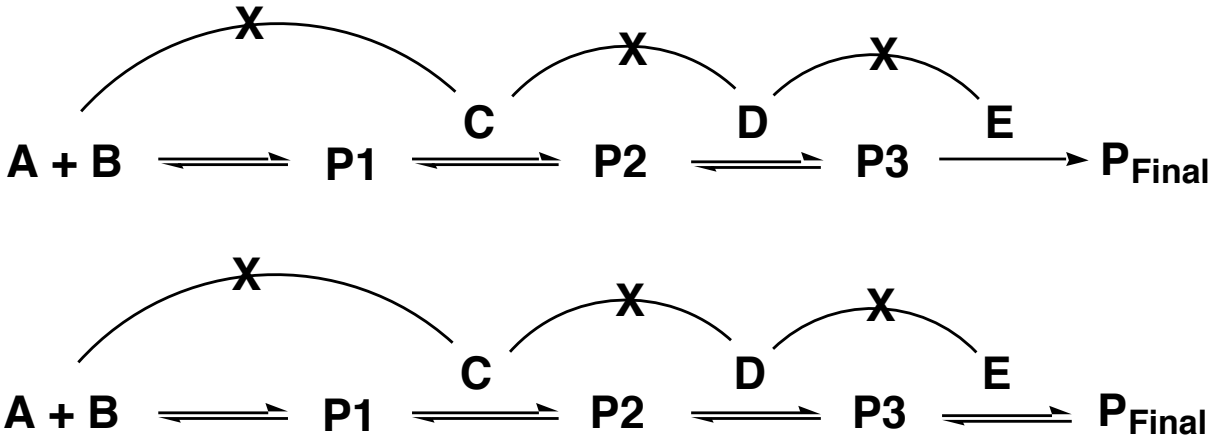
Multicomponent Reaction (MCR)

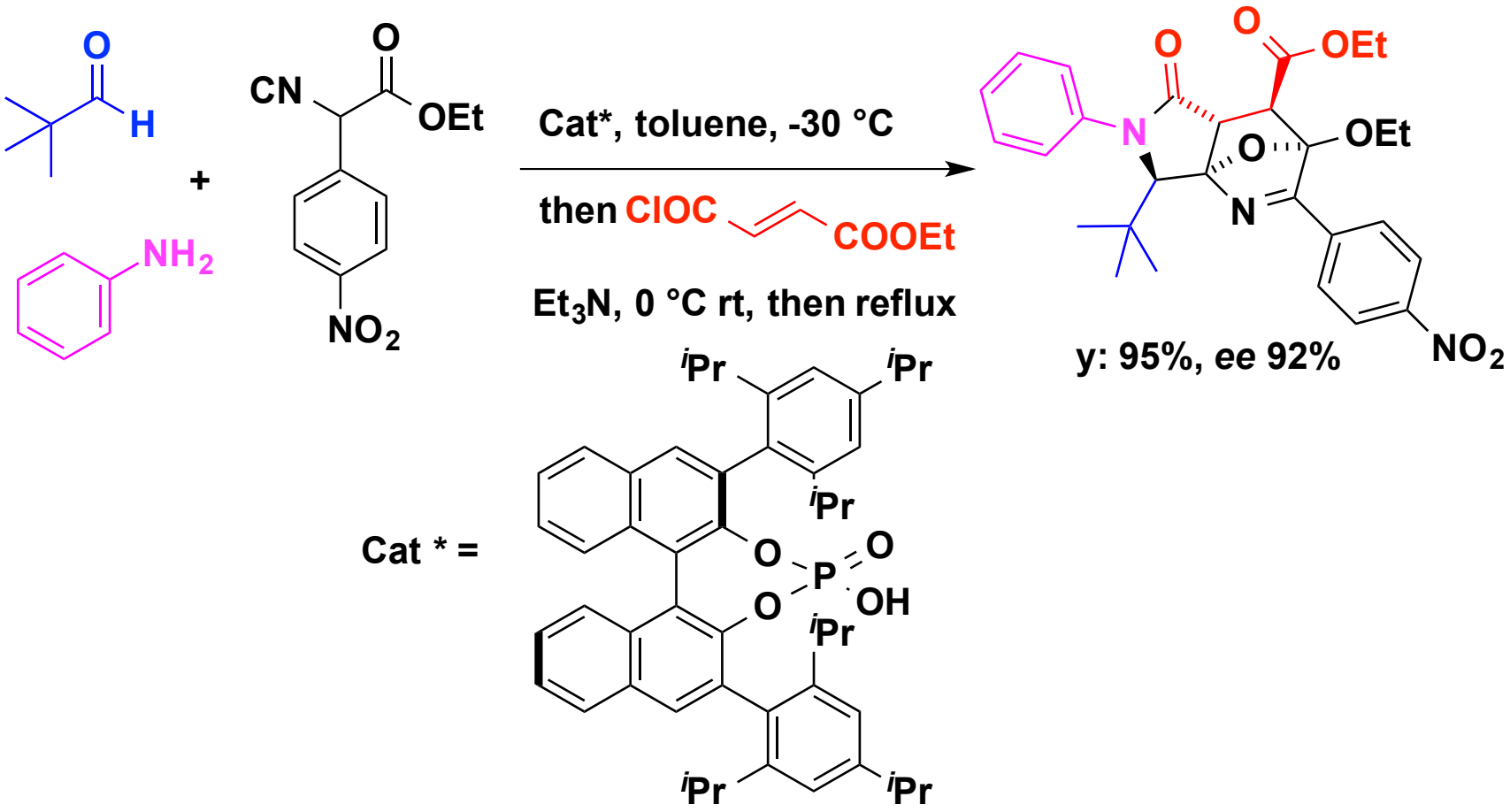
Definition and Principle

A process in which three or more reactants are combined in a single reaction vessel to produce a product that incorporates substantial portions of all the components. A sequence of bimolecular events that proceed according to the Domino principle, i.e., the subsequent reactions result as a consequence of the functionality formed in the previous step.



Monographs: a) "***Multicomponent Reaction***" Wiley-VCH, Eds: J. Zhu, H. Bienayme, **2005**
b) **"Multicomponent reactions in Organic Synthesis"** Wiley VCH,
Eds: J. Zhu, Q. Wang, M.-X. Wang, **2014.**

Multicomponent Synthesis of Heterocycles



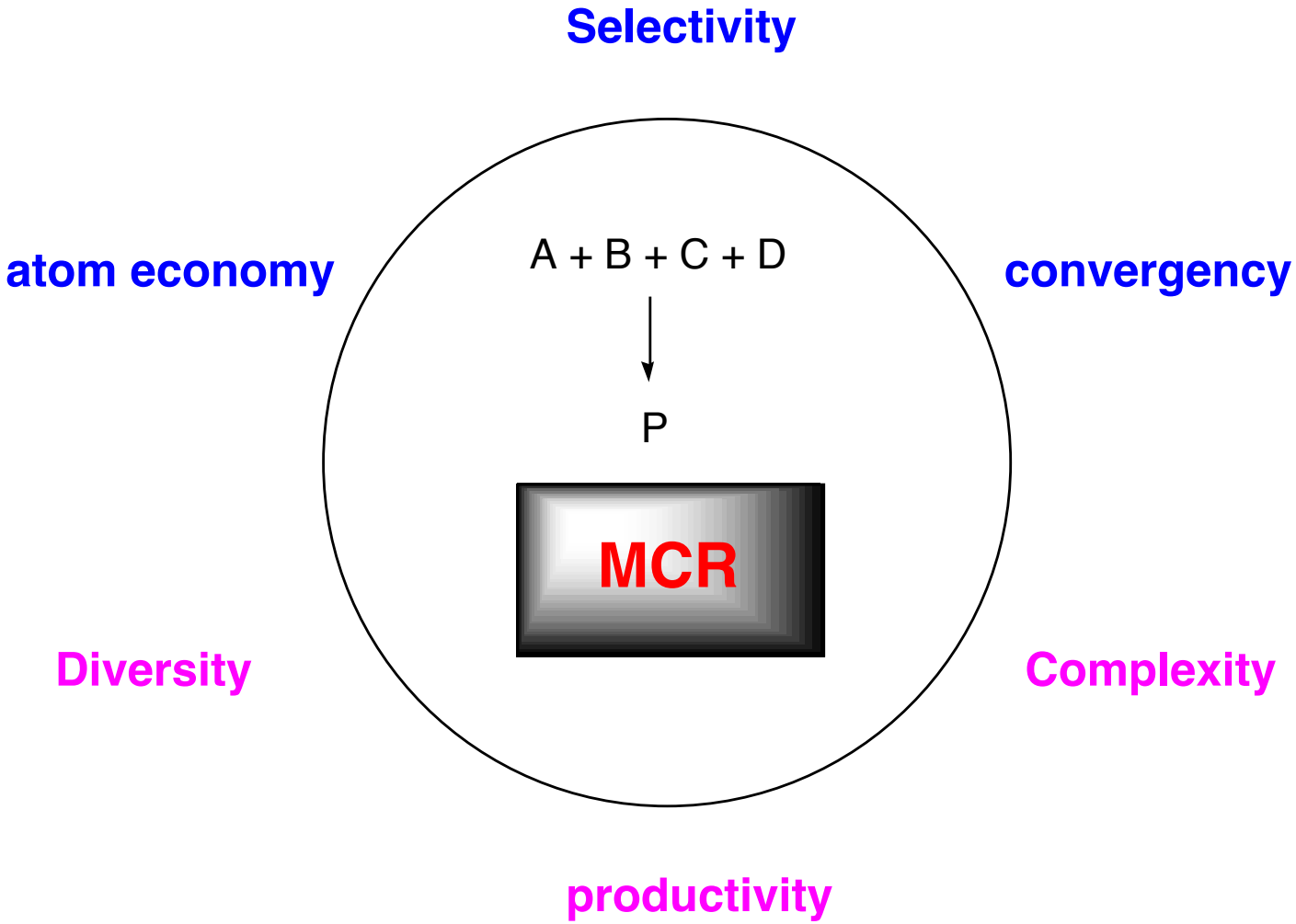
1 C-O, 2 C-N, 3 C-C bonds formed (total 6)

5 contiguous stereocenters including 2 quaternary ones

Bonne, D.; Dekhane, M.; Zhu, J. *Angew. Chem. Int. Ed.* **2007**, 46, 2485-2488.

Su, Y.; Bouma, M. J.; Alcaraz, L.; Stocks, M.; Furber, M.; Masson, G.; Zhu, J. *Chem. Eur. J.* **2012,** *18*, 12624-12627.

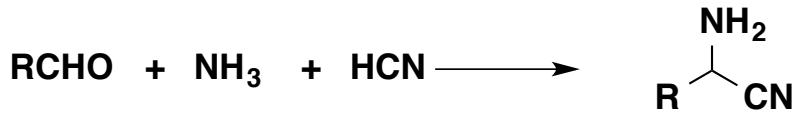
Advantages of Multicomponent Reactions



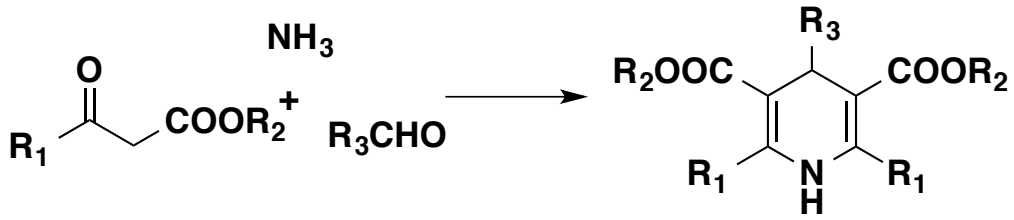
Monographs: "***Multicomponent Reaction***" Wiley-VCH, Eds: J. Zhu, H. Bienayme, **2005**
"Multicomponent reactions in Organic Synthesis" Wiley VCH, Eds: J. Zhu, Q. Wang, M.-X. Wang, **2014**

MCR in Natural Product Synthesis: B. B. Touré, D. G. Hall, *Chem. Rev*. **2009**, *109*, 4439-4486.

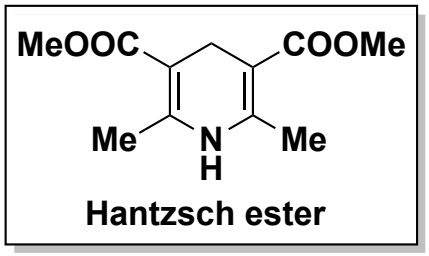
Textbook MCRs



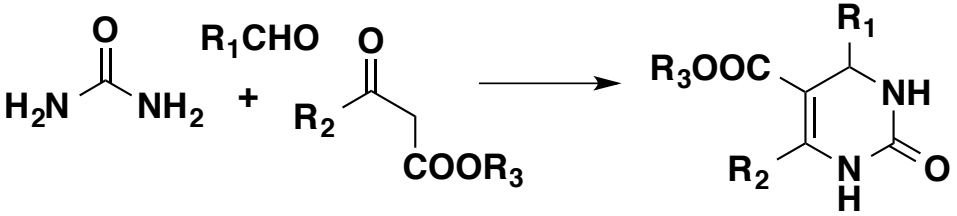
Strecker, 1850



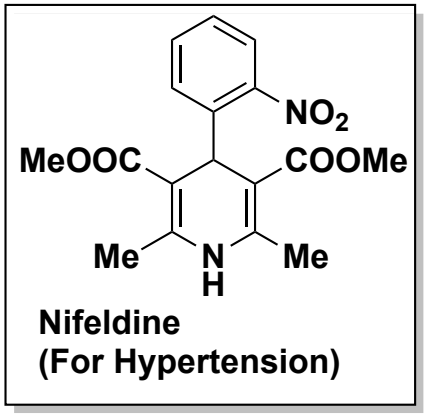
Hantzsch, 1882



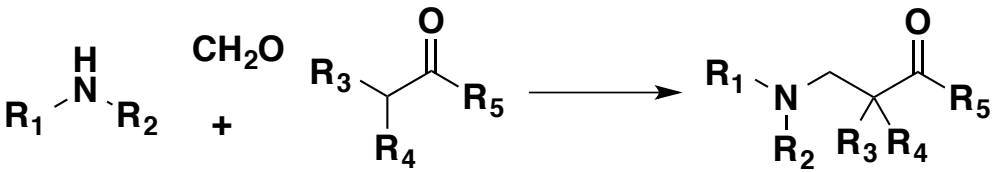
Hantzsch ester



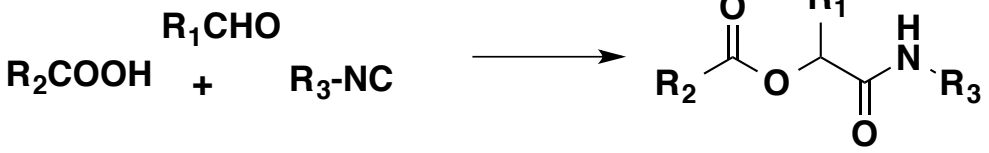
Biginelli, 1891



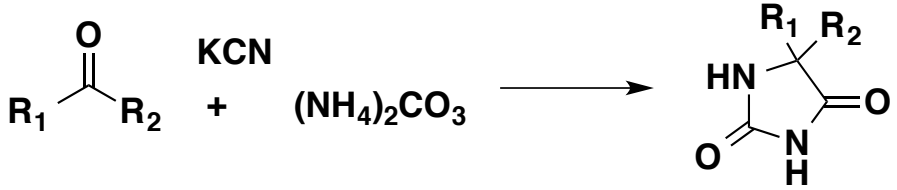
Nifeldine
(For Hypertension)



Mannich, 1912

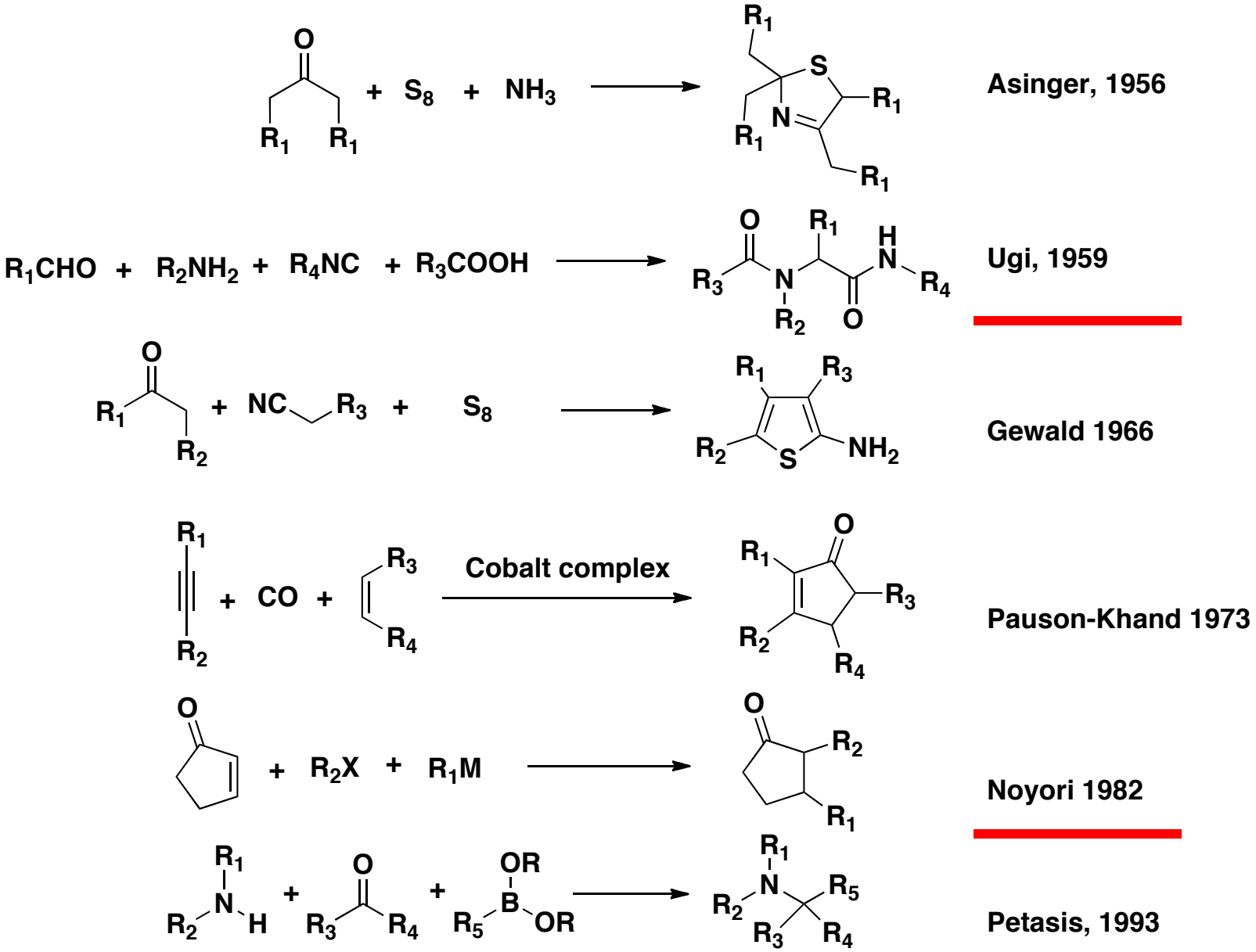


Passerini, 1921

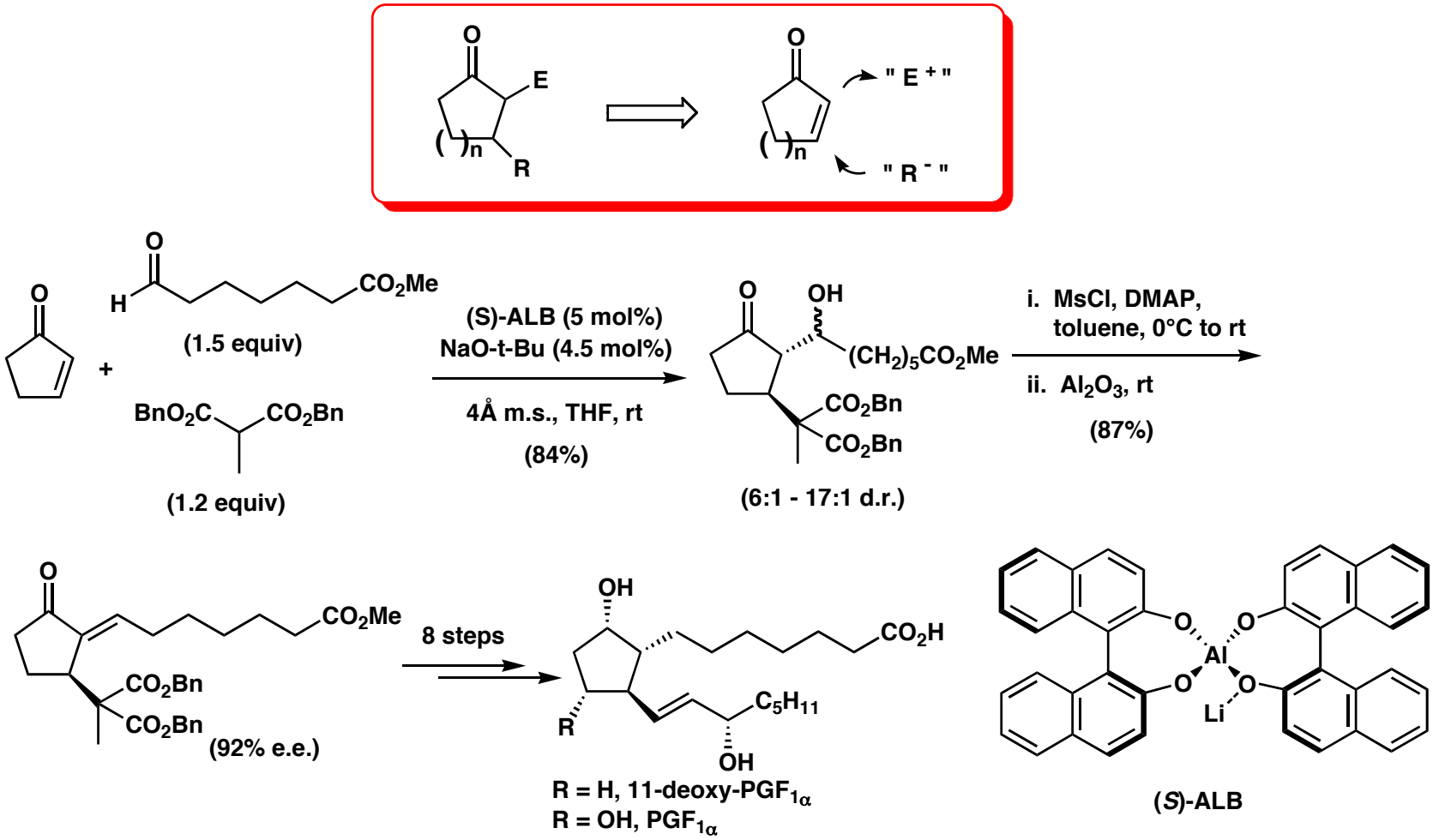


Bucherer-Bergs 1934

Textbook MCRs

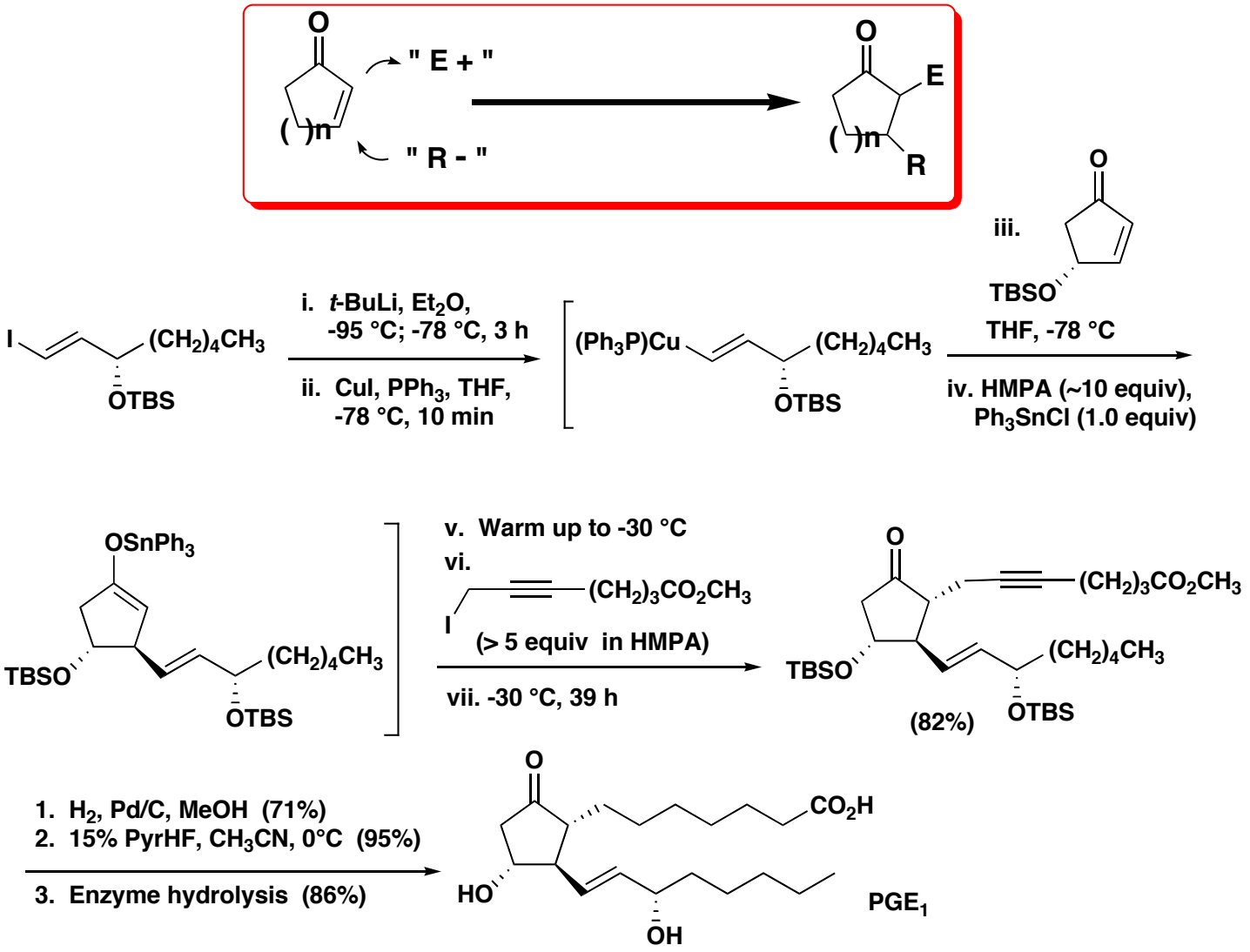


Michal Addition/Aldol Sequence



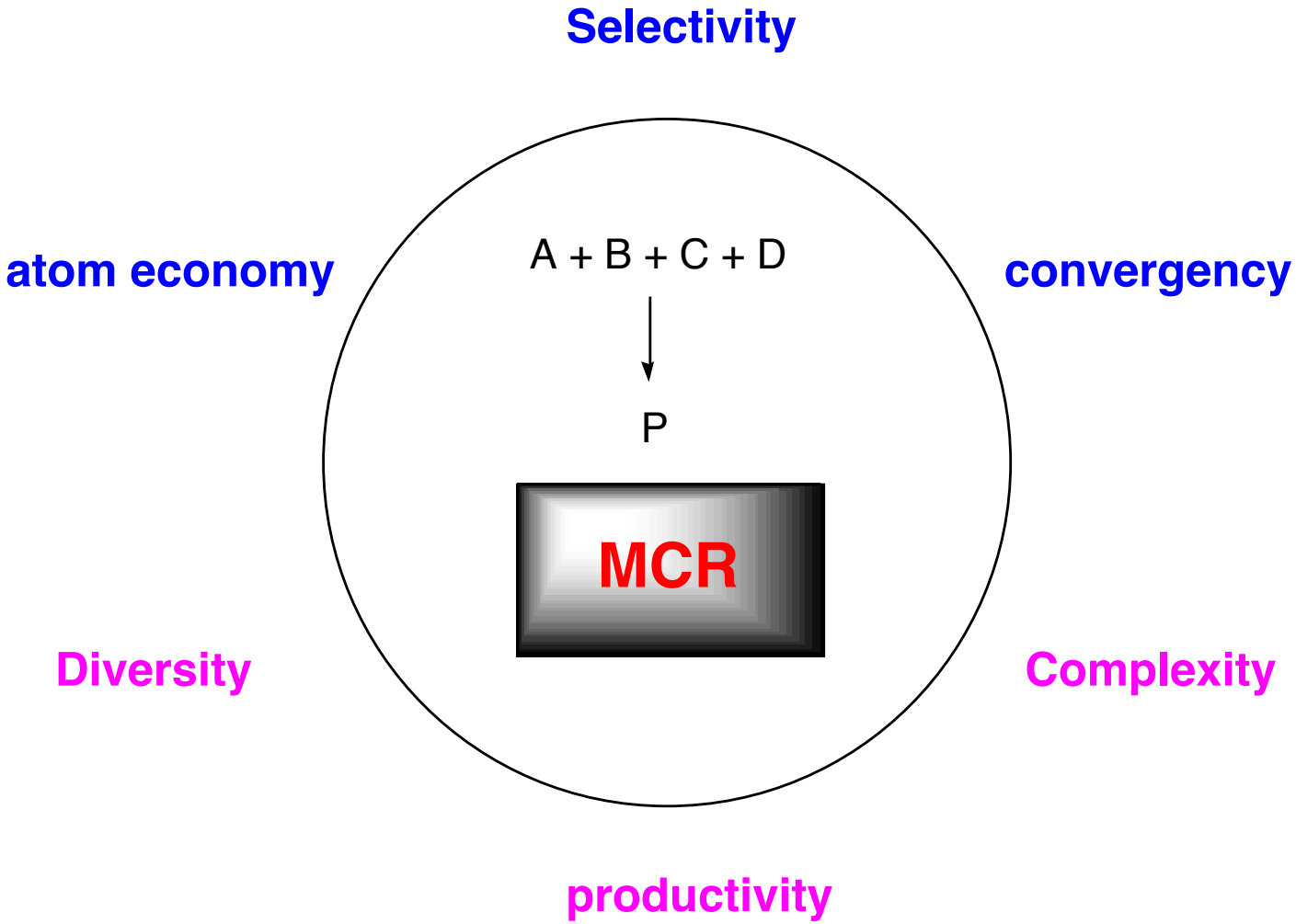
Shibasaki, *J. Org. Chem.* **1998**, *63*, 3666-3672; *Syn Org Chem JPN* **1998,** *56*, 344-356.
Reviews: *Org React*. **1990**, *38*, 225-653; **1992**, *41*, 135-631.
Ma, J. A. *Anegw. Chem. Int. Ed*. **2006**, *45*, 354-366.

Michal Addition/Alkylation Sequence



C.J. Sih, J.B. Heather, R. Sood, P. Price, G. Peruzzotti, L.-F.H. Lee, S.S. Lee, *J. Am. Chem. Soc.* **1975**, *97*, 865-874.

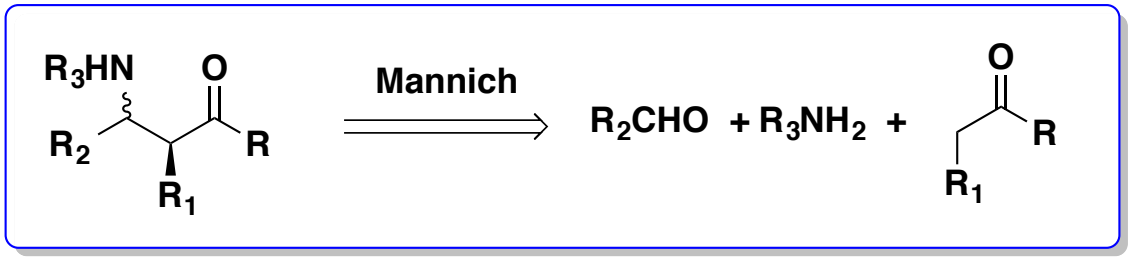
Advantages of Multicomponent Reactions

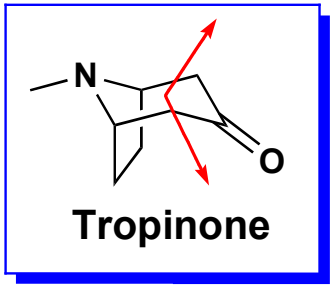


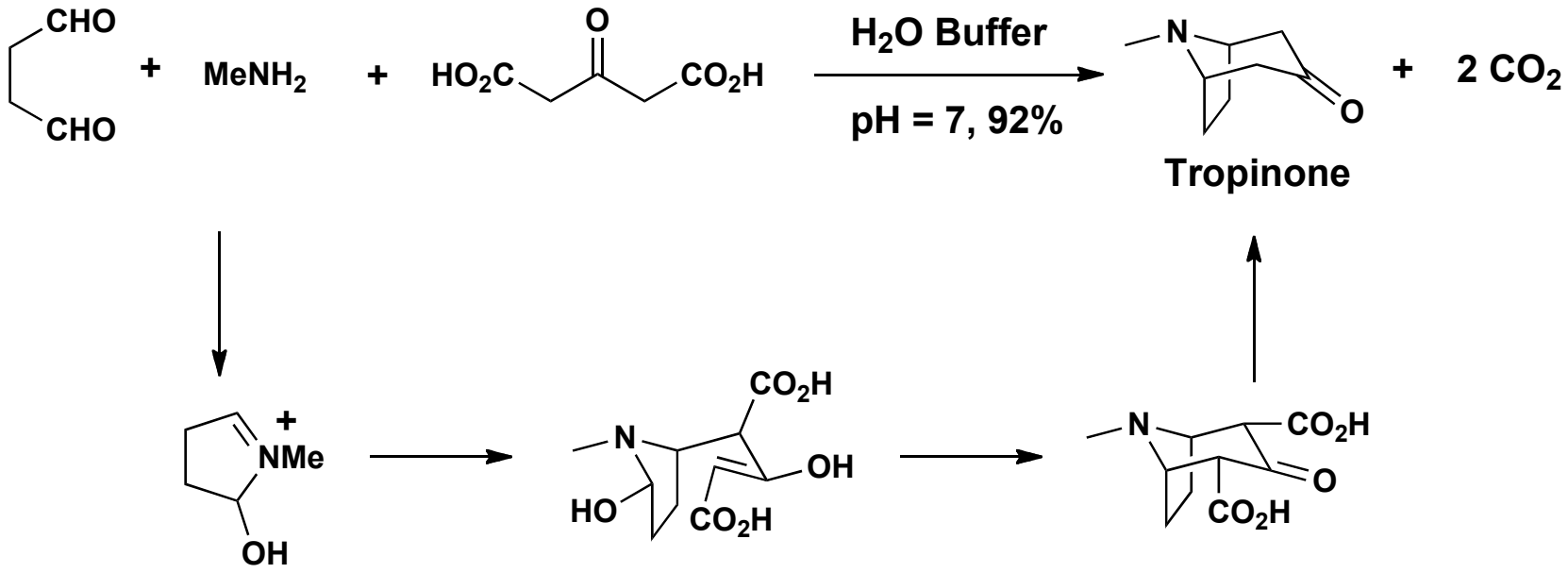
Monographs: "***Multicomponent Reaction***" Wiley-VCH, Eds: J. Zhu, H. Bienayme, **2005**
"Multicomponent reactions in Organic Synthesis" Wiley VCH, Eds: J. Zhu, Q. Wang, M.-X. Wang, **2014**

MCR in Natural Product Synthesis: B. B. Touré, D. G. Hall, *Chem. Rev*. **2009**, *109*, 4439-4486.

Robinson's Three-Component Synthesis of Tropinone



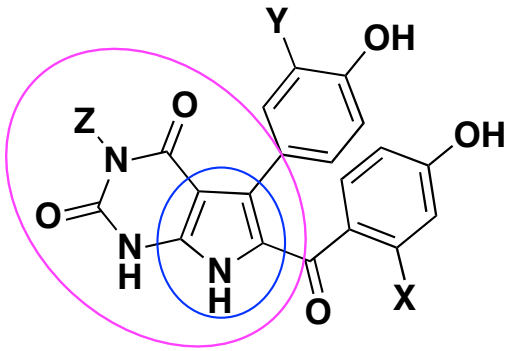




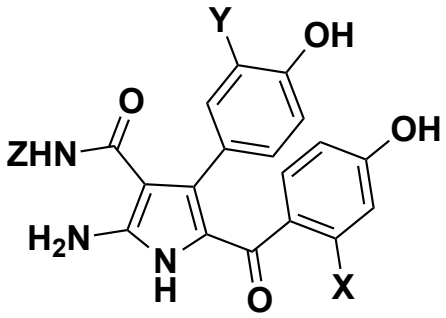
Key: Double Mannich Reactions

R. Robinson, *J. Chem. Soc.* **1917**, *111*, 762-768.

Rigidins



Rigidin A X = Y = Z = H
Rigidin B X= OMe, Y = Z = H
Rigidin C Y = OMe, X = Z = H
Rigidin D X = Y = OMe, Z = H
Rigidin E X = Y = H, Z = Me



Isolated from marine tunicates collected near Okinawa and New Guinea displayed potent calmodulin antagonist activities

Structural fetaures:

Pyrrolopyrimidine

Fully substituted 2-aminopyrrole unit

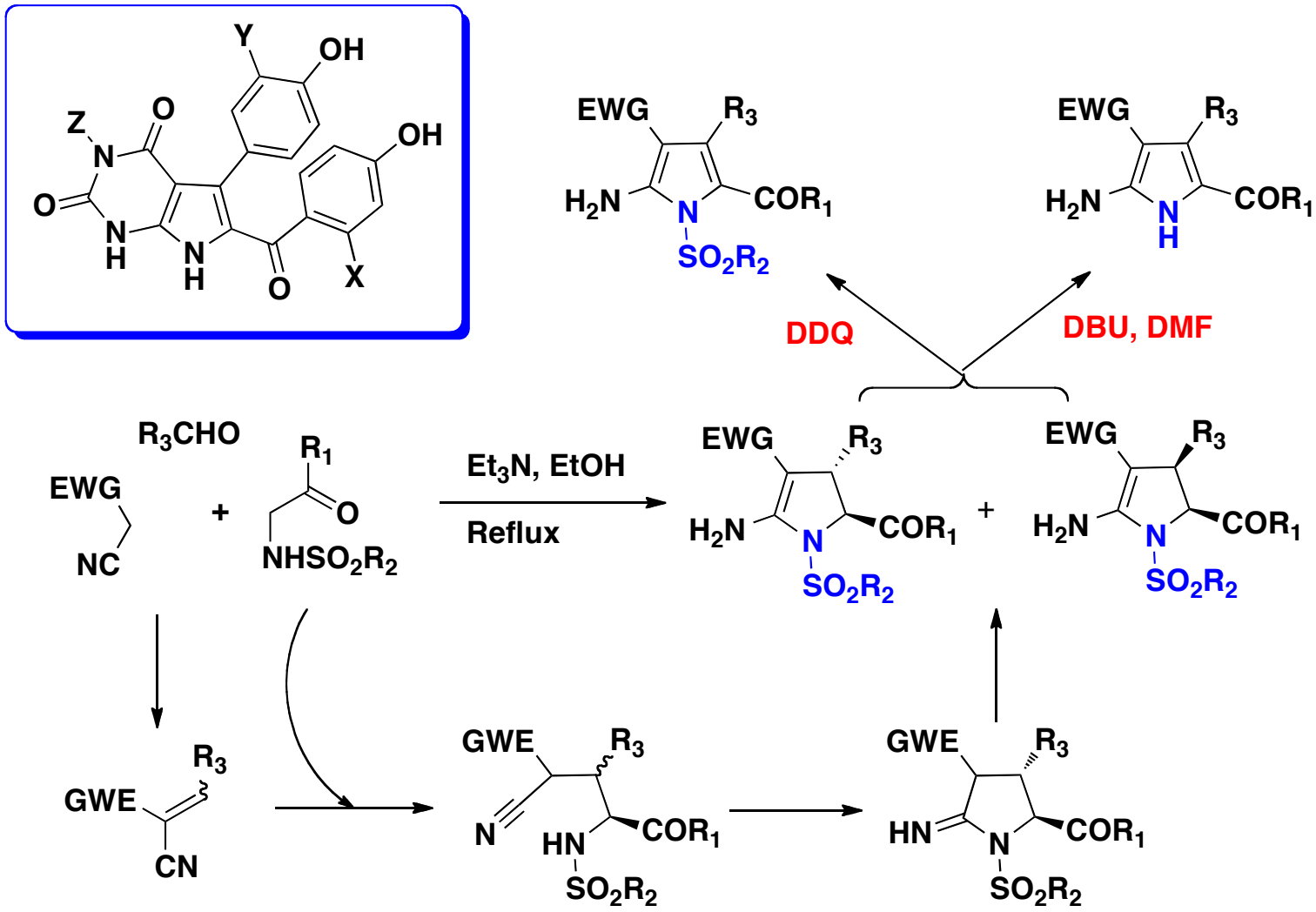
A multicomponent Synthesis???

Kobayshi, J.; Cheng, J.; Kikuchi, Y.; Ishibashi, Y.; Yamamura, S.; Ohizumi, Y.; Ohta, T.; Nozoe, S. *Tetrahedron,* **1990***, 31*, 4617-4620.

Tsuda, M.; Nozawa, K.; Shimbo, K.; Kobayashi, J. *J. Nat. Prod*. **2003**, *66*, 292–294.

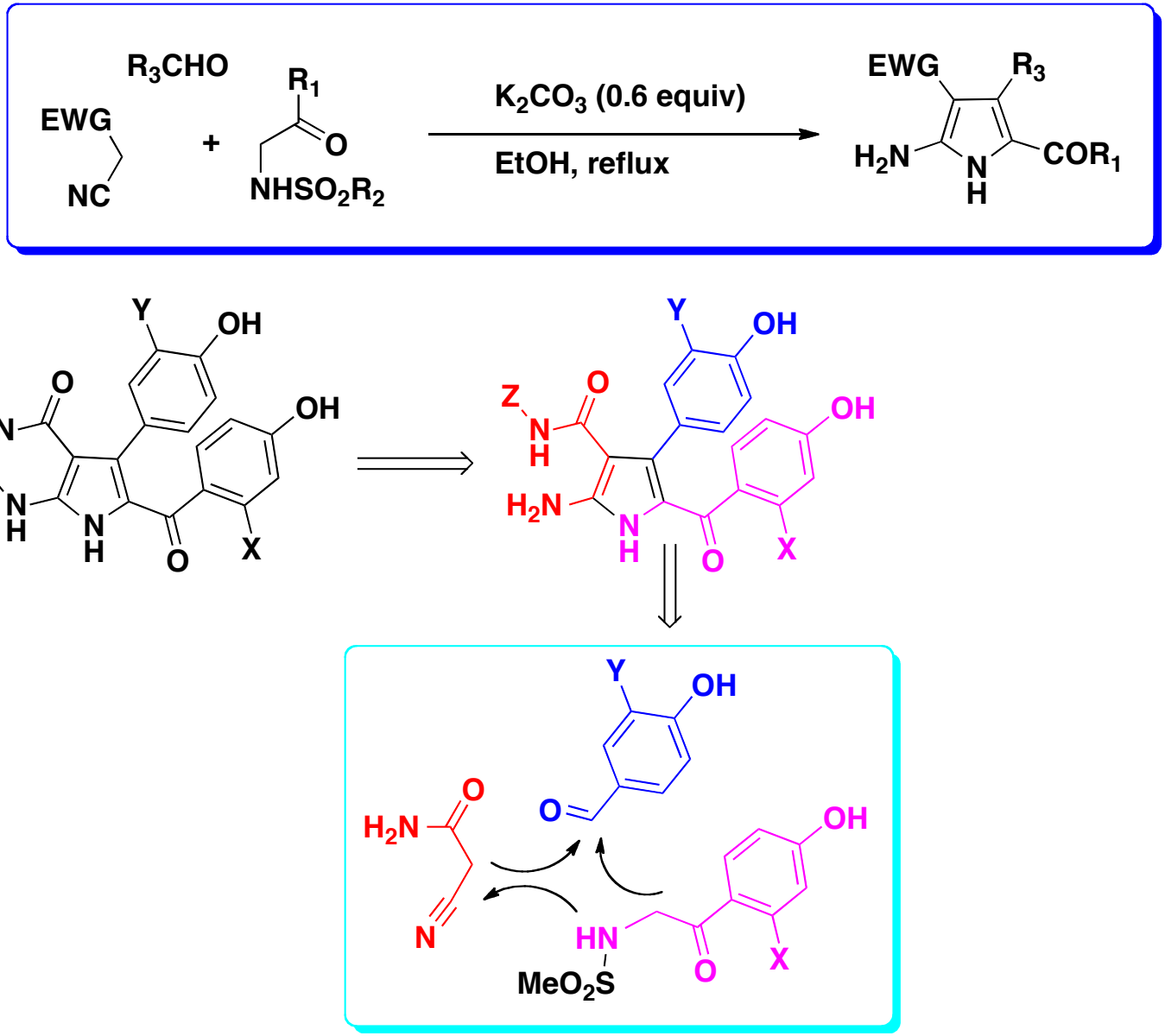
Davis, R.; Christensen, L.; Richardson, A.; da Rocha; Ireland, C. *Mar. Drugs* **2003**, *1*, 27–33

Three-component synthesis of Pyrroline and Pyrrole



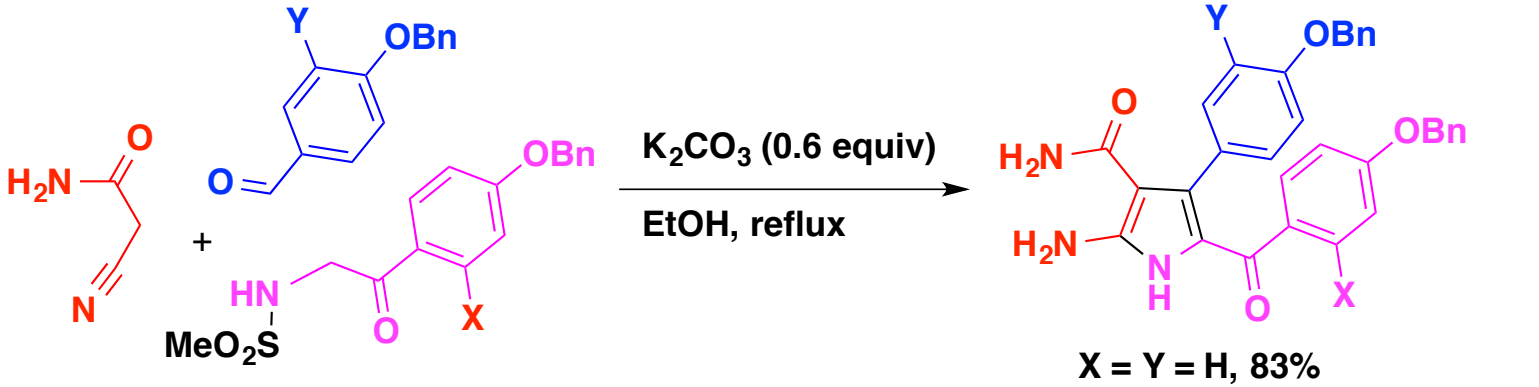
Magedov, I. V. et al. *Bioorg. Med. Chem. Lett*. **2008**, *18*, 1392-1396.

Three-component Synthesis of 2-Aminopyrrole

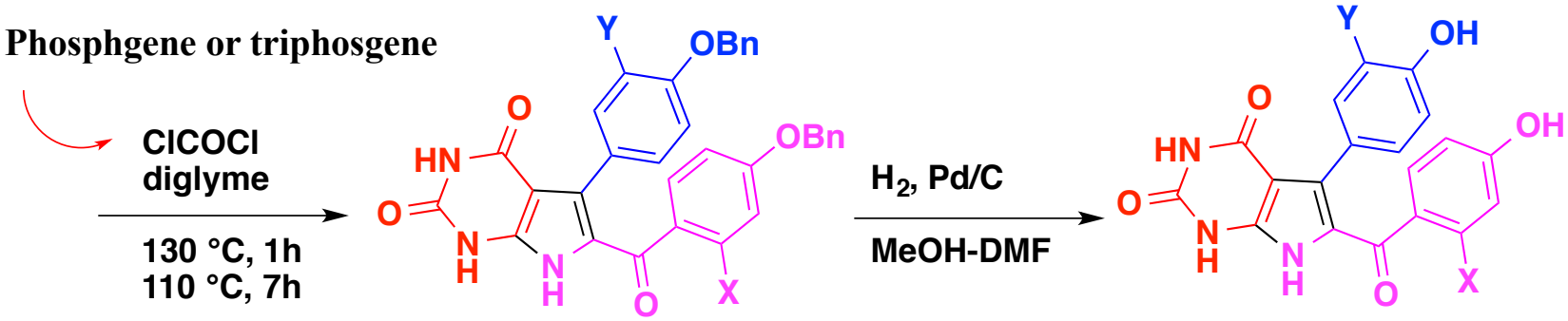


Magedov, I. V. et al. *Org. Lett.* **2011**, *13*, 1118.

Three-step Total Synthesis of Regidins



X = Y = H, 83%
X = OMe, Y = H, 86%
X = H, Y = OMe, 86%
X = Y = OMe, 84%

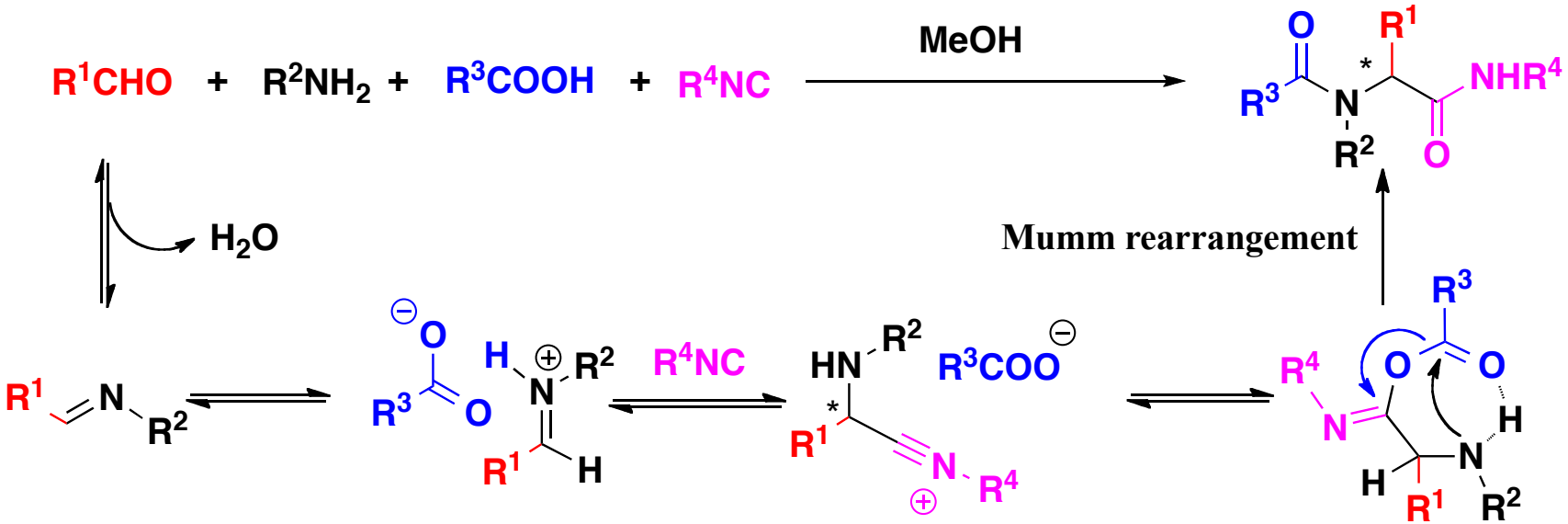


X = Y = H, 81%
X = OMe, Y = H, 74%
X = H, Y = OMe, 76%
X = Y = OMe, 72%

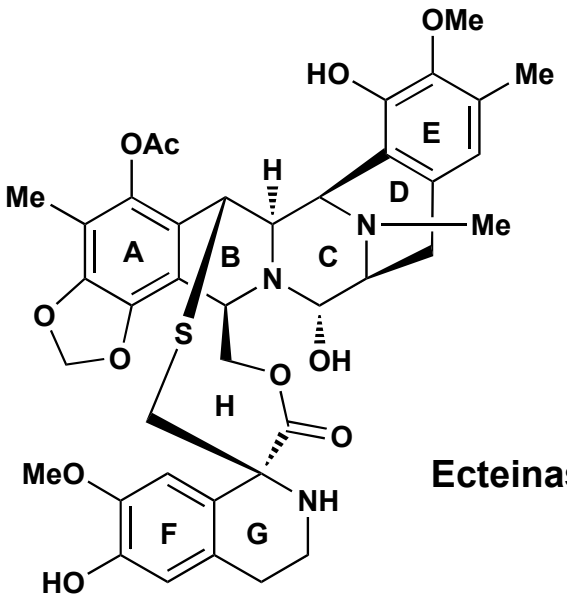
X = Y = H, 95%
X = OMe, Y = H, 95%
X = H, Y = OMe, 96%
X = Y = OMe, 93%

Magedov, I. V. et al. *Org. Lett*. **2011**, *13*, 1118.

Deep Insight into Structure: Ugi 4CR and Ecteinascidin-743



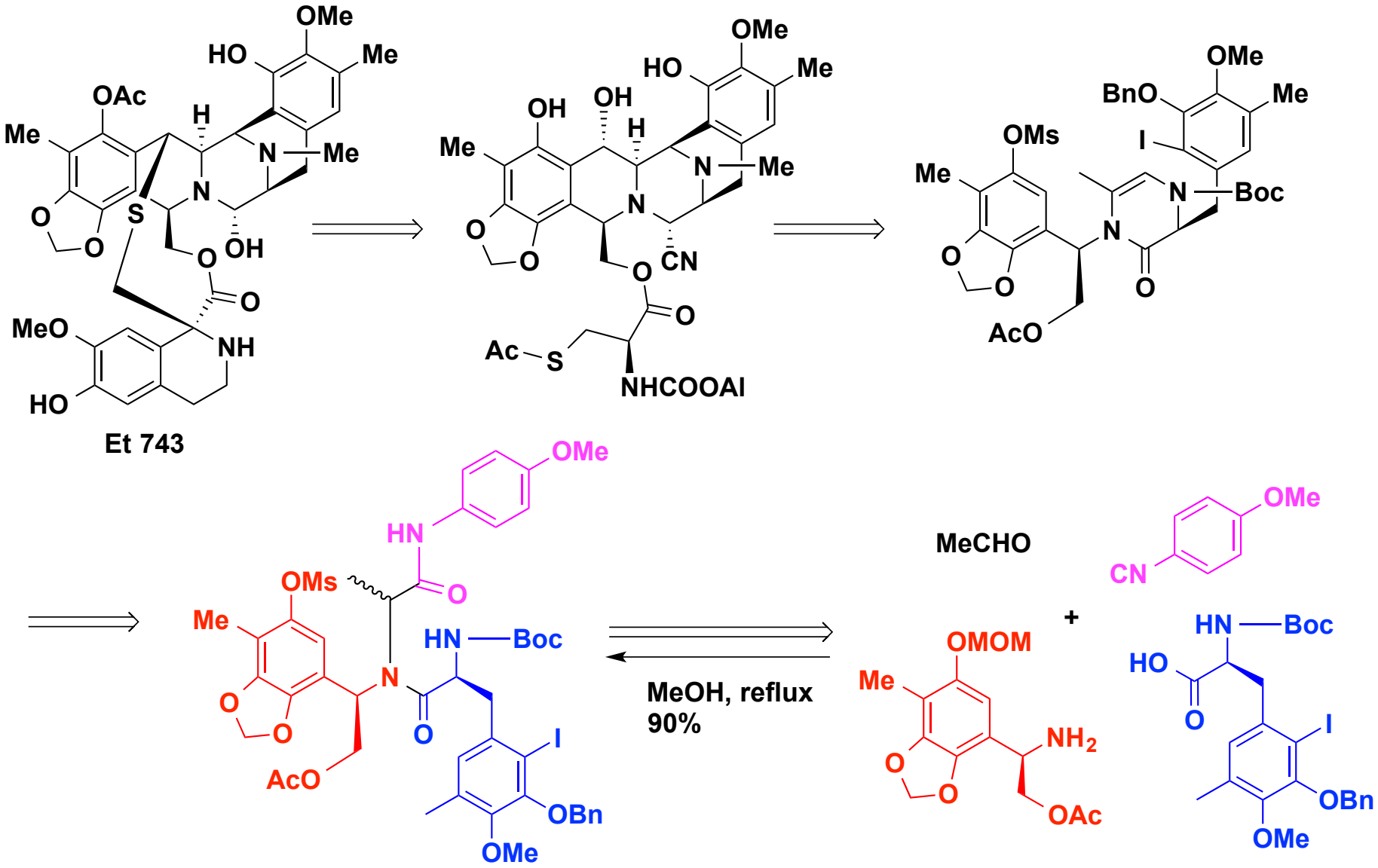
R^1, R^2, R^3, R^4 = aliphatique, aromatique



Ecteinascidin 743

Rev on Isonitrile-based MCRs, see:
Dömling, A. *Chem. Rev.* **2006**, *106*, 17-89.

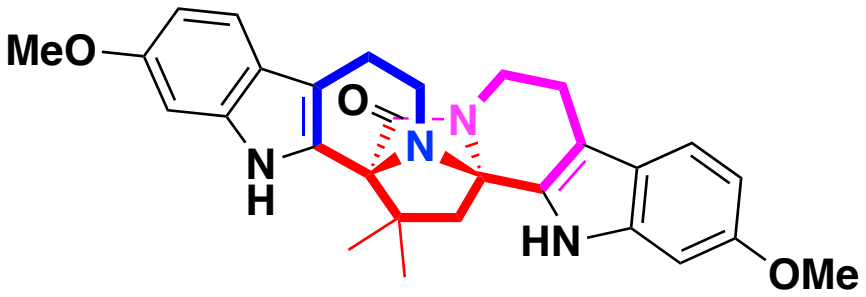
Fukuyama's Synthesis of Ecteinascidin-743: Retro-Synthetic Analysis



T. Fukuyama *et al. J. Am. Chem. Soc*. **2002**, *124*, 6552-6554.

Two other total syntheses: Corey, E. J.; Gin, D. Y.; Kania, R. S. *J. Am. Chem. Soc*. **1996**, *118*, 9202-9203
Chen, J.; Chen, X.; Bois-Choussy, M.; Zhu, J. *J. Am. Chem. Soc*. **2006**, *128*, 87-89.

(+)-Peganumine A: an Octacyclic Alkaloid



(+)–Peganumine A

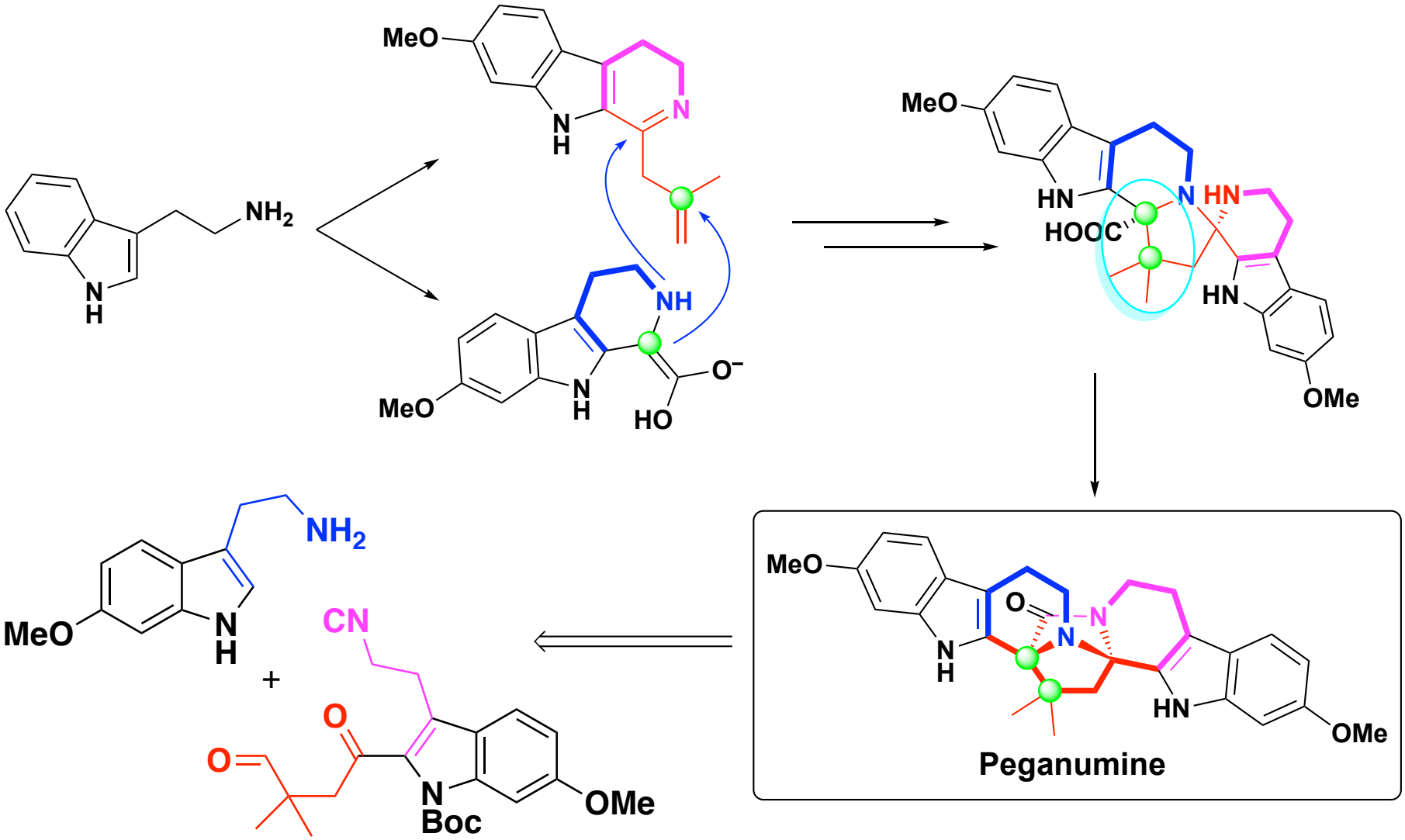
Relative stereochemistry: by X-ray
Absolute configuration: based on CD, ECD spectroscopic studies
Bioactivity: Low μM activity against MCF-7, PC-3, HepG2 and HL-60 cancer cell lines
Isolation yield: Extremely low (3.5 mg from 15.4 kg of the seeds)

Completely new skeleton:

an octacyclic indole alkaloid
two quaternary stereocenters,
two spirocycles embedded in an unusal 2,7-diazabicyclo[2.2.1]heptan-3-one unit

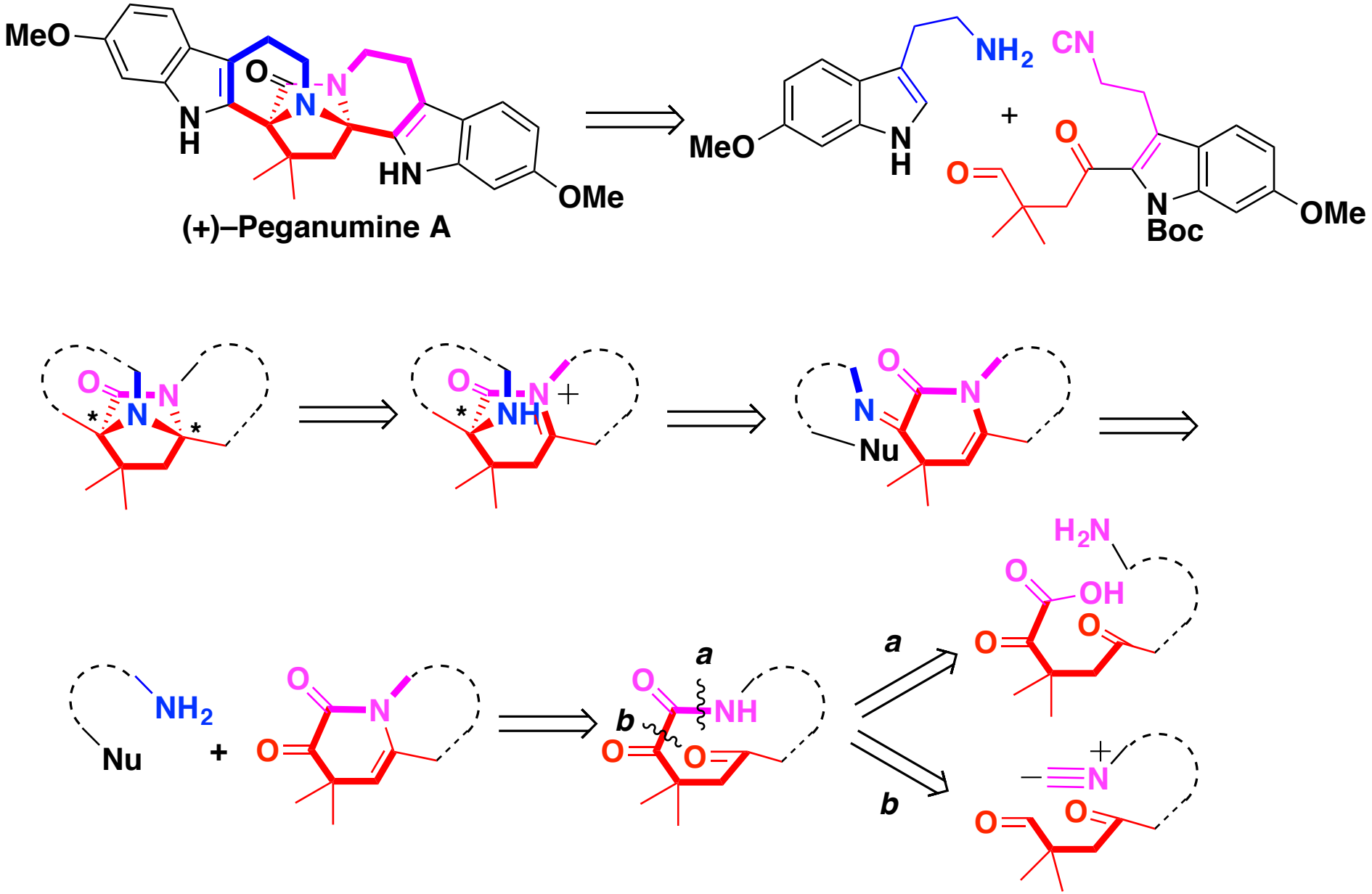
Hua, H.-M. *et al Org. Lett.* **2014**, *16*, 4028

(+)-Peganumine A: Biosynthetic Hypothesis and Synthesis Design

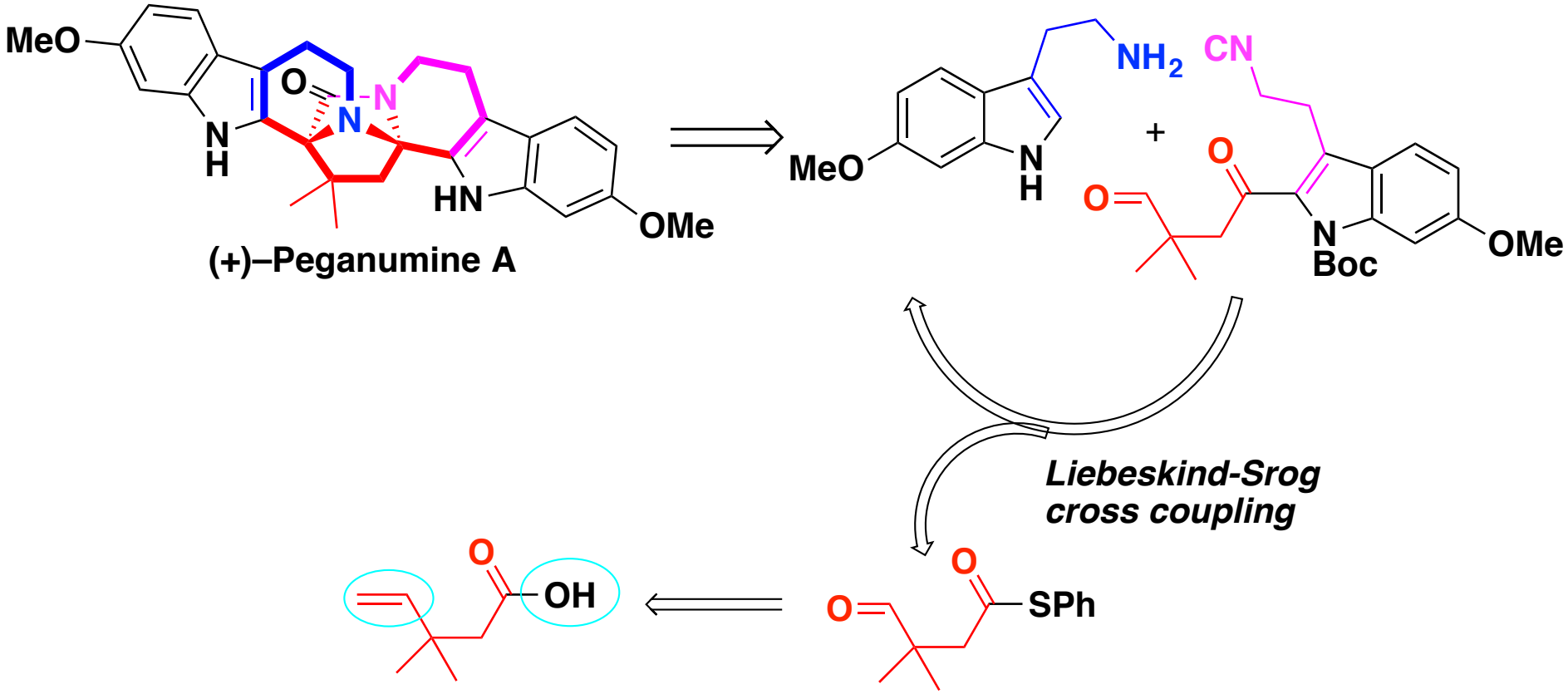


Biosynthesis hypothesis: Hua, H.-M. *et al Org. Lett.* **2014**, *16*, 4028

Peganumine A: Retro-synthetic Analysis



Peganumine A: Retro-synthetic Analysis



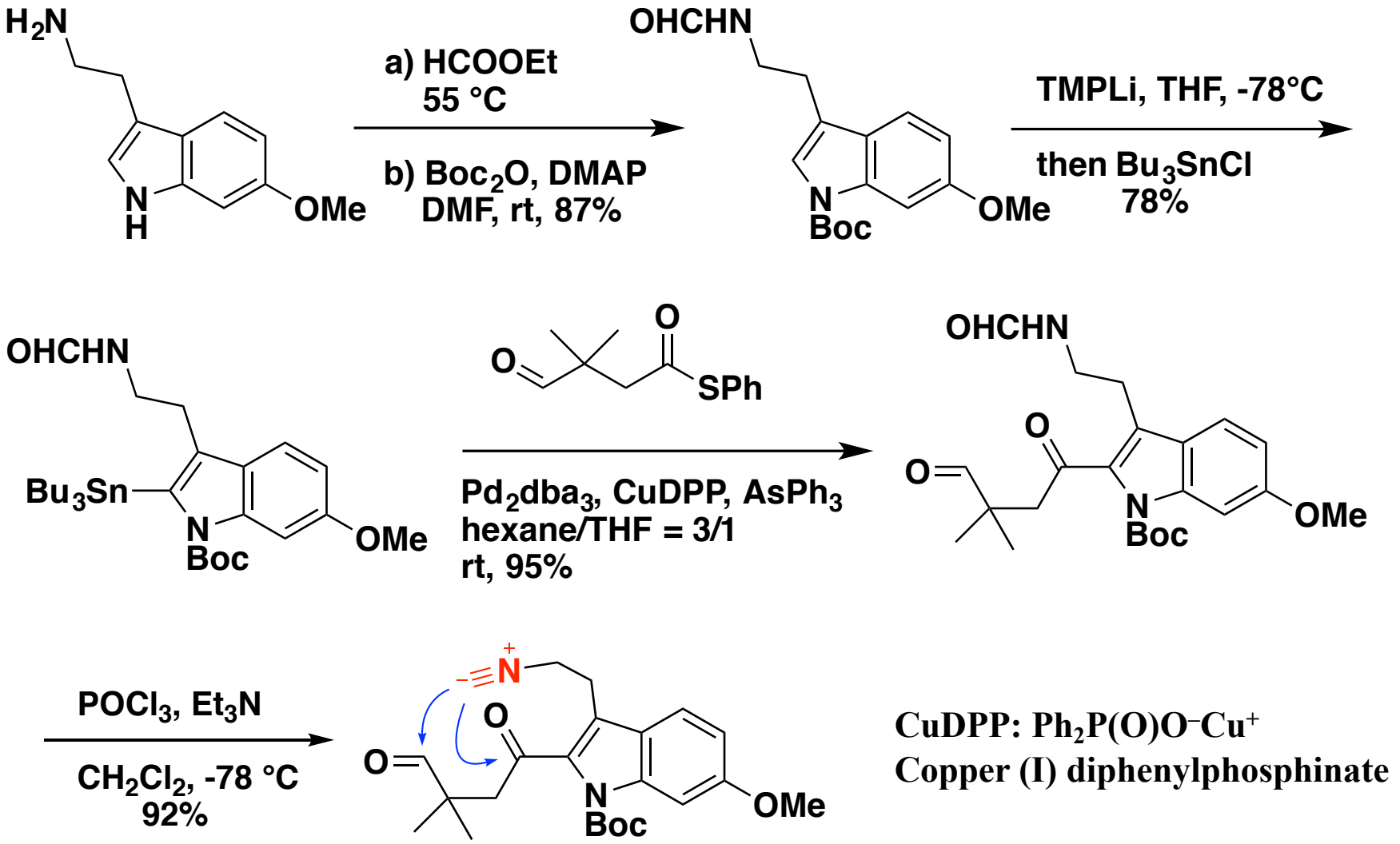
Liebeskind-Srogl cross coupling:

Liebeskind, L. S.; Srogl, J. *J. Am. Chem. Soc*. **2000**, *122*, 11260.

Yang, H.; Li, H.; Wittenberg, R.; Egi, M.; Huang, W.; Liebeskind, L. S. *J. Am. Chem. Soc*. **2007**, *129*, 1132

For a review, see: Prokopcová, H.; Kappe, C. O. *Angew. Chem., Int. Ed*. **2009**, *48*, 2276.

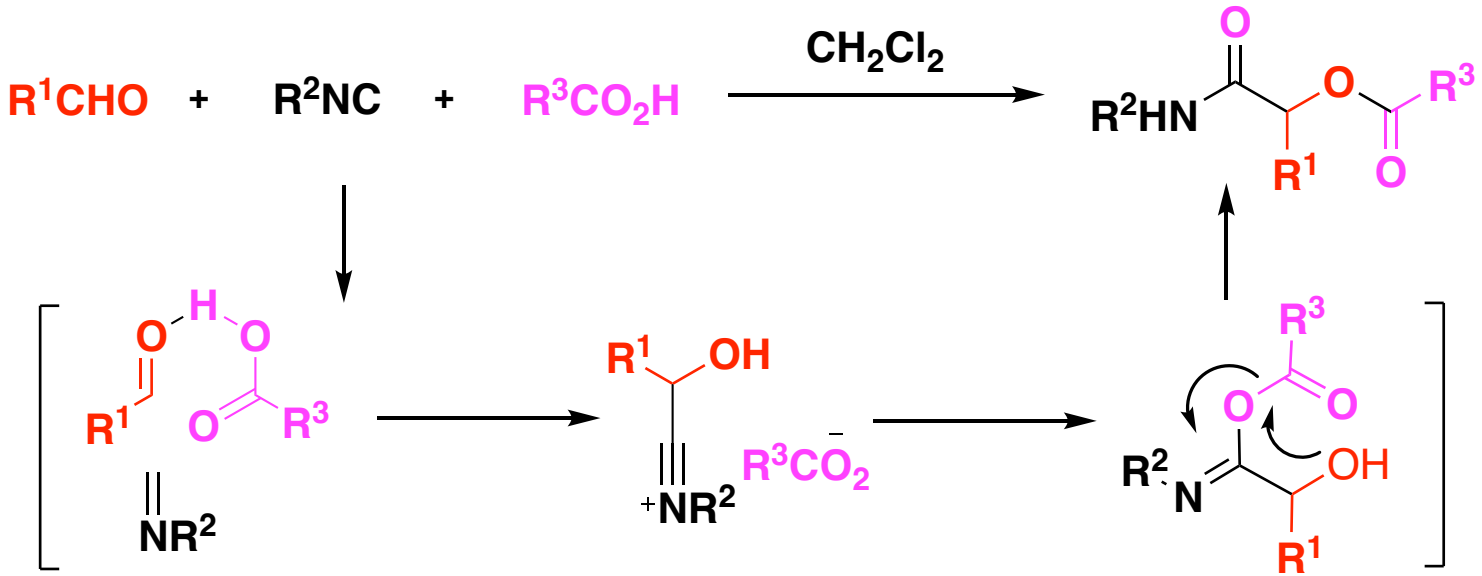
Synthesis of Functionalized Tryptamine



CuDPP: $Ph_2P(O)O^-Cu^+$
Copper (I) diphenylphosphinate

Piemontesi, C.; Wang, Q.; Zhu, J. *J. Am. Chem. Soc.* **2016**, *138*, 11148-11151.

Passerini Three-component Reaction

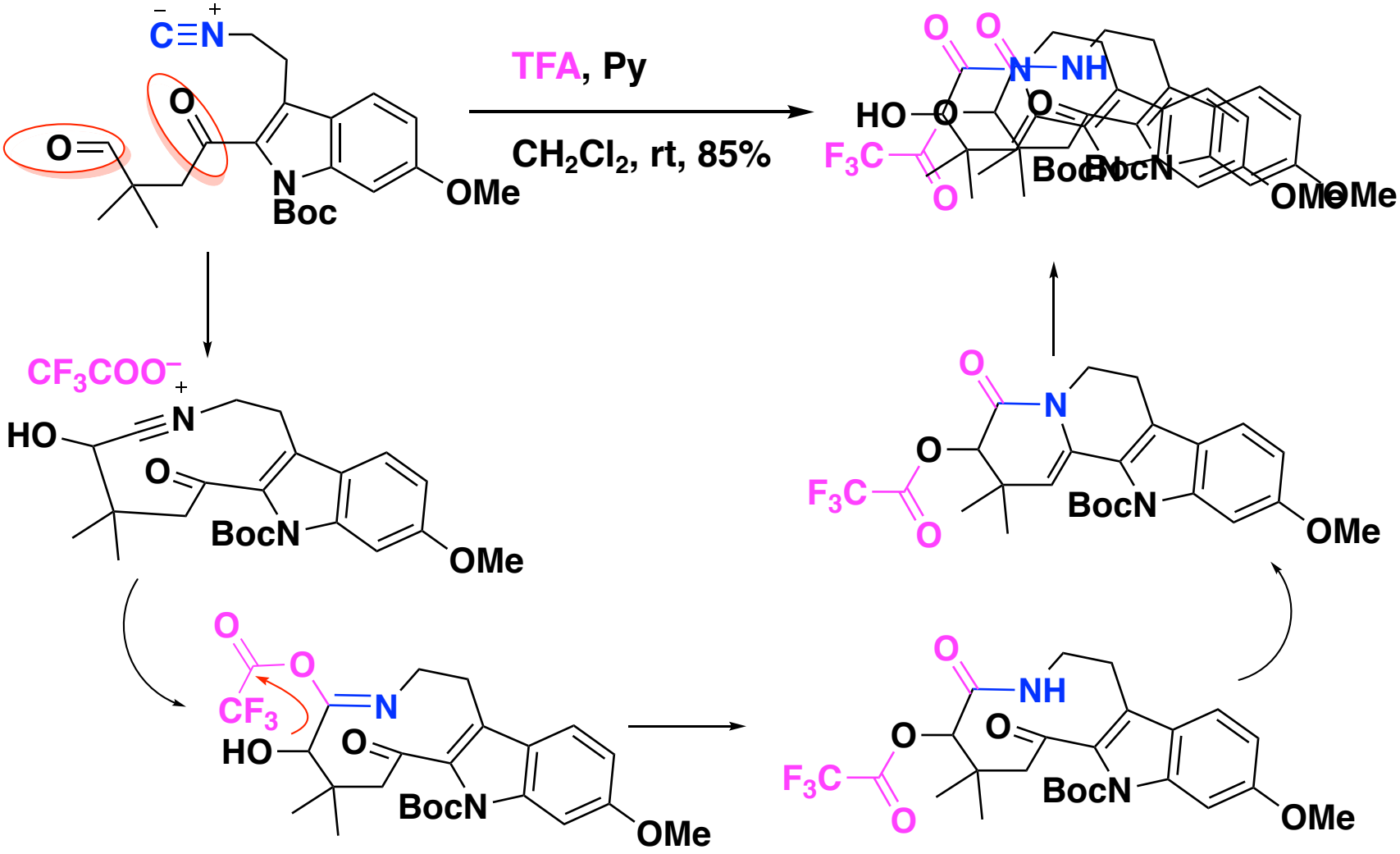


For reviews on multicomponent synthesis of macrocycles:

Wessjohann, L. A.; Rivera, D. G.; Vercillo, O. E. *Chem. Rev*. **2009**, *109*, 796.

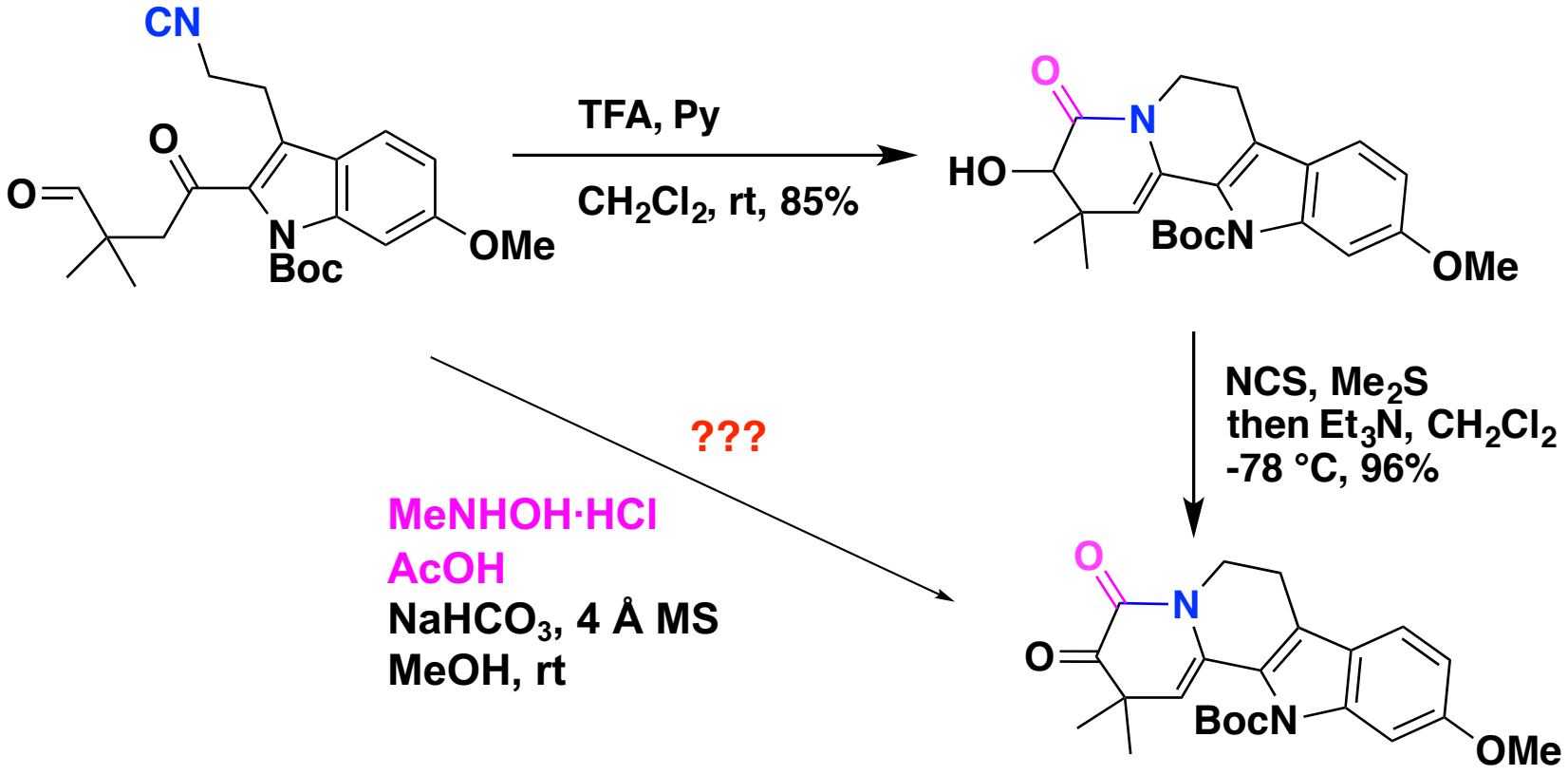
Masson, G.; Neuville, L.; Bughin, C.; Fayol, A.; Zhu, J. in "*Synthesis of Heterocycles via Multicomponent Reactions II*" (Eds. R. V. A. Orru, E. Ruijter), **2010**, Springe, Heidelberg**.**

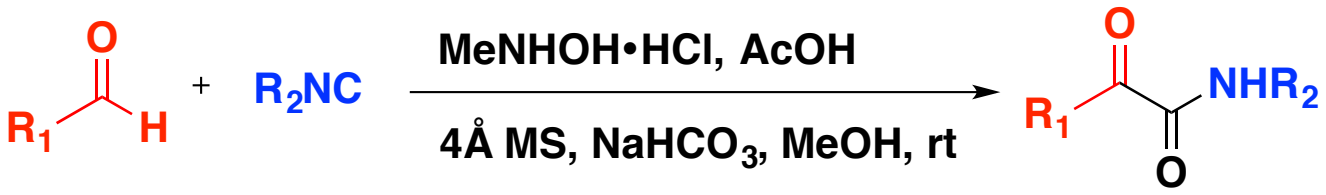
Intramolecular Three-center-two-component Passerini Reaction



Formation of a tetracycle, a hydroxy amide unit with the creation of one C-N, one C=O, one C-C bonds

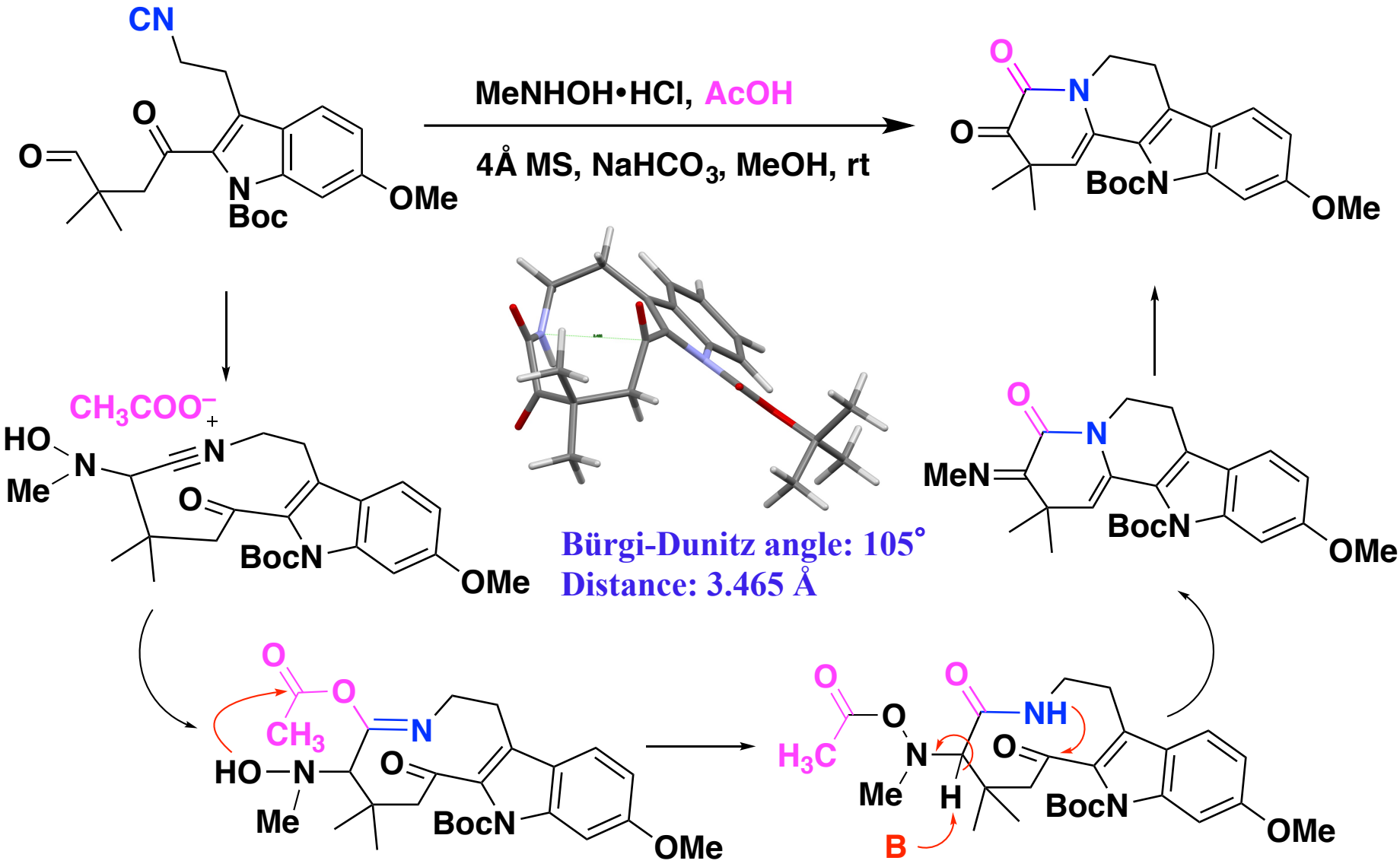
Intramolecular Three-center-two-component Passerini Reaction



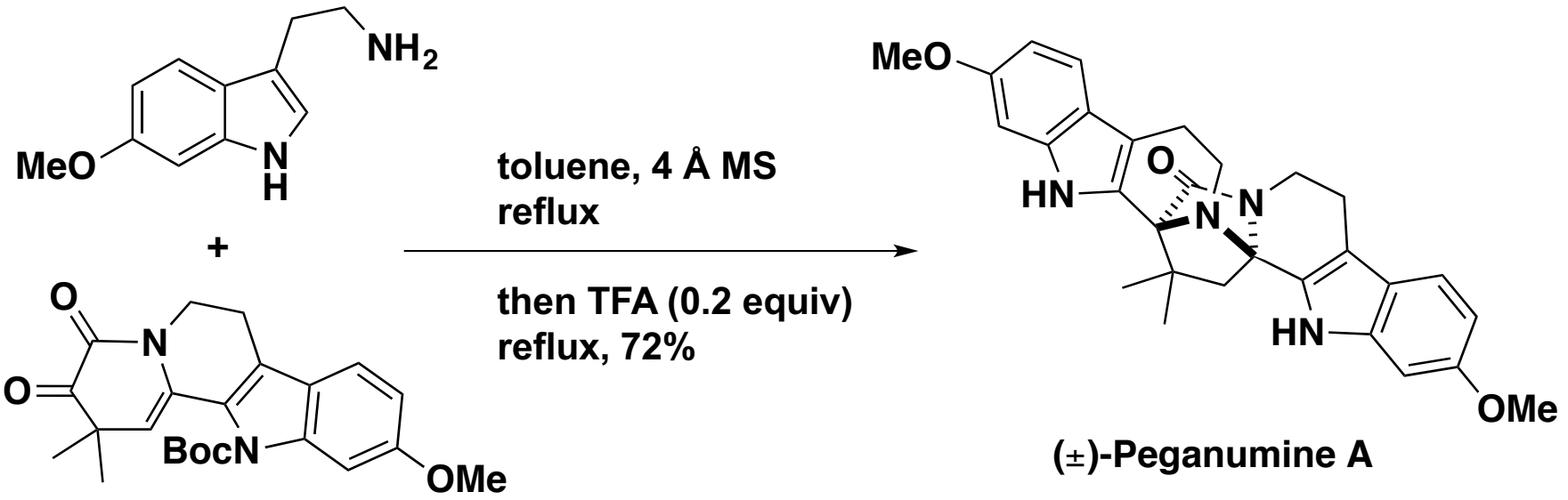


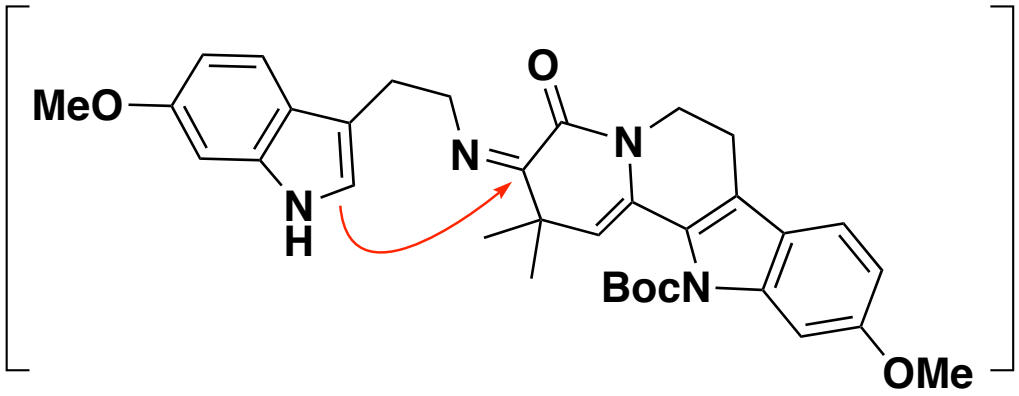
Grassot, J. M.; Masson, G.; Zhu, J. *Angew. Chem. Int. Ed.* **2008**, *47*, 947.

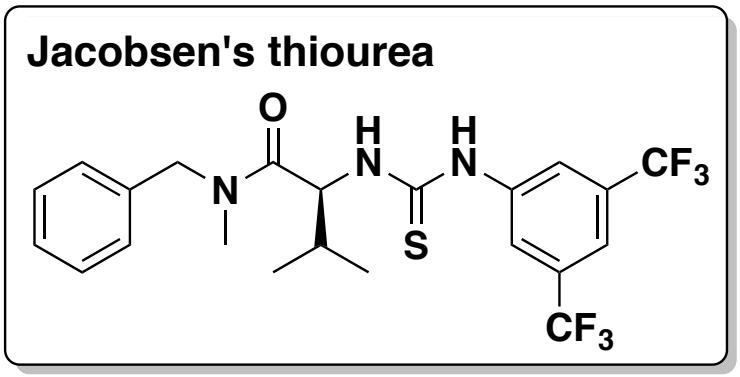
Hydroxyamine-mediated Oxidative Coupling of Aldehyde with Isocyanide



Total Synthesis of (±)-Peganumine A

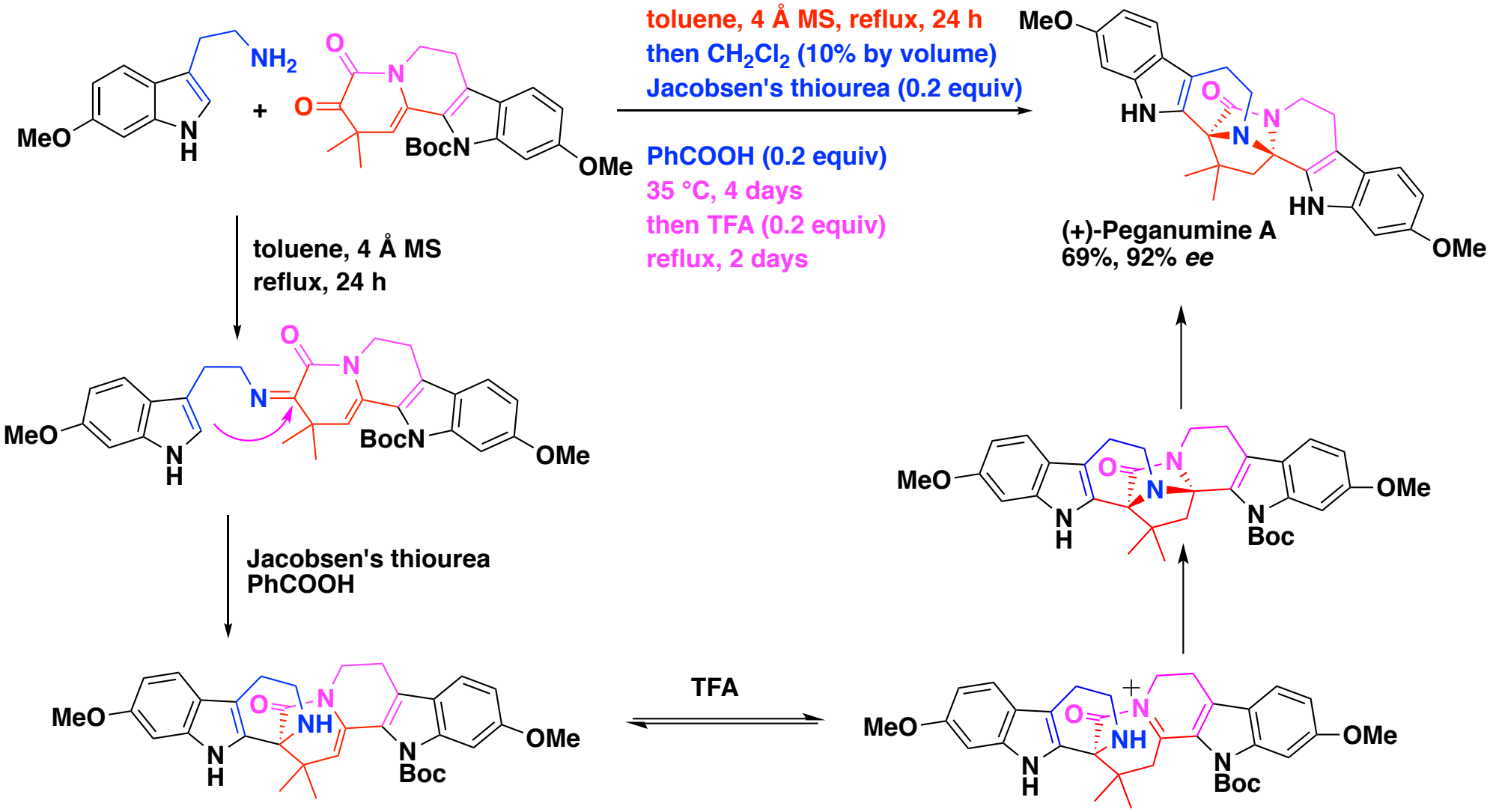






Jacobsen, E. et al. *J. Am. Chem. Soc.* **2004**, *126*, 10558
Jacobsen, E. et al. *Org. Lett.* **2009**, *11*, 887.

Total Synthesis of (+)-Peganumine A

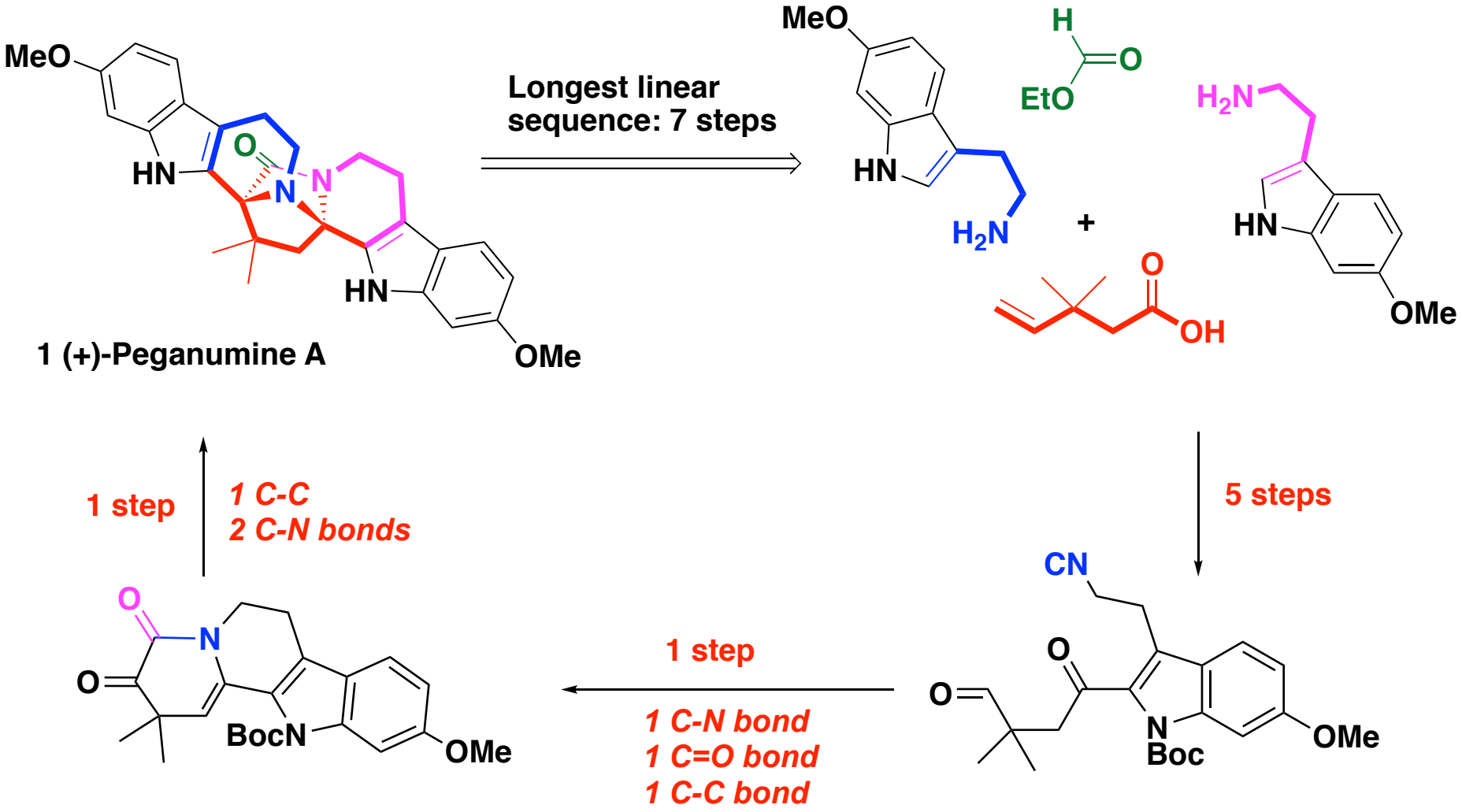


1 C-C, 2 C-N bonds, two quaternary stereocenters

2 Spirocycles, concurrent formation of the 2,7-diazabicyclo[2.2.1]heptan-3-one unit

Piemontesi, C.; Wang, Q.; Zhu, J. *J. Am. Chem. Soc.* **2016**, *138*, 11148.

Total Synthesis of (–)-Peganumine A: Combined Use of MCR and Domino Process



Piemontesi, C.; Wang, Q.; Zhu, J. *J. Am. Chem. Soc.* **2016**, *138*, 11148.

Summary of Peganumine A Synthesis

1) **Liebeskind-Srog Cross Coupling**
2) **Isocyanide chemistry**
3) **Passerini three-component reaction**
4) **Ugi four-component reaction**
5) **Enantioselective Pictet-Spingler reaction**
6) **Corey-Kim Oxidation of alcohol to ketone**
7) **Transannular cyclization**