Tetrahedron Letters Vol. 22, pp 719 - 722 0040-4039/81/0215-0719$02.00/0

A DIASTEREOSELECTIVE ROUTE TO (±)-ISORETRONECANOL

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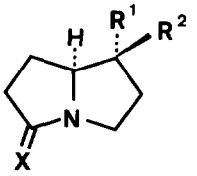
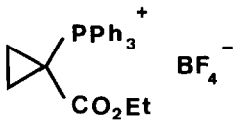
Abstract: N-Unsubstituted imides react with 1-carboethoxycyclopropyltriphenylphosphonium tetrafluoroborate to yield N-acyl-Δ^2-pyrroline, pyrrolizidine, and indolizidine derivatives.

There is much interest[1] in 1-substituted pyrrolizidine derivatives because of the wide distribution of alkaloids containing these compounds and their wide range of physiological properties[2,3,14].

We report on the total synthesis of one of the simplest members of this series of alkaloids - (±)-isoretronecanol (1a). The key step in this approach is the reaction of sodium succinimide with 1-carboethoxycyclopropyltriphenylphosphonium tetrafluoroborate (2)[4] in boiling xylene. Separation of the crude product by silicagel column-chromatography and purification by crystallization from n-hexane affords 1-carboethoxy-$\Delta^{1,8}$-dehydro-5-oxo-pyrrolizidine (3)[5,6] in 84.1 % yield[7] (m.p. 62°C). Subsequent reduction of the double bond with platinum dioxide in acetic acid[8] proceeds quantitatively with high stereoselectivity. The purity of the colourless oil was determined by GLC analysis, which revealed the presence of 2.5 % of (±)-exo-1-carboethoxy-5-oxo-pyrrolizidine (1d) beside 97.5 % of the thermodynamically less stable (±)-endo-ester 1c[9,10]. 1c is converted into (±)-isoretronecanol (1a)[11] by reduction with lithium aluminium hydride in 83.2 % yield.





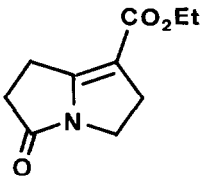
1a $R^1 = H,\ R^2 = CH_2OH,\ X = H_2$

b $R^1 = CH_2OH,\ R^2 = H,\ X = H_2$

c $R^1 = H,\ R^2 = CO_2Et,\ X = O$

d $R^1 = CO_2Et,\ R^2 = H,\ X = O$

2



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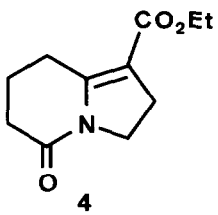

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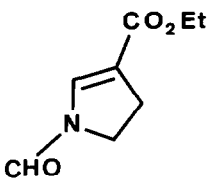

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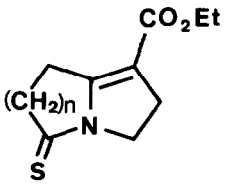
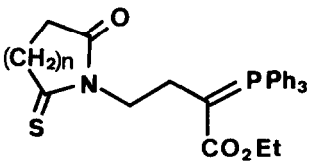
Since 1c epimerizes to 1d with 1,5-diaza-bicyclo(4.3.0)non-5-en in boiling benzene (60 %)[8] the synthetic pathway described herein also provides an approach to (±)-trachelathamidine (1b).

The reaction of the cyclopropylphosphonium salt 2 with the anions of glutarimide and diformylimide under the reported conditions results in the production of the indolizidine 4 (68.4 %), and the pyrrolidine 5 (47.3 %) respectively.

We also investigated the possibility of converting monothioimides into the annelated bicycles, since A. Gossauer[12] reports that thioimides should react with phosphoranes readily and regiospecifically at the thiocarbonyl group[13]. Under basic conditions in boiling xylene the reaction of monothiosuccinimide and monothioglutarimide with 2 leads disappointingly to low yields of the expected products 3 (27.9 %), and 4 (14.6 %), the thioderivatives 6a (19.7 %), and 6b (6 %) and the products of the nucleophilic ring opening 7a (29.2 %) and 7b (13.7 %) are found as well.



6a n = 1
b n = 2



7a n = 1
b n = 2

We are working on the application of this methodology to the synthesis of more complex pyrrolizidines and of the mitomycin skeleton.

This investigation was supported by the Deutschen Forschungsgemeinschaft.

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2. W.W. Huskin, and D.H.G. Crout, J.C.S. Perkin I 1977, 538.
3. A recent review: D.J. Robins, Adv. Heterocycl. Chem. 24, 247 (1979); see also: W.N. Speckamp, and P.M.M. Nossin, Tetrahedron Lett. 1979, 4411; H.W. Pinnick, and Y.H. Chang, J. Org. Chem. 43, 4662 (1978); D.J. Robins, and S. Sakdarat, J.C.S. Chem. Commun. 1979, 1734; H.W. Pinnick, and Y.H. Chang, Tetrahedron Lett. 1979, 837; S.R. Wilson, and A. Sawicki, J. Org. Chem. 44, 287 (1979).
4. P.L. Fuchs, J. Amer. Chem. Soc. 96, 1607 (1974).
5. The structures of all new compounds are supported by IR, ^{1}H-NMR, MS and correct analytical data.
6. The reaction presumably involves nucleophilic ring opening of the cyclopropylphosphonium salt 2 to give a stabilized ylide (see compounds 7), which subsequently undergoes an intramolecular Wittig reaction. As Wittig reactions often are sterically hindered, we first treated 1-carboethoxycyclopentan-2-one with 2 and obtained the expected pentalene derivative[8].
7. IR: (KBr) ν (cm^{-1}) = 1715 (s, -CO_2Et), 1680 (s, N-CO-), 1645 (s, C=C). ^{1}H-NMR: ($CDCl_3$) δ (ppm) = 1.28 (t, J = 7 Hz, 3H, -CH_3), 2.85 (m, 4H),

3.10 (unsym. t, J = 9 Hz, 2H), 3.62 (m, 4H), 4.16 (q, J = 7 Hz, 2H, $-CH_2-O-$). ^{13}C-NMR: ($CDCl_3$) δ (ppm) = 171.105 (s), 164.346 (s), 159.472 (s), 101.326 (s), 58.672 (t), 40.020 (t), 32.806 (t), 31.116 (t), 20.263 (t), 13.634 (q).

8. P. Wernsmann, Diplomarbeit. Münster 1980.
9. IR: (NaCl) ν (cm^{-1}) = 1725 (s, $-CO_2Et$), 1690 (s, -CO-N). ^{1}H-NMR: ($CDCl_3$) δ (ppm) = 1.19 (t, J = 7 Hz, 3H, $-CH_3$), 1.5-1.8 (m, 1H), 2.0-2.74 (m, 6H), 2.78-3.16 (m, 2H), 3.6-3.9 (m, 1H), 4.4 (t, J = 7 Hz, 2H, $-CH_2-O-$). ^{13}C-NMR: ($CDCl_3$) δ (ppm) = 174.290 (s), 171.495 (s), 62.052 (d), 59.542 (t), 44.309 (d), 40.085 (t), 32.741 (t), 29.232 (t), 20.848 (t), 13.114 (q).
10. Under the conditions of GLC separation (Carbowax, 12 %, 4 m, 220°C or OV 17, 4 %, 1.7 m, 180°C) the epimerisation of 1c to the thermodynamically more stable exo-isomer 1d cannot be excluded; therefore the amount of 1d herein determined is considered to be the lowest limit.
11. The melting point of the picrate (192-194°C, from EtOH) corresponds closely with that reported in the literature[3] (190-192°C). The IR spectrum is in accordance with a published spectrum of an authentic sample: N.K. Kochetkov, A.M. Likhosherstov, and A.S. Lebedeva, Zh. Obshch. Khim. 31, 3461 (1961). Also does the ^{1}H-NMR spectrum: S. Danishefsky, R. McKee, and R.K. Singh, J. Amer. Chem. Soc. 99, 4783 (1977).
12. A. Gossauer, R.P. Hinze, and H. Zilch, Angew. Chem. 89, 429 (1977); A. Gossauer, L. Ernst, F. Rößler, and H. Zilch, Liebigs Ann. Chem. 1979, 1309.
13. We aimed at the regioselective annelation of substituted monothioimides.
14. For a recent synthesis of (±)-isoretronecanol see: G.A. Kraus, K. Neuenschwander, Tetrahedron Lett. 1980, 3841.

(Received in Germany 15 November 1980)