# A New Method for the Preparation of Non-Terminal Alkynes: Application to the Total Synthesis of Tulearin A and C

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Current Literature
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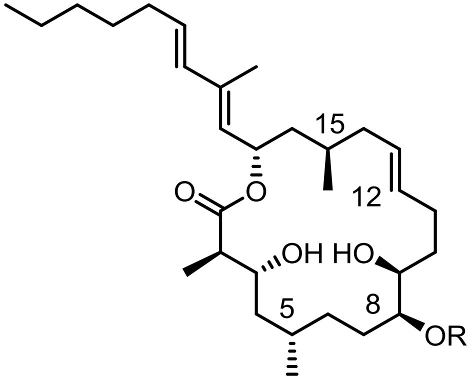
# Tulearin Natural Products

Isolated from marine Madagascan sponge
*Fascaplysinopsis genus*
(Salary Bay north of Tulear)

**Biological activity:**

- Tulearin A exhibits potent antiproliferative activity against 2 human leukemic cell lines (K562, UT7).
- ~60% inhibition of proliferation with 0.5μg/mL

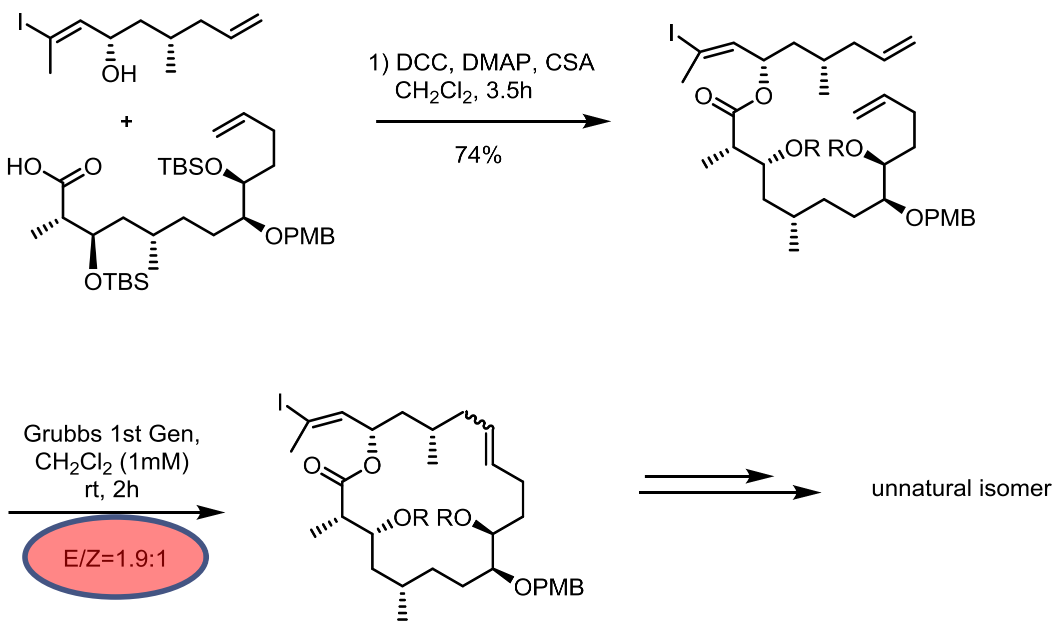



tulearin A, R = C(O)$NH_2$
tulearin C, R = H

*Org. Lett*, **2008**, 10, 153-156

# Synthesis of a Stereoisomer of Tulearin A

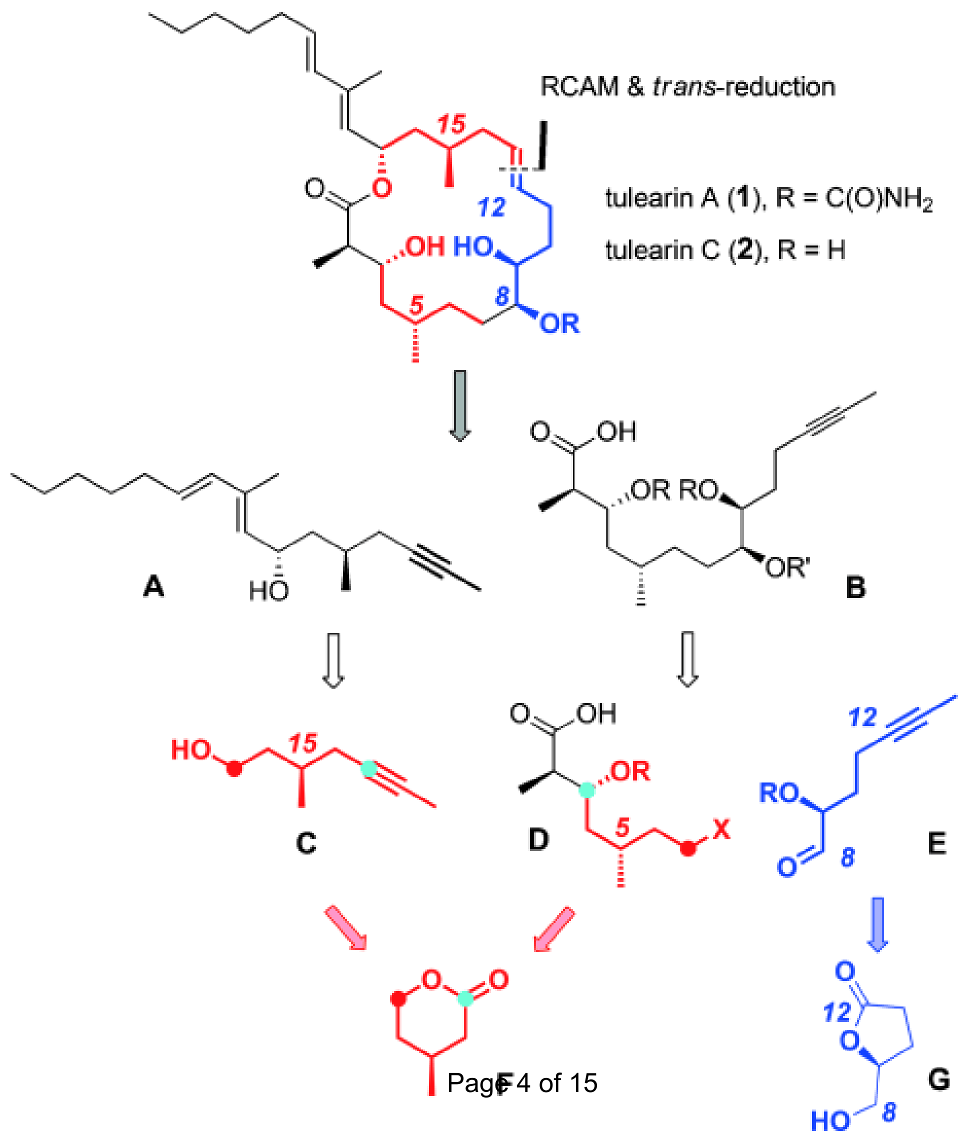
- Cossy and Curran were the first to synthesize an unnatural isomer of Tulearin A via ring closing olefin metathesis
- Relative and absolute stereochemistry were assigned by X-Ray crystallography by Kashman and co-workers in 2009.



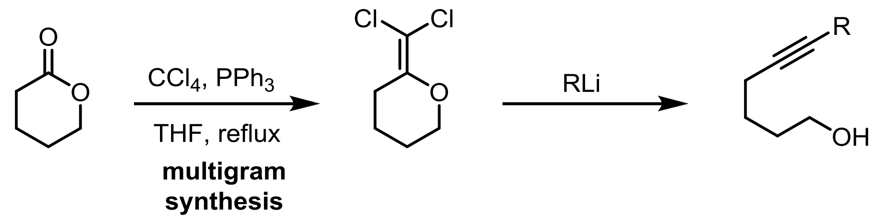

*Tet. Lett*. **2009**, 50, 3820-3822

*Org. Lett*. **2009**, 11, 3282-3285

# Fürstner's Approach: Retrosynthetic Analysis



# Synthesis of Non-Terminal Alkynes

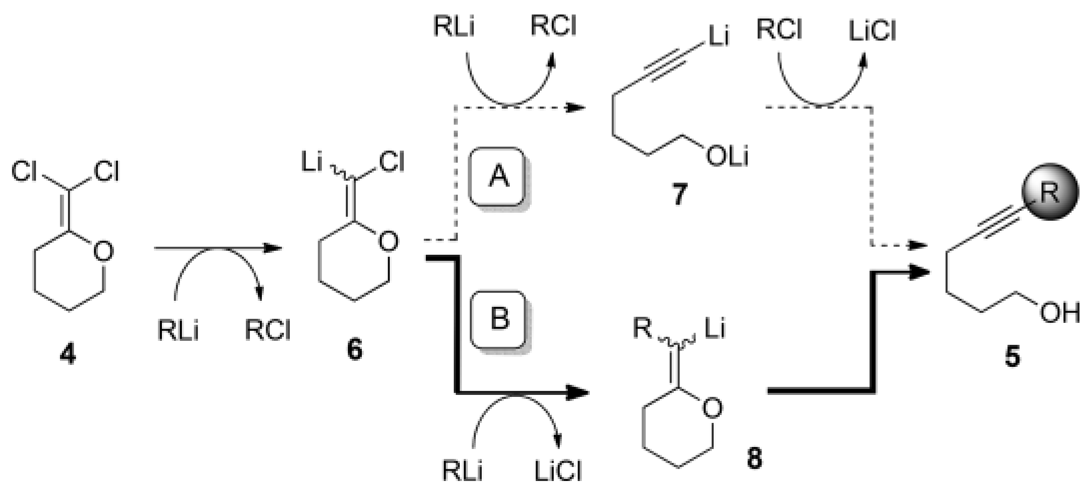



| Entry | RLi | Solvent | Temp [°C] | t [h] | Additives (mol%) | Yield [%][b] |
|---|---|---|---|---|---|---|
| **1** | MeLi (2.1eq) | $Et_2O$ | RT | 96 | | 50[c] |
| **2** | MeLi (5eq) | $Et_2O$ | RT | 48 | | 90 |
| **3** | MeLi | THF | RT | 2 | | 80 (GC) |
| **4** | MeLi | $Et_2O$ | RT | 4 | $Cu(acac)_2$ (10) | 89 |
| **5** | MeLi | $Et_2O$ | RT | 2 | $Fe(acac)_3$ (10) + 1,2-diaminobenzene (50) | 70 |
| **6** | *n*BuLi | $Et_2O$ | RT | 4 | | 76 |
| **7** | *s*BuLi | $Et_2O$ | -78 | 1 | | 84 |
| **8** | *t*BuLi | $Et_2O$ | -78 | 1 | | 82 |
| **9** | PhLi | $Et_2O$ | -78 | <1 | | [d] |
| **10** | $Me_3SiCH_2Li$ | $Et_2O$ | RT | 4 | | 86 |
| **11** | $Me_2PhSiLi$ | $Et_2O$ | -78 | 6 | | 83 |

***$Cu(acac)_2$ and $Fe(acac)_3$ catalysts facilitate the metal/halogen exchange***

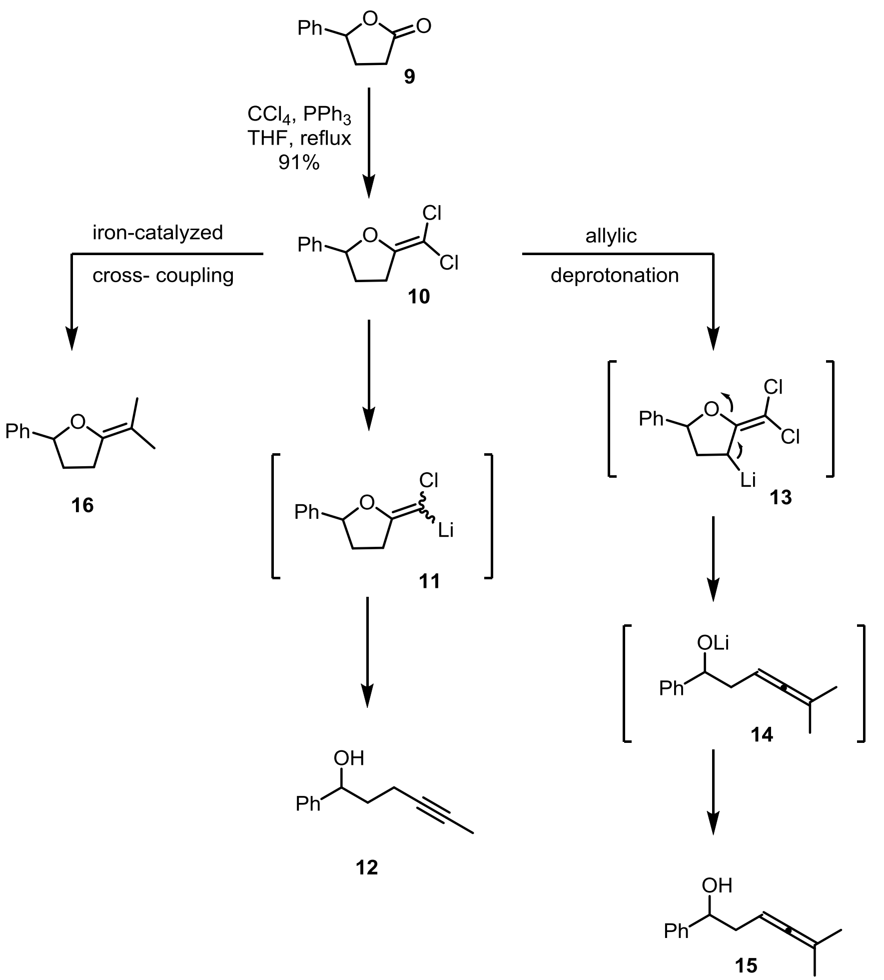
- ❑ PhLi was unsuitable (got readily oxidized with formation of biphenyl)
- ❑ $MeMgBr/Me_2Zn$ gave no conversion

# Mechanistic Explanation




***Pathway B*** *supported by a control experiment using 1-chloro-1-heptyne: treatment with MeLi merely furnished 1-heptyne after aqueous work-up suggesting that a lithium acetylide was formed but not trapped by the methyl chloride generated in situ.*

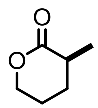
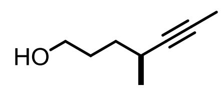
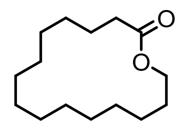
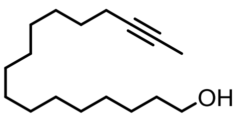
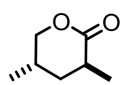
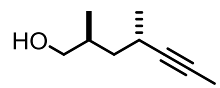
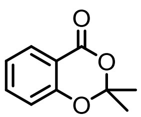
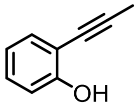
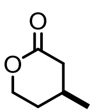
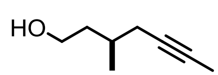
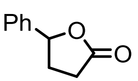
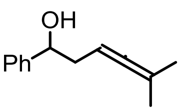
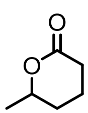
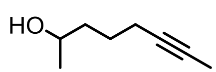
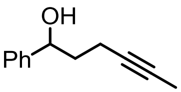
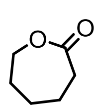
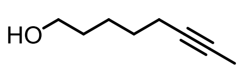
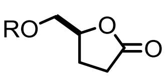
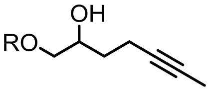
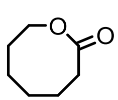
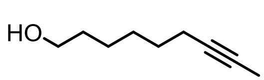
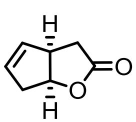
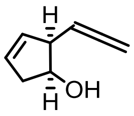
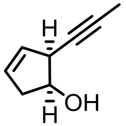
# Optimization Studies of γ-Butyrolactone Derived *gem*-Dichloro-Olefins




| Entry | Solvent | t [h] | Additives [mol%] | Yield [%] 12 | 15 | 16 |
|---|---|---|---|---|---|---|
| 1 | $Et_2O$ | 72 | - | 60 | 10 | <5 (GC) |
| 2 | THF | 3 | - | 25 | 58 | <5 (GC) |
| 3 | $Et_2O$ | 20 | $Cu(acac)_2$ (10) | 58 | 5 (GC) | <5 (GC) |
| 4 | $Et_2O$ | 4 | $FeCl_2$ (10) | 32 | <5 (GC) | 46 |
| 5 | $Et_2O$ | 2 | $Fe(acac)_3$ (5) + 1,2-diaminobenzene (25) | 85 | <5 (GC) | <5 (GC) |

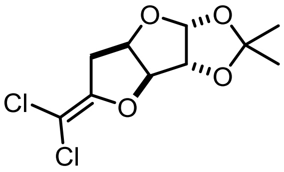
***Suppression of allene unit by addition of catalytic amounts of $Cu(acac)_2$ or $Fe(acac)_3$/1,2-diaminobenzene***

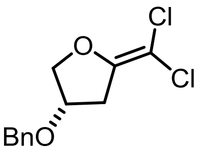
# Scope of Methodology

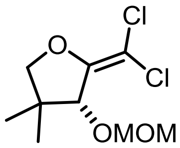
| Substrate | Dichloro-olefination [%] | Method | Product | Yield [%} | Substrate | Dichloro-olefination [%] | Method | Product | Yield [%} |
|---|---|---|---|---|---|---|---|---|---|
|  | 81 | C |  | 92 |  | 30 | B |  | 80 |
|  | [d] | B |  | 56 |  | 88 | A<br>C |  | <20<br>60 |
|  | 92 | A<br>B<br>C |  | 90<br>77<br>85 |  | 91 | A |  | 58 |
|  | 95 | A<br>B |  | 89<br>88 | | | D |  | 85 |
|  | 92 | B |  | 88 |  | 87<br>62<br>88 | D |  | R=MOM, 83%<br>R=PMB, 69%<br>R=Bn, 70% |
|  | 92 | B<br>C |  | 88 |  | 95 | A |  | 84 |
| | | | | | | | D |  | 80 |

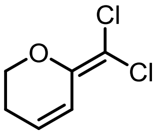
**Method A:** MeLi (5eq), $Et_2O$, rt
**Method B:** MeLi (5eq), THF, rt
**Method C:** MeLi (5 eq), $Et_2O$, $Cu(acac)_2$ (10 mol%)
**Method D:** MeLi (5eq), $Et_2O$, $Fe(acac)_3$ (5-10 mol%) 1,2-diaminobenzene (25-50 mol%), rt

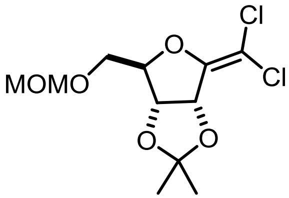
# Substrate Limitations



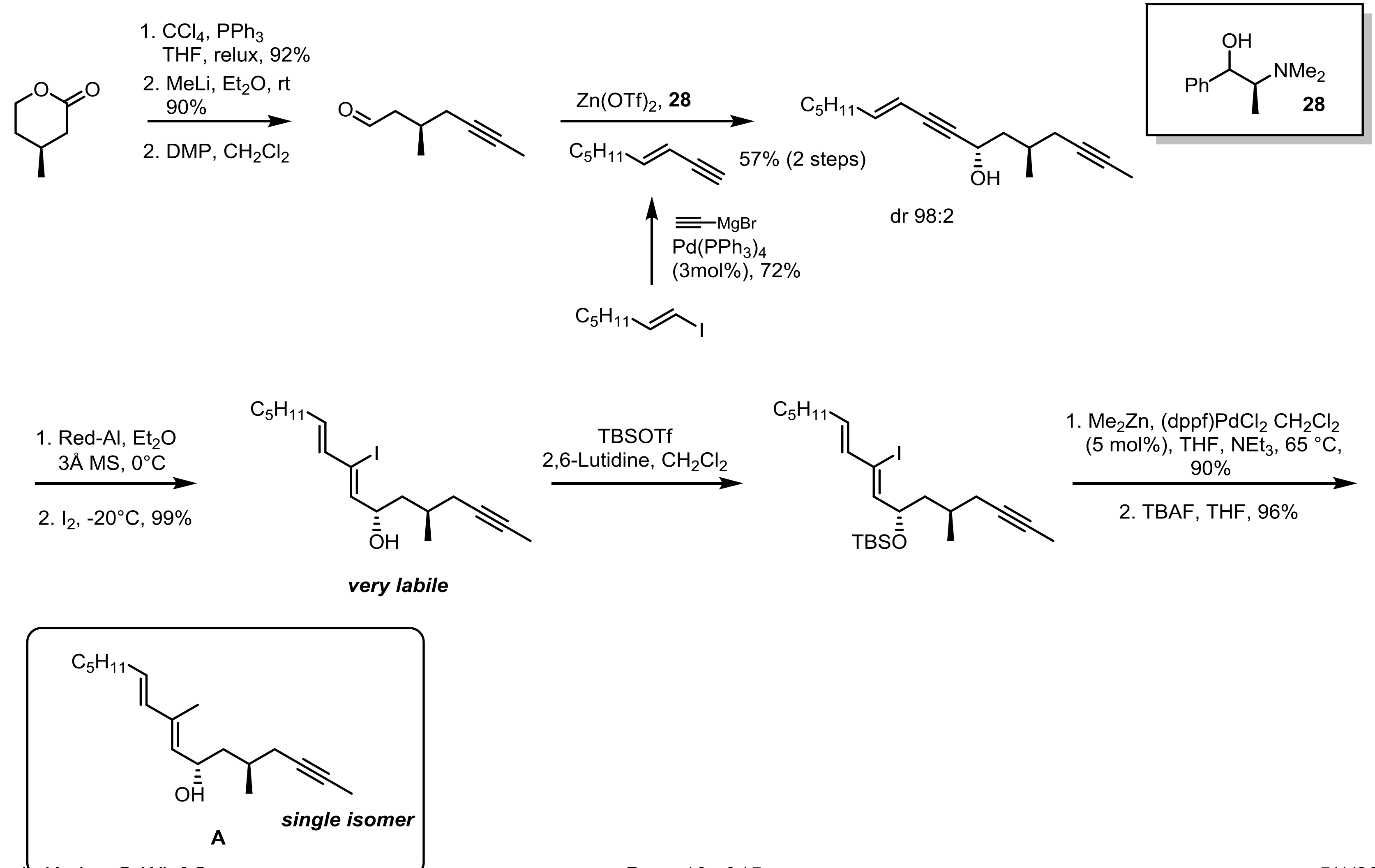



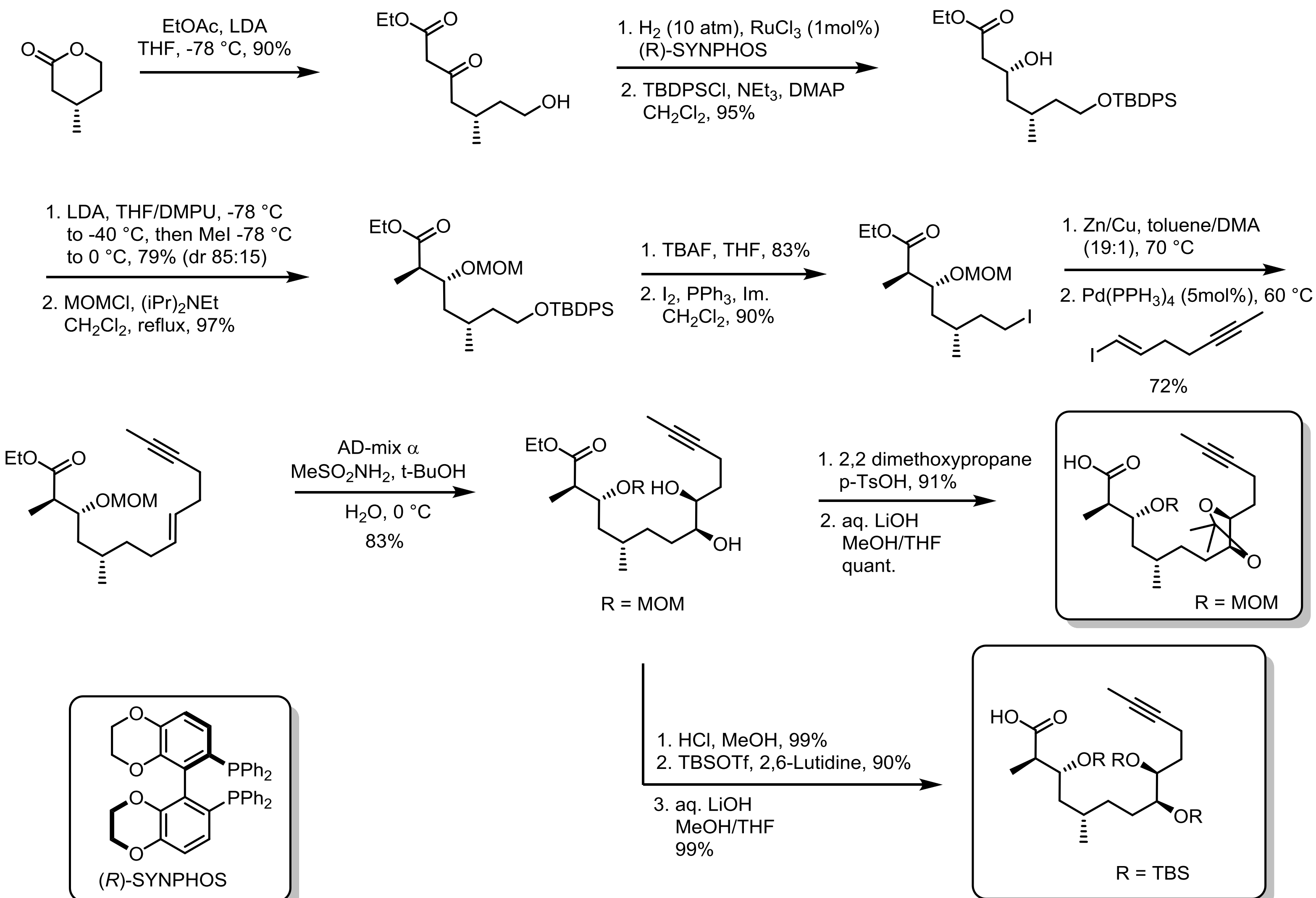




Decomposition for substrates containing oxygen substituents α and/or β to the former lactone carbonyl

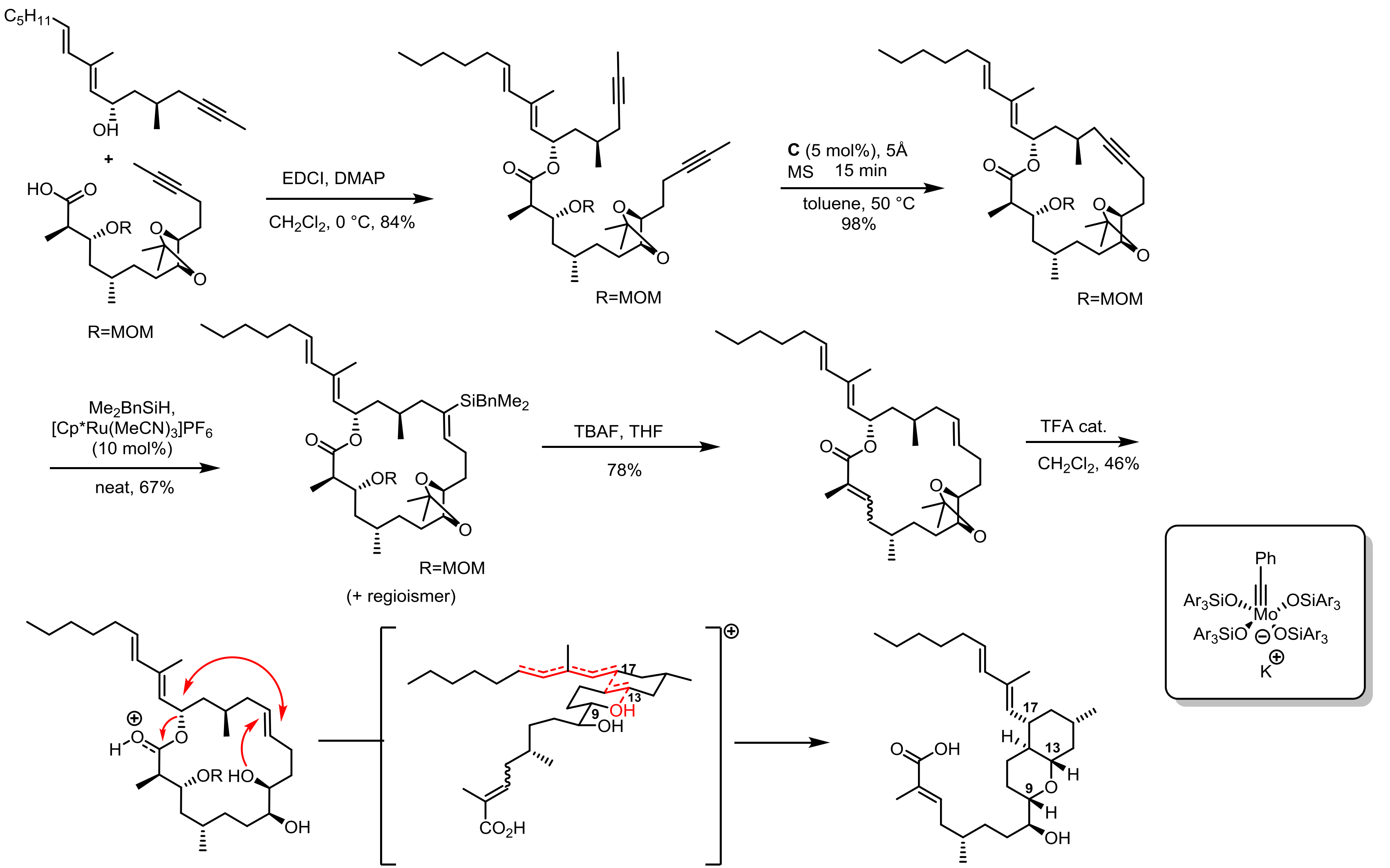
# Total Synthesis of Tulearin C: Synthesis of Fragment A



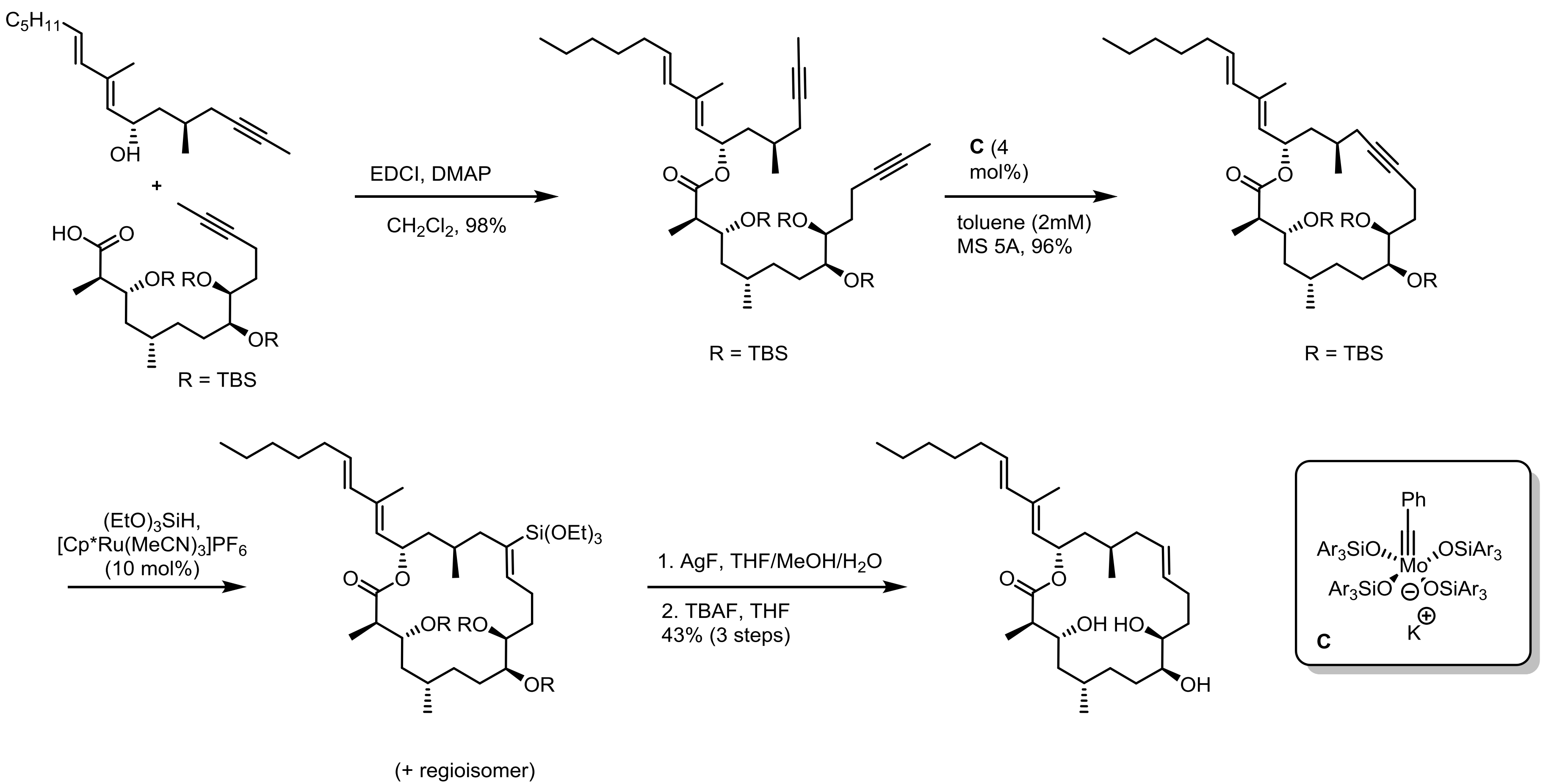
# Synthesis of Fragment B



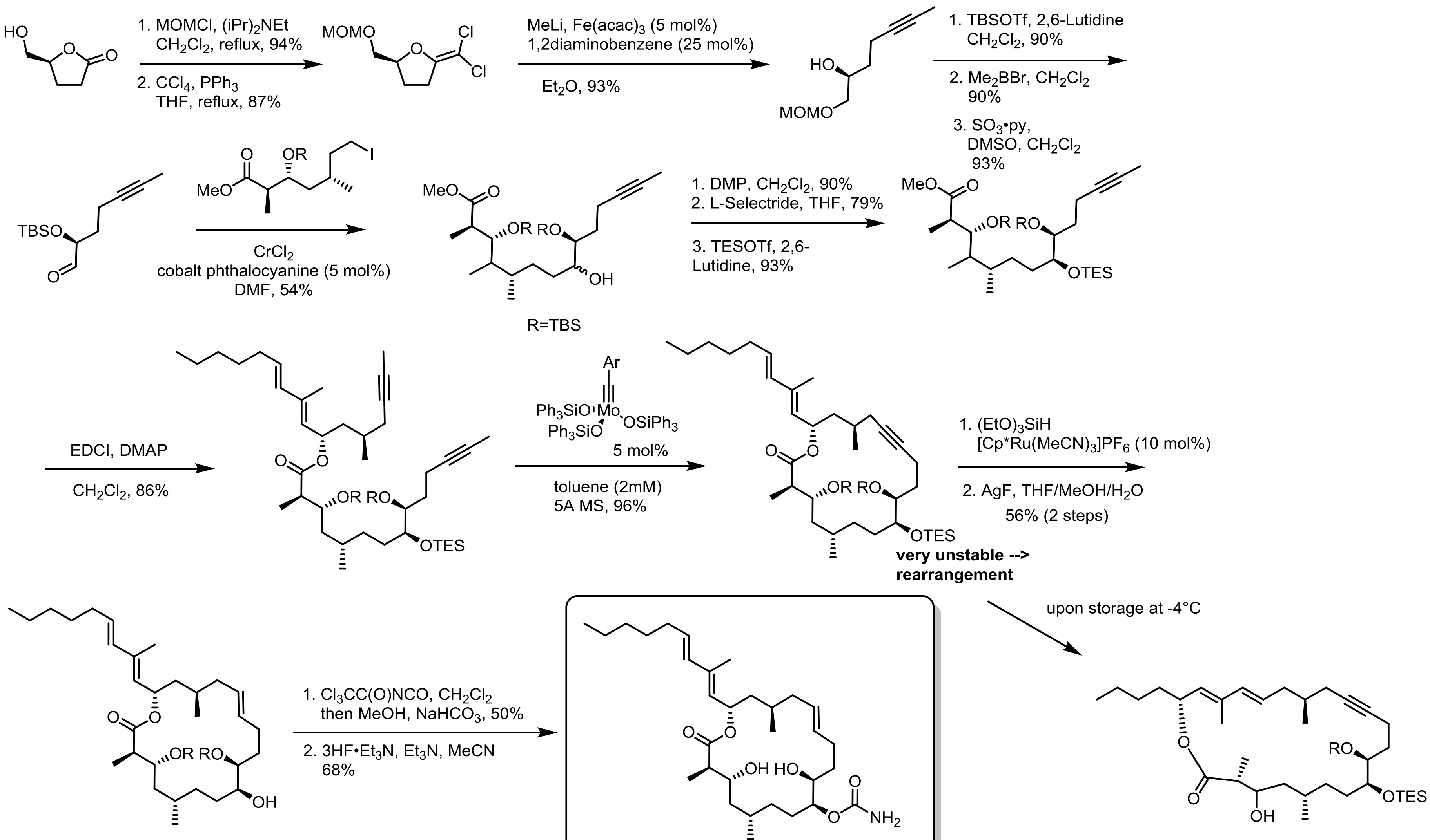
# Synthesis of Fragment B



# End Game Strategy



# Total Synthesis of Tulearin A



# Conclusion

- New methodology affords ***non-terminal alkynes*** in excellent yield
- Methodology offers entry into ***chiral building blocks*** required for both total syntheses in excellent yield and optical purity
- Highlights the ***remarkable selectivity profile*** of the latest generation Mo-catalysts