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

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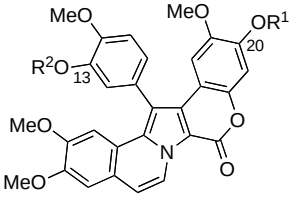
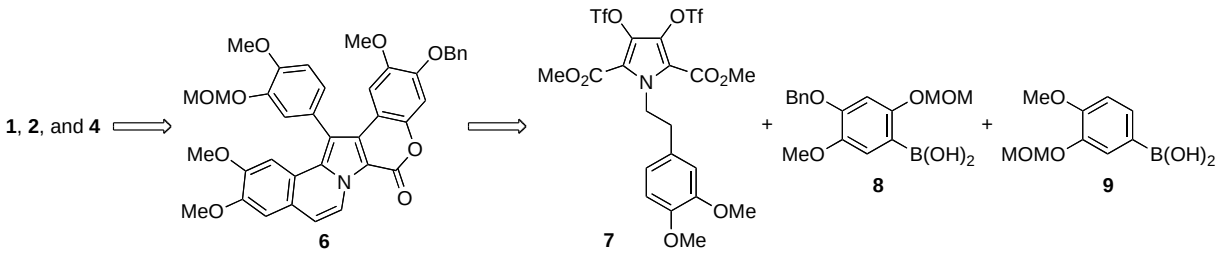
Abstract – A divergent synthesis of three sulfate derivatives of lamellarin α, namely, lamellarin α 13-sulfate (**2**), 20-sulfate (**1**), and 13,20-disulfate (**4**) has been achieved *via* a common intermediate (**6**) in which 13-OH and 20-OH of the lamellarin core are differentially protected by 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-SO_3 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



lamellarin α 20-sulfate (**1**) (R^1=SO_3Na, R^2=H)
lamellarin α 13-sulfate (**2**) (R^1=H, R^2=SO_3Na)
lamellarin α (**3**) (R^1=R^2=H)
lamellarin α 13,20-disulfate (**4**) (R^1=R^2=SO_3Na)
20*O*-benzyl-13*O*-isopropyllamellarin α (**5**) (R^1=Bn, R^2=*i*-Pr)

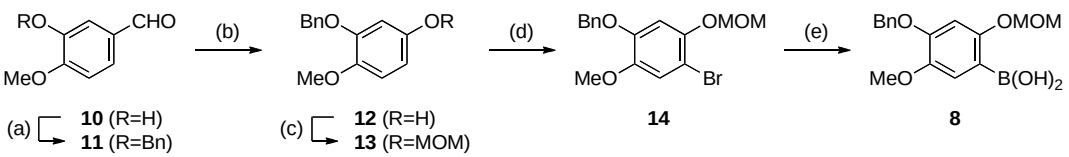
20-OH was effected by a sequence involving selective debenzylation of 20-OBn, 2,2,2-trichloroethylsulfonation of the resulting 20-OH, deprotection of 13-O*i*-Pr, and final reductive cleavage of the 2,2,2-trichloroethyl ester moiety.[5,6] For the structure-activity relationship studies concerning integrase inhibition and anti-HIV activity, we needed to prepare lamellarin α 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-O*i*-Pr under the standard BCl_3 conditions. Thus, we designed a new lamellarin α 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 α 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

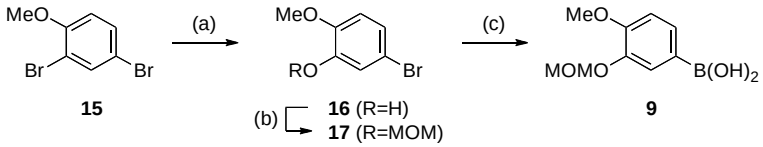
The synthesis of arylboronic acid (**8**) is shown in Scheme 2. Isovanillin (**10**) was benzylated with benzyl bromide to give *O*-benzylisovanillin (**11**) in 86% yield.[7] Baeyer-Villiger oxidation of **11** with *m*-chloroperbenzoic acid (*m*CPBA) followed by methanolysis afforded the phenol (**12**) 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 *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-



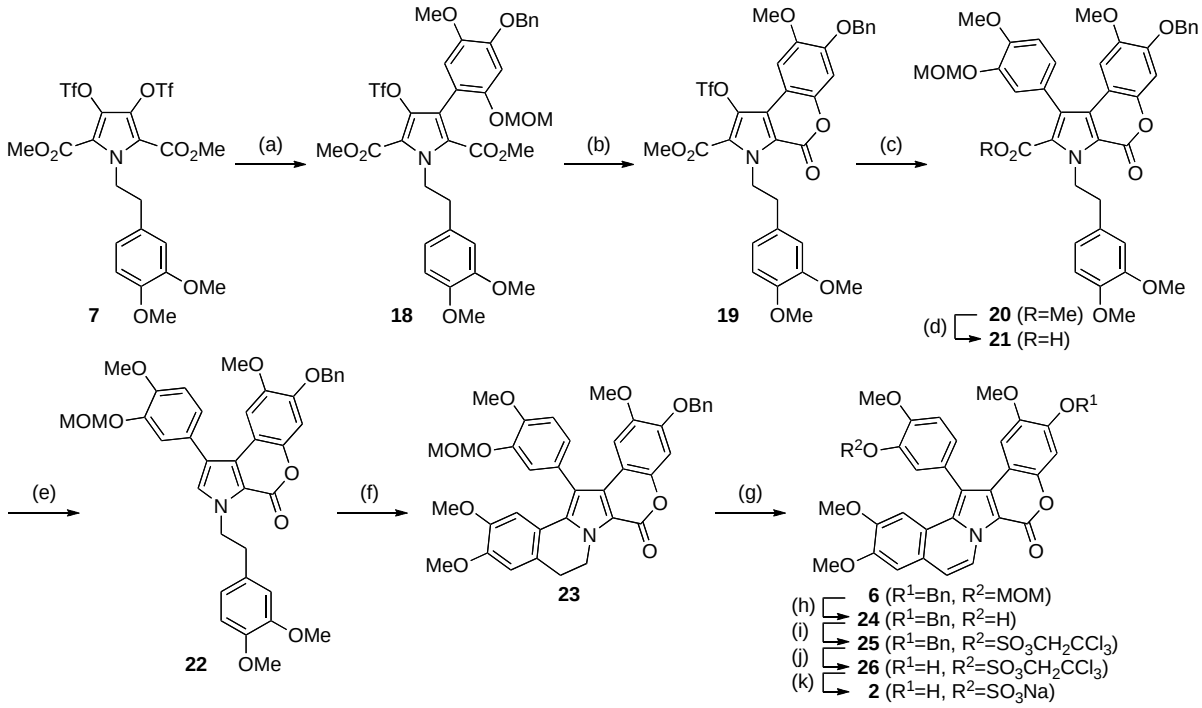
Scheme 2. *Reagents and conditions:* (a) BnBr (1.1 equiv), K_2CO_3, acetone, reflux, 4.5 h (86%); (b) (1) *m*CPBA (1.5 equiv), CH_2Cl_2, 0 °C, 3 h, (2) K_2CO_3, MeOH, rt, 1.5 h (90%); (c) MOM-Cl (1.5 equiv), *i*-Pr_2NEt, CH_2Cl_2, 0 °C, 1 h then rt, 48 h (87%); (d) NBS (1.0 equiv), DMF, 0 °C, 1 h (97%); (e) (1) *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.[8] 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:* (a) (1) *n*-BuLi (1.1 equiv), THF, –78 °C, 1 h, (2) $B(OMe)_3$ (1.5 equiv), –78 °C, 1 h then rt, 1 h, (3) AcOH, H_2O_2, rt, 16 h (78%); (b) MOM-Cl (1.5 equiv), K_2CO_3, acetone, 0 °C, 1 h then reflux, 19 h (96%); (c) (1) *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 (72%).

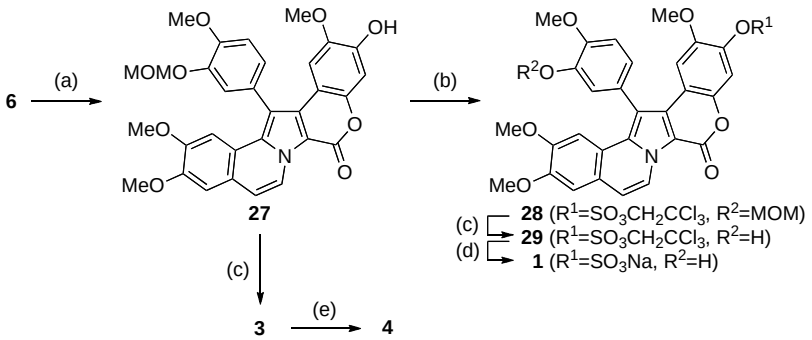
The synthesis of lamellarin α 13-sulfate (**3**) was shown in Scheme 4. Suzuki-Miyaura coupling of the



Scheme 4. *Reagents and conditions:* (a) **8** (1.2 equiv), $Pd(PPh_3)_4$ (2 mol%), Na_2CO_3, water, THF, reflux, 3 h (74%); (b) (1) concd HCl, MeOH, reflux, 1 h, (2) *p*-TsOH, CH_2Cl_2, reflux, 2 h (93%); (c) **9** (2.0 equiv), $Pd(PPh_3)_4$ (8 mol%), Na_2CO_3, water, THF, reflux, 8 h (95%); (d) (1) 40% aqueous KOH, EtOH, reflux, 2 h, (2) PPTS, CH_2Cl_2, reflux, 24 h (61%); (e) Cu_2O (1.0 equiv), quinoline, 220 °C, 10 min (83%); (f) PIFA (1.2 equiv), $BF_3{\cdot}OEt_2$, CH_2Cl_2, –40 °C, 1.5 h (62%); (g) DDQ (1.0 equiv), CH_2Cl_2, reflux, 30 h (87%); (h) concd HCl, MeOH-CH_2Cl_2 (1:2), 45 °C, 2 h (99%); (i) $CCl_3CH_2OSO_2Cl$ (2.0 equiv), Et_3N, DMAP, CH_2Cl_2, rt, 5 h (89%); (j) H_2, 10% Pd-C, EtOAc, rt, 4 h (61%); (k) (1) Zn powder (3.0 equiv), HCO_2NH_4 (6.0 equiv), THF-MeOH (1:1), rt, 2 h, (2) Amberlite IRC-50 (Na^+ form), MeOH, (3) Sephadex LH-20, MeOH–CH_2Cl_2 (1:1) (61%).

bistriflate (**7**) with 1.2 equiv of an arylboronic acid (**8**) under the standard conditions [$Pd(PPh_3)_4$ (2 mol%), Na_2CO_3, 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 $Pd(PPh_3)_4$ afforded **20** in 95% yield. Compound (**20**) was converted into the acid (**21**) by alkaline hydrolysis followed by acid-catalyzed relactonization 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 conditions[11] using phenyliodine bis(trifluoroacetate) (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/HCO_2NH_4 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/HCO_2NH_4 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) H_2, 10% Pd-C, EtOAc, rt, 2 h (99%); (b) $CCl_3CH_2OSO_2Cl$ (2.0 equiv), Et_3N, DMAP, CH_2Cl_2, rt, 2.5 h (69%); (c) concd HCl, MeOH-CH_2Cl_2 (1:2), 45 °C, 5 h (**29**, 81%; **3**, 99%); (d) (1) Zn powder (3.0 equiv), HCO_2NH_4 (6.0 equiv), THF-MeOH (1:1), rt, 4 h, (2) Amberlite IRC-50 (Na^+ form), MeOH, (3) Sephadex LH-20, MeOH–CH_2Cl_2 (1:1) (85%); (e) (1) pyridine-SO_3, DMF-pyridine (4:1), 65 °C, 2 h, (2) Amberlite IRC-50 (Na^+ form), MeOH, (3) Sephadex LH-20, MeOH–CH_2Cl_2 (1:1) (69%).

hydrochloric acid in methanol produced lamellarin α (**3**) in 99% yield. Treatment of **3** with pyridine-SO_3 complex in DMF-pyridine followed by ion exchange over Amberlite IRC-50 (Na^+ form) and Sephadex purification afforded lamellarin α 13,20-disulfate (**4**)[14] 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.

ACKNOWLEDGEMENTS

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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-d_6): 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); ^{13}C NMR (100 MHz, 8 mg of **2** in 0.7 mL of DMSO-d_6): δ 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 $C_{29}H_{22}NNa_2O_{11}S$ $[(M+Na)^+]$: 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-d_6): 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); ^{13}C NMR (100 MHz, 17 mg of **1** in 0.7 mL of DMSO-d_6): δ 54.4, 55.0, 55.5, 55.9, 104.7, 105.8, 106.9, 108.0, 108.7, 111.4, 111.5, 112.8, 113.4, 118.2 (118.16), 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 $C_{29}H_{22}NNa_2O_{11}S$ $[(M+Na)^+]$: 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-d_6): 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); ^{13}C NMR (100 MHz, DMSO-d_6): 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 $C_{29}H_{21}NNa_3O_{14}S_2$ $[(M+Na)^+]$: 740.0097. Found: 740.0145.