Stereoselective Total Synthesis of Natural (+)-Streptazolin via a Palladium-Catalyzed Enyne Bicyclization Approach

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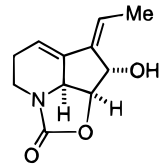
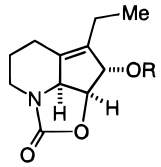
Abstract: The natural *Z* isomer of (+)-streptazolin (**1**), isolated from cultures of *Streptomyces viridochromogenes*, was synthesized in an optically pure form for the first time on the basis of a palladium-catalyzed enyne bicyclization approach in 12 steps and 4.3% overall yield from (3*R*,4*R*)-3,4-bis(benzyloxy)succinimide (**5**). The requisite enyne **13** for palladium-catalyzed bicyclization was prepared from **5** via *N*-acyliminium ion cyclization of the acetoxy lactam **9**, partial reduction of **10** with DIBALH−BuLi, and conversion to the dibromo olefin **12**. The best result in the palladium-catalyzed bicyclization was obtained when treated with 30 mol % $Pd(OAc)_2$ and *N*,*N*′-bis(benzylidene)-ethylenediamine (BBEDA) as the ligand in benzene at reflux, thus affording a 93:7 mixture of the 1,2,4a,7a,6,7-hexahydro-5*H*-1-pyrindine (*Z*)-**14** along with its isomerized product (*Z*)-**15** in 84% total yield. The isomerization of the 1,4-diene in (*Z*)-**14** to the 1,3-diene was achieved by treatment with triiron dodecacarbonyl to generate the stable tricarbonyl(η^4-1,3-diene)iron complex **16**, which was then converted to the glycol **17**. Treatment of **17** with sodium methoxide followed by ordinary chromatography on silica gel resulted in isolation of chemically and enantiomerically pure (+)-streptazolin (**1**).

Streptazolin (**1**), isolated from cultures of *Streptomyces viridochromogenes* (strain Tü 1678)[1] for the first time in 1981 and later discovered by a chemical screening of *Streptomyces luteogriseus* (strain FH-S 1307)[2] or the high-producing strain *Streptomyces* sp. (strain FH-S 2184),[3] is a unique antibiotic which possesses the structural feature of an unusual ring system (hexahydro-1*H*-1-pyrindine) embodying an internal urethane unit and an exocyclic ethylidene side chain.[4] This antibiotic has been claimed to be unstable and readily polymerizes during the isolation and purification although it may be kept for some time in diluted solutions at low temperatures. For this reason, structural investigations based on X-ray[5] and extensive NMR analyses were carried out using its crystalline stable derivative *O*-acetyldihydrostreptazolin (**3**) transformed from **1** by catalytic hydrogenation followed by O-acetylation. To enhance the stability and solubility, streptazolin (**1**) and dihydrostreptazolin (**2**) have been converted to the glucopyranosides.[6] While **1** exhibits limited antimicrobial activities, some Diels−Alder adducts with naphthoquinones have been reported[7] to have striking bactericidal, fungicidal, protozoacidal, and antitumor activity as effective as adriamycin on leukemia L1210 cells as well as improvement of the chemical stability. In view of the unique structural feature and promising pharmacological activity profile, this antibiotic has posed an interesting challenge. Indeed, the pioneering synthetic studies toward **1** have been published by the two groups of Kozikowski[8] and Overman.[9] In both syntheses, the lack of stereoselectivity in the introduction of the ethylidene side chain by the Wittig reaction of the cyclic ketone led to streptazolin as a 1:2 mixture of the ethylidene stereoisomers with its incorrect *E* isomer predominating. Since the *E*/*Z* 1,3-diene isomers of streptazolin thus formed were found to be inseparable and to have the tendency to readily polymerize due to the conjugated diene system, this mixture was, without isolation, immediately hydrogenated to the stable dihydro or tetrahydro derivatives for isolation and characterization.[8,9]



(+)-Streptazolin (**1**)



2, R = H
3, R = Ac

We initiated a synthetic program to overcome this problem in these syntheses associated with preponderant formation of the undesired (*E*)-ethylidene isomer of streptazolin under the Wittig conditions. Preparation of stereodefined exocyclic alkenes seems an important objective for development,[10] since various types of biologically active natural products containing an exocyclic alkenyl moiety other than streptazolin are known. However, the difficulties associated with controlling exocyclic alkene geometry have been recognized even in a more general sense. In our own involvement in this area, we have recently reported[11] a solution to this problem through utilizing intramolecular chromium−nickel-mediated cyclization[12] in the total synthesis of the dendrobatid alkaloids allopumiliotoxins.

[⊗] Abstract published in *Advance ACS Abstracts,* January 15, 1996.

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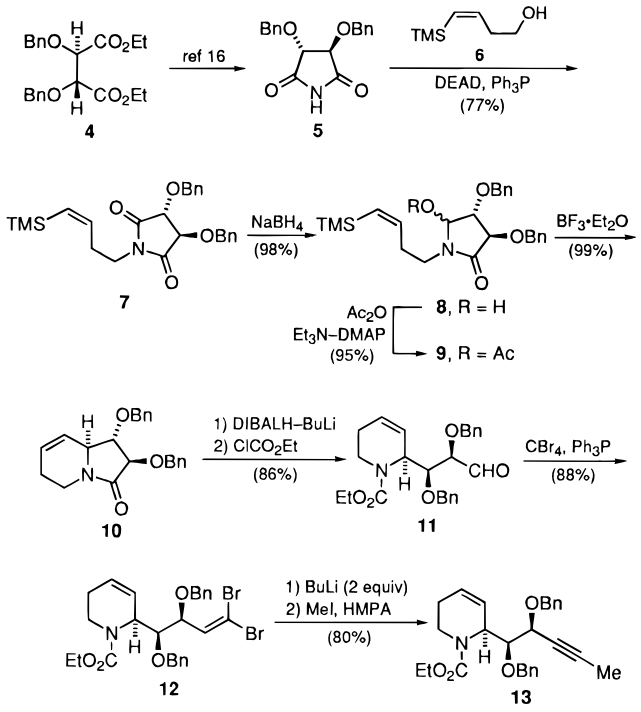
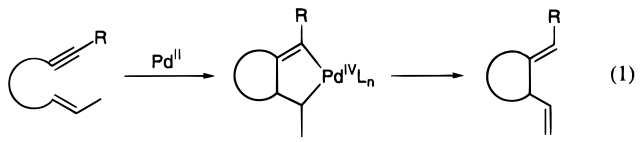
Scheme 1



With these issues in mind, we envisioned that this problem might be resolved by using the strategy based on the carbocyclization by palladium-catalyzed ene type reaction of enyne compounds via palladacycles (eq 1) broadly developed by



(1)

Trost.[13] This approach would allow a direct, highly stereoselective incorporation of the *E* configuration (corresponds to the *Z* configuration in **1**) at the exocyclic alkylidene group. We herein present our highly stereoselective total synthesis of the natural *Z* isomer of (+)-streptazolin (**1**) in a *chemically and enantiomerically pure* form for the first time based on a palladium-catalyzed enyne bicyclization approach.

The synthesis began by preparation of an enyne compound adequate for palladium-catalyzed bicyclization as outlined in Scheme 1. Our initial plan for this centered on the construction of an optically active indolizidinone (i.e., **10**) based on the *N*-acyliminium ion−vinylsilane cyclization protocol previously developed by Overman's group.[9,14] The dibenzyl ether **4**, prepared from diethyl L-tartrate by a modified Yamamoto procedure[15] (BnBr, NaH, Bu_4NI, DMF, room temperature) in 92% yield, was converted to the cyclic imide **5** according to the method of Kakisawa.[16] Mitsunobu coupling of **5** with (*Z*)-4-(trimethylsilyl)-3-butenol (**6**)[17] provided the *N*-butenylimide **7** (77% yield), which was converted to the acetoxy lactam **9** via reduction of the one of the carbonyl groups with $NaBH_4$ followed by O-acetylation (Ac_2O, DMAP) of **8** (obtained as an essentially single diastereomer) in 93% overall yield. Treatment of **9** with $BF_3{\cdot}Et_2O$ at room temperature induced *N*-acyliminium ion cyclization to produce the indolizidinone **10** as a single diastereomer in 99% yield. The partial reduction of the tertiary amide moiety in **11** was cleanly attained by using the aluminum ate complex from DIBALH and butyllithium.[18] The amino aldehyde thus obtained via hemiaminal ring opening was protected at nitrogen in situ with the ethoxycarbonyl group to give the tetrahydropyridine **11** in 86% overall yield. Treatment of **11** with carbon tetrabromide and triphenylphosphine afforded the dibromo olefin **12** (88%), which was then transformed into the requisite enyne **13** (80%) by treatment with 2 equiv of BuLi and then iodomethane in the presence of HMPA.

Palladium-catalyzed bicyclization of **13** was carried out at a 0.02 M substrate concentration at reflux. Although with 5−10 mol % $Pd(OAc)_2$ (in benzene) the reaction was slow, increasing the quantity of the catalyst to 30 mol % allowed the reaction rate to be enhanced and resulted in the bicyclic products in 85% total yield as a mixture of the (*Z*)-ethylidene isomers ((*Z*)-**14** and its isomerized product (*Z*)-**15**) and the (*E*)-ethylidene isomers ((*E*)-**14** and its isomerized product (*E*)-**15**) in a *Z*/*E* ratio of 70:30 (Table 1, entry 1). In this case, the actual yield for the required ene adduct (*Z*)-**14** was very poor (38%), and more seriously, the *Z* and *E* isomers were inseparable by ordinary chromatography. The same reaction using $Pd(OAc)_2(PPh_3)_2$ was very sluggish; heating for 24 h resulted in no reaction, but addition of AcOH (2 equiv) brought the reaction to completion in 4 h (Table 1, entry 2). In the latter case, however, the product was again a mixture of (*Z*)-**14**, (*Z*)-**15**, (*E*)-**14**, and (*E*)-**15** in 88% total yield. Although the *Z*/*E* product ratio was slightly improved to 78:22 by this process, these reaction conditions greatly produced isomerization to the (*Z*)-enamide (*Z*)-**15.** The actual yield for the desired (*Z*)-**14** was thus only 8%.

Use of *N*,*N*′-bis(benzylidene)ethylenediamine (BBEDA) as the ligand dramatically improved the selectivity, leading to formation of a 93:7 mixture of (*Z*)-**14** and (*Z*)-**15** in 84% yield with no detection of the *E* isomers (Table 1, entry 4). These isomers that were produced were easily separable by column chromatography, and that both compounds (*Z*)-**14** and (*Z*)-**15** individually obtained indeed possess the *Z* geometry as well as the cis ring junction was evidenced by NOESY (Figure 1). We thus could obtain pure (*Z*)-**14** in 73% yield from **13**. When the same reaction using $Pd(OAc)_2$−BBEDA was performed in the presence of a proton source such as acetic acid or water, the reaction was completed in a shorter time compared with the reaction without these proton sources (Table 1, entries 5 and 6). In each case, none of the *E* isomers was detected in the product, but a somewhat lower selectivity for (*Z*)-**14** due to its isomerization to (*Z*)-**15** was observed.

With correct (*Z*)-ethylidene stereochemistry and the configuration at all stereocenters in hand, the only remaining problem was the isomerization of the 1,4-diene in (*Z*)-**14** to the 1,3-diene. Thus, (*Z*)-**14** was treated with 2 equiv of triiron dodecacarbonyl, freshly prepared from iron pentacarbonyl by treatment with Et_3N and then HCl,[19] in 1,2-dichloroethane (reflux, 5 h) (Scheme 2).

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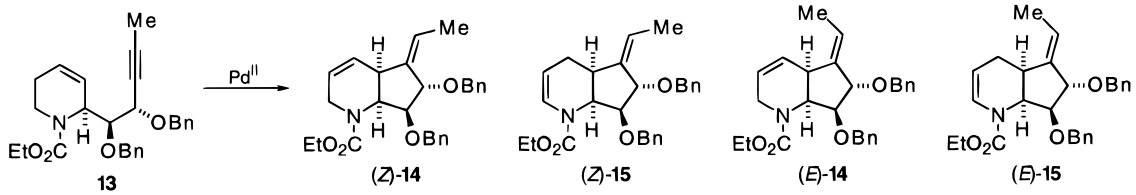
Table 1. Palladium-Catalyzed Bicyclization of Enyne **13**



entry[a]	catalyst (mol %)	solvent	time (h)	product ratio[b] (*Z*)-**14**:(*Z*)-**15**:(*E*)-**14**:(*E*)-**15**	yield (%)[c]
1	$Pd(OAc)_2$ (30)	benzene	10	45:25:27:3	85
2	$Pd(OAc)_2(PPh_3)_2$ (30)	benzene containing AcOH (2 equiv)	4	9:69:6:16	88
3	$Pd(OAc)_2$−BBEDA[d] (10)	benzene	26	92:8:0:0	80
4	$Pd(OAc)_2$−BBEDA (30)	benzene	7	93:7:0:0	84
5	$Pd(OAc)_2$−BBEDA (30)	benzene containing AcOH (2 equiv)	3	81:19:0:0	93
6	$Pd(OAc)_2$−BBEDA (30)	benzene saturated with water	1.5	85:15:0:0	85

[a] All reactions were run at a substrate concentration of 0.02 M at reflux. [b] HPLC determination. [c] HPLC determination using 2-naphthol as an internal standard. [d] BBEDA = *N*,*N*′-bis(benzylidene)ethylenediamine.

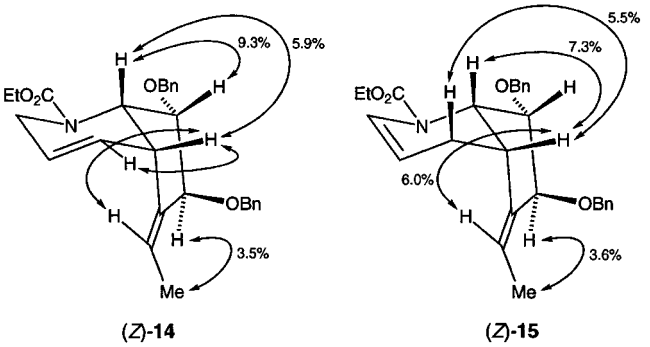
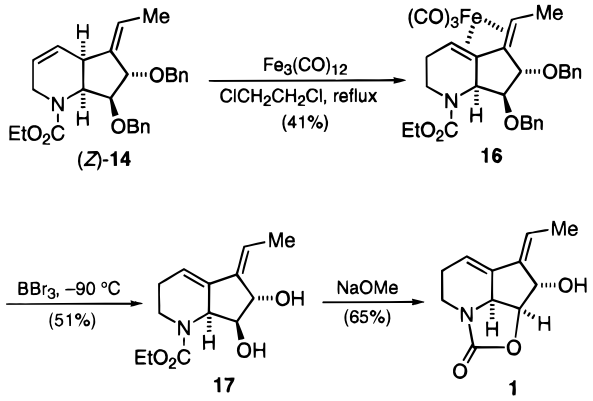


Figure 1. Some selected NOEs for (*Z*)-ethylidene isomers (*Z*)-**14** and (*Z*)-**15**.

Scheme 2



After workup, chromatography and recrystallization from hexane provided the stable tricarbonyl(η^4-1,3-diene)iron complex **16** as a yellow crystalline compound having mp 68 °C in 41% yield. This complexation is very advantageous not only because of the stabilization of the conjugated diene system but also because of the greater ease of structural identification by X-ray crystallography (Figure 2).[20] This served primarily to confirm the absolute and relative stereochemistry of **16** but also to unambiguously established the *Z* geometry of the exocyclic ethylidene.

(20) Crystal data for **16**: monoclinic space group $P2_1$, $Z = 2$, $a = 8.255(4)$ Å, $b = 14.015(4)$ Å, $c = 12.230(4)$ Å, $\beta = 92.94(3)°$, $d_{calcd} = 1.348$ g cm^{-3}, $\lambda = 1.541\,78$ Å. Of the 2324 reflections measured at $2\theta_{max} = 120.2°$, 2212 unique reflections were used in the structure solution by direct methods. Refinement on F^2 converged at $R = 3.8\%$, w$R_F{}^2 = 5.1\%$, with GOF = 1.19.

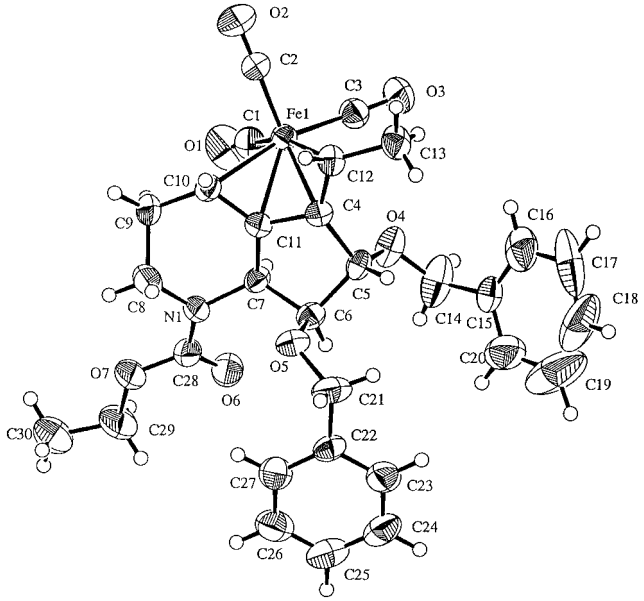


Figure 2. ORTEP drawing of the X-ray crystal structure of the complex **16** ($C_{30}H_{31}NO_7Fe$). Selected bond lengths (Å) and angles (deg): Fe−C4 = 2.076(6), Fe−C10 = 2.209(6), Fe−C11 = 2.067(5), Fe−C12 = 2.143(6), N−C7 = 1.479(9), N−C8 = 1.45(1), C4−C5 = 1.512(9), C4−C11 = 1.404(8), C4−C12 = 1.421(8), C5−C6 = 1.562(9), C6−C7 = 1.516(9), C7−C11 = 1.525(9), C8−C9 = 1.54(1), C9−C10 = 1.506(9), C10−C11 = 1.401(10), C12−C13 = 1.504(9); C5−C4−C11 = 108.6(6), C5−C4−C12 = 132.9(6), C11−C4−C12 = 118.4(6), Fe−C10−C9 = 129.1(5), Fe−C10−C11 = 65.5(3), C9−C10−C11 = 113.5(5), C4−C11−C7 = 108.9(6), C4−C11−C10 = 124.9(6), C7−C11−C10 = 126.0(5), Fe−C12−C4 = 67.8(3), Fe−C12−C13 = 125.1(5), C4−C12−C13 = 120.4(6).

Exposure of **16** to BBr_3 in CH_2Cl_2 at −90 °C led to removal of the $Fe(CO)_3$ fragment and the benzyl protecting groups, affording the glycol **17** in 51% yield. On treatment with sodium methoxide in methanol at reflux, **17** underwent oxazolidinone formation. After usual workup, purification and isolation were performed by conventional chromatographic techniques to provide (+)-streptazolin (**1**) as a colorless clean oil in 65% yield. The synthetic sample of (+)-streptazolin had spectroscopic data (^{1}H NMR, IR) identical to those reported[1] for natural product. The specific rotation, $[\alpha]^{27}_D$ +21.5° (*c* 0.65, $CHCl_3$), was also in agreement with the literature data[1] ($[\alpha]^{25}_D$ +22° (*c* 2.8, $CHCl_3$)).

In summary, the highly stereoselective total synthesis of chemically and enantiomerically pure (+)-streptazolin (**1**) was

accomplished in an overall yield of 4.3% by a 12-step sequence from (3*R*,4*R*)-3,4-bis(benzyloxy)succinimide (**5**). This synthesis representing a new and efficient approach to the natural isomer of streptazolin was devised in the stereoselective construction of the (*Z*)-ethylidene group by utilizing a palladium-catalyzed enyne cyclization as the key step.

Experimental Section

General Procedures. All melting points were measured on Yanaco MP-5000 micro melting point apparatus and are uncorrected. Optical rotation were recorded on a JEOL DIP-4 instrument. IR spectra were performed with a Perkin-Elmer FTIR spectrometer. Nuclear magnetic resonance (^{1}H and ^{13}C NMR) spectra were taken with a Varian Gemini-300, a Bruker AM-400, or a AM-500 spectrometer. Residual chloroform (7.26 ppm) was used as the internal reference for ^{1}H NMR spectra measured in $CDCl_3$. ^{13}C chemical shifts were reported on the δ scale relative to $CDCl_3$ as an internal reference (77.1 ppm), and the degree of substitution of each carbon atom was determined by DEPT composed 90° and 135° pulsed sequence experiments. Mass spectra were measured on a Hitachi M-80 or a VG Auto Spec spectrometer at 70 eV. Thin-layer chromatography (TLC) was performed on Merck silica gel 60 F_{254} TLC plates, and Merck silica gel 60 (230−400 mesh) was used for column chromatography. HPLC analysis was performed on a 6.0 × 150 mm 5 μm Shim-pack CLC-SIL column with hexane−EtOAc (7:1) as eluent at a flow rate of 1 mL/min and 254 nm detection using a JASCO PU-980 pump equipped with a JASCO UV-970 detector.

(3*R*,4*R*)-1-[(*Z*)-4-(Trimethylsilyl)-3-butenyl]-3,4-bis(benzyloxy)-pyrrolidine-2,5-dione (7). To a stirred, cooled (0 °C) mixture of **5** (4.70 g, 15.1 mmol), (*Z*)-4-(trimethylsilyl)-3-butenol (**6**) (2.40 g, 16.6 mmol), PPh_3 (5.15 g, 19.6 mmol), and THF (150 mL) was added DEAD (3.68 g, 21.1 mmol), and the mixture was stirred under Ar at room temperature for 30 min. Condensation in vacuo followed by chromatography on silica gel (hexane−EtOAc, 15:1) gave **7** (5.10 g, 77%) as a colorless oil: $[\alpha]^{27}_D$ +108.8° (*c* 1.0, $CHCl_3$); IR (neat) 2953, 1718, 1398, 1348, 1249, 1118, 1070, 839 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.35−2.51 (2 H, m), 3.47−3.65 (2 H, m), 4.37 (2 H, s), 4.76 (2 H, $^1/_2$ AB q, J = 11.6 Hz), 5.00 (2 H, $^1/_2$ AB q, J = 11.6 Hz), 5.64 (1 H, d, J = 14.0 Hz), 6.19 (1 H, td, J = 14.0, 7.3 Hz), 7.23−7.45 (10 H, m); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 0.1 (3 carbons), 31.5, 38.1, 73.5 (2 carbons), 78.5 (2 carbons), 128.3 (6 carbons), 128.6 (4 carbons), 133.2, 136.6 (2 carbons), 143.0, 172.6 (2 carbons); EIMS *m/z* (relative intensity) 438 (M^+ + 1, 1), 421 (8), 346 (3.2), 318 (1), 294 (3), 250 (2), 225 (100), 182 (10.2), 157 (5.4), 134 (1.6), 111 (2.4). Anal. Calcd for $C_{25}H_{31}NO_4Si$: C, 68.62; H, 7.14; N, 3.20. Found: C, 68.70; H, 7.20; N, 3.35.

(3*R*,4*R*)-1-[(*Z*)-4-(Trimethylsilyl)-3-butenyl]-3,4-bis(benzyloxy)-5-hydroxypyrrolidin-2-one (8). To a stirred, cooled (0 °C) solution of **7** (3.70 g, 8.45 mmol) in MeOH (80 mL) was added $NaBH_4$ (640 mg, 16.9 mmol) in small portions, and the mixture was stirred at 0 °C for 30 min. After addition of H_2O (20 mL), the mixture was concentrated in vacuo to ca. one-third volume and extracted with CH_2Cl_2 (3 × 50 mL). The combined extracts were washed with brine (80 mL), dried ($MgSO_4$), and concentrated to dryness. The residue was purified by chromatography on silica gel (hexane−EtOAc, 4:1) to give **8** (3.64 g, 98%) as a colorless oil: IR (neat) 3346, 2953, 1685, 1455, 1358, 1249, 1114, 1064, 839, 764, 737, 698 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.12 (9 H, s), 2.33−2.51 (2 H, m), 2.63 (1 H, dd, J = 10.4, 1.6 Hz), 3.24−3.32 (1 H, m), 3.49−3.57 (1 H, m), 3.84 (1 H, dd, J = 4.0, 2.4 Hz), 4.03 (1 H, d, J = 4.0 Hz), 4.60 (2 H, m), 4.76 (1 H, $^1/_2$ AB q, J = 11.7 Hz), 4.94 (1 H, dd, J = 8.0, 2.4 Hz), 4.98 (1 H, $^1/_2$ AB q, J = 11.7 Hz), 5.63 (1 H, d, J = 14.3 Hz), 6.25 (1 H, td, J = 14.3, 7.3 Hz), 7.26−7.40 (10 H, m).

(3*R*,4*R*)-1-[(*Z*)-4-(Trimethylsilyl)-3-butenyl]-5-acetoxy-3,4-bis-(benzyloxy)pyrrolidin-2-one (9). To a stirred solution of **8** (3.64 g, 8.24 mmol) in CH_2Cl_2 (80 mL) were sequentially added acetic anhydride (1.10 g, 10.8 mmol), triethylamine (1.10 g, 10.9 mmol), and 4-(dimethylamino)pyridine (800 mg, 6.55 mmol), and the mixture was stirred at room temperature for 30 min. After addition of saturated aqueous $NaHCO_3$ (50 mL), the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 70 mL). The combined organic phases were washed with saturated aqueous NH_4Cl (100 mL) and then brine (100 mL) and dried ($MgSO_4$). Removal of the solvent in vacuo followed by chromatography on silica gel (hexane−EtOAc, 8:1) afforded **9** (3.79 g, 95%) as a colorless oil: $[\alpha]^{26}_D$ +31.6° (*c* 1.0, $CHCl_3$); IR (neat) 2953, 2897, 1718, 1608, 1455, 1427, 1364, 1218, 1162, 1104, 1019, 839 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.12 (9 H, s), 2.10 (3 H, s), 2.30−2.51 (2 H, m), 3.06 (1 H, ddd, J = 14.0, 8.4, 5.9 Hz), 3.60 (1 H, ddd, J = 14.2, 8.4, 7.0 Hz), 3.93 (1 H, dd, J = 2.8, 1.4 Hz), 4.04 (1 H, d, J = 2.8 Hz), 4.56 (1 H, $^1/_2$ AB q, J = 11.9 Hz), 4.62 (1 H, $^1/_2$ AB q, J = 11.9 Hz), 4.76 (1 H, $^1/_2$ AB q, J = 11.9 Hz), 4.96 (1 H, $^1/_2$ AB q, J = 11.9 Hz), 5.63 (1 H, d, J = 14.1 Hz), 6.11 (1 H, d, J = 1.4 Hz), 6.22 (1 H, dt, J = 7.3, 14.1 Hz), 7.22−7.43 (10 H, m); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 0.1 (3 carbons), 21.0, 31.5, 40.4, 72.0, 72.7, 79.3, 81.9, 85.4, 127.8 (2 carbons), 128.0, 128.1, 128.2 (2 carbons), 128.4 (2 carbons), 128.5 (2 carbons), 132.5, 137.0, 137.3, 143.7, 170.2, 171.3; EIMS *m/z* (relative intensity) 481 (M^+, 1), 466 (2), 423 (1.4), 390 (0.3), 366 (0.4), 330 (2.3), 286 (0.9), 210 (100), 181 (0.7), 155 (0.5), 111 (0.9). Anal. Calcd for $C_{27}H_{35}NO_5Si$: C, 67.33; H, 7.32; N, 2.91. Found: C, 67.29; H, 7.39; N, 2.96.

(1*S*,2*R*,8a*S*)-1,2-Bis(benzyloxy)-1,2,3,5,6,8a-hexahydroindolidin-3-one (10). To a stirred solution of **9** (3.79 g, 7.87 mmol) in CH_2Cl_2 (160 mL) was added dropwise BF_3·Et_2O (2.23 g, 15.7 mmol), and the mixture was stirred at room temperature for 2 h. After addition of saturated aqueous $NaHCO_3$ (80 mL), the mixture was stirred for 30 min, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL), and the combined organic layers were washed with saturated aqueous NH_4Cl (100 mL) and then brine (100 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by chromatography on silica gel (hexane−EtOAc, 4:1) to give **10** (2.72 g, 99%) as a colorless oil: $[\alpha]^{26}_D$ +63.2° (*c* 1.15, $CHCl_3$); IR (neat) 2871, 1708, 1455, 1437, 1358, 1302, 1110, 736, 698 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.01−2.10 (1 H, m), 2.17−2.30 (1 H, m), 2.80 (1 H, dt, J = 4.9, 11.8 Hz), 3.83 (1 H, t, J = 7.3 Hz), 3.88−3.96 (1 H, m), 4.25 (1 H, dd, J = 13.1, 6.7 Hz), 4.35 (1H, dd, J = 7.2, 1.4 Hz), 4.61 (1 H, $^1/_2$ AB q, J = 11.7 Hz), 4.71 (1 H, $^1/_2$ AB q, J = 11.7 Hz), 4.84 (1 H, $^1/_2$ AB q, J = 11.5 Hz), 5.18 (1 H, $^1/_2$ AB q, J = 11.5 Hz), 5.72−5.87 (2 H, m), 7.21−7.47 (10 H, m); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 23.9, 35.3, 56.1, 72.6 (2 carbons), 82.1, 84.3, 125.2, 126.1, 127.8 (4 carbons), 127.8, 127.9, 128.4 (4 carbons), 137.6, 137.7, 168.9; EIMS *m/z* (relative intensity) 351 (M^+ + 2, 0.5), 243 (3.1), 172 (0.3), 153 (1.4), 137 (4.7). Anal. Calcd for $C_{22}H_{23}NO_3$: C, 75.62; H, 6.63; N, 4.01. Found: C, 75.51; H, 6.79; N, 3.90.

(2*S*)-1-Carbethoxy-2-[(1*S*,2*S*)-1,2-bis(benzyloxy)-4,4-dibromo-3-butenyl]-1,2,5,6-tetrahydropyridine (12). DIBALH (0.9 M) in hexane (4.2 mL, 3.78 mmol) was diluted with THF (10 mL), and to this solution was added 1.6 M BuLi in hexane (2.4 mL, 3.78 mmol) at 0 °C. The mixture was stirred under Ar at 0 °C for 30 min. The newly created solution of LiAlHBu(*i*-Bu)$_2$ reagent in hexane−THF (3.78 mmol) was added dropwise to a solution of **10** (1.10 g, 3.15 mmol) in THF (30 mL), and the mixture was stirred under Ar at room temperature. After 5 min, 1 N NaOH (20 mL) and CH_2Cl_2 (50 mL) were added under cooling, and the mixture was stirred for 5 min. A solution of ethyl chloroformate (684 mg, 6.30 mmol) in CH_2Cl_2 (2 mL) was added, and stirring was continued under Ar at room temperature. After 1 h, the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined layers were washed with brine, dried ($MgSO_4$), concentrated, and passed through a short column of silica gel (hexane−EtOAc, 8:1) to give (2*S*)-1-carbethoxy-2-[(1*S*,2*R*)-1,2-bis(benzyloxy)-2-formylethyl]-1,2,5,6-tetrahydropyridine (**11**) (1.15 g, 86%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.14−1.34 (3 H, m), 1.92−2.34 (2 H, m), 2.95−3.08 (1 H, m), 3.83−3.97 (2 H, m), 3.98−4.27 (3 H, m), 4.45−4.93 (5 H, m), 5.80−6.03 (2 H, m), 7.20−7.43 (10 H, m), 9.69 (1 H, br s).

The above material **11** is immediately used for the following reaction. Thus, a solution of **11** (1.15 g, 2.72 mmol), CBr_4 (1.80 g, 5.44 mmol), and triphenylphosphine (2.89 g, 10.9 mmol) in CH_2Cl_2 (60 mL) was stirred at room temperature. After 15 min, the mixture was concentrated in vacuo and subjected to chromatography on silica gel (hexane−EtOAc, 10:1) to afford **12** (1.38 g, 88%) as a yellow oil: $[\alpha]^{24}_D$ −116.4° (*c* 1.3, $CHCl_3$); IR (neat) 2929, 1696, 1455, 1429, 1337, 1257, 1119, 1110, 1072, 1029, 698 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21−

1.30 (3 H, m), 1.92−2.28 (2 H, m), 3.01−3.18 (1 H, m), 3.71−4.24 (4 H, m), 4.32 (1 H, dd, J = 9.1, 6.7 Hz), 4.42−4.57 (2 H, m), 4.60−4.66 (2 H, m), 4.79 (1 H, $^1/_2$ AB q, J = 11.3 Hz), 5.75−5.82 (1 H, m), 5.95−6.05 (1 H, m), 6.05−6.15 (1 H, m), 7.23−7.41 (10 H, m); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 14.7, 24.5 (24.8), 38.4 (38.9), 53.1, 61.5, 71.6, 75.4, 81.3, 82.3 (83.4), 93.2, 124.2, 124.6, 127.7 (4 carbons), 127.9 (2 carbons), 128.3 (4 carbons), 136.6, 138.0 (2 carbons), 155.3; EIMS *m/z* (relative intensity) 581 (M^+ + 4, 21), 579 (M^+ + 2, 31), 577 (M^+, 21), 536 (13), 534 (17), 532 (13), 500 (24), 498 (24), 490 (55), 488 (100), 486 (55), 473 (27), 471 (28), 427 (20), 425 (29), 423 (200). Anal. Calcd for $C_{22}H_{23}NO_3$: C, 53.90; H, 5.04; N, 2.42. Found: C, 53.85; H, 5.00; N, 2.44.

(2*S*)-1-Carbethoxy-2-[(1*S*,2*S*)-1,2-bis(benzyloxy)-3-pentynyl]-1,2,5,6-tetrahydropyridine (13). To a stirred, cooled (−78 °C) solution of **12** (1.13 g, 1.95 mmol) in THF (20 mL) was added 1.66 M BuLi in hexane (0.235 mL, 3.90 mmol) via syringe, and the mixture was stirred at the same temperature. After 1 h, HMPA (700 mg, 3.91 mmol) and iodomethane (1.38 g, 9.72 mmol) were added, and the mixture was stirred at −78 °C for 2 h and allowed to cool to room temperature. After stirring was further continued at room temperature for 24 h, the mixture was diluted with Et_2O (40 mL) and aqueous saturated NH_4Cl (5 mL) was added. The mixture was stirred for 30 min and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 50 mL), and combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated. The residue was purified by chromatography on silica gel (hexane−EtOAc, 10:1) to give **13** (675 mg, 80%) as a colorless oil: $[\alpha]^{23}_D$ −94.9° (*c* 0.7, $CHCl_3$); IR (neat) 2920, 1696, 1455, 1429, 1280, 1246, 1200, 1110, 739, 699 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.17−1.31 (3 H, m), 1.91 (3 H, br s), 1.92−2.24 (2 H, m), 3.10−3.27 (1 H, m), 3.85−4.30 (5 H, m), 4.51−4.90 (5 H, m), 5.70−6.03 (2 H, m), 7.23−7.41 (10 H, m); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 3.7, 14.6, 24.7, 38.4 (39.1), 53.1 (53.3), 61.2, 71.1, 71.2, 72.0, 75.2, 83.1 (83.9), 84.5, 123.6, 124.1, 127.6 (2 carbons), 127.7 (2 carbons), 128.0 (2 carbons), 128.3 (4 carbons), 138.2 (2 carbons), 155.4; EIMS *m/z* (relative intensity) 433 (M^+, 0.1), 403 (0.1), 373 (0.1), 342 (1.1), 312 (0.3), 274 (100), 252 (0.2), 234 (1.1), 206 (0.5), 181 (0.1), 155 (100), 126 (0.2); HRMS calcd for $C_{27}H_{31}NO_4$ (M^+) 433.2253, found 433.2251.

General Procedure for Palladium-Catalyzed Bicyclization of Enyne 13. To a 0.02 M solution of **13** in benzene, benzene containing AcOH, or benzene saturated with water was added the catalyst (30 mol % or 10 mol %) as shown in Table 1, and the mixture was stirred at reflux. After the amount of time indicated in Table 1, the mixture was passed through a short column of silica gel and eluted with EtOAc. The combined solutions were concentrated in vacuo, and a solution of β-naphthol (1.00 mg) in hexane−EtOAc (7:1) was added to the residue. The resulting solution was used for determinations of the product ratio and the yield by HPLC analysis. The results are summarized in Table 1.

Data for (1*S*,6*S*,8*S*,9*S*)-8,9-bis(benzyloxy)-2-carbethoxy-7(*Z*)-ethylidene-2-azabicyclo[4.3.0]non-4-ene ((*Z*)-**14**): $[\alpha]^{26}_D$ −163.2° (*c* 0.75, $CHCl_3$); IR (neat) 2927, 2862, 1695, 1455, 1417, 1374, 1328, 1093, 1028, 698 cm^{-1}; ^{1}H NMR (400 MHz, pyridine-d_5, 60 °C) δ 1.22 (3 H, t, J = 7.0 Hz), 1.74 (3 H, dd, J = 6.9, 1.6 Hz), 3.43 (1 H, br d, J = 8.9 Hz), 4.05 (1 H, dd, J = 17.8, 2.4 Hz), 4.25 (2 H, q, J = 7.0 Hz), 4.12−4.72 (7 H, m), 5.25 (1 H, br s), 5.68 (1 H, dd, J = 10.2, 3.2 Hz), 5.80−5.88 (2 H, m), 7.24−7.49 (10 H, m); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 14.7, 14.8, 38.5, 42.5, 53.9, 61.3, 71.0, 72.2, 79.0, 82.1, 121.2 and 121.6 (due to the carbamate rotamers), 125.9, 127.0, 127.5 (2 carbons), 127.6 (2 carbons), 127.7, 127.9, 128.4 (4 carbons), 138.2, 138.4, 141.8, 156.0; EIMS *m/z* (relative intensity) 433 (M^+, 0.1), 403 (0.1), 373 (0.1), 342 (1.1), 312 (0.3), 274 (100), 252 (0.2), 234 (1.1), 206 (0.5), 181 (0.1), 155 (100), 126 (0.2); HRMS calcd for $C_{27}H_{31}NO_4$ (M^+) 433.2253, found 43.2264.

Data for (1*S*,6*S*,8*S*,9*S*)-8,9-bis(benzyloxy)-2-carbethoxy-7(*Z*)-ethylidene-2-azabicyclo[4.3.0]non-3-ene ((*Z*)-**15**): $[\alpha]^{24}_D$ −127.2° (*c* 0.75, $CHCl_3$); IR (neat) 2980, 2915, 2858, 1708, 1662, 1445, 1411, 1375, 1333, 1318, 1279, 1110, 1072 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.14 and 1.32 (total 3 H, t, J = 7.1 Hz, and t, J = 6.9 Hz, respectively, in ca 1:1 due to the carbamate rotamers), 1.69 (3 H, dd, J = 6.6, 14.3 Hz), 2.02−2.23 (2 H, m), 2.61−2.74 (1 H, m), 4.00−4.24 (3 H, m), 4.25−4.62 (6 H, m), 4.83−4.87 and 4.87−5.01 (total 1 H, each m, in ca 1:1 due to the carbamate rotamers), 5.80 (1 H, br qd, J = 7.0, 2.1 Hz), 6.91 and 7.01 (total 1 H, br d, J = 9.0 Hz, and br d, J = 8.7 Hz, respectively, in ca. 1:1 due to the carbamate rotamers), 7.20−7.39 (10 H, m); ^{1}H NMR (400 MHz, pyridine-d_5, 60 °C) δ 1.23 (3 H, br s), 1.81 (3 H, d, J = 6.8 Hz), 2.29 (1 H, td, J = 16.4, 6.8 Hz), 2.35−2.43 (1 H, m), 2.81 (1 H, td, J = 9.1, 8.5 Hz), 4.27 (2 H, br s), 4.39 (2 H, br s), 4.46−4.88 (5 H, m), 5.06 (1 H, br s), 5.88 (1 H, q, J = 6.9 Hz), 7.10−7.45 (11 H, m); ^{13}C NMR (100.6 MHz, $CDCl_3$), a 1:1 mixture of the carbamate rotamers, δ 14.4, 14.6, 14.8 (overlapping signals for the rotamers), 28.2, 28.3, 36.9 (overlapping signals for the rotamers), 55.8, 56.0, 61.7, 61.8, 71.5, 71.8, 71.9, 72.3, 79.4, 79.5, 81.3 (overlapping signals for the rotamers), 82.1, 82.3, 104.3, 104.7, 124.5, 124.7, 125.3, 125.6, 127.2, 127.5 (2 carbons), 127.6, 127.8, 127.9, 128.2, 128.3, 128.4 (2 carbons), 137.9 (signals at δ 127.2 to 137.9 are all overlapping due to the rotamers), 138.4, 138.7, 143.8, 144.1, 153.3, 153.8; EIMS *m/z* (relative intensity) 434 (M^+ + 1, 89), 326 (28), 236 (28), 107 (100).

Data for (1*S*,6*S*,8*S*,9*S*)-8,9-bis(benzyloxy)-2-carbethoxy-7(*E*)-ethylidene-2-azabicyclo[4.3.0]non-4-ene ((*E*)-**14**): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.16−1.33 (3 H, m), 2.01 (3 H, d, J = 9.5 Hz), 3.62−4.27 (6 H, m), 4.35−4.63 (5 H, m), 4.77−4.83 (1 H, m), 4.93−5.01 (1 H, m), 5.18 (1 H, dd, J = 10.2, 2.2 Hz), 5.38−5.31 (1 H, m), 7.28−7.41 (1 H, m).

Preparation of (*Z*)-14. Method A. A benzene (92.5 mL) solution containing **13** (800 mg, 1.85 mmol), AcOH (222 mg, 3.70 mmol), and the $Pd(OAc)_2$−BBEDA complex (256 mg, 0.556 mmol) were treated as described above for 3 h. After being passed through a short column and concentrated as described above, the reaction product was subjected to column chromatography on silica gel (hexane−EtOAc, 10:1). The first fractions contained (*Z*)-**15** (128 mg, 16%), and the second fractions provided desired (*Z*)-**14** (584 mg, 73%).

Method B. A solution of **13** (1.18 g, 2.72 mmol) in benzene (136 mL) saturated with water and the $Pd(OAc)_2$−BBEDA complex (376 mg, 0.816 mmol) was treated for 1.5 h and worked up as described above in method A to afford (*Z*)-**15** (142 mg, 12%) and (*Z*)-**14** (814 mg, 69%).

(1*S*,8*S*,9*S*)-Tricarbonyl[(η^4-5,6,7,1′)-8,9-bis(benzyloxy)-2-carbethoxy-7(*Z*)-ethylidene-2-azabicyclo[4.3.0]non-5-ene]iron (16). To a solution of $Fe_3(CO)_{12}$ (1.78 g, 3.54 mmol) in 1,2-dichloroethane (5 mL) was added a solution of (*Z*)-**14** (767 mg, 1.77 mmol), and the mixture was stirred at reflux under Ar. During this reaction the initial dark green color changed to dark brown. After 5 h, the mixture was filtered through Celite with EtOAc (90 mL), and the filtrate was concentrated in vacuo, dried ($MgSO_4$), and purified by chromatography on silica gel (hexane−EtOAc, 15:1) to provide **16** (417 mg, 41%) as yellow crystals which were recrystallized from hexane to yield yellow plates: mp 68 °C; $[\alpha]^{30}_D$ −28.3° (*c* 1.05, $CHCl_3$); IR (KBr) 2923, 2871, 2035, 1981, 1953, 1687, 1456, 1420, 1385, 1349, 1246, 1212, 1123, 1089, 1073, 1036, 1016 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.80−0.87 (1 H, m), 1.13−1.38 (5 H, m), 1.46−1.70 (2 H, m), 2.19−2.28 (1 H, m), 3.95−4.30 (3 H, m), 4.46−4.73 (5 H, m), 4.99 (1 H, br s), 7.21−7.48 (10 H, m); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 14.7, 15.7, 27.0, 44.9, 47.6, 51.1, 52.0, 59.3, 61.4, 72.5, 73.4, 81.4,, 86.6, 106.6, 107.0, 127.9, 128.0, 128.4, 128.5, 137.5, 138.2, 155.8, 211.4; EIMS *m/z* (relative intensity) 489 (M^+ − $(CO)_3$, 39), 433 (2), 398 (14), 342 (5), 307 (5), 278 (7), 221 (7), 118 (30), 83 (100), 70 (6). Anal. Calcd for $C_{30}H_{31}NO_7Fe$: C, 62.84; H, 5.45; N, 2.44. Found: C, 62.88; H, 5.06; N, 2.40.

(1*S*,8*S*,9*S*)-2-Carbethoxy-7(*Z*)-ethylidene-8,9-dihydroxy-2-azabicyclo[4.3.0]non-5-ene (17). To a stirred, cooled (−90 °C) solution of **16** (130 mg, 0.226 mmol) in CH_2Cl_2 (6 mL) was added a solution of BBr_3 (283 mg, 1.13 mmol) in CH_2Cl_2 (2 mL), and the mixture was stirred at −90 °C. After 30 min, the mixture was diluted with $CHCl_3$ (5 mL), the reaction was quenched by addition of a solution of 29% aqueous ammonia (2 mL) in MeOH (6 mL), and the mixture was stirred at −90 °C for 1 h and then at room temperature for 1 h. The mixture was concentrated in vacuo, diluted with EtOAc (10 mL), washed with brine (2 mL), and dried ($MgSO_4$). Evaporation of the solvent followed by chromatography on silica gel (EtOAc−hexane, 2:1) gave **17** (29.0 mg, 51%) as a colorless oil: IR (neat) 3407, 2930, 1680, 1432, 1384, 1350, 1289, 1210, 1117 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30 (3 H, t, J = 7.2 Hz), 1.90 (3 H, d, J = 7.2 Hz), 2.12−2.33 (2

H, m), 2.95−3.10 (1 H, m), 3.97−4.13 (1 H, m), 4.13−4.27 (3 H, m), 4.45 (2 H, br s), 4.60 (1 H, br d, $J = 2.4$ Hz), 4.71 (1 H, br d, $J = 5.3$ Hz), 6.20 (1 H, q, $J = 7.2$ Hz), 6.23−6.30 (1 H, m); EIMS *m/z* (relative intensity) 253 (M^+, 100), 234 (31), 206 (31), 180 (11), 162 (24), 134 (31), 110 (24).

Being unstable on standing, this material was immediately used for the next reaction.

(+)-Streptazolin (1). The above diol **17** (24.2 mg, 0.0963 mmol) was added to a 2.5% solution of NaOMe in MeOH (1 mL), and the mixture was refluxed for 30 min. The mixture was diluted with EtOAc (20 mL), washed with water (10 mL) and then brine (10 mL), and dried ($MgSO_4$). Evaporation of the solvent in vacuo followed by purification by chromatography on silica gel (EtOAc−hexane, 1:1) provided **1** (13.0 mg, 65%) as a colorless oil: $[\alpha]^{27}_D$ +21.5° (*c* 0.65, $CHCl_3$); IR (neat) 3418, 2955, 2924, 2854, 1734, 1655, 1446, 1380, 1219, 1202, 1097, 1039 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.83 (1 H, br s), 1.91 (3 H, d, $J = 7.3$ Hz), 2.13−2.25 (1 H, m), 2.51 (1 H, dtd, $J = 16.7, 7.2, 3.3$ Hz), 3.36−3.51 (2 H, m), 4.26−4.31 (1 H, m), 4.73 (1 H, d, $J = 6.8$ Hz), 4.88 (1 H, br s), 6.02−6.07 (1 H, m), 6.15 (1 H, q, $J = 7.3$ Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 14.9, 22.8, 39.9, 59.1, 74.5, 81.5, 118.9, 123.7, 139.1, 142.8, 159.3; EIMS *m/z* (relative intensity) 207 (M^+, 100), 192 (7), 178 (11), 162 (14), 149 (21), 134 (30), 119 (23), 111 (7), 105 (16), 97 (10), 91 (28.5), 56 (87.5); HRMS calcd for $C_{11}H_{13}NO_3$ (M^+) 207.0895, found 207.0896.

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