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# A formal synthesis to (+)-nephrosteranic acid from chiral nitroalkyl derivatives

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ABSTRACT

A concise and versatile formal synthesis to (+)-nephrosteranic acid was accomplished from a common nitroderivative **2** in a sequence of six steps. The adduct **2** was obtained via a highly *syn*-diastereoselective conjugate addition of 1-dodecyl nitronate ion to chiral enoate *Z*-**5** (yield = 80%; de = 95%), derived from D-(+)-mannitol.



(+)-Nephrosteranic acid belongs to the paraconic acid family which is involved in many important biological activities including antitumor,[1] antifungal,[2] antibacterial,[2,3] and anti-inflammatorial.[4] Structurally, this family comprises a carboxyl group in C-4 position, a methyl or methylene group in C-3 position and different alkyl substituents in C-5 position in varied spatial arrangements. A double bond between C-3 and C-4 is also encountered (Fig. 1).

Today, nearly 25 different paraconic acids have been isolated from diverse natural sources,[5] such as various species of mosses, lichens, and fungus. Interestingly, some paraconic acids were isolated in both enantiomeric forms.[5a]

There are a number of racemic[6] as well as enantioselective total[7–10] and formal syntheses[11] to paraconic acids that utilize distinct synthetic strategies.

Based on our strategy, which utilizes chiral nitroderivatives obtained via chiron approach as useful synthetic intermediates in natural products syntheses, we report a versatile and concise route for the formal synthesis of (+)-nephrosteranic acid from nitroderivative **2**, obtained from D-(+)-mannitol (Scheme 1).

We hypothesized that (+)-nephrosteranic acid precursor **1** could be synthesized via a transformation of the 1,2-diacetonide group of **4** in the necessary carboxyl group by a one-pot sequence (deprotection, vicinal diol oxidative cleavage and oxidation of the corresponding formed aldehyde). On the other hand, the intermediate **4** would be obtained via one-pot sequence involving the *anti*-diastereoselective reduction of keto function of **3** with simultaneous lactonization. The β-acylester **3** would be formed via an oxidative Nef reaction[12,13] of the intermediate **2**. This would be synthesized via a *syn*-selective conjugate addition of 1-dodecyl nitronate anion to the known *Z*-enoate **5**,[14] obtained from D-(+)-mannitol, similar to that described by us.[15]

Initially the nitroderivative **2** was synthesized via a *syn*-stereoselective conjugate addition of 1-dodecyl nitronate anion, generated by treatment of 1-nitrododecane (**6**)[16] with DBU (1 equiv), to *Z*-enoate **5**. This was easily synthesized from D-(+)-mannitol in three steps.[14] As expected,[15b] **2** was obtained in high de (95%) at the C-3 stereocenter and as a mixture of epimers at C–$NO_2$ stereocenter (1.0:1.2) (Scheme 2).

The *syn* stereochemistry of **2** was unambiguously determined by transformation of the mixture of nitroderivatives **2** in the butyrolactone **7**[21] (Scheme 2). As previously reported,[15b,15c] the cis-relationship between H-3 and H-4 in lactone **7,** and thus the *syn*-stereochemistry in adduct **2**, was determined by the coupling constant ($J_{3,4}$) 7.8 Hz and confirmed by NOE effect. Irradiation at H-4 ($\delta$ 4.58) led to an enhancement of 2.6% in intensity of H-3 ($\delta$ 3.48).

To explain the kinetic *syn*-selectivity in **2**, we proposed a twisted *antiperiplanar* approach[15b] of the nitronate anion to the less hindered enoate *Re* face of the Felkin-Anh type transition state model A[17] (Fig. 2). The attack of the prochiral *re* face of the nitronate ion to *Z*-**5** should be more favorable since the more bulky group ($-C_{11}H_{23}$) of the incoming nucleophile assumes the less hindered outside position. In this manner, an additional stereocenter bearing the nitro group (C–$NO_2$) with the *S* stereochemistry should be formed. However, due to fast equilibration in the basic media, this stereochemical information is lost and an epimeric mixture is obtained.

Scheme 3 shows the steps of conversion of **2** in **1**. Thus, the transformation of **2** into ketone **3** was accomplished, in 71% yield and de = 95%, using the Nef reaction. Several protocols were investigated and Gissot's protocol ($NaNO_2$ 2.0 equiv/DMSO:$H_2O$/60 °C)[13] was used. Initially, this protocol furnished the ketone **3** in 40% yield and the corresponding oxime derivative as a byproduct in 25% yield. After a small modification ($NaNO_2$, 6 equiv was used instead 2 equiv), we were able to obtain the ketone in high yield without the formation of byproducts. Gissot's protocol beyond leading to the best yield, utilizes a neutral medium that inhibits a possible epimerization in the C-3 stereocenter.

The diastereoselective reduction of keto group of **3** was accomplished using sodium borohydride in THF, in the presence of $MnCl_2$[18] as a metal-chelating agent leading to the direct production (reduction followed by lactonization) of lactone derivative **4** in 84%

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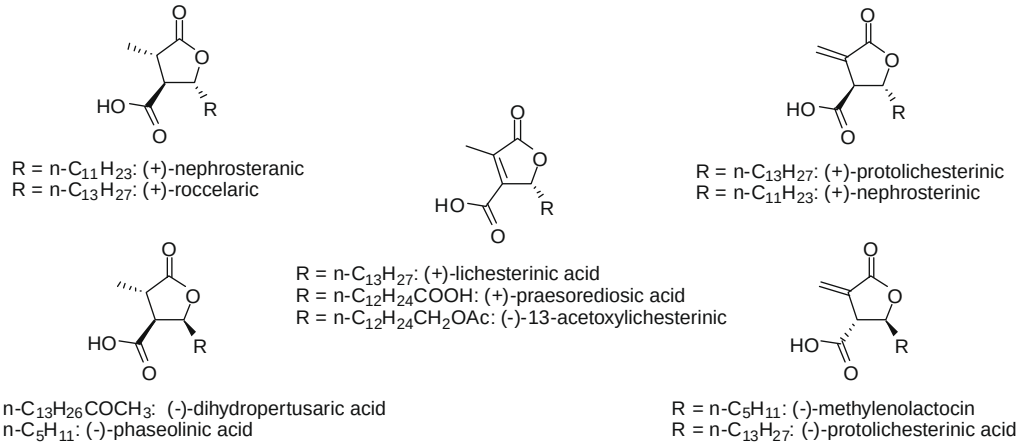
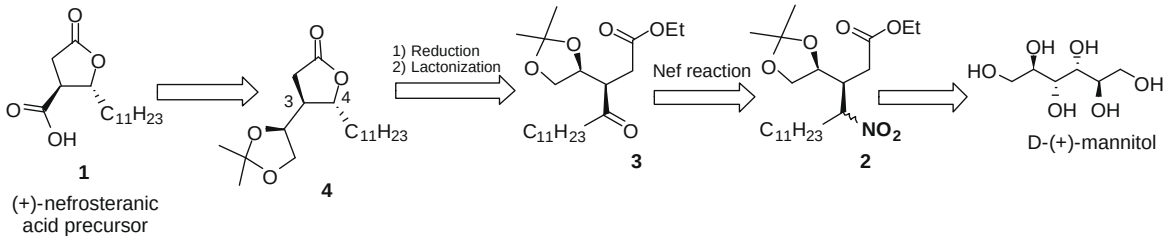
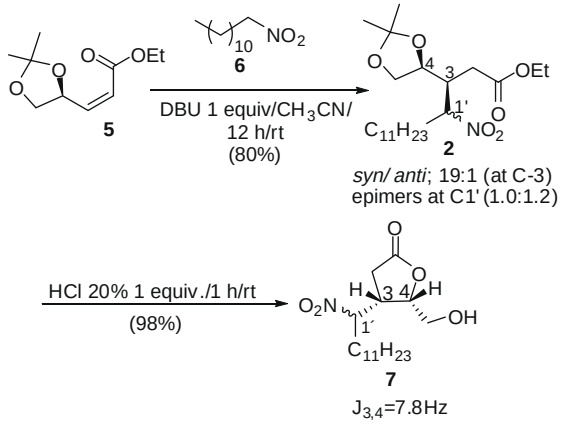


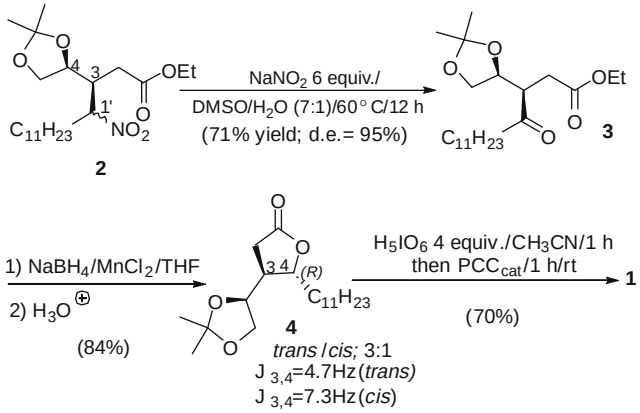

**Figure 1.** Some paraconic acids found in nature.




**Scheme 1.** Retroanalysis to obtain **1** from **2**.




**Scheme 2.** Synthesis of **3** from ***Z*-5**.




**Scheme 3.** Synthesis of **1** from **2**.

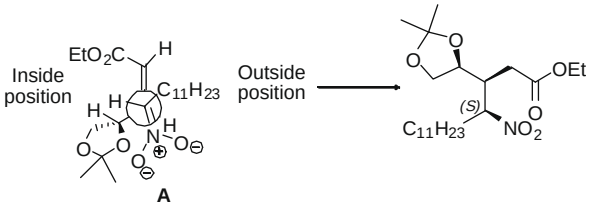
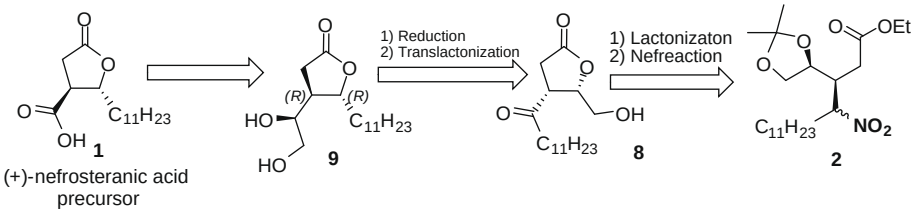


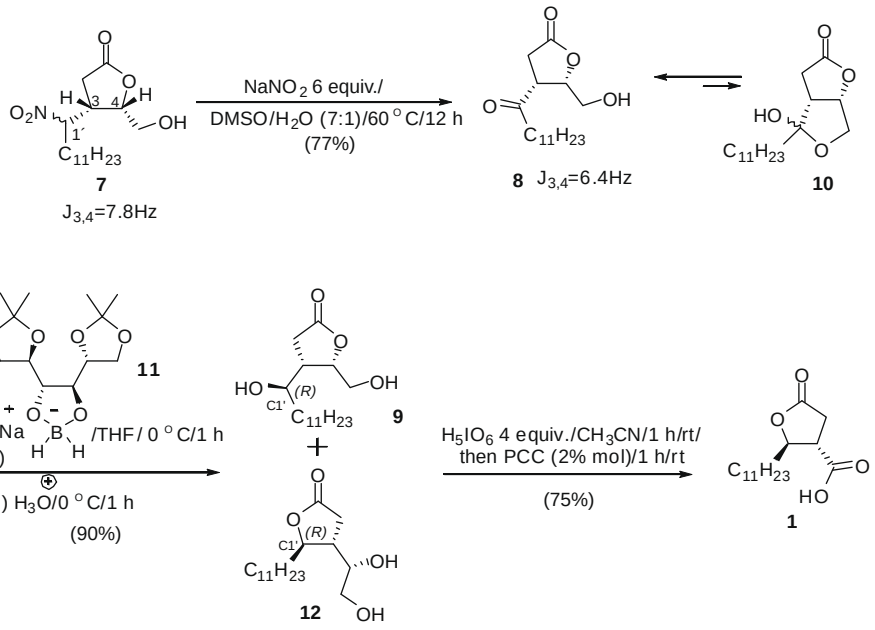

**Figure 2.** Twisted *antiperiplanar* approach of prochiral nitronate (*re* face) in type Felkin-Anh transition state model A.

yield as an epimeric ratio at C4 of 3:1. Other reductive systems were investigated ($NaBH_4$, $NaBH_4/CeCl_3$, K-Selectride, and DIBAL)[19] but were found to be less selective. Treatment of ketal derivative **4** with periodic acid ($H_5IO_6$ 4.0 equiv) led to the corresponding diol which suffered subsequent oxidative cleavage to necessary aldehyde. This was oxidized to (+)-nephrosteranic acid precursor **1** via the addition of catalytic amount of PCC (0.02 mol) using the remaining periodic acid of the media as reoxidant.[20] The three steps were processed in one-pot, in a global 70% yield with maintenance of the trans-stereoselectivity.

Due to the low stereoselectivity obtained in the reduction step of **3**, we propose as an alternative modification in the route originally imagined to **1** (Scheme 4). Thus, **1** could be synthesized from diol derivative **9** by a similar sequence employed in **4** (vicinal diol oxidative cleavage and the oxidation of the corresponding aldehyde formed). On the other hand, **9** would be obtained by an *anti*-diastereoselective reduction of the keto-derivative **8**, followed by a translactonization mediated by acid. Finally, **8** would be obtained from a common intermediate **2** via a lactonization step followed by a Nef reaction.




**Scheme 4.** Retroanalysis to obtain **1** from **2**.




**Scheme 5.** Synthesis of **1** from **2**.

Thus, as proposed the mixture of butyrolactones **7** obtained from lactonization of **2** (Scheme 2) was submitted to Nef reaction using Gissot's protocol leading to keto-butyrolactone derivative **8** ($J_{3,4}$ = 6.4 Hz) in equilibrium with its furanosidic form **10**, in 77% yield and diastereoisomeric excess of 95% (Scheme 5). The keto group in **8** was diastereoselectively reduced with the use of the chiral hydride $NaBH_2$ (mannitol diacetonide) **11**[22] prepared in 80% yield from D-(+)-mannitol diacetonide/$NaBH_4$/THF/2 h/rt. As verified by $^1$H NMR, a mixture of butyrolactones **9** and **12** was formed in 90% yield as an epimeric ratio at C1′ of 6:1 (*R*:*S*). The butyrolactone mixture was reacted, in one-pot, with $H_5IO_6$ (1 h) and then with a catalytic amount of PCC (0.02% mol, 1 h) to produce the desired (+)-nephrosteranic acid precursor **1**[23] in 75% yield and 85.7% de. The confirmation of the chemical stereostructure to **1** was accomplished by comparison with spectroscopic data of the same compound synthesized via the first route. A separation of the diastereoisomeric mixture of **1** could be accomplished in a similar manner described by Barros[7d] or Amador[9e] through esterification and chromatography separation. As already related,[7d,8a] a trans-stereoselective introduction of methyl group at α-carbonyl position of **1** will lead to the total synthesis of (+)-nephrosteranic acid.

The advantages of this route include the use of the readily available and inexpensive starting materials and operational simplicity besides the potential to obtain different paraconic acids, whereas varied carbonic chains can be efficiently introduced at *Z*-enoate **5** using the conjugate addition of different nitronate anions, in high *syn*-diastereoselectivity and good yields. Whereas both enantiomeric forms of acceptor **5** can be easily obtained from natural vitamin C[24] or D-(+)-mannitol[14] both enantiomers of paraconic acids can also be synthesized. On the other hand, the reduction step can be directed to the necessary stereochemistry using diverse commercial chiral hydrides.

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21. (4*S*,5*S*)-5-(Hydroxymethyl)-4-(1-nitrododecyl)dihydrofuran-2(3*H*)-one (**9**):white solid; one of the diastereoisomer at C1′ separated by chromatography: $^{1}$H NMR (400 MHz, $CDCl_3$) $\delta$ ppm 4.96 (dt, $J$ = 11.0, 6.3 Hz, 1H) 4.58 (dt, $J$ = 7.7, 1.4 Hz, 1H) 4.00 (d, $J$ = 13.2 Hz, 1H) 3.73 (d, $J$ = 13.3 Hz, 1H) 3.40 (dddd, $J$ = 12.2, 10.7, 9.6, 7.9 Hz, 1H) 3.29 (s, 1H) 2.66 (dd, $J$ = 16.9, 12.5 Hz, 1H) 2.48 (dd, $J$ = 16.9, 9.5 Hz, 1H) 1.81–1.92 (m, 2H) 1.17–1.38 (m, 18H) 0.88 (t, $J$ = 7.0, 6.6 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ ppm 175.80, 87.05, 80.43, 61.39, 40.25, 33.58, 31.80, 29.47, 29.33, 29.22, 29.14, 28.81, 24.72, 22.58, 14.02, IR (KBr): 3444, 2954, 2920, 2853, 1775, 1554, 1470, 1421, 1371, 1069. MS (70 eV) $m/z$ (%) 203 (2), 191 (2), 147 (5), 109 (10), 95 (20), 81 (30), 69 (40), 55 (70), 43 (100).
22. Based on works of: Brown, H. C.; Cho, B. T.; Park, W. S. *J. Org. Chem.* **1987**, *52*, 4020–4024.
23. (2*R*,3*S*)-5-Oxo-2-undecyltetrahydrofuran-3-carboxylic acid (**1**):pale yellow solid, diastereoisomeric mixture (6:1), major isomer: $^{1}$H NMR (400 MHz, $CDCl_3$) 4.63 (td, $J$ = 7.5, 4.7 Hz, 1H), 3.09 (ddd, $J$ = 9.5, 8.3, 7.0 Hz, 1H), 2.94 (dd, $J$ = 17.9, 8.3 Hz, 1H), 2.82 (dd, $J$ = 17.9, 9.7 Hz, 1H), 1.71–1.86 (m, 2H), 1.19–1.38 (m, 21H), 0.88 (t, $J$ = 6.6 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) 175.39, 175.01, 81.90, 45.35, 35.33, 31.86, 29.55, 29.46, 29.35, 29.28, 29.14, 25.13, 22.63, 14.05 IR (KBr): 3133, 2955, 2921, 2851, 1749, 1238, 721. MS (70 eV) $m/z$ (%): 266 (([M$^+$]-18, 5), 238 (10), 225 (10), 140 (20), 127 (30), 118 (50), 101 (65), 83 (50), 55 (100).
24. (a) Hubschwerlen, C. *Synthesis* **1986**, 962–964; (b) Hubschwerlen, C.; Specklin, J. L.; Higelin, J. *Org. Synth.* **1995**, *72*, 1–5.