A Stereoselective Synthesis of (+)-Gonyautoxin 3

Total Synthesis of (+)-Lithospermic Acid by Asymmetric Intramolecular Alkylation via Catalytic C-H Bond Activation

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Short Literature
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Introduction to C-H Insertion Chemistry

This process can be thought of as a “net oxidation.”

Initial heteroatom insertion into a C-H $\sigma$-bond:

Difficulties: competing aziridination, poor regioselectivity

Breslow and Sloan, Tetrahedron Lett. 1968, 5349
**Du Bois’s C-H Amination**

**Question:** Is there a way to perform the insertion *regioselectively*?

By employing a carbamate, the nitrogen selectively inserts to form oxazolidinones. Also, full retention of the stereocenter is observed.

Espino, Wehn, Chow, and Du Bois 2001

Espino, Wehn, Chow, and Du Bois 2001

Kim, Mulcahy, Espino, and Du Bois 2006
Natural Product Relevance

**Saxitoxin**
*Du Bois, 2006*

**dibromophakellstatin**
*Romo, 2003*

**palau'amine**
*Good Luck!!*

**Gonyautoxin 3**
**Du Bois’s Strategy**

Modification of the $\pi$-bond was previously undisclosed.
Gonyautoxin 3

- **L-serine**
  - Reactions:
    - DCC, Et$_3$N, CH$_2$Cl$_2$ → 65% yield
  - Further reactions:
    - 1) TBDPSCI
    - 2) DIBAL
    - 1) Pd($PPh_3)_4$
    - BF$_3$•OEt$_2$

Yields:
- 64% yield
- 94% yield
- 54% over 3 steps (20:1 dr)
- 87% yield

Chemical structures and reactions shown in the diagram.
Other types of oxidations resulted in complete consumption but no pdt formation.
As with saxitoxin, the **ketal** is the more stable structure.

**Epimerization** of the sulfate carbon occurs on standing to obtain a 1:3 mixture, $\beta:\alpha$. 
Ellman’s Rh-Catalyzed C-H Insertion

Unlike the previous chemistry, no oxidant is required and formation of C-C bonds is possible.

Initial coordination to the imine directs the oxidative addition to the ortho position.

Thalji, Ellman, and Bergman, *JACS*, 2004, 126, 7192-7193
Ellman’s Rh-Catalyzed C-H Insertion

Enantioselectivity is possible through the use of phosphoramidate ligands.

Enantioselectivity is observed in the reactions:

1. 94% yield, 95% ee
2. 90% yield, 70% ee
3. 95% yield, 96% ee
Ellman’s Synthesis of Lithospermic Acid

(+)-lithospermic acid

Knöevenagel → Rh-catalysis
Ellman’s Synthesis of Lithospermic Acid

1. Reaction with CBr₄, PPh₃ to form 1,2-dibromo-4-methoxybenzene: 88% yield

2. Treatment with n-BuLi to form a lithiobenzene derivative: 93% yield

3. Reaction with ClCO₂Me to form a carboxylic acid derivative: 59% yield

4. Reaction with MeOH:py to form a 1,3-dioxynaphthalene derivative

5. Reaction with NH₂Ph to form a Schiff base

6. Reaction with Rh(I) and ferrocenyl-PCy₂, then HCl to form the final product: 89% yield

*ee not sufficient*
Ellman’s Synthesis of Lithospermic Acid

\[
\text{CHO} \quad \text{CBr}_4, \text{PPh}_3 \quad 88\% \text{ yield}
\]

\[
\text{CHO} \quad \text{ClCO}_2\text{Me} \quad 93\% \text{ yield}
\]

\[
\text{CHO} \quad \text{[RhCl(coe)_2]_2} \quad \text{FcPCy}_2 \quad \text{toluene, 75 °C then HCl}
\]

56% yield

*single enantiomer after recryst.*
Ellman’s Synthesis of Lithospermic Acid

80% yield

85% yield

10:1 anti: syn

1) Me₃SnOH
2) TMSI, quinoline 100 °C

33% yield over 2 steps