VIP Natural Product Synthesis

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An Efficient Formal Synthesis of the Human Telomerase Inhibitor (±)-γ-Rubromycin**

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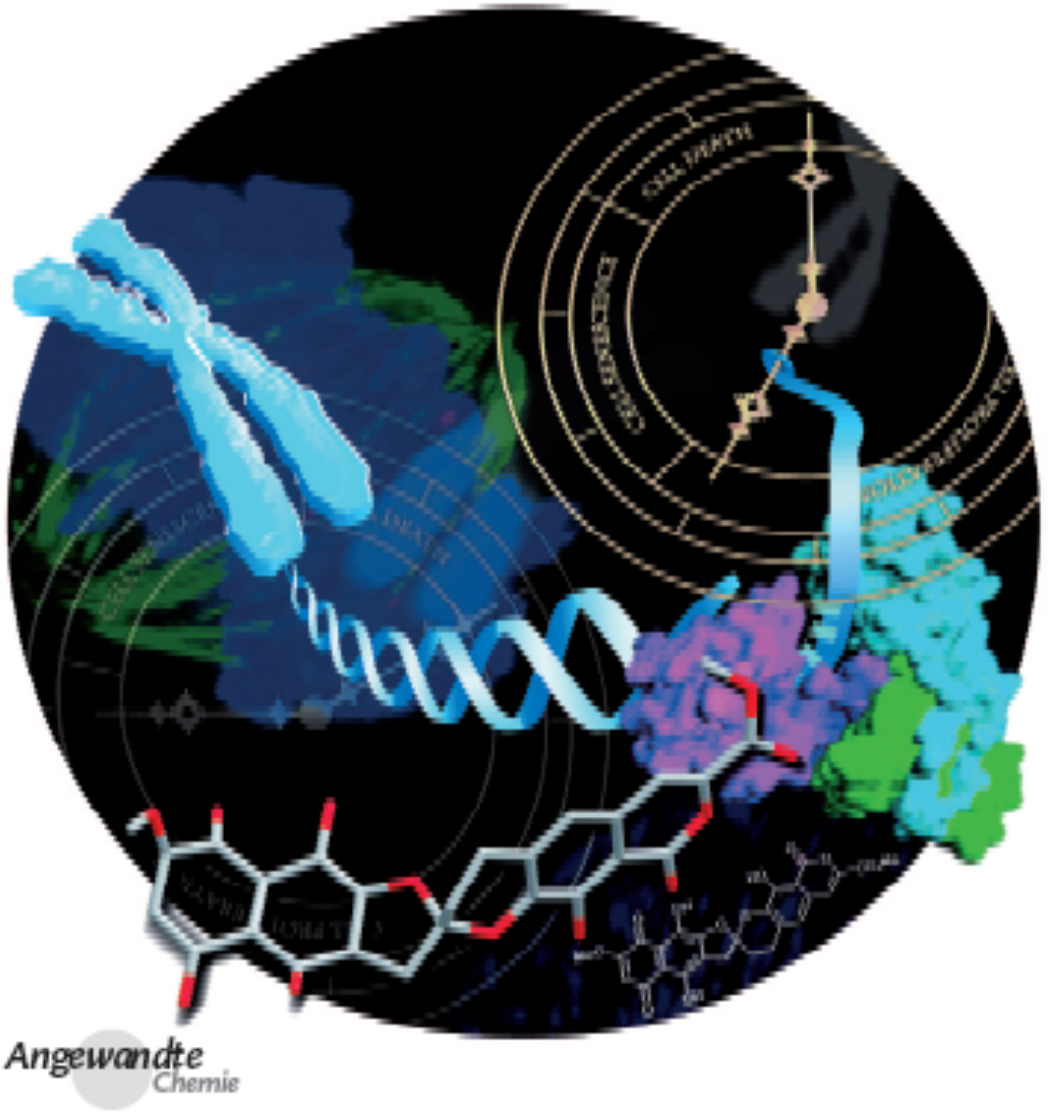
Rachel A. Byerly

Current Literature

December 26, 2009



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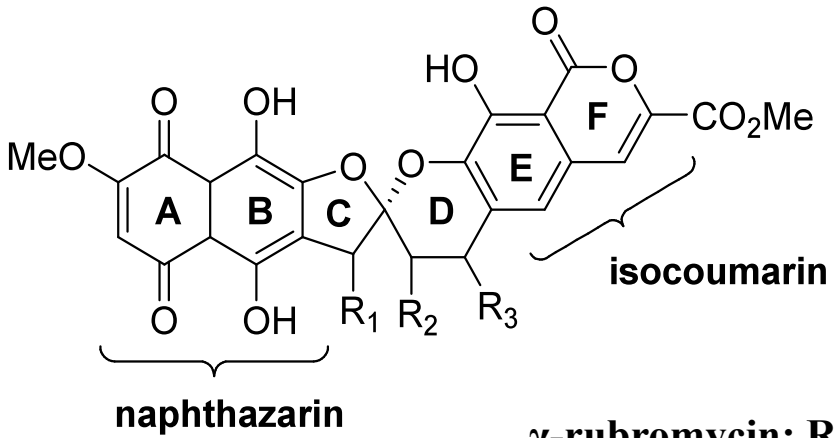
Rubromycins



γ-rubromycin: $R^1 = R^2 = R^3 = H$

- structurally related family of antibiotics
- densely oxygenated naphthazarin ring and isocoumarin moiety linked through a unique aromatic 5,6-spiroketal ring system
- antimicrobial and anticancer properties
- β- and γ-rubromycin display potent activity against human telomerase (IC_{50} = 3 μM), the reverse transcriptase of HIV-1, and the moloney murine leukemia virus
- α-rubromycin, lacking the aryl spiroketal moiety, has decreased inhibitory potency toward telomerase (IC_{50} > 200 μM), suggesting that the spiroketal core is the essential pharmacophore for the inhibition of telemorase

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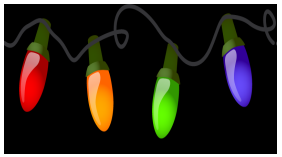
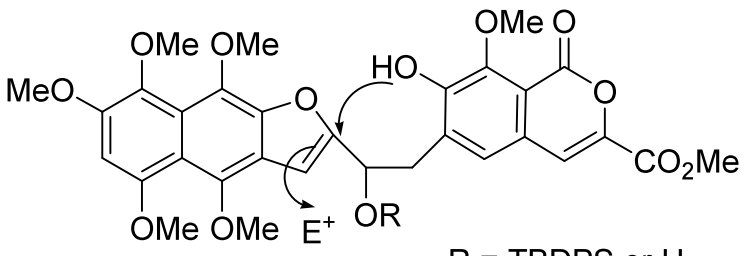
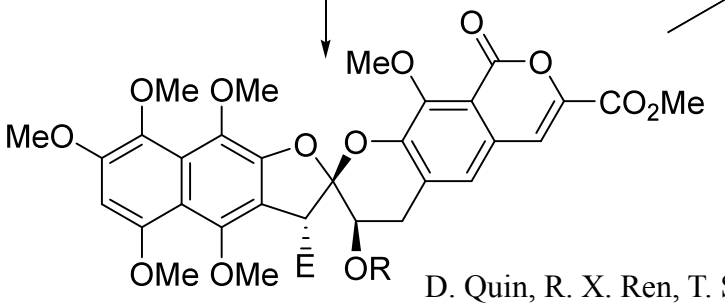
Danishefsky's Mitsunobu strategy for spiroketalization





R = TBDPS or H

3



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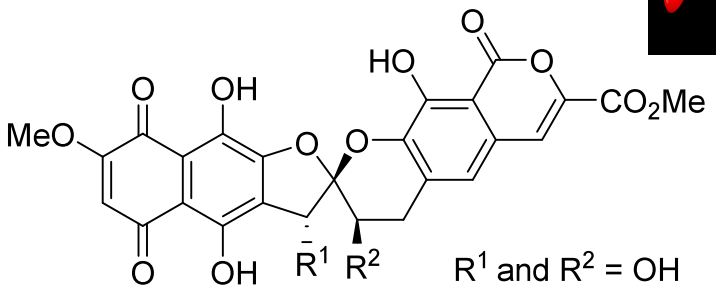


R^1 and R^2 = OH

2

Aglycone

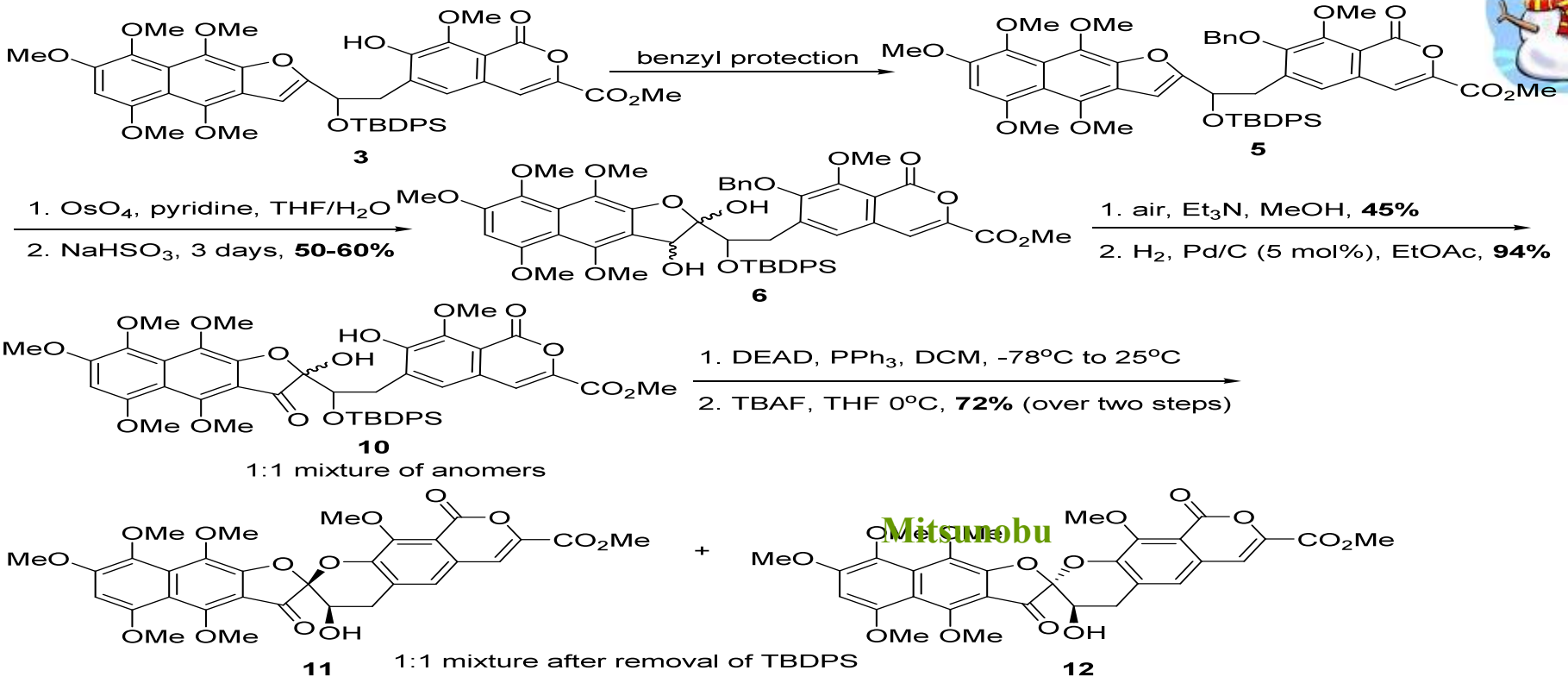
Danishefsky and co-workers envisioned **3** as a substrate for an oxidative dearomatization-spiroketalization toward heliquinomycinone, **2**, the aglycone of the naturally occurring helicase inhibitor heliquinomycin

D. Quin, R. X. Ren, T. Siu, C. Zheng, S. J. Danishefsky, *Angew. Chem. Int. Ed.* **2001**, *40*, *4709*

- sought E^+ that could be introduced concomitantly with nucleophilic spirocyclization; **unsuccessful**
- using halonium equivalents (NBS, NIS, NCS, or iodine) in the presence of sodium bicarbonate allowed for oxidative demethylation and quinone formation; similar results in attempt to epoxidize the furanoid ring
- important constraining factor: electron richness of the pentamethoxy-naphthalene moiety in **3**
- this methoxy decoration pattern set up to readily do pairwise oxidative demethylations to produce ring **A** or ring **B** quinones with subsequent deactivation of the furan double bond.
- no reaction occurred with metal-based reagents, $Pd(OAc)_2$, $Ti(OAc)_3$, Re_2O_7, or Hg^{II} salts in attempt to activate the furan double bond for Nu^- attack
- unable to carry out transformation **3** to **4**

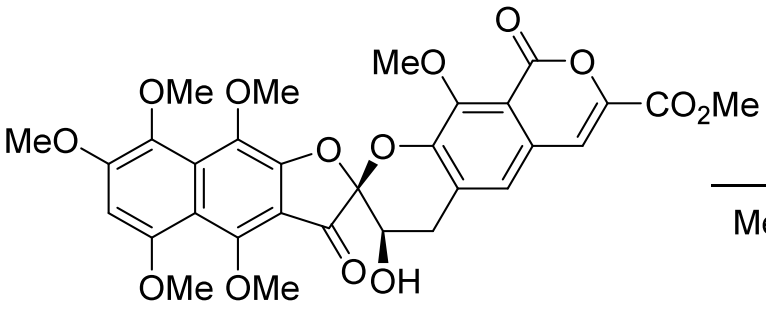
T. Siu, D. Quin, S. J. Danishefsky, *Angew. Chem. Int. Ed.* **2001**, *40*, 4713

Danishefsky's Mitsunobu strategy, continued



T. Siu, D. Quin, S. J. Danishefsky, *Angew. Chem. Int. Ed.* **2001**, *40*, 4713

Danishefsky's Mitsunobu strategy, continued, finishing Aglycone

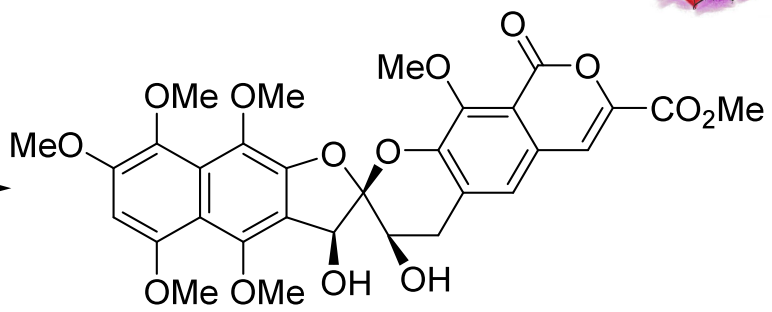


11

$Me_4NBH(OAc)_3$,

MeCN/acetic acid (5:1)

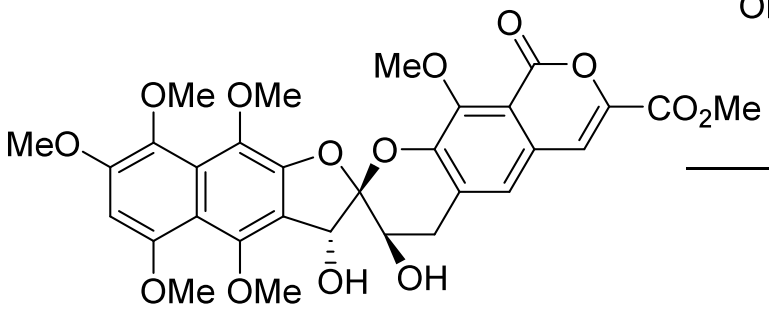
72%



14

$BF_3 \cdot OEt_2$ (O.5 equiv), DCM

64%

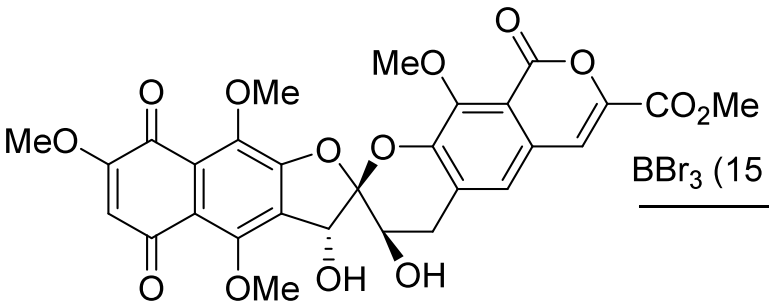


15

cerium ammonium nitrate,

$MeCN/H_2O$ (5:1), 0°C

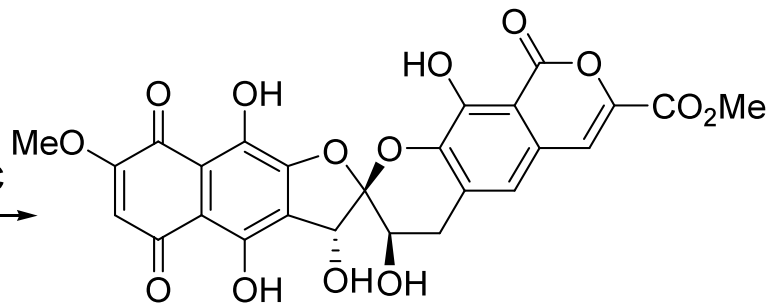
77%



17

BBr_3 (15 equiv), DCM, -78°C

52%



2

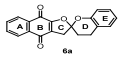
Aglycone

Danishefsky has the only successful synthesis **to date** for this class of natural products

T. Siu, D. Quin, S. J. Danishefsky, *Angew. Chem. Int. Ed.* **2001**, *40*, 4713

Kita's double Pummerer-type reaction pathway

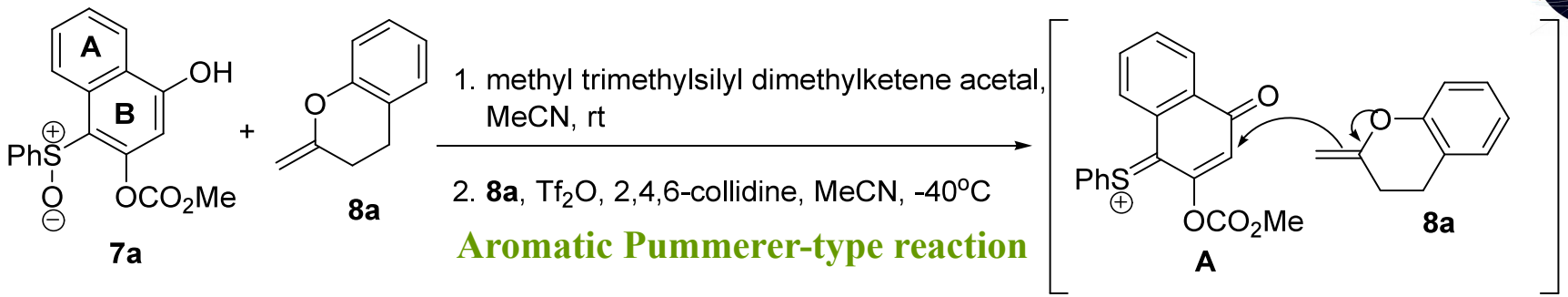
- present convergent synthesis of **I** and the first total synthesis of (+/-)-γ-rubromycin
- develop an effective, convergent route to the pentacyclic ketal, **6a**, the core structure of these natural products
- successful application of two kinds of aromatic Pummerer-type reactions of sulfinyl naphthol derivatives
- the first reaction enables the novel one-step construction of the bisbenzannelated spiroketal unit
- the second reaction allows the unique rearrangement of a "bent" pentacyclic ketal to a linearly fused pentacyclic ketal with the concurrent formation of the B-ring paraquinone
- offers convergent access to a wide range of substituted bisbenzannelated spiroketals from naphthol derivatives
- potential use in the development of new drugs derived from natural products that contain bisbenzannelated spiroketal structures

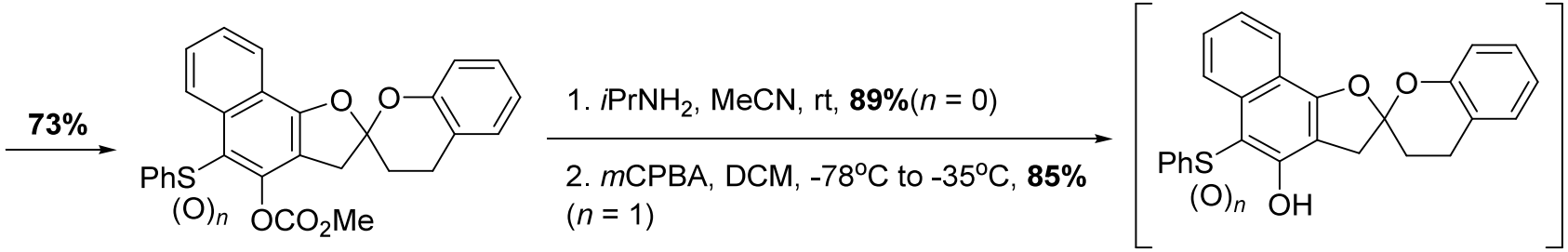


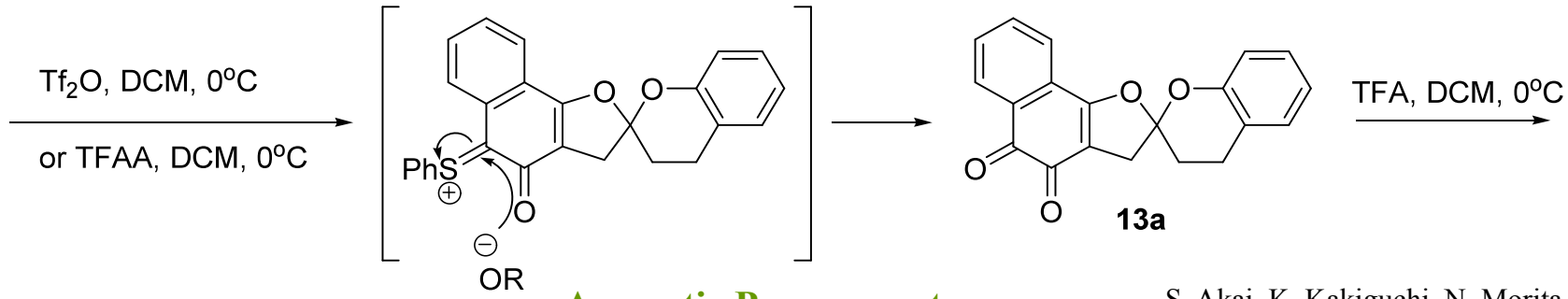
(+/-)-γ-rubromycin

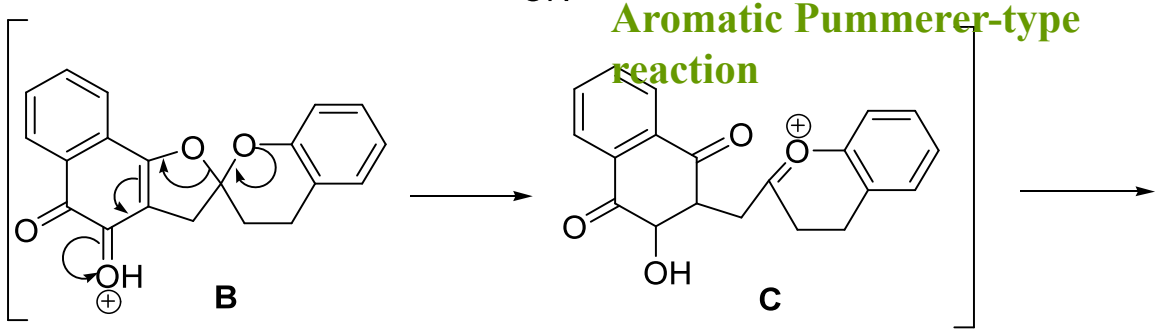
S. Akai, K. Kakiguchi, N. Morita, Y. Kita, et. al. *Angew. Chem. Int. Ed.* **2007**, *46*, 7458-7461

Kita's approach to 6a

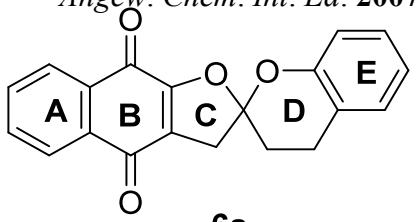








S. Akai, K. Kakiguchi, N. Morita, Y. Kita, et. al. *Angew. Chem. Int. Ed.* **2007**, *46*, 7458-7461



However…

- in spite of Danishefsky and Kita's investigations, an efficient and flexible strategy for the total synthesis of these natural products has not been forthcoming
- most striking problem in the synthesis is the acid-mediated spiroketalization to construct the unique 5,6-bisbenzannelated spiroketal core
- comprehensive modeling studies by Kozlowski, Reiβig, and coworkers has concluded that the presence of electron-withdrawing groups in the isocoumarin unit markedly decreases the nucleophilicity of the phenolic hydroxyl group, a factor that prohibits the critical spiroketalization step

Title Paper: Retrosynthesis of γ-rubromycin

γ - rubromycin (**1**)

6

7

8

9

17

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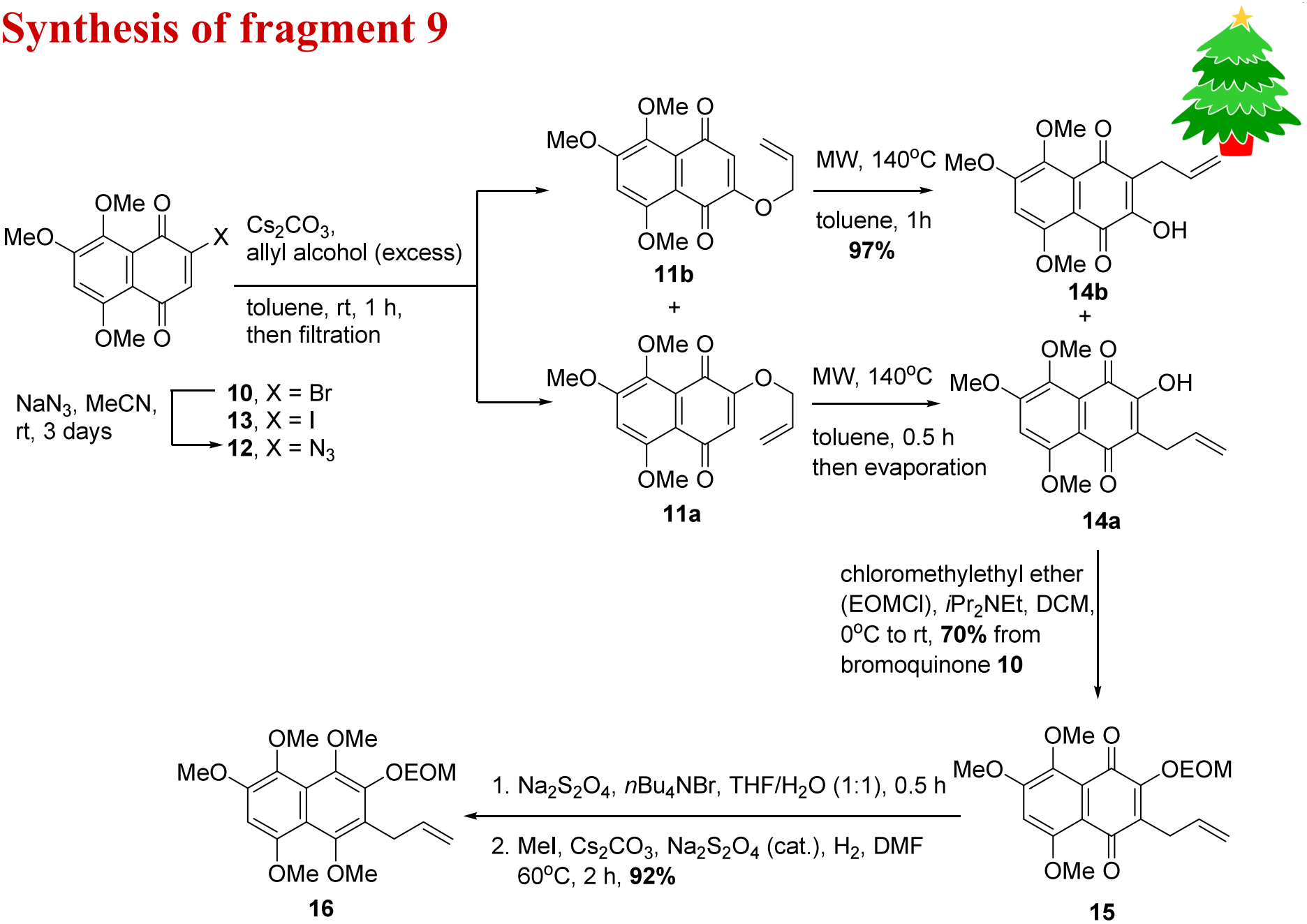
Synthesis of fragment 9



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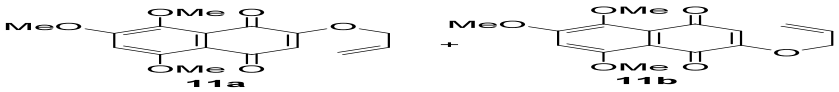
Synthesis of fragment 9, continued

Leaving-group effect on regiochemical outcome of allyloxidation



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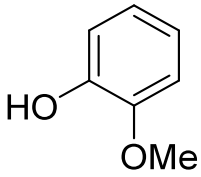
	X	Yield	(**11a**/**11b**)
13	I	86%	0:100
10	Br	64%	60:40
12	N_3	80%	100:0

- the high regioselectivity observed can be attributed to a combination of steric and bond-dipole effects
- decreasing the steric bulk at the C-X bond (I > Br >> N_3) facilitates the desired *ipso* substitution
- if the azide fragment is considered as a pseudohalogen, increased C-X bond polarization may also lead to *ipso* attack being favored over *ortho* substitution (absolute electronegativity: I = 6.7, Br = 7.5, and N_3 = 7.7 eV)

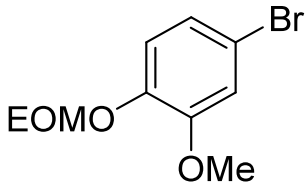
Synthesis of fragment 17



18

1. NBS, DMF, 0°C, 0.5 h, **83%**

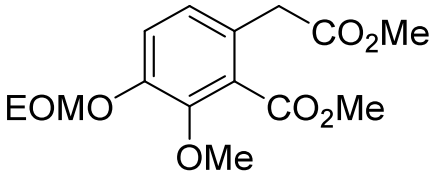
2. EOMCl, *i*Pr_2NEt, DCM, 0°C to rt, **89%**



19

LDA, THF, 0°C, 0.5 h, then

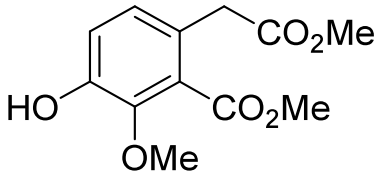
dimethyl malonate, 0°C, 0.5 h,
then **19**, THF, 0°C, **71%**



20

$NaHSO_4/SiO_2$, DCM

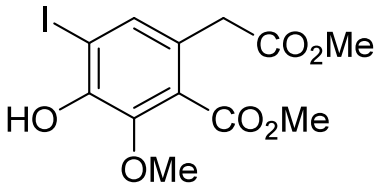
rt, 16 h, **92%**



21

$NaHCO_3$,

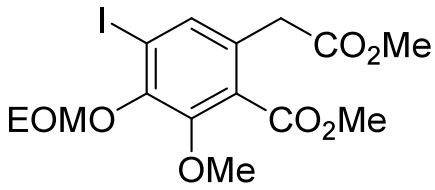
tetramethylammonium
dichloroiodate, DCM, rt,
2 h, **51%**



22

EOMCl, *i*Pr_2NEt, DCM,

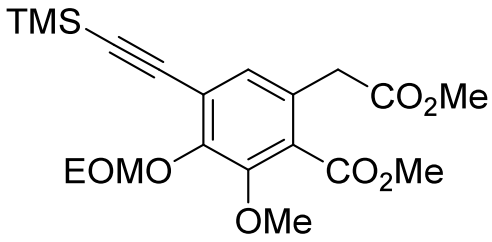
0°C to rt, **93%**



23

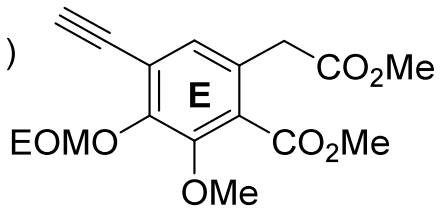
trimethylsilylacetylene, Et_3N,

CuI (15 mol%), PPh_3 (25 mol%),
$Pd(OAc)_2$ (10 mol%), DMF, rt,
16 h, **98%**



K_2CO_3, THF/MeOH (1:1)

rt, 1.5 h, **91%**



17

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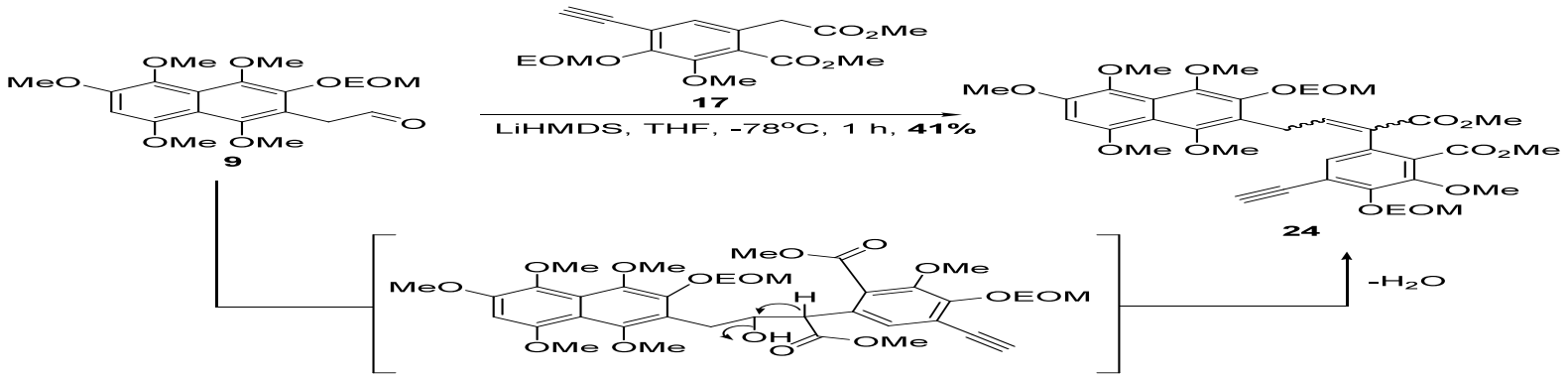
Attempted lithiated acetylide coupling



- attempts to generate the lithiated acetylide of isocoumarin precursor **17** afforded adduct **24** instead, which resulted from the aldol condensation of aldehyde **9** with the ester enolate derived from **17**

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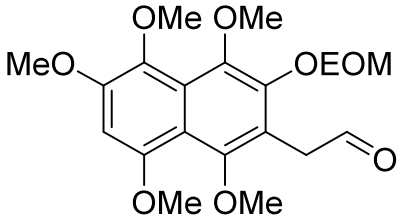
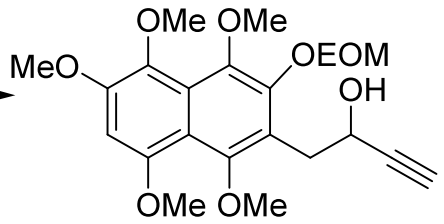
Coupling strategy re-routed…



9

ethynyl magnesium

bromide (0.5 M in THF), THF, 0°C, 1 h, **90%**



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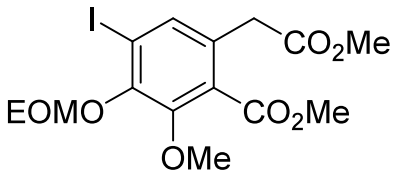
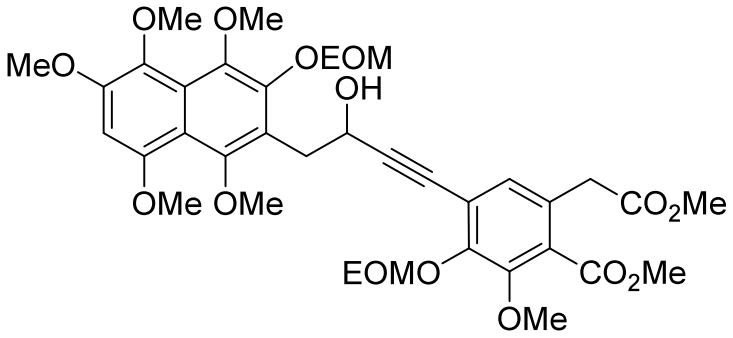


23

$[Pd(PPh_3)_4]$ (10 mol%), CuI (15 mol%), Cs_2CO_3, DMF, 6 h, **8 (91%)**, **26 (trace)**



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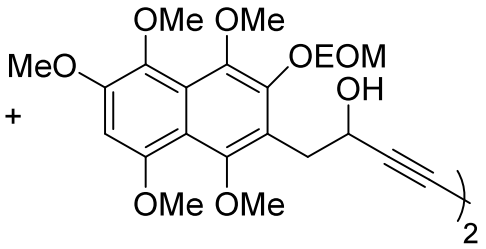
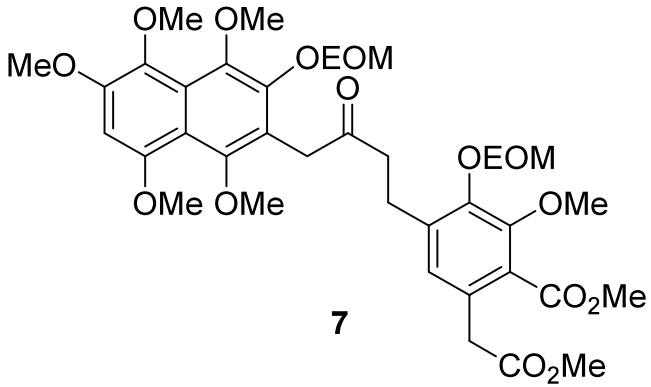


26

1. Pd/C, H_2, $NaHCO_3$, EtOAc, 3 h, **99%**

2. IBX, DMSO, 60°C, 0.5 h, **95%**



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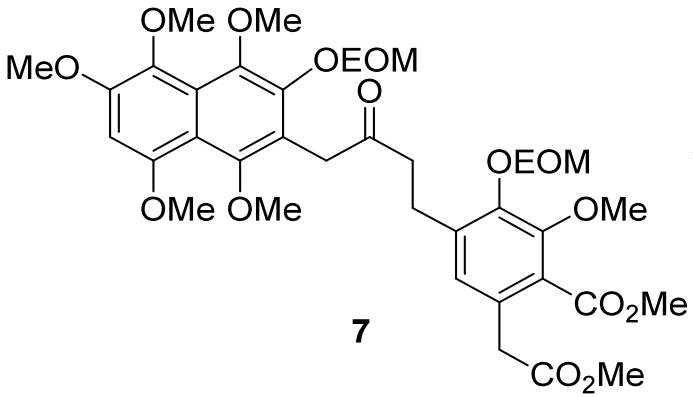
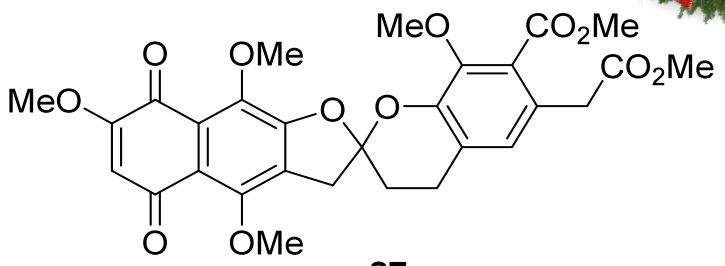
Coupling strategy re-routed, continued…



7

$NaHSO_4/SiO_2$, DCM,

rt, 4 h, **80%**

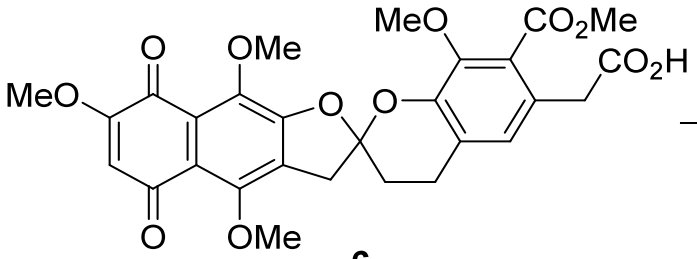


27

1. 10% KOH, MeOH, 0°C to rt, 16 h

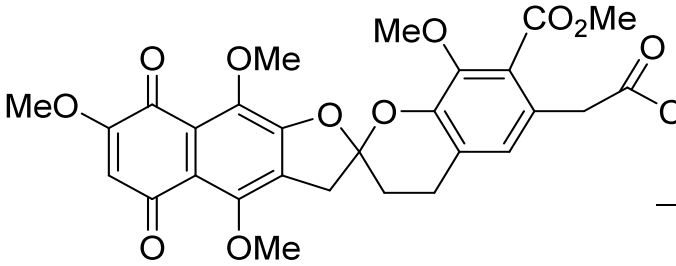
2. cerium (IV) ammonium nitrate, $MeCN/H_2O$ (5:1), 0°C, 0.5 h

(58% over two steps)



6

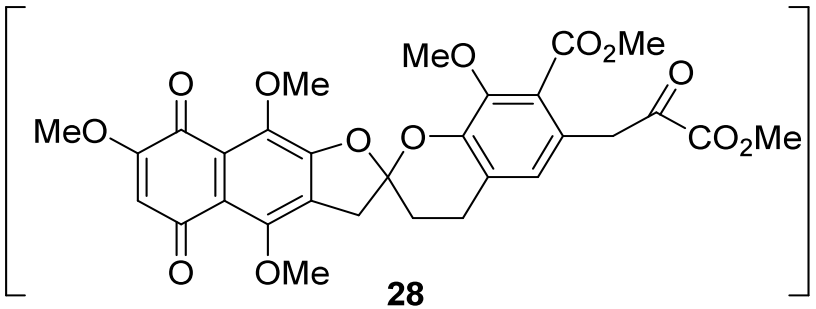
(triphenylphosphoranylidene) acetonitrile, EDCI, DMAP, DCM, rt, **46%**



27

dimethyldioxirane,

MeOH, 0°C



28

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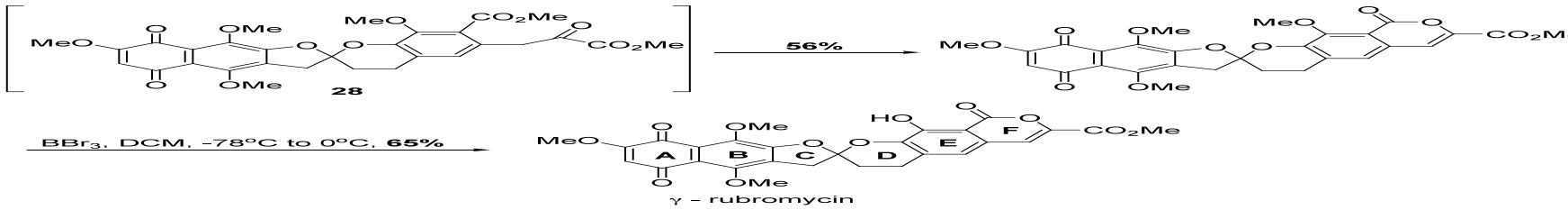
Coupling strategy re-routed, continued…



Angew. *Chem*. Int. *Ed*. **2009**, *48*, 7996-8000

Conclusions

- completion of an efficient formal total synthesis of (+/-)-γ-rubromycin in **17** steps from 1,2,4-trimethoxybenzene
- synthesis significantly shorter than Kita's approach and produces (+/-)-γ-rubromycin in a much better overall yield
- demonstrates the previously unrealized applications of acid-mediated spiroketalization for the synthesis of the challenging rubromycin family of natural products
- this synthetic route makes use of a novel regioselective allyloxylation of a 2-azido-1,4-naphthoquinone to facilitate a subsequent Claisen rearrangement
- future work will focus on extension of this synthetic strategy to the synthesis of purpuromycin and naphthoquinone analogues