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Total Synthesis of Isomalabaricane Triterpenoids

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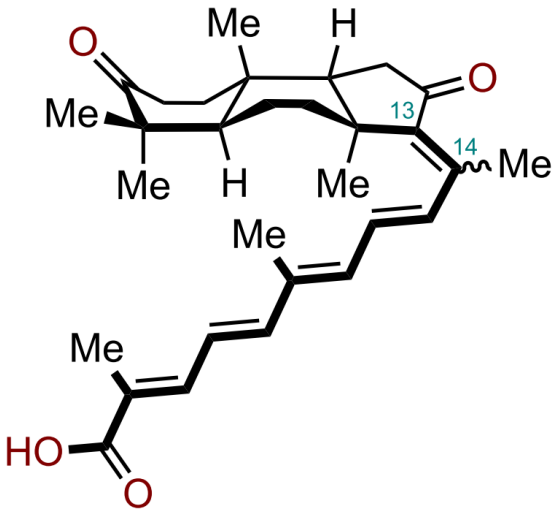


$\Delta^{13(14)}$ = *E*, **rhabdastrellic acid A (1)**

IC_{50} = 1.46 μM (HL-60)

$\Delta^{13(14)}$ = *Z*, **stelletin E (2)**

IC_{50} = 3.9 nM (HCT-116)

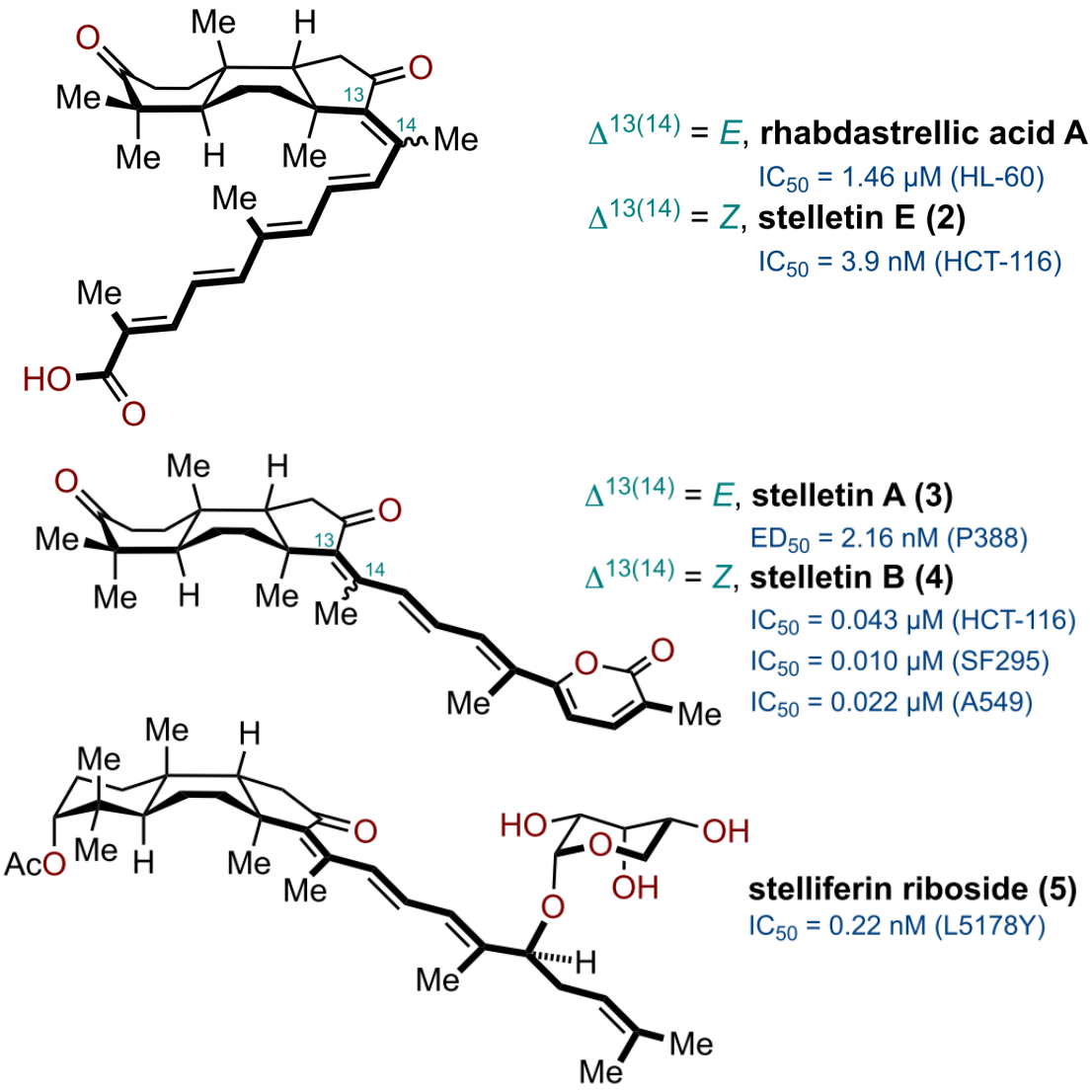
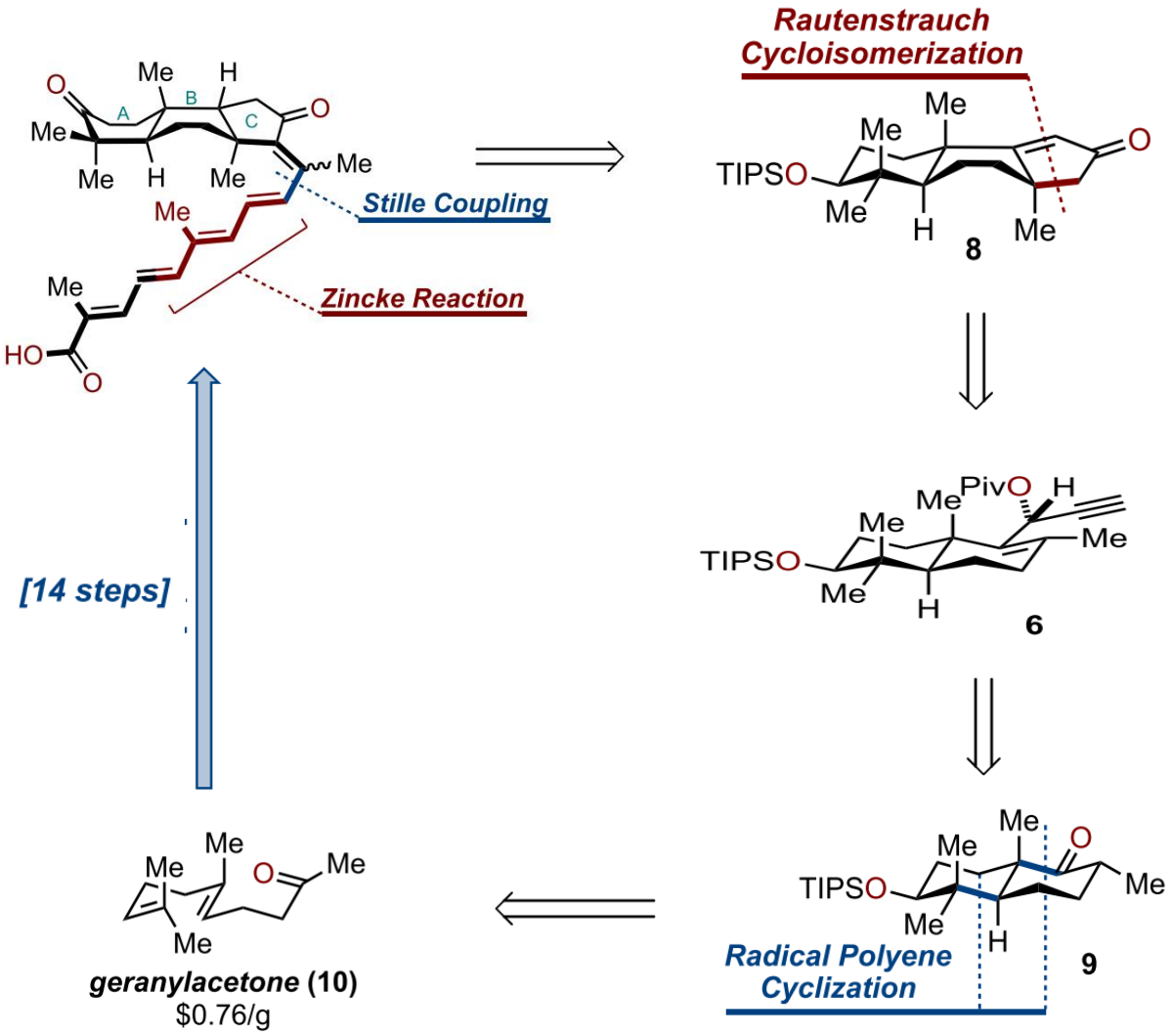
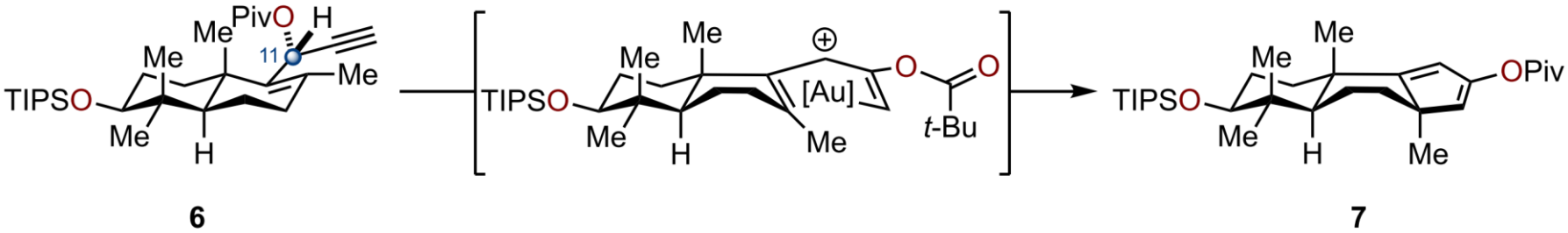


Figure 1. Selected isomalabaricane triterpenoids.

(a) Retrosynthetic approach to the isomalabaricanes.



(b) Mechanism of the Rautenstrauch rearrangement.



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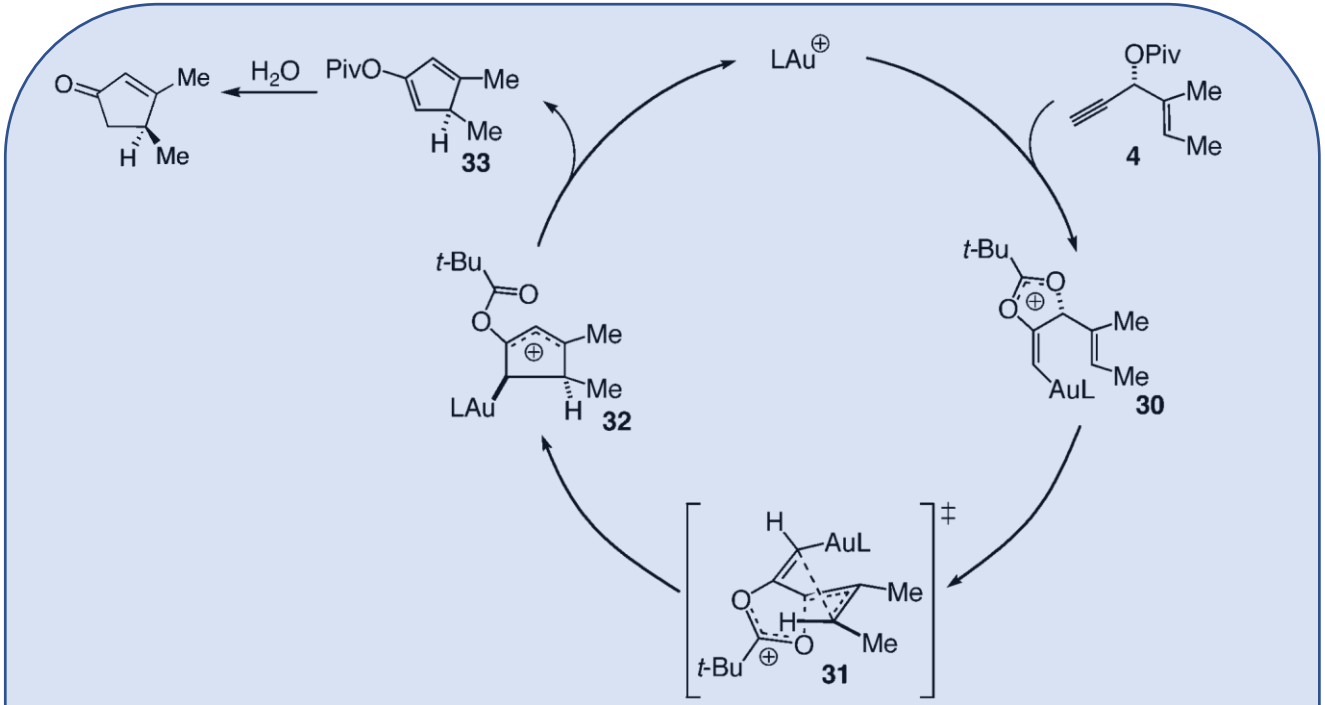
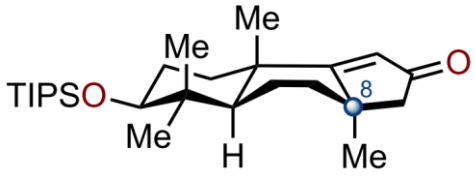


H_3O^+



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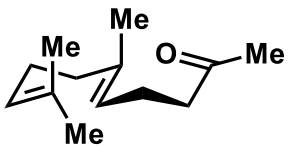
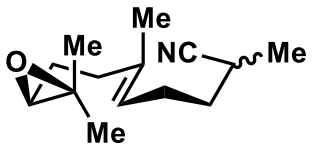
J. Am. Chem. Soc. **2005**, *127*, 5802



geranylacetone (10)

1. TosMIC, *t*-BuOK
94%

2. NBS, THF/H_2O
then K_2CO_3
82%, *d.r. = 1:1*



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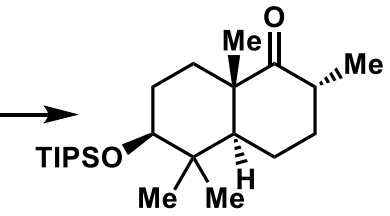
3. Cp_2TiCl_2, Zn
70%, *d.r. = 5:1*

4. TIPSOTf
95%



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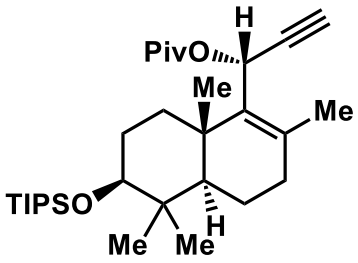
5. LDA, CH_2Cl_2
then $LiClO_4$
80%

6. C_2H_2, n-BuLi
then PivCl
82%, *d.r. > 20:1*



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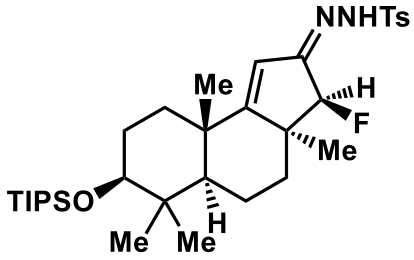
7. $[Au(PPh_3)Cl]$
AgOTf, Selectfluor

then NH_2NHTs
81%, *d.r. > 20:1*



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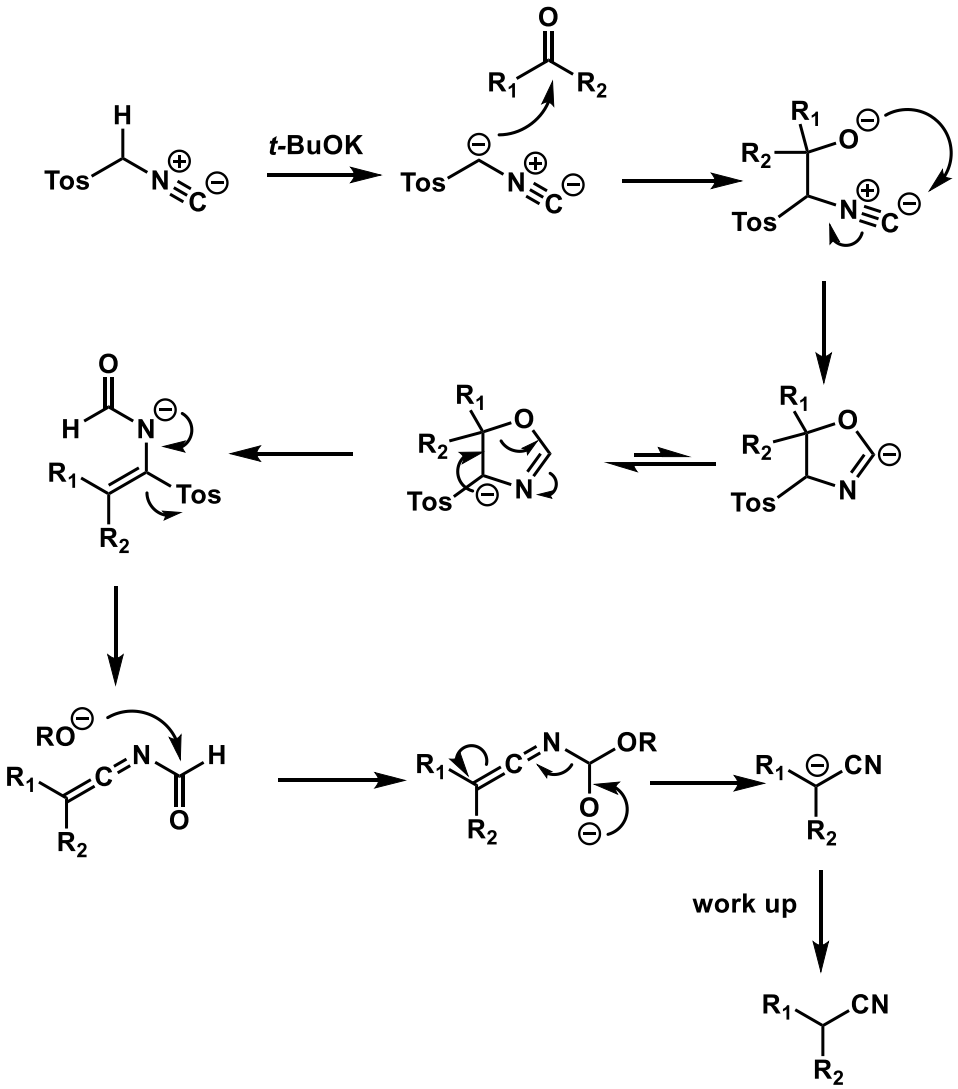
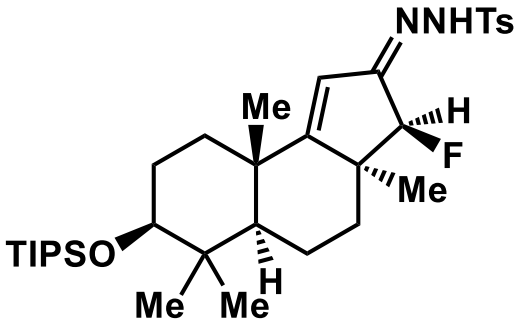
van Leusen reductive cyanation of the ketone



J. Org. Chem. **1977**, *42*, 3114

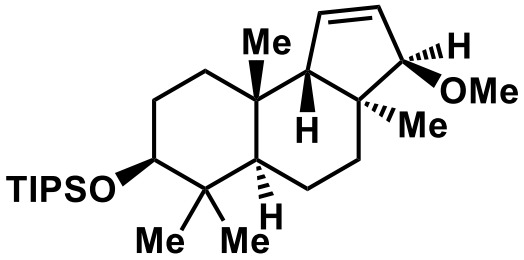


12

8. MeOH, Et_3N

then CatBH, CsOAc

58%, *d.r. > 20:1*



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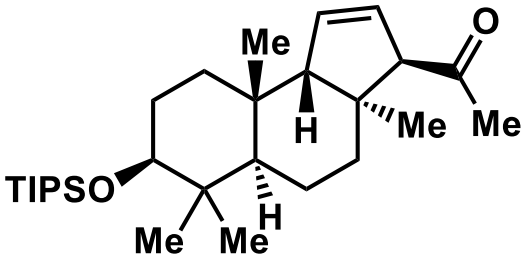
gram scale synthesis

64%

9. Cp_2ZrCl_2, *n*-BuLi

then CuOAc, AcCl



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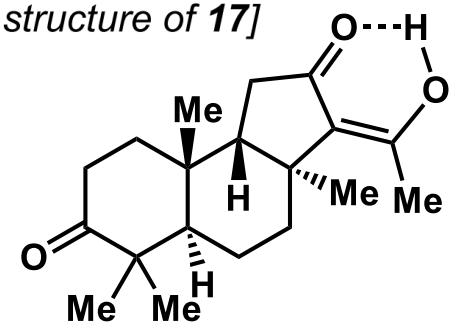
10. BH_3, TfOH

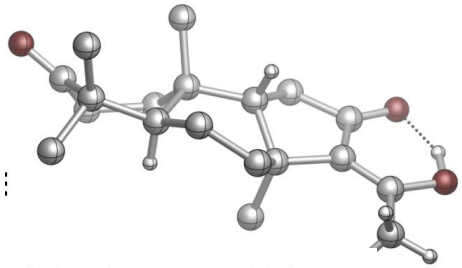
then H_2O_2

11. IBX

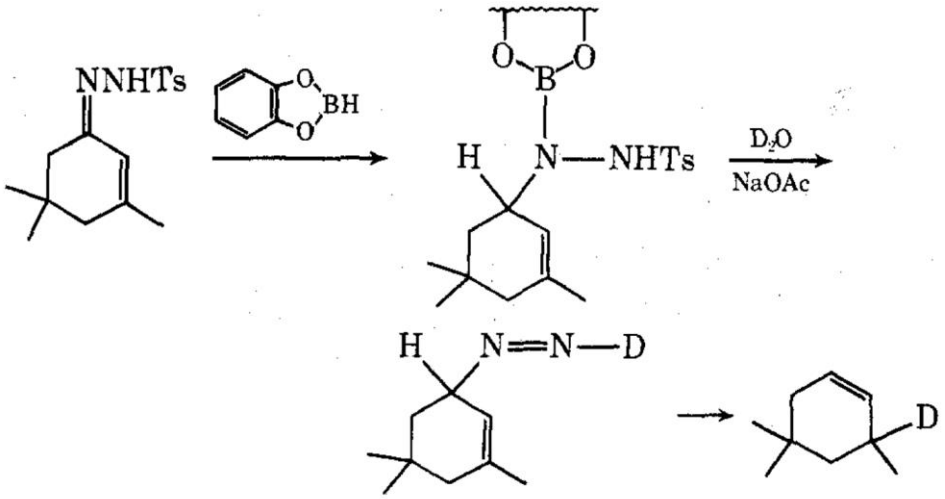
80% over 2 steps



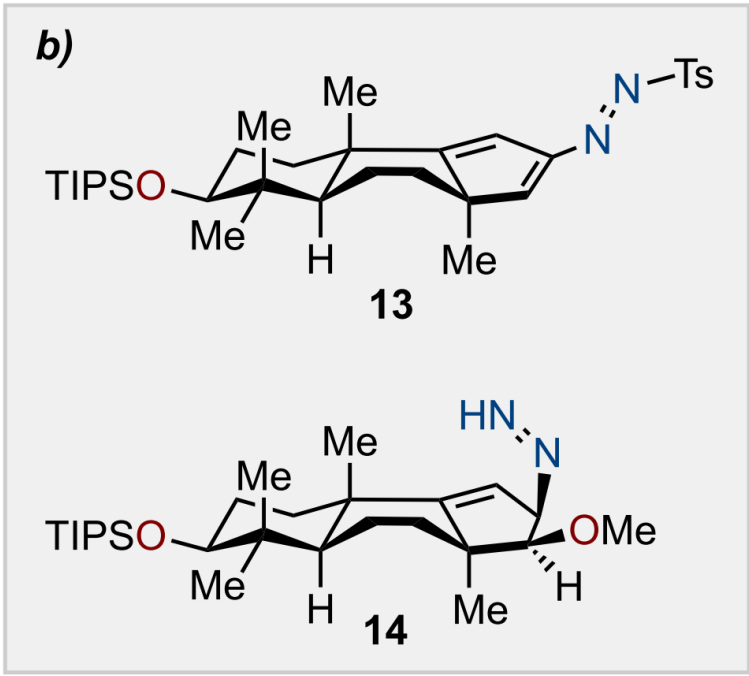
17

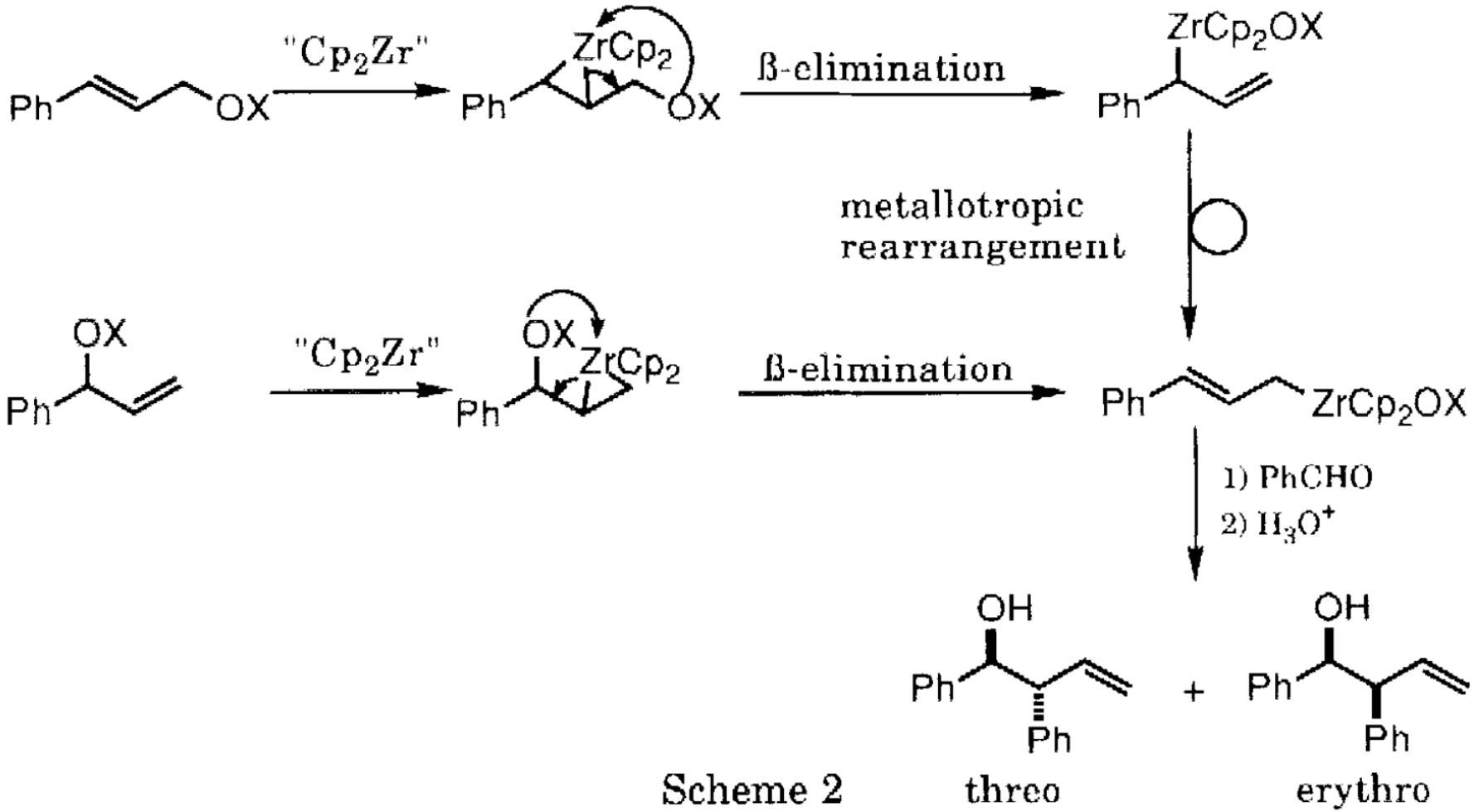


*[single crystal X-ray structure of **17**]*



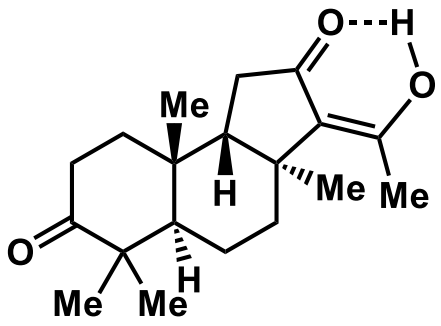
J. Org. Chem. **1976**, *41*, 574





Scheme 2

Tetrahedron Lett. **1992**, *33*, 1295



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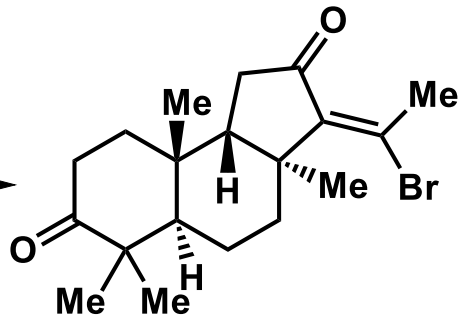
12. $(COBr)_2$

DMF



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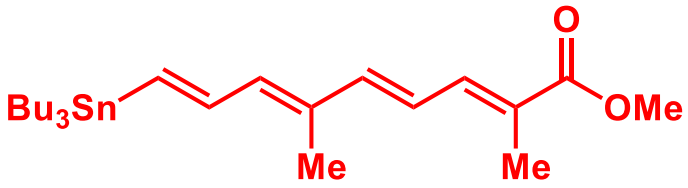

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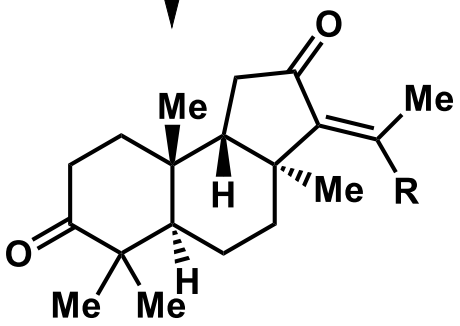
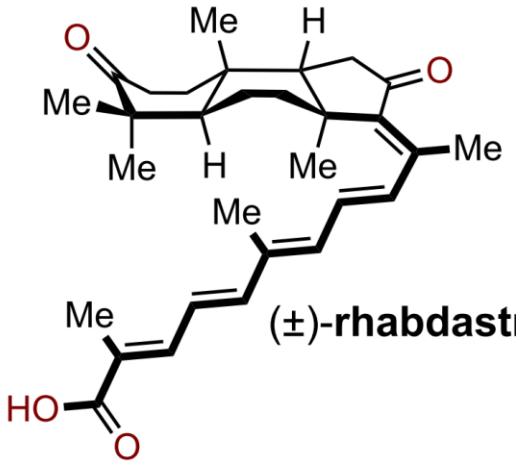
13. $Pd_2(dba)_3$
Ph_3As, 20
NMP, 70 °C
45%



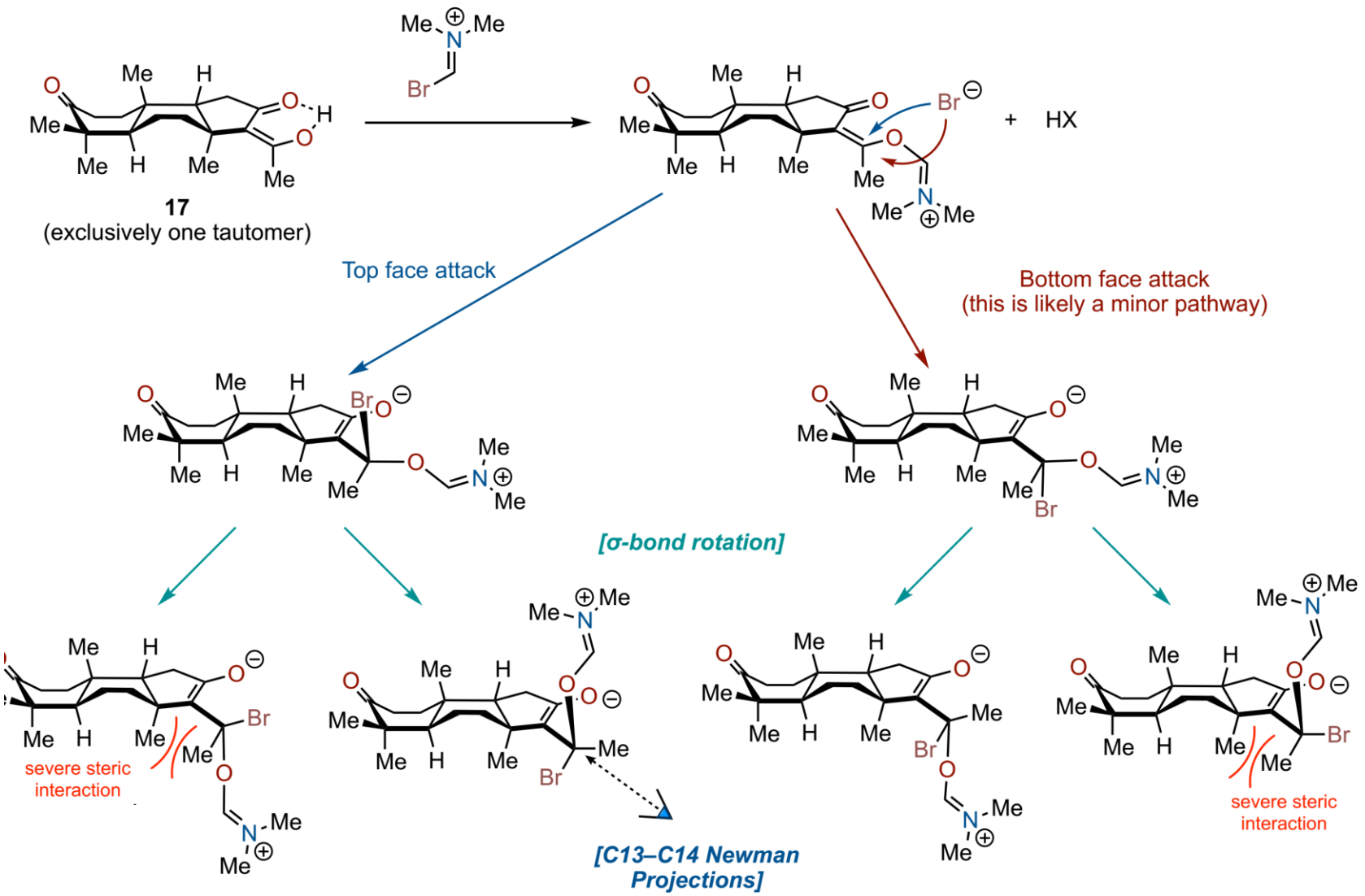
14. Me_3SnOH
98%, *d.r. = 8:1*

or

14. LiOH
96%, *d.r. = 1.9:1*



(±)-rhabdastrellic acid A (1)


17
(exclusively one tautomer)
+ HX
Top face attack
Bottom face attack
(this is likely a minor pathway)
[σ-bond rotation]
severe steric
interaction
severe steric
interaction
[C13–C14 Newman
Projections]