Identification of an Unexpected 2-Oxonia[3,3]sigmatropic Rearrangement/Aldol Pathway in the Formation of Oxacyclic Rings. Total Synthesis of (+)-Aspergillin PZ.

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Current Litetature
Juraj Rehák
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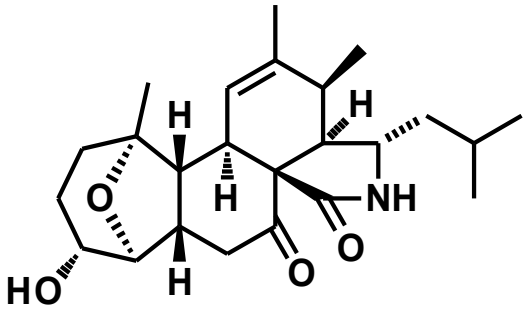
(+)-Aspergillin PZ



(+)-Aspergillin PZ

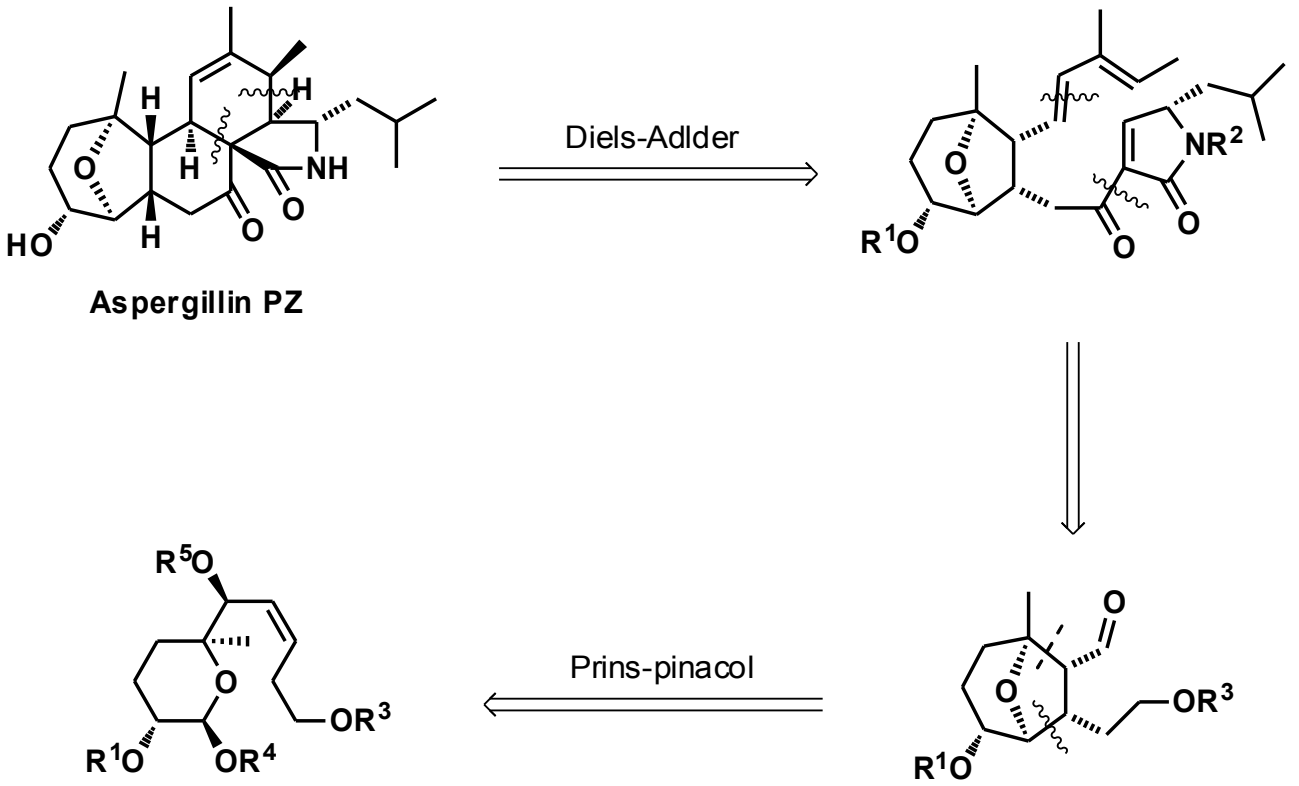
The (+)-Aspergillin PZ was isolated from the soil fungus *Aspergillus awamori.* The isolation and identification were reported by by Pei and coworkers in 2002.(1)

The structure of aspergillin PZ was proved by 2D NMR studies and X-ray analysis. The aspergilin PZ has pentacyclic structure with isoindolone moiety and unusual 12-oxatricyclo[6.3.1.$0^{2,7}$]dodecane ring system.

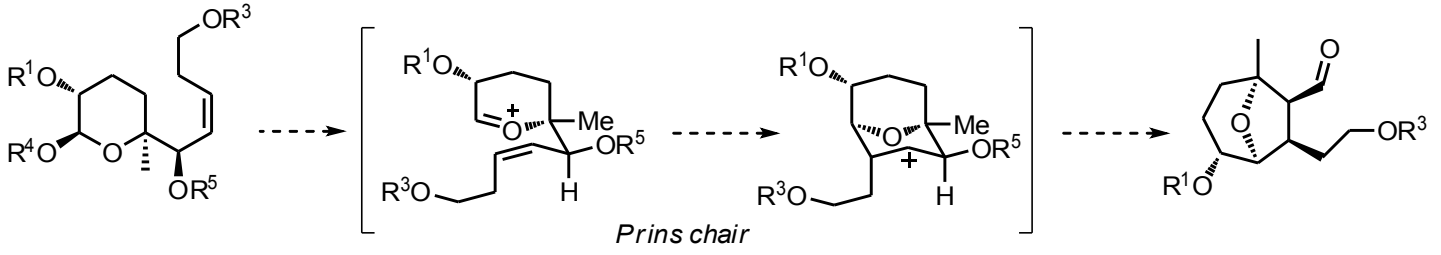
Pei and coworkers also described morphological deformation of the conidia of *Pyricularia oryzae* at 0.089 μM induced by aspergillin PZ.(1)

(1) Zhang, Y.; Wang, T.; Pei, Y.; Hua, H.; Feng, B. *J. Antibiot.* **2002**, *55*, 693–695.

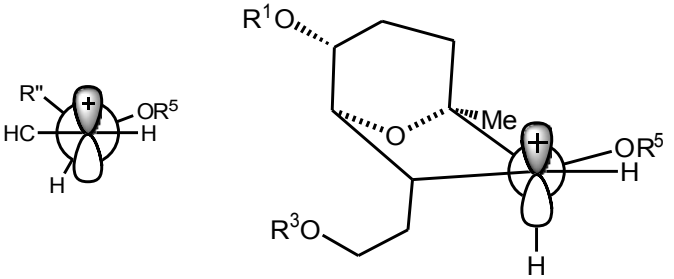
Retrosynthetic analysis of (+)-Aspergillin PZ.

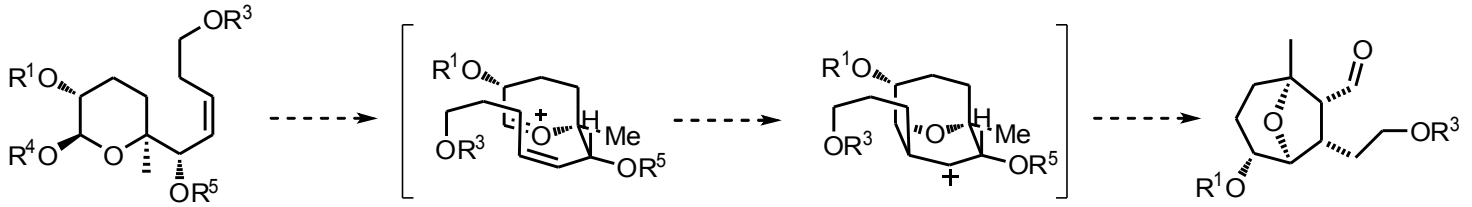


Stereochemical analysis of the Prins-pinacol reaction

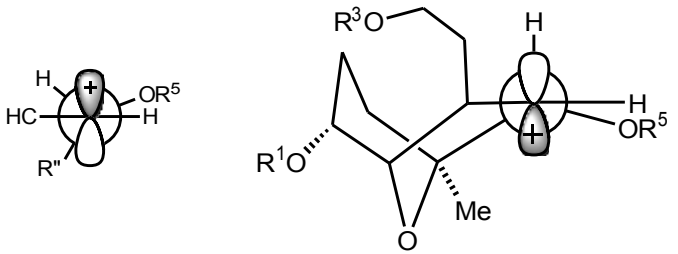


Prins chair

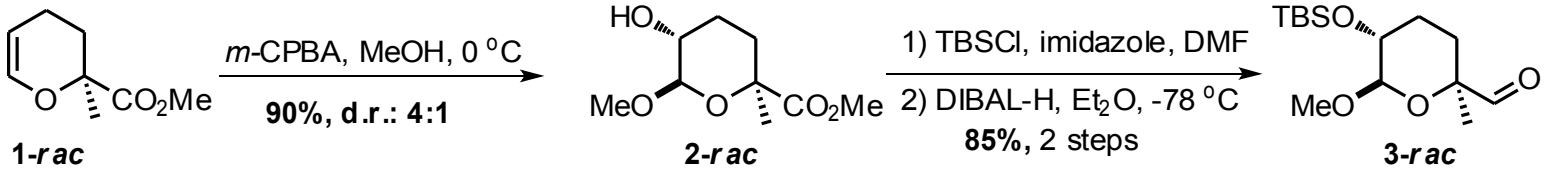




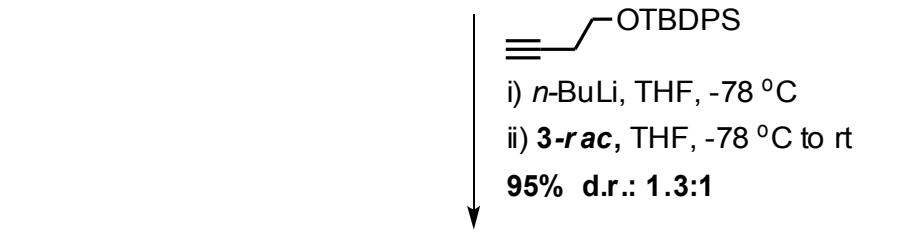
Prins boat

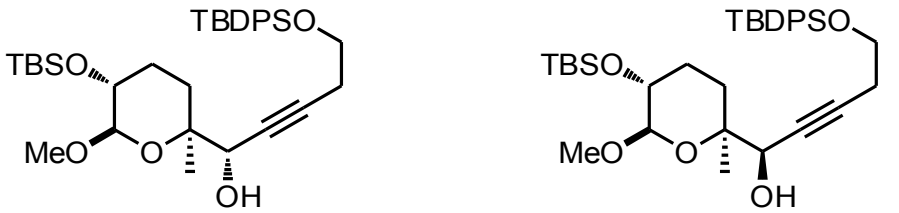


Synthesis of the Prins-pinacol *rac*-precursors.

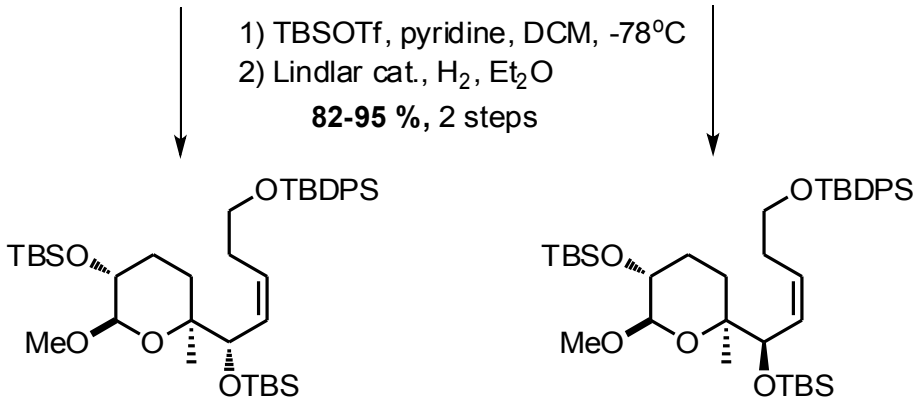


1-*rac* **2-*rac*** **3-*rac***



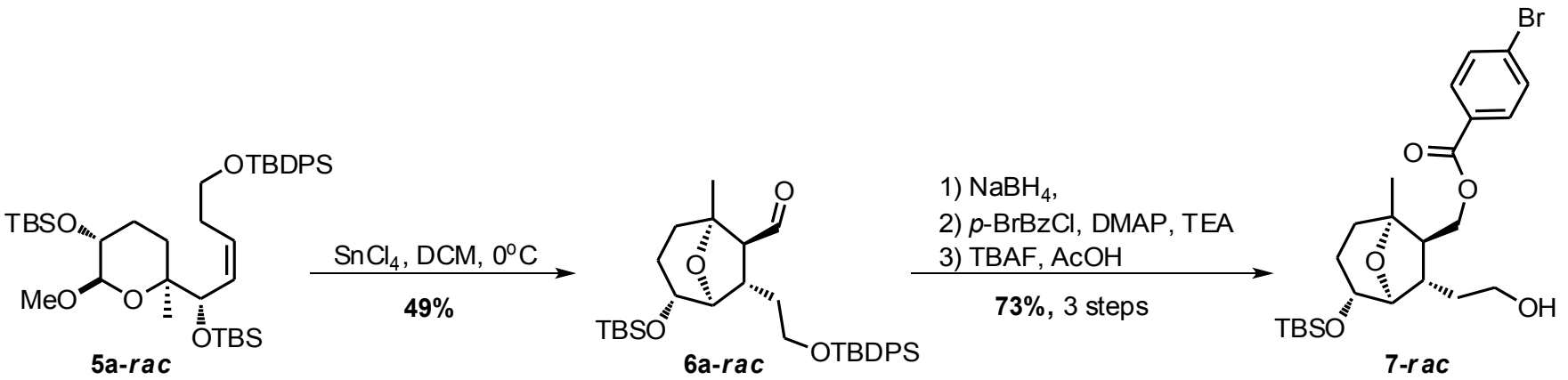


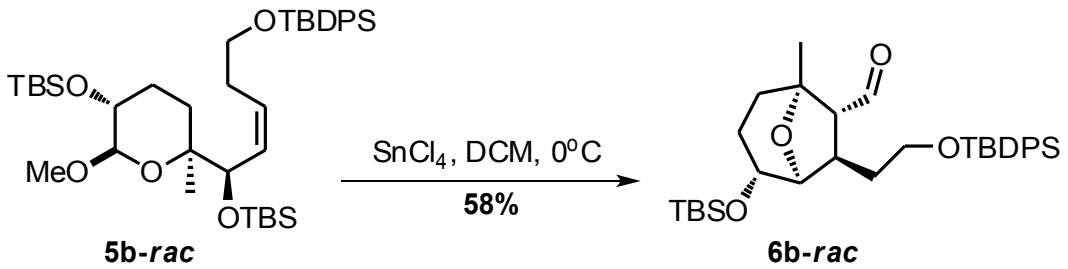
4a-*rac* **4b-*rac***



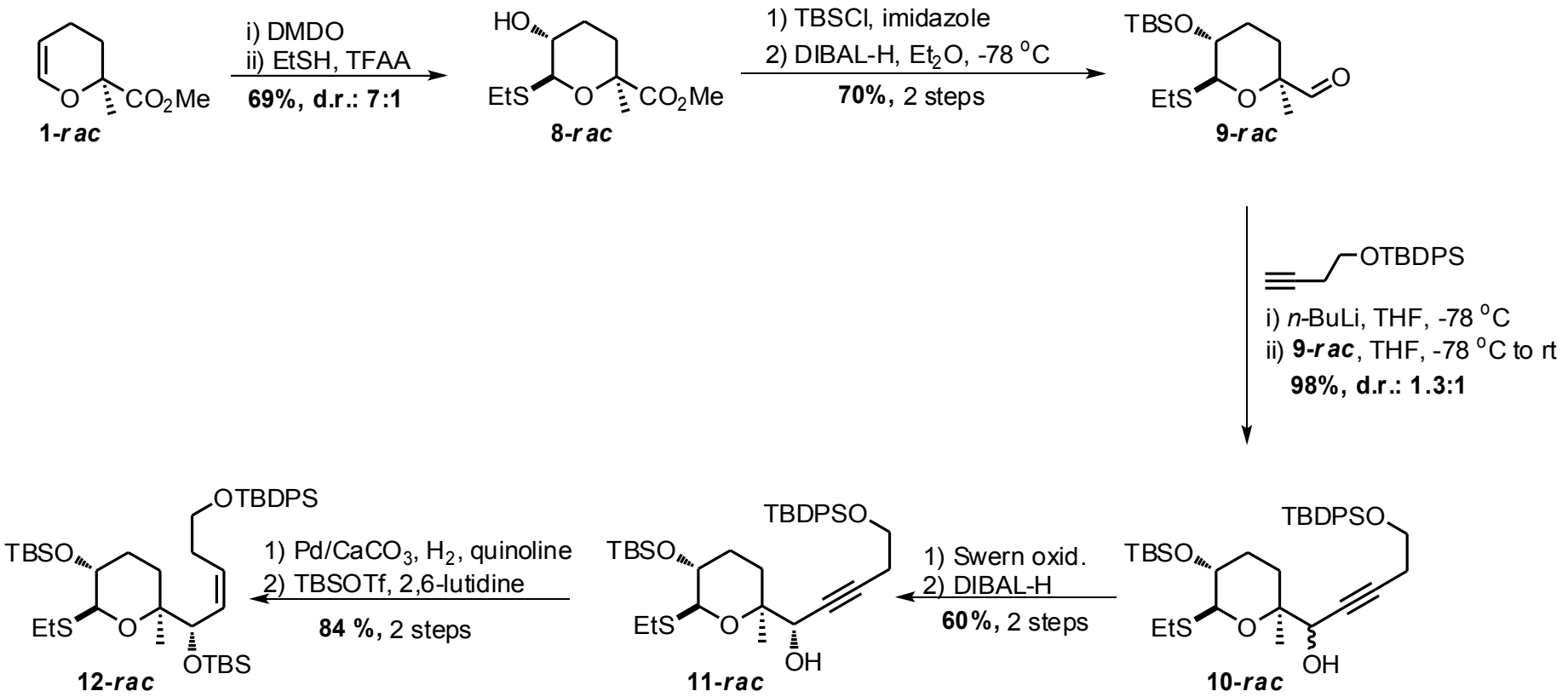
5a-*rac* **5b-*rac***

Unexpected formation of the trans aldehydes

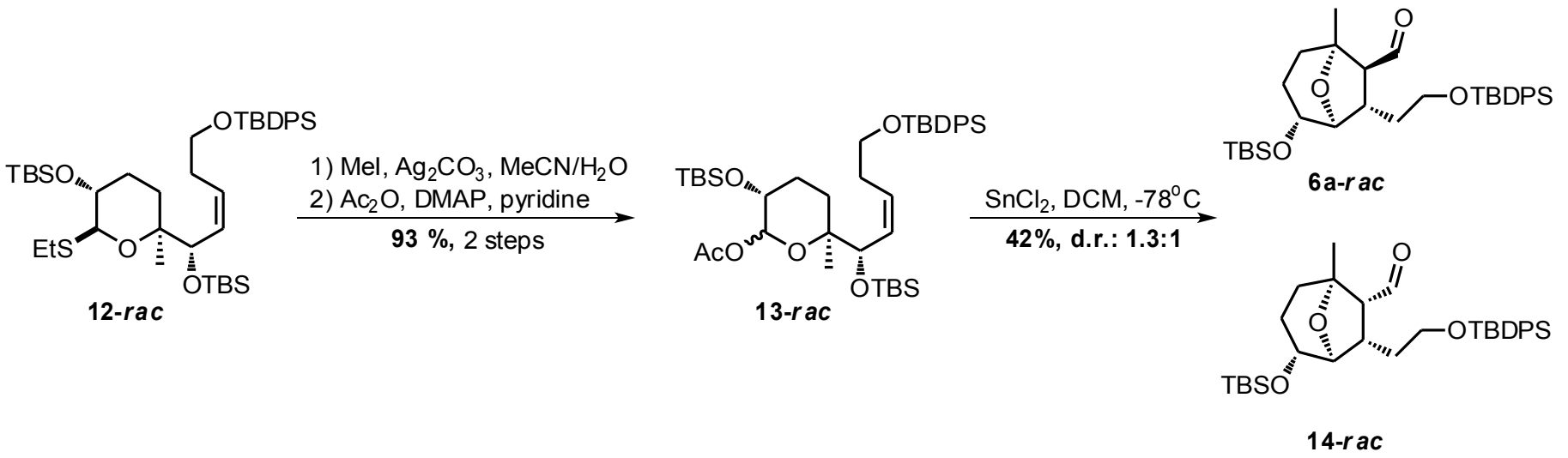




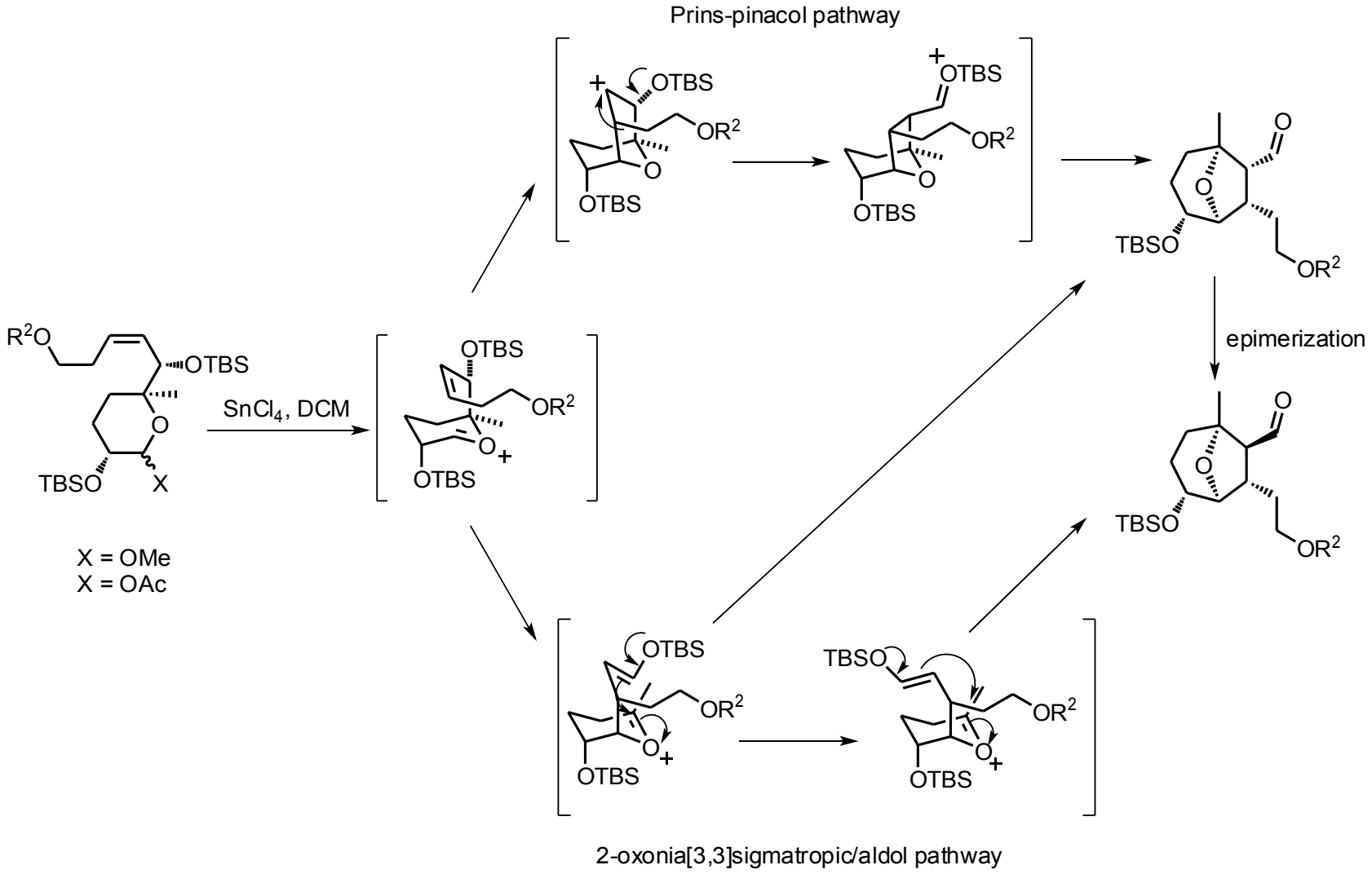
Synthesis of the Prins-pinacol *rac*-glycosyl acetate.



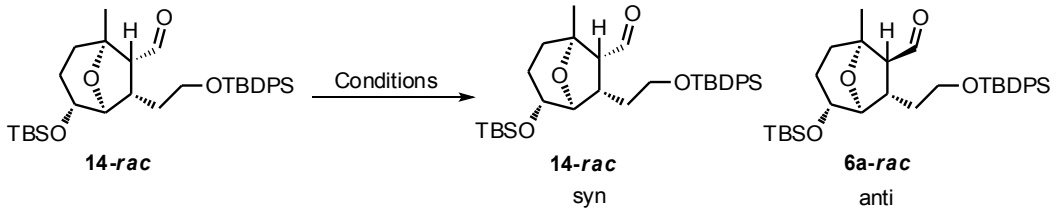
Initiation of the Prins-pinacol cascade at low temperature from glycosyl acetate 13-*rac*



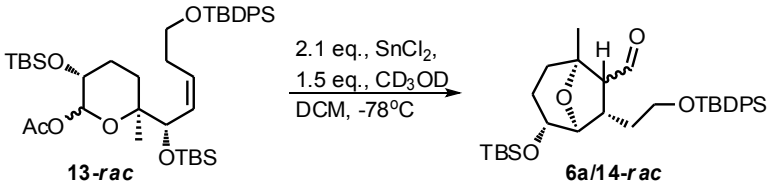
Potential Prins-pinacol and 2-oxonia[3,3]sigmatropic/aldol pathways.



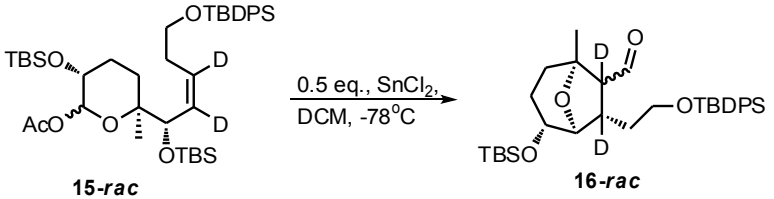
Deuterium labeling experiments and epimerization of cis aldehyde epimer 14-rac under various reaction conditions



14-*rac* **14-*rac*** syn **6a-*rac*** anti



13-*rac* **6a/14-*rac***

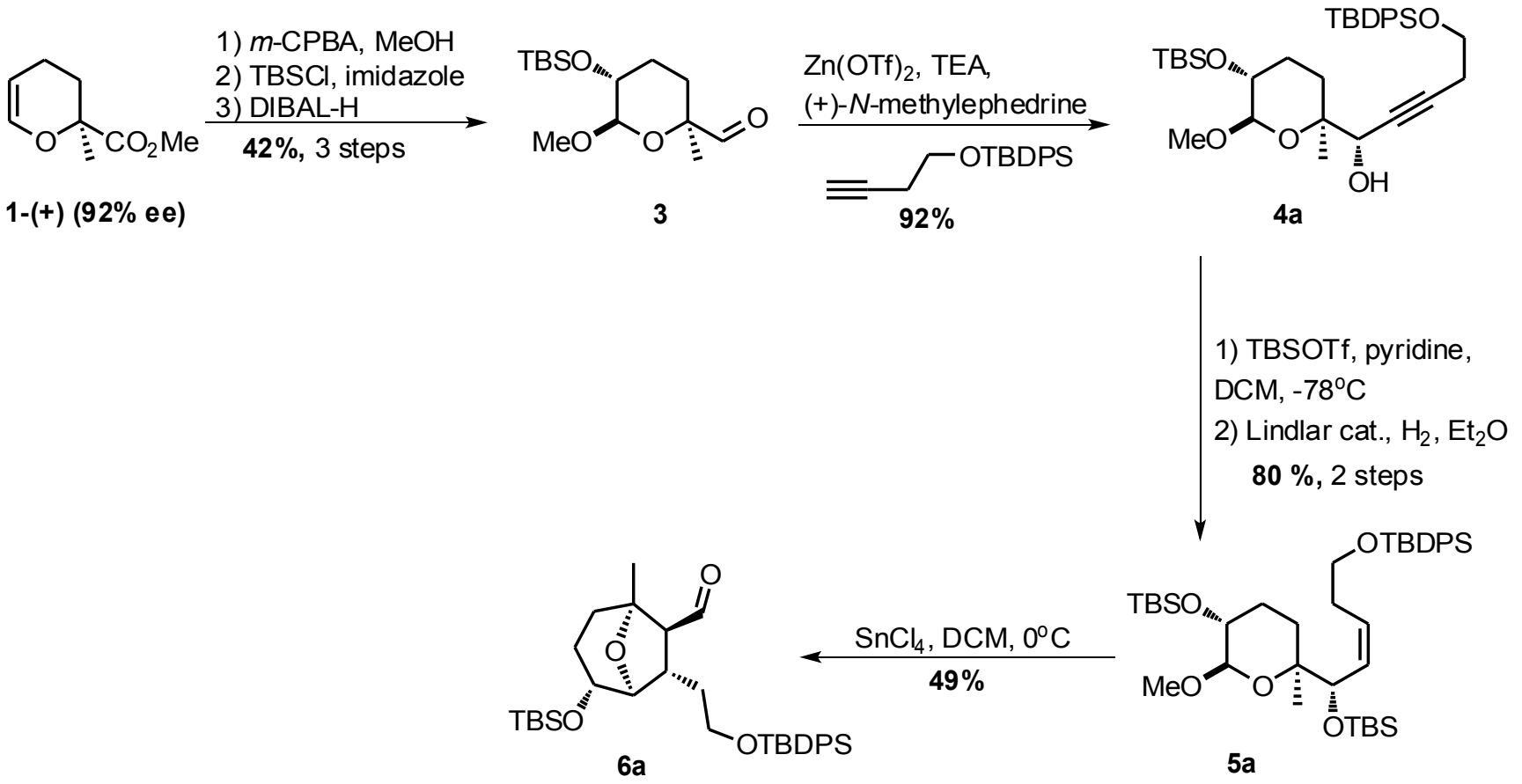


15-*rac* **16-*rac***

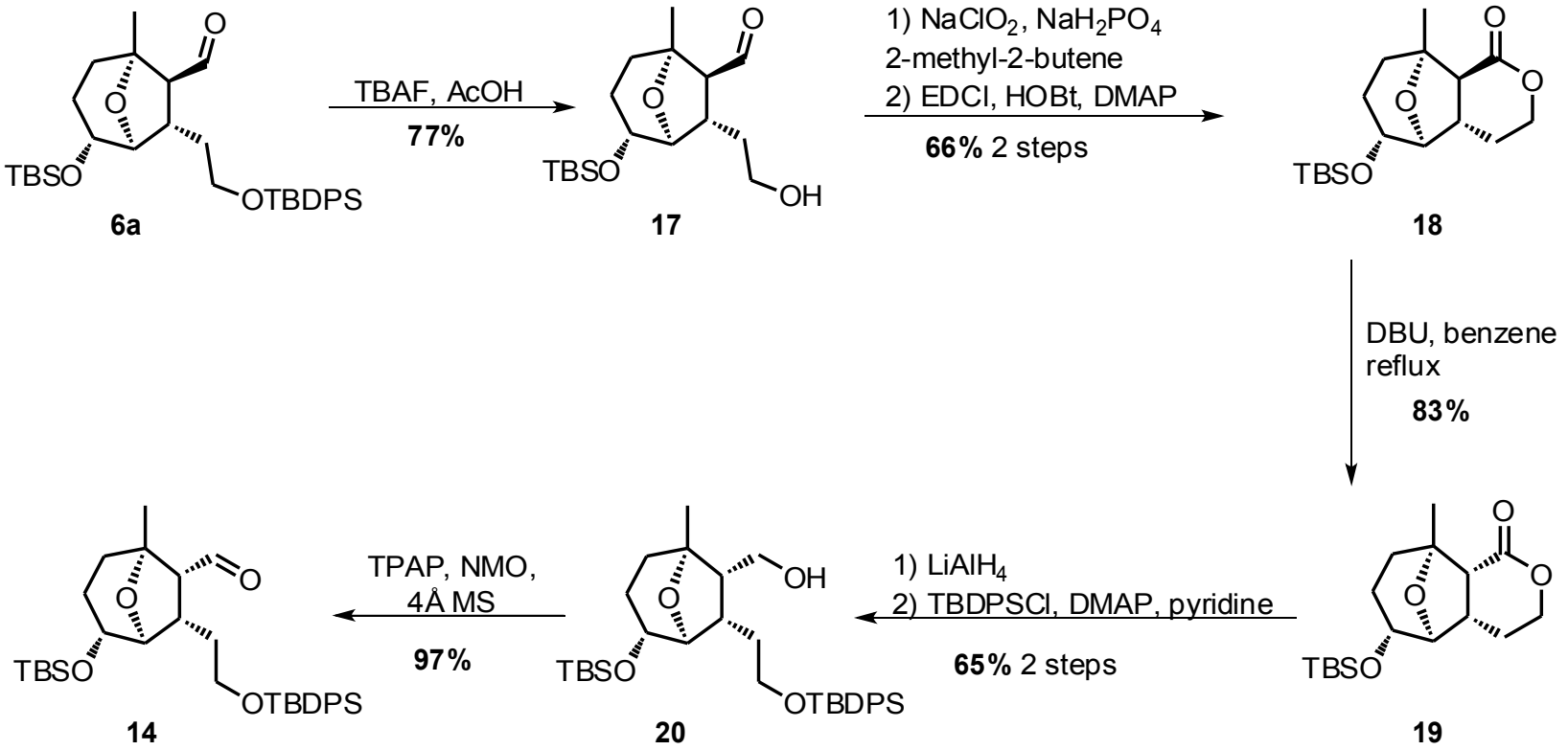
Entry	Conditions	cis	trans
1	BDU, toluene, r.t. 12 h	-	100%
2	TEA, DCM. -78 °C→r.t. 12 h	100%	-
3	0.5 eq. $SnCl_4$, DCM, -78 °C, 30 min	100%	-
4	0.5 eq. $SnCl_4$, DCM, 0 °C, 15 min	34%	66%
5	0.15 eq. $HN(Tf)_2$, DCM, -78 °C→ 0 °C, 30 min	100%	-
6	0.15 eq. $HN(Tf)_2$, DCM, 0 °C, 30 min	20%	80%

Ratio of cis/trans determined by integration of 1H NMR spectra

Synthesis of enantioenriched *trans*-8-oxabicyclooctyl aldehyde.

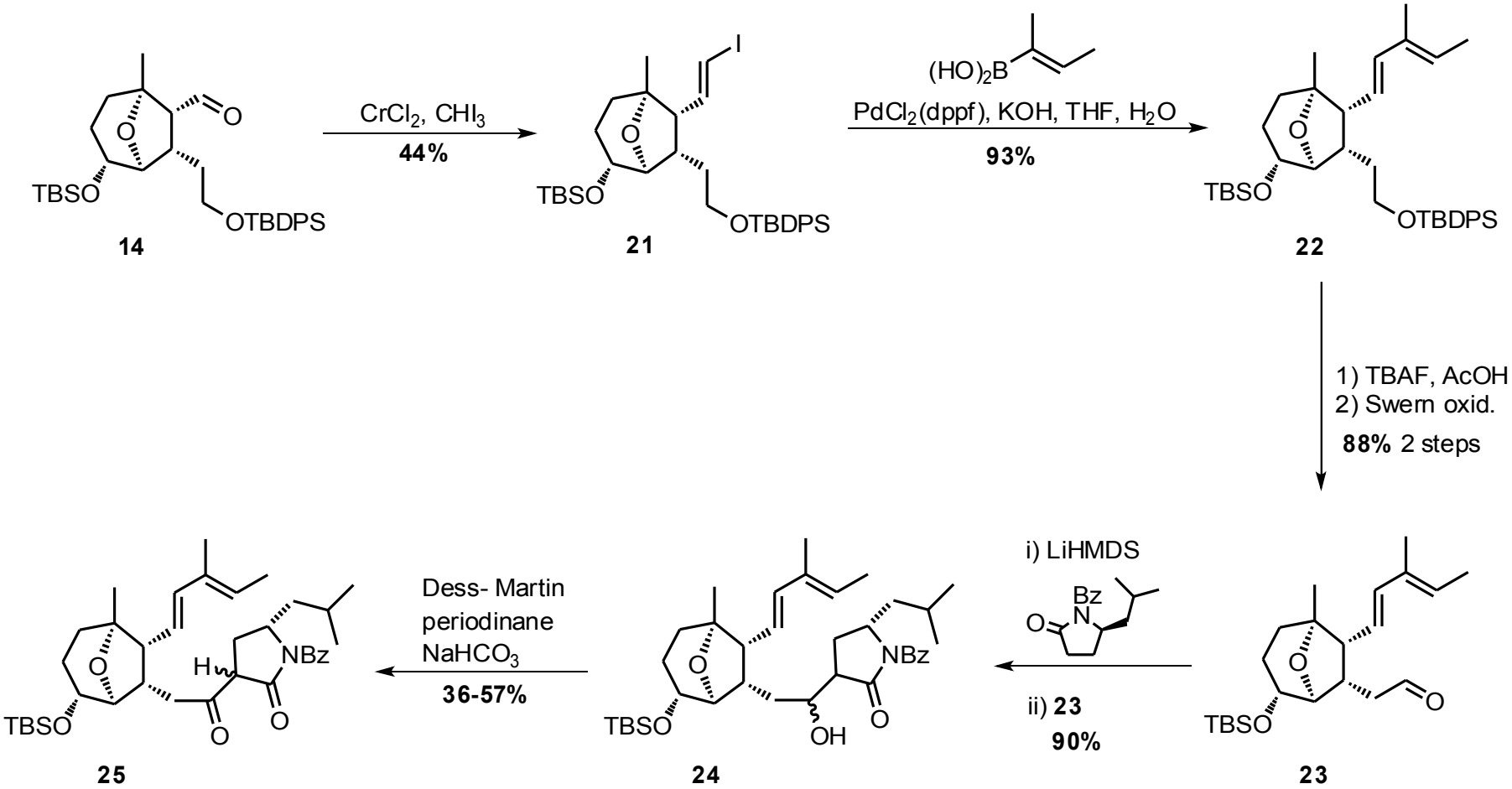


Preparation of cis-8-oxabicyclooctyl aldehyde.

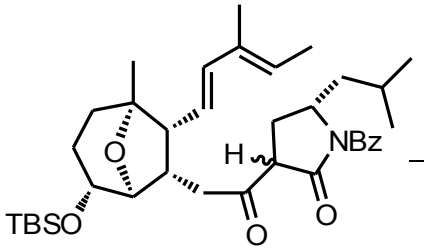


cis-aldehyde **14** in 27% overall yield from its *trans* epimer **6a**.

Preparation of Diels-Alder precursor.



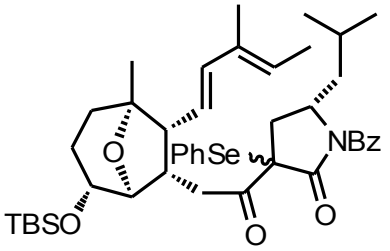
Completion of the (+)-Aspergillin PZ.



25

i) LiHMDS
ii) PhSeCl

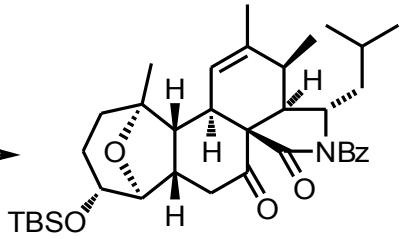
83%



26

1) H_2O_2, m-CPBA
-50 °C to 0 °C
2) toluene 100 °C

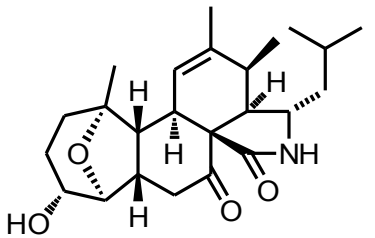
56%, 2 steps



27

1) NaOH, H_2O, MeOH
2) TBAF, THF

67%, 2 steps



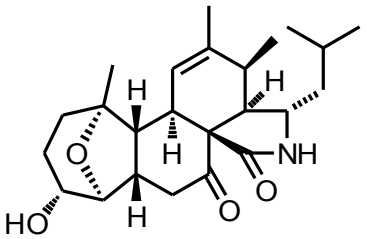
(+)-Aspergillin PZ

Conclusion.

Autors showed evidence that the cascade transformation can take place by a 2-oxonia[3,3]sigmatropic/aldol pathway as well as by the more common Prins-pinacol mechanism.

The (+)-Aspergillin PZ was synthesized in owerall 0.23 % yield after 25 steps.

The syntetic sample of (+)-Aspergillin PZ was tested against two highly invasive tumor lines (A2058 melanoma and DU145 prostate cancer) and no useful activity (IC 50 >10 μM) was found in either cell line.



(+)-Aspergillin PZ