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Synthesis, modification, and evaluation of (*R*)-de-*O*-methyllasiodiplodin and analogs as nonsteroidal antagonists of mineralocorticoid receptor

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ABSTRACT

Macrolide (*R*)-de-*O*-methyllasiodiplodin (**1**), discovered to be a potent nonsteroidal antagonist of the mineralocorticoid receptor (MR), was synthesized via an efficient method and evaluated for MR antagonistic activity together with its analogs. Among all the tested compounds, compounds **18a**, 18b and **18c**, exhibited more potent antagonistic activity against MR with IC_{50} values ranging from 0.58 to 1.11 μM. Generally, it was obviously demonstrated that acetylation at phenolic hydroxyl groups and the ring size in analogs of **1** were very important for MR antagonist activity.

The mineralocorticoid receptor (MR), also called aldosterone receptor, is a member of the super family of nuclear receptor. MR is activated by steroids including aldosterone, cortisol and corticosterone.[1–4] MR activation results in sodium transport, increasing blood pressure, urinary protein excretion and potassium levels.[5] However, abnormal activation of MR by elevated level of aldosterone and salt imbalance cause hypertension and other effects detrimental to the cardiovascular system. Thus, MR antagonists are expected to be beneficial to patients with hypertension and other cardiovascular diseases, such as heart failure.[6]

Despite the great achievements in exploring MR ligand in 50 years, only two steroidal MR antagonists, spironolactone and eplerenone, have been brought to the market for the treatment of hypertension and heart failure. Results of randomized aldactone evaluation study (RALES) has demonstrated that spironolactone in standard therapy reduced risk of death by 30% and improved cardiac function of patients with severe heart failure.[7] Other results from Eplerenone Post Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) indicated that eplerenone, when added to optimal medical therapy, resulted in improved survival and reduced hospitalization among patients with acute myocardial infarction complicated by left ventricular dysfunction and heart failure.[8]

However, spironolactone lacks selectivity against other steroid nuclear homone receptors, primarily androgen receptor and progesterone receptor, and has undesirable side effect, such as gynecomastia in men and menstrual irregularity in women, that limited its long term use.[9] In contrast, eplerenone is more selective, but less potent than spironolactone in vitro.[10] Meanwhile, steroidal MR antagonists were developed slowly due to complexity in chemical synthesis, lacking of selectivity and unwanted side effects. In recent years novel classes of nonsteroidal MR antagonists have just begun to emerge.[6,11]

A great number of macrolide compounds with remarkable bioactivities have been isolated and synthesized to date.[12] The twelve-membered macrolides, (*R*)-de-*O*-methyllasiodiplodin (**1**) and (*R*)-lasiodiplodin (**1a**) (see Fig. 1), which were isolated from plants[13] as well as from fungus,[14] exhibit efficient inhibition of prostaglandin biosynthesis,[13c,15,16] antimicrobial activities[14b] and significant antitumor activities.[16] Recently, **1** was reported to be a potent inhibitor of pancreatic lipase (PL), an enzyme playing a key role in the efficient digestion of triglycerides and being a target for treating obesity,[17] with an IC_{50} value of 4.73 μM.[18]

In our screening program to search for nonsteroidal MR antagonist, **1** was found to exhibit potent antagonistic effect against MR with an IC_{50} value of 8.93 μM (unpublished data). The compound **1** is the first macrolide compound found to behave as MR antagonist to date, different from the other nonsteroidal MR antagonists.[6,11]

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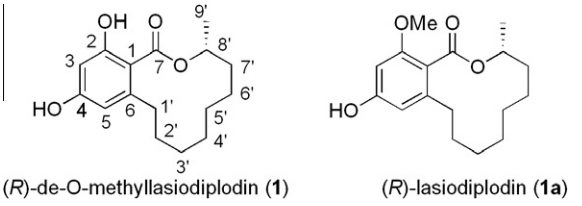


Figure 1. Structures of (*R*)-de-*O*-methyllasioplodin (**1**) and (*R*)-lasiodiplodin (**1a**).

The MR antagonistic activity of **1** sparked our great interest in its further investigation and optimization, but the low amount of the available sample from natural sources is a bottle-neck for additional structural derivatization/modification and structure–activity relationship (SAR) studies.

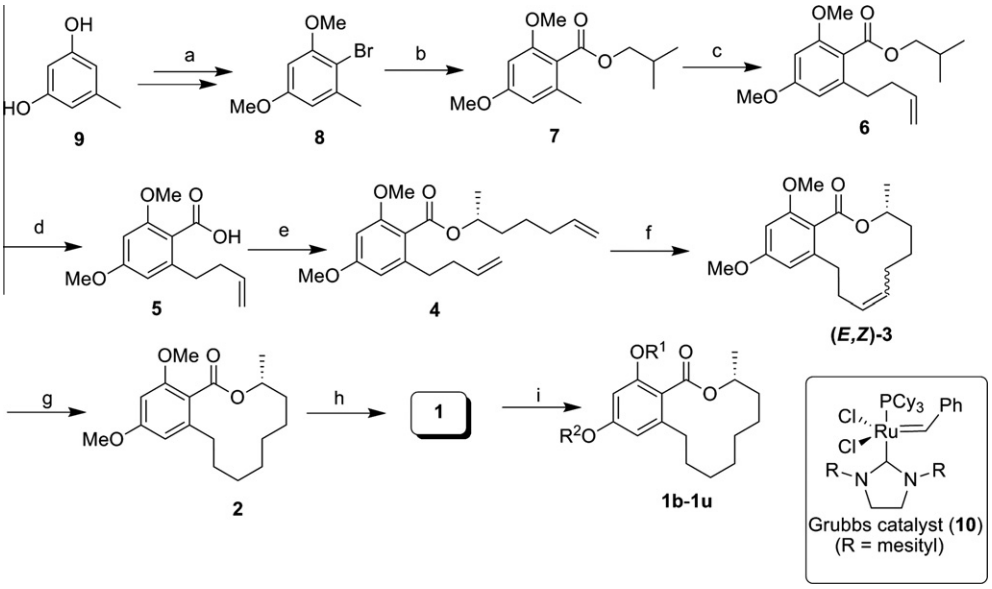
The first asymmetric total synthesis of **1**, a precursor in the synthesis of **1a**, was published in 1990 with 18 steps in 0.8% overall yield[19] but the synthetic route was too complicated and low yielding. Especially, the yield of the last demethylation step was only 17%. In 1996, a shorter route, using the Ring-closing-metathesis (RCM) reaction as the key step, was reported by Alois Fürstner and Kindler.[20] However, the carboxylation step via a Kolbe–Schmitt reaction under CO_2 (40 atm) and 120 °C for 12 h can not be considered a routine procedure for an average synthetic laboratory. Herein we report a more facile and efficient route for the preparation of **1** with higher yield and simple synthetic steps.

Scheme 1 shows the synthetic route for the preparation of macrolide **1**. Compound **8** was prepared from the commercially available orcinol monohydrate (**9**) in two steps with 99% overall yield by following procedures described in the literature.[21] The lithiation of the bromo derivative **8** by *n*-BuLi in dry THF at −78 °C followed by treatment with isobutyl chloroformate gave the required ester **7** in 89% yield,[21] which was converted to **6** in 90% yield with 3-chloropropene in dry THF at −78 °C catalyzed by LDA.[22] Saponification of **6** with KOH in refluxing EtOH (90%) for 12 h afforded the carboxylic acid **5** in 98% yield. Esterification of **5** with (*S*)-hept-6-en-2-ol obtained in a Grignard reaction,[23] afforded (*R*)-**4** in 85% yield under Mitsunobu conditions,[24] then **4** was converted to **3**, a mixture of geometrical isomers [(*E*):(*Z*) = 1.5:1], in 80% yield by the classical RCM reaction catalyzed by the second generation Grubbs catalyst (**10**, 3 mol %) in refluxing CH_2Cl_2 for 1 h.[20] A subsequent catalytic hydrogenation of the double bond provided (*R*)-**2** in 94% yield in EtOH at room temperature overnight. Then **2** was treated with BBr_3 in dry CH_2Cl_2 at 0 °C for 15 min and quenched with H_2O under reduced pressure to afford the target compound **1**,[25] the physical and spectral data of which were in agreement with the literature data.[13,19] By performing the quenching under reduced pressure, the yield of the last step was increased to 57%, a remarkable increase from the 17% yield of the literature procedure.[19]

In order to discover initial information about SAR of **1** and find more potent MR antagonists than **1**, 20 derivatives (**1b–1u**) of **1** were synthesized (see Scheme 1 and Table 1). Compound **1b** was prepared from **1** by reacting with CH_2N_2/Et_2O in methanol at room temperature.[26] Treatment of **1** (1 equiv) with ethyl iodide or bromoalkane (1.5 equiv) catalyzed by potassium carbonate in acetone provided **1c–1l**,[27] with anhydride (2.5 equiv) catalyzed by triethylamine in dichloromethane provided **1n–1q**, and with acyl chloride catalyzed by triethylamine in dichloromethane at room temperature provided **1r–1u**, respectively.[28] Compound **1m** was obtained by treating **1** epichlorohydrin (2.5 equiv) catalyzed by potassium carbonate in refluxing acetone.[29]

To evaluate the antagonistic activity of these derivatives against MR, yeast two-hybrid assay was preformed according to our previously published papers.[30,31] The pGADT7-hSRC-1(aa.613-773) and pGBKT7-rMR-LBD (aa.725-981) were constructed and transformed into AH109 yeast cells. To assess the reliability of the yeast two-hybrid system, we firstly determined the activity of corticosterone in stimulating MR_LBD/SRC1 interaction with EC_{50} of 33 nM. Then the activities of the derivatives were determined using the same assay.

The results are shown in Table 1. Only four compounds were found to have MR antagonistic effect besides **1**, and compound **1n** was the most potent antagonist with an IC_{50} value of 2.78 μM. Among compounds **2–4**, only *Z*-**3** was active against



Scheme 1. Reagents and conditions: (a) reaction conditions of the two steps are specified in Ref.[9], 99% over two steps; (b) *n*-BuLi, isobutyl chloroformate, dry THF, −78 to 0 °C, 3 h, 89%; (c) LDA, 3-chloropropene, dry THF, −78 to 0 °C, 3 h, 90%; (d) KOH, 90% EtOH, reflux, 12 h, then 10% HCl, 98%; (e) EtOOC–N=N–COOEt, PPh_3, (*S*)-hept-6-en-2-ol, THF, rt, 1.5 h, 85%; (f) **10** (3 mol %), CH_2Cl_2, reflux, 1 h, 80%; (g) H_2 (1 atm), 10% Pd/C, EtOH, rt, overnight, 94%; (h) BBr_3, dry CH_2Cl_2, 0 °C, 15 min, 57%; (i) CH_2N_2/Et_2O, MeOH, rt, overnight for **1b**, 73%; EtI, K_2CO_3, acetone, rt, overnight for **1c**, 45% and **1d**, 46%; bromoalkane, K_2CO_3, acetone, reflux, 2.5 h for **1e–1i**, 23–48%, and rt, overnight for **1j–1l**, 33–86%; epichlorohydrin, K_2CO_3, acetone, reflux, 4 h for **1m**, 46%; anhydride or acyl chloride, Et_3N, CH_2Cl_2, rt, overnight for **1n–1u**, 66–93%.

Table 1
Inhibitory activity of **1** and its analogs presented as IC_{50} (μM)

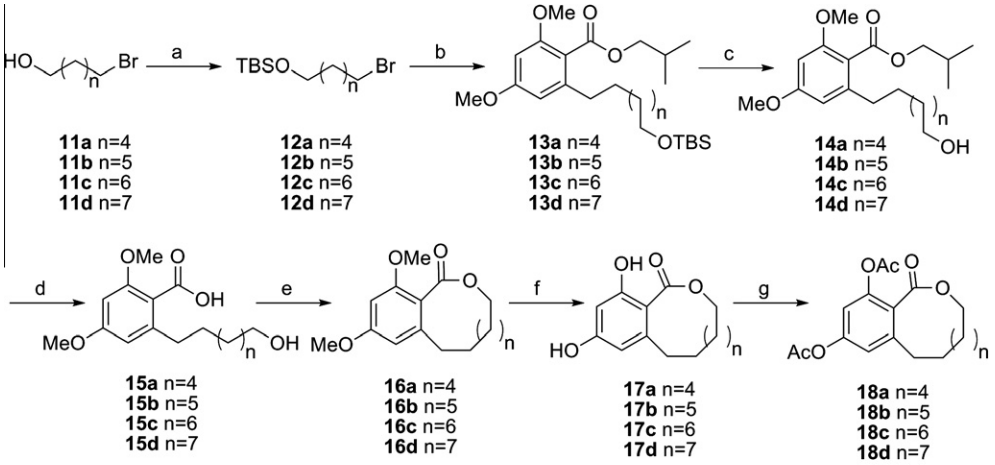
Compounds	R^1	R^2		Compounds	R^1	R^2	
4	Me	Me	–[a]	**1i**	CH_2=$CHCH_2$	CH_2=$CHCH_2$	–
E-3	Me	Me	–	**1j**	H	Bn	–
Z-3	Me	Me	16.55	**1k**	Bn	Bn	–
2	Me	Me	–	**1l**	*p*-NO_2-Bn	*p*-NO_2-Bn	–
1a	Me	H	–	**1m**	H	CH_2OCHCH_2	–
1	H	H	8.93	**1n**	Ac	Ac	2.78
1b	H	Me	–	**1o**	EtCO	EtCO	31.72
1c	H	Et	–	**1p**	*n*-ProCO	*n*-ProCO	–
1d	Et	Et	–	**1q**	*i*-ProCO	*i*-ProCO	–
1e	*n*-Bu	*n*-Bu	–	**1i**	Bz	Bz	–
1f	H	Pr	–	**1s**	*p*-Br-Bz	*p*-Br-Bz	–
1g	Pr	Pr	–	**1t**	*p*-Cl-Bz	*p*-Cl-Bz	–
1h	H	CH_2=$CHCH_2$	–	**1u**	*p*-Ts	*p*-Ts	6.51

[a] Inactive.

MR, indicating that to some extent the configuration of lactonic ring had an impact on the antagonistic activity against MR. By comparison with compounds **1a**, **1**, **1b**, and **2**, it was found that not only dimethylates but also monomethylates led to inhibitory effect loss, and only compound **1** without methylate was active with an IC_{50} value of 8.93 μM. The reason was speculated that maybe methylate of phenolic hydroxyl group decreased its hydrophilicity and affinity to MR consequently, and the similar results were obtained from **1c–1m** without inhibitory activity against MR. Intriguingly, compound **1n**, diacetylate of compound **1**, exhibited a more potent antagonistic effect against MR than **1,** with an IC_{50} value of 2.78 μM. So it was decided to continue acetylation of **1** with the purpose of finding more potent derivatives. However, the activity of derivatives from **1o** to **1t** decreased or lost with increase in the amount of carbon atoms or steric hindrance of substituent groups. It is interesting to note that although *p*-toluene sulfonyl group causes large steric effect, **1u** had potent antagonistic effect against MR with an IC_{50} value of 6.51 μM. Possible explanation is that the sulphur or oxygen atoms in substituent groups are helpful to increase affinity to MR.

Base on this information in hand and in order to investigate the impact of different ring size of the lactone on the MR inhibitory effect, another synthesis program was initiated to further explore this series by preserving diacetylate moiety and introducing different ring size of the lactone without chiral methyl moiety. The synthetic route is shown in Scheme 2. The compounds **11** were reacted with *tert*-butyldimethylsily (TBS) chloride in CH_2Cl_2 to result in the protected derivatives **12** in 90–96% yield,[32] which were converted to **13** with **7** in dry THF at −78 °C catalyzed by LDA.[22] The compounds **14** were obtained from **13** by TBS-deprotection of hydroxyl groups using concentrated HCl at room temperature in acetone[33] in 60–70% overall yield for two steps. Saponification of **14** with KOH in refluxing EtOH (90%) for 12 h afforded the carboxylic acid **15** in 74–81% yield, which were converted to **16** in 52–62% yield under Mitsunobu conditions.[24] Then **16** were treated with BBr_3 in dry dichloromethane at 0 °C for 15 min and quenched with H_2O under reduced pressure to afford **17** in 35–44% yield. Treatment of **17** with acetic anhydride catalyzed by triethylamine at room temperature in CH_2Cl_2 provided **18** in 80–88% yield.[28]

The activity results of **17** and **18** are shown in Table 2. Except for **17**, all compounds **18** were active against MR. Clearly, diacetylation can increase antagonistic effect against MR. It was speculated that the permeability change caused by the acetyl group leads to increase the antagonistic activity of **1n** and **18**. The compounds **18a**, **18b** and **18b** were more potent active than **1n**, indicating that the chiral methyl moiety was unnecessary for the MR antagonistic effect. The removal of methyl moiety can promote antagonistic activity against MR, most probably because of decreasing steric



Scheme 2

Scheme 2. Reagents and conditions: (a) TBSCl, DMAP, Et_3N, CH_2Cl_2, rt, 5 h, 90–96%; (b) LDA, **7**, dry THF, −78 to 0 °C, 3 h; (c) concd HCl, acetone, rt, 10 min, 60–70% for two steps b and c; (d) KOH, 90% EtOH, reflux, 12 h, then 10% HCl, 74–81%; (e) EtOOC–N=N–COOEt, PPh_3, THF, rt, 1.5 h, 52–62%; (f) BBr_3, dry CH_2Cl_2, 0 °C, 15 min, 35–44%; (g) Ac_2O, Et_3N, dry CH_2Cl_2, rt, overnight, 80–88%.

Table 2
Inhibitory activity of **17** and **18**

Compounds	*n*	IC_{50} (μM)
17a	4	—[a]
18a	4	0.58
17b	5	—
18b	5	1.11
17c	6	—
18c	6	0.82
17d	7	—
18d	7	2.90

[a] Inactive.

Table 3
Inhibitory activity of **1n** and **18** against GR, ERα and PR

Compounds	IC_{50} (μM)		
	GR	ERα	PR
1n	—[a]	8.36	—
18a	—	—	—
18b	—	—	—
18c	—	—	3.06
18d	—	>10	3.22

[a] Inactive.

hindrance to some extent. It is important to point out that all compounds **18** lacking the chiral methyl moiety were more potent than **1**, which provided a very simple but efficient way to design macrolide MR antagonist. In addition, the ring size of the lactone is significant for antagonistic effect against MR. For instance, the activity of **18a**-**18c** were better than **18d**, and especially the compound **18a**, bearing 11-membered lactonic ring, had the best antagonistic effect against MR with an IC_{50} value of 0.58 μM, 14.4- and 3.8-fold increase in inhibitory effect compared with **1** and **1n**, respectively.

In order to test the antagonistic activity of compounds **1n** and **18** against other panel of related steroid nuclear hormone receptors including glucocorticoid receptor (GR), estrogen receptor (ERα) and progestogen receptor (PR), mammalian one-hybrid assay was performed according to our previous methods.[34,35] The plasmids including UAS-TK-Luc, pRL-SV40 and pGAL4-nuclear receptor (GR, ERα or PR)-LBD were transiently co-transfected into HEK293T cells. Relative activities were measured using Dual-Luciferase Assay System kit (Promega). The results are shown in Table 3. From the data shown below, compounds **1n** and **18d** exhibited antagonistic activity against ERα, **18c** and **18d** exhibited antagonism against PR, but **18a** and **18b** had no effects on PR and ERα, and none of them had effects on GR.

In summary, (*R*)-de-*O*-methyllasiodiplodin (**1**) was synthesized via an efficient route with nine steps in 28.3% overall yield, and evaluated for MR antagonist activity together with its analogs. Some more potent MR antagonists were found, such as **18a**, **18b** and **18**c with IC_{50} values ranging from 0.58 to 1.11 μM, providing a novel MR antagonist chemtype. Initial evaluation of antagonistic activity against MR indicated that the acetylation at phenolic hydroxyl groups in analogs of **1** can increase the antagonistic effect against MR and the ring size of the lactone was also very crucial for its activity. The further study on SAR about this new class of MR antagonists is ongoing.

Acknowledgments

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A. Supplementary data

Supplementary data (Experimental details and ^1H and ^{13}C NMR spectra of compounds) associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2010.12.101.

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25. Experimental section and spectral data for (*R*)-de-O-methyllasioplodin (**1**): To a stirred solution of **2** (1.00 g, 3.26 mmol) in anhydrous dichloromethane under nitrogen, BBr_3 (25 mmol, 2.41 mL) was added at 0 °C and stirred for 15 min at the same temperature. To the resulting mixture, then H_2O (15 mL) was added and it was evacuated for 5 min. The residue was extracted with CH_2Cl_2 (3 × 30 mL). The organic layer was dried with $MgSO_4$ and concentrated. The residue was subjected to chromatography with petroleum ether/acetone (3:1) to give the desired products **1** as a white solid (0.52 g, 57%). $[\alpha]_D^{20}$ +29.2 (*c* 0.25, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 1.36 (3H, d, *J* = 6.2 Hz), 1.40–1.99 (12H, m), 2.50 (1H, m, benzylic H), 3.28 (1H, td, *J* = 3.7, 11.4 Hz benzylic H), 5.17 (1H, m, HCOCO), 6.22 (1H, d, *J* = 2.6 Hz,), 6.27 (1H, d, *J* = 2.6 Hz), 11.98 (1H, s, 2-OH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.1 (CH_3), 21.1 (CH_2), 24.1 (CH_2), 24.6 (CH_2), 27.2 (CH_2), 30.7 (CH_2), 31.0

(CH_2), 33.5 (CH_2), 75.1 (CH), 101.3 (CH), 105.5 (C), 110.7 (CH), 149.4 (C), 160.1 (C), 165.3 (C), 171.9 (C). ESI-MS: *m/z* 279.1 $[M+H]^+$, 301.1 $[M+Na]^+$.

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