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# Total Synthesis of Meayamycin and *O*-Acyl Analogues

**Christopher Gartshore**[a], **Shinji Tadano**[a], **Prem B. Chanda**[a], **Anindya Sarkar**[a], **Naidu S. Chowdari**[b], **Sanjeev Gangwar**[b], **Qian Zhang**[b], **Gregory D. Vite**[b,c], **Jelena Momirov**[a], **Dale L. Boger**[a,*]

[a]Department of Chemistry and Skaggs Institute for Chemical Biology, The Scripps Research Institute, 10550 N. Torrey Pines Road, La Jolla, California 92037, USA

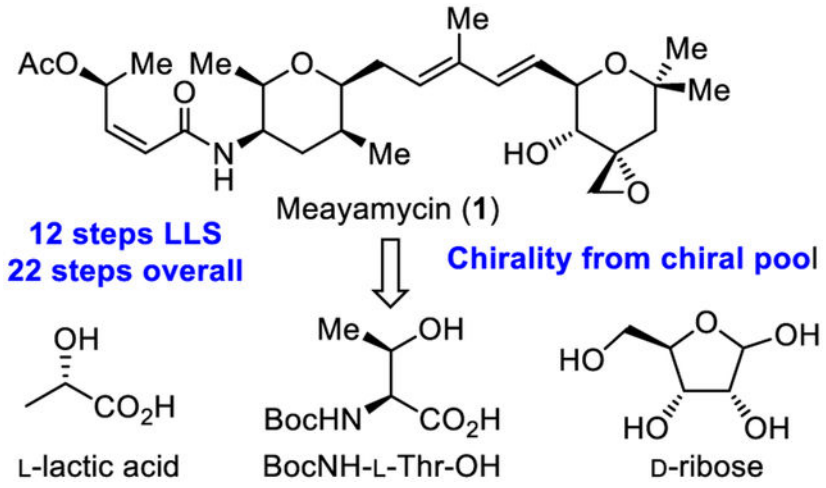
[b]Bristol Myers Squibb Research & Development, 700 Bay Road, Redwood City, California 94063, USA

[c]Bristol Myers Squibb Research & Development, PO Box 4000, Princeton, New Jersey 08543 USA

## Abstract

A short, scalable total synthesis of meayamycin is described by an approach that entails a longest linear sequence of 12 steps (22 steps overall) from commercially available chiral pool materials (ethyl L-lactate, BocNH-Thr-OH, and D-ribose) and introduces the most straightforward preparation of the right-hand subunit detailed to date. The use of the approach in the divergent synthesis of a representative series of *O*-acyl analogues is exemplified.

## Graphical abstract




*Corresponding Author dale.boger@outlook.com.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Full experimental details and $^{1}H$ and $^{13}C$ NMR spectra (PDF).

FR901464, isolated by Fujisawa Pharmaceutical Company from pseudomonas sp. No. 2663,[1] is the first member of a growing class of potent antitumor antibiotics that includes the spliceostatins[2] and thailanstatins.[3] Initial total syntheses of FR901464 confirmed the assigned structure and relative stereochemistry within each noncontiguous subunit and permitted assignment of absolute stereochemistry. These were disclosed first by Jacobsen and co-workers (40 steps),[4] utilizing a powerful asymmetric hetero Diels–Alder reaction to form the two tetrahydropyrans, and shortly thereafter by Kitahara (41 steps),[5] enlisting the chiral pool to access the two tetrahydropyrans. Subsequent total syntheses by Koide[6] (28 steps) and later by Ghosh[7] (22 steps) provided more expedient assembly of the two highly substituted and functionalized tetrahydropyran rings.[8] In addition to demonstrating the critical role of the epoxide,[4] Jacobsen defined the instability of FR901464 and further showed that removal of the right-hand subunit tertiary alcohol not only abrogated this instability, but also enhanced biological potency.[4] In an extension of these observations, Koide latter found that replacement of the tertiary alcohol with a methyl group (vs H)[4] not only avoided the rapid compound degradation but also improved potency as much as 100-fold.[6] Such synthetic analogues, named the meayamycins (Figure 1), represented an early contribution to the growing number of natural products and analogues in the class accessed by total synthesis.[4-13] In 2007, Yoshida disclosed that FR901464 binds a subunit of the spliceosome disrupting conversion of pre-mRNA to mRNA.[14] Shortly thereafter, Koide established that the meayamycins act in an analogous manner.[15] The mechanism by which spliceosome inhibition is achieved has been shown to be effective in selectively controlling both cancer cell proliferation and metastasis with selected members exhibiting efficacious in vivo antitumor activity.[16]

In a program that explores natural product analogues as therapeutics[17] or components of antibody-drug conjugates, we targeted the potent meayamycins with the objective of developing a short, scalable total synthesis. After several iterations on the approach, each subunit used to assemble **1** herein is derived from chiral pool starting materials with all 8 chiral centers introduced or controlled by chirality found in inexpensive commercial starting materials (Figure 1). The approach provided **1** in a longest linear sequence of 12 steps (22 steps overall),[18] complementary to an improved approach recently disclosed by Koide (11 longest linear sequence, 24 steps overall).[19]

The most challenging subunit is the right-hand tetrahydropyran **7,** bearing three of the stereocenters and the essential epoxide. Intermediate **7** was accessed in four steps from known aldehyde **2,**[20] itself prepared from D-ribose in three steps (Scheme 1). Grignard addition of 2-methylallylmagnesium chloride (2 equiv) to aldehyde **2** (THF, 5 h, 0–25 °C, 5 h, 61–65%) provided **3** as an inconsequential diastereomeric mixture. Dess–Martin periodinane (DMP) oxidation (1.5 equiv DMP, $CH_2Cl_2$, 0 °C, 3 h, 78–88%) and subsequent acid-catalyzed acetonide deprotection, alkene isomerization, and 6-endo-trig cyclization of the distal alcohol provided cyclic ketone **6**. Initial optimization of this reaction found that treatment of **3** with pyridinium *p*-toluenesulfonate (PPTS) in MeOH (0.2 equiv PPTS, 60 °C, 4 h) afforded principally the corresponding diol and subsequent addition of aqueous 1 M HCl ($MeOH/H_2O$ 9:1, 60 °C, 2–4 h) completed the isomerization of the double bond into conjugation with the ketone to provide **5**. Without purification, treatment of crude **5,** already

containing substantial amounts of **6,** with Amberlyst-15 ($CHCl_3$, 12 h, 80 °C, 12 h) completed the distal alkoxy conjugate addition to provide **6** (76% overall). Conversion of **6** to **7** was achieved by diastereoselective epoxide introduction (73%) following Koide's protocol.[21] In addition to the concise nature of the synthesis of **7** (4–5 steps, 32% from **2**; 7–8 steps, 20% from D-ribose), the approach avoids the generation of diastereomers and provides full control of the absolute stereochemistry.

The central tetrahydropyran, bearing four chiral centers, was accessed by an approach that relied on the chiral pool to set the absolute stereochemistry (Scheme 2). Although inspired by Koide's original synthesis,[6] it is substantially shorter (5 vs 8 steps) and enlists further optimized protocols for overlapping steps. Analogous improvements were independently reported by Koide earlier this year for synthesis of intermediate lactone **12**.[19] Additional subtle improvements are also highlighted herein for the original conversion[6] of **12** to **15**.[18] Central to the synthesis of **15** was use of the known starting material **9,**[22] the BocNH-L-Thr derived variant of Garner's aldehyde, available in three steps from BocNH-L-Thr (1 equiv MeONHMe, 1.2 equiv EDCI, 1.2 equiv HOBt, 2 equiv ($i$Pr$_2$)NEt, $CH_2Cl_2$, 25 °C, 22 h; 0.2 equiv PPTS, 10 equiv $MeC(OMe)_2Me$, THF, reflux, 18 h, 85-88% for two steps), including the reported DIBAL-H reduction of the Weinreb amide (2 equiv DIBAL-H, $CH_2Cl_2$, −78 °C, 3 h).[22] A *Z*-selective modified Wadsworth–Horner–Emmons reaction of **10**[23] with aldehyde **9** provided the α,β-unsaturated ester **11** (86% for two steps, 4.6:1 *Z*:*E*) where preferential generation of the *Z*-isomer facilitates but may not be required for an ensuing lactonization. Acid-catalyzed *N,O*-ketal cleavage effected with 10-camphorsulfonic acid (CSA) and in situ lactonization (0.05 equiv CSA, MeOH, 23 °C, 74%) provided **12** in a single step. The subsequent alkene reduction of **12** proceeded with lower diastereoselectivity (6:1 vs 10:1) than reported and provided **13** contaminated with lactone ethanolysis product in our hands under conditions reported (2 mol % $PtO_2$, $H_2$, EtOH, 23 °C, 2 h, 98%).[6] For our purposes, this was reoptimized to provide **13** in high yield (quantitative) and excellent diastereoselectivity (10:1, THF > EtOH, $i$PrOH, EtOAc) through use of THF as solvent (23 °C, 15 h) without competitive solvent lactone ring opening.

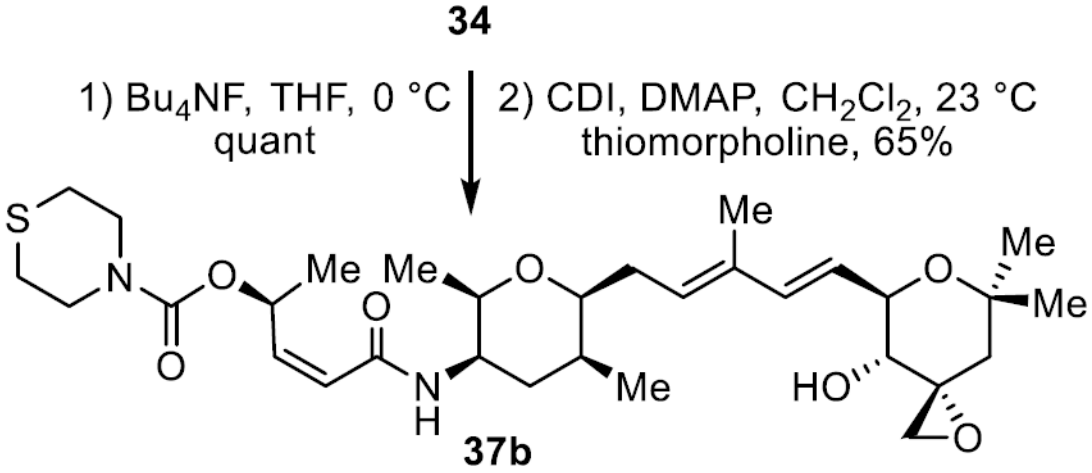
More substantial optimizations were required for implementation of the Koide[6] two-step conversion of **13** to **15**. Significant amounts of double addition product were observed when the reaction of allylmagnesium chloride (1.9 equiv) with **13** was conducted as detailed, likely accounting for the lower overall conversion of **13** to **15** than reported herein. Although a reduction in the amount of allylmagnesium chloride (1.3–1.6 equiv) attenuated the over addition, increasing amounts of recovered starting **13** offset any improvement in this selectivity. However, by lowering the reaction temperature (−98 vs −78 °C) and adjusting the reaction solvent (2-MeTHF vs THF), **14** was obtained in excellent yield (85-87%) with minimal over addition (6%) or recovered starting lactone (7%). Final diastereoselective reduction of the lactol provided **15** in improved conversions (49%) provided triethylsilane (10 equiv) and trifluoroethanol (TFE, 8 equiv) were also added at −78 °C and stirred for 10 min prior to addition of $BF_3$-$OEt_2$ (4 equiv). The entire sequence and latter reaction were conducted on gram scales, completing the synthesis of the central subunit (24% overall, 8 steps from BocNH-L-Thr).

The left-hand subunit was assembled by several approaches, two of which are illustrated in Scheme 3 that were employed depending on the target structure (e.g., **1** vs *O*-acyl analogues). For meayamycin (**1**) itself, we first implemented a straightforward approach starting with the commercially available optically active alcohol **16**. Its acetal protection with ethyl vinyl ether (96%), alkyne carboxylation with $Boc_2O$ and acetal deprotection without intermediate purification of **18** (80-89%, 2 steps) provided **19**. Alcohol acetylation (82%) followed by stereoselective reduction of the alkyne to the cis alkene with Lindlar's catalyst and subsequent *t*-butyl ester deprotection (96%, 2 steps) provided **22**. The conversion of **16** to **20** could be accomplished without purification of intermediates to provide **20** in yields as high as 81% (>7 g scale) and **22** in 78% overall yield (6 steps). A more versatile subunit **27,** permitting late-stage divergent[24] functionalization and avoiding a coupling isomerization, was also employed. Compound **27** was prepared with small variations on the approach described by Kitahara[5] and itself adopted from earlier unrelated studies.[25] Commercial ethyl L-lactate protected as its TBDPS ether[25d] (98%) was reduced with DIBAL-H ($Et_2O$, −78 °C, 3 h) to the aldehyde **24**[25d] and subjected to *Z*-selective Wadsworth–Horner–Emmons olefination with **25**[23] (THF, −78 to −55 °C, 10 h), affording **26** in high yield (95%, two steps) and stereoselectivity (>99:1 *Z*:*E*). Methyl ester hydrolysis (LiOH, 90%) completed the synthesis of **27**, which was conducted on gram scales and required 4 steps (84% overall) from ethyl L-lactate.

The initial assemblage of the subunits for meayamycin paralleled earlier approaches and is summarized in Scheme 4.[6] Deprotection of **15** (10% TFA–$CH_2Cl_2$, 23 °C) followed by acylation of the liberated amine with **22** (1.2 equiv HATU, 4 equiv $i$Pr$_2$NEt, MeCN, 23 °C, 3–6 h, 69%) provided **28**. Cross metathesis of **28** with methacrolein (20 equiv) provided the α,β-unsaturated aldehyde **29** (0.2 equiv Grubbs II[26] cat., $CH_2Cl_2$, 23 °C, 36–48 h, 60–80%) or 0.01 equiv Grela cat.,[27] $CH_2Cl_2$, 23 °C, 12 h, 60%) followed by Wittig olefination afforded **30** (1.5 equiv $Ph_3P^+MeBr^-$, 1.4 equiv tBuOK, THF, 0– 23 °C, 4 h, 57–65%). Final cross metathesis of **30** with the right-hand subunit **7** (0.2 equiv Grela cat., 0.3 equiv benzoquinone (*p*-BQ), $ClCH_2CH_2Cl$, 45 °C, 12 h) notably without the protection of the secondary alcohol provided meayamycin (**1**) in yields as high as 54% and on scales up to 130 mg. This completed a synthesis of **1** by an approach that required a longest linear sequence of 12 steps (22 steps overall) from commercial materials and introduced what we suggest is the most straightforward preparation of a right-hand subunit detailed to date.

A further improved approach is also summarized in Scheme 4 and enlisted **27** in place of **22**. Introduction of the meayamycin *O*-acetyl group may be accomplished at any stage in this alternative sequence and is exemplified with the conversion of **31** to **28** by silyl ether deprotection and acetylation. It uses the left-hand subunit **27** available in four steps, proceeds in higher overall yields because of the more robust stability of the alcohol substituent, avoids a problematic *Z* to *E* isomerization of the left-hand subunit that we observed during the coupling introduction of **22** to provide **28,** proceeds with a more reproducible cross metathesis reaction in the conversion of **33** to **34** (0.3 equiv Grela cat., 0.4 equiv *p*-BQ, $ClCH_2CH_2Cl$, 40 °C, 12 h, 44–52%), and permits a late stage diversification of the *O*-acyl substituent. Without optimization, this latter feature was exemplified by the preparation of carbamate **37b** from **34** ($Bu_4NF$, THF, 0 °C, quant.; 3 equiv

carbonyldimidazole (CDI), 0.2 equiv 4-dimethylaminopyridine (DMAP), $CH_2Cl_2$, 23 °C then thiomorpholine), eq 1.




(1)

As this latter approach was in development, an initial series of meayamycin *O*-acyl analogues, including meayamycin B,[12] was prepared from the alcohol derived from acetate hydrolysis of **30** ($K_2CO_3$, MeOH, 95%) or later by TBDPS deprotection of **33** ($Bu_4NF$, THF, 23 °C, 4 h, quant), its acylation to access alternative and representative more stable carbamates,[12] and final cross-metathesis of the resulting **37a–c** with **7,** Figure 2.

The results of their initial evaluation, along with that of **1** and intermediate alcohol **35** are summarized in Figure 2. Whereas the removal of the *O*-acyl substituent reduced potency **(35)** as previously disclosed,[12] the more stable carbamate replacements for the acetate **(37a–c)** matched the activity of **1**. These observations, and those not reported herein,[18] complement those disclosed initially by Koide[12] and Webb[11] and more recently by Nicolaou[10] on the thailanstatins and help define a site and functionality available for productive modification on the stand-alone drugs themselves or for linkage as antibody-drug conjugates.

Finally, and as these studies were concluding, we reexamined an alternative sequence for assembling **33** from (Scheme 5). This entailed first elaborating **15** to **39** through cross metathesis with acrolein and subsequent Wittig olefination prior to introduction of the left-hand amide. In the absence of the labile acetate and *Z*-alkene found in the left-hand subunit, the transformations proved easier to implement and proceeded in higher conversions. In prior studies, acid-catalyzed Boc deprotection (10% TFA, $CH_2Cl_2$, 23 °C) conducted on **39** was reported to result in diene isomerization[6] and we confirmed these observations. However, we found that Boc deprotection under alternative conditions (1 N HCl, EtOAc, 23 °C, 15 min) did not suffer competitive isomerization and the liberated free amine could be coupled with **27** (1.2 equiv HATU, $i$Pr$_2$NEt, MeCN, 25 °C, 15 h) to provide **33** in excellent yields, providing a viable alternative in future studies.

Herein, a short scalable total synthesis of meayamycin is described by an approach that entails a longest linear sequence of 12 steps (22 steps overall) from inexpensive commercially available chiral pool materials (ethyl L-lactate, BocNH-Thr-OH, and D-ribose). It introduces the most straightforward preparation of the ornate right-hand subunit that contains the essential epoxide by an approach amenable to structural modifications. Its use in the divergent synthesis of *O*-acyl analogues is exemplified that helps define a site for productive modification on the stand-alone drugs or for linkage as antibody-drug conjugates.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## ACKNOWLEDGMENT

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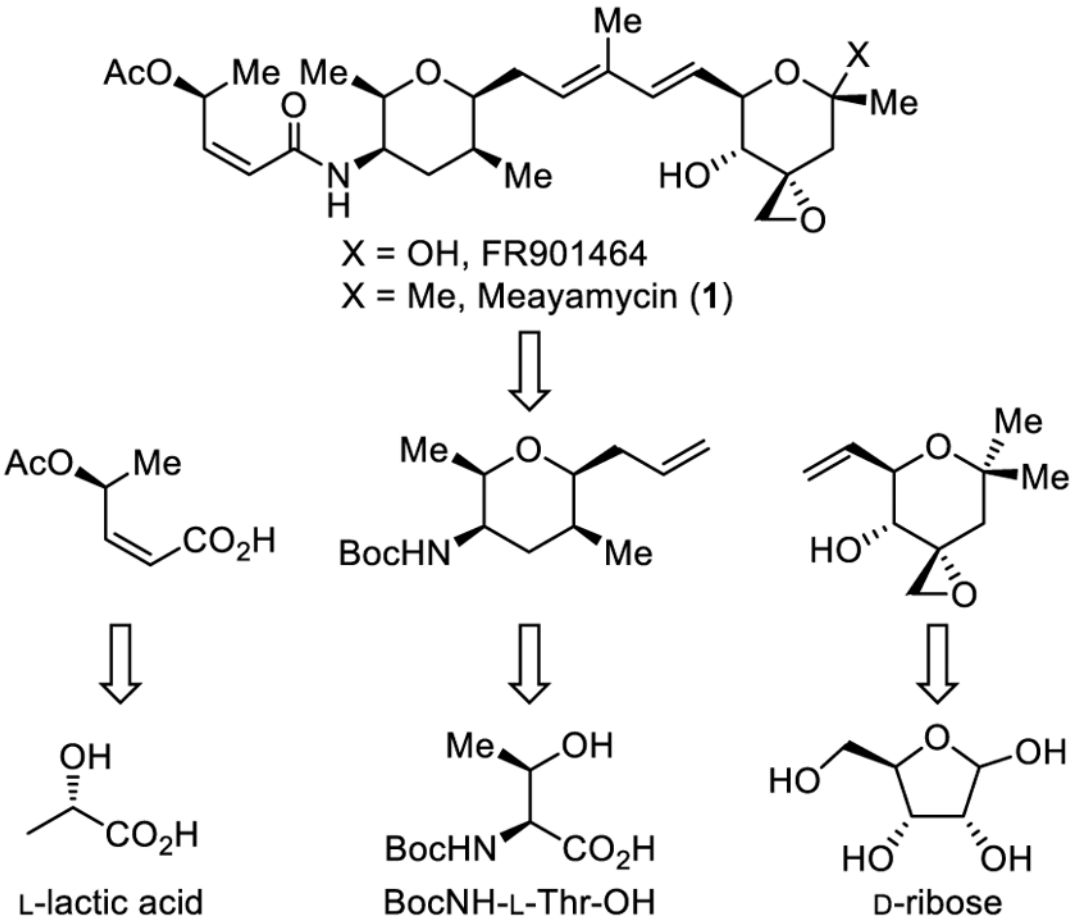
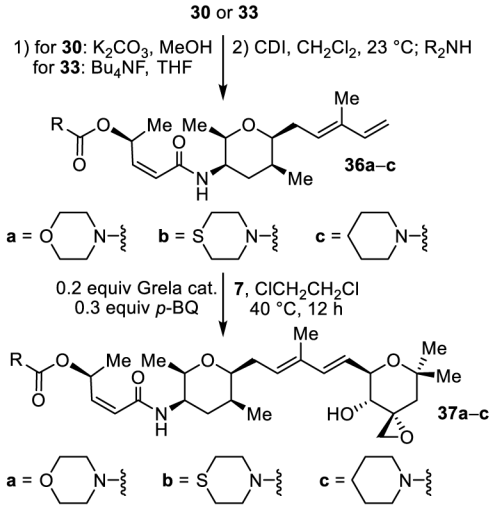



**Figure 1.**
Target structures, key intermediates, and chiral pool starting materials.



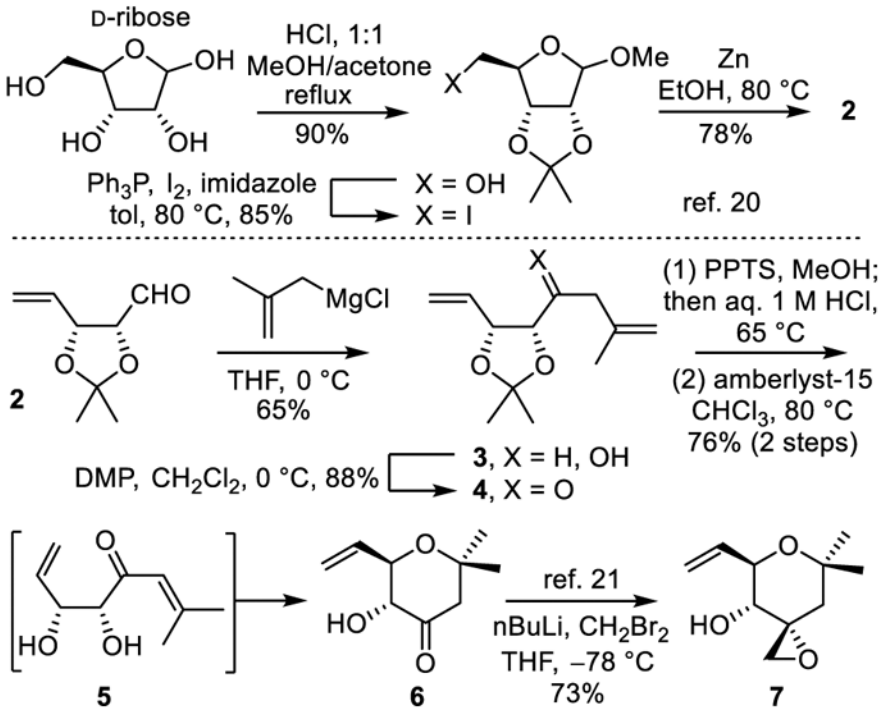

In vitro cytotoxic activity

| compd | cell line[a] | $IC_{50}$ (nM) |
|---|---|---|
| **1**, meayamycin | L1210 | 0.54 |
| | HCT116 | 0.56 |
| | HCT116/VM46 | 0.51 |
| **35** | L1210 | 7.8 |
| | HCT116 | 9.7 |
| | HCT116/VM46 | 7.4 |
| **37a**, meayamycin B | L1210 | 0.51 |
| | HCT116 | 0.49 |
| | HCT116/VM46 | 0.55 |
| **37b** | L1210 | 0.60 |
| | HCT116 | 0.48 |
| | HCT116/VM46 | 0.52 |
| **37c** | L1210 | 0.44 |
| | HCT116 | 0.68 |
| | HCT116/VM46 | 0.59 |

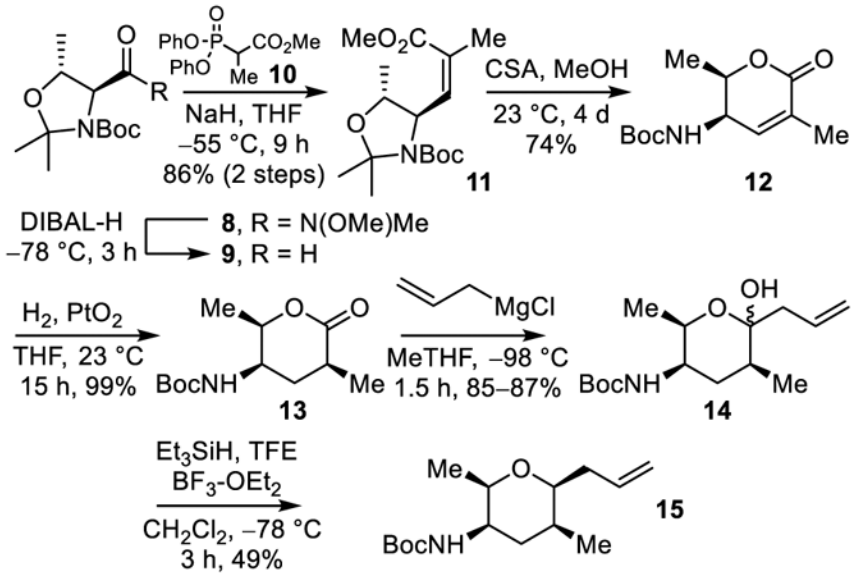
[a]L1210 (mouse leukemia), HCT116 (human colon cancer), HCT116/VM46 (resistant HCT116, Pgp overexpression), MCF-7 (human breast cancer)

**Figure 2.**

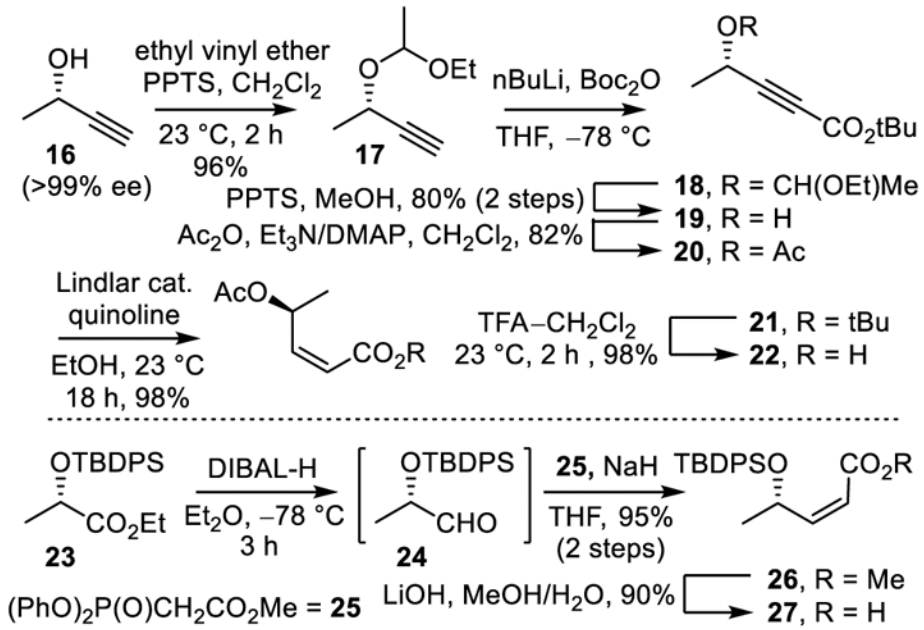
*O*-Acyl analogues, synthesis and activity.



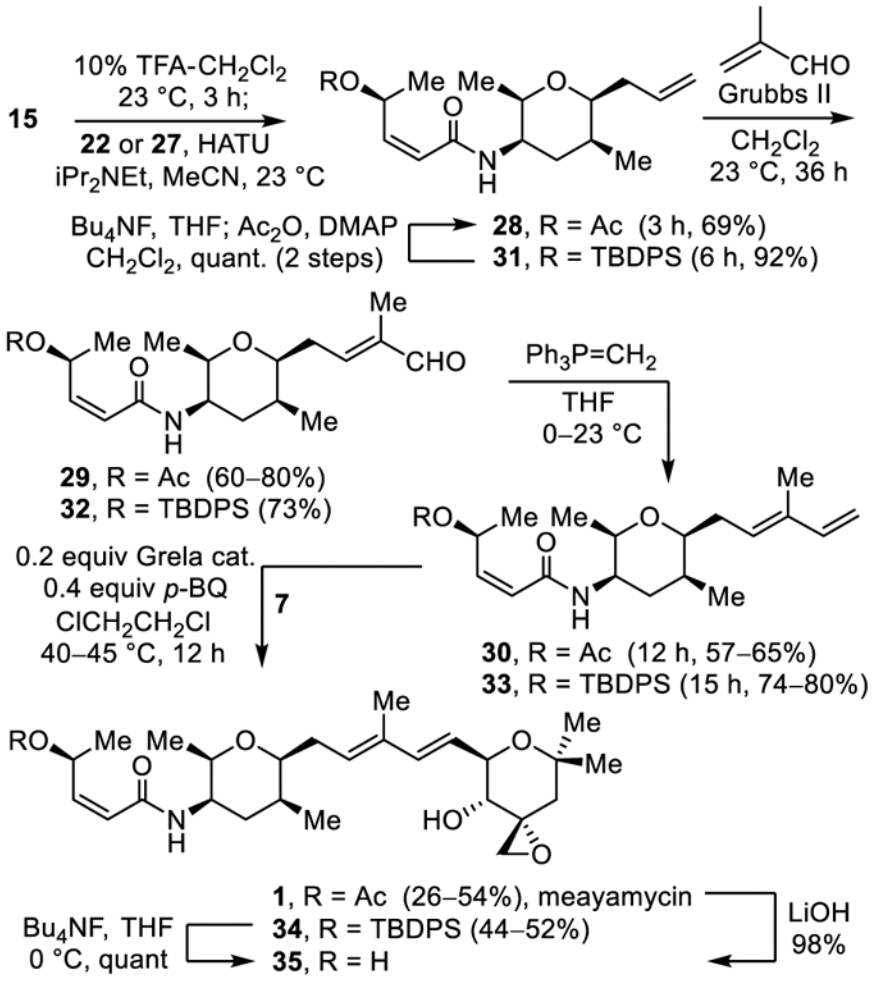

**Scheme 1.**



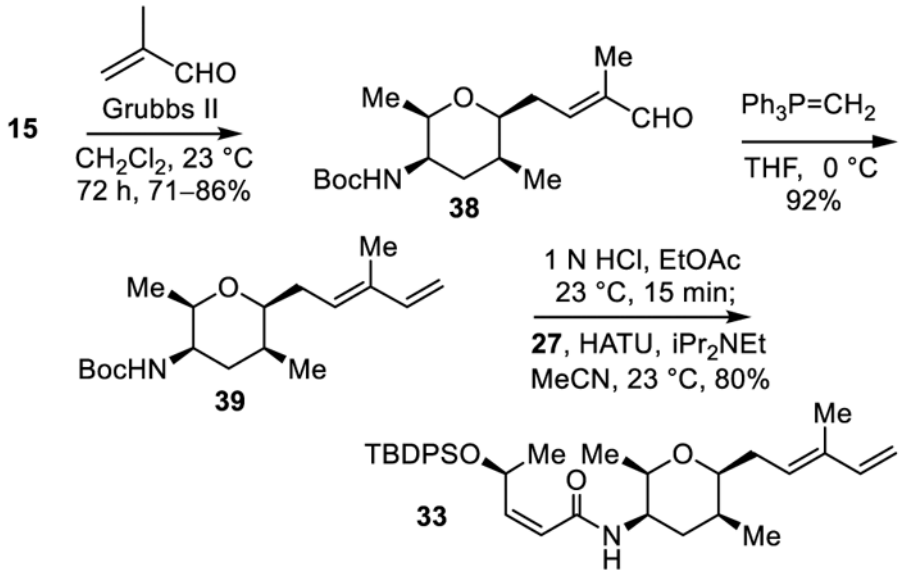

**Scheme 2.**




**Scheme 3.**




**Scheme 4.**




**Scheme 5.**