The First Total Synthesis of (±)-Napyradiomycin A1

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(±)-Napyradiomycin A1 has been stereoselectively synthesized through a tandem Michael-Dieckmann type reaction and the introduction of a side chain and two chlorine atoms onto the pyranonaphthoquinone core.

Napyradiomycin A1 (**1**), which is a member of the pyranonaphthoquinone group, was isolated from strains of *Chainia rubra*[1] and *Streptomyces* sp.[2] Although napyradiomycin A1 (**1**) was first found by the Umezawa group to inhibit the growth of Gram-positive bacteria,[1] the Fujisawa group reported **1** to be a novel non-steroidal estrogen-receptor antagonist.[2]

The structure was determined by NMR and X-ray analyses to have a chloro-pyranonaphthoquinone core bound with a side chain.[3]

Recently, we have synthesized polycyclic natural products including pyranonaphthoquinones by using tandem Michael-Dieckmann type reactions, which were explored extensively in our laboratories.[4–6] This transformation is ideally suited for the synthesis of napyradiomycin A1 (**1**), since the tricyclic core **9** arises from benzofuranone **6** and dihydropyranone **7**.

Herein, we report the first total synthesis of (±)-napyradiomycin A1 (**1**).

From both structural and retrosynthetic standpoints, napyradiomycin A1 (**1**) is reasonably expected to be constructed from the tricyclic core **9** and the side chain **10** as outlined in Figure 1. Especially, the core **9** can be prepared from the benzofuranone **6** and the dihydropyranone **7** as mentioned above. The former **6** is derived from 2,4-dihydroxybenzoic acid (**2**).

Key elements of the approach include the stereo- and regioselective introduction of two chlorine atoms and one side chain onto the pyranonaphthoquinone structure.

The synthesis commenced with conversion of 2,4-dihydroxybenzoic acid (**2**) into the *N*, *N*-diethylamide **3**[7] in 3 steps (Scheme 1).

The regioselective introduction of a formyl group onto **3** was carried out by *ortho* lithiation[8] of the amido group to give **4** in a quantitative yield. Treatment of **4** with $PhSO_2Na$ in AcOH to give **5** was followed by methoxymethylation of the deprotected hydroxy group to afford **6**.

The crucial Michael-Dieckmann type reaction[6] was conducted by lithiation of **6** followed by exposure to **7**, which was prepared according to Obrecht's procedure.[9] The resulting tricyclic compound was oxidized to the quinone **8**. Chlorination of **8** with SO_2Cl_2 afforded **9**.

The side chain segment **10** was prepared from geranyl chloride by treatment with tributyltin lithium according to the modified Naruta's procedure.[10]

Michael addition of the side chain segment to **9** was achieved using the stannyl derivative **10**, which was in turn lithiated to give the enol **11** (55%) with its diastereomer (5%). The addition was expected to occur from the opposite site of the chlorine atom to give the *trans* compound **11**, because the chlorine atom was present in a *quasi-axial* position due to repulsion by the vicinal methyl groups.

Another chlorination of **11** proceeded smoothly to give **12** in a quantitative yield. Selective deoxygenation at C4 in **12** to give **16** failed to occur under various conditions. After extensive experimentation, we were able to convert **12** into **16** in 4 steps through the unsaturated ketone **14**. The ketone **12** was reduced with a highly hindered KPh_3BH[11] to give a 5 : 1 diastereomeric mixture of the alcohol **13**. This was treated with 2,2'-dipyridyl disulfide and tributylphosphine to afford the α,β-unsaturated ketone **14**.[12] The selective 1,4-hydride reduction of **14** was carried out with KPh_3BH again to give exclusively the tetrahydropyran **15**.

At this stage, the fusion point in **15** proved to be extremely resistant to chlorination under standard conditions including LHMDS and NCS. However, it was discovered that the crucial chlorination could be accomplished by exposure of **15** to KHMDS followed by treatment with NCS, affording the desired compound **16** as a single product. The chlorination was anticipated to occur at the convex site of **15** to give **16** preferentially.

Finally, de-*O*-protection afforded (±)-napyradiomycin A1 (**1**) as a syrup, which was identical in NMR, IR and mass spectral analyses with the natural product.[13]

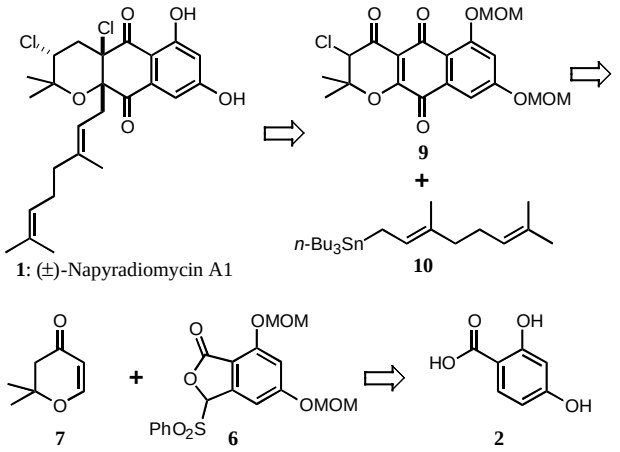

Figure 1.

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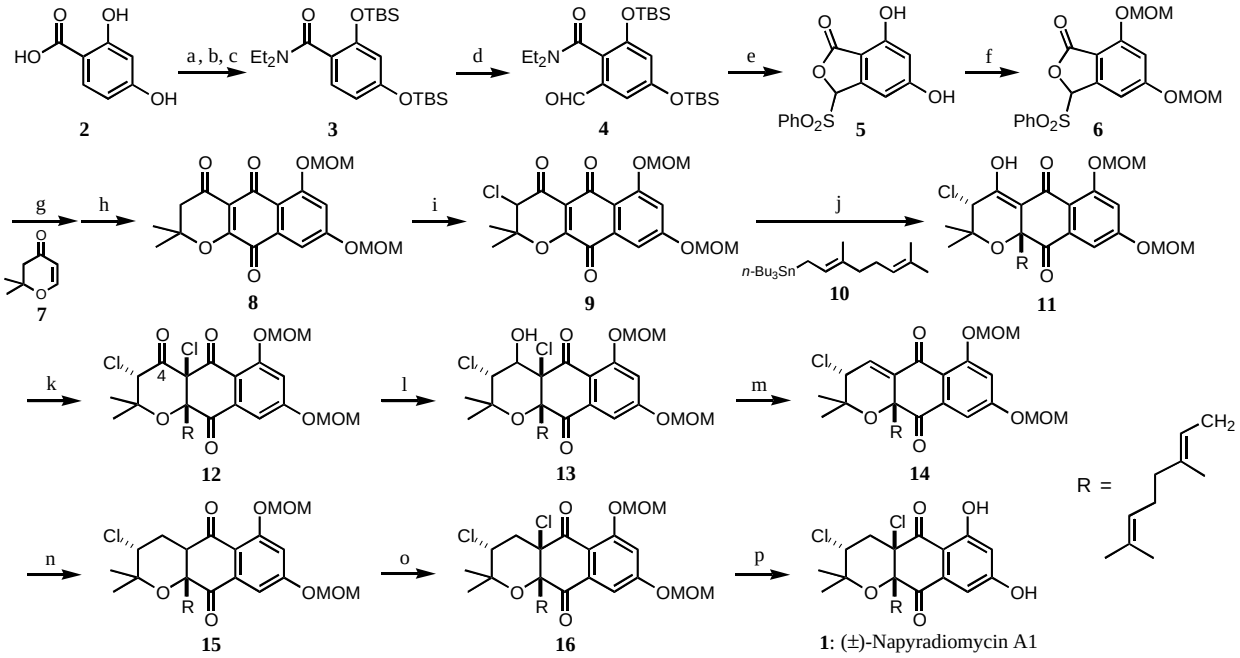
This paper is dedicated to Professor Teruaki Mukaiyama on the occasion of his 75th birthday.



Scheme 1. a) H_2SO_4/MeOH, reflux, 72 h, quant. b) TBSCl, NaH/THF, 0 °C, 30 min, quant. c) Et_2NH, Me_3Al/PhMe, reflux, 10 h, quant. d) *s*-BuLi, TMEDA, DMF/THF, -78 °C, 1 h, quant. e) $PhSO_2Na$/AcOH, 80 °C, 12 h, 80%. f) MOMCl, *i*-Pr_2NEt/DMF, 0 °C, 1 h, 88%. g) *t*-BuOLi/THF, -78 °C – rt, 2 h. h) MnO_2/$CHCl_3$, rt, 30 min, 2 steps 64%. i) SO_2Cl_2/CH_2Cl_2, -40 °C, 40 min, 77%. j) *n*-BuLi, CuI, LiBr/THF, -78 °C, 1 h, 55%. k) NCS/1,2-dimethoxyethane, rt, 40 min, quant. l) KPh_3BH/THF, -78 °C, 30 min, 61%. m) $(PyS)_2$, *n*-Bu_3P/PhMe, rt, 5 min, 76%. n) KPh_3BH/THF, 0 °C, 30 min, 72%. o) NCS, KHMDS/THF, -

References and Notes

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7 Selected data for key compounds: ^{1}H NMR spectra (*J* in Hz; 400 and 600 MHz) were measured in $CDCl_3$, unless otherwise noted. **1**: ^{1}H NMR δ 1.19 (3H, s), 1.33 (3H, s), 1.51 (3H, s), 1.52 (3H, s), 1.57-1.62 (4H, m), 1.63 (3H, s), 2.42 (1H, dd, J = 14.0 and 11.0), 2.48 (1H, dd, J = 14.0 and 5.0), 2.70 (2H, br d, J = 8.0), 4.43 (1H, dd, J = 11.0 and 5.0), 4.71 (1H, t, J = 8.0), 4.91 (1H, m), 6.21 (1H, br s), 6.70 (1H, d, J = 2.5), 7.16 (1H, d, J = 2.5), 11.83 (1H, s); IR (KBr) 1700, 1641, 1614, 1253, 1076 cm^{-1}, **3**: ^{1}H NMR δ 0.19 (6H, s), 0.21 (6H, s), 0.95 (9H, s), 0.97 (9H, s), 0.98 (3H, t, J = 7.0), 1.22 (3H, t, J = 7.0), 3.02-3.31 (2H, m), 3.35-3.69 (2H, m), 6.31 (1H, d, J = 2.0), 6.47 (1H, dd, J = 8.0 and 2.0), 7.04 (1H, d, J = 8.0), **6**: mp 117–118 °C; ^{1}H NMR δ 3.48 (3H, s), 3.53 (3H, s), 5.25 (1H, d, J = 7.0), 5.27 (1H, d, J = 7.0), 5.30 (1H, d, J = 7.0), 5.35 (1H, d, J = 7.0), 6.01 (1H, s), 6.93 (1H, d, J = 2.0), 7.19 (1H, d, J = 2.0), 7.54 (2H, ddd, J = 7.5, 7.5 and 1.5), 7.68 (1H, dddd, J = 7.5, 7.5, 1.5 and 1.5), 7.89 (2H, dd, J = 7.5 and 1.5), **8**: mp 123–124 °C; ^{1}H NMR δ 1.57 (6H, s), 2.72 (2H, s), 3.49 (3H, s), 3.53 (3H, s), 5.27 (2H, s), 5.29 (2H, s), 7.16 (1H, d, J = 2.5), 7.41 (1H, d, J = 2.5), **9**: ^{1}H NMR δ 1.59 (3H, s), 1.70 (3H, s), 3.49 (3H, s), 3.54 (3H, s), 4.16 (1H, s), 5.28 (2H, s), 5.30 (2H, s), 7.18 (1H, d, J = 2.5), 7.44 (1H, d, J = 2.5), **11**: ^{1}H NMR δ 1.15 (3H, s), 1.45 (3H, d, J = 1.5), 1.57 (3H, s), 1.59 (3H, s), 1.69 (3H, s), 1.95–2.06 (4H, m), 2.38 (1H, dd, J = 14.0 and 8.0), 2.46 (1H, dd, J = 14.0 and 7.5), 3.50 (3H, s), 3.57 (3H, s), 4.42 (1H, s), 5.04 (1H, m), 5.10 (1H, ddq, J = 8.0, 7.5 and 1.5), 5.26 (1H, d, J = 7.0), 5.28 (1H, d, J = 7.0), 5.33 (1H, d, J = 7.0), 5.35 (1H, d, J = 7.0), 7.12 (1H, d, J = 2.0), 7.28 (1H, d, J = 2.0), 16.12 (1H, s), **13**: ^{1}H NMR δ 1.18 (3H, s), 1.47 (3H, s), 1.51 (3H, s), 1.55 (3H, s), 1.66 (3H, s), 1.68-1.83 (4H, m), 2.53 (1H, dd, J = 14.5 and 8.0), 2.64 (1H, d, J = 2.5), 2.72 (1H, dd, J = 14.5 and 7.5), 3.48 (3H, s), 3.53 (3H, s), 4.31 (1H, dd, J = 2.5 and 2.5), 4.64 (1H, d, J = 2.5), 4.90 (1H, dd, J = 8.0 and 7.5), 4.98 (1H, br s), 5.22 (1H, d, J = 7.0), 5.26 (1H, d, J = 7.0), 5.28 (1H, d, J = 7.0), 5.29 (1H, d, J = 7.0), 7.05 (1H, d, J = 2.0), 7.35 (1H, d, J = 2.0), **14**: ^{1}H NMR (C_6D_6) δ 1.18 (3H, s), 1.43 (3H, s), 1.46 (3H, s), 1.56 (3H, d, J = 1.0), 1.59 (3H, s), 1.82–1.98 (4H, m), 2.55 (1H, dd, J = 15.0 and 7.5), 2.68 (1H, dd, J = 15.0 and 8.0), 2.98 (3H, s), 3.21 (3H, s), 4.25 (1H, d, J = 2.0), 4.67 (1H, d, J = 7.0), 4.68 (1H, d, J = 7.0), 4.96 (1H, d, J = 6.5), 4.99 (1H, d, J = 6.5), 5.04 (1H, m), 5.25 (1H, ddq, J = 8.0, 7.5 and 1.0), 7.00 (1H, d, J = 2.0), 7.17 (1H, d, J = 2.0), 7.71 (1H, d, J = 2.0), **15**: ^{1}H NMR (C_6D_6) δ 1.28 (3H, s), 1.38 (3H, s), 1.46 (3H, s), 1.53 (3H, s), 1.67 (3H, d, J = 1.0), 1.93-2.07 (5H, m), 2.16 (1H, ddd, J = 14.0, 4.5 and 4.0), 2.51 (1H, dd, J = 14.5 and 7.5), 2.56 (1H, dd, J = 14.5 and 8.0), 3.01 (3H, s), 3.18 (1H, dd, J = 13.0 and 4.0), 3.19 (3H, s), 3.47 (1H, dd, J = 12.0 and 4.5), 4.72 (1H, d, J = 6.5), 4.74 (1H, d, J = 6.5), 4.93 (2H, s), 5.13 (1H, m), 5.33 (1H, dd, J = 8.0 and 7.5), 7.21 (1H, d, J = 2.0), 7.83 (1H, d, J = 2.0), **16**: ^{1}H NMR (C_6D_6) δ 1.25 (3H, s), 1.38 (3H, s), 1.44 (6H, s), 1.58 (3H, s), 1.63–1.74 (4H, m), 2.41 (1H, dd, J = 14.0 and 4.0), 2.54 (1H, dd, J = 14.0 and 12.0), 2.99 (3H, s), 3.01 (1H, dd, J = 13.5 and 7.5), 3.13 (1H, dd, J = 13.5 and 9.0), 3.17 (3H, s), 4.53 (1H, dd, J = 12.0 and 4.0), 4.67 (1H, d, J = 7.0), 4.69 (1H, d, J = 7.0), 4.88 (1H, d, J = 6.0), 4.90 (1H, d, J = 6.0), 4.95 (1H, m), 5.13 (1H, dd, J = 9.0 and 7.5), 7.17 (1H, d, J = 2.0), 7.73 (1H, d, J = 2.0).
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13 The authentic sample of natural napyradiomycin A1 was kindly provided by Dr. H. Naganawa, Institute of Microbial Chemistry.

Additions and Corrections

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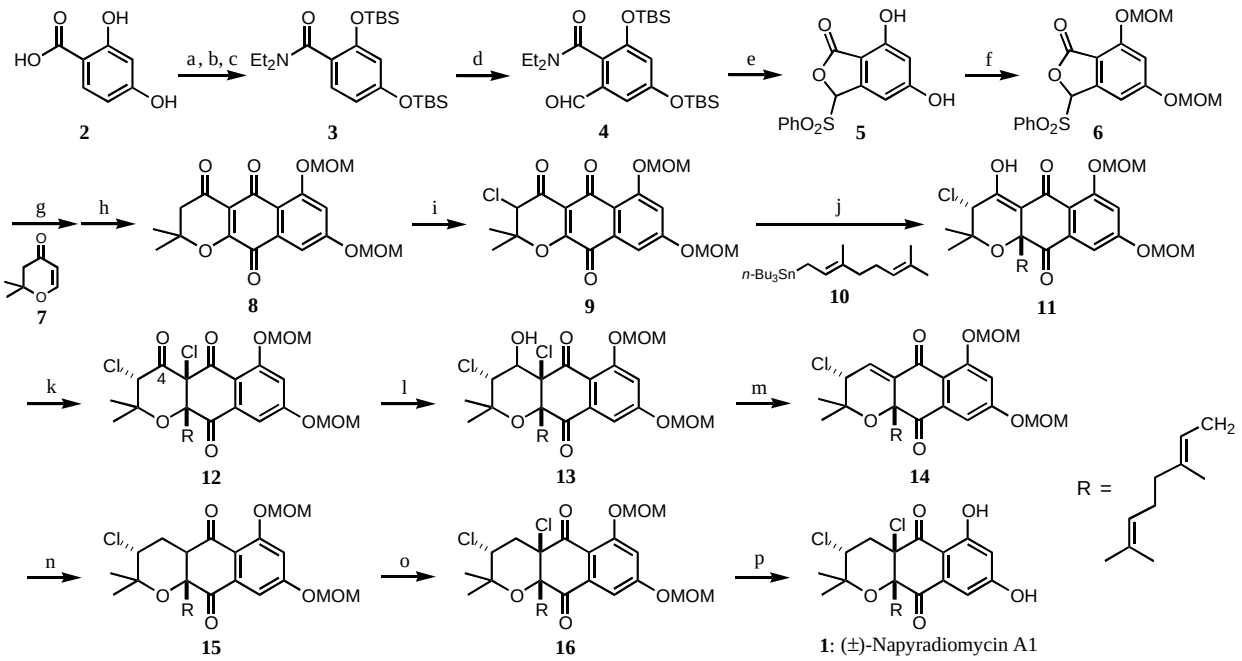
Page 15, the caption of Scheme 1 is incomplete. This mistake was caused on the publishing process. Scheme 1 and its caption should appear as given below.



Scheme 1. a) H_2SO_4/MeOH, reflux, 72 h, quant. b) TBSCl, NaH/THF, 0 °C, 30 min, quant. c) Et_2NH, Me_3Al/PhMe, reflux, 10 h, quant. d) *s*-BuLi, TMEDA, DMF/THF, -78 °C, 1 h, quant. e) $PhSO_2Na$/AcOH, 80 °C, 12 h, 80%. f) MOMCl, *i*-Pr_2NEt/DMF, 0 °C, 1 h, 88%. g) *t*-BuOLi/THF, -78 °C – rt, 2 h. h) $MnO_2/CHCl_3$, rt, 30 min, 2 steps 64%. i) SO_2Cl_2/CH_2Cl_2, -40 °C, 40 min, 77%. j) *n*-BuLi, CuI, LiBr/THF, -78 °C, 1 h, 55%. k) NCS/1,2-dimethoxyethane, rt, 40 min, quant. l) KPh_3BH/THF, -78 °C, 30 min, 61%. m) $(PyS)_2$, *n*-Bu_3P/PhMe, rt, 5 min, 76%. n) KPh_3BH/THF, 0 °C, 30 min, 72%. o) NCS, KHMDS/THF, -78 °C, 3 h, 81%. p) PPTS/*t*-BuOH, 90 °C, 18 h, 91%.