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Progress toward the total synthesis of mirabalin isomers

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Dedicated to Prof. Stephen Hanessian for his outstanding contributions to the field of organic chemistry

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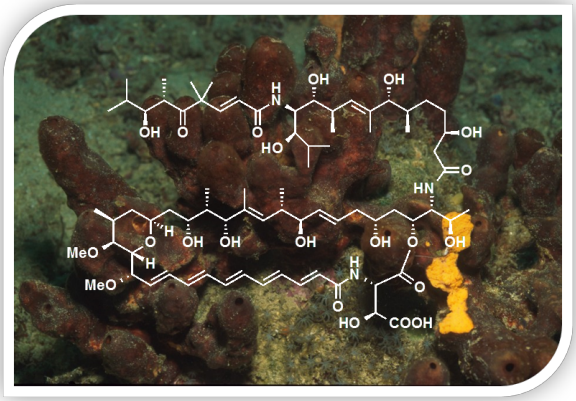
Abstract

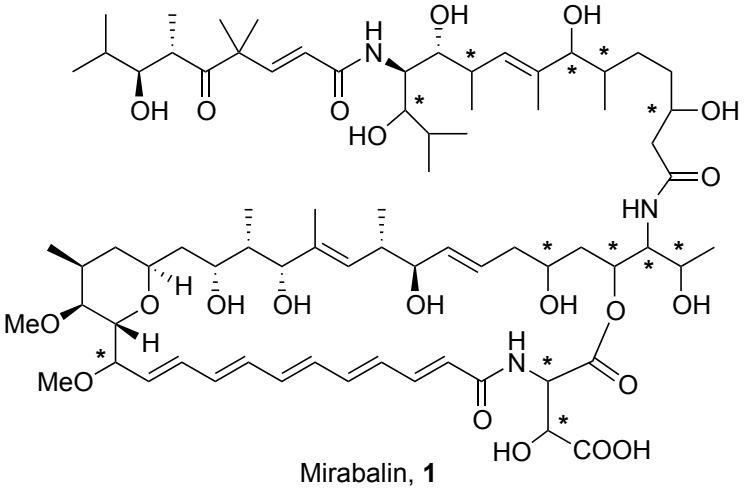
Key fragments of the cytotoxic marine macrolide mirabalin have been synthesized, by using a flexible strategy based on asymmetric reductions to control the hydroxy- and carbamate-bearing stereocenters. In particular, ruthenium or rhodium-mediated asymmetric hydrogenation and transfer hydrogenation were used in combination with a dynamic kinetic resolution to control two contiguous stereocenters in a single step.



Keywords: Marine macrolides, asymmetric hydrogenation, asymmetric transfer hydrogenation, enantioselectivity, diastereoselectivity

Introduction

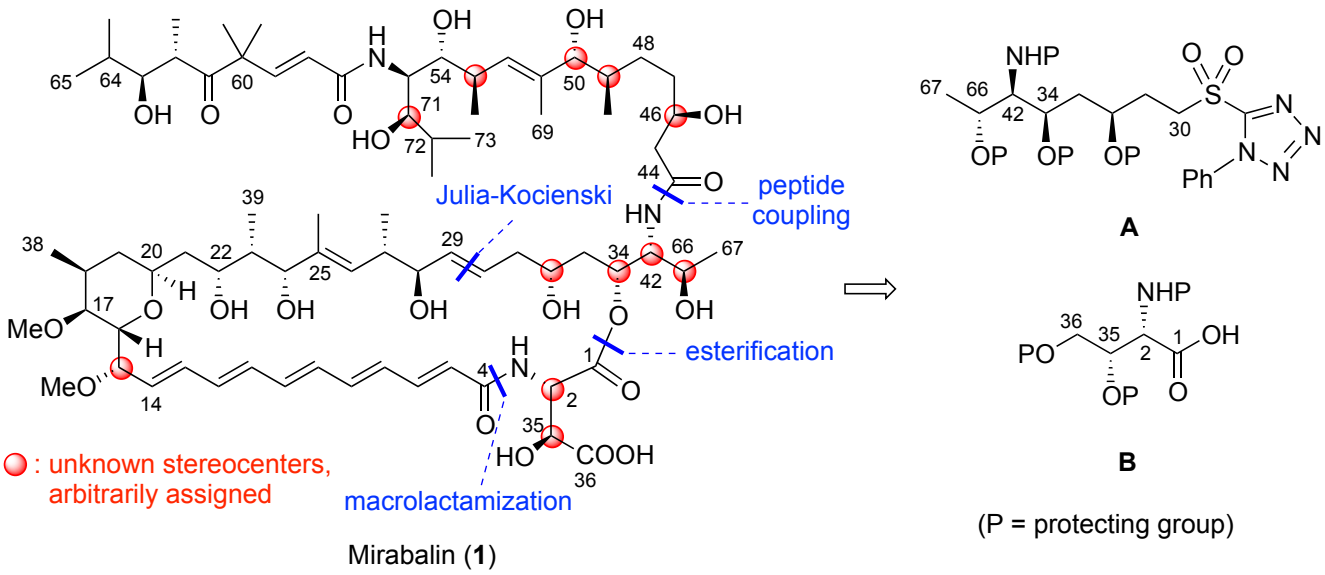
Lithistid demosponges are an assemblage of sponges predominantly found in deeper waters.[1,2] They are regarded as an excellent source of structurally diverse and bioactive secondary metabolites.[3-5] In particular, numerous novel macrolides have been isolated from the *Theonellidae* family exhibiting excellent biological activities.[6-7] Among them, mirabalin, a macrocycle, has been extracted from *Siliquariaspongia mirabilis*, a lithistid demosponge collected from the archipelago of Chuuk, Micronesia (Figure 1).[8,9] This macrocycle exhibits potent cytotoxicity toward human colon tumor cell line HCT-116 with an IC_{50} of 0.27 μM. Morever, it has been found that the macrocycle ring is crucial to mirabalin antitumor activity. Indeed, no inhibition of the tumor cells growth was observed when treated with the linear polyketide side-chain. From a structural point of view, mirabalin exhibits a 35-membered macrocyclic lactam-lactone possessing a fully conjugated pentaene system along with a tetrasubstituted tetrahydropyran ring. In addition, a linear polyketide side-chain is linked to the macrocyclic ring with an amide linkage. An investigation combining advanced NMR and MS techniques allowed the partial elucidation of the structure of mirabalin. Undeniably, because of the large number of stereocenters and the low amount of material available, the absolute configurations of 12 out of the 25 stereocenters could not be assigned. Nevertheless, the geometry for each of the double bonds was established unambiguously (Figure 1).



Mirabalin, **1**

Figure 1. Picture of *Siliquariaspongia mirabilis* and the structure of mirabalin (**1**)[9].

As part of our ongoing studies on the total synthesis of natural products,[10-17] and intrigued by the structural intricacy of this macrolide, we embarked on a study aiming at developing a flexible, convergent and modular route to one isomer of mirabalin where the configurations of the twelve unknown stereocenters were arbitrarily fixed (Scheme 1). Recently, we reported a synthetic strategy toward the C44−C65 polyketide side chain[18] and toward the C14−C29 fragment of mirabalin,[19] as well as a straightforward method to construct the pentaene moiety C4-C14.[20] Scheme 1 shows the mirabalin global retrosynthetic plan with late stage esterification, peptide coupling and C=C bond formation to access the macrocycle by macro-lactamization, suggesting **A** and **B** as suitable key intermediates for the sake of convergence.



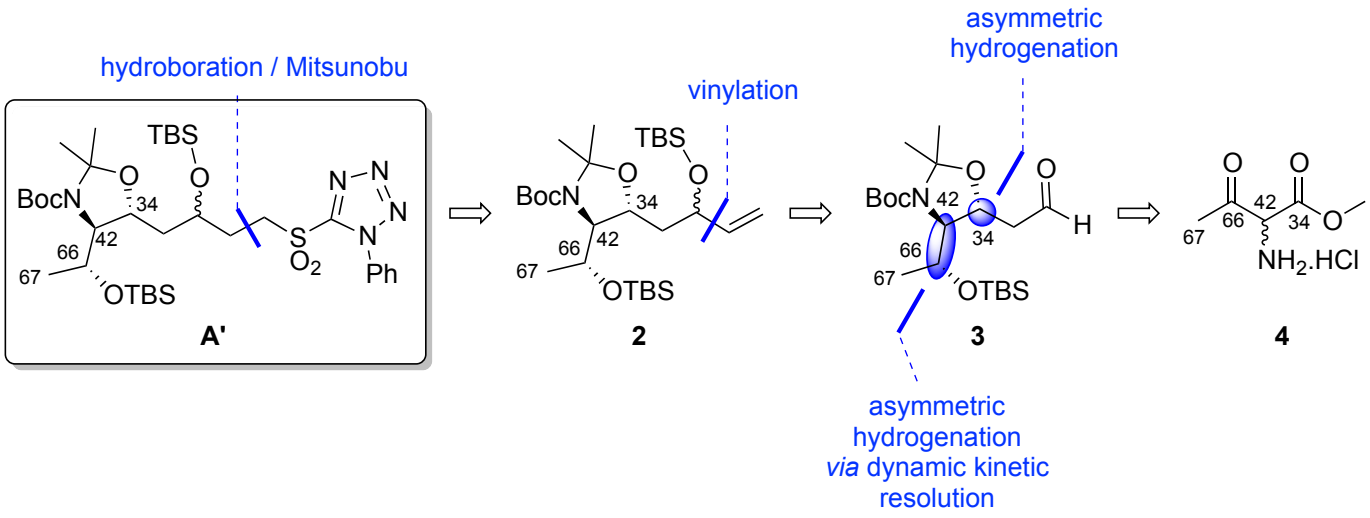
Scheme 1. Global retrosynthetic plan for mirabalin (**1**)

Herein, we report a flexible synthesis of fragments **A** and **B** but also details about the synthesis of isomers of the C44−C65 side chain of mirabalin.

Results and Discussion

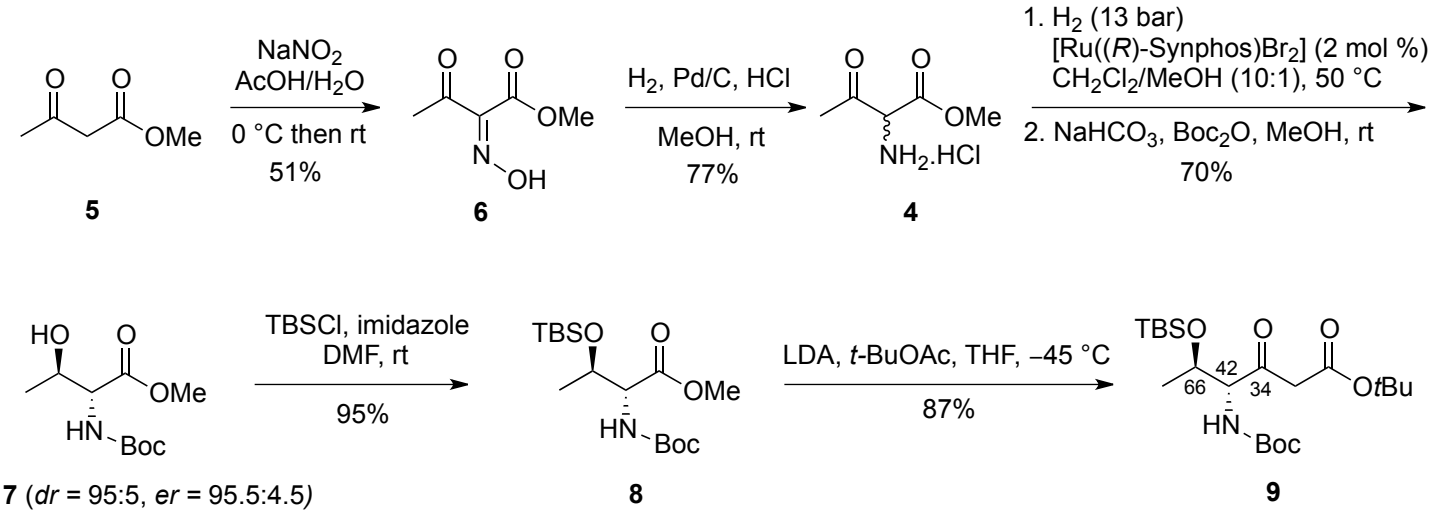
Synthesis of fragment A

Our retrosynthetic analysis was based on known methods for the introduction of the phenyltetrazolyl sulfone moiety by a hydroboration/Mitsunobu/oxidation sequence applied to alkene **2**. We therefore envisaged that the aldehyde **3** represented a useful intermediate in the synthesis of the unsaturated compound **2**, and aldehyde **3** could be obtained from α-amino β-ketoester **4** after asymmetric hydrogenation[21-23] *via* a dynamic kinetic resolution,[24-26] Claisen condensation and asymmetric hydrogenation (Scheme 3).[27-29]



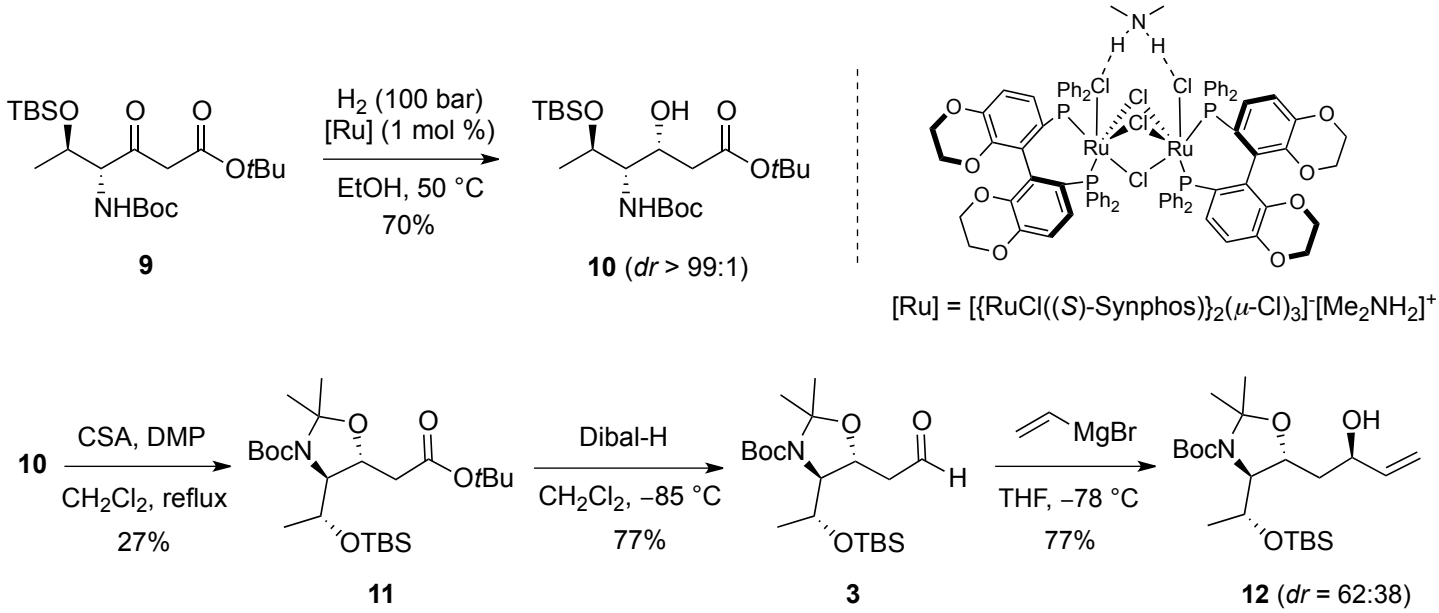
Scheme 2. Retrosynthetic analysis of fragment **A** (compound **A'**).

Our synthesis began with the preparation of the hydrochloride ammonium salt **4** in two steps from methyl acetoacetate **5** after nitrosation followed by hydrogenolysis of the oxime **6** under acidic conditions. To control the *anti* configuration at C66 and C42, a ruthenium-catalyzed asymmetric hydrogenation through dynamic kinetic resolution of the racemic α-amino β-keto ester hydrochloride **4** was envisaged. Using this method, the corresponding *anti*-aminoalcohol was successfully prepared with 90% diastereomeric excess and 91% enantiomeric excess. The reaction was performed in CH_2Cl_2/MeOH (10:1) at 50 °C under 13 bar of H_2 using 2 mol% of the *in situ* prepared [Ru((*R*)-Synphos)]Br_2] catalyst[30] (Scheme 3). Protection of the amino group as a carbamate and conversion of the hydroxy function into a TBS ether delivered compound **8**. The ensuing fully protected amino hydroxy ester **8** was then submitted to a Claisen condensation with *tert*-butyl acetate under basic conditions to deliver β-keto ester **9** in 87% yield (Scheme 3).



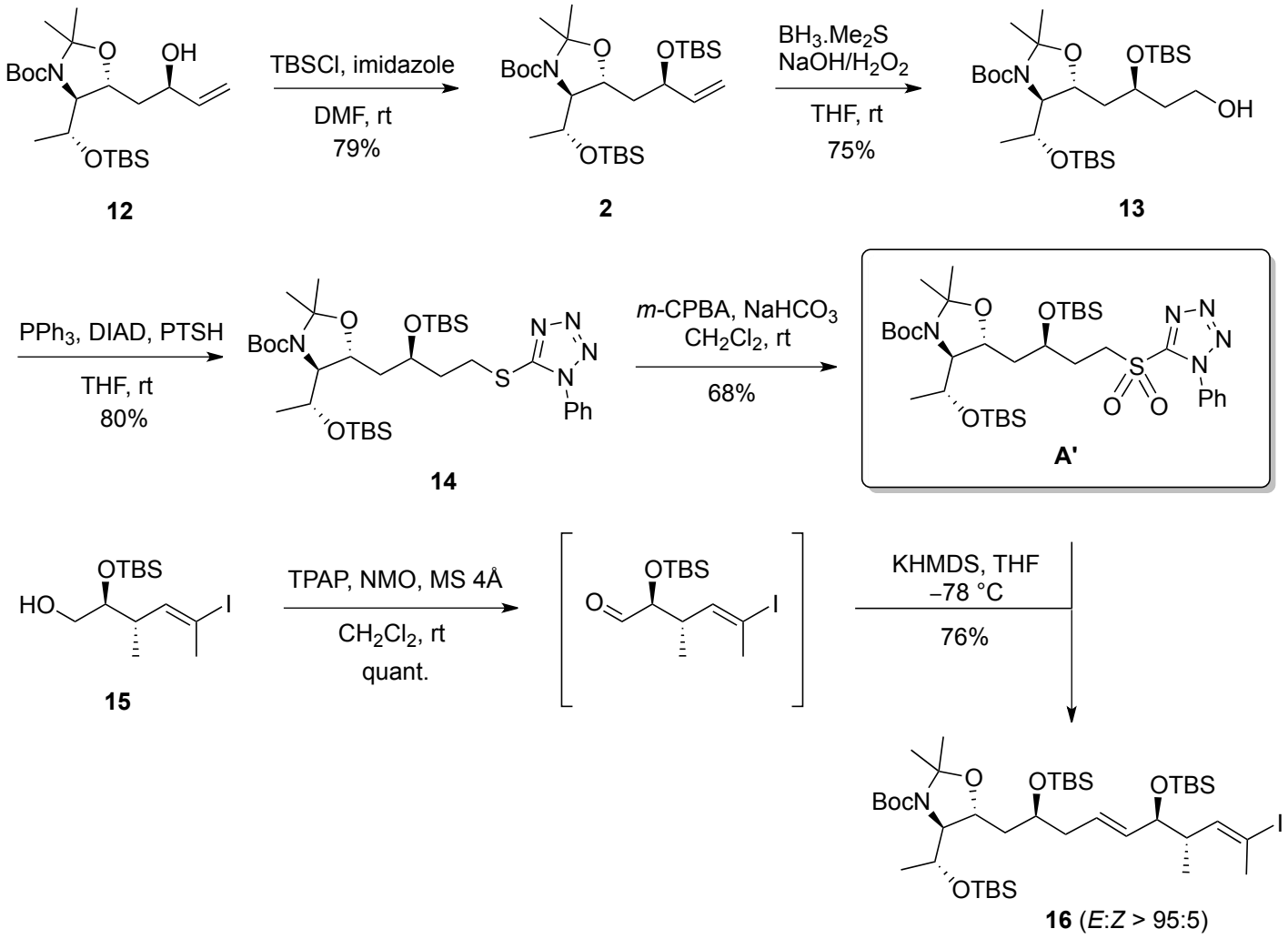
Scheme 3. Preparation of β-keto ester **9.**

We then turned our attention to the asymmetric hydrogenation of ketone **9** (Scheme 4). Different conditions varying catalyst loading and hydrogen pressure were screened using the binuclear complex [{RuCl((*S*)-Synphos)}$_2$(μ-Cl)$_3$][Me_2NH_2][30] in EtOH at 50 °C. No influence of the catalyst loading was observed on the stereochemical outcome of the reaction. However, changing the hydrogen pressure from 70 to 100 bar afforded a better result in terms of diastereoselectivity (*dr* switching from 74:26 to >99:1). With these optimized conditions in hand, the synthesis was pursued with the protection of aminoalcohol **10** to the oxazolidine **11**. It was found that the starting material **10** was not fully converted during the reaction and the acidic conditions led to the cleavage of the TBS group on both compounds **10** and **11**. The yield was modest and variable despite several experimentations. Nevertheless, compound **11** was converted to aldehyde **3** with Dibal-H in 77% yield. Addition of vinylmagnesium bromide to aldehyde **3** at low temperature provided the desired allylic alcohol **12** in 77% yield with a diastereoselectivity of 62:38. The two stereoisomers were separated by flash column chromatography and the synthesis of compound **A'** was carried out with the major diastereomer, the absolute configuration of which was determined by Mosher analysis (Scheme 4).[31]



Scheme 4. Preparation of alcohol **12.**

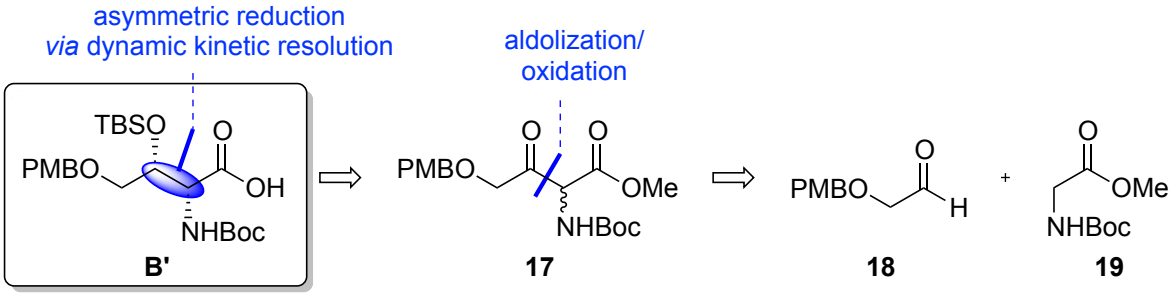
After protection of alcohol **12** (TBSCl, imid, DMF, rt), hydroboration/oxidation of the obtained compound **2** furnished the desired product **13** in 75% yield. Formation of thioether **14** was accomplished using a Mitsunobu reaction[32,33] applied to alcohol **13** (1-phenyl-1*H*-tetrazole-5-thiol, DIAD, PPh_3, THF, rt) and the thioether **14** was converted to the corresponding sulfone in 68% yield by oxidation with *m*-CPBA (Scheme 5). Thus, compound **A'** was obtained in 14 steps in 1.1% overall yield from methyl acetoacetate **5** and three contiguous stereocenters were controlled using asymmetric hydrogenation. To appreciate the feasibility of our envisaged retrosynthetic plan, we performed a Julia-Kocienski olefination[34] between compound **A'** and the aldehyde generated from alcohol **15**[35] (corresponding to the C25-C28 fragment of the macrocycle, Scheme 1). Pleasingly, the desired *E*-alkene was obtained in 76% yield with tight control of the double bond geometry (*E*/*Z* > 95:5) (Scheme 5).



Scheme 5. Synthesis of compound **A'** and subsequent Julia-Kocienski olefination.

Synthesis of fragment B

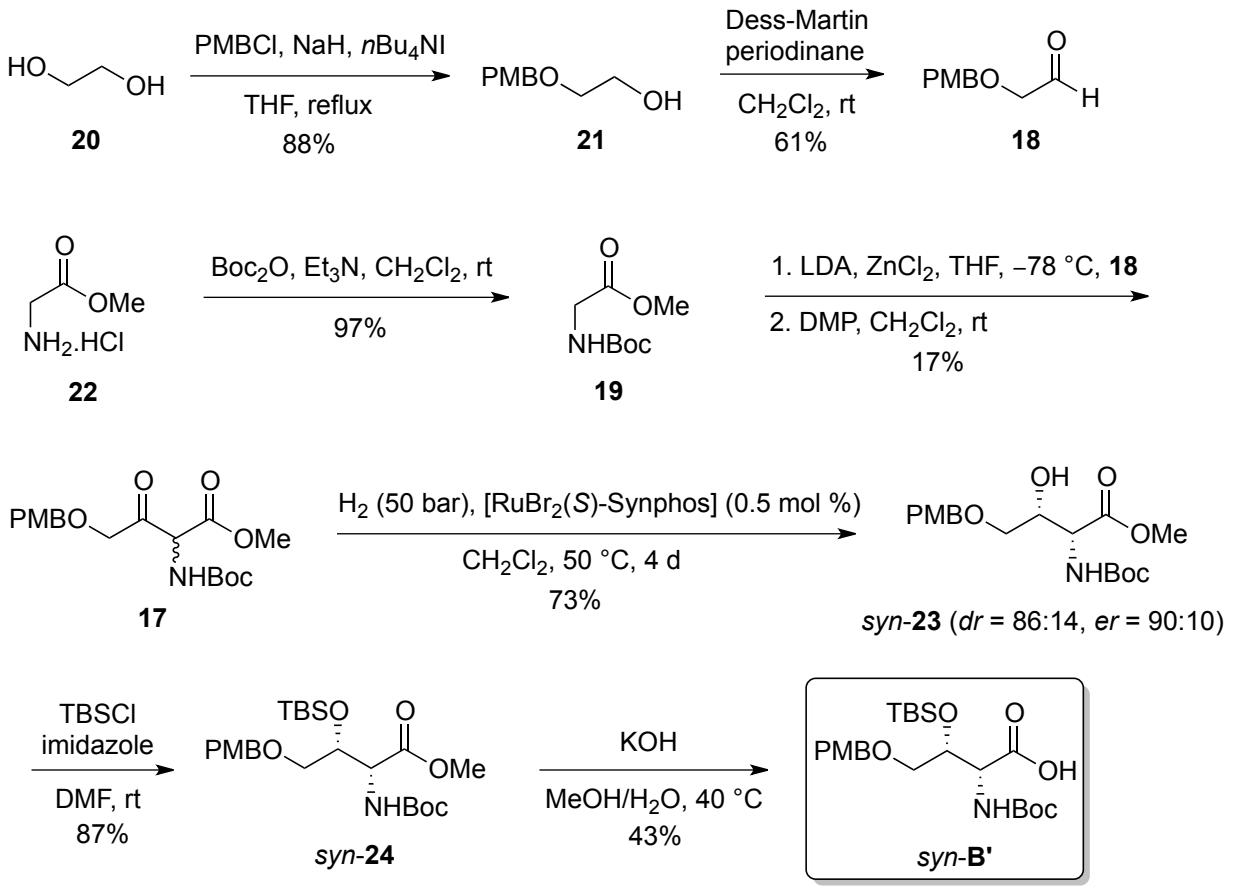
The retrosynthetic analysis for the construction of the second major building block **B** is summarized in Scheme 6 for compound **B'**. Our strategy focused on the flexibility in term of stereochemistry. For this purpose, asymmetric hydrogenation and transfer hydrogenation[36-40] were chosen as complementary methods to access all four stereoisomers of compound **B'**.



Scheme 6. Retrosynthetic analysis of fragment **B** (compound **B'**).

The synthesis of the α-carbamate β-ketoester **17** proceeded as shown in Scheme 7. After PMB-monoprotection of ethane-1,2-diol **20** and Dess-Martin oxidation of the obtained **21**, aldehyde **18** was isolated in 61% yield. The other partner **19** was prepared by simple *N*-Boc protection of glycine methyl ester hydrochloride **22** in 97% yield. Thereafter, reaction of the zinc derivative of **19** with aldehyde **18** furnished the corresponding α-carbamate β-hydroxy ester whose oxidation afforded the desired β-keto ester **17**. It is noteworthy that, after thorough investigation, only the use of Dess-Martin periodinane in the absence of $NaHCO_3$ allowed the oxidation, albeit in low yield; other attempts using IBX, Parikh-Doering, Ley-Griffith, Swern, Fétizon or pyridinium dichromate reagents led only to degradation products. With the desired keto ester **17** in hand, we focused on the asymmetric reduction of **17** *via* dynamic kinetic resolution.

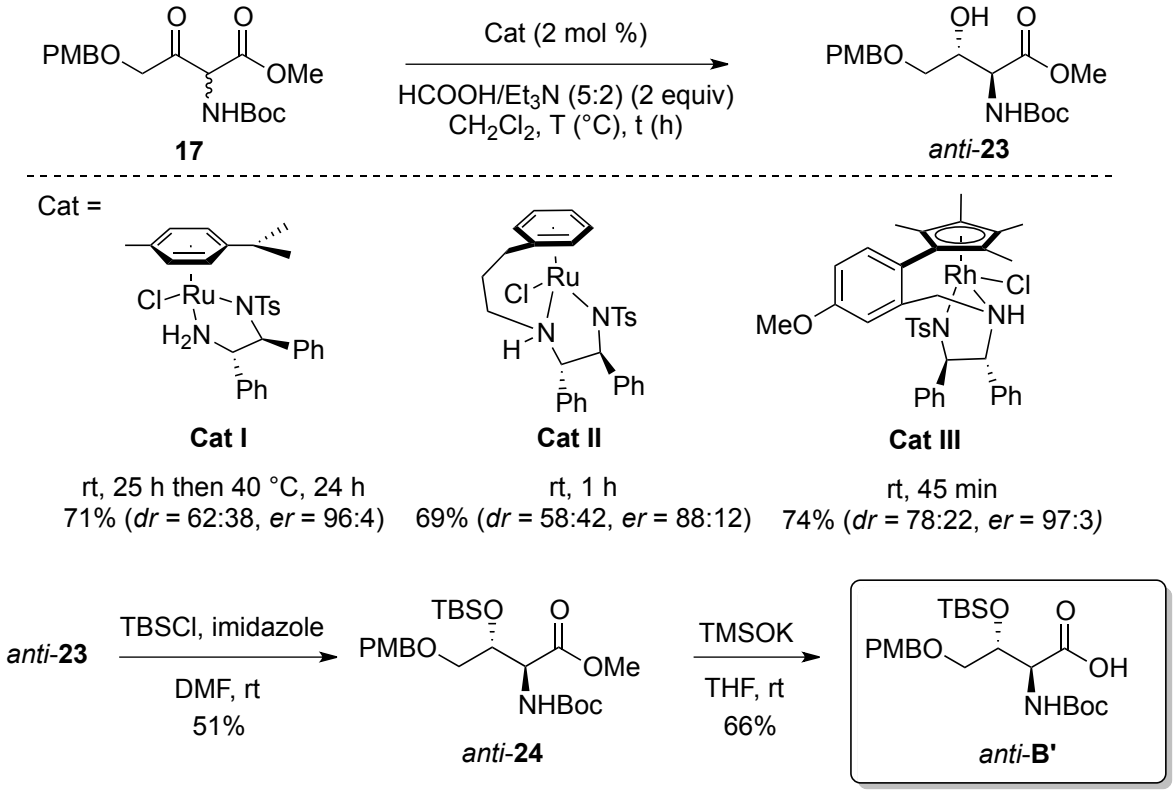
After careful optimization of the reaction parameters, compound *syn*-**23** was obtained in 73% yield with good diastereomeric ratio (*dr* = 86:14) and enantioselectivity (*er* = 90:10) by using 0.5 mol% of the complex [$RuBr_2$((*S*)-Synphos)] prepared *in situ* from [Ru(COD)(2-methylallyl)$_2$],[30] under 50 bar of hydrogen pressure at 50 °C in dichloromethane. Subsequent TBS protection of the hydroxyl gave *syn*-**24** and the desired compound *syn*-**B'** was finally obtained by hydrolysis of the methyl ester to the corresponding carboxylic acid (Scheme 7).



Scheme 7. Synthesis of compound *syn*-**B'** through asymmetric hydrogenation.

To obtain the *anti*-isomer of fragment **B**, we turned our attention to the use of asymmetric transfer hydrogenation of **17** in combination with dynamic kinetic resolution. Preliminary screening employing different catalysts **Cat I**,[41] **Cat II**,[42] and **Cat III**[43,44] with HCOOH/Et_3N (5:2) as the hydrogen donor demonstrated that faster reaction times as well as better diastereoselectivities in favor of compound *anti*-**23** (*dr* = 78:22) were obtained with catalyst **Cat III**. Moreover, the catalytic charge could be decreased from 2 mol% to 0.1

mol% without any loss of stereoselectivity and compound **23** was isolated with a comparable 70% yield. It is noteworthy that at this point of the synthesis inseparable mixtures of *syn*- and *anti*-isomers were obtained. To complete the synthesis of fragment **B**, the newly formed hydroxy-ester **23** was protected by using TBSCl and imidazole in 51% yield before hydrolysis of the ester with TMSOK yielded the fully protected compound *anti*-**B'**. Gratifyingly, flash chromatography allowed separation of the *syn*- and *anti*-isomers (Scheme 8).

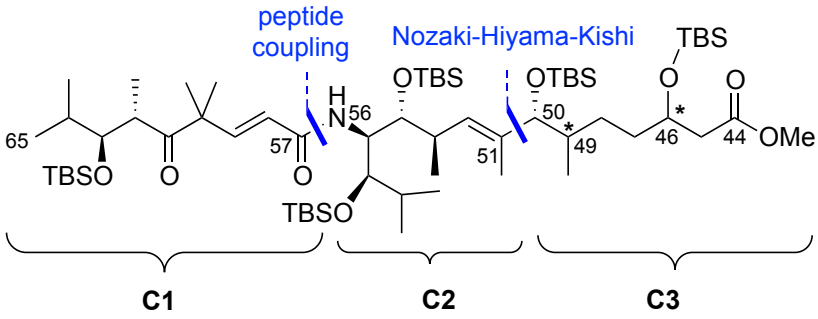


Scheme 8. Synthesis of compound *anti*-**B'** through asymmetric transfer hydrogenation.

Thus, compound *anti*-**B'** was synthesized in 7 steps starting from ethylene glycol **20** in 2.2% overall yield. This strategy inherently makes the synthesis flexible because all the four stereoisomers of fragment **B** can be synthesized by simply changing the configuration of the chiral ligand and by moving from asymmetric hydrogenation to asymmetric transfer hydrogenation.

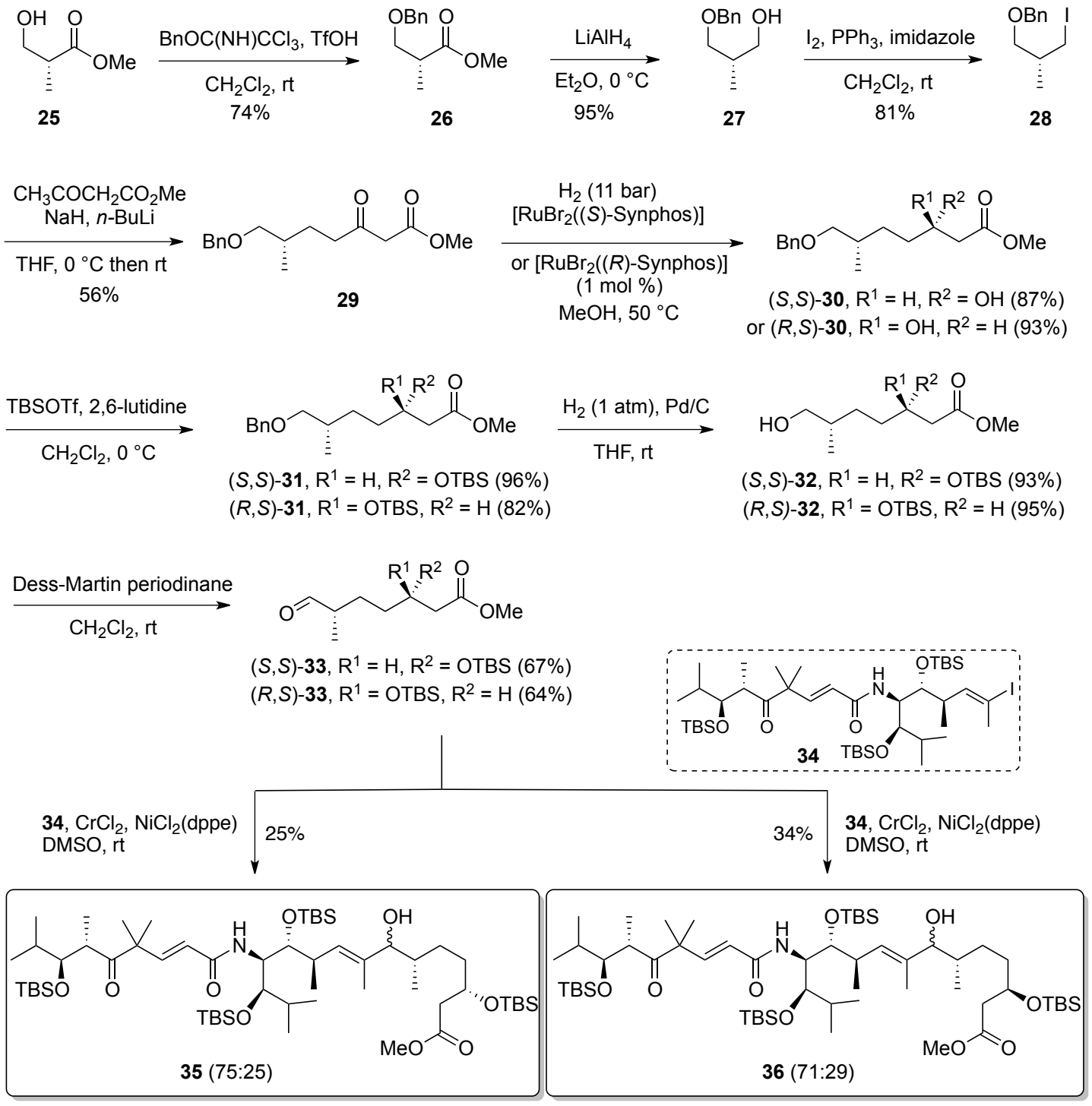
Synthesis of stereoisomers of the C44−C65 side chain

As outlined above, flexibility of our synthetic plan was essential as the configurations of several stereogenic centers remain unknown. We decided to prepare other isomers of the north fragment of the targeted molecule (C44-C65 fragment, the two relevant stereocenters are highlighted with a star on Scheme 9). As such, it was shown previously that the C44-C65 part of the molecule could easily be synthesized after assembly of fragments **C1**, **C2** and **C3** (Scheme 9).[18] Herein, we focused our attention to the modifications of the two C46 and C49 stereocenters of fragment **C3**. The stereogenic center at C46 would be easily modulated by simply changing the configuration of the upstream Roche ester, while modification of the configuration at the C49 stereocenter would be achieved by switching the ligand configuration during the asymmetric hydrogenation, thus allowing access to new isomers of the side chain.



Scheme 9. Retrosynthetic analysis of mirabalin side chain C44-C65.

The synthesis began with the benzyl protection of (*R*)-Roche ester **25** followed by reduction of the resulting ester **26** to **27** using $LiAlH_4$. Garegg iodination[45] (I_2, PPh_3, imid, CH_2Cl_2, rt) of the latter afforded iodide **28**, which was used for the alkylation of methyl acetoacetate[46] to provide the key β-keto ester **29** (Scheme 10). With convenient amounts of compound **29** in hand, ruthenium-catalyzed asymmetric hydrogenation of the ketone was tackled. This transformation was accomplished using the *in situ* generated chiral complexes either [$RuBr_2$((*S*)-Synphos)] or [$RuBr_2$((*R*)-Synphos)]. The stereochemical outcome of the reaction was controlled by choosing the appropriate configuration of the Synphos ligand and the reaction afforded (*S*,*S*)-**30** and (*R*,*S*)-**30** in 87% and 93% yields, respectively, as single diastereomers. The protection of these alcohols (TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C) yielded (*S*,*S*)-**31** and (*R*,*S*)-**31** which were subjected to debenzylation conditions (H_2, Pd/C) to give (*S*,*S*)-**32** and (*R*,*S*)-**32**, and subsequent Dess-Martin oxidation afforded aldehydes (*S*,*S*)-**33** and (*R*,*S*)-**33** required for the Nozaki-Hiyama-Kishi[47,48] coupling with (*E*)-iodoalkene **34**.[18] This reaction was performed in DMSO using $CrCl_2$ (14 equiv) in the presence of a catalytic amount of $NiCl_2$(dppe) (6 mol%). Under these conditions, alcohols **35** and **36** were obtained in 25% and 34% yields, respectively (quantitative yields based on the recovered starting material) as a mixture of diastereomers (*dr* = 75:25 for **35**, *dr* = 71:29 for **36**) which were separated by flash chromatography on silica gel.



Scheme 10. Synthesis of stereoisomers **35** and **36** of the C44-C65 side chain of mirabalin.

In summary, the facile synthesis of two new isomers **35** and **36** of the C44-C65 part of mirabalin demonstrated the high flexibility of the synthetic plan offered by using asymmetric reduction and one can envisage to access other stereoisomers using this versatile reduction.

Conclusions

In conclusion, the synthesis of several key fragments of mirabalin **1** was achieved using flexible and robust methods based on asymmetric hydrogenation and transfer hydrogenation. The C30–C67 fragment (compound **A'**) as well as two isomers of the C1–C36 subunits (compounds *syn*-**B'** and *anti*-**B'**) have been prepared. Moreover the synthesis of two isomers of the C44-C65 part of mirabalin has been achieved. Most importantly, the flexibility of this approach provides a platform for modification of several unknown stereocenters. The assembly of the different fragments is currently being pursued in our laboratory.

Experimental Section

General. All air and/or water sensitive reactions were carried out under an argon atmosphere. Tetrahydrofuran and diethyl ether were distilled from sodium-benzophenone. Dichloromethane was distilled from calcium hydride. Reactions were monitored by thin layer chromatography carried out on precoated silica gel plates (E. Merck ref. 5554 60 F254) and revealed with either an ultra-violet lamp (λ= 254 nm), a potassium permanganate solution (3 g $KMnO_4$, 20 g K_2CO_3, 0.25 mL AcOH, 300 mL H_2O), a ninhydrin solution (1 g ninhydrin, 100 mL EtOH/H_2SO_4: 95/5) or a Kagi-Mosher solution (8 mL *p*-anisaldehyde, 16 mL H_2SO_4, 800 mL AcOH). The nuclear magnetic resonance 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. Data are reported as follows: chemical shifts (δ), multiplicity (recorded as s singlet; d, doublet; t, triplet; q, quartet; quint, quintet; sxt, sextet; sep, septet; m, multiplet; dd, doublet of doublets; dt, doublet of triplets; td, triplet of doublets; br, broad), integration and coupling constants. Melting points (mp) were determined on a Büchi apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. High resolution mass spectrometric (HRMS) analyses were measured on LTQ-Orbitrap (Thermo Fisher Scientific) at Pierre et Marie Curie University. Enantiomeric excesses were determined by HPLC using a chiral stationary phase column (Chiralpak IA) and eluting with a hexane/isopropanol mixture as indicated.

Methyl (*Z*)-2-(hydroxyimino)-3-oxobutanoate (**6**). A solution of methyl acetoacetate **5** (15 g, 129 mmol, 1 equiv) in acetic acid (100 mL) was cooled to 0 °C and a suspension of $NaNO_2$ (22.3 g, 323 mmol, 2.5 equiv) in water (75 mL) was added dropwise, the temperature of the reaction mixture being kept below 5 °C. After evolution of the brown fumes, the stirring was maintained 1.5 h at 0 °C and then at rt until completion of the reaction, monitored by TLC (1 h). The reaction mixture was then diluted and extracted with Et_2O. The combined organic layers were washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, concentrated under reduced pressure and the crude mixture was purified by silica gel column chromatography (cyclohexane/EtOAc: 6/4) to give the desired product **6** (9.54 g, 51%) as a white solid. mp 39 °C; R_f (cyclohexane/EtOAc: 8/2) 0.17; IR (film): 3353, 1742, 1681, 1415, 1317, 1244, 1070, 1000 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.33 (s, 1H), 3.91 (s, 3H), 2.41 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ193.9, 162.1, 151.0, 52.8, 25.3.

Methyl 2-amino-3-oxobutanoate hydrochloride (**4**). To a solution of oxime **6** (7.34 g, 51 mmol, 1 equiv) in MeOH (126 mL) was added Pd/C 10% (1.79 g, 1.68 mmol, 0.033 equiv). 2N HCl in Et_2O (84.2 mL, 168.3 mmol, 3.3 equiv) was added dropwise to the resulting mixture and the argon atmosphere was replaced with hydrogen (balloon). The reaction mixture was stirred at rt under atmospheric pressure of hydrogen for 24 h (reaction monitored by TLC). The suspension was then filtered on a celite pad and washed with MeOH. The filtrate was concentrated under reduced pressure and the yellow solid was washed with EtOAc to give the title

compound **4** as a white solid (6.57 g, 77%). mp 148 °C; IR (film): 3419, 2986, 1745, 1727, 1469, 1279, 1241, 1164, 1131, 1089, 878 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 9.08 (s, 3H), 5.26 (s, 1H), 3.79 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 196.7, 164.2, 61.2, 53.6, 28.2.

Methyl (2*R*,3*R*)-2-[(*tert*-butoxycarbonyl)amino]-3-hydroxybutanoate (**7**). (*R*)-Synphos (377 mg, 0.59 mmol, 0.022 equiv) and [Ru(COD)(η^3-2-methylallyl)$_2$] (171 mg, 0.54 mmol, 0.02 equiv) were placed in a reaction tube and the vessel was purged with argon. Anhydrous acetone (20 mL) previously degassed by three vacuum-argon cycles was added at rt. To this suspension was added dropwise methanolic HBr (6.6 mL, 0.044 equiv of a 0.18N solution prepared by adding 48% aqueous HBr in degassed methanol) and the suspension was stirred at room temperature for 30 min. The suspension immediately turned yellow, then an orange precipitate appeared and the solvent was thoroughly evaporated under vacuum to give the catalyst as an orange-brown solid [$RuBr_2$((*R*)-Synphos)], which was used directly. The β-keto ester hydrochloride **4** (4.5 g, 26.9 mmol, 1 equiv) was then added followed by previously degassed anhydrous CH_2Cl_2 (20 mL) and degassed alcoholic solvent MeOH (2 mL). The reaction vessel was degassed by three vacuum-argon cycles and then placed under argon in a 250 mL stainless steel autoclave. The argon atmosphere was replaced with hydrogen by three cycles of pressurizing and the pressure adjusted to 13 bar. The autoclave was heated at 50 °C and stirring was maintained for 23 h. After cooling, the reaction mixture was concentrated under reduced pressure to afford the crude β-hydroxy ester. It was then dissolved in degassed MeOH (50 mL) and $NaHCO_3$ (9.02 g, 107.4 mmol, 4 equiv) and di-*tert*-butyl dicarbonate (5.86 g, 26.9 mmol, 1 equiv) was added. The mixture was stirred under ultrasonic irradiation during 4 h. The solvent was removed under reduced pressure and the crude mixture was purified by silica gel column chromatography (petroleum ether/EtOAc: 6/4) to give the desired product **7** (4.37 g, 70%) as a white solid. R_f (cyclohexane/EtOAc: 6/4) 0.28; $[\alpha]_D^{20}$ −19.0 (*c* 0.63, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 5.46 (s, 1H), 4.36 (s, 1H), 4.17 − 4.05 (m, 1H), 3.76 (s, 3H), 2.55 (s, 1H), 1.43 (s, 9H), 1.20 (d, *J* 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 156.1, 80.5, 68.9, 59.0, 52.4, 28.2, 18.8. Enantio- and diastereoselectivities were determined by HPLC after the asymmetric hydrogenation step on the corresponding benzamide derivative. HPLC : Chiralpak AS-H, hexane/*i*PrOH 94/6, 1 mL/min, λ = 215 nm; t_R [*syn*] = 33.8 min, t_R [*anti*] = 37.3 min, t_R [*syn*] = 41.4 min, t_R [*anti*] = 50.4 min.

Methyl (2*R*,3*R*)-2-[(*tert*-butoxycarbonyl)amino]-3-[(*tert*-butyldimethylsilyl)oxy]butanoate (**8**). To a solution of **7** (7.23 g, 31 mmol, 1 equiv) in dry DMF (28 mL) were added successively imidazole (0.876 g, 12.87 mmol, 3 equiv) and TBSCl (1.62 g, 10.73 mmol, 2.5 equiv) at rt. The mixture was stirred for 23 h at rt, then brine and Et_2O were added. The aqueous phase was extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (SiO_2, petroleum ether/EtOAc: 96/4) to give **8** (10.23 g, 95%) as a colorless oil. R_f (cyclohexane/EtOAc: 95/5) 0.26; $[\alpha]_D^{20}$ −27.6 (*c* 0.78, $CHCl_3$); IR (film): 2955, 2935, 2858, 1721, 1498, 1365, 1253, 1168, 834, 778 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.26 (d, *J* 8.6 Hz, 1H), 4.23 (dd, *J* 8.2, 3.4 Hz, 1H), 4.12 − 4.02 (m, 1H), 3.74 (s, 3H), 1.44 (s, 9H), 1.23 (d, *J* 6.4 Hz, 3H), 0.86 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 155.1, 79.7, 69.9, 59.6, 51.9, 28.3, 25.6, 20.4, 17.9, –4.6, –5.1.

***tert*-Butyl (4*R*,5*R*)-4-[(*tert*-butoxycarbonyl)amino]-5-[(*tert*-butyldimethylsilyl)oxy]-3-oxohexanoate (9)**

To a solution of diisopropylamine (14.1 mL, 100.4 mmol, 3.6 equiv) in dry THF (175 mL) was added *n*-butyllithium (49 mL, 97.7 mmol, 2M, 3.5 equiv) at 0 °C and the mixture was stirred at 0 °C for 45 min. The solution was then cooled to −45 °C and *tert*-butyl acetate (15 mL, 111.6 mmol, 4 equiv) was added. The resulting mixture was stirred for 1.5 h at −45 °C before a solution of **8** (9.7 g, 27.9 mmol, 1 equiv) in 50 mL of dry THF was added *via* cannula (rinsed with 25 mL). The reaction mixture was stirred at −45 °C for 22 h. The solution was then warmed to 0 °C before the reaction was quenched with 200 mL of saturated NH_4Cl. The aqueous phase was extracted with EtOAc and the combined organic layers were washed with saturated

$NaHCO_3$ and brine. The organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford the crude mixture which was purified by flash column chromatography (SiO_2, petroleum ether/EtOAc: 92/8) to yield the desired compoud **9** (10.5 g, 87%) as a colorless oil. R_f (cyclohexane/EtOAc: 9/1) 0.49; $[\alpha]_D^{20}$ −13.2 (*c* 2.05, $CHCl_3$); IR (film) : 2979, 2931, 2859, 1714, 1500, 1367, 1253, 1161, 833 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.22 (d, *J* 8.4 Hz, 1H), 4.29 (dd, *J* 7.1, 6.4 Hz, 1H), 4.02 (quint, *J* 6.2 Hz, 1H), 3.59 (d, *J* 16.0 Hz, 1H), 3.45 (d, *J* 16.1 Hz, 1H), 1.46 (s, 9H), 1.43 (s, 9H), 1.23 (d, *J* 6.3 Hz, 3H), 0.87 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.5, 165.9, 155.2, 82.0, 79.9, 70.2, 64.3, 50.4, 28.3, 27.9, 25.7, 20.7, 17.9, −4.7, −5.0; HRMS (ESI): calculated for $C_{21}H_{41}O_6NSiNa$: 454.2595, found : 454.2592.

***tert*-Butyl (3*R,4S,*5*R)*-4-[(*tert*-butoxycarbonyl)amino]-5-[(*tert*-butyldimethylsilyl)oxy]-3-hydroxyhexanoate** (**10**) A degassed solution of **9** (100 mg, 0.23 mmol, 1 equiv) in EtOH (3.8 mL) was prepared in a reaction tube and the vessel was purged with argon. Solid catalyst [{RuCl((*S*)-Synphos)}$_2$(μ-Cl)$_3$][Me_2NH_2] (3.9 mg, 0.0023 mmol, 0.01 equiv) was then added and the reaction vessel was degassed by three vacuum-argon cycles and then placed under argon in a 250 mL stainless steel autoclave. The argon atmosphere was replaced with hydrogen by three cycles of pressurizing and the pressure adjusted to 100 bar. The autoclave was heated at 50 °C and stirring was maintained for 6 h. After cooling, the reaction mixture was concentrated under reduced pressure to afford the crude product which was purified by flash chromatography (SiO_2, petroleum ether/*i*Pr_2O: 8/2) to afford the desired compound **10** (70 mg, 70%) as a colorless oil. R_f (cyclohexane/EtOAc: 9/1) 0.41; $[\alpha]_D^{20}$ −25.0 (*c* 0.88, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 5.22 (d, *J* 9.2 Hz, 1H), 4.61 (dd, *J* 4.8, 8.5 Hz, 1H), 4.13 (m, 1H), 3.57 (bs, 1H), 3.31 (dd, *J* 3.5, 9.3 Hz, 1H), 2.40 (dd, *J* 8.5, 16.0 Hz, 1H), 2.33 (dd, *J* 4.9, 16.1 Hz, 1H), 1.46 (s, 9H), 1.44 (s, 9H), 1.27 (d, *J* 6.4 Hz, 3H), 0.88 (s, 9H), 0.08 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 155.7, 80.9, 79.3, 71.8, 66.0, 56.9, 40.0, 28.4, 28.1, 25.7, 20.7, 17.8, −4.7, −5.1; HRMS (ESI): calculated for $C_{21}H_{43}O_6NSiNa$ $[M + Na]^+$: 456.2757, found : 456.2752.

***tert*-Butyl (4*S,5R*)-5-[2-(*tert*-butoxy)-2-oxoethyl]-4-(*R*)-1-{[(*tert*-butyldimethylsilyl)oxy]ethyl}-2,2-dimethyl-oxazolidine-3-carboxylate** (**11**). To a solution of ester **10** (2.6 g, 6 mmol, 1 equiv) in dry CH_2Cl_2 (100 mL) was added distilled dimethoxypropane (3.9 mL, 32 mmol, 5.3 equiv) and (±)-camphorsulfonic acid (0.265 g, 1.14 mmol, 0.19 equiv) at rt. The mixture was stirred at reflux for 1 h. The solution was then cooled to rt and saturated $NaHCO_3$ was added. The aqueous phase was extracted with CH_2Cl_2 and the combined organic layers were washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (SiO_2, petroleum ether/EtOAc: 93/7 to 8/2 to 6/4) to afford the desired compound **11** (0.757 g, 27%) as a white solid. R_f (cyclohexane/EtOAc: 8/2, ninhydrin) 0.68; $[\alpha]_D^{20}$ −21.5 (*c* 0.79, $CHCl_3$); ^1H NMR (300 MHz, C_6D_6) δ 5.00 − 4.77 (m, 1H), 4.60 (s, 1H), 3.72 (s, 1H), 2.77 − 2.05 (m, 2H), 1.59 (bs, 6H), 1.38 (s, 9H), 1.35 (s, 9H), 1.06 (d, *J* 6.4 Hz, 3H), 0.94 (s, 9H), 0.09 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6) δ 169.2, 152.3, 79.9, 79.4 (2C), 72.2, 67.5, 66.5, 42.7, 28.5, 28.2, 28.0, 27.3, 26.2, 21.2, 18.3, −4.4, −4.5; HRMS (ESI): calculated for $C_{24}H_{47}O_6NSiNa$ $[M + Na]^+$: 496.3070, found : 496.3065.

***tert*-Butyl (4*S,5R*)-4-{(*R*)-1-[(*tert*-butyldimethylsilyl)oxy]ethyl}-2,2-dimethyl-5-(2-oxoethyl)oxazolidine-3-carboxylate** (**3**). Diisobutylaluminum hydride (1 M solution in toluene, 2.3 mL, 2.3 mmol, 1.5 equiv) was added to a cooled (–85 °C) solution of the ester **11** (733 mg, 1.5 mmol, 1 equiv) in CH_2Cl_2 (19 mL). After 1.5 h at –85 °C, Rochelle salt was added at –85 °C and the resulting mixture was warmed to rt and stirred overnight. The biphasic solution was extracted with CH_2Cl_2. The combined organic extracts were washed with Rochelle salt and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography (pentane/EtOAc: 9/1) to afford compound **3** (1.23 g, 77%) as a colorless oil. R_f (cyclohexane/EtOAc: 8/2, ninhydrin) 0.41; $[\alpha]_D^{20}$ −35.4 (*c* 0.79, $CHCl_3$); IR (film): 3439, 2978, 2937, 2856, 1697, 1463, 1376, 1257, 1079, 838, 777, 741 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 9.44 (dd, *J* 2.9, 1.5 Hz, 1H), 4.76 (ddd, *J*

8.4, 5.6, 4.3 Hz, 1H), 4.70 (bs, 1H), 3.50 (bs, 1H), 2.27 (ddd, *J* 16.0, 8.4, 2.9 Hz, 1H), 2.13 (ddd, *J* 16.0, 4.3, 1.5 Hz, 1H), 1.58 (bs, 6H), 1.41 (s, 9H), 0.96 (s, 9H), 0.95 (bs, 3H), 0.10 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6) δ 198.5, 152.2, 94.5, 79.5, 69.8, 67.6, 65.4, 49.6, 28.3, 27.2, 27.1, 26.0, 20.9, 18.1, −4.3, −4.7; HRMS (ESI): calculated for $C_{20}H_{39}O_5NSiNa$ $[M + Na]^+$: 424.2495, found : 424.2490.

***tert*-Butyl (4*S*,5*R*)-4-{(*R*)-1-[(*tert*-butyldimethylsilyl)oxy]ethyl}-5-((*R*)-2-hydroxybut-3-en-1-yl)-2,2-dimethyl-oxazolidine-3-carboxylate** (**12**). A 0.7 M solution of vinyl magnesium bromide in THF (4.8 mL, 3.33 mmol, 3 equiv) was added to a solution of aldehyde **3** (447 mg, 1.11 mmol, 1 equiv) in dry THF (1.9 mL) at –78 °C. The mixture was stirred at –78 °C for 4 h. Saturated NH_4Cl was added at –78 °C and the solution was warmed to rt. The aqueous phase was extracted with EtOAc and the combined organic layers were washed with saturated NH_4Cl, dried over $MgSO_4$, filtered and concentrated under vacuum. Purification of the crude material by flash chromatography (SiO_2, pentane/*i*Pr_2O: 8/2 to pentane/EtOAc: 8/2) afforded **12** (major diastereomer, 231 mg, 48%) as well as the minor diastereoisomer (137 mg, 29%) as colorless oils. R_f (cyclohexane/EtOAc: 8/2, ninhydrin) 0.46 (minor), 0.37 (major); $[\alpha]_D^{20}$ (major): −35.8 (*c* 0.74, $CHCl_3$); ^{1}H NMR (major) (300 MHz, $CDCl_3$) δ 5.82 (ddd, 1H, *J* 17.2, 10.4, 5.6 Hz), 5.35 (dd, 1H, *J* 17.2, 1.7 Hz), 5.06 − 4.99 (m, 1H), 4.72 (s l, 1H), 4.56 (ddd, 1H, *J* 9.9, 5.5, 3.3 Hz), 4.38 (m, 1H), 3.60 (bs, 1H), 2.69 (s, 1H), 2.02 − 1.48 (m, 8H), 1.41 (s, 9H), 1.01 (d, 3H, *J* 5.2 Hz), 0.96 (s, 9H), 0.11 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (major) (75 MHz, C_6D_6) δ 150.2, 141.2, 114.1, 94.4, 79.4, 74.1, 71.4, 68.3, 65.4, 43.9, 28.3, 27.4, 27.1, 26.0, 21.0, 18.1, −4.3, −4.7; HRMS (ESI): calculated for $C_{22}H_{43}O_5NSiNa$ $[M + Na]^+$: 452.2808, found : 452.2803.

***tert*-Butyl (4*S*,5*R*)-5-((*R*)-2-((*tert*-butyldimethylsilyl)oxy)but-3-en-1-yl)-4-((*R*)-1-((*tert*-butyldimethylsilyl)oxy) ethyl)-2,2-dimethyloxazolidine-3-carboxylate** (**2**). To a solution of **12** (146 mg, 0.34 mmol, 1 equiv) in dry DMF (1 mL) were added successively TBSCl (75 mg, 0.5 mmol, 1.5 equiv) and imidazole (46 mg, 0.68 mmol, 2 equiv) at 0 °C. The mixture was stirred for 19 h at rt, then brine and EtOAc were added. The aqueous phase was extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (SiO_2, petroleum ether/*i*Pr_2O: 95/5) to give **2** (146 mg, 79%) as a colorless oil. R_f (cyclohexane/EtOAc: 85/15, ninhydrin) 0.79; $[\alpha]_D^{20}$ −11.7 (*c* 0.74, $CHCl_3$); IR (film): 2957, 2930, 2858, 1695, 1471, 1464, 1364, 1256, 1082, 836, 776 cm^{-1}; ^{1}H NMR (300 MHz, C_6D_6) δ 5.95 (ddd, *J* 17.2, 10.3, 6.8 Hz, 1H), 5.29 (d, *J* 17.1 Hz, 1H), 5.05 (d, *J* 10.3 Hz, 1H), 4.90 − 4.21 (m, 3H), 3.63 (bs, 1H), 2.17 − 1.54 (m, 8H), 1.43 (s, 9H), 1.01 (bs, 12H), 0.96 (s, 9H), 0.14 (s, 3H), 0.12 (s, 3H), 0.11 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (75 MHz, C_6D_6) δ 152.2, 141.2, 114.8, 93.8, 79.2, 72.1, 71.2, 68.1, 65.4, 45.4, 28.3, 27.4, 27.1, 26.1, 26.0, 21.1, 18.3, 18.1, −4.2, −4.6 (2C), −4.7; HRMS (ESI): calculated for $C_{28}H_{57}O_5NSi_2Na$ $[M + Na]^+$: 566.3673, found : 566.3668.

***tert*-Butyl (4*S*,5*R*)-5-{(*S*)-2-[(*tert*-butyldimethylsilyl)oxy]-4-hydroxybutyl}-4-{(*R*)-1-[(*tert*-butyldimethylsilyl)-oxy]ethyl}-2,2-dimethyloxazolidine-3-carboxylate** (**13**). To a solution of **2** (137 mg, 0.25 mmol, 1 equiv) in dry THF (1.4 mL) was added $BH_3.Me_2S$ (2M in THF, 0.25 mL, 0.75 mmol, 3 equiv) at 0 °C. The mixture was stirred at 0 °C for 1 h then allowed to rise to rt. NaOH 3M (1.25 mL, 3.75 mmol, 15 equiv) and 35% H_2O_2 in H_2O (0.32 mL, 3.75 mmol, 15 equiv) were added at 0 °C and the resulting solution was stirred at rt for 1 h. Saturated NH_4Cl was added and the aqueous phase was extracted with CH_2Cl_2. The combined organic layers were washed with saturated NH_4Cl, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, petroleum ether/EtOAc: 9/1 to 8/2) to give **13** (105 mg, 75%) as a pale yellow oil. R_f (cyclohexane/EtOAc: 8/2, ninhydrin) 0.41; ^{1}H NMR (400 MHz, C_6D_6, 50 °C) δ 4.74 − 4.60 (m, 1H), 4.52 (ddd, *J* 9.8, 5.7, 3.0 Hz, 1H), 4.27 (m, 1H), 3.82 − 3.63 (m, 2H), 3.58 (dd, *J* 5.7, 3.1 Hz, 1H), 2.04 − 1.85 (m, 2H), 1.82 − 1.67 (m, 2H), 1.62 (bs, 3H), 1.44 (s, 9H), 1.43 (bs, 3H), 1.11 (d, *J* 6.5 Hz, 3H), 0.97 (s, 9H), 0.97 (s, 9H), 0.13 (s, 3H), 0.13 (s, 3H), 0.12 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (100 MHz, C_6D_6, 50 °C) δ 152.6, 94.7, 79.6,

72.3, 69.2, 69.0, 66.6, 59.8, 44.9, 38.9, 28.6, 27.7, 27.3, 26.3, 26.2, 21.4, 18.3, 18.3, −3.9, −4.1, −4.4, −4.5; HRMS (ESI): calculated for $C_{28}H_{59}O_6NSi_2Na$ $[M + Na]^+$: 584.3779, found : 584.3773.

***tert*-Butyl (4*S,5R*)-5-{(*R*)-2-[(*tert*-butyldimethylsilyl)oxy]-4-{[(1-phenyl-1*H*-tetrazol-5-yl)thio]butyl}-4-{[(*R*)-1-(*tert*-butyldimethylsilyl)oxy]ethyl}-2,2-dimethyloxazolidine-3-carboxylate** (**14**). To a solution of **13** (107 mg, 0.19 mmol, 1 equiv) in dry THF (1.6 mL) were successively added triphenylphosphine (60 mg, 0.23 mmol, 1.2 equiv), 1-phenyl-1*H*-tetrazole-5-thiol (41 mg, 0.23 mmol, 1.2 equiv) and DIAD (0.12 mL, 0.23 mmol, 1.2 equiv) dropwise at rt. The mixture was stirred at rt for 22.5 h. Saturated $NaHCO_3$ was added and the aqueous phase was extracted with EtOAc. The combined organic phases were washed with saturated $NaHCO_3$, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, petroleum ether/*i*Pr_2O: 9/1 to petroleum ether/EtOAc: 9/1) to give **14** (109 mg, 80%) as a pale yellow oil. R_f (cyclohexane/EtOAc: 8/2, ninhydrin, UV) 0.63; ^{1}H NMR (400 MHz, $CDCl_3$, 50 °C) δ 7.62 − 7.48 (m, 5H), 4.46 (bs, 1H), 4.33 (ddd, *J* 10.0, 5.7, 2.9 Hz, 1H), 4.15 − 4.06 (m, 1H), 3.58 − 3.40 (m, 3H), 2.24 − 2.13 (m, 1H), 2.06 − 1.86 (m, 2H), 1.84 − 1.74 (m, 1H), 1.56 (s, 3H), 1.49 (s, 9H), 1.46 (s, 3H), 1.11 (d, *J* 6.5 Hz, 3H), 0.91 (s, 9H), 0.89 (s, 9H), 0.09 (s, 6H), 0.07 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 50 °C) δ 154.6, 152.7, 134.4, 130.1, 129.9, 124.2, 94.6, 80.1, 71.7, 69.0, 68.7, 66.3, 44.2, 35.8, 29.9, 28.7, 27.4, 27.2, 26.2, 26.1, 21.4, 18.2 (2C), −4.0, −4.1, −4.3 (2C); HRMS (ESI): calculated for $C_{35}H_{63}O_5N_5Si_2SNa$ $[M + Na]^+$: 744.3986, found : 744.3981.

tert*-Butyl (4*S,5R*)-5-{(*R*)-*2*[(*tert*-butyldimethylsilyl)oxy]-4-[(1-phenyl-1*H*-tetrazol-5-yl)sulfonyl]butyl}-4-{(*R)*-1-[(*tert*-butyldimethylsilyl)oxy]ethyl}-2,2-dimethyloxazolidine-3-carboxylate** (A'***). To a solution of **14** (95 mg, 0.13 mmol, 1 equiv) in dry CH_2Cl_2 (2 mL) were added $NaHCO_3$ (33 mg, 0.39 mmol, 3 equiv) and *m*-CPBA (67 mg, 0.39 mmol, 3 equiv) at 0 °C. The mixture was stirred for 14 h at rt. Saturated $Na_2S_2O_3$ was added at 0 °C and the mixture was diluted with CH_2Cl_2. The white solid was filtered and the aqueous layer was extracted with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, pentane / *i*Pr_2O: 9/1 to 8/2) to give **A'** (67 mg, 68%) as a pale yellow oil. R_f (cyclohexane/EtOAc: 8/2, ninhydrin, UV) 0.58; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74-7.65 (m, 2H), 7.65 − 7.55 (m, 3H), 4.54 (bs, 1H), 4.41 − 4.24 (m, 1H), 4.18 − 4.05 (m, 1H), 3.94 − 3.74 (m, 2H), 3.43 (bs, 1H), 2.36 − 2.21 (m, 1H), 2.19 − 2.05 (m, 1H), 1.80 − 1.60 (m, 2H), 1.55 (bs, 3H), 1.47 (s, 9H), 1.44 (bs, 3H), 1.08 (d, *J* 6.6 Hz, 3H), 0.89 (s, 9H), 0.86 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H), 0.05 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.7, 152.7, 133.3, 131.6, 129.9, 125.2, 94.4, 80.2, 70.3, 68.1, 67.7, 64.7, 52.8, 43.4, 30.3, 28.6, 27.0 (2C), 26.1, 26.0, 21.2, 18.1, 18.1, −4.1, −4.3, −4.6 (2C); HRMS (ESI): calculated for $C_{35}H_{63}O_7N_5Si_2SNa$ $[M + Na]^+$: 776.3884, found : 776.3879.

(2*S*,3*S*)(*E*)-2-[(*tert*-Butyldimethylsilyl)oxy]-5-iodo-3-methylhex-4-en-1-ol (**15**). To a solution of (2*S*,3*S*,*E*)-2-((*tert*-butyldimethylsilyl)oxy)-5-iodo-3-methylhex-4-en-1-ol[19] (150 mg, 0.31 mmol, 1 equiv) in EtOH (70 mL) was added PPTS (7.8 mg, 0.03 mmol, 0.1 equiv) at rt. After 24 h at rt, the mixture was concentrated under reduced pressure. Purification by flash chromatography on silica gel (petroleum ether/Et_2O = 100:0 to 80:20) afforded the alcohol **15** as a pale yellow oil (55 mg, 47%) and bis-protected alcohol was recovered (57 mg, 38%). $[\alpha]_D^{20}$ –35.5 (*c* 0.64, $CHCl_3$); IR (neat): 3416, 1636, 1471, 1462, 1378, 1361, 1525, 1150, 1098, 1046, 1006 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.01 (dq, *J* 10.2, 1.5 Hz, 1H), 3.61 – 3.48 (m, 3H), 2.69 (m, 1H), 2.38 (d, *J* 1.5 Hz, 3H), 1.71 (brt, *J* 6.0 Hz, 1H), 0.97 (d, *J* 6.9 Hz, 3H), 0.90 (s, 9H), 0.10 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.5, 94.5, 75.8, 64.3, 38.3, 27.9, 25.9, 18.0 (3C), 16.5, –4.4, –4.5; MS (EI) *m*/*z*: 339 (4), 313 (9, [M-*t*Bu]$^+$), 255 (20), 195 (37), 186 (5), 185 (11), 181 (10), 175 (11), 119 (5), 117 (14), 115 (12), 111 (7), 105 (30), 103 (23), 94 (9), 93 (9), 77 (11), 75 (98), 73 (100).

***tert*-Butyl (4*S,5R*)-5-{(2*S*,4*E*,6*R*,7*S*,8*E*)-2,6-bis[(*tert*-butyldimethylsilyl)oxy]-9-iodo-7-methyldeca-4,8-dien-1-yl}-4-{(*R*)-1-[(*tert*-butyldimethylsilyl)oxy]ethyl}-2,2-dimethyloxazolidine-3-carboxylate** (**16**). To a solution of **15** (40 mg, 0.11 mmol, 1 equiv) in dry CH_2Cl_2 were added at rt MS 4Å (30 mg), TPAP (3 mg, 0.01 mmol, 0.08

equiv) and NMO (15 mg, 0.13 mmol, 1.2 equiv). The mixture was stirred for 2 h at rt and filtered over a pad of celite (CH_2Cl_2). The crude aldehyde was used directly into the next step. To a solution of **A** (55 mg, 0.07 mmol, 1 equiv) in dry THF (1.5 mL) was added dropwise KHMDS (0.15 mL, 0.07 mmol, 0.5 M in toluene, 1.05 equiv) at –78 °C. The brown solution was stirred for 30 min at –78 °C before adding dropwise a solution of the crude aldehyde (40 mg, 0.11 mmol, 1.5 equiv) in THF (0.5 mL). The mixture was stirred 2 h at –78 °C then 1 h at rt. An aqueous solution of NH_4Cl was added and the phases were separated. The aqueous layer was extracted twice with EtOAc. The combined organic layers were washed with water, dried over Na_2SO_4 and concentrated under reduced pressure. Purification by flash chromatography on silica gel (SiO_2, pentane/Et_2O: 100/0 to 95/5) afforded **16** as a colorless oil (50 mg, 76%, *E*/*Z* > 95:5, mixture of rotamers). $[\alpha]_D^{20}$ −33.0 (*c* 0.78, $CHCl_3$); IR (neat): 1692, 1462, 1387, 1365, 1253, 1178, 1079, 1025 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 6.18 (dq, *J* 10.0, 1.5 Hz, 1H), 5.84 (m, 1H), 5.54 (ddt, J 15.9, 6.5, 1.1 Hz), 4.70 (bs, 1H), 4.56 (ddd, *J* 9.3, 5.9, 3.6 Hz, 1H), 4.18 (m, 1H), 3.90 (t, *J* 6.5 Hz, 1H), 3.64 (dd, *J* 5.9, 2.7 Hz, 1H), 2.54 (m, 1H), 2.45 (m, 1H), 2.37 (m, 1H), 2.27 (d, *J* 1.5 Hz, 3H), 2.01 – 1.86 (m, 2H), 1.73 (s, 3H), 1.64 (s, 3H), 1.45 (s, 9H), 1.15 (d, *J* 6.6 Hz, 3H), 1.01 (s, 9H), 1.00 (s, 18H), 0.90 (d, J 6.9 Hz, 3H), 0.16 – 0.14 (m, 9H), 0.12 – 0.09 (m, 9H); ^{13}C NMR (100 MHz, C_6D_6) δ 152.4, 144.4, 134.3, 128.3, 94.5, 93.7, 79.4, 77.2, 72.1, 70.3, 68.8, 66.4, 43.8, 43.1, 39.4, 28.5 (3C), 27.9 (2C), 27.5, 26.23 (3C), 26.16 (3C), 26.12 (3C), 21.4, 18.30, 18.25, 18.23, 16.0, –3.9, –4.0, –4.26, –4.29, –4.5 (2C); HRMS (ESI): calculated for $C_{41}H_{82}INO_6Si_3Na$ $[M + Na]^+$: 918.4387, found : 918.4382.

2-[(4-Methoxybenzyl)oxy]ethan-1-ol (**21**). To a slurry of NaH (60% dispersion in oil, 7.0 g, 110 mmol, 1 equiv) in dry THF (300 mL) were added dropwise ethylene glycol **20** (28.8 mL, 510 mmol, 3 equiv), tetrabutylammonium iodide (7.1 g, 17 mmol, 0.1 equiv) and *para*-methoxylbenzyl chloride (23.2 mL, 9.8 mmol, 1 equiv) at 0 °C. The mixture was stirred for 4 h under reflux and a saturated aqueous ammonium chloride solution was added. The aqueous layer was extracted with EtOAc and the combined organic layers were washed with brine, dried, filtered and concentrated. Flash chromatography (SiO_2, petroleum ether/EtOAc: 55/45) gave the alcohol **21** as a yellow oil (27.45 g, 88%). R_f (cyclohexane/EtOAc:6/4, $KMnO_4$, UV) 0.29; ^1H NMR (300 MHz, $CDCl_3$) δ 7.28 (d, *J* 8.6 Hz, 2H), 6.89 (d, *J* 8.6 Hz, 2H), 4.49 (s, 2H), 3.81 (s, 3H), 3.78 – 3.66 (m, 2H), 3.56 (t, *J* 4.9 Hz, 2H), 2.57 (t, *J* 6.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2, 129.9, 129.3, 113.7, 72.8, 71.0, 61.7, 55.1.

2-[(4-Methoxybenzyl)oxy}acetaldehyde (**18**). Dess-Martin periodinane (2.54 g, 6 mmol, 1.1 equiv) was added to a solution of alcohol **21** (1 g, 5.5 mmol, 1 equiv) in dry CH_2Cl_2 (30 mL) at 0 °C. After stirring 3 h at rt, the reaction was quenched with saturated $NaHCO_3$ and the mixture was stirred vigorously until two clear layers were obtained. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure to a crude mixture which was purified by flash chromatography (SiO_2, petroleum ether/EtOAc: 6/4) to give the alcohol **18** as a yellow oil (0.605 g, 61%). R_f (cyclohexane/EtOAc:4/6, $KMnO_4$, UV) 0.59; ^1H NMR (300 MHz, $CDCl_3$) δ 9.69 (s, 1H), 7.28 (d, *J* 8.7 Hz, 2H), 6.89 (d, *J* 8.7 Hz, 2H), 4.55 (s, 2H), 4.06 (d, *J* 0.7 Hz, 2H), 3.80 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.6, 159.6, 129.7, 128.8, 113.9, 74.9, 73.2, 55.2.

Methyl (*tert*-butoxycarbonyl)glycinate (**19**). Glycine methyl ester hydrochloride **22** (7.28 g, 58 mmol, 1 equiv) was suspended in CH_2Cl_2 (200 mL) and Et_3N (9 mL, 64 mmol, 1.1 equiv) was added at 0 °C. The mixture was stirred for 30 min at 0 °C and Boc_2O (13.95 g, 64 mmol, 1.1 equiv) was added at rt. The reaction was stirred for 26 h at rt and H_2O (150 mL) was added. The mixture was extracted with CH_2Cl_2 and the organic phase was washed with 100 mL of HCl (1 N), 100 mL of saturated Na_2CO_3 and 100 mL of brine. The organic layer was dried over $MgSO_4$, filtered, and the solvent was removed under reduced pressure. Flash chromatography of the crude mixture (SiO_2, petroleum ether/EtOAc: 7/3) gave the desired compound **19** as a colorless oil (10.59

g, 97%). R_f (cyclohexane/EtOAc:1/1, $KMnO_4$) 0.63; ^1H NMR (300 MHz, $CDCl_3$) δ 5.00 (bs, 1H), 3.92 (d, *J* 5.5 Hz, 2H), 3.75 (s, 3H), 1.45 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 155.7, 80.0, 52.2, 42.2, 28.3.

Methyl 2-[(*tert*-butoxycarbonyl)amino]-4-[(4-methoxybenzyl)oxy]-3-oxobutanoate (**17**). To a solution of diisopropylamine (11.6 mL, 82.5 mmol, 3.3 equiv) in THF (90 mL), was added dropwise at –78 °C, a 2.3 M solution of *n*BuLi in THF (33 mL, 75 mmol, 3 equiv). The solution was stirred for 30 min at –78 °C then transferred *via* cannula to a solution of **19** (4.7 g, 25 mmol, 1 equiv) and $ZnCl_2$ (4.09 g, 30 mmol, 1.2 equiv) in dry THF (55 mL). The mixture was stirred 45 min at –78 °C and a solution of **18** (5.82 g, 32.3 mmol, 1.3 equiv) in dry THF (35 mL) was added *via* cannula. The resulting solution was stirred for 30 min at –78 °C before it was hydrolyzed with saturated NH_4Cl and extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, the solvent was evaporated *in vacuo*, and the crude product was purified by flash chromatography (SiO_2, petroleum ether/EtOAc: 6/4). The corresponding alcohol was obtained as a colorless oil (6.94 g, 75%). Dess-Martin periodinane (14.1 g, 27.2 mmol, 1.8 equiv) was added to a solution of this alcohol (6.70 g, 18.1 mmol, 1 equiv) in dry CH_2Cl_2 (160 mL) at 0 °C. After stirring 3.5 h at rt, the reaction was quenched with saturated $NaHCO_3$ and the mixture was stirred vigorously until two clear layers were obtained. The layers were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude mixture was purified by flash chromatography (SiO_2, cyclohexane/EtOAc: 8/2) to give the ketone **17** as a colorless oil (1.54 g, 23%). R_f (cyclohexane/EtOAc: 1/1, $KMnO_4$, UV) 0.65; ^1H NMR (300 MHz, $CDCl_3$) δ 7.19 (d, *J* 8.7 Hz, 2H), 6.80 (d, *J* 8.7 Hz, 2H), 5.65 (d, *J* 7.4 Hz, 1H), 5.10 (d, *J* 7.6 Hz, 1H), 4.44 (s, 2H), 4.35 (d, *J* 17.0 Hz, 1H), 4.20 (d, *J* 17.0 Hz, 1H), 3.71 (s, 3H), 3.65 (s, 3H), 1.35 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.7, 166.6, 159.4, 154.7, 129.6, 128.7, 113.7, 80.5, 72.9 (2C), 60.0, 55.1, 53.0, 28.0.

Methyl (2*R*,3*R*)-2-[(*tert*-butoxycarbonyl)amino]-3-hydroxy-4-[(4-methoxybenzyl)oxy]butanoate (*syn*-**23**). (*S*)-Synphos (2.9 mg, 4.5 μmol, 0.011 equiv) and [Ru(COD)(η^3-2-methylallyl)$_2$] (1.3 mg, 4.1 μmol, 0.01 equiv) were placed in a reaction tube and the vessel was purged with argon. Anhydrous acetone (1.5 mL) previously degassed by three vacuum-argon cycles was added at rt. To this suspension was added dropwise methanolic HBr (47 μL, 0.009 equiv of a 0.19N solution prepared by adding 48% aqueous HBr in degassed methanol) and the suspension was stirred at room temperature for 30 min. The suspension immediately turned yellow, then an orange precipitate appeared and the solvent was thoroughly evaporated under vacuum to give the catalyst as an orange-brown solid [$RuBr_2$((*S*)-Synphos)], which was used directly. A solution of β-ketoester hydrochloride **17** (150 mg, 0.41 mmol, 1 equiv) in degassed anhydrous CH_2Cl_2 (1.5 mL) was then added. The reaction vessel was degassed by three vacuum-argon cycles and then placed under argon in a 250 mL stainless steel autoclave. The argon atmosphere was replaced with hydrogen by three cycles of pressurizing and the pressure adjusted to 120 bar. The autoclave was heated at 50 °C and stirring was maintained for 96 h. After cooling, the reaction mixture was concentrated under reduced pressure to afford the crude β-hydroxy ester which was purified by flash chromatography (SiO_2, cyclohexane/EtOAc: 6/4) to give syn-**23** (110 mg, 73%) as a colorless oil. R_f (cyclohexane/AcOEt: 1/1, $KMnO_4$, UV) 0.47; ^1H NMR (300 MHz, $CDCl_3$) δ 7.27-7.18 (m, 2H), 6.90-6.82 (m, 2H), 5.40 (d, 1H, *J* 9.0 Hz), 4.45 (s, 2H, H_6), 4.39 (dd, 1H, *J* 16.1, 6.2 Hz), 4.23 (br s, 1H), 3.78 (s, 3H), 3.72 (s, 3H), 3.51 (dd, 1H, *J* 8.9, 5.4 Hz), 3.43 (m, 1H), 2.98 (br s, 1H), 1.43 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.4, 159.3, 155.8, 129.6, 129.4, 113.8, 80.3, 73.1, 70.7, 70.3, 55.2, 52.5, 52.3, 28.2; HPLC : Chiralpak IA, hexane/*i*PrOH 95/5, 1 mL/min, λ = 215 nm; t_R [*syn*] = 37.71 min, t_R [*syn*] = 42.65 min, t_R [*anti*] = 50.56 min, t_R [*anti*] = 61.98 min.

Methyl (2*R*,3*R*)-2-[(*tert*-butoxycarbonyl)amino]-3-[(*tert*-butyldimethylsilyl)oxy]-4-[(4-methoxybenzyl)oxy]-butanoate (*syn*-**24**). To a solution of *syn*-**23** (97 mg, 0.26 mmol, 1 equiv) in dry DMF (0.5 mL) were added successively imidazole (54 mg, 0.79 mmol, 3 equiv) and TBSCl (99 mg, 0.66 mmol, 2.5 equiv) at rt. The mixture

was stirred for 18 h at rt, then saturated aqueous NaCl and *i*Pr_2O were added. The aqueous phase was extracted with *i*Pr_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (SiO_2, petroleum ether/EtOAc: 9/1) to give *syn*-**24** (111 mg, 87%) as a colorless oil. R_f (cyclohexane/AcOEt: 7/3, ninhydrin, UV) 0.67; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, 2H, *J* 8.5 Hz), 6.91-6.83 (m, 2H), 5.13 (d, 1H, *J* 9.9 Hz), 4.55 (dd, 1H, *J* 10.0, 1.4 Hz), 4.43 (s, 2H), 4.41-4.32 (m, 1H), 3.80 (s, 3H), 3.71 (s, 3H), 3.43 (dd, 1H, *J* 9.7, 6.4 Hz), 3.35 (dd, 1H, *J* 9.3, 5.8 Hz), 1.47 (s, 9H), 0.82 (s, 9H), 0.01 (s, 3H), -0.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8, 159.2, 156.0, 130.0, 129.4, 113.7, 79.8, 73.1, 71.5, 70.7, 55.7, 55.2, 52.2, 28.3, 25.6, 17.9, –4.5, –5.4.

(2*R*,3*R*)-2-[(*tert*-Butoxycarbonyl)amino]-3-[(*tert*-butyldimethylsilyl)oxy]-4-[(4-methoxybenzyl)oxy]butanoic acid (*syn*-**B'**). To a solution of *syn*-**24** (48 mg, 0.099 mmol, 1 equiv) in water/MeOH (0.2 mL:1.4 mL) was added at rt an aqueous solution of potassium hydroxide (400 μL, 0.20 mmol, 2 équiv, 0.5 M). The mixture was stirred at 40 °C for 4 h, then quenched with a 1M HCl solution. The aqueous layer was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash chromatography (SiO_2, CH_2Cl_2/MeOH: 8/2) afforded *syn*-**B'** as a colorless oil (20 mg, 43%). R_f (cyclohexane/AcOEt: 8/2, ninhydrin, UV) 0.15; $[\alpha]_D^{20}$: –7.3 (*c* 0.78, $CHCl_3$); ^{1}H NMR (300 MHz, MeOD) δ 7.30-7.22 (m, 2H), 6.92-6.85 (m, 2H), 4.44 (br s, 2H), 4.39 (br s, 2H), 3.78 (s, 3H), 3.43-3.34 (m, 2H), 1.47 (s, 9H), 0.85 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (75 MHz, MeOD) δ 174.4, 160.8, 157.9, 131.3, 130.6, 114.7, 80.9, 74.0, 72.9, 71.6, 56.8, 55.6, 28.7, 26.3, 18.9, –4.3, –5.0.

Methyl (2*S*,3*R*)-2-[(*tert*-butoxycarbonyl)amino]-3-hydroxy-4-[(4-methoxybenzyl)oxy]butanoate (*anti*-**23**). A reaction vessel fitted with a rubber septum equipped with a balloon of argon was charged with the ester **17** (124 mg, 0.34 mmol, 1 equiv) and CH_2Cl_2 (2.5 mL). 126 μL of a 0.0027 M solution of **Cat III** [RhCl(Cp*)((*R*,*R*)-teth-TsDPEN)] (0.1 mol%) in CH_2Cl_2 was added and the resulting mixture was subjected to three vacuum/argon cycles before the azeotropic mixture HCOOH/NEt_3 (5/2) (0.17 mL, 0.68 mmol, 2 equiv) was added dropwise. The reaction mixture was stirred at rt for 4 h (monitored by TLC). Saturated $NaHCO_3$ was added and the aqueous layer was extracted with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The conversion and the diastereoisomeric ratio were determined by ^{1}H NMR analysis of the crude product. The crude product was purified by flash chromatography (SiO_2, pentane/EtOAc: 7/3) to afford compound *anti*-**23** (88 mg, 70%). R_f (cyclohexane/AcOEt: 6/4, $KMnO_4$, UV) 0.33; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 – 7.21 (m, 2H), 6.87 (d, *J* 8.6 Hz, 2H), 5.58 (d, *J* 7.1 Hz, 1H), 4.45 (s, 2H), 4.42 – 4.15 (m, 2H), 3.79 (s, 3H), 3.73 (s, 3H), 3.55 – 3.41 (m, 2H), 2.87 (d, *J* 4.0 Hz, 1H), 1.43 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.4, 159.3, 155.9, 129.6, 129.5, 113.8, 80.0, 73.1 (2C), 70.7, 70.3, 55.2, 52.5, 28.2; HPLC : Chiralpak IA, hexane/*i*PrOH 95/5, 1 mL/min, λ = 215 nm; t_R [*syn*] = 37.71 min, t_R [*syn*] = 42.65 min, t_R [*anti*-(*R*,*S*)] = 50.56 min, t_R [*anti*-(*S*,*R*)] = 61.98 min (major).

Methyl (2*S*,3*R*)-2-[(*tert*-butoxycarbonyl)amino]-3-[(*tert*-butyldimethylsilyl)oxy]-4-[(4-methoxybenzyl)oxy]-butanoate (*anti*-**24**). To a solution of *anti*-**23** (173 mg, 0.47 mmol, 1 equiv) in dry DMF (1 mL) were added successively imidazole (64 mg, 0.94 mmol, 2 equiv) and TBSCl (107 mg, 0.71 mmol, 1.5 equiv) at rt. The mixture was stirred for 33 h at rt, then brine and *i*Pr_2O were added. The aqueous phase was extracted with *i*Pr_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (SiO_2, petroleum ether/EtOAc: 9/1) to give *anti*-**24** (115 mg, 51%) as a colorless oil. R_f (cyclohexane/EtOAc:8/2, ninhydrin, UV) 0.45; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, *J* 8.2 Hz, 2H), 6.87 (d, *J* 8.2 Hz, 1H), 5.13 (d, *J* 10.0 Hz, 1H), 4.56 – 4.35 (m, 2H), 4.45 (s, 2H), 3.80 (s, 3H), 3.72 (s, 3H), 3.46 – 3.33 (m, 2H), 1.47 (s, 9H), 0.85 (s, 9H), 0.01 (s, 3H), –0.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8, 159.2, 156.0, 130.0, 129.4, 113.8, 79.8, 73.1, 71.6, 70.7, 55.7, 55.2, 52.2, 29.7, 28.3, 25.7, –4.5, –5.4.

(2*S*,3*R*)-2-[(*tert*-Butoxycarbonyl)amino]-3-[(*tert*-butyldimethylsilyl)oxy]-4-[(4-methoxybenzyl)oxy]butanoic acid (*anti*-**B'**). To a solution of *anti*-**24** (93 mg, 0.19 mmol, 1 equiv) in THF (3 mL) was added at rt a 2 M solution of TMSOK (0.76 mL, 1.52 mmol, 8 equiv) in THF. After 1.5 h, the reaction medium was quenched with a 10% aqueous solution of citric acid (5 mL). The phases were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography (SiO_2, CH_2Cl_2/MeOH: 9/1) afforded *anti*-**B'** as a pale yellow oil (59 mg, 66%). R_f (CH_2Cl_2/MeOH:9/1, ninhydrin, UV) 0.26; ^{1}H NMR (300 MHz, MeOD) δ 7.30 – 7.22 (m, 2H), 6.92 – 6.85 (m, 2H), 4.44 (bs, 2H), 4.39 (bs, 2H), 3.78 (s, 3H), 3.43 – 3.34 (m, 2H), 1.47 (s, 9H), 0.85 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (75 MHz, MeOD) δ 174.4, 160.8, 157.9, 131.3, 130.6, 114.7, 80.9, 74.0, 72.9, 71.6, 56.8, 55.6, 28.7, 26.3, 18.9, –4.3, –5.0.

Methyl (*R*)-3-(benzyloxy)-2-methylpropanoate (**26**). To a solution of (*R*)-Roche ester **25** (200 mg, 1.69 mmol, 1 equiv) in CH_2Cl_2 (3 mL) was added at 0 °C benzyl trichloroacetimidate (640 mg, 2.54 mmol, 1.5 equiv). A solution of CF_3SO_3H in CH_2Cl_2 (0.85 M, 100 µL, 0.09 mmol, 0.05 equiv) was added at 0 °C and the mixture was stirred at room temperature for 44 h. After filtration, the filtrate was concentrated under reduced pressure and saturated aqueous $NaHCO_3$ (15 mL) was added. The aqueous layer was extracted with EtOAc, the combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (SiO_2, petroleum ether/Et_2O: 95/5) to afford the desired product **26** (262 mg, 74%) as a yellow oil. R_f (cyclohexane/EtOAc: 9/1, UV, $KMnO_4$) 0.30; $[\alpha]_D^{20}$ –8.0 (c 1.60, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 7.38 – 7.24 (m, 5H), 4.53 (s, 2H), 3.70 (s, 3H), 3.66 (dd, *J* 9.2, 7.3 Hz, 1H), 3.50 (dd, *J* 9.1, 5.9 Hz, 1H), 2.86 – 2.72 (m, 1H), 1.18 (d, *J* 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.4, 138.3, 128.5, 127.7 (2C), 73.2, 72.1, 51.8, 40.3, 14.1.

(*S*)-3-(Benzyloxy)-2-methylpropan-1-ol (**27**). To a suspension of $LiAlH_4$ (287 mg, 7.56 mmol, 1.5 equiv) in Et_2O (7.5 mL) was added dropwise a solution of **26** (1.05 g, 5.04 mmol, 1 equiv) in Et_2O (7.5 mL) at 0 °C. The mixture was stirred for 1.5 h and 600 mg of SiO_2 were added at 0 °C, followed by water (1 mL), an aqueous solution of 15% NaOH (3 mL) and water again (1 mL). $MgSO_4$ was added, the mixture was filtered and the solvent was removed under reduced pressure to afford the desired product **27** (866 mg, 95%) as a colorless oil. R_f (cyclohexane/EtOAc: 8/2, $KMnO_4$) 0.19; $[\alpha]_D^{20}$ –22.2 (c 0.45, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.39 – 7.24 (m, 5H), 4.52 (s, 2H), 3.68 – 3.52 (m, 3H), 3.43 (dd, *J* 9.0, 8.1 Hz, 1H), 2.52 (s, 1H), 2.15 – 2.02 (m, 1H), 0.89 (d, *J* 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.2, 128.6, 127.9, 127.7, 75.6, 73.5, 68.0, 35.7, 13.6.

(*R*)-[(3-Iodo-2-methylpropoxy)methyl]benzene (**28**). To a solution of PPh_3 (1.40 g, 5.33 mmol, 1.2 equiv) in CH_2Cl_2 (15 mL) cooled to 0 °C were successively added imidazole (453 mg, 6.66 mmol, 1.5 equiv) and I_2 (1.52 g, 5.99 mmol, 1.35 equiv). A solution of **27** (800 mg, 4.44 mmol, 1 equiv) in CH_2Cl_2 (2.5 mL) was added and the mixture was stirred at room temperature for 2 h. The solvent was removed under reduced pressure and saturated aqueous $Na_2S_2O_3$ was added. The aqueous layer was extracted with Et_2O and the combined organic layers were washed with water and brine, dried over $MgSO_4$ and concentrated under reduced pressure. Pentane was added, the suspension was filtered and the solvent was removed under reduced pressure. The crude mixture was purified by flash column chromatography (SiO_2, petroleum ether/toluene: 83/7) to afford the desired product **28** (1.04 g, 81%) as a yellow oil. R_f (cyclohexane/EtOAc: 98/2, phosphomolybdic acid) 0.23; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.40 – 7.24 (m, 5H), 4.53 (s, 2H), 3.40 (dd, *J* 9.3, 5.2 Hz, 1H), 3.35 – 3.26 (m, 3H), 1.87 – 1.70 (m, 1H), 1.00 (d, *J* 6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.5, 128.5, 127.8 (2C), 74.3, 73.3, 35.3, 17.8, 14.1.

Methyl (*S*)-7-(benzyloxy)-6-methyl-3-oxoheptanoate (**29**). To a suspension of NaH (60% dispersion in mineral oil) (91 mg, 2.27 mmol, 1.5 equiv) in THF (3 mL) was added dropwise methyl acetoacetate (0.16 mL, 1.52 mmol, 1 equiv) at 0 °C. The mixture was stirred at 0 °C for 10 min and a 2.28 M solution of *n*BuLi (0.73 mL, 1.67

mmol, 1.1 equiv) was added dropwise. The mixture was stirred at 0 °C for 10 min and a solution of **28** (484 mg, 1.67 mmol, 1.1 equiv) in THF (2.5 mL) was added dropwise. The mixture was stirred at room temperature for 23 h. A 10% aqueous solution of HCl (8 mL) and AcOEt (8 mL) were added and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with water and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (SiO_2, petroleum ether/EtOAc: 98/2 then 85/15) to afford the desired product **29** (238 mg, 56%) as a yellow oil. R_f (cyclohexane/EtOAc: 8/2, $KMnO_4$) 0.40; $[\alpha]_D^{20}$ –5.8 (c 0.60, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.38 – 7.25 (m, 5H), 4.48 (s, 2H), 3.73 (s, 3H), 3.43 (s, 2H), 3.29 (d, *J* 5.9 Hz, 2H), 2.68 – 2.47 (m, 2H), 1.85 – 1.68 (m, 2H), 1.57 – 1.40 (m, 1H), 0.92 (d, *J* 6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 202.9, 167.8, 138.7, 128.5, 127.7, 127.7, 75.6, 73.2, 52.5, 49.1, 40.9, 33.0, 27.5, 17.1.

Methyl (3*R*,6*S*)-7-(benzyloxy)-3-hydroxy-6-methylheptanoate *(R,S)*-(**30**). Ru(COD)[η^3-$(CH_2)_2CHCH_3]_2$ (4.1 mg, 0.0129 mmol, 0.02 equiv.) and (*R*)-SYNPHOS (9.1 mg, 0.0142 mmol, 0.022 equiv.) were placed in a Schlenk tube, which was purged with argon. Anhydrous acetone (0.7 mL), previously degassed by three vacuum-argon cycles, and a 0.165 M solution of methanolic hydrobromic acid (0.17 mL, 0.0285 mmol, 0.044 equiv.) were successively added. The suspension was stirred at room temperature for 30 min. The solvent was evaporated under vacuum to provide the catalyst as an orange solid. A solution of **29** (180 mg, 0.647 mmol, 1 equiv) in previously degassed MeOH (1 mL) was added and the mixture was stirred under 11 bar of H_2 at 50 °C for 22 h. The solvent was evaporated under reduced pressure and the crude mixture was purified by flash column chromatography (petroleum ether/AcOEt: 8/2) to afford the desired product (*R*,*S*)-**30** (168 mg, 93%) as a yellow oil. R_f (cyclohexane/EtOAc: 7/3, $KMnO_4$) 0.28; $[\alpha]_D^{20}$ –14.8 (c 0.50, $CHCl_3$); ^{1}H NMR (C_6D_6, 300 MHz) δ 7.34 – 7.28 (m, 2H), 7.23 – 7.06 (m, 3H), 4.33 (s, 2H), 3.91 – 3.80 (m, 1H), 3.28 (s, 3H), 3.17 (dd, *J* 8.9, 5.8 Hz, 1H), 3.10 (dd, *J* 8.9, 6.2 Hz, 1H), 2.78 (d, *J* 3.7 Hz, 1H), 2.22 (dd, *J* 16.2, 8.0 Hz, 1H), 2.15 (dd, *J* 16.2, 4.2 Hz, 1H), 1.79 – 1.54 (m, 2H),1.43 – 1.22 (m, 2H), 1.16 – 1.01 (m, 1H), 0.91 (d, *J* 6.6 Hz, 3H); ^{13}C NMR (C_6D_6, 75 MHz) δ 173.2, 139.5, 128.6, 127.8, 127.6, 75.8, 73.2, 68.4, 51.1, 41.5, 34.4, 33.9, 29.9, 17.5.

Methyl (3*S*,6*S*)-7-(benzyloxy)-3-hydroxy-6-methylheptanoate (*S,S*)-(**30**). (*S*,*S*)-**30** was obtained in 87% yield using (*S*)-SYNPHOS and the same protocol as for (*R*,*S*)-**30**. R_f (cyclohexane/EtOAc: 7/3, $KMnO_4$) 0.33; $[\alpha]_D^{20}$ +6.8 (c 0.40, $CHCl_3$); ^{1}H NMR (C_6D_6, 300 MHz) δ 7.34 – 7.28 (m, 2H), 7.23 – 7.06 (m, 3H), 4.33 (s, 2H), 3.92 – 3.79 (m, 1H), 3.27 (s, 3H), 3.17 (dd, *J* 8.9, 6.0 Hz, 1H), 3.11 (dd, *J* 8.9, 6.3 Hz, 1H), 2.75 (s, 1H), 2.22 (dd, *J* 16.2, 8.3 Hz, 1H), 2.14 (dd, *J* 16.2, 4.0 Hz, 1H), 1.78-1.61 (m, 1H), 1.52 – 1.08 (m, 4H), 0.90 (d, *J* 6.7 Hz, 3H); ^{13}C NMR (C_6D_6, 75 MHz) δ 173.1, 139.5, 128.4, 127.8, 127.7, 75.9, 73.2, 68.3, 51.1, 41.6, 33.8, 33.8, 29.8, 17.4.

Methyl (3*R*,6*S*)-7-(benzyloxy)-3-[(*tert*-butyldimethylsilyl)oxy]-6-methylheptanoate (*R*,*S*)-(**31**). To a solution of (*R*,*S*)-**30** (137 mg, 0.49 mmol, 1 equiv) in CH_2Cl_2 (3 mL) cooled to 0 °C were successively added 2,6-lutidine (0.45 mL, 1.96 mmol, 4 equiv) and TBSOTf (0.40 mL, 3.42 mmol, 7 equiv). The mixture was stirred at 0 °C for 3 h and quenched by saturated aqueous NH_4Cl at 0 °C. The aqueous layer was extracted with CH_2Cl_2, the combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude mixture was purified by silica gel column chromatography (pentane/AcOEt: 97/3) to afford the desired product (*R*,*S*)-**31** (159 mg, 82%) as a yellow oil. R_f (cyclohexane/AcOEt: 7/3, $KMnO_4$) 0.75; $[\alpha]_D^{20}$: –15.8 (c 0.45, $CHCl_3$). ^{1}H NMR (C_6D_6, 300 MHz) δ 7.34 – 7.28 (m, 2H), 7.24 – 7.06 (m, 3H), 4.33 (s, 2H), 4.26 – 4.16 (m, 1H), 3.37 (s, 3H), 3.17 (dd, *J* 8.9, 6.0 Hz, 1H), 3.12 (dd, *J* 8.9, 6.2 Hz, 1H), 2.45 (dd, *J* 14.7, 7.7 Hz, 1H), 2.29 (dd, *J* 14.7, 4.8 Hz, 1H), 1.78 – 1.62 (m, 1H), 1.62-1.40 (m, 3H), 1.22-1.04 (m, 1H), 0.98 (s, 9H), 0.92 (d, *J* 6.7 Hz, 3H), 0.11 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (C_6D_6, 75 MHz) δ 171.7, 139.5, 128.6, 128.4, 127.7, 75.8, 73.2, 70.1, 51.0, 42.5, 35.3, 34.0, 29.2, 26.1, 18.3, 17.4, –4.3, –4.6.

Methyl (3*S*,6*S*)-7-(benzyloxy)-3-((*tert*-butyldimethylsilyl)oxy)-6-methylheptanoate (*S*,*S*)-(**31**). Compound (*S*,*S*)-**31** was obtained in 96% yield following the same protocol as for compound (*S*,*R*)-**31**. R_f

(cyclohexane/AcOEt: 7/3, $KMnO_4$) 0.68; $[\alpha]_D^{20}$: +11.5 (c 0.75, $CHCl_3$); ^1H NMR (C_6D_6, 300 MHz) δ 7.34 – 7.28 (m, 2H), 7.24 – 7.06 (m, 3H), 4.33 (s, 2H), 4.25 – 4.15 (m, 1H), 3.37 (s, 3H), 3.18 (dd, *J* 8.9, 6.0 Hz, 1H), 3.12 (dd, *J* 8.9, 6.2 Hz, 1H), 2.45 (dd, *J* 14.7, 7.7 Hz, 1H), 2.29 (dd, *J* 14.7, 4.8 Hz, 1H), 1.78 – 1.62 (m, 1H, H_7), 1.59 – 1.40 (m, 3H), 1.22 – 1.04 (m, 1H), 0.98 (s, 9H), 0.92 (d, *J* 6.7 Hz, 3H), 0.11 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (C_6D_6, 75 MHz) δ 171.7, 139.5, 128.6, 127.7, 127.6, 75.8, 73.2, 70.1, 51.0, 42.6, 35.3, 34.0, 29.2, 26.1, 18.3, 17.3, –4.3, –4.6.

Methyl (3*R*,6*S*)-3,7-dihydroxy-6-methylheptanoate (*R*,*S*)-(**32**). To a solution of (*R*,*S*)-**31** (138 mg, 0.35 mmol, 1 equiv) in THF (1.8 mL) was added palladium on carbon 10% (56 mg, 0.05 mmol, 0.15 equiv). The medium was purged with argon and three vaccum–H_2 cycles were made. The mixture was stirred at room temperature for 22 h under 1 atm of H_2, filtered on celite and concentrated under reduced pressure. The crude mixture was purified on silica gel column chromatography (petroleum ether/MTBE: 6/4) to afford the desired product (*R*,*S*)-**32** (102 mg, 95%) as a colorless oil. R_f (cyclohexane/AcOEt: 7/3, $KMnO_4$) 0.38; $[\alpha]_D^{20}$: –17.8 (c 0.75, $CHCl_3$); ^1H NMR (C_6D_6, 300 MHz) δ 4.24 – 4.14 (m, 1H), 3.38 (s, 3H), 3.21 (dd, *J* 10.4, 5.7 Hz, 1H), 3.15 (dd, *J* 10.4, 5.9 Hz, 1H), 2.44 (dd, *J* 14.7, 7.6 Hz, 1H), 2.29 (dd, *J* 14.7, 4.8 Hz, 1H), 1.59 – 1.26 (m, 4H), 1.12 – 1.00 (m, 1H), 0.98 (s, 9H), 0.82 (d, *J* 6.6 Hz, 3H), 0.11 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (C_6D_6, 75 MHz) δ 171.8, 70.0, 67.8, 51.1, 42.4, 36.0, 35.2, 28.6, 26.1, 18.3, 16.8, –4.3, –4.6.

Methyl (3*S*,6*S*)-3,7-dihydroxy-6-methylheptanoate (*S*,*S*)-(**32**). Compound (*S*,*S*)-**32** was obtained in 93% yield following the same procedure than for compound (*S*,*R*)-**32**. R_f (cyclohexane/AcOEt: 7/3, $KMnO_4$) 0.43; $[\alpha]_D^{20}$: +13.7 (c 0.80, $CHCl_3$); ^1H NMR (C_6D_6, 300 MHz) δ 4.23 – 4.13 (m, 1H), 3.37 (s, 3H), 3.23 (dd, *J* 10.3, 5.5 Hz, 1H), 3.16 (dd, *J* 10.3, 6.0 Hz, 1H), 2.45 (dd, *J* 14.7, 7.8 Hz, 1H), 2.28 (dd, *J* 14.7, 5.0 Hz, 1H), 1.58 – 1.24 (m, 4H), 1.13 – 1.00 (m, 1H), 0.98 (s, 9H), 0.82 (d, *J* 6.6 Hz, 3H), 0.11 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (C_6D_6, 75 MHz) δ 171.8, 70.1, 67.8, 51.1, 42.5, 36.1, 35.2, 28.6, 26.1, 18.3, 16.8, –4.4, –4.6.

Methyl (3*R*,6*S*)-3-hydroxy-6-methyl-7-oxoheptanoate (*R*,*S*)-(**33**). To a solution of (*R*,*S*)-**32** (82 mg, 0.27 mmol, 1 equiv) in CH_2Cl_2 (1 mL) was added DMP (171 mg, 0.40 mmol, 1.5 equiv) and the mixture was stirred at room temperature for 3 h. After dilution with Et_2O, the organic layer was successively washed with saturated aqueous $Na_2S_2O_3$ and a saturated solution of $NaHCO_3$. The aqueous layer was extracted with AcOEt, the combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude mixture was purified by silica gel column chromatography (petroleum ether/*i*Pr_2O: 8/2) to afford the desired product (*R*,*S*)-**33** (52 mg, 64%) as a colorless oil. R_f (cyclohexane/AcOEt: 6/4, $KMnO_4$) 0.68; ^1H NMR (C_6D_6, 300 MHz) δ 9.26 (d, *J* 1.6 Hz, 1H), 4.17 – 4.06 (m, 1H), 3.37 (s, 3H), 2.38 (dd, *J* 14.8, 7.4 Hz, 1H), 2.19 (dd, *J* 14.8, 5.0 Hz, 1H), 1.78 (sxtd, *J* 6.9, 1.5 Hz, 1H), 1.56-1.44 (m, 1H), 1.39 – 1.25 (m, 2H), 1.19 – 1.05 (m, 1H), 0.95 (s, 9H), 0.75 (d, *J* 7.1 Hz, 3H), 0.09 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (C_6D_6, 75 MHz) δ 203.0, 171.5, 69.5, 51.1, 46.1, 42.3, 34.9, 26.0, 25.8, 18.2, 13.3, –4.4, –4.6.

Methyl (3*S*,6*S*)-3-hydroxy-6-methyl-7-oxoheptanoate (*S*,*S*)-(**33**). Compound (*S*,*S*)-**33** was obtained in 67% yield following the same procedure than for compound (*S*,*R*)-**33**. R_f (cyclohexane/AcOEt: 6/4, $KMnO_4$) 0.62; $[\alpha]_D^{20}$: +12.0 (c 0.40, $CHCl_3$); ^1H NMR (C_6D_6, 300 MHz) δ 9.27 (d, *J* 1.6 Hz, 1H), 4.16 – 4.06 (m, 1H), 3.37 (s, 3H), 2.39 (dd, *J* 14.8, 7.4 Hz, 1H), 2.19 (dd, *J* 14.8, 5.1 Hz, 1H), 1.79 (sxtd, *J* 6.5, 1.4 Hz, 1H), 1.56 – 1.41 (m, 1H), 1.40 – 1.24 (m, 2H), 1.20 – 1.06 (m, 1H), 0.95 (s, 9H), 0.74 (d, *J* 7.0 Hz, 3H), 0.09 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (C_6D_6, 75 MHz) δ 203.0, 171.5, 69.5, 51.1, 46.1, 42.4, 34.8, 26.0, 25.9, 18.2, 13.2, –4.4, –4.6.

Methyl (3*S*,6*S*,10*R*,11*R*,12*R*,13*R*)(*E*)-3,11,13-tris[(*tert*-butyldimethylsilyl)oxy]-12-{(6*S*,7*S*)(*E*)-7-[(*tert*-butyldimethylsilyl)oxy]-4,4,6,8-tetramethyl-5-oxonon-2-enamido}-7-hydroxy-6,8,10,14-tetramethylpentadec-8-enoate (**35**). To a solution of **34** (145 mg, 0.16 mmol, 1.4 equiv) and (*S*,*S*)-**33** (36 mg, 0.12 mmol, 1 equiv) in freshly distilled DMSO (4.1 mL) were successively added $CrCl_2$ (230 mg, 1.87 mmol, 16 equiv) and $NiCl_2$(dppe) (3.8 mg, 0.007 mmol, 0.06 equiv). Three vacuum/argon cycles were performed and the mixture was stirred at

room temperature for 21 h. A mixture of sodium serinate/AcOEt 1/1 (20 mL) was added at 0 °C and the medium was stirred at room temperature for 1 h. After filtration, the aqueous layer was extracted with AcOEt, the combined organic layers were washed with water and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude mixture was purified by silica gel column chromatography (pentane/*i*Pr_2O: 8/2 to 7/3 and 5/5) to afford the minor diastereomer (8 mg) and the major diastereomer (24 mg) as yellow oils (total yield: 25%).

Major diastereomer: R_f (cyclohexane/*i*Pr_2O:5/5, Kagi-Mosher) 0.38; ^{1}H NMR (C_6D_6, 300 MHz) δ 7.30 (d, *J* 15.5 Hz, 1H), 6.03 (d, *J* 9.8 Hz, 1H), 5.97 (d, *J* 15.5 Hz, 1H), 5.63 (d, *J* 9.2 Hz, 1H), 4.52 – 4.43 (m, 1H), 4.32 – 4.22 (m, 1H), 4.11 (dd, *J* 3.6, 0.9 Hz, 1H), 3.95 – 3.85 (m, 1H), 3.70 – 3.64 (m, 2H), 3.39 (s, 3H), 3.24 – 3.12 (m, 1H), 2.85 – 2.71 (m, 1H), 2.50 (dd, *J* 14.7, 7.7 Hz, 1H), 2.37 (dd, *J* 14.7, 4.6 Hz, 1H), 2.11 – 1.98 (m, 1H), 1.89 – 1.77 (m, 1H), 1.77 – 1.68 (m, 1H), 1.68 – 1.59 (m, 6H), 1.46 (m, 2H), 1.25 (s, 3H), 1.24 (s, 3H), 1.18 (dd, J 6.8, 5.4 Hz, 6H), 1.11 (d, *J* 7.1 Hz, 3H), 1.04 (s, 9H), 1.02 (s, 9H), 1.01 (s, 9H), 0.98 (s, 9H), 0.97 – 0.94 (m, 3H), 0.94 – 0.90 (m, 6H), 0.89 (d, *J* 5.6 Hz, 3H), 0.25 (s, 3H), 0.19 (s, 3H), 0.16 (s, 3H), 0.16 (s, 3H), 0.15 (s, 3H), 0.14 (s, 3H), 0.12 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (major isomer) (100 MHz, C_6D_6) δ 211.9, 171.7, 165.5, 149.2, 139.1, 128.3, 123.1, 83.7, 79.5, 78.9, 76.1, 70.4, 54.6, 51.3, 51.0, 45.1, 42.7, 40.0, 36.2, 35.2, 31.6, 31.4, 30.2, 28.8, 26.7, 26.4, 26.3, 26.1, 23.9, 23.0, 20.0, 19.9, 18.9, 18.8, 18.3, 18.0, 16.7, 16.6, 16.6, 16.3, 11.1, –2.6, –2.8, –3.4 (2C), –3.7, –4.2, –4.6 (2C). MS (ESI: NH_3) *m/z* 1093 $[M+Na]^+$, 1088 $[M+NH_4]^+$.

Methyl (3*R*,6*S*,10*R*,11*R*,12*R*,13*R*)(*E*)-3,11,13-tris[(*tert*-butyldimethylsilyl)oxy]-12-{(6*S*,7*S*)(*E*)-7-[(*tert*-butyldimethylsilyl)oxy]-4,4,6,8-tetramethyl-5-oxonon-2-enamido}-7-hydroxy-6,8,10,14-tetramethylpentadec-8-enoate (**36**). Compound **36** was obtained in 34% yield as a colorless oil from **34** (112 mg, 0.125 mmol, 1.2 equiv) and (*R*,*S*)-**33** (32 mg, 0.104 mmol, 1 equiv) following the same procedure than for compound **35**. ^{1}H NMR (major isomer) (400 MHz, C_6D_6) δ 7.36 (d, *J* 15.5 Hz, 1H), 6.09 (d, *J* 9.7 Hz, 1H), 5.97 (d, *J* 15.5 Hz, 1H), 5.42 (d, *J* 10.2 Hz, 1H), 4.23 (d, *J* 2.1 Hz, 2H), 4.15 (t, *J* 9.6 Hz, 1H), 3.92 (dd, *J* 9.2, 1.7 Hz, 1H), 3.62 (dd, *J* 9.6, 1.5 Hz, 1H), 3.55 (d, *J* 9.3 Hz, 1H), 3.36 (s, 3H), 3.21 (dd, *J* 9.2, 6.8 Hz, 1H), 2.78 – 2.73 (m, 1H), 2.46 (dd, *J* 14.8, 7.7 Hz, 1H), 2.26 (dd, *J* 14.8, 4.7 Hz, 1H), 2.03 – 2.00 (m, 2H), 1.83 (d, *J* 1.2 Hz, 3H), 1.77 – 1.72 (m, 1H), 1.36 (s, 3H), 1.27 (s, 3H), 1.18 – 1.14 (m, 11H), 1.10 (d, *J* 7.1 Hz, 3H), 1.02 (s, 18H), 0.995 (s, 9H), 0.991 (s, 9H), 1.02 – 0.90 (m, 12H), 0.18 (s, 3H), 0.17 (s, 3H), 0.15 (s, 6H), 0.15 (s, 3H), 0.13 (s, 3H), 0.12 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (major isomer) (100 MHz, C_6D_6) δ 211.9, 171.7, 165.5, 149.2, 139.1, 128.7, 123.1, 83.9, 79.5, 78.9, 76.1, 70.3, 54.6, 51.3, 51.0, 45.1, 42.7, 40.0, 36.5, 35.4, 32.4, 31.6, 31.4, 30.2, 30.0, 29.8, 28.7, 26.7, 26.4, 26.3, 26.1, 23.9, 23.1, 23.0, 19.9, 18.9, 18.8, 18.0, 16.3, 14.4, 11.1, –2.6, –2.8, –2.8, –3.5, –3.7, –4.2, –4.5, –4.6; MS (ESI, NH_3) : *m/z* 1071 $[M+H]^+$, 1093 $[M+Na]^+$, 1088 $[M+NH_4]^+$.

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