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Synthesis of the C21–C34 fragment of antascomicin B

John M. Hutchison¹, Andrew S. Gibson, David T. Williams, and Matthias C. McIntosh*

University of Arkansas, 119 Chemistry Building, Fayetteville, AR 72701, USA

Abstract

The C21–C34 fragment of the potent FKBP12-binding macrolide antascomicin B was prepared using Ireland-Claisen and allylic diazene rearrangements to establish the C26/C27 and the C23 stereocenters, respectively. Directed hydrogenation installed the C29 β -configuration. The fragment possesses **7** of the **11** fixed stereocenters contained in the natural product.

Keywords

Ireland-Claisen rearrangement; Allylic diazene rearrangement; Directed hydrogenation; Natural product

The antascomicins are a small family of macrolides isolated in China from soil bacteria of the genus *Micromonospora* that exhibit very strong binding to FKBP12.¹ The most potent of these, antascomicin B, binds with an IC₅₀ of 0.7 nM, equivalent to that of FK-506 and rapamycin.^{2–4} Unlike the latter compounds, which are clinically used to suppress graft rejection in organ transplant patients, the antascomicins possess no immunosuppressive effects. They lack the so-called effector domain that is responsible for binding a second protein, calcineurin for FK-506 and mTOR for rapamycin.

However, FKBP12 and other immunophilins have been found in a variety of other tissues,⁵ including the nervous system. Small molecule FKBP binders have been demonstrated to stimulate neurite outgrowth and hence have potential for use in the treatment of neurodegenerative diseases.⁶ In addition, FKBP12 has multiple isoforms, and it may be biochemically or therapeutically useful to selectively inhibit a particular isoform.⁷

Similarly, the development of inhibitors of specific peptidylprolyl isomerases such as FKBP12 may find clinical applications.⁸ Antascomicin B offers a platform from which these issues can be explored.

In 2008 we reported a model study of the C22–C34 fragment of antascomicin B lacking the C31 and C32 hydroxyl groups.⁹ We report herein the successful completion of the corresponding fully substituted and differentially protected fragment.

Our approach to C21–C34 fragment **1** involves a directed hydrogenation to install the C29 stereocenter (Scheme 1). The remote C23 stereocenter of diene **2** would be installed via our

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*Corresponding author. mcintosh@uark.edu (M.C. McIntosh).

¹Current address: Auburn University Montgomery, 7061 Senators Dr., Montgomery, AL 36117, USA.

Supplementary data

Supplementary data (experimental procedures, characterization data, ¹H and ¹³C NMR spectra of all new compounds; crystal structure and cif file of compound **9'**, the C31 benzyloxycarbonyl variant of compound **9**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.09.027.

recently reported acyclic 1,3-reductive transposition methodology¹⁰ from hydrazone **3**. The hydrazone would in turn be derived from pentenoic acid derivative **4**, which is the product of Ireland-Claisen rearrangement of allylic ester **5**.¹¹

The synthesis would begin with the known trihydroxy cyclohexenone **6** (Scheme 2), which is available in racemic form in five steps from benzoquinone.¹² However, an efficient asymmetric route to **6** was not available. We, therefore, undertook a racemic synthesis of fragment **1** while simultaneously developing a practical, scalable asymmetric approach to **6**. The latter has been successfully realized.¹³ We report herein the racemic synthesis of fragment **1**.

Selective *bis*-silylation of triol **6**, followed by alkene hydrogenation gave hydroxy ketone **7**. Although we had initially also protected the C31 hydroxyl group, additions of propynyl MgBr or Li to the triply protected substrate were inefficient, unselective, or selective for the undesired isomer. We noted scattered reports in the literature describing the addition of organometallic nucleophiles to cyclohexanones bearing unprotected β -hydroxyl groups that provided 1,3-*syn*-diols with high diastereoselectivity.¹⁴ In those cases, however, the hydroxyl groups were fixed in an axial position. In at least one case,^{14d} an isomeric equatorial alcohol gave the opposite facial selectivity. Hence enone **7** would presumably need to adopt an all axial conformation to exhibit high diastereoselectivity. Gratifyingly, the addition of propynyl MgBr to β -hydroxy ketone **7** did indeed afford a single 1,3-*syn*-diol diastereomer **8** in good yield.^{15,16} This was in stark contrast to the propynyl MgBr addition to the corresponding model compound lacking the C31 and C32 oxygens, which was completely unselective.⁹

Regioselective protection of the C31 2° alcohol of diol **8** as the *t*-Bu carbonate was achieved by treatment of the diol with just over 1 equiv of *n*-BuLi (Scheme 3). Acylation of the 3° hydroxyl group was performed in a similar fashion to give propargyl ester **9**. Hydrogenation of alkyne **9** using Pd/BaSO₄ gave *Z*-alkene **5** in high yield.

Ireland-Claisen rearrangement of the highly sterically congested allylic ester **5** was effected by treatment with LDA and TMSCl at -78 °C, followed after 10 min by HOAc (Scheme 4). The HOAc served to protonate excess base and prevent enolization of the rearrangement product.¹⁷ The rearrangement presumably proceeded via a chair-like transition state corresponding to *Z*-ketene acetal **5'** in which the larger OTBS-substituted C30 carbon was oriented in the pseudo-equatorial position. Pentenoic acid **4** was obtained in very good yield as a single diastereomer based on ¹H NMR and ¹³C NMR analyses. Carboxylic acid **4** was then converted to Weinreb amide **10**.¹⁸ Addition of the Li anion of iodide **11**¹⁹ provided enone **12**. Conversion of enone **12** to hydrazone **3** was sluggish, but highly selective for the desired *E*-isomer.

We then sought to employ our 1,3-reductive transposition methodology to deliver diene **2** (Scheme 4). This example would constitute the most highly substituted and oxygenated system thus far attempted. The conditions we employed previously largely followed Kabalka's protocol.²⁰ After reduction of the hydrazone with catecholborane was complete, solid NaOAc hydrate was added and the mixture heated under reflux.

However, reduction of hydrazone **3** required significantly higher loading of catecholborane than was needed in the simpler systems. Three charges of 6 equiv each were ultimately needed to effect the reduction.²¹ The high loading necessitated an intermediate wash after reduction to decompose the excess borane. The crude isolate was then treated with NaOAc and heated under reflux in CHCl₃ to provide 1,4-*syn* isomer **2**, presumably via allylic diazene **3'**. The 1,4-*syn* configuration is a consequence of allylic strain directed rearrangement.^{22,23} Cleavage of the TBS groups was best effected sequentially, with the

C30 group undergoing deprotection upon treatment with HOAc/H₂O, and the C31 TBS group requiring Bu₄NF to give alcohol **13** in good overall yield.

As in the model system, we pursued a directed hydrogenation approach to install the C29 stereocenter, although we recognized potential problems arising from the more highly substituted cyclohexane ring. Presumably, the directed hydrogenation would need to occur from the higher energy all axial conformation of diene **13** to selectively provide the β -configuration at C29 (Scheme 5). Although a few examples of directed hydrogenation of alkenes possessing unprotected diols have been reported,²⁴ it was nevertheless a concern that the high affinity of Crabtree-type Ir(I) catalysts for alcohols would result in sequestering of the catalyst by either the diol or an alcohol-carbonate combination and prevent effective reduction.

In the event, directed hydrogenation of diene **13** did provide the desired configuration at C29,²⁵ although a high loading of catalyst (ca. 40 mol %) was indeed required. For the purposes of characterization, we found it helpful to convert diol **1** to the corresponding *bis-p*-nitrobenzoate **14**.

In summary, a differentially protected C21–C34 fragment of antascomicin B has been prepared in a highly stereocontrolled sequence. The synthesis was 14 steps from the known trihydroxycyclohexenone **6**, or 19 steps from benzoquinone. Further progress toward the antascomicins will be presented in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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25. The C29 configuration was confirmed by the 10.0 Hz *trans*-diaxial coupling between the C29 and C30 protons in *bis*-p-nitrobenzoate ester **14**.

Scheme 1.
Retrosynthesis of C21-C34 fragment **1**.

Scheme 2.
Synthesis of allylic ester **5**.

Scheme 3.
Synthesis of hydrazone **3**.

Scheme 4.
Synthesis of C22–C34 fragment **1**.

Scheme 5.
Directed hydrogenation of 28-C29 alkene.