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Synthesis of 3-(3-Hydroxypropyl)-phthalide and Pedicellosine

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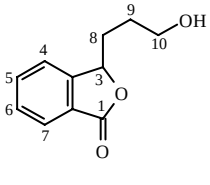
Abstract: 3-(3-hydroxypropyl)-phthalide **1**, a phthalide isolated from the flowers of *G. pedicellata* Wall, has been synthesized in high yield from 2-carboxybenzaldehyde **3** in 2 steps. Reaction of **1** with 2,3-dihydroxybenzoic acid afforded pedicellosine **2**, another phthalide from the leaves of *G. pedicellata* Wall.

Keywords: 3-(3-hydroxypropyl)-phthalide, pedicellosine, synthesis.

3-(3-Hydroxypropyl)-phthalide **1** and pedicellosine **2** are two of the phthalides isolated from the flowers and leaves of *Gentiana pedicellate* Wall, respectively[1]. Since the extract of *Gentiana pedicellate* Wall is used in treatment of many diseases[2], and naturally occurring phthalide always has bioactivities[3], it is deemed worth while to search for synthesis of the two phthalides, which has not been synthesized before.



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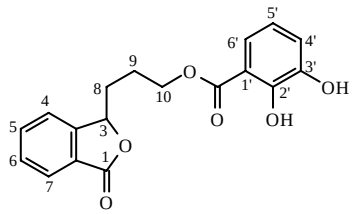

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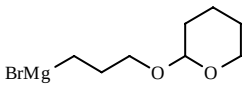

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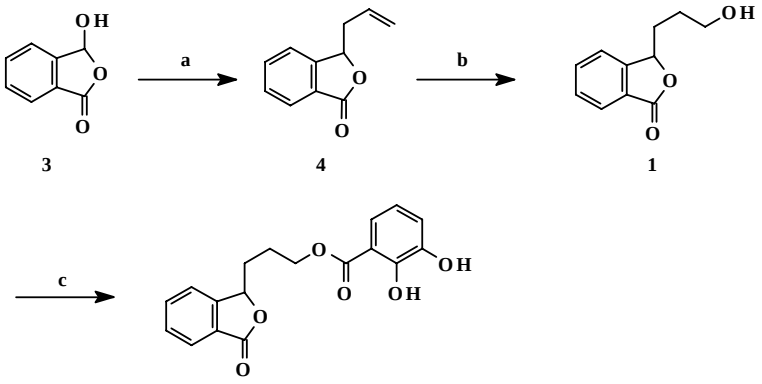
We initially attempt to obtain **1** by condensation of 2-carboxybenzaldehyde **3** with 2.5 eq of the Grignard reagent **5** in THF and several efforts were made. Unfortunately, no addition reaction was found even after the mixture had been refluxed for 48h.

We had to prepare **1** in an indirect way (**Scheme 1**). Condensing **3** with allylmagnesium bromide gave 3-allyl-phthalide **4** in 88% yield. Hydroboration of **4** with $BH_3 \rceil SMe_2$, following oxidation with H_2O_2/OH^- gave the terminal alcohol **1** in 82% yield. The lactone of **4** was not reduced in this reaction. We found it was not necessary to protect the phenol groups of 2,3-dihydroxybenzoic acid, and **1** was esterified directly in the presence of DCC/DMAP to give pedicellosine **2** in fairly good yield (74%).

Scheme 1



a: CH_2CHCH_2MgBr, THF;
b: BH_3⎤SMe_2, THF, then H_2O_2/OH^-;
c: 2,3-dihydroxybenzoic acid, DCC/DMAP, CH_2Cl_2.

References and Notes

1. a) J. Garcia *et al*., *Planta Medica*, **1989**, *55*, 405.
   b) E. M. Mpondo *et al*., *ibid*, **1987**, *53*, 297.
2. S. Ghosal *et al*., *ibid*, **1983**, *49*, 240.
3. M. Lin *et al*., *Yaoxue xuebao*, **1979**, *14*, 529.
4. **1:** oil; IR: 3413, 2944, 1758, 1288, 1058 cm^{-1}; ^{1}HNMR (80Mz, $CDCl_3$) δ: 7.87-7.40 (m, 4H, Ar-H), 5.50 (dd, 1H, J=7.1, 3.8, H-3), 3.65 (t, 2H, J=6.1, H-10), 2.21 (m, 1H, H-8a), 1.88 (m, 1H, H-8b), 1.77-1.60 (m, 2H, H-9); MS m/z (%): 192 (M^+,12), 174 (3), 146 (34), 133 (100), 105 (34), 77 (27).
   2: oil; IR: 3080, 1761, 1670, 1306, 1151 cm^{-1}; ^{1}HNMR (400Mz, $CDCl_3$) δ: 7.93 (d, 1H, J=7.4, H-7), 7.70 (t, 1H, J=7.4, H-5), 7.56 (t, 1H, J=7.5, H-4), 7.46 (d, 1H, J=8, H-6), 7.35 (dd, 1H, J=7.4, 1.4, H-6'), 7.12 (dd, 1H, J=8.0, 1.2, H-4'), 6,80 (t, 1H, J=8.1, H-5'), 5.57 (dd, 1H, J=7.6, 3.5, H-3), 4.41(m, 2H, H-10), 2.29 (m, 1H, H-8a), 2.00-1.88 (m, 3H, H-8b, H-9); MS (70ev, 230°C) m/z (%): 328 (M^+, 12), 175 (100), 136 (50),133 (40),107 (3),105 (5),77 (3).

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