Tetrahedron 64 (2008) 6263–6269

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Concise route to defined stereoisomers of the hydroxy acid of the chondramides

Anke Schmauder, Sven Müller, Martin E. Maier *

Institut für Organische Chemie, Universität Tübingen, Auf der Morgenstelle 18, 72076 Tübingen, Germany

ARTICLE INFO

Article history:
Received 21 March 2008
Received in revised form 25 April 2008
Accepted 28 April 2008
Available online 30 April 2008

ABSTRACT

The use of Kobayashi vinylogous aldol reaction in the reaction with acetaldehyde led to *anti*-aldol product **11**. After reductive removal of the chiral auxiliary, the primary alcohol was converted to the allyliodide **14**. This compound could be engaged in an Evans alkylation reaction, leading eventually to hydroxy acid **19**. Inclusion of a Mitsunobu inversion reaction on the sequence starting with *ent*-**11** led to hydroxy ester **30**, featuring a 6,7-*syn*-configuration. These hydroxy acids should help to elucidate the correct stereostructure of the chondramide depsipeptides.

1. Introduction

Screening of the fermentation broth of the myxobacteria *Chondromyces crocatus* led to the isolation of four antifungal and cytostatic depsipeptides, the chondramides A–D (**1**–**4**) (Fig. 1).[1,2] They are comprised of a tripeptide subunit and a 7-hydroxy-trimethyloctenoic acid. The tripeptide sector consists of an alanine followed by a *N*-methyl-tryptophan and a β-tyrosine. In two of the chondramides, the tryptophan is chlorinated in the 2-position. The β-tyrosine unit of chondramides A and B additionally contains an α-methoxy substituent. The chondramides are similar to some cyclodepsipeptides that have been isolated from marine sponges. These macrocycles include jasplakinolide[3] (**5**), the geodiamolides,[4] neosiphoniamolide,[5] and the seragamides.[6]

All these marine depsipeptides, except for the chondramides, share the same polyketide ω-hydroxy acid (**6**) (Fig. 2). The major difference between the chondramide and jasplakinolide ω-hydroxy acid is a putative acetyl versus lactoyl starter unit for the biosynthesis of the polyketide part.[7] Accordingly, the macrocycle of jasplakinolide has a ring size of 19, whereas the chondramides consist of a smaller, 18-membered ring. Both hydroxy acids, **6** and **7**, feature non-bonded interactions that restrict the conformation of the polyketide part but should also govern the conformation of the whole macrocyclic system. Thus, one can identify a *syn*-pentane and a 1,3-allylic interaction.[8] Even though one would expect different shapes for jasplakinolide and the chondramides,[9] they show similar biological activity. These depsipeptides interfere with the microfilament fibers of the cytoskeleton. Thus, they exert their cytostatic effect by inducing actin polymerization.

Since the stereochemistry of jasplakinolide is known, a number of syntheses have appeared for the natural product[10] as well as the ω-hydroxy acid.[10,11] On the other hand, for the chondramide just the constitution was published.[1b] Due to the structural similarity to jasplakinolide, structure **3** for chondramide C was proposed by Ghosh et al.[12] However, this seems not to be correct.[13] We became interested in the chondramides as lead structure for targeting the actin of certain species.[14] One major reason for choosing the chondramides is the fact that the ω-hydroxy acid **7** as a straight polyketide should be much more easier to synthesize than the jasplakinolide hydroxy acid **6**. This fact also stimulated the design of simpler analogs of acid **6**.[15] Typical routes to acid **6** are based on aldehyde **8**. Extension is done either by reaction with 2-propenyl-magnesium bromide followed by Claisen rearrangement or by the sequence Wittig reaction, conversion to an allylic halide, and asymmetric alkylation.[10,11] Since the preparation of **8** already requires a number of steps, the synthesis of hydroxy acid **6** in large amounts is cumbersome. In order to delineate the stereostructure of the chondramides, we designed an aldol approach that would allow the facile preparation of various stereoisomers of **7**. In this paper we describe the realization of this goal by employing a vinylogous aldol reaction.[16,17]

2. Results

Our target was a hydroxy ester so that in the synthesis of the depsipeptide, the ester bond to the tripeptide sector would be formed first. The macrocyclic ring would then be closed by the formation of an amide bond. Deprotonation and silylation of the unsaturated imide **9** gave the vinylketene silyl *N*,*O*-acetal **10** (Scheme 1).[16] Reaction of **10** with distilled acetaldehyde (2 equiv) in presence of $TiCl_4$ (1 equiv) in CH_2Cl_2 at −80 °C provided a good yield of the *anti*-aldol adduct **11**, probably via transition state **A** (Scheme 1). Following silylation of the hydroxyl function with $^tBuPh_2SiCl$ (TBDPSCl), the chiral auxiliary was removed from **12** by

* Corresponding author. Tel.: +49 7071 2975247; fax: +49 7071 295137.
E-mail address: martin.e.maier@uni-tuebingen.de (M.E. Maier).

0040-4020/$ – see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2008.04.109

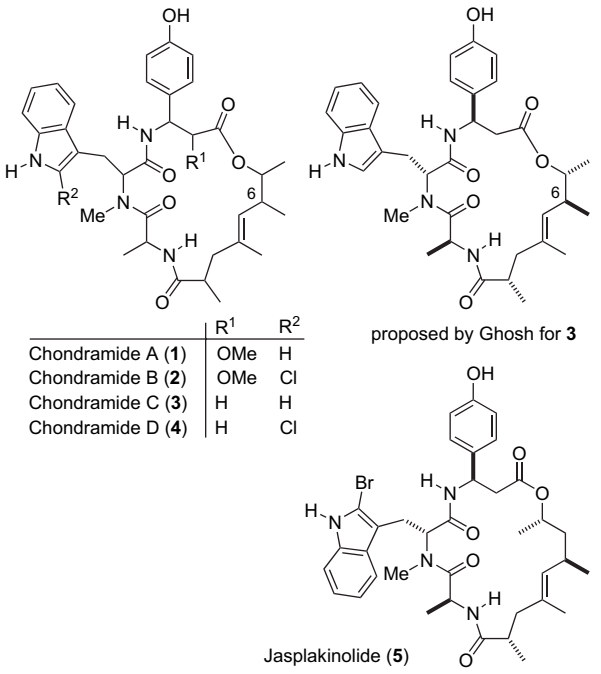


Figure 1. Structures of the chondramides and of jasplakinolide (**5**).

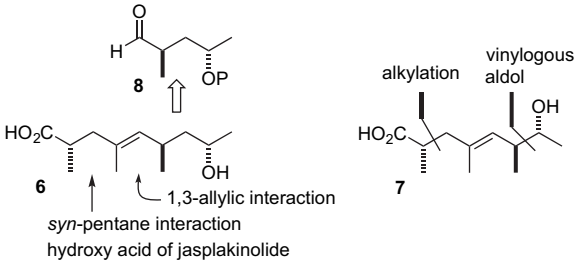
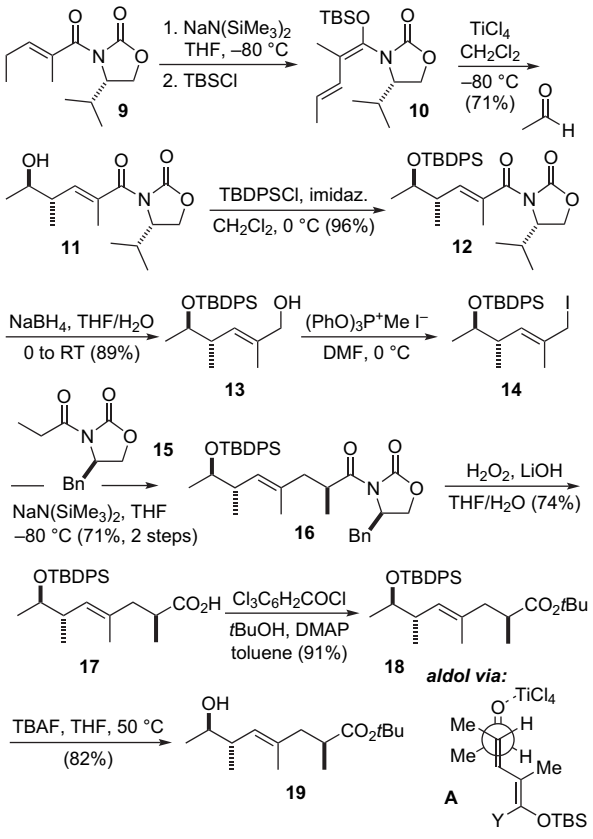


Figure 2. The ω-hydroxy acids of jasplakinolide and the chondramides. The stereochemistry of **7** reflects the Ghosh proposal.

reduction with sodium borohydride in aqueous THF.[18] This provided the allylic alcohol **13**. The subsequent conversion of **13** to the corresponding allylic iodide turned out to be non-trivial and many reagents gave **14** only in moderate yield. However, methyltriphenoxyphosphonium iodide gave rise to allylic iodide **14** in good yield.[19,20] Since the double bond of **14** can undergo isomerization during flash chromatography, iodide **14** was used crude for the subsequent alkylation of propionyloxazolidinone[21] **15**. Using standard conditions, that is, deprotonation of **15** with $NaN(SiMe_3)_2$ in THF followed by addition of iodide **14** furnished compound **16** in 71% yield based on alcohol **13**. Hydrolysis of the carboxylic acid derivative **16** led to the OH-protected acid **17**. Esterification of the acid with ^{t}BuOH under Yamaguchi conditions[22] gave ester **18**. Finally, cleavage of the silyl ether using TBAF provided hydroxy ester **19**, suitable for esterification with the tripeptide fragment of the chondramides.

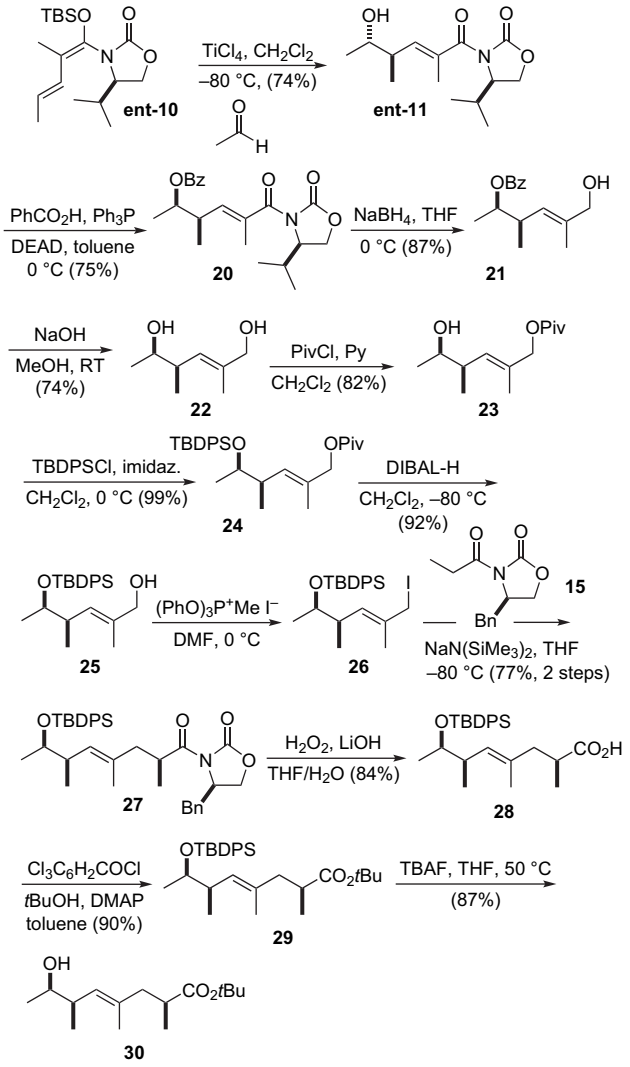
In a related manner the vinylogous aldol reaction with acetaldehyde was carried out with *ent*-**10** providing the aldol product *ent*-**11** (74% yield) (Scheme 2). Access to the 6,7-*syn*-diastereomer should be possible by Mitsunobu inversion.[23] This was demonstrated on aldol product *ent*-**11** using benzoic acid. However, this also might be possible by reaction of a hydroxy ester such as **19** or *ent*-**19** with the tripeptide acid. In the case of *ent*-**11** we obtained the benzoate **20**. Reductive removal of the chiral auxiliary delivered allylic alcohol **21**.



Scheme 1. Synthesis of the 6,7-*anti*-hydroxy ester **19** by vinylogous aldol reaction.

To be on the safe side the benzoate was replaced by a robust silyl protecting group. This was achieved in a simple four-step sequence consisting of benzoate cleavage under basic conditions, selective pivaloylation of the primary alcohol to give **23**, silylation of the secondary hydroxyl group, and reductive removal of the pivaloyl

group using DIBAL-H leading to alcohol **25**. Using the same sequence of steps as shown before (cf. Scheme 1), the allylic alcohol **25** could be transformed to the 6,7-*syn*-hydroxy ester **30** via a sequence of iodination to **26**, asymmetric alkylation with **15** providing **27** (77%, two steps), saponification (84%) to the acid **28**, esterification with ^{t}BuOH (90%) yielding ester **29**, and cleavage of the silyl ether.



Scheme 2. Synthesis of the hydroxy ester **30** via *ent*-**11** followed by Mitsunobu inversion at C7.

3. Conclusion

We could illustrate a very concise strategy to stereoisomers of the 7-hydroxy acid of the chondramides. Work is now in progress to prepare the corresponding chondramide derivatives in order to delineate the correct stereostructure of the chondramides. The advantage of the approach is that gram amounts of the acids can be prepared.

4. Experimental

4.1. General

^{1}H and ^{13}C NMR: Bruker Avance 400, spectra were recorded at 295 K either in $CDCl_3$ or in acetone-d_6. Chemical shifts are calibrated with respect to the residual proton and carbon resonance of the solvent: $CDCl_3$ (δ_H 7.25 ppm, δ_C 77.0 ppm); acetone-d_6 (δ_H 2.40 ppm, δ_C 29.8 ppm). HRMS (FT-ICR): Bruker Daltonic APEX 2 with electron spray ionization (ESI). Analytical LC–MS: HP 1100 Series connected with an ESI MS detector Agilent G1946C; positive mode with fragmentor voltage of 40 eV; column: Nucleosil 100-5, C-18 HD, 5 μm, 70×3 mm Machery-Nagel; eluent: NaCl solution (5 mM)/acetonitrile; gradient: 0–10–15–17–20 min with 20–80–80–99–99% acetonitrile; flow rate: 0.5 mL min^{-1}. Flash chromatography: J. T. Baker silica gel 43–60 μm. Thin-layer chromatography: Machery-Nagel Polygram Sil G/UV254. Perkin–Elmer 341 Polarimeter, Na-lamp, 589 nm, 1 dm cuvette, 25 °C. Solvents were distilled prior to use; petroleum ether with a boiling range of 40–60 °C was used. Reactions were generally run under a nitrogen atmosphere.

4.1.1. *(4S)-3-((1′E,3′E)-1′-{[tert-Butyl(dimethyl)silyl]oxy}-2′-methyl-1′,3′-pentadienyl)-4-isopropyl-1,3-oxazolidin-2-one (**10**)*[16]

To a stirred solution of acylated oxazolidinone **9** (8.00 g, 35.5 mmol) in THF (380 mL) was added dropwise $NaN(SiMe_3)_2$ (9.8 g, 53.3 mmol), dissolved in THF (60 mL) at −80 °C. After 90 min, ^{t}BuMe$_2$SiCl (TBSCl, 16.1 g, 106.5 mmol) in THF (80 mL) was added and the mixture was stirred for 30 min. The reaction mixture was treated with saturated NH_4Cl solution (100 mL) and allowed to warm to room temperature. The aqueous layer was extracted with ethyl acetate (2×200 mL). The combined organic layers were washed with water (100 mL) and saturated NaCl solution (100 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 7:1) to give ketene acetal **10** (11.12 g, 92%) as a colorless oil. R_f=0.33 (petroleum ether/EtOAc, 7:1); $[\alpha]_D^{20}$ −55.6 (*c* 1.00, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm]=0.13, 0.18 (2s, 3H each, Si(C*H*$_3$)$_2$C(CH$_3$)$_3$), 0.91 (d, *J*=6.9 Hz, 6H, CH(C*H*$_3$)$_2$), 0.96 (s, 9H, Si(CH$_3$)$_2$C(C*H*$_3$)$_3$), 1.73–1.79 (m, 6H, 2′-CH$_3$, 5′-H), 1.85–2.00 (m, 1H, C*H*(CH$_3$)$_2$), 3.92–4.04 (m, 1H, 4-H), 4.11 (dd, *J*=8.4, 8.4 Hz, 1H, 5-H), 4.30 (dd, *J*=8.8, 8.8 Hz, 1H, 5-H), 5.62 (qd, *J*=15.4, 6.7 Hz, 1H, 4′-H), 6.19 (d, *J*=15.5 Hz, 1H, 3′-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ [ppm]=−4.9, −4.3 (Si(*C*H$_3$)$_2$C(CH$_3$)$_3$), 12.3 (2′-CH$_3$), 16.3 (CH(*C*H$_3$)$_2$), 18.0 (Si(CH$_3$)$_2$*C*(CH$_3$)$_3$), 18.3 (CH(*C*H$_3$)$_2$), 18.8 (C-5′), 25.6 (Si(CH$_3$)$_2$C(*C*H$_3$)$_3$), 29.3 (*C*H(CH$_3$)$_2$), 59.4 (C-4), 64.4 (C-5), 115.0 (C-2′), 124.3 (C-4′), 128.1 (C-3′), 134.7 (CO), 155.9 (CO); HMRS (ESI): $[M+Na]^+$ calcd for $C_{18}H_{33}NO_3Si$ 362.2122, found 362.2121.

4.1.2. *(4S)-3-[(2′E,4′S,5′R)-5′-Hydroxy-2′,4′-dimethyl-2′-hexenoyl]-4-isopropyl-1,3-oxazolidin-2-one (**11**)*

To a stirred solution of acetaldehyde (0.91 mL, 16.04 mmol) in CH_2Cl_2 (40 mL) at −80 °C were added a 1.0 M solution of $TiCl_4$ in CH_2Cl_2 (8.02 mL, 8.02 mmol) and a solution of oxazolidinone **10** (2.72 g, 8.02 mmol) in CH_2Cl_2 (40 mL) dropwise resulting in a color change from yellow to red. After stirring for 16 h at −80 °C, the reaction mixture was quenched with pyridine (5 mL). Saturated Rochelle salt solution (15 mL) and saturated $NaHCO_3$ (15 mL) solution were added and the mixture was allowed to warm to room temperature The aqueous layer was extracted with ethyl acetate (2×50 mL). The combined organic layers were washed with water and saturated NaCl solution, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 2:1) to give alcohol **11** (1.53 g, 71%) as a colorless solid; mp 53 °C. R_f=0.28 (petroleum ether/EtOAc, 2:1); $[\alpha]_D^{20}$ +2.5 (*c* 1.00, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm]=0.89 (d, *J*=6.9 Hz, 3H, CH(C*H*$_3$)$_2$), 0.90 (d, *J*=6.9 Hz, 3H, CH(C*H*$_3$)$_2$), 0.95 (d, *J*=6.6 Hz, 3H, 4′-CH$_3$), 1.22 (d, *J*=6.1 Hz, 3H, 6′-H), 1.92 (d, *J*=1.5 Hz, 3H, 2′-CH$_3$), 2.25–2.36 (m, 1H, C*H*(CH$_3$)$_2$), 2.41–2.52 (m, 1H, 4′-H), 3.21 (d, *J*=2.0 Hz, 1H, OH), 3.44–3.53 (m, 1H, 5′-H), 4.16 (dd, *J*=9.0, 5.7 Hz, 1H, 5-H), 4.31 (dd, *J*=9.0, 9.0 Hz, 1H, 5-H), 4.55 (ddd, *J*=10.2, 5.6, 4.6 Hz, 1H, 4-H), 5.74–5.80 (m, 1H, 3′-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ [ppm]=13.9 (2′-CH$_3$), 15.2 (CH(*C*H$_3$)$_2$), 16.1 (4′-CH$_3$), 17.8 (CH(*C*H$_3$)$_2$), 20.0 (C-6′), 28.4 (*C*H(CH$_3$)$_2$), 41.9 (C-4′), 58.0 (C-4), 63.4 (C-5), 71.6 (C-5′), 131.2 (C-2′), 142.1 (C-3′), 154.5 (CO), 171.5 (CO); HMRS (ESI): $[M+Na]^+$ calcd for $C_{14}H_{23}NO_4$ 292.15193, found 292.15191.

*4.1.3. (4S)-3-((2′E,4′S,5′R)-5′-{[tert-Butyl(diphenyl)silyl]oxy}-2′,4′-dimethyl-2′-hexenoyl)-4-isopropyl-1,3-oxazolidin-2-one (**12**)*

To a stirred solution of aldol product **11** (1.53 g, 5.70 mmol) in CH_2Cl_2 (25 mL) at 0 °C were added imidazole (1.16 g, 17.09 mmol) and a catalytic amount of DMAP. The mixture was stirred for 10 min before TBDPSCl (2.96 mL, 11.39 mmol) was added. The mixture was allowed to warm to room temperature. After stirring for 20 h, the reaction mixture was quenched with water and the aqueous layer was extracted with CH_2Cl_2 (2×30 mL). The combined organic layers were dried over $NaSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 7:1) to afford silyl ether **12** (2.78 g, 96%) as a colorless oil. R_f=0.37 (petroleum ether/EtOAc, 7:1); $[\alpha]_D^{20}$ +8.0 (*c* 1.00, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm]=0.89 (d, *J*=6.6 Hz, 3H, $CH(CH_3)_2$), 0.90 (d, *J*=6.8 Hz, 3H, $CH(CH_3)_2$), 1.01–1.08 (m, 15H, $Si(Ph)_2C(CH_3)_3$, 4′-CH_3, 6′-H), 1.69 (d, *J*=1.3 Hz, 3H, 2′-CH_3), 2.30–2.40 (m, 1H, $CH(CH_3)_2$), 2.48–2.57 (m, 1H, 4′-H), 3.87 (qd, *J*=9.7, 3.6 Hz, 1H, 5′-H), 4.15 (dd, *J*=8.9, 5.6 Hz, 1H, 5-H), 4.29 (dd, *J*=8.9, 8.9 Hz, 1H, 5-H), 4.50 (ddd, *J*=9.7, 5.3, 4.5 Hz, 1H, 4-H), 6.02–6.07 (m, 1H, 3′-H), 7.31–7.44 (m, 6H, H_{ar}), 7.64–7.74 (m, 4H, H_{ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ [ppm]=13.4 (2′-CH_3), 15.0 ($CH(CH_3)_2$), 15.0 (4′-CH_3), 17.8 ($CH(CH_3)_2$), 19.4 ($Si(Ph)_2C(CH_3)_3$), 20.3 (C-6′), 27.0 ($Si(Ph)_2C(CH_3)_3$), 28.2 ($CH(CH_3)_2$), 39.9 (C-4′), 58.2 (C-4), 63.3 (C-5), 72.0 (C-5′), 127.4 (C_{ar}), 127.6 (C_{ar}), 129.4 (C_{ar}), 129.6 (C_{ar}), 130.9 (C-2′), 134.0 (C_{ar}), 134.6 (C_{ar}), 135.9 (C_{ar}), 141.0 (C-3′), 153.5 (CO), 172.0 (CO); HMRS (ESI): $[M+Na]^+$ calcd for $C_{30}H_{41}NO_4Si$ 530.26971, found 530.26963.

*4.1.4. (2E,4S,5R)-5-{[tert-Butyl(diphenyl)silyl]oxy}-2,4-dimethyl-2-hexen-1-ol (**13**)*

To a stirred solution of oxazolidinone **12** (2.86 g, 5.63 mmol) in THF (66 mL) at 0 °C was added $NaBH_4$ (1.07 g, 28.15 mmol) in H_2O (33 mL). The reaction mixture was allowed to warm to room temperature and stirred for 6 h, before the reaction mixture was quenched with saturated NH_4Cl solution (200 mL). The aqueous layer was extracted with CH_2Cl_2 (2×40 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (petroleum ether/EtOAc, 6:1) to afford alcohol **13** (1.92 g, 89%) as a colorless oil. R_f=0.28 (petroleum ether/EtOAc, 6:1); $[\alpha]_D^{20}$ −1.2 (*c* 1.00, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm]=0.96 (d, *J*=6.9 Hz, 3H, 4-CH_3), 0.99 (d, *J*=6.1 Hz, 3H, 6-H), 1.05 (s, 9H, $Si(Ph)_2C(CH_3)_3$), 1.14 (br s, 1H, OH), 1.45 (d, *J*=1.3 Hz, 3H, 2-CH_3), 2.40–2.51 (m, 1H, 4-H), 3.71–3.79 (m, 1H, 5-H), 3.92 (br s, 2H, 1-H), 5.20–5.25 (m, 1H, 3-H), 7.31–7.49 (m, 6H, H_{ar}), 7.64–7.72 (m, 4H, H_{ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ [ppm]=13.7 (2-CH_3), 15.4 (4-CH_3), 19.4 ($Si(Ph)_2C(CH_3)_3$), 19.6 (C-6), 27.0 ($Si(Ph)_2C(CH_3)_3$), 39.2 (C-4), 69.0 (C-1), 72.6 (C-5), 127.4 (C_{ar}), 127.5 (C_{ar}), 129.0 (C-3), 129.4 (C_{ar}), 129.5 (C_{ar}), 134.4 (C-2), 134.7 (C_{ar}), 134.8 (C_{ar}), 135.9 (C_{ar}); HMRS (ESI): $[M+Na]^+$ calcd for $C_{24}H_{34}O_2Si$ 405.22203, found 405.22214.

*4.1.5. (2E,4S,5R)-5-{[tert-Butyl(diphenyl)silyl]oxy}-2,4-dimethyl-1-iodo-2-hexene (**14**)*

To a stirred solution of alcohol **13** (1.76 g, 4.60 mmol) in DMF (6 mL) at 0 °C was added methyltriphenoxyphosphonium iodide (2.55 g, 5.64 mmol) in DMF (5 mL) dropwise. The reaction mixture was allowed to warm to room temperature and stirred for 30 min. The reaction mixture was diluted with hexane (70 mL) and the organic layer was washed with cold aqueous 1 N NaOH (2×15 mL) and water (2×15 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo to afford iodide **14** (2.32 g, crude) as yellow oil. The crude product was used for the next reaction without further purification. R_f=0.38 (petroleum ether/EtOAc, 40:1); ^{1}H NMR (400 MHz, acetone-d_6): δ [ppm]=0.97 (d, *J*=7.1 Hz, 3H, 4-CH_3), 0.99 (d, *J*=6.4 Hz, 3H, 6-H), 1.06 (s, 9H, $Si(Ph)_2C(CH_3)_3$), 1.60 (d, *J*=1.3 Hz, 3H, 2-CH_3), 2.36–2.48 (m, 1H, 4-H), 3.80–3.89 (m, 1H, 5-H), 3.97–4.05 (m, 2H, 1-H), 5.67 (d, *J*=9.7 Hz, 1H, 3-H), 7.37–7.50 (m, 6H, H_{ar}), 7.66–7.76 (m, 4H, H_{ar}); ^{13}C NMR (100 MHz, acetone-d_6): δ [ppm]=15.4 (C-1), 15.6 (4-CH_3), 17.3 (2-CH_3), 19.9 ($Si(Ph)_2C(CH_3)_3$), 20.2 (C-6), 27.4 ($Si(Ph)_2C(CH_3)_3$), 40.7 (C-4), 73.3 (C-5), 128.4 (C_{ar}), 128.5 (C_{ar}), 130.4 (C_{ar}), 130.6 (C_{ar}), 132.8 (C-3), 134.2 (C_{ar}), 134.7 (C_{ar}), 135.3 (C-2), 136.6 (C_{ar}).

*4.1.6. (4R)-4-Benzyl-3-((2′S,4′E,6′S,7′R)-7′-{[tert-butyl-(diphenyl)silyl]oxy}-2′,4′,6′-trimethyloct-4′-enoyl)-1,3-oxazolidin-2-one (**16**)*

To a stirred solution of $NaN(SiMe_3)_2$ (2.78 g, 15.18 mmol) in THF (20 mL) was added (4*R*)-4-benzyl-3-propionyl-1,3-oxazolidin-2-one[21] (**15**) (3.22 g, 13.8 mmol) in THF (7 mL) at −80 °C. After 1 h, iodide **14** (2.27 g crude, about 4.6 mmol) in THF (3 mL) was added and the reaction mixture was allowed to warm to −50 °C. After stirring the reaction mixture at this temperature for 18 h, the mixture was quenched with saturated NH_4Cl solution (10 mL) and allowed to warm to room temperature. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2×40 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (petroleum ether/EtOAc, 7:1) to give oxazolidinone **16** (1.954 g, 71% over two steps) as a colorless oil. R_f=0.21 (petroleum ether/EtOAc, 7:1); $[\alpha]_D^{20}$ −33.8 (*c* 1.00, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm]=1.04 (d, *J*=6.6 Hz, 6H, 8′-H, 6′-CH_3), 1.13 (s, 9H, $Si(Ph)_2C(CH_3)_3$), 1.15 (d, *J*=6.6 Hz, 3H, 2′-CH_3), 1.49 (s, 3H, 4′-CH_3), 2.05 (dd, *J*=13.0, 8.4 Hz, 1H, 3′-H), 2.44–2.52 (m, 1H, 6′-H), 2.56 (dd, *J*=13.2, 6.1 Hz, 1H, 3′-H), 2.75 (dd, *J*=13.2, 9.9 Hz, 1H, CH_2Ph), 3.32 (dd, *J*=13.2, 3.1 Hz, 1H, CH_2Ph), 3.79–3.87 (m, 1H, 7′-H), 3.94–4.04 (m, 1H, 2′-H), 4.18–4.27 (m, 2H, 5-H), 4.70–4.78 (m, 1H, 4-H), 5.18 (d, *J*=9.4, 1H, 5′-H), 7.23–7.26 (m, 1H, H_{ar}), 7.42 (m, 10H, H_{ar}), 7.75 (m, 4H, H_{ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ [ppm]=15.3 (4′-CH_3), 15.5 (6′-CH_3), 16.2 (2′-CH_3), 19.4 (C-8, $Si(Ph)_2C(CH_3)_3$), 27.0 ($Si(Ph)_2C(CH_3)_3$), 35.6 (C-2′), 38.1 (CH_2Ph), 39.3 (C-6′), 44.1 (C-3′), 55.3 (C-4), 65.9 (C-5), 72.4 (C-7′), 127.3 (C_{ar}), 127.3 (C_{ar}), 127.5 (C_{ar}), 128.9 (C_{ar}), 129.3 (C_{ar}), 129.4 (C_{ar}), 129.5 (C_{ar}), 130.4 (C-5′), 132.2 (C_{ar}), 134.3 (C-4′), 134.9 (C_{ar}), 135.3 (C_{ar}), 135.9 (C_{ar}), 153.1 (CO), 177.1 (CO); HMRS (ESI): $[M+Na]^+$ calcd for $C_{37}H_{47}NO_4Si$ 620.31666, found 620.31640.

*4.1.7. (2S,4E,6S,7R)-7-{[tert-Butyl(diphenyl)silyl]oxy}-2,4,6-trimethyloct-4-enoic acid (**17**)*

To a solution of oxazolidinone **16** (1.95 g, 3.27 mmol) in THF (35 mL) was added H_2O_2 (30% in water, 1.34 mL, 13.07 mmol) at 0 °C, followed by the addition of a solution of $LiOH\cdot H_2O$ (0.274 g, 6.54 mmol) in water (17 mL). The reaction mixture was allowed to warm to room temperature and after stirring for 15 h, saturated $Na_2S_2O_3$ solution (5 mL) and saturated $NaHCO_3$ solution (5 mL) were added. The aqueous layer was extracted with CH_2Cl_2 (2×20 mL) and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. Flash chromatography (petroleum ether/EtOAc, 5:1) of the residue provided acid **17** (1.13 g, 79%) as a colorless oil. R_f=0.24 (petroleum ether/EtOAc, 5:1); $[\alpha]_D^{20}$ −15.8 (*c* 1.00, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm]=0.95 (d, *J*=6.4 Hz, 6H, 8-H, 6-CH_3), 1.06 (s, 9H, $Si(Ph)_2C(CH_3)_3$), 1.08 (d, *J*=6.9 Hz, 3H, 2-CH_3), 1.36 (s, 3H, 4-CH_3), 2.01 (dd, *J*=13.6, 8.0 Hz, 1H, 3-H), 2.29–2.45 (m, 2H, 3-H, 6-H), 2.51–2.62 (m, 1H, 2-H), 3.71–3.80 (m, 1H, 7-H), 5.07 (d, *J*=9.4 Hz, 1H, 5-H), 7.31–7.45 (m, 6H, H_{ar}), 7.64–7.74 (m, 4H, H_{ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ [ppm]=15.4 (6-CH_3), 15.7 (4-CH_3), 16.2 (2-CH_3), 19.4 ($Si(Ph)_2C(CH_3)_3$), 19.5 (C-8), 27.0 ($Si(Ph)_2C(CH_3)_3$), 37.8 (C-2), 39.4 (C-6), 43.8 (C-3), 72.5 (C-7), 127.4 (C_{ar}), 127.5 (C_{ar}), 129.4 (C_{ar}), 129.5 (C_{ar}), 130.3 (C-5), 131.8 (C-4), 134.3 (C_{ar}), 134.9 (C_{ar}), 135.9 (C_{ar}), 136.0 (C_{ar}), 183.1 (CO); HMRS (ESI): $[M+Na]^+$ calcd for $C_{27}H_{38}O_3Si$ 461.24824, found 461.24824.

4.1.8. *tert*-Butyl (2*S*,4*E*,6*S*,7*R*)-7-{[*tert*-butyl(diphenyl)silyl]oxy}-2,4,6-trimethyloct-4-enoate (**18**)

To a stirred solution of acid **17** (0.237 g, 0.54 mmol) in toluene (5 mL) were added Et_3N (0.225 mL, 1.62 mmol) and 2,4,6-trichlorobenzoyl chloride (0.085 mL, 0.54 mmol). After 30 min, ^{t}BuOH (0.103 mL, 1.08 mmol) and DMAP (0.264 g, 2.16 mmol) were added and the mixture was stirred for 1 h at room temperature. The reaction mixture was quenched with saturated $NaHCO_3$ solution (5 mL) and the aqueous layer was extracted with EtOAc (2×10 mL). The combined organic layers were dried over $NaSO_4$, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (petroleum ether/EtOAc, 30:1) to afford ester **18** (0.242 g, 91%) as a colorless oil. R_f=0.28 (petroleum ether/EtOAc, 30:1); $[\alpha]_D^{20}$ −11.9 (*c* 1.00, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm]=0.95 (d, *J*=6.1 Hz, 3H, 8-H), 0.97 (d, *J*=6.9 Hz, 3H, 6-CH_3), 1.01 (d, *J*=6.9 Hz, 3H, 2-CH_3), 1.06 (s, 9H, Si(Ph)$_2$C(CH_3)$_3$), 1.35 (d, *J*=1.0 Hz, 3H, 4-CH_3), 1.41 (s, 9H, C(CH_3)$_3$), 1.94 (dd, *J*=13.5, 7.5 Hz, 1H, 3-H), 2.29 (dd, *J*=13.5, 7.4 Hz, 1H, 3-H), 2.35–2.48 (m, 2H, 2-H, 6-H), 3.70–3.80 (m, 1H, 7-H), 5.03 (d, *J*=9.4 Hz, 1H, 5-H), 7.32–7.44 (m, 6H, H_{ar}), 7.64–7.73 (m, 4H, H_{ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ [ppm]=15.3 (6-CH_3), 15.7 (4-CH_3), 16.8 (2-CH_3), 19.3 (C-8), 19.4 (Si(Ph)$_2$*C*(CH_3)$_3$), 27.0 (Si(Ph)$_2$C(CH_3)$_3$), 28.1 (C(*C*H$_3$)$_3$), 38.8 (C-6), 39.2 (C-2), 44.2 (C-3), 72.5 (C-7), 79.2 (*C*(CH_3)$_3$), 127.3 (C_{ar}), 127.5 (C_{ar}), 129.3 (C_{ar}), 129.3 (C_{ar}), 129.5 (C_{ar}), 129.6 (C-5), 132.5 (C-4), 134.4 (C_{ar}), 135.0 (C_{ar}), 135.9 (C_{ar}), 175.9 (CO); HMRS (ESI): [M+Na]$^+$ calcd for $C_{31}H_{46}O_3Si$ 517.31084, found 517.31077.

4.1.9. *tert*-Butyl (2*S*,4*E*,6*S*,7*R*)-7-hydroxy-2,4,6-trimethyloct-4-enoate (**19**)

To a stirred solution of silyl ether **18** (0.23 g, 0.46 mmol) in THF (5 mL) was added $Bu_4NF\cdot 3H_2O$ (TBAF, 0.58 g, 1.84 mmol) and the mixture was stirred for 14 h at 55 °C. Thereafter, the solvent was removed in vacuo and flash chromatography (petroleum ether/EtOAc, 6:1) of the residue provided hydroxy ester **19** (0.097 g, 82%) as a colorless oil. R_f=0.23 (petroleum ether/EtOAc, 6:1); $[\alpha]_D^{20}$ −37.6 (*c* 1.00, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm]=0.89 (d, *J*=6.9 Hz, 3H, 6-CH_3), 1.05 (d, *J*=6.9 Hz, 3H, 2-CH_3), 1.13 (d, *J*=6.1 Hz, 3H, 8-H), 1.40 (s, 9H, C(CH_3)$_3$), 1.63 (d, *J*=0.8 Hz, 3H, 4-CH_3), 1.78 (s, 1H, OH), 2.03 (dd, *J*=13.9, 6.7 Hz, 1H, 3-H), 2.25–2.38 (m, 2H, 3-H, 6-H), 2.45–2.55 (m, 1H, 2-H), 3.39–3.48 (m, 1H, 7-H), 4.98 (d, *J*=9.7 Hz, 1H, 5-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ [ppm]=16.7 (4-CH_3), 16.8 (6-CH_3), 17.0 (2-CH_3), 20.0 (C-8), 28.0 (C(*C*H$_3$)$_3$), 38.9 (C-2), 40.6 (C-6), 43.8 (C-3), 71.7 (C-7), 79.9 (*C*(CH_3)$_3$), 129.0 (C-5), 135.3 (C-4), 175.7 (CO); HMRS (ESI): [M+Na]$^+$ calcd for $C_{15}H_{28}O_3$ 279.19307, found 279.19305.

4.1.10. (4*R*)-3((2′*E*,4′*R*,5′*R*)-5′-(Benzoyloxy)-2′,4′-dimethyl-2′-hexenoyl)-4-isopropyl-1,3-oxazolidin-2-one (**20**)

To a stirred solution of Ph_3P (9.07 g, 34.89 mmol) and benzoic acid (6.34 g, 51.88 mmol) in toluene (120 mL) was added DEAD (40% in toluene, 17.44 mL, 38.05 mmol) at 0 °C. Then a solution of alcohol *ent*-**11** (2.33 g, 8.65 mmol) in toluene (20 mL) was added dropwise and the reaction mixture was allowed to warm to room temperature. After stirring for 16 h, the reaction mixture was concentrated in vacuo and the residue purified by flash chromatography (petroleum ether/EtOAc, 5:1) to give benzoate **20** (2.42 g, 75%) as a colorless solid; mp 74.9 °C. R_f=0.22 (petroleum ether/EtOAc, 5:1); $[\alpha]_D^{20}$ −48.7 (*c* 1.00, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm]=0.89 (d, *J*=7.4 Hz, 3H, CH(*CH*$_3$)$_2$), 0.91 (d, *J*=7.6 Hz, 3H, CH(*CH*$_3$)$_2$), 1.08 (d, *J*=6.6 Hz, 3H, 4′-CH_3), 1.36 (d, *J*=6.4 Hz, 3H, 6′-H), 1.93 (d, *J*=1.3 Hz, 3H, 2′-CH_3), 2.30–2.43 (m, 1H, *CH*(CH_3)$_2$), 2.81–2.93 (m, 1H, 4′-H), 4.17 (dd, *J*=8.9, 5.3 Hz, 1H, 5-H), 4.30 (dd, *J*=8.8, 8.8 Hz, 1H, 5-H), 4.46–4.52 (m, 1H, 4-H), 5.01–5.10 (m, 1H, 5′-H), 5.80–5.88 (m, 1H, 3′-H), 7.42 (t, *J*=7.6 Hz, 2H, H_{ar}), 7.54 (t, *J*=7.4 Hz, 1H, H_{ar}), 8.02–8.08 (m, 2H, H_{ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ [ppm]=14.0 (2′-CH_3), 15.0 (CH(*CH*$_3$)$_2$), 16.1 (2′-CH_3), 17.8 (CH(*CH*$_3$)$_2$, C-6′), 28.2 (*CH*(CH_3)$_2$), 38.3 (C-4′), 58.2 (C-4), 63.4 (C-5), 74.4 (C-5′), 128.3 (C_{ar}), 129.6 (C_{ar}), 130.6 (C_{ar}), 131.8 (C-2′), 132.8 (C_{ar}), 138.4 (C-3′), 153.5 (CO), 166.0 (CO), 171.7 (CO); HMRS (ESI): [M+Na]$^+$ calcd for $C_{21}H_{27}NO_5$ 396.17814, found 396.17804.

4.1.11. (2*E*,4*R*,5*R*)-5-(Benzoyloxy)-2,4-dimethyl-2-hexen-1-ol (**21**)

To a stirred solution of acylated oxazolidinone **20** (4.72 g, 12.63 mmol) in THF (140 mL) was added $NaBH_4$ (2.39 g, 63.1 mmol) in water (70 mL) at 0 °C. The reaction mixture was warmed to room temperature and after stirring for 3 h, it was treated with saturated NH_4Cl solution (40 mL). The aqueous layer was extracted with CH_2Cl_2 (2×80 mL) and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (petroleum ether/EtOAc, 4:1) to afford primary alcohol **21** (2.74 g, 87%) as a colorless oil. R_f=0.23 (petroleum ether/EtOAc, 4:1); $[\alpha]_D^{20}$ −25.1 (*c* 1.00, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm]=1.04 (d, *J*=6.9 Hz, 3H, 4-CH_3), 1.28 (d, *J*=6.4 Hz, 3H, 6-H), 1.49 (br s, 1H, OH), 1.69 (d, *J*=1.02 Hz, 3H, 2-CH_3), 2.70–2.82 (m, 1H, 4-H), 4.01 (s, 2H, 1-H), 4.96–5.05 (m, 1H, 5-H), 5.27–5.34 (m, 1H, 3-H), 7.43 (t, *J*=7.6 Hz, 2H, H_{ar}), 7.54 (t, *J*=7.4 Hz, 1H, H_{ar}), 8.02 (m, 2H, H_{ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ [ppm]=14.1 (2-CH_3), 16.8 (4-CH_3), 17.6 (C-6), 37.3 (C-4), 68.7 (C-1), 75.0 (C-5), 127.1 (C-3), 128.3 (C_{ar}), 129.5 (C_{ar}), 130.7 (C_{ar}), 132.8 (C_{ar}), 135.8 (C-2), 166.2 (CO); HMRS (ESI): [M+Na]$^+$ calcd for $C_{15}H_{20}O_3$ 271.13047, found 271.13061.

4.1.12. (2*E*,4*R*,5*R*)-2,4-Dimethyl-2-hexene-1,5-diol (**22**)

To a stirred solution of benzoate **21** (2.67 g, 10.74 mmol) in MeOH (180 mL), NaOH (2.15 g, 53.68 mmol) was added at 0 °C. The reaction mixture was allowed to warm to room temperature, and after 20 h the solution was concentrated in vacuo. The residue was diluted with water and extracted with CH_2Cl_2 (2×50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (CH_2Cl_2/MeOH, 15:1) to give diol **22** (1.15 g, 74%) as a colorless oil. R_f=0.16 (CH_2Cl_2/MeOH, 15:1); $[\alpha]_D^{20}$ +26.7 (*c* 1.00, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm]=0.96 (d, *J*=6.6 Hz, 3H, 4-CH_3), 1.11 (d, *J*=6.4 Hz, 3H, 6-H), 1.67 (d, *J*=1.0 Hz, 3H, 2-CH_3), 1.94 (br s, 1H, OH), 2.17 (br s, 1H, OH), 2.41–2.53 (m, 1H, 4-H), 3.57–3.68 (m, 1H, H-5), 3.97 (s, 2H, 1-H), 5.22–5.30 (m, 1H, 3-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ [ppm]=14.1 (2-CH_3), 16.2 (4-CH_3), 20.1 (C-6), 39.2 (C-4), 68.6 (C-1), 71.8 (C-5), 127.7 (C-3), 135.7 (C-2); HMRS (ESI): [M+Na]$^+$ calcd for $C_8H_{16}O_2$ 167.10425, found 167.10417.

4.1.13. (2′*E*,4′*R*,5′*R*)-5′-Hydroxy-2′,4′-dimethyl-2′-hexenyl pivalate (**23**)

To a stirred solution of diol **22** (0.19 g, 1.35 mmol) in CH_2Cl_2 (5 mL) and pyridine (1.09 mL, 13.45 mmol) was added pivaloyl chloride (0.17 mL, 1.35 mmol) dropwise at 0 °C, followed by stirring the reaction mixture for 1 h. Then, water was added and the layers were separated. The aqueous layer was extracted with EtOAc (2×20 mL). The combined organic layers were washed with 1 N HCl (10 mL), saturated $NaHCO_3$ solution (10 mL), and saturated NaCl solution (10 mL), then dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (petroleum ether/EtOAc, 5:1) to afford pivalate **23** (0.31 g, 82%) as a colorless oil. R_f=0.18 (petroleum ether/EtOAc, 5:1); $[\alpha]_D^{20}$ +25.8 (*c* 1.00, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm]=0.97 (d, *J*=6.6 Hz, 3H, 4′-CH_3), 1.10 (d, *J*=6.4 Hz, 3H, 6′-H), 1.18 (s, 9H, C(CH_3)$_3$), 1.60–1.66 (m, 4H, 2′-CH_3, OH), 2.37–2.48 (m, 1H, 4′-H), 3.53–6.63 (m, 1H, 5′-H), 4.37–4.48 (m, 2H, 1′-H), 5.22–5.29 (m, 1H, 3′-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ [ppm]=14.2 (2′-CH_3), 16.4 (4′-CH_3), 20.5 (C-6′), 27.2 (C(*C*H$_3$)$_3$), 38.8 (*C*(CH_3)$_3$), 39.6 (C-4′), 69.7 (C-1′), 71.8 (C-5′), 130.7 (C-3′), 131.1 (C-2′), 178.3 (CO); HMRS (ESI): [M+Na]$^+$ calcd for $C_{13}H_{24}O_3$ 251.16177, found 251.16176.

*4.1.14. (2′E,4′R,5′R)-5′-{[tert-Butyl(diphenyl)silyl]oxy}-2′,4′-dimethyl-2′-hexenyl pivalate (**24**)*

To a stirred solution of alcohol **23** (1.17 g, 5.12 mmol) in CH_2Cl_2 (50 mL) at 0 °C were added imidazole (1.05 g, 15.35 mmol) and a catalytic amount of DMAP. The mixture was stirred for 10 min, before TBDPSCl (2.66 mL, 10.23 mmol) was added. The mixture was allowed to warm to room temperature and after 20 h the reaction mixture was quenched with water. The aqueous layer was extracted with CH_2Cl_2 (2×30 mL) and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 30:1) to afford pivalate **24** (2.362 g, 99%) as a colorless oil. R_f=0.20 (petroleum ether/EtOAc, 30:1); $[\alpha]_D^{20}$ +3.3 (*c* 1.00, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm]=0.96 (d, *J*=6.9 Hz, 6H, 4′-CH_3, 6′-H), 1.04 (s, 9H, Si(Ph)$_2$C(CH_3)$_3$), 1.19 (s, 9H, C(CH_3)$_3$), 1.60 (d, *J*=1.02 Hz, 3H, 2′-H), 2.39–2.52 (m, 1H, 4′-H), 3.68–3.78 (m, 1H, 5′-H), 4.41 (s, 2H, 1′-H), 5.31–5.37 (m, 1H, 3′-H), 7.32–7.45 (m, 6H, H_{ar}), 7.63–7.72 (m, 4H, H_{ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ [ppm]=14.2 (2′-CH_3), 16.3 (4′-CH_3), 19.4 (Si(Ph)$_2$*C*(CH_3)$_3$), 20.7 (C-6′), 27.0 (Si(Ph)$_2$C(*C*H$_3$)$_3$), 27.2 (C(*C*H$_3$)$_3$), 38.8 (*C*(CH_3)$_3$), 39.9 (C-4′), 70.1 (C-1′), 73.4 (C-5′), 127.3 (C_{ar}), 127.5 (C_{ar}), 129.4 (C_{ar}), 129.5 (C_{ar}), 129.9 (C-2′), 132.2 (C-3′), 134.2 (C_{ar}), 135.0 (C_{ar}), 135.9 (C_{ar}), 178.3 (CO); HMRS (ESI): $[M+Na]^+$ calcd for $C_{29}H_{42}O_3Si$ 489.27954, found 489.27941.

*4.1.15. (2E,4R,5R)-5-{[tert-Butyl(diphenyl)silyl]oxy}-2,4-dimethyl-2-hexen-1-ol (**25**)*

To a stirred solution of pivalate **24** (2.36 g, 5.06 mmol) in CH_2Cl_2 (70 mL) at −80 °C was added DIBAL-H (1 M in hexane, 12.65 mL, 12.65 mmol) in a dropwise fashion. After 1 h, the reaction mixture was quenched with saturated Rochelle salt solution (20 mL), allowed to warm to room temperature, and stirred vigorously for 1 h. The aqueous layer was extracted with CH_2Cl_2 (2×30 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. Flash chromatography (petroleum ether/EtOAc, 6:1) provided alcohol **25** (1.79 g, 92%) as a colorless oil. R_f=0.26 (petroleum ether/EtOAc, 6:1); $[\alpha]_D^{20}$ −3.8 (*c* 1.00, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm]=0.98 (d, *J*=6.9 Hz, 3H, 4-CH_3), 0.99 (d, *J*=6.4 Hz, 3H, 6-H), 1.06 (s, 9H, Si(Ph)$_2$C(CH_3)$_3$), 1.19 (br s, 1H, OH), 1.60 (s, 3H, 2-CH_3), 2.38–2.50 (m, 1H, 4-H), 3.70–3.79 (m, 1H, 5-H), 3.93 (d, *J*=5.9 Hz, 2H, 1-H), 5.25–5.31 (m, 1H, 3-H), 7.32–7.46 (m, 6H, H_{ar}), 7.60–7.76 (m, 4H, H_{ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ [ppm]=14.0 (2-CH_3), 16.2 (4-CH_3), 19.4 (Si(Ph)$_2$*C*(CH_3)$_3$), 21.1 (C-6), 27.1 (Si(Ph)$_2$C(*C*H$_3$)$_3$), 39.8 (C-4), 69.0 (C-1), 73.4 (C-5), 127.3 (C_{ar}), 127.4 (C_{ar}), 129.4 (C-3), 129.4 (C_{ar}), 129.5 (C_{ar}), 134.2 (C_{ar}), 134.3 (C_{ar}), 134.9 (C-2), 136.0 (C_{ar}), 136.0 (C_{ar}); HMRS (ESI): $[M+Na]^+$ calcd for $C_{24}H_{34}O_2Si$ 405.2203, found 405.22237.

*4.1.16. (2E,4S,5R)-5-{[tert-Butyl(diphenyl)silyl]oxy}-2,4-dimethyl-1-iodo-2-hexene (**26**)*

To a stirred solution of alcohol **25** (1.78 g, 4.66 mmol) in DMF (3 mL) at 0 °C was added methyltriphenoxyphosphonium iodide (2.58 g, 5.59 mmol) in DMF (3 mL) dropwise. The reaction mixture was allowed to warm to room temperature and stirred for 30 min. The mixture was diluted with hexane (70 mL) and then washed with cold aqueous 1 N NaOH (2×15 mL) and with water (2×15 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo to afford iodide **26** (2.33 g, crude) as a yellow oil. This crude product was used for the next reaction without further purification. R_f=0.38 (petroleum ether/EtOAc, 40:1); ^{1}H NMR (400 MHz, acetone-d_6): δ [ppm]=0.93 (d, *J*=6.6 Hz, 3H, 4-CH_3), 0.98 (d, *J*=6.4 Hz, 3H, 6-H), 1.05 (s, 9H, Si(Ph)$_2$C(CH_3)$_3$), 1.74 (d, *J*=1.0 Hz, 3H, 2-CH_3), 2.38–2.51 (m, 1H, 4-H), 3.74–3.85 (m, 1H, 5-H), 3.97–4.06 (m, 2H, 1-H), 5.66 (d, *J*=9.9 Hz, 1H, 3-H), 7.35–7.49 (m, 6H, H_{ar}), 7.68–7.75 (m, 4H, H_{ar}); ^{13}C NMR (100 MHz, acetone-d_6): δ [ppm]=15.9 (C-1), 15.9 (4-CH_3), 17.5 (2-CH_3), 19.9 (Si(Ph)$_2$*C*(CH_3)$_3$), 21.0 (C-6), 27.5 (Si(Ph)$_2$C(*C*H$_3$)$_3$), 41.4 (C-4), 74.1 (C-5), 128.4 (C_{ar}), 128.5 (C_{ar}), 130.4 (C_{ar}), 130.6 (C_{ar}), 133.3 (C-3), 133.6 (C_{ar}), 134.7 (C_{ar}), 135.5 (C-2), 136.6 (C_{ar}), 136.7 (C_{ar}).

*4.1.17. (4R)-4-Benzyl-3-((2′S,4′E,6′R,7′R)-7′-{[tert-butyl(diphenyl)-silyl]oxy}-2′,4′,6′-trimethyl-4′-octenoyl)-1,3-oxazolidin-2-one (**27**)*

To a stirred solution of NaN($SiMe_3$)$_2$ (2.82 g, 15.36 mmol) in THF (20 mL) was added (4*R*)-4-benzyl-3-propionyl-1,3-oxazolidin-2-one[21] (**15**) (3.26 g, 13.97 mmol) in THF (7 mL) at −80 °C. After 1 h, iodide **26** (2.29 g crude, about 4.66 mmol) in THF (3 mL) was added and the reaction mixture was allowed to warm to −50 °C. After stirring the reaction mixture at this temperature for 18 h, it was quenched with saturated NH_4Cl solution (10 mL) and allowed to warm to room temperature. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2×40 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (petroleum ether/EtOAc, 7:1) to give oxazolidinone **27** (2.14 g, 77% over two steps) as a colorless solid; mp 115.8 °C. R_f=0.36 (petroleum ether/EtOAc, 7:1); $[\alpha]_D^{20}$ −23.8 (*c* 1.00, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm]=1.00 (d, *J*=1.8 Hz, 3H, 6′-CH_3), 1.02 (d, *J*=2.3 Hz, 3H, 8′-H), 1.10 (s, 9H, Si(Ph)$_2$C(CH_3)$_3$), 1.14 (d, *J*=6.6 Hz, 3H, 2′-CH_3), 1.68 (s, 3H, 4′-CH_3), 2.02 (dd, *J*=13.4, 9.0 Hz, 1H, 3′-H), 2.38–2.61 (m, 1H, 6′-H, 3′-H), 2.71 (dd, *J*=13.2, 9.9 Hz, 1H, CH_2Ph), 3.32 (dd, *J*=13.4, 3.2 Hz, 1H, CH_2Ph), 3.70–3.82 (m, 1H, 7′-H), 3.88–4.02 (m, 1H, 2′-H), 4.14–4.27 (m, 2H, 5-H), 4.64–4.77 (m, 1H, 4-H), 5.16 (d, *J*=9.7 Hz, 1H, 5′-H), 7.21–2.24 (m, 1H, H_{ar}), 7.29–7.49 (m, 10H, H_{ar}), 7.69–7.77 (m, 4H, H_{ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ [ppm]=15.8 (4′-CH_3), 16.1 (6′-CH_3), 17.0 (2′-CH_3), 19.4 (Si(Ph)$_2$*C*(CH_3)$_3$), 21.1 (C-8), 27.1 (Si(Ph)$_2$C(*C*H$_3$)$_3$), 35.7 (C-2′), 38.0 (CH_2Ph), 40.5 (C-6′), 43.5 (C-3′), 55.4 (C-4), 66.0 (C-5), 73.7 (C-7′), 127.3 (C_{ar}), 127.4 (C_{ar}), 128.9 (C_{ar}), 129.3 (C_{ar}), 129.4 (C_{ar}), 129.4 (C_{ar}), 131.1 (C-5′), 131.3 (C_{ar}), 134.3 (C-4′), 135.1 (C_{ar}), 135.4 (C_{ar}), 135.9 (C_{ar}), 153.0 (CO), 177.1 (CO); HMRS (ESI): $[M+Na]^+$ calcd for $C_{37}H_{47}NO_4Si$ 620.31666, found 620.31677.

*4.1.18. (2S,4E,6R,7R)-7-{[tert-Butyl(diphenyl)silyl]oxy}-2,4,6-trimethyloct-4-enoic acid (**28**)*

To a solution of oxazolidinone **27** (2.04 g, 3.41 mmol) in THF (35 mL) was added H_2O_2 (30% in water, 1.39 mL, 13.65 mmol) at 0 °C, followed by the addition of a solution of LiOH·H_2O (0.286 g, 6.82 mmol) in water (17 mL). The reaction mixture was allowed to warm to room temperature and after stirring for 15 h, saturated $Na_2S_2O_3$ solution (5 mL) and saturated $NaHCO_3$ solution (5 mL) were added. The aqueous layer was extracted with CH_2Cl_2 (2×20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. Flash chromatography (petroleum ether/EtOAc, 5:1) of the residue provided acid **28** (1.26 g, 84%) as a colorless oil. R_f=0.27 (petroleum ether/EtOAc, 5:1); $[\alpha]_D^{20}$ +4.7 (*c* 1.00, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm]=0.95 (d, *J*=6.4 Hz, 6H, 8-H, 6-CH_3), 1.05 (s, 9H, Si(Ph)$_2$C(CH_3)$_3$), 1.07 (d, *J*=7.1 Hz, 3H, 2-CH_3), 1.57 (s, 3H, 4-CH_3), 1.99 (dd, *J*=13.5, 8.4 Hz, 1H, 3-H), 2.31–2.47 (m, 2H, 3-H, 6-H), 2.52–2.64 (m, 1H, 2-H), 3.64–3.73 (m, 1H, 7-H), 5.05 (d, *J*=9.4 Hz, 1H, 5-H), 7.31–7.45 (m, 6H, H_{ar}), 7.63–7.73 (m, 4H, H_{ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ [ppm]=16.1 (6-CH_3), 16.1 (4-CH_3), 17.1 (2-CH_3), 19.4 (Si(Ph)$_2$*C*(CH_3)$_3$), 21.1 (C-8), 27.1 (Si(Ph)$_2$C(*C*H$_3$)$_3$), 37.6 (C-2), 40.6 (C-6), 43.6 (C-3), 73.8 (C-7), 127.3 (C_{ar}), 127.4 (C_{ar}), 129.3 (C_{ar}), 129.4 (C_{ar}), 131.0 (C-5), 131.1 (C-4), 134.3 (C_{ar}), 135.1 (C_{ar}), 135.9 (C_{ar}), 136.0 (C_{ar}), 183.0 (CO); HMRS (ESI): $[M+Na]^+$ calcd for $C_{27}H_{38}O_3Si$ 461.24824, found 461.24845.

*4.1.19. tert-Butyl (2S,4E,6R,7R)-7-{[tert-butyl(diphenyl)silyl]oxy}-2,4,6-trimethyloct-4-enoate (**29**)*

To a stirred solution of acid **28** (1.20 g, 2.74 mmol) in toluene (24 mL) were added Et_3N (1.14 mL, 8.21 mmol) and 2,4,6-trichlorobenzoyl chloride (0.43 mL, 2.74 mmol). After 30 min, ^{t}BuOH (0.52 mL, 5.47 mmol) and DMAP (1.34 g, 10.94 mmol) were added and the mixture was stirred for 1 h at room temperature. The reaction mixture was quenched with saturated $NaHCO_3$ solution (10 mL) and the aqueous layer was extracted with EtOAc (2×40 mL). The combined organic layers were dried over Na_2SO_4,

filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (petroleum ether/EtOAc, 30:1) to afford ester **29** (1.23 g, 90%) as a colorless oil. R_f=0.31 (petroleum ether/EtOAc, 30:1); $[\alpha]_D^{20}$ +3.1 (*c* 1.00, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm]=0.95 (d, *J*=6.9 Hz, 3H, 8-H, 6-CH_3), 1.02 (d, *J*=7.1 Hz, 3H, 2-CH_3), 1.05 (s, 9H, Si(Ph)$_2$C(CH_3)$_3$), 1.41 (s, 9H, C(CH_3)$_3$), 1.55 (s, 3H, 4-CH_3), 1.91 (dd, *J*=13.7, 7.9 Hz, 1H, 3-H), 2.33 (dd, *J*=13.7, 6.6 Hz, 1H, 3-H), 2.37–2.49 (m, 2H, 2-H, 6-H), 3.62–3.71 (m, 1H, 7-H), 5.03 (d, *J*=9.4 Hz, 1H, 5-H), 7.30–7.45 (m, 6H, H_{ar}), 7.63–7.73 (m, 4H, H_{ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ [ppm]=16.4 (6-CH_3), 16.6 (4-CH_3), 17.0 (2-CH_3), 19.4 (Si(Ph)$_2$*C*(CH_3)$_3$), 21.2 (C-8), 27.1 (Si(Ph)$_2$C(*C*H$_3$)$_3$), 28.1 (C(*C*H$_3$)$_3$), 38.6 (C-6), 40.5 (C-2), 43.4 (C-3), 73.8 (C-7), 79.7 (*C*(CH_3)$_3$), 127.3 (C_{ar}), 127.4 (C_{ar}), 129.3 (C_{ar}), 129.4 (C_{ar}), 130.1 (C-5), 131.8 (C-4), 134.3 (C_{ar}), 135.1 (C_{ar}), 136.0 (C_{ar}), 136.0 (C_{ar}), 176.1 (CO); HMRS (ESI): $[M+Na]^+$ calcd for $C_{31}H_{46}O_3Si$ 517.31084, found 517.31041.

*4.1.20. tert-Butyl (2S,4E,6R,7R)-7-hydroxy-2,4,6-trimethyloct-4-enoate (**30**)*

To a stirred solution of silyl ether **29** (1.18 g, 2.39 mmol) in THF (25 mL) was added $Bu_4NF\cdot 3H_2O$ (TBAF, 1.51 g, 4.79 mmol) and the mixture was stirred for 14 h at 55 °C. The solvent was removed in vacuo and flash chromatography (petroleum ether/EtOAc, 6:1) of the residue provided hydroxy ester **30** (0.534 g, 87%) as a colorless oil. R_f=0.18 (petroleum ether/EtOAc, 6:1); $[\alpha]_D^{20}$ +19.1 (*c* 1.00, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm]=0.95 (d, *J*=6.6 Hz, 3H, 6-CH_3), 1.04 (d, *J*=6.9 Hz, 3H, 2-CH_3), 1.10 (d, *J*=6.4 Hz, 3H, 8-H), 1.41 (s, 9H, C(CH_3)$_3$), 1.53 (br s, 1H, OH), 1.62 (d, *J*=1.27 Hz, 3H, 4-CH_3), 1.97 (dd, *J*=13.9, 6.7 Hz, 1H, 3-H), 2.35 (dd, *J*=13.7, 7.4 Hz, 1H, 3-H), 2.39–2.53 (m, 2H, 6-H, 2-H), 3.53–3.62 (m, 1H, 7-H), 4.96–5.04 (m, 1H, 5-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ [ppm]=16.4 (4-CH_3), 16.7 (6-CH_3), 16.9 (2-CH_3), 20.3 (C-8), 28.1 (C(*C*H$_3$)$_3$), 38.8 (C-2), 39.7 (C-6), 43.9 (C-3), 72.0 (C-7), 79.9 (*C*(CH_3)$_3$), 128.8 (C-5), 133.8 (C-4), 175.8 (CO); HMRS (ESI): $[M+Na]^+$ calcd for $C_{15}H_{28}O_3$ 279.19307, found 279.19315.

Acknowledgements

Financial support by the Deutsche Forschungsgemeinschaft (grant Ma 1012/13-2), the NIH, and the Fonds der Chemischen Industrie is gratefully acknowledged. We thank Graeme Nicholson (Institute of Organic Chemistry) for measuring the HRMS spectra.

Supplementary data

Procedures for *ent*-**10** and *ent*-**11**, copies of NMR spectra. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.04.109.

References and notes

1. (a) Kunze, B.; Jansen, R.; Sasse, F.; Höfle, G.; Reichenbach, H. *J. Antibiot.* **1995**, *48*, 1262–1266; (b) Jansen, R.; Kunze, B.; Reichenbach, H.; Höfle, G. *Liebigs Ann.* **1996**, 285–290.
2. For recent reviews, covering depsipeptides, see: (a) Hamada, Y.; Shioiri, T. *Chem. Rev.* **2005**, *105*, 4441–4482; (b) Hughes, R. A.; Moody, C. J. *Angew. Chem.* **2007**, *119*, 8076–8101; *Angew. Chem., Int. Ed.* **2007**, *46*, 7930–7954.
3. (a) Zabriskie, T. M.; Klocke, J. A.; Ireland, C. M.; Marcus, A. H.; Molinski, T. F.; Faulkner, D. J.; Xu, C.; Clardy, J. C. *J. Am. Chem. Soc.* **1986**, *108*, 3123–3124; (b) Crews, P.; Manes, L. V.; Boehler, M. *Tetrahedron Lett.* **1986**, *27*, 2797–2800.
4. (a) Chan, W. R.; Tinto, W. F.; Manchand, P. S.; Todaro, L. J. *J. Org. Chem.* **1987**, *52*, 3091–3093; (b) Tinto, W. F.; Lough, A. J.; McLean, S.; Reynolds, W. F.; Yu, M.; Chan, W. R. *Tetrahedron* **1998**, *54*, 4451–4458; (c) Coleman, J. E.; Van Soest, R.; Andersen, R. J.; Kelsey, R. G. *J. Nat. Prod.* **1999**, *62*, 1137–1141.
5. D'Auria, M. V.; Paloma, L. G.; Minale, L.; Zampella, A.; Debitus, C.; Perez, J. *J. Nat. Prod.* **1995**, *58*, 121–123.
6. Tanaka, C.; Tanaka, J.; Bolland, R. F.; Marriott, G.; Higa, T. *Tetrahedron* **2006**, *62*, 3536–3542.
7. Rachid, S.; Krug, D.; Kunze, B.; Kochems, I.; Scharfe, M.; Zabriskie, T. M.; Bloecker, H.; Müller, R. *Chem. Biol.* **2006**, *13*, 667–681.
8. (a) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841–1860; (b) Hoffmann, R. W. *Angew. Chem.* **2000**, *112*, 2134–2150; *Angew. Chem., Int. Ed.* **2000**, *39*, 2054–2070.
9. Marimganti, S.; Wieneke, R.; Geyer, A.; Maier, M. E. *Eur. J. Org. Chem.* **2007**, 2779–2790.
10. (a) Grieco, P. A.; Hon, Y. S.; Perez-Medrano, A. *J. Am. Chem. Soc.* **1988**, *110*, 1630–1631; (b) Chu, K. S.; Negrete, G. R.; Konopelski, J. P. *J. Org. Chem.* **1991**, *56*, 5196–5201; (c) Rama Rao, A. V.; Gurjar, M. K.; Nallaganchu, B. R.; Bhandari, A. *Tetrahedron Lett.* **1993**, *34*, 7085–7088; (d) Hirai, Y.; Yokota, K.; Momose, T. *Heterocycles* **1994**, *39*, 603–612; (e) Ashworth, P.; Broadbelt, B.; Jankowski, P.; Kocienski, P.; Pimm, A.; Bell, R. *Synthesis* **1995**, 199–206; (f) Ghosh, A. K.; Moon, D. K. *Org. Lett.* **2007**, *9*, 2425–2427.
11. (a) Schmidt, U.; Siegel, W.; Mundinger, K. *Tetrahedron Lett.* **1988**, *29*, 1269–1270; (b) Hirai, Y.; Yokota, K.; Yamazaki, T.; Momose, T. *Heterocycles* **1990**, *30*, 1101–1119; (c) Kang, S.-K.; Lee, D.-H. *Synlett* **1991**, 175–176; (d) Rama Rao, A. V.; Gurjar, M. K.; Nallaganchu, B. R.; Bhandari, A. *Tetrahedron Lett.* **1993**, *34*, 7081–7084; (e) Shioiri, T.; Imaeda, T.; Hamada, Y. *Heterocycles* **1997**, *46*, 421–442; (f) Wattanasereekul, S.; Maier, M. E. *Adv. Synth. Catal.* **2004**, *346*, 855–861.
12. Bai, R.; Covell, D. G.; Liu, C.; Ghosh, A. K.; Hamel, E. *J. Biol. Chem.* **2002**, *277*, 32165–32171.
13. Müller, S. University of Tübingen, unpublished results.
14. (a) Khan, A.; Su, C.; German, M.; Storch, G. A.; Clifford, D. B.; Sibley, L. D. *J. Clin. Microbiol.* **2005**, *43*, 5881–5887; (b) Sahoo, N.; Beatty, W.; Heuser, J.; Sept, D.; Sibley, L. D. *Mol. Biol. Cell* **2006**, *17*, 895–906.
15. Marimganti, S.; Yasmeen, S.; Fischer, D.; Maier, M. E. *Chem.—Eur. J.* **2005**, *11*, 6687–6700.
16. (a) Shirokawa, S.; Kamiyama, M.; Nakamura, T.; Okada, M.; Nakazaki, A.; Hosokawa, S.; Kobayashi, S. *J. Am. Chem. Soc.* **2004**, *126*, 13604–13605; (b) Shirokawa, S.-i.; Shinoyama, M.; Ooi, I.; Hosokawa, S.; Nakazaki, A.; Kobayashi, S. *Org. Lett.* **2007**, *9*, 849–852.
17. For a recent application, see: Jiang, X.; Liu, B.; Lebreton, S.; De Brabander, J. K. *J. Am. Chem. Soc.* **2007**, *129*, 6386–6387.
18. Prashad, M.; Kim, H.-Y.; Lu, Y.; Liu, Y.; Har, D.; Repic, O.; Blacklock, T. J.; Giannousis, P. *J. Org. Chem.* **1999**, *64*, 1750–1753.
19. Landauer, S. R.; Rydon, H. N. *J. Chem. Soc.* **1953**, 2224–2234.
20. Evans, D. A.; Dow, R. L.; Shih, T. L.; Takacs, J. M.; Zahler, R. *J. Am. Chem. Soc.* **1990**, *112*, 5290–5313.
21. Gage, J. R.; Evans, D. A. *Org. Synth.* **1989**, *68*, 77–82; *Org. Synth.* **1993**, *Coll. Vol.*, 528–531.
22. Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989–1993.
23. (a) Hughes, D. L. *Org. React.* **1992**, *42*, 335–656; (b) Dembinski, R. *Eur. J. Org. Chem.* **2004**, 2763–2772.