Synthesis of the Tetrahydroisoquinoline Alkaloid (±)-Renieramycin G and a (±)-Lemonomycinone Analogue from a Common Intermediate

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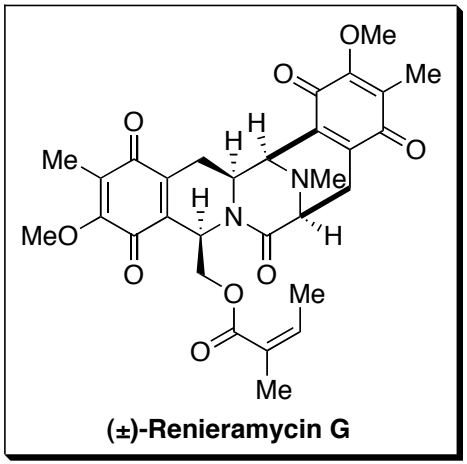
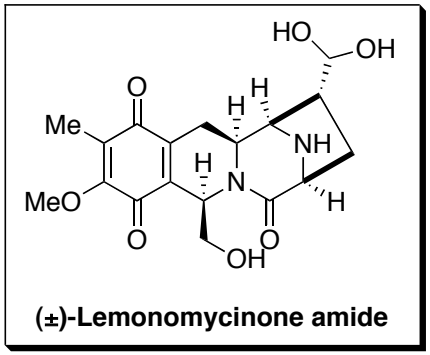
Department of Chemistry and Biochemistry, University of Texas at Austin

J. Am Chem. Soc. **2005**, *ASAP*.



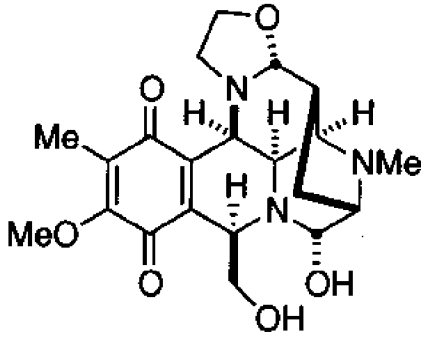
(±)-Renieramycin G



(±)-Lemonomycinone amide

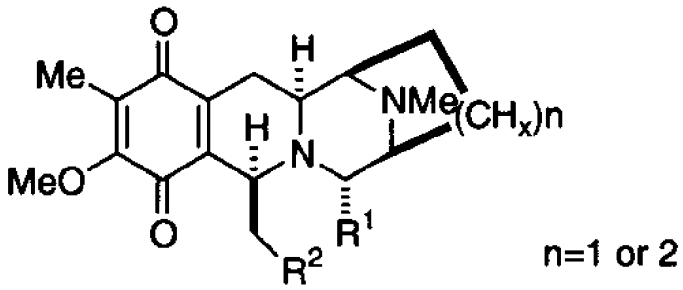
Tetrahydroisoquinoline Antitumor Antibiotics

■ The tetrahydroquinoline family of antitumor antibiotics has been studied since naphthriydinomycin was isolated in 1974 by Kluepfel *et al*.



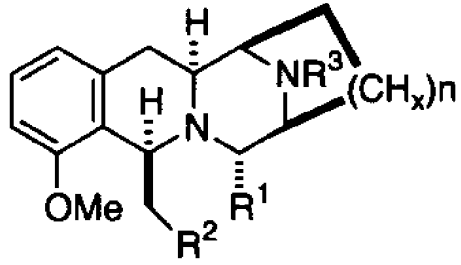
Naphthyridinomcyin

■ The two core structures of this family are the quinone **A** and the aromatic core **B**. To date, nearly 60 natural products in this family have been isolated, and hundreds of synthetic analogues have been reported.



n=1 or 2

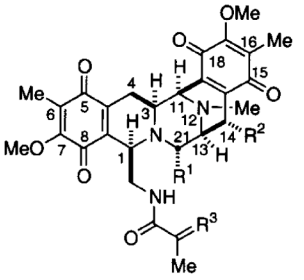
A



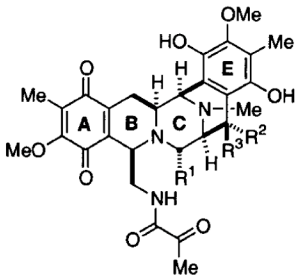
B

Scott, J. D.; Williams, R. M. *Chem. Rev.* **2002**, *102*, 1669.

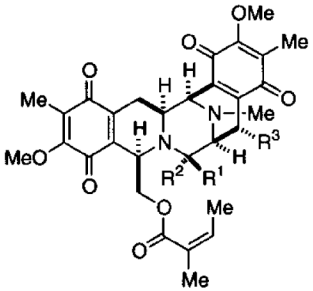
Tetrahydroisoquinoline Antitumor Antibiotics



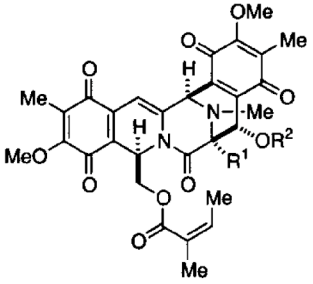
Saframycin A (**3**) R^1=CN, R^2=H, R^3=O
B (**4**) R^1=R^2=H, R^3=O
C (**5**) R^1=H, R^2=OMe, R^3=O
G (**6**) R^1=CN, R^2=OH, R^3=O
H (**7**) R^1=CN, R^2=H, R^3=OH, CH_2COMe
S (**8**) R^1=OH, R^2=H, R^3=O



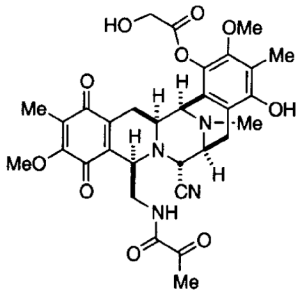
Saframycin D (**9**) R^1=H, R^2,R^3=O
E (**10**) R^1=R^3=H, R^2=OH
F (**11**) R^1=CN, R^2,R^3=O



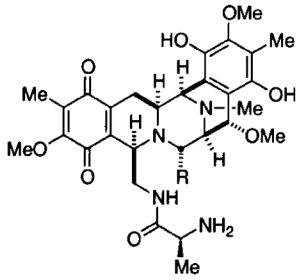
Renieramycin A (**138**) R^1=R^2=H, R^3=OH
B (**139**) R^1=R^2=H, R^3=OMe
C (**140**) R^1,R^2=O, R^3=OH
D (**141**) R^1,R^2=O, R^3=OEt
E (**142**) R^1=H,R^2=OH, R^3=H
F (**143**) R^1=H,R^2=OH, R^3=OMe
G (**144**) R^1=R^2=O, R^3=H



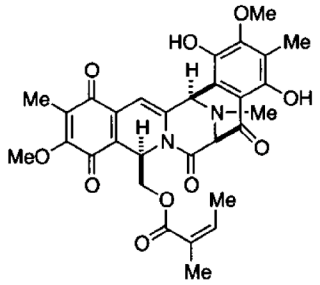
145 R^1=OH, R^2=H
146 R^1=H, R^2=Me



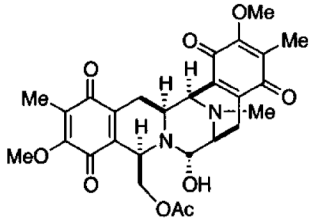
Saframycin R (**12**)



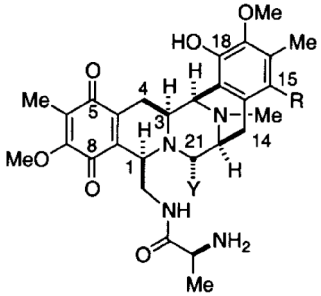
Saframycin Mx1 (**13**) R=OH
Mx2 (**14**) R=H



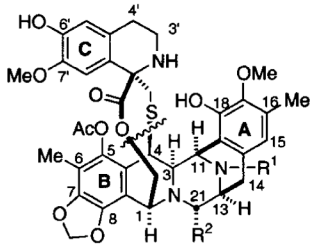
Renieramycin H (**147**)



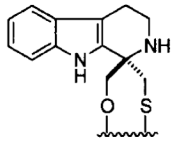
Jorumycin (**148**)



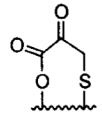
safracin A (**159**) R=Y=H
B (**160**) R=H, Y=OH
161 R=Br, Y=OH
162 R=H, Y=CN



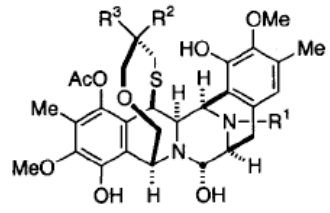
Et 743 (**170**) R^1=Me, R^2=OH
Et 729 (**171**) R^1=H, R^2=OH
Et 745 (**172**) R^1=Me, R^2=H
Et 759B (**173**) R^1=Me, R^2=OH, S-oxide
Et 770 (**174**) R^1=Me, R^2=CN
175 R^1=Me,O R^2=OH
176 R^1=CHO, R^2=OMe



Et 736 (**177**) R^1=Me, R^2=OH
Et 722 (**178**) R^1=H, R^2=OH



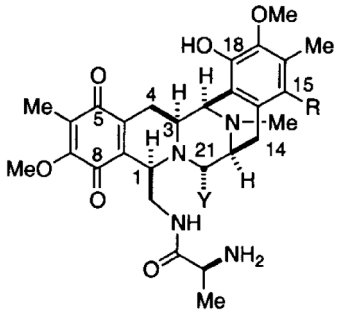
Et 594 (**179**) R^1=Me, R^2=OH



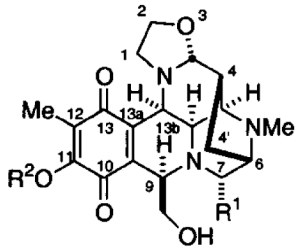
Et 597 (**180**) R^1=Me, R^2=NH_2, R^3=H
Et 583 (**181**) R^1=H, R^2=NH_2, R^3=H
Et 596 (**182**) R^1=Me, R^2, R^3=O

Scott, J. D.; Williams, R. M. *Chem. Rev.* **2002**, *102*, 1669

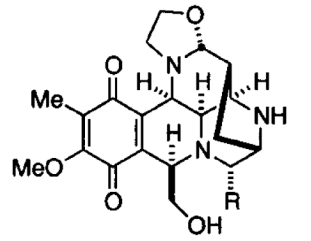
Tetrahydroisoquinoline Antitumor Antibiotics



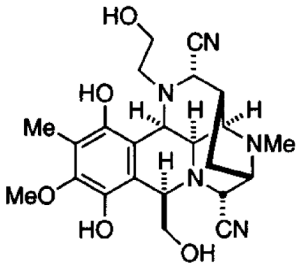
safracin A (**159**) R=Y=H
B (**160**) R=H, Y=OH
161 R=Br, Y=OH
162 R=H, Y=CN



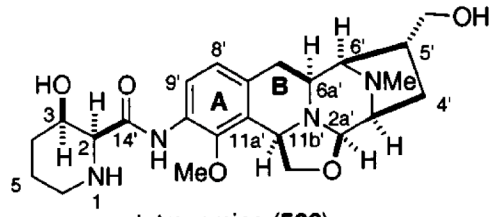
naphthridinomycin (**243**) R^1 = OH, R^2 = Me
SF-1739 HP (**244**) R^1 = OH, R^2 = H
cyanocycline A (**245**) R^1 = CN, R^2 = Me
cyanocycline F (**246**) R^1 = CN, R^2 = H



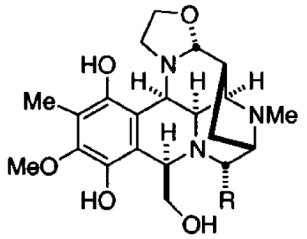
cyanocycline B (**247**) R = CN
(**248**) R = OH



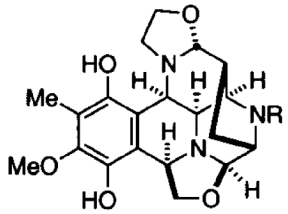
cyanocycline D (**251**)



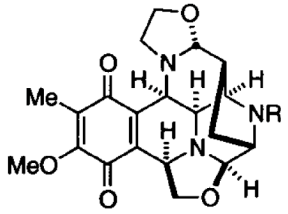
tetrazomine (**566**)



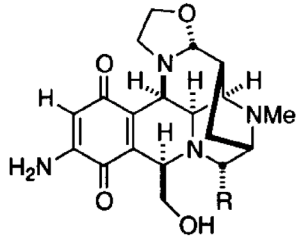
cyanocycline C (**249**) R = CN
(**250**) R = OH



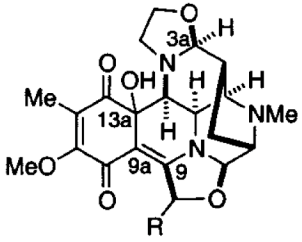
bioxalomycin α_1 (**252**) R = H
bioxalomycin α_2 (**253**) R = Me



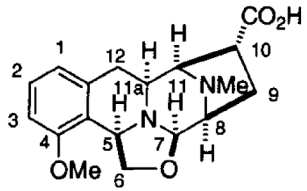
bioxalomycin β_1 (**254**) R = H
bioxalomycin β_2 (**255**) R = Me



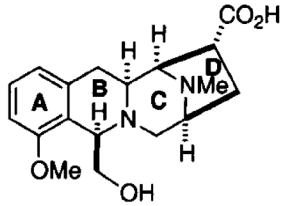
Dnacin A_1 (**349a**) R = CN
B_1 (**349b**) R = OH



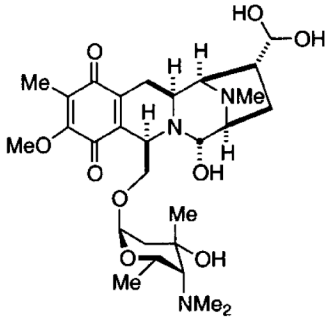
Aclindomycin A (**350a**) R = H
Aclindomycin A (**350b**) R = OH



Quinocarcin (**351**)



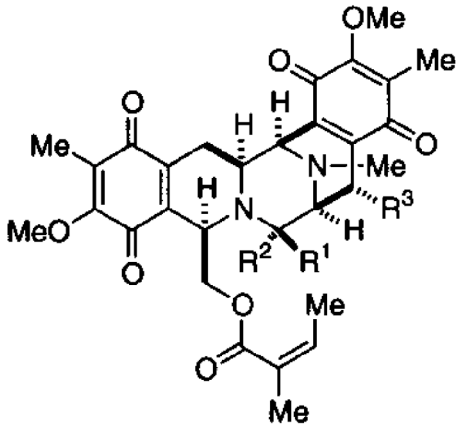
Quinocarcinol (**352**)



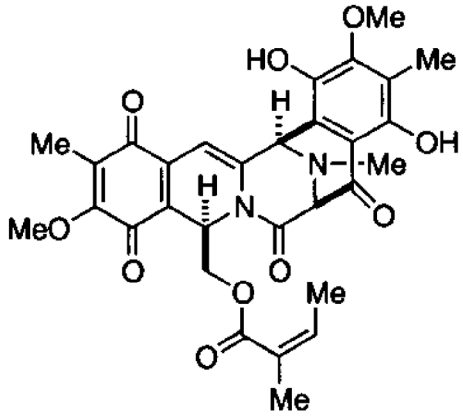
Lemonomycin (**608**)

Scott, J. D.; Williams, R. M. *Chem. Rev.* **2002**, *102*, 1669.

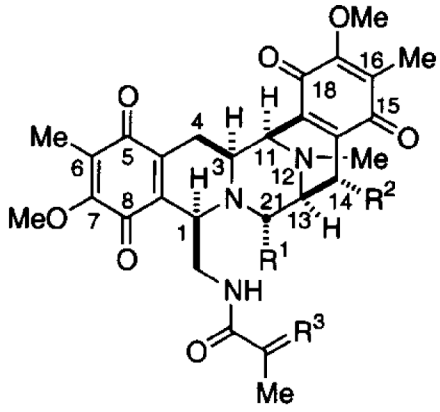
Renieramycins: Isolation and Biological Activity



Renieramycin A (**138**) R^1=R^2=H, R^3=OH
B (**139**) R^1=R^2=H, R^3=OMe
C (**140**) R^1,R^2=O, R^3=OH
D (**141**) R^1,R^2=O, R^3=OEt
E (**142**) R^1=H,R^2=OH, R^3=H
F (**143**) R^1=H,R^2=OH, R^3=OMe
G (**144**) R^1=R^2=O, R^3=H



Renieramycin H (**147**)



Saframycin A (**3**) R^1=CN, R^2=H, R^3=O
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G (**6**) R^1=CN, R^2=OH, R^3=O
H (**7**) R^1=CN, R^2=H, R^3=OH, CH_2COMe
S (**8**) R^1=OH, R^2=H, R^3=O

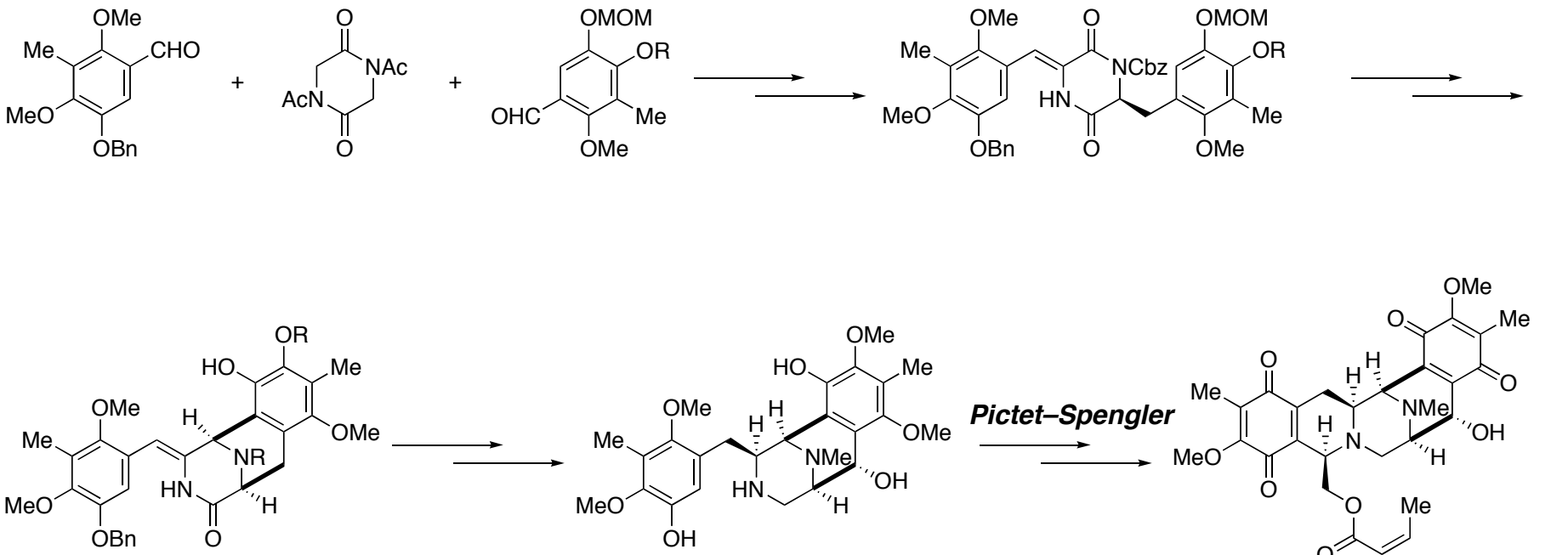
■ Renieramycines are isolated from various marine sponges belonging to genera *Reniera, Xestospongia, Haliclona, Cribrochalina,* and *Neopetrosia*.

■ The ring systems and their relative stereochemistry are identical with those of saframycins which exhibit strong cytotoxicity against cultured cells and antitumor activity against several experimental tumors.

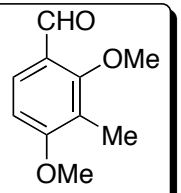
■ Renieramycins A–D, and H have moderate antimicrobial activities. Renieramycin G has cytotoxicity against human cancer cells with MIC values of 0.5 and 1.0 *μ*g/mL against KB and LoVo cell lines, respectively.

Total Synthesis of Renieramycins

Fukuyama: First Total Synthesis of (±)-Renieramycin A



29 steps from

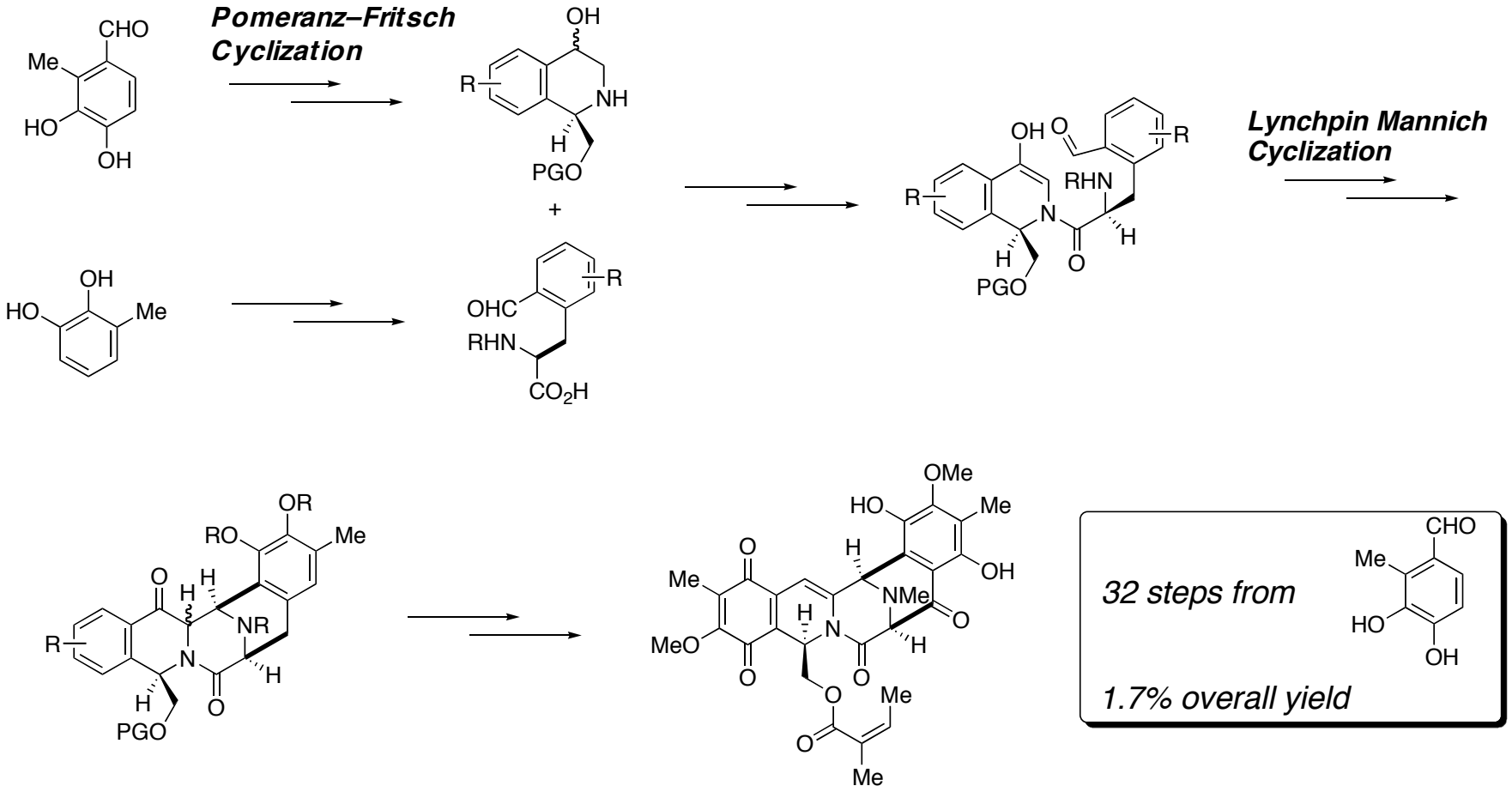


0.5% overall yield

Fukuyama, T. *et al. Tetrahedron Lett.* **1990**, *31*, 5989.

Total Synthesis of Renieramycins

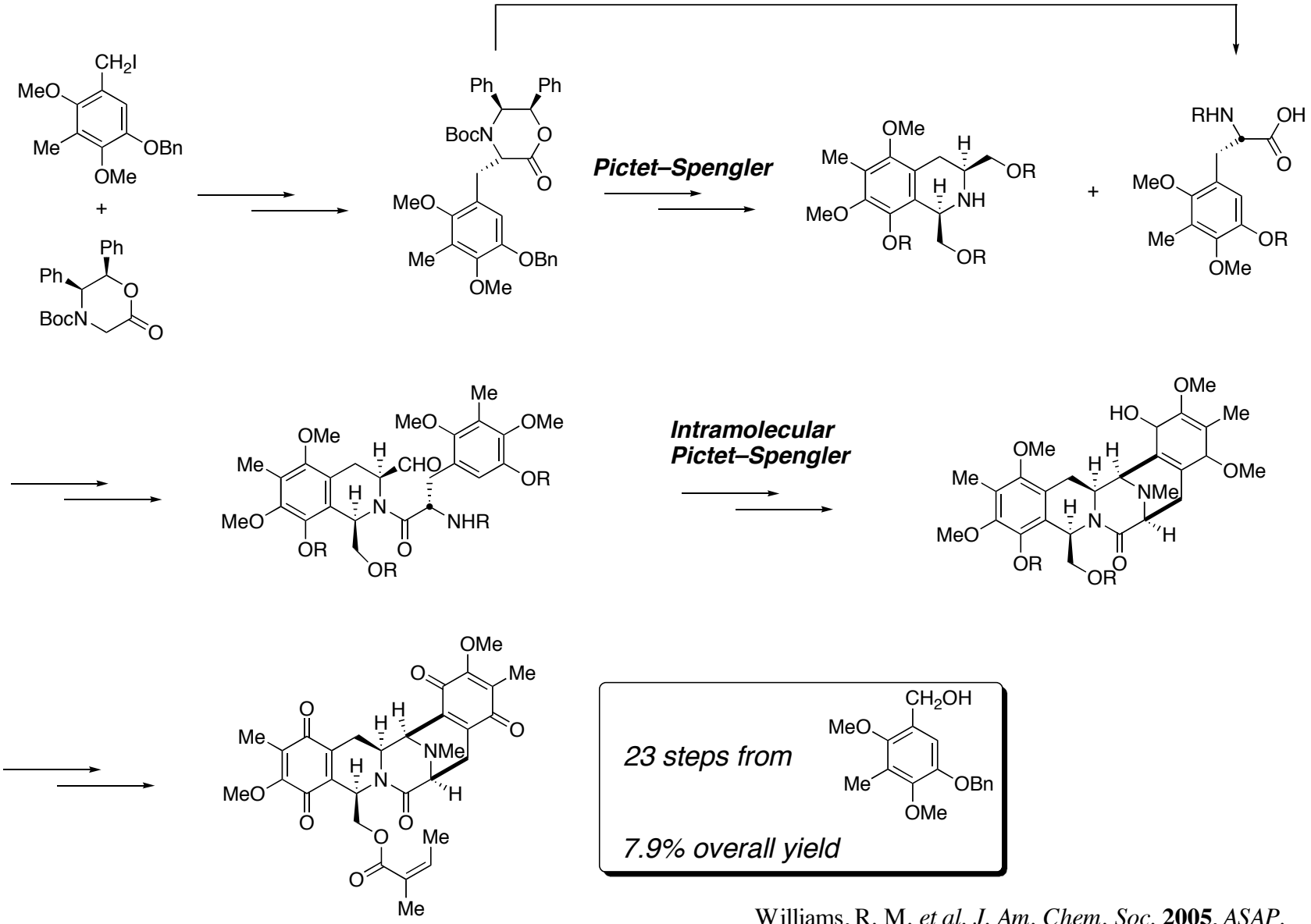
Danishefsky: First Asymmetric Total Synthesis of Cribrostatin IV (Renieramycin H)



Danishefsky, S. J. *et al. J. Am. Chem. Soc.* **2005**, *127*, 4596.

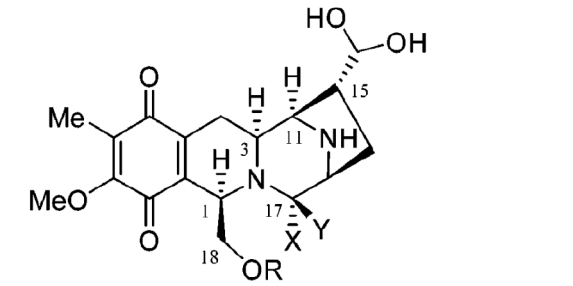
Total Synthesis of Renieramycins

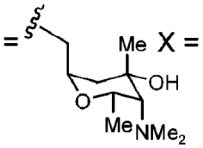
Williams: First Asymmetric Total Synthesis of (–)-Renieramycin G



Williams, R. M. *et al. J. Am. Chem. Soc.* **2005**, *ASAP*.

Lemonomycin: Isolation and Biological Activity



Lemonomycin (R =  Me X = OH, Y = H)

Lemonomycinone (R = H, X = OH, Y = H)
Lemonomycinone amide (R = H, X,Y = O)

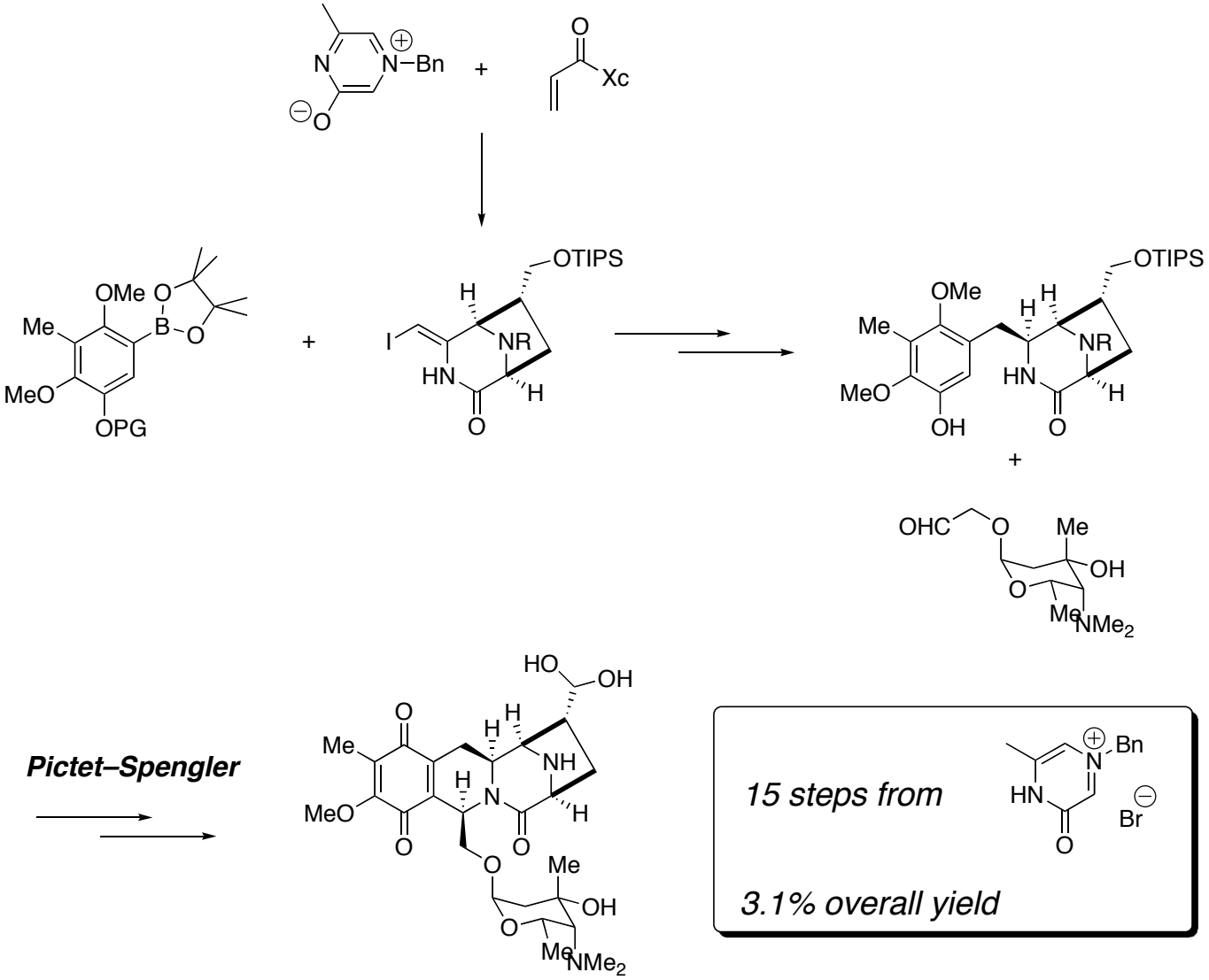
■ Lemonomycin was isolated in 1964 from *Streptomyces candidus.* However, the structure was not elucidated until 2000.

■ Lemonomycin contains the unusual aldehyde hydrate and the sugar moiety, and is the only member in this family of tetrahydroisoquinoline antibiotics.

■ Lemonomycin has interesting antibiotic activity against methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus faecium*, as well as cytotoxicity against a human colon tumor cell line.

Total Synthesis of Lemonomycin

Stoltz: First Asymmetric Total Synthesis of (–)-Lemonomycin

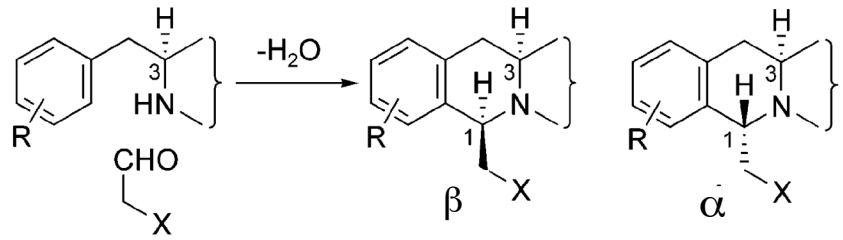


Stoltz, B. M. *et al. J. Am. Chem. Soc.* **2003**, *125*, 15000.

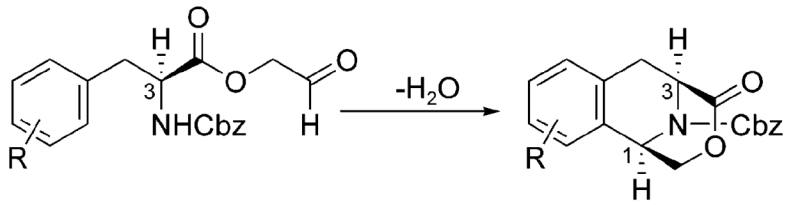
New Strategy for the 1,3-cis-Substituted Tetrahydroisoquinolines

Pictet–Spengler Approach

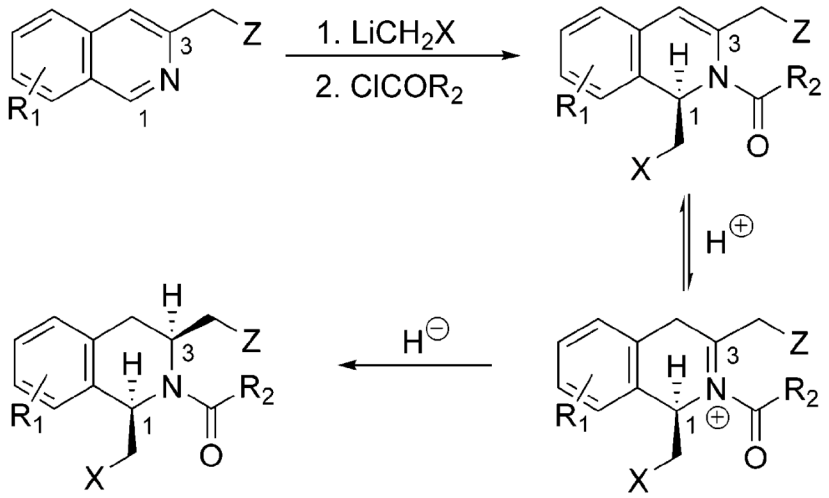
Intermolecular



Intramolecular

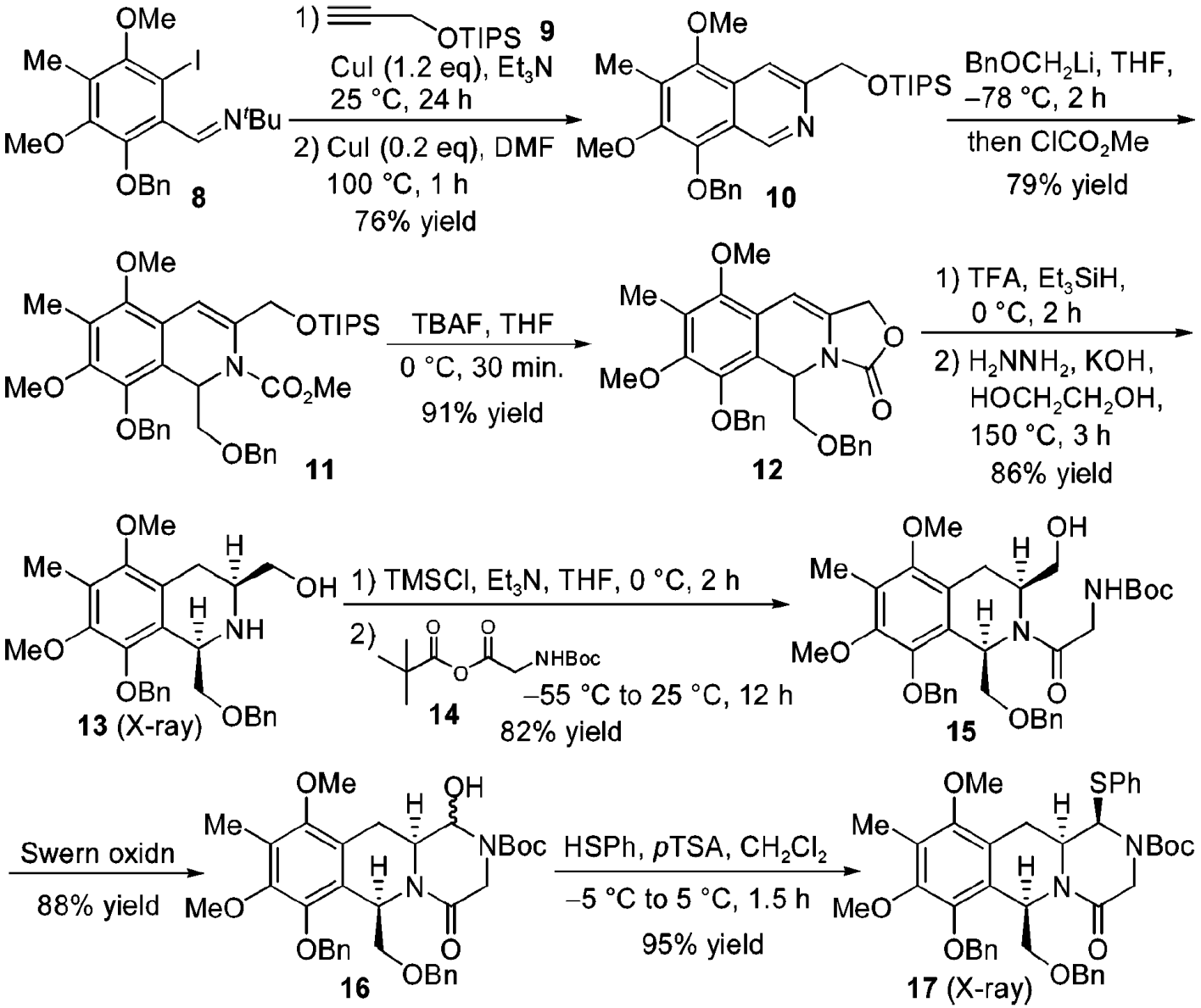


C1 Nucleophilic Addition Approach



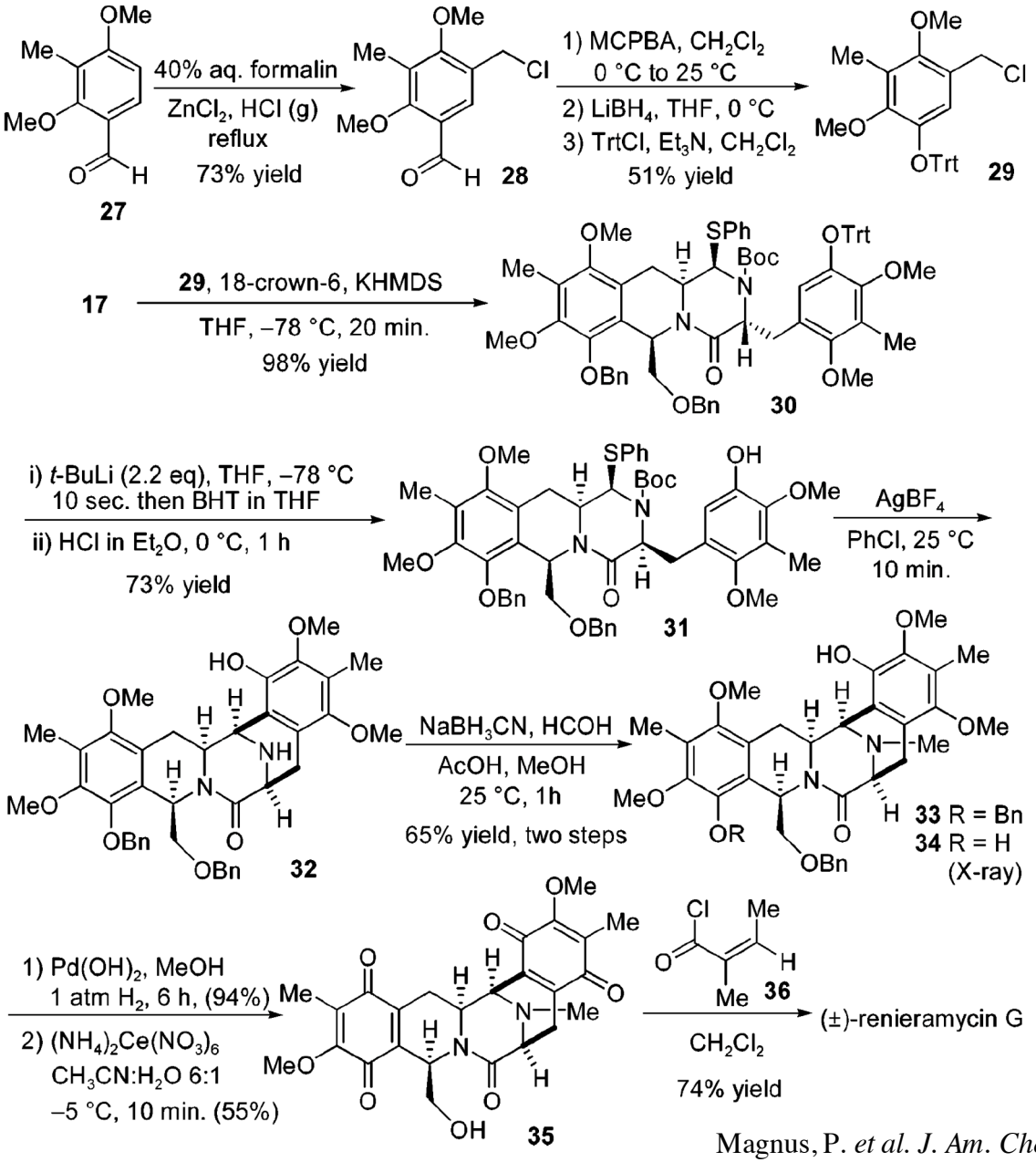
Magnus, P. *et al. Org. Lett.* **2003**, *5*, 2181.

Synthesis of Common Intermediate



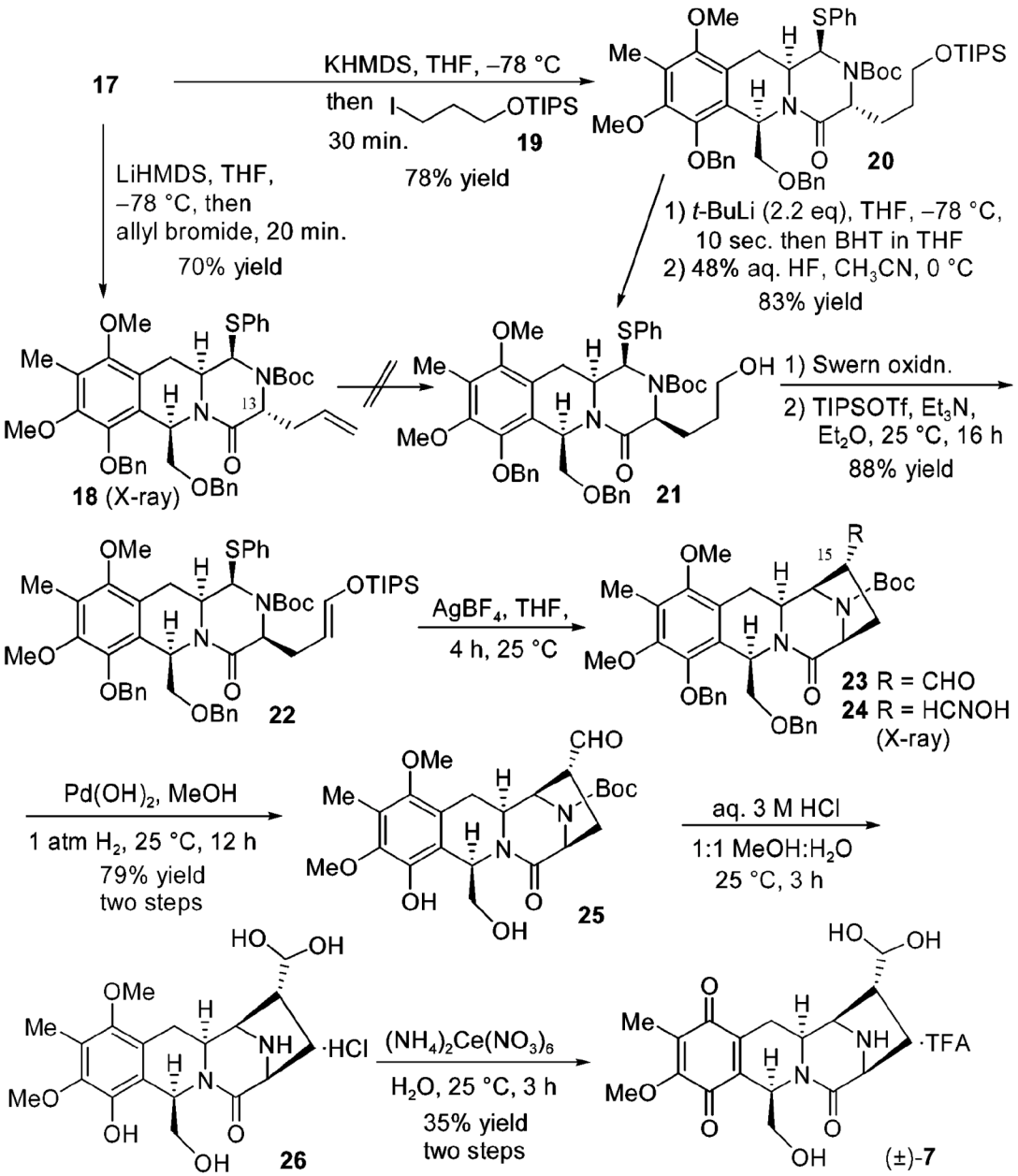
Magnus, P. *et al. J. Am. Chem. Soc.* **2005**, *ASAP*.

(±)-Renieramycin G



Magnus, P. *et al. J. Am. Chem. Soc.* **2005**, *ASAP*.

(±)-Lemonomycinone Amide



Magnus, P. *et al. J. Am. Chem. Soc.* **2005**, *ASAP*

Summary

■ A general approach to both mono- and bistetrahydroisoquinoline alkaloids from a common advanced intermediate has been developed.