Natural Product Synthesis

DOI: 10.1002/ange.201301978

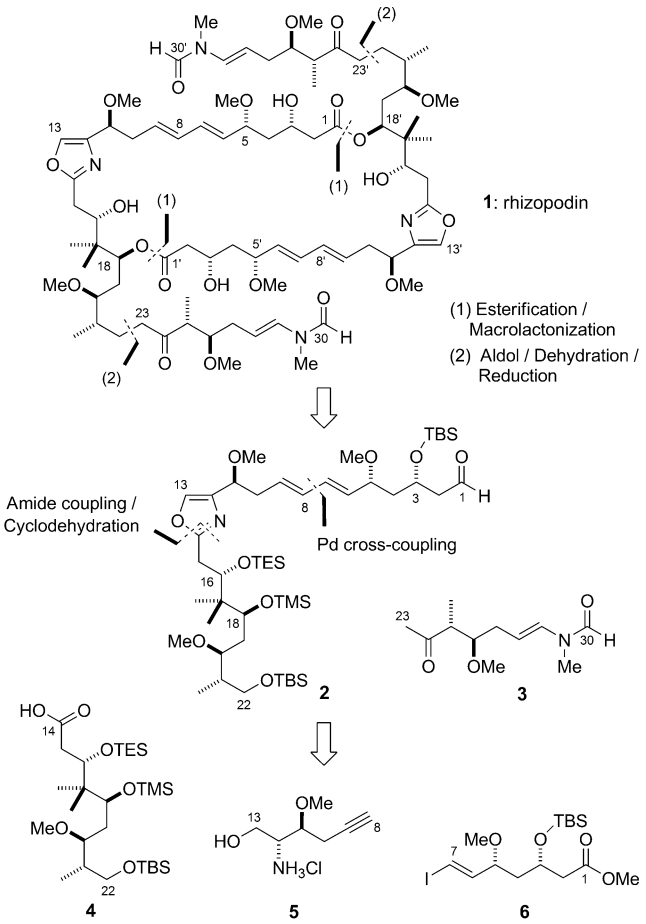
Total Synthesis of (−)-Rhizopodin**

Stephen M. Dalby, Jake Goodwin-Tindall, and Ian Paterson**

Dedicated to Professor K. C. Nicolaou

Rhizopodin (**1**, Scheme 1) is a structurally complex macrocyclic polyketide,[1–3] isolated from the myxobacterium *Myxococcus stipitatus* by Höfle and Reichenbach in 1993.[3a] Rhizopodin exhibits potent antiproliferative activity and exerts a strong cytostatic effect against a range of cancer cell lines. This activity is mediated through highly selective actin binding, inhibiting actin polymerization and leading to capping of the growing microfilament, severely disrupting cytoskeletal dynamics in vivo.[2a] The principal progenitors of this specific actin-recognition and antimicrofilament function are rhizopodin's characteristic *N*-methyl-*N*-vinylformamide-terminating side-chain tails, while the macrocyclic head serves to stabilize the protein-bound complex, modulating the precise biological response.[4] These tails are highly conserved within a number of related macrolides but the unique dimeric nature of rhizopodin, which presents two side-chains, elicits extraordinary antimicrofilament activity through the formation of a ternary actin complex.[3b] With growing recognition of actin as an alternative therapeutic target to tubulin,[2b] rhizopodin represents a unique and important lead structure for the treatment of cancer and other diseases such as stroke and cystic fibrosis, as well as a novel molecular probe for study of the cytoskeleton.

Originally characterized as a monomeric macrolide,[3a] the C_2-symmetric dimeric structure of rhizopodin was established through subsequent X-ray crystallographic studies of its actin-bound complex.[3b] This also enabled the full configurational assignment[3c,d] of rhizopodin's 18 stereocenters, 14 of which are embedded within its 38-membered macrodiolide core together with two oxazole rings and two diene motifs, while the remaining stereocenters reside on the side-chains. Despite the intensity of research efforts,[5] it is testament to the severe challenge presented[2b,6] that only a single completed synthesis has been claimed.[7,8] We now report a modular total synthesis of rhizopodin, which reveals some remarkable and unpredictable macrocyclic behavior, making its successful execution critically dependent on the choice of protecting groups.



Scheme 1. Retrosynthetic analysis and key fragments for the synthesis of rhizopodin (**1**). TBS = *tert*-butyldimethylsilyl, TES = triethylsilyl, TMS = trimethylsilyl.

Scheme 1 depicts the main retrosynthetic disconnections and key fragments **2**–**6** devised for rhizopodin. Principal simplification was made by disassembly of the C_2-symmetric macrocycle into truncated monomer **2** and side-chain subunit **3**. Macrocycle formation might then occur through either direct or sequential esterification, followed by bidirectional aldol coupling of the known methyl ketone **3**[6a] to the preformed macrodiolide core. The oxazole and diene motifs of monomer **2** would be exploited as ideal sites for mild and effective fragment coupling; amide-bond formation between C14–C22 carboxylic acid **4** and C8–C13 amino alcohol **5** followed by cyclodehydration would generate the oxazole, while Pd-mediated coupling of vinyl iodide **6** and a suitable C8 vinyl metal derivative would forge the (6*E*,8*E*)-diene. Importantly, the selection of various silyl ethers to differ-

[*] Dr. S. M. Dalby, J. Goodwin-Tindall, Prof. Dr. I. Paterson
University Chemical Laboratory, University of Cambridge
Lensfield Road, Cambridge, CB2 1EW (UK)
E-mail: sd344@cam.ac.uk
ip100@cam.ac.uk
Homepage: http://www-paterson.ch.cam.ac.uk

[**] This work was supported by the EPSRC (J.G.-T.) and Clare College, Cambridge (S.M.D.). We thank the EPSRC National Mass Spectrometry Centre (Swansea) for mass spectra.

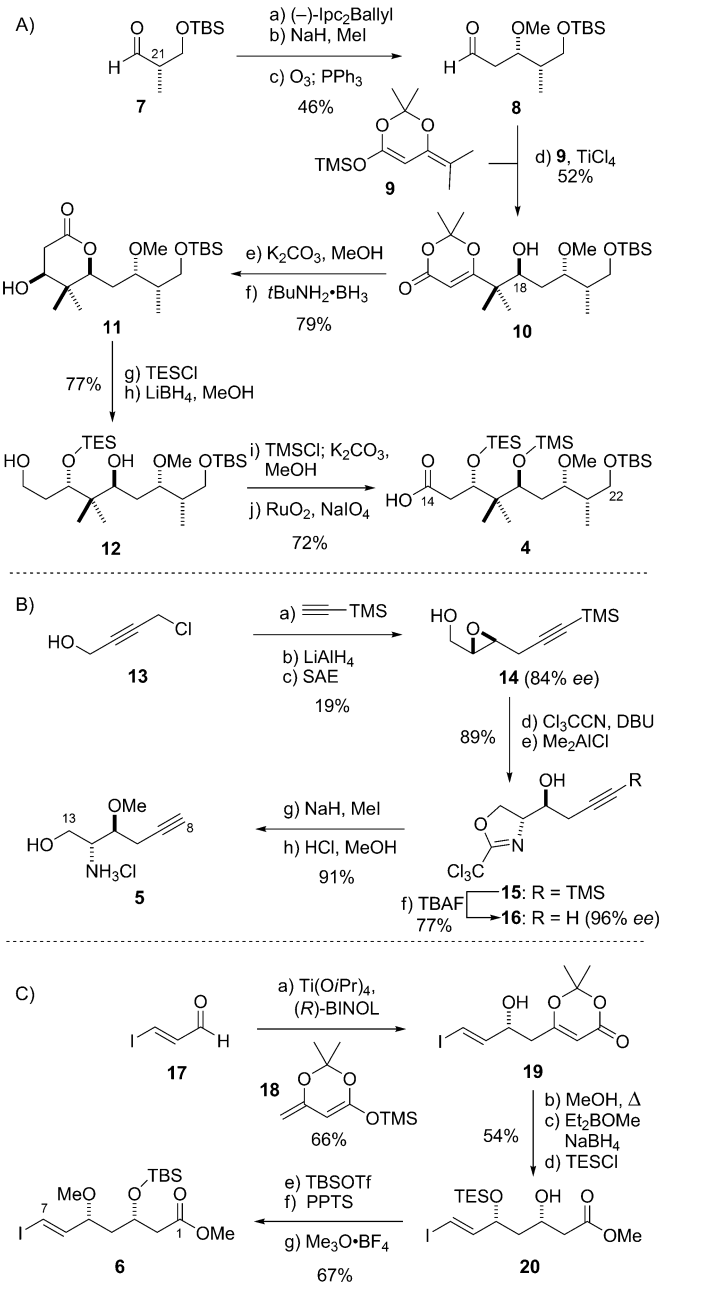
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201301978.

entiate the hydroxy groups (TBS at C3 and C22, TES at C16 and TMS at C18) was critical, made on the basis of an iterative series of studies which each failed to generate rhizopodin in the final deprotection sequence, as discussed later. In particular, the choice of the labile TMS ether at C18 to be carried through many steps was certainly high risk and would greatly limit our selection of reagents and reaction conditions.

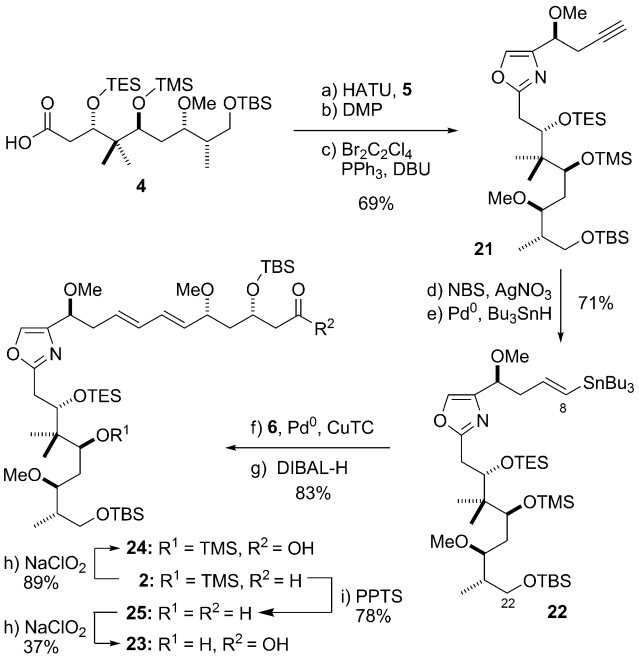
As shown in Scheme 2 A, the synthesis of carboxylic acid **4** utilized Roche ester-derived aldehyde **7** as the source of the C21 methyl-bearing stereocenter.[9] Brown allylation[10] of **7** provided the corresponding homoallylic alcohol (>20:1 d.r.), which was methylated (NaH, MeI, >95%) and subjected to ozonolysis (O_3; Ph_3P, 74%) to provide aldehyde **8**. Chelation-controlled ($TiCl_4$) Mukaiyama aldol addition of silyl ketene acetal **9** installed the C18 stereocenter and the adjacent *gem*-dimethyl moiety as part of dioxinone **10** with excellent stereocontrol (20:1 d.r.).[11] Methanolysis (K_2CO_3, MeOH, 90%) of **10** led to a δ-lactone, which then underwent stereoselective reduction ($tBuNH_2{\cdot}BH_3$, 88%) to afford β-hydroxy lactone **11** as a 10:1 mixture of chromatographically separable diastereoisomers.[12–14] Silylation of the hydroxy group (TESCl, imid, 93%) and reductive opening of the δ-lactone ($LiBH_4$, THF/MeOH, 83%)[15] afforded 1,5-diol **12**. Protection as its bis-TMS ether (TMSCl, imid) followed by controlled methanolysis (K_2CO_3, MeOH) then gave the corresponding primary alcohol. Testament to the lability of the TMS ether was its immediate incompatibility with conventional Pinnick oxidation conditions to generate the C14 carboxylic acid. Fortunately, this was overcome using catalytic RuO_2 and $NaIO_4$, which provided enantiomerically pure fragment **4** in 10% overall yield.

Amino alcohol **5** was prepared from propargylic alcohol **13** (Scheme 2 B).[16] Copper-mediated coupling with TMS acetylene led to a diyne (CuI, K_2CO_3, 74%),[17] which underwent regioselective reduction with $LiAlH_4$ to afford the corresponding (*E*)-allylic alcohol (>20:1 *E*:*Z*). Sharpless asymmetric epoxidation[18] ($Ti(OiPr)_4$, (+)-DIPT, *t*BuOOH, 87%, 84% *ee*) then provided epoxide **14**, which facilitated incorporation of the requisite nitrogen at C12 through regioselective Me_2AlCl-mediated epoxide opening of the derived trichloroacetimidate (Cl_3CCN, DBU) to provide oxazoline **15** (89%).[19] Removal of the TMS group afforded alkyne **16** as a colorless solid, which was recrystallized to provide material of 96% *ee*.[14] Methylation (NaH, MeI, 95%), followed by hydrolysis of the oxazoline (HCl, MeOH, 96%) then delivered **5** in 12% overall yield.

The polyacetate structure of vinyl iodide **6** was conveniently assembled through a catalytic asymmetric vinylogous Mukaiyama aldol reaction[20] of (*E*)-iodoacrolein **17**[21] with silyl ketene acetal **18**



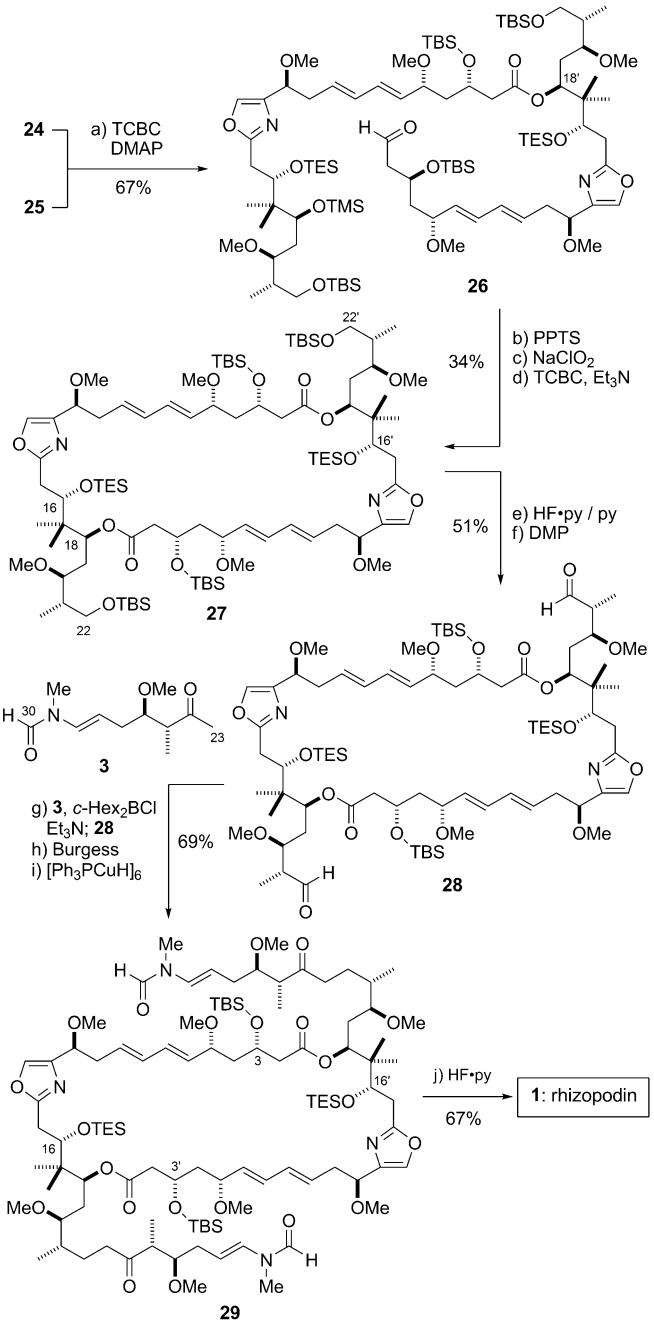
Scheme 2. A) Preparation of carboxylic acid **4**. B) Preparation of amino alcohol **5**. C) Preparation of vinyl iodide **6**. Reagents and conditions: A) a) (−)-Ipc_2BOMe, allylMgBr, Et_2O, −78 °C, 65% (d.r. > 20:1), b) NaH, MeI, THF, >95%; c) O_3, CH_2Cl_2, −78 °C; PPh_3, 74%; d) $TiCl_4$, **9**, CH_2Cl_2, −78 °C, 52% (d.r. 20:1); e) K_2CO_3, MeOH, 90%; f) $tBuNH_2{\cdot}BH_3$, citric acid, MeOH, 88% (d.r. 10:1); g) TESCl, imid, CH_2Cl_2, 93%; h) $LiBH_4$, THF/MeOH, 83%; i) TMSCl, imid, CH_2Cl_2; K_2CO_3, MeOH, 87% (over 2 steps); j) RuO_2, $NaIO_4$, CCl_4, MeCN, pH 7 buffer, 83%; B) a) CuI, K_2CO_3, NaI, TMSC≡CH, DMF, 74%; b) $LiAlH_4$, Et_2O, 29% (*E*:*Z* > 20:1); c) (+)-DIPT, $Ti(OiPr)_4$, *t*BuOOH, CH_2Cl_2, −30 °C, 87% (84% *ee*); d) Cl_3CCN, DBU, CH_2Cl_2, 0 °C; e) Me_2AlCl, CH_2Cl_2, 0 °C to RT, 89% (over 2 steps); f) TBAF, THF, 77%; g) NaH, MeI, THF, >95%; h) HCl, MeOH, 96%; C) a) $Ti(OiPr)_4$, (*R*)-BINOL, CaH_2, **18**, CH_2Cl_2, −20 °C, 66% (94% *ee*); b) MeOH, PhMe, reflux, >95%; c) $NaBH_4$, Et_2BOMe, THF, −78 °C, 86% (d.r. 10:1); d) TESCl, imid, CH_2Cl_2, −10 °C, 66% (76% brsm); e) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C, 85%; f) PPTS, MeOH/CH_2Cl_2 (1:7), 93%; g) $Me_3O{\cdot}BF_4$, Proton Sponge, 85%. (*R*)-BINOL = (*R*)-(+)-1,1′-Bi(2-naphthol), DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DIPT = diisopropyl tartrate, DMF = *N*,*N*-dimethylformamide, DMAP = 4-(dimethylamino)pyridine, DMP = Dess–Martin periodinane, imid = imidazole, Ipc = isopinocampheyl-borane, PPTS = pyridinium *para*- toluenesulfonate, SAE = Sharpless asymmetric epoxidation, TBAF = tetrabutylammonium fluoride.



Scheme 3. Preparation of monomers **24** and **25**. Reagents and conditions: a) HATU, *i*Pr_2NEt, **5**, CH_2Cl_2, 0 °C, 89%; b) DMP, $NaHCO_3$, CH_2Cl_2; c) $Cl_4C_2Br_2$, *i*Pr_2NEt, PPh_3, DBU, CH_2Cl_2, 78% (over 2 steps); d) NBS, $AgNO_3$, Me_2CO, 86%; e) Bu_3SnH, $Pd_2(dba)_3$, PPh_3, THF, 83%; f) **6**, $[Pd(PPh_3)_4]$, CuTC, $Ph_2PO_2NBu_4$, DMF, >95%; g) DIBAL-H, CH_2Cl_2, −78 °C, 87%; h) $NaClO_2$, NaH_2PO_4, *t*BuOH/H_2O, 89% for **24**, 37% for **23**; i) PPTS, MeOH/CH_2Cl_2 (1:19), 78% (88% brsm). dba = dibenzylideneacetone, HATU = *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluroniumhexafluorophos-phate, NBS = *N*-bromosuccinimide, TC = thiophene-2-carboxylate.

(Scheme 2C), which afforded dioxinone **19** in 94% *ee*.[22,23] Methanolysis of **19** followed by Narasaka reduction[24] provided the corresponding 1,3-*syn* diol (86%, 10:1 d.r.). Regioselective silylation of the allylic alcohol effected diol differentiation and provided β-hydroxy ester **20**. Silylation of the remaining alcohol (TBSOTf, 2,6-lutidine, 85%) and removal of the TES ether (PPTS, MeOH/CH_2Cl_2, 93%) led to an allylic alcohol, which upon methylation with Meerwein's salt ($Me_3O{\cdot}BF_4$, Proton Sponge, 85%) afforded vinyl iodide **6** in 23% overall yield.

With an effective means to prepare multi-gram quantities of each of these fragments, their union and formation of the targeted monomer **2** was tackled (Scheme 3). Amide coupling of carboxylic acid **4** with amino alcohol **5** was smoothly executed (HATU, *i*Pr_2NEt, 89%), where the lower operating temperature of HATU proved critical to avoid competing TMS removal/lactonization.[25] Oxidation of the ensuing alcohol with DMP[26] followed by cyclodehydration under the modified Robinson–Gabriel conditions developed by Wipf[27] afforded oxazole **21** (78%). Forging the C6–C9 diene commenced through preparation of the corresponding bromoalkyne (NBS, $AgNO_3$, 86%), which then enabled a highly regioselective Pd-catalyzed hydrostannylation ($[Pd_2(dba)_3]$, Ph_3P, Bu_3SnH, 83%)[28] to afford the requisite (*E*)-vinyl stannane coupling partner **22** for vinyl iodide fragment **6**. Pleasingly, the anticipated Stille cross-coupling reaction proceeded in excellent yield under Fürstner conditions.[29]



Scheme 4. Completion of the total synthesis of rhizopodin (**1**). Reagents and conditions: a) TCBC, DMAP, PhH, 67%; b) PPTS, MeOH/CH_2Cl_2 (1:19), 69%; c) $NaClO_2$, NaH_2PO_4, *t*BuOH/H_2O, 78%; d) TCBC, Et_3N, THF; DMAP, PhH, 63%; e) HF·py/py, THF, 58%; f) DMP, $NaHCO_3$, CH_2Cl_2, 88%; g) **3**, *c*-Hex_2BCl, Et_3N, Et_2O, −78 to 0 °C, 94%; h) $Et_3NSO_2NCO_2Me$, THF, 81%; i) $[Ph_3PCuH]_6$, PhMe, 91%; j) HF·py, THF, 67%. py = pyridine; TCBC = 2,4,6-trichlorobenzoyl chloride.

Reduction of the ester by treatment with DIBAL-H then afforded aldehyde **2**, thus completing this key truncated monomer intermediate in 18 steps. Oxidation adjustment was necessitated by the lability of the TMS ether to ester hydrolysis conditions.

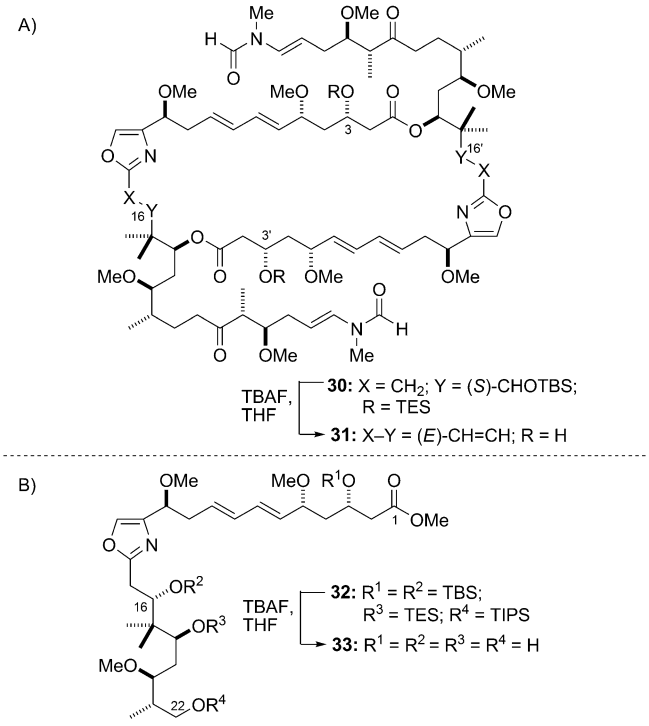
At this stage, our attention turned to the challenging assembly of the 38-membered rhizopodin macrocycle. Initial

studies, focused on the direct dimerization of the truncated *seco*-acid **23**, were discouraging, delivering a mixture of oligomers containing predominantly the corresponding monomeric macrocycle.[30] In response, a more controlled, sequential approach was undertaken, for which **2** was processed through separate oxidation ($NaClO_2$, 89%) or controlled silyl deprotection (PPTS, $MeOH/CH_2Cl_2$, 78%, 88% brsm) to give carboxylic acid **24** or alcohol **25**, respectively.

As shown in Scheme 4, fragment linkage was then initiated through acylation of the C18′ hydroxy by exposure of a mixture of **24** and **25** to TCBC and DMAP to provide ester **26**.[31] Removal of the remaining TMS group (PPTS, $MeOH/CH_2Cl_2$, 69%) to reveal the C18 hydroxy and oxidation of the aldehyde ($NaClO_2$, 78%) afforded a truncated *seco*-acid, which under Yamaguchi macrolactonization conditions (TCBC, DMAP)[32] pleasingly delivered macrodiolide **27**. At this stage, installation of the characteristic side-chains could be undertaken.[6a] This required selective cleavage of the primary TBS groups (C22/C22′), which proved an extremely delicate operation, owing to the comparable lability of the C16/C16′ TES ethers.[33] After some optimization, access to the requisite 22,22′-diol was achieved through carefully controlled exposure of **27** to HF·py/py, which, after a sequence of recycling, proceeded in 58% overall yield. Oxidation with DMP then afforded dialdehyde **28**, in readiness for bidirectional aldol coupling with methyl ketone **3**.[6a] In the event, exposure of **28** to the dicyclohexylboron enolate of **3** (*c*-Hex_2BCl, Et_3N) delivered the double aldol adduct in excellent yield. Controlled dehydration of this bis-β-hydroxy ketone with Burgess reagent[34] followed by conjugate reduction of the ensuing bis-(*E*)-enone[35] then afforded the protected rhizopodin derivative **29**.

In earlier studies,[36] we had prepared other protected versions of rhizopodin by synthetic routes analogous to that described above. Deprotection of the corresponding tetra-PMB ether was complicated by accompanying oxidation of the C5 allylic ether (DDQ) and general lability under Lewis-acidic conditions sufficient for complete PMB cleavage.[5f,37] The tetra-silyl ether **30** (Scheme 5A, regioisomeric to **29**) presented a further synthetic impasse, owing mainly to the remarkable stability of the C16/C16′ TBS ethers, which, despite an exhaustive search of deprotection conditions[38] (including neat HF·py) could not be successfully removed. Notably, **30** is almost identical to the final intermediate reported by Menche (tetra-TBS) which was claimed to afford rhizopodin upon treatment with TBAF.[7,39] In our hands however, compound **30** had failed to yield any detectable rhizopodin under such conditions, providing instead only the doubly eliminated macrodiolide **31**, having (15*E*,15′*E*)-alkenes in conjugation with the oxazole rings.[40] By contrast, the comparable acyclic monomer **32** (Scheme 5B) underwent silyl deprotection to give tetraol **33** with TBAF, without any observed elimination, suggesting a subtle macrocyclic conformational effect may be operative, in which the bulky TBS ethers adjacent to the C17 *gem*-dimethyl group favor an elimination pathway to give **31**.

This surprising and highly frustrating background had led us to carefully reassess our protecting group strategy, leading



Scheme 5. Global deprotection studies with: A) Rhizopodin derivative **30** (isomeric to **29**) and B) acyclic truncated monomer **32**.

to **29** (Scheme 4) bearing the more labile TES ethers at C16/C16′ which might be successfully removed under sufficiently mild conditions to circumvent the accompanying elimination. Gratifyingly, submission of this second-generation tetra-silyl ether to HF·py in THF proved fruitful in this task, delivering the previously elusive (−)-rhizopodin (**1**, 67%, $[\alpha]_D^{20}=-39.6$ ($c=0.25$, MeOH) vs Ref. [3c] $[\alpha]_D^{20}=-53.4$ ($c=1$, MeOH)). To our satisfaction, all ^1H and ^{13}C NMR spectroscopic data for this synthetic material correlated with those reported for natural rhizopodin A.[3c–d]

In conclusion, we have achieved a highly convergent total synthesis of the actin-binding macrodiolide rhizopodin (**1**), proceeding in 29 steps and 0.2% yield from aldehyde **7**. This route features a uniformly high level of stereocontrol combined with expedient fragment assembly, and should be amenable to the synthesis of useful quantities of this otherwise scarce anticancer agent, along with analogues and hybrids, for evaluation as new tools for the study of the actin cytoskeleton and as potential therapeutic agents. Surprisingly, the selection of TES rather than TBS ethers, located at C16/C16′ within the macrocycle and close to the oxazole rings, proved crucial to enable the final deprotection. This finding further underscores the unknown challenges that are often faced in tackling the chemical synthesis of such complex polyketides.

Received: March 8, 2013
Published online: May 6, 2013

Keywords: actin · anticancer agents · macrolides · protecting groups · total synthesis

[1] a) S. M. Dalby, I. Paterson, *Curr. Opin. Drug Discov. Devel.* **2010**, *13*, 777; b) G. M. Cragg, P. G. Grothaus, D. J. Newman, *Chem. Rev.* **2009**, *109*, 3012; c) I. Paterson, E. A. Anderson, *Science* **2005**, *310*, 451.

[2] a) T. M. A. Gronewold, F. Sasse, H. Lünsdorf, H. Reichenbach, *Cell Tissue Res.* **1999**, *295*, 121; b) K.-S. Yeung, I. Paterson, *Angew. Chem.* **2002**, *114*, 4826; *Angew. Chem. Int. Ed.* **2002**, *41*, 4632.

[3] a) F. Sasse, H. Steinmetz, G. Höfle, H. Reichenbach, *J. Antibiot.* **1993**, *46*, 741; b) G. Hagelueken, S. C. Albrecht, H. Steinmetz, R. Jansen, D. W. Heinz, M. Kalesse, W.-D. Schubert, *Angew. Chem.* **2009**, *121*, 603; *Angew. Chem. Int. Ed.* **2009**, *48*, 595; c) R. Jansen, H. Steinmetz, F. Sasse, W. D. Schubert, G. Hagelüken, S. C. Albrecht, R. Müller, *Tetrahedron Lett.* **2008**, *49*, 5796; d) N. Horstmann, D. Menche, *Chem. Commun.* **2008**, 5173.

[4] a) R. D. Perrins, G. Cecere, I. Paterson, G. Marriott, *Chem. Biol.* **2008**, *15*, 287; b) J. S. Allingham, V. A. Klenchin, I. Rayment, *Cell. Mol. Life Sci.* **2006**, *63*, 2119; c) G. Kustermans, J. Piette, S. Legrand-Poels, *Biochem. Pharmacol.* **2008**, *76*, 1310; d) J. S. Allingham, A. Zampella, M. V. D'Auria, I. Rayment, *Proc. Natl. Acad. Sci. USA* **2005**, *102*, 14527.

[5] a) Z. Chen, L. Song, Z, Xu, T. Ye, *Org. Lett.* **2010**, *12*, 2036; b) T. K. Chakraborty, K. K. Pulukuri, M. Sreekanth, *Tetrahedron Lett.* **2010**, *51*, 6444; c) T. K. Chakraborty, M. Sreekanth, K. K. Pulukuri, *Tetrahedron Lett.* **2011**, *52*, 59; d) M. Kretschmer, D. Menche, *Org. Lett.* **2012**, *14*, 382; e) K. K. Pulukuri, T. K. Chakraborty, *Org. Lett.* **2012**, *14*, 2858; f) M. Dieckmann, S. Rudolph, S. Dreisigacker, D. Menche, *J. Org. Chem.* **2012**, *77*, 10782.

[6] For work from our group on other actin-binding macrolides, see: a) I. Paterson, K. Ashton, R. Britton, G. Cecere, G. Chouraqui, G. J. Florence, H. Knust, J. Stafford, *Chem. Asian J.* **2008**, *3*, 367; b) I. Paterson, C. Watson, K.-S. Yeung, P. A. Wallace, R. A. Ward, *J. Org. Chem.* **1997**, *62*, 452; c) I. Paterson, K.-S. Yeung, R. A. Ward, J. D. Smith, J. G. Cumming, S. Lamboley, *Tetrahedron* **1995**, *51*, 9467.

[7] M. Dieckmann, M. Kretschmer, P. Li, S. Rudolph, D. Herkommer, D. Menche, *Angew. Chem.* **2012**, *124*, 5765; *Angew. Chem. Int. Ed.* **2012**, *51*, 5667.

[8] For the synthesis of the monomeric analogue, monorhizopodin, and 16-epi-monorhizopodin, see: K. C. Nicolaou, X. Jiang, P. J. Lindsay-Scott, A. Corbu, S. Yamashiro, A. Bacconi, V. M. Fowler, *Angew. Chem.* **2011**, *123*, 1171; *Angew. Chem. Int. Ed.* **2011**, *50*, 1139.

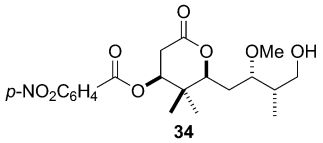
[9] I. Paterson, G. J. Florence, K. Gerlach, J. P. Scott, N. Sereinig, *J. Am. Chem. Soc.* **2001**, *123*, 9535.

[10] a) H. C. Brown, B. Singaram, *J. Org. Chem.* **1984**, *49*, 945; b) P. K. Jadhav, K. S. Bhat, P. T. Perumal, H. C. Brown, *J. Org. Chem.* **1986**, *51*, 432.

[11] The remaining mass balance was largely accounted for by reaction of silyl ketene acetal **9** at the α-position. An alternative procedure involving sequential isobutyrate Mukaiyama aldol reaction followed by Claisen condensation of the derived acetate was also investigated. See the Supporting Information for full details.

[12] K. Hinterding, S. Singhanat, L. Oberer, *Tetrahedron Lett.* **2001**, *42*, 8463.

[13] Alcohol **11** was derivatized as the crystalline *p*-nitrobenzoate ester **34**, for which X-ray crystallographic analysis confirmed the desired relative stereochemistry. See the Supporting Information for details.



34

[14] CCDC 924917 (**34**), 782547 (**16**), and 924918 (**19**) 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.

[15] K. Soai, A. Ookawa, *J. Org. Chem.* **1986**, *51*, 4000.

[16] V. Bagutski, N. Moszner, F. Zeuner, U. K. Fischer, A. de Meijere, *Adv. Synth. Catal.* **2006**, *348*, 2133.

[17] S. Durand, J.-L. Parrain, M. Santelli, *Synthesis* **1998**, 1015.

[18] a) Y. Gao, R. M. Hanson, J. M. Klunder, S. Y. Ko, H. Masamune, K. B. Sharpless, *J. Am. Chem. Soc.* **1987**, *109*, 5765; b) R. M. Hanson, K. B. Sharpless, *J. Org. Chem.* **1986**, *51*, 1922.

[19] S. Hatakeyama, H. Matsumoto, H. Fukuyama, Y. Mukugi, H. Irie, *J. Org. Chem.* **1997**, *62*, 2275.

[20] a) M. De Rosa, A. Soriente, A. Scettri, *Tetrahedron: Asymmetry* **2000**, *11*, 3187; b) S. E. Denmark, J. R. Heemstra, Jr., G. L. Beutner, *Angew. Chem.* **2005**, *117*, 4760; *Angew. Chem. Int. Ed.* **2005**, *44*, 4682; c) I. Paterson, R. D. M. Davies, A. C. Heimann, R. Marquez, A. Meyer, *Org. Lett.* **2003**, *5*, 4477.

[21] B. M. Trost, M. U. Frederiksen, J. P. N. Papillon, P. E. Harrington, S. Shin, B. T. Shireman, *J. Am. Chem. Soc.* **2005**, *127*, 3666.

[22] A related approach was employed by Nicolaou et al.; see Ref. [8].

[23] X-ray crystallographic analysis confirmed the desired absolute configuration for **19**. See Ref. [14] and the Supporting Information for details.

[24] K. Narasaka, F.-C. Pai, *Tetrahedron* **1984**, *40*, 2233.

[25] L. A. Carpino, A. El-Faham, C. A. Minor, F. J. Albericio, *J. Chem. Soc. Chem. Commun.* **1994**, 201.

[26] D. B. Dess, J. C. Martin, *J. Am. Chem. Soc.* **1991**, *113*, 7277.

[27] P. Wipf, T. H. Graham, *J. Org. Chem.* **2001**, *66*, 3242.

[28] a) C. D. J. Boden, G. Pattenden, T. Ye, *J. Chem. Soc. Perkin Trans. 1* **1996**, 2417; b) H. X. Zhang, F. Guibé, G. Balavoine, *J. Org. Chem.* **1990**, *55*, 1857.

[29] a) J. K. Stille, B. L. Groh, *J. Am. Chem. Soc.* **1987**, *109*, 813; b) A. Fürstner, J.-A. Funel, M. Tremblay, L. C. Bouchez, C. Nevado, M. Waser, J. Ackerstaff, C. C. Stimson, *Chem. Commun.* **2008**, 2873.

[30] This is consistent with results obtained by Nicolaou et al.; see Ref. [8].

[31] M. Hikota, Y. Sakurai, K. Horita, O. Yonemitsu, *Tetrahedron Lett.* **1990**, *31*, 6367.

[32] J. Inanaga, K. Hirata, H. Saeki, T. Katsuki, M. Yamaguchi, *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.

[33] Potential solutions to this issue explored included an unsuccessful protecting group-free approach, involving preparation and manipulation of the corresponding macrocyclic hexaol.

[34] E. M. Burgess, H. R. Penton, Jr., E. A. Taylor, *J. Org. Chem.* **1973**, *38*, 26.

[35] W. S. Mahoney, D. M. Brestensky, J. M. Stryker, *J. Am. Chem. Soc.* **1988**, *110*, 291.

[36] This work was carried out prior to the publication of Menche et al.; see Ref. [7].

[37] P. Wipf, T. H. Graham, *J. Am. Chem. Soc.* **2004**, *126*, 15346.

[38] P. G. M. Wuts, T. Greene, *Greene's Protective Groups in Organic Synthesis*, 4th ed., Wiley, Hoboken, **2006**.

[39] The Supporting Information in Ref. [7] indicates however, that neither this, nor the preceding compound, were purified or characterized. The synthesis of 0.14 mg of rhizopodin was claimed as proceeding in 14% yield over the final 3 steps.

[40] The Nicolaou group also expressed concern about the lability of the C16 alcohol, "*whose facile elimination toward the oxazole moiety was considered to be potentially problematic*"; see Ref. [8].

