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De novo asymmetric synthesis of the mezzettiaside family of natural products via the iterative use of a dual B-/Pd-catalyzed glycosylation‡

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Abstract

The first synthesis of any and all members of the mezzettiaside family of natural products has been achieved. The reported synthesis features the iterative use of the Taylor catalyst in a dual nucleophilic boron/electrophilic palladium catalyzed regioselective glycosylation. In addition, the *de novo* approach utilizes atomless protecting groups and the minimal use of protecting groups (2 chloroacetates for the synthesis of 10 natural products). These divergent syntheses occurred in a range of 13 to 22 longest linear steps and required only 41 total steps to prepare the entire family of mezzettiasides.

Introduction

The mezzettiasides are a family of partially acetylated oligorhamnose natural products that were isolated from the fruit and bark of several medicinally relevant *Mezzettia leptopoda* Annonaceae plants located in the Malaysian island of Borneo.[1] These anticancer natural products were shown to consist of α-1,3-linked L-*rhamno*-di-, tri- and tetra-saccharides with differing patterns of acetylation (Fig. 1). Initial testing of the mezzettiasides revealed their μg/mL cytotoxicity against three human cell lines (KB, Col2 and Lu1).[2]

As part of a program aimed at the synthesis and biological investigation of anticancer/antibiotic oligosaccharide natural products,[3] we became interested in the synthesis of mezzettiasides. This interest came out of our synthesis and study of a related class of tri- and tetrasaccharide natural products, the cleistriosides and cleistetrosides, [4] where we found the pattern of acetylation had a significant effect on the biological activity. As a continuation of these studies, we desired access to all ten members of the mezzettiaside natural products.

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‡Electronic supplementary information (ESI) available: Experimental procedures, ^{1}H and ^{13}C NMR spectra and correlation studies. See DOI: 10.0000/x0xx00000x

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Author Contributions
S.O.B conducted all the synthetic work. N.G.A. was responsible for the NMR structure elucidation/confirmation. E.U.S. and G.A.O. provided guidance. All authors contributed to the preparation of the manuscript.

Complete experimental procedures and spectral data for all new compounds. This material is available free of charge via the internet at DOI: 10.1039/x0xx00000x

While re-isolation of these materials from the various sources was considered, we instead decided upon a *de novo* asymmetric synthetic approach, [5] as this approach would nicely position us for further structure activity relationship (SAR) studies.[6] We were particularly intrigued at the possibility of efficiently assembling all members of the mezzettiasides via a divergent approach that would minimize the use of protecting groups. Herein, we disclose our successful *de novo* asymmetric approach to all ten members of the mezzettiaside where all the stereocenters in the represented natural products were derived from achiral acetyl furan (**1**).

Retrosynthetically, we envisioned that the three tetrasaccharide (**5-7**) and the four trisaccharide (**2-4** & **8**) mezzettiasides could be obtained from a common pyranone containing trisaccharide intermediate **13** (Scheme 1). In turn, trisaccharide **13** as well as, the three disaccharide natural products (**9-11**) could be prepared from pyran containing rhamnoside **12**. Finally allylic alcohol **12** could be obtained from achiral 2-acetyl furan (**1)** using our *de novo* approach to carbohydrates. [7] Key to the success of this approach is the strategic use of atomless/minimal protecting groups (enone of a pyranone as a masked triol and a chloroacetate as the only protecting group) in combination with the iterative use of a highly stereo- and regio-selective organoboron/Pd-catalyzed glycosylation (*i.e.*, a dual nucleophilic/electrophilic catalysis).[8,9]

Results and discussion

Our synthesis began with pyranone **14**, which can be prepared in optically pure form in 3 steps from achiral furan **1**.[7, 10] Glycosylation of 1-octanol with pyranone **14** using our typical conditions ($Pd_2(dba)_3$•$CHCl_3$/4PPh_3 in CH_2Cl_2)[6] gave enone **15** (93%). Luche reduction ($NaBH_4$/$CeCl_3$) of enone **15** gave allylic alcohol **16** (80%). The C-4 hexanoate ester was installed by a Steglich esterification (DCC/$C_5H_{11}CO_2H$/DMAP) and an Upjohn dihydroxylation (OsO_4/$NMO_{(aq)}$) was used to diastereoselectively install the C-2/3 *rhamno*-stereochemistry (**16** to **17a**) (75%, 2 steps).[11]

We next investigated on a catalytic regio-/stereoselective glycosylation of the C-3 hydroxyl of **17a**. When the Pd-glycosylation was performed on diol **17a,** a 1:2 mixture of regioisomer (C-3 vs C-2) was produced. Previously, we have found that the tin acetal of similar diols can react regioselectively (~7:1) under similar Pd-glycosylation conditions.[4] The tin acetal **17b** formation, however, was difficult to optimize, as conversion to the crude tin acetal must be complete to get good yields and regioselectivities. When this 2-step procedure was performed under optimal conditions, a 5:1 mixture of C-3 to C-2 regioisomers was obtained (68%) (Table 1).

A practical alternative to this difficult to execute procedure emerged when we replaced the stochiometric tin reagent with the catalytic boron reagent developed by Taylor ($Ph_2BOCH_2CH_2NH_2$) resulting in a dual B-nucleophilic/Pd-electrophilic catalyzed glycosylation.[12,13] For instance, when the Taylor catalyst was added to our typical glycosylation conditions (2.5% $Pd_2(dba)_3$•$CHCl_3$/4$PPh_{3,}$ 15 mol% $Ph_2BOCH_2CH_2NH_2$ in CH_2Cl_2) a 2.5:1 mixture of C-3 to C-2 regioisomers was obtained. This ratio was significantly increased to 6:1, when the solvent system was changed from CH_2Cl_2 to

CH_3CN/THF (10:1). Varying the percentage of the boron catalyst from 10 to 30 percent found the optimal B/Pd ratio to be 6:1 for this glycosylation reaction. Presumably the anionic nature of the borinate complex **17c** makes it an ideal coupling partner with the cationic Pd-π-allyl complex (*e.g.*, intermediate **18**, Fig. 2), whereas the more polar solvent improves the turnover rate for the formation of borinate **17c**. Thus, rendering it significantly more reactive than the neutral diol **17a** and as a result requiring on catalytic amounts to impart excellent regiocontrol.

Under our optimized conditions (2.5 mol% $Pd_2(dba)_3 \bullet CHCl_3/4PPh_3$, 30 mol% $Ph_2BOCH_2CH_2NH_2$ in CH_3CN/THF(10:1)) a mixture of **17a**/**14** (1:1.1) was coupled in an 77% yield with good regiocontrol (7.5:1). It is worth noting that when the C-4 ester is smaller (*e.g.*, OAc), significantly better regiocontrol (16:1) was observed in this B-/Pd-dual catalyzed glycosylation (*e.g.*, **23** to **24**, Scheme 5). The mixture of regioisomeric products **19** and **20** was difficult to separate at preparative scales. This was easily solved by protecting the remaining hydroxyl group **19** and **20** as a chloroacetate (**21**) and reducing the enone to give pure allylic alcohol **12** in 85% after silica gel chromatography.

The allylic alcohol portion of **12** could be easily elaborated into the three disaccharide members of the mezzettiasides **9-11** (Scheme 3). Synthesis of mezzettiaside-**9** was accomplished in four steps (64%). Specifically, the allylic alcohol **12** underwent chloroacetylation at the C-4 position ($(ClAc)_2O$, 10 mol% DMAP in Py), followed by an Upjohn dihydroxylation ($OsO_4/NMO_{(aq)}$), bis-acetylation (Ac_2O/Py) and finally bis-deprotection of the two chloroacetate groups (thiourea, $NaHCO_3$ and n-Bu_4NI) [14] to give mezzettiaside-**9**. When the chloroacetylation step was removed from the above sequence, the resulting three steps sequence provides mezzettiaside-**11**, in overall good yield (66%). The regioisomeric diacetate mezzettiaside-**10** was prepared by a slightly different sequence. The allylic alcohol **12** was C-4 acetylated, dihydroxylated, and regioselectively acetylated via orthoester formation to give the protected disaccharide **22** (68%, 3 steps). Once again, selective removal to the C-2 chloroacetate group gave mezzettiaside-**10** (86%). In addition to being an intermediate for the synthesis of mezzettiaside-**10**, disaccharide **22** proved to be the launching point for the syntheses of the remaining tri- and tetrasaccharide members of the mezzettiasides (Schemes 4-6).

The application of this approach to the trisaccharide mezzettiasides **2-4** and **8**, began with the Pd-catalyzed glycosylation of disaccharide **22** with pyranone **14** to give trisaccharide **13** (68%). A four step post glycosylation sequence was used to convert trisaccharide **13** into mezzettiaside **8**. This involved a two-step post-glycosylation transformation ($NaBH_4/CeCl_3$ and $OsO_4/NMO_{(aq)}$) of the enone functionality of **13** into a *rhamno*-sugar, an orthoester mediated axial acetylation at C-2 followed by chloroacetate deprotection to give mezzettiaside **8** (53%, 4 steps).

The key tris-*rhamno*-trisaccharide intermediate **23** for the synthesis of mezzettiaside **2, 3** and **4** was synthesized from trisaccharide **13** by incorporating a C-4 acetylation into the above post-glycosylation sequence ($NaBH_4/CeCl_3$, Ac_2O/Py and $OsO_4/NMO_{(aq)}$), (Scheme 4). Mezzettiaside **4** was obtained by removing the chloroacetate protecting group (**23** to **4**, 82%). The required C-2 acetylation in mezzettiaside **2** was achieved via orthoester while the

C-3 acetate for mezzettiaside **3** was obtained via Taylor borinate catalyzed acetylation of **23**.[12] Finally removal of chloroacetate gave mezzettiaside **2** and mezzettiaside **3** in 64% and 58% overall yield respectively (Scheme 4).

As with disaccharide **22**, trisaccharide **23** served as a point of divergence for the route to the final three tetrasaccharide mezzettiasides **5-7** (Scheme 5). The route to the tetrasaccharide natural products began with a second regioselective C-3 glycosylation (**23** and **14**). This was accomplished once again with use of the Taylor catalyst in the dual B-nucleophilic/Pd-electrophilic catalyzed glycosylation (2.5 mol% $Pd_2(dba)_3$•$CHCl_3$/4PPh_3, 15 mol% $Ph_2BOCH_2CH_2NH_2$ in THF/CH_3CN) to give tetrasaccharide enone **24** in excellent yield 76%. In contrast to **17a** with a more hindered C-4 hexanoate, for diol **23** with a C-4 acetate, only 15 mol% boron catalyst was needed to achieve near complete regiocontrol (>16:1) in the glycosylation. The resulting enone was converted into a *rhamno*-sugar **25** by a successive Luche reduction and Upjohn dihydroxylation (73%, 2 steps). As before, a regioselective C-3 acetylation using catalytic borinate followed by chloroacetate deprotection converted compound **25** into mezzettiaside-**5** (58%, 2 steps). In contrast, a C-2 acetylation via orthoester and a successive chloroacetate deprotection gave mezzettiaside-**6** (**25** to **6;** 61%, 2 steps). Whereas, a direct chloroacetate deprotection of **25** provided the final tetrasaccharide natural product, mezzettiaside-**7** (83%).

Comparison of the spectral data (^1H, ^{13}C NMR) for synthetic mezzettiasides with the data reported for the isolated materials was complicated by the choice of mixed solvent systems (CD_3OD/C_6D_6) used in the isolation work. The same features that allow for increase resolution of the ^1H and ^{13}C spectra from the use of CD_3OD/C_6D_6 also lead to the increased sensitivity to small changes in solvent ratio and water impurities. In addition, slightly different chemical shifts are obtained depending on which solvent is used as the reference standard. This problem with carbohydrate natural products has been previously observed by us[15] and others.[16] By exercising with great care in the solvent ratios we were able to generate ^{13}C NMR spectra for nine of the ten mezzettiasides were the shifts fell within (+/−) 0.5 ppm. Unfortunately, for mezzettiaside **8**, we were unsuccessful at finding the identical solvent system to reproduce the spectra of the natural material. Using the reported ratio ($CD_3OD:C_6D_6$ (6:1)) the difference in ^{13}C NMR shifts was as high as (+/−) 0.9 ppm. It should be noted that the multiplicities and coupling constants in ^1H NMR were in agreement with that found for the synthetic material and consistent with the structure reported. In order to confirm the 3D-structure of the synthetic material, a detailed NMR studies were conducted on synthetic mezzettiaside-**8** (see, SI) as well as mezzettiasides-**3** and **4**. Thus, we believe that the structure of the synthetic and isolated mezzettiaside-**8** are the same. In this regard, we recommend future comparisons to mezzettiaside NMR data should be to the $CDCl_3$ and C_6D_6 spectra for the mezzettiasides reported herein.

Conclusions

In conclusion, we have successfully completed the first total synthesis of any and all members of the mezzettiaside family of natural products. This divergent synthesis of all 10 mezzettiasides occurred in a range of 13 to 22 longest linear steps. A more notable measure of efficiency is that the entire family of natural products was prepared in only 41 total steps

(~ 4 steps/natural product). This highly efficient, regio- and stereo-selective divergent synthesis relied on the strategic use of a novel dual B-/Pd-catalyzed glycosylation, which was used to construct two of the four-glycosidic bonds in progressively more complex settings. Additional efficiencies were achieved by the use of numerous regioselective acetylation as well as an atomless-protecting group strategy which minimized the number of protecting groups required to only two chloroacetate for 10 natural products. The synthesis was amenable for the preparation of significant quantities of each member of the mezzettiasides (5-15 mg) for further biological studies, which will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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11. In general, we have found the $NaBH_4$ (with and without $CeCl_3$) reduction of α-pyranones (**13, 15, 19** and **24**) and the OsO_4 catalyzed dihydroxylation of the resulting allylic alcohol (*e.g.*, **12, 16**) to proceed with virtually complete diastereocontrol, see refs: 4, 6, 7 10.

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13. While the Taylor catalyst has been used in regioselective glycosylations (glycosylbromide with excess Ag_2O, ref. 12), this is the first example of its use to catalytically induce regiocontrol in a catalyzed glycosylation.

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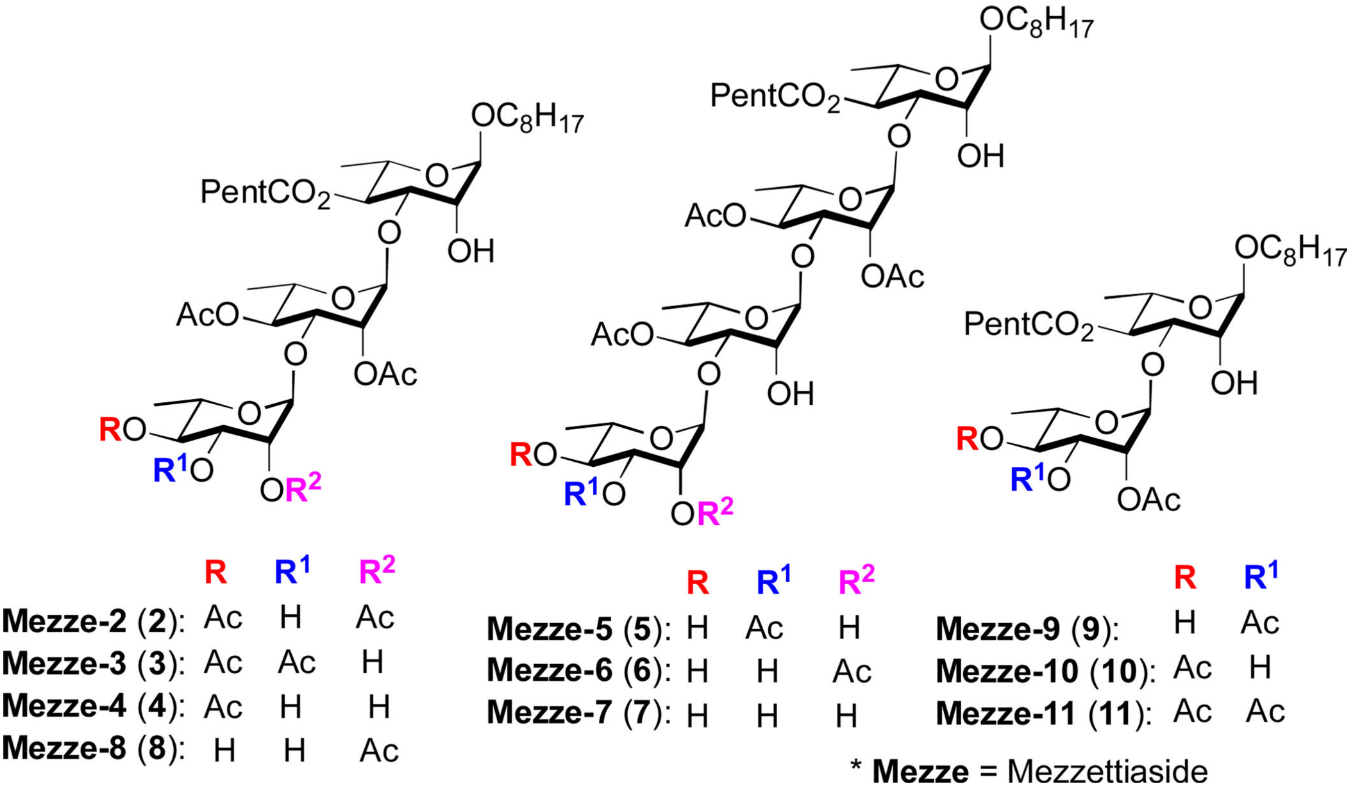


	R	R¹	R²
Mezze-2 (**2**):	Ac	H	Ac
Mezze-3 (**3**):	Ac	Ac	H
Mezze-4 (**4**):	Ac	H	H
Mezze-8 (**8**):	H	H	Ac

	R	R¹	R²
Mezze-5 (**5**):	H	Ac	H
Mezze-6 (**6**):	H	H	Ac
Mezze-7 (**7**):	H	H	H

	R	R¹
Mezze-9 (**9**):	H	Ac
Mezze-10 (**10**):	Ac	H
Mezze-11 (**11**):	Ac	Ac

* **Mezze** = Mezzettiaside

Figure 1.

The mezzettiaside family of natural products

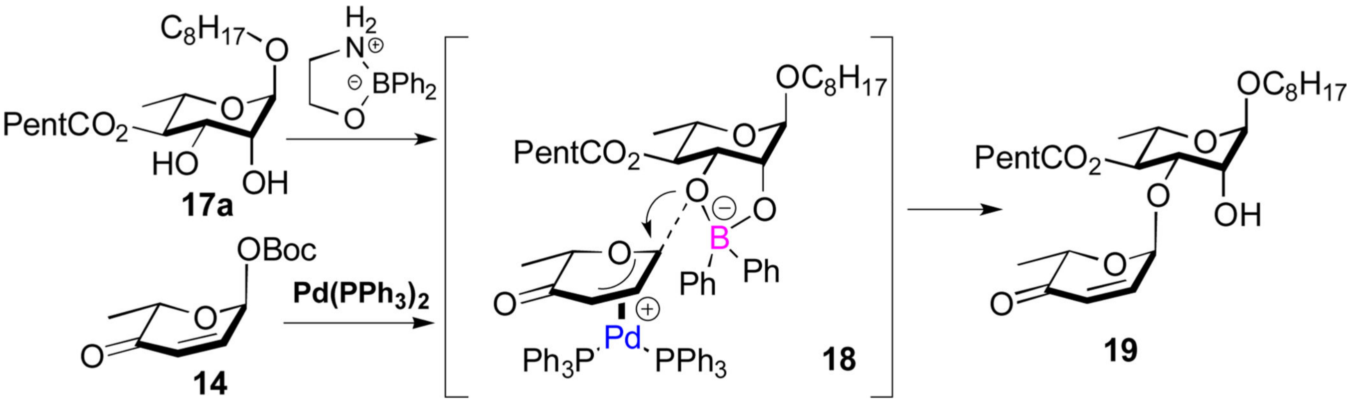
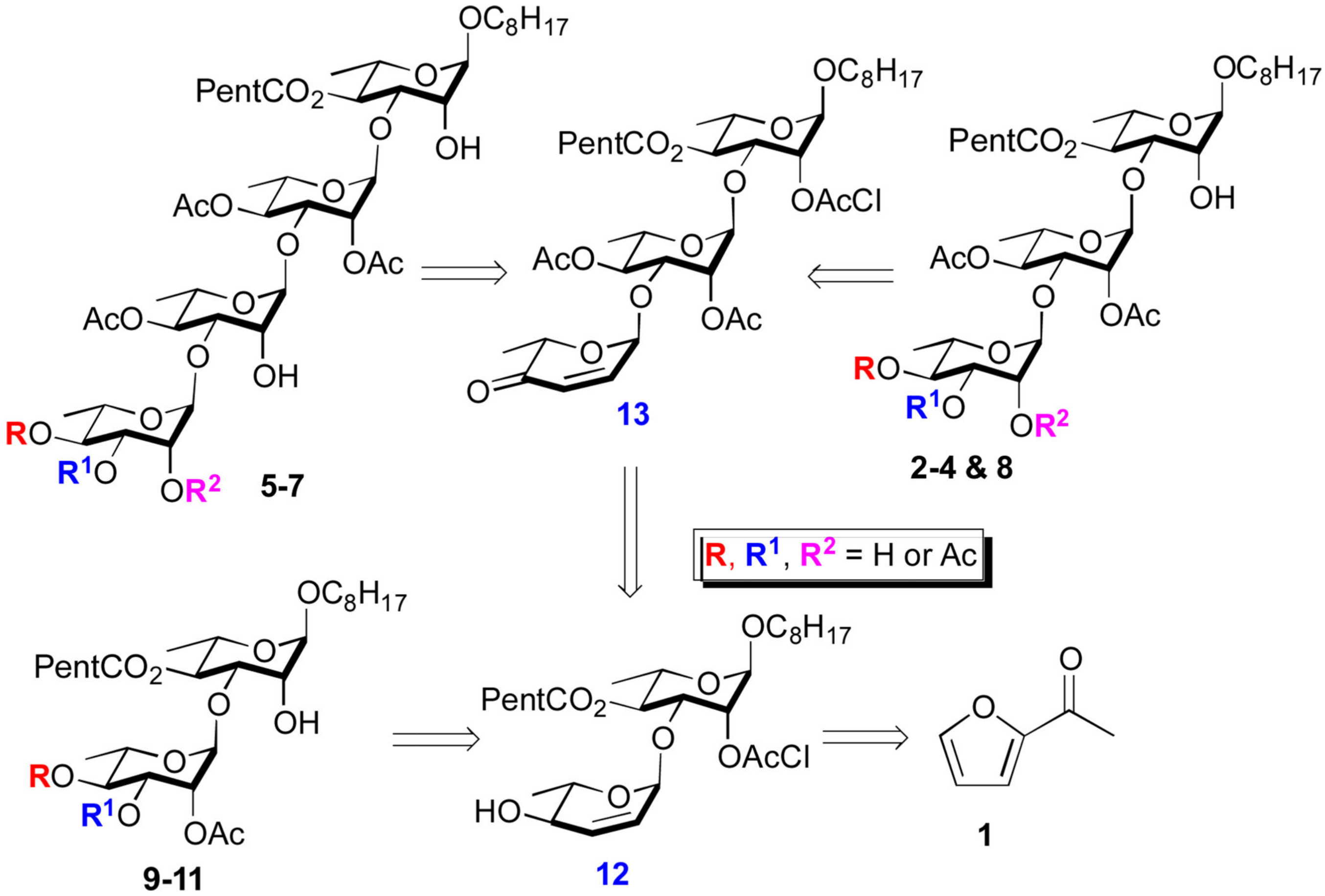


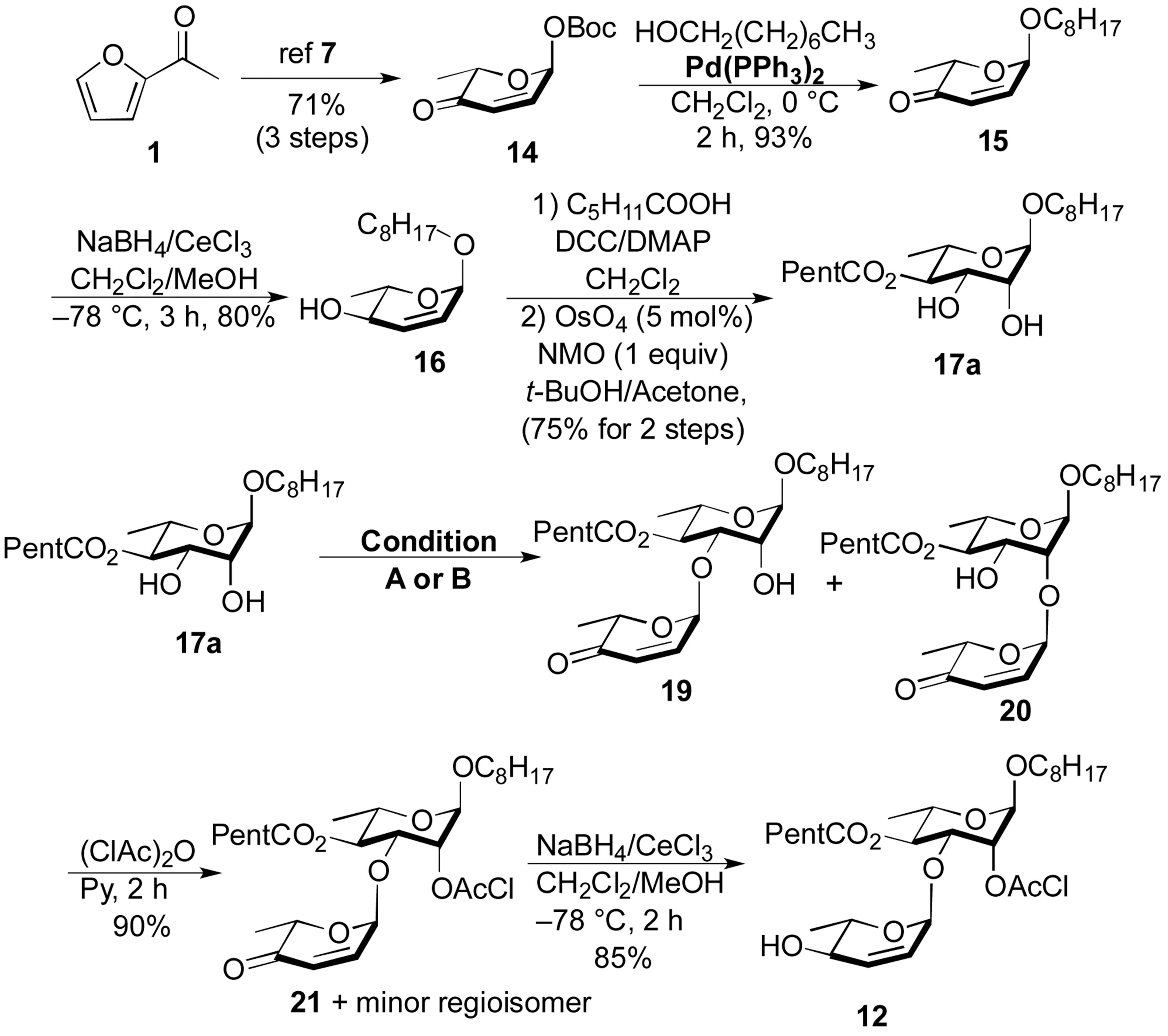
Figure 2.

Plausible transition state for glycosylation via dual catalysis



Scheme 1.

Retrosynthetic analysis of mezzettiasides



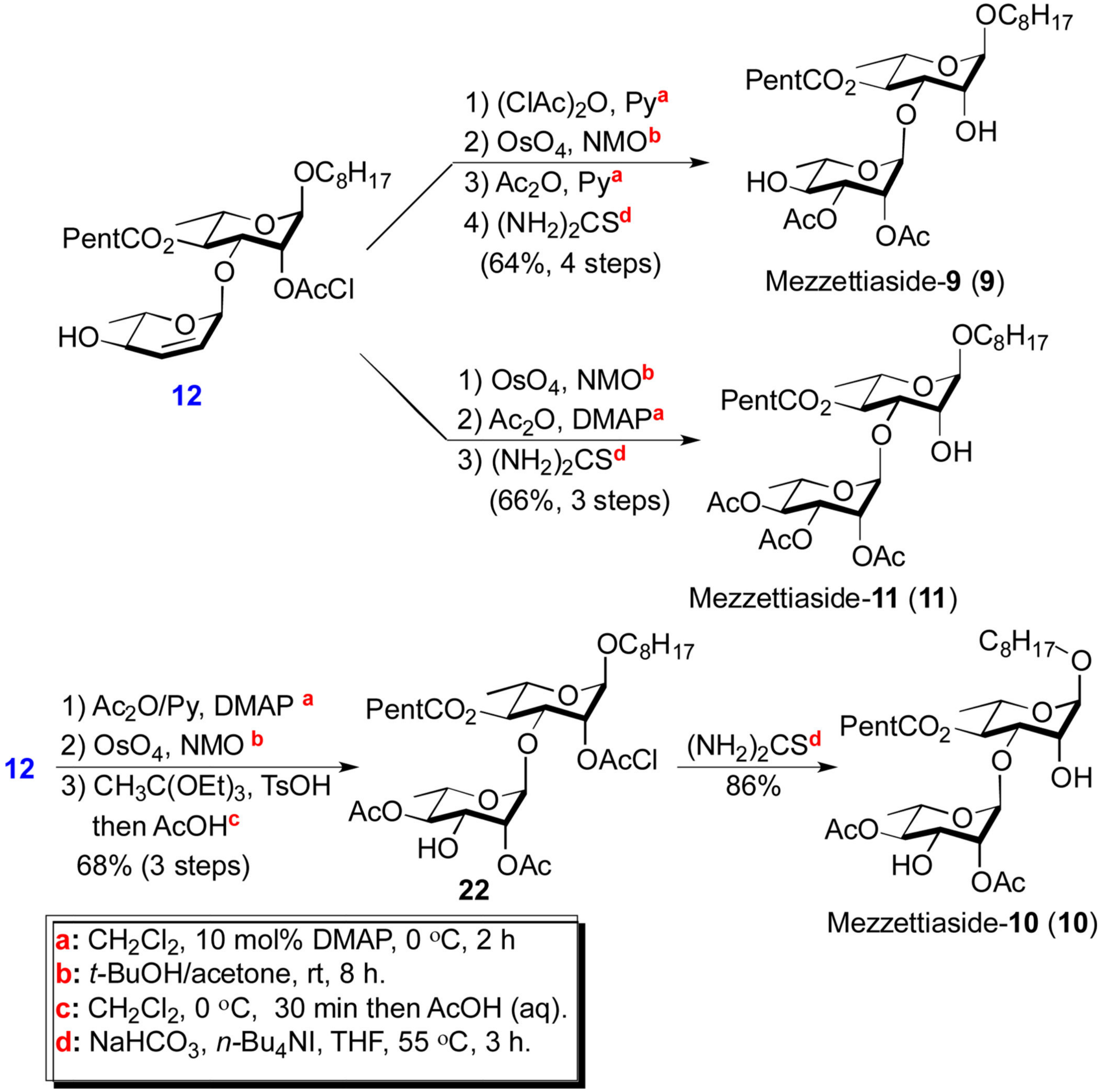
Condition A: 30 mol% $Ph_2BOCH_2CH_2NH_2$, CH_3CN/THF then **14**, **$Pd(PPh_3)_2$,** 74% (7.5:1)

Condition B: n-$Bu_2Sn{=}O$, toluene/reflux then **14 $Pd(PPh_3)_2$,** CH_2Cl_2, 68% (5:1)

$Pd(PPh_3)_2$ = 2.5 mol% $Pd_2(dba)_3$•$CHCl_3$/4PPh_3

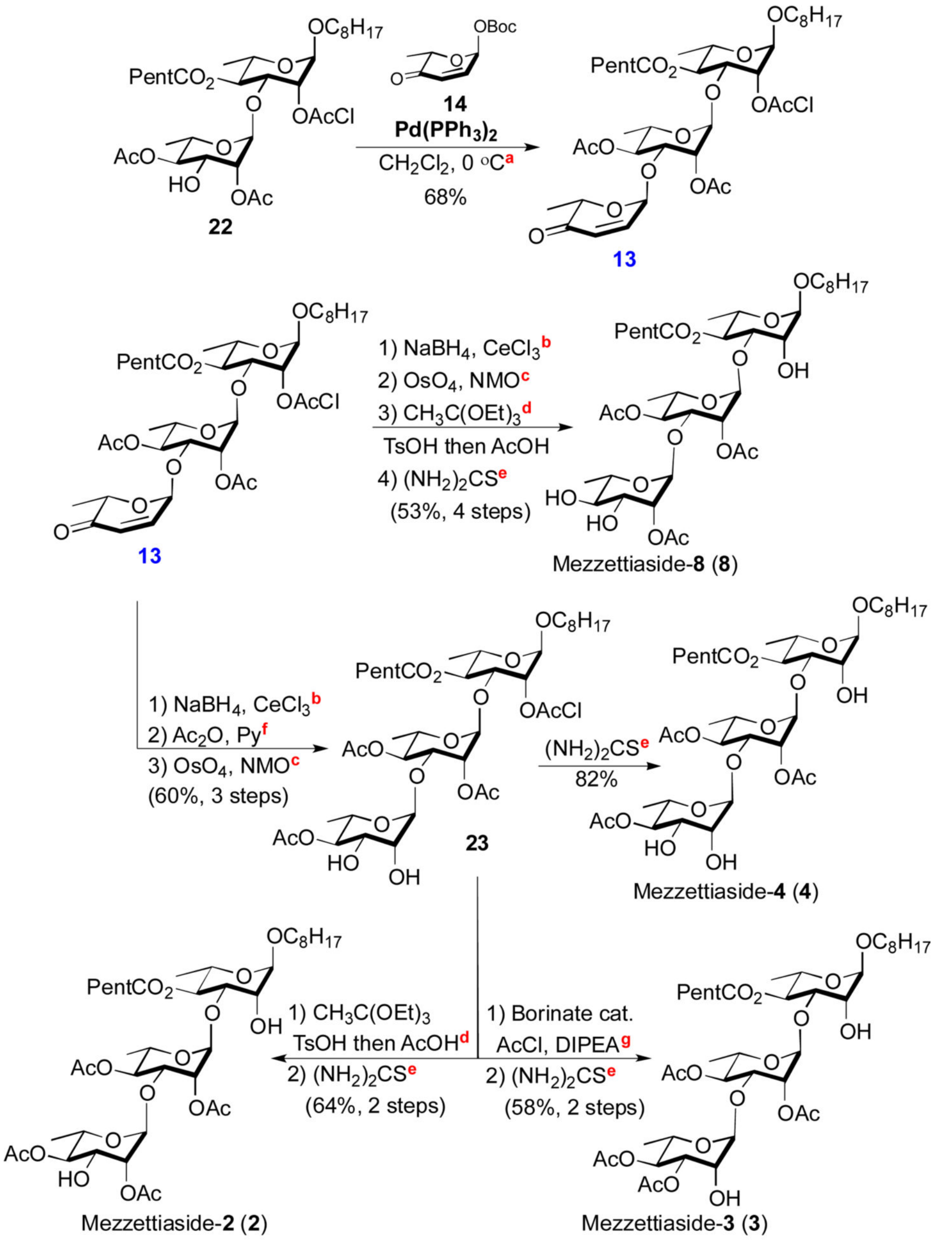
Scheme 2.

Synthesis of key disaccharide intermediate **12**



Scheme 3.

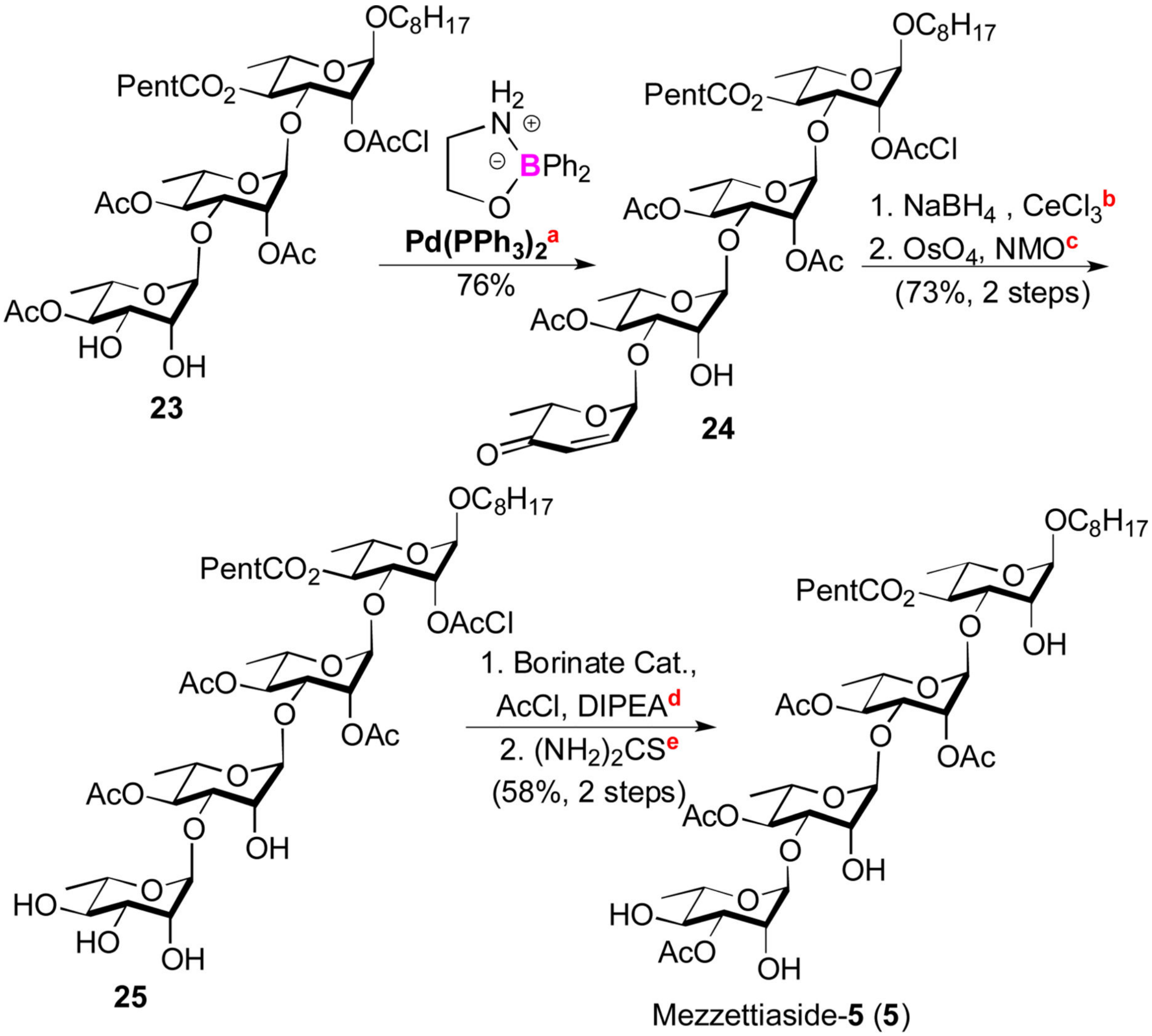
Synthesis of mezzettiaside-**9, 10 & 11**



a: **$Pd(PPh_3)_2$** = 2.5 mol% $Pd_2(dba)_3$•$CHCl_3$/5 mol% PPh_3; **b:** CH_2Cl_2/MeOH, –78 °C, 2 h. **c:** *t*-BuOH/Acetone, 0 °C, 6 h; **d:** CH_2Cl_2, 0 °C, 30 min then AcOH (aq). **e:** $NaHCO_3$, *n*-Bu_4NI, THF, 55 °C, 3 h; **f:** CH_2Cl_2, DMAP, 0 °C; **g:** CH_3CN/THF, 0 °C, 3 h.

Scheme 4.

Synthesis of mezzettiaside-**2, 3, 4 & 8**



a: 14, CH_3CN/THF (1:0.1), 0 °C, 6 h. (15 mol% cat.)

Pd(PPh₃)₂ = 2.5 mol% $Pd_2(dba)_3 \cdot CHCl_3/4PPh_3$

b: $CH_2Cl_2/MeOH$, –78 °C, 2 h.

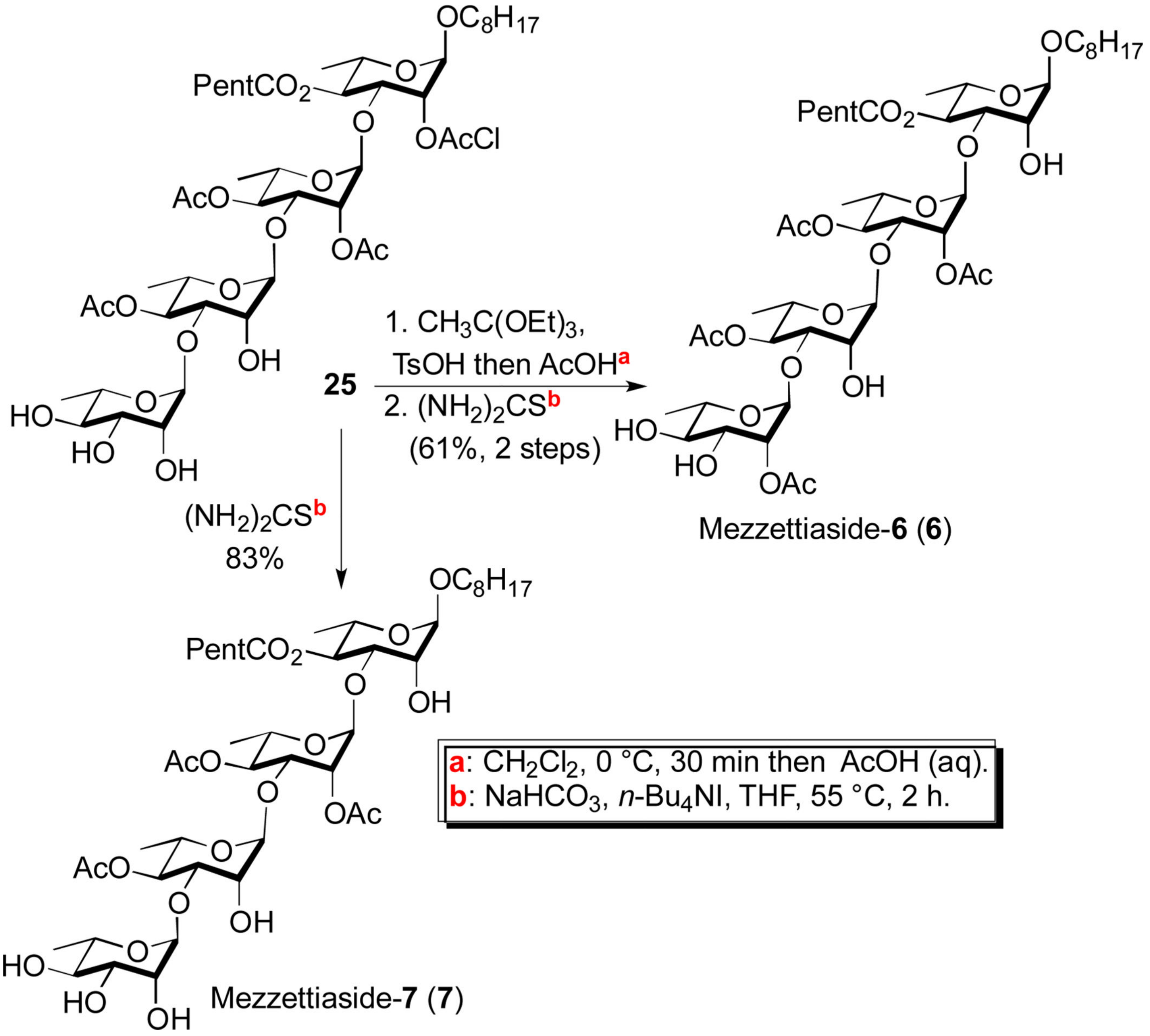
c: *t*-BuOH/acetone

d: 15 mol% cat., CH_3CN/THF, 0 °C, 5 h.

e: $NaHCO_3$, *n*-Bu_4NI, THF, 55 °C, 2 h.

Scheme 5.

Synthesis of mezzettiaside-**5**

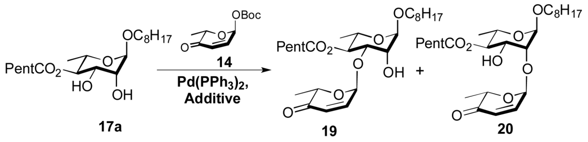


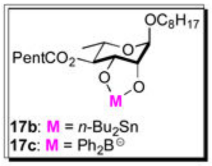
Scheme 6.

Synthesis of the tetrasaccharide mezzettiaside-**6 & 7**

Table 1

Boron vs Tin mediated regioselective glycosylation





Boron Cat.= $Ph_2BOCH_2CH_2NH_2$

Additive	solvent(s)	19:20	yield
none	CH_2Cl_2	1:2	61%
$Bu_2Sn{=}O$ (1.1 equiv)	CH_2Cl_2	5:1	68%
Boron cat. (15 mol%)	CH_2Cl_2	2.5:1	61%
Boron cat. (10 mol%)	CH_3CN/CH_2Cl_2 (1:0.2)	3:1	65%
Boron cat. (15 mol%)	CH_3CN/THF (1:0.1)	6:1	74%
Boron cat. (30 mol%)	CH_3CN/THF (1:0.1)	7.5:1	77%