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A CONVERGENT TOTAL SYNTHESIS OF (-)-ANAMARINE FROM D-GLUCOSE[1]

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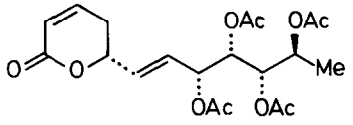
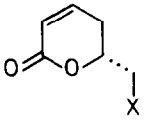
Summary: The di-acetonide of 6-deoxy-*aldehydo*-D-glucose 12 and (*S,S*)-2-ethoxy-6-triphenylphosphoniomethyl-dihydropyran iodide 8 are elaborated from D-glucose each in practicable procedures of 5 and 10 steps, resp., and subsequently joined to give, after oxidation, deprotection and acetylation, (-)-anamarine (*ent*-1). The synthesis proves the absolute configuration of natural (+)-anamarine (1).

A novel C_{12} compound isolated in 1979 from the flowers and leaves of a Peruvian *Hyptis* species and named anamarine[2] was shown to have constitution 1 on the basis of ^{1}H-, ^{13}C-NMR and X-ray crystallographic data[3], featuring *R*-configuration in the pyranoid ring and a rather unusual L-gluco arrangement in the C_6-side chain.

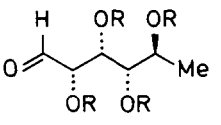


1



A

+

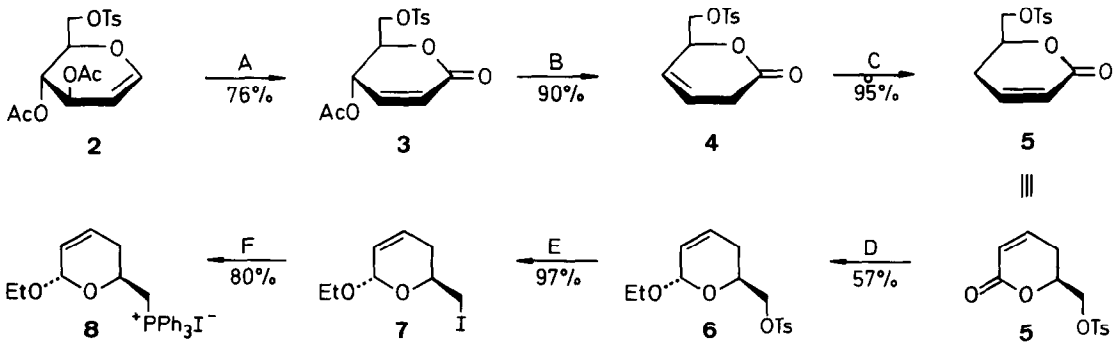


B

Conceptually, the most direct synthetic approach to enantiomerically pure 1 would lie in the elaboration of both C_6-halves from a suitable six-carbon sugar whereby the generation of the side chain portion (synthon B) from 6-deoxy-L-glucose appeared most obvious. Conversion of a hexose into the pyranoid enelactone segment (synthon A, in a form suitable for Wittig reactions) was considered of practicable value and, hence, reasonable only if number of steps and overall yields attainable are in sound proportions. In this communication we wish to describe investigations towards realization of this concept, by elaboration of synthons A and B — as their enantiomers though — from D-glucose, and their junction in a Wittig reaction, leading to the synthesis of the (-)-anamarine (*ent*-1).

Preparation of the pyranoid six-carbon half started from the known[4] di-O-acetyl-6-O-tosyl-D-glucal 2, accessible from D-glucose in four steps, of which the first two (tosylation and acetylation, 30%) and the following ones (HBr treatment and Zn reduction) may be combined into two consecutive one-pot operations, allowing overall yields of 25% on a 60-80 g scale of product[5]. BF_3-catalyzed peroxidation[6] smoothly gave the enelactone 3 (m.p. 92-93°, $[\alpha]_D^{20}$ +91°, chloroform), which on exposure to zinc amalgam/HCl in ether[7,8] underwent reductive cleavage of the allylic acetoxy group with concomitant shift of the double bond into the unconjugated position. The resulting 4 (m.p. 73°, $[\alpha]_D^{20}$ -35°, chloroform), however, on brief treatment with base quantitatively transposed the olefinic double bond into conjugation to yield the (6*S*)-tosyloxymethyl-dihydropyranone 5[9].

Since conversion of 5 into the respective phosphonium salt is not realizable[10], the corresponding ethoxy-dihydropyrane 6 (syrup, a 20:1 α/β-mixture on the basis of ^{1}H-NMR) was prepared by DIBAL reduction and subsequent acetalization. Displacement of the tosyloxy group in 6 by iodide proceeded smoothly to give 7 as a syrup, which on fusion with triphenylphosphane afforded the desired phosphonium salt 8 in nicely crytalline form[9] and respectable yield (cf. formula scheme), particularly when considering the entirely different course of this reaction at the enelactone stage[10]. Thus, an enantiomerically pure six-carbon synthon, suitable for the construction of the pyranoid portion of compounds of type 1 via Wittig reactions, may be obtained from D-glucose in 10 steps and an overall yield of 7.2% (or 29% for 2 → 8); since the lowest yielding steps are at the outset of the conversion D-glucose → 8 (i.e. 25% for generation of 2) this approach is considered to be of practical utility.



Key

A: MCPBA/BF_3 in CH_2Cl_2, -30° → 0°C, 30 min.

B: Zn-Hg/HCl in THF, 1 h, 0°C.

C: DBU/THF, 2 h, 25°C.

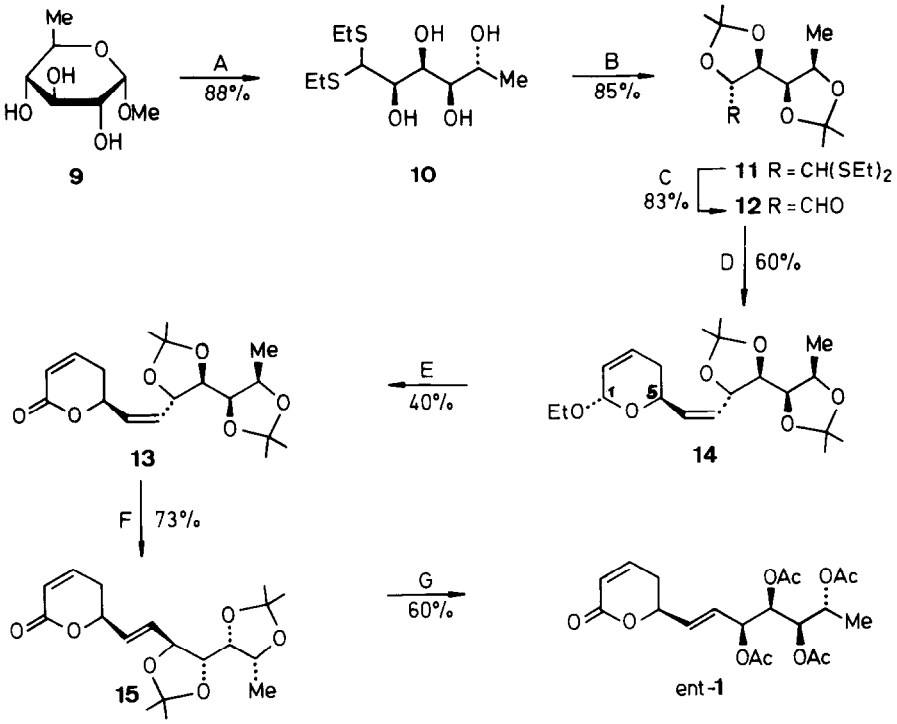
D: DiBAL/THF, -65°C, then EtOH/BF_3 in CH_2Cl_2, 6 h, 25°C.

E: NaI in EtCOMe, 6 h, 80°C.

F: PPh_3, fusion, 18 h.

The obvious generation of the side-chain six-carbon synthon B (in its enantiomeric form) from the readily accessible[11] methyl 6-deoxy-D-glucoside 9 followed standard procedures, fixation in the open-chain tautomer being effected by thioacetalization 9 → 10[12]. Subsequent acetonation proceeded uniformly when P_2O_5 was used as the catalyst[13] to give the di-O-isopropylidene derivative 11[9] with two 1,3-dioxolane rings as evidenced on the basis of ^{13}C-NMR data[14]. The synthon B-concluding liberation of the aldehyde function 11 → 12 was accomplished by MeI/$CdCO_3$-induced desulfurization to afford 12 as a syrup of $[\alpha]_D^{20}$ -44° ($CHCl_3$).

Well aware of the potential complications associated with the deprotonation of phosphonium salts of type 8 — in furanoid systems reversible ß-elimination occurs[15] — we allowed 8 to react with n-butyllithium in THF/HMPA (2:1) at -78°, and, subsequently, with aldehyde 12 for 15 min, whereupon the mixture was warmed to -10° and quenched[16]. These conditions produce an approximate (^{1}H-NMR) 8:1-mixture of 14 and its 5-epimer, both of Z-configuration ($J_{6,7}$ 11.2 Hz). Their separation was best achieved after BF_3-catalyzed peroxidation to the enelactone 13, which is highly crystalline[9] and whose structure and configuration was unequivocally established by ^{1}H-NMR[9] and X-ray analysis[17].



Key

A: 2N HCl, 12 h reflux, then EtSH/ $ZnCl_2$, 3 d, 25°C.

B: Me_2CO/P_2O_5, 1 h, 25°C.

C: MeI/$CdCO_3$ in Me_2CO/H_2O, 2 d, 25°C.

D: nBuLi + 8 in THF/HMPA (2:1), -78° → 0°C, 1 h.

E: MCPBA/BF_3 in CH_2Cl_2, -30° — 0°C, 30 min.

F: Ph_2S_2/hv in benzene, 5 h, 25°C.

G: TFA, 10 min, 25°C, then Ac_2O/Pyr.

Isomerization of 13 to the E-isomer 15 (syrup, -93° in chloroform, $J_{6,7}$ 15.6 Hz) was accomplished by irradiation in the presence of diphenyldisulfide. The concluding steps, deacetonation and acetylation proceeded smoothly to give (-)-anamarine (*ent*-1), which was isolated in amorphous form and with a rotation of -15°; it was pure by TLC, microanalysis, a fully analyzable ^{1}H-NMR spectrum[9], and ^{13}C-NMR data. Comparison of synthetic *ent*-1 with the *Hyptis*-derived 1 — kindly provided by Prof. Valverde[2] — showed perfect identity of TLC behaviour in a series of solvent systems, of ^{1}H-NMR[9] and of ^{13}C-NMR[2] data. The fact that *ent*-1 could not be induced to crystallize yet — 1 exhibits a m.p. 110-112°C[3] — may be due to the scarcity of synthetic material, and is not considered detrimental; more important appears to be the near-identity of rotational values, with opposite sign though, i.e. -15° for *ent*-1 versus +18.8° for 1[18].

This total synthesis of (-)-anamarine (*ent*-1), in turn, proves the absolute configuration of the natural (+)-1 as well as that of olguine, which have been inferred from the anomalous dispersion effects of oxygen atoms and by analogy with related compounds[2,3]. The construction of 1 from L-glucose or, more economically, from D-gulonolactone along similar synthetic veins is currently being addressed.

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5. F.D. Klingler, Dissertation, Technische Hochschule Darmstadt, 1985; 2 had a m.p. of 103° and rotations of +18° (chloroform) and +40° (methanol).
6. P. Jarglis and F.W. Lichtenthaler, *Tetrahedron Lett.*, 1982, *23*, 3781.
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9. Selected physical data (m.p.; $[\alpha]_D^{20}$ in $CHCl_3$ at c = 0.5-1; ^{1}H-NMR at 300 MHz in $CDCl_3$) of:

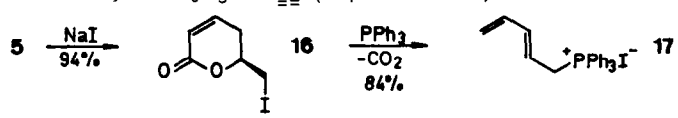
   5: 79.5°C; -81°; δ 2.42 and 2.53 (two 1H-m, 4-H_2), 4.20 (two 1H-dd, 6-H_2), 4.65 (ddt, 5-H), 6.01 (ddd, 2-H), 6.89 (ddd, 3-H); $J_{2,3}$ 9.8, $J_{2,4}$ 1.2 and 2.5, $J_{3,4}$ 2.8 and 5.7, $J_{4,4}$ 18.4, $J_{4,5}$ 4.8 and 11.0, $J_{5,6}$ 4.5 and 4.8, $J_{6,6}$ 10.8 Hz.

   8: 161-163°C; +20°; δ 2.40 and 2.70 (two 1H-m, 4-H_2), 3.67 and 4.72 (two 1H-ddd, 6-H_2), 4.75 (d, 1-H), 5.60 (ddt, 2-H), 6.00 (m, 3-H); $J_{2,3}$ 10.2, $J_{5,6}$ 2.1 and 10.6, $J_{6,6}$ 15.6, $J_{6,P}$ 10.6 and 14.2 Hz.

   11: 52°C; -96°; δ 1.42 (3H-d, 6-Me), 3.90 (d, 1-H), 4.00 (dd, 3-H), 4.24 (dd, 4-H), 4.29 (dd, 2-H), 4.41 (quint., 5-H); $J_{1,2}$ 5.1, $J_{2,3}$ 8.1, $J_{3,4}$ 1.0, $J_{4,5}$ 6.8, $J_{5,6}$ 6.4 Hz.

   13: 149°C; -65°; δ 1.43 (3H-d, 12-Me), 2.45 (m, 2 H, 4-H_2), 3.56 (dd, 9-H), 3.82 (dd, 10-H), 4.41 (quint., 11-H), 4.64 (dt, 8-H), 5.47 (m, 5-H), 5.60 (ddd, 7-H), 5.89 (ddd, 6-H), 6.07 (dt, 2-H), 6.89 (ddd, 3-H), $J_{2,3}$ 9.8, $J_{2,4}$ 1.6 and 2.0, $J_{3,4}$ 3.6 and 4.6, $J_{4,5}$ 6.5 and 9.0, $J_{5,6}$ 8.4, $J_{5,7}$ 1.1, $J_{6,7}$ 11.3, $J_{6,8}$ 0.9, $J_{7,8}$ 8.5, $J_{8,9}$ 8.7, $J_{9,10}$ 1.3, $J_{10,11}$ 6.6, $J_{11,12}$ 6.4 Hz.

   ent-1: amorphous; -15°; δ 1.19 (3H-s, 12-Me), 2.03, 2.07, 2.08 and 2.13 (four 3H-s, 4 Ac), 2.45 (m, 2 H, 2-H_2), 4.92 (quint., 11-H), 4.96 (m, 5-H), 5.18 (dd, 10-H), 5.31 (dd, 9-H), 5.37 (dd, 8-H), 5.83 (m, 2 H, 6/7-H), 6.06 (ddd, 2-H), 6.89 (ddd, 3-H), $J_{2,3}$ 9.8, $J_{2,4}$ 1.5 and 2.2, $J_{3,4}$ 3.4 and 5.1, $J_{4,5}$ 5.7 and 9.4, $J_{5,6}$ 3.6, $J_{5,7}$ 0.6, $J_{6,7}$ 15.6, $J_{7,8}$ 5.6, $J_{8,9}$ 7.4, $J_{9,10}$ 3.4, $J_{10,11}$ 6.7, $J_{11,12}$ 6.4 Hz.
10. The iodo derivative 16 (syrup, -98°, chloroform), on exposure to triphenylphosphine under a variety of conditions, mainly gave 17 (m.p. 194-195°).



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12. M.p. 97-98°, -47.7° (water); for the L-*gluco* analog of 10, the same m.p. and a rotation of +47.1° (water) has been reported: E. Zissis, N.K. Richtmeyer, and C.S. Hudson, *J. Am. Chem. Soc.*, 1951, *73*, 4714.
13. In adaption of conditions introduced by T. van Es (*Carbohydr. Res.*, 1974, *32*, 370).
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16. These conditions were adapted from those used by J.A. Secrist III and S.-R. Wu (*J. Org. Chem.*, 1979, *44*, 1434) for Wittig reaction of a galactose-derived 6-phosphonium salt.
17. We are grateful to Prof. H.J. Lindner, of this institute, for determining the X-ray crystal structural analysis of 13, which will be published elsewhere.
18. The rotation for the *Hyptis*-derived 1, originally given as +28.2° (*c* 0.52, $CHCl_3$)[3], was kindly redetermined by Prof. Valverde to be +18.8° (*c* 0.75, $CHCl_3$).

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