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A short, stereoselective, and common approach for the synthesis of 4,5-disubstituted δ-lactones simplactone B and its C-5 analogue☆

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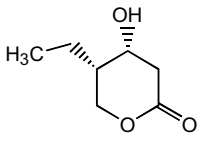
Abstract—A short, stereoselective, and a common approach for the synthesis of 4,5-disubstituted δ-lactones simplactone B and its analogue using Evans protocol is described.

1. Introduction

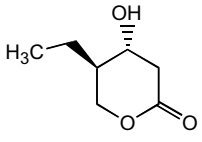
Many natural products, which contains γ- and δ-lactone moieties isolated from marine and terrestrial natural sources differing in chain length, branching and functionalization of alkyl chain, possesses interesting and peculiar biological activities.[1] Hitherto a number of γ- and δ-lactones are isolated, possessing activities like antifungal and antibiotic activities. Among these, recently simplactone A and B compounds were isolated from the Caribbean sponge,[2] *Plakortis simplex* and these compounds possesses in vitro cytotoxic activity against WEHI 164. Some other interesting δ-lactones are homomevanolactone,[3] a structural isomer of simplactones, malyngolide,[4a,b] etc.,[4c] which possess long alkyl chains.

Some of the γ- and δ-lactones, which contain long alkyl chain unit mainly possess antibiotic and antifungal activities. Cafieri et al.[2] expressed that incorporation of long alkyl chains may increase the activity of simplactones. Herein we report the novel and short strategy for the synthesis of simplactone B and its C-5 analogue using asymmetric aldol reaction. This strategy is also helpful to make analogues with various chain lengths. Sato et al.[5] synthesized simplactones A and B and they proposed that these spectral values are identical with the proposed (isolated) simplactones B and A, respectively, rather A and B. Our synthesis gives strong evidence to the above statement because the spectral data of simplactone B which we synthesized is identical with the proposed (isolated) simplactone A (see Scheme 1).

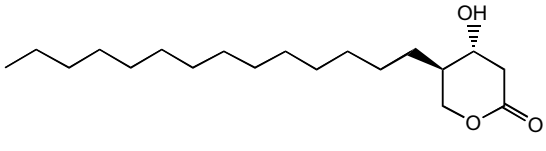
Our synthetic route for simplactones involves Evans asymmetric aldol methodology to set up the stereochemistry of the two contiguous stereogenic centers. Compound **4** was coupled with corresponding different



Simplactone A **1**
(Proposed)



simplactone B **2**
(Proposed)



C-5 analogue of simplactone **3**

Keywords: Chiral auxiliary; Evans-asymmetric aldol methodology; Tempo oxidation; δ-Lactones; Cytotoxic activity.
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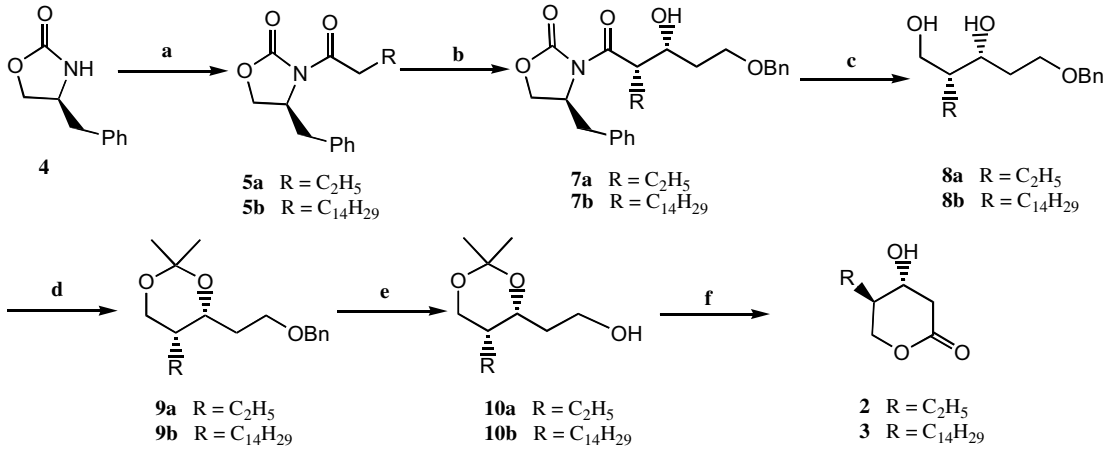

Scheme 1. Reagents and condition: (a) $CH_3CH_2CH_2COOH$ (for **5a**), $C_{15}H_{31}COOH$ (for **5b**), pivaloyl chloride, Et_3N, LiCl, THF, −20 °C, 5 h, 95% for **5a**, 96% for **5b**; (b) Bu_2BOTf, Et_3N, −78 °C, 1 h, then $CHO(CH_2)_2OBn$ (**6**), −78 °C to −10 °C, 2 h, 82%, for **7a**, 81% for **7b**; (c) aq $NaBH_4$, THF, 0 °C to rt, 2 h, 96% for **8a**, 95% for **8b**; (d) 2,2-DMP, CH_2Cl_2, PTSA (Cat amount), rt, 8 h, 97% for **9a**, 95% for **9b**; (e) Li/liq NH_3, −78 °C, 0.5 h, 91%, for **10a**, 92% for **10b**; (f) NaOCl, TEMPO free radical, TBAI (cat. amount), NaBr, EtOAc, toluene, H_2O, $NaHCO_3$, rt, then PTSA, CH_2Cl_2, rt, 3 h, 72% for **2**, 73% for **3**.

acids in the presence of pivaloyl chloride and triethyl amine to get **5a**,**b**. Treatment of the boron enolate[6] derived from compounds **5a**,**b** with the aldehyde **6** provided **7a** in 82% and **7b** in 81% yield, which were converted to diols **8a**,**b** after removing the oxazolidinone auxiliary with aq $NaBH_4$. Then the diols underwent acetonide protection using 2,2-DMP to get compounds **9a**,**b**, which on treatment with Li/liq NH_3 conditions yielded **10a**,**b**. Under Tempo oxidation conditions **10a** and **b** were converted to acids, which were simultaneously treated with PTSA in DCM to afford lactones **2** and **3**, in one pot. The spectral data of **2** is well in agreement with the reported values, whose optical rotation value ($[\alpha]_D^{25}$ −23.1 (*c* 1, $CHCl_3$)) is matching with the synthetic compound prepared by Sato et al. {lit.[5] (synthetic) $[\alpha]_D^{25}$ −23.9 (*c* 0.8, $CHCl_3$)}. Whereas optical rotation value of natural product is lower than the synthetic compounds. {lit.[2] (natural) $[\alpha]_D^{25}$ −3 (*c* 0.002, $CHCl_3$)}.

We have evaluated both lactones **2** and **3** for cytotoxic activity against human breast cancer cell lines (HBL-100) by MTT method.[7] Compound **3**[8] (C-5 analogue) possesses moderate cytotoxic activity with IC_{50} of 0.176 μM, whereas on these cell lines lactone **2** has not shown any activity. This clearly shows that side chain length variation of these lactones will certainly influence the activity.

In summary we have developed a short and highly stereoselective synthesis of δ-lactones using the well-known diastereoselective Evans protocol which is useful to make analogues of different chain lengths for more therapeutic activity.

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8. Spectral data for compound **3**: $[\alpha]_D^{25}$ −3.07 (*c* 1.1, $CHCl_3$); Mp: 74 °C; (^{1}H NMR, 400 MHz, $CDCl_3$): δ 0.9 (t, 3H, J = 6.2), 1.2–1.45 (m, 24H), 1.51–1.62 (m, 1H), 1.77–1.95 (m, 2H), 2.5 (dd, 1H, J = 6.1, 17.7), 2.84 (dd, 1H, J = 5.3, 16.9), 3.92 (t, 2H, J = 10.1), 4.46 (dd, 1H, J = 3.8, 11.5); (^{13}C, 75 MHz, $CDCl_3$): 170.3, 69.3, 68.4, 41.1, 38.2, 31.9, 29.6, 29.4, 29.3, 28.8, 26.8, 22.6, 14.03. FABMS: (M^++1) 313.