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Synthesis of C13–C22 fragment of the marine sponge polyketide callystatin A†

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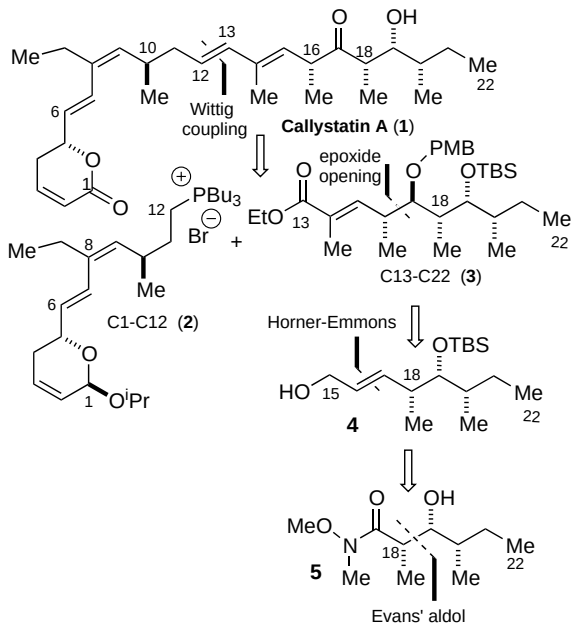
Abstract—We wish to report here our initial efforts towards the total synthesis of callystatin A, describing the synthesis of the C13–C22 fragment. This asymmetric approach uses an efficient *syn*-aldol reaction, and a diastereoselective epoxidation of an allylic alcohol with *m*-CPBA followed by epoxide opening with Me_2CuLi.

In 1997, Kobayashi and co-workers reported the isolation of callystatin A (**1**), a potent antitumor polyketide from the marine sponge *Callyspongia truncata* (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]



Scheme 1.

Callystatin A (**1**), a polyketide with a terminal α,β-unsaturated lactone and two diene systems shows remarkably high activity (IC_{50} = 0.01 ng/mL) against KB tumor cells.

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 analogs.[3,4] The approach described here to the C13–C22 fragment might give access to callystatin A and additional derivatives with potential relevance to biological studies.[4,5]

Our disconnection, summarized in Scheme 1, involved cleavage of the C12–C13 bond to give fragments C1–C12 (**2**) and C13–C22 (**3**).[6] Unsaturated ester **3** is viewed as arising from an allylic alcohol **4** by selective epoxidation followed by epoxide opening with Me_2CuLi. The allylic alcohol **4** may be further dissected in a straightforward manner to give Weinreb amide **5**. Of the available options, we speculate that the desired *syn–syn* stereocenters in **5** might be established through a boron enolate mediated aldol reaction.

Synthesis of fragment C13–C22 began with the known acyloxazolidinone **6**, which was most conveniently prepared by acylation of the corresponding (*S*)-oxazolidinone (Scheme 2).[7] Asymmetric aldol addition of the boron enolate derived from oxazolidinone **6** with 2-(*S*)-methylbutanal **7** gave the aldol adduct **8** as a crystalline solid (mp 88°C) in 89% yield and >95:5 diastereoselectivity (Scheme 2).[8] Exchange of the oxazolidinone auxiliary in the all *syn*-aldol **8** with *N*,*O*-dimethylhydroxyl-

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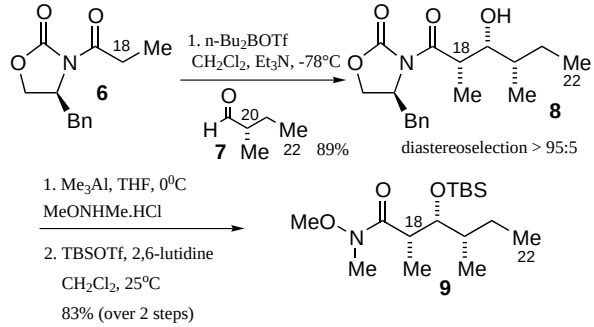
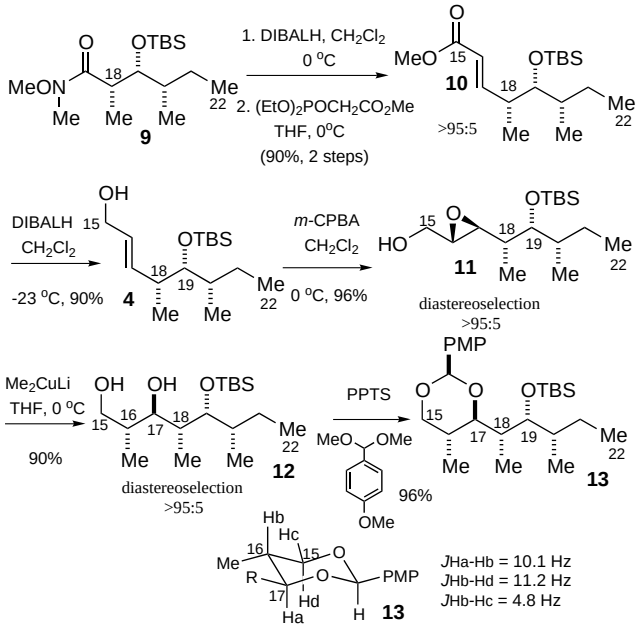


Scheme 2.

amine generated the Weinreb amide, whose purification was facilitated by isolation of the recyclable oxazolidinone chiral auxiliary (92%) by efficient crystallization from the reaction mixture.[9] Subsequent protection of the alcohol functionality as its TBS ether cleanly provided the Weinreb amide **9**, in 83% yield (over two steps).

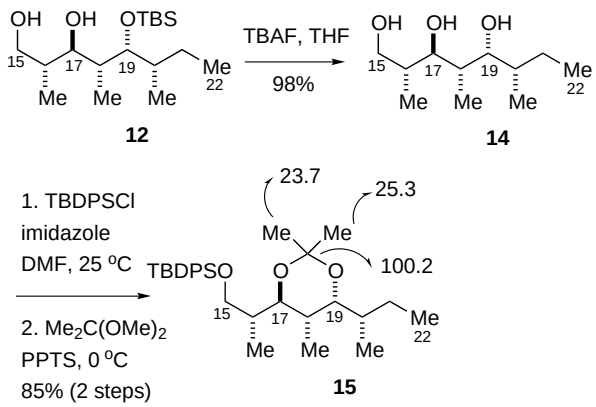
This amide was smoothly reduced to the aldehyde on treatment with diisobutylaluminum hydride at 0°C (Scheme 3). This unpurified aldehyde was directly subjected to a Horner–Emmons homologation with the required phosphonate reagent to give α,β-unsaturated ester **10** in 90% isolated yield over the two-step sequence.[10] Reduction of **10** with 2.2 equiv. of diisobutylaluminum hydride at −23°C gave allylic alcohol **4** (90% yield). Epoxidation of allylic alcohol **4** with *m*-CPBA proceeded with complete stereoselectivity from the opposite side of the C19 *tert*-butyldimethylsilyl group to yield the *anti*-epoxy alcohol **11** as a single product in high purity (96% yield, >95:5).[6,11] It is noteworthy that the diastereoselectivity associated with this epoxidation was exceptional and compared in both yield and selectivity to related transformations described earlier by Isobe et al. and later by Miyashita et al.[11] Epoxide opening proceeded smoothly with high regioselectivity after treatment of the epoxy alcohol **11** with Me_2CuLi to give diol **12** in 90% yield and >95:5 selectivity, possessing the *anti-anti–syn-syn* stereochemistry for the five contiguous stereocenters.[12] Although the hydroxyl function at C17 in diol **12** should be converted to a ketone carbonyl later in the synthesis, this epoxidation/epoxide opening sequence enabled control of the C16 stereocenter. Formation of *p*-methoxybenzylidene acetal **13** was accomplished by treatment of the corresponding diol with *p*-methoxybenzaldehyde dimethyl acetal and a catalytic amount of PPTS (96% yield). The use of CSA instead of PPTS in this reaction gave the secondary alcohol with loss of the TBS protecting group. The stereochemical outcome of the epoxide opening was determined by coupling constant analysis in the ^1H NMR spectra of benzylidene acetal **13**. The large vicinal coupling constants between Ha–Hb (10.1 Hz) and Hb–Hd (11.2 Hz), together with the small observed value between Hb–Hc (4.8 Hz) unambiguously established the proposed 1,2-*anti* relative stereochemistry between C16 and C17.



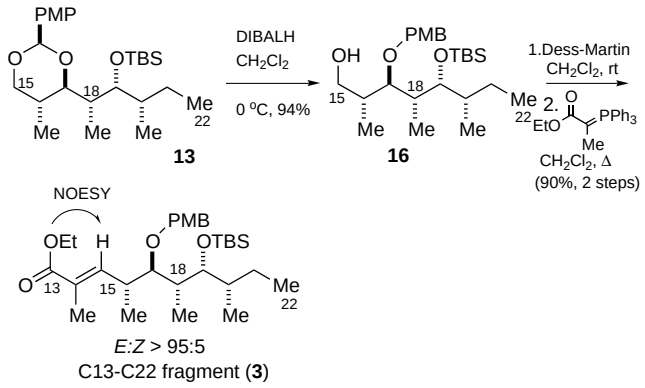
Scheme 3.

The stereochemistry of the secondary alcohols at C17 and C19 was determined on the basis of the ^{13}C NMR analysis of the corresponding 1,3-diol acetonide **15** (Scheme 4). Treatment of diol **12** with TBAF in THF gave triol **14** in 98% yield. A sequence of selective protection of the primary alcohol functionality in **14** followed by treatment with 2,2-dimethoxypropane and catalytic amounts of PPTS gave acetonide **15** in 85% yield for the two steps. ^{13}C NMR observed resonances at 23.7, 25.3, and 100.2 are characteristic of an *anti* acetonide.[13]

Selective DIBALH-mediated acetal cleavage in **13** gave the desired *p*-methoxybenzyl ether alcohol **16** in 94% yield with complete regioselectivity (Scheme 5).[14] Dess–Martin periodinane oxidation[15] of **16** under standard conditions followed by Wittig[10] type coupling with carboethoxyethylidene–triphenylphosphorane in refluxing CH_2Cl_2 gave α,β-unsaturated ester **3** (*E:Z*>95:5) in 90% overall yield for the two-step sequence, corresponding to the C13–C22 fragment of callystatin A.



Scheme 4.



Scheme 5.

The *E*-geometry for ester **3** was confirmed by the illustrated NOESY interaction between vinylic hydrogen at C15 and hydrogens of the ethyl group. Ester **3** is a very useful intermediate to be used in the synthesis of callystatin A, by the same strategies already used by others[4].

The 12-step sequence from **6** to **3** proceeded in an overall yield of 42% and is amenable to a multigram scale-up. Thus, the synthesis of C13–C22 fragment of callystatin A has been described. Notable features of this approach include an efficient *syn* aldol reaction, a diastereoselective epoxidation of an allylic alcohol followed by epoxide opening with Me_2CuLi, and a diastereoselective Wittig coupling. As a result, the route to the C13–C22 fragment presented here is, in principle, readily applicable for the preparation of callystatin A and additional analogs. Efforts are being undertaken to complete the total synthesis of callystatin A and these studies will be described in a full account of this work.[16]

Acknowledgements

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16. New compounds and the isolatable intermediates gave satisfactory ^1H and ^{13}C NMR, IR, HRMS and analytical data. Yields refer to chromatographically and spectroscopically homogeneous materials.