RSC Advances

PAPER

View Article Online
View Journal | View Issue

Cite this: *RSC Adv.*, 2020, **10**, 19655

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

Anju Gehlawat,[a] Ranjana Prakash[a] and Satyendra Kumar Pandey *[ab]

Received 1st May 2020
Accepted 14th May 2020

DOI: 10.1039/d0ra04267f

rsc.li/rsc-advances

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 silyl 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 total[5] and formal[6] synthesis of paraconic acids such as (+)-nephrosteranic acid are documented in literature. More recently, Appayee and co-workers 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

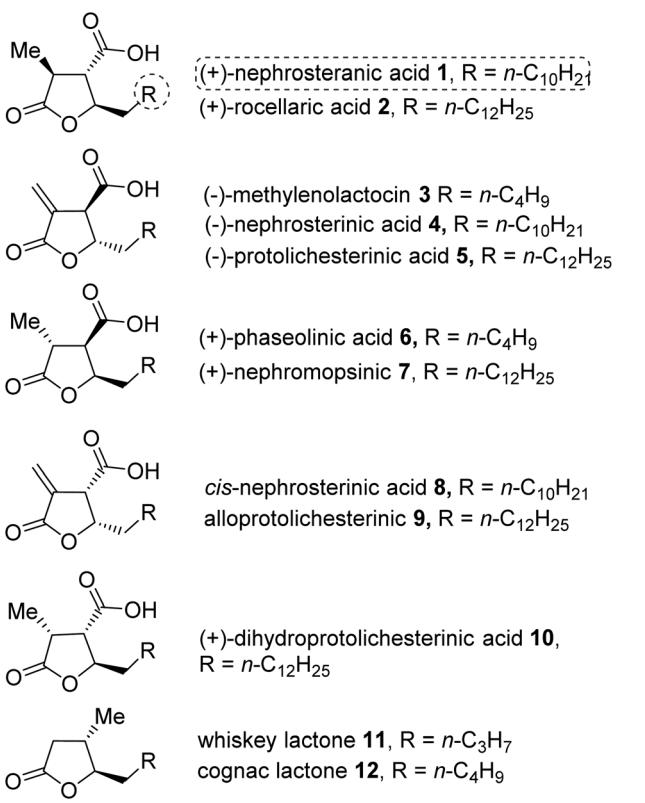
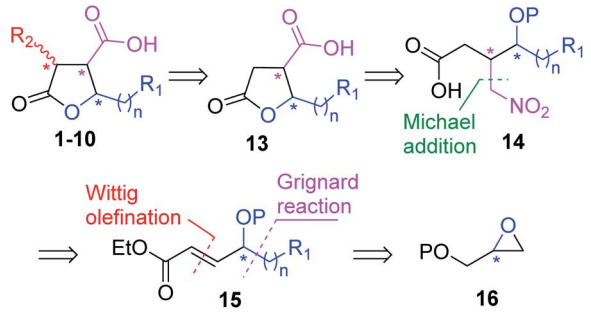


Fig. 1 Representative structures of γ-butyrolactone based paraconic acids and lactones.

[a]*School of Chemistry and Biochemistry, Thapar Institute of Engineering and Technology, Patiala-147 001, India. E-mail: skpandey@thapar.edu*

[b]*Department of Chemistry, Institute of Science, Banaras Hindu University, Varanasi-221 005, India. E-mail: skpandey.chem@bhu.ac.in*

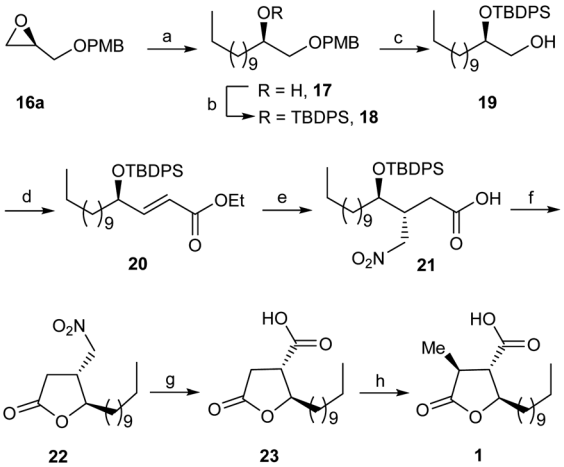
† Electronic supplementary information (ESI) available. See DOI: 10.1039/d0ra04267f



Scheme 1 Retrosynthetic general approach of γ-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 CH_3NO_2 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 **16a**[9] 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 (TBDPSCl) 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 conditions[10] followed by treatment with (ethoxycarbonylmethylene)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 °C to α,β-unsaturated aldehyde intermediate and successive conjugate Michael addition[11] of nitromethane in the presence of (*S*)-diphenylprolinol silyl ether (10 mol%) afforded the nitroaldehyde adduct which on



Scheme 2 Reagents and conditions: (a) $C_{10}H_{21}MgBr$, CuI, 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) PPh_3=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) $NaNO_2$, acetic acid, DMSO, rt, 24 h, 94%; (h) NaHMDS, CH_3I, dry THF, −78 °C, 3 h, 93%.

subsequent oxidation with oxone[12] 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 (±)-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[13] 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 conditions[14] 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, $CHCl_3$), {lit.[5s] $[\alpha]_D^{27}$ + 27.2 (*c* 1.45, $CHCl_3$)}. 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 variations in all the positions of the ring and extension to other analogues.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

S. K. P. is thankful to the Science and Engineering Research Board, New Delhi, for generous funding of the project (grant no. EMR/2016/003649). A. G. thank UGC, New Delhi for research fellowships.

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