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Synthetic efforts toward the synthesis of octalactins

Minh-Thu Dinh [a], Samir Bouzbouz [a,*,†], Jean-Louis Péglion [b], Janine Cossy [a,*]

[a] Laboratoire de Chimie Organique associé au CNRS, ESPCI, 10 rue Vauquelin, 75231 Paris Cedex 05, France
[b] Laboratoire Servier, 11 rue des Moulineaux, 92150 Suresnes, France

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ABSTRACT

Octalactin B was synthesized from the commercially available methyl-3-butenoate and isobutyraldehyde, using enantioselective allyl- and crotyltitanations to control the stereogenic centers at C3, C4, C7, C8, and C13. Moreover, the two other key-step reactions are a cross-metathesis reaction and a lactonization, using the effective anhydride MNBA, to build up the eight-membered ring lactone.

1. Introduction

Octalactin A was isolated from the marine bacterium *Streptomyces* sp. in 1991,[1] together with the related compound, octalactin B (Fig. 1). The structure of octalactin A was established by X-ray crystallographic analysis and the absolute configuration of the stereogenic centers in octalactin A and octalactin B were established independently by synthesis.[2,3] In addition, octalactin A exhibits potent cytotoxicity in tests with B-16-F10 murine melanoma and HCT-116 human colon tumor cell lines, whereas octalactin B was completely inactive. However, it has been shown that octalactin B can be transformed easily to octalactin A by a one-step epoxidation. Because of their structural complexity and their interesting biological properties, octalactins have solicited considerable interest among organic chemists and three total syntheses,[2,4] two formal syntheses as well as the preparation of several fragments of octalactins have been reported.[5] An excellent review by Shiina has been published recently on the synthesis of octalactins A and B.[6] Here, we would like to report two approaches for obtaining octalactins.

2. First approach

At first, we have envisaged the synthesis of octalactin B from the linear polyhydroxyester **A**, with the purpose of examinating the regioselectivity of the possible lactonizations under kinetic or thermodynamic control. In order to synthesize fragment **A**, the key steps would be enantioselective crotylmetalations to control all the stereogenic centers, an aldol reaction to built up the C10–C11 bond, and a cross-metathesis (CM) to construct the C5–C6 bond. Compound of type **A** would be synthesized from an aldol condensation between a ketone of type **B** and an aldehyde of type **C**. Compound **B** would be obtained from aldehyde of type **D**, which would be the result of a CM between hydroxyester **2** and acrolein. An enantioselective crotylmetalation applied to **1′** would allow the access to **2** (Scheme 1).

The unstable ester-aldehyde **1′** was prepared by ozonolysis of the commercially available methyl-3-butenoate (**1**) (O_3, CH_2Cl_2, −78 °C then Me_2S, MeOH/CH_2Cl_2, rt) and treated directly with the highly face selective crotyltitanium complex (*R*,*R*)Ti-**I** (Et_2O, −78 °C) to afford the desired hydroxyester **2** in 79% overall yield based on (*R*,*R*)Ti-**I** (2 steps), with a diastereomeric excess superior to 95% and with an enantiomeric excess (ee) of 94%.[7] In order to obtain aldehyde **5**, that would allow the introduction of the stereogenic centers at C7 and C8, a CM between **2** and acrolein (4.7 equiv) was achieved using Hoveyda-Grubbs catalyst ([Ru]-**I** (7.2 mol %), CH_2Cl_2, rt, 20 h) and the unsaturated aldehyde **3** was formed in 86% isolated yield (conversion of **2**=85%). After protection of **3** (TBSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C), followed by an hydrogenation step (Pd/C 10%, AcOEt, 1 h), aldehyde **5** was isolated in quantitative yield and treated directly with the highly face selective crotyltitanium complex (*S*,*S*)Ti-**I** (Et_2O, −78 °C). As after purification by flash chromatography, the homoallylic alcohol could not be separated from the Taddol, resulting from the (*S*,*S*)Ti-**I** complex, the mixture was treated with TBSOTf (2,6-lutidine,

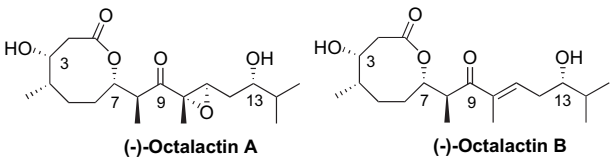

Figure 1.

* Corresponding authors. Tel.: +33 1 40 79 44 29; fax: +33 1 40 79 46 60.
E-mail address: janine.cossy@espci.fr (J. Cossy).
† Present address: UMR 6014, Laboratoire de Chimie Pharmaceutique, UFR Médecine et Pharmacie, CNRS, 22Bd Gambetta, Rouen, France.

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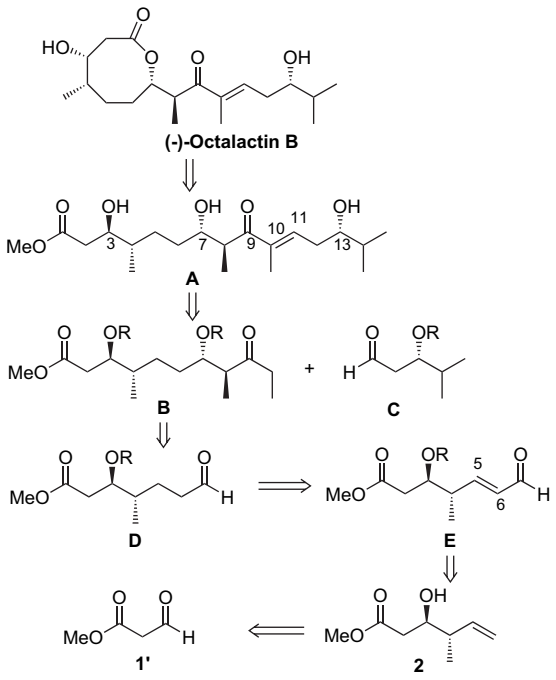
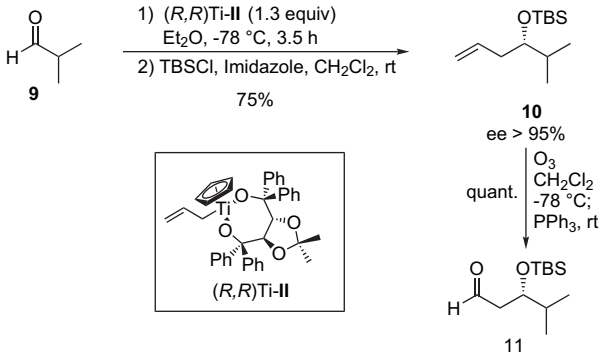


Scheme 1.

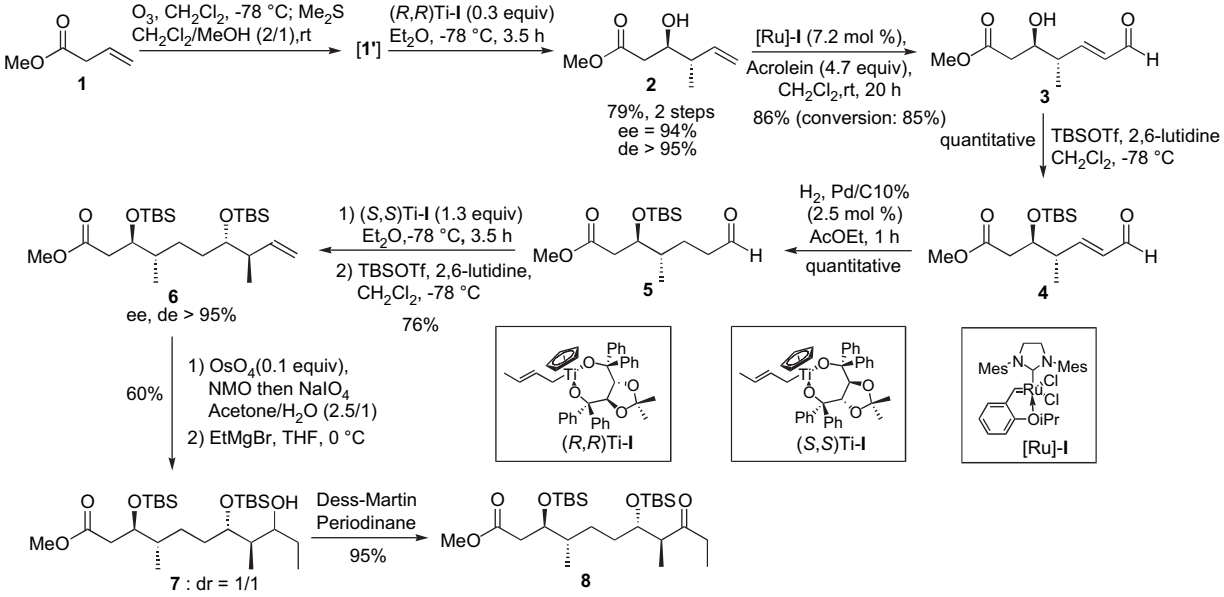
CH_2Cl_2, −78 °C) to furnish, after purification by flash chromatography on silica gel, the desired compound **6**, which corresponds to the C1–C9 fragment (76% yield). Compound **6** was then transformed to ethylketone **8** via alcohol **7** in 3 steps. After oxidative cleavage of the double bond [OsO_4, NMO, acetone/H_2O (2.5:1) then $NaIO_4$], ethylmagnesium bromide was directly added to the non-purified obtained aldehyde to produce the corresponding alcohol **7** in 60% yield. Its oxidation using the Dess–Martin periodinane (DMP) (CH_2Cl_2, rt) afforded the desired ethylketone **8** (95% yield) (Scheme 2).

In parallel, the optically active hydroxyaldehyde **11**, which represents the C11–C15 fragment of octalactins, was prepared from isobutyraldehyde **9**. The addition of the allyltitanium complex (*R*,*R*)Ti-**II** (Et_2O, −78 °C) to isobutyraldehyde **9** led to the desired homoallylic alcohol,[8] which was protected by using TBSCl (imidazole, CH_2Cl_2). After purification by flash chromatography on silica gel, the protected homoallylic alcohol **10** was isolated in 75% yield with an ee superior to 95%. The transformation of **10** to the desired hydroxyaldehyde **11** was realized by ozonolysis (O_3, CH_2Cl_2, −78 °C then PPh_3, rt, quantitative) (Scheme 3).

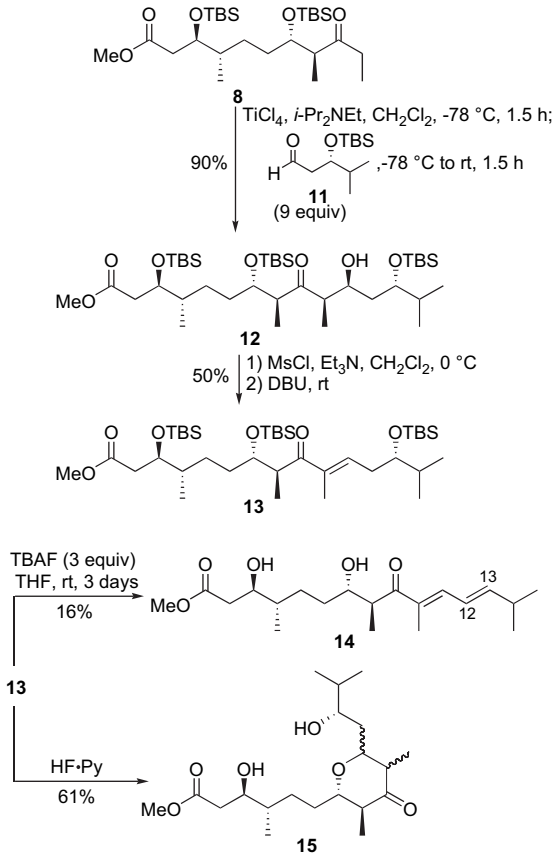


Scheme 3.

Having compounds **8** and **11** in hand, an aldolisation between these two compounds was performed. The generation of the (*Z*)-titanium enolate from **8** ($TiCl_4$, *i*-Pr_2NEt, CH_2Cl_2, −78 °C, 1.5 h) followed by the addition of **11** (9 equiv, −78 °C to rt, 1.5 h), led to the aldol product **12** in 90% with a good diastereoselectivity (superior to 95%). The required unsaturated ketone **13**, precursor of the compound of type **A**, was prepared in a one-pot reaction by mesylation (MsCl, Et_3N, CH_2Cl_2, 0 °C) followed by addition of DBU at rt. After this two-step sequence, enone **13** was isolated in 50% yield. In order to obtain the polyhydroxyester **A**, compound **13** has to be deprotected. At first, **13** was treated with tetrabutylammonium fluoride (TBAF) (THF, rt, 3 days), but unfortunately, under these conditions, the only product that could be isolated was diene **14** in 16% yield. Furthermore, when **13** was treated with HF·Py (THF, rt), tetrahydropyranone **15**, which comes from an intramolecular 1,4-addition of the hydroxy group at C7 to the enone, was formed and isolated as an inseparable mixture of diastereomers (1:1) in 61% yield (Scheme 4). Due to these results, a second approach to octalactins was considered from aldehyde **5** (Scheme 4).



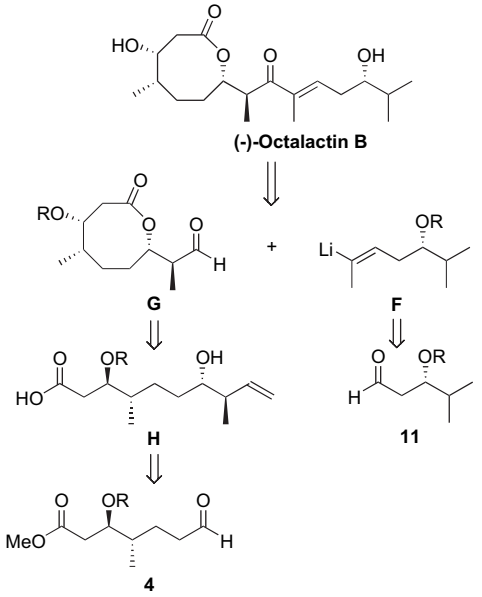
Scheme 2.



Scheme 4.

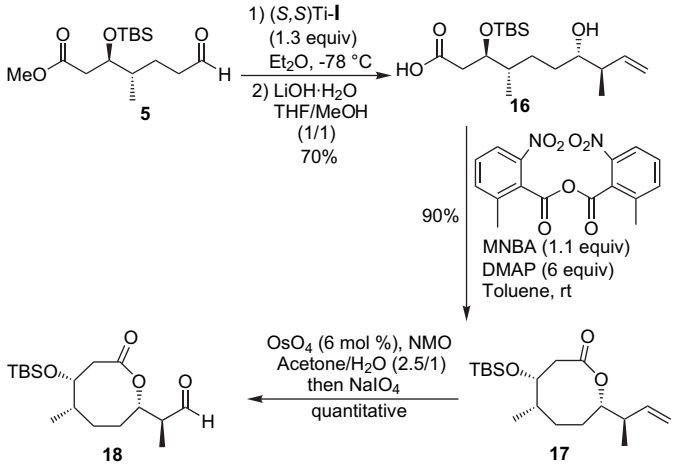
3. Second approach

In the second approach, octalactins would be obtained by a chemoselective addition of a vinyllithium reagent of type **F** on an aldehyde-lactone of type **G**. In this approach, the stereogenic centers would be also controlled by enantioselective crotylmetalations and the lactone of type **G** would be derived from the hydroxyacid **H**, which would be prepared from aldehyde **4**. The synthesis of the vinyllithium reagent **F** was envisaged from the protected hydroxyaldehyde **11**, which was previously obtained (Scheme 5).



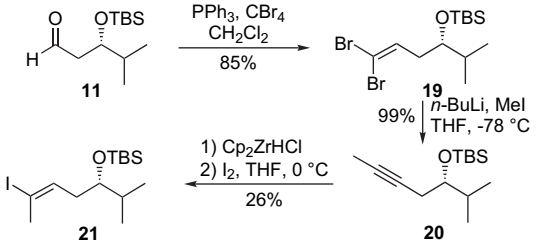
Scheme 5.

As previously, aldehyde **5** was treated with the highly face selective crotyltitanium complex (*S*,*S*)Ti-**I** (Et_2O, −78 °C) and then transformed to the corresponding carboxylic acid. As after purification by flash chromatography, the homoallylic alcohol could not be separated from the Taddol resulting from the (*S*,*S*)Ti-**I** complex, the mixture was directly treated with $LiOH·H_2O$ (THF/MeOH 1:1) to furnish the carboxylic acid **16**, which was isolated with an overall yield of 70% from aldehyde **5**. The obtained seco-acid **16** was cyclized to form the eight-membered ring lactone **17** in 90% yield using the effective anhydride, 2-methyl-6-nitrobenzoic anhydride (MNBA) (1.1 equiv), and DMAP (6 equiv) in toluene at rt. After oxidative cleavage of the double bond in **17** (OsO_4, NMO then $NaIO_4$), aldehyde **18** was isolated quantitatively (Scheme 6).[9]



Scheme 6.

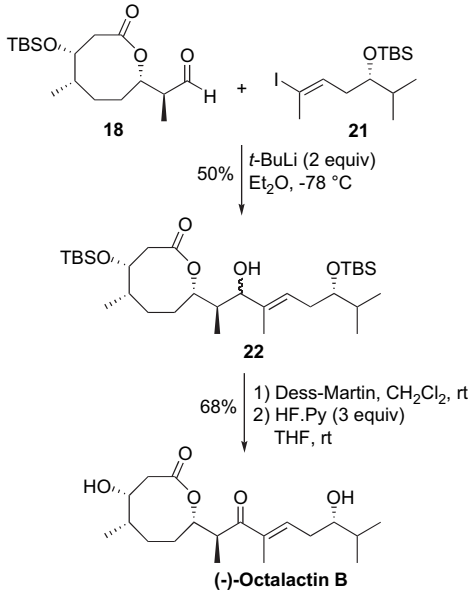
In parallel, the vinyliodide **21**, precursor of the vinyllithium reagent of type **F**, was prepared from **11** in three steps. After transformation of **11** to dibromide **19**, by treatment of **11** with PPh_3/CBr_4 (CH_2Cl_2, yield 85%), this compound was transformed to the acetylenic compound **20** (*n*-BuLi, MeI, THF, −78 °C) in 99% yield. The hydrozirconation of **20** (Cp_2ZrHCl, benzene, 40 °C) followed by iodolysis (I_2, THF, 0 °C) furnished the desired vinyliodide **21** (Scheme 7).



Scheme 7.

After a halogen-metal exchange (*t*-BuLi, Et_2O, −78 °C), the desired vinyllithium reagent prepared from vinyliodide **21** was added to aldehyde-lactone **18** at −78 °C to afford the desired allylic alcohol **22** in 50% yield without any noticeable diastereoselectivity, which has no consequence on the synthesis of octalactins as the hydroxy group at C9 has to be transformed to a ketone. This allylic alcohol **22** was then transformed to octalactin B in two steps. After a Dess–Martin oxidation (CH_2Cl_2, rt), followed by a deprotection (HF·Py, THF, rt), octalactin B was isolated in 68% yield. The optical

rotation of the synthetic octalactin B revealed to be −37 (*c* 0.7, $CHCl_3$), which is close to the optical rotation of the isolated natural product [−12.3 (*c* 5.6, $CHCl_3$)], compared to the optical rotations of the previously synthesized octalactin B,[2–4] which are approximately 10 times larger than that reported for the natural product itself.[1] Unfortunately, we could not have access to the racemic octalactin B and could not verify the optical purity by HPLC. It is worth noting that octalactin B can be transformed easily to octalactin A by epoxidation[4] [*t*-BuO_2H, $VO(acac)_2$] (Scheme 8).



Scheme 8.

Octalactin B was obtained in 14.5% overall yield in 12 steps from methyl-3-butenoate (**1**) by using highly enantioselective crotyltitanation of aldehydes and a CM reaction. This synthesis represents one of the shortest syntheses of octalactin B.

4. Experimental section

4.1. General

Diethyl ether (Et_2O) and tetrahydrofuran (THF) were distilled prior to use. All other reagents and solvents were obtained from commercial sources and used without further purification. Reactions were routinely carried out under an atmosphere of dry argon with magnetic stirring.

4.2. First approach of octalactins

*4.2.1. (+)-3-Hydroxy-4-methylhex-5-enoic acid methylester (**2**)*

A solution of methyl-3-butenoate (3 g, 30 mmol) in CH_2Cl_2 (60 mL) was stirred under O_3 bubbling at −78 °C. After 2.5 h, MeOH (30 mL) and Me_2S (30 mL, 40.5 mmol) were added and the resulting mixture was stirred for 3.5 h at rt. After concentration, aldehyde **1′** was obtained as a colorless oil and directly engaged to the next step. To a suspension of complex (*R*,*R*)-TaddolTiCpCl (5 g, 11.5 mmol) in Et_2O (160 mL) at −40 °C, was added crotylmagnesium chloride (45 mL, 0.35 M in THF, 15.7 mmol). The mixture was stirred at 0 °C for 1.5 h, then cooled at −78 °C and the freshly obtained aldehyde **1′** was added to the mixture. After 3.5 h of stirring at −78 °C, the mixture was hydrolyzed with water (100 mL) with strong stirring overnight at rt. The mixture was then filtered over Celite and the organic layer was extracted with Et_2O (3×100 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under vacuum. Purification of the residue by flash chromatography on silica gel (petroleum ether/Et_2O 8:2) afforded product **2** (1.2 g, 79%) as a yellow liquid. R_f=0.60 (petroleum ether/AcOEt 6:4). $[\alpha]_D^{20}$ +25.2 (*c* 1.0, $CHCl_3$). IR (neat) 3450, 2940, 1740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.72 (ddd, *J*=16.5, 10.9, 8.0 Hz, 1H), 5.03 (dd, *J*=16.5, 1.3 Hz, 1H), 5.01 (dd, *J*=8.0, 1.3 Hz, 1H), 3.75 (m, 1H), 3.62 (s, 3H), 2.69 (br s, 1H), 2.40 (d, *J*=3.0 Hz, 1H), 2.38 (d, *J*=7.5 Hz, 1H), 2.22 (m, 1H), 1.00 (d, *J*=6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2 (s), 139.4 (d), 115.8 (t), 71.0 (d), 51.5 (q), 43.2 (d), 38.6 (t), 15.6 (q); MS (EI) *m*/*z*: 158 (M^+, 0), 127 (10), 103 (100), 71 (76); HRMS calcd: 181.0841 [$(M+Na)^+$, M=$C_8H_{14}O_3$]; found: 181.0843.

*4.2.2. (+)-3-Hydroxy-4-methyl-7-oxohept-5-enoic acid methylester (**3**)*

To a solution of **2** (145 mg, 0.91 mmol) in CH_2Cl_2 (8 mL) were added Hoveyda-Grubbs catalyst [Ru]-**I** (41 mg, 0.065 mmol) and acrolein (280 μL, 4.23 mmol) and the resulting mixture was stirred at rt overnight. After concentration, the crude oil was purified by flash chromatography on silica gel (petroleum ether/Et_2O 1:1) to afford **3** (126.3 mg, 86% corrected yield for 85% conversion) as a brown oil. R_f=0.4 (petroleum ether/AcOEt 6:4). $[\alpha]_D^{20}$ +18.9 (*c* 0.4, $CHCl_3$). IR (neat) 3437, 2921, 2851, 1729, 1686 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.46 (d, *J*=7.9 Hz, 1H), 6.86 (dd, *J*=15.8, 7.9 Hz, 1H), 6.08 (ddd, *J*=15.8, 7.9, 1.1 Hz, 1H), 3.99 (dt_{app}, *J*=12.4, 3.5 Hz, 1H), 3.64 (s, 3H), 3.30 (d, *J*=3.5 Hz, 1H), 2.50 (m, 1H), 2.43 (d, *J*=3.4 Hz, 1H), 2.40 (d, *J*=8.3 Hz, 1H), 1.11 (d, *J*=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.0 (d), 173.0 (s), 159.0 (d), 133.3 (d), 70.7 (d), 51.9 (q), 42.2 (d), 39.0 (t), 15.7 (q); MS (EI) *m*/*z*: 186 (M^+, 0), 155 [$(M-OMe)^+$, 2], 137 [$(M-OMe-H_2O)^+$, 2], 109 [$(M-OMe-H_2O-CHO)^+$, 4], 103 (26), 84 (100), 71 (42), 55 (40).

*4.2.3. (−)-3-[(tert-Butyldimethylsilyl)oxy]-4-methyl-7-oxohept-5-enoic acid methylester (**4**)*

To a solution of **3** (172.6 mg, 0.93 mmol) in CH_2Cl_2 (9 mL) at −78 °C were added 2,6-lutidine (0.8 mL, 6.8 mmol) and TBSOTf (1 mL, 4.3 mmol). The mixture was stirred for 2 h at −78 °C and then hydrolyzed with a saturated $NaHCO_3$ aqueous solution (50 mL). The organic layer was extracted with CH_2Cl_2 (3×50 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum to afford crude product. Purification on silica gel (petroleum ether/AcOEt 8:2) afforded **4** (278 mg, quantitative) as a yellow oil. R_f=0.3 (petroleum ether/AcOEt 9:1). $[\alpha]_D^{20}$ −1.0 (*c* 1.4, $CHCl_3$). IR (neat) 2940, 1740, 1690 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.42 (d, *J*=7.9 Hz, 1H), 6.75 (dd, *J*=15.8, 7.9 Hz, 1H), 6.04 (ddd, *J*=15.8, 7.9, 1.1 Hz, 1H), 4.12 (dt_{app}, *J*=9.4, 3.4 Hz, 1H), 3.55 (s, 3H), 2.56 (m, 1H), 2.38 (dd, *J*=15.2, 6.7 Hz, 1H), 2.27 (dd, *J*=15.2, 6.0 Hz, 1H), 1.06 (d, *J*=7.1 Hz, 3H), 0.82 (s, 9H), 0.01 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.0 (d), 171.7 (s), 159.0 (d), 133.3 (d), 71.9 (d), 51.6 (q), 42.7 (d), 40.0 (t), 25.7 (3q), 17.9 (s), 15.2 (q), −3.6 (q), −4.7 (q); MS (EI) *m*/*z*: 300 (M^+, 0), 285 (1), 269 (9), 243 (41), 217 (49), 183 (56), 141 (54), 89 (81), 73 (100).

*4.2.4. (+)-3-[(tert-Butyldimethylsilyl)oxy]-4-methyl-7-oxoheptanoic acid methylester (**5**)*

A mixture of **4** (1.66 g, 5.52 mmol), Pd/C (10%) (17 mg, 0.16 mmol) in AcOEt (20 mL) was stirred under a hydrogen atmosphere for 1 h at rt then filtered over Celite. The filtrate was concentrated under vacuum to afford **5** (1.67 g, quantitative) as a colorless oil. R_f=0.7 (petroleum ether/AcOEt 8:2). $[\alpha]_D^{20}$ +20.1 (*c* 0.8, $CHCl_3$). IR (neat) 2920, 1730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.72 (t, *J*=1.5 Hz, 1H), 4.05 (ddd, *J*=7.5, 5.0, 3.6 Hz, 1H), 3.61 (s, 3H), 2.46–2.39 (m, 2H), 2.39–2.32 (m, 2H), 1.75–1.52 (m, 2H), 1.33 (m, 1H), 0.85 (d, *J*=6.7 Hz, 3H), 0.80 (s, 9H), 0.00 (s, 3H), −0.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.0 (d), 172.4 (s), 72.6 (d), 51.4 (q), 41.8 (t), 38.3 (d), 38.1 (t), 25.6 (3q), 24.2 (t), 17.9 (s), 14.2 (q), −4.7 (q), −4.9 (q); MS (EI) *m*/*z*: 302 (M^+, 0), 245 [$(M-t\text{-}Bu)^+$, 46], 217 [$(M-t\text{-}Bu-CHO)^+$, 39], 203

[(M−*t*-Bu−HO−Me)$^+$, 9], 185 [(M−*t*-Bu−CHO−OMe)$^+$, 23], 171 [(M−*t*-Bu−CHO−OMe−CH_2)$^+$, 98], 89 (100), 73 (76), 59 (33).

4.2.5. (+)-3,7-Bis-[(tert-butyldimethylsilyl)oxy]-4,8-dimethyldec-9-enoic acid methylester (**6**)

To a suspension of complex (*R*,*R*)-TaddolTiCpCl (611 mg, 0.93 mmol) in Et_2O (16 mL) at −40 °C, was added crotylmagnesium chloride (2.8 mL, 0.35 M in THF, 0.98 mmol). The resulting mixture was stirred for 1.5 h at 0 °C then cooled to −78 °C and aldehyde **5** (216 mg, 0.71 mmol) was added to the reaction mixture. After 3.5 h of stirring at −78 °C, the mixture was hydrolyzed with water (20 mL) with strong stirring for 1 h at rt. The mixture was then filtered over Celite and the organic layer was extracted with AcOEt (3×50 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was dissolved in CH_2Cl_2 (8 mL) and cooled to −78 °C. To this solution was added 2,6-lutidine (0.1 mL, 0.86 mmol) and TBSOTf (0.2 mL, 0.87 mmol) and the resulting mixture was stirred for 1.5 h at −78 °C. After hydrolysis with a saturated $NaHCO_3$ aqueous solution (50 mL), the organic layer was extracted with CH_2Cl_2 (3×50 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (petroleum ether/AcOEt 95:5) to afford **6** (157.8 mg, 76% in 2 steps) as a colorless oil. R_f=0.7 (petroleum ether/AcOEt 95:5). $[\alpha]_D^{20}$ +42.7 (*c* 1.1, $CHCl_3$). IR (neat) 2950, 1740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.74 (m, 1H), 4.98–4.90 (m, 2H), 4.05 (m, 1H), 3.61 (s, 3H), 3.45 (m, 1H), 2.38–2.21 (m, 3H), 1.60–1.00 (m, 5H), 0.94 (d, *J*=6.7 Hz, 3H), 0.84 (d, *J*=6.7 Hz, 3H), 0.84 (s, 9H), 0.80 (s, 9H), 0.00 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9 (s), 140.9 (d), 114.3 (t), 76.0 (d), 73.0 (d), 51.4 (q), 43.1 (d), 39.4 (d), 37.9 (t), 31.6 (t), 28.6 (t), 25.9 (3q), 25.7 (3q), 18.1 (s), 17.9 (s), 15.2 (q), 13.9 (q), −4.2 (q), −4.4 (q), −4.6 (q), −4.9 (q); MS (EI) *m*/*z*: 472 (M^+, 0), 457 (3), 441 [(M−OMe)$^+$, 1], 415 (62), 385 [(M−OMe−*t*-Bu)$^+$, 28], 283 (30), 185 (65), 171 (56), 159 (38), 89 (50), 73 (100).

4.2.6. 3,7-Bis[(tert-butyldimethylsilyl)oxy]-9-hydroxy-4,8-dimethylundecanoic acid methylester (**7**)

To a solution of **5** (63.5 mg, 0.134 mmol) in a mixture of acetone/water (2.5 mL/1 mL) were added NMO (0.7 g, 0.59 mmol) and OsO_4 (3.5 mg, 0.0138 mmol). The mixture was stirred for 2 h at rt, then $NaIO_4$ (120 mg, 0.56 mmol) was added and the mixture was stirred 2 h. After filtration, the organic layer was extracted with AcOEt (3×50 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was dissolved in THF (15 mL) and the solution was cooled at 0 °C. Ethylmagnesium bromide (50 μL, 3 M in Et_2O, 0.14 mmol) was added and the mixture was stirred for 20 min at 0 °C. After hydrolysis with a saturated NH_4Cl aqueous solution (50 mL), the organic layer was extracted with AcOEt (3×50 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (petroleum ether/AcOEt 95:5) to afford alcohol **7** (40.4 mg, 60% in 3 steps) as a diastereomeric mixture (1:1) and as a colorless oil. For the two diastereomers: IR (neat) 3800, 1890 cm^{-1}. MS (EI) *m*/*z*: 504 (M^+, 0), 417 [(M−OMe−*t*-Bu)$^+$, 5], 359 [(M−OMe−2×*t*-Bu)$^+$, 4], 257 (54), 201 (31), 171 (28), 149 (37), 89 (49), 73 (100). Diastereomer **7a**: R_f=0.6 (petroleum ether/AcOEt 9:1). ^1H NMR (400 MHz, $CDCl_3$) δ 4.00 (m, 1H), 3.81 (t_{app}, *J*=6.4 Hz, 1H), 3.62 (td, *J*=6.8, 2.6 Hz, 1H), 3.57 (s, 3H), 3.50 (br s, 1H), 2.30 (dd, *J*=14.7, 8.3 Hz, 1H), 2.20 (dd, *J*=14.7, 4.3 Hz, 1H), 1.60–1.30 (m, 4H), 1.30–1.00 (m, 4H), 0.88 (d, *J*=7.1 Hz, 3H), 0.84 (d, *J*=7.5 Hz, 3H), 0.80–0.75 (m, 21H), 0.00 (s, 3H), −0.02 (s, 3H), −0.04 (s, 3H), −0.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6 (s), 79.2 (d), 72.8 (d), 71.9 (d), 51.5 (q), 39.4 (d), 38.1 (t), 37.8 (d), 33.2 (t), 28.5 (t), 27.4 (t), 25.8 (3q), 25.7 (3q), 17.9 (2s), 14.3 (q), 11.2 (q), 10.5 (q), −4.2 (q), −4.6 (q), −4.7 (q), −4.8 (q). Diastereomer **7b**: R_f=0.5 (petroleum ether/AcOEt 9:1). ^1H NMR (400 MHz, $CDCl_3$) δ 4.02 (dt_{app}, *J*=11.0, 5.5 Hz, 1H), 3.68 (t_{app}d, *J*=7.7, 5.5 Hz, 1H), 3.58 (s, 3H), 3.37 (td, *J*=10.8, 3.8 Hz, 1H), 2.31 (dd, *J*=19.8, 11.0 Hz, 1H), 2.24 (dd, *J*=19.8, 5.5 Hz, 1H), 1.62–1.00 (m, 9H), 0.88 (t, *J*=10.0 Hz, 3H), 0.82 (s, 9H), 0.81 (d, *J*=6.5 Hz, 3H), 0.77 (s, 9H), 0.72 (d, *J*=6.7 Hz, 3H), 0.00 (2s, 6H), −0.03 (s, 3H), −0.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9 (s), 75.9 (d), 75.2 (d), 73.1 (d), 51.5 (q), 42.9 (d), 39.5 (d), 37.9 (t), 32.0 (t), 29.7 (t), 27.5 (t), 25.9 (3q), 25.7 (3q), 18.0 (s), 17.9 (s), 13.8 (q), 12.5 (q), 9.4 (q), −4.2 (2q), −4.5 (q), −4.9 (q).

4.2.7. (+)-3,7-Bis[(tert-butyldimethylsilyl)oxy]-4,8-dimethyl-9-oxoundecanoic acid methylester (**8**)

To a solution of **6** (348 mg, 0.68 mmol) in CH_2Cl_2 (15 mL) was added Dess–Martin periodinane (842 mg, 1.98 mmol). The resulting mixture was stirred for 2.5 h at rt and then hydrolyzed with a mixture of $Na_2S_2O_3$ (1.5 M)/$NaHCO_3$ (40 mL/40 mL) aqueous solution. After extraction with CH_2Cl_2 (3×100 mL), the combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude product was purified by flash chromatography on silica gel (petroleum ether/AcOEt/Et_3N 94:5:1) to afford ketone **7** (329 mg, 95%) as a colorless oil. R_f=0.7 (petroleum ether/AcOEt 9:1). $[\alpha]_D^{20}$ +32.6 (*c* 1.0, $CHCl_3$). IR (neat) 2940, 1740, 1720 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.06 (dt_{app}, *J*=8.1, 4.0 Hz, 1H), 3.90 (dt_{app}, *J*=8.1, 4.0 Hz, 1H), 3.62 (s, 3H), 2.68 (quint, *J*=7.1 Hz, 1H), 2.45 (q, *J*=7.0 Hz, 2H), 2.34 (dd, *J*=9.8, 4.3 Hz, 1H), 2.29 (dd, *J*=14.7, 4.3 Hz, 1H), 1.60–1.10 (m, 5H), 0.99 (d, *J*=7.1 Hz, 3H), 0.96 (d, *J*=7.1 Hz, 3H), 0.91 (d, *J*=6.7 Hz, 3H), 0.82 (s, 9H), 0.81 (s, 9H), 0.00 (2s, 6H), −0.03 (s, 3H), −0.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.3 (s), 172.8 (s), 73.8 (d), 73.2 (d), 51.4 (q), 50.1 (d), 39.6 (d), 38.0 (t), 37.0 (t), 31.7 (t), 29.7 (t), 25.9 (3q), 25.8 (3q), 22.7 (s), 17.9 (s), 13.8 (q), 12.6 (q), 7.3 (q), −4.5 (q), −4.6 (q), −4.9 (2q); MS (EI) *m*/*z*: 502 (M^+, 0), 445 [(M−OMe−Me)$^+$, 21], 359 [(M−OMe−2×*t*-Bu)$^+$,78], 199 (100), 171 (40), 75 (48).

4.2.8. 3,7,13-Tris[(tert-butyldimethylsilyl)oxy]-11-hydroxy-4,8,10,14-tetramethyl-9-oxopentadecanoic acid methylester (**12**)

To a solution of **7** (348 mg, 1 M in CH_2Cl_2, 0.68 mmol) in CH_2Cl_2 (7 mL) were added $TiCl_4$ (0.86 mL, 0.86 mmol) and Hünig's base (0.20 mL, 1.15 mmol). The resulting dark brown mixture was stirred for 3 h at −78 °C and then aldehyde **11** (200 mg, 0.98 mmol) was introduced as a 0.2 M CH_2Cl_2 solution. After 2 h of stirring at −78 °C, the mixture was hydrolyzed with a saturated NH_4Cl aqueous solution (50 mL). After extraction with AcOEt (3×50 mL), the combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (petroleum ether/AcOEt/Et_3N 94:5:1) and product **12** (448 mg, 90%) was isolated as a colorless oil. R_f=0.6 (petroleum ether/AcOEt 9:1). $[\alpha]_D^{20}$ +17.2 (*c* 0.6, $CHCl_3$). IR (neat) 3510, 2960, 1740, 1700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.20 (d, *J*=10.8 Hz, 1H), 4.09 (dt_{app}, *J*=11.4, 5.2 Hz, 1H), 3.95 (dt_{app}, *J*=10.5, 5.3 Hz, 1H), 3.75 (m, 1H), 3.66 (s, 3H), 3.03 (br s, 1H), 2.92 (t_{app}, *J*=9.3 Hz, 1H), 2.56 (qd, *J*=9.5, 4.0 Hz, 1H), 2.40 (dd, *J*=19.4, 11.4 Hz, 1H), 2.30 (dd, *J*=19.4, 5.2 Hz, 1H), 1.83 (m, 1H), 1.60–1.40 (m, 5H), 1.30–1.20 (m, 2H), 1.16 (d, *J*=7.3 Hz, 3H), 0.97 (d, *J*=6.9 Hz, 3H), 0.90–0.80 (m, 36H), 0.09 (s, 3H), 0.08 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H), −0.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 218.2 (s), 172.7 (s), 73.8 (d), 73.5 (d), 73.2 (d), 66.8 (d), 51.9 (d), 51.4 (q), 48.9 (t), 39.6 (d), 38.0 (t), 35.5 (t), 33.4 (d), 31.4 (t), 26.1 (t), 25.9 (3q), 25.8 (3q), 25.7 (3q), 18.4 (s and q), 18.1 (s), 17.9 (s), 17.0 (q), 13.8 (q), 12.4 (q), 9.8 (q), −4.2 (2q), −4.5 (q), −4.6 (q), −4.7 (q), −4.9 (q). HRMS calcd: 755.5110 [(M+Na)$^+$, M=$C_{38}H_{80}O_7Si_3$]; found: 755.5116.

4.2.9. (+)-3,7,13-Tris[(tert-butyldimethylsilyl)oxy]-11-hydroxy-4,8,10,14-tetramethyl-9-oxopentadecanoic acid methylester (**13**)

To a stirring solution of **12** (234 mg, 0.32 mmol) in CH_2Cl_2 (5 mL) at 0 °C were added Et_3N (50 μL, 0.26 mmol) and MsCl (30 μL,

0.36 mmol). After 3 h of stirring at 0 °C, the mixture was hydrolyzed with a saturated aqueous NH_4Cl (50 mL) solution and the organic layer was extracted with CH_2Cl_2 (3×50 mL), dried, filtered, and concentrated under vacuum. The residue was dissolved in CH_2Cl_2 (4 mL) and DBU (24 μL, 0.16 mmol) was added. The resulting mixture was stirred for 2 h at rt, concentrated, and the residue was purified by preparative TLC (petroleum ether/AcOEt 95:5) to afford **13** (112 mg, 49%) as a colorless oil. R_f=0.9 (petroleum ether/AcOEt 9:1). $[\alpha]_D^{20}$ +30.7 (*c* 1.1, $CHCl_3$). IR (neat) 2950, 1740, 1660 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.69 (m, 1H), 4.05 (m, 1H), 3.96 (m, 1H), 3.61 (s, 3H), 3.55 (m, 1H), 3.36 (m, 1H), 2.38–2.22 (m, 4H), 1.66 (m, 1H), 1.50–0.90 (m, 5H), 1.00–0.60 (m, 42H), 0.05-−0.20 (m, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.9 (s), 172.8 (s), 139.9 (d), 138.4 (s), 75.9 (d), 73.8 (d), 73.1 (d), 51.4 (q), 43.3 (d), 39.8 (d), 37.9 (t), 33.5 (t), 33.4 (d), 31.8 (t), 25.8 (3q), 25.7 (3q), 25.6 (3q), 25.6 (t), 18.0 (2s), 18.0 (q), 17.9 (s), 17.7 (q), 14.0 (q), 13.8 (q), 11.9 (q), −5.0 (2q), −4.9 (2q), −4.6 (q), −4.5 (q). HRMS calcd: 737.5004 [$(M+Na)^+$, $M=C_{38}H_{78}O_6Si_3$]; found: 737.5011.

*4.2.10. 3,7-Dihydroxy-4,8,10,14-tetramethyl-9-oxo-pentadeca-10,12-dienoic acid methylester (**14**)*

To a solution of **12** (123.3 mg, 0.172 mmol) in THF (1 mL) was added TBAF (550 μL, 1 M in THF, 0.55 mmol) and the resulting mixture was stirred for 3 days at rt. After hydrolysis with a saturated NH_4Cl aqueous solution (10 mL), the organic layer was extracted with AcOEt (3×20 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was purified by chromatography on silica gel (petroleum ether/AcOEt 6:4) to afford product **14** (9.7 mg, 16%) as a colorless oil. R_f=0.3 (petroleum ether/AcOEt 6:4). ^1H NMR (400 MHz, $CDCl_3$) δ 6.98 (d, *J*=10.5 Hz, 1H), 6.33 (ddd, *J*=15.0, 10.5, 1.0 Hz, 1H), 6.08 (dd, *J*=15.0, 7.0 Hz, 1H), 3.80 (m, 1H), 3.65 (s, 3H), 3.60 (m, 1H), 3.25 (m, 1H), 3.00–2.80 (m, 2H), 2.50–2.30 (m, 4H), 1.81 (s, 3H), 1.09 (d, *J*=7.1 Hz, 3H), 1.01 (d, *J*=6.7 Hz, 3H), 0.95–0.70 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.4 (s), 173.9 (s), 151.7 (d), 140.2 (d), 134.0 (s), 123.6 (d), 74.3 (d), 71.8 (d), 51.8 (q), 43.7 (d), 38.0 (d), 37.8 (t), 32.4 (t), 32.0 (d), 28.4 (t), 21.9 (q), 16.2 (q), 15.0 (q), 13.5 (q), 11.5 (q).

*4.2.11. 3-Hydoxy-6-[6-(2-hydroxy-3-methylbutyl)-3,5-dimethyl-4-oxotetrahydropyran-2-yl]-4-methyl-hexanoic acid methylester (**15**)*

To a solution of **13** (66 mg, 0.092 mmol) in THF was added HF·Py (100 μL, 0.65 mmol) and the resulting mixture was stirred for 20 h at rt. After hydrolysis with a saturated $NaHCO_3$ aqueous solution, the organic layer was extracted with AcOEt (3×20 mL), dried over $MgSO_4$, filtered, concentrated under vacuum, and the residue was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH 95:5) to afford pyranone **15** (21.1 mg, 61%) as a non separable mixture of diastereomers. Only the major diastereomer is reported. R_f=0.6 (CH_2Cl_2/MeOH 95:5). ^1H NMR (400 MHz, $CDCl_3$) δ 3.90–3.50 (m, 4H), 3.50 (s, 3H), 2.50–2.20 (m, 6H), 1.65–1.40 (m, 8H), 1.20–0.70 (m, 9H), 1.10 (d, *J*=7.1 Hz, 3H), 0.98 (d, *J*=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.1 (s), 173.8 (s), 78.9 (d), 73.6 (d), 71.6 (d), 71.5 (d), 51.8 (q), 47.3 (d), 47.1 (d), 38.1 (t), 37.2 (t), 37.0 (d), 34.0 (d), 28.7 (t), 27.4 (t), 18.6 (q), 17.6 (q), 15.1 (q), 11.5 (q), 9.6 (q); MS (EI) *m*/*z*: 311 (17), 171 (100).

4.3. Second approach of octalactins

*4.3.1. (+)-3-[(tert-Butyldimethylsilyl)oxy]-7-hydroxy-4,8-dimethyldec-9-enoic acid (**16**)*

To a suspension of complex (*S*,*S*)-TaddolTiCpCl (1.52 g, 2.43 mmol) in Et_2O (10 mL) at 0 °C, was added crotylmagnesium chloride (6.3 mL, 0.35 M in THF, 2.22 mmol). The resulting mixture was stirred for 1 h at 0 °C then cooled at −78 °C and aldehyde **5** (564 mg, 1.86 mmol) was added to the mixture, which was allowed to stir for 3.5 h at −78 °C. After hydrolysis with water (20 mL) with a strong stirring for 2 h at rt, the mixture was filtered over Celite and the organic layer was extracted with AcOEt (3×100 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was dissolved in a mixture of THF/MeOH 1:1 (2 mL/2 mL) and LiOH (1.12 mL, 5 M in water, 5.64 mmol) was added. After 5 h of stirring at rt, the mixture was hydrolyzed with a saturated NH_4Cl aqueous solution (50 mL). The organic layer was extracted with AcOEt (3×50 mL), washed with brine, dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude product was purified by flash chromatography on silica gel (petroleum ether/AcOEt 7:3) to afford acid **16** (448 mg, 70% in 2 steps) as a colorless oil. R_f=0.6 (petroleum ether/AcOEt 6:4). $[\alpha]_D^{20}$ +5.4 (*c* 1.2, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 6.40 (br s, 1H), 5.71 (ddd, *J*=16.6, 10.9, 8.3 Hz, 1H), 5.05 (d, *J*=16.6 Hz, 1H), 5.03 (dd, *J*=8.3, 1.2 Hz, 1H), 4.08 (ddd, *J*=6.0, 4.3, 4.1 Hz, 1H), 3.35 (dd, *J*=11.3, 6.0 Hz, 1H), 2.36 (d, *J*=6.0 Hz, 2H), 2.13 (m, 1H), 1.57 (m, 1H), 1.45–1.10 (m, 5H), 0.97 (d, *J*=6.8 Hz, 3H), 0.83 (d, *J*=6.8 Hz, 3H), 0.80 (s, 9H), 0.00 (s, 3H), −0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.6 (s), 140.1 (d), 116.5 (t), 74.6 (d), 72.9 (d), 44.1 (d), 39.0 (d), 37.8 (t), 31.9 (t), 28.5 (t), 25.7 (3q), 18.0 (s), 16.3 (q), 13.9 (q), −4.6 (q), −4.8 (q); MS (EI) *m*/*z*: 269 [$(M-H_2O-t\text{-}Bu)^+$, 19], 251 [$(M-2H_2O-t\text{-}Bu)^+$, 2], 157 (28), 139 (47), 95 (35), 75 (100). Anal. Calcd for $C_{18}H_{36}O_4Si$: C, 62.74; H, 10.53. Found: C, 62.44; H, 10.54.

*4.3.2. (−)-4-[(tert-Butyldimethylsilyl)oxy]-5-methyl-8-(1-methyl-allyl)oxocan-2-one (**17**)*

To a mixture of MNBA (203 mg, 0.58 mmol) and DMAP (370 mg, 3.03 mmol) in toluene (100 mL), was added dropwise, over a 30 min period, a solution of acid **16** (180 mg, 0.52 mmol) in toluene (150 mL) then the resulting solution was stirred for 3 h at rt. After hydrolysis with a saturated Na_2CO_3 aqueous solution (150 mL), the organic layer was extracted with AcOEt (3×150 mL) and the combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was purified by chromatography on silica gel (petroleum ether/AcOEt 9:1) to afford lactone **17** (204 mg, 90%) as a colorless oil. R_f=0.6 (petroleum ether/AcOEt 9:1). $[\alpha]_D^{20}$ −58.6 (*c* 1.3, $CHCl_3$). IR (neat) 2956, 2929, 2856, 1722 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.77 (ddd, *J*=14.6, 9.8, 7.9 Hz, 1H), 5.05–4.92 (m, 2H), 4.18 (ddd, *J*=12.0, 5.0, 3.0 Hz 1H), 3.90 (td, *J*=4.3, 1.3 Hz, 1H), 2.62 (d, *J*=4.9 Hz, 2H), 2.33 (m, 1H), 1.87 (m, 1H), 1.76–1.42 (m, 4H), 1.03 (d, *J*=7.1 Hz, 3H), 0.98 (d, *J*=7.1 Hz, 3H), 0.86 (s, 9H), 0.13 (s, 3H), −0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4 (s), 139.5 (d), 115.7 (t), 81.0 (d), 72.9 (d), 42.4 (d), 39.8 (t), 38.7 (d), 31.5 (t), 25.8 (4q), 23.4 (t), 18.1 (s), 16.3 (q), −4.1 (q), −5.0 (q); MS (EI) *m*/*z*: 326 (M^+, 0), 269 [$(M-t\text{-}Bu)^+$, 26], 251 [$(M-t\text{-}Bu-H_2O)^+$, 8], 225 [$(M-t\text{-}Bu-H_2O-CCH_2)^+$, 12], 185 (59), 145 (38), 135 (49), 101 (56), 75 (100).

*4.3.3. (−)-2-[6-(tert-Butyldimethylsilyl)oxy]-5-methyl-8-oxo-oxocan-2-ylpropionaldehyde (**18**)*

To a solution of **16** (52 mg, 0.16 mmol) in a mixture of acetone/H_2O (2.5 mL/1 mL) were added NMO (0.11 g, 0.94 mmol) and OsO_4 (2.5 mg, 0.01 mmol). The resulting mixture was stirred for 2 h at rt then $NaIO_4$ (0.2 g, 0.94 mmol) was added and the mixture was stirred 5 min. After hydrolysis with a saturated NH_4Cl aqueous solution (50 mL), the organic layer was extracted with AcOEt (3×50 mL) and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under vacuum to give the unstable aldehyde **18** (52 mg, quantitative) as a brown oil. R_f=0.6 (petroleum ether/AcOEt 8:2). $[\alpha]_D^{20}$ −54.6 (*c* 1.6, $CHCl_3$). IR (neat) 1721, 1461 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.55 (d, *J*=1.5 Hz, 1H), 4.47 (ddd, *J*=15.0, 7.1, 3.6 Hz, 1H), 3.78 (d_{app}, *J*=6.8 Hz, 1H), 2.64–2.50 (m, 3H), 1.81 (m, 1H), 1.61–1.39 (m, 4H), 1.08 (d,

J=7.1 Hz, 3H), 0.99 (d, J=7.1 Hz, 3H), 0.73 (s, 9H), 0.00 (s, 3H), −0.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.4 (d), 170.8 (s), 76.8 (d), 72.7 (d), 50.6 (d), 39.7 (t), 38.5 (d), 31.4 (t), 25.8 (3q), 25.8 (d), 23.0 (t), 10.4 (q), 18.1 (s), −4.1 (q), −5.0 (q); MS (EI) m/z: 328 (M^+, 0), 271 [(M−t-Bu)$^+$, 12], 253 [(M−H_2O−t-Bu)$^+$, 5], 243 [(M−CO−t-Bu)$^+$, 12], 145 (46), 101 (61), 75 (100), 73 (53).

4.3.4. (−)-4-[(tert-Butyldimethylsilyl)oxy]-5-methylhex-1-ene (**10**)

To a suspension of complex (*R*,*R*)-TaddolTiCpCl (5.79 g, 9.17 mmol) in Et_2O (130 mL) at −40 °C, was added allylmagnesium chloride (5 mL, 2 M in THF, 10 mmol). After 1.5 h of stirring at 0 °C, the mixture was cooled at −78 °C and isobutyraldehyde **8** (0.64 mL, 7.0 mmol) was added. The mixture was stirred for 3.5 h at −78 °C and then hydrolyzed with water (100 mL), with vigorous stirring at rt overnight. After filtration of the mixture over Celite, the organic layer was extracted with Et_2O (3×100 mL) and the combined layers were washed with brine (100 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was dissolved in CH_2Cl_2 (15 mL), then TBSCl (1.2 g, 8.4 mmol) and imidazole (953 mg, 14 mmol) were added. After 2 h of stirring at rt, the mixture was hydrolyzed with water (100 mL) and the organic layer was extracted with CH_2Cl_2 (3×100 mL). The combined layers were washed with brine (100 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was purified by chromatography on silica gel (petroleum ether/AcOEt 95:5) to afford alcohol **10** (1.2 g, 75% in 2 steps) as a yellow oil. R_f=0.9 (petroleum ether/AcOEt 98:2). $[\alpha]_D^{20}$ +8.6 (c 1.6, $CHCl_3$). IR (neat) 3080, 2920, 2820, 1640 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.78 (m, 1H), 5.03–4.94 (m, 2H), 3.44 (ddd, J=10.3, 5.8, 1.3 Hz, 1H), 2.16 (dt_{app}, J=12.8, 1.1 Hz, 1H), 2.15 (dt_{app}, J=5.8, 1.1 Hz, 1H), 1.65 (m, 1H), 0.86 (s, 9H), 0.86–0.81 (m, 6H), 0.01 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.8 (d), 116.2 (t), 76.5 (d), 38.6 (t), 32.5 (d), 25.9 (3q), 18.6 (q), 18.5 (q), 18.3 (s), −4.2 (q), −5.2 (q); MS (EI) m/z: 228 (M^+, 0), 187 (57), 171 (100), 99 (45), 73 (86).

4.3.5. (−)-3-[(tert-Butyldimethylsilyl)oxy]-4-methyl pentanal (**11**)[9]

A solution of **10** (397 mg, 1.73 mmol) in CH_2Cl_2 (10 mL) was stirred under O_3 bubbling at −78 °C. After 15 min, PPh_3 (0.4 g, 1.52 mmol) was added and the mixture was allowed to stir at rt for 2 h. After concentration under vacuum, the residue was purified by flash chromatography on silica gel (petroleum ether/AcOEt 98:2) to afford the unstable aldehyde **11** (397 mg, quantitative) as a colorless oil. R_f=0.9 (petroleum ether/AcOEt 95:5). $[\alpha]_D^{20}$ −15.4 (c 0.8, $CHCl_3$). IR (neat) 2950, 1720 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.77 (dd, J=3.0, 1.9 Hz, 1H), 3.99 (dt_{app}, J=7.1, 4.5 Hz, 1H), 2.49 (ddd, J=15.8, 7.1, 3.0 Hz, 1H), 2.38 (ddd, J=15.8, 4.5, 1.9 Hz, 1H), 1.75 (m, 1H), 0.84 (d, J=6.7 Hz, 3H), 0.83 (d, J=6.7 Hz, 3H), 0.83 (s, 9H), 0.02 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.6 (d), 72.4 (d), 47.2 (t), 34.0 (d), 25.7 (3q), 18.3 (q), 18.0 (s), 17.2 (q), −4.5 (q), −4.6 (q); MS (EI) m/z: 230 (M^+, 0), 173 (100), 129 (87), 101 (88).

4.3.6. (+)-tert-Butyl-(4,4-dibromo-1-isopropylbut-3-enyloxy)-dimethylsilane (**19**)

To a solution of PPh_3 (660 mg, 2.51 mmol) in CH_2Cl_2 (4 mL) at −78 °C were added CBr_4 (500 mg, 1.51 mmol) then a solution of aldehyde **11** (200 mg, 0.94 mmol) in CH_2Cl_2 (1 mL). The resulting stirring mixture was allowed to reach 0 °C for 15 min then hydrolyzed with a saturated $NaHCO_3$ aqueous solution (50 mL) and the organic layer was extracted with CH_2Cl_2 (5×50 mL), washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (petroleum ether) to afford **19** (363 mg, 85%) as a colorless oil. R_f=0.9 (petroleum ether/AcOEt 98:2). $[\alpha]_D^{20}$ +0.45 (c 1.1, $CHCl_3$). IR (neat) 2955, 2927, 2855, 1462 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.40 (t, J=7.3 Hz, 1H), 3.48 (dd, J=11.2, 5.0 Hz, 1H), 2.18 (dd, J=7.3, 6.4 Hz, 1H), 2.15 (dd, J=6.4, 4.9 Hz, 1H), 1.62 (m, 1H), 0.83 (s, 9H), 0.81 (d, J=6.7 Hz, 6H), 0.00 (s, 3H), −0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.2 (d), 88.1 (s), 75.2 (d), 37.3 (t), 33.3 (d), 25.8 (3q), 22.7 (s), 18.1 (q), 17.8 (q), −4.4 (q), −4.6 (q); MS (EI) m/z: 386 (M^+, 0), 343 (7), 329 (23), 257 (63), 203 (32), 187 (90), 139 (29), 73 (100).

4.3.7. (+)-tert-Butyl-(1-isopropylpent-3-enyloxy)dimethylsilane (**20**)

To a solution of (73 mg, 0.189 mmol) in THF (2 mL) at −78 °C was added dropwise *n*-BuLi (200 μL, 2.52 M in hexanes, 0.50 mmol) and the resulting mixture was stirred at −78 °C for 45 min. Then MeI (60 μL, 0.964 mmol) was added dropwise and the mixture was allowed to reach rt for 3 h. After hydrolysis with a saturated NH_4Cl aqueous solution (50 mL), the organic layer was extracted with Et_2O (3×50 mL), and the combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was purified by chromatography on silica gel (petroleum ether) to afford **20** (46 mg, 99%) as a colorless oil. R_f=0.8 (petroleum ether). $[\alpha]_D^{20}$ +17.8 (c 0.03, $CHCl_3$). IR (neat) 2956, 2928, 2856 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.50 (td_{app}, J=6.2, 3.6 Hz, 1H), 2.16 (m, 1H), 2.15 (m, 1H), 1.82 (m, 1H), 1.69 (t, J=2.6 Hz, 3H), 0.82 (s, 9H), 0.78 (d, J=6.7 Hz, 3H), 0.76 (d, J=4.8 Hz, 3H), 0.00 (s, 3H), −0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 76.8 (s), 76.7 (s), 75.7 (d), 32.2 (d), 25.8 (3q), 24.8 (t), 19.1 (q), 18.1 (s), 16.1 (q), 3.5 (q), −4.3 (q), −4.7 (q); MS (EI) m/z: 240 (M^+, 0), 183 (84), 111 (52), 73 (100). Anal. Calcd for $C_{14}H_{28}OSi$: C, 69.93; H, 11.74. Found: C, 69.85; H, 11.74.

4.3.8. (−)-tert-Butyl-(4-iodo-1-isopropylpent-3-enyloxy)-dimethylsilane (**21**)

To a suspension of Cp_2ZrHCl (1.45 g, 5.61 mmol) in freshly and degassed benzene (5 mL), was added dropwise at rt a solution of **20** (498 mg, 2.06 mmol) in benzene (5 mL). The resulting mixture was stirred for 2 h at 40 °C in darkness then cooled at 0 °C and a solution of I_2 (1 g, 3.90 mmol) in THF (10 mL) was added dropwise. After 20 min of stirring at 0 °C and hydrolysis by a saturated $Na_2S_2O_3$ aqueous solution (50 mL), the mixture was stirred for 15 min at rt then filtered over Celite. The organic layer was extracted with AcOEt (3×50 mL) and the combined layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was purified by chromatography on silica gel (petroleum ether) affording vinyliodide **21** (198 mg, 26%) as a colorless oil. R_f=0.68 (petroleum ether). $[\alpha]_D^{20}$ −6.0 (c 1.8, $CHCl_3$). IR (neat) 2955, 2927, 2855, 1678 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.15 (t_{app}, J=7.5 Hz, 1H), 3.46 (td, J=6.9, 4.7 Hz, 1H), 2.35 (s, 3H), 2.17–2.04 (m, 2H), 1.68 (m, 1H), 0.86 (s, 9H), 0.86 (d, J=8.6 Hz, 3H), 0.83 (d, J=6.0 Hz, 3H), 0.03 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.6 (d), 94.5 (s), 75.8 (d), 34.7 (t), 33.0 (d), 27.6 (q), 25.9 (3q), 18.7 (q), 18.1 (s), 17.4 (q), −4.2 (q), −4.6 (q); MS (EI) m/z: 368 (M^+, 0.5), 311 (45), 255 (45), 239 (24), 187 (100), 73 (78). Anal. Calcd for $C_{14}H_{29}IOSi$: C, 45.65; H, 7.94. Found: C, 46.08; H, 7.92.

4.3.9. (−)-4-[(tert-Butyldimethylsilyl)oxy]-8-{6-[(tert-butyldimethylsilyl)oxy]-2-hydroxy-1,3,7-trimethyloct-3-enyl}-5-methyloxocan-2-one (**22**)

To a solution of **20** (73.1 mg, 0.198 mmol) in Et_2O (1 mL) at −78 °C was added dropwise *t*-BuLi (250 μL, 1.7 M in pentane, 0.425 mmol). The resulting solution was stirred for 30 min at −78 °C, then a solution of aldehyde **18** (61.2 mg, 0.186 mmol) in Et_2O (1 mL) was added dropwise. After stirring at −78 °C for 45 min, the mixture was hydrolyzed with a saturated NH_4Cl aqueous solution (20 mL). The organic layer was extracted with AcOEt (3×20 mL) and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was purified by chromatography on silica gel (petroleum ether/AcOEt 8:2) affording product **22** (56 mg, 50%) as a mixture of diastereomers (1:3). Major diastereomer **22a**: R_f=0.2 (petroleum ether/AcOEt 9:1). $[\alpha]_D^{20}$ −5.0 (c 0.8, $CHCl_3$). IR (neat) 3460, 2955, 2925, 2854, 1786, 1715, 1251, 1185 cm^{-1}; ^{1}H NMR

(400 MHz, $CDCl_3$) δ 5.42 (t_{app}, J=7.0 Hz, 1H), 4.36 (td_{app}, J=12.0, 3.7 Hz, 1H), 4.23 (br s, 1H), 3.91 (d, J=6.4 Hz, 1H), 3.46 (m, 1H), 2.76 (dd, J=12.8, 1.8 Hz, 1H), 2.61 (dd, J=12.8, 6.7 Hz, 1H), 2.18–2.14 (m, 2H), 1.93 (m, 1H), 1.83 (m, 1H), 1.65–1.53 (m, 5H), 1.50 (s, 3H), 1.00 (d, J=7.0 Hz, 3H), 0.87 (s, 9H), 0.85 (s, 9H), 0.83 (d, J=6.8 Hz, 3H), 0.81 (d, J=6.8 Hz, 3H), 0.72 (d, J=7.0 Hz, 3H), 0.14 (2s, 6H), 0.01 (s, 3H), 0.00 (s, 3H), one OH does not appear in the spectrum; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7 (s), 136.9 (s), 120.7 (d), 79.0 (d), 76.6 (d), 74.1 (d), 72.6 (d), 40.1 (d), 39.7 (t), 38.7 (d), 32.4 (d), 32.3 (2t), 25.9 (3q), 25.8 (3q), 23.5 (t), 18.9 (q), 18.1 (2s), 16.9 (2q), 14.0 (q), 8.9 (q), −4.1 (2q), −4.6 (q), −5.0 (q). Minor diastereomer **22b**: R_f=0.4 (petroleum ether/AcOEt 9:1). $[\alpha]_D^{20}$ −28 (c 0.8, $CHCl_3$). IR (neat) 3435, 2955, 2927, 2855, 1711, 1250, 1179 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.36 (t_{app}, J=6.8 Hz, 1H), 4.70 (m, 1H), 3.90 (d_{app}, J=6.6 Hz, 1H), 3.74 (d, J=9.5 Hz, 1H), 3.45 (m, 1H), 2.75 (dd, J=13.0, 1.7 Hz, 1H), 2.61 (m, 1H), 2.13 (t_{app}, J=6.8 Hz, 2H), 2.00 (m, 1H), 1.89 (m, 1H), 1.70–1.60 (m, 5H), 1.01–0.74 (m, 33H), 0.01–0.00 (m, 12H), one OH does not appear in the spectrum; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3 (s), 136.6 (s), 125.9 (d), 80.5 (d), 77.6 (d), 76.5 (d), 72.6 (d), 40.1 (d), 39.9 (t), 38.5 (d), 32.6 (d), 32.3 (t), 28.3 (t), 26.1 (q), 25.9 (3q), 25.8 (3q), 23.0 (t), 18.7 (q), 18.1 (s), 18.0 (s), 17.0 (q), 11.3 (q), 10.9 (q), −4.1 (2q), −4.6 (q), −5.0 (q). HRMS calcd: 593.4033 [$(M+Na)^+$, $M=C_{31}H_{62}O_5Si$]; found: 593.4036.

4.3.10. Octalactin B

To a solution of **22** (23.9 mg, 0.042 mmol) in CH_2Cl_2 (2 mL) was added Dess–Martin periodinane (18 mg, 0.042 mmol) and the resulting mixture was stirred for 1 h at rt. After hydrolysis with a mixture of saturated $NaHCO_3/Na_2S_2O_4$ 1:1 (20 mL/20 mL) aqueous solutions, the organic layer was extracted with CH_2Cl_2 (3×20 mL), and the combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was dissolved in THF (3 mL) and to the resulting solution was added HF·Py (0.25 mL, 0.25 mmol). After 20 h of stirring at rt, the mixture was hydrolyzed with water (20 mL) and the organic layer was extracted with AcOEt (3×20 mL). The combined organic layers were washed with brine, dried, filtered, and concentrated. The residue was purified by preparative TLC (toluene/isopropyl alcohol 9:1), to afford octalactin B (9.8 mg, 68%) as a brown oil. R_f=0.2 (petroleum ether/AcOEt 6:4). $[\alpha]_D^{20}$ −37 (c 0.7, $CHCl_3$). IR (neat) 3432, 2958, 2929, 2877, 1709, 1658 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.80 (t_{app}, J=7.0 Hz, 1H), 4.65 (t_{app}, J=12.0 Hz, 1H), 3.97 (d, J=6.1 Hz, 1H), 3.50–3.42 (m, 2H), 2.98 (dd, J=13.2, 1.7 Hz, 1H), 2.66 (dd, J=13.2, 6.1 Hz, 1H), 2.41–2.30 (m, 2H), 2.10 (br s, 2H), 1.71 (s, 3H), 1.67–1.09 (m, 6H), 1.06 (d, J=7.1 Hz, 3H), 0.98 (d, J=7.1 Hz, 3H), 0.90 (d, J=6.7 Hz, 3H), 0.89 (d, J=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.3 (s), 172.7 (s), 141.5 (d), 137.4 (s), 79.4 (d), 75.8 (d), 71.3 (d), 44.2 (d), 39.2 (t), 37.9 (d), 34.0 (t), 33.9 (d), 32.2 (t), 22.6 (t), 22.0 (q), 18.7 (q), 17.4 (q), 15.0 (q), 11.7 (q); MS (EI) m/z: 340 (M^+, 0), 279 (17), 207 (48), 167 (37), 149 (100). HRMS calcd: 363.2147 [$(M+Na)^+$, $M=C_{19}H_{32}O_5$]; found: 363.2149.

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References and notes

1. Fenical, W.; Roman, M.; Tapiolas, D. M. *J. Am. Chem. Soc.* **1991**, *113*, 4682.
2. Buszek, K. R.; Sato, N.; Jeong, Y. *J. Am. Chem. Soc.* **1994**, *116*, 5511.
3. Total synthesis of (+)-*ent*-octalactin A: McWilliams, J. C.; Clardy, J. *J. Am. Chem. Soc.* **1994**, *116*, 8378.
4. (a) O'Sullivan, P. T.; Burh, W.; Fuhry, M. A. M.; Harrison, J. R.; Davies, J. E.; Feeder, N.; Marshall, D. R.; Burton, J. W.; Holmes, A. B. *J. Am. Chem. Soc.* **2004**, *126*, 2194; (b) Shiina, I.; Hashizume, M.; Yamai, Y.; Oshiumi, H.; Shimazaki, T.; Takasuma, Y.; Ibuka, R. *Chem.—Eur. J.* **2005**, *11*, 6601.
5. (a) Buszek, K. R.; Jeong, Y. *Tetrahedron Lett.* **1995**, *36*, 7189; (b) Andrus, M. B.; Argade, A. B. *Tetrahedron Lett.* **1996**, *37*, 5049; (c) Kodama, M.; Matsushita, M.; Terada, Y.; Takeuchi, A.; Yoshio, S.; Fukuyama, Y. *Chem. Lett.* **1997**, 117; (d) Inoue, S.; Iwabuchi, Y.; Irie, H.; Hatakeyama, S. *Synlett* **1998**, 735; (e) Garcia, J.; Bach, J. *Tetrahedron Lett.* **1998**, *39*, 6761; (f) Bach, J.; Berenguer, R.; Garcia, J.; Vilarrasa. *Tetrahedron Lett.* **1995**, *36*, 3425; (g) Hulme, A. N.; Howells, G. E. *Tetrahedron Lett.* **1997**, *38*, 8245; (h) Shimoma, F.; Kusaka, H.; Wada, K.; Azami, H.; Yasunami, M.; Suzuki, T.; Hagiwara, H.; Ando, M. *J. Org. Chem.* **1998**, *63*, 920; (i) Harrison, J. R.; Holmes, A. B.; Collins, I. *Synlett* **1999**, 972; (j) Buszek, K. R.; Sato, N.; Jeong, Y. *Tetrahedron Lett.* **2002**, *43*, 181.
6. (a) Shiina, I. *Chem. Rev.* **2007**, *107*, 239; (b) Aird, J. I.; Hulme, A. N.; White, J. W. *Org. Lett.* **2007**, *9*, 631.
7. The diastereoselectivity and the enantioselectivity as well as the absolute configuration of the stereogenic centers were determined by ^{1}H NMR from the corresponding mandelic esters, according to Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovec, J. M. *J. Org. Chem.* **1986**, *51*, 2370.
8. The alcohol was previously prepared by Hafner, A.; Duthaler, R.; Marti, R.; Rihs, G.; Rothe Streit, P.; Schwarzenbach, F. *J. Am. Chem. Soc.* **1992**, *114*, 2321.
9. Dinh, M.-T.; Bouzbouz, S.; Peglion, J.-L.; Cossy, J. *Synlett* **2005**, 2851.