JOC Article

Asymmetric Synthesis of Fused Bicyclic α-Amino Acids Having a Hexahydro-cyclopenta[*c*]pyridine Skeleton via Intramolecular Pauson−Khand Reaction of 1-Sulfonimidoyl-Substituted 5-Azaoct-1-en-7-ynes

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An asymmetric synthesis of fused bicyclic amino acids having a hexahydro-cyclopenta[*c*]pyridine skeleton and carrying besides an enone structural element a substituent at the *β*-position is described. The key steps of the synthesis are a highly selective allylation of *N*-*tert*-butylsulfonyl imino ester with bis(allylsulfoximine)titanium complexes and a highly diastereoselective Pauson−Khand cycloaddition of sulfonimidoyl-substituted *γ*,*δ*-unsaturated α-amino acid esters carrying a substituent at the *β*-position and a propargyl group at the N-atom. The cyclization is accompanied by a reductive cleavage of the sulfoximine group of the primary cyclization product. Surprisingly, the removal of the sulfoximine group proceeds with inversion of the configuration at the S-atom and gives *N*-methyl-phenylsulfinamide with ≥98% ee. Deprotection of the bicyclic *N*-*tert*-butylsulfonyl-protected amino acid ester was accomplished through treatment with CF_3SO_3H under anhydrous conditions. The enantio- and diastereomerically pure sulfoximine-substituted *γ*,*δ*-unsaturated α-amino acid esters used as starting material were obtained through a highly regio- and diastereoselective allylation of *N*-*tert*-butylsulfonyl imino ester with acyclic bis(allylsulfoximine)-titanium complexes, described previously.

Introduction

The synthesis of conformationally constrained α-amino acids and their incorporation into peptides are currently topics of high interest.[1,2] The restricted conformational flexibility of such peptidomimetics can have large effects on their biological activity and metabolic stability.[2] Much sought after are fused bicyclic α-amino acids having the N-atom incorporated into a ring system.[3] Many of these amino acids display interesting pharmacological activities,[4] and they have served as building blocks for the synthesis of peptidomimetics.[1] We have been interested in the asymmetric synthesis of the bicyclic amino acid esters **1**, which contain a hexahydro-cyclopenta[*c*]pyridine skeleton and carry besides an enone structural element a substituent at the *β*-position (Scheme 1). Because of the cyclopentenone ring of **1**, synthesis of a large number of highly substituted analogues can be envisioned. With the exception of the *N*-tosyl-substituted parent compound (R = H),[5] amino acids of type **1** were not known up to now. The bicyclic amino acid esters **1** and their derivatives should be interesting building blocks for the syn-

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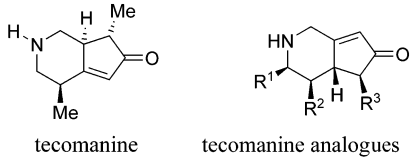
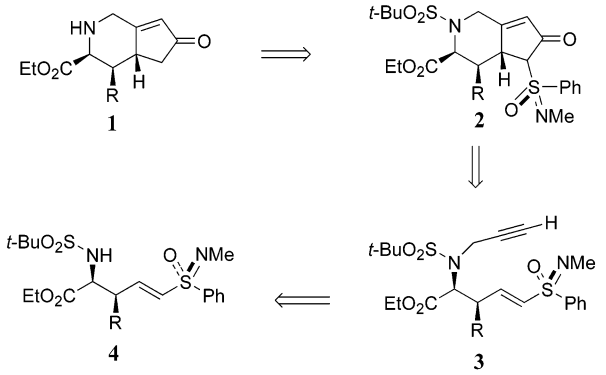


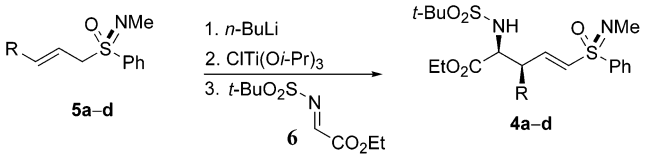
FIGURE 1. Tecomanine and potential analogues.

SCHEME 1. Retrosynthetic Analysis of Bicyclic Amino Acid Derivatives 1



thesis of peptidomimetics, and they could exhibit interesting biological activities as bicyclic analogues of pipecolic acid.[6] Besides these applications, amino acid esters **1** could perhaps also serve as starting materials for the synthesis of analogues of the alkaloid tecomanine, which shows a strong hypoglycemic activity (Figure 1).[7] We envisioned a synthesis of **1** through a Pauson−Khand cycloaddition[8] of the sulfonimidoyl-substituted enynes **3**, derived from the (*syn*,*E*)-configured γ,δ-unsaturated α-amino acid esters **4**. We have recently described a flexible asymmetric synthesis of **4** through a highly regio- and diastereoselective allylation of *N*-*tert*-butylsulfonyl imino ester with acyclic bis(allylsulfoximine)titanium complexes.[9] Support for the feasibility of a Pauson−Khand cycloaddition of enynes **3** came from the work of Bolton et al., who showed that the cycloaddition of the parent *N*-tosyl-substituted enyne (R = H) being devoid, however, of a substituent at the δ-position, proceeded with high diastereoselectivity to give the corresponding bicyclic *N*-tosyl amino acid.[5] Although intramolecular Pauson−Khand reactions involving sulfonyl- and sulfinyl-substituted alkenes have been described,[10] it remained to be seen whether alkenyl sulfoximines of type **3** are also amendable to a [2+2+1]-cycloaddition. *N*-Methyl sulfoximines are Lewis bases,[11] a feature that could perhaps prevent cobalt complexes of **3** from undergoing such a cycloaddition. In the final step of the synthesis of **1** it was planned to remove the sulfonimidoyl group of **2** reductively.[12]

SCHEME 2. γ-Amino Alkylation of Allylic Sulfoximines 5



a: R = Me, **b**: R = *i*-Pr, **c**: R = *c*C_6H_{11}, **d**: R = Ph

TABLE 1. Asymmetric Synthesis of the Amino Acid Derivatives 4a−d

allylic sulfoximine	amino acid derivative	chemical yield (%)	isolated yield (%)	dr
5a	**4a**	90	67	≥99:1
5b	**4b**	93	85	≥99:1
5c	**4c**	92	77	≥99:1
5d	**4d**	96	82	≥99:1

Results and Discussion

Synthesis of the Enynes. The enantio- and diastereomerically pure α-amino acid derivatives **4a−d** were obtained in good yields (Scheme 2, Table 1) through the successive treatment of the allylic sulfoximines **5a−d**[13] with *n*-BuLi, 2 equiv of $ClTi(Oi\text{-}Pr)_3$, and the *N*-*tert*-butylsulfonyl α-imino ester **6** in THF at −78 °C.[9] Because of the much more facile cleavage of *N*-*tert*-butylsulfonylamines as compared to *N*-tosylamines,[14] the amino alkylation of **5a−d** was carried out with **6**, whose synthesis we have reported recently,[9] and not with the corresponding *N*-tosyl analogue.[15] Treatment of sulfonamides **4a−d** with propargyl bromide in DMF in the presence of Cs_2CO_3 afforded the enynes **3a−d**, respectively (Scheme 3, Table 2) in high yields.

Pauson−Khand Reaction. Treatment of enynes **3a−d** with 1.1 equiv of $Co_2(CO)_8$ for 30 min in THF led to their complete conversion to the cobalt complexes **7a−d**, which were isolated by chromatography but not further characterized (vide infra). We were pleased to see that complexes **7a−d** gave upon treatment with 6 equiv of *N*-morpholine-*N*-oxide (NMO) in two portions over a period of 4 h at −78 °C and warming the reaction mixture to room temperature directly the sulfonimidoyl-free bicyclic amino acid derivatives **9a−d** in approximately 95% purity. The bicyclic amino acid derivatives were generally obtained as single diastereomers (^{1}H NMR) (Table 3, entries 1−4), except in the case of the phenyl-substituted

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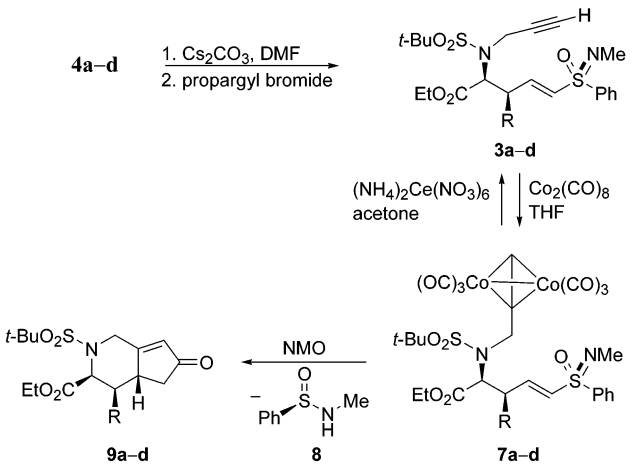
SCHEME 3. Synthesis and Pauson–Khand Cycloaddition of Enynes 3



a: R = Me, **b**: R = *i*-Pr, **c**: R = *c*C_6H_{11}, **d**: R = Ph

TABLE 2. Synthesis of Enynes 3a–d

amino acid derivative	enyne	yield (%)
4a	**3a**	95
4b	**3b**	94
4c	**3c**	91
4d	**3d**	96

TABLE 3. Pauson–Khand Cycloaddition of Enynes 3a–d

						sulfinamide **8**	
entry	enyne	conditions[a]	amino acid derivative	yield (%)	dr[b]	yield (%)	ee[c] (%)
1	**3a**	I	**9a**	49	≥98:2	70	≥98
2	**3b**	I	**9b**	51	≥98:2	68	≥98
3	**3c**	I	**9c**	55	≥98:2	66	≥98
4	**3d**	I	**9d**	60	93:7	71	≥98
5	**3b**	II	**9b**	35	85:15	*d*	*e*
6	**3b**	III	**9b**	30	66:34	*d*	*e*

[a] I: THF, −78 °C, 3 equiv of NMO, 1 h, rt, 1 h, −78 °C, 3 equiv of NMO. II: CH_2Cl_2, 0 °C, 3 equiv of NMO, 1 h, rt, 1 h, 0 °C, 3 equiv of NMO. III: MeCN, 81 °C, 2 h. [b] Determined by ^{1}H NMR spectroscopy. [c] Determined by GC on chiral stationary phase. [d] Not isolated. [e] Not determined.

amino acid **9d**, which, under the conditions used, was contaminated with a small amount of its diastereomer (entry 4). Preparative HPLC of **9a–c** afforded the pure bicyclic enones in medium to good overall yields, based on **3a–c**. Surprisingly, treatment of **3b** with NMO in CH_2Cl_2 at 0 °C gave **9b** with lower diastereoselectivity and yield (Table 3, entry 5). The ^{1}H NMR spectra of **9a–d** in [D_6]-benzene at room temperature showed an overlap and a line broadening of the signals of 1-H and 3-H. We tentatively ascribe the line broadening to a restricted rotation around the N–S bond. The configuration of **9b** was assigned by ^{1}H NOE experiments in [D_6]-benzene at 50 °C. Recording the spectra at the higher temperature resulted in a better line separation and a sharpening of the signals of 1-H and 3-H. The NOE experiment revealed strong NOE's between 3-H and 4-H, 4-H and 5-Hα, and 4a-H and 5-H*β*, respectively, which proved their cis relationship (Figure 2). The lack of NOE's between 4-H and 4a-H, and 4a-H and 5-Hα is indicative

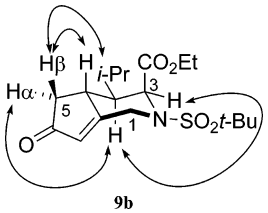


FIGURE 2. Observed NOE's of amino acid derivative **9b**.

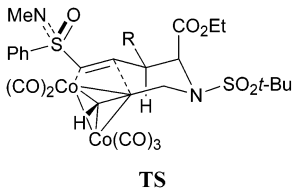


FIGURE 3. Transition state model for the Pauson–Khand cycloaddition of eynes **3**.

of their trans relationship. According to the magnitudes of the vicinal coupling constants $J_{4-H,4a-H} = 12.4$ Hz and $J_{3-H,4-H} = 5.2$ Hz of **9b** in $CDCl_3$, its six-membered ring adopts in solution preferentially a chairlike conformation in which the ester group is in a pseudoaxial and the R substituent in a pseudoequatorial position. This was supported by the magnitudes of the vicinal coupling constants of **1d** (vide infra). Because of similar chemical shifts and magnitudes of coupling constants, the same configuration was assigned to **9a**, **9c**, and **9d**.

The highly diastereoselective formation of **9a–d** could be rationalized by assuming that the intramolecular addition of the C–Co bond to the double bond occurs via the transition state **TS** in which the ester group is placed in a pseudoaxial position while the substituent at the *β*-position, the double bond, and the *tert*-butylsulfonyl group are placed in pseudoequatorial positions (Figure 3).

We were surprised to see that the Pauson–Khand reaction of **3a–d** was accompanied by a reductive cleavage of the sulfonimidoyl group of **2a–d**, which ought to be the primary cyclization products (cf. Scheme 1). In all cases the (*R*)-configured sulfinamide **8**[12,16] with ≥98% ee was isolated as a second reaction product in similar yields as **9a–d**. Thus, the reductive cleavage of the sulfonimidoyl group of **2a–d** had occurred under inversion of configuration at the S-atom. It is interesting to note in this context that intramolecular Pauson–Khand reactions involving alkenyl sulfones and alkenyl sulfoxides are apparently not accompanied by a desulfurization of the corresponding α-sulfonyl- and α-sulfinyl-substituted cyclopentenone derivatives.[10] To see whether the desulfurization is caused in some way by NMO, the Pauson–Khand reaction of **3b** was carried out in boiling MeCN by omitting NMO (Table 3, entry 6). Under these conditions the sulfonimidoyl free amino acid derivative **9b** was also obtained, albeit with a much lower diastereoselectivity and yield. Finally the structure of the cobalt complexes **7a–d** was probed by chemical means to evaluate whether it is the complex formation that causes the reductive removal of the sulfonimidoyl group. Treat-

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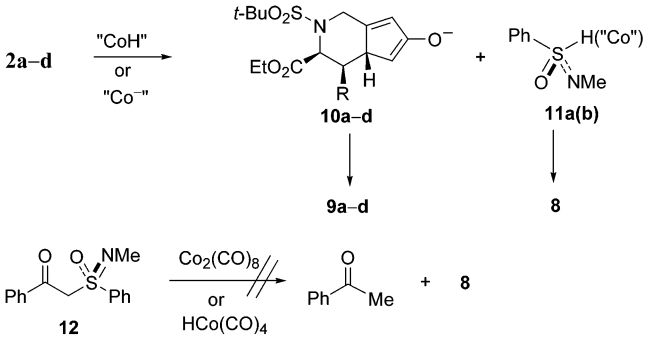
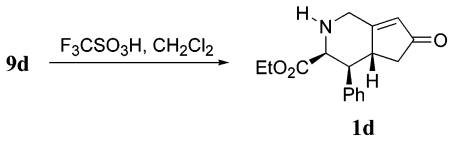


FIGURE 4. Putative substitution of the sulfonimidoyl group of the keto sulfoximines with inversion at the S-atom and model experiments.

ment of complex **7a** with $(NH_4)_2Ce(NO_3)_6$ in acetone[17] led to a quantitative recovery of sulfoximine **3a** (cf. Scheme 3). Therefore we conclude that the desulfurization occurs after the Pauson–Khand process at the stage of **2a–d**. Reductive defunctionalizations during Pauson–Khand reactions have been described previously for α-halo cyclopentenone derivatives.[18] It has been suggested that an allylic hydridocobalt complex,[19] derived from the alkyne cobalt complex, is responsible for the reduction of the α-halo ketone.[18b] The formation of sulfinamide **8** with inversion of configuration would lend support to the notion that the reduction of **2a–d** may be caused at least in part by an allylic hydridocobalt complex derived from **7a–d**, since the alternative reduction of **2a–d** by a single electron-transfer mechanism should proceed under retention of configuration at the S-atom (Figure 4).[11,12] Thus, reaction of **2a–d** with such a hydridocobalt species could give enolates **10a–d** and the S–H sulfoximine **11a**. Protonation of the former during workup and isomerization of the latter compound would afford **9a–d** and **8**, respectively. However, we have not been able to isolate reaction products, which might have given information as to the intermediate formation of such hydridocobalt complexes, nor did we carry out experiments to trap such putative allylic cobalt complexes derived from **7a–d**. Besides the hydridocobalt mechanism, a substitution of the sulfonimidoyl group of **2a–d** with nucleophilic cobalt compounds could also be envisioned,[20] which might be present in the reaction mixture, with formation of a cobalt–sulfinamide complex **11b**, which upon workup could deliver **8**. Two simple test reactions were carried out with the ketosulfoximine **12**[21] as a model compound for **2a–d**. However, treatment of **12** with either $Co_2(CO)_8$ or $HCo(CO)_4$, which was prepared from $Co_2(CO)_8$ and hydrogen as an equilibrium mixture,[22] did not lead to cleavage of the starting material, which was recovered in almost quantitative yield.

SCHEME 4. Deprotection of the Amino Group



In concluding the asymmetric synthesis of amino acid esters of type **1**, the amino acid derivative **9d** was treated with 3 equiv of CF_3SO_3H in CH_2Cl_2 for 30 min, which afforded the amino acid ester **1d** in 85% yield (Scheme 4). In contrast to the ^1H NMR spectra of the *N*-sulfonyl derivatives **9a–d** the ^1H NMR spectrum of the amino acid derivative **1d** exhibited sharp signals, which allowed an analysis. According to the magnitudes of the coupling constants $J_{3-H,4-H} = 5.3$ Hz and $J_{4-H,4a-H} = 12.4$ of **1d** the amino acid derivative adopts in solution a chairlike conformation similar to that of **9a–d**.

Conclusion and Summary

We have demonstrated that the Pauson–Khand cycloaddition of 1-sulfonimidoyl-substituted 5-azaoct-1-en-7-ynes carrying an ester group at C–4 and a substituent at C–3 provides a highly diastereoselective access to fused bicyclic amino acids containing the hexahydrocyclopenta[*c*]pyridine skeleton. The starting materials for the synthesis of the 5-azaoct-1-en-7-ynes were obtained enantio- and diastereomerically pure through a highly selective allylation of *N*-*tert*-butylsulfonyl imino ester with enantiomerically pure bis(allylsulfoximine)titanium complexes. A notable feature of this Pauson–Khand cyclization involving alkenyl sulfoximines is the concomitant reductive cleavage of the sulfonimidoyl group of the cyclization products, which, remarkably, proceeds under inversion of configuration at the S-atom. The mechanism of this transformation is not known at present and further investigations are required for a better understanding.

Experimental Section

General Procedure for the Synthesis of Sulfonimidoyl-Substituted *N*-Propargyl Amino Acid Esters 3 (*GP1*). To a solution of the amino acid ester **4** (1 mmol) in DMF (5 mL) was added Cs_2CO_3 (1.2 mmol). After the suspension had been stirred for 15 min at room temperature, it was cooled in an ice bath to 0 °C. Propargyl bromide was added (2.0 mmol, 80% in toluene) and the mixture was allowed to warm to room temperature and stirred overnight. Then DMF was removed in vacuo and aqueous NH_4Cl (10 mL) was added to the residue. The aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (EtOAc) gave **3** as a light yellow oil.

General Procedure for the Pauson–Khand Reaction (*GP2*). To a solution of ester **3** (1 mmol) in THF (100 mL) was added $Co_2(CO)_8$ (1.1 mmol). The brown solution was stirred until TLC indicated complete conversion of the starting material (30 min). The solution was cooled to −78 °C and NMO was added (3 mmol). After the mixture had been stirred for 1 h at −78 °C, it was warmed to room temperature within 1 h and then cooled to −78 °C. An additional portion of NMO (3 mmol) was added and the mixture was stirred first for 1 h at −78 °C and then for 1 h at room temperature. Then the mixture was filtered through a pad of Celite, which was subsequently washed with EtOAc. Concentration of the organic phase in vacuo and flash chromatography (EtOAc) of the

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residue afforded **9** of 95% purity and sulfinamide **8** as a white solid. The ee value of sulfinamide **8** was determined by GC: heptakis-(2,3-di-*O*-methyl-6-*O*-*tert*-butyldimethylsilyl)-*β*-cyclodextrin (Hydrodex-*β*-6-TBDM, Macherey & Nagel), 25 m, 0.25 mm, 100 kPa, T = 120 °C, 2 min; 5 K/min 160 °C, 5 min; 5 K/min 200 °C, 30 min. $R_t(S)$ = 21.2 min; $R_t(R)$ = 23.5 min.

(+)-(*E*,*S*$_S$,2*S*,3*R*)-5-[*N*-Methyl-*S*-phenylsulfonimidoyl]-3-methyl-2-[(2-methyl-propane-2-sulfonyl)-prop-2-ynyl-amino]-pent-4-enoic Acid Ethyl Ester (3a). Following *GP1*, reaction of sulfoximine **4a** (1.0 g, 2.32 mmol) with Cs_2CO_3 (983 mg, 2.78 mmol) and propargyl bromide (0.52 mL, 4.64 mmol, 80% in toluene) afforded the *N*-propargyl amino ester derivative **3a** (1.03 g, 95%) as a light yellow oil. $[\alpha]_D$ +46.4 (*c* 1.33, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.13 (t, J = 6.9 Hz, 3 H), 1.32 (d, J = 6.7 Hz, 3 H), 1.41 (s, 9 H), 2.26 (t, J = 1.7 Hz, 1 H), 2.74 (s, 3 H), 3.18 (m, 1 H), 3.76 (dq, J = 10.9, 7.2 Hz, 1 H), 3.97 (dq, J = 10.9, 7.2 Hz, 1 H), 4.08−4.20 (br m, 1 H), 4.25 (d, J = 9.9 Hz, 1 H), 4.40 (br d, J = 19.3 Hz, 1 H), 6.48 (d, J = 14.8 Hz, 1 H), 6.79 (dd, J = 14.8, 8.9 Hz, 1 H), 7.50−7.60 (m, 3 H), 7.83−7.89 (m, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.9 (d), 17.8 (d), 24.6 (d), 29.2 (d), 35.3 (u), 37.1 (d), 61.4 (u), 62.6 (u), 64.2 (d), 72.7 (u), 80.0 (u), 128.7 (d), 129.4 (d), 131.7 (d), 132.8 (d), 138.8 (u), 146.0 (d), 169.8 (u). IR ($CHCl_3$) $\tilde{\nu}$ 3302 (w), 3272 (w), 2980 (m), 2938 (m), 2877 (w), 2805 (w), 1737 (s), 1630 (w), 1447 (m), 1383 (w), 1323 (s), 1247 (s), 1132 (s), 1080 (w), 1024 (m), 973 (w), 868 (m), 814 (w) cm^{-1}. MS (EI, 70 eV) *m*/*z* (rel intensity, %) 467 [M$^+$ − 1] (3), 347 (21), 271 (14), 223 (30), 209 (17), 194 (16), 182 (12), 163 (12), 149 (17), 140 (40), 131 (20), 125 (54), 120 (19), 107 (16), 82 (16), 77 (13), 57 (100). Anal. Calcd for $C_{22}H_{32}N_2O_5S_2$ (468.63): C, 56.38; H, 6.88; N, 5.98. Found: C, 56.73; H, 6.71; N, 5.81.

(−)-(3*S*,4*R*,4a*R*)-2,3,4,4a,5,6-Hexahydro-4-methyl-2-(2-methyl-propane-2-sulfonyl)-6-oxo-1*H*-cyclopenta[*c*]pyridine-3-carboxylic Acid Ethyl Ester (9a). Following *GP2*, reaction of **3a** (262 mg, 0.56 mmol) with $Co_2(CO)_8$ (210 mg, 0.61 mmol) and NMO (392 mg, 3.36 mmol) gave **9a** (94 mg, 49%) as a white solid and **8** (61 mg, 70%) of ≥98% ee as a white solid.

8: $[\alpha]_D$ −168.3 (*c* 0.91, acetone).

9a: mp 112 °C; $[\alpha]_D$ −44.2 (*c* 1.82, CH_2Cl_2). ^{1}H NMR (C_6D_6, 300 MHz) δ 0.63 (d, J = 6.9 Hz, 3 H), 0.92 (t, J = 7.2 Hz, 3 H), 1.12 (s, 9 H), 1.35 (m, 1 H), 1.53 (dd, J = 18.3, 3.0 Hz, 1 H), 2.11 (dd, J = 18.3, 6.7 Hz, 1 H), 2.36 (br m, 1 H), 3.91 (q, J = 6.9 Hz, 2 H), 4.35−4.67 (br m, 3 H), 5.65 (s, 1 H). ^{13}C NMR (C_6D_6, 75 MHz) δ 14.1 (d), 16.4 (d), 24.1 (d), 39.8 (u), 40.7 (d), 41.7 (d), 45.8 (u), 60.9 (u), 61.0 (d), 61.4 (u), 129.0 (d), 170.6 (u), 171.8 (u), 204.9 (u). IR (KBr) $\tilde{\nu}$ 3677 (w), 3443 (m), 2980 (m), 2937 (m), 1732 (s), 1708 (s), 1636 (s), 1479 (m), 1452 (m), 1384 (m), 1320 (s), 1260 (m), 1209 (s), 1175 (s), 1125 (s), 1064 (w), 1024 (m), 1002 (m), 953 (m), 916 (m), 898 (m), 861 (w), 834 (w), 808 (w) cm^{-1}. MS (CI, methane) *m*/*z* (rel intensity, %) 344 [M$^+$ + 1] (28), 252 (11), 224 (100). HRMS (EI, 70 eV, M$^+$−[$C_4H_9SO_2$]) calcd for $C_{12}H_{16}NO_3$ 222.113018, found 222.113145.

Preparation of the Dicobalt Carbonyl Alkyne Complex 7a and Its Oxidative Demetalation with Ceric Ammonium Nitrate. To a stirred solution of **3a** (103 mg, 0.22 mmol) in dry acetone (10 mL) was added $Co_2(CO)_8$ (83 mg, 0.24 mmol) and the mixture was stirred at room temperature. After 1 h TLC showed the complete consumption of **3a** and the mixture was cooled to −78 °C. A solution of $(NH_4)_2Ce(NO_3)_6$ (0.84 g, 1.54 mmol) in dry acetone (20 mL) was added. After the mixture had been stirred for 2 h at −78 °C, it was warmed to room temperature and stirred for an additional hour. Then the mixture was poured into brine (20 mL) and extracted with diethyl ether (5 × 10 mL). The combined organic layers were washed with brine and dried ($MgSO_4$). Concentration in vacuo gave **3a** (99 mg, 96%) as a light yellow oil.

(−)-(3*S*,4*R*,4a*R*)-2,3,4,4a,5,6-Hexahydro-6-oxo-4-phenyl-1*H*-cyclopenta[*c*]-pyridine-3-carboxylic Acid Ethyl Ester (1d). To a solution of **9d** (137 mg, 0.33 mmol) in CH_2Cl_2 (15 mL) was added a 0.25 M solution of F_3CSO_3H in CH_2Cl_2 (4 mL) at room temperature. The mixture was stirred 1 h and 2 M NaOH (1 mL) was added. After 5 min the mixture was diluted with aqueous NH_4Cl (10 mL). Then it was extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic phases were dried ($MgSO_4$). Flash chromatography (EtOH:*n*-hexane, 2:1) gave **1d** (82 mg, 85%) as a yellow liquid that turned brown upon standing in air. $[\alpha]_D$ −2.5 (*c* 0.61, CH_2Cl_2). ^{1}H NMR (C_6D_6, 400 MHz) δ 0.64 (t, J = 7.1 Hz, 3 H), 1.22 (br s, 1 H), 1.60 (dd, J = 18.4, J = 2.8 Hz, 1 H), 2.23 (dd, J = 18.4, 6.6 Hz, 1 H), 2.28 (dd, J = 5.3, 12.4 Hz, 1 H), 3.21 (d, J = 14.3 Hz, 1 H), 3.53 (d, J = 5.3 Hz, 1 H), 3.60−3.70 (m, 3 H), 4.00 (d, J = 14.3 Hz), 5.73 (t, J = 1.5 Hz), 6.92−6.95 (m, 2 H), 6.99−7.09 (m, 3 H). ^{13}C NMR (C_6D_6, 100 MHz,) δ 13.8 (d), 39.2 (d), 41.3 (u), 43.4 (u), 53.5 (d), 59.7 (u), 60.9 (d), 126.8 (d), 127.1 (d), 127.4 (d), 128.4 (d), 139.3 (u), 171.2 (u), 176.8 (u), 205.3 (u). IR ($CHCl_3$) $\tilde{\nu}$ 3324 (m), 3062 (m), 2983 (s), 2935 (m), 1725 (s), 1628 (m), 1545 (m), 1497 (w), 1449 (m), 1377 (m), 1190 (s), 1076 (w), 1030 (s), 934 (w), 901 (w), 856 (m) cm^{-1}. MS (EI, 70 eV) *m*/*z* (rel intensity, %) 285 [M$^+$] (2), 212 (100), 184 (15), 167 (8), 155 (7), 141 (11), 128 (11), 118 (12), 117 (20), 115 (32), 103 (11), 94 (14), 91 (80), 80 (10), 78 (14), 77 (30). HRMS (EI, 70 eV) calcd for $C_{18}H_{19}NO_3$ 285.136493, found 285.136329.

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Supporting Information Available: General experimental details, experimental details and characterization of compounds not described in the experimental part, and ^{1}H and ^{13}C NMR spectra of **1d** and of **9a**−**d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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