Natural Product Synthesis

Concise and Practical Synthesis of Latrunculin A by Ring-Closing Enyne–Yne Metathesis**

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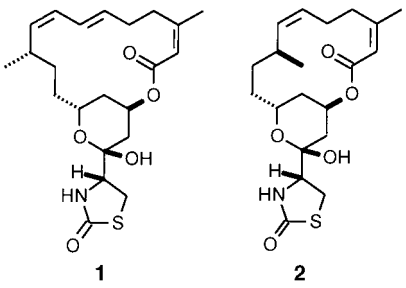
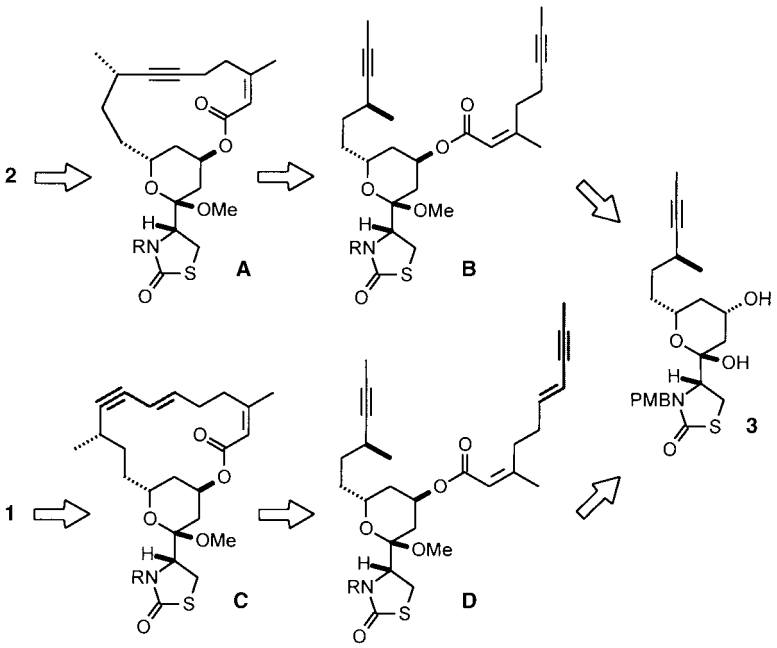
Incubation of eukaryotic cells with micromolar concentrations of the marine natural product latrunculin A (**1**) or its ring-contracted congener



latrunculin B (**2**) results in a selective perturbation or even complete disruption of the actin cytoskeleton.[1,2] Thereby, the potency and rapid onset of action are highly reminiscent of genetic knockout experiments, and thus allow study of the many biological properties of actin by what might be considered a prototype "chemical genetics" approach.[3] This crucial and highly complex subcellular protein network determines the shape and mechanical properties of the cells and is responsible for motility processes as fundamental as exo- and endocytosis. The recent discovery of an actin-dependent checkpoint in mitosis also relied on the use of **1**, thus increasing the interest in this and related probe molecules even further.[4]

It is hardly surprising, therefore, that this family of scarce macrolides has also attracted the interest of the synthetic community to culminate in three successful total synthesis campaigns.[5–7] In this context, we reported an efficient route to latrunculin B (**2**) based upon the use of ring-closing alkyne metathesis (RCAM)[8,9] for the formation of the macrocycle.[7] Although this approach is inherently flexible and should therefore be amenable to the synthesis of all other members of this series, two important aspects deserved further consideration before it was adapted to the total synthesis of the parent compound **1**.

While access to **2** relies on a regular RCAM reaction[8,9] of a properly protected diyne of type **B** to cycloalkyne **A** followed by Lindlar reduction, the envisaged extension of this strategy to the synthesis of **1** implies a metathetic event between an alkyne and a conjugated enyne (**D**→**C**, Scheme 1). Only if this transformation occurs strictly chemoselectively at the triple bonds without affecting the adjacent olefin[10] might latrunculin A come into reach. Such alkyne-selective enyne–yne metathesis reactions were disclosed only recently and have never been used in a similarly complex setting.[11] Moreover, as the resulting products are necessarily strained, the efficiency of this reaction strongly depends on the ring size formed, with the smallest successful example reported to date comprising 18 ring atoms.[11] It was therefore by no means clear if this methodology was applicable to the



Scheme 1. Retrosynthetic analyses of latrunculin A and B which both converge to the common building block **3**. PMB = *para*-methoxybenzyl.

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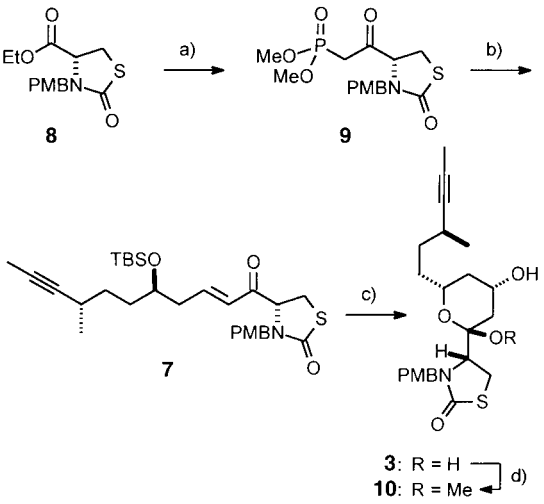
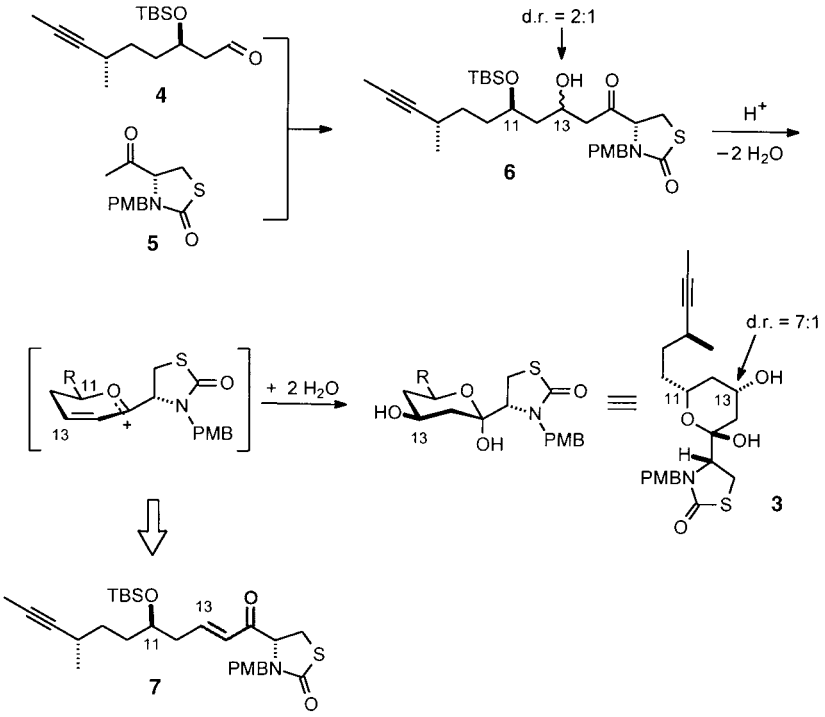
stereoselective formation of the diene moiety of **1** which is embedded into the 16-membered ring of a rigid bicyclic skeleton.

The second aspect that deserves further consideration is of practical relevance. While compound **3** as the key building block en route to **2** can also be used for the total synthesis of **1** (see Scheme 1), its preparation relies on an aldol reaction which is not fully satisfactory. Specifically, exposure of aldehyde **4** to the titanium enolate derived from ketone **5** at −78 °C provides product **6** as an inseparable 2:1 mixture of the corresponding diastereomers (Scheme 2).[7] This mixture equilibrates to a more favorable ≈7:1 ratio of isomeric hemiketals on acid-catalyzed cleavage of the O-TBS group at C-11 (latrunculin B numbering), most likely by a retro-Michael/Michael manifold that involves a transient oxocarbenium ion.[7,12] If this mechanistic hypothesis is correct, however, it might be possible to obtain **3** also from the α,β-unsaturated ketone **7** by protonation and addition of water through a sterically and stereoelectronically preferred equatorial trajectory. It seemed lucrative to pursue this idea as it



Scheme 3. Improved synthesis of the key building block **3**: a) $(MeO)_2P(O)CH_3$, *n*BuLi, THF, −78 °C, 60%; b) $Ba(OH)_2 \cdot 8H_2O$ (activated at 140 °C), THF, aldehyde **4**, 75%; c) aq. HCl, THF, 63%; d) MeOH, camphorsulfonic acid (cat.), quantitative.

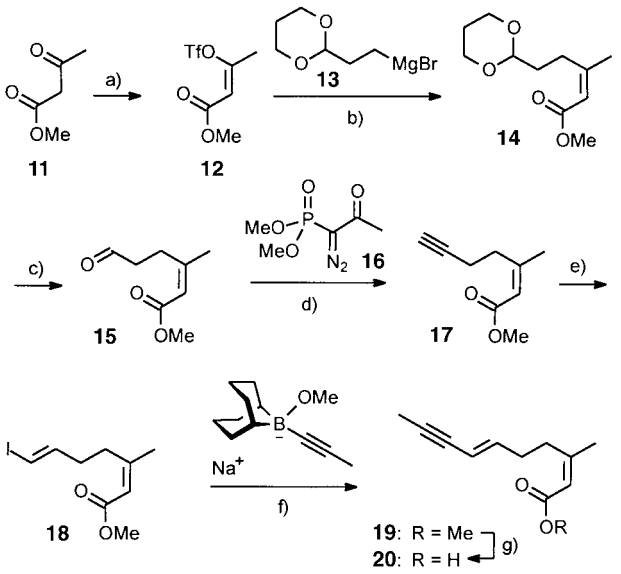


Scheme 2. Established aldol route to the key building block **3** and rationale for the stereochemical equilibration observed upon hemiketal formation. TBS = *tert*-butyldimethylsilyl.

may allow us to replace the somewhat capricious aldol reaction by a simple olefination, which requires neither the handling of sensitive compounds nor the use of low temperatures and should therefore be much more robust, practical, and scaleable.

As shown in Scheme 3, this strategy turned out highly rewarding. Thus, reaction of ester **8** (derived from cysteine in two high-yielding steps)[7] with deprotonated $(MeO)_2P(O)CH_3$ afforded ketophosphonate **9**, ready for condensation with aldehyde **4** (obtained in multigram quantities from (+)-citronellene in seven steps, as previously described).[7] After some experimentation it was found that this Horner–Wadsworth–Emmons reaction proceeded best when activated $Ba(OH)_2$ was used as the base.[13] Exposure of the resulting alkene **7** to aqueous HCl gave the desired hydrated hemiketal **3** in approximately 9:1 ratio; the individual isomers were separable after transformation into the corresponding methyl glycosides **10**. Importantly, this outcome does not only corroborate the proposed equilibration mechanism (see Scheme 2) but also opens a convenient route to this essential building block.

The required acid part was obtained from enol triflate **12**[14] by using iron-catalyzed cross-coupling chemistry previously developed in our laboratory (Scheme 4).[15,16] To this end, substrate **12** was treated with the commercially available organomagnesium reagent **13** in the presence of $[Fe(acac)_3]$ as a cheap and benign precatalyst to give product **14** on a multigram scale.[17] Cleavage of the acetal, conversion of the resulting aldehyde **15** into the corresponding alkyne **17** with the aid of the Ohira–Bestmann reagent **16**,[18] followed by hydrozirconation/iodination[19] provided the desired alkenyl iodide **18** as a single isomer.[20] Conversion of this compound into enyne **19** turned out to be surprisingly difficult, and only the "9-methoxy-9-BBN" variant of the Suzuki reaction (9-MeO-9-BBN, MeC≡CNa, $[Pd(PPh_3)_4]$ catalyst), as previously described by our group, gave satisfactory and reproducible results.[21] Enyne **19** was saponified with KOH in aqueous THF, whereas other bases commonly used for ester hydrolyses led to the decomposition of the material and/or partial epimerization of its *Z*-configured enoate moiety.



Scheme 4. Preparation of the acid part: a) (1) NaH, CH_2Cl_2; (2) Tf_2O, 82%; b) Grignard reagent **13**, [Fe(acac)$_3$] (15 mol%), −30°C, THF, 67–83%; c) aq. HCOOH, reflux; d) reagent **16**, K_2CO_3, MeOH, 80% (over both steps); e) [$Cp_2Zr(H)Cl$], CH_2Cl_2, then I_2, 56%; f) 9-MeO-9-BBN, NaC≡CMe, [$Pd(PPh_3)_4$] (5 mol%), THF, reflux, 77%; g) KOH, aq. THF, 82%. Tf = trifluoromethanesulfonyl, acac = acetylacetonate, Cp = cyclopentadienyl, BBN = borabicyclo[3.3.1]nonane.

Coupling of the fragments now in hand required the consecutive formation of triflate **21** and substitution with the sodium salt of acid **20** (see Scheme 5). All attempts to perform this esterification under Mitsunobu conditions were unrewarding. We were pleased to note that the resulting product **22** underwent productive enyne–yne metathesis to give the desired product **23** in the presence of catalytic amounts of [Mo{N(*t*Bu)(Ar)}$_3$] (**26**), activated in situ with CH_2Cl_2 as previously described.[22,23] This success, however, was thwarted by our inability to cleave the remaining N-PMB group from the thiazolidinone ring with either 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) or cerium ammonium nitrate (CAN). Although we were apprehensive that this step might be problematic,[24] it seemed likely that the high ring strain of the cyclic enyne **23** promotes its degradation by rendering the single-electron oxidation of this reactive entity more facile than the cleavage of the PMB group.

To test this hypothesis, cleavage of the N-PMB group prior to ring closure was attempted. It was gratifying to note that this change in the order of events paved the way to the target. Thus, treatment of the acyclic enyne **22** with CAN afforded product **24** in acceptable yield. Although this compound could not be cyclized owing to the known incompatibility of complex **26** with N-unprotected amides,[22] conversion into the Teoc derivative **25** allowed the crucial enyne–yne metathesis to proceed with rigorous chemoselectivity at the triple bonds to form the highly strained 16-membered cyclic product **27** in 70% yield. Not only is this the smallest ring size ever to be formed by ring-closing enyne–yne metathesis[11] but the compatibility with the dense and diverse array of functional groups also attests to the excellent application profile of this emerging methodology. *Z*-Selective semihydrogenation of the triple bond in **27** with Lindlar's catalyst in the presence of a large excess of quinoline to suppress overreduction followed by consecutive cleavage of the Teoc group and the methyl glycoside in **28** under standard conditions furnished latrunculin A (**1**). The spectroscopic and analytical data for the product were in excellent agreement with those already reported.[1,5,6]

In summary, a concise and efficient synthesis of the strongly actin-binding marine natural product latrunculin A has been achieved. The chosen route features the first successful implementation of a ring-closing enyne–yne metathesis reaction into a total synthesis and is largely catalysis-based overall. Furthermore, a practical solution for the preparation of the key intermediate **3** has been developed that clearly surpasses prior art. As this building block can also serve as a convenient platform for the preparation of non-natural analogues of both **1** and **2**, we are now in a favorable position for a synthesis-driven evaluation of the still largely unknown structure–activity profile of this important class of bioactive macrolides. Our investigations along these lines will be reported shortly.

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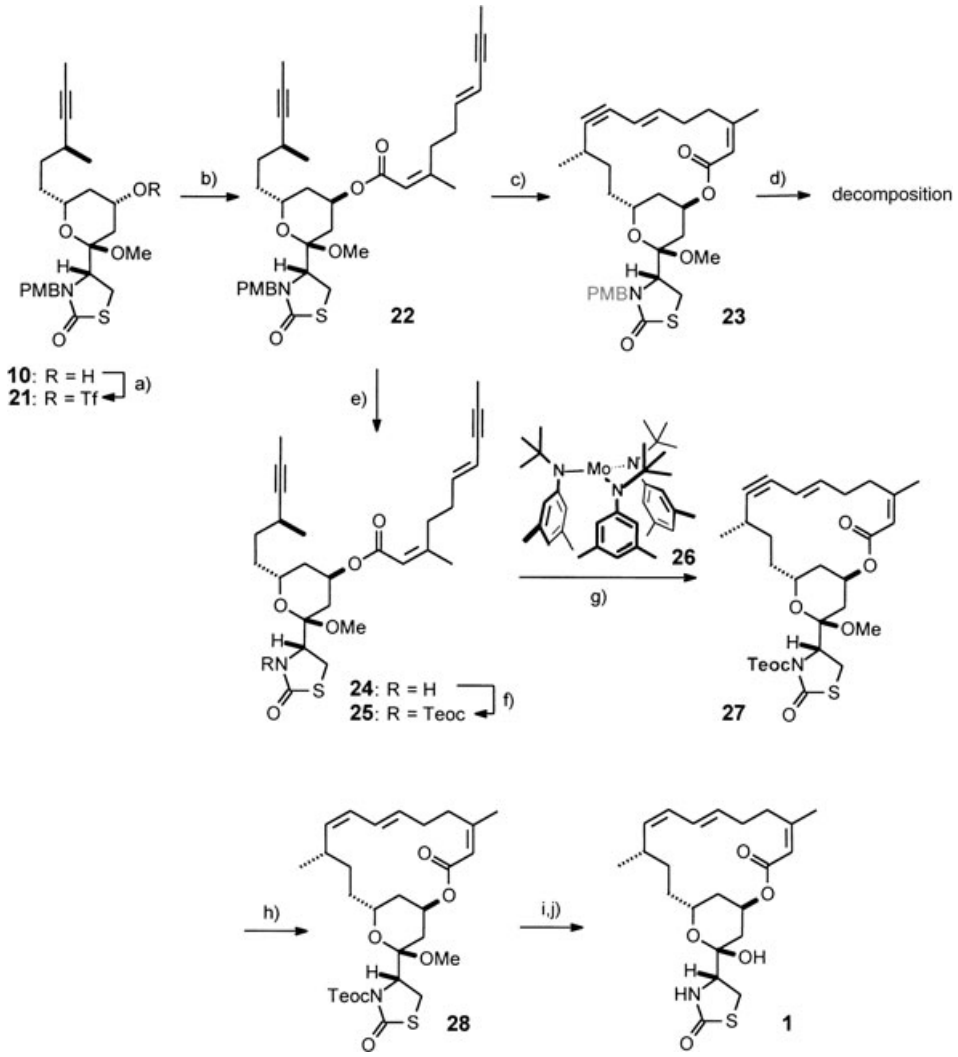

Scheme 5. Ring-closing enyne–yne metathesis and completion of the total synthesis of **1**: a) Tf_2O, pyridine, CH_2Cl_2, −78 °C; b) sodium salt of **20**, 15-crown-5, THF, 74% (over both steps); c) complex **26** (10 mol%), CH_2Cl_2/toluene, 80 °C, 36% (unoptimized); d) CAN, MeCN/H_2O, 0 °C→RT; e) CAN, MeCN/H_2O, 54%; f) $Me_3SiCH_2CH_2OH$, triphosgene, pyridine, CH_2Cl_2, then compound **24**, DMAP/$(iPr)_2NEt$, 81%; g) complex **26** (10 mol%), CH_2Cl_2/toluene, 80 °C, 70%; h) H_2 (1 atm), Lindlar catalyst, quinoline, CH_2Cl_2, 82%; i) TBAF, THF, 62%; j) aq. HOAc, 60 °C, 80%. Teoc = trichloroethoxycarbonyl, CAN = cerium ammonium nitrate, DMAP = 4-dimethylaminopyridine, TBAF = tetra-*n*-butylammonium fluoride.

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[14] Enol triflate **12** was previously formed in 61% yield from methyl acetoacetate and $PhN(Tf)_2$ with KHMDS as the base (see ref. [7]). Note that the new protocol that employs NaH and Tf_2O is significantly more productive (82%) and readily scaleable (8 g).

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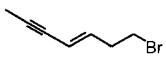
[17] A more direct approach to **19** by cross-coupling of enol triflate **12** with bromide **29** was unsuccessful as the latter could not be converted into the corresponding Grignard reagent.



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[24] Smith et al. reported that they failed to deprotect the *N*-PMB group from the corresponding macrocyclic diene prepared by an entirely different route (see ref. [5]).

