DIVERGENT SYNTHESIS OF LAMELLARIN α 13-SULFATE, 20-SULFATE, and 13,20-DISULFATE

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Abstract – A divergent synthesis of three sulfate derivatives of lamellarin α, namely, lamellarin α 13-sulfate (2), 20-sulfate (1), and 13,20-disulfate (4) has been achieved via a common intermediate (6) in which 13-OH and 20-OH of the lamellarin core are differentially protected by MOM and benzyl groups, respectively. Compound (6) in turn was prepared using sequential Suzuki-Miyaura coupling of 3,4-dihydroxypyrrole bistriflate (7) as a key reaction.

Lamellarins and the related marine pyrrole alkaloids have attracted considerable attention due to their unique structures and highly useful biological activities.1 Lamellarin α 20-sulfate (1) was isolated from the unidentified ascidian collected from the Arabian Sea near Trivandrum, India, by Faulkner and co-workers.2 They demonstrated that 1 inhibits HIV-1 integrase selectively and growth of the HIV-1 virus in cell culture.2 Because cytotoxicity of 1 is quite low, this natural product has been regarded as a new type of lead compound for development of anti-HIV agents. An attempted synthesis of lamellarin α 20-sulfate (1) and 13-sulfate (2) from lamellarin α (3) by titration with DMF-SO3 complex was reported by Faulkner and coworkers in 2002.3 Unfortunately, however, they obtained only lamellarin 13,20-disulfate (4) in low yield. Recently, we reported the first total synthesis of lamellarin α 20-sulfate (1) from the differentially protected lamellarin α (5).4 The selective introduction of sulfate group at
20-OH was effected by a sequence involving selective debenzylation of 20-OBn, 2,2,2-trichloroethylsulfonation of the resulting 20-OH, deprotection of 13-Oi-Pr, and final reductive cleavage of the 2,2,2-trichloroethyl ester moiety.\(^5\)\(^6\) For the structure-activity relationship studies concerning integrase inhibition and anti-HIV activity, we needed to prepare lamellarin \(\alpha\) 13-sulfate (2) and 13,20-disulfate (4) also. It was revealed, however, the synthesis of 2 from 5 was difficult because debenzylation at 20-OBn occurred simultaneously during deprotection at 13-Oi-Pr under the standard BCl\(_3\) conditions. Thus, we designed a new lamellarin \(\alpha\) derivative (6) in which 13-OH was protected by a more labile methoxymethyl (MOM) group. In this communication, we report a divergent synthesis of lamellarin \(\alpha\) sulfate derivatives (1), (2), and (4) from the common intermediate (6) which in turn can be obtained from 3,4-dihydroxypyrrole bistriflate (7) and arylboronic acids (8), (9) using the previously established procedure developed in our laboratories (Scheme 1).\(^4\)\(^5\)

Scheme 1

The synthesis of arylboronic acid (8) is shown in Scheme 2. Isovanillin (10) was benzylated with benzyl bromide to give \(O\)-benzylisovanillin (11) in 86% yield.\(^7\) Baeyer-Villiger oxidation of 11 with \(m\)-chloroperbenzoic acid (\(m\)CPBA) followed by methanolysis afforded the phenol (12) in 90% yield. After MOM protection of the phenolic hydroxy group, the resulting 13 was regioselectively brominated by \(N\)-bromosuccinimide (NBS) to give 14 in 97% yield. Bromine–lithium exchange of 14 with \(\text{tert}\)-butyllithium followed by treatment with trimethyl borate afforded the desired arylboronic acid (8). Another arylboronic acid (9) was prepared according to the procedure shown in Scheme 3. C-2-

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\begin{align*}
\text{RO} & \quad \text{CHO} & \text{BnBr} (1.1 \text{ equiv}), K_2CO_3, \text{acetone, reflux, 4.5 h (86\%) } \\
10 \text{ (R=H)} & \quad 11 \text{ (R=Bn)} & \\
\text{(a)} & \quad \text{(b)} & \\
\text{MeO} & \quad \text{MeO} & \\
\text{MeO} & \quad \text{MeO} & \\
\text{MeO} & \quad \text{MeO} & \\
\text{MeO} & \quad \text{MeO} & \\
\text{MeO} & \quad \text{MeO} & \\
\text{MeO} & \quad \text{MeO} & \\
\end{align*}
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\begin{align*}
\text{Br} & \quad \text{OR} & \text{BnO} \quad \text{OMOM} \\
12 \text{ (R=H)} & \quad 13 \text{ (R=MOM)} & \\
\text{(c)} & \quad \text{(d)} & \\
\text{MeO} & \quad \text{MeO} & \\
\text{MeO} & \quad \text{MeO} & \\
\text{MeO} & \quad \text{MeO} & \\
\text{MeO} & \quad \text{MeO} & \\
\text{MeO} & \quad \text{MeO} & \\
\end{align*}
\]

\[
\begin{align*}
\text{Br} & \quad \text{OMOM} & \\
14 & \quad 8 & \\
\text{(e)} & \quad \text{(f)} & \\
\text{MeO} & \quad \text{MeO} & \\
\text{MeO} & \quad \text{MeO} & \\
\text{MeO} & \quad \text{MeO} & \\
\text{MeO} & \quad \text{MeO} & \\
\text{MeO} & \quad \text{MeO} & \\
\end{align*}
\]

Scheme 2. Reagents and conditions: (a) BnBr (1.1 equiv), K\(_2\)CO\(_3\), acetone, reflux, 4.5 h (86%); (b) (1) \(m\)CPBA (1.5 equiv), CH\(_2\)Cl\(_2\), 0 °C, 3 h, (2) K\(_2\)CO\(_3\), MeOH, rt, 1.5 h (90%); (c) MOM-Cl (1.5 equiv), \(i\)-Pr\(_2\)NEt, CH\(_2\)Cl\(_2\), 0 °C, 1 h then rt, 48 h (87%); (d) NBS (1.0 equiv), DMF, 0 °C, 1 h (97%); (e) (1) \(\text{tert}\)-BuLi (2.1 equiv), THF, –78 °C, 1 h, (2) B(OMe)\(_3\), 1.5 equiv, –78 °C, 1 h then rt, 1 h (99%).
selective bromine–lithium exchange of commercially available 2,4-dibromoanisole (15) followed by boration and oxidation gave the phenol (16) in 78% yield. After MOM protection of the phenolic hydroxy group, the resulting 17 was converted into the arylboronic acid (9) via bromine–lithium exchange with tert-butyllithium followed by treatment with trimethyl borate.

![Scheme 3. Reagents and conditions:](image)

The synthesis of lamellarin α 13-sulfate (3) was shown in Scheme 4. Suzuki-Miyaura coupling of the

![Scheme 4. Reagents and conditions:](image)
bistriflate (7) with 1.2 equiv of an arylboronic acid (8) under the standard conditions [Pd(PPh3)4 (2 mol%), Na2CO3, water, THF, reflux, 3 h]9 gave the mono-arylated pyrrole (18) in 74% yield. Compound (18) was converted into the lactone (19) by treatment with hydrochloric acid in methanol followed by acid-catalyzed lactonization in 93% yield. The second cross-coupling of 19 with an arylboronic acid (9) (2.0 equiv) using 8 mol% of Pd(PPh3)4 afforded 20 in 95% yield. Compound (20) was converted into the acid (21) by alkaline hydrolysis followed by acid-catalyzed relaxtonization in 61% yield. Decarboxylation of 21 in hot quinoline in the presence of copper(I) oxide produced 22.10 Intramolecular oxidative biaryl coupling of 22 under Kita’s conditions11 using phenylidene bis(trifluoracetate) (PIFA)-boron trifluoride etherate afforded the cyclized product (23) in 62% yield. Treatment of 23 with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in refluxing dichloromethane produced the common intermediate (6). Deprotection of the MOM group by treatment with hydrochloric acid in methanol afforded 24, which was reacted with 2,2,2-trichloroethyl chlorosulfate in dichloromethane to give the mixed sulfate (25) in 89% yield.6 Hydrogenolysis of 25 over palladium on charcoal for 4 h at room temperature afforded debenzylated 26 in 61% yield. Final reductive deprotection of the 2,2,2-trichloroethyl ester with Zn/HCO2NH4 followed by ion exchange over Amberlite IRC-50 (Na+ form) and Sephadex purification produced lamellarin α 13-sulfate (2)12 in 61% yield.

The syntheses of lamellarin α 20-sulfate (1) and lamellarin α 13,20-disulfate (4) are shown in Scheme 5. Compound (6) was debenzylated by hydrogenolysis over palladium on charcoal to give 27 in 99% yield. 2,2,2-Trichloroethylsulfonation of 27 in a similar manner as described above provided 28 in 69% yield. Selective removal of MOM protecting group provided 29 in 81% yield. Treatment of 29 with Zn/HCO2NH4 followed by ion exchange over Amberlite IRC-50 (Na+ form) and Sephadex purification produced lamellarin α 20-sulfate (1)13 in 85% yield. Deprotection of MOM group from 27 with

Scheme 5. Reagents and conditions: (a) H2, 10% Pd-C, EtOAc, rt, 2 h (99%); (b) CCl3CH2OSO2Cl (2.0 equiv), Et3N, DMAP, CH2Cl2, rt, 2.5 h (69%); (c) concd HCl, MeOH-CH2Cl2 (1:2), 45 °C, 5 h (29, 81%; 3, 99%); (d) (1) Zn powder (3.0 equiv), HCO2NH4 (6.0 equiv), THF-MeOH (1:1), rt, 4 h, (2) Amberlite IRC-50 (Na+ form), MeOH, (3) Sephadex LH-20, MeOH–CH2Cl2 (1:1) (85%); (e) (1) pyridine-SO3, DMF-pyridine (4:1), 65 °C, 2 h, (2) Amberlite IRC-50 (Na+ form), MeOH, (3) Sephadex LH-20, MeOH–CH2Cl2 (1:1) (69%).
hydrochloric acid in methanol produced lamellarin α (3) in 99% yield. Treatment of 3 with pyridine-SO₃ complex in DMF-pyridine followed by ion exchange over Amberlite IRC-50 (Na⁺ form) and Sephadex purification afforded lamellarin α 13,20-disulfate (4) in 69% yield. The spectroscopic data of 1 and 4 are identical with those previously reported.³,⁴

In conclusion, we have succeeded in a divergent synthesis of lamellarin α 20-sulfate (1), 13-sulfate (2), and 13,20-disulfate (4) using 6 as a common intermediate. The synthesis of the other lamellarin sulfate derivatives and their structure-activity relationship studies are in progress.

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REFERENCES AND NOTES
12. Lamellarin α 13-sulfate (2). Mp 265-280 °C (dec.) (sealed capillary); IR (KBr): 3422, 1684, 1432, 1267, 1049 cm⁻¹; ¹H NMR (400 MHz, 8 mg of 2 in 0.7 mL of DMSO-d₆): δ 3.31 (s, 3H), 3.37 (s, 3H), 3.85 (s, 3H), 3.87 (s, 3H), 6.39 (s, 1H), 6.46 (s, 1H), 7.07 (s, 1H), 7.16 (dd, J= 2.0 and 8.3 Hz, 1H), 7.19 (d, J= 7.3 Hz, 1H), 7.26 (d, J= 8.3 Hz, 1H), 7.36 (s, 1H), 7.71 (d, J= 2.0 Hz, 1H), 9.03 (d, J= 7.3 Hz, 1H); ¹³C NMR (100 MHz, 8 mg of 2 in 0.7 mL of DMSO-d₆): 54.4, 54.5, 55.5, 56.2, 103.2, 103.8, 104.9, 105.5, 107.9, 109.3, 111.4, 113.9, 118.2, 122.2, 123.3, 124.2, 126.0, 127.2, 130.9, 133.5, 143.8, 147.2, 148.4, 148.8, 149.7, 150.3, 154.9. HRFABMS m/z. Calcd for C₂₉H₂₂NNa₂O₁₁S [(M+Na)+]: 638.0709. Found: 638.0662.

13. Lamellarin α 20-sulfate (1). Mp 258-268 °C (dec.) (sealed capillary) [lit.⁴, mp 263-269 °C (dec.) (sealed capillary)]; IR (KBr): 3422, 1698, 1485, 1418, 1273, 1047 cm⁻¹; ¹H NMR (400 MHz, 17 mg of 1 in 0.7 mL of DMSO-d₆): δ 3.34 (s, 3H), 3.37 (s, 3H), 3.84 (s, 3H), 3.87 (s, 3H), 6.82 (s, 1H), 6.86 (dd, J= 1.9 and 8.2 Hz, 1H), 7.02 (d, J= 1.9 Hz, 1H), 7.16 (d, J= 8.2 Hz, 1H), 7.18 (s, 1H), 7.26 (d, J= 7.4 Hz, 1H), 7.34 (s, 1H), 7.57 (s, 1H), 9.02 (d, J= 7.4 Hz, 1H); ¹³C NMR (100 MHz, 17 mg of 1 in 0.7 mL of DMSO-d₆): δ 54.4, 55.0, 55.4, 55.9, 104.7, 105.8, 106.9, 108.0, 108.7, 111.4, 111.6, 112.8, 113.4, 118.2 (118.24), 120.7, 122.0, 124.2, 127.0, 127.9, 133.4, 143.2, 145.1, 146.6, 148.3, 148.8, 149.0, 149.8, 154.1. HRFABMS m/z. Calcd for C₂₉H₂₂NNa₂O₁₁S [(M+Na)+]: 638.0709. Found: 638.0750.

14. Lamellarin α 13,20-disulfate (4). Mp 205-210 °C (dec.) (sealed capillary) [lit.³, mp > 260 °C (chars)]; IR (KBr): 1699, 1486, 1419, 1272, 1050 cm⁻¹; ¹H NMR (400 MHz, DMSO-d₆): δ 3.37 (s, 3H), 3.39 (s, 3H), 3.86 (s, 3H), 3.88 (s, 3H), 6.73 (s, 1H), 7.12 (s, 1H), 7.21 (dd, J= 2.1 and 8.3 Hz, 1H), 7.29 (d, J= 8.3 Hz, 1H), 7.34 (d, J= 7.4 Hz, 1H), 7.42 (s, 1H), 7.58 (s, 1H), 7.75 (d, J= 2.1 Hz, 1H), 9.08 (d, J= 7.4 Hz, 1H); ¹³C NMR (100 MHz, DMSO-d₆): δ 54.5, 55.0, 55.6, 56.2, 104.8, 105.6, 107.0, 108.1, 108.6, 111.0, 111.5, 112.9, 114.0, 118.3, 122.0, 123.1, 124.2, 125.9, 126.3, 128.2, 133.6, 143.1, 143.9, 145.0, 146.7, 149.1, 150.0, 150.6, 154.2. HRFABMS m/z. Calcd for C₂₉H₂₁NNa₃O₁₄S₂ [(M+Na)+]: 740.0097. Found: 740.0145.