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Tetrahedron Letters 47 (2006) 2439–2442
Tetrahedron Letters

Total synthesis of an antitubercular lactone antibiotic, (+)-tubelactomicin A

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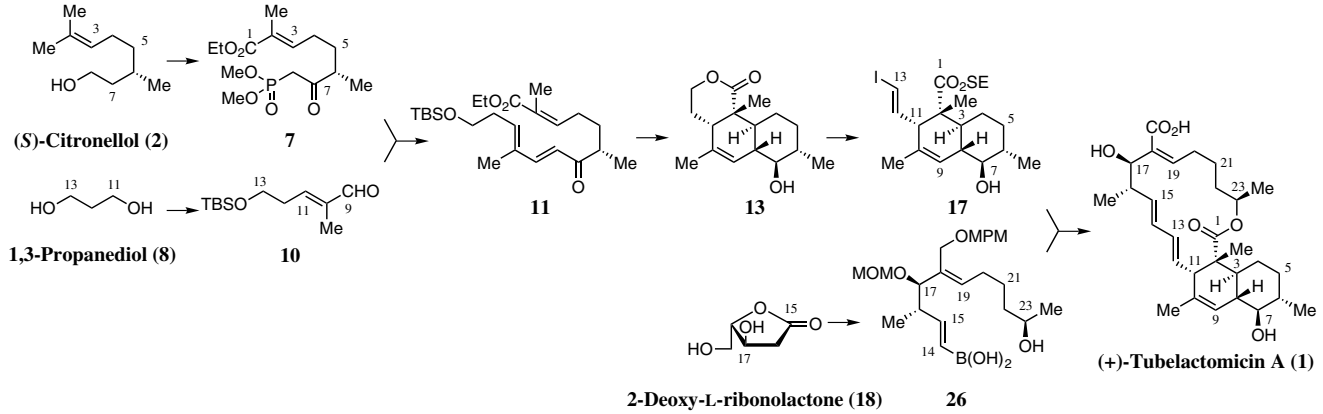
Received 28 December 2005; revised 23 January 2006; accepted 23 January 2006
Available online 20 February 2006

Abstract—(+)-Tubelactomicin A (**1**), an antitubercular lactone, has been synthesized from (*S*)-citronellol (**2**) and 2-deoxy-L-ribonolactone (**18**) through intramolecular Diels–Alder reaction, Suzuki–Miyaura coupling, and Shiina macrolactonization.

(+)-Tubelactomicin A (**1**) was isolated from the culture broth of *Nocardia* sp. MK703-102F1 to show strong and specific antimicrobial activities against drug-resistant *Mycobacterium*.[1] The structure was determined by X-ray crystallographic analysis to be the 16-membered lactone fused with a trans decalin skeleton.[2] As the morbidity of tuberculosis with the drug-resistant strains has increased worldwide, new effective drugs are needed for treatment of *Mycobacterium tuberculosis*. The interesting chemical structure, combined with its antitubercular activities, has made (+)-tubelactomicin A (**1**) an attractive target for synthesis, although the total synthesis has already been accomplished by the Tadano group using intramolecular Diels–Alder reaction.[3]

Independently, we report herein the total synthesis of (+)-tubelactomicin A (**1**).

The approach involves the construction and coupling of components **7**, **10**, and **26** (Scheme 1), wherein stereoselective Suzuki–Miyaura coupling reaction[4] was chosen for the key C13–C14 bond-forming reaction to assemble the C1–C13 and C14–C23 subunits[5] (**17** and **26**). The segments **7** and **10** were derived from (*S*)-citronellol (**2**)[6] and 1,3-propanediol (**8**), respectively, while the segment **26** was from 2-deoxy-L-ribonolactone (**18**).[7] The intramolecular Diels–Alder reaction[8–10] of **11** and subsequent stereoselective hydride reduction to give **13** formed the basis for controlling the configuration of 6



Scheme 1.

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doi:10.1016/j.tetlet.2006.01.140

of 9 stereogenic centers including a quaternary carbon in (+)-tubelactomicin A (**1**).

O-Benzylation of **2** successively followed by ozonolysis and hydride reduction gave alcohol **3** (Scheme 2).

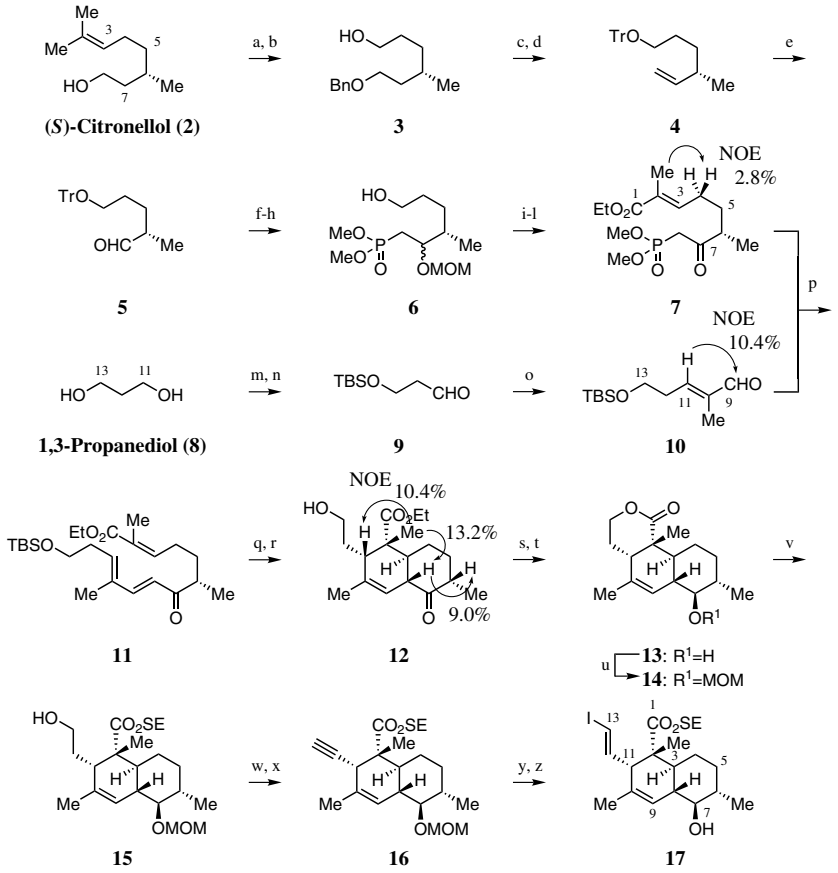
After tritylation, the *O*-benzyl group was submitted to a 2,3-rearrangement[11] with *n*-butyl lithium to give olefin **4**. Ozonolysis of **4** was followed by reaction with lithio dimethyl methylphosphonate, methoxymethylation of the resultant alcohol, and finally de-*O*-tritylation to provide phosphonate **6**. This was converted into the key segment **7** in four steps: IBX oxidation, Horner–Wadsworth–Emmons reaction, de-*O*-methoxymethylation, and then IBX oxidation.

Segment **10** was readily prepared from **8** by silylation and oxidation to give aldehyde **9** followed by Wittig olefination.

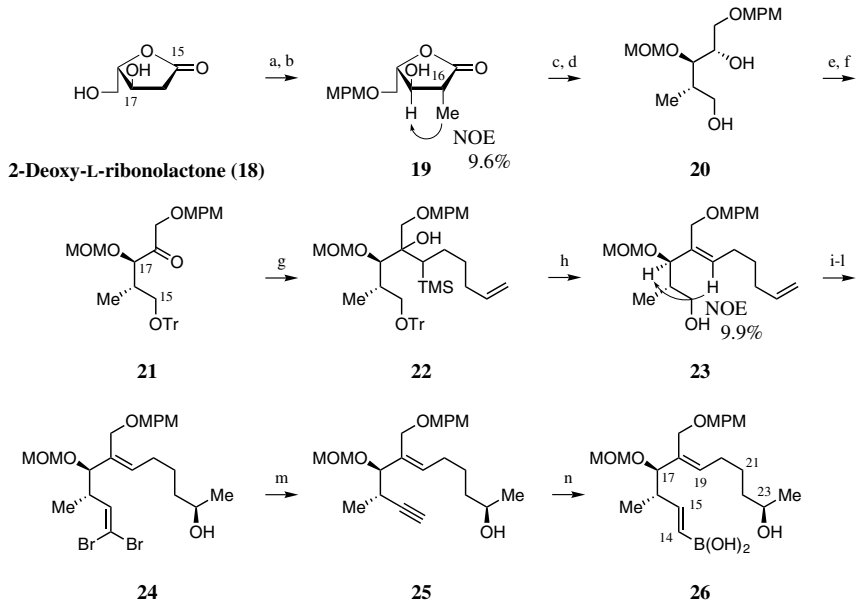
The configurations of both segments **7** and **10** were confirmed by the ^{1}H NMR studies.

Coupling of **7** and **10** was effected using $Ba(OH)_2$ under mild conditions[12] to give the desired product **11**.[13] The intramolecular Diels–Alder reaction of **11** afforded the requisite adduct as a single product as expected from the favored transition state.[8–10] De-*O*-silylation of the adduct gave **12**, which was stereoselectively reduced to **13** and then transformed to the methoxymethyl ether **14**. Their structures were supported by the ^{1}H NMR studies. Reaction of **14** with sodium TMS-ethylate gave the hydroxyl ester **15** without the undesired lactone formation. The alcohol was oxidized to the aldehyde, which was treated with Comins' reagent[14] to give the desired acetylene **16**. This was converted to the key vinyl iodide **17** according to the reported procedures.[15]

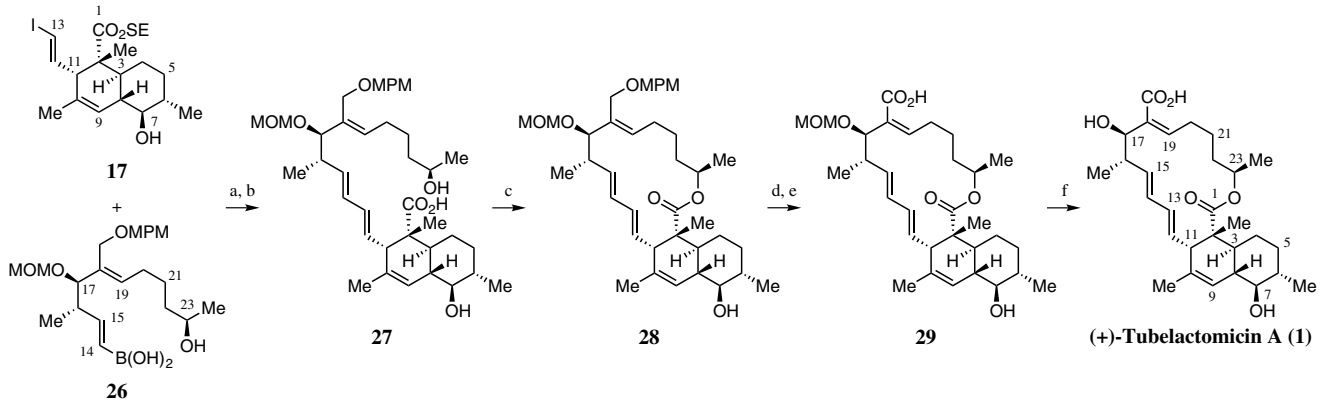
Synthesis of the segment **26** began with selective *O*-protection of **18** and stereoselective introduction of a *C*-methyl group[16] (Scheme 3). *O*-Methoxymethylation of **19** and subsequent hydride reduction afforded diol **20**, which was selectively tritylated and then oxidized to ketone **21**. Installation of the trimethylsilylated side



Scheme 2. Reagents and conditions: (a) BnCl, NaH/DMF, 0 °C, 3 h; (b) O_3/CH_2Cl_2, −78 °C, 1 h, then $NaBH_4$, −78 °C to rt, 12 h, 84% in two steps; (c) TrCl, Et_3N, DMAP/$Cl(CH_2)_2Cl$, 50 °C, 12 h; (d) *n*-BuLi/THF, −78 °C to rt, 1 h, 76% in two steps; (e) O_3/CH_2Cl_2, −78 °C, 1 h, then PPh_3, −78 °C to rt, 12 h, 95%; (f) dimethyl methylphosphonate, *n*-BuLi/THF, −78 °C, 1 h; (g) MOMCl, *i*-Pr_2NEt/MeCN, 50 °C, 4 h; (h) aq AcOH, rt, 12 h, 48% in three steps; (i) IBX/PhMe–DMSO, 50 °C, 3 h; (j) triethyl 2-phosphonopropionate, *i*-Pr_2NEt, LiCl/MeCN, rt, 5 h; (k) HCl/aq THF, 65 °C, 1 d; (l) IBX/PhMe–DMSO, 50 °C, 5 h, 60% in four steps; (m) TBSCl, imidazole/MeCN, 0 °C, 1 h; (n) IBX/PhMe–DMSO, 50 °C, 1 h; (o) 2-(triphenylphosphoranylidene)-propionaldehyde/PhMe, 90 °C, 5 h, 47% in three steps; (p) $Ba(OH)_2{\cdot}8H_2O$/aq THF, rt, 3 h, 85%; (q) BHT/xylene, 130 °C, 3 d; (r) $BF_3{\cdot}OEt_2$/MeCN, rt, 10 min, 68% in two steps; (s) $NaBH(OAc)_3$/1,4-dioxane, 95 °C, 12 h; (t) CSA/$Cl(CH_2)_2Cl$, 70 °C, 12 h; (u) MOMCl, *i*-$Pr_2NEt/Cl(CH_2)_2Cl$, 50 °C, 6 h, 39% in three steps; (v) $TMS(CH_2)_2ONa$/THF, 50 °C, 5 min, 68%; (w) IBX/PhMe–DMSO, 50 °C, 1 h; (x) 2-[*N*,*N*-bis(trifluoromethylsulfonyl)amino]-5-chloropyridine, KHMDS/THF, 0 °C, 30 min, 60% in two steps; (y) HCl/aq THF, 60 °C, 3 h; (z) Cp_2ZrHCl/PhH, rt, 1 h, then I_2, rt, 1 h, 50% in two steps.



Scheme 3. Reagents and conditions: (a) *p*-methoxybenzyl 2,2,2-trichloroacetimidate, CSA/CH_2Cl_2, rt, 12 h; (b) MeI, LDA/THF, −78 °C to rt, 6 h, 60% in two steps; (c) MOMCl, *i*-Pr_2NEt/MeCN, 50 °C, 4 h; (d) LAH/THF, 0 °C, 30 min, 85% in two steps; (e) TrCl, Et_3N/$Cl(CH_2)_2Cl$, 50 °C, 12 h; (f) IBX/PhMe–DMSO, 50 °C, 30 min, 90% in two steps; (g) vinyltrimethylsilane, 4-bromo-1-butene, *t*-BuLi/THF, −78 °C to rt, 1 h, 65%; (h) $BF_3{\cdot}OEt_2$/CH_2Cl_2, 0 °C, 1 h, 75%; (i) $PdCl_2$/aq DMF, 0 °C, 12 h; (j) IBX/PhMe–DMSO, 50 °C, 3 h; (k) CBr_4, PPh_3/CH_2Cl_2, 0 °C, 10 min, 68% in three steps; (l) (*S*)-CBS, catecholborane/THF–CH_2Cl_2, −78 °C, 8 h; (m) *n*-BuLi/THF, 0 °C, 10 min, 59% in two steps; (n) catecholborane/THF, reflux, 3 d, 61%.



Scheme 4. Reagents and conditions: (a) $Pd_2(dba)_3$, $AsPh_3$, TlOEt/aq THF, rt, 10 min, 35%; (b) TBAF/THF, 0 °C to rt, 3 h, 95%; (c) MNBA, DMAP/CH_2Cl_2, rt, 12 h, 80%; (d) DDQ/aq CH_2Cl_2, rt, 4 h; (e) NiO_2/aq NaOH, 50 °C, 30 min, 85% in two steps; (f) HCl/aq THF, rt, 1 d, 80%.

chain gave the diastereomeric **22**, which was converted into olefin **23**.[17] The stereochemistry was also confirmed by the ^1H NMR studies.

The terminal vinyl group of **23** was selectively oxidized to the methyl ketone under Wacker conditions, which was followed by oxidation of the primary alcohol to give the intermediary aldehyde. The aldehyde portion reacted with CBr_4 and PPh_3 to give the dibromomethylene. Sequentially, the methyl ketone portion was stereoselectively reduced with (*S*)-CBS to afford the desired **24** with a little undesired isomer.[18] Exposure of the crude sample to the *n*-butyl lithium provided acetylene **25**, which was transformed to the alkenylboronic acid **26** by hydroboration with catecholborane followed by hydrolysis on silica gel.

Cross-coupling of **17** and **26** gave,[4] after deprotection, the desired seco acid **27** (Scheme 4). Macrolactonization proceeded smoothly under Shiina's conditions[19] to deliver lactone **28**.

To complete the total synthesis, removal of the *O*-MPM group was successively followed by selective NiO_2 oxidation[20] of the resultant allyl alcohol to the carboxylic acid **29** and de-*O*-methoxymethylation to give (+)-tubelactomicin A (**1**). The analytical data of **1** were consistent with those reported previously.[2,3]

Acknowledgments

We are grateful to the 21COE 'Center for Practical Nano-Chemistry' the Consolidated Research Institute for Advanced Science and Medical Care, a Grant-in-Aid for Scientific Research (A), and Scientific Research on Priority Areas 16073220 from Ministry of Education, Culture, Sports, Science and Technology (MEXT) for the financial supports of our program.

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13. ^{1}H NMR (600 MHz: δ, ppm from TMS, and J in Hz) spectra were in $CDCl_3$ solution, unless otherwise stated. Selected data; compound **1**: $[\alpha]_D^{23}$ +100 (*c* 0.40, MeOH). ^{1}H NMR [in acetone-d_6]: δ 1.03 (3H, d, $J = 6.0$ Hz, Me-6), 2.38 (1H, d, $J = 10.0$ Hz, H-11), 4.71 (1H, m, H-23), 5.27 (1H, dd, $J = 14.0$ and 10.0 Hz, H-12), 5.73 (1H, dd, $J = 15.0$ and 6.0 Hz, H-15). Compound **11**: $[\alpha]_D^{26}$ +20 (*c* 0.91, $CHCl_3$). ^{1}H NMR: δ 1.13 (3H, d, $J = 7.0$ Hz, Me-6), 1.80 (3H, s, Me-2), 2.80 (1H, ddq, $J = 7.0$, 7.0, and 7.0 Hz, H-6), 6.15 (1H, d, $J = 16.0$ Hz, H-8), 7.25 (1H, d, $J = 16.0$ Hz, H-9). Compound **12**: $[\alpha]_D^{26}$ +36 (*c* 1.10, $CHCl_3$). ^{1}H NMR: δ 1.03 (3H, d, $J = 6.0$ Hz, Me-6), 1.20 (3H, s, Me-2), 2.43 (1H, dddq, $J = 12.0$, 6.0, 6.0, and 1.0 Hz, H-6), 2.76 (1H, d, $J = 12.0$ Hz, H-8), 5.55 (1H, s, H-9). Compound **17**: $[\alpha]_D^{24}$ +122 (*c* 0.26, $CHCl_3$). ^{1}H NMR: δ 1.05 (3H, d, $J = 6.0$ Hz, Me-6), 1.12 (3H, s, Me-2), 2.91 (1H, ddq, $J = 9.0$, 9.0, and 6.0 Hz, H-7), 5.82 (1H, s, H-9), 6.30 (1H, dd, $J = 14.0$ and 10.0 Hz, H-12). Compound **20**: $[\alpha]_D^{27}$ +32 (*c* 0.87, $CHCl_3$). ^{1}H NMR: δ 0.89 (3H, d, $J = 7.0$ Hz, Me-16), 3.55 (1H, dd, $J = 9.6$ and 5.6 Hz, CH_2-18), 3.64 (1H, dd, $J = 9.6$ and 3.0 Hz, CH_2'-18), 3.71 (1H, dd, $J = 7.6$ and 3.0 Hz, H-17), 3.82 (1H, m, H-18). Compound **23**: $[\alpha]_D^{23}$ +21 (*c* 0.60, $CHCl_3$). ^{1}H NMR: δ 0.96 (3H, d, $J = 7.0$ Hz, Me-16), 3.52 (2H, dd, $J = 6.0$ and 6.0 Hz, H-15), 3.99 (1H, d, $J = 7.0$ Hz, H-17), 5.68 (1H, t, $J = 7.0$ Hz, H-19), 5.77 (1H, ddd, $J = 17.0$, 10.0, and 7.0 Hz, H-23). Compound **25**: $[\alpha]_D^{23}$ +62 (*c* 0.54, $CHCl_3$). ^{1}H NMR: δ 1.15 (3H, d, $J = 7.0$ Hz, Me-16), 1.25 (3H, d, $J = 7.0$ Hz, Me-23), 2.04 (1H, d, $J = 3.0$ Hz, H-14), 3.76 (1H, m, H-23), 5.71 (1H, t, $J = 7.0$ Hz, H-19). Compound **28**: $[\alpha]_D^{23}$ +149 (*c* 0.31, $CHCl_3$). ^{1}H NMR: δ 1.04 (3H, d, $J = 7.0$ Hz, Me-6), 2.34 (1H, d, $J = 10.0$ Hz, H-11), 4.68 (1H, m, H-23), 5.29 (1H, dd, $J = 14.0$ and 10.0 Hz, H-12), 5.63 (1H, dd, $J = 16.0$ and 7.0 Hz, H-15).
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