Tetrahedron Letters,Vol.26,No.1,pp 75 - 78,1985
Printed in Great Britain

0040-4039/85 $3.00 + .00

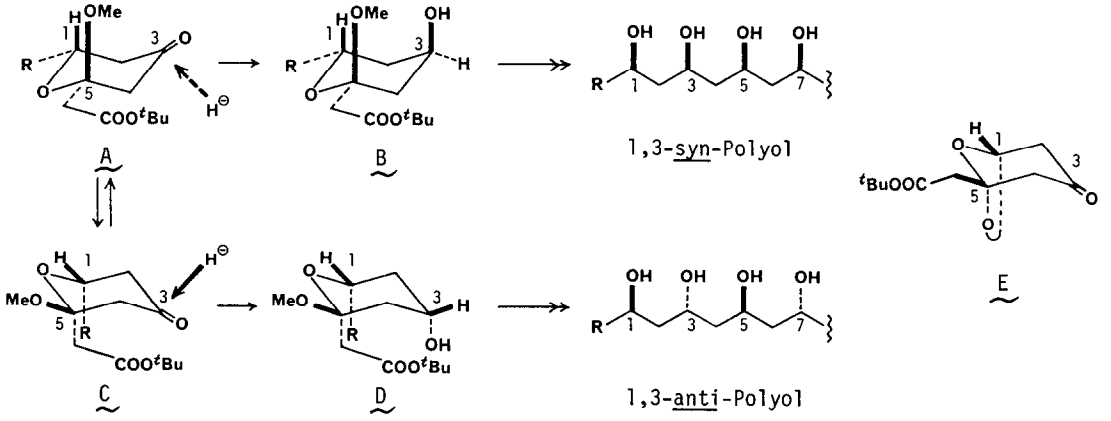
STEREOSELECTIVE SYNTHESIS OF THE OPTICALLY ACTIVE FUNCTIONALIZED 1,3,5-ALL-ANTI-TRIOL

Tadashi Nakata,* Shigeto Nagao, and Takeshi Oishi*
RIKEN (The Institute of Physical and Chemical Research)
Wako-shi, Saitama 351-01, Japan

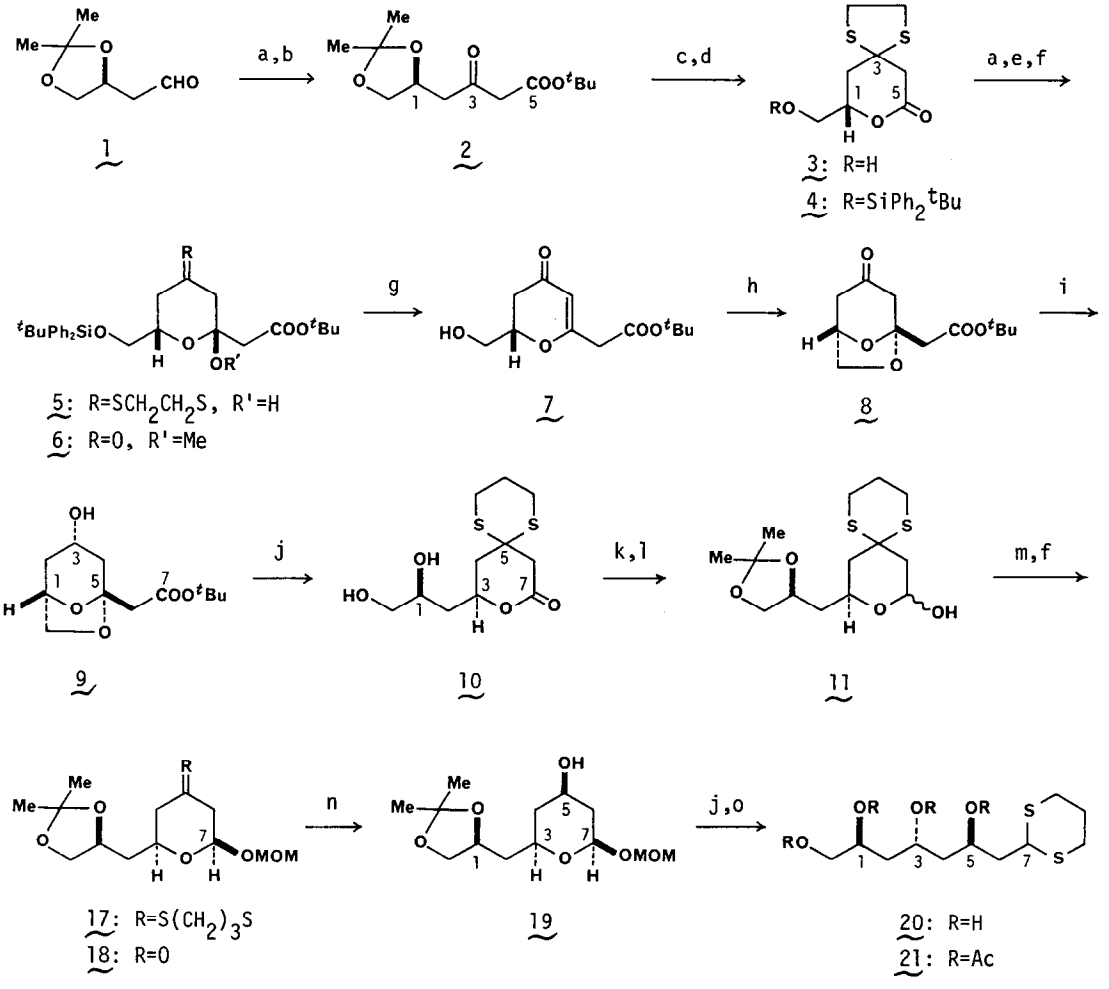
Summary: The optically active 1,3,5-all-anti-triol 20 was synthesized starting from (S)-(-)-malic acid with complete stereoselection, based on the stereoselective reduction of cyclic β-keto acetal and successive transthioacetalization.

Structural studies on polyene macrolide antibiotics have been extensively undertaken using modern techniques. However, even relative configurations of 1,3-polyols characterizing this type of antibiotics have not been determined yet, except for amphotericin B.[1] Therefore, development of a method for the synthesis of stereochemically defined 1,3-polyol functions is a prerequisite for successful total synthesis. We recently developed a highly stereocontrolled method for the synthesis of 1,3-syn-polyol based on the stereoselective reduction of a six-membered β-keto acetal A and successive transthioacetalization.[2] We now report the synthesis of the optically active 1,3,5-all-anti-triol derivative 20 with virtually complete stereoselection by slightly modifying the synthetic strategy for 1,3-syn-polyol.[3]

Our strategy for 1,3-anti-polyol synthesis is as follows. K-Selectride reduction of A, a key intermediate for the synthesis of 1,3-syn-polyol, took place from the less hindered α-side to produce exclusively 3β(axial)-alcohol B, corresponding to 1,3-syn-diol.[2] However, if A is converted to the other conformer C by ring inversion, the reduction should take place from the less hindered β-side producing 3α(axial)-alcohol D, corresponding to 1,3-anti-diol. The problem is how to fix the thermodynamically unstable conformer C. This difficulty was simply overcome by converting A [R=$(CH_2)_nOH$] into a ketone having a bicyclic acetal structure exemplified by E.



Treatment of aldehyde 1,[4] prepared from (S)-(-)-malic acid, with LDA and MeCOO-t-Bu followed by PCC oxidation[5] afforded β-keto ester 2 in 65% yield. Thioacetalization of 2 with ethanedithiol and $BF_3 \cdot Et_2O$ produced δ-lactone 3, and the hydroxyl group was protected with t-$BuPh_2SiCl$[6] giving δ-lactone 4[7] in 64% yield. Reaction of 4 with lithium enolate of t-butyl acetate in THF at -78°C afforded hemiacetal 5[7] as a single product in 93% yield.[8] Treatment of 5 with $CH(OMe)_3$ and DL-10-camphorsulfonic acid (CSA) in MeOH-CH_2Cl_2 (78%) and successive dethioacetalization with NBS in aq MeCN gave ketone 6[7] (93%). Desilylation of 6 with n-Bu_4NF was accompanied by an elimination of MeOH affording enone 7[7] in 76% yield. CSA treatment of 7 in CH_2Cl_2 gave the desired bicyclic acetal 8[7] in 48% yield (77% based on the consumed 7) along



1

2

3: R=H
4: R=$SiPh_2{}^tBu$

5: R=SCH_2CH_2S, R'=H
6: R=O, R'=Me

7

8

9

10

11

17: R=$S(CH_2)_3S$
18: R=O

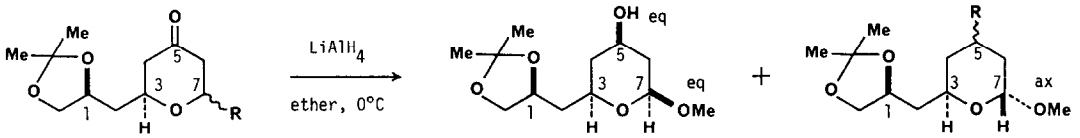
19

20: R=H
21: R=Ac

a: LDA/MeCOO-t-Bu/THF/-78°C, b: PCC/3A molecular sieves/CH_2Cl_2/rt, c: $HSCH_2CH_2SH/BF_3 \cdot Et_2O$/$CH_2Cl_2$/rt, d: t-$BuPh_2SiCl$/imidazole/DMF/rt, e: $CH(OMe)_3$/CSA/MeOH/CH_2Cl_2/rt, f: NBS/$AgNO_3$/Na_2CO_3/aq MeCN/0°C, g: n-$Bu_4NF \cdot 3H_2O$/THF/rt, h: CSA/CH_2Cl_2/rt, i: K-Selectride/THF/-78°C, j: $HS(CH_2)_3SH/BF_3 \cdot Et_2O/CH_2Cl_2$, k: $Me_2C(OMe)_2$/CSA/CH_2Cl_2/rt, l: DIBAH/toluene/-78°C, m: $BrCH_2OMe$/i-Pr_2NEt/CH_2Cl_2/reflux, n: $LiAlH_4/Et_2O$/0°C, o: Ac_2O/pyridine/rt

with the recovered 7 (38%). Reduction of 8 with K-Selectride in THF at -78°C took place, as expected, from the less hindered β-side to produce 3α(axial)-hydroxy isomer 9[7] as a single product in 82% yield. The configuration of the C-3 hydroxyl group was assigned as axial by ^{1}H NMR analysis ($W_{1/2}$=10 Hz; C-3 H). On treatment of 9 with 1,3-propanedithiol and $BF_3 \cdot Et_2O$ in CH_2Cl_2 at -40°C, transthioacetalization and lactone formation between the newly developed C-3 hydroxyl group and the t-butyl ester took place and the desired δ-lactone 10[7] was produced in 96% yield. Since δ-lactone 10 contains the same β-thioacetal-δ-lactone moiety having hydroxyl group on the side chain as 3, the repetition of the same reaction sequence would produce the higher homologue of 1,3-anti-polyol.

Here, we examined the termination of this reaction. After the protection of the glycol moiety as an acetonide (79%), δ-lactone 10 was reduced with DIBAH to lactol 11 in 84% yield.[9] Treatment of 11 with $CH(OMe)_3$ and CSA in MeOH-CH_2Cl_2 and successive dethioacetalization produced a 4 : 5 mixture of 7β- and 7α-methoxy acetals 12[7] and 13[7]. In $LiAlH_4$ reduction, 7β(equatorial)-methoxy acetal 12 gave only the desired 5β(equatorial)-alcohol 14[7], while 7α(axial)-methoxy acetal 13 yielded a 3 : 2 mixture of 5β(equatorial)-alcohol 15[7] and its isomer 16[7]. These results suggest that the anomeric alkoxy group should be fixed to equatorial



12: R=β-OMe
13: R=α-OMe

14

15: R=β-OH
16: R=α-OH

in order to induce the complete 3,5-anti stereoselection. After several attempts, alkylation of 11 with $BrCH_2OMe$ and i-Pr_2NEt in CH_2Cl_2 under reflux was found to afford exclusively the required 7β(equatorial)-MOM ether 17[7] in 98% yield.[10] MOM ether 17 was converted by NBS treatment to ketone 18[7] in 79% yield. $LiAlH_4$ reduction of 18 yielded only the expected 5β(equatorial)-hydroxy isomer 19[7] in quantitative yield.[11] The stereochemistry of 19 was confirmed based on the NMR data ($W_{1/2}$=25 Hz; C-5 H: $J_{6\beta,7\alpha}$=9.8 Hz). Thus, $LiAlH_4$ reduction of the β-keto cyclic acetal having an equatorial alkoxy group at the anomeric position was proved to be an attractive alternative to the aforementioned K-Selectride reduction of the β-keto bicyclic acetal. Finally, treatment of 19 with 1,3-propanedithiol and $BF_3 \cdot Et_2O$ in CH_2Cl_2 gave 1,3,5-all-anti-triol derivative 20 in 59% yield. Acetylation of 20 with Ac_2O in pyridine afforded the corresponding tetraacetate 21[7] in 78% yield.

Thus, a highly stereoselective method for the optically active 1,3-anti-polyol was established. Application of the newly developed methods for the synthesis of 1,3-syn- and anti-polyols to the synthesis of natural products involving 1,3-syn- and/or anti-polyol functions is under investigation.

Acknowledgement: This work was supported in part by a Grant-in-Aid (No 57218096) for Scientific Research from the Ministry of Education, Science, and Culture.

References and Notes

1. P. Ganis, G. Avitabile, W. Mechlinski, and C. P. Schaffner, J. Am. Chem. Soc., 93, 4560 (1971).
2. T. Nakata, S. Takao, M. Fukui, T. Tanaka, and T. Oishi, Tetrahedron Lett., 24, 3873 (1983). Other approaches for 1,3-syn-polyol synthesis are cited therein. See also, B. H. Lipshutz and J. A. Kozlowski, J. Org. Chem., 49, 1147 (1984).
3. Other approaches for 1,3-anti-diol synthesis; P. Ma, V. S. Martin, S. Masamune, K. B. Sharpless, and S. M. Viti, J. Org. Chem., 47, 1378 (1982); A. R. Chamberlin and R. L. Mulholland, Jr., Tetrahedron, 40, 2297 (1984); K. Narasaka and F.-C. Pai, Chemistry Lett., 1415 (1980), Tetrahedron, 40, 2233 (1984).
4. S. Hanessian, A. Ugolini, and M. Therien, J. Org. Chem., 48, 4427 (1983).
5. E. J. Corey and J. W. Suggs, Tetrahedron Lett., 2647 (1975).
6. S. Hanessian and P. Lavallee, Can. J. Chem., 53, 2975 (1975).
7. ^{1}H NMR spectra were taken on a JEOL GX-400 instrument in $CDCl_3$ and the optical rotations were measured in $CHCl_3$.
4: $[\alpha]_D^{28}$ +8.1° (c=1.33); NMR: δ 2.97 (d, J=17.6 Hz; C-4α H), 3.18 (dd, J=17.6, 2.5 Hz; C-4β H). 5: $[\alpha]_D^{25}$ +6.1° (c=1.03); NMR: δ 2.12 (dd, J=13.7, 2.0 Hz; C-4α H), 2.38 (dd, J=13.7, 2.0 Hz; C-4β H), 5.29 (d, J=2.0 Hz; OH). 6: $[\alpha]_D^{26}$ +22.0° (c=1.30); IR (neat): 1725 cm^{-1}; NMR: δ 3.23 (s; OMe). 7: $[\alpha]_D^{26}$ +116.7° (c=1.04); NMR: δ 5.42 (s; C-4 H). 8: $[\alpha]_D^{25}$ -28.6° (c=0.8); NMR: δ 2.84 (d, J=16.6 Hz; C-4β H), 4.89 (td, J=4.9, 1.5 Hz; C-1 H). 9: $[\alpha]_D^{25}$ -31.6° (c=0.8); NMR: δ 2.16 (dd, J=14.8, 4.8 Hz; C-4β H), 4.07 (m, $W_{1/2}$=10 Hz; C-3β H). 10: NMR: δ 2.94 (d, J=17.1 Hz; C-6β H), 3.20 (dd, J=17.1, 2.0 Hz; C-6α H). 12: NMR: δ 3.55 (s; OMe), 4.61 (dd, J=8.9, 2.8 Hz; C-7α H). 13: NMR: δ 3.37 (s; OMe), 5.11 (broad d, J=4.1 Hz; C-7β H). 14: NMR: δ 3.50 (s; OMe), 3.85 (tt, J=11.2, 4.9 Hz, $W_{1/2}$=29 Hz; C-5α H). 15: NMR: δ 3.32 (s; OMe), 4.11 (tt, J=11.2, 4.9 Hz; C-5α H). 16: NMR: δ 3.39 (s; OMe), 4.05 (m, $W_{1/2}$=10 Hz; C-5β H). 17: NMR: δ 3.41 (s; OMe), 5.05 (dd, J=9.5, 2.0 Hz; C-7α H). 18: IR (neat): 1725 cm^{-1}; NMR: δ 4.98 (dd, J=8.9, 2.8 Hz; C-7α H). 19: $[\alpha]_D^{22}$ +93.8° (c=0.5); NMR: δ 3.88 (m, $W_{1/2}$=25 Hz; C-5α H), 4.70 (dd, J=9.8, 2.2 Hz; C-7α H). 21: $[\alpha]_D^{22}$ -5.2° (c=1.09); NMR: δ 2.026, 2.047, 2.059, 2.071 (each s; 4 x OAc), 4.03 (dd, J=7.6, 6.3 Hz; C-7 H).
8. Cf. A. J. Duggan, M. A. Adams, P. J. Brynes, and J. Meinwald, Tetrahedron Lett., 4323 (1978).
9. The axial and equatorial ratio of the anomeric hydroxyl groups of 11 is estimated to be ca. 1 : 4 (in $CDCl_3$), the latter predominating.
10. Since the anomeric axial hydroxyl group of 11 is in the 1,3-diaxial relationship with one of the C-S bond of the thioacetal group, the equatorial hydroxyl group should be alkylated much faster with large and effective $BrCH_2OMe$ than the axial hydroxyl group under basic conditions. As the equatorial anomer is consumed, the axial one would be epimerized to the other, the equatorial MOM derivative 17 being ultimately accumulated.
11. Cf. D. C. Wigfield and S. Feiner, Can. J. Chem., 56, 789 (1978).

(Received in Japan 18 September 1984)