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A short synthesis of (±)-tecomanine via a Pauson–Khand-based route

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Abstract—The *N*-carboethoxy precursor to (±)-tecomanine has been prepared in 11 steps from 2-methyl-1-buten-3-yne. The key step, Pauson–Khand cyclization of a methylated 5-aza-6-nonen-1-yne succeeds, but only in low yield, a consequence of the dialkyl substitution about the azaenyne framework. Nevertheless, the overall sequence to that point is one of the more efficient to be described. © 2003 Elsevier Science Ltd. All rights reserved.

1. Introduction

Tecomanine, **1**, a substance with powerful hypoglycemic activity, is one of a number of naturally-occurring alkaloids with cyclopentanopyridine- or cyclopentanopiperidine-based structures.[1] First isolated by Hammouda and Motawi,[2] tecomanine has been synthesized in several ways.[3] We chose to explore the possibility that tecomanine might be efficiently accessed via direct Pauson–Khand cyclization of a suitably substituted alkenylalkynylamine precursor **2**, without the need to introduce the methyl groups subsequent to cycloaddition (Fig. 1). It is well-known that acyclic internal alkenes often fare poorly in the Pauson–Khand process, but we hoped that recent advances in the state of the art in Pauson–Khand chemistry would enable us to develop conditions to overcome that problem.[4] As to the choice of group R in the substrate, that would also be dictated by the limitations of the cyclization process. During the course of our investigations, Whitby, et al. reported the synthesis of tecomanine using a related zirconocene-based cyclization strategy.[3f] We report herein the results of our efforts.

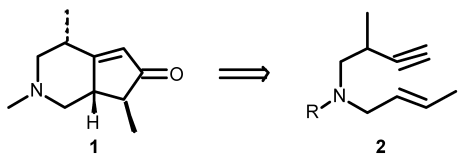

Figure 1. Pauson–Khand approach to tecomanine.

Keywords: alkaloid; amine; cyclopentenone; Pauson–Khand reaction; tecomanine.

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2. Results and discussion

Our synthesis of cyclization substrate **2** differed from that of Whitby, et al. in several ways. Theirs utilized addition of a 1,2-butadienylaluminum reagent to paraformaldehyde to obtain 2-methyl-3-butyn-1-ol. The tosylate of the latter was then coupled with *N*-methyl-2-buten-1-amine, which had been obtained as an *E*/*Z* mixture by alkylation of *N*-methyltrifluoroacetamide with crotyl chloride.

We instead chose to protect the terminal carbon of 2-methylbutenyne, allowing a sequence of epoxidation, ring opening, and displacement to give the protected 2-methyl-3-butyn-1-amine **7** in 35% overall yield (Scheme 1).

The method of Nussbaumer and Stütz[5] for reductive ring opening of epoxide **4** using DIBAL-H was the key to obtaining **5** with 100% regioselectivity and free of any allenic isomer. Applying Mitsunobu's method[6] to the conversion of **5** into the corresponding amine **7** was similarly effective. With the latter in hand our first thought was to prepare the *N*-trifluoroacetyl derivative for N-crotylation, followed by deprotection of the alkyne terminus: any subsequent Pauson–Khand would stand little chance of success with both an internal alkene and a silylated alkyne. However, this route proved problematic: although partial desilylation of **7** was observed during the N-acylation/N-alkylation sequence, all attempts to complete the deprotection of the alkyne terminus led to significant formation of allenic material. Fortunately, we found that desilylation could be carried out immediately after N-trifluoroacetylation without complication. Subsequent alkylation at nitrogen with crotyl chloride followed by hydrolysis and carbamate formation gave cyclization precursor **12** in 36% overall yield (Scheme 2).

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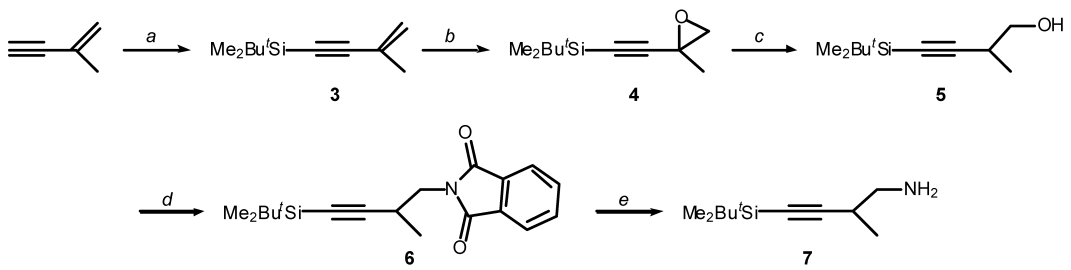
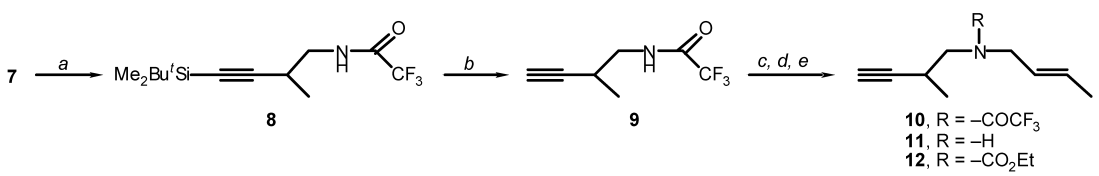


Scheme 1. (a) *n*-BuLi, THF, then *t*-BuMe$_2$SiCl, −78°C to room temperature, 12 h (90%); (b) *m*-ClC$_6$H$_4$CO$_3$H, CH$_2$Cl$_2$, 0°C, 12 h (75%); (c) *i*-Bu$_2$AlH, THF, -35 to 0°C, 3 h (83%); (d) phthalimide, Ph$_3$P, DEAD, THF, 0°C to room temperature, 48 h (81%); (e) N$_2$H$_4$, EtOH, 85°C, 3 h (75%).



Scheme 2. (a) (CF$_3$CO)$_2$O, Et$_2$O, 0°C to room temperature, 1 h (98%); (b) *n*-Bu$_4$N$^+$ F$^-$, THF, 65°C, 4 h (72%); (c) KH, THF, 0°C to room temperature, 0.5 h, then 18-crown-6, *trans*-CH$_3$CH=CHCH$_2$Cl, 65°C, 6 h (62%); (d) KOH, MeOH, 0°C, 1 h (98%); (e) Et$_3$N, THF, EtOCOCl, 0°C to room temperature, 1 h (85%).

Pauson–Khand cyclizations of allyl 3-butynyl amines have been reported by several groups. The first, by Brown and Pauson, described cyclization of the *N*-acetyl derivative of the parent compound in 30–44% yields, with the best conditions being heating to 70°C of the silica-adsorbed substrate.[7] Bolton succeeded in cyclizing several *N*-tosyl systems in yields up to 90+%, using NMO activation of Co$_2$(CO)$_8$ in CH$_2$Cl$_2$ both in solution and polymer supported.[8] These studies also include the only report of attempted cyclizations of substrates with internal double bonds prior to our work, the phenyl derivative shown in Figure 2, below, being the best example, proceeding in 51% yield. Though encouraging, this successful result does not quite emulate our situation, because the Pauson–Khand process has been found to be much more tolerant of phenyl substitution than alkyl substitution at the reactive centers of the substrate.[4]

Krafft,[9] Alcaide and Sierra,[10] Pérez-Castells,[11] Kotha,[12] and most recently Magnus[13] have reported cyclizations of a variety of allylic amines. In all cases the nitrogen is substituted with a conjugating moiety, and any of several promoters (amine oxides, molecular sieves, thioethers) are used to give in some cases quite satisfactory yields. An Rh-based variant is also known.[14]

Prior to testing carbamate **12** under Pauson–Khand conditions we had previously attempted cyclizations of several related substrates, including *N*-acetyl and *N*-tosyl analogs of **12**, under a variety of conditions—thermal, solid phase, and promoted. Only in the case of tosyl derivative **13** was any enone formation observed—a 6% yield of **15** upon treatment with Co$_2$(CO)$_8$ in CH$_2$Cl$_2$ followed by addition of TMANO under an O$_2$ atmosphere. Interestingly, in other preliminary studies we found that butenyl butynyl ethers and amines lacking the propargylic methyl substituent gave somewhat superior results: yields in the 20–25% range were obtained, although in the case of the ether evidence for some reduction to the saturated cyclopentanone under Pauson–Khand conditions was observed (IR absorption at 1727 cm^{-1}).[7] In any event, after considerable experimentation, cyclization of **12** itself was finally achieved upon treatment with Co$_2$(CO)$_8$ and NMO in CH$_2$Cl$_2$, although the 16% yield of the product **14** was still disappointingly low (Fig. 3). As this compound has been previously converted into tecomanine, it does constitute a formal synthesis of the

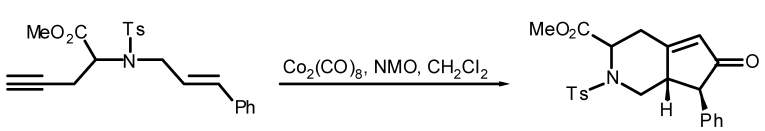


Figure 2. Pauson–Khand cyclization of a phenyl-substituted allyl butynyl amine derivative.

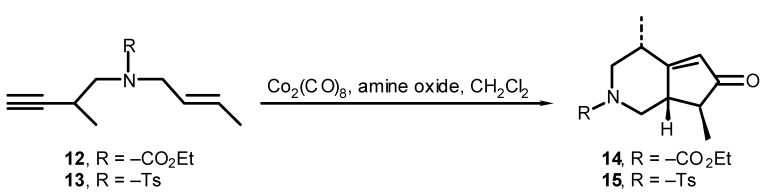


Figure 3. Pauson–Khand cyclizations of **12** and **13**.

natural product. Unfortunately, the low yield in the final step prevents it from being similarly efficient to syntheses previously described.[3a,b]

3. Conclusions

An efficient synthesis of 2-butenyl 2-methyl-3-butynyl amine derivatives, potential precursors to tecomanine and related structures via Pauson–Khand cyclization, has been achieved. The cyclization itself proceeds only poorly, however, a consequence of the dialkyl substitution on the alkene cyclization component. It is thus clear that, barring appropriate improvements in the tolerance of the process for sterically encumbered substrates, Pauson–Khand-based routes to targets such as these should be designed to take advantage of the superior reactivity of the simpler allyl analogs: tecomanine has been successfully synthesized by methylation at the α-carbon of the cyclization products of the latter compounds.[3e]

4. Experimental

4.1. General

Solvents were purified and dried according to standard procedures. All reactions were carried out under an atmosphere of dry N_2, unless indicated otherwise. All NMR spectra were recorded at 298 K in $CDCl_3$ at 300 MHz (^{1}H) or 75 MHz (^{13}C). High resolution mass spectrometry was provided by Dr Robert Barkley at the Mass Spectrometry Facility at the University of Colorado at Boulder. Column chromatography was done using flash techniques with silica gel (60–200 mesh) as the solid phase. Radial chromatography was done on a Chromatotron using plates of either 1, 2, or 4 mm film thickness. The solid phase used was silica gel 60 PF, and compounds were visualized by UV. Capillary gas chromatography was done on a Shimadzu 14A GC using a DB-101 column with a flame ionization detector (FID) detector. Conditions: initial temperature 150°C; hold time 2.0 min; ramp 5°/min; final temperature 240°C; hold time 5.0 min.

4.1.1. 4-(*tert*-Butyldimethylsilyloxy)-2-methyl-1-buten-3-yne (3).[15] A solution of 2.0 g (29.4 mmol) of 2-methyl-1-buten-3-yne in 10 mL of THF was cooled to −78°C. To the cooled solution was added 11.74 mL of *n*-BuLi (2 M in THF) dropwise. The mixture was stirred at −78°C for 30 min. To the cooled solution was added a solution of 4.43 g of *tert*-butyldimethylsilyl chloride (29.4 mmol) in 10 mL of THF. The reaction was allowed to warm slowly to room temperature and was stirred for 12 h. The reaction was quenched with 100 mL of water, the layers separated, the aqueous layer extracted with 4×100 mL of pentane, and the combined organic layers dried ($MgSO_4$) and evaporated. The product was purified by column chromatography (pentane, R_f=0.93) to yield 4.77 g of **3** (90% yield) as a pale yellow oil. ^{1}H NMR δ 5.34 (s, 1H), 5.24 (s, 1H), 1.89 (s, 3H), 0.95 (s, 9H), 0.12 (s, 6H). ^{13}C NMR δ 127.0, 122.6, 107.1, 91.3, 26.1, 23.4, 16.6, -4.6. HRMS for $C_{11}H_{20}Si$ (M^+): calcd 180.1334, found 180.1333.

4.1.2. 1-(*tert*-Butyldimethylsilyl)-3,4-epoxy-3-methyl-1-butyne (4). A solution of 1.56 g (5.54 mmol) of MCPBA in 5 mL of CH_2Cl_2 was cooled to 0°C. A solution of 1.0 g of **3** (5.54 mmol) in CH_2Cl_2 was added via cannula. The solution was the stirred at 0°C for 30 min, then allowed to warm to room temperature, stirred overnight, and then treated with 10 mL of sat'd aq $NaCO_3$. The layers were separated, the aqueous layer was extracted with 3×10 mL of CH_2Cl_2, the combined extracts dried ($MgSO_4$) and evaporated. The product was purified by column chromatography (CH_2Cl_2, R_f=0.76) to yield 0.82 g of **4** (75% yield) as a light orange oil. ^{1}H NMR δ 3.10 (d, *J*=5.8 Hz, 1H), 2.74 (d, *J*=5.51 Hz, 1H), 1.55 (s, 3H), 0.93 (s, 9H), 0.10 (s, 6H). ^{13}C NMR δ 105.3, 85.6, 55.6, 47.3, 26.0, 22.9, 16.5, -4.8. Anal for $C_{11}H_{20}SiO$: calcd C 67.28%, H 10.27%, found C 66.80%, H 10.34%.

4.1.3. 4-(*tert*-Butyldimethylsilyl)-2-methyl-3-butyn-1-ol (5). A solution of 1.0 g (5.1 mmol) of **4** in 5 mL of THF was cooled to -35°C. To the solution was added 5.1 mL of DIBAL-H (1 M in THF). The mixture was then allowed to warm slowly over 3 h to 0°C. The reaction mixture was quenched with 1 mL of MeOH, diluted with 10 mL of Et_2O, and then poured into an equal volume of a sat'd soln of Rochelle's salt. The mixture was warmed to room temperature and stirred overnight. The layers were separated, the aqueous layer extracted with 3×15 mL of Et_2O, the combined extracts dried ($MgSO_4$) and evaporated. Purification by column chromatography (1:1 hexane/Et_2O, R_f=0.65) gave 0.85 g of **5** (83% yield) as a colorless liquid. ^{1}H NMR δ 3.54 (dd, 1H, *J*=5.3, 10.7 Hz), 3.51 (dd, 1H, *J*=5.3, 10.7 Hz), 2.70, (m, 1H), 1.73 (bs, 1H), 1.17 (d, 3H, *J*=6.6 Hz), 0.93 (s, 9H), 0.09 (s, 6H); ^{13}C NMR δ 108.8, 84.7, 66.7, 31.4, 30.4, 26.0, 17.0, -4.5. Anal for: $C_{11}H_{22}SiO$: calcd C 66.60%, H 11.18%, found C 66.67%, H 11.19%.

4.1.4. *N*-[4-(*tert*-Butyldimethylsilyl)-2-methyl-3-butynyl]phthalimide (6). To a solution of 0.74 g (5.04 mmol) of phthalimide in 10 mL of THF was added 1.32 g of PPh_3 and 1.0 g of **5**. The mixture was cooled to 0°C, and 0.97 mL (5.04 mmol) of diethyl azodicarboxylate in 5 mL of THF was added dropwise. The mixture was warmed to room temperature and stirred in the dark for 48 h. The solvent evaporated, and the product was purified by column chromatography (CH_2Cl_2, R_f=0.66) to yield 1.34 g of **6** (81% yield) as a yellow liquid. ^{1}H NMR δ 7.84 (dd, 2H, *J*=2.2, 5.5 Hz), 7.72 (dd, 2H, *J*=2.9, 5.5 Hz), 3.83 (dd, 1H, *J*=8.4, 13.6 Hz), 3.62 (dd, 1H, *J*=7.4, 13.2 Hz), 3.12 (m, 1H), 1.20 (d, 3H, *J*=6.6 Hz), 0.78 (s, 9H), -0.03 (s, 6H); ^{13}C NMR δ 168.0, 133.9, 132.0, 123.2, 108.0, 83.3, 42.8, 25.8, 18.3, 16.2, 8.3, -4.8; HRMS for $C_{19}H_{25}NO_2Si$ (M^+): calcd 327.1655, found 327.1646.

4.1.5. 4-(*tert*-Butyldimethylsilyl)-2-methyl-3-butyn-1-amine (7). A solution of 1.0 g (3.05 mmol) of **6** in 10 mL of 95% EtOH was treated with 6.1 mL of a 1.0 M solution of hydrazine hydrate in 95% ethanol. The mixture was refluxed for 3 h, cooled to 0°C, and made slightly acidic. Sat'd aq $NaHCO_3$ was added and the mixture was extracted with 3×20 mL of Et_2O. The combined extracts were washed with sat'd aq $NaHCO_3$ and brine, and dried (KOH). The solvent was evaporated and the product purified by column chromatography (20% EtOH in Et_2O, R_f=0.59) to give

0.45 g of **7** (75% yield) as a colorless liquid. ^{1}H NMR δ 2.73 (dd, 1H, J=5.9, 11.8 Hz), 2.63 (dd, 1H, J=7.6, 11.8 Hz), 2.52 (m, 1H), 1.50 (br s, 2H), 1.17 (d, 3H, J=7.1 Hz), 0.92 (s, 9H), 0.09 (s, 6H); ^{13}C NMR δ 110.3, 83.8, 48.0, 31.3, 26.0, 18.1, 16.4, -4.5; FTIR (neat): 3369, 3293, 2163 cm^{-1}.

4.1.6. *N*-[4-(*tert*-Butyldimethylsilyl)-2-methyl-3-butynyl]trifluoroacetamide (8). To a solution of 1.0 g (5.06 mmol) of **7** in 5 mL of Et_2O was added dropwise at 0°C a solution of 1.07 mL (7.59 mmol) of trifluoroacetic anhydride in 3 mL of Et_2O. The mixture was brought to room temperature, stirred for 1 h, and cooled to 0°C, at which point 2.0 mL of water was added and the mixture stirred for 5 min. Sat'd aq $NaHCO_3$ was added, the layers separated, the aqueous layer extracted with 3×10 mL of Et_2O, and the combined extracts dried ($MgSO_4$). Evaporation and column chromatography (1:1 hexane/Et_2O, R_f=0.74) gave 1.45 g of **8** (98% yield) as a colorless liquid. ^{1}H NMR δ 6.72 (br s, 1H), 3.54 (m, 1H), 3.21 (m, 1H), 2.78 (m, 1H), 1.20 (d, 3H, J=7.0 Hz), 0.90 (s, 9H), 0.05 (s, 6H); ^{13}C NMR δ 107.5, 85.9, 44.3, 27.2, 26.0, 18.2, 16.3, -4.6; FTIR (neat): 2169, 1722 cm^{-1}; HRMS for $C_{13}H_{22}F_3NOSi$ (M^+): calcd 293.1423, found 293.1433. Anal for $C_{13}H_{22}F_3NOSi$: calcd C 53.22%, H 7.56%, found C 53.34%, H 7.62%.

4.1.7. *N*-[2-Methyl-3-butynyl]trifluoroacetamide (9). To a solution of 1.17 g (4.00 mmol) of **8** in 5 mL of THF was added 6.0 mL (6.0 mmol) of 1.0 M tetrabutylammonium fluoride in THF. The mixture was heated to 40°C for 3 h. After cooling to 0°C and acidification, sat'd aq $NaHCO_3$ was added, the layers separated, the aqueous layer extracted with 3×15 mL of Et_2O, and the combined extracts dried ($MgSO_4$). Evaporation and column chromatography (1:1 hexane/Et_2O, R_f=0.52) gave 0.52 g of **9** (72% yield) as a colorless liquid. ^{1}H NMR δ 6.60 (br s, 1H), 3.58 (m, 1H), 3.24 (m, 1H), 2.79 (m, 1H), 2.17 (d, 1H, J=2.2 Hz), 1.23 (d, 3H, J=7.0 Hz); ^{13}C NMR δ 117.6, 84.7, 70.6, 65.7, 44.2, 25.9, 25.5; FTIR (film): 3313, 2119, 1711 cm^{-1}; HRMS for $C_7H_8F_3NO$ (M^+): calcd 179.0558, found 179.0565.

4.1.8. *N*-[(*E*)-2-Butenyl]-*N*-[2-methyl-3-butynyl]trifluoroacetamide (10). To a suspension of 0.15 g (3.7 mmol) of KH in 3 mL of THF was added dropwise at 0°C a solution of 0.66 g (3.7 mmol) of **9** in 2 mL of THF. The mixture was stirred for 30 min, warmed to room temperature, treated with a solution of 0.51 mL (5.2 mmol) of crotyl chloride and 20 mg of 18-crown-6 in 2 mL of THF, and heated to reflux for 6 h. After cooling to 0°C, 2 mL of water was added, the solution was made acidic, sat'd aq $NaHCO_3$ was added, the layers separated, the aqueous layer extracted with 3×15 mL of Et_2O, and the combined extracts dried ($MgSO_4$). Evaporation and column chromatography (4:1 hexane/Et_2O, R_f=0.63) gave 0.60 g of **10** (70% yield) as a colorless liquid. ^{1}H NMR δ 5.75 (m, 1H), 5.40 (m, 1H), 4.15 (d, 2H, J=6.8 Hz), 3.50 (m, 1H), 3.25 (m, 1H), 3.00 (m, 1H), 2.10 (d, 1H, J=2.2 Hz), 1.75 (d, 3H, J=6.9 Hz), 1.20 (d, 3H, J=6.9 Hz); ^{13}C NMR δ 131.2, 124.8, 105.0, 86.0, 70.0, 50.8, 50.54, 50.45, 24.0, 18.4, 17.6; FTIR (film): 3313, 2116, 1697, 966 cm^{-1}; HRMS for $C_{11}H_{14}F_3NO$ (M^+): calcd 233.1027, found 233.1035.

4.1.9. *N*-(2-Methyl-3-butynyl)-(*E*)-2-buten-1-amine (11). A solution of 0.80 g (6.8 mmol) of **10** in 5 mL of MeOH was cooled to 0°C and treated with 2 pellets of solid KOH. After warming to room temperature and stirring for 1 h, the layers were separated and the aqueous phase extracted with 5×5 mL of Et_2O, and the combined extracts dried ($MgSO_4$). Evaporation and column chromatography (1:1 hexane/Et_2O, R_f=0.36) gave 0.44 g of **11** (94% yield) as a colorless liquid. ^{1}H NMR δ 5.60 (m, 2H), 3.20 (d, 2H, J=4.8 Hz), 2.80 (m, 4H), 2.10 (d, 1H, J=2.2 Hz), 1.70 (d, 3H, J=6.6 Hz), 1.20 (d, 3H, J=6.3 Hz); ^{13}C NMR δ 130.0, 126.9, 105.1, 87.8, 70.0, 54.9, 51.5, 26.8, 18.7; FTIR (film): 3309, 2112, 968 cm^{-1}; HRMS for $C_9H_{15}N$ (M^+): calcd 137.1204, found 137.1207.

4.1.10. Ethyl *N*-[(*E*)-2-Butenyl]-*N*-(2-methyl-3-butynyl)-carbamate (12). A solution of 0.32 g (2.3 mmol) of **11** and 0.32 mL (2.3 mmol) of Et_3N in 5 mL of THF was treated dropwise at 0°C with a solution of 0.18 mL (2.3 mmol) of ethyl chloroformate in 5 mL of THF. The mixture was stirred for 1 h and allowed to warm to room temperature. Water was added, the layers were separated and the aqueous phase extracted with 3×10 mL of Et_2O, and the combined extracts dried ($MgSO_4$). Evaporation and column chromatography (1:1 hexane/Et_2O, R_f=0.61) gave 0.41 g of **12** (85% yield) as a colorless liquid. ^{1}H NMR δ 5.60 (m, 1H), 5.40 (m, 1H), 4.17 (q, 2H, J=7.1 Hz), 4.1–3.8 (m, 2H), 3.4–3.2 (m, 2H), 2.80 (m, 1H), 2.02 (d, 1H, J=2.1 Hz), 1.70 (d, 3H, J=6.7 Hz), 1.23 (t, 3H, J=7.0 Hz), 1.19 (d, 3H, J=7.2 Hz); ^{13}C NMR δ 156.5, 128.1, 126.4, 86.8, 69.4, 61.2, 51.7, 50.9, 49.7, 44.3, 25.3, 18.2, 17.6, 14.6; FTIR (film): 2114, 1701 cm^{-1}; HRMS for $C_{12}H_{19}NO_2$ (M^+): calcd 209.1365, found 209.1424.

4.1.11. *N*-[(*E*)-2-Butenyl]-*N*-(2-methyl-3-butynyl)-*p*-toluenesulfonamide (13). A solution of 0.42 g (2.2 mmol) of *p*-toluenesulfonyl chloride in 2 mL of pyridine was treated dropwise at 0°C with a solution of 0.30 g (2.2 mmol) of **11** in 1 mL of pyridine. The mixture was stirred for 1.5 h at 0°C, treated with 2 mL of water, the layers separated, the aqueous phase extracted with 3×5 mL of Et_2O, and the combined extracts dried ($MgSO_4$). Evaporation and column chromatography (1:1 hexane/Et_2O, R_f=0.65) gave 0.50 g of **13** (78% yield) as a colorless liquid. ^{1}H NMR δ 7.70 (d, 2H, J=8.1 Hz), 7.40 (d, 2H, J=8.1 Hz), 5.60 (m, 1H), 5.20 (m, 1H), 3.80 (d, 2H, J=6.6 Hz), 3.15 (m, 2H), 2.80 (m, 1H), 2.48 (s, 3H), 2.04 (d, 1H, J=2.2 Hz), 1.60 (d, 3H, J=6.3 Hz), 1.21 (d, 3H, J=6.6 Hz); ^{13}C NMR δ 143.1, 137.0, 129.5, 129.4, 127.1, 125.3, 86.3, 69.7, 52.1, 51.7, 50.8, 25.7, 18.1, 17.4; FTIR (film): 3290, 2114, 1599, 1161 cm^{-1}; HRMS for $C_{16}H_{21}NO_2S$ (M^+): calcd 291.1293, found 291.1291.

4.1.12. Ethyl (4*R,7*S**,7a*S**)-4,7-Dimethyl-6-oxo-1,2,3,4,7,7a-hexahydro-6*H*-2-pyridine-2-carboxylate (14).**[3b] To a solution of 0.42 g (0.124 mmol) of $Co_2(CO)_8$ in 0.30 mL of freshly distilled CH_2Cl_2 was added a solution of 0.241 g (0.124 mmol) of **12** in 0.30 mL of CH_2Cl_2. The solution was allowed to stir for 2 h, cooled to 0°C, and treated with a solution of 0.090 g (0.77 mmol) of NMO in 0.30 mL of CH_2Cl_2. The mixture was warmed to room temperature and stirred overnight, at which time the reaction appeared to be complete by TLC, and the solvent was evaporated. The residue was taken up in a small amount of

CH_2Cl_2 and passed through a silica plug. Purification by radial chromatography (4:1 hexane/ethyl acetate) gave 4.7 mg of **13** (16% yield), a colorless oil, displaying NMR and IR spectra identical to those reported.[3b]

4.1.13. Ethyl (4*R,7*S**,7a*S**)-4,7-Dimethyl-6-oxo-1,2,3,4,7,7a-hexahydro-6*H*-2-pyrindine-2-carboxylate (15).** To a solution of 0.17 g (0.050 mmol) of $Co_2(CO)_8$ in 5.0 mL of freshly distilled CH_2Cl_2 was added a solution of 0.15 g (0.050 mmol) of **12** in 5.0 mL of CH_2Cl_2. The solution was allowed to stir for 1 h, the atmosphere was changed to O_2, and a solution of 0.050 g (0.70 mmol) of TMANO in 2.0 mL of CH_2Cl_2 was added slowly, dropwise. The mixture was stirred for 2 h, at which time an additional 0.190 g (2.50 mmol) of TMANO in 5.0 mL of CH_2Cl_2 was added slowly and the mixture stirred for an additional 12 h. The mixture was passed through a silica plug, eluting with Et_2O. Purification by preparative HPLC (4:1 hexane/ethyl acetate) gave 5.0 mg of **15** (6% yield) as a colorless oil. ^{1}H NMR δ 7.63 (d, 2H, J=8.1 Hz), 7.32 (d, 2H, J=8.1 Hz), 5.86 (s, 1H), 4.22 (m, 1H), 3.77 (d, 1H, J=11.4 Hz), 3.03 (m, 1H), 2.84 (m, 1H), 2.47 (dd, 1H, J=3.3, 11.8 Hz), 2.43 (s, 3H), 1.98 (m, 1H), 1.87 (m, 1H), 1.38 (d, 3H, J=7.0 Hz), 1.23 (d, 3H, J=7.4 Hz); ^{13}C NMR δ 179.9, 143.9, 129.8, 127.2, 126.6, 105.0, 52.1, 51.9, 45.0, 44.5, 36.7, 21.5, 17.8, 17.7, 14.4; FTIR (film): 1707, 1599 cm^{-1}.

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