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Total Syntheses of the Actin-Binding Macrolides Latrunculin A, B, C, M, S and 16-*epi*-Latrunculin B

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Abstract: The latrunculins are highly selective actin-binding marine natural products and as such play an important role as probe molecules for chemical biology. A short, concise and largely catalysis-based approach to this family of bioactive macrolides is presented. Specifically, the macrocyclic skeletons of the targets were forged by ring-closing alkyne metathesis (RCAM) or enyne–yne metathesis of suitable diyne or enyne–yne precursors, respectively. This transformation was best achieved with the aid of $[(t\mathrm{Bu})(\mathrm{Me_2C_6H_3})\mathrm{N}]_3\mathrm{Mo}$ (**37**) as precatalyst activated in situ with CH_2Cl_2, as previously described. This catalyst system is strictly chemoselective for the triple bond and does not affect the olefinic sites of the substrates. Moreover, the molybdenum-based catalyst turned out to be broader in scope than the Schrock alkylidyne complex $[(t\mathrm{BuO})_3\mathrm{W}{\equiv}\mathrm{CCMe_3}]$ (**38**), which afforded cycloalkyne **35** in good yield but failed in closely related cases. The required metathesis precursors were assembled in a highly convergent fashion from three building blocks derived from acetoacetate, cysteine, and (+)-citronellene. The key fragment coupling can either be performed via a titanium aldol reaction or, preferentially, by a sequence involving a Horner–Wadsworth–Emmons olefination followed by a protonation/cyclization/diastereoselective hydration cascade. Iron-catalyzed C–C-bond formations were used to prepare the basic building blocks in an efficient manner. This synthesis blueprint gave access to latrunculin B (**2**), its naturally occurring 16-epimer **3**, as well as the even more potent actin binder latrunculin A (**1**) in excellent overall yields. Because of the sensitivity of the 1,3-diene motif of the latter, however, the judicious choice of protecting groups and the proper phasing of their cleavage was decisive for the success of the total synthesis. Since latrunculin A and B had previously been converted into latrunculin S, C and M, respectively, formal total syntheses of these congeners have also been achieved. Finally, a previously unknown acid-catalyzed degradation pathway of these bioactive natural products is described. The cysteine-derived ketone **18**, the tetrahydropyranyl segment **31** serving as the common synthesis platform for the preparation of all naturally occurring latrunculins, as well as the somewhat strained cycloalkyne **35** formed by the RCAM reaction en route to **2** were characterized by X-ray crystallography.

Keywords: alkynes · macrolides · metathesis · molybdenum · natural products · total synthesis

Introduction

The major constituents of the cytoskeleton of eukaryotic cells are the microtubules and the actin microfilaments. The latter form a complex three-dimensional network that determines the overall shape, structure and mechanical stability of the cells and keeps the various organelles in place. Even though the expression "cytoskeleton" is therefore appropriate, it must not be misunderstood as a static entity. Rather, all its components are inherently dynamic in nature, undergoing constant cycles of highly regulated polymerization/depolymerization processes. As a result of these dynamic phenomena at the molecular level, actin filaments are also responsible for motility processes as fundamental as cytokinesis, exocytosis, and endocytosis, force development in muscles, as well as for all kinds of active cell movement.[1]

The vast knowledge about the many fundamental roles of actin stems, to a large extent, from the use of small molecules that selectively bind to and interfere with the cytoskeleton.[2] While the cytochalasins were the first chemical

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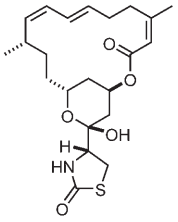
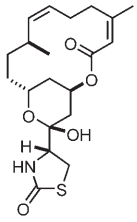
probes to find widespread use in this context,[3] it is the family of the latrunculins which now defines the standard in the field due to their more potent and better defined mode of action.[4] These marine natural products were originally isolated as the ichthyotoxic principles of the Red Sea sponge *Negombata magnifica* (formerly *Latrunculia magnifica*), but were later also found in a variety of taxonomically unrelated organisms from different habitats.[5–12]


latrunculin A (**1**)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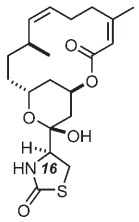
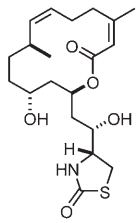
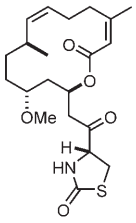
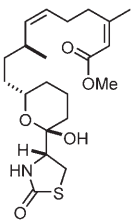
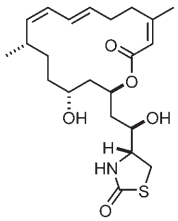
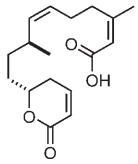

16-*epi*-Lat B (**3**)


Lat C (**4**)


Lat D (**5**)


Lat M (**6**)


Lat S (**7**)


latrunculeic acid (**8**)

The most notable response of eukaryotic cells to incubation with low micromolar concentrations of **1** or **2** is the rapid and selective disassembly of existing actin filaments without damage to the microtubular system.[4,13] This striking effect can be explained by the selective formation of 1:1 complexes of latrunculin with the actin monomers (G-actin, globular actin) which thereby lose their ability to polymerize to intact protein fibers (F-actin, fibrous actin). The binding site of **1** has been located in the vicinity of the nucleotide-binding cleft formed by the four domains of the protein.[14,15] This mechanism of action engenders a host of biological responses:[4,13] thus, non-muscular cells almost immediately lose their normal shapes even though the resulting deformed cells usually continue to grow and metabolize. Likewise, the latrunculins inhibit force development in muscles, alter actin-mediated adhesive interactions in tissue, inhibit fertilization and early development of sea urchin eggs or mouse oocytes, disturb microfilament-mediated processes in meiosis, and affect protein kinase C signaling pathways. Even an actin-dependent checkpoint in mitosis has recently been discovered, which seems to be evolutionary highly conserved.[16] Overall, the remarkable specificity and rapid onset of action of **1–7** are reminiscent of genetic knockout experiments that inactivate a single constituent within the hierarchical organization of a living cell. The use of the latrunculins, therefore, represents a prototype case of a "forward chemical genetics" approach to molecular biology.[17]

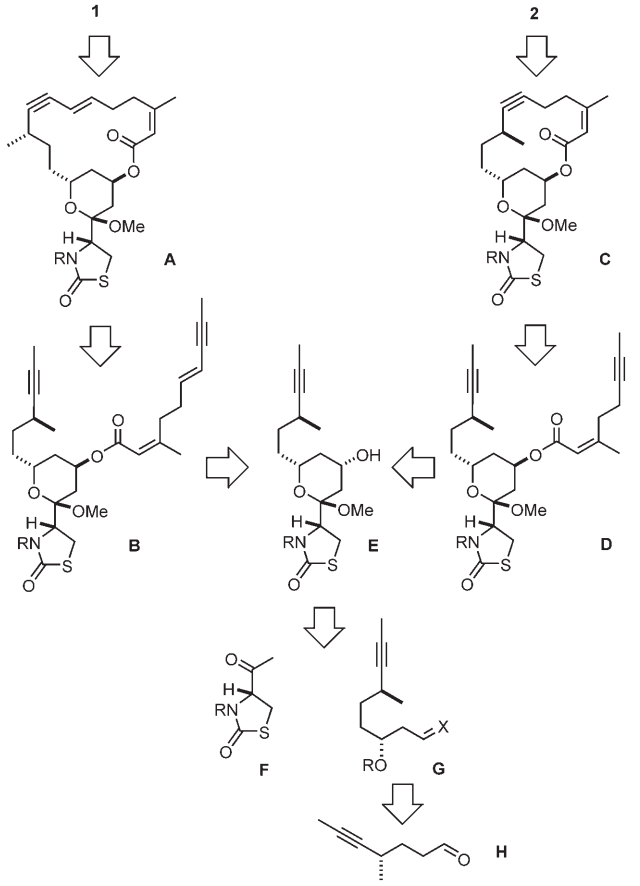
Intrigued by this fascinating biological and biochemical background, the demanding and labile structures of **1–8**, the almost complete lack of understanding of pertinent structure/activity relationships (SAR) in this series,[18] as well as the short supply of these highly valuable marine natural products,[19] we launched a program aiming at the total synthesis, structural modification and biological evaluation of the latrunculins and nonnatural analogues. Described herein is the development of a convergent and productive synthesis route that opened access to all relevant naturally occurring members of this family of actin-destabilizing macrolides.[20] The accompanying paper in this issue outlines how digression from the underlying blueprint during a "diverted total synthesis" campaign provided for the first time important information about the basic structural requirements for actin binding.[21,22] The insights acquired were then translated into the design of a truncated latrunculin analogue of enhanced biological potency.

Results and Discussion

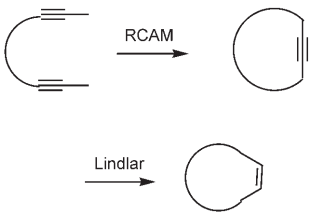
Retrosynthetic and strategic considerations: Latrunculin A and B had been the targets of previous total syntheses reported by Smith[23] and White.[24] Both groups developed elegant solutions featuring two common design elements, namely a Wittig olefination for the formation of the (*Z*)-alkene and a Mitsunobu reaction to close the lactone ring. Our retrosynthetic analysis (Scheme 1) is conceptually different as the (*Z*)-olefin itself was chosen as the site for macrocyclization. This manoeuvre should not only provide an opportunity to capitalize upon catalysis but might also allow us to scrutinize methodology previously developed in this laboratory.

Specifically, it was envisaged to rely on ring-closing alkyne metathesis (RCAM) for the formation of the carbon framework (Scheme 2).[25–27] In contrast to the more widely practiced ring-closing alkene metathesis (RCM) reaction,[28] RCAM ensures a *stereoselective* entry into macrocyclic (*Z*)-alkenes when combined with a Lindlar semireduction of the cycloalkynes primarily formed. The projected RCAM cases **B**→**A** and **D**→**C**, however, are highly demanding since the catalyst must rigorously distinguish between the triple- and the double bonds of the substrates; whereas the former must be activated, the latter must remain untouched. This condition is particularly stringent for latrunculin A (**1**) where one of the olefins of the cyclization precursor **B** is conjugated and hence electronically coupled with the π-system of the alkyne that needs to react with the metathesis catalyst.

A valuable fringe benefit of such a metathetic transform would be a significant gain in flexibility. As illustrated in Scheme 1, the syntheses of latrunculin A and B then require only the attachment of different acid segments to alcohol **E** serving as a common synthesis platform; esterifications of **E** with other acid derivatives should enable further structural variations as part of a synthesis-driven mapping of the SAR



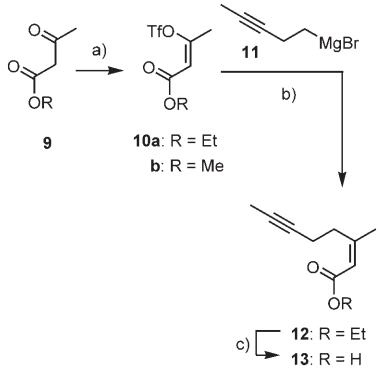
Scheme 1. Convergent retrosynthetic analysis of latrunculin A (**1**) and latrunculin B (**2**).



Scheme 2. Stereoselective synthesis of (*Z*)-alkenes by ring-closing alkyne metathesis (RCAM) followed by Lindlar hydrogenation.

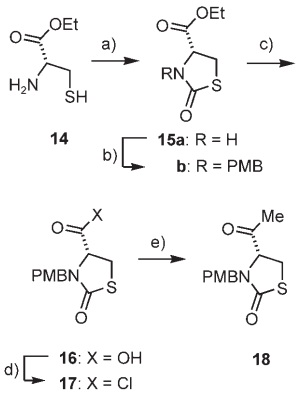
at a later stage. The required alcohol **E** can be dissected by an aldol transform into the known ketone **F**[23,24] and the acetylenic component **G** that invites disassembly into the predecessor aldehyde **H** by a diastereoselective allylation transform. The convergent character of this retrosynthetic analysis should ultimately allow for modifications of every substructure embedded into the frame of the natural compounds.

Preparation of the building blocks: As outlined above, latrunculin B (**2**) poses fewer selectivity issues than latrunculin A during the envisaged metathetic ring closure and was therefore chosen as the primary testing ground. The required acid component **13** was easily prepared from acetoacetate **9** (R = Me, Et) via enol triflate **10** formed upon treatment with NaH and Tf_2O. This reagent combination gave consistently better results than KHMDS/PhN$(Tf)_2$ originally used for this purpose.[20a] Reaction of **10** with the Grignard reagent **11** derived from 1-bromo-3-pentyne in the presence of [Fe$(acac)_3$] as cheap and benign precatalyst[29,30] resulted in an almost instantaneous, stereoselective and essentially quantitative cross-coupling with formation of the desired product **12**,[31] which was then saponified under standard conditions (Scheme 3).



Scheme 3. a) NaH, CH_2Cl_2, 0 °C, then Tf_2O, 82 % (R = Me); or: KHMDS, Ph-N$(Tf)_2$, THF, −78 °C → RT, 61 % (R = Et); b) Grignard reagent **11** (fast addition), [Fe$(acac)_3$] (10 mol %), THF, −30 °C, 97 % (R = Et); c) aq. NaOH, MeOH, 92 %.

Iron catalysis was also instrumental in the preparation of the required ketone **18** (Scheme 4). While the conversion of L-cysteine ethyl ester hydrochloride into thiazolidinone **15a**, its subsequent *N*-alkylation (either with freshly prepared *p*-methoxybenzyl bromide (PMPBr) and NaH[20a] or, more conveniently, with commercial *p*-methoxybenzyl chloride, cat. KI and K_2CO_3), and saponification of the resulting ester **15b** proceeded smoothly, significant problems were encoun-



Scheme 4. a) Carbonyl diimidazole, THF, 88 %; b) PMBCl, K_2CO_3, NaI cat., DMF, 76 %; or: NaH, PMBBr, −15 °C → RT, THF, 84 %; c) aq. KOH, 1,4-dioxane/H_2O, 97 %; d) 1-chloro-2,*N*,*N*-trimethylprop-1-en-1-ylamine,[32] THF, −18 °C; e) [Fe$(acac)_3$] (1.5 mol %), MeMgBr, THF, −78 °C → 0 °C, 80 % (99 % *ee* after recrystallization).

tered during the attempted conversion of acid **16** into the methyl ketone **18** according to the literature procedure.[23] Although described as high yielding, the reaction of the acid chloride **17** with MeMgBr gave highly variable (20–60%) but mostly disappointingly low yields (ca. 35%) in our hands despite considerable experimentation. Attempts to improve this unsatisfactory outcome by addition of either catalytic or stoichiometric amounts of CuBr to the reaction mixture failed completely, resulting only in the decomposition of the starting material.

Therefore we were pleased to see that the application of iron catalysis led to a significant improvement. As previously reported by our group, [Fe(acac)$_3$] serves as an efficient, cheap and non-toxic catalyst for the cross-coupling of Grignard reagents with functionalized acid chlorides at low temperatures.[29,30,33] In the present case, this method allowed for the formation of ketone **18** in well reproducible 80% yield. Although the known predisposition of amino acid chlorides for racemization is responsible for a slight decrease in optical purity, a single recrystallization of the crude material (*ee* 87%) from hexane conveniently solved this problem (*ee* 99%, HPLC). The rotatory power of product **18** was recorded as $[\alpha]_D = -62.2°$, which is significantly higher than the literature value of $[\alpha]_D = -38°$ reported for the sample prepared by the uncatalyzed route.[23] Figure 1 depicts the structure of optically pure **18** in the solid state.

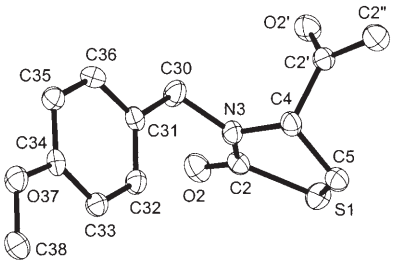
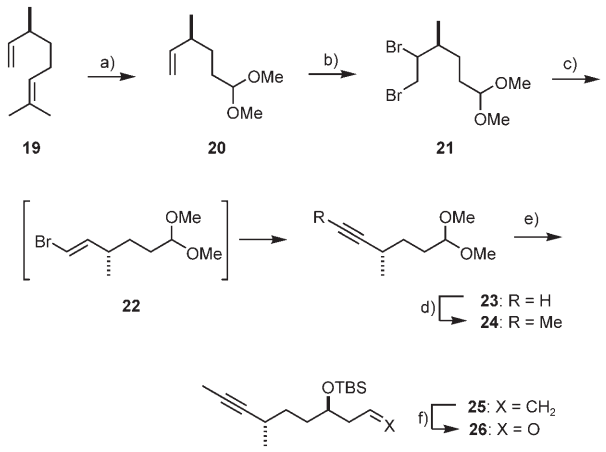


Figure 1. Molecular crystal structure of ketone **18** in the solid state. Anisotropic displacement parameters are drawn at the 50% probability level.

The preparation of the third building block commenced with a selective ozonolysis of the more highly substituted double bond of (*S*)-citronellene **19** followed by conversion on a multigram scale of the resulting aldehyde into dimethylacetal **20** under standard conditions (Scheme 5).[34,35] The subsequent bromination of the remaining olefin had to be performed with 4-dimethylaminopyridinium bromide perbromide in the presence of 4-dimethylaminopyridine (DMAP) as the reagent,[36] because attempted addition of Br_2 led to partial decomposition of the material. The outcome of the elimination of the resulting vicinal dibromide **21** strongly depended on the chosen base. Thus, treatment of **21** with *n*BuLi reconverted this compound to alkene **20** (most likely via metal–halogen exchange followed by a reductive elimination), whereas the use of LiHMDS cleanly afforded the desired alkyne **23** in 90% yield on a multigram scale. This elimination occurs in a stepwise fashion: at ambient temperature, the (*E*)-configured alkenyl bromide **22** is formed selectively, which undergoes a *syn*-elimination in the presence of excess base when the temperature is raised to 50°C. As expected,[37] the optical purity of the adjacent chiral center was not compromised during this elimination process.

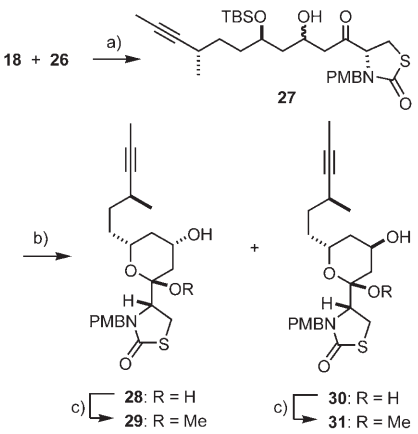


Scheme 5. a) i) O_3, CH_2Cl_2, −78°C, then Me_2S; ii) $HC(OMe)_3$, K10 montmorilonite, 75%; b) 4-dimethylaminopyridinium bromide perbromide, 0°C → RT, DMAP, CH_2Cl_2, 87%; c) LiHMDS, THF, 50°C, 90%; d) BuLi, MeI, THF/DMPU, −78°C → RT, 95%; e) i) aq. HCl, THF; ii) (−)-Ipc$_2$B(allyl), −100°C, Et_2O; iii) TBSCl, imidazole, DMF, 78% (over three steps); f) O_3, MeOH, Sudan red 7B, then Me_2S, 94%.

C-Methylation of the resulting terminal alkyne **23** proceeded smoothly, thus setting the stage for the installation of the missing chiral center. To this end, the acetal moiety of **24** was cleaved with aqueous HCl and the resulting aldehyde was immediately subjected to a Brown allylation with (−)-(Ipc)$_2$B(allyl) in Et_2O at −100°C.[38,39] Even though addition of 8-hydroxyquinoline as a boron sequestering agent greatly facilitated the work up, the still somewhat impure material was directly subjected to an O-silylation with TBSCl and imidazole. This three-step procedure afforded the required homoallylic alcohol **25** in 78% overall yield (based on acetal **24**) in diastereomerically pure form (*de* > 99%) on a multigram scale and was considerably more effective than alternative allylation methods. Ozonolysis of the double bond cleanly gave aldehyde **26**, provided that the reaction was performed in MeOH as solvent. Thereby it is advantageous to add small amounts of Sudan red 7B to the reaction mixture, which is decolorized just before the triple bond starts to react with excess ozone. This simple indicator[40] greatly facilitates the scale up and ensures that this chemoselective oxidation can be stopped in time once the olefin has been consumed.

Fragment coupling—the aldol route: The envisaged aldol reaction between ketone **18** and aldehyde **26** turned out to be more difficult than anticipated from the available literature.[23,24] Specifically, the use of the lithium enolate derived from **18** and LDA at low temperature never gave more than 40% of the desired product, while transmetallation with an-

hydrous $CeCl_3$, as previously recommended,[24] led only to a slight improvement (57%). Gratifyingly, however, recourse to established titanium aldol methodology[41] resulted in an appreciable 73% yield of compound **27** as a 2:1 mixture of diastereomers (Scheme 6). No attempt was made to improve

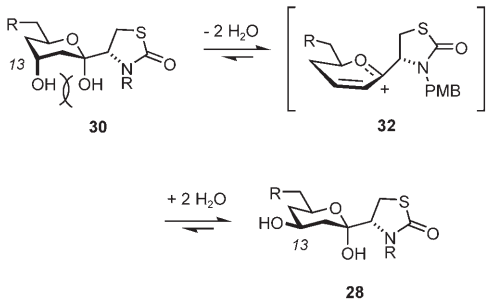


Scheme 6. a) $TiCl_4$, $(iPr)_2NEt$, CH_2Cl_2, −78°C, 73% (d.r. 2:1); b) aq. HCl, THF; c) camphorsulfonic acid cat., MeOH, **29** (64%, over both steps), **30** (21%, over both steps).

on this result as the stereochemical outcome could be conveniently dealt with in the next step. For the success of the titanium aldol reaction it was essential to allow for complete enolization of the ketone with $TiCl_4$ and Hünig's base by raising the temperature of the reaction mixture to 0°C for 2 h, whereas the addition step had to be performed and quenched at −78°C to avoid undesired elimination of the titanium aldolate primarily formed.

Stirring of product **27** with aqueous HCl effected cleavage of the TBS group and the spontaneous cyclization of the resulting diol to the corresponding hemiacetals **28** and **30**. It was noted, however, that the diastereomeric ratio of these products changed with time and was always significantly better than the 2:1 ratio of the aldol substrate. Extending the reaction time to 15 h led to a 7:1 mixture of diastereomers, which are separable by flash chromatography.

This outcome likely reflects an equilibration process which has precedence in the latrunculin series (Scheme 7).[42] It is assumed that hemiacetal **30** with an axially oriented -OH group at C13 (Lat-B numbering) is predisposed to eliminate H_2O to relieve the strain resulting from the unfavorable 1,3-transannular interaction with the anomeric hydroxyl group. The loss of a second molecule of H_2O will then rapidly ensue under the acidic conditions due to the stabilized character of the incipient oxocarbenium cation **32**. If the reaction is reversible, however, re-addition of water should disfavor the diastereomer featuring an unfavorable 1,3-transannular contact: although the hemiacetal will again be axially disposed due to the anomeric effect, the second incoming nucleophile prefers an equatorial trajectory for stereoelectronic and steric reasons. Such a retro-Michael/Michael addition scenario readily explains the accu-



Scheme 7. Proposed mechanism of the observed equilibration process upon hemiacetal formation.

mulation of isomer **28**, as experimentally observed. Even though the stereochemical assignments for both isomers are evident from the coupling constants of the protons on the tetrahydropyran ring in the NMR spectra after locking the anomeric center as the corresponding methyl glycosides **29** and **31**, additional confirmation came from the crystal structure analysis of the minor isomer. As can be seen from Figure 2, the -OH group as well as the methyl glycoside in **31** are axially disposed on the tetrahydropyran chair, whereas both alkyl side chains are equatorially oriented. The thiazolidinone ring adopts an envelope conformation.

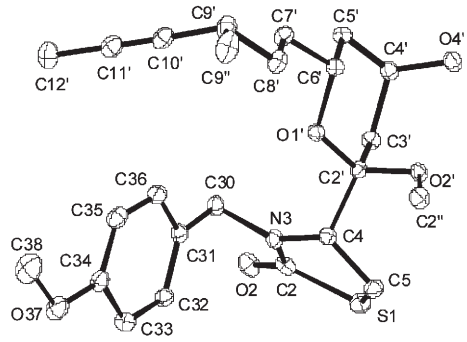
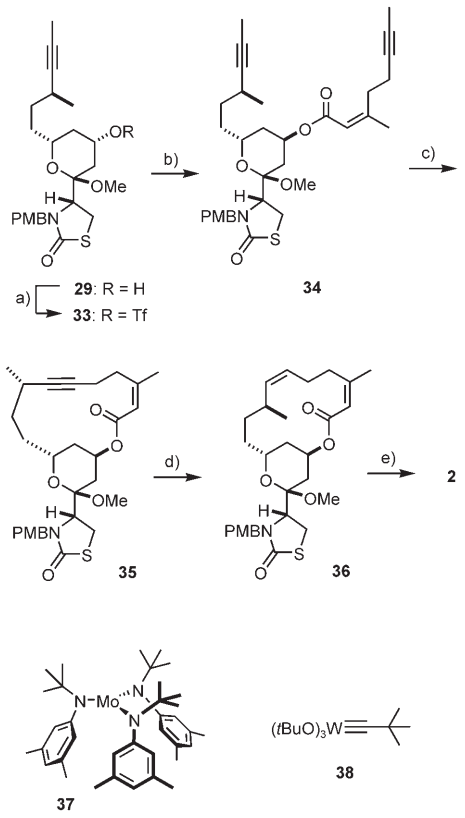


Figure 2. Molecular crystal structure of the minor glycoside **31** in the solid state. Anisotropic displacement parameters are drawn at the 50% probability level.

Completion of the total syntheses of latrunculin B, C and M: With secured stereochemical information in hand, the stage was set for the introduction of the ester segment and closure of the macrocyclic ring by RCAM (Scheme 8). In order to process the major isomer **29** with the equatorially oriented -OH at C13, the esterification has to occur with inversion of configuration. A Mitsunobu reaction seemed optimal,[43] not least because the syntheses of latrunculin A and B reported by Smith and White both relied on this transformation to form the macrolactone moiety.[23,24] Despite this encouraging precedence, the attempted *intermolecular* Mitsunobu reaction of alcohol **29** with acid **13** under a variety of conditions gave only traces of the desired ester **34**. Whether or not this failure reflects the entropic price of the intermolecular setting as compared to the intramolecular



Scheme 8. a) Tf_2O, pyridine, CH_2Cl_2, −20 °C; b) Na salt of acid **13**, [15]crown-5, THF, 58 %; c) complex **37** (5 mol %), toluene/CH_2Cl_2, 80 °C, 70 %; d) H_2, Lindlar catalyst, CH_2Cl_2, quant.; e) CAN, MeCN/H_2O, 78 %.

cases previously reported in the literature[23,24] has not been investigated further. Rather, the desired ester was prepared by a two-step protocol involving formation of the corresponding triflate **33** followed by nucleophilic substitution with the sodium salt of acid **13** in the presence of [15]crown-5 as additive. Although small amounts of an elimination product were also formed, diyne **34** as the required substrate for the envisaged macrocyclization was obtained in 58 % isolated yield over two steps.

It was gratifying to see that the key RCAM reaction **34** → **35** worked exceptionally well in the presence of Mo[N-(*t*Bu)(Ar)]$_3$ (**37**) (Ar = 3,5-dimethylphenyl) as precatalyst which was activated in situ with CH_2Cl_2 as previously described by our group.[27,44,45] Neither does the dense array of functional groups nor the branching substituent α to one of the alkynes interfere with this catalytic system.[46] The chemoselective reaction of the triple bonds in the presence of a pre-existing alkene in **34** constitutes an intriguing chemical feature, auguring well for the even more demanding latrunculin A case (see below). This rigorous distinction of the transition metal catalyst between different types of π-bonds corroborates our previous findings that alkyne- and alkene metathesis are orthogonal in nature.[47,48] The use of the Schrock alkylidyne [(*t*BuO)$_3$W≡CCMe$_3$] (**38**)[49] as catalyst also provided cycloalkyne **35** albeit in slightly lower yield (63 %). The strained character of this product is evident from the molecular crystal structure depicted in Figure 3, which shows that the alkyne unit deviates from linearity. Moreover, the diaxial orientation of the anomeric MeO- and the ester moiety on the central tetrahydropyran chair are clearly visible.

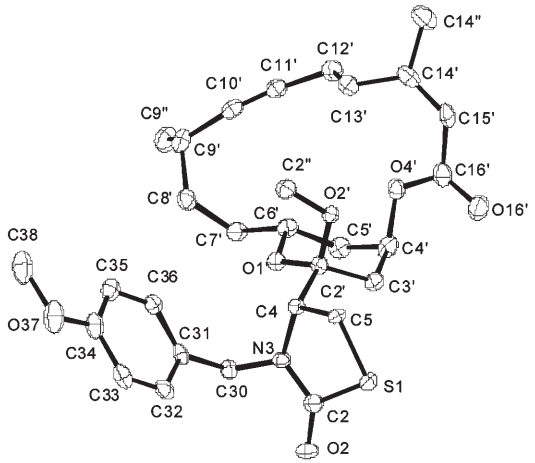
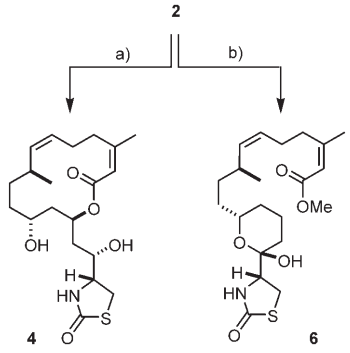


Figure 3. Molecular crystal structure of compound **35** in the solid state. Anisotropic displacement parameters are drawn at the 50 % probability level.

Cycloalkyne **35** was then subjected to a Lindlar reduction to ensure the stereoselective formation of the (*Z*)-alkene entity. In contrast to the latrunculin A case (see below), this hydrogenation is rather slow and stops accurately at the semi-reduction stage, without any overreduction being detected. Finally, concurrent cleavage of the *N*-PMB (PMB = *p*-methoxybenzyl) group and the methyl glycoside in **36** with cerium ammonium nitrate (CAN) in aqueous MeCN delivered latrunculin B (**2**), the analytical and spectroscopic data of which matched those reported in the literature in all regards. Although this final deprotection had previously been described as fairly low yielding,[23] we were pleased to find that it occurred in satisfactory yield (78 %) simply on prolongation of the reaction time; thereby it is the cleavage of the methyl glycoside which is rate-determining. Since Kashman et al. have already shown that latrunculin B can be converted into latrunculin C (**4**) as well as into latrunculin M (**6**),[42a] formal total syntheses of these extremely scarce members of this class of bioactive marine natural products have also been completed (Scheme 9).

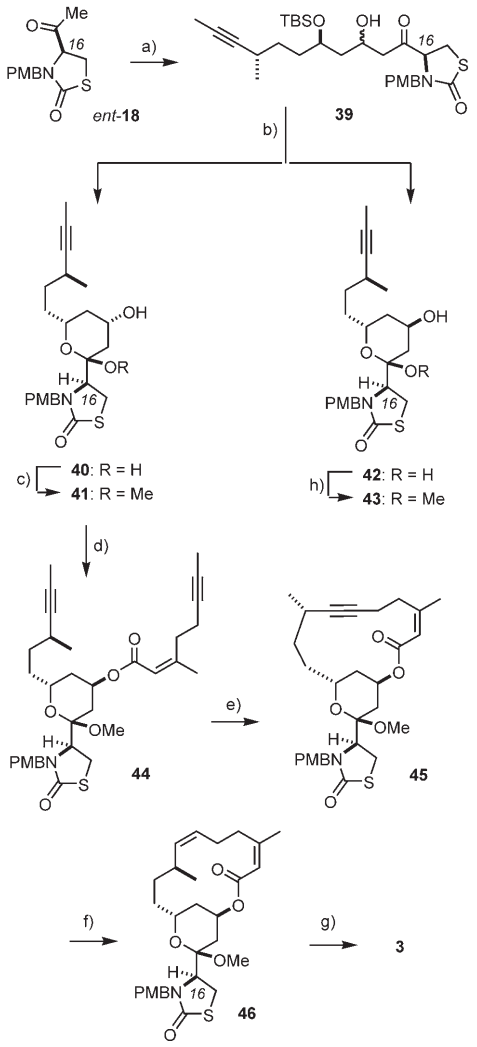
16-*epi*-Latrunculin B: Although colonizing the densely populated coral reefs of the Red Sea, the sponge *Negombata magnifica* is conspicuously free from predation in its natural habitat due to an efficient chemical defense mechanism based on the ichthyotoxic properties of the latrunculins.[5] All members of this family originally isolated invariably feature an (*R*)-configured thiazolidinone ring; this particular heterocycle had not been known as a naturally occurring structural motif before. It was therefore quite surprising that a recent sample collection showed that the sponge also pro-



Scheme 9. a) $NaBH_4$, MeOH, 73% (**4** + epimer, d.r. 1:1); b) i) MeOH, $BF_3{\cdot}Et_2O$, 76%; ii) Et_3SiH, $BF_3{\cdot}Et_2O$, CH_2Cl_2, 16%; iii) HOAc, 44%; iv) CH_2N_2, quant., cf. ref. [42a].

duces minute amounts of 16-*epi*-latrunculin B (**3**) embodying the enantiomeric (*S*)-configured thiazolidinone moiety.[11] Since compound **3** exhibits antiviral and cytotoxic properties, the gross structure of the latrunculins can obviously accommodate some stereochemical diversity without annihilation of the biological effects. Therefore it was of particular interest to prepare this natural product and to evaluate its actin-binding capacity.

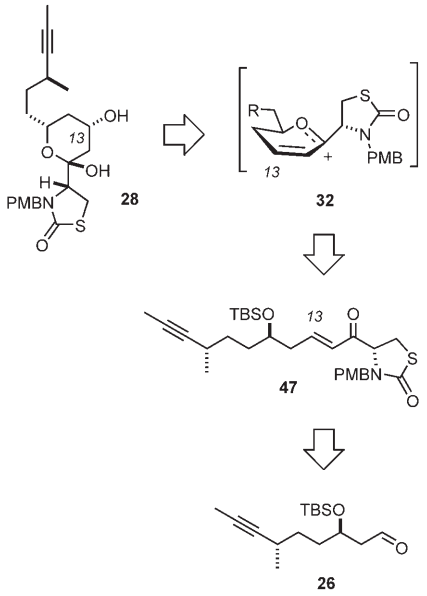
Because of the flexibility inherent to our synthesis plan, this goal was easily attained (Scheme 10). It sufficed to replace ketone **18** used en route to latrunculin B by the enantiomeric building block *ent*-**18** (prepared from D-cysteine by the iron-catalyzed methodology described above) and to follow the same reaction sequence from there on. As depicted in Scheme 10, this led to the first total synthesis of 16-*epi*-latrunculin (**3**) without incident. The analytical data of the synthetic sample are in excellent agreement with those of the natural product, including the chiroptical properties.[11] As will be outlined in the accompanying paper,[21] **3** effectively induces actin de-polymerization, although it is slightly less potent than its diastereomer latrunculin B (**2**).



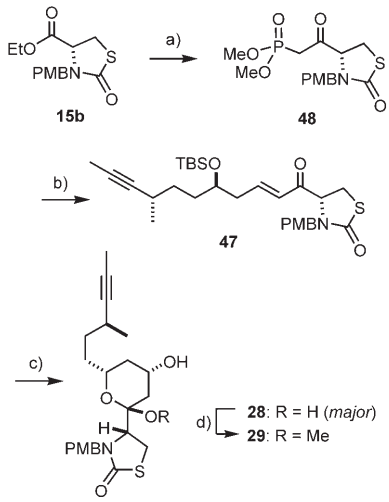
Scheme 10. Total synthesis of 16-*epi*-latrunculin B (**3**). a) $TiCl_4$, Hünig base, aldehyde **26**, CH_2Cl_2, −78°C, 78%, d.r. 1.7:1; b) aq. HCl (1M), THF, 86%, d.r. = 2.1:1; c) camphorsulfonic acid (CSA) cat., MeOH, 81%; d) Tf_2O, pyridine, CH_2Cl_2, −78°C → −40°C, then sodium salt of acid **13**, [15]crown-5, THF, 0°C, 45%; e) complex **37** (15 mol%), toluene/CH_2Cl_2, 80°C, 82%; f) H_2, Lindlar catalyst, CH_2Cl_2, 86%; g) CAN, MeCN/H_2O, 54%; h) CSA cat., MeOH, decomp.

"Second-generation" fragment coupling: The results summarized above show that our RCAM-based synthesis route opens ready access to the latrunculin family and analogues thereof. To make it even more practical and concise, the assembly process leading to alcohol **28** as the common synthesis platform was reconsidered. Thereby, it was the proposed mechanism for the observed epimerization of the aldol products **27** during cyclization of the tetrahydropyranyl ring that suggested an alternative tactic that would allow us to avoid the somewhat capricious aldol reaction altogether (Scheme 7). Specifically, one can envisage generating the putative oxocarbenium ion **32**, responsible for the accumulation of the thermodynamically favored glycoside **28**, with the equatorially oriented hydroxyl group at C13 (Lat B numbering), by protonation of the α,β-unsaturated ketone **47**, which in turn could derive from aldehyde **26** through a standard olefination reaction (Scheme 11).

As can be seen from Scheme 12, this revised strategy turned out to be highly rewarding. Thus, reaction of ester **15b** with deprotonated $(MeO)_2P(O)CH_3$ afforded the somewhat labile ketophosphonate **48** ready for condensation with aldehyde **26**. After some experimentation it was found that this Horner–Wadsworth–Emmons reaction proceeded best using activated $Ba(OH)_2$ as the base,[50] whereas more classical protocols involving *t*BuOK, NaH or Cs_2CO_3 led to poor conversions and/or significant degradation. Gratifyingly, exposure of the resulting alkene **47** to aqueous HCl gave the desired hydrated hemiketals **28** and **30** in a ≈9:1 ratio. As described above, the individual isomers are separable after transformation to the corresponding methyl glycosides **29** and **31**, respectively. Overall, this outcome provides compelling evidence for the proposed equilibration mechanism (cf. Scheme 7) and opens a convenient access to the essential building block **29**.



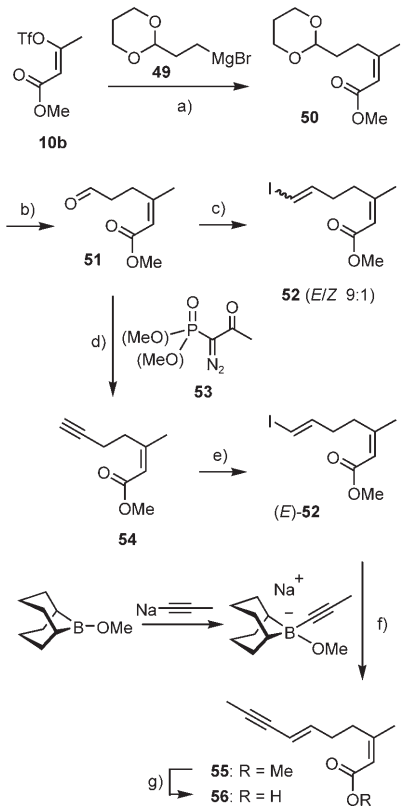
Scheme 11. Revised retrosynthetic analysis of building block **28**.



Scheme 12. a) $(MeO)_2P(O)CH_3$, *n*BuLi, THF, −78 °C, 60 %; b) $Ba(OH)_2{\cdot}8H_2O$ (preactivated at 140 °C), THF, aldehyde **26**, 75 %; c) aq. HCl, THF, 64 %; d) MeOH, camphorsulfonic acid (CSA) cat., 92 %.

Latrunculin A and S: With a good supply of alcohol **29** being secured, the total synthesis of latrunculin A (**1**) as the most potent actin-binding macrolide of this series was tackled. As outlined in the Results and Discussion section (Scheme 1), this target constitutes a particularly stringent test for ring-closing alkyne metathesis (RCAM).[25] Not only must the chosen catalyst be able to rigorously distinguish between the π-system of the alkynes on the one hand and the olefins on the other hand, even though the latter are conjugated and hence electronically coupled, but the metathesis event also has to build up considerable strain: note that the resulting product embodies an (*E*)-configured olefin in addition to the a priori linear acetylene moiety in its bicyclic *meta*-bridged edifice that incorporates a 16-membered ring. Although model studies on alkyne-selective enyne–yne metathesis reactions provided encouraging precedence with regard to the chemoselectivity issue, the smallest cycle so far to be successfully forged by this transformation was an 18-membered ring.[51] Therefore it was by no means clear if RCAM is applicable to the projected total synthesis of latrunculin A.

The required acid segment was again obtained by the iron-catalyzed cross-coupling methodology developed in our laboratory (Scheme 13).[29,30,33] To this end, enol triflate **10b**



Scheme 13. a) Grignard reagent **49**, $[Fe(acac)_3]$ (15 mol %), −30 °C, THF, 67–83 %; b) aq. HCOOH, reflux; c) $CrCl_2$, CHI_3, THF, 91 %; d) reagent **53**, K_2CO_3, MeOH, 80 % (over both steps); e) $[Cp_2Zr(H)]Cl$, CH_2Cl_2, then I_2, 67 %; f) 9-MeO-9-BBN, NaC≡CMe, $[Pd(PPh_3)_4]$ (5 mol %), THF, reflux, 77 %; g) KOH, $MeOH/H_2O$, 60 °C, 72 %.

was reacted with the commercially available functionalized Grignard reagent **49** in the presence of $[Fe(acac)_3]$ as a cheap and benign precatalyst to give product **50**. Although a somewhat higher catalyst loading (15 mol %) was required, this convenient reaction provided multigram amounts of the desired compound in isomerically pure form.[52]

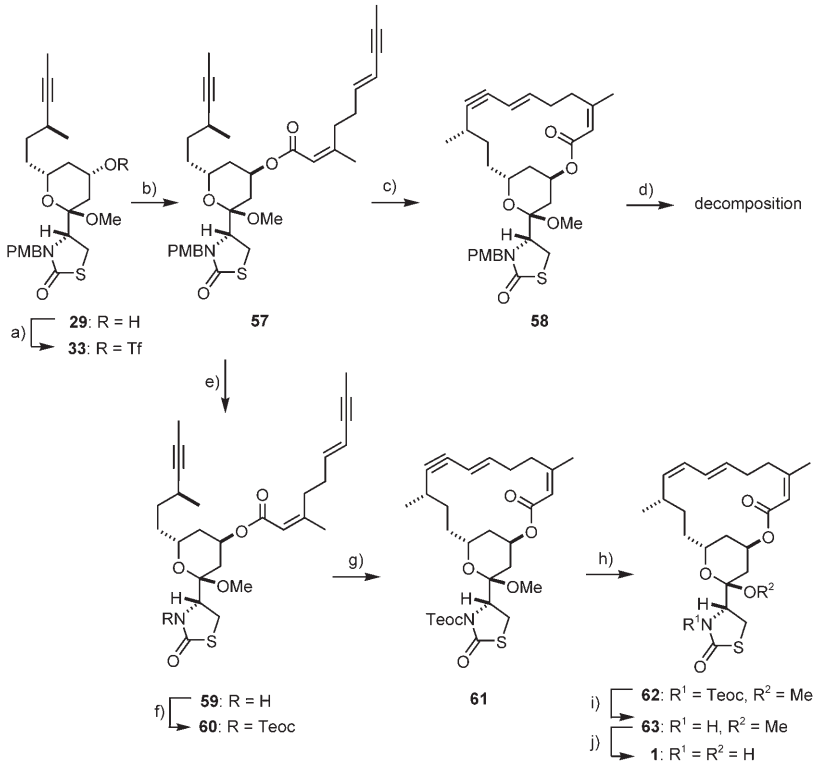
Conversion of this compound into the required acid segment **56** was initially attempted by cleavage of the acetal and subsequent Takai olefination of the resulting aldehyde **51** with $CHI_3/CrCl_2$.[53] Unfortunately, however, this reaction gave an inseparable 9:1 mixture of (*E*)- and (*Z*)-**52** and was therefore abandoned. A more appropriate solution was found by transforming the aldehyde into the corresponding alkyne **54** using the Ohira–Bestmann reagent **53**,[54] followed

by hydrozirconation/iodination,[55] which gave alkenyl iodide (*E*)-**52** as a single isomer. Conversion of this compound into enyne **55** turned out to be surprisingly difficult, and only the "9-methoxy-9-BBN" variant of the Suzuki reaction (9-MeO-9-BBN, MeC≡CNa, $[Pd(PPh_3)_4]$ cat.) developed by our group gave satisfactory and reproducible results.[56,57] Saponification of **55** to **56** was achieved with KOH in aqueous THF, while other bases commonly used for ester hydrolyses led to the decomposition of the material and/or partial isomerization of its (*Z*)-configured enoate.

Coupling of the fragments now in hand required the consecutive formation of triflate **33** and substitution with the sodium salt of acid **56** in the presence of [15]crown-5, whereas all attempts to perform this esterification under Mitsunobu conditions[43] were once again unrewarding (Scheme 14). We were pleased to note that the resulting product **57** underwent productive enyne–yne metathesis to give the desired product **58** in the presence of catalytic amounts of $[\{(t\text{Bu})(\text{Ar})\text{N}\}_3\text{Mo}]$ (**37**) activated in situ with CH_2Cl_2.[27] In contrast to the latrunculin B series, attempted RCAM with the aid of the Schrock alkylidyne $[(t\text{BuO})_3\text{W}{\equiv}\text{CCMe}_3]$ (**38**)[49] as catalyst resulted in the decomposition of the substrate only. The success of the molybdenum-based RCAM, however, was thwarted by our inability to cleave the remaining *N*-PMB group off the thiazolidinone ring with either DDQ or CAN. Although we were apprehensive that this step might be problematic,[58] the high ring strain of the cyclic enyne **58** might facilitate the degradation by single electron oxidation at a rate competitive to productive PMB-cleavage even further.

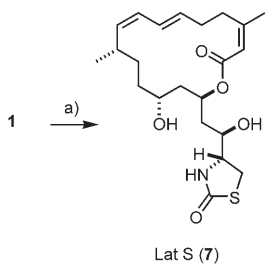
Therefore the *N*-PMB substituent was replaced by a more dischargeable protecting group *prior* to ring closure. This was made possible by the observation that the acyclic enyne **57**—in contrast to its cyclic congener **58**—allows the *N*-PMB moiety to be cleaved with CAN in aqueous MeCN. Because unprotected amides are known to be incompatible with the alkyne metathesis catalyst **37**,[27] compound **59** was converted into the corresponding Teoc derivative **60**, since this particular carbamate had already served well in a previous total synthesis of latrunculin A.[23] It was gratifying to note that compound **60** underwent the crucial ring closure in a rigorously chemoselective fashion at the triple bonds, delivering the highly strained 16-membered product **61** in 70% isolated yield. This is the smallest ring size formed by ring-closing enyne–yne metathesis so far,[51] providing an excellent outlook for future applications of this methodology.

Whereas the Lindlar hydrogenation performed in the latrunculin B series was rather slow and even on prolonged exposure of the substrate to the catalyst stopped accurately at the (*Z*)-alkene stage (see above), the corresponding *semi*-reduction of enyne **61** had to be conducted in the presence of a large excess of quinoline and required careful monitoring. Consecutive cleavage of the Teoc group in the resulting 1,3-diene **62** and of the remaining methyl glycoside in **63** furnished latrunculin A (**1**) in high overall yield. Its spectroscopic and analytical data are in excellent agreement with those reported in the literature (cf. Experimental Section).[5,23,24] Since latrunculin A had previously been converted by simple borohydride reduction into latrunculin S (**7**), a minor metabolite of the Okinawan sponge *Fasciospongia rimosa*,[9] a formal total synthesis of this rather scarce congener has also been achieved (Scheme 15).

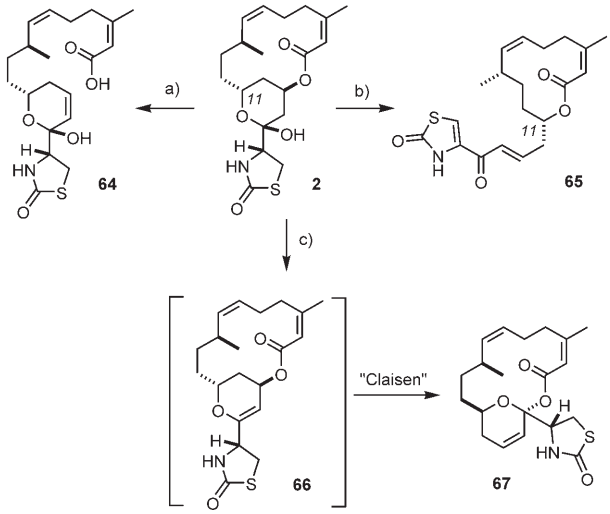


Scheme 14. a) Tf_2O, pyridine, CH_2Cl_2, $-78 \rightarrow -40\,^{\circ}C$; b) sodium salt of acid **56**, [15]crown-5, THF, 74% (over both steps); c) complex **37** (10 mol%), CH_2Cl_2/toluene, 80 °C, 36% (unoptimized); d) CAN, MeCN/H_2O; e) CAN, MeCN/H_2O, 51%; f) $Me_3SiCH_2CH_2OH$, triphosgene, pyridine, CH_2Cl_2, then compound **57**, DMAP/$(i\text{Pr})_2$NEt, 81%; g) complex **37** (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%.

A novel degradation pathway: The sensitivity of the latrunculins towards acid as well as base and their pronounced bias to open the macrocycle are well precedented in the literature (Scheme 16).[5,42,59] In line with the results discussed above, it is reasonable to assume that this cleavage is en-



Scheme 15. a) $NaBH_4$, MeOH, 52% (+ 42% of isomer), cf. ref. [9].

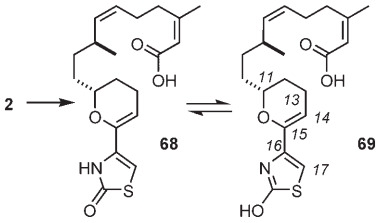


Scheme 16. Known degradation pathways of latrunculin B (**2**): a) $SOCl_2$, pyridine, then aq. HCl (1 M), cf. ref. [42a]; b) Ac_2O, pyridine, cf. ref. [59]; c) $SOCl_2$, pyridine, then silica gel, cf. ref. [59].

thalpically driven by relief of the 1,3-transannular interaction between the anomeric -OH group and the lactone moiety on the tetrahydropyran ring.

Different types of products can result from this process depending on the chosen reaction conditions, including simple derivatives of the *seco*-acid such as **64**.[42a] More interesting are product **67**, assumed to derive from a Claisen-type rearrangement of the putative intermediate **66**, as well as compound **65**, originating from a mechanistically somewhat obscure acyl shift to the alcohol group at C11 originally engaged in the tetrahydropyran ring.[59] In view of this detailed prior knowledge, we were surprised to find an as yet unknown degradation pathway.

Specifically, stirring of latrunculin B (**2**) in $CHCl_3$ that is not rigorously acid free resulted in the rapid and virtually quantitative formation of acid **69** (Scheme 17). Loss of water from the hemiacetal group likely triggers the formation of stabilized carbenium ions which ultimately result in the "aromatization" of the heterocycle with formation of the 2-hydroxythiazole ring (or its keto tautomer **68**). Characteristic NMR spectroscopic features of this novel product are i) the appearance of new signals in the olefinic/aromatic region of the ^{13}C NMR spectrum ($\delta = 98.0$ (C14), 143.5 (C15), 131.6 (C16), 95.7 (C17)) while the former signals of these carbon atoms in **2** disappear, ii) the shift of C11 from $\delta = 62.5$ in **2** to $\delta = 77.3$ ppm in **69**, and iii) a new, strongly down-field shifted proton at $\delta_H = 11.27$ ppm (-NH ⇄ -OH). All other spectroscopic data confirm this structure assignment.



Scheme 17. Novel degradation pathway of latrunculin B (**2**) in acidic $CDCl_3$.

Conclusion

The investigation summarized above resulted in concise and largely catalysis-based syntheses of the strongly actin-binding marine natural products latrunculin A, B, C, M, S and 16-*epi*-latrunculin B. The chosen approach also bears witness to the maturity of alkyne metathesis in general, a method that has received attention only recently.[25–27,47,48] Particularly notable is the first successful implementation of a ring-closing enyne–yne metathesis reaction[51] in a total synthesis campaign, highlighting the striking chemoselectivity of this transformation. A most valuable benefit of the metathesis approach is its inherent flexibility:[60] variation of a single component amongst the three basic building blocks allowed the synthesis route to be redirected from latrunculin B (**2**) as the initial target to either its 16-epimer **3** or to its ring expanded congener **1**. Because high yielding routes to the individual components have been developed and many more variations can be envisaged, a favorable position has been reached for a synthesis-driven mapping of the still largely unknown structure/activity profile of this important class of bioactive macrolides. Our investigations along these lines are disclosed in the accompanying paper.[21,22]

Experimental Section

General methods: All reactions were carried out in flame-dried glassware under Ar. The solvents were purified by distillation over the drying agents indicated and were transferred under Ar: THF, Et_2O (Mg/anthracene), CH_2Cl_2 (P_4O_{10}), MeCN, Et_3N (CaH_2), MeOH (Mg), DMF (Desmodur, dibutyltin dilaurate), hexane, toluene (Na/K). Flash chromatography: Merck silica gel 60 (230–400 mesh). NMR: Spectra were recorded on Bruker DPX 300, AV 400, or DMX 600 spectrometers in the solvents indicated; chemical shifts (δ) are given in ppm relative to TMS, coupling constants (J) in Hz. The solvent signals were used as references and the chemical shifts converted to the TMS scale ($CDCl_3$: $\delta_C \equiv 77.0$ ppm; residual $CHCl_3$ in $CDCl_3$: $\delta_H \equiv 7.24$ ppm; CD_2Cl_2: $\delta_C \equiv 53.8$ ppm; residual CH_2Cl_2 in CD_2Cl_2: $\delta_H \equiv 5.32$ ppm). Where indicated, the signal assignments are unambiguous; the numbering Scheme is arbitrary and is shown in the inserts. The assignments are based upon 1D and 2D spectra recorded using the following pulse sequences from the Bruker standard pulse program library: DEPT; COSY (cosygs and cosydqtp); HSQC (invietgssi) optimized for $^1J(C,H) = 145$ Hz; HMBC (inv4gslplrnd) for corre-

lations via ^{n}J(C,H); HSQC-TOCSY (invietgsml) using an MLEV17 mixing time of 120 ms. IR: Nicolet FT-7199 spectrometer, wavenumbers ($\tilde{\nu}$) in cm^{-1}. MS (EI): Finnigan MAT 8200 (70 eV), ESI-MS: Finnigan MAT 95, accurate mass determinations: Bruker APEX III FT-MS (7 T magnet). Melting points: Büchi melting point apparatus B-540 (corrected). Elemental analyses: H. Kolbe, Mülheim/Ruhr. All commercially available compounds (Fluka, Lancaster, Aldrich) were used as received.

Preparation of the building blocks

3-Trifluoromethanesulfonyloxy-but-2-enoic acid methyl ester (10b, R = Me, Method A): At 0 °C, methyl acetoacetate **9** (R = Me, 4 mL, 43.02 mmol) was added dropwise to a well stirred suspension of NaH (1.03 g, 43.02 mmol) in CH_2Cl_2 (200 mL). After 2 h, triflic anhydride (7.24 mL, 43.02 mmol) was added dropwise and the cooling bath was removed. The reaction was quenched with sat. aq. $NaHCO_3$ and the product was extracted three times with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and evaporated, and the residue was purified by flash chromatography on silica gel (EtOAc/hexanes 1:20) to give triflate **10b** as a pale yellow liquid (8.31 g, 82 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.18 (s, 3H), 3.79 (s, 3H), 5.77 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.2, 52.2, 112.6, 117.0 (q, J = 318 Hz), 155.7, 162.9; IR (film): $\tilde{\nu}$ = 2959, 1733, 1689, 1422, 1388, 1322, 1296, 1253, 1196, 1138, 1124, 1046, 988, 929, 903, 856, 779, 760, 720 cm^{-1}; MS (EI): m/z (%): 248 (34), 217 (37), 216 (17), 169 (20), 153 (19), 98 (11), 87 (38), 69 (100), 59 (36), 43 (48), 39 (12); HRMS (EI): m/z: calcd for $C_6H_7F_3O_5S$: 247.99663; found: 247.99637 [M^+].

Triflate 10a (R = Et, method B):[61] A solution of KHMDS (46 mL, 0.5 M in toluene, 23 mmol) was added dropwise to a solution of ethyl acetoacetate **9** (R = Et, 2.5 g, 19 mmol) in THF (20 mL) at −78 °C. After stirring for 30 min at that temperature, a solution of *N*-phenyl-bis(trifluoromethanesulfonimide) (8.2 g, 23 mmol) in THF (20 mL) was introduced and the resulting mixture was allowed to warm to room temperature overnight. The red solution was diluted with ether and consecutively washed with water, aq. citric acid (10 %), sat. aq. $NaHCO_3$ (5 %), and brine before being dried (Na_2SO_4) and evaporated. Purification of the residue by flash chromatography (ethyl acetate/hexanes 1:10) afforded triflate **10a** as a pale yellow oil (3.1 g, 61 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.30 (t, J = 7.1 Hz, 3H), 2.17 (d, J = 1.0 Hz, 3H), 4.24 (q, J = 7.1 Hz, 2H), 5.75 (q, J = 1.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0, 20.9, 61.3, 112.9, 118.4 (q, J = 318 Hz), 155.0, 162.3; IR (film): $\tilde{\nu}$ = 2988, 1733, 1687, 1427, 1208, 1143, 1125, 1048, 928, 861, 780, 621 cm^{-1}; MS (EI): m/z (%): 262 (52) [M^+], 234 (40), 217 (97), 216 (56), 153 (20), 87 (85), 85 (24), 84 (58), 69 (100).

Ester 12 (R = Et): A freshly prepared solution of 3-pentynylmagnesium bromide **11** (0.5 M in THF, 3.0 mL, 1.5 mmol) was rapidly added to a solution of triflate **10a** (160 mg, 0.61 mmol) and [Fe(acac)$_3$] (22 mg, 10 mol %) in THF (5 mL) at −30 °C and the resulting mixture was stirred for 25 min. The cooling bath was removed, the mixture was diluted with ether, the reaction was quenched with water and brine, and the organic phase was dried (Na_2SO_4) and evaporated. Purification of the residue by flash chromatography (ethyl acetate/hexanes 1:30) provided ester **12** as a colorless oil (107 mg, 97 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.27 (t, J = 7.1 Hz, 3H), 1.76 (t, J = 2.6 Hz, 3H), 1.94 (d, J = 1.0 Hz, 3H), 2.30–2.36 (m, 2H), 2.79 (t, J = 7.4 Hz, 2H), 4.14 (q, J = 7.1 Hz, 2H), 5.70 (q, J = 1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 3.5, 14.3, 17.8, 25.6, 32.7, 59.6, 76.1, 78.4, 117.0, 158.6, 166.2; IR (film): $\tilde{\nu}$ = 2979, 2920, 2859, 1715, 1648, 1444, 1377, 1235, 1176, 1141, 1063, 1029, 734, 604 cm^{-1}; MS (EI): m/z (%): 180 (16) [M^+], 152 (21), 151 (28), 135 (29), 108 (10), 107 (100), 106 (23), 105 (21), 91 (63), 79 (32), 77 (12), 53 (21).

Acid 13: Aq. NaOH (1 M, 7 mL, 7 mmol) was added to a solution of ester **12** (0.53 g, 3.2 mmol) in MeOH (5 mL) and the mixture was stirred overnight at room temperature. After evaporation of the MeOH, the residue was diluted with *tert*-butyl methyl ether, the organic layer was separated and discarded. The aqueous phase was acidified with conc. HCl until pH ≈1 was reached and repeatedly extracted with ethyl acetate. The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated to give a yellow solid. Recrystallization from hexane/Et_2O afforded acid **13** as white crystals (0.44 g, 92 %). M.p. 75–77 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1. 76 (t, J = 2.5 Hz, 3H), 1.98 (d, J = 1.3 Hz, 3H), 2.31–2.36 (m, 2H), 2.80 (t, J = 7.4 Hz, 2H), 5.73 (br s, 1H), 11.66 (br s, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 3.4, 17.7, 25.9, 32.8, 76.4, 78.2, 116.6, 161.8, 171.4; IR (KBr): $\tilde{\nu}$ = 2983, 1690, 1627, 1266, 1199, 939, 855, 710 cm^{-1}; MS (EI): m/z (%): 152 (14) [M^+], 137 (23), 107 (100), 91 (78), 79 (29), 77 (24), 65 (13), 53 (59); elemental analysis calcd (%) for $C_9H_{12}O_2$: C 71.03, H 7.95; found: C 70.88, H 8.06.

(−)-2-Oxothiazolidine-4-carboxylic acid ethyl ester (15a):[23] Carbonyldiimidazole (57.63 g, 0.355 mol) was added in small portions to a slurry of cysteine ethyl ester hydrochloride **14** (65.87 g, 0.355 mol) in THF (1 L). The mixture was stirred at ambient temperature for 20 h. Filtration through a pad of silica gel, evaporation of the filtrate and flash chromatography of the residue (hexanes/EtOAc 3:2 → 1:1) afforded the title compound as an oil (54.80 g, 88 %). $[\alpha]_D^{20}$ = −51.8° (*c* 3.14, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.82 (br s, 1H), 4.39 (ddd, J = 0.9, 5.0, 8.3 Hz, 1H), 4.21 (q, J = 7.1 Hz, 2H), 3.65 (dd, J = 8.3, 11.4 Hz, 1H), 3.54 (dd, J = 5.0, 11.4 Hz, 1H), 1.25 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.7, 170.0, 62.2, 56.0, 31.7, 14.0, 13.9; MS (EI): m/z (%): 175 (22), 102 (10), 74 (60).

(−)-3-(4-Methoxybenzyl)-2-oxo-thiazolidine-4-carboxylic acid ethyl ester (15b)[23]

Method A: A solution of ester **15a** (50.20 g, 0.287 mol) in THF (350 mL) was slowly added over a period of 45 min to a slurry of NaH (7.00 g, 0.29 mol) in THF (500 mL) at −15 °C. The mixture was stirred at this temperature for 3 h until a clear solution was formed. Freshly prepared 4-methoxybenzyl bromide (115.43 g, 0.574 mol) in THF (200 mL) was introduced and stirring was continued for 20 h before the reaction was quenched with sat. aq. NH_4Cl (500 mL). The aqueous phase was extracted with *tert*-butyl methyl ether (2 × 500 mL), the combined organic phases were dried ($MgSO_4$) and evaporated, and the residue was purified by flash chromatography (hexanes/EtOAc 3:1) to give the title compound as a colorless oil that solidifies upon standing (70.67 g, 84 %).

Method B: PMB-Cl (2.52 g, 16.21 mmol) was added dropwise to a well stirred suspension of K_2CO_3 (2.79 g, 20.26 mmol), a catalytic amount of NaI and ester **15a** (2.36 g, 13.5 mmol) in DMF (50 mL). After 6 h at room temperature, diethyl ether (50 mL) was added and the resulting mixture was washed three times with brine. The resulting organic layer was dried over $MgSO_4$, filtered, and evaporated, and the residue purified as described above to give product **15b** as a white solid (3.3 g, 76 %). $[\alpha]_D^{20}$ = −96.7° (*c* 1.3, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.14 (d, J = 8.6 Hz, 2H), 6.84 (d, J = 8.7 Hz, 2H), 5.05 (d, J = 14.8 Hz, 1H), 4.22 (q, J = 7.2 Hz, 3H), 4.10 (dd, J = 3.1, 8.5 Hz, 1H), 3.97 (d, J = 14.8 Hz, 1H), 3.77 (s, 3H), 3.45 (dd, J = 8.6, 11.4 Hz, 1H), 3.31 (dd, J = 3.1, 11.4 Hz, 1H), 1.28 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.5, 169.9, 159.4, 129.8, 127.5, 114.2, 62.1, 59.3, 55.3, 47.3, 29.0, 14.1; MS (EI): m/z (%): 295 (2), 167 (2), 134 (2), 121 (33).

(−)-3-(4-Methoxybenzyl)-2-oxo-thiazolidine-4-carboxylic acid (16): A solution of ester **15b** (1.09 g, 3.69 mmol) and KOH (0.64 g, 11.4 mmol) in 1,4-dioxane (14 mL) and water (10 mL) was stirred for 1 h. For work up, aq. HCl (3 M, 10 mL) and *tert*-butyl methyl ether (60 mL) were added, the phases were separated, and the aqueous phase was extracted with *tert*-butyl methyl ether (2 × 25 mL). The combined organic layers were washed with brine (2 × 10 mL), dried ($MgSO_4$), filtered and evaporated to give acid **16** as a colorless oil (0.96 g, 97 %). $[\alpha]_D^{20}$ = −67.5° (*c* 1.2, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.51 (br s, 1H), 7.19 (d, J = 8.4 Hz, 2H), 6.82 (d, J = 8.5 Hz, 2H), 5.07 (d, J = 14.8 Hz, 1H), 4.15 (dd, J = 2.4, 8.6 Hz, 1H), 3.97 (d, J = 14.8 Hz, 1H), 3.74 (s, 3H), 3.47 (dd, J = 9.0, 11.4 Hz, 1H), 3.36 (dd, J = 2.4, 11.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.4, 172.3, 159.4, 129.8, 127.2, 114.3, 58.9, 55.3, 47.3, 29.0.

(−)-4-Acetyl-3-(4-methoxybenzyl)-thiazolidin-2-one (18): 1-Chloro-2,*N*,*N*-trimethylprop-1-en-1-ylamine (0.50 mL, 3.78 mmol)[32] was added at −78 °C to a solution of acid **16** (0.200 g, 0.748 mmol) in THF (5 mL) and the resulting mixture was kept at −18 °C for 40 h. The resulting solution of acid chloride **17** was then cooled to −78 °C and a mixture of [Fe(acac)$_3$] (3.9 mg, 0.011 mmol) and MeMgBr (3 M in THF, 0.55 mL, 1.65 mmol) was added. After stirring for 30 min at 0 °C, the reaction was quenched with sat. aq. NH_4Cl (10 mL), the aqueous phase was extracted with *tert*-butyl methyl ether (2 × 75 mL), the combined organic layers were dried ($MgSO_4$), filtered and evaporated, and the residue was puri-

fied by flash chromatography (hexanes/EtOAc 3:1) to yield ketone **18** as an oil which solidified upon standing (*ee* 87.4%). Recrystallization from hexane furnished the product as white thin needles (0.16 g, 80%, *ee* 99%). $[\alpha]_D^{20}=-62.2°$ (*c* 0.97, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=$ 7.08 (d, $J=8.6$ Hz, 2H), 6.82 (d, $J=8.7$ Hz, 2H), 4.96 (d, $J=14.7$ Hz, 1H), 4.07 (dd, $J=3.9$, 9.3 Hz, 1H), 3.86 (d, $J=14.7$ Hz, 1H), 3.75 (s, 3H), 3.47 (dd, $J=9.3$, 11.5 Hz, 1H), 3.08 (dd, $J=3.9$, 11.5 Hz, 1H), 2.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=$204.4, 171.5, 159.4, 129.8, 127.1, 114.2, 65.4, 55.2, 47.3, 27.6, 26.1; MS (EI): *m/z* (%): 265 (<1), 222 (8), 121 (60) (215).

Acetal 20: Ozone was bubbled through a solution of (*S*)-citronellene **19** [8.2 g, 59 mmol; $[\alpha]_D^{20}=+11.1°$ (*c* 1.40, CH_2Cl_2); *ee* 91%] in dry CH_2Cl_2 (200 mL) at −78°C until TLC showed complete consumption of the substrate. After the solution had been flushed with Ar for 15 min, Me_2S (9.2 g, 148 mmol) was added and the mixture was stirred for 90 min at ambient temperature. Excess Me_2S was then removed under reduced pressure and the remaining solution was poured into a suspension of montmorilonite K10 (30 g) in trimethyl orthoformate (65 mL, 59.3 mmol) which had previously been vigorously stirred for 30 min. After stirring for 20 min, the mixture was filtered and the filtrate was extracted with sat. aq. $NaHCO_3$ and water before being dried (Na_2SO_4) and evaporated. Purification of the residue by flash chromatography (ethyl acetate/hexanes 1:40) afforded acetal **20** as a colorless liquid (7.00 g, 75%); *ee*= 91% (HP 6890; 25 m Lipodex G); $[\alpha]_D^{20}=+8.7°$ (*c* 1.14, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=1.05$ (d, $J=6.8$ Hz, 3H), 1.34 (m, 2H), 1.58 (m, 2H), 2.11 (m, 1H), 3.30, 3.31 (2s, 6H), 4.34 (t, $J=5.7$ Hz, 1H), 4.93 (d, $J=10.4$ Hz, 1H), 4.96 (d, $J=17.2$ Hz, 1H), 5.67 (ddd, $J=7.6$, 10.4, 17.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=$20.2, 30.3, 31.3, 37.7, 52.6, 52.7, 104.7, 113.0, 144.3; IR (film): $\tilde{\nu}=$ 3077, 2954, 2932, 2829, 1640, 1456, 1385, 1193, 1127, 1058, 995, 912 cm^{-1}; MS (EI): *m/z* (%): 157 (0.2) [M^+], 95 (29), 75 (100), 71 (22), 67 (8), 58 (6), 55 (7), 41 (15).

Dibromide 21: 4-(Dimethylamino)pyridinium bromide perbromide (25.4 g, 70 mmol)[36] was added in portions to a solution of alkene **20** (7.4 g, 47 mmol) and DMAP (8.6 g, 70 mmol) in CH_2Cl_2 (75 mL) at 0°C. After stirring for 4 h, the yellow mixture was gradually warmed to room temperature. For work-up, the mixture was washed with sat. aq. $NaHCO_3$ and water, the organic phase was dried (Na_2SO_4) and evaporated, and the residue was purified by flash chromatography (ethyl acetate/hexanes 1:40) to give dibromide **21** (d.r. 1:1.2) as a colorless oil (12.9 g, 87%). ^{1}H NMR (400 MHz, $CDCl_3$, mixture of isomers): $\delta=$0.92, 1.06 (2d, $J=$ 6.5, 6.7 Hz, 3H), 1.18–1.78 (m, 4H), 2.00–2.14 (m, 1H), 3.33 (s, 6H), 3.66–3.86 (m, 2H), 4.19–4.24, 4.34–4.29 (2m, 3H), 4.36, 4.38 (2t, $J=5.5$, 5.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, mixture of isomers): $\delta=$13.4, 18.4, 25.4, 29.9, 30.8, 33.7, 34.1, 34.4, 35.1, 52.7, 52.8, 52.9, 59.4, 60.8, 104.4, 104.4; IR (film): $\tilde{\nu}=$ 2954, 2829, 1458, 1384, 1192, 1148, 1126, 1056, 600 cm^{-1}; MS (EI): *m/z* (%): 317 (0.2) [M^+], 287 (6), 93 (5), 75 (100), 47 (5), 41 (6).

Alkyne 23: A solution of dibromide **21** (12.7 g, 40 mmol) in THF (25 mL) was added to a solution of LiHMDS (20.2 g, 121 mmol) in THF (75 mL) at ambient temperature. The reaction mixture was stirred for 13 h at 50°C. For work-up, the mixture was diluted with ether and the organic layer was repeatedly washed with water until the aqueous phase remained neutral. The organic phase was then washed with brine, dried (Na_2SO_4) and evaporated, and the residue was purified by flash chromatography (ethyl acetate/hexanes 1:20) to give alkyne **23** as a colorless oil (5.6 g, 90%). *ee* 91% (HP 6890N, 25 m Ivadex1/PS 086lg 404); $[\alpha]_D^{20}=+25.8°$ (*c* 1.2, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=1.19$ (d, $J=$ 6.9 Hz, 3H), 1.42–1.56 (m, 2H), 1.66–1.88 (m, 2H), 2.05 (d, $J=2.4$ Hz, 1H), 2.41–2.50 (m, 1H), 3.32, 3.33 (2s, 6H), 4.38 (t, $J=5.7$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=$20.9, 25.5, 30.1, 31.5, 52.4, 52.8, 68.6, 88.5, 104.2; IR (film): $\tilde{\nu}=$ 3296, 2956, 2936, 2831, 2111, 1455, 1387, 1192, 1126, 1056, 634 cm^{-1}; MS (EI): *m/z* (%): 155 (0.4) [M^+], 125 (16), 109 (8), 91 (8), 77 (10), 75 (100), 71 (48), 65 (5), 55 (5), 53 (11), 51 (7), 47 (12), 45 (9), 41 (33).

Alkyne 24: *n*BuLi (24.6 mL, 1.6 M, 39.4 mmol) was added at −78°C over a period of 20 min to a solution of the terminal alkyne **23** (5.6 g, 35.8 mmol) in THF (50 mL). The resulting mixture was stirred for 10 min at −78°C and at 0°C for 90 min to ensure complete deprotonation. The mixture was then cooled again to −78°C before DMPU (13 mL, 107.5 mmol) was introduced. After stirring for another 10 min, MeI (4.5 mL, 71.7 mmol) was added and the mixture was stirred for 13 h while it was allowed to reach ambient temperature. Ether (200 mL) was added and the resulting phase was washed with water (3×100 mL) and brine, dried (Na_2SO_4), and concentrated. Purification of the crude product by flash chromatography (ethyl acetate/hexanes 1:20) afforded alkyne **24** as a colorless oil (5.8 g, 95%). *ee* 91% (HP 6890N, 25 m Ivadex1/PS 086lg 404); $[\alpha]_D^{20}=+21.4°$ (*c* 0.76, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=1.14$ (d, $J=6.9$ Hz, 3H), 1.35–1.51 (m, 2H), 1.63–1.86 (m, 2H), 1.78 (d, $J=2.4$ Hz, 3H), 2.39 (m, 1H), 3.32, 3.33 (2s, 6H), 4.38 (t, $J=5.8$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=$2.9, 20.9, 25.3, 29.8, 31.5, 51.9, 52.3, 75.4, 82.8, 103.9; IR (film): $\tilde{\nu}=$ 2955, 2933, 2829, 1454, 1386, 1193, 1130, 1062 cm^{-1}; MS (EI): *m/z* (%): 169 (0.3) [M^+], 139 (8), 109 (11), 101 (7), 91 (7), 79 (11), 75 (100), 71 (8), 67 (6), 47 (10), 41 (12).

Compound 25: Aq. HCl (30 mL, 10% w/w) was added to a solution of alkyne **24** (5.0 g, 30 mmol) in THF (55 mL). After stirring for 90 min, the reaction mixture was diluted with ether and washed with sat. aq. $NaHCO_3$ and water before being dried (Na_2SO_4) and evaporated. The residue was dissolved in ether (15 mL) and the resulting solution was slowly added along the side of the flask to a solution of (−)-B-allyl(diisopinocampheyl)borane (12.5 g, 38 mmol)[38] in diethyl ether (40 mL) at −100°C. After stirring for 1 h, MeOH (2 mL) was introduced and the cooling bath was removed. After reaching ambient temperature, the diethyl ether was evaporated and the residue was treated with a solution of 8-hydroxyquinoline (6.4 g, 44 mmol) in MeOH (80 mL) and stirred overnight. The resulting precipitate was filtered off and the filtrate was evaporated. Flash chromatography (ethyl acetate/hexanes 1:40) gave the allylic alcohol which still contained traces of terpene impurities (3.9 g). This material was dissolved in DMF (35 mL), to which imidazole (3.25 g, 48 mmol) and TBSCl (4.6 g, 30 mmol) were added. After stirring at ambient temperature for 15 h, the reaction mixture was diluted with hexane and successively washed with aq. HCl (5%), sat. aq. $NaHCO_3$ and water, dried (Na_2SO_4), and evaporated. Purification of the residue by flash chromatography (ethyl acetate/hexanes 1:20) provided compound **25** as a colorless oil (6.4 g, 78% over 3 steps). *de* 99% (HPLC); $[\alpha]_D^{20}=+28.2°$ (*c* 0.66, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=0.05$ (s, 6H), 0.89 (s, 9H), 1.12 (d, $J=6.9$ Hz, 3H), 1.38–1.65 (m, 4H), 1.78 (d, $J=$ 2.4 Hz, 3H), 2.15–2.27 (m, 2H), 2.34 (m, 1H), 3.71 (qt, $J=5.8$ Hz, 1H), 5.00–5.07 (m, 2H), 5.82 (ddt, $J=14.4$, 10.4, 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=-4.5$, −4.4, 3.4, 18.2, 21.4, 25.9, 26.0, 32.7, 34.4, 41.8, 71.9, 75.7, 83.8, 116.6, 135.5; IR (film): $\tilde{\nu}=$ 3077, 2956, 2930, 2858, 1641, 1472, 1462, 1361, 1255, 1076, 1004, 913, 836, 774 cm^{-1}; MS (EI): *m/z* (%): 279 (0.2) [M^+], 239 (48), 223 (32), 181 (13), 147 (20), 107 (38), 99 (20), 75 (100), 73 (85), 59 (13); HRMS (EI): *m/z*: calcd for $C_{17}H_{33}OSi$: 281.23007; found: 281.22982 [M^++H].

Aldehyde 26: Ozone was bubbled through a solution of compound **25** (2.0 g, 7.13 mmol) in MeOH (50 mL) containing Sudan red 7B (0.5 mL, 0.05% in MeOH) until the pink color disappeared. At that point, the mixture was purged with argon for 10 min before Me_2S (5 mL) was added. After stirring for 2 d at ambient temperature, the solution was evaporated and the residue was purified by flash chromatography (ethyl acetate/hexanes 1:30) to give aldehyde **26** as a colorless oil (1.9 g, 94%). $[\alpha]_D^{20}=+12.5°$ (*c* 0.58, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=0.06$, 0.08 (2s, 6H), 0.88 (s, 9H), 1.13 (d, $J=6.9$ Hz, 3H), 1.34–1.80 (m, 4H), 1.78 (d, $J=2.4$ Hz, 3H), 2.30–2.58 (m, 3H), 4.23 (qt, $J=5.8$ Hz, 1H), 9.81 (t, $J=2.5$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=-4.7$, −4.4, 3.4, 18.0, 21.4, 25.8, 25.9, 32.5, 35.5, 50.8, 68.1, 76.0, 83.3, 202.2.

Aldol route to latrunculin B and 16-*epi*-latrunculin B

Aldol product 27: A solution of $TiCl_4$ (1 M in CH_2Cl_2, 0.76 mL, 0.76 mmol) was added dropwise to a solution of ketone **18** (182 mg, 0.69 mmol) in CH_2Cl_2 (3 mL) at −78°C. The resulting brown suspension was stirred for 10 min before a solution of $(i\text{Pr})_2$NEt (1 M in CH_2Cl_2, 0.96 mL, 0.96 mmol) was added. The mixture was stirred for 1 h at −78°C and for 2 h at 0°C. The resulting deep red, clear solution was cooled to −78°C before a solution of aldehyde **26** (2.5 mL, 0.25 M in CH_2Cl_2, 0.62 mmol) was slowly introduced. After stirring for 3 h at −78°C the reaction was quenched at that temperature with saturated

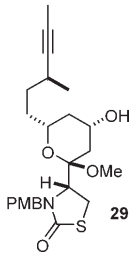
NH_4Cl (15 mL) and the cooling bath was removed. When ambient temperature was reached, water was added to the mixture to dissolve the white precipitate. The phases of the resulting nearly colorless biphasic system were separated, the aqueous layer was extracted three times with CH_2Cl_2 and the combined organic phases were successively washed with sat. aq. $NaHCO_3$ and brine. After drying over Na_2SO_4, the solvent was evaporated and the residue was purified by flash chromatography (ethyl acetate/hexanes 1:3) to provide aldol **27** as a 2:1 mixture of diastereomers (250 mg, 73%). ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 0.10–0.12 (m, 6H), 0.90, 0.91 (2s, 9H), 1.12, 1.13 (2d, J = 6.9 and 6.9 Hz, 3H), 1.26–1.87 (m, 9H), 2.30–2.66 (m, 3H), 3.18, 3.27 (2dd, J = 3.2, 11.6 Hz and 3.3, 11.5 Hz, 1H), 3.46–3.52 (m, 1H), 3.34, 3.69 (2brs, 1H, OH), 3.78, 3.80 (2d, J = 14.7 and 14.8 Hz, 1H), 3.77, 3.78 (2s, 3H), 3.93–4.03 (m, 1H), 4.24, 4.30 (2dd, J = 3.3, 9.4 Hz and 3.2, 9.5 Hz, 1H), 4.36–4.42 (m, 1H), 4.94, 5.00 (2d, J = 14.8 and 14.7 Hz, 1H), 6.84, 6.85 (2d, J = 8.6 and 8.6 Hz, 2H), 7.12, 7.16 (2d, J = 8.6 and 8.6 Hz, 2H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ = −5.0, −4.9, −4.8, −4.3, 3.2, 17.8, 17.9, 21.3, 21.4, 25.6. 25.7, 26.1, 26.2, 27.0, 27.2, 32.3, 33.2, 34.0, 35.5, 41.4, 42.6, 46.6, 46.7, 47.2, 55.2, 55.3, 65.3, 65.9, 66.1, 67.3, 71.5, 72.6, 75.9, 83.4, 114.1, 114.2, 127.8, 128.0, 129.8, 130.0, 159.5, 171.5, 171.7, 205.5, 205.9.

Compound 39: Prepared as described above using aldehyde **26** and ketone *ent*-**18**. The two diastereomeric products are separable by flash chromatography and show the following spectroscopic and analytical data. Major isomer: $[\alpha]_D^{20}$ = +59.0 (*c* 1.38, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.12 (d, J = 8.6 Hz, 2H), 6.85 (d, J = 8.8 Hz, 2H), 5.09 (d, J = 14.7 Hz, 1H), 4.48–4.39 (m, 1H), 4.13 (dd, J = 9.1, 4.0 Hz, 1H), 4.03–3.96 (m, 1H), 3.87 (d, J = 14.7 Hz, 1H), 3.79 (s, 3H), 3.60 (d, J = 2.0 Hz, 1H), 3.45 (dd, J = 11.4, 9.1 Hz, 1H), 3.25 (dd, J = 11.4, 3.8 Hz, 1H), 2.61 (dd, J = 16.4, 8.3 Hz, 1H), 2.43–2.30 (m, 1H), 2.38 (dd, J = 16.4, 3.8 Hz, 1H), 1.85–1.76 (m, 1H), 1.78 (d, J = 2.3 Hz, 3H), 1.70–1.60 (m, 2H), 1.53 (ddd, J = 14.4, 5.6, 2.3 Hz, 1H), 1.43–1.28 (m, 2H), 1.14 (d, J = 6.8 Hz, 3H), 0.89 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 206.2 (C), 171.8 (C), 159.5 (C), 129.9 (CH), 127.5 (C), 114.3 (CH), 83.4 (C), 76.0 (C), 71.1 (CH), 65.4 (CH), 64.9 (CH), 55.3 (CH_3), 47.3 (CH_2), 46.7 (CH_2), 41.3 (CH_2), 34.0 (CH_2), 33.1 (CH_2), 27.3 (CH_2), 26.1 (CH), 25.8 (CH_3), 21.4 (CH_3), 18.0 (C), 3.4 (CH_3), −4.6 (CH_3), −4.8 (CH_3); IR (film): $\tilde{\nu}$ = 3443, 2972, 1725, 1678, 1513, 1081 cm^{-1}; HRMS (ESI+): *m*/*z*: calcd for $C_{29}H_{45}NO_5SSi$+Na: 570.2683; found: 570.2685. Minor isomer: $[\alpha]_D^{20}$ = +10.9 (*c* 1.16, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.15 (d, J = 8.6 Hz, 2H), 6.83 (d, J = 8.6 Hz, 2H), 4.99 (d, J = 14.7 Hz, 1H), 4.27 (dd, J = 9.6, 3.5 Hz, 1H), 4.23–4.14 (m, 1H), 4.02–3.93 (m, 1H), 3.82 (d, J = 14.7 Hz, 1H), 3.79 (s, 3H), 3.59–3.56 (m, 1H), 3.46 (dd, J = 11.6, 9.6 Hz, 1H), 3.18 (dd, J = 11.6, 3.5 Hz, 1H), 2.61 (dd, J = 15.2, 8.8 Hz, 1H), 2.38–2.29 (m, 2H), 1.80–1.69 (m, 1H), 1.78 (d, J = 2.5 Hz, 3H), 1.62–1.48 (m, 3H), 1.47–1.37 (m, 1H), 1.35–1.23 (m, 1H), 1.13 (d, J = 6.8 Hz, 3H), 0.90 (s, 9H), 0.12 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 205.7 (C), 171.7 (C), 159.4 (C), 130.1 (CH), 127.7 (C), 114.2 (CH), 83.4 (C), 76.1 (C), 73.0 (CH), 68.5 (CH), 65.8 (CH), 55.3 (CH_3), 47.3 (CH_2), 46.3 (CH_2), 42.5 (CH_2), 35.6 (CH_2), 32.1 (CH_2), 26.8 (CH_2), 26.2 (CH), 25.8 (CH_3), 21.5 (CH_3), 17.9 (C), 3.4 (CH_3), −4.0 (CH_3), −4.8 (CH_3); IR (film): $\tilde{\nu}$ = 3488, 2930, 2857, 1725, 1673, 1513, 1248 cm^{-1}; HRMS (ESI+): *m*/*z*: calcd for $C_{29}H_{45}NO_5SSi$+Na: 570.2683; found: 570.2685 [M^++Na].

Glycosides 29 and 31: Aq. HCl (1 mL, 10% *w*/*w*) was added to a solution of compound **27** (440 mg, 0.80 mmol) in THF (10 mL) and the resulting mixture was stirred at room temperature for 14 h. Saturated aq. $NaHCO_3$ was added and the resulting solution extracted three times with CH_2Cl_2. The combined organic phases were washed with brine, dried over Na_2SO_4, and evaporated, and the residue was purified by flash chromatography (ethyl acetate/hexanes 1:1) to give hemiacetal **28** (240 mg) and its epimer **30** (90 mg) as colorless oils each. Because both compounds are prone to isomerization, they were further processed without delay.

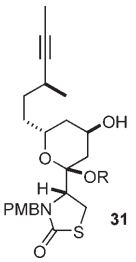
For this purpose, a catalytic amount of camphor-10-sulfonic acid was added to a solution of compound **28** (250 mg, 0.577 mmol) in MeOH (7 mL) and the resulting mixture was stirred at ambient temperature overnight. For work-up, sat. aq. $NaHCO_3$ was introduced and the aqueous phase was repeatedly extracted with CH_2Cl_2.

The combined organic layers were washed with brine, dried (Na_2SO_4), and evaporated. Purification of the residue by flash chromatography (ethyl acetate/hexane 1:2) afforded glycoside **29** as a colorless solid (232 mg, 64% over both steps). $[\alpha]_D^{20}$ = +34.4° (*c* 0.52, CH_2Cl_2): ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 1.17–1.26 (m, 1H), 1.18 (d, J = 6.9 Hz, 3H), 1.40–1.50 (m, 2H), 1.56–1.76 (m, 2H), 1.75 (d, J = 2.4 Hz, 3H), 1.83–2.0 (m, 3H), 2.18 (ddd, J = 1.8, 4.7, 12.5 Hz, 1H), 2.37–2.48 (m, 1H), 3.04 (s, 3H), 3.22–3.33 (m, 2H), 3.55–3.61 (m, 1H), 3.79 (s, 3H), 3.84 (dd, J = 2.9, 9.1 Hz, 1H), 3.98–4.06 (m, 1H), 4.28 (d, J = 14.5 Hz, 1H), 5.06 (d, J = 14.5 Hz, 1H), 6.88 (d, J = 8.6 Hz, 2H), 7.25 (d, J = 8.6 Hz, 2H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 3.3, 21.6, 25.4, 26.3, 33.6, 34.3, 37.1, 40.9, 47.2, 47.5, 55.3, 59.1, 64.7, 70.3, 76.1, 83.3, 103.1, 114.0, 129.1, 129.8, 159.3, 172.5; IR (film): $\tilde{\nu}$ = 2942, 1670, 1612, 1512, 1446, 1403, 1248, 1033 cm^{-1}; MS (EI): *m*/*z* (%): 447 (0.4) [M^+], 225 (34), 207 (20), 175 (20), 151 (26), 147 (37), 133 (55), 121 (100), 109 (24); HRMS (ESI+): *m*/*z*: calcd for $C_{24}H_{33}NO_5S$+Na: 470.19772; found: 470.19777 [M^++Na].



29

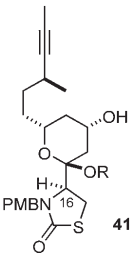
By following the same procedure, the corresponding epimeric hemiacetal **30** (90 mg, 0.208 mmol) was converted into glycoside **31**. White crystals (75 mg, 21% over both steps). $[\alpha]_D^{20}$ = +43.2° (*c* 0.50, CH_2Cl_2); ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 1.19 (d, J = 6.9 Hz, 3H), 1.43–1.53 (m, 2H), 1.56–1.65 (m, 2H), 1.74–1.93 (m, 3H), 1.75 (d, J = 2.4 Hz, 3H), 2.04 (ddd, J = 2.0, 2.8, 14.4 Hz, 1H), 2.38–2.49 (m, 1H), 3.14 (s, 3H), 3.24–3.34 (m, 2H), 3.57 (d, J = 9.6 Hz, 1H, OH), 3.77–3.80 (m, 1H), 3.80 (s, 3H), 3.89–3.95 (m, 1H), 4.07–4.12 (m, 1H), 4.27 (d, J = 14.5 Hz, 1H), 5.04 (d, J = 14.5 Hz, 1H), 6.89 (d, J = 8.6 Hz, 2H), 7.25 (d, J = 8.6 Hz, 2H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 3.2, 21.7, 25.4, 26.3, 32.5, 33.5, 34.2, 38.1, 47.3, 47.7, 55.3, 59.2, 64.1, 66.2, 76.1, 83.3, 103.6, 114.1, 129.0, 129.8, 159.3, 172.5; IR (film): $\tilde{\nu}$ = 2942, 1672, 1611, 1512, 1444, 1402, 1248, 1029 cm^{-1}; MS (EI): *m*/*z* (%): 447 (<0.3) [M^+], 225 (38), 207 (15), 193 (10), 175 (12), 151 (32), 147 (23), 133 (39), 121 (100), 109 (10); HRMS (ESI+): *m*/*z*: calcd for $C_{24}H_{34}NO_5S$: 448.21577; found: 448.21580 [M^++H].



31

Compound 41: Prepared as described above using aldol **39** as the starting material.

The major isomer showed the following spectroscopic and analytical properties: $[\alpha]_D^{20}$ = +57.2 (*c* 0.95, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.15 (d, J = 8.3 Hz, 2H), 6.87 (d, J = 8.7 Hz, 2H), 5.23 (d, J = 15.4 Hz, 1H), 4.22 (d, J = 15.4 Hz, 1H), 4.15–4.01 (m, 1H), 3.94 (dd, J = 8.3, 4.5 Hz, 1H), 3.80 (s, 3H), 3.59–3.47 (m, 1H), 3.39–3.31 (m, 2H), 3.01 (s, 3H), 2.40–2.28 (m, 1H), 2.10 (ddd, J = 12.8, 4.9, 1.9 Hz, 1H), 1.98 (dt, J = 12.4, 2.3 Hz, 1H), 1.76 (d, J = 2.6 Hz, 3H), 1.73–1.15 (m, 7H), 1.11 (d, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.3 (C), 159.0 (C), 128.6 (C), 128.5 (CH), 114.1 (CH), 102.4 (C), 82.2 (C), 76.0 (C), 69.9 (CH), 64.6 (CH), 56.9 (CH), 55.3 (CH_3), 47.7 (CH_3), 46.7 (CH_2), 40.0 (CH_2), 37.7 (CH_2), 33.3 (CH_2), 32.8 (CH_2), 26.2 (CH_2), 25.9 (CH), 21.4 (CH_3), 3.5 (CH_3); IR (film): $\tilde{\nu}$ = 3433, 2970, 2943, 1672, 1512, 1029 cm^{-1}; HRMS (ESI+): *m*/*z*: calcd for $C_{24}H_{33}NO_5S$+Na: 470.1975; found: 470.1977 [M^++Na].



41

Diyne 34: NaH (19 mg, 60% in mineral oil, 0.469 mmol) was added to a solution of acid **13** (74 mg, 0.485 mmol) in THF (5 mL) and the resulting mixture was refluxed for 1 h. Upon cooling to ambient temperature a white precipitate formed which was used in the subsequent step.

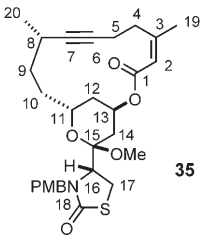
Pyridine (25 μL, 0.313 mmol) and Tf_2O (32 μL, 0.188 mmol) were successively added to a solution of compound **29** (60 mg, 0.134 mmol) in CH_2Cl_2 (5 mL) at −20 °C and the resulting mixture was stirred for 1 h at that temperature. The pale pink solution was transferred into a separation funnel containing aq. $KHSO_4$ (10 mL, 10%) and ice. The aqueous layer was extracted with CH_2Cl_2, the combined organic phases were

dried over Na_2SO_4, and the solvent was carefully evaporated while keeping the temperature at 0 °C. The residue was dissolved in THF (3 mL) and added to the suspension of the sodium salt of acid **13** described above. [15]Crown-5 ether was then introduced until a homogeneous solution had formed which was stirred overnight at ambient temperature. Ether was added and the solution was successively washed with aq. NaOH (10%, 0 °C), sat. aq. $NaHCO_3$, and brine before it was dried (Na_2SO_4) and evaporated. Purification of the crude product by flash chromatography ($CHCl_3$/ethyl acetate 25:1) afforded diyne **34** as a colorless oil (45 mg, 58% over both steps). $[\alpha]_D^{20} = +43.0°$ (*c* 0.5, CH_2Cl_2); ^{1}H NMR (400 MHz, CD_2Cl_2): $\delta = 1.18$ (d, $J = 6.9$ Hz, 3H), 1.41–1.61 (m, 3H), 1.72–1.95 (m, 11H), 1.93 (d, $J = 1.4$ Hz, 2H), 2.07 (td, $J = 2.0$, 15.0 Hz, 1H), 2.28–2.34 (m, 2H), 2.39–2.48 (m, 1H), 2.69–2.87 (m, 2H), 3.09 (s, 3H), 3.23–3.27 (m, 2H), 3.78–3.83 (m, 1H), 3.79 (s, 3H), 3.90–3.96 (m, 1H), 4.31 (d, $J = 14.4$ Hz, 1H), 5.04 (d, $J = 14.4$ Hz, 1H), 5.15–5.20 (m, 1H), 5.67 (d, $J = 1.4$ Hz, 1H), 6.88 (d, $J = 8.6$ Hz, 2H), 7.26 (d, $J = 8.6$ Hz, 2H); ^{13}C NMR (100 MHz, CD_2Cl_2): $\delta = 3.2$, 3.3, 17.8, 21.7, 25.3, 25.4, 26.3, 30.1, 32.8, 33.4, 34.2, 34.8, 47.3, 47.4, 55.3, 59.4, 65.8, 66.2, 76.0, 76.1, 78.4, 83.3, 101.6, 114.0, 117.6, 129.0, 129.8, 158.1, 159.2, 165.6, 172.7; IR (film): $\tilde{\nu} = 2919$, 1702, 1672, 1512, 1443, 1247, 1173, 1092, 1032 cm^{-1}; MS (EI): *m*/*z* (%): 359 (19), 208 (14), 207 (95), 175 (37), 147 (43), 135 (100), 133 (33), 121 (97), 107 (21), 91 (16); HRMS (ESI+): *m*/*z*: calcd for $C_{29}H_{37}NO_6S+Na$: 550.22393; found: 550.22450 [M^++Na].

Diyne 44: Prepared as described above from acid **13** and alcohol **41**. $[\alpha]_D^{20} = +59.0$ (*c* 1.04, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.15$ (d, $J = 8.3$ Hz, 2H), 6.86 (d, $J = 8.7$ Hz, 2H), 5.72 (d, $J = 1.1$ Hz, 1H), 5.24–5.11 (m, 2H), 4.26 (d, $J = 15.5$ Hz, 1H), 3.90 (dd, $J = 9.4$, 3.8 Hz, 2H), 3.80 (s, 3H), 3.41–3.18 (m, 2H), 3.09 (s, 3H), 2.89–2.72 (m, 2H), 2.40–2.29 (m, 3H), 2.03 (d, $J = 3.4$ Hz, 2H), 1.96 (d, $J = 1.1$ Hz, 3H), 1.86–1.78 (m, 1H), 1.77–1.74 (m, 6H), 1.73–1.34 (m, 5H), 1.11 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 173.0$ (C), 165.7 (C), 159.0 (C), 158.0 (C), 128.8 (C), 128.6 (CH), 117.8 (CH), 114.1 (CH), 100.6 (C), 83.3 (C), 78.5 (C), 77.2 (C), 76.2 (C), 76.0 (C), 65.5 (CH), 65.4 (CH), 57.6 (CH), 55.3 (CH_3), 47.8 (CH_3), 46.9 (CH_2), 34.3 (CH_2), 33.4 (CH_2), 32.8 (CH_2), 32.7 (CH_2), 31.4 (CH_2), 26.3 (CH_2), 26.0 (CH), 25.6 (CH_3), 21.4 (CH_3), 17.9 (CH_2), 3.5 (CH_3); IR (film): $\tilde{\nu} = 2973$, 1704, 1676, 1513, 1082 cm^{-1}; HRMS (ESI+): *m*/*z*: calcd for $C_{33}H_{43}NO_6S+Na$: 604.2705; found: 604.2709 [M^++Na].

Cycloalkyne 35: CH_2Cl_2 (30 μL) was added to a solution of [Mo{N-(*t*Bu)(Ar)}$_3$] (**37**) (1.3 mg, 5 mol%, Ar = 3,5-dimethylphenyl)[27] in toluene (0.5 mL).

This catalyst solution was transferred into a flask containing a solution of diyne **34** (25 mg, 0.043 mmol) in toluene (2 mL). The resulting mixture was stirred at 80 °C for 20 h before it was filtered through a pad of silica gel. Evaporation of the filtrate followed by flash chromatographic purification of the residue (ethyl acetate/hexanes 1:4) gave cycloalkyne **35** as white crystals (16 mg, 70%). $[\alpha]_D^{20} = +61.3°$ (*c* 0.75, CH_2Cl_2); ^{1}H NMR (600 MHz, CD_2Cl_2): $\delta =$ 5.74 (quint., $J = 1.2$ Hz, 1H, H2), 2.90 (ddd, $J = 8.0$, 9.0, 12.7 Hz, 1H, H4a), 2.59 (dddd, $J =$ 1.0, 5.1, 7.3, 12.6 Hz, 1H), 2.37 (m, 1H, H5a), 2.34 (m, 1H, H5b), 2.45 (m, 1H, H8), 1.63 (m, 1H, H9a), 1.44 (m, 1H, H9b), 1.67 (m, 1H, H10a), 1.58 (m, 1H, H10b), 4.71 (dtd, $J = 1.8$, 6.8, 11.6 Hz, 1H, H11), 2.30 (ddt, $J = 1.8$, 3.1, 14.2 Hz, 1H, H12a), 1.37 (ddd, $J = 2.6$, 11.7, 14.3 Hz, 1H, H12b), 5.35 (quint., $J = 2.9$ Hz, 1H, H13), 2.10 (ddd, $J = 2.0$, 2.8, 14.7 Hz, 1H, H14a), 1.95 (dd, $J = 3.5$, 14.7 Hz, 1H, H14b), 3.80 (ddd, $J = 1.1$, 6.1, 9.0 Hz, 1H, H16), 3.48 (dd, $J = 8.9$, 11.7 Hz, 1H, H17a), 3.40 (dd, $J = 6.0$, 11.7 Hz, 1H, H17b), 1.86 (d, $J = 1.4$ Hz, 3H, H19), 1.14 (d, $J = 7.0$ Hz, 3H, H20), 3.79 (br s, 1H, OH), 5.68 (s, 1H, NH); ^{13}C NMR (150 MHz, CD_2Cl_2): $\delta = 165.3$ (C1), 118.2 (C2), 156.1 (C3), 32.7 (C4), 18.3 (C5), 79.6 (C6), 86.3 (C7), 25.6 (C8), 31.3 (C9), 34.1 (C10), 63.9 (C11), 33.4 (C12), 68.8 (C13), 31.0 (C14), 97.7 (C15), 61.6 (C16), 28.8 (C17), 174.7 (C18), 24.2 (C19), 22.7 (C20); IR (film): $\tilde{\nu} = 2935$, 1695, 1672, 1512, 1444, 1276, 1248, 1214, 1093, 1031 cm^{-1}; MS (EI): *m*/*z* (%): 305 (100), 287 (20), 273 (13), 255 (26), 227 (15), 213 (23), 203 (15), 149 (11), 121 (91). HRMS (ESI+): *m*/*z*: calcd for $C_{29}H_{37}NO_6S+Na$: 550.22393, found: 550.22450 [M^++Na].



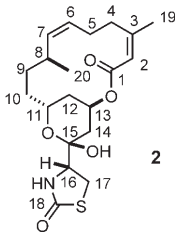
35

Cycloalkyne 45: Prepared analogously from diyne **44**; colorless syrup (22 mg, 82%). $[\alpha]_D^{20} = +66.3$ (*c* 1.17, $CDCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.14$ (d, $J = 8.7$ Hz, 2H), 6.85 (d, $J = 8.7$ Hz, 2H), 5.65 (d, $J =$ 1.1 Hz, 1H), 5.28–5.21 (m, 1H), 5.15 (d, $J = 15.1$ Hz, 1H), 4.92–4.79 (m, 1H), 4.24 (d, $J = 15.1$ Hz, 1H), 3.90 (dd, $J = 9.0$, 3.8 Hz, 1H), 3.79 (s, 3H), 3.40–3.26 (m, 3H), 3.13 (s, 3H), 2.48–2.21 (m, 4H), 2.20–2.07 (m, 2H), 2.00 (dd, $J = 15.4$, 4.1 Hz, 1H), 1.88 (d, $J = 1.5$ Hz, 3H), 1.75–1.61 (m, 3H), 1.50–1.36 (m, 2H), 1.12 (d, $J = 7.2$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 172.9$, 165.9, 159.0, 156.2, 128.9, 128.7, 119.1, 114.1, 101.0, 86.2, 80.9, 66.8, 65.0, 57.7, 55.3, 47.9, 47.0, 33.9, 33.8, 33.3, 31.2, 21.1, 26.4, 26.3, 25.1, 22.0, 19.0; IR (film): $\tilde{\nu} = 2938$, 1697, 1673, 1512, 1276, 1248 cm^{-1}; HRMS (ESI+): *m*/*z*: calcd for $C_{29}H_{37}NO_6S+Na$: 550.2239; found: 550.2239 [M^++Na].

Compound 36: A catalytic amount of Lindlar catalyst was added to a solution of cycloalkyne **35** (15 mg, 0.028 mmol) in CH_2Cl_2 (3 mL). The flask was evacuated three times and filled with hydrogen and the reaction mixture was vigorously stirred overnight. The catalyst was filtered off through a pad of silica gel and the filtrate was evaporated to give cycloalkene **36** in analytically pure form as a white foam (15 mg, quant.). $[\alpha]_D^{20} =$ +117° (*c* 0.75, $CHCl_3$); ^{1}H NMR (400 MHz, CD_2Cl_2): $\delta = 0.98$ (d, $J =$ 6.6 Hz, 3H), 1.24–1.95 (m, 8H), 1.90 (d, $J = 1.3$ Hz, 3H), 2.04–2.41 (m, 3H), 2.70–2.85 (m, 2H), 3.14 (s, 3H), 3.18–3.29 (m, 2H), 3.78–3.83 (m, 1H), 3.79 (s, 3H), 4.22–4.30 (m, 1H), 4.33 (d, $J = 14.4$ Hz, 1H), 5.01 (d, $J = 14.4$ Hz, 1H), 5.06–5.13 (m, 1H), 5.28 (dd, $J = 3.0$, 11.4 Hz, 1H), 5.60 (d, $J = 1.3$ Hz, 1H), 6.87 (d, $J = 8.6$ Hz, 2H), 7.23 (d, $J = 8.6$ Hz, 2H); ^{13}C NMR (100 MHz, CD_2Cl_2): $\delta = 21.9$, 24.3, 25.4, 26.7, 29.4, 30.0, 31.5, 32.4, 35.1, 35.6, 47.5, 47.6, 55.3, 59.3, 63.4, 67.6, 102.3, 114.0, 118.6, 128.1, 129.1, 129.9, 135.0, 155.0, 159.2, 165.9, 172.7; IR (film): $\tilde{\nu} = 2925$, 2854, 1700, 1670, 1512, 1453, 1274, 1247, 1089, 1028, 734 cm^{-1}.

Compound 46: Prepared analogously by Lindlar reduction of cycloalkyne **45**; colorless oil (16 mg, 86%). $[\alpha]_D^{20} = +115.8$ (*c* 0.91, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.14$ (d, $J = 8.3$ Hz, 2H), 6.86 (d, $J = 8.8$ Hz, 2H), 5.69 (d, $J = 1.3$ Hz, 1H), 5.26 (td, $J = 11.2$, 2.8 Hz, 1H), 5.18 (d, $J =$ 15.7 Hz, 1H), 5.18–5.13 (m, 1H), 5.06 (td, $J = 10.9$, 1.5 Hz, 1H), 4.26 (d, $J = 15.7$ Hz, 1H), 4.20–4.08 (m, 1H), 3.90 (dd, $J = 9.1$, 4.0 Hz, 1H), 3.79 (s, 3H), 3.38–3.26 (m, 2H), 3.13 (s, 3H), 2.79–2.63 (m, 2H), 2.39–2.29 (m, 1H), 2.24 (dt, $J = 15.4$, 2.0 Hz, 1H), 2.20–2.07 (m, 2H), 1.97 (d, $J = 15.4$, 4.0 Hz, 1H), 1.91 (dd, $J = 15.4$, 4.0 Hz, 1H), 1.76–1.11 (m, 6H), 0.92 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 172.9$, 166.2, 159.0, 153.9, 135.2, 128.9, 128.4, 127.7, 118.9, 114.1, 101.3, 67.2, 63.0, 57.9, 55.3, 47.8, 46.8, 35.6, 34.9, 32.3, 31.5, 29.6, 26.5, 26.2, 24.4, 22.6, 22.0; IR (film): $\tilde{\nu} = 2954$, 1700, 1673, 1512, 1275, 1248, 1022 cm^{-1}; HRMS (ESI+): *m*/*z*: calcd for $C_{29}H_{39}NO_6S+Na$: 552.2389; found: 552.2396 [M^++Na].

Latrunculin B (2): Cerium ammonium nitrate (CAN, 31 mg, 0.057 mmol) was added to a vigorously stirred suspension of cycloalkene **36** (12 mg, 0.023 mmol) in MeCN/water 2:1 (0.5 mL). After 20 min, the mixture became homogeneous and stirring was continued for additional 3 h. For work-up, the solution was extracted three times with CH_2Cl_2, the combined organic layers were dried (Na_2SO_4) and the solvent was evaporated. Purification of the residue by flash chromatography (ethyl acetate/hexanes 1:2) afforded latrunculin B (**2**) as a colorless oil (7 mg, 78%). $[\alpha]_D^{20} = +122°$ (*c* 0.55, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.95$ (d, $J =$ 6.3 Hz, 3H), 1.07–2.39 (m, 11H), 1.90 (d, $J =$ 1.3 Hz, 3H), 2.60–2.80 (m, 2H), 3.39 (dd, $J = 6.3$, 11.6 Hz, 1H), 3.47 (dd, $J = 8.8$, 11.6 Hz, 1H), 3.81–3.85 (m, 1H), 3.87 (s, 1H, OH), 4.24 (br t, $J = 10.6$ Hz, 1H), 5.05 (dt, $J = 1.5$, 11.2 Hz, 1H), 5.25 (dt, $J = 3.0$, 11.2 Hz, 1H), 5.43–5.46 (m, 1H), 5.68 (d, $J = 1.3$ Hz, 1H), 5.77 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): see Table 1; IR (film): $\tilde{\nu} = 3328$, 2952, 1678, 1278, 1092, 1057 cm^{-1}.



2

16-*epi*-Latrunculin B (3): Prepared analogously from compound **46** (5.6 mg, 54%). $[\alpha]_D^{24} = +85$ (*c* 0.24, $CHCl_3$) [lit.: $[\alpha]_D^{24} = +76$ (*c* 0.2, $CHCl_3$)];[11] ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 5.67$ (d, $J = 1.3$ Hz, 1H), 5.51 (br s, 1H), 5.31–5.21 (m, 1H), 5.24 (dd, $J = 11.4$, 2.8 Hz, 1H), 5.08–5.00

Table 1. Comparison of the ^{13}C NMR ($CDCl_3$) data of latrunculin B (**2**). Numbering scheme as shown above.

No	Kashman (75 MHz)[5]	Smith (125 MHz)[23]	This synthesis (100 MHz)
20	22.3	22.2	22.2
19	24.1	23.9	24.0
5	26.9	26.8	26.9
17	28.7	28.7	28.7
8	28.9	28.9	28.8
9	31.2	31.0	30.9
10	31.2	31.1	31.2
14	31.8	31.6	31.4
12	35.4	35.3	35.3
4	35.8	35.8	35.8
16	61.8	61.5	61.3
11	62.6	62.5	62.5
13	68.7	68.7	68.6
15	97.7	97.8	97.8
2	118.0	117.8	117.8
6	127.6	127.4	127.4
7	135.9	135.8	135.8
3	154.7	154.4	154.5
1	165.6	165.4	165.3
18	175.3	174.8	174.7

(m, 1H), 4.39–4.30 (m, 1H), 3.86 (ddd, $J=8.4$, 8.3, 1.0 Hz, 1H), 3.40 (dd, $J=11.1$, 8.6 Hz, 1H), 3.28 (dd, $J=11.6$, 8.3 Hz, 1H), 3.28 (br s, 1H), 2.80 (ddd, $J=12.9$, 12.1, 4.8 Hz, 1H), 2.69–2.57 (m, 1H), 2.48–2.35 (m, 1H), 2.25–2.12 (m, 2H), 2.03–1.92 (m, 2H), 1.76–1.46 (m, 5H), 1.42–1.36 (m, 1H), 1.18–1.09 (m, 1H), 0.97 (d, $J=6.6$ Hz, 3H); ^{13}C NMR (75 MHz, CD_2Cl_2): $\delta=175.1$, 165.9, 155.7, 135.8, 128.3, 118.4, 97.0, 68.1, 63.3, 63.2, 36.0, 35.9, 32.8, 31.6, 29.9, 29.5, 29.4, 27.1, 24.5, 22.4; IR (film): $\tilde{\nu}$ = 3342, 2923, 2854, 1685, 1260, 1029, 796 cm^{-1}; HRMS (ESI+): *m/z*: calcd for $C_{20}H_{29}NO_5S+Na$: 418.1664; found: 418.1664 [M^++Na].

Second-generation fragment coupling

Dimethyl 2-((*R*)-3-(4-methoxybenzyl)-2-oxothiazolidin-4-yl)-2-oxoethylphosphonate (48): *n*BuLi (1.34 mL, 1.55 M in hexanes, 2.09 mmol) was added dropwise to a solution of dimethylmethylphosphonate (0.22 mL, 2.09 mmol) in THF (11 mL) at −78 °C. After 20 min, a solution of ester **15b** (0.103 g, 0.348 mmol) in THF (5 mL) was added dropwise. After stirring for 30 min, the reaction was quenched with sat. aq. NH_4Cl. The product was extracted with ethyl acetate, the combined organic layers were dried over anhydrous $MgSO_4$, filtered and evaporated, and the residue was purified by flash chromatography on silica gel (ethyl acetate) to give product **48** as a white solid (74.3 mg, 60%). $[\alpha]_D^{20}=-15.0$ (*c* 0.9, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): $\delta=2.9$ (m, 1H), 3.15 (m, 1H), 3.23 (dd, $J=3.2$, 11.7 Hz, 1H), 3.44 (dd, $J=9.6$, 11.6 Hz, 1H), 3.6–3.73 (m, 7H), 3.77 (d, $J=14.8$ Hz, 1H), 4.31 (dd, $J=2.3$, 9.1 Hz, 1H), 4.92 (d, $J=14.8$ Hz, 1H), 6.79 (d, $J=8.5$ Hz, 2H), 7.9 (d, $J=8.5$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=26.6$, 37.0 (d, $J=129$ Hz), 46.9, 53.0 (d, $J=5.7$ Hz), 54.9, 65.3, 113.9, 127.2, 129.5, 159.1, 171.3, 197.1; IR (film): $\tilde{\nu}$ = 3476, 2958, 2852, 1724, 1659, 1610, 1584, 1512, 1443, 1395, 1352, 1303, 1243, 1174, 1111, 1019, 945, 917, 871, 848, 807, 777, 759, 703, 662 cm^{-1}; MS (EI): *m/z* (%): 373 (1), 355 (4), 222 (8), 151 (10), 124 (19), 122 (10), 121 (100), 109 (5), 94 (4); HRMS (ESI+): *m/z*: calcd for $C_{15}H_{20}NO_6PS+Na$: 396.06467; found: 396.06504 [M^++Na].

Enone 47: $Ba(OH)_2{\cdot}8H_2O$ (57 mg, 0.18 mmol) was heated at 140 °C during 2 h under vacuum before it was cooled to ambient temperature and suspended in THF (1 mL). A solution of phosphonate **48** (84 mg, 0.22 mmol) in THF (5 mL) was added and the suspension was stirred for 30 min before a solution of aldehyde **26** (63.4 mg, 0.22 mmol) in THF (5 mL) and water (125 μL) was added dropwise. After stirring for 3 h, the reaction was quenched with sat. aq. NH_4Cl (5 mL), the aqueous layer was extracted three times with EtOAc, and the combined organic layers were dried over anhydrous $MgSO_4$, filtered and evaporated. The crude material was purified by column chromatography on silica gel (EtOAc/hexane 1:3) to give enone **47** as a colorless oil (91 mg, 75%). $[\alpha]_D^{20}=-10.9$ (*c* 1.11, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): $\delta=0.04$ (s, 3H), 0.058 (s, 3H), 0.87 (s, 9H), 1.13 (d, $J=6.8$ Hz, 3H), 1.35–1.45 (m, 2H), 1.46–1.56 (m, 1H), 1.60–1.71 (m, 2H), 1.77 (d, $J=2.5$ Hz, 3H), 2.32–2.41 (m, 3H), 3.12 (dd, $J=11.4$, 4.8 Hz, 1H), 3.46 (dd, $J=11.4$, 9.2 Hz, 1H), 3.79 (s, 3H), 3.75–3.85 (m, 2H), 4.26 (dd, $J=9.3$, 4.5 Hz, 1H), 5.08 (d, $J=14.9$ Hz, 1H), 6.24 (dt, $J=15.7$, 1.3 Hz, 1H), 6.84 (d, $J=8.8$ Hz, 2H), 7.03 (dt, $J=15.7$, 7.6 Hz, 1H), 7.11 (d, $J=8.8$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=-4.3$, 3.7, 18.3, 21.7, 26.0, 26.1, 28.1, 32.8, 35.2, 40.8, 47.5, 55.5, 64.0, 71.1, 76.2, 83.6, 114.4, 126.7, 127.6, 130.2, 148.8, 159.7, 172.2, 194.8; IR (film): $\tilde{\nu}$ = 2951, 2929, 2857, 1677, 1628, 1612, 1586, 1513, 1461, 1442, 1389, 1360, 1302, 1248, 1174, 1109, 1072, 1034; 1004, 984, 939, 834, 774, 735, 662 cm^{-1}; MS (EI): *m/z* (%): 530 (1), 472 (19), 239 (4), 222 (4), 122 (8), 121 (100), 73 (11); HRMS (ESI+): *m/z*: calcd for $C_{29}H_{44}NO_4SSi$: 530.27604; found: 530.27608 [M^++H].

Compound 29: A solution of enone **47** (488.7 mg, 0.92 mmol) in THF (5 mL) and HCl (20% w/w, 5 mL) was stirred overnight at ambient temperature. The mixture was diluted with ethyl acetate (10 mL) and washed with aq. sat. $NaHCO_3$. The aqueous layer was extracted three times with EtOAc, the combined organic layers were dried over anhydrous $MgSO_4$, filtered and evaporated. The crude material was purified by flash chromatography on silica gel (EtOAc/hexanes 1:1) to give minor isomer **30** (25 mg, 6.9%) and the major α-isomer **28** (226 mg, 57%). The products were used without delay in the next reaction.

Compound **28** (226 mg) was dissolved in MeOH (20 mL) and a catalytic amount of (±)-camphorsulfonic acid was introduced. The reaction was stirred overnight before it was quenched with sat. aq. $NaHCO_3$. The aqueous layer was repeatedly extracted with CH_2Cl_2 and the combined organic phases were dried ($MgSO_4$), filtered and evaporated. The residue was purified by flash chromatography on silica gel (EtOAc/hexane 1:1) to give glycoside **29** as a white solid (214.9 mg, 92%). The analytical data are compiled above.

Total synthesis of latrunculin A

5-[1,3]Dioxan-2-yl-3-methyl-pent-2-enoic acid methyl ester (50): At −30 °C, a solution of the Grignard reagent **49** (50 mL, 0.5 M in THF, 25 mmol) was quickly added to a solution of triflate **10b** (5.9 g, 25 mmol) and [Fe(acac)$_3$] (1.32 g, 3.75 mmol) in dry THF (200 mL). After stirring for 1 h, the reaction was quenched with water, the aqueous phase was repeatedly extracted with diethyl ether, the combined organic layers were dried ($MgSO_4$), filtered and evaporated, and the residue was purified by flash chromatography on silica gel (EtOAc/hexanes 1:10) to give product **50** as a colorless liquid (3.59 g, 67%). ^1H NMR (400 MHz, $CDCl_3$): $\delta=$ 1.33 (m, 1H), 1.76 (m, 2H), 1.89 (s, 3H), 2.07 (m, 1H), 2.7 (m, 2H), 3.67 (s, 3H), 3.75 (m, 2H), 4.1 (m, 2H), 4.56 (t, $J=5$ Hz, 1H), 5.67 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=25.4$, 26.0, 28.3, 51.0, 67.1, 102.2, 116.3, 160.3, 166.8; IR (film): $\tilde{\nu}$ = 2953, 2850, 1715, 1646, 1433, 1402, 1377, 1333, 1283, 1233, 1194, 1141, 1088, 1074, 1044, 1019, 1004, 946, 927, 889, 851, 736 cm^{-1}; MS (EI): *m/z* (%): 214 (5), 183 (5), 138 (16), 113 (8), 100 (25), 97 (10), 87 (100), 67 (6), 59 (15), 41 (16); HRMS (EI): *m/z*: calcd for $C_{11}H_{18}O_4$: 214.12051; found: *m/z* 214.12032 [M^+].

3-Methyl-hept-2-en-6-ynoic acid methyl ester (54): A solution of ketal **50** (1.10 g, 5.14 mmol) in formic acid (10 mL, 80% in water) was refluxed overnight. After cooling, diethyl ether was added and the aqueous phase was washed with sat. aq. $NaHCO_3$. The aqueous layer was repeatedly extracted with diethyl ether, the combined organic layers were dried ($MgSO_4$), filtered, and carefully evaporated. Due to its volatility and instability, aldehyde **51** thus obtained was used directly in the next reaction without further purification.

K_2CO_3 (1.1 g, 7.971 mmol) was added to a stirred mixture of crude aldehyde **51** (0.8 g, 5.12 mmol) and Ohira's reagent **53** (1.1 g, 5.73 mmol) in dry methanol (10 mL) at 0 °C. The cooling bath was removed and the reaction was allowed to stir overnight at ambient temperature. The reaction was quenched with sat. aq. NH_4Cl (10 mL), the aqueous layer was repeatedly extracted with diethyl ether, the combined organic layers were dried ($MgSO_4$), filtered and carefully evaporated, and the residue was purified by flash chromatography on silica gel (Et_2O/hexanes 1:4) to give alkyne **54** as a colorless liquid (572 mg, 80%). ^1H NMR (400 MHz, $CDCl_3$): $\delta=$ 1.95 (s, 3H), 1.96 (t, $J=2.7$ Hz, 1H), 2.38 (dt, $J=7.4$, 2.7 Hz, 2H), 2.84 (t,

J=7.4 Hz, 2H), 3.68 (s, 3H), 5.72 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=17.7, 26.0, 32.4, 51.2, 69.2, 83.9, 117.25, 158.8, 166.9; IR (film): $\tilde{\nu}$ = 3298, 2950, 1712, 1647, 1434, 1377, 1330, 1279, 1236, 1207, 1189, 1170, 1140, 1062, 1005, 920, 859, 737 cm^{-1}; MS (EI): m/z (%): 152 (2), 137 (7), 124 (4), 121 (18), 111 (11), 93 (100), 77 (45); HRMS (CI): m/z: calcd for $C_9H_{14}O_2$: 153.09155; found: 153.09146 [M^++H].

7-Iodo-3-methyl-hepta-2,6-dienoic acid methyl ester ((*E*)-52): [Cp_2Zr(H)Cl] (0.59 g, 2.29 mmol) was added to a solution of alkyne **54** (0.30 g, 1.97 mmol) in CH_2Cl_2 (10 mL) at 0°C and the resulting mixture was stirred for 30 min at that temperature. A solution of I_2 (0.55 g, 2.29 mmol) in CH_2Cl_2 (5 mL) was then added dropwise and stirring was continued for 2 h. The reaction was quenched with sat. aq. $Na_2S_2O_3$ (10 mL), the aqueous layer was repeatedly extracted with CH_2Cl_2, the combined organic layers were dried ($MgSO_4$), filtered and evaporated, and the residue was purified by flash chromatography on silica gel (pentane → Et_2O/pentane 1:10) to give vinyliodide (*E*)-**52** as a colorless liquid (367 mg, 67%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.81 (s, 3H), 2.15 (m, 2H), 2.64 (t, J=7.4 Hz, 2H), 3.61 (s, 3H), 5.63 (s, 1H), 6.00 (d, J= 14.4 Hz, 1H), 6.47 (dt, J=14.2, 14.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=25.6, 32.4, 34.8, 51.3, 75.6, 117.0, 145.8, 167.0; IR (film): $\tilde{\nu}$ = 2947, 1713, 1646, 1433, 1377, 1237, 1200, 1153, 1075, 940, 919, 851 cm^{-1}; MS (EI): m/z (%): 280 (1), 249 (6), 221 (2), 167 (29), 153 (32), 121 (2), 93 (100), 77 (14), 39 (30); HRMS (EI): m/z: calcd for $C_9H_{13}IO_2$: 279.99602; found: 279.99568 [M^+].

3-Methyl-deca-2,6-dien-8-ynoic acid methyl ester (55): 9-MeO-9-BBN (2.16 mL, 12.84 mmol) was added dropwise to a stirred suspension of NaC≡CCH_3 (0.80 g, 12.84 mmol) in THF. After 10 min, [$Pd(PPh_3)_4$] (185 mg, 0.16 mmol) and vinyliodide (0.90 g, 3.21 mmol) were successively added and the resulting brown mixture was stirred at 60°C for 4 h, during which time a white precipitate was formed. For work-up, all volatile materials were evaporated under reduced pressure and the residue was purified by flash chromatography on silica gel (Et_2O/pentane 1:5) to give ester **55** as a colorless liquid (477.6 mg, 77%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.80 (s, 3H), 1.85 (s, 3H), 2.19 (m, 2H), 2.64 (t, J=7.5 Hz, 2H), 3.60 (s, 3H), 5.40 (dt, J=15.8, 1.6 Hz, 1H), 5.61 (s, 1H), 5.98 (dt, J=15.8, 7.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=3.8, 24.9, 31.1, 32.2, 50.4, 77.8, 84.1, 110.2, 116.0, 141.5, 158.9, 166.2; IR (film): $\tilde{\nu}$ = 2917, 2854, 2225, 1715, 1647, 1434, 1377, 1282, 1227, 1189, 1163, 1140, 1088, 1041, 1005, 953, 919, 852, 734 cm^{-1}; MS (EI): m/z (%): 192 (10), 177 (10), 160 (35), 145 (21), 133 (50), 132 (18), 131 (11), 117 (29), 105 (21), 79 (100), 77 (84); HRMS (EI): m/z: calcd for $C_{12}H_{16}O_2$: 192.11503; found: 192.11535 [M^+].

3-Methyl-deca-2,6-dien-8-ynoic acid (56): KOH (24 mL, 0.5 M in water) was added dropwise to a cooled (0°C) solution of ester **55** (477.6 mg, 2.48 mmol) in methanol (15 mL) and H_2O (4 mL). The reaction was then stirred at 60°C for 3 h before it was quenched with aqueous HCl (1 M, 12 mL). A standard extractive work up followed by flash chromatography of the crude product (EtOAc/hexanes 1:1) afforded acid **56** as a white solid (320 mg, 72%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.91 (s, 6H), 2.28 (m, 2H), 2.71 (t, J=7.5 Hz, 2H), 5.49 (dt, J=15.8, 1.6 Hz, 1H), 5.70 (s, 1H), 6.04 (dt, J=14.8, 7.0 Hz, 1H), 11 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=3.8, 25.2, 31.0, 32.4, 77.8, 84.2, 110.3, 115.8, 141.3, 161.9, 170.7; IR (KBr): $\tilde{\nu}$ = 2914, 2586, 2361, 2220, 2160, 2018, 1970, 1932, 1682, 1633, 1441, 1373, 1288, 1258, 1194, 952, 875, 802, 714 cm^{-1}; MS (EI): m/z (%): 178 (10), 160 (11), 149 (10), 145 (12), 133 (32), 119 (11), 117 (11), 105 (11), 91 (16), 79 (100), 77 (80); HRMS (EI): m/z: calcd for $C_{11}H_{14}O_2$: 178.09938; found: 178.09950 [M^+].

Compound 57: NaH (52 mg, 60% in mineral oil, 1.31 mmol) was added to a solution of acid **56** (242 mg, 1.36 mmol) in dry THF (3 mL). The mixture was refluxed for 1 h. After cooling to ambient temperature, a white precipitate appeared.

Tf_2O (92 μL, 0.54 mmol) was added at −78°C to a solution of alcohol **29** (203 mg, 0.45 mmol) and pyridine (73 μL, 0.9 mmol) in CH_2Cl_2 and the resulting mixture was stirred at −40°C during 2 h. The mixture was transferred in a separation funnel containing aqueous $KHSO_4$ (10%) and ice. The product was repeatedly extracted with CH_2Cl_2 and the combined organic layers were dried (Na_2SO_4), filtered and carefully evaporated at 0°C.

A solution of the crude triflate **33** thus formed in THF (3 mL) was added dropwise at 0°C to the suspension of the sodium salt of acid **56**. [15]Crown-5 ether was added until a clear solution was formed. The cooling bath was removed after 1 h and the mixture was allowed to stir at ambient temperature for 24 h. The reaction was quenched with sat. aq. $NaHCO_3$, the aqueous phase was repeatedly extracted with EtOAc, the combined organic layers were dried (Na_2SO_4), filtered, and evaporated, and the residue was purified by flash chromatography on silica gel (EtOAc/hexanes 1:8) to give ester **57** as a white solid (205 mg, 74%). $[\alpha]_D^{20}$=+40.3 (c 1.37, CH_2Cl_2); ^{1}H NMR (400 MHz, CD_2Cl_2): δ=1.10 (d, J=6.8 Hz, 3H), 1.35–1.55 (m, 3H), 1.66 (s, 3H), 1.79 (s, 3H), 1.81 (s, 3H), 1.67–1.85 (m, 2H), 1.99 (dt, J=1.5, 1.9 Hz, 1H), 2.75 (q, J=7.2 Hz, 1H), 2.35 (m, 1H), 2.62 (t, J=7.7 Hz, 1H), 3 (s, 3H), 3.24 (m, 1H), 3.73 (s, 3H), 3.74 (m, 1H), 3.76 (m, 1H), 4.25 (d, J=14.5 Hz, 1H), 4.9 (d, J= 14.5 Hz, 1H), 5.15 (s, 1H), 5.35 (d, J=5.4 Hz, 1H), 5.55 (s, 1H), 5.95 (dt, J=15.6, 6.8 Hz, 1H), 6.8 (d, J=8.6 Hz, 2H), 7.2 (d, J=8.6 Hz, 2H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ=3.9, 4.6, 22.3, 25.6, 26.1, 27.0, 30.8, 32.1, 33.1, 34.1, 34.9, 35.5, 48.1, 56.0, 60.1, 66.4, 66.9, 76.7, 78.8, 84.0, 85.1, 102.3, 111.2, 114.7, 118.1, 129.7, 130.5, 142.7, 159.2, 156.0, 166.3, 173.4; IR (KBr): $\tilde{\nu}$ = 2918, 2856, 1703, 1670, 1611, 1585, 1511, 1442, 1401, 1377, 1360, 1334, 1302, 1280, 1246, 1215, 1195, 1172, 1138, 1107, 1090, 1071, 1030, 978, 955, 845, 820, 757, 735, 662 cm^{-1}; MS (EI): m/z (%): 607 (1), 385 (16), 207 (55), 175 (18), 161 (31), 147 (26), 133 (37), 122 (10), 121 (100), 105 (16), 79(16); HRMS (ESI+): m/z: calcd for $C_{35}H_{45}NO_2S$+Na: 630.28694; found: 630.28653 [M^++Na].

Compound 58: CH_2Cl_2 (30 μL) was added dropwise to a solution of [Mo{N(*t*Bu)(Ar)}$_3$] (**37**) (Ar=3,5-dimethylphenyl, 2 mg, 2.9 μmol)[27] in toluene (0.5 mL). The resulting brown mixture was added to a solution of diyne **57** (18 mg, 0.029 mmol) in toluene (5 mL) and the mixture was stirred at 80°C during 20 h. After cooling, the solution was filtered through a pad of silica gel, the filtrate was evaporated and the residue was purified by flash chromatography (EtOAc/hexanes 1:5) to give cycloalkyne **58** as a white solid (6 mg, 36%). ^{1}H NMR (400 MHz, CD_2Cl_2): δ=1.10 (d, J=7.3 Hz, 3H), 1.3–1.6 (m, 4H), 1.65–1.8 (m, 6H), 1.9 (s, 3H), 1.95–2.2 (m, 3H), 2.3 (m, 1H), 2.6 (m, 1H), 3.1 (s, 3H), 3.2 (d, J=5.8 Hz, 2H), 3.5 (m, 1H), 3.7 (s, 3H), 3.78 (t, J=5.8 Hz, 1H), 4.05 (m, 1H), 4.25 (d, J=14.3 Hz, 1H), 4.92 (d, J=14.3 Hz, 1H), 5 (t, J=3.1 Hz, 1H), 5.17 (d, J=15.6 Hz, 1H), 5.65 (s, 1H), 5.75 (m, 1H), 6.78 (d, J=8.6 Hz, 2H), 7.13 (d, J=8.6 Hz, 2H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ=21.8, 23.8, 25.6, 25.9, 30.6, 30.8, 30.8, 30.9, 33.8, 33.9, 47.4, 47.6, 55.3, 61.6, 66.0, 66.1, 80.7, 91.8, 101.4, 110.8, 114.0, 118.6, 129.1, 130.0, 141.9, 155.8, 159.3, 166.5, 172.7; IR (KBr): $\tilde{\nu}$ = 2934, 1715, 1669, 1612, 1585, 1513, 1439, 1396, 1377, 1323, 1312, 1286, 1253, 1231, 1194, 1177, 1160, 1135, 1084, 1026, 1009, 970, 930, 873, 846, 835, 820, 794, 756, 735, 715, 681, 663 cm^{-1}; MS (EI): m/z (%): 552 (1), 504 (1), 331 (28), 257 (17), 151 (100), 121 (80), 91 (10); HRMS (ESI+): m/z: calcd for $C_{31}H_{39}NO_6S$+Na: 576.23958; found: 576.23947 [M^++Na].

Compound 59: CAN (229 mg, 0.42 mmol) was added to a stirred solution of compound **57** (51 mg, 0.084 mmol) in acetonitrile (18 mL) and water (6 mL). After 1 h, saturated aqueous $NaHCO_3$ (10 mL) was introduced and the aqueous layer was repeatedly extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered and evaporated, and the residue was purified by flash chromatography on silica gel (EtOAc/hexanes 1:5) to give product **59** as a colorless oil (21 mg, 51%). $[\alpha]_D^{20}$= +33 (c 0.1, CH_2Cl_2); ^{1}H NMR (400 MHz, CD_2Cl_2): δ=1.05 (d, J= 6.8 Hz, 3H), 1.10–1.65 (m, 7H), 1.69 (s, 3H), 1.8 (s, 3H), 1.82 (s, 3H), 1.89 (m, 1H), 2.14–2.22 (m, 2H), 2.26–2.36 (m, 1H), 2.65 (dd, J=7.6, 7.5 Hz, 2H), 3.13 (s, 3H), 3.17–3.31 (m, 2H), 3.77–3.76 (m, 1H), 4–4.2 (m, 1H), 5.09 (m, 1H), 5.38 (d, J=15.6 Hz, 1H), 5.4 (s, 1H), 5.58 (s, 1H), 5.94 (dt, J=7.2, 15.6 Hz, 1H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ= 3.2, 3.9, 21.3, 25.0, 26.1, 28.2, 29.5, 31.4, 31.4, 32.4, 33.0, 33.5, 34.5, 47.8, 56.8, 65.7, 65.9, 83.4, 84.5, 99.9, 110.5, 110.7, 117.4, 142.0, 158.7, 165.7, 174.2; IR (film): $\tilde{\nu}$ = 3225, 2918, 2855, 1682, 1646, 1440, 1377, 1336, 1278, 1226, 1164, 1138, 1089, 1036, 991, 956, 839, 722, 685, 657 cm^{-1}; MS (EI): m/z (%): 385 (12), 279 (11), 278 (53), 208 (14), 207 (100), 175 (33), 170 (10), 162 (10), 161 (61), 147 (51), 133 (84), 107 (21), 105 (36), 91 (21), 79 (54); HRMS (ESI+): m/z: calcd for $C_{27}H_{37}NO_5S$+Na: 510.22902; found: 510.22287 [M^++Na].

Compound 60: Pyridine (11 μL, 0.14 mmol) was added dropwise at 0 °C to a solution of 2-trimethylsilylethanol (20.5 μL, 0.14 mmol) and triphosgene (13.6 mg, 0.046 mmol) in CH_2Cl_2 (2 mL). After stirring for 30 min, the resulting mixture was added dropwise at 0 °C to a solution of compound **59** (14 mg, 0.028 mmol), ethyl(diisopropyl)amine (49 μL, 0.287 mmol) and a catalytic amount of DMAP in CH_2Cl_2 (2 mL). The reaction was stirred for 24 h before it was quenched with sat. aq. $NaHCO_3$ (10 mL) and the aqueous layer was extracted three times with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$, filtered and evaporated, and the residue was purified by flash chromatography (EtOAc/hexanes 1:5) to give product **60** as a white solid (14.7 mg, 81 %). $[\alpha]_D^{20} = +20.9$ (*c* 0.74, CH_2Cl_2); ^{1}H NMR (400 MHz, CD_2Cl_2): $\delta = 0.07$ (s, 9H), 1.07–1.14 (m, 3H), 1.13 (d, $J = 6.8$ Hz, 3H), 1.4–1.65 (m, 5H), 1.73 (m, 1H), 1.76 (s, 3H), 1.87 (s, 3H), 1.89 (s, 3H), 1.86–1.89 (m, 1H), 2.04–2.11 (m, 1H), 2.22–2.3 (m, 2H), 2.33–2.41 (m, 1H), 2.71 (m, 2H), 3.23 (d, $J = 11.6$ Hz, 1H), 3.24 (s, 3H), 3.52 (dd, $J = 9.6$, 11.6 Hz, 1H), 3.82–3.9 (m, 1H), 4.19–4.27 (m, 1H), 4.35–4.42 (m, 1H), 4.88 (d, $J = 9.6$ Hz, 1H), 5.14 (s, 1H), 5.46 (d, $J = 15.9$ Hz, 1H), 5.66 (s, 1H), 6.02 (dt, $J = 15.9$, 6.8 Hz, 1H); ^{13}C NMR (100 MHz, CD_2Cl_2): $\delta = 0.1$, 5.0, 5.7, 19.3, 23.1, 26.7, 27.0, 27.8, 32.2, 33.2, 34.2, 34.6, 35.3, 35.9, 49.6, 60.8, 67.44, 67.5, 67.7, 77.7, 79.9, 85.2, 86.3, 102.8, 112.3, 119.2, 143.8, 152.3, 160.4, 167.4, 172.5; IR (film): $\tilde{\nu}$ = 2952, 2919, 2858, 1774, 1732, 1702, 1646, 1451, 1335, 1314, 1263, 1227, 1166, 1139, 1120, 1093, 1069, 1035, 955, 937, 857, 836, 761, 696, 664 cm^{-1}; MS (EI): *m*/*z* (%): 616 (1), 410 (10), 394 (20), 385 (21), 350 (20), 208 (14), 207 (100), 175 (24), 161 (53), 147 (33), 133 (48), 105 (18), 79(22), 73 (43); HRMS (ESI+): *m*/*z*: calcd for $C_{33}H_{49}NO_7SSi$+Na: 654.28967; found: 654.28905 [M^++Na].

Cycloalkyne 61: CH_2Cl_2 (30 μL) was added dropwise to a solution of [Mo{N(*t*Bu)(Ar)}$_3$] (**37**) (Ar = 3,5-dimethylphenyl, 1.4 mg, 2.3 μmol)[27] in toluene (0.5 mL). The brown mixture was added to a solution of diyne **60** (14.7 mg, 0.023 mmol) in toluene (20 mL) and the resulting mixture was stirred at 80 °C during 20 h. After cooling, the mixture was filtered through a short pad of silica gel which was carefully rinsed with EtOAc. The filtrate was evaporated and the residue was purified by flash chromatography on silica gel (EtOAc/hexanes 1:4) to give cycloalkyne **61** as a white solid (9.4 mg, 70 %). $[\alpha]_D^{20} = +36.6$ (*c* 0.46, CH_2Cl_2); ^{1}H NMR (400 MHz, CD_2Cl_2): $\delta = 0.07$ (s, 9H), 1.05–1.12 (m, 1H), 1.12 (d, J = 6.8 Hz, 3H), 1.3–1.47 (m, 3H), 1.52–1.61 (m, 3H), 1.69–1.78 (m, 1H), 1.81 (s, 3H), 1.93–1.96 (m, 1H), 2–2.13 (m, 3H), 2.34–2.43 (m, 1H), 2.61–2.68 (m, 1H), 3.27 (d, $J = 11.6$ Hz, 1H), 3.31 (s, 3H), 3.54 (dd, $J = 11.6$, 9.6 Hz, 1H), 3.57–3.68 (m, 1H), 4.04–4.12 (m, 1H), 4.14–4.21 (m, 1H), 4.32–4.39 (m, 1H), 4.87 (d, $J = 9.6$ Hz, 1H), 5.04–5.08 (m, 1H), 5.23 (d, $J = 15.6$ Hz, 1H), 5.73 (s, 1H), 5.81 (m, 1H); ^{13}C NMR (100 MHz, CD_2Cl_2): $\delta = -1.8$, 17.5, 21.8, 23.8, 25.9, 30.8, 30.8, 30.9, 30.9, 33.4, 33.6, 48.1, 59.4, 65.7, 66.0, 80.1, 91.9, 100.6, 110.8, 118.5, 141.8, 150.6, 155.8, 166.4, 170.7; IR (KBr): $\tilde{\nu}$ = 2931, 1772, 1708, 1651, 1443, 1378, 1317, 1264, 1234, 1167, 1142, 1093, 1034, 958, 937, 856, 836, 761, 695 cm^{-1}; MS (EI): *m*/*z* (%): 562 (1), 331 (15), 257 (13), 221 (5), 152 (10), 151 (100), 105 (9), 91 (12), 73 (50), 55 (8); HRMS (ESI+): *m*/*z*: calcd for $C_{29}H_{43}NO_7SSi$+Na: 600.24272; found: 600.24217 [M^++Na].

Compound 62: Lindlar catalyst (10 mg, 10 % w/w) was added to a solution of enyne **61** (20.5 mg, 36.51 μmol) and quinoline (40 μL) in CH_2Cl_2 (3 mL). The mixture was vigorously stirred under a hydrogen atmosphere (1 bar) for 5 h. The catalyst was filtered off through a short path of silica gel which was carefully rinsed with EtOAc, the combined filtrates were evaporated and the residue was purified by flash chromatography on silica gel (EtOAc/hexanes 1:3) to give diene **62** as a white solid (17.2 mg, 82 %). $[\alpha]_D^{20} = +198$ (*c* 0.9, CH_2Cl_2); ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 0.06 (s, 9H), 1.02 (d, $J = 6.3$ Hz, 3H), 1.11 (t, $J = 8.8$ Hz, 2H), 1.25–1.47 (m, 4H), 1.5–1.6 (m, 3H), 1.82–1.91 (m, 1H), 1.92 (s, 3H), 2.0–2.4 (m, 4H), 2.85 (m, 1H), 3.21 (d, $J = 11.6$ Hz, 1H), 3.33 (s, 3H), 3.45 (m, 1H), 3.53 (dd, $J = 11.6$, 11.5 Hz, 1H), 4.02–4.21 (m, 1H), 4.33–4.43 (m, 1H), 4.90 (d, $J = 9.3$ Hz, 1H), 5.00 (dd, $J = 10.2$, 10.0 Hz, 1H), 5.09 (br s, 1H), 5.59 (s, 1H), 5.82 (m, 1H), 6.05 (dd, $J = 10.5$, 10.4 Hz, 1H), 6.39 (dd, J = 14.1, 11.8 Hz, 1H); ^{13}C NMR (100 MHz, CD_2Cl_2): $\delta = -1.8$, 17.5, 21.6, 24.9, 25.2, 29.7, 29.9, 30.9, 31.3, 31.4, 32.3, 34.8, 47.9, 59.1, 63.2, 65.8, 66.8, 101.1, 118.1, 125.0, 127.8, 132.3, 135.7, 150.6, 158.1, 166.2, 170.6; IR (KBr): $\tilde{\nu}$ = 2952, 2923, 2854, 1776, 1741, 1693, 1633, 1443, 1348, 1351, 1265, 1226, 1186, 1127, 1089, 1035, 988, 973, 949, 913, 860, 834, 781, 752, 696 cm^{-1}; MS (EI): *m*/*z* (%): 564 (1), 507 (2), 460 (16), 335 (25), 334 (22), 333 (100), 315 (15), 301 (17), 283 (38), 73 (61); HRMS (ESI+): *m*/*z*: calcd for $C_{29}H_{45}NO_7SSi$+Na: 602.25837, found: 602.25890 [M^++Na].

Compound 63: TBAF (37 μL, 1 M in THF, 37.8 μmol) was added at 0 °C to a stirred solution of diene **62** (19.9 mg, 34.3 μmol) in THF (2 mL). After stirring for 15 min, the mixture was filtered through a plug of silica gel, the filtrate was evaporated, and the residue was purified by flash chromatography (EtOAc/hexanes 1:2) to give product **63** as a white solid (8.9 mg, 62 %). $[\alpha]_D^{20} = +295$ (*c* 0.05, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.97$ (d, $J = 6.3$ Hz, 3H), 1.04–1.12 (m, 1H), 1.35–1.45 (m, 3H), 1.65–1.67 (m, 1H), 1.75–2.65 (m, 2H), 1.88 (s, 3H), 2.09–2.15 (m, 2H), 2.2–2.34 (m, 4H), 2.74 (m, 1H), 3.3 (s, 3H), 3.17–3.32 (m, 1H), 3.35–3.45 (m, 1H), 4.15 (dd, $J = 8.0$ Hz, 2H), 5.0 (dd, $J = 10.4$ Hz, 1H), 5.17 (br m, 1H), 5.48 (br s, 1H), 5.65 (s, 1H), 5.78–5.85 (m, 1H), 6.04 (d, $J = 10.6$ Hz, 1H), 6.37 (dd, $J = 14.5$, 11.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 21.9$, 25.3, 28.2, 29.3, 29.8, 30.9, 31.3, 31.6, 32.4, 35.4, 48.1, 56.9, 63.3, 66.9, 100.1, 118.5, 125.2, 127.8, 132.4, 135.9, 158.0, 166.6, 174.7; IR (KBr): $\tilde{\nu}$ = 3226, 2952, 2926, 1682, 1455, 1434, 1377, 1350, 1325, 1275, 1220, 1185, 1132, 1087, 1068, 1040, 1026, 984, 951, 910, 867, 769, 726, 683 cm^{-1}; MS (EI): *m*/*z* (%): 421 (20), 385 (25), 301 (100); HRMS (ESI+): *m*/*z*: calcd for $C_{23}H_{33}NO_5S$+Na: 458.19772; found: 458.19762 [M^++Na].

(+)-Latrunculin A (1): A solution of compound **63** (8.1 mg, 25 μmol) in AcOH (6 mL) and water (4 mL) was stirred at 60 °C for 2 h. After cooling, the mixture was diluted with EtOAc (10 mL) and washed with sat. aq. $NaHCO_3$ to neutralize the acid. The aqueous phase was repeatedly extracted with EtOAc and the combined organic layers were dried over anhydrous $MgSO_4$, filtered and evaporated. The residue was purified by flash chromatography on silica gel (EtOAc/hexanes 1:2) to give latrunculin A (**1**) as a white solid (6.3 mg, 80 %). $[\alpha]_D^{20} = +145$ (*c* 0.05, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.98$ (d, $J = 6.3$ Hz, 3H), 1.01–1.14 (m, 1H), 1.24–1.98 (m, 6H), 1.93 (s, 3H), 2.04–2.07 (m, 1H), 2.23–2.34 (m, 2H), 2.62–2.77 (m, 2H), 2.86–2.95 (m, 1H), 3.37–3.52 (m, 1H), 3.82–3.93 (m, 2H), 4.2–4.3 (m, 1H), 5.01 (dd, $J = 10.6$, 10.5 Hz, 1H), 5.42 (m, 1H), 5.65–5.69 (m, 1H), 5.69 (br s, 1H), 5.74 (s, 1H), 5.97 (dd, $J = 10.7$, 10.6 Hz, 1H), 6.40 (dt, $J = 14.0$, 12.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): see Table 2; IR (KBr): $\tilde{\nu}$ = 3302, 2952, 2854, 1670, 1435, 1377, 1351, 1279, 1231, 1190, 1060, 1050, 1029, 985, 953, 904, 865, 806, 753, 726, 686, 663 cm^{-1}; MS (EI): *m*/*z* (%): 403 (28), 385 (15), 335 (41), 334 (23), 333 (100), 327 (13), 315 (15), 301 (17), 285 (10), 205 (11), 175 (11), 170 (14), 159 (11), 147 (14), 135 (12), 133 (14), 131 (14), 121 (19), 119 (15), 117 (16), 109 (11), 107 (25), 105 (19), 93 (30), 91 (22), 81 (30), 79 (41), 55 (25); HRMS (ESI+): *m*/*z*: calcd for $C_{22}H_{31}NO_5S$+Na: 444.18207; found: 444.18233 [M^++Na].

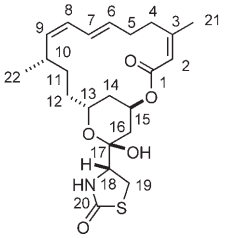
X-ray crystallographic study: Data were recorded using an Bruker-AXS KappaCCD-diffractometer with graphite-monochromated $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å). The crystal was mounted in a stream of cold nitrogen gas. The structures were solved by direct methods (SHELXS-97)[62] and refined by full-matrix least-squares techniques against F^2 (SHELXL-97).[63] Hydrogen atoms were inserted from geometry consideration using the HFIX option of the program.

Selected X-ray crystallographic data for ketone 18: $C_{13}H_{13}NO_3S$, M_r = 263.30 g mol^{-1}, colorless, crystal size 0.24 × 0.10 × 0.04 mm, orthorhombic, $P2_12_12_1$ [No. 19], $a = 5.3552(2)$, $b = 10.6947(3)$, $c = 23.0315(8)$ Å, V = 1319.07(8) Å^3, $Z = 4$, $\rho_{calcd} = 1.326$ Mg m^{-3}, $\mu = 0.245$ mm^{-1}, $T = 100$ K, 18482 reflections collected, 4193 independent reflections, 3286 reflections with $I > 2\sigma(I)$, $\theta_{max} = 31.00°$, 165 refined parameters, $R = 0.067$, wR^2 = 0.152, $S = 1.077$, largest diff. peak and hole = 0.5/−0.3 e Å^{-3}.

Selected X-ray crystallographic data for compound 31: $C_{24}H_{33}NO_5S$, M_r = 447.57 g mol^{-1}, colorless, crystal size 0.24 × 0.15 × 0.06 mm, monoclinic, $P2_1$ [No. 4], $a = 8.43580(10)$, $b = 7.20150(10)$, $c = 19.4502(3)$ Å, β = 100.4800(10)°, $V = 1161.90(3)$ Å^3, $Z = 2$, $\rho_{calcd} = 1.279$ Mg m^{-3}, μ = 0.174 mm^{-1}, $T = 100$ K, 18915 reflections collected, 7388 independent reflections, 6536 reflections with $I > 2\sigma(I)$, $\theta_{max} = 31.02°$, 412 refined parameters, $R = 0.037$, $wR^2 = 0.087$, $S = 1.015$, largest diff. peak and hole = 0.3/−0.2 e Å^{-3}.

Selected X-ray crystallographic data for compound 35: $C_{29}H_{37}NO_6S$, M_r = 527.66 g mol^{-1}, colorless, crystal size 0.57 × 0.05 × 0.04 mm, orthorhombic,

Table 2. Comparison of the ^{13}C NMR ($CDCl_3$) data reported for latrunculin A (**1**). Numbering scheme as shown in the insert.



No	Kashman[5] (75 MHz)	White[24] (100 MHz)	Smith[23] (125 MHz)	This synthesis (100 MHz)
1	166.0	165.3	165.3	165.4
2	117.6	117.3	117.3	117.3
3	158.3	158.5	158.4	158.4
4	32.7	32.6	32.7	32.7
5	30.6	30.4	30.4	30.5
6	131.8	131.8	131.8	131.8
7	126.3	126.0	126.0	126.0
8	127.3	127.1	127.2	127.2
9	136.5	136.5	136.5	136.5
10	29.2	29.2	29.2	29.2
11	31.8	31.4	31.4	31.5
12	31.2	31.0	31.0	31.0
13	62.3	62.3	62.3	62.3
14	35.1	34.9	34.9	34.9
15	68.1	68.2	68.2	68.2
16	32.1	31.7	31.8	31.8
17	96.9	97.3	97.3	97.3
18	62.1	61.2	61.3	61.4
19	28.7	28.7	28.7	28.7
20	175.5	174.6	174.6	174.8
21	24.7	24.5	24.5	24.5
22	21.8	21.6	21.6	21.6

$P2_12_12_1$ [No. 19], $a=8.21710(10)$, $b=20.8618(3)$, $c=31.8352(5)$ Å, $V=5457.30(13)$ Å^3, $Z=8$, $\rho_{calcd}=1.284$ Mg m^{-3}, $\mu=0.162$ mm^{-1}, $T=100$ K, 49602 reflections collected, 15781 independent reflections, 10411 reflections with $I>2\sigma(I)$, $\theta_{max}=30.07°$, Gaussian absorption correction (min. 0.95/max. 0.99), 660 refined parameters, $R=0.087$, $wR^2=0.180$, $S=0.966$, largest diff. peak and hole $=0.5/-0.4$ e Å^{-3}.

CCDC-229442–229444 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif/

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