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Total Synthesis of (±)-Butyl Ester of Rosmarinic Acid

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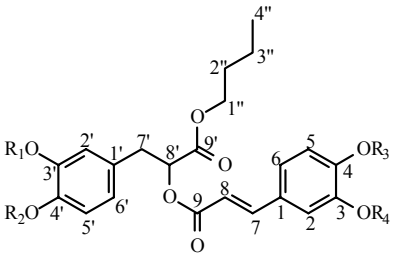
Abstract: (±)-Butyl ester of rosmarinic acid **1** was synthesized by 5-step reactions through the two key intermediates **2** and **3**, the total yield was 23.9% and 25.1%, respectively.

Keywords: Butyl ester of rosmarinic acid, piperonal.

Rosmarinic acid, a well-known natural product firstly isolated from *rosemary* by Scarpati and Oriente in 1958[1], possesses various kinds of biological activities such as antioxidant[2] and antibacterial[3]. Recently, the synthesis and biological activities of related compounds of rosmarinic acid have received much attention, such as 4, 4′-*O*-di-β-D-glucopyranosyl rosmarinic acid[4], methyl ester of rosmarinic acid[5-6] and rabdosiin[7].

Butyl ester of rosmarinic acid **1 (Scheme 1)** was isolated from *Isodon oresbius* in 1999[8]. However, there was no report of synthesis and biological activities of this compound. In order to study its biological activities, a new short route for its synthesis was designed **(Scheme 1)**.

Scheme 1



1 $R_1=R_2=R_3=R_4=H$
2 R_1, R_2=—CH_2—, $R_3=R_4$=Bn
3 R_1, R_2=—CH_2—, R_3, R_4=—CH_2—

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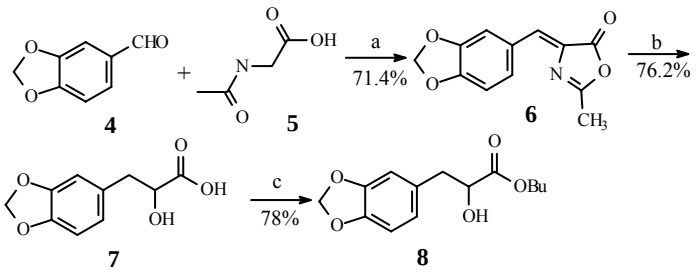
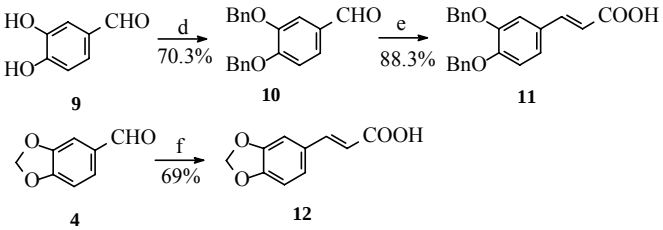
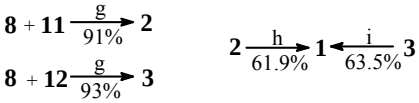
Scheme 2 Synthesis of the intermediate **8**



Scheme 3 Synthesis of intermediates **11** and **12**



Scheme 4



Regents and conditions: a) aceturic acid, Ac_2O, NaOAc, 120℃, 5 h; b) HCl, 100℃, 3 h, then Zn/Hg, HCl, 4 h; c) H_2SO_4, CH_2Cl_2, *n*-BuOH, 24 h; d) K_2CO_3, ethanol, $PhCH_2Cl$, reflux, 5 h; e) malonic acid, pyridine, piperidine, 110℃, 4 h; f) malonic acid, pyridine, piperidine, 110℃, 3 h; g) DCC, DMAP, CH_2Cl_2, -20℃, 10 h; h) BBr_3, -78℃, 1.5 h; i) BBr_3, -78℃, 3 h.

The key step is the synthesis of the intermediate **8** which was prepared from piperonal **4** as shown in **Scheme 2**. According to classic Erlenmeyer-Plöchl method[9], piperonal **4** reacted with excess of aceturic acid **5** in the presence of anhydrous NaOAc in Ac_2O to give azlactone **6** as slight yellow crystals. We adopted "one-pot" procedure in which **6** was refluxed with 3 mol/L hydrochloric acid, and then zinc amalgam was added to give **7**. **8** was obtained by esterification of **7** with *n*-BuOH in 78% yield.

The other two intermediates **11** and **12** were prepared from 3, 4-dihydroxy benzaldehyde **9** and **4** as shown in **Scheme 3**. **9** was treated with benzyl chloride to afford **10**. **10** or **4** was condensed with malonic acid to yield the intermediate **11** or **12**, respectively.

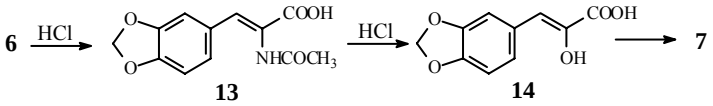
The title compound **1** was prepared from the intermediates **2** and **3** as shown in **Scheme 4**. Esterification of **8** with **11** and **12** gave **2** and **3**, which were treated with BBr_3 to give **1**. Benzyl can be more easily removed than methylene in the above

procedure.

The mechanism of formation of **7** from **6** can be postulated as shown in **Scheme 5**. The azlactone **6** was treated with 0.2 mol/L HCl to afford the enamine intermediate **13**. **13** can be easily hydrolyzed with 3 mol/L HCl to afford the intermediate **14;** it was reduced to give the intermediate **7**.

In summary, we have presented a concise approach of preparation of (±)-**1**; the synthetic route from **2** is more facile than from **3,** because it is more amenable to large-scale synthesis. Biological evaluation and asymmetric synthesis of **1** are in progress.

Scheme 5



13 **14**

References and Notes

1. M. L. Scarpati, G. Oriente, *Ricerca Sci.*, **1958,** *28*, 2329.
2. J. H. Chen, C.T. Ho, *J. Agric. Food Chem.*, **1997**, *45*, 2374.
3. M. Kuhnt, A. Probstle, H. Rimpier, R. Bauer, M. Heinrich, *Planta Med.*, **1995**, *61*, 227.
4. T. Satake, K. Kamiya, Y. Saiki, *et al*, *Chem. Pharm. Bull.*, **1999**, *47*, 1444.
5. T. Motoyuki, O. Yasuyuki, *Planta Med*., **1998**, *64*, 555.
6. E. Reimann, H. J. Mass, T. Pflug, *Monatsh. Chem.*, **1997**, *128*, 995.
7. D. E. Bogucki, J. L. Charlton, *Can. J. Chem.*, **1997**, *75*, 1783.
8. H. Huang, Q.R. Chao, R.X. Tan, *Planta Med.*, **1999**, *65*, 92.
9. H. E. Carter, *Org. Reactions*, **1946**, *3*, 198.
10. Spectral data of compound **2**: ^{1}HNMR (300MHz, $CDCl_3$, δ ppm): 7.61 (d, 1H, J=15.9 Hz, =CH-), 7.49-7.31 (m, 10H, ArH), 7.14 (d, 1H, J=2.0 Hz, ArH), 7.08 (dd, 1H, J=8.4 Hz, 2.0 Hz, ArH), 6.92 (d, 1H, J=8.4 Hz, ArH), 6.78 (d, 1H, J=1.4 Hz, ArH), 6.74 (d, 1H, J=8.0 Hz, ArH), 6.70 (dd, 1H, J=8.0 Hz, 1.4 Hz, ArH), 6.30 (d, 1H, J=15.9 Hz, =CH-), 5.93 (s, 2H, OCH_2O), 5.30 (t, 1H, J=6.6 Hz, CHO-), 5.20 (s, 2H, -OCH_2Ph), 5.19 (s, 2H, -OCH_2Ph), 4.16 (t, 2H, J=6.6 Hz, -OCH_2-), 3.12 (t, 2H, J=6.6 Hz, CH_2Ar), 1.65-1.58 (m, 2H, CH_2), 1.41-1.28 (m, 2H, CH_2), 0.92 (t, 3H, J=7.2 Hz, CH_3); IR (KBr, cm^{-1}): 1743, 1716, 1634, 1596; EI-MS: *m/z* 608 (M^+, 0.2), 91 (100); HREI-MS: *m/z* 608.2457 (calcd. for $C_{37}H_{36}O_8$, 608.2410).
11. Spectral data of compound **3**: ^{1}HNMR (300MHz, $CDCl_3$, δ ppm): 7.60 (d, 1H, J=15.9 Hz, =CH-), 7.03 -6.68 (m, 6H, ArH), 6.28 (d, 1H, J=15.9Hz, =CH-), 5.98 (s, 2H, OCH_2O), 5.91 (s, 2H, OCH_2O), 5.27 (t, 1H, J=6.6 Hz, CHO-), 4.13 (t, 2H, J=6.4 Hz, CH_2O-), 3.11 (d, 2H, J=6.6 Hz, CH_2Ar), 1.67-1.52 (m, 2H, CH_2), 1.38-1.24 (m, 2H, CH_2), 0.90 (t, 3H, J=7.2 Hz, CH_3); EI-MS: *m/z* 440 (M^+, 1), 248 (89), 192 (100), 135 (45); IR (KBr, cm^{-1}): 1743, 1716, 1629, 1601. HREI-MS: *m/z* 440.1484 (calcd. for $C_{24}H_{24}O_8$, 440.1471).
12. Spectral data of compound **1**: ^{1}HNMR (300MHz, DMSO-d_6, δ ppm): 7.48 (d, 1H, J=15.9 Hz, H-7), 7.06 (d, 1H, J=1.8 Hz, H-2), 7.04 (dd, 1H, J=7.8 Hz, 1.8Hz, H-6), 6.77 (d, 1H, J=7.8 Hz, H-5), 6.65 (d, 1H, J=1.8 Hz, H-2′), 6.63 (d, 1H, J=7.8 Hz, H-5′), 6.49 (dd, 1H, J=7.8 Hz,

1.8 Hz, H-6′), 6.26 (d, 1H, J=15.9 Hz, H-8), 5.08 (t, 1H, J=6.6 Hz, H-8′), 4.03 (t, 2H, J=6.0 Hz, H-1″), 2.95 (d, 2H, J=6.6 Hz, H-7′), 1.52-1.38 (m, 2H, H-2″), 1.36-1.28 (m, 2H, H-3″), 0.84 (t, 3H, J=7.2 Hz, H-4″); ^{13}CNMR (75MHz, DMSO-d_6, δ ppm): 169.5 (C-9′), 165.9 (C-9), 148.6 (C-4), 146.3 (C-3), 145.5 (C-7), 144.9 (C-3′), 144.1 (C-4′), 125.6 (C-1′), 125.3 (C-1), 121.7 (C-6), 120.1 (C-6′), 116.7 (C-2′), 115.7 (C-5), 115.4 (C-5′), 114.9 (C-2), 112.9 (C-8), 72.9 (C-8′), 64.4 (C-1″), 36.2 (C-7′), 30.0 (C-2″), 18.4 (C-3″), 13.5 (C-4″); IR (KBr, cm^{-1}): 3379, 1716, 1604; FAB-MS: *m/z* 417 (M^++1, 0.1), 163 (100); HRFAB-MS: *m/z* 417.1534 $[M+H]^+$ (calcd. for $C_{22}H_{25}O_8$, 417.1549).

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