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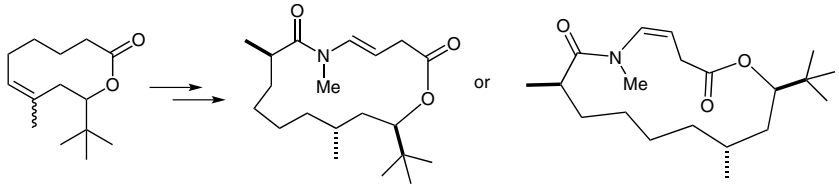
Total Synthesis of Laingolide A Diastereomers

Gaétan Pomey
Phannarath Phansavath*

PSL Research University, Chimie ParisTech-CNRS, Institut de Recherche de Chimie Paris, 75005 Paris, France
phannarath.phansavath@chimie-paristech.fr



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Abstract The first total syntheses of two (±)-laingolide A diastereomers were achieved in 11 and 12 steps, respectively. The key steps include a tandem cross-dimerization/oxonia-Cope reaction and an intramolecular dehydrative cyclization for the formation of either the *trans*- or *cis*-enamide moieties.

Key words natural products, total synthesis, macrocycles, ring expansion, oxonia-Cope reactions

Laingolide (**1**),[1] an unprecedented 15-membered macrolide structure containing a *trans*-*N*-methyl enamide moiety, was isolated in 1996 from the blue-green alga *Lyngbya bouillonii* (Cyanophyceae) collected in Papua New Guinea (Figure 1). This marine cyanobacterium proved to be an exceptionally rich source of secondary metabolites, because two other macrolides, laingolide A (**2**) and madangolide (**3**), were also isolated from the same organism a few years later.[2] More recently, investigation of several collections of *L. bouillonii* from shallow patch reefs in Apra Harbor, Guam, gave laingolide B (**4**), a chlorinated analogue of laingolide A.[3]

All members of the laingolide family decomposed during characterization studies, preventing the testing of the compounds for bioactivity and impeding the assignment of their relative and absolute stereochemistries. Interestingly, however, (–)-palmyrolide A (**5**), a structurally related neuroactive macrolide isolated from a marine cyanobacterial assemblage composed of *Leptolyngba cf.* species and *Oscillatoria* species showed promising biological properties, significantly inhibiting calcium(2+) ion oscillations in murine cerebrocortical neurons with an IC_{50} value of 3.70 μM.[4] Several total syntheses of this compound have recently

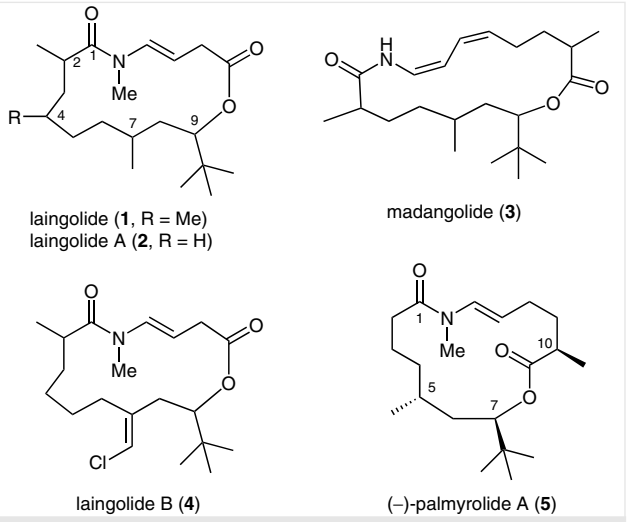
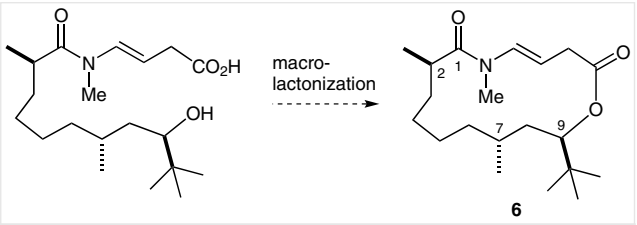


Figure 1 Structures of laingolide (**1**), laingolide A (**2**), madangolide (**3**), laingolide B (**4**), and palmyrolide A (**5**)

appeared in the literature.[5] The first of those, reported by Maio and co-workers,[5a,b] permitted the determination of the absolute stereochemistry of palmyrolide A and a revision of the initially suggested relative stereochemistry between the C(5) methyl and the C(7) *tert*-butyl stereocenters. The interaction of synthetic (–)-palmyrolide A diastereomers and nonnatural analogues with voltage-gated sodium channels was also examined.[6] Because of their structural similarity to palmyrolide A, laingolide derivatives are potentially interesting secondary metabolites and, as part of our work on the total synthesis of relevant biomolecules,[7] we decided to study a route to laingolide A isomers. Here, we report the first total synthesis of two laingolide A diastereomers, involving a tandem cross-dimeriza-

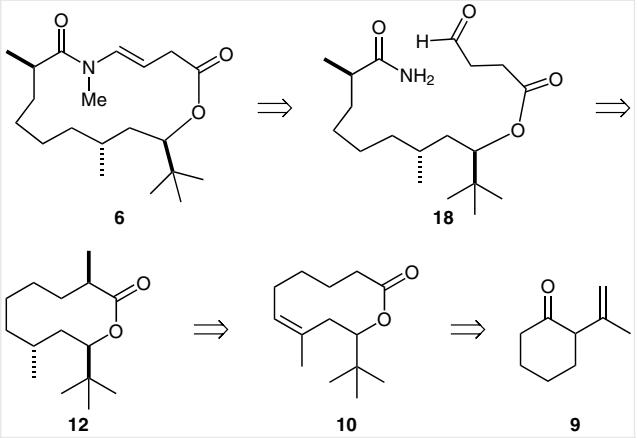
tion/oxonia-Cope reaction and an intramolecular dehydrative cyclization to install either the *trans*- or *cis*-enamide moieties.

The relative configuration of the three stereogenic centers at C(2), C(7), and C(9) of the target isomer **6** of laingolide A was chosen on the basis of the stereochemistry of the parent compound (–)-palmyrolide A, and our first approach relied on a Yamaguchi esterification for the final macrocyclization step (Scheme 1).



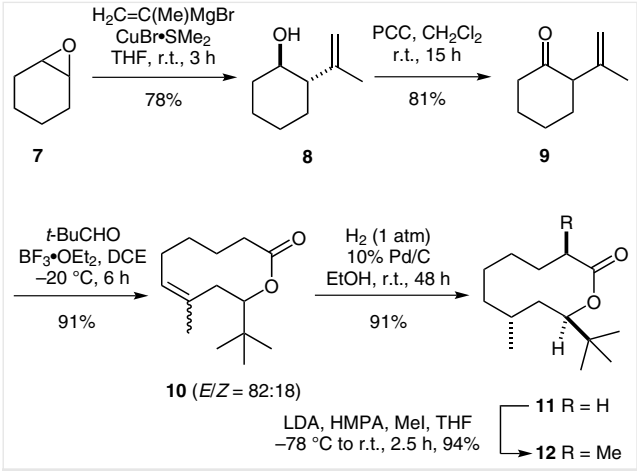
Scheme 1 First macrocyclization approach

However, despite considerable experimentation, we were unable to prepare the required cyclization precursor. Therefore, we planned an alternative route involving, as the key macrocyclization step, a dehydrative cyclization of compound **18** to install the *trans*-enamide moiety (Scheme 2), an approach successfully adopted by Sudhakar et al.[5d] in their total synthesis of (–)-palmyrolide A. The primary amide-containing macrocyclization precursor **18** might be obtained from the ten-membered lactone **12** by ring opening with ammonia followed by introduction of a masked aldehyde segment. Compound **12** might, in turn, be obtained from lactone **10** after diastereoselective hydrogenation of the alkene function and stereoselective α-methylation. Finally, compound **10** might be obtained from the α–substituted cyclohexanone **9** and pivalaldehyde through a tandem cross-dimerization/oxonia-Cope rearrangement, an elegant method reported by Wang and Goeke[8] for the efficient and straightforward preparation of macrolactones.



Scheme 2 Retrosynthetic strategy for the laingolide A diastereomer **6**

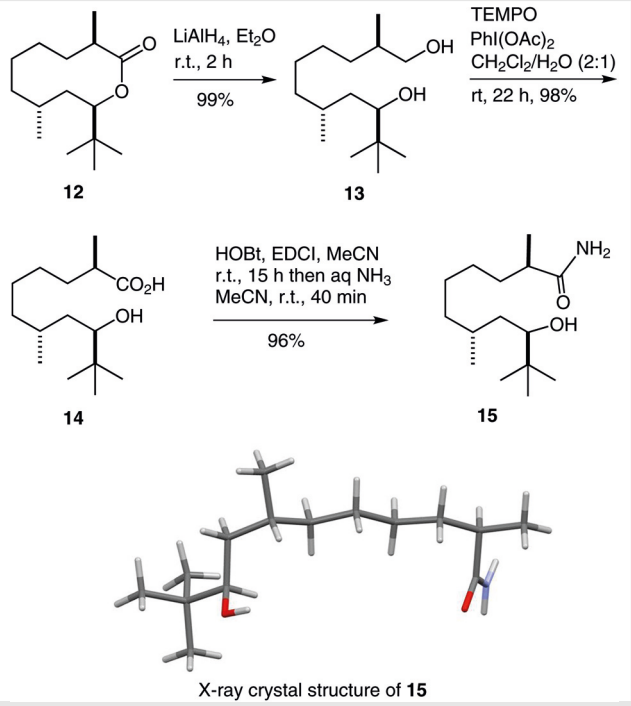
Our synthesis began with the copper-catalyzed epoxide opening of cyclohexene oxide (**7**) with isopropenylmagnesium bromide to give *trans*-2-isopropenylcyclohexanol (**8**; Scheme 3).[9] Oxidation of the alcohol **8** with pyridinium chlorochromate then gave the corresponding cyclohexanone **9** in 81% yield.[9b] Subsequent oxonia-Cope [6+4] ring enlargement[8] of ketone **9** was carried out by treatment with pivalaldehyde in the presence of 20 mol% of boron trifluoride etherate to give a good yield of lactone **10** as a 82:18 mixture of the *E*- and *Z*-isomers. We expected that hydrogenation of this mixture would produce both the *cis*- and *trans*-products with respect to the C(7) and C(9) stereocenters.



Scheme 3 Preparation of lactone **12**

To our surprise, however, reduction of the *E*/*Z* mixture of the trisubstituted alkene **10** with palladium/carbon under a hydrogen atmosphere proceeded in a highly stereoconvergent manner, giving lactone **11** as a single *trans*-diastereomer.[10,11] Subsequent methylation of the ten-membered lactone with lithium diisopropylamide and iodomethane in the presence of hexamethylphosphoramide gave the corresponding C(2)-methylated product as a single diastereomer with a *cis*-relationship between the stereocenters at C(2) and C(9).[12] Having obtained the diastereomerically pure lactone **12**, we needed to introduce the primary amide moiety required for the macrocyclization step. To achieve this, we initially planned to prepare hydroxy amide **15** by direct ring opening of the lactone **12** with ammonia (Scheme 4).

However, in our hands, the addition of ammonia to **12** under a variety of conditions failed to give the desired amide **15**, probably because of the steric hindrance provided by the contiguous *tert*-butyl substituent at C(9), as observed by Gerwick et al.[4] in their attempts to hydrolyze the lactone of (–)-palmyrolide A. We therefore prepared amide



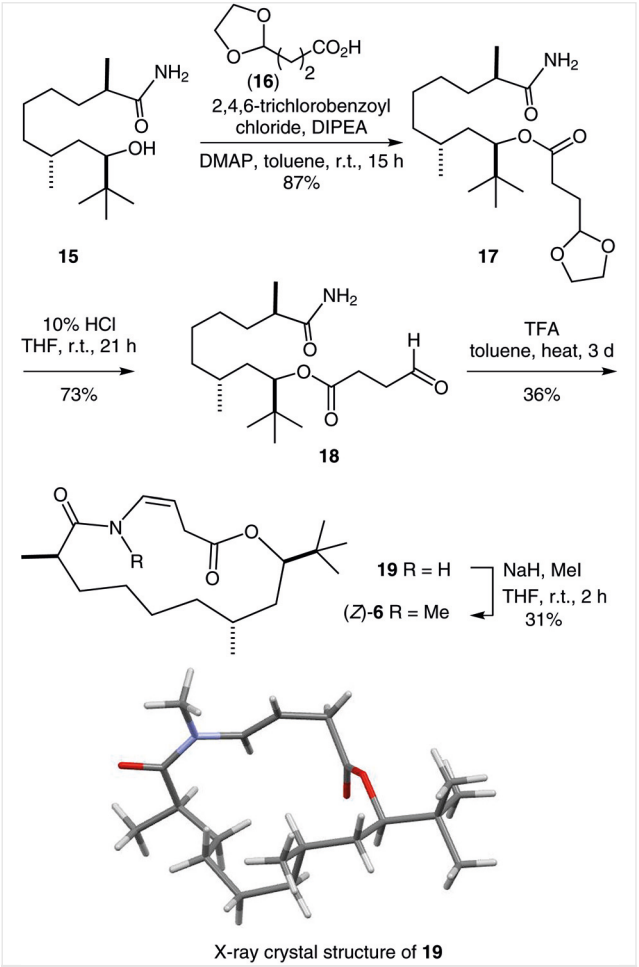
Scheme 4 Synthesis of hydroxy amide **15**; HOBt = 1*H*-1,2,3-benzotriazol-1-ol

15 in three steps: reduction of lactone **12** with lithium aluminum hydride to give the corresponding diol **13**, chemoselective oxidation of the primary alcohol group of **13** with a combination of 2,2,6,6-tetramethylpiperidinyl-1-oxyl (TEMPO) and [bis(acetyloxy)iodo]benzene (BAIB),[13] and coupling of the resulting carboxylic acid **14** with aqueous ammonia in the presence of *N*-ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide (EDCI) and 1*H*-1,2,3-benzotriazol-1-ol (HOBt).[14] An X-ray crystallographic analysis of amide **15** unambiguously confirmed its relative configuration (Scheme 4). Subsequent esterification of **15** with 3-(1,3-dioxolan-2-yl)propanoic acid (**16**)[15] in the presence of 2,4,6-trichlorobenzoyl chloride, diisopropylethylamine, and 4-(*N*,*N*-dimethylamino)pyridine under Yamaguchi conditions[5b,16] gave ketal **17** in 87% yield (Scheme 5).

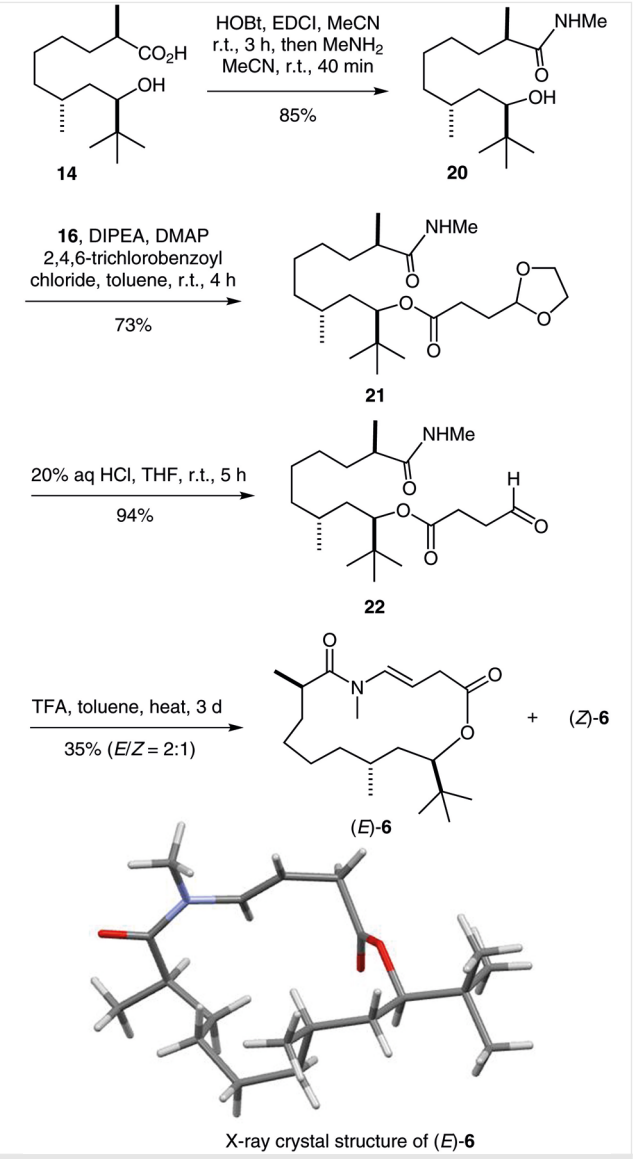
Hydrolysis of ketal **17** with 10% hydrochloric acid gave the macrocyclization precursor **18**, which underwent dehydrative cyclization in refluxing toluene containing trifluoroacetic acid to give a 36% yield of the macrolactone **19**, bearing a *cis*-enamide moiety instead of the desired *trans*-isomer. The structure of **19** was confirmed by an X-ray crystal analysis. The possibility of internal hydrogen bonding between the hydrogen on the nitrogen atom and the lactone carbonyl group, which is prevented in the *trans*-isomer, might account for the preferential formation of the *cis*-enamide, as suggested by Reddy and co-workers[5e] for the parent compound (–)-palmyrolide A. Finally, N-methylation of macrolactone **19** using sodium hydride and iodomethane in tetrahydrofuran allowed us to complete the first total synthesis of a member of the laingolide family. Thus, the *cis*-isomer (*Z*)-**6** of laingolide A was obtained in 12 steps from commercially available cyclohexene oxide (**7**).

To synthesize our initially target, the *trans*-laingolide A isomer (*E*)-**6**, we decided to perform the macrocyclization step with a precursor bearing a secondary *N*-methyl amide to prevent intramolecular N–H–O hydrogen bonding in the resulting enamide. To this end, we prepared amide **20** from carboxylic acid **14** by treatment with HOBt, EDCI, and methylamine. After a Yamaguchi esterification with 3-(1,3-dioxolan-2-yl)propanoic acid (**16**), acidic hydrolysis of ketal **21** gave the required cyclization precursor **22** (Scheme 6).

Heating the amido aldehyde **22** in refluxing toluene in the presence of trifluoroacetic acid this time gave the *trans*-laingolide A isomer (*E*)-**6** as the major product, the structure and relative configuration of which were unambiguously confirmed by X-ray analysis.



Scheme 5 Total synthesis of the *cis*-isomer of laingolide A [(*Z*)-**6**]



Scheme 6 Total synthesis of the *trans*-isomer of laingolide A [(*E*)-**6**]

In conclusion, we have completed the first total synthesis of two diastereomers of laingolide A. This short synthesis relies on a tandem cross-dimerization/oxonia-Cope reaction and an intramolecular dehydrative cyclization, and proceeds in 11 or 12 steps and 6.72 and 3.2% overall yields, respectively. To establish the relative configuration of natural laingolide A, syntheses of the three remaining *trans*-diastereomers are currently in progress in our laboratories and will be reported in due course.

All air- and/or water-sensitive reactions were carried out under an atmosphere of argon. Reaction solvents were purified before use. THF and Et_2O were distilled from Na–benzophenone; CH_2Cl_2 was distilled from CaH_2. Reactions were monitored by TLC using precoated silica gel plates (Merck, ref. 5554 60 F254). The TLC plates were visualized by means of UV radiation (λ = 254 nm) or a *p*-anisaldehyde staining solution (Kagi–Mosher). NMR spectra were recorded on a Bruker AC 300 (^{1}H: 300 MHz, ^{13}C: 75 MHz) or an Avance 400 (^{1}H: 400 MHz, ^{13}C: 100 MHz) instrument. The chemical shifts are expressed in ppm referenced to residual $CHCl_3$ (7.26 ppm for ^{1}H and 77.16 for ^{13}C). IR spectra were recorded on a JACSO FTIR 4100 spectrometer. Melting points were determined on a Stuart Scientific SMP1 apparatus and are uncorrected. High-resolution mass spectra were obtained by using an LTQ-Orbitrap (Thermo Fisher Scientific) at Pierre et Marie Curie University.

Crystallographic data for compounds **15**, **19**, and **6** have been deposited with the accession numbers CCDC 1032052, 1032053, and 1032054, respectively, and can be obtained free of charge from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: +44(1223)336033; E-mail: deposit@ccdc.cam.ac.uk; Web site: www.ccdc.cam.ac.uk/conts/retrieving.html.

trans-2-Isopropenylcyclohexanol (8)[9b]

A 0.5 M solution of CH_2=C(Me)MgBr in THF (300 mL, 150 mmol, 1.1 equiv) was added to a slurry of CuBr·Me_2S (1.40 g, 6.82 mmol, 0.05 equiv) in THF (100 mL) at –50 °C, and the mixture was stirred for 10 min at –50 °C. Cyclohexene oxide (13.4 g, 136.4 mmol, 1 equiv) was added and the mixture was stirred for 3 h at r.t., poured into sat. aq NH_4Cl (100 mL), and extracted with Et_2O (4 × 50 mL). The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash chromatography [silica gel, PE–EtOAc (9:1)] to give a yellow oil; yield: 14.97 g (78%); R_f = 0.38 (cyclohexane–EtOAc, 7:3).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.89 (br s, 1 H), 4.85 (br s, 1 H), 3.42 (td, *J* = 10.1, 4.4 Hz, 1 H), 2.10–2.01 (m, 1 H), 1.99–1.84 (m, 2 H), 1.81–1.62 (m, 6 H), 1.38–1.11 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 146.8, 112.9, 70.8, 54.7, 34.2, 30.3, 25.8, 25.0, 19.3.

2-Isopropenylcyclohexanone (9)

PCC (39.7 g, 184.0 mmol, 2 equiv) was added to a solution of alcohol **8** (12.9 g, 92.0 mmol, 1 equiv) in CH_2Cl_2 (200 mL), and the mixture was stirred overnight at r.t. Silica gel (100 g) was then added slowly, followed by Et_2O (600 mL). The solids were removed by filtration and the filtrate was concentrated under vacuum. The residue was purified by flash chromatography [silica gel, PE–CH_2Cl_2 (1:1)] to give a yellow oil; yield: 10.25 g (81%); R_f = 0.21 (cyclohexane–CH_2Cl_2, 1:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.90 (d, *J* = 1.4 Hz, 1 H), 4.70 (s, 1 H), 2.98 (dd, *J* = 11.0, 4.7 Hz, 1 H), 2.46–2.21 (m, 2 H), 2.10–1.97 (m, 2 H), 1.97–1.80 (m, 2 H), 1.80–1.58 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 211.0, 143.5, 112.8, 58.5, 42.2, 32.2, 27.7, 24.9, 21.4.

(7*E*)- and (7*Z*)-10-*tert*-Butyl-8-methyl-3,4,5,6,9,10-hexahydro-2*H*-oxecin-2-one [(*E*)-10, and (*Z*)-10][8]

BF_3·OEt_2 (660 μL, 5.3 mmol, 0.2 equiv) was added dropwise to a solution of ketone **9** (3.7 g, 26.8 mmol, 1 equiv) and *t*-BuCHO (3.49 mL, 32.1 mmol, 1.2 equiv) in DCE (50 mL) at –20 °C. The mixture was stirred for 2.5 h at –20 °C, the reaction was quenched with sat. aq $NaHCO_3$ (30 mL), and the mixture was extracted with EtOAc (3 × 15 mL). The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash chromatog-

raphy [silica gel, PE–CH_2Cl_2 (6:4)] to give a mixture of two diastereomers as a pale-yellow oil; yield: 5.46 g (91%; *E*/*Z* = 82:18). For analytical purposes, a sample of this mixture was separated by flash chromatography [silica gel, PE–CH_2Cl_2 (6:4)] to give pure (*E*)-**10** and (*Z*)-**10**.

(*E*)-10

R_f = 0.47 (cyclohexane–CH_2Cl_2, 1:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.02–4.98 (m, 1 H), 4.78 (dd, *J* = 10.9, 3.2 Hz, 1 H), 2.47 (ddd, *J* = 10.9, 9.1, 1.8 Hz, 1 H), 2.17–1.91 (m, 5 H), 1.92–1.78 (m, 2 H), 1.78–1.61 (m, 1 H), 1.57 (s, 3 H), 1.46–1.27 (m, 1 H), 0.94 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.2, 133.5, 130.1, 81.2, 41.2, 36.1, 33.5, 30.2, 28.7, 26.4, 25.6, 17.2.

(*Z*)-10

R_f = 0.34 (cyclohexane–CH_2Cl_2, 1:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.12 (d, *J* = 11.6 Hz, 1 H), 4.76 (dd, *J* = 11.7, 2.0 Hz, 1 H), 2.54 (t, *J* = 12.6 Hz, 1 H), 2.43–2.17 (m, 3 H), 2.08–1.95 (m, 1 H), 1.91–1.57 (m, 7 H), 1.57–1.37 (m, 1 H), 0.96 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.8, 132.4, 129.1, 79.4, 35.5, 33.8, 32.2, 29.0, 27.3, 26.2, 24.8, 24.6.

10-(*tert*-Butyl)-8-methyloxecan-2-one (11)

A solution of the 82:18 *E*/*Z* mixture of lactone **10** (10.8 g, 48.1 mmol, 1 equiv) in EtOH (1 L) was treated with 10% Pd/C (2.0 g, 1.9 mmol, 0.04 equiv). The argon atmosphere was replaced with H_2 and the mixture was stirred at r.t. under H_2 (balloon) for 48 h. The suspension was then filtered through a Celite pad that was washed with CH_2Cl_2 (200 mL). The filtrate was concentrated under reduced pressure, and the residue was purified by flash chromatography [silica gel, PE–CH_2Cl_2 (7:3)] to give a yellow oil; yield: 9.89 g (91%); R_f = 0.42 (cyclohexane–CH_2Cl_2, 1:1).

IR (neat): 2954, 2870, 1726, 1468, 1366, 1263, 1082, 969, 640 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.71 (dd, *J* = 7.6, 2.5 Hz, 1 H), 2.33–2.23 (m, 2 H), 2.01–1.60 (m, 5 H), 1.60–1.39 (m, 3 H), 1.39–1.18 (m, 2 H), 1.18–0.70 (m, 1 H), 0.91 (s, 9 H), 0.89 (d, *J* = 7.0 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.9, 78.6, 35.1, 34.8, 32.0, 31.3, 29.4, 27.3, 26.3, 23.3, 22.6, 21.5.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{26}O_2$ + Na: 249.1825; found: 249.1827.

10-(*tert*-Butyl)-3,8-dimethyloxecan-2-one (12)

A 2.4 M solution of BuLi in hexanes (40.0 mL, 96.0 mmol, 2 equiv) and HMPA (20.1 mL, 109.7 mmol, 2.3 equiv) were successively added to a solution of *i*-Pr_2NH (14.8 mL, 105.0 mmol, 2.2 equiv) in THF (30 mL) at –50 °C. The mixture was stirred for 20 min at –50 °C and then a solution of lactone **11** (10.8 g, 47.7 mmol, 1 equiv) in THF (40 mL) was added. The mixture was stirred for 30 min at –20 °C then added through a cannula to a solution of MeI (8.9 mL, 143.1 mmol, 3 equiv) in THF (30 mL) at r.t. The resulting solution was stirred for 2.5 h, mixed with sat. aq NH_4Cl (100 mL), and extracted with Et_2O (3 × 30 mL). The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated under vacuum. The residue was purified by flash chromatography [silica gel, PE–CH_2Cl_2 (7:3)] to give a single diastereomer as a colorless oil; yield: 10.8 g (94%); R_f = 0.42 (cyclohexane–CH_2Cl_2, 1:1).

IR (neat): 2956, 2871, 1725, 1466, 1365, 1267, 1074, 964 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.73 (dd, *J* = 6.7, 3.3 Hz, 1 H), 2.49–2.38 (m, 1 H), 1.98–1.31 (m, 10 H), 1.16 (d, *J* = 7.1 Hz, 3 H), 1.09–0.70 (m, 1 H), 0.91 (s, 9 H), 0.85 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 177.0, 78.4, 41.9, 35.0, 31.9, 31.5, 31.4, 29.2, 26.6, 25.4, 22.1, 21.2, 17.8.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{28}O_2$ + Na: 263.1981; found: 263.1985.

2,7,10,10-Tetramethylundecane-1,9-diol (13)

$LiAlH_4$ (496 mg, 13.1 mmol, 2 equiv) was added in portions to solution of lactone **12** (1.57 g, 6.5 mmol, 1 equiv) in Et_2O (80 mL) at 0 °C. The mixture was stirred at r.t. for 2 h and then H_2O (30 mL) was carefully added. The mixture was filtered and the filtrate was extracted with Et_2O (3 × 15 mL). The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated under vacuum. The residue was purified by flash chromatography [silica gel, PE–EtOAc (7:3)] to give a colorless oil; yield: 1.59 g (99%); R_f = 0.48 (cyclohexane–EtOAc 1:1).

IR (neat): 3293, 2927, 2865, 1464, 1362, 1076, 1029, 989, 902, 644 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.44 (dd, *J* = 10.5, 6.0 Hz, 1 H), 3.35 (dd, *J* = 10.5, 6.5 Hz, 1 H), 3.24 (d, *J* = 10.0 Hz, 1 H), 2.21 (br s, 1 H), 1.72 (br s, 1 H), 1.66–1.49 (m, 2 H), 1.49–0.94 (m, 10 H), 0.94–0.68 (m, 6 H), 0.84 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 77.6, 68.2, 39.4, 35.8, 35.5, 35.0, 33.1, 29.9, 27.2, 27.1, 25.8, 21.1, 16.6.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{32}O_2$ + Na: 267.2294; found: 267.2299.

9-Hydroxy-2,7,10,10-tetramethylundecanoic Acid (14)

TEMPO (1.18 g, 7.59 mmol, 0.2 equiv) and $PhI(OAc)_2$ (30.5 g, 94.8 mmol, 2.5 equiv) were added to a solution of diol **13** (9.27 g, 37.9 mmol, 1 equiv) in 2:1 CH_2Cl_2/H_2O (180 mL). The mixture was stirred at r.t. for 22 h then poured into sat. aq $Na_2S_2O_3$ (60 mL) and extracted with EtOAc (3 × 40 mL). The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated under vacuum. The residue was purified by flash chromatography [silica gel, PE–EtOAc (7:3)] to give a yellow oil; yield: 9.57 g (98%); R_f = 0.22 (cyclohexane–EtOAc, 1:1).

IR (neat): 3438, 2933, 2867, 1707, 1464, 1366, 1223, 1072, 982, 642 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.28 (dd, *J* = 10.2, 1.7 Hz, 1 H), 2.45 (sextet, *J* = 6.9 Hz, 1 H), 1.75–0.69 (m, 12 H), 1.16 (d, *J* = 6.9 Hz, 3 H), 0.91 (d, *J* = 6.7 Hz, 3 H), 0.88 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 182.9, 77.9, 39.5, 39.3, 35.4, 35.0, 33.7, 30.0, 27.6, 26.8, 25.8, 21.1, 16.9.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{30}O_3$ + Na: 281.2087; found: 281.2089.

9-Hydroxy-2,7,10,10-tetramethylundecanamide (15)

EDCI (18.8 mg, 0.098 mmol, 1.2 equiv) and 1*H*-1,2,3-benzotriazol-1-ol hydrate (13.3 mg, 0.098 mmol, 1.2 equiv) were added to a solution of acid **14** (21 mg, 0.081 mmol, 1 equiv) in MeCN (1 mL). The mixture was stirred overnight at r.t., and then 20% aq NH_3 (400 µL, 4.35 mmol) was added. The mixture was stirred for 40 min at r.t., poured into H_2O (10 mL), and extracted with EtOAc (3 × 5 mL). The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated under vacuum. The residue was purified by flash chromatography [silica gel, EtOAc–PE (8:2)] to give a white solid; yield: 20 mg (96%); mp 95–96 °C; R_f = 0.23 (EtOAc–cyclohexane, 9:1).

IR (neat): 3458, 2964, 2947, 2932, 2858, 1665, 1614, 1464, 1289, 1172, 1073, 1006, 975, 731, 651 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 5.92 (br s, 1 H), 5.61 (br s, 1 H), 3.25 (d, *J* = 10.0 Hz, 1 H), 2.24 (sextet, *J* = 6.7 Hz, 1 H), 1.71–1.48 (m, 3 H), 1.47–0.90 (m, 9 H), 1.12 (d, *J* = 6.9 Hz, 3 H), 0.89 (d, *J* = 6.7 Hz, 3 H), 0.86 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 179.6, 77.6, 41.0, 39.4, 35.4, 35.0, 34.3, 29.9, 27.8, 26.9, 25.8, 21.1, 17.9.

HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{15}H_{31}NO_2$ + Na: 280.2247; found: 280.2247.

9-Amino-1-*tert*-butyl-3,8-dimethyl-9-oxononyl 3-(1,3-Dioxolan-2-yl)propanoate (17)

DIPEA (145 µL, 0.83 mmol, 1.7 equiv) and 2,4,6-trichlorobenzoyl chloride (153 µL, 0.98 mmol, 2 equiv) were added to a mixture of amide **15** (126 mg, 0.49 mmol, 1 equiv), DMAP (150 mg, 1.23 mmol, 2.5 equiv), and carboxylic acid **16** (100 mg, 0.68 mmol, 1.4 equiv) in toluene (2.7 mL). The mixture was stirred overnight at r.t., the reaction was quenched with H_2O (10 mL), and the mixture was extracted with EtOAc (3 × 5 mL). The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated under vacuum. The residue was purified by flash chromatography [silica gel, EtOAc–PE (7:3)] to give a colorless oil; yield: 165 mg (87%); R_f = 0.25 (EtOAc–cyclohexane, 9:1).

IR (neat): 3360, 2964, 2361, 1727, 1666, 1466, 1368, 1262, 1170, 1137, 1070, 980, 905 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 5.79 (br s, 2 H), 4.90 (t, *J* = 4.3 Hz, 1 H), 4.80 (m, 1 H), 3.96–3.80 (m, 4 H), 2.42 (t, *J* = 7.4 Hz, 2 H), 2.21 (sextet, *J* = 6.8 Hz, 1 H), 2.03–1.89 (m, 2 H), 1.63–0.88 (m, 11 H), 1.11 (d, *J* = 6.9 Hz, 3 H), 0.83 (s, 9 H), 0.82 (d, *J* = 6.9 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 179.7, 173.2, 103.3, 78.9, 65.1, 40.8, 37.2, 35.0, 34.7, 34.1, 29.2, 29.1, 28.7, 27.4, 26.4, 26.0, 20.9, 17.8.

(4*Z*)-15-*tert*-Butyl-8,13-dimethyl-1-oxa-6-azacyclopentadec-4-ene-2,7-dione (19)

A solution of amino ester **17** (525 mg, 1.36 mmol, 1 equiv) in THF (20 mL) was treated with 10% aq HCl (20 mL, 57 mmol), and the mixture was stirred for 21 h at r.t. Sat. aq $NaHCO_3$ (100 mL) was slowly added and then the mixture was extracted with Et_2O (3 × 30 mL). The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated under vacuum to give aldehyde **18** as a yellow oil; yield: 340 mg (73%).

A solution of the crude aldehyde **18** (200 mg, 0.59 mmol, 1 equiv) in toluene (80 mL) containing 4 Å MS (1.2 g) was treated with TFA (227 µL, 2.95 mmol, 5 equiv), and the mixture was stirred at the reflux for 1 h. It was then cooled to r.t., filtered, and poured into sat. aq $NaHCO_3$ (30 mL) and extracted with EtOAc (3 × 15 mL). The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated under vacuum. The residue was purified by flash chromatography [silica gel, PE–EtOAc (9:1)] to give white solid **19**; yield: 70 mg (36%); mp 85–86 °C; R_f = 0.38 (cyclohexane–EtOAc, 8:2).

IR (neat): 3371, 2963, 2931, 2357, 1690, 1660, 1501, 1460, 1371, 1298, 1279, 1252, 1196, 1075, 1041, 975, 957, 937, 815, 791, 762 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.36 (br d, *J* = 10.8 Hz, 1 H), 6.92 (ddd, *J* = 8.9, 2.4, 2.3 Hz, 1 H), 4.93 (dd, *J* = 10.4, 0.8 Hz, 1 H), 4.75 (td, *J* = 9.2, 5.0 Hz, 1 H), 3.08 (ddd, *J* = 13.7, 5.0, 2.5 Hz, 1 H), 2.99 (dd, *J* = 13.7, 9.5 Hz, 1 H), 2.55 (sextet, *J* = 6.5 Hz, 1 H), 1.91–1.71 (m, 2 H), 1.40–0.98 (m, 9 H), 1.12 (d, *J* = 6.9 Hz, 3 H), 0.87 (s, 9 H), 0.77 (d, *J* = 6.3 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.0, 173.2, 126.3, 98.1, 79.5, 39.9, 38.8, 34.4, 33.1, 32.7, 32.2, 26.3, 26.0, 25.2, 22.3, 20.9, 15.4.

HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{19}H_{33}NO_3$ + Na: 346.2352; found: 346.2347.

(4*Z*)-15-*tert*-Butyl-6,8,13-trimethyl-1-oxa-6-azacyclopentadec-4-ene-2,7-dione [(*Z*)-6]

A 60% dispersion of NaH in mineral oil (3.4 mg, 0.085 mmol, 1.1 equiv) and MeI (7 µL, 0.105 mmol, 1.5 equiv) were added successively to a solution of dione **19** (25 mg, 0.077 mmol, 1 equiv) in THF (1 mL) at 0 °C. The mixture was stirred at r.t. for 2 h, the reaction was quenched with H_2O (5 mL), and the mixture was extracted with EtOAc (3 × 5 mL). The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated under vacuum. The residue was purified by flash chromatography [silica gel, cyclohexane–EtOAc (8:2)] to give an oil; yield: 8 mg (31%); R_f = 0.18 (cyclohexane–EtOAc, 8:2).

^1H NMR (300 MHz, $CDCl_3$): δ = 6.46 (dd, *J* = 7.7, 1.8 Hz, 1 H), 5.67 (ddd, *J* = 7.7, 3.4, 0.6 Hz, 1 H), 4.96 (dd, *J* = 12.3, 3.1 Hz, 1 H), 3.30 (dd, *J* = 12.2, 6.7 Hz, 1 H), 3.06 (s, 3 H), 2.97 (ddd, *J* = 18.6, 3.4, 2.2 Hz, 1 H), 2.80 (ddd, *J* = 18.6, 5.6, 3.4 Hz, 1 H), 1.73–1.11 (m, 11 H), 1.06 (d, *J* = 6.7 Hz, 3 H), 0.88 (s, 9 H), 0.83 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 177.5, 170.5, 132.6, 122.6, 78.1, 38.3, 36.7, 36.5, 36.3, 34.8, 33.5, 31.3 29.8, 27.2, 26.3, 26.2, 20.9, 18.2.

HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{20}H_{35}NO_3$ + Na: 360.2509; found: 360.2503.

9-Hydroxy-*N*,2,7,10,10-pentamethylundecanamide (20)

A solution of **14** (4.15 g, 16.1 mmol, 1 equiv) in MeCN (40 mL) was treated with EDCI (3.70 g, 19.3 mmol, 1.2 equiv) and 1*H*-1,2,3-benzotriazol-1-ol (2.6 g, 19.3 mmol, 1.2 equiv). The mixture was stirred for 3 h at r.t., and then a solution of 2 M solution of $MeNH_2$ in MeOH (40 mL, 80 mmol, 5 equiv) was added. The mixture was stirred for a further 40 min at r.t., then poured into H_2O (40 mL) and extracted with EtOAc (3 × 20 mL). The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated under vacuum. The residue was purified by flash chromatography [silica gel, EtOAc–PE (8:2)] to give a pale-yellow amorphous solid; yield: 3.70 g (85%); mp 80–81 °C; R_f = 0.30 (EtOAc–cyclohexane, 9:1).

IR (neat): 3299, 2931, 2868, 1650, 1555, 1462, 1410, 1366, 1246, 1074 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 5.65 (br s, 1 H), 3.25 (dd, *J* = 10.2, 1.7 Hz, 1 H), 2.78 (d, *J* = 4.8 Hz, 3 H), 2.14 (sextet, *J* = 6.9 Hz, 1 H), 1.72–1.49 (m, 3 H), 1.49–1.05 (m, 8 H), 1.10 (d, *J* = 6.9 Hz, 3 H), 1.05–0.68 (m, 1 H), 0.89 (d, *J* = 6.7 Hz, 3 H), 0.86 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 177.4, 77.6, 41.7, 39.4, 35.4, 35.0, 34.5, 29.9 27.9, 26.9, 26.3, 25.8, 21.1, 18.0.

HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{16}H_{33}NO_2$ + Na: 294.2403; found: 294.2402.

1-*tert*-Butyl-3,8-dimethyl-9-(methylamino)-9-oxononyl 3-(1,3-Dioxolan-2-yl)propanoate (21)

A mixture of amide **20** (3.23 g, 11.9 mmol, 1 equiv), DMAP (3.63 g, 29.7 mmol, 2.5 equiv), and carboxylic acid **16** (2.44 g, 16.7 mmol, 1.4 equiv) in toluene (60 mL) was treated with DIPEA (3.52 mL, 20.2 mmol, 1.7 equiv) and 2,4,6-trichlorobenzoyl chloride (3.72 mL, 23.8 mmol, 2 equiv). The mixture was stirred for 4 h at r.t., the reaction was quenched with H_2O (40 mL), and the mixture was extracted with EtOAc (3 × 20 mL). The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated under vacuum. The residue was purified by flash chromatography [silica gel, EtOAc–PE (8:2)] to give a colorless oil; yield: 3.47 g (73%); R_f = 0.32 (EtOAc–cyclohexane, 9:1).

IR (neat): 3301, 2959, 2933, 2875, 1730, 1648, 1550, 1367, 1251, 1169, 1137, 1071, 1039 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 5.79 (br s, 1 H), 4.92 (t, *J* = 4.3 Hz, 1 H), 4.85–4.75 (m, 1 H), 4.00–3.76 (m, 4 H), 2.77 (d, *J* = 4.8 Hz, 3 H), 2.49–2.35 (m, 2 H), 2.15 (sextet, *J* = 6.8 Hz, 1 H), 2.06–1.91 (m, 2 H), 1.69–1.49 (m, 1 H), 1.49–1.05 (m, 9 H), 1.09 (d, *J* = 6.9 Hz, 3 H), 1.05–0.90 (m, 1 H), 0.84 (s, 9 H), 0.90–0.75 (m, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 177.5, 173.2, 103.3, 78.9, 65.1, 41.5, 37.2, 35.0, 34.8, 34.2, 29.3, 29.1, 28.7, 27.5, 26.28, 26.27, 26.0, 20.9, 17.9.

HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{22}H_{41}NO_5$ + Na: 422.2877; found: 422.2879.

1-*tert*-Butyl-3,8-dimethyl-9-(methylamino)-9-oxononyl 4-Oxobutanoate (22)

A solution of ester **21** (1.89 g, 4.75 mmol, 1 equiv) in THF (50 mL) was treated with 20% aq HCl (50 mL), and the mixture was stirred for 5 h at r.t. Sat. aq $NaHCO_3$ (400 mL) was added slowly and the mixture was extracted with Et_2O (3 × 100 mL). The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated under vacuum. The residue was purified by flash chromatography [silica gel, EtOAc–PE (8:2)] to give a colorless oil; yield: 1.58 g (94%); R_f = 0.32 (EtOAc–cyclohexane, 9:1).

IR (neat): 3314, 2961, 2932, 2872, 1728, 1648, 1549, 1463, 1370, 1235, 1174, 1073, 963, 648 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 9.82 (s, 1 H), 5.69 (br s, 1 H), 4.86–4.75 (m, 1 H), 2.79 (d, *J* = 4.8 Hz, 3 H), 2.82–2.73 (m, 2 H), 2.67–2.57 (m, 2 H), 2.15 (sextet, *J* = 6.8 Hz, 1 H), 1.67–1.50 (m, 1 H), 1.50–1.04 (m, 9 H), 1.11 (d, *J* = 6.8 Hz, 3 H), 1.04–0.75 (m, 4 H), 0.86 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 200.4, 177.5, 172.3, 79.5, 41.6, 38.7, 37.2, 35.0, 34.8, 34.3, 29.4, 27.6, 26.9, 26.4, 26.3, 26.0, 20.9, 18.0.

HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{20}H_{37}NO_4$ + Na: 378.2615; found: 378.2616.

***(4E)*-15-*tert*-Butyl-6,8,13-trimethyl-1-oxa-6-azacyclopentadec-4-ene-2,7-dione [(*E*)-6]**

A solution of amino ester **22** (200 mg, 0.562 mmol, 1 equiv) in toluene (120 mL) containing 4 Å MS (1.2 g) was treated with TFA (217 µL, 2.81 mmol, 5 equiv), and the mixture was stirred at the reflux with a Dean–Stark apparatus for 3 d. The mixture was then cooled to r.t., filtered, poured into sat. aq $NaHCO_3$ (50 mL), and extracted with EtOAc (3 × 20 mL). The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated under vacuum. The residue was purified by flash chromatography [silica gel, PE–EtOAc (9:1)] to give (*E*)-**6** as a white solid [yield: 45 mg (24%)], together with (*Z*)-**6** as an oil [yield: 21 mg (11%)].

(*E*)-6

Mp 94–95 °C; R_f = 0.39 (cyclohexane–EtOAc, 7:3).

IR (neat): 2956, 2930, 2857, 1713, 1674, 1640, 1462, 1259, 1154, 1095, 959, 804, 649, 641 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.08 (d, *J* = 14.0 Hz, 1 H), 5.09 (dt, *J* = 14.1, 7.2 Hz, 1 H), 4.90 (dd, *J* = 12.0, 1.6 Hz, 1 H), 3.07 (s, 3 H), 3.04–2.96 (m, 2 H), 2.91 (sextet, *J* = 6.5 Hz, 1 H), 1.68–0.91 (m, 11 H), 1.13 (d, *J* = 6.6 Hz, 3 H), 0.86 (s, 9 H), 0.76 (d, *J* = 6.2 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.9, 171.6, 133.2, 103.1, 78.0, 38.0, 36.8, 35.1, 34.8, 34.7, 33.5, 30.9, 26.2, 26.1, 26.0, 25.5, 20.3, 17.4.

HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{20}H_{35}NO_3$ + Na: 360.2509; found: 360.2512.

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Supporting Information

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(11) To ascertain that no enrichment in *trans*-**11** at the expense of the *cis*-isomer occurred during the purification process, a sample of pure (*Z*)-**10** was subjected to the hydrogenation reaction and the *trans*-isomer was obtained exclusively.

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