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A Macrocyclic Approach to Tetracycline Natural Products. Investigation of Transannular Alkylations and Michael Additions

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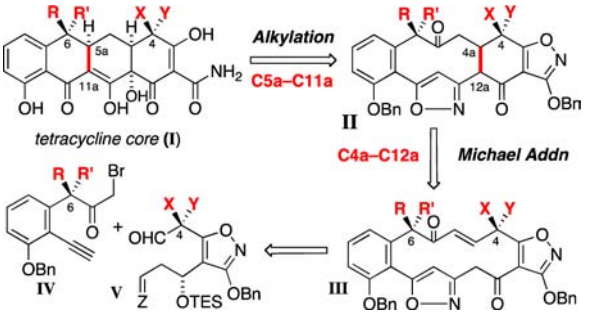
ABSTRACT



A new approach to the tetracycline core structure is presented. The pivotal intermediate is identified as macrocycle III. The two interior bonds (C4a−C12a and C5a−C11a) are to be constructed through sequential transannular Michael additions (III−II) and compression-promoted transannular isoxazole alkylations from intermediate II.

The tetracycline antibiotics, such as (−)-tetracycline (**1**)[1] and (−)-oxytetracycline (**2**),[2] have been the subject of sustained research since their discovery in 1948[3] (Figure 1). More recent isolates with intriguing anticancer properties, SF2575 (**3**)[4] and TAN-1518A/B (**4**, **5**),[5] have expanded both the structural complexity and known biological activity of this natural product family.

Herein, we report a new approach to the construction of the tetracycline nucleus involving advanced macrocyclic intermediate **III** (*vide supra*).[6] From this intermediate, a subsequent stereoselective transannular Michael addition (C4a−C12a) followed by an internal alkylation (C5a−C11a) is planned for the formation of the two internal C−C bonds.[7]

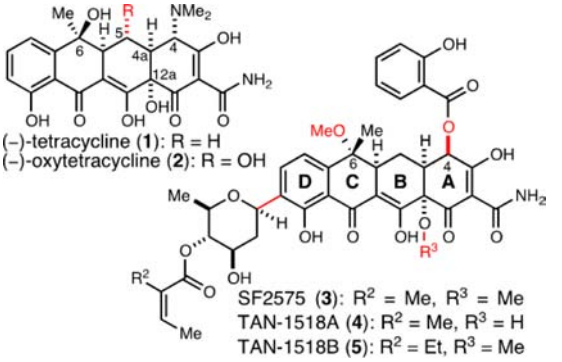


Figure 1. Representative tetracycline natural products.

(1) (a) Booth, J. H.; Morton, J., II; Petisi, J. P.; Wilkinson, R. G.; Williams, J. H. *J. Am. Chem. Soc.* **1953**, *75*, 4621. (b) Conover, L. H.; Moreland, W. T.; English, A. R.; Stephens, C. R.; Pilgrim, F. J. *J. Am. Chem. Soc.* **1953**, *75*, 4622–4623.

(2) Finlay, A. C.; Hobby, G. L.; P'an, S. Y.; Regna, P. P.; Routien, J. B.; Seeley, D. B.; Shull, G. M.; Sobin, B. A.; Solomons, I. A.; Vinson, J. W.; Kane, J. H. *Science* **1950**, *111*, 85.

(3) Duggar, B. M. *Ann. N.Y. Acad. Sci.* **1948**, *51*, 177–181.

(4) Hatsu, M.; Sasaki, T.; Watabe, H.; Miyadoh, S.; Nagasawa, M.; Shomura, T.; Sezaki, M.; Inouye, S.; Kondo, S. *J. Antibiot.* **1992**, *45*, 320–324. (b) Hatsu, M.; Sasaki, T.; Gomi, S.; Kodama, Y.; Sezaki, M.; Inouye, S.; Kondo, S. *J. Antibiot.* **1992**, *45*, 325–330.

(5) Horiguchi, T.; Hayashi, K.; Tsubotani, S.; Iineuma, S.; Harada, S.; Tanida, S. *J. Antibiot.* **1994**, *47*, 545–556.

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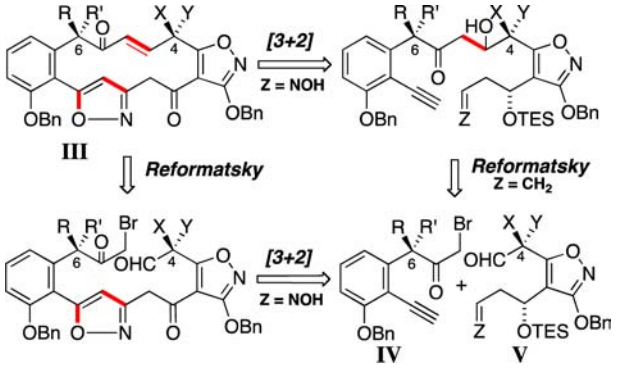
It is anticipated that the transannular ring strain inherent in intermediate ***II*** *should enhance the facility of the alkylation step*. This communication focuses on the stereochemical outcome of this transannular Michael addition (cf. **III**–**II**) and provides some preliminary results on the strain-enhanced transannular alkylation event.

This synthesis plan exploits the resident carbonyl group polarities derived from the biosynthetic origin of the tetracyclines while also incorporating flexibility dependent upon the identities of the substituents at the C4- and C6-positions. We have incorporated the popular Stork–Hagedorn benzyloxyisoxazole synthon for the vinylogous carbamic acid moiety.[8] The 1,3-diketone proximal to the D-ring is masked as a second isoxazole synthon. This heterocycle maintains the C=O derived functional group polarity while also enabling reagent-selective activation of either the C11a or C12a position.

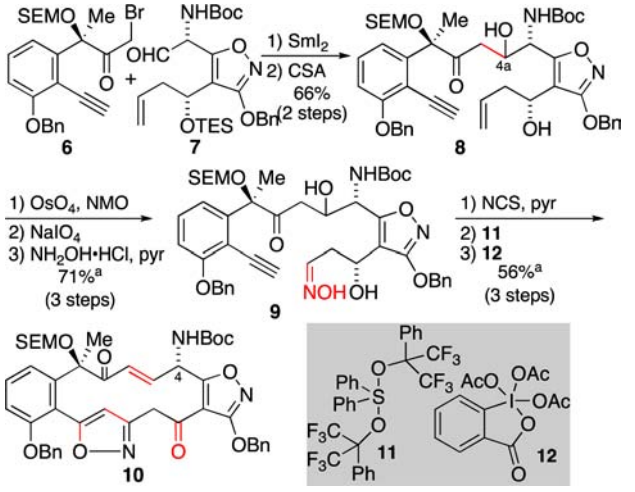
Scheme 1. Complementary Approaches to Macrocycle Synthesis



Macrocycle Synthesis. To maximize convergency, two complementary disconnections for the deconstruction of **III** have been explored: a nitrile-oxide cycloaddition and a Reformatsky aldol addition (Scheme 1).[9] Due to the orthogonality of these two reactions, minor variations in the coupling partners provide access to either option. In practice, both assemblage variants have been utilized to synthesize the macrocycles discussed herein.

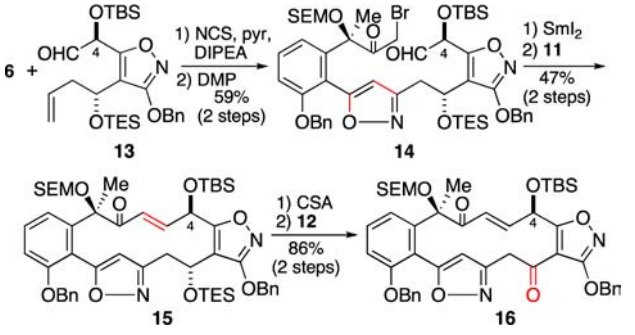
NHBoc macrocycle **10** was constructed via an initial Reformatsky aldol to couple fragments **6** and **7**,[10] affording **8** in reasonable yield after deprotection (Scheme 2).[11] The two aldol diastereomers were separated at this point and carried on individually to **10**. It is noteworthy that the two C4a alcohol diastereomers did not efficiently dehydrate under the identical conditions. Conversion of **8** to oxime **9** via a three-step procedure was uneventful. Macrocyclization was effected in good yield via the implementation of dipolar cycloaddition conditions reported by Mulzer,[12] producing macrocycle **10** after selective dehydration[13] and oxidation.

Scheme 2. Synthesis of the α-NHBoc Macrocycle **10**



[a] Yield reported corresponds to the major aldol diastereomer.

Scheme 3. Synthesis of the β-OTBS Macrocycle **16**



The alternate macrocycle synthesis strategy was arbitrarily employed for the synthesis of C4-β-OTBS macrocycle **16** (Scheme 3). An initial nitrile-oxide cycloaddition was performed to couple subunits **6** and **13**, producing **14** after primary alcohol oxidation. A Reformatsky aldol macrocyclization was then implemented to afford macrocycle **15** after dehydration. Two remaining functional group manipulations were performed to convert the TES-silyl ether to elaborated macrocycle **16**. The C4-α-OTBS macrocycle **17** was synthesized in direct analogy to **16** (*cf.* Scheme 4).

(6) For related strategies, see: (a) Evans, D. A.; Ripin, D. H. B.; Halstead, D. P.; Campos, K. R. *J. Am. Chem. Soc.* **1999**, *121*, 6816–6826. (b) Evans, D. A.; Starr, J. T. *J. Am. Chem. Soc.* **2003**, *125*, 13531–13540. (c) Scheerer, J. R.; Lawrence, J. F.; Wang, G. C.; Evans, D. A. *J. Am. Chem. Soc.* **2007**, *129*, 8968–8969.

(7) The numbering of the tetracycline structure is maintained in the illustrated macrocyclic intermediates.

(8) Stork, G.; Hagedorn, A. A., III. *J. Am. Chem. Soc.* **1978**, *100*, 3609–3611.

(9) Please see the Supporting Information for information regarding fragment syntheses.

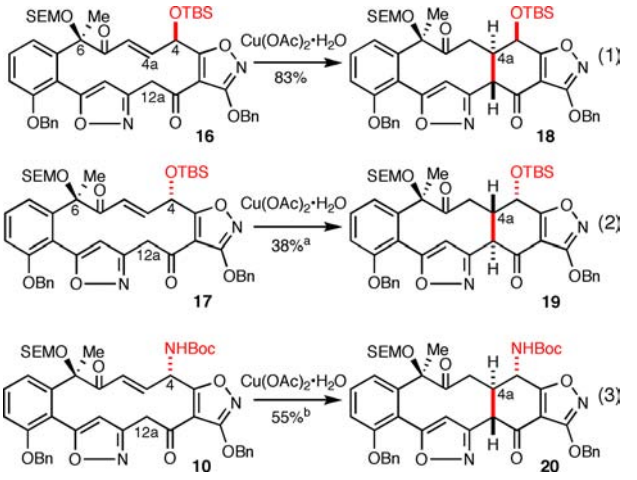
(10) Please see the Supporting Information for fragment syntheses.

(11) (a) Moslin, R. M.; Jamison, T. F. *J. Am. Chem. Soc.* **2006**, *128*, 15106–15107. (b) Sparling, B. A.; Moslin, R. M.; Jamison, T. F. *Org. Lett.* **2008**, *10*, 1291–1294.

(12) Enev, V. S.; Drescher, M.; Mulzer, J. *Tetrahedron* **2007**, *63*, 5930–5939.

(13) Arhart, R. J.; Martin, J. C. *J. Am. Chem. Soc.* **1972**, *94*, 5003–5010.

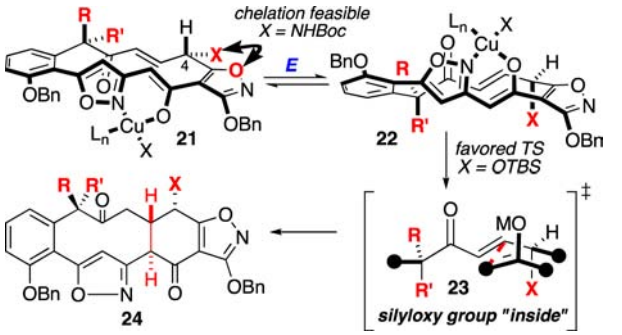
Scheme 4. Transannular C4a–C12a Michael Bond Constructions



Transannular Michael Additions. With reliable methods for macrocycle construction in hand, attention was directed to the Michael addition study to form the A-ring and to establish the C4a-stereocenter. Following optimization, we were able to establish conditions to promote this reaction employing $Cu(OAc)_2 \bullet H_2O$ to mediate the transformation (Scheme 4). We hypothesize that enolization occurs through bidentate Cu(II) complexation, followed by acetate-mediated deprotonation. Previously, we had used ligand–$Cu(OAc)_2$ complexes for a catalytic enantioselective Henry reaction.[14]

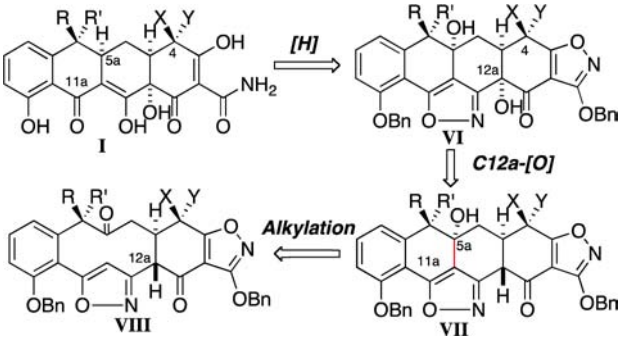
Each of the Michael additions depicted in Scheme 4 was highly diastereoselective; only one isomer was observed in each instance. These cases highlight the importance of the C4-substituent and its influence on the stereochemical outcome. For example, the Michael addition employing macrocycle **16** afforded **18** (eq 1), containing the correct C4a configuration when compared to the antibiotic tetracyclines.[15] Michael addition of the diastereomeric macrocycle **17** produced the alternate C4a diastereomer **19** (eq 2). Since the relative orientation of oxygen substituents at the C4- and C6-positions is now inverted with respect to **18**, Michael adduct **19** is appropriately configured for ent-anticancer tetracyclines. Lastly, the transannular Michael addition employing the C4–NHBoc substituent **10** afforded an appropriate C4–C4a product diastereomer for the antibiotic tetracyclines (eq 3). The diastereochemical outcome of the Michael additions of the substrates **17** and **10** is surprising (eq 2 vs 3). This result was unanticipated considering that both macrocycles **10** and **17** contain the same configuration at C4 and both the NHBoc group and OTBS substituents are comparable in size.

Scheme 5. Rationalization of Michael Selectivities for **17** and **10**



Enolate conformational analysis provides a rationalization for the observed stereochemical outcomes (Scheme 5). Upon enolization, it is likely that macrocycles **10** and **17** proceed to two major enolate conformers **21** and **22**.[16] When the C4-substituent is an NHBoc group, chelation between the boc group and the proximal isoxazole nitrogen could reinforce conformer **21** that proceeds to the observed product.[17] However, experimental results suggest that the C4-silyloxy systems are reacting through enolate conformers **22**.[18] While ground state conformational preferences undoubtedly affect transition state barrier heights, the transition state stabilization imparted by the orientation of the C4-OR substituent in the axial conformation was unexpected. Studies on the effects of related intermolecular cuprate additions have been reported;[19] however, they are not relevant to the present cases where conformational rigidity is strongly reinforced. *While the origin of this substituent effect is currently not understood, it is possible that transition state dipole minimization between the resident C4-OR substituent and the developing enolate might be a significant factor within the conformational constraints of this system.*

Scheme 6. Synthesis Plan for Tetracycline Core



(14) Evans, D. A.; Seidel, D.; Rueping, M.; Lam, H. W.; Shaw, J. T.; Downey, C. W. *J. Am. Chem. Soc.* **2003**, *125*, 12692–12693.

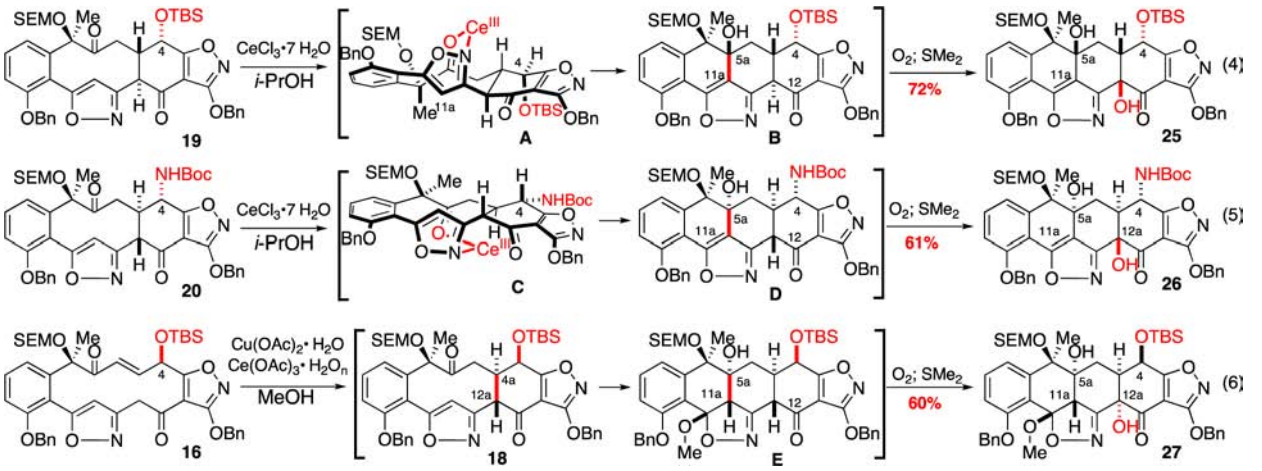
(15) Stereospecific displacement of a suitably functionalized C4-substituent with a nucleophilic nitrogen (such as dimethylamine or azide) would produce the correct C4/C4a stereoarray for the antibiotic tetracyclines.

(16) Macrocycle **16** would proceed to analogous enantiomeric enolates.

(17) At this point we have no definitive evidence that chelation is involved in this transformation.

(18) (a) Seeman, J. I. *Chem. Rev.* **1983**, *83*, 83–134. (b) Seeman, J. I. *J. Chem. Educ.* **1986**, *1*, 42–48.

Scheme 7. Ce(III)- and Cu(II)/Ce(III)-Mediated Multistep Transformations



Preliminary Transannular Alkylations. With the successful development of transannular Michael additions appropriate for either the antibiotic or (ent)-anticancer tetracyclines, we are now integrating these results into a synthesis plan. Future work will entail the execution of several transformations including the obligatory transannular alkylation step (Scheme 6).

In accordance with the proposed endgame, we report preliminary studies on the transannular isoxazole alkylation. We anticipated that a mild Lewis acid would facilitate coupling of the isoxazole and proximal ketone to produce **VII** from **VIII**. In a subsequent transformation, we would then tackle C12a-hydroxylation in the conversion of **VII** to **II**.

In practice we have discovered that $CeCl_3 \cdot 7H_2O$ is capable of facilitating both transformations in an atmosphere of molecular oxygen (Scheme 7).[20] Exposure of either **19** or **20** to these conditions smoothly furnished products **25** and **26**, respectively, after peroxide reduction with dimethyl sulfide. Both reactions are exceedingly selective, producing a single detectable diastereomer. Importantly, while Michael product **19** proceeds to **25**, which contains a cis C4a/C12a ring fusion (eq 4), Michael product **20** proceeds to a trans ring fusion (eq 5). Considering that the cis C4a/C12a ring fusion is nearly ubiquitous within the tetracycline family, these results suggest that a viable total synthesis endeavor will employ the C4-silyloxy macrocycle **16** rather than **10**.

Following further optimization, we have also discovered that all three processes (Michael addition, transannular alkylation, and C12a-oxidation) can be merged into a single multistep transformation. Treatment of macrocycle **16** with 5 mol % $Cu(OAc)_2 \cdot H_2O$ and 4 equiv of $Ce(OAc)_3 \cdot H_2O_n$ under an atmosphere of molecular oxygen yields **27** as a single diastereomer in 60% yield (eq 6). Several features of this reaction deserve comment. Due to the ability of Cu(II) to facilitate enolate chlorination in the presence of chloride ions, we found it necessary to utilize $Ce(OAc)_3 \cdot H_2O_n$ in the cascade rather than $CeCl_3 \cdot 7H_2O$. Additionally, since the Michael addition requires methanol as solvent, we found that the intermediate oxocarbenium ion produced following isoxazole substitution was trapped by solvent to form methanol adduct **E**. Lastly, under these conditions, there is no longer a requirement for reduction of the intermediate peroxide with dimethyl sulfide since this is now accomplished *in situ*.

These preliminary transannular alkylation studies coupled with our newfound understanding of the stereochemical consequence of the C4-substitutent within the Michael addition provide exciting new avenues of research. Incorporation of the results from this work into a larger synthesis effort will be reported in due course.

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Supporting Information Available. Complete experimental details, proton and carbon NMR spectra for all new compounds, and stereochemical determination. This material is available free of charge via the Internet at http://pubs.acs.org.

(19) Yamamoto, Y.; Chounan, Y.; Nishii, S.; Ibuka, T.; Kitahara, H. *J. Am. Chem. Soc.* **1992**, *114*, 7652–7660.

(20) Oxidation of 1,3-dicarbonyl compounds with Ce(III) is known; please see: Christoffers, J.; Werner, T. *Synlett*. **2002**, *1*, 119–121.

The authors declare no competing financial interest.