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Synthesis of the Alkaloids (-)-Heliotridane and (-)-Isoretronecanol *via* π-Allyltricarbonyliron Lactam Complexes.

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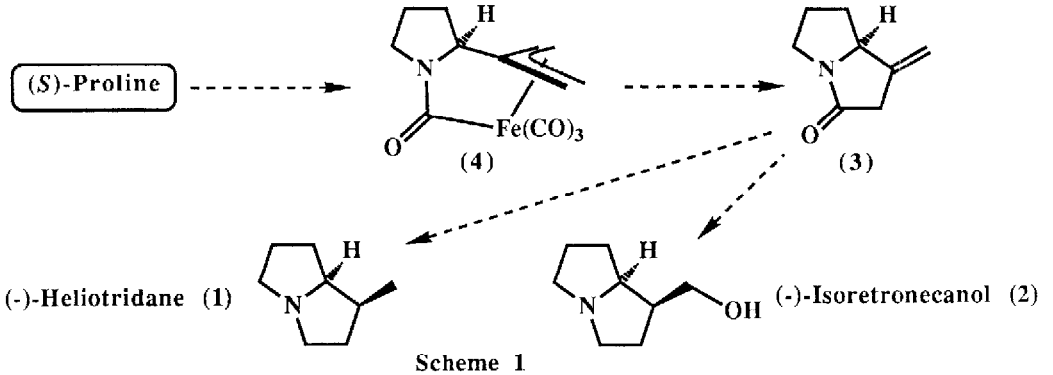
Abstract: *A novel synthesis of the pyrrolizidine alkaloids (-)-heliotridane (1) and (-)-isoretronecanol (2) is described. The key steps involve the conversion of a proline-derived carbamate (10) into the π-allyltricarbonyliron lactam complex (4) and the exhaustive carbonylation of this to give the pivotal intermediate γ-lactam (3). Lactam (3) has been converted into the title compounds by standard methods.*

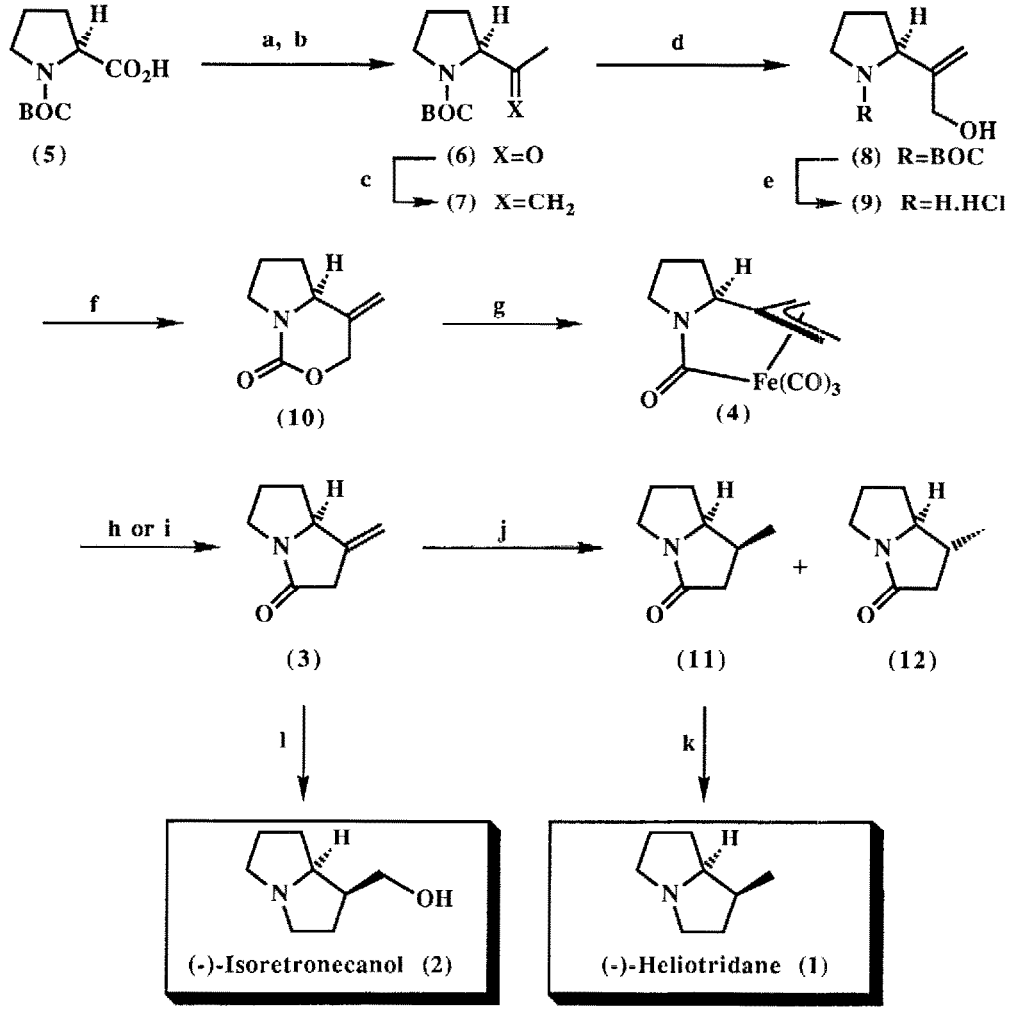
The chemistry of π-allyltricarbonyliron lactone and lactam complexes has been investigated by our group for several years.[1,2,3] The synthetic utility of these complexes arises from the ability to oxidise them to the corresponding β-lactones and lactams and to carbonylate the lactone complexes to give δ-lactones. Several natural products have been synthesised using this methodology.[1,4,5] We recently reported a new method for the preparation of iron lactone complexes *via* 1,2-diol cyclic sulphites[3] and, in the course of extending this procedure to the synthesis of the corresponding lactam complexes, we have devised a new route to pyrrolizidine alkaloids.

Although many approaches to the synthesis of necine bases such as heliotridane (**1**) and isoretronecanol (**2**) have been reported,[6,7] few of these give enantiomerically pure material.[8-10] We considered the possibility that both of these alkaloids might be prepared from the unsaturated γ-lactam (**3**) which, in turn, might arise from oxidation or carbonylation of the unusual π-allyltricarbonyliron lactam complex (**4**). It was hoped that complex (**4**) could be obtained in enantiomerically pure form from (*S*)-proline (scheme 1). This letter describes the successful accomplishment of this goal.



Scheme 1

Commercially available (*S*)-*N*-BOC-proline (**5**) was converted into the corresponding *N*-methyl-*N*-methoxy amide[11] *via* an acyl imidazolide. Treatment of this intermediate amide with methyl magnesium chloride gave the ketone (**6**)[12,13] in excellent yield (scheme 2). Wittig reaction of ketone (**6**) with methylene triphenylphosphorane produced the corresponding alkene (**7**)[12] in 98% yield.



a. CDI, THF, r.t. 1h; MeONHMe.HCl; 24h (98%); b. MeMgCl (3 eq.), THF, 0°C, 5h; r.t., 16h (91%); c. $Ph_3P{=}CH_2$ (2 eq.), Et_2O, 0°C, 2h (98%); d. SeO_2, ^tBuOOH (2 eq.), CH_2Cl_2, 35°C, 4h (58%); e. HCl, $CHCl_3$, r.t., 15min (100%); f. MeOCOCl, Et_3N, CH_2Cl_2, r.t., 4h; NaH, PhMe, r.t., 2h (60%); g. $Fe_2(CO)_9$, PhH, .))), 4h (98%); h. $Ce(NH_4)_2(NO_3)_6$ (4 eq.), MeCN, -30°C, 3h (26%);i. CO (305 atm.), C_6H_6, 105°C, 48h (80%); j. H_2, 10% Pd/C, EtOAc, r.t., 16h (73%); k. $LiAlH_4$ (ref. 18); l. BH_3, THF, reflux, 1.5h; NaOH, H_2O_2, 1h; HCl, MeOH, reflux, 2h (ref. 18).

Scheme 2

The conversion of this alkene into the alcohol (**8**) was achieved by allylic oxidation using stoichiometric selenium dioxide in the presence of ^{t}butyl hydroperoxide.[14] This reaction produced the required allylic alcohol (**8**)[12] in modest yield (58%) together with minor amounts of the corresponding enal (from overoxidaton) and the product of allylic oxidation α to nitrogen. Deprotection of the nitrogen atom was accomplished by treatment of a chloroform solution of (**8**) with dissolved HCl and the hydrochloride salt (**9**) was used without further purification.

The cyclic carbamate (**10**)[12] was prepared from (**9**) in 60% yield using methyl chloroformate. We were pleased to discover that treatment of the carbamate (**10**) with diiron nonacarbonyl in benzene under ultrasonication[15] gave the π-allyltricarbonyliron lactam complex (**4**)[12] in an excellent 98% yield.[16,17] This is the first time that a cyclic carbamate has been used to produce a π-allyltricarbonyliron lactam complex.

Because the allyl unit of this complex is joined to the rest of the molecule *via* the central carbon, both oxidation and exhaustive carbonylation should produce the same unsaturated lactam. The oxidative removal of iron using ceric ammonium nitrate in acetonitrile at low temperature was found, however, to give a poor yield of the γ-lactam (**3**) (26%). Exhaustive carbonylation under the conditions developed for lactone complexes (70°C, 250 atm.) failed to give any product. More forcing conditions (105°C, 305 atm.) were found to be necessary and the lactam (**3**)[12,18] was obtained in good yield (80%). This reaction constitutes the first conversion of a π-allyltricarbonyliron lactam complex into the corresponding lactam by exhaustive carbonylation.

Hydrogenation of (**3**) using 10% palladium on charcoal gave the amides, (**11**) and (**12**), in a ratio of 7:2 respectively (scheme 2). Mori has reported[19] the conversion of racemic (**11**) into (±)-heliotridane (**1**) and of racemic (**12**) into (±)-pseudoheliotridane and our work thus constitutes formal syntheses of these products in enantiomerically pure form. The racemic lactam (**5**) has also been converted into (±)-isoretronecanol (**4**) by treatment with diborane.[19] Following this procedure, we obtained (-)-isoretronecanol which was isolated as its stable picrate salt.[20]

In summary, we have developed an efficient, novel synthesis of two pyrrolizidine alkaloids. The pivotal intermediate (**3**) may also be suitable for conversion into other alkaloid natural products such as (-)-supinidine.[22] The general approach outlined here should also be applicable to the synthesis of other pyrrolizidine and indolizidine alkaloids.

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16. The corresponding cyclic sulphamidite and sulphamidate behave in a similar way to the carbamate (**10**). This work will be described elsewhere.
17. Preparation of complex (**4**): A mixture of $Fe_2(CO)_9$ (350 mg, 1.0 mmol) and the carbamate (**10**) (26 mg, 0.17 mmol) in dry benzene (15 ml) was sonicated under Ar for 4h. Toluene (5 ml) was added and the mixture was filtered through talc. Most of the solvent was removed under reduced pressure to leave a green solution in toluene. Flash chromatography on silica (2 g) eluting with petroleum ether (b.p. 40-60°C)-diethyl ether (gradient 2:1 to 0:1) gave the iron complex (**4**) (46 mg, 98%) as needles, m.p.110-115°C (slow dec.); $[\alpha]_D^{20}$ +88.5 (c= 0.26, $CHCl_3$); $\upsilon_{max.}$ (film) 2007 s (CO), 1981 s (CO), and 1568 cm^{-1} (C=O); δ_H(500 MHz, $CDCl_3$) 1.74 (1H, m, one of CH_2CH_2C), 1.9-2.0 (1H, m, one of CH_2CH_2C), 2.01-2.06 (1H, m, one of CH_2CH_2C), 2.13 (1H, br s, allyl-H_{endo}), 2.13-2.19 (1H, m, one of CH_2CH_2C), 2.56 (1H, br s, allyl-H_{endo}), 2.98 (1H, ddd, J 2.8, 9.3, 11.7 Hz, one of CH_2N), 3.60 (1H, br s, allyl-H_{exo}), 3.62 (1H, dt, J 11.7, 8.4 Hz, one of CH_2N), 3.89 (1H, dd, J 5.2, 10.6 Hz, CHN), and 4.11 (1H, d, J 2.8 Hz, allyl-H_{exo}).
18. For lactam (**3**): $[\alpha]_D^{20}$ -125 (c= 0.44, $CHCl_3$); $\upsilon_{max.}$ (film) 2964, 1696 (C=O), 1663 (C=C), and 1388 cm^{-1}; δ_H(500 MHz, $CDCl_3$) 1.4-1.5 (1H, m, one of CH_2CH_2), 1.97-2.14 (3H, m, three of CH_2CH_2), 3.06-3.12 (2H, m, one of CH_2N and obscured br d, J 21 Hz, one of CH_2CO), 3.42 (1H, br.d, J 21 Hz, one of CH_2CO), 3.68 (1H, dt, J 11.6, 8.0 Hz, one of NCH_2), 4.34-4.37 (1H, m, NCH), 5.02-5.03 (1H, m, C=CH), and 5.04-5.05 (1H, m, C=CH).
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