ORGANIC LETTERS

2013
Vol. 15, No. 16
4154–4157

First Total Synthesis of the Proposed Structure of Batatin VI

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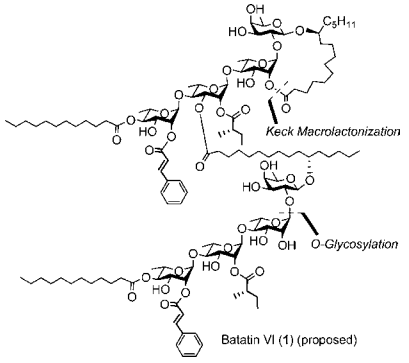
Received June 28, 2013

ABSTRACT



The first total synthesis of batatin VI, an architecturally novel resin glycoside dimer, has been achieved via a convergent [5 + 3] glycosidic coupling approach. An improved protocol for the construction of the key 18-membered macrolactone core using a Keck macrolactonization method was introduced. However, the synthesized compound was not identical to the natural batatin VI.

Plants of the morning glory family (Convolvulaceae) have been cultivated for over 2000 years and were widely used in folk medicine for treating various diseases. Chemical studies on their glycosidic components have led to isolation of a large number of resin glycosides, a class of amphiphilic glycolipids with a characteristic macrolactone backbone.[1] The hydrophobic aglycons usually found in these secondary metabolites are chiral hydroxyaliphatic acids mainly including jalapinolic acid (11(*S*)-hydroxyhexadecanoic acid) and convolvulinolic acid (11(*S*)-hydroxytetradecanoic acid).[2] Yet the hydrophilic carbohydrate sections typically consist of four to six monosaccharides such as D-glucose, D-fucose, L-rhamnose, and D-quinovose. These sugar residues are often modified with some fatty acids. The macrocycle is formed through an intramolecular esterification between the carboxyl group of aglycon and one hydroxy group of the complex oligosaccharide chain.

Merremin, the first glycolipid ester-type dimer, was isolated by Noda et al. in 1995.[3] To date, several members of this type of compound have been identified.[3−7] They feature intriguing structures that are composed of two units of the same resin glycosidic acid. The carboxyl group of aglycon in the acyclic unit esterifies with one hydroxy group of the macrocyclic unit to form the dimer. Bioassays disclose that these dimeric resin glycosides possess a broad spectrum of activities such as increasing the release of γ-aminobutyric acid (GABA) and glutamic acid,[5] a high vasorelaxant effect,[5] and inhibition of multidrug efflux pumps.[7b]

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(1) For reviews, see: (a) Lu, S.-F.; Guo, Z.-W.; O'Yang, Q.-Q.; Hui, Y.-Z. *Youji Huaxue* **1997**, *17*, 488. (b) Pereda-Miranda, R.; Bah, M. *Curr. Top. Med. Chem.* **2003**, *3*, 111. (c) Pereda-Miranda, R.; Rosas-Ramírez, D.; Castañeda-Gómez, J. In *Progress in the Chemistry of Organic Natural Products*, Vol. 92, Chapter 2; Kinghorn, A. D., Falk, H., Kobayashi, J., Eds.; Springer-Verlag: New York, 2010; p 77 and references cited therein.

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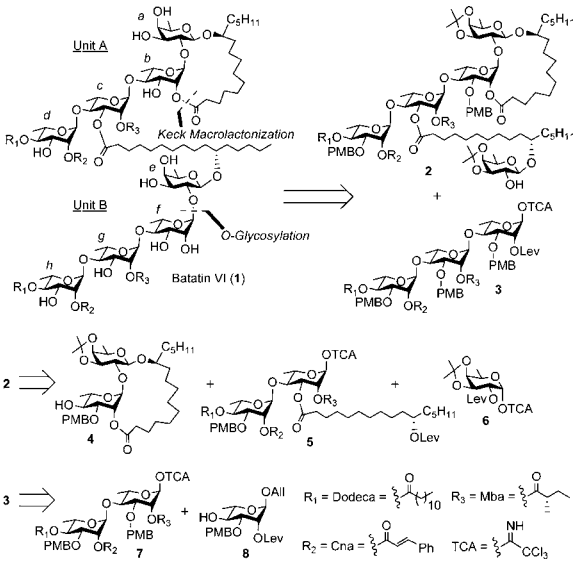
10.1021/ol4020255
Published on Web 07/30/2013

Scheme 1. Retrosynthetic Analysis

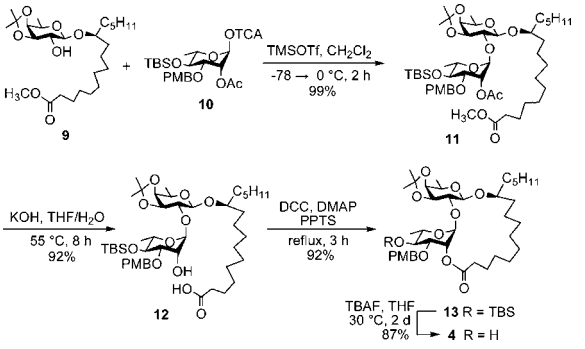


However, studies on their systematic structure−activity relationship are still very limited.

Despite that several total syntheses of resin glycosides have been accomplished,[1c,8] no synthetic work on their dimers has been reported to date. In a continuing investigation on the synthesis of resin glycosides,[9] we have developed an efficient route to optically active methyl 11(*S*)-jalapinolate starting from commercially available (*R*)-glycidol.[9a] Then, by use of a macrolactonization strategy, we realized the total synthesis of batatoside L[9b] and the construction of the 20- and 21-membered macrolactone rings of merremoside-type resin glycosides.[9a] Here, we describe the first total synthesis of the proposed structure of dimeric batatin VI (**1**, Scheme 1). This natural product along with three analogues was isolated by Pereda-Miranda et al. from the tuberous roots of sweet potato (*Ipomoea batatas*).[6b] Structural characterization revealed that **1** is the first example of an ester-type dimer of heterotetrasaccharide operculinic acid C.[10] The ester linkage between the macrocycle-containing unit A and the acyclic unit B is located at C-3 of the rhamnose moiety c in unit A. Moreover, each monomeric unit is acylated with fatty acids including *n*-dodecanoic (Dodeca), *trans*-cinnamic (Cna), and 2(*S*)-methylbutyric (Mba) acids.

As retrosynthetically outlined in Scheme 1, we envisioned that **1** could be obtained in a highly convergent manner via a [5 + 3] glycosidic coupling between pentasaccharide alcohol **2** and trirhamnosyl trichloroacetimidate **3**. The assembly of **2** would in turn involve a sequential [2 + 2 + 1] glycosylation of three building blocks: the heterodisaccharide acceptor **4**, the dirhamnosyl donor **5**, and the fucopyranosyl donor **6** (see Supporting Information). Besides, imidate **3** could be easily derived from glycosylation of compound **7**[9b] with **8**. To guarantee the expected 1,2-*trans* stereochemistry of each glycosylation, an acyl-type functionality acting as a neighboring participating group was incorporated at the 2-position of each donor. Furthermore, in order to simplify the protection/deprotection

Scheme 2. Preparation of Macrolactone Acceptor **4**



manipulation, only three types of protecting groups, i.e. *p*-methoxybenzyl (PMB), levulinoyl (Lev), and isopropylidene groups, were employed.

Our studies on the total synthesis of batatin VI (**1**) began with the preparation of the macrolactone alcohol **4** (Scheme 2). By use of the Schmidt glycosylation conditions,[11] the known **9**[12c] was reacted with monosaccharide **10** (see Supporting Information) in CH_2Cl_2 promoted by catalytic amounts of TMSOTf to furnish **11** in quantitative yield. Glycoside **11** was then saponified with KOH in a THF/H_2O (9:1) cosolvent at 55 °C to release the 2′-OH and the aglycon carboxyl groups, giving seco-acid **12** in 92% yield.

With the precursor **12** in hand, efforts were focused on the key ring-closing process. Producing the unique macrolactone core in these natural products has been considered a major synthetic challenge, in which two methodologies have been adopted so far.[1c,8] One is a macrolactonization approach.[12] For instance, the Corey−Nicolaou protocol was used, respectively, by the Schmidt,[12a] Yu,[12b,c] and our[9b] groups for the total synthesis of calonyctin A1, tricolorin A, and batatoside L. While the Yamaguchi method was utilized by Heathcock[12d−f] and

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Table 1. Optimization of Keck Macrolactonization of **12**[a]

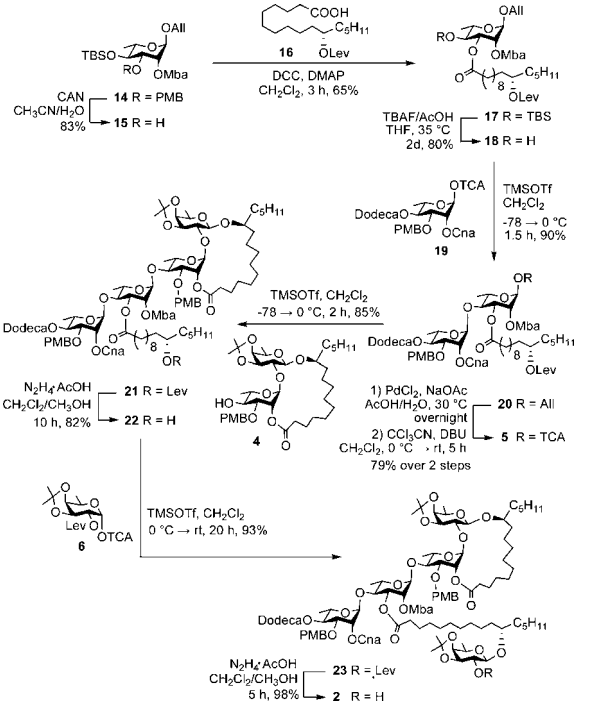
entry	reagent	solvent	time (h)	yield of **13**[b]
1	DCC, pyridine, PPTS	DCE	2	45%
2	DCC, pyridine, PPTS	DCE	12	36%
3	DCC, Et_3N, PPTS	DCE	3	25%
4	**DCC, DMAP, PPTS**	**DCE**	**3**	**92%**
5	DCC, DMAP, DMAP·HCl	DCE	5	77%
6	DCC, DMAP, PPTS	toluene	3	63%

[a] All reactions were run with **12** (1 equiv, 1 mM), DCC (10 equiv), base (pyridine or Et_3N or DMAP, 100 equiv), and a proton source (PPTS or DMAP·HCl, 10 equiv) in DCE or toluene under reflux. [b] Isolated yields.

Sakairi,[12g] respectively, in the synthesis of tricolorin A and other resin glycosides. But this strategy suffers from either long reaction times (5−7 days)[12a−c,9b] or modest cyclization yields (60−71%).[12d−g] The other protocol is an olefin ring closing metathesis (RCM) strategy,[13] by which the Fürstner group[13a−g] and later a team from the Eisai Research Institute[13h] built up the macrolidic systems and succeeded in synthesizing a series of complex resin glycosides. But in this approach, the need to selectively reduce the formed disubstituted C═C double bond in the tether without affecting the unsaturated ester substituents on the sugar chain required careful planning.

In order to improve the efficiency of the macrocycle formation, we decided to explore another protocol. Thus, the Keck macrolactonization[14,15] in which the activated ester intermediate is formed *in situ* and does not need to be isolated was chosen for this purpose (see Table 1). Initially, the hydroxy acid **12** was subjected to the modified Keck conditions (DCC, pyridine, PPTS, 1,2-dichloroethane (DCE), reflux, 2 h),[15a] which provided the desired large ring derivative **13** in 45% yield (Table 1, entry 1). Elongation of the reaction time gave a lower 36% yield (entry 2). After a series of screenings (entries 1−4), it was found that the base is crucial for this reaction. When **12** was macrolactonized with a combination of DCC, DMAP, and PPTS in DCE under reflux for 3 h, the yield of the product **13** was dramatically enhanced to 92% (entry 4). Switching the proton source and the solvent to DMAP·HCl and toluene, respectively, resulted in decreased yields (entries 5−6). Thus, a more reliable approach to gain access to the

Scheme 3. Synthesis of Pentasaccharide Acceptor **2**



macrocyclic framework of resin glycosides via the Keck protocol has been established. This protocol offers a significant advantage over the previous method in terms of a shorter reaction time, simpler operation, and higher yield.

Subsequent desilylation of **13** with TBAF in THF gave the required lactone alcohol **4** in 87% yield (Scheme 2).

The next task was to prepare the pentasaccharide acceptor **2** (Scheme 3). In the event, treatment of compound **14**[9b] with ceric ammonium nitrate (CAN) in aqueous acetonitrile gave alcohol **15**. Then, we attempted to couple **15** with chiral jalapinolic acid derivative **16** (see Supporting Information). However, this was met with difficulty probably due to the steric hindrance around the secondary 3-OH of **15**. A number of condensation reagents, such as EDCI/DMAP, TBTU/DBU, and DCC/DMAP, were examined. At last, the DCC/DMAP system was found to be the most effective, and the desired **17** was isolated in 65% yield. Then, exposure of **17** to TBAF buffered with HOAc in THF[16] at 35 °C for 2 days generated an 80% yield of acceptor **18**. On activation with TMSOTf, this compound was readily coupled to rhamnosyl imidate **19**[9b] at −78 → 0 °C in CH_2Cl_2 to form disaccharide **20**. The anomeric center of **20** was then unmasked by a $PdCl_2$-catalyzed deallylation. Activation of the resulting crude hemiacetal was performed by treatment with CCl_3CN and DBU[11b] to give the desired imidate **5** in 79% yield over two steps.

Then, our attention was directed to the connection of macrocycle acceptor **4** with the fully elaborated donor **5**

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(15) For selected examples of the use of Keck macrolactonization in the total synthesis of macrolides, see: (a) Kasai, Y.; Ito, T.; Sasaki, M. *Org. Lett.* **2012**, *14*, 3186. (b) Hanessian, S.; Ma, J.; Wang, W. *J. Am. Chem. Soc.* **2001**, *123*, 10200. (c) Mulzer, J.; Mantoulidis, A.; Oehler, E. *J. Org. Chem.* **2000**, *65*, 7456.

(16) Smith, A, B., III; Ott, G. R. *J. Am. Chem. Soc.* **1996**, *118*, 13095. TBAF buffered with HOAc has been screened as the best chioce for the deprotection of the TBS ether. The use of other reagents such as TBAF in THF or PPTS led to a 1:1 mixture of **17** and the acyl transfer isomer.

(Scheme 3). But this coupling reaction led to only a 45% yield of the desired **21** under the same Schmidt glycosylation conditions. We reasoned that the unsatisfying outcome might arise from the lability of the donor **5** in the presence of the Lewis acid (TMSOTf). This prompted us to survey another method, i.e., the inverse glycosylation procedure to minimize the exposure of the imidate donor to the Lewis acidic solutions.[17] In such a glycosylation process, the acceptor **4** was premixed with a catalytic amount of TMSOTf (0.4 equiv) and 4 Å molecular sieves in dry CH_2Cl_2 prior to the gradual addition of a CH_2Cl_2 solution of the donor **5** (2.0 equiv) at −78 °C. As a result, the unwanted donor hydrolysis was effectively prevented and the yield of **21** was greatly improved to 85%. Subsequently, selective hydrolysis of the levulinate in **21** under mild basic conditions ($N_2H_4 \cdot AcOH$, CH_2Cl_2/CH_3OH, rt) yielded tetrasaccharide alcohol **22** in 82% yield.

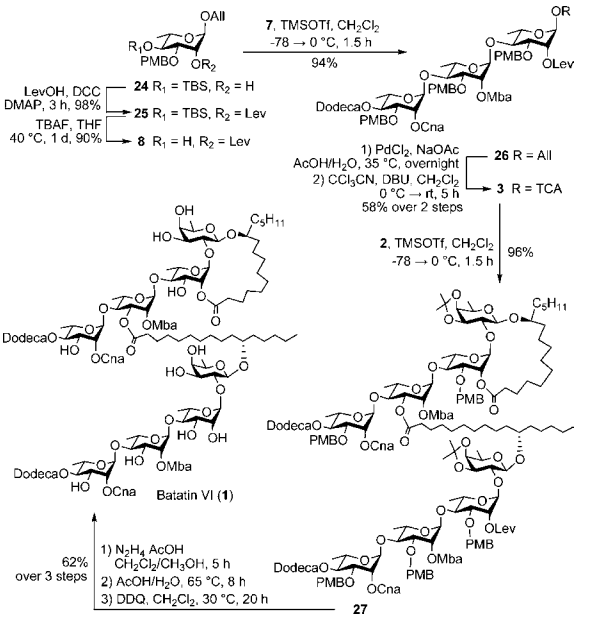
The glycosylation of **22** with the fucose donor **6** also proved to be challenging (Scheme 3). When the glycosylation was carried out under the same conditions as those used for **9** → **11**, only small amounts of product were detected. This is likely due to the steric hindrance of the flexible jalapinolic acid chain. After extensive experimentation, we were pleased to find that, by increasing the amount of **6** to 8 equiv[18] and by conducting this reaction at ambient temperature for 20 h, the expected **23** could be successfully obtained in 93% yield and with complete β-stereoselectivity. This compound was subsequently treated again with $N_2H_4 \cdot AcOH$ to remove the Lev group, affording the corresponding **2** in excellent yield.

Meanwhile, the preparation of trisaccharide intermediate **3** was investigated (Scheme 4). Reaction of monosaccharide **24**[9b] with levulinic acid (LevOH) afforded **25** that underwent a clean 4-*O*-desilylation with TBAF to give alcohol **8**. Glycosidic coupling of **8** with the known donor **7** resulted in a 94% yield of trirhamnoside **26** which was easily converted into **3** utilizing the same two-step transformation procedure (58% yield over two steps).

Finally, the stage was set to bring the fragments **2** and **3** together via *O*-glycosylation (Scheme 4). Under the similar TMSOTf-activated inverse glycosylation conditions, the coupling between **2** and **3** (1.6 equiv) proceeded very well to furnish protected octasaccharide **27** in 96% yield as the sole product. Global deprotection of **27** involved (i) cleavage of the Lev group with $N_2H_4 \cdot AcOH$, (ii) removal of the isopropylidene acetals under acidic conditions (AcOH, H_2O), and (iii) oxidation deprotection of the PMB ethers with DDQ, which gave the target **1** in 62% yield over three steps after chromatographic purification.

Unfortunately, the NMR data of our synthetic material was not in full agreement with those of the naturally occurring batatin VI.[19] The most significant deviation in the ^1H NMR is observed at H-3 of the sugar f in unit B ($\Delta\delta_H$ = 1.4 ppm). Moreover, clear differences ($\Delta\delta_C \geq 1$ ppm) in most anomeric C-1 signals are also observed. The structures of the synthetic intermediates **23** and **26** were evidently determined through the use of NMR and ESI-MS analysis. Complete analysis of 1D (^1H, ^{13}C, 400 MHz) and 2D (gCOSY, HMQC, and HMBC) NMR spectroscopy of **1** confirmed that all the anomeric centers, the linkages of sugar residues, and the substitution positions of ester groups were installed exactly as assigned in the published structure of batatin VI by the Pereda-Miranda group[6b] (see Supporting Information for details). Consequently, a structural revision of batatin VI may be required.[20]

Scheme 4. Completion of Total Synthesis of Batatin VI (**1**)



In summary, the first total synthesis of the proposed structure of batatin VI has been accomplished in a highly convergent manner. The key steps include an improved protocol for the closure of the 18-membered lactone via a Keck macrolactonization and two inverse glycosylation procedures for the prevention of hydrolysis of the donors. The present work provides a facile entry into the natural ester-type resin glycoside dimers. Structural reconsideration of batatin VI is currently underway.

Acknowledgment. The financial support from the NSFC (21172156, 21021001), the 973 program (2010CB833202), and the Ministry of Education (NCET-08-0377, 2010018-1110082) is highly appreciated.

Supporting Information Available. Experimental details, ^1H and ^{13}C NMR spectra for all new compounds, and 2D NMR spectra for **1**, **23**, and **26**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(17) Schmidt, R. R.; Behrendt, M.; Toepfer, A. *Synlett* **1990**, 694. The inverse glycosylation technique has also played a key role in Fürstner and Yang's resin glycoside syntheses; see refs 13d, 13e, and 9b, respectively.

(18) Donor **6** was unable to be recovered as it decomposed to the corresponding hemiacetal during the glycosylation.

(19) The NMR spectra of both the natural (ref 6b) and the synthetic samples were recorded in pyridine-d_5.

(20) For a recent total synthesis of the proposed structure of a natural glycolipid, see: Kondoh, A.; Arlt, A.; Gabor, B.; Fürstner, A. *Chem.—Eur. J.* **2013**, *19*, 7731.