# Efficient Synthesis of the C1–C13 Fragment of Bistramide A

Loic Tomas, Thibault Bechet, Erwann Jeanneau, David Gueyrard,* Peter G. Goekjian*

Université de Lyon, ICBMS – UMR CNRS 5246, LCO2 – Glycochimie, Université Claude Bernard Lyon 1, Bat. 308 CPE LYON, 43, Bd du 11 Novembre 1918, 69622 Villeurbanne, France
Fax +33(4)72448109; E-mail: gueyrard@univ-lyon1.fr; E-mail: goekjian@univ-lyon1.fr

*Received 26 October 2011*

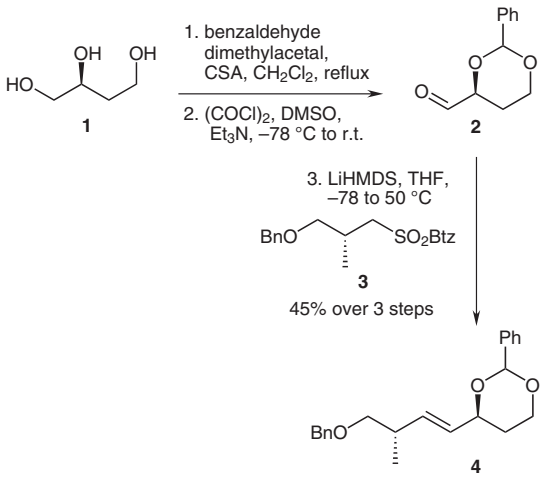
**Abstract:** Herein we report an efficient synthesis of the C1–C13 fragment of bistramide A from (*S*)-1,2,4-butanetriol and Roche ester in 14 steps and 13% overall yield.

**Key words:** bistramide, tetrahydropyran, oxa-Michael, Julia-modified olefination

Bistramide A is a member of a small family of natural products isolated from *Lissoclinum bistratum*, an ascidian.[1] The bistramides exhibit a variety of biological activities,[2] most notably antiproliferative.[3] This biological activity can be attributed to the activation of protein kinase C δ[4] and/or to the binding of bistramide A to actin.[5]

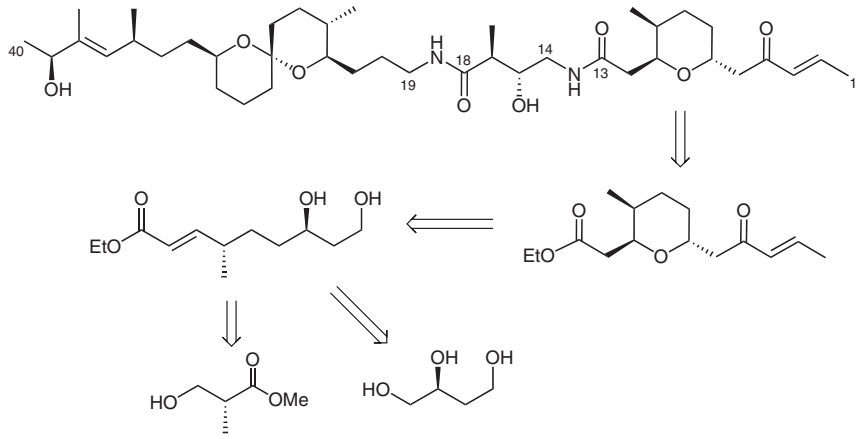
Due to its original structure and biological profile, several groups have reported the total synthesis of bistramide A and C.[6] The bistramide A is composed of a spiroketal unit (C19–C40), a central amino acid fragment (C14–C18), and a tetrahydropyran ring (C1–C13). We report here a convenient approach for the preparation of the C1–C13 fragment from chiral, inexpensive, and commercially available starting materials: (*S*)-1,2,4-butanetriol and Roche ester (Scheme 1).

The synthesis of the C1–C13 fragment starts with the protection of 1,3-diol of triol **1** as a benzylidene protective group. The oxidation of the primary alcohol provide the aldehyde **2** which is coupled with the sulfone **3** in a modified Julia olefination with LiHMDS as a base to give the alkene **4** as a mixture of geometric isomers (*E*/*Z* = 2.5:1, Scheme 2)



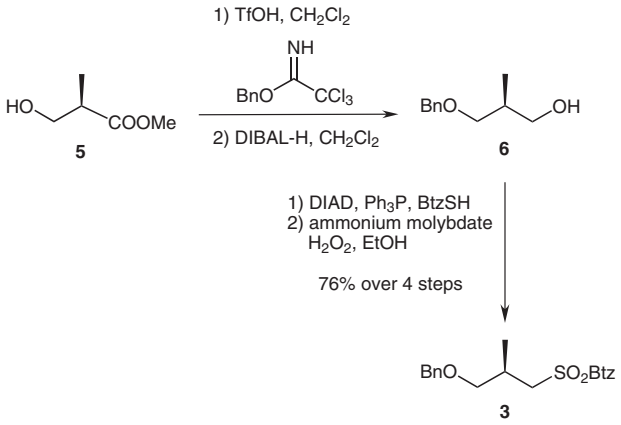

**Scheme 2** Formation of the alkene **4**

The benzothiazolyl sulfone **3** was prepared through a four-step sequence from Roche ester. Benzylation of the alcohol under acidic conditions followed by reduction of the ester provides the alcohol **6**. This intermediate is transformed into the sulfone through a Mitsunobu–oxidation sequence in 76% yield over four steps (Scheme 3).



**Scheme 1** Retrosynthetic approach for the C1–C13 fragment

*SYNLETT* 2012, 23, 215–218
Advanced online publication: 09.12.2011
DOI: 10.1055/s-0031-1290097; Art ID: D28511ST




**Scheme 3** Synthesis of the sulfone from Roche ester

We first attempted the simultaneous reduction of the alkene and hydrogenolysis of the benzyl ether and benzylidene groups in compound **4** using hydrogen and a $Pd(OH)_2$ or Pd/C catalyst under $H_2$ at 1 bar. In this case, we hydrogenated the double bond without deprotecting the benzyl ether or benzylidene. When we increased the hydrogen pressure, we obtained the triol as a major compound, albeit in very moderate yield (45%). In an attempt to selectively hydrogenate the double bond and remove the benzyl group, we prepared the corresponding alkene with a paramethoxybenzylidene protective group and attempted the selective hydrogenolysis conditions ($H_2$/Raney Ni) described by Panek.[6c] However, in our hands, we were unable to obtain the primary alcohol after three days.

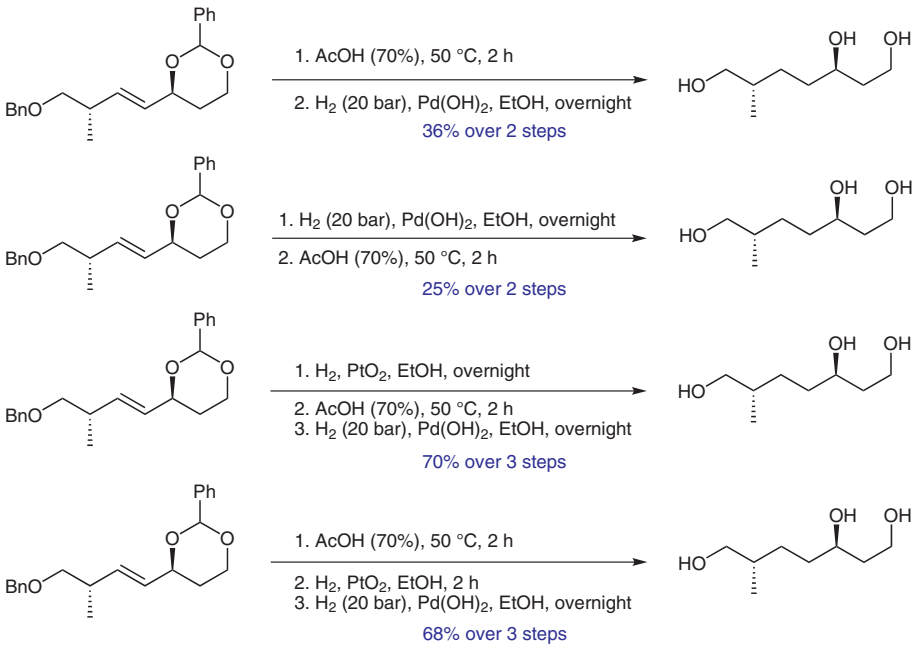
We therefore decided to optimize the formation of the triol **7**. In the reaction described above, several minor products were identified corresponding to hydrogenolysis of the carbon–oxygen bonds of the butanetriol moiety, thus suggesting the need for a sequential cleavage of the three functional groups. Several reactions were run changing the order of the different steps (Scheme 4).

Palladium-catalyzed hydrogenation of the double bond before or after acid hydrolysis of the benzylidene group provided surprisingly low yields of the triol product. However, selective hydrogenation of the double bond over $PtO_2$ prior to hydrogenolysis of the benzyl group gave considerably better results. After optimization, a three-step sequence allowed us to prepare the triol in 70% overall yield. The 1,3-diol was reprotected as the benzylidene **8**, and the primary alcohol was converted to the corresponding aldehyde by Swern oxidation. Finally, the Michael acceptor **9** was prepared through a Horner–Wadsworth–Emmons reaction as a *E*/*Z* mixture (96:4, Scheme 5).

The key step is an intramolecular Michael addition under kinetic control. This methodology, already employed by Bates et al.[7] and Piva et al.[8] to synthesize the bistramide tetrahydropyran, was evaluated on the *E*-isomer of the diol **9** (Table 1).

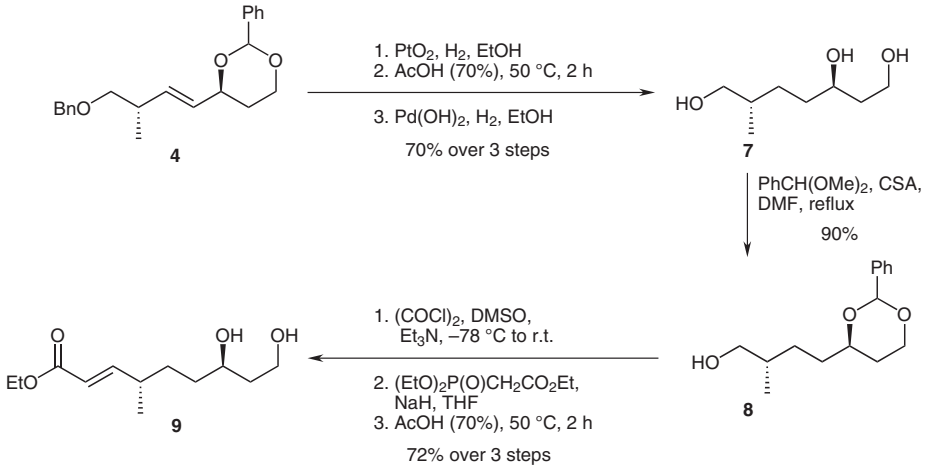
The first experiment, carried out under the conditions described by Piva et al. (Table 1, entry 1), showed that potassium *tert*-butoxide gives a better ratio than sodium hydride.[8] The conversion of the starting material is good, and the selectivity is in favor of the 2,6-*trans*-disubstituted tetrahydropyran (2:1 mixture). The selectivity can be increased to 2.2:1 reducing the number of equivalents of base (Table 1, entry 2).

Increasing of the number of equivalents of the base (Table 1, entry 3) leads in the mixture of side products in which the major compound was isolated and identified as a dimeric macrolide. The structure of this product has been confirmed by NMR, MS, and X-ray crystallography




**Scheme 4** Optimization of the hydrogenolysis–hydrogenation sequence




**Scheme 5** Synthesis of the Michael acceptor

**Table 1** Optimization of the Oxa-Michael Cyclization on the *E*-Isomer

| Entry | Time (min) | Temp (°C) | Solvent | Base (equiv) | Conv. (%) | Selectivity |
|---|---|---|---|---|---|---|
| 1 | 25 | –78 | THF | KO*t*-Bu (1.1) | >95 | 2.0:1 |
| 2 | 25 | –78 | THF | KO*t*-Bu (0.6) | >95 | 2.2:1 |
| 3 | 25 | –78 | THF | KO*t*-Bu (1.4) | >95 | mixture |
| 4 | 9 | –78 | toluene | KO*t*-Bu (0.6) | 78 | 2.5:1 |
| 5 | 25 | –78 | toluene | KO*t*-Bu (0.6) | >95 | 2.4:1 |
| 6 | 25 | –78 | toluene | KHMDS (0.6) | >95 | 1.3:1 |
| 7 | 1200 | –15 | toluene | DBU (3) | 17 | 1.2:1 |
| 8 | 25 | –15 | toluene–*t*-BuOH (3:2) | KO*t*-Bu (0.6) | <5 | n.d. |
| 9 | 240 | –10 | toluene–*t*-BuOH (3:2) | KO*t*-Bu (0.6) | 67 | 2.0:1 |
| 10 | 5 | 0 | toluene–*t*-BuOH (3:2) | KO*t*-Bu (0.6) | >95 | 2.3:1 |

(Figure 1).[9] This compound can be related to clavosolide[10] or cyanolide,[11] but, to our knowledge, this compound is the first example of dimeric macrolide including two 2,6-*trans*-tetrahydropyran units.

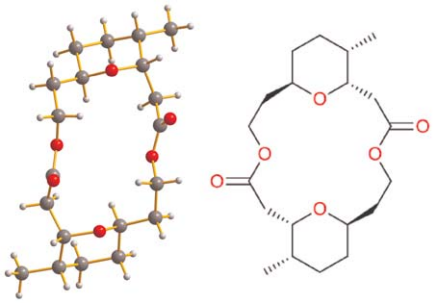


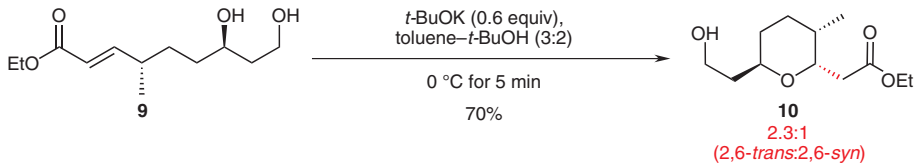
**Figure 1** X-ray crystal structure of the side product

The use of a less polar solvent (toluene) allowed us to increase the selectivity to 2.4:1 (Table 1, entry 5). We then studied the importance of the reaction time. Reducing this parameter allows to enhance the selectivity to 2.5:1, but the reaction is not complete (conversion approximately 78%).

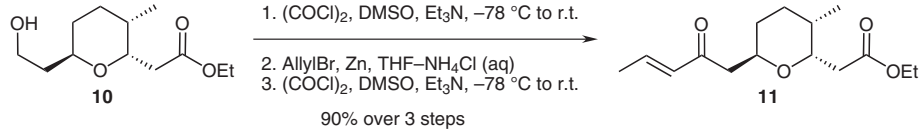
At this stage we looked at the nature of the base on the selectivity. The treatment of the diol with a strong base such as KHMDS (Table 1, entry 6) provided the tetrahydropyran with excellent conversion but poor selectivity (1.3:1). On the other hand, the use of a weaker base such as DBU offered a low conversion and did not increase the selectivity (Table 1, entry 7).

At last, we also explored the possibility to trap the kinetic product and to reduce the retroaddition process by addition of a protic solvent (*t*-BuOH).[12] In a toluene–*t*-BuOH mixture (3:2), the reaction is very slow at –15 °C (Table 1, entry 8), the conversion of the starting material is partial (67%) after four hours at –10 °C (Table 1, entry 9). Finally, we found that the selectivity is good (2.3:1) at 0 °C for five minutes (Scheme 6, Table 1, entry 10).[13]

Finally, the selectivities observed are in the same range compared to previous work on similar structures.[7,8]




**Scheme 6** Michael addition under kinetic control




**Scheme 7** Completion of the synthesis of the C1–C13 fragment

The achievement of the C1–C13 fragment of bistramide A was accomplished by the Swern oxidation of the primary alcohol to afford the corresponding aldehyde which is submitted to an allylation reaction with zinc powder.[8] Finally, a Swern oxidation of the allylic alcohol furnished the α,β-unsaturated ketone after in situ isomerisation of the double bond in basic media.[14] Thus, the C1–C13 fragment of bistramide A is obtained in 90% over the last three steps (Scheme 7).

In conclusion, an efficient and robust synthesis of the C1–C13 fragment of bistramide A has been developed in 14 steps and 13% overall yield from the inexpensive chiral starting materials (*S*)-1,2,4-butanetriol and Roche ester. The key step of this synthesis is an oxa-Michael cyclization under kinetic conditions to provide the 2,6-*trans*-tetrahydropyran ring. During this step, we also isolated a dimeric macrolide related to two families of natural products: clavosolides and cyanolides.

**Supporting Information** for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

## Acknowledgment

The authors thank the European Commission (contract N° LSHB-CT-2004-503467) for financial support. The Ministère de l'Enseignement Supérieur et de la Recherche is acknowledged for a research fellowship (L.T.). We also thank the CCSM for mass measurements.

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(9) $^1$H NMR (300 MHz, $CDCl_3$): δ = 0.82 (d, *J* = 6.9 Hz, 3 H), 1.32 (m, 2 H), 1.62 (m, 4 H), 2.00 (m, 1 H), 2.20 (dd, *J* = 2.9, 14.5 Hz, 1 H), 2.87 (dd, *J* = 12.7, 14.5 Hz, 1 H), 3.78 (m, 1 H), 3.96 (m, 1 H), 4.33 (m, 1 H) ppm. ESI-MS: *m/z* = 391.2 $[M + Na]^+$. CCDC 843221 contains the supplementary crystallographic data for this structure. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.ac.uk/data_request/cif.
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(13) $^1$H NMR (400 MHz, $CDCl_3$): δ = 0.82 (d, *J* = 7.0 Hz, 3 H), 1.28 (t, *J* = 7.2 Hz, 3 H), 1.32–1.39 (m, 1 H), 1.53–1.69 (m, 6 H), 1.93–2.06 (m, 1 H), 2.33 (dd, *J* = 4.1, 13.5 Hz, 1 H), 2.80 (dd, *J* = 11.8, 13.5 Hz, 1 H), 2.94–3.01 (m, 1 H), 3.55–3.66 (m, 1 H), 3.68–3.75 (m, 1 H), 3.81–3.91 (m, 1 H), 4.16 (q, *J* = 7.1 Hz, 2 H), 4.28 (dt, *J* = 4.9, 4.9, 11.8 Hz, 1 H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 172.9 (C), 74.7 (CH), 68.0 (CH), 61.1 ($CH_2$), 60.2 ($CH_2$), 38.3 ($CH_2$), 33.1 (CH), 32.6 ($CH_2$), 31.8 ($CH_2$), 26.8 ($CH_2$), 17.4 ($CH_3$), 14.2 ($CH_3$). ESI-MS: *m/z* = 253 $[M + Na]^+$. ESI-HRMS: *m/z* calcd for $C_{12}H_{22}O_4Na$ $[M + Na]^+$: 253.1410; found: 253.1412.
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