A TOTAL SYNTHESIS OF (±)-CORYDALIC ACID METHYL ESTER[1]

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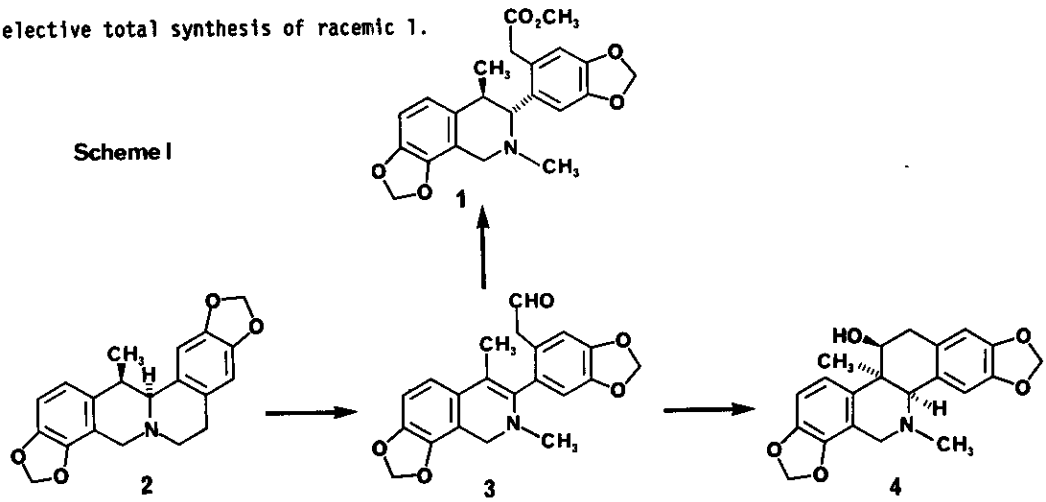
Abstract-A highly stereoselective synthesis of (±)-corydalic acid methyl ester (1) is reported. The key step involved cyclocondensation of the lithio derivative of amide 6 with imine 7 which afforded the trans-3-aryl-4-methyl-3,4- dihydro-1(2H)-isoquinolone 5 which was further elaborated to 1.

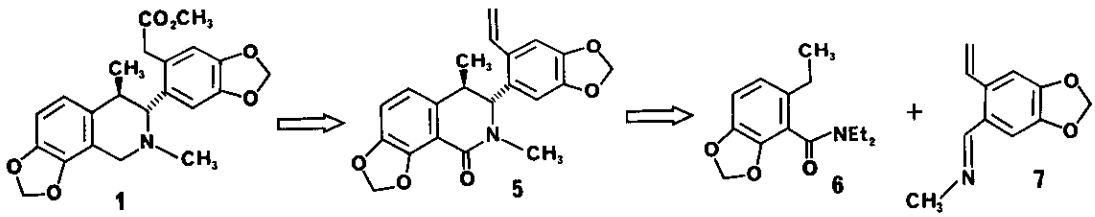
We have reported that 3-aryl-3,4-dihydro-1(2H)-isoquinolones are conveniently prepared by cyclocondensation of lithiated N,N-diethyl-o-toluamides with benzaldimines.[3,4] In order to further explore the generality of this methodology we undertook a synthesis of corydalic acid methyl ester (1), an alkaloid which has been isolated along with protoberberine and benzo[c]phenanthridine alkaloids from Corydalis incisa Pers.[5] Corydalic acid methyl ester is presumably derived biogenetically from aldehyde 3, a hypothetical intermediate in the well documented biosynthetic conversion of the tetrahydroprotoberberine alkaloids (e.g. tetrahydrocorysamine, 2) to the benzo[c]phenanthridines (e.g. corynoline, 4)[6] (Scheme I). Racemic corydalic acid methyl ester (1) has been the subject of a modestly stereoselective total synthesis[6] and of a biomimetic synthesis from the protoberberine alkaloid corysamine.[7] We now report the application of the cycloaddition methodology to a highly stereoselective total synthesis of racemic 1.

Scheme I

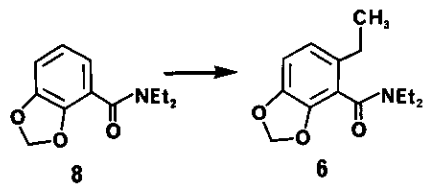


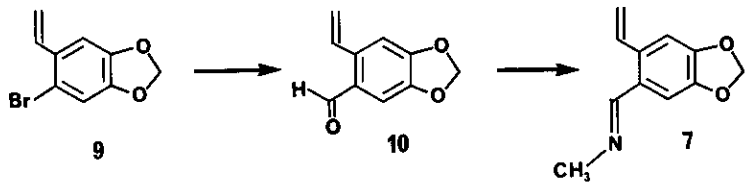
A retrosynthetic analysis (Scheme II) led to 5 as an ideal intermediate for conversion to corydalic acid methyl ester (1). Based on our earlier work,[4] it was anticipated that 5 would be stereospecifically produced from condensation of the lithio derivative of amide 6 with imine 7. These latter two intermediates were readily available from 2,3-methylenedioxybenzoic acid and piperonal, respectively, as shown in Scheme III. Alkylation of the lithio species derived from the N,N-diethyl-2,3-methylenedioxybenzamide (8) (sec-BuLi, TMEDA, THF, -70°C) with ethyl iodide afforded 6 in 55% yield. Imine 7 was prepared from the known bromo compound 9 (available by treatment of 6-bromopiperonal with methylene triphenylphosphorane)[8,9] by conversion to aldehyde 10 (1. n-BuLi; 2. DMF, acid workup) and treatment with aqueous methylamine (CH_2Cl_2, molecular sieves) in 86% overall yield.

Scheme II



Scheme III

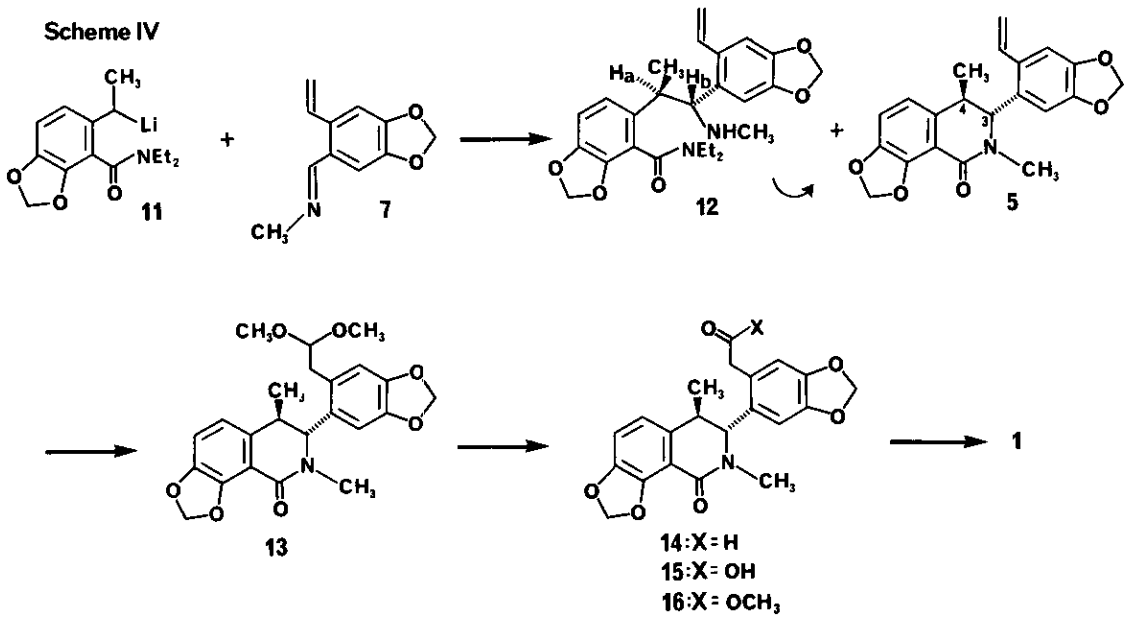




In the key step (Scheme IV) one equivalent of imine 7 was added to a -70°C solution of lithio species 11 (derived from treatment of 6 with LDA) in THF and the resulting mixture was stirred 2 h at -60°C and allowed to warm to room temperature. Workup[10] afforded adduct 12[11] as the main product (50% yield) along with the desired trans cycloadduct 5[12] (28% yield). Based on an analysis of the ^1H nmr spectrum[11], adduct 12 appeared to be a single

stereoisomer and the stereochemical assignment was based on the large coupling (10.5 Hz) of H_aH_b which is consistent with the completely staggered conformation expected for stereoisomer 12. Treatment of 12 with t-BuLi (2 equiv, THF, -70°C with warming to -30°C) gave clean conversion to 5 (84% yield). Thus, the overall yield of cycloadduct 5 was 70%. The trans stereochemistry of 5 follows from the small H_aH_b coupling constant (1.3 Hz) which is typical of trans-3,4-disubstituted dihydroisoquinolones.[4,13] We believe that the synthesis of 5 is stereospecific although we cannot discount the possibility that a small amount (<5%) of the cis-stereoisomer may have eluded chromatographic isolation.[14]

Scheme IV



Treatment of 5 with thallium trinitrate [7,15] in methanol gave dimethyl acetal 13 which was hydrolyzed (5% HCl, acetone, 50-60°C) to aldehyde 14. Oxidation of 14 ($KMnO_4$, benzene, water, Bu_4NBr)[16] to acid 15 followed by esterification with diazomethane afforded the known ester 16 (60% overall from 5) previously converted to corydalic acid methyl ester by Cushman and Wong.[6] Compound 16 had a melting point and ^1H nmr and mass spectral properties in accord with those reported.[17] Conversion of 16 to (±)-corydalic acid methyl ester (1) was accomplished according to the two-step procedure described by Cushman and Wong[6,18] (1. $POCl_3$; 2. $NaBH_4$, 66%; mp 145-147°C (acetone, pet. ether) lit. mp 144-147°C[6]). The synthetic 1 had ^1H nmr and mass spectral data in agreement with the literature[5-7] and was identical by tlc with an authentic sample.

Thus, we have utilized the lithiated toluamide-benzaldimine cycloaddition process in a convergent, highly stereoselective total synthesis of (±)-corydalic acid methyl ester which proceeded in 28% overall yield from the readily available intermediates 6 and 7.

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1. Contribution No. 760 from the Institute of Organic Chemistry.

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10. The reaction was quenched with aqueous ammonium chloride and extracted with CH_2Cl_2. The CH_2Cl_2 was evaporated and the residue was dissolved in EtOAc. Compound 12 crystallized from the EtOAc extract and 5 was isolated by medium pressure chromatography (EtOAc).

11. Compound 12: mp 210-214°C (EtOAc); ^{1}H nmr ($CDCl_3$) δ 1.10(t, 3H, J=7 Hz), 1.14(d, 3H, J=6.9 Hz), 1.34(t, 3H, J=7 Hz), 2.27(s, 3 H), 3.13(dq, 1H, J=6.9, 10.5 Hz), 3.28(m, 1 H), 3.45 (m, 2 H), 3.84(m, 1 H), 4.59(d, 1H, J=10.5 Hz), 5.36(dd, 1 H, J=0.8, 10.8 Hz), 6.01(d, 1H, J=1.4 Hz), 6.03(s, 2 H), 6.07 (d, 1H, J=1.4 Hz), 7.00(m, 3 H) 7.06 (d, 1H, J=8 Hz), 7.16(d, 1H, J=8 Hz); ms 438(M^+).

12. Compound 5: mp 199-202°C (EtOAc); ^{1}H nmr ($CDCl_3$) δ 1.40(d, 3H, J=7 Hz), 2.96(dq, J=1.3, 7 Hz), 3.06 (s, 3 H),4.66(d, 1H, J=1.3 Hz), 5.34(dd, 1H, J=1.1, 10.8 Hz), 5.60(dd, 1H, J=1.1, 17 Hz), 5.84 (d, 1H, J=1.4 Hz), 5.90(d, 1H, J=1.4 Hz), 6.12(d, 1H, J=1.3 Hz), 6.15(d, 1H, J=1.3 Hz), 6.34(s, 1H), 6.40(d, 1H, J=7.8 Hz), 6.75(d, 1H, J=7.8 Hz) 6.82(dd, 1H, J=10.8, 17 Hz), 6.97 (s, 1H); ms 365 (M^+).

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14. It is probable that the cis isomer, even if formed, would equilibrate to the trans under the strongly basic conditions. These points will be addressed in a full paper.

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17. Compound 16: mp 193-194°C(EtOAc, hexane); lit. mp 190-192°C(reference 6).

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