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(+)-Colletodiol

Synthesis from (S,S)-Tartaric Acid and (R)-3-Hydroxy-butyric Acid

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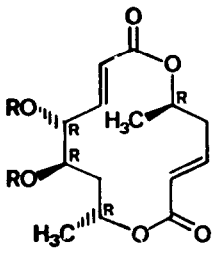
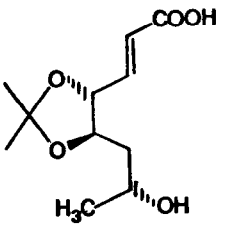
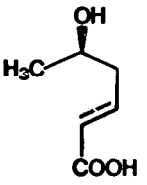
Summary: *E-(R)-5-Hydroxy-2-hexenoic acid (4) and the acetonide of E-(4R,5R,7R)-trihydroxy-2-octenoic acid (3) are joined to give, after deprotection, (+)-colletodiol (1). The syntheses of the two hydroxy-acids from poly-(R)-3-hydroxy-butanoate (PHB) and (-)-tartaric acid, respectively, are outlined.*

Of the unsymmetrical[1], antibiotic 14-membered macrodiolides colletodiol (1)[2], grahamimycin[3], and their congeners, only (-)-grahamimycin A_1 has been synthesized[4] so far. Several attempts towards the synthesis of colletodiol failed[5,6]. In our own, numerous approaches[5], this failure was mainly due to the pronounced tendency, under esterification conditions, for HOR-elimination from the 4.5-position of the hexenoic acid moiety of colletodiol.







1: R = H (colletodiol)

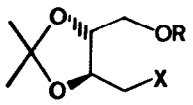
2: R-R = $C(CH_3)_2$

3

4

In an act of desperation, we have now subjected a 1:1 mixture of the two carboxylic acids 3 and 4 to esterifying macrocyclization conditions[7]. We isolated without difficulty, albeit in only a few percent yield, the known[2] acetonide 2 of colletodiol. Deprotection[8] furnished colletodiol 1, identical in every respect with an authentic sample. Details are given in the accompanying table which also lists conditions, yields, and some other character-

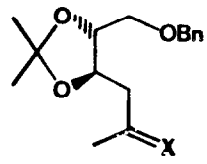
istic data for the syntheses of 3 and 4, many intermediates of which should be useful enantiomerically pure building blocks, also for other target structures[9a].



5: X = OH, R = H

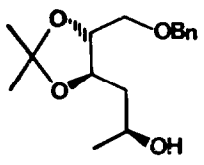
6: X = OH, R = $CH_2C_6H_5$(≡Bn)

7: X = Br, R = Bn



8: X = $S(CH_2)_3S$

9: X = O



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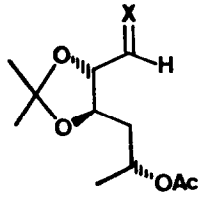
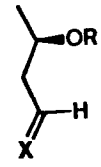


12: X = H/OBn

13: X = H/OH

14: X = O

E-15: X = CH-$COOCH_3$

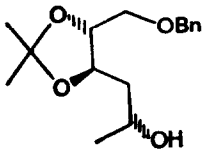


16: R = $CH(CH_3)OC_2H_5$(EE), X = H/OH

17: R = EE, X = O

E-18: R = EE, X = $CHCOOCH_3$

E-19: R = H, X = $CHCOOCH_3$



11

The synthesis of the trihydroxy-acid derivative 3 starts from the now commercially available diol 5 [from (-)-tartaric acid[9a]]. Monobenzylation to 6 abolishes the C_2-symmetry of the molecule[9], substitution of the remaining OH-group by a bromine (→ 7) and hence by a 2-methyl-1.3-dithian-2-yl group (→ 8), with subsequent Hg(II)-assisted thioacetal hydrolysis produces the ketone 9. Non-stereoselective borohydride reduction, separation of the epimers by flash chromatography, and acetylation of 10 with inversion and of 11 with retention of configuration[10] concludes the overall diastereoselective conversion 9 → 12. Debenzylation (→ 13), *Swern* oxidation (→ 14), *Wittig-Horner* olefination (→ 15), and hydrolysis of both ester groups furnishes the hydroxyacid 3 in *ca.* 23 % yield for the ten steps from the diol 5.

The methyl ester 19 of the C_6-hydroxy-acid 4 was obtained following procedures described for the preparation of the racemic material[11] and of the analogous *t*-butyl-ester with (S)-

-configuration[4a], see 16-19 and the table. The starting material is PHB, readily depolymerizable[12] to ethyl (R)-3-hydroxy-butanoate, from which 4 is made in six steps with a total yield of 57 %.

Table. - *Methods, reaction conditions, and batch sizes used for the conversions leading to colletodiol (1). Yields, some physical properties of intermediates, and leading references are also given. Correct elemental analyses of most and spectroscopic characterization of all compounds are fully compatible with the structures 1-19.*

6: 83.2 g (89 %) from 59.9 g **5** and 65.1 g $C_6H_5CH_2Br$ (DMF, -50°C → 0°C, 2 h); $[\alpha]_D = -7.4^\circ$ (c = 1.17, $CHCl_3$).

7: 79.8 g (85 %) from 75 g **6**, 200 g CBr_4 and 158 g $(C_6H_5)_3P$ (Et_2O/CH_2Cl_2 3:2, 35 min.[13]), $CHBr_3$ was removed by crystallization at -30°C), $[\alpha]_D = +2.0^\circ$ (c = 1.64, $CHCl_3$).

9: 27.1 g (70 %) from 44 g **7** and 31.4 g 2-methyl-1,3-dithian (→ **8**), hydrolysis with 160 g $HgCl_2$ and 160 g $CaCO_3$ (CH_3CN/H_2O, 16 h); $[\alpha]_D = +5.4^\circ$ (c = 5.29, $CHCl_3$).

10 + **11**: 8.8 g (99 %) from 8.8 g **9** and 2.13 g $NaBH_4$ (90 % MeOH, 40°C, 1 h). Separation of 5 g amounts by flash-chromatography (Ø of the column 8 cm) with CH_2Cl_2: $CH_3COOC_2H_5$ 9:1. Recovery: 82.8 %; **10**: $[\alpha]_D = +9.5^\circ$ (c = 1.23, $CHCl_3$), **11**: $[\alpha]_D = +2.5^\circ$ (c = 1.20, $CHCl_3$).

12: 4.1 g (70.7 %) from 2.1 g **10**, 1.1 equiv. DEAD, 1.1 equiv. $(C_6H_5)_3P$ and 1.05 equiv. CH_3COOH ($C_6H_5CH_3/C_6H_6$ 1:1, 23°C, 16 h)[14] and 2.9 g **11** (2 g $Ti(OC_2H_5)_4$ in 200 ml $CH_3COOC_2H_5$[12]), 77°C, 24 h), after chromatography ($CH_2Cl_2/CH_3COOC_2H_5$ 9:1); $[\alpha]_D = +11.7^\circ$ (c = 0.63, $CHCl_3$).

13: 2.9 g (quant.) from 4.1 g **12** with $Pd(OH)_2/C$ ($CH_3COOC_2H_5$, 23°C, 30 min.); $[\alpha]_D = +27^\circ$ (c = 1.0, $CHCl_3$).

E-15: 1.6 g (73 %) from 1.8 g **13** via *Swern* oxidation (→ **14**) and *Wittig* reaction with excess $(C_6H_5)_3PCHCOOCH_3$ in DMF; $[\alpha]_D = +9.5^\circ$ (c = 0.93, $CHCl_3$).

E-19: cf. ref.[11]; $[\alpha]_D = -16.9^\circ$ (c = 1.05, $CHCl_3$).

3: 0.7 g (99 %) from 0.88 g **15** with 7 equiv. 0.5 N LiOH aq. (THF, 23°C, 2 h).

4: 1.07 g (97 %) from 1.22 g **19** with 1.4 equiv. 1 N NaOH aq. (H_2O/THF 1:1, 23°C, 1 h); $[\alpha]_D = -11^\circ$ (c = 0.99, C_2H_5OH).

1: m.p. 160.8°C-161.8°C, $[\alpha]_D = +28^\circ \pm 10^\circ$ (c = 0.2, $CHCl_3$) (ref.[2]): 162°C-164°C; +36° (c = 1.0, $CHCl_3$)), ^{13}C-NMR (25.2 MHz) and ^1H-NMR (300 MHz) identical with those of natural product[2].

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References and Footnotes

1) There is also a group of C_2-symmetrical, 16-membered natural macrodiolides, such as pyrenophorin, vermiculin, conglobatin, and elaiophylin. For leading references see the most recent paper describing our own synthetic efforts in this area: M.A. *Sutter* and *D. Seebach*, Liebigs Ann. Chem. *1983*, 939.

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8) *Y. Quindon, H.E. Morton*, and *Ch. Yoakim*, Tetrahedron Lett. *24*, 3969 (1983).

9) a: Cf. also the review article: *D. Seebach* and *E. Hungerbühler*, Modern Synthetic Methods 1980, Editor: *R. Scheffold*, Sauerländer, Aarau. - b: Mono-benzoylation: *N. Cohen, B.L. Banner, R.J. Lopresti, F. Wong, M. Rosenberger, Y.-Y. Liu, E. Thom*, and A.A. *Liebmann*, J. Am. Chem. Soc. *105*, 3661 (1983).

10) Isomer 11 was shown to have the correct configuration by deprotection to 1.3-dideoxy--D-lyxo-hexitol, $[\alpha]_D = +11.5^{\circ}$; cf. *J. Němec, Z. Keßurtová, K. Keßurt*, and *J. Jarý*, Collect. Czech. Chem. Commun. *33*, 2097 (1968).

11) *E. Hungerbühler, D. Seebach*, and *D. Wasmuth*, Helv. Chim. Acta *64*, 1467 (1981).

12) *D. Seebach* and *M.F. Züger*, Helv. Chim. Acta *65*, 495 (1982). - *P. Schnurrenberger, M.F. Züger*, and *D. Seebach*, Helv. Chim. Acta *65*, 1197 (1982). - Both, PHB and the monomeric ester are now commercially available.

13) *M. Downie, J.B. Holmes*, and *J.B. Lee*, Chem. Ind. London *1966*, 900.

14) *O. Mitsunobu* and *M. Eguchi*, Bull. Chem. Soc. Jap. *44*, 3427 (1971).

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