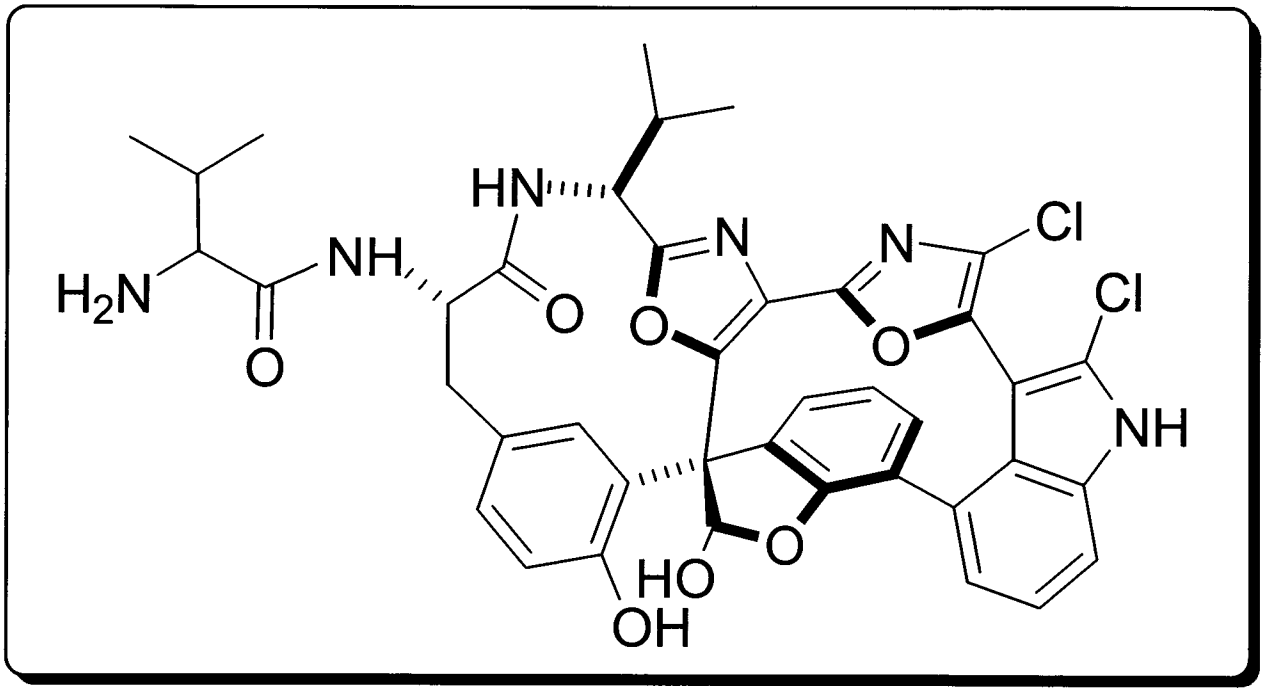
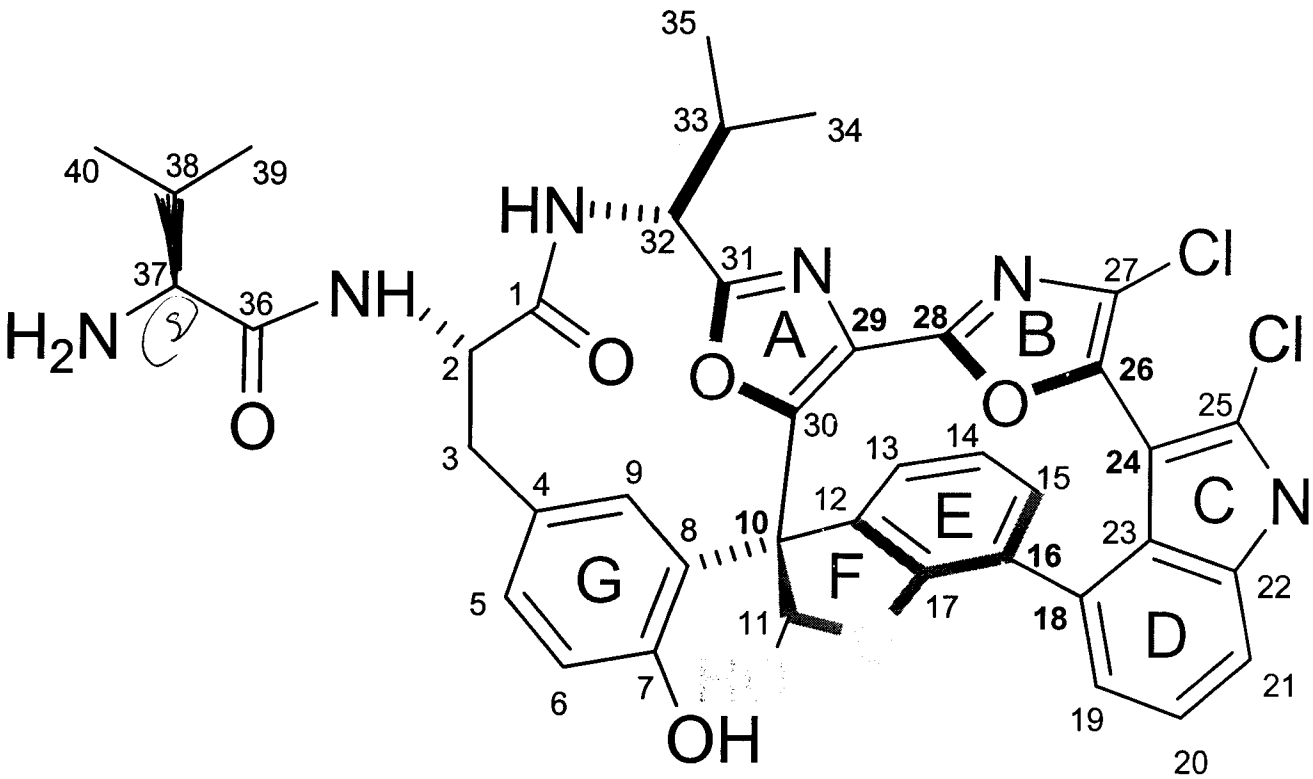
Ramzi F. Sweis
April 24, 2001

Advances in The Synthesis of Diazonamide A



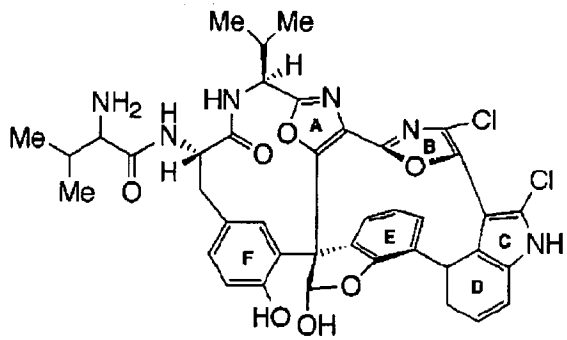
- Isolated in 1991 from Diazona chinensis collected from the ceilings of caves along the northwest coast of Siquijor Island in the Philippines
- Potent in vitro cytotoxicity to human colon carcinoma and B-16 murine melanoma cancer cells (IC_{50}<15 ng/mL)
- *"represents one of the most enticing natural products isolated in recent years and a serious challenge to synthetic chemists" K.C. Nicolaou*

Retro-synthetic Issues to address

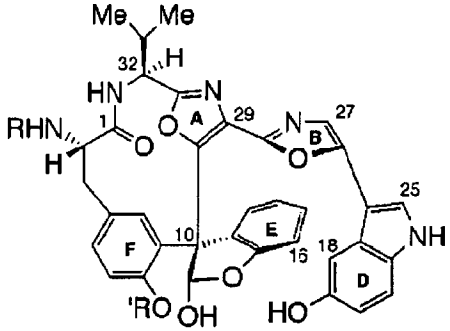


- C_{10} quaternary center
- Synthesis of E,F benzofuran
- Indole / bioxazole system
- 4 possible atropisomers (C_{16}-C_{18} and C_{24}-C_{29})

The Harran Approach



1 diazonamide A



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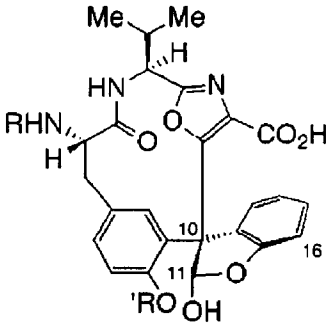
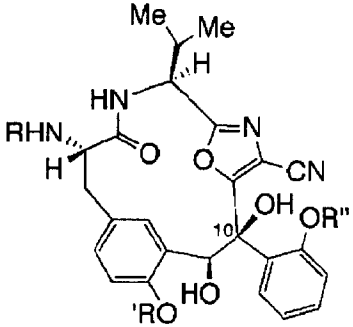


3

Ring contracting pinacol rearrangement



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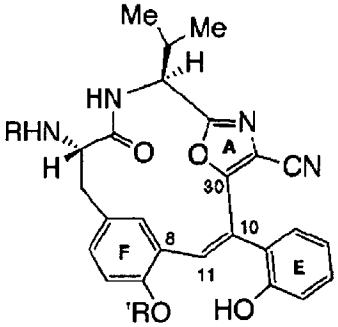
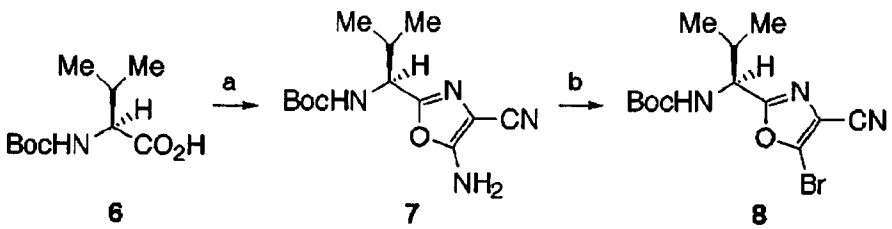
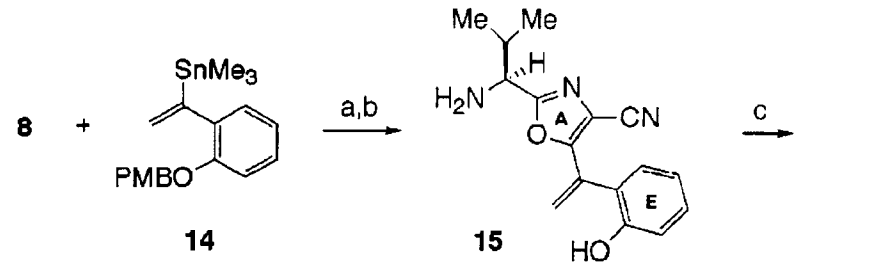


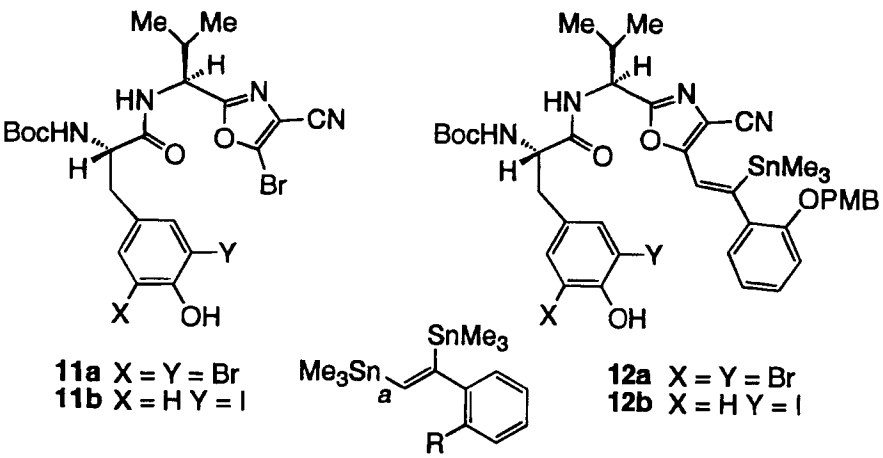
5

Heck Endocyclization



[a] a) aminomalononitrile *p*-toluenesulfonate, EDC, pyridine, rt (64%).
b) *t*-BuONO, $CuBr_2$, CH_3CN, 0°C (50-55%).



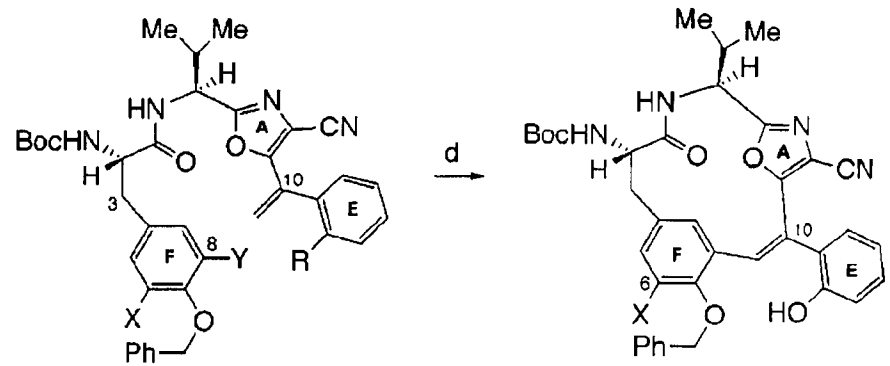


11a X = Y = Br
11b X = H Y = I

12a X = Y = Br
12b X = H Y = I

13a R = H
13b R = OMe
13c R = OPMB

Bromide couples before iodide giving wrong regiochemistry!



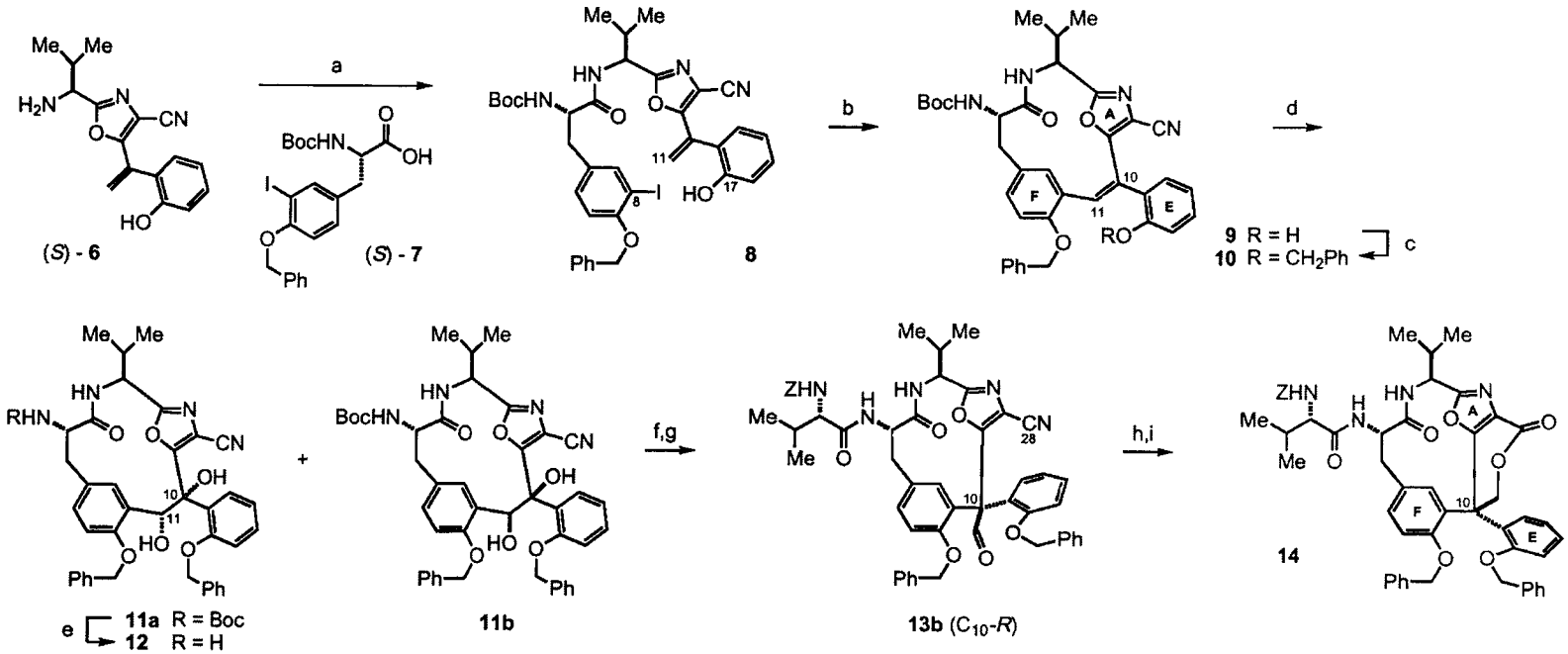
16a X = H Y = I R = H
16b X = H Y = I R = OH
16c X = H Y = I R = OMe
16d X = H Y = I R = OPMB
16e X = Y = Br R = OH
16f X = Y = Br R = OPMB

17a X = H
17b X = Br

[a] a) 2 mol % $PdCl_2(CH_3CN)_2$, DMF, rt (94%). b) 2.5 eq. BBr_3, CH_2Cl_2 -78°C (91%). c) **9b** or **10b**, TBTU, DIPEA, CH_3CN, rt (89% for **16b**, 86% for **16e**). d) 10 mol % $Pd_2(dba)_3$, Ag_3PO_4, THF, reflux, 11h (66% for **17a**, 41% for **17b** based on recovered **16e**).

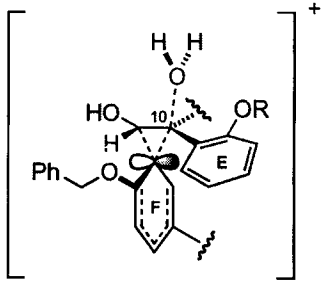
free phenol necessary for successful cyclization

Pinacol Ring-Contraction

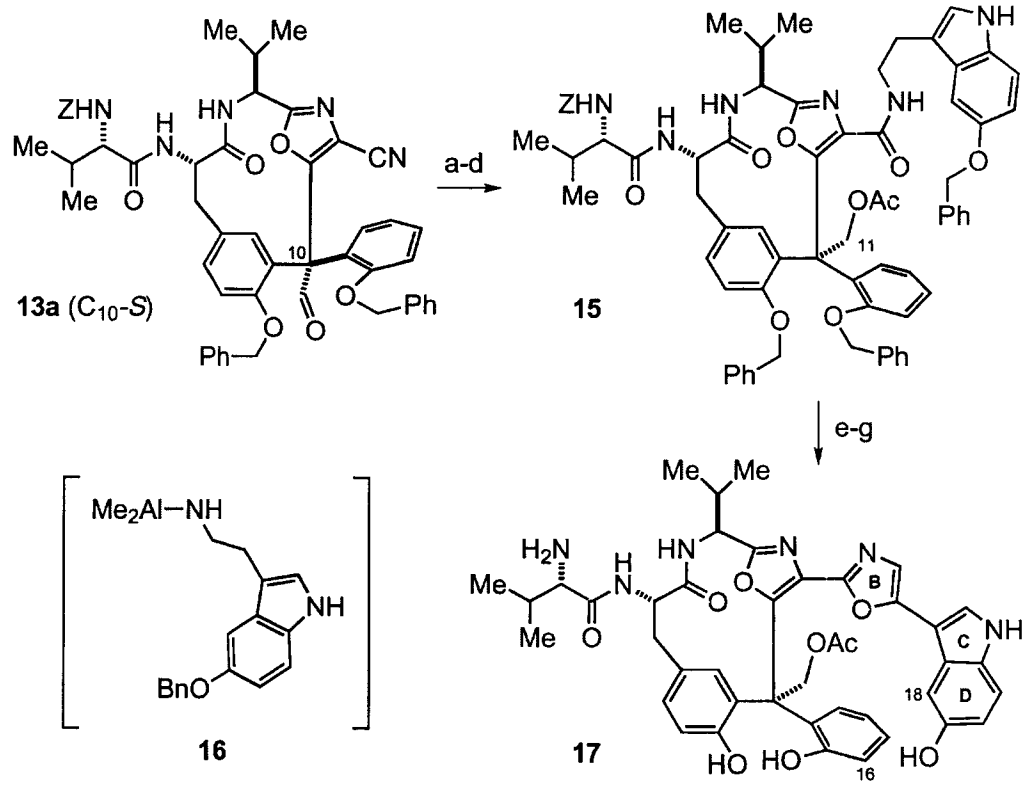


Scheme 2. a) TBTU, DIPEA, DMF, RT (89 %); b) $[Pd_2(dba)_3]$ (3 mol %), 2-(di-*tert*-butylphosphanyl)biphenyl (6 mol %), Ag_3PO_4, THF (0.025 M), 90 °C, 69 %, 82 % based on recovered **8**; c) DEAD, PPh_3, $PhCH_2OH$, THF, 97 %; d) 1. OsO_4, DMAP (2 equiv), *t*BuOH/H_2O, RT; 2. H_2S, THF, −50 °C, 57–60 %, **11a**:**11b** = 5:1; e) *p*TsOH (1 equiv), toluene, 95 °C, 1 h, 90 %; f) *p*TsOH (3.0 equiv), toluene, 95 °C, 2.2 h; g) *N*-Z-L-Val-OH, TBTU, DIPEA, DMF, 25 % from **11b**; h) $NaBH_4$, MeOH/THF, −10 °C, 82 %; i) (+)-10-camphorsulfonic acid (1 equiv), PhH, 45 °C, 24 h, 57 %.

*Obtained 5:1 selectivity of **11a:11b** (wrong major isomer since ring contraction occurs with inversion) at C_{10}*

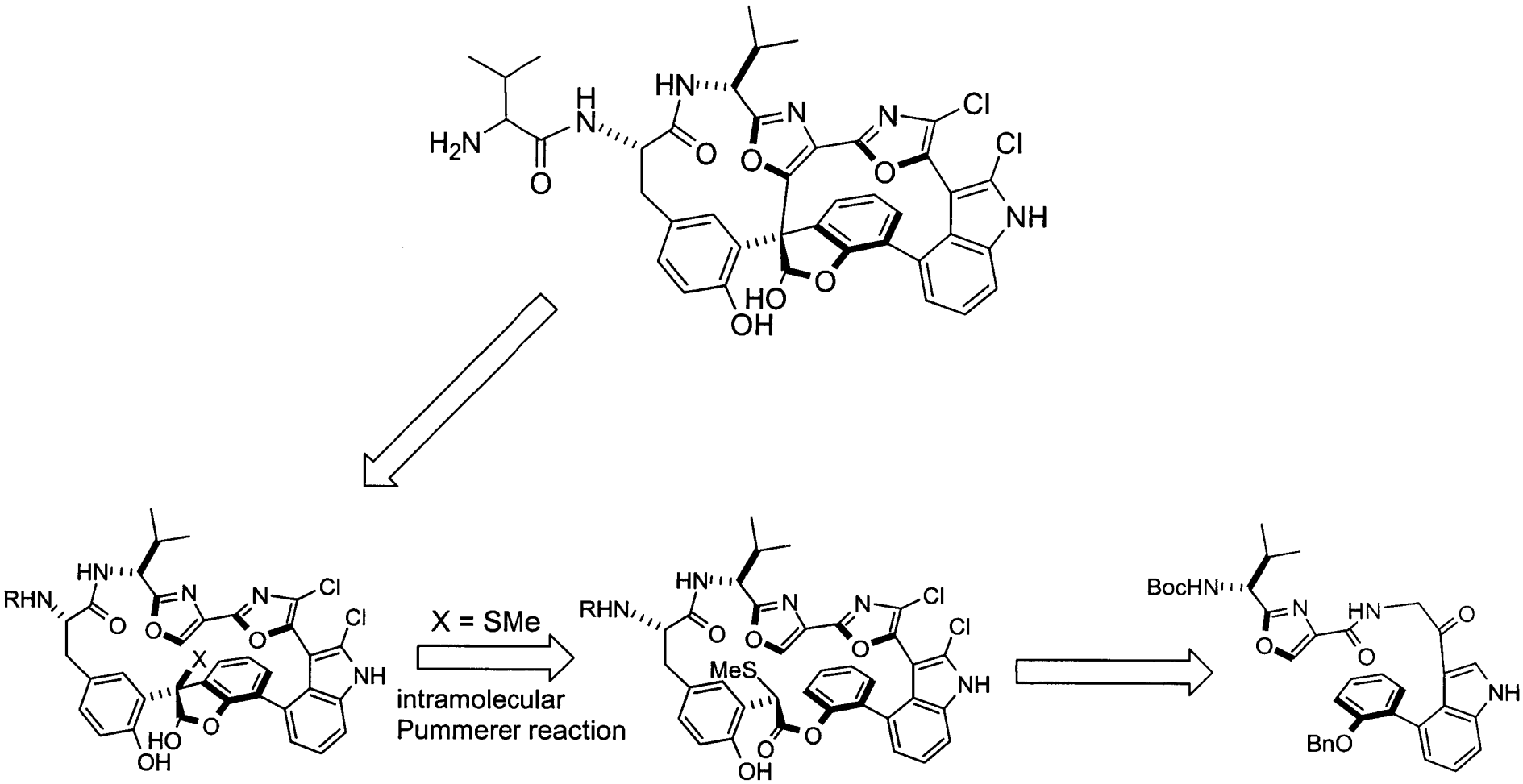


Final Serotonin Installation

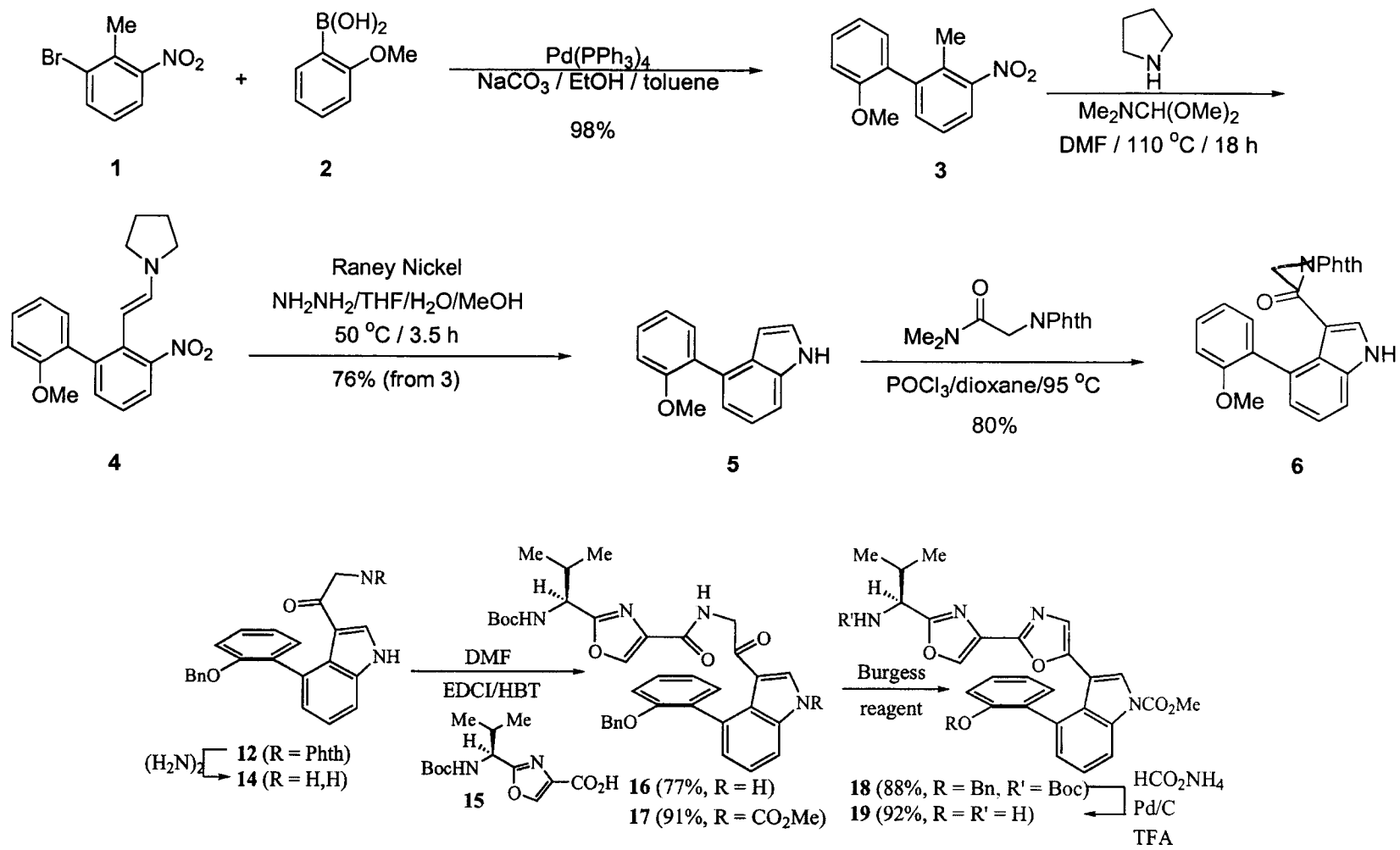


Scheme 3. a) $NaBH_4$, MeOH/THF, −10 °C, 85 %; b) (+)-10-camphorsulfonic acid (1.4 equiv), PhH, 60 °C, 6.5 h, 81 %; c) **16**, toluene/CH_2Cl_2, RT, 88 %; d) Ac_2O, pyridine, CH_2Cl_2, 0 °C, 95 %; e) DDQ, THF/H_2O, RT, 92 %; f) PPh_3, $(CCl_3)_2$, Et_3N, CH_2Cl_2, RT, 94 %; g) Pd/C (10 %), HCO_2H, Et_3N, MeOH/H_2O, RT, 90 %.

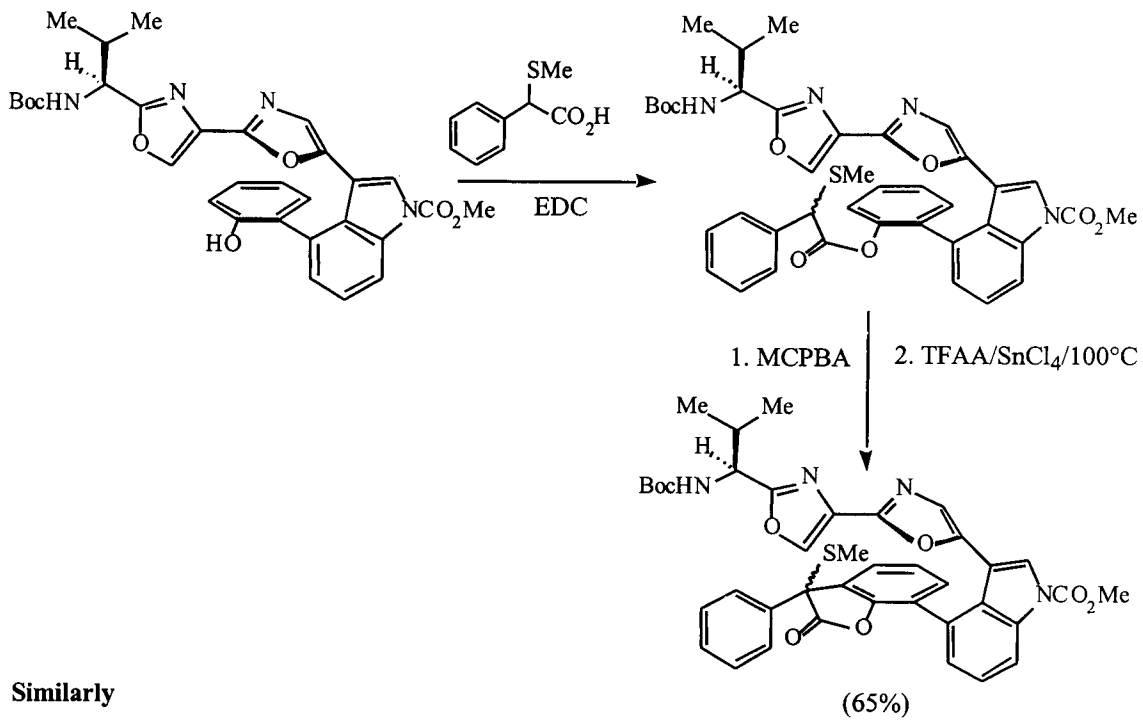
The Magnus Approach



Indole / Bisoxazole Synthesis

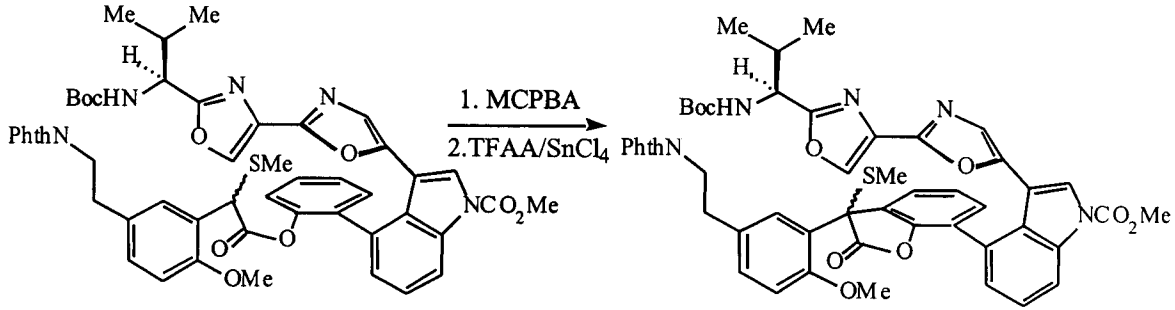


Pummerer Reaction to Form Benzofuranone



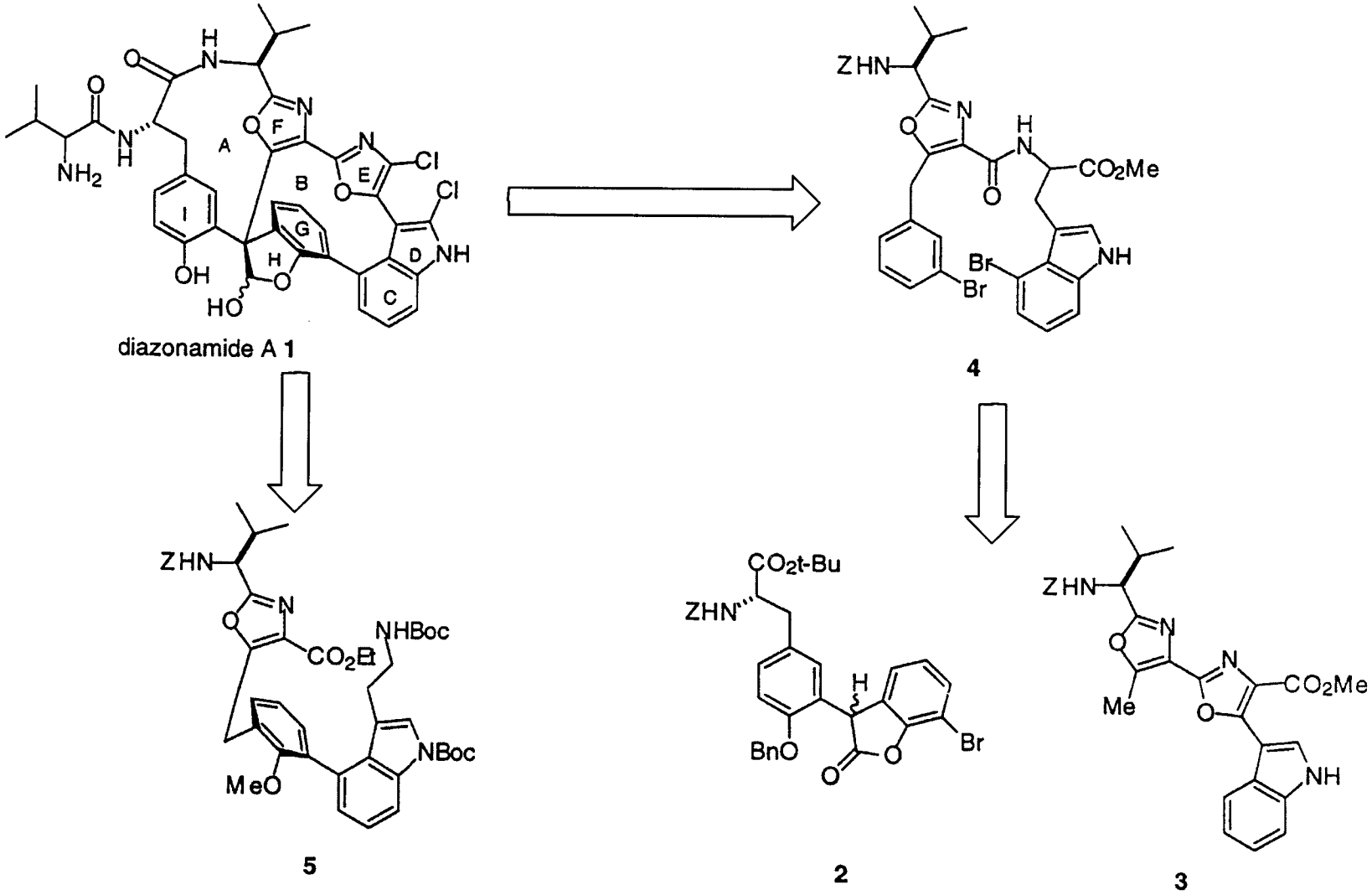
(65%)

Similarly

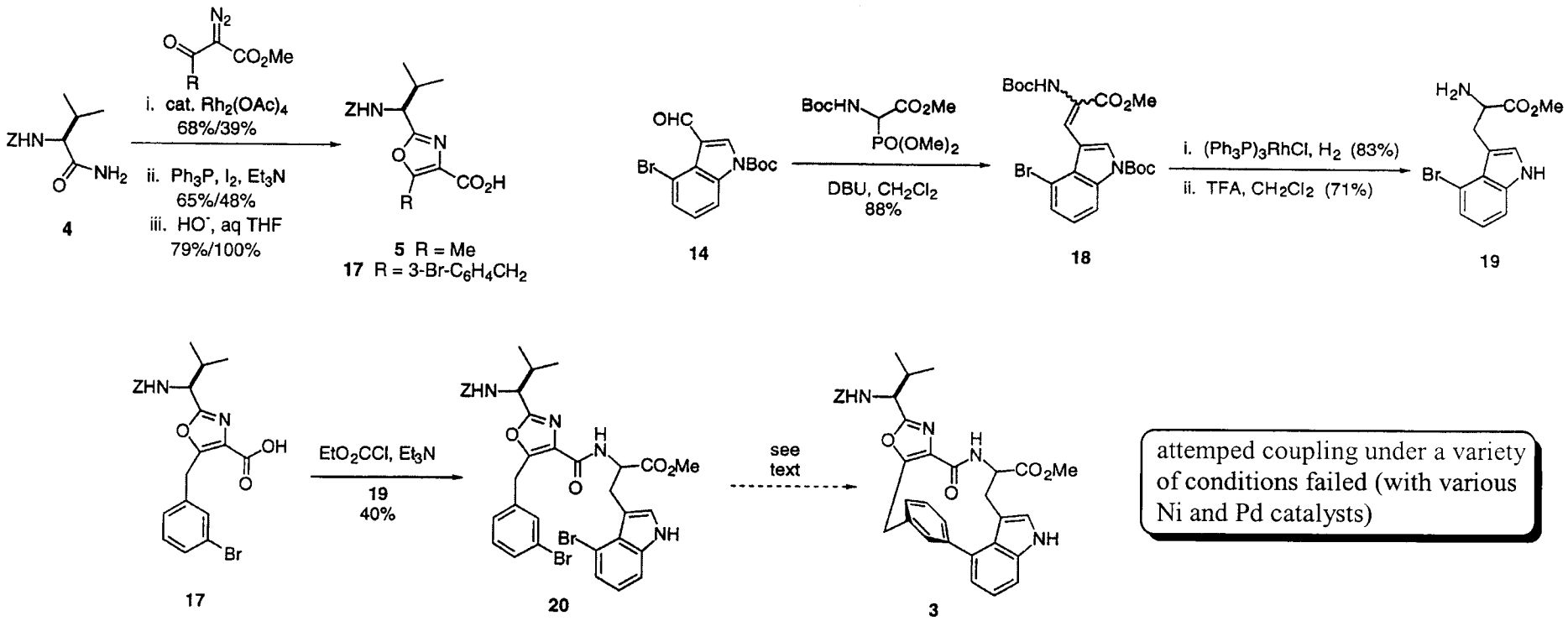


(45%)

The Moody Approach

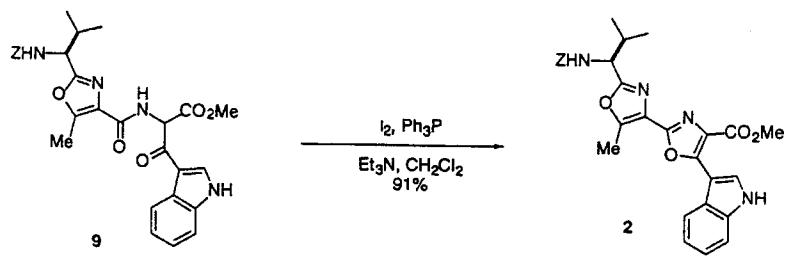


The Intramolecular Biaryl Coupling

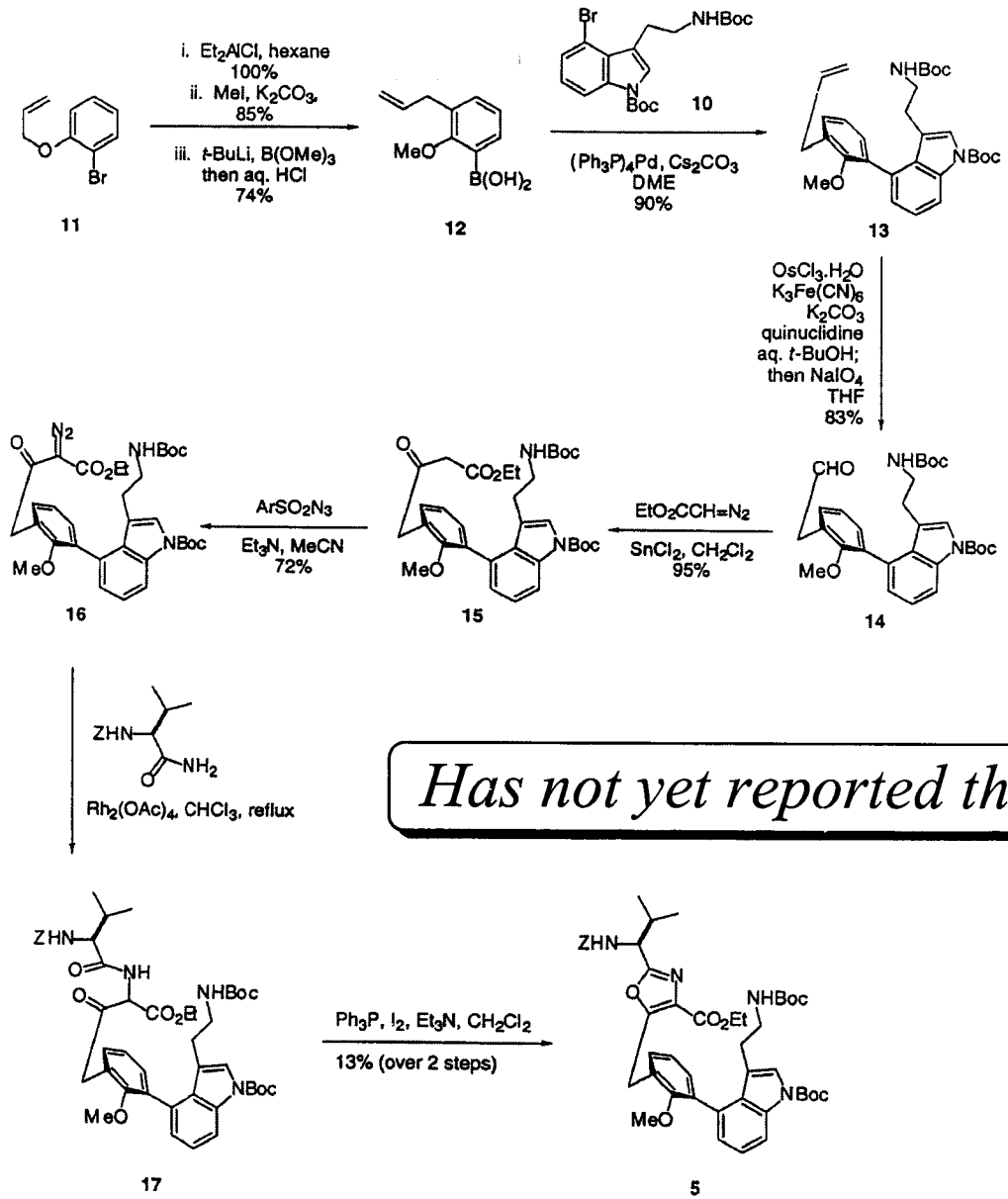


attemped coupling under a variety of conditions failed (with various Ni and Pd catalysts)

Bisoxazole made by:

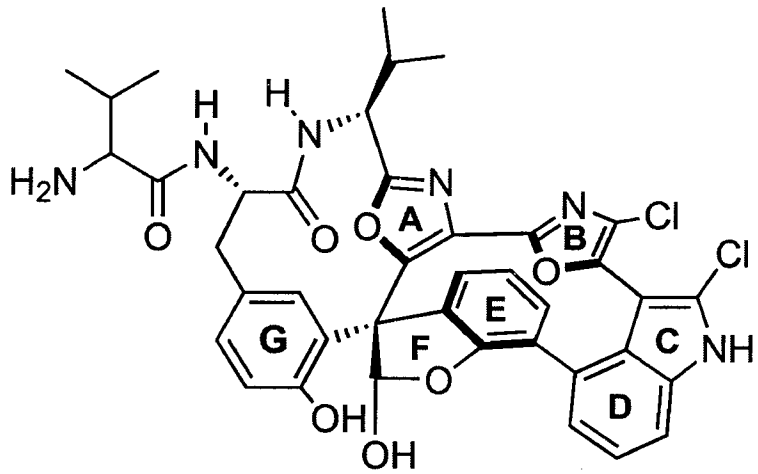


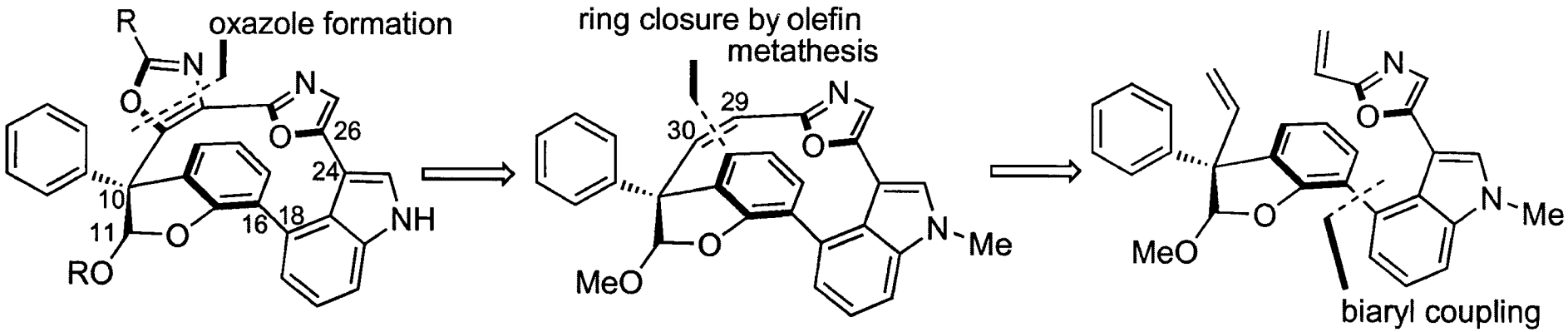
Intermolecular Biaryl Coupling



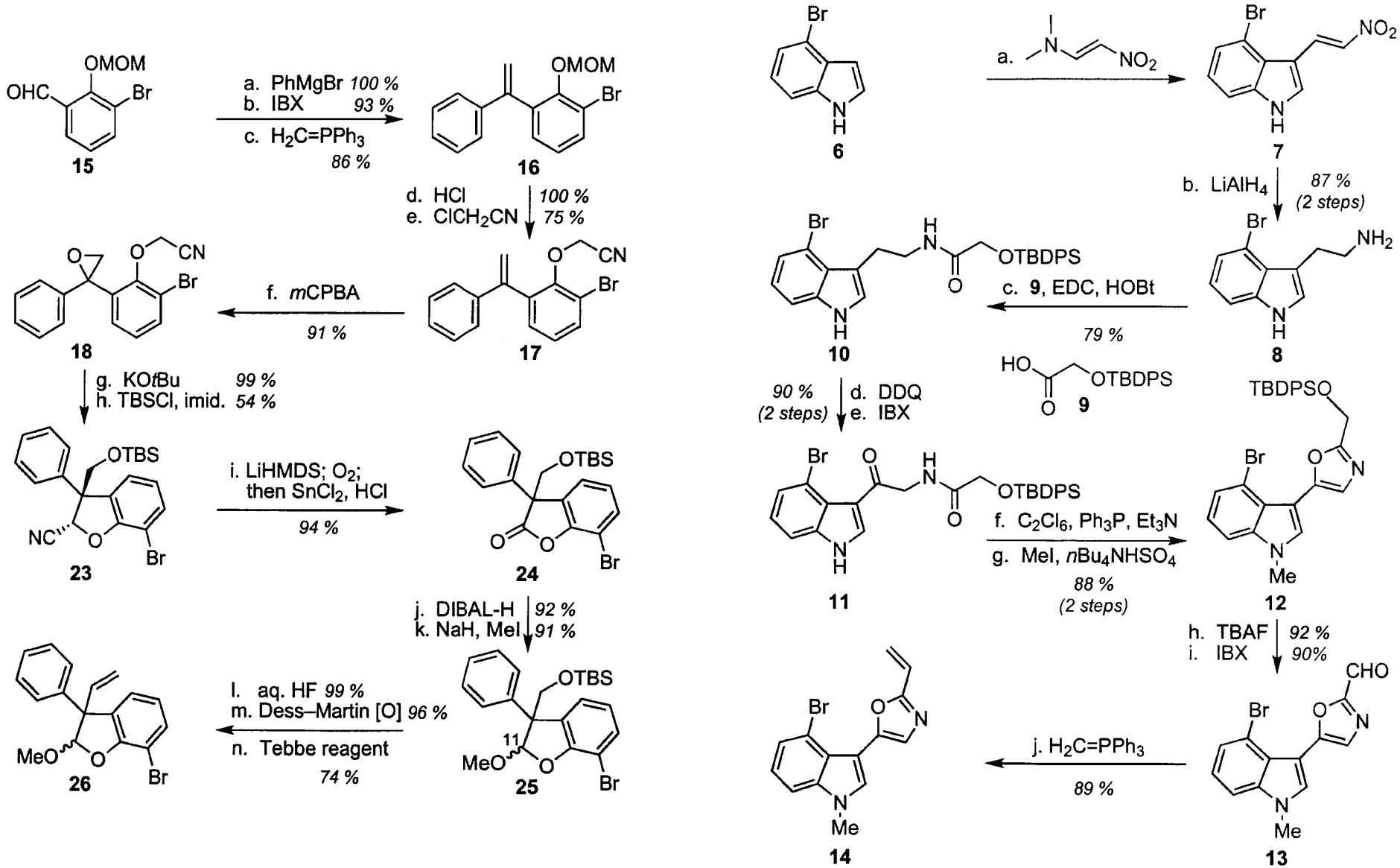
Has not yet reported the cyclization

The Nicolaou Approach

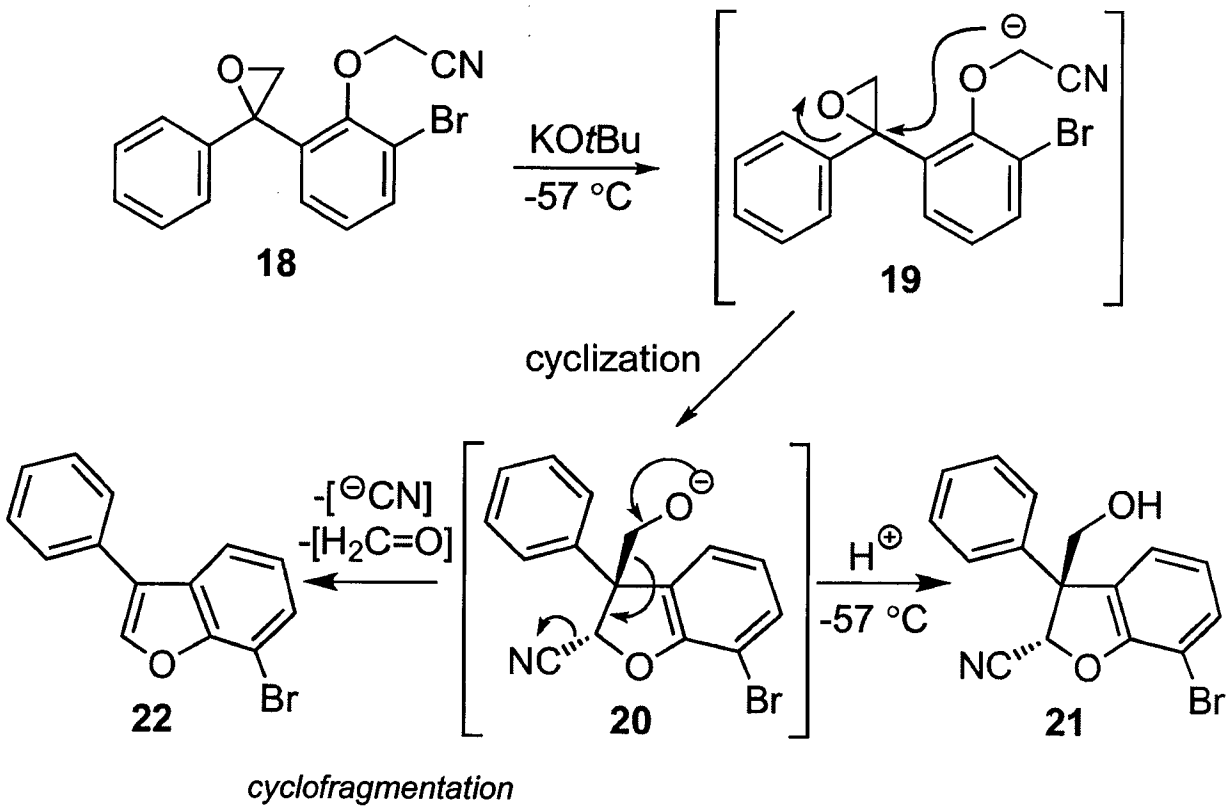




Synthesis of Biaryl Coupling Partners

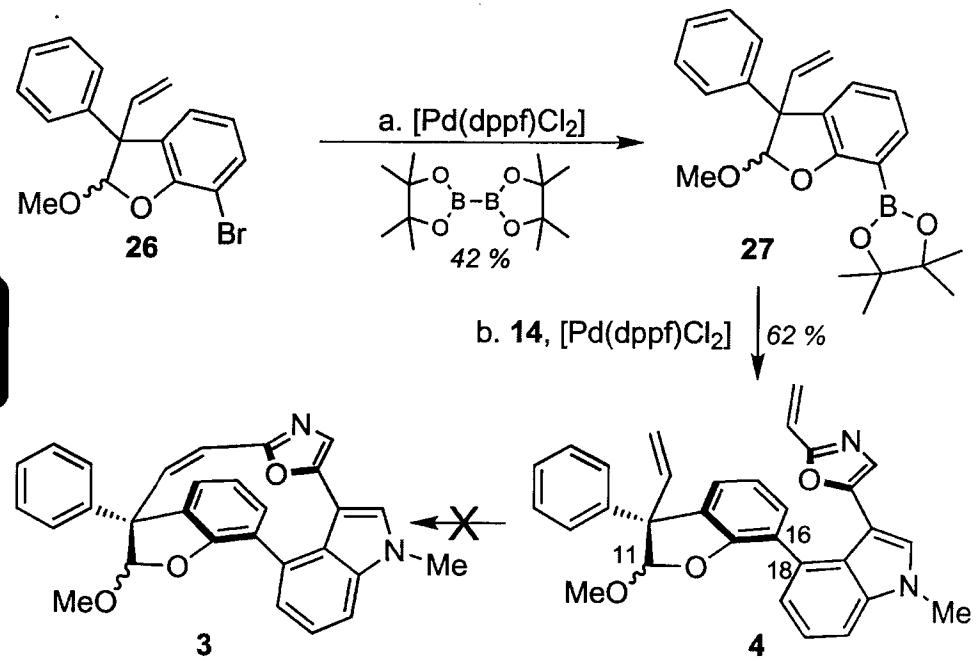


Cyclization / Epoxide Opening Reaction



Side product 22 is also predominant if Wittig is used instead of Tebbe

Final Biaryl Coupling and RCM

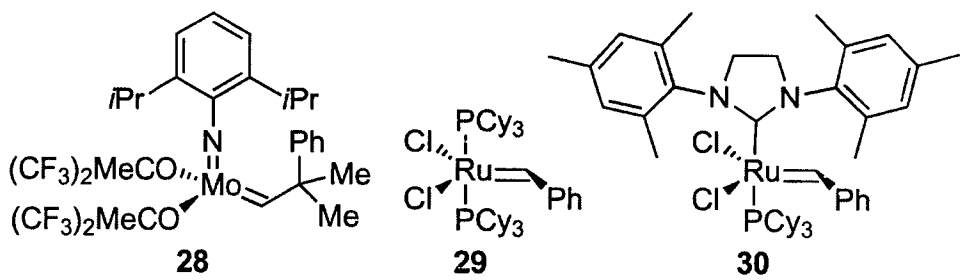


Efforts to prepare the boronic acid of either 14 or 26 failed with nBuLi, $B(OMe)_3$

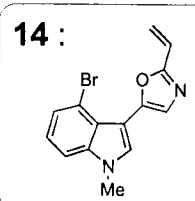
15 mol % Pd used, in DME, 85 °C, 2h

only recovered starting material or decomposition observed for RCM attempts

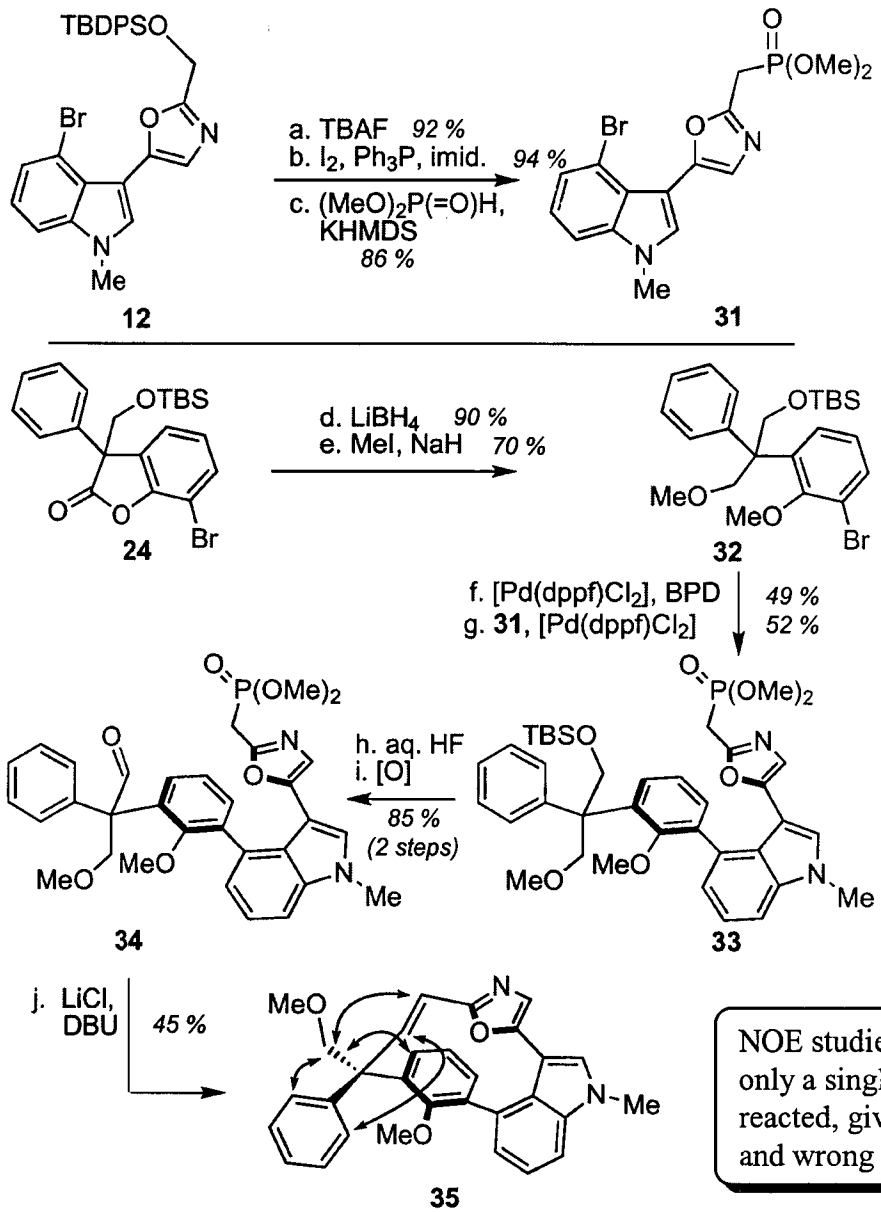
4 was a mixture of four diastereomers : two C_{11} epimers and two atropisomers (C16-C18)



14 :



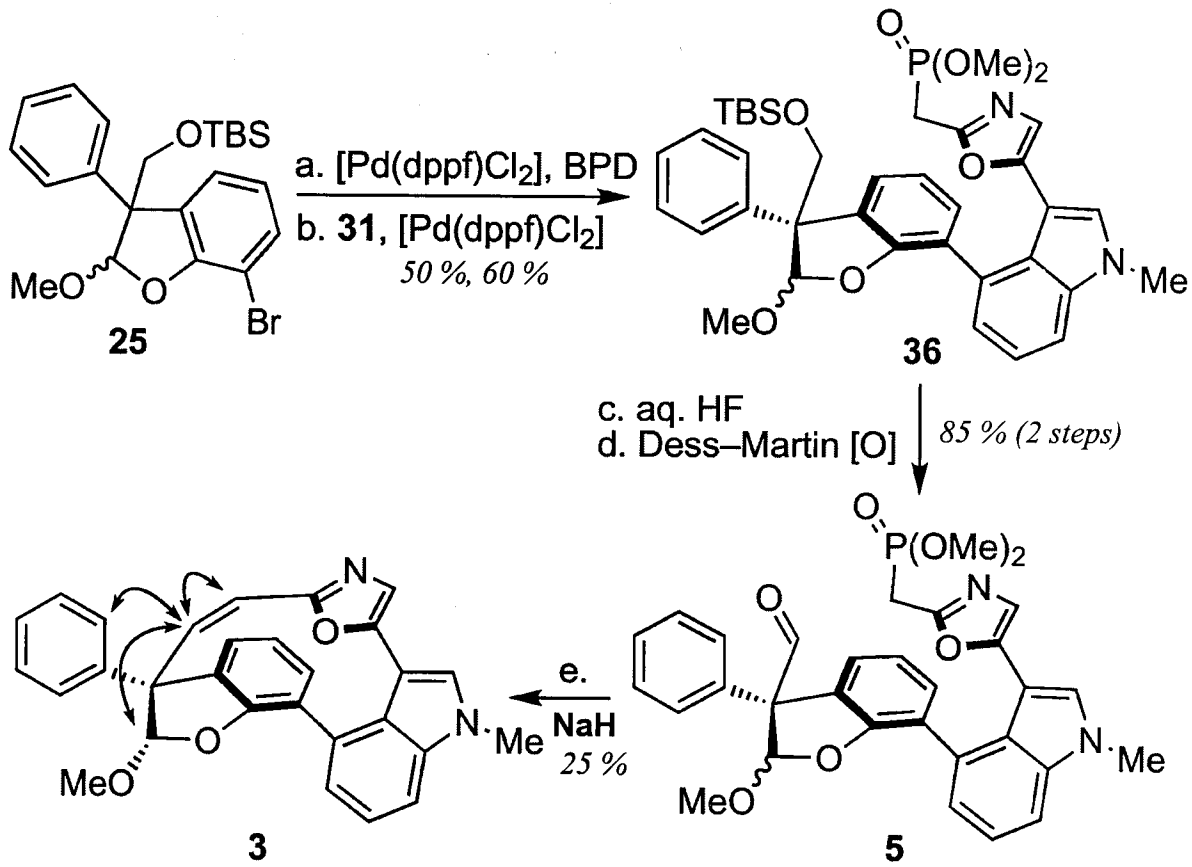
Back to More Traditional Olefinations

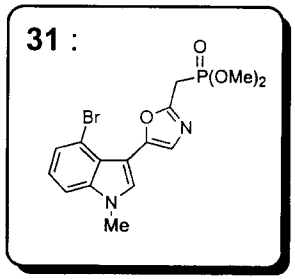


Lactone opened first due to the previous cyclofragmentation when Wittig (with CH_2PPh_3) was tried (assumed same with HWE).

NOE studies showed that only a single isomer of **34** reacted, giving trans olefin and wrong C_{10} config.

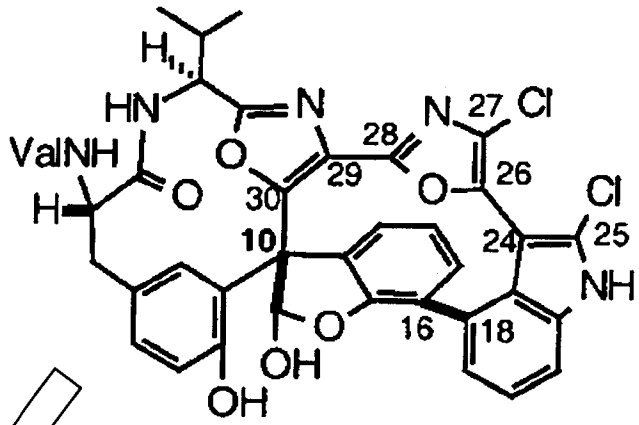
An Educated Assumption is Still an Assumption

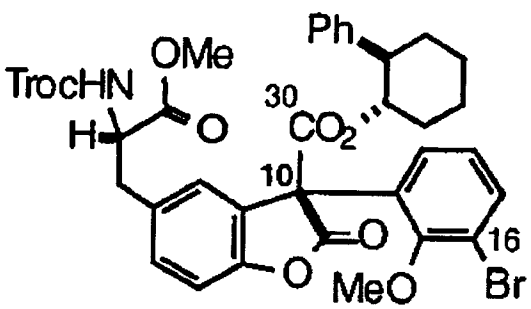




- even though **36** and **5** were a mixture of 4 diastereomers, **3** was only one
- first complete synthesis of the heterocyclic core
- multigram quantities of **25** and **31** have been made

The Vedejs Approach





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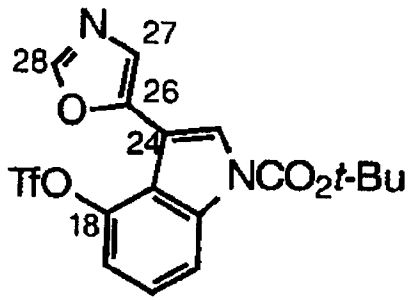
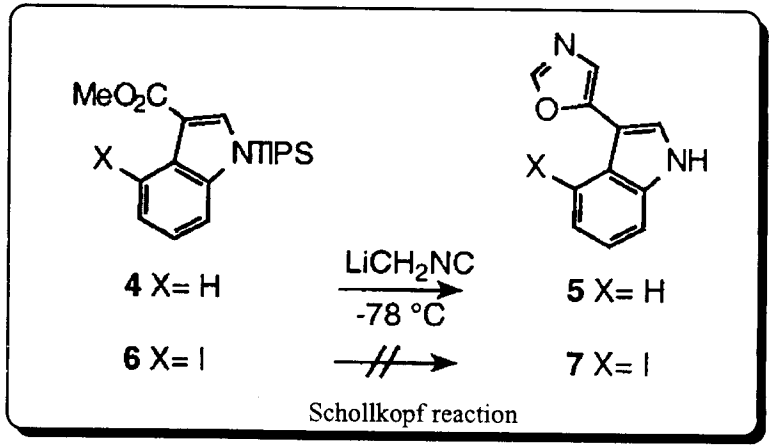
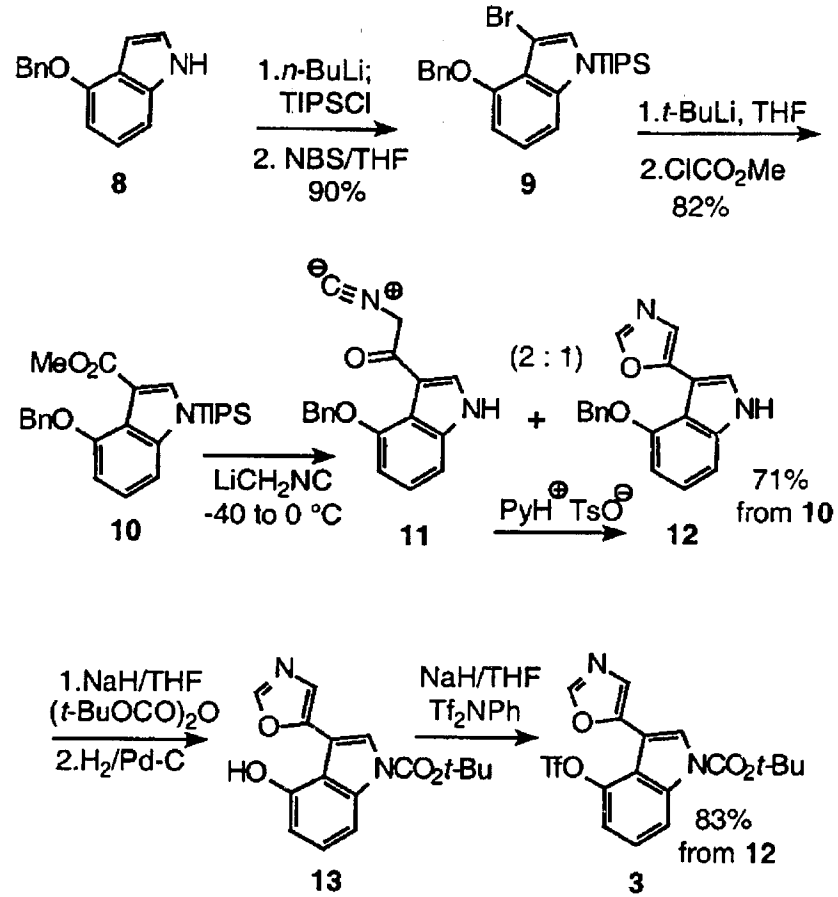


3

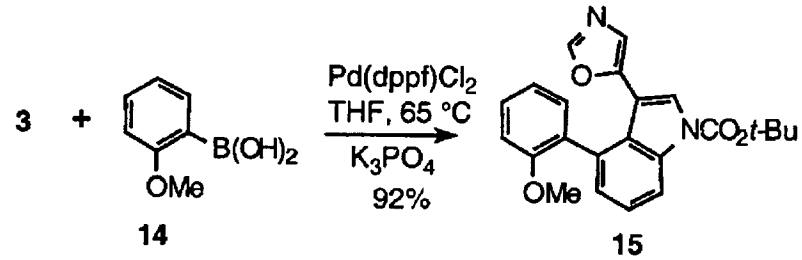
Reason for using triflate:



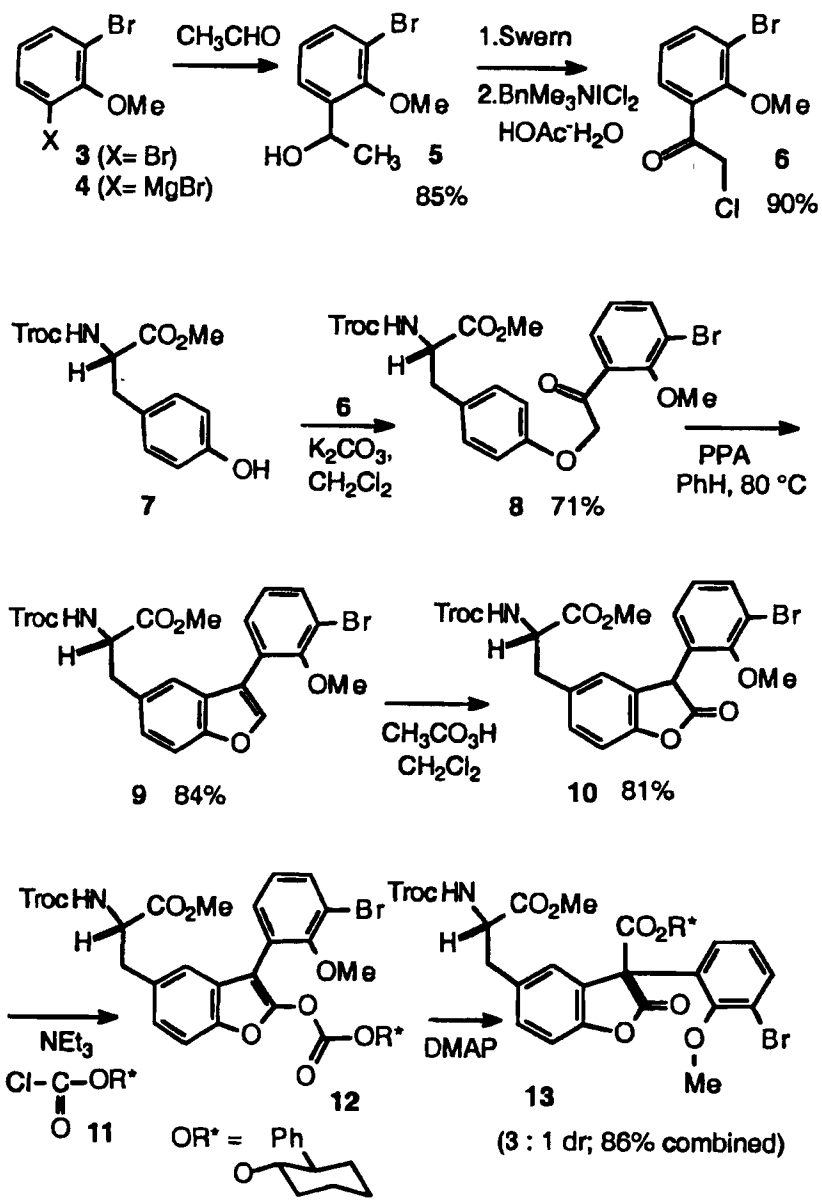
Preparation of the Indole Triflate



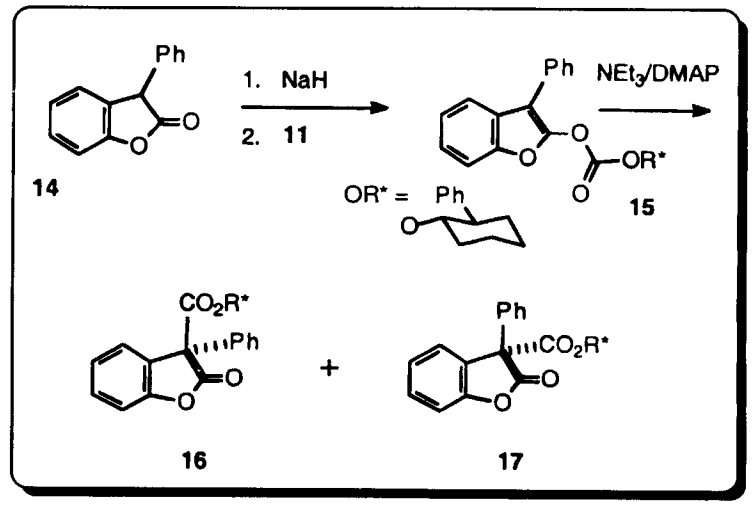
Feasibility test of indole cross-coupling



Preparation of Benzofuranone

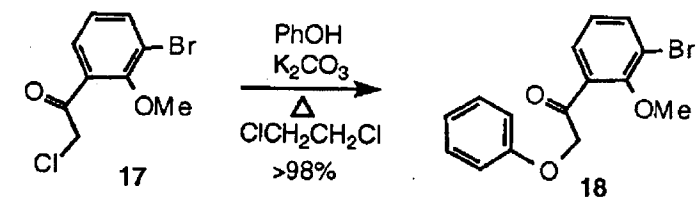


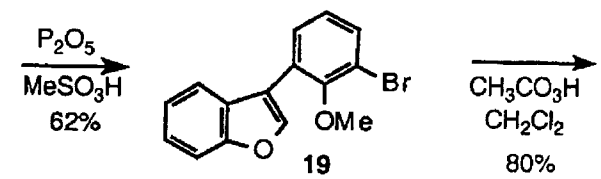
model study to determine C_{10} configuration:



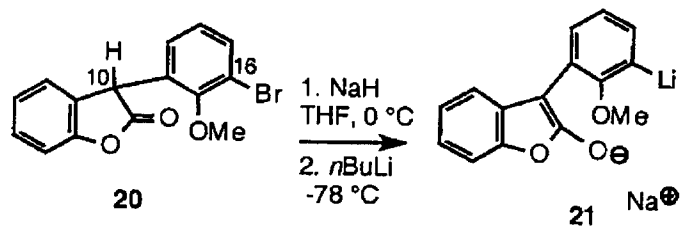
- key rearrangment faster than with **12** (2 min vs. hours)
- 8:1 selectivity of **16:17** (major assigned by X-ray crystallography)
- **13** was assigned major based on C_{10} configuration of **16**.

Biaryl Coupling of Indole and Benzofuranone

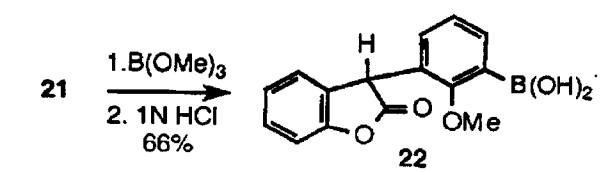


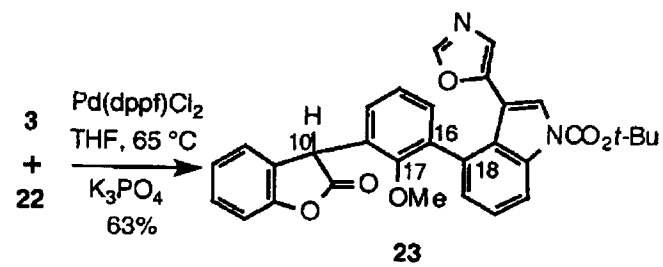


lactone carbonyl protected as enolate before installation of boronic acid



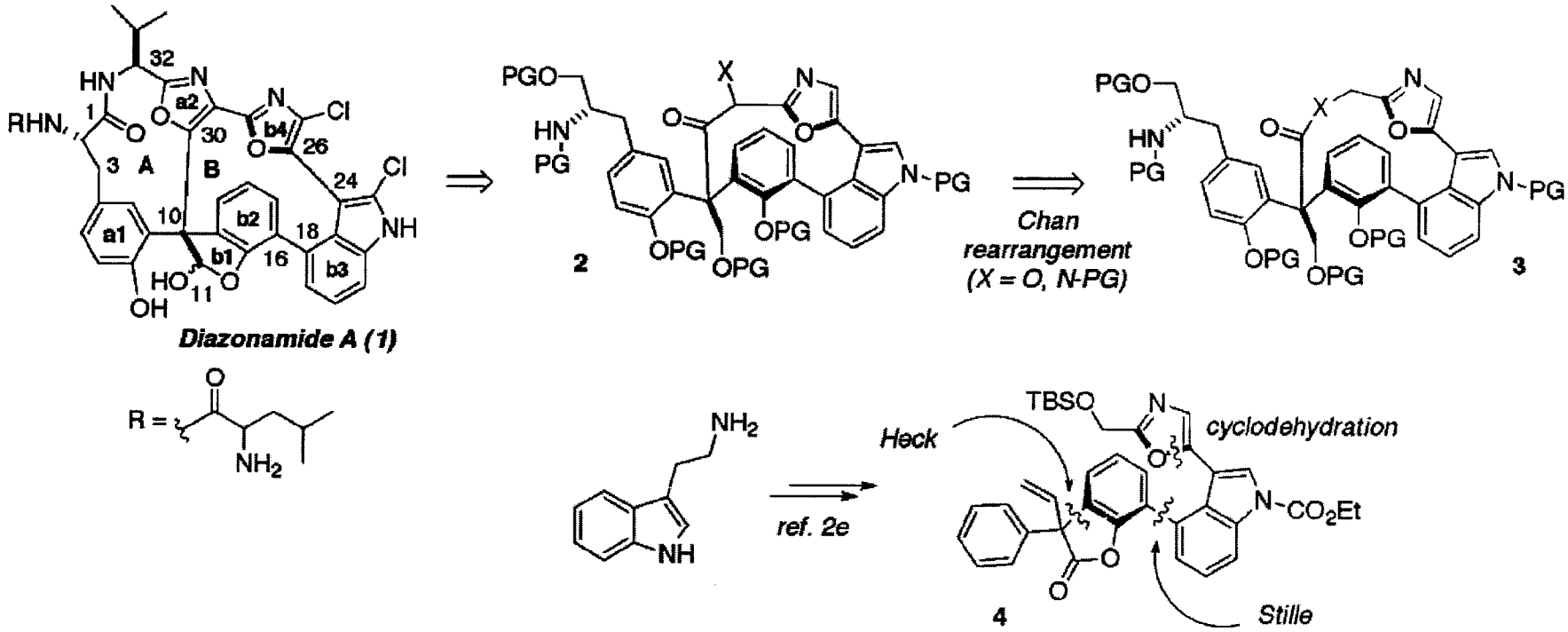
incorporation of C_{10} carboxyl group *after* installation of boronic acid





two signals observed for C_{17} methoxy group, C_{10} methine, and several aromatic H's. The two isomeric structures correspond to atropisomers of C_{16}-C_{18} bond. (coalescence seen at 105 °C and 115 °C for methine and methoxy signals)

The Wipf Approach



The Stille / Asymmetric Heck Sequence

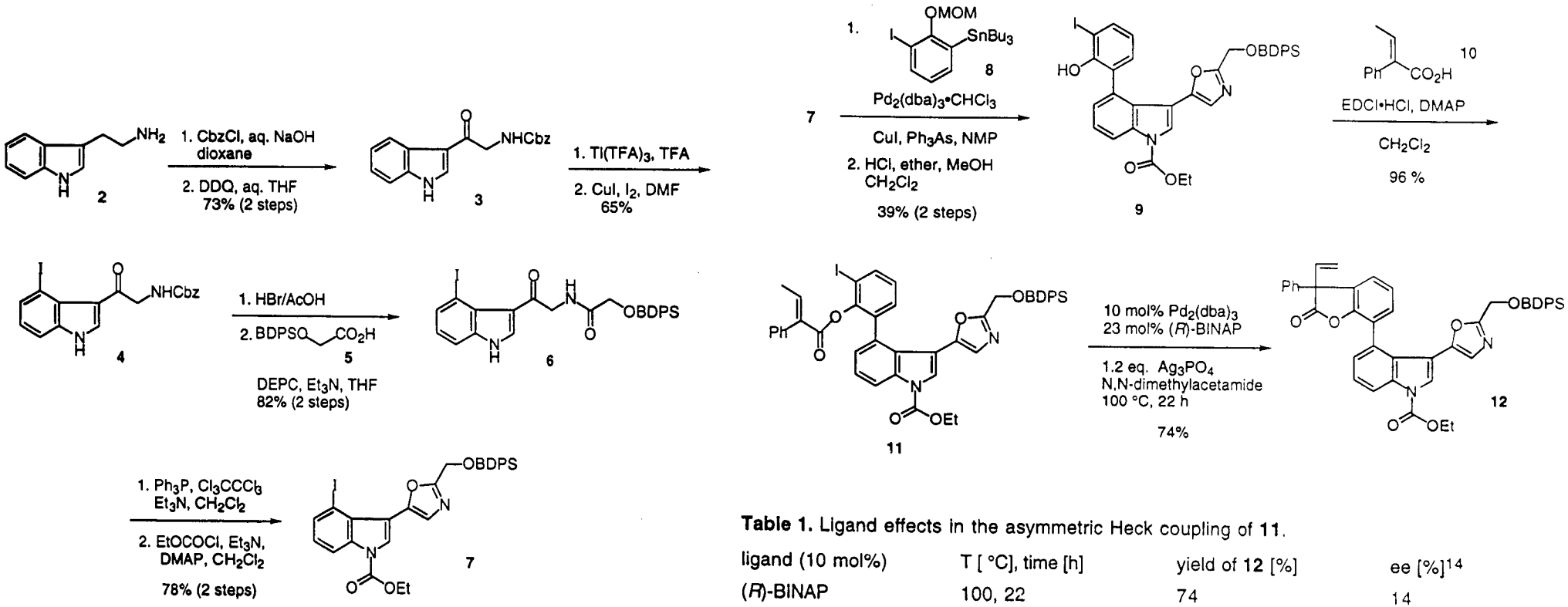
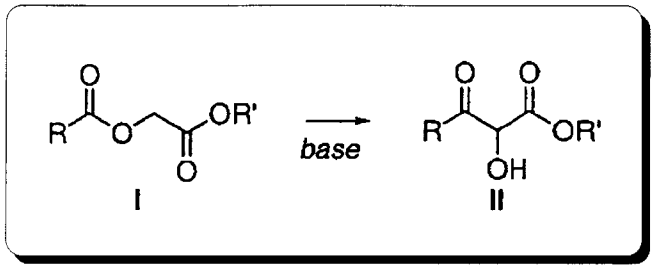


Table 1. Ligand effects in the asymmetric Heck coupling of **11**.

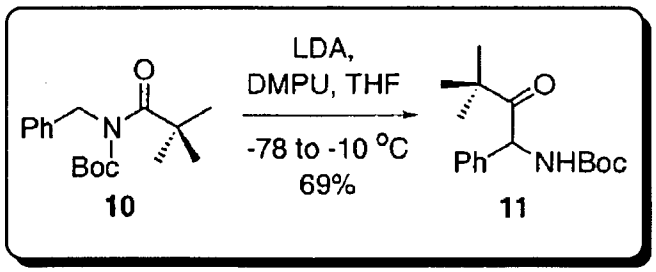
ligand (10 mol%)	T [°C], time [h]	yield of **12** [%]	ee [%][14]
(*R*)-BINAP	100, 22	74	14
(*R*)-BINAP	80, 59	47	19
(*R*)-Tol-BINAP	100, 21	67	19
(*R,R*)-DIOP	100, 21	27	16
(*R,S*)-BPPFA	100, 19	42	3
Cl_2Pd-(*R*)-BINAP	100, 14	72	12
(*S*)-BINAs	100, 20	19	3

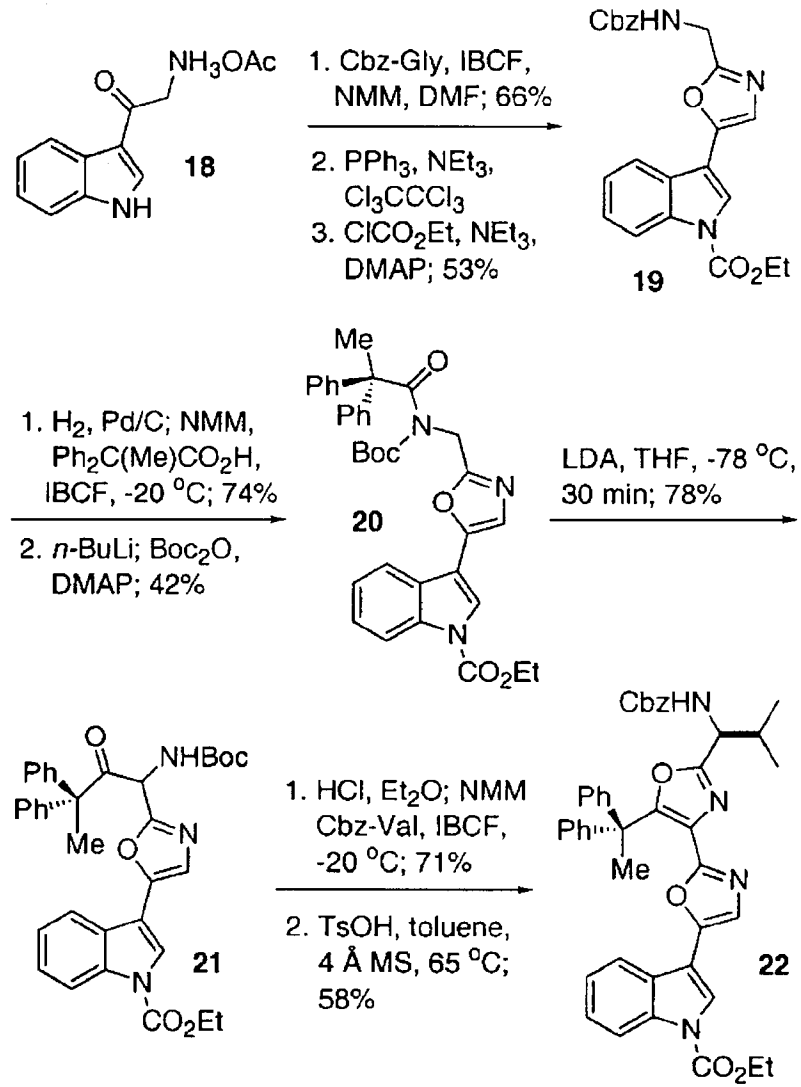
Synthesis of the Bisoxazole via the Chan Reaction

original Chan reaction:



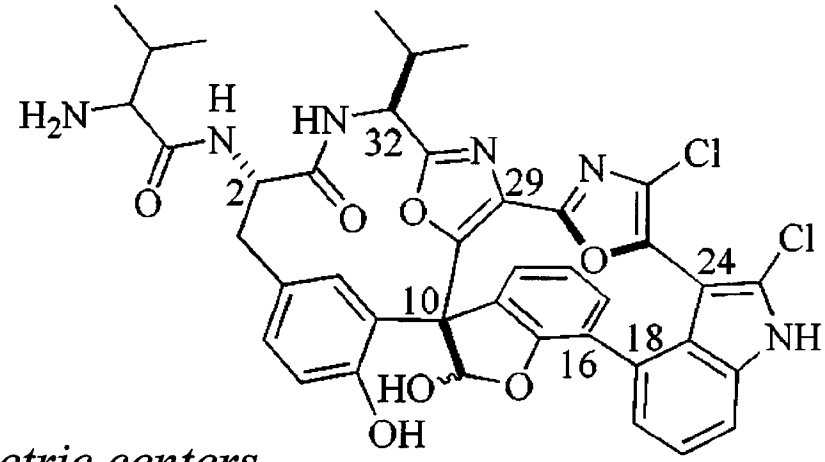
model for benzyl migration in amide:





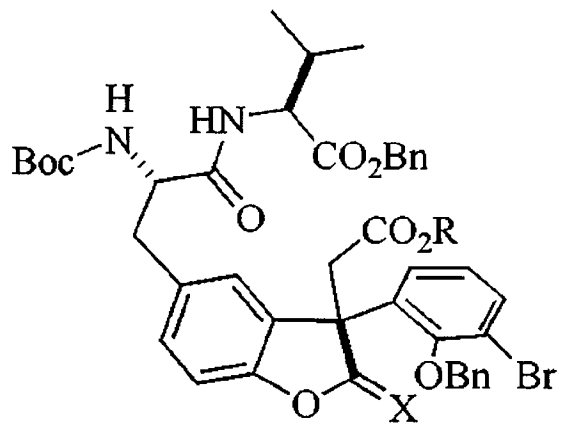
22 produced in >90% enantiomeric purity

The Wood Approach



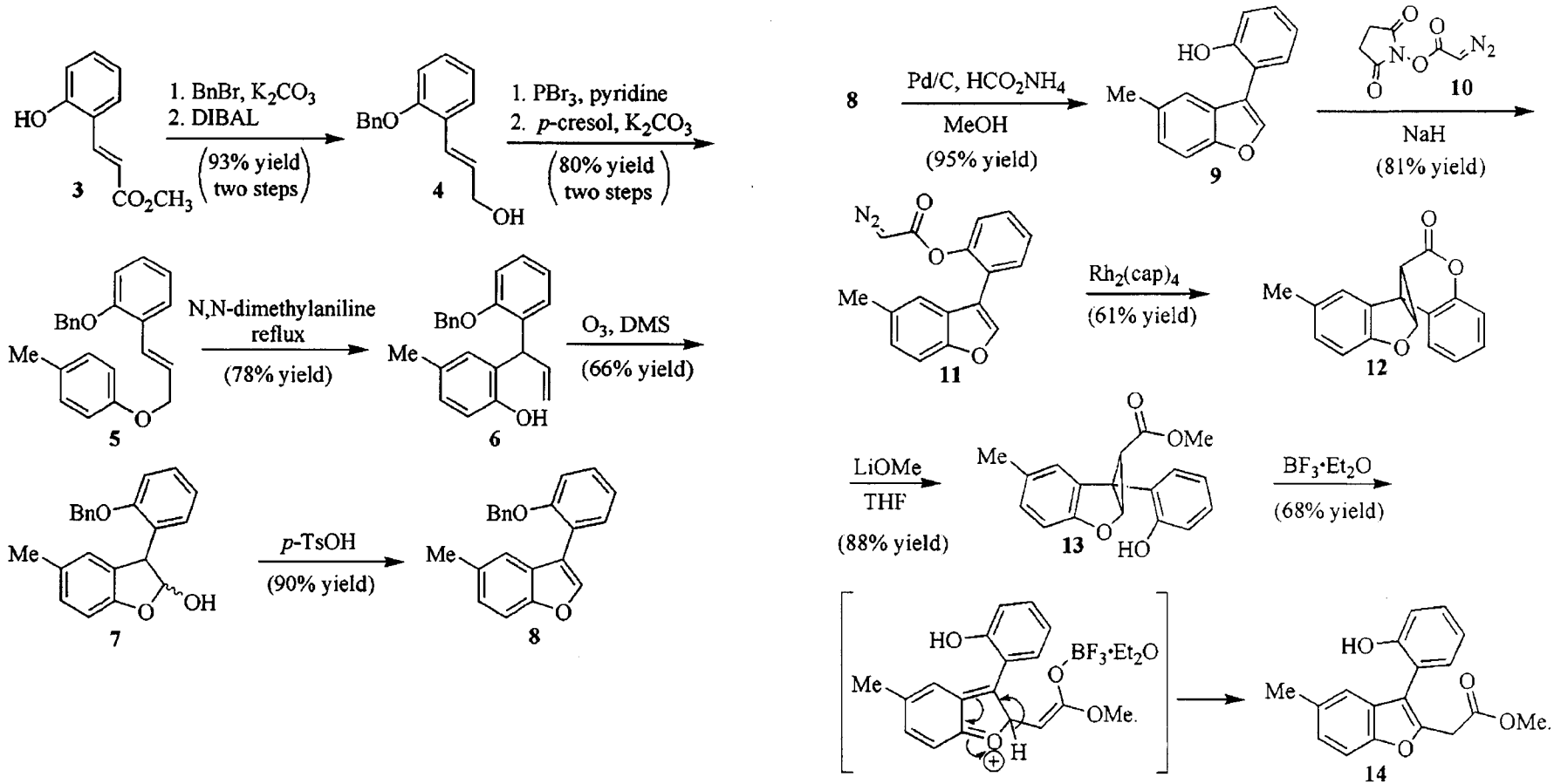
1, Diazonamide A

employ the three asymmetric centers, C_{32}, C_2, and C_{10},,on the left macrocycle to set the axial chirality on right side.



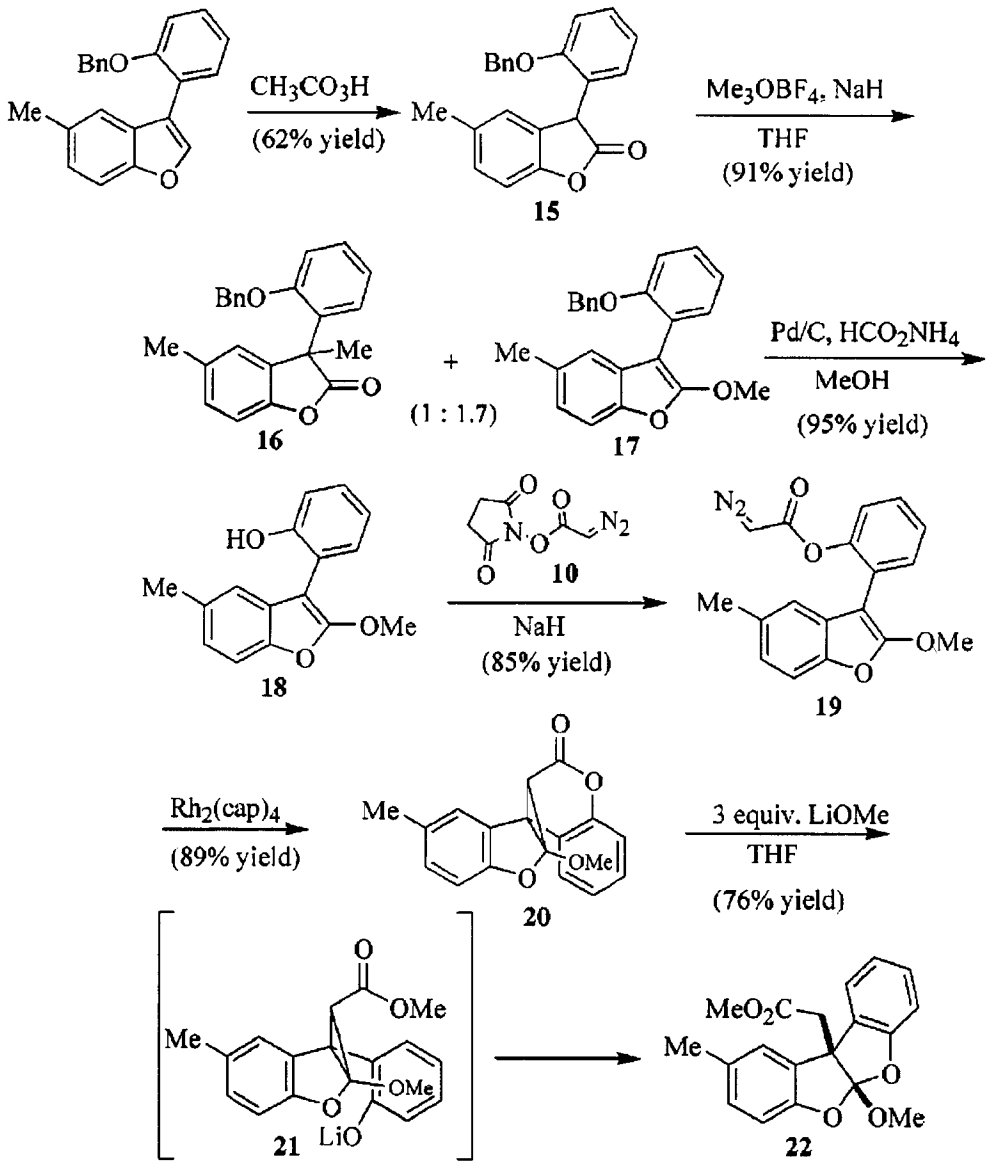
2a: X = OH, H
2b: X = O

Cyclopropanation / Ring Opening to set C(10)



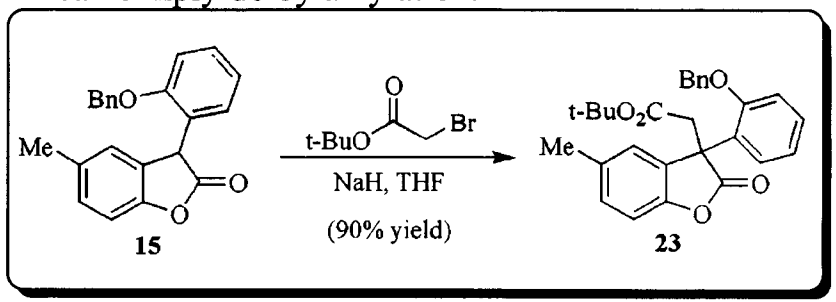
unfortunately, wrong cyclopropane bond was cleaved!

Scission of the Correct Cyclopropane Bond

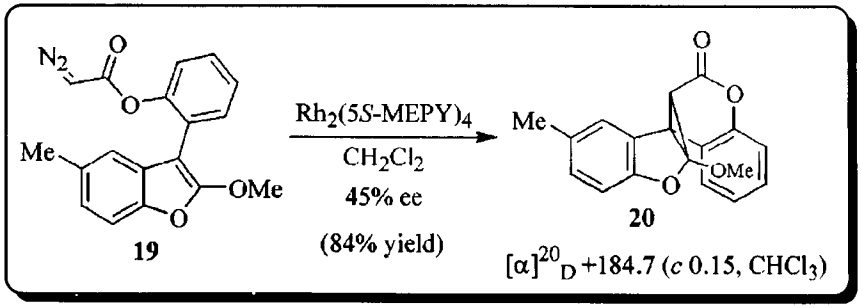


use of an alkoxy group at C_2 of benzofuran to directring opening

Since C_2 alkoxy is necessary, can simply do by alkylation:



Asymmetric cyclopropanation



"Whereas the alkylation approach is ideally suited for the advancement of material, the cyclopropanation / ring opening sequence provides a means of introducing asymmetry"

Who has the Best Approach?

Investigator	Pros	Cons
Harran	ring contracting pinacol rearrangment can set C_{10} config.	orthophenolic coupling does not work, substrate favors wrong isomer for osmylation
Magnus	high yield for biaryl coupling before indole synthesis Pummerer reaction for benzofuranone	has not addressed oxazole-benzofuran linkage or setting C_{10} config.
Moody	Rhodium carbenoid NH insertion to make oxazoles, addressed synthesis of all fragments	has not been able to construct macrocycle, intramolecular biaryl coupling fails
Nicolaou	only one to construct the macrocyclic heterocycle, novel epoxide opening to make benzofuran	many low yielding steps late, has yet to address polyoxazole synthesis
Vedejs	key asymmetric rearrangement to set C_{10} config., first successful coupling of hindered 4-trifloxyindole	modest 3:1 selectivity for C_{10} isomers, bisoaxazole synthesis to form macrocycle not yet addressed
Wipf	asymmetric Heck to set C_{10}, Chan reaction to make bisoxazole	low ee's with asymmetric Heck, Chan reaction on macrocycle not addressed
Wood	Use of asymmetric cyclopropanation nice way to set C_{10} config.	Has yet to report on approaches to the heterocyclic rings in the molecule

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