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Synthesis of (−)-Tetracycline

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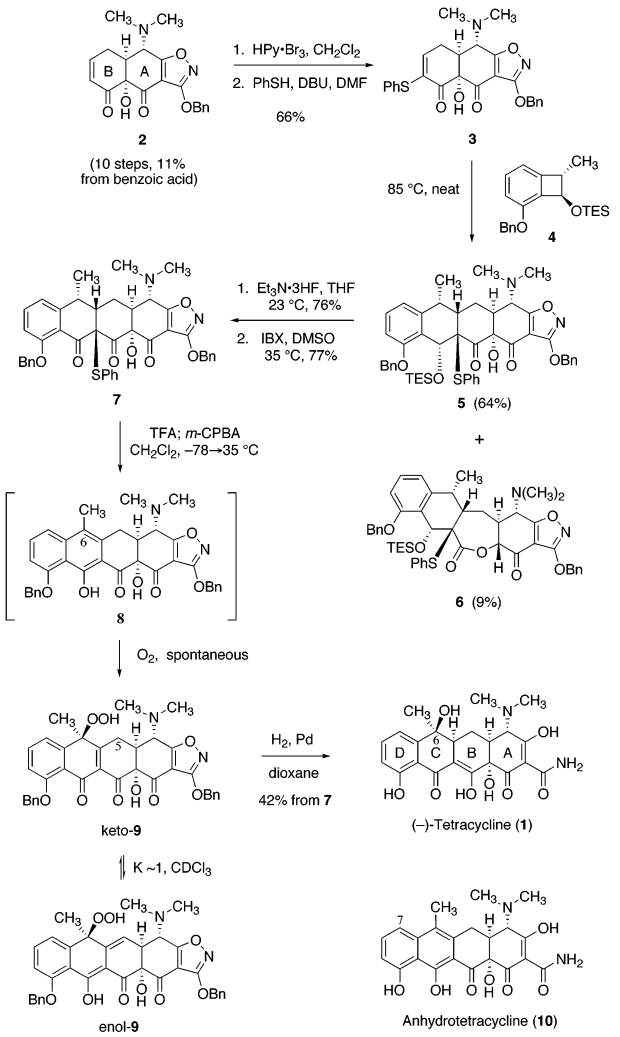
The tetracycline antibiotics have been widely used in human and veterinary medicine for more than 50 years.[1] Their broad-spectrum antibacterial activity and structural complexity have motivated enormous efforts toward the development of a laboratory synthetic route for their preparation, with many landmark achievements;[2] however, to date, tetracycline (**1**) has been prepared from a nontetracycline starting material only once, in a 34-step sequence from D-glucosamine (0.002% yield).[3] Here, we report a second synthesis of (−)-**1**, proceeding in 17 steps from benzoic acid (1.1% yield).

Our synthesis of (−)-**1** began with the tricyclic AB precursor **2**, prepared in 10 steps (11% yield, >95% ee) from benzoic acid.[4] In prior work, we had shown that the enone **2** could be transformed into many structurally diverse 6-deoxytetracycline derivatives in just four steps.[4] Here, we demonstrate that **2** can also be transformed into (−)-tetracycline (**1**), in seven steps (10% yield, Scheme 1). Toward this end, we first introduced a phenylthio substituent in the α-position of the enone **2**, which served to activate the molecule toward Diels−Alder cycloaddition[5] and, later, as a means to desaturate the C-ring and introduce oxygen at C6 (vide infra). This was accomplished by α-bromination of **2** with pyridinium hydrobromide perbromide to form an intermediate vinyl bromide, then bromide displacement with thiophenol and 1,8-diazabicyclo[5.4.0]-undec-7-ene in *N*,*N*-dimethylformamide at 0 °C, forming the vinyl sulfide **3** in 66% yield (two steps).

The triethylsilyloxybenzocyclobutene derivative **4** served as the Diels−Alder diene precursor and was synthesized in five steps (49% yield) from 2-bromo-3-(benzyloxy)benzyl alcohol by direct application of methods described by Durst et al. (see Supporting Information).[6] Heating a neat mixture of **3** (1 equiv) and **4** (7.7 equiv) at 85 °C for 48 h produced the endo-Diels Alder cycloadduct **5** in 64% yield. The excess diene precursor (**4**) could be recovered in >95% yield by flash column chromatography, which also served to remove a seven-membered ring lactone byproduct (**6**, 9% yield), believed to arise by a retro-Dieckmann type fragmentation of **5**.[7] The cycloadduct **5** was crystallized from methanol; X-ray analysis of the crystals obtained confirmed the gross stucture of **5** and all stereochemical assignments (see Supporting Information). In contrast to the success of the Diels−Alder reaction of **3** and **4**, all attempts to bring about the cycloaddition of hydroxyl-protected variants of enone **3** (or **2**) with the diene precursor **4** or with dienes such as isobenzofuran derivatives,[8] both with or without Lewis acid additives, failed to produce detectable amounts of cycloadducts.[9] Prior work from the Danishefsky laboratory had established that *trans*-1,2-bis-(*tert*-butyldimethylsilyoxy)benzocyclobutene produces an *o*-quinodimethane intermediate of sufficient reactivity to undergo thermal cycloaddition with the unactivated dienophile cyclohexenone, and they provide additional experimental data that support the idea that the presence of the free α-hydroxyl group within enone **3** is an important feature of the successful Diels−Alder cyclization that we observe.[10]

Scheme 1



To complete the synthesis of (−)-tetracycline, we first cleaved the triethylsilyl ether group of the Diels−Alder adduct **5** (triethylamine trihydrofluoride, 76%) and oxidized the hydroxyl group that was liberated with *o*-iodoxybenzoic acid in dimethyl sulfoxide[11] (77% yield). The resulting 2-(phenylthio)-1,3-diketone (**7**) was then oxidized with *m*-chloroperoxybenzoic acid in the presence of trifluoroacetic acid (to prevent oxidation of the dimethylamino group) to form an intermediate sulfoxide(s) that was observed to eliminate upon warming to 35 °C, giving the anyhydrotetracycline derivative **8**. Attempted isolation of **8** was complicated by the fact that it underwent spontaneous, stereoselective autoxidation in the air at ambient temperature, an observation that was used to advantage preparatively. Thus, dissolution of the crude naphthol **8** in chloroform and stirring of the resulting solution in the air produced the hydroperoxide **9**. The latter product was not isolated,

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but was subjected to hydrogenation in the presence of palladium black, affording (−)-tetracycline (**1**) in 42% yield (from **7**) after purification by preparative HPLC. The synthetic product was shown to be identical to an authentic sample of natural tetracycline in all respects.

The transformation of the naphthol **8** to the hydroperoxide **9** is functionally equivalent to the transformation of 7-chloroanhydrotetracycline to 7-chlorotetracycline (aureomycin) by photooxygenation−reduction, first demonstrated by Scott and Bedford.[12] Later, the same transformation was successfully applied to anhydrotetracycline (**10**) by the use of a dye-sensitized photooxygenation procedure.[13] Both transformations were reported to be highly stereoselective. In the case of photooxygenation of anhydrotetracycline (**10**), the stereoselectivity of the transformation observed was attributed to selective ene reaction of singlet oxygen with the (pseudoaxial) 5-β-hydrogen atom.[13] Two observations in the present work are noteworthy with respect to these precedents. First, is the fact that ^{1}H NMR analysis of the oxygenation reaction (**8** → **9**, $CDCl_3$) showed that the keto form of **9** (keto-**9**) was formed exclusively as the direct product of the reaction. After standing for several hours, solutions of keto-**9** in $CDCl_3$ were observed to undergo equilibration with the enol form (enol-**9**, $K \approx 1$). This observation rules out the possibility that enol-**9** is the direct product of the oxygenation of **8** and thus discounts the possible involvement of an ene mechanism involving C5.[14] The second observation concerns the extraordinary facility of the oxygenation of substrate **8**, which far exceeds that of anhydrotetracycline (**10**).[13,15] Reaction of **8** to form **9** at 23 °C is evident within minutes of exposure to the air in daylight; only with the rigorous exclusion of light is the oxidation prevented. These observations are reminiscent of the autoxidation of 2-naphthols bearing bulky 1-alkyl groups reported several years ago, also producing hydroperoxide products.[16] Although we cannot rule out a mechanism involving singlet oxygen in the transformation of **8** to **9** (by Diels−Alder reaction, then 1,4-endoperoxide hemiketal opening), a simple photoinitiated free-radical autoxidation mechanism may be operative instead.[17] The data thus far do not allow us to distinguish these possibilities. In either case, stereoelectronic factors seem most plausible to account for the stereochemistry of oxygen addition to **8** (generating a pseudoaxial hydroperoxy group), but whether the basis for the greater reactivity of **8** relative to anhydrotetracycline is related to the modification of the A-ring by the incorporation of the Stork−Hagedorn 3-benzyloxyisoxazole protective group[18] or to benzylation of the D-ring phenol is not known.

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Supporting Information Available: Experimental procedures, listings of spectral data, and X-ray crystal structure data for the cycloadduct **5** (CIF, PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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