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Total Synthesis and Biological Evaluation of Monorhizopodin and 16-*epi*-Monorhizopodin**

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For many years, polyketide natural products have provided the scientific community with a rich source of novel molecular architectures, many of which have become important therapeutics for clinical use.[1] In 1993, the polyketide rhizopodin was isolated from the myxobacterium *Myxococcus stipitatus*. [2] It was shown to display an interesting array of biological properties, including potent anti-tumor activity against a range of cancer cell lines in the low nanomolar range and the ability to inhibit the polymerization of actin. [2,3] Despite its original structural assignment as the 19-membered monomeric lactone **1a** (monorhizopodin), recent studies revealed dimeric structure **2** to be the correct architecture of rhizopodin (Figure 1). [4] These molecules have started to attract attention from the synthetic community, although no total syntheses have been reported to date. [5]

We were intrigued as to whether the originally proposed structure (**1a**) for monorhizopodin might exhibit comparable biological properties to its parent dimer (**2**), since these molecules contain several common structural elements, including an enamide side-chain, crucial for biological activity. X-ray crystallographic analysis of a rhizopodin-actin complex indicated that the binding of **2** to actin was largely due to favorable van der Waals interactions between the enamide side-chain and certain hydrophobic residues in the binding cleft. [6] Thus, the construction of **1a** might shed light on the effect of the macrocycle itself upon the binding affinity of these compounds. Herein, we describe a highly convergent and enantioselective total synthesis of monorhizopodin (**1a**) and its C16 epimer (**1b**), as well as preliminary biological evaluation of these compounds.

Scheme 1 depicts, in retrosynthetic format, the outline of the synthetic strategy employed for the construction of monorhizopodin (**1a**) and 16-*epi*-monorhizopodin (**1b**). Thus, rupture of the macrolactone and the C22–C23 and C29–N bonds led, after functional group adjustments, to hydroxy carboxylic acid **3** and ketophosphonate **4** as potential precursors to the target molecules. Disassembly of **3** at the indicated bond (C15–C16) through a SmI_2 -mediated Barbier reaction revealed iodoester **5** and aldehyde **6** as the required building blocks for its construction. Finally, disconnection of the diene system of **5** through a Stille coupling traced the origins of this compound to vinyl iodide **7** and oxazole-containing vinyl stannane **8**. The choice for the SmI_2 -mediated Barbier coupling over the more conventional Grignard reaction was based on the remarkably mild nature of the former reagent, [7] considered to be essential for the survival of the resulting secondary alcohol, whose facile elimination toward the oxazole moiety was considered to be an issue.

The synthesis of monorhizopodin (**1a**) and its 16-*epi*-diastereoisomer (**1b**) commenced with the construction of the requisite building blocks in their enantiomerically pure forms, starting with ketophosphonate **4**. Thus, as shown in Scheme 2, enantioselective crotylation of aldehyde **9** [8] with (–)-(Ipc)₂-*trans*-crotyl borane following Brown's protocol afforded alcohol **10** in 91% yield as a >10:1 mixture of diastereomers and >95% *ee*. Methylation (NaH, MeI, 76% yield) and ozonolytic cleavage of the terminal olefin (O₃; Ph₃P, 84% yield) of the latter compound led to aldehyde **12** through intermediate **11**. Reaction of aldehyde **12** with the lithium species derived from dimethyl methylphosphonate and *n*BuLi, followed by DMP oxidation of the resulting mixture of diastereomeric alcohols, furnished ketophosphonate **4** in 98% overall yield.

Aldehyde **6** was synthesized from known diol **13** [9] as summarized in Scheme 3. Thus, acetone formation from **13** [Me₂C(OMe)₂, (±)-CSA (cat.), 96% yield] followed by ozonolysis of the resulting olefin (**14**, O₃; Ph₃P, 83% yield) led to aldehyde **15**, which was subjected to reagent-controlled crotylation under the Brown conditions [(+)-(Ipc)₂-*cis*-crotyl borane] to afford secondary alcohol **16** in 75% yield as a single diastereomer. Methylation of **16** (NaH, MeI) was followed by ozonolysis (O₃; Ph₃P) and NaBH₄ reduction to give primary alcohol **18**, whose silylation [TBDPSCl, imid., DMAP (cat.)] led to acetone

TBDPS ether **19**, *via* intermediates **17** and **18**, in 75% overall yield for the four steps. Liberation of the 1,3-diol system of **19** required mild acid conditions (PPTS) and recycling (3×) in order to avoid significant degradation of the TBDPS ether and resulted in 56% yield (plus 33% recovered starting material) of diol **20**. Selective oxidation of the primary hydroxyl group of the latter [PhI(OAc)₂, TEMPO (cat.)], followed by TES protection (TESOTf, 2,6-lut.), furnished, through intermediate **21**, the required aldehyde **6** (75% overall yield for the two steps).

Scheme 4 summarizes the construction of vinyl iodide **7**. Following a procedure developed by Denmark and co-workers, α,β -unsaturated aldehyde **22**[10] was treated with silyl ketene acetal **23**[11] in the presence of catalyst **24** and SiCl₄[12] to afford secondary alcohol **25** in 69% yield and >90% *ee*. Exposure of **25** to KHMDS and benzaldehyde afforded benzylidene acetal **26** (71% yield), whose stereochemical configuration was confirmed by nOe studies. Subsequent reaction of **26** with (±)-CSA in MeOH revealed dihydroxy methyl ester **27** through acetal cleavage and transesterification (54% yield plus 44% recovered starting material). Selective protection of the hydroxyl group proximal to the ester moiety was achieved through δ -lactone formation (K₂CO₃; *p*TsOH, 96% overall yield) within **27** and silylation (TBSCl, DMAP, 84% yield), leading to TBS ether **29** *via* hydroxy compound **28**. Subsequent opening of the δ -lactone moiety of **29** (NaOMe, 86% yield), followed by methylation (Me₃OBf₄, 2,6-di-*t*-butyl-4-methyl pyridine, 80% yield) and iodination (NIS, 96% yield), furnished vinyl iodide **7** *via* intermediates **30** and **31**.

Vinyl stannane **8** was constructed from known oxazole aldehyde **32** [13] and converted to advanced iodide **5** as summarized in Scheme 5. Thus, treatment of **32** with allenyl-tri-*n*-butylstannane in the presence of Ti(O*i*Pr)₄ and (*S*)-BINOL afforded alcohol **33** in 60% yield and >95% *ee*. [14] Methylation of **33** (NaH, MeI, 93% yield) followed by desilylation (aq. HF, 86% yield) led to primary alcohol **35** *via* **34**. Regio- and stereoselective addition of tri-*n*-butyltin hydride to the terminal acetylene of **35** was achieved through palladium catalysis [Pd₂(dba)₃, Cy₃P·HBF₄, *i*Pr₂NEt, (*n*Bu)₃SnH, 67% yield] to afford vinyl stannane **8**. Coupling of this stannane with vinyl iodide **7** in the presence of CuTC[15] led to alcohol **36** (75% yield), which was converted to the desired advanced iodide **5** by sodium iodide through its mesylate (MsCl, Et₃N; NaI, 96% overall yield).

With fragments **4–6** now available, the stage was set for their coupling and elaboration to the targeted molecules monorhizopodin (**1a**) and its 16-*epi*-diastereoisomer (**1b**). As shown in Scheme 6, a mixture of **5** (1.0 equiv) and **6** (1.5 equiv) was exposed to the action of SmI₂ in THF to afford a 1:1 diastereomeric mixture of alcohols **37** at C16 (56% yield). Given the complexity of these substrates, the performance of SmI₂ in this coupling reaction is remarkable and provides further testament for the power of this reagent in organic synthesis. [7] Having achieved coupling of the key fragments, the resulting mixture of alcohols (**37**) was oxidized through the action of DMP to afford ketone **38** in 95% yield. Saponification of the methyl ester of **38** (LiOH, 60 °C) followed by TES removal (PPTS) then led to hydroxy acid **3** (62% overall yield), which was now primed for macrolactonization. It was after screening of several conditions that we found that optimal results could be obtained by employing the Shiina protocol.[16] Thus, slow addition of hydroxy acid **3** to a toluene solution of MNBA and DMAP at 60 °C afforded keto macrolactone **39** in good yield. Due to its tailing TLC properties, this ketone was difficult to purify and, therefore, was reduced with NaBH₄ in the presence of CeCl₃ in MeOH at –20 °C to give hydroxy compounds **40a** and **40b** as a chromatographically separable mixture of diastereomers (*ca.* 2:1 in favor of **40a**; under the high dilution conditions employed in the macrolactonization process, no dimeric material was observed). Interestingly, reduction of ketone **39** with NaBH₄ alone delivered alcohol **40b** exclusively. Other reducing agents led to unsatisfactory results. The

stereochemical configurations of diastereomers **40a** and **40b** were determined by the Rychnovsky ^{13}C NMR method,[17] employing the acetonides obtained from **40a** and **40b** upon reductive macrolactone opening, selective primary alcohol TBDPS protection, and acetonide formation [**40a** gave *anti*-acetonide **40a'** (^{13}C NMR, δ = 101.61 ppm), whilst **40b** gave *syn*-acetonide **40b'** (^{13}C NMR, δ = 99.04 ppm); see Supporting Information). In preparation for the side-chain attachment, the silyl protecting groups of diastereomer **40a** (corresponding to the C16 rhizopodin configuration) were removed (TBAF, AcOH) to afford triol **41a** in 89% yield. The latter compound was then converted to its *tris*-TES derivative **42a** (TESOTf, 2,6-lut., 66% yield) which underwent selective mono-desilylation (PPTS, 89% yield) and oxidation ($\text{SO}_3\cdot\text{py}$, 81% yield) to afford aldehyde **44a** through primary alcohol **43a**. This aldehyde was then reacted with ketophosphonate **4** in the presence of $\text{Ba}(\text{OH})_2$ to afford the corresponding α,β -unsaturated ketone (65%), which was reduced with Stryker's reagent, leading to its saturated counterpart (**45a**) in 87% yield. At this juncture, all that remained to complete the synthesis of monorhizopodin (**1a**) was global deprotection and installation of the enamide moiety. To this end, *tris*-silylated ketone **45a** was first exposed to TASf (to produce triol **46a**, 70% yield) and thence to $\text{PhI}(\text{OAc})_2/\text{TEMPO}$ (cat.) to furnish, through selective oxidation of the primary alcohol, dihydroxy aldehyde **47a** (74% yield). The latter was condensed with *N*-methyl formamide (PPTS, 4 Å MS, 80 °C) to afford monorhizopodin (**1a**) in 78% yield as a mixture of *E:Z* geometrical isomers (*ca.* 2:1 in favor of the *E* isomer). Following the same sequence, 16-*epi*-monorhizopodin (**1b**) was also synthesized from diastereoisomer **40b** (see Supporting Information). The ^1H and ^{13}C NMR and IR spectroscopic data of **1a** and **1b** were similar to those reported for rhizopodin (**2**).[4] The monomeric structures of these compounds were confirmed by their mass spectral data.

With synthetic samples of monorhizopodin (**1a**) and 16-*epi*-monorhizopodin (**1b**) available to us, we were in a position to evaluate their biological properties in actin polymerization and cytotoxicity assays. As shown in Figure 2, monorhizopodin (**1a**) exhibited potent inhibitory activity of actin polymerization, as expected from its enamide side-chain structural motif. This activity, which is mimicked by monorhizopodin's 16-*epi*-isomer (**1b**), albeit with somewhat lower potency, is comparable to that of latrunculin A (LatA, see figure 2), which was used as a standard in this assay. However, neither monorhizopodin (**1a**) nor 16-*epi*-monorhizopodin (**1b**) exhibited cytotoxicity against MDA-MB-231 breast cancer cells (up to 100 μM concentrations), presenting an interesting dichotomy and a puzzle regarding their divergence from rhizopodin (**2**). Although further investigations are needed to explain this phenomenon, we hypothesize that either these compounds are unable to displace G-actin binding proteins, such as profilin,[18] within cells, or that they fail to penetrate the cell membrane to reach their target.

In conclusion, a highly convergent total synthesis of monorhizopodin (**1a**) and 16-*epi*-monorhizopodin (**1b**) has been developed, rendering these monomeric homologues of the powerful antitumor agent rhizopodin (**2**) available for biological investigations. Preliminary studies showed these compounds to be endowed with actin-binding properties but devoid of any associated cytotoxicity, posing interesting questions regarding the role of the dimeric nature of rhizopodin (**2**) in its mode of action. Further studies directed toward the elucidation of the mechanism of action and the differences of rhizopodin (**2**) and its monomeric homologues, (**1a**) and (**1b**), as well as the total synthesis of the former are in progress.

Supplementary Material

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References

1. a) Newman DJ, Cragg GM. *J Nat Prod.* 2007; 70:461–477. [PubMed: 17309302] b) Newman DJ, Grothaus PG. *Chem Rev.* 2009; 109:3012–3043. [PubMed: 19422222]
2. Sasse F, Steinmetz H, Höfle G, Reichenbach H. *J Antibiot.* 1993; 46:741–748. [PubMed: 8514628]
3. Gronewold TM, Sasse F, Lünsdorf H, Reichenbach H. *Cell Tissue Res.* 1999; 295:121–129. [PubMed: 9931358]
4. Jansen R, Steinmetz H, Sasse F, Schubert WD, Hagelüken G, Albrecht SC, Müller R. *Tetrahedron Lett.* 2008; 49:5796–5799.
5. a) Cheng Z, Song L, Xu Z, Ye T. *Org Lett.* 2010; 12:2036–2039. [PubMed: 20380407] b) Chakraborty TK, Pulkuri KK, Sreekanth M. *Tetrahedron Lett.* 2010; 51:6444–6446. c) Chakraborty TK, Sreekanth M, Pulkuri KK. *Tetrahedron Lett.* 2010; 51:1016–1019. [PubMed: 2010.10.142]
6. Hagelüken G, Albrecht SC, Steinmetz H, Jansen R, Heinz DW, Kalesse M, Schubert WD. *Angew Chem.* 2009; 121:603–606. *Angew Chem Int Ed.* 2009; 48:595–598.
7. For selected reviews on the use of SmI_2 in organic synthesis, see: a) Nicolaou KC, Ellery SP, Chen JS. *Angew Chem.* 2009; 121:7276–7301. *Angew Chem Int Ed.* 2009; 48:7140–7165. b) Gopalaiiah K, Kagan HB. *New J Chem.* 2008; 32:607–637. c) Jung DY, Kim YH. *Synlett.* 2005:3019–3032. d) Edmonds DJ, Johnston D, Procter DJ. *Chem Rev.* 2004; 104:3371–3403. [PubMed: 15250745] For specific examples relevant to the present application, see: e) Wu J, Panek JS. *Angew Chem.* 2010; 122:6301–6304. *Angew Chem Int Ed.* 2010; 49:6165–6168. f) Williams DR, Berliner MA, Stroup BW, Nag PP, Clark MP. *Org Lett.* 2005; 7:4099–4102. [PubMed: 16146361] g) Williams DR, Kiryanov AA, Emde U, Clark MP, Berliner MA, Reeves JT. *Proc Natl Acad Sci.* 2004; 101:12058–12063. [PubMed: 15277662]
8. Luo J, Li H, Wu J, Xing X, Dai WM. *Tetrahedron.* 2009; 65:6828–6833.
9. Bode J, Gauthier DR, Carreira EM. *Chem Commun.* 2001:2560–2561.
10. Su Q, Dakin LA, Panek JS. *J Org Chem.* 2007; 72:2–24. [PubMed: 17194076]
11. Denmark SE, Beutner GL, Wynn T, Eastgate MD. *J Am Chem Soc.* 2005; 127:3774–3789. [PubMed: 15771512]
12. Denmark SE, Fujimori S. *J Am Chem Soc.* 2005; 127:8971–8973. [PubMed: 15969572]
13. Li DR, Zhang DH, Sun CY, Zhang JW, Yang L, Chen J, Liu B, Su C, Zhou WS, Lin GQ. *Chem Eur J.* 2006; 12:1185–1204. [PubMed: 16267861]
14. Keck GE, Krishnamurthy D, Chen X. *Tetrahedron Lett.* 1994; 35:8323–8324.
15. Allred GD, Liebeskind LS. *J Am Chem Soc.* 1996; 118:2748–2749.
16. Shiina I, Kubota M, Oshiumi H, Hashizume M. *J Org Chem.* 2004; 69:1822–1830. [PubMed: 15058924]
17. Rychnovsky SD, Rogers BN, Richardson TI. *Acc Chem Res.* 1998; 31:9–17.
18. Carlsson L, Nyström LE, Sundkvist I, Markey F, Lindberg U. *J Mol Biol.* 1977; 115:465–483. [PubMed: 563468]

Figure 1.
Structures of monorhizopodin (**1a**), 16-*epi*-monorhizopodin (**1b**) and rhizopodin (**2**).

Figure 2. Inhibition of actin polymerization by monorhizopodin (**1a**). The concentration of actin was 5 μ M, that of monorhizopodin (**1a**) as indicated. For the corresponding graphs obtained with 16-*epi*-monorhizopodin (**1b**) and further details of the assay, see Supplementary Information. LatA = latrunculin A.

Scheme 1.

Retrosynthetic analysis of monorhizopodin (**1**). TBS = *tert*-butyldimethylsilyl, TBDPS = *tert*-butyldiphenylsilyl, TES = triethylsilyl.

Scheme 2.

Construction of ketophosphonate **4**. Reagents and conditions: a) $(-)-(Ipc)_2$ -*trans*-crotyl borane (1.2 equiv), $BF_3 \cdot OEt_2$ (1.2 equiv), THF, $-78^\circ C$, 1 h; 3 $NNaOH$ (aq.), H_2O_2 , Et_2O , $25^\circ C$, 10 h, 91%, *d.r.* >10:1; b) NaH (1.5 equiv), MeI (1.5 equiv), THF, 0 to $25^\circ C$, 1 h, 76%; c) O_3 , CH_2Cl_2 , $-78^\circ C$; then PPh_3 (1.5 equiv), $25^\circ C$, 1 h, 84%; d) $MeP(O)(OMe)_2$ (5.5 equiv), $nBuLi$ (5.5 equiv), THF, $-78^\circ C$, 1 h; **12** (1.0 equiv), $-78^\circ C$, 2.5 h; DMP (1.4 equiv), CH_2Cl_2 , $25^\circ C$, 10 min, 98% for 2 steps. Ipc = isopinocampheyl, aq. = aqueous, THF = tetrahydrofuran, DMP = Dess–Martin periodinane.

Scheme 3.

Construction of aldehyde **6**. Reagents and conditions: a) ($\pm$)-CSA (0.010 equiv), $\text{Me}_2\text{C(OMe)}_2$, DMF, 25 °C, 2 h, 96%; b) O_3 , CH_2Cl_2 , -78 °C; then PPh_3 (2.0 equiv), 25 °C, 1 h, 83%; c) (+)-(Ipc) $_2$ -*cis*-crotyl borane (1.2 equiv), $\text{BF}_3\cdot\text{OEt}_2$ (1.2 equiv), THF, -78 °C, 1 h; 3*N*NaOH (aq.), H_2O_2 , Et_2O , 25 °C, 10 h, 75%; d) NaH (1.3 equiv), MeI (2.0 equiv), THF, 0 to 25 °C, 1 h, 89%; e) O_3 , CH_2Cl_2 , -78 °C; then PPh_3 (2.0 equiv), 25 °C, 1 h; NaBH_4 (1.1 equiv), MeOH, 0 °C, 30 min, 86% for 2 steps; f) TBDPSCI (1.1 equiv), imidazole (1.3 equiv), DMAP (0.10 equiv), CH_2Cl_2 , 0 to 25 °C, 1 h, 98%; g) PPTS (1.0 equiv), CH_2Cl_2 , MeOH, 25 °C, 16 h, 56% (33% recovered **19**); h) TEMPO (0.30 equiv), PhI(OAc)_2 (3.0 equiv), CH_2Cl_2 , 25 °C, 12 h, 85%; i) TESOTf (1.2 equiv), 2,6-lutidine (2.4 equiv), CH_2Cl_2 , -78 °C, 30 min, 88%. DMAP = 4-dimethylaminopyridine, PPTS = pyridinium *para*-toluenesulfonate, TEMPO = 2,2,6,6-tetramethyl-1-piperidinyloxy.

Scheme 4.

Construction of vinyl iodide **7**. Reagents and conditions: a) **23** (1.2 equiv), cat. (R,R) -**24** (0.015 equiv), SiCl_4 (1.1 equiv), $i\text{Pr}_2\text{NEt}$ (0.20 equiv), CH_2Cl_2 , -78°C , 2 h, 69%; b) PhCHO (3.3 equiv), KHMDS (0.30 equiv), THF , 0°C , 1 h, 71%; c) $(\pm)$ - CSA (0.30 equiv), MeOH , 25°C , 20 h, 54% (44% recovered **26**); d) K_2CO_3 (2.0 equiv), MeOH , H_2O , 25°C , 15 min; $p\text{TsOH}$ (1.0 equiv), THF , 25°C , 1 h, 96% for 2 steps; e) TBSCl (2.4 equiv), DMAP (3.9 equiv), CH_2Cl_2 , 25°C , 2 h, 84%; f) NaOMe (2.0 equiv), MeOH , 0°C , 1 h, 86%; g) Me_3OBF_4 (4.0 equiv), 2,6-di-*t*-butyl-4-methyl pyridine (5.0 equiv), CH_2Cl_2 , 25°C , 12 h, 80%; h) NIS (3.0 equiv), MeCN , 60°C , 10 h, 96%. KHMDS = potassium hexamethyldisilazide, CSA = camphorsulfonic acid, $p\text{TsOH}$ = *para*-toluenesulfonic acid, NIS = *N*-iodosuccinimide.

Scheme 5.

Synthesis of vinyl stannane **8** and advanced iodide **5**. Reagents and conditions: a) $\text{Ti}(\text{O}i\text{Pr})_4$ (1.0 equiv), $(S)\text{-BINOL}$ (1.0 equiv), 4 Å MS, CH_2Cl_2 , 40 °C, 1 h; **32** (1.0 equiv), allenyl-tri-*n*-butylstannane (1.2 equiv), -24 °C, 72 h, 60% (24% recovered **32**); b) NaH (2.0 equiv), MeI (2.0 equiv), THF, 0 to 25 °C, 1 h, 93%; c) 48% aq. HF (2.0 equiv), MeCN, 25 °C, 3 h, 86%; d) $\text{Pd}_2(\text{dba})_3$ (0.0050 equiv), $\text{Cy}_3\text{P HBF}_4$ (0.020 equiv), $i\text{Pr}_2\text{NEt}$ (0.040 equiv), $(\text{nBu})_3\text{SnH}$ (1.2 equiv), CH_2Cl_2 , 25 °C, 10 min, 67%; e) **7** (1.0 equiv), **8** (1.0 equiv), CuTC (10.0 equiv), NMP, 0 °C, 30 min, 75%; f) MsCl (1.2 equiv), Et_3N (1.5 equiv), CH_2Cl_2 , -78 °C, 30 min; NaI (5.0 equiv), acetone, 25 °C, 1 h, 96% for 2 steps. BINOL = 1,1'-bi(2-naphthol), dba = dibenzylidene acetone, CuTC = copper(I) thiophene-2-carboxylate, NMP = *N*-methyl-2-pyrrolidinone.

Scheme 6.

Fragment coupling and completion of the total synthesis of monorhizopodin (**1a**). Reagents and conditions: a) **5** (1.0 equiv), **6** (1.5 equiv), SmI_2 (3.0 equiv), THF, 25 °C, 5 min, 56%; b) DMP (3.0 equiv), CH_2Cl_2 , 25 °C, 15 min, 95%; c) $\text{LiOH} \cdot \text{H}_2\text{O}$ (6.0 equiv), $(\text{CH}_3)_2\text{CHOH}:\text{THF}:\text{H}_2\text{O}$ (4:1:1), 60 °C, 1 h; PPTS (1.0 equiv), CH_2Cl_2 , MeOH, 25 °C, 12 h, 62% for 2 steps; d) **3** (1.0 equiv in THF-toluene 1:1, syringe-pump slow addition), MNBA (2.0 equiv), DMAP (6.0 equiv), 4 Å MS, toluene, 60 °C, 20 h; NaBH_4 (3.0 equiv), $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ (10.0 equiv), MeOH, -20 °C, 30 min, 70% for 2 steps, *d.r.* 2:1; e) TBAF (10.0 equiv), AcOH (10.0 equiv), DMF, 25 °C, 12 h, 89%; f) TESOTf (10.0 equiv), 2,6-lutidine (20 equiv), CH_2Cl_2 , -78 °C, 30 min, 66%; g) PPTS (0.10 equiv), CH_2Cl_2 , MeOH, 25 °C, 30 min, 89%; h) $\text{SO}_3 \cdot \text{py}$ (2.0 equiv), $i\text{Pr}_2\text{NEt}$ (6.0 equiv), CH_2Cl_2 , DMSO, 25 °C, 30 min, 81%; i) **4** (2.0 equiv), $\text{Ba}(\text{OH})_2$ (0.5 equiv), THF, H_2O , 25 °C, 2 h, 65%; j) $[\text{CuH}(\text{PPh}_3)]_6$ (1.0

equiv), benzene, 25 °C, 8 h, 87%; k) TASF (5.0 equiv), DMF, 25 °C, 8 h, 70%; l) TEMPO (0.10 equiv), PhI(OAc)₂ (2.0 equiv), CH₂Cl₂, 25 °C, 4 h, 74%; m) HN(Me)CHO (20 equiv), PPTS (0.14 equiv), 4 Å MS, C₆H₆, 80 °C, 8 h, 78%. MNBA = 2-methyl-6-nitrobenzoic anhydride, TBAF = tetra-*n*-butylammonium fluoride, py = pyridine, DMSO = dimethylsulfoxide, TASF = tris(dimethylamino)sulfonium difluorotrimethylsilicate.