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The Asymmetric Total Synthesis of (+)-Salvianolic acid A

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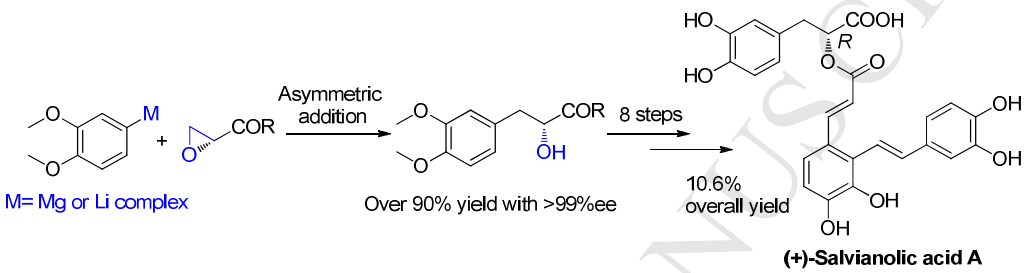
Abstract: An asymmetric synthesis of (+)-salvianolic acid A with cardioprotective properties, has been accomplished in a convergent manner in eight steps and 10.6% overall yield. This synthesis features an asymmetric addition of organometallics to optically pure 2,3-epoxypropionate in the presence of $BF_3 \cdot Et_2O$, Ru(III)-catalyzed directed C−H olefination, and I_2-catalyzed isomerization reaction.

Keywords: Asymmetric addition; Aryl metal reagents; Phenyl-D-lactic acid; C–H activation; Salvianolic acid A



Introduction

(+)-Salvianolic acid A (Sal-A, **1**), the water-soluble phenolic acids firstly isolated from the root of Chinese herb Danshen (*Salvia miltiorrhiza*) in 1984 by Lian-niang Li and co-workers,[1] has recently attracted considerable interest due to its reported significant activities, such as antioxidant effect,[2] cardioprotective effect,[3] antiplatelet and antithrombotic effect,[4] suppressing lipopolysaccharide-induced NF-κB signaling pathway,[5] as well as inhibiting tumor migration and invasion by inactivating transgelin 2.[6] However, the follow-up development of Sal-A was limited by its low contents in *Salvia miltiorrhiza* for a long time (<0.05% content in the roots of Danshen). Therefore, since the early 1990s, numerous efforts in the fields of chemistry have been undertaken in an effort to solve the resource of Sal-A (Fig. 1).

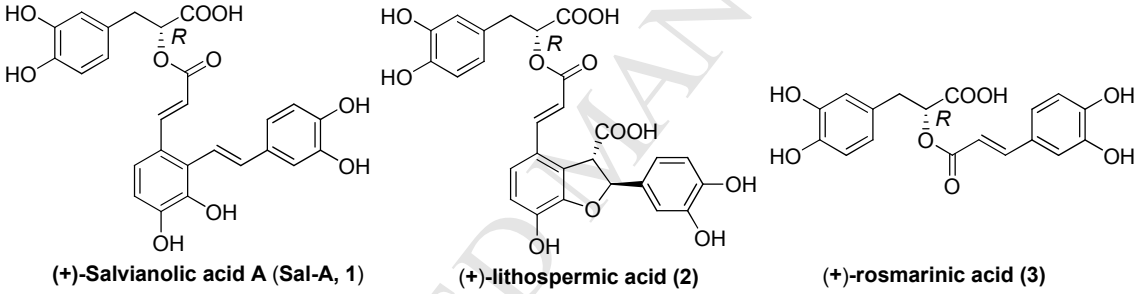


Fig. 1 Structures of known salvianolic acid compounds

In 1999, Zhou and co-workers studied the water soluble chemical constituents of *Salvia miltiorrhiza*, and found that Sal-A could be generated from (+)-lithospermic acid (**2**) by taking off one molecule of CO_2 as well as furan ring opening.[7] As a consequence, many kinds of methods for the semi-synthesis of Sal-A were developed through degrading the water extract of *Salvia miltiorrhiza* in the presence of different Lewis acid under high temperature.[8] Additionally, in 2014, Chen and co-workers reported the total synthesis of Sal-A using an uneconomically methyl-protected rosmarinic acid as the key chiral sources.[9] Obviously, the formally asymmetric total synthesis of Sal-A has not been reported up to now. So, as part of our interest to explore the cardioprotective properties of Sal-A, we plan to devise an effective route that is amenable to the preparation of structural variants. Herein, we wish to report our

method for the asymmetric synthesis of (+)-salvianolic acid A.

Our retrosynthetic analysis of (+)-salvianolic acid A (**1**) is outlined in Figure 2. Strategic disconnection of C9-C10 resulted in (+)-*β*-(3,4-dimethoxyphenyl) lactic acid **2** and tetramethyl salvianolic acid F **3**, which could be easily achieved in the presence of esterification agents. As for the optically pure phenyl-D-lactic acid **2**, we planned to prepare via metal-participated asymmetric reaction of aryl metal reagents **4** with the optically pure 2,3-epoxypropionate **5** or **5'**, which could be obtained from commercially available L-serine.[10] Additionally, salvianolic acid F **3** could be readily made through Wittig reaction of ylide reagent from corresponding benzyl bromide with formyl-substituted caffeic acid **6**, while the acrylic acid group of **6** could be achieved by Rh (III)-catalyzed directed C-H olefination using an aldehyde directing group.[11]

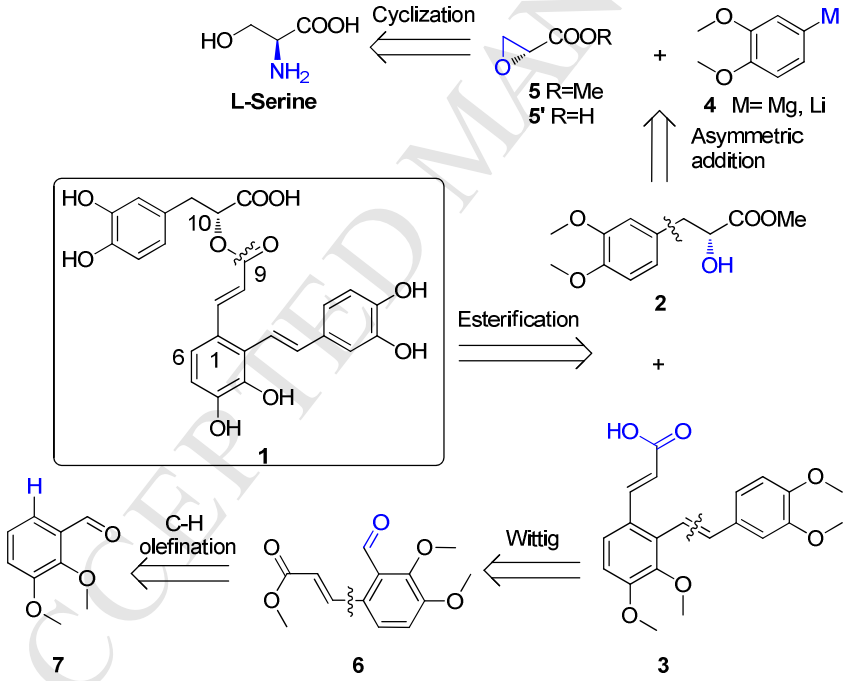


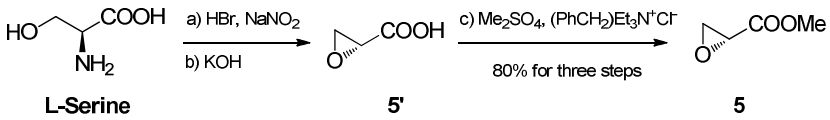
Fig. 2 Retrosynthesis of (+)-salvianolic acid A

Results and Discussion

Following the above-mentioned synthetic plan, we began our experimental efforts to prepare the optically pure 2,3-epoxypropionate intermediate **5** and/or **5'** (Scheme 1). The reaction of L-serine with nitrous acid (a mixture $NaNO_2$-HBr)

afforded the (−)-2-bromo-3-hydroxypropionic acid, which in turn was subsequently cyclized with KOH in EtOH at 0 °C to give (+)-2,3-epoxy propionic acid **5'**,[10] followed by methyl esterification with Me_2SO_4 in the presence of $(PhCH_2)Et_3N^+Cl^-$ to produce the (*R*)-chirality in intermediate **5** with 80% yield via a three-step sequence.

Scheme 1. Synthesis of *R*-(+)-2,3-epoxypropionate intermediate **5** and **5'**[a]



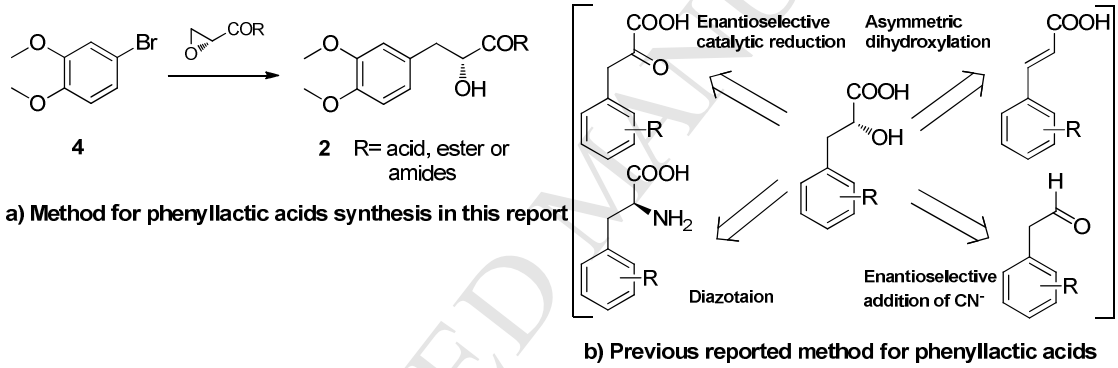
[a] Reagents and conditions: (a) 48% HBr (2 equiv.), $NaNO_2$(1.2 equiv), KBr (3 equiv.), H_2O, -10 °C, 3 h; then warmed to 0 °C, 12 h, N_2. (b) KOH (2 equiv.), EtOH, -15 °C, 2 h; then warmed to 0 °C, 16 h. (c) Me_2SO_4 (3 equiv.), $(PhCH_2)Et_3N^+Cl^-$ (1 equiv.), CH_2Cl_2, rt, 24 h; 80% yield for three steps.

With the optically pure 2,3-epoxypropionate **5** and **5'** in hand, we were ready to test the key step of stereoselective addition reaction with organic metal reagents (Table 1). Initially, we used aryl magnesium reagent to react with the (*R*)-chirality intermediate **5'** under -40 °C for the synthesis of (+)-*β*-(3,4-dimethoxyphenyl) lactate **2'**, but which was obtained only in 68% yield with 78% ee (Table 1, entry 1). Considering that the reaction of organocuprates nucleopilic reagents with 2-substituted epoxy propionate could show a preference for C3 attack with high enantioselectivity,[12] we then tried to use the aryl magnesocuprate and/or aryl lithium cuprate of compound **4** to react with the (*R*)-chirality intermediate **5'**, and the desired product **2'** was obtained smoothly in 63-75% yields with >99% ee (Table 1, entries 2-3). More interestingly, when a catalytic amount of $BF_3 \cdot Et_2O$ was added into the aryl lithium cuprate reaction system (1.5 equivalents), phenyl lactate **2'** was easily achieved in 82% yield with >99% ee under -78 °C for 30 min (Table 1, entry 4). Beside, phenyl lactate **2'** could also be achieved in 87% yield with >99% ee under -15 °C for 30 min when used $BF_3 \cdot Et_2O$ and aryl magnesolithium reaction system (Table 1, entry 5).[13] The reaction needed 1.5 equivalents of organic metallic reagents due to the existed free carboxylic acid moiety could consme some amount of organic metallic reagents, while the $BF_3 \cdot Et_2O$ could increase the reactivity of epoxy group and result

in increasing yields.

Having established the optimized reaction conditions, we also briefly investigated the scope of the reaction, and pleased to find that the optically pure epoxypropionate and epoxypropionamides could easily react with aryl magnesolithium in the presence of $BF_3 \cdot Et_2O$ and append the desired products in 95-96% yields with 99% ee (Table 1, entries 6-8). Among them, the Danshensu-ecysteine analog conjugate with cardiovascular-protective effect, could be smoothly synthesized with high stereoselectivity (Table 1, entry 8).[14] Obviously, this method, which showed advantages of good functional group tolerance, high stereoselectivity and yields, could be an alternative protocol for the synthesis of phenyllactic acids (Table 1, 1b).[15]

Table 1. Synthesis of (+)-*β*-(3,4-dimethoxyphenyl) lactate analogues



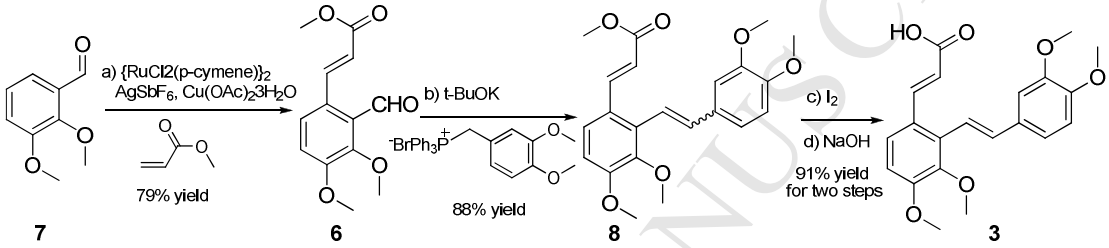
Entry	metallic reagents	Additive (20 mol%)	R	T (^oC)	yield (%)	ee (%)
1[a]	Mg	-	OH	-40 ^oC	68	78
2[a]	Mg, CuBr	-	OH	-40 ^oC	63	>99
3[a]	*n*-BuLi, CuBr	-	OH	-78 ^oC	70	>99
4[a]	*n*-BuLi, CuBr	$BF_3 \cdot Et_2O$	OH	-78 ^oC	82	>99
5[a]	*i*PrMgCl, LiCl	$BF_3 \cdot Et_2O$	OH	-15 ^oC	87	>99
6[b]	*i*PrMgCl, LiCl	$BF_3 \cdot Et_2O$	OMe	-15 ^oC	95	>99
7[b]	*i*PrMgCl, LiCl	$BF_3 \cdot Et_2O$	HN COOMe	-15 ^oC	96	>99
8[b]	*i*PrMgCl, LiCl	$BF_3 \cdot Et_2O$	S COOMe NHBoc	-15 ^oC	95	>99

[a] Using 1.5 equiv of organic metal reagents. [b] Using 1.05 equiv of organic metal reagents.

Next, we turned our attention to prepare the tetramethyl salvianolic acid F **3**. Reacting 2,3-dimethoxyl aromatic aldehyde **7** with methyl acrylate in the presence of a catalytic amount of $[\{RuCl_2(p\text{-cymene})\}_2]$, $AgSbF_6$, and $Cu(OAc)_2 \cdot 3H_2O$ under an

open atmosphere for 16 h afforded the intermediate **6** in 79% yield. Then, **6** was reacted with veratryl triphenylphosphine halide salt under the Wittig olefination reaction conditions to afford the cis-trans isomerization coexisted intermediate **8** in 88% yield (*Z*/*E* = 25:1). Then, **8** was subjected to an isomerization reaction using catalytic amount of iodine at room temperature for 24 h (*Z*/*E* = 1:50),[16] and subsequently hydrolyzed by an NaOH aqueous solution for 12 h to produce the key intermediate **3** in 91% yield.

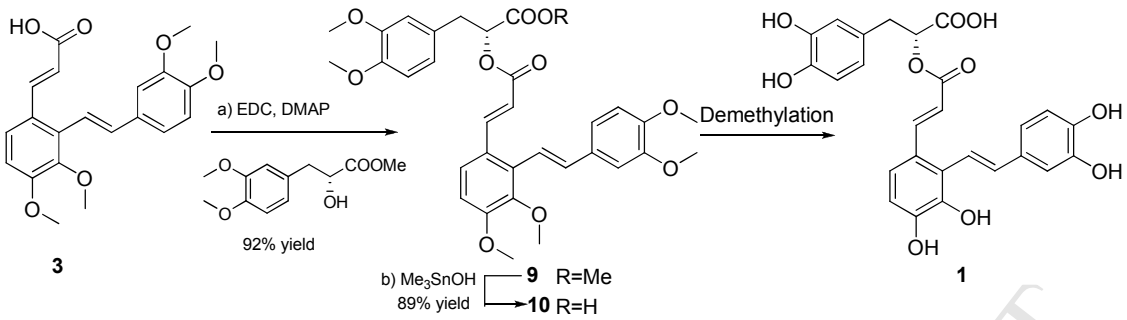
Scheme 2. Synthesis of tetramethyl salvianolic acid F **3**[a]



[a] Reagents and conditions: (a) Methyl acrylate (1.5 equiv.), [{$RuCl_2$(*p*-cymene)}$_2$] (3 mol %), $AgSbF_6$ (20 mol %), and $Cu(OAc)_2 \cdot 3H_2O$ (50 mol %), DCE, 100 ^oC, 16 h, 79%. (b) Veratryl phosphonium salt (1.1 equiv.), *t*-BuOK (1.2 equiv.), THF, 0-5°C; 30 min, 80 °C, 30 min; 80 °C → rt. (c) I_2 (5 mol %), DCM, rt, 20 h. (d) NaOH (2 equiv.) THF-H_2O (4:1), rt, 6 h; 91% yield for two steps.

These results encouraged us to perform the ester condensation and the two-step demethylation procedures that would complete the synthesis of (+)-salvianolic acid A (Scheme 3). By treating methyl lactate **2** with acrylic acid **3** in the presence of EDC and DMAP at room temperature for overnight, methyl ester of hexamethyl salvianolic acid A **9** was obtained in 92% yield. Conversion of methyl ester **9** to hexamethyl salvianolic acid A **10** reached 89% yield in the presence of Me_3SnOH reagent.[17] However, the subsequent demethylation of compound **10** using BBr_3 only gave trace amount of the desired product (+)-salvianolic acid A **1** (Table 2, entry 1).[9]

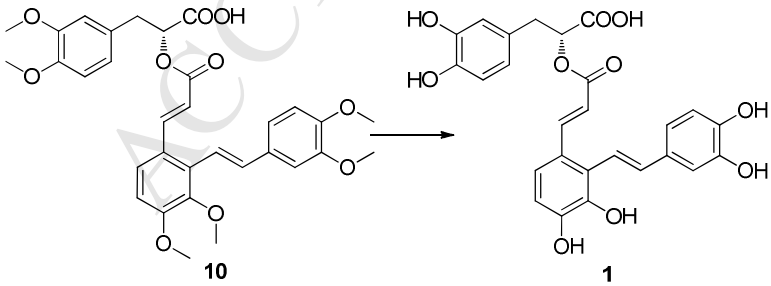
Scheme 3. Synthesis of (+)-salvianolic acid A **1**[a]



[a] Reagents and conditions: (a) Methyl lactate **2** (1.1 equiv.), EDC-HCl (2 equiv.), DMAP (2 equiv.), CH_2Cl_2, 0 to 23 ^oC, o/n, 92%. (b) Me_3SnOH (3 equiv.), DCE, 80 ^oC, 24 h, 89%.

To complete this final reaction, a series of demethylation conditions were further studied, and it was found that TMSI-quinoline complex gave decomposition products (Table 2, entry 3),[18] while iodotrimethylsilane (TMSI) afforded trace amount of the desired product **1** (Table 2, entry 2). Besides, it is worth noting that the desired product **1** and it's demethyl analogues were precipitated when the reactions were performed in DCM using BBr_3 and/or TMSI as demethylation reagents (Table 2, entries 1-2). In consideration of the insolubility of **1** in DCM, and the excess of BBr_3 might be sensitive to the ester group that caused the ester bond degradation of **1**, we tried to carry out the demethylation reaction in DCM/Et_2O (4:1) for three times at 0 and -78 ^oC using BBr_3 as demethylation reagent (Table 2, entries 5-6),[19] and finally obtained the desired product (+)-salvianolic acid A **1** in 8% and 27% yields separately.

Table 2. Completion of the Synthesis of (+)-salvianolic acid A **1**



entry	reagent[a]	T (^oC)	yield (%)
1	BBr_3, DCM	0	trace
2	TMSI, DCM	0	trace
3	TMSI, quinoline	100	decomposition
4[b,c]	BBr_3, DCM/Et_2O	0	8
5[b,c]	BBr_3, DCM/Et_2O	-78 to 0	27

[a] Reagent (6 equiv.). [b] Reaction for three times (BBr_3, 2 equiv.). [c] The ratio of DCM/Et_2O is 4:1.

Conclusions

In summary, an efficient, asymmetric synthesis of (+)-salvianolic acid A was

accomplished in 8 steps and 10.6% overall yield starting from 4-bromo-1,2-dimethoxybenzene **4** and (*R*)-methyl oxirane-2-carboxylate **5**. In which, the asymmetric addition of optically pure 2,3-epoxypropionate with aryl metal reagents and $BF_3 \cdot Et_2O$ could provide the enantiomerically pure phenyllactic acids in high yields. Due to this efficient synthesis, the preparation of (+)-salvianolic acid A analogues for cardioprotection is also in progress.

Experimental Section

The experimental procedures, product characterization data, and ^{1}H and ^{13}C NMR spectra were fully supplied in supporting information.

Acknowledgments

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