.

Retrosynthesis



lyconadin A (**1**) **4**



5 **6** **7**

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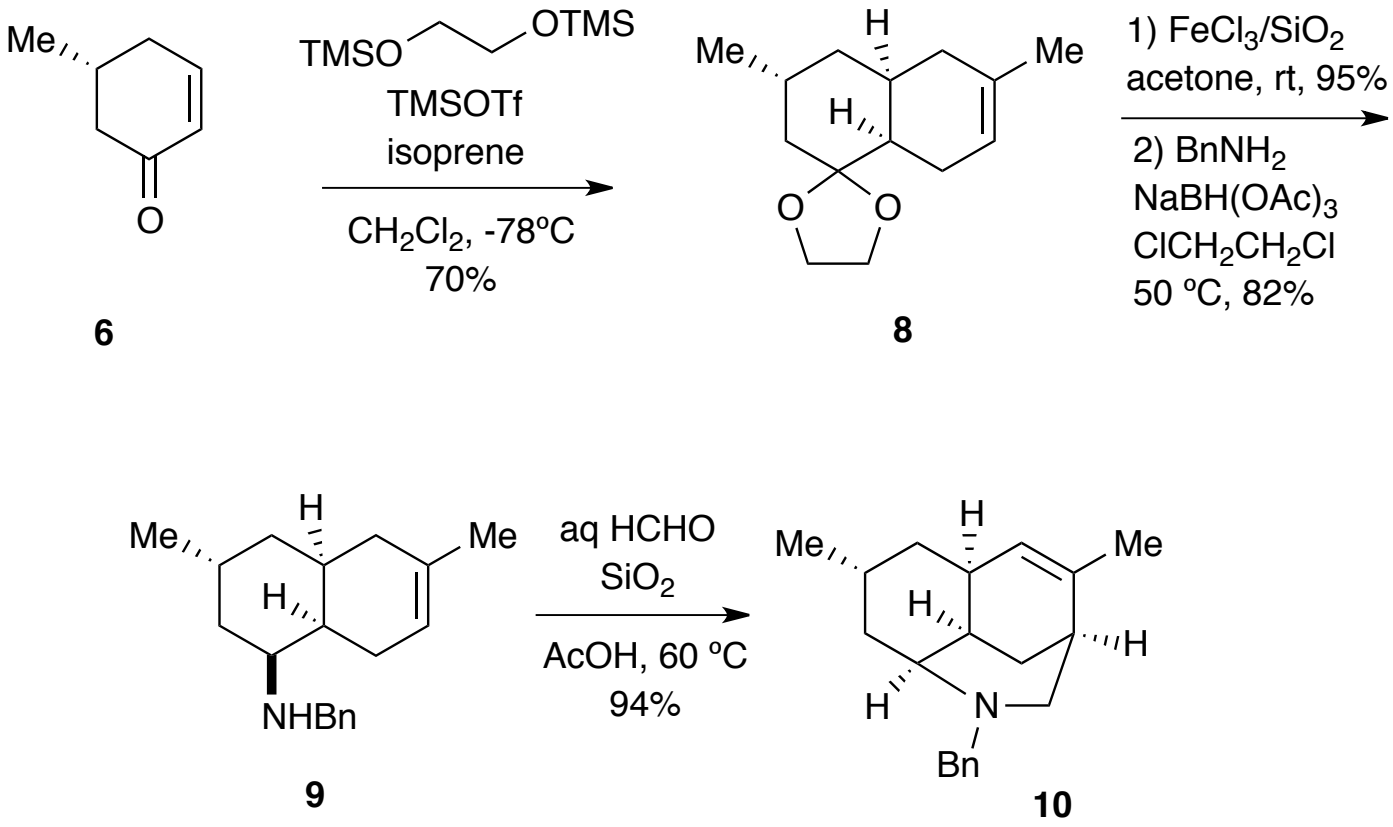
Diels-Alder Reaction and Aza-Prins Reaction



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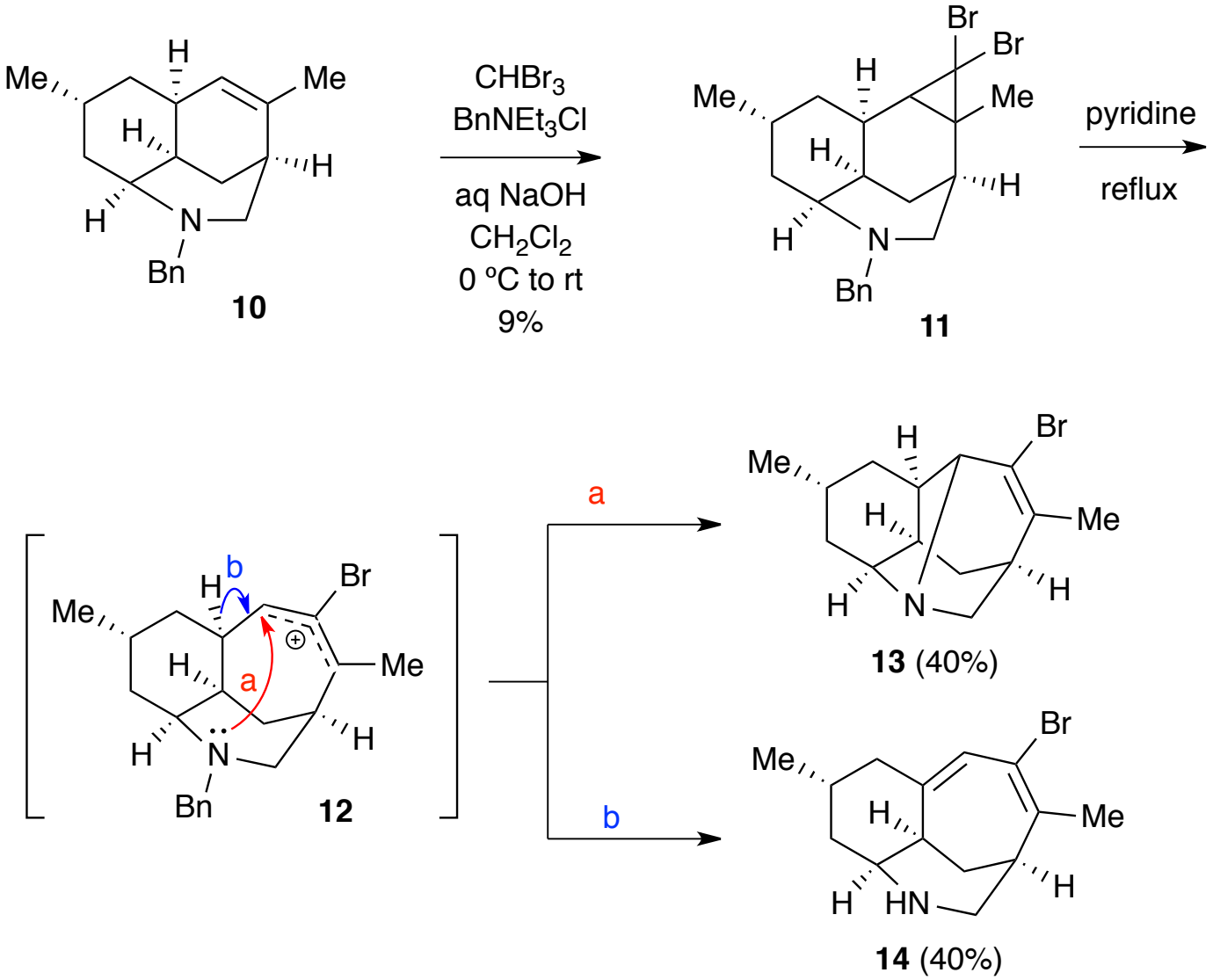
Attempted Formation of Tetracyclic Core



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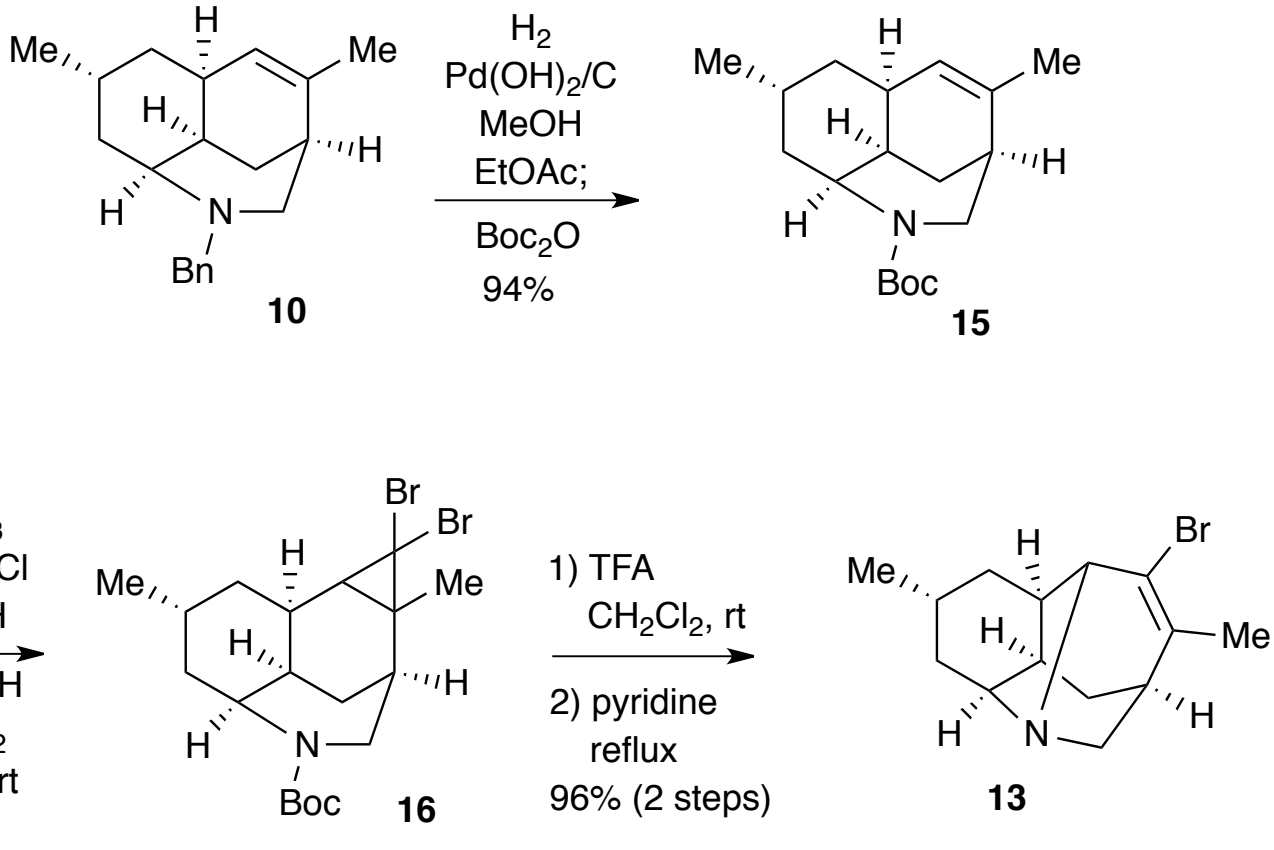
Construction of Tetracyclic Skeleton



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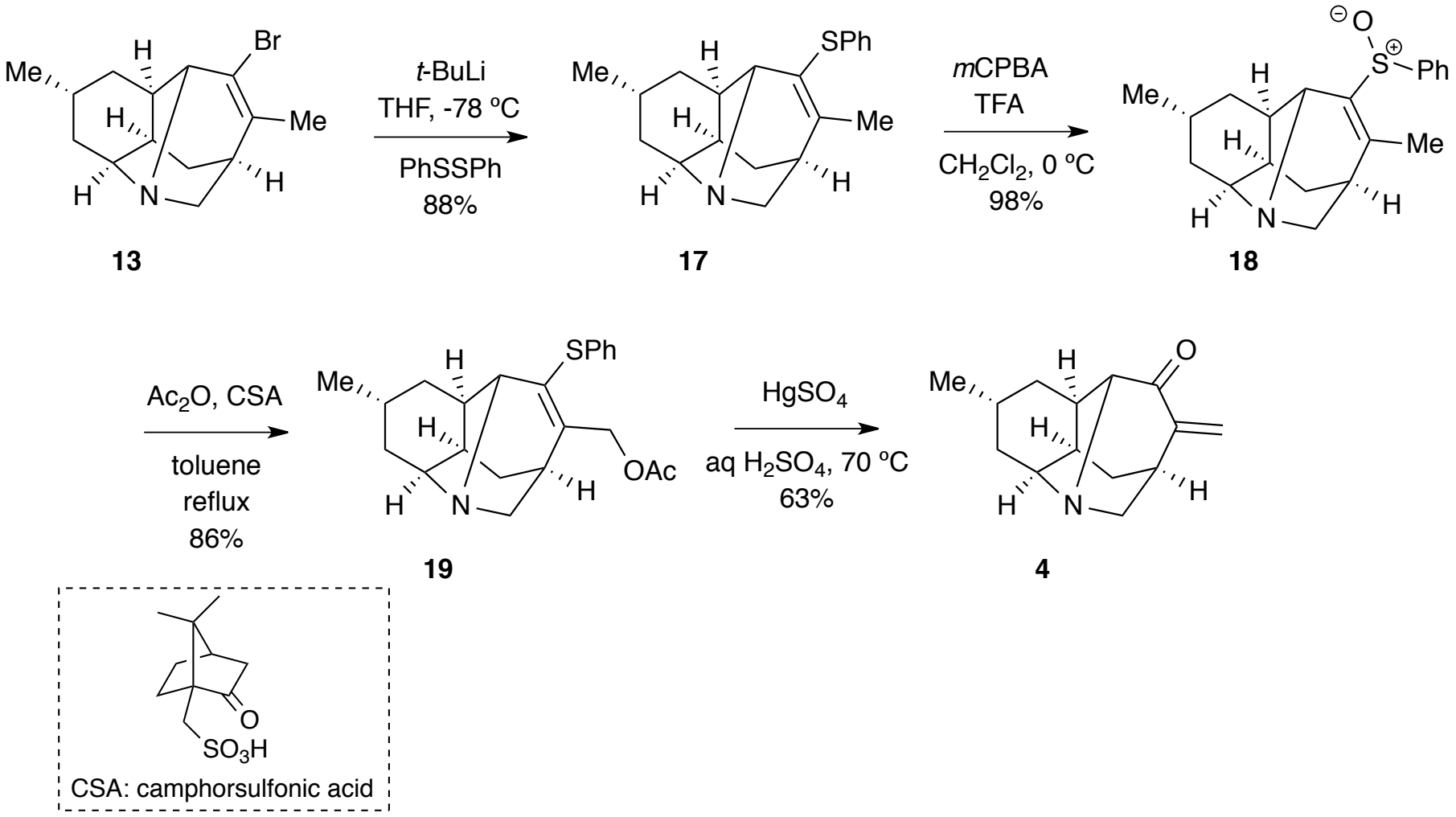
*Transformation into Enone **4** via Vinylogous Pummerer Rearrangement*



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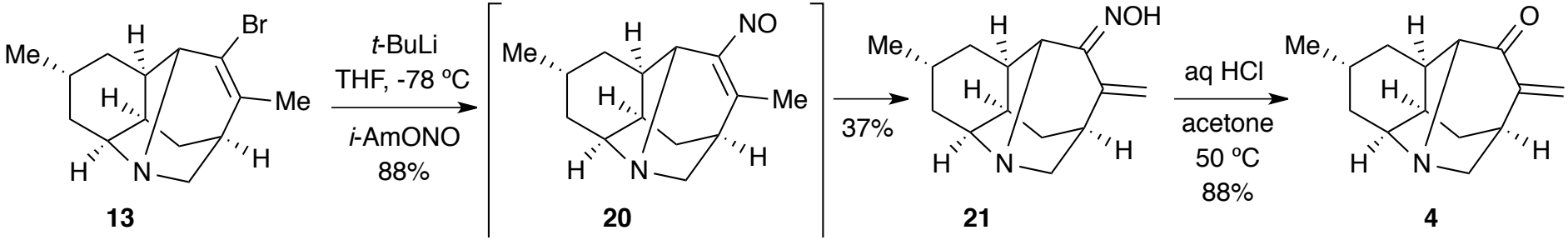
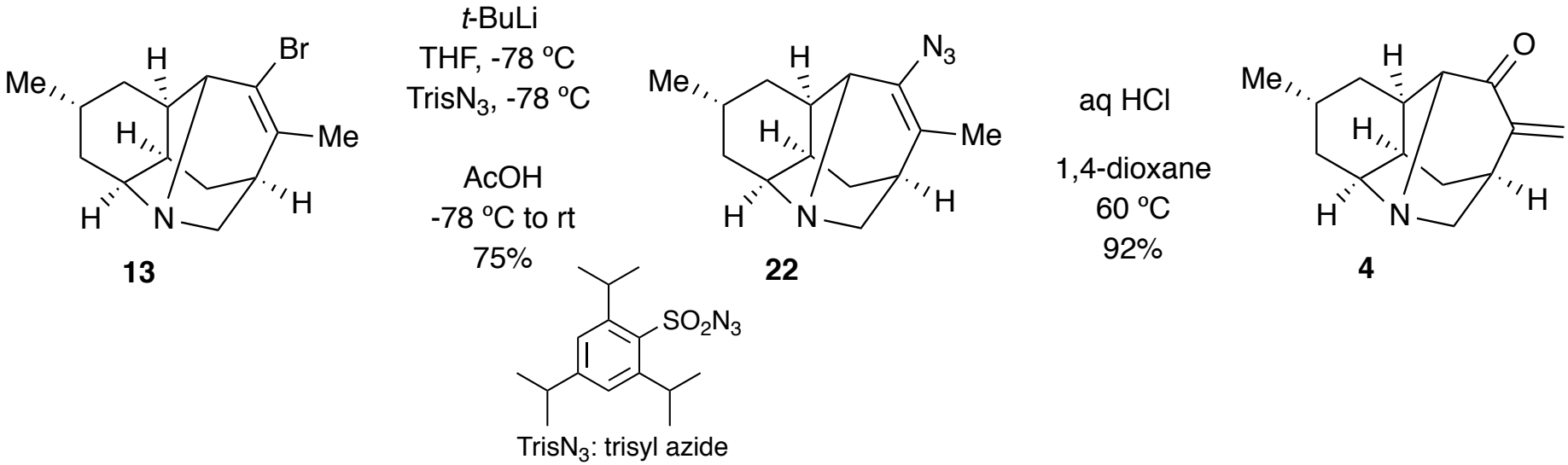
*Transformation into Enone **4** through an Oxime*



*Transformation into Enone **4** through an Azide*



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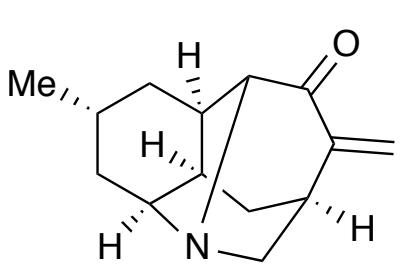
Completion of Synthesis of Lyconadine A



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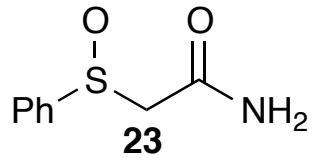
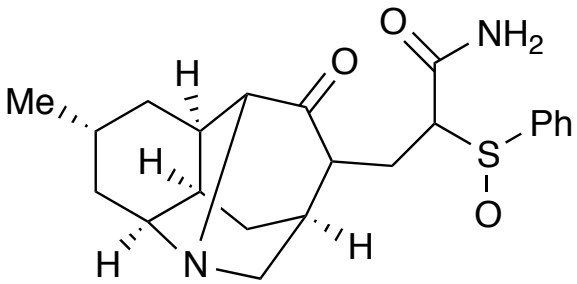


23

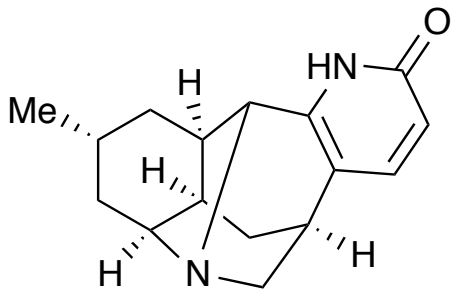
NaH, THF
0 ºC



24

HCl

MeOH, rt
90%



lyconadin A (**1**)

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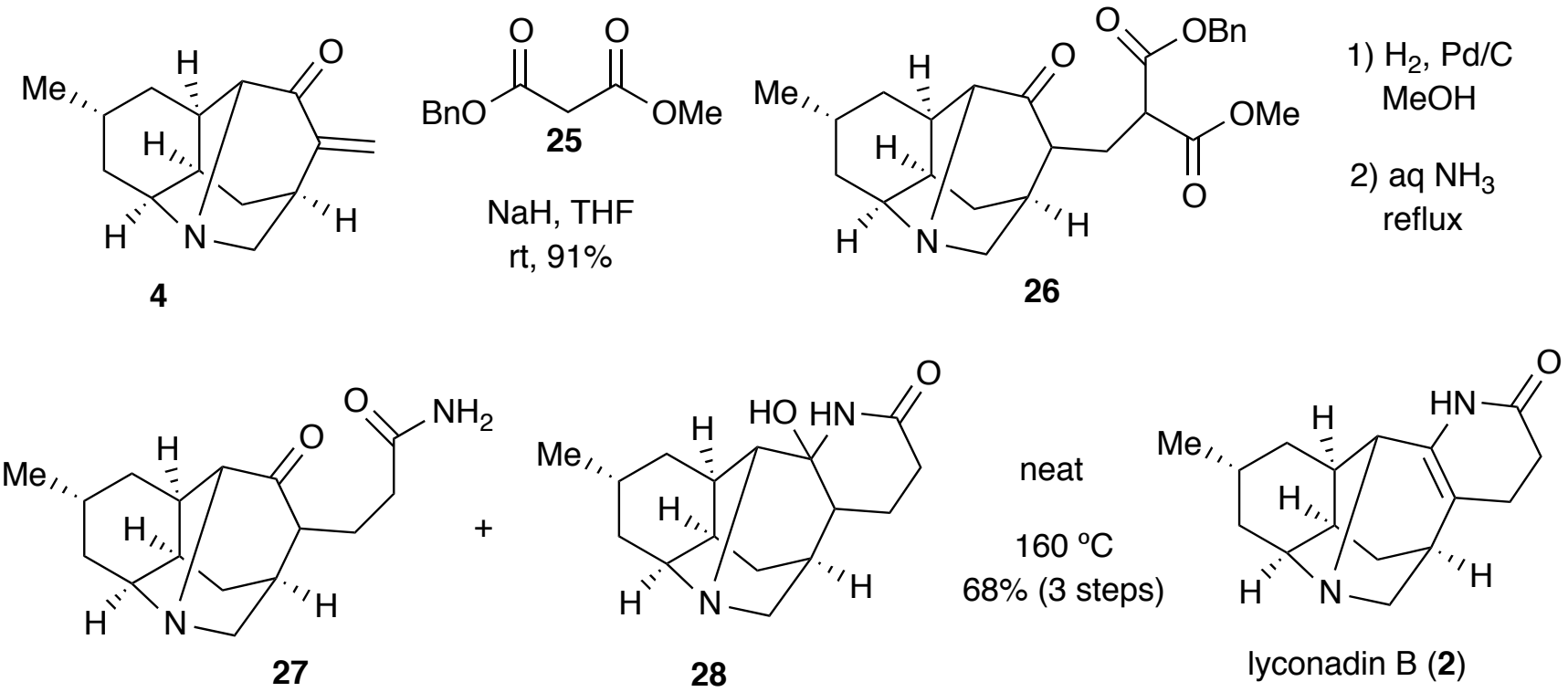
Synthesis of Lyconadine B



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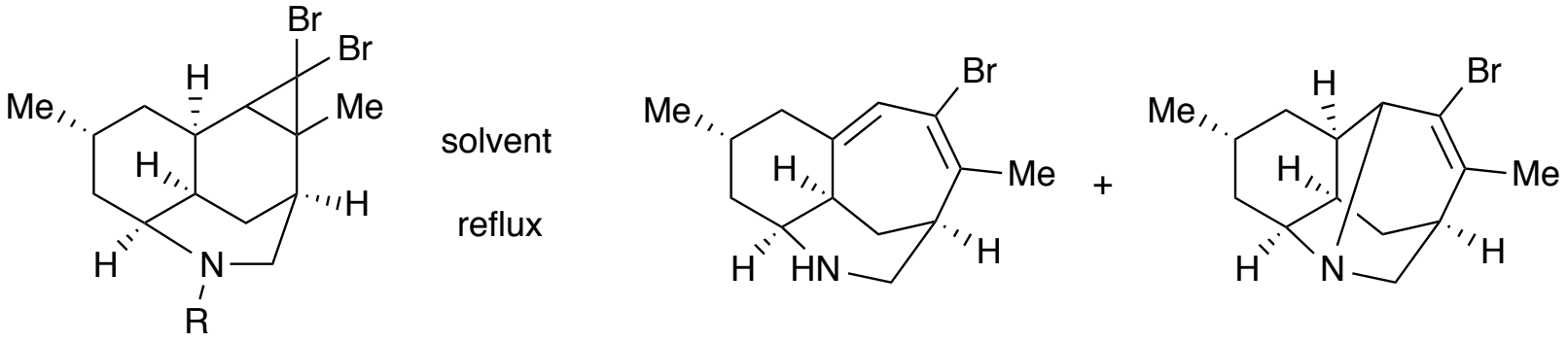
Cleavage of Dibromocyclopropane Ring



29a-e **30a-e** **13**

entry	R	substrate	solvent	yield[a] (%) 30a–e	yield[a] (%) 13
1	Boc	29a	pyridine	20	46
2	Ts	29b	AcOH	43	51
3	*p*-Ns	29c	AcOH	51	42
4	*o*-Ns	29d	AcOH	89	trace
5	H	29e·HCl	AcOH	62	20
6	H	29e·HCl	HCO_2H	74	*b*

[a]Isolated yields. [b]Compound **13** could not be detected.

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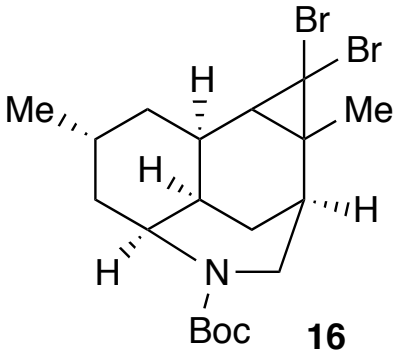
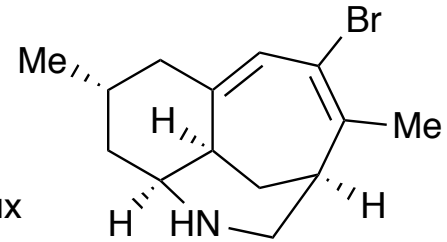
Synthesis of Lyconadine C



16

aq HCl
HCO_2H

rt then reflux

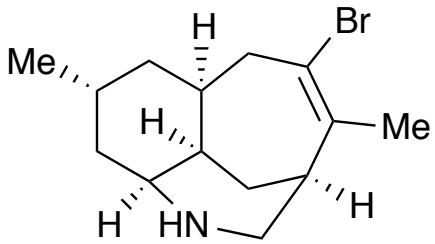


30e

$TsNHNH_2$
NaOAc

$DME\text{-}H_2O$
85 ºC

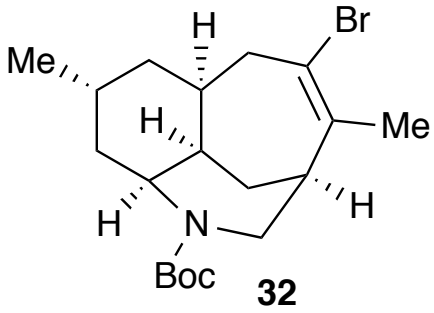
63% (2 steps)



31

Boc_2O

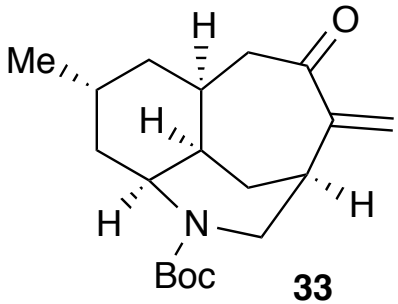
CH_2Cl_2
rt, 96%



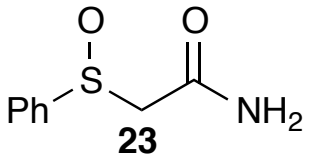
32

*m*CPBA

CH_2Cl_2,rt
43%



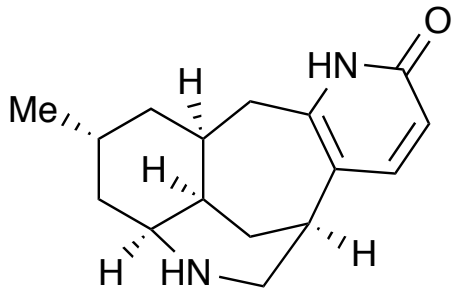
33



23

NaH, THF
0 ºC to 40 ºC

HCl, MeOH
40 ºC, 63%



lyconadin C (**3**)

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Conclusion

- Completed the total syntheses of lyconadin A, B and C.

- Synthetic highlights include:

the highly fused tetracyclic skeleton: a combination of an aza-Prins reaction and an electrocyclic ring opening, followed by formation of a C–N bond.

enone **4** compound was prepared from three methods via sulfide, oxime, or azide intermediates.