A TOTAL SYNTHESIS OF (+)-CORYDALIC ACID METHYL ESTER

Robin D. Clark and Jahangir
Institute of Organic Chemistry, Syntex Research, Palo Alto, California 94304, U.S.A.

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-toluidines with benzaldimines. 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[ε]phenanthridine alkaloids from Corydalis incisa Pers. 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. tetrahydrocoryamine, 2) to the benzo[c]phenanthridines (e.g. corynoline, 4) (Scheme 1). Racemic corydalic acid methyl ester (1) has been the subject of a modestly stereoselective total synthesis and of a biomimetic synthesis from the protoberberine alkaloid coryamine. We now report the application of the cycloaddition methodology to a highly stereoselective total synthesis of racemic 1.

Scheme 1
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, 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) by conversion to aldehyde 10 (1. n-BuLi; 2. DMF, acid workup) and treatment with aqueous methylamine (CH₂Cl₂, molecular sieves) in 86% overall yield.

Scheme II

| 1 | 5 | 6 | 7 |

Scheme III

| 8 | 6 |

| 9 | 10 | 11 |

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 afford adduct 12 as the main product (50% yield) along with the desired trans cycloadduct 5 (28% yield). Based on an analysis of the ¹H nmr spectrum, adduct 12 appeared to be a single
stereoisomer and the stereochemical assignment was based on the large coupling \(10.5\,\text{Hz}\) of \(\alpha_{\beta}\), which is consistent with the completely staggered conformation expected for stereoisomer 12. Treatment of 12 with \(\text{BuLi}\) (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 \(\delta_{\alpha_{\beta}}\) coupling constant (1.3 Hz) which is typical of trans-3,4-disubstituted dihydroisoquinolones.\(^4\)\(^\dagger\)\(^\dagger\) 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.\(^4\)\(^\dagger\)\(^\dagger\)

**Scheme IV**

\[
\begin{align*}
\text{H} & \text{c} & \text{Li} & \text{N} & \text{O} & \text{O} & \text{O} \\
\text{CH} & \text{N} & \text{CH} & \text{N} & \text{CH} & \text{O} & \text{O}
\end{align*}
\]

Treatment of 5 with thallium trinitrate \(^7\)\(^\dagger\)\(^\dagger\)\(^\dagger\) in methanol gave dimethyl acetal 13 which was hydrolyzed (5% \(\text{HCl}\), acetone, 50-60°C) to aldehyde 14. Oxidation of 14 (\(\text{KMnO}_4\), benzene, water, \(\text{Bu}_4\text{NBr}\))\(^6\) 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 \(^1\text{H}\) nmr and mass spectral properties in accord with those reported.\(^7\)\(^\dagger\)\(^\dagger\)\(^\dagger\) Conversion of 16 to \((\pm)\)-corydalic acid methyl ester (1) was accomplished according to the two-step procedure described by Cushman and Wong\(^6\)\(^\dagger\)\(^\dagger\)\(^\dagger\) (1. \(\text{POCl}_3\); 2. \(\text{NaBH}_4\), 66%; mp 145-147°C (acetone, pet. ether) lit. mp 144-147°C\(^6\)). The synthetic 1 had \(^1\text{H}\) nmr and mass spectral data in agreement with the literature\(^5\)\(^\dagger\)-\(^7\)\(^\dagger\) and was identical by tlc with an authentic sample.

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

We thank Dr. J. Muchowski for his encouragement and valuable discussions during the course of this work and Lani Russell for preparing the manuscript. We are grateful to Professor Mark Cushman for providing an authentic sample of 1.

REFERENCES AND NOTES

10. The reaction was quenched with aqueous ammonium chloride and extracted with CH₂Cl₂. The CH₂Cl₂ 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); ¹H nmr (CDCl₃) 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), 3.20 (m, 1H), 3.45 (m, 2H), 3.84 (m, 1H), 4.59 (d, 1H, J=10.5 Hz), 5.36 (dd, 1H, J=0.8, 10.8 Hz), 6.01 (d, 1H, J=1.4 Hz), 6.03 (s, 2H), 6.07 (d, 1H, J=1.4 Hz), 7.00 (m, 3H), 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); ¹H nmr (CDCl₃) δ 1.40 (d, 3H, J=7 Hz), 2.96 (dq, J=1.3, 7 Hz), 3.06 (s, 3H), 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⁺).
14. It is probable that the cis isomer, even if formed, would equilibrate with the trans under the strongly basic conditions. These points will be addressed in a full paper.
17. Compound 16: mp 193-194°C(EtOAc, hexane); lit. mp 190-192°C(reference 6).

Received, 30th November, 1987