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STEREOSELECTIVE SYNTHESIS OF THE FUNCTIONALIZED SYN-1,3,5,7-TETRAOL

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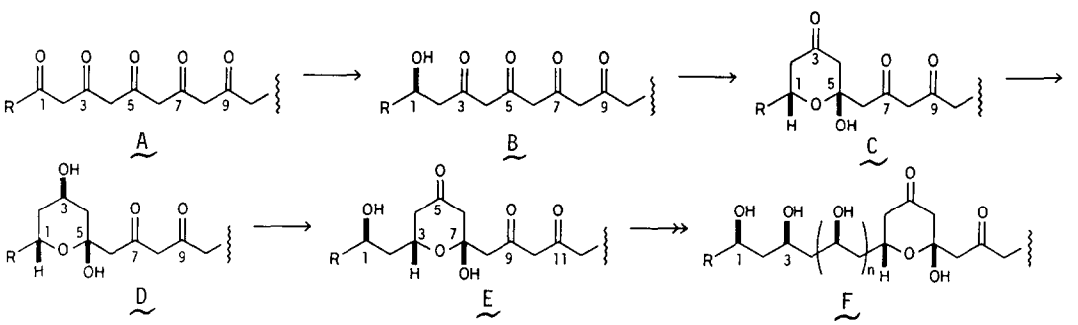
Summary The syn-1,3,5,7-tetraol derivative 21 was synthesized with complete stereoselection based on the stereoselective reduction of a six-membered β-keto hemiacetal and a subsequent hemiacetal ring opening

We previously reported a highly stereocontrolled reduction of the various acyclic ketones by means of $Zn(BH_4)_2$ [1] The stereoselectivity of the reduction is considered to be governed by the stability of a zinc mediated cyclic transition state. Therefore, if a functionalized acyclic ketone which is in equilibrium with a corresponding cyclic ketone is designed and the equilibrium lies to the latter, a well established stereocontrol in a cyclic system would be operative in this compound and after reduction, the resulting cyclic alcohol is convertible to the desired acyclic alcohol by simply shifting the equilibrium to this direction We now report the synthesis of syn-1,3,5,7-tetraol with virtually complete stereoselection based primarily on this line

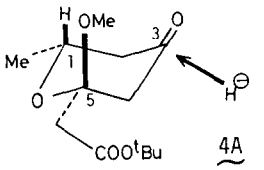
A 1,3-polyol system is often found in polyoxygenated natural products such as polyene macrolide antibiotics and although several excellent methods have been reported,[2] the synthesis of stereochemically defined polyols is still highly required These polyols are presumed to be produced biogenetically from the corresponding polyketide precursor A by NAD(P)H reduction Our synthetic strategy is basically related to this biogenetic pathway and is schematically shown below If a terminal ketone in A is reduced to an alcohol, the resulting B will be



cyclized to the six-membered β-keto hemiacetal C and therefore, the reducing reagent may attack from the less hindered α-side producing the 3β-hydroxy compound D. Opening of the hemiacetal ring in D and the successive ring closure between the newly produced C-3 hydroxyl group and C-7 ketone is now possible to produce the isomeric hemiacetal E. Since E contains again the same β-keto hemiacetal structure as C, the higher homologue of syn-1,3-polyol such as F will be

produced by repetition of the same reaction sequence In this scheme, it is noteworthy that a six-membered β-keto hemiacetal is serving as a chiral syn-1,3-polyol chain producing unit

In the actual synthesis, the above scheme was modified to a more practical one The β-thioacetal-δ-lactone 1 [mp 78-80°C, NMR δ 1 41 (d, J=6 4 Hz, Me), 2 97 (d, J=17 6 Hz, C-4α H)],[3] prepared from ethyl β-hydroxy butyrate,[4] was treated with CH_3COOt-Bu and LDA in THF at -78°C to produce the hemiacetal 2 [mp 107-109°C, NMR δ 2 49, 2.50 (ABq, J=15 Hz, C-6 H_2)] as a single product in 94% yield [5] The hemiacetal 2 was converted to the acetal 3 by methylation with $CH(OMe)_3$ and CSA, which was treated with NBS to afford the ketone 4 [NMR δ 3.25 (s, OMe)] in 74% yield. Stereostructure of 4 was determined based on the NOE measurement, enhancement of C-1 H signal (6.9%) observed upon irradiation of C-5 OMe suggested that C-1 H and C-5 OMe should be syn-diaxial [6] Therefore, in the reduction of 4, the hydride would attack the C-3 keto group preferentially from the less hindered equatorial side (see conformer 4A) In order to enhance the stereoselectivity of the reduction, we chose the sterically bulky reagent "Selectride" as reducing agent [7] Reduction of 4 with K-Selectride in THF at -78°C gave only the expected 3β-hydroxy isomer 5 [NMR δ 1 84 (dd, J=14 4, 3.6 Hz, C-4α H)] in 96% yield The configuration of the C-3 hydroxyl group was assigned as 3β-axial by the coupling constant (J=3.6 Hz) between C-3 H and C-4α axial H in the NMR spectrum Subsequent treatment of 5 with excess 1,3-propanedithiol and $BF_3 \cdot Et_2O$ in CH_2Cl_2 at -40°C produced the δ-lactone 6 [NMR δ 1 27 (d, J=6 1 Hz, Me), 2 93 (d, J=17.1 Hz, C-6α H)] in 80% yield [8] In this reaction, transthioacetalization and lactonization took place successively releasing the C-1 hydroxyl group from the hemiacetal ring as expected Since the product 6 has the same β-thioacetal-δ-lactone moiety as the starting material 1, the same reaction sequence described above is expected to be repeated



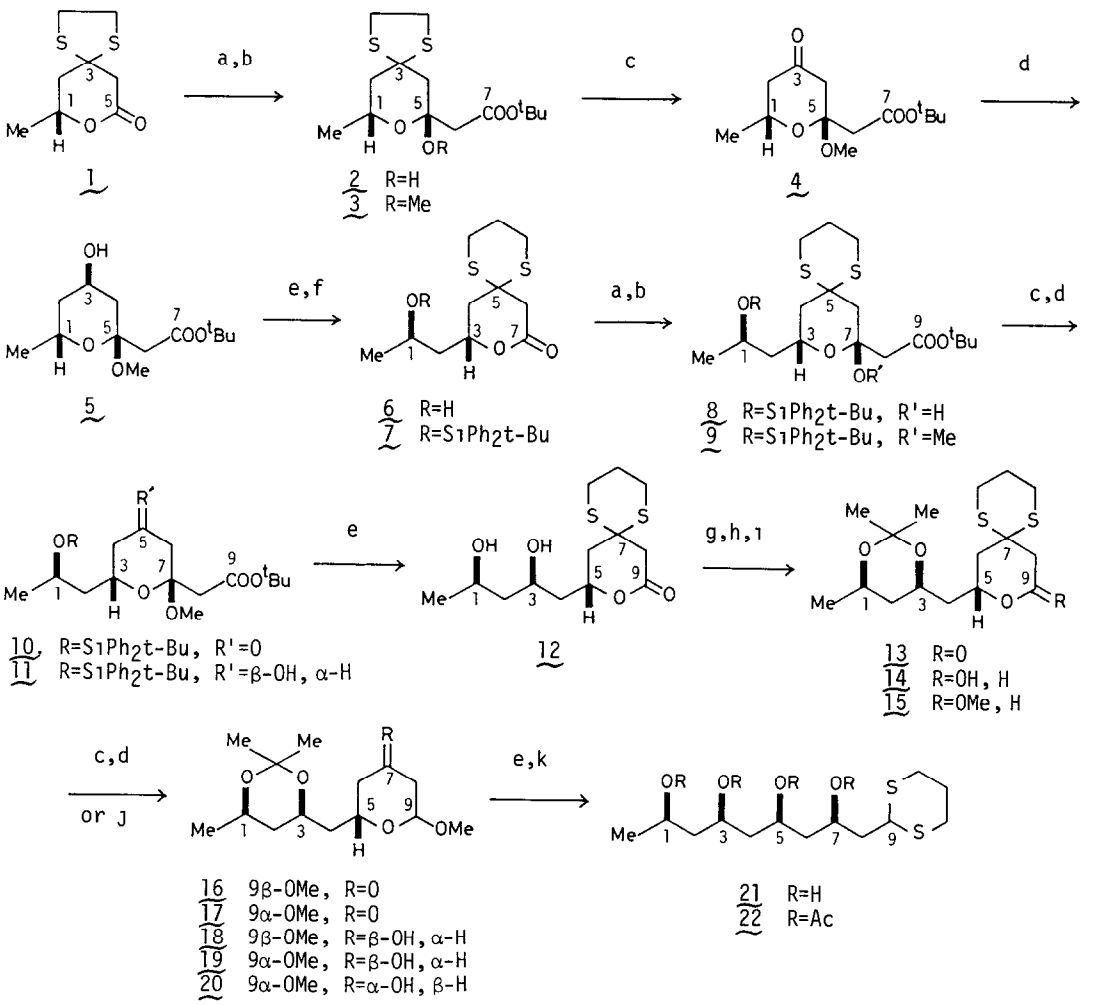
4A

Indeed, the δ-lactone 6, after protection of the C-1 hydroxyl group as the t-butyldiphenylsilyl ether (81%), was successfully converted to the δ-lactone 12 in five steps (i~v), (i) introduction of C-2 unit (CH_3COOt-Bu/LDA/THF/-78°C 7→8, 74% yield), (ii) methylation of hemiacetal ($CH(OMe)_3$/CSA/CH_2Cl_2/MeOH/rt 8→9), (iii) dethioacetalization (NBS/$AgNO_3$/Na_2CO_3/aq MeCN/0°C 9→10), (iv) reduction (K-Selectride/THF/-78°C 10→11, 65% yield from 8), (v) transthioacetalization and successive lactonization (1,3-propanedithiol/$BF_3 \cdot Et_2O$/CH_2Cl_2/-40~-20°C 11→12, 74% yield) [8,9] K-Selectride reduction of 10 proceeded with complete stereoselection and afforded the desired 5β-hydroxy isomer 11 The stereochemistry of the C-5β hydroxyl group in 11 was confirmed based on the NMR data ($J_{5,6\alpha}$=3.7 Hz) The lactone 12 contains again the same β-thioacetal-δ-lactone moiety as 1 and 6, which shows that from this unique unit the ethanol moiety whose secondary hydroxyl group is syn to the β-hydroxyl group is newly produced through a series of the reactions (one cycle, five steps, i~v) Therefore, further repetition of the same reaction sequence would, in principle, produce the higher homologue of syn-1,3-polyol

Having confirmed the repeatability of the sequence (i~v), we then examined the termination of the reaction After protection of the C-1,3 dihydroxyl group in 12 as an acetonide, 13 was reduced with DIBAH to give the lactol 14 in 60% yield Subsequent methylation [$CH(OMe)_3$/PPTS] of 14 followed by NBS treatment yielded a 1 1 mixture of the 9β- and 9α-methoxy ketones, 16 [NMR δ 3.37 (s, OMe)] and 17 [NMR δ 3.54 (s, OMe)], in 90% yield. The mixture of 16 and 17, without separation,[10] was reduced with K-Selectride to give a mixture of 18, 19, and 20 in a

ratio of 100 84 32 (73% yield).[11] Namely, reduction of the 9β-methoxy ketone 16 produced only the 7β-hydroxy compound 18 as expected,[12] while the 9α-methoxy ketone 17 gave the undesired 7α-hydroxy isomer 20 along with the 7β-hydroxy compound 19 On the other hand, reduction of the mixture of 16 and 17 with KS-Selectride in THF gave only the 7β-hydroxy compounds 18 and 19 in a ratio of 1 1 (39% yield) [13] Finally, on treatment with 1,3-propanedithiol and BF_3 Et_2O at 0°C, the 7β-hydroxy compounds, 18 and 19, were effectively converted to the syn-1,3,5,7-tetraol 21 in 69% yield, which was acetylated (Ac_2O/py/rt) to give the syn-1,3,5,7-tetraacetate 22 [NMR δ 2 032, 2 057, 2 065, 2 068 (each s, 4xAc)]

A practical method for the synthesis of the functionalized syn-1,3-polyol system was thus established The synthesis of optically active natural products containing syn-1,3-polyol system is now in progress.



a CH_3COOt-Bu/LDA/THF/-78°C, b $CH(OMe)_3$/CSA/CH_2Cl_2/MeOH/rt, c NBS/$AgNO_3$/Na_2CO_3/aq MeCN/0°C, d K-Selectride/THF/-78°C, e 1,3-propanedithiol/BF_3 Et_2O/CH_2Cl_2, f t-$BuPh_2SiCl$/imidazole/DMF/rt, g $Me_2C(OMe)_2$/CSA/CH_2Cl_2/rt, h DIBAH/toluene/-78°C, i $CH(OMe)_3$/PPTS/CH_2Cl_2/rt, J KS-Selectride/THF/-30∼-10°C, k Ac_2O/pyridine/rt

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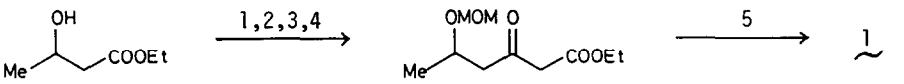
References and Notes

1. T. Nakata and T Oishi, Tetrahedron Lett., 21, 1641 (1980), T Nakata, T Tanaka, and T. Oishi, ibid., 22, 4723 (1981), T. Nakata, T Tanaka, and T. Oishi, ibid., in press.
2 P. A. Bartlett and K K. Jernstedt, J. Am. Chem. Soc , 99, 4829 (1977), P. A. Bartlett and K. K. Jernstedt, Tetrahedron Lett., 21, 1607 (1980), P A Bartlett, J. D Meadows, E. G. Brown, A. Morimoto, and K. K Jernstedt, J. Org Chem , 47, 4013 (1982), G Cardillo, M Orena, G Porzi, and S. Sandri, J. Chem. Soc. Chem. Comm , 465 (1981), M Hirama and M Uei, Tetrahedron Lett., 23, 5307 (1982), D M. Floyd and A W Fritz, ibid., 22, 2847 (1981), J M. Finan and Y. Kishi, ibid., 23, 2719 (1982), P. Ma, V S Martin, S Masamune, K B. Sharpless, and S. M Viti, J. Org. Chem., 47, 1378 (1982), K C Nicolaou and J Uenishi, J. Chem. Soc. Chem. Comm., 1292 (1982), K Narasaka and H C. Pai, Chem Lett , 1415 (1980)
3 The NMR spectra of the compounds (1~22) were obtained in $CDCl_3$ on a JEOL FX-400 or GX-400 spectrometer (400 MHz).
4 The starting material 1 was synthesized by the route shown below The optically active β-hydroxy esters are readily prepared. Therefore, when these compounds are used, the optically active 1 and thence optically active 1,3-polyols can be synthesized.



1) $MeOCH_2Cl$/i-Pr_2NEt, 2) DIBAH (or $LiAlH_4$, PCC), 3) CH_3COOt-Bu/LDA, 4) Jones oxidation, 5) ethanedithiol/BF_3 Et_2O

5. cf. A J. Duggan, M A Adams, P J Brynes, and J Meinwald, Tetrahedron Lett., 4323 (1978)
6 The present result was confirmed by NOE difference spectrum
7 cf. H C Brown and S. Krishnamurthy, Aldrichimica Acta, 12, No 1, 3 (1979)
8. The reaction mixture was directly separated by silicagel column or PTLC after excess 1,3-propanedithiol was removed in vacuo
9 The reaction was carried out until the silyl group was completely removed (ca. 7 hr).
10 No attempt was made to separate the mixture, although the analytical TLC indicated the two separated spots
11 The ratio was determined by NMR data The three isomers, 18, 19, and 20, are separable on preparative TLC. NMR 18 δ3.390 (s, OMe), 4 07 (m, $W_{h/2}$=10 Hz, C-7 H), 19 δ3 493 (s, OMe), 4.33 (m, $W_{h/2}$=7.4 Hz, C-7 H), 20 δ3.489 (s, OMe), 3 84 (m, $W_{h/2}$=24 Hz, C-7 H)
12 cf. S Danishefsky, J. F. Kerwin Jr , and S Kobayashi, J Am Chem Soc , 104, 358 (1982)
13 Although TLC analysis of the reaction mixture showed almost no by-product, the yield was rather low The yield is not optimized yet

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