Substituted Oxocanes by Intramolecular Allylboration Reactions. Entry to an Efficient Synthesis of (+)-Laurencin

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Abstract: Δ^5-Oxocenes, such as *cis*-3-hydroxy-2-vinyl-Δ^5-oxocenes, can be generated by an intramolecular aldehyde−allylboration reaction. This allowed a rapid and stereoselective access to the trisubstituted oxocene **24** which had been transformed by the Holmes group into (+)-laurencin. The key feature of this effective intramolecular allylboration reaction is that both the aldehyde and the allylboronate functionality have been generated in a masked form in situ. They are liberated by an aqueous workup which initiates the ring closure reaction.

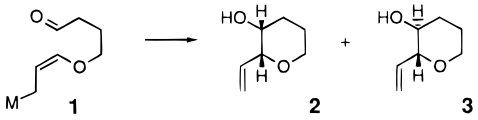
Introduction

Interest in saturated and unsaturated six- to nine-membered oxygen heterocycles has been stimulated by the discovery of the polyether toxins,[1] such as brevetoxin,[2] ciguatoxin,[3] the halichondrins,[4] maitotoxin,[5] or yessotoxin.[6] In his classical account of the first brevetoxin synthesis[7] Nicolaou devoted a whole section to the "oxocene-problem", which he addressed as an ill-famous, hard-to-overcome obstacle. Nicolaou himself developed some ingenious routes to ring-fused oxocenes, yet this left the challenge to uncover general inroutes to this class of oxygen heterocycles.

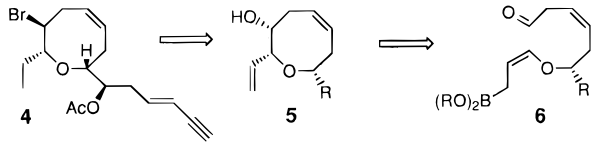
Driven by the interest in the polyether toxins, most progress has been made in the synthesis of fused tetrahydropyran rings.[8] Successful routes include ring closure of γ-hydroxy epoxides,[9] intramolecular Michael addition of a hydroxy group to an α,β-unsaturated ester,[10] and ring closing metathesis reactions[11] as well as intramolecular allylmetalation reactions of aldehydes, cf. Scheme 1.

Studies by the groups of Y. Yamamoto and J. D. Martin have shown that the trialkyltin or trimethylsilyl derivatives **1** cyclize

Scheme 1



Scheme 2



by the action of boron trifluoride etherate to give mainly the trans-disubstituted tetrahydropyran **3**.[12−15] This reaction has been implemented into the synthesis of multifused heterocyclic systems.[16] In contrast, the report[17] that **1** (M = Bu_3Sn) is cyclized to the cis-disubstituted tetrahydropyran **2** by the action of trifluoromethanesulfonic acid has not found further application in synthesis. Our interest in intramolecular allylboration reactions as a route to heterocyclic compounds[18] led us to the allylboronate **1** (M = $B(OR)_2$), which cyclized exclusively to the cis-disubstituted tetrahydropyran **2**.[19] It was therefore attractive to extend these studies to the synthesis of the ill-famous oxocane and oxocene ring systems. Laurencin (**4**),[20] a long known natural oxocene-derivative, was chosen as a target, cf. Scheme 2.

The ethyl side chain in laurencin (**4**) can be derived from a vinyl group; therefore, the *cis*-hydroxy compound **5** appears as

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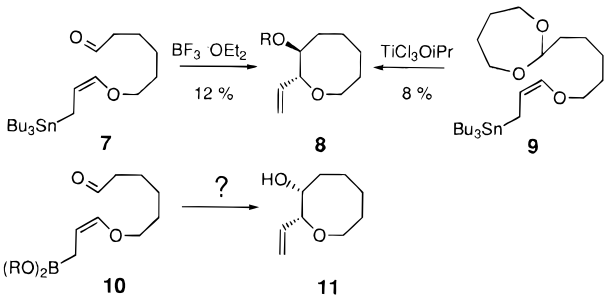
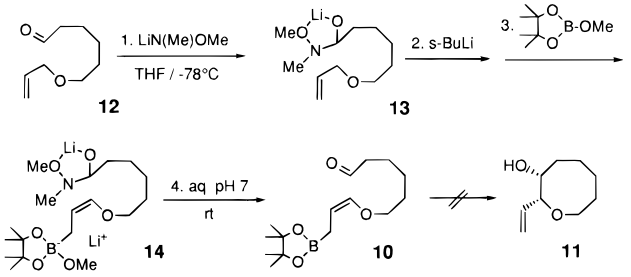
Scheme 3



Scheme 4



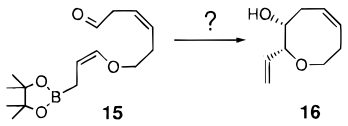
a reasonable precursor because the substitution of a hydroxyl group under inversion of configuration had already been realized in previous syntheses of laurencin.[21] The Δ^5-oxocene **5** should be the product of an intramolecular allylboration of **6**. The point to be clarified, though, is whether the resident stereogenic center in **6** would induce ring closure to **5** with the desired relative configuration.

Allylmetalation Reactions Leading to Oxocanes

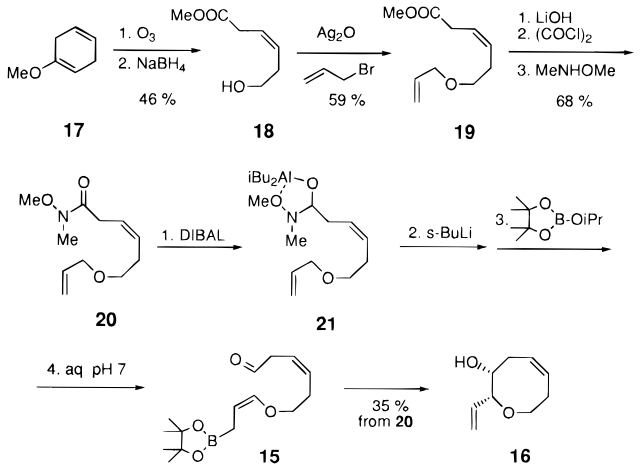
The formation of an oxocane ring by an intramolecular aldehyde/allylstannation reaction had been studied before. Both the Yamamoto[12] and the Martin[16] group found that the simple oxocane **8** can be obtained by an intramolecular allylstannation reaction, albeit in low yield; cf. Scheme 3. They found that cyclization yields could be raised to between 30 and 65%, when substituents or a Z-double bond in the precursor molecule induced a conformation favorable for cyclization. While these routes led to the trans-disubstituted oxocane **8**, we report here our efforts to reach cis-disubstituted oxocanes **11** by cyclization of the allylboronate **10**.

A problem germane to all intramolecular allylmetalation reactions is the necessity to generate an aldehyde function in the presence of the acid-labile allylmetal moiety or vice versa. In the case of the allyltin compound **1** this has been attained by a mild oxidiation of a primary alcohol[13] or a by oxidative cleavage of a 1,2-diol.[15] We envisioned an approach to **10**, by which the aldehyde function is temporarily masked during the generation of the allylboronate function. This could be achieved by an in situ protection of the type advocated by Comins.[22] In view of the high stability of the adducts[23] of organolithium compounds to Weinreb amides,[24] we opted for a route to **10** described in Scheme 4. In this route the allylboronate moiety is also generated in a masked form, as the ate complex **14**. Only upon aqueous workup will both reactive functionalities, the aldehyde and the allylboronate, be liberated which then should enter into a ring closure reaction.

Scheme 5



Scheme 6



Thus, allyloxyhexanal (**12**) was treated with lithium *N*-methoxy-*N*-methyl amide to generate **13**. Subsequent addition of *sec*-butyllithium should metalate the allyl ether moiety.[25] The resulting organolithium compound was trapped by addition of an trialkylborate. Finally, hydrolysis liberated both the allylboronate and the aldehyde functions in **10**. To our dismay, none of the desired cyclization product **11** could be obtained from this reaction sequence. We suspect that ring closure of **10** was not able to compete with polymerization.

However, the reaction sequence delineated in Scheme 4 had worked fine to generate the allylboronate **1** (M = $B(OR)_2$)[19] which cyclized readily to **2**. We were therefore confident that the model system **15** with a Z-double bond should have a higher predisposition for cyclization, cf. ref 16.

Nevertheless, projecting the aldehyde **15** as a cyclization precursor entailed a further problem: The double bond in **15** is β,γ- to the aldehyde function. We were therefore afraid that treatment of the Δ^3-analog of **12** with a lithium amide base would lead to enolization rather than to masking of the aldehyde function by addition. Thus, we decided to generate the aldehyde function as well directly in a masked form. This we hoped to attain by a DIBAH reduction of the Weinreb amide **20**, cf. Scheme 6.

Following an earlier approach by Corey[26] the methoxycyclohexadiene **17** was used as a source of a Z-double bond in the alcohol **18**. The latter was allylated to give the ether **19**. Attempts to convert **19** directly into the Weinreb amide **20**[24,27] failed. We therefore took a more roundabout way to **20** via saponification and formation of the acid chloride. The Weinreb amide was then carried through in a one-pot reaction sequence to the aldehyde **15**: DIBAL reduction of the Weinreb amide to generate the aluminum chelate **21**, lithiation of the allyloxy system with *sec*-butyllithium, borylation with a pinacol borate ester and, finally, liberation of the reactive groups by aqueous

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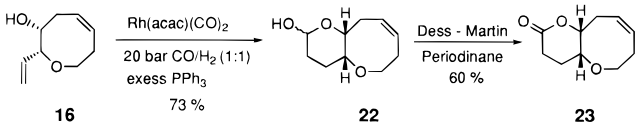
Scheme 7



pH 7 buffer solution. To our delight, this sequence resulted in the formation of the oxocene **16** in 32% overall yield. While this yield is still far from optimal, the result nevertheless shows that the Z-double bond present in **15** raised the chances for the intramolecular versus the intermolecular allylboration reaction.

The oxocene **16** was obtained as a single diastereomer. The relative configuration of the two new stereogenic centers in **16** was not evident from the ^{1}H-NMR spectra of the flexible oxocene ring. We therefore converted the alcohol **16** into a more rigid bicyclic derivative **23**. This was effected by hydroformylation of **16** to an anomeric mixture of the lactols **22**, followed by oxidation to the lactone **23**, cf. Scheme 7.

The two bridgehead protons in **23** showed a 2−3 Hz coupling. Their disposition on the same side of the bicyclic framework was also proven by a strong NOE contact between them.

The conversion of **20** into **16** set the stage for a direct access to the oxocene ring system of laurencin. Even if the overall yield of this transformation is only moderate, this will be partially compensated by the high stereoselectivity and by the low number of steps required to build the oxocene ring system.

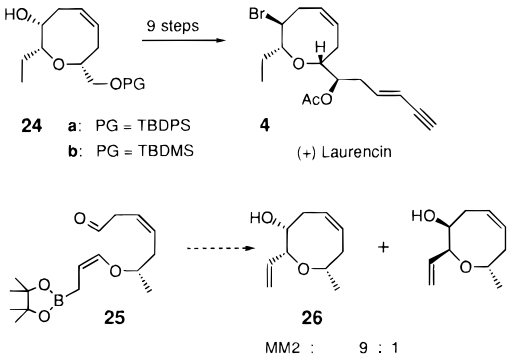
An Entry into an Efficient Laurencin Synthesis

Our route to Δ^5-oxocenes seemed well suited to interface with a recent synthesis of laurencin (**4**) carried out by the Holmes group.[28] In their synthesis the intermediate **24a** has been converted in nine operations into the enantiomerically pure (+)-laurencin (**4**). We therefore wanted to reach the intermediate **24** by an intramolecular allylboration of the aldehyde **34**. We had, however, first to address the question, whether asymmetric induction from the resident stereogenic center in **34** would lead to the desired stereoisomer of **35**. We therefore carried out MM2-calculations on the transition states for the intramolecular allylboration of **25**, in which the methyl group serves as a model for the side chain in laurencin. We used the force field parameters developed by Gennari[29] to model transition states of the allylboronate aldehyde additions.

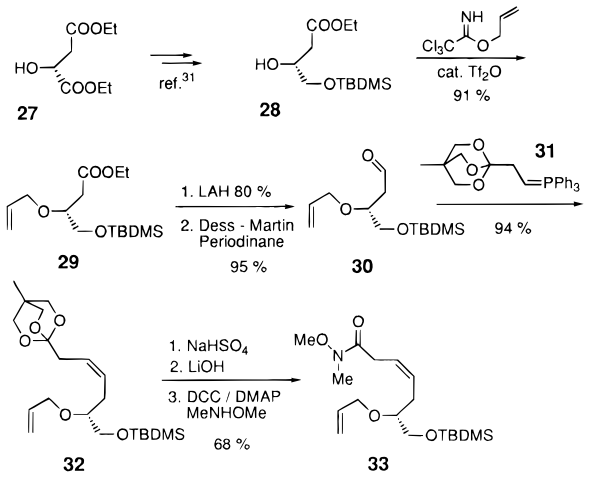
These calculations led us to expect an ca. 9:1 preference in favor of **26**, i.e., the relative configuration required for laurencin, on the ring closure of **25**. This was in keeping with the high levels of asymmetric induction from resident stereocenters found before[30] in intramolecular allylboration reactions leading to six-membered carbocycles.

The starting point of our synthesis was the alcohol **28**[31] derived from the ethyl ester **27** of unnatural malic acid.[32] Attempts to allylate **28** under the usual basic conditions resulted in partial migration of the silyl protecting group.[33] Allylation to **29** was, however, cleanly accomplished with allyl trichloroacetimidate and a catalytic amount of trifluoromethane-sulfonic anhydride (91%). The ester group in **29** was now converted to the aldehyde **30** by standard lithium aluminium hydride reduction to the alcohol followed by Dess−Martin oxidation (75%). We intended to use a Wittig reaction with the known[34] phosphorane **31** to arrive at the Z-double bond in **32**. Using the route described by Keinan[35,36] the Wittig reaction furnished the desired **32** in 94% yield with a *Z/E* ratio of 96:4. The transformation of the OBO ester **32** into the Weinreb amide **33** was carried out as a one-pot sequence in 68% yield, involving saponification to the carboxylic acid and DCC initiated formation of the amide.

Scheme 8



Scheme 9



At this point we were ready to launch the one-pot cyclization to the oxocene **35**. DIBAL reduction of the Weinreb amide **33**, metalation with *sec*-butyllithium, borylation with the pinacol borate ester and, finally, liberation of both the aldehyde and the allylboronate function by aqueous pH 7 buffer solution generated the reactive target **34** which cyclized in 38% yield overall to the desired **35**. NOE cross-peaks in the ^{1}H-NMR spectra between the hydrogens at C-2, C-3, and C-8 indicated that all substituents at the oxocene ring were in a cis arrangement. Since we observed no diastereomeric product, we conclude that the cyclization proceeded under high asymmetric induction from the resident stereogenic center present in **31**.

At this point we had to address the selective hydrogenation of **35** to **24b**. High selectivities for hydrogenations of terminal double bonds have been reported for ruthenium catalysts.[37] We had, however, no luck with these for the selective hydrogenation of **35**. After screening a variety of hydrogenation catalysts, we

(28) Holmes, A. B. Personal communication, 1996. Cf. the accompanying paper.

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(36) The conversion of the bromoethyl compound into the iodo ethyl compound worked better, when using sodium iodide, sodium bicarbonate in butanone as solvent.

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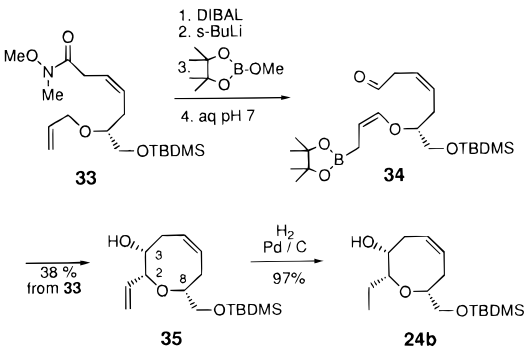
Scheme 10



found that simple palladium on carbon differentiated well enough between the two double bonds in **35** to realize a selective hydrogenation to **24b** in 97% yield. Careful monitoring of the progress of the hydrogenation reaction was, however, necessary. Finally, the TBDMS group was cleaved from **24b**, and the resulting diol was selectively reprotected with TBDPS chloride to furnish **24a** which showed ^{1}H- and ^{13}C-NMR spectra identical to those kindly provided by Dr. A. B. Holmes.

If our route to the oxocene **24b** (16% overall yield from **28**) is implemented into the Holmes synthesis of laurencin, this amounts to a 18-step synthesis with an overall yield of 3%. Comparison with the other approaches to laurencin[21,38,39] makes it clear that direct ring closure reactions, as the one developed here and the one utilized by Overman,[39] characterize the most efficient ways to laurencin.

Apart from opening an efficient route to laurencin, the heterocyclization reaction by intramolecular allylboration of an aldehyde function presented here has the novel feature that both the reactive aldehyde and the allylboronate moiety are initially generated in a masked form in situ and are liberated simultaneously by spontaneous hydrolysis of the precursor functions.

Experimental Section

All temperatures quoted are not corrected: ^{1}H-NMR, ^{13}C-NMR: Bruker AMX-500; Bruker AC-300; boiling range of petroleum ether: 40−60 °C; pH 7 buffer: 56.2 g $NaH_2PO_4 \times 2\ H_2O$ + 213.2 g $Na_2HPO_4 \times 2\ H_2O$ in 1.0 L of water; flash chromatography: silica gel Si 60 E. Merck AG, Darmstadt, 40−63 μm.

Methyl (3*Z*)-6-(2-Propenyloxy)-3-hexenoate (19). A solution of methyl (3*Z*)-6-hydroxy-3-hexenoate[26] **18** (0.64 g, 4.4 mmol), Ag_2O (1.0 g, 4.4 mmol), allyl bromide (0.87 mL, 10 mmol), and 20 mL anhydrous diethyl ether was refluxed for 8 h under exclusion of light in an nitrogen atmosphere. The reaction was maintained at room temperature over night. The solvent and excess of allyl bromide were removed in vacuo. The resulting residue was purified by flash chromatography (10:1 petroleum ether/*tert*-butyl methyl ether) to afford **19** (0.40 g, 49%) as a colorless liquid. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.31 (m, 2H), 3.10 (d, J = 5.5 Hz, 2H), 3.43 (t, J = 6.8 Hz, 2H), 3.66 (s, 3H), 3.95 (dt, J = 5.6 and 1.4 Hz, 2H), 5.14 (dq, J = 10.3 and 1.5 Hz, 1H), 5.24 (dq, J = 17.1 and 1.7 Hz, 1H), 5.62 (m, 2H), 5.88 (ddt, J = 10.5, 17.2 and 5.6 Hz, 1H); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 28.1, 32.8, 51.8, 69.3, 71.8, 116.8, 122.7, 129.3, 134.7, 172.2. Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.00; H 8.51.

***N*-Methoxy-*N*-methyl-(3*Z*)-6-(2-propenyloxy)-3-hexenoicamide (20).** To a solution of the ester **19** (234 mg, 1.27 mmol), DME (5 mL), and water (3 mL) was added 2 mL of an aqueous LiOH solution (5 M) at room temperature. It was stirred for 10 min and then carefully brought to pH 2−3 with 2 M aqueous HCl. The reaction mixture was diluted with ether (10 mL), and the aqueous layer was extracted three times with 5 mL each of *tert*-butyl methyl ether. The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated. The residue (214 mg) was dissolved in anhydrous CH_2Cl_2 (8 mL). To this solution $(COCl)_2$ (240 mg, 1.89 mmol) and a catalytic amount of DMF was added under ice-cooling. The mixture was maintained at 0 °C for 30 min and at room temperature for 15 min. The solvent and excess of $(COCl)_2$ were removed in vacuo, and the residue was diluted with CH_2Cl_2 (5 mL). *N*,*O*-Dimethylhydroxylamine hydrochloride (136 mg, 1.39 mmol) and pyridine (224 μL, 2.77 mmol) were added under ice-cooling. The mixture was stirred for 40 min at room temperature. Aqueous HCl (1 mL, 2 M solution) was added, and the aqueous layer was extracted twice with 3 mL each of CH_2Cl_2. The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated. The resulting residue was purified by flash chromatography (1:1 petroleum ether/*tert*-butyl methyl ether) to yield **20** (183 mg, 68%) as a pale yellow liquid. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 2.37 (dq, J = 5.7 and 0.96 Hz, 2H), 3.17 (s, 3H), 3.23 (d, J = 5.9 Hz, 2H), 3.45 (t, J = 7.0 Hz, 2H), 3.68 (s, 3H), 3.97 (dt, J = 1.4 and 5.6 Hz, 2H), 5.16 (dq, J = 1.7 and 10.5 Hz, 1H), 5.25 (dq, J = 1.6 and 17.3 Hz, 1H), 5.60−5.67 (m, 2H), 5.90 (ddt, J = 5.6, 10.3 and 17.3 Hz, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 28.4, 31.1, 32.3 (broad), 61.3, 69.6, 71.9, 116.7, 123.7, 128.8, 134.9. The resonance for the carbonyl-C-atom of the amide was missing. Anal. Calcd for $C_{11}H_{19}NO_3$: C, 61.95; H, 8.98. Found: C, 61.86; H 9.16.

(2*R,3*R**)-3-Hydroxy-2-vinyl-3,4,7,8-tetrahydro-2*H*-oxocin (16).** To a solution of the Weinreb amide **22** (183 mg, 0.85 mmol) and anhydrous THF (10 mL) was added DIBAH (0.82 mL, 1.02 mmol, 1.24 M solution in petroleum ether) dropwise via a syringe at −78 °C. The reaction was maintained at −78 °C for 90 min. A solution of *s*-BuLi (1.3 M in 92:8 cyclohexane/hexane, 1.44 mL, 1.87 mmol, purchased from Acros) was added dropwise via a syringe, and the resulting bright yellow solution was stirred for 60 min at −78 °C. A solution of 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (380 mg, 2.04 mmol) in THF (2 mL) was added via a syringe within 5 min. The cooling bath was removed, and the reaction mixture was allowed to reach room temperature. It was diluted with petroleum ether (10 mL), and pH 7 phosphate buffer (10 mL) was added under vigorous stirring. The mixture was maintained at ambient temperature for 3 h and then extracted three times with 10 mL each of ether. The combined organic layer was washed with brine (10 mL), dried (Na_2SO_4), and concentrated. The resulting residue was purified by flash chromatography (1:1 petroleum ether/ether) to afford the Δ^5-oxocene **16** (41.0 mg, 32%) as a single diastereomer. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.94 (s, broad, 1H), 2.16 (m, 1H), 2.34 (m, 1H), 2.43−2.63 (m, 2H), 3.42 (m, 1H), 3.76 (s, broad, 1H), 3.96 (ddd, J = 3.7, 6.0 and 12.0 Hz, 1H), 4.02 (m, 1H), 5.21 (dq, J = 2.0 and 10.6 Hz, 1H), 5.34 (dq, J = 1.8 and 17.3 Hz, 1H), 5.76−5.91 (m, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 29.4, 32.7, 70.4, 74.4, 81.8, 115.6, 128.8, 130.6, 136.9. Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H 9.15. Found: C, 70.34; H 9.35.

(1*R,8*R**)-2,9-Dioxabicyclo[6.4.0]dodec-5-en-10-one (23).** Triphenylphosphine (0.10 g, 0.39 mmol, 100 equiv) was added to a solution of $Rh(CO)_2acac$ (1.0 mg, 1.9 mol%) in anhydrous benzene (5 mL), and the mixture was stirred for 10 min. Homoallylic alcohol **16** (33 mg, 0.21 mmol) was added, and the reaction mixture was transferred into an autoclave through a cannula. An atmosphere of CO (10 bar) and H_2 (10 bar) was established, and the mixture was stirred at 70 °C for 2 h. The reaction vessel was flushed with nitrogen, and the solvent was removed in vacuo. The residue was purified by flash chromatography (1:1 petroleum ether/*tert*-butyl methyl ether) to yield 28 mg of the lactol **22** as an anomeric mixture. The product was dissolved in anhydrous CH_2Cl_2 (5 mL) and pyridine (0.12 mL, 1.5 mmol), and Dess−Martin periodinane (76 mg, 0.18 mmol) was added under ice-cooling. The mixture was maintained at 0 °C for 30 min. After TLC indicated complete oxidation, the mixture was concentrated, and the residue was purified by flash chromatography (1:2 petroleum ether/ether) to afford the desired lactone **23** (16 mg, 60%): ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.86−2.11 (m, 3H), 2.36−2.47 (m, 2H), 2.55−2.84 (m, 3H), 3.34 (dt, J = 12.0 and 1.3 Hz, 1H), 3.76 (dt, J = 3.3 and 3.6 Hz, 1H), 4.10 (dt, J = 3.5 and 12.2 Hz, 1H), 4.36 (ddd, J = 2.7, 4.9 and 11.5 Hz, 1H), 5.69 (m, 1H), 5.92 (m, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 25.1, 25.8, 29.7, 30.3, 72.2, 72.7, 83.0, 126.8, 132.0, 170.8;

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HRMS (EI) *m/z* 182.0938 (182.0943 calcd for $C_{10}H_{14}O_3$) *m/z* 183.0979 (183.0976 calcd for $^{13}C_1C_9H_{14}O_3$).

Ethyl 4-[(*tert*-Butyldimethylsilyl)oxy]-(3*R*)-(2-propenyloxy)butanoate (29). Four drops of trifluoromethane sulfonic anhydride were added to a solution of ethyl 4-[(*tert*-butyldimethylsilyl)oxy]-(3*R*)-2-hydroxybutanoate (**28**)[31] (3.22 g, 12.3 mmol) and allyl trichloroacetimidate (4.05 g, 20.0 mmol) in petroleum ether (25 mL), and the mixture was stirred for 3 days at room temperature. The precipitated trichloroacetamide was filtered off. The filtrate was washed with saturated aqueous $NaHCO_3$ and brine, dried with Na_2SO_4, and concentrated. The resulting residue was purified by flash chromatography (10:1 petroleum ether/*tert*-butyl methyl ether) to yield 3.39 g (91%) of the allylated alcohol **39** as a colorless liquid. $[\alpha]^{25}_D$ +17.1° (*c* 0.52, CH_2Cl_2); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.04 (s, 6H), 0.87 (s, 9H), 1.25 (t, J = 7.2 Hz, 3H), 2.45 (dd, J = 7.9 and 15.6 Hz, 1H), 2.58 (dd, J = 4.8 and 15.6 Hz, 1H), 3.54 (dd, J = 5.9 and 10.3 Hz, 1H), 3.69 (dd, J = 5.3 and 10.4 Hz, 1H), 3.85 (m, 1H), 4.06 (m, overlayed by the adjacent quartett, 2H), 4.13 (q, J = 7.2 Hz, 2H), 5.13 (qd, J = 1.4 and 10.3 Hz, 1H), 5.24 (qd, J = 1.7 and17.2 Hz, 1H), 5.87 (ddt, J = 10.3, 17.3 and 5.6 Hz, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ −5.4 (2 C), 14.2, 18.3, 25.9 (3 C), 37.6, 60.4, 64.8, 71.5, 76.6, 116.7, 135.1, 171.7. Anal. Calcd for $C_{15}H_{30}O_4Si$: C, 59.56; H 10.00. Found: C, 59.40; H 10.22.

4-[(*tert*-Butyldimethylsilyl)oxy]-(3*R*)-(2-propenyloxy)butanal (30). A solution of the ester **29** (0.30 g, 1.0 mmol) in THF (1 mL) was added dropwise via a syringe at 0 °C to a suspension of lithium aluminium hydride (29 mg, 0.75 mmol) in THF (5 mL). TLC indicated the reaction to be complete after 10 min. Saturated aqueous K_2CO_3 solution was added dropwise to the reaction mixture under ice-cooling until there was no more evolution of gas. The mixture was stirred at room temperature for 15 min, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography (2:1 petroleum ether/*tert*-butyl methyl ether) to yield the alcohol (0.21 g, 80%) as a colorless oil. $[\alpha]^{20}_D$ +29.5° (*c* 0.66, CH_2Cl_2); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.06 (s, 6H), 0.88 (s, 9H), 1.78 (m, 2H), 2.67 (t, J = 5.1 Hz, 1H), 3.58 (m, 2H), 3.67−3.79 (m, 3H), 4.04 (ddt, J = 1.4, 4.5, and 12.6 Hz, 1H), 4.18 (ddt, J = 1.4, 5.5, and 12.6 Hz, 1H), 5.16 (qd, J = 1.3 and 10.3 Hz, 1H), 5.23 (qd, J = 1.7 and 17.2 Hz, 1H), 5.91 (ddt, J = 10.4, 17.2, and 5.7 Hz, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ −5.4 (2 C), 18.3, 25.9 (3 C), 34.4, 60.4, 65.3, 71.2, 79.1, 117.0, 135.0. Anal. Calcd for $C_{13}H_{28}O_3Si$: C, 59.95; H 10.84. Found: C, 59.80; H 10.91.

Dess−Martin periodinane (0.59 g, 1.4 mmol) was added to a solution of the alcohol (0.26 g, 1.0 mmol) in anhydrous CH_2Cl_2 (10 mL), pyridine (0.79 mL, 10 mmol), and approximately 100 mg of powdered molecular sieves at 0 °C. It was stirred at room temperature for 2 h, filtered, and concentrated. The residue was purified by flash chromatography (5:1 petroleum ether/*tert*-butyl methyl ether) to yield 0.24 g (95%) of the desired aldehyde **30** as a colorless liquid. $[\alpha]^{20}_D$ +17.4° (*c* 0.80, CH_2Cl_2); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.04 (s, 6H), 0.87 (s, 9H), 2.61 (m, 2H), 3.57 (dd, J = 6.1 and 10.4 Hz, 1H), 3.73 (dd, J = 4.9 and 10.4 Hz, 1H), 3.91 (q, J = 5.9 Hz, 1H), 4.07 (m, 2H), 5.16 (qd, J = 1.3 and 10.3 Hz, 1H), 5.24 (qd, J = 1.6 and 17.2 Hz, 1H), 5.87 (ddt, J = 10.4, 17.2 and 5.6 Hz, 1H), 9.80 (t, J = 2.2 Hz, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ −5.3 (2 C), 18.2, 25.8 (3 C), 46.3, 64.4, 71.1, 75.0, 117.0, 134.8, 201.0. Anal. Calcd for $C_{13}H_{26}O_3Si$: C, 60.42; H 10.14. Found: C, 60.50; H 10.28.

1-[6-[(*tert*-Butyldimethylsilyl)oxy]-(5*R*)-(2-propenyloxy)-(2*Z*)-hexenyl]-4-methyl-2,6,7-trioxabicyclo[2.2.2]octane (32). NaHMDS (0.7 mL of a 2 M solution in THF) was added to a stirred suspension of 2-(4-methyl-2,6,7-trioxabicyclo[2.2.2]octyl)ethyltriphenylphosphonium iodide[34,35,36] (0.82 g, 1.5 mmol) in anhydrous THF (15 mL) via a syringe at room temperature. The reaction mixture was stirred at 45 °C for 3 h and then cooled to −78 °C. A solution of aldehyde **30** (0.22 g, 0.87 mmol) in THF (2 mL) was added dropwise, and the mixture was allowed to warm to room temperature over night. It was diluted with ether (10 mL) and quenched with water (10 mL). The aqueous layer was extracted three times with 10 mL each of *tert*-butyl methyl ether. The combined organic layer was washed with brine, dried (Na_2SO_4), and concentrated. The resulting residue was purified by flash chromatography (5:1 petroleum ether/*tert*-butyl methyl ether containing 0.5% triethylamine) to yield the alkene **32** (0.33 g, 94%) as a 96:4 mixture of *Z*/*E* diastereomers. $[\alpha]^{20}_D$ −1.6° (*c* 0.75, CH_2Cl_2); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.03 (s, 6H), 0.78 (s, 3H), 0.87 (s, 9H), 2.25 (m, 2H), 2.46 (m, 2H), 3.39 (m, 1H), 3.57 (m, 2H), 3.88 (s, 6H), 4.06 (m, 2H), 5.11 (qd, J = 1.8 Hz, and 10.5 Hz, 1H), 5.23 (qd, J = 1.8 Hz and 17.3 Hz, 1H), 5.57 (m, 2H), 5.88 (ddt, J = 10.3, 17.2 and 5.6 Hz, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ −5.4, −5.3, 14.5, 18.3, 25.9 (3 C), 29.5, 30.4, 35.0 65.3, 71.1, 72.6 (3 C), 79.7, 108.8, 116.2, 123.2, 128.1, 135.6. Anal. Calcd for $C_{21}H_{38}O_5Si$: C, 63.28; H 9.61. Found: C, 63.01; H 9.81.

***N*-Methoxy-*N*-methyl-7-[(*tert*-butyldimethylsilyl)oxy]-(6*R*)-(2-propenyloxy)-(3*Z*)-heptenoic-amide (33).** To a solution of the OBO ester **32** (0.70 g, 1.76 mmol) in DME (5 mL) was added under ice-cooling 5 mL of an aqueous $NaHSO_4$ solution which was adjusted to pH 3−4. The cooling bath was removed, and the mixture was stirred until TLC indcated complete comsumption of the starting material (approximately 3 h). The aqueous layer was extracted four times with 5 mL each of ethyl acetate. The combined organic layer was washed with brine and concentrated. The residue was dissolved in DME (10 mL) and cooled to 0 °C followed by addition of 5 mL of an aqueous LiOH (2 M) solution. The mixture was maintained at room temperature for 1 h and the brought to pH 5−6 by dropwise addition of aqueous HCl (1 M). The aqueous layer was extracted four times with 10 mL each of *tert*-butyl methyl ether. The combined organic layer was washed with brine, dried with Na_2SO_4, and concentrated to yield 0.56 g (1.76 mmol) of the crude acid. This was taken up in anhydrous CH_2Cl_2 (10 mL), and *N*,*O*-dimethylhydroxylamine hydrochloride (0.17 g, 1.77 mmol), *N*-methylpiperidine (0.18 g, 1.77 mmol), DMAP (22 mg, 0.18 mmol), and DCC (0.37 g 1.77 mmol) were added. The mixture was maintained at room temperature over night, filtrated over zeolite, and concentrated. The resulting residue was purified by flash chromatography (1:1 petroleum ether/*tert*-butyl methyl ether) to afford 0.43 g (68%) of the desired Weinreb amide **33** as a pale yellow liquid. $[\alpha]^{20}_D$ −0.57° (*c* 1.25, CH_2Cl_2); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.04 (s, 6H), 0.87 (s, 9H), 2.29 (m, 2H), 3.16 (s, 3H), 3.26 (m, 2H), 3.43 (m, 1H), 3.54 (dd, J = 5.2 and 10.6 Hz, 1H), 3.62 (dd, J = 5.7 and 10.6 Hz, 1H), 3.67 (s, 3H), 4.07 (m, 2H), 5.12 (qd, J = 1.8 and 10.3 Hz, 1H), 5.24 (qd, J_q = 1.6 and 17.3 Hz, 1H), 5.67 (m, 2H), 5.88 (ddt, J = 10.4, 17.2 and 5.6 Hz, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ −5.4 (2 C), 18.3, 25.9 (3 C), 29.8, 31.1 (broad), 32.3 (very broad), 61.2, 65.0, 71.2, 79.5, 116.4, 123.7, 128.5, 135.4. The resonance for the carbonyl-C-atom of the amide was missing. Anal. Calcd for $C_{18}H_{35}NO_4Si$: C, 60.46; H, 9.87. Found: C, 60.44; H 9.81.

(8*R*)-[(*tert*-Butyldimethylsilyl)oxy]methyl-(3*R*)-hydroxy-(2*R*)-vinyl-3,4,7,8-tetrahydro-2*H*-oxocin (35). DIBAH (1.12 mL, 0.89 M in petroleum ether) was added via a syringe over 15 min at −78 °C to a solution of the Weinreb amide **33** (357 mg, 1.00 mmol) in THF (10 mL). The mixture was maintained at −78 °C for 90 min. Addition of 1.62 mL *s*-BuLi (2.10 mmol, 1.3 M in cyclohexane/hexane 92:8) via syringe produced a yellow color. The mixture was stirred for 30 min. A solution of 2-methoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (347 mg, 2.20 mmol) in THF (2 mL) was added, and the cooling bath was removed. After warming to room temperature the mixture was poured into a vigorous stirred bilayer system of ether (20 mL) and pH 7 buffer (20 mL). It was stirred over night, and the aqueous layer was extracted three times with 10 mL each of ether. The combined organic layer was washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography (5:1 petroleum ether/ether) to yield 112 mg (38%) of the desired product as a single diastereomer. $[\alpha]^{20}_D$ −38.4° (*c* 0.5, CH_2Cl_2); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.07 (s, 6H), 0.89 (s, 9H), 1.77 (d, J = 7.6 Hz, OH), 2.29−2.39 (m, 3H), 2.60 (m, 1H), 3.44 (m, 1H), 3.49 (m, 1H), 3.74 (dd, J = 5.5 and 10.0 Hz, 1H), 3.77 (m, broad, 1H), 4.16 (m, sharp, 1H), 5.23 (dt, J = 2.0 and 10.6 Hz, 1H), 5.46 (dt, J = 2.0 and 17.2 Hz, 1H), 5.76−5.88 (m, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ −5.3 (2 C), 18.3, 25.9 (3 C), 30.7, 32.8, 65.9, 74.5, 81.3, 81.5, 115.9, 129.3, 129.9, 136.7. Anal. Calcd for $C_{16}H_{30}O_3Si$: C, 64.38; H, 10.13. Found: C, 64.24; H 10.16.

(8*R*)-[(*tert*-Butyldimethylsilyl)oxy]methyl-(3*R*)-hydroxy-(2*R*)-ethyl-3,4,7,8-tetrahydro-2*H*-oxocin (24b). A solution of the diene **35** (43.0 mg, 144 μmol), anhydrous methanol (3 mL), and a catalytic amount of Pd/C (purchased from Fluka) was stirred in an H_2 atmosphere at room temperature. The reaction was monitored by ^{1}H-NMR spectroscopy. After 30 min all olefinic signals for the vinyl group had dissappeared. The reaction mixture was filtered over zeolite and

concentrated resulting in 42.0 mg (97%) of the desired oxocene **24b** as a colorless liquid. $[\alpha]^{20}_D$ −11.3° (*c* 0.39, CH_2Cl_2); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.05 (2 sharp s, 2 × 3H), 0.89 (s, 9H), 0.94 (t, J = 7.4 Hz, 3H), 1.35−1.49 (m, 1H), 1.56−1.74 (m, 1H), 1.81 (m, broad, 1H), 2.29 (m, 3H), 2.54 (dt, J = 12.5 and 9.0 Hz, 1H), 3.46 (m, 3H), 3.69 (m, 2H), 5.69−5.89 (m, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ −5.4, −5.3, 10.5, 18.3, 25.9 (3 C), 30.3, 33.5, 65.6, 74.3, 81.4, 82.4, 129.0, 129.5. Anal. Calcd for $C_{16}H_{32}O_3Si$: C, 63.95; H, 10.73. Found: C, 63.78; H 10.75.

(8*R*)-(*tert*-Butyldiphenylsilyloxy)methyl-(3*R*)-hydroxy-(2*R*)-ethyl-3,4,7,8-tetrahydro-2*H*-oxocin (24a). To a solution of the TBS ether **25b** (9.0 mg, 33 μmol) and THF (1 mL) was added TBAF (70 μL of a 1 M solution in THF) under ice-cooling. The mixture was stirred at room temperature for 1 h and concentrated, and the residue was purified by flash chromatography using ether as the eluent to yield 6.1 mg of the diol which was not further characterized. Under a nitrogen atmosphere *tert*-butyldiphenylsilyl chloride (31.5 μL, 0.12 mmol) and imidazole (8.2 mg, 0.12 mmol) were added under ice-cooling to a solution of the diol (21 mg, 0.11 mmol) in CH_2Cl_2 (3 mL). The mixture was maintained at 0 °C for 2 h and then quenched with water (2 mL). The aqueous layer was extracted three times with 3 mL each of CH_2Cl_2. The combined organic layer was dried with Na_2SO_4 and concentrated. The resulting residue was purified by flash chromatography (3:1 petroleum ether/ether) to afford 34 mg (67%) of the TBDPS ether **24a** as a colorless oil: $[\alpha]^{20}_D$ +0.6° (*c* 1.7, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.93 (t, J = 7.4 Hz, 3H), 1.13 (s, 9H), 1.46 (m, 1H), 1.69 (m, 1H), 1.80 (broad, 1H), 2.37 (m, 3H), 2.58 (m, 1H), 3.46 (m, 1H), 3.50−3.62 (m, 2H), 3.71 (m, 1H), 3.79 (m, 1H), 5.86−5.88 (m, 2H), 7.46 (m, 6H), 7.75 (m, 4H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 10.3, 19.0, 25.7, 26.7 (3 C), 30.2, 33.3, 66.2, 74.1, 80.9, 82.2, 127.4 (4 C), 128.9, 129.2, 129.4 (2 C), 133.5 (2 C), 135.4 (4 C). The spectroscopic data for **24a** are identical to those kindly provided by Dr. A. B. Holmes (Cambridge, UK).

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