Total Synthesis of (−)-N-Methylwelwitindolinone C Isothiocyanate Based on a Pd-Catalyzed Tandem Enolate Coupling Strategy
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Structural Features of the Target
- Multi-fused ring system
- Pendant alkene
- Isothiocyanate
  (can be replaced by other functionality in series)

Previous Syntheses Include:

Retrosynthesis

Common Intermediate to Others in the Family

Pd-Catalyzed Tandem Annulation

MeCN addition

**Forward Synthesis**

\[
\text{Forward Synthesis}
\]

**Acid chloride formation:** 13a

**Wittig Reaction:** 14

The E-olefin is favored under standard Wittig conditions with a stabilized reagent.

**Route to 12:** Martin, S. F. Org. Lett. 2010, 12, 2492–2495.
Stereochemistry set by this center

9

Pd$_2$(dba)$_3$ (20 mol%) XPhos (80 mol%) t-BuOK (2 equiv)
toluene, 110 °C "100%"
2:1 dr ("all-syn")

AcO

NC

Br

O

Me

Me

H

Me

Me

- via -

Also isolated from unoptimized runs

TBSO

NC

H

Br

O

Me

Me

H

Me

Me

D

E

Either cyclization can proceed first.
Subjecting E to the reaction conditions gives a 10:1 dr; which is why the authors suggest allylation first is preferred over arylation first.

9 to 8:

AcO

NC

Br

OK

Oxidative Addition

Pd$^0$

AcO

NC

Br

Pd

OK

- KBr

Reductive Elimination

NC

Pd

O

NC

Pd

O

- Pd$^0$

Enolate Formation

8

Reactive Elimination

[Pd]

NC

K

Pd$^0$

Inner-Sphere Attack

NC

OK

Oxidative Addition

Pd$^0$

NC

OK

The reverse (i.e., allylation first) may also occur.
Experimental evidence: top right of this page

Hard nucleophiles in the Tsuji-Trost reaction attack palladium in its coordination sphere rather than the carbon allyl fragment in an outer-sphere fashion.
More on the (slightly) preferred stereochemistry for 8:
1) Explicit "upward" facing proton directs the allyl-containing fragment "down." Also, bulky OTBS fragment promotes anti oxidative addition of the allyl acetate.

2) Addition of enolate via coordination of Pd then

3) Reductive elimination gives the all syn product. Base in solution gives enolate then

4) The original stereocenter directs the second enolate addition from the "bottom" face only. Addition to the top face is geometrically unfeasible.

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TBSO
AcO
NC
Br
O
Me
Me
Me
Me
9

1) [Pd]
NC
Br
O
Me
Me
Me
Me

2) OTBS
NC
Br
O
Me
Me
Me
Me

3) [Pd]
NC
Br
O
Me
Me
Me
Me

4) TBSO
NC
Br
O
Me
Me
Me
Me

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8 major diastereomer

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TBSO
NC
O
Me
Me
Me
Me
8

1) TBAF, THF, RT
2) DMP, NaHCO₃, CH₂Cl₂, rt

[1]
NC
O
Me
Me
Me
Me

21

[2]
t-BuOLi, MeI
DMF, -40 °C
63%, 3 steps from 9

Me
O
Me
Me
7

KHMD
Comins Reagent
THF, -78 °C
91%

Me
O
Me
Me

22

Methyl approach is substrate-controlled (bowl shape).
**Dess-Martin Oxidation (G to 26)**

![Chemical structure diagram](attachment:image.png)


**26 to 27:**

![Chemical structure diagram](attachment:image.png)

Magnesium monoperxyphthalate (MMPP)