Total Synthesis of (-)-Conophylline and (-)-Conophyllidine

Yuku Han-ya, Hidetoshi Tokuyama, and Tohru Fukuyama

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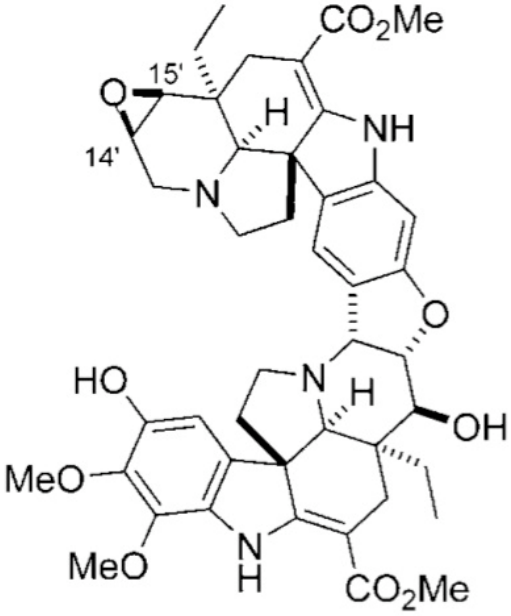
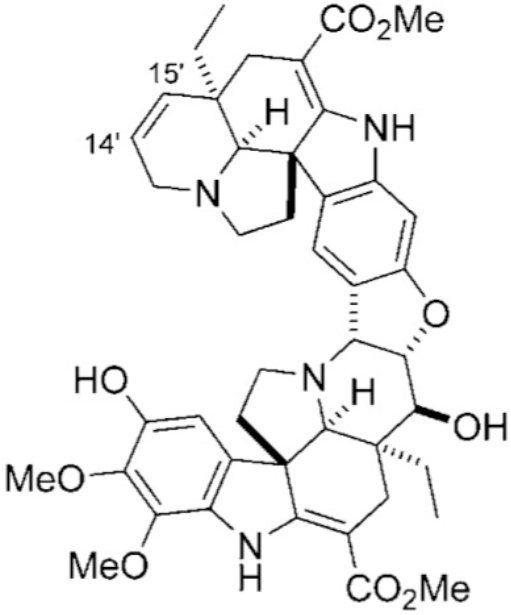


(–)-conophylline (**1**)



(–)-conophyllidine (**2**)

Benjamin R. Eyer
Wipf Group- Current Literture
June 18, 2011

Isolation, Structural Determination and Biological Activity

- *Tabernaemontana divaricata*
  - –Popular garden plant in native to India
  - –Significant variation in alkaloid natural products

- 2 kg of ground leaves from Petaling Jaya, Malaysia
  - –650 mg of conophylline
  - –43 mg of conophyllidine

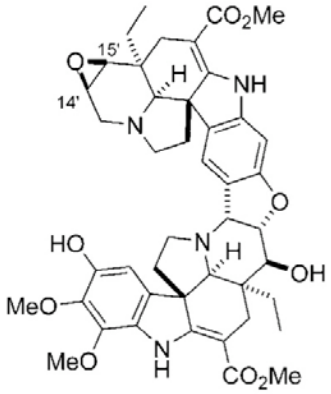
- Characterized by ^{1}H- and ^{13}C-NMR, MS, IR, UV, MP and X-ray crystallography

Kam T.S.; Loh K.-Y.; Lim, L.-H.; Loong, Chuah, C.-H.; Wei, C. *Tet. Let.* **1992**, 33, 969.
Kam T.S.; Loh K.-Y; Wei, C. *J. Nat. Prod.* **1993**, 56, 1865.
Image from: http://www.jungleseeds.com/SeedShop/Conservatory2.htm

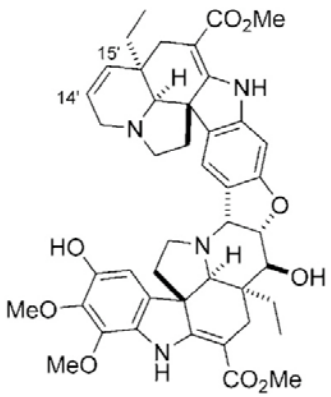
- Bis(indole) alkaloid with two pentacyclic aspidosperma skeletons

- Potent inhibitor the ras function
  - –Potential chemotherapeutic drug

- Induces beta cell differentiation
  - –Regeneration treatment for Diabetes Type I



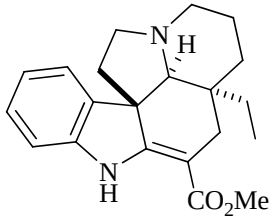
(–)-conophylline (**1**)



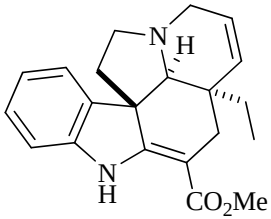
(–)-conophyllidine (**2**)

Umezawa, K.; Ohse, T.; Yamamoto, T.; Koyano, T.; Takahashi, Y. *Anticancer Res*. **1994**, 14, 2413.
Amino, N.; Ohse, T.; Koyano, T.; Umezawa, K. *Anticancer Res*. **1996**, 16, 55.
Ogata, T.; Li, L.; Yamada, S.; Yamamoto, Y.; Tanaka, Y.; Takei, I.; Umenzawa, K.; Kojima, I. *Diabetes*. **2004**, 53, 2596.

(±)-Vincadifformine and (-)-Tabersonine



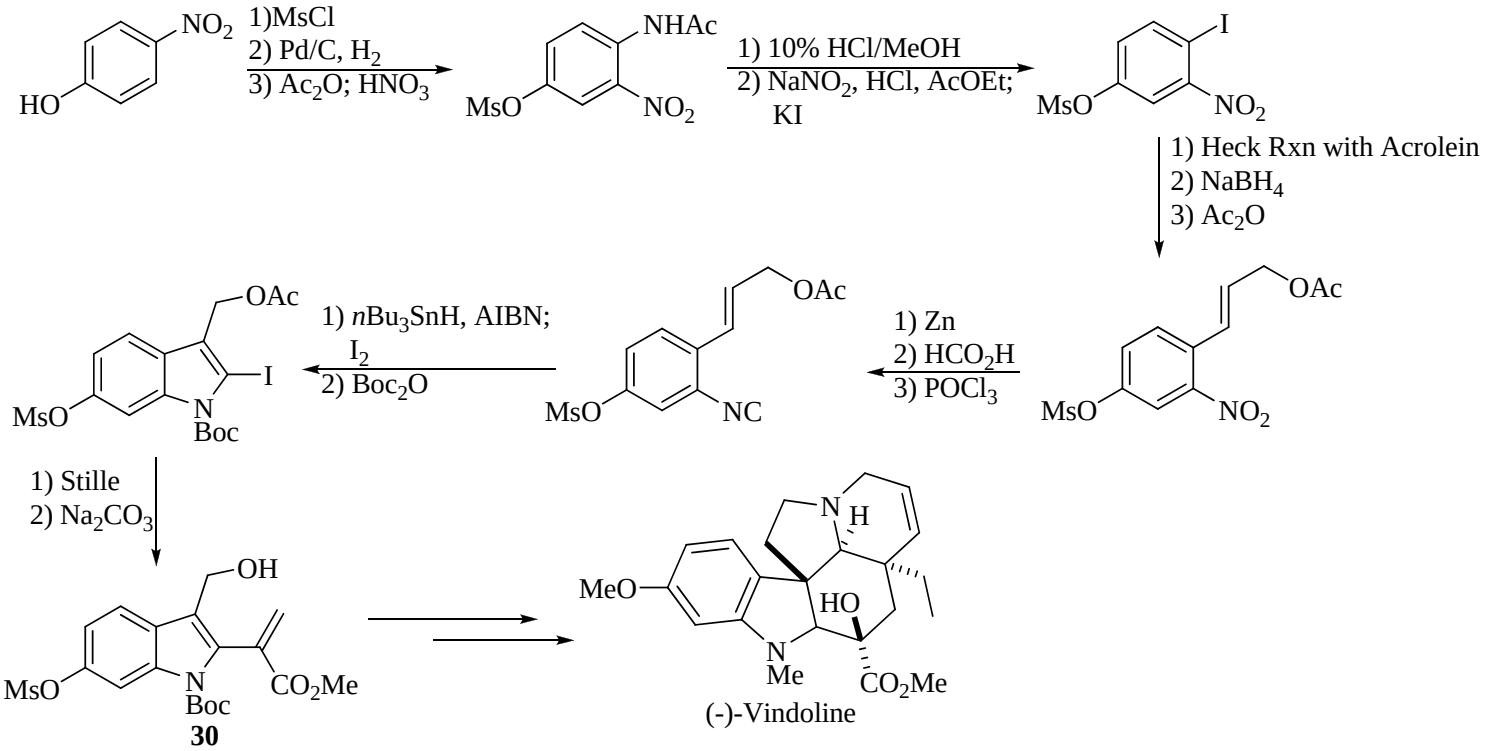
(±)-Vincadifformine



(-)-Tabersonine

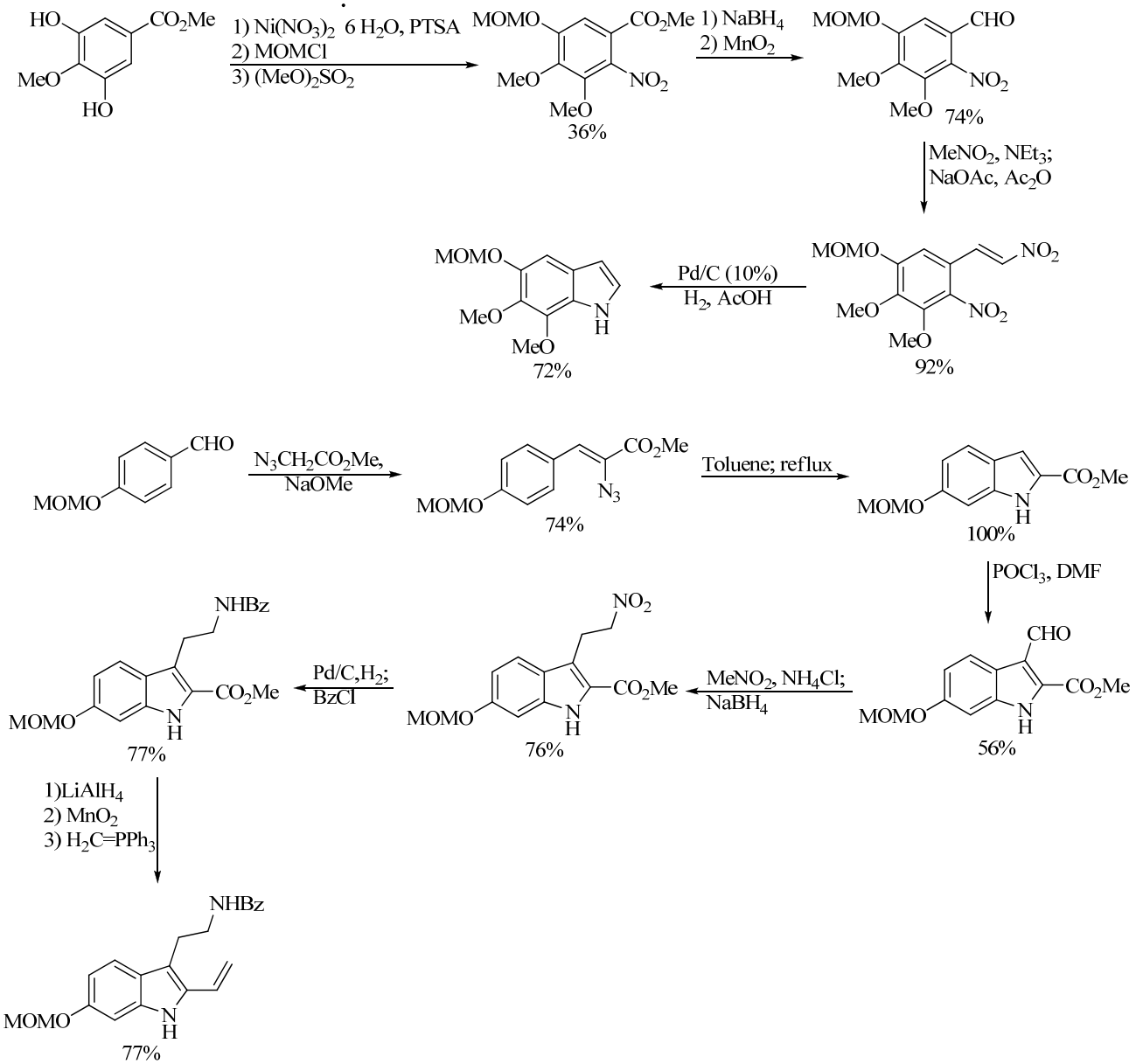
Kobayashi, S.; Peng, G.; Fukuyama, T. *Tet. Let.* **1999**, 40, 1519.

(-)-Vindoline



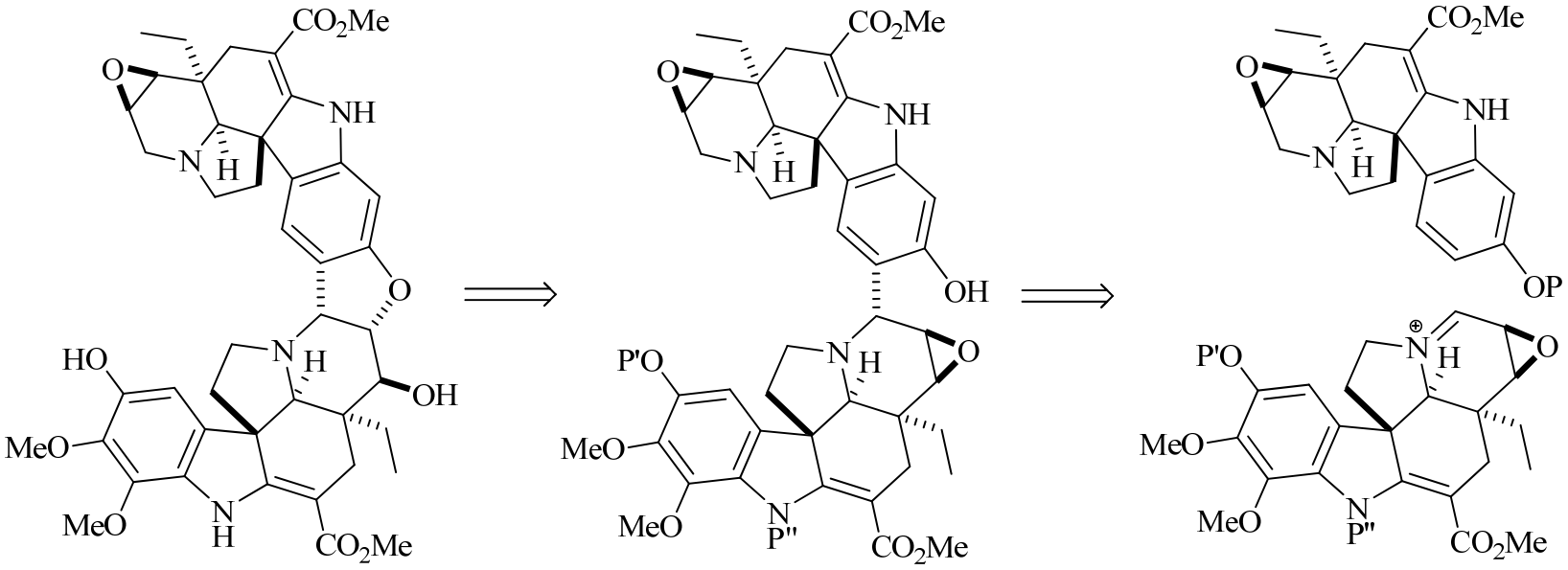
Kobayashi, S.; Ueda, T.; Fukuyama, T. *Synlett.* **2000**, 883.

Synthesis of the Indole Core Structures of Conophylline



Ando, S.; Okamoto, Y.; Umezawa, K.; Otsuka, M. *J. Heterocycl. Chem.* **2008**, 45, 1803.

Retrosynthetic Analysis



(-)-conophylline (**1**) **3** **5**

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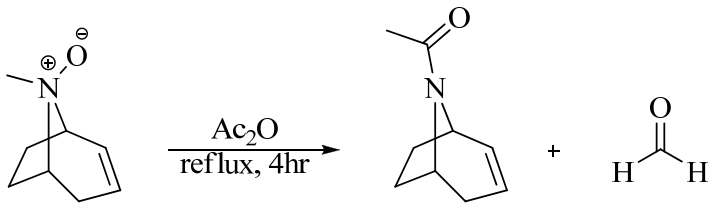
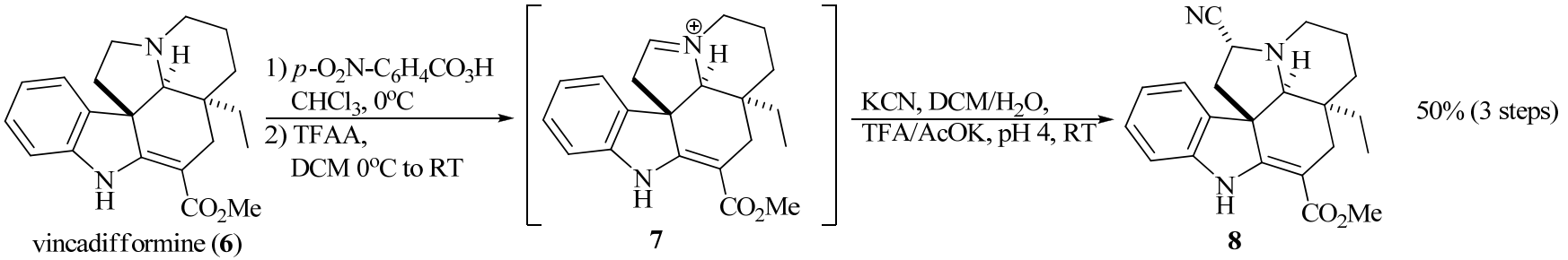
Polonovski-Potier Reaction

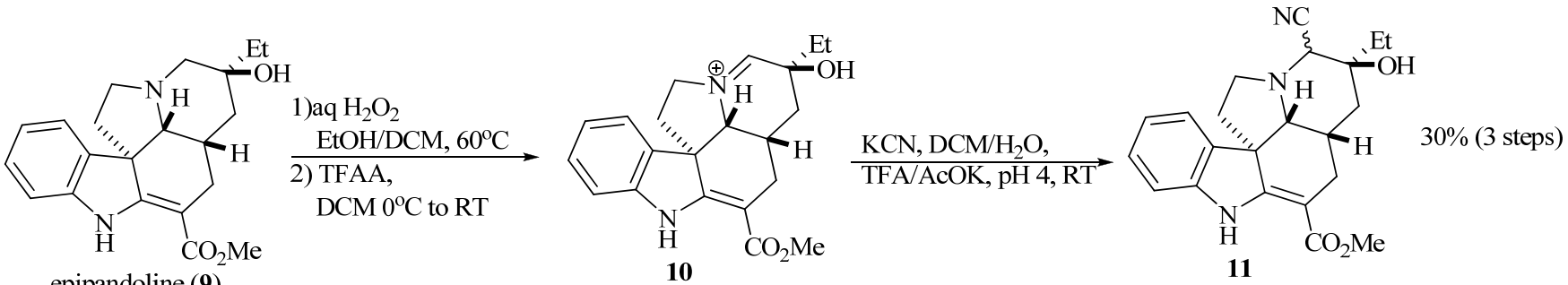
- Potier Modification
  - TFAA in place of Ac_2O or AcCl
  - Allowed for milder reaction conditions
  - Can be stopped at iminium ion



Polonovski, M; Polonovski, M. *Bull. soc. chim.* **1927**, 1190.
Polonovski, M. *Bull. soc. chim. Belg.* **1930**, 39, 1190.
Cave, A.; Kan-Fan, C.; Potier, P.; Le Man, J. *Tetrahedron*. **1967**, 23, 4681.



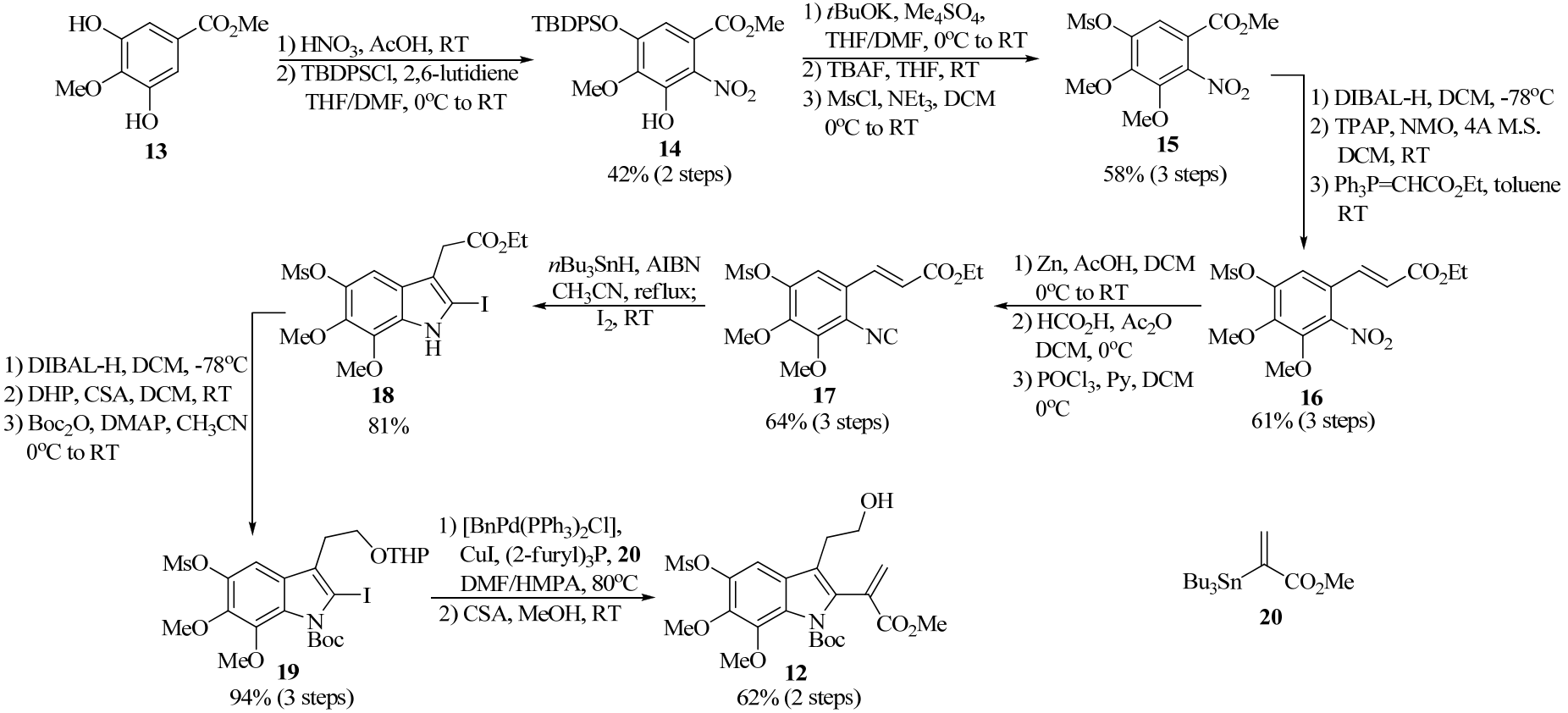
vincadifformine (**6**) **7** **8**



epipandoline (**9**) **10** **11**

Henriques, A.; Kan, C.; Chiaroni, A.; Richie, C.; Husson, H.-P.; Kan, S.-K.; Lounasmaa, M. *J. Org. Chem.* **1982**, 47, 803

Title Paper: Synthesis of Indole **12**



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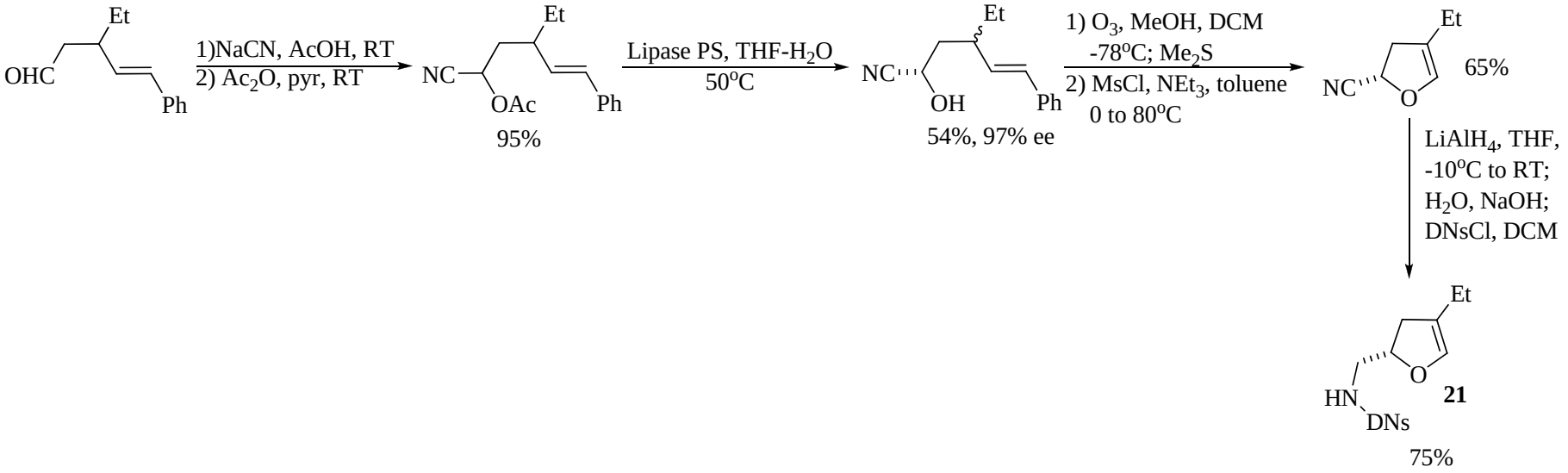
Title Paper: Synthesis of Dinitrobenzenesulfonamide **21**



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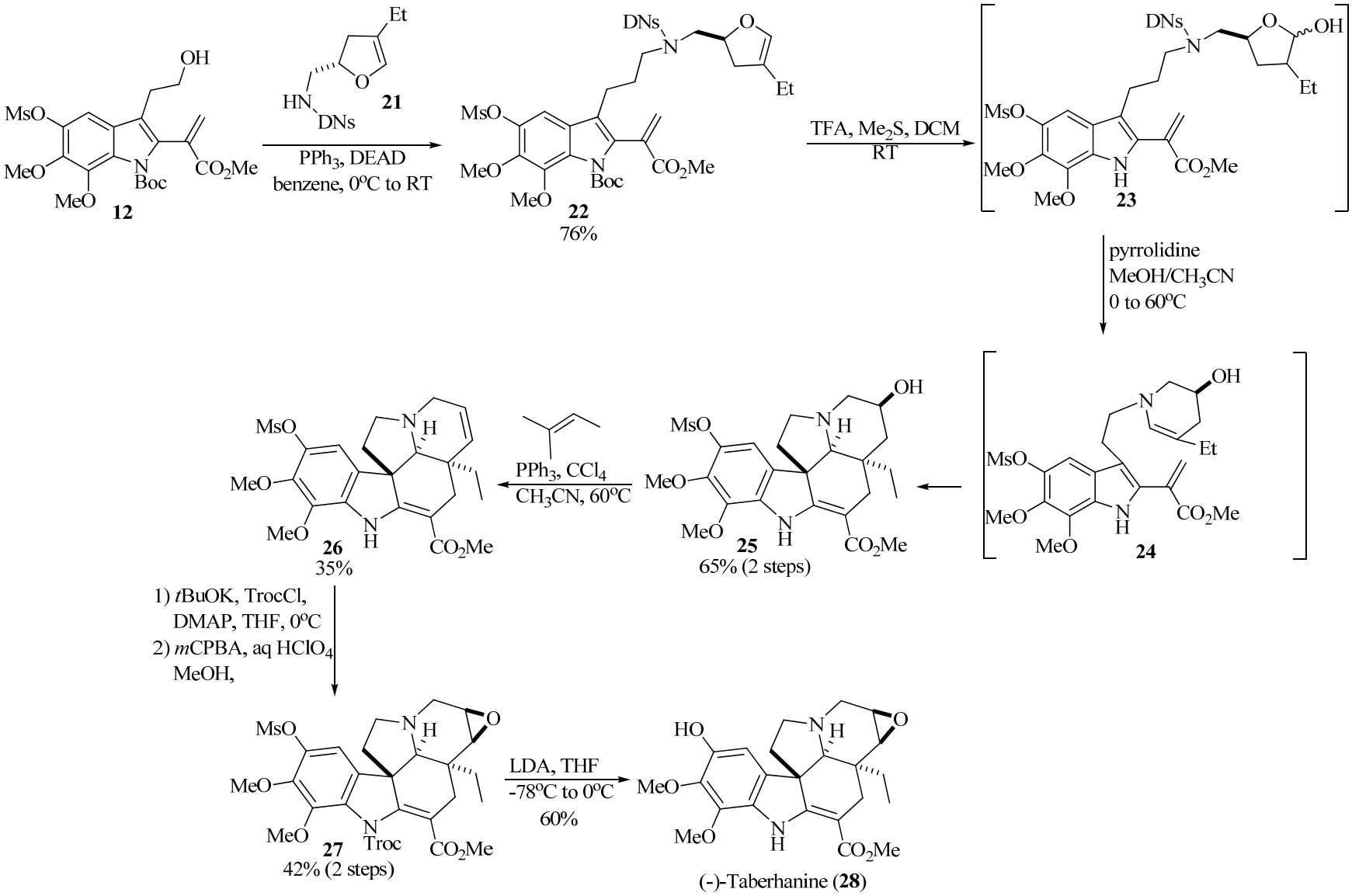
Kobayashi, S.; Peng, G.; Fukuyama, T. *Tet. Let.* **1999**, 40, 1519.
Yokoshima, T; Kobayashi, S.; Ueda, T.; Sato, A.; Kuboyama, T,; Tokuyama, H; Fukuyama, T. *JACS.* **2002**, 124, 2137.

Title Paper: Synthesis of lower indole segment **27**



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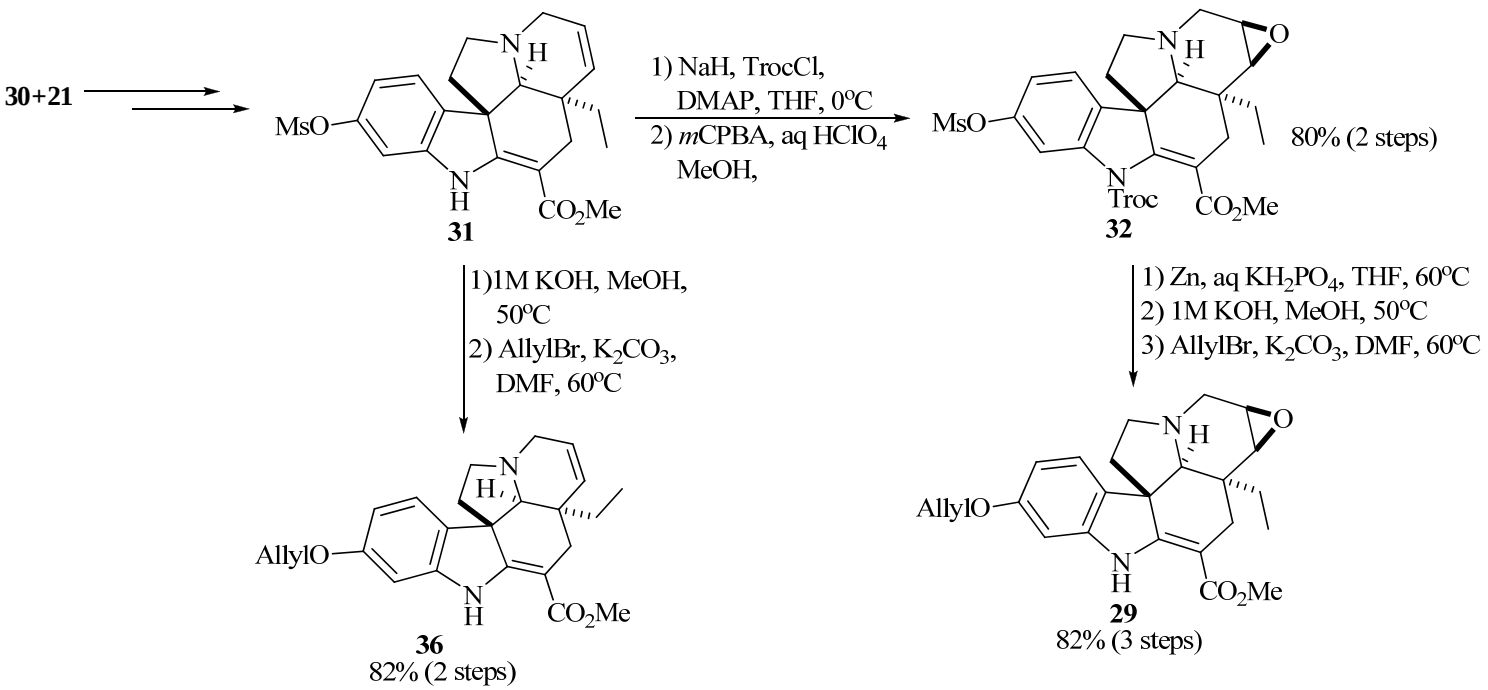
Title Paper: Synthesis of upper indole **29** and **36**



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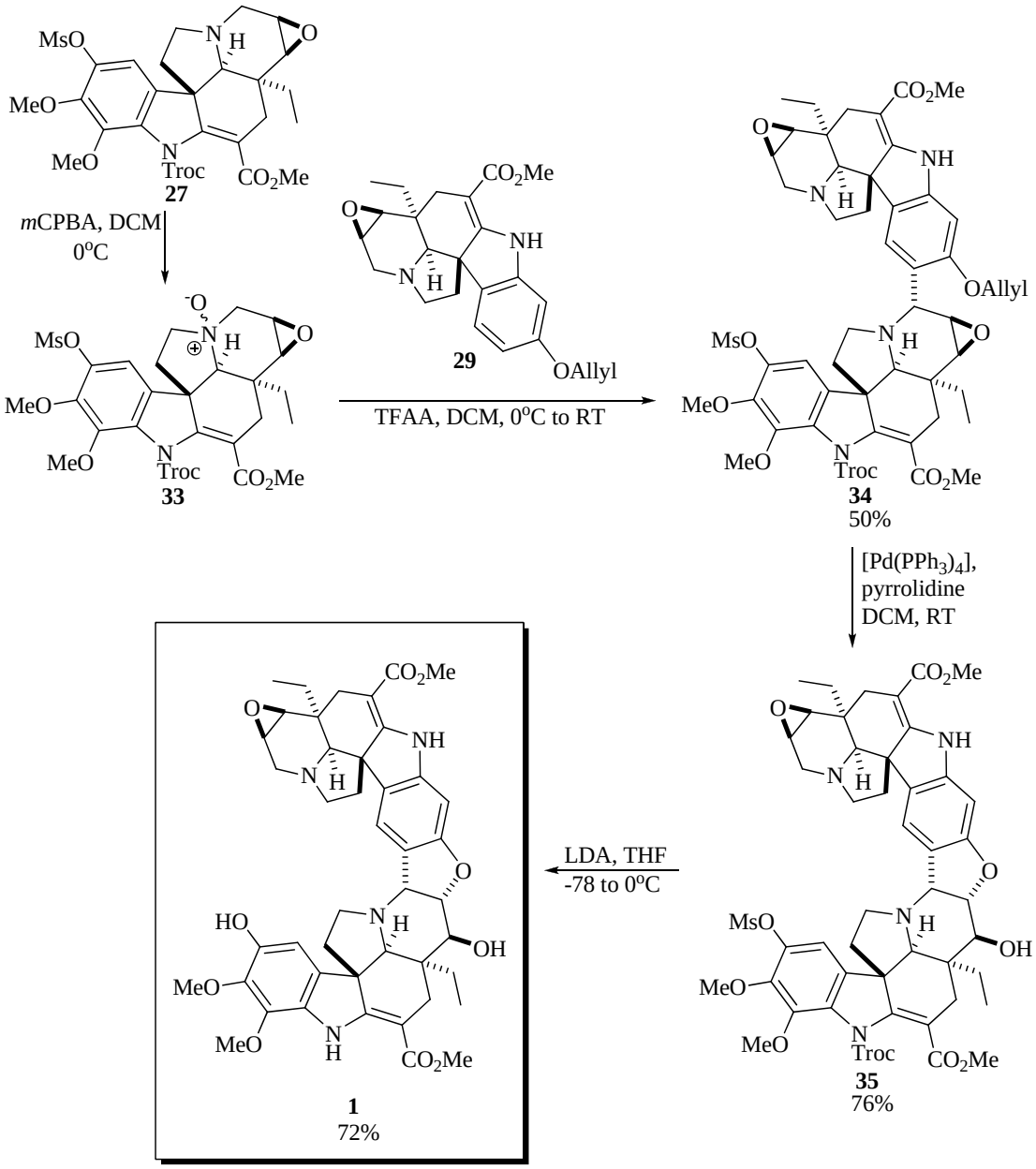
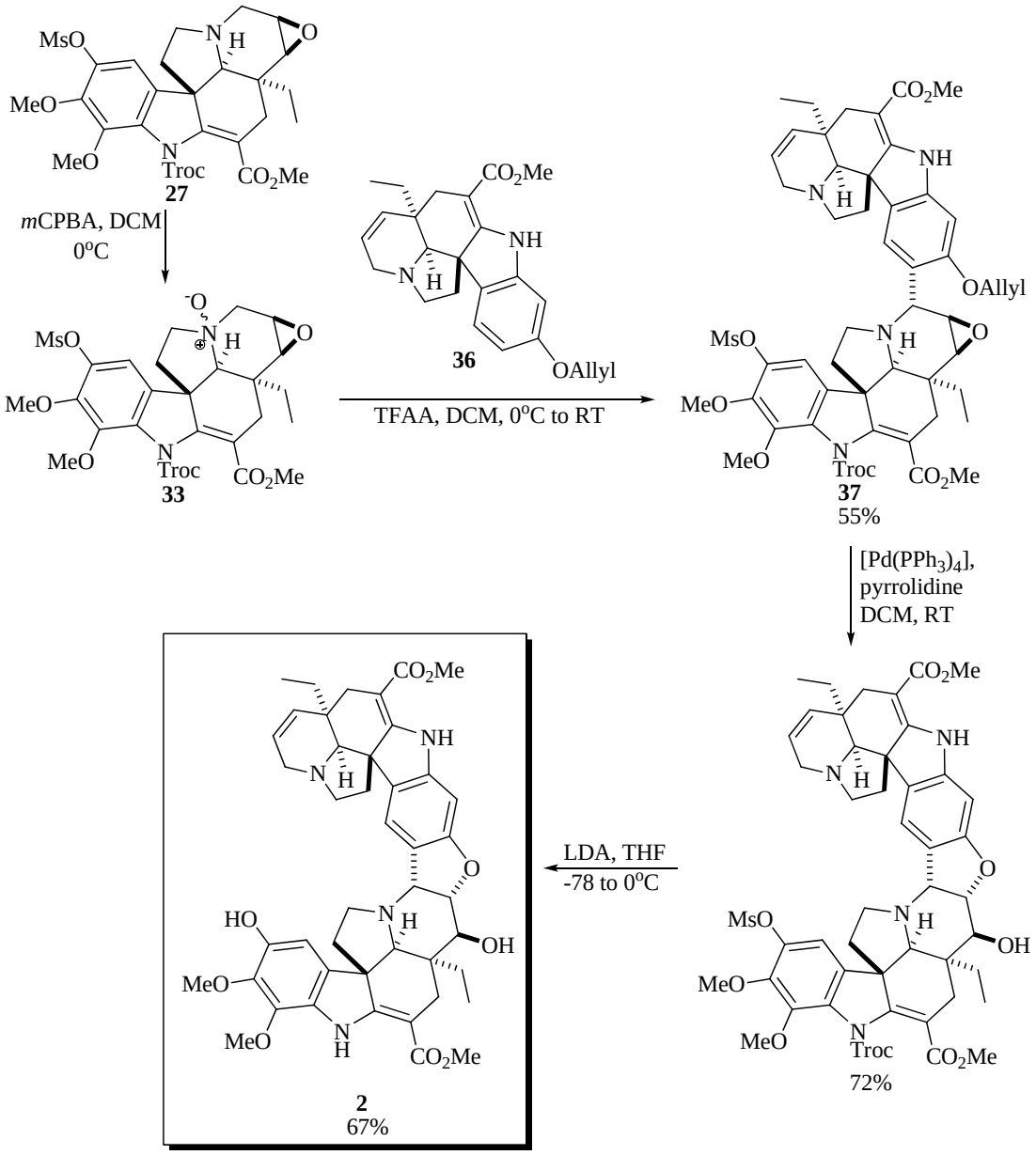
Title Paper: Completion of (-)-conophylline (**1**)



Han-ya, Y.; Tokuyama, H.; Fukuyama, T. *Angew Chem. Int. Ed.* **2011**, 50, 4884.

Title Paper: Completion of (-)-conophyllidine (**2**)



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Conclusions

- First total synthesis of (-)-conophylline and its congener (-)-conophyllidine via a convergent route
- Key Steps
  - Tin-mediated radical cyclization to produce indole core
  - Stereoselective intramolecular Michael addition/Mannich reaction cascade
  - Potentially biomimetic cascade to couple two pentacyclic aspidosperma skeletons utilizing a regio- and diastereoselective Polonovski-Potier reaction
- Convergent route leaves open the possibility for SAR analysis to probe biological activity