A Caveat in the Application of the Exciton Chirality Method to *N*,*N*-Dialkyl Amides. Synthesis and Structural Revision of AT2433-B1

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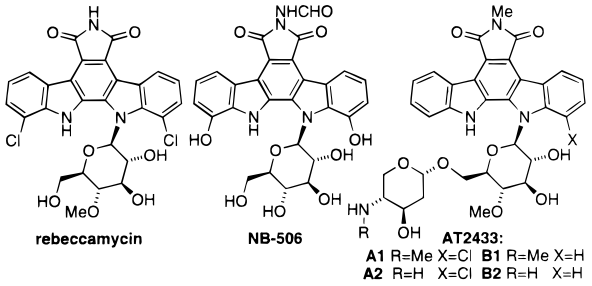
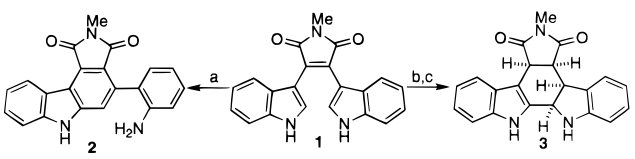
Circular dichroism (CD) is a powerful technique for absolute stereochemical assignment.[1,2] Dibenzoyl derivatives of vicinal 1,2-amino alcohols exhibit strong anisotropic absorption of circularly polarized light due to the interaction between gauche benzoyl chromophores. This differential absorption is expressed as an exciton couplet in the CD spectrum. The diagnostic relationship between exciton couplet and absolute stereochemistry is the basis for the exciton chirality method. The benzamide configuration is critical for stereochemical assignment.[3] For amino alcohol derivatives, *E* and *Z* amides possess an enantiotopic relationship between chromophores that produces opposite CD curves. This deceptive effect of *N*,*N*-dialkyl amide conformation was revealed during the first total synthesis of the antitumor antibiotic AT2433-B1[4,5] from *Actinomadura melliaura*.

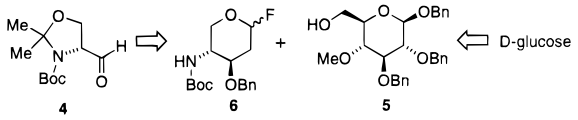


The Mannich dimerization of indoles[6] provides an efficient method for the construction of indolocarbazole glycosides[7] because the indoline products can efficiently capture unprotected, unactivated carbohydrates.[8−10] This mild glycosylation is stereoselective and produces the equatorial *N*-glycoside. The aminodisaccharide moiety of the AT2433 natural products challenges traditional methods for indole glycosylation and provides an opportunity to validate the efficiency of carbohydrate capture by indolines. Total synthesis serves an important role in new drug development by confirming structural assignment, revealing fundamental patterns of reactivity, and expanding the range of available derivatives. Derivatives have been particularly important for understanding and improving the efficacy of topoisomerase inhibitors such as camptothecin, rebeccamycin, and NB-506.[11,12]

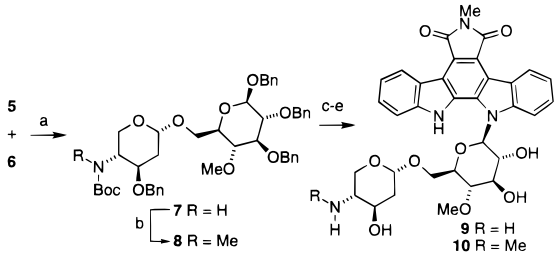
Scheme 1



Scheme 2



Scheme 3



Mannich cyclization of *N*-methylarcyriarubin A **1** is accompanied by an undesired opening of the indoline ring to give carbazole **2**.[13,14] The corresponding bisindolylsuccinimide, however, cyclizes efficiently in neat trifluoroacetic acid (TFA) to afford indoline (±)-**3** as the *cis-syn-cis* diastereomer (Scheme 1).

The two carbohydrate subunits of AT2433 were ultimately derived from D-glucose[15] and D-serine. The stereochemistry of the amino sugar was established by Roush allylboration of D-Garner's aldehyde.[16]

Coupling of the primary alcohol **5** was performed under Mukaiyama−Nicolaou conditions with little control of anomeric stereochemistry (Scheme 3).[17] For the synthesis of AT2433-B1, carbamate **7** was *N*-methylated to give **8**. Disaccharide **8** was debenzylated and coupled with 3 equiv of indoline **3** in refluxing methanol. Oxidation with DDQ afforded the fully aromatic indolocarbazole glycoside. Deprotection of the Boc group completed the synthesis but was accompanied by a significant amount of hydrolysis, the 2-deoxyglycoside being labile.

Both glycoside **10** and AT2433-B1 exist in two conformations in d_6-DMSO. At room temperature (slow exchange), or at 150

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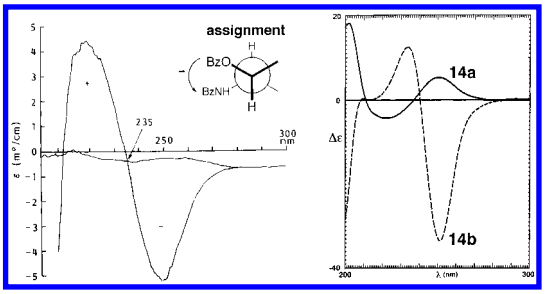
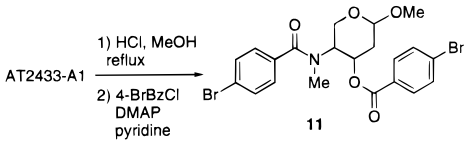
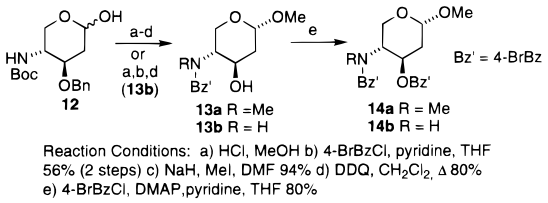


Figure 1. (a) CD spectrum of **11**. (b) CD spectra of **14a** and **14b**. All spectra were recorded in acetonitrile at a 40 mM concentration.

Scheme 4



Scheme 5

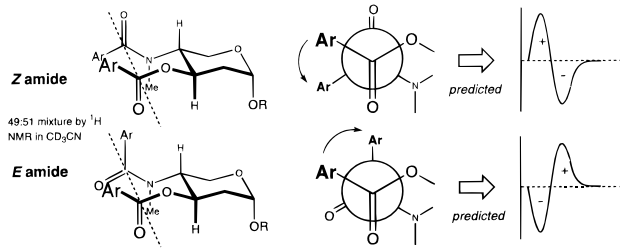


°C (rapid exchange), the NMR spectra were similar, but did not match. In addition, glycoside **9** (prepared by the same route) did not match authentic AT2433-B2. The tetraacetate of **9** was prepared and the stereochemistry of the β-glucoside moiety and the connectivity were confirmed using *J* analysis and HMBC, respectively. At this point we were confident that **9** corresponded with AT2433-B2 in the following ways: (i) the connectivity was the same, (ii) the structure of the 4-*O*-methyl-β-D-glucoside was secure, and (iii) the relative stereochemistry of the amino sugars was the same.

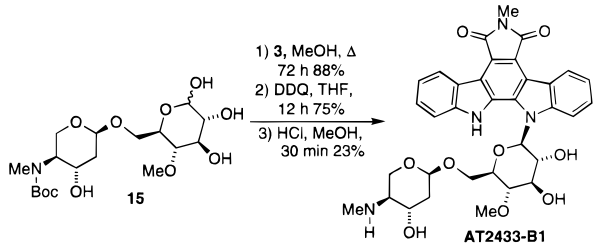
We were led to reconsider the absolute stereochemistry of the amino sugar moiety. Other natural products isolated from *Actinomadura* (calicheamicin and esperamicin) possess the enantiomer of the AT2433 amino sugar.[18,19] The absolute stereochemistry of the AT2433 amino sugar was originally assigned by application of the exciton chirality method to a dibenzoyl derivative **11** derived from methanolysis of AT2433-A1.[4] The absolute stereochemistry was assigned as 3*R*, 4*R* based on the negative chirality of the exciton couplet (Figure 1a).

To verify the absolute configuration of the amino sugar moiety, independent synthesis of pyranoside **11** was required. Lactol **12** was converted to **14a** by the route shown in Scheme 5. Suprisingly the exciton couplet for synthetic **14a** exhibited positive chirality (Figure 1b), whereas amino alcohol derivatives with the same absolute configuration as **14a** should exhibit negative chirality.[20] To remove any doubts about the configuration of amino alcohol derivative **14a**, the absolute stereochemistry of intermediate **13b**

Scheme 6



Scheme 7



was confirmed by Mosher's ester analysis. The discrepancy between **10** and AT2433-B1 was now clear; the puzzling results of the CD were not.

To explain the discrepancy between the CD of **14a** and **11**, we directed our attention to the tertiary amide moiety. Molecular modeling indicates only a small energy difference between *E* and *Z* amide conformations of **14a**, and this is supported by the existence of a 1:1 ratio of signals in the ^{1}H NMR (in CD_3CN).[21] As shown in Scheme 6 **the aryl chromophores in the *E* amide adopt a clockwise orientation, whereas the aryl chromophores in the *Z* amide adopt a counterclockwise orientation. Thus, *E* and *Z* amides should give opposite Cotton effects.** The resulting CD spectrum is dictated by two factors that are difficult to predict: (i) the relative population of conformers and (ii) the degree to which the two chromophores interact in each conformer. These combined effects can generate either positive or negative chirality, depending on which conformation dominates the CD spectrum.

Figure 1b highlights the deceptive effects of *N*,*N*-dialkyl amide conformation. The negative chirality of *N*-alkyl amide **14b** corrrectly correlates with the amino alcohol configuration; the positive chirality of *N*,*N*-dialkyl amide **14a** does not. The diminished amplitude of the CD curve of **14a** corroborates the opposing effects of *E* and *Z* conformers.[22]

Having established the correct configuration of the amino sugar as 3*S*, 4*S* (rather than 3*R*, 4*R*), we repeated our original synthesis with L-Garner's aldehyde and prepared the enantiomer of pyranosyl fluoride **6**. Glycosylation with glucoside **5**, installation of the methyl group, and debenzylation provided disaccharide **15**. *N*-Glycosylation, oxidation, and deprotection of the Boc group provided material identical with AT2433-B1 (Scheme 7).

This work has capitalized upon a Mannich cyclization/glycosylation route for the synthesis of indolocarbazole glycosides. It has led to a structural revision of the AT2433 series of antitumor antibiotics. Finally this work exposes the need for caution when *N*,*N*-dialkyl amides are involved in determination of absolute stereochemistry of amino alcohols using exciton chirality.

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Supporting Information Available: Procedures and characterization data for compounds **3**, **5**−**10**, **12**−**15**, and results of mechanics and semiempirical calculations for conformations of **14a** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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