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Total synthesis of (±) aspidostomide B, C, regioisomeric *N*-methyl aspidostomide D and their derivatives

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ABSTRACT

A full account of the total synthesis of aspidostomide B, C, their analogues and our synthetic efforts towards the synthesis of aspidostomide D, which led to the synthesis of regioisomeric *N*-methyl aspidostomide D, its analogues via epoxide opening strategy is presented. The synthesis of regioisomeric *N*-methyl aspidostomide D involves an efficient, five-step sequence, with 36.3% overall yield, starting from 3,4,5-tribromo-1H-pyrrole-2-carboxylic acid. The key features of this protocol are intramolecular cyclization, dehydration, oxidation, and a Lewis acid-mediated regioselective epoxide ring opening by C-3 position of 2,5-dibromo-1H-indole to furnish the title compounds.

Introduction

Natural products are chemical substances which are derived from natural sources such as plants, animals or microorganism, which have been used traditionally as drugs, drug candidates or lead compounds for novel drugs [1]. Natural products are also an attractive source for generating new anti-bacterial compounds. Marine natural products consist of several halogenated metabolites which have shown antibacterial properties. Bryozoans are a rich source of biologically active compounds which have been studied extensively over the past few years.

Bromopyrrole is a privileged structure that frequently occurs in marine natural products and pharmaceuticals, many of which exhibit simple to the complex structure and display an extraordinarily broad range of biological activities [2]. For example, longamide B, hanishin [3], agesamides A, B [4], mukanadins A-C [5], slagenins B and C [6], agelamadins A, B and F [7], agelastatin A-F [8].

Recently Palermo and co-workers have isolated bromopyrrole containing natural products such as aspidostomides D, E, F and aspidazide A (**1–4**, Fig. 1) from the Patagonian bryozoan *Aspidostoma giganteum*. These compounds have dibromotyrosine or bromotryptophan structural moieties, which forms either linear amides or cyclic amides with a bromopyrrole carboxylic acid as a common structural motif [9].

Because of these diverse molecular architectures and prominent biological activities, our group became interested in the synthesis of marine natural products and their analogues. In our ongoing studies, we recently reported syntheses of brominated marine natural products wilsoniamine A, B, amathamide D, F, convolutamine F, H and lutamide A, C [10], and ianthelliformisamines A-C, their analogues as well as antibacterial evaluation [11]. As a continuation, we aimed to synthesize aspidostomide D (**1**) which eventually led to the synthesis of regioisomeric *N*-methyl aspidostomide D through epoxide opening strategy and total synthesis of aspidostomide B, C and their analogues have been synthesized.

Results and discussion

Aspidostomide D contains a 6,7,8-tribromopyrrolo[1,2-*a*]pyrazin-1(2H)-one moiety which is connected to C-3 position of 2,5 dibromo-1H-indole **11r** [12]. Retrosynthetic analysis for aspidostomide D **1** is shown in Scheme 1. Epoxide **9** was identified as a suitable building block. It was envisaged that the target **1** and its regioisomer **1a** could be secured via an epoxide ring opening of **9** with the nucleophilic C-3 position of 2,5-dibromo-1H-indole **11r** in presence of Lewis acids. Epoxide could be derived via oxidation of alkene **8**, obtained by dehydration of cyclized product **7**. Trans-

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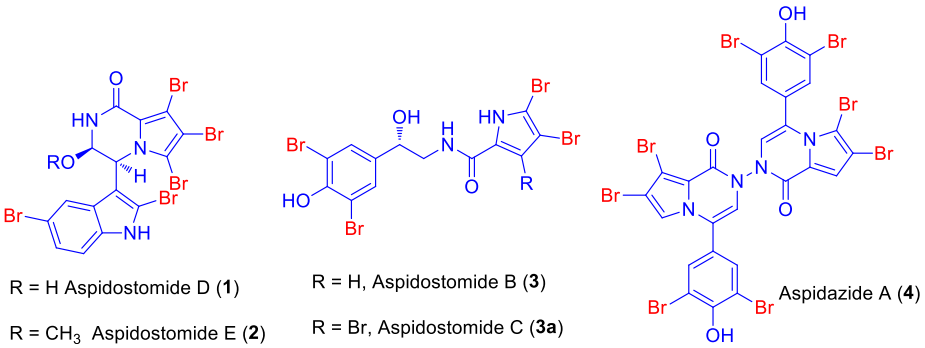
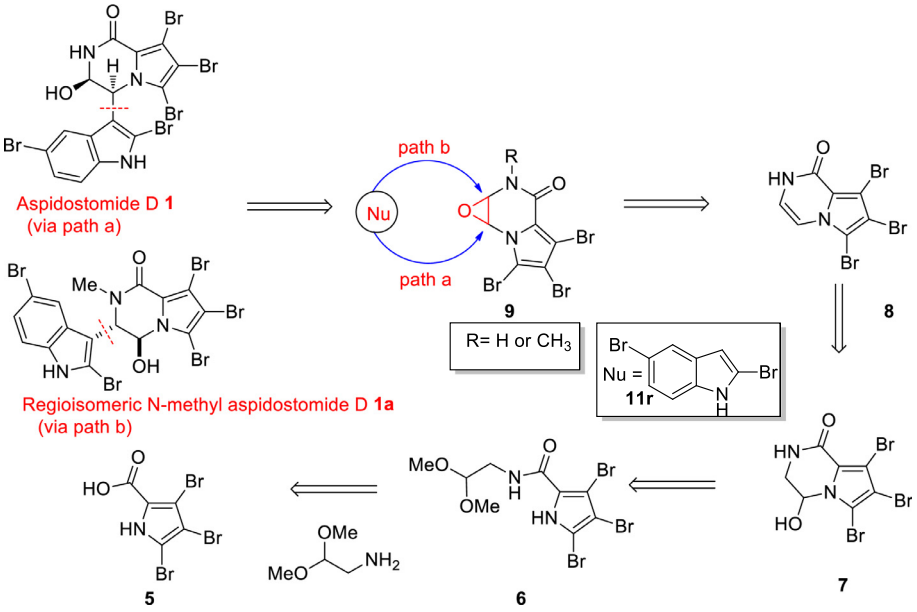
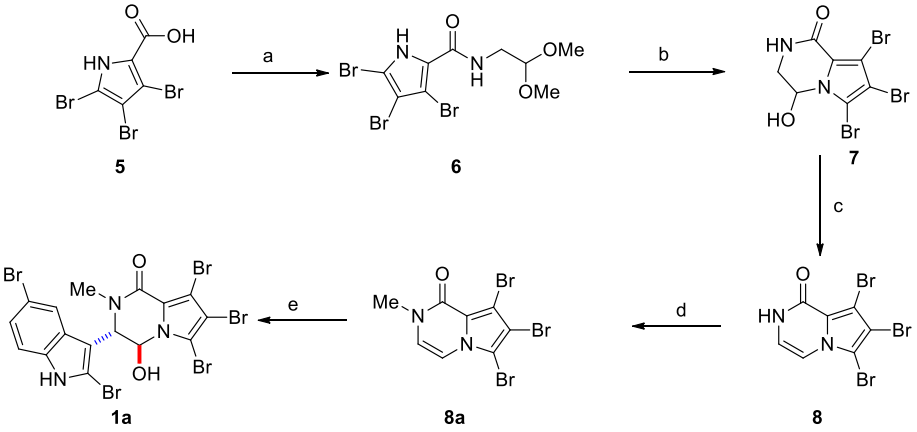


Fig. 1. Structures of the aspidostomides B-E and aspidazide A (**1**–**4**).



Scheme 1. Retrosynthetic analysis of aspidostomide D and its regioisomer.



Scheme 2. Synthesis of regioisomeric *N*-methyl aspidostomide D. **Reaction conditions:** (a) oxalyl chloride (3.5 mmol, 7 equiv) DMF (15 mg, 0.4 equiv), amino acetaldehyde dimethyl acetal (0.650 mmol, 1.3 equiv), pyridine (1.25 mmol, 2.5 equiv), CH_2Cl_2, 0 °C - rt, 14 h, (87%). (b) 2 N HCl (2.5 equiv), acetone, rt, 16 h, (94%). (c) CF_3COOH, 80 °C, 1 h, (94%). (d) NaH 60% dispersion in mineral oil (1.61 mmol, 2 equiv), MeI (3.2 mmol, 3 equiv), DMSO, 0 °C - rt, 12 h, (83%). (e) i, *m*CPBA, 65–75% (0.389 mmol, 1.5 equiv), $NaHCO_3$ (0.779 mmol, 3.0 equiv), CH_2Cl_2, 0 °C - rt, 2 h. ii, $LiClO_4$ (0.249 mmol, 1.0 equiv), 2,5-dibromo-1H-indole **11r**, (0.249 mmol, 1.0 equiv), CH_3CN, 80 °C, 6 h, 57% (over two steps).

formation of **5** through routine amine coupling followed by hydrolysis and intramolecular cyclization of the resulting amide **6** would furnish **7**.

As depicted in Scheme 2, the synthesis commenced by an amine coupling between 3,4,5-tribromo-1H-pyrrole-2-carboxylic acid **5** and amino acetaldehyde dimethyl acetal. Preparation of **5** was accomplished from the commercially available pyrrole-2-carboxaldehyde according to modified literature protocol via oxidation with Ag_2O followed by bromination reaction with Br_2/AcOH [13]. The coupling reaction initially furnished poor yield (33%) of amide **6** with DCC/DMAP which was significantly improved (87%) by performing the reaction with oxalyl chloride and catalytic amount of DMF in presence of amino acetaldehyde dimethyl acetal and pyridine [14]. Preparation of **7** from **6** was accomplished in good yield (94%) via *in situ* hydrolysis followed by cyclisation using 2 M HCl/acetone [14] at ambient temperature. Initially, the dehydration reaction was performed using TsCl/Et_3N which gave poor yield (14%) of the desired product. A significant improvement (94%) was achieved by performing the reaction with TFA [15] as a solvent at 80 °C to obtain **8**. Attempts to transform **8** to epoxide **9** under usual conditions such as *m*CPBA/$NaHCO_3$ and oxone/$NaHCO_3$ were unsuccessful. However, converting the free amide NH in **8** to the corresponding *N*-methyl derivative **8a** by treating with NaH/MeI followed by epoxidation with *m*CPBA and ring opening of fragile crude epoxide in the presence of $LiClO_4$, furnished **1a** in good yield (57%, over two steps), as single regioisomeric ring opening product.

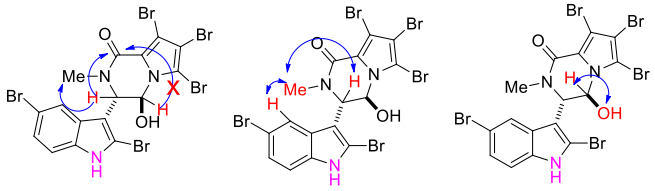


Fig. 2. HMBC, NOESY and COSY correlation of **1a**.

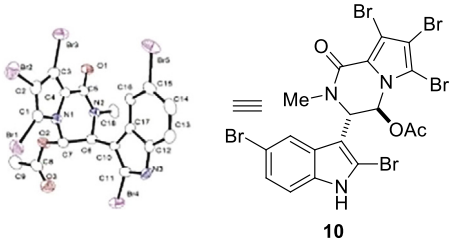


Fig. 3. X-ray crystal structure of compound **10** [17].

We anticipated that Lewis acid catalyzed epoxide opening of compound **9** would give us a mixture of both regioisomers **1** and **1a** via path '*a* and *b*' respectively as shown in Scheme 1. We assumed that both the nitrogen lone pairs will not interfere in the reaction as pyrrole nitrogen lone pair is involved in aromaticity whereas amide nitrogen lone pair is in resonance with a keto group. But contrary to our expectation, we observed selectively one regioisomer **1a**.

The structural assignment for **1a** was based on ^1H, ^{13}C NMR and HRMS data which was further supported by 2D NMR correlations (Fig. 2).

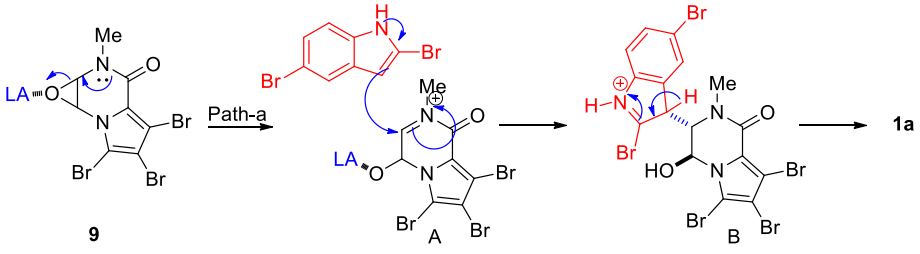
An unambiguous structural proof was obtained by performing a single crystal X-ray analysis of the corresponding acylated product **10**, prepared by performing the acylation reaction of **1a** with Ac_2O in presence of DMAP/Et_3N/CH_2Cl_2 [16] in good yield (Fig. 3).

Based on the product formed, we proposed a plausible mechanism to explain the observed selectivity as depicted in Scheme 3. Amide nitrogen is possibly assisting the epoxide opening followed by nucleophilic attack of C-3 position of 2,5-dibromo-1H-indole **11r** followed by aromatization leading to compound **1a**.

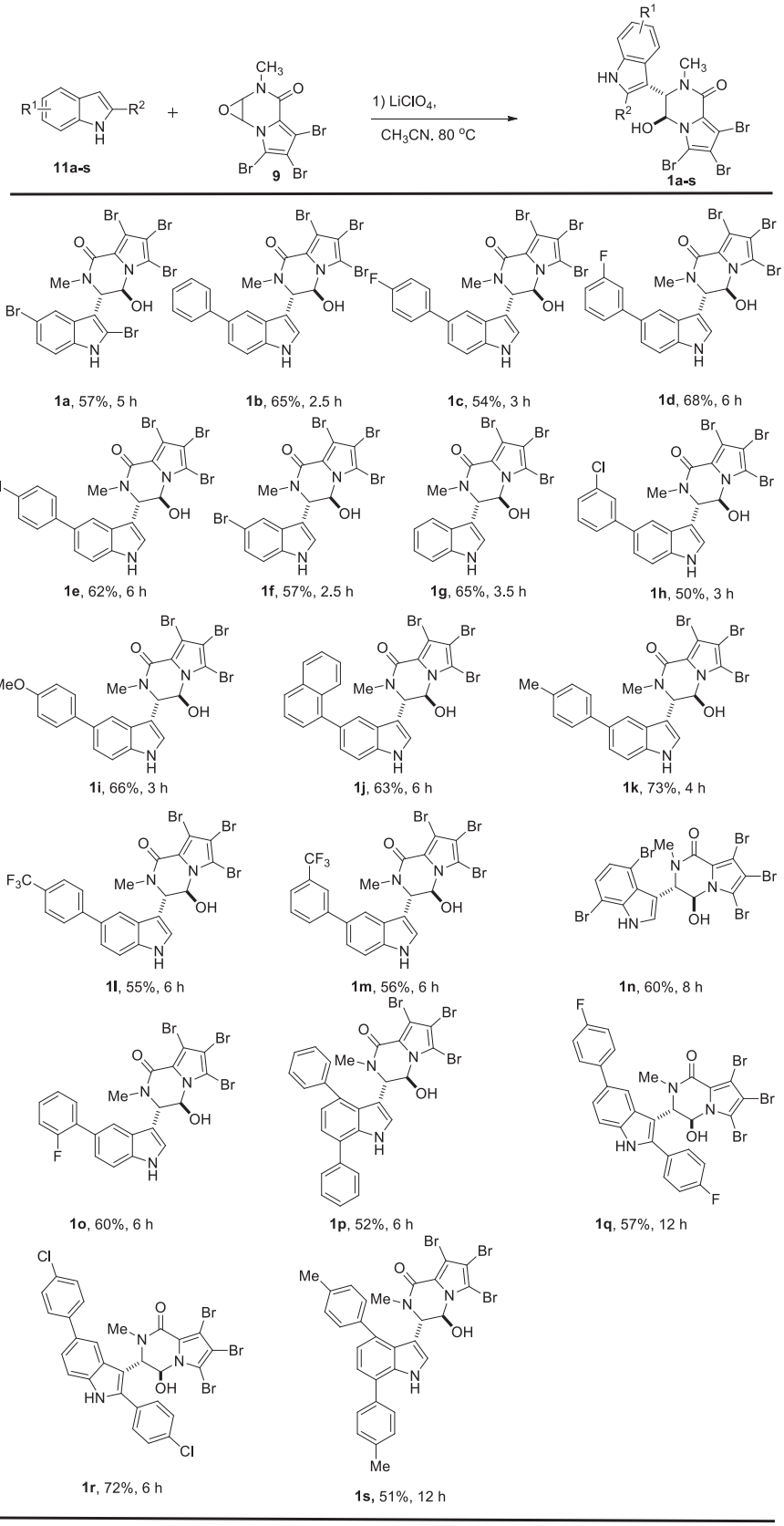
Additionally, we have synthesized a variety of different regioisomeric *N*-methyl aspidostomide D analogues **1a-s** (a total of **19** analogues, as shown in Scheme 4) by employing various indole derivatives **11a-s**, having different substitutions. The same reaction procedure as for **1a** (*vide supra*) was used to obtain moderate to good yields, as shown in Scheme 4. The indole derivatives **11a-s** were synthesized by using Suzuki cross-coupling [12,18].

Aspidostomides B and C contain a dibromotyrosine moiety which is connected with bromopyrrole carboxylic acid via amide functionality.

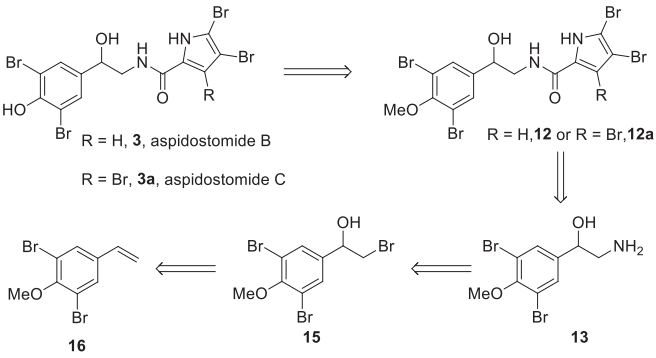
Retrosynthetic analysis of our approach for aspidostomides B and C is shown in Scheme 5. Intermediate **12** or **12a** was identified as a suitable building block. It was imagined that the target **3** and **3a** could be secured via demethylation of **12** or **12a**. Intermediate **12** or **12a** could be derived via routine acid amine coupling of **13** with a bromopyrrole carboxylic acid. Amino alcohol **13** could be



Scheme 3. Proposed mechanism for the synthesis of regioisomeric *N*-methyl aspidostomide D.



Scheme 4. Synthesis of a regioisomeric *N*-methyl aspidostomide D and its analogues. **Reaction conditions**: $LiClO_4$ (1.0 equiv), indole derivatives **11a-s** (1.0 equiv), epoxide **9** (1.0 equiv), anhydrous CH_3CN, 80 °C, 2.5–12 h, under nitrogen atmosphere.



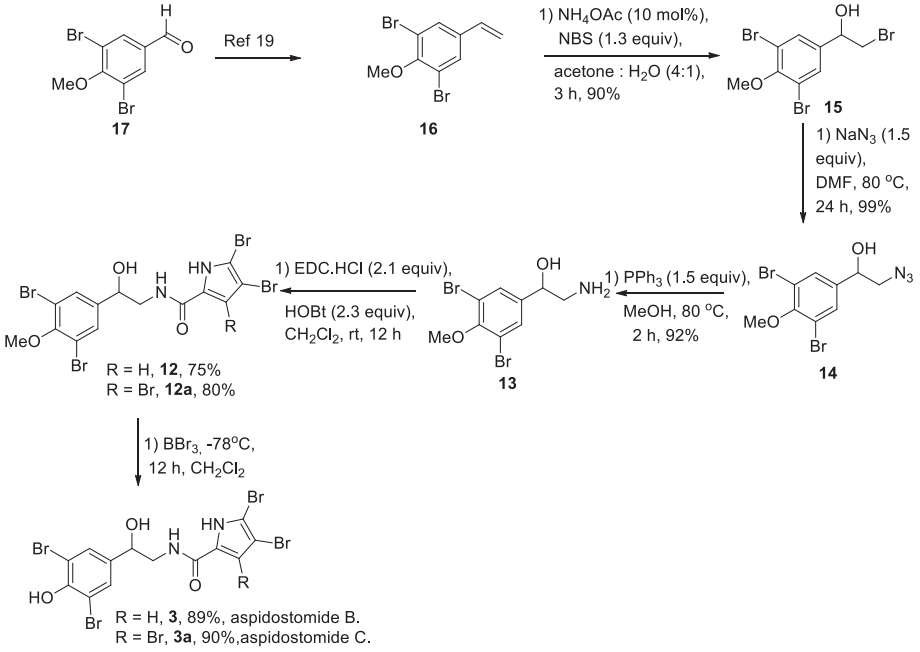
Scheme 5. Retrosynthetic analysis of aspidostomide B and C.

derived via azidation of **15** followed by reduction. Conversion of **16** to **15** through bromohydrin of the resulting alkene would furnish **15**.

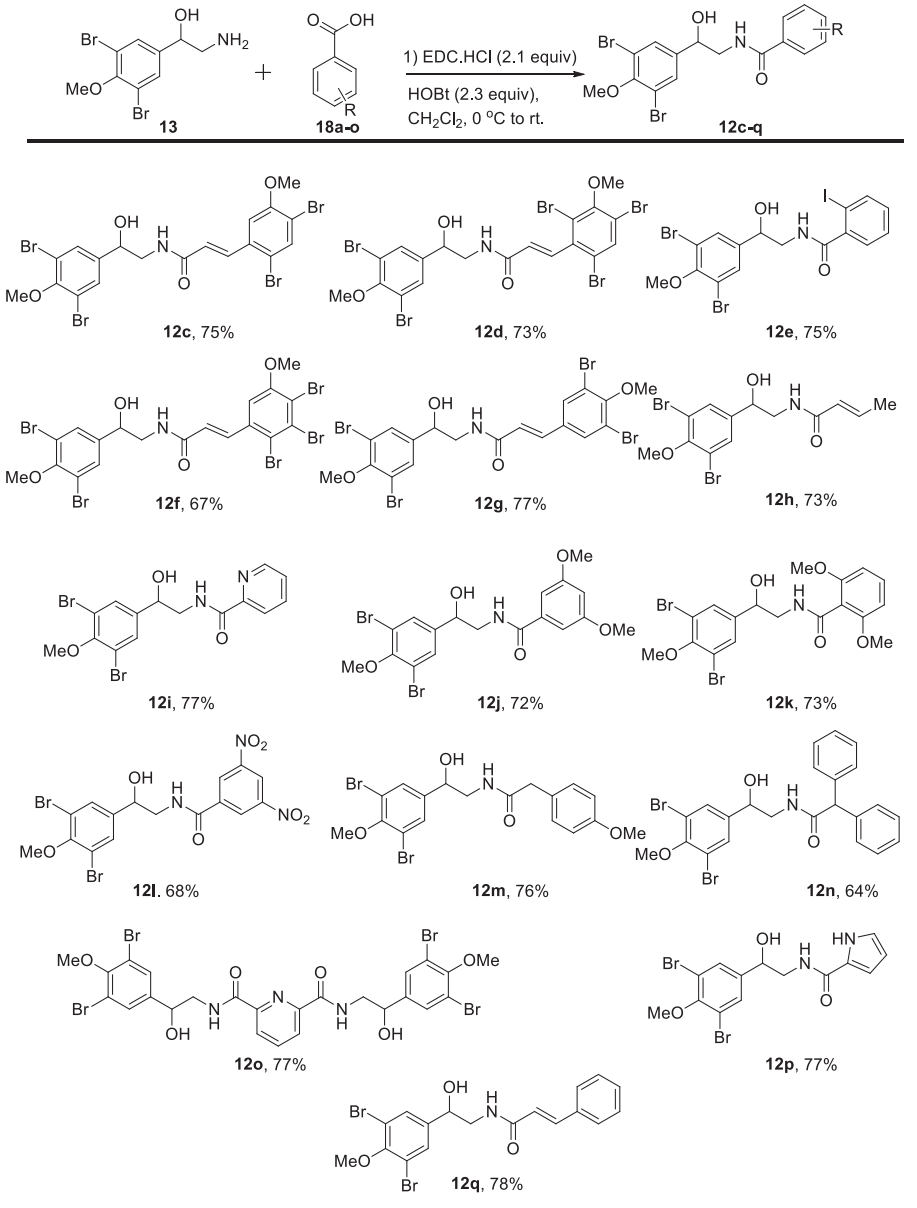
As depicted in Scheme 6, the synthesis of aspidostomide B and C was commenced by the preparation of known aldehyde **17** from commercially accessible 4-hydroxy benzaldehyde as reported earlier.[19] The aldehyde **17** was treated $CH_3P(C_6H_5)Br$ in presence of KO^tBu under Wittig olefination conditions to furnish olefin **16** in 82% yield. The olefin was subjected to bromohydroxylation in presence of NBS and a catalytic amount of ammonium acetate in a mixture of acetone, water (4:1) to furnish compound **17** in 90% yield. The bromo group in **15** was replaced with NaN_3 to furnish **14** in nearly quantitative yield. Reduction of **14** with PPh_3 in MeOH at 80 °C was accomplished in excellent yield to obtain **13** [10]. Amidation of the free $-NH_2$ in **13** with 4,5-dibromo pyrrole carboxylic acid and 3,4,5-tribromo pyrrole carboxylic acid by using EDC.HCl/HOBt [11] in CH_2Cl_2, at 0 °C to room temperature gave the corresponding amide products **12** and **12a** in good yield (75 and 80%, respectively). Attempts to transform **12** and **12a** to **3** and **3a** under nucleophilic demethylation conditions such as CH_3SNa/DMF, NaHMDS/HMPA were unsuccessful. A significant transformation of **12** or **12a** to **3** or **3a** was accomplished by performing reaction with BBr_3/CH_2Cl_2 at −78 °C to obtain the desired products in good yield (89 and 90%, respectively).

Additionally, we have synthesized a variety of O-methyl aspidostomide B and C their analogues **12c-q** (a total of **15** analogues, as shown in Scheme 7) by employing various acid derivatives **18a-o**, having different substitutions. The same reaction procedure as for **12** or **12a** (*vide supra*) was used to obtain good yields, as shown in Scheme 7.

In summary, we have synthesized a regioisomeric *N*-methyl aspidostomide D **1a** via regioselective epoxide ring opening reaction with 2,5-dibromo-1H-indole **11r** in presence of $LiClO_4$. This strategy was extended to synthesize a variety of synthetic regioisomeric *N*-methyl aspidostomide D analogues, by varying indole derivatives. First total synthesis of aspidostomide B, C and their analogues has been reported.



Scheme 6. Synthesis of (±) aspidostomide B and C.



Scheme 7. Synthesis of O-methyl aspidostomide B & C analogues. **Reaction conditions**: EDC.HCl (2.1 equiv), HOBt (2.3 equiv), corresponding derivatives **12c-q** (1.2 equiv), compound **13** (1.0 equiv), anhydrous CH_2Cl_2, 0 °C to rt, 12 h.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2019.151040.

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