HETEROCYCLES, Vol. 76, No. 2, 2008, pp. 1001 - 1005. © The Japan Institute of Heterocyclic Chemistry
Received, 26th March, 2008, Accepted, 26th May, 2008, Published online, 29th May, 2008. COM-08-S(N)62

# SYNTHESIS OF γ-VALEROLACTONES AS THE TEA CATECHIN METABOLITES[†]

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**Abstract** – The synthesis of optically active γ-valerolactones in order to characterize the absolute configuration of the one of the (-)-epicatechin gallate metabolites was described. The determination of stereochemistry at C(4) position of γ-valerolactone suggested that C(3) position of tea catechins was converted to the C(4) position of γ-valerolactone by maetabolism.

The green tea catechins are known as one of the strongest bioactive groups among the polyphenols. They have diverse biological activities: free-radical scavenging,[1] antibacterial,[2] antiviral,[3] anticancer,[4] antiinflammatory activities,[5] and inhibitory activities against DNA polymerases.[6] We have been reported the synthetic studies of monomer catechin derivatives[7] and the stereoselective synthesis of procyanidin oligomers[8] consisting of (+)-catechin and (-)-epicatechin with their bioactivities. With the potentially beneficial role of tea catechins in human health becoming increasingly significant, the metabolic fate of tea catechins in the body has recently become a subject of considerable interest and is beginning to be elucidated to some extent with respect to (-)-epicatechin, (-)-epigallocatechin, and (-)-epigallocatechin gallate. The catechins undergo extensive metabolism including methylation, glucuronidation, and sulfation.[9,10] Mitsui Norin group described the identification of (-)-epicatechin gallate metabolites in the rat bile and urine.[11] The microbial degradation of these compounds in the colon resulted in the formation of γ-valerolactones,[12, 13] which are detectable in the plasma and urine following consumption of green tea. We report here a synthesis of catechin metabolites as the optically active form in order to characterize the absolute configuration of the one of the (-)-epicatechin gallate metabolites.

[†]Dedicated to Prof. Dr. Ryoji Noyori on the occasion of his 70th birthday.

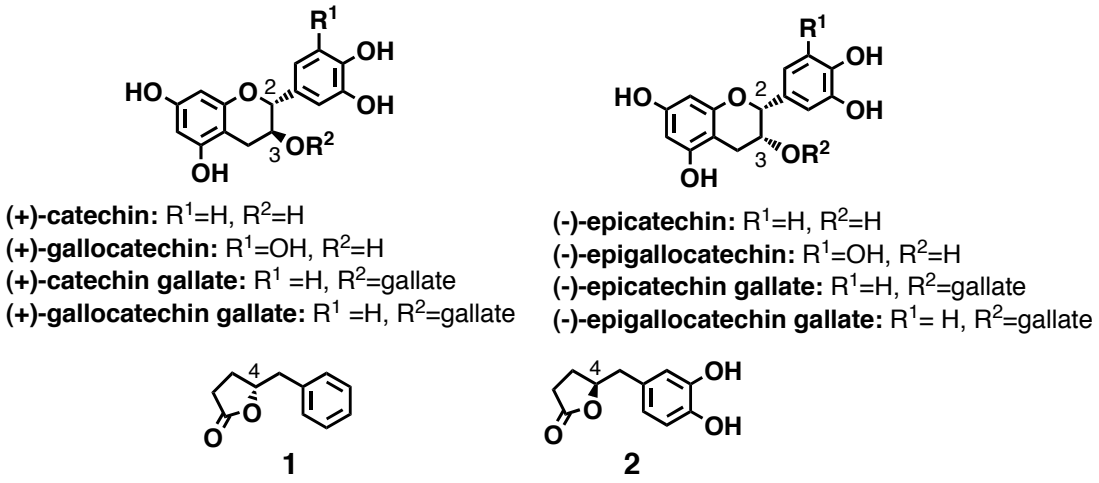
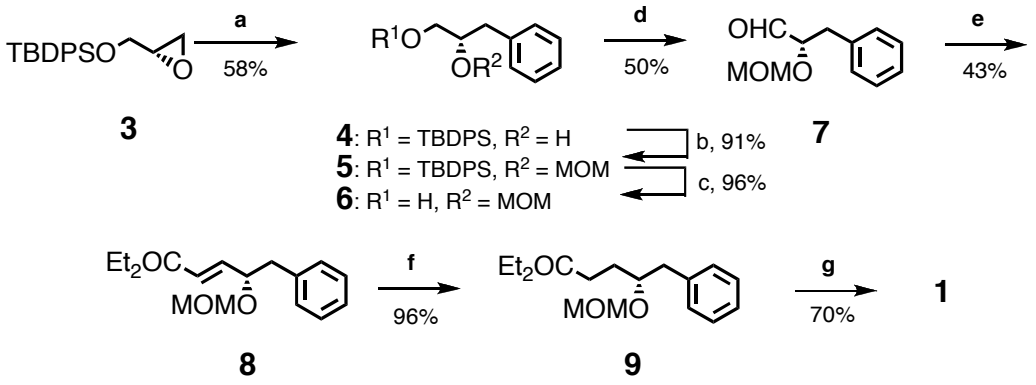



**Figure 1. Structure of catechin, epicatechin derivatives and γ-valerolactones**

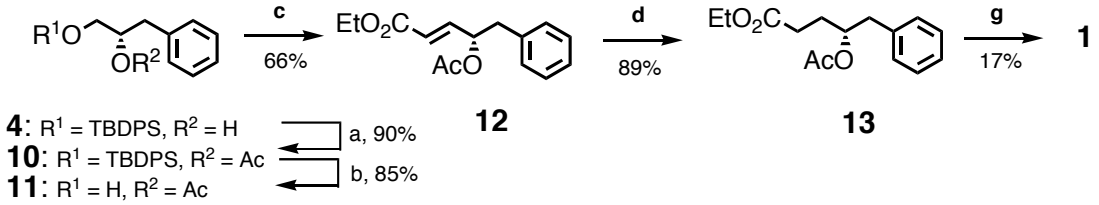
In 2005, the synthesis of tea catechin metabolites as a racemic form was reported by J. D. Lambert group.[14] We synthesized (*R*)-5-phenyl-γ-valerolactone (**1**) as a model compound described as shown in **Scheme 1**. Starting from chiral epoxide (**3**),[15] **3** was treated with phenylmagnesium bromide to afford **4** in 58% yield. The hydroxy group of **4** was protected with MOM (methoxymethyl) group in 91% and TBDPS (*tert*-butyldiphenylsilyl) group was deprotected by TBAF (tetrabutylammonium fluoride) to give **6** in 96% yield. PDC oxidation and following Wittig olefination gave the *trans* α,β-unsaturated ester (**8**) in 22% yield for the two-step sequences. Saturated ester was obtained from **8** with 10% Pd-C under hydrogen atmosphere in 96% yield. The removal of MOM group and lactone formation was achieved under acidic conditions to give **1**[16,17] in 70% yield.

A modification of the synthesis outlined above was employed for changing the protecting group from MOM to acetyl (Ac) group (**Scheme 2**). Acetyl protected alcohol was prepared from **4** by acetylation in 90% and TBDPS group was removed by TBAF in the presence of acetic acid to give **11** in 85% yield.



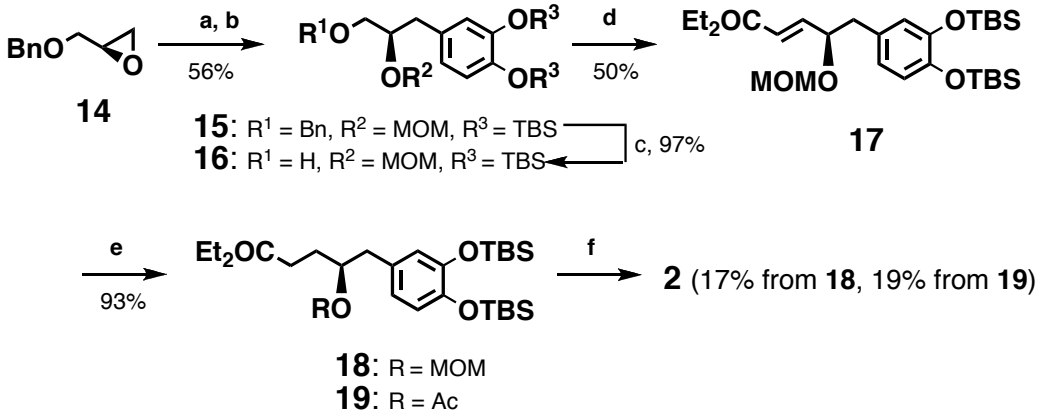

**Scheme 1. Reagents and conditions:** (a) phenylmagnesium bromide, THF, -78 °C to rt; (b) MOMCl, *i*-$Pr_2NEt$, $CH_2Cl_2$; (c) TBAF, THF, rt; (d) PDC, $CH_2Cl_2$; (e) $Ph_3PCHCO_2Et$, $CH_2Cl_2$; (f) 10% Pd-C/$H_2$, EtOAc; (g) HCl, MeOH

The α,β-unsaturated ester (**12**) was obtained by Swern oxidation of **11** and following Wittig olefination under one-pot conditions in 66% yield. Hydrogenolysis over 10% Pd-C gave saturated ester **13** in 89% yield. The acetyl group was hydrolyzed with $K_2CO_3$ in methanol to form **1** in 17% yield.




**Scheme 2. Reagents and conditions:** (a) $Ac_2O$, $Et_3N$, DMAP, $CH_2Cl_2$; (b) TBAF, AcOH, THF, rt; (c) $(COCl)_2$, DMSO, $Et_3N$, $CH_2Cl_2$ and then $Ph_3PCHCO_2Et$, $CH_2Cl_2$; (d) 10% Pd-C/$H_2$, EtOAc; (g) $K_2CO_3$, MeOH

Catechol compounds, (*S*)-5-(3,4-dihydroxyphenyl)-γ-valerolactone (**2**) was next synthesized from the coupling of epoxide (**14**) and di-silyl protected catechol bromide (**Scheme 3**). Bromide was treated with *n*-BuLi in THF in the presence of $BF_3$•$Et_2O$ at -78 °C and THF solution of **14** was added to the solution, obtained alcohol was protected by MOM group under usual condition to give **15** in 56% yield. After Bn group was removed, alcohol (**16**) was oxidized to aldehyde by Swern oxidation and following Wittig olefination under one-pot conditions gave α,β-unsaturated ester (**17**) in 49% yield. Final γ-lactone formation was preceded under acidic conditions, γ-lactone (**2**) was obtained from **18** in 17% yield. To improve the reaction yield, the γ-lactone formation was studied on acetate (**19**)[18] under alkaline conditions, desired γ-lactone (**2**)[19] was obtained only in 19% yield. The spectroscopic data, MS, $^1$H NMR and $^{13}$C NMR, agreed with those of authentic 5-(3,4-dihydroxyphenyl)-γ-valerolactone. However, the optical rotation




**Scheme 3. Reagents and conditions:** (a) 3,4-bis(*tert*-butyldimethylsilyloxy)-bromobenzene, *n*-BuLi, $BF_3$-$OEt_2$, THF, -78 °C to rt; (b) MOMCl, *i*$Pr_2$NEt, $CH_2Cl_2$; (c) 10% Pd-C/$H_2$, EtOAc; (d) $(COCl)_2$, DMSO, $Et_3N$, $CH_2Cl_2$ and then $Ph_3PCHCO_2Et$, $CH_2Cl_2$; (e) 10% Pd-C/$H_2$, EtOAc; (f) HCl, MeOH; (g) $K_2CO_3$, MeOH

value, $[\alpha]_D^{26}$ +39.6 (*c* 0.1, MeOH), was opposite value and three times larger than reported value, [12] $[\alpha]_D$ -12 (*c* 0.1, MeOH).

In summary, we describe method for the synthesis of one of metabolites of the green tea catechins. We have determined the absolute stereochemistry of metabolite. This results suggest that stereochemistry at C(3) position of tea catechins reflects to the stereochemistry at C(4) position of γ-valerolactone. The difference of optical rotation value between synthetic sample and metabolite became clear, the metabolic fate of tea catechins still remains to be clarified.

## REFERENCES AND NOTES


1. T. Ariga, I. Koshiyama, and D. Fukushima, *J. Agric. Food Chem.,* 1998, **52**, 2717.
2. T. Fukai, T. Ishigami, and Y. Hara, *Agric. Biol. Chem.*, 1991, **55**, 1895.
3. M. Nakayama, K. Suzuki, M. Toda, S. Okubo, Y. Hara, and T. Shimamura, *Antiviral Res.*, 1993, **21**, 289.
4. Y. Xu, C.-T. Ho, S. G. Amin, C. Han, and F.-L. Chung, *Cancer Res.*, 1992, **52**, 3875.
5. C. S. Yang, J. M. Landau, M. T. Huang, and H. L. Newmark, *Annual Review of Nutrition*, 2001, **21**, 381.
6. Y. Mizushina, A. Saito, A. Tanaka, N. Nakajima, I. Kuriyama, M. Takemura, T. Takeuchi, F. Sugawara, and H. Yoshida, *Biochem. Biophys. Res. Commun.*, 2005, **333**, 101.
7. K. Matsubara, A. Saito A. Tanaka, N. Nakajima, R. Akagi, M. Mori, and Y. Mizushina, *DNA & Cell Biol.*, 2006, **25**, 95; K. Matsubara, A. Saito A. Tanaka, N. Nakajima, R. Akagi, M. Mori, and Y. Mizushina, *Life Sciences*, 2007, **80**, 1578.
8. A. Saito and N. Nakajima, *J. Syn. Org. Chem. Jpn,* 2005, **63**, 982. and references therein.
9. J. D. Lambert and C. S. J. Yang, *J. Nutr.*, 2003, **133**, 3262s; C. S. Yang, P. Maliakal, and X. Meng, *Ann. Reu. Pharmacol. Toxicol.,* 2002, **42**, 25.
10. H. Lu, X. Meng, C. Li, S. Sang, C. Patten, S. Sheng, S, J. Hong, N. Bai, B. Winnik, C. T. Ho, and C. S. Yang, *Drug Metab. Dispos.*, 2003, **31**, 452; H. Lu, X. Meng, and C. S. Yang, *Drug Metab. Dispo*s., 2003**, 31**, 572; J. D. Lambert, M. J. Lee, H. Lu, X. Meng, J. Ju, J. Hong, D. N. Seril, M. G. Sturgill, and C. S. Yang, *J. Nutr.*, 2003, **133**, 4172.
11. T. Kohri, M. Suzuki, and F. Nanjo*, J. Agric. Food Chem.*, 2003, **51**, 5561; T. Kohri, N. Matsumoto, M. Yamakawa, M. Suzuki, F. Nanjo, Y. Hara, and N. Oku, *J. Agric. Food Chem.*, 2001, **49**, 4102.
12. M. R. Meselhy, N. Nakamura, and M. Hattori, *Chem. Pharm. Bull.*, 1997, **45**, 888.
13. K. G. Duweler and P. Rohdwald, *Pharmazie*, 2000, **55**, 5; C. Li, M.-J. Lee, S. Sheng, X. Meng, S. Prabhu, B. Winnik, B. Huang, J. Y. Chung, S. Yan, C.-T. Ho, and C. S. Yang, *Chem. Res. Toxicol.*, 2000, **13**, 177.

14. J. D. Lambert, J. E. Rice, J. Hong, Z. Hou, and C. S. Yang, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 873.
15. The chiral epoxide (**3**) was synthesized from (*S*)-solketal in 4 step sequences in 58% yield; tosylation, 80% AcOH treatment, *tert*-butyldiphenylsilyl protection, $K_2CO_3$ treatment.
16. Data for (*R*)-5-phenyl-γ-valerolactone (**1**): $[\alpha]_D^{26}$ -22.1 (*c* 0.28, $CHCl_3$) [lit.,[17] $[\alpha]_D^{25}$ +24.7 (*c* 1, $CHCl_3$)]; $^1$H-NMR (400 MHz, $CDCl_3$) δ 7.36-7.22 (5H, m), 4.74 (1H, dddd, *J* = 6.1, 6.3, 6.8, 7.6 Hz), 3.10 (1H, dd, *J* = 6.1, 13.9 Hz), 2.93 (1H, dd, *J* = 6.3, 13.9 Hz), 2.47 (1H, dt, *J* = 17.6, 9.2 Hz), 2.38 (1H, ddd, *J* = 4.6, 9.3, 17.5 Hz), 2.26 (1H, dddd, *J* = 4.9, 6.8, 9.7, 12.9 Hz), 1.96 (1H, ddt, *J* = 7.6, 12.9, 9.3 Hz); $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 177.0, 135.9, 129.4, 128.6, 127.0, 80.8, 41.3, 28.6, 27.1; ESI-MS (*m/z*) 177 $(M+H)^+$, 199 $(M+Na)^+$; ESI-HRMS *m/z* $(M+Na)^+$: calcd for $C_{11}H_{12}O_2Na$, 199.0756; found. 199.0730.
17. S. P. Kotkar, G. S. Suryavanshi, and A. Sudalai, *Tetrahedron Asymmetry*, 2007, **18**, 1795.
18. Acetate (**19**) was synthesized from **14** in 5 steps, 26% yield with the same synthetic manner of **13** describing at Scheme 2.
19. Data for (*S*)-5-(3,4-dihydroxyphenyl)-γ-valerolactone (**2**): $[\alpha]_D^{26}$ +39.6 (*c* 0.1, MeOH); $^1$H-NMR (400 MHz, $CD_3OD$) δ 6.68 (1H, d, *J* = 8.0 Hz), 6.67 (1H, d, *J* = 2.0 Hz), 6.60 (1H, dd, *J* = 2.0, 8.0 Hz), 4.75-4.69 (1H, m), 2.86 (1H, dd, *J* = 6.1, 14.1 Hz), 2.77 (1H, dd, *J* = 6.1, 14.1 Hz), 2.47 (1H, ddd, *J* = 8.8, 9.8, 17.8 Hz), 2.32 (1H, ddd, *J* = 4.9, 9.5, 17.8 Hz), 2.22 (1H, dddd, *J* = 4.9, 6.8, 9.7, 12.9 Hz), 1.94 (1H, ddt, *J* = 7.3, 12.7, 9.7 Hz); $^{13}$C-NMR (100 MHz, $CD_3OD$) δ 180.5, 146.5, 145.4, 129.3, 122.1, 117.9, 116.6, 83.5, 41.7, 29.7, 28.1; IR (neat, $cm^{-1}$) 3331 (w), 1742 (s), 1604 (w), 1517 (m), 1444 (m), 1356 (m), 1281 (m), 1179 (s), 1113 (m), 1015 (m), 987 (m), 925 (m), 871 (m), 805 (m); ESI-MS (*m/z*) 209 $(M+H)^+$; ESI-HRMS *m/z* $(M+H)^+$: calcd for $C_{11}H_{13}O_4$, 209.0809; found. 209.0808.