Stereocontrolled Synthesis of (±)-12a-Deoxytetracycline

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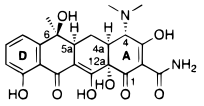
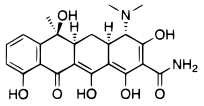
Tetracycline (**1**)[1] has been one of the major antibiotics for almost half a century. The difficult problems implied by its sensitive functionality and demanding stereochemistry have, predictably, attracted the attention of chemists for several decades.[2] Muxfeldt's construction of terramycin,[2a] 5a-hydroxytetracycline, was—and is—an impressive achievement in total synthesis. It, nevertheless, did not control the introduction of the center at C4a and would not, in any case, be easily extended to tetracycline itself. A remarkable reconstruction of tetracycline has been achieved recently[3] from anhydrotetracycline. If the 12a-hydroxylation[4] of synthetically available[2c] 12a-deoxyanhydrotetracycline could be verified, this would constitute a formal, if indirect, total synthesis of tetracycline.

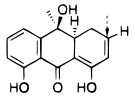
We describe here a stereospecific total synthesis of (±)-12a-deoxytetracycline (**2**) which solves the longstanding problem of establishing the proper relative stereochemistry of the C5a and C4a centers.



tetracycline (**1**)



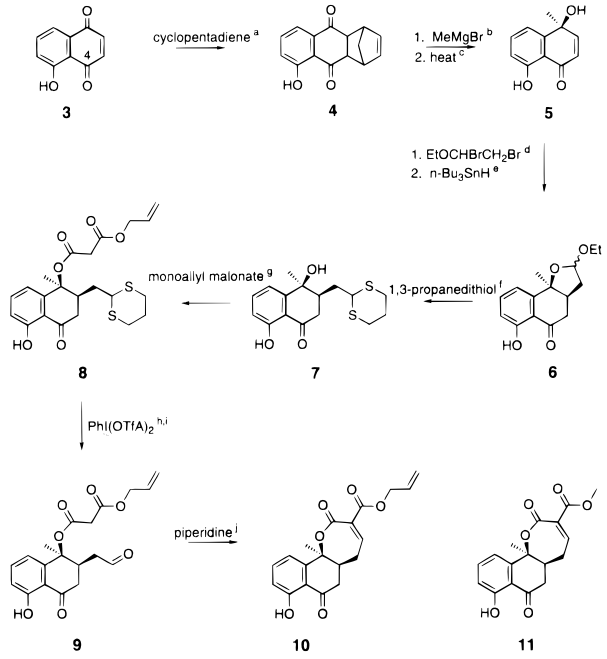
12a-deoxytetracycline (**2**)



A

Early observations by Shemyakin and his co-workers, as well as extensive previous work in these laboratories,[5] have shown that conjugate nucleophilic additions to a linear tricyclic system such as **A** results in addition, largely or entirely, from the α side and, thus, to the incorrect stereochemistry at C4a. We became intrigued, however, by the fact that α addition of a nucleophile to a *nonlinear* tricyclic structure such as is present in the seven-membered unsaturated lactones **10** or **11** would now generate the *correct* relative stereochemistry at C4a (vide infra). As our first target for the construction of **10**, we selected the naphthofuran derivative **6** which we planned to assemble from dihydroxynaphthalenone **5**. The latter should result from the addition of a methyl group to the readily available[6] 5-hydroxy-1,4-naphthoquinone (**3**), but competitive 1,4-addition to the latter made it desirable to protect its double bond temporarily as the cyclopentadiene adduct **4**. Addition of methylmagnesium bromide proceeded with the expected regioselectivity[7] and, after thermolysis, provided **5** in 75% overall yield from **3**. The tertiary hydroxyl of **5** could now be used to establish the correct relationship between centers at C5a and C6 of **2** by taking advantage of the predictable regio- and stereochemistry of the radical-mediated haloacetal cyclization:[8] Condensation of **5** with the dibromide from ethyl vinyl ether gave the mixed bromoacetal which underwent the anticipated radical cyclization upon treatment with tributylstannane to form **6** as a single isomer (except, of course, for the irrelevant ethoxy group), in 88% overall yield from **5** (see Scheme 1).

Scheme 1[a]



[a] (a) $CHCl_3$, 30 min, rt, 100%. (b) (2 equiv), THF, −78°C to rt, 78%. (c) *p*-xylene, 19 h, 100%. (d) *N*,*N*-dimethylaniline, CH_2Cl_2, 4 h, Δ, 98%. (e) (1.2 equiv), AIBN (0.1 equiv), Ph, 1.5 h, Δ, 90%. (f) BF_3·Et_2O, CH_2Cl_2, 0 °C, 15 min, 88%. (g) 1, trifluoroacetic anhydride; 2, add **7**, DME, 1.5 h, 92%. (h) (2.5 equiv), CH_2Cl_2, MeOH, 2.5 h, 92%. (i) 5% aq HCl, THF, 18 h. (j) (11 equiv), HOAc (40 equiv), 4 Å molecular sieves, Ph, 0 °C to rt, 2.5 h, 97% (from **8**).

Elaboration of the naphthofuran **6** toward the unsaturated lactone **10** was initiated by reaction of **6** with 1,3-propanedithiol to give the dithiane **7**, the tertiary hydroxyl of which was esterified by reaction with the monoallyl ester of malonic acid, in the presence of trifluoroacetic anhydride, to form **8** (presumably via the ketene). Liberation of the aldehyde function was best achieved by transacetalization to the dimethyl acetal,[9] followed by aqueous acid, to give **9** which was readily cyclized

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(1) (a) Blackwood, R. K. *Handb. Exp. Pharmacol.* Hlavka, J. J., Boothe, J. H., Eds.; Springer Verlag: New York, 1985; Vol. 18, p 59. (b) Durckheimer, W. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 721. (c) Mitschner, L. A. *Medicinal Research Series: The Chemistry of the Tetracycline Antibiotics*; Marcel Dekker: New York, 1978; Vol. 9. (d) Clive, D. L. J. *Q. Rev., Chem. Soc.* **1968**, *22*, 435.

(2) (a) Johnson, F. In *The Total Synthesis of Natural Products*; Apsimon, J., Ed.; Wiley Interscience: New York, 1973; Vol. I, p 331. (b) Muxfeldt, H.; Hans, G.; Hardtmann, G.; Kathawala, F.; Mooberry, J. B.; Vedejs, E. *J. Am. Chem. Soc.* **1979**, *101*, 689. (c) Stork, G.; Hagedorn, A. I., III. *J. Am. Chem. Soc.* **1978**, *100*, 3611. (d) Muxfeldt, H.; Dopp, H.; Kaufmann, J. E.; Schneider, J.; Hansen, P. E.; Sasaki, A.; Geiser, T. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 497. (e) Barton, D. H. R. *Pure Appl. Chem.* **1971**, *25*, 5. (f) Barton, D. H. R.; Magnus, P. D. *J. Chem. Soc. C* **1971**, 2165 and following papers. (g) Korst, J. J.; Johnston, J. D.; Butler, K.; Bianco, E. J.; Conover, L. H.; Woodward, R. B. *J. Am. Chem. Soc.* **1968**, *90*, 439. (h) Gurevich, A. I.; Karapetyan, M. G.; Kolosov, M. N.; Korobko, V. G.; Onoprienko, V. V.; Popravko, S. A.; Shemyakin, M. M. *Tetrahedron Lett.* **1967**, 131. (i) Conover, L. H.; Butler, K.; Johnston, J. D.; Korst, J. J.; Woodward, R. B. *J. Am. Chem. Soc.* **1962**, *84*, 3223. (j) Kende, A. S.; Fields, T. L.; Boothe, J. H.; Kushner, S. *J. Am. Chem. Soc.* **1961**, *83*, 439.

(3) Wassermann, H. H.; Lu, T.-J.; Scott, I. A. *J. Am. Chem. Soc.* **1986**, *108*, 4237.

(4) Gurevich, A. I.; Karapetyan, M. G.; Kolosov, M. N. *Khim Prir. Soedin.* **1966**, 141.

(5) Gurevich, A. I.; Karapetyan, M. G.; Kolosov, M. N.; Korobko, V. G.; Onoprienko, V. V.; Popravko, S. A.; Shemyakin, M. M. *Tetrahedron Lett.* **1967**, *131* and unpublished observations in this laboratory by Dr. Hagedorn.

(6) Among the numerous methods which have been used to oxidize 1,5-naphthalenediol to 5-hydroxy-1,4-naphthoquinone, we selected the periodate method of Pinto, A. V.; Ferreira, V. F.; Pinto, M. do C. *Synth. Commun.* **1985**, *15*, 1177. It was modified to make it suitable for ∼50 g scale preparation by reducing the amount of periodate to 2.2 equiv and using aqueous THF as solvent rather than DMF. This gave the quinone, also known as juglone, in 83% yield, after purification.

(7) This selectivity is, obviously, due to conjugative deactivation of the C4 carbonyl; cf.: Shemyakin, M. M.; Kolosov, M. N.; Karapetyan, M. G.; Chaman, E. S. *Dokl. Akad. Nauk SSSR* **1957**, *112*, 669.

(8) Stork, G.; Mook, R., Jr.; Biller, S. A.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **1983**, *105*, 3741.

(9) Stork, G.; Zhao, K. *Tetrahedron Lett.* **1989**, *30*, 287.

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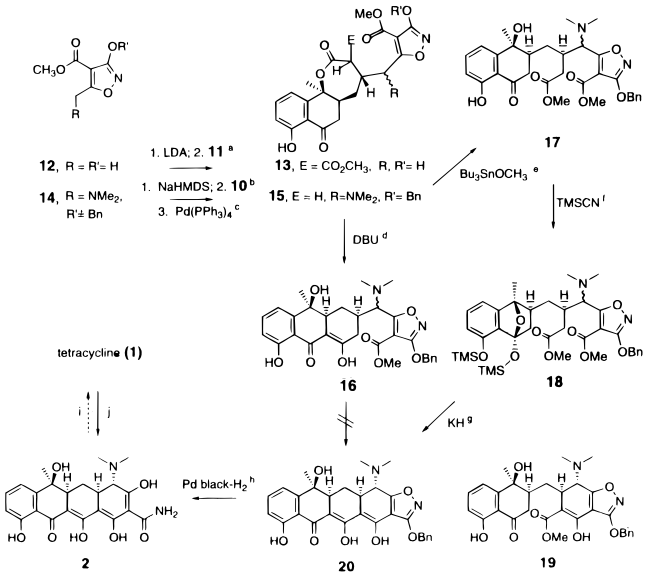
Scheme 2[a]



[a] (a) 1, LDA (3 equiv) in THF, −78 °C; 1 equiv **12** in THF 2. **11** (1 eq) in THF; −78 °C, 30 min, satd NH_4Cl, then 2N HCl, 75%. (b) NaHMDS (4.5 equiv), **14**, THF, −78 °C to −20 °C, 1.5 h. **10** in THF, −78 °C; −78 to −50 °C, 2.5 h, then 10% aq HCl. (c) (0.02 equiv); PPh_3 (0.02 equiv) ethylhexanoic acid (3.5 equiv), 4 Å molecular sieves, EtOAc, CH_2Cl_2, 95% (of **16** from **10**). (d) (0.5 equiv), 4 Å molecular sieves, Ph, 89%. (e) (5 equiv), $PhCH_3$, 60 °C, 5 h, 97%. (f) (8 equiv), KCN (0.5 equiv) 18-crown-6 (0.1 equiv), CH_2Cl_2. (g) (∼25 eq), THF, −78 to 0 °C, 3 h; then, rt to 50 °C, 30 min, ∼59% (h) H_2 (1 atm), THF, MeOH, 3 h, 94%. (i) See ref 19. (j) Reference 18.

to the desired unsaturated lactone **10**,[10] thus obtained in a gratifying ∼45% overall yield from 5-hydroxynaphthoquinone (**3**).

The seven-membered unsaturated lactone **10** is quite flexible and access to either its α or its β face might appear formally possible, but we thought it likely that the transition state for conjugate addition would be less crowded and of lower energy with a rather bulky addend on the α rather than the β side of the molecule. This would generate the correct C4a stereochemistry. We were especially interested to find whether such a Michael addition could be effected with an isoxazole system because, as we had shown earlier in the synthesis of C_{12a} deoxyanhydrotetracycline,[2c] a suitably designed isoxazole can play the role of a stable surrogate for the sensitive functionality of the tetracycline A ring.

We were encouraged to find that, indeed, when methyl 3-hydroxy-5-methyl-4-isoxazolecarboxylate (**12**)[2c] was added to 3 equiv of LDA in THF at −78 °C, followed by 1 equiv of the unsaturated lactonic ester **11**, a crystalline adduct was obtained in over 75% yield. It was shown to be **13** by X-ray crystallography[11] (see Scheme 2).

This favorable result encouraged us to examine the possibility of constructing a precursor of 12a-deoxytetracycline which would already bear the 4-dimethylamino group. To that end, the conjugate addition of the anion of the more elaborate isoxazole **14**[12] to the unsaturated lactonic ester **10** was investigated. With careful control of temperature, this proved very successful and led, after palladium^0-catalyzed removal[13] of the now superfluous allyl ester group of the initial lactonic ester adduct, to a 95% yield of the decarboxylated adduct **15** as a single isomer.

At this point, the goal of setting, stereospecifically, the three asymmetric centers at positions C4a, C5a, and C6 of **2** had been reached, and we were ready to face the problem of closing rings A and B. The closure of the B ring could be achieved very easily by base-catalyzed intramolecular Claisen cyclization of **15** to **16**. This might appear to be a major step in the right direction, except for the fact that previous intense efforts in our laboratory with structures like **16** had failed[14] to achieve closure of ring A by a second Claisen cyclization. We could only confirm this result, once again. Closure of the troublesome ring A *before* ring B became a possibility when we found that cleavage of the lactone system of **15** to form the diester **17** could be achieved efficiently with methoxytributylstannane. Protection of the ring C ketone of **17** to prevent initial closure to the unwanted BCD system of **16** via the siloxyketal **18** (cyanotrimethylsilane, catalytic potassium cyanide, 18-crown-6), achieved the welcome result of simultaneously protecting the keto, tertiary hydroxyl, and phenolic groups in rings C and D.

Dieckmann cyclization of crude **18**[15] now proceeded readily with KH (−78 to 0 °C, 3 h, followed by raising the temperature to 50 °C for 30 min) to give, presumably via **19**, the fully cyclized system **20**. Hydrogenolysis (Pd black, H_2, THF/methanol) now gave (94% yield) (±)-12a-deoxytetracycline (**2**)[16] which showed identical spectral (^{1}H NMR in DMSO and in pyridine; ^{13}C-NMR; MS; UV−vis) and chromatographic[17] properties with a sample derived from natural (−)-tetracycline (**1**).[18,19]

Acknowledgment. We are grateful to the National Institutes of Health and the National Science Foundation for financial support and to Dr. Vinka Parmakovich for mass spectral analyses.

Supporting Information Available: Detailed experimental procedures and copies of relevant ^{1}H-NMR for compounds starting with **4**, as well as ^{13}C-NMR and IR data (30 pages). Ordering information is given on any current masthead page.

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(10) Methoxycarbonyl lactone **11** was produced in the same manner as used for **10**, using the monomethyl ester of malonic acid.

(11) We thank Dr. Michael Chiang for this determination.

(12) Isoxazole **14** can be prepared from trimethylorthoacetate and dimethyl malonate, as detailed in the supporting information. It was first prepared several years ago, by a different route, by Dr. M. Mansuri.

(13) Jeffrey, P. D.; McCombie, S. W. *J. Org. Chem.* **1982**, *47*, 587. The alkoxycarbonyl group is required to enhance nucleophilicity of the conjugated lactone because attempted conjugate addition in its absence gave no adduct, presumably because the seven-membered unsaturated lactone does not readily achieve planarity, so that the conjugated ester external to the lactone becomes essential.

(14) Kahne, D. Ph.D. Thesis, Columbia University, New York, NY, 1986.

(15) The extreme moisture sensitivity of compound **18** made its isolation difficult. Attempts to chromatograph it on a variety of adsorbents destroyed the silyl hemiacetal. Its structure was established by CI-MS, NMR, and IR spectroscopy.

(16) The material was purified on MN Polyamid SC6 eluting with a gradient of acetonitrile (with 0.1% TFA) to methanol/acetonitrile (1:1 with 0.1% TFA). Trace amounts of additional impurities were removed by triturating the solid chromatographed product in refluxing anhydrous methanol.

(17) Thin layer chromatographic behavior (on both MN Polygram Polyamid-6 and Merck Polyamid 11 F_{254}) of both synthetic and natural **2** matched when eluted with methanol, water, acetic acid (3:10:1) and acetonitrile, water, TFA (100:100:1).

(18) (a) Blackwood, R. K.; Rennhard, H. H.; Stephens, C. R. *J. Am. Chem. Soc.* **1960**, *82*, 5194. (b) Green, A.; Boothe, J. H. *J. Am. Chem. Soc.* **1960**, *82*, 3950.

(19) Methods have been claimed[20] for the stereospecific 12a-oxidation of **2**. We are not aware, however, that a reproducible method for the oxidation of **2** to **1** is available. We were unable to duplicate the platinum−oxygen reaction of ref 20b which gave us a mixture of 12 different products, none of which had an HPLC retention time consonant with that of tetracycline. (We thank Dr. P. E. Sum of Wyeth-Ayerst Research for this determination). It appears that the best that has been reported for the 12a oxidation of a tetracycline relative bearing a dimethylamino group at C4 (but lacking substituents at C6) is the 6.5% obtained in ref 20c.

(20) (a) Holmlund, C. E.; Andres, W. W.; Shay, A. J. *J. Am. Chem. Soc.* **1959**, *81*, 4748. (b) Muxfeldt, H.; Buhr, G.; Bangert, R. *Angew. Chem., Int. Ed. Engl.* **1962**, *1*, 177. (c) Korst, J. J.; Johnston, J. D.; Butler, K.; Bianco, E. J.; Conover, L. H.; Woodward, R. B. *J. Am. Chem. Soc.* **1968**, *90*, 439. (d) See also: Davies, A. K.; McKellar, J. F.; Phillips, G. O.; Reid, H. G. *J. Chem. Soc., Perkin Trans. 2* **1979**, 369.