Synthesis of Theaflavins via Biomimetic Oxidative Coupling Reactions

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Received: 11.12.2012; Accepted after revision: 07.01.2013

Abstract: Biomimetic synthesis of theaflavins from catechins was accomplished by using 2-nitrobenzenesulfonyl (Ns) as a protecting group for phenols to minimize undesired side reactions of the electron-rich aromatic rings. This enabled the construction of the complex benzotropolone core in a single-step oxidative coupling reaction.

Key words: theaflavins, 2-nitrobenzensulfonyl group, polyphenol, biomimetic synthesis, benzotropolone

Theaflavin (**1**; Figure 1), one of the polyphenols that are major constituents of tea,[1] is an oxidative dimer of catechin derivatives[2] and has various biological activities.[3] Although many synthetic studies of catechin derivatives have been reported,[4] there are only a few reports of the biomimetic synthesis of **1** using enzymatic oxidation.[5] Recently, Nakatsuka and Yanase's group reported a novel oxidative coupling of *ortho*-quinone **4** and pyrogallol derivative **5** based on the proposed biosynthetic route (Scheme 1).[6] Although their model reactions proceeded in excellent yield, application of this approach to the synthesis of theaflavin has not been reported to date,[7] probably because the oxidation precursors and theaflavin itself are unstable under strongly oxidizing conditions. We have developed the 2-nitrobenzensulfonyl (Ns) group[8] for protecting reactive phenols, and we envisioned that application of Ns group would enable the efficient synthesis of theaflavins from catechins. Herein, we report the syntheses of theaflavin (**1**) and its derivatives from catechins by means of biomimetic oxidative coupling reactions.

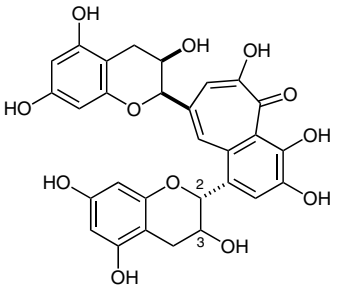
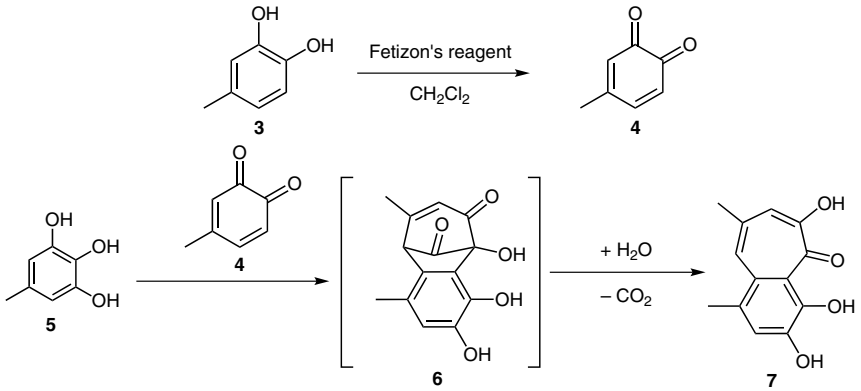


Figure 1 Structures of theaflavin (**1**) and neotheaflavin (**2**)

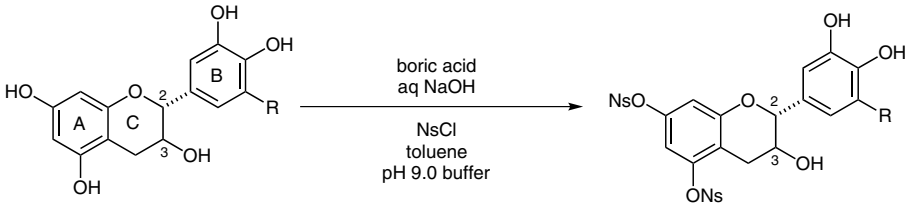
Recently, we reported a regioselective synthesis of methylated epigallocatechin gallate from epigallocatechin by utilizing Ns groups as protecting groups for phenols.[9] For the synthesis of theaflavin, we initially investigated the selective incorporation of Ns groups into the A-ring of catechin (CC) (**9**), epicatechin (EC) (**10**) and epigallocatechin (EGC) (**11**), as shown in Scheme 2.

Regioselective protection of the A-ring with Ns groups was performed by utilizing the bridged boric ester **8**[10] between neighboring phenolic hydroxyl groups on the B-ring as an intermediate. Thus, the boric ester was formed by treatment of **9** with boric acid in the presence of aqueous NaOH, and then reaction with NsCl followed by acidic hydrolysis of boric ester provided **12** exclusively. Similar reactions of **10** and **11** proceeded smoothly to pro-



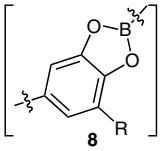
Scheme 1 Coupling reaction of *ortho*-quinone **4** and pyrogallol derivative **5** reported by Nakatsuka and Yanase

SYNLETT 2013, 24, 0479–0482
Advanced online publication: 23.01.2013
DOI: 10.1055/s-0032-1318131; Art ID: ST-2012-U1061-L



Entry	Catechin	Product	Yield (%)
1	**9** R = H, 2,3-*trans*	Ns-CC (**12**)	70
2	**10** R = H, 2,3-*cis*	Ns-EC (**13**)	63
3[a]	**11** R = OH, 2,3-*cis*	Ns-EGC (**14**)	52

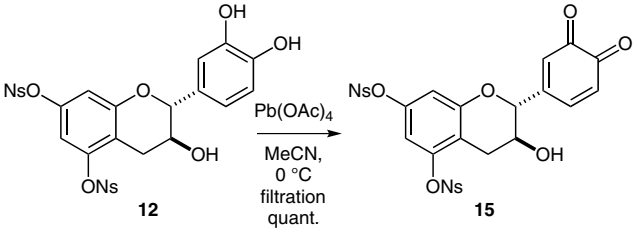
[a] Three equivalents of NsCl were used.



Scheme 2 Regioselective incorporation of Ns group into the A-ring of **9**, **10** and **11**

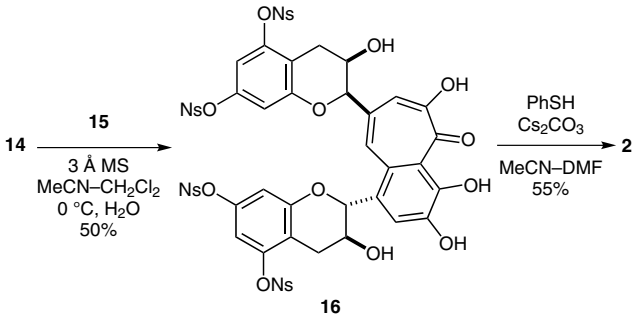
vide **13** and **14**, respectively. Although the boric ester intermediate of **11** has a phenolic hydroxyl group remaining on the B-ring, steric hindrance is expected to prevent its reaction with NsCl.

Having succeeded in selective protection of the A-ring, the next challenge is oxidation of the catechol group in **12** and **13**. First, we optimized the oxidation conditions using **12**, which is derived from less expensive **9**. As shown in Scheme 3, the best result was obtained by oxidation with $Pb(OAc)_4$ in MeCN at 0 °C, affording the desired quinone **15** quantitatively. The use of $Pb(OAc)_4$ as an oxidant offers the advantage of easy removal of the reduced lead salt from the reaction medium by filtration through Celite after completion of the reaction. Furthermore, the electron-withdrawing nature of the Ns group would enhance the stability of the A-ring in the presence of the strong oxidant $Pb(OAc)_4$. Although other oxidants, such as Fetizon's reagent and $PhI(OAc)_2$, were tested, the chemical yields were unsatisfactory. Since the resulting *ortho*-quinone **15** was not stable on silica gel, crude **15**, obtained by simple filtration, was used directly in the next reaction.



Scheme 3 Oxidation of **12** to *ortho*-quinone **15**

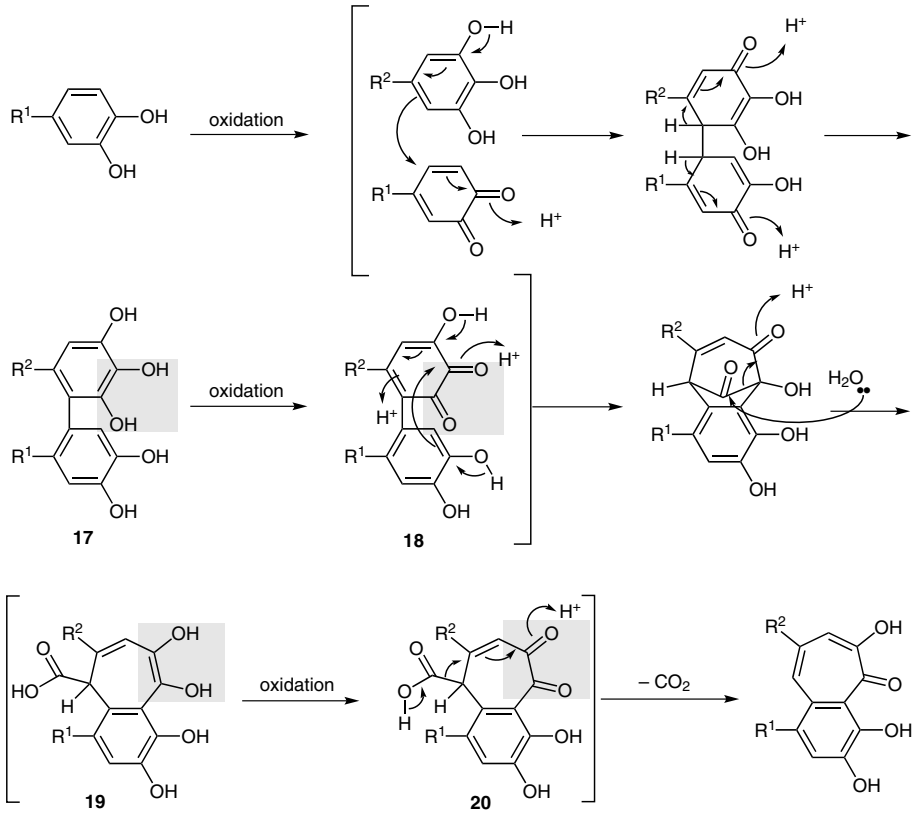
With **15** in hand, we tested the coupling reaction with pyrogallol derivative **14** (Scheme 4). Gratifyingly, treatment of three equivalents of **15** with **14** in a mixture of MeCN and CH_2Cl_2, followed by addition of H_2O, afforded the desired compound **16** in moderate yield. Considering the reaction mechanism illustrated in Scheme 5, at least two equivalents of *ortho*-quinone should theoretically be consumed in the oxidation steps of **17** to **18** and **19** to **20**. Furthermore, the addition of 3 Å MS to the reaction mixture before the addition of H_2O was essential for efficient conversion. 3 Å MS might play a significant role in the oxidation step from **17** to **18**, although the precise mechanism remains unclear. After separation from **12** (generated by reduction of **15**), deprotection of the Ns groups of **16** was accomplished by treatment with thiophenol and cesium carbonate to provide neotheaflavin (**2**).[11] During the coupling and deprotection processes, no appreciable decomposition of benzotropolone was observed.



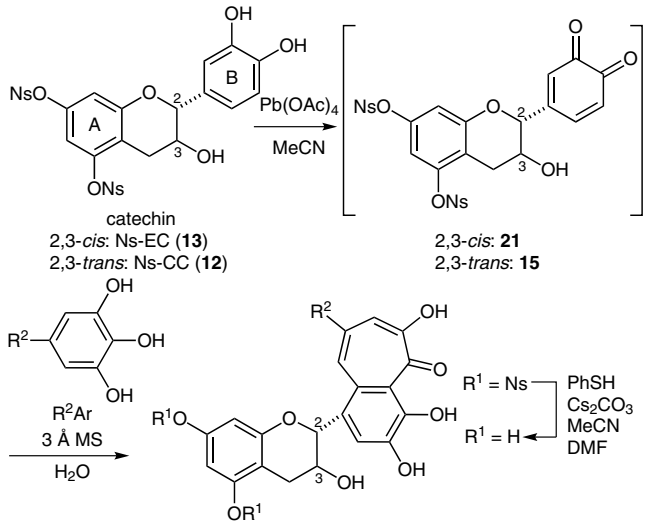
Scheme 4 Synthesis of neotheaflavin (**2**) by oxidative coupling reaction of **14** and **15**

This benzotropolone ring-forming reaction was also applicable to the synthesis of theaflavin (**1**) and its derivatives, as shown in Scheme 6. Upon treatment of Ns-protected epicatechin (**13**) with $Pb(OAc)_4$, the desired oxidation reaction proceeded smoothly to provide *ortho*-quinone **21**. The coupling reaction with **14** was carried out without purification of the *ortho*-quinone intermediate to give a benzotropolone intermediate. Finally, deprotection of the Ns groups afforded theaflavin (**1**). Decreased yield of **1** in comparison with **2** might be a result of instability of the *ortho*-quinone intermediate derived from *cis*-dihydrobenzopyran **13**. This oxidation–coupling strategy was also applied to pyrogallol (**22**) and gallate **24** to give **23** and **25**, respectively (Scheme 6). Since compounds similar to **25**, derived from oxidative coupling of gallate derivatives, have been isolated from tea,[12] this method should be useful for synthesizing derivatives for SAR studies.

In summary, we have accomplished a short-step biomimetic syntheses of theaflavin (**1**), neotheaflavin (**2**) and their derivatives by utilizing Ns as a protecting group for phenols. As far as we know, this is the first example of the



Scheme 5 Proposed mechanism of the coupling reaction of quinone and pyrogallol according to Nakatsuka and Yanase



Entry	Catechin	R^2Ar	Product	Yield (%) (2 steps from R^2Ar)
1[a]	**13**	**14**	**1**	11
2	**12**	**22** R^2 = H	**23** (2,3-*trans*)	13
3	**12**	**24** R^2 = CO_2Me	**25** (2,3-*trans*)	24

[a] 2-$H_2NC_6H_4SH$ was used instead of PhSH.

Scheme 6 Synthesis of theaflavin (**1**) and its derivatives

chemical syntheses of theaflavins. Further application of this approach is underway in our laboratory.

Acknowledgments

The authors thank Dr. Masayuki Suzuki (Mitsui Norin Co., Ltd) for providing samples of (–)-EGC, (–)-EC and (–)-GC. This work was financially supported by a grant from the Shizuoka Prefecture and

Shizuoka City Collaboration of Regional Entities for the Advancement of Technological Excellence, a grant from the Japan Science and Technology Agency (JST), and a Grant-in-Aid for Scientific Research on Priority Areas (No 12045232) from the Ministry of Education, Culture, Sports, Science and Technology (MEXT) of Japan. We also thank Professors Tsutomu Nakayama, Masahiko Hara, and Takeshi Ishii (Department of Food and Nutritional Science, University of Shizuoka) for valuable discussions.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(11) **Synthetic Procedure for 2**: To a solution of **12** (1.0 g, 1.5 mmol) in MeCN (15 mL) was added $Pb(OAc)_4$ (806 mg, 4.5 mmol) at 0 °C. The resulting suspension was stirred for 10 min at 0 °C. The reaction mixture was added to benzene, and then the mixture was filtered through a pad of Celite. Then the filtrate was evaporated under reduced pressure, and the resulting crude product **15** was dissolved in MeCN–CH_2Cl_2 (1:4, 25 mL). To the solution of **15** were added MS 3A (1.0 g) and **14** (342 mg, 505 μmol) in MeCN–CH_2Cl_2 (1:4, 10 mL) at 0 °C. The resulting suspension was stirred for 20 min at 0 °C. After the addition of H_2O the mixture was stirred for 5 min at r.t. The reaction mixture was filtered, and the filtrate was extracted with EtOAc, the organic phase was washed with H_2O, and evaporated under reduced pressure. The residue was purified by silica gel flash column chromatography (CH_2Cl_2–MeOH, 98:2) to afford **16** (327 mg, 50%) as an orange amorphous solid.
To a suspension of Cs_2CO_3 (501 mg, 0.17 mmol) and thiophenol (0.17 mL, 1.7 mmol) in MeCN–DMF (1:2, 2.7 mL) was added the solution of **16** (223 mg, 0.17 mmol) in MeCN (3.0 mL) at 0 °C After stirring at 0 °C for 2 h, the reaction was quenched with aq 1 M HCl and extracted with EtOAc. The organic phase was evaporated under reduced pressure. The residue was purified by preparative TLC (CH_2Cl_2–MeOH, 9:1) to afford **2** (53 mg, 55%) as an orange amorphous solid.
Spectral Data for 2: $[\alpha]_D^{20}$ –122.1 (*c* = 0.20, acetone). ^{1}H NMR (500 MHz, acetone-d_6): δ = 8.83 (br s, 1 H), 8.27 (s, 1 H), 7.77 (s, 1 H), 7.67 (s, 1 H), 6.08 (s, 1 H), 6.04 (s, 1 H), 5.96 (s, 1 H), 5.95 (s, 1 H), 5.62 (d, *J* = 5.0 Hz, 1 H), 5.02 (s, 1 H), 4.38 (br s, 1 H), 4.10–4.16 (m, 1 H), 2.75–3.00 (m, 3 H), 2.66 (dd, *J* = 16.0, 9.0 Hz, 1 H). HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{29}H_{24}O_{12}Na$: 587.1159; found: 587.1130

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