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The synthesis of 8-substituted tetracycline derivatives, the first 8-position carbon–carbon bond

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Abstract

The synthesis of C8-functionalized tetracyclines using Stille coupling is described. These derivatives are the first reported with a carbon–carbon bond in the 8-position of a tetracycline negating total synthesis routes to 8-substituted tetracyclines.

Keywords: antibacterials; antibiotics; coupling reactions; polycyclic aromatic compounds.

Since 1944 tetracyclines have been important for the treatment of bacterial infections when chlortetracycline was introduced into clinical use. The advantages of these compounds were that they inhibited a much wider spectrum of gram-positive and gram-negative organisms. In subsequent years, lengthy programs directed at the chemical modification of tetracyclines yielded few medically useful derivatives. As a result, numerous chemical modifications of tetracyclines have been reported at all conceivable positions except for the C8 position.[1–3] Many researchers feel that the synthesis of 8-substituted tetracylines falls strictly within the realms of total synthesis.[4] In 1979 Glatz et al. reported the total synthesis of racemic 6-demethyl-6-deoxy-8-hydroxy-tetracycline.[5] The reportedly poor antimicrobial activity attributed to this compound was likely due to the epimerization at C4 and not the substitution at C8.[6] In fact, dactylocyclines are a class of clinical isolates bearing a C8 methoxy substituent and show potent antimicrobial activity against tetracycline resistant bacteria.[7,8] These molecules are the first known tetracycline glycosides and the first naturally occurring C6 *epi* tetracyclines. Unfortunately, efforts directed toward chemical modification of tetracyclines subsided in the early 1980's due to bacterial resistance and the advent of new antibiotics leaving this interesting class of compounds relatively unexplored.

Recently, access to 6-demethyl-6-deoxy-8-chloro-tetracyclines has been described in a communication by Sum et al. via a diazonium rearrangement reaction (Schemes 1 and 2).[9] However, there has been no report utilizing this halogenated substrate as an intermediate for further modification. The absence of reported modifications to the 8-halotetracyclines is surprising in light of

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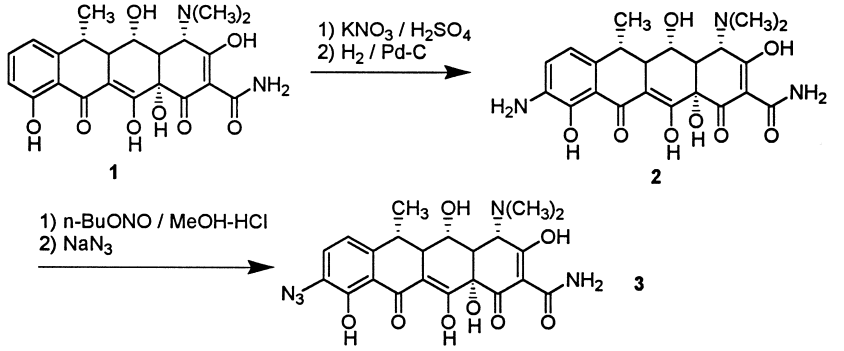
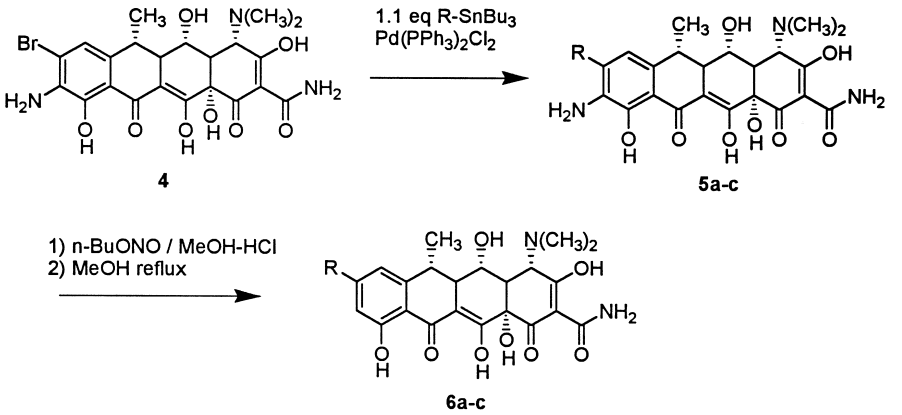
the number of cross-coupling reactions which will tolerate a polyhydroxylated substrate such as tetracycline. Research in our laboratory has focused on utilizing transition metal-catalyzed carbon–carbon formation for preparing a number of novel C7- or C9-substituted tetracycline derivatives.[10] Fortuitously, these reactions are very high yielding, easy to carry out, and in most cases improve the antimicrobial activity of the compound. This chemistry was easily extended to the preparation of C8-substituted tetracyclines in good yield. This methodology eliminates the need for total synthesis routes to C8-substituted tetracyclines and allows suitable quantities of material to easily be prepared for biological evaluation.



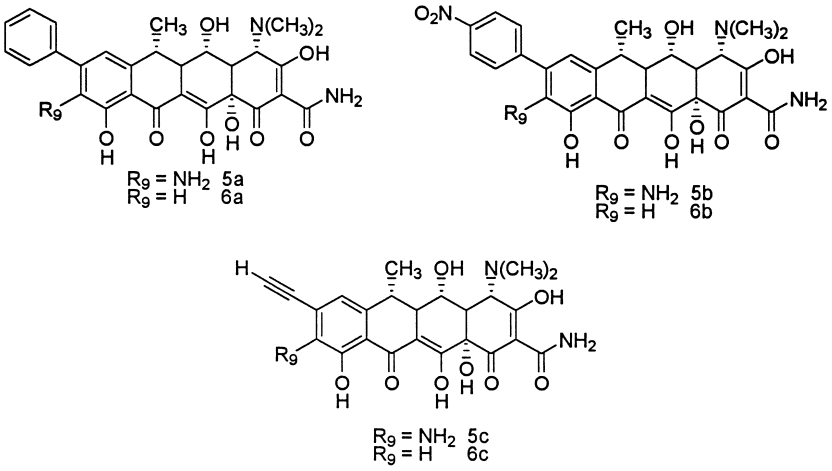
Scheme 1.



Scheme 2.

Treatment of doxycyline **1** with potassium nitrate in concentrated sulfuric acid followed by reduction with H_2 and Pd/C affords 9-aminodoxycycline **2** in 79% yield. Diazotization with *n*-butylnitrite in 1.0N methanolic HCl followed by treatment with NaN_3 affords 9-azidodoxycycline **3**. Sum et al. have described the preparation of 9-amino-8-chlorodoxycycline by bubbling HCl gas through a methanolic solution of **3**. However, Stille coupling performed on the chloro compound resulted in low yields presumably due to the difficulty of oxidative addition to the active palladium species.[11] Since it is well known that aryl bromides undergo oxidative addition much more readily than the corresponding aryl chlorides, the reaction conditions were modified to give the C8

bromodoxycycline. Thus, the treatment of **3** with HBr/HOAc afforded 9-amino-8-bromodoxycycline **4** in 56% isolated yield.[12] The reaction of **4** with 1.1 equivalents of phenyl tri-*n*-butyltin or 4-nitrophenyl tri-*n*-butyl tin in the presence of a palladium catalyst gives good yields of the cross-coupled product **5a** and **5b**, respectively, with no significant side products or homo-coupling products observed.[13] Similarly, the reaction of **4** with tri-*n*-butylstannylacetylene gave 9-amino-8-ethynyldoxycycline **5c** in excellent yield. The C9 amino group may be removed via diazotization followed by heating in methanol to afford the 8-substituted doxycyclines **6a–c** (Scheme 3). In addition, the potential for 8,9-disubstituted tetracyclines opens up the exciting possibility of extending the aromatic ring system by tandem cyclization reactions.



Scheme 3.

In summary, we have demonstrated a concise approach to the synthesis of novel 8-substituted tetracycline derivatives which previously were only available by total synthesis. This method should be advantageous for several reasons. This general method allows the synthesis of a large number of derivatives which are critical for structure–activity relationships and biological evaluation. Extension of this methodology to other tetracyclines such as minocycline, sancycline, and chlortetracycline may be easily accomplished under similar conditions. These compounds are amenable to further structural modification which may lead to a compound with antimicrobial activity against multi-antibiotic resistant bacteria. Presently, biological assessment of these compounds is being undertaken and the synthesis of derivatives with unique pharmacophores may shed light on the importance of functionalization in this position.

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12. *9-Amino-8-bromodoxycyline*: ^{1}H NMR (methanol *d*-4, 400 MHz) δ 6.94 (s, 1H), 4.47 (s, 1H), 3.77 (s, 1H), 3.54 (m, 1H), 3.16 (s, 1H), 2.96 (s, 7H), 2.81 (m, 2H), 2.58 (m, 3H), 1.47 (d, J = 6.13 Hz, 3H). MS (FAB) 538 and 540 amu (isotopic pattern confirming the presence of bromine).
13. Typical coupling procedure: 25 mg of 9-amino-8-bromodoxycycline (**4**), 3 mg of $Pd(PPh_3)_2Cl_2$, 1 mg of $AsPh_3$, and 1 mg of CuI is dissolved in 5 ml of toluene with stirring. Then 8.0 μl of phenyl tri-*n*-butyltin is added and the solution refluxed for 6 h under nitrogen. The solution is cooled to room temperature, filtered, the solvent removed, and the crude residue purified by preparative thin layer chromatography. Yield: 23 mg (93%); ^{1}H NMR (methanol *d*-4, 400 MHz) δ 7.78 (m, 5H), 6.71 (s, 1H), 3.95 (s, 1H), 3.65 (s, 1H), 2.79 (s, 7H), 2.52 (m, 3H), 1.53 (d, J = 6.41 Hz, 3H).