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SYSNTHESIS OF 3-*O*-ACYLATED EPICATECHIN DERIVATIVES *VIA* SEQUENTIAL ONE-POT MULTI-STEP REACTIONS

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Abstract – An effective approach for the synthesis of epicatechin derivatives based on sequential one-pot multi-step reactions is described. Reductive etherification of the disulfanyl derivative was promoted with a catalytic amount of TfOH, providing the cis-substituted benzopyran derivative in a stereoselective manner.

Epigallocatechin gallate (EGCG **1**) is a member of the catechin family composed of *cis*-2-aryl-3-hydroxybenzopyran and exhibits various biological activities, including antitumor activity and proteasome, uPA, and several tyrosine kinase inhibitory activities (Scheme 1).[1] The 2,3 *cis*-stereochemistry is an important factor for most of the biological activities. Recently Kan and co-workers have reported that the dehydroxyl derivative **2** exhibited improved anti-influenza virus activity in comparison with EGCG.[2] Therefore, the epicatechin skeleton would be an effective template for developing new drug candidates and biochemical probes. However, most of the established chemical approaches for the synthesis of the epicatechin derivatives are based on indirected methods involving epimerization of the C3 hydroxyl group on the catechin skeleton with 2,3 *trans*-stereochemistry.[2,3] We have recently developed an effective direct method for the synthesis of epicatechin 3-acylates gallate via

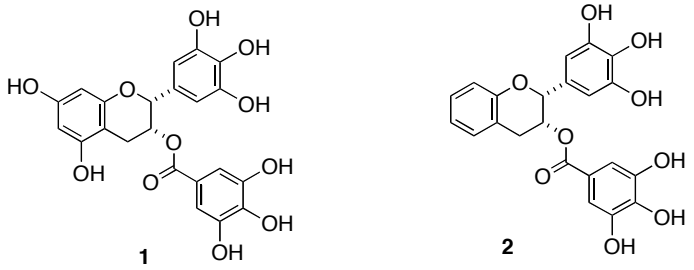
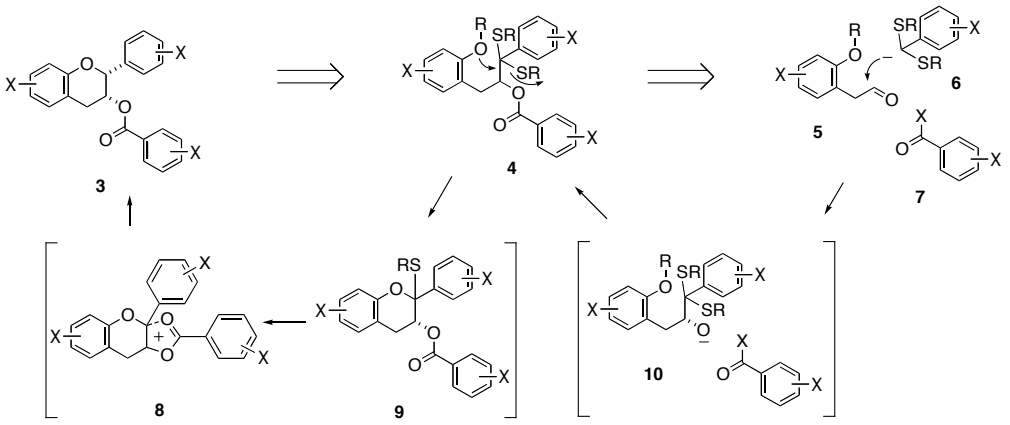


Figure 1 Structures of epigallocatechin gallate (**1**) and its derivative **2**

reductive cyclization of β-acyloxyl ketone[4] and reported on the application to the solid-phase synthesis of epigallocatechin gallate derivatives[5]. In this paper, we describe an efficient direct solution-phase approach for the synthesis of epicatechin derivatives based on sequential one-pot reactions.

Our strategy for the synthesis of the epicatechin derivative **3** based on sequential one-pot multi-step reactions involves (1) coupling of aldehyde **5**, dithioacetal **6** and acid chloride **7** and (2) reductive cyclization of the acyclic precursor **4** to epicatechin derivative **3**. The coupling of three building blocks can be achieved by 1,2 addition of dithioacetal **6** with aldehyde **5**, followed by acylation of resulting alkoxide **10** with acid chloride **7** in one-pot. The dithioacetal acyclic precursor **4** would undergo reductive etherification via *S*, *O*-acetal **9** to provide the epicatechin derivative **3**. The neighboring group participation of the acyloxyl group in **8** allows the direct synthesis of epicatechin derivative **3** from **4**. The three-component coupling strategy would be effective and suitable for the combinatorial synthesis of epicatechin libraries with the variable substitutions in all three aromatic rings.

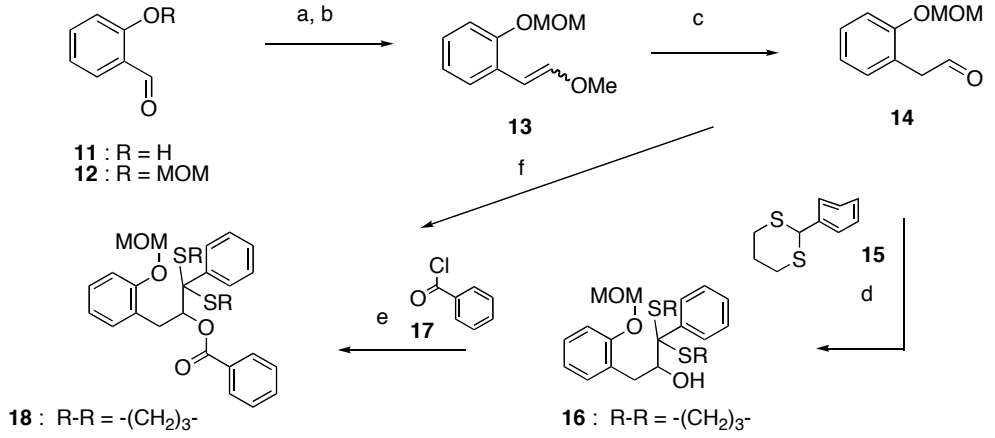


Scheme 1 Strategy for the synthesis of epicatechin 3-acylate **3.**

The synthesis of the acyclic precursor is shown in Scheme 2. Treatment of salicylaldehyde **11** with methoxymethyl chloride under the basic conditions provided the *O*-protected salicylaldehyde **12** in a quantitative yield. Wittig reaction of aldehyde with methoxymethyl triphenylphosphonium chloride under the basic conditions gave the methylvinyl ether **13** in 88% yield. Treatment of the methylvinyl ether **13** with 1 M HCl in AcOEt solution resulted in chemoselecitve hydrolysis of the vinylether **13** to provide aldehyde **14** in 81% yield.

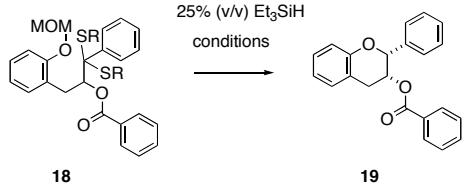
The stepwise synthesis of the acyclic precursor **18** from three building blocks **14**, **15** and **17** was conducted. Treatment of 2-phenyl-1,3-dithiane (**15**) with butyl lithium at -78 ºC for 0.5 h, followed by addition of aldehyde **14** provided alcohol **16** in 80% yield. The resulting alcohol **16** was treated with the acid chloride **17** in the presence of DMAP for 2 days at room temperature to provide the acyclic precursor **18** in 96% yield. Next one-pot synthesis of **18** was examined. The coupling of aldehyde **14** and dithiane **15** was achieved by the same protocol. Subsequently, benzoyl chloride **17** and DMAP were added to the

reaction mixture to afford the acyclic precursor **18** in 64% yield based on **14**. The one-pot yield was comparable to total yield in the stepwise synthesis.



Scheme 2 Reagents and conditions: (a) MOMCl, DIEA, DCM, quant. (b) Ph_3PCH_2OMeCl, tBuLi, THF, 0 °C, 88%. (c) 1 M HCl in AcOEt, 81%. (d) 15, nBuLi, 80%. (e) 17, DMAP, DCM, 2 days, 96%. (f) 15, nBuLi, then 17, DMAP, THF, 3 h, 64%.

The reductive cyclization of thioacetal **18** to the epicatechin derivative **19** was conducted. Table in Scheme 3 shows reaction conditions and analytical results of the crude materials by HPLC-MS based on UV absorption. We first used trifluoroacetic acid (TFA) as a promoter, which was effective for reductive cyclization of the corresponding ketone derivative.[4] However, TFA was not suitable for the activation of dithioacetal **18**. After the optimization of the reactions, we found that exposure of thioacetal **18** to 1% TfOH in dichloromethane in the presence of 25% triethylsilane at 0 °C promoted the deprotection of the MOM group and subsequent reductive etherification to provide *cis*-chroman **19** in 68% yield and with excellent selectivity (Entry 11). The relative stereochemistry was determined by ^{1}H NMR analysis coupling constant of the C2 proton (<1.0 Hz).[6]



Entry	Acid	Solvent	Temp.	Purity (%)[a]	Isolated Yield (%)
1	5% TFA	CH_2Cl_2	RT	7	-
2	25% TFA	CH_2Cl_2	RT	33	-
3	1% TfOH	CH_2Cl_2	RT	52	-
4	5% TfOH	CH_2Cl_2	RT	31	-
5	10% TfOH	CH_2Cl_2	RT	24	-
6	25% TfOH	CH_2Cl_2	RT	22	-
7	1% TfOH	THF	RT	0	-
8	10% TfOH	THF	RT	0	-
9	1% TfOH	CH_3CN	RT	10	-
10	1% TfOH	CH_3OH	RT	0	-
11	1% TfOH	CH_2Cl_2	0 °C	60	68
12	1% TfOH	CH_2Cl_2	-78 °C	20	-

[a]Purity was estimated by HPLC analysis based on UV absorption (254 nm)

Scheme 3

In conclusion, we described an efficient solution-phase approach for the synthesis of epicatechin 3-acylates based on sequential one-pot multi-step reactions. The dithioacetal **18** smoothly underwent reductive etherification to provide the *cis*-epicatechin 3-acylate derivative **19** via the neighboring group participation of the C3 benzoyloxyl group, although it requires stronger acidic conditions than the

corresponding ketone derivatives **4**. This method would be effective for the synthesis of various epicatechin derivatives in solution-phase.

ACKNOWLEDGEMENTS

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6. **(2*R**,3*R**)-2-phenylchroman-3-yl benzoate** (**19**): white solid; IR (solid) 1704, 1582, 1488cm^{-1}; ^{1}H NMR(400 MHz, $CDCl_3$): δ = 7.87 (brd, *J* = 7.5Hz, 2 H), 7.51 (m, 3 H), 7.36-7.25 (m, 5 H), 7.20 (m, 1 H), 7.10 (d, *J* = 7.5Hz, 1 H), 7.04 (d, *J* = 7.5Hz, 1 H), 6.93 (t, *J* = 7.5Hz, 1 H),5.68 (m, 1 H), 5.27 (s, 1 H), 3.42 (dd, *J* = 17.5, 4.4 Hz, 1 H), 3.16 (dd, *J* = 17.5, 2.2 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$); δ = 165.8, 154.3, 133.0, 130.0, 129.8, 129.7, 128.3, 128.2, 128.1, 127.7, 126.4, 121.1, 118.4, 116.8, 77.7, 68.9, 31.0.