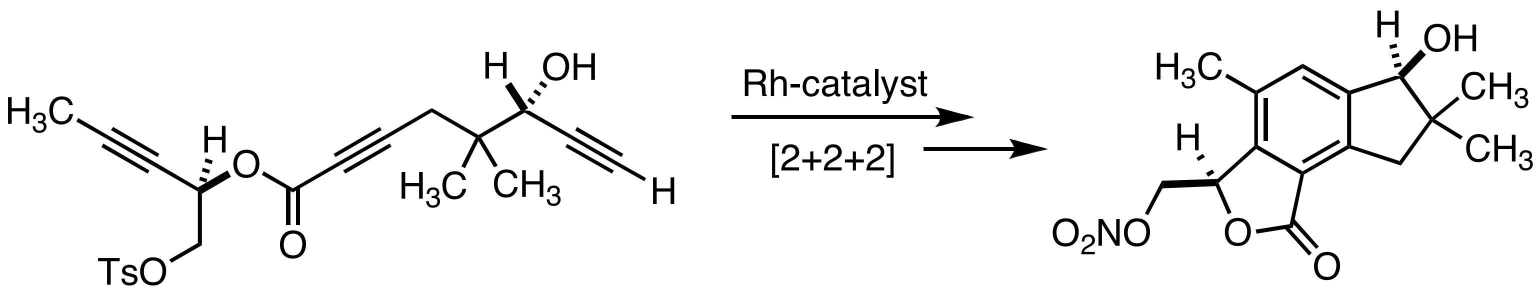
Total Syntheses of the Marine Illudalanes Alcyopterosin I, L, M, N, and C

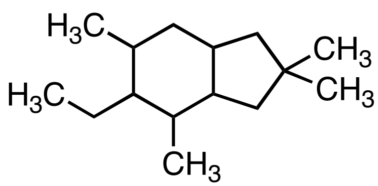
Welsch, T.; Tran, H.-A.; Witulski, B. *Org. Lett.* **2010**, *ASAP.*
DOI: 10.1021/ol102432q



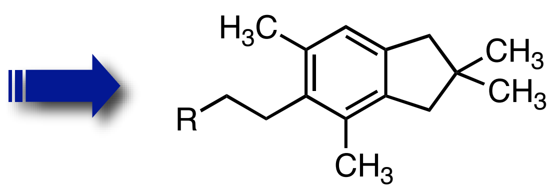
alcyopterosin M

Kara George
Wipf Group Current Literature
4 December 2010

Illudalane Sesquiterpenes: Alcyopterosin

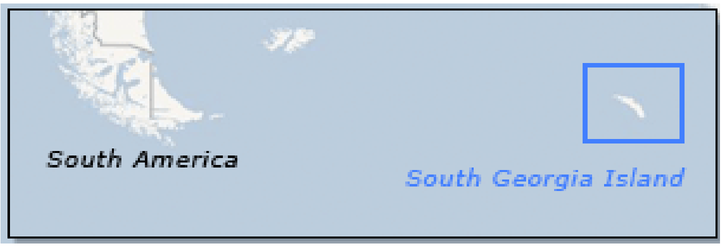


Illudalane Skeleton



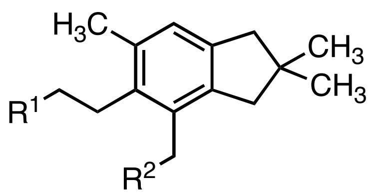
Alcyopterosin Skeleton
R= Cl or ONO_2

- The illundalane sesquiterpenes are a rare class of natural products typically isolated from fungi and ferns
- The alcyopterosin subclass are the first illudalanes isolated from marine sources
- Alcyopterosins have an aromatized six-membered ring and almost all members have either a Cl atom or a nitrate ester present on the ethylene side chain
- Alcyopterosins A-O were first isolated in 2000 by Palermo and co-workers from the sub-Antarctic deep sea soft coral *Alcyonium paessleri*
- Recently, nine additional alcyopterosins were isolated from the Antarctic soft coral *Alcyonium grandis* by Gavagnin and co-workers in 2009

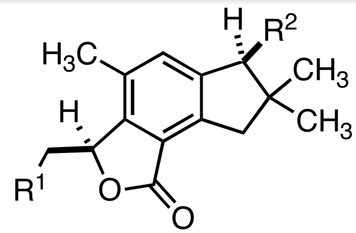


Fraga, B. M.; *Nat. Prod. Rep.* **2008**, *25*, 1180.
Palermo, J. A.; Rodriguez Brasco, M. F.; Spagnuolo, C.; Seldes, A. M. *J. Org. Chem.* **2000**, *65*, 4482.
Carbone, M.; Nunez-Pons, L.; Castelluccio, F.; Avila, C.; Gavagnin, M. *J. Nat. Prod.* **2009**, 72, 1357.

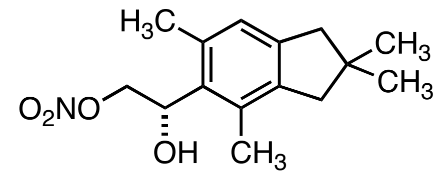
Alcyopterosins: Structure and Biological Activity



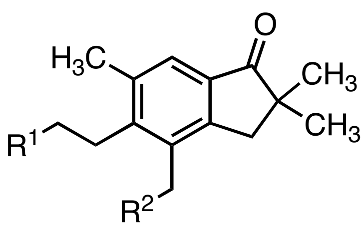
	R^1	R^2
alcyopterosin A	Cl	H
alcyopterosin B	ONO_2	H
alcyopterosin D	Cl	OH
alcyopterosin G	ONO_2	OH
alcyopterosin O	OH	OH



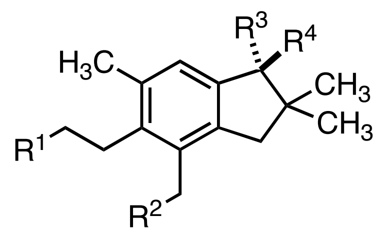
	R^1	R^2
alcyopterosin E	ONO_2	H
alcyopterosin L	Cl	OH
alcyopterosin M	ONO_2	OH



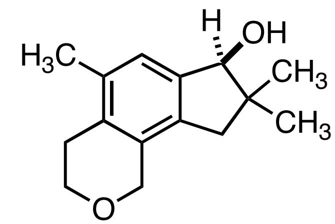
alcyopterosin F



	R^1	R^2
alcyopterosin C	ONO_2	H
alcyopterosin J	ONO_2	OH
alcyopterosin N	OH	H



	R^1	R^2	R^3	R^4
alcyopterosin H	ONO_2	H	OH	H
alcyopterosin K	Cl	OH	H	OH

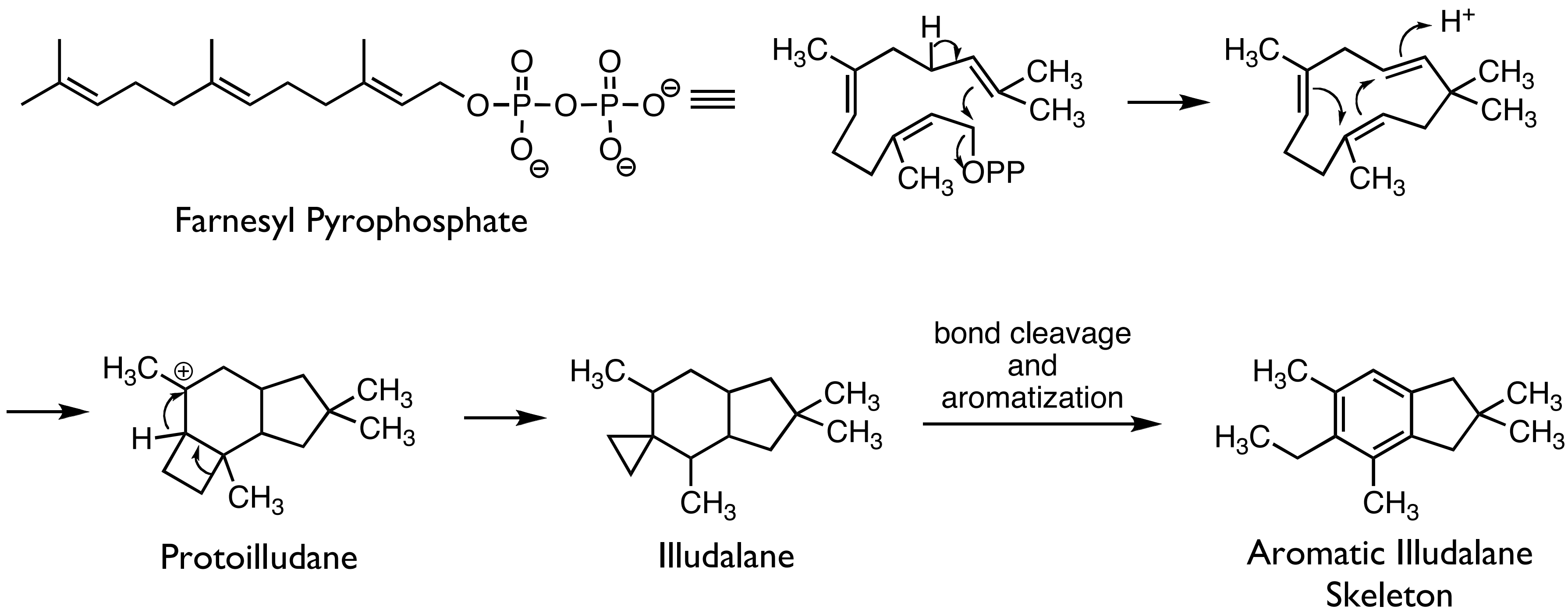


alcyopterosin I

- Alcyopterosin E showed cytotoxicity toward Hep-2 (human larynx carinoma) cell line and both alcyopterosin A and C were cytotoxic toward the HT-29 (human colon carinoma) cell line
- Alcyopterosin A and its analogs also exhibit DNA-binding properties

Palermo, J. A.; Rodriguez Brasco, M. F.; Spagnuolo, C.; Seldes, A. M. *J. Org. Chem.* **2000**, *65*, 4482.
Finkielsztein, L. M.; Bruno, A. M.; Renou, S. G.; Moltrasio Iglesias, G. Y. *Bioorg. Med. Chem.* **2006**, *14*, 1863.

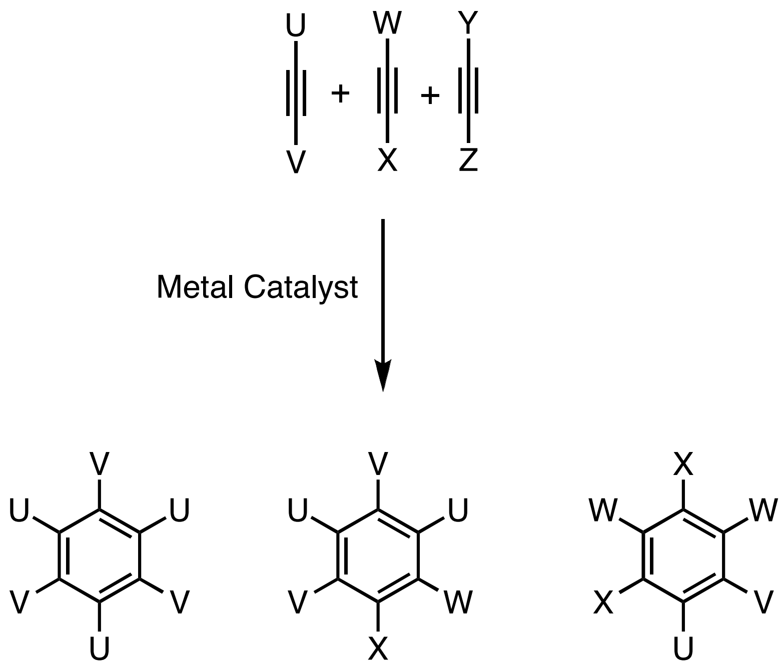
Alcyopterosins: Proposed Biosythesis



Cane, D. E.; Nachbar, R. B. *Tetrahedron Lett.* **1980**, *21*, 437.
Hanssen, H.-P.; Abraham, W.-R. *Tetrahedron.* **1988**, *44*, 2175.
Morisaki, N.; Furukawa, J.; Kobayashi, H.; Iwasaki, S.; Nozoe, S.; Okuda, S. *Tetrahedron Lett.* **1985**, *26*, 4755.

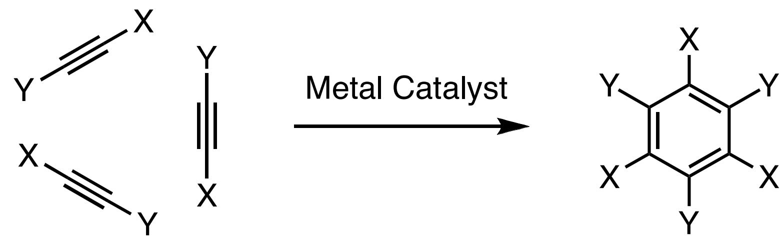
Synthetic Approaches to Alcyopterosins

- Reppe's cyclotrimeriation of acetylenes

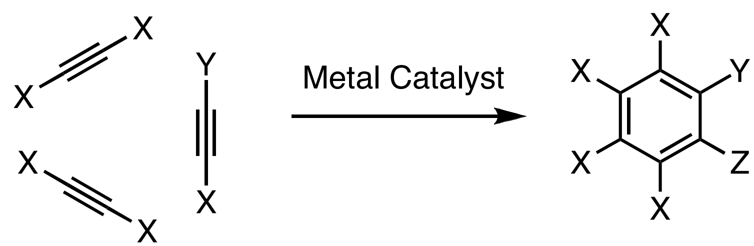


38 homo- and cross-coupled products possible!

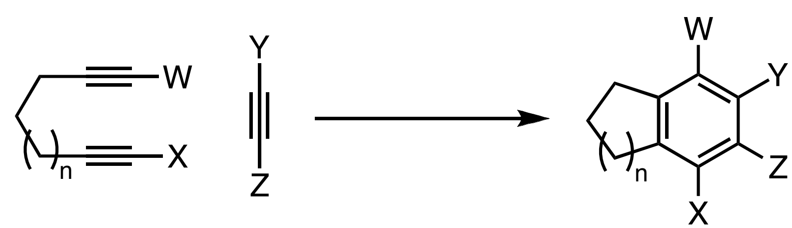
- Homo-coupling of acetylenes



- Cross-coupling using at least one symmetrical acetylene



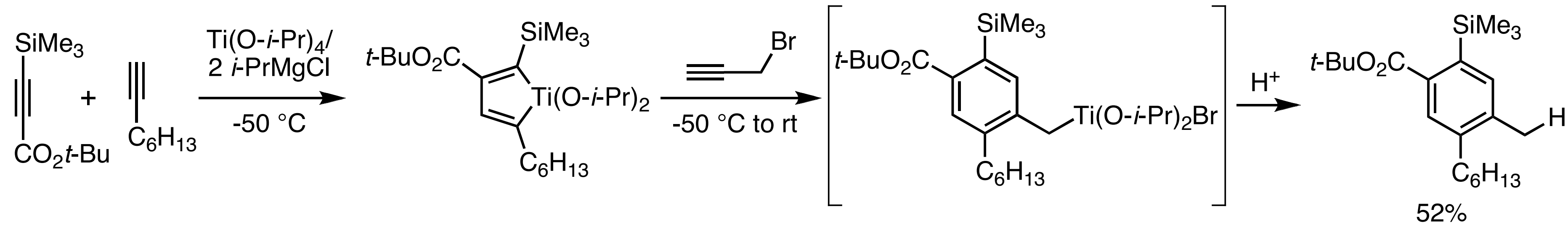
- Cross-coupling of tethered alkynes



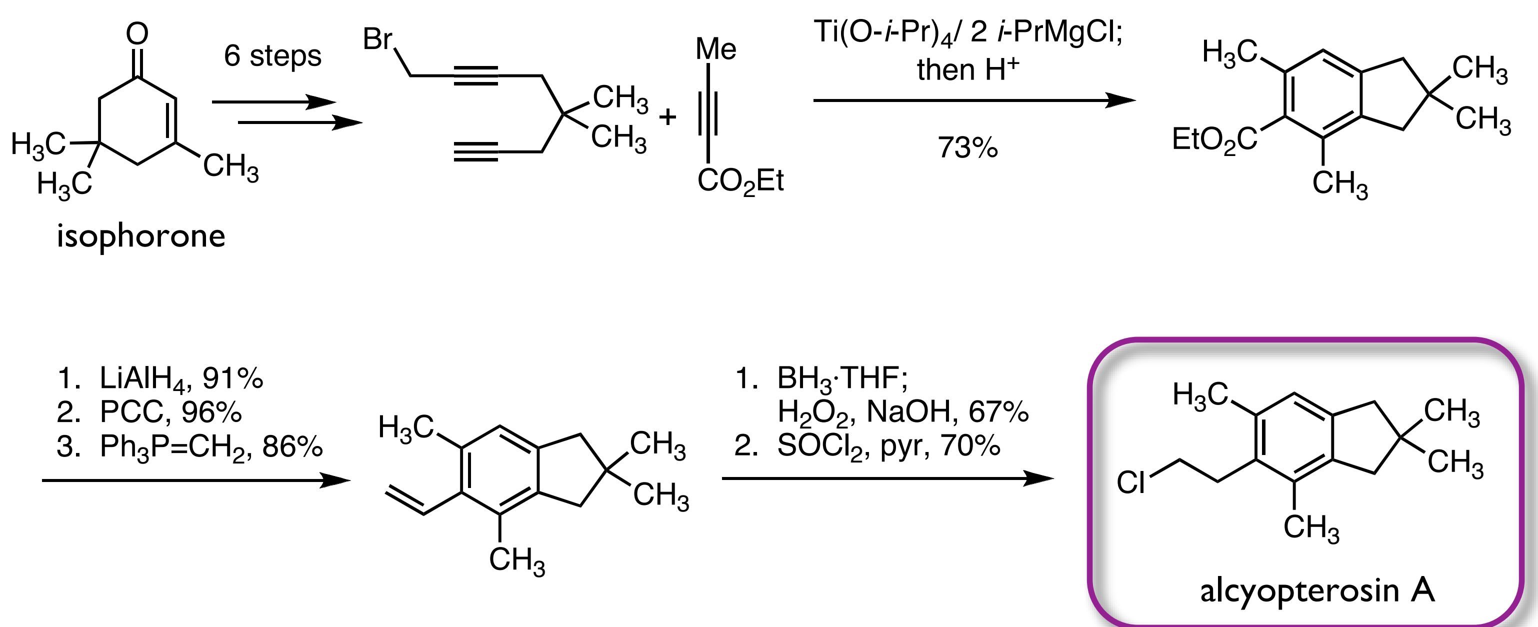
Jones, D. M. Ph. D. disertation, The Florida State University, 2010.

Synthetic Approaches to Alcyopterosins

- One-Pot Metalative Reppe reaction developed by Sato and co-workers



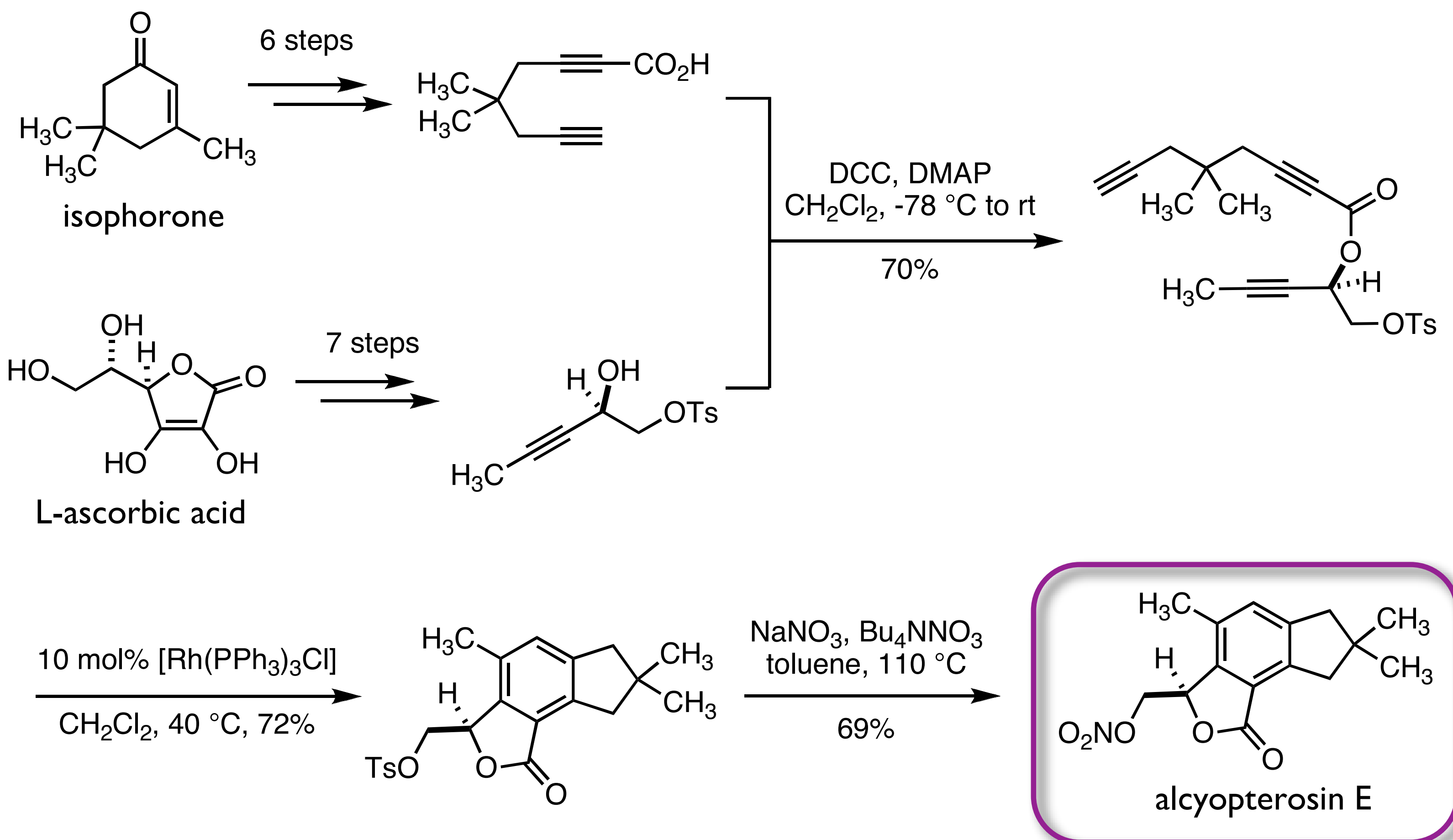
- First synthesis of alcyopterosin A



Tanaka, R.; Nakano, Y.; Suzuki, D.; Urabe, H.; Sato, F. *J. Am. Chem. Soc.* **2002**, *124*, 9682.

Synthetic Approaches to Alcyopterosins

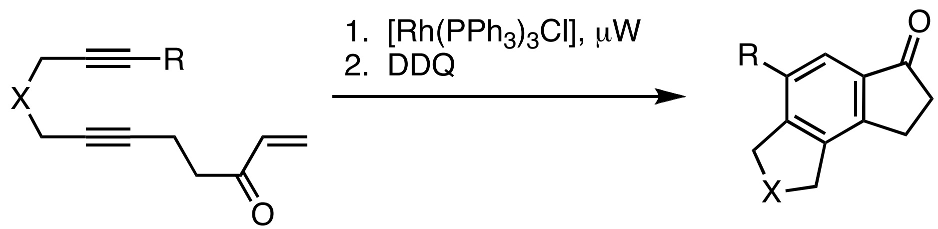
- The first total synthesis of alcyopterosin E by Witulski and co-workers
  - catalytic intramolecular alkyne cyclotrimerization with electron deficient alkynes



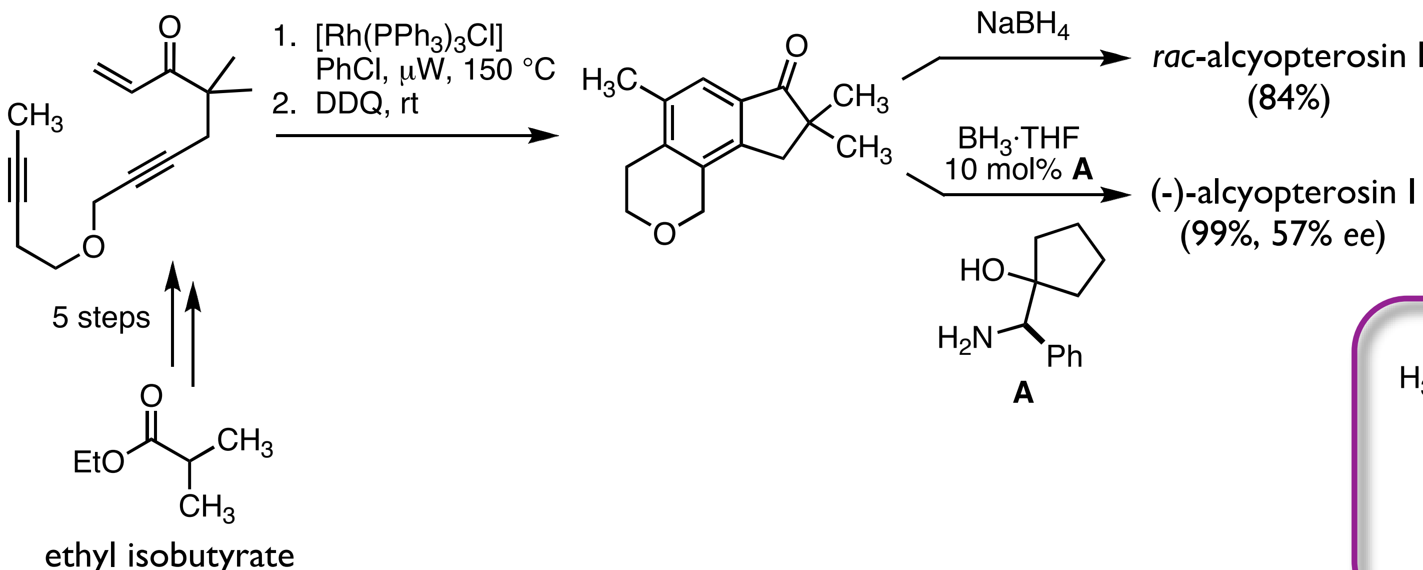
Witulski, B.; Zimmermann, A.; Gowans, N. D. *Chem. Comm.* **2002**, 2984.

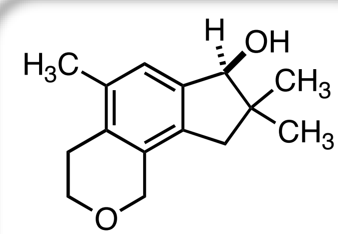
Synthetic Approaches to Alcyopterosins

- Microwave promoted Rh(I)-catalyzed [2+2+2] cyclization of diynes with α,β-unsaturated enones developed by Snyder and co-workers



- First total synthesis of alcyopterosin I

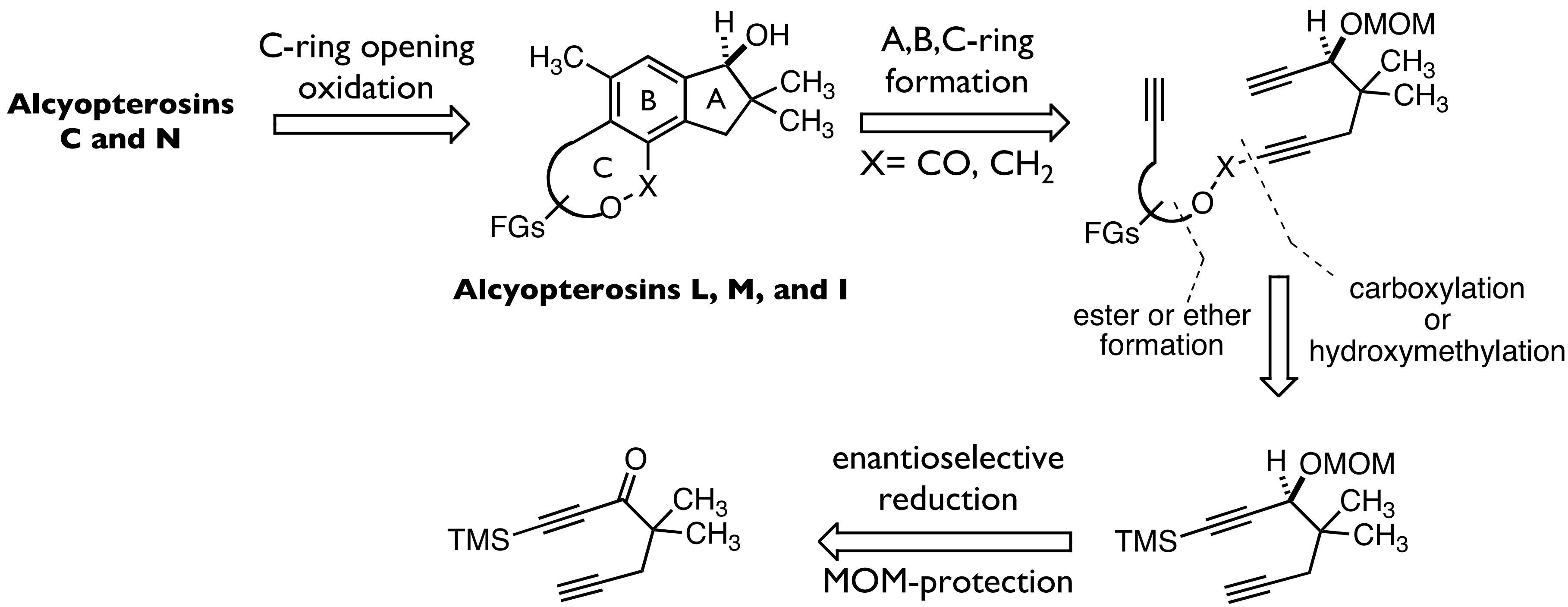




alcyopterosin I

Jones, A. L.; Snyder, J. K. *J. Org. Chem.* **2009**, *74*, 2907.

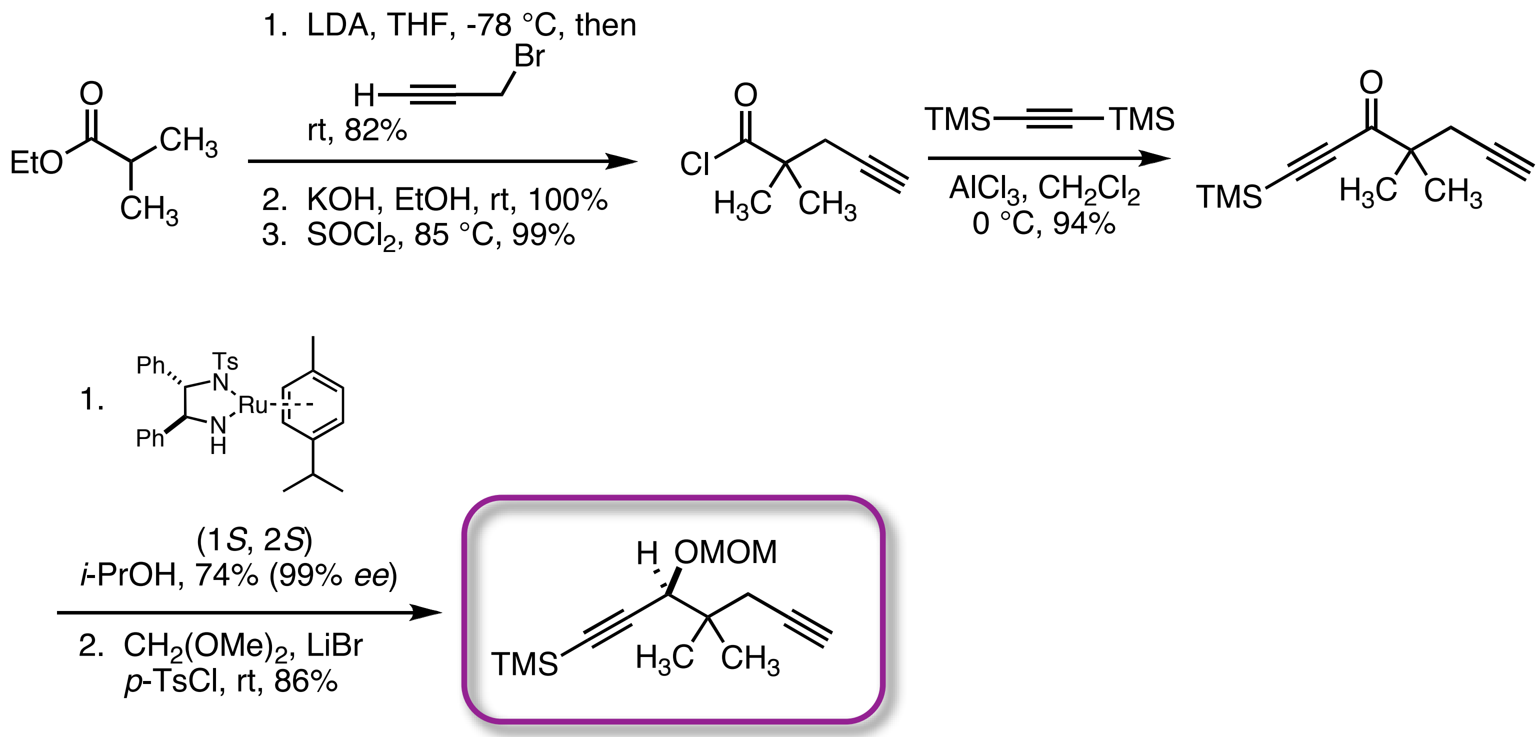
Title Paper: Synthetic Strategy



- One step formation of the ABC-ring system via a transition metal catalyzed [2+2+2] cycloaddition reaction
- Variable tether lengths would provide access to angular fused [5-6-6] and [5-6-5]
- Take advantage of readily accessible chiral building blocks

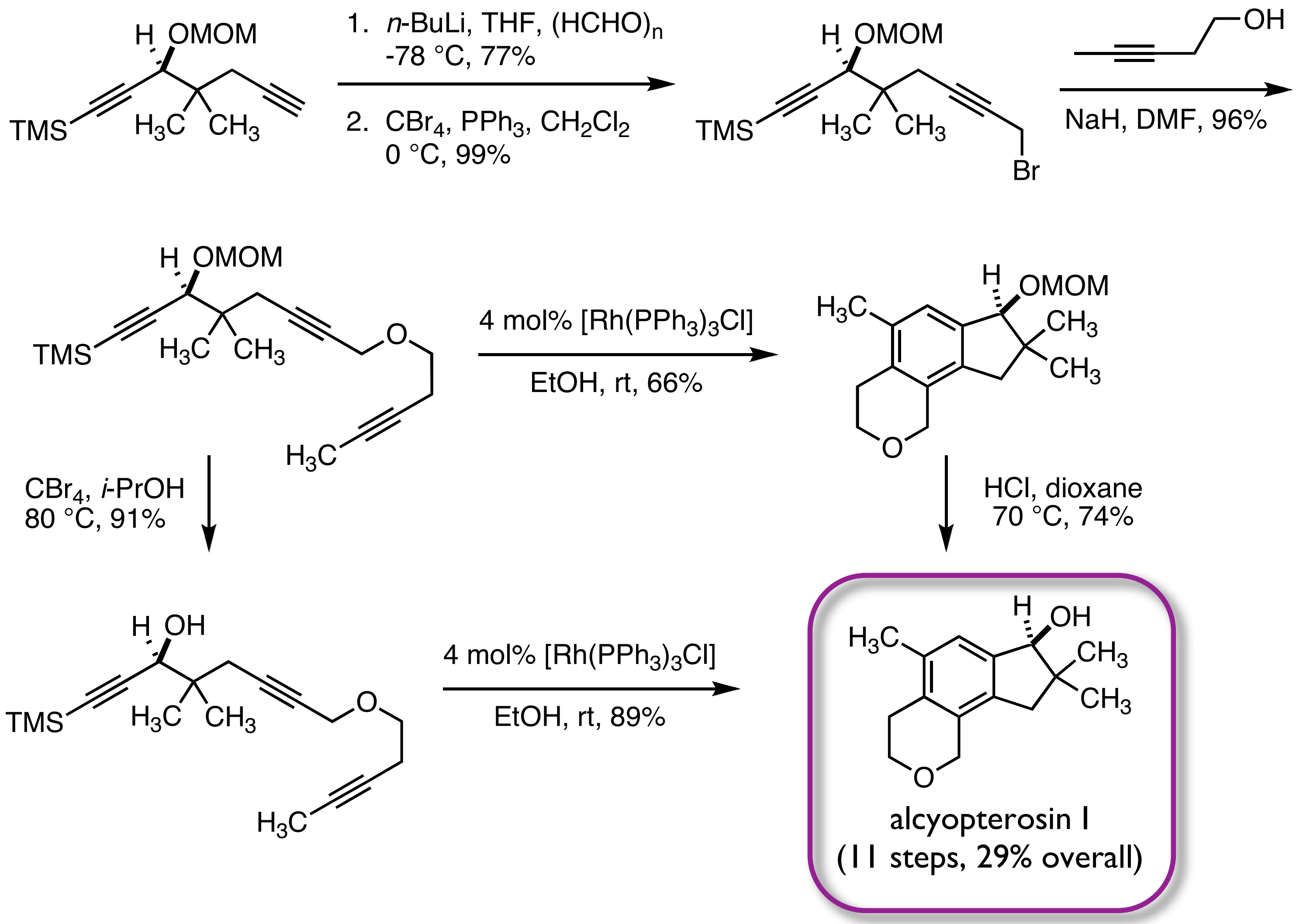
Welsch, T.; Tran, H.-A.; Witulski, B. *Org. Lett.* **2010**, DOI: 10.1021/ol102432q.

Preparation of Key Chiral Building Block



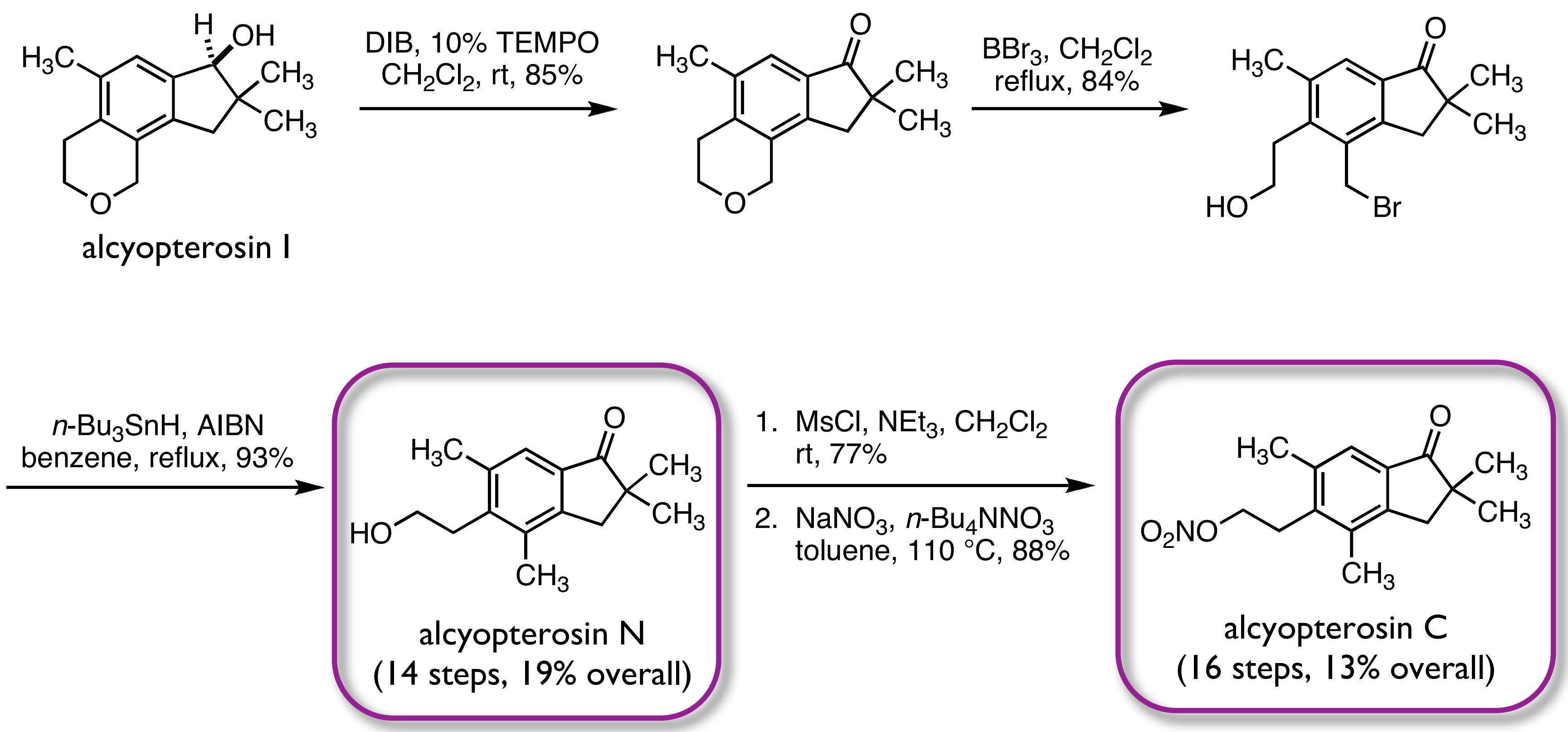
Welsch, T.; Tran, H.-A.; Witulski, B. *Org. Lett.* **2010**, DOI: 10.1021/ol102432q.

Synthesis of Alcyopterosin I



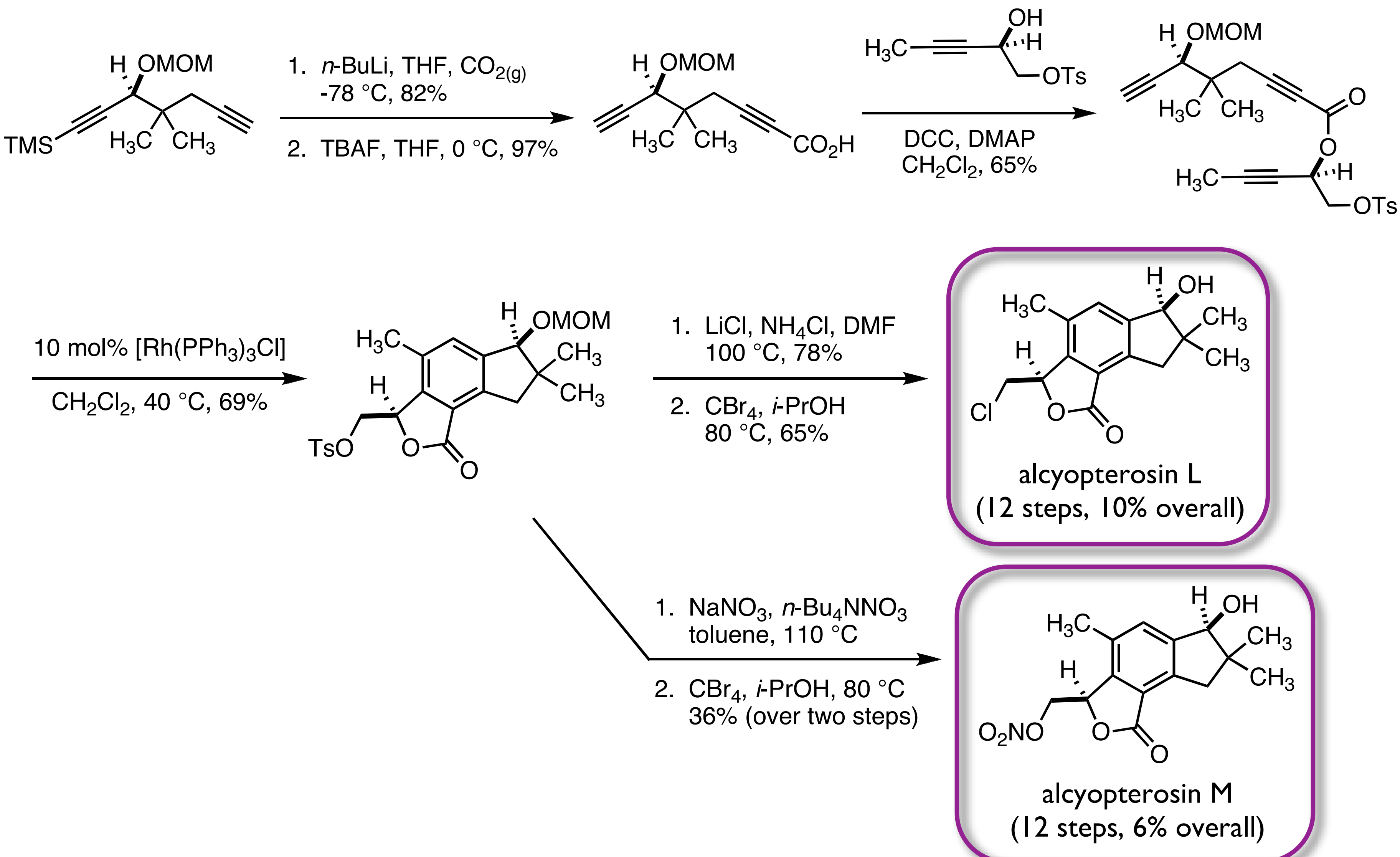
Welsch, T.; Tran, H.-A.; Witulski, B. *Org. Lett.* **2010**, DOI: 10.1021/ol102432q.

Synthesis of Alcyopterosins N and C



Welsch, T.; Tran, H.-A.; Witulski, B. *Org. Lett.* **2010**, DOI: 10.1021/ol102432q.

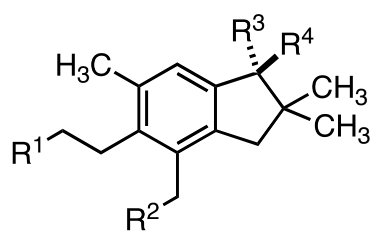
Synthesis of Alcyopterosins L and M



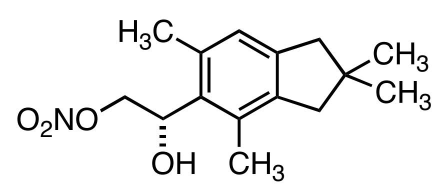
Welsch, T.; Tran, H.-A.; Witulski, B. *Org. Lett.* **2010**, DOI: 10.1021/ol102432q.

Conclusions

- The authors successfully synthesized a set of the rare marine alcyopterosins using a modular approach which features a Rh-catalyzed [2+2+2] alkyne cyclotrimerization
- Application of this approach allowed for:
  - The enantioselective total synthesis of alcyoptersin I
  - The first total enantioselective syntheses of alcyopterosins L and M
  - The total synthesis of alcyopterosin N and the first total synthesis of alcyopterosin C
- Further development of this approach could provide access to the alcyopterosins F, H, and K



	R^1	R^2	R^3	R^4
alcyopterosin H	ONO_2	H	OH	H
alcyopterosin K	Cl	OH	H	OH



alcyopterosin F