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An efficient enantioselective approach to multifunctionalized γ -butyrolactone: concise synthesis of (+)-nephrosteranic acid†

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A short, efficient and novel approach for multifunctionalized γ -butyrolactone paraconic acids and its application to the total synthesis of (+)-nephrosteranic acid from readily available PMB (R)-glycidyl ether as a starting material are described. Key transformations include asymmetric Michael addition catalyzed by chiral diphenylprolinol silvl ether and stereoselective α -methylation.

Bioactive natural products containing a multifunctionalized γ -butyrolactone moiety are found abundantly in nature.¹ The paraconic acids (1–10) containing multifunctionalized γ -butyrolactone were isolated from various species of lichens, fungi, moss and cultures of *Penicillium* sp.² These acids possess interesting biological activities such as antitumor, antibacterial, antibiotic, antifungal/antiviral and growth regulatory properties.³ The whiskey lactone 11 and cognac lactone 12 have great commercial interest because they are potential key components in the flavor of aged alcoholic beverages.⁴ Architecturally, the paraconic acid family comprises a variable length alkyl chain at the C5 position, a C4 carboxyl group and methyl or methylene substituents at the C3 position, which play an important role in the biological activities of the paraconic acids (Fig. 1).

Intrigued by the unique structural features and biological activities of paraconic acids, hitherto, several total³ and formal⁶ synthesis of paraconic acids such as (+)-nephrosteranic acid are documented in literature. More recently, Appayee and coworkers disclosed an elegant approach for the stereodivergent synthesis of chiral paraconic acids via dynamic kinetic resolution of 3-acylsuccinimides.⁷ As part of our research program aimed at developing the asymmetric synthesis of bioactive natural molecules,⁸ we became attentive in developing a flexible and general approach for the synthesis of multifunctionalised γ -butyrolactone paraconic acids. Herein, we are reporting a short, efficient and novel general approach for the synthesis of paraconic acids and its application to the enantioselective synthesis of (+)-nephrosteranic acid 1 using organocatalyzed Michael addition reaction as key step.

Our general retrosynthetic route for asymmetric synthesis of γ -butyrolactone based paraconic acids and its application to enantioselective synthesis of (+)-nephrosteranic acid **1** was envisaged via the retrosynthetic approach as displayed Scheme 1. We envisioned that the γ -butyrolactone **13** could be used as a key intermediate from which paraconic acids **1–10** including

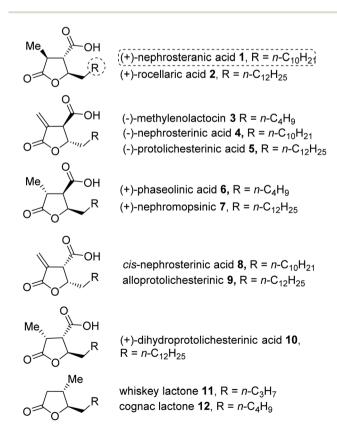


Fig. 1 Representative structures of γ -butyrolactone based paraconic acids and lactones.

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Scheme 1 Retrosynthetic general approach of $\gamma\text{-butyrolactone}$ based some paraconic acids and lactones.

(+)-nephrosteranic acid 1 would be synthesized via methylenation or stereoselective methylation at the C3 centre. The γ butyrolactone 13 could be achieved from protected nitro-acid derivative 14 via deprotection and in situ lactonization followed by Nef reaction. The nitro-acid derivative 14 in turn could be synthesized from (R)- or (S)-diphenylprolinol silyl ether catalyzed Michael addition of CH₃NO₂ to α,β-unsaturated aldehyde intermediate obtained from the controlled DIBAL-H reduction of olefinic ester derivative 15 followed by oxidation. The α,β -unsaturated ester 15 could be obtained from protected (R)- or (S)-glycidol 16 by treatment with suitable Grignard reagents, secondary alcohol protection, primary alcohol deprotection and oxidation followed by 2C-Wittig olefination reaction. The desired stereochemistry of paraconic acids 1-10 could be achieved by simply altering the (R)- and (S)-configuration of glycidyl ether and/or by using catalyst (R)- or (S)diphenylprolinol silyl ether during Michael addition reaction. Thus, in principle, C3, C4 and C5 chiral centres in paraconic acids could be easily manipulated and accessed by this approach.

As depicted in Scheme 2, the synthesis of (+)-nephrosteranic acid 1 as a representative target compound of paraconic acids was commenced from readily available PMB (R)-glycidyl ether 16a9 which was subjected to copper-catalyzed (CuI) regioselective ring opening with the Grignard reagent, derived from decyl bromide to furnish the alcohol derivative 17 in 85% yield. The alcohol derivative 17 on silyl protection with tert-butyldiphenylsilyl chloride (TBDPSCI) and imidazole with DMAP in catalytic amount afforded the silyl ether derivative 18 in 95% yield which on PMB ether cleavage using CAN (ceric ammonium nitrate) at 0 °C to rt furnished the terminal alcohol derivative 19 in 91% yield. The alcohol derivative 19 on oxidation under Swern conditions¹⁰ followed by treatment with (ethoxyearbonylmethylene)triphenylphosphorane in THF afforded the trans-olefinic ester derivative 20 in 92% yield. Our next goal was to carry out the synthesis of multifunctionalized γ-butyrolactone. Towards this end, trans-olefinic ester 20 on controlled reduction with DIBAL-H at $-78\ ^{\circ}\text{C}$ to $\alpha,\beta\text{-unsaturated}$ aldehyde intermediate and successive conjugate Michael addition11 of nitromethane in the presence of (S)-diphenylprolinol silyl ether (10 mol%) afforded the nitroaldehyde adduct which on

Scheme 2 Reagents and conditions: (a) $C_{10}H_{21}MgBr$, Cul, dry THF, -30 °C, 6 h, 85%; (b) TBDPSCl, imidazole, cat. DMAP, CH_2Cl_2 , 0 °C-rt, 8 h, 95%; (c) CAN, $CH_3CN: H_2O(4:1, v/v)$, 0 °C-rt, 2 h, 91%; (d) (i) $(COCl)_2$, DMSO, Et_3N , CH_2Cl_2 , -78 °C to -60 °C, 3 h; (ii) PPh₃-CHCOOEt, THF, rt, 20 h, 92% (over two steps); (e) (i) DIBAL-H, CH_2Cl_2 , -78 °C, 1 h; (ii) (S)-diphenylprolinol silyl ether (10 mol%), CH_3NO_2 , benzoic acid, MeOH, rt, 16 h; (iii) oxone, DMF, rt, 12 h, 84% (over 3 steps); (f) TBAF, dry THF, rt, 2 h, 95%; (g) NaNO₂, acetic acid, DMSO, rt, 24 h, 94%; (h) NaHMDS, CH_3 l, dry THF, -78 °C, 3 h, 93%.

subsequent oxidation with oxone¹² furnished the nitro-acid derivative **21** in excellent yield.

Further to demonstrate the stereochemistry during the conjugate Michael addition of nitromethane to α,β -unsaturated aldehyde intermediate we carried out the reaction with racemic catalyst (\pm)-diphenylprolinol silyl ether to get the nitroaldehyde adduct which on subsequent oxidation with oxone afforded the *anti-/syn*-nitro acid diastereomers (dr, 1 : 1) in 83% combined yield. However, on the other hand, in presence of (S)-diphenylprolinol silyl ether catalyst the conjugate addition of nitromethane on α,β -unsaturated aldehyde intermediate obtained from 20 followed by oxidation with oxone furnished the *anti*-nitro acid derivative 21 as a single diastereomer in 84% yield.

The *anti*-nitro acid derivative **21** on TPS deprotection and concomitant cyclisation with TBAF (tetra-*n*-butylammonium fluoride) furnished the γ -butyrolactone derivative **22** in 95% yield. The nitro- γ -butyrolactone derivative **22** was subjected to treatment with sodium nitrite and acetic acid under Nef reaction conditions¹⁴ to afford the γ -butyrolactone acid derivative **23** in 94% yield. Finally, stereoselective methylation at α -position of acid derivative **23** was carried out with methyl iodide and NaHMDS in dry THF to furnish the target compound (+)-nephrosteranic acid **1** in 93% yield ($[\alpha]_D^{25} + 27.18$ (*c* 1.50, CHCl₃), {lit.^{5s} $[\alpha]_D^{27} + 27.2$ (*c* 1.45, CHCl₃)}. The spectral and physical properties of the (+)-nephrosteranic acid **1** were in full agreement with reported values.^{5a}

Conclusions

In summary, we have developed an efficient and enantioselective route to multifunctionalized γ -butyrolactone paraconic acids and its application to the synthesis of the (+)-nephrosteranic acid 1 from readily accessible PMB (R)-glycidyl ether as starting material. Pivotal reaction sequence comprises asymmetric Michael addition catalyzed by (S)-diphenylprolinol silyl ether and stereoselective α -methylation. The overall yield for the (+)-nephrosteranic acid 1 was 47%. The synthetic route presented has further potential for the stereochemical varia-

tions in all the positions of the ring and extension to other

Conflicts of interest

Paper

analogues.

There are no conflicts to declare.

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