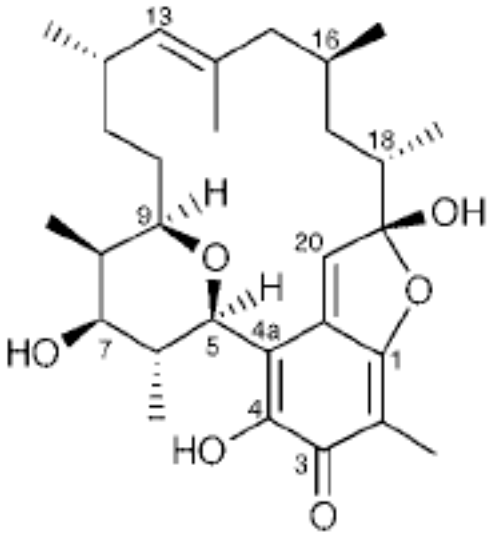
Total Synthesis of Kendomycin- An Odyssey in C-Aryl Glycoside Synthesis



1

kendomycin

Literature Talk
Oct. 28 2004
Vijay Gopalsamuthiram

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3] Marques, M.B.M.; Pichlmair, S.; Martin, J.H.; Mulzer, J. *Synthesis* **2002**, 18, 2766

4] Pichlmair, S.; Marques, M.; Green, M.P.; Martin, H.J.; Mulzer, J. *Org.Lett.* **2003**, *5*, 4657

5] Mulzer, J.; Pichlmair, S.; Green, M.P.; Marques, M.B.M.; Martin, H.J. *Proc.Nat.Acad.Sci.***2004**, 11980

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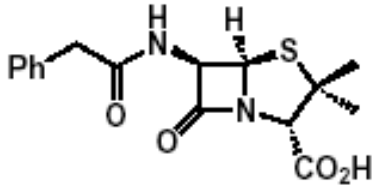
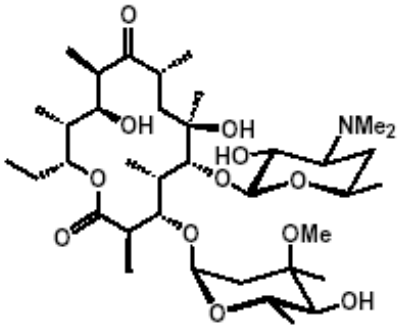
War Against Staphylococcus Aureus- Highly Infectious Bacterial Strains



2

Figure 1. Structure of penicillin (**2**).



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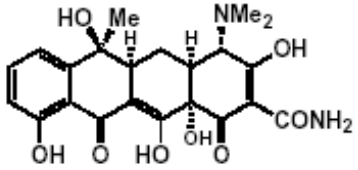

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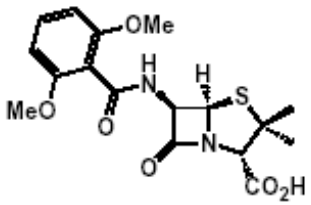

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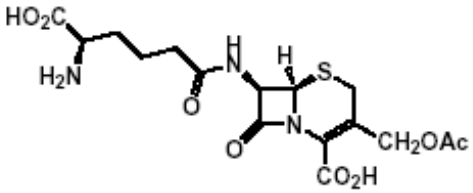
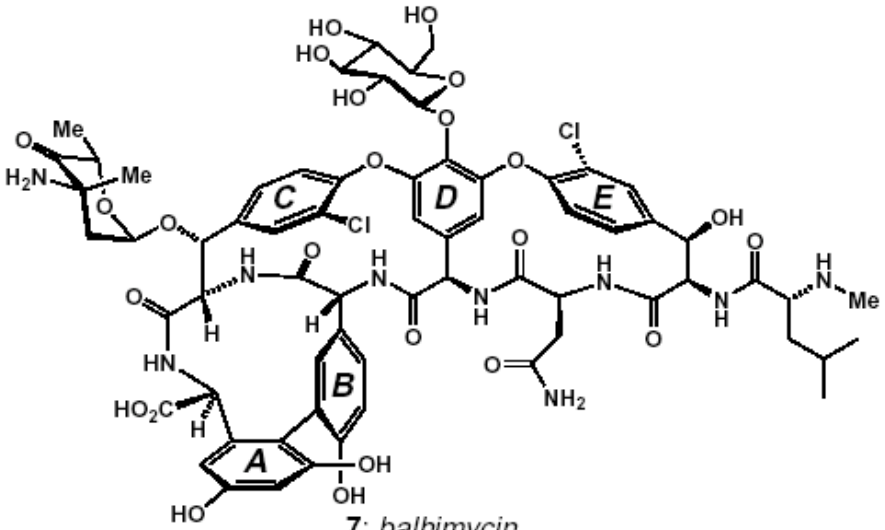


6

Figure 3. Classical antibiotics: erythromycin B (**3**), tetracycline (**4**), methicillin (**5**), and cephalosporin C (**6**).

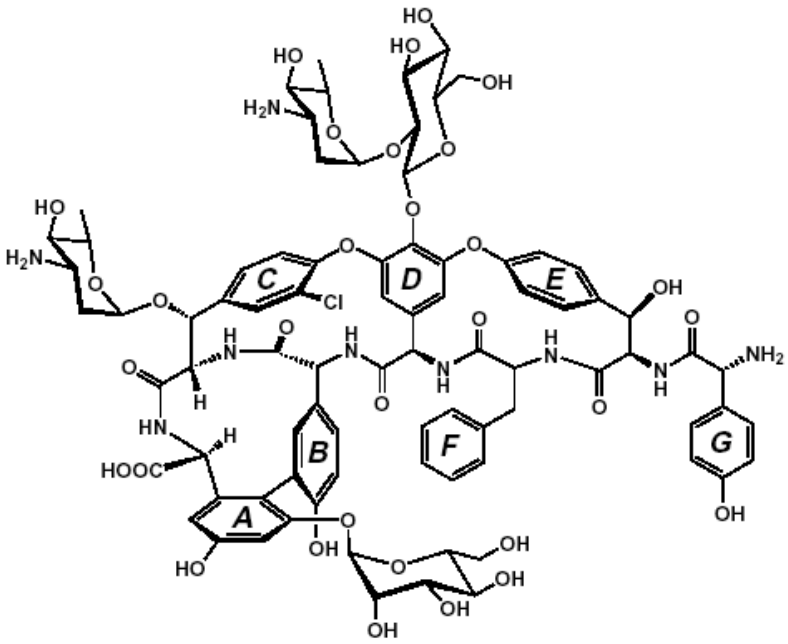
Cell cultures of *S. aureus* (A).

Glycopeptide Antibiotics as Last Line of Defense Against Bacterial Infection

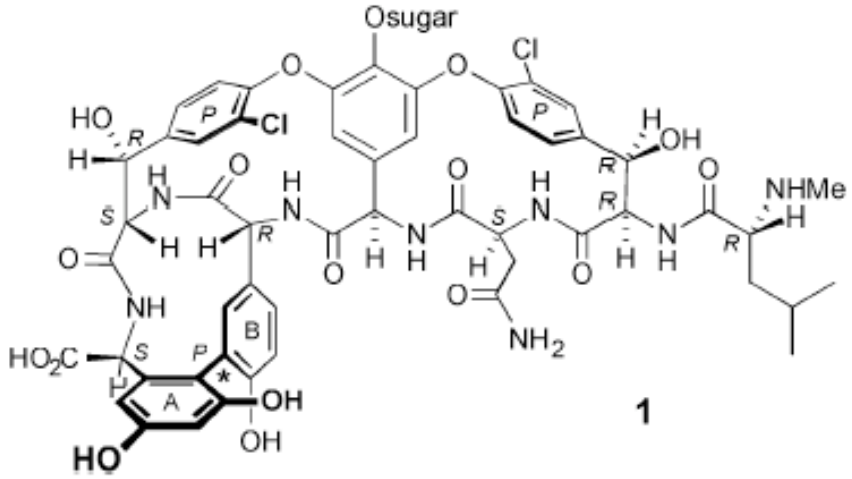


7: *balhimycin*

[***type I***: *contain aliphatic chains in AA-1 and AA-3*]



tinoidin A

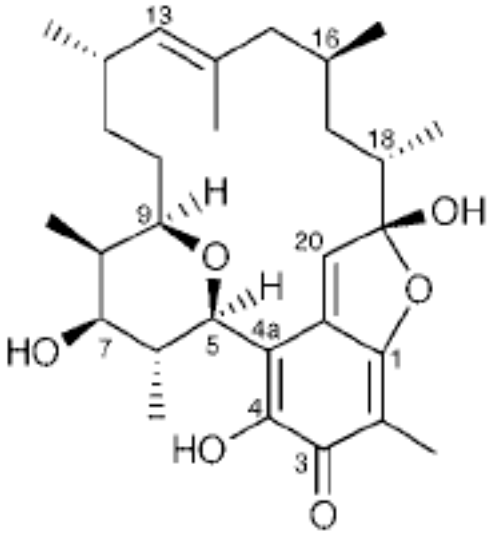


1

And other Semisynthetic Analogs

Figure 1. Vancomycin.

Kendomycin [(-)TAN 2162] - A C-Aryl Glycoside



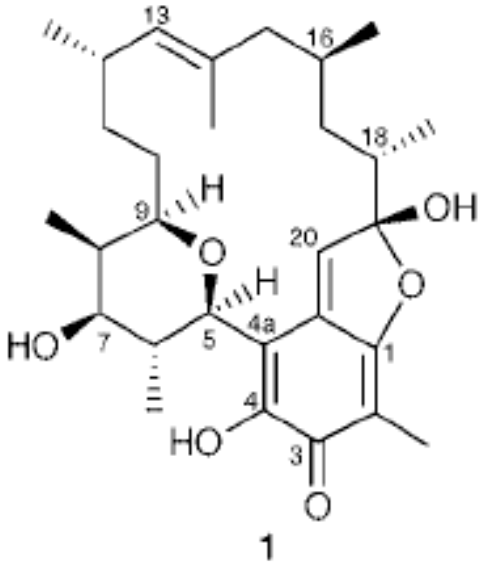
1

Interesting Facts

- Polyketide isolated from different *Streptomyces* sp. by Funahashi in **1996**
- Potent endothelin receptor antagonist and antiosteoporotic compound
- Re-isolated by Zeeck in **2000 (70 mg/l)** from Streptomyces violaceoruber and was shown to degrade natural rubber
- Remarkable Antibacterial activity against Gram positive and Gram negative bacteria particularly against Staphylococcus aureus strains
- Highly cytotoxic against tumor cell lines
- Biosynthesis has been proposed recently by Zeeck

Structure Elucidation

"Ansa bridge Stereochemistry"



1

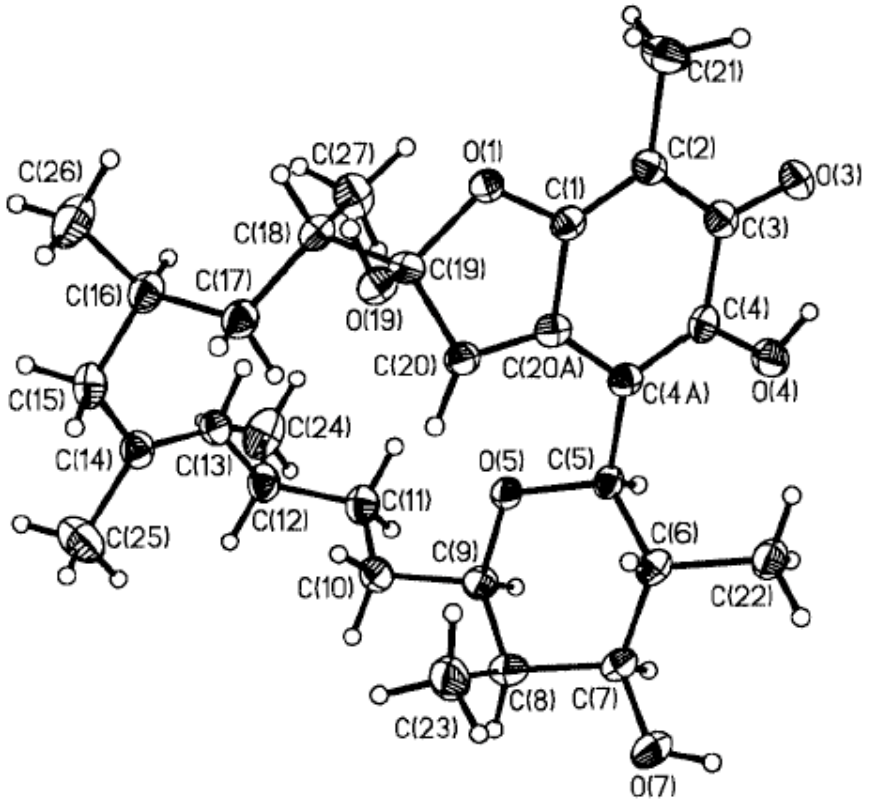
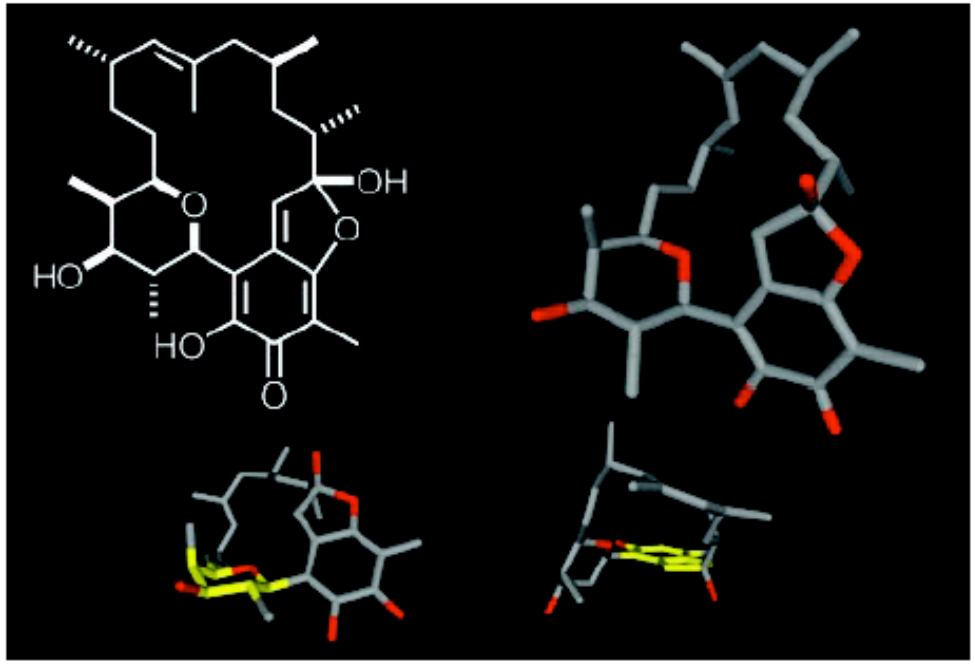


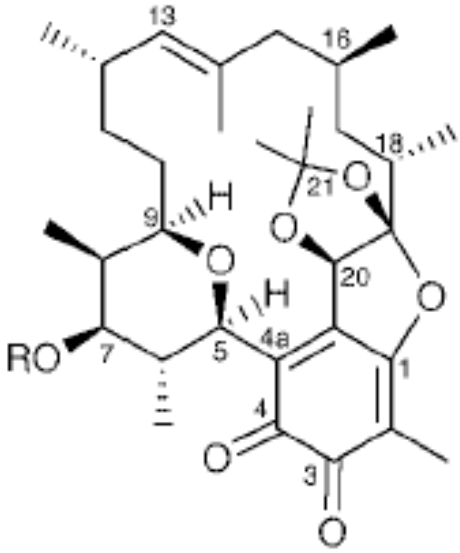
Fig. 1 Perspective view of kendomycin **1**. Only the relative configuration resulted from the X-ray analysis. The given absolute configuration was determined using Mosher's methodology. Crystallographic numbering is shown.

Stereotetrad Absolute Configuration Determination



$FeCl_3$

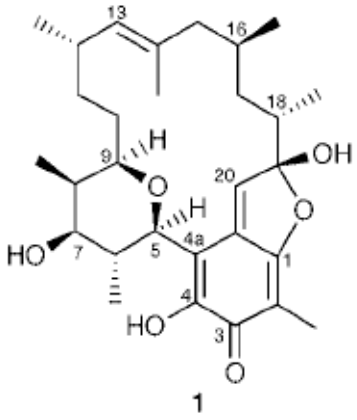
acetone



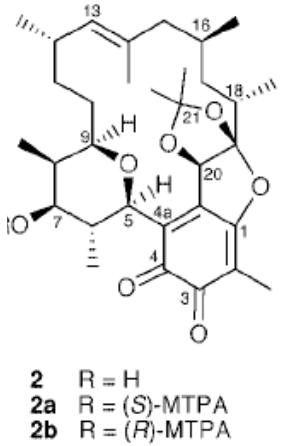
2 R = H
2a R = (*S*)-MTPA
2b R = (*R*)-MTPA

Fig. 1. Structure of kendomycin (**1**) with different views of the crystal structure.

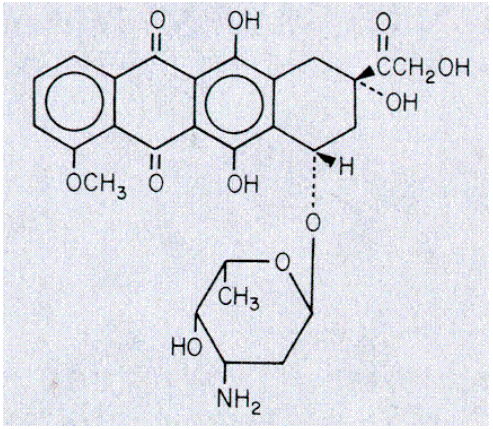
Cytotoxicity Profile Comparison with Cis-Platin



1



2 R = H
2a R = (*S*)-MTPA
2b R = (*R*)-MTPA



Doxorubicin

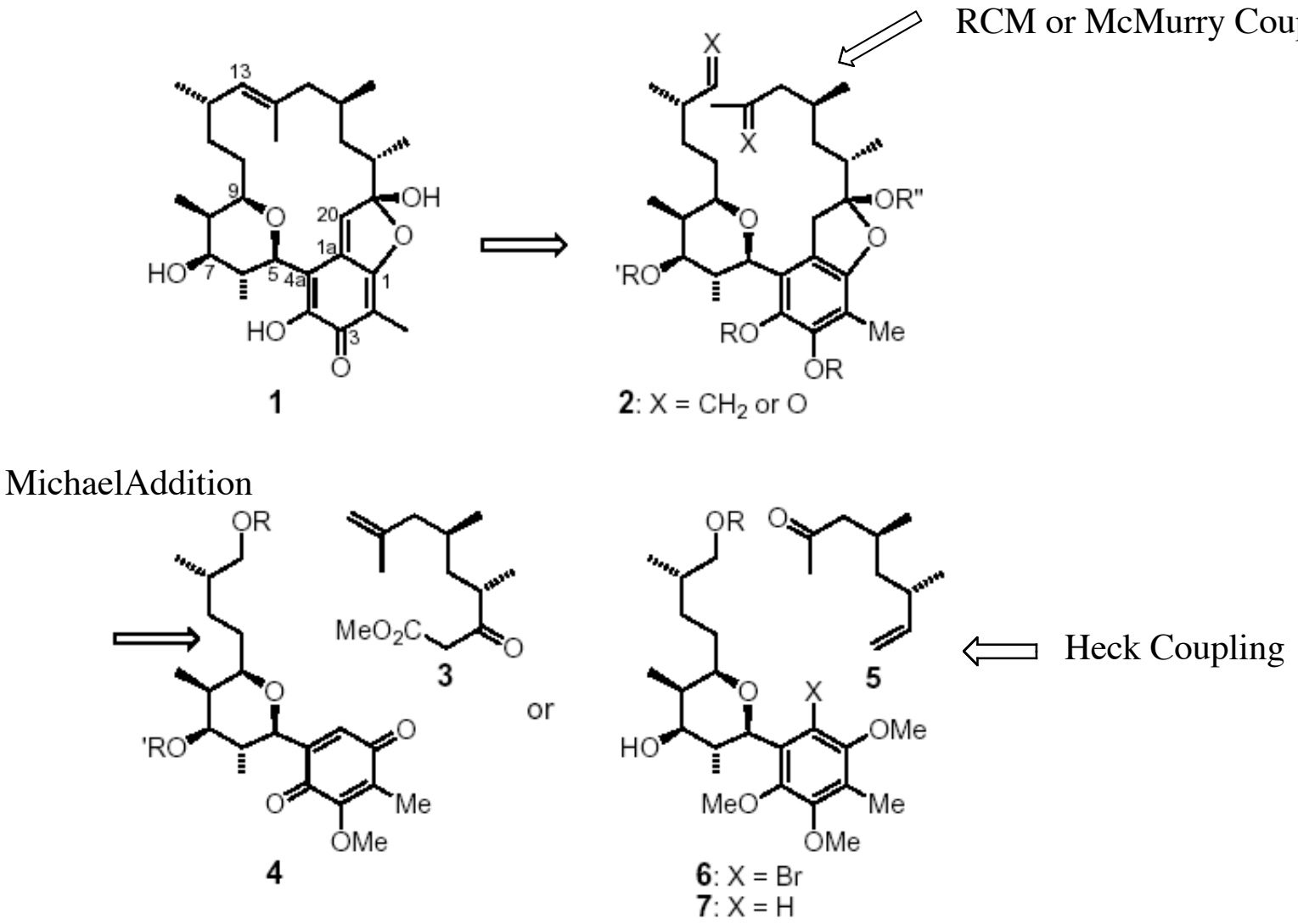
Cis-Platin

Table 3 Cytotoxic activity of **1** and **2** (in μmol l^{-1})

	HMO2[a]		HEP G2[b]		MCF7[c]	
Compound	GI_{50}[d]	TGI[e]	GI_{50}	TGI	GI_{50}	TGI
1	<0.1	0.2	<0.1	0.2	<0.1	0.5
2	0.1	0.4	0.8	48	0.2	0.6
Doxorubicin	<0.1	0.1	0.3	1.0	<0.1	0.2
Cisplatin	0.2	1.5	0.5	5.0	0.1	10

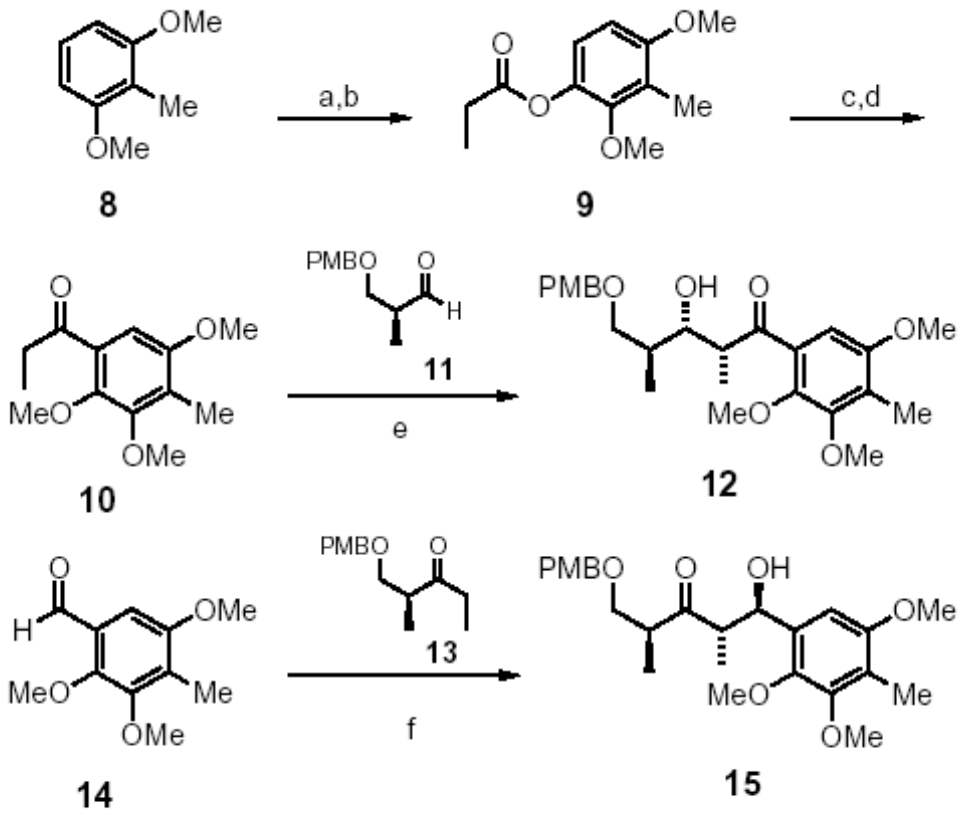
[a] Stomach adenocarcinoma. [b] Hepatocellular carcinoma.
[c] Breast adenocarcinoma. [d] 50% growth inhibition. [e] Total growth inhibition.

Mulzer's First Generation Approach



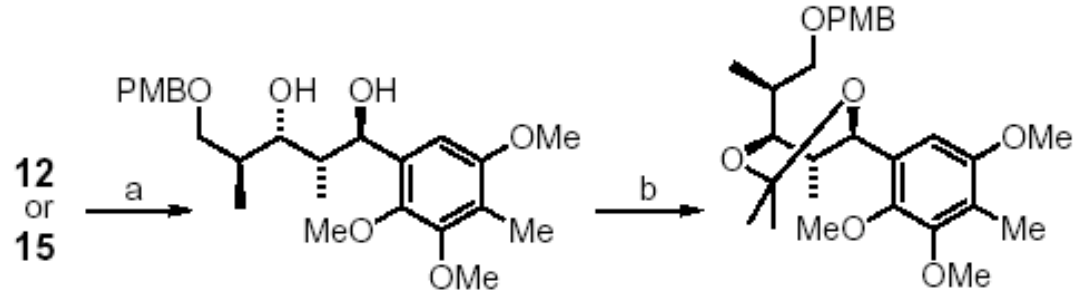
Scheme 1. Retrosynthesis of kendomycin (**1**).

Syn and Anti Aldol reactions towards Fragments 12 and 15

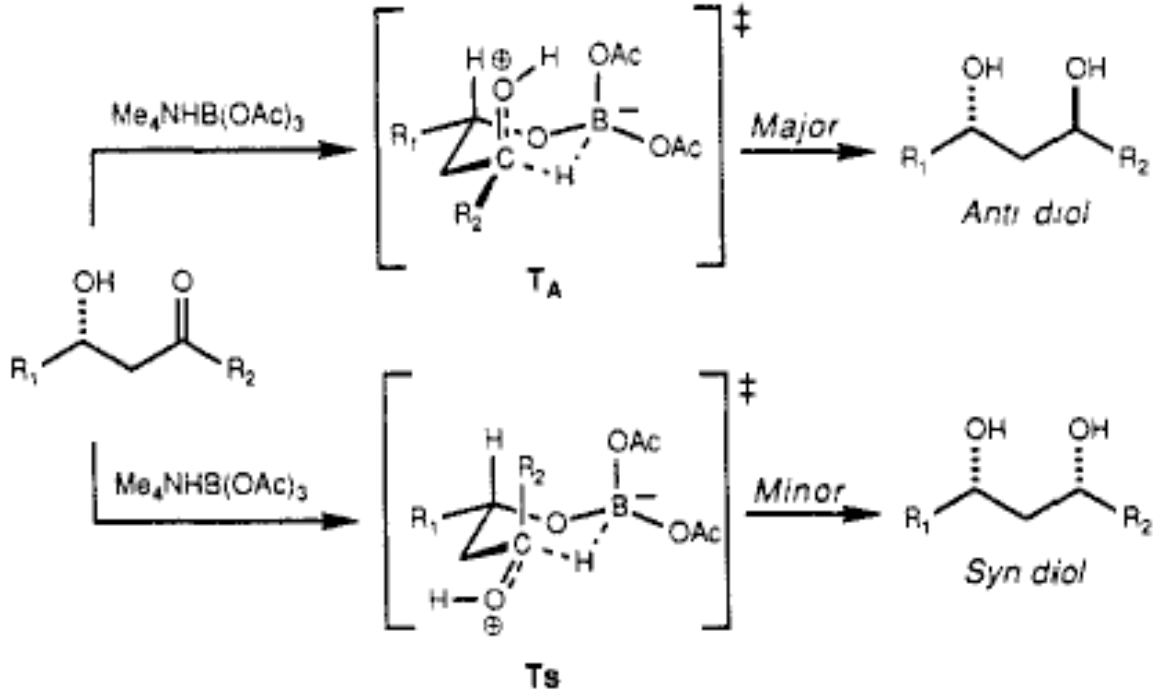


Scheme 2. a) EtCOCl, $TiCl_4$, benzene, 0 °C, 0.5 h, 96 %; b) mCPBA, CH_2Cl_2, RT, 85 %; c) BF_3OMe_2, 90 °C, 3 h, 76 %; d) $(MeO)_2SO_2$, K_2CO_3, acetone, RT, 40 h, 99 %; e) **10**, LiHMDS, −78 °C, THF, 0.75 h, $Ti(OiPr)_3Cl$, −78 → −40 °C, 1 h, −78 °C, addition of **11**, −78 → −40 °C, 3 h, then aq. NH_4F, 58 %; f) **13**, NEt_3, $(c\text{-}C_6H_{11})_2BCl$, Et_2O, −78 → −40 °C, −40 °C, 1.5 h, −78 °C, addition of **14**, −78 → 15 °C, 16 h, then $NaBO_3$, 62 %. mCPBA = *m*-chloroperbenzoic acid; LiHMDS = lithium hexamethyldisilazanide; PMB = *p*-methoxybenzyl.

Synthesis of Acetonide 17

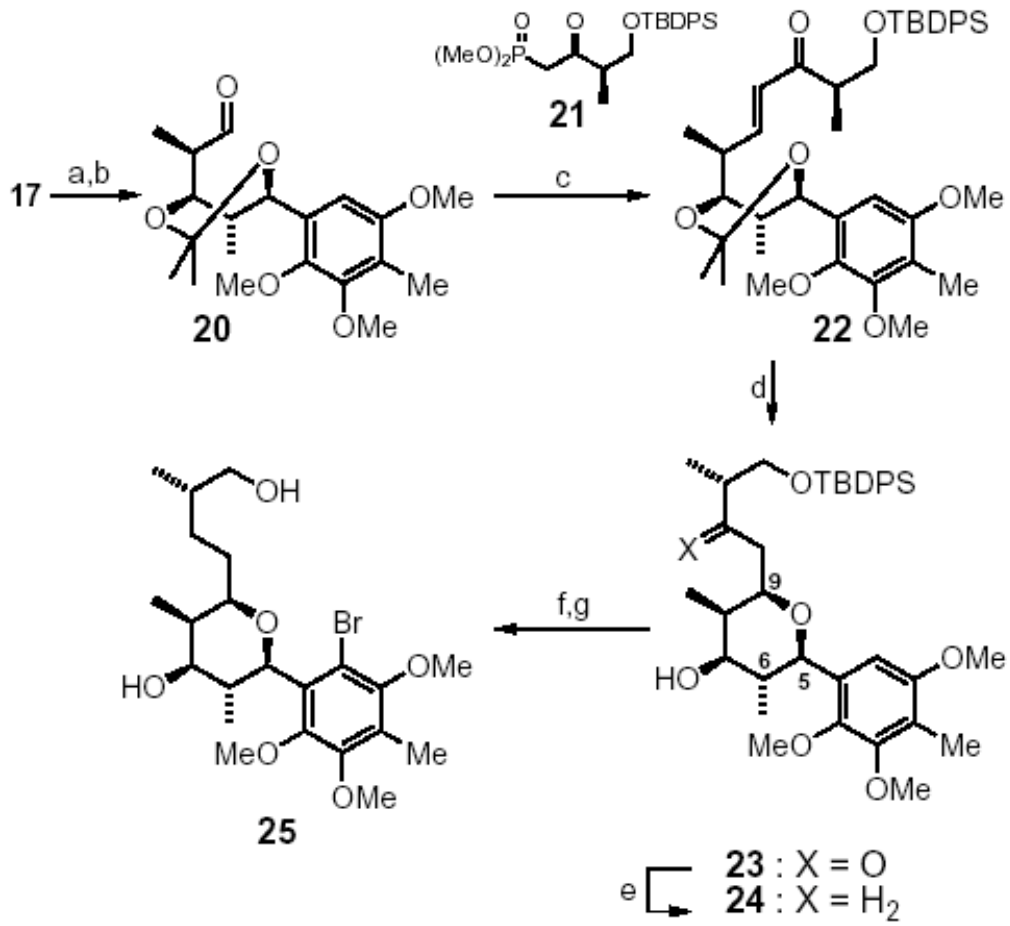


Scheme 3. a) $Me_4NBH(OAc)_3$, MeCN:AcOH (1:1), $-30 \rightarrow 20\,^{\circ}C$, 16 h, 92–95 %; b) $(MeO)_2CHMe_2$, RT, 18 h, 88–93 %;



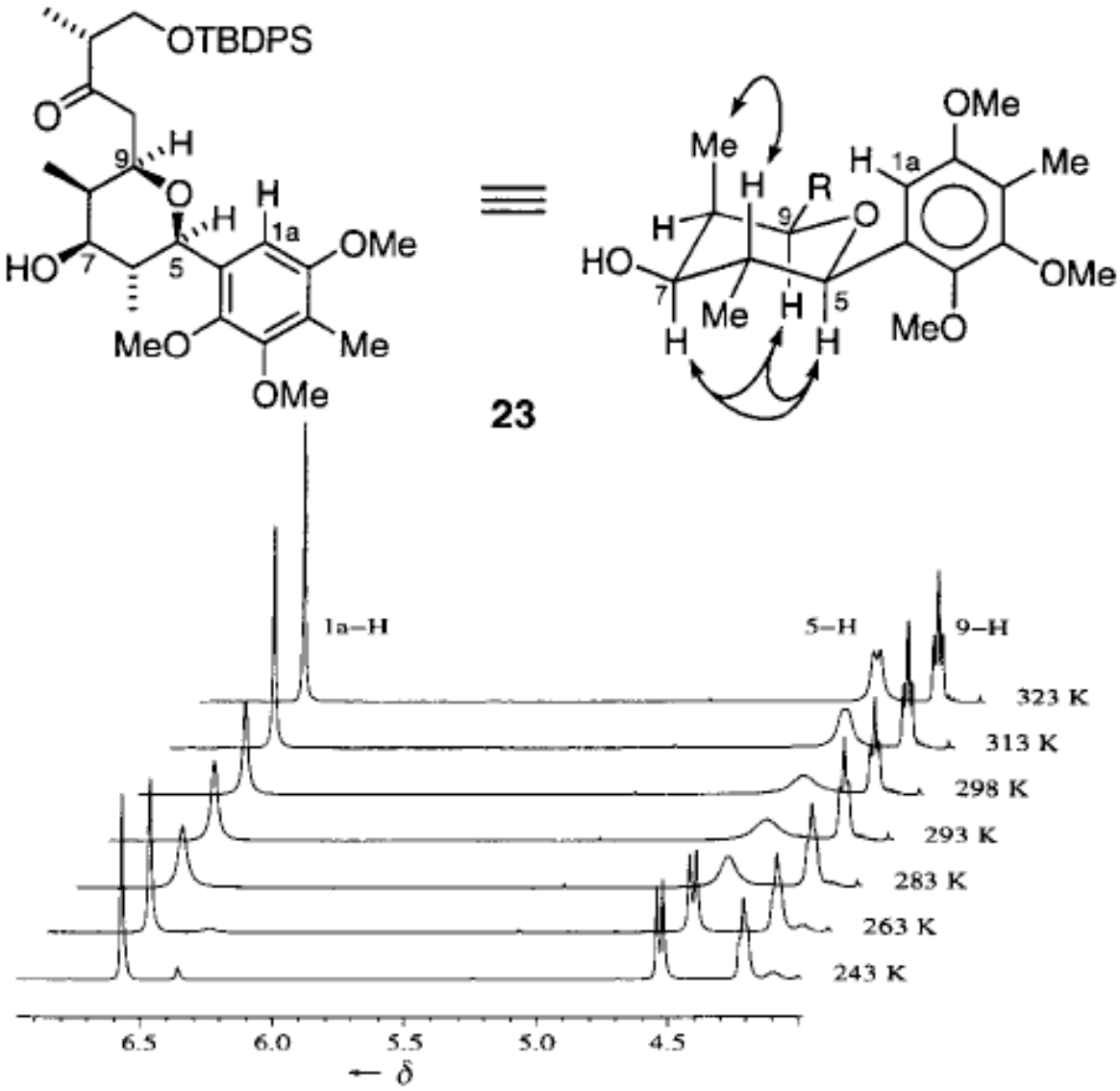
Evans, D.A.; Chapman, K.T.; Carreira, E.M. *J.Am.Chem.Soc.***110**, 3560

Preparation of Aryl Bromide 25



Scheme 4. a) DDQ, 4-Å molecular sieves, CH_2Cl_2:pH 7 buffer (15:1), 0.5 h, 83 %; b) DMSO, $(COCl)_2$, CH_2Cl_2, −78 °C, 1.5 h, then NEt_3, −78 → 0 °C, 0.25 h; c) **21**, LiOH, Et_2O, 15 min, RT, then addition of **20**, RT, 4 h, 85 %; d) MeOH:HCl_{aq}(0.2 M) (5:1), RT, 6 h, 92 % (*ds* = 97:3); e) 1. *p*-$TsNHNH_2$, EtOH, 4-Å molecular sieves, reflux, 4 h; 2. $NaCNBH_3$, $ZnCl_2$, EtOH, reflux, 8 h, 65 %; f) MeOH:HCl_{aq}(2 M) (5:1), RT, 4 h, 97 %; g) NBS, CH_3CN, 40 °C, 12 h, 75 %.

Atropisomerism about sp^2-Sp^3 C-C Bond in 23



Broad signals in HNMR for H's at C-5, C-6 and C1a were observed due to dynamic effect

No signals in 13C were observed for C5, C6 and C1a

At Lower temperature Benzylic H's showed a doublet $J_{1,2}$ = 10.7 Hz

Rotamer Identification by NOE

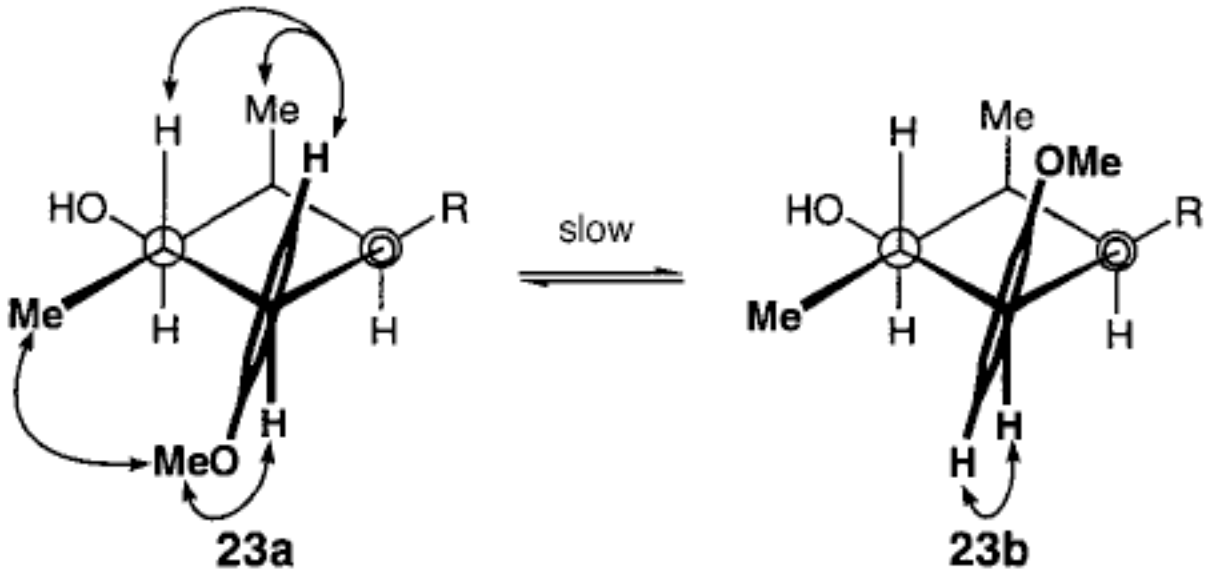


Figure 1. Hindered rotation in compound **23**. Top: structural formulas and indication of the NOEs in the THP unit; middle: NMR spectra of **23** at various temperatures showing the region containing the signals for 1a-, 5-, and 9-H; bottom: NOE interactions of the aromatic *ortho* substituents at −40 °C in the main isomer **23a** and the minor isomer **23b**.

Rotamer ratio at -40 °C = 93:7

9-epi 23 shows sharp signals over entire temp range due to axial disposition of C-9 substituent that leads to twist conformation of THP ring and thereby greater degree of rotational freedom of aryl residue

Rotamer Distribution in 25

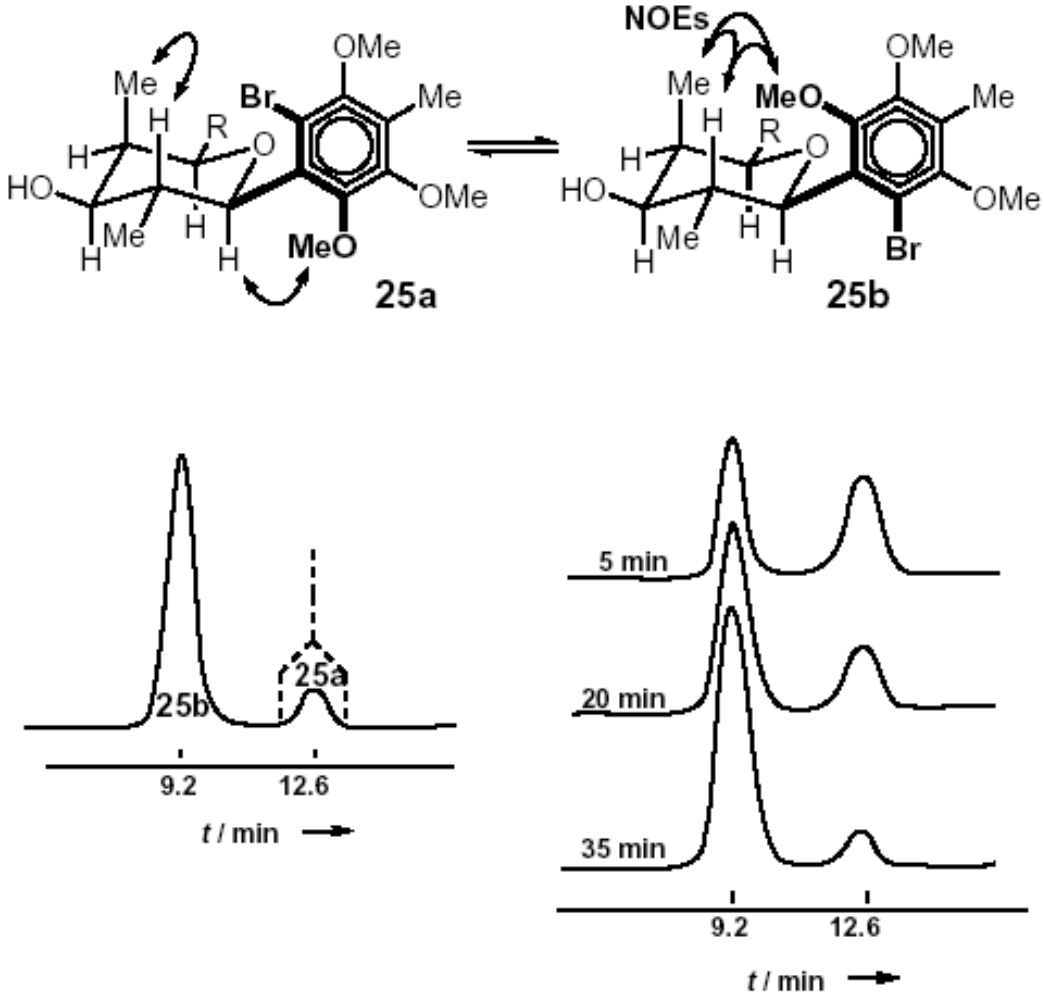
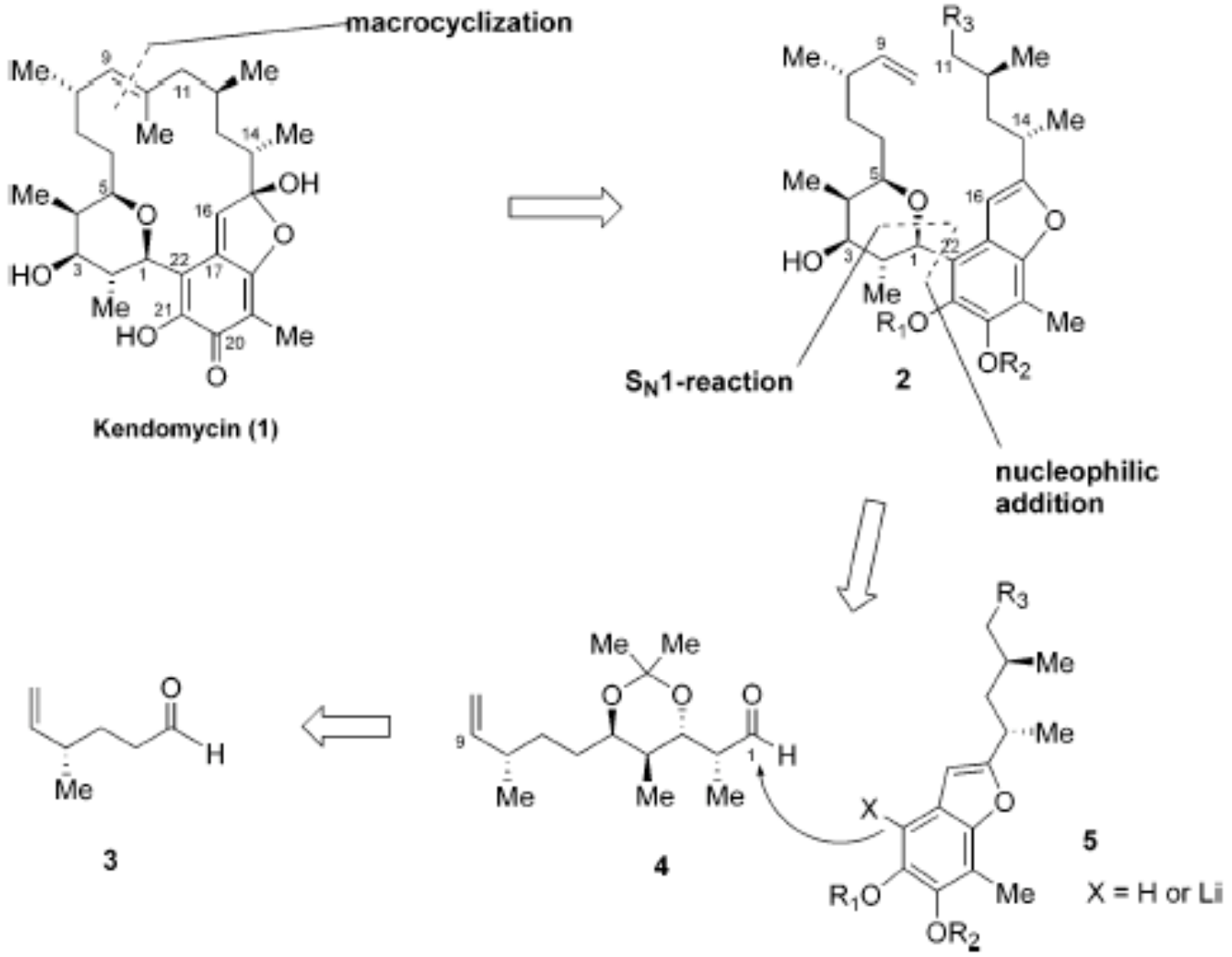


Figure 2. Atropisomerism of compound **25**. Top: NOE interactions in the THP unit of **25a** and **25b**; bottom left: HPLC separation of the rotamers **25a** and **25b**; bottom right: HPLC chromatograms of an pure solution of **15a**, analyzed after the given time intervals.

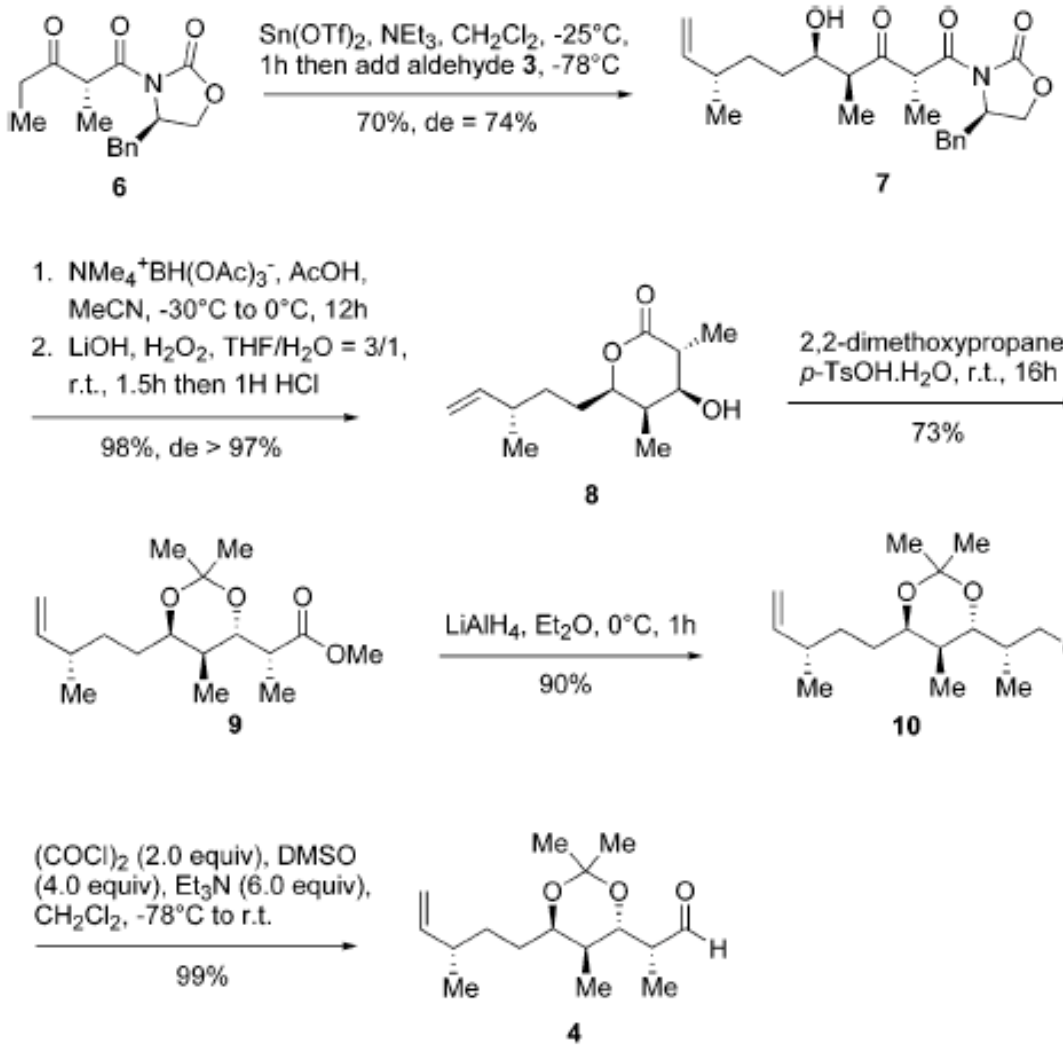
Second Generation Approach

Scheme 1. Retrosynthetic Analysis of **1**



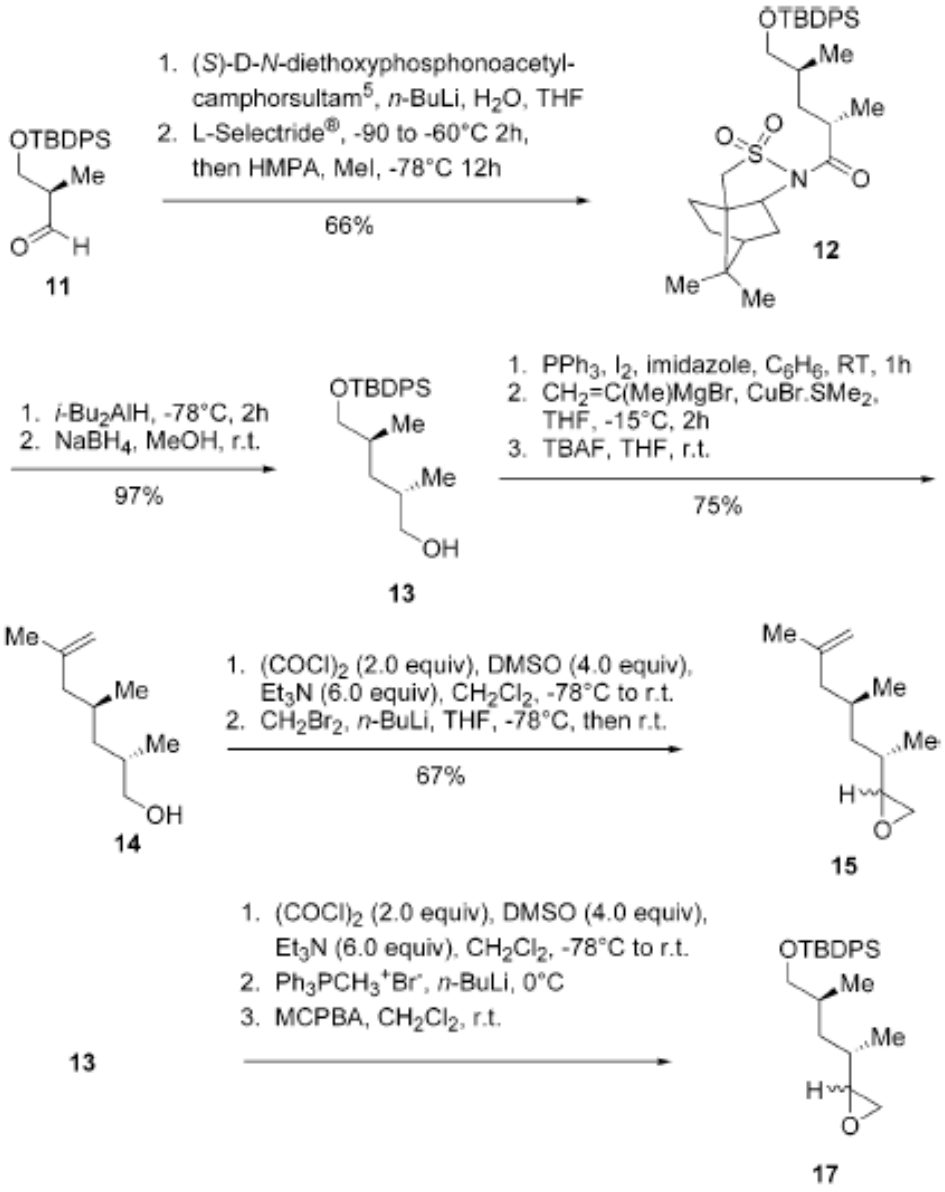
Evans β- Keto Imide Aldol in Preparation of 4

Scheme 2

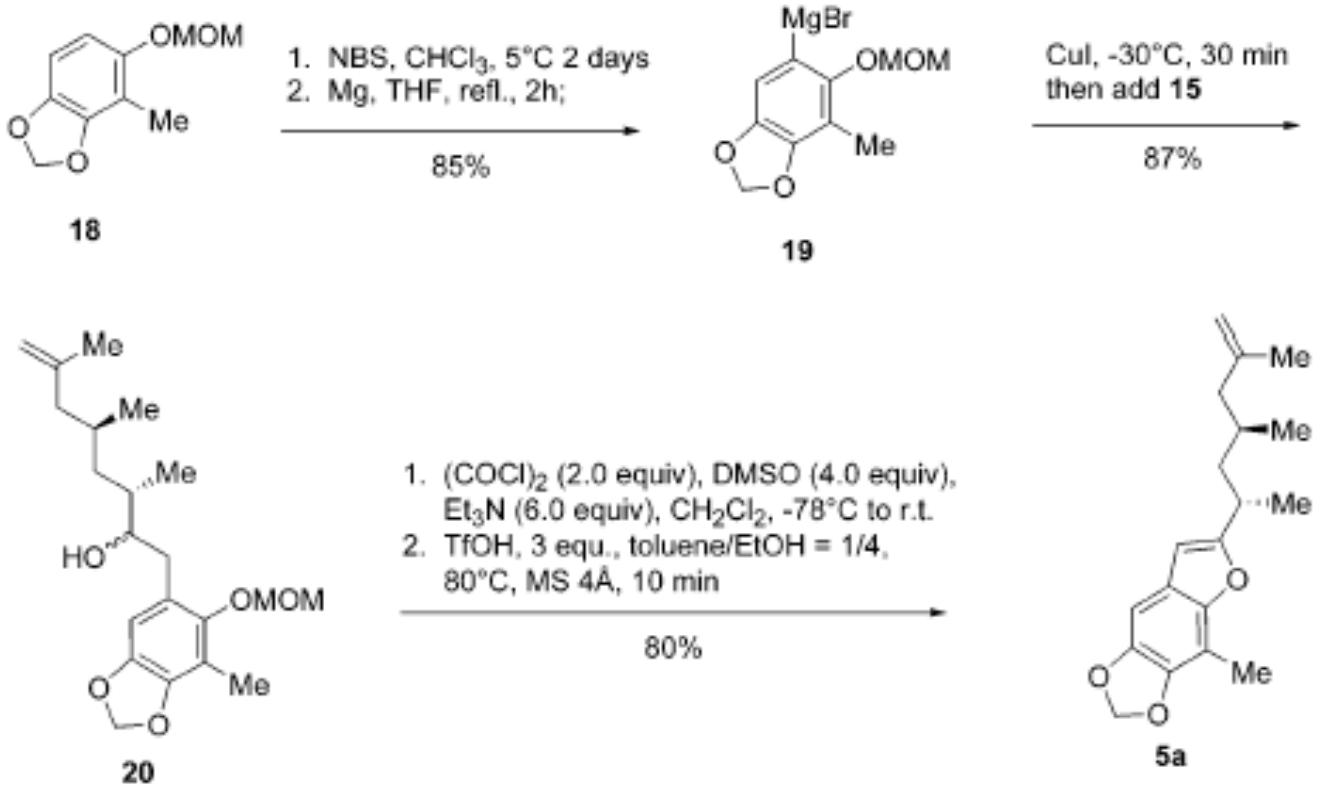


Oppolzer's Sultam in Synthesis of 17

Scheme 3[a]

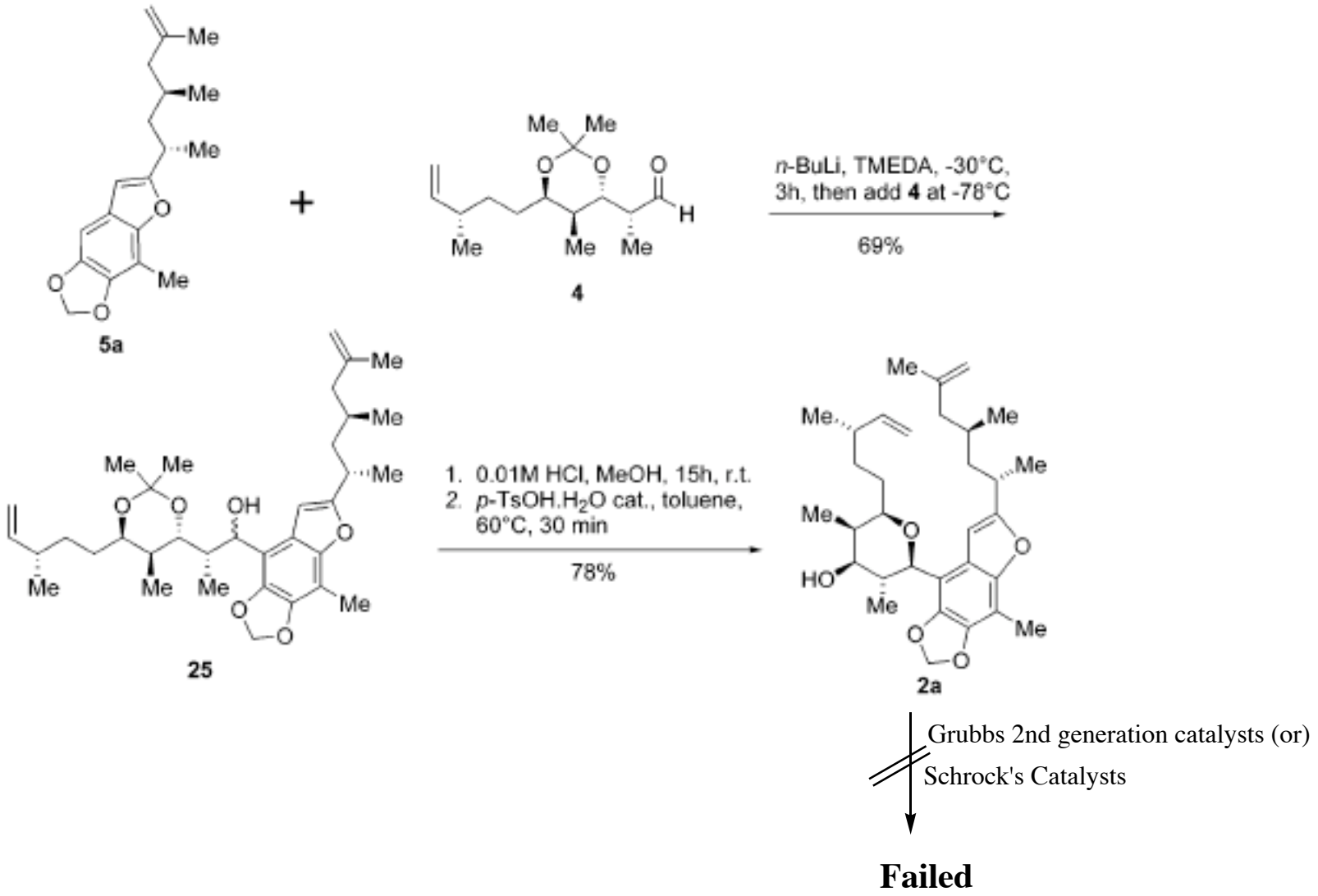


Synthesis of Benzofuran 5a

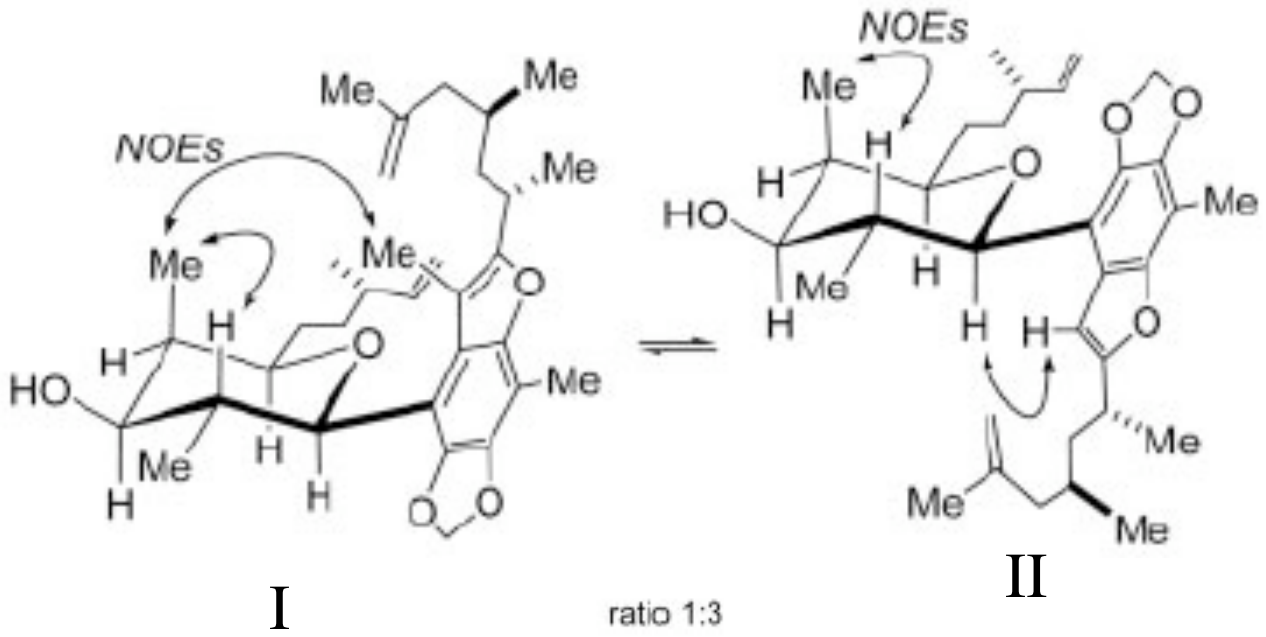


Ring Closing Metathesis of Precursor 2a

Scheme 5 [a]

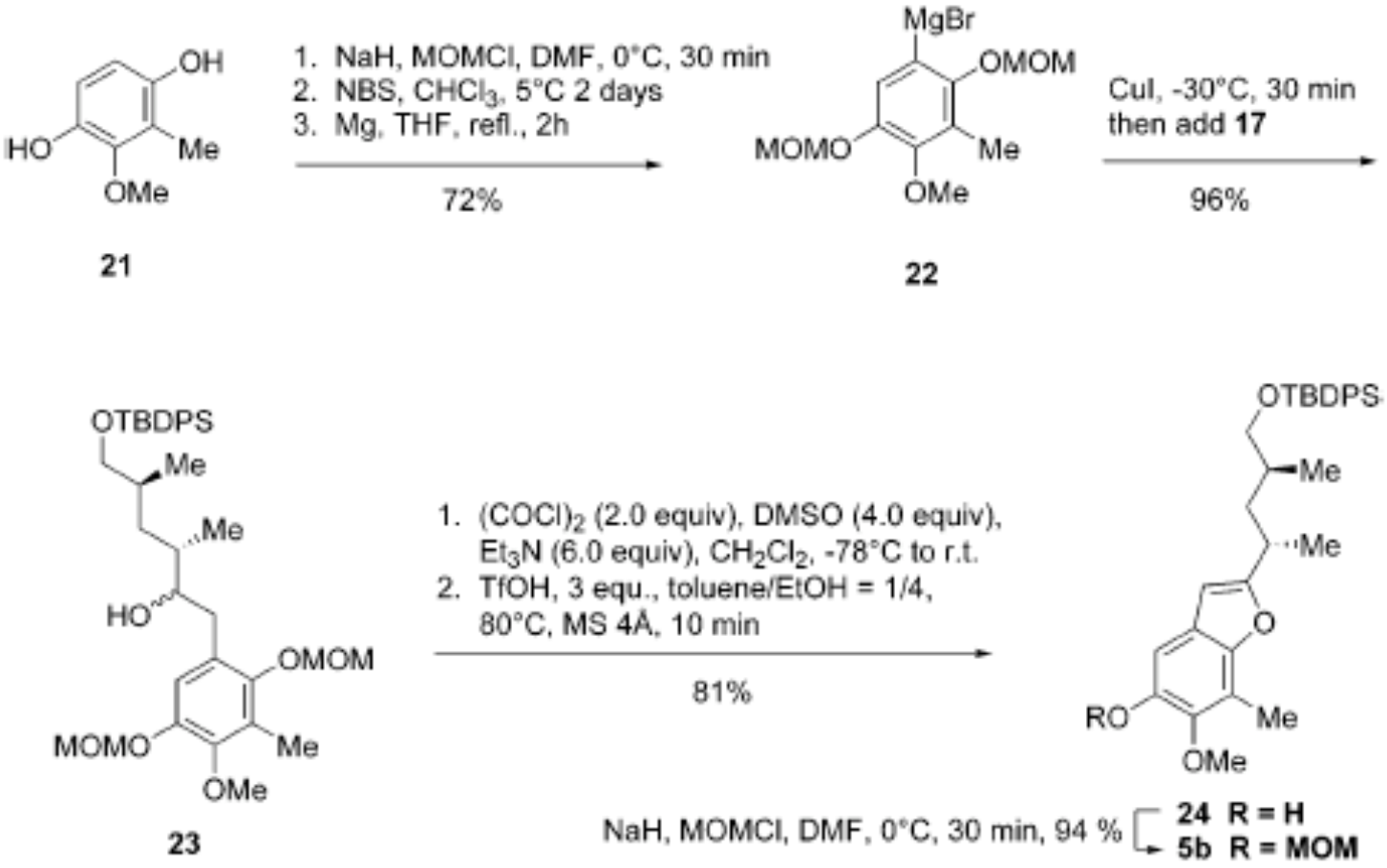


Unfavorable Rotamer Distribution in 2a

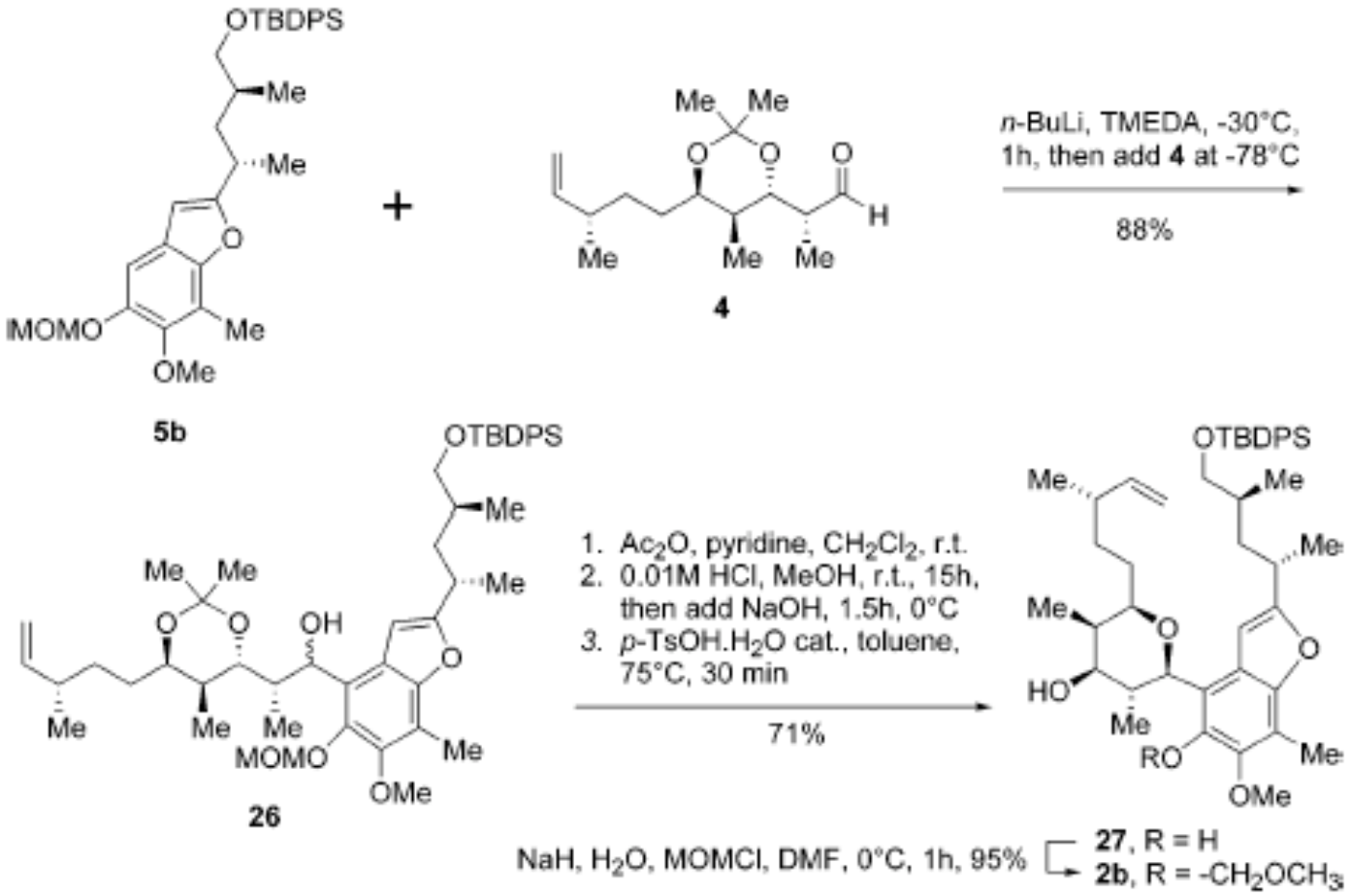


I ratio 1:3 II

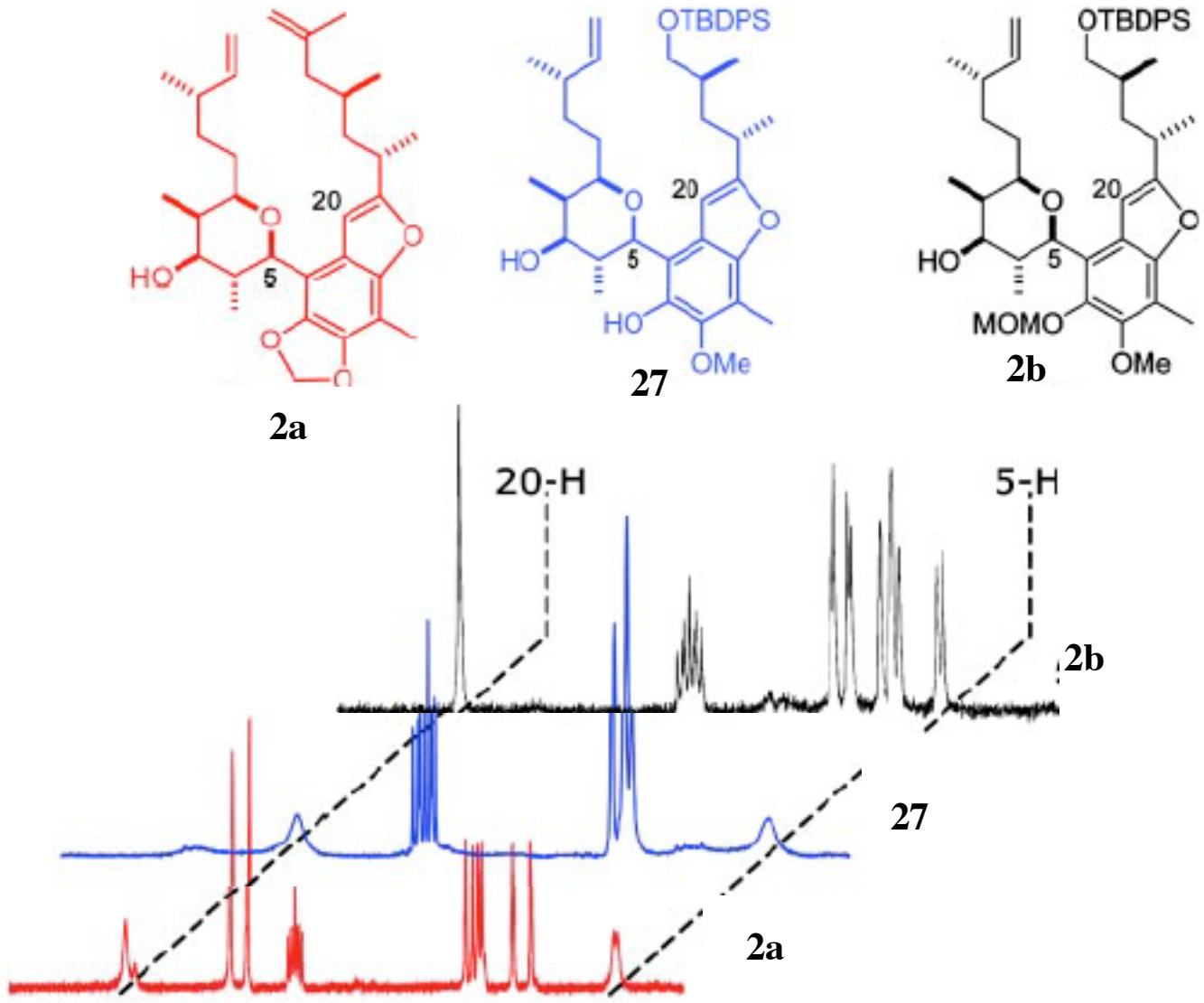
Third Generation Approach Synthesis of Benzofuran 5b



Direced Ortho Metalation in Synthesis of Benzofuran 2b

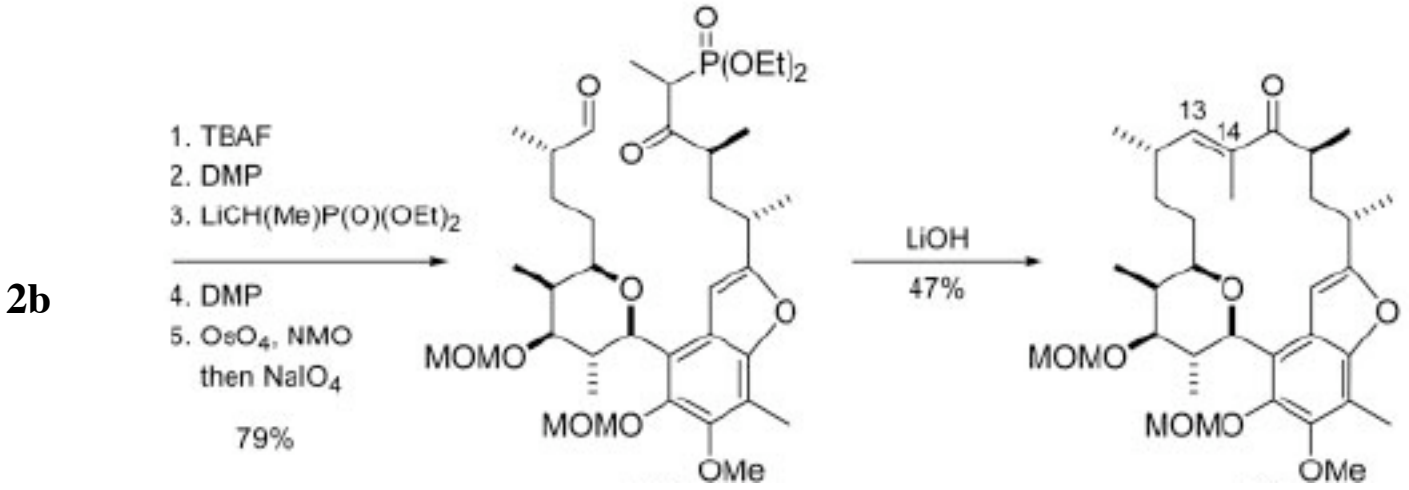


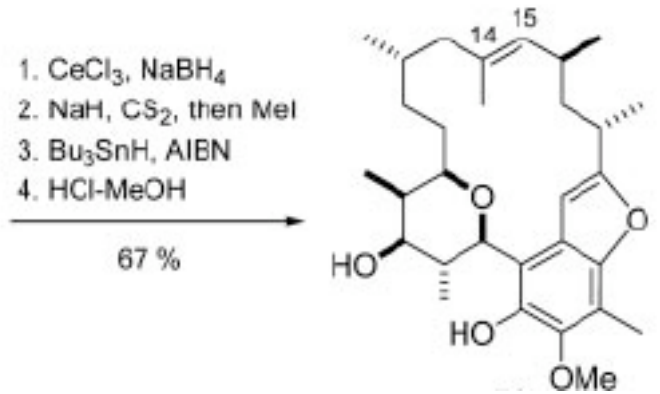
Atropisomerism in 2a, 27 and 2b



^{1}H NMR spectra of tetrahydropyran-arene compounds at 27°C.

HWE Macrocyclization





Undesired Double Bond Migration, Back to the Start…….

Uemura's Approach

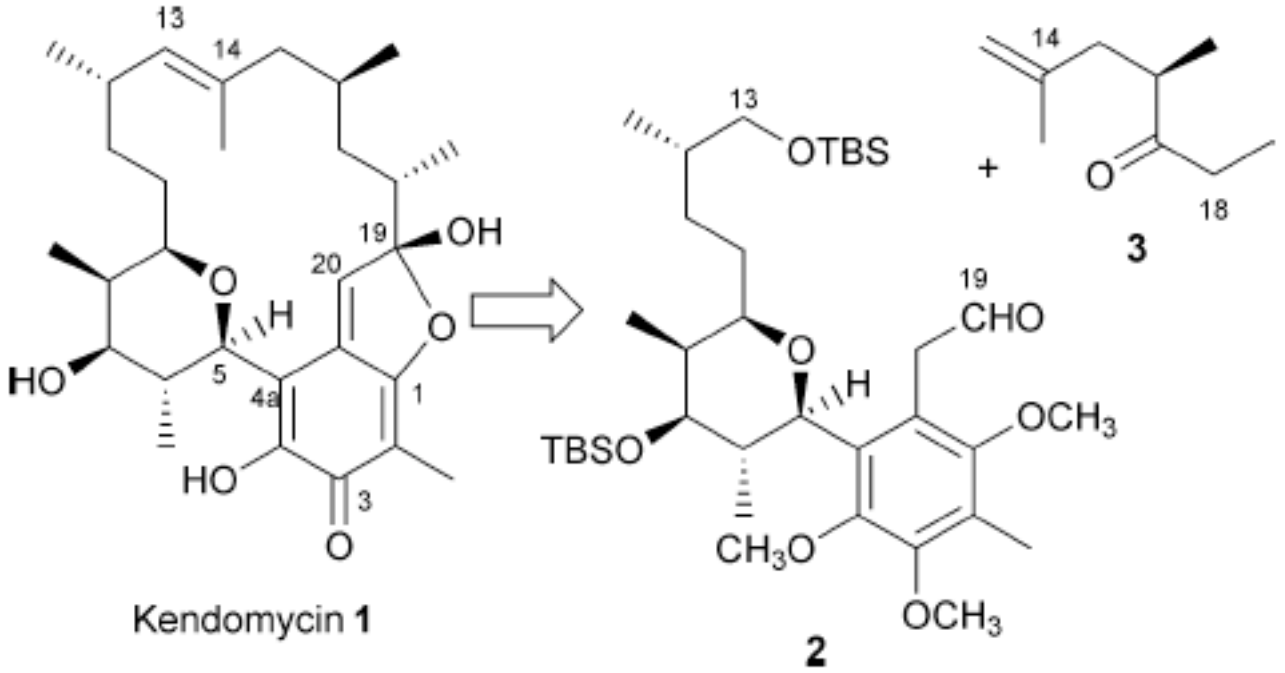
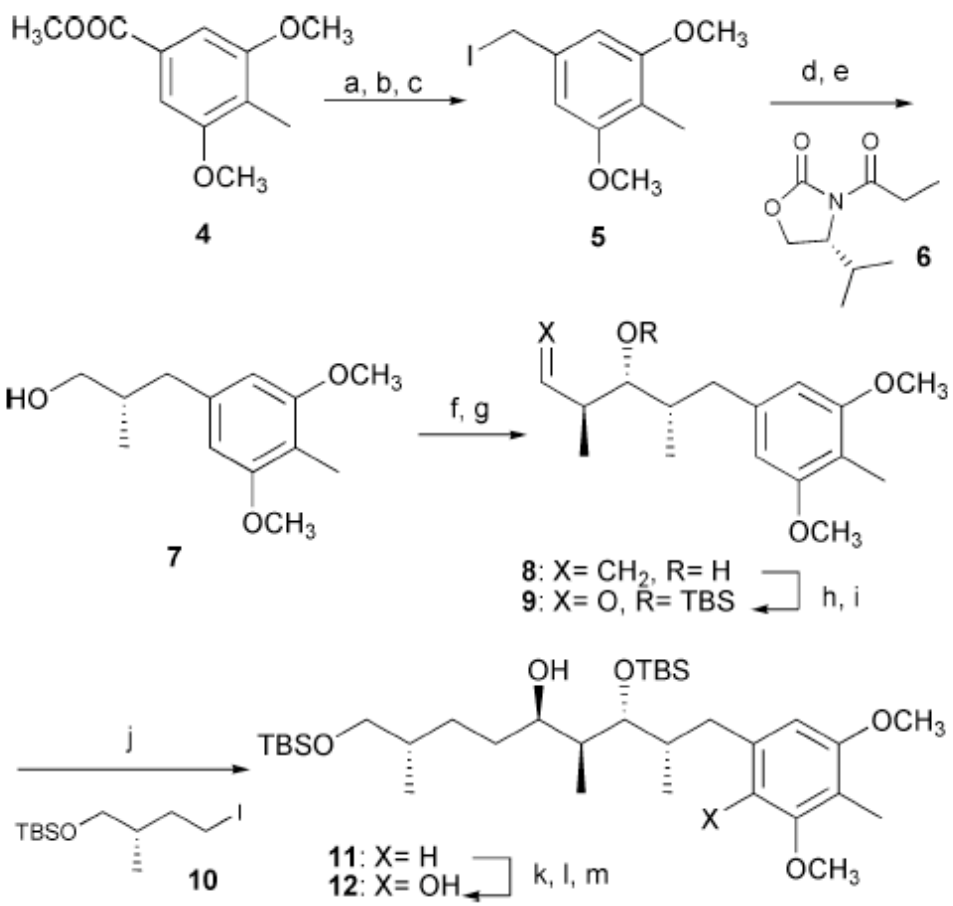


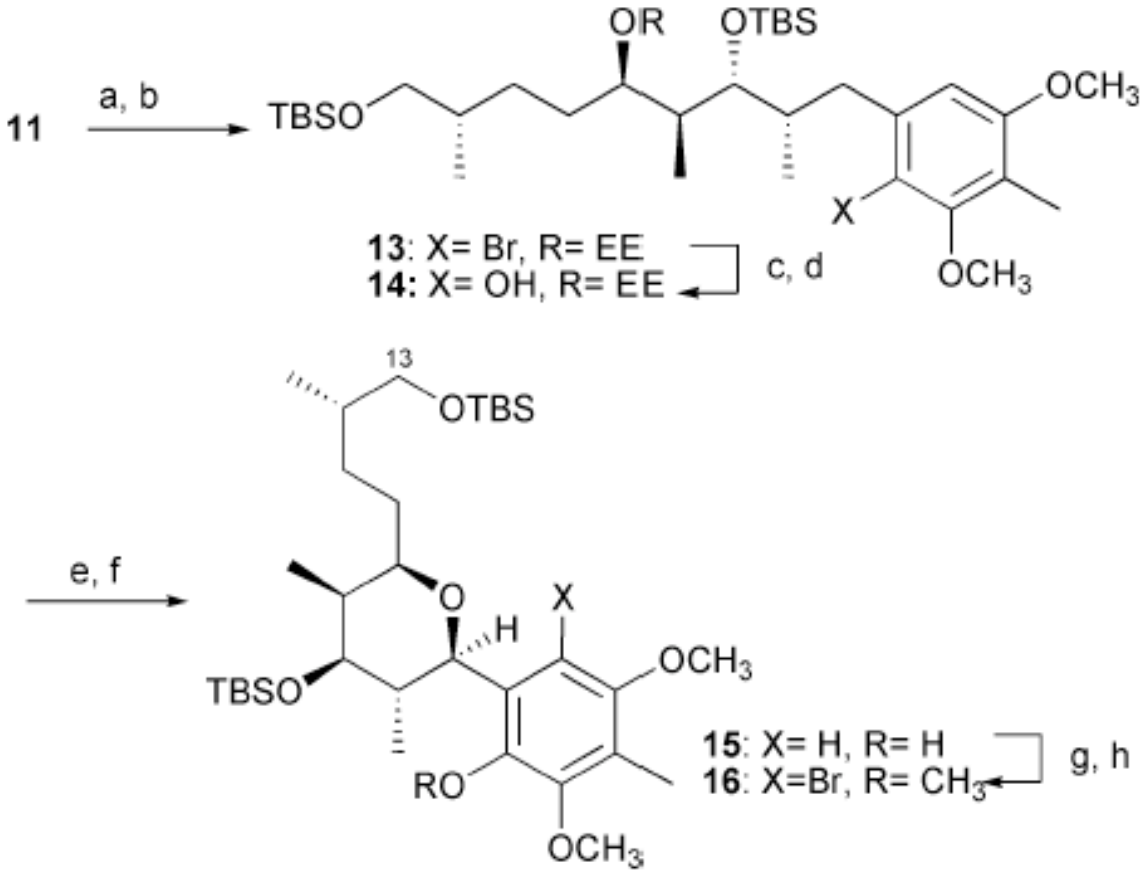
Fig. 1 Retrosynthetic analysis of kendomycin.

Evans Alkylation and Roush Allylboration to 12



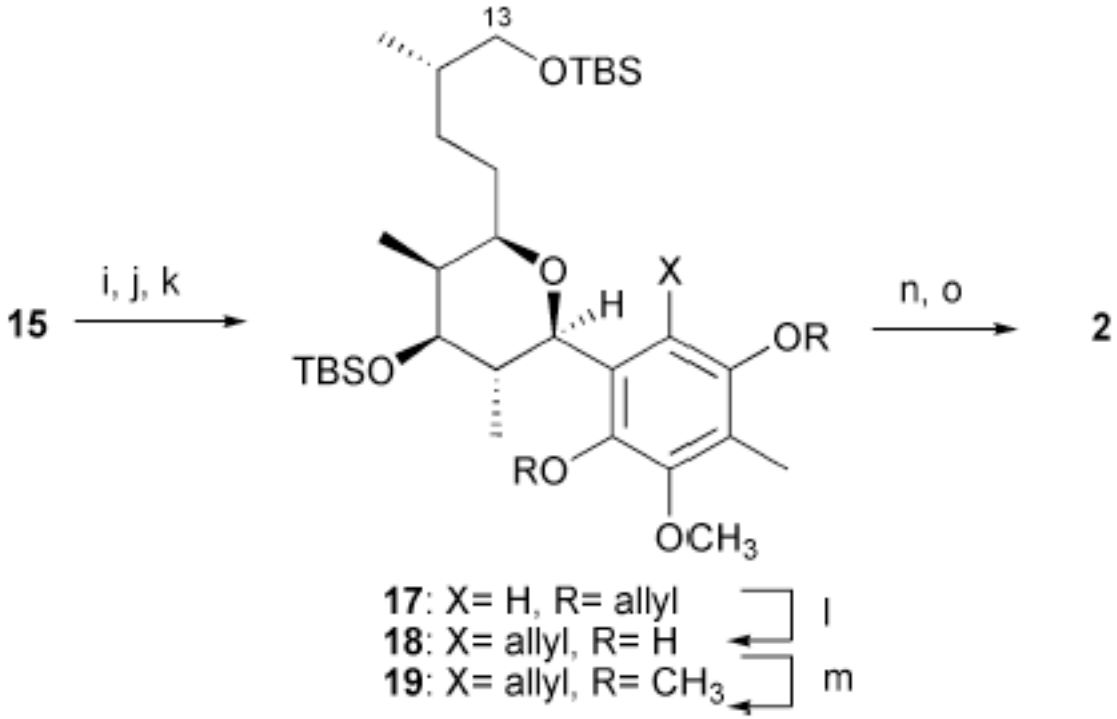
Scheme 1 a) $LiAlH_4$, THF, 40 °C; b) CH_3I, NaH, THF, 0 °C, 96% in 2 steps; c) NaI, BF_3 etherate, CH_3CN, room temp., 82%; d) **6**, NaHMDS, THF, −78 °C; e) $LiAlH_4$, THF, −78 °C to 0 °C, 91% in 2 steps; f) Dess–Martin periodinane, CH_2Cl_2, room temp.; g) (*R*,*R*)-diisopropyl tartrate, (*E*)-crotyl boronate, MS4A, toluene, −78 °C, 71% in 2 steps; h) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 100%; i) OsO_4, $NaIO_4$, aq. THF, room temp.; j) **10** (3 equiv.), *t*-BuLi (6 equiv.), THF, −78 °C, yield of major isomer **11** 62% in 2 steps; k) Ac_2O, DMAP, pyridine, room temp., 100%; l) mCPBA (3 equiv.), CH_2Cl_2, room temp.; m) DIBAL-H, CH_2Cl_2, −78 °C, 66% in 2 steps.

Synthesis of Fragment 16



Scheme 2 a) Pyridinium bromide perbromide, K_2CO_3, CH_2Cl_2, 0 °C to room temp.; b) ethyl vinyl ether, PPTS, room temp., 98% in 2 steps; c) *n*-BuLi (2.5 equiv.), then $B(OCH_3)_3$, THF, −78 °C; d) H_2O_2, sat. Na_2CO_3 aq., 82% in 2 steps; e) PPTS, *n*-propanol, room temp., 94%; f) Ag_2O, CH_2Cl_2, room temp., 94%; g) CH_3I, K_2CO_3, acetone, reflux, 100%; h) pyridinium bromide perbromide, CH_2Cl_2, room temp., 40%;

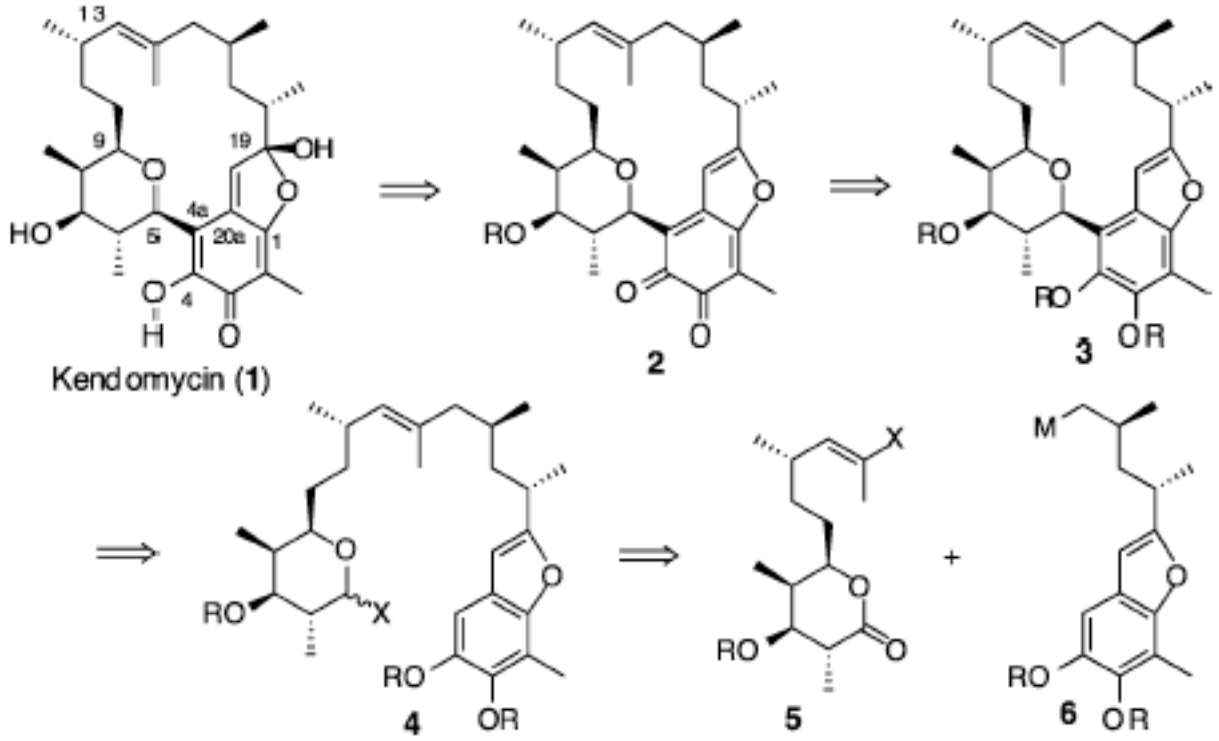
Preparation of Advanced Intermediate 2



i) $(CF_3COO)_2IPh$, K_2CO_3, CH_3CN, H_2O, room temp.; j) $Na_2S_2O_4$, THF, H_2O, 0 °C, 83% in 2 steps; k) allyl bromide, K_2CO_3, acetone, reflux, 100%; l) *N*,*N*-dimethylaniline, reflux, 1.5 h, 66%; m) CH_3I, K_2CO_3, acetone, reflux, 100%; n) OsO_4, NMO, aq. acetone, room temp., 82%; o) $NaIO_4$, ethanol, room temp., 96%.

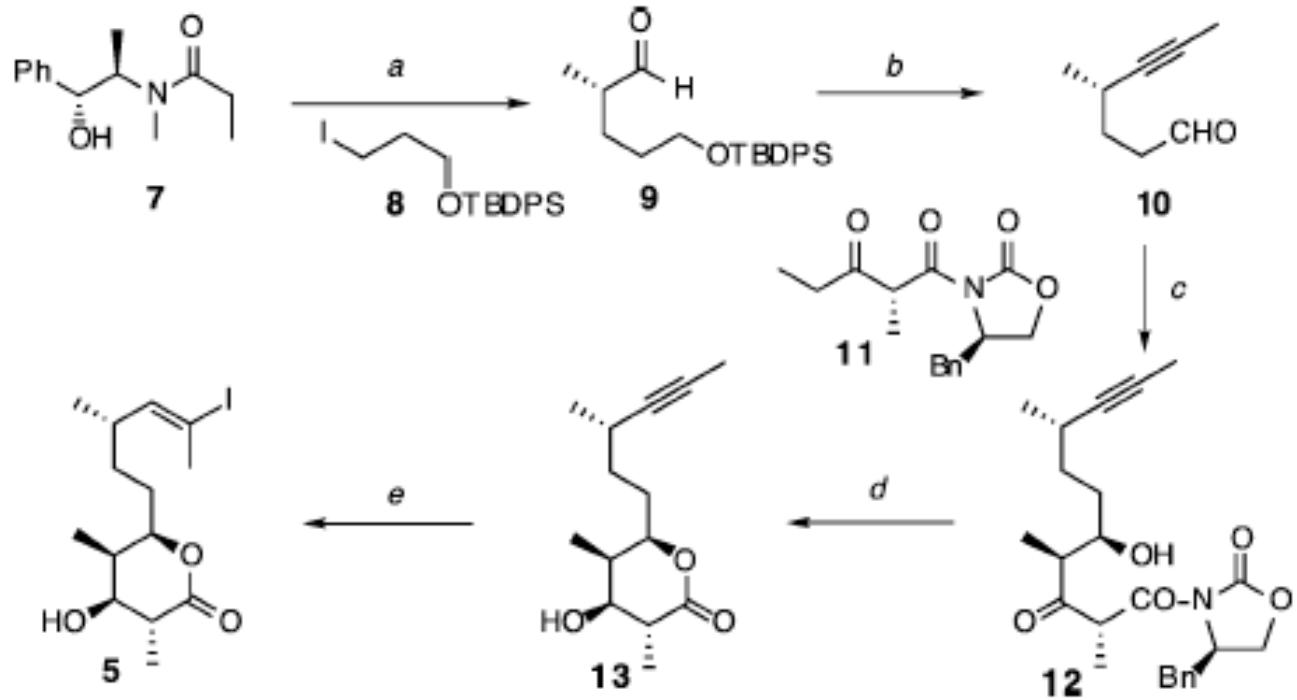
Lee's Strategy to Kendomycin

Scheme 1. Structure and Retrosynthetic Analysis of Kendomycin



Evans 2,4 Anti Aldol Approach to 5

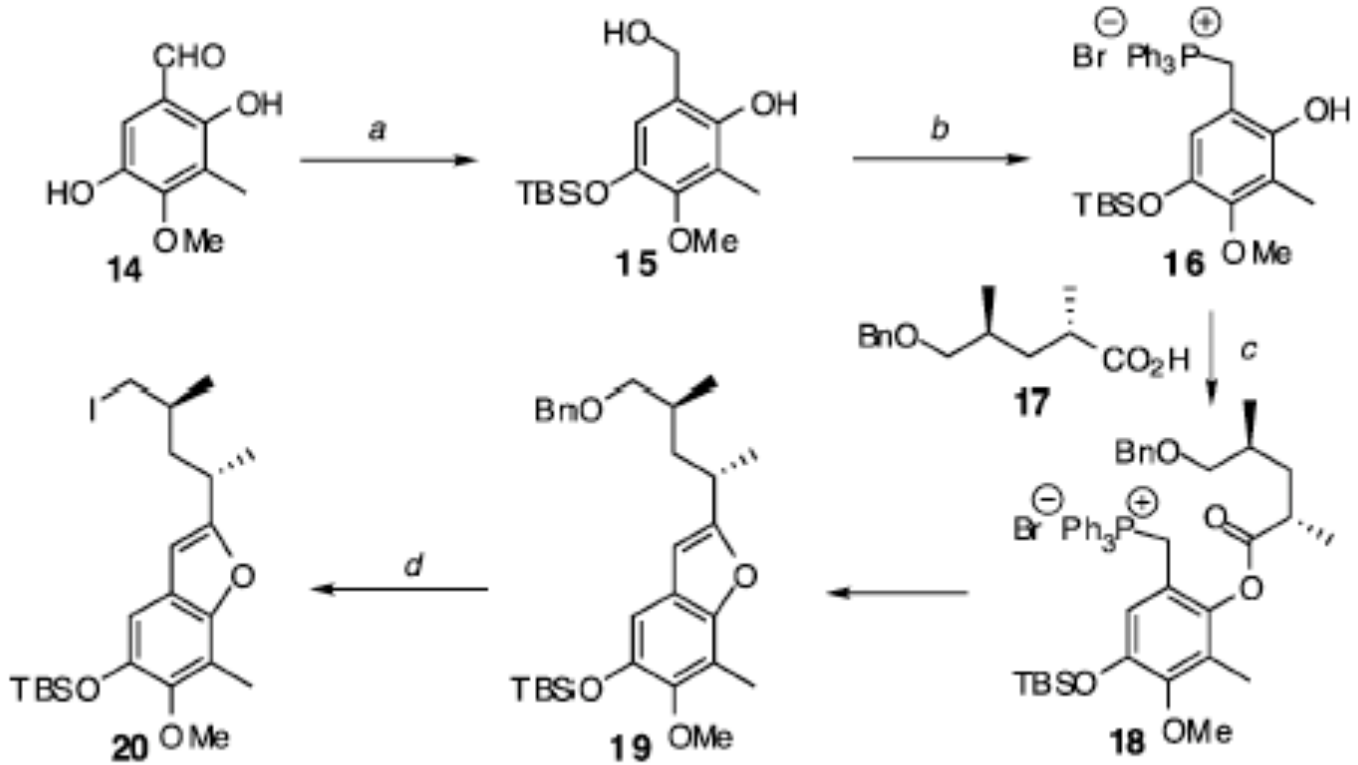
Scheme 2. Synthesis of the Tetrahydropyran Domain[a]



[a] Reagents and conditions: (a) ref 7; (b) (i) CBr_4, PPh_3, Zn, DCM, 83%, (ii) *n*-BuLi, MeI, THF, 99%, (iii) TBAF, THF, 99%, (iv) Dess−Martin, DCM, 85%; (c) $Sn(OTf)_2$ TEA, DCM, −78 °C, 82% (dr = 7:1); (d) (i) $NaBH(OAc)_3$, AcOH, 5 °C, 84% (dr = 20:1), (ii) DBU, DCM, 90%; (e) (i) cat. $Pd(OAc)_2$−PCy_3, *n*-Bu_3SnH, hexanes−THF, (ii) I_2, DCM, 83% (dr = 7−10:1).

Intramolecular Wittig Olefination in Synthesis of Benzofuran 20

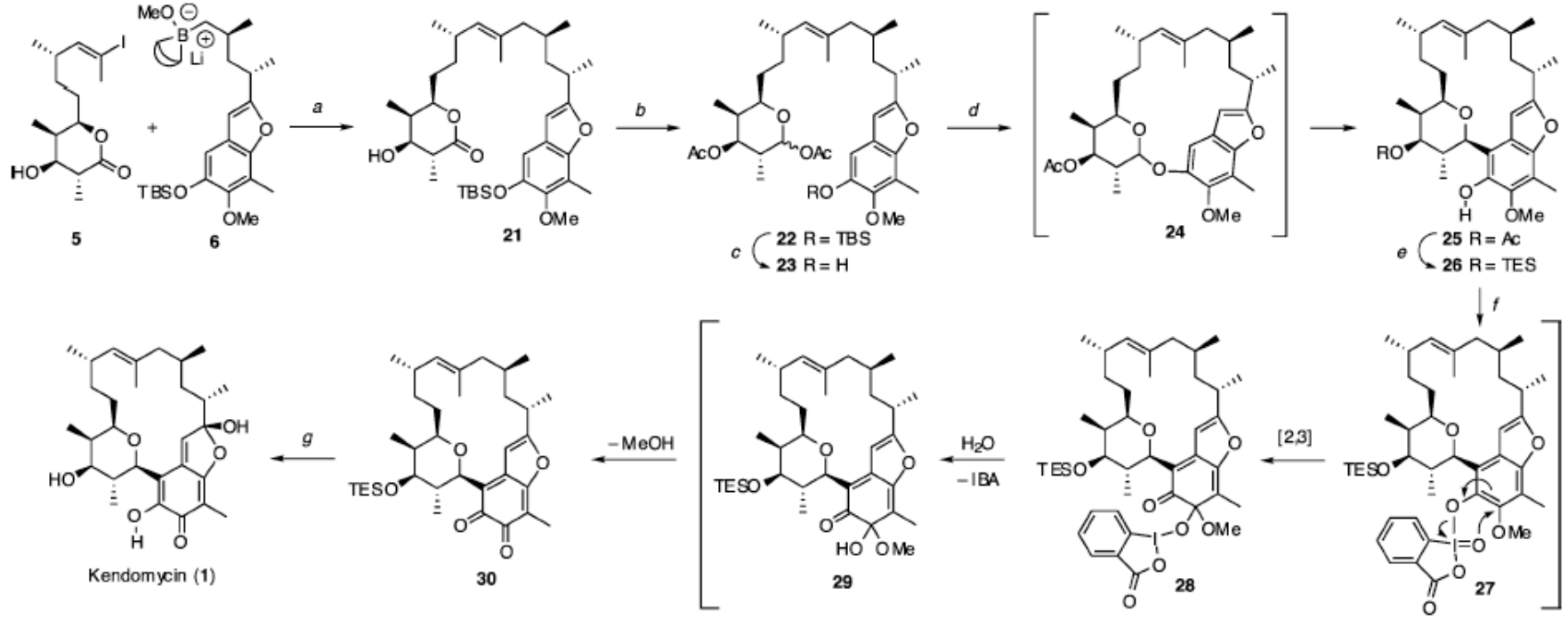
Scheme 3. Synthesis of the Benzofuran Domain[a]



[a] Reagents and conditions: (a) (i) TBSCl, imidazole, DCM, (ii) Dibal-H, DCM, −78 °C, 95%; (b) Ph_3P·HBr, CH_3CN, 78%; (c) DCC/DMAP, DCM, then TEA, toluene, reflux, 93%; (d) (i) 10 mol % Pd/C, H_2, EtOAc−CH_3OH, 99%, (ii) I_2/PPh_3, imidazole, DCM, 96%.

Suzuki Coupling of Fragments 5 and 6

Scheme 4. Suzuki–Miyaura Merger of the Key Fragments, Macroglycosidation, and Completion of the Total Synthesis of Kendomycin (**1**)[a]



[a] Reagents and conditions: (a) 4% $PdCl_2$(dppf), 3 M aq K_3PO_4, Et_2O–THF–DMF, 86%; (b) Dibal-H, toluene, then Ac_2O, pyridine, 79%; (c) TBAF, THF, 91%; (d) $SnCl_4$, 4 Å MS, $CHCl_3$, 40–70%; (e) (i) MeONa/MeOH, 87%, (ii) TESOTf, Et_3N, DCM, 98%; (f) IBX, DMF, 62% (g) aq HF, CH_3CN, 50%.