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Stereoselective synthesis of the C1–C13 fragment of bistramide A

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ABSTRACT

The C1–C13 fragment of bistramide A was prepared from 5-hexenoic acid in 15 linear steps and in 16% overall yield. The core 2,6-trans-tetrahydropyran ring was obtained via a kinetically controlled oxa-Michael cyclization from the corresponding chiral α,β-unsaturated hydroxyester. This precursor was prepared by using a diastereoselective alkylation reaction using Davies Superquat auxiliary and a diastereoselective Roush's allylboration as key steps.

Bistramide A is a member of a family of bioactive cyclic polyethers isolated from the marine ascidian *Lissoclinum bistratum* near New Caledonia.[1,2] This macrolide induces sodium channel inhibition[3] and has immunomodulating properties.[4] In addition, bistramide A exhibits high cytotoxicity and has significant effects on cell cycle regulation,[2,5] in particular a potent antiproliferative profile.[6] The mode of action of bistramide A to explain this antiproliferative activity was initially attributed to a highly selective activation of protein kinase C isotope δ.[7] More recent studies have identified actin as the primary cellular receptor of bistramide A establishing this marine metabolite as a potential lead for a new class of anticancer agents.[8–10]

The disconnection of bistramide A amide linkages leads to three fragments: a central γ-aminoacid residue connected to a tetrahydropyran subunit (C1–C13 fragment Fig. 1) and a spiroketal subunit. All syntheses of this target macrolide reported so far have been designed on this convergent approach.[11–14] In the first total synthesis of bistramide A by Kozmin et al. providing the full structural and stereochemical assignment of this complex molecule, the construction of the C1–C13 fragment was based on a ring-closing metathesis reaction to form an intermediate unsaturated δ-lactone. After hydrogenation, this compound was then transformed into the tetrahydropyran ring via a key C-glycosidation to introduce the C1–C4 enone fragment.[11] The same strategy to access the tetrahydropyran subunit from the saturated δ-lactone was applied in two other syntheses.[12,14] The intermediate δ-lactone was in these cases obtained by lactonization of an appropriate hydroxyester precursor. Panek and co-workers have described the synthesis of the C1–C13 fragment through a [4 + 2]-annulation utilizing a chiral *syn*-(*Z*)-crotylsilane reagent.[13,15] Depending on the crotylsilane stereochemistry, this methodology enabled the access to all eight possible stereoisomers of the tetrahydropyran subunit, which allowed the recently published synthesis and screening of a 35-member analog library of bistramide A.[16] As a part of a program devoted to the discovery of new modulators of protein kinases, we were interested in the total synthesis of bistramide A and analogs. In parallel to our work on the formation of tetrahydropyran analogs of the C1–C13 subunit,[17,18] our objective was to design a novel diastereoselective synthesis of this fragment, which we disclose herein.

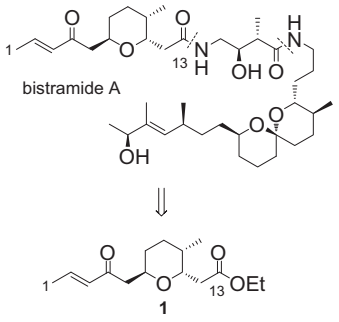

Figure 1. Fragment C1–C13 of bistramide A.

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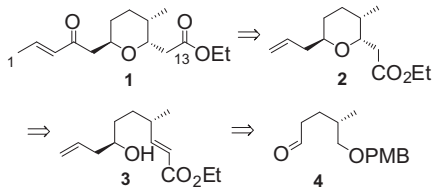
The retrosynthetic analysis is shown in Scheme 1. The enone moiety is accessible in a straightforward manner from allyl-substituted tetrahydropyran **2**. This substrate may be constructed through a Wittig reaction and a diastereoselective allylation reaction on aldehyde **4**, which can be derived from 5-hexenoic acid.

The synthesis of aldehyde **4** depicted in Scheme 2 was achieved from 5-hexenoic acid, which is commercially available but can also be prepared on a large scale in one step from inexpensive cyclohexanone.[19] This acid was converted into chiral *N*-acyl compound **5** with Davies' 4-isopropyl-5,5-dimethyl Superquat auxiliary.[20] The asymmetric alkylation of *N*-acyl enolate derived from **5** with methyl iodide furnished methylated product **6** which could be isolated as a single diastereoisomer in 86% yield after recrystallization. Rapid treatment of **6** with $LiAlH_4$ yielded alcohol **7** and the recovery of the chiral auxiliary. A PMB protection of **7** followed by an oxidative cleavage of olefin **8** delivered aldehyde **4** in high yield.

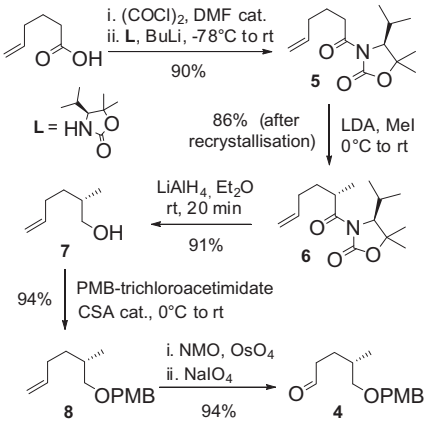
Aldehyde **4** was next subjected to a diastereoselective allylation reaction with chiral diisopropyl tartrate allylboronate according to Roush's methodology (Scheme 3).[21] The corresponding homoallylic alcohol was thus obtained in high yield as a 4:1 mixture of diastereoisomers, from which the desired isomer **9** could be isolated in 73% yield. A TBS protection of the resulting secondary alcohol, followed by PMB deprotection of **10**, afforded primary alcohol **11**, which was oxidized in the presence of Dess–Martin periodinane.[22] A Wittig reaction between aldehyde **12** and commercially available (carbethoxymethylene) triphenylphosphorane provided the geometric (*E*)-isomer **13** in 94% yield. Removal of the TBS-protecting group under acidic conditions[23] provided the target Michael acceptor **3** in quantitative yield.

The key transformation of this synthesis was the intramolecular oxa-Michael cyclization and its stereochemical outcome from functionalized Michael acceptor **3**. Previous studies on nor-methyl derivatives have shown that NaH-promoted conjugate addition (−78 °C to rt) could afford 2,6-trans disubstituted tetrahydropyrans as the major stereoisomer.[18,24,25] Preliminary attempts[26] in the presence of NaH or *t*-BuOK indicated that cyclization occurred very rapidly at −78 °C while *t*-BuOK gave a higher ratio in favor of the desired isomer than NaH. Therefore less basic *t*-BuOK was used instead of NaH. Treatment of **3** for 25 min at −78 °C in the presence of 1.1 equiv of *t*-BuOK provided a 3:1 mixture of cyclization products in favor of the 2,6-trans isomer in 96% yield (Scheme 4).[27] The reaction had to be carried out under kinetic conditions (low temperature, short reaction time) in order to avoid the formation of the thermodynamic cycloadduct *epi*-**2**. Indeed, when the reaction was allowed to warm up to rt or when cycloadduct *epi*-**2** was resubmitted under the reaction conditions, this starting material was recovered unchanged in both cases. The diastereomers were separable by column chromatography and tetrahydropyran **2** could be isolated in 72% yield. The relative 2,6-trans relationship of the protons adjacent to the oxygen in THP **2** was attributed on the basis of the values of the chemical shifts of these protons (4.30 and 3.64 ppm) which are higher for the trans-isomer than for the cis-isomer *epi*-**2** (3.42 and 3.32 ppm).

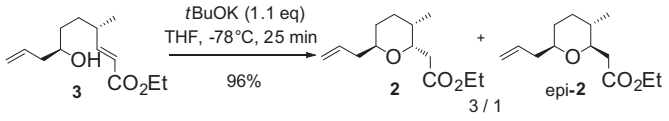
The completion of the C1–C13 fragment was achieved in three steps from **2** according to a sequence previously reported by Kitching and co-workers (Scheme 5).[28] Oxidative cleavage of the terminal olefin afforded the corresponding intermediate aldehyde, which was directly subjected to an allylation reaction with zinc powder and allyl bromide under biphasic conditions.[29] Homoallylic alcohol **14** was thus obtained in 92% yield over two steps and subjected to oxidation under Swern conditions.[30] Use of excess



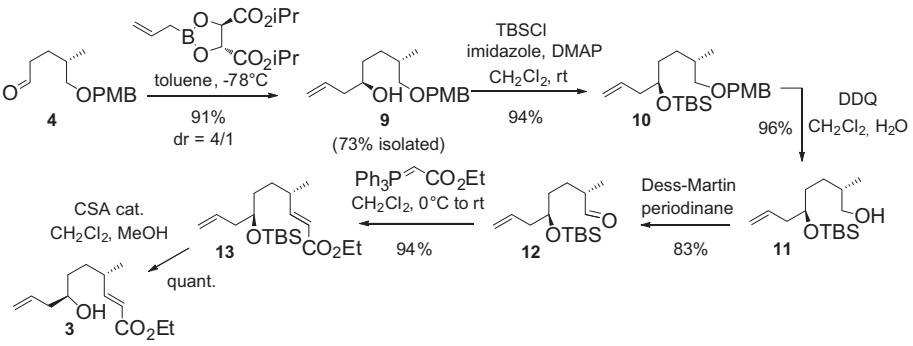
Scheme 1. Retrosynthetic analysis.



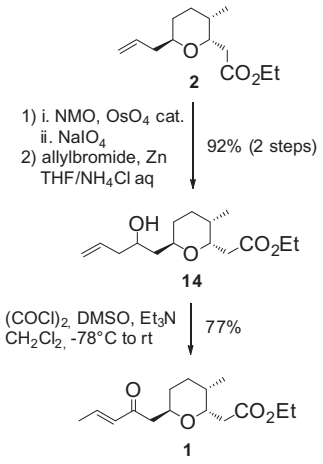
Scheme 2. Synthesis of aldehyde **4**.



Scheme 4. Oxa-Michael cyclization.



Scheme 3. Synthesis of Michael acceptor **3**.



Scheme 5. Completion of the fragment C1–C13.

triethylamine in this last step enabled the in situ isomerization of the resulting α,β-unsaturated ketone into conjugation to provide target enone **1** in 77% yield.[31]

In conclusion, a diastereoselective synthesis of the C1–C13 fragment of bistramide A has been achieved in 15 steps with a 16% overall yield. The core-trisubstituted tetrahydropyran was accessed through a key oxa-Michael cyclization under kinetic conditions to control its 2,6-trans relative stereochemistry.

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23. Treatment of ω-silyloxy-α,β-unsaturated esters under basic conditions (TBAF) is known to yield tetrahydropyrans by a tandem deprotection/cyclization process. See, for example: (a) Horita, K.; Hachiya, S.; Nagasawa, M.; Hikota, M.; Yonemitsu, O. *Synlett* **1994**, 38–40; (b) Noda, A.; Aoyagi, S.; Machinaga, N.; Kibayashi, C. *Tetrahedron Lett.* **1994**, *35*, 8235–8240.
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26. Preliminary experiments on a 1/1 diastereomeric mixture of alcohols **3** performed at −78 °C with NaH and *t*-BuOK, respectively, showed that higher amounts of the desired isomer was obtained in the presence of *t*-BuOK.
27. To a solution of alcohol **3** (0.27 mmol, 60 mg) in THF (2 mL) at −78 °C was added *t*-BuOK (0.29 mmol, 33 mg). After 25 min stirring at −78 °C, a saturated solution of NH_4Cl (3 mL) was added and the mixture warmed up to rt. Extraction was carried out with Et_2O (3 × 3 mL). The organic phase was dried over $MgSO_4$, filtered, and was concentrated in vacuo. The purification of the residue was done by flash column chromatography (hexanes/EtOAc, 98:2) furnished cycloadduct **2** in 72% yield (0.19 mmol, 43 mg) as a colorless oil. R_f = 0.7 (hexanes/EtOAc, 90:10). ^{1}H NMR δ 0.81 (d, *J* = 7.0 Hz, 3H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.27–1.40 (m, 2H), 1.61–1.67 (m, 2H), 1.86–1.98 (m, 1H), 2.07–2.26 (m, 2H), 2.31 (dd, J_{AB} = 14.0 Hz, *J* = 4.5 Hz, 1H), 2.71 (dd, J_{AB} = 14.0 Hz, *J* = 10.6 Hz, 1H), 3.60–3.68 (m, 1H), 4.14 (qt, *J* = 7.1, 1.1 Hz, 2H), 4.30 (dt, *J* = 10.7, 4.7 Hz, 1H), 4.98 (br d, *J* = 10.4 Hz, 1H), 5.03 (br d, *J* = 17.5 Hz, 1H), 5.78 (ddt, *J* = 17.1, 10.2, 7.0 Hz, 1H). ^{13}C NMR δ 14.3, 16.7, 26.7, 30.3, 32.9, 33.2, 40.2, 60.5, 69.2, 74.2, 116.4, 135.3, 172.1. IR (film) *ν* 3071, 2976, 2952, 2932, 1737, 1438, 1370, 1285, 1191, 1711, 1037, 911 cm^{-1}. HRMS (ESI) calcd for $C_{13}H_{22}O_3Na^+$ [M+Na$^+$] 249.1467, found 249.1468. $[\alpha]_D^{25} = -60.4$ (*c* = 0.98, $CHCl_3$). Isomer *epi*-**2**: isolated as a colorless oil (0.059 mmol, 13 mg, 22%). R_f = 0.5 (hexanes/EtOAc, 95:5). ^{1}H NMR δ 0.82 (d, *J* = 6.4 Hz, 3H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.20–1.40 (m, 3H), 1.58–1.78 (m, 2H), 2.10 (dd, J_{AB} = 14.2 Hz, *J* = 6.4 Hz, 1H), 2.25 (dd, J_{AB} = 14.2 Hz, *J* = 7.2 Hz, 1H), 2.35 (dd, J_{AB} = 14.5 Hz, *J* = 9.5 Hz, 1H), 2.60 (dd, J_{AB} = 14.5 Hz, *J* = 3.5 Hz, 1H), 3.28–3.36 (m, 1H), 3.42 (td, *J* = 9.5, 3.5 Hz, 1H), 4.15 (q, *J* = 7.1 Hz, 2H), 4.96–5.06 (m, 2H), 5.78 (ddt, *J* = 17.1, 10.2, 6.8 Hz, 1H).
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31. To a solution of freshly distilled oxalyl chloride (0.09 mmol, 8 μL) in dry DCM (1.2 mL) cooled at −78 °C was added dry DMSO (0.19 mmol, 13 μL). After 15 min of stirring, a solution of alcohol **14** (0.078 mmol, 21 mg) in dry DCM (0.8 mL) was added at −78 °C. The mixture was stirred for a further 20 min at that temperature before adding dropwise a solution of freshly distilled Et_3N (4 mmol, 550 μL) in DCM (2 mL). The reaction mixture was allowed to warm up to rt and stirred for 24 h. The mixture was then diluted with DCM (10 mL) and washed with saturated aqueous solutions of $NaHCO_3$ (10 mL), NH_4Cl (10 mL), and NaCl (5 mL). The organic layer was dried over $MgSO_4$, filtered, and was concentrated in vacuo. The crude residue was purified by flash column chromatography on silica gel (hexanes/EtOAc, 85:15) to yield enone **1** (0.060 mmol, 16 mg) as a colorless oil in 77% yield. R_f = 0.5 (hexanes/EtOAc, 80/20). ^{1}H NMR δ 0.81 (d, *J* = 7.0 Hz, 3H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.27–1.43 (m, 2H), 1.59–1.78 (m, 2H), 1.87–1.95 (m, 1H), 1.89 (dd, *J* = 7.0, 1.7 Hz, 3H), 2.34 (dd, J_{AB} = 14.5 Hz, *J* = 4.7 Hz, 1H), 2.51 (dd, J_{AB} = 15.2 Hz, *J* = 6.2 Hz, 1H), 2.71 (dd, J_{AB} = 14.5 Hz, *J* = 10.0 Hz, 1H), 2.78 (dd, J_{AB} = 15.2 Hz, *J* = 6.4 Hz, 1H), 4.05–4.32 (m, 3H), 4.28 (br dt, *J* = 9.8, 4.9 Hz, 1H), 6.11 (dq, *J* = 15.7, 1.7 Hz, 1H), 6.83 (dq, *J* = 15.7, 6.8 Hz, 1H). ^{13}C NMR δ 14.3, 16.7, 18.4, 26.6, 30.6, 32.8, 33.1, 45.9, 60.6, 66.7, 74.3, 132.6, 143.3, 172.0, 198.4. HRMS (ESI) calcd for $C_{15}H_{24}O_4Na^+$ [M+Na$^+$] 291.1572, found 291.1572. $[\alpha]_D^{25} = -50.0$ (*c* = 0.4, $CHCl_3$). Literature: $[\alpha]_D^{25} = -54.0$ (*c* = 0.1, $CHCl_3$) for the acid derivative.[16]