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The biomimetic synthesis of SNF4435C and SNF4435D, and the total synthesis of the polyene metabolites aureothin, *N*-acetyl-aureothamine and spectinabilin

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Abstract—Full details of the biomimetic conversion of polyene metabolite spectinabilin (**5**) into the isomeric natural products SNF4435C (**1**) and SNF4435D (**2**) by a cascade of *E*/*Z*-isomerizations and electrocyclizations are reported. Additionally, short total syntheses of the related natural products (±)-aureothin (**3**), (±)-*N*-acetyl-aureothamine (**4**) and (±)-spectinabilin (**5**) are presented. The key steps in the synthesis of (±)-**3**, (±)-**4** and (±)-**5** are the construction of the tetrahydrofuran motif using a palladium-catalyzed cycloaddition and the ruthenium-catalyzed cross metathesis of alkene **17** to form the common intermediate, boronic ester **24**, which was further transformed using a trans-selective Suzuki coupling with a dibromide and a stereospecific Negishi-type methylation.
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1. Introduction

In recent years, a plethora of polypropionates metabolites have been isolated from various terrestrial and marine systems as phylogenetically diverse as bacteria and sponges. Several of these compounds not only feature interesting biological activities, including immunosuppression, cytotoxicity and antibacterial effects, but also possess structurally interesting and complex motifs. Our continued interest in polypropionate natural products and biomimetic synthesis motivated us to consider the recently isolated nitrophenyl pyrones SNF4435C (**1**) and SNF4435D (**2**) reported by Snow Brand Milk Products Co., Ltd, Japan as targets for synthesis (Fig. 1).[1–3]

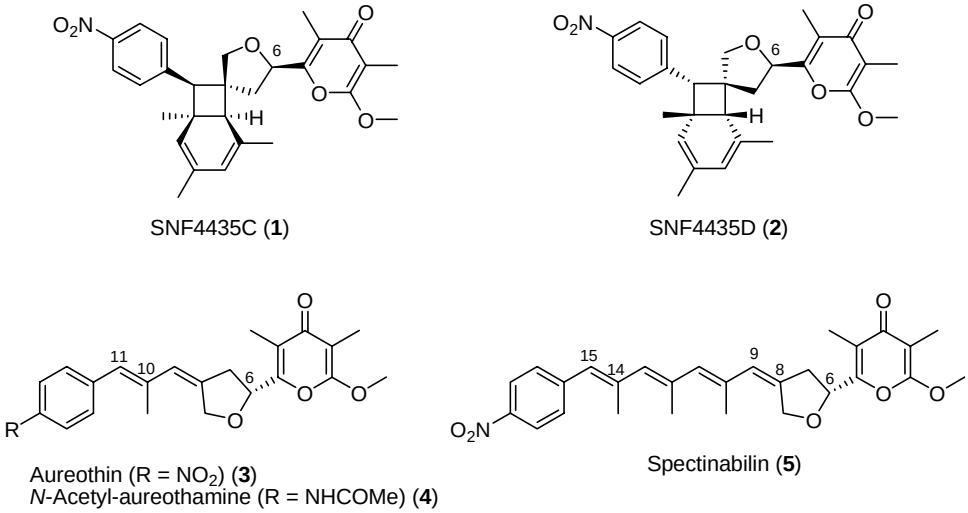

Figure 1. Metabolites from Streptomyces.

Keywords: Metabolite; Total synthesis; Metathesis; C–C coupling reaction; Biomimetic synthesis; Electrocyclization; Isomerization.
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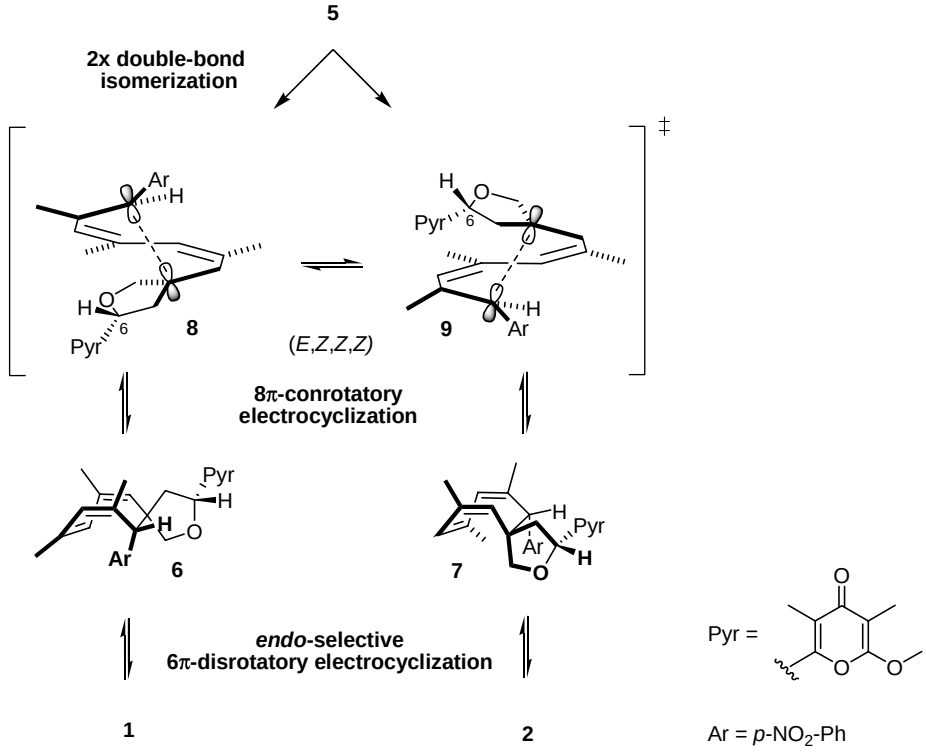
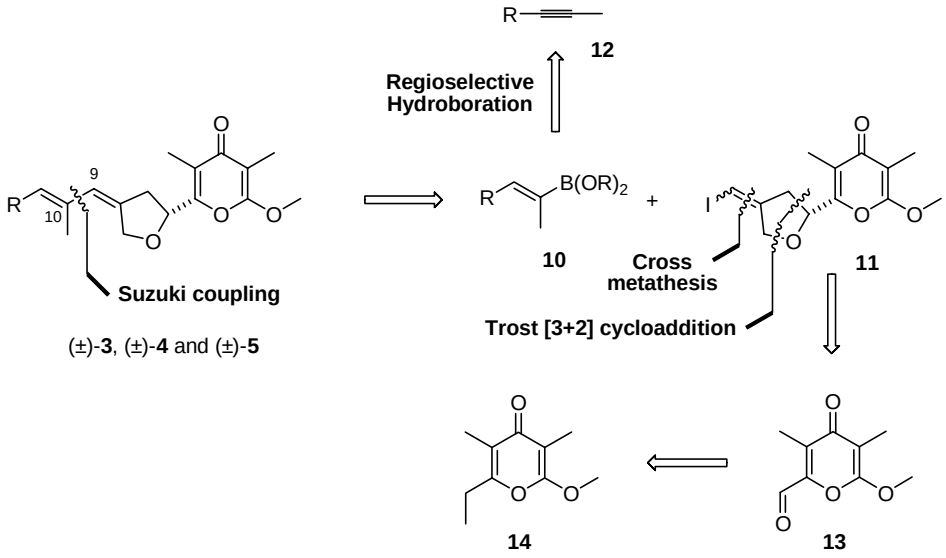
Biologically, the SNF compounds are potent immunosuppressants, exhibiting activities at submicromolar concentrations, isolated from a strain of *Streptomyces spectabilis* found in a soil sample collected on the main island of Okinawa, Japan. Structurally, the SNF compounds are pentacyclic structures featuring a rare hexasubstituted bicyclo[4.2.0] core connected to a spirofuran unit, which in turn is linked to a γ-pyrone moiety. The tetrahydrofuran ring-substituted γ-pyrone motif is also found in the related polyenes aureothin (**3**) (*Streptomyces thioluteu*),[4,5] *N*-acetyl-aureothamine (**4**) (*Streptomyces netropsis*)[6] and spectinabilin (**5**) (*S. spectabilis*).[7–9] *N*-Acetyl-aureothamine (**4**) has been shown to be a highly selective agent against *Helicobacter pylori*, a common cause of chronic gastritis.[6] Recently, studies on the biosynthesis of **3** have revealed that two novel oxygenases are involved.[10,11] An *N*-oxygenase catalyzes the oxidation of *p*-aminobenzoate to the corresponding nitro compound, which serves as starter unit for the polyketide synthase (PKS) resulting in **3**.[10] Secondly, a cytochrome P450 monooxygenase catalyzes the formation of the exomethylene tetrahydrofuran ring.[11] The biosynthesis of **5** is likely to proceed in a similar manner.[12]

It is apparent that spectinabilin (**5**) is a constitutional isomer of **1** and **2**. Interestingly, it has been isolated from the same actinomycete producing the SNF compounds.[3] These observation have led us[13,14] and others[15,16] to propose a biogenetic hypothesis for the transformation of **5** into **1** and **2**,[17] resembling Black's hypothesis for the formation of the endiandric acids,[18] which has been experimentally corroborated by the work of Nicolaou.[19] We envisaged that **1** and **2** could be formed from **5** via a cascade of *E*/*Z*-isomerizations and electrocyclisations. Firstly, the (*E*,*E*,*E*,*Z*)-configuration of **5** could be changed to (*E*,*Z*,*Z*,*Z*) via double *E* to *Z* isomerization. Secondly, the transformed (*E*,*Z*,*Z*,*Z*)-isomer of **5** could undergo a thermally allowed conrotatory 8π-electrocyclization with some bias towards **6** versus **7** via 1,3-asymmetric induction from the C6-stereocenter, followed by an *endo*-selective disrotatory 6π-electrocyclization to form **1** and **2** (Scheme 1). The transition structures **8** and **9** may possess a helical geometry in accord with studies of conrotatory 8π-electrocyclizations using ab initio molecular orbital theory.[20]

In the course of this work, Parker and co-workers have synthesized (−)-**1** and (+)-**2**, both of approximately 70% ee, by forming the (*E*,*Z*,*Z*,*Z*)-isomer in situ via a Stille coupling.[16] Similarly (−)-aureothin (**3**) of 27% ee has previously been synthesized,[21] but the approach employed lacked efficiency (0.01% overall yield) and we believed that it would not be compatible with the more complex tetraene **5**. In order to achieve the synthesis of tetraene **5**, we initially chose the simpler dienes **3** and **4** as model systems.[22] It is reported that both **3**[21] and **5**[9] are prone to racemization even under mild conditions due to the labile C6-proton. Accordingly, any intermediate bearing similar allylic proton(s) in the γ-position to the ketone of a γ-pyrone motif may suffer from such racemization/epimerization. Therefore, we chose instead to devise novel synthesis of (±)-**3**, (±)-**4** and (±)-**5**. We have previously communicated our main findings in these synthetic endeavors and in the biomimetic conversion of **5** to **1** and **2**.[14,22] We now report full details of these studies.



Scheme 1. Biogenetic hypothesis for the formation of **1** and **2** from **5**.

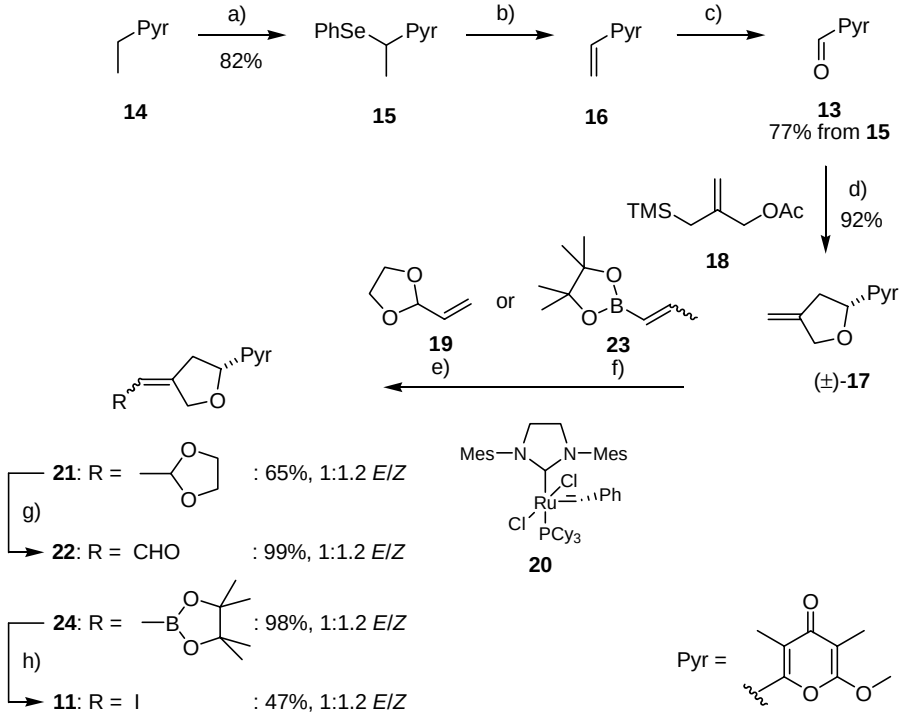


Scheme 2. First retrosynthesis of (±)-**3**, (±)-**4** and (±)-**5**.

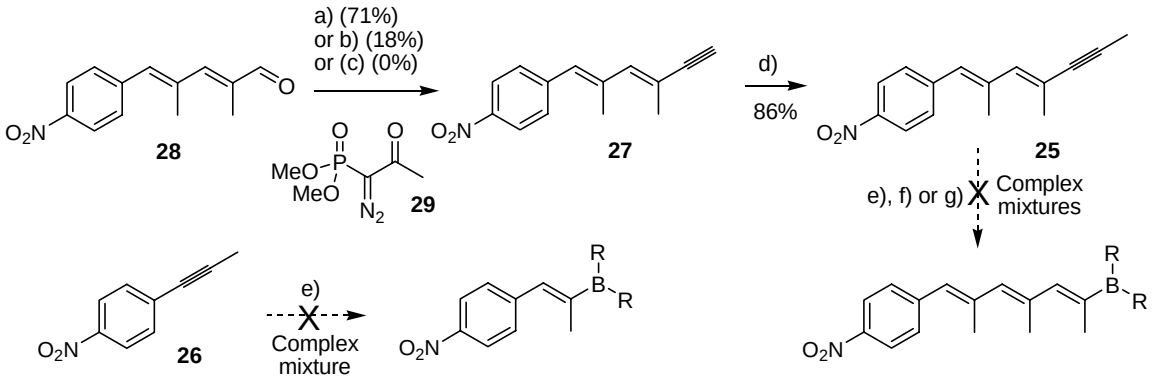
2. Results and discussion

2.1. Synthesis of key boronic ester 24 and initial synthetic studies towards (±)-3, (±)-4 and (±)-5

Our initial retrosynthetic analysis of the polyenes **3**–**5** revealed that the C9–C10 double bond may be formed from the Suzuki coupling of boronic ester **10** with the advanced intermediate, alkenyl iodide **11** (Scheme 2). The former would be formed by regioselective hydroboration of alkyne **12**. We believed that subjection of known aldehyde **13**[21,23] to a sequence of Trost [3+2] cycloaddition, cross metathesis (CM) and iodination should furnish **11**. Our synthesis of **11** started from ethyl pyrone **14**, which was converted to the phenylselenyl compound **15**, and oxidation–elimination of **15** yielded the unstable alkene **16** (Scheme 3). **16** was subjected to the Lemieux–Johnson protocol[24] to afford aldehyde **13** in excellent overall yield (63% from **14**). This route to **13** is a considerable improvement compared to the previously reported route.[23] We were pleased to find that aldehyde **13** reacted smoothly with the palladium-bound trimethylenemethane complex generated from 2-[(tributylstannyl)methyl]-2-propen-1-yl acetate and $Pd(OAc)_2/PPh_3$ to afford the alkene **17** in 88%



Scheme 3. Synthesis of tetrahydrofuran fragments **11** and **24**. (a) KHMDS, PhSeBr, THF, −78 °C→rt; (b) $NaIO_4$, cat. $NaHCO_3$, aq MeOH, rt; (c) cat. OsO_4, $NaIO_4$, aq THF, rt; (d) **18**, 5 mol% $Pd(PPh_3)_4$, 10 mol% $In(acac)_3$, PhMe, reflux; (e) **19** (3.0 equiv), 5 mol% **20**, CH_2Cl_2, reflux; (f) **23** (2.0 equiv), 5 mol% **20**, CH_2Cl_2, reflux; (g) PTSA, acetone–H_2O, rt; (h) I_2, aq NaOH, THF, rt.



Scheme 4. Synthesis of alkyne **25** and attempted hydroborations of **25** and **26**. (a) $TMSCHN_2$, LHMDS, THF, −78 °C; (b) $Ph_3PCHBr^+Br^-$, KO′Bu, THF, −78 °C; (c) **29**, K_2CO_3, MeOH, rt; (d) LHMDS, MeI, rt; (e) catecholborane, neat, 70 °C; (f) 9-BBN; (g) pinacolborane.

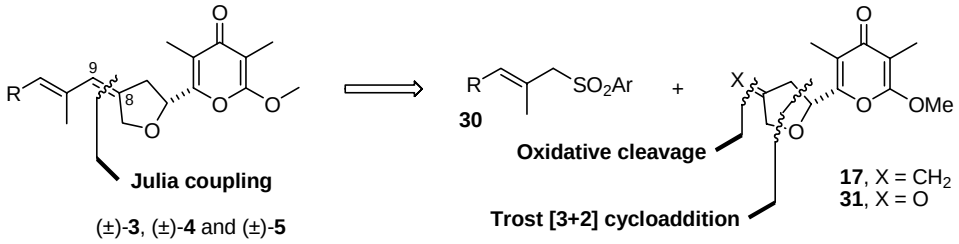
yield.[25] A minor improvement in yield (93%) was observed by employing the silyl acetate **18** instead and $In(acac)_3$ as co-catalyst.[26] Pleasingly, the sequence **14**→**17** can be performed without column chromatography; simple crystallizations of the crude products from CH_2Cl_2-pentanes is sufficient.

The recent report of 1,1-disubstituted alkenes as excellent substrate for CM with alkenyl boronic esters led us to attempt such transformations with **17**.[27] Initially, we attempted the CM with **19** and catalyst **20**. In our hands, this led to a good yield of acetal **21** provided that **19** was added slowly to the reaction mixture to suppress homodimerisation of itself. Treatment of acetal **21** with PTSA smoothly furnished **22**, a potentially useful building block. On the other hand, boronic ester **23** reacted with **17** without the need for slow addition and furnished **24** in almost quantitative yield, albeit with low *E*/*Z*-selectivity.[28] The stereochemistry of (*E*)-**24** and (*Z*)-**24** was confirmed by NOE experiments. **24** could easily be converted to the required iodides **11** in 47% yield (14% recovered **24**) with retention of the *E*/*Z* ratio (1:1.2 *E*/*Z*) upon treatment with I_2 and NaOH in aq THF.[27a]

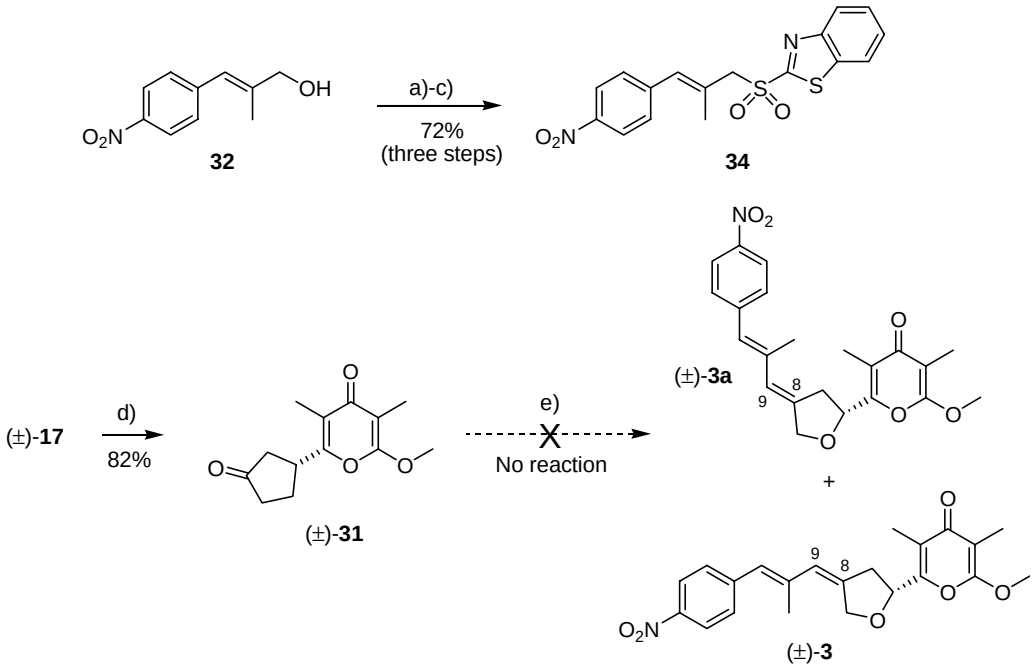
Next, we turned our attention towards the hydroboration of the alkynes **25** and **26**[29] (Scheme 4). Initially, alkyne **27** was synthesized by reacting known aldehyde **28** with the lithium anion of $TMSCHN_2$.[30] The use of a Wittig dehalogenation procedure instead furnished a lower yield (18%) of **27**,[31] while employing the Ohira reagent **29**[32] only led to the decomposition of **28**. Subsequently, facile methylation of **27** provided **25**. To our disappointment, the hydroboration of either **25** or **26** under a variety of conditions proved fruitless, as this only led to intractable tarry product mixtures. Instead, we decided to evaluate a modified Julia coupling of sulfone **30** with (±)-aureonone **31** for the disconnection of the C8–C9 double bond in (±)-**3**, (±)-**4** and (±)-**5** (Scheme 5). The known alcohol **32** reacted with MsCl and Et_3N to afford a mesylate **33**, which was then efficiently converted to sulfone **34** [substitution of **33** with the sodium anion of 2-mercaptobenzothiazole to the yield a sulfide **35**, followed by ammonium molybdate-mediated oxidation to **34**].[33] (±)-Aureonone **31** was easily obtained from alkene (±)-**17** by oxidative cleavage with OsO_4/$NaIO_4$, and the spectral data (IR, ^1H and ^{13}C NMR) were in excellent agreement with those previously reported.[21] Unfortunately, treatment of the lithium anion of sulfone **34** with aureonone **31** did not provide detectable amounts of **3** and/or **3a** presumably due to the stability of the anion of **34**. We were therefore impelled to consider alternative pathways to (±)-**3**, (±)-**4** and (±)-**5** (Scheme 6).

2.2. Completion of the synthesis of (±)-aureothin (3), (±)-*N*-acetyl-aureothamine (4) and (±)-spectinabilin (5)

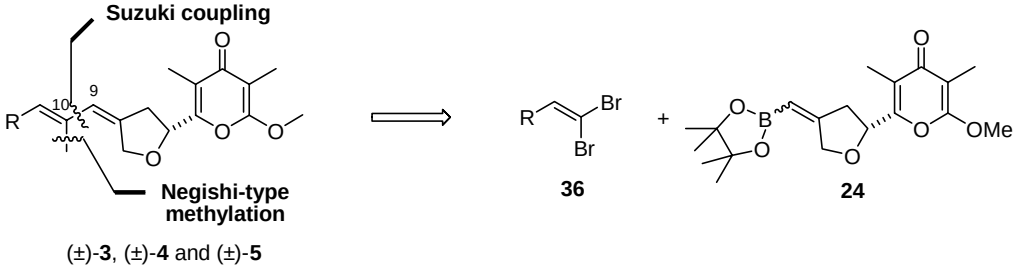
Since we had already established an efficient route to **24**, the use of it in a trans-selective Suzuki coupling with a dibromide **36** to form the C9–C10 double bond followed by a Negishi-type methylation seemed an attractive approach to (±)-**3**, (±)-**4** and (±)-**5** (Scheme 7). Therefore, the Suzuki coupling of **24** and **37**[34] was examined under the influence of various bases (Scheme 8 and Table 1). While NaOH afforded exclusively the dehydrohalogenated product, alkyne **38** (entry 1), Tl_2CO_3 gave rise to a mixture of products, **38**, **39** and **40** (entry 2). Gratifyingly, the use of TlOEt afforded (*E*)-**40** and (*Z*)-**40** as a separable mixture of isomers (1:1.2 *E*/*Z*) in 72% yield (entry 3).[35] The stereochemistry of the C9–C10 double-bond of (*Z*)-**40**,



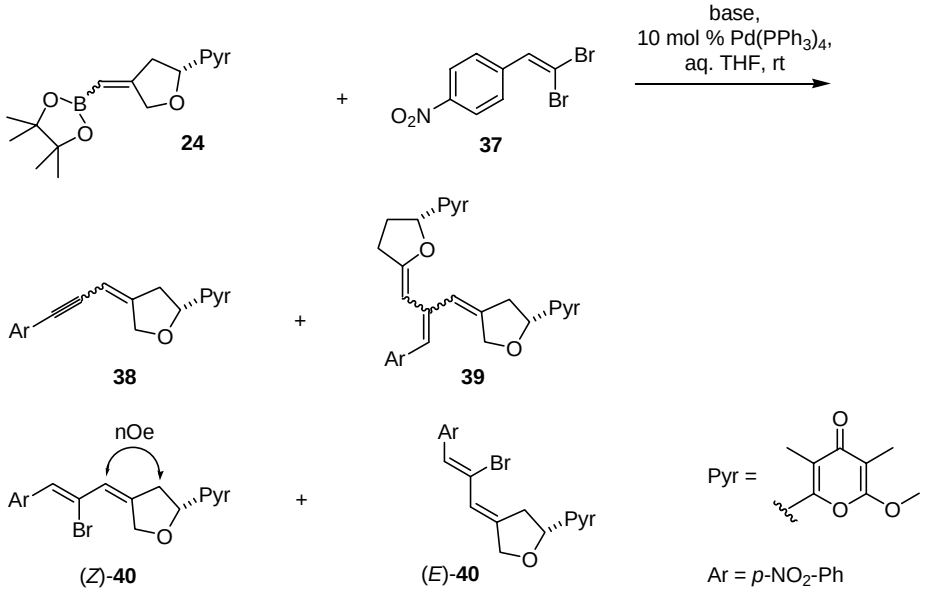
Scheme 5. Second retrosynthesis of (±)-**3**, (±)-**4** and (±)-**5**.



Scheme 6. Synthesis of Julia–Kocienski fragment **34** and (±)-aureonone **31**, and attempted Julia–Kocienski coupling to form (±)-**3** and/or (±)-**3a**. (a) MsCl, Et_3N, CH_2Cl_2, −10→−15 °C; (b) 2-mercaptobenzothiazole, NaH, DMF, 0 °C→rt; (c) $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$, H_2O_2, EtOH:THF, 0 °C→rt; (d) OsO_4, $NaIO_4$, aq THF, rt; (e) LHMDS, **34**, THF, −78 °C→rt.



Scheme 7. Third retrosynthesis of (±)-**3**, (±)-**4** and (±)-**5**.



Scheme 8. Influence of base on Suzuki coupling of **24** with **37** (see Table 1).

Table 1. Influence of base on the Suzuki coupling of **24** with **37** (see Scheme 8)[a,b,c]

Entry	Base (equiv)	Yield **38** (%)	Yield **39** (%)	Yield **40** (%)
1	NaOH (1.5)	70	—	—
2	Tl_2CO_3 (1.5)	20	20	20
3	TlOEt (1.8)	—	—	72

[a] The ratio of **38**, **39** and **40** was determined by ^{1}H NMR analysis of the crude product.
[b] Compounds **38** and **40** were obtained as 1:1.2 *E*/*Z* mixtures of isomers.
[c] Compound **39** was obtained as a mixture of isomers.

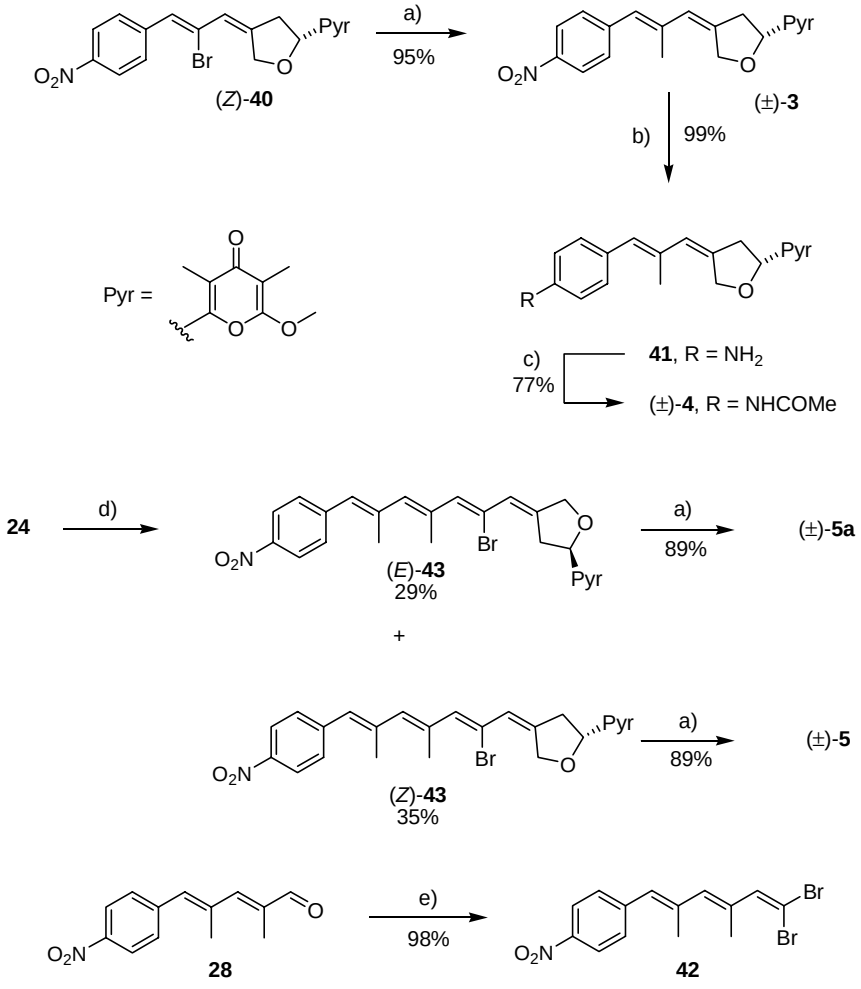
was confirmed by a NOESY experiment. The precursor (*Z*)-**40** of (±)-aureothin (**3**) was methylated under the recently reported Negishi-type conditions (cat. Pd(^{t}Bu$_3$P), Me_2Zn) to afford (±)-**3** in excellent yield with complete retention of stereochemistry (Scheme 9).[36] (±)-**3** was subjected to Zn-mediated reduction under aqueous conditions to furnish pure (±)-aureothamine (**41**) in high yield,[4] which was then acetylated to afford the antibiotic (±)-*N*-acetyl-aureothamine (**4**).[6] The spectral data for (±)-**3**[21] and (±)-**4**[6] (IR, ^{1}H and ^{13}C NMR) were in excellent agreement with those previously reported.

In a similar manner boronic ester **24** was subjected to Suzuki coupling with dibromide **42** (made from aldehyde **28**[37]) to afford the isomers (*E*)-**43** and (*Z*)-**43** in a combined yield of 64%, which could be separated by silica gel chromatography. The light sensitive (*Z*)-**43** reacted smoothly with Me_2Zn under palladium catalysis to yield (±)-spectinabilin (**5**) in 89% yield, while (*E*)-**43** was converted to **5a**, the (*E*,*E*,*E*,*E*)-isomer of **5**. (±)-**5** exhibited identical ^{1}H NMR spectra to that of an authentic sample, and the spectral data (^{1}H, ^{13}C NMR and IR) were in excellent agreement with those previously reported.[7] The previously tentative assignment[7] of the (*E*,*E*,*E*,*Z*)-geometry to **5** was confirmed by 1D NOE experiments.

2.3. The biomimetic conversion of (±)-5 to (±)-1 and (±)-2

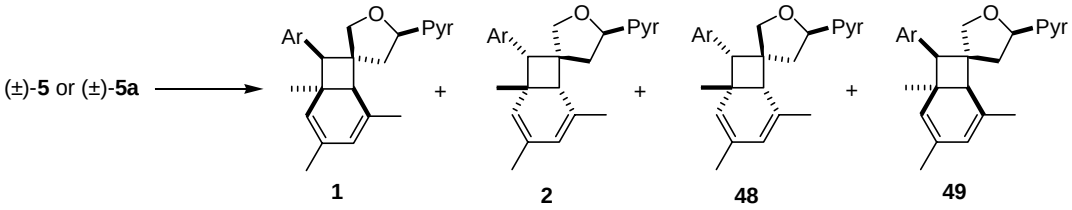
Since we were not aware of the specific conditions by which Nature might convert **5** to **1** and **2**, we examined three types of reaction conditions in attempts to affect the required *E*/*Z* isomerizations and initiate the cascade of electrocyclizations in vitro: light, heat and a Pd(II) source.

During initial exposure of **5** to sunlight in solution, it underwent *E* to *Z* isomerization of the C14–C15 double bond as observed by ^{1}H NMR. The same is true for the C10–C11 double bond in aureothin (**3**). Unfortunately, prolonged exposure of (±)-**5** in solution to sunlight resulted ultimately in very complex product mixtures in which neither **1** nor **2**



Scheme 9. Completion of the total synthesis of (±)-**3**, (±)-**4** and (±)-**5**. (a) Me_2Zn, 2 mol% Pd(^{t}Bu$_3$P)$_2$, THF, rt; (b) Zn, NH_4Cl, aq acetone, rt; (c) AcCl, pyridine, CH_2Cl_2, 0 °C; (d) **42**, 10 mol% $Pd(PPh_3)_4$, TlOEt, aq THF, rt; (e) CBr_4, Zn, PPh_3, pyridine, CH_2Cl_2, rt.

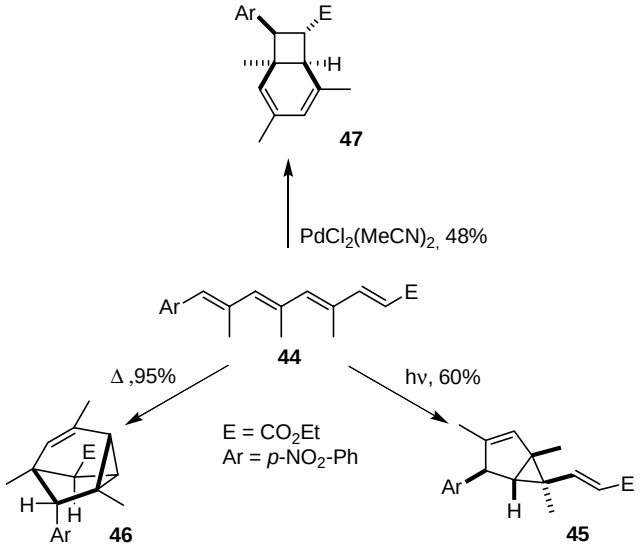
Table 2. Synthesis of (±)-SNF4435C (**1**), (±)-SNF4435D (**2**) and isomers **48** and **49** from (±)-**5** and (±)-**5a**[a,b]



Entry	Substrate	$PdCl_2(MeCN)_2$ (Mol%)	Temperature (°C)	Ratio/**1**:**2**:**48**:**49**[c]	Yield (%)
1	**5**	0	70	3.6:1.0:0:0	23
2	**5**	25	20	4.5:1.0:4.5:1.7	<5[d]
3	**5**	25	70	2.8:1.1:2.1:1.0	40
4	**5**	25	50	3.9:1.0:2.8:1.2	nd
5	**5**	25	110	2.9:1.0:2.0:1.1	nd
6	**5**	100	70	nd	~0
7	**5a**	25	70	2.0:1.0:5.7:3.0	31

[a] Reactions were performed in DMF in the dark.
[b] nd, not determined.
[c] Ratio of **1**, **2**, **48** and **49** was determined from analysis of ^{1}H NMR spectra of crude product.
[d] Estimated from analysis of ^{1}H NMR spectra of crude product.

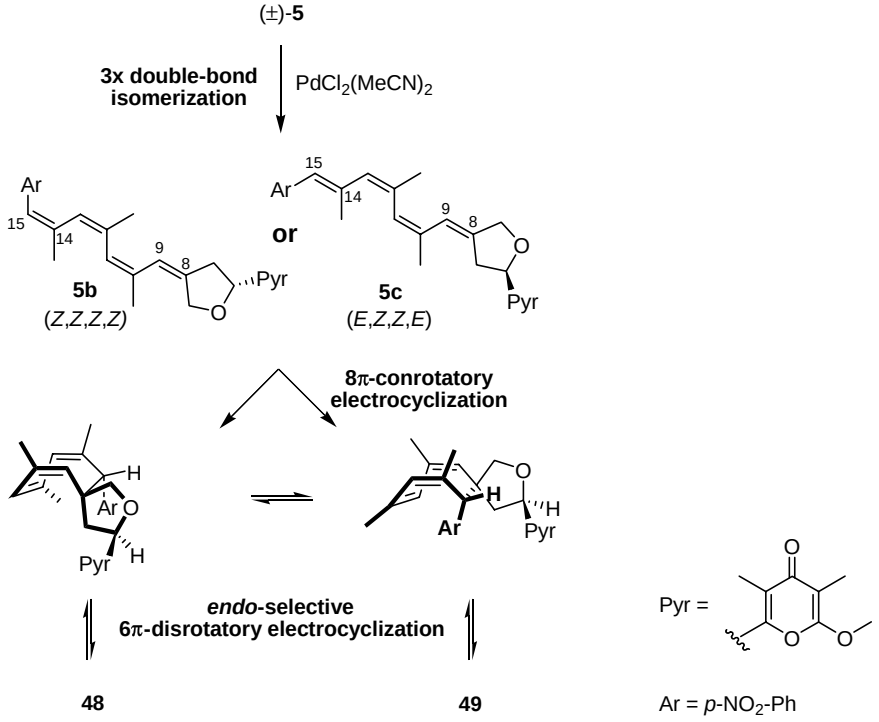
could be detected by ^{1}H NMR. On the other hand, heating a solution of (±)-**5** in DMF at 70 °C for 3 days resulted in 23% of (±)-**1** and (±)-**2** as a 3.6:1 mixture after extensive purification by preparative TLC (Table 2, entry 1). Interestingly, the related tetraene **44** having an electron-withdrawing ester group behaved differently (Scheme 10). The crispatene core structure **45** was produced when **44** was subjected to light, while heat afforded the tricyclic structure **46** in high yield (Scheme 10).[37,38]



Scheme 10. Cascade electrocyclization pathways of tetraene ester **44**.

Previous results in our group have demonstrated that the bicyclo[4.2.0]octadiene core of **1** and **2** can be obtained from (*E*,*E*,*E*,*E*)-tetraenes by employing a palladium(II) source ($PdCl_2(MeCN)_2$) for the requisite *E* to *Z* isomerization, that is, (*E*,*E*,*E*,*E*) to (*E*,*Z*,*Z*,*E*), exemplified by the conversion of **44** to **47** in 48% yield.[13,37,38] However, when **5** was subjected to the standard conditions at rt only small amounts of **1** and **2** could be detected, suggesting that the *E*/*Z*-isomerizations were too slow at this temperature (entry 2). By varying both the catalyst loading and temperature, we found the best conditions to involve heating a solution of **5** in DMF with 25 mol% $PdCl_2(MeCN)_2$ at 70 °C for 1 day in the dark (entry 3). This afforded 22% of (±)-SNF4435C (**1**) and (±)-SNF4435D (**2**) in a slightly different ratio of 2.5:1 compared to that resulting from heating alone (entry 1 vs 3). Surprisingly, 18% of two unexpected isomers **48** and **49** could also be isolated in a 2.1:1 ratio from the reaction mixture. Apparently, their formation is intrinsically related to the use of the Pd(II) source, as neither **48** nor **49** could be detected by heating alone. Lower temperatures led to a more complex reaction mixture (entry 4), whereas elevated temperatures or higher catalyst loading led to increased decomposition (entries 5 and 6). Also, the individual ratios **1**:**2** and **48**:**49** decreased with increasing temperature, while the overall ratio of **1** and **2** to **48** and **49** remained nearly constant (entries 2–4). Interestingly, the ratios of **1** and **2** are close throughout to that found in Nature (2.3:1),[2a] thus supporting our biogenetic hypothesis for their formation. The 1,3-diastereoselection induced from the C6-stereocenter in the 8π-electrocyclization step is almost of the same magnitude for **48** and **49** compared to **1** and **2**, resulting in roughly equal ratios **1**:**2** and **48**:**49**.

The formation of **48** and **49** is consistent with the 8π/6π-electrocyclization cascade of either of the (*Z*,*Z*,*Z*,*Z*)- and (*E*,*Z*,*Z*,*E*)-isomers, **5b** and **5c** (Scheme 11). We have not observed this 'over-isomerization' previously with similar tetraenes, for example, **44**.[13,37] X-ray structures have indicated a lack of planarity of the polyene backbone of structures similar to **5**, for example, **44**, presumably due to 1,3-steric interactions between the methyl groups.[37] Firstly, such interactions for the reactive (*E*,*Z*,*Z*,*Z*)-isomer of **5** may be partly relieved in conformations like **8** and **9** thus facilitating the subsequent cascade of electrocyclizations (Scheme 1). Secondly, it should lead to a decrease in the



Scheme 11. Mechanistic rationale for the formation of isomers **48** and **49**.

conjugation of the C8–C9 double bond with the electron deficient *p*-nitrophenyl ring. The more electron-rich C8–C9 double bond is expected to be more prone to isomerizations with the cationic palladium moiety versus the C14–C15 double bond.[39] Hence, we favor that **48** and **49** may be formed predominately via the (*E*,*Z*,*Z*,*E*)-isomer **5c**. In support of this was the observation that subjection of the (*E*,*E*,*E*,*E*)-isomer **5a** to the Pd(II) conditions provided 23% of a 1.9:1 mixture of **48** and **49** and minor amounts of **1** and **2** (8%) (entry 7).

3. Conclusion

We have developed short and efficient synthesis of the metabolites (±)-aureothin (**3**), (±)-*N*-acetyl-aureothamine (**4**) and (±)-spectinabilin (**5**) by using several palladium-catalyzed reactions to assemble the congested polyene structures (23, 17, and 18% overall yield, respectively, from ethyl pyrone **14**). In addition, the key boronic ester **24** was synthesized via ruthenium-catalyzed cross metathesis of alkene **17**. Alternative routes to (±)-**3**, (±)-**4** and (±)-**5** via hydroboration or a modified Julia coupling proved ineffective. The successful biomimetic conversion of spectinabilin (**5**) to SNF4435C (**1**) and SNF4435D (**2**) shows that our biogenetic hypothesis connecting these natural products is chemically viable. The isolation of the isomers **48** and **49** was demonstrated to be a side effect of the Pd(II) conditions employed for the *E*/*Z*-isomerizations. Due to the lower efficiency of the biomimetic conversion and the general complexity of the product mixtures, we can only speculate that Nature uses efficient enzyme-mediated *E*/*Z*-isomerizations of **5**, which the subsequent cyclization cascade may benefit from as well.[40]

4. Experimental

4.1. General experimental

Unless otherwise stated, all reactions were carried out under nitrogen. Tetrahydrofuran (THF) and dichloromethane (CH_2Cl_2) were dried by passing through activated alumina columns. *N*,*N*-dimethylformamide (DMF) was dried over 3 Å molecular sieves. Pentanes of bp 30–40 °C were used exclusively. All reagents were purchased at the highest commercial quality and used without further purification. NMR spectra were recorded at 200, 400 or 500 MHz (^{1}H NMR), and calibrated to the residual solvent peak. The following abbreviations are used for NMR data: s, singlet; d, doublet; t, triplet; qn, quintet; m, multiplet; br, broad; app, apparent. Coupling constants are rounded to nearest 0.5 Hz. The following abbreviations are used for IR data: s, strong; m, medium; w, weak; br, broad. Room temperature (rt) is 22 °C. Column chromatography was carried out using Sorbsil C60 (40–63 mm, 230–240 mesh) silica gel. Preparative thin-layer chromatography was performed on Whatman precoated silica gel $60_{F\text{-}254}$ glass-supported plates with 1.0 mm thickness. Reactions were monitored by thin-layer chromatography (TLC) analysis. Spots were visualized by exposure to ultraviolet (UV) light (254 nm), or by staining with a 5% solution of phosphomolybdenic acid (PMA) in ethanol or basic aq potassium permangante ($KMnO_4$) and then heating. Crystallization solvents are in parenthesis. Melting points are uncorrected. All compounds synthesized were determined to be >95% pure by ^{1}H NMR. Compounds **14**,[41] **23**,[27] **26**,[29] **28**,[37] **32**[37] were prepared according to literature procedures.

4.1.1. (±)-2-Methoxy-3,5-dimethyl-6-(1-(phenylselenyl)-ethyl)-4*H*-pyran-4-one (15). To a solution of THF (20 mL) containing γ-pyrone **14**[41] (1.50 g, 8.23 mmol) at −78 °C

was added slowly a solution of KHMDS (19.8 mL, 0.5 M in toluene, 9.90 mmol) with stirring. The resulting solution was allowed to stir for 30 min at −78 °C after which time the reaction had developed a bright orange-red color. A solution of phenyl selenium bromide (2.34 g, 9.9 mmol) in THF (5 mL) was then added dropwise, and the reaction mixture was allowed to warm to rt over the course of 1 h. Satd aq NH_4Cl (30 mL) was added, and the aqueous layer was extracted with EtOAc three times. The combined organics were washed with brine and dried over $MgSO_4$, and the solvent was removed by evaporation in vacuo. The residue was subjected to column chromatography (pentanes/EtOAc, gradient elution) to give **15** as a white solid (2.28 g, 82%). Mp 103–105 °C (CH_2Cl_2/pentanes); R_f=0.4 (1:1 pentanes/EtOAc); IR (KBr) 1660 (s), 1618 (m), 1592 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.63 (s, 3H), 1.72 (t, J=7.0 Hz, 1H), 1.83 (s, 3H), 3.81 (s, 3H), 4.41 (q, J=7.0 Hz, 1H), 7.21–7.26 (m, 2H), 7.31–7.37 (m, 1H), 7.47–7.50 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 6.9, 9.6, 18.4, 36.1, 55.1, 99.2, 117.8, 127.3, 129.1 (3C), 136.8 (2C), 157.1, 161.7, 180.5; HRMS (ESI) *m/e* calcd for $C_{16}H_{19}O_3{}^{80}Se$ (MH^+) 339.0499, found 339.0489.

4.1.2. 2-Methoxy-3,5-dimethyl-6-vinyl-4*H*-pyran-4-one (16). To a solution of phenylselenyl pyrone **15** (4.22 g, 12.5 mmol) in MeOH (90 mL) and H_2O (57 mL) was added a catalytic quantity of $NaHCO_3$ followed by $NaIO_4$ (5.35 g, 25.0 mmol) at rt. The resulting mixture was stirred for 1 h at rt. The methanol was removed by evaporation in vacuo, and the aqueous layer was extracted twice with CH_2Cl_2. The combined organics were dried over $MgSO_4$ and evaporated to dryness to yield a light yellow solid. The resulting crude alkene **16** was carried on to the next step without further purification. A small amount was purified for characterization purposes by column chromatography (CH_2Cl_2/EtOAc, gradient elution) to yield **16** as a white solid. Mp 95–98 °C (CH_2Cl_2/pentanes); R_f=0.6 (1:1 pentanes/EtOAc); IR (KBr) 1657 (s), 1601 (m), 1572 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.86 (s, 3H), 2.03 (s, 3H), 4.02 (s, 3H), 5.53 (d, J=11.0 Hz, 1H), 5.93 (d, J=17.0 Hz, 1H), 6.71 (dd, J=11.0, 17.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 6.9, 9.5, 55.3, 99.7, 119.0, 119.4, 126.6, 151.3, 161.8, 181.0; HRMS (ESI) *m/e* calcd for $C_{10}H_{13}O_3$ (MH^+) 181.0865, found 181.0865.

4.1.3. 6-Methoxy-3,5-dimethyl-4-oxo-4*H*-pyran-2-carbaldehyde (13).[21,24] To a solution of crude alkene **16** (see above) in THF–H_2O (1/1 v/v, 180 mL) was added $NaIO_4$ (5.35 g, 25.0 mmol) followed by the slow addition of OsO_4 (1.9 mL, 4% w/w in H_2O, 0.31 mmol). The resulting mixture was stirred for 1 h at rt. The THF was removed by evaporation in vacuo, and the remaining aqueous phase was extracted twice with CH_2Cl_2. The combined organics were dried over $MgSO_4$, and evaporated to dryness in vacuo. The crude aldehyde was purified by crystallization from CH_2Cl_2-pentanes to yield **13** (1.76 g, 77% for two steps) as a white, crystalline solid. Mp 143–145 °C (CH_2Cl_2/pentanes); R_f=0.45 (1:1 CH_2Cl_2/EtOAc); IR (KBr) 1694 (s), 1648 (s), 1590 (s), 1174 (s); ^{1}H NMR (200 MHz, $CDCl_3$) δ_H 1.90 (s, 3H), 2.35 (s, 3H), 4.09 (s, 3H), 10.1 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ_C 7.1, 8.3, 55.8, 102.4, 130.3, 147.3, 162.3, 179.9, 182.9; HRMS (ESI) *m/e* calcd for $C_9H_{11}O_4$ (MH^+) 183.0657, found 183.0660.

4.1.4. (±)-2-Methoxy-3,5-dimethyl-6-(4-methylene-tetrahydrofuran-2-yl)-4*H*-pyran-4-one (17). A solution of $In(acac)_3$ (229 mg, 0.555 mmol) and $Pd(PPh_3)_4$ (321 mg, 0.278 mmol) in toluene (20 mL) was stirred for 10 min at rt. To the resulting yellow suspension was added a solution of aldehyde **13** (1.01 g, 5.54 mmol) in toluene (40 mL) and **18** (1.50 mL, 7.22 mmol). The reaction mixture heated at reflux for 5 h. The mixture was cooled to rt, and evaporated to dryness in vacuo. The residue was filtered through a pad of silica gel eluting with 1:1 CH_2Cl_2/EtOAc to afford (±)-**17** as a white solid, that was further purified by crystallization from CH_2Cl_2 with pentanes (1.21 g, 92%). Mp 115–117 °C (CH_2Cl_2/pentanes); R_f=0.3 (1:1 CH_2Cl_2/EtOAc); IR (KBr) 1667 (s), 1606 (s), 1458 (s), 1322 (s); ^{1}H NMR (200 MHz, $CDCl_3$) δ_H 1.83 (s, 3H), 2.01 (s, 3H), 2.71–2.98 (m, 2H), 3.93 (s, 3H), 4.42 (br d, J=13.0 Hz, 1H), 4.54 (br d, J=13.0 Hz, 1H), 5.02 (qn, J=2.0 Hz, 1H), 5.10 (qn, J=2.0 Hz, 1H), 5.18 (dd, J=6.5, 7.5 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ_C 6.8, 9.3, 35.9, 55.2, 71.7, 74.8, 99.7, 105.1, 119.7, 146.4, 155.0, 162.0, 180.5; HRMS (ESI) *m/e* calcd for $C_{13}H_{17}O_4$ (MH^+) 237.1127, found 237.1131.

4.1.5. (±)-(*E*)- and (±)-(*Z*)-2-(4-((1,3-Dioxolan-2-yl)-methylene)-tetrahydrofuran-2-yl)-6-methoxy-3,5-dimethyl-4*H*-pyran-4-one (21). To a solution of catalyst **20** (17 mg, 0.02 mmol) and pyrone (±)-**17** (95 mg, 0.40 mmol) in CH_2Cl_2 (2 mL) was added over a period of 3 h a solution of 2-vinyl-1,3-dioxolane (**19**) (120 μL, 1.20 mmol) in CH_2Cl_2 (3 mL) at reflux. The resulting solution was heated for a further 2 h at reflux, and then cooled to rt. The solvent was removed by evaporation in vacuo, and the residue was subjected to column chromatography (1:1 pentanes/EtOAc → EtOAc) to afford a 1:1.2 *E*/*Z* mixture of **21** (81 mg, 65%) as a viscous oil. R_f=0.35 (1:1 CH_2Cl_2/EtOAc); IR (film) 2930 (s), 1672 (s), 1664 (s), 1584 (br, s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.82 (s, 2×3H), 2.00 (s, 2×3H), 2.77–3.08 (m, 2×2H), 3.83–4.05 (m, 2×4H), 3.92 (s, 2×3H), 4.46 (d, J=13.5 Hz, 1H), 4.57 (d, J=14.5 Hz, 1H), 4.58 (d, J=13.5 Hz, 1H), 4.72 (d, J=14.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 6.9 (2C), 9.4 (2C), 32.4, 36.3, 55.4 (2C), 64.9 (4C), 69.1, 71.9, 73.8, 75.1; HRMS (ESI) *m/e* calcd for $C_{16}H_{21}O_6$ (MH^+) 309.1338, found 309.1335.

4.1.6. (*E*)- and (*Z*)-2-(5-(6-Methoxy-3,5-dimethyl-4-oxo-4*H*-pyran-2-yl)-dihydrofuran-3(2*H*)-ylidene)acetaldehyde (22). To a solution of acetal **21** (432 mg, 1.40 mmol) in acetone (25 mL) was added water (200 μL) and *p*-toluenesulfonic acid (40 mg, 0.21 mmol). The resulting solution was stirred for 1 h. Satd aq $NaHCO_3$ (5 mL) was added, and the acetone was removed in vacuo. The aqueous phase was extracted with CH_2Cl_2 twice. The combined organic layers were washed with brine and dried over $MgSO_4$. Removal of the solvent in vacuo yielded pure **22** (366 mg, 99%) as 1:1.2 *E*/*Z* mixture and as an unstable oil, which required no further purification. R_f=0.45 (1:1 CH_2Cl_2/EtOAc); IR (film) 1665 (s), 1593 (s), 1266 (s) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ_H 1.83 (s, 3H), 1.84 (s, 3H), 2.96–3.51 (m, 2×2H), 3.88 (s, 3H), 3.90 (s, 3H), 4.63 (d, J=17.0 Hz, 1H), 4.78 (d, J=17.0 Hz, 1H), 4.87 (d, J=17.5 Hz, 1H), 5.09 (d, J=17.5 Hz, 1H), 5.23 (t, J=6.5 Hz, 1H), 5.32 (t, J=7.0 Hz, 1H), 6.09–6.15 (m, 1H), 6.26–6.32 (m, 1H), 9.70 (d, J=4.5 Hz, 1H), 9.85 (d, J=6.5 Hz, 1H);

^{13}C NMR (50 MHz, $CDCl_3$) δ_C 6.8 (2C), 9.4 (2C), 33.5, 37.2, 55.2, 55.3, 71.2, 72.4, 73.3, 75.4, 100.1 (2C), 119.8, 120.2, 120.5 (2C), 153.5 (2C), 162.0 (2C), 162.9, 163.2, 180.3 (2C), 189.3, 190.1; HRMS (ESI) *m/e* calcd for $C_{14}H_{17}O_5$ (MH^+) 265.1076, found 265.1079.

4.1.7. (±)-(*E*)- and (±)-(*Z*)-2-Methoxy-3,5-dimethyl-6-(4-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methylene)-tetrahydrofuran-2-yl)-4*H*-pyran-4-one (24). To a solution of alkene **17** (869 mg, 3.68 mmol) and alkenyl boronic ester **23**[27] (1.24 g, 7.36 mmol) in CH_2Cl_2 (5 mL) was added catalyst **20** (156 mg, 0.184 mmol). The resulting was heated at reflux for 3 h, cooled to rt and evaporated to dryness in vacuo. The residue was subjected to column chromatography (CH_2Cl_2/EtOAc, gradient elution) to afford **24** (1.31 g, 98%) as a 1:1.2 *E*/*Z* mixture and as an oil. R_f=0.35 (4:1 CH_2Cl_2/EtOAc); IR (film) 3054 (m), 2982 (s), 1665 (s), 1595 (s); ^{1}H NMR (200 MHz, $CDCl_3$) δ_H 1.22 (s, 2×3H), 1.23 (s, 2×6H), 1.25 (s, 2×3H), 1.82 (s, 3H), 1.83 (s, 3H), 2.00 (s, 3H), 2.01 (s, 3H), 2.77–3.22 (m, 2×2H), 3.89 (s, 3H), 3.90 (s, 3H), 4.45 (br d, J=14.5 Hz, 1H), 4.58 (br d, J=14.5 Hz, 1H), 4.58 (br d, J=15.5 Hz, 1H), 4.79 (d, J=15.5 Hz, 1H), 5.13–5.25 (m, 2H), 5.33 (qn, J=2.0 Hz, 1H), 5.45 (qn, J=2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 6.7 (2C), 9.2, 9.3, 24.5, 24.6 (2C), 24.6, 24.7 (4C), 35.8, 38.8, 55.0, 55.1, 72.0, 73.4, 73.7, 75.3, 83.0 (2C), 83.1 (2C), 95.6 (2C), 99.5 (2C), 119.5, 119.7, 154.9, 155.1, 161.9 (2C), 162.6, 163.2, 180.4, 180.5; HRMS (ESI) *m/e* calcd for $C_{19}H_{28}BO_6$ (MH^+) 363.1979, found 363.1975.

4.1.8. (*E*)- and (*Z*)-2-(4-(Iodomethylene)-tetrahydrofuran-2-yl)-6-methoxy-3,5-dimethyl-4*H*-pyran-4-one (11). To boronic ester **24** (362 mg, 1.0 mmol) in THF (2.5 mL) was added NaOH (1.0 mL, 3.0 M in H_2O, 3.00 mmol). The solution was stirred vigorously at rt for 10 min. The mixture was titrated with iodine (7.0 mL, 0.2 M in THF, 1.40 mmol) at such rate that only towards the end of addition was the mixture allowed to develop a persistent red color (~2 h). Satd aq sodium thiosulfate (0.5 mL) and water (4 mL) were added. The aqueous phase was extracted with CH_2Cl_2 twice and the combined organics were dried over $MgSO_4$. The solvent was removed in vacuo, and the residue was subjected to column chromatography (10:1→1:1 CH_2Cl_2/EtOAc) to afford **11** (169 mg, 47%) as a 1.2:1 *E*/*Z* mixture followed by recovered **24** (51 mg, 14%) both as clear oils. Data for **11**: R_f=0.3 (5:1 CH_2Cl_2/EtOAc); IR (film) 3054 (w), 2957 (w), 1664 (s), 1590 (s), 1467 (s), 1265 (s) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ_H 1.82 (s, 3H), 1.83 (s, 3H), 1.98 (s, 3H), 2.01 (s, 3H), 2.71–3.03 (m, 2×2H), 3.22 (s, 2×3H), 4.29–4.57 (m, 2×2H), 5.26 (dd, J=6.5, 7.5 Hz, 1H), 5.34 (dd, J=6.0, 7.5 Hz, 1H), 6.10–6.17 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ_C 6.8 (2C), 9.4 (2C), 37.9, 40.3, 55.4 (2C), 67.5, 68.2, 71.7, 74.1, 76.0, 76.1, 99.9 (2C), 119.9, 120.4, 149.8, 150.7, 154.1, 154.5, 162.0 (2C), 180.4 (2C); HRMS (ESI) *m/e* calcd for $C_{13}H_{16}IO_4$ (MH^+) 363.0093, found 363.0098.

4.1.9. 1-((1*E*,3*E*)-2,4-Dimethylhexa-1,3-dien-5-ynyl)-4-nitrobenzene (27). To a solution of LHMDS (6.0 mL, 1.0 M in THF, 6.00 mmol) in THF (25 mL) was added dropwise $TMSCHN_2$ (3.0 mL, 2.0 M in Et_2O, 6.00 mmol) at −78 °C. The resulting was stirred for 30 min, and then a solution of aldehyde **28**[36] (1.16 g, 5.00 mmol) in THF (20 mL) was added dropwise at −78 °C. The resulting mixture was stirred for 1 h at −78 °C, and allowed to warm slowly to rt. Satd aq NH_4Cl (10 mL) was added. The aqueous phase was extracted twice with CH_2Cl_2, and the combined organics were washed with brine and dried over $MgSO_4$. The solvent was removed in vacuo, and the residue was subjected to column chromatography (50:1 pentanes/EtOAc) to furnish **27** (802 mg, 71%) as a yellow paste. R_f=0.6 (9:1 pentanes/EtOAc); IR (KBr) 2283 (m), 1594 (m), 1514 (m), 1342 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 2.1 (s, 6H), 2.99 (s, 1H), 6.50 (s, 1H), 7.33 (s, 1H), 7.45 (d, J=8.5 Hz, 2H), 8.31 (d, J=8.5 Hz, 2H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ_C 19.2, 19.9, 77.0, 87.8, 119.8, 123.9 (2C), 130.0 (2C), 134.0, 138.7, 141.4, 144.5, 146.5; HRMS (CI(NH_3)) calcd for $C_{14}H_{17}N_2O_2$ (MNH_4^+) 245.1290, found 245.1286.

4.1.10. 1-((1*E*,3*E*)-2,4-Dimethylhepta-1,3-dien-5-ynyl)-4-nitrobenzene (25). To a stirred solution of alkyne **27** (773 mg, 3.40 mmol), in THF (20 mL), was added LHMDS (4.1 mL, 1.0 M solution in THF, 4.1 mmol) dropwise at rt. MeI (1.70 mL, 27.3 mmol) was added after 5 min. Water (10 mL) was added after another 10 min. The organic layer was separated, and the aqueous layer extracted with CH_2Cl_2 twice. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. Purification of the crude oil using column chromatography (50:1 pentanes/EtOAc) gave **25** as a yellow solid (707 mg, 86%). Mp 54–55 °C (CH_2Cl_2/pentanes); R_f=0.55 (9:1 pentanes/EtOAc); IR (KBr) 1587 (s), 1522 (m), 1337 (s) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ_H 2.03 (s, 3H), 2.08 (s, 6H), 6.31 (s, 1H), 6.43 (s, 1H), 7.43 (d, J=8.5 Hz, 2H), 8.21 (d, J=8.5 Hz, 2H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ_C 4.8, 19.4, 20.3, 84.0, 86.0, 121.5, 123.9 (2C), 129.1, 130.0 (2C), 138.7, 139.1, 144.8, 146.4; HRMS (CI(NH_3)) calcd for $C_{15}H_{16}NO_2$ (MH^+) 242.1181, found 242.1178.

4.1.11. (*E*)-2-Methyl-3-(4-nitrophenyl)allyl methanesulfonate (33). To a solution of alcohol **32**[37] (2.55 g, 13.2 mmol) in CH_2Cl_2 (50 mL) was added Et_3N (2.76 mL, 19.8 mmol) at 0 °C, followed by the dropwise addition of MsCl (1.22 mL, 15.8 mmol) at −10 °C. The resulting solution was stirred at −10 to −15 °C for 1 h, then satd aq NH_4Cl (10 mL) was added. The organic phase was washed with water and brine, and dried over $MgSO_4$. The solvent was removed by evaporation in vacuo to yield a crude yellow-orange oil, that was purified by passing through a plug of silica gel eluting with 2:1 pentanes/EtOAc to yield **33** (3.48 g, 97%) as a unstable yellow solid. R_f=0.35 (2:1 pentanes/EtOAc); ^{1}H NMR (200 MHz, $CDCl_3$) δ_H 1.97 (s, 3H), 3.08 (s, 3H), 4.78 (s, 2H), 6.68 (s, 1H), 7.43 (d, J=8.5 Hz, 2H), 8.20 (d, J=8.5 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ_C 15.4, 37.9, 74.4, 123.6 (2C), 128.2, 129.6 (2C), 134.7, 142.9, 146.6; HRMS (ESI) *m/e* calcd for $C_{11}H_{14}NO_5S$ (MH^+) 272.0593, found 272.0588.

4.1.12. (*E*)-2-(2-Methyl-3-(4-nitrophenyl)allylthio)benzo[*d*]thiazole (35). To a solution of 2-mercaptobenzothiazole (1.76 g, 10.5 mmol) in DMF (10 mL) was added sodium hydride (420 mg, 60 w/w % in oil, 10.5 mmol) slowly at 0 °C. The resulting suspension was stirred for 20 min at 0 °C. A solution of mesylate **33** (950 mg, 3.50 mmol) in DMF (5 mL) was added at 0 °C, and the mixture was allowed to warm to rt

then stirred for 2 h. Satd aq $NaHCO_3$ (10 mL) was added, and the aqueous phase was extracted with CH_2Cl_2 twice. The combined organics were dried over $MgSO_4$ and evaporated to dryness in vacuo. The residue was subjected to column chromatography (20:1 pentanes/EtOAc) to afford **35** (1.07 g, 89%) as a light yellow solid. Mp 114–116 °C (CH_2Cl_2/pentanes); R_f=0.1 (20:1 pentanes/EtOAc); IR (KBr) 1593 (m), 1507 (s), 1425 (s), 1338 (s) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ_H 2.06 (s, 3H), 4.20 (s, 2H), 6.70 (s, 1H), 7.28–7.48 (m, 4H), 7.77 (d, J=8.0 Hz, 1H), 7.90 (d, J=8.0 Hz, 1H), 8.17 (d, J=9.0 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ_C 17.3, 43.1, 121.0, 121.6, 123.4 (2C), 124.4, 126.1, 127.7, 129.4 (2C), 135.3, 137.1, 143.9, 146.2, 153.0, 165.8; HRMS (CI(NH_3)) *m/e* calcd for $C_{17}H_{15}N_2O_2S_2$ (MH^+) 343.0575, found 343.0567.

4.1.13. (*E*)-2-(2-Methyl-3-(4-nitrophenyl)allylsulfonyl)-benzo[*d*]thiazole (34). To a solution of sulfide **35** (599 mg, 1.75 mmol) in THF–EtOH (2/1, 30 mL) was added at 0 °C a solution of ammonium heptamolybdate tetrahydrate (433 mg, 0.35 mmol) in H_2O_2 (1.5 mL, 33% w/w, 17.5 mmol) over a period of 5 min. The resulting solution was allowed to warm to rt, and it was stirred for 20 h. A solution of Na_2SO_3 (2 g) in H_2O (20 mL) was added, and the aqueous phase was extracted with CH_2Cl_2 (3×30 mL). The combined organics were washed with brine and dried over $MgSO_4$, and then the solvent was removed by evaporation in vacuo. The residue was subjected to column chromatography (7:1 pentanes/EtOAc, then CH_2Cl_2) to give **34** (544 mg, 83%) as a white solid. Mp 115–117 °C (CH_2Cl_2/pentanes); R_f=0.6 (CH_2Cl_2); IR (KBr) 1595 (m), 1511 (s), 1337 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 2.11 (s, 3H), 4.37 (s, 2H), 6.42 (s, 1H), 7.19 (d, J=8.5 Hz, 2H), 7.62 (app t, J=7.0 Hz, 1H), 7.67 (app t, J=7.0 Hz, 1H), 8.01 (d, J=8.0 Hz, 1H), 8.13 (d, J=8.5 Hz, 2H), 8.25 (d, J=8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 19.0, 65.0, 122.3, 123.5 (2C), 125.5, 127.9, 128.3, 128.7, 129.5 (2C), 133.9, 136.9, 142.7, 146.6, 152.6, 165.2; HRMS (CI(NH_3)) *m/e* calcd for $C_{17}H_{15}N_2O_4S_2$ (MH^+) 375.0473, found 375.0475.

4.1.14. (±)-Aureonone (31).[21] To a solution of alkene **17** (165 mg, 0.70 mmol) in THF–H_2O (1/1, 6 mL) was added $NaIO_4$ (299 mg, 1.40 mmol) followed by OsO_4 (0.22 mL, 4% w/w in H_2O, 0.018 mmol) at rt. The resulting solution was stirred for 15 h, and the THF was removed by evaporation in vacuo, and the aqueous phase was extracted twice with CH_2Cl_2. The combined organics were dried over Na_2SO_4, and evaporated to dryness. The residue was subjected to column chromatography (3:1 CH_2Cl_2/EtOAc) to yield **31** (136 mg, 82%) as a white solid. Mp 119–121 °C (CH_2Cl_2/pentanes); R_f=0.25 (2:1 CH_2Cl_2/EtOAc); IR (KBr) 2927 (w), 1755 (s), 1666 (s), 1593 (s), 1328 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 1.84 (s, 3H), 2.05 (s, 3H), 2.71 (dd, J=6.0, 18.0 Hz, 1H), 2.87 (dd, J=8.0, 18.0 Hz, 1H), 3.89 (s, 3H), 4.05 (d, J=17.0 Hz, 1H), 4.16 (d, J=17.0 Hz, 1H), 5.54 (dd, J=6.0, 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 6.9, 9.5, 39.2, 55.4, 70.6, 73.0, 100.4, 120.9, 153.3, 161.9, 190.2, 212.3; HRMS (ESI) *m/e* calcd for $C_{12}H_{15}O_5$ (MH^+) 239.0919, found 239.0919. The IR, ^1H and ^{13}C NMR spectral data were in excellent agreement with those previously published.[21]

4.1.15. 1-(2,2-Dibromovinyl)-4-nitrobenzene (37).[34] To a solution of PPh_3 (7.87 g, 30.0 mmol), Zn powder (1.96 g, 30.0 mmol) and pyridine (2.4 mL, 30 mmol) in CH_2Cl_2 (50 mL) was added portionwise solid CBr_4 (9.95 g, 30.0 mmol) at rt. The resulting suspension was stirred for 30 min. A solution of *p*-nitrobenzaldehyde (1.51 g, 10.0 mmol) in CH_2Cl_2 (25 mL) was added slowly at rt. The resulting reaction mixture was stirred for 2 h. Water (25 mL) was added. The organic phase was diluted with pentanes (~150 mL) with stirring and the resulting suspension was filtered through a pad of Celite®, and evaporated to dryness in vacuo. The residue was subjected to column chromatography (pentanes/EtOAc, gradient elution) to afford **37** (2.67 g, 87%) as an orange solid. Mp 101–103 °C (CH_2Cl_2/pentanes); R_f=0.75 (10:1 pentanes/EtOAc); IR (KBr) 1586 (s), 1512 (s), 1342 (s), 860 (s); ^1H NMR (200 MHz, $CDCl_3$) δ_H 7.55 (s, 1H), 7.69 (d, J=9.0 Hz, 2H), 8.21 (d, J=9.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 94.0, 123.7 (2C), 129.1 (2C), 134.8, 141.4, 147.1; HRMS (ESI) *m/e* calcd for $C_8H_6^{79}Br_2NO_2$ (MH^+) 305.8765, found 305.8770. The ^1H and ^{13}C NMR spectral data are in good agreement with those previously published.[34]

4.1.16. (±)-2-((*E*)-4-((*Z*)-2-Bromo-3-(4-nitrophenyl)allylidene)-tetrahydrofuran-2-yl)-6-methoxy-3,5-dimethyl-4*H*-pyran-4-one ((*E*)-40) and (±)-2-((*Z*)-4-((*Z*)-2-bromo-3-(4-nitrophenyl)allylidene)-tetrahydrofuran-2-yl)-6-methoxy-3,5-dimethyl-4*H*-pyran-4-one ((*Z*)-40). To a solution of dibromide **37** (169 mg, 0.55 mmol), boronic ester **24** (181 mg, 0.50 mmol) and $Pd(PPh_3)_4$ (58 mg, 0.05 mmol) in THF–H_2O (3/1, 10 mL) was added slowly TlOEt (71 μL, 1.00 mmol) at rt. The resulting suspension was stirred for 75 min at rt. Brine (5 mL) and CH_2Cl_2 (20 mL) was added, and the separated aqueous layer was extracted twice with CH_2Cl_2. The combined organics were dried over $MgSO_4$ and the solvent was removed in vacuo. The crude product **40** was obtained as a 1:1.2 *E*/*Z* mixture as determined by ^1H NMR, which was subjected to column chromatography (pentanes/EtOAc, gradient elution) to afford (*E*)-**40** (69 mg, 30%) followed by (*Z*)-**40** (98 mg, 42%) as yellow solids. Data for (*E*)-**40**: Mp 117–119 °C (CH_2Cl_2/pentanes); R_f=0.5 (1:1 CH_2Cl_2/EtOAc); IR (KBr) 1667 (s), 1607 (s), 1514 (s), 1343 (s); ^1H NMR (400 MHz, $CDCl_3$) δ_H 1.82 (s, 3H), 2.01 (s, 3H), 3.11–3.40 (m, 2H), 3.94 (s, 3H), 4.59 (br s, J=14.0 Hz, 1H), 4.71 (br d, J=14.0 Hz, 1H), 5.27 (dd, J=6.0, 7.5 Hz, 1H), 6.25 (br s, 1H), 6.93 (s, 1H), 7.76 (d, J=8.5 Hz, 2H), 8.19 (d, J=8.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 6.9, 9.5, 34.4, 55.4, 73.0, 75.4, 100.0, 120.2, 121.3, 123.3, 123.4 (2C), 129.3, 129.8 (2C), 141.9, 144.2, 146.9, 154.3, 162.1, 180.5; HRMS (Cl(NH_3)) *m/e* calcd for $C_{21}H_{21}^{79}BrNO_6$ (MH^+) 462.0552, found 462.0562. Data for (*Z*)-**40**: Mp 146–148 °C (CH_2Cl_2/pentanes); R_f=0.4 (1:1 CH_2Cl_2/EtOAc); IR (KBr) 1665 (s), 1603 (s), 1510 (s), 1345 (s); ^1H NMR (200 MHz, $CDCl_3$) δ_H 1.85 (s, 3H), 2.03 (s, 3H), 2.98 (br dd, J=6.0, 16.5 Hz, 1H), 3.14 (br dd, J=7.5, 16.5 Hz, 1H), 3.95 (s, 3H), 4.87 (br d, J=15.0 Hz, 1H), 5.05 (br d, J=15.0 Hz, 1H), 5.19 (dd, J=6.0, 7.5 Hz, 1H), 6.39 (br s, 1H), 6.83 (s, 1H), 7.77 (d, J=8.5 Hz, 2H), 8.23 (d, J=8.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 6.9, 9.4, 38.0, 55.4, 70.1, 73.2, 100.1, 120.2, 122.6, 123.1, 123.5 (2C), 129.2, 129.8 (2C), 141.9, 144.8,

147.0, 154.5, 162.1, 180.5; HRMS ($Cl(NH_3)$) *m/e* calcd for $C_{21}H_{21}^{79}BrNO_6$ (MH^+) 462.0552, found 462.0555.

4.1.17. (±)-Aureothin (3).[4,21] To a solution of bromide (*Z*)-**40** (69.5 mg, 0.15 mmol) and $Pd(^tBu_3P)_2$ (1.5 mg, 3 μmol) in THF (3 mL) was added slowly Me_2Zn (150 μL, 0.30 mmol) at rt. The resulting was stirred for 30 min at rt, and then satd aq NH_4Cl (1 mL) was added carefully, followed by brine (1 mL). The mixture was extracted twice with CH_2Cl_2, and the combined organics were dried over $MgSO_4$ and evaporated to dryness in vacuo. The residue was subjected to column chromatography (CH_2Cl_2/EtOAc, 1:1) to afford (±)-aureothin (**3**) (57 mg, 95%) as a light sensitive crystalline, yellow solid. Mp 173–175 °C (CH_2Cl_2/pentanes); R_f=0.45 (1:1 CH_2Cl_2/EtOAc); IR (KBr) 1666 (s), 1586 (s), 1510 (m), 1332 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.83 (s, 3H), 2.01 (s, 3H), 2.03 (s, 3H), 2.95 (br dd, *J*=6.0, 16.0 Hz, 1H), 3.05 (br dd, *J*=6.0, 16.0 Hz, 1H), 3.93 (s, 3H), 4.74 (br d, *J*=14.0 Hz, 1H), 4.86 (br d, *J*=14.0 Hz, 1H), 5.13 (t, *J*=6.0 Hz, 1H), 6.19 (br s, 1H), 6.36 (s, 1H), 7.38 (d, *J*=8.5 Hz, 2H), 8.18 (d, *J*=8.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 6.9, 9.4, 17.7, 38.2, 55.2, 70.1, 73.2, 99.9, 120.1, 123.5 (2C), 125.9, 128.3, 129.5 (2C), 138.6, 140.6, 144.2, 146.0, 154.6, 162.0, 180.5; HRMS (ESI) *m/e* calcd for $C_{22}H_{24}NO_6$ (MH^+) 398.1604, found 398.1600. The IR, ^{1}H and ^{13}C NMR spectral data are in excellent agreement with those previously published.[21]

4.1.18. (±)-Aureothamine (41)[4] To a solution of (±)-aureothin (**3**) (80.5 mg, 0.20 mmol) in acetone–H_2O (5/1, 10 mL) was added Zn powder (165 mg, 2.52 mmol) and solid NH_4Cl (225 mg, 4.20 mmol) at rt. The bright yellow suspension was heated at reflux for 15 min. The resulting almost colorless mixture was cooled to rt and concentrated under reduced pressure. The aqueous mixture was extracted several times with CH_2Cl_2, and the combined organics were dried over $MgSO_4$ and evaporated to dryness in vacuo. The residue was filtered through a pad of silica gel eluting with 1:1 CH_2Cl_2/EtOAc to afford (±)-**41** (73.5 mg, 99%) as a white, crystalline solid. Mp 177–179 °C (CH_2Cl_2/pentanes); R_f=0.25 (1:1 CH_2Cl_2/EtOAc); IR (KBr) 3454 (s), 3343 (s), 3227 (m), 1660 (s), 1582 (s), 1326 (s); ^{1}H NMR (200 MHz, $CDCl_3$) δ_H 1.84 (s, 3H), 2.00 (s, 3H), 2.02 (s, 3H), 2.87 (dd, *J*=6.0, 15.5 Hz, 1H), 3.04 (dd, *J*=7.5, 15.5 Hz, 1H), 3.93 (s, 3H), 4.73 (br d, *J*=14.0 Hz, 1H), 4.86 (br d, *J*=14.0 Hz, 1H), 5.12 (dd, *J*=6.0, 7.5 Hz, 1H), 6.14 (br s, 1H), 6.24 (s, 1H), 6.67 (d, *J*=8.5 Hz, 2H), 7.09 (d, *J*=8.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 6.9, 9.4, 17.5, 38.2, 55.2, 70.1, 73.0, 99.8, 114.7 (2C), 119.7, 127.1, 127.8, 130.2 (2C), 130.8, 132.1, 136.4, 145.1, 155.2, 162.1, 180.6; HRMS (ESI) *m/e* calcd for $C_{22}H_{26}NO_4$ (MH^+) 368.1862, found 368.1863.

4.1.19. (±)-*N*-Acetyl-aureothamine (4).[6] To a solution of aureothamine (**41**) (35.5 mg, 97 μmol) in CH_2Cl_2 (1.5 mL) was added pyridine (16 μL, 0.20 mmol) at 0 °C. Acetyl chloride (11 μL, 0.15 mmol) was added slowly to the resulting solution. The mixture was stirred for 45 min at 0 °C. Satd aq NH_4Cl (2 mL) was added, and the aqueous phase was extracted twice with CH_2Cl_2. The combined organics were dried over $MgSO_4$, and the solvent was removed in vacuo. The residue was subjected to column chromatography (CH_2Cl_2/EtOAc, 1:1) to afford (±)-**4** as a white solid (30.5 mg, 77%). Mp 175–177 °C (CH_2Cl_2/pentanes); R_f=0.2 (1:1 CH_2Cl_2/EtOAc); IR (KBr) 1683 (s), 1661 (s), 1572 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.84 (s, 3H), 2.00 (s, 3H), 2.02 (s, 3H), 2.17 (s, 3H), 2.90 (dd, *J*=6.5, 16.0 Hz, 1H), 3.04 (dd, *J*=7.5, 16.0 Hz, 1H), 3.94 (s, 3H), 4.73 (d, *J*=14.0 Hz, 1H), 4.85 (d, *J*=14.0 Hz, 1H), 5.13 (dd, *J*=6.5, 7.5 Hz, 1H), 6.15 (s, 1H), 6.28 (s, 1H), 7.20 (d, *J*=8.5 Hz, 2H), 7.52 (d, *J*=8.5 Hz, 2H), 7.94 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 6.9, 9.4, 17.5, 24.5, 38.2, 55.3, 70.1, 73.1, 99.9, 119.5 (2C), 119.8, 126.7, 129.6 (2C), 130.1, 133.2, 134.2, 136.8, 137.6, 155.2, 162.2, 168.5, 180.7; HRMS (ESI) *m/e* calcd for $C_{24}H_{28}NO_5$ (MH^+) 410.1967, found 410.1967. The IR, ^{1}H and ^{13}C NMR spectral data are in excellent agreement with those previously published.[6]

4.1.20. 1-((1*E*,3*E*)-6,6-Dibromo-2,4-dimethylhexa-1,3,5-trienyl)-4-nitrobenzene (42). To a solution of PPh_3 (11.8 g, 45.0 mmol), Zn powder (2.94 g, 45.0 mmol) and pyridine (3.6 mL, 45.0 mmol) in CH_2Cl_2 (150 mL) was added portionwise solid CBr_4 (14.9 g, 45.0 mmol) at rt. The resulting was stirred for 30 min. A solution of aldehyde **28** (3.47 g, 15.0 mmol) in CH_2Cl_2 (50 mL) was added slowly. The resulting reaction mixture was stirred for 2 h then water (50 mL) was added. The organic phase was diluted with pentanes (~400 mL) with stirring and the resulting suspension was filtered through a pad of Celite®, and evaporated to dryness in vacuo. The residue was subjected to column chromatography (20:1→10:1 pentanes/EtOAc) to afford **42** (5.67 g, 98%) as a light sensitive yellow-orange solid. Mp 76–78 °C (CH_2Cl_2/pentanes); R_f=0.55 (9:1 pentanes/EtOAc); IR (KBr) 1590 (m), 1513 (m), 1340 (m); ^{1}H NMR (250 MHz, $CDCl_3$) δ_H 2.08 (3H, s), 2.13 (3H, s), 6.22 (1H, s), 6.50 (1H, s), 7.02 (1H, s), 7.44 (d, *J*=8.5 Hz, 2H), 8.22 (d, *J*=8.5 Hz, 2H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ_C 18.1, 19.5, 85.5, 124.0, 129.6, 130.0, 134.3, 137.8, 138.0, 141.4, 144.6, 146.5; HRMS ($Cl(NH_3)$) *m/e* calcd for $C_{14}H_{17}^{79}Br_2N_2O_2$ (MNH_4^+) 402.9657, found 402.9655.

4.1.21. (±)-2-((*Z*)-4-((2*Z*,4*E*,6*E*)-2-Bromo-4,6-dimethyl-7-(4-nitrophenyl)hepta-2,4,6-trienylidene)-tetrahydrofuran-2-yl)-6-methoxy-3,5-dimethyl-4*H*-pyran-4-one (43) and (±)-2-((*E*)-4-((2*Z*,4*E*,6*E*)-2-bromo-4,6-dimethyl-7-(4-nitrophenyl)hepta-2,4,6-trienylidene)-tetrahydrofuran-2-yl)-6-methoxy-3,5-dimethyl-4*H*-pyran-4-one (43). To a solution of dibromide **42** (852 mg, 2.20 mmol), boronic ester **24** (724 mg, 2.00 mmol) and $Pd(PPh_3)_4$ (231 mg, 0.20 mmol) in THF–H_2O (3/1, 40 mL) was added slowly TlOEt (283 μL, 4.00 mmol) at rt. The resulting suspension was stirred for 30 min at rt. Brine (20 mL) and CH_2Cl_2 (40 mL) was added, and the separated aqueous layer was extracted twice with CH_2Cl_2. The combined organics were dried over $MgSO_4$ and the solvent was removed in vacuo. The crude product **43** was obtained as a 1:1.2 *E*/*Z* mixture as determined by ^{1}H NMR. The crude product was subjected to column chromatography (2:1→1:1 pentanes/EtOAc) to afford (*E*)-**43** (315 mg, 29%) as a stiff red foam followed by (*Z*)-**43** (380 mg, 35%) as an yellow solid, both as light sensitive compounds. Data for (*E*)-**43**: R_f=0.25 (1:1 pentanes/EtOAc); IR (KBr) 1665 (s), 1594 (s), 1512 (s), 1339 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.83 (s, 3H), 2.01 (s, 3H), 2.07 (s, 3H), 2.17 (s, 3H), 3.10

(dd, J=5.0, 17.0 Hz, 1H), 3.24 (dd, J=7.5, 17.0 Hz, 1H), 3.94 (s, 3H), 4.58 (d, J=13.5 Hz, 1H), 4.65 (d, J=13.5 Hz, 1H), 5.25 (dd, J=5.0, 7.5 Hz, 1H), 6.11 (s, 1H), 6.28 (s, 1H), 6.44 (s, 1H), 6.50 (s, 1H), 7.42 (d, J=8.5 Hz, 2H), 8.18 (d, J=8.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 6.8, 9.4, 19.2, 18.6, 34.2, 55.4, 72.8, 75.2, 99.8, 118.1, 120.0, 122.0, 123.5 (2C), 129.0, 129.5 (2C), 134.2, 135.7, 137.5, 138.7, 141.4, 144.3, 145.9, 154.7, 162.0, 180.5; HRMS (ESI) *m/e* calcd for $C_{27}H_{29}^{79}BrNO_6$ (MH^+) 542.1178, found 542.1181. Data for (*Z*)-**43**: Mp 101–103 °C (CH_2Cl_2/pentanes); R_f=0.15 (1:1 pentanes/EtOAc); IR (KBr) 1665 (s), 1594 (s), 1512 (s), 1339 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.84 (s, 3H), 2.02 (s, 3H), 2.08 (s, 3H), 2.17 (s, 3H), 2.91 (dd, J=5.0, 16.0 Hz, 1H), 3.08 (dd, J=7.5, 16.0 Hz, 1H), 3.95 (s, 3H), 4.80 (d, J=15.0 Hz, 1H), 4.96 (d, J=15.0 Hz, 1H), 5.16 (dd, J=5.0, 7.5 Hz, 1H), 6.24 (s, 1H), 6.28 (s, 1H), 6.34 (s, 1H), 6.51 (s, 1H), 7.44 (d, J=9.0 Hz, 2H), 8.19 (d, J=9.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 6.9, 9.4, 18.6, 19.2, 37.8, 55.4, 70.1, 73.1, 99.9, 117.9, 119.9, 123.2, 123.5 (2C), 129.1, 129.6 (2C), 134.2, 135.6, 137.5, 138.7, 141.9, 144.3, 146.0, 154.9, 162.1, 180.5; HRMS (ESI) *m/e* calcd for $C_{27}H_{29}^{79}BrNO_6$ (MH^+) 542.1178, found 542.1177.

4.1.22. (±)-Spectinabilin (5).[7] To a solution of bromide (*Z*)-**43** (1.01 g, 1.86 mmol) and Pd(^{t}Bu$_3$P)$_2$ (19 mg, 37.2 μmol) in THF (40 mL) was added slowly Me_2Zn (1.87 mL, 2.0 M in PhMe, 3.74 mmol) at rt. The resulting was stirred for 45 min at rt. Satd aq NH_4Cl (10 mL) was added carefully, followed by brine (10 mL). The mixture was extracted twice with CH_2Cl_2, and the combined organics were dried over $MgSO_4$ and evaporated to dryness in vacuo. The residue was subjected to column chromatography (silica gel, 2:1 CH_2Cl_2/EtOAc) to afford (±)-**5** (795 mg, 89%) as a light sensitive yellow solid. Mp 133–135 °C (CH_2Cl_2/pentanes); R_f=0.55 (1:1 CH_2Cl_2/EtOAc); IR (KBr) 1667 (s), 1601 (s), 1517 (s), 1338 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.85 (s, 3H), 2.00 (s, 3H), 2.02 (s, 3H), 2.04 (s, 3H), 2.09 (s, 3H), 2.89 (dd, J=6.0, 15.5 Hz, 1H), 3.02 (dd, J=7.5, 15.5 Hz, 1H), 3.94 (s, 3H), 4.71 (d, J=14.0 Hz, 1H), 4.81 (d, J=14.0 Hz, 1H), 5.12 (dd, J=6.0, 7.5 Hz, 1H), 5.83 (s, 1H), 5.96 (s, 1H), 6.08 (s, 1H), 6.46 (s, 1H), 7.42 (d, J=9.0 Hz, 2H), 8.18 (d, J=9.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 6.8, 9.4, 17.8, 19.4, 19.6, 38.2, 55.2, 70.0, 73.1, 99.8, 119.9, 123.5 (2C), 126.8, 128.1, 129.5 (2C), 133.9, 134.3, 135.2, 135.6, 137.7, 139.3, 144.6, 145.8, 155.0, 162.0, 180.6; HRMS (ESI) *m/e* calcd for $C_{28}H_{32}NO_6$ (MH^+) 478.2230, found 478.2241. The IR, ^{1}H and ^{13}C NMR spectral data are in excellent agreement with those previously published.[7]

4.1.23. (±)-2-Methoxy-3,5-dimethyl-6-((*E*)-4-((2*E*,4*E*,6*E*)-2,4,6-trimethyl-7-(4-nitrophenyl)hepta-2,4,6-trienylidene)-tetrahydrofuran-2-yl)-4*H*-pyran-4-one (5a). To a solution of bromide (*E*)-**43** (195 mg, 0.36 mmol) and Pd(^{t}Bu$_3$P)$_2$ (3.5 mg, 7.2 μmol) in THF (7.5 mL) was added slowly Me_2Zn (360 μL, 2.0 M in PhMe, 0.72 mmol) at rt. The resulting was stirred for 20 min at rt. Satd aq NH_4Cl (3 mL) was added carefully, followed by brine (3 mL). The mixture was extracted twice with CH_2Cl_2, and the combined organics were dried over $MgSO_4$ and evaporated to dryness in vacuo. The residue was subjected to column chromatography (silica gel, 2:1 CH_2Cl_2/EtOAc) to afford (±)-**5a** (153 mg, 89%) as a light sensitive orange foam. R_f=0.55 (1:1 CH_2Cl_2/EtOAc); IR (film) 1666 (s), 1595 (s), 1514 (s), 1340 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.84 (s, 3H), 2.02 (s, 3H), 2.04 (s, 3H), 2.07 (s, 3H), 2.08 (s, 3H), 2.98 (dd, J=6.0, 16.5 Hz, 1H), 3.16 (dd, J=7.5, 16.5 Hz, 1H), 3.94 (s, 3H), 4.53 (d, J=13.0 Hz, 1H), 4.63 (d, J=13.0 Hz, 1H), 5.22 (dd, J=6.0, 7.5 Hz, 1H), 5.94 (s, 1H), 5.97 (s, 1H), 5.98 (s, 1H), 6.46 (s, 1H), 7.42 (d, J=8.5 Hz, 2H), 8.19 (d, J=8.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 6.9, 9.4, 18.2, 19.5, 19.6, 34.3, 55.3, 73.8, 75.7, 99.8, 119.8, 123.5 (2C), 125.4, 128.1, 129.5 (2C), 133.9, 134.4, 135.6, 135.7, 137.0, 139.4, 144.6, 145.8, 155.0, 162.1, 180.6; HRMS (ESI) *m/e* calcd for $C_{28}H_{32}NO_6$ (MH^+) 478.2230, found 478.2228.

4.1.24. (±)-SNF4435C (1), (±)-SNF4435D (2), and isomers 48 and 49 from (±)-5. To (±)-spectinabilin (**5**) (311 mg, 0.65 mmol) was added $PdCl_2(MeCN)_2$ (42 mg, 0.163 mmol) and then dry DMF (10 mL). The resulting red-brown solution was heated in the dark at 70 °C for 23 h. At the end of the reaction, a precipitate of palladium black had formed and the solution had a pale yellowish color. After cooling to rt the reaction mixture was evaporated to dryness in vacuo. The residue was directly subjected to column chromatography (2:1 pentanes/EtOAc) to afford a slightly impure mixture of **1**, **2**, **48** and **49** (160 mg). The mixture was subjected to preparative TLC (1:1 hexanes/Et_2O, multiple elutions) to afford a 2.1:1 mixture of **48** and **49** (56 mg, 18%) as a yellowish stiff foam, followed by a 2.5:1 mixture of **1** and **2** (68.5 mg, 22%) as a yellowish stiff foam. (±)-SNF4435C (**1**) and (±)-SNF4435D (**2**) could be separated by preparative TLC (3:1 pentanes/EtOAc, multiple elutions) to provide **1** and **2** as pale yellow solids.

Data for mixture of **48** and **49**: R_f=0.2 (2:1 pentanes/EtOAc); IR (KBr) 2954 (m), 2856 (m), 1667 (s), 1601 (s), 1519 (s), 1346 (s); HRMS (ESI) *m/e* calcd for $C_{28}H_{32}NO_6$ (MH^+) 478.2230, found 478.2236. Data for **48**: ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.26 (s, 3H), 1.64 (s, 3H), 1.69 (s, 3H), 1.76 (s, 3H), 1.80 (s, 3H), 2.05 (dd, J=10.0, 14.0 Hz, 1H), 2.46 (dd, J=6.5, 14.0 Hz, 1H), 2.74 (s, 1H), 3.56 (s, 1H), 3.91 (s, 3H), 4.02 (d, J=9.0 Hz, 1H), 4.06 (d, J=9.0 Hz, 1H), 4.14 (dd, J=6.5, 10.0 Hz, 1H), 5.20 (s, 1H), 5.61 (s, 1H), 7.61 (d, J=8.5 Hz, 2H), 8.81 (d, J=8.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 6.8, 9.0, 22.2, 22.9, 30.7, 32.0, 42.3, 49.1, 52.6, 55.2, 63.3, 75.0, 81.5, 99.9, 119.5, 122.3, 123.3 (2C), 124.0, 129.5 (2C), 130.7, 130.8, 145.1 (2C), 154.7, 162.0, 180.4. Data for **49**: ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.22 (s, 3H), 1.75 (s, 3H), 1.77 (s, 3H), 1.86 (s, 3H), 1.91–1.94 (m, 1H), 1.92 (s, 3H), 2.57 (dd, J=6.5, 13.0 Hz, 1H), 2.72 (s, 1H), 3.42 (s, 3H), 3.61 (s, 1H), 3.78 (d, J=9.0 Hz, 1H), 4.04 (d, J=9.0 Hz, 1H), 4.85 (dd, J=6.5, 10.0 Hz, 1H), 5.00 (s, 1H), 5.73 (s, 1H), 7.49 (d, J=8.5 Hz, 2H), 8.81 (d, J=8.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 6.7, 9.4, 22.2, 22.3, 30.5, 32.3, 43.2, 51.9, 54.6, 54.9, 58.6, 75.5, 80.6, 99.8, 119.6, 123.1 (3C), 124.4, 130.6 (2C), 130.9, 131.4, 143.6, 147.0, 154.9, 162.0, 180.4.

Data for mixture of (±)-**1** and (±)-**2**: HRMS (ESI) *m/e* calcd for $C_{28}H_{32}NO_6$ (MH^+) 478.2230, found 478.2238. Data for (±)-SNF4435C (**1**): R_f=0.16 (2:1 pentanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.30 (s, 3H), 1.72 (s, 3H), 1.74 (s, 3H), 1.84 (s, 3H), 1.89 (s, 3H), 2.43

(d, J=8.5 Hz, 2H), 2.84 (s, 1H), 3.64 (s, 1H), 3.96 (s, 3H), 3.96 (d, J=10.0 Hz, 1H), 4.32 (d, J=10.0 Hz, 1H), 4.76 (t, J=8.5 Hz, 1H), 4.94 (s, 1H), 5.58 (s, 1H), 7.54 (d, J=9.0 Hz, 2H), 8.20 (d, J=9.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 6.9, 9.4, 22.2, 23.0, 30.4, 42.9, 46.3, 51.1, 51.8, 55.5, 63.6, 70.5, 73.5, 100.2, 119.6, 122.0, 123.6 (2C), 123.8, 129.1 (2C), 130.4, 131.0, 145.1, 146.9, 155.0, 162.0, 180.5. Data for (±)-SNF4435D (**2**): R_f=0.15 (2:1 pentanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.30 (s, 3H), 1.73 (s, 3H), 1.79 (s, 3H), 1.84 (s, 3H), 1.97 (s, 3H), 2.28 (dd, J=9.5, 13.0 Hz, 1H), 2.48 (dd, J=7.0, 13.0 Hz, 1H), 2.73 (s, 1H), 3.53 (s, 3H), 3.74 (s, 1H), 3.83 (d, J=9.0 Hz, 1H), 4.18 (d, J=9.0 Hz, 1H), 4.89 (s, 1H), 4.93 (dd, J=7.0, 9.5 Hz, 1H), 5.70 (s, 1H), 7.47 (d, J=9.0 Hz, 2H), 8.15 (d, J=9.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 6.8, 9.4, 22.1, 22.5, 30.7, 43.0, 45.4, 51.1, 54.8, 55.2, 61.0, 70.6, 72.5, 99.9, 119.7, 121.9, 123.2 (2C), 124.4, 129.9 (2C), 131.2, 131.3, 144.0, 146.9, 154.9, 161.9, 180.5. The spectral data (^{1}H and ^{13}C NMR) for (±)-**1** and (±)-**2** in $CDCl_3$ are in excellent agreement with those previously reported.[3] The spectral data (^{1}H and ^{13}C NMR) for (±)-**1** and (±)-**2** in DMSO-d_6 are also in excellent agreement with those previously reported.[2b] Minor errors in the reported data for (−)-**1** (^{13}C NMR) and (+)-**2** (^{1}H and ^{13}C NMR) in $CDCl_3$ by Parker and co-workers are evident by comparison to their own included copies of spectra, thus making slight differences from ours.[16]

4.1.25. (±)-SNF4435C (1), (±)-SNF4435D (2), 48 and 49 from (±)-5a. To (±)-**5a** (115 mg, 0.24 mmol) was added $PdCl_2(MeCN)_2$ (15.5 mg, 0.06 mmol) and then dry DMF (3 mL). The resulting red-brown solution was heated in the dark at 70 °C for 23 h. Towards the end a precipitate of palladium black had formed and the solution had a pale yellowish color. After cooling to rt the reaction mixture was evaporated to dryness in vacuo. The residue was subjected to preparative TLC (3:1→2:1 pentanes/EtOAc, multiple elutions) to afford a 1.9:1 mixture of **48** and **49** (26 mg, 23%) as a yellowish foam, followed by a 2:1 mixture of (±)-**1** and (±)-**2** (9 mg, 8%) as a yellow foam. The spectral data (^{1}H and ^{13}C NMR) for (±)-**1** and (±)-**2** were identical to those above.

4.1.26. (±)-SNF4435C (1) and (±)-SNF4435D (2) from (±)-5. To (±)-spectinabilin (**5**) (100 mg, 0.21 mmol) was added dry DMF (3 mL). The resulting yellow solution was heated at 70 °C for 72 h in the dark. The resulting yellow-orange solution was evaporated to dryness in vacuo. The residue was subjected to preparative TLC (3:1 pentanes/EtOAc, multiple elutions) twice to afford (±)-**1** (18 mg, 18%) and (±)-**2** (5 mg, 5%) as yellow foams. The spectral data (^{1}H and ^{13}C NMR) for (±)-**1** and (±)-**2** were identical to those above.

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