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SYNTHESIS OF ENANTIOMERICALLY ENRICHED 2-SUBSTITUTED PYRROLIDINE ANALOGUES OF NORHYGRINE. APPLICATION OF THE HETERO-DIELS-ALDER ADDITION OF SULFUR DIOXIDE

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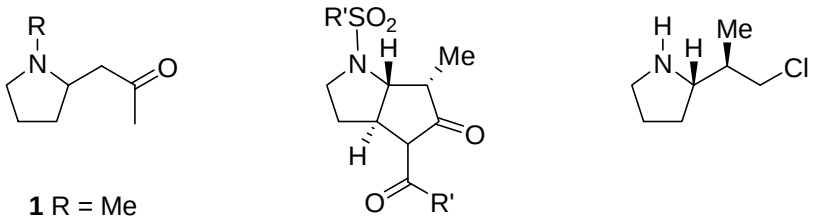
Dedicated to Professor Yoshito Kishi on the occasion of his 70th birthday

Abstract – The Vogel's reaction cascade (one-pot hetero-Diels-Alder addition of SO_2, ionization of the sultines into zwitterions and their quenching by electron-rich alkenes) has been applied to the preparation of enantiomerically-enriched (1*S*)-2((2*R*)-1-benzoylpyrrolidin-2-yl)pentan-3-one (**14**). Reaction of SO_2 with (-)-(1*E*,3*Z*)-2-methyl-1-((1*S*)-1-phenylethoxy)penta-1,3-dien-3-ol benzoate (**5**: derived from (*S*)-1-phenylethanol (97% ee)) and allyltrimethylsilane in the presence of a Lewis acid at -78°C provides (-)-(2*Z*,1'*S*,4*S*,5*S*)-4-methyl-5-(1'-phenylethoxy)octa-2,7-dien-3-ol benzoate (**9**). Selective cleavage of the benzyl ether of **9** and subsequent S_N2 displacement with $Ph_2P(O)N_3$ provided an azide **11** that was converted into **14**.

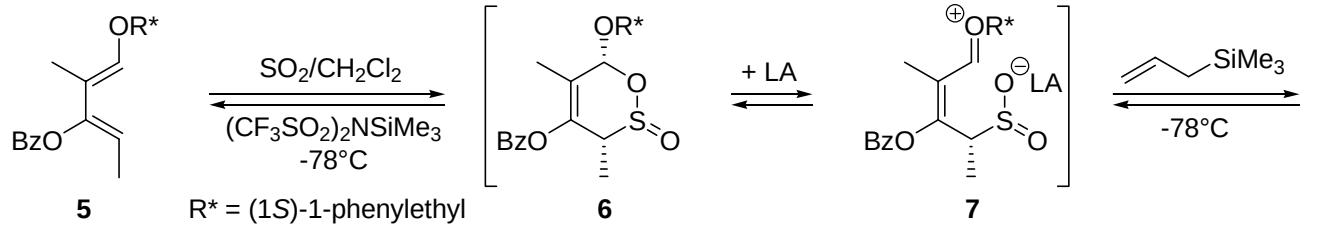
Pyrrolidines are found in Nature[1] and as pharmacophores in drugs.[2] The active ingredients of toxic herbs are often pyrrolidine derivatives.[3] Simple derivatives such as hygrine (**1**) and norhygrine (**2**) are present in several plants.[4] Recently, enantiomerically pure "*trans*-lactams" of type **3** have been shown to be potent human cytomegalovirus (HCMV) protease inhibitors.[5] HCMV is one of the nine known human herpes viruses.[6]



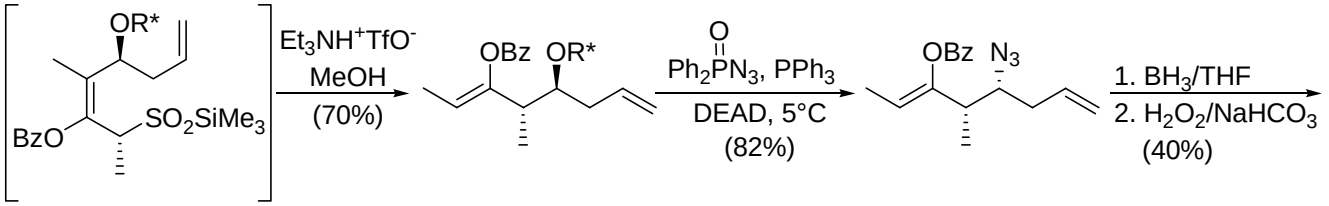
1 R = Me
2 R = H

3 **4**

Although several reports[7] present synthesis of pyrrolidine derivatives, relatively few are the methods for the enantioselective preparation of 2-substituted pyrrolidines analogues of **1** – **2**.[8] A close analogue of the system described here would be compound **4** (derived from (*R*)-α-methyl benzylamine).[8b] We disclosed here our synthesis of (1*S*)-2-((2*R*)-1-benzoylpyrrolidin-2-yl)pentan-3-one (**14**), a new compound derived from enantiomerically enriched (97%) (-)-(1*E*,3*Z*)-2-methyl-1-((1*S*)-1-phenylethoxy)penta-1,3-dien-3-ol benzoate (**5**), a diene obtained in three steps from inexpensive (1*S*)-1-phenylethanol (97% ee).[9] The method uses new organic chemistry of sulfur dioxide developed in our laboratory.[10]

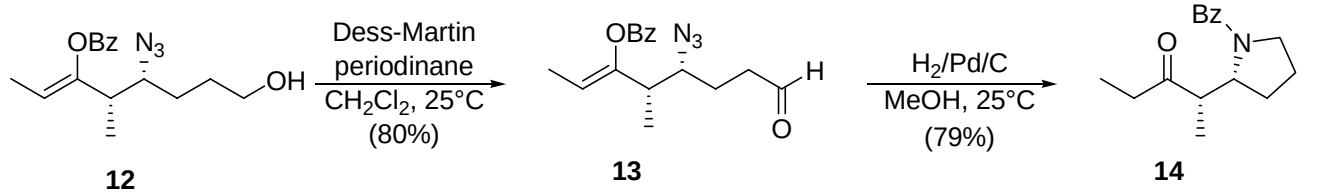


5 R* = (1*S*)-1-phenylethyl **6** **7**



8 **11**

CF_3COOH,anisole, CH_2Cl_2, 0-15°C, (75%) → **9** R = R*, **10** R = H

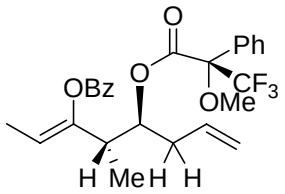


12 **13** **14**

In the presence of an excess of sulfur dioxide in CH_2Cl_2 and a catalytic amount of $(CF_3SO_2)_2NSiMe_3$ (Lewis acid promoter) diene (**5**) equilibrates with the corresponding sultine **6**. At -78°C the latter is ionized into zwitterions **7** that is quenched by allyltrimethylsilane giving sulfinate **8**. After SO_2 evaporation at -78°C, treatment of the crude reaction mixture with $Et_3NH^+CF_3SO_3^-$ (made *in situ* from Et_3N, $CF_3SO_3SiMe_3$ and MeOH) buffer in anhydrous methanol (-78 to -50°C) led to desulfinylation producing **9**.[11] Cleavage of the (1*S*)-phenylethyl ether moiety of **9** was induced by CF_3COOH (10 equiv.) in CH_2Cl_2 containing one equivalent of anisole. This gave **10** in 75% yield, together with 15% of

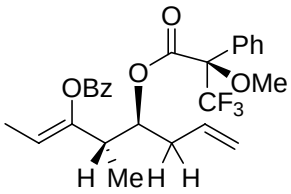
(3*S*,4*S*)-4-methyl-5-oxooct-1-en-3-ol benzoate (product of benzoyl group migration). The enantiomeric excess of alcohol **10** was the same as that of the (1*S*)-phenylethanol used to prepare diene **5** (97% ee), as proven by ^{19}F-NMR ($CDCl_3$) of the (*S*)-MTPA and (*R*)-MTPA Mosher's ester **10S** and **10R**. The (3*S*)-absolute configuration of **10** was suggested by the ^{1}H-chemical shifts of $H_2C(2)$ and H-C(4) of **10S** and **10R**[12] and confirmed by X-ray radiocrystallography of a derivative of the enantiomer of **10**.[11]

10*S*



δ_H: 2.78 2.54 & 2.34 ppm

10*R*



δ_H: 2.76 2.60 & 2.42 ppm

Reaction of alcohol **10** with $Ph_2P(O)N_3$ in the presence of diethyl azodicarboxylate and triphenylphosphine[13] provided azide **11** in 82% yield. Hydroboration followed by oxidation of alkene **11** (BH_3·THF, work-up with 30% aq. H_2O_2)[14] gave alcohol **12** (40%) and unreacted **11** (22%). Dess-Martin oxidation of **12** furnished aldehyde **13** (80%). Reduction of azide **13** with H_2/10% Pd/C in MeOH led to **14**, resulting from the conversion of the azide into a primary amine that cyclized with the aldehyde forming an intermediate imine that was hydrogenated into a pyrrolidine. Migration of the benzoyl group from the enol ester to the nitrogen atom of pyrrolidine finally produced **14**.

This note demonstrates that the new organic chemistry of sulfur dioxide developed to generate polyketide and polypropionate fragments[11] can be used to prepare enantiomerically enriched pyrrolidine analogue of hygrine and norhygrine.

EXPERIMENTAL

General, see ref. 9. ^{1}H-NMR assignments were confirmed by 2D-(COSY, NOESY)-^{1}H-NMR spectra.

(-)-(6*Z*,1'*S*,4*S*,5*S*)-5-Methyl-5-(1'-phenylethoxy)octa-1,6-dien-6-yl benzoate (**9**). Allyltrimethylsilane (0.2 mL, 1.26 mmol) and 0.5 M $(CF_3SO_2)NH$ in CH_2Cl_2 (0.25 mL, 1.26 mmol) were mixed in CH_2Cl_2 (7 mL) and stirred at 20°C for 10 min. Then SO_2 (ca. 7 mL) dried over a column of P_2O_5 and Al_2O_3 was transferred through the vacuum line to the frozen solution (-196°C). The mixture was allowed to melt and to warm to -78°C. After 30 min at this temperature a mixture of (-)-(1*E*,3*Z*)-2-methyl-1-((1*S*)-1-phenylethoxy)penta-1,3-dien-3-ol benzoate (**5**) [9] (1.45 g, 4.2 mmol) and allyltrimethylsilane (1.34 mL, 8.4 mmol) in anh. CH_2Cl_2 (0.7 mL) was added dropwise under vigourous stirring at -78°C. The mixture was stirred at -78°C for 24 h. Sulfur dioxide and CH_2Cl_2 were evaporated at -78°C under vacuum for 2 h. Then a premixed solution of Et_3N (0.76 mL, 5.45 mmol), $CF_3SO_3SiMe_3$ (0.76 mL, 4.2 mmol) in anh. MeOH (2 mL) was

added at -78°C under vigorous stirring . The temperature was allowed to reach -50°C over 3 h. The reaction mixture was poured into a ice-cold sat. aq. soln. of $NaHCO_3$ (50 mL) and extracted with CH_2Cl_2 (30 mL, 3 times). The combined org. extracts were washed successively, with sat. aq. soln. of $NaHCO_3$ (20 mL), brine (10 mL) and dried (Na_2SO_4). After solvent evaporation *in vacuo* the residue was purified by flash chromatography on silica gel (light petroleum ether/EtOAc 96:4) giving 1.07 g (70%) colorless oil. $[\alpha]_D^{25}$ = -34, $[\alpha]_{577}^{25}$ = -41, $[\alpha]_{546}^{25}$ = -36, $[\alpha]_{435}^{25}$ = -54, $[\alpha]_{405}^{25}$ = -63 (*c* = 1.04, $CHCl_3$). IR (film) ν: 3065, 2975, 2925, 1730, 1695, 1600, 1450, 1260, 1175, 1090 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H: 8.08 (*d*, 2H, ^3J = 7.4, Bz), 7.65 (*t*, 1H, ^3J = 7.7, Bz), 7.50 (*t*, 2H, ^3J = 7.7, Bz), 7.23-7.20 (*m*, 2H, Ph), 7.17-7.14 (*m*, 3H, Ph), 5.69 (*dxdxt*, 1H, ^3J = 17.3, ^3J = 10.2, ^3J = 7.0, H-C(2)), 5.33 (*q*, 1H, ^3J = 7.0, H-C(7)), 5.06-4.96 (*m*, 2H, H-C(1)), 4.50 (*q*, 1H, ^3J = 6.4, H-C(1')), 3.50 (*dxt*, 1H, ^3J = 7.7, ^3J = 4.2, H-C(4)), 2.97 (*m*, 1H, H-C(5)), 2.28-2.15 (*m*, 2H, H-C(3)), 1.58 (*d*, 3H, ^3J = 7.0, H-C(8)), 1.44 (*d*, 3H, ^3J = 6.4, H-C(2')), 1.20 (*d*, 3H, ^3J = 7.0, Me-C(5)). ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ_C: 164.1 (*s*, CO), 150.2 (*s*, C(6)), 143.6 (*s*, Ar), 136.0 (*d*, ^1J(C,H) = 153, Ar), 133.2 (*d*, ^1J(C,H) = 160, Ar), 129.9 (*d*, ^1J(C,H) = 165, Ar), 128.4 (*d*, ^1J(C,H) = 163, Ar), 128.0 (*d*, ^1J(C,H) = 162, Ar), 127 (*d*, ^1J(C,H) = 160, Ar), 126.8 (*d*, ^1J(C,H) = 160, Ar), 116.1 (*t*, ^1J(C,H) = 145, C(1')), 75.7 (*d*, ^1J(C,H) = 143, C(4)), 39.6 (*d*, ^1J(C,H) = 128, C(5)), 34.8 (*t*, ^1J(C,H) = 121, C(3)), 23.9 (*q*, ^1J(C,H) = 129, C(2')), 11.6 (*q*, ^1J(C,H) = 128, 4 Me), 11.0 (*q*, ^1J(C,H) = 128, C(8)). MS-MALDI: Calcd for $C_{24}H_{28}O_3Na^+$ 387.1936 (*M*+Na^+); found: 387.1935. Anal. Calcd for $C_{24}H_{28}O_3$ (364.48): C 79.9, H 7.74. Found: C 79.12, H 7.72.

(+)-(6*Z*,4*S*,5*S*)-4-Hydroxy-5-methylocta-1,6-dien-6-yl benzoate (**10**). To a solution of (-)-**9** (3.9 g, 10.7 mmol) and anisole (1.22 mL, 10.7 mmol) in CH_2Cl_2 (65 mL) at 0°C was added CF_3COOH (8.1 mL, 0.11 mol). The resulting brownish-pink solution was let to reach +15°C in 2.5 h. Then it was neutralized with solid $NaHCO_3$, filtered and evaporated *in vacuo*. The residue was purified by flash chromatography (light petroleum ether/EtOAc 95:5): 2.09 g (75%) of **10**, and 0.42 g (15%) of (3*S*,4*S*)-4-methyl-5-oxooct-1-en-3-ol benzoate. Data of **10**. colorless oil. R_f = 0.29 (petroleum ether/EtOAc = 9:1). $[\alpha]_D^{25}$ = +24, $[\alpha]_{577}^{25}$ = +26, $[\alpha]_{435}^{25}$ = +39, $[\alpha]_{405}^{25}$ = +39 (*c* = 0.41, $CHCl_3$). IR (film) ν: 3515, 3070, 2975, 2920, 1735, 1715, 1690, 1600, 1450, 1285, 1260, 1175, 1095, 1070 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H: 8.14 (*d*, ^3J = 8.4, ^4J = 1.3, H-C(Bz)), 7.64 (*txt*, ^3J = 7.0, ^4J = 1.3, H-C(Bz)), 7.51 (*t*, 2H, ^3J = 8.3, H-C(Bz)), 5.94 (*dxdxdxd*, 1H, ^3J = 16.6, ^3J = 10.2, ^3J = 7.7, ^3J = 6.4, H-C(2)), 5.39 (*q*, 1H, ^3J = 7.0, H-C(7)), 5.12 (*dxq*, 1H, ^3J = 16.6, ^2J = 1.3, ^4J = 1.3, Ha-C(1)), 5.09 (*dxdxd*, 1H, ^3J = 10.2, ^2J = 1.2, ^4J = 1.2, Hb-C(1)), 3.43 (*dxtxd*, 1H, ^3J = 8.3, ^3J =3.8, ^3J = 2.6, H-C(4)), 3.26 (*d*, 1H, ^3J = 2.6, HO-C(4)), 2.44 (*dxq* + *m*, 2H, ^3J =8.9, ^3J =7.0, H-C(5)), Ha-C(3)), 2.16 (*dxt*, 1H, ^2J = 14.5, ^3J = 7.7, Hb-C(3)), 1.53 (*d*, 3H, ^3J =7.0, H-C(2')), 1.12 (*d*, 3H, ^3J = 7.0, CH_3-C(5)). ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ_C: 165.5, 149.4, 135.1, 133.8, 130.2, 128.8, 128.7, 117.1,

114.6, 71.4, 45.8, 38.0, 14.5, 11.1. MS-MALDI: Calcd for $C_{16}H_{20}O_3Na^+$ 283.1310; found: 283.1389. Anal. Calcd for $C_{16}H_{20}O_3$ (260.33): C 73.82, H 7.74. Found: C 73.76, H 7.80.

(6*Z*,4*S*,5*S*)-5-Methyl-4-(((2*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropionyl)oxy)octa-1,6-dien-6-yl benzoate (**10*R***). To a solution of (+)-**10** (26 mg, 0.10 mmol) in pyridine (0.5 mL) at -15°C was added (*S*)-1-methoxy-1-trifluoromethyl-1-phenylacetyl chloride (50 mg, 0.20 mmol). The resulting mixture was allowed to reach 20°C and stirred for 2 h. It was then chilled to -20°C and *N*,*N*-dimethylaminoethanol (20 mg, 0.20 mmol) was added. The mixture was allowed to warm to -20°C and stirred for 1 h. It was diluted with Et_2O (30 mL), washed successively with a sat. aq. soln. of $CuSO_4$ (7 mL, 4 times), water (10 mL) 10% aq. soln. of citric acid (7 mL, 4 times), sat. aq. soln. of $NaHCO_3$ (5 mL, 3 times), dried (Na_2SO_4) and evaporated *in vacuo*. Yield: 44 mg (93%) of **10*R***. All the NMR measurements were done on the crude sample. Data of **10*R***: colorless oil. R_f = 0.44 (petroleum ether/EtOAc 9:1). ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H: 8.09 (*dd*, 2H, ^3J = 8.0, ^4J = 1.3, H-C(Bz)), 7.64 (*tt*, 1H, ^3J = 7.0, ^4J = 1.3, H-C(Bz)), 7.58-7.32 (*m*, 7H, H-C(Ar)), 5.78 (*dxdxdxd*, 1H, ^3J = 17.3, ^3J = 10.0, ^3J = 8.0, ^3J = 6.2, H-C(2)), 5.30 (*dxdxd*, 1H, ^3J = 8.0, ^3J = 6.8, ^3J = 4.3, H-C(4)), 5.24 (*q*, 1H, ^3J = 6.8, H-C(7)), 5.12 (*dm*, 1H, ^3J = 17.3, Ha-C(1)), 5.12 (*dm*, 1H, ^3J = 10.0, Hb-C(1)), 3.54 (br. *q*, 3H, $^5J_{H,F}$ = 1.2, CH_3O-C(2")), 2.76 (*quint*, 1H, ^3J = 6.8, H-C(5)), 2.60 (*dxdxdxd*, 1H, ^2J = 14.8, ^3J = 5.7, ^3J = 3.8, ^4J = 1.9, Ha-C(3)), 2.42 (*dt*, 1H, ^2J = 14.8, ^3J = 8.0, Hb-C(3)), 1.44 (*d*, 3H, ^3J = 7.4, H-C(8)), 1.01 (*d*, 3H, ^3J = 7.0, CH_3-C(5)). ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ_C: 166.2, 164.0, 148.0, 133.4, 133.3, 132.4, 130.1, 129.5, 129.4, 128.6, 128.3, 127.5, 123.4 (*q*, $^1J_{C,F}$ = 288, CF_3), 118.6, 133.8, 77.2, 55.6, 41.5, 35.1, 13.4, 11.2. ^{19}F-NMR ($CDCl_3$, 376.7 MHz) δ_F: -71.78 (*s*, CF_3). MS-MALDI: Calcd for $C_{26}H_{27}F_3O_5Na^+$ 499.1708; found: 499.1712.

(6*Z*,4*S*,5*S*)-5-Methyl-4-(((2*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropionyl)oxy)octa-1,6-dien-6-yl benzoate (**10*S***). Same procedure as that for **10*R***, using (*R*)-1-methoxy-1-trifluoromethyl-1-phenylacetyl chloride. Yield: 94%. Colorless oil, R_f = 0.44 (petroleum ether/EtOAc 9:1). ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H: 8.11 (*dd*, 2H, ^3J = 7.4, ^4J = 1.2, H-C(Bz)), 7.64 (*tt*, 1H, ^3J = 7.4, ^4J = 1.2, H-C(Bz)), 7.58-7.35 (*m*, 7H, H-C(Ar)), 5.78 (*dxdxdxd*, 1H, ^3J = 15.4, ^3J = 10.0, ^3J = 8.6, ^3J = 6.2, H-C(2)), 5.34 (*m*, 2H, H-C(4), H-C(7)), 5.04 (br. *d*, 1H, ^3J = 15.4, Ha-C(1)), 5.12 (br. *d*, 1H, ^3J = 10.0, Hb-C(1)), 3.55 (br. *q*, 3H, $^5J_{H,F}$ = 1.2, CH_3O-C(2")), 2.79 (*quint*, 1H, ^3J = 6.8, H-C(5)), 2.54 (*dxdxt*, 1H, ^2J = 14.8, ^3J = 6.2, ^3J = 2.0, ^4J = 2.0, Ha-C(3)), 2.34 (*dt*, 1H, ^2J = 14.8, ^3J = 7.4, Hb-C(3)), 1.50 (*d*, 3H, ^3J = 6.8, H-C(8)), 1.15 (*d*, 3H, ^3J = 6.8, CH_3-C(5)). ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ_C: 166.2, 164.0, 148.3, 133.5, 132.6, 132.4, 130.2, 129.6, 129.2, 128.6, 128.4, 127.6, 123.5 (*q*, $^1J_{C,F}$ = 288, CF_3), 118.7, 133.8, 77.1, 55.5, 41.5, 35.2, 14.0, 11.3. ^{19}F-NMR ($CDCl_3$, 376.7 MHz) δ_F: -71.65 (*s*, CF_3). MS-MALDI: Calcd for $C_{26}H_{27}F_3O_5Na^+$ 499.1708; found: 499.1724.

(+)-(6*Z*,4*R*,5*R*)-4-Azido-5-methylocta-1,6-dien-6-yl benzoate (**11**). To a chilled (-30°C) solution of (+)-**10** (1.34 g, 5.13 mmol) and Ph_3P (1.42 g, 5.28 mmol) in THF (45 mL) were sequentially added diethyl azodicarboxylate (DEAD, 0.84 mL, 5.38 mmol) and $Ph_2P(O)N_3$ (1.17 mL, 5.38 mmol). The resulting mixture was allowed to reach +5°C in 2 h and stirred at this temperature for 2 more hours. Then it was poured into brine (50 mL) and the aqueous phase was extracted with Et_2O (30 mL, 3 times). The combined organic layers were washed with brine (30 mL) dried (Na_2SO_4), filtered and evaporated. The resulting oil was purified by flash chromatography on silica gel (light petroleum ether/EtOAc 95:5) yielding 1.2 g (82%), colorless oil, R_f = 0.72 (light petroleum ether/EtOAc 9:1). $[\alpha]_D^{25}$ = +1.0, $[\alpha]_{577}^{25}$ = +1.5, $[\alpha]_{546}^{25}$ = +2.3, $[\alpha]_{435}^{25}$ = +7.9, $[\alpha]_{405}^{25}$ = +11.0 (*c* = 0.48, $CHCl_3$). IR (film) ν: 2980, 2920, 2100, 1735, 1695, 1450, 1260, 1090 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H: 8.14 (*dxd*, 2H, ^3J = 7.4, H-C(Bz)), 7.64 (*t*, 1H, ^3J = 7.4, H-C(Bz)), 7.51 (*t*, 2H, ^3J = 7.4, H-C(Bz)), 5.83 (*dxdxt*, 1H, ^3J =17.2, ^3J = 10.5, ^3J = 6.8, H-C(2)), 5.35 (*q*, ^3J = 6.8, H-C(7)), 5.19 (*dxq*, 1H, ^3J = 16.6, ^4J = 1.2, Ha-C(1)), 5.14 (*dxq*, 1H, ^3J = 9.8, ^4J = 1.9, Hb-C(1)), 3.53 (*dxt*, 1H, ^3J = 8.6, ^3J = 5.5, H-C(4)), 2.57 (*qxd*, 1H, ^3J = 6.8, ^3J = 5.5, H-C(5)), 2.45, 2.37 (2*m*, ABXY, ^2J = 14.8, ^3J = 8.6, ^3J = 6.8, H_2C(3)), 1.56 (*d*, 3H, ^3J = 6.8, H-C(8)), 1.20 (*d*, 3H, ^3J = 6.8, CH_3-C(5)). ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ_C: 164.1, 149.5, 134.2, 133.5, 130.1, 129.4, 128.6, 118.3, 113.3, 64.4, 42.4, 37.0, 13.3, 11.1. MS-CI (NH_3) *m/z*: 304 ([*M*+19]$^+$, 100), 303 ([*M*+18]$^+$, 71), 287 ([*M*+2]$^+$, 77), 286 ([*M*+1]$^+$, 244 (20), 243 (22), 190 (24), 189 (33), 137 (100) 136 (100), 106 (100), 105 (100). MS-MALDI: Calcd for $C_{16}H_{19}N_3O_2Na^+$ 308.1375; found: 308.1343. Anal. Calcd for $C_{16}H_{19}N_3O_2$ (285.34): C 67.35, H 6.71, N 14.73. Found: C 67.39, H 6.64, N 14.69.

(6*Z*,4*R*,5*S*)-4-Azido-1-hydroxy-5-methyloct-6-en-6-yl benzoate (**12**). To a solution of (+)-**11** (0.125 g, 0.44 mmol) in THF (2 mL) was added 1 M solution of BH_3·THF in THF (0.22 mL, 0.22 mmol) at 0°C. The resulting mixture was stirred at 0°C for 2 h. It was cooled to -78°C and quenched with MeOH (0.14 mL). Then water (0.7 mL), $NaHCO_3$ (0.24 g) and 30% aq. soln. of H_2O_2 (0.4 mL) were added successively. The mixture was stirred at 5°C for 7 h. EtOAc (20 mL) was added, phases were separated, and organic phase was washed with brine, dried (Na_2SO_4), filtered and evaporated. The resulting oil was purified by flash column chromatography on silica gel (light petroleum ether/EtOAc 7:3) yielding 53 mg (40%) of **12** and unreacted (+)-**11** (28 mg, 22%). Data of **12**: colorless oil, R_f = 0.37 (light petroleum ether/EtOAc 7:3), ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H: 8.12 (*dd*, 2H, ^3J = 8.4, H-C(Bz)), 7.62 (*t*, 1H, ^3J = 7.4, H-C(Bz)), 7.50 (*t*, 2H, ^3J = 7.8, H-C(Bz)), 5.34 (*q*, 1H, ^3J = 7.4, H-C(7)), 3.66 (*t*, 2H, ^3J = 5.8, H-C(1)), 3.44 (*dxdxd*, 1H, ^3J = 9.0, ^3J = 6.4, ^3J = 3.2, H-C(4)), 2.56 (*qxd*, 1H, ^3J = 7.0, ^3J = 6.4, H-C(5)), 1.88 (br. *s*, 1H, HO-C(1)), 1.84-1.72, 1.66-1.58 (2*m*, 4H, H-C(2), H-C(3)), 1.55 (*d*, 3H, ^3J = 7.0, H-C(8)), 1.20 (*d*, 3H, ^3J = 7.0,

CH_3-C(5)). ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ_C: 164.3, 149.5, 133.6, 130.1, 129.3, 128.7, 113.3, 64.9, 62.2, 43.1, 29.7, 29.0, 13.5, 11.1. MS-MALDI: Calcd for $C_{16}H_{21}N_3O_2K^+$ 342.1220; found: 342.1255.

(6*Z*,4*R*,5*S*)-4-Azido-6-benzoyloxy-5-methyl-6-octenal (**13**). To a solution of alcohol **12** (38 mg, 0.127 mmol) in CH_2Cl_2 (1 mL) was added Dess-Martin periodinane (0.135 g, 0.318 mmol) at 0°C. The resulting mixture was stirred at 25°C for 1 h. It was quenched by addition of sat. aq. soln. of $NaHCO_3$ (2 mL) followed by $Na_2S_2O_3$·5 H_2O (0.5 g). Extractive work-up (CH_2Cl_2, 3 mL, 3 times), drying (Na_2SO_4) and evaporation provided the crude product which was purified by flash column chromatography on silica gel (light petroleum ether/EtOAc 8:2) giving 29 mg (80%), colorless oil. R_f = 0.74 (CH_2Cl_2/Et_2O 95:5). IR (film) ν: 2980, 2920, 2110, 1730, 1695, 1600, 1455, 1260, 1090 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H: 9.18 (*s*, 1H, H-C(1)), 8.13 (*dxd*, 2H, ^3J = 8,4, ^4J = 1.2, H-C(Bz)), 7.64 (*txt*, 1H, ^3J = 7.4, ^4J = 1.2, H-C(Bz)), 7.51, *t*, 2H, ^3J = 7.8, H-C(Bz)), 5.37 (*q*, 1H, ^3J = 6.8, H-C(7)), 3.44 (*dxdxd*, 1H, ^3J = 9.8, ^3J = 6.2, ^3J = 3.1, H-C(4)), 2.71-2.55 (*m*, 2H, H-C(2)), 2.05 (*dxdxdxd*, 1H, ^2J = 14.3, ^3J = 8.0, ^3J = 6.8, ^3J = 3.6, Ha-C(3)), 1.80 (*dxdxdxd*, 1H, ^2J = 14.3, ^3J = 9.8, ^3J = 8.0, ^3J = 5.5, Hb-C(3)), 1.55 (*d*, 3H, ^3J = 6.8, H-C(8)), 1.22 (*d*, 3H, ^3J = 6.8, CH_3-C(5)). MS-MALDI: Calcd for $C_{16}H_{19}N_3O_3Na^+$ 324.1324; found: 324.1387.

(1*S*)-2-((2*R*)-1-Benzoylpyrrolidin-2-yl)pentan-3-one (**14**). To a solution of **13** (25 mg, 0.084 mmol) in MeOH (1 mL) was added Pd/C (10% Pd on C) (5 mg) and the resulting suspension was stirred under H_2 atmosphere (1 bar) for 3 h. Filtration of catalyst and evaporation of solvent provided 17 mg (79%) of pure **14**, colorless oil. R_f = 0.12 (CH_2Cl_2/Et_2O 95:5). ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H: 7.50-7.37 (*m*, 5H, H-C(Bz)), 4.40 (*dt*, 1H, ^3J = 8.3, ^3J = 5.8, H-C(2')), 3.55 (*dq*, 1H, ^3J = 7.0, ^3J = 5.1, H-C(2)), 3.44 (*dd*, 2H, ^3J = 9.0, ^3J = 3.8, H-C(5')), 2.50 (*q*, 2H, ^3J = 7.0, H-C(4)), 2.17-2.01 (*m*, 2H, H-C(3')), 1.88-1.81, 1.70-1.58 (2*m*, 2H, H-C(4')), 1.17 (*d*, 3H, ^3J = 7.0, H-C(1)), 1.05 (*t*, 3H, ^3J = 7.0, H-C(5)). ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ_C: 214.4, 170.4, 137.0, 130.3, 128.3, 127.4, 60.0, 51.3, 45.8, 36.5, 26.9, 25.2, 13.6, 7.8. MS-MALDI: Calcd for $C_{16}H_{21}N_2O_2Na^+$ 282.1470; found: 282.1478.

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