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A NEW STEREOCONTROLLED SYNTHESIS OF (+)-PEDERINE. UNUSUAL CONFORMATION AROUND C-10—C-11 BOND IN PEDERINE DERIVATIVES

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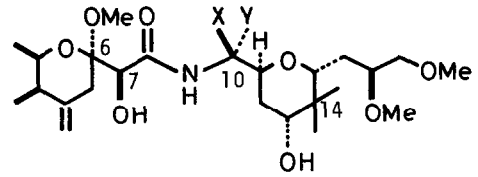
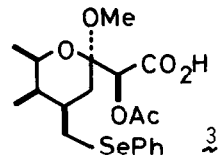
Abstract: Kinetically controlled epimerization of a dihydro-10-epipederine derivative 13 through an alkoxy exchange reaction at C-10 afforded a dihydropederine derivative 12, which was converted into pederine 1.

In previous papers we reported the first total synthesis of the potent insect poison, (+)-pederine 1.[1,2] In the final step of the synthesis, however, the ratio of pederine 1 to (+)-10-epipederine 2 was not satisfactory (1:3). In the present paper we wish to show that the ratio can be inverted to 60:14. In essence, the new synthesis involves as key steps connection of (+)-selenoacid 3 and methyl pedimidate 5 obtained from (+)-pedamide 4,[1] selective conversion of a (+)-dihydro-10-epipederine derivative 13 into a (+)-dihydropederine derivative 12 by acid catalyzed double alkoxy-exchange reaction[3] and generation of the exo-double bond at a later step.



X=OMe, Y=H 1
X=H, Y=OMe 2



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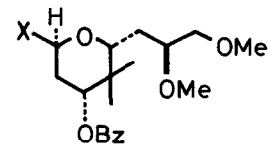
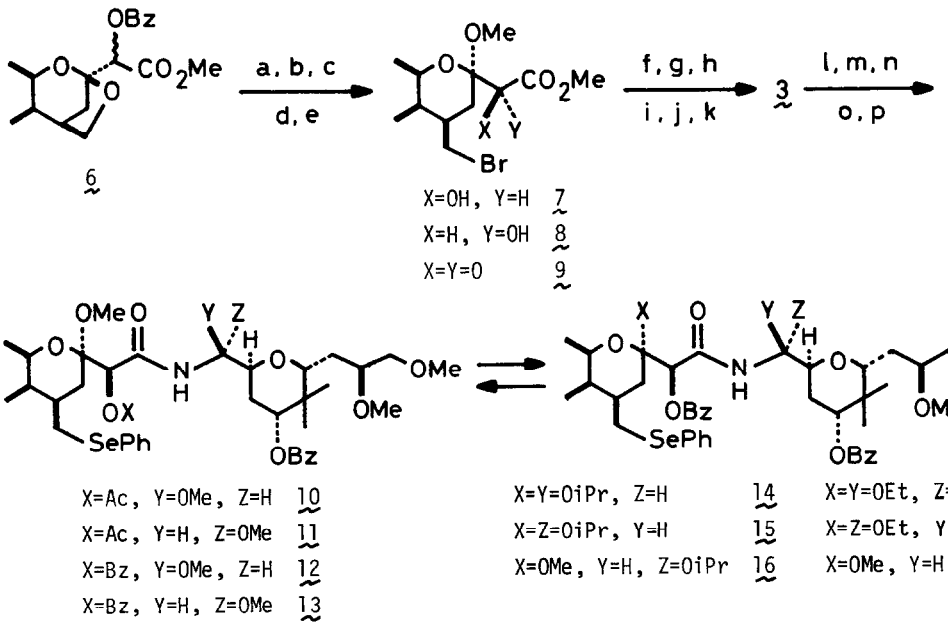


X=CONH$_2$ 4
X=C(OMe)=NH 5

Preparation of the (+)-selenoacid 3[4a] originated with a 2,7-dioxabicyclo[3.2.1]octane derivative 6,[4a] which was synthesized through a similar route to the racemic one[5] from (+)-2,3-epoxybutane. Compound 6 was first converted into a 1:1 mixture of two tetrahydropyrans, (+)-7[4a] and (+)-8[4a] by the sequence of reactions (Fig 1). The mixture gave on oxidation with Collins reagent a (+)-ketone 9[4b] as a single product in 47% overall yield[6] from 6. Reduction of 9 with sodium borohydride (MeOH, -78 °C) afforded the desired β-alcohol 7 in 75% yield[6] together with a 15% yield[6] of the epimer 8, which was recycled. Conversion of 7 into 3 was effected in 45% overall yield (Fig 1). Methyl pedimidate 5,[4b] obtained from (+)-pedamide 4,[1] and 3 were connected together through the N-(1-methoxyalkyl)amide linkage by the sequence of reactions[1] (Fig 1) to give an epimeric mixture of N-(1-methoxyalkyl)amides, 10[4b] and 11[4b] in 72% overall yield from 4. Conversion of the acetyl group into a benzoyl group[7] afforded after separation a 18% yield of

Fig 1



6

X=OH, Y=H 7
X=H, Y=OH 8
X=Y=O 9

X=Ac, Y=OMe, Z=H 10
X=Ac, Y=H, Z=OMe 11
X=Bz, Y=OMe, Z=H 12
X=Bz, Y=H, Z=OMe 13

X=Y=OiPr, Z=H 14
X=Z=OiPr, Y=H 15
X=OMe, Y=H, Z=OiPr 16

X=Y=OEt, Z=H 17
X=Z=OEt, Y=H 18
X=OMe, Y=H, Z=OEt 19

(a) $Ph_3P{\cdot}Br_2$, MeCN, reflux, 3 h [A. G. Anderson, Jr. and F. J. Freenor, J. Am. Chem. Soc., 86, 5037 (1964)] (b) AcCl, MeOH, r.t., 12 h (c) MeONa, MeOH, r.t., 20 min (d) $CrO_3{\cdot}2Py$, CH_2Cl_2, r.t., 1 h (e) $NaBH_4$, MeOH, -78 °C, 30 min (f) BzCl, DMAP, Py, r.t., 12 h (g) $(PhSe)_2$, $NaBH_4$, MeOH, reflux, 2 h (h) Et_3N, H_2O, MeOH, r.t., 12 h (i) Ac_2O, Py, r.t., 12 h (j) $HN(c\text{-}C_6H_{11})_2$, AcOEt, r.t., 30 min (k) 1N-HCl, AcOEt, r.t., 5 min (l) $SOCl_2$ (1.4 equiv.), Py (1.9 equiv.), CH_2Cl_2, r.t., 5 min (m) 5 (0.67 equiv.), Et_3N (1.9 equiv.), CH_2Cl_2, r.t., 2 h (n) $NaBH_4$, EtOH, 0 °C, 30 min (o) 1N-LiOH, MeOH, r.t., 2 h (p) BzCl, DMAP, Py, r.t., 12 h.

the (+)-dihydropederine derivative 12 and a 62% yield[6] of the (+)-dihydro-10-epipederine derivative 13.[4b]

Treatment of 13 with AcCl (0.67 M) in isopropanol (r.t.) afforded after 7 days selectively 6α,10α-diisopropoxy compound 15 as a single and thermodynamically stable product through initial formation of the kinetically controlled product 6α,10β-diisopropoxy isomer 14. Kinetically controlled methoxylation of 15 with AcCl (0.23 M) in methanol (r.t., 4.5 h) proceeded stereoselectively to give at 58% conversion a 60% yield[6] (based on consumed 15) of 10β-methoxy compound 12 and a 14% yield[6] of 10α-methoxy compound 13, the 10α-isopropoxy compound being recovered in 42% yield in the form of 6α-methoxy compound 16.[4b] The recovered amide in turn afforded the same mixture of 12, 13 and 16 almost quantitatively by the similar HCl treatment in methanol (r.t., 3.5 h). At 100% conversion the ratio of 12:13 was 2:3. Similar treatment of 13 in ethanol gave 17[4b] and 18[4b] in a ratio of 1:4 at equilibrium, through initial formation of 17. Methoxylation (MeOH, 0.23 M AcCl) of 18 proceeded more slowly (r.t., 10 h) than that of 15, and afforded at 50% conversion 12 and 13 in 2:1 ratio.[8] The stereochemistry at C-10 of the above described alkoxy isomers was inferred from δ values of their NH protons. The NH protons of 10R and 10S pederine derivatives generally exhibit peaks at δ 7.7-8.0 and δ 6.6-6.8, respectively (Table 1).

As a rule 10S derivatives were more stable than 10R derivatives.

The dihydropederine derivative 12 thus obtained was converted into (+)-pederine 1 in three steps and 73% overall yield[6] by (1) oxidation with sodium periodate (MeOH, r.t., 1 h), (2) elimination of phenylselenic acid in a mixture of benzene and triethylamine (reflux, 30 min), and (3) debenzoylation (1N-LiOH, MeOH, r.t., 3 h). The synthetic pederine was identical with the natural product in all respects (IR, ^{1}H-nmr, mp, mmp, $[\alpha]_D$, and TLC mobilities with several different solvent systems).

The small $J_{10\text{-}11}$ values for acyl derivatives of 10R- and 10S-pederine series (Table 1) indicated that in both series H_{10} and H_{11} are arranged in a gauche form, contrary to expectation based on naive conformational analysis. Partial conformations 20 and 21 were assigned to 10S and 10R compounds respectively (Fig 2), since (a) the presence of conformation 20 in a diacyl pederine derivative in crystalline state has already been demonstrated by X-ray[9] (b) stability of conformation 20 is reasonably explained by the attractive O/O gauche effect,[10] out of the two possible O/O gauche conformations for the 10S compounds, 20 is estimated to be preferred (c) δ values for the amide proton (Table 1) show the presence of a hydrogen bond between NH and the ethereal oxygen atom in the 10-epi compounds. On the other hand exchange of the C-10 methoxyl group by a ethoxyl group of 12 produced a small but distinctive shielding effect (Table 1) on 14β-methyl group. A similar effect (Table 1) was observed in the 10-epi compounds 13 and 18, in which the alkoxyl group is necessarily situated upon the ring, supporting the above conformation 21.[11]

Fig 2

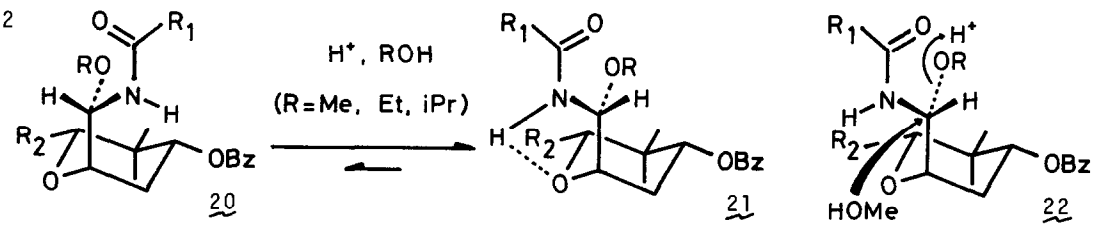


Table 1

	Compound	$\delta_{N\text{-}H}$	$J_{NH\text{-}10}$ (Hz)	$J_{10\text{-}11}$ (Hz)	$\delta_{14\text{-dimethyl}}$ α	$\delta_{14\text{-dimethyl}}$ β
10S	10	6.61	9.77	4.15	1.003	1.003
	12	6.69	9.77	3.67	1.003	0.996
	17	6.75	9.76	4.15	1.009	0.961
	dibenzoyl 1	6.77	9.77	4.40	1.008	0.988
10R	11	7.73	9.28	3.91	1.033	0.920
	13	7.80	9.77	3.42	1.044	1.030
	16	7.94	9.77	3.66	1.066	0.965
	18	7.80	9.27	3.67	1.048	1.014
	19	7.87	9.28	3.42	1.055	1.002

The spectral data were obtained at 400 MHz in $CDCl_3$.

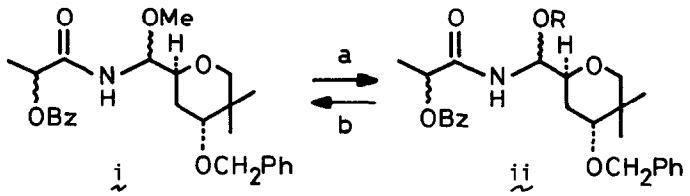
Increased thermodynamic stability of the 1OR compounds over the corresponding 1OS compounds is well understood by ascribing it to the presence of the NH····O hydrogen bond in the former compounds (Fig 2). Observed decreasing rate order isopropoxy > ethoxy > methoxy epi-compounds in the alkoxy exchange reaction in methanol is accounted for by the conformational instability of the starting materials. On the basis of these preferred conformations 20 and 21, kinetically controlled conversions of 1OR compounds 15, 16, 18 and 19 into 12 and 1OS compounds 14 and 17 into 13 are nicely rationalized by transition states such as 22, in which methanol attacks from the less hindered site (Fig 2).

References and Notes

(1) F. Matsuda, M. Yanagiya, and T. Matsumoto, Tetrahedron Lett., 23, 4043 (1982).

(2) M. Yanagiya, F. Matsuda, K. Hasegawa, and T. Matsumoto, Tetrahedron Lett., 23, 4039 (1982), and references cited therein.

(3) In the course of studying reactivities of model N-(1-alkoxyalkyl)amides i[4b] and ii[4b] (both diastereomeric mixture) under acidic conditions, it turned out that an alkoxy-exchange reaction of N-(1-alkoxyalkyl)amides takes place almost quantitatively in an alcoholic solvent (r.t., 0.23 M AcCl) as shown below. A large alkoxyl group in ii accelerated the reaction. Contrary to expectation, however, all attempts to achieve direct epimerization of 2 or dibenzoyl 2 by acid treatment in methanol were fruitless because of their lability under acidic conditions. Compounds 12 and 13 were stable to acids.



i ii

R=Et (a) EtOH, 1.5 h
(b) MeOH, 25 min
R=iPr (a) iPrOH, 4 h
(b) MeOH, 15 min

(4) (a) Satisfactory spectral and analytical data were obtained for this compounds. (b) Satisfactory spectral data were obtained for this compound.

(5) K. Tsuzuki, T. Watanabe, M. Yanagiya, and T. Matsumoto, Tetrahedron Lett., 4745 (1976).

(6) Isolated yield (silica gel chromatography).

(7) This conversion was essential for separation of the epimers. The C-7 acetoxyl compounds were labile under acidic conditions.

(8) Treatment of 13 in methanol (0.67 M AcCl, r.t., 3 h) gave an equilibrium mixture of 12 and 13 almost quantitatively. The ratio of 12:13 was 1:3.

(9) A. Furusaki, T. Watanabe, T. Matsumoto, and M. Yanagiya, Tetrahedron Lett., 6301 (1968).

(10) N. S. Zefirov, L. G. Gurvich, A. S. Shashkov, M. Z. Krimer and E. A. Vorobera, Tetrahedron, 32, 1211 (1976).

(11) However, pederine and 10-epipederine shows in $CDCl_3$ J_{10-11} 8.05 and 6.0 Hz respectively, indicating large population of the H_{10}/H_{11} anti conformer in pederine. The reason is not clear at present.

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