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A Concise Synthesis of the Octalactins

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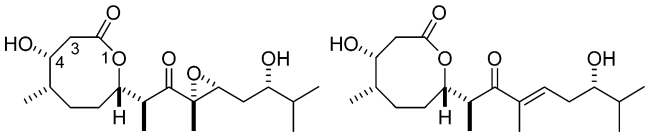
Abstract: The total synthesis of octalactins A and B has been achieved in 15 steps (longest linear sequence) and 10% overall yield from commercially available materials. Key steps include the Paterson−Aldol reaction for the rapid assembly of the carbonate **46**, methylenation of **46** and subsequent Claisen rearrangement of the corresponding alkenyl-substituted cyclic ketene acetal to provide the core unsaturated medium-ring lactone **47**, and the use of enzyme-mediated acetate deprotection in the presence of a medium-ring lactone.

Introduction

In 1991, Fenical and Clardy reported the isolation of the saturated eight-membered lactones octalactin A (**1**) and B (**2**) from a marine-derived actinomycete of the genus *Streptomyces* collected from a gorgonian octocoral.[1,2] The structure and relative stereochemistry of **1** and **2** were assigned by a combination of spectroscopic analysis and X-ray crystallography; the absolute stereochemistry of the metabolites was established by total synthesis.[3,4] Biological evaluation of these natural products demonstrated that octalactin A (**1**) was significantly cytotoxic in tests with B-16-F10 murine melanoma and HCT-116 human colon tumor cell lines, whereas octalactin B (**2**) was completely inactive.[1,5] The therapeutic potential of octalactin A (**1**) coupled with the unusual structural features of both metabolites and the challenges associated with the construction of such systems has rendered the octalactins attractive targets for total synthesis.



1 **2**

In the first total synthesis of the octalactins,[3] Buszek used the Gerlach modification[6] of the Corey−Nicolaou lactonization[7,8] to form the central eight-membered lactone of **1** and **2**. This synthesis demonstrated for the first time that it was feasible to construct an eight-membered lactone from a saturated *seco*-acid precursor using a direct lactonization. This methodology has further been extended by Buszek.[9] Latterly, the Buszek group have demonstrated the utility of ring-closing metathesis for the construction of the key eight-membered lactone core of **1** and **2** as well as documenting a large-scale route for the synthesis of **1**.[10,11] A completely different approach was adopted by McWilliams and Clardy for the synthesis of ***ent*-1** and ***ent*-2**.[4] Their elegant synthesis involved a Baeyer−Villiger ring expansion for the conversion of a cycloheptanone into the corresponding eight-membered lactone core of **1** and **2**. Many other groups have reported formal total syntheses and approaches toward the octalactins.[12−17] Our own approach to medium-ring oxacycles has been based on ring expansion reactions of cyclic ketones and ketene acetals to produce both saturated[18−23] and unsaturated[23−29] medium-ring lactones. In

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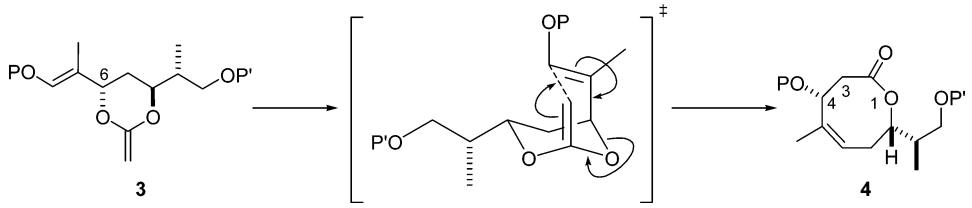
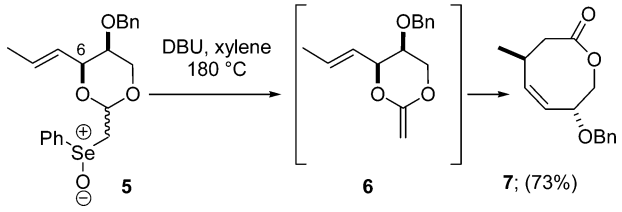


Figure 1. Transfer of stereochemical information during the Claisen rearrangement.

Scheme 1. Synthesis of the Lactone **7**



particular, we have exploited the Claisen rearrangement of alkenyl-substituted ketene acetals to prepare unsaturated medium-ring lactones, a reaction first reported by Petrzilka,[30] although we have demonstrated that a direct lactonization approach to unsaturated medium-ring lactones is also feasible.[23] Herein we report a short total synthesis of the octalactins based on the two-carbon ring expansion reaction of an alkenyl-substituted ketene acetal to form an unsaturated eight-membered ring lactone which is stereoselectively hydrogenated to produce the core saturated lactone of **1** and **2**. A notable feature of our approach is the faithful transfer of stereochemical information from the sp^3 center at C6 and the *E*-alkene in **3** to the sp^3 center at C4 and the *Z*-alkene in the lactone **4**, presumably through the chairlike transition state of the Claisen rearrangement (Figure 1).[27−29]

Results and Discussion

Synthesis of a Model System. At the outset of this work, we had demonstrated that it was possible to synthesize diastereomerically pure disubstituted seven- and eight-membered lactones by Claisen rearrangement of the corresponding vinyl-substituted ketene acetals.[27] For example, heating a solution of the selenoxides **5** and DBU in xylene in a sealed tube at 180 °C afforded the diastereomerically pure lactone **7** with complete transfer of stereochemical information (Scheme 1).

Before we embarked upon the synthesis of the octalactins, it was necessary to demonstrate that it would be possible to synthesize an eight-membered lactone such as **9** containing a 5,6-trisubstituted double bond with concomitant introduction of the C4 substituent by transfer of stereochemical information from the sp^3 center (C6) of the alkene-substituted ketene acetal **8** (Scheme 2).[28,29]

For synthetic simplicity, we selected the racemic lactone **9** as our initial target with the knowledge that the phenyldimethylsilyl group could potentially be transformed into the desired hydroxy substituent by Fleming−Tamao oxidation later in the synthesis.[31] Claisen rearrangement of the alkenyl-substituted ketene acetal **8** derived from the corresponding *anti*-1,3,-diol would likely proceed via a chair−chair transition state (Scheme 2) to deliver the desired *cis*-disubstituted lactone **9**; previous work had indicated that the synthesis of medium-ring lactams proceeded more efficiently from alkenyl-substituted ketene aminals derived from *anti*-1,3-amino alcohols than from the corresponding syn diastereomers.[32]

The unsaturated lactone **9** was prepared by the route outlined in Scheme 3. Aldol reaction of the boron enolate derived from acetophenone **10** with TMS-propynal **11**[33] provided the β-keto alcohol **12** in good yield (74%). Hydroxy-directed anti reduction of **12** was effected using the Evans protocol[34] to provide the diol **13** as a single diastereomer (mp 92−94 °C from EtOAc/hexane) as judged by 200 MHz ^{1}H NMR. The TMS protecting group was removed (NaOH, MeOH), and the acetonide **14** was formed under standard conditions. Silylcupration of **14** was conducted according to the Fleming protocol[35] and the resultant alkenylcuprate was quenched with methyl iodide furnishing the (*E*)-alkene **15a** in respectable yield.[36] While this reaction is known to be very efficient for simpler acetylenes, the yields for this system were variable even with strict monitoring of the reaction conditions. At this stage, it was possible to confirm the relative stereochemistry of the substituents on the acetonide **15a** and hence the diol **13**. In line with the results of Rychnovsky,[37,38] the ^{13}C NMR chemical shifts of the methyl groups of the acetonide **15a** were at δ 25.0 and 25.1 indicating that **15a** adopts a twist-boat conformation and is therefore derived from an *anti*-diol.[39] Acetonide removal transformed **15a** into the corresponding diol which was converted into the selenoacetal **17** in the presence of phenylselanylacetaldehyde diethylacetal **16**[30] and PPTS. The selenides **17** were isolated as a mixture of diastereomers, and no attempt was made to separate them, although they both appeared to undergo selenoxide

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(33) Kruithof, K. J. H.; Schmitz, R. F.; Klumpp, G. W. *Tetrahedron* **1983**, *39*, 3073−3081.
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(36) If the silylcupration reaction was prematurely quenched then the corresponding (*E*)-disubstituted olefin **15b** was isolated (J_{alkene} = 18.9 Hz). The alkene **15b** arises via protonation of the vinyl copper intermediate. By analogy, the stereochemistry of vinyl silane **15a** was assigend as (*E*).
(37) Rychnovsky, S. D.; Yang, G.; Powers, J. P. *J. Org. Chem.* **1993**, *58*, 5251−5255.
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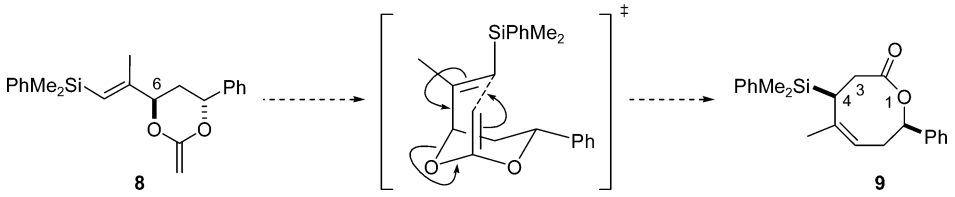
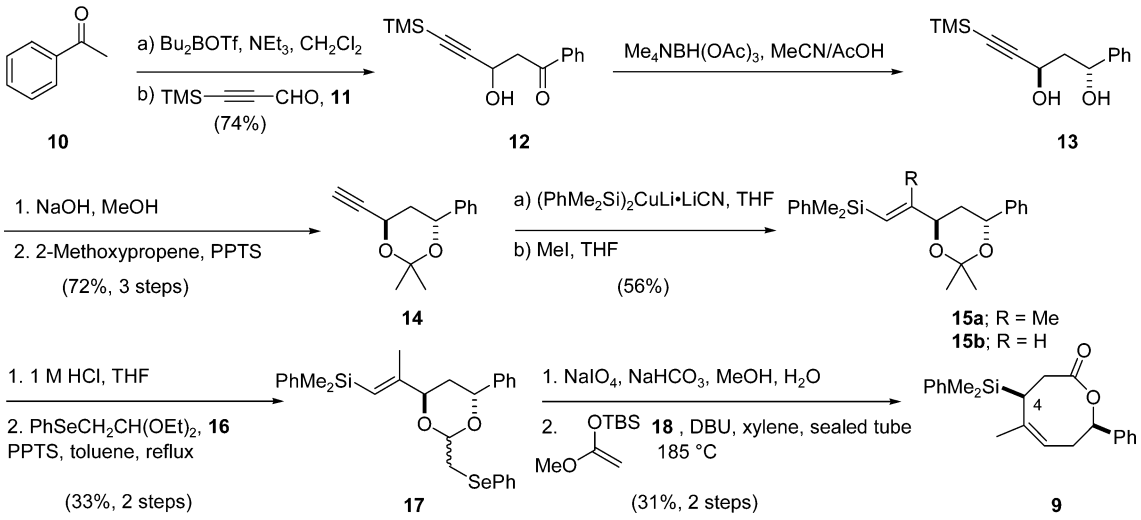
(39) Due to the sterically undemanding nature of a terminal acetylene (A-value = 0.41−0.52 kcal mol^{-1}) alkynyl-substituted acetonides of *anti*-1,3-diols generally exist as an equilibrium mixture of chair and twist-boat conformers.[37] For these systems, Rychnovsky has shown that the difference in the ^{13}C NMR chemical shifts for the methyl groups of the acetonide ($\Delta\delta$) are usually <5 ppm. For the alkynyl-substituted acetonide **14**, $\Delta\delta$ = 5.8 ppm indicating that **14** was most likely derived from an *anti*-1,3-diol. Confirmation of this stereochemical assignment was therefore made on the vinyl silane **15a**.

Scheme 2. Proposed Claisen Rearrangement of the Ketene Acetal **8**



Scheme 3. Synthesis of the Lactone **9**



elimination and Claisen rearrangement with equal facility. The selenides were oxidized to the corresponding selenoxides which, on being heated as a dilute solution in xylene in a sealed tube at 180 °C in the presence of DBU and the silyl ketene acetal **18**, provided the ketene acetal **8** which underwent in situ Claisen rearrangement to provide the desired eight-membered lactone **9** in 31% yield. The use of the ketene acetal **18** as a trap for "$PhSe^+$" had previously been shown to enhance related Claisen ring expansion reactions which were sensitive to side reactions involving disproportion promoted by "$PhSe^+$".[32] The lactone **9** was isolated as a single diastereomer indicating complete transfer of stereochemical information between C6 in **8** and C4 in **9**. Due to overlapping ^{1}H NMR signals from several key protons on the ring, assignment of the relative stereochemistry of **9** on the basis of ^{1}H NMR NOE experiments proved inconclusive. The stereochemistry of **9** was therefore tentatively assigned as cis on the basis of the likely chair−chair transition state of the Claisen rearrangement which places the phenyl group in a pseudoequatorial position (see Scheme 2).[23]

The success of this strategy toward a disubstituted eight-membered lactone bearing a trisubstituted double bond, which was the most stereochemically demanding Claisen rearrangement which we had realized at that time, encouraged us to press on with the total synthesis of the octalactins. However, due to the capricious nature of the silylcupration reaction used to generate **15a**, we decided to investigate the possibility of carrying a protected hydroxy group through the synthesis from the outset.

Retrosynthetic Analysis and Synthetic Planning. As had been previously demonstrated, octalactin A (**1**) may be synthesized from octalactin B (**2**) by hydroxy directed epoxidation.[4] Our initial target was therefore the enone **2**. The retrosynthetic analysis of **2** (Scheme 4) depends on the convergent union of the aldehyde **19** with the vinyl iodide **23** using the Nozaki−Hiyama−Kishi reaction[40] (NHK reaction), a process which has precedent from a previous synthesis of **2**.[3] The vinyl iodide **23** was to be generated by hydrozirconation of the corresponding acetylene which would be available through elaboration of the boronic acid **24** according to the procedure of Yamamoto;[41] Andrus has also used this methodology for the synthesis of the side chain of the octalactins.[15] The saturated eight-membered lactone **19** was to be prepared by substrate controlled hydrogenation of the trisubstituted ring-alkene **4**.[42] A key test of the synthetic strategy would be the stereoselective reduction of the double bond in **4**, and we anticipated that the reduction would occur preferentially from the face opposite the C4 and C8 substituents. Success in the model Claisen rearrangement study implied that we would be able to prepare the unsaturated lactone **4** by [3,3]-sigmatropic rearrangement of the alkenyl-substituted ketene acetal **3** which was to be generated either by in situ selenoxide elimination from **20** or by methylenation of the carbonate **21** using dimethyltitanocene.[28] The synthesis therefore relied upon the preparation of the triol derivative **20** or **21**. The *anti*-1,3-diol precursor to **20** and **21** would be necessary in order to set the desired stereochemistry at C4 in the lactone **4**, and based on previous experience, we were confident that Claisen rearrangement from the derived alkenyl-substituted ketene acetal **3** would occur in good yield.[32] The elegant aldol methodology of Paterson,[43−45] based on Ipc boron enolates, was to be used to prepare **22** which would undergo *anti*-selective reduction[34]

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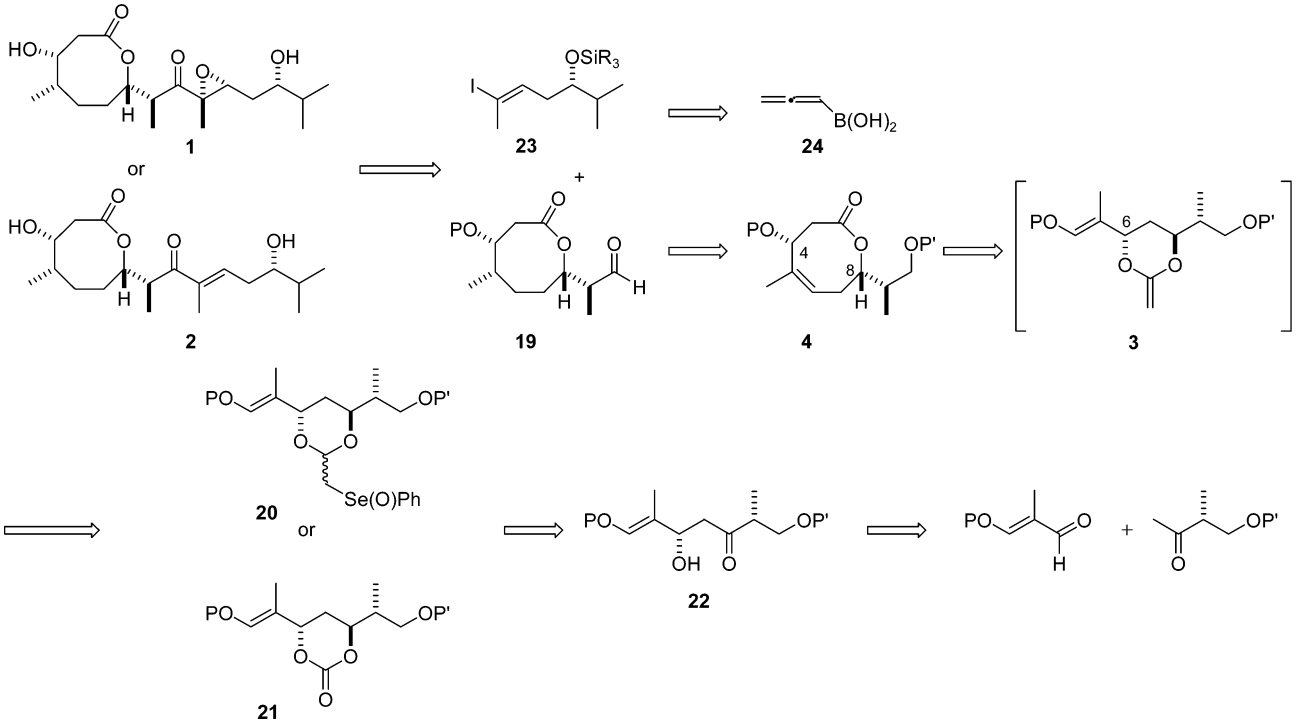
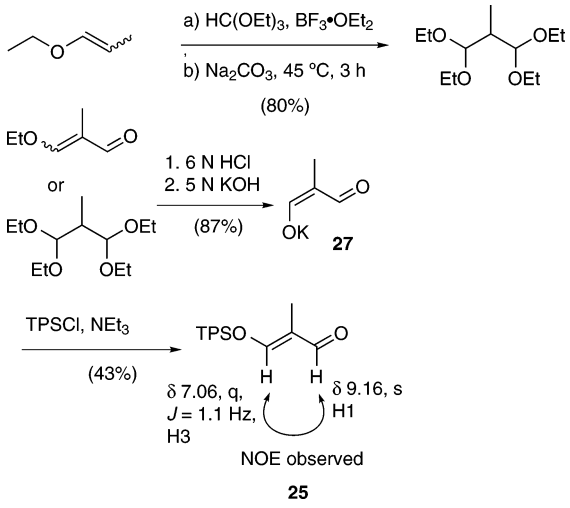
Scheme 4. Retrosynthetic Analysis of the Octalactins[a]



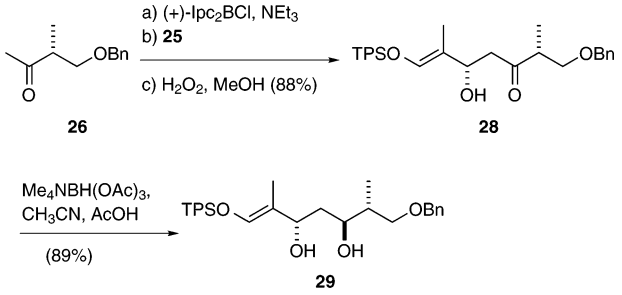
[a] P,P′ = protecting groups.

Scheme 5. Synthesis of the Aldehyde **25**



to provide the desired diol. Note that this strategy combines the requirement of an *anti*-1,3-diol with the use of substrate-induced stereocontrol to generate the required absolute stereochemistry at C4 and C8 in the lactone **4**. Not only does the Claisen rearrangement induce the C4 stereocenter in **4**, but it also produces the desired (*Z*)-trisubstituted double bond at the expense of the C6 stereocenter in the ketene acetal **3**. As in the synthesis of many complex natural products, the choice of protecting groups would prove crucial to the success of our plan. At the outset of the synthesis, we chose to prepare the vinylogous silyl ester **25** (Scheme 5) and the known benzyl-protected methyl ketone **26** (Scheme 6).[43] This choice was guided, in part, by Clardy's synthesis of the octalactins where a silyl group had been used to protect the oxygen functionality at C4 of **1** and **2**.[4]

Scheme 6. Synthesis of the Diol **29**

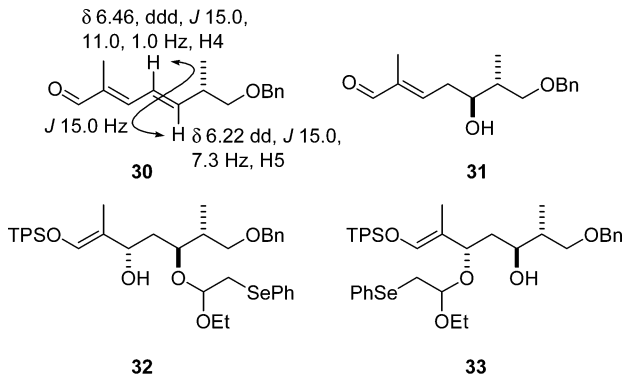


First Generation Synthesis of the Core Saturated Eight-Membered Lactone. The construction of the required core eight-membered lactone began with the convergent aldol union of the silyloxy aldehyde **25** with the methyl ketone **26**. The aldehyde **25**[46] was prepared from the enolate **27** by adaptation of a literature procedure (Scheme 5).[47] The salt **27** is readily obtained from either tetraethoxymethylpropane or 3-ethoxymethacrolein via acid-catalyzed hydrolysis followed by addition of potassium hydroxide.[46,48,49] The stereochemistry of **25** was assigned by ^{1}H NMR NOE measurements; a strong reciprocal NOE was observed between H1 and H3 with no NOE being observed between H3 and the methyl group. The known methyl ketone **26** was prepared from (*R*)-methyl-3-hydroxy butyrate.[43]

The aldol reaction of the Ipc-boron enolate derived from the methyl ketone **26**, and the aldehyde **25** afforded the 1,4-*syn*-*β*-hydroxy ketone **28** in good yield and reasonable diastereoselectivity (71%) (Scheme 6).[43−45,50] Attempted formation of

(46) Ullrich, F.-W.; Rotscheidt, K.; Breitmaier, E. *Chem. Ber.* **1986**, *119*, 1737−1744.
(47) The corresponding trimethylsilyl-protected aldehyde has been prepared.[46]
(48) Klimo, V. T.; Skoldinov, A. P. *Chem. Abstr.* **1960**, *54*, 20870.
(49) Isler, O.; Zeller, P. (Hoffmann-La Roche) Ger., 1,011,881, 11 Jul 1957. *Chem. Abstr.* **1959**, *53*, P15116e.
(50) Cowden, C. J.; Paterson, I. *Org. React.* **1997**, *51*, 1−200.

Chart 1



the Mosher esters from **28** was unsuccessful and resulted in decomposition of the substrate. The stereochemistry of the major diastereomer **28** was therefore tentatively assigned as 1,4-*syn* on the basis of precedent.[43,44] The decomposition of **28** under the conditions for Mosher ester formation indicated the delicate nature of the compound and hinted at the problems that we were soon to face. *Anti*-reduction[34] of the aldol **28** provided the corresponding *anti*-diol **29**. The diol **29** was relatively unstable and was therefore stored as a dilute solution in ethyl acetate at −20 °C and was not purified by column chromatography. Attempted formation of the acetonide derived from **29** to allow stereochemical assignment resulted in decomposition. However, the stereochemistry of the diol could be assigned by comparison of the ^{1}H NMR with the ^{1}H NMR of **15a** (see Supporting Information).

We have gained extensive expertise in the formation of medium-ring lactones (and lactams[32,51−53]) by the Claisen rearrangement of alkenyl-substituted ketene acetals (and aminals). In these studies, we have generally formed the ketene acetal according to the original procedure of Petrzilka,[30] namely by pyrolytic selenoxide elimination from the corresponding acetal. These acetals are formed by acid-catalyzed acetal exchange between phenylselanylacetaldehyde diethyl acetal **16** and the 1,*n*-diol. More recently, we have reported a complementary method for the formation of ketene acetals via methylenation of the corresponding carbonates using a titanium-methylidene reagent.[28] The carbonates (e.g., **21**) are formed at low temperature under mildly basic conditions thus complementing the acid-catalyzed formation of the selenoacetals.

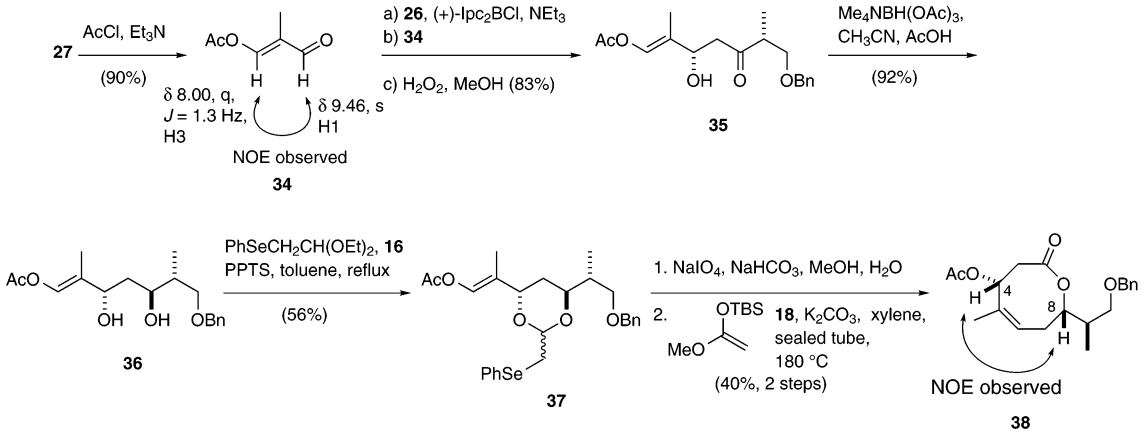
Exposure of the diol **29** to our standard conditions for selenoacetal formation (acetal **16**, PPTS, toluene at reflux) yielded the diene **30** (Chart 1), the structure of which was assigned as the 2(*E*),4(*E*) isomer ($J_{4,5}$ = 15.0 Hz). The diene is assumed to arise via acid-catalyzed elimination of the hydroxy groups at C3 and C5 of **29**. A wide variety of protic and Lewis acids were screened in an effort to form the desired cyclic selenoacetal; however, all efforts met with failure. Either starting material (**29**) was recovered, or more usually, the diol **29** decomposed or was transformed into the aldehyde **30**. The synthesis of the selenoacetal **16** involves the addition of phenylselenyl chloride to ethyl vinyl ether in the presence of basic ethanol.[30] A plausible strategy for the formation of the required 1,3-dioxane could involve generation of the mixed acetals **32** and **33** under mild basic conditions followed by mild intramolecular transacetalization. Addition of a mixture of ethyl vinyl ether and phenylselenyl chloride to a solution of the diol **29** and diisopropylethylamine in ethanol provided the two mixed acetals **32** and **33** as a 2:1 mixture in a combined yield of 55%. The structures of the regioisomeric acetals were assigned on the basis of ^{1}H NMR COSY experiments. Treatment of the major acetal **33** with a range of mild protic and Lewis acids resulted in formation of either the diene **30** or the α,β-unsaturated aldehyde **31**. Indeed heating a solution of the acetal **33** in toluene at reflux in the presence of 4 Å molecular sieves resulted in formation of the diene **30** indicating the acute acid sensitivity of the mixed acetal. In a further series of experiments, formation of the desired acetal was attempted using Noyori's protocol[54] (TMS-triflate and the bis-TMS ether derived from **29**), but these conditions resulted in decomposition of the substrate.

A further method which would potentially allow access to the desired ketene acetal would involve reaction of a titanium methylidene carbene with the cyclic carbonate derived from the 1,3-diol **29**.[28] However, the difficulty in forming the Mosher esters of the aldol **28** was most probably a result of the very facile elimination that occurs when the hydroxy group in **28** is made into a good leaving group. Therefore formation of corresponding cyclic carbonate derived from **29** was likely to prove challenging. Indeed exposure of the diol **29** to either triphosgene[55] or carbonyldiimidazole[56] resulted in decomposition. By this stage, it was apparent that the silylenol ether was too electron rich and was promoting β-elimination reactions under both acidic and basic conditions. We therefore switched our attention to the use of an electron-withdrawing enol-acetate substituent to be derived from the aldehyde **34** (Scheme 7). At this stage, we were also mindful of the impending challenge of selective deacetylation of the C4 acetoxy substituent in the presence of a medium-ring lactone at a late stage in the synthesis.

The enol acetate **34** was synthesized in an analogous manner to that used for the enol silane **25** by reaction of the salt **27**[46] with acetyl chloride (Scheme 7); the stereochemistry of the product **34** was assigned by ^{1}H NMR NOE experiments. The Paterson−Aldol reaction[43−45,50] between **26** and **34** proceeded without incident to provide the 1,4-*syn*-aldol **35** with good diastereocontrol (88% de as judged by 400 MHz ^{1}H NMR). The absolute configuration at the newly formed stereocenter was assigned using Kakisawa's extension of Mosher's method (see Supporting Information).[57] *Anti*-selective reduction of the keto-alcohol **35** with tetramethylammonium triacetoxyborohydride[34] provided the *anti*-diol **36** as a single diastereomer; the relative stereochemistry of **36** was assigned as anti on the basis of much precedent. Exposure of **36** to phenylselanylacetaldehyde diethyl acetal[30] **16** and PPTS in toluene at reflux in the presence of 4 Å molecular sieves provided the corresponding selenoacetals **37** in 56% optimized yield as a mixture of acetal diastereomers. These reactions have been shown to be highly

(51) Evans, P. A.; Holmes, A. B.; Collins, I.; Raithby, P. R.; Russell, K. *Chem. Commun.* **1995**, 2325−2326.
(52) Evans, P. A.; Holmes, A. B.; Russell, K. *J. Chem. Soc., Perkin Trans. 1* **1994**, 3397−3409.
(53) Evans, P. A.; Holmes, A. B.; Russell, K. *Tetrahedron Lett.* **1992**, *33*, 6857−6858.
(54) Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 1357.
(55) Burk, R. M.; Roof, M. B. *Tetrahedron Lett.* **1993**, *34*, 395−398.
(56) Kutney, J. P.; Ratcliffe, A. H. *Synth. Commun.* **1975**, *5*, 47−52.
(57) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092−4096.

Scheme 7. Synthesis of the Lactone **38**



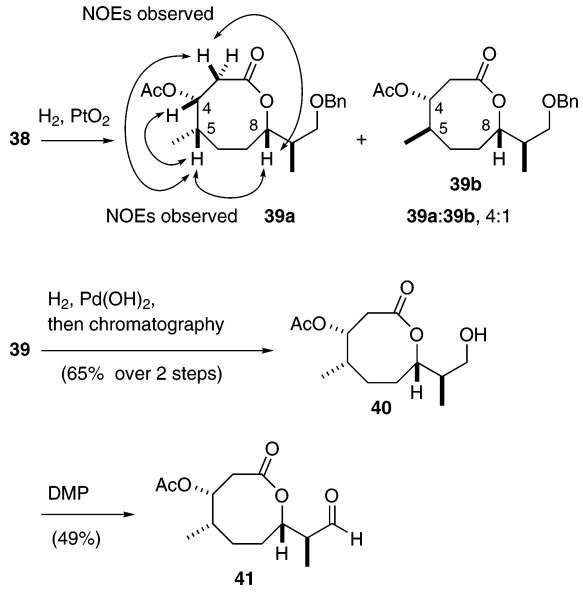
susceptible to the presence of residual acetic acid from the triacetoxyborohydride reduction. If the final product is not carefully washed with saturated sodium hydrogencarbonate solution, it is impossible to form the acetals **37**; the only products observed are the aldehydes **30** and **31**. Even with these precautions, a more polar highly UV active component (the hydroxy-aldehyde **31**) was always observed. It was therefore not possible to completely suppress the formation of the elimination product **31** even when the olefin carried an electron-withdrawing group. The oxidation of the selenides **37** to the corresponding selenoxides proceeded without event. Heating the selenoxides using our standard conditions (xylene at reflux in the presence of DBU)[23] provided the desired eight-membered lactone **38** in poor yield (22%) along with recovered selenides **37** (25%). The low yield in this case was attributed to the known thermal cleavage of acetate esters by DBU[58] and to disproportionation reactions mediated by "$PhSe^{+}$".

As previously noted, the selenides are most likely formed by reduction of the selenoxides with diphenyl diselenide.[28] The diphenyl diselenide is produced by the disproportionation of the benzeneseleninic acid which is a product of the selenoxide elimination. The disproportionation may be suppressed by the use of non-nucleophilic bases and the addition of a nucleophilic silyl ketene acetal (e.g. **18**) as a selenium scavenger. After much experimentation, it was discovered that heating the selenoxides in a sealed tube in xylene at 180 °C in the presence of potassium carbonate and **18** furnished the desired lactone **38** in an optimized yield of 40% as well as 24% of recovered selenides. Use of silyl-ketene aminals as selenium scavengers[27] or the addition of mild bases gave inferior yields of the lactone. In all cases, **38** was isolated as a single diastereomer.

Many of the hydrogen atoms adorning the ring of the lactone **38** showed vicinal ^{1}H NMR coupling constants of approximately 7 Hz, indicating that the ring was conformationally mobile and that the conformers were in "fast exchange" on the NMR time scale. Nevertheless, the stereochemistry of the lactone **38** could be assigned on the basis of ^{1}H NMR NOE data; a reciprocal NOE was observed between H4 (δ 5.65, t, J = 7.2 Hz, 1H) and H8 (δ 4.66, q, J = 7.5 Hz, 1H) in the lactone **38**, indicating that these two substituents were on the same face of the ring. The formation of the (4*R*)-lactone **38** may be explained by the preference for the Claisen rearrangement to adopt a chairlike

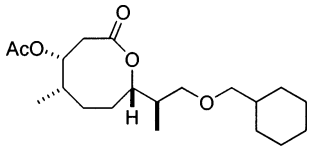
(58) Baptistella, L. H. B.; dos Santos, J. F.; Ballabio, K. C.; Marsaioli, A. J. *Synthesis* **1989**, 436−438.

Scheme 8. Conversion of the Lactone **38** into the Aldehyde **41**



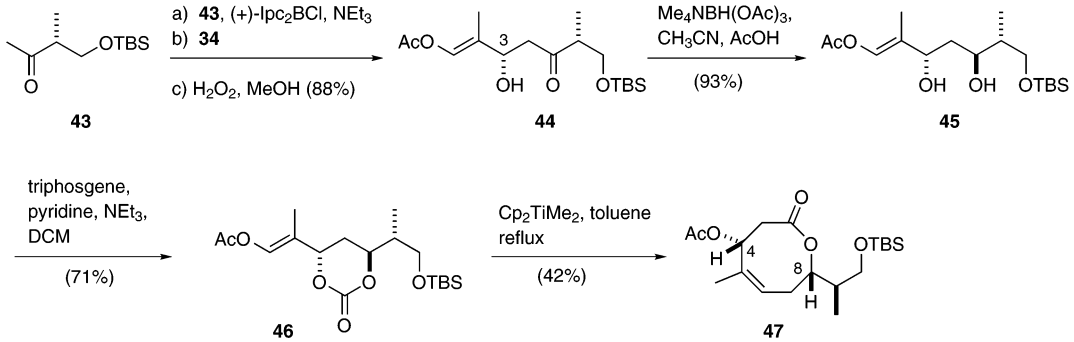
transition state with the α-methylbenzyloxyethyl side chain adopting a pseudoequatorial position (see Figure 1).

Transformation of the lactone **38** into the aldehyde **41** required for the side chain coupling necessitated the removal of the benzyl protecting group and the hydrogenation of the trisubstituted double bond from the top face as drawn. In initial catalyst screens, it was shown that palladium hydroxide effected the hydrogenolysis of the benzyl group with concomitant hydrogenation of the olefin to provide **40**. However, the product was isolated as a 1:1 mixture of C5 diastereomers. The use of Adams catalyst (PtO_2) provided the saturated lactones **39** as a mixture of inseparable C5 diastereomers (**39a**:**39b**, 4:1) (Scheme 8); careful monitoring of the reaction was required to minimize subsequent reduction of the benzyl group to a cyclohexylmethyl group, giving **42**.



The stereochemistry of the major lactone **39a** was assigned on the basis of a ^{1}H NMR NOESY experiment. An NOE was

Scheme 9. Synthesis of the TBS-Protected Lactone **47**



observed between H5 (δ 1.77−1.72, m, 1H) and H8 (4.45−4.40, m, 1H) and between H5 and H4 (δ 5.00, brd, J = 6.2 Hz, 1H). Further NOEs supported the assignment of the structure as shown and indicated that hydrogenation of **38** had occurred preferentially on the face of the olefin opposite to both the C4 and C8 side chains. Although we had not experienced any difficulty in hydrogenating the trisubstituted ring-double bond in **38** to provide **39**, Buszek and co-workers,[3] in the first synthesis of the octalactins, had found it impossible to hydrogenate a disubstituted double bond between C6 and C7 in a similar medium-ring lactone. However, if the reduction of the disubstituted double bond was delayed until installation of the complete octalactin side chain, then the hydrogenation could be accomplished with ease.[11] The benzyl group in **39** was removed by hydrogenolysis in the presence of palladium hydroxide, providing the primary alcohol **40** (9:1 mixture of C5 diastereomers after purification by flash chromatography) which was oxidized using the Dess−Martin periodinane[59−61] to provide the aldehyde **41** in 49% yield in readiness for side chain introduction. We had now managed to construct the core of the octalactins utilizing our Claisen rearrangement methodology. However, the modest yields encountered in the later stages of the synthesis meant that this route was unattractive for delivery of sufficient material for the completion of the synthesis.

Second Generation Synthesis of the Core Saturated Eight-Membered Lactone. Some of the difficulties associated with the first generation synthesis of the core lactone **41** resulted from our use of a benzyl protecting group. This group had interfered with the hydrogenation of the trisubstituted double bond in **38** and its removal by hydrogenolysis had not been high yielding. We therefore elected to use a more labile silyl ether protecting group. Furthermore, the formation of the selenides **37** under acidic conditions occurred in moderate yield and also resulted in the formation of some elimination products. We therefore decided to use our more recently developed methodology for the formation of ketene acetals from carbonates via methylenation with dimethyltitanocene.[28] Although we had already demonstrated that it was possible to form medium-ring lactones from alkenyl-substituted cyclic carbonates by exposure to dimethyltitanocene in toluene at reflux,[28] the use of a substrate bearing an acetate protecting group would provide a further test of this methodology; would it be possible to selectively methylenate a carbonate carbonyl group in the presence of an acetate carbonyl group?

The synthesis of the *anti*-diol **45** followed the same course as the synthesis of **36** (Scheme 9). Thus, 1,4-*syn*-selective aldol reaction between the Ipc boron enolate of the ketone **43**[62] and the aldehyde **34** proceeded without incident to provide **44**[43−45,50] (the stereochemistry at C3 was assigned on the basis of precedent).[63] Evans[34] *anti*-reduction then delivered the diol **45** (94% de) in good yield. Exposure of the diol **45** to our optimized conditions for carbonate formation (triphosgene, pyridine, triethylamine, 4 Å molecular sieves, dichloromethane, −78 → 0 °C)[28] provided the unstable cyclic carbonate **46** in good yield (71%). Treatment of the carbonate **46** with dimethyltitanocene in toluene at reflux[28,64] for 30 min resulted in methylenation and subsequent Claisen rearrangement to provide the desired eight-membered lactone **47** in reasonable yield (42%) after purification by flash chromatography. The stereochemistry of **47** [δ 5.70 (t, J = 7.4 Hz, 1H, H4), 5.43 (t, J = 6.2 Hz, 1H, H6), 4.67 (dt, J = 5.0, 9.3 Hz, 1H, H8)] was initially assigned by comparison of the ^{1}H NMR spectrum with the benzyl-protected lactone **38** [δ 5.65 (t, J = 7.2 Hz, 1H, H4), 5.42 (t, J = 6.7 Hz, 1H, H6), 4.66 (q, J = 7.5 Hz, 1H, H8)] and was proven by crystal structure analysis of a later translactonization product **48** (vide infra). Although the yield for the Claisen rearrangement to form the lactone **47** was similar to the selenium-based route to form **38**, the formation of the carbonate **46** occurred in significantly higher yield (71%) compared with the formation of the selenoacetals (56%). Furthermore, the conversion of the carbonate **46** into the lactone **47** occurred in toluene at reflux under relatively concentrated conditions (0.053 M), whereas the formation of the lactone **38** from the selenoxides derived from **37** required heating at 180 °C in a sealed tube at lower concentration (0.017 M). We[28] and others[65−67] had previously shown that it is possible to perform chemoselective methylenations of carbonyl groups using titanium based reagents; however, we believe that this is the first report of the selective methylenation of a carbonate carbonyl group in the presence of an ester carbonyl group. A plausible explanation for this chemoselectivity is that the lone pair electrons of the carbonate carbonyl group interact more readily with the bulky electrophilic titanium carbene generated from dimethylti-

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(60) Ireland, R. E.; Liu, L. B. *J. Org. Chem.* **1993**, *58*, 2899.
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(62) The enantiomer of the ketone **43** is known. Denmark, S. E.; Fujimori, S. *Synlett* **2001**, 1024−1029.
(63) Based on the isolated yield of diastereomerically pure **44**, the lower limit of the de of the aldol reaction of **43** and **34** is 76%.
(64) Petasis, N. A.; Bzowej, E. I. *J. Am. Chem. Soc.* **1990**, *112*, 6392−6394.
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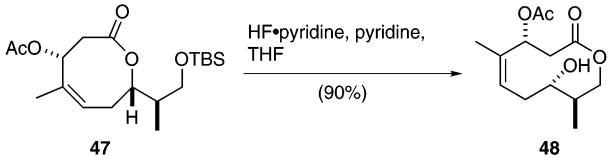
(67) Bartlett, P. A.; Nakagawa, Y.; Johnson, C. R.; Reich, S. H.; Luis, A. *J. Org. Chem.* **1988**, *53*, 3195−3210.

Scheme 10. Deprotection with Concommitant Translactonization



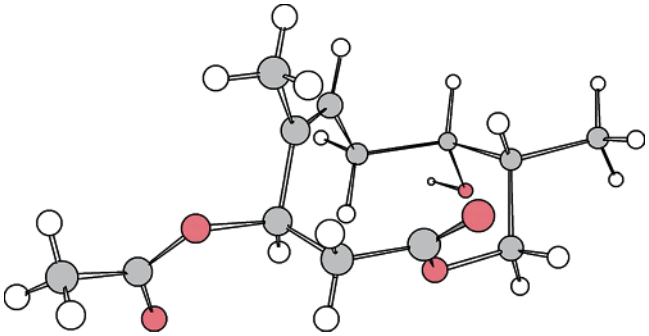


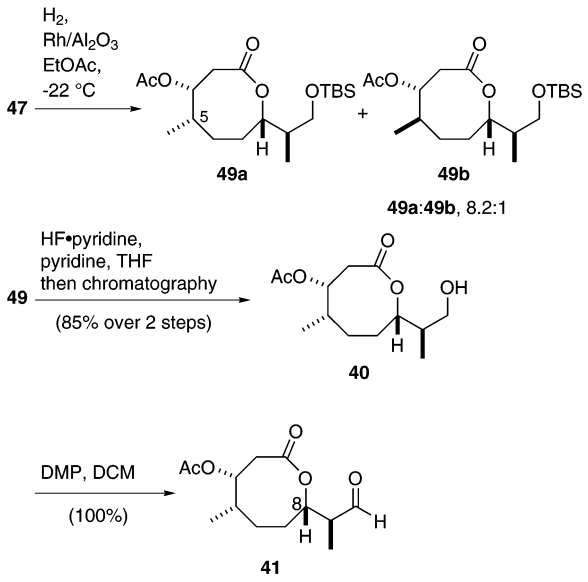
Figure 2. Chem-3D representation of the X-ray crystal structure of the lactone **48**. The acetate group carbonyl oxygen atom is disordered.

tanocene[68] than the lone pairs of the enol acetate carbonyl group. This may be mainly a steric effect as the alkyl groups of the carbonate **46** are "tied-back" into a six-membered ring rendering the carbonate carbonyl group lone pairs more available (and more basic) than those of the enol acetate of **46**.[69] Furthermore, the lone pairs of the enol acetate carbonyl group are likely to be less basic than those of a standard acetate ester.

With the lactone **47** in hand, we had the choice of either introducing the side chain and then hydrogenating the trisubstituted double bond or vice versa. Exposure of **47** to HF·pyridine (Scheme 10) resulted in cleavage of the silyl group and translactonization to provide the crystalline ten-membered lactone **48** in excellent yield. The lactone **48** formed crystals suitable for X-ray structure determination which allowed assignment of the relative (and hence absolute) stereochemistry of C4 in **47**. The structure is shown in Figure 2.[70] We have noted this type of ring-expansion reaction previously,[26] and the reaction is likely driven by the thermodynamic stability of the ten-membered lactone **48** compared with the desilylated eight-membered lactone derived from **47**.[71]

Due to the rearrangement encountered during desilylation of **47**, we elected to hydrogenate the trisubstituted double bond of **47** before desilylation. We switched our attention to the use of rhodium on alumina as the use of Adams catalyst had effected the transformation of **38** into **39** with moderate diastereoselectivity. In an initial encouraging experiment, the desired product, the saturated lactones **49**, was isolated as an inseparable 5:1 mixture of diastereomers (by ^{1}H NMR analysis), although this result was not reproducible in subsequent experiments (Scheme 11). The stereochemistry at C5 of the lactones **49** was assigned by comparison of the ^{1}H NMR spectra of **49a** [δ_H 5.03 (d, J =

Scheme 11. Synthesis of the Aldehyde **41**



6.1 Hz, 1H, H4)] and **49b** [δ_H 4.77 (ddd, J = 8.6, 5.0, 3.6 Hz, 1H, H4)] with **39a** [δ_H 5.00 (d, J = 6.0 Hz, 1H, H4)] and **39b** [δ_H 4.76 (ddd, J = 8.8, 5.1, 3.7 Hz, 1H, H4)] and ultimately rests with the conversion of the major diastereomer **49a** into the octalactins.

As discussed above, the benzyl-protected lactone **38** exists as a mixture of medium-ring conformers at room temperature. Due to similarities in the ^{1}H NMR spectrum it is most likely that the lactone **47** also exists as a mixture of medium-ring conformers. Therefore we postulated that the selectivity of the hydrogenation might be increased by conducting the reaction at lower temperature. In the event, a stepwise lowering of the temperature at which the hydrogenation was conducted improved the selectivity. At −22 °C, the saturated lactones were formed in excellent yield and with good selectivity (8.2:1) in favor of the desired diastereomer **49a**; further lowering of the reaction temperature led to poor conversion and no improvement in selectivity. Removal of the silyl ether protecting group from a mixture of the lactones **49** with HF·pyridine provided the alcohol **40** and the corresponding C5 epimer which were readily separable by flash chromatography.[72] Oxidation of the alcohol **40** with freshly prepared Dess−Martin periodinane[59−61] provided the acid-sensitive unstable aldehyde **41** which was purified by filtration through Florisil and used immediately. Use of older batches of the periodinane resulted in significant epimerization of the methyl group adjacent to the aldehyde in **41**, and the product was isolated in much poorer yield (see Scheme 8).

By the judicious choice of protecting groups, and the use of a cyclic carbonate (**46**) as a Claisen rearrangement precursor, we had secured an efficient, reproducible, and scalable synthesis

(68) The Petasis olefination has been shown to proceed by way of a titanium carbene. Hughes, D. L.; Payack, J. F.; Cai, D.; Verhoeven, T. R.; Reider, P. J. *Organometallics* **1996**, *15*, 663−667. Meurer, E. C.; Santos, L. S.; Pilli, R. A.; Eberlin, M. N. *Org. Lett.* **2003**, *5*, 1391−1394.

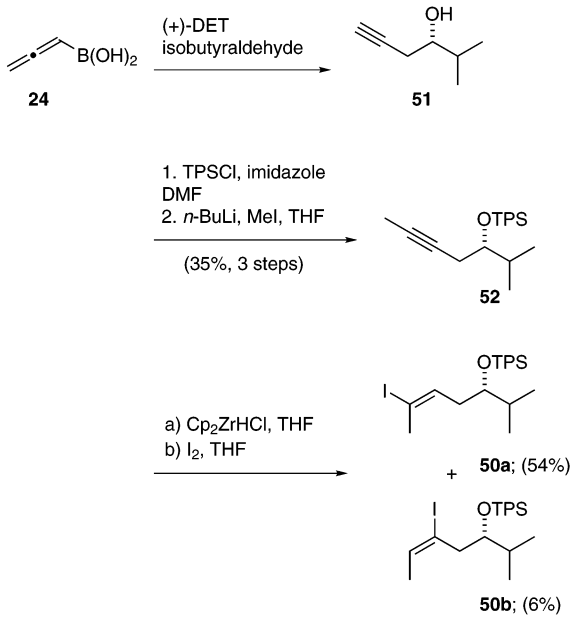
(69) The hydrogen-bond basicity pK_{HB} of carbonates and esters has been measured. Besseau, F.; Laurence, C.; Berthelot, M. *J. Chem Soc., Perkin Trans. 2* **1994**, 485−489.

(70) Compound **48**, $C_{13}H_{20}O_5$, MW 256.30, was obtained as clear colorless crystals, space group $P3_1$, a = 12.843(2) Å, c = 7.107(3) Å, V = 1015.2(5) Å^3, Z = 3, D_{calcd} = 1.258 g cm^{-3}, $F(000)$ = 414. More detailed crystal structure data can be viewed in the Supporting Information.

(71) Wiberg, K. B.; Waldron, R. F. *J. Am. Chem. Soc.* **1991**, *113*, 7697−7705.

(72) The eight-membered lactone **40** did not undergo translactonization under the reaction conditions.

Scheme 12. Synthesis of the TPS-Protected Vinyl Iodide **50**

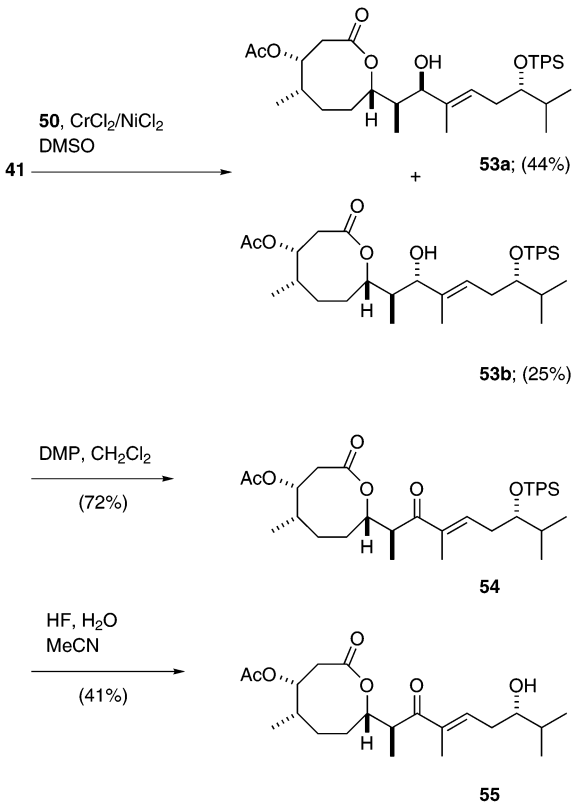


of the core eight-membered lactone of the octalactins, thus allowing us access to significant quantities of the aldehyde **41**. All that remained for the completion of the natural products was to elaborate the C8 side chain.

Side Chain Synthesis. The vinyl iodide **50** was synthesized in a manner similar to the route developed by Andrus.[15] Thus the known boronic acid **24** was synthesized from propargyl bromide and trimethylborate according to the procedure of Yamamoto.[41] Addition of (+)-diethyl tartrate allowed formation of the corresponding enantiomerically pure boronic ester derivative (Scheme 12). Subsequent reaction with isobutyraldehyde provided the homopropargylic alcohol **51** in 80% ee (Mosher ester analysis; see Supporting Information). The volatile alcohol **51** was stored as a solution in toluene and was converted to the corresponding silyl ether as required (TPSCl, imidazole, DMF). Methylation of the terminal acetylene occurred in quantitative yield (*n*-BuLi, MeI) to provide **52**. Finally, following the route of Buszek,[3] hydrozirconation of the internal acetylene **52** using Schwartz's reagent (4 equiv) in THF, equilibration at room temperature for 4 h, followed by the addition of a solution of iodine in THF provided the vinyl iodides **50a** (δ 5.98, tq, J = 7.5, 1.3 Hz, 1H, H3) and **50b** (δ 6.20, q, J = 7.0 Hz, 1H, H2) as a 9:1 inseparable mixture of regioisomers in reasonable yield (60%).

Fragment Coupling and Completion of the Syntheses. The final stages of the synthesis involved coupling of the side chain **50a** with the aldehyde **41**. Initial studies focused on the use of the Nozaki−Hiyama−Kishi (NHK) reaction to effect this transformation.[40] Thus treatment of a solution of the aldehyde **41** and the mixture of vinyl iodides **50** in DMSO with 11 equiv of $CrCl_2$/0.1% $NiCl_2$ provided the desired coupled products **53a** and **53b** as a mixture of diastereomers in good overall yield (69%) (Scheme 13). Pleasingly, only the less-hindered vinyl iodide **50a** underwent the coupling reaction. The absolute stereochemistry of the secondary alcohols **53** was proved using Kakisawa's extension of Mosher's method[57] (see Supporting Information), thus demonstrating that the coupling reaction had occurred with modest Felkin−Anh selectivity as expected.[3,40]

Scheme 13. Side Chain Coupling

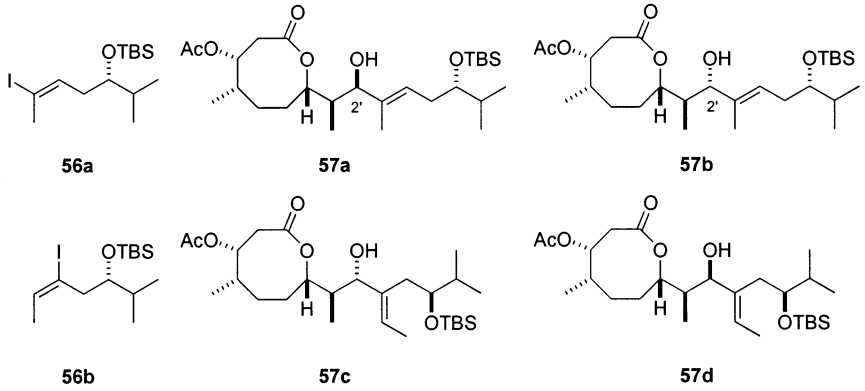


All that remained for the synthesis of octalactin B (**2**) was oxidation of the allylic alcohols to a ketone followed by protecting group removal. The formation of the ketone **54** from a mixture of alcohols **53** occurred without event. However, removal of the silyl protecting group with aqueous HF was inefficient (41% yield). It appeared that the long reaction time (40 h) required for removal of the bulky silyl protecting group was causing decomposition of the substrate **54**, the product **55**, or both.[73] Our attention therefore turned to the use of the TBS-protected vinyl iodide **56a** in the coupling reaction, as Buszek had demonstrated that removal of this protecting group occurred with good efficiency.[3] The vinyl iodide **56a** was synthesized in an analogous manner to the TPS-protected vinyl iodide **50a** but with three important modifications. First, benzene was used as the solvent for the hydrozirconation; second, the vinyl zirconium intermediates were allowed to equilibrate for 4 h at 40 °C before addition of iodine; and third, an aqueous workup procedure was employed.[74] The vinyl iodides **56a** and **56b** were isolated as a 10:1 mixture of regioisomers in a combined yield of 79%. The previously optimized procedure for side chain coupling provided the desired products **57a** and **57b**. However, ^{1}H NMR indicated the presence of two inseparable impurities, assigned as **57c** and **57d**, that had resulted from coupling of the regioisomeric iodide **56b** (Chart 2). Surprisingly the difference in steric bulk of a TBS-ether compared with a TPS-ether in the vinyl iodides **50** and **56** is sufficient to influence the outcome of the NHK coupling reaction.

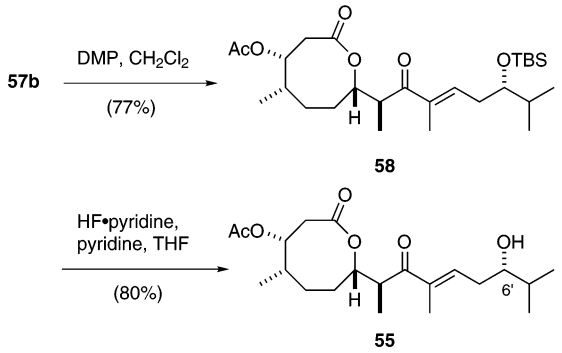
The reaction with the pure vinyl iodide **56a** (obtained by careful flash chromatography in hexane) provided the desired

(73) Clardy reported a similar low yield for removal of the corresponding side chain TPS group.[4]
(74) Nakatsuka, M.; Ragan, J. A.; Sammakia, T.; Smith, D. B.; Uehling, D. E.; Schreiber, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 5583−5601.

Chart 2



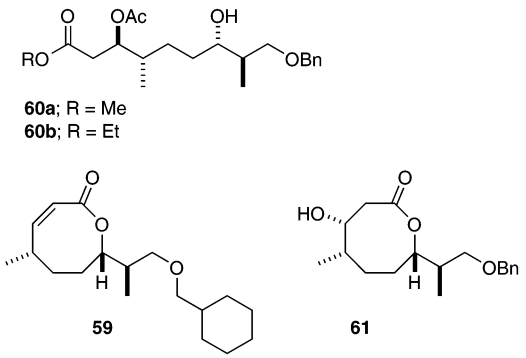
Scheme 14. Synthesis of Acetyl-Protected Octalactin B



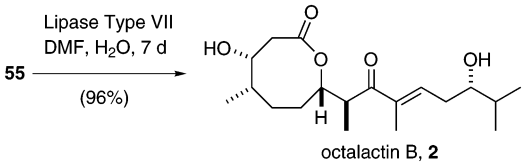
products **57a** and **57b** in excellent yield (91%) as a 1.8:1 mixture of separable diastereomers. Surprisingly the ^{1}H NMR spectra of **57a** and **57b** differed significantly from the ^{1}H NMR spectra of **53a** and **53b**. Nevertheless, we presumed that the reaction had proceeded under Felkin−Anh control (vide supra), and thus the major diastereomer was assigned the (2′*R*)-configuration **57a** and the minor diastereomer was assigned the (2′*S*)-configuration **57b**. Oxidation of the minor diastereomer **57b** with the Dess−Martin periodinane[59−61] provided the ketone **58** (Scheme 14). Pleasingly, deprotection of the silyl group with HF·pyridine provided the alcohol **55** in good yield (80%). The ^{1}H NMR spectrum of **55** indicated the presence of a minor impurity (<10%) [δ 6.81 (t, J = 6.7 Hz, 1H)]. The impurity was identified as being the C6′ side chain epimer. The epimer arises from the moderate enantiomeric excess (80%) obtained in the synthesis of the (*S*)-alkynol **51** from the allenyl boronic acid **24**. The minor impurity was removed by preparative thin-layer chromatography after deprotection of the acetate ester (vide infra).

All that remained for the synthesis of octalactin B (**2**) was the deprotection of the acetate group. The lactones **39a** and **42** were used as model substrates to test this transformation. Unfortunately, attempted deprotection of the acetate group in these systems under a wide variety of conditions (NH_3, MeOH, 0 °C; KCN, EtOH, 5 °C; DBU, toluene; DBU, MeOH; K_2CO_3, MeOH; Et_3N, THF, water, MeOH; NH_2-NH_2, water, pyridine, AcOH; BF_3·OEt_2, MeCN, water)[75,76] resulted in decomposition of the substrate, formation of the α,β-unsaturated lactone **59**, or formation of ring-opened products **60** which retained the acetate group (Chart 3).[77]

Chart 3



Scheme 15. Synthesis of Octalactin B

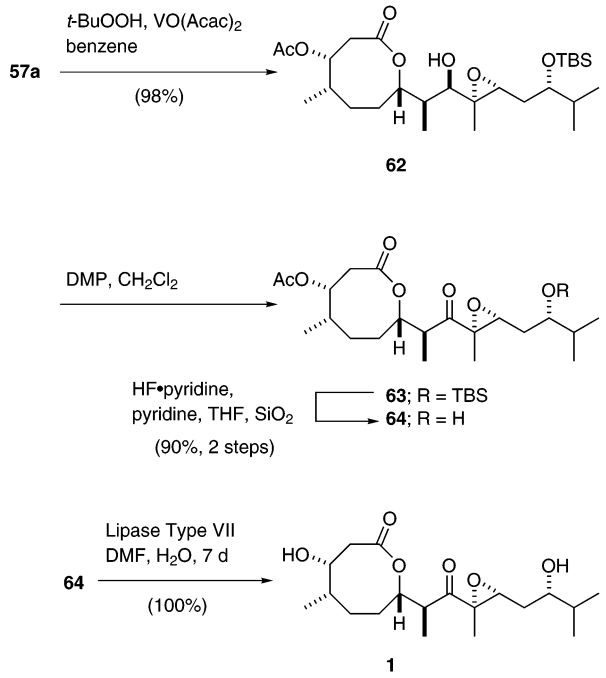


Our attention therefore turned to the use of an enzymatic method for the final deprotection.[75,78] After much experimentation, it was discovered that lipase type VII from *Candida cylindracea* (an enzyme known to accommodate bulky esters in its active site[78]) could be used for the deprotection. Thus exposure of **39a** to the enzyme in diethyl ether containing 3% pH 7 buffer provided a small quantity of the desired hydroxylactone **61** after stirring for 22 days (Chart 3). Complete conversion could be achieved after 7 days if the reaction was conducted in 10% DMF/pH 7 buffer.[79] In the real system, exposure of **55** to the lipase in 10% DMF/pH 7 buffer provided octalactin B (**2**) {$[\alpha]_D^{24}$ −123 (*c* 0.04 in $CDCl_3$), lit.[3] $[\alpha]_D$ −126} in 96% yield as a clear and colorless oil (Scheme 15).

The spectral data (^{1}H NMR, ^{13}C NMR, IR, MS) for our synthetic sample of **2** were in complete agreement with the data reported by Buszek for synthetic (−)-octalactin B[3] and that

(75) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley & Sons: New York, 1999.
(76) Ishido, Y.; Nakazki, N.; Sakairi, N. *Chem. Commun.* **1976**, 832−833.
(77) Due to problems with the deprotection of the acetate ester in the presence of a medium-ring lactone, we explored the possiblity of synthesizing the corresponding lactone bearing a chloroacetate protecting group. Clardy had previously demonstrated that this group is more labile than a medium-ring lactone to treatment with ammonia in THF.[4] Unfortunately it has not so far proved possible to synthesize the chloroacetate-protected aldehyde corresponding to **34**.
(78) Wong, C.-H.; Whitesides, G. M. *Enzymes in Synthetic Organic Chemistry*; Pergamon: Oxford, 1994; Vol. 12.
(79) We are much indebted to Prof. C. -H. Wong for advice in using DMF as a cosolvent for this reaction and for screening a range of other lipases.

Scheme 16. Synthesis of Octalactin A



reported for the isolated natural product by Fenical and Clardy.[1] The optical rotation of the synthetic natural product was approximately 10 times larger than that reported for the natural product, as noted by Buszek[3] and Clardy;[4] this is likely due to a calculational error in the original isolation paper.[1]

In the original synthetic approaches to octalactin A (**1**), a vanadium-directed allylic epoxidation had been used to install the required epoxide. The proof of the stereochemical outcome of this reaction had relied on application of the Sharpless mnemonic[80] and comparison of spectral data from the synthetic and natural samples. We adopted this approach to complete the synthesis of octalactin A (**1**). Thus, in a manner similar to that reported by Buszek,[3] we subjected the major allylic alcohol **57a** to hydroxy directed epoxidation[80] [$VO(acac)_2$, *tert*-butyl hydroperoxide] to provide **62** as a single diastereomer (Scheme 16); however, we had no method of assigning the relative stereochemistry at the epoxide stereocenters. The stereochemistry of the epoxide moiety was ultimately proven by conversion of **62** into octalactin A **1** and the use of X-ray crystal structure analysis, which indicated that the reaction had proceeded according to the model proposed by Sharpless.[80] Attempts to epoxidize the minor diastereomer **57b** from the same face as the hydroxy group failed.[3]

Oxidation of **62**[59−61] provided the corresponding ketone **63** which was desilylated on exposure to HF·pyridine giving **64**.[81] Finally, enzymatic hydrolysis of the acetate protecting group[78] provided octalactin A **1** {$[\alpha]_D^{20}$ −153 (*c* 0.14 in $CHCl_3$), lit.[3] $[\alpha]_D$ −156 (*c* 0.7 in $CHCl_3$)} in quantitative yield as a colorless crystalline solid mp 154−157 °C (ether) {lit.[1] mp 155−157 °C ($CHCl_3$/EtOAc)}. Octalactin A had spectral data (^{1}H NMR, ^{13}C NMR, IR, MS) in complete agreement with the published data.[1,3]

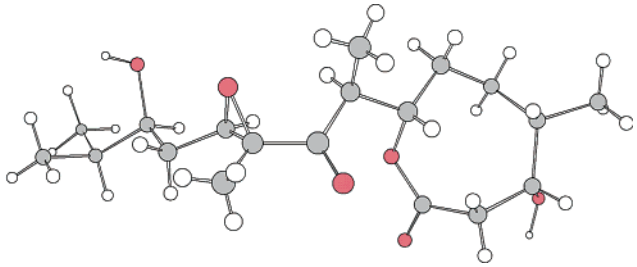


Figure 3. Chem-3D representation of the X-ray crystal structure of synthetic octalactin A (**1**).

The optical rotation of our synthetic sample of **1** was approximately an order of magnitude greater than that published for the natural sample[1] (vide supra). Synthetic octalactin A (**1**) formed crystals suitable for X-ray structure determination; the structure is shown in Figure 3 and confirms our previous stereochemical assignments.[82]

Conclusion

In summary, we have reported above an efficient synthesis of the octalactins. The synthesis of octalactin A (**1**) proceeds in 15 steps (longest linear sequence) and 10% overall yield (86% average yield per step) from commercially available materials. We have demonstrated the utility of the Paterson−Aldol reaction for the rapid assembly of the Claisen rearrangement precursor **46**, transfer of stereochemical information during the Claisen rearrangement of alkenyl-substituted cyclic ketene acetals in the formation of Δ^5-oxocenes, as well as documenting the use of our recently developed carbonate methylenation strategy for the formation of ketene acetals[28] and the use of enzyme-mediated acetate deprotection in the presence of a medium-ring lactone. Further examples of the use of the Claisen rearrangement for the construction of medium-ring natural products and natural product fragments will be reported in due course.

Experimental Section

For general experimental techniques, see Supporting Information.

(*E*)-3-Acetoxy-2-methylpropenal 34. To a suspension of **27**[46](see Supporting Information) (4.0 g, 32.3 mmol) in Et_2O (30 mL) and triethylamine (6.5 mL, 47.1 mmol) at −10 °C was added a solution of acetyl chloride (3.36 mL, 47.1 mmol) in Et_2O (10 mL) dropwise via syringe at such a rate as to maintain the temperature below −5 °C. The reaction mixture was warmed to ambient temperature over 1.5 h and was stirred for an additional 6 h during which time a brown precipitate formed. The reaction was quenched with water (50 mL) and was extracted with Et_2O (3 × 30 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Purification by flash chromatography (ethyl acetate/hexane, 9:1) provided the title compound **34** as a clear colorless oil (3.2 g, 25 mmol, 79%); R_f 0.5 (ethyl acetate/hexane, 2:3); ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.46 (s, 1H), 8.01 (q, J = 1.3 Hz, 1H), 2.29 (s, 3H), 1.77 (d, J = 1.3 Hz, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 166.5, 152.9, 124.4, 20.6, 7.0; IR ($CHCl_3$) 1743 (CO) cm^{-1}; HRMS (EI) *m*/*z* 128.0462 (128.0473 calcd for $C_6H_8O_3$, M).

(*E*),3(*S*),6(*R*)-1-Acetoxy-7-(*tert*-butyldimethylsiloxy)-3-hydroxy-2,6-dimethyl-hept-1-ene-5-one 44. To a solution of (+)-chlorodiisopinocampheylborane (2.29 g, 7.10 mmol) in Et_2O (150 mL) cooled to 0 °C was added Et_3N (1.04 mL, 7.40 mmol) followed by a solution of the ketone **43** (1.05 g, 4.80 mmol) in Et_2O (15 mL). The resultant white

(80) Sharpless, K. B.; Verhoeven, T. R. *Aldrichimica Acta* **1979**, *12*, 63−74.
(81) The ^{1}H NMR of **64** indicated the presence of a slight impurity arising from coupling of the minor enantiomer of the vinyl iodide present in the scaelmic mixture of iodides derived from **51**. As for **55**, this minor component was removed by preparative thin-layer chromatography after deprotection of the acetate ester.
(82) Compound **1**, (−)-octalactin A, $C_{19}H_{32}O_6$, MW 356.46, was obtained as a clear colorless crystal, space group $P2_12_12_1$, a = 9.961(4) Å, b = 20.869(5) Å, c = 9.596(4) Å, α = 90°, β = 90°, γ = 90°, V = 1994.8(12) Å^3, Z = 4, D_{calcd} = 1.187 g cm^{-3}, F(000) = 776. More detailed crystal data can be viewed in the Supporting Information.

suspension was stirred for 2.5 h. The mixture was then cooled to −78 °C, and a solution of aldehyde **34** (1.27 g, 10.0 mmol) in Et_2O (60 mL) was added dropwise via syringe. After the mixture was stirred for 2 h at −78 °C, it was left to warm slowly to −20 °C in a freezer. After 15 h, the mixture was warmed to 0 °C and stirred for 40 min. The reaction was quenched with a mixture of methanol (150 mL), pH 7 buffer (75 mL), and H_2O_2 (100 v/v, 19 mL) and stirred vigorously at 0 °C for 10 min followed by warming to ambient temperature and stirring for 1 h. The mixture was poured into water (150 mL) and was extracted with EtOAc/hexane, 1:1 (2 L). The aqueous layer was saturated with solid sodium chloride and was re-extracted with the same solvent mixture (2 × 250 mL). The combined organic extracts were washed with brine (200 mL), dried ($MgSO_4$), and concentrated in vacuo. Purification by flash chromatography (EtOAc/hexane, 10:1 → 5:1) afforded the title compound **44** (1.44 g, 4.20 mmol, 88%) as a clear colorless oil; R_f 0.16 (hexane/ethyl acetate, 5:1); $[\alpha]_D^{20}$ −62.2 (*c* 3.7, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.20 (s, 1H), 4.55 (m, 1H), 3.78−3.60 (m, 2H), 3.14 (s, 1H), 2.85−2.70 (m, 3H), 2.14 (s, 3H), 1.70 (s, 3H), 1.02 (d, J = 6.9 Hz, 3H), 0.86 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 214.3, 167.9, 132.3, 122.0, 68.8, 65.6, 49.1, 47.8, 25.8, 20.7, 18.2, 12.6, 9.9, −5.6; IR ($CHCl_3$) 3491 (OH), 1758 (CO), 1710 (CO) cm^{-1}; MS (CI, NH_3) *m*/*z* (rel intensity) 362 [8, $(M + NH_4)^+$]; HRMS (CI, NH_3) *m*/*z* 362.2363 (362.2363 calcd for $C_{17}H_{36}NO_5Si$, MNH_4).

(*E*),3(*S*),5(*S*),6(*R*)-1-Acetoxy-7-(*tert*-butyldimethylsilyloxy)-2,6-dimethyl-hept-1-ene-3,5-diol 45. To a solution of tetramethylammonium triacetoxyborohydride (3.76 g, 14.3 mmol) in acetonitrile (40 mL) and acetic acid (10 mL) at −45 °C was added via cannula a cooled solution of the aldol **44** (1.40 g, 4.08 mmol) in acetonitrile (10 mL, 5 mL rinse). The reaction mixture was stirred at −35 °C for 24 h and then quenched with saturated aqueous sodium potassium tartrate (40 mL). The mixture was allowed to warm to ambient temperature, stirred for 50 min, and then poured onto ice, neutralized with saturated aqueous sodium hydrogen carbonate (200 mL), and extracted with CH_2Cl_2 (200 mL). The aqueous layer was saturated with solid sodium chloride and re-extracted with CH_2Cl_2 (2 × 200 mL). The combined organic layers were washed with saturated aqueous sodium hydrogencarbonate (2 × 150 mL), dried (Na_2SO_4), and concentrated to give the title compound **45** as a clear colorless oil (1.31 g, 3.80 mmol, 93%). The relatively unstable diol **45** was used without purification. For characterization purposes, flash chromatography (ethyl acetate/hexane, 2:3) of the residue yielded the pure compound; R_f 0.31 (ethyl acetate/hexane, 2:3); $[\alpha]_D^{22}$ −17.0 (*c* 0.87, $CDCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.19 (s, 1H), 4.38 (br s, 1H), 3.81−3.74 (m, 2H), 3.82 (dd, J = 10.1, 7.1 Hz, 1H), 3.81−3.74 (m, 1H), 3.60−3.54 (m, 2H), 2.10 (s, 3 H), 1.83−1.77 (m, 2H), 1.65 (s, 3H), 0.86 (s, 9H), 0.78 (d, J = 6.9 Hz, 3H), 0.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.0, 131.7, 123.9, 74.8, 70.1, 68.8, 39.0, 38.6, 25.8, 20.7, 18.0, 13.3, 10.0, −5.6, −5.7; IR ($CDCl_3$) 3423 (OH), 1748 (CO) cm^{-1}; HRMS (electrospray, Q-TOF) *m*/*z* 369.2103 (369.2073 calcd for $C_{17}H_{34}O_5SiNa$, MNa).

(*E*),4(*S*),6(*S*)-6-(2-Acetoxy-1-methyl-vinyl)-4-[(*R*)-2-(*tert*-butyldimethylsilyloxy)-1-methyl-ethyl]-[1,3]dioxan-2-one 46. The diol **45** (118.0 mg, 0.20 mmol) was dissolved in CH_2Cl_2 (6 mL), pyridine (166 μL, 2.05 mmol), and triethylamine (569 μL, 4.10 mmol). Crushed 4 Å molecular sieves (250 mg) were added, and the reaction mixture was cooled to −78 °C. A solution of triphosgene (80.8 mg, 0.273 mmol) in CH_2Cl_2 (3 mL) was added dropwise via syringe. The suspension was stirred for 25 min after which it was warmed to 0 °C and quenched with saturated aqueous ammonium chloride solution (10 mL). The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4), and concentrated in vacuo. The mixture was filtered through a plug of silica to give the title compound **46** (90.0 mg, 0.24 mmol, 71%) which was used without further purification. The ^{1}H NMR spectrum indicated the presence of an inseparable impurity (judged from integration to be < 5%), corresponding to the carbonate formed from the 1,3-*syn*-diol. For characterization purposes, a small sample was purified by flash chromatography (ethyl acetate/hexane, 2:3); R_f 0.3 (ethyl acetate/hexane, 2:3); $[\alpha]_D^{20}$ +24.1 (*c* 0.61, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (qu, J = 1.3 Hz, 1H), 4.95 (t, J = 6.6 Hz, 1H), 4.50 (dt, J = 7.6, 6.6 Hz, 1H), 3.72 (dd, J = 10.1, 4.8 Hz, 1H), 3.60 (dd, J = 10.1, 4.8 Hz, 1H), 2.16 (s, 3H), 2.15−1.99 (m, 3H), 1.72 (d, J = 1.2 Hz, 3H), 0.95 (d, J = 7.0 Hz, 3H), 0.87 (s, 9H), 0.04 (d, J = 2.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 149.0, 133.8, 117.9, 63.5, 45.8, 38.9, 26.6, 25.9, 20.6, 18.2, 12.3, 10.2, 8.6, −5.6, −5.8; IR ($CDCl_3$) 1752 (CO) cm^{-1}; HRMS (Electrospray, Q-TOF) *m*/*z* 395.1872 (395.1866 calcd for $C_{18}H_{32}O_6SiNa$, MNa).

(*Z*),4(*R*),8(*S*)-4-Acetoxy-8-[(*R*)-2-(*tert*-butyldimethylsiloxy)-1-methyl-ethyl]-5-methyl-3,4,7,8-tetrahydro-oxocin-2-one 47. To the carbonate **46** (0.98 g, 2.64 mmol) in toluene (500 mL) was added dimethyl titanocene (603 mg, as a 0.24 M solution in toluene, 2.90 mmol) via syringe. The mixture was excluded from light and heated at 110 °C for 30 min. After allowing the mixture to cool, it was concentrated in vacuo to 30 mL and filtered through a plug of silica (hexane/ethyl acetate, 1:1). The concentrated residue was subjected to flash chromatography (hexane/ethyl acetate, 19:1) to give the title compound **47** (392 mg, 1.10 mmol, 42%) as a light yellow oil; R_f (hexane/ethyl acetate, 3:1) 0.61; $[\alpha]_D^{20}$ −17.0 (*c* 2.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.70 (t, J = 7.4 Hz, 1H), 5.43 (t, J = 6.2 Hz, 1H), 4.67 (dt, J = 9.3, 5.0 Hz, 1H), 3.67 (dd, J = 9.7, 4.9 Hz, 1H), 3.54 (dd, J = 9.7, 3.3 Hz, 1H), 3.18 (dd, J = 14.2, 7.4 Hz, 1H), 2.89 (dd, J = 14.2, 7.4 Hz, 1H), 2.52−2.35 (m, 2H), 2.11 (s, 3H), 1.87 (m, 1H), 1.74 (s, 3H), 0.98 (d, J = 6.8 Hz, 3H), 0.90 (s, 9H), 0.04 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 170.0, 137.6, 121.7, 79.0, 69.9, 64.2, 42.5, 40.3, 31.2, 25.9, 20.9, 19.7, 18.3, 13.1, −5.5, −5.6; IR (film) 1739 (CO), 1693 (CO) cm^{-1}; MS (CI, NH_3) *m*/*z* (rel intensity) 371 [42, $(M + H)^+$]; HRMS (CI, NH_3) *m*/*z* 371.2254 (371.2254 calcd for $C_{19}H_{35}O_5Si$, MH).

4(*R*),5(*S*),8(*S*)-4-Acetoxy-8-[(*R*)-2-(*tert*-butyldimethylsiloxy)-1-methyl-ethyl]-5-methyl-oxocan-2-one 49a. To a solution of the lactone **47** (5 mg, 13.4 μmmol) in EtOAc (5 mL) was added 5% rhodium on alumina (6 mg, 2.6 μmol Rh). This mixture was stirred vigorously under an atmosphere of H_2 at −22 °C for 20 h. Filtration of the mixture through a plug of silica (eluting with EtOAc) followed by concentration in vacuo and purification by flash chromatography (hexane/ethyl acetate, 9:1) afforded the reduced lactones **49** as an 8.2:1 mixture of C5 epimers (4.8 mg, 12.8 μmol, 96%) as a clear colorless oil. The diastereoisomers were inseparable at this stage and were characterized as a mixture; R_f (hexane/ethyl acetate, 9:1) 0.10; ^{1}H NMR (400 MHz, $CDCl_3$ major diastereomer) δ 5.03 (d, J = 5.7 Hz, 1H), 4.45 (m, 1H), 3.78 (dd, J = 9.8, 3.9 Hz, 1H), 3.44 (dd, J = 9.8, 3.6 Hz, 1H), 2.95 (dd, J = 13.4, 6.2 Hz, 1H), 2.78 (dd, J = 13.4, 1.7 Hz, 1H), 2.10 (s, 3H), 1.95−1.65 (m, 5H), 1.34−1.22 (m, 1H), 1.03 (d, J = 6.6 Hz, 3H), 1.00 (d, J = 7.0 Hz, 3H), 0.88 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$ major diastereomer) δ 170.9, 78.0, 73.2, 64.1, 40.0, 36.8, 36.0, 30.5, 25.8, 21.8, 20.9, 18.8, 13.4; IR (film) 1736 (CO) cm^{-1}; MS (CI, NH_3) *m*/*z* (rel intensity) 390 [25, $(M + NH_4)^+$], 373 [100, $(M + H)^+$]; HRMS (CI, NH_3) *m*/*z* 373.2410 (373.2410 calcd for $C_{19}H_{37}O_5Si$, MH).

4(*R*),5(*S*),8(*S*)-4-Acetoxy-8-[(*R*)-2-hydroxy-1-methyl-ethyl]-5-methyl-oxocan-2-one 40. To a solution of the lactones **49** (38 mg, 0.102 mmol) in THF (2.0 mL) at 0 °C was added crushed glass followed by pyridine (150 μL) and 70% HF·pyridine (100 μL). The mixture was warmed to ambient temperature and was stirred for 20 h. Additional HF·pyridine (70 μL) was added, and the mixture was stirred for a further 3 h. The mixture was then filtered through a short wide plug of silica, eluting with EtOAc. The eluent was evaporated, and the residue was purified by flash column chromatography (ethyl acetate/hexane, 2:1) yielding the separated diastereomeric products as clear oils (total yield 26.5 mg, 0.102 mmol, 100%); R_f (major diastereomer) 0.16 (ethyl acetate/hexane, 2:1); $[\alpha]_D^{20}$ −88 (*c* 0.57, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.03 (d, J = 6.3 Hz, 1H), 4.46−4.39 (m, 1H), 3.77 (dd, J = 10.5, 4.3 Hz,

1H), 3.57 (dd, J = 10.5, 4.2 Hz, 1H), 2.94 (dd, J = 13.5, 6.4 Hz, 1H), 2.81 (dd, J = 13.5, 2.3 Hz, 1H), 2.09 (s, 3H), 1.94−1.65 (m, 5H), 1.03 (d, J = 7.0 Hz, 3H), 1.00 (d, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 170.8, 78.9, 73.3, 64.1, 39.8, 36.3, 35.5, 31.7, 21.0, 13.4, 1.0; IR (film) 3454 (OH), 1720 (CO) cm^{-1}; MS (CI, NH_3) m/z (rel intensity) 259 [20, $(M + H)^+$]; HRMS (CI, NH_3) m/z 259.1545 (259.1546 calcd for $C_{13}H_{23}O_5$ MH). Anal. Calcd for $C_{13}H_{22}O_5$: C, 60.5; H, 8.6. Found: C, 60.6; H, 8.6.

4(*R*),5(*S*),8(*S*)-4-Acetoxy-5-methyl-8-[(*S*)-1-methyl-2-oxoethyl]-oxocan-2-one, 41. To a solution of **40** (12.0 mg, 46 μmol) in CH_2Cl_2 (3 mL) was added the Dess Martin periodinane (67 mg, 160 μmol). After 2 h at ambient temperature, wet CH_2Cl_2 (1 mL) was added and the mixture was stirred another 30 min. The solvent was exchanged with EtOAc by careful evaporation, and the insoluble Dess Martin reagent was filtered off by quickly passing the mixture through a short wide plug of Florisil (EtOAc/hexane, 3:1) giving the crude title compound **41** (12 mg, 46 μmol, 100%). The unstable aldehyde **41** was used in the next step without further purification; R_f (EtOAc/hexane, 7:3) 0.4; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.72 (d, J = 1.2 Hz, 1H), 5.06 (d, J = 6.1 Hz, 1H), 4.70 (ddd, J = 13.5, 7.5, 3.4 Hz, 1H), 3.00 (dd, J = 13.5, 6.6 Hz, 1H), 2.87 (dd, J = 13.5, 1.9 Hz, 1H), 2.78 (dqn, J = 1.2, 7.5 Hz, 1H), 2.10 (s, 3H), 1.94−1.52 (m, 5H), 1.15 (d, J = 7.5 Hz, 3H), 1.00 (d, J = 6.6 Hz, 3H).

4(*R*),5(*S*),8(*S*)-4-Acetoxy-8-[(*E*),1(*R*),2(*R*),6(*S*)-6-(*tert*-butyldimethylsilyloxy)-2-hydroxy-1,3,7-trimethyl-oct-3-enyl]-5-methyl-oxocan-2-one 57a and 4(*R*),5(*S*),8(*S*)-4-Acetoxy-8-[(*E*),1(*R*),2(*S*),6(*S*)-6-(*tert*-butyldimethylsilyloxy)-2-hydroxy-1,3,7-trimethyl-oct-3-enyl]-5-methyl-oxocan-2-one 57b. The aldehyde **41** (8.0 mg, 0.031 mmol) was azeotropically evaporated twice with toluene (2 × 2 mL) and dried under high vacuum in a Schlenk flask prior to use. DMSO (1 mL) was added via syringe followed by the vinyl iodide **56a** (44.9 mg, 0.122 mmol) as a solution in DMSO via cannula (0.5 mL, 0.5 mL rinse). A mixture of 1% $NiCl_2$ in $CrCl_2$ (38.1 mg, 0.31 mmol) was preweighed in a glovebox and added to the reaction mixture under a stream of argon. The dark green solution was stirred at ambient temperature with the exclusion of light for 24 h, after which time the reaction mixture was quenched with saturated aqueous ammonium chloride solution (8 mL) and extracted with EtOAc (5 × 10 mL). The combined organic layers were washed with brine (10 mL) and dried (Na_2SO_4). Concentration in vacuo was followed by flash chromatography (ethyl acetate/hexane, 1:4) to provide the diastereomeric allylic alcohols **57a** (9.0 mg, 0.018 mmol, 58%) and **57b** (5.1 mg, 0.010 mmol, 33%) as clear colorless oils. Data for **57a**: R_f 0.3 (hexane/ethyl acetate, 3:1); $[\alpha]_D^{20}$ −27.6 (c 0.25, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.47 (t, J = 6.9 Hz, 1H), 5.05 (d, J = 5.4 Hz, 1H), 4.48−4.44 (m, 1H), 4.28 (s, 1H), 3.49 (m, 1H), 2.95 (dd, J = 13.5, 6.2 Hz, 1H), 2.87 (d, J = 13.5 Hz, 1H), 2.20 (m, 2H), 2.11 (s, 3H), 1.95−1.86 (m, 2H), 1.84−1.62 (m, 5H), 1.38 (s, 1H), 1.32−1.22 (m, 3H), 1.04 (d, J = 7.0 Hz, 3H), 0.89 (s, 9H), 0.87 (d, J = 7.0 Hz, 3H), 0.85 (d, J = 7.0 Hz, 3H), 0.76 (d, J = 7.0 Hz, 3H), 0.04 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 170.8, 136.8, 120.8, 79.2, 77.0, 73.9, 73.3, 40.0, 36.5, 35.6, 32.8, 32.5, 32.3, 25.9, 24.5, 21.3, 21.0, 18.9, 18.1, 17.1, 14.1, 8.8, −4.2, −4.6; IR (film) 3477 (OH), 1731 (CO) cm^{-1}; MS (CI, NH_3) m/z (rel intensity) 516 [40, $(M + NH_4)^+$], 499 [8, $(M + H)^+$]; HRMS (CI, NH_3) m/z 516.3712 (516.3720 calcd for $C_{27}H_{54}O_6NSi$, MNH_4). Anal. Calcd for $C_{27}H_{50}O_6Si$: C, 65.0; H, 10.1. Found: C, 64.9; H, 10.0.

Data for **57b**: R_f 0.13 (ethyl acetate/hexane, 1:3); $[\alpha]_D^{22}$ −49.2 (c 0.6, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.42 (dd, J = 7.0, 0.5 Hz, 1H), 5.04 (d, J = 6.0 Hz, 1H), 4.80 (dt, J = 12.3, 3.9 Hz, 1H), 3.76 (dd, J = 8.7, 2.1 Hz, 1H), 3.48 (dt, J = 4.4, 5.9 Hz, 1H), 2.98 (dd, J = 13.5, 6.2 Hz, 1H), 2.85 (dd, J = 13.3, 1.9 Hz, 1H), 2.21−2.15 (m, 3H), 2.10 (s, 3H), 1.68−1.63 (m, 1H), 1.61 (s, 3H), 1.03 (d, J = 6.8 Hz, 3H), 0.89 (s, 9H), 0.87 (d, J = 7.0 Hz, 3H), 0.85 (d, J = 6.8 Hz, 3H), 0.80 (d, J = 7.0 Hz, 3H), 0.03 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 170.8, 136.4, 126.4, 80.4, 77.9, 76.5, 73.3, 39.8, 36.3, 35.9, 32.7, 32.2, 28.3, 25.9, 24.2, 21.5, 21.0, 18.7, 17.2, 11.1, 10.9, −4.2, −4.6; IR (film) 3467 (OH), 1742 (CO) cm^{-1}; MS (CI, NH_3) m/z (rel intensity) 516 [15, $(M + NH_4)^+$], 499 [18, $(M + H)^+$]; HRMS (CI, NH_3) m/z 499.3445 (499.3455 calcd for $C_{27}H_{51}O_6Si$, MH).

4(*R*),5(*S*),8(*S*)-4-Acetoxy-8-[(*E*),1(*S*),6(*S*)-6-(*tert*-butyl-dimethyl-siloxy)-1,3,7-trimethyl-2-oxo-oct-3-enyl]-5-methyl-oxocan-2-one 58. To a solution of **57b** (11.2 mg, 22.5 μmol) in CH_2Cl_2 (2 mL) was added the Dess Martin periodinane (38 mg, 90 μmol). The mixture was stirred at ambient temperature for 3 h. The solvent was exchanged with EtOAc, and the reagent was removed by passing the mixture through a short plug of silica, eluting with EtOAc. The crude product was purified by column chromatography (hexane/ethyl acetate, 3:1) to furnish the title compound **58** (9.5 mg, 77%) as a colorless oil; R_f 0.25 (hexane/ethyl acetate, 3:1); $[\alpha]_D^{22}$ −95.8 (c 0.36, $CDCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.76 (t, J = 6.6 Hz, 1H), 5.07 (d, J = 5.7 Hz, 1H), 4.79 (ddd, J = 12.0, 9.1, 2.9 Hz, 1H), 3.63 (td, J = 6.0, 5.0 Hz, 1H), 3.48 (m, 1H), 2.98 (dd, J = 13.6, 2.2 Hz, 1H), 2.92 (dd, J = 13.7, 6.0 Hz, 1H), 2.45−2.31 (m, 2H), 2.09 (s, 3H), 1.94−1.64 (m, 5H), 1.77 (s, 3H), 1.05 (d, J = 2.1 Hz, 3H), 1.03 (d, J = 1.8 Hz, 3H), 0.90 (m, 12H), 0.89 (s, 3H), 0.06 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.0, 170.7, 170.5, 141.2, 136.8, 78.6, 77.2, 75.8, 73.1, 44.5, 36.4, 35.5, 33.6, 33.3, 31.9, 25.8, 24.0, 21.7, 20.9, 18.1, 17.9, 15.1, 11.9, −4.3, −4.5; IR (film) 1732 (CO), 1665 (CO) cm^{-1}; MS (CI, NH_3) m/z (rel intensity) 514 [4, $(M + NH_4)^+$], 497 [6, $(M + H)^+$]; HRMS (CI, NH_3) m/z 497.3297 (497.3298 calcd for $C_{27}H_{49}O_6Si$, MH).

4(*R*),5(*S*),8(*S*)-4-Acetoxy-8-[(*E*),1(*S*),6(*S*)-6-hydroxy-1,3,7-trimethyl-2-oxo-oct-3-enyl]-5-methyl-oxocan-2-one 55. Crushed glass (150 mg) was added to a solution of **58** (6.3 mg, 12.6 μmol) in THF (2.0 mL) at 0 °C followed by anhydrous pyridine (300 μL) and 70% HF·pyridine (150 μL). The cooling bath was removed, and the mixture was stirred for 48 h at ambient temperature with additional HF·pyridine (100 μL) being added after 24 h. The mixture was filtered through a short wide plug of silica (EtOAc). Evaporation was followed by flash chromatography (hexane/ethyl acetate, 1:1) to give the title compound **55** (3.8 mg, 9.9 μmol, 80%) as a clear colorless oil; R_f 0.21 (hexane/ethyl acetate, 1:1); $[\alpha]_D^{22}$ −126.6 (c 0.29, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.87 (t, J = 7.1 Hz, 1H), 5.05 (brs, 1H), 4.72 (ddd, J 12.2, 9.3, 3.0 Hz, 1H), 3.59−3.50 (m, 2H), 2.95−2.89 (m, 2H), 2.48−2.32 (m, 2H), 2.09 (s, 3H), 1.90−1.67 (m, 7H), 1.35−1.27 (m, 3H), 1.05 (d, J = 5.5 Hz, 3H), 1.04 (d, J = 5.2 Hz, 3H), 0.97 (d, J = 3.6 Hz, 3H), 0.95 (d, J = 3.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.3, 170.7, 141.5, 137.5, 79.1, 75.9, 73.0, 44.4, 36.4, 35.5, 34.0, 33.9, 32.0, 30.9, 29.7, 24.0, 21.7, 21.0, 18.7, 17.4, 15.0, 11.8; IR (film) 3468 (OH), 1731 (CO), 1661 (CO) cm^{-1}; MS (FAB) m/z (rel intensity) 383 [50, $(M + H)^+$]; HRMS (CI, NH_3) m/z 383.2435 (383.2434 calcd for $C_{21}H_{35}O_6$, MH).

4(*R*),5(*S*),8(*S*)-4-Hydroxy-8-[(*E*),1(*S*),6(*S*)-6-hydroxy-1,3,7-trimethyl-2-oxo-oct-3-enyl]-5-methyl-oxocan-2-one, (−)-Octalactin B, 2. To a solution of **55** (2.8 mg, 7.3 μmol) in 10% DMF/pH 7 buffer (2.0 mL) was added type VII lipase from *Candida cylindracea* (Fluka; 35.3 mg). The flask was sealed, and the mixture was excluded from light and stirred at ambient temperature for a period of 6 d, adding 13 mg, 9.0 mg, 13 mg, 5 mg of enzyme on days 2, 3, 4, and 5, respectively. Water was added to the mixture, and the aqueous layer was extracted with Et_2O (5 × 10 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), and filtered. The eluent was passed through a short wide plug of silica (Et_2O). Concentration of the eluent was followed by flash chromatography (ethyl acetate/hexane, 3:1) and PTLC to give the title natural product (−)-octalactin B, **2** (2.4 mg, 7.0 μmol, 96%), as an oil; R_f 0.15 (hexane/ethyl acetate, 1:2); $[\alpha]_D^{24}$ −123 (c 0.04, $CDCl_3$) {lit.[3] $[\alpha]_D$ −126}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.86 (t, J = 7.0 Hz, 1H), 4.75 (t, J = 10.7 Hz, 1H), 4.03 (brs, 1H), 3.56−3.51 (m, 2H), 3.05 (dd, J = 13.3, 1.5 Hz, 1H), 2.72 (dd, J = 13.3, 6.5 Hz, 1H), 2.45 (m, 1H), 2.35 (m, 1H), 1.96 (d, J = 4.8 Hz, 1H), 1.81−1.74 (m, 2H), 1.78 (s, 3H), 1.73−1.68 (m, 3H), 1.24−1.18 (m, 1H), 1.14 (d, J = 7.1 Hz, 3H), 1.05 (d, J = 7.2 Hz, 3H), 0.98 (d, J = 6.6 Hz, 3H), 0.96 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ

203.3, 172.5, 141.4, 137.5, 79.4, 75.9, 71.4, 44.2, 39.2, 38.0, 34.1, 33.9, 32.2, 22.6, 22.0, 18.7, 17.4, 15.0, 11.7; IR (film) 3444 (OH), 1714 (CO), 1660 (CO) cm^{-1}; HRMS (FAB) *m*/*z* 364.2225 (364.2226 calcd for $C_{19}H_{33}O_5Na$, MH + Na).

4(*R*),5(*S*),8(*S*)-4-Acetoxy-8-{2-[3-((*S*)-2-(*tert*-butyldimethylsilyloxy)-3-methyl-butyl)-2(*R*),3(*R*)-2-methyl-oxiranyl]-1(*R*),2(*R*)-2-hydroxy-1-methyl-ethyl}-5-methyl-oxocan-2-one 62. To a stirred solution of **57a** (24.0 mg, 48 μmol) in benzene (3 mL) was added *t*-BuOOH (27 μL, 144 μmol) and $VO(acac)_2$ (3 mg, 11.3 μmol). The mixture was stirred at ambient temperature for 1 h. Concentration in vacuo was followed by flash chromatography (hexane/ethyl acetate, 3:1), which gave the title compound **62** (23.8 mg, 46 μmol, 98%) as a clear colorless oil; R_f 0.08 (hexane/ethyl acetate, 4:1); $[\alpha]_D^{23}$ −14.3 (*c* 0.91, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.04 (d, J = 5.5 Hz, 1H), 4.47 (m, 1H), 4.02 (s, 1H), 3.60 (q, J = 5.2 Hz, 1H), 3.29 (dd, J = 7.8, 3.1 Hz, 1H), 2.94 (dd, J = 13.7, 5.8 Hz, 1H), 2.88 (dd, J = 13.7, 2.2 Hz, 1H), 2.10 (s, 3H), 1.97−1.76 (m, 6H), 1.69−1.59 (m, 2H), 1.33−1.28 (m, 1H), 1.28−1.25 (m, 1H), 1.21 (s, 3H), 1.07 (d, J = 7.0 Hz, 3H), 0.91 (d, J = 2.2 Hz, 3H), 0.89 (s, 12H), 0.83 (d, J = 7.0 Hz, 3H), 0.06 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 170.8, 78.5, 75.3, 73.2, 70.2, 60.8, 55.5, 39.3 36.4, 35.5, 32.8, 32.8, 32.5, 25.9, 24.4, 21.6, 21.0, 18.6, 18.2, 18.1, 14.9, 9.5, −4.3, −4.6; IR ($CHCl_3$) 3476 (OH), 1738 (CO) cm^{-1}; MS (CI, NH_3) *m*/*z* (rel intensity) 532 [20, $(M + NH_4)^+$], 515 [9, $(M + H)^+$]; HRMS *m*/*z* 515.3404 (515.3404 calcd for $C_{27}H_{51}O_7Si$, MH).

4(*R*),5(*S*),8(*S*)-4-Acetoxy-8-{2-[3-((*S*)-2-(*tert*-butyldimethylsilyloxy)-3-methyl-butyl)-2(*S*),3(*R*)-2-methyl-oxiranyl]-1(*S*)-methyl-2-oxo-ethyl}-5-methyl-oxocan-2-one 63. To a solution of the epoxide **62** (12.0 mg, 23 μmol) in CH_2Cl_2 (2 mL) was added the Dess Martin periodinane (51.0 mg, 120 μmol) under a stream of argon. The suspension was stirred for 2 h at 25 °C. The solvent was exchanged for EtOAc on a rotary evaporator while ensuring the mixture did not go dry. The resultant white suspension was filtered through a short wide plug of silica to provide the title compound **63** (11.9 mg, 23 μmol, 100%) as a clear colorless oil; R_f 0.23 (hexane/ethyl acetate, 4:1); $[\alpha]_D^{22}$ −124.0 (*c* 0.59, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.05 (brs, 1H), 4.67 (ddd, J = 12.4, 9.4, 3.0 Hz, 1H), 3.68 (dd, J = 10.4, 5.9 Hz, 1H), 3.16 (dd, J = 7.1, 4.0 Hz, 1H), 2.96−2.83 (m, 3H), 2.08 (s, 3H), 1.92−1.68 (m, 5H), 1.65−1.55 (m, 2H), 1.43 (s, 3H), 1.32−1.25 (m, 1H), 1.03 (d, J = 6.9 Hz, 3H), 1.01 (d, J = 7.2 Hz, 3H), 0.92−0.88 (m, 12H), 0.86 (d, J = 6.8 Hz, 3H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.8, 170.7, 170.1, 77.3, 74.9, 73.0, 62.4, 57.9, 43.5, 36.4, 35.5, 33.1, 32.3, 31.7, 25.9, 25.9, 23.9, 21.6, 20.9, 18.2, 18.1, 17.4, 13.4, 13.3, −4.4, −4.6; IR ($CHCl_3$) 1738 (CO), 1708 (CO) cm^{-1}; MS (CI, NH_3) *m*/*z* (rel intensity) 530 [4, $(M + NH_4)^+$]; HRMS *m*/*z* 530.3512 (530.3513 calcd for $C_{27}H_{52}NO_7Si$, MNH_4).

4(*R*),5(*S*),8(*S*)-4-Acetoxy-8-{2-[3-((*S*)-2-hydroxy-3-methyl-butyl)-2(*S*),3(*R*)-2-methyl-oxiranyl]-1(*S*)-methyl-2-oxo-ethyl}-5-methyl-oxocan-2-one 64. To a solution of the silyl ether **63** (5.0 mg, 98 μmol) in THF (2 mL) stirred at 0 °C was added crushed glass (150 mg) followed by pyridine (300 μL) and 70% HF·pyridine (150 μL). The mixture was warmed to ambient temperature and stirred for 24 h. The resulting white suspension was diluted with EtOAc (3 mL) and filtered through a small wide plug of silica (EtOAc). The eluent was concentrated in vacuo and purified by flash chromatography (hexane/ethyl acetate, 2:1) to give the title compound **64** (3.5 mg, 88 μmol, 90%) as a clear colorless oil; R_f 0.19 (hexane/ethyl acetate, 2:1); $[\alpha]_D^{22}$ −126.3 (*c* 0.24, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.03 (d, J = 5.7 Hz, 1H), 4.60 (m, 1H), 3.57 (t, J = 6.2 Hz, 1H), 3.47 (m, 1H), 3.02−2.83 (m, 4H), 2.07 (s, 3H), 1.90−1.58 (m, 6H), 1.43 (s, 3H), 1.32−1.22 (m, 2H), 1.04 (d, J = 7.0 Hz, 3H), 1.00 (d, J = 7.0 Hz, 3H), 0.93 (d, J = 6.8 Hz, 3H), 0.92 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.6, 170.8, 170.6, 79.2, 77.2, 74.3, 72.8, 62.5, 58.8, 42.4, 36.5, 35.5, 34.0, 32.1, 31.8, 23.8, 21.9, 20.9, 18.3, 17.6, 13.5, 12.5; IR ($CHCl_3$) 3470 (OH), 1734 (CO), 1709 (CO) cm^{-1}; MS (CI, NH_3) *m*/*z* (rel intensity) 416 [12, $(M + NH_4)^+$], 399 [18, $(M + H)^+$]; HRMS *m*/*z* 399.2386 (399.2383 calcd for $C_{21}H_{35}O_7$, MH).

4(*R*),5(*S*),8(*S*)-4-Hydroxy-8-{2-[3-((*S*)-2-hydroxy-3-methyl-butyl)-2(*S*),3(*R*)-2-methyl-oxiranyl]-1(*S*)-methyl-2-oxo-ethyl}-5-methyl-oxocan-2-one, (−)-Octalactin A, 1. To a vigorously stirred solution of the acetate ester **64** (2.0 mg, 50 μmol) in 10% DMF/pH 7 buffer (1 mL) was added type VII lipase from *Candida cylindracea* (Fluka, 20 mg). This mixture was stirred with the exclusion of light for 7 days, additional enzyme (20 mg) being added on days 2 and 4. The suspension was extracted with ether (3 × 5 mL), and the combined organic layers were filtered through a short wide plug of silica (Et_2O), washed with brine (5 mL), and dried (Na_2SO_4). The solvent was removed in vacuo, and purification by flash chromatography (ethyl acetate/hexane, 1:1) gave the synthetic natural product (−)-octalactin A, **1** (2.0 mg, 50 μmol, 100%), as a colorless solid which was crystallized from ether; mp 154−157 °C (ether){lit.[1] 155−157 °C ($CHCl_3$/EtOAc}; $[\alpha]_D^{20}$ −153.1 (*c* 0.14, $CHCl_3$), {lit.[3] $[\alpha]_D$ −156 (*c* 0.7 in $CHCl_3$)}; R_f 0.09 (ethyl acetate/hexane, 1:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.60 (t, J = 10.3 Hz, 1H), 4.03 (brs, 1H), 3.55 (t, J = 6.2 Hz, 1H), 3.58−3.48 (m, 1H), 3.00−2.93 (m, 2H), 2.79 (br d, J = 3.1 Hz, 0.5H, OH), 2.72 (dd, J = 13.4, 6.3 Hz, 1H), 1.89 (br d, J = 3.1 Hz, 0.5H, OH), 1.79−1.57 (m, 6H), 1.44 (s, 3H), 1.23−1.18 (m, 1H), 1.13 (d, J = 7.1 Hz, 3H), 1.00 (d, J = 7.0 Hz, 3H), 0.94 (d, J = 6.8 Hz, 3H), 0.92 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.5, 172.5, 79.3, 74.5, 71.3, 62.4, 58.9, 42.4, 39.2, 38.0, 34.0, 32.2, 32.0, 22.4, 22.1, 18.5, 17.6, 13.5, 12.6; IR ($CHCl_3$) 3458 (OH), 1708 (CO), 1462 cm^{-1}; HRMS (Q-TOF) *m*/*z* 379.2122 (379.2097 calcd for $C_{19}H_{32}O_6Na$, MNa).

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Supporting Information Available: Experimental procedures for the synthesis of **9**, **12**−**15**, the diol derived from **15a**, **17**, **25**, **27**, **28**−**39a**, **42**, **43**, **48**, **50**−**54**, and **56**; ^{1}H NMR analysis of **29**, **35**, **51**, and **53a**; CIF files and ORTEP plots of **48** and **1** (the data has been deposited with the Cambridge Crystallographic Database); ^{1}H and ^{13}C NMR spectra of synthetic octalactins A (**1**) and B (**2**) and tabulated comparisons with the natural octalactins. This material is available free of charge via the Internet at http://pubs.acs.org.

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