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Samarium(II) promoted stereoselective synthesis of antiproliferative *cis*-β-alkoxy-γ-alkyl-γ-lactones

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Abstract—Samarium(II) iodide promotes the stereoselective synthesis of *cis*-β-alkoxy-γ-alkyl-γ-lactones under mild conditions starting from linear precursors. The in vitro antiproliferative activities were examined in the human solid tumor cell lines from diverse origin A2780, SW1573, and WiDr. From the growth inhibition data a structure–activity relationship was obtained. Overall the results point to the relevant role of *cis*-β-alkoxy-γ-alkyl-γ-lactones as novel scaffolds for the development of new anticancer drugs.

Lactones are common structural elements present in several natural products that are known to exhibit diverse biological and pharmacological activities. In particular, γ-lactones display a broad biological profile including strong antibiotic, antihelmintic, antifungal, antitumor, antiviral, antiinflammatory, and cytostatic properties, which makes them interesting lead structures for the development of new drugs.[1]

Several syntheses of lactones are available in the literature.[2] However, reports on the synthesis of *cis*-β,γ-disubstituted-γ-lactones compared with that of the *trans* form are limited.[3] Moreover, in the construction of the two stereogenic centers in β,γ-disubstituted-γ-lactone tedious stepwise methods have been employed.[4]

Samarium(II) iodide (SmI_2) is a mild single-electron reducing agent that has been widely used in the field of organic chemistry.[5] This reagent has been employed in the past to obtain substituted γ-lactones in modest to high yields (17–82%), by the intermolecular coupling of aldehydes or ketones with α,β-unsaturated esters.[6] More recently, it has been reported the synthesis of β-alkoxy-γ,γ-dialkyl-γ-lactones from ketones and β-alkoxyacrylates.[7]

Within our program directed at the synthesis of novel antitumor compounds[8] and bioactive substances of marine origin,[9] these synthetically challenging structures have attracted our interest in the development of new methodologies for their synthesis. We report herein on the synthesis of β-alkoxy-γ-alkyl-γ-lactones by means of one-pot SmI_2-mediated coupling of *n*-octanal with β-alkoxyacrylates. To the best of our knowledge, we describe for the first time the intermolecular coupling of β-alkoxyacrylates with aldehydes in a stereoselective manner and promoted by SmI_2. The antitumor profile of the obtained γ-lactones was evaluated in vitro against a panel of the human solid tumor cell lines A2780 (ovarian cancer), WiDr (colon cancer), and SW1573 (non-small cell lung cancer, NSCLC).

The general synthetic pathway used to obtain the compounds in this study is outlined in Scheme 1. The necessary β-alkoxyacrylates are prepared in high yields (69–72%) in THF from the appropriate alcohol **1**, an

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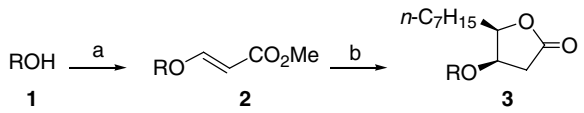


Scheme 1. Reagents and conditions: (a) $HC{\equiv}CCO_2Me$, $(n\text{-}Bu)_3P$, THF, 51–72%; (b) *n*-octanal, SmI_2, MeOH, THF, 0 °C, 11–52%.

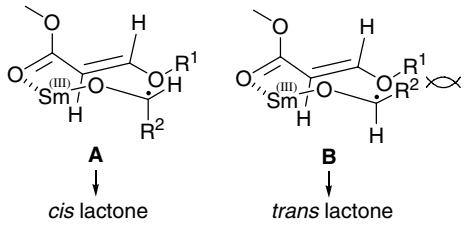


Figure 1. Proposed diastereoisomeric control for the formation of *cis*-β-alkoxy-γ-alkyl-γ-lactone **3**.

equimolar amount of methyl propyolate, and half an equivalent of tri-*n*-butyl phosphine. Then, the β-alkoxyacrylate **2** is reacted with *n*-octanal promoted by SmI_2 to give the corresponding γ-lactone **3** in modest yields.[10] The spectral data of selected γ-lactones **3** are given.[11] Interestingly, the stereochemistry of the substituents on the ring is *cis*.[12] Traces of the corresponding *trans* isomer are not detected. According to this methodology a series of derivatives were prepared and the results obtained are given in Table 1.

We propose a chelation-control model such as illustrated in Figure 1 for the reaction of β-alkoxyacrylates **2** with aldehydes. The ketyl radical generated from the reduction of aldehydes can coordinate with the Sm(III) cation. Subsequent chelation of the carbonyl oxygen atom of the β-alkoxyacrylate **2** forms a complex, where two nearly alternated approaches of the ketyl radical to the double bond are possible. The A approach provides the *cis*-γ-lactone **3** and the B approach gives the *trans* compound. In the latter, a steric hindrance can be present between R^1 and R^2 groups. The destabilizing effect may account for the diastereoisomeric control observed in this reaction.

The in vitro antiproliferative activity was evaluated using the National Cancer Institute (NCI) protocol.[13] We screened growth inhibition and cytotoxicity against the panel of human solid tumor cell lines A2780, SW1573, and WiDr after 48 h of drug exposure using the sulforhodamine B (SRB) assay.[14] The growth inhibition data are listed in Table 2. The results allow us to classify the compounds according to their activity profile. Taken as a whole, compounds **3a** and **3e–f** appear as the most active products from the series with similar performance against the three tumor cell lines. Thus,

Table 1. β-Alkoxyacrylates **2a–h** and *cis*-β-alkoxy-γ-alkyl-γ-lactones **3a–f**

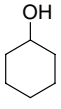
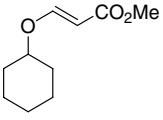
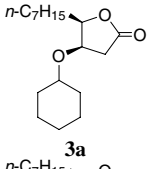
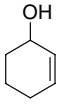
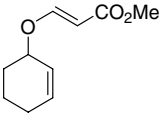
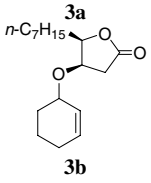
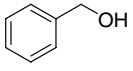
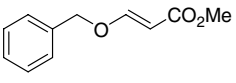
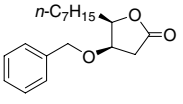
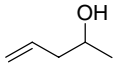
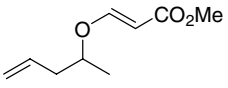
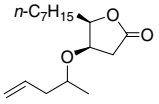
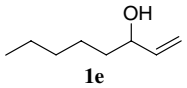
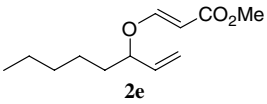
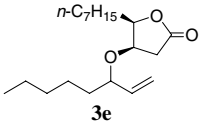
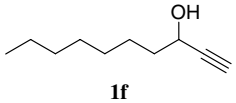
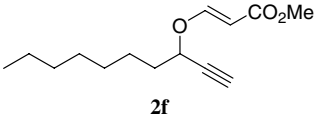
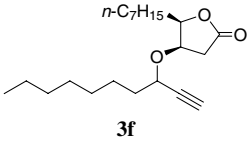
ROH	β-Alkoxyacrylate	Yield (%)	Lactone (*racemic*)	Yield (%)
 **1a**	 **2a**	69	 **3a**	52
 **1b**	 **2b**	72	 **3b**	24
 **1c**	 **2c**	70	 **3c**	15
 **1d**	 **2d**	51	 **3d**	35
 **1e**	 **2e**	60	 **3e**	20
 **1f**	 **2f**	72	 **3f**	11

Table 2. In vitro antiproliferative activity of *cis*-β-alkoxy-γ-alkyl-γ-lactones against human solid tumor cells[a]

Compound	A2780			SW1573			WiDr		
	GI_{50}	TGI	LC_{50}	GI_{50}	TGI	LC_{50}	GI_{50}	TGI	LC_{50}
3a	16 (±3.1)	31 (±4.5)	61 (±5.7)	18 (±2.3)	36 (±2.8)	71 (±6.5)	16 (±3.8)	33 (±5.1)	71 (±9.2)
3b	84 (±27)			23 (±4.1)	49 (±8.7)	95 (±8.3)	50 (±24)		
3c	63 (±13)			52 (±7.9)			44 (±9.0)		
3d	48 (±14)			33 (±12)	83 (±30)		39 (±13)		
3e	19 (±6.4)	42 (±12)	88 (±15)	27 (±2.3)	78 (±27)	96 (±8.3)	27 (±8.2)	81 (±34)	97 (±5.0)
3f	22 (±3.2)	51 (±23)	80 (±18)	32 (±7.1)	83 (±30)	97 (±4.5)	32 (±12)	86 (±25)	

[a] Values are given in μM and are means of two to four experiments, standard deviation is given in parentheses. GI_{50} represents 50% growth inhibition, TGI total growth inhibition, and LC_{50} 50% cell killing. TGI and LC_{50} values are given only if they are less than 100 μM, which is the maximum concentration test.

GI_{50} and TGI values were in the range 16–32 and 31–86 μM, respectively. These lactones were able to show LC_{50} values within the experimental range with the exception of compound **3f** against WiDr cells.

A second group comprises derivatives **3b–d**, which showed modest activity against A2780 ovarian and WiDr colon cancer cells with GI_{50} values in the range 39–84 μM. For these drug-cell line combinations TGI and LC_{50} values could not be reached at the maximum test concentration, that is, 100 μM. Interestingly, differences in activity were observed for lactones **3b–d** against lung cancer cells. While compound **3c** showed a comparable modest activity in all cell lines, derivatives **3b** and **3d** exerted larger activity against lung cancer cells. The activity profile of compound **3b** was better, showing specificity for SW1573 cells comparable to those of **3a** and **3e–f**.

Even though the experiments are preliminary, we found that these synthetic derivatives considerably induced growth inhibition or even cytotoxicity in human solid tumor cells. Taking as a whole, the results are consistent with considering γ-lactones as an essential structure with the substituents on the ring modulating the biological activity. The outcome of the assay brings up a dual behavior for derivative **3b**. While this γ-lactone may be considered as a lead for further development of traditional cytotoxic agents for lung cancer, a new strategy can be foreseen for colon and ovarian cancer cells: compound **3b** may be considered as a cytostatic drug against these cancer cells.

In conclusion, we have reported a samarium(II) iodide promoted method for the synthesis of *cis*-β-alkoxy-γ-alkyl-γ-lactones from linear precursors. This general methodology allows the quick production of a variety of γ-lactones that are anticipated to be useful for the discovery of novel bioactive compounds. On the basis of growth inhibition parameters, a structure–activity relationship was obtained.

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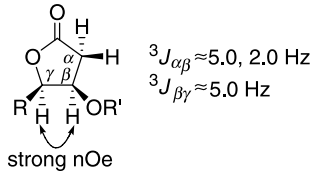
10. General procedure for the SmI_2 promoted synthesis of *cis*-β-alkoxy-γ-alkyl-γ-lactones: to a solution of **2** (0.405 mmol) in dry THF (4 mL, 0.1 M) at 0 °C were added sequentially under nitrogen atmosphere *n*-octanal (0.405 mmol), dry MeOH (1.22 mmol), and SmI_2 (1.22 mmol, 0.1 M in THF). The resultant mixture was stirred at 0 °C for 1 h, after which time it was diluted with EtOAc (25 mL) and a saturated solution of sodium thiosulfate was added (50 mL). The aqueous phase was extracted with EtOAc (3× 25 mL), the combined organic layers were dried under anhydrous $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The residue was purified by chromatography on silica gel (EtOAc/hexane, 1:9) to give γ-lactone **3**.
11. Compound **3a**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.88 (t, J = 7.0 Hz, 3H), 1.25–1.51 (m, 16H), 1.60–1.87 (m, 6H), 2.54 (dd, J = 17.4, 2.1 Hz, 1H), 2.64 (dd, J = 17.4, 5.2 Hz, 1H), 3.25 (m, 1H), 4.17 (ddd, J = 5.0, 5.0, 2.1 Hz, 1H), 4.37 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.0 (q), 22.6 (t), 23.7 (t), 23.8 (t), 25.4 (t), 25.6 (t), 28.5 (t), 29.1 (t), 29.4 (t), 31.4 (t), 31.7 (t), 33.0 (t), 37.1 (t), 72.9 (t), 76.6 (d), 84.5 (d), 175.5 (s).
    Compound **3b**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.89 (t, J = 7.0 Hz, 3H), 1.18–2.03 (m, 18H), 2.57 (dd, J = 17.5, 2.4 Hz, 1H), 2.67 (dd, J = 17.5, 5.4 Hz, 1H), 3.84 (m, 1H), 4.24 (ddd, J = 5.4, 5.4, 2.4 Hz, 1H), 4.39 (m, 1H), 5.69–5.74 (m, 1H), 5.87 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1 (q), 18.8 (t), 22.6 (t), 25.1 (t), 25.2 (t), 25.4 (t), 28.1 (t), 28.6 (t), 29.1 (t), 29.4 (t), 31.7 (t), 37.0 (t), 37.2 (t), 71.7 (d), 72.1 (d), 73.3 (d), 84.5 (d), 126.2 (d), 127.3 (d), 131.6 (d), 132.0 (d), 176,0 (s).
    Compound **3c**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.89 (t, J = 6.6 Hz, 3H), 1.18–1.51 (m, 9H), 1.74–1.91 (m, 3H), 2.63 (dd, J = 17.6, 5.0 Hz, 1H), 2.70 (dd, J = 17.6, 2.3 Hz, 1H), 4.17 (ddd, J = 5.0, 5.0, 2.3 Hz, 1H), 4.40 (m, 1H), 4.41 (d, J = 11.9 Hz, 1H), 4.61 (d, J = 11.9 Hz, 1H), 7.29 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.8 (q), 22.4 (t), 25.2 (t), 28.3 (t), 28.9 (t), 29.2 (t), 31.5 (t), 35.5 (t), 71.1 (t), 74.8 (d), 84.1 (d), 127.4 (d), 127.8 (d), 128.3 (d), 136.9 (s), 174.9 (s).
    Compound **3d**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.89 (t, J = 7.0 Hz, 6H), 1.11 (d, J = 6.0 Hz, 3H), 1.13 (d, J = 6.0 Hz, 3H), 1.20–1.45 (m, 20H), 1.72 (m, 4H), 2.18 (m, 4H), 2.53 (dd, J = 16.9, 1.9 Hz, 2H), 2.62 (dd, J = 16.9, 4.9 Hz, 2H), 3.46 (m, 2H), 4.15 (ddd, J = 4.2, 4.2, 1.9 Hz, 2H), 4.37 (m, 2H), 5.07 (m, 4H), 5.75 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.8 (q), 18.7 (q), 20.3 (q), 22.4 (t), 25.1 (t), 25.3 (t), 28.3 (t), 28.9 (t), 29.2 (t), 31.5 (t), 36.5 (t), 37.1 (t), 40.4 (t), 41.1 (t), 72.8 (d), 73.6 (d), 73.8 (d), 74.7 (d), 84.2 (d), 84.4 (d), 117.2 (t), 134.1 (d), 175.3 (s).
    Compound **3e**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.88 (m, 6H), 1.15–1.92 (m, 19H), 2.35 (m, 1H), 2.54 (dd, J = 17.3, 2.2 Hz, 1H), 2.64 (dd, J = 17.3, 5.3 Hz, 1H), 3.67 (m, 1H), 4.14 (ddd, J = 5.3, 5.3, 2.2 Hz, 1H), 4.37 (m, 1H), 5.19 (m, 2H), 5.67 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.0 (q), 24.8 (t), 25.3 (t), 25.6 (t), 28.5 (t), 28.7 (t), 28.9 (t), 29.0 (t), 29.1 (t), 29.4 (t), 29.5 (t), 31.6 (t), 31.7 (t), 35.4 (t), 37.6 (t), 74.5 (d), 76.6 (d), 79.5 (d), 82.7 (d), 84.5 (d), 117.2 (d), 118.1 (d), 138.2 (t), 139.5 (t), 175.5 (s).
    Compound **3f**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.90 (t, J = 6.9 Hz, 12 H), 1.22–1.52 (m, 38H), 1.59 (bs, 2H), 1.72 (m, 4H), 1.81 (m, 4H), 2.44 (d, J = 1.8 Hz, 1H), 2.49 (d, J = 1.8 Hz, 1H), 2.49 (dd, J = 17.7, 1.7 Hz, 2H), 2.62 (dd, J = 17.7, 4.7 Hz, 2H), 4.06 (ddd, J = 4.7, 4.7, 1.7 Hz, 2H), 4.48 (m, 2H), 4.48 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1 (q), 22.6 (t), 24.9 (t), 25.0 (t), 25.1 (t), 25.6 (t), 28.4 (t), 28.6 (t), 29.1 (t), 29.2 (t), 29.4 (t), 29.5 (t), 31.7 (t), 35.6 (t), 36.0 (t), 37.2 (t), 67.3 (d), 70.4 (d), 72.8 (d), 74.3 (d), 74.5 (d), 75.7 (d), 83.0 (s), 84.3 (d), 84.4 (d), 175.2 (s).
12. The *cis* relative stereochemistry for γ-lactone **3** was determined by nOe studies and ^{1}H–^{1}H coupling constants.



13. In this method, for each drug a dose–response curve is generated and three levels of effect can be calculated, when possible. The effect is defined as percentage of growth (PG), where 50% growth inhibition (GI_{50}), total growth inhibition (TGI), and 50% cell killing (LC_{50}) represent the drug concentration at which PG is +50, 0, and −50, respectively Skehan, P.; Storeng, P.; Scudeiro, D.; Monks, A.; McMahon, J.; Vistica, D.; Warren, J. T.; Bokesch, H.; Kenney, S.; Boyd, M. R. *J. Natl. Cancer Inst.* **1990**, *82*, 1107.
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