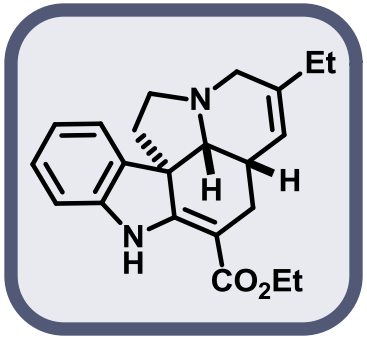
Applications of Ring Closing Metathesis : Total Synthesis of (±)-Pseudotabersonine



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Tetrahedron 2015, 71, 7323-7331

Presented By: Nutthawat Chuanopparat
Renaud Group
11.02.2016

Professor Stephen F. Martin

Univ. of New Mexico (BS, 1968)

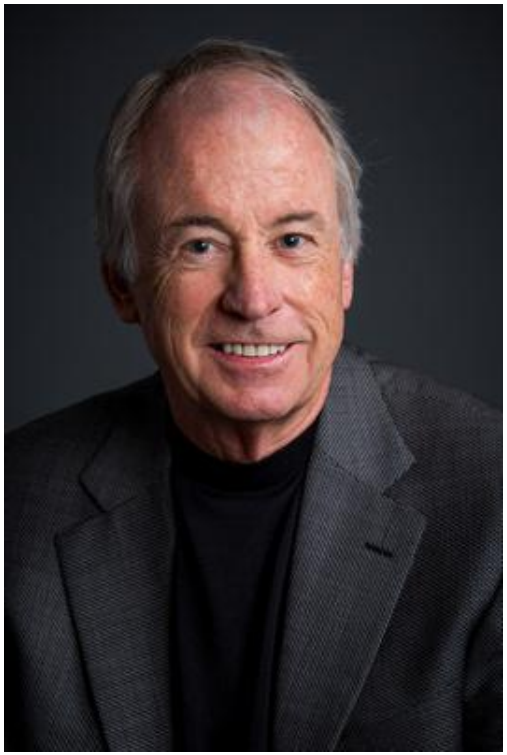
Princeton Univ. (MA, 1970; PhD, 1972)

Postdoctoral research:

Univ. of Munich (1972-73)

Massachusetts Institute of Technology (1973-74)

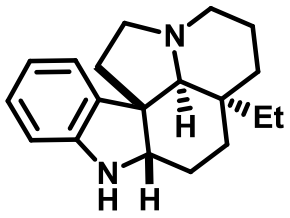
Univ. of Texas; Assist. Professor (1974-80);
Assoc. Professor (1980-86);
Professor (1986-)



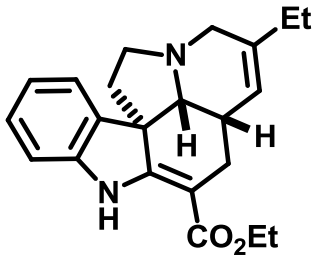
Research interests:
-Synthesis of Natural Products and Bioactive Compounds
-Molecular Recognition in Protein-Ligand Interactions

Introduction

- Psuedotabersonine is a member of the Aspidosperma family, indole alkaloids.
- It was isolated from *Pandaca caducifolia* in 1975 by Razafindrambao and Debray
- Kuehne and Grieco reported two elegant syntheses of this compound in 1992 and 1993, repectively.



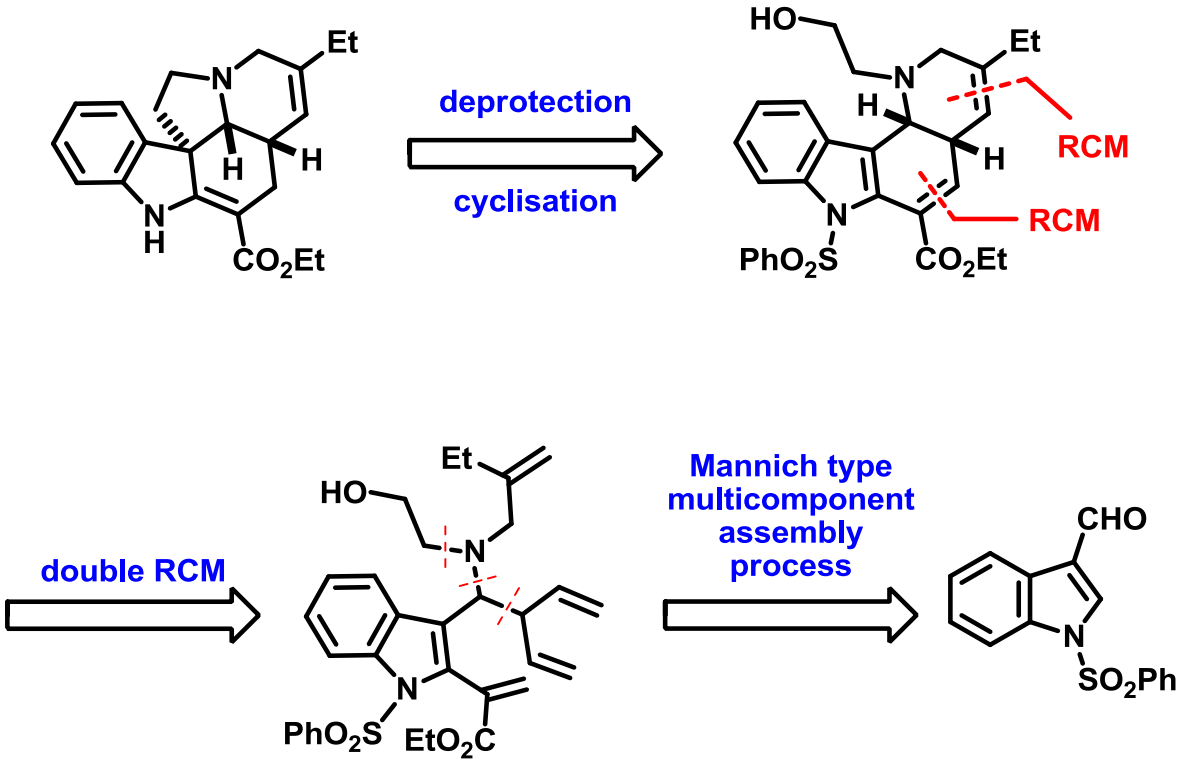
aspidospermidine



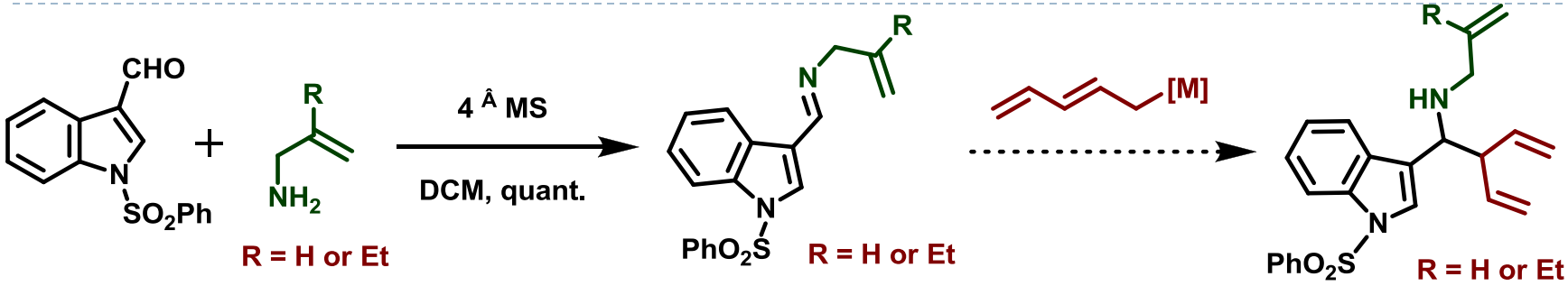
pseudotabersonine

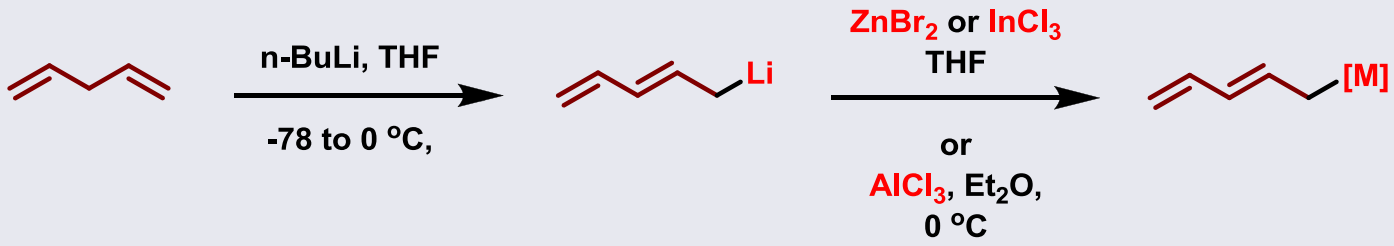
a). Zeches, M.; Debray, M. M.; Ledouble, G.; Le Men-Olivier, L.; Le Men, J. Phytochemistry 1975, 14, 1122–1124.
b). Bornmann, W. G.; Kuehne, M. E. J. Org. Chem. 1992, 57, 1752–1760.
c). Carroll, W. A.; Grieco, P. A. J. Am. Chem. Soc. 1993, 115, 1164–1165.

Retrosynthesis

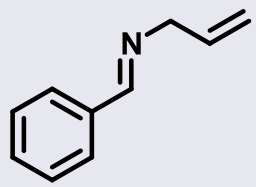


Synthesis of Tetraene

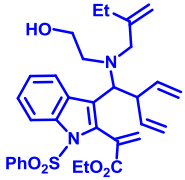




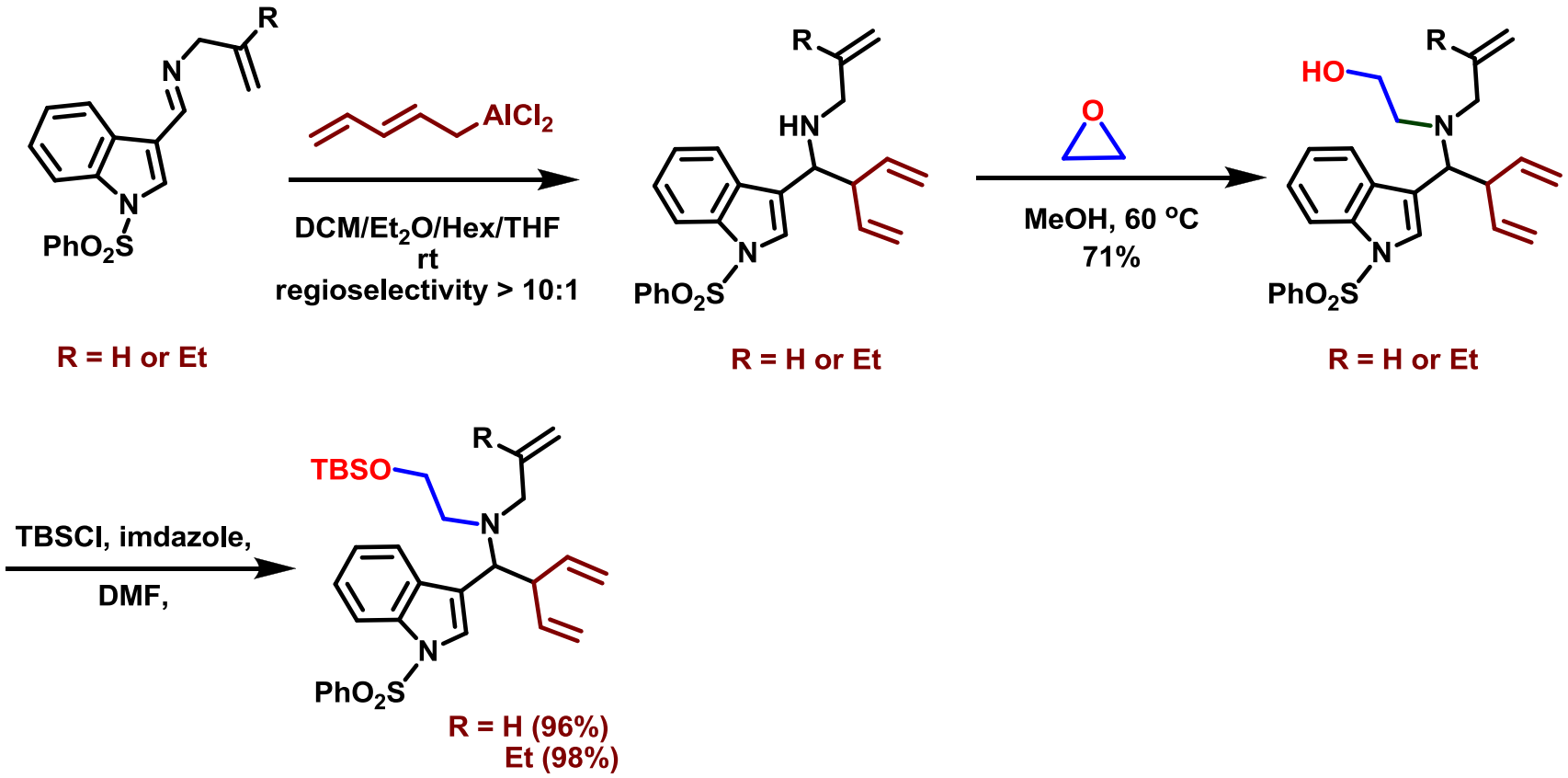
Entry	MX_n	Branched : Linear (Determined by ^{1}H-NMR)	%Conv.
1	Li	1 : 3	30
2	ZnBr	1 : 10	100
3	$InCl_2$	1 : 4	50
4	$AlCl_2$	7.5 : 1	100

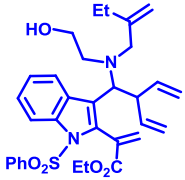


Gerard, F.; Miginiac, P. Bull. Soc. Chim. Fr. 1974, 11, 2527-2533.
Deck, J. A.; Martin, S. F. Org. Lett. 2010,12, 2610-2613.
S. Okamoto, Fumie Sato Journal of Organometallic Chemistry 2001, 624, 151–156



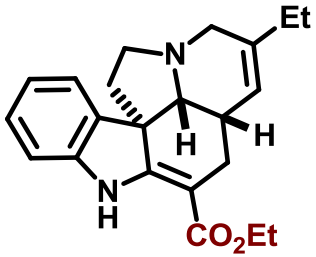
Synthesis of Tetraene (cont.)



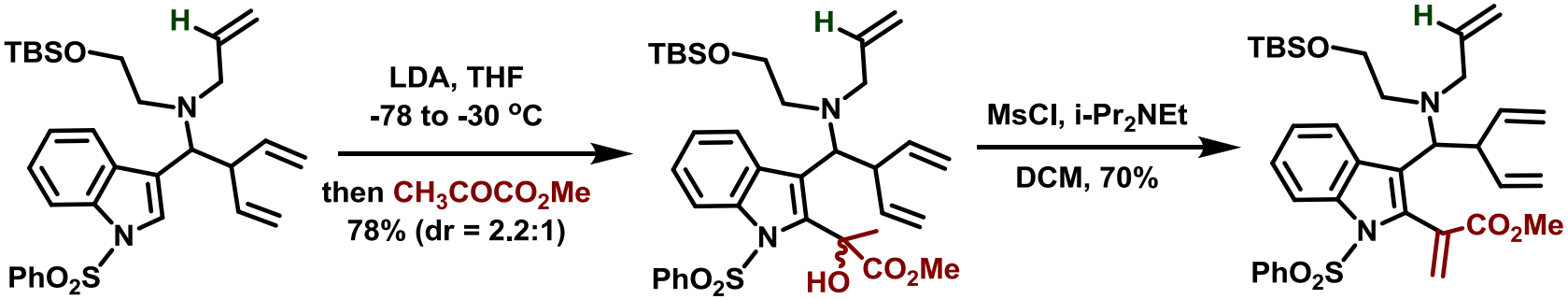


Synthesis of Tetraene (cont.)

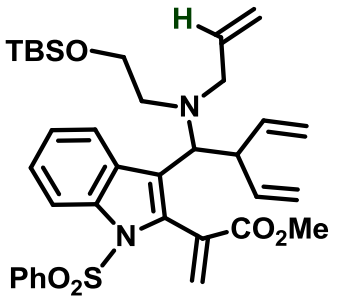
Model Study

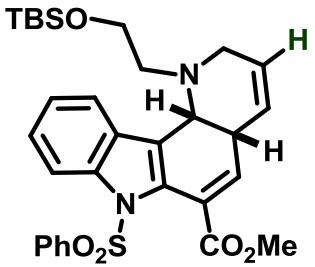


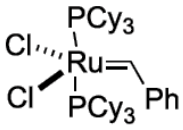
pseudotabersonine



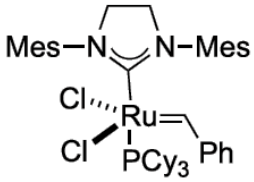
Model Study: Double RCM Reaction



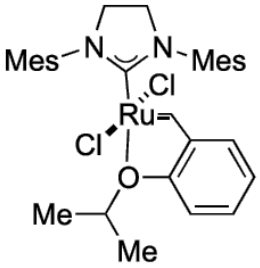




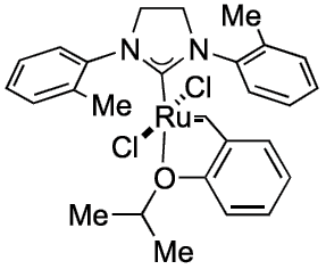
Grubbs I



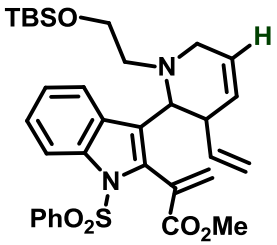
Grubbs II



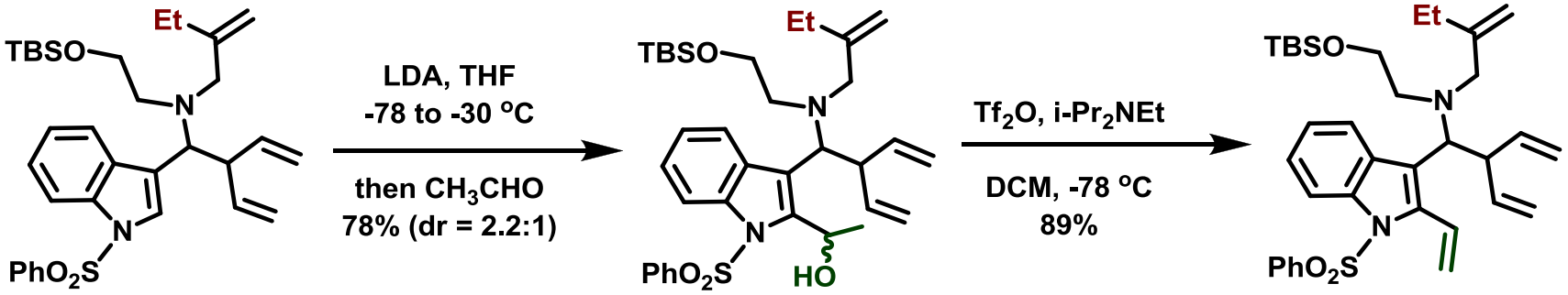
Hoveyda-Grubbs II



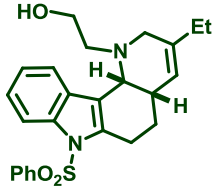
Grubbs-Stewart

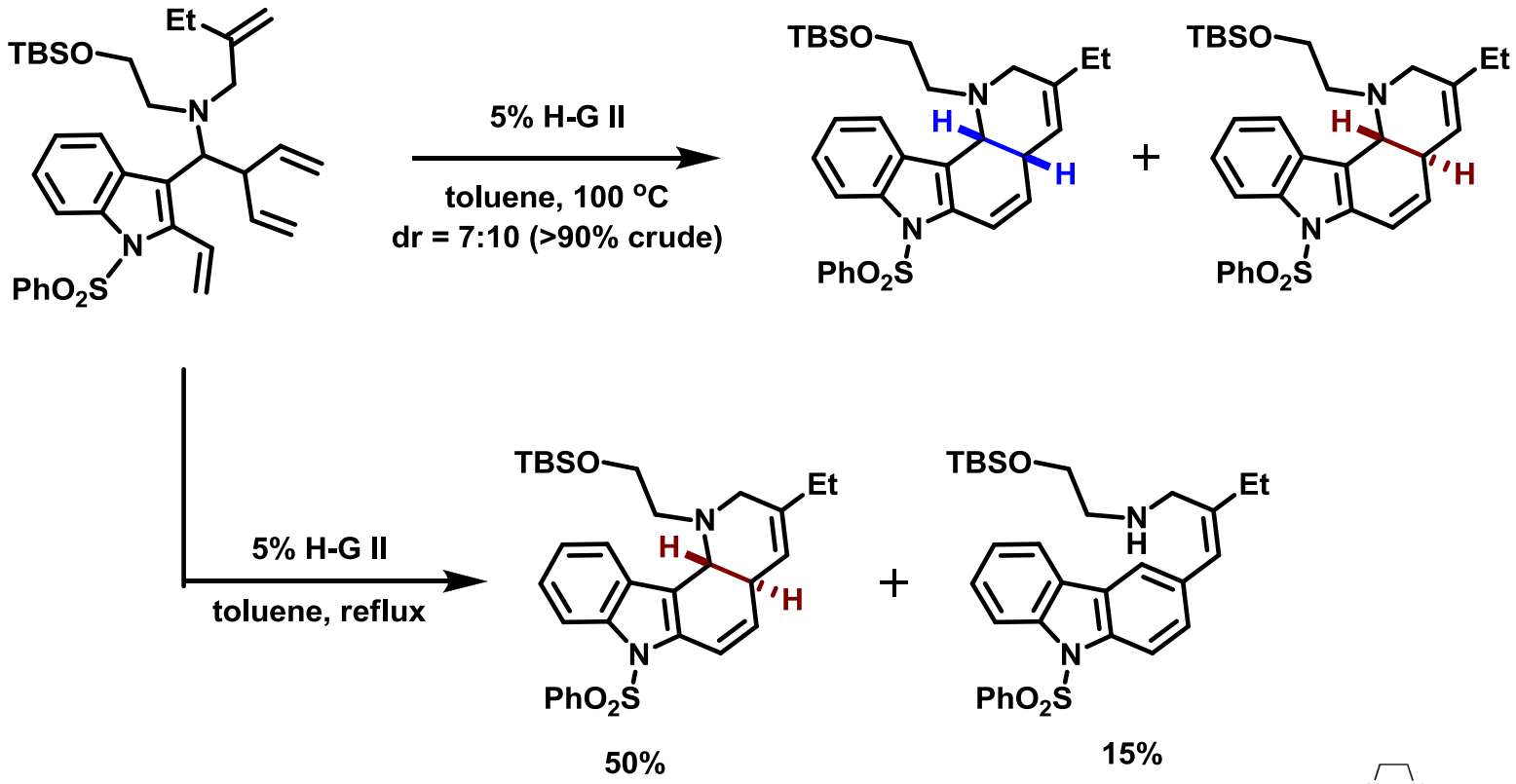


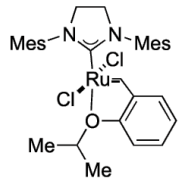
Synthesis of Tetraene (cont.)



Double RCM of Tetraene



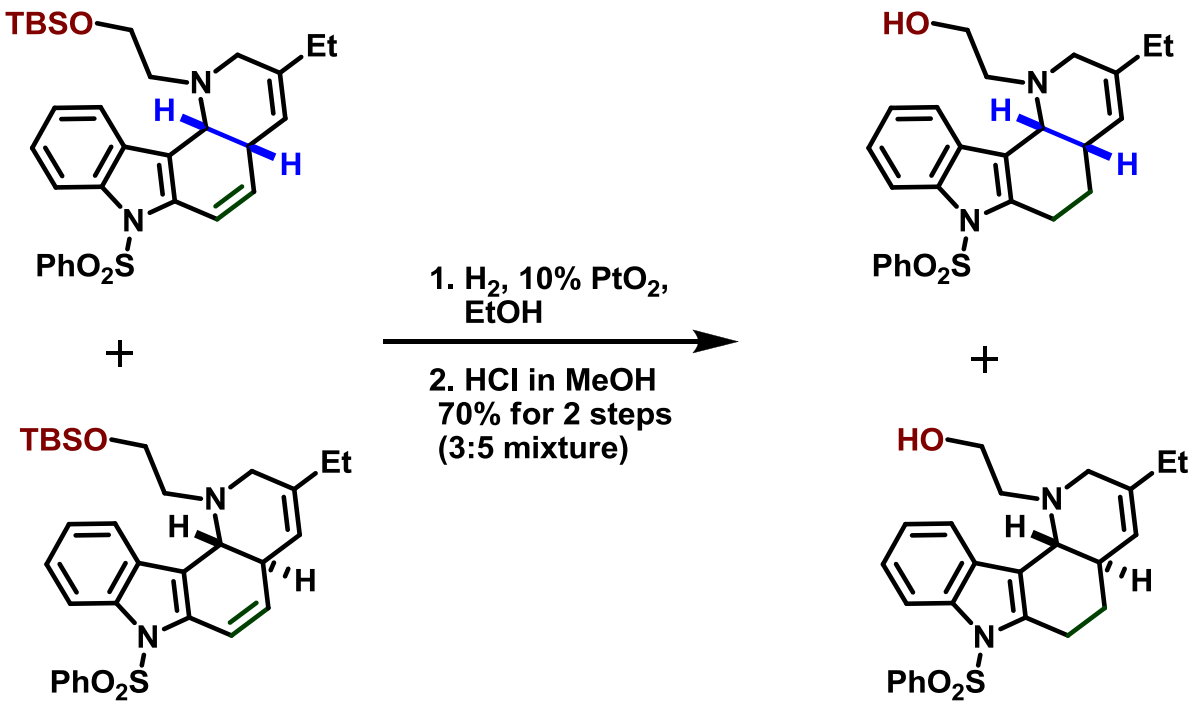




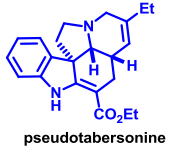
Hoveyda-Grubbs II

The ratio was determined by comparison the 1H NMR of the corresponding H3 of the crude double RCM reaction mixture

Construction of Tetracycles

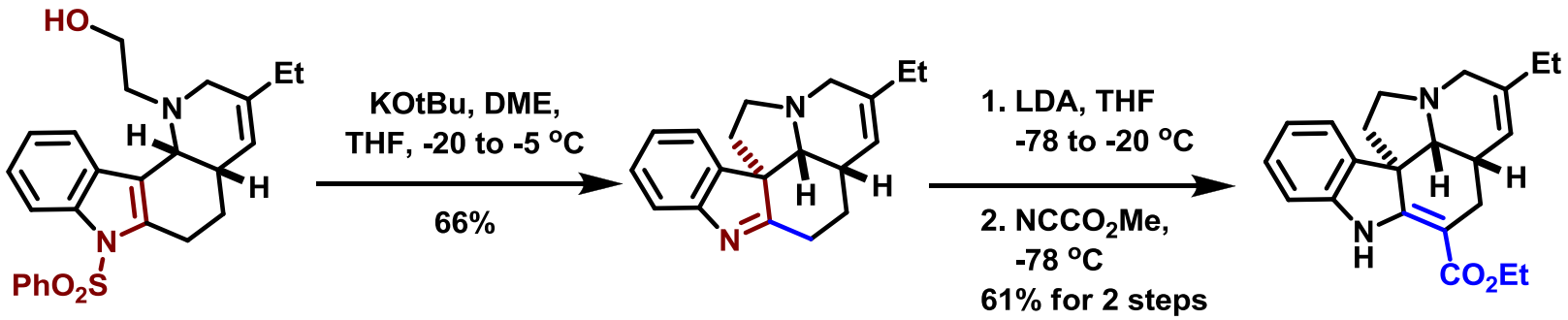


The ratio was determined by comparison the 1H NMR of the corresponding H3 of the crude reaction mixture



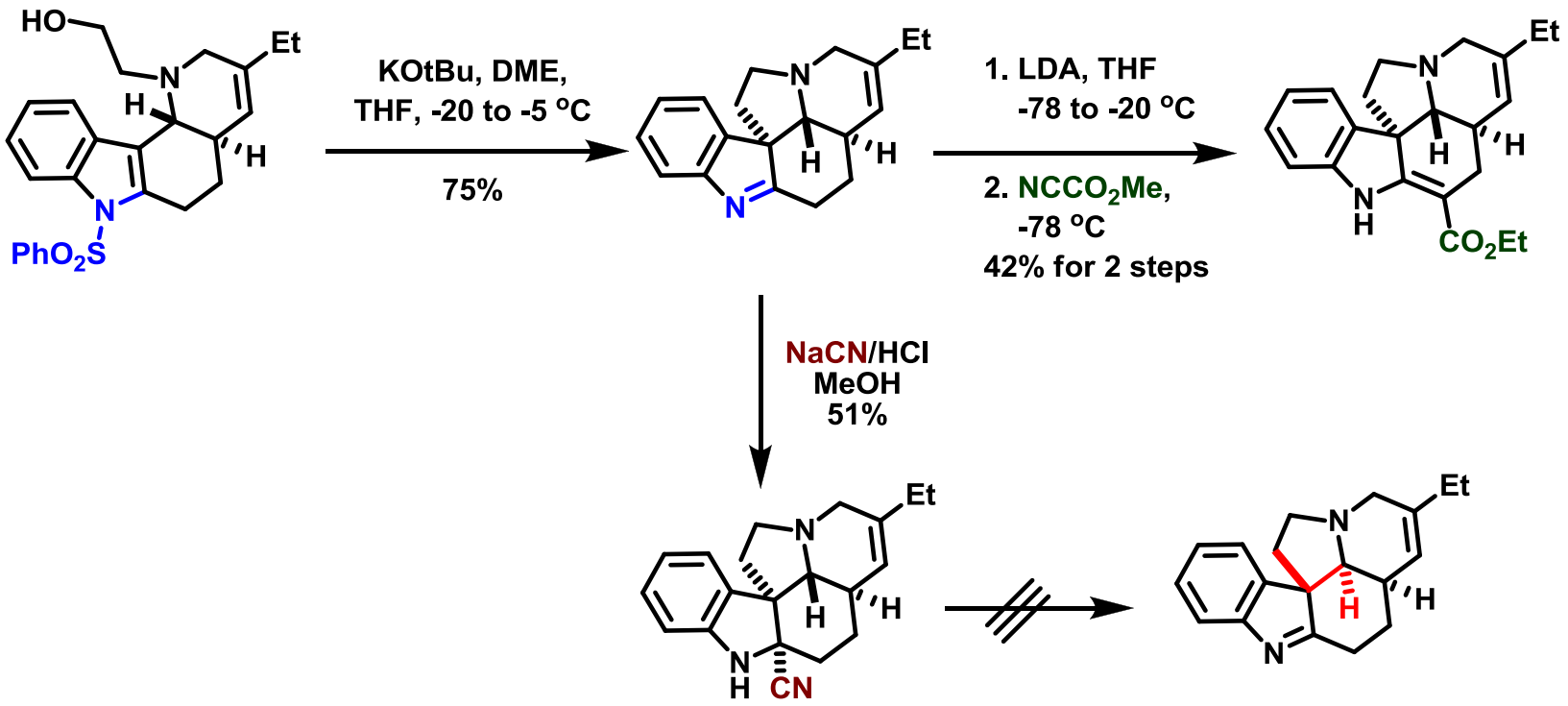
pseudotabersonine

Synthesis of (±)-Pseudotabersonine



Kozmin, S. A.; Rawal, V. H. J. Am. Chem. Soc. 1998, 120, 13523-13524
Overman, L. E.; Sworin, M.; Burk, R. M. J. Org. Chem. 1983, 48, 2685-2690.

Synthesis of (±)-14-epi-Pseudotabersonine



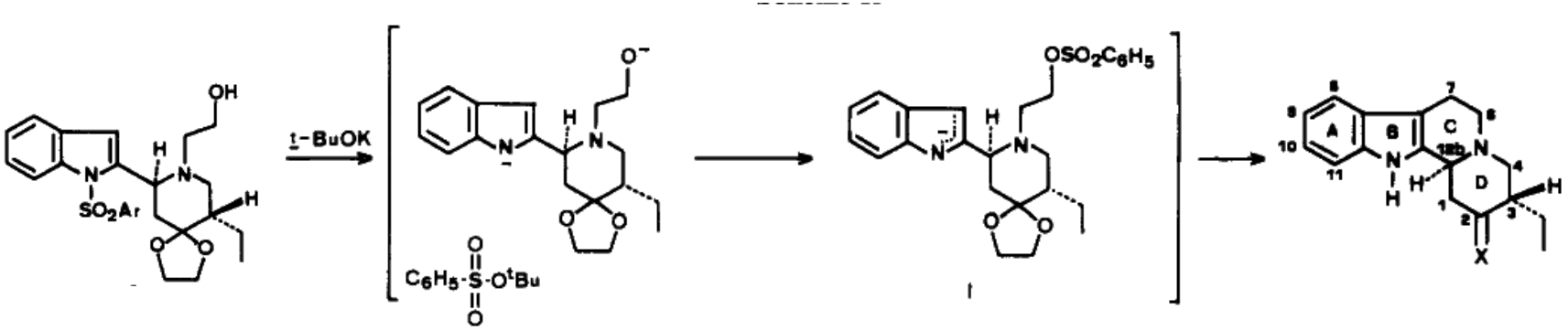
Conclusions

- **The synthesis was accomplished**
  - **in 11 steps**
  - **with 5% overall yield.**

- **Key reactions**
  - **Mannich-like multicomponent assembly process,**
  - **Double RCM**
  - **one-pot deprotection/protection/cyclisation reactions**

Thank You
for
Your Kind Attention

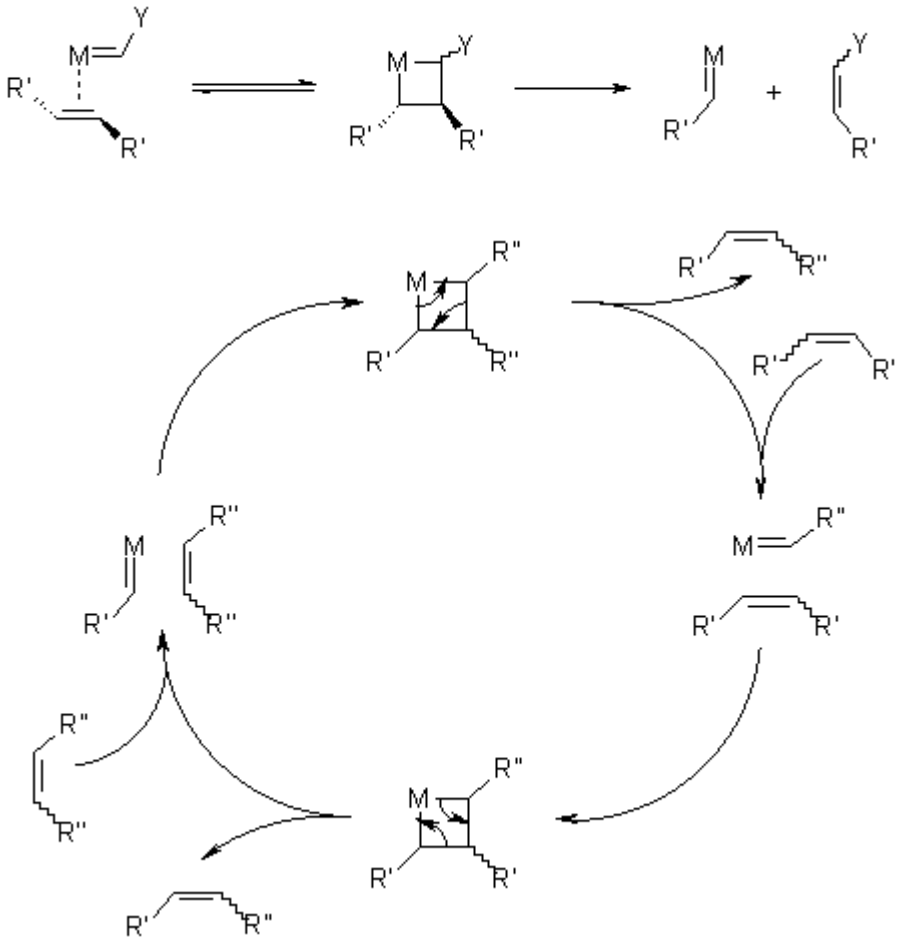
One-pot *N*-deprotection/*O*-sulfonylation

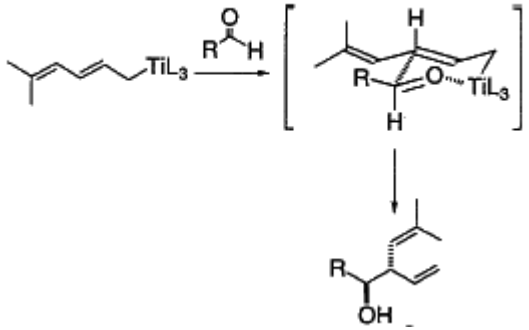


Scheme II shows a possible pathway to rationalize the formation of tetracycles **21** and **22**. *tert*-Butyl benzenesulfonate, formed in the deprotection of the indole nitrogen by *t*-BuOK, can act as a sulfonylating agent upon the piperidine ethoxy substituent to give the intermediate I. Further deplacement of the sulfonate group by the ambident indolyl anion, either by C(3) or by the nitrogen, would lead to compounds **21** and **22**.

J. Org. Chem. **1989**, *54*, 5591–5597

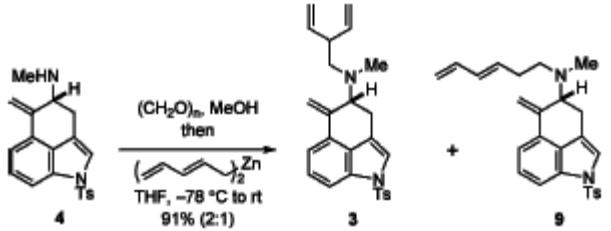
RCM





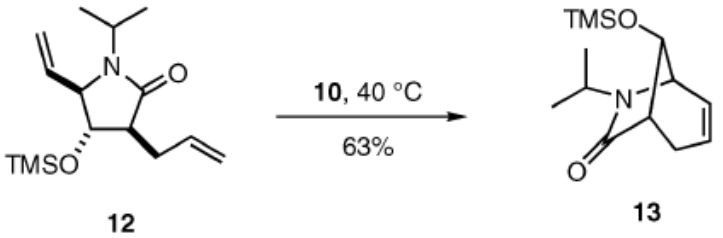
The predominant production of γ-addition product(s) **2** and the diastereoselectivity observed for the reaction shown in entry 11 can be explained by assuming that the generated allyltitanium would exist mostly as a primary alkyl derivative in order to avoid the steric repulsion, and the addition reaction with carbonyl compounds proceeds through the six-membered chair-like transition structure illustrated in Eq. (3), in which the substituent at the γ-position of the allylic titaniums is in the preferred equatorial position [3,4].

Journal of Organometallic Chemistry 624 (2001) 151–156



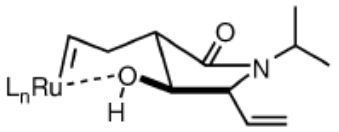
ORGANIC LETTERS 2010, 12 (11), 2610-2613

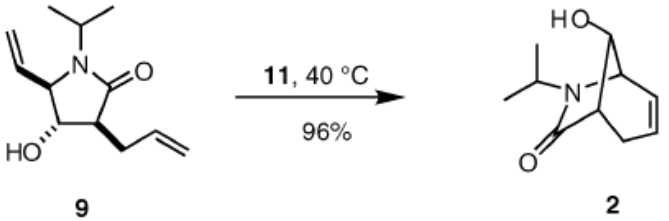
Why they have to protect OH for RCM



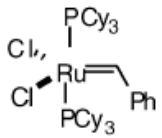
12 13

problems with this catalyst.[12] That the hydroxyl group was indeed the source of the problem was confirmed in a separate experiment where the TMS ether **12** was found to cyclize smoothly in the presence of **10** to give **13** (Scheme 3). It is perhaps instructive to consider a possible cause for the lack of the observed reactivity of **9** toward **10**, even though such reasoning is presently speculative. On the basis of steric considerations, **10** would likely react preferentially with the less hindered allylic carbon−carbon double bond of **9**. If the proximal hydroxy group then coordinated with the ruthenium ion as in **14**, the complex could then be locked in a conformation that would be unreactive toward further metathesis because of the relative orientation of the carbene and the pendant vinyl group.

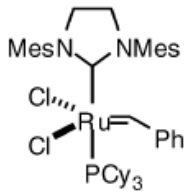




9 2



10



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