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Total syntheses of strychnos alkaloids

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Abstract-
Total syntheses of racemic dihydromossambine, lagunamine, echitamidine, alstogustine, epi-alstogustine and strychnine were obtained from two alternative synthetic strategies.

Syntheses of dihydromossambine (1), lagunamine (2), echitamidine (3) and strychnine (4) were achieved by two alternative synthetic pathways for construction of the pentacyclic framework of these alkaloids. Path A is based on an intramolecular Diels-Alder reaction of indoloacrylate and enamine functions while in path B a new electrocylic rearrangement and cyclization provides the tetracyclic core for further elaboration. For illustration and comparison, complete reaction schemes are shown for echitamidine (3) and strychnine (4).

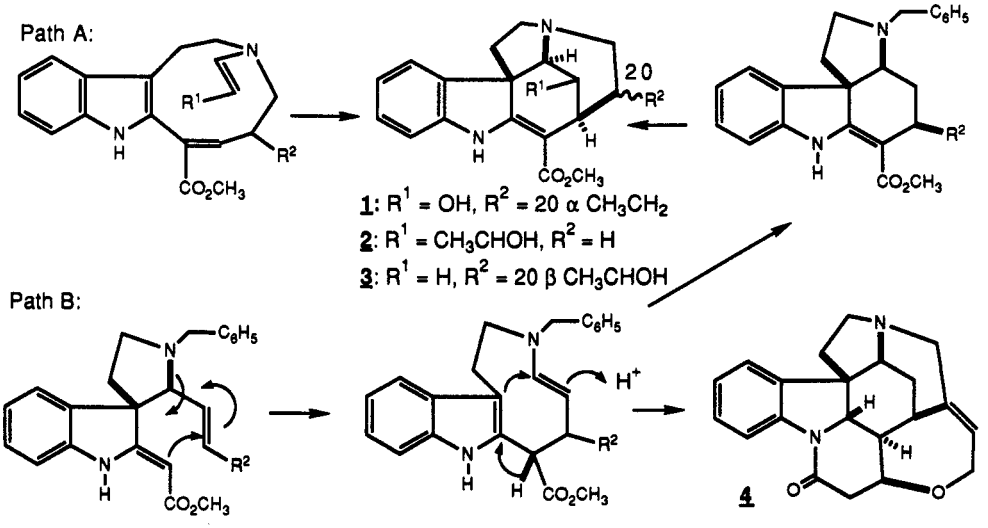
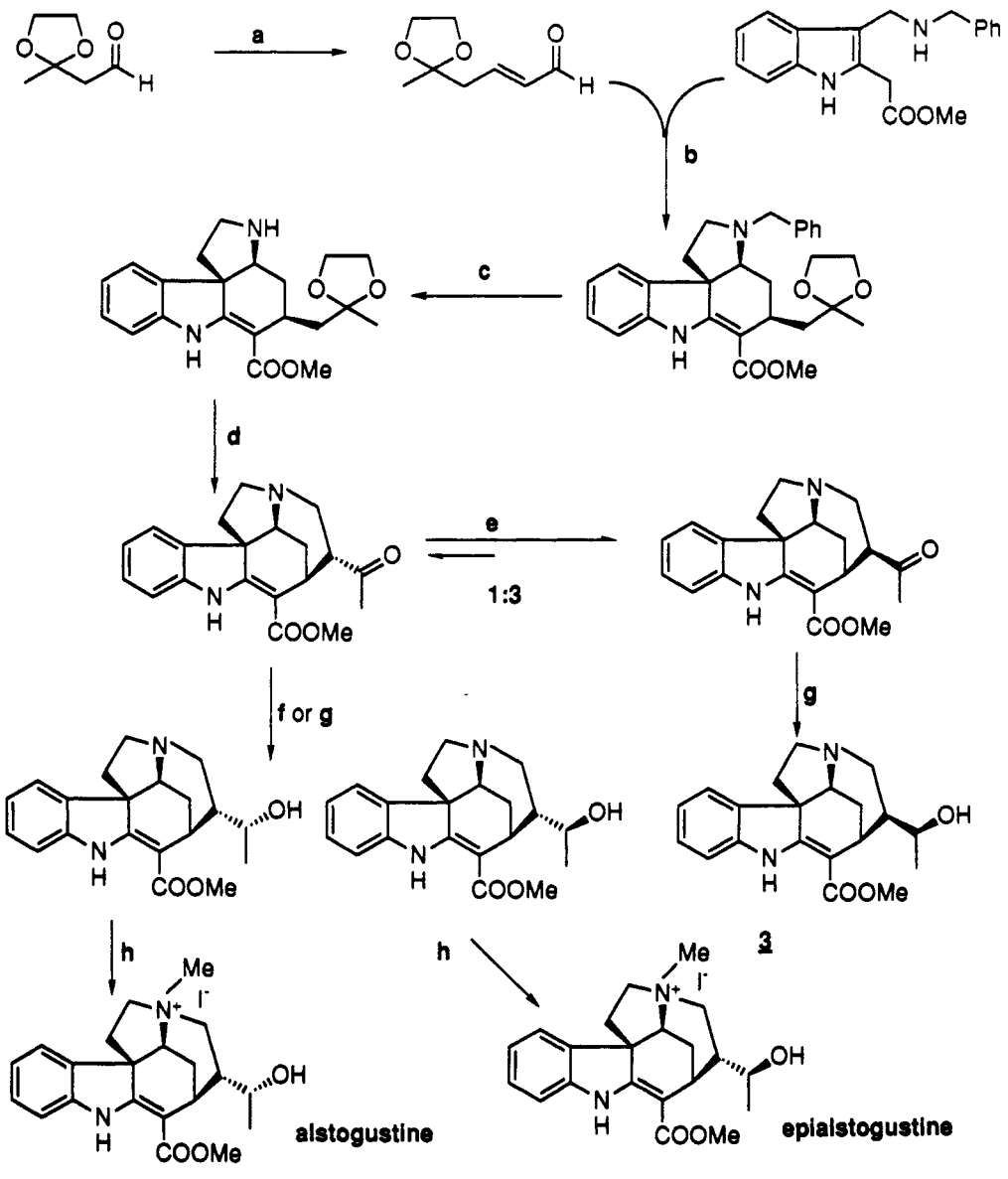


Fig. 1: Two alternative strategies for construction of strychnos alkaloids



Reagents: **a.** Ph_3P=CHCHO, $CHCl_3$, 60 °C, 20 h, 86 %. **b.** 4 Å molecular sieves, $BF_3{\cdot}Et_2O$, toluene, reflux, 3 days, 30 %. **c.** 10 % Pd-C, $HCOONH_4$, MeOH, EtOAc, reflux, 3 h. **d.** (1) HCHO (g), MeOH, 0° C; (2) HCl, 0° C to reflux, 2 h; (3) HCl-H_2O, 15 min. 83 % for 4 steps. **e.** NaOMe, MeOH, r.t. **f.** $NaBH_4$, $CeCl_3{\cdot}5H_2O$, 0° C, MeOH, 91 %. **g.** $NaBH_4$, 0° C to r.t., MeOH. **h.** MeI, MeOH, r.t.

Fig. 3: Synthesis of **echitamidine** (**3**) by path B

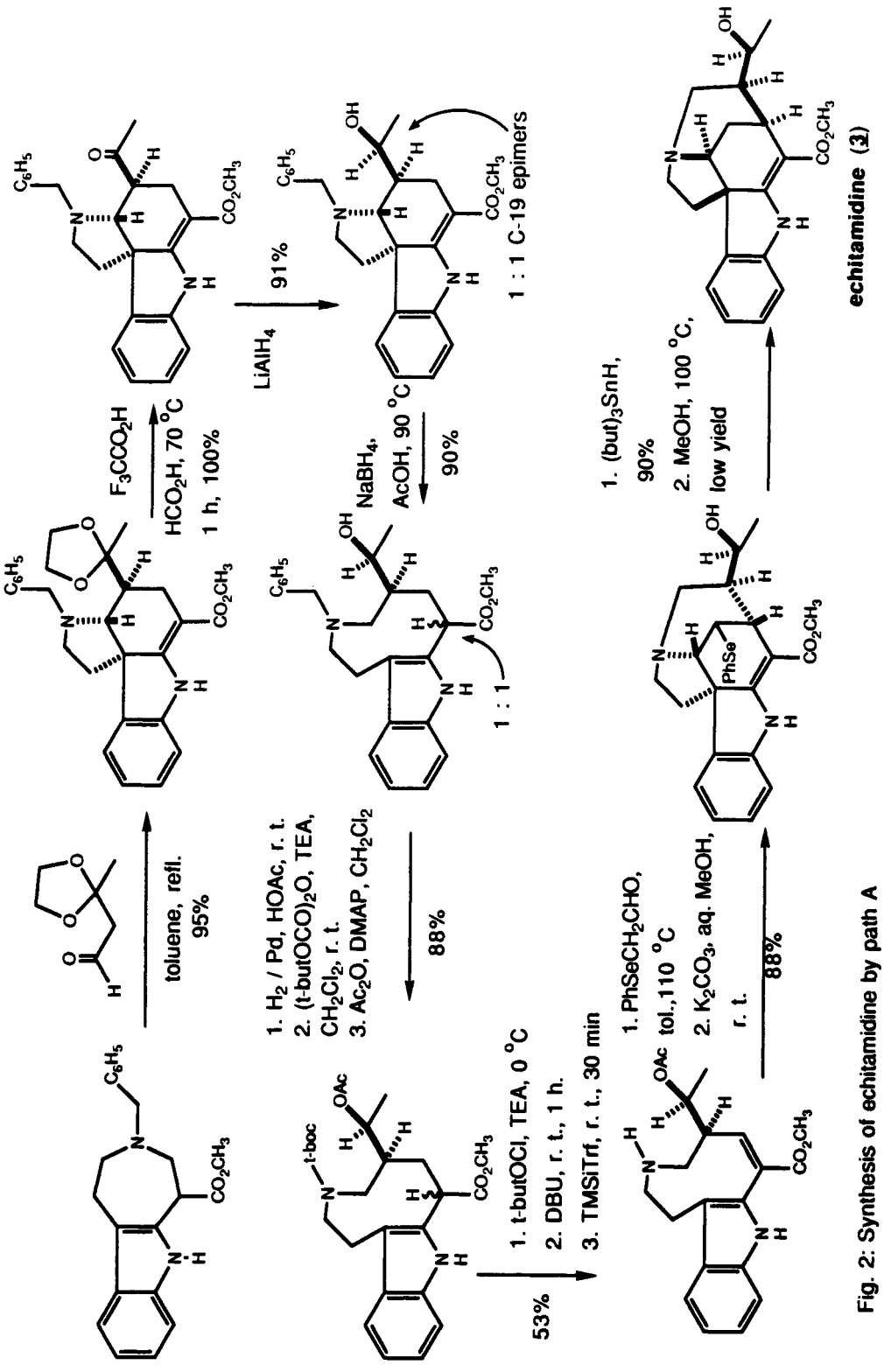
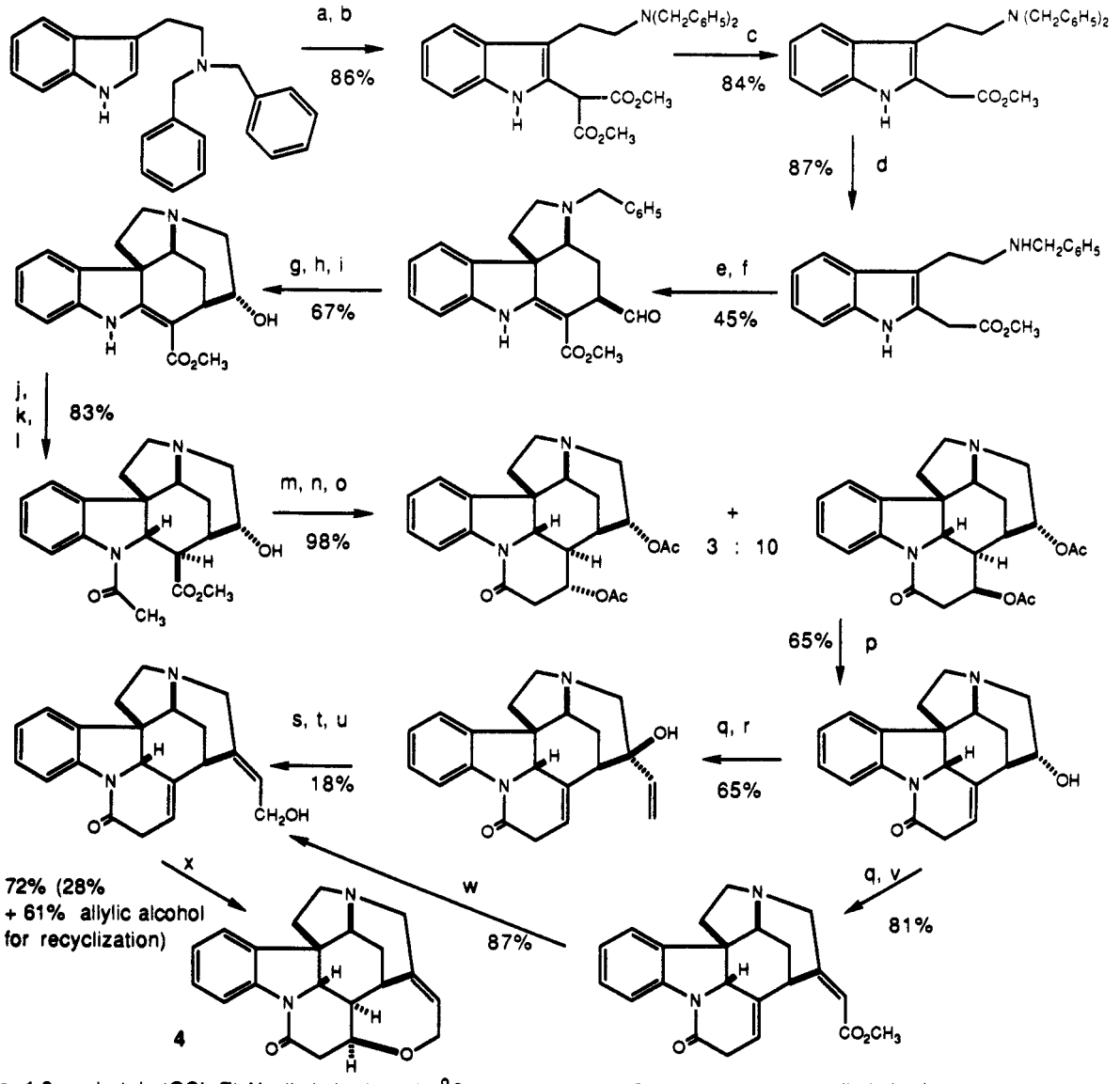


Fig. 2: Synthesis of echitamidine by path A



a: 1.3 equiv.*t*- butOCl, Et_3N, diethyl ether,-78 °C, 3h; **b**: 1.1 eqiv.Tl-dimethylmalonate, diethyl ether, -78 °C to r. t., 4h; **c**: 1.1 equiv. LiCl, 0.25 equiv. Et_3NHCl, DMF, 130 °C, 2.5 h; **d**: H_2,10%Pd/C, HOAc, r.t.; **e**: 1.5 equiv. 4,4-dimethoxybut-2-ene-1-al, 0.03 equiv. BF_3Et_2O, 4Å Molecular Sieves,toluene,18h reflux; **f**: 10% $HClO_4$, THF, r.t., 5h; **g**: 3.5 equiv. Me_3SI, 3.5 equiv. *n*-butLi, THF, -20 °C,followed by addition of aldehyde; **h**: reflux in MeOH, 24h; **i**: H_2, 10% Pd/C, MeOH; **j**: $NaBH_3CN$, HOAc, r. t., 30 min; **k**: Ac_2O, pyridine, r.t.,12 h; **l**: 4.0 equiv. NaOMe, MeOH, 0 °C, 40 min; **m**: 3.2 equiv. $LiN(SiMe_3)_2$, THF, reflux 30 min; **n**: $NaBH_4$, MeOH, 0 °C, 1h; **o**: Ac_2O, pyridine, 12h, r.t.; **p**: 10 equiv. DBU, dioxane : water (5:1), 100 °C, 10 h; **q**: Swern oxid.; **r**: 1.1 eqiv. $CH_2CHMgBr$, THF, 0 °C, 30 min; **s**: Ac_2O, Et_3N, DMAP, r. t. 24 h; **t**: $PdCl_2(MeCN)_2$, F_3CCO_2H, 46%; **u**: KOH,THF; Swern oxid. eql. 2:1; $NaBH_4$, $CeCl_3$; 42% overall; **v**: $(ETO)_2POCH_2CO_2CH_3$, hv equilib. 8:1; **w**: DIBALH, BF_3, -70°C; **x** :KOH, EtOH, 85 °C, 6h.

Fig. 4: Synthesis of rac. Strychnine (**4**) by path B