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TOTAL SYNTHESIS OF (±) PSEUDOPHRYNAMINOL

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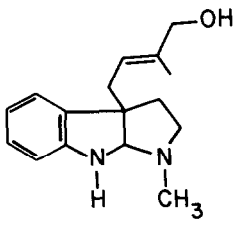
Summary: The first synthesis of (±) pseudophrynaminol, a unique pyrrolo [2,3b] indole recently isolated from the Australian frog *Pseudophryne coriacea*, is described.

Recently pseudophrynaminol **1** and pseudophrynamine A **2** were isolated from the skin of the Australian frog *Pseudophryne coriacea*.[1] Although the biological significance of these compounds for *P. coriacea* is unknown, they may protect the animal from predation, perhaps by acting as foul-tasting substances or neurotoxins since other indole alkaloids isolated from amphibian skin serve these roles.[2,3]



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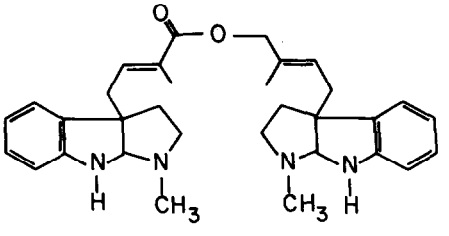

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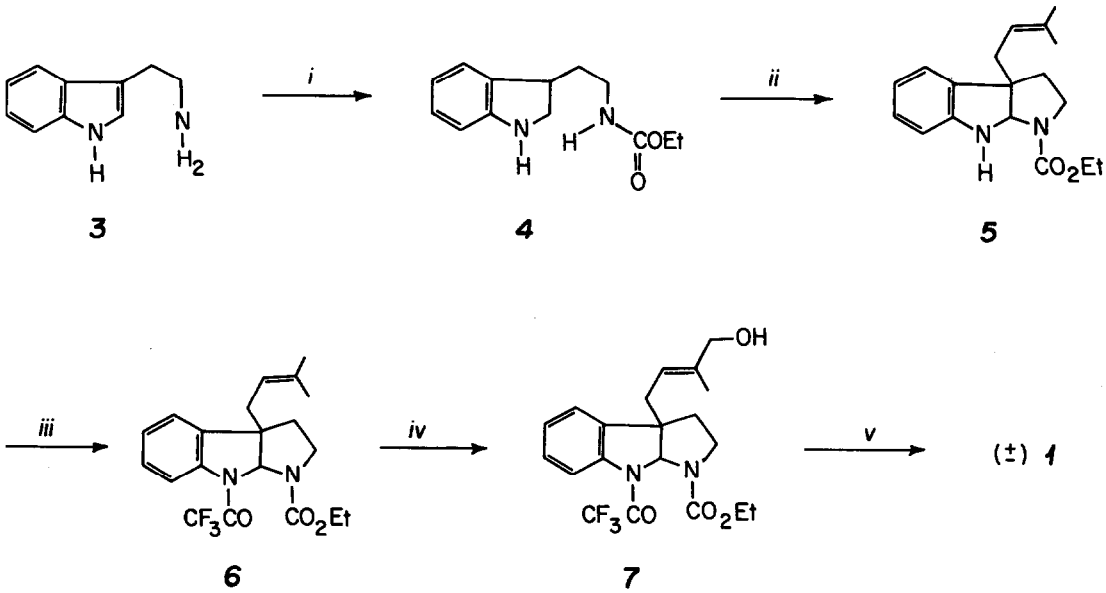
In an effort to provide sufficient quantities of **1** for extensive biological testing (only 1.5 mg of **1** could be isolated from 166 frogs),[1] we developed a convenient synthesis of (±) **1** from tryptamine **3** in five steps.

As shown in the Scheme, **3** was protected in the first step as the ethoxycarbonyl derivative **4** in 95-100% yield. **4** then underwent a Mg^{2+}-mediated, tandem electrophilic addition-cyclization under S_N1 conditions with 4-bromo-2-methyl-2-butene to form the monoprenylated, pyrrolo [2,3b] indole **5**[4] cleanly in 21-23% yield using a modification of the conditions of Christophersen et al.[5] (An alternative approach to **5**,

SCHEME



i. *EtOCCl (1.1 eq), Et_3N (1.1 eq), p-dioxane, r.t.*

ii. *4-bromo-2-methyl-2-butene (1.0 eq. 180 min. addition/reaction time), $Mg(NO_3)_2{\cdot}6H_2O$ (3.0 eq), pH 2.9 buffer (8 g CH_3CO_2Na/20 mL H_2O/100 mL CH_3CO_2H), r.t.*

iii. *$(CF_3CO)_2O$ (1.1 eq), Et_3N (1.1 eq), CH_2Cl_2, r.t.*

iv. *SeO_2 (0.5 eq), $(CH_3)_3COOH$ (2.0 eq), CH_2Cl_2, r.t.*

v. *$LiAlH_4$ (2.0 mole eq), ether, reflux.*

based on Nakagawa et al.'s reported 45-50% yield synthesis of the methoxycarbonyl analogue,[6] is also potentially employable[7].) The key intermediate **5** was next converted to the trifluoroacetyl derivative **6**[8] (85%) in order to improve the yield in the subsequent oxidation step.[9] Following a general procedure by Umbreit and Sharpless,[10] regioselective oxidation of **6** with selenium dioxide/t-butyl hydroperoxide generated the desired E alcohol **7**[11] in >95% stereochemical purity (by ^{1}H-NMR) and in 27% yield.[12] Finally, reduction of **7** with lithium aluminum hydride in refluxing ether gave (±) **1** in 45% yield (2.3% overall from tryptamine). (±) **1** is identical to the natural product in all its spectral characteristics. A full paper describing mass spectral analyses, NMR studies, and reaction studies in this project will be forthcoming. This synthesis is a direct stereospecific route to pseudophrynaminol from readily available starting materials. The pathway is suitable for preparation of many analogs.

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References

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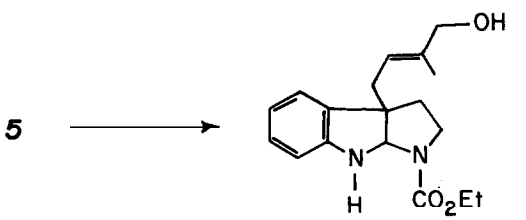
2. J. W. Daly and T. F. Spande, *Alkaloids: Chemical and Biological Perspectives*; S. W. Pelletier, Ed.; Wiley: New York, 1986, vol. 4, Ch. 1, pp. 1-274.
3. C. W. Myers and J. W. Daly, *Sci. Am.* **1983**, 248, 120.
4. ^{1}H-NMR of **5**($CDCl_3$, TMS reference, 300 MHz): δ_a1.24 (t) and δ_b1.33 (t) (two rotamers, 3H total. $J_a = J_b$ = 7.1-7.2 Hz), 1.53 (s, 3H), 1.71 (s, 3H), 2.13-2.17 (m, 2H), 2.35-2.39 (m, 2H), 3.02-3.06 (m, 1H), 3.55-3.75 (two rotamers, apparent quartets, J = 7.1-7.2 Hz for both, 2H total), 5.10 (s, 1H), 5.07-5.18 (m,1H and D_2O exchangeable proton, 2H total), 6.60 (d, 1H, J = 7.7 Hz) 6.73-6.76 (m, 1H), 7.05 (d, 1H, J = 7.5 Hz), 7.09 (d, 1H, J = 1.4 Hz).
   IR of **5** (60 mg/ml in CH_2Cl_2, cm^{-1}): 3360, 2920, 1690, 1610, 1480, 1465, 1420.
5. P. Muthusubramanian, J.S. Carlé, C. Christophersen, *Acta. Chem. Scand.* **1983**, B37, 803.
6. M. Nakagawa, K. Matsuki, T. Hino, *Tet. Lett.* **1983**, 24, 2171.
7. Personal communication from Drs. M. Nakagawa and T. Hino (experimental methods from M.S. Thesis by K. Matsuki).
8. ^{1}H-NMR of **6** ($CDCl_3$, TMS reference, 300 MHz): δ1.23 (t, 3H, J = 7.1 Hz), 1.50 (s, 3H), 1.64 (s, 3H), 1.70-1.82 (m, 1H), 2.09-2.38 (m, 1H), 2.40-2.50 (m, 1H), 2.86-2.96 (m, 6 distinct lines, 1H), 3.69 (t, 1H), 4.08-4.17 (m, 2H), 4.97 (t, 1H), 6.06 (s, 1H), 7.19-7.36 (m, 4H), 7.97 (br s, 1H).
   ^{19}F-NMR of **6** ($CFCl_3$, $CDCl_3$ reference, 282 MHz): δ -68.8 (br s). IR of **6** (neat, NaCl disks, cm^{-1}): 2940, 1690 (broad), 1600, 1480-1400.
9. We were able to synthesize the desired E alcohol **8** directly from **5** (same oxidation conditions as **6**→**7**) but in only 17% yield.



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10. M. A. Umbreit and K. B. Sharpless, *J. Am. Chem. Soc.* **1977**, 99, 5526.

11. ^{1}H-NMR of **7** ($CDCl_3$, TMS reference, 300 MHz): δ1.22 (t, 3H), 1.54 (s, 3H), 1.68 (br s, 1H (OH)), 2.11-2.33 (m, 2H), 2.41-2.57 (m, 2H), 2.87-2.97 (m, 6 distinct lines, 1H), 3.67-3.88 (m, 1H), 3.93 (s, 2H), 4.03-4.22 (m, 2H), 5.28 (t, 1H), 6.08 (s, 1H), 7.20-7.36 (m, 3H), 7.97 (br s, 1H).

12. This yield only applies to reactions performed on a 100 mg scale. On a 500 mg scale, the isolated yield drops to 16%.

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