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Synthesis of Several Cleistrioside and Cleistetroside Natural Products via a Divergent De Novo Asymmetric Approach

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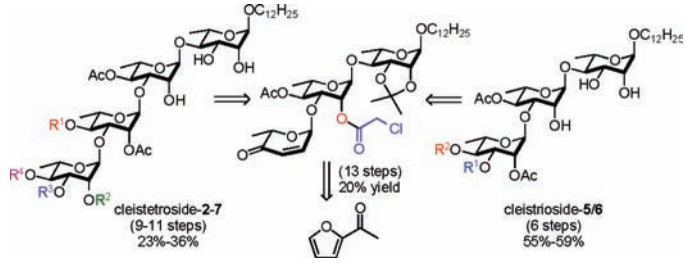
ABSTRACT



The de novo asymmetric syntheses of several partially acylated dodecanyl tri- and tetra-rhamnoside natural products (cleistriosides-5 and 6 and cleistetrosides-2 to 7) have been achieved (19−24 steps). The divergent route requires the use of three or less protecting groups. The asymmetry was derived via Noyori reduction of an acylfuran. The rhamno-stereochemistry was installed by a diastereoselective palladium-catalyzed glycosylation, ketone reduction and dihydroxylation.

The quest to find new natural products with interesting biological activity has led to the discovery of several partially acylated dodecanyl tri- and tetra-rhamnoside natural products with significant antibacterial activity from *Cleistopholis patens* and *glauca* (Figure 1).[1] For instance, cleistrioside-**5** (**1**) and cleistetroside-**2** (**3**) have shown significant antimicrobial activity against several methicillin-resistant *Staphylococcus aureus* (e.g., ATCC 33592 0.5 μg/mL for **3** and 8 μg/mL for **1**). Due to limited supplies of the isolated materials, only two members (**1** and **3**) of this class of natural products have been extensively studied for biological activity and only cleistetroside-**2** (**3**) has succumbed to total synthesis.[2] However, some related acylated rhamnoside natural products have possessed anticancer activity.[3]

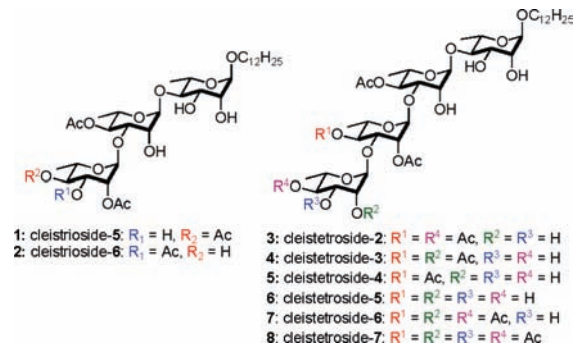


Figure 1. Targeted cleistriosides and cleistetrosides.

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(1) (a) Ngnokam, D.; Tsopmo, A.; Ayafor, J. F.; Nuzillard, J. M.; Sterner, O. *Bull. Chem. Soc. Ethiop.* **2003**, *17*, 177–180. (b) Hu, J.-F.; Garo, E.; Hough, G. W.; Goering, M. G.; O'Neil-Johnson, M.; Eldridge, G. R. *J. Nat. Prod.* **2006**, *69*, 585–590. (c) Seidel, V.; Bailleul, F.; Waterman, P. G. *J. Nat. Prod.* **2000**, *63*, 6–11. (d) Seidel, V.; Bailleul, F.; Waterman, P. G. *Phytochemistry* **1999**, *52*, 465–472.

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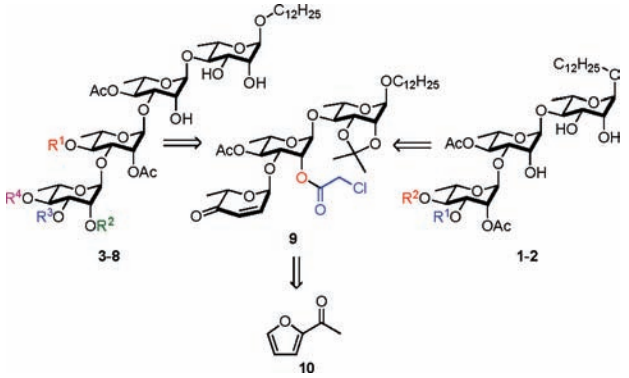
As part of a program of de novo synthesis and study of biologically active partially acylated rhamnoside natural products,[4] we became interested in their synthesis and biological study. Key to the synthetic efficiency of this approach is the use of a divergent strategy and the minimal use of protecting groups. Herein we describe our successful development of a divergent de novo approach to eight members of this class of natural products.

Retrosynthetically, we envisioned that the eight oligosaccharides could be efficiently prepared from a common trisaccharide intermediate **9** (Scheme 1), where the pyranone

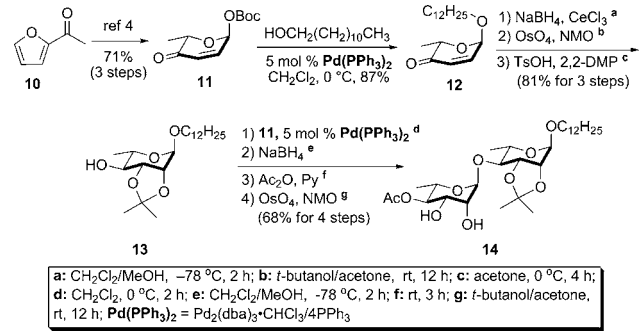
Scheme 1. Retrosynthetic Analysis



ring could be elaborated into the required *rhamno*-mono- and disaccharide with the use of one or less protecting groups.[5] In turn, the key intermediate **9** could be stereoselectively prepared from achiral acetyl furan **10** via our de novo asymmetric approach. The route as envisioned should allow for the selective preparation of the eight target molecules (**1**−**8**) with the use of one acetonide and one or two chloroacetate groups.

Our synthesis started with the commercially available pyranone **11** (Scheme 2), which also can be synthesized from achiral acetyl furan **10** in three steps (71%).[6] Exposure of the pyranone **11** and dodecyl alcohol to our typical Pd-catalyzed glycosylation conditions (2.5 mol % $Pd_2(dba)_3$·$CHCl_3$ and 10 mol % of PPh_3 in CH_2Cl_2 at 0 °C)[7] produced

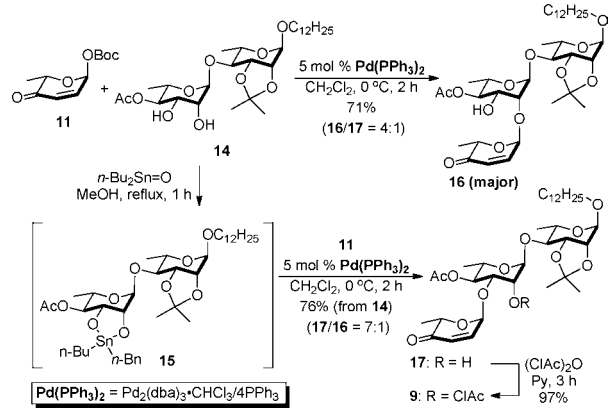
Scheme 2. Approach to the Disaccharide **14**



pyranone **12** in 87% yield with complete α-selectivity. A Luche reduction and Upjohn dihydroxylation diastereoselectively produced a *rhamno*-triol, which was then regioselectively protected as acetonide **13** (81%, three steps). Using a similar 4-step sequence the free equatorial hydroxyl group at C4 in **13** was glycosylated. This began with our Pd-catalyzed glycosylation of **13**, followed by $NaBH_4$ reduction, acetylation (Ac_2O/Py) of the resulting allylic alcohol and finally Upjohn dihydroxylation, which provided diol **14** (68% yield for the four steps).

With the diol **14** in hand, we then turned our attention to the regioselective glycosylation of C3 hydroxyl group of the diol **14** (Scheme 3). We first investigated a C2 protection/

Scheme 3. Regioselective Glycosylation



C3 glycosylation strategy but failed to find a suitable procedure to selectively install an acetate-orthogonal protecting group that would selectively react at the C2 position. So, we turned to the selective glycosylation of diol **14**. Exposing **14** to our typical Pd-catalyzed glycosylation with pyranone **11** gave a 4:1 ratio of regioisomeric trisaccharides **16** and **17**, with the undesired isomer **16** being the major product (71% of **16**).

Given that tin ethers were known to react with Pd-π-allyl intermediates and that the stannylene complex of 2,3-*manno*-

(2) (a) Zhang, Z.; Wang, P.; Ding, N.; Song, G.; Li, Y. *Carbohydr. Res.* **2007**, *342*, 1159–1168. (b) Cheng, L.; Chen, Q.; Du, Y. *Carbohydr. Res.* **2007**, *342*, 1496–1501.

(3) Cui, B.; Chai, H.; Santisuk, T.; Reutrakul, V.; Farnsworth, N. R.; Cordell, G. A.; Pezzuto, J. M.; Kinghorn, A. D. *J. Nat. Prod.* **1998**, *61*, 1535–1538.

(4) (a) Shan, M.; O'Doherty, G. A. *Org. Lett.* **2010**, *12*, 2986–2989. (b) Shan, M.; O'Doherty, G. A. *Org. Lett.* **2006**, *8*, 5149–5152.

(5) (a) Shan, M.; Xing, Y.; O'Doherty, G. A. *J. Org. Chem.* **2009**, *74*, 5961–5966. (b) Guo, H.; O'Doherty, G. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 5206–5208. (c) Guo, H.; O'Doherty, G. A. *J. Org. Chem.* **2008**, *73*, 5211–5220.

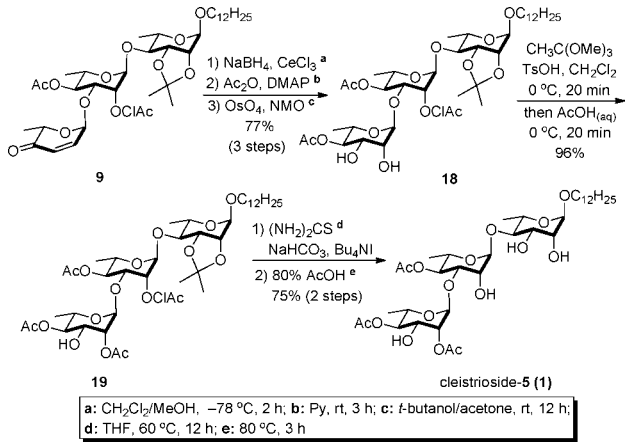
(6) We have reported lower yields for this sequence on larger scale (56%). The pyranone asymmetry is derived from a Noyori reduction; see refs (a) Li, M.; Scott, J. G.; O'Doherty, G. A. *Tetrahedron Lett.* **2004**, *45*, 1005–1009. (b) Babu, R. S.; O'Doherty, G. A. *J. Carb. Chem.* **2005**, *24*, 169–177. (c) Guo, H.; O'Doherty, G. A. *Org. Lett.* **2005**, *7*, 3921–3924.

(7) (a) Babu, R. S.; O'Doherty, G. A. *J. Am. Chem. Soc.* **2003**, *125*, 12406–12407. (b) Babu, R. S.; Zhou, M.; O'Doherty, G. A. *J. Am. Chem. Soc.* **2004**, *126*, 3428–3429.

diols were known to direct alkylation[8]/acylation[9] and silylation[10] to the C3 hydroxyl group, we decided to use the 2,3-*O*-*cis*-stannylene acetal **15** to try to switch the regioselectivity of the Pd-catalyzed glycosylation. In practice, we treated diol **14** with a slight excess of the *in situ* generated $Bu_2Sn(OMe)_2$ before proceeding with our normal Pd-catalyzed glycosylation procedure. To our delight, exposure of the stannylene acetal complex **15** and pyranone **11** to our typical conditions gave the desired glycosylation product **17** in 76% yield (1:7, **16**/**17**). Subsequent chloroacetylation of the C2-hydroxyl group using chloroacetic anhydride in the presence of catalytic amount of DMAP in pyridine provided **9** in excellent yield (97%).

With access to the key intermediate **9** for our proposed divergent synthesis, we embarked on the synthesis of the two cleistriosides (**1** and **2**) via postglycosylation/deprotection sequences (Schemes 4 and 5). As before, a sequential Luche

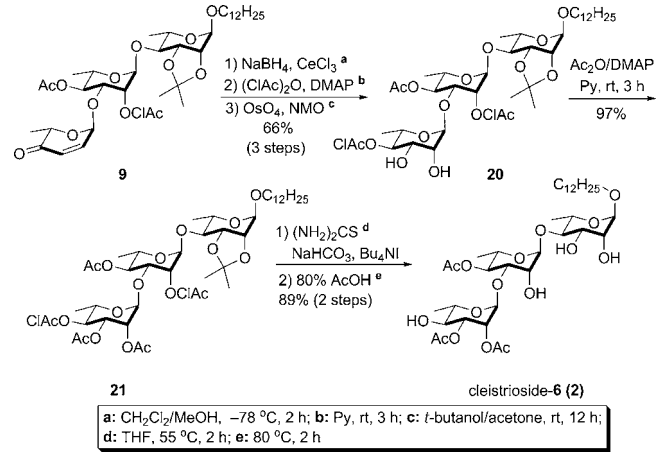
Scheme 4. Approach to Cleistrioside-**5**



reduction, acetylation and Upjohn dihydroxylation installed the *rhamno*-stereochemistry producing diol **18** in 77% yield (for 3 steps). Selective acetylation of the C2 axial hydroxyl group of diol **18** was successfully achieved using orthoester chemistry forming **19** ($CH_3C(OCH_3)_3$/*p*-TsOH then 90% AcOH/H_2O, 96%).[11] Removal of chloroacetyl group using thiourea (3 equiv) in the presence of $NaHCO_3$ (3.3 equiv.) and catalytic Bu_4NI,[12] followed by deprotection of the acetonide group using 80% AcOH/H_2O[2a] furnished the target cleistrioside-**5** (75% yield, two steps).

The same intermediate **9** was used to synthesize the other trisaccharide, cleistrioside-**6** (Scheme 5). For example,

Scheme 5. Approach to Cleistrioside-**6**



switching a chloroacetylation for acetylation step in the postglycosylation sequence of **9** gave **20** (66% yield, 3 steps). A subsequent per-acetylation (**21** in 97%) and similar deprotection sequence generated the target cleistrioside-**6** (89% yield, 2 steps).

We believed that the key intermediate **9** from these two syntheses could also be used for the further divergent synthesis of the desired cleistetrosides (**3**−**8**). This would require a further branching point at the above trisaccharides **19** and **20**, which vary by an acetyl vs chloroacetyl group at C4 in the third sugar (Schemes 6 and 7).

We first turned our attention to the synthesis of the five required protected cleistetrosides (**22**−**26**) from the pivotal intermediate **19** (Scheme 6). Sequential Pd-catalyzed glycosylation, $NaBH_4$ reduction and Upjohn dihydroxylation of **19** afforded the desired triol **22** (64% yield, three steps), which was then peracetylated to give **23** (96% yield). By incorporating an acylation step in the synthesis of **22** tetrasaccharide **25** was prepared from **19** (60% yield, four steps). Whereas, the incorporation of two additional steps (chloroacylation at C4 and orthoester mediated acylation of the axial alcohol at C2) gave the tetrasaccharide **24** (44% yield, 5 steps). Once again, using orthoester chemistry ($CH_3C(OCH_3)_3$/TsOH; AcOH/H_2O) on **25** allowed for the installation of a C2 acetyl group affording the desired C2/C4 diacetate **26** in good yield (93%).

We then turned our attention to the synthesis of the final required protected cleistetroside (**27**) from the remaining pivotal intermediate **20** (Scheme 7). As before, a selective acetylation of the C2 hydroxyl group of diol **20** using orthoester chemistry followed by sequential Pd-catalyzed glycosylation, $NaBH_4$ reduction, and Upjohn dihydroxylation generated triol **27** (58%, 4 steps).

(8) (a) David, S.; Thieffry, A.; Veyrieres, A. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1796–1801. (b) Fernandex, P.; Jimenez-Barbero, J.; Martin-Lomas, M. *Carbohydr. Res.* **1994**, *254*, 61–79.

(9) (a) Ogawa, T.; Nozaki, M.; Matsui, M. *Carbohydr. Res.* **1978**, *60*, C7–C10. Ogawa, T.; Matsui, M. *Carbohydr. Res.* **1977**, *56*, C1–C6. Ogawa, T.; Matsui, M. *Tetrahedron* **1981**, *37*, 2363–2369. (b) Roelens, S. *J. Org. Chem.* **1996**, *61*, 5257–5263. (c) Bredenkamp, M. W.; Spies, H. S. C. *Tetrahedron Lett.* **2000**, *41*, 543–546. Bredenkamp, M. W.; Spies, H. S. C.; van der Merwe, M. J. *Tetrahedron Lett.* **2000**, *41*, 547–550.

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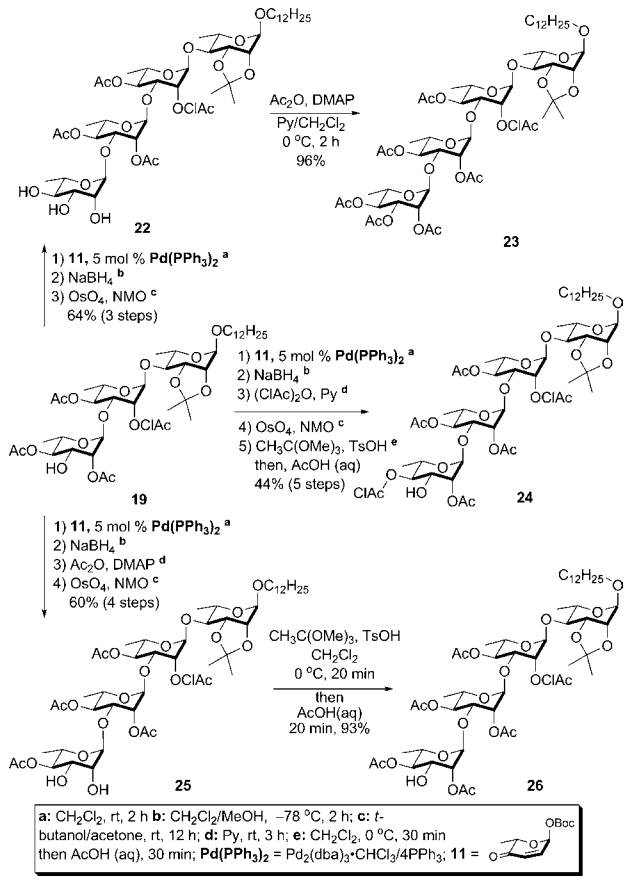
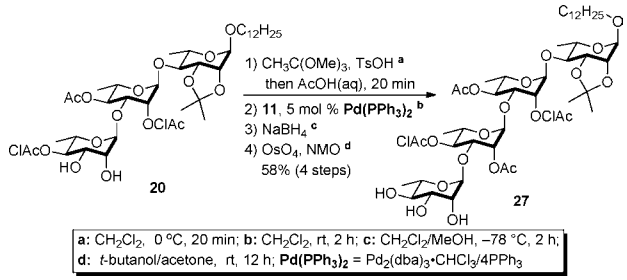
Scheme 6. Synthesis of the Key Intermediates of **22**−**26**



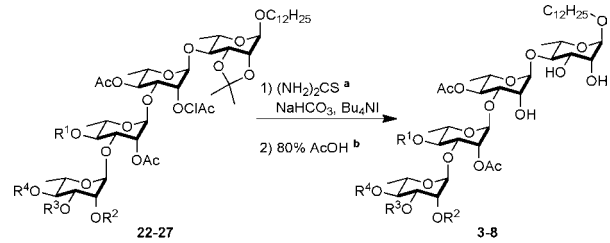
Finally a nearly identical deprotection protocol that was used for the preparation of cleistriosides-**5** and -**6** (Schemes

Scheme 7. Synthesis of the Key Intermediate **27**



4 and 5) could be used for the desired cleistetrosides (Scheme 8). Thus, exposure of all the protected tetrasaccharides **22**−**27** to the typical alkylative cyclization deprotection procedure ($(NH_2)_2CS/NaHCO_3/Bu_4NI$) cleanly removed all the chloroacetyl groups. Similarly, exposure of the products to 80%

Scheme 8. Completion of the Total Synthesis of Cleistetrosides **3**−**8**



25 → **3**: cleistetroside-**2**: $R^1 = R^4 =$ Ac, $R^2 = R^3 =$ H (2 Steps & 74% yield)
24 → **4**: cleistetroside-**3**: $R^1 = R^2 =$ Ac, $R^3 = R^4 =$ H (2 Steps & 83% yield)
22 → **5**: cleistetroside-**4**: $R^1 =$ Ac, $R^2 = R^3 = R^4 =$ H (2 Steps & 65% yield)
27 → **6**: cleistetroside-**5**: $R^1 = R^2 = R^3 = R^4 =$ H (2 Steps & 62% yield)
26 → **7**: cleistetroside-**6**: $R^1 = R^2 = R_4 =$ Ac, $R^3 =$ H (2 Steps & 85% yield)
23 → **8**: cleistetroside-**7**: $R^1 = R^2 = R^3 = R^4 =$ Ac (2 Steps & 93% yield)

aqueous AcOH completed the total synthesis of all desired cleistetrosides in excellent yields. All the synthetic cleistriosides (**1** and **2**) and cleistetrosides (**3**−**8**) had physical and spectral data that matched that reported in the literature (see: Supporting Information).

In conclusion, a short and enantioselective total synthesis of two cleistriosides and six cleistetrosides has been achieved. The synthetic approach is amenable to the installation of all the sugar carbons for these biologically active natural products from achiral acetyl furan (**10**). The sugar absolute stereochemistry was installed by means of a highly enantioselective Noyori reduction and the anomeric stereochemistry by a Pd-catalyzed glycosylation. The remaining *rhamno*-stereochemistry was installed by highly diastereoselective postglycosylation ketone reduction and alkene dihydroxylation. The synthesis also features an organotin mediated regioselective glycosylation achieving the desired reversal diol glycosylation regioselectivity. All the functionalities on the sugar moiety have been established via corresponding postglycosylation transformations with only two protecting groups used. The route to the tetrasaccharide is comparable in terms of total steps to the previous approaches and is more amenable to the synthesis of all members of this family of oligosaccharide natural products. The preparation and further biological investigation of other analogues are ongoing and will be reported in due course.

Acknowledgment. We are grateful to the NIH (GM090259) and NSF (CHEM-0749451) for their generous support of our research program.

Supporting Information Available: Complete experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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