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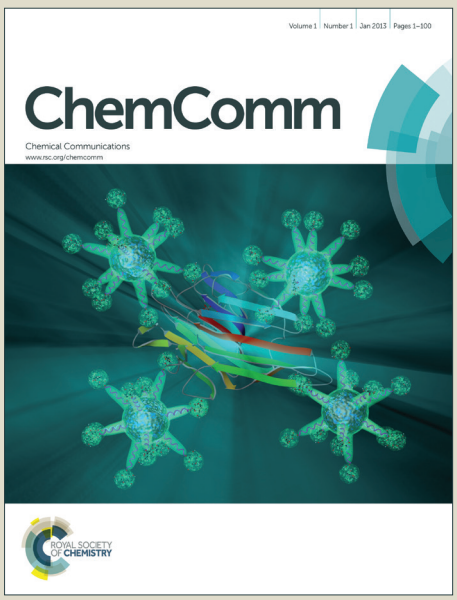

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A concise total synthesis of puberulic acid, potent antimalarial agent

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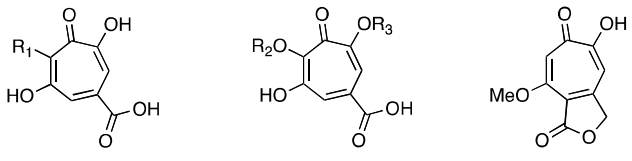
Efficient and practical total synthesis of puberulic acid has been accomplished via 8 steps, with 54% overall yield, and only two C-C bond formations, without introduction of oxygen atoms into the core skeleton. The construction of a tropolone framework as the key transformation was achieved by multi-tandem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

Malaria, 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* appear rapidly and increasingly. Therefore, the development of novel antimalarial drugs with new modes of action and structures is urgently and constantly required.

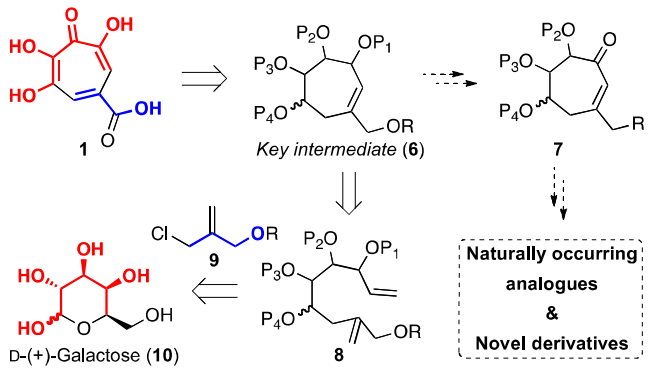
In the course of our group's screening programme to discover compounds with promise as antimalarial drugs from metabolites of microorganisms, some troponoids (**Fig. 1**), namely puberulic acid (**1**),[2] stipitatic acid (**2**),[3] and viticolins A-C (**3**-**5**), have been isolated from a culture broth of *Penicillium viticola* FKI-4410.[4] The unique structure of a highly-oxygenated tropolone framework and the promising antimalarial activity led us to pursue the 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.



	R_1	R_2	R_3
Puberulic acid (**1**)	OH		
Stipitatic acid (**2**)	H		
Viticolin A (**3**)		Me	H
Viticolin B (**4**)		Me	Me
Viticolin C (**5**)			

Fig. 1 Structure of antimalarial troponoids

Total synthesis of **1** has 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 creation of numerous analogues and novel derivatives from a key synthetic intermediate (**Scheme 1**).



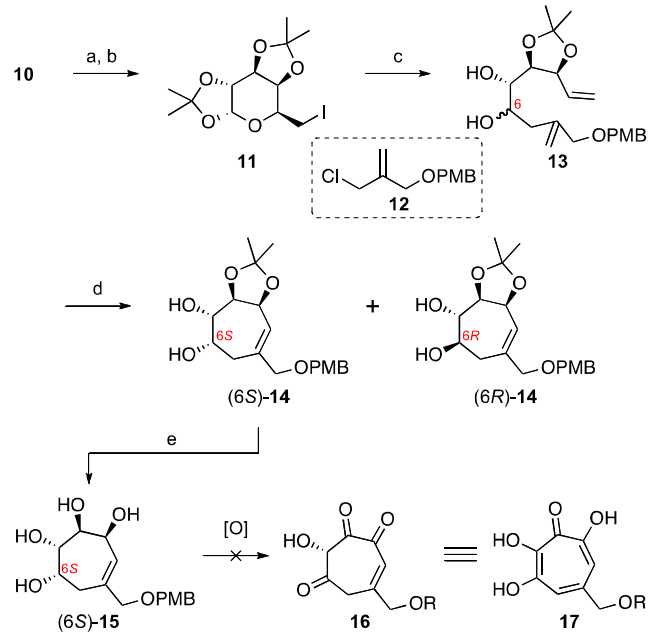
Scheme 1 Synthetic strategy of puberulic acid (**1**)

The unique tropolone framework, the highly-oxygenated 7-membered aromatic ring of **1**, would be 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-oxidation of three hydroxyl groups on **6**. Divergence to derive other naturally occurring analogues and novel derivatives would be permitted via the enone **7**, which could be led by stepwise oxidation of **6**.

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

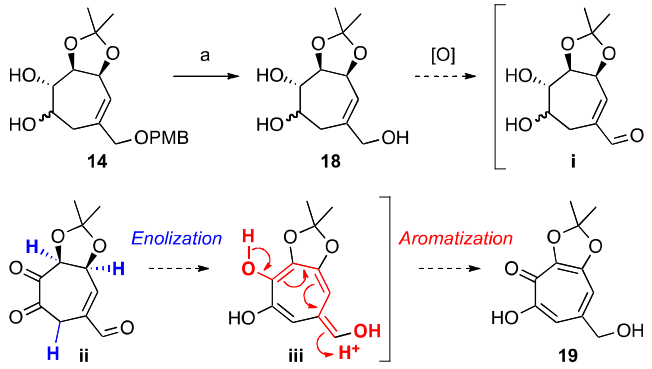
backbone of the target compound. The sugar is generally useful as the chiral pool, and often utilized in the syntheses of complex natural products as the chiral source.[10] In spite of the sugar being cheaply available, its application as the frame source is infrequent. Therefore, in our synthetic strategy, we proposed to utilize the shadow of the sugar to project the skeleton, allowing maximum use of its atomic structure. So the cyclization precursor **8** was planned to be driven by Barbier-type addition with allyl chloride **9** to D-(+)-galactose (**10**).[11]

Iodide **11** could be accessed from **10** by known reaction,[12] that is protection with an acetonide group and subsequent Appel reaction. For Barbier-type addition, **11** was treated with Zn in THF/H_2O to generate the aldehyde intermediate. Continuously, allyl chloride **12**[13] was added to the reaction mixture to provide 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 cyclic diol **14** as a separable mixture in excellent yield. The stereochemistry at the C6 position was determined by NMR spectroscopy after the protection of the diol moiety of **14** with an acetonide group.[14] After removal of the acetonide group of a major single diastereomer (6*S*)-**14** with *p*-toluenesulfonic acid, the key aromatization by multi-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 at the aromatization failed under any oxidation conditions, probably because the retro-aldol reaction was caused due to intricate oxidation of four adjacent hydroxyl groups. Additionally, it was assumed that competition due to elimination of hydroxyl groups at the β-position of the generated carbonyl group afforded various byproducts (**Scheme 2**).



Scheme 2 Multi-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 (10 mol%), CH_2Cl_2, reflux, 97%; (e) TsOH•H_2O, MeOH, r.t., 99% (from (6*S*)-**14**)

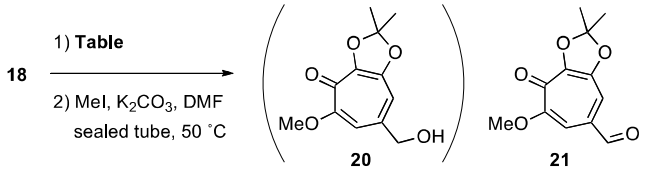
Accordingly, oxidation of the hydroxyl group on the 7-membered ring did not bear fruit.[15] We focused on the exocyclic primary alcohol and subsequently planned to oxidize the triol **18**, which could be led by deprotection of the PMB group (**Scheme 3**). In the case of multi-oxidation of the triol **18**, primary hydroxyl group would be oxidized firstly to afford 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 shift of intermediate **iii** to give the troponoid **19**.



Scheme 3 Strategy of the aromatization by multi-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 was known to chelate with some metals,[16] oxidants without metal catalysts were particularly selected. In actuality, all compounds constructing 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 of tropolone framework. In entry 1, IBX oxidation, which is generally useful for the oxidation of vicinal diol, caused decomposition of the substrate. Next, we attempted several activated DMSO mediated oxidations. Although Swern oxidation, which is one of the principal methods, gave complex mixture (Entry 2), Parikh-Doering oxidation afforded the desired compound **21** and its regioisomer,[18] which fortunately had a higher oxidation state than the supposed one (Entry 3). It was therefore hoped that oxidation using IBS[19] would afford carboxylic acid, but decomposition was observed (Entry 4). Based on these results, multi-tandem oxidation was found to proceed only under Parikh-Doering condition to construct the desired functionalized tropolone framework.

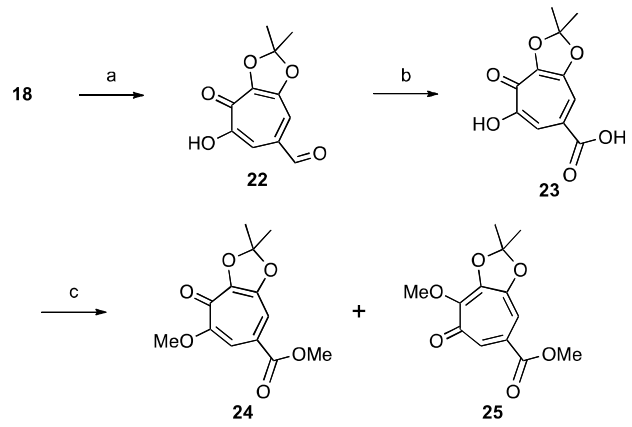
Table 1 Multi-oxidation of triol **18**



Entry	Condition	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.

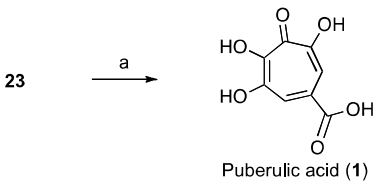
[a]regioisomer of α-methoxy carbonyl part, [b]isolated yield

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



Scheme 4 Synthesis of methyl ester **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**)

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



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

In conclusion, with D-(+)-galactose as the starting material, the C-C and C-O bond backbone of the target compound was subjected to Barbier-type addition and RCM to afford the aliphatic-triol. Parikh-Doering oxidation of the triol underwent multi-tandem oxidation through tautomerization, to construct 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 application of this efficient total synthetic route. Based on our synthetic methods, comprehensive synthesis of novel derivatives and structure-activity relationship studies of this class of compounds are currently in progress.

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Notes and references

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Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/c000000x/

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 Electronic Supplementary Information for the reaction condition and spectroscopic data.
15 Although the oxidation of diols **14** was also performed, desired diketone didn't generate in 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 Electronic Supplementary Information for the analytical conditions and chromatograms.
18 The structures of **21** and its regioisomer were determined by NOE analysis (see the Electronic Supplementary Information for the detail).
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.