

Yondelis
(trabectedin)

Pharma Mar S.A., Johnson & Johnson
FDA Approved 2015



Ecteinascidia turbinata
mangrove tunicate
found in the Caribbean
Sea, Gulf of Mexico, and
Mediterranean Sea

Image via Sean Nash:

<https://www.flickr.com/photos/nashworld/4525673461> Rinehart, K. L. (2000), Antitumor compounds from tunicates. *Med. Res. Rev.*, 20: 1-27.

Extracts of the sea squirt were found to have anti-tumor properties in 1969, but the compounds responsible for that activity were not elucidated until much later. Ecteinascidin 743 was first isolated and characterized by Kenneth Rinehart at UIUC in 1986.

In vitro IC₅₀ values for ecteinascidin 743

tumor cell line	IC ₅₀ (μM)
P388 (murine leukemia)	0.00034
L1210 (murine leukemia)	0.00066
A549 (lung)	0.00026
HT29 (colon)	0.00046
MEL-28 (melanoma)	0.00050

In vivo ecteinascidin 743 activity

model	activity	tumor free (d)
MX-1 (breast)	9/10 CR	9/10 (23)
MEXF989 (melanoma)	6/6 CR	6/6 (35)
LXFL529 (NSCLC)	3/4 CR	3/7 (33)
HOC22 (ovarian)	5/6 CR	5/6 (120)
MRIH121 (renal)	5/5 PR	-/5 (39)
PC2 (prostate)	5/5 PR	-/5 (20)

Early biological studies were accomplished using isolated material, but in order for clinical trials to be run, a synthetic route to these compounds needed to be developed.

Facts about trabectedin:

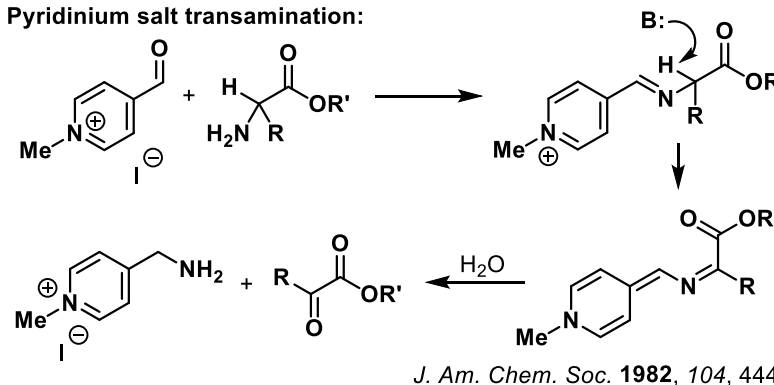
- Approved in 2015 by the FDA for the treatment of soft-tissue sarcoma
- Also undergoing trials for other cancers
- Orphan Drug status for STS
- Cost of treatment: ~40,500 USD
- Mechanism of action: binds to DNA in the minor groove, specifically in areas rich with guanine, affects DNA/RNA/protein synth.; stops cell cycle
- Current industrial route is Pharma Mar semisynthesis; however, a shorter semisynthetic route was patented in 2017

Other synthetic approaches:

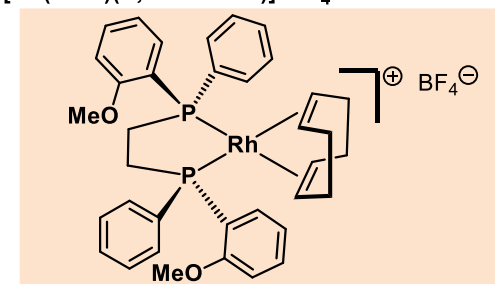
Fukuyama et al. *J. Am. Chem. Soc.* **2002**, 124, 6552.
Zhu et al. *J. Am. Chem. Soc.* **2006**, 128, 87.
Danishefsky et al. *ACIE* **2006**, 45, 1754.
Williams and Dan J. *Org. Chem.* **2008**, 73, 9594.
Fukuyama et al. *J. Am. Chem. Soc.* **2013**, 135, 13684.
Zhang et al. *Eur. J. Org. Chem.* **2017**, 975.
Zhang et al. WO2017219917

<https://www.reuters.com/article/us-johnson-johnson-fda/fda-clears-jjs-chemotherapy-for-certain-soft-tissue-sarcomas-idUSKCN0SH1U920151023>

Pyridinium salt transamination:

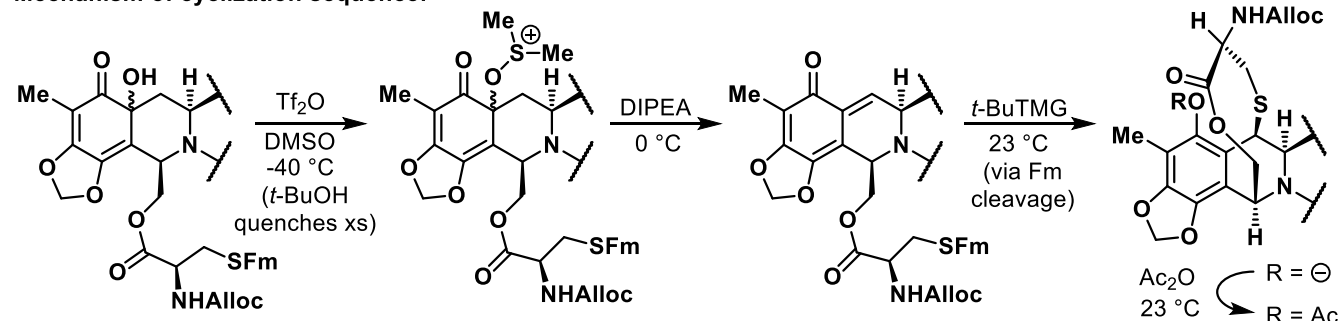


[Rh(COD)(R,R-DIPAMP)]⁺BF₄⁻

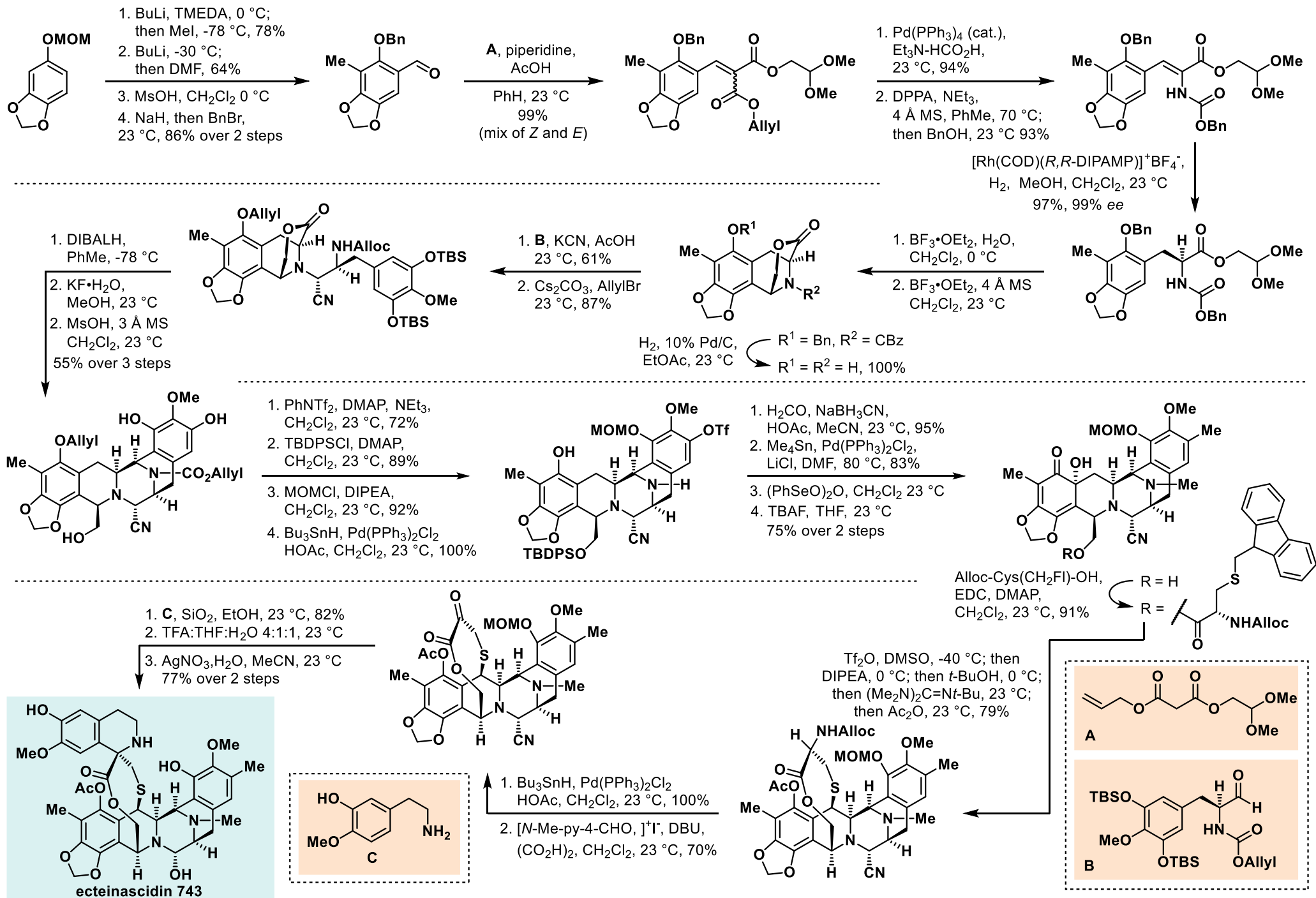


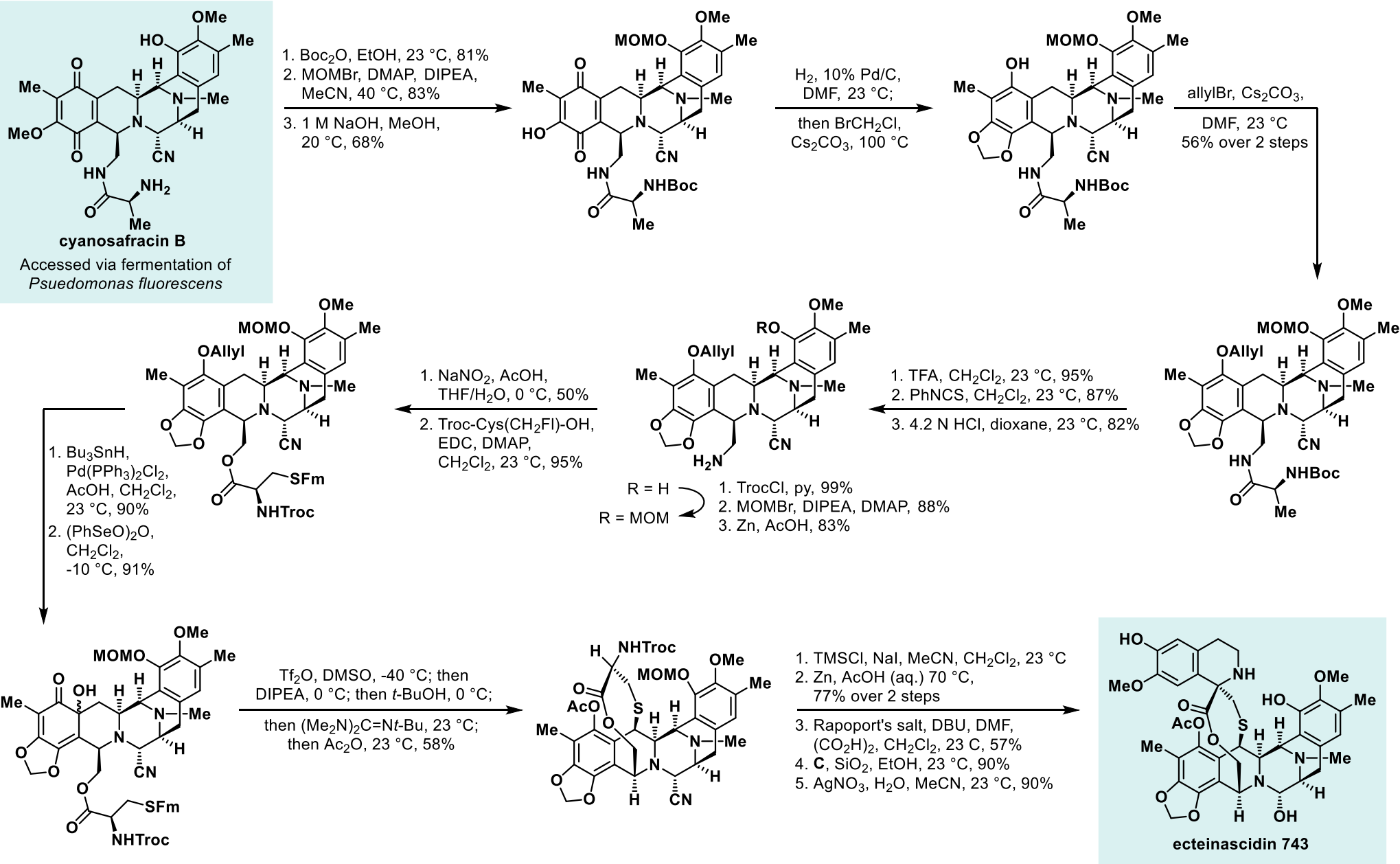
Asymm. hydrog. cat. developed by W. Knowles
Acc. Chem. Res. **1983**, 16, 106.

Mechanism of cyclization sequence:



Drug of the Week: Trabectedin

Corey synthesis: *J. Am. Chem. Soc.* **1996**, *118*, 9202.

Pharma Mar semisynthetic route: *Organic Letters*, **2000**, *2*, 2545.For modifications of this route, see: *J. Org. Chem.* **2003**, *68*, 8859; WO200069862A2; WO200187895A1; WO2011147828A1