

## SYNTHESIS OF BOTH ENANTIOMERS OF FOUR DIFFERENT MACROCYCLIC LACTONES

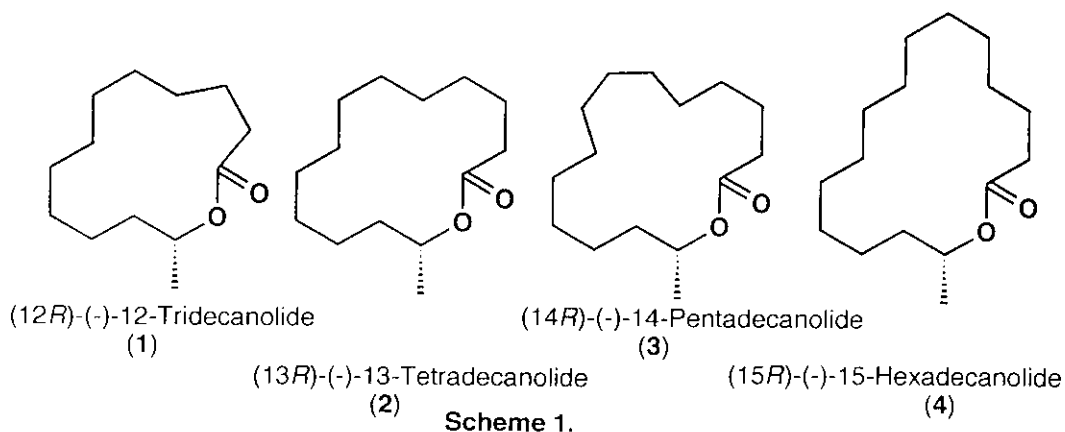
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Dedicated to Professor Dr. Dieter Seebach, on the occasion of his 60th birthday.

**Abstract---** Both enantiomers of macrocyclic lactones, 12-tridecanolide (**1**), 13-tetradecanolide (**2**), 14-pentadecanolide (**3**) and 15-hexadecanolide (**4**), were synthesized utilizing (S)-(-)- $\beta$ -hydroxythioacetal (**5**) as the chiral building block. Key steps are the C-alkylation of a dianion derived from **5** with alkyl dibromides followed by conversion of functional groups and the two macrolactonization. The both enantiomers of **1~4** have been obtained by reductive desulfurization of the dithiane moiety.

12-Tridecanolide (**1**), 13-tetradecanolide (**2**), 14-pentadecanolide (**3**) and 15-hexadecanolide (**4**) were isolated by Kaiser and Lamparsky<sup>1</sup> as trace components of Galbanam oleo-gum-resin, the dried latex of *Ferula galbaniflua* BOISSIER et BÜHSE and *F. rubicaulis* BOISSIER (*Umbelliferae*). Galbanum is widely used in perfumery. These macrocyclic lactones possess an interesting musk-like fragrance. The absolute configurations of these natural



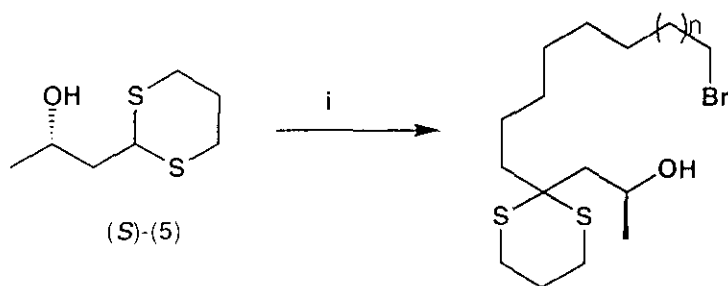
macrocyclic lactones were determined as (*R*) by the syntheses of Gerlach<sup>2</sup> and Hesse<sup>3</sup>

Recently, Bestmann *et al.*<sup>4</sup> synthesized (*R*)-(-)-**1**, **2** and **4** from bromoacetals and (*R*)-1,2-epoxypropane. Tochtermann *et al.*<sup>5</sup> synthesized both enantiomers of 13-tetradecanolide (**2**) using ring enlargement reactions.

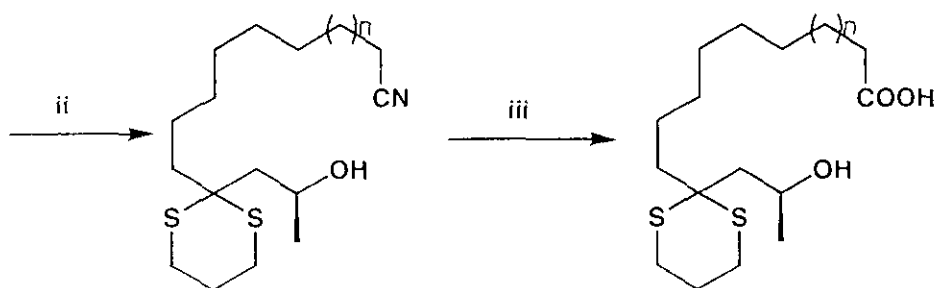
In this paper, we report the synthesis of both enantiomers of 12-tridecanolide (**1**), 13-tetradecanolide (**2**), 14-pentadecanolide (**3**) and 15-hexadecanolide (**4**) from (*S*)-(-)- $\beta$ -hydroxythioacetal [(*S*)-(-)-1-(1,3-dithian-2-yl)-2-propanol] (**5**)<sup>6</sup> as a chiral building block.

Optically active  $\beta$ -hydroxythioacetal (*S*)-(**5**) was easily obtained by the Baker's yeast asymmetric reduction of (1,3-dithian-2-yl)acetone in good yield (85% yield) with excellent optical purity (>99% ee) and has already been used as a building block for the synthesis of natural products.<sup>6,7</sup>

The transformation of (*S*)-**5** into the dianion (**6**) was achieved by reaction with 2.2 eq. of *n*-BuLi in THF at -20 °C. The dianion (**6**) was treated with 1.1 eq. of alkyl dibromide (**7a**, dibromooctane; **7b**, dibromononane; **7c**, dibromodecane; **7d**, dibromoundecane) and the C-alkylation products (*S*)-(**8**) were obtained. The reaction of (*S*)-**8** with NaCN in aq. EtOH afforded the nitriles (*S*)-(**9**), which on successive alkaline hydrolysis gave the hydroxy acids (*S*)-(**10**). The remaining problem was the ring closure step, which was achieved either with retention of configuration by Gerlach's modification<sup>8</sup> of the Mukaiyama-Corey method<sup>9</sup> or with



(8a) n=1 57%  $[\alpha]_D^{24} + 17.6^\circ$  (c 0.83 CHCl<sub>3</sub>)  
 (8b) n=2 57%  $[\alpha]_D^{25} + 16.1^\circ$  (c 2.10 CHCl<sub>3</sub>)  
 (8c) n=3 55%  $[\alpha]_D^{21} + 15.6^\circ$  (c 0.69 CHCl<sub>3</sub>)  
 (8d) n=4 53%  $[\alpha]_D^{26} + 14.4^\circ$  (c 0.64 CHCl<sub>3</sub>)



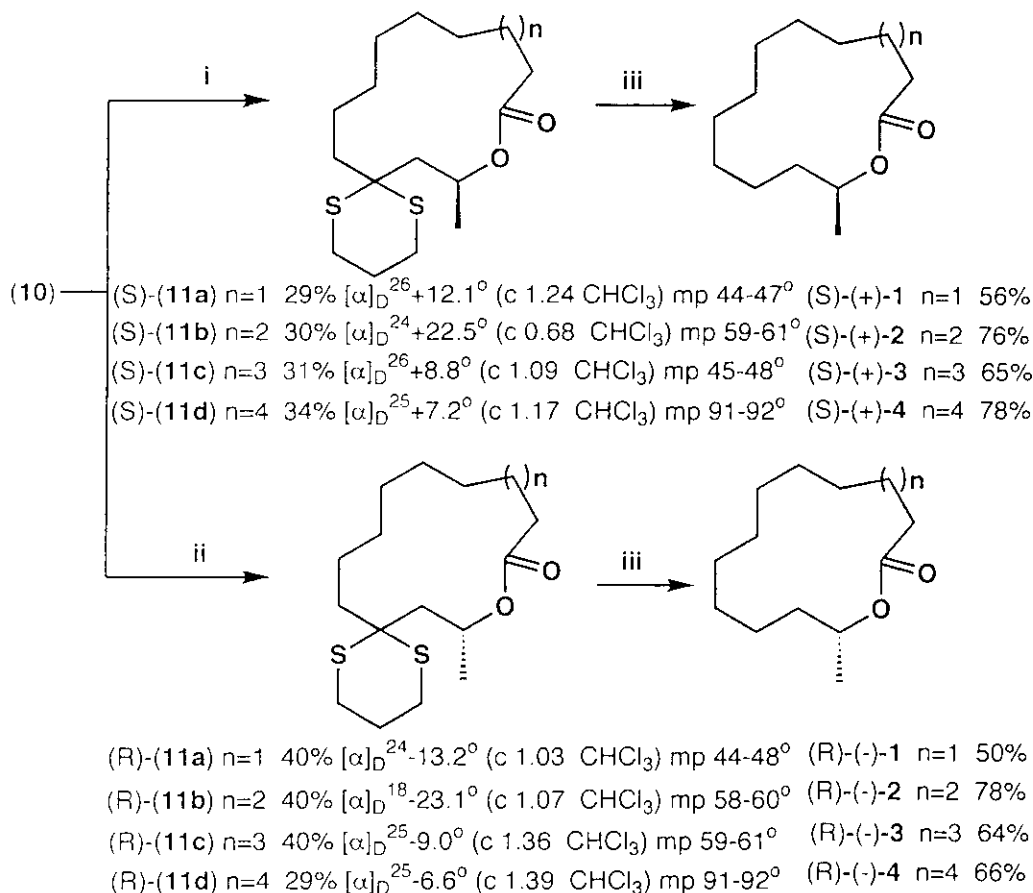
(9a) n=1 86%  $[\alpha]_D^{22} + 19.5^\circ$  (c 0.73 CHCl<sub>3</sub>) (10a) n=1 85%  $[\alpha]_D^{23} + 18.2^\circ$  (c 0.94 CHCl<sub>3</sub>) mp 28-31°  
 (9b) n=2 88%  $[\alpha]_D^{22} + 18.1^\circ$  (c 0.72 CHCl<sub>3</sub>) (10b) n=2 89%  $[\alpha]_D^{26} + 17.1^\circ$  (c 0.93 CHCl<sub>3</sub>) mp 75-77°  
 (9c) n=3 86%  $[\alpha]_D^{22} + 17.8^\circ$  (c 1.61 CHCl<sub>3</sub>) (10c) n=3 85%  $[\alpha]_D^{19} + 16.7^\circ$  (c 0.99 CHCl<sub>3</sub>) mp 35-37°  
 (9d) n=4 88%  $[\alpha]_D^{20} + 17.2^\circ$  (c 0.57 CHCl<sub>3</sub>) (10d) n=4 84%  $[\alpha]_D^{26} + 16.0^\circ$  (c 1.02 CHCl<sub>3</sub>) mp 78-80°

**Scheme 2.** Reagents and conditions: (i) 2.4 eq. n-BuLi, THF, alkyl dibromide (7a, dibromooctane. 7b, dibromononane. 7c, dibromodecane. 7d, dibromoundecane), -20 °C; (ii) NaCN, EtOH-H<sub>2</sub>O, reflux; (iii) KOH, EtOH-H<sub>2</sub>O, reflux.

inversion at the chiral centre using a Mitsunobu lactonization method.<sup>10</sup>

Lactonization method 1: hydroxy acids (S)-(10) were cyclized via the pyridinethiol esters on refluxing in toluene in the presence of AgClO<sub>4</sub><sup>9</sup> to give dithiolactones (S)-(11) with retention of configuration.

Lactonization method 2: the reaction of hydroxy acids (S)-(10) with diethyl azodicarboxylate and triphenylphosphine went to completion within 1 day at reflux giving the inverted configuration dithiolactones (R)-(11). Therefore we are able to obtain both enantiomers of dithiolactones (11).



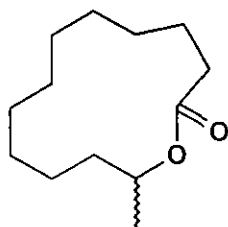
**Scheme 3.** Reagents and conditions: (i) 1) Ph<sub>3</sub>P, dipyridyl disulfide, MeCN, 2) AgClO<sub>4</sub>, toluene, reflux; (ii) Ph<sub>3</sub>P, diethyl azodicarboxylate, toluene, reflux; (iii) Raney Ni, EtOH, reflux.

Finally, dithiolactones (S)-(1) and (R)-(1) were reduced to methylene units with W-2 Raney Ni in refluxing EtOH providing the target lactones (-)-(1) and (+)-(1), (-)-(2) and (+)-(2), (-)-(3) and (+)-(3), (-)-(4) and (+)-(4), respectively.

The <sup>1</sup>H-, <sup>13</sup>C-NMR and IR spectra of synthetic lactones (1)~(4) completely coincided with those of natural products.

In summary, we have achieved the synthesis of both enantiomers of four different macrocyclic lactones (1)~(4) from (S)-(-)-β-hydroxythioacetal (5) and alkyl dibromides. The (S)-(-)-β-hydroxythioacetal (5) should also be useful as a chiral building block for other purposes. The new strategy described here also offers an approach to other macrocyclic

lactones of differing ring size, because many alkyl dibromides are readily available.

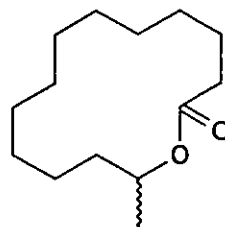


(12*R*)-(-)-1  $[\alpha]_D^{23} -19.4^\circ$  (c 1.15, CHCl<sub>3</sub>)

(12*S*)-(+)-1  $[\alpha]_D^{25} +18.4^\circ$  (c 0.85, CHCl<sub>3</sub>)

lit.,<sup>1</sup>  $[\alpha]_D^{20} -20.8^\circ$  (c 0.13, CHCl<sub>3</sub>)

lit.,<sup>4</sup>  $[\alpha]_D -17.5^\circ$  (c 1.95, EtOH)



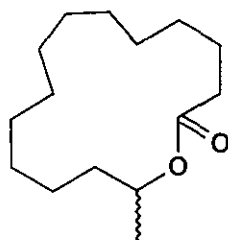
(13*R*)-(-)-2  $[\alpha]_D^{21} -36.5^\circ$  (c 1.14, CHCl<sub>3</sub>)

(13*S*)-(+)-2  $[\alpha]_D^{20} +32.8^\circ$  (c 0.30, CHCl<sub>3</sub>)

lit.,<sup>1</sup>  $[\alpha]_D -33.8^\circ$  (c 1.04, CHCl<sub>3</sub>)

lit.,<sup>2</sup>  $[\alpha]_D -34.5^\circ$  (c 1.64, CHCl<sub>3</sub>)

lit.,<sup>5</sup>  $[\alpha]_D -38.2^\circ$  (c 2.0, CHCl<sub>3</sub>)

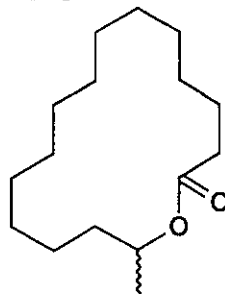


(14*R*)-(-)-3  $[\alpha]_D^{23} -25.5^\circ$  (c 0.58, CHCl<sub>3</sub>)

(14*S*)-(+)-3  $[\alpha]_D^{25} +22.9^\circ$  (c 0.44, CHCl<sub>3</sub>)

lit.,<sup>1</sup>  $[\alpha]_D^{20} -20.2^\circ$  (c 0.59, CHCl<sub>3</sub>)

lit.,<sup>2</sup>  $[\alpha]_D -23.8^\circ$  (c 1.48, CHCl<sub>3</sub>)



(15*R*)-(-)-4  $[\alpha]_D^{26} -15.4^\circ$  (c 1.01, CHCl<sub>3</sub>)

(15*S*)-(+)-4  $[\alpha]_D^{25} +19.1^\circ$  (c 1.22, CHCl<sub>3</sub>)

lit.,<sup>1</sup>  $[\alpha]_D^{20} -16.5^\circ$  (c 1.03, CHCl<sub>3</sub>)

lit.,<sup>4</sup>  $[\alpha]_D -18.9^\circ$  (c 1.06, CHCl<sub>3</sub>)

**Scheme 4.** Configuration and specific rotation value

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