A SHORT AND EFFICIENT SYNTHESIS OF (±)-ISORETRONECANOL AND (±)-TRACHELANTHAMIDINE

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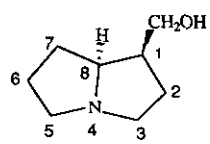
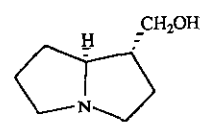
Abstract- Radical decarboxylation of N-protected proline in the presence of dimethyl fumarate gave a thiopyridyl adduct 5 which was readily transformed into isoretronecanol 1 and trachelanthamidine 2.

Pyrrolizidine alkaloids have stimulated a great deal of interest because of their diverse biological activities.[1] The two simplest members of the necine family only (isoretronecanol 1 and trachelanthamidine 2) have been the target of a large number of synthesis.[2]A recent review covers literature dealing with the synthesis of the pyrrolizidine framework from 1978 up to 1987.[2d]

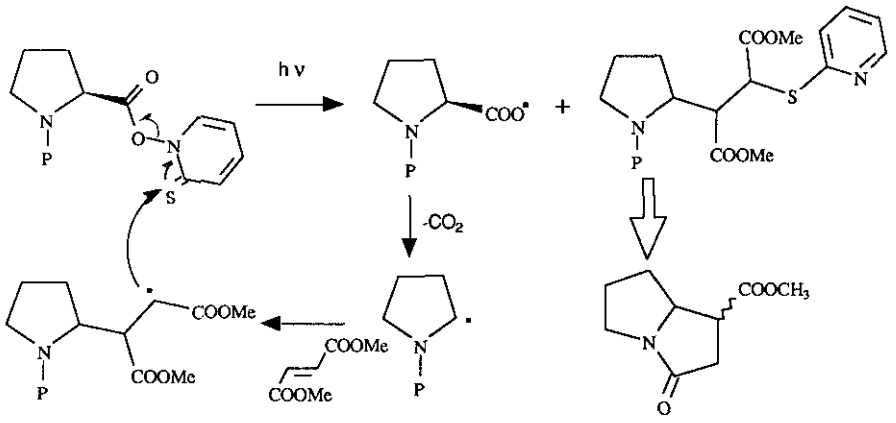


1 Isoretronecanol



2 Trachelanthamidine

During the course of our study on Barton's radical decarboxylation of amino acids, we had shown that trapping of the radical derived from the thiohydroxamate derivative of N-protected proline by an electron deficient olefin was quite efficient.[3] We, therefore, thought that if the same radical was trapped by dimethyl fumarate, it would lead readily to a precursor of isoretronecanol 1 (Scheme I). The desulfurization followed by deprotection of the amine should provide the bicyclic framework. The reduction of the bicyclic product had been previously described in the literature.[2]



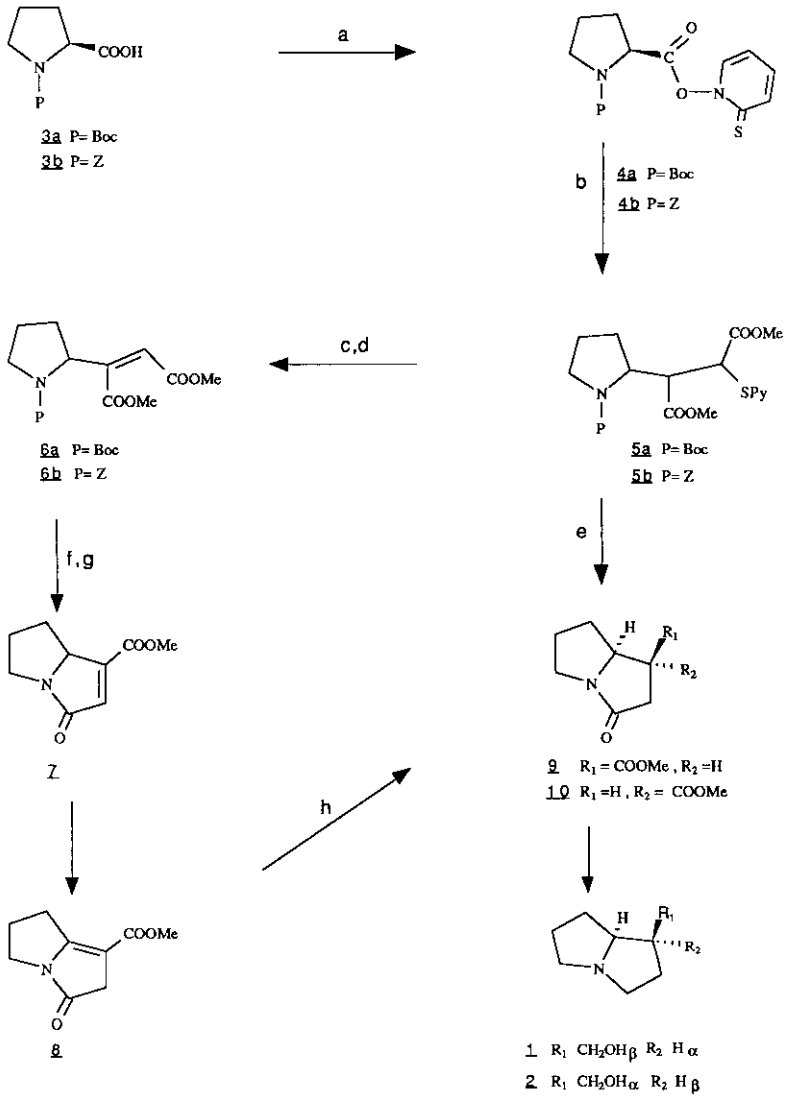
Scheme I

The thiohydroxamic derivative 4a was prepared from Boc L-proline 3a (Boc= t-butyloxycarbonyl) according to the procedure already described.[3] Irradiation of 4a with 2 X 100 W tungsten lamps in the presence of dimethyl fumarate (5 equiv.) led to the adduct 5a[4] as a mixture of diastereoisomers in 82% yield. In order to determine if there was any stereoselectivity during the addition of the intermediate radical on the olefin, the thiopyridyl group was removed through thermolysis in refluxing toluene of the intermediate sulfoxides obtained by oxidation of 5a with meta-chloroperbenzoic acid. The ratio of epimers at C_1 (1:2) was deduced from nmr spectrum of the olefinic product 6a.[5]

Cleavage of the Boc group by treatment of 6a with trifluoroacetic acid followed by careful neutralization with aqueous ammonia of the trifluoracetate salt gave the bicyclic product 7 in 73% yield.[6] Purification of this product on silica gel caused the double bond to migrate to a tetrasubstituted position and yielded a crystalline product 8.[2b,c,6] Catalytic hydrogenation of 8 provided the saturated compound 9.[2a,b,c] The reduction with $LiAlH_4$ of 9 gave (±)-isoretronecanol, the picrate of which had mp 187-188°C (lit. 188-189°C [2c]).

In a similar manner, starting from Z- L-proline 3b (Z= benzyloxycarbonyl) the sequence of reactions shown on Scheme II led to the addition product 5b and then to the olefin 6b in 67 and 46 % yields respectively. In this case, the ratio of epimers at C_1 was 1:1 as estimated from the nmr spectrum of 6b.[7] The sulfur adduct 5b[4] was transformed in one step through Raney nickel treatment[8] in refluxing methanol into the bicyclic compound in 42% yield. HPLC analysis[9] of the resulting product showed that it was a mixture of the two epimers 9 and 10, which could be separated by column chromatography on silica gel.

Thus, this approach using radical chain mechanism provides us with a straightforward entry to pyrrolizidine framework starting from readily available N-protected proline.



Scheme II

a:N-Methylmorpholine, iso-ButOCOCl, 2-mercaptopyridine 1-oxide sodium salt, 1 h, -15°C ; b: 1h, dimethyl fumarate (5 equiv.), room temperature; c: MCPBA (1 equiv.), $CHCl_3$, 1 h; d: reflux in toluene, 1 h; e: when P=Z, washed Raney nickel in methanol, reflux, 90 min; f: when P=Boc, trifluoroacetic acid,1 h,room temperature; g: neutralization with 17% NH_4OH; h: H_2 , Pd/C, atm. pressure, room temperature.

REFERENCES AND NOTES

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3. D.H.R. Barton, Y. Herve, P. Potier, and J. Thierry, Tetrahedron, 1987, 43, 4297.
4. 5a ^{1}H Nmr ($CDCl_3$, 80 MHz) δ 1.47 and 1.53(2s,9H), 1.69-2.20(m,4H), 2.91-3.57(m,3H), 3.57 and 3.65(2s,3H), 4.02-4.52(m,1H), 5.02-5.45(m,1H), 6.89-7.65(m,3H),8.30-8.50(m,1H); ms m/z 425 (MH^+).
   5b ^{1}H Nmr ($CDCl_3$, 80 MHz) δ 1.72-2.20(m,4H), 3.12-3.55(m,3H), 3.55 and 3.61(2s,3H), 4.55-4.98(m,1H), 4.98-5.43(m,3H), 6.82-7.66(m,8H), 8.25-8.50 (m,1H); ms m/z 458 ($M^{+\cdot}$) 254.
5. The oxidation reaction was carried out using one equivalent of meta-chloroperbenzoic acid in chloroform for one hour at room temperature. The solution in toluene of the sulfoxides so obtained was refluxed for one hour. Yield after column chromatography around 61%. 6a ^{1}H-Nmr ($CDCl_3$, 200 MHz) δ 1.40 and 1.46(2s,9H,Boc), 2.16-2.25(m,2H), 2.25-2.48(m,1H), 3.26-3.48(m,2H), 3.80(s,6H),5.25-5.46(m,1H,CHN), 6.60(s,1H,C=CH)
6. 7 crystallizes from ether, mp 80°C. ^{1}H Nmr ($CDCl_3$,200 MHz) δ 1.03-1.36(m, 1H,C(7)H, 2.13-2.50(m,3H,C(6)2H,C(7)H), 3.23-3.43(m,1H,C(5)H), 3.43-3.69(m,1H,C(5)H), 3.86(s,3H,$COOCH_3$), 4.36-4.56(m,1H,C(8)H), 6.70(s,1H, C(2)H. 8 was not reported as a solid in ref. 2b. It crystallizes from ether mp 80-81°C. ^{1}H Nmr($CDCl_3$,200 MHz) δ 2.36(quint.,2H,C(7)2H), 2.81 -3.01(m,2H,C(6)2H), 3.4-3.66(m,4H,C(2)2H,C(5)2H).
7. 6b ^{1}H-Nmr ($CDCl_3$, 400 MHz) δ 1.73-1.98(m,1H), 1.91-2.25(m,2H), 2.28-2.48(m,1H), 3.36-3.58(m,1H), 3.70(s,7H), 5.04 and 5.08(2s,2H,CH_2-Ar), 6.60 and 6.68(2s,1H,C=CH), 7.29 and 7.33(2s,5H,Ar)
8. The reagent used was Raney nickel from Aldrich washed with methanol to neutral pH. The reagent was added to a solution of the addition product 5b in methanol and the reaction mixture was refluxed for one and half hour. The reagent was filtered and the solvent was removed under vacuum. Chromatography on silica gel SDS Chromagel 60 A CC 40-60μ gave the two isomers 9 and 10.
9. HPLC on a RESOLVE Waters 5μ spherical silica gel column, mobile phase: ethyl acetate/heptane (1/1), flow rate 2 ml/mn, showed a mixture of 9 and 10 (1/2.5), retention time 9 t = 6.4 min, 10 t = 9.8 min.

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