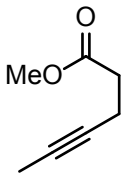
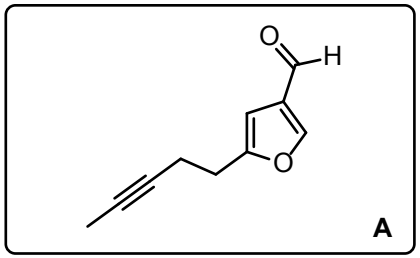
Total Synthesis of Nakadomarin A

Mark G. Nilson, Raymond L. Funk

Org. Lett. **2010**, *12*, 4912 – 4915.

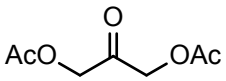


1 – 4

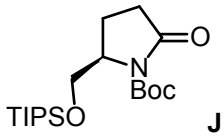


A

1) $PO(OMe)_2CH_2Li$
2) NaH, **1**
3) cat. HCl, MeOH, 50 °C
4) $(COCl)_2$, DMSO, NEt_3



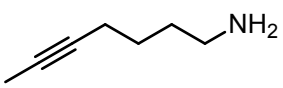
1



J

5 – 8

5) $LiBHEt_3$ then *i*-Pr_2NEt, DMAP, TFAA
6) DMF, $(COCl)_2$ then sat. aq. Na_2CO_3
7) **2** then $NaBH_4$
8) **3**, NEt_3



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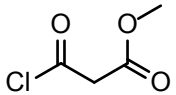
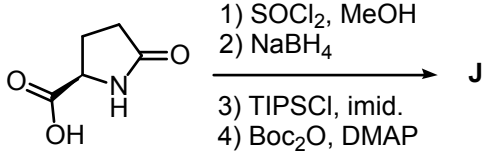


3

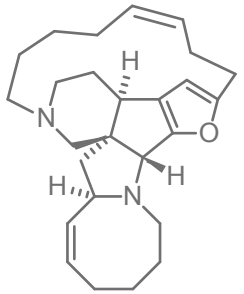
How would you make starting material **J**?

from D-pyroglutamic acid:

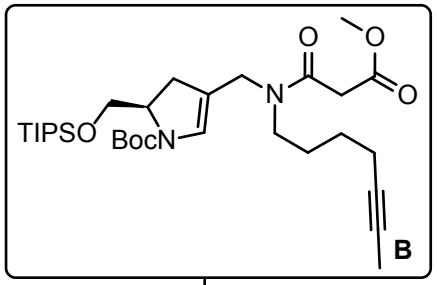


1) $SOCl_2$, MeOH
2) $NaBH_4$
3) TIPSCl, imid.
4) Boc_2O, DMAP

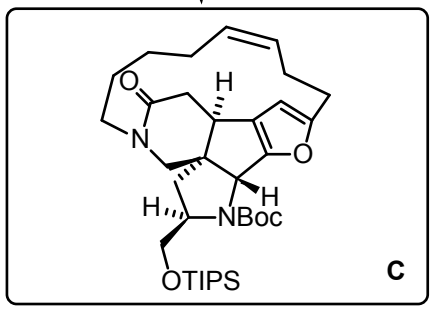
J



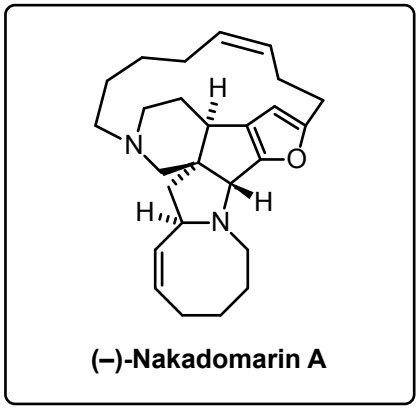
(–)-Nakadomarin A



9 – 14

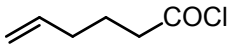


15 – 21



(–)-Nakadomarin A

9) **A**, $PhCO_2H$, piperidine, PhH, 80 °C
10) $InCl_3$ (10 mol%), DCM, 40 °C
11) KOH; acidic work up; PhMe, reflux
12) (*t*-BuO)$_3$W≡C-*t*-Bu (25 mol%), PhCl, 80 °C
13) H_2, Lindlar cat., quinoline, MeOH

14) TBAF
15) IBX, DMSO
16) Tebbe reagent
17) TFA
18) NEt_3, 

19) Grubbs I, DCM, 40 °C
20) Alane

What is the mechanism in step 10?
see next page

12) What other catalysts can be used for this transformation? - *see next page*

13) Name another system to accomplish this transformation. - *Pd/BaSO$_4$, quinoline*
also see. Chem. Rev. **2013**, *113*, 1313–1350

16) How do you make the Tebbe reagent?

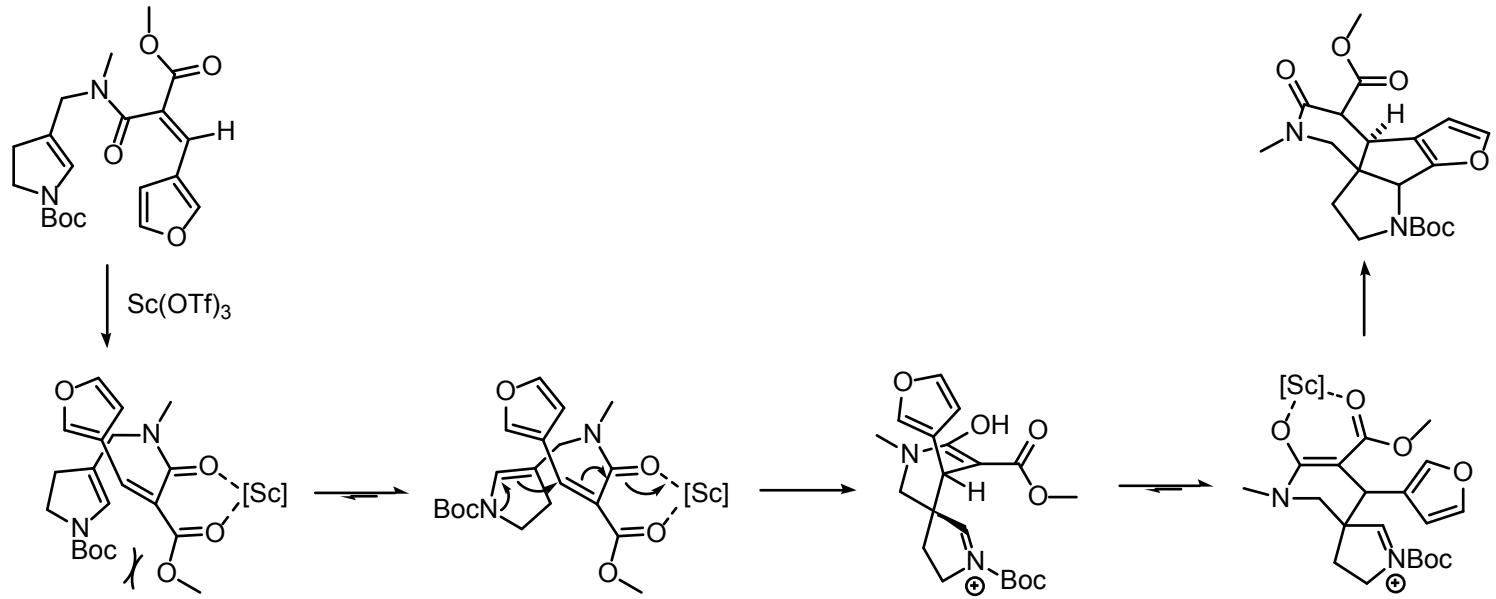
$Cp_2TiCl_2 + Al(Me)_3 \longrightarrow Cp_2TiCH_2AlClMe_2$

What other Ti-based methylenation methods do you know?
Lombardo, Petasis, Nysted/TiCl$_4$

20: How do you make the reagent?
$3\ LiAlH_4 + AlCl_3 \longrightarrow 4\ \mathbf{AlH_3} + 3\ LiCl$

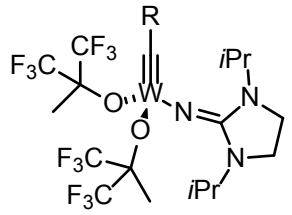
Mechanism of step 10:

model study: Org. Lett., **2006**, *8*, 3833 – 3836.

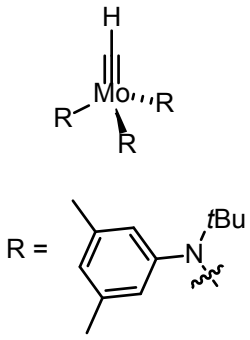


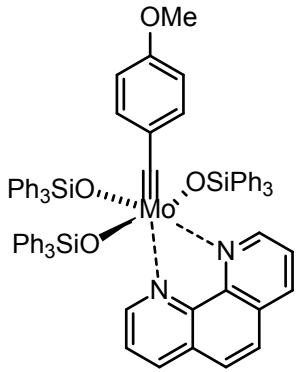
Step 12: Catalysts for Alkyne Metathesis (examples):

Montreux and Blachard: $Mo(CO)_6$ and resorcinol; Problem: low FG tolerance. resorcinol and related phenols are often even used in excess, high temp.



R = Ph, *t*-Bu





see also: *Angew. Chem. Int. Ed.* **2013**, *52,* 2794 – 2819.

bench stable precatalyst