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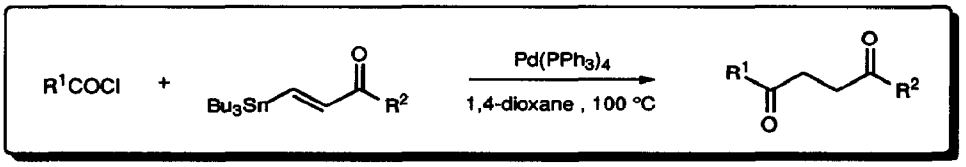
A Concise Synthesis of (±)-Monomorine I by way of a Palladium-Catalyzed Reductive Coupling

Ana M. Castaño, Juan M. Cuerva, and Antonio M. Echavarren*

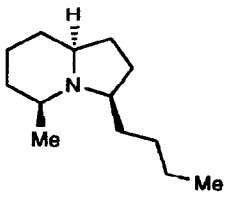
Departamento de Química Orgánica, Universidad Autónoma de Madrid, Cantoblanco, 28049 Madrid, Spain

Abstract: A seven steps synthesis of the indolizidine alkaloid (±)-monomorine I is described starting from 2-methylpiperidine. The key step of the synthesis is a palladium-catalyzed reductive coupling reaction of an acid chloride with a β-stannanyl enone to give a 1,4-diketone.

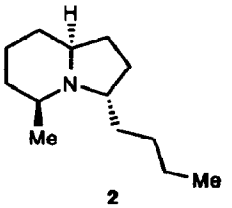
We have recently developed a new method for the synthesis of 1,4-diketones by a palladium-catalyzed coupling of acid chlorides with β-stannyl enones.[1] The reaction is general and tolerates the presence of double bonds conjugated with a single carbonyl group. Interestingly, the reduction of the intermediate α,β-unsaturated 1,4-diketone is catalyzed by palladium complexes and promoted by Bu_3SnCl, formed as a byproduct in the coupling process.[2]



Herein we report an application of this reaction to a concise synthesis of the indolizidine alkaloid monomorine I (**1**),[3] a substance isolated from the ant *Monomorium pharaonis*.[4] Its C-3 epimer, indolizidine 195B (gephirothoxine 195 B) (**2**), is also a natural product isolated from the skin of the poisonous tropical frog *Dentrobates histrionicus*.[5,6] Other 3,5-disubstituted indolizidine alkaloids have been isolated from different species of ants[7] and amphibians.[8] A new reduction reaction promoted by Bu_3SnCl and catalyzed by palladium was observed in the course of the synthesis.



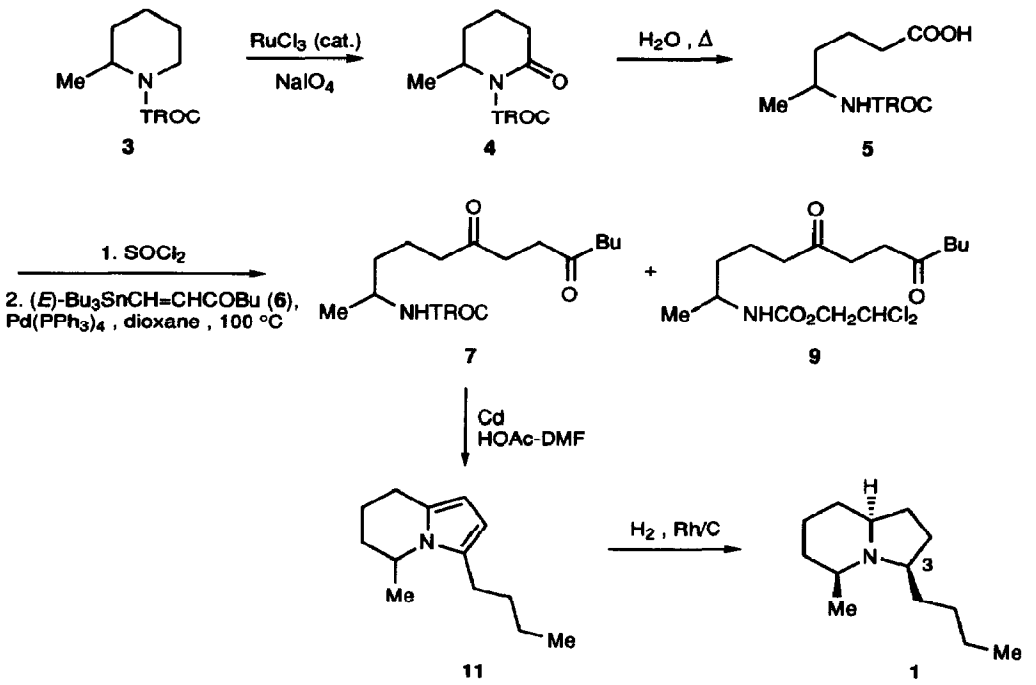
1



2

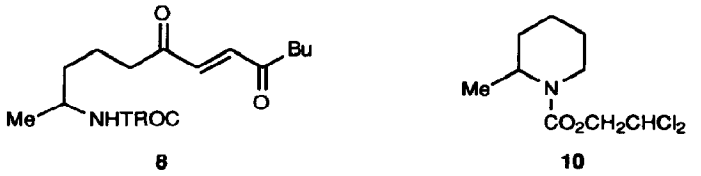
2-Methyl-*N*-(2,2,2-trichloroethoxycarbonyl)piperidine (TROC-2-methylpiperidine) (**3**) was prepared in 96 % yield by acylation of commercially available 2-methylpiperidine with TROC-Cl under Schotten-Baumann conditions (Scheme 1).[9] Oxidation of the C-6 methylene to give the imide **4** (88 %) was accomplished with RuO_4, generated under catalytic conditions according to the procedure of Sharpless.[10]

Hydrolysis of **4** led cleanly to acid **5** in 89 % yield. The oxidation of carbamate **3** with aqueous $KMnO_4$ at 100 °C[11] gave **5** in one step, albeit in rather low yield (17 %).



Scheme 1

Coupling of the acid chloride of **5** with β-stannyl enone **6**[2,12] proceeded in the presence of $Pd(PPh_3)_4$ as the catalyst in dioxane (100 °C, 24 h) to give **7** (45 % yield).[1,2] The moderate yield obtained in this coupling was due in part to the competitive cyclization of the acid chloride to imide **4**. When the coupling reaction was carried out at 40 °C for 4 h, the α,β-unsaturated 1,4-diketone **8** was obtained in 49 % yield.[13]

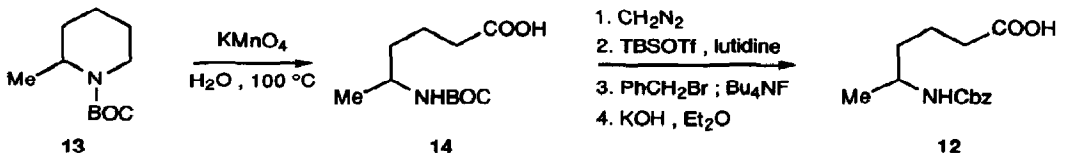


Small amounts (*ca.* 5 %) of a byproduct **9** with a 2,2-dichloroethoxycarbonyl protective group were also isolated in the coupling reaction carried out under refluxing conditions for long reaction times. This surprising reduction was promoted by Bu_3SnCl in a process catalyzed by palladium catalysts. Thus, treatment of **3** with Bu_3SnCl in dioxane under reflux in the presence of $Pd(PPh_3)_2Cl_2$ as the catalyst gave dichloroethoxycarbonyl derivative **10** (24 h, 11 % yield).

Deprotection of the TROC protective group with Zn and HOAc in THF at 23 °C in the presence of KH_2PO_4[14] led to a 1:1 mixture of the desired pyrrole **11** and **9**. Higher temperatures led to extensive decomposition of **11**. Further treatment of carbamate **9** under the reduction conditions failed to give **11**. Better

results were obtained by reductive cleavage of the protective group by sonication with Cd in a 1:1 mixture of DMF and HOAc at 23 °C[15] leading cleanly to **11** in 96 % yield.

We have originally expected that the use of benzyloxycarbonyl (Cbz) protective group would have allowed for its direct removal under hydrogenolytic conditions with simultaneous reduction of the pyrrole ring. The starting carboxylic acid **12** could be prepared in very poor yield by oxidation of *N*-(benzyloxycarbonyl)-2-methylpiperidine.[16] An alternative synthesis is shown in Scheme 2 starting from BOC-protected piperidine **13**, prepared quantitatively by reaction of 2-methylpiperidine with $(BOC)_2O$ in refluxing THF. Oxidation[11] of **13** led to **14** (32 % yield), which, after treatment with excess ethereal diazomethane was submitted to the protective group exchange developed by Ohfune.[17] Final saponification[18] led to **12** in 36 % yield (four steps). Unfortunately, the acid chloride of **12** gave only decomposition products after treatment with stannane **6** under the reductive coupling conditions.[1,2]



13 **14** **12**

Scheme 2

Catalytic hydrogenation of **11** with 1-3 atm of H_2 at 23 °C in the presence of PtO_2 or Rh/Al_2O_3[3a,b,19] in EtOH gave negative results. Addition of small amounts of acids (HOAc, TFA, or HCl) led to decomposition of the pyrrole **11** along with traces of **1** and its three diastereomers. The best results were obtained by using Rh/C as the catalysts (1 atm H_2, EtOH, 25 °C, 24 h)[8a,19] leading to the formation of a mixture of **1** two of ist diastereomers **15** and **16** in a 2:2:1 ratio (60 % yield).[20]

15 **16**

In summary, the developed synthesis of (±)-**1** is concise and demonstrates the application of the reductive coupling reaction for the synthesis of fuctionalized 1,4-diketones. If desired, this synthesis could also be applied for the preparation of either antipode of **1** starting from known optically pure 2-methylpiperidine.[21,22]

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9. ***Selected physical and spectral data.*** **3**: oil; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 4.84 (d, J = 12.0 Hz, 1 H), 4.51 (d, J = 12.0 Hz, 1 H), 4.53 - 4.47 (m, 1 H), 4.09-3.99 (m, 1 H), 3.03-2.89 (m, 1 H), 1.7-1.4 (m, 6 H), 1.21 (d, J = 7.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 153.55, 95.94, 75.01, 46.98, 39.32, 30.00, 25.50, 18.50, 15.91; HRMS calcd for $C_{11}H_{21}Cl_3NO_4$ 273.0090; found 273.0082. **4**: oil; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 4.79 (s, 2 H), 4.50-4.40 (m, 1 H), 2.56-2.48 (m, 2 H), 2.1-1.5 (m, 4), 1.31 (d, J = 6.5 Hz, 3 H). **5**: mp 67-68 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) δ 7.50 (d, J = 8.3 Hz, 1 H), 4.77 (br s, 2 H), 3.27 (m, 1 H), 2.18 (m, 2 H), 1.56-1.27 (m, 4 H), 1.05 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 178.78, 154.06, 95.71, 74.48, 47.31, 36.54, 36.24, 33.54, 21.07; Anal. Calcd for $C_9H_{14}Cl_3NO_4$: C, 35.26; H, 4.60; N, 4.47. Found: C, 35.51; H, 4.90; N, 4.59. **7**: oil; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 4.91 (d, J = 8.3 Hz, 1 H), 4.71 (s, 2 H), 3.73 (m, 1 H), 2.74-2.59 (m, 4 H), 2.54-2.41 (m, 4 H), 1.70-1.22 (m, 8 H), 1.18 (d, J = 6.6 Hz, 3 H), 0.90 (t, J = 7.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 209.68, 209.14, 154.00, 74.37, 47.36, 42.49, 42.16, 36.06, 36.03, 35.97, 25.93, 22.28, 21.05, 20.04, 13.78 (the CCl_3 was not observed); Anal. Calcd for $C_{16}H_{26}Cl_3NO_4$: C, 47.72; H, 6.51; N, 3.49. Found: C, 47.93; H, 6.60; N, 3.58. **8**: mp 52-53 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.86 (m, 2 H), 4.79 (d, J = 8.4 Hz, 1 H), 4.72 (m, 2 H), 3.76 (m, 1 H), 2.70-2.61 (m, 4 H), 1.78-1.20 (m, 8 H), 1.20 (d, J = 6.6 Hz, 3 H), 0.92 (t, J = 7.3 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 200.57, 200.03, 153.99, 136.43, 136.03, 95.70, 74.41, 47.21, 41.35, 40.93, 36.19, 25.80, 22.22, 21.04, 19.88, 13.75; Anal. Calcd for $C_{16}H_{24}Cl_3NO_4$: C, 47.96; H, 6.04; N, 3.49. Found: C, 47.74; H, 6.09; N, 3.45. **9**: mp 70-72 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.84 (t, J = 6.0 Hz, 1 H), 4.81 (br d, J = 7 Hz, 1 H), 4.39 (d, J = 6.0 Hz, 2 H), 3.68 (septet, J = 6.5 Hz, 1 H), 2.75-2.60 (m, 4 H), 2.54-2.41 (m, 4 H), 1.7-1.2 (m, 8 H), 1.16 (d, J = 6.6 Hz, 3 H), 0.90 (t, J = 7.3 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 209.67, 209.15, 154.59, 69.11, 68.64, 47.19, 42.48, 42.16, 36.03, 35.97, 25.93, 22.28, 21.03, 20.01, 13.77 (the CCl_3 was not observed); Anal. Calcd for $C_{16}H_{27}Cl_2NO_4$: C, 52.18; H, 7.39; N, 3.80. Found: C, 52.50; H, 7.65; N, 3.85. **11**: oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.87 (d, J = 3.4 Hz, 1 H), 5.77 (d, J = 3.4 Hz, 1 H), 4.29 (m, 1 H), 2.95-2.60 (m, 2 H), 2.57-2.50 (m, 2 H), 2.05-1.37 (m, 8 H), 1.33 (d, J = 6.5 Hz, 3 H), 0.97 (t, J = 7.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 131.09, 127.20, 104.55, 103.05, 46.84, 31.05, 30.26, 25.72, 23.40, 22.79, 21.47, 16.25, 13.99; MS *m/z* 191 (M^+).
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19. A recently published report describes an alternative synthesis of pyrrole **11**.[3b] The catalytic hydrogenation of **11** with Rh/Al_2O_3 in MeOH furnished a mixture of four indolizidines (**1**, **2**, **15**, and **16** in a 33:23:40:3 ratio, 78 % yield).
20. Chromatography on an alumina column (50:1 hexane-EtOAc) allowed for the separation of **1**. Oligomerization of the pyrrole **11** was a side reaction in the catalytic hydrogenation experiments.
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