Natural Product Synthesis

Catalysis-Based Total Synthesis of Latrunculin B**

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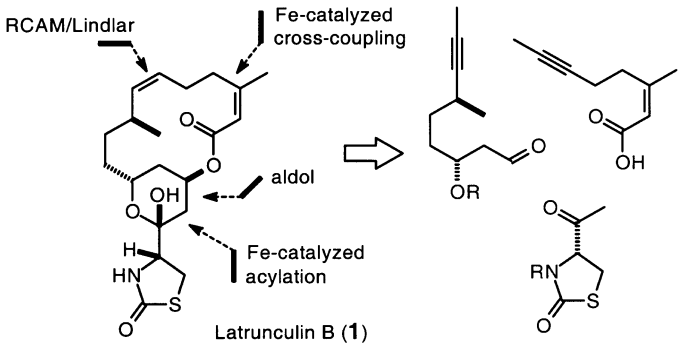
Actin is one of the two major components of the cytoskeleton and not only determines the shape and mechanical properties of eukaryotic cells but is also responsible for cell motility processes as fundamental as cytokinesis or exo- and endocytosis. Our present knowledge about the many biological roles of actin derives to a large extent from a "chemical genetics" approach based on probe molecules able to dissect this highly sophisticated and inherently dynamic microfilament structure.[1] Among them, the latrunculins gained particular importance because of their striking selectivity and the surprisingly rapid onset of action.[2] They form 1:1 complexes with actin monomers that are incapable of polymerizing to the intact protein filament network.[3] Latrunculin B (**1**) and congeners were originally isolated as the ichthyotoxic principles of the Red Sea sponge *Latrunculia magnifica* and were also found later in taxonomically unrelated organisms from different marine habitats.[4,5]

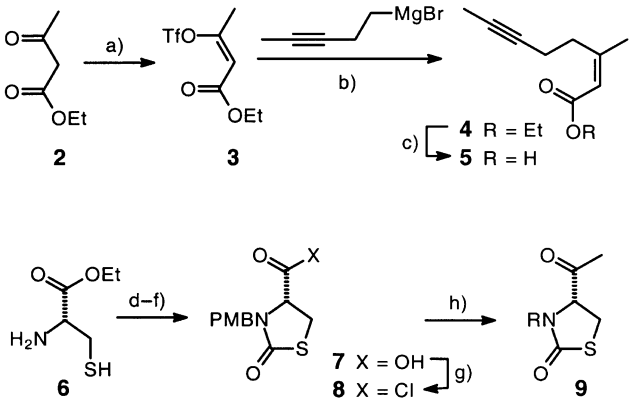
Despite the truly remarkable properties of the latrunculins and their widespread use as biochemical tools, the understanding of the structure–activity relationships (SAR) of these exquisite actin binders is fairly limited.[6] As a first step towards a synthesis-driven mapping of the structural elements essential for biological activity, a concise total synthesis of latrunculin B (**1**) was devised which is flexible enough to allow structural variations at a later stage. This flexibility was ensured by disconnecting **1** into three simple building blocks (Scheme 1) that are easy to modify and can be efficiently assembled through aldol chemistry, esterification, and formation of the macrocycle by the novel ring-closing alkyne metathesis (RCAM)/Lindlar reduction manifold.[7] Therefore, this new approach not only complements the previous total syntheses of **1** and its homologue latrunculin A based on macrolactonization,[8,9] but also illustrates the relevance of novel catalytic transformations recently developed in this laboratory.

The required acid component **5** was easily prepared from ethyl acetoacetate (**2**) via triflate **3** (Scheme 2). Reaction of the latter with the Grignard reagent derived from 1-bromo-3-pentyne in the presence of [Fe(acac)$_3$] as precatalyst afforded the desired product **4** in almost quantitative yield; the reaction proceeded stereoselectively and very rapidly under notably mild conditions. To the best of our knowledge, this is the first case of an iron-catalyzed cross-coupling reaction of an enol triflate. As such, it adds to the now rapidly growing number of examples in which cheap and benign iron salts serve as substitutes for established palladium or nickel catalysts in a variety of cross-coupling processes in general.[10,11]

In full accord with this notion, the synthesis of the cysteine-derived ketone **9** also takes advantage of iron catalysis (Scheme 2). Acid chloride **8** was prepared from **6** through standard reactions. Although **9** had previously been made by an uncatalyzed addition of MeMgBr to **8**,[8] we found the corresponding Fe-catalyzed process to be much more reliable and convenient; again, the rapid reaction rate is an additional bonus. The fact that attempted reactions of **8** with Me_2CuLi led to complete decomposition of the starting material also bears witness to the superiority of the iron-catalyzed procedure.[12] Although acid chloride **8** is inherently prone to racemization, one recrystallization of the crude material sufficed to adjust the *ee* of ketone **9** to 99%.



Scheme 1. Retrosynthetic analysis of latrunculin B.



Scheme 2. Synthesis of two building blocks by iron-catalyzed cross-coupling reactions: a) KHMDS, PhN(Tf)$_2$, THF, −78°C, 61%; b) [Fe(acac)$_3$] (10 mol%), THF, −30°C, 97%; c) aqueous NaOH, MeOH, 92%; d) CDI, THF, 71%; e) NaH, PMBBr, THF, 77%; f) aq. KOH, Et_2O, 98%; g) 1-chloro-2,*N*,*N*-trimethylprop-1-en-1-ylamine, THF, −18°C; h) [Fe(acac)$_3$] (1.5 mol%), MeMgBr, THF, −78°C→0°C, 80%. HMDS = hexamethyldisilazide, Tf = trifluoromethanesulfonyl, acac = acetylacetone, CDI = *N*,*N*′-carbonyldiimidazole, PMB = *p*-methoxybenzyl.

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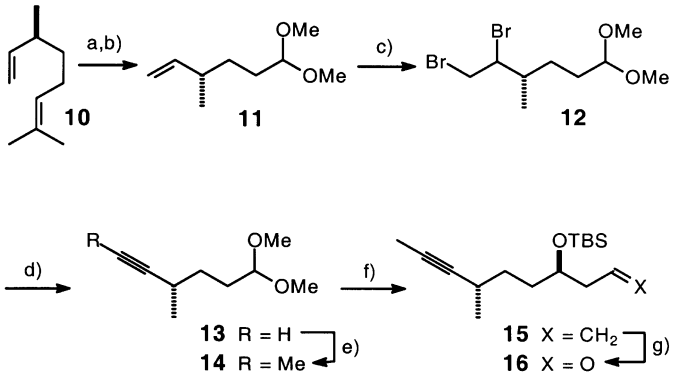
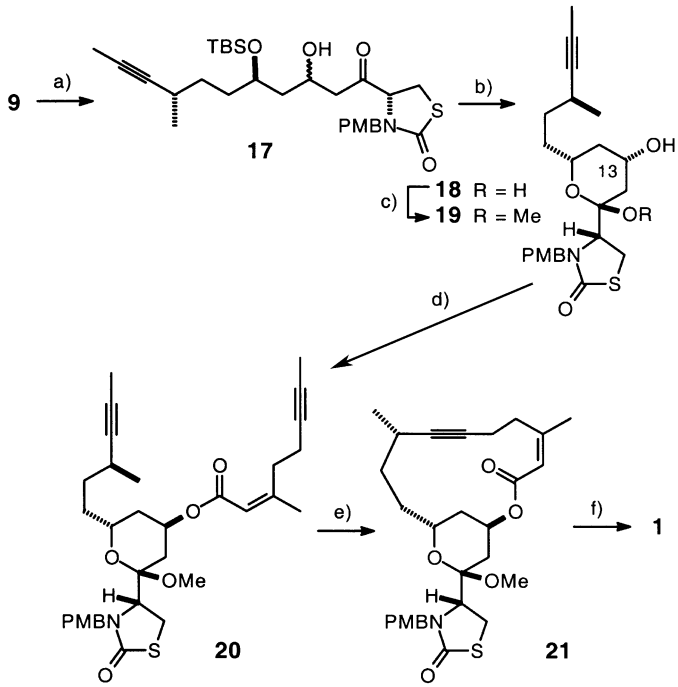
The third building block was derived from (+)-citronellene (**10**; 91% *ee*) by selective ozonolysis of the more highly substituted double bond and acetalization of the resulting aldehyde.[13] Bromination of **11** provided **12**, which was treated with LiHMDS to give **13** (Scheme 3). Alkyne **13** was



Scheme 3. Synthesis of the third building block: a) O_3, CH_2Cl_2, $-78\,^{\circ}C$, then Me_2S; b) $HC(OMe)_3$, K10 montmorillonite, 75%; c) 4-dimethylaminopyridinium bromide perbromide, DMAP, CH_2Cl_2, 87%; d) LiHMDS, THF, 90%; e) BuLi, MeI, THF/DMPU, 95%; f) 1) aqueous HCl, THF; 2) (−)-Ipc_2B(allyl), $-100\,^{\circ}C$, Et_2O; (iii) TBSCl, imidazole, DMF, 78%; g) O_3, MeOH, Sudan red 7B, then Me_2S, 94%. DMAP = 4-dimethylaminopyridine, DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone, Ipc = isopinocampheyl, TBS = *tert*-butyldimethylsilyl, DMF = *N*,*N*-dimethylformamide.



Scheme 4. Completion of the total synthesis: a) $TiCl_4$, iPr_2NEt, CH_2Cl_2, $-78\,^{\circ}C$, 73%; b) aqueous HCl, THF; c) CSA, MeOH, 64% (over two steps); d) 1) Tf_2O, pyridine, CH_2Cl_2, $-10\,^{\circ}C$; 2) Na salt of **5**, 15[crown]-5, THF, 58%; e) [Mo{N(*t*Bu)(3,5-$Me_2C_6H_3$)}$_3$] (5 mol%), toluene, CH_2Cl_2, $80\,^{\circ}C$, 70%; f) 1) H_2, Lindlar catalyst, CH_2Cl_2, quant.; 2) CAN, $MeCN/H_2O$, 78%. CSA = (+)-10-camphorsulfonic acid, CAN = ceric ammonium nitrate.

then methylated by reaction with BuLi and MeI. Deprotection of the acetal in **14**, allylation of the resulting aldehyde with (−)-Ipc_2B(allyl),[14] and subsequent protection of the alcohol with a TBS group furnished **15** in diastereomerically pure form (d.r. > 99.5:0.5). Selective ozonolysis of its alkene entity afforded the required product **16** for further elaboration.

Reaction of aldehyde **16** with the titanium enolate[15] derived from ketone **9** gave aldol **17** as a mixture (2:1) of diastereomers (Scheme 4). No attempt was made to improve this result as the stereochemical outcome was conveniently rectified at the next step by an equilibration process, which is well-precedented in the latrunculin series.[6a,8] Thus, acid-catalyzed cleavage of the TBS group in **17** delivered hemiacetal **18** (d.r. up to 7:1). Under these conditions, a transient oxonium ion is formed, which undergoes rapid loss of the axial OH group at C13; as 1,3-diaxial interactions are avoided during the re-addition of water to this intermediate, the formation of product **18** with an equatorially disposed OH function at that site is highly favored. Glycosylation with MeOH, conversion of product **19** into the corresponding triflate, and reaction with the sodium salt of acid **5** furnished diyne **20**, the substrate for the envisaged macrocyclization by RCAM.

This reaction proceeded exceptionally well in the presence of [Mo{N(*t*Bu)(3,5-$Me_2C_6H_3$)}$_3$] precatalyst, which was activated in situ with CH_2Cl_2 as recently described by our group.[16] Neither the dense array of functional groups nor the branching methyl substituent α to one of the alkyne units interfere with this catalytic system.[17] The chemoselective reaction of the triple bonds in the presence of a preexisting alkene is another noteworthy aspect of this transformation. The somewhat strained cycloalkyne **21** (Table 1) thus formed was subjected to a Lindlar reduction to ensure the stereoselective formation of the *Z*-alkene entity, followed by

Table 1: Selected data for **21** and **1**.

21: $[\alpha]_D^{20} = +61.3°$ ($c = 0.75$, CH_2Cl_2); IR (ATR): $\tilde{\nu} = 2935, 1695, 1672, 1512, 1444, 1276, 1248, 1214, 1093, 1031\ cm^{-1}$; ^1H NMR (400 MHz, CD_2Cl_2): $\delta = 1.43$ (d, 3H, $J = 6.9$ Hz), 1.40–1.57 (m, 2H), 1.86 (d, 3H, $J = 1.3$ Hz), 1.75–1.90 (m, 4H), 2.08–2.40 (m, 5H), 2.49–2.53 (m, 1H), 3.14 (s, 3H), 3.17–3.32 (m, 4H), 3.79 (s, 3H), 3.83 (dd, 1H, $J = 3.3$ Hz, 9.0 Hz), 4.33 (d, 1H, $J = 14.4$ Hz), 4.91–4.99 (m, 1H), 5.00 (d, 1H, $J = 14.4$ Hz), 5.19–5.22 (m, 1H), 5.58 (d, 3H, $J = 1.3$ Hz), 6.87 (d, 2H, $J = 8.6$ Hz), 7.22 ppm (d, 2H, $J = 8.6$ Hz); ^{13}C NMR (100 MHz, CD_2Cl_2): $\delta = 19.05, 21.86, 24.99, 25.42, 26.33, 29.76, 31.09, 33.37, 33.92, 34.24, 47.36, 47.47, 55.28, 59.23, 65.66, 67.09, 80.96, 86.23, 101.98, 113.93, 118.73, 129.06, 130.00, 156.83, 159.22, 165.74, 172.59$ ppm; MS (ESI, 70 eV): *m/z* (%): 305 (100), 287 (20), 273 (13), 255 (26), 227 (15), 213 (23), 203 (15), 149 (11), 121 (91); HRMS: calcd for $C_{29}H_{37}NNaO_6S$ [*M*+Na$^+$]: 550.223930, found: 550.22450.

1: $[\alpha]_D^{20} = +122°$ ($c = 0.55$, $CHCl_3$); IR (ATR): $\tilde{\nu} = 3328, 2952, 1678, 1278, 1092, 1057\ cm^{-1}$; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 0.95$ (d, 3H, $J = 6.3$ Hz), 1.07–2.39 (m, 11H), 1.90 (d, 3H, $J = 1.3$ Hz), 2.60–2.80 (m, 2H), 3.39 (dd, 1H, $J = 6.3$ Hz, 11.6 Hz), 3.47 (dd, 1H, $J = 8.8$ Hz, 11.6 Hz), 3.81–3.85 (m, 1H), 3.87 (s, 1H, OH), 4.24 (br t, 1H, $J = 10.6$ Hz), 5.05 (dt, 1H, $J = 1.5$ Hz, 11.2 Hz), 5.25 (dt, 1H, $J = 3.0$ Hz, 11.2 Hz), 5.43–5.46 (m, 1H), 5.68 (d, 1H, $J = 1.3$ Hz), 5.77 ppm (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 22.2, 24.0, 26.9, 28.7, 28.8, 30.9, 31.2, 31.4, 35.3, 35.8, 61.3, 62.5, 68.7, 97.8, 117.8, 127.4, 135.8, 154.5, 165.3, 174.7$ ppm.

concurrent cleavage of the *N*-PMB group and the methyl glycoside with CAN. Although this final deprotection was previously described as low-yielding,[8] we were pleased to find that it provided **1** (Table 1) in satisfactory yield (78%) simply upon prolongation of the reaction time.

In summary, a concise, productive, and inherently flexible route to latrunculin B (**1**) has been outlined based on Fe-catalyzed cross-coupling reactions[10–12] and alkyne metathesis[16,18] as the key steps. The longest linear sequence comprises 16 steps, which were performed in 14 operations, and provides an overall yield of approximately 6%. An extension of this approach to the synthesis of a focused library of latrunculin analogues is underway and will be reported in due course.

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