Literature Report 5

Asymmetric Total Synthesis of Brasilicardins

Reporter: Zi-Biao Zhao

Checker: Xiao-Yong Zhai

Date: 2019-1-21

Yoshimura, F.; Itoh, R.; Torizuka, M.; Mori, G.; Tanino, K.*
Angew. Chem. Int. Ed. **2018**, *57*, 17161.

CV of Prof. Keiji Tanino

Background:

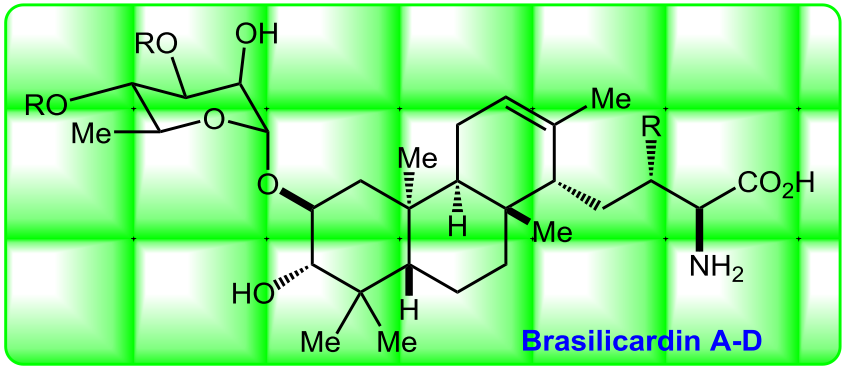
- **1981-1985** B.S., Tokyo Institute of Technology.
- **1985-1987** M.S., Tokyo Institute of Technology,
- **1994** Ph.D., Tokyo Institute of Technology.
- **1990-1998** Assistant Professor, Tokyo Institute of Technology.
- **1998-1999** Assistant Professor, Hokkaido University.
- **1999-2006** Associate Professor, Hokkaido University.
- **2006-now** Professor, Hokkaido University.

Research:

- Total synthesis of complex natural product.

Contents

Introduction

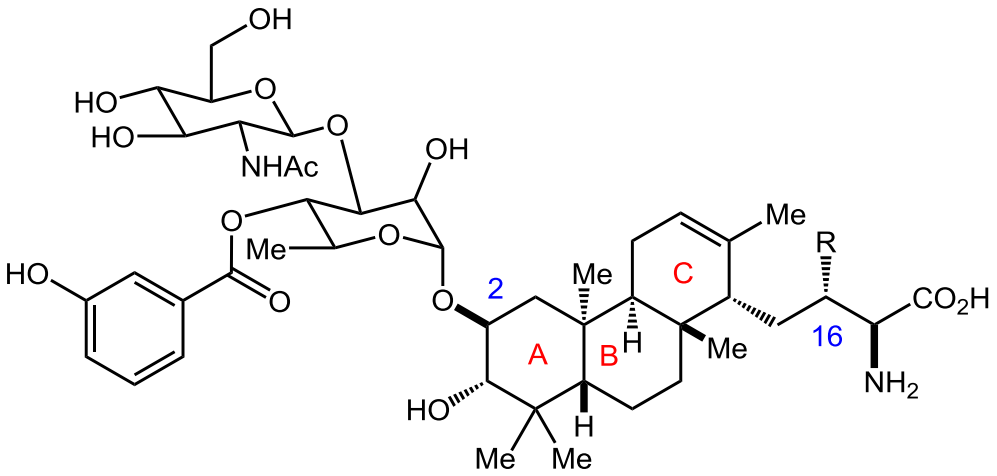


(放线菌培养液)

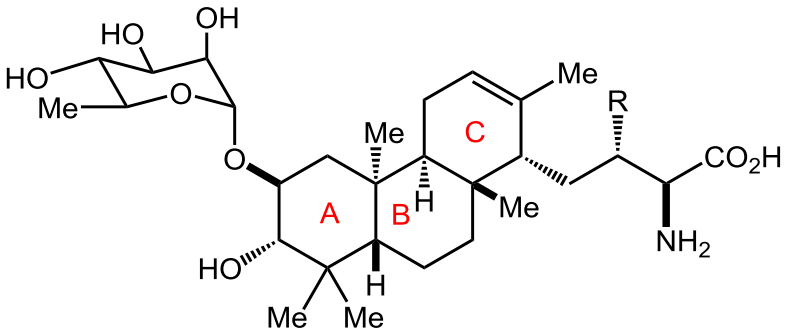
- Brasilicardins A-D are bacterial diterpenoid natural products isolated from the cultured broth of the actinomycete *Nocardia brasiliensis* IFM 0406;
- Exhibiting diverse biological activities such as Brasilicardin A displays potent immunosuppressive activity (IC_{50} = 0.05 nm).

Shigemori, H.; Komaki, H.; Kobayashi, J. *J. Org. Chem.* **1998**, *63*, 6900.

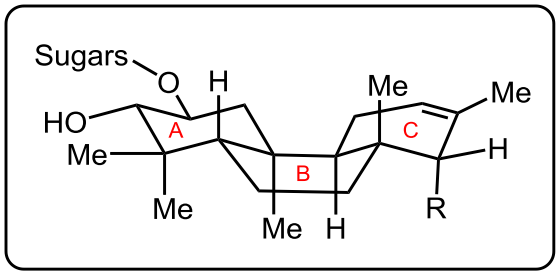
Structures of Brasilicardins



Brasilicardin A (1): R = OMe
Brasilicardin B (2): R = H



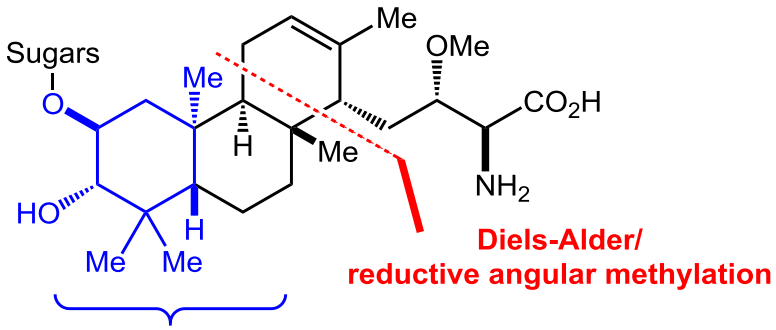
Brasilicardin C (3): R = OMe
Brasilicardin D (4): R = H



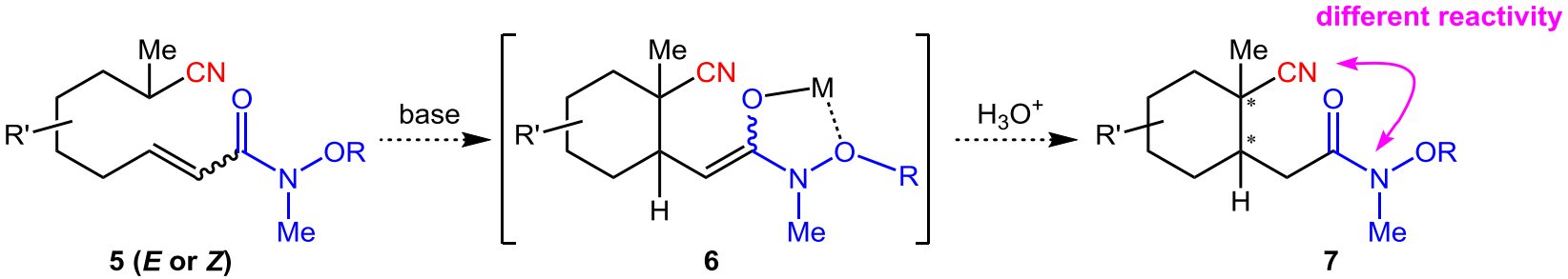
***anti-syn-anti*-fused perhydrophenanthrene skeleton of brasilicardins**

Background and Synthetic Plan

a: Anada-Hashimoto approch

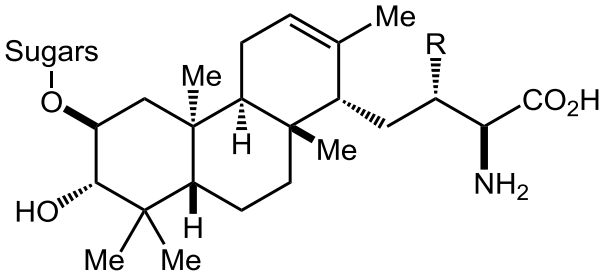


b: Our key technology



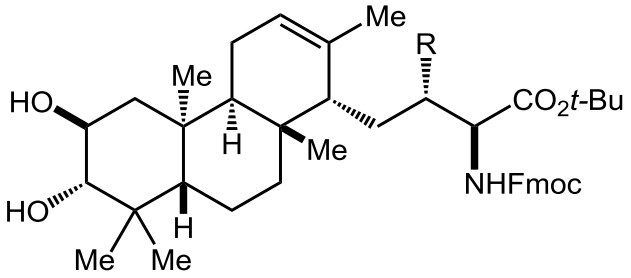
Anada, M. *et al*. *Org. Lett*. **2017**, *19*, 5581.
Tanino, K. *et al*. *Angew. Chem. Int. Ed.* **2018**, *57*, 17161.

Retrosynthetic Analysis



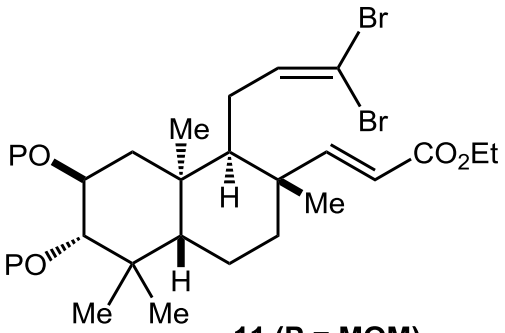
Brasilicardins A-D (**1-4**):
R = OMe or H

Glycosylation



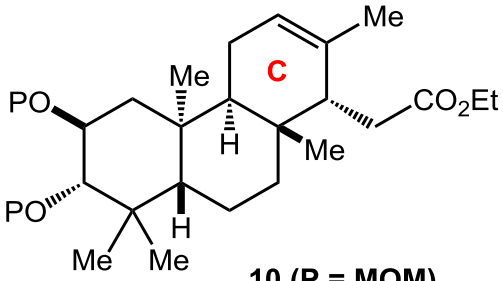
8 (R = OMe)
9 (R = H)

Construction of amino acid



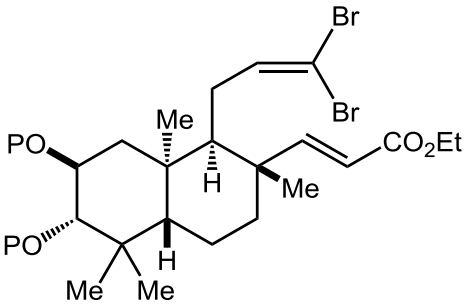
11 (P = MOM)

Intramolecular conjugate addition



10 (P = MOM)

Retrosynthetic Analysis



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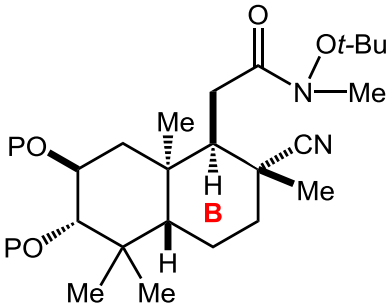
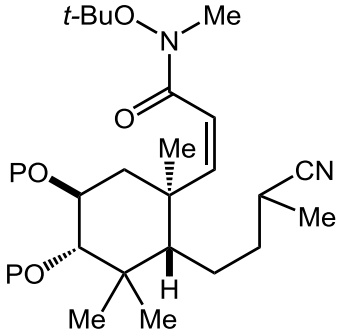
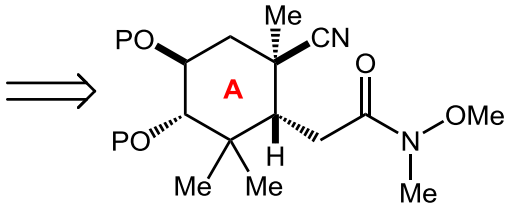


12 (P = MOM)

Intramolecular conjugate addition

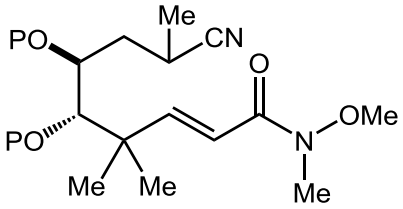


13 (P = MOM)

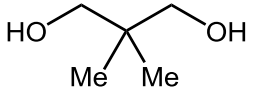


14 (P = MOM)

Intramolecular conjugate addition

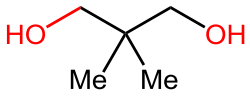


15 (P = MOM)



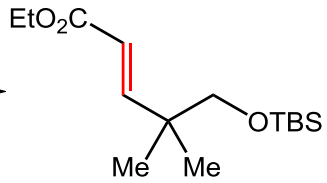
16

Synthesis of The Compound 14



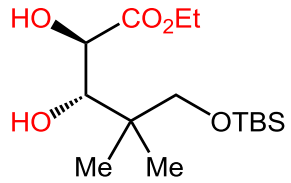
16

1) NaH, TBSCl
2) $(COCl)_2$, DMSO, Et_3N
then $(EtO)_2P(O)CH_2CO_2Et$
DBU, LiCl, MeCN
96% (2 steps)



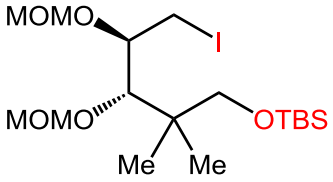
17

(DHQ)PHN, $K_2OsO_2(OH)_4$
$K_3Fe(CN)_6$, K_2CO_3, $MeSO_2NH_2$
t-BuOH-H_2O, 0 °C
>99%



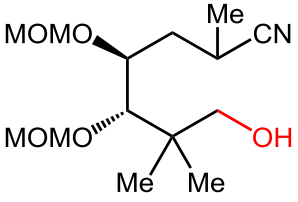
18
(95% ee)

1) MOMCl, *i*-Pr_2NEt
2) $LiAlH_4$, 0 °C
3) I_2, PPh_3, imidazole
96% (3 steps)



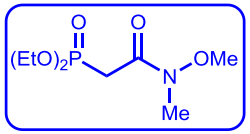
19

1) EtCN, LDA,
HMPA, -78 °C
2) TBAF, 50 °C
98% (2 steps)

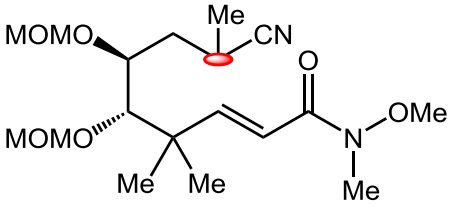


20
(dr = 55:45)

1) TPAP, NMO
2) NaHMDS

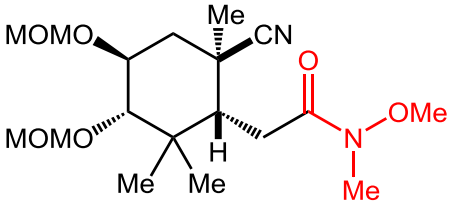


76% (2 steps)



15
(dr = 60:40)

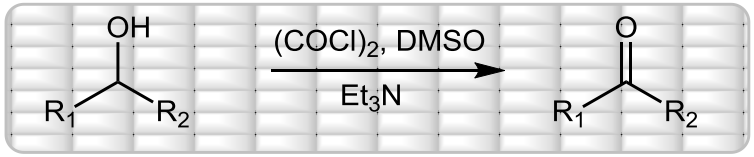
NaHMDS
THF, -78 °C
93% (dr>99:1)

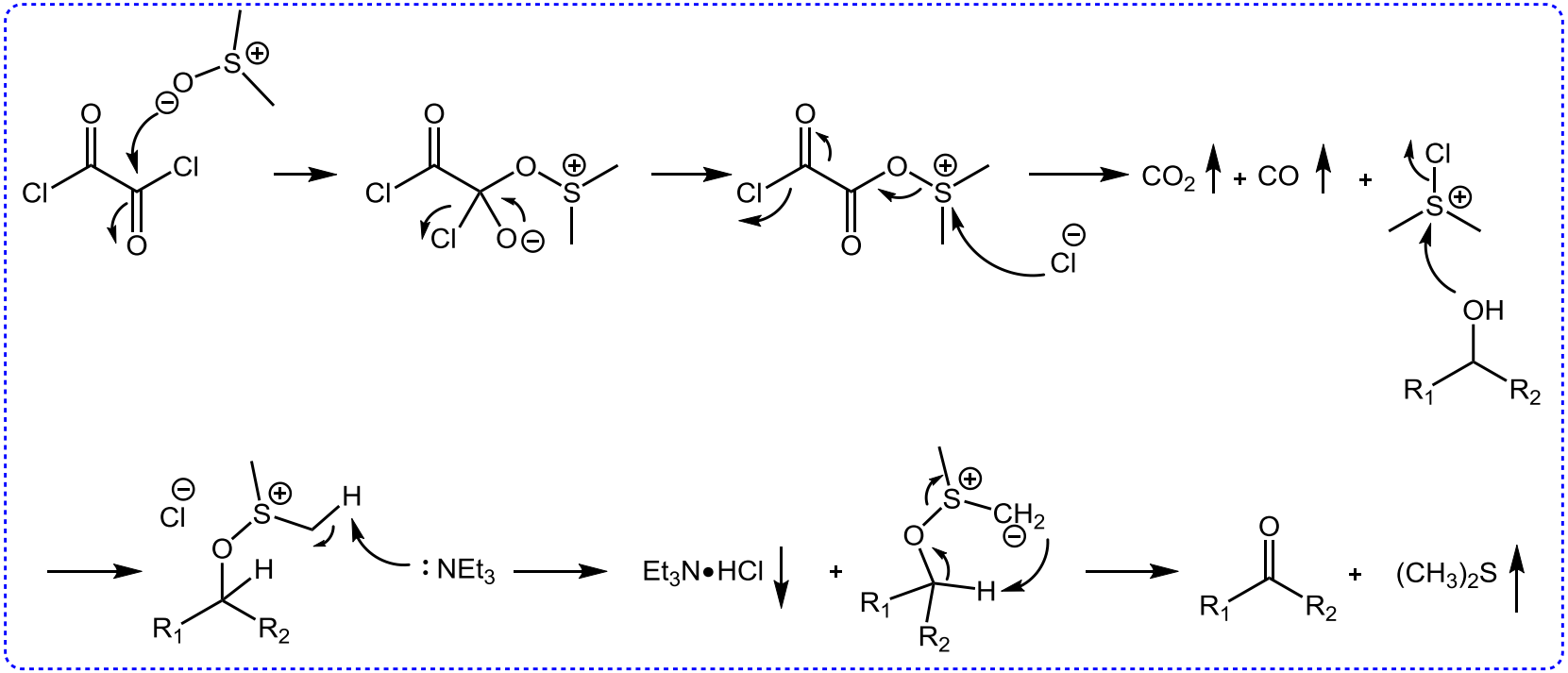


14

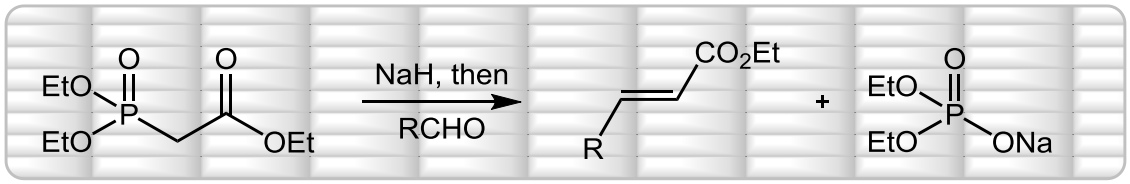
1) DIBAL, THF, -78 °C
2) $Ph_3P(CH_2OMe)Cl$, *t*-BuOK
93% (2 steps)

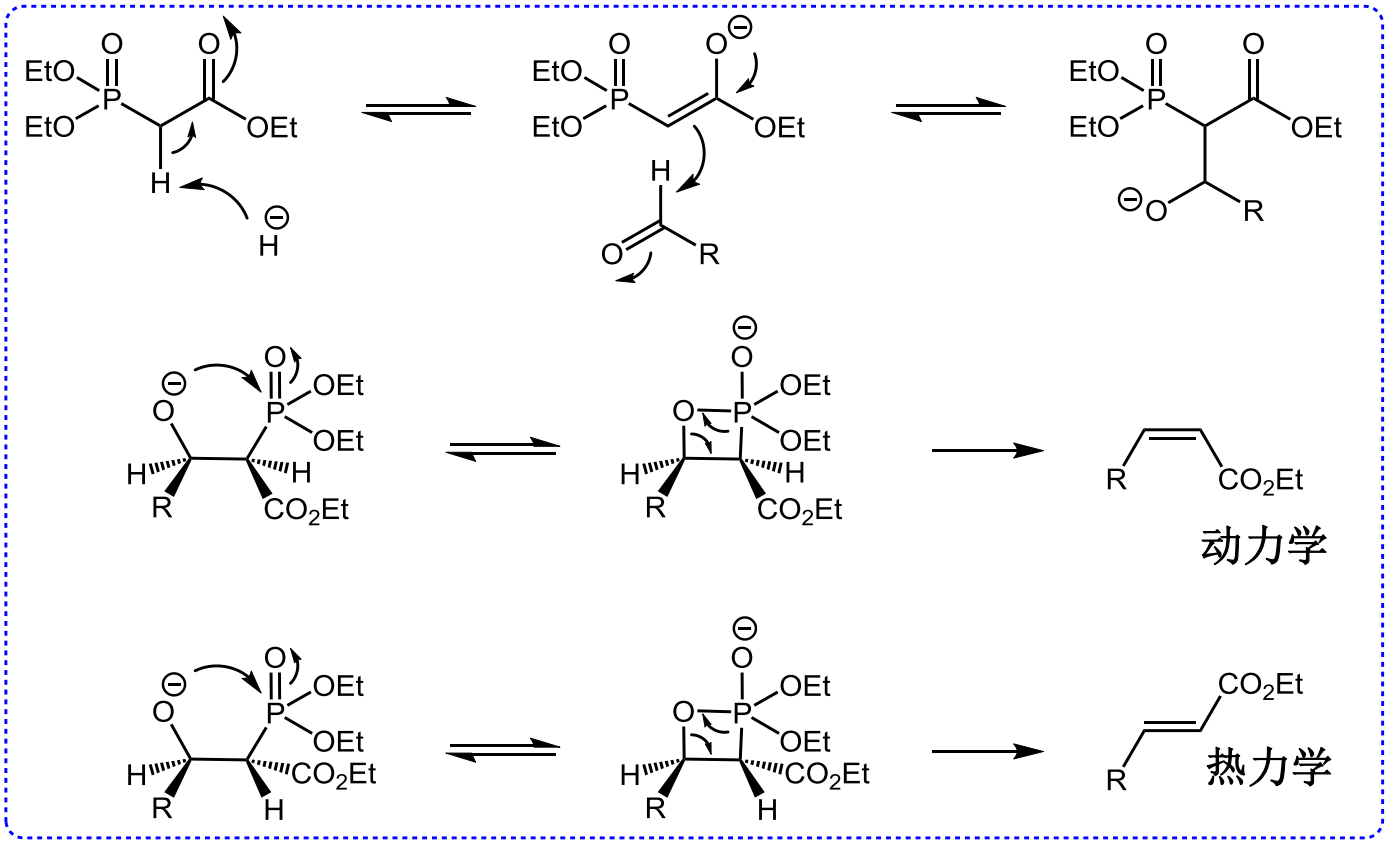
Swern Oxidation



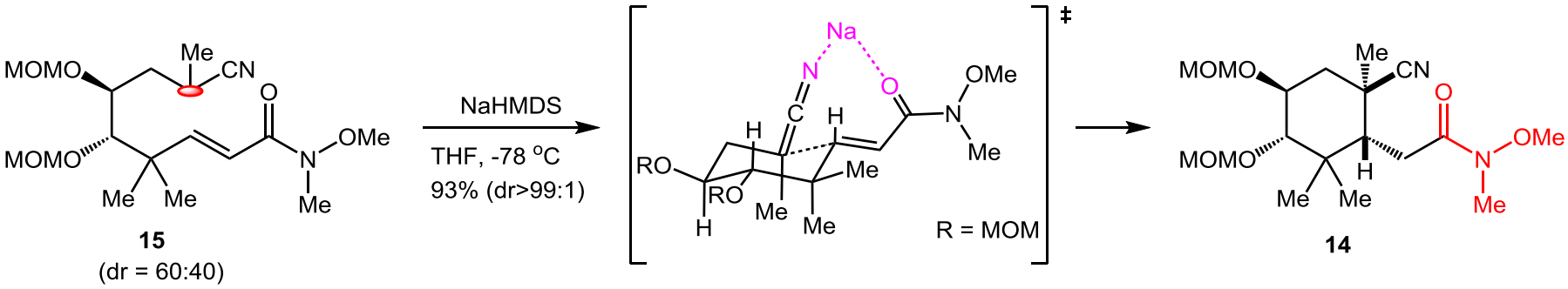


Horner-Wadsworth-Emmons Reaction (HWE)

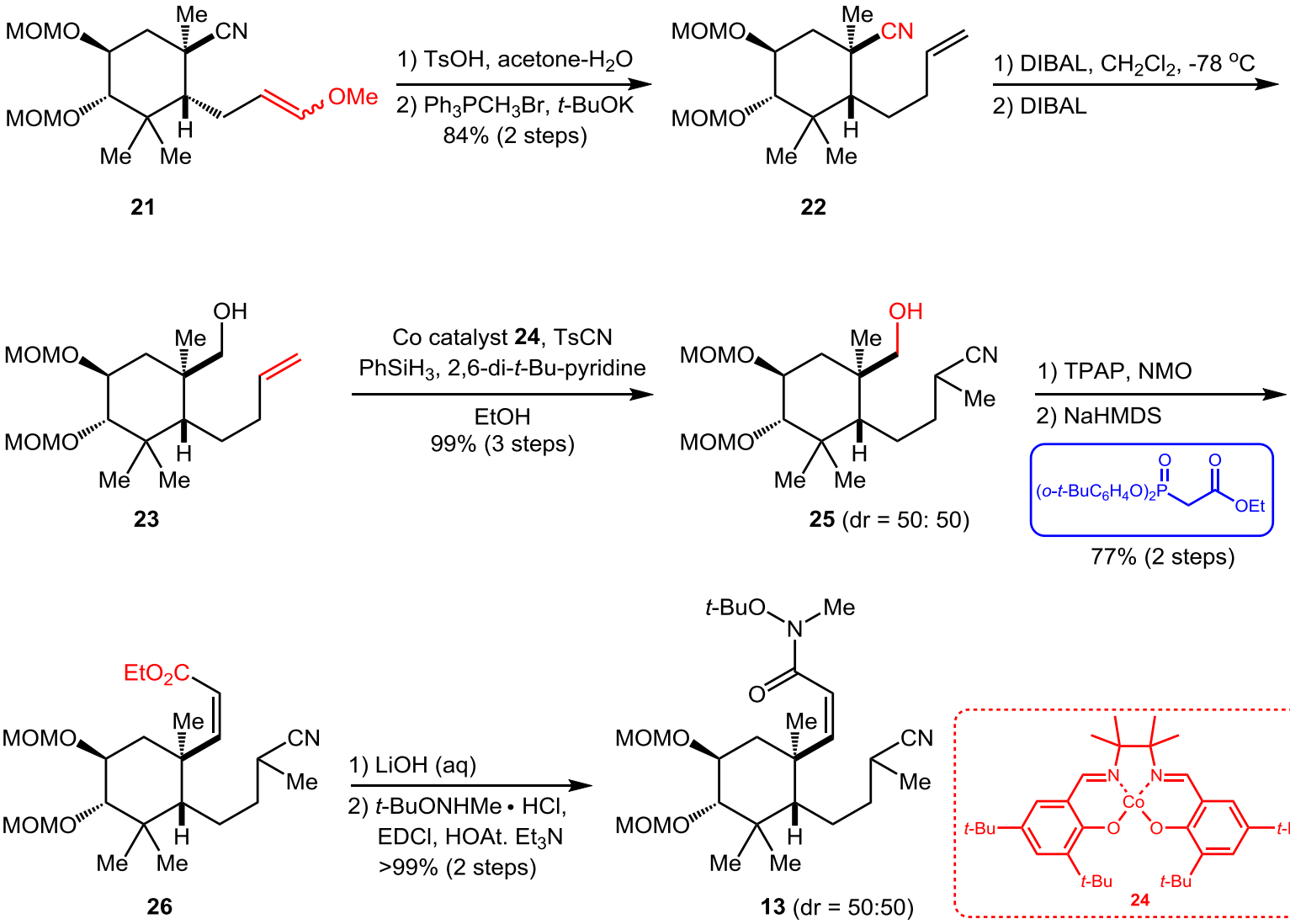




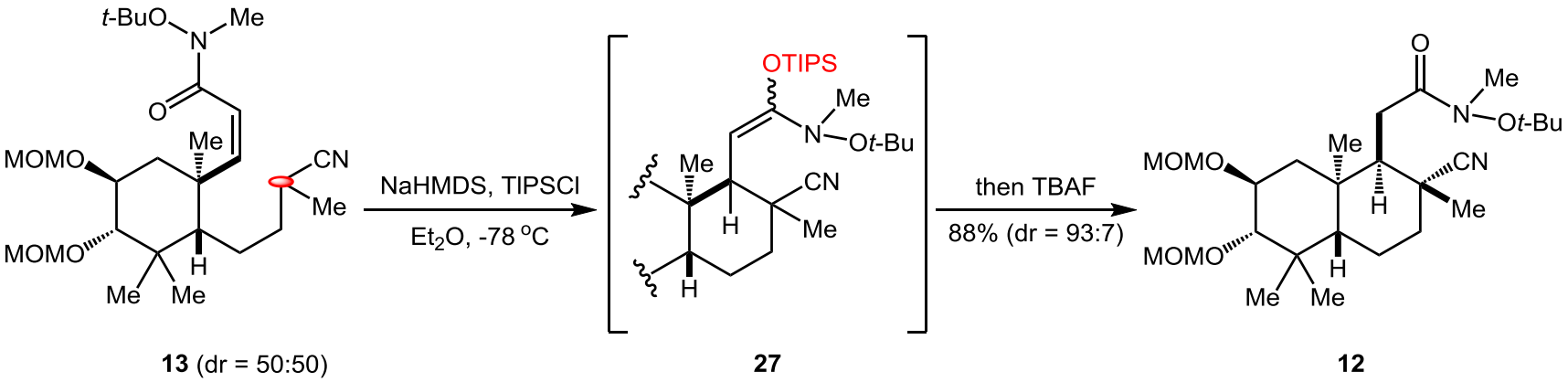
Plausible Transition Model Leading to 14



Synthesis of The Compound 13



Synthesis of The Compound 12

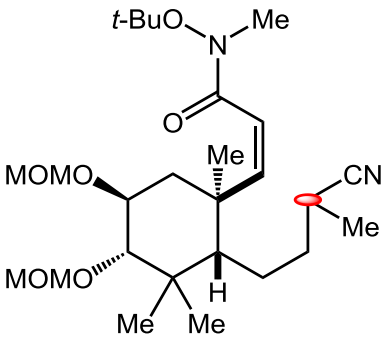


13 (dr = 50:50)

27

12

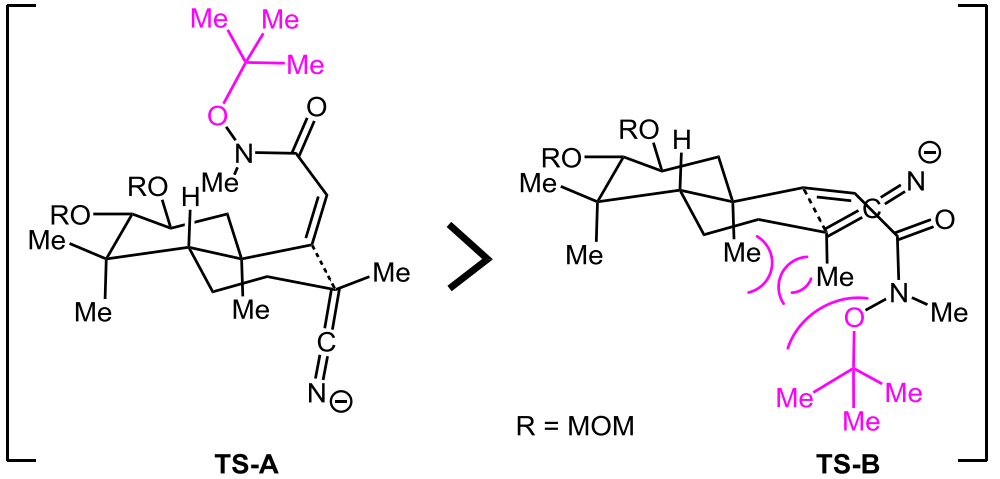
Plausible Transition State Model



13 (dr = 50:50)

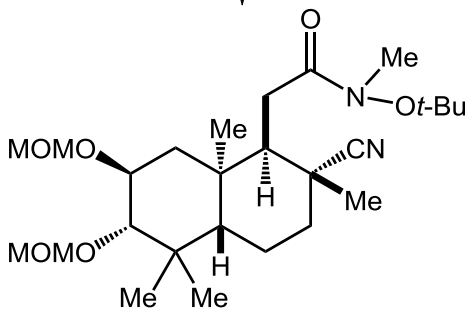
NaHMDS, TIPSCl

Et_2O, -78 °C



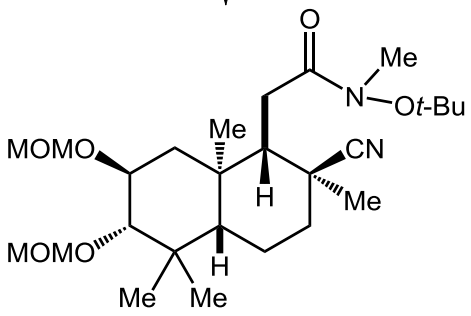
TS-A **TS-B**

then TBAF



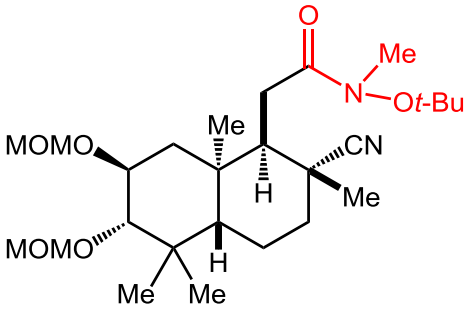
12

88% (dr = 93:7)



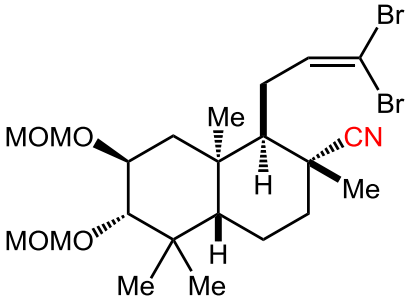
12'

Synthesis of The Compound 10



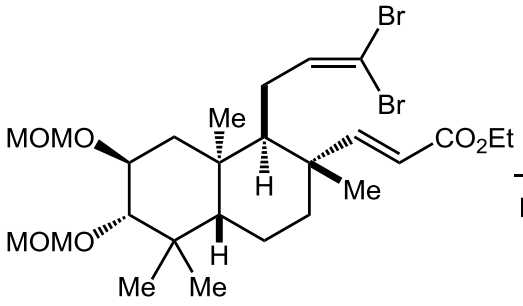
12

1) DIBAL, THF, -78 °C
2) CBr_4, PPh_3, Et_3N
76% (2 steps)



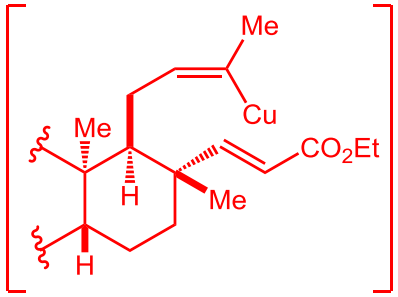
28

1) DIBAL, CH_2Cl_2, -78 °C
2) $(EtO)_2P(O)CH_2CO_2Et$
NaHMDS
96% (2 steps)



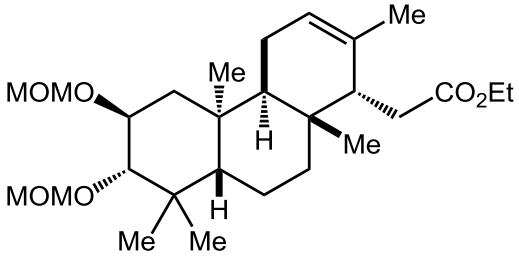
11

Me_2CuLi
Et_2O, -78 °C



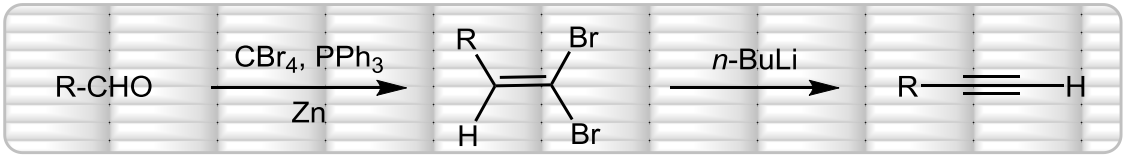
29

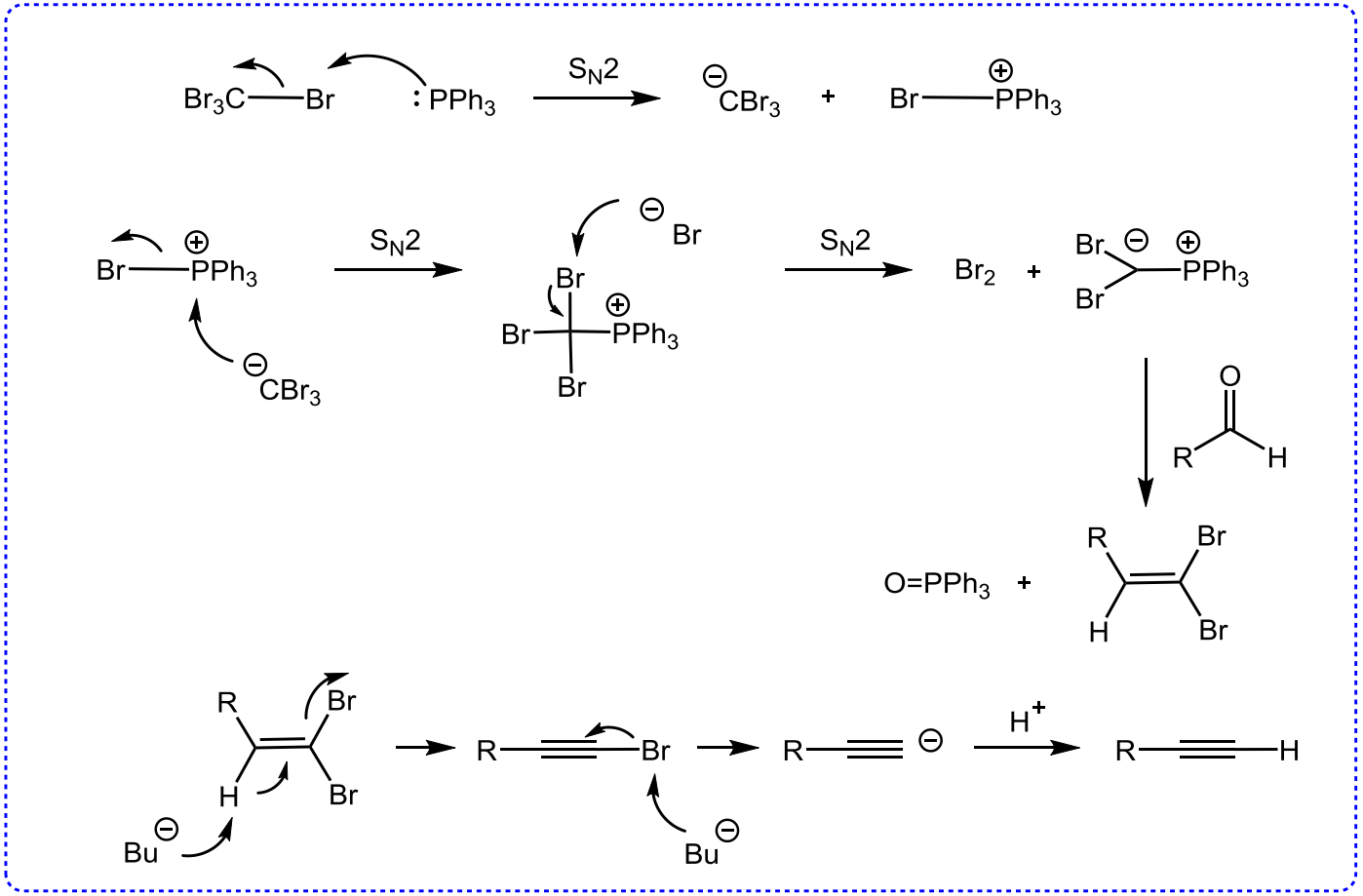
-40 °C
83%
(dr>99:1)



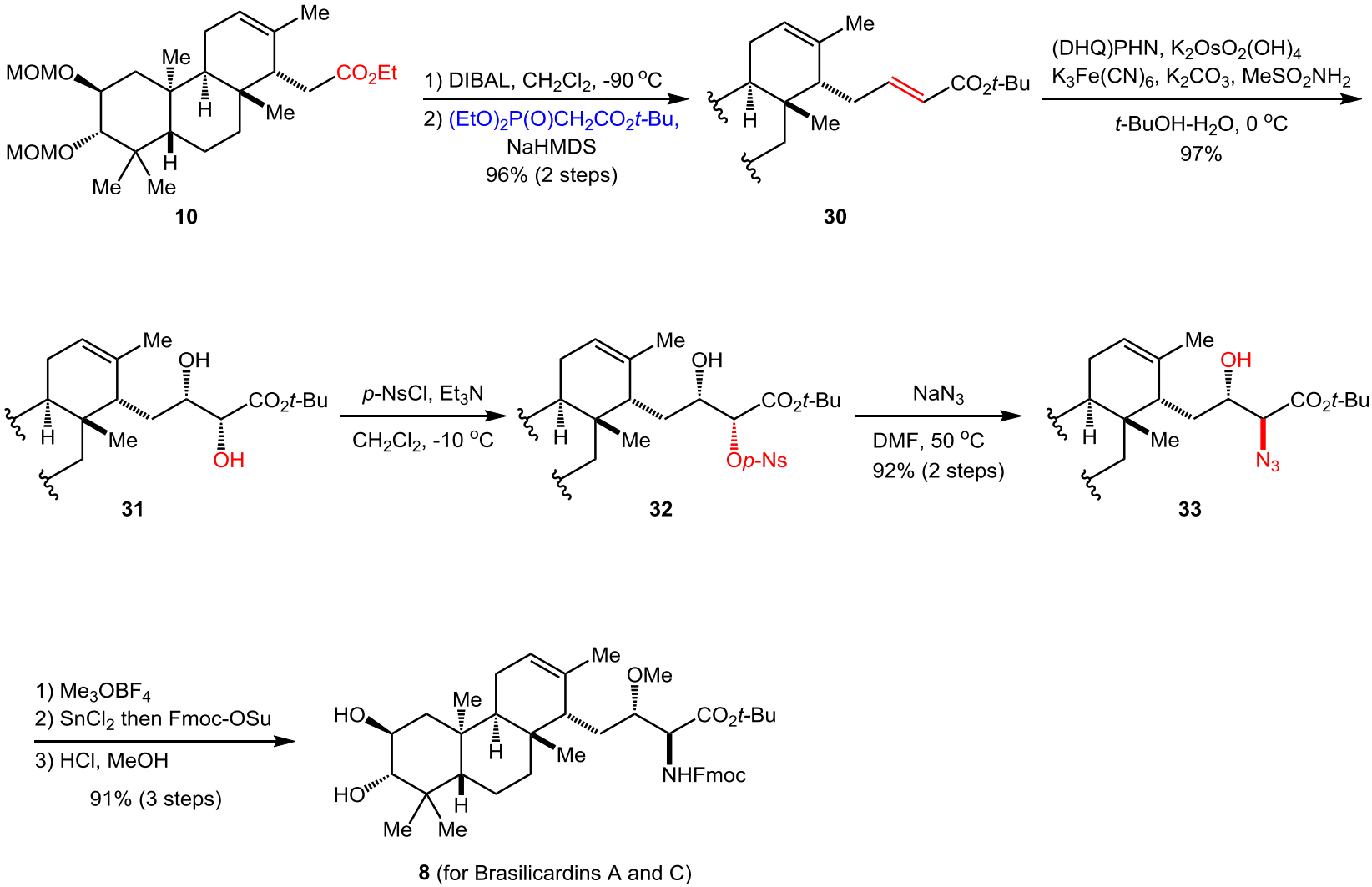
10

Corey-Fuchs Reaction

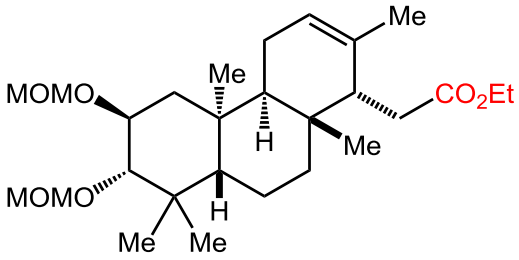




Synthesis of The Compound 8



Synthesis of The Compound 9

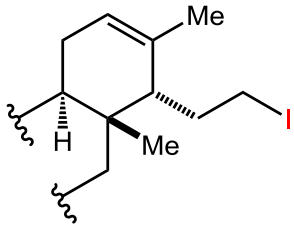


10

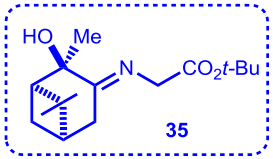
1) $LiAlH_4$

2) I_2, PPh_3, imidazole

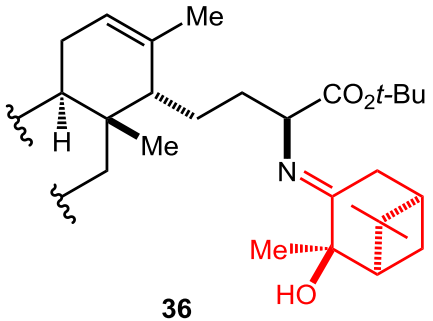
98% (2 steps)



34



KHMDS, THF, -65 °C



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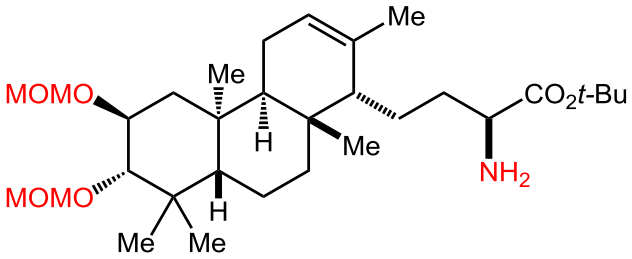
citric acid (aq.)

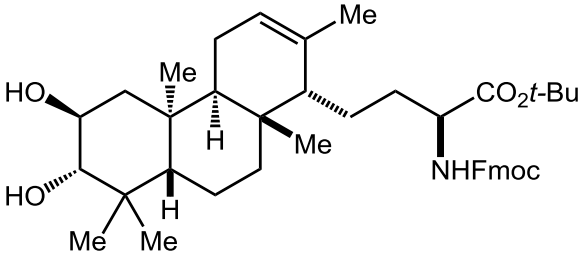


37

1) FmocCl, $NaHCO_3$

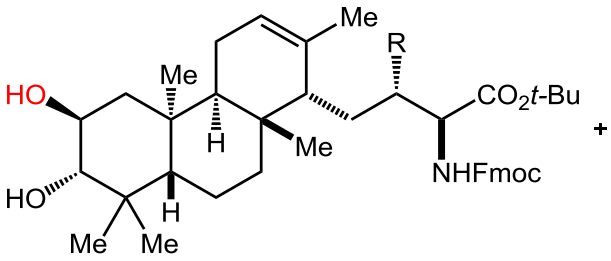
2) HCl, MeOH

88% (4 steps)

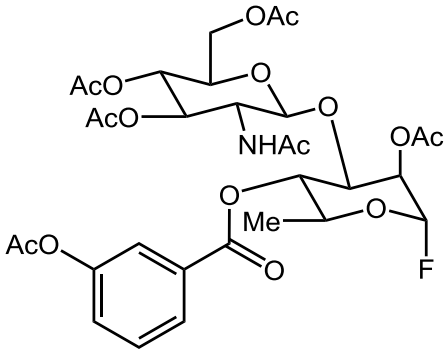


9 (for Brasilicardins B and D)

Synthesis of The Compound 39 or 40



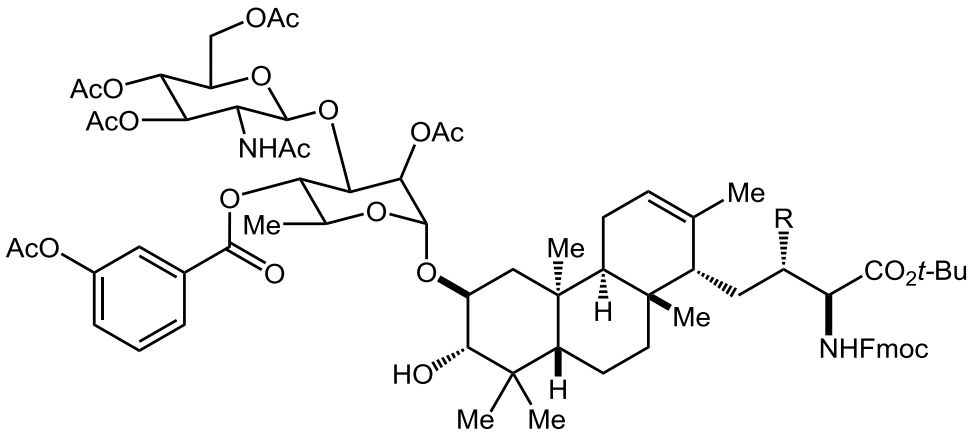
+



8 (R = OMe)
9 (R = H)

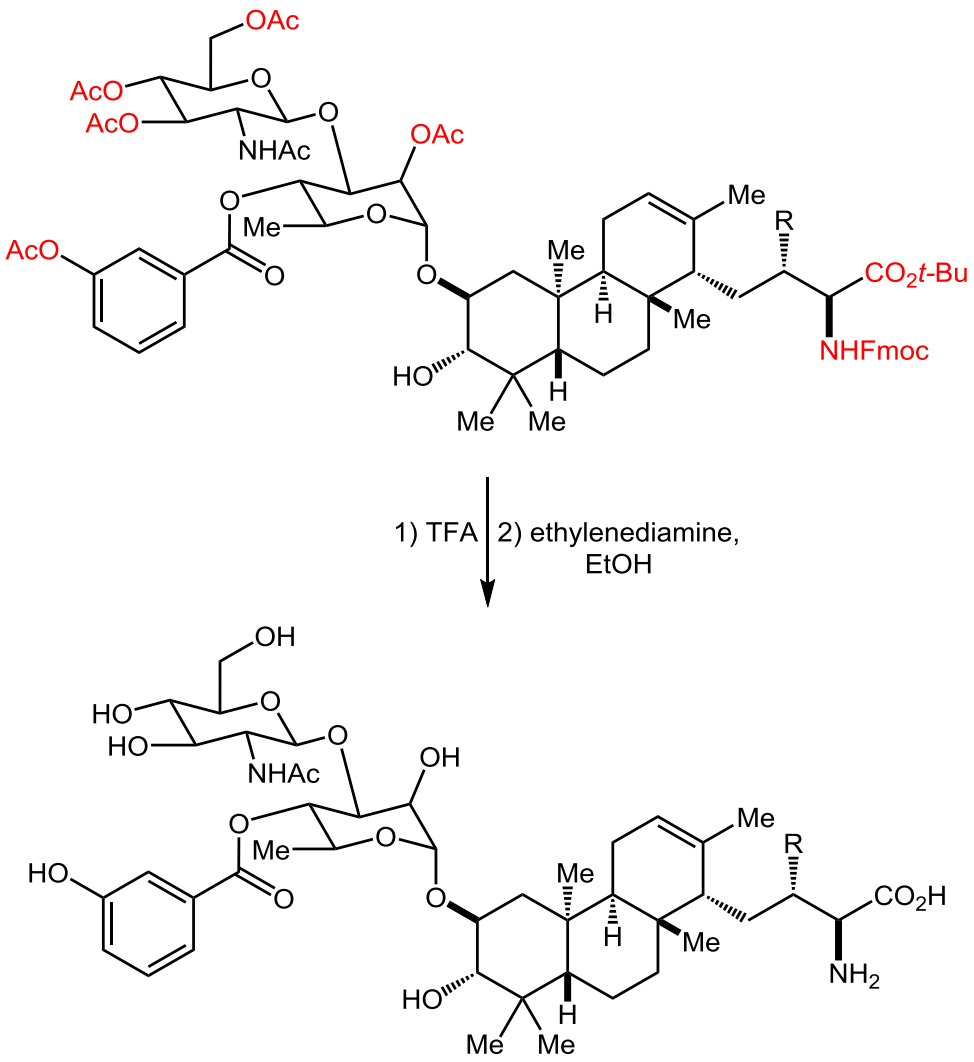
38 (α-anomer exclusively)

Cp_2HfCl_2, AgOTf
DTBMP, MS4Å
CH_2Cl_2



39 (R = OMe) + recovery of **8** (43%)
40 (R = H) + recovery of **9** (61%)

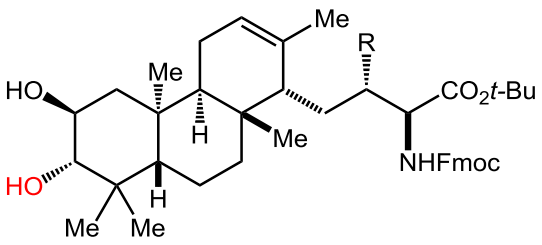
Total Synthesis of Brasilicardins A/B



39 (R = OMe) + recovery of **8** (43%)
40 (R = H) + recovery of **9** (61%)

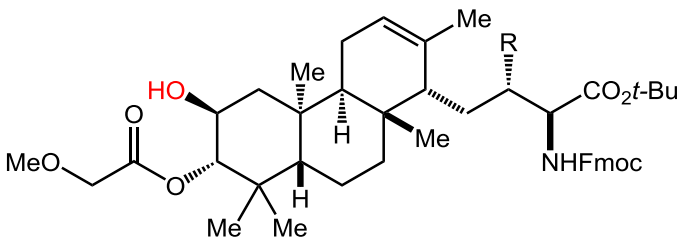
Brasilicardin A (**1**, R =OMe): 43% (3 steps from **8**)
Brasilicardin B (**2**, R =H): 37% (3 steps from **8**)

Total Synthesis of Brasilicardins C/D

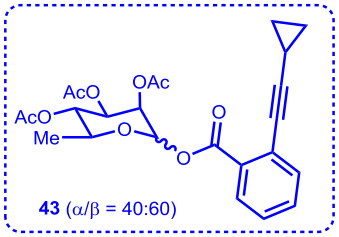


8 (R = OMe)
9 (R = H)

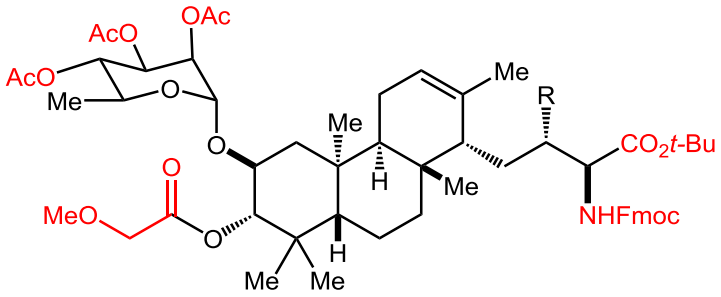
1) TBSOTf, 2,6-lutidine, -90 °C
2) $MeOCH_2COCl$, pyridine
3) HF•pyridine



41 (R = OMe): 86% from **8**
42 (R = H): 87% from **9**

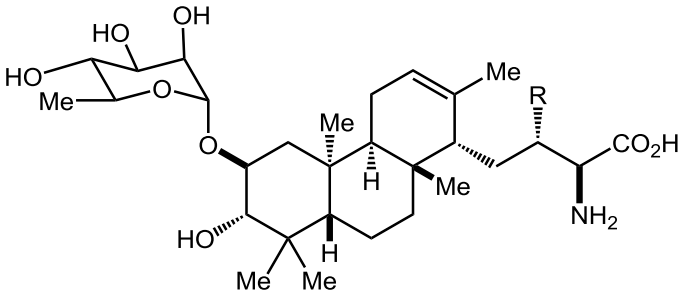


$Ph_3PAuNTf_2$, MS4Å
CH_2Cl_2, 0 °C



44 (R = OMe)
45 (R = H)

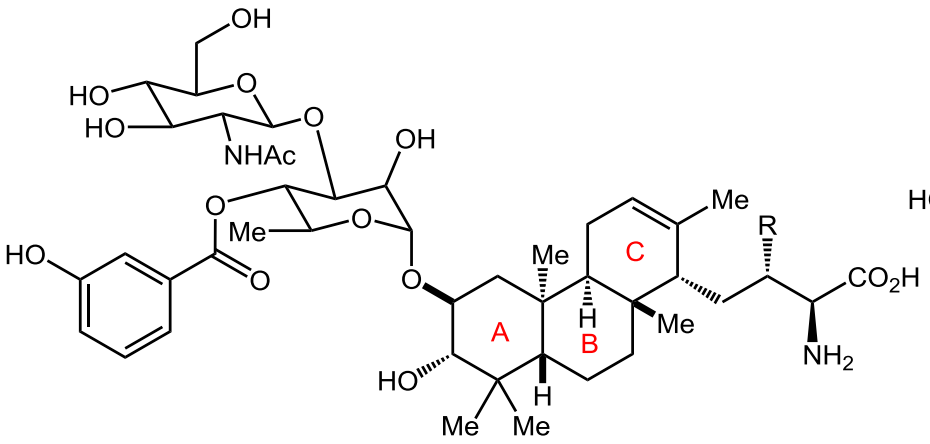
1) TFA
2) LiOH (aq.)
45 °C



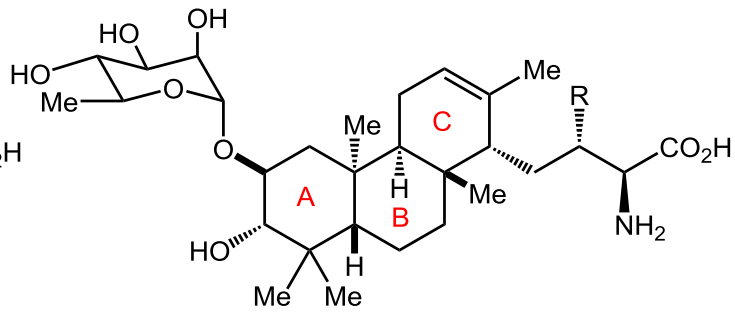
Brasilicardin C (**3**, R =OMe): 94% (3 steps from **41**)
Brasilicardin D (**4**, R =H): 92% (3 steps from **42**)

Summary

Tanino's work:



Brasilicardin A (1): R = OMe
Brasilicardin B (2): R = H



Brasilicardin C (3): R = OMe
Brasilicardin D (4): R = H

- The asymmetric total syntheses of Brasilicardin A (39 linear steps, 6.8% yield), Brasilicardin B (37 linear steps, 6.5% yield), Brasilicardin C (42 linear steps, 12% yield), Brasilicardin D (40 linear steps, 14% yield).
- Intramolecular nitrile Michael addition; Stereoselective installation of the amino acid component; Regio- and stereoselective glycosylation.

The First Paragraph

Brasilicardins A–D are bacterial diterpenoid natural products isolated from the cultured broth of the actinomycete Nocardia brasiliensis IFM 0406, which exhibit diverse biological activities. Among these congeners, brasilicardin **A** displays potent immunosuppressive activity (IC_{50} = 0.05 nm). Although the mechanism of the immunosuppressive action of **A** has not been clarified in detail, it has been suggested that it is induced by amino acid deprivation via the inhibition of the amino acid transporter system **L**. Currently used immunosuppressive clinical agents such as tacrolimus and cyclosporin **A** often cause side effects such as nephrotoxicity and arterial hypertension; therefore, an alternative to them is desired.

The First Paragraph

In this context, **A** is considered to be a promising drug candidate. Thus, **A** has been studied with keen interest, particularly in the context of the development of new immunosuppressive drugs. However, further biological and pharmacological studies of **A** have not been conducted because of its limited availability from natural sources; therefore, efficient chemical syntheses of **A** and its derivatives and simplified analogues are required to aid further studies.

The Last Paragraph

In conclusion, we have developed a stereoselective synthetic route to synthesize brasilicardins with potent immunosuppressive activity; we accomplished the asymmetric total syntheses of brasilicardin A-D from readily available commercial materials. The synthesis features 1) the development of a novel intramolecular nitrile Michael addition; 2) a Michael addition based strategy for the stereoselective formation of the highly strained *anti*-*syn*-*anti*-fused perhydrophenanthrene skeleton (the ABC-ring system); 3) stereoselective installation of the amino acid component to the terpenoid core; and 4) regio- and stereoselective glycosylation using glycosyl fluoride or *o*-alkynylbenzoate as the glycosyl donor.

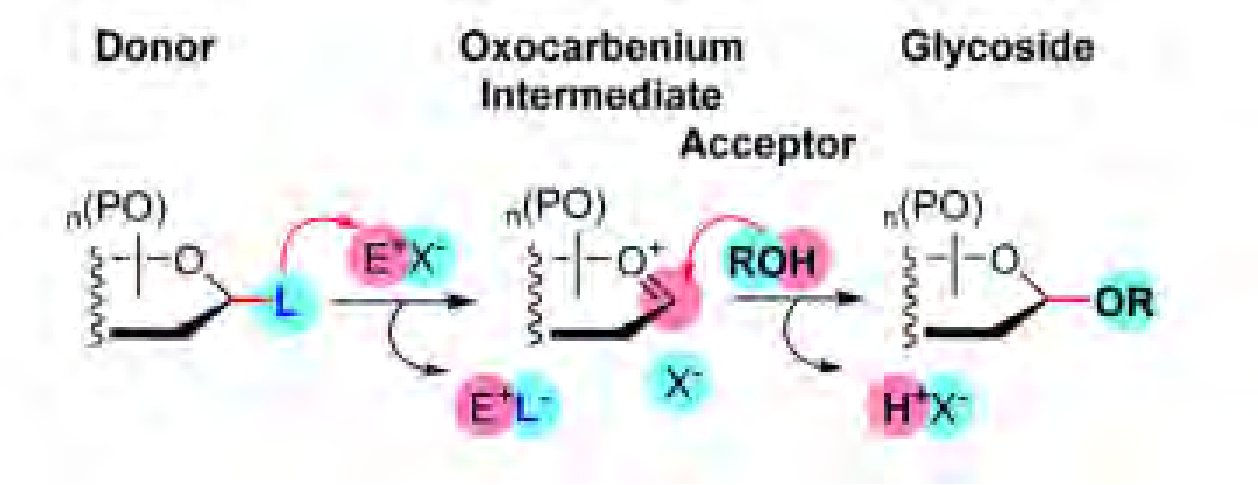
The Last Paragraph

Our strategy allowed the unified synthesis of all brasilicardins from the common late-stage intermediate utilizing appropriate installation methods for an amino acid and glycosylation. The novel synthetic route developed here should accelerate the synthesis and biological studies of brasilicardins and a wide variety of their analogues that were previously inaccessible by syntheses or from natural products, as well as aid in obtaining in-depth SAR for the development of new immunosuppressive drugs.

Acknowledgement

Thanks
for your attention

A Typical Glycosylation Reaction



Two Protocol About Glycosylation Reaction

Yu, B. *Acc. Chem. Res*. **2018**, *51*, 507.