En Route to New Bioactive Compounds from Natural Feedstock: Protection and Reduction of Quinic Acid

TAMPEREEN TEKNILLINEN YLIOPISTO
TAMPERE UNIVERSITY OF TECHNOLOGY

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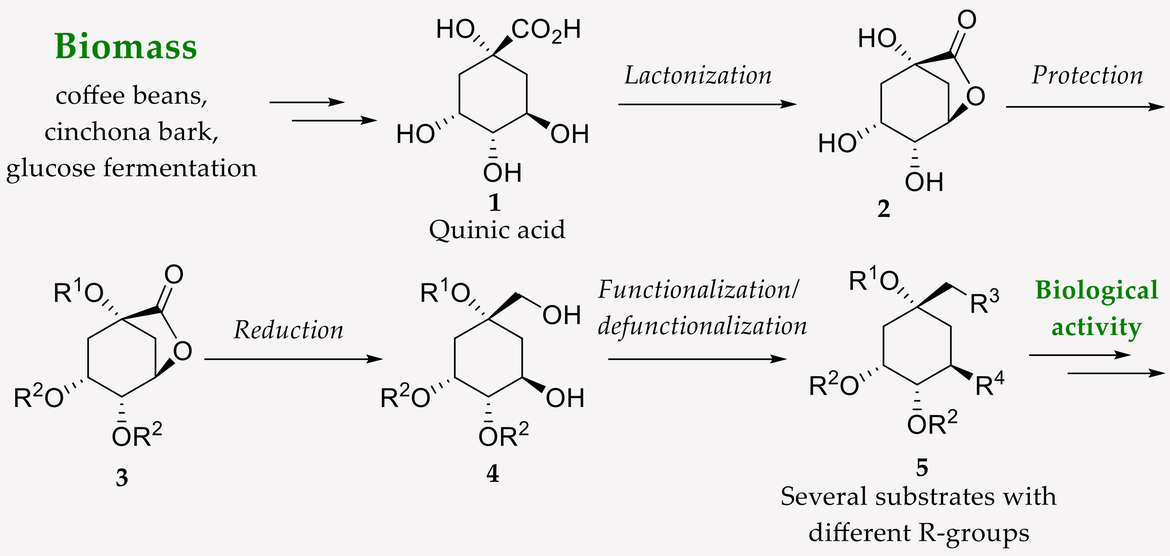
Holmstedt, S.; Koivuporras, A.; Candeias, N. R.

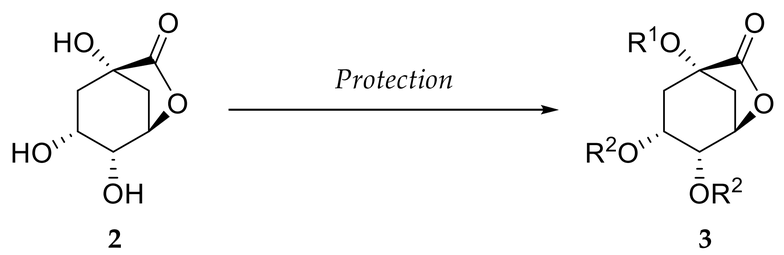
Laboratory of Chemistry and Bioengineering, Tampere University of Technology, Korkeakoulunkatu 10, 33720 Tampere, Finland, suvi.holmstedt@tut.fi



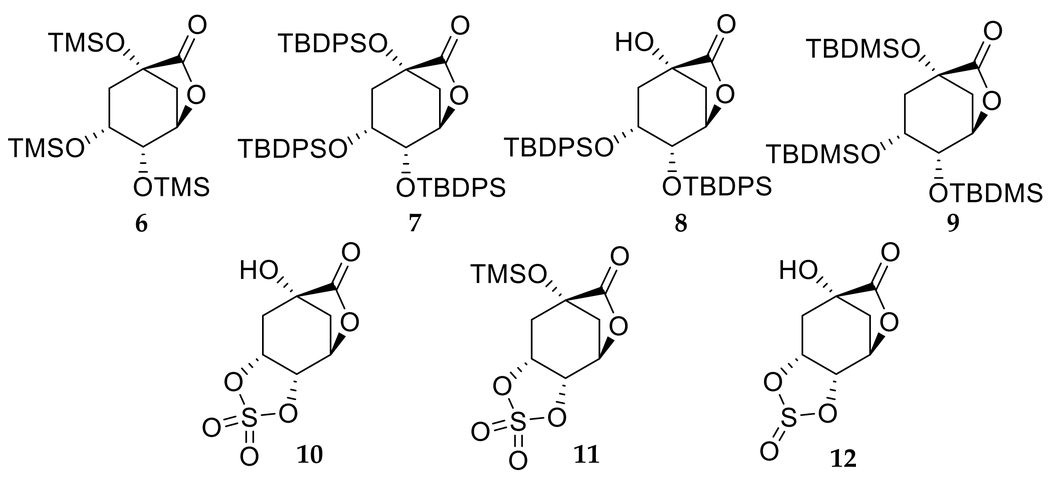
The use of biomass-derived compounds allows to utilize cheap chiral molecules as starting materials and create potential drug precursors, among other uses.[1-2] This study is based on quinic acid **1**, a natural chiral polyol, which is a cheap material and synthetically attractive due to its multiple functional groups.[3-4] Quinic acid was transformed into its corresponding lactone and different protecting groups using the tridimensional arrangement of the vicinal diol framework were explored, allowing the preparation of seven different lactone derivatives. Reduction of the lactone exposes a primary hydroxyl functionality that can be further explored due to its higher reactivity. By functionalization/defunctionalization of those hydroxyl groups, a library of different quinic acid derivatives was synthesized and is currently being tested against HT29 human colorectal adenocarcinoma cells.

Protection of alcohol groups

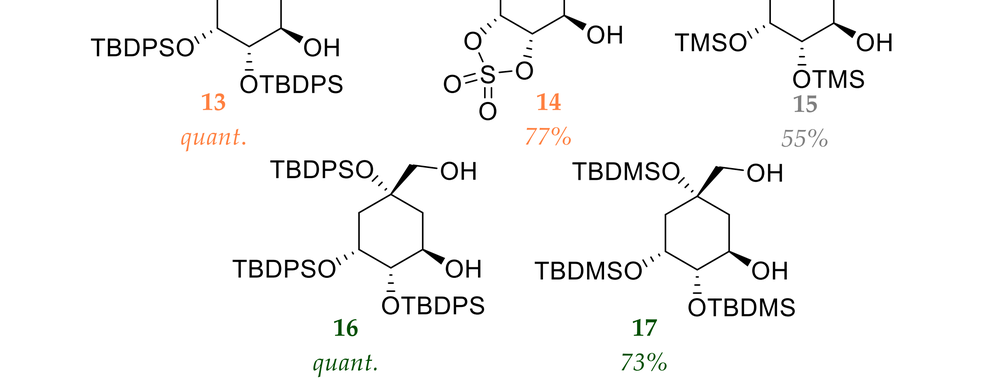
The lactone **2** derived from quinic acid **1** was protected with different silyl or sulfur based protection groups. The vicinal diol framework in quinide **2** allows the use of either acyclic (entries 1-4) or cyclic (entries 5-6) protection groups, in reasonable to excellent yields.



Entry	Protective group	Conditions	Yield (%)
1	TMS, **6**	Et_3N, TMSCl, ACN	*quant.*
2	TBDPS, **7**	Imidazole, TBDPS-Cl, ACN	*98*
3	TBDPS, **8**	Imidazole, TBDPS-Cl, ACN	*38*
4	TBDMS, **9**	Imidazole, TBDMS-Cl, ACN	*70*
5	SO_2, cyclic, R^2-R^2, **10** R^1=TMS, **11**	i) SO_2Cl_2, Et_3N, ACN ii) TMS-Cl, Et_3N, THF	*79* *77*
6	S=O, cyclic, R^2-R^2, **12**	$SOCl_2$, Et_3N, ACN	*55*



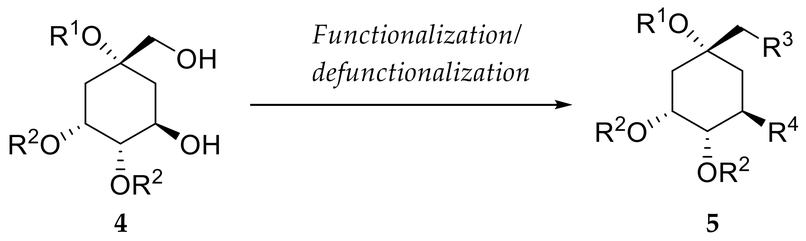
Reduction of lactone moiety



The protected lactones were reduced by using either $NaBH_4$, $LiAlH_4$ or DIBAL to yield the corresponding diols. Presence of bulky protection groups allowed the reductions to be achieved in excellent yields. However, amongst the sulfur protected lactones, only **10** could be efficiently reduced without cleavage of the protective groups.

Future work

By exploring the different reactivities of primary, secondary and tertiary hydroxyls, their selective functional group interconversions or defunctionalization will be explored in order to increase the library of potential bioactive compounds.



Conclusions

Biomass-based quinic acid was transformed into several different lactone derivatives, which were further reduced into their corresponding diols. Altogether 12 new substrates were synthetized with good to excellent yields and the biological properties of these new chiral entities will be studied.

Further functionalization/defunctionalization of the available library will allow its facile expansion. Besides the well known biological properties of quinic acid, its backbone can be found in many natural products, which makes it an attractive starting material for total synthesis.

References

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