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# Convergent synthesis of S-8921, a new potent hypocholesterolemic arylnaphthalene lignan analog

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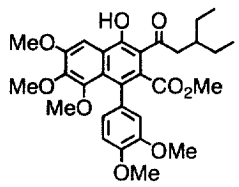
**Abstract**

We established a convergent synthesis of S-8921 (**1**), a unique hypocholesterolemic lignan analog, in 9 steps, including concise preparations of phthalide **7** and acylpropenoate **10**, and their regio- and stereocontrolled tandem anionic reactions leading to precursor **11** as a key step. 

*Keywords:* coupling reactions, condensations, Fridel-Crafts reactions, lignans, Michael reactions, regiocontrol

Hypocholesterolemic agents can help prevent atherosclerosis, which can result from long-lasting high levels of serum cholesterol. Atherosclerosis is a serious risk factor of coronary heart disease.

We have been trying to develop an efficient hypocholesterolemic agent, and our biologists found that S-8921 (**1**), an arylnaphtalene lignan analog, displays remarkable hypocholesterolemic activity (58% reduction of serum cholesterol at 1 mg/kg p.o. in cholesterol and bile acid loaded rats) [1] through strong inhibition of intestinal bile acid reabsorption via the ileal $Na^+$/bile acid cotransporter [2].




S-8921 (**1**)

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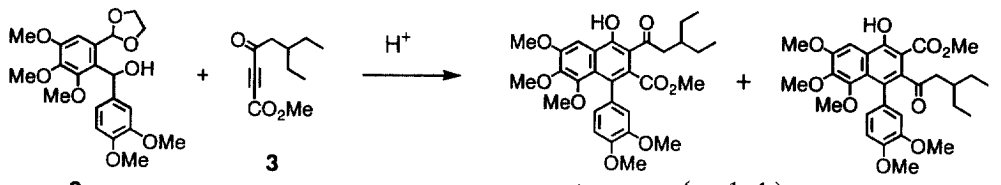
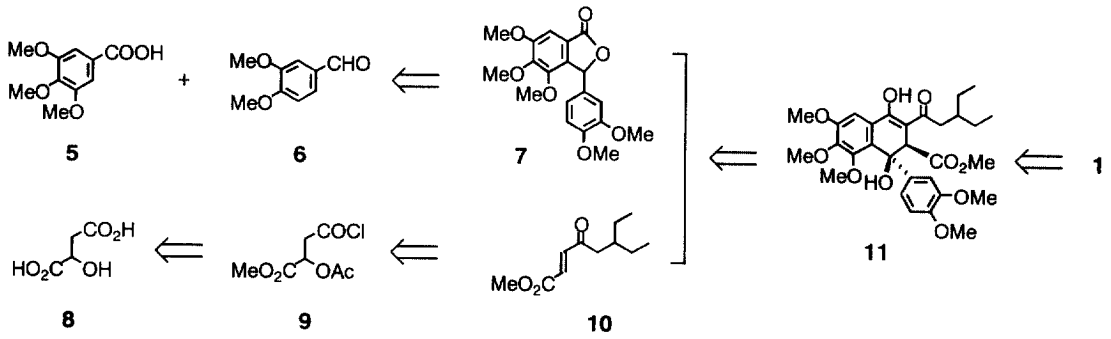
These findings made S-8921 an attractive candidate for a novel cholesterol-lowering drug, overcoming disadvantages of already marketed bile acid sequestrants, such as requiring large-quantity administration and nonspecifically capturing anionic nutrients. In this paper we report the convergent synthesis of a new potent hypocholesterolemic agent, S-8921 (**1**).

For the first synthesis of S-8921 (**1**)[3], we employed conventional Diels-Alder reaction and tried the reaction between isobenzofuran equivalent **2** and acylpropiolate **3** under acidic condition [4] as shown in Scheme 1. However, it was nonselective as anticipated, giving a mixture of **1** and its regioisomer **4** in nearly equal amounts, and therefore we decided to develop a more efficient synthetic procedure.




Scheme 1

Our synthetic plan, shown in Scheme 2, involved concise preparations of phthalide **7** and acylpropenoate **10**, and their regio- and stereocontrolled coupling leading to key intermediate **11**.

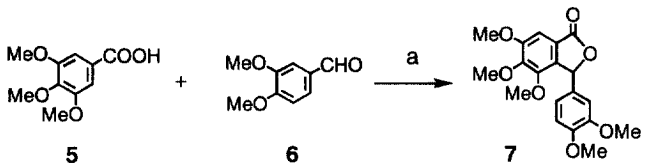



Scheme 2

We envisioned that the latter coupling process could be favorably performed by consecutive anionic reactions, namely, Michael addition and Claisen reaction. As for the two building blocks, we supposed that the phthalide **7** could be obtained in a single-step operation by Friedel-Crafts type reaction utilizing trimethoxybenzoic acid **5** and dimethoxybezaldehyde **6**, while alkylation of acylchloride **9** derived from (±)-malic acid (**8**) and subsequent removal of acetic acid were expected to conveniently afford the acylpropenoate **10** .

Synthesis of phthalide 7 (Scheme 3)

As we anticipated that the reactivity of trimethoxybenzoic acid **5** toward dimethoxybezaldehyde **6** might be low because of the presence of the electron-withdrawing carboxy group, we concentrated on seeking acids which could effectively activate counterpart **6**. The best choice was PPA, with the other acids working scarcely or only poorly. Thus we allowed **5** and **6** to react in the presence of PPA to yield **7** in 46% after single crystallization.

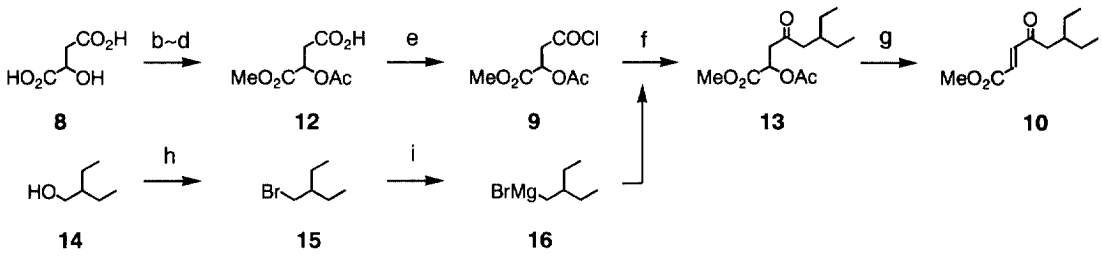



**Reagents and Conditions:** a) PPA, PhCl, 80 °C, 46%

Scheme 3

Synthesis of acylpropenoate **10** (Scheme 4)

(±)-Malic acid (**8**) was converted into the *O*-acetylated monomethylester **12** in 72% yield in one pot by a sequence of reactions involving *O*-acetylation, dehydration and methanolysis, which was then chlorinated by a conventional method to yield acid chloride **9**. The key reaction, namely, the alkylation of **9** was performed by $Li_2CuCl_4$ [5] catalyzed cross-coupling reaction using 2-ethylbutylmagnesium bromide **16**, obtained from the corresponding alcohol **14**, to preferentially afford the desired ketone **13**. No further alkylation of the ketonic group in **13** was observed under the conditions used. Lastly, treatment of **13** with triethylamine in toluene afforded acylpropenoate **10**, which was easily isolated as crystalline material by cooling the reaction mixture. The overall yield of **10** based on **12** was 55%.

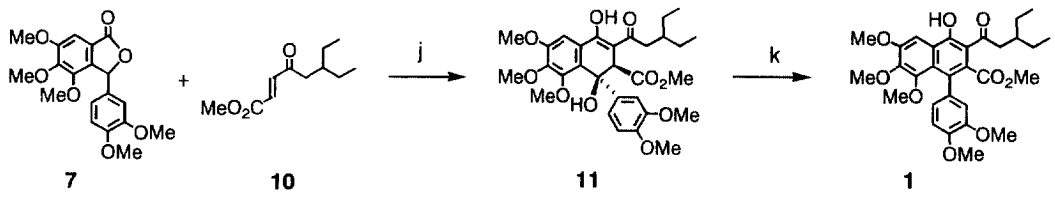



**Reagents and Conditions:** **b)** $Ac_2O$, 80° C; **c)** AcCl, 40° C; **d)** MeOH, 72% for b,c,d; **e)** $SOCl_2$, DMF(cat.); **f)** $Li_2CuCl_4$ (0.05 eq.), **16**, THF, -15° C; **g)** $Et_3N$, PhMe, then crystallization at -50° C, 55% for e,f,g; **h)** $PBr_3$, 77%; **i)** Mg, THF

Scheme 4

Synthesis of S-8921 (1) (Scheme 5)

With both building blocks, namely phthalide **7** and acylpropenoate **10** in hand, we embarked on their coupling under basic condition [6], the most crucial part in our synthesis. We soon realized the reaction was highly dependent on the base and the solvent being employed. Screening revealed that a combination of $LiN(TMS)_2$ and THF-DMF was the best choice, producing the key intermediate **11** in a highly regio- and stereoselective manner (**11**:other regio- and stereoisomers = >10:1). Simple crystallization of the reaction mixture obtained under the above condition afforded pure **11** in 68% yield. Finally, dehydration of **11** was very smoothly effected by treatment with MsOH to furnish crystalline S-8921 (**1**) in 91% yield.




7 10 11 1

**Reagents and Conditions: j)** **7**, $LiN(TMS)_2$ ( 2.0 eq.), THF, DMF -78 °C, then **10**, -78 °C→0 °C, 68%; **k)** MsOH, $CH_3CN$ 91%

Scheme 5

In conclusion, we accomplished the highly convergent synthesis of S-8921 (**1**), which consists of only nine steps and was satisfactorily applied to its preparation in more than ten-kilogram scale.

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