

Aldol Reactions of Dioxanes Derived  
from Tartaric Acid. A Total Synthesis of  
(+)-Nephrosteranic Acid

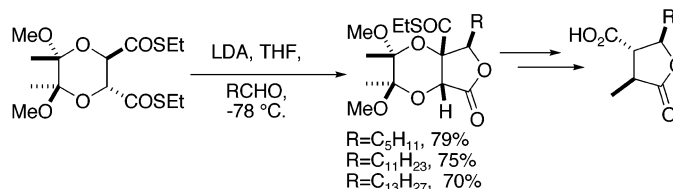
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## ABSTRACT



A general enantioselective synthesis of the paraconic acids was developed. The key step was a highly stereoselective aldol reaction between a dioxane dithioester derived from L-tartaric acid and a suitable aldehyde.

Paraconic acids are a family of chiral trisubstituted  $\gamma$ -butyrolactones with a carboxylic acid at the  $\beta$  position, isolated from various species of moss, lichens, and fungus. They possess important biological activities, such as antitumor, antibiotic, antifungal, and antibacterial.<sup>1</sup> Due to their important potential pharmacological applications, several total and formal total syntheses of members of this class of compounds have been described in both racemic and optically active forms.<sup>2–4</sup> Surprisingly, (+)-nephrosteranic acid **1**<sup>2</sup> (Figure 1), with an 11-carbon alkyl chain at the  $\gamma$  position, has been the least often prepared of the most common members of this important group of natural products.

Here, we describe the enantioselective syntheses of natural (+)-nephrosteranic acid **1**, the natural enantiomer, and the formal syntheses of the analogues **2–7** (Figure 1). (+)-

Tartaric acid was used as the starting material, a useful chiral building block, for the asymmetric synthesis of natural products.<sup>5</sup> Seebach<sup>6</sup> and Evans<sup>7</sup> have previously used the enolates prepared from dioxolanes derived from tartaric acid for aldol reactions and the synthesis of complex polyhydroxylated molecules. The dioxane **8** (Scheme 1), readily available from tartaric acid,<sup>8</sup> was predicted to be a good

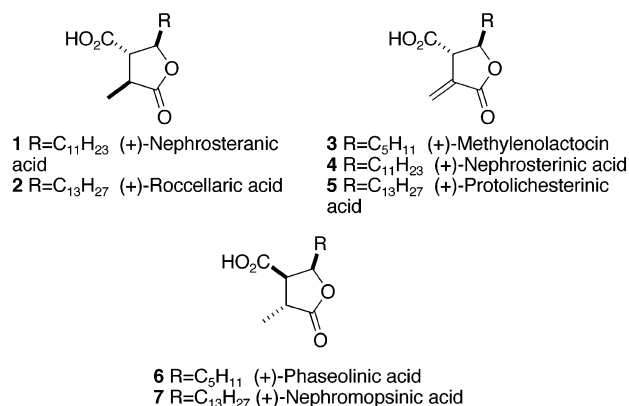
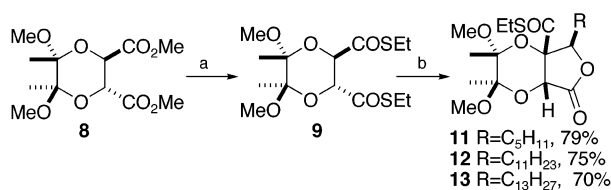


Figure 1.

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Scheme 1<sup>a</sup>

<sup>a</sup> Key: (a) EtSH, CH<sub>2</sub>Cl<sub>2</sub>, Me<sub>3</sub>Al, 0 °C/rt, 99%; (b) LDA, THF, RCHO, -78 °C.

candidate for stereoselective aldol reactions since it has a conformationally rigid structure which could enhance diastereoselectivity. Preliminary studies on the deprotonation of (2*R*,3*R*,5*R*,6*R*)-dimethoxy-2,3-dimethyl-1,4-dioxane-5,6-dicarboxylate **8** derived from tartaric acid<sup>6,8</sup> showed that the ester enolates underwent a novel ring contraction reaction. To avoid this, it was converted to its dithioester **9** by treatment with ethanethiol and trimethylaluminum (Scheme 2). Treatment of **9** with 2.2 equiv of LDA and quenching

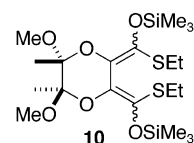


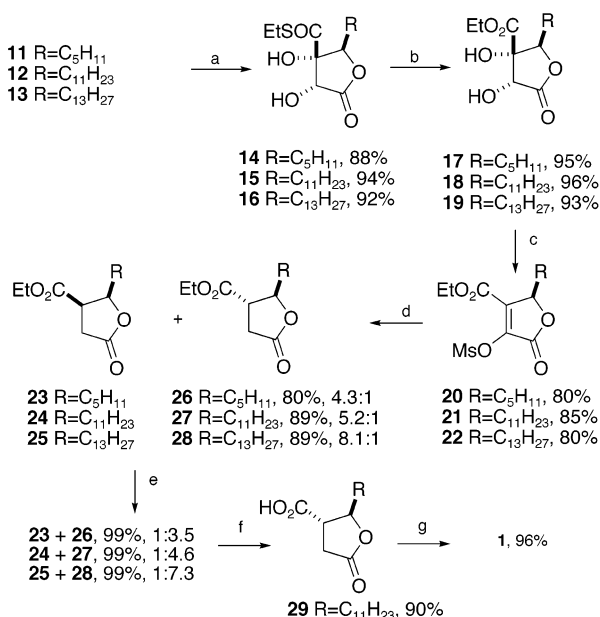
Figure 2.

acetal would serve as an effective chiral adjunct and direct reactions of the bis enolate.

In the presence of 2.2 equiv of LDA, the dienolate of dioxane **9** was generated, which upon quenching with a suitable aldehyde formed the corresponding lactones **11**–**13** in good yields (typically 75%) and with very high stereoselectivity, since only one of the possible isomers was isolated (Scheme 1). The absolute configuration of the lactone obtained was assigned as (4*R*,5*S*), by comparison with previous unpublished results.<sup>9</sup> Lactones **11**–**13** were the key intermediates for the synthesis of the target compounds. The synthesis of (+)-nephrosteranic acid was completed in order to verify this assignment.

Hydrolysis of the dioxane acetal of aldol product **12** was easily accomplished with ethanedithiol and BF<sub>3</sub>·OEt<sub>2</sub> to afford the diol **15** in 94% yield (Scheme 2). Transesterification with 1 equiv of sodium ethoxide in ethanol afforded the ethyl ester **18**, also in very good yield (96%). Mesylation occurred with spontaneous elimination (Scheme 2) to afford the labile enolmesylate **21** in 85% yield.

Catalytic hydrogenation (10% Pd/C) of **21** was effected in the presence of sodium acetate at 50 bar of H<sub>2</sub> during which three processes took place: (i) hydrogenation of the double bond, (ii) elimination of the remaining mesylate group, and finally (iii) hydrogenation of this newly formed double bond. The amount of palladium present was crucial to the success of this reaction. If insufficient Pd was added, double-bond isomerization competed efficiently with the hydrogenation and the eventual major product became **31**

Scheme 2<sup>a</sup>

<sup>a</sup> Key: (a) BF<sub>3</sub>·OEt<sub>2</sub>, HS(CH<sub>2</sub>)<sub>2</sub>SH, CH<sub>2</sub>Cl<sub>2</sub>, 80 °C; (b) NaOEt, EtOH, THF, 0 °C; (c) MsCl, (*i*-Pr)<sub>2</sub>NEt, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C; (d) H<sub>2</sub>, Pd/C, NaOAc, MeOH, AcOEt, rt; (e) DBU, CH<sub>2</sub>Cl<sub>2</sub>, rt; (f) HCl 6 N, dioxane, 110 °C; (g) NaN(TMS)<sub>2</sub>, MeI, THF, -78 °C.

with TMSCl afforded an unstable low-melting solid compound ([α]<sub>D</sub><sup>20</sup> +26.2 (*c* 0.88 CH<sub>2</sub>Cl<sub>2</sub>)), which presented a simple <sup>1</sup>H NMR spectrum with signals for a TMS group but no methine protons. MS and <sup>13</sup>C NMR also supported the conclusion that this product was the bis ketene acetal **10** (Figure 2), which indicated that both acidic protons were easily removed. Chiral information, except at the acetal, is lost on deprotonation; however, it was predicted that this

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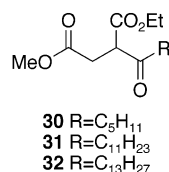
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(9) This assignment is based upon the structure of the principal lactonic aldol product, obtained by reaction of dienolate **10** with benzaldehyde, determined by X-ray crystallography, Lou, J. D. Ph.D. Dissertation, New University of Lisbon, Oeiras, 2001.



**Figure 3.**

(Figure 3). We think that Pd(II) was generated in situ and this promoted the isomerization.<sup>10</sup> Similarly, hydrogenation of mesylates **20** and **22** with insufficient palladium afforded ketodiester **30** and **32**, respectively.

The two saturated diastereoisomers **24/27** (89%) were obtained with a cis/trans ratio of 5.2:1. Isomerization with DBU<sup>4e,f</sup> (**3d**) afforded mainly the trans isomer (1:4.6 **24/27**, 99%), as expected. After acid-catalyzed hydrolysis,<sup>4b</sup> the acid **29** was exclusively obtained in 90% yield and the cis starting material recovered unreacted. The final reaction,  $\alpha$ -alkylation with methyl iodide and sodium bis(trimethylsilyl)amide as the base,<sup>4b</sup> furnished (+)-nephrosteranic acid **1**, [ $\alpha$ ]<sub>D</sub><sup>25</sup> +27.8 (*c* 0.6, CHCl<sub>3</sub>) (lit.<sup>2b</sup> [ $\alpha$ ]<sub>D</sub><sup>25</sup> +27.2 (*c* 1.45, CHCl<sub>3</sub>), enantiomer lit.<sup>2a</sup> -28.1 (*c* 1.02, CHCl<sub>3</sub>)) in 96% yield, and 3% of starting material **29** was recovered. The overall yield was 43%, and the same reaction sequence was followed for the 5-carbon and 13-carbon chain analogues (Scheme 2). From lactone **11**, the esters **23** and **26** were prepared, and conversion of these compounds to (+)-phaseolinic acid **6**

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(Figure 1) and (+)-methylenolactocin **3** (Figure 1) by hydrolysis and alkylation, as for the C-11 analogues, has been reported in the literature.<sup>4b</sup> Similarly, from lactone **13** were obtained esters **25** and **28**, and again these would furnish (+)-roccellaric acid **2**<sup>3b</sup> and (+)-protolichesterinic acid **5** by applying the same methodology. It is interesting to notice that the length of the carbon side chain influenced the diastereoselectivity of the hydrogenation reaction, with larger groups favoring the cis isomer. The same tendency, but for the trans isomer, was noticed in the isomerization reaction with DBU. The flexibility of this strategy is also supported by the fact that the enantiomers of all these compounds can be synthesized starting from (–)-tartaric acid. Cis-4,5 derivatives such as (+)-nephromopsinic acid **7** (Figure 1) should also be attainable if the isomerization with DBU is eliminated.

In conclusion, the aldol reactions of enolates derived from dioxane **9** afford, stereoselectively, lactones having the correct stereochemistry for an efficient and general enantioselective route to natural paraconic acids. This has been demonstrated by the total synthesis of (+)-nephrosteranic acid and the formal syntheses of other members of this family of natural products.

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**Supporting Information Available:** Experimental procedures and spectroscopic data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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