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(15) A 4-ft glass column of 1% QF 1 was used for the GC analysis. The GC–MS operating conditions were as follows: column temperature, 170 °C; flash heater, 225 °C; separator, 240 °C; ion source 250 °C; trap current, 65 μA; ionizing voltage, 70 eV.
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Roy A. Johnson,* Eldon G. Nidy
Lubomir Baczynskyj, Robert R. Gorman
Experimental Chemistry Research
Physical and Analytical Chemistry Research, and
Experimental Biology Research, The Upjohn Company
Kalamazoo, Michigan 49001
Received July 18, 1977

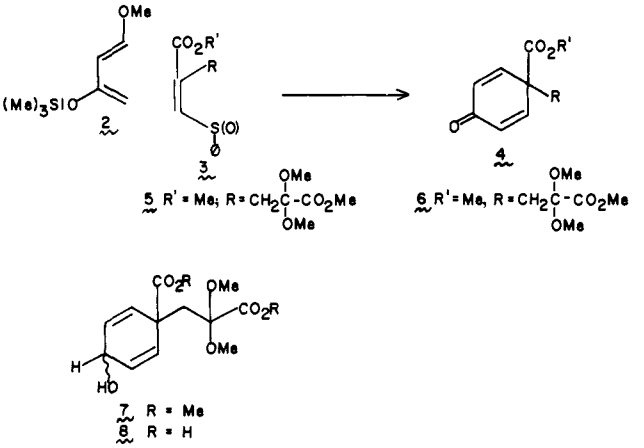
Total Synthesis of Disodium Prephenate

Sir:

Prephenic acid (**1**), stable only in its dicarboxylate form (**1a, 1b**), is the central intermediate in the biological production of the aromatic rings of phenylalanine and tyrosine.[1] Its existence was inferred and established after extensive research by Davis.[2] Given the fragility of prephenate and the paucity of degradative and analytical data, the formulation of its structure by Weiss et al.[3] was an accomplishment of considerable magnitude. The stereochemistry of prephenic acid was surmised to be that shown in **1** by Plieninger and co-workers[4,5] by the paper chromatographic comparison of the 2,4-DNP derivative of tetrahydroprephenic acid, with a sample of known stereochemistry obtained through synthesis.

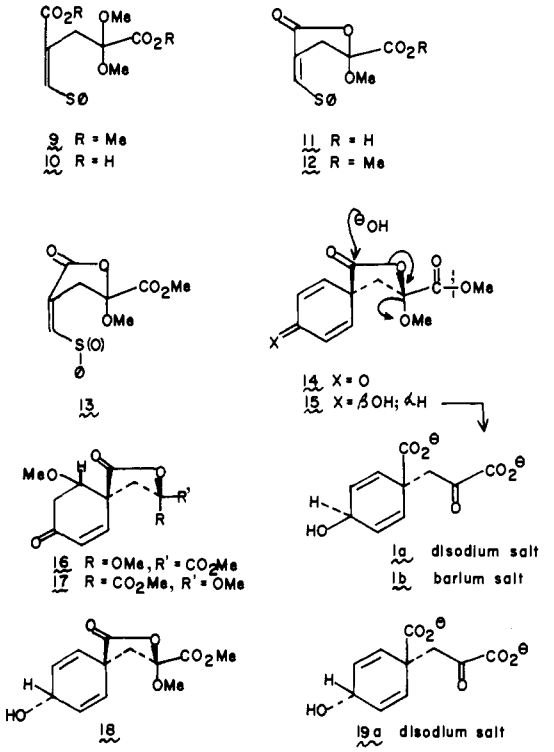
The lability of prephenate and its compactly arranged functionality pose an implicit challenge to its total synthesis. Below we describe the total synthesis of disodium prephenate.

Our general approach was recently described.[6] It involves a new synthesis of compounds such as **4,** themselves systems of marginal stability to acids[7] and bases.[8a] Such systems are obtained by unraveling of the Diels–Alder adducts of diene **2**[8b] with dienophiles of the type **3.** Through the use of the specific dienophile, **5,** we obtained dienone **6.** This was converted to a 7:5 mixture (separated into its components) of **7.** Unfortunately, the side-chain ketone could not be redeemed from the dimethyl acetal by treatment of either epimer of **7** with acids, under a variety of conditions, owing to dienol–benzene rearrangement.[9] Moreover, both epimers of **8** suffered rapid conversion of phenylpyruvic acid dimethyl acetal even at pH 3.5 under conditions where the ketal was stable.[6]



We reasoned that it would be advantageous to store the C_{10}-carboxy and C_8-keto functions in a concurrently protected form from which both groups might be unmasked in a single step under alkaline circumstance. Methoxylactone **15** seemed eminently suitable for this purpose. Its precursor dienone **14,** might be expected to arise from a Diels–Alder dynamic using **2** and **13.** This proposition was reduced to practice.

Saponification (5 equiv of KOH, 1:1 methanol–water, room temperature, 36 h) of the readily available **9**[6] afforded a 92% yield of **10,**[10] mp 108–110 °C. Treatment of **10** with 2:1 aqueous HCl (0.012 N)–THF (room temperature, 73 h) afforded acid **11** which upon reaction with diazomethane and



chromatography on silica gel (elution with 40:1 benzene–ethyl acetate), gave a 54% yield of **12.**[10a,11a] Reaction of **12** with *m*-chloroperoxybenzoic acid (1 equiv, methylene chloride, −20–0 °C, 3 h) afforded the needed sulfoxide **13**[10a,11b] in 69% yield.

Heating of **2** and **13** (neat, 120 °C, 20 h) and treatment with 2.3% acetic acid in ethyl acetate followed by rapid chromatography on silica gel (elution with 4:1 benzene –ethyl acetate) gave a 41% crude yield of **14** contaminated with ~15% methoxy epimers **16** and **17.** In related cases,[8b] such contaminants can readily be removed by chromatography on silica gel. In the case at hand, dienone **14** is unstable to slow chromatography of the type required to separate it from **16** and **17.** Fortunately, homogeneous **14,**[10] mp 128–130 °C, was obtained by crystallization from ether but only in 17% yield. For our subsequent operations it was easier to use homogeneous **14** though dienols **15** and **18** (vide infra) could be obtained in pure form starting with crude **14.**

Treatment of **14** with 9-BBN[12] (3 equiv, THF, 0 °C to room temperature, 3 h) afforded a 3:2 ratio of **15:18.** These were separated by chromatography on silica gel. Each epimer was treated with 1.25 equiv of sodium hydroxide in aqueous methanol (14 h, room temperature). After lyophilization, the resultant disodium salts were dissolved in D_2O and their NMR spectra measured at 250 MHz.[13]

Starting with dienol **15**[10a,14] (R_f[15] 0.61, 9:1 chloroform–ethanol), there was thus obtained synthetic disodium prephenate **1a.** Its NMR spectrum[13,16] was identical with that of an authentic sample prepared from authentic barium prephenate by ion exchange (Dowex 50W-X8 Na^+ form).

From dienol **18**[10a,17] (R_f[15] 0.53, 9:1 chloroform–ethanol) there was obtained disodium epiprephenate **19a.** The NMR spectrum of **19a**[18] is similar in character but clearly different in detail (at 250 MHz) from that of **1a.**

We believe that this total synthesis will permit the introduction of isotopic perturbations into the prephenate system which will be of assistance in biosynthetic inquiries. Also, it would be of interest to ascertain, through analogue synthesis and biological examination, the effect of structural variations in the prephenate system on enzymic recognitions. In this connection, of course, the epiprephenate system will be of interest.

Finally, we would note that, with some yield improvements, total synthesis may well be the most effective method for obtaining prephenate salts.

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(10) The structure of this compound is in accord with (a) its infrared and NMR spectral properties and (b) its combustion analysis within 0.4% of theory.
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(14) Dienol **15**: δ ($CDCl_3$) 2.07 (s, OH), 2.51 (s, CH_2), 3.49 (s, $ROCH_3$), 3.88 (s, RCO_2CH_3), 4.46 (ddt, J_1 = 3.9, J_2 = 3.8, J_3 = 1.0 Hz, C*H*OH), 5.71 (ddd, J_1 = 9.9, J_2 = 2.2, J_3 = 1.0 Hz, vinyl H at C_3 or C_5), 6.02 (ddd, J_1 = 9.9, J_2 = 2.2, J_3 = 1.0 Hz, vinyl H at C_5 or C_3), 6.18 (ddd, J_1 = 9.9, J_2 = 3.8, J_3 = 1.5 Hz, vinyl H at C_2 or C_6), 6.25 (ddd, J_1 = 9.9, J_2 = 3.9, J_3 = 1.5 Hz, vinyl H at C_6 or C_2) ppm; $\bar{\nu}$($CHCl_3$) 3520, 1783, 1754 cm^{-1}.
(15) R_f values were determined on commercial (E. M. Merck) precoated silica gel (60F-254 TLC) plates.
(16) **1a:** δ^{13} (D_2O) 4.50 (tt, J_1 = 3.1, J_2 = 1.4 Hz, C*H*OH), 5.92 (dd, J_1 = 10.4, J_2 = 3.1 Hz, vinyl hydrogens at C_2 and C_6), 6.01 (dd, J_1 = 10.4, J_2 = 1.4 Hz, vinyl hydrogens at C_3 and C_5) ppm. The methylene protons at C_7 are exchanged in basic D_2O.
(17) **18:** δ ($CDCl_3$) 1.80 (br, s, OH), 2.53 (d, J = 14.2 Hz, H_A at C_7), 2.56 (d, J = 14.2 Hz, H_B at C_7), 3.48 (s, $ROCH_3$), 3.88 (s, RCO_2CH_3), 4.71 (ddt, J_1 = 3.0, J_2 = 2.7, J_3 = 1.9 Hz, C*H*OH), 5.64 (dt, J_1 = 9.9, J_2 = 1.9 Hz, vinyl H at C_3 or C_5), 5.97 (dt, J_1 = 9.9, J_2 = 1.9 Hz, vinyl H at C_5 or C_3), 6.09 (ddd, J_1 = 9.9 Hz, J_2 = 2.7 Hz, J_3 = 1.9 Hz, vinyl H at C_2 or C_6), 6.17 (ddd, J_1 = 9.9, J_2 = 3.0, J_3 = 1.9 Hz, vinyl H at C_6 or C_2) ppm; $\bar{\nu}$($CHCl_3$) 3623, 3436, 1786, 1754 cm^{-1}.
(18) **19a:** δ^{13} (D_2O) 4.55 (tt, J_1 = 3.1, J_2 = 1.5 Hz, C*H*OH), 5.89 (dd, J_1 = 10.3, J_2 = 3.1 Hz, vinyl hydrogens at C_2 and C_6), 5.99 (dd, J = 10.3, 1.5 Hz, vinyl hydrogens at C_3 and C_5). The methylene protons at C_7 are exchanged in D_2O.

Samuel Danishefsky,* Masahiro Hirama
Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260
Received August 22, 1977.

Synthesis of Oligoribonucleotides

Sir:

During the past decade major advances in the synthesis of oligodeoxyribonucleosides have been made. The Khorana diester approach has contributed significantly to the synthesis of a gene sequence.[1] Further the modern triester approach initiated by Letsinger[2] and expanded by Eckstein[3] and Reese[4] has allowed the rapid synthesis of oligodeoxynucleotides in large quantities. Recently Narang has used the triester method to synthesize a 21-unit deoxynucleotide corresponding to the lactose operator of *Escherichia coli.*[5] Unfortunately, because of the presence of the 2′-hydroxyl group, developments in the oligoribonucleotide area have been much slower.

There are three major problems in ribonucleotide synthesis: (1) the selection of suitable protecting groups for the hydroxyl, amino, and phosphate groups; (2) the actual synthesis of nucleosides protected on the 2′-hydroxyl and/or on the 2′- and 5′-hydroxyls; (3) the condensation of the protected nucleosides to nucleotides. Usually several steps are required[6,7] to satisfy requirement 2 and then usually in very low overall yields. The condensation reactions are usually slow and accompanied by low yields, although van Boom[8] has recently reported yields of 40–80% in condensation steps.

Two recent developments have occurred which allow us to present a remarkably simple and rapid synthesis of ribonucleotides. The first development was our application of silyl protecting groups to nucleosides.[9-11] These procedures have now been extended to all of the common ribonucleosides.[12] The only products isolated from the silylation reactions of ribonucleosides are those in which only the hydroxyl groups are protected. Further it is possible to obtain a 2′,5′-disilylated ribonucleoside (**1**) from the parent nucleoside in 40–60% yields in a 30-min reaction.[10,12] Compounds **1** are easily separated