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Modular Total Syntheses of the Marine-Derived Resorcylic Acid Lactones Cochliomycins A and B Using a Late-Stage Nozaki–Hiyama–Kishi Macrocyclization Reaction

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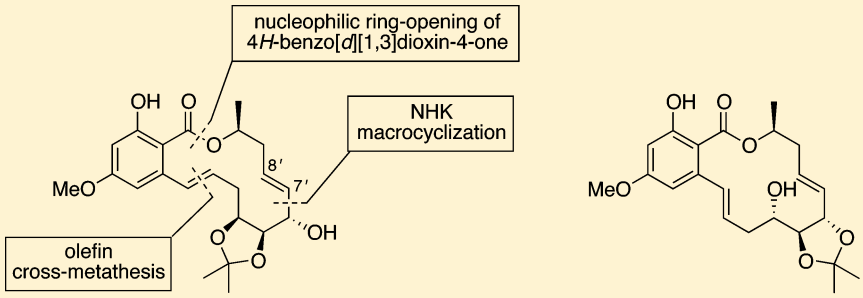
Supporting Information



ABSTRACT: The natural products cochliomycin A (**1**) and cochliomycin B (**2**), two resorcylic acid lactones obtained from marine sources, have been prepared in a concise and stereocontrolled manner from the readily accessible building blocks **4**–**6**. Olefin cross-metathesis, *trans*-esterification and Nozaki–Hiyama–Kishi (NHK) macrocyclization reactions were employed in the key steps. Hydrolysis of the immediate precursor to cochliomycin B affords the resorcylic acid lactone zeaenol (**24**).

INTRODUCTION

The 14-membered and benzannulated macrolides known as the resorcylic acid lactones (RALs) are mycotoxins that have been isolated from a range of fungi.[1] The first members of what is now a rather large family of natural products were described more than 50 years ago,[2] and new ones continue to be reported on a regular basis.[1,3] The extraordinary range of biological properties displayed by the RALs, which include (among other things) antimalarial, antiviral, antifungal, nematocidal, and antiparasitic activities, has attracted significant attention[1] although probably not as much as the capacities of some of them to act as potent and highly selective inhibitors of kinases[1] and the chaperone heat shock protein 90 (Hsp90).[1,4] As such, certain RALs have come to be regarded as important leads for the development of new oncolytic agents. Certainly, an impressive range of derivatization and analoguing programs[4,5] has been launched on this basis and such efforts have even led to a number of clinical trials.[4]

The biogenesis of the polyketide-derived RALs has become an increasing focus of attention[6] not least because of the potential to modify (reprogram) the pathways involved and so generate, hopefully in significant quantity, structurally diverse/novel variants that might display enhanced properties. While the biomimetic construction of certain RALs has also been reported,[7] the vast majority of the successful efforts directed toward the total synthesis of such systems has involved annulation of the requisite macrolide onto a resorcylic acid derivative.[1] Many of these syntheses have been summarized in recent reviews,[1] but new ones continue to be reported.[8] A good fraction, if not most of these, employ ring closing metathesis or macrolactonization protocols for assembling the requisite 14-membered heterocycle.[9]

In 2012, Wang and co-workers reported on the isolation of cochliomycins A, B, and C (**1**–**3**, respectively) from the marine fungus *Cochliobolus lunatus* (M351) associated with the gorgonian *Dichotella gemmacea* found in the South China Sea.[1e,10] These RALs are unusual for several reasons. First of all, they contain acetonide residues that cannot be artifacts arising from the isolation process because acetone was not employed for this purpose.[11] Second, they have been isolated from marine rather than terrestrial sources, and third, when evaluated as an antifouling agent (against larval settlement of the barnacle *Balanus Amphitrite*) cochliomycin A (**1**) proved to be a very active compound indeed (EC_{50} of 1.2 μg/mL).[12] Compound **1**, the only one of the trio obtained in sufficient amount for extended biological evaluation, was essentially inactive when tested against the A549 and HepG2 tumor cell lines but exhibited moderate antibacterial activity against *Staphylococcus aureus*.

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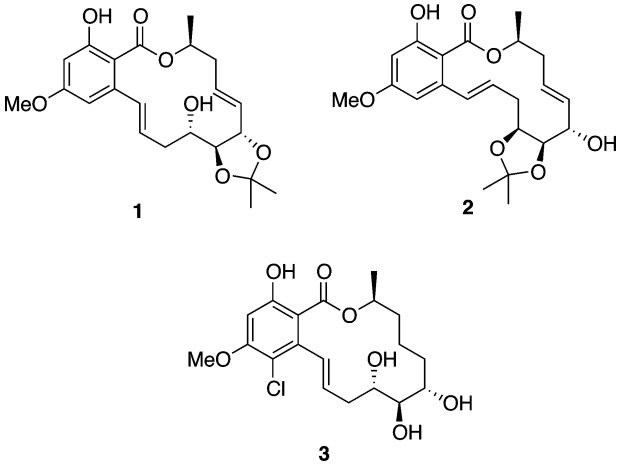
Interestingly, cochliomycin B (**2**) was observed[10] to rearrange to congener **1** on standing in $CDCl_3$, thus hinting at a possible challenge associated with the synthesis of the former natural product. Very recently the Wang group reported[3b] on the isolation of three further, nonacetonide-containing cochliomycins (D, E, and F) from a related fungus [*C. lunatus* (TA26−46)] associated with a zoanthid *Palythoa haddoni* that was also found in the South China Sea. Two of these compounds also displayed potent antifouling properties although neither was as active as congener **1**.



The rather intriguing structures, chemical behaviors, and biological properties of the cochliomycins, when considered together with our earlier studies on the synthesis of the RALs L-783,290 (a MEK inhibitor)[13] and L-783,277,[9c] prompted us to pursue the total synthesis of natural product **2**, the thus far untested member of the cochliomycin family and an established precursor to congener **1**. Herein we report on the realization of this objective using a highly modular approach and which exploited a late-stage and highly stereoselective Nozaki−Hiyama−Kishi (NHK) reaction to effect the necessary macrocyclization process.[9d,14] We also report on the conversion of a derivative of cochliomycin B (**2**) into isomer **1** as well as the generation of the corresponding triol, itself a natural product.

During the course of the work detailed below, Du and co-workers reported syntheses of both cochliomycins A[8c] and B[8d] using macrocyclization and RCM protocols, respectively, for the pivotal lactone ring-forming step. Nanda and co-workers have also recently detailed total syntheses of cochliomycin A[15] and 5′-*epi*-cochliomycin C[8a] using a late-stage RCM protocol in each instance. The Nanda and Du groups demonstrated, independently, that treatment of compounds **1** and **2**, respectively, with mineral acid in protic solvent or cosolvent results in cleavage of the associated acetonide residues, thus delivering the corresponding triol, a previously reported RAL known as zeaenol and the structure of which had been established by single-crystal X-ray analysis.[16] By such means the structures assigned to cochliomycins A and B were substantiated.

RESULTS AND DISCUSSION

Identifying the Required Building Blocks. An inspection of the structure of cochliomycin B (**2**) (Figure 1) reveals that disconnections of the macrolide residue could be carried out at the styrenyl double bond, at the lactone linkage, and between the sp^3-hybridized carbon bearing the free hydroxyl group and the adjacent sp^2-hybridized carbon of the nonconjugated double

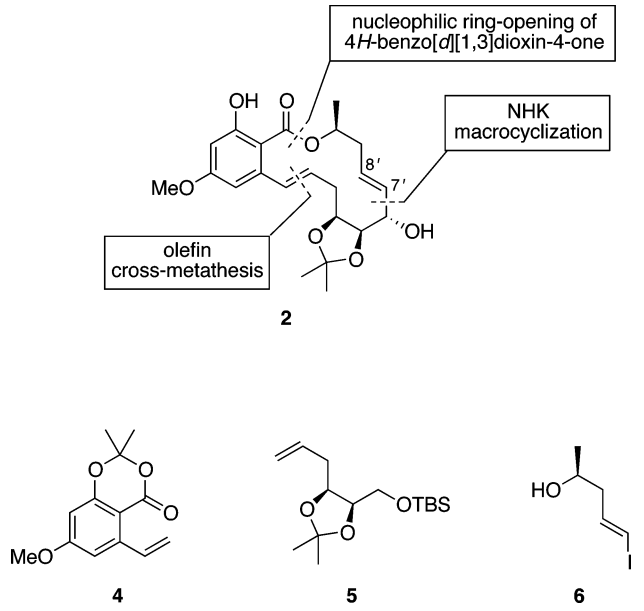


Figure 1. Key disconnections associated with cochliomycin B and identification of building blocks **4**, **5**, and **6**.

bond. In the forward (synthetic) direction the styrene-type double bond could be established through an olefin cross metathesis (OCM) reaction of potential building blocks **4** and **5** while treatment of the product of that process with the conjugate base derived from alcohol **6** would be expected to effect, via a *trans*-esterification reaction, ring cleavage of the associated [1,3]dioxin-4-one moiety, thereby simultaneously establishing the required ester/lactone linkage and revealing the free phenolic residue associated with the target **2**. This type of process has been successfully applied in a number of settings.[5c,8b−d,17] It was thought the third bond, the formation of which would establish the target macrocycle, could be installed through an intramolecular NHK reaction in which the participating functionalities would be the *E*-configured iodo-alkene moiety arising from building block **6** and a carbonyl residue obtained by deprotection of the silyl-protected primary alcohol within the product of the above-mentioned *trans*-esterification reaction and oxidation of this to the aldehyde. While NHK reactions have been employed previously in macrocyclization processes[9d,14] including, on one occasion, in the formation of a RAL,[9d] we are unaware of its use in the synthesis of such systems that incorporate a *trans*-configured $\Delta^{7',8'}$-double bond.

Synthesis of the 4*H*-Benzo[*d*][1,3]dioxin-4-one 4. Building block **4** has been reported previously.[17,18] Thus, following the protocol detailed by Srihari,[18b] commercially available 2,4,6-trihydroxybenzoic acid (**7**, Scheme 1) was converted into the lactone **8** (76% based on recovered starting material) by treating a solution of the former compound with a mixture of trifluoroacetic acid (TFA) and the corresponding anhydride (TFAA). Subjection of compound **8** (as the nucleophile) to a Mitsunobu reaction with methanol and using a combination of Ph_3P and diethyl azodicarboxylate (DEAD) resulted in the completely regioselective *O*-methylation of the non-hydrogen-bonded phenolic residue within the substrate and thereby generating ether **9** in 81% yield. Conversion of compound **9** into the corresponding triflate **10** (96%) was readily achieved under standard conditions, and this was then engaged in a Stille cross-coupling reaction with tri-*n*-butylvinyl-

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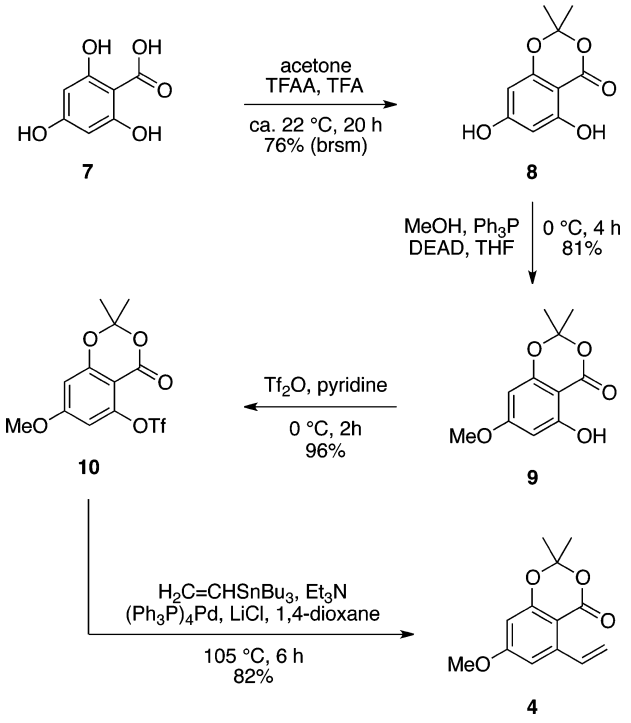
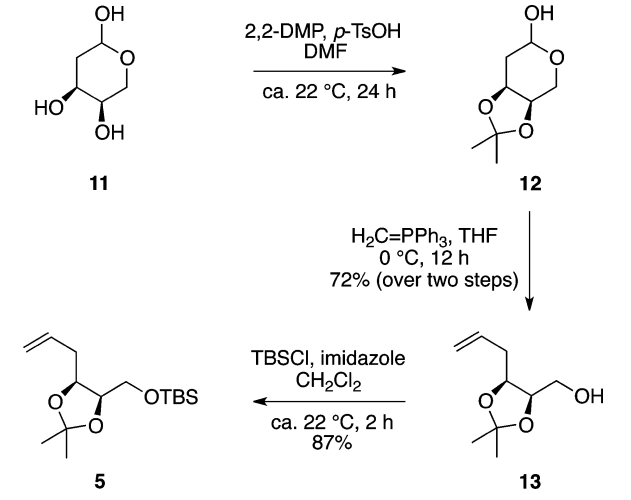
Scheme 1. Synthesis of Building Block 4



stannane in the presence of $(Ph_3P)_4Pd$, triethylamine, and lithium chloride to afford the target styrene **4** in 82% yield. The spectral data obtained on compound **4** were in complete accord with those reported earlier.[18b]

Synthesis of Acetonide 5. While building block **5** has been obtained in seven steps from commercially available isopropylidene-*D*-erythrono-1,4-lactone,[19] a more concise (three-step) synthesis from *D*-2-deoxyribose (**11**) is shown in Scheme 2.

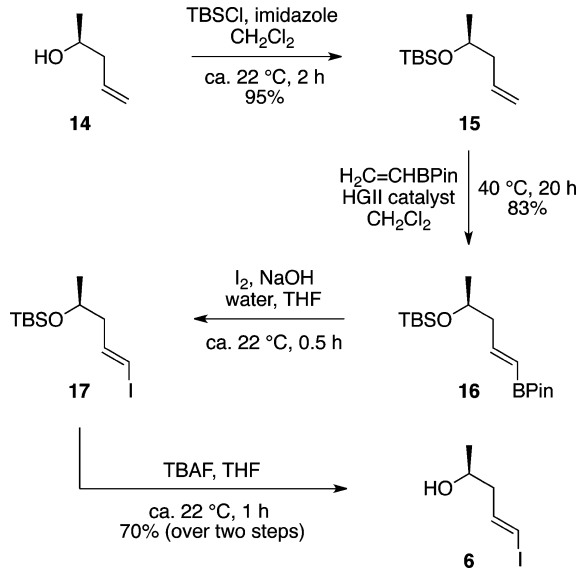
Scheme 2. Synthesis of Building Block 5



Thus, the readily derived acetonide, **12**, of compound **11** was subjected, using a protocol defined by Geng and Danishefsky,[5a] to a Wittig olefination reaction with in situ generated triphenylphosphonium methylide, thereby affording the previously reported[5a] unsaturated alcohol **13** (72% from **11**). Application of a conventional *O*-silylation procedure using *tert*-butyldimethylsilyl (TBS) chloride to the last compound then afforded ether **5** that was obtained in 87% yield. All the spectral data acquired on compound **5** were in complete accord with the assigned structure and matched those reported previously.[19]

Synthesis of Iodoalkene 6. The reaction sequence employed in the synthesis of the final building block, namely compound **6**, is shown in Scheme 3 and started with

Scheme 3. Synthesis of Building Block 6



commercially available (*S*)-(+)-4-penten-2-ol (**14**) that was first converted into the previously reported[6a] TBS-ether **15** (95%) under standard conditions. Engagement of compound **15** in an OCM reaction with the commercially available pinacol ester of vinylboronic acid using the Hoveyda–Grubbs second generation (HGII) catalyst[20] then afforded the expected boronate ester **16**[21] with the illustrated *E*-geometry about the associated double bond being assigned on the basis of the observation of a 17.5 Hz coupling between the vicinally related olefinic protons. Treatment of compound **16** with molecular iodine in the presence of sodium hydroxide, under conditions defined by Grubbs and Morrill,[22] resulted in an *ipso*-deborylation reaction that proceeded with retention of configuration of the alkene geometry and so affording the iodoalkene **17** (70% from **15**). Product **17** has been obtained previously by Sellès and Lett[23] over four steps from trimethylsilylacetylene and by using a hydrozirconation/iododezirconation protocol in the key step.

Treatment of compound **17** with tetra-*n*-butylammonium fluoride (TBAF) afforded the target building block **6**[24] (99%) as a clear, colorless oil. The derived spectral data were in complete accord with the assigned structure, and most notably, the vicinal coupling between the olefinic protons was 15.0 Hz, as would be expected for an *E*-configured alkene.

Coupling of Building Blocks 4–6 and the Ring-Closing NHK Reaction Leading to Cochliomycin B. With the requisite building blocks, viz. compounds **4**–**6**, in hand, the assembly of them so as to establish a synthesis of cochliomycin B was the remaining task. In the event, and as foreshadowed in the original analysis (see above) of the target structure, terminal olefins **4** and **5** were subjected to an OCM reaction (Scheme 4) using the HGII catalyst[20] and by such means the *E*-configured styrene **18** was obtained in 86% yield. Accordingly, the stage was now set for the pivotal lactone ring-opening/*trans*-esterification reaction. To such ends, NaH was added to a magnetically stirred

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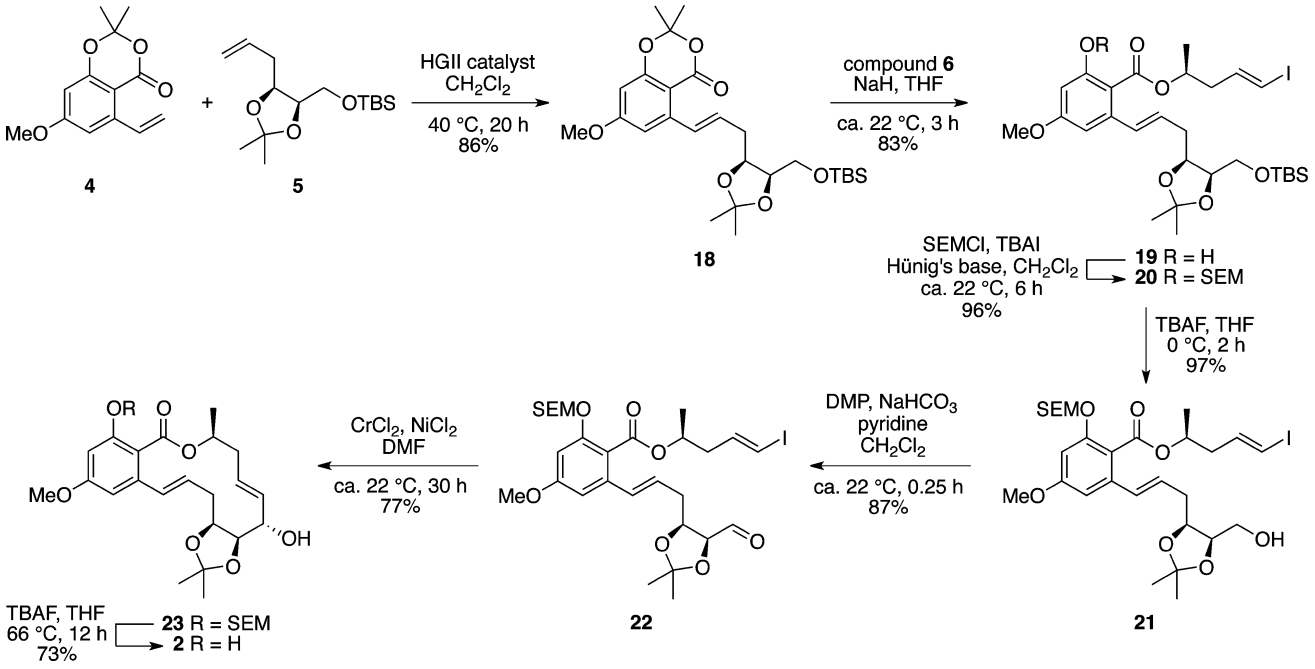
Scheme 4. Assembly of Building Blocks 4–6 and Completion of the Synthesis of Cochliomycin B (2)



solution of alcohol **6** and lactone **18** in THF maintained at ca. 22 °C, thereby generating the ester **19** (83%) that incorporates a free phenolic group. Even if it was pleasing to have obtained this last compound, all attempts to oxidize the alcohol resulting from cleavage of the associated TBS ether only led to complex mixtures of products, probably because of concomitant or competing oxidation of the phenolic moiety. As a result, compound **19** was protected as the corresponding SEM ether **20** (96%) under conventional conditions and this was then treated with TBAF in THF at 0 °C so as to selectively remove the TBS ether residue and thus provide the 1°-alcohol **21** in readiness for oxidation to the corresponding aldehyde. While, because of the propensity for acetonide group migration, compound **21** proved to be sensitive, when it was subjected to oxidation with the Dess–Martin periodinane (DMP) in dichloromethane that had been buffered with a combination of anhydrous sodium bicarbonate and pyridine then the desired aldehyde **22** could be obtained in 87% yield. Upon subjection of the last compound to reaction with a combination of 10 mol equiv of $CrCl_2$ and catalytic amounts (5 mol %) of $NiCl_2$ in DMF under high-dilution conditions at ca. 22 °C for 30 h,[9d] then the desired NHK macrocyclization reaction took place and thus provided SEM-protected cochliomycin B (**23**) in 77% yield. No evidence could be obtained for the coproduction of the epimeric 2°-alcohol in this remarkably selective macrocyclization reaction. In the final step of the synthesis, compound **23** was treated with TBAF in THF at 66 °C, thus effecting cleavage of the SEM ether and so producing cochliomycin B (**2**) in 73% yield.

The spectral data acquired on compound **2** were in complete accord with the assigned structure. Furthermore, a comparison of the so-derived ^{1}H and ^{13}C NMR spectral data with those reported[10] for the natural product (Table 1) revealed a particularly good match. However, the specific rotation of the synthetically derived material was of the opposite sign (and of different magnitude) to that reported for cochliomycin B {$[\alpha]_D$ −17.7 (*c* 1.41, CH_3OH) for synthetic material vs $[\alpha]_D$ +7.3 (*c* 0.05, CH_3OH) for the natural product}. This discrepancy is attributed to contamination of the natural product by quantities of the strongly dextrorotatory isomer cochliomycin A (**1**). Interestingly, despite suggestions[10] that natural product **2** slowly isomerizes to congener **1** on standing in $CDCl_3$, we have not observed such a process in this solvent, at least when it had been passed through basic alumina before use.

Conversion of the SEM-Derivative of Cochliomycin B into Cochliomycin A and the RAL Zeaenol. In the course of manipulating the precursor **23** to cochliomycin B (**2**), it was observed that, on treating the former compound with HCl in methanol containing traces of water at room temperature for 1 h, the SEM-ether residue was cleaved and the acetonide moiety migrated (no specific order of events implied). As a result cochliomycin A (**1**) was formed in 91% yield (Scheme 5). A comparison of the ^{1}H and ^{13}C NMR spectral data derived from this material with those reported[10] for the natural product revealed an excellent match (Table 2). The specific rotation of the synthetically derived material was of the same sign as

Scheme 5. Conversion of Compound 23 into Cochliomycin A (1) and Zeaenol (24)

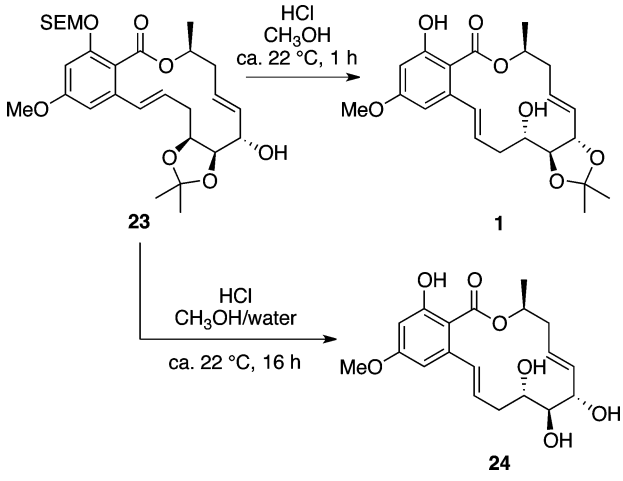


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Table 1. Comparison of the ^{13}C and ^{1}H NMR Data Recorded for Synthetically Derived Compound 2 with Those Reported for Cochliomycin B

^{13}C NMR (δ_C)		^{1}H NMR (δ_H)	
cochliomycin B[a]	compound **2**[b]	cochliomycin B[c]	compound **2**[d]
170.6	170.5	11.50, s, 1H	11.50, s, 1H
164.8	164.7	7.00, dd, *J* = 15.6 and 2.4 Hz, 1H	7.01, dd, *J* = 15.5 and 2.4 Hz, 1H
164.1	164.0	6.40, d, *J* = 2.4 Hz, 1H	6.40, d, *J* = 2.6 Hz, 1H
142.6	142.5	6.39, d, *J* = 2.4 Hz, 1H	6.39, d, *J* = 2.6 Hz, 1H
134.5	134.4	6.07, ddd, *J* = 15.6, 9.0, and 4.8 Hz, 1H	6.07, ddd, *J* = 15.5, 8.8, and 4.9 Hz, 1H
132.9	132.8	5.56,[e] ddd, *J* = 15.6, 9.0, and 3.6 Hz, 1H	5.65, ddd, *J* = 15.6, 9.2, and 3.5 Hz, 1H
130.5	130.4	5.46, m, 1H	5.49−5.40, complex m, 2H
126.3	126.2	5.44, m, 1H	–
107.9	107.7	4.36, ddd, *J* = 12.0, 4.8, and 3.6 Hz, 1H	4.36, ddd, *J* = 11.5, 4.8, and 3.0 Hz, 1H
107.7	107.7	4.12, t, *J* = 9.0 Hz, 1H	4.12, dd, *J* = 9.7 and 8.3 Hz, 1H
104.6	104.4	3.85, dd, *J* = 9.0 and 4.8 Hz, 1H	3.84, dd, *J* = 9.7 and 4.6 Hz, 1H
100.1	100.0	3.81, s, 3H	3.82, s, 3H
79.5	79.4	2.76, m, 1H	2.76, dtd, *J* = 15.7, 3.1, and 2.9 Hz, 1H
77.4	77.3	2.59, m, 1H	2.59, ddd, *J* = 15.7, 11.0, and 9.3 Hz, 1H
70.6	70.5	2.50, m, 1H	2.50, ddd, *J* = 15.7, 9.3, and 3.8 Hz, 1H
69.7	69.6	2.44, m, 1H	2.43, dtd, *J* = 15.5, 5.2, and 2.2 Hz, 1H
55.5	55.4	1.52, s, 3H	1.54, s, 3H
38.3	38.2	1.44, d, *J* = 6.6 Hz, 3H	1.46, d, *J* = 6.4 Hz, 3H
31.4	31.3	1.42, s, 3H[f]	1.42, s, 3H
28.5	28.4	–	3.03, broadened s, 1H (OH)
25.9	25.9	–	–
18.8	18.8	–	–

[a]Obtained from ref 10 and recorded in $CDCl_3$ at 150 MHz. [b]Recorded in $CDCl_3$ at 100 MHz. [c]Obtained from ref 10 and recorded in $CDCl_3$ at 600 MHz. [d]Recorded in $CDCl_3$ at 400 MHz. [e]We assume this is a transcription error and that the true value is 5.65. [f]Signal due to OH group proton not observed.

Table 2. Comparison of the ^{13}C and ^{1}H NMR Data Recorded for Synthetically Derived Compound 1 with Those Reported for Cochliomycin A

^{13}C NMR (δ_C)		^{1}H NMR (δ_H)	
cochliomycin A[a]	compound **1**[b]	cochliomycin A[c]	compound **1**[d]
170.7	170.7	11.49, s, 1H	11.50, s, 1H
164.7	164.7	7.16, dd, *J* = 15.6 and 2.4 Hz, 1H	7.17, dd, *J* = 15.5 and 2.3 Hz, 1H
163.7	163.9	6.46, d, *J* = 2.4 Hz, 1H	6.47, d, *J* = 2.6 Hz, 1H
142.0	142.1	6.39, d, *J* = 2.4 Hz, 1H	6.39, d, *J* = 2.6 Hz, 1H
134.0	134.0	5.99, ddd, *J* = 15.6, 8.4, and 4.8 Hz, 1H	6.00, ddd, *J* = 15.3, 8.1, and 5.2 Hz, 1H
132.6	132.7	5.72, ddd, *J* = 15.0, 10.2, and 3.0 Hz, 1H	5.73, ddd, *J* = 15.3, 10.5, and 3.1 Hz, 1H
129.5	129.5	5.52, ddt, *J* = 15.0, 9.6, and 1.2 Hz, 1H	5.52, ddt, *J* = 15.4, 8.8, and 1.5 Hz, 1H
126.4	126.4	5.44, m, 1H	5.45, dtd, *J* = 11.8, 6.4, and 3.7 Hz, 1H
108.4	108.5	4.56, t, *J* = 8.4 Hz, 1H	4.57, t, *J* = 8.3 Hz, 1H
107.1	107.2	4.20, ddd, *J* = 12.0, 4.8, and 2.4 Hz, 1H	4.21, ddd, *J* = 12.3, 4.9, and 2.3 Hz, 1H
104.3	104.4	3.89, dd, *J* = 8.4 and 2.4 Hz, 1H	3.90, dd, *J* = 7.9 and 2.3 Hz, 1H
100.0	100.1	3.81, s, 3H	3.82, s, 3H
81.4	81.4	2.75, m, 1H	2.76, ddt, *J* = 14.9, 5.3, and 2.9 Hz, 1H
75.2	75.2	2.50, m, 1H	2.65−2.45, complex m, 2H
70.5	70.5	2.42, m, 1H	2.43, m, 1H
68.7	68.8	2.25, m, 1H	2.29, m, 1H
55.4	55.4	1.44, d, *J* = 6.6 Hz, 3H	1.45, d, *J* = 6.4 Hz, 3H
37.8	37.8	1.43, s, 3H	1.44, s, 3H
36.0	36.0	1.36, s, 3H[e]	1.38, s, 3H
26.9	27.0	–	–
26.9	26.9	–	–
19.2	19.2	–	–

[a]Obtained from ref 10 and recorded in $CDCl_3$ at 150 MHz. [b]Recorded in $CDCl_3$ at 100 MHz. [c]Obtained from ref 10 and recorded in $CDCl_3$ at 600 MHz. [d]Recorded in $CDCl_3$ at 400 MHz. [e]Signal due to OH group proton not observed.

reported for cochliomycin A {$[\alpha]_D$ +34.4 (*c* 1.99, CH_3OH) for synthetic material vs $[\alpha]_D$ +10.5 (*c* 0.43, CH_3OH) for the natural product}. The discrepancy in the magnitudes of these values is attributed to the evident impurities present in the naturally

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Table 3. Comparison of the ^{13}C and ^{1}H NMR Data Recorded for Synthetically Derived Compound 24 with Those Reported for Zeaenol

^{13}C NMR (δ_C)		^{1}H NMR (δ_H)	
zeaenol[a]	compound **24**[b]	zeaenol[c]	compound **24**[d]
171.0	171.2	11.85, s, 1H	11.87, s, 1H
165.0	165.3	7.12, d, J = 15.5 Hz, 1H	7.10, d, J = 15.4 Hz, 1H
163.9	164.0	6.44, d, J = 2.7 Hz, 1H	6.43, d, J = 2.6 Hz, 1H
142.9	142.8	6.39, d, J = 2.7 Hz, 1H	6.38, d, J = 2.6 Hz, 1H
133.4	133.7	5.98, dt, J = 15.5 and 6.1 Hz, 1H	5.97, dt, J = 15.6 and 6.2 Hz, 1H
131.3	131.5	5.82, ddd, J = 15.5, 10.1, and 4.0 Hz, 1H	5.83, ddd, J = 14.7, 10.2, and 3.9 Hz, 1H
128.9	129.2	5.71, dd, J = 15.5 and 7.4 Hz, 1H	5.69, dd, J = 15.6 and 7.4 Hz, 1H
128.7	128.5	5.32, m, 1H	5.36−5.27, complex m, 1H
107.5	107.6	4.26, dd, J = 8.1 and 7.4 Hz, 1H	4.25, t, J = 7.9 Hz, 1H
103.8	103.9	3.98, ddd, J = 8.1, 2.0, and 1.3 Hz, 1H	3.95, t, J = 7.8 Hz, 1H
99.9	100.1	3.82, s, 3H	3.80, s, 3H
77.2	77.2	3.59, dd, J = 8.1 and 2.0 Hz, 1H	3.59, broadened d, J = 8.4 Hz, 1H
72.3	73.2	–	3.24, broad s, 1H
72.3	72.0	2.53, m, 2H	–
71.4	71.5	2.51, m, 1H	2.72−2.34, complex m, 6H
55.3	55.4	2.43, m, 1H	–
37.5	37.8	1.41, d, J = 6.1 Hz, 3H[e]	1.45, d, J = 6.2 Hz, 3H
35.9	36.0	–	–
19.3	19.7	–	–

[a]Obtained from ref 16 and recorded in $CDCl_3/CD_3OD$ at 125 MHz. [b]Recorded in $CDCl_3$ at 100 MHz [c]Obtained from ref 16 and recorded in $CDCl_3$ at 500 MHz. [d]Recorded in $CDCl_3$ at 400 MHz. [e]Signal due to OH group proton not observed/reported.

derived material and the small quantities of this that were isolated from the producing organism.

Exposure of compound **23** to HCl in 9:1 v/v methanol/water at room temperature for 16 h resulted in cleavage of both the SEM and acetonide moieties and, thereby, the formation of the corresponding triol **24** (84%) that represents the structure of the RAL known as zeaenol[16] and which has been isolated from the plant pathogenic fungus *Drechslera portulacae*. The structure of the naturally derived zeaenol was established by single-crystal X-ray analysis[16] as was that of the synthetic material produced by the pathway just described. Details of this second analysis are presented in the Experimental Section and the Supporting Information. A comparison of the ^{1}H and ^{13}C NMR spectral data derived from this material with those reported[16] for the natural product revealed an excellent match (Table 3). There was also good agreement between the specific rotations of the synthetic and naturally derived materials {$[\alpha]_D$ −93.8 (*c* 4.80, CH_3OH) vs $[\alpha]_D$ −92 (*c* 0.52, CH_3OH)}.

CONCLUSION

The modular nature of the cochliomycin B (**2**) synthesis reported here has provided this natural product in just 11 steps (longest linear sequence), thus delivering sufficient material for an extended assessment of its biological properties, including its capacity to serve as an antifouling agent. A reaction sequence of the same length has been employed to generate congener **1** (cochliomycin A), a demonstrably potent antifouling agent, while a sequence with the same number of steps leads to the corresponding triol zeaenol (**24**), a rather phytotoxic and therefore potentially useful compound.

The use of an OCM process in conjunction with a NHK macrocyclization reaction provides the capacity to generate other highly functionalized and generally more biologically active RALs. Work directed toward such ends is now underway in our laboratories, and results will be reported in due course, as will the outcomes of studies of the ecological properties of compounds **1**, **2**, and **24**.

EXPERIMENTAL SECTION

General Experimental Procedures. Unless otherwise specified, proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded at 18 °C in base-filtered $CDCl_3$ on a spectrometer operating at 400 MHz for proton and 100 MHz for carbon nuclei. ^{1}H NMR data are recorded as follows: chemical shift (δ) [multiplicity, coupling constant(s) J (Hz), relative integral] where multiplicity is defined as s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet or combinations of the above. In relevant cases, the signal due to residual $CHCl_3$ appearing at δ_H 7.26 and the central resonance of the $CDCl_3$ "triplet" appearing at δ_C 77.0 were used to reference ^{1}H and ^{13}C NMR spectra, respectively. Samples were analyzed by infrared spectroscopy (ν_{max}) as thin films on KBr plates. Low- and high-resolution electron impact (EI) mass spectra were recorded on a double focusing, triple sector machine. Low- and high-resolution ESI mass spectra were recorded on a triple-quadrupole mass spectrometer operating in positive ion mode. Melting points are uncorrected. Analytical thin layer chromatography (TLC) was performed on aluminum-backed 0.2 mm thick silica gel 60 F_{254} plates. Eluted plates were visualized using a 254 nm UV lamp and/or by treatment with a suitable dip followed by heating. These dips included phosphomolybdic acid/ceric sulfate/sulfuric acid (conc.)/water (37.5 g/7.5 g/37.5 g/720 mL), potassium permanganate/potassium carbonate/5% sodium hydroxide aqueous solution/water (3 g/20 g/5 mL/300 mL), and *p*-anisaldehyde or vanillin/sulfuric acid (conc.)/ethanol (15 g/2.5 mL/250 mL). Flash chromatographic separations were carried out following protocols defined by Still et al.[25] with silica gel 60 (40−63 μm) as the stationary phase and using the AR- or HPLC-grade solvents indicated. Starting materials, reagents, drying agents, and other inorganic salts were generally commercially available and were used as supplied. Tetrahydrofuran (THF), methanol, and dichloromethane were dried using a solvent purification system that is based upon a technology originally described by Grubbs et al.[26] Where necessary, reactions were performed under an argon atmosphere.

Compound 8. Trifluoroacetic anhydride (28.5 mL) and acetone (5.00 mL) were added sequentially to a magnetically stirred suspension of 2,4,6-trihydroxybenzoic acid monohydrate (5.03 g, 26.8 mmol) in

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trifluoroacetic acid (38.0 mL) maintained at 0 °C, and the ensuing mixture was then left to warm to room temperature. After 20 h the reaction mixture was concentrated under reduced pressure, and the residue was diluted with ethyl acetate (70 mL). The solution thus obtained was washed with $NaHCO_3$ (2 × 50 mL of a saturated aqueous solution) and then brine (1 × 50 mL). The separated organic phase was dried (Na_2SO_4), filtered, and then concentrated under reduced pressure. The ensuing light-yellow oil was subjected to flash chromatography (silica, 4:1 v/v hexane/ethyl acetate) to afford, after concentration of the relevant fractions (R_f = 0.25), compound **8**[18b] (3.13 g, 56% or 76% brsm) as a white, crystalline solid, mp 196−198 °C (lit.[18b] mp 202 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.45 (s, 1H), 6.08 (d, J = 2.2 Hz, 1H), 5.95 (d, J = 2.2 Hz, 1H), 5.63 (broad s, 1H), 1.73 (s, 6H); IR (KBr) ν_{max} 3189, 1658, 1639, 1480, 1351, 1272, 1167, 1160, 1094, 813 cm^{-1}; MS (ESI, +ve) m/z 233 (40%), 211 (50), 153 (100); HRMS (ESI) [M + Na]$^+$ calcd for $C_{10}H_{10}O_5$ 233.0426, found 233.0426.

The combined aqueous phases obtained from the workup process described above were treated with an excess of concentrated HCl, and the precipitate so formed was collected by filtration to give 2,4,6-trihydroxybenzoic acid (1.35 g, 27% recovery) as a white, crystalline solid that was identical, in all respects, with the authentic material.

Compound 9. Diethyl azodicarboxylate (3.30 mL, 20.7 mmol) was added to a magnetically stirred solution of phenol **8** (3.11 g, 14.8 mmol) and triphenylphosphine (4.27 g, 16.3 mmol) in THF (25 mL) containing CH_3OH (660 μL, 16.3 mmol) and maintained at 0 °C under a nitrogen atmosphere. After 4 h the reaction mixture was concentrated under reduced pressure, and the residue thus obtained was subjected to flash chromatography (silica, 9:1 → 4:1 v/v 40−60 petroleum spirit/ethyl acetate gradient elution) to afford, after concentration of the relevant fractions (R_f = 0.45 in 4:1 v/v 40−60 petroleum spirit/ethyl acetate), the title compound **9**[18b] (2.68 g, 81%) as a white, crystalline solid, mp 105−107 °C (lit.[18b] mp 108 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.45 (s, 1H), 6.15 (d, J = 2.0 Hz, 1H), 6.01 (d, J = 2.0 Hz, 1H), 3.82 (s, 3H), 1.74 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.7, 165.2, 163.1, 156.8, 106.9, 95.7, 94.6, 93.0, 55.8, 25.6; IR (KBr) ν_{max} 1695, 1636, 1581, 1353, 1189, 1156 cm^{-1}; MS (ESI, +ve) m/z 247 (8%), 225 (33), 167 (100); HRMS (ESI) [M + H]$^+$ calcd for $C_{11}H_{12}O_5$ 225.0763, found 225.0764.

Compound 10. Trifluoromethanesulfonic anhydride (3.0 mL, 17.7 mmol) was added to a magnetically stirred mixture of phenol **9** (2.65 g, 11.8 mmol) and pyridine (24 mL) maintained at 0 °C under a nitrogen atmosphere. The ensuing mixture was stirred at 0 °C for 1.5 h and then diluted with ethyl acetate (100 mL), and the resulting solution was washed with $CuSO_4$ (3 × 50 mL of a saturated aqueous solution), water (1 × 50 mL), and brine (1 × 50 mL) before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The resulting light-yellow oil was subjected to flash chromatography (silica, 1:0 → 4:1 v/v hexane/ethyl acetate gradient elution) and so affording, after concentration of the relevant fractions (R_f = 0.3 in 4:1 v/v 40−60 petroleum spirit/ethyl acetate), the title compound **10**[18b] (4.05 g, 96%) as a white, crystalline solid, mp 68−71 °C (lit.[18b] mp 58 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.54 (d, J = 2.0 Hz, 1H), 6.49 (d, J = 2.0 Hz, 1H), 3.89 (s, 3H), 1.75 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5, 158.7, 157.1, 149.8, 118.7 (q, J = 320 Hz), 106.5, 105.3, 101.0, 100.8, 56.2, 25.4; IR (KBr) ν_{max} 1746, 1629, 1578, 1429, 1285, 1211, 1149, 1057, 969, 819 cm^{-1}; MS (ESI, +ve) m/z 379 (58%), 357 (100), 299 (45); HRMS (ESI) [M + H]$^+$ calcd for $C_{12}H_{11}F_3O_7S$ 357.0256, found 357.0255.

Compound 4. 1,4-Dioxane (40 mL) was added to a Schlenk flask containing triflate **10** (1.40 g, 3.9 mmol), $(Ph_3P)_4Pd$ (450 mg, 10 mol %), and lithium chloride (1.25 g, 29.4 mmol), and the ensuing mixture was deoxygenated with argon. Triethylamine (1.47 mL, 10.6 mmol) and tri-*n*-butylvinyltin (1.27 mL, 4.3 mmol) were then added sequentially, and the deoxygenation process was repeated. The ensuing mixture was heated at 105 °C for 5 h while also being stirred magnetically and then allowed to cool to room temperature before ethyl acetate (100 mL) and water (100 mL) were added. The separated aqueous phase was extracted with ethyl acetate (2 × 50 mL), and the combined organic phases were washed with brine (2 × 50 mL) before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The resulting light-yellow oil was subjected to flash chromatography (silica, 4:1 v/v hexane/ethyl acetate elution), and the relevant fractions (R_f = 0.4) were subjected to further flash chromatography (silica, 4:1 → 3:2 v/v 40−60 petroleum spirit/dichloromethane gradient elution) and so affording, after concentration of the relevant fractions (R_f = 0.33), compound **4**[18b] (752 mg, 82%) as a white, crystalline solid, mp 89−91 °C (lit.[18b] mp 96 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (dd, J = 17.3 and 10.5 Hz, 1H), 6.74 (d, J = 2.2 Hz, 1H), 6.33 (d, J = 2.2 Hz, 1H), 5.65 (dd, J = 17.3 and 1.5 Hz, 1H), 5.40 (dd, J = 10.5 and 1.5 Hz, 1H), 3.86 (s, 3H), 1.71 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.8, 159.9, 158.5, 143.8, 135.4, 117.4, 108.4, 105.0, 103.7, 100.6, 55.5, 25.5; IR (KBr) ν_{max} 2994, 1723, 1606, 1571, 1290, 1276, 1202, 1158, 1038 cm^{-1}; MS (ESI, +ve) m/z 257 (95%), 235 (28), 177 (100); HRMS (ESI) [M + H]$^+$ calcd for $C_{13}H_{14}O_4$ 235.0970, found 235.0970.

Compound 12. Calcium sulfate (1.01 g, 7.5 mmol) was added to a magnetically stirred solution of 2-deoxy-D-ribose (**11**) (2.00 g, 14.9 mmol) in DMF (30 mL) maintained under nitrogen, and the ensuing mixture was cooled to −10 °C. 2,2-Dimethoxypropane (3.7 mL, 29.8 mmol) and *p*-toluenesulfonic acid (28 mg, 10 mol %) were then added sequentially, and the resulting mixture was stirred at −10 °C for 24 h before being filtered through a silica cartridge (30 g) that was eluted with hexane/ethyl acetate (1:1 v/v mixture). The filtrate was concentrated under reduced pressure, and the ensuing clear, colorless oil was subjected to flash chromatography (silica, 3:1 → 1:1 v/v hexane/ethyl acetate gradient elution) and so affording, after concentration of the relevant fractions (R_f = 0.5 in ethyl acetate), the title compound **12**[5a] (2.59 g, >95%) as a clear, colorless oil comprised of a ca. 3:1 mixture of anomers and containing traces of DMF. ^{1}H NMR (300 MHz, $CDCl_3$) δ (major anomer) 5.26 (dt, J = 7.0 and 4.0 Hz, 1H), 4.48 (dt, J = 6.5 and 4.0 Hz, 1H), 4.24−4.11 (complex m, 1H), 3.95 (dd, J = 12.5 and 3.0 Hz, 1H), 3.69 (dd, J = 12.5 and 3.5 Hz, 1H), 3.14 (d, J = 3.5 Hz, 1H), 2.24 (dt, J = 15.0 and 4.0 Hz, 1H), 1.78 (ddd, J = 15.0, 7.0, and 4.0 Hz, 1H), 1.50 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 109.3, 108.6, 91.5, 90.7, 71.4, 71.1, 70.6, 70.4, 61.9, 60.7, 32.9, 32.0, 27.9, 27.1, 25.5, 25.2; IR (KBr) ν_{max} 3412, 2984, 2936, 1664, 1456, 1380, 1372, 1244, 1216, 1113, 1061, 1035, 1003, 870, 852 cm^{-1}; MS (ESI, +ve) m/z 197 (100%); HRMS (ESI) [M + Na]$^+$ calcd for $C_8H_{14}O_4$ 197.0790, found 197.0789.

Compound 13. *n*-Butyllithium (22.3 mL of a 2.0 M solution in hexanes, 44.6 mmol) was added dropwise to a magnetically stirred solution of methyltriphenylphosphonium bromide (16.0 g, 44.7 mmol) in THF (70 mL) maintained at −78 °C under a nitrogen atmosphere. The resulting mixture was left to warm to ca. 22 °C and after 0.5 h at this temperature was recooled to −78 °C and then treated with a solution of DMF-contaminated lactol **12** (2.60 g, ca. 14.9 mmol) in THF (30 mL). After the addition was complete the reaction mixture was slowly warmed to ca. 22 °C, and after 16 h at this temperature it was treated, successively, with NH_4Cl (100 mL of a saturated aqueous solution) and ethyl acetate (100 mL). The separated organic phase was washed with brine (2 × 50 mL) before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Subjection of the resulting light-yellow oil to flash chromatography (silica, 4:1 v/v hexane/ethyl acetate elution) afforded, after concentration of the relevant fractions (R_f = 0.2), the title compound **13**[5a] (1.85, 72%) as a clear, colorless oil, $[\alpha]_D^{20}$ +15.5 (*c* 6.3, $CHCl_3$) {lit.[5a] $[\alpha]_D^{20}$ +54.8 (*c* 0.26, $CHCl_3$)}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.85 (m, 1H), 5.28−5.03 (complex m, 2H), 4.37−4.12 (complex m, 2H), 3.66 (d, J = 5.5 Hz, 2H), 2.52−2.36 (complex m, 1H), 2.36−2.21 (complex m, 1H), 1.87 (broadened s, 1H), 1.50 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.1, 117.3, 108.2, 77.7, 76.2, 61.5, 33.6, 28.1, 24.4; IR (KBr) ν_{max} 3412, 2986, 2935, 1642, 1381, 1372, 1252, 1217, 1064 cm^{-1}; MS (ESI, +ve) m/z 195 (100%); HRMS (ESI) [M + Na]$^+$ calcd for $C_9H_{16}O_3$ 195.0997, found 195.0997.

Compound 5. *tert*-Butyldimethylsilyl chloride (770 mg, 4.56 mmol) was added to a magnetically stirred solution of alcohol **12** (523 mg, 3.04 mmol) and imidazole (414 mg, 6.08 mmol) in dichloromethane (30 mL) maintained at ca. 22 °C under a nitrogen atmosphere. After 2 h the reaction mixture was diluted with dichloromethane (50 mL), and the resulting solution was washed with HCl (1 × 20 mL aqueous solution), $NaHCO_3$ (1 × 30 mL of a saturated aqueous solution), and then brine (1 × 20 mL). The separated organic phase was dried ($MgSO_4$), filtered,

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and concentrated under reduced pressure. Subjection of the resulting light-yellow oil to flash chromatography (silica, 19:1 v/v 40−60 petroleum spirit/diethyl ether elution and then 3:7 → 1:1 v/v 40−60 petroleum spirit/dichloromethane gradient elution) afforded, after concentration of the relevant fractions (R_f = 0.35 in 1:1 v/v 40−60 petroleum spirit/dichloromethane), the title compound **5** (757 mg, 87%) as a clear, colorless oil, $[\alpha]_D^{20}$ −21.4 (*c* 5.4, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.90 (m, 1H), 5.05−5.19 (complex m, 2H), 4.21 (m, 1H), 4.12 (m, 1H), 3.70 (m, 1H), 3.64 (m, 1H), 2.27−2.49 (complex m, 2H), 1.44 (s, 3H), 1.35 (s, 3H), 0.90 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.2, 116.8, 107.9, 77.7, 77.0, 61.8, 33.8, 28.1, 25.9, 25.5, 18.2, −5.4, −5.5; IR (KBr) ν_{max} 2955, 2931, 2858, 1642, 1472, 1463, 1379, 1368, 1255, 1217, 1100, 913, 837, 776 cm^{-1}; MS (ESI, +ve) *m*/*z* 309 (100%); HRMS (ESI) $[M + Na]^+$ calcd for $C_{15}H_{30}O_3Si$ 309.1862, found 309.1862.

Compound 15. *tert*-Butyldimethylsilyl chloride (2.96 g, 17.3 mmol) was added to a magnetically stirred solution of (*S*)-4-penten-2-ol (1.41 g, 14.4 mmol) and imidazole (2.68 g, 35.5 mmol) in dichloromethane (50 mL) maintained at ca. 22 °C under a nitrogen atmosphere. The ensuing mixture was stirred at this temperature for 16 h before being diluted with dichloromethane (50 mL), and the resulting solution was washed with HCl (1 × 50 mL of 1 M aqueous solution), $NaHCO_3$ (1 × 50 mL of a saturated aqueous solution), and then brine (1 × 50 mL). The separated organic phase was then dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Subjection of the resulting light-yellow oil to flash chromatography (silica, 1:0 → 19:1 v/v hexane/dichloromethane gradient elution) afforded, after concentration of the relevant fractions (R_f = 0.35 in 19:1 v/v 40−60 petroleum spirit/dichloromethane), the title compound **15**[6a] (3.13 g, 95%) as a clear, colorless oil, $[\alpha]_D^{20}$ +6.2 (*c* 3.2, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.98−5.67 (complex m, 1H), 5.16−4.92 (complex m, 2H), 3.84 (sextet, *J* = 6.0 Hz, 1H), 2.19 (m, 2H), 1.13 (d, *J* = 6.0 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.6, 116.5, 68.4, 44.3, 25.9, 23.4, 18.2, −4.5, −4.7; IR (KBr) ν_{max} 2958, 2930, 2858, 1642, 1472, 1376, 1255, 1129, 1091, 1046, 1004, 913, 835, 774 cm^{-1}; HRMS (ESI, +ve) $[M + H]^+$ calcd for $C_{11}H_{24}OSi$ 201.1675, found 201.1675.

Compound 16. A magnetically stirred mixture of silyl ether **15** (3.13 g, 15.6 mmol) and vinylboronic acid pinacol ester (4.0 mL, 23.4 mmol) in dichloromethane (80 mL) maintained under argon was heated at reflux 0.5 h and then cooled to room temperature. The HGII catalyst (245 mg, 2.5 mol %) was then added to the reaction mixture that was then again heated at reflux. After 16 h the cooled reaction mixture was concentrated under reduced pressure, and the yellow residue thus obtained was subjected to flash chromatography (silica, 1:0 → 1:1 v/v hexane/dichloromethane gradient elution), affording, after concentration of the relevant fractions (R_f = 0.3 in 1:1 v/v 40−60 petroleum spirit/dichloromethane), the title compound **16**[21] (4.09 g, 83%) as a clear, colorless oil, containing traces of vinyl boronate, $[\alpha]_D^{20}$ +9.3 (*c* 1.01, $CHCl_3$) {lit.[9d] $[\alpha]_D^{23}$ (for *ent*-**16**) −8.1 (*c* 1.12, CH_2Cl_2)}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.60 (dt, *J* = 17.5 and 7.0 Hz, 1H), 5.46 (d, *J* = 17.5 Hz, 1H) 3.89 (m, 1H), 2.43−2.10 (complex m, 2H), 1.27 (s, 12H), 1.15 (d, *J* = 6.0 Hz, 3H), 0.88 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.3, 121.2 (broad), 83.0, 66.2, 46.4, 25.9, 24.7, 23.7, 18.2, −4.6, −4.8; IR (KBr) ν_{max} 2978, 2930, 2858, 1641, 1363, 1321, 1255, 1146, 1084, 1003, 835, 811, 774 cm^{-1}; MS (ESI, +ve) *m*/*z* 349 (100%); HRMS (ESI) $[M + Na]^+$ calcd for $C_{17}H_{35}{}^{11}BO_3Si$ 349.2346, found 349.2346.

Compound 6. NaOH (2.40 mL of a 3 M aqueous solution, 7.9 mmol) was added to a magnetically stirred solution of boronate **16** (714 mg, 2.19 mmol) in THF (22 mL) maintained under a nitrogen atmosphere at ca. 22 °C. After 0.25 h a solution of molecular iodine (1.20 g, 5.3 mmol) in THF (5 mL) was added dropwise, and after a further 0.66 h the reaction mixture was diluted with ethyl acetate (50 mL). The separated organic phase was washed with $Na_2S_2O_3$ (1 × 30 mL of a saturated aqueous solution) and brine (1 × 30 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The resulting light-yellow oil (presumed to contain silyl ether **17**) was dissolved in THF (22 mL), and the solution thus obtained was treated with TBAF (1.14 g, 4.4 mmol) while being maintained at ca. 22 °C under a nitrogen atmosphere. After 16 h the reaction mixture was diluted with ethyl acetate (50 mL), and the resulting solution was washed with brine (1 × 50 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Subjection of the resulting light-yellow oil to flash chromatography (silica, 1:0 → 4:1 v/v hexane/ethyl acetate gradient elution) afforded, after concentration of the relevant fractions (R_f = 0.2 in 4:1 v/v 40−60 petroleum spirit/ethyl acetate), compound **6** (325 mg, 70%) as a clear, pale-yellow oil, $[\alpha]_D^{20}$ +17.9 (*c* 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.55 (dt, *J* = 14.4 and 7.5 Hz, 1H), 6.14 (d, *J* = 14.4 Hz, 1H), 3.87 (m, 1H), 2.31−2.09 (complex m, 2H), 1.54 (broad s, 1H), 1.20 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.5, 77.4, 66.5, 45.4, 22.8; IR (KBr) ν_{max} 3352, 2968, 2928, 1606, 1455, 1423, 1374, 1271, 1121, 1074, 948 cm^{-1}; MS (EI, 70 eV) *m*/*z* 212 ($M^{+\bullet}$, 15%), 168 (100); HRMS (EI) $M^{+\bullet}$ calcd for $C_5H_9{}^{127}IO$ 211.9697, found 211.9698.

Compound 18. The HGII catalyst (270 mg, 8 mol %) was added to a magnetically stirred solution of styrene **4** (3.18 g, 10.4 mmol) and acetonide **5** (1.54 g, 5.4 mmol) in CH_2Cl_2 (5.4 mL) maintained under an argon atmosphere. The resulting mixture was heated at 40 °C for 16 h and then (after solvent loss) at 60 °C for 72 h. The cooled reaction mixture was concentrated under reduced pressure, and the residue thus obtained was subjected to flash chromatography (silica, 1:0 → 17:3 v/v hexane/ethyl acetate and then 1:0 → 9:1 v/v dichloromethane/diethyl ether elution). Concentration of the relevant fractions (R_f = 0.4 in 17:3 v/v 40−60 petroleum spirit/ethyl acetate and 0.5 in 9:1 v/v dichloromethane/diethyl ether) afforded compound **18** (2.28 g, 86%) as a clear, colorless oil, $[\alpha]_D^{20}$ −22.2 (*c* 0.99, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 16.0 Hz, 1H), 6.80 (d, *J* = 2.5 Hz, 1H), 6.35 (d, *J* = 2.5 Hz, 1H), 6.31 (dt, *J* = 16.0 and 7.0 Hz, 1H), 4.31 (dt, *J* = 9.0 and 5.0 Hz, 1H), 4.17 (dt, *J* = 7.0 and 5.5 Hz, 1H), 3.85 (s, 3H), 3.78−3.60 (complex m, 2H), 2.68−2.49 (complex m, 2H), 1.70 (s, 6H), 1.47 (s, 3H), 1.37 (s, 3H), 0.91 (s, 9H), 0.09 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.7, 160.2, 158.7, 143.8, 131.3, 130.1, 108.2, 108.0, 104.9, 103.7, 100.3, 77.8, 77.1, 61.9, 55.6, 33.2, 28.2, 25.9, 25.7, 25.6, 18.3, −5.4 (four signals obscured or overlapping); IR (neat) ν_{max} 2931, 2857, 1731, 1605, 1574, 1378, 1273, 1205, 1160, 1071, 837 cm^{-1}; MS (ESI, +ve) *m*/*z* 515 (100%); HRMS (ESI) $[M + Na]^+$ calcd for $C_{26}H_{40}O_7Si$ 515.2441, found 515.2451.

Compound 19. Sodium hydride (320 mg of a 60% dispersion in mineral oil, 8.0 mmol) was added to a magnetically stirred solution of alcohol **6** (1.10 g, 5.2 mmol) and acetonide **18** (1.97 g, 4.0 mmol) in THF (20 mL) maintained at ca. 22 °C under a nitrogen atmosphere. The ensuing mixture was stirred for 1.5 h at this temperature and then treated with $NaHCO_3$ (20 mL of a saturated aqueous solution) and ethyl acetate (40 mL). The separated organic phase was washed with brine (1 × 40 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Subjection of the ensuing residue to flash chromatography (silica, 1:0 → 4:1 v/v hexane/ethyl acetate gradient elution) afforded, after concentration of the relevant fractions (R_f = 0.5 in 4:1 v/v 40−60 petroleum spirit/ethyl acetate), compound **19** (1.93 g, 83%) as a clear, colorless oil, $[\alpha]_D^{20}$ +17.3 (*c* 1.54, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.68 (s, 1H), 7.01 (d, *J* = 16.0 Hz, 1H), 6.54 (m, 1H), 6.49 (d, *J* = 2.5 Hz, 1H), 6.39 (d, *J* = 2.5 Hz, 1H), 6.19 (d, *J* = 14.5 Hz, 1H), 5.99 (dt, *J* = 16.0 and 7.0 Hz, 1H), 5.23 (sextet, *J* = 6.0 Hz, 1H), 4.27 (dt, *J* = 9.5 and 5.0 Hz, 1H), 4.15 (dt, *J* = 7.5 and 5.5 Hz, 1H), 3.83 (s, 3H), 3.75 (dd, *J* = 10.5 and 8.0 Hz, 1H), 3.67 (dd, *J* = 10.5 and 5.0 Hz, 1H), 2.64−2.54 (complex m, 1H), 2.54−2.37 (complex m, 3H), 1.45 (s, 3H), 1.37 (d, *J* = 6.0 Hz, 3H), 1.36 (s, 3H), 0.91 (s, 9H), 0.09 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 165.1, 164.1, 143.3, 140.9, 133.1, 128.9, 108.6, 107.9, 103.8, 99.8, 78.2, 77.8, 77.3, 70.8, 61.9, 55.4, 42.0, 33.1, 28.2, 25.9, 25.6, 19.6, 18.3, −5.3, −5.4; IR (KBr) ν_{max} 2931, 2856, 1648, 1609, 1572, 1317, 1256, 1213, 1160, 836 cm^{-1}; MS (ESI, +ve) *m*/*z* 669 (100%); HRMS (ESI) $[M + Na]^+$ calcd for $C_{28}H_{43}{}^{127}IO_7Si$ 669.1721, found 669.1722.

Compound 20. SEM-Cl (200 μL, 1.1 mmol) and DIPEA (300 μL, 1.8 mmol) were added sequentially and dropwise to a magnetically stirred solution of compound **19** (580 mg, 0.9 mmol) and TBAI (330 mg, 0.1 mmol) in dichloromethane (4 mL) maintained under nitrogen at room temperature at ca. 22 °C. After 2 h the reaction mixture was quenched with brine (20 mL) and water (20 mL) and then extracted with dichloromethane (3 × 50 mL). The organic layers were combined

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and washed with brine (1 × 100 mL) before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The resulting light-yellow oil was subjected to flash chromatography (silica, 22:3 v/v 40−60 petroleum spirit/diethyl ether elution), thus affording, after concentration of the appropriate fractions (R_f = 0.25), compound **20** (668 mg, 96%) as a clear, colorless oil, $[\alpha]_D^{20}$ −7.2 (*c* 7.9, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.69 (d, *J* = 2.3 Hz, 1H), 6.66 (d, *J* = 2.3 Hz, 1H), 6.59 (m, 1H), 6.46 (m, 1H), 6.28 (m, 1H), 5.26−5.16 (complex m, 4H), 4.23 (m, 1H), 4.13 (m, 1H), 3.81 (s, 3H), 3.80−3.65 (complex m, 6H), 2.61−2.32 (complex m, 4H), 1.43 (s, 3H), 1.34 (s, 3H), 0.95 (m, 3H), 0.89 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H), 0.00 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 161.1, 155.7, 141.5, 137.2, 130.5, 128.3, 116.5, 108.0, 103.4, 100.6, 93.3, 77.7, 77.6, 77.2, 69.9, 66.4, 61.9, 55.5, 42.0, 33.3, 28.2, 25.9, 25.6, 19.6, 18.3, 18.0, −1.4, −5.3, −5.4; IR (KBr) ν_{max} 2953, 2929, 1726, 1601, 1577, 1258, 1161, 1104, 1050, 836 cm^{-1}; MS (ESI, +ve) *m*/*z* 799 (100%); HRMS (ESI) $[M + Na]^+$ calcd for $C_{34}H_{57}{}^{127}IO_8Si_2$ 799.2534, found 799.2555.

Compound 21. TBAF (2.88 mL of a 1.0 M solution in THF, 2.88 mmol) was added to a magnetically stirred solution of compound **20** (1.12 g, 1.44 mmol) in THF (30 mL) maintained at 0 °C under a nitrogen atmosphere. The ensuing mixture was stirred for 2 h at this temperature and then filtered through a short pad of TLC-grade silica gel (2.8 g), and the solids thus retained were washed with diethyl ether (50 mL). The filtrate was concentrated under reduced pressure, and the residue thus obtained was subjected to flash chromatography (silica, 4:1 → 1:4 v/v 40−60 petroleum spirit/diethyl ether gradient elution) to afford, after concentration of the relevant fractions (R_f = 0.2 in 4:1 v/v 40−60 petroleum spirit/diethyl ether), compound **21** (931 mg, 96%) as a clear, pale-yellow oil, $[\alpha]_D^{20}$ −6.2 [*c* 6.2, $(CH_3)_2CO$]. ^{1}H NMR [400 MHz, $(CD_3)_2CO$] δ 6.78 (d, *J* = 2.3 Hz, 1H), 6.69 (d, *J* = 2.3 Hz, 1H), 6.66 (m, 1H), 6.50 (d, *J* = 15.9 Hz, 1H), 6.40−6.25 (complex m, 2H), 5.29 (ABq, *J* = 11.1 Hz, 2H), 5.19 (m, 1H), 4.28 (m, 1H), 4.18 (m, 1H), 3.83 (s, 3H), 3.80 (dd, *J* = 8.4 and 8.0 Hz, 2H), 3.70−3.58 (complex m, 2H), 2.88 (broad s, 1H), 2.61−2.38 (complex m, 4H), 1.39 (s, 3H), 1.33 (d, *J* = 6.3 Hz, 3H), 1.29 (s, 3H), 0.97 (7, *J* = 8.2 Hz, 2H), −0.02 (s, 9H); ^{13}C NMR [100 MHz, $(CD_3)_2CO$] δ 167.5, 161.9, 156.4, 143.0, 137.9, 131.4, 128.9, 117.9, 108.3, 103.6, 101.2, 93.8, 78.9, 78.2, 77.5, 70.6, 66.9, 61.6, 55.8, 42.4, 34.2, 28.5, 25.8, 19.9, 18.5, 1.2; IR (KBr) ν_{max} 3482, 2951, 1723, 1601, 1578, 1262, 1162, 1108, 1049, 836 cm^{-1}; MS (ESI, +ve) *m*/*z* 685 (100%); HRMS (ESI) $[M + Na]^+$ calcd for $C_{28}H_{43}{}^{127}IO_8Si$ 685.1670, found 685.1672.

Compound 22. DMP (900 mg, 2.11 mmol) was added to a magnetically stirred mixture of alcohol **21** (931 mg, 1.41 mmol), pyridine (50 μL), and $NaHCO_3$ (260 mg, 3.10 mmol) in dichloromethane (140 mL) maintained at ca. 22 °C. After 0.25 h pyridine (140 μL) was added to the reaction mixture that was then filtered through a pad of TLC-grade silica gel (14 g) with the solids thus retained being washed with diethyl ether (100 mL). The combined filtrates were concentrated under reduced pressure, and the residue thus obtained was subjected to flash chromatography (silica, 6:2.5:0.5 → 6:3:1 v/v/v dichloromethane/40−60 petroleum spirit/ethyl acetate gradient elution) to afford, after concentration of the relevant fractions (R_f = 0.4 in 6:3:1 v/v/v dichloromethane/40−60 petroleum spirit/ethyl acetate), compound **22** (810 mg, 87%) as a clear, pale-yellow oil, $[\alpha]_D^{20}$ +2.2 [*c* 4.4, $(CH_3)_2CO$]. ^{1}H NMR [400 MHz, $(CD_3)_2CO$] δ 9.71 (d, *J* = 2.8 Hz, 1H), 7.77 (d, *J* = 2.3 Hz, 1H), 6.70 (d, *J* = 2.3 Hz, 1H), 6.66 (dt, *J* = 14.5 and 7.0 Hz, 1H), 6.51 (broadened d, *J* = 15.8 Hz, 1H), 6.36−6.27 (complex m, 2H), 5.30 (ABq, *J* = 11.3 Hz, 2H), 5.19 (m, 1H), 4.58 (m, 1H), 4.46 (dd, *J* = 7.1 and 2.8 Hz, 1H), 3.84 (s, 3H), 3.80 (m, 2H), 2.57 (m, 1H), 2.52−2.38 (complex m, 3H), 1.55 (s, 3H), 1.39 (s, 3H), 1.33 (d, *J* = 6.3 Hz, 3H), 0.97 (m, 2H), −0.01 (s, 9H); ^{13}C NMR [100 MHz, $(CD_3)_2CO$] δ 202.3, 167.4, 162.0, 156.4, 143.0, 137.6, 130.0, 129.8, 118.0, 111.0, 103.8, 101.4, 93.8, 82.7, 78.6, 78.2, 70.7, 67.0, 55.8, 42.4, 34.3, 27.8, 25.6, 19.9, 18.5, 1.2; IR (KBr) ν_{max} 2952, 1728, 1601, 1262, 1162, 1108, 1051, 836 cm^{-1}; MS (ESI, +ve) *m*/*z* 683 ($[M + Na]^+$, 20%), 661 (38), 242 (88), 117 (100); HRMS (ESI) $[M + Na]^+$ calcd for $C_{28}H_{41}{}^{127}IO_8Si$ 683.1513, found 683.1514.

Compound 23. While being maintained under an atmosphere of nitrogen, anhydrous $CrCl_2$ (1.55 g, 12.3 mmol) and then $NiCl_2$ (8 mg, 5 mol %) were added to a magnetically stirred solution of aldehyde **22** (832 mg, 1.23 mmol) in dry DMF (250 mL, freshly distilled from CaH_2). The resulting mixture was flushed with and then deoxygenated using argon for 0.5 h. The reaction vessel was then sealed, and the contents were stirred at ca. 22 °C for 30 h before being quenched with water (ca. 750 mL) and then extracted with diethyl ether (3 × 250 mL). The combined organic layers were washed with "half-brine" (2 × 250 mL) before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The resulting light-yellow oil was subjected to flash chromatography (silica, 1:1 → 1:4 v/v 40−60 petroleum spirit/diethyl ether gradient elution) to afford, after concentration of the appropriate fractions (R_f = 0.25 in 3:2 v/v 40−60 petroleum spirit/ethyl acetate), the title compound **23** (507 mg, 77%) as a pale-yellow oil, $[\alpha]_D^{20}$ +48.3 [*c* 6.8, $(CH_3)_2CO$]. ^{1}H NMR [400 MHz, $(CD_3)_2CO$] δ 6.66 (d, *J* = 2.3 Hz, 1H), 6.50 (m, 2H), 6.06 (m, 1H), 5.90 (m, 1H), 5.58 (dd, *J* = 15.9 and 6.1 Hz, 1H), 5.31 (m, 1H), 5.25 (ABq, *J* = 7.0 Hz, 2H), 4.26 (m, 1H), 4.11 (m, 1H), 3.95 (dd, *J* = 9.5 and 4.8 Hz, 1H), 3.81 (s, 3H), 3.78 (m, 2H), 3.43 (broadened s, 1H), 2.62 (m, 1H), 2.50−25 (complex m, 3H), 1.43 (s, 3H), 1.34 (d, *J* = 6.3 Hz, 3H), 1.32 (s, 3H), 0.96 (m, 2H), −0.01 (s, 9H); ^{13}C NMR [100 MHz, $(CD_3)_2CO$] δ 167.7, 161.8, 156.5, 137.9, 132.3, 131.0, 130.9, 130.3, 117.5, 107.9, 106.5, 101.1, 93.8, 81.9, 77.3, 70.6, 69.4, 66.9, 55.8, 38.9, 34.4, 28.7, 26.2, 21.2, 18.5, 1.3; IR (KBr) ν_{max} 3517, 2927, 2852, 1724, 1600, 1578, 1250, 1162, 1104, 1055, 971, 836 cm^{-1}; MS (ESI, +ve) *m*/*z* 557 (100%); HRMS (ESI) $[M + Na]^+$ calcd for $C_{28}H_{42}O_8Si$ 557.2547, found 557.2548.

Compound 2 (Cochliomycin B). TBAF (2.0 mL of a 1.0 M solution in THF, 2.0 mmol) was added to a magnetically stirred solution of compound **23** (107 mg, 0.20 mmol) in THF (2 mL), and the ensuing mixture was heated at reflux for 24 h while being maintained under nitrogen. The cooled reaction mixture was filtered through a pad of TLC-grade silica gel (0.5 g), and the solids thus retained were washed with diethyl ether (20 mL). The combined filtrates were concentrated under reduced pressure, and the ensuing light-yellow oil was subjected to flash chromatography (silica, 4:1 v/v diethyl ether/40−60 petroleum spirit elution). Concentration of the relevant fractions (R_f = 0.3) afforded compound **2** (58 mg, 73%) as a white, amorphous solid, mp 134−136 °C, $[\alpha]_D^{20}$ −17.7 (*c* 1.41, CH_3OH). ^{1}H NMR (400 MHz, $CDCl_3$) δ see Table 1; ^{13}C NMR (100 MHz, $CDCl_3$) δ see Table 1; IR (KBr) 3514, 2984, 2935, 1702, 1647, 1609, 1573, 1382, 1370, 1356, 1320, 1260, 1216, 1160, 1118, 1059, 965, 851 cm^{-1}; MS (ESI, +ve) *m*/*z* 427 (100%); HRMS (ESI) $[M + Na]^+$ calcd for $C_{22}H_{28}O_7$ 427.1733, found 427.1733.

Compound 1 (Cochliomycin A). Compound **23** (53.4 mg, 0.10 mmol) was treated with HCl (10 mL of a 0.1 M solution in dry CH_3OH), and the resulting mixture stirred at ca. 22 °C and then, after 1 h, quenched with anhydrous K_2CO_3 and filtered through a pad of TLC-grade silica gel (0.2 g). The solids thus retained were washed with diethyl ether (20 mL), and the combined filtrates were concentrated under reduced pressure. The resulting light-yellow oil was subjected to flash chromatography (silica, diethyl ether elution) to afford, after concentration of the relevant fractions (R_f = 0.25), compound **1** (36.8 mg, 91%) as a white solid, mp 154−155 °C, $[\alpha]_D^{20}$ +34.4 (*c* 1.99, CH_3OH). ^{1}H NMR (400 MHz, $CDCl_3$) δ see Table 2; ^{13}C NMR (100 MHz, $CDCl_3$) δ see Table 2; IR (KBr) ν_{max} 3479, 2983, 2932, 1647, 1608, 1571, 1317, 1256, 1210, 1159, 1116, 1042, 965 cm^{-1}; MS (ESI, +ve) *m*/*z* 427 (100%); HRMS (ESI) $[M + Na]^+$ calcd for $C_{22}H_{28}O_7$ 427.1733, found 427.1728.

Compound 24 (Zeaenol). Compound **23** (107 mg, 0.20 mmol) was treated with HCl (20 mL of a 1 M solution in 9:1 v/v CH_3OH/water). The resulting mixture was stirred magnetically at ca. 22 °C for 16 h before being quenched with anhydrous K_2CO_3 and then filtered through a pad of TLC-grade silica gel (0.5 g), and the solids thus retained were washed with dichloromethane/CH_3OH (50 mL of a 4:1 v/v mixture). The combined filtrates were concentrated under reduced pressure, and the resulting light-yellow oil was subjected to flash chromatography (silica, 9:1 v/v dichloromethane/CH_3OH elution). Concentration of the relevant fractions (R_f = 0.3) then gave a white solid that upon recrystallization (chloroform/CH_3OH) afforded compound **24** (85.8 mg, 84%) as a white, crystalline solid, mp 176−178 °C, $[\alpha]_D^{20}$ −93.8 (*c* 4.8, CH_3OH). ^{1}H NMR (400 MHz, $CDCl_3$) δ see Table 3; ^{13}C NMR (100 MHz, $CDCl_3$) δ see Table 3; IR (KBr) ν_{max} 3386, 2917,

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1644, 1607, 1572, 1315, 1257, 1160, 1052, 964 cm^{-1}; MS (ESI, +ve) *m/z* 387 ($[M + Na]^+$, 30%), 139 (100); HRMS (ESI) $[M + Na]^+$ calcd for $C_{19}H_{24}O_7$ 387.1420, found 387.1449.

Crystallographic Data. *Compound* **2**. $C_{22}H_{28}O_7$, M = 404.46, *T* = 150 K, monoclinic, space group $P2_1$, *Z* = 4, *a* = 8.5036(1) Å, *b* = 26.1166(3) Å, *c* = 9.3544(1) Å; β = 94.3007(9)°; *V* = 2071.62(4) $Å^3$, D_x = 1.297 g cm^{-3}, 7438 unique data ($2\theta_{max}$ = 144.4°), *R* = 0.033 [for 7084 reflections with $I > 2.0\sigma(I)$]; *Rw* = 0.084 (all data), *S* = 1.00.

Compound **24**. $C_{19}H_{24}O_7 \cdot H_2O$, M = 382.41, *T* = 150 K, monoclinic, space group *C*2, *Z* = 4, *a* = 16.8112(2) Å, *b* = 4.9796(1) Å, *c* = 23.1742(3) Å, β = 105.1099(15)°, *V* = 1872.91(5) $Å^3$, D_x = 1.356 g cm^{-3}, 3061 unique data ($2\theta_{max}$ = 144.8°), *R* = 0.031 [for 2944 reflections with $I > 2.0\sigma(I)$]; *Rw* = 0.077 (all data), *S* = 1.00.

Structure Determinations. Images were measured on a CCD diffractometer (CuKα, mirror monochromator, λ = 1.54184 Å), and data were extracted using the CrysAlis package.[27] Structures were solved by direct methods (SIR92).[28] The structures of compounds **2** and **24** were refined using the CRYSTALS program package.[29] Atomic coordinates, bond lengths and angles, and displacement parameters for compounds **2** and **24** have been deposited at the Cambridge Crystallographic Data Centre (CCDC Nos. 1029428 and 1029429 for compounds **2** and **24**, respectively). These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Crystallographic data (CIFs), anisotropic displacement ellipsoid plots derived from the single-crystal analyses of compounds **2** and **24**; ^1H and ^{13}C NMR spectra for compounds **1**, **2**, **4**−**6**, **8**−**10**, **12**, **13**, **15**, **16**, and **18**−**24**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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