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A STEREOSELECTIVE SYNTHESIS OF THE ANT TRAIL PHEROMONE (±)-MONOMORINE I

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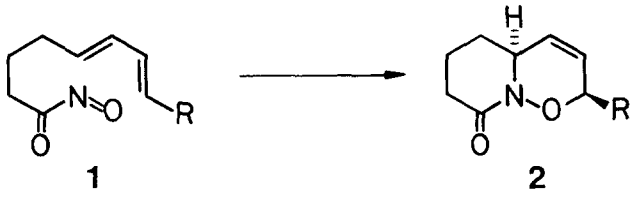
Abstract: A stereoselective synthesis of the ant trail pheromone monomorine I is described utilizing a bicyclic 1,2-oxazine intermediate.

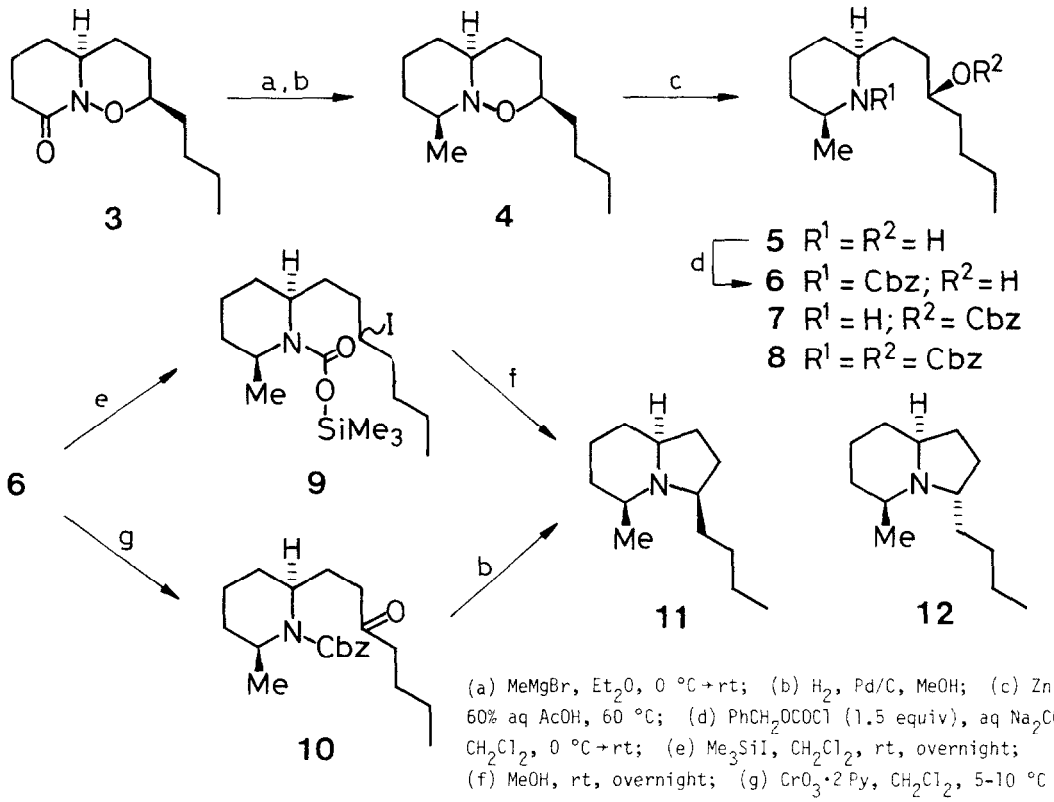
Recently we have demonstrated that the bicyclic 1,2-oxazine 2, formed by intramolecular "hetero Diels-Alder reaction" of the N-acyl nitroso compound 1 (eq 1), is a versatile intermediate for the synthesis of an indolizidine alkaloid gephyrotoxin 223AB.[1] In a continuation of our research in this area, we now wish to report the successful extension of this reaction to the synthesis of monomorine I (11). This substance, isolated as one of the trail pheromones from Pharaoh ants (Monomorium pharaonis L.),[2] has been determined its relative stereochemistry by nonstereoselective synthesis.[3,4] More recently, a stereospecific synthesis of racemic 11[5] and a chiral synthesis of the (-)-enantiomer of natural 11[6] were reported.



1 2 (1)

Our synthesis was initiated with the Grignard reaction of the bicyclic 1,2-oxazine 3[1] using MeMgBr in ether (0 °C → room temperature) to generate the unstable enamine, which was then immediately hydrogenated (Pd/C, MeOH) leading to a single isomer 4 in 70% overall yield: ^{1}H NMR ($CDCl_3$) δ 0.90 (t, J = 7.0 Hz, 3 H), 1.09 (d, J = 6.6 Hz, 3 H), 1.20-2.45 (series of m, 18 H), 3.86 (m, 1 H). Compound 4 was subjected to N-O bond cleavage by treatment with zinc in 60% aqueous acetic acid (60 °C, 9 h) to give the amino alcohol 5 in 68% yield: mp 69-71 °C; ^{1}H NMR ($CDCl_3$) δ 0.90 (t, J + 7.0 Hz, 3 H), 1.10 (d, J = 6.6 Hz, 3 H), 1.20-2.45 (series of m, 16 H), 2.65 (m, 2 H), 3.3-3.8 (br, 2 H with m, 1 H at δ 3.51). Treatment of 5 with benzyl chloroformate (1.5 equiv, aqueous Na_2CO_3, CH_2Cl_2) afforded the benzyl carbamate 6 (53% yield): IR ($CHCl_3$) 3550-3330, 1680 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.90 (t, J = 7.0 Hz, 3 H), 1.18 (d, J = 6.6 Hz, 3 H), 1.25-1.17 (16 H), 3.60, 4.19, 4.38 (br, 1 H each), 5.13 (s, 2 H), 7.25-7.44 (5 H). This reaction was accompanied by the formation of 7 (6%) and 8 (32%) which could readily be reverted to starting 5 by hydrogenolysis (Pd/C, MeOH) in quantitative yield. Thus the actual yield of 6 based on recovered 5 was 85%.

When exposed to iodotrimethylsilane at room temperature (CH_2Cl_2), 6 underwent C-O bond cleavage[7] along with iodination to produce the silyl ester 9. In situ cyclization was carried out by treating 9 in methanol at room temperature to provide (±)-monomorine I (11) and its C-3 epimer (12) in 42% and 40% yield from 6, respectively. Synthetic 11 so produced exhibited the



(a) MeMgBr, Et_2O, 0 °C → rt; (b) H_2, Pd/C, MeOH; (c) Zn, 60% aq AcOH, 60 °C; (d) $PhCH_2OCOCl$ (1.5 equiv), aq Na_2CO_3, CH_2Cl_2, 0 °C → rt; (e) Me_3SiI, CH_2Cl_2, rt, overnight; (f) MeOH, rt, overnight; (g) $CrO_3 \cdot 2$ Py, CH_2Cl_2, 5-10 °C

spectra (^{1}H NMR,[8] ^{13}C NMR, mass) identical with authentic (-)-monomorine I. Synthetic 12 showed ^{13}C NMR data identical with the published data.[3c] An appreciated improvement of the diastereoselectivity in the cyclization to monomorine I was obtained by the following sequence. With compound 6 in hand, the ketone 10 was prepared by Collins oxidation in 94% yield: IR ($CHCl_3$) 1715, 1680 cm^{-1}. On catalytic hydrogenation of 10, (±)-monomorine I (11) was obtained in 71% yield, along with (±)-3-epimonomorine I (12) in 15% yield.

Further work to investigate the utility of bicyclic 1,2-oxazines for the synthesis of nitrogenous natural product is currently being carried out in our laboratories.

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References and Notes

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(8) The chemical shift values reported for (-)-monomorine I in ref 6 are all shifted downfield by ca. 0.5 ppm probably due to incorrect calibration.

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