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TOTAL SYNTHESIS AND UNAMBIGUOUS STEREOCHEMICAL ASSIGNMENT OF DISODIUM PREPHENATE

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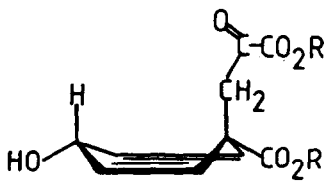
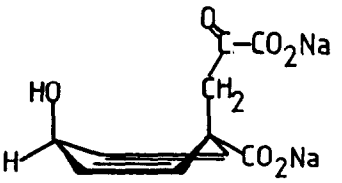
Prephenic acid (1a), in form of its salts, represents the essential intermediate in the biosynthesis of aromatic compounds, starting from carbohydrates[1]. Most of bacteria, micro-organisms and lower plants follow this pathway. During a long period of investigations, *Davis*[2] could assure the existence of 1. The formulation of the structural formula by *Weiss*[3], deduced only from the rearrangement by acid and alkali, the catalytic hydrogenation, the uv, and the analysis of the barium salt 1b is a masterpiece, considering that similar 2,5-cyclohexadienols became known only much later. Because of its exceptional constitution, possessing the labile dienol- and pyruvate-skeletons, prephenic acid (1a) is only stable in form of its salts 1b and 1c for a longer time[4].



1



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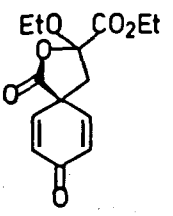


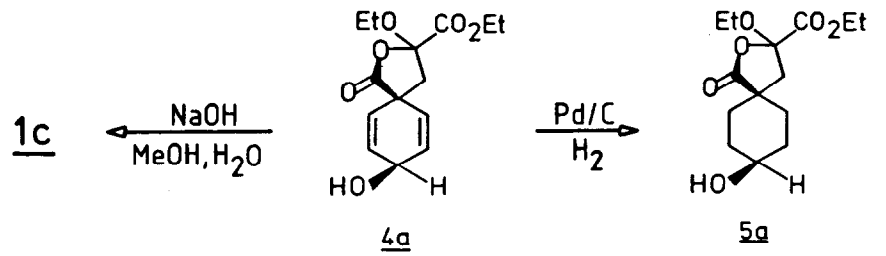
3

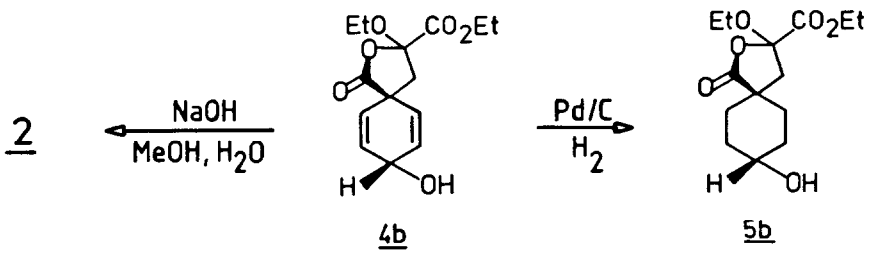
1a R= H
1b R=½Ba
1c R= Na

The synthesis of prephenic acid is as fascinating as it is difficult, because of its high tendency to aromatize. Many unsuccessful attempts of the synthesis were prosecuted[4-6].
So far, pure barium prephenate (1b) has been isolated from culture filtrates of special mutants of Escherichia coli, a tyrosine auxotroph of Salmonella typhimurium and a triple mutant of Neurospora crassa[7]. Recently, *Danishefs-*

ky and *Hirama*[8] succeeded in the total synthesis of 1c, using a Diels-Alder route. Our general advance implying a new synthesis of dienones *via* seleno enones was recently described[9].

The convenient intermediate for the synthesis of 1 is the dienone 3, a compound of extreme lability[10]. 3 was reduced with 9-BBN[11] to a mixture of the diastereomers 4a and 4b (ratio 4a:4b = 4:3)[12]. Separation was completed by chromatography on silica gel. After careful hydrolysis under alkaline conditions and following lyophilization, 4a gave a sample of disodium prephenate (1c). The ^1H NMR spectrum (in D_2O) was identical with those, reported in literature[7,8].





The other diastereomer 4b gave in the same manner a disodium salt 2. The two spectra were very similar but clearly different in detail. Thus, the difference in the two broad triplets of the allylic hydrogens is only $\Delta = 0.05$ ppm - the signal of prephenate 1c at higher field[13]. The signals of the two methylene protons could be obtained at 3.17 ppm (1c) and at 3.22 ppm (2), while *Danishefsky*[8] didn't get them (exchange in basic D_2O). Both of the disodium salts 1c and 2 could easily be transferred to phenylpyruvate by adding acid and afterwards alkali (λ_{max}=320 nm, pH 9).

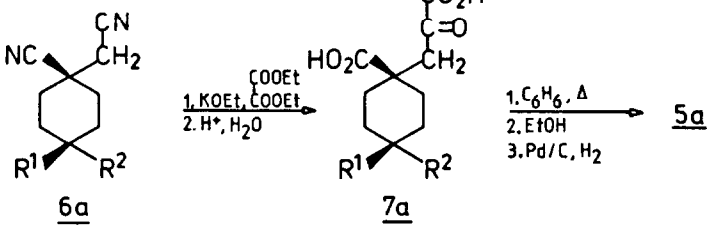
Now, we can prove the configuration of the dienols 4a and 4b by synthetical compounds of well-known configuration. The connecting links for stereochemical assignment were the spiro alcohols 5a and 5b, which could be synthesized in a stereospecific way, outlined in Scheme 1 (with regard to clearness, only one epimer 5a is shown; the synthesis of 5b takes the same course).

Starting materials for the synthesis of 5a and 5b were the two dinitriles

6a and 6b, which could be easily separated from each other by recrystallization[14,15].

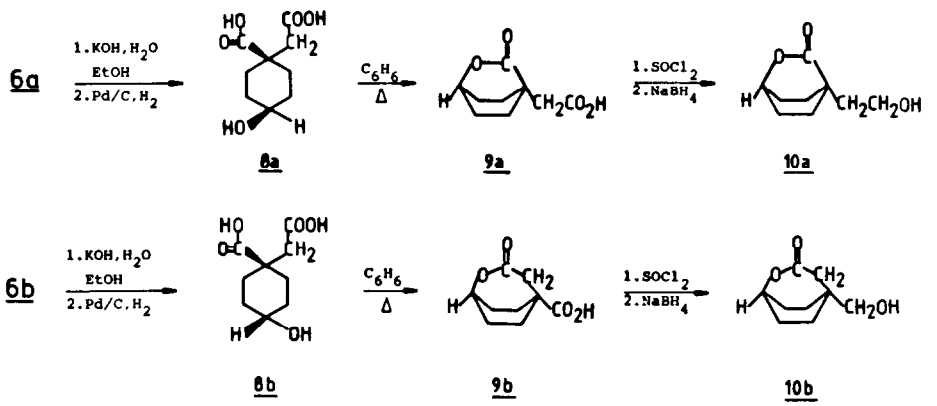
Scheme 1

	R^1	R^2
6a, 7a	$OCH_2C_6H_5$	H
6b, 7b	H	$OCH_2C_6H_5$



The configuration of the latter, previously[14] conjectured by different rates of esterification, could now be established in the following way, outlined in Scheme 2; the two isomers 10a and 10b could easily be assigned by their ^1H NMR spectra.

Scheme 2



Finally, the cyclohexadienols 4a and 4b were hydrogenated over 10% Pd/C. The NMR spectrum of the hydrogenated 4a was identical with the spectrum of 5a,

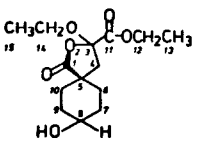


Table 1. 60 MHz ^1H NMR spectra ($CDCl_3$) of compounds 5a and 5b in ppm from TMS (multiplicity, coupling constants [Hz])

	OH	8-H	12-H	14-H	13-H	15-H	4-H	cyclohex.-H
5a	2.7	3.80	4.3(q,7.2)	3.72(m)	1.3(t)	1.2(t,7.2)	2.30(s)	2.5-1.0
5b	2.1	3.70	4.3(q,7.1)	3.70(m)	1.3(t)	1.2(t,7.2)	2.38 [a]	2.3-0.8

[a] J_{AB} = 13.8 Hz

synthesized independently, while the product of the hydrogenation of 4b was identical with 5b.

Table 2. ^{13}C Chemical Shifts ($CDCl_3$) of 5a and 5b (in ppm relative to TMS)

	C-1	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10	C-11
5a	179.18	102.95	43.26	44.17	29.90[a)]	29.45	66.26	29.45	30.15[a)]	167.96[c)]
5b	180.01	103.25	43.28	43.81	32.87[b)]	31.13	68.62	31.13	32.23[b)]	167.85[d)]

a,b) These signal assignments may be reversed

c) Remaining ^{13}C signals of 5a: C-12: 61.93; C-13: 14.09; C-14: 62.42; C-15: 15.37

d) 5b: C-12: 61.98; C-13: 14.09; C-14: 62.48; C-15: 15.38

In this way, the stereochemical assignment of prephenate proposed 1961 by paper chromatographical comparison[16)] of hydrogenated prephenate with synthetic tetrahydroprephenates could now be confirmed without doubt.

References and Notes

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