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Total Synthesis of (−)-Callystatin A

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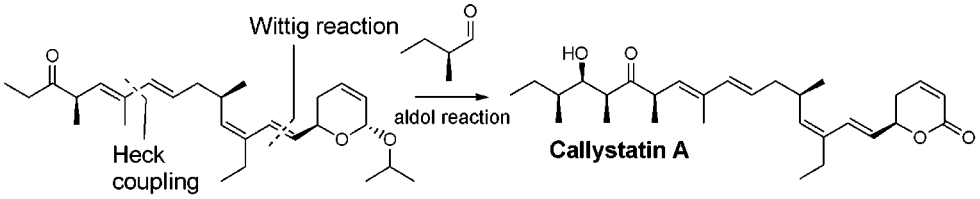
ABSTRACT



The enantioselective synthesis of callystatin A is described. The pivotal step in the synthesis is the stereoselective aldol reaction that generates the *β*-hydroxy ketone moiety. Utilizing the allylic strain within the ethyl ketone precursor, we were able to generate the *all-syn* configuration of callystatin A. For the construction of the two diene moieties, both a Heck coupling and a Wittig reaction were employed.

Callystatin A[1] was isolated from *Callyspongia truncata* and its structure determined by Kobayashi and co-workers. In 1998 they also reported the first total synthesis which was followed by those from Crimmins[1d] and Smith.[1e] Callystatin belongs to a group of natural products that is characterized by an unsaturated lactone moiety and two diene systems separated by two sp^3-hybridized carbons.

This structural motif is also present in leptomycin,[2] ratjadone,[3] kazusamycin, and anguinomycin.[4] Our interest in this group of natural products most recently produced the first total synthesis of ratjadone and the evaluation of the structure−activity relationships (SAR) for this compound.[5a] Within that series, the lactone as well as the diene moieties are crucial for the biological activity whereas the hydroxyl moiety can be modified without losing the tumor growth inhibitory effect.[5] In this context we started the synthesis of callystatin in which the fragments potentially crucial for antitumor activity are assembled before the aldol reaction is performed as the final coupling step.

This strategy not only circumvents the drawbacks of selective protecting group transformations but also allows for the rapid synthesis of structural analogues and derivatives for cellular target identification.[5b,c] The structure of callystatin reveals the diene systems as attractive sites for retrosynthetic disassembly. We dissected callystatin into four major frag-

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(2) (a) Hammamoto, T.; Seto, H.; Beppu, T. *J. Antibiot.* **1983**, *36*, 646. (b) Hurley, T. R.; Bunge, R. H.; Willer, N. E.; Hokanson, G. C.; French, J. C. *J. Antibiot.* **1986**, *39*, 1651. (c) Schaumberg, J. P.; Hokanson, G. C.; French, J. C. *J. Chem. Soc., Chem. Commun.* **1984**, 1450. (d) Absolute stereochemistry and total synthesis of leptomycin B: Kobayashi, M.; Wang, W.; Tsutsui, Y.; Sugimoto, M.; Murakami, N. *Tetrahedron Lett.* **1998**, *39*, 8291.

(3) Isolation:(a) Gerth, K.; Schummer, D.; Höfle, G.; Irschik, H.; Reichenbach, H. *J. Antibiot*. **1995**, *48*, 973. (b) Schummer, D.; Gerth, K.; Reichenbach, H.; Höfle, G. *Liebigs Ann.* **1995**, 685. Syntheses: (c) Christmann, M.; Bhatt, U.; Quitschalle, M.; Claus, E.; Kalesse, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 4364. (d) Bhatt, U.; Christmann, M.; Quitschalle, M.; Claus, E.; Kalesse, M. *J. Org. Chem.* **2001**, *66*, 1885. (e) Williams, D. R.; Ihle, D. C.; Plummer, S. V. *Org. Lett.* **2001**, *3*, 1383.

(4) (a) Kazusamycin: Komiyama, K.; Okada, K.; Oka, H.; Tomisaka, S.; Miyano, T.; Funayama, S.; Umezawa, I. *J. Antibiot.* **1985**, *38*, 220. (b) Anguinomycins: Hayakawa, Y.; Adachi, K.; Koneshima, N. *J. Antibiot.* **1987**, *40*, 1349. (c) Hayakawa, Y.; Sohda, K.; Shin-ya, K.; Hidaka, T.; Seto, H. *J. Antibiot.* **1995**, *48*, 954. (d) Leptofuranins: Hayakawa, Y.; Sohda, K.; Seto, H. *J. Antibiot.* **1996**, *49*, 980.

(5) (a) Kalesse, M.; Christmann, M.; Bhatt, U.; Quitschalle, M.; Claus, E.; Saeed, A.; Burzlaff, A.; Kasper, C.; Haustedt, L. O.; Hofer, E.; Scheper, T.; Beil, W. *ChemBioChem* **2001**, in press. For SAR of callystatin A, see: (b) Murakami, N.; Sugimoto, M.; Kobayashi, M. *Bioorg. Med. Chem.* **2001**, *9*, 57. (c) Murakami, N.; Sugimoto, M.; Nakajima, T.; Kawanishi, M.; Tsutsui, Y.; Kobayashi, M. *Bioorg. Med. Chem.* **2000**, *8*, 2651.

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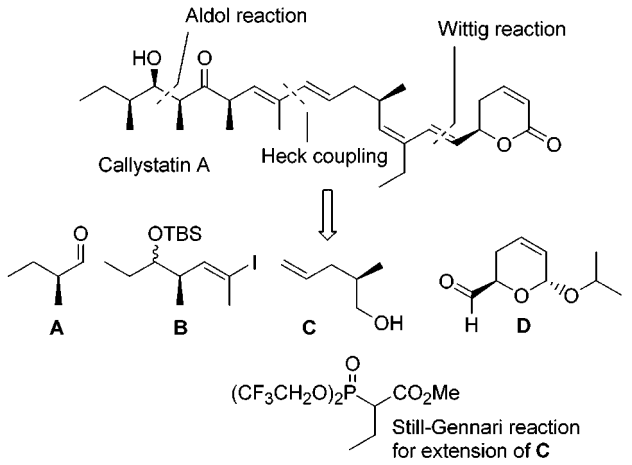
Scheme 1. Retrosynthetic Analysis of Callystatin **A**

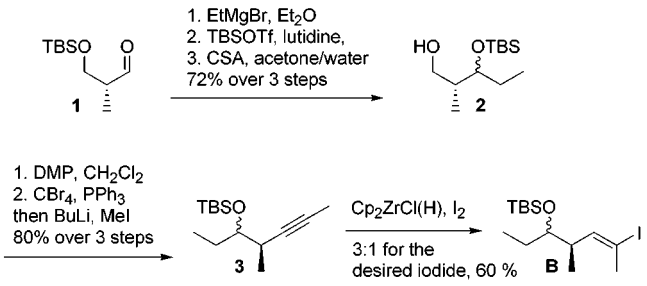


ments (Scheme 1), chiral aldehyde **A**, vinyl iodide **B**, alcohol **C**, and aldehyde **D**. In the synthetic direction, fragments **B** and **C** are joined by a Heck coupling followed by oxidation and extension with the Still−Gennari reagent. After formation of the corresponding bromide, a Wittig reaction between phosphine **6** and aldehyde **D** furnishes the majority of the carbon skeleton.

The synthesis of fragment **B** commences with known aldehyde **1**[6] derived from (*S*)-3-hydroxyisobutyric acid. Addition of EtMgBr[7] followed by TBS protection and selective liberation of the primary hydroxyl group with CSA in acetone/water generates alcohol **2**.

Oxidation with the Dess−Martin periodinane[8] and a subsequent Corey−Fuchs reaction[9] in which the anion was alkylated with MeI established the acetylenic compound **3**. Treatment with the Schwartz reagent[10] and quenching the anion with I_2 generated a 3:1 mixture of regioisomers of which the desired major fragment **B** was easily separated by flash chromatography (Scheme 2). The synthesis of

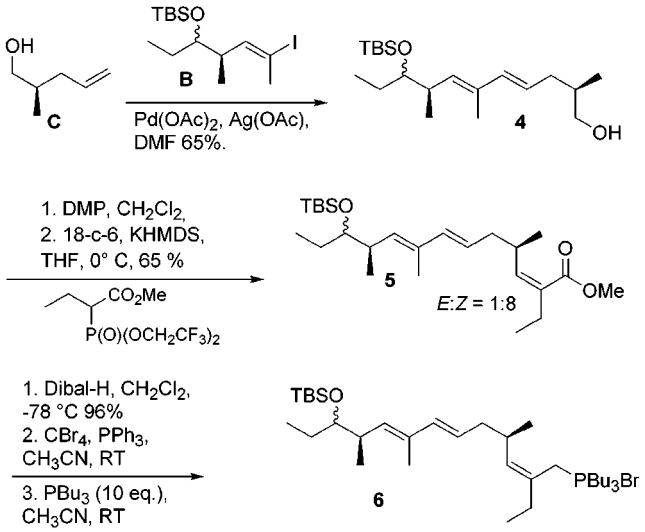
Scheme 2. Synthesis of the Vinyl Iodide **B**



fragment **6** (Scheme 3) was initiated with a Heck coupling[11] between vinyl iodide **B** and the known alcohol **C**.[12] Swern oxidation[13] of **4** followed by Still−Gennari reaction[14] estab-

(6) Burke, S. D.; Cobb, J. E.; Takeuchi, K. *J. Org. Chem.* **1990**, *55*, 2138.

Scheme 3. Synthesis of Fragment **6**



lished the *Z*-configured α,*β*-unsaturated ester **5**. Dibal-H reduction and subsequent transformation into the bromide under Appel[1d] conditions followed by treatment with tributylphosphine furnished tributylphosphonium salt **6** (Scheme 3).

Wittig reaction of **6** with aldehyde **D**[15] using KO*t*Bu in toluene[1d] provided precursor **7** which contained the complete carbon skeleton necessary for the pivotal aldol reaction.

Deprotection of the secondary hydroxyl group was accomplished with TBAF in THF. The following Swern oxidation provided ethyl ketone **8** in 73% yield over two steps (Scheme 4). The ketone was then treated with LiHMDS at −78 °C in THF to generate the *Z*-enolate. After the reaction mixture had been stirred for 20 min, aldehyde **A** was added in one portion and the reaction was quenched after 15 min at −78 °C with a saturated NH_4Cl solution. The aldol step generated the two *syn*-isomers in a 2:1 ratio in favor of the *all-syn* isomer (19,20-*syn* **9**). Acid-catalyzed cleavage of the acetal and subsequent oxidation with MnO_2 in CH_2Cl_2 and pyridine furnished callystatin A (Scheme 4). The spectroscopic data were identical in all respects to those reported for the natural material (e.g., ^1H and ^{13}C NMR, HRMS, optical rotation). Having the aldol reaction established in the end-game of the synthesis circumvents the

(7) The addition of EtMgBr gave a 4:1 mixture of stereoisomers of which the *anti* isomer was the major component.

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(9) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *13*, 3769.

(10) Schwartz, J.; Labinger, J. A. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 333.

(11) Jeffery, T. *J. Chem. Soc., Chem Commun.* **1991**, 324.

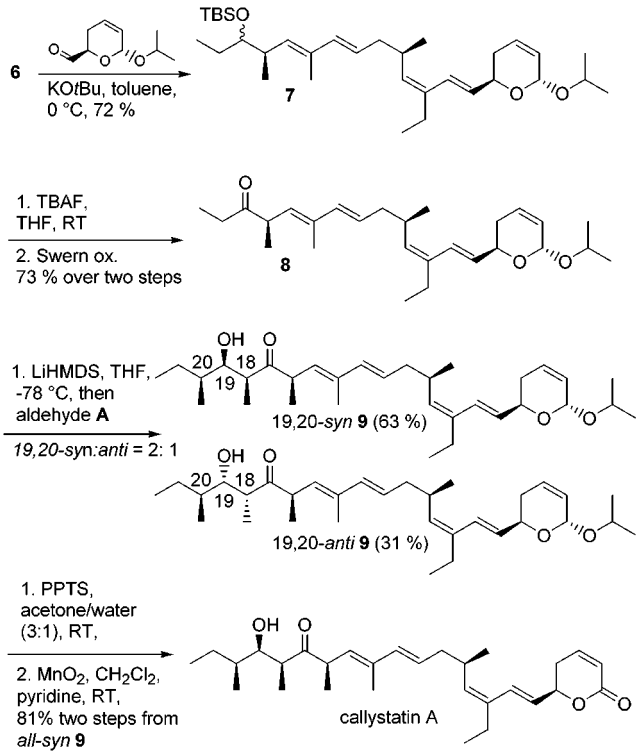
(12) (a) Overman, L. E.; Robinson, L. A.; Zablocki, J. *J. Am. Chem. Soc.* **1992**, *114*, 368. (b) Schinzer, D.; Bauer, A.; Schieber, J. *Synlett* **1998**, 861.

(13) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165.

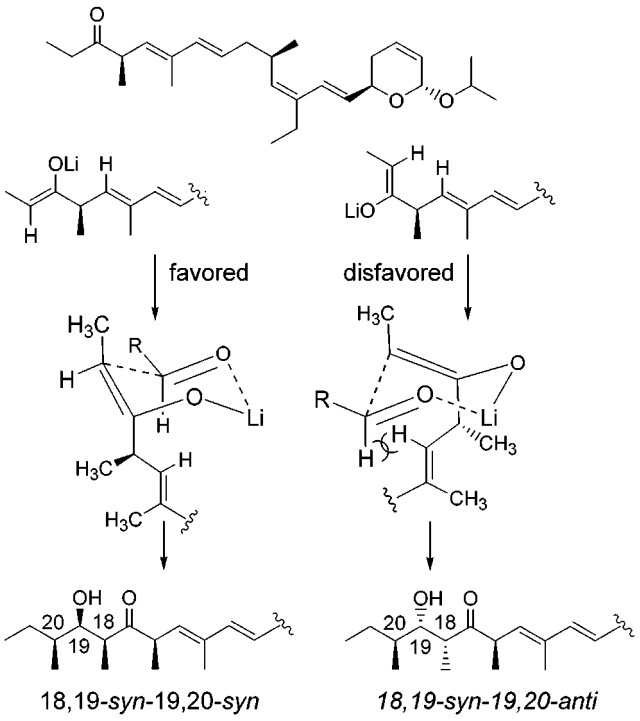
(14) (a) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405. The phosphonate was generated according to Morimoto, Y.; Matsuda, F.; Shirahama, H. *Tetrahedron.* **1996**, *52*, 10609.

(15) Quitschalle, M.; Christmann, M.; Bhatt, U.; Kalesse, M. *Tetrahedron Lett.* **2001**, *42*, 1263.

Scheme 4. Synthesis of Callystatin A



Scheme 5[a]



[a] Allylic strain imparted by the orientation of the substituents α to the enolate favors the linear chain conformation as depicted. That same sterically congested α center then dictated facial selectivity in the aldol reaction with the aldehyde approaching from the opposite side of the methyl group.

problem of removing a TBS group from a secondary alcohol in the presence of a sensitive lactone moiety or having to discriminate between two secondary hydroxyl groups.

The minor isomer (19,20-*anti* **9**)[16] was also subjected to the final transformations and it could be seen that the diastereomeric callystatin differs significantly from the natural one (see Supporting Information) in its ^{1}H NMR spectra. We rationalized the observed selectivity for the major isomer in the aldol step with a Zimmerman−Traxler transition state[17] in which pseudo 1,3 diaxial interactions between the ketone side chain and the aldehyde proton are minimized (Scheme 5).[18] This strategy now allows the rapid assembly of analogues that differ from the natural product in the hydroxy ketone region. The results from biological testings of both isomers as well as additional analogues will be reported in due course.

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Supporting Information Available: Spectroscopic data and experimental procedures for compounds **B**, **4**, **5**, **6**, **7**, **8**, **9**, and callystatin. This material is available free of charge via Internet at http://pubs.acs.org.

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(16) The stereochemistry of the minor isomer was assigned on the basis of the transition state model.

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