Total Synthesis of (±) Mitomycin C via Isomitomycin A intermediate

Tohru Fukuyama*, Lihu Yang

Presented by William Reid
Tohru Fukuyama

- Tohru Fukuyama was born in Anjo, Aich, in 1948.
- Ph.D. in 1977 under Professor Y. Kishi at Harvard.
- Postdoctoral for one year at Harvard.
- Joined the faculty of Rice University as an assistant Professor in 1979.
- Became a full Professor in 1988.
- In 1995, he moved to the University of Tokyo, where he is currently Professor of Pharmaceutical Sciences.

http://chemistry.rice.edu/FacultyDetail.aspx?RiceID=609
Awards

• 218 Publications

• The PSJ Award (Pharmaceutical Society of Japan Award (2006))

• ACS Award for Creative Work in Synthetic Organic Chemistry (2004)

• ISHC Senior Award in Heterocyclic Chemistry (2003)

• Synthetic Organic Chemistry Award, Japan (2002)

• ACS Arthur C. Cope Scholar Award (1993)

http://en.wikipedia.org/wiki/Tohru_Fukuyama
Mitomycin C

- Isolated from *Streptomyces caespitosus* or *Streptomyces lavendulae*
- Potent antitumor agent
- Used extensively in chemotherapy
- Has been shown to be a DNA crosslinker

- First synthesized by Kishi (Kishi, Y. *J. Nat. Prod.* 1979, 42, 549.)
- Was later synthesized by Fukuyama (Fukuyama, T.; Yang, L.-H. *J. Am. Chem. SOC.* 1987, 109, 7881.)
Mitomycin C
Retrosynthesis

Mitomycin C

Isomitomycin A

MeO

Me

OMe

Me

OMe

MeO

Me

OMe

MeO

Me

OMe

N₃

OBn

Ph
Isomitomycin A
Scheme 1
The Starting Material

Scheme 3

12
\[ \text{(h) } \text{NH}_3, \text{MeOH}, 23 \, ^\circ\text{C}; \text{NaBH}_4. \]

13
\[ \text{(i) CSA (0.3 equiv), MeOH, 23 \, ^\circ\text{C}.} \]
Scheme 4

(j) $H_2$ (1 atm), 10% Pd/C, EtOH.
(k) DDQ, acetone/H$_2$O (20:1), -78 °C.

(i) NH$_3$, MeOH, 23 °C, 5 h.

Mitomycin C
Mitomycin Rearrangement

Isomitomycin C

Mitomycin C
Conclusion

• The synthetic mitomycin C was identical with an authentic sample in both TLC behavior and spectroscopic properties.

• The overall yield of (±)-1 from commercially available 2,6-dimethoxytoluene is 10%.
Questions