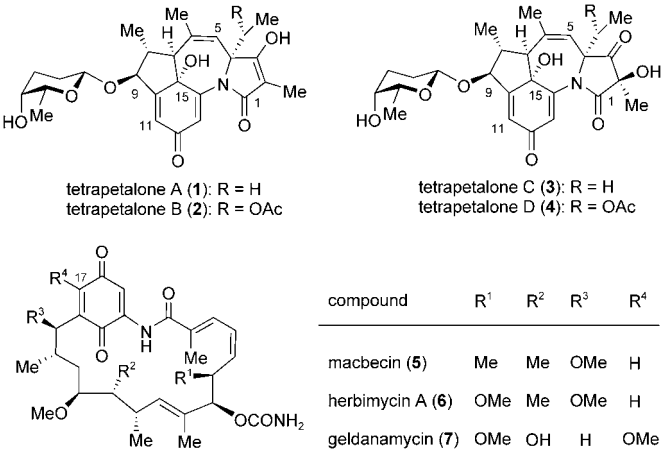
Natural Product Synthesis

# Synthesis of the Tetracyclic Core of the Tetrapetalones through Transannular Oxidative [4+3] Cyclization**

*Xiang Wang and John A. Porco, Jr.**

A series of novel soybean lipoxygenase (SBL) inhibitors, tetrapetalones A–D (**1**–**4**, Scheme 1), were recently isolated




| compound | $R^1$ | $R^2$ | $R^3$ | $R^4$ |
|---|---|---|---|---|
| macbecin (**5**) | Me | Me | OMe | H |
| herbimycin A (**6**) | OMe | Me | OMe | H |
| geldanamycin (**7**) | OMe | OH | H | OMe |

***Scheme 1.*** Chemical structures of the tetrapetalones A–D (**1**–**4**) and representative ansamycin natural products **5**–**7**.

by Komoda et al.[1] from the culture filtrate of the *Streptomyces* sp. strain USF-4727.[2] These tetrapetalones showed moderate inhibition of SBL ($IC_{50} = 190$–$360\ \mu M$ for **1**–**4**) comparable to the well-known lipoxygenase inhibitors nordihydroguaiaretic acid (NDGA, $IC_{50} = 290\ \mu M$) and kojic acid ($IC_{50} = 110\ \mu M$). The structure of tetrapetalone A (**1**) was first determined by $^1H$ NMR NOESY spectroscopic analysis and modified Mosher analysis,[1a] and then was subsequently revised by $^1H$–$^{15}N$ HMBC techniques, detailed NOE analysis, and chemical derivatization.[1b] The tetrapetalones B–D (**2**–**4**) were structurally characterized shortly thereafter and were shown to have similar inhibitory activities against SBL. The tetrapetalones possess an unprecedented tetracyclic skeleton bearing an appended β-rhodinosyl moiety. The unique structural feature of the tetracyclic core and its similarity to

[*] X. Wang, Prof. J. A. Porco, Jr.
Department of Chemistry and
Center for Chemical Methodology and Library Development
Boston University, 590 Commonwealth Avenue
Boston, MA 02215 (USA)
Fax: (+1) 617-353-6466
E-mail: porco@chem.bu.edu

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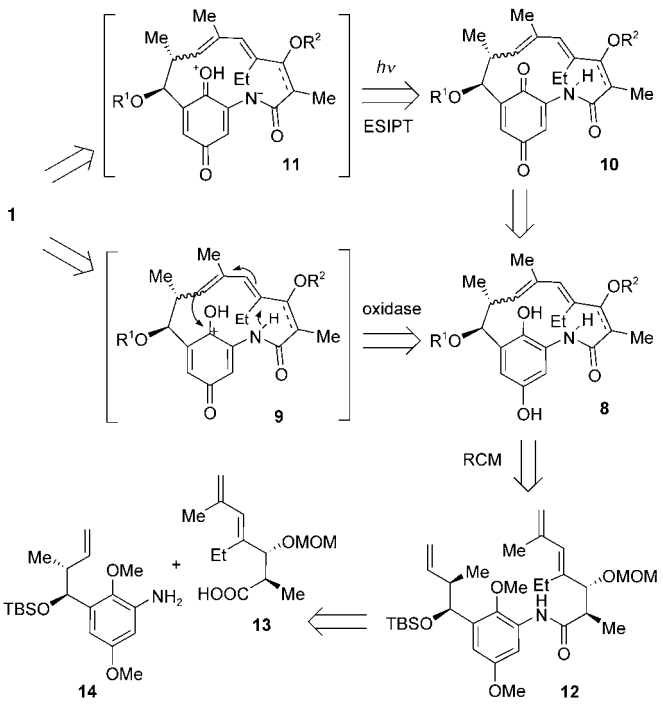
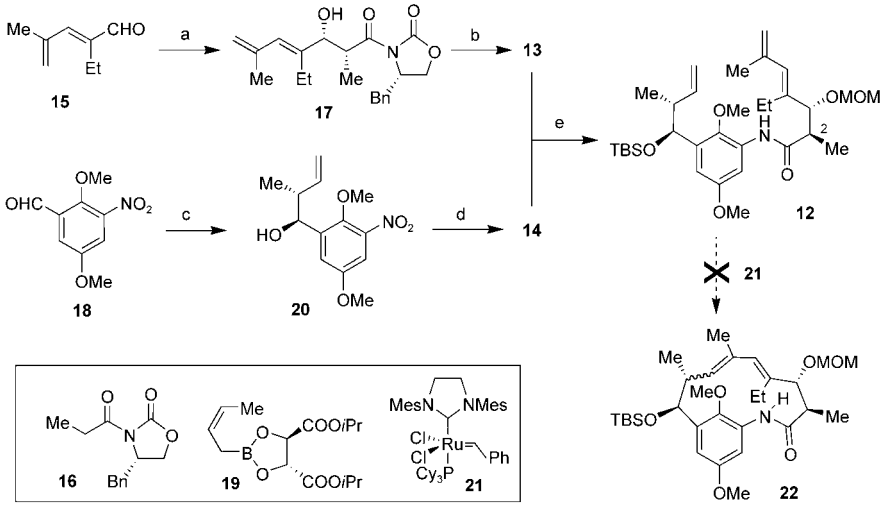
the ansamycin antibiotics[3,4] attracted our interest and prompted consideration of synthetic approaches.

The ansamycins are important antibiotics possessing antibacterial, antifungal, and antitumor activities.[5] For example, geldanamycin (**7**) has been shown to inhibit the chaperone activity of heat shock protein 90 (Hsp90) by noncovalent binding to its ATP/ADP binding site.[6] A synthetic analogue, 17-allylamino-17-demethoxygeldanamycin, has entered phase I clinical trials.[7] The benzylic ansamycin natural products (representative members are shown in Scheme 1) vary in oxidation level from a monophenol (for example, reblastatin),[3h] hydroquinone (for example, cytotrienin A),[3f] to a benzylquinone (for example, **5**–**7**), each bearing a highly functionalized polyketide *ansa* chain. It is likely that the biosynthesis of the benzylic ansamycins involves oxidation of the aromatic core after construction of the macrolactam unit.[8] We considered whether the tetrapetalones may be derived from a macrocyclic ansamycin precursor because of structural similarities between the tetrapetalones and the ansamycins. During oxidation of hydroquinone **8**, however, the arene-derived oxonium ion **9** may be trapped by the diene fragment, which subsequently reacts with the amide nitrogen atom to form the tetracyclic skeleton of **1**–**4** (Scheme 2).[9] It is also possible that the desired quinone **10** may undergo excited-state intramolecular proton transfer (ESIPT)[10] under UV irradiation to afford dipole **11**, which further reacts with the diene fragment to form the tetracycle. To investigate these and other possible transannular[11] [4+3] cyclization processes,[12,13] we developed a retrosynthetic analysis for tetrapetalone A to target the preparation of both hydroquinone **8** and quinone **10**. We considered ring-closing metathesis (RCM)[14] of acyclic substrate **12**, which may be derived from condensation of the acid **13** and aniline **14**, as a route to develop a convergent synthetic pathway to these precursors.




***Scheme 2.*** Retrosynthetic analysis of tetrapetalone A (**1**). TBS = *tert*-butyldimethylsilyl. MOM = methoxymethyl.

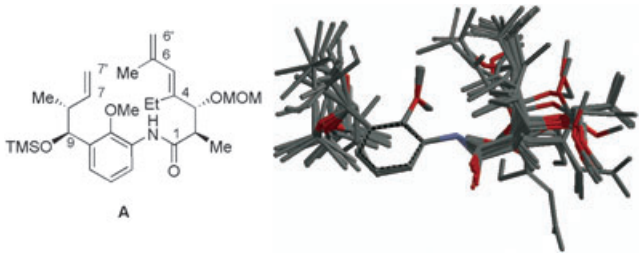
Synthesis of the requisite diene acid **13** commenced with the Evans *syn*-aldol condensation[15] of dienal **15**[16] and chiral oxazolidinone **16** to afford chiral alcohol **17** as a single diastereomer (Scheme 3). Methoxymethyl (MOM) protection of the alcohol and hydrolysis of the chiral auxilary afforded **13** (85% yield, three steps). Asymmetric crotylation[17] of aldehyde **18**[4a] using the chiral *cis*-crotylboronate **19** derived from L-diisopropyltartrate (L-dipt) afforded chiral alcohol **20** (100% yield, single diastereomer). Silylation followed by reduction of the nitro group[18] afforded the desired aniline **14** (62% yield, two steps). Coupling of fragments **13** and **14** using *N*,*N*-bis(2-oxo-3-oxazolidinyl)phosphorodiamidic chloride (BOPCl)[19] led to epimerization of the α chiral center (C2, Scheme 3) of the amide product **12**. The use of an acid chloride proved to be feasible in the preparation of **12** (82%) without epimerization. However, treatment of acyclic triene **12** with the Grubbs second generation catalyst **21** did not produce the desired cyclic diene **22**. $^1$H NMR spectroscopic analysis of the crude reaction mixture indicated that the ruthenium catalyst had reacted with the monosubstituted olefin, with no evidence of metathesis of the 1,1-disubstituted olefin. We believe that the 1,1-disubstituted olefin was



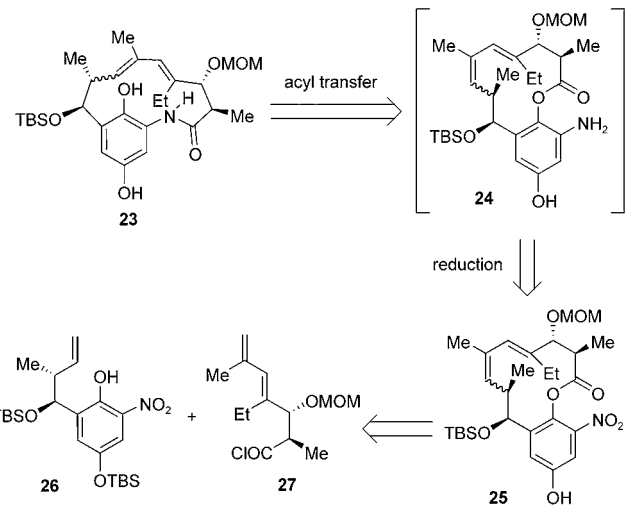

***Scheme 3.*** RCM approach to macrolactam **22**. a) **16**, $Bu_2BOTf$, $Et_3N$, $CH_2Cl_2$, −78→0°C; b) 1. MOMCl, DIPEA; 2. LiOH, $H_2O_2$, THF, $H_2O$ (85% yield over 3 steps); c) **19**, $CH_2Cl_2$, −78→25°C (100% yield); d) 1. TBSOTf, $Et_3N$, −78°C; 2. $NaBH_4$, $S_8$, THF, 65°C (62% yield over 2 steps); e) **13**, $(COCl)_2$, cat. DMF, $CH_2Cl_2$, 0→25°C; then **14**, $Et_3N$, 82% yield. MOMCl = chloromethyl methyl ether, DIPEA = diisopropylethylamine, TBSOTf = *tert*-butyldimethylsilyl triflate, DMF = *N*,*N*-dimethylformamide, Mes = mesitylene, Cy = cyclohexyl, Bn = benzyl.

unreactive in this case and that the two *meta*-substituted side chains are likely to be positioned away from each other because of "*meta* bridging" of the aromatic substituents. Therefore, the macrocyclic RCM was prohibited by both the reactivity of the olefin and the conformational strain within the substrate **12**.[4f] A conformational search on model **A** by molecular mechanics force field (MMFF) studies[20] (Scheme 4) suggested a possible rationale: the smallest




***Scheme 4.*** Conformers of the "*meta*-bridged" acyclic model.

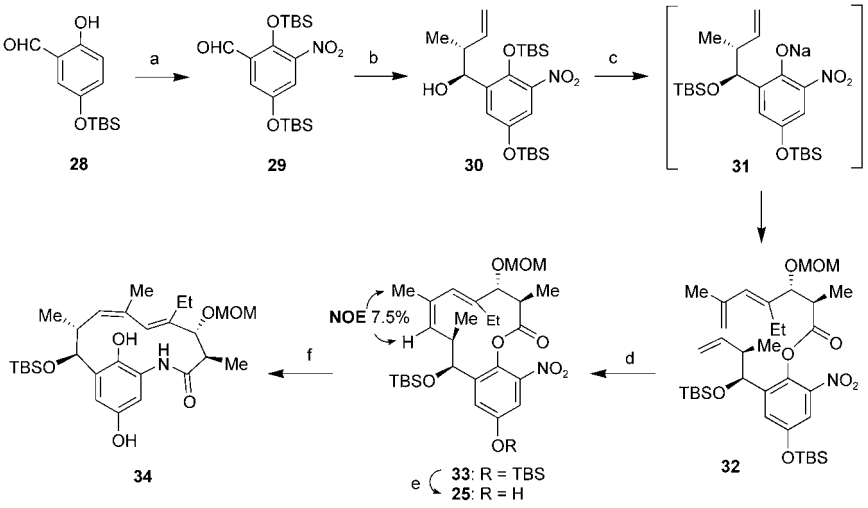



***Scheme 5.*** Revised retrosynthetic analysis for macrolactam **23**.

distance between the C6′ and C7′ atoms is 6.2 Å among the low-energy conformers ($E_{rel}$ = 0–5.2 kcal mol$^{-1}$) of model **A**. Therefore, the conformational strain of the "*meta*-bridged" framework may provide a significant barrier for macrocyclization of substrate **12**.

Since the direct macrocyclic RCM approach did not afford the desired macrocycle, we next considered that macrolactam **23** (Scheme 5) may be derived from an "*ortho*-bridged" macrolactone **24** through intramolecular acyl transfer[21] (ring expansion). Lactone **24** may be prepared from selective reduction of the nitro group of **25**, which may be obtained from nitrophenol **26** and acyl chloride **27**. A TBS group was chosen to protect the phenol of **26**, to facilitate removal at a later stage.

Synthesis of the revised C7–C15 fragment began with nitration of phenol **28**[22] followed by silylation to afford bis(silyl) ether **29** (70%, two steps; Scheme 6). Asymmetric crotylation of **29** using *cis*-crotyl boronate **19**[17] produced chiral alcohol **30** as a single diastereomer in quantitative yield. Deprotonation of the secondary alcohol of **30** using sodium hexamethyldisilazane (NaHMDS; THF, −78 °C) generated a sodium phenoxide species **31** in situ through intramolecular transfer of a silyl group.[23,24] Subsequent addition of acyl chloride **27**, $Et_3N$, and DMAP afforded phenol ester **32**. To our delight, triene **32** underwent smooth RCM macrocyclization to afford cyclic diene **33** after treatment with the Grubbs second generation catalyst **21** (80 °C, 30 min). NOE analysis showed that the newly formed olefin possessed a *Z* configuration. Selective desilylation of **33** (TBAF/AcOH) afforded nitrophenol **25** (85%, two steps).




***Scheme 6.*** Synthesis of ansamycin **34**. a) 1. $Cu(NO_3)_2{\cdot}3H_2O$, $Ac_2O$, 0→25 °C; 2. TBSCl, $Et_3N$, DMF, 70% yield over 2 steps; b) **19**, $CH_2Cl_2$, −78→25 °C, 99% yield; c) NaHMDS, THF, −78 °C; then **27**, $Et_3N$, DMAP, −78→25 °C, 85% yield; d) **21**, benzene, 80 °C; e) TBAF/HOAc, THF, 0 °C, 85% yield over 2 steps; f) $Pd/CaCO_3$, $Et_3N$, THF, 1 atm $H_2$; then silica gel, EtOAc. DMAP = 4-*N*,*N*-dimethylaminopyridine, DMF = *N*,*N*-dimethylformamide; HMDS = 1,1,1,3,3,3-hexamethyldisilazane; TBAF = tetrabutylammonium fluoride.

We next evaluated conditions for the selective reduction of the aryl nitro group in the presence of the diene functionality. We found that application of standard conditions for reduction of the nitro group, such as $SnCl_2$[25] and $NaBH_4/S_8$,[18] to substrate **25** not only reduced the nitro group but also hydrolyzed the ester, and no desired macrolactam **34** was formed. The use of Pd/C[26] or $Pd/CaCO_3$[27] in a hydrogen atmosphere was found to reduce both the diene and nitro groups. However, $Pd/CaCO_3$ chemoselectively reduced the nitro group of **25** when 10% triethylamine was employed as a cosolvent. Filtration of the reaction mixture through silica gel followed by elution with EtOAc cleanly afforded the desired acyl migration product **34**. It is interesting to note that use of the Lindlar catalyst[4b] resulted in formation of trace amounts of the desired product, presumably because of the catalyst poison $PbO_2$ and the sensitivity of aniline **24** to the oxidant.

With hydroquinone **34** in hand, we next evaluated the crucial biomimetic transannular oxidative [4+3] cyclization.[28] Out of the possible oxidants to effect the transformation of hydroquinones to quinones, we first chose $PhI(OAc)_2$[29] for the activation of hydroquinone. After considerable experimentation, we found that hydroquinone **34** was readily oxidized, with oxidative oligomerization as a major side reaction. Addition of a dilute solution of **34** in $CH_2Cl_2$ to a solution of $PhI(OAc)_2$ in $CH_2Cl_2$ at 0 °C over 15 minutes provided tetracycle **35** (42 %, two steps; Scheme 7). The structure of **35** was determined by NOESY spectroscopic analysis as shown in Scheme 7. Three stereocenters were formed (see inset, Scheme 7), and out of these, the configurations at the C4 and C7 atoms are the same as those of the natural products **1**–**4** but the configuration at C15 is reversed (*S*).

A conformational search of substrate **34** was performed by using MMFF studies to investigate the stereochemical outcome of this highly diastereoselective transannular [4+3] cyclization.[20] The macrocycle is positioned underneath the aromatic ring in the ground-state conformer (see inset, Scheme 7), thus establishing an *S* configuration for the C15 stereocenter. Allylic strain forces the C8–H bond to be eclipsed to the C6–C5 bond, which controls the configuration at C7. Since the ground-state conformer of **34** shows that C5–C6 is *s-trans*, we believe that the transannular cyclization may, in fact, be a stepwise process. After the diene reacts with the arene-derived oxonium ion, intermediate **36** may rotate to obtain a suitable conformation for reaction with the amide nitrogen atom. Furthermore, calculations indicated that the atropisomer of the macrolactam **34** that leads to the correct configuration at C15 is approximately 4.1 kcal mol$^{-1}$ higher in energy than the ground-state conformer (see the Supporting Information).[30]

In summary, a novel $I^{III}$-promoted transannular oxidative [4+3] cyclization has been developed to construct the tetracyclic skeleton of the tetrapetalones. A convergent strategy to access the macrocyclic ansamycin precursor has been developed that involves a one-pot, base-mediated silyl transfer/acylation process for fragment coupling and a tandem reduction of the nitro group/acyl transfer process for construction of the highly strained, bicyclic system. This novel strategy provides an alternative approach to the construction of macrolactams as precursors to the ansamycin antibiotics and analogues. Synthetic studies toward the total synthesis of tetrapetalone A (**1**) and development of related oxidative [4+3] cyclization processes are currently being investigated and will be reported in due course.

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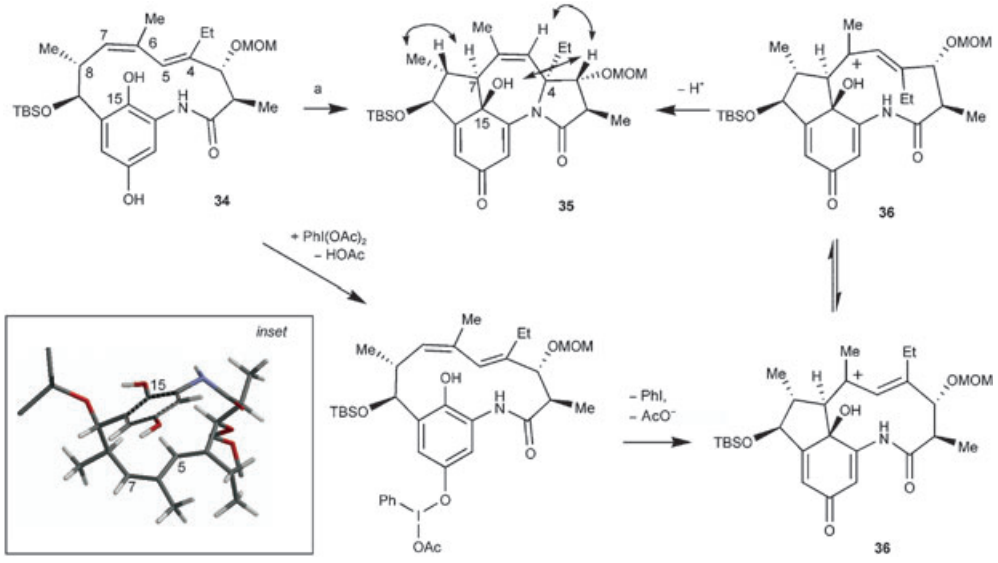


***Scheme 7.*** $I^{III}$-promoted transannular oxidative [4+3] cyclization. a) $PhI(OAc)_2$, $CH_2Cl_2$, 0 °C (42 % yield over 2 steps).

  

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