Application of Isatoic Anhydride Chemistry to the Synthesis of Racemic Paraensine

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The alkaloid paraensine was obtained in racemic form in 84% overall yield by a two step reaction sequence which involves a hetero ring opening of *N*-methylisatoic anhydride with the lithium enolate of 4,5-dihydro-4,5,5-trimethyl-2(3*H*)-furanone followed by a thermal cyclization.

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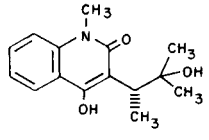
In a previous publication from this laboratory 4-hydroxy-3-(2-hydroxyalkyl)-1-methyl-2(1*H*)-quinolones were efficiently prepared from the reaction of *N*-methylisatoic anhydride with γ- and δ-lactone derivatives [1]. Recently, several quinolin-2-one alkaloids were isolated from the heartwood of the Brazilian tree *Euxylophora paraensis* (Rutaceae). One of the alkaloids, paraensine (**1**), is optically active and by means of X-ray crystallographic analysis its structure and absolute stereochemistry were elucidated [2].



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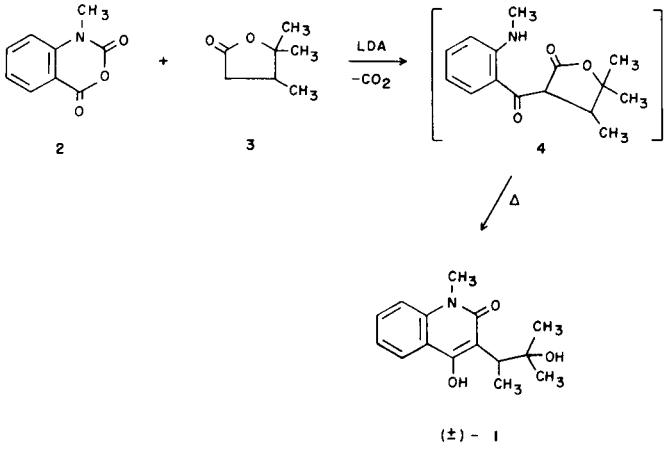
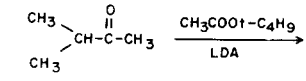
The similarity between the skeletal structure of paraensine and our previously described 3-(2-hydroxyalkyl)-2-quinolones makes this molecule ideally suited for synthesis utilizing that methodology.



2 3 4

(±) - 1

The required reactants, *N*-methylisatoic anhydride (**2**) and 4,5-dihydro-4,5,5-trimethyl-2(3*H*)-furanone (**3**), are readily available. *N*-Methylisatoic anhydride can be purchased commercially [3] and is very inexpensive. Lactone 3 is easily prepared in two steps. The initial reaction, an Aldol condensation of 3-methyl-2-butanone (**5**) with lithio *t*-butyl acetate, proceeds cleanly to give the β-hydroxyester **6** in high yield. Subsequent cyclization to the lactone was accomplished with concentrated sulfuric acid according to the method of Dobrev and Ivanov [4].



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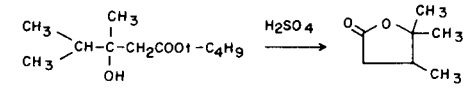

6 3

The reaction of **2** with the lithium enolate of the butyrolactone derivative **3** proceeds very rapidly with both starting materials being consumed upon completion of the addition of **2**. The intermediate β-ketolactone **4**, when heated in toluene for 90 minutes, cyclizes with concomitant fission of the lactone ring to directly produce racemic paraensine in high yield (84% overall). The product crystallizes directly from the reaction mixture and is isolated analytically pure simply by filtration. All spectral data from our product is identical to the published spectra for the natural product [2].

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover Unimelt apparatus and are uncorrected. The infrared spectra were recorded on either Perkin-Elmer Model 257 and 457, or Analect FX-6200 spectrophotomers. Absorption frequencies are quoted in reciprocal centimeters. The proton nmr spectra were recorded on EM-360 and Jeol FX-90-Q spectrometers using TMS as an internal reference. Chemical shifts are quoted in parts per million (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet).

The carbon-13 magnetic resonance spectra were obtained in the Fourier transform mode on a Jeol FX-200 spectrometer system. The spectra were obtained at an observing frequence of 50.1 MHz. Sample concentrations were ca. 0.1 molar in 5 (od) sample tubes. General nmr spectral and instrumental parameters employed were: Internal deuterium lock to the solvent; spectral width of 10000 Hz; a pulse width of 3 μs

corresponding to a 45° pulse angle, and a pulse repetition time of 1.8 seconds. For all spectra, 16K time-domain points were used. All shifts reported are referenced to internal TMS and are estimated to be accurate to ±0.05 ppm.

Enolate generating reactions were conducted under a nitrogen atmosphere using tetrahydrofuran which was freshly distilled over lithium aluminum hydride. No attempt has been made to optimize the yields of the described reactions.

3-Hydroxy-3,4-dimethylpentanoic Acid *t*-Butyl Ester (**6**).

To a solution of 12.5 g (0.12 mole) of diisopropylamine in 250 ml of tetrahydrofuran (at 0°) was added 75 ml of a 1.65 *M* solution of *n*-butyllithium in hexane. After stirring for five minutes, a solution of 12.8 g (0.11 mole) of *t*-butyl acetate in 50 ml of tetrahydrofuran was added dropwise. The mixture was then cooled to -78° and stirring was continued for 1.5 hours. Then a solution of 8.6 g (0.1 mole) of 3-methyl-2-butanone (**5**) in 100 ml of tetrahydrofuran was added dropwise. After stirring at -78° for 2 hours, the mixture was allowed to warm to -40° at which point 250-300 ml of 2*N* hydrochloric acid was added. This mixture was poured into 250 ml of water and was extracted twice with ether. The organic phase was washed with water until neutral and was dried over magnesium sulfate.

The solvent was removed under reduced pressure to give 14.6 g (72%) of essentially pure **6** [2]. This was used in the next reaction without further purification; ir (neat): 3506, 1710 cm^{-1}; nmr (deuteriochloroform): δ 3.78 (s, 1H), 2.39 (d, 2H, J = 2.5 Hz), 2.0-1.56 (m, 1H), 1.5 (s, 9H), 1.16 (s, 3H), 0.98 (d, 3H, J = 3.5 Hz), 0.9 (d, 3H, J = 3.5 Hz).

4,5-Dihydro-4,5,5-trimethyl-2(3*H*)-furanone (**3**).

Ester **6** was converted to the lactone **3** by treatment with concentrated sulfuric acid according to the prodedure of Dobrev and Ivanov [4]; ir (neat): 1779 cm^{-1}; nmr (deuteriochloroform): δ 2.8-2.1 (m, 3H), 1.45 (s, 3H), 1.28 (s, 3H), 1.1 (d, 3H, J = 6.7 Hz).

(±)-Paraensine ((±)-**1**).

To a solution of 2.0 g (0.02 mole) of diisopropylamine in 75 ml of tetrahydrofuran (at -30°) was added 1.28 g (0.02 mole) of *n*-butyllithium (1.65 *M* in hexane) [5]. After cooling to -65°, a solution of 1.28 g (0.01 mole) of **3** in 20 ml of tetrahydrofuran was added dropwise and the mixture was stirred at -65° for 1 hour. To this was slowly added a solution of 1.77 g (0.01 mole) of *N*-methylisatoic anhydride (**2**) in 30 ml of tetrahydrofuran. After stirring at -65° for 10 minutes, the reaction was quenched with 100 ml of saturated ammonium chloride solution. The organic phase was separated and the aqueous layer was extracted twice with methylene chloride. The organic solutions were combined and dried over sodium sulfate. The solvent was removed under reduced pressure to give 2.8 g of a yellow solid (acyclic intermediate **4**). The solid was dissolved in 35 ml of toluene and the solution was refluxed for 90 minutes (after 45 minutes a precipitate formed). The mixture was allowed to cool to room temperature and the precipitate was filtered and washed with ether to give 2.2 g (84%) of (±)-**1**, mp 213-216°, lit [2] mp 217-218°; ir (chloroform): 3604, 3140, 1631 cm^{-1}; nmr (deuteriochloroform): δ 11.20 (s, 1H, enol OH), 8.06 (dd, 1H), 7.65-7.10 (m, 3H), 3.77 (q, 1H), 3.71 (s, 3H, NCH_3), 3.46 (s, 1H, OH), 1.50 (s, 3H), 1.31 (d, 3H, J = 7 Hz), 1.28 (s, 3H); ^{13}C-nmr (deuteriochloroform): δ 164.28, 157.94, 138.70, 130.36, 123.97, 121.48, 117.37, 113.51, 112.70, 75.59, 40.22, 30.03, 29.27, 28.68, 12.64.

Anal. Calcd. for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.32; N, 5.36. Found: C, 68.88; H, 7.51; N, 5.33.

REFERENCES AND NOTES

[1] G. M. Coppola, *J. Heterocyclic Chem.*, in press.

[2] L. Jurd, M. Benson, and R. Y. Wong, *Aust. J. Chem.*, **36**, 759 (1983).

[3] The 1984 Chem Sources-U.S.A lists 22 suppliers.

[4] A. Dobrev and C. Ivanov, *Synthesis*, 562 (1977).

[5] An Extra equivalent of LDA is required to satisfy the highly acidic proton of the developing β-ketolactone **4**.