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Total synthesis and absolute stereochemistry of (+)-batzellaside B and its C8-epimer, a new class of piperidine alkaloids from the sponge *Batzella sp.*

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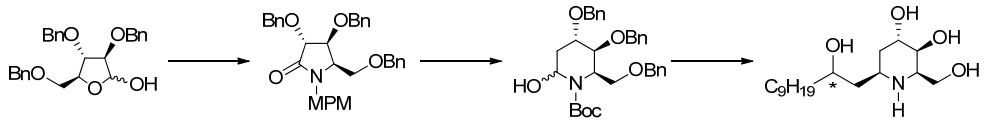

L-arabinose tribenzyl ether

(1*S*,3*S*,4*S*,5*R*,8*S*)-(+)-batzellaside B
(1*S*,3*S*,4*S*,5*R*,8*R*)-8-*epi*-batzellaside B

Pergamon

TETRAHEDRON
LETTERS

Total synthesis and absolute stereochemistry of (+)-batzellaside B and its C8-epimer, a new class of piperidine alkaloids from the sponge *Batzella sp.*

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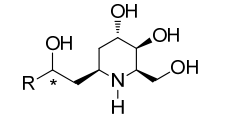
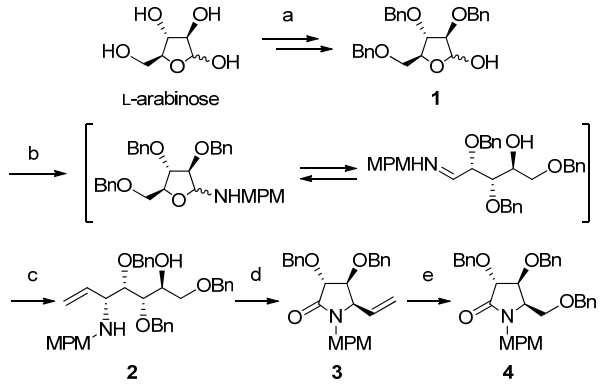
Abstract—The first total synthesis of (+)-batzellaside B and its C8-epimer was completed from a known L-arabinose-derived tribenzyl ether in 22 steps with overall yields of 3.9% and 5.4%, respectively. The absolute configuration of (+)-batzellaside B was unambiguously determined to be 1*S*,3*S*,4*S*,5*R*,8*S* by the Mosher analysis of a synthetic intermediate prepared through a separate route.



batzellaside A; R = $C_{10}H_{21}$
B; R = C_9H_{19}
C; R = $C_{11}H_{23}$

The batzellasides are a novel class of *C*-alkylated iminosugars originally isolated from *Batzella sp.*, a sponge collected off the west coast of Madagascar, on the basis of the first example of iminosugars from marine organism.[1] In addition to antibacterial potency against *Staphylococcus epidermidis* with MIC values less than 6.3 μg/mL, their unique structural properties provide an intriguing extension of the iminosugar frameworks due to the fact that they are biosynthetically related to a variety of plant-derived alkaloids rather than marine-derived ones, thereby attracting attention to the research field of contemporary drug discovery. Unfortunately, the low natural abundance of batzellasides has limited their availability, further impeding complete understanding of the absolute configurations and extensive studies on the development of biologically potent analogues. Although total synthesis would address this supply problem, no reports, to our knowledge, have appeared previously describing successful studies on the synthesis of these compounds. In this publication, we report our initial efforts in the first total synthesis and absolute stereochemical assignment of (+)-batzellaside B as a representative example among constituent members of the batzellaside family.



Scheme 1. *Reagents and conditions*: (a) see ref. 2; (b) $MPMNH_2$, toluene, reflux, 5 h; (c) CH_2=CHMgCl, THF, -78 to 0 °C, 2 h; 81% (two steps); (d) PCC, MS 4Å, CH_2Cl_2, 0 °C to rt, 1 h; 64%; (e) i, OsO_4, NMO, acetone, rt, 4 days; ii, $NaIO_4$, THF-H_2O (1:1), 0 °C to rt, 3 days; iii, $NaBH_4$, MeOH, 0 °C to rt, 24 h; iv, BnBr, Ag_2O, DMF, rt, 24 h; 90% (four steps).

Our strategy for the target-directed synthesis involves the use of commercially available L-arabinose as an appropriate chiral source for the required stereocenters (Scheme 1). The synthesis began with the preparation of 2,3,5-tri-*O*-benzyl-L-arabinose **1** by following the published procedure.[2] Reaction of **1** with *p*-

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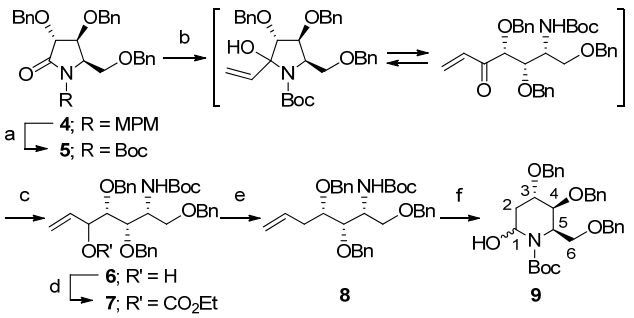
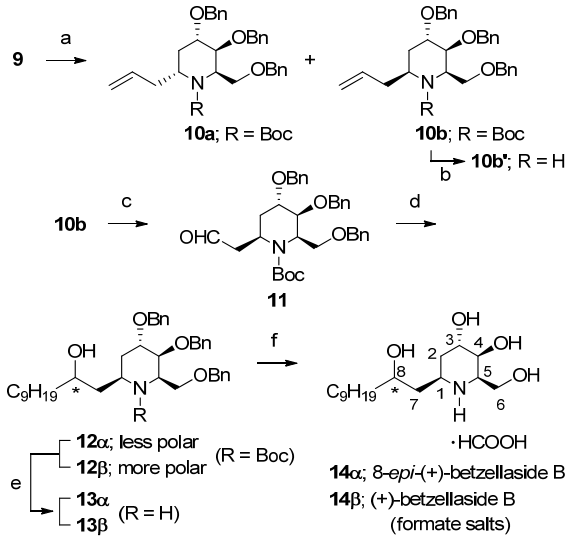
methoxyphenylmethyl amine ($MPMNH_2$) in refluxing toluene led to complete consumption of the substrate and clean formation of aminal intermediate, which would exist in equilibrium with the corresponding γ-hydroxy imine. In agreement with our previous findings on similar reactions,[3] this equilibrium was shifted toward the ring-opened form through treatment of this mixture with vinylmagnesium chloride, facilitating the *syn*-selective reaction to provide the diastereomerically pure adduct **2** in 81% yield from **1**. When the secondary hydroxyl group of **2** was converted into the carbonyl group upon treatment with pyridinium chlorochromate (PCC), in situ cyclization took place to give γ-lactam **3** in 64% yield, whose stereochemistry at the C5 center was established by comparison of its ^{13}C NMR spectrum with that for the antipode of **3**.[4] Oxidative cleavage of the vinyl group in **3** by a two-step procedure of dihydroxylation with *N*-methylmorpholine-*N*-oxide (NMO) and OsO_4 followed by reaction with $NaIO_4$ gave aldehyde, which was subjected to successive $NaBH_4$ reduction and benzyl protection without purification, giving the corresponding benzyl ether **4** in 90% over four steps.



Scheme 2. *Reagents and conditions*: (a) i, CAN, MeCN-H_2O (9:1), 0 °C to rt, 2.5 h; ii, Boc_2O, Et_3N, DMAP, CH_2Cl_2, 0 °C, 2 h; 77% (two steps); (b) CH_2=CHMgCl, THF, -78 °C, 1.5 h; (c) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, 0 °C, 2 h; 81% (two steps); (d) $ClCO_2Et$, py, 0 °C to rt, 12 h; quant.; (e) $Pd(PPh_3)_4$, HCO_2NH_4, Et_3N, toluene, reflux, 30 min; 86%; (f) i, OsO_4, NMO, acetone, rt, 24 h; ii, $NaIO_4$, THF-H_2O (1:1), 0 °C to rt, 3.5 h; 98% (two steps).

At this point, we envisioned that replacement of the MPM moiety of **4** with the Boc functionality would offer potential advantages making the lactam carbonyl more reactive in nucleophilic processes due to reduced conjugation of the amide bonding associated with delocalization of the nitrogen electron pair in the second carbonyl system.[5] Accordingly, treatment of **4** with ceric ammonium nitrate (CAN) removed the MPM group to give unsubsituted γ-lactam, which was then converted to the Boc-protected **5** with $(Boc)_2O$ in 77% for two steps (Scheme 2). As expected, the reaction of **5** with vinylmagnesium chloride resulted in nucleophilic addition to the carbonyl group on the γ-lactam ring to afford the corresponding hemiaminal. This product could be reduced under the Luche conditions due to spontaneous equilibrium with the acyclic enone at ambient temperature, giving rise to acyclic allyl alcohol **6** in 81% for two steps.[6] This compound was then deoxygenated in two steps by quantitative transformation into the ethyl carbonate **7** followed by catalytic transfer hydrogenolysis using ammonium formate and triethylamine in the presence of tetrakis(triphenylphosphine)palladium to give acyclic olefin **8** in 86% without isolation of the internal olefinic product of **8**.[7] Then, the piperidine ring system was constructed by conversion of the olefinic endgroup of **8** to aldehyde through the dihydroxylation-oxidation sequence, which underwent spontaneous in situ cyclization to form the heterocyclic hemiaminal **9** in excellent yield (98% for two steps).



Scheme 3. *Reagents and conditions*: (a) CH_2=$CHCH_2SnBu_3$, TBSOTf, toluene, -78 °C, 9 h; 30% (**10a**), 66% (**10b**); (b) MeOH-HCl, rt, 2h, 81%; (c) i, OsO_4, NMO, acetone-H_2O (3:2), rt, 24 h; ii, $NaIO_4$, THF-H_2O (1:1), 0 °C to rt, 4 h; 91% (two steps); (d) $C_9H_{19}MgBr$, THF, -78 °C to 0 °C, 4.5 h; 45% (**12α**), 45% (**12β**); (e) MeOH-HCl, rt, 12 h; (**13α**) 90%; (**13β**) 84%; (f) i, H_2, Pd/C (10% Pd), MeOH-HCl, rt, 11 days; ii, HCO_2H, MeOH, rt; (**14α**); 90% (**14β**); 70%.

Having the hemiaminal intermediate in hand, our next objective was introduction of a carbon side chain at the C1 position of the six-membered piperidine ring system (Scheme 3). Thus, a Lewis acid mediated allylation of **9** was carried out by using allyltributylstannane and *tert*-butyldimethylsilyl triflate (TBSOTf) in toluene at -78°C.[8] Under these conditions, the reaction took place in a stereoselective manner to form a 1:2 diastereomeric mixture of the C1-allylated products **10a,b** in 96%, which could be separated in part by column chromatography on silica gel. Unfortunately, our initial attempts to determine the absolute configuration of the newly formed stereocenter based on the ^1H NMR analysis of the major isomer **10b** failed due to overlapping resonances for the C1 methine proton and protons of the Boc groups. Alternatively, *N*-unsubstituted piperidine analogue **10b'** prepared by treatment of **10b** with HCl in methanol was assumed to provide well-separated resonances in the ^1H NMR spectrum. Indeed, **10b'** showed clearly distinguishable multiplicities in the ^1H NMR spectrum, giving *J* coupling constants of $^3J_{H2eq\text{-}H3}$ = 2.8 Hz, $^3J_{H2ax\text{-}H3}$ = 11.7 Hz, $^3J_{H1\text{-}H2eq}$ = 2.8 Hz, and $^3J_{H1\text{-}H2ax}$ = 2.7 Hz. Analysis of the given *J* values allowed us to visualize the three-dimensional

structure of the substituted piperidine ring system, demonstrating the desired 1,5-*syn* relative orientation of the substituents with (*S*)-configuration at the C1 position of **10b** (see Supplementary data).

In the next step, we subjected **10b** to dihydroxylation-oxidation sequence under the above reaction conditions. These reactions took place very efficiently to give the corresponding aldehyde **11** in 91% yield for two steps. Introduction of the alkyl side chain by Grignard addition furnished a 1:1 mixture of diastereomeric alcohols **12** in 90% yield, being separated by chromatography on silica to provide less and more polar fractions **12α** and **12β**, respectively. After acid-catalyzed independent removal of the Boc groups of the diastereomers **12α,β** (90 and 84% yield, respectively), the resulting *N*-unsubstituted piperidine analogues **13α,β** were then hydrogenated in the presence of 10% Pd/C and HCl under H_2 atmosphere to give HCl salts of the fully deprotected products,[9] which were subjected to counteranion exchange through treatment with formic acid in methanol to afford the corresponding formate salts **14α,β** in 90 and 70% yield, respectively.

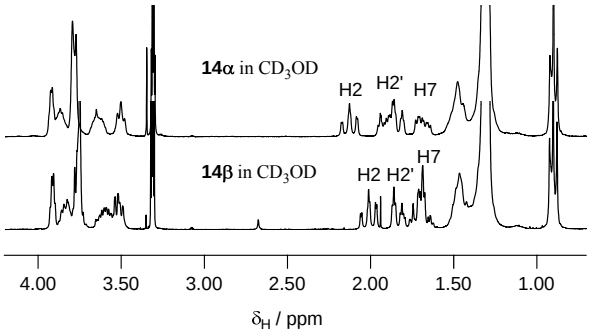
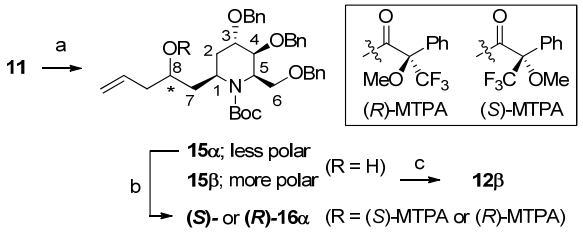


Figure 1. Comparison of ^{1}H NMR spectra of **14α** and **14β**.

Figure 1 depicts the ^{1}H NMR spectra of these final products. Remarkably, the spectral shape observed for **14β** closely matches that for formate salt of (+)-batzellaside B, which has been given in the literature.[1] On the other hand, inspection of the ^{1}H NMR spectrum of **14α** revealed that resonances assignable to the protons at the C2 position (H2 and H2') were significantly shifted downfield relative to those of **14β**, accompanied by noticeable changes in spectral shapes of the H2' and H7 with even less resolved multiplets. In addition, the ^{13}C NMR chemical shifts for **14β** are completely consistent with literature data of structurally related batzellaside A,[1] whereas significant differences in the corresponding spectral data are evident in the case of **14α**. From these observations, it is evident that **14β** can be assigned as the formate salt of (+)-batzellaside B and **14α** should be its C8-epimer.[10]

After the completion of the total synthesis, we turned next to spectroscopic determination of the absolute stereochemistry of the final products. Unfortunately, an attempt to determine the absolute configurations at the C8 chiral centers of **14α** and **14β** by employing the Mosher's method[11] failed due to indistinguishable proton resonances. Therefore, we explored an separate route involving the intermediacy of a structurally simpler system so as to validate the Mosher analysis (Scheme 4). Based on these considerations, **11** was allylated by following the Barbier-type protocol[12] to give a mixture of less and more polar diastereomeric isomers **15α** and **15β**, respectively. After separation of each component by silica-gel column chromatography, we subjected **15α** to derivatization with (*R*)- and (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (MTPA-Cl) to convert into the corresponding (*S*)- and (*R*)-**16α**, respectively. Model projection performed according to the empirical method with the $\Delta\delta_{SR}$ (= $\delta_S - \delta_R$, ppm) value distributions[11b] for (*S*)- and (*R*)-**16α** allowed precise determination of the absolute stereochemistry, indicating the absolute configurations at C8 for **15α** and **15β** to be *R* and *S*, respectively (Figure 2). Meanwhile, **15β** was shown to undergo the cross metathesis with 1-heptene and subsequent hydrogenation to result in exclusive production of **12β** as evidenced by identity of the ^{1}H NMR resonances (see Supplementary data). Consequently, the definitive conclusion drawn from the correlation of the above structure/absolute configuration relationship is that the C8 stereochemistries of **14α** and **14β** should be *R* and *S*, respectively.



Scheme 4. *Reagents and conditions*: (a) CH_2=$CHCH_2Br$, Mg, THF, -40 °C, 1 h then -30 °C, 2 h; 58% (**15α**), 27% (**15β**); (b) (*R*)- or (*S*)-MTPA-Cl, py, rt, 24 h (for (*S*)-**16α**), 5 days (for (*R*)-**16α**); 46% ((*S*)-**16α**), 81% ((*R*)-**16α**); (c) i, 1-octene, Grubbs II complex, toluene, rt, 4.5 h; ii, H_2, Pd/C(en), MeOH, rt, 12 h; 61% (for two steps).

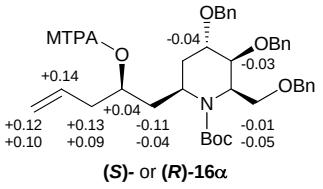


Figure 2. Model projection for the $\Delta\delta_{SR}$ value distributions in ppm (600 MHz, $CDCl_3$).

In conclusion, we have completed the total synthesis of (+)-batzellaside B and its C8-epimer from a known L-arabinose-derived tribenzyl ether in 22 steps with overall yields of 3.9% and 5.4%, respectively. In the course of our synthetic studies the absolute configuration of (+)-batzellaside B also has been unambiguously determined to be 1*S*,3*S*,4*S*,5*R*,8*S* by the modified Mosher analysis of the synthetic intermediate prepared through the separate route. The present study represents the first total synthesis of this class of natural products as well as the first report revealing

the unspecified absolute stereochemistry. Efforts to provide a more facile and efficient route to this class of natural products and to explore synthetic access to homologous batzellaside derivatives are in progress.

Acknowledgments

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Supplementary data

Supplementary data (spectroscopic data for all intermediates, structural analysis of **10b'**, details of the transformation of **15β** into **12β**) associated with this article can be found, in the online version.

References and notes

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4. On the basis of the coincidence spectral data and the mechanistic sequence identical to the literature procedure employing D-antipode of **1**, it is reasonable to assume that **3** would have the (*R*)-configuration at the newly formed stereocenter, see ref. 3a.
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6. On the basis of simple ^{1}H NMR spectral data, it is reasonable to assume that **6** was formed as a single diastereomer.
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9. The crude HCl salts were purified on DOWEX 50W-X8 (H^+ form resin) column with aqueous NH_3 at 0.7 M prior to use.
10. The observed optical rotation of **14β** ($[\alpha]_D^{25}$ +9.3 (*c* 0.5, MeOH)) close to that for the natural product (lit. $[\alpha]_D^{25}$ +10 (*c* 0.5, MeOH), see ref. 1) indicated their structural and stereochemical identity.
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