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The first total synthesis of lymphostin

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Abstract—Lymphostin (**1**), a novel immunosuppressant, has been synthesized from tryptophan through six kinds of regioselectively oxidative reactions.

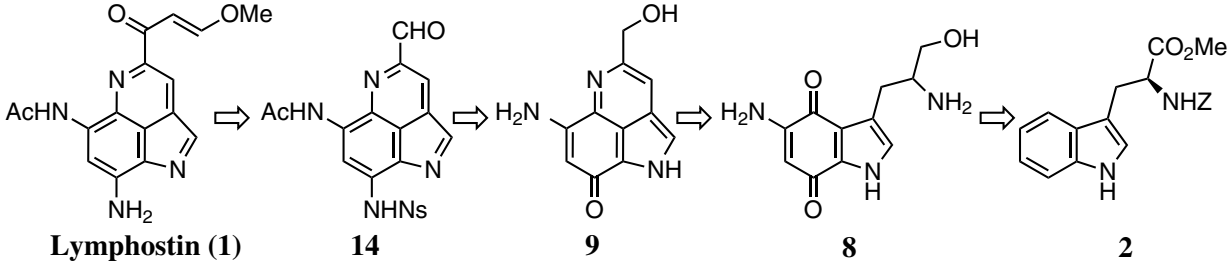
Lymphostin (**1**) was isolated by the Kyowa Hakko group from a culture broth of *Streptomyces* sp. as an immunosuppressant to show potent inhibitory activity against lymphocyte kinase.[1] The structure was elucidated by thorough NMR studies to be a novel tricyclic aromatic alkaloid with a pyrroloquinoline skeleton.[2] In addition to its novel mechanism of action, impinging on a crucial biological cascade, the structure of **1** interested us as a focused target for total synthesis. We have proposed lymphostin (**1**) to be biogenetically produced from tryptophan.

Herein, we report the implementation of a novel biomimetic strategy for the first total synthesis of lymphostin (**1**). The critical element of the synthetic plan was inspired by our proposed biosynthetic sequence as shown in the retrosynthetic perspective to assemble the tricyclic core **14** from the quinone **8** through cyclization and oxidation to give the intermediary iminoquinone **9** (Scheme 1).

In the event, the starting *N*-carbobenzyloxy-L-tryptophan methyl ester (**2**) was converted to the racemic keto-alcohol **3** in a quantitative yield by hydride reduction and DDQ oxidation (Scheme 2 and Table 1). The selective introduction of a hydroxyl group onto the phenyl portion proceeded on oxidative reaction with $Tl(OCOCF_3)_3$ followed by treatment with $CuSO_4{\cdot}5H_2O$ to give the phenol **4**.[3,4] This was deoxygenated by $NaBH_3CN$ to give **5**,[5] which was oxidized by $NO(SO_3K)_2$ to the quinone **6** in high yield.

Regioselective reaction of **6** with benzylamine to afford **7**[6] was followed by hydrogenolysis to the diamino derivative **8**. This was cyclized concomitant with aromatization by heating in DMF with air to give the desired iminoquinone **9**, which was acetylated to **10**.[7]

The transformation of the quinone **10** to the diaminopyrroloquinoline **12** was examined under a variety of conditions, and realized by the introduction of an azido



Scheme 1.

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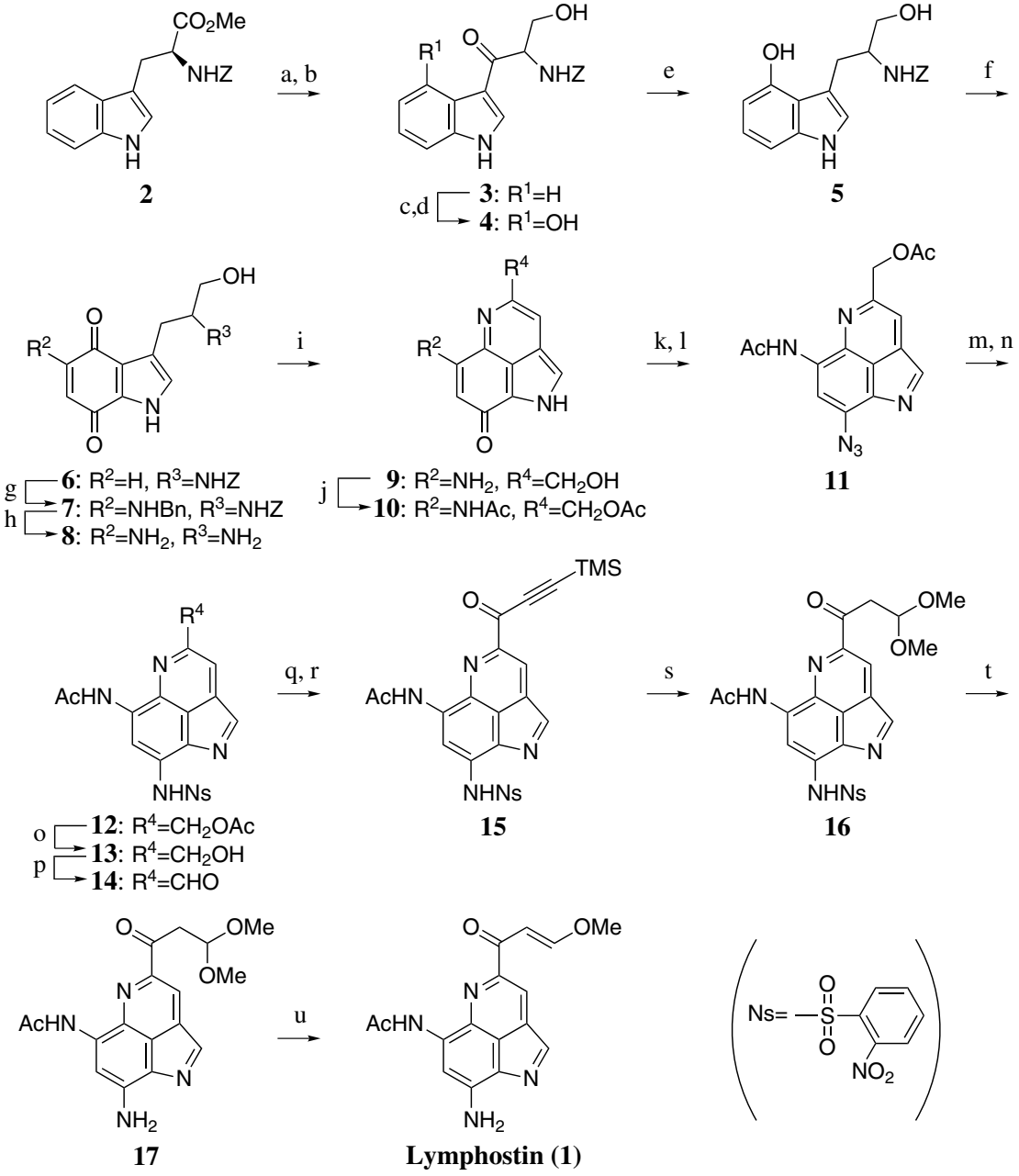

Scheme 2. Reagents and conditions: (a) $LiBH_4$/THF, rt, 1 h then reflux, 1 h; (b) DDQ/aq THF, rt, 1 h, 95% in two steps; (c) $Tl(OCOCF_3)_3$/TFA, rt, 1 h; (d) $CuSO_4 \cdot 5H_2O$/DMF, 130 °C, 10 min, 59% in two steps; (e) $NaBH_3CN$, $BF_3 \cdot Et_2O$/THF, rt, 4 h, 85%; (f) $NO(SO_3K)_2$/acetone-pH 7 phosphate buffer, rt, 2 h, 82%; (g) $BnNH_2$, air/PhH, rt, 4 h, 79%; (h) H_2, Pd–C/EtOH, rt, 2 h, quant.; (i) air/DMF, 70 °C, 1 h; (j) C_6F_5OAc/DMF, rt, 12 h, 66% in two steps; (k) Tf_2O, Py/CH_2Cl_2, −78 °C, 1 h; (l) *n*-Bu_4NN_3/CH_2Cl_2, −78 °C to rt, 12 h, 68% in two steps; (m) H_2, Lindlar cat./EtOH, rt, 2 h; (n) NsCl, Py/$ClCH_2CH_2Cl$, 50 °C, 1 h, 75% in two steps; (o) aq acetone, rt, 5 days, quant.; (p) PCC, Al_2O_3/AcOH/CH_2Cl_2, rt, 4 h, 80%; (q) trimethylsilylacetylene, *n*-BuLi/THF, −78 °C, 2 h; (r) MnO_2/acetone/CH_2Cl_2, rt, 12 h, 69% in two steps; (s) K_2CO_3/MeOH, rt, 5 h, 73%; (t) PhSH, K_2CO_3/DMF, rt, 12 h, 75%; (u) MS 4A/DMSO, 90 °C, 7 days, 64%.

group, and subsequent reduction. Treatment of **10** with Tf_2O followed by *n*-Bu_4NN_3 afforded the tautomerized azide **11**, which was reduced on the Lindlar catalyst and protected by an *o*-nitrobenzenesulfonyl (Ns) group[8] to afford **12**. De-O-acetylation of **12** to **13** was quantitatively carried out only with aqueous acetone. The alcohol **13** was oxidized to the aldehyde **14**, which was followed successively by reaction with trimethylsilylacetylene and oxidation with MnO_2 to give the ethynyl ketone **15**.[9] This was transformed to the dimethyl acetal **16** by alkaline methanol and de-N-protected by alkaline thiophenol to the amine **17**.

In the final stage, methanol was eliminated from **17**[10] to give lymphostin (**1**). This was identical in all respects with the natural product,[11] completing the total synthesis.

At the heart of the synthesis of lymphostin (**1**) described herein are six kinds of oxidative reactions, which were regioselectively accomplished.

Table 1. Physico-chemical properties of compounds

Compounds	Mp (°C)	^{1}H NMR (600 MHz; δ ppm; J Hz) ^{13}C NMR (150 MHz; δ ppm) MS (m/z) IR (KBr; cm^{-1})	Compounds	Mp (°C)	^{1}H NMR (600 MHz; δ ppm; J Hz) ^{13}C NMR (150 MHz; δ ppm) MS (m/z) IR (KBr; cm^{-1})
1	276–277 Crystals (*i*-PrOH)	^{1}H NMR (DMSO-d_6): δ 2.35 (3H, s), 3.95 (3H, s), 7.64 (1H, d, J = 12.5 Hz), 7.88 (1H, d, J = 12.5 Hz), 8.15 (1H, s), 8.23 (2H, br s), 8.38 (1H, s), 8.63 (1H, s), 10.16 (1H, br s) ^{13}C NMR (DMSO-d_6): δ 24.3, 58.4, 101.7, 110.6, 117.3, 124.3, 124.8, 133.5, 136.4, 139.5, 145.6, 147.5, 150.1, 163.8, 169.5, 188.5 FAB-MS: 311 [M+H]$^+$ IR (KBr): 3448, 1685, 1654, 1632, 1596, 1500, 1363, 1350, 1241, 1132, 1078	**11**	Wax	^{1}H NMR (MeOH-d_4): δ 2.15 (3H, s), 2.33 (3H, s), 5.47 (2H, s), 7.78 (1H, s), 8.03 (1H, s), 8.06 (1H, s) MALDI-TOF-MS: 325 [M+H]$^+$ IR (KBr): 3428, 2346, 1735, 1658, 1560, 1540, 1457, 1421, 1388, 1236, 1218, 1106, 1087
3	153 Needles (EtOAc)	^{1}H NMR (MeOH-d_4): δ 3.84 (1H, dd, J = 11.5 & 6.0 Hz), 3.96 (1H, dd, J = 11.5 & 5.0 Hz), 5.09 (1H, d, J = 13.0 Hz), 5.11 (1H, dd, J = 6.0 & 5.0 Hz), 5.12 (1H, d, J = 13.0 Hz), 7.21 (1H, ddd, J = 7.5, 7.5 & 1.0 Hz), 7.24 (1H, ddd, J = 7.5, 7.5 & 1.0 Hz), 7.27–7.38 (5H, m), 7.45 (1H, ddd, J = 7.5, 1.0 & 0.5 Hz), 8.25 (1H, ddd, J = 7.5, 1.0 & 0.5 Hz) FAB-MS: 339 [M+H]$^+$	**12**	218 (decomp.) Needles (MeOH)	^{1}H NMR (MeOH-d_4): δ 2.09 (3H, s), 2.28 (3H, s), 5.36 (2H, s), 7.80 (1H, ddd, J = 8.0, 8.0 & 1.0 Hz), 8.02 (1H, dd, J = 8.0 & 1.0 Hz), 8.05 (1H, dd, J = 8.0 & 1.0 Hz), 8.10 (1H, s), 8.11 (1H, ddd, J = 8.0, 8.0 & 1.0 Hz), 8.14 (1H, s), 8.26 (1H, s) FAB-MS: 484 [M+H]$^+$
4	196–197 Crystals (EtOAc)	^{1}H NMR (MeOH-d_4): δ 3.83 (1H, dd, J = 11.0 & 6.5 Hz), 3.95 (1H, dd, J = 11.0 & 6.5 Hz), 5.09 (1H, d, J = 14.0 Hz), 5.13 (1H, d, J = 14.0 Hz), 5.17 (1H, dd, J = 6.5 & 6.5 Hz), 6.55 (1H, d, J = 8.0 Hz), 6.91 (1H, d, J = 8.0 Hz), 7.12 (1H, dd, J = 8.0 & 8.0 Hz), 7.25–7.37 (5H, m), 8.31 (1H, s) FAB-MS: 355 [M+H]$^+$	**13**	225 (decomp.) Needles (EtOAc)	^{1}H NMR (DMSO-d_6): δ 2.16 (1H, br s), 2.20 (3H, s), 5.50 (2H, s), 7.88 (1H, ddd, J = 8.0, 8.0 & 1.0 Hz), 8.00 (1H, br s), 8.07 (1H, dd, J = 8.0 & 1.0 Hz), 8.08 (1H, s), 8.10 (1H, dd, J = 8.0 & 1.0 Hz), 8.11 (1H, s), 8.22 (1H, s), 8.23 (1H, ddd, J = 8.0, 8.0 & 1.0 Hz), 10.03 (1H, br s) MALDI-TOF-MS: 442 [M+H]$^+$
6	165 (decomp.) Prisms (acetone)	^{1}H NMR (MeOH-d_4): δ 2.81 (1H, dd, J = 14.5 & 10.0 Hz), 3.04 (1H, dd, J = 14.5 & 5.0 Hz), 3.56 (1H, dd, J = 11.0 & 5.0 Hz), 3.59 (1H, dd, J = 11.0 & 5.5 Hz), 3.92 (1H, dddd, J = 10.0, 5.5, 5.0 & 5.0 Hz), 4.92 (1H, d, J = 11.5 Hz), 5.03 (1H, d, J = 11.5 Hz), 6.50 (1H, d, J = 10.5 Hz), 6.53 (1H, d, J = 10.5 Hz), 6.96 (1H, s), 7.19–7.31 (5H, m) FAB-MS: 355 [M+H]$^+$	**14**	194–195 (decomp.) Amorphous	^{1}H NMR (MeOH-d_4): δ 2.18 (3H, s), 7.85 (1H, ddd, J = 8.0, 8.0 & 1.5 Hz), 7.90 (1H, dd, J = 7.5 & 1.5 Hz), 8.07 (1H, s), 8.09 (1H, s), 8.13 (1H, dd, J = 8.0 & 1.0 Hz), 8.16 (1H, ddd, J = 8.0, 7.5 & 1.0 Hz), 8.25 (1H, s), 10.03 (1H, s) FAB-MS: 440 [M+H]$^+$
7	>300 Crystals (MeOH)	^{1}H NMR (MeOH-d_4): δ 2.79 (1H, dd, J = 12.0 & 10.0 Hz), 3.01 (1H, dd, J = 12.0 & 6.0 Hz), 3.56 (1H, dd, J = 12.5 & 6.0 Hz), 3.57 (1H, dddd, J = 10.0, 6.0, 6.0 & 2.5 Hz), 3.60 (1H, dd, J = 12.5 & 2.5 Hz), 4.39 (2H, s), 4.93 (1H, d, J = 13.0 Hz), 5.04 (1H, d, J = 13.0 Hz), 5.08 (1H, s), 6.75 (1H, s), 7.16–7.32 (10H, m) FAB-MS: 460 [M+H]$^+$	**15**	244–246 (decomp.) Amorphous	^{1}H NMR (MeOH-d_4): δ 0.06 (9H, s), 2.23 (3H, s), 8.03 (1H, ddd, J = 8.0, 8.0 & 1.0 Hz), 8.06 (1H, s), 8.08 (1H, dd, J = 8.0 & 1.0 Hz), 8.12 (1H, dd, J = 8.0 & 1.0 Hz), 8.15 (1H, s), 8.17 (1H, ddd, J = 8.0, 8.0 & 1.0 Hz), 8.30 (1H, s) FAB-MS: 536 [M+H]$^+$
8	216–218 (decomp.) Crystals (MeOH)	^{1}H NMR (MeOH-d_4): δ 2.87 (1H, dd, J = 14.5 & 7.5 Hz), 2.96 (1H, dd, J = 14.5 & 7.0 Hz), 3.42 (1H, dddd, J = 7.5, 7.0, 6.5 & 4.0 Hz), 3.49 (1H, dd, J = 11.5 & 6.5 Hz), 3.68 (1H, dd, J = 11.5 & 4.0 Hz), 5.39 (1H, s), 6.83 (1H, s) ^{13}C NMR (MeOH-d_4): δ 28.2, 54.4, 63.6, 98.2, 120.2, 121.3, 123.9, 136.5, 154.1, 180.1, 180.4 FAB-MS: 236 [M+H]$^+$	**16**	>300 Amorphous	^{1}H NMR (MeOH-d_4): δ 2.21 (3H, s), 3.28 (6H, s), 3.72 (2H, d, J = 6.0 Hz), 4.93 (1H, t, J = 6.0 Hz), 7.98 (1H, ddd, J = 8.0, 7.5 & 1.0 Hz), 8.06 (1H, s), 8.12 (1H, dd, J = 8.0 & 1.0 Hz), 8.14 (1H, s), 8.15 (1H, dd, J = 8.0 & 1.0 Hz), 8.20 (1H, ddd, J = 8.0, 7.5 & 1.0 Hz) 8.29 (1H, s) FAB-MS: 528 [M+H]$^+$

Table 1 (*continued*)

Compounds	Mp (°C)	^{1}H NMR (600 MHz; δ ppm; J Hz) ^{13}C NMR (150 MHz; δ ppm) MS (m/z) IR (KBr; cm^{-1})	Compounds	Mp (°C)	^{1}H NMR (600 MHz; δ ppm; J Hz) ^{13}C NMR (150 MHz; δ ppm) MS (m/z) IR (KBr; cm^{-1})
10	182 (decomp.) Amorphous	^{1}H NMR (MeOH-d_4): δ 2.16 (3H, s), 2.33 (3H, s), 5.43 (2H, s), 7.71 (1H, s), 7.99 (1H, s), 8.02 (1H, s) ^{13}C NMR (DMSO-d_6): δ 21.1, 24.9, 67.3, 117.6, 118.1, 119.9, 120.0, 124.0, 125.0, 140.8, 142.3, 147.3, 170.4, 170.6, 173.6 MALDI-TOF-MS: 300 $[M+H]^+$ IR (KBr): 3442, 1739, 1685, 1592, 1508	**17**	288–290 (decomp.) Amorphous	^{1}H NMR (DMSO-d_6): δ 2.33 (3H, s), 3.32 (6H, s), 3.78 (2H, d, J = 5.5 Hz), 5.05 (1H, t, J = 5.5 Hz), 8.21 (1H, s), 8.30 (2H, br s), 8.52 (1H, s), 10.05 (1H, br s) FAB-MS: 343 $[M+H]^+$

It seems likely that the chemistry and insights developed for this total synthesis will find wider application.

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