Pergamon

Tetrahedron Letters 43 (2002) 8883–8885

TETRAHEDRON LETTERS

Synthesis of C1–C11 fragment of callystatin A†

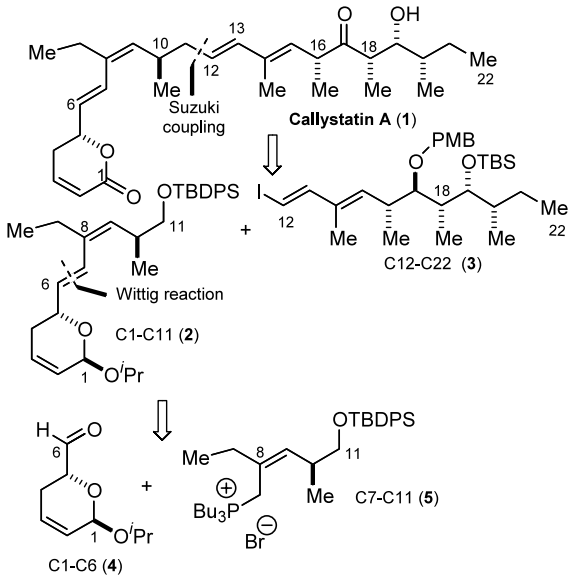
Luiz C. Dias* and Paulo R. R. Meira

Instituto de Química, Universidade Estadual de Campinas, UNICAMP, C.P. 6154, 13083-970 Campinas, SP, Brazil

Received 25 September 2002; accepted 2 October 2002

Abstract—We wish to describe here our continuing efforts towards the total synthesis of the marine sponge polyketide callystatin A, describing the synthesis of the C1–C11 fragment. © 2002 Elsevier Science Ltd. All rights reserved.

In 1997, Kobayashi and co-workers reported the isolation of (−)-callystatin A (**1**), a potent antitumor polyketide from the marine sponge *Callyspongia truncata*, collected from Goto Islands, Nagasaki Prefecture, Japan (Scheme 1).[1] The relative as well as the absolute stereochemistry of (−)-callystatin A was established by a combination of spectroscopic methods and chemical synthesis.[2–5] (−)-Callystatin A (**1**), a polyketide with a terminal α,β-unsaturated lactone and two diene systems shows remarkably high activity ($IC_{50} = 10$ pg/mL) against KB tumor cell lines and 20 pg/mL against L1210 cells.



Scheme 1.

As the natural supply is extremely restricted, and attracted by its potent cytotoxicity, we initiated a project directed towards its total synthesis. An efficient and flexible synthesis is essential to provide further material for more extensive biological studies, along with access to novel analogues.[3–6] We have recently described a very efficient synthesis of the C13–C22 fragment of (−)-callystatin A.[7] The approach described here to the C1–C11 fragment might give access to (−)-callystatin A and additional derivatives with potential relevance to biological studies.[8]

Our disconnection, summarized in Scheme 1, involved cleavage of the C11–C12 bond to give fragments C1–C11 (**2**) and C12–C22 (**3**).[9] Fragment C1–C11 is viewed as arising from coupling between aldehyde **4**, a masked α,β-unsaturated lactone, corresponding to the C1–C6 fragment and phosphonium salt **5** (C7–C11).

The α,β-unsaturated lactone fragment found in callystatin A is a common structural motif in polyketide natural products. Among the strategies available to the synthesis of this lactone, a ring-closing metathesis using Grubb's catalyst is one of the most common.[10] Of the remaining available options, we speculate that the desired aldehyde **4** might be most conveniently prepared from D-malic acid.[11]

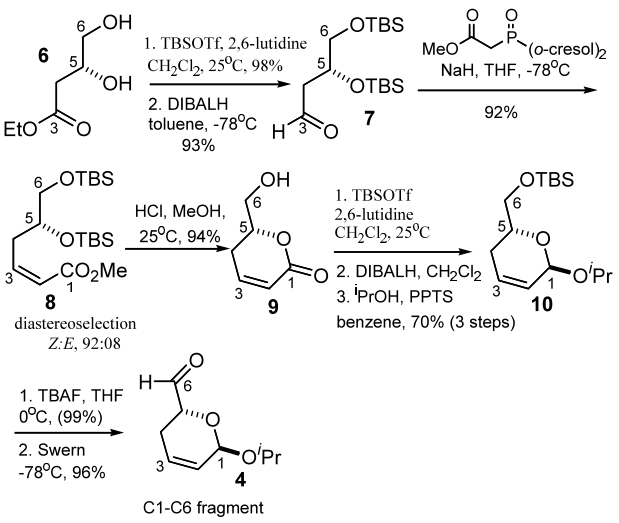
The synthesis of fragment C1–C6 began with full protection of diol **6** (easily prepared from D-malic acid) as its TBS ether to give the corresponding ester in 98% yield.[11] This ester was smoothly reduced to aldehyde **7** (93% yield) on treatment with diisobutylaluminum hydride in toluene at −78°C (Scheme 2).

This unpurified aldehyde was directly subjected to a Horner–Wadsworth–Emmons homologation with the required phosphonate reagent under Ando's conditions

* Corresponding author. Tel.: +55-019-3788-3021; fax: +55-019-3788-3023; e-mail: ldias@iqm.unicamp.br

† This paper is dedicated to the Brazilian Chemical Society (SBQ).

0040-4039/02/$ - see front matter © 2002 Elsevier Science Ltd. All rights reserved.
PII: S0040-4039(02)02200-1

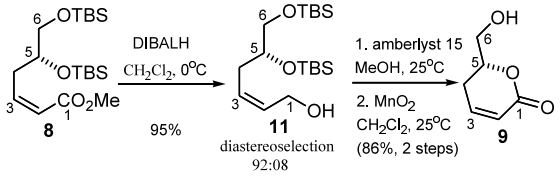


Scheme 2.

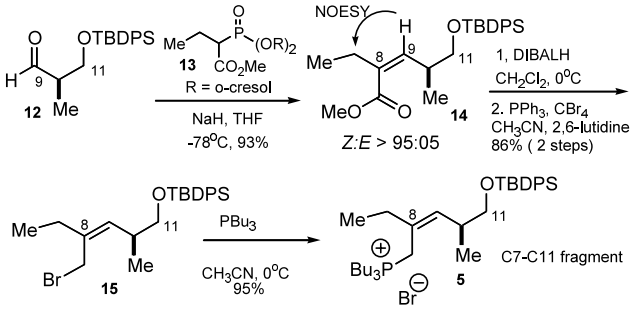
to give (*Z*)-α,β-unsaturated ester **8** (*Z*:*E*=92:08) in 92% isolated yield.[12] Treatment of *Z*-ester **8** with 1N HCl in MeOH gave lactone **9** in 94% yield. At this point, in order to avoid partial racemization at C5 at the aldehyde stage, the carbonyl group in **9** should be masked as an acetal, which can be easily hydrolyzed later on in the synthesis under mild conditions and subsequently oxidized to regenerate the desired α,β-unsaturated lactone.[5,13] Protection of the primary alcohol functionality in **9** as its TBS ether followed by careful DIBALH reduction gave an intermediate lactol that was treated with ^{i}PrOH in the presence of catalytic amounts of PPTS to provide isopropyl acetal **10** in 70% overall yield over the three-step sequence. The next step involved TBS removal in **10** with TBAF in THF (99% yield) followed by Swern oxidation of the OH-function under standard conditions to give aldehyde **4** (96% yield).[13,14]

An alternative approach to lactone **9** involved reduction of (*Z*)-ester **8** with 2.2 equiv. of diisobutylaluminum hydride at 0°C to give allylic alcohol **11** in 95% yield (Scheme 3). Formation of lactone **9** was accomplished by treatment of allylic alcohol **11** with Amberlyst 15® resin in MeOH at room temperature, followed by subsequent treatment of the resulting triol with MnO_2, in 86% yield over the two-step sequence.

Our approach to fragment C7–C11 began with a Horner–Wadsworth–Emmons homologation reaction of aldehyde **12** with β-ketophosphonate **13** under Ando's conditions to give (*Z*)-α,β-unsaturated ester **14** (*Z*:*E*>95:05) with a trisubstituted *Z*-double bond in



Scheme 3.

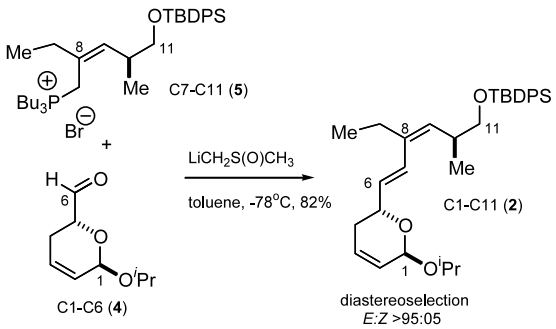


Scheme 4.

93% isolated yield (Scheme 4).[12,15,16] The *Z*-geometry for ester **14** was confirmed by the illustrated NOESY interaction between vinylic hydrogen at C9 and hydrogens of the ethyl group. A sequence of DIBALH reduction followed by treatment of the intermediate allylic alcohol with PPh_3, CBr_4 in CH_3CN gave bromide **15** in 86% yield over the two-step sequence. Reaction of bromide **15** with PBu_3 gave phosphonium salt **5** in 95% yield.[17]

With fragments C1–C6 and C7–C11 in hands, their coupling was undertaken (Scheme 5). Treatment of a mixture of aldehyde **4** and phosphonium salt **5** with $LiCH_2S(O)CH_3$ in toluene at −78°C, cleanly provided diene **2** in 82% yield (*E*:*Z* >95:5), corresponding to the C1–C11 fragment of (−)-callystatin A.[5,17]

The 10-step sequence from **6** to **2** (longest linear sequence) proceeded in an overall yield of 42% and is easily amenable to a gram scale-up. Thus, the synthesis of C1–C11 fragment of (−)-callystatin A has been described. Notable features of this approach include an efficient preparation of the α,β-unsaturated lactone fragment from diol **6**, and Wittig and Horner–Wadsworth–Emmons reactions to establish the double bonds at C2–C3, C6–C7 and C8–C9. As a result, the route to the C1–C11 fragment presented here is, in principle, readily applicable for the preparation of (−)-callystatin A and additional analogs. We have now finished the synthesis of C1–C11 and C13–C22 fragments of (−)-callystatin A. Efforts are being undertaken to improve the synthesis of both fragments as well as to complete the total synthesis of (−)-callystatin A and these studies will be described in a full account of this work.[18]



Scheme 5.

Acknowledgements

We are grateful to FAPESP and CNPq for financial support. We also thank Professor Carol H. Collins, from IQ-UNICAMP, for helpful suggestions about English grammar and style.

References

1. Kobayashi, M.; Higuchi, K.; Murakami, N.; Tajima, H.; Aoki, S. *Tetrahedron Lett*. **1997**, *38*, 2859.
2. Murakami, N.; Wang, W.; Aoki, M.; Tsutsui, Y.; Higuchi, K.; Aoki, S.; Kobayashi, M. *Tetrahedron Lett*. **1997**, *38*, 5533.
3. (a) Hamamoto, T.; Seto, H.; Beppu, T. *J. Antibiot*. **1983**, *36*, 646; (b) Absolute stereochemistry and synthesis of leptomycin B: Kobayashi, M.; Wang, W.; Tsutsui, Y.; Sugimoto, M.; Murakami, N. *Tetrahedron Lett*. **1998**, *39*, 8291.
4. Murakami, N.; Sugimoto, M.; Kobayashi, M. *Bioorg. Med. Chem*. **2001**, *9*, 57.
5. For total syntheses of callystatin A, see: (a) Murakami, N.; Wang, W.; Aoki, M.; Tsutsui, Y.; Sugimoto, M.; Kobayashi, M. *Tetrahedron Lett*. **1998**, *39*, 2349; (b) Crimmins, M. T.; King, B. W. *J. Am. Chem. Soc*. **1998**, *120*, 9084; (c) Smith, A. B., III; Brandt, B. M. *Org. Lett*. **2001**, *3*, 1685; (d) Kalesse, M.; Quitschalle, M.; Khandavalli, C. P.; Saeed, A. *Org. Lett*. **2001**, *3*, 3107; (e) Vicario, J. L.; Job, A.; Wolberg, M.; Muller, M.; Enders, D. *Org. Lett*. **2002**, 4, 1023; (f) Marshall, J. A.; Bourbeau, M. P. *J. Org. Chem*. **2002**, *67*, 2751; (g) Lautens, M.; Stammers, T. A. *Synthesis* **2002**, 1993.
6. For a previous synthesis of C13–C22 fragment of callystatin A, see: (a) Marshall, J. A.; Fitzgerald, R. N. *J. Org. Chem*. **1999**, *64*, 4477; (b) Marshall, J. A.; Schaaf, G. M. *J. Org. Chem*. **2001**, *66*, 7825.
7. (a) Dias, L. C.; Meira, P. R. R. *Tetrahedron Lett*. **2002**, *43*, 185; (b) Dias, L. C.; Meira, P. R. R. *Tetrahedron Lett*. **2002**, *43*, 1593.
8. For a very interesting review about the chemistry and biology of the leptomycin family, see: Kalesse, M.; Christmann, M. *Synthesis* **2002**, 981.
9. The numbering of **1** as well as of each intermediate follows that suggested in Ref. 1.
10. For a recent review with several examples of α-pyrones prepared using ring-closing metathesis (RCM), see: Ramachandran, P. V. *Aldrichimica Acta* **2002**, *35*, 23.
11. (a) Mori, K.; Takigawa, T.; Matsuo, T. *Tetrahedron* **1979**, *35*, 933; (b) Saito, S.; Ishikawa, T.; Kuroda, A.; Koga, K.; Moriwake, T. *Tetrahedron* **1992**, *48*, 4067.
12. (a) Ando, K. *J. Org. Chem*. **1997**, *62*, 1934; (b) Ando, K. *J. Org. Chem*. **1998**, *63*, 8411; (c) Ando, K. *J. Org. Chem*. **1999**, *64*, 8406; (d) Ando, K.; Oishi, T.; Hirama, M.; Ohno, H.; Ibuka, T. *J. Org. Chem*. **2000**, *65*, 4745.
13. Very recently, Hansen has described the preparation of the corresponding aldehyde from lactone **9** by Swern oxidation: Hansen, T. V. *Tetrahedron: Asymmetry* **2002**, *13*, 547.
14. Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165.
15. (a) Burke, S. D.; Cobb, J. E.; Takeuchi, K. *J. Org. Chem*. **1990**, *55*, 2138; (b) Thomas, E. J.; Whitehead, J. W. F. *J. Chem. Soc., Perkin Trans. 1* **1989**, 507.
16. For an interesting paper dealing with the construction of the C8–C9 (*Z*) trisubstituted olefin of callystatin A and analogues, see: Arefolov, A.; Langille, N. F.; Panek, J. S. *Org. Lett*. **2001**, *3*, 3281.
17. Tamura, R.; Saegusa, K.; Kakihana, M.; Oda, D. *J. Org. Chem*. **1988**, *53*, 2723.
18. New compounds and the isolatable intermediates gave satisfactory ^{1}H and ^{13}C NMR, IR, HRMS and analytical data. Yields refer to chromatographically and spectroscopically homogeneous materials.