Tetrahedron Letters,Vol.28,No.51,pp 6437-6440,1987 0040-4039/87 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

A CONVERGENT TOTAL SYNTHESIS OF (+)-ANAMARINE FROM (*R,R*)-TARTRATE AND D-GULONOLACTONE[1]

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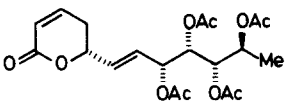
Abstract The (R,R)-6-alkoxy-2-triphenylphosphoniomethyl-dihydropyran iodide **2** and the di-acetonide of 6-deoxy-aldehydo-L-glucose **3** are elaborated from (R,R)-tartrate and D-gulonolactone, resp., and subsequently joined to yield (+)-anamarine (**1**), identical with the Hyptis-derived product.

Anamarine, a C_{12} compound isolated from the flowers and leaves of an unclassified Peruvian Hyptis species was shown to have constitution **1** on the basis of ^{1}H-, ^{13}C-NMR and X-ray crystallographic data[2], featuring R-configuration in the pyranoid ring and L-gluco arrangement in the C_6-side chain. A total synthesis of (-)-anamarine (ent-**1**), has recently been accomplished in this laboratory[3], which proved the absolute configuration of the natural product (**1**), and also allowed to clarify its rotational value to be +18.8° ($CHCl_3$)[4] instead of the +28.2° originally reported[2].



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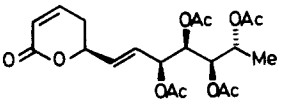
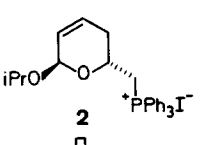


ent-**1**

In our approach to ent-**1**[3], both the pyranoid C_6-portion and the six-carbon side chain were elaborated from D-glucose[5]. The synthesis of **1**, however, if one excludes the obvious possibility of repeating the same sequence of reactions with the rather inaccessible L-glucose as the educt, presents a quite different challenge in synthetic design and assembly. In this paper we present an operationally novel approach for the construction of the two C_6-segments **2** and **3** in enantiomerically pure form, utilizing (R,R)-tartaric acid and D-gulonolactone as the readily available precursors.[7]



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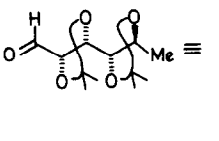

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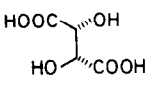
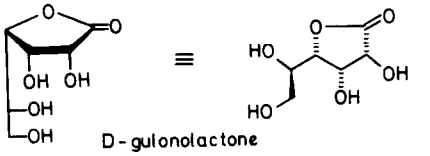
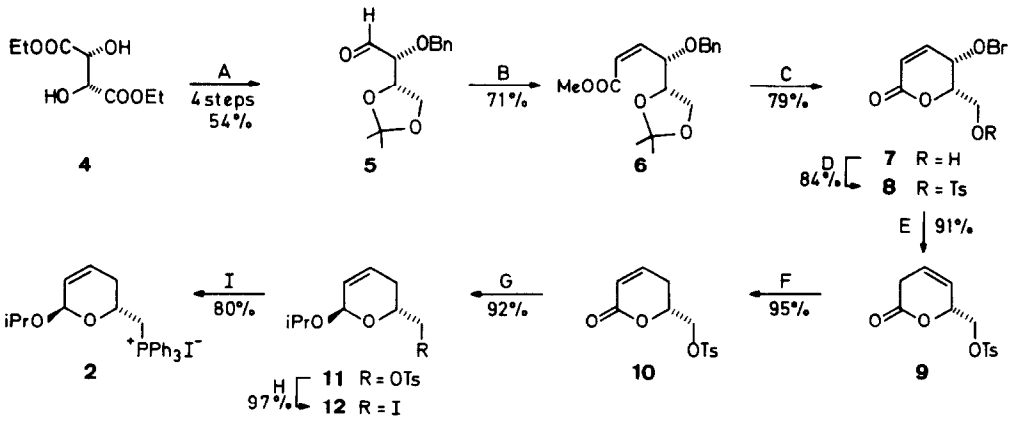


(R,R)-tartrate



D-gulonolactone

Preparation of the pyranoid six-carbon half followed well-established procedures in the first few steps,[8,9] i.e. the conversion of diethyl tartrate (**4**) into the L-threose derivative **5**, suitably blocked for an ensuing C_2-extension (**5** → **6**[9]) and subsequent hydrolysis/lactonization to yield enelactone **7**[9] in an overall yield of 30% for the 6 steps involved. Tosylation readily afforded the crystalline **8**[11], which on exposure to zinc amalgam/HCl in ether underwent reductive cleavage of the allylic benzyloxy group with concomitant shift of the double bond into the unconjugated position.[12] The resulting **9** (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 (6R)-tosyloxymethyl-dihydropyranone **10** (m.p. 79.5°, +81°, chloroform).

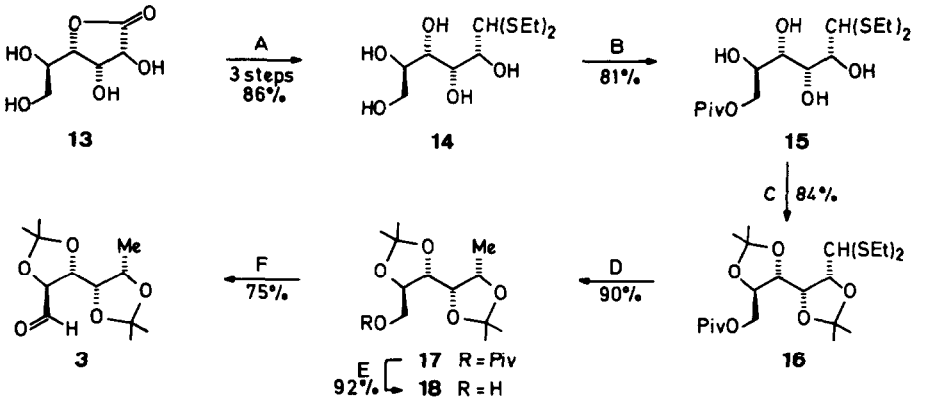


Key A: 4 steps: C_6H_5CHO/TsOH in benzene, 80°C, H_2O↓, 89%.
→ $LiAlH_4/AlCl_3$ in Et_2O/CH_2Cl_2, -40°C to reflux, 91%[8].
→ Me_2CO/TsOH, 94%[9].
→ PCC/Al_2O_3, CH_2Cl_2, NaOAc, 71%[9,10].
B: Ph_3P=CHCOOMe in MeOH, 1 h, 25°C[9].
C: LiOH in THF/MeOH → TFA/H_2O (9:1)[9].
D: TsCl/pyr., 15 h, 0°C.
E: Zn-Hg/HCl in THF, 1 h, 0°C.
F: DBU/THF, 2 h, 25°C.
G: DIBAL/THF, -65°C, then EtOH/BF_3 in CH_2Cl_2, 6 h, 25°C.
H: NaI in EtCOMe, 6 h, 80°C.
I: Ph_3P, fusion, 16 h.

Whilst displacement of the tosyloxy group by iodide is readily feasible under standard conditions, the generation of the respective enelactone phosphonium salt therefrom is not since the relatively harsh phosphonylation conditions required also induce decarboxylation to yield the 2,5-pentadienyl phosphonium salt instead.[3] Thus, the corresponding isopropyloxy-dihydropyran **11** [syrup, $[\alpha]_D^{20}$ +40° (c 3, $CHCl_3$)] was prepared by DIBAL reduction and subsequent acetalization. Iodination of **11** proceeded smoothly to provide syrupy **12**, which on fusion with triphenylphosphane afforded the desired phosphonium salt **2** in crystalline form[11] and respectable yield (cf. formula scheme). Accordingly, an enantiomerically pure six-carbon synthon, suitable for the construction of the pyranoid portion of targets of type **1** via Wittig reactions, may be obtained from (R,R)-tartrate with an overall yield of 16% for the 12 simple, large-scale adaptable steps.

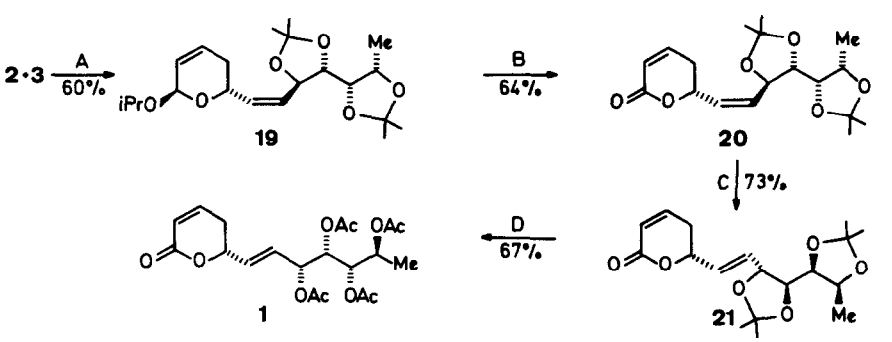
On the other hand, generation of the side-chain six-carbon segment **3** started from D-gulonolactone (**13**) as readily accessible progenitor, which via known[13] 3-step procedure was converted into the diethyl dithioacetal of D-gulose **14**. Selective pivaloylation of the primary hydroxy group provided **15** (m.p. 91-92°C, $[\alpha]_D^{20}$ -8°, $CHCl_3$), subsequent P_2O_5-induced acetonation proceeded with remarkable uniformity — traces of a second product are detectable — to afford the 2,3:4,5-di-O-isopropylidene derivative **16** (syrup, $[\alpha]_D^{20}$ +59°). The side-chain synthon concluding operations utilized

standard procedures for desulfurization (**16** → **17**[11]), depivaloylation[14] (→ **18**, oil, $[\alpha]_D^{20}$ +67°, $CHCl_3$), and PCC-oxidation, to give **3**[11]; an overall yield of 36%, based on D-gulonolactone has thereby been obtained, which implies a reasonably satisfactory 88% per functional change.



Key A: 3 steps[12]: Me_3SiCl/pyr., imidazole → DIBAL in toluene, -65°C → EtSH/HCl, 0°C.
B: PivCl/pyr., -10 → 40°C.
C: P_2O_5/acetone, 6 h, 25°C.
D: Raney-Ni in EtOH, 1 h reflux.
E: $tBuOK/H_2O/Et_2O$, 2 h, 0 → 25°C.
F: PCC/Al_2O_3, NaOAc, 5 h, 25°C.

The conjunction of the two synthons and elaboration of the target molecule mainly followed the synthetic veins used previously for ent-**1**[3]. Ylid formation in phosphonium salts of type **2** being encumbered with reversible β-eliminative ring opening[15], and, hence, potential epimerization at at C-5, the Wittig reaction had to be carried out with particular care. Best results gave conditions (i.e. A in key to last formula scheme) adapted from those used for the Wittig reaction of a galactose-derived 6-phosphonium salt[16]. The approximate (^1H NMR) 9:1 mixture of **19** (syrup, 60% after chromatographic separation, $[\alpha]_D^{20}$ +27°, $CHCl_3$) and its C-5 epimer resulting therefrom, is best separated at the stage of the highly crystalline enelactone **20** (mp 149-150°C, $[\alpha]_D^{20}$ +65°), which is readily obtained on acetal hydrolysis and subsequent PCC oxidation (**19** → **20**). Isomerization of **20** to the E-isomer **21**[11] was effected by irradiation in the presence of diphenyldisulfide. The concluding steps, deacetonation and acetylation proceeded smoothly to give (+)-anamarine (**1**), which was isolated in amorphous form and with rotational value of +15.9° (c 0.8,



Key A: nBuLi in THF/HMPA (2:1), -78° → 0°C, 1 h.
B: 0.1 N HCl/Me_2CO (1:2), 0°C, 15 min → $NaHCO_3$ → PCC/Al_2O_3/NaOAc, CH_2Cl_2.
C: $Ph_2S_2/h\nu$ in benzene, 5 h, 25°C.
D: TFA, 10 min, 25°C, then Ac_2O/Pyr..

$CHCl_3$) as compared to +18.8° for the Hyptis-derived **1**[2,4]. A sample of natural **1**, kindly provided by Prof. Valverde[2], ent-**1**[3], and the synthetic **1** exhibited perfect identity of TLC behaviour in a series of solvent systems, of ^{1}H NMR[3], and ^{13}C NMR[2] data.

REFERENCES AND NOTES

1. Enantiomerically Pure Building Blocks from Sugars, 6. — This work was supported by the Deutsche Forschungsgemeinschaft. — Part 5: M. Brehm, W.G. Dauben, P. Köhler, F.W. Lichtenthaler, Angew. Chem., **99** (1987), in press.
2. A. Alemany, C. Márquez, C. Pascual, S. Valverde, M. Martinez-Ripoll, J. Fayos, A. Perales, Tetrahedron Lett., **1979**, 3583.
3. F.W. Lichtenthaler, K. Lorenz, W.Y. Ma, Tetrahedron Lett., **28** (1987) 47.
4. Ref. 3, footnote 18.
5. A second synthesis of ent-**1**[6] has appeared most recently (submitted May 1987), using the same basic approach, the same six-carbon synthons, and the same methodology in the ensuing five steps, for which the overall yields were lower despite of modifying conditions (e.g. Jones oxidant instead of MCPBA) and, in part, changing the order in which the manipulations were executed. Prof. Valverde had been provided a preprint of our work[3] in Nov. 1986.
6. S. Valverde, A. Hernandez, B. Herradon, R.M. Rabanal, M. Martin-Lomas, Tetrahedron, **43** (1987) 3499.
7. Essential portions of this work were presented at the 4th European Carbohydrate Symposium, Darmstadt, 13-17 July 1987, Abstract A-70.
8. D. Seebach and E. Hungerbühler, "Modern Synthetic Methods" (R. Scheffold, Ed.), Salle and Sauerländer, Frankfurt, 1980, p. 152 ff.
9. S. Valverde, B. Herradon, M. Martin-Lomas, Tetrahedron Lett., **26** (1985) 3731.
10. D.R. Williams, F.D. Klingler, Tetrahedron Lett., **28** (1987) 869.
11. Selected physical data (m.p.; $[\alpha]_D^{20}$ in $CHCl_3$ at c = 1-2; ^{1}H-NMR at 300 MHz in $CDCl_3$) of:
    2: 168-170°C; -12.8°; δ 2.38 and 2.63 (two 1H-m, 4-H_2), 3.65 and 4.64 (two 1H-ddd, 6-H_2), 4.89 (d, 1-H), 5.56 (ddt, 2-H), 5.97 (m, 3-H); $J_{1,2}$ 2.8, $J_{2,3}$ 10.2, $J_{2,4}$ 1.0 and 2.8, $J_{4,4}$ 18.0, $J_{4,5}$ 10.5, $J_{5,6}$ 2.3 and 10.5, $J_{6,6}$ 15.7, $J_{6,P}$ 10.5 and 14.2 Hz.
    3: syrup; δ 1.39 (3H-d, 6-Me), 3.97 (dd, 3-H), 4.10 (dd, 4-H), 4.34 (dd, 2-H), 4.42 (quint., 5 H), 9.82 (d, 1-H), $J_{1,2}$ 1.8, $J_{2,3}$ 7.9, $J_{3,4}$ 2.1, $J_{4,5}$ 6.5, $J_{5,6}$ 6.6 Hz.
    8: 107°C; +169°; δ 2.45 (3H-s, Ph-Me), 4.07 (dd, 4-H), 4.26 and 4.42 (two 1H-dd, 6-H_2), 4.54 and 4.58 (two 1H-d, $PhCH_2$), 4.64 (dt, 5-H), 6.14 (d, 2-H), 6.87 (dd, 3-H); $J_{2,3}$ 9.8, $J_{3,4}$ 5.4, $J_{4,5}$ 3.1, $J_{5,6}$ 6.2 and 6.8, $J_{6,6}$ 10.4 Hz.
    17: syrup; +47.8°, δ 1.23 (9H-s, 3 Piv-Me), 1.37, 1.41, 1.45 and 1.53 (four 3H-s, 4 isopropylidene-Me), 1.39 (3H-d, 6-Me), 3.73 (dd, 3-H), 4.03 (dd, 4-H), 4.19 (m, 2-H), 4.24 (2H-m, 1-H_2), 4.42 (quint., 5-H), $J_{2,3}$ 8.5, $J_{3,4}$ 1.6, $J_{4,5}$ 6.6, $J_{5,6}$ 6.4 Hz.
    21: syrup; +92.5°; δ 1.37, 1.43, 1.45 and 1.53 (four 3H-s, 4 isopropylidene-Me), 1.39 (3H-d, 12-Me), 2.42 and 2.50 (dddd and ddt, 1 H each, 4-H_2), 3.58 (dd, 9-H), 3.96 (dd, 10-H), 4.40 (quint., 11-H), 4.42 (dd, 8-H), 4.96 (ddt, 5-H), 5.85 (ddd, 7-H), 5.99 (ddd, 6-H), 6.06 (ddd, 2-H), 6.89 (ddd, 3-H); $J_{2,3}$ 9.8, $J_{2,4}$ 1.4 and 2.3, $J_{3,4}$ 3.2 and 5.2, $J_{4,4'}$ 18.2, $J_{4,5}$ 5.3 and 10.0, $J_{5,6}$ 6.2, $J_{5,7}$ 0.9, $J_{6,7}$ 15.5, $J_{6,8}$ 0.5, $J_{7,8}$ 7.4, $J_{8,9}$ 8.7, $J_{9,10}$ 1.5, $J_{10,11}$ 6.6, $J_{11,12}$ 6.4 Hz.
12. For precedents of this deoxygenation see I. Elphimoff-Felkin, P. Sarda, Org. Synth., **56** (1977) 101; F.W. Lichtenthaler, F.D. Klingler, P. Jarglis, Carbohydr. Res., **132** (1984) C1, and ref. 3.
13. F. Gillard, J.-J. Riehl, Tetrahedron Lett., **24** (1983) 587.
14. Unlike other saponification procedures this "anhydrous hydroxide" method (P.G. Gassman, W.N. Schenk, J. Org. Chem., **42** (1977) 918) was found very effective.
15. E.E. Schweizer, W.S. Creasy, K.K. Light, E.T. Shaffer, J. Org. Chem., **34** (1969) 212; J.A. Secrist III, S.R. Wu, ibid., **42** (1977) 4084.
16. J.A. Secrist III, S.R. Wu, J. Org. Chem., **44** (1979) 1434.

(Received in Germany 28 September 1987)