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The first total synthesis of a tetracyclic antibiotic, (−)-tetrodecamycin

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Abstract—(−)-Tetrodecamycin (**1**) has been synthesized from optically active butenolide through stereoselective SmI_2-mediated pinacol cyclization and newly developed deoxygenation.

(−)-Tetrodecamycin (**1**) has been isolated from the culture broth of *Streptomyces* sp. MJ885-mF8 to show antimicrobial activities especially against *Pasteurella piscicida*, which is well known as the causative bacteria of pseudotuberculosis in cultured fishes.[1] The structure is distinguished by a tetronic acid-containing 6-6-7-5-membered tetracyclic core, the one cyclohexane ring of which is fully and diversely substituted.[2] Moreover, the quaternary carbons are located at C7 and C13.[3] The imposing structure and potential medicinal importance of this molecule have attracted a great deal of attention from other researchers since the disclosure of the structure,[4–6] although the total synthesis has not been reported yet.

Herein, we report the first total synthesis of (−)-tetrodecamycin (**1**).

From the retrosynthetic perspective, we envisioned that the 6-6-7-membered tricyclic core **17** would be accessible from the aldehyde **16** by a Baylis–Hillman-type reaction (Scheme 1).[7] In another critical step, we planned an efficient construction of **16** through the formation of the *cis*-diol by the SmI_2-mediated pinacol cyclization of the keto-aldehyde **10**,[8] which would be stereospecifically derived from our reported lactone **3**[9–11] through the unsaturated ketone **7** by reaction with cyclohexanone followed by reductive opening of the lactone ring.

The synthesis was initiated with the stereoselective conversion of the optically active butenolide **2** into the 2,3-dimethyl derivative **3** in three steps by our reported procedures (Scheme 2).[9–11] Reaction of the lithiated **3** with cyclohexanone was followed by dehydration to stereoselectively give the quaternary product **4**[12] as expected from our previous synthesis.[10] The structure was confirmed by X-ray crystallographic analysis.[13] Hydride reduction of **4** to the diol was successively followed by selective *O*-benzylation and silylation to give **6**.

Regioselective oxidation of **6** with SeO_2 gave the α,β-unsaturated ketone **7** as a single product in 86% yield.[14] The 1,4-reduction of **7** was achieved by a couple of $NaBH_4$ and $NiCl_2{\cdot}6H_2O$[15] to give a diastereomeric mixture of **8** and **9** in 77% and 15%, respectively, although the undesired **9** was recycled by epimerization to the desired **8** in alkaline MeOH. The structure of **8** was also determined by the X-ray analysis.[13]

De-*O*-tritylation of **8** and subsequent PCC oxidation gave the keto-aldehyde **10**. This was submitted to SmI_2-mediated cyclization in question to stereoselectively give the requisite *cis*-diol **11** as a single product resulting from the most stable transition state of the chelation-controlled reaction.[8] The configuration was confirmed by the X-ray analysis of the following acetonide **12**.[13] Michael addition of **12** to diethyl acetylenedicarboxylate gave a mixture of **13** and **14** in 75% and 15% yield, respectively, the stereochemistry of which was defined by the NMR studies,[12] especially by the chemical shifts of the olefin protons.[16]

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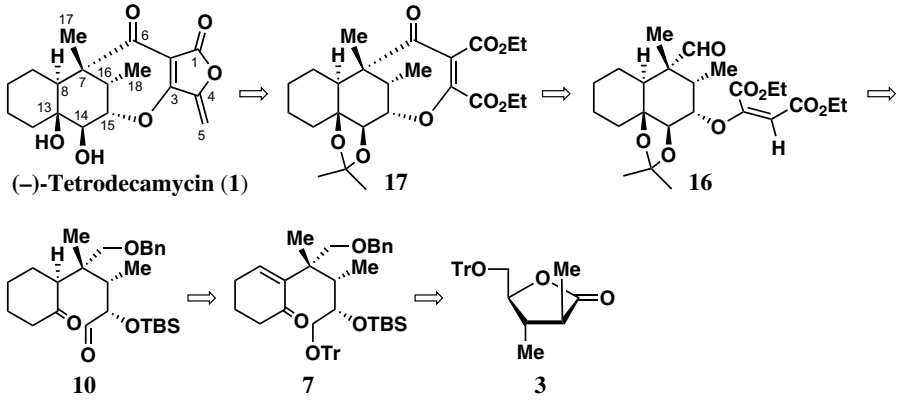
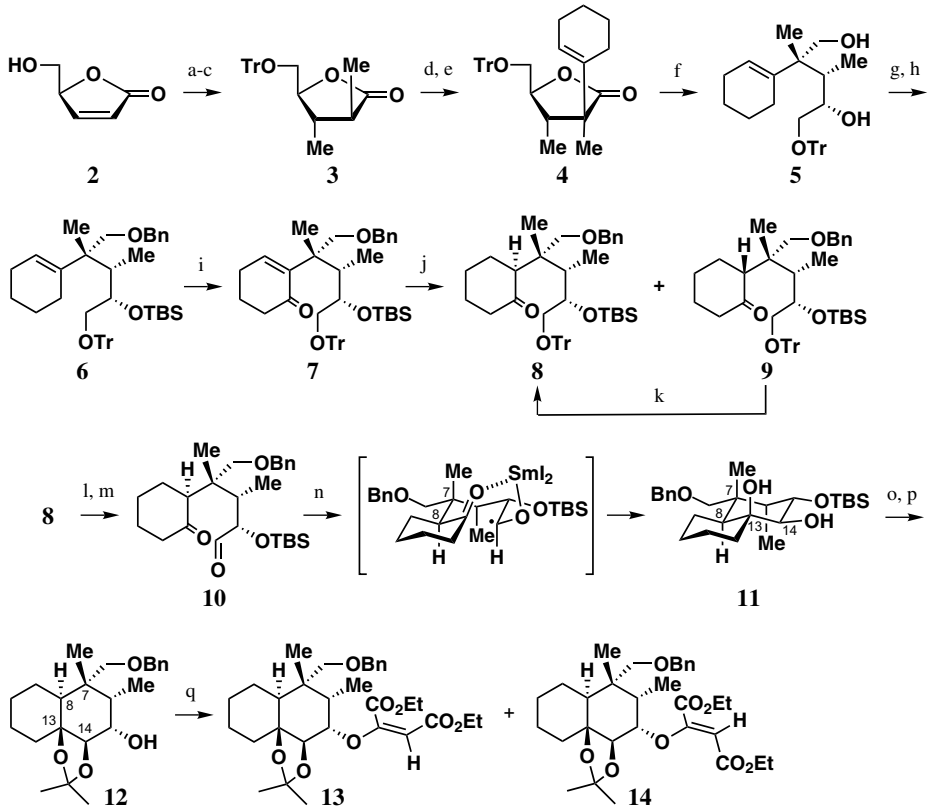


Scheme 1.

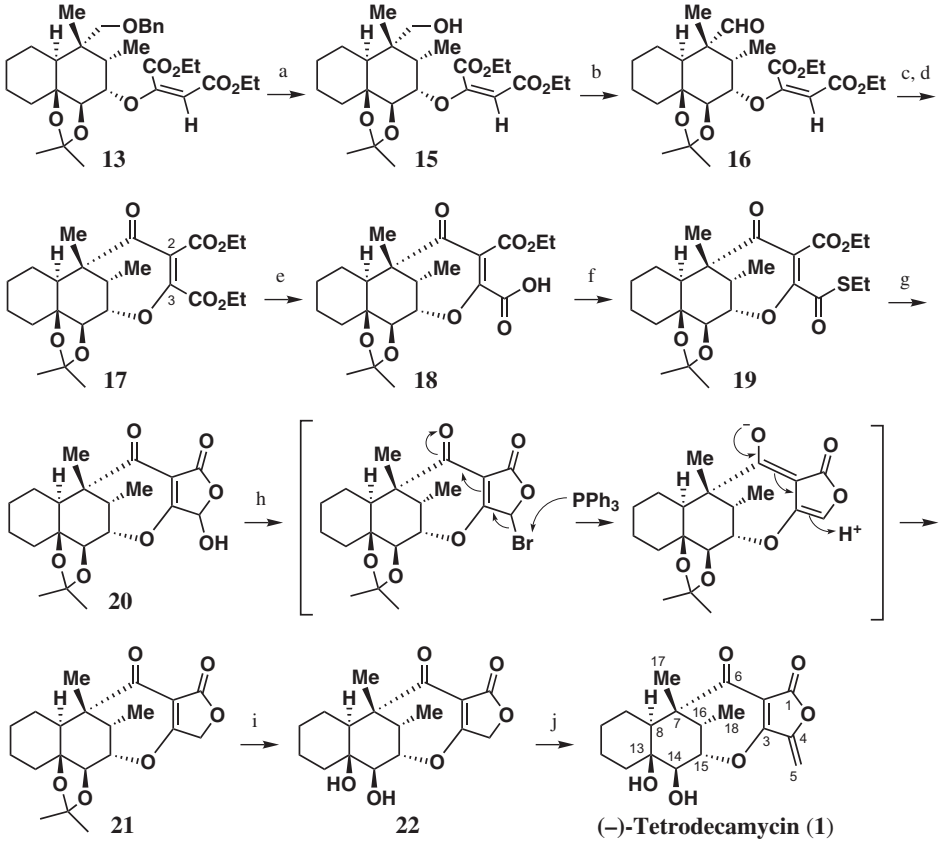


Scheme 2. Reagents and conditions: (a) TrCl, NH_4NO_3/DMF, rt, 16 h; (b) MeMgBr, CuBr·SMe_2, TMSCl, HMPA/THF, −78 °C to −50 °C, 20 min; (c) MeI, LDA/THF, −78 °C, 20 min, 81% in three steps; (d) cyclohexanone, LDA/THF, −78 °C, 10 min; (e) $SOCl_2$/Py, 0 °C, 1 h, 91% in two steps; (f) $LiBH_4$/THF, 65 °C, 38 h; (g) BnBr, K_2CO_3, 18-crown-6-ether/MeCN, 50 °C, 8 h; (h) TBSCl, DBU/MeCN, 65 °C, 20 h, 88% in three steps; (i) SeO_2/aq dioxane, 90 °C, 17 h, 86%; (j) $NaBH_4$, $NiCl_2·6H_2O$/MeOH–CH_2Cl_2, 0 °C, 10 min, **8**: 77%, **9**: 15%; (k) KOH/MeOH, 60 °C, 2 h, 60%; (l) Et_2AlCl/CH_2Cl_2, −78 °C to 0 °C, 0.5 h; (m) PCC, Al_2O_3/CH_2Cl_2, rt, 6 h; (n) SmI_2, *t*-BuOH/THF, −78 °C, 0.5 h, 73% in three steps; (o) 2-methoxypropene, PPTS/CH_2Cl_2, rt, 8 h; (p) TBAF/THF, 50 °C, 15 h, 71% in two steps; (q) diethyl acetylenedicarboxylate, KH/$ClCH_2CH_2Cl$, 75 °C, 6 h, **13**: 75%, **14**: 15%.

Reductive de-*O*-benzylation of the desired olefin **13** gave the alcohol **15**, which was oxidized to aldehyde **16** (Scheme 3). After some experimentation, treatment of **16** with NaHMDS constructed smoothly the seven-membered ring to afford a 5:1 diastereomeric mixture of the alcohols,[7] which was oxidized to a single product **17** as expected.

The stage was now set for further elaboration to tetrodecamycin.

In the diester **17**, the C2 ester is anticipated to be less reactive than the C3 ester for saponification because of the tautomerization with the ring oxygen atom. In the event, **17** was selectively hydrolyzed to the mono-acid



Scheme 3. Reagents and conditions: (a) H_2, Pd–C/EtOH, rt, 2 h; (b) PCC, Al_2O_3/CH_2Cl_2, rt, 6 h, 88% in two steps; (c) NaHMDS/THF, −78 °C, 10 min; (d) IBX/PhMe–DMSO, rt, 3 h, 81% in two steps; (e) Na_2CO_3/aq THF, rt, 15 h, 91%; (f) EtSH, WSCI·HCl, Py/CH_2Cl_2, rt, 1 h, 74%; (g) Et_3SiH, Lindlar cat./acetone, rt, 0.5 h, 80%; (h) CBr_4, PPh_3/CH_2Cl_2, rt, 0.5 h, 75%; (i) 70% aq TFA, 50 °C, 10 h, 85%; (j) $CH_2{=}N^+Me_2I^-$, *i*-Pr_2NEt/1,4-dioxane, rt, 12 h, then MeI, rt, 11 h, 63%.

18. The acid **18** was transformed to the thioester **19**, which was reduced by Et_3SiH to the aldehyde with concomitant cyclization to the diastereomeric acetal **20**.[17] The formation of lactone **21** was then tested from **18** or **20** under a variety of conditions, and finally the best result was realized from **20** by our newly developed procedures. Deoxygenation of the acetal **20** was effected in one operation using CBr_4 and PPh_3 to furnish lactone **21** by bromination[18] followed by debromination with PPh_3 and subsequent protonation.[19]

We then turned our attention to the introduction of the *exo*-methylene group onto the tetronic acid moiety. Deacetonation of **21** afforded diol **22**, which, upon treatment with Eschenmoser's reagent,[20] underwent introduction of an *exo*-methylene group to give (−)-tetrodecamycin (**1**). This was identical in all respects with the natural product,[21] completing the first total synthesis to establish the absolute structure.

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12. ^{1}H NMR (600 MHz: δ, ppm from TMS, and J in Hz) spectra were in $CDCl_3$ solution, unless otherwise stated. Selected data; Tetrodecamycin (**1**): $[\alpha]_D^{26}$ −6.0 (*c* 0.42, MeOH). δ 1.01 (3H, d, $J = 7.5$, H-18), 1.12 (1H, ddddd, $J = 13.0$, 13.0, 13.0, 3.0 and 3.0, H-10), 1.25 (3H, s, H-17), 1.22–1.29 (1H, m, H-12), 1.34 (1H, dd, $J = 12.5$ and 4.0, H-8), 1.42 (1H, ddddd, $J = 13.0$, 13.0, 13.0, 3.0 and 3.0, H-11), 1.48–1.53 (1H, m, H-9), 1.54–1.65 (2H, m, H-9′ and H-11′), 1.76–1.83 (1H, m, H-10′), 2.07 (1H, s, OH-13), 2.09 (1H, ddd, $J = 14.0$, 5.0 and 2.5, H-12′), 2.65 (1H, dq, $J = 3.0$ and 7.5, H-16), 3.17 (1H, d, $J = 6.5$, OH-14), 3.62 (1H, d, $J = 6.5$, H-14), 4.81 (1H, dd, $J = 3.0$ and 0.5, H-15), 5.27 (1H, d, $J = 2.5$, H-5), 5.37 (1H, d, $J = 2.5$, H-5′). Compound **4** [needles from *i*-PrOH, mp 154 °C (decomp.)]: $[\alpha]_D^{24}$ +12 (*c* 1.53, $CHCl_3$). δ 0.73 (3H, d, $J = 6.5$, H-18), 1.19 (3H, s, H-17), 2.65 (1H, dq, $J = 10.0$ and 6.5, H-16), 4.08 (1H, ddd, $J = 10.0$, 4.0 and 3.0, H-15), 5.62–5.68 (1H, m, H-9). Compound **8** (prisms from MeOH, mp 115 °C): $[\alpha]_D^{23}$ +3.6 (*c* 0.82, $CHCl_3$). δ 0.70 (3H, d, $J = 7.5$, H-18), 2.51 (1H, dd, $J = 12.0$ and 4.0, H-8), 4.08 (1H, ddd, $J = 8.0$, 2.5 and 1.5, H-15). Compound **10**: δ 1.05 (3H, d, $J = 7.5$, H-18), 2.06 (1H, ddd, $J = 12.5$, 6.0 and 3.0, H-12), 2.37 (1H, ddd, $J = 12.5$, 12.5 and 6.0, H-12′), 2.82 (1H, dd, $J = 12.5$ and 4.0, H-8), 3.95 (1H, dd, $J = 3.5$ and 3.0, H-15), 9.43 (1H, d, $J = 3.0$, H-14). Compound **12** (needles from EtOAc, mp 135 °C): $[\alpha]_D^{28}$ +26 (*c* 1.57, MeOH). δ 1.10 (3H, d, $J = 6.5$, H-18), 1.43 (3H, s, IP-Me), 1.45 (3H, s, IP-Me), 1.90 (1H, dd, $J = 12.0$ and 3.0, H-8), 3.45–3.51 (1H, m, H-15), 3.89 (1H, d, $J = 2.5$, H-14). Compound **13**: δ 0.92 (3H, d, $J = 7.0$, H-18), 3.22 (2H, s, H-6), 4.15 (2H, q, $J = 7.0$, –OCH_2–), 4.31 (1H, dq, $J = 10.5$ and 7.0, –OCH_2–), 4.33 (1H, dq, $J = 10.5$ and 7.0, –OCH_2–), 4.39–4.46 (1H, m, H-15), 5.23 (1H, s, H-2). Compound **14**: δ 1.01 (3H, d, $J = 7.0$, 18-Me), 6.10 (1H, s, H-2). Compound **16**: δ 0.99 (3H, d, $J = 7.0$, H-18), 4.11 (1H, d, $J = 2.5$, H-14), 4.15 (1H, dd, $J = 2.5$ and 1.5, H-15), 5.39 (1H, s, H-2), 9.42 (1H, s, H-6). Compound **19**: δ 1.07 (3H, d, $J = 7.5$, H-18), 2.90 (1H, dq, $J = 13.0$ and 7.0, –SCH_2–), 2.92 (1H, dq, $J = 13.0$ and 7.0, –SCH_2–), 4.20 (1H, d, $J = 2.5$, H-14), 4.31 (1H, dq, $J = 10.5$ and 7.0, –OCH_2–), 4.33 (1H, dq, $J = 10.5$ and 7.0, –OCH_2–), 4.51 (1H, dd, $J = 2.5$ and 0.5, H-15). Compound **20** (diastereomeric mixture): δ 1.00 (3H, d, $J = 6.5$, H-18), 1.03 (3H, d, $J = 6.5$, H-18), 5.77–5.85 (2H, br, OH-4), 5.90 (1H, s, H-4), 5.95 (1H, s, H-4). Compound **22**: $[\alpha]_D^{21}$ +97 (*c* 0.43, MeOH). (acetone-d_6): δ 0.96 (3H, d, $J = 7.0$, H-18), 3.70 (1H, d, $J = 6.5$, H-14), 4.63 (1H, d, $J = 16.0$, H-4), 4.66 (1H, d, $J = 16.0$, H-4′), 4.80 (1H, d, $J = 3.0$, H-15), 5.02 (1H, d, $J = 6.5$, OH-14).
13. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 290461 for **4**, CCDC 288233 for **8**, and CCDC 288691 for **12**. Copies of the data can be obtained, free charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44-0-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].
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21. An authentic sample of (−)-tetrodecamycin was kindly provided by Dr. Tomio Takeuchi, Inst. Microb. Chem.