Total synthesis and structure validation of (+)-bistramide C†‡

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The convergent total synthesis of the marine natural product (+)-bistramide C confirms the *a priori* assignments of its relative and absolute configurations, which were originally based on the combined application of $[\alpha]_D$ analysis, NMR, and synthesis.

The bistramides or bistratenes have posed structural puzzles to the scientific community from the very beginning of their isolation from the marine ascidian *Lissoclinum bistratum*. Gouiffès *et al.* obtained bistramide A from New Caledonia,[1] shortly before the report of Hawkins *et al.* of the isolation of bistratenes A and B from the coast of Heron Island.[2] Bistratenes A and B turned out to be identical to bistramides A and B, and the originally proposed macrocyclic scaffold[2] was corrected by 2D INADEQUATE spectroscopy.[1b] Even the 1992 structural reassignment did not shed light on any relative or absolute configuration, leaving instead the possibility of 2048 possible stereoisomers for the natural product. Since bistramides demonstrate attractive biological properties, including antiproliferative effects,[3] sodium channel blockage,[4] and unique protein kinase Cδ activation,[5] it was of interest to elucidate their actual configuration. We embarked on solving this problem by combining novel computational and optical rotation analyses,[6] NMR spectroscopy and organic synthesis, and in 2002 reported a prediction for the relative and absolute configuration of (+)-bistramide C (**1**) as well as a total synthesis of a stereoisomer.[7,8] In 2004, Kozmin *et al.* completed an elegant synthesis of (+)-bistramide A (**2**) and were able to confirm our stereochemical prediction for the parent structure in this family.[9] We now report the first total synthesis of (+)-bistramide C which further validates our *a priori* structure assignment and presents improved methodology for the convergent preparation of this natural product.

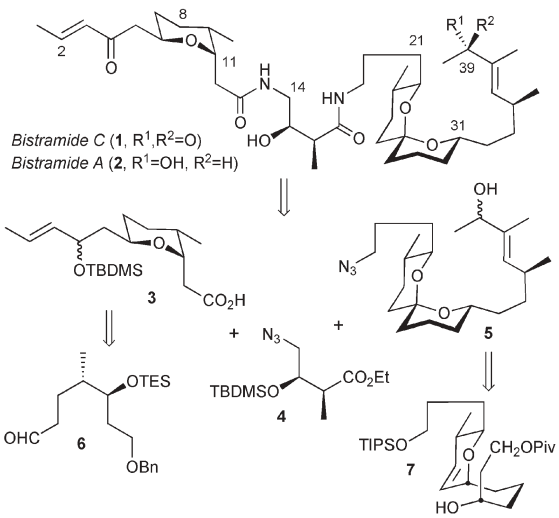
The major features of our retrosynthetic strategy were a triple convergency and a late-stage linkage of acid **3** to ester **4** and spiroketal **5** by azide couplings (Scheme 1). The synthesis of pyran **3** was based on asymmetric carbometalation[10] followed by a tandem etherification–allylation[11] of aldehyde **6**, whereas a hypervalent iodine mediated C–H insertion was used to convert alcohol **7** into the spiroketal **5**.

The preparation of segment **3** showcases the MAO-mediated asymmetric methylalumination of terminal alkene **8** (Scheme 2).[10] In the presence of 2.8 mol% of Erker's chiral zirconocene **9**, the β-methylated alcohol **10** was obtained in 78% yield and 83% ee.

Oxidation with NaOCl and catalytic TEMPO, followed by a Horner–Wadsworth–Emmons reaction provided enoate **11** in 84% yield. The linear chain was further elaborated into 1,3-diol **12** *via* a DiBAl-H reduction followed by a Sharpless asymmetric epoxidation and reductive opening of the resulting epoxy alcohol with Red-Al in toluene. The primary alcohol was selectively protected as a benzyl ether in 87% yield. Following a TBAF deprotection of the silyl ether, the resultant 1,5-diol **13** was bis-protected with TES-OTf. The primary silyl ether was preferentially cleaved upon exposure to a dilute solution of acetic acid.[12] Subsequently, the alcohol product was oxidized to the key aldehyde intermediate **14**.

Aldehyde **14** provided us with an opportunity to utilize Evans' methodology for the construction of *trans*-2,6-substituted tetrahydropyrans *via* a tandem etherification–allylation process.[11] Thus, treatment of **14** with catalytic $BiBr_3$ and excess allyltrimethylsilane afforded **15** in 72% yield and >5:1 diastereomeric ratio. We recognized the potential to manipulate the termini of both pyran side chains simultaneously. Thus, oxidation of **15** with ozone followed by *in situ* reduction with PPh_3 transformed the benzyl ether into the benzoate ester and the allyl group into the aldehyde. Treatment of a −100 °C solution of this aldehyde-ester with a −78 °C solution of propenyl lithium in Et_2O resulted in the exclusive addition of the organolithium reagent to the aldehyde function. The secondary allylic alcohol was obtained as a >10:1 mixture of epimers, but the configuration of the major isomer was inconsequential for the bistramide C synthesis and was not assigned. Silyl protection of the allylic alcohol, cleavage of the benzoate **16** with NaOMe in MeOH, and two-step oxidation led to the requisite carboxylic acid fragment **3**.

For the preparation of spiroketal segment **5**, the D-glucal derived **17**[7] was converted to the primary triflate (Scheme 3).



Scheme 1 Retrosynthetic strategy for **1**.

† Electronic supplementary information (ESI) available: spectroscopic data and copies of ^1H and ^{13}C NMR, DEPT, COSY, HSQC, HMBC, and NOESY for **1**. See http://www.rsc.org/suppdata/cc/b5/b505100b/
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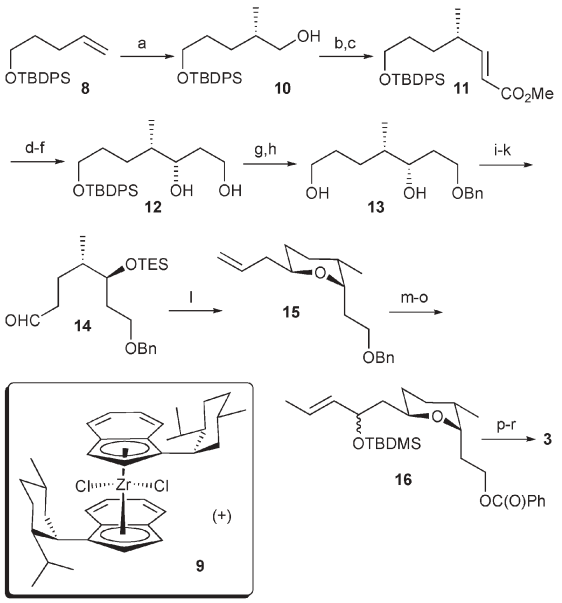
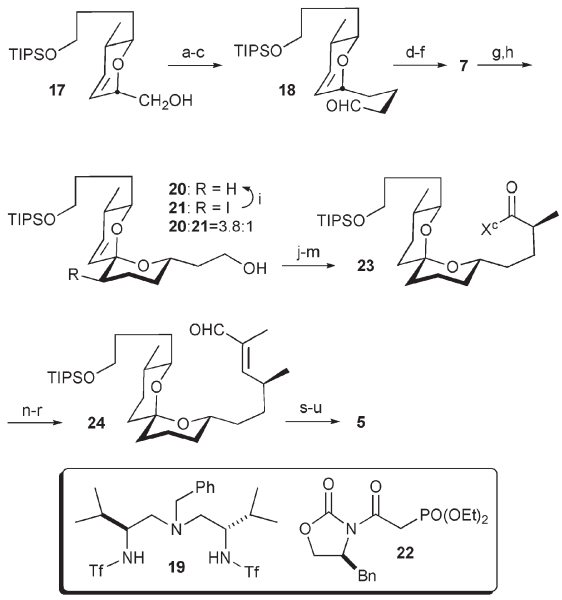


Scheme 2 (a) $AlMe_3$ (4.3 equiv), **9** (2.8 mol%), MAO (1.5 equiv), CH_2Cl_2, 3–5 °C, 15 h; then, O_2, −20 °C to rt, 78%; (b) NaOCl, TEMPO, KBr, $NaHCO_3/Na_2CO_3$, CH_2Cl_2, 0 °C, 3 h, 92%; (c) trimethylphosphonacetate, DBU, LiCl, CH_3CN, 0 °C to rt, 6 h, 91%; (d) DiBAl-H, CH_2Cl_2, −78 °C, 2 h, 98%; (e) TBHP, D-(−)-DIPT, $Ti(O\text{-}iPr)_4$, 4Å MS, CH_2Cl_2, −20 °C, 15 h, 96%; (f) Red-Al, toluene, −78 °C to rt, 13 h, quant.; (g) NaH, THF, 0 °C; then, BnBr, $n\text{-}Bu_4NI$, 0 °C to rt, 36 h, 87%; (h) TBAF, THF, 0 °C to rt, 15 h, 98%; (i) TES-OTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 30 min, quant.; (j) H_2O, AcOH, THF (1:3:10), 0 °C to rt, 4 h, 79%; (k) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, 0 °C to rt, 2 h, 81%; (l) allyl-TMS, $BiBr_3$ (cat.), CH_3CN, rt, 23 h, 72%; (m) O_3/O_2, methyl pyruvate, CH_2Cl_2, −78 °C, 30 min; then, PPh_3, −78 °C to rt, 16 h, 60–65%; (n) *trans*-2-propenyl bromide, *t*-BuLi, Et_2O, −78 °C (45 min) to 0 °C to −78 °C; then addition to −100 °C solution of aldehyde in Et_2O; (o) TBDMS-Cl, imid., CH_2Cl_2, 0 °C to rt, 21 h, 82%; (p) NaOMe, MeOH/THF, 0 °C to rt, 24 h, 90%; (q) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, 0 °C to rt, 1 h; (r) $NaClO_2$, $NaH_2PO_4{\cdot}H_2O$, 2-methyl-2-butene, *t*-BuOH, rt, 1 h, 67%.

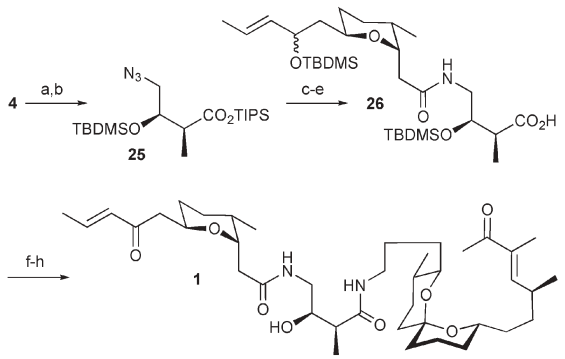


Scheme 3 (a) Tf_2O, pyr., CH_2Cl_2, −45 °C to 0 °C, 45 min; then, $(CH_2CHCH_2)_2Cu(CN)Li_2$ (1.5 equiv), THF, −78 to −60 °C, 4 h, 79%; (b) 9-BBN, THF, 0 °C to rt, 14 h; then, 0.5 M NaOH, 30% H_2O_2, 0 °C to rt, 65%; (c) Dess–Martin periodinane, CH_2Cl_2, 0 °C to rt, 1 h, 77%; (d) **19** (30 mol%), $AlMe_3$, acetyl bromide, $(iPr)_2NEt$, CH_2Cl_2, −50 °C, 20 h; (e) LAH, Et_2O, 0 °C to rt, 1 h 15 min, 88%; (f) pivaloyl chloride, pyr., rt, 24 h, 83%; (g) $PhI(OAc)_2$, I_2, CCl_4, *hv*, rt, 2 h; (h) LAH, Et_2O, 0 °C to rt, 2 h, 26%; (i) $(n\text{-}Bu)_3SnH$, AIBN, 80 °C, 14 h, 94% (j) PCC, NaOAc, CH_2Cl_2, rt, 1.5 h, 84%; (k) **22**, $(iPr)_2NEt$, LiCl, THF, 12 h, 87%; (l) Pt/C, H_2, MeOH, rt, 1.5 h, 79%; (m) NaHMDS, MeI, THF, −78 °C, 4.5 h, 67%; (n) $LiBH_4$, EtOH, Et_2O, −25 °C to 0 °C (2.5 h) to 5 °C (12 h), 77%; (o) Dess–Martin periodinane, CH_2Cl_2, rt, 25 min, 77%; (p) $EtO_2CC(Me)=PPh_3$, toluene (degassed), rt, 10 d; (q) LAH, THF, 0 °C to rt, 2 h, 68%; (r) Dess–Martin periodinane, 0 °C to rt, 1 h 10 min, 93%; (s) MeMgBr, Et_2O, 0 °C, 93%; (t) TBAF, THF, 0 °C to rt, 18 h, quant.; (u) Ms_2O, $(iPr)_2NEt$, CH_2Cl_2, 0 °C to rt, 1 h; then, NaN_3, DMF, 70 °C, 48 h, 49%.

Nucleophilic displacement of the triflate with allylmagnesium bromide in the presence of catalytic CuBr·DMS was capricious, and after extensive experimentation we determined that the corresponding higher-order allyl cuprate[13] was a more reliable method for the desired side chain extension. Selective hydroboration–oxidation of the terminal olefin followed by Dess–Martin oxidation provided the key aldehyde intermediate **18**. We employed Nelson's acyl halide-aldehyde condensation methodology (AAC)[14] for the installation of the (*S*)-configured stereocenter at the bistramide C(31). The Al(III)-triamine complex was prepared *in situ* from the (*S*)-valinol-derived triamine ligand **19** and $AlMe_3$. This catalyst proved to be quite effective in facilitating the condensation of acetyl bromide and **18** in high yield and excellent diastereoselectivity (>95% de). Reduction of the β-lactone with LAH and pivaloylation of the primary alcohol delivered the spirocyclization precursor **7** as a single diastereomer in 73% overall yield from aldehyde **18**.

Oxidative spirocyclization[15] in the presence of iodobenzene diacetate and iodine transformed **7** into a mixture of partially iodinated spiroketals **20** and **21** upon irradiation with a 250 W tungsten lamp. Following the reductive removal of the pivaloate and oxidation of the primary alcohol to the aldehyde with PCC, the α,β-unsaturated oxazolidinone was obtained in 87% yield *via* a Horner–Wadsworth–Emmons reaction with phosphonate **22**.[16] Catalytic hydrogenation of both alkenes with Pt/C in MeOH delivered the precursor for the late-stage methylation at bistramide C(34). The methyl group was installed in 67% yield using the alkylation conditions reported by Evans.[17] Next, the chiral auxiliary X^c in **23** was reductively removed, and oxidation of the intermediate alcohol led to the aldehyde. Wittig reaction, followed by reduction of the resultant enoate with lithium aluminum hydride and oxidation of the allylic alcohol to the α,β-unsaturated aldehyde transformed **23** into **24** in an overall yield of 37%. An unselective low temperature addition of methylmagnesium bromide to **24** followed by TBAF deprotection of the silyl group gave the intermediate diol in high yield. Finally, the key azide fragment **5** was accessed by selective mesylation of the 1° alcohol followed by an S_N2-displacement of the crude mesylate with sodium azide.

The stage was now set for the final segment condensation. The γ-amino carboxylate **4**,[7] derived in six steps and 35% yield from D-malic acid, was converted to azide **25** *via* saponification of the ethyl ester and temporary re-protection of the resultant carboxylic acid as the TIPS ester in a two-step yield of 82%. This late-stage protective group switch was due to an unexpectedly



Scheme 4 (a) $LiOH{\cdot}H_2O$, EtOH, 0 °C to rt, 15 h; (b) TIPS-Cl, NEt_3, THF/DMF (1:1), 0 °C, 30 min, 82%; (c) H_2 (1 atm), Pd/C, THF, rt, 3.5 h; (d) **3**, PyBOP, NEt_3, CH_2Cl_2, rt, 16 h; (e) TBAF (0.1 M), THF, 0 °C, 25 min, 86%; (f) **5**, PPh_3 (1.0 M in THF), H_2O, THF (degassed), rt, 41 h; then, **26**, PyBOP, $(i\text{Pr})_2\text{NEt}$, DMF, rt, 47 h, 58%; (g) PPTS, MeOH, rt, 48 h; (h) Dess–Martin periodinane (15 wt% in CH_2Cl_2), CH_2Cl_2, 0 °C to rt, 1 h, 77%.

facile hydrolysis of the newly-formed amide bond in the coupling product with **3** under a variety of ester saponification conditions. Reduction of azide **25** under standard catalytic hydrogenation conditions followed by a PyBOP-mediated condensation of the resultant amine with acid **3** led to the desired C(13) amide. The labile amino ester intermediate was submitted to the acylation reaction without purification. Subsequent to a fluoride-induced deprotection of the TIPS ester, carboxylic acid **26** was obtained in an overall yield of 86%. Prior to the final segment coupling, spiroketal azide **5** was treated with PPh_3 in degassed THF at room temperature. Upon the completion of the redox reaction, the solvent was removed *in vacuo* and the crude amine was treated with a DMF solution of **26**, followed by PyBOP and Hünig's base. The diamide product was isolated in a two step yield of 58%. Global deprotection under mildly acidic conditions followed by selective oxidation[7] of the two allylic alcohols provided target molecule **1**. The overall yield of the longest linear sequence, 31 steps from triacetyl-D-glucal *via* spiroketal **5**, was 0.03%. The spectroscopic properties (^1H and ^{13}C NMR, CD, $[\alpha]_D$) of **1** were in agreement with those obtained from an authentic sample of (+)-bistramide C. Accordingly, our original assignment[7] of the stereochemistry of the natural product was confirmed.

In conclusion, key methodology highlights of this total synthesis are a MAO-mediated asymmetric methylalumination of a terminal alkene, a tandem bismuth(III)-initiated cyclization–allylation for the formation of a 2,6-*trans*-substituted pyran, and a hypervalent iodine promoted remote functionalization–spiroketalization reaction.

Total synthesis continues to play an important role in the structure elucidation of natural products, in particular those obtained from the marine environment or rare life forms.[18] Both synthesis and NMR methodology are significantly augmented by the judicious use of chiroptical tools such as optical rotatory dispersion (ORD) and circular dichroism (CD) that give direct information about the absolute configuration of an analyte.[6]

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