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

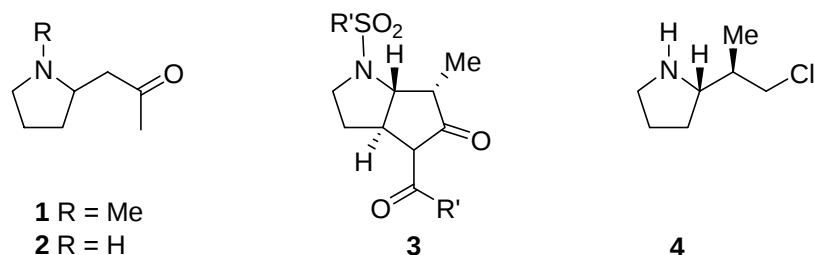
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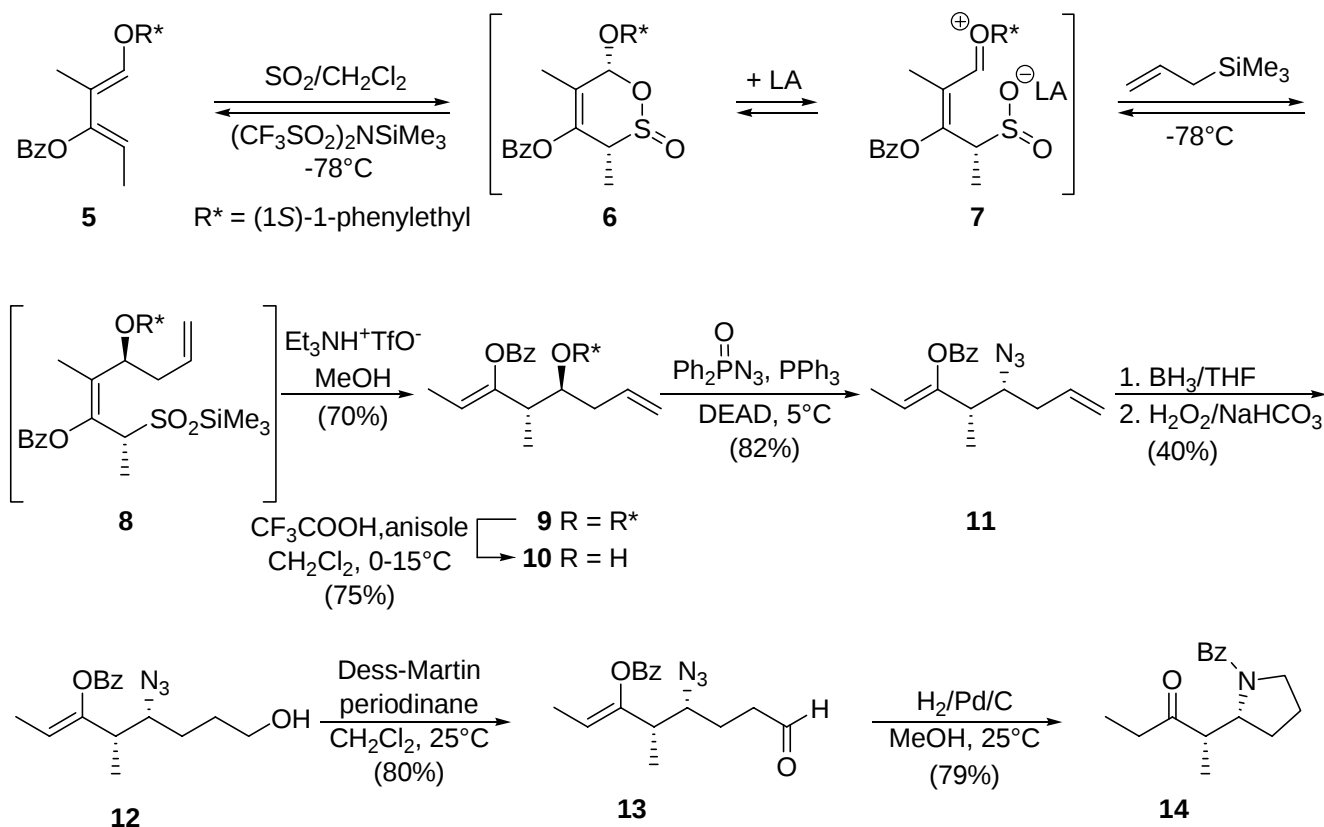
Dedicated to Professor Yoshito Kishi on the occasion of his 70th birthday

Abstract – The Vogel's reaction cascade (one-pot hetero-Diels-Alder addition of SO₂, 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 SO₂ 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 Ph₂P(O)N₃ provided an azide **11** that was converted into **14**.

Pyrrolidines are found in Nature¹ 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

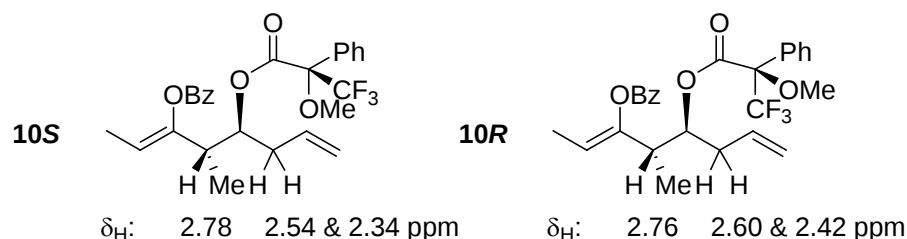


Although several reports⁷ present synthesis of pyrrolidine derivatives, relatively few are the methods for the enantioselective preparation of 2-substituted pyrrolidines analogues of **1** – **2**.⁸ A close analogue of the system described here would be compound **4** (derived from (*R*)- α -methyl benzylamine).^{8b} 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



In the presence of an excess of sulfur dioxide in CH_2Cl_2 and a catalytic amount of $(\text{CF}_3\text{SO}_2)_2\text{NSiMe}_3$ (Lewis acid promoter) diene (**5**) equilibrates with the corresponding sulfone **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 $\text{Et}_3\text{NH}^+\text{CF}_3\text{SO}_3^-$ (made *in situ* from Et_3N , $\text{CF}_3\text{SO}_3\text{SiMe}_3$ 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 ^1H -chemical shifts of $\text{H}_2\text{C}(2)$ and $\text{H}-\text{C}(4)$ of **10S** and **10R**¹² and confirmed by X-ray radiocrystallography of a derivative of the enantiomer of **10**.¹¹



Reaction of alcohol **10** with $\text{Ph}_2\text{P}(\text{O})\text{N}_3$ in the presence of diethyl azodicarboxylate and triphenylphosphine¹³ provided azide **11** in 82% yield. Hydroboration followed by oxidation of alkene **11** ($\text{BH}_3\cdot\text{THF}$, 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 $\text{H}_2/10\% \text{Pd/C}$ 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 fragments¹¹ can be used to prepare enantiomerically enriched pyrrolidine analogue of hygrine and norhygrine.

EXPERIMENTAL

General, see ref. 9. ^1H -NMR assignments were confirmed by 2D-(COSY, NOESY)- ^1H -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 $(\text{CF}_3\text{SO}_2)\text{NH}$ 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 vigorous 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), $\text{CF}_3\text{SO}_3\text{SiMe}_3$ (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. $[\alpha]_{\text{D}}^{25} = -34$, $[\alpha]_{577}^{25} = -41$, $[\alpha]_{546}^{25} = -36$, $[\alpha]_{435}^{25} = -54$, $[\alpha]_{405}^{25} = -63$ ($c = 1.04$, CHCl_3). IR (film) ν : 3065, 2975, 2925, 1730, 1695, 1600, 1450, 1260, 1175, 1090 cm^{-1} . $^1\text{H-NMR}$ (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)). $^{13}\text{C-NMR}$ (100.6 MHz, CDCl_3) δ_{C} : 164.1 (s, CO), 150.2 (s, C(6)), 143.6 (s, Ar), 136.0 (d, $^1J(\text{C,H}) = 153$, Ar), 133.2 (d, $^1J(\text{C,H}) = 160$, Ar), 129.9 (d, $^1J(\text{C,H}) = 165$, Ar), 128.4 (d, $^1J(\text{C,H}) = 163$, Ar), 128.0 (d, $^1J(\text{C,H}) = 162$, Ar), 127 (d, $^1J(\text{C,H}) = 160$, Ar), 126.8 (d, $^1J(\text{C,H}) = 160$, Ar), 116.1 (t, $^1J(\text{C,H}) = 145$, C(1')), 75.7 (d, $^1J(\text{C,H}) = 143$, C(4)), 39.6 (d, $^1J(\text{C,H}) = 128$, C(5)), 34.8 (t, $^1J(\text{C,H}) = 121$, C(3)), 23.9 (q, $^1J(\text{C,H}) = 129$, C(2')), 11.6 (q, $^1J(\text{C,H}) = 128$, 4 Me), 11.0 (q, $^1J(\text{C,H}) = 128$, C(8)). MS-MALDI: Calcd for $\text{C}_{24}\text{H}_{28}\text{O}_3\text{Na}^+$ 387.1936 ($M+\text{Na}^+$); found: 387.1935. Anal. Calcd for $\text{C}_{24}\text{H}_{28}\text{O}_3$ (364.48): C 79.9, H 7.74. Found: C 79.12, H 7.72.

(+)-(6Z,4S,5S)-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 $+15^{\circ}\text{C}$ 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 (3S,4S)-4-methyl-5-oxooct-1-en-3-ol benzoate. Data of **10**. colorless oil. $R_{\text{f}} = 0.29$ (petroleum ether/EtOAc = 9:1). $[\alpha]_{\text{D}}^{25} = +24$, $[\alpha]_{577}^{25} = +26$, $[\alpha]_{435}^{25} = +39$, $[\alpha]_{405}^{25} = +39$ ($c = 0.41$, CHCl_3). IR (film) ν : 3515, 3070, 2975, 2920, 1735, 1715, 1690, 1600, 1450, 1285, 1260, 1175, 1095, 1070 cm^{-1} . $^1\text{H-NMR}$ (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)). $^{13}\text{C-NMR}$ (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.

(6Z,4S,5S)-5-Methyl-4-(((2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropionyl)oxy)octa-1,6-dien-6-yl benzoate (**10R**). 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 **10R**. All the NMR measurements were done on the crude sample. Data of **10R**: colorless oil. R_f = 0.44 (petroleum ether/ EtOAc 9:1). ^1H -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, $^5J_{\text{H,F}}$ = 1.2, $\text{CH}_3\text{O-C}(2'')$), 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, $\text{CH}_3\text{-C}(5)$). ^{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*, $^1J_{\text{C,F}}$ = 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 $\text{C}_{26}\text{H}_{27}\text{F}_3\text{O}_5\text{Na}^+$ 499.1708; found: 499.1712.

(6Z,4S,5S)-5-Methyl-4-(((2S)-3,3,3-trifluoro-2-methoxy-2-phenylpropionyl)oxy)octa-1,6-dien-6-yl benzoate (**10S**). Same procedure as that for **10R**, using (*R*)-1-methoxy-1-trifluoromethyl-1-phenylacetyl chloride. Yield: 94%. Colorless oil, R_f = 0.44 (petroleum ether/ EtOAc 9:1). ^1H -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, $^5J_{\text{H,F}}$ = 1.2, $\text{CH}_3\text{O-C}(2'')$), 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, $\text{CH}_3\text{-C}(5)$). ^{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*, $^1J_{\text{C,F}}$ = 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 $\text{C}_{26}\text{H}_{27}\text{F}_3\text{O}_5\text{Na}^+$ 499.1708; found: 499.1724.

(+)-(6Z,4R,5R)-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 $\text{Ph}_2\text{P}(\text{O})\text{N}_3$ (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). $[\alpha]_{\text{D}}^{25}$ = +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} . $^1\text{H-NMR}$ (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, H₂C(3)), 1.56 (*d*, 3H, 3J = 6.8, H-C(8)), 1.20 (*d*, 3H, 3J = 6.8, CH₃-C(5)). $^{13}\text{C-NMR}$ (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 ($[\text{M}+19]^+$, 100), 303 ($[\text{M}+18]^+$, 71), 287 ($[\text{M}+2]^+$, 77), 286 ($[\text{M}+1]^+$, 244 (20), 243 (22), 190 (24), 189 (33), 137 (100) 136 (100), 106 (100), 105 (100). MS-MALDI: Calcd for $\text{C}_{16}\text{H}_{19}\text{N}_3\text{O}_2\text{Na}^+$ 308.1375; found: 308.1343. Anal. Calcd for $\text{C}_{16}\text{H}_{19}\text{N}_3\text{O}_2$ (285.34): C 67.35, H 6.71, N 14.73. Found: C 67.39, H 6.64, N 14.69.

(6Z,4R,5S)-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 $\text{BH}_3\cdot\text{THF}$ 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), $^1\text{H-NMR}$ (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,

CH₃-C(5)). ¹³C-NMR (100.6 MHz, CDCl₃) 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 C₁₆H₂₁N₃O₂K⁺ 342.1220; found: 342.1255.

(6Z,4R,5S)-4-Azido-6-benzoyloxy-5-methyl-6-octenal (**13**). To a solution of alcohol **12** (38 mg, 0.127 mmol) in CH₂Cl₂ (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 NaHCO₃ (2 mL) followed by Na₂S₂O₃·5 H₂O (0.5 g). Extractive work-up (CH₂Cl₂, 3 mL, 3 times), drying (Na₂SO₄) 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 (CH₂Cl₂/Et₂O 95:5). IR (film) ν: 2980, 2920, 2110, 1730, 1695, 1600, 1455, 1260, 1090 cm⁻¹. ¹H-NMR (400 MHz, CDCl₃) δ_H: 9.18 (s, 1H, H-C(1)), 8.13 (*dxd*, 2H, ³*J* = 8.4, ⁴*J* = 1.2, H-C(Bz)), 7.64 (*txt*, 1H, ³*J* = 7.4, ⁴*J* = 1.2, H-C(Bz)), 7.51, *t*, 2H, ³*J* = 7.8, H-C(Bz)), 5.37 (*q*, 1H, ³*J* = 6.8, H-C(7)), 3.44 (*dxdxd*, 1H, ³*J* = 9.8, ³*J* = 6.2, ³*J* = 3.1, H-C(4)), 2.71-2.55 (*m*, 2H, H-C(2)), 2.05 (*dxdxdxd*, 1H, ²*J* = 14.3, ³*J* = 8.0, ³*J* = 6.8, ³*J* = 3.6, Ha-C(3)), 1.80 (*dxdxdxd*, 1H, ²*J* = 14.3, ³*J* = 9.8, ³*J* = 8.0, ³*J* = 5.5, Hb-C(3)), 1.55 (*d*, 3H, ³*J* = 6.8, H-C(8)), 1.22 (*d*, 3H, ³*J* = 6.8, CH₃-C(5)). MS-MALDI: Calcd for C₁₆H₁₉N₃O₃Na⁺ 324.1324; found: 324.1387.

(1S)-2-((2R)-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 H₂ 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 (CH₂Cl₂/Et₂O 95:5). ¹H-NMR (400 MHz, CDCl₃) δ_H: 7.50-7.37 (*m*, 5H, H-C(Bz)), 4.40 (*dt*, 1H, ³*J* = 8.3, ³*J* = 5.8, H-C(2')), 3.55 (*dq*, 1H, ³*J* = 7.0, ³*J* = 5.1, H-C(2)), 3.44 (*dd*, 2H, ³*J* = 9.0, ³*J* = 3.8, H-C(5')), 2.50 (*q*, 2H, ³*J* = 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, ³*J* = 7.0, H-C(1)), 1.05 (*t*, 3H, ³*J* = 7.0, H-C(5)). ¹³C-NMR (100.6 MHz, CDCl₃) 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 C₁₆H₂₁N₂O₂Na⁺ 282.1470; found: 282.1478.

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