The First Total Synthesis of Natural (–)-Tetracycline

Kuniaki Tatsuta,* Takuji Yoshimoto, Hiroki Gunji, Yoshiya Okado, and Masaaki Takahashi
Department of Applied Chemistry, School of Science and Engineering, Waseda University, 3-4-1 Ohkubo, Shinjuku-ku, Tokyo 169-8555

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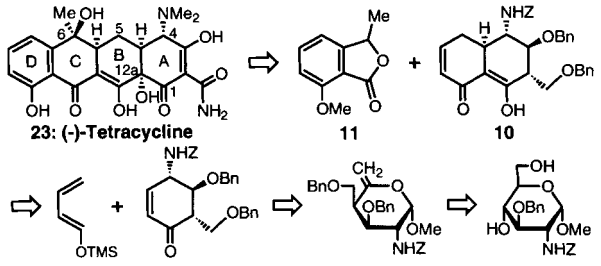
Natural (–)-tetracycline has been stereoselectively synthesized from D-glucosamine through [4 + 2] cycloaddition and Michael-Dieckmann type reaction.

For almost half a century, tetracycline (**23**) has been well-known as a major antibiotic from the viewpoint of its unique structural features as well as antibacterial activities.[1] The total synthesis of tetracycline families was initiated by Woodward's 6-demethyl-6-deoxytetracycline synthesis in 1962,[2] followed by Muxfeldt's terramycin synthesis in 1968,[3] and culminated by Stork's 12a-deoxytetracycline synthesis in 1996.[4] However, all these syntheses have been accomplished only in racemic forms. The total synthesis of natural (–)-tetracycline (**23**) remained an unanswered challenge, despite the remarkable achievements as described above.



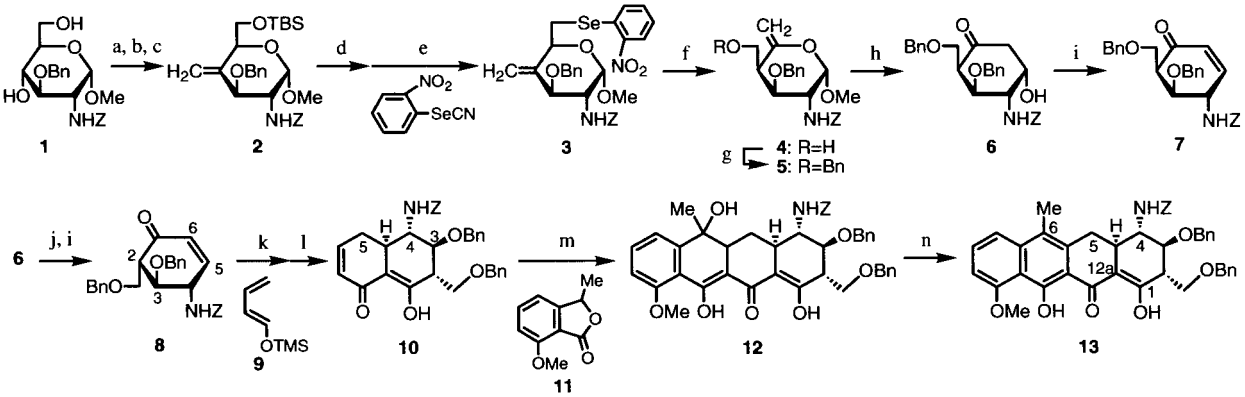
Scheme 1.

Herein, we describe the first total synthesis of (–)-tetracycline (**23**) from D-glucosamine, which stereospecifically constructs the densely and sensitively functionalized A ring.

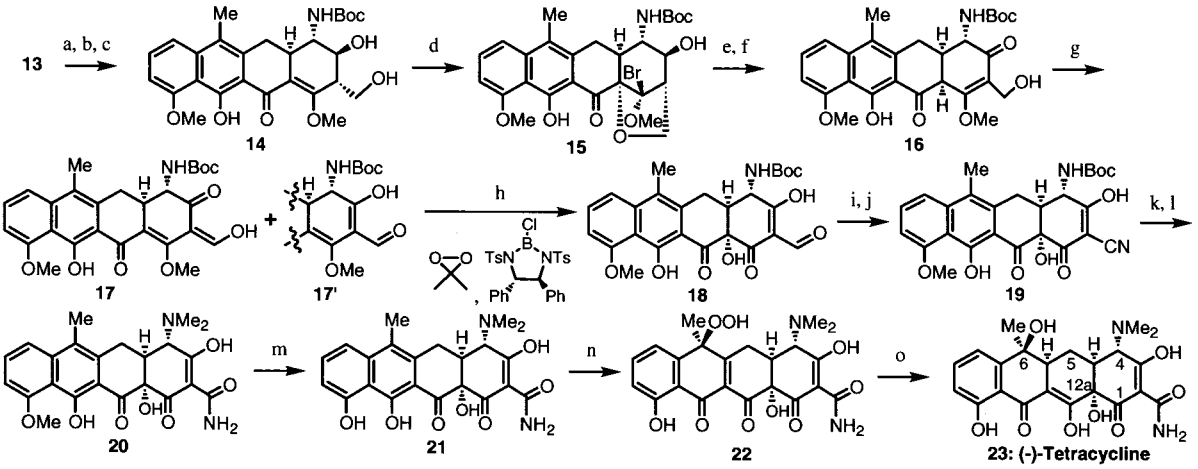
From the retrosynthetic perspective (Scheme 1), the tetracyclic structure is expected to be accessible by tandem Michael-Dieckmann type reaction of **10** with **11**. The suitably substituted chiral intermediate **10** would be synthesized by Diels-Alder reaction of the cyclohexenone **8** and the silyloxybutadiene **9**. The regio- and stereoselectivities are established as a consequence of the dienophile geometry according to Gleiter's theory.[5] Compound **8** could be obtained from **1** through Ferrier reaction of **5**.

As a viable synthetic relay from anhydrotetracycline (**21**) to tetracycline (**23**) has been reported by Wasserman and Scott[6] via a two-step hydration at the 5a,6-position, **21** was our first target. A reliable 12a-hydroxylation is required for the synthesis of **21**, although evidence of such hydroxylation has been reported.[4,7]

The starting **1**, which was prepared from D-glucosamine,[8] was converted into the olefin **2** by selective silylation, oxidation and Wittig olefination (Scheme 2). After de-*O*-silylation of **2**, the resulting alcohol was led to the selenide **3**.[9] Treatment of **3** with borane followed by H_2O_2 oxidation gave stereoselectively the alcohol **4** by simultaneous formation of a new olefin group. Benzylation of **4** gave **5**,[10] which was submitted to Ferrier reaction with $HgCl_2$[11] to give the cyclohexanone **6**. The [4 + 2] cycloaddition of **7**, which was derived from **6** by dehydration, with the butadiene **9** did not proceed because of the steric repulsion. Therefore, **6** was epimerized at C2 and dehydrated to the isomer **8**.[10] This cycloaddition with **9** in the presence of 2,6-di-*tert*-butyl-4-methylphenol (DBMP) proceeded from the β-face of **8** regio- and stereoselectively as expected.[5] This highly stereoselective reaction gave a labile adduct, which upon acidic oxidation was transformed to the α,β-unsaturated ketone **10**.[10] The tandem Michael-Dieckmann type reaction[12] of **10** with the isobenzofuranone **11**[13] gave the tetracyclic compound **12**, which was in turn aromatized to **13**[10] in high yield. The struc-



Scheme 2. a) TBSCl/Py, 2 h, 93% b) DMSO, DCC, Py-TFA/Et_2O, 70 min, 97% c) $[Ph_3PCH_3]Br$, *n*-BuLi/THF, -78 °C - rt, 1 h, 91% d) 1%HCl-MeOH, 10 min, 93% e) PBu_3/THF, 1 h, 90% f) BH_3•THF/THF, 0 - 45 °C, 1 h, then H_2O_2, NaOH/THF-H_2O, 45 °C, 16 h, 69% g) BnBr, BaO, $Ba(OH)_2$•$8H_2O$/DMF, 18 h, 84% h) $HgCl_2$, THF-H_2O, 13 h, 67% i) MsCl, TEA/CH_2Cl_2, 0 °C, 15 min, ~82% j) DBU/PhMe, -30 °C, 50 min, quant. k) DBMP/PhMe, 170 °C, 43 h, 72% l) CrO_3, H_2SO_4, acetone-H_2O, 0 °C, 10 min, 85% m) LDA/THF, -40 °C, 15 min, 80% n) $SOCl_2$, TEA/CH_2Cl_2, -30 °C, 10 min, 90%



Scheme 3. a) BBr_3/CH_2Cl_2, -78 °C, 15 min b) H_2, Pd-black, $(Boc)_2O$, TEA/dioxane-H_2O, 1 h, 2steps 92% c) $TMSCHN_2$, *i*-Pr_2NEt/THF-MeOH, 2 h, 72% d) Br_2, $(Bu_3Sn)_2O$, MS-4A/CH_2Cl_2, -78 °C, 15 min, 85% e) Dess-Martin periodinane/MeCN-CH_2Cl_2, 15 min, 91% f) Zn/AcOH, 2 min g) Dess-Martin periodinane/MeCN-CH_2Cl_2, 15 min, 2 steps 62%, **17**:**17'**=5:1 h) TEA/CH_2Cl_2, -78 °C, 30 min, 60% i) NH_2OH•HCl, TEA/ MeOH, 30 min j) CDI/THF, 45 min, 2 steps 80% k) Polyphosphoric acid, 100 °C, 45 min, 68% l) aq. $HCHO/HCO_2H$, 80 °C, 1 h, 80% m) BBr_3/ CH_2Cl_2, 0 °C - rt, 15 h, 88% n) O_2, hv, TPP/$CHCl_3$, 20 - 40 °C, 10 min, 75% o) 3 atm H_2, Pt-black/dioxane, 8 h, 62%

tures of **10** and **13** were reasonably confirmed by NMR studies.

After selective de-*O*-benzylation of **13** with BBr_3 (Scheme 3), the alcohol was converted into **14** by exchange of the *N*-protecting group followed by *O*-methylation of the enol. The direct oxidation of **14** gave no desired products **17** and **17'**. Treatment of **14** with Br_2 gave stereoselectively the bromide **15**.[10] The opening of the pyran ring was examined under a variety of conditions, but in vain. Dess-Martin oxidation of **15** was followed by treatment with Zn in AcOH[14] to provide the keto-alcohol **16**[10] with migration of the resulting double bond. This was oxidized to a mixture of the enols **17** and **17'**. Though the process suffered from the loss of the valuable asymmetry at C12a, it was expected that the mixture would be a useful intermediate provided that epoxidation could be achieved at the α-face. The mixture was submitted to epoxidation using dimethyldioxirane with the chiral cyclic borane,[15] where the reaction occurred from the α-face as expected, affording predominantly the C12a alcohol **18**.[10] This was transformed to the nitrile **19**[10] by our newly developed method. Hydrolysis of **19** to give the amide with concomitant removal of the *N*-Boc group was followed by *N*-dimethylation to produce **20**. De-*O*-methylation gave anhydrotetracycline (**21**),[10] which was identical with a naturally derived sample in all respects.[6]

The final stage was to introduce stereoselectively the hydroxy group into the C6 position according to the reported procedures.[6] By photooxidation of **21**, the peroxide **22** was obtained. The hydrogenolysis of **22** on Pd-C gave no significant product,[4] while the desired reduction proceeded smoothly on Pt black to give (−)-tetracycline (**23**) in a fairly good yield, which was neutralized with HCl in MeOH to give the hydrochloride.[10] This was identical with the hydrochloride of natural (−)-tetracycline in all respects,[16] completing the first total synthesis.

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References and Notes

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10 Selected data for key compounds: Optical rotations (22 °C) and ^{1}H-NMR spectra (*J* in Hz; 400, 500 and 600 MHz) were measured in $CHCl_3$ and $CDCl_3$, respectively, unless otherwise noted. **5**: $[\alpha]_D$ +61°(*c* 1.0); ^{1}H-NMR δ 3.03 (1H, ddd, *J* = 5, 5 and 8, H-4), 4.48 (1H, s, H-6), 4.66 (1H, s, H'-6), **8**: mp 75 °C; $[\alpha]_D$ +50°(*c* 1.0); ^{1}H-NMR δ 2.57 (1H, d, *J* = 9, H-2), 4.02 (1H, dd, *J* = 8 and 9, H-3), 6.10 (1H, dd, *J* = 2 and 10, H-6), 6.76 (1H, br d, *J* = 10, H-5), **10**: mp 173 °C; $[\alpha]_D$ -16°(*c* 1.0); ^{1}H-NMR δ 2.15 (1H, br d, *J* = 12 and 18, H_β-5), 2.56 (1H, ddd, *J* = 6, 6 and 18, H_α-5), 3.78 (1H, ddd, *J* = 10, 10 and 10, H-4), 3.87 (1H, dd, *J* = 10 and 10, H-3), **13**: mp 204 °C(dec.); $[\alpha]_D$ +397°(*c* 0.33); ^{1}H-NMR (C_5D_5N) δ 2.24 (3H, s, Me-6), 3.04 (1H, ddd, *J* = 4, 10 and 14, H-4a), 4.40 (1H, ddd, *J* = 10, 10 and 10, H-4), 4.46 (1H, dd, *J* = 10 and 10, H-3), **15**: $[\alpha]_D$ -99°(*c* 0.46); ^{1}H-NMR δ 2.74 (1H, ddd, *J* = 4, 10 and 10, H-4a), 3.57 (1H, dd, *J* = 7 and 9, CH-2), 4.08 (1H, dd, *J* = 7 and 7, CH'-2), **16**: $[\alpha]_D$ -93°(*c* 0.27); ^{1}H-NMR δ 2.92 (1H, dddd, *J* = 2, 4, 5 and 11, H-4a), 4.20 (1H, d, *J* = 4, H-12a), 4.46 (1H, dd, *J* = 6 and 12, CH-2), 4.54 (1H, dd, *J* = 8 and 12, CH'-2), **18**: $[\alpha]_D$ -106°(*c* 0.35, MeOH); ^{1}H-NMR (CD_3OD) δ 2.66 (1H, ddd, *J* = 3, 4 and 11, H-4a), 4.04 (1H, d, *J* = 12, H-4), 9.75 (1H, s, CHO), **19**: $[\alpha]_D$ -360°(*c* 0.12); ^{1}H-NMR δ 2.79 (1H, dd, *J* = 5 and 13, H-4a), 4.54 (1H, d, *J* = 6, H-4); IR (neat) 2204 cm^{-1}, **21**: $[\alpha]_D$ -86°(*c* 0.40, 0.1 M HCl); ^{1}H-NMR δ 2.47 (9H, s, N-Me and Me-6), 3.33 (1H, d, *J* = 11, H-4), **23**·HCl: $[\alpha]_D$ -261°(*c* 0.50, 0.1 M HCl); ^{1}H-NMR (CD_3OD-DCl/D_2O) δ 1.65 (3H, s, Me-6), 1.93 (1H, ddd, *J* = 11, 13 and 13, H_β-5), 2.25 (1H, ddd, *J* = 3, 5 and 13, H_α-5), 3.04 (6H, s, N-Me).
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16 The authentic sample was prepared by purification of commercially available sample.