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Total Synthesis of (+)-18-*epi*-Latrunculol A

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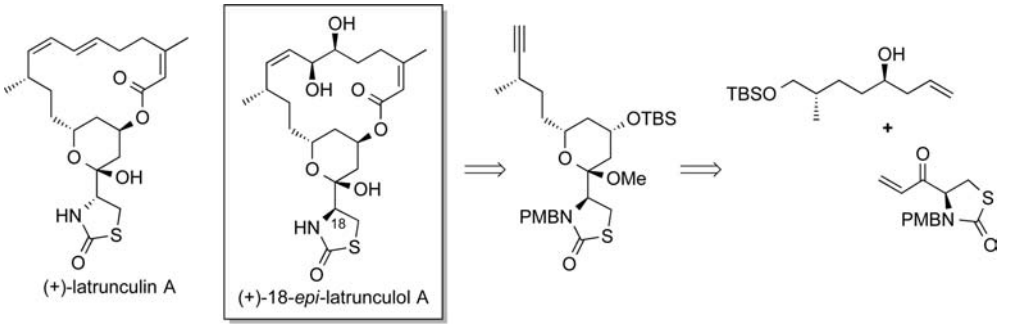
ABSTRACT



An enantioselective total synthesis of the cytotoxic latrunculin congener (+)-18-*epi*-latrunculol A has been achieved. Key steps in the synthetic route include an acid-mediated enone cyclization/equilibration sequence, a Carreira alkynylation, and a late-stage Mitsunobu macrolactonization to construct the macrolide skeleton.

The latrunculins comprise a family of sponge-derived, architecturally intriguing macrolides widely studied due to their aggressive inhibition of actin polymerization and cytotoxicity against human cancer cell lines.[1] The parent compound, latrunculin A, is commonly employed as a molecular probe to explore the effects of actin depolymerization;[1b] however, due to the ubiquity of actin in the cytoskeleton of living organisms, latrunculin A displays nonselective cytotoxicity and, as such, is currently considered inappropriate for drug development.[2]

In 2008, Crews and co-workers reported the structural assignment and an initial bioactivity assesment of several novel latrunculin congeners derived from two sponges, *Cacospongia mycofijiensis* and *Negombata magnifica*.[3] Surprisingly, one of the analogues, (+)-18-*epi*-latrunculol A (**1**), was found to exhibit selective, solid tumor cytotoxicity[4] when tested against HCT-116 (5.5 μM) and MDA-MB-435 (> 50 μM) *but* was devoid of actin depolymerization activity. Thus (+)-**1** may in fact hold promise as a potential lead for cancer chemotherapy.

In view of our long-standing interest in the latrunculins,[5] in conjunction with the unique biological properties and unknown mode of cytotoxicity, we embarked on the development of a viable, preparative-scale total synthesis of (+)-18-*epi*-latrunculol A (**1**), both to validate the assigned structure and absolute stereochemistry and to provide material for further biological evaluation. Although to date there have been no reported synthetic approaches toward (+)-18-*epi*-latrunculol A (**1**), the synthesis of latrunculins A and B has attracted considerable attention,[6] in addition to our efforts.[5] Herein we report the first total synthesis and structural validation of (+)-18-*epi*-latrunculol A (**1**).

(1) (a) Spector, I.; Shochet, N.; Kashman, Y.; Groweiss, A. *Science* **1983**, *4584*, 493–495. (b) Ayscough, K. R.; Stryker, J.; Pokala, N.; Sanders, M.; Crews, P.; Drubin, D. G. *J. Cell Biol.* **1997**, *2*, 399–416.

(2) Newman, D.; Cragg, G. *J. Nat. Prod.* **2004**, *8*, 1216–1238.

(3) Amagata, T.; Johnson, T. A.; Cichewicz, R. H.; Tenney, K.; Mooberry, S. L.; Media, J.; Edelstein, M.; Valeriote, F. A.; Crews, P. *J. Med. Chem.* **2008**, *51*, 7234–7242.

(4) Valeriote, F.; Grieshaber Charles, K.; Media, J.; Pietraszkewicz, H.; Hoffmann, J.; Pan, M.; McLaughlin, S. *J. Exp. Ther. Oncol.* **2002**, *2*, 228–236.

(5) (a) Zibuck, R.; Liverton, N. J.; Smith, A. B. *J. Am. Chem. Soc.* **1986**, *108* (9), 2451–2453. (b) Smith, A. B.; Noda, I.; Remiszewski, S. W.; Liverton, N. J.; Zibuck, R. *J. Org. Chem.* **1990**, *55*, 3977–3979. (c) Zibuck, R.; Liverton, N. J.; Smith, A. B. *J. Am. Chem. Soc.* **1992**, *114*, 2995–3001.

(6) (a) Furstner, A.; De Souza, D.; Turet, L.; Fenster, M. D. B.; Parra-Rapado, L.; Wirtz, C.; Mynott, R.; Lehmann, C. W. *Chem.—Eur. J.* **2007**, *13*, 115–134. (b) Furstner, A.; Nagano, T.; Mueller, C.; Seidel, G.; Mueller, O. *Chem.—Eur. J.* **2007**, *13*, 1452–1462. (c) White, J. D.; Kawasaki, M. *J. Org. Chem.* **1992**, *57*, 5292–5300. (d) White, J. D.; Kawasaki, M. *J. Am. Chem. Soc.* **1990**, *112*, 4991–4993.

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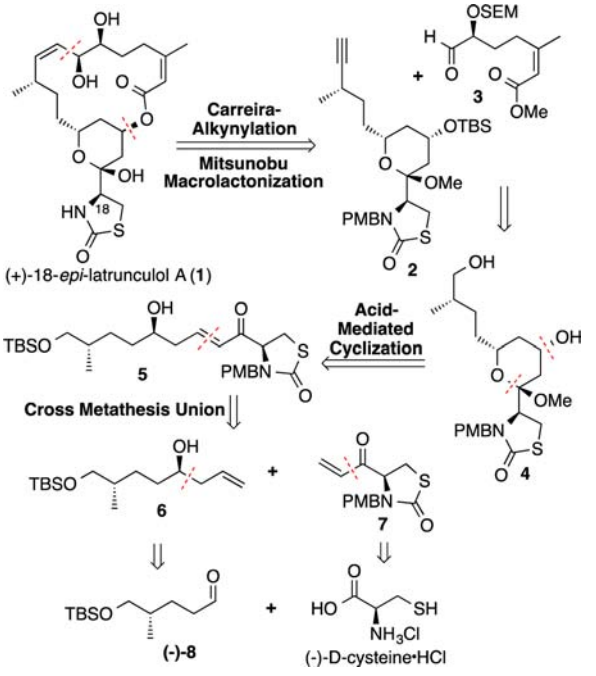
Our synthetic strategy was planned around our original effective route to latrunculin A.[5b] Important modifications however were incorporated to ensure access to the (+)-enantiomer, as illustrated in Scheme 1.

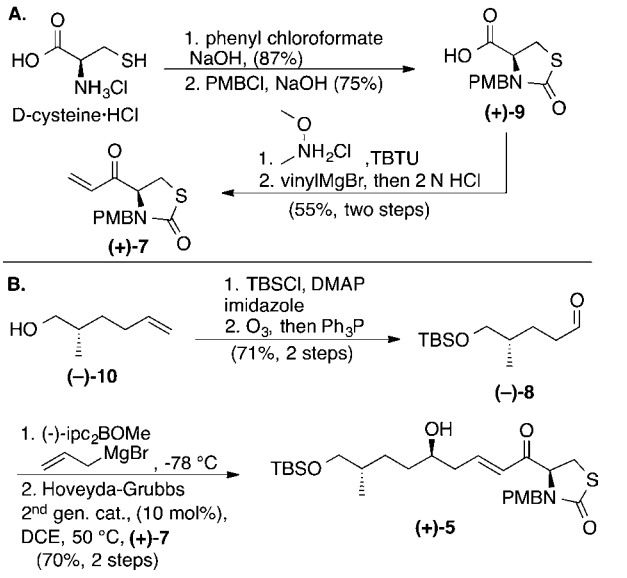
Scheme 1. Retrosynthetic Analysis of (+)-18-*epi*-Latrunculol A (**1**)



As with latrunculin A, we envisioned use of a late-stage Mitsunobu macrolactonization[7] to access the 16-membered lactone with requisite stereoinversion, in this case with incorporation of a Carreira alkynylation[8] to unite alkyne **2** with aldehyde **3** under mild conditions. A Seyferth–Gilbert homologation would then be employed to construct alkyne **2** from alcohol **4**.[9] Methoxy ketal **4**, in turn, would result from an acid-mediated cyclization of enone **5**, which would be readily constructed *via* a functional group tolerant cross metathesis.[10] Finally, the cross metathesis partners **6** and **7** would be available respectively from known aldehyde (−)-**8**[11] and D-cysteine.

We began the synthesis of (+)-*epi*-latrunculol A (**1**) *via* conversion of D-cysteine (Scheme 2A) to thiazolidinone (+)-**9**, employing phenyl chloroformate, followed by chemoselective protection with *p*-methoxy benzyl chloride

Scheme 2. Synthesis of (A) (+)-**7** and (B) (+)-**5**



(PMBCl).[12] In turn, (+)-**9** was converted to the Weinreb amide[13] and then treated with vinyl magnesium bromide to yield enone (+)-**7** in 36% overall yield (4 steps) from D-cysteine.

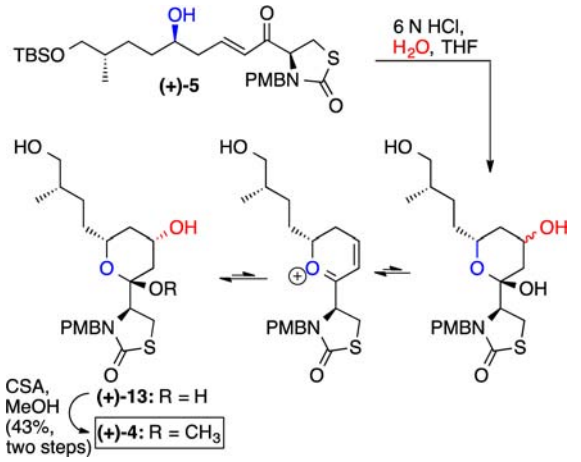
To construct cyclization precursor **5** (Scheme 2B), known aldehyde (−)-**8** was readily available from (−)-**10**[14] *via* TBS protection and ozonolysis. Brown allylation,[15] followed by cross metathesis union employing the Hoveyda–Grubbs second generation catalyst between the resulting homoallylic alcohol and enone (+)-**7**, proceeded smoothly to provide cyclization precursor (+)-**5** in a 70% yield for the two steps, after separation of the minor epimeric alcohol resulting from the Brown allylation.

The critical acid-mediated cyclization of (+)-**5** to lactol (+)-**13** was then achieved by treatment with a THF/6 N HCl mixture (1.3:1/v:v) followed by protection as the methyl ketal (MeOH/CSA) to furnish (+)-**4** as a single diastereomer, presumably *via* the reaction sequence outlined in Scheme 3.[5,6]

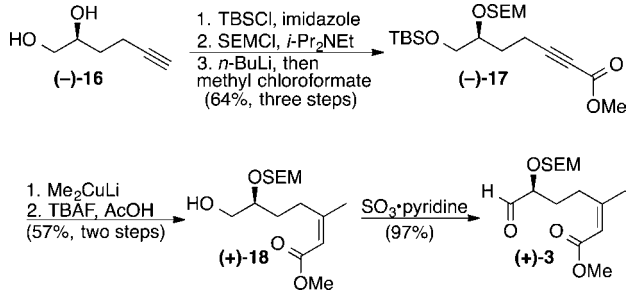
Turning to the requisite northern hemisphere aldehyde (+)-**3**, construction entailed six steps, beginning with known diol (−)-**16** (Scheme 4).[16] A two-step chemoselective protection strategy, followed by addition of the derived alkynyl anion to methyl chloroformate, delivered alkynoate (−)-**17** in 64% yield over the three steps. Conjugate addition of Me_2CuLi to (−)-**17** was then followed by removal of the TBS group with acetic acid buffered TBAF to furnish enoate (+)-**18**, importantly without isomerization of the sensitive *Z*-enone. Parikh–Doering oxidation[17]

(7) Mitsunobu, O. *Synthesis* **1981**, *1*, 1–28.
(8) Frantz, D.; Fassler, R.; Carreira, E. *J. Am. Chem. Soc.* **2000**, *8*, 1806–1807.
(9) (a) Seyferth, D.; Marmor, R. S.; Hilbert, P. *J. Org. Chem.* **1971**, *36*, 1379–1386. (b) Gilbert, J. C.; Weerasooriya, U. *J. Org. Chem.* **1982**, *47*, 1837–1845.
(10) (a) Kingsbury, J. S.; Harrity, J. P. A.; Bonitatebus, P. J.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *4*, 791–799. (b) Chatterjee, A. K.; Choi, T.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125* (37), 11360–11370.
(11) Marshall, J.; Yanik, M. *J. Org. Chem.* **2001**, *4*, 1373–1379.
(12) Seki, M.; Hatsuda, M.; Mori, Y.; Yoshida, S.; Yamada, S.; Shimizu, T. *Chem.—Eur. J.* **2004**, *23*, 6102–6110.
(13) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *39*, 3815–3818.
(14) Tomas, L.; af Gennas, G. B.; Hiebel, M. A.; Hampson, P.; Gueyrard, D.; Pelotier, B.; Yli-Kauhaluoma, J.; Piva, O.; Lord, J. M.; Goekjian, P. G. *Chem.—Eur. J.* **2012**, *24*, 7452–7466.
(15) Brown, H. C.; Jadhav, P. K. *J. Am. Chem. Soc.* **1983**, *7*, 2092–2093.
(16) Ramharter, J.; Mulzer, J. *Org. Lett.* **2009**, *11*, 1151–1153.
(17) Parikh, J.; Doering, W. *J. Am. Chem. Soc.* **1967**, *89*, 5505–5507.

Scheme 3. Synthesis of Ketal (+)-**4**



Scheme 4. Synthesis of Aldehyde (+)-**3**

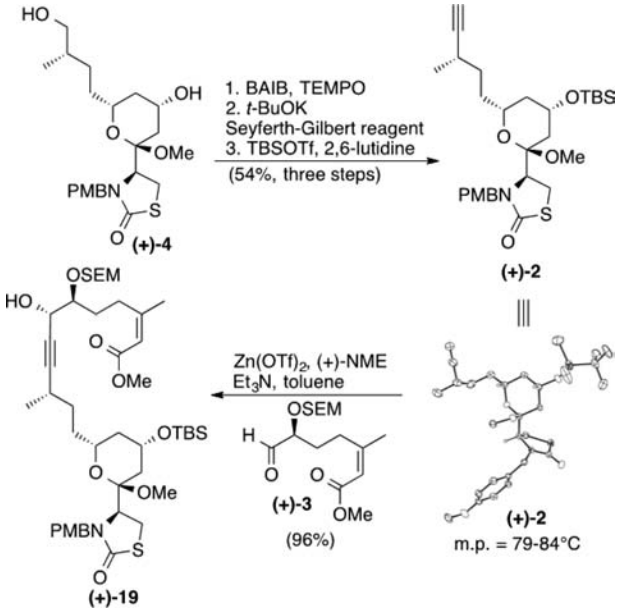


completed the construction of aldehyde (+)-**3**, the latter requiring minimal purification.

In preparation for fragment union (Scheme 5), selective oxidation of diol (+)-**4**,[17] followed in turn by alkyne formation exploiting the Seyferth–Gilbert reagent[9,19] and TBS protection, delivered crystalline alkyne (+)-**2**; the structure and absolute stereochemistry were confirmed by single crystal X-ray analysis. Although aldehyde (+)-**3** proved sensitive to a variety of basic conditions, union of (+)-**2** with (+)-**3** *via* Carreira alkynylation[8] pleasingly delivered adduct (+)-**19** as a single diastereomer in high yield.

We next turned to explore the semihydrogenation of (+)-**19**; surprisingly no alkyne reduction was observed when either Lindlar or P-2 nickel catalysts[20] were utilized under a hydrogen atmosphere. We reasoned this may be due to possible steric encumbrance. To visualize the steric environment around the alkyne, MM2 modeling was undertaken. Our focus quickly shifted, however, when we recognized the methyl ester group in (+)-**19** was in precisely the required conformation for Mitsunobu macrolactonization. With this information, coupled with the idea that ring strain from an alkyne residing within a 16-membered macrolactone ring might aid in the required semireduction, we turned to the construction of the corresponding alkyne seco-acid.

Scheme 5. Synthesis of Propargylic Alcohol (+)-**19**



Protecting group manipulation first furnished acetonide (+)-**20** (Scheme 6). Hydrolysis of the ester with sodium hydroxide in ethanol was then followed by treatment with Ph_3P and diethyl azodicarboxylate (DEAD) to provide the macrolactone with full consumption of the starting material. The macrolactone however proved inseparable from the reduced DEAD byproduct, *via* standard silica column chromatography.

However, subjecting the mixture to ceric ammonium nitrate (CAN) in an acetonitrile/water mixture (3:1) not only removed the PMB protecting group but also furnished pure macrolactone (+)-**21** in 35% yield for the three steps after flash chromatography on silica gel.

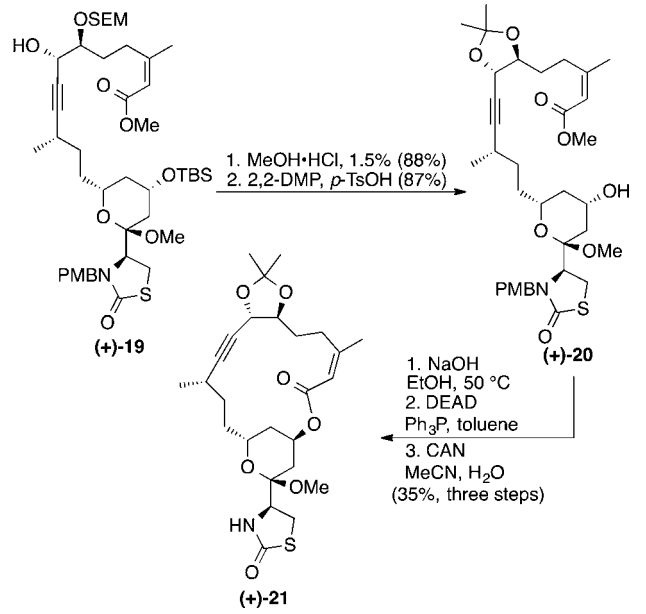
For comparison, the Mitsunobu macrolactonization employed in our original synthesis of latrunculin A[5b,c] occurred in only 31% yield, with the resulting macrolactone being either unstable or unreactive under all conditions employed to remove the PMB protecting group. A similar resilient amide PMB protecting group was encountered by Fürstner et al. in their synthesis of latrunculin A, likewise resulting in a protecting group adjustment.[6] For the synthesis of (+)-18-*epi*-latrunculol A, we had, however, reasoned that the macrolactone derived *via* Mitsunobu macrolactonization (Scheme 6) might withstand ceric ammonium nitrate (CAN)-mediated oxidative removal of the PMB protecting group, given the lack of the sensitive conjugated diene present in latrunculin A. Moving forward, global deprotection of (+)-**21** was achieved in high

(18) DeMico, A.; Margarita, R.; Parlanti, L.; Vescovi, A.; Piancatelli, G. *J. Org. Chem.* **1997**, *62*, 6974–6977.

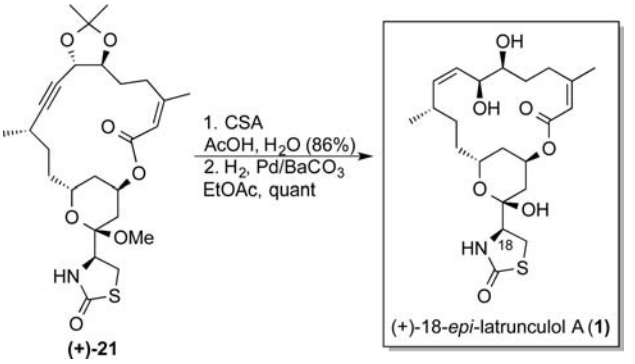
(19) Ohira–Bestmann conditions resulted in epimerization.

(20) Brown, C. A.; Ahuja, V. K. *J. Chem. Soc., Chem. Commun.* **1973**, 553–554.

Scheme 6. Synthesis of Macrolactone (+)-**21**



Scheme 7. Synthesis (+)-18-*epi*-Latrunculol A (**1**)



yield (86%) by heating in aqueous acetic acid with catalytic camphorsulfonic acid (Scheme 7).

Semihydrogenation of the penultimate alkyne however again proved unfruitful, employing either poisoned catalytic palladium or P-2 nickel catalysts under an atmosphere of hydrogen. We did however eventually discover that hydrogenation using excess palladium on carbon (without poison; ca. 1.2 equiv) provided (+)-18-*epi*-latrunculol A (**1**), albeit in a modest yield of 29% yield, but remarkably without over-reduction. The semireduction was further improved by utilizing barium carbonate as a less adsorbent solid support, to furnish (+)-**1** now in near-quantitative yield. Pleasingly, the spectral data of totally synthetic (+)-18-*epi*-latrunculol A (**1**) [i.e., ^{1}H and ^{13}C NMR (500 and 125 MHz, respectively), HRMS parent ion identification, and chiroptic properties] proved identical in all respects to those reported for the natural (+)-18-*epi*-latrunculol A (**1**).[3]

In summary, the total synthesis of (+)-18-*epi*-latrunculol A (**1**) has been achieved with a longest linear sequence of 15 steps from known aldehyde (−)-**8** in an overall yield of 3.5%. The key features of this work comprise an acid-mediated enone cyclization/equilibration sequence, followed by a Carreira alkynylation, and conclude with a late-stage Mitsunobu macrolactonization that leads to an effective asymmetric route, permitting access to (+)-18-*epi*-latrunculol A (**1**) and potentially to a diverse set of analogues. Biological testing, currently underway, will be reported in due course.

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Supporting Information Available. Experimental details and spectroscopic and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.