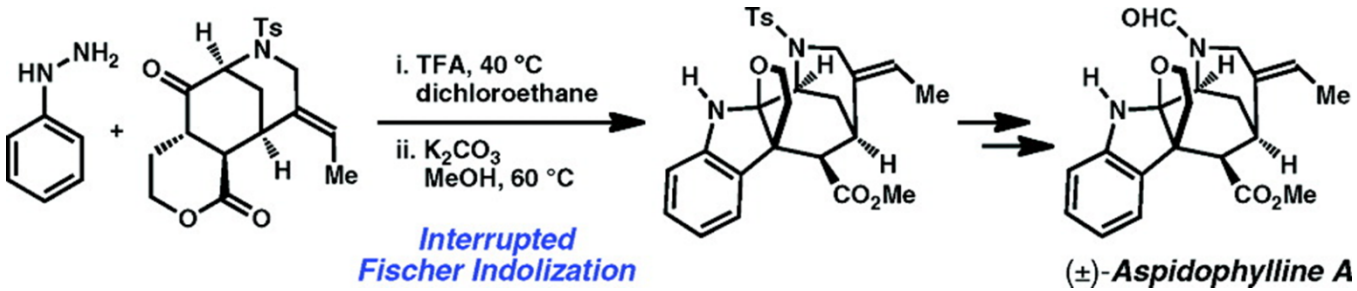
Total Synthesis of (±)-Aspidophylline A

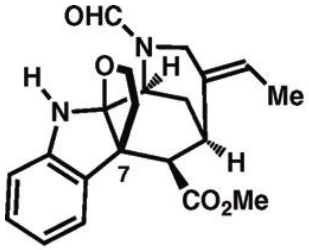
Liansuo Zu, Ben W. Boal, and Neil K. Garg. *J. Am. Chem. Soc*, 2011, ASAP
DOI: 10.1021/ja203227q



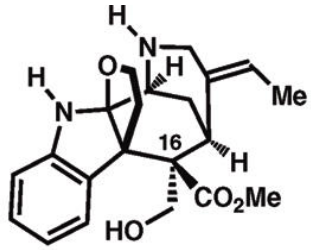
Liming Cao
Wipf Group Current Literature
6/18/2011

Indole alkaloids: Aspidophylline A

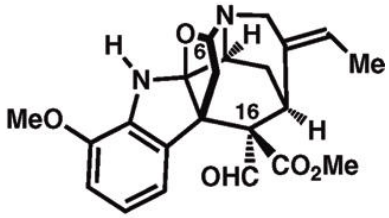
- The Apocynaceae family of plants is a particularly rich source of indole alkaloids, and found predominantly in Southeast Asia.



Aspidophylline A (1)



Aspidodasycarpine (2)

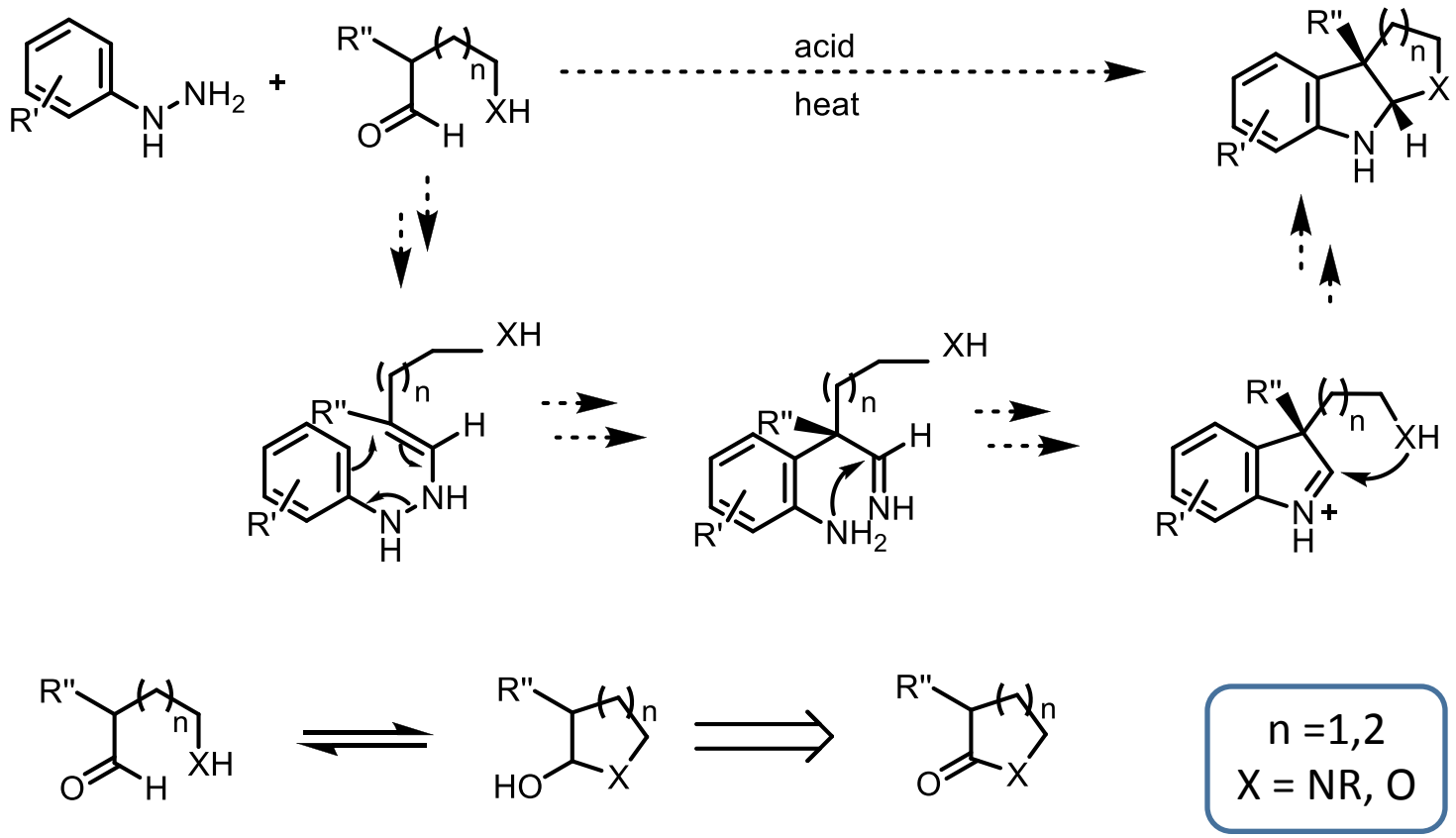


Vincarinine (3)

- Aspidophylline A was first isolated by Kam and co-workers in 2007 from the stem-bark of *K. singapurensis.*
- Aspidophylline A was found to reverse drug resistance in resistant KB cells.
- Synthetic challenges: the tricyclic furoindoline motif, a cyclohexyl ring containing five contiguous stereogenic centers, and a bridged [3.3.1] bicycle.

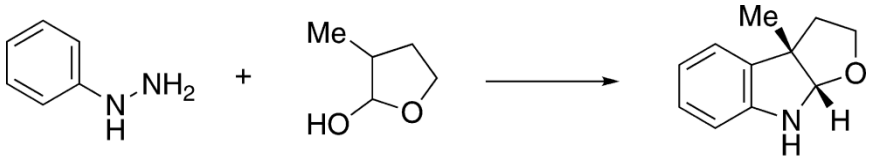
Kam, T.-S. *Alkaloids: Chem. Biol. Perspect*.**1999**, 14, 285–435
Kam, T.-S.; Choo, Y. M. *Alkaloids (San Diego)*. **2006**, 63, 181–337
Subramaniam, G.; Hiraku,O.; Hayashi, M.; Koyano, T.; Komiyama, K.; Kam, T.-S. J. *Nat. Prod.* **2007**, 70, 1783–1789.
http://www.natureloveyou.sg/Plants-K.html

Interrupted Fischer Indolization



Boal, B. W.;Schammel, A. W.; Garg, N. K. *Org. Lett*. **2009**, 11, 3458–3461.
Schammel, A. W.; Boal, B. W.; Zu, L.; Mesganaw, T.; Garg, N. K. *Tetrahedron* **2010**, 66, 4687–4695

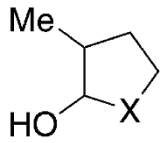
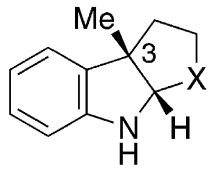
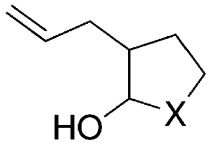
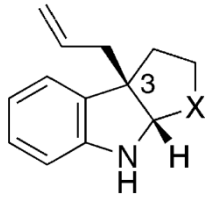
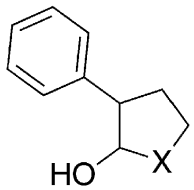
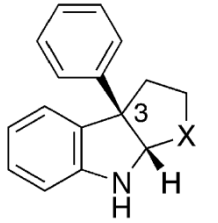
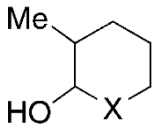
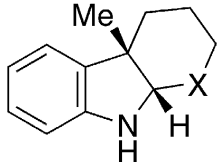
Previous work



acid source	conditions	yield[a](%)
PCl_3	Benzene,60℃	<5
$ZnCl_2$	EtOH,100℃	<5
TsOH	EtOH, H_2O,60℃	51
TFA	CH_3CN,60℃	64
5% HCl	CH_3CN, 60℃	70
4%H_2SO_4	CH_3CN,60℃	87
AcOH	AcOH,60℃	52
AcOH	1:1AcOH/H_2O,60℃	89[b]

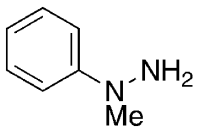
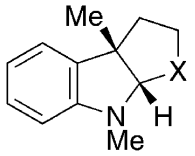
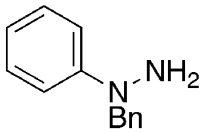
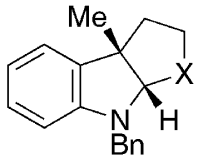
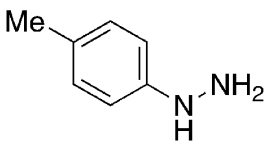
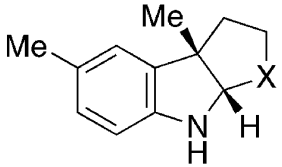
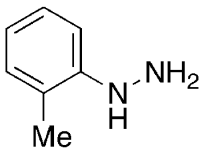
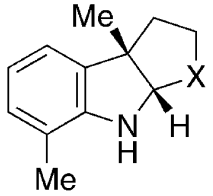
[a] Yields determined by ^1H NMR analysis.
[b] Isolated yield.

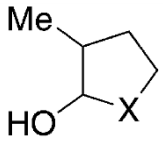
Boal, B. W.;Schammel, A. W.; Garg, N. K. *Org. Lett*. **2009**, 11, 3458–3461.

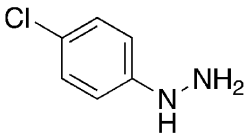
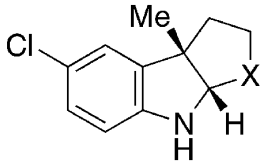
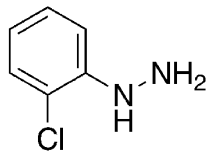
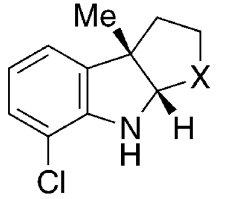
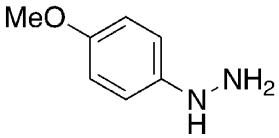
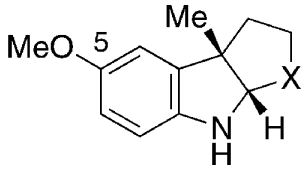
aldehyde surrogate		product	yield[c](%)
	X[a] =O		89%
	X[b]=NTs		88%
	X[a]=O		89%
	X[b]=NTs		68%
	X[a]=O		75%
	X[b]=NTs		70%
	X[a]=O		65%
	X[b]=NTs		81%

[a] 1:1 AcOH/H_2O, 60℃; [b] 1:1 AcOH/H_2O, 60℃;
[c] Isolated yield.

Previous work

hydrazine		product	yield[f](%)
	X[b]=O		89%
	X[c] =NTs		88%
	X[a] =O		89%
	X[d] =NTs		68%
	X[a] =O		75%
	X[d]=NTs		70%
	X[a] =O		65%
	X[d] =NTs		81%

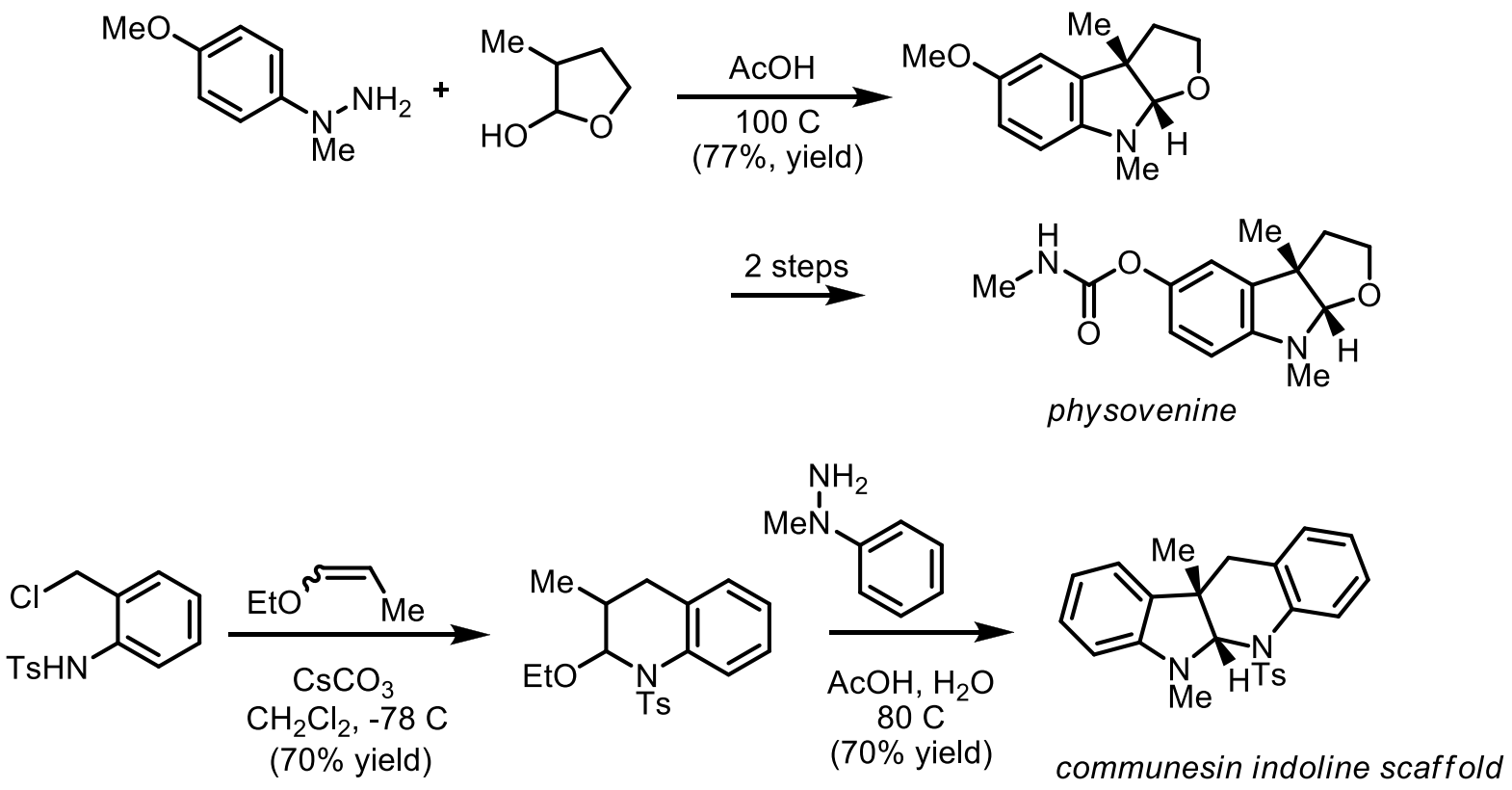


hydrazine		product	yield[f](%)
	X[a] =O		89%
	X[d]=NTs		88%
	X[a] =O		75%
	X[d]=NTs		70%
	X[a] =O		65%
	X[e]=NTs		81%

[a] 1:1 AcOH/ H_2O, 60℃; [b] AcOH, 60℃; [c] AcOH, 23℃; [d] AcOH, 100℃; [e] AcOH, 75℃; [f] Isolated yield.

Boal, B. W.;Schammel, A. W.; Garg, N. K. *Org. Lett*. **2009**, 11, 3458–3461.

Previous work



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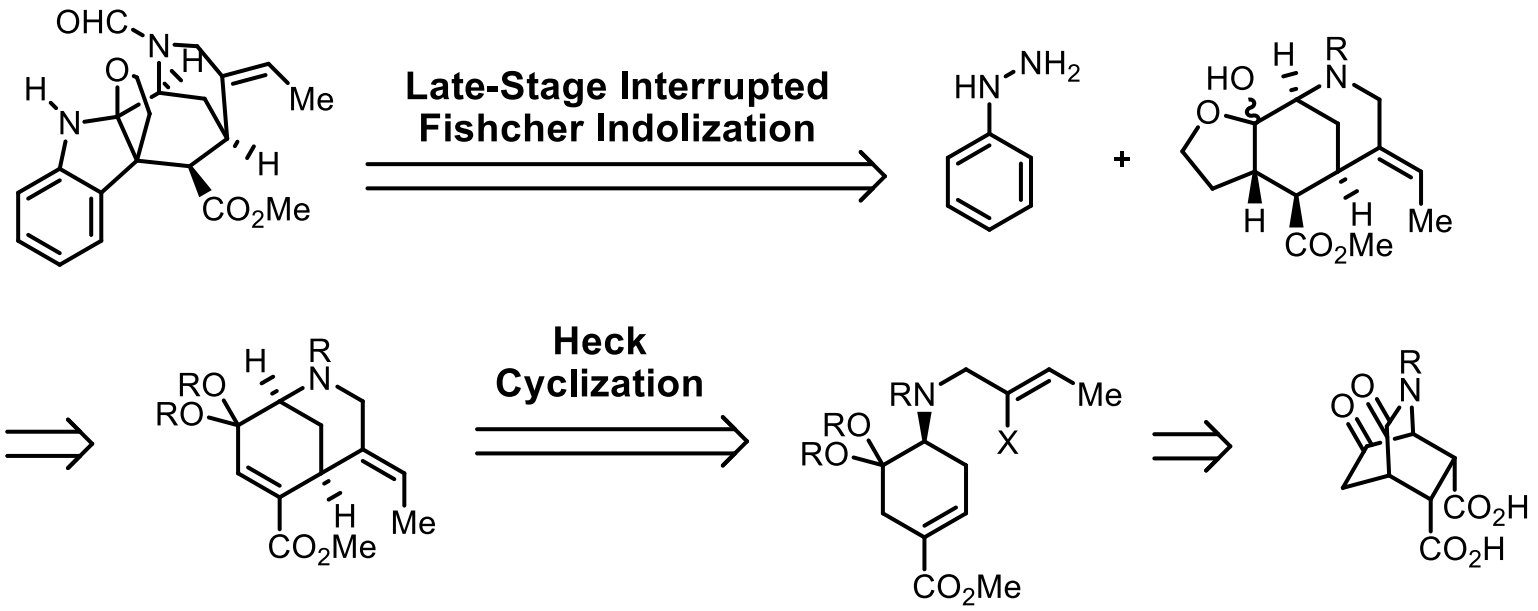
Schammel, A. W.; Boal, B. W.; Zu, L.; Mesganaw, T.; Garg, N. K. *Tetrahedron* **2010**, 66, 4687–4695

Retrosynthetic Analysis



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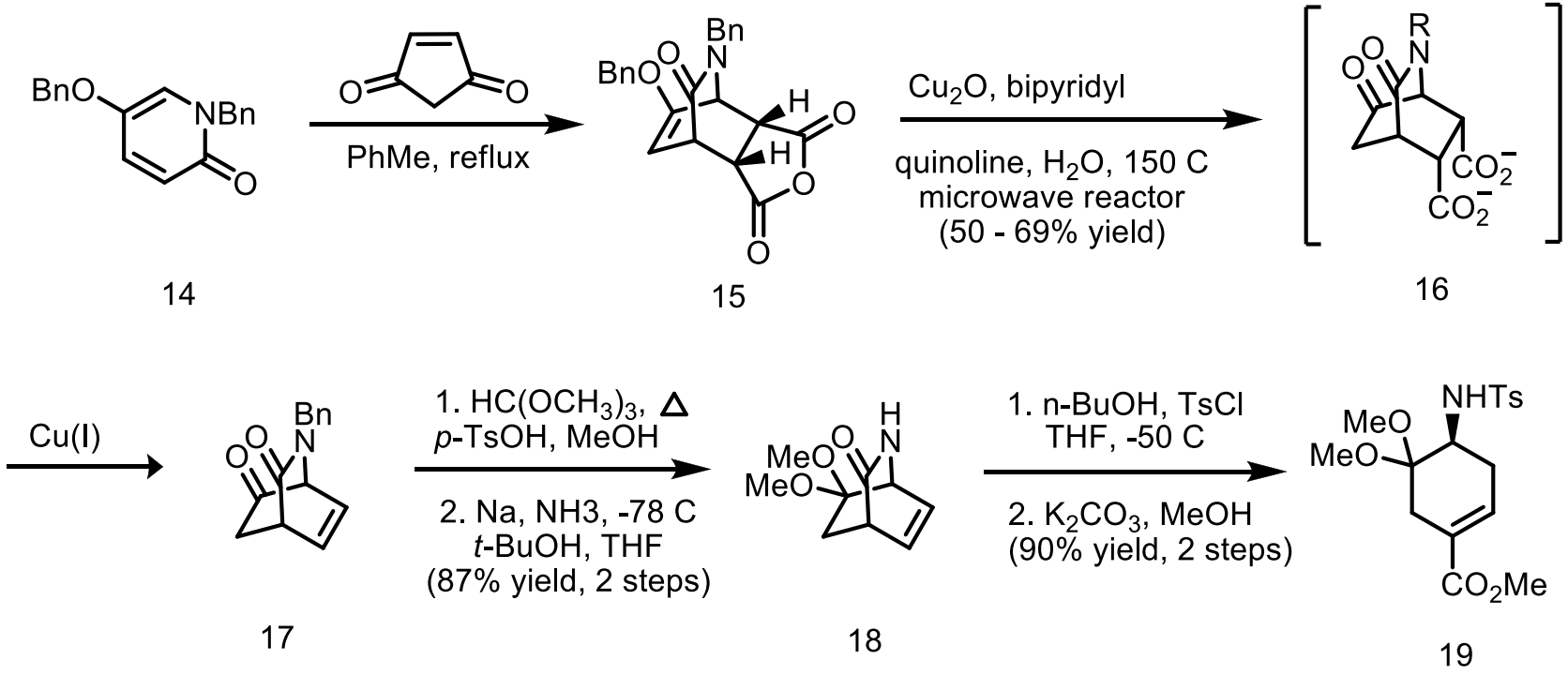
Total Synthesis of (±)-Aspidophylline A



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Herdeis, C., Hartke, C. *Heteroycles* **1989**, 29, 287-296.

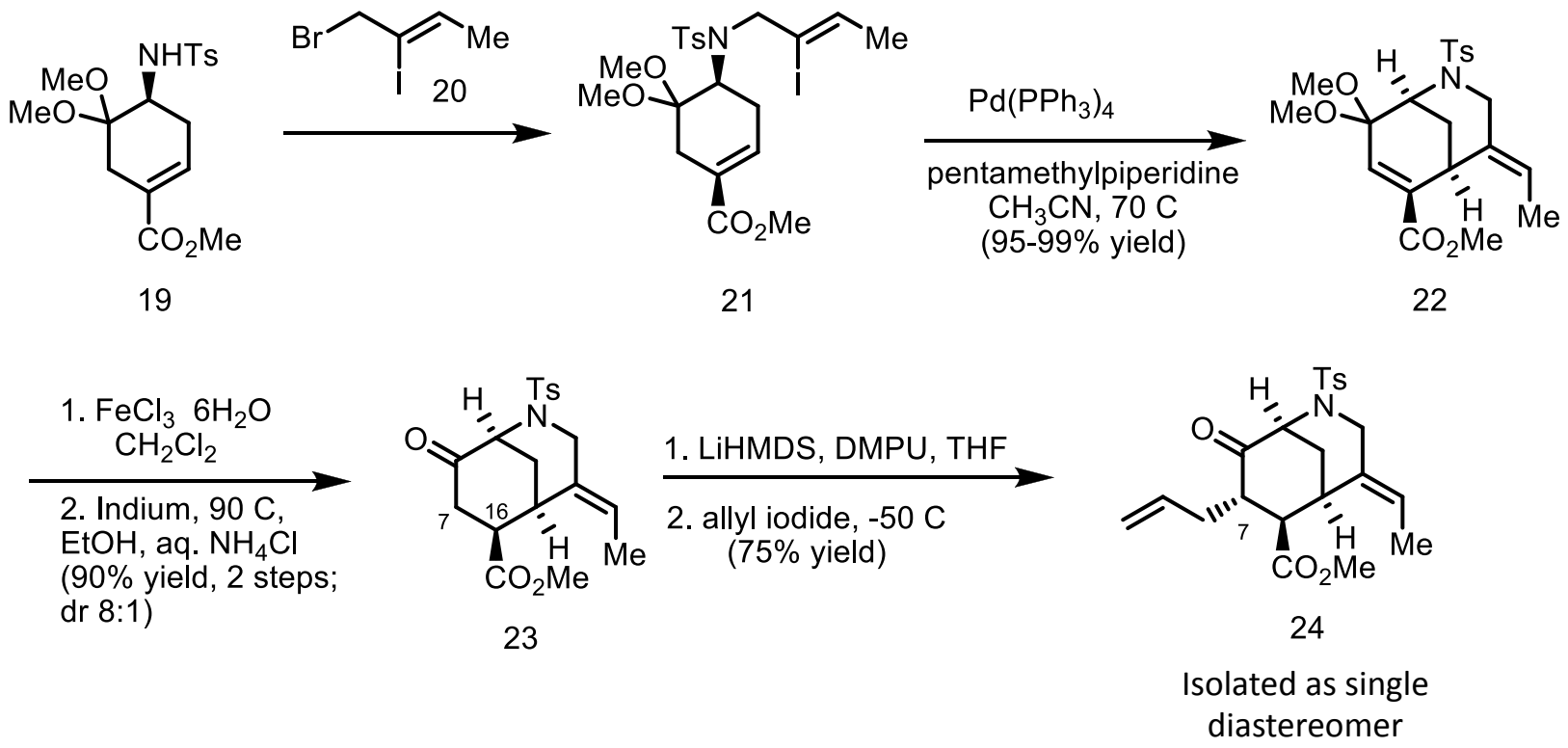
Fessner, W. D.; Sedelmeier, G.; Spurr, P. R.; Rihs, G.; Prinzbach, H. *J. Am. Chem. Soc*. **1987**, 109, 4626–4642.

Snow, R. A.; Degenhardt, C. R.; Paquette, L. A. *Tetrahedron Lett.* **1976**, 17, 4447–4450.

Ensley, H. E.; Buescher, R. R.; Lee, K. *J. Org. Chem*. **1982**, 47, 404–408.

Martin, D. B. C.; Vanderwal, C. D. *J. Am. Chem. Soc*. **2009**, 131, 3472–3473.

Total Synthesis of (±)-Aspidophylline A



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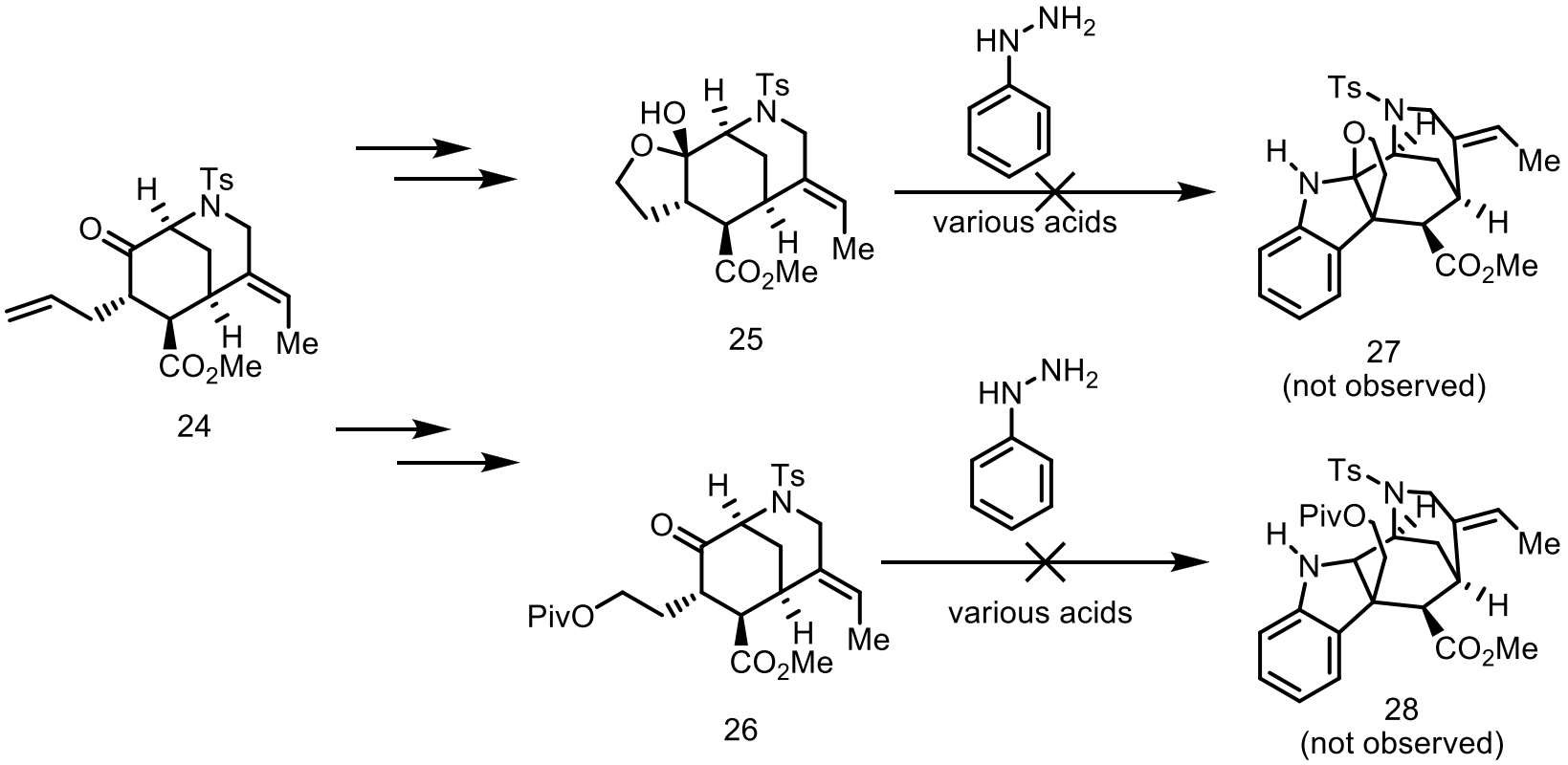

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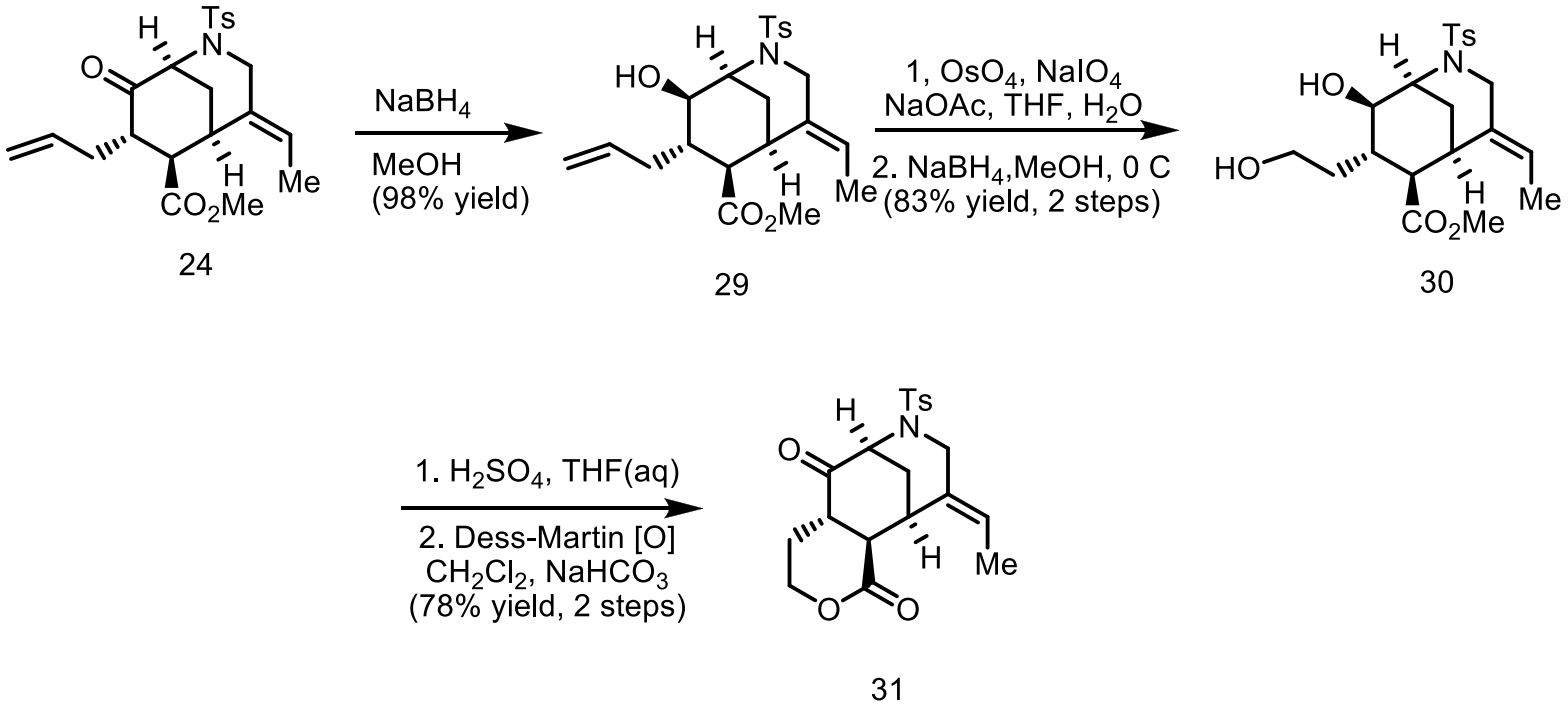

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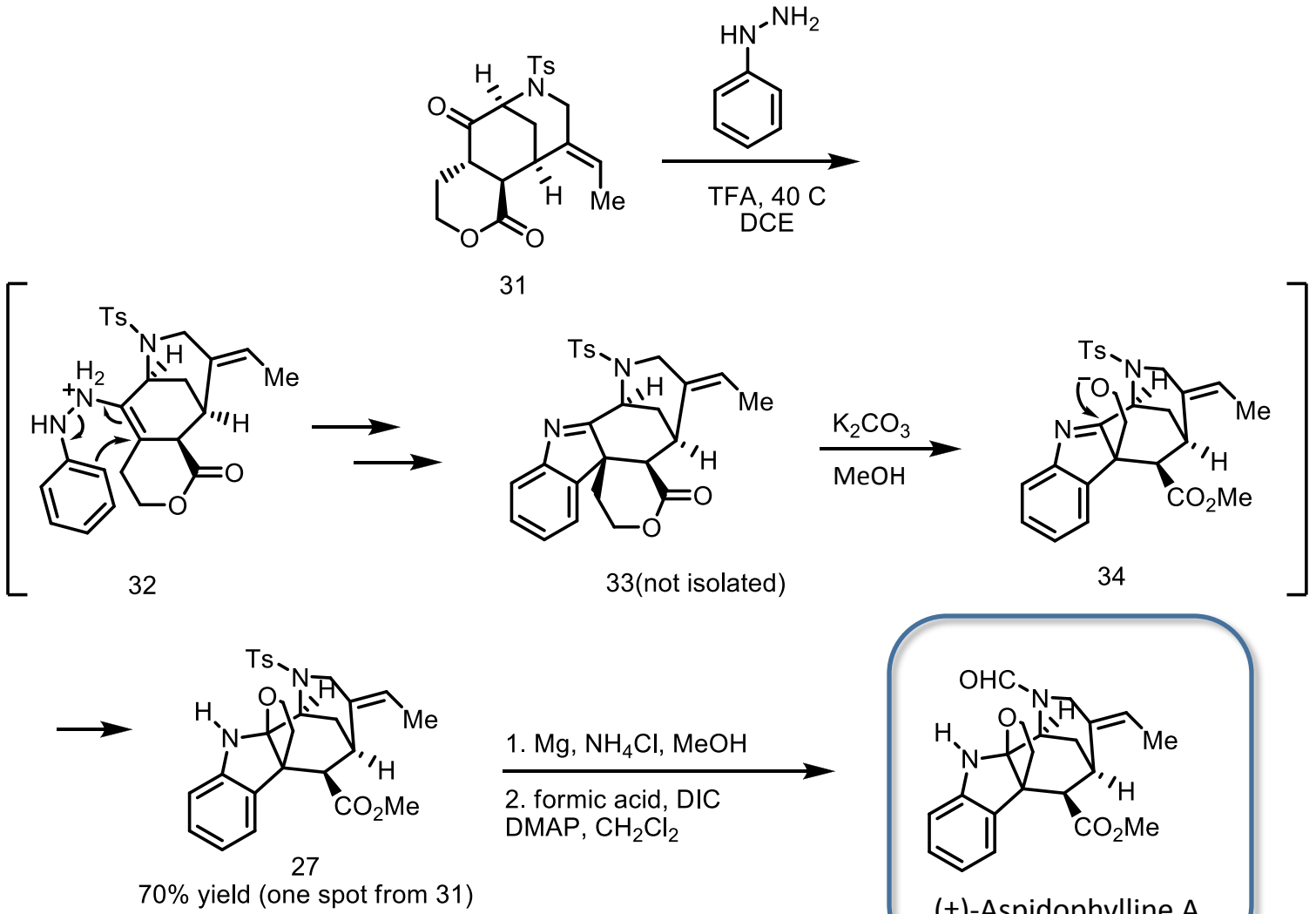

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Conclusion

- The author achieved the first total synthesis of (±)-Aspidophylline A in 18 steps.
- The route features a number of key transformations, including:

1. an oxidative bis(decarboxylation)
2. a Heck cyclization
3. a late stage Interrupted Fischer indolization

- The synthesis of (±)-Aspidophylline A validates the interrupted Fischer indolization approach to intricate indoline-containing natural products and sets the stage for future synthetic endevours.