

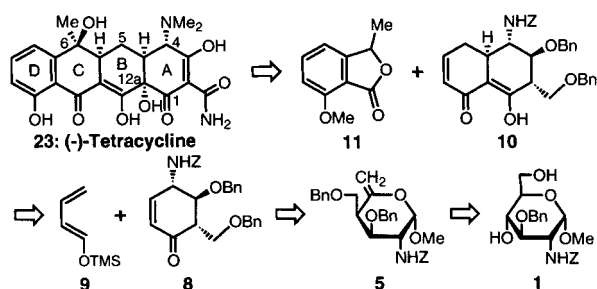
The First Total Synthesis of Natural (–)-Tetracycline

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.

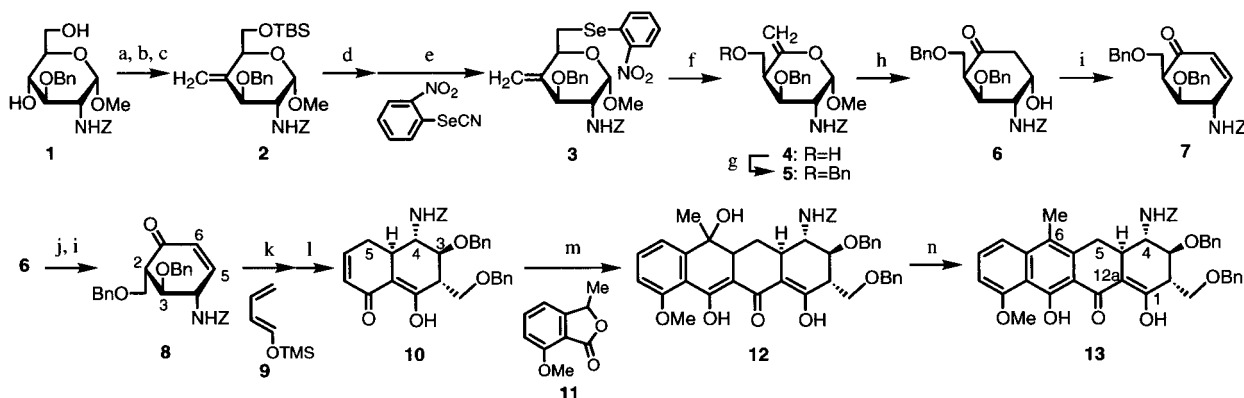
Herein, we describe the first total synthesis of (–)-tetracycline (**23**) from D-glucosamine, which stereospecifically constructs the densely and sensitively functionalized A ring.

From the retrosynthetic perspective (Scheme 1), the tetra-

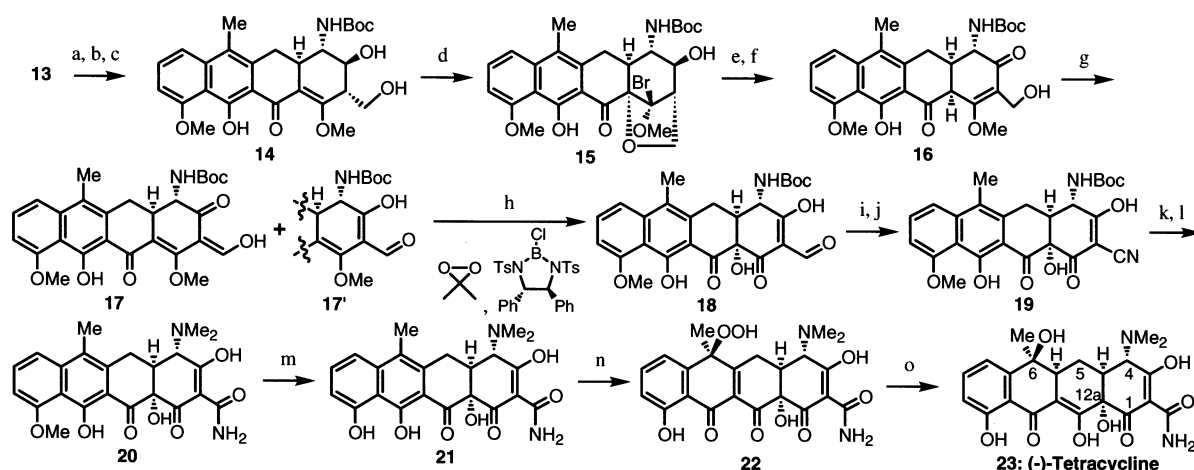
cyclic structure is expected to be accessible by tandem Michael-Dieckmann type reaction of **10** with **11**. The suitably substituted chiral intermediate **10** would be synthesized by Diels-Alder reaction of the cyclohexenone **8** and the silyloxybutadiene **9**. The regio- and stereoselectivities 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 Scott⁶ 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 H₂O₂ oxidation gave stereoselectively the alcohol **4** by simultaneous formation of a new olefin group. Benzoylation of **4** gave **5**,¹⁰ which was submitted to Ferrier reaction with HgCl₂¹¹ 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 reaction¹² 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/Et₃O, 70 min, 97% c) [Ph₃PCH₃]₄Br, *n*-BuLi/THF, -78 °C - rt, 1 h, 91% d) 1% HCl-MeOH, 10 min, 93% e) PBu₃/THF, 1 h, 90% f) BH₃·THF/THF, 0 - 45 °C, 1 h, then H₂O₂, NaOH/THF-H₂O, 45 °C, 16 h, 69% g) BnBr, BaO, Ba(OH)₂·8H₂O/DMF, 18 h, 84% h) HgCl₂, THF-H₂O, 13 h, 67% i) MsCl, TEA/CH₂Cl₂, 0 °C, 15 min, ~82% j) DBU/PhMe, -30 °C, 50 min, quant. k) DBMP/PhMe, 170 °C, 43 h, 72% l) CrO₃, H₂SO₄, acetone-H₂O, 0 °C, 10 min, 85% m) LDA/THF, -40 °C, 15 min, 80% n) SOCl₂, TEA/CH₂Cl₂, -30 °C, 10 min, 90%



Scheme 3. a) $\text{BBr}_3/\text{CH}_2\text{Cl}_2$, -78°C , 15 min b) H_2 , Pd-black, $(\text{Boc})_2\text{O}$, TEA/dioxane- H_2O , 1 h, 2 steps 92% c) TMSCHN_2 , $i\text{-Pr}_2\text{NEt}/\text{THF-MeOH}$, 2 h, 72% d) Br_2 , $(\text{Bu}_3\text{Sn})_2\text{O}$, $\text{MS-4A}/\text{CH}_2\text{Cl}_2$, -78°C , 15 min, 85% e) Dess-Martin periodinane/ $\text{MeCN-CH}_2\text{Cl}_2$, 15 min, 91% f) Zn/AcOH , 2 min g) Dess-Martin periodinane/ $\text{MeCN-CH}_2\text{Cl}_2$, 15 min, 2 steps 62%, $17:17'=5:1$ h) TEA/ CH_2Cl_2 , -78°C , 30 min, 60% i) $\text{NH}_2\text{OH}\cdot\text{HCl}$, TEA/ MeOH, 30 min j) CDI/THF , 45 min, 2 steps 80% k) Polyphosphoric acid, 100°C , 45 min, 68% l) aq. $\text{HCHO}/\text{HCO}_2\text{H}$, 80°C , 1 h, 80% m) $\text{BBr}_3/\text{CH}_2\text{Cl}_2$, 0°C - rt, 15 h, 88% n) O_2 , hv, TPP/CHCl_3 , $20-40^\circ\text{C}$, 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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- Selected data for key compounds: Optical rotations (22°C) and ^1H -NMR spectra (J in Hz; 400, 500 and 600 MHz) were measured in CHCl_3 and CDCl_3 , respectively, unless otherwise noted. **5**: $[\alpha]_D^{+61}(c\ 1.0)$; ^1H -NMR δ 3.03 (1H, ddd, $J = 5, 5$ and $8, \text{H-4}$), 4.48 (1H, s, H-6), 4.66 (1H, s, H'-6), **8**: mp 75°C ; $[\alpha]_D^{+50}(c\ 1.0)$; ^1H -NMR δ 2.57 (1H, d, $J = 9, \text{H-2}$), 4.02 (1H, dd, $J = 8$ and $9, \text{H-3}$), 6.10 (1H, dd, $J = 2$ and $10, \text{H-6}$), 6.76 (1H, br d, $J = 10, \text{H-5}$), **10**: mp 173°C ; $[\alpha]_D^{-16}(c\ 1.0)$; ^1H -NMR δ 2.15 (1H, br d, $J = 12$ and $18, \text{H}_\alpha\text{-5}$), 2.56 (1H, ddd, $J = 6, 6$ and $18, \text{H}_\alpha\text{-5}$), 3.78 (1H, ddd, $J = 10$ and $10, \text{H-4}$), 3.87 (1H, dd, $J = 10$ and $10, \text{H-3}$), **13**: mp $204^\circ\text{C}(\text{dec.})$; $[\alpha]_D^{+397}(c\ 0.33)$; ^1H -NMR ($\text{C}_2\text{D}_2\text{N}$) δ 2.24 (3H, s, Me-6), 3.04 (1H, ddd, $J = 4, 10$ and $14, \text{H-4a}$), 4.40 (1H, ddd, $J = 10, 10$ and $10, \text{H-4}$), 4.46 (1H, dd, $J = 10$ and $10, \text{H-3}$), **15**: $[\alpha]_D^{-99}(c\ 0.46)$; ^1H -NMR δ 2.74 (1H, ddd, $J = 4, 10$ and $10, \text{H-4a}$), 3.57 (1H, dd, $J = 7$ and $9, \text{CH-2}$), 4.08 (1H, dd, $J = 7$ and $7, \text{CH'-2}$), **16**: $[\alpha]_D^{-93}(c\ 0.27)$; ^1H -NMR δ 2.92 (1H, dddd, $J = 2, 4, 5$ and $11, \text{H-4a}$), 4.20 (1H, d, $J = 4, \text{H-12a}$), 4.46 (1H, dd, $J = 6$ and $12, \text{CH-2}$), 4.54 (1H, dd, $J = 8$ and $12, \text{CH'-2}$), **18**: $[\alpha]_D^{-106}(c\ 0.35, \text{MeOH})$; ^1H -NMR (CD_3OD) δ 2.66 (1H, ddd, $J = 3, 4$ and $11, \text{H-4a}$), 4.04 (1H, d, $J = 12, \text{H-4}$), 9.75 (1H, s, CHO), **19**: $[\alpha]_D^{-360}(c\ 0.12)$; ^1H -NMR δ 2.79 (1H, dd, $J = 5$ and $13, \text{H-4a}$), 4.54 (1H, d, $J = 6, \text{H-4}$); IR (neat) 2204 cm^{-1} , **21**: $[\alpha]_D^{-86}(c\ 0.40, 0.1\text{ M HCl})$; ^1H -NMR δ 2.47 (9H, s, N-Me and Me-6), 3.33 (1H, d, $J = 11, \text{H-4}$), **23-HCl**: $[\alpha]_D^{-261}(c\ 0.50, 0.1\text{ M HCl})$; ^1H -NMR ($\text{CD}_3\text{OD-DCI}/\text{D}_2\text{O}$) δ 1.65 (3H, s, Me-6), 1.93 (1H, ddd, $J = 11, 13$ and $13, \text{H}_\beta\text{-5}$), 2.25 (1H, ddd, $J = 3, 5$ and $13, \text{H}_\alpha\text{-5}$), 3.04 (6H, s, N-Me).
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