ChemComm

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Chem. Commun.*, 2014, **50**, 8715

Received 28th April 2014,
Accepted 17th May 2014

DOI: 10.1039/c4cc03134b

www.rsc.org/chemcomm

A concise total synthesis of puberulic acid, a potent antimalarial agent†

Goh Sennari,[a] Tomoyasu Hirose,[ab] Masato Iwatsuki,[ab] Satoshi Ōmura*[b] and Toshiaki Sunazuka*[ab]

Efficient and practical total synthesis of puberulic acid has been accomplished *via* 8 steps, with 54% overall yield, and only two C–C bond formations, without the introduction of oxygen atoms into the core skeleton. Construction of the tropolone framework as the key transformation was achieved by multi-tandem oxidation of the aliphatic-triol, from D-(+)-galactose as the starting material.

Malaria, which is caused by species of *Plasmodium* parasites, is one of the world's three gravest infectious diseases, and remains a major global health problem.[1] Although many antimalarial agents have been continually developed, drug-resistant *Plasmodia* rapidly and increasingly appear. Therefore, the development of novel antimalarial drugs with new modes of action and structures is urgently and constantly required.

In the course of our group's screening programme to discover metabolites with promise as antimalarial drugs from microorganisms, some troponoids (Fig. 1), namely puberulic acid (**1**),[2] stipitatic acid (**2**),[3] and viticolins A–C (**3–5**), were isolated from a culture broth of *Penicillium viticola* FKI-4410.[4] The unique structure of a highly-oxygenated tropolone framework, and promising antimalarial activity, led us to pursue synthetic studies to provide clarification of detailed structure–activity relationships. Consequently, we decided to establish a new total synthetic route for puberulic acid (**1**), the compound exhibiting the most potent antimalarial properties.

Total synthesis of **1** has been previously achieved by two groups: R. B. Johns *et al.*[5] and M. G. Banwell *et al.*[6] In both routes, the tropolone framework was constructed by ring expansion from cyclopropanized benzene derivatives. However, we planned a different efficient and practical total synthetic route to allow for the creation of numerous analogues and novel derivatives from a key synthetic intermediate (Scheme 1).

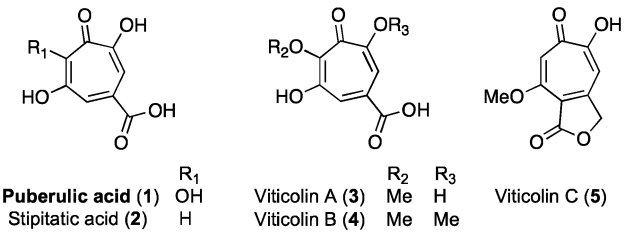
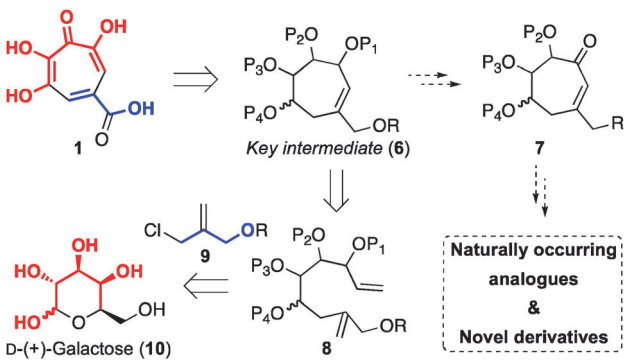


Fig. 1 Structures of antimalarial troponoids.



Scheme 1 Synthetic strategy for puberulic acid (**1**).

The unique tropolone framework, the highly-oxygenated 7-membered aromatic ring of **1**, was constructed by functionally tolerated ring-closing metathesis (RCM)[7,8] to afford the aliphatic 7-membered cyclic compound **6** as a key intermediate, followed by multi-tandem oxidation of the three hydroxyl groups on **6**. Divergence to produce other naturally occurring analogues and novel derivatives is permitted *via* the enone **7**, which could be derived from stepwise oxidation of **6**.

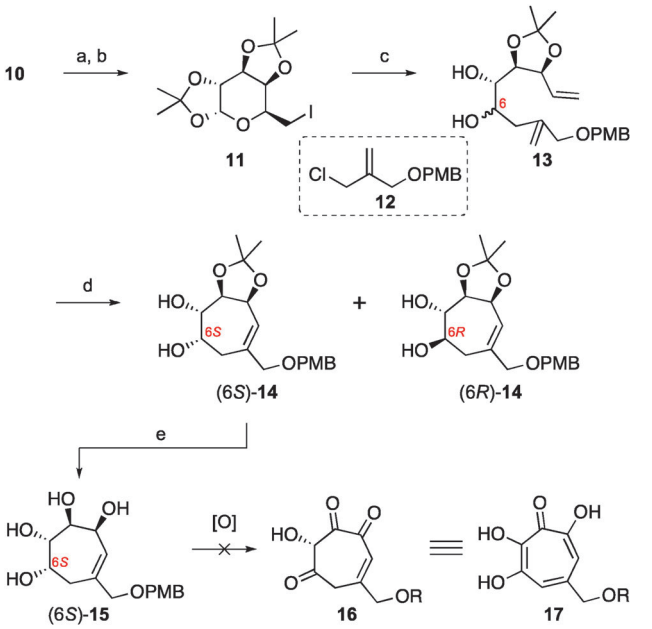
With respect to synthetic efficiency, one of the most important tasks in synthesis planning is to envisage the production of the target compound using minimal bond-forming reactions.[9] In this reaction, the target compound has a low molecular weight and simple planar structure which is highly-oxygenated and has no asymmetric carbons. We envisaged that this characteristic

[a] *Graduate School of Infection Control Sciences, Kitasato University, Japan*
[b] *Kitasato Institute for Life Sciences, Kitasato University, 5-9-1 Shirokane, Minato-ku, Tokyo 108-8641, Japan. E-mail: omuras@insti.kitasato-u.ac.jp, sunazuka@lisci.kitasato-u.ac.jp; Fax: +81 3-5791-6340; Tel: +81 3-5791-6340*

† Electronic supplementary information (ESI) available. See DOI: 10.1039/c4cc03134b

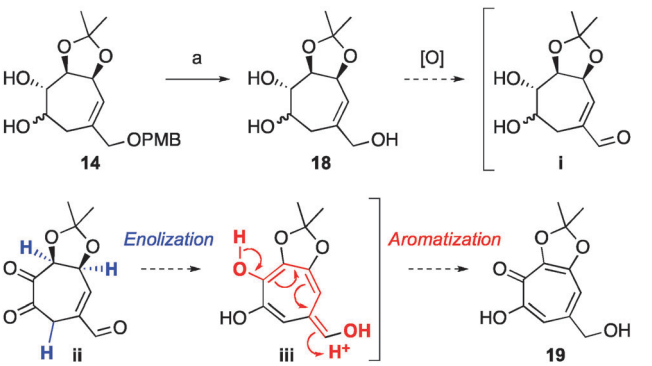
compound could be synthesized using only two C–C bond-forming reactions, and selected a sugar, D-(+)-galactose, as the starting material, which contains the C–C and C–O bonds in the backbone of the target compound. The sugar is generally useful in chiral pool synthesis, and often utilized in the syntheses of complex natural products as the chiral source.[10] In spite of the sugar being cheaply available, its application as a framework source is infrequent. Therefore, in our synthetic strategy, we proposed to utilize the structure of the common sugar without being conscious of its three-dimensional information, allowing maximum use of its atomic structure. Therefore, we planned to drive the cyclization precursor **8** by a Barbier-type addition with allyl chloride **9** to D-(+)-galactose (**10**).[11]

The iodide **11** could be accessed from **10** by a known reaction,[12] that is, protection with an acetonide group, and subsequent Appel reaction. For the Barbier-type addition, **11** was treated with Zn in THF–H_2O to generate the aldehyde intermediate. Allyl chloride **12**[13] was continuously added to the reaction mixture to produce the diene **13** as a 2.3 : 1 (6*S* : 6*R*) separable mixture of diastereomers. Then, RCM of the diastereomixture of **13** using the Grubbs 2nd catalyst (10 mol%) afforded the cyclic diol **14** as a separable mixture in excellent yield. The stereochemistry at the C6 position was determined by NMR spectroscopy after the diol moiety of **14** was protected with an acetonide group.[14] After removal of the acetonide group from the major single diastereomer (6*S*)-**14** with *p*-toluenesulfonic acid, the key aromatization step by multi-tandem oxidation of tetraol (6*S*)-**15** was investigated. We expected that if three hydroxyl groups of tetraol were oxidized, the aromatization *via* tautomerization would occur immediately to give the desired troponoid **17**. However, all efforts to achieve the aromatization failed under any oxidation conditions, probably because the retro-aldol reaction occurred due to the intricate process of oxidising of four adjacent hydroxyl groups. Additionally, it was assumed that competition, due to the elimination of hydroxyl groups at the β-position of the generated carbonyl group, afforded various byproducts (Scheme 2).



Scheme 2 Multi-tandem oxidation of tetraol **15**. (a) $ZnCl_2$, H_2SO_4, acetone, r.t., 97%; (b) I_2, PPh_3, imidazole, PhMe, 70 °C, 97%; (c) Zn, THF/H_2O, then **12**, r.t., 96% (6*S* : 6*R* = 2.3 : 1); (d) Grubbs 2nd catalyst (10 mol%), CH_2Cl_2, reflux, 97%; (e) TsOH·H_2O, MeOH, r.t., 99% (from (6*S*)-**14**).

Accordingly, oxidation of the hydroxyl group on the 7-membered ring did not bear any fruit.[15] We focused on the exocyclic primary alcohol, and subsequently planned to oxidize the triol **18**, which could be preceded by deprotection of the PMB group (Scheme 3). On multi-tandem oxidation of the triol **18**, the primary hydroxyl group would be oxidized first to afford the conjugate aldehyde **i**. Oxidation of two hydroxyl groups on the 7-membered ring would then occur to afford the tricarbonyl compound **ii**. Aromatization would proceed *via* tautomerization, and subsequent proton shifts in the intermediate **iii**, to give the troponoid **19**.

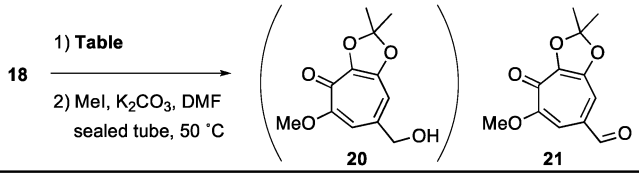


Scheme 3 Strategy for the aromatization through multi-tandem oxidation of triol **18**. (a) DDQ, CH_2Cl_2/pH 7 buffer (9 : 1), 0 °C, 94%.

Several oxidation methods (shown in Table 1) were performed. In these investigations, since the tropolone framework is known to chelate with some metals,[16] oxidants without metal catalysts were specifically selected. In actuality, all compounds which possess the tropolone framework could not be monitored and purified with silica gel, so the reaction was monitored with LC-UV,[17] and purification was conducted after protection of the hydroxyl group on the tropolone framework. In entry 1, IBX oxidation, which is generally useful for the oxidation of vicinal diols, caused decomposition of the substrate. Next, we attempted several activated DMSO-mediated oxidations. Although Swern oxidation, which is one of the principal methods for oxidation, gave a complex mixture (entry 2), Parikh–Doering oxidation afforded the desired compound **21**, and its regioisomer,[18] which fortunately had a higher oxidation state than that which was predicted (entry 3). It was therefore hoped that oxidation using IBS,[19] which can be generated *in situ* from pre-MIBSK with oxone, would afford the carboxylic acid, but decomposition was observed (entry 4). Based on these results, multi-tandem oxidation was found to proceed only under Parikh–Doering conditions to construct the desired functionalized tropolone framework.

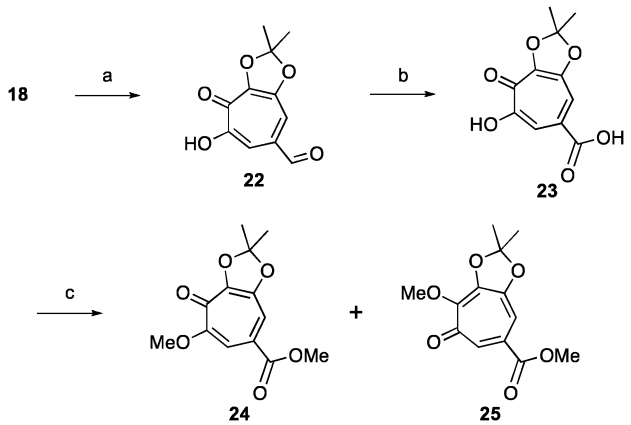
Although the desired compound was in hand, it was envisaged that aldehyde **21** and its isomer were labile during

Table 1 Multi-tandem oxidation of triol **18**



Entry	Conditions	Result (2 steps)
1	IBX, DMSO, r.t.	Decomp.
2	$(COCl)_2$, DMSO, CH_2Cl_2, −78 °C then Et_3N, −78 °C	Complex mixture
3	SO_3·pyridine, DMSO, Et_3N, CH_2Cl_2, 0 °C to r.t.	**21** and regioisomer:[a] 28% (1 : 1)[b]
4	Pre-MIBSK, powdered Oxone®, MeCN, 70 °C, then H_2O, 70 °C	Decomp.

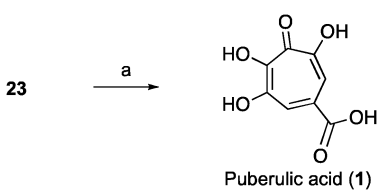
[a] Regioisomer of α-methoxy carbonyl part. [b] Isolated yield.



Scheme 4 Synthesis of methyl esters **24** and **25**. (a) SO_3·pyridine, DMSO, Et_3N, CH_2Cl_2, 0 °C to r.t.; (b) $NaClO_2$, NaH_2PO_4·$2H_2O$, 2-methyl-2-butene, THF/*t*-BuOH/H_2O (1 : 1 : 1), r.t.; (c) $TMSCHN_2$, PhH/MeOH (9 : 1), r.t., 42% (**24** : **25** = 1 : 1, 3 steps from triol **18**).

purification using silica gel. Thus, we decided to proceed with the next step without protection and purification. The multi-tandem oxidation of triol **18**, and subsequent Pinnick oxidation afforded carboxylic acid **23**, which was detected after protection with a methyl group, and purification (Scheme 4).

Since it was found that the desired carboxylic acid **23** could be generated by two oxidation steps, we investigated the deprotection of the acetonide group in the final step. As a result, deprotection was clearly carried out by treatment with HBr–AcOH[6] to generate puberulic acid (**1**) (Scheme 5). As **1** could also not be purified using silica gel, several purification methods were tried, and we found that the compounds, including other tropolonoids, could be purified using reverse-phase chromatography.



Scheme 5 Synthesis of puberulic acid (**1**). (a) 33% HBr–AcOH, sealed tube, 120 °C, 65% (3 steps from triol **18**).

This method could be applied to facilitate complete and substantial synthesis, allowing us to achieve our goal of the efficient and practical large-scale synthesis of puberulic acid (**1**).

In conclusion, with D-(+)-galactose as the starting material, the C–C and C–O backbone of the target compound was subjected to Barbier-type addition and RCM to afford the aliphatic-triol. The triol underwent multi-tandem oxidation through tautomerization by Parikh–Doering oxidation to give the desired functionalized tropolone framework. After several conversions of the functional group, total synthesis of **1** was accomplished *via* 8 steps, with 54% overall yield, and only two C–C bond formations. Furthermore, we achieved large-scale synthesis of puberulic acid by applying this efficient total synthetic route. Based on our synthetic methods, comprehensive synthesis of novel derivatives and structure–activity relationship studies on this class of compounds are currently in progress.

We thank Dr K. Nagai and Ms. N. Sato (School of Pharmacy, Kitasato University) for various instrumental analyses. This work was supported by a grant from the 21st Century Center of Excellence Program (to M. Iwatsuki), a Kitasato University Research Grant for Young Researchers, and the Ministry of Education, Science, Sports and Culture of Japan, through a Grant-in-Aid for Young Scientists (B, 25860082).

Notes and references

1 World Health Organization, *World Malaria Report*, 2013.
2 J. H. Birkinshaw and H. Raistrick, *Biochem. J.*, 1932, **26**, 441.
3 J. H. Birkinshaw, A. R. Chambers and H. Raistrick, *Biochem. J.*, 1942, **36**, 242.
4 (*a*) M. Iwatsuki, S. Takada, M. Mori, A. Ishiyama, M. Namatame, A. Nishihara-Tsukashima, K. Nonaka, R. Masuma, K. Otoguro, K. Shiomi and S. Ōmura, *J. Antibiot.*, 2011, **64**, 183; (*b*) K. Nonaka, R. Masuma, M. Iwatsuki, K. Shiomi, K. Otoguro and S. Ōmura, *Mycoscience*, 2011, **52**, 338.
5 R. B. Johns, A. W. Johnson and J. Murray, *J. Chem. Soc.*, 1954, 198.
6 M. G. Banwell, M. P. Collis, M. F. Mackay and S. L. Richards, *J. Chem. Soc., Perkin Trans. 1*, 1993, 1913.
7 R. H. Grubbs, S. J. Miller and G. C. Fu, *Acc. Chem. Res.*, 1995, **28**, 446.
8 Recently, only one example has been reported for the construction of the tropolone framework by RCM: D. Arican and R. Brückner, *Org. Lett.*, 2013, **15**, 2582.
9 (*a*) R. M. Wilson and S. J. Danishefsky, *J. Org. Chem.*, 2007, **72**, 4293; (*b*) M. Willot, L. Radtke, D. Könning, R. Fröhlich, V. H. Gessner, C. Strohmann and M. Christmann, *Angew. Chem., Int. Ed.*, 2009, **48**, 9105.
10 For recent review, see: S. Hanessian, *J. Org. Chem.*, 2012, **77**, 6657.

11 I. Hanna and L. Richard, *Org. Lett.*, 2000, **17**, 2651.
12 Z. Yu, L. Ya-Peng and Z. Li, *J. Carbohydr. Chem.*, 2008, **27**, 113.
13 Z. Kałuża, A. Kazimierski, K. Lewandowski, K. Suwińska, B. Szczęsna and M. Chmielewski, *Tetrahedron*, 2003, **59**, 5893.
14 See the ESI† for the reaction condition and spectroscopic data.
15 Although the oxidation of diols **14** was also performed, the desired diketone was not generated under any conditions.
16 S. R. Pittre, A. Ganzhorn, J. Hoflack, K. Islam and J.-M. Hornsperger, *J. Am. Chem. Soc.*, 1997, **119**, 14.
17 See the ESI† for the analytical conditions and chromatograms.
18 The structures of **21** and its regioisomer were determined by NOE analysis (see the ESI† for details).
19 (*a*) M. Uyanik, M. Akakura and K. Ishihara, *J. Am. Chem. Soc.*, 2009, **131**, 251; (*b*) M. Uyanik and K. Ishihara, *Org. Synth.*, 2012, **89**, 105.

