Asymmetric Total Synthesis of (−)-Pironetin Employing the SAMP/RAMP Hydrazone Methodology**

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Dedicated to Professor Alain Krief on the occasion of his 65th birthday

Abstract: A convergent asymmetric total synthesis of pironetin (1), a polyketide with immunosuppressive, antitumor, and plant-growth regulating activities is described. The synthesis was realized by coupling between the C8–C14 2 and C7–C2 15 fragments, respectively, by using a Mukaiyama-aldol reaction. The stereogenic centers of each fragment were generated by employing the SAMP/RAMP hydrazone (SAMP = (S)-1-amino-2-methoxymethylpyrrolidine, RAMP = (R)-1-amino-2-methoxy-methylpyrrolidine) methodology as a key step. An asymmetric α-alkylation of diethyl ketone permitted the introduction of the C10 stereogenic center of 2, whereas the stereocenters C4 and C5 of 15 were installed by an asymmetric aldol reaction. Finally, the formation of the α,β-unsaturated γ-lactone was achieved by ring-closing metathesis in the presence of catalytic amounts of titanium tetraisopropoxide.

Keywords: aldol reaction · asymmetric synthesis · hydrazones · metathesis · natural products · pironetin

Introduction

Pironetin (1) (PA-48153C) was first isolated in 1993 by Yoshida et al.[1] from the fermentation broth of Streptomyces prunicolor PA-48153, and then in 1994 by Kobayashi and co-workers[2] from Streptomyces sp. NK10958. This natural lactone displays very interesting and diverse biological activities. Pironetin shows a potent immunosuppressive effect on the responses of both T and B-lymphocytes to mitogens, whereas immunosuppressants cyclosporin A (CsA) and FK-506 only antagonize T-cell activation.[1a] Apart from being an immunosuppressive agent with an original mode of action, pironetin also exhibits a strong regulating activity in plant growth.[1] More importantly, it has recently been identified as a strong antitumor agent, which influences the dynamic of the tubulin-microtubules system inhibiting the polymerization of tubulin.[3] Its uniqueness comes from its ability to bind covalently to the α-subunit of tubulin in contrast to colchicine, vinblastin, or rhizoxin which bind to different sites of β-tubulin.[3a] Based on all these characteristics, pironetin 1 is considered to be a very attractive research target and several total syntheses have already been described in the literature.[4] However, this metabolite suffers from problems of toxicity and side effects; therefore, some structural modifications of the natural product have been studied in order to reduce its toxicity and increase its specificity.[3]

Due to its unique properties and low extraction yields from nature, it was our aim to establish an efficient total synthesis of pironetin 1, which also enabled an easy access for the preparation of other structural analogues. We envisaged its synthesis by employing the SAMP/RAMP hydrazone (SAMP = (S)-1-amino-2-methoxymethylpyrrolidine, RAMP = (R)-1-amino-2-methoxymethylpyrrolidine) alkylation[3] and aldolization[5a,6] methodology developed earlier by our group.

Our retrosynthetic analysis was initially based on the asymmetric aldol reaction between the ketone 2 and the lactone-aldehyde 3, in which the stereogenic center C10 could be introduced by hydrazone α-alkylation, and the C4 and C5 centers by a hydrazone aldol reaction (Scheme 1).
Results and Discussion

For the synthesis of ketone 2, the stereogenic center at C₁₀ was generated by asymmetric α-alkylation of 3-pentanone via its SAMP-hydrazone derivative 4 with (E)-crotyl bromide. After removal of the chiral auxiliary from the product hydrazone 5 by standard acidic conditions in a two-phase system, ketone 2 was obtained with 98% ee (ee = enantiomeric excess) and with good yield over two steps (Scheme 2).

To introduce the stereogenic centers C₄ and C₅ of the lactone aldehyde building block ent-3,[⁷] we used the syn-selective asymmetric aldol reaction via titanium azoenolates of SAMP hydrazones.[⁶,⁷] Butanal SAMP hydrazone 6 was treated with titanium tetrachloride and Hünig's base to provide the titanated hydrazone as a deep-red solution in dichloromethane. Subsequent trapping with the aldehyde 7, followed by protection as a TBS (TBS = tert-butyldimethylsilyl) ether, furnished the syn-configured SAMP hydrazone ent-8 as the major diastereomer (de = 55%, de ≥ 96% after HPLC, ee = 96%; de = diastereomeric excess) with good yield. Oxidative cleavage of the chiral auxiliary by using magnesium monoperoxyphtalate hexahydrate (MMPP)[⁸] afforded the corresponding nitrile without racemization in 92% yield. Its reduction with DIBAL-H (DIBAL-H = diisobutylaluminum hydride), followed by Wittig olefination of the corresponding aldehyde ent-9 gave the olefin ent-10 in good yield. After TBS deprotection and esterification with acrylic acid, the diene precursor of the metathesis ent-11 was isolated in 75% yield over two steps. Ring-closing meta-

Several oxidation attempts were studied on 12 by using classical conditions, such as pyridinium chlorochromate,[⁹] pyridinium dichromate,[¹⁰] DMP (DMP = Dess–Martin periodinane),[¹¹] TPAP/NMO (TPAP = tetra-n-propylammonium perruthenate, NMP = N-methyl-2-pyrrolidinone)[¹²] and the Swern oxidation.[¹³] Unfortunately, only traces of aldehyde were observed and were accompanied by decomposition products of the starting alcohol in all cases. Consequently, we had to modify our first strategy.

In the new approach, the lactone formation was envisaged at the end of the synthesis by means of a transition-metal-catalyzed ring-closing metathesis of the diene 13. We considered a Mukaiyama-aldol reaction between the alkylated ketone 2 and the aldehyde 15 to create the C₇–C₉ bond. The stereogenic center at C₉ may be controlled by a samarium-iiodide-mediated Tishchenko reduction of the β-hydroxyketone 14 (Scheme 4).

For the synthesis of the aldehyde 15, planned to be used in the aldol reaction with 2, the benzyl group of 10 was removed with calcium in liquid ammonia, and the resulting primary alcohol was oxidized under Swern conditions to

![Scheme 1. Retrosynthetic analysis of pironetin.](image)

![Scheme 2. Synthesis of the α-alkylated ketone 2: a) 1)LiTMP, THF, 0°C, 30 min; 2) (E)-crotyl bromide, –110°C; b) pentane/4% HCl, RT, 1 h, 78% over two steps, 98% ee (CSP GC analysis, Lipodex E).](image)

![Scheme 3. Attempts to synthesize the aldehyde ent-3: a) TiCl₄, DIPEA (DIPEA = disopropyl ethyl amine), dichloromethane, –78°C–RT; b) TBSOTf, lutidine, dichloromethane, –78°C, 80% over two steps, 96% ee, 55% de (de ≥ 96% after HPLC); c) MMPP, EtOH, buffer pH 7, RT, 92%; d) DIBAL–H, THF, 0°C–RT, 86%; e) Ph₃P=CH₂, THF, –78°C–RT, 92%; f) TBAF, THF, RT, 97%; g) acryl acid, DMAP, DDC, dichloromethane, 0°C–RT, 77%; h) Grubbs first-generation catalyst, Ti(OiPr)₄, dichloromethane, reflux, 96%; i) TiCl₄, dichloromethane, 0°C–RT, 91%.](image)
afford the desired aldehyde 15 in 83% yield over two steps. Deprotonation of the ketone 2 by using diphenyltetramethyldisilazane and n-butyllithium followed by trapping with a mixture of trimethylsilyl chloride and triethylamine furnished the Z enolate 16, which was used directly in a Mukaiyama-aldol reaction in the presence of triethylamine to give the ester 13.\(^\text{19}\) \(^\text{13}^\text{C}NMR spectroscopic analysis of the acetonide methyl group chemical shifts (δ = 24.9 and 25.0 ppm) of 21, easily achieved from 20 in two steps, proved the anti relationship between C7 and C6. The formation of the δ-lactone was carried out by employing the ring-closing metathesis with Grubbs first-generation catalyst and a catalytic amount of titanium isopropoxide.\(^\text{9}\) Finally, the removal of the acetate group provided the title natural product pironetin (1) in 80% yield (Scheme 6).\(^\text{4g}\)

The resulting alcohol 17 was easily converted to the acetonide 19 in two steps by removal of the acetate group and acetonide formation to determine the configuration. The anti relationship between C9 and C7 was established by \(^\text{13}^\text{C}NMR spectroscopy (the acetonide methyl group chemical shifts of 19, δ = 23.8 and 26.0 ppm). The alcohol on C9 was converted to the methyl ether by using proton sponge and Meerwein’s reagent (Me3OBF4) in dichloromethane.\(^\text{17}\) The cleavage of the TBS ether\(^\text{18}\) furnished the alcohol 20, which was then treated with acryloid chloride in THF in the presence of triethylamine to give the ester 13.\(^\text{19}\) \(^\text{13}^\text{C}NMR spectroscopic analysis of the acetonide methyl group chemical shifts (δ = 24.9 and 25.0 ppm) of 21, easily achieved from 20 in two steps, proved the anti relationship between C7 and C6. The formation of the δ-lactone was carried out by employing the ring-closing metathesis with Grubbs first-generation catalyst and a catalytic amount of titanium isopropoxide.\(^\text{9}\) Finally, the removal of the acetate group provided the title natural product pironetin (1) in 80% yield (Scheme 6).\(^\text{4g}\)
Conclusion

A convergent asymmetric total synthesis of pironetin (1) has been accomplished. The creation of the stereogenic centers at C₆, C₇, and C₈ were realized by employing the SAMP/RAMP hydrazone alkylation and aldolization methodology. The formation of the C₇=C₈ bond was carried out by a Mukaiyama-aldol reaction between ketone 2 and aldehyde 15, which installed the stereogenic centers C₇ and C₈ simultaneously. The last stereogenic center C₉ was introduced by means of a samarium-mediated Tishchenko reduction and the formation of the α,β-unsaturated δ-lactone was achieved by ring-closing metathesis. Our new approach should permit easy access to various stereoisomers and structural analogues. Indeed, all the configurations of the stereogenic centers of pironetin can be simply controlled by auxiliary exchange between SAMP and RAMP in the alkylation and aldol reactions or by modification of the experimental conditions for the aldol reaction between the fragments 2 and 15 as well as for the reduction of the δ-hydroxy ketone. Moreover, as it has already been described by our laboratory, the asymmetric α-alkylation of ketones by means of the SAMP/RAMP hydrazone methodology allows the introduction of a large variety of substituents R₁ in the C₁₀ position.

Experimental Section

General methods: Solvents were dried and purified prior to use. THF was freshly distilled over sodium metal under argon. Dichloromethane, dimethyl sulfoxide (DMSO), and triethylamine were distilled over KOH, CaH₂, and K₂CO₃, respectively. Analytical glass-backed TLC plates (silica gel 60 F₂₅₄) and silica gel (60, 40–63 μm) were purchased from Merck, Darmstadt. Reagents of commercial quality were used from freshly opened containers unless otherwise stated. Optical rotations were measured on a Perkin–Elmer P241 polarimeter and with solvents of Merck UVASOL quality. Microanalyses were obtained with a Heraeus CHN-O-RAPID, Vario EL elemental analyzer. ¹H and ¹³C NMR spectra were obtained on a Varian VXR 300, Gemini 300 (both 300 and 75 MHz), Varian Inova 400 (400 MHz and 100 MHz), or Varian Unity 500 (500 and 125 MHz) with TMS as the internal standard. IR spectra were recorded on a Perkin–Elmer FTIR 1760 spectrometer. Mass spectrometry was carried out on a Varian MAT 212, EI 70 eV, 1 mA and a Finnigan MAT SSQ7000, Cl 100 eV (relative intensities are reported in brackets). High-resolution mass spectra were recorded on a Finnigan MAT 95.

(E)-5-Benzyl-3-(tert-butyl(dimethyl)silyloxy)-2-ethylpentanal (13a-Si-d): A solution of crude product (5.0 mmol, 1.0 equiv) in CH₂Cl₂ (15 mL) under argon, the dark-red solution was stirred for 30 min at –78°C, then diisopropylethylamine (6.00 mmol, 1.2 equiv) was added over 7.5 min under argon. The dark-red solution was stirred for 30 min and a solution of hydrazone 1 (11.4 mmol, 1.0 equiv) in THF (20 mL) was added at 0°C. After stirring for 4 h at the same temperature, the mixture was cooled to –110°C and (E)-1-bromo-2-ene (68 mmol, 0.9 equiv) was slowly added in order to maintain the low temperature. After stirring for a further 30 min at –110°C, the mixture was allowed to warm up to room temperature overnight. The reaction was quenched with pH 7 buffer solution (330 mL) and then diluted with Et₂O (200 mL). The aqueous phase was extracted with Et₂O (3 × 150 mL), the combined organic layers were washed with brine, dried (MgSO₄), and concentrated under reduced pressure. The resulting crude ketone hydrazone 5 was distilled in pentane (140 mL) and cooled to –78°C for 2 h. An aqueous solution of HCl (4N, 60 mL) was added and the reaction mixture was vigorously stirred at room temperature for 1 h. The aqueous layer was separated, extracted with Et₂O (3 × 50 mL), and the organic extracts were combined, washed with brine (100 mL), dried (MgSO₄), filtered, and concentrated under reduced pressure. The crude product was purified by silica-gel flash chromatography (pentane/Et₂O 100:0) to afford the aldehydes 2 (7.5 g, 78% over two steps) as a clear liquid. [α]D²⁰ = +23.9 (c = 1.07 in CHCl₃); ¹H NMR (400 MHz, CDCl₃); δ = 5.49–5.39 (1H, 1H, 1H), 5.29–5.20 (1H, 1H), 2.43 (3d, J = 7.1 Hz, 2.2 Hz, 2H), 2.33–2.24 (1H, 1H), 2.06–1.97 (1H, 1H), 1.62 (dd, J₂,₂H = 6.2, 1.2 Hz, 3H), 1.04 (d, J₁,₁H = 7.1 Hz, 3H), 1.02 ppm (t, J₁,₁H = 7.1 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃); δ = 214.8, 128.2, 127.3, 46.4, 36.3, 34.6, 18.1, 16.3, 7.9 ppm; IR (film, CHCl₃). F = 3022, 2970, 2934, 2857, 1714, 1457, 1413, 1376, 1106, 1021, 969 cm⁻¹; MS (EI); m/z (%): 140 [M⁺]*, 112, 111, 83, 83, 67, 57, 56, 55, 53; elemental analysis calculated (%) for C₉H₁₆O (140.12): C 77.09, H 11.50; found: C 76.83, H 11.38.

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The combined organic layers were washed with brine (20 mL), dried over MgSO$_4$, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (pentane/EtO$_2$O 60:40) to give the corresponding alcohol (900 mg, 3.45 mmol, 82%) as a colorless oil. 

Acidic (1S,2S)-1-(2-Benzoyloxyethyl)-2-ethyl-but-3-enyl ester (ent-10): A solution of tetrabutylammonium fluoride (TBFA) in THF (16.4 mmol, 5.9 equiv) was added to a solution of ent-10 (970 mg, 2.87 mmol, 1.0 equiv) in THF (13 mL) under argon at room temperature. The reaction mixture was stirred for 16 h and was then quenched by addition of water (13 mL), followed by extractions with EtO$_2$O (3 × 10 mL). The combined organic layers were washed with brine (20 mL), dried over MgSO$_4$, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (pentane/EtO$_2$O 60:40) to give the corresponding alcohol (820 mg, 97%) as a colorless oil.

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MgSO₄, filtered, and concentrated in vacuo. Purification by silica-gel flash chromatography (EtOAc 100%) gave the desired product enr-12 (353 mg, 91%) as a colorless liquid. [α]D = −79.2 (c = 1.00 in CHCl₃); 

'H NMR (400 MHz, CDCl₃): δ = 0.04 (ddd, J = 17.0, 1.8, 0.5 Hz, 1H), 0.50 (ddd, J = 17.3, 1.9, 0.8 Hz, 1H), 0.98 (ddd, J = 6.6, 4.9, 1.8 Hz, 1H), 2.14–2.06 (m, 1H), 1.62–1.52 (m, 1H), 1.28–1.17 (m, 1H), 0.88 (s, 9H), 0.87 (t, J = 7.4 Hz, 3H), 0.09 (s, 3H), 0.05 ppm (s, 3H); 

'^C NMR (100 MHz, CDCl₃): δ = 202.3, 182.0, 137.5, 70.5, 52.5, 48.3, 25.8, 23.0, 18.0, 11.9, −4.5, −4.4 ppm; IR (film, CHCl₃): ν = 3097, 2954, 2802, 2719, 2727, 1466, 1360, 1255, 1091, 1003, 838, 777, 673, 552 ppm; MS (Cl−): m/z (%): 287 [M+1]⁻, 241, 213, 199, 187, 159, 125, 127, 107, 81.

(E)-5S,7K,10R,11R)-10-(tert-Butyldimethylsilyloxy)-11-ethyl-8-hydroxy-5,7-dimethyltrideca-2,12-diene-6-one (17): nBuLi (3.86 mmol, 2 equiv) was added to a solution of diphenyltetrachlorosilane (3.86 mmol, 2 equiv) in THF (7.7 mL) under argon at 0°C. After 10 min of stirring, the solution was cooled to −78°C and a solution of the ketone 2 (270 mg, 1.93 mmol, 1 equiv) in THF (1 mL) was added. After stirring for 1 h at −78°C, a solution of TMSCI (7.2 mmol, 4 equiv) and Et₂N (1.93 mmol, 1 equiv) in THF (1 mL) was added. The reaction was stirred for 15 min at −78°C, and then for 5 h at room temperature. The mixture was partitioned between pentane (100 mL) and saturated aqueous NaHCO₃ (50 mL). The pentane layer was dried (Na₂SO₄), filtered, and concentrated under reduced pressure. The crude product was used in the next step without purification.

BF₂OEt₂ (7.72 mmol, 4 equiv) was added to a stirred solution of enolide 16 (1.93 mmol, 1 equiv) and aldehyde 15 (1.93 mmol, 1 equiv) in anhydrous dichloromethane (15 mL) under argon at −78°C. The reaction was stirred at −78°C for 3 h and then partitioned between dichloromethane (100 mL) and saturated aqueous NaHCO₃ (50 mL). The aqueous layer was added to a stirred solution of dichloromethane (3×30 mL). The combined organic extracts were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. A short purification by flash chromatography (pentane/ EtOAc 95:5, 100:100) afforded a mixture of diastereoisomers (700 mg, 92% over two steps) as a clear oil, which contained 57% of the desired diastereoisomer 14 (399 mg).

The mixture of 4-hydroxyketone (1.77 mmol, 1.0 equiv) was dissolved in anhydrous THF (7.1 mL) under argon. To this was added freshly distilled acetaldehyde (7.08 mmol, 4.0 equiv). The solution was cooled to −15°C (methanol/ice bath) and a freshly prepared 0.1 mol solution of SmI₂ in THF (4 mL, 0.4 equiv) was added dropwise (30 min). The initial blue color disappeared within 15 s. After stirring for 1 h at −15°C, the reaction mixture was quenched by the addition of Et₂O (20 mL) and saturated aqueous NaHCO₃ (10 mL). The aqueous layer was extracted with Et₂O (3×3 mL) under argon. The organic layers were washed with brine (80 mL), dried over MgSO₄, filtered, and concentrated in vacuo. After short filtration on silica gel (pentane/EtOAc 80:20), the corresponding alcohol (500 mg, quantitative, clear oil) was used directly in the next step. 

'H NMR (400 MHz, CDCl₃): δ = 0.83 (s, 3H), 3.96 (dd, J = 17.0, 1.8 Hz, 1H), 1.04 (t, J = 7.4 Hz, 3H), 0.67 (s, 9H), 0.65 (s, 9H), 0.28 ppm (s, 3H); IR (film, CHCl₃): ν = 3428, 2949, 1471, 1469, 1341, 1282, 1184, 1089, 973, 885, 768, 668 ppm; MS (Cl-): m/z (%): 259 [M+1]⁻, 243, 189, 173, 131, 127, 109, 83.

DMSO (8 mL) and Et₃N (9.69 mmol, 5.0 equiv) were added to a solution of the alcohol (500 mg, 1.94 mmol, 1.0 equiv) in dichloromethane (8 mL) under argon. The solution was cooled to 0°C and SO₂/pyridine complex (9.69 mmol, 5.0 equiv) was added. After 30 min of stirring, the reaction mixture was diluted with Et₂O (20 mL) and washed with a saturated solution of NH₄Cl (15 mL). The organic solution was dried over MgSO₄, filtered, and concentrated in vacuo. Purification by flash chromatography on silica gel (pentane/EtOAc 95:5, 90:10) afforded the aldehyde 15 (414 mg, 83% over two steps) as a colorless oil. 

'H NMR (400 MHz, CDCl₃): δ = 0.90 (s, 3H), 1.06 (t, J = 7.4 Hz, 3H), 0.77 (t, J = 7.4 Hz, 3H), 0.05 ppm (s, 3H); IR (film, CHCl₃): ν = 3429, 3094, 2955, 2819, 2727, 1727, 1460, 1360, 1255, 1091, 1003, 920, 838, 777, 673, 552 ppm; MS (Cl−): m/z (%): 287 [M+1]⁻, 241, 213, 199, 187, 159, 125, 127, 107, 81.

Acetic acid (E)=([R],[S],[S],[R]-1)·[1R,(2R)]-10-(tert-Butyldimethylsilyloxy)-3-ethyl-pent-4-enyl-3-hydroxy-2,4-dimethyl-oct-6-enyl ester (18): Proton sponge (0.74 mmol, 5 equiv) and Me₅OBF₄ (0.74 mmol, 5 equiv) were added to a solution of alcohol 17 (65 mg, 0.148 mmol, 1 equiv) in dichloromethane (2 mL) under argon at room temperature. The heterotronic mixture was stirred for 6 h at 40°C and then overnight at room temperature in the dark. The brownish mixture was poured into dichloromethane (10 mL) and washed with aqueous HCl (1 M, 3×5 mL). The organic layer was dried over Na₂SO₄, filtered, and concentrated in vacuo. Purification by flash chromatography (pentane/EtOAc 90:10) afforded 18 (35.6 mg, 53%, 69% based on the recovered start material) as a colorless oil. 

'H NMR (400 MHz, CDCl₃): δ = 5.74 (ddd, J = 17.3, 1.9, 0.8 Hz, 1H), 5.05 (ddd, J = 17.3, 1.9, 0.8 Hz, 1H), 1.47–1.37 (m, 1H), 1.37–1.27 (m, 1H), 0.89 (s, 3H), 0.88 (t, J = 7.4 Hz, 3H), 0.28 (dd, J = 7.4 Hz, 3H), 0.82 (dd, J = 7.4 Hz, 3H), 0.80 (dd, J = 7.4 Hz, 3H), 0.10 (s, 3H), 0.06 ppm (s, 3H); IR (film, CHCl₃): ν = 3400, 3350, 3094, 2954, 2819, 2727, 1727, 1460, 1360, 1255, 1091, 1003, 920, 838, 777, 673, 552 ppm; MS (Cl−): m/z (%): 455 [M+1]⁻, 395, 363, 325, 309, 250, 249, 231, 199, 179, 137, 113, 83.
Acrylic acid (E)-1R,3R,5S,5S)-3-acetoxy-1(R)-1-ethylallyl-5-methoxy-6-dimethylamino-8-enzyme ester (13): Et3N (0.53 mmol, 5 equiv) was added to a solution of the alcohol (20 mg, 0.10 mol, 1 equiv) in dry THF (1 mol) under argon at 0°C. A solution of acryloyl chloride (0.53 mmol, 5 equiv) in dry CH2Cl2 (1 mL) was added dropwise to the mixture and stirred for a further 30 min at 0°C. Brine was added and the aqueous phase was quickly extracted with Et2O (3 × 5 mL). The combined organic layers were washed with brine, dried (MgSO4), filtered, and concentrated under reduced pressure. Purification by flash chromatography (pentane/EtO2:90:10) afforded 13 (20 mg, 48% not optimized) as a colorless oil. 1H NMR (200 MHz, CDCl3): δ = 6.39 (dd, 1J = 17.3, 14.4 Hz, 1H), 6.11 (dd, 1J = 17.3, 10.4 Hz, 1H), 5.80 (dd, 1J = 10.4, 1.4 Hz, 1H), 5.56 (dd, 1J = 17.3, 10.4, 9.1 Hz, 1H), 5.30–5.32 (m, 2H), 5.25 (dd, 1J = 9.3, 4.1 Hz, 1H), 5.12 (dd, 1J = 10.4, 2.0 Hz, 1H), 5.04 (dd, 1J = 17.3, 2.0 Hz, 1H), 4.91–4.93 (m, 1H), 3.91 (d, 1J = 6.3, 3.0 Hz, 1H), 3.41 (s, 3H), 2.90 (s, 2H). 13C NMR (200 MHz, CDCl3): δ = 172.4, 139.0, 120.7, 112.5, 108.3, 105.7, 104.5, 102.1, 93.3, 63.0, 58.1, 54.7, 53.8, 50.1, 42.0, 31.6. HRMS: m/z: calcd for C11H21O3: [M+H]+ 209.1385; found: 209.1388.

Acetic acid (E)-(1R,3R,5S,5S)-1(2R,3R)-3-ethyl-6-oxo-3,6-dihydro-2H-pyran-2-ylmethyl-3-methoxy-2,4-dimethyl-6-enzyme ester (22): A solution of 17 (0.05 mol) in dichloromethane (0.4L, 0.0155 mmol) was added to a stirred solution of diene 13 (20 mg, 0.0155 mol, 1.0 equiv) in dichloromethane (17 mL, 0.003 mol) under argon at room temperature. The resulting solution was refluxed at 40°C for 30 min and then Grubbs first-generation catalyst (0.001 mol, 0.2 equiv) in dichloromethane (1 mL) was added. The mixture reacted with stirring for another 20 h. The mixture cooled to room temperature, and the solvent was partially evaporated. The residue was purified by flash chromatography on silica gel (pentane/EtO2:50:50) to provide the lactone (22) (60 mg, 32% not optimized, 39% based on the recovered start material) as a brown oil. 1H NMR (400 MHz, CDCl3): δ = 7.03 (dd, 1J = 9.6, 6.0 Hz, 1H), 6.12 (dd, 1J = 9.6, 1.1 Hz, 1H), 5.51–5.34 (m, 2H), 5.30–5.24 (m, 1H), 4.50–4.43 (m, 1H), 3.39 (s, 3H), 2.88 (dd, 1J = 9.3, 1.6 Hz, 1H), 2.17 (s, 3H), 2.30–2.22 (m, 1H), 1.72–1.70 (m, 1H), 1.82–1.70 (m, 2H), 1.67 (dd, 1J = 5.5, 3.1 Hz, 1H), 1.64–1.47 (m, 2H), 0.97 (t, 1J = 7.4 Hz, 3H), 0.89 (m, 1J = 5.5, 3.1 Hz), 0.82 ppm (dd, 1J = 6.3, 3.1 Hz). 13C NMR (100 MHz, CDCl3): δ = 170.6, 164.0, 150.3, 129.9, 126.4, 120.7, 85.0, 77.4, 70.8, 61.2, 39.0, 38.1, 38.0, 35.6, 33.9, 21.1, 20.3, 17.8, 12.2, 10.8, 10.1 ppm. The data are in accordance with those described in the literature.[4]
The synthesis was carried out in the enantiomeric series. The aldol reaction with the RAMP hydrazone gave the same yield, enantio- and diastereoselectivities as compared to the SAMP hydrazone.


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