Natural Product Synthesis

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Total Synthesis of (−)-Reidispongiolide A, an Actin-Targeting Marine Macrolide**

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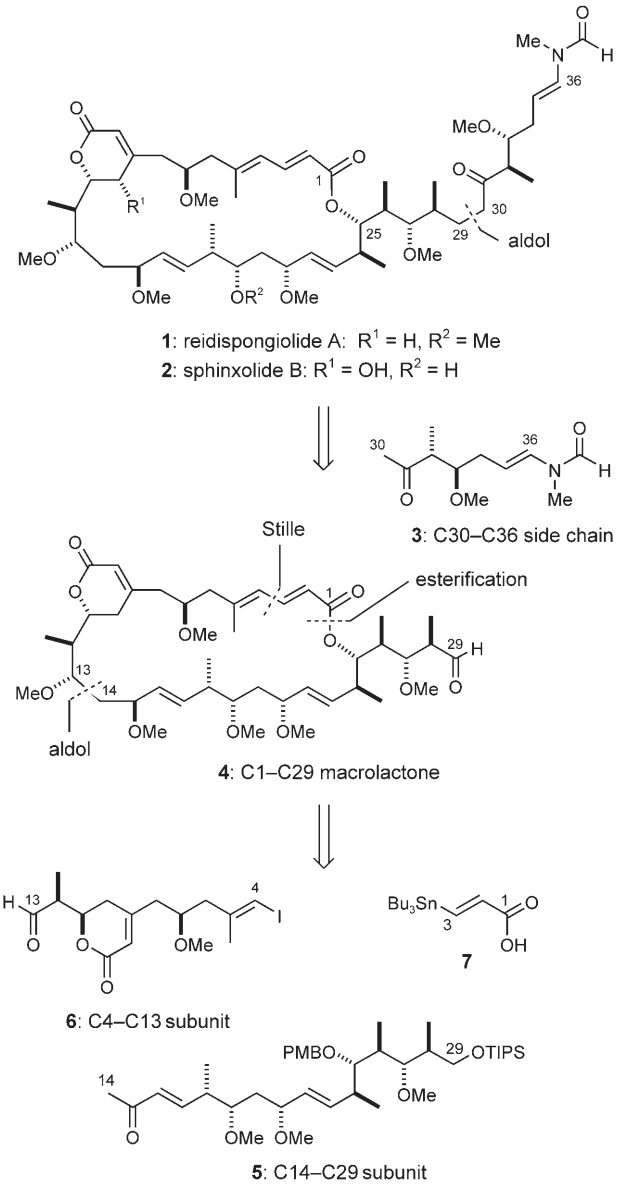
Reidispongiolide A (**1**), isolated by D'Auria et al. from the sponge *Reidispongia coerulea*, which was collected off the coast of New Caledonia,[1] and sphinxolide B (**2**)[2] are representative members of a structurally unique family of cytotoxic marine macrolides.[3] Their interaction with actin in the cell cytoskeleton leads to microfilament destabilization, and they show potent antiproliferative activity (for example, $IC_{50} = 0.04$ and 0.01 μg mL^{-1} against human colon carcinoma HT29) and the ability to circumvent multidrug resistance. This profile makes these macrolides valuable molecular probes in cell biology and promising lead compounds for the development of novel chemotherapeutic agents that target actin.[4,5] Their structures comprise a highly oxygenated 26-membered macrolactone, containing a δ-lactone ring, and appended with an elaborate side chain at C25 which terminates in an *N*-vinylformamide group. Through the combination of degradation fragment[2d,6,7] synthesis and detailed NMR analysis, we determined the stereochemistry of the entire reidispongiolide macrolide to be that shown in **1** (Scheme 1).[8] Subsequently, Rayment and co-workers[9] reported the X-ray crystal structure of actin-bound reidispongiolide A, assigning the complete configuration and revealing its intriguing mechanism of microfilament destabilization. The sparse natural supply of the reidispongiolides[1] and sphinxolides[2] makes total synthesis of paramount importance, not only to support further biological applications but also to enable structure–activity relationship (SAR) studies. Herein, we report the first total synthesis of reidispongiolide A based on a highly convergent modular assembly process that evolved from our stereochemical analysis groundwork.[7a,8]

As outlined in Scheme 1, our synthetic strategy for reidispongiolide A involves a late-stage introduction of the C30–C36 side-chain segment **3**, which incorporates the sensitive *N*-vinylformamide functionality, through a suitable aldol coupling with the macrolactone aldehyde **4**. We elected to disassemble the macrolide **4** into key subunits **5** (C14–C29) and **6** (C4–C13) based on an envisaged second aldol coupling to introduce the stereocenter at C13. The remaining subunit **7**



Scheme 1. Synthetic strategy for reidispongiolide A (**1**) that involves the key building blocks **3**, **5**, and **6**.

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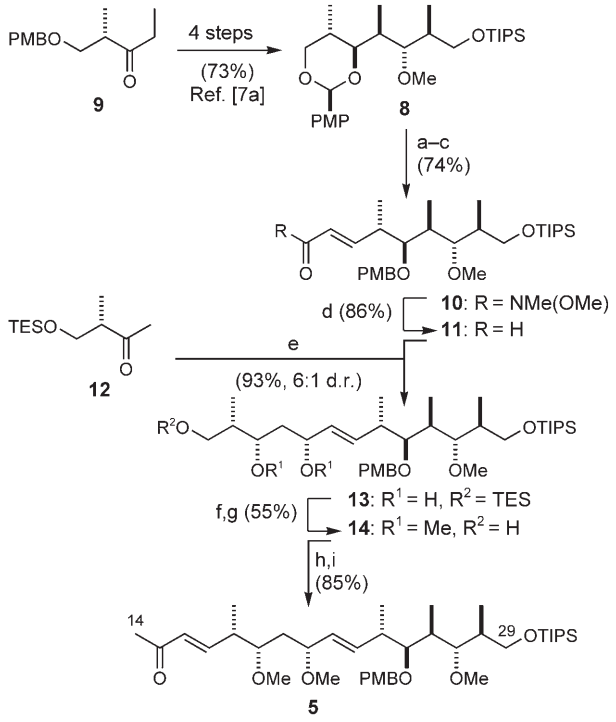
would then provide inherent flexibility whereby macrolide formation might arise through sequential $C(sp^2)$–$C(sp^2)$ coupling and esterification of the hydroxy group at C25, in either order. Another attractive aspect of this approach is that the three subunits **3**, **5**, and **6** resemble the reidispongiolide degradation fragments originally reported by D'Auria and co-workers,[6] which we had initially targeted for determination of the stereochemistry.[7a,8]

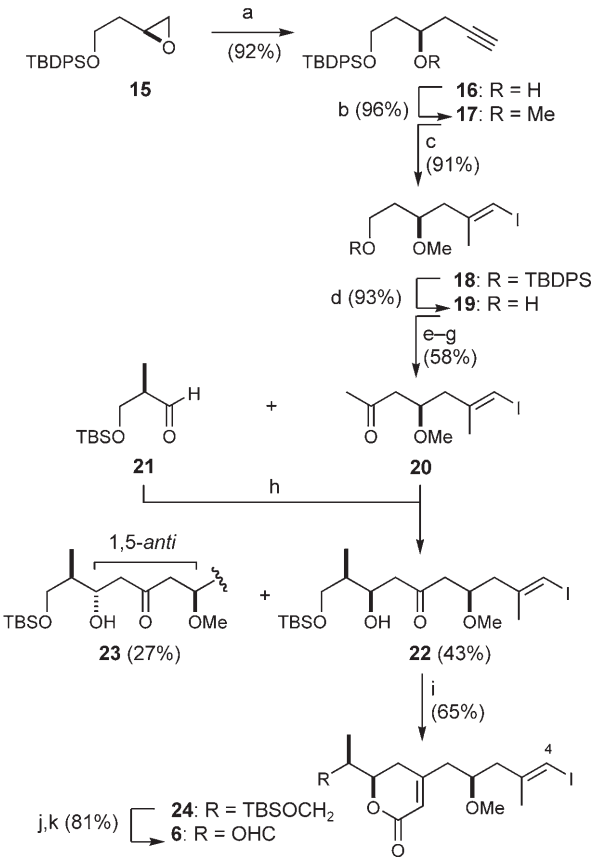
As shown in Scheme 2, the synthesis of the C14–C29 subunit **5** began with the construction of PMP-acetal **8**,



Scheme 2. Synthesis of the C14–C29 subunit **5**. a) DIBAL-H, TBME; b) DMP, $NaHCO_3$, CH_2Cl_2; c) $(MeO)MeNC(O)CH_2P(O)(OEt)_2$, LiCl, Et_3N, MeCN; d) DIBAL-H, THF, −78 °C; e) 1. (−)-Ipc_2BCl, Et_3N, Et_2O, 0 °C; 2. **11**, −78 °C; 3. $LiBH_4$, −78 °C; f) NaH, MeI, THF, 0 °C to RT; g) PPTS (cat.), MeOH; h) DMP, $NaHCO_3$, CH_2Cl_2, 0 °C to RT; i) $MeC(O)CH_2P(O)(OMe)_2$, LiCl, Et_3N, MeCN. DIBAL-H = diisobutylaluminum hydride, DMP = Dess–Martin Periodinane, Ipc = isopinocampheyl, PMB = *para*-methoxybenzyl, PMP = *para*-methoxyphenyl, PPTS = pyridinium *para*-toluenesulfonate, TBME = *tert*-butylmethyl ether, TES = triethylsilyl, TIPS = triisopropylsilyl.

accessible in four steps from the ethyl ketone (*S*)-**9**[10] by using our boron aldol methodology to install the required stereochemistry, as reported previously.[7a] Regioselective DIBAL-H opening of the acetal in **8** was best performed in TBME, followed by Dess–Martin oxidation of the resulting primary alcohol to give the corresponding aldehyde which underwent olefination under LiCl/Et_3N Horner–Wadsworth–Emmons (HWE) conditions[11] to afford the Weinreb amide **10** (72 %, $E:Z > 20:1$). Reduction of **10** with DIBAL-H provided the aldehyde **11** in readiness for a 1,4-*syn* boron aldol reaction[7a,12] with the methyl ketone (*S*)-**12**.[10] Enolization of **12** with the matched chiral reagent (−)-Ipc_2BCl and addition of aldehyde **11** at −78 °C, followed by the in situ reduction[13] of the intermediate boron aldolate with $LiBH_4$, afforded the 1,3-*syn* diol **13** (93 %, 6:1 d.r.). Having installed all the required stereochemistry of subunit **5**, a chain extension to the enone was now needed. Bis-*O*-methylation of **13** with NaH and MeI, followed by selective cleavage of the TES ether gave alcohol **14**. Dess–Martin oxidation of **14** gave the corresponding aldehyde that was combined with dimethyl (2-oxopropyl)-phosphonate to install the *E*-enone motif in **5** (90 %, $E:Z > 20:1$). By using this approach, the C14–C29 subunit **5** was synthesized efficiently on a multigram scale in 13 steps and 20 % overall yield from (*S*)-**9**.

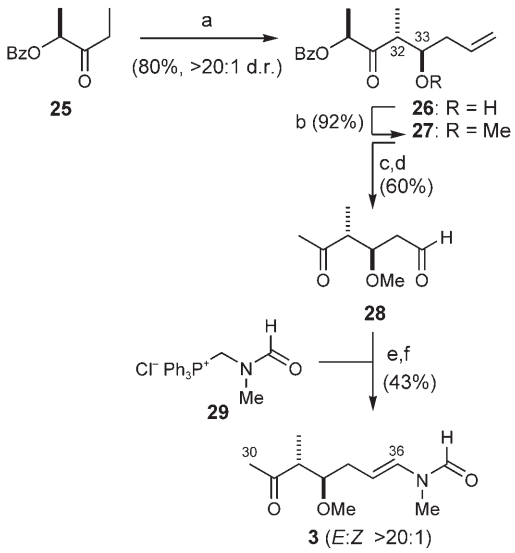
Preparation of the C4–C13 subunit **6** (Scheme 3) began with the opening of (*S*)-epoxide **15**[14] with the lithium anion of trimethylsilylacetylene in the presence of $BF_3{\cdot}Et_2O$ to afford **16** after desilylation. The conversion into methyl ether **17** (NaH, MeI) was followed by a Negishi carbometalation[15] (Me_3Al, $[Cp_2ZrCl_2]$) with an I_2 quench to provide the (*E*)-vinyl iodide **18** (91 %). Desilylation of **18** using TBAF gave



Scheme 3. Synthesis of the C4–C13 subunit **6**. a) 1. *n*BuLi, HCCTMS, $BF_3{\cdot}Et_2O$, THF, −78 °C; 2. K_2CO_3, MeOH, RT; b) NaH, MeI, THF, 0 °C to RT; c) 1. $AlMe_3$, $[Cp_2ZrCl_2]$, DCE, 60 °C; 2. I_2, THF, −20 °C; d) TBAF, THF; e) $(COCl)_2$, DMSO, CH_2Cl_2; Et_3N, −78 °C to RT; f) MeMgI, THF, −78 to −50 °C; g) PCC, celite, CH_2Cl_2; h) 1. (−)-Ipc_2BCl, Et_3N, Et_2O, 0 °C; 2. **21**, −78 °C; i) 1. $(EtO)_2P(O)CH_2CO_2H$, 2,4,6-$Cl_3(C_6H_2)COCl$, Et_3N, DMAP, PhMe; 2. $Ba(OH)_2$, wet THF; j) HF·py, py, THF, 0 °C to RT; k) TEMPO, $PhI(OAc)_2$, CH_2Cl_2. TBDPS = *tert*-butyldiphenylsilyl, TMS = trimethylsilyl, DCE = 1,2-dichloroethane, TBAF = tetrabutylammonium fluoride, PCC = pyridinium chlorochromate, DMAP = 4-*N*,*N*′-dimethylaminopyridine, DMSO = dimethylsulfoxide, py = pyridine, TEMPO = 4-amino-2,2,6,6-tetramethylpiperidine-1-oxyl.

alcohol **19** (93%), which was converted into methyl ketone **20** (58%, 3 steps). Enolization of **20** with (−)-Ipc_2BCl/Et_3N,[12b] followed by addition of aldehyde (*R*)-**21** at −78°C, provided the separable adducts **22** and **23** in 43% and 27% yield, respectively. In this demanding mismatched situation, the combination of Felkin–Anh induction from the α-chiral aldehyde **21** and Ipc-ligand influence imparted only moderate levels of aldol stereocontrol in favor of **22**, albeit overturning the inherent 1,5-*anti* stereoinduction[8,16] arising from the β-methoxy group in **20**, which is directed towards formation of the epimeric adduct **23**. Treatment of **22** with diethylphosphonoacetic acid generated the corresponding ester[8] that underwent $Ba(OH)_2$-promoted HWE cyclization[17] to give the dihydropyrone **24** (65%). Cleavage of the TBS ether with HF·py and oxidation[18] of the resulting alcohol with TEMPO and $PhI(OAc)_2$ completed the C4–C13 subunit **6** in 11 steps and 10% overall yield from (*S*)-**15**.

The synthesis of the remaining subunit **3** utilized our lactate aldol chemistry[19] to install the *anti* relationship at C32/C33 (Scheme 4). Thus, enolization of ethyl ketone (*S*)-



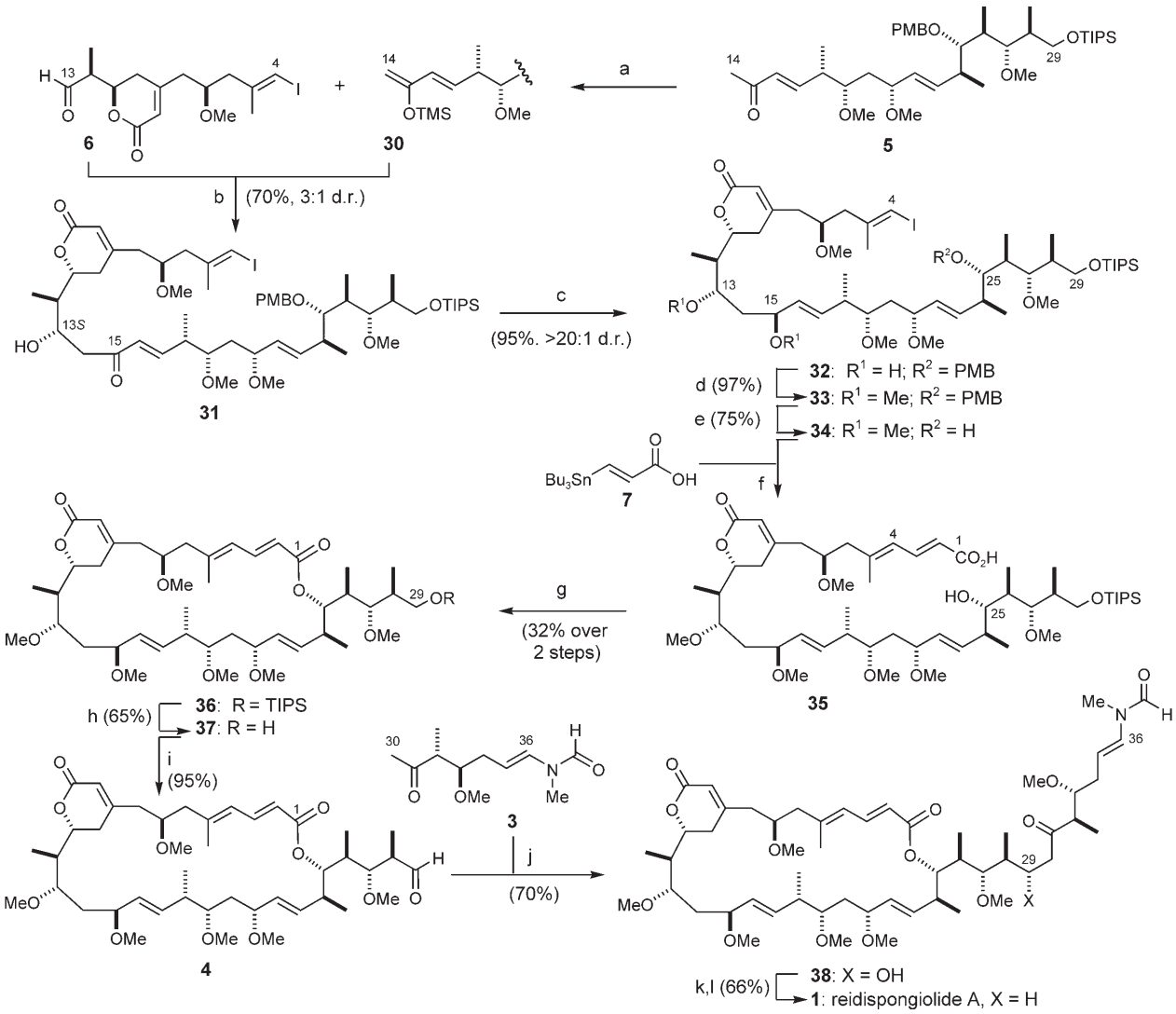
Scheme 4. Synthesis of the C30–C36 side chain **3**. a) 1. *c*Hex_2BCl, Me_2NEt, 0°C; 2. $H_2C{=}CHCH_2CHO$, −78°C; b) $Me_3O{\cdot}BF_4$, proton sponge, CH_2Cl_2, 0°C to RT; c) MeLi, Et_2O, −78 to −20°C; d) OsO_4 (cat.), $NaIO_4$, THF, H_2O; e) LiHMDS, THF, −78°C; f) I_2 (cat.), CH_2Cl_2, dark. Bz = benzoyl, *c*Hex = cyclohexyl, LiHMDS = lithium hexamethyldisilazide.

25[19a,c] with *c*Hex_2BCl and Me_2NEt followed by addition of freshly prepared 3-butenal[20] provided the adduct **26** (91%, >20:1 d.r.). Treatment of **26** with $Me_3O{\cdot}BF_4$ afforded ketone **27** (92%), which underwent methyl addition (MeLi) with concomitant benzoyl cleavage, followed by dihydroxylation and in situ oxidative cleavage of both 1,2-diols to provide δ-ketoaldehyde **28** (60%). At this point, installation of the sensitive *N*-vinylformamide functionality was required. By using our Wittig protocol,[21] treatment of aldehyde **28** with the ylide derived from phosphonium salt **29** (LiHMDS, −78°C) gave the (*Z*)-alkenylformamide as the predominant isomer (52%, *Z*:*E* 1.5:1). Iodine-mediated isomerization then provided the desired (*E*)-alkenylformamide **3** cleanly (82%; obtained as a mixture of rotamers by NMR analysis), which completed the C30–C36 side-chain segment in 6 steps and 19% overall yield from (*S*)-**25**.

With the three key subunits in hand, attention was now focused on their union, which began with a Mukaiyama aldol reaction[22] of **5** and **6** to introduce the stereocenter at C13 that relied on Felkin–Anh induction from the aldehyde **6** (Scheme 5). Enolization of methyl ketone **5** with LiHMDS at −78°C and trapping with TMSCl provided silyl enol ether **30**. Exposure of **6** and **30** to $BF_3{\cdot}Et_2O$ in CH_2Cl_2 at −95°C provided the desired (13*S*)-adduct **31** preferentially (70%, 3:1 d.r.). Evans–Saksena reduction[23] of **31** with $Me_4NBH(OAc)_3$ then gave the 1,3-*anti* diol **32** (95%, >95:5 d.r.). Conversion of **32** into the corresponding bismethyl ether **33**[24] with $Me_3O{\cdot}BF_4$ (97%) enabled the chromatographic removal of the minor diastereomer that arose from the Mukaiyama aldol coupling. In preparation for macrocycle formation, oxidative cleavage of the PMB ether at C25 in **33** with DDQ then gave **34** (75%).

Installation of the C1–C4 linker subunit **7** was now needed. Initial studies focused on the esterification of **34** with **7**, but led to degradation and/or recovery of starting materials under a variety of conditions. Gratifyingly, reversing the order of this coupling sequence proved successful. In practice, the Pd-mediated Stille coupling[25] of vinyl stannane **7** with the vinyl iodide **34** installed the *E*,*E* diene in *seco*-acid **35**, which underwent Yamaguchi macrolactonization[26] to provide the desired 26-membered macrocycle **36** (32% over 2 steps). At this stage, the ^1H and ^{13}C NMR spectra of **36** showed good correlations with the macrocyclic region of reidispongiolide A, further supporting our proposed stereostructure. Cleavage of the TIPS ether at C29 with HF·py and Dess–Martin oxidation of the resulting alcohol **37** provided the macrocyclic aldehyde **4** (62%). Attention was now directed on the challenging introduction of the full side chain of reidispongiolide A. After careful optimization, it was found that addition of **4** to the boron enolate of **3** (*c*Hex_2BCl/Et_3N) provided the aldol adduct **38** cleanly as a single isomer (70%), attributable to 1,5-*anti* stereoinduction[16] from the β-methoxy group in **3** as well as 1,4-*syn* induction.[27] Finally, dehydration of this β-hydroxy ketone with the Burgess reagent[28] (88%), followed by 1,4-reduction[29] of the intermediate *E* enone with $[\{Ph_3PCuH\}_6]$ gave reidispongiolide A (**1**) in 75% yield. All spectroscopic data (^1H and ^{13}C NMR, IR, MS) for the synthetic material were in excellent agreement with that reported[1,30] for natural reidispongiolide A, and correlated with an authentic sample, including HPLC comparison. As reidispongiolide A has a relatively low magnitude of specific rotation ($[\alpha]_D = -10.0$ ($c = 0.02$, MeOH) compared with $[\alpha]_D = -4.8$ in Ref. [1]), we also carried out a chiroptical correlation using circular dichroism spectra,[30] thereby conclusively defining the relative and absolute configuration.

In summary, we have completed a highly stereocontrolled synthesis of reidispongiolide A that proceeds in 0.9% overall yield with a longest linear sequence of 24 steps from **9**, and unequivocally established its relative and absolute configuration as depicted in structure **1**, in agreement with our earlier



Scheme 5. Subunit assembly and completion of reidispongiolide A. a) LDA, TMSCl, Et_3N, THF, −78 °C; b) $BF_3{\cdot}Et_2O$, CaH_2, CH_2Cl_2, −95 to −78 °C; c) $Me_4NBH(OAc)_3$, MeCN, AcOH, −30 °C; d) $Me_3O{\cdot}BF_4$, proton sponge, CH_2Cl_2, 0 °C; e) DDQ, pH 7 buffer, CH_2Cl_2; f) $[Pd_2(dba)_3]$, iPr_2NEt, NMP; g) 1. 2,4,6-$Cl_3(C_6H_2)COCl$, Et_3N, PhMe; 2. DMAP; h) HF·py, py, THF; i) DMP, CH_2Cl_2; j) 1. *c*Hex_2BCl, Et_3N, Et_2O, 0 °C; 2. **4**, −78 to 0 °C, 1 h; k) $Et_3NSO_2NCO_2Me$, THF; l) $[\{Ph_3PCuH\}_6]$, PhMe, H_2O. LDA = lithium diisopropylamide, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, dba = dibenzylideneacetone, NMP = 1-methyl-2-pyrrolidinone.

stereochemical analysis and the X-ray structure of the actin complex reported by Rayment and co-workers.[9] This constitutes the first total synthesis of any member of the reidispongiolide/sphinxolide family of cytotoxic marine macrolides. In combination with the available structural data on actin-bound reidispongiolide and related marine macrolides,[5,9] the design of novel analogues with tailored functional properties can now be envisaged.

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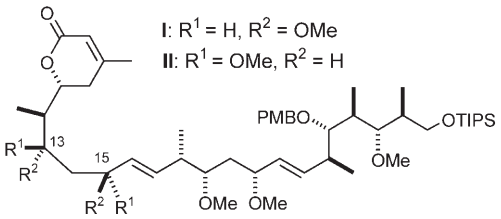

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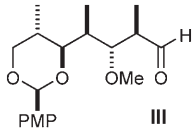
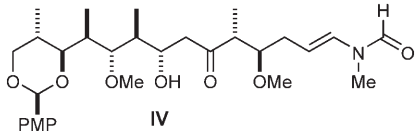


III



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