Iterative Methodology for the Stereocontrolled Synthesis of Polyol Chains Employing 2-Acetylthiazole as Lactaldehyde Equivalent

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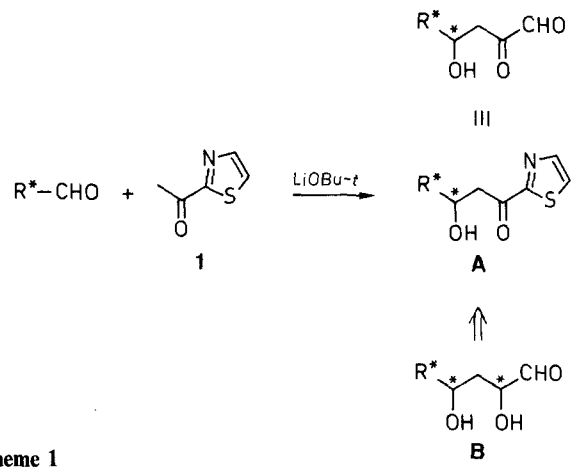
Received 7 December 1992; revised 2 February 1993

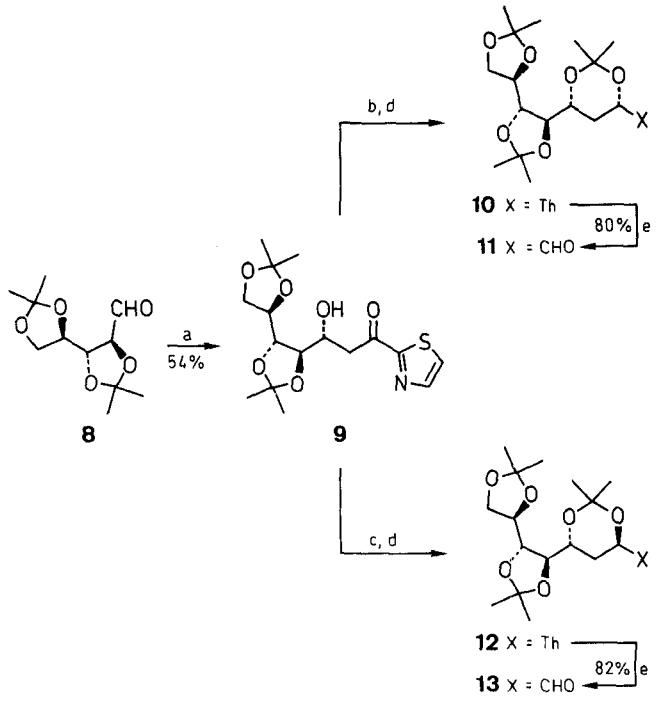
The *anti*-diastereoselective addition (ds 90–92%) of the lithium enolate of 2-acetylthiazole to chiral (poly)alkoxy aldehydes and the stereocontrolled ketone reduction of the resultant aldols using diisobutylaluminum hydride/tetramethylammonium triacetoxyborohydride followed by the aldehyde unmasking from the thiazole ring, afford three-carbon higher homologue aldehydes bearing a *syn*- or *anti*-1,3-diol unit. The iterative repetition of the sequence provides a route to polyhydroxylated chains having 1,3- and 1,2-diol units. In this methodology 2-acetylthiazole serves as the surrogate of lactaldehyde and its lithium enolate as the equivalent of the α-hydroxypropanal β-anion synthon.

Given the thiazole to formyl equivalence,[1] the addition of the lithium enolate of 2-acetylthiazole (2-ATT, **1**) to chiral alkoxy aldehydes[2] provides a convenient method for the installation of a masked 4-hydroxy-2-oxobutanal fragment in a (poly)alkoxy chain R* (Scheme 1). This carbon–carbon bond forming reaction occurs with high stereoselectivity favoring attack *anti* to the resident α-alkoxy group of the aldehyde.[3] The β-hydroxy ketone **A** prepared in this way is suitable for different synthetic elaborations. Intramolecular ketalization of the carbonyl and thiazole to aldehyde unmasking, leads to a pyranose bearing a formyl group at C-1 (aldosulose),[3] whereas the ketone reduction followed by the aldehyde liberation, affords a 1,3-dihydroxybutanal derivative **B**.[2,4] In the latter sequence, 2-ATT (**1**) appears to serve as the surrogate of lactaldehyde and its lithium enolate as the equivalent of the β-anion of this aldehyde, i.e. a synthon which is not directly accessible by enolization of lactaldehyde.[5] We now wish to describe the iterative application of this protocol to the synthesis of polyol chains. Either *syn*- and *anti*-1,3-diol units are assembled by stereocontrolled reduction of the aldol carbonyl using suitable metal hydride reducing agents. The numerous natural products of polyacetate and polypropionate origin such as polyene and polyol macrolide antibiotics[6] in which are embodied 1,3-polyol segments, have stimulated in recent years several synthetic strategies for the construction of 1,3-dioxygenated carbon chains.[7] Particularly attractive are methods which involve a reiteration of key chemical manipulations since they allow to extension of the chain to any required length and provide potentially automatable procedures suitable for robot synthesis.



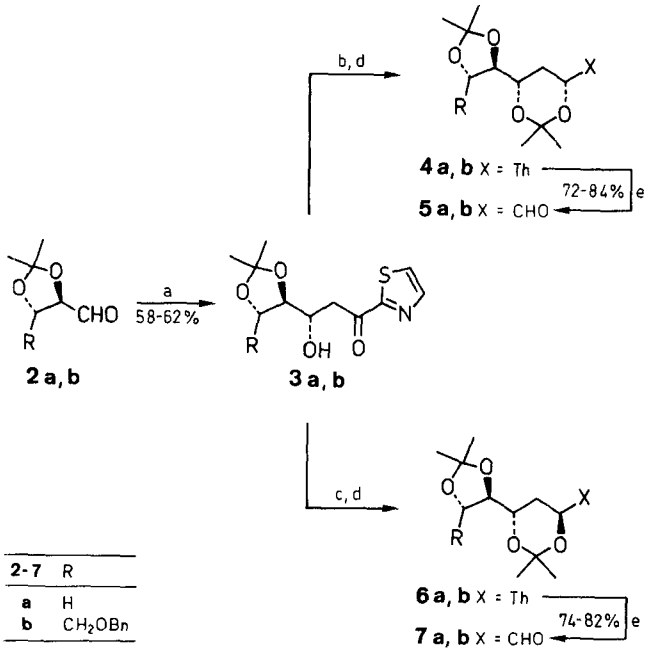
Scheme 1

The addition of the lithium enolate of 2-ATT (**1**) to 2,3-*O*-isopropylidene-D-glyceraldehyde (**2a**) (Scheme 2) and pentose 2,3:4,5-di-*O*-isopropylidene-D-arabinose (**8**) (Scheme 3) to give the corresponding *anti*-adducts **3a** and **9**, respectively, has already been described.[3] Under the same conditions, 4-*O*-benzyl-2,3-*O*-isopropylidene-L-threose (**2b**) (Mukaiyama aldehyde)[8] (Scheme 2) and 2-ATT (**1**) afforded the aldol **3b** with a good level of diastereoselectivity (ds 95%) and satisfactory isolated chemical yield (62%). The *anti*-configuration of **3b** (Felkin–Anh adduct)[9] was assigned based on precedent cases of aldol condensation of the lithium enolate of **1** with α,β-dialkoxy aldehydes.[3]



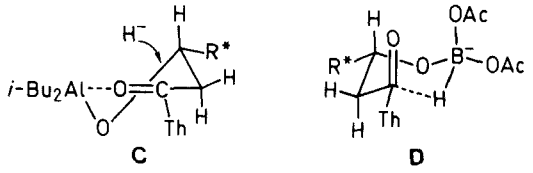
a) 2-ATT (**1**)/LiOBu-*t*/THF, −50°C, 2 h. b) DIBALH/THF, −78°C, 1 h. c) TETABH/MeCN/AcOH, −40°C, 24 h. d) acetone/DMP/CSA, r.t., 2 h. e) 1. MeI/MeCN, reflux, 16 h; 2. $NaBH_4$/MeOH, r.t., 30 min; 3. $HgCl_2$/MeCN/H_2O, r.t., 15 min.

Scheme 3



Scheme 2

Since various methods are available for the reduction of β-hydroxy ketones in a predictable and stereoselective manner,[10] two appropriate metal hydride reducing agents were employed for the *syn*- and *anti*-selective reduction of β-hydroxy 2-thiazolyl ketones **3a, b**, and **9**. Treatment of these compounds with diisobutylaluminum hydride (DIBALH) in tetrahydrofuran afforded *syn*-1,3-diol diastereomers which were isolated and characterized as the acetonide derivatives (isopropylidenedioxy derivatives) **4a, b**, and **10**. Alternatively, the reduction with tetramethylammonium triacetoxyborohydride (TETABH) in acetonitrile/acetic acid mixture and acetonization of the resultant diols, afforded the *anti*-1,3-diol acetonides **6a, b**, and **12**. In all cases the reduction occurred with high levels of diastereoselectivity and the products were isolated in fairly good yields (Table 1). The stereochemistry of the isopropylidenedioxy derivatives, was confirmed by the substantial differences displayed by their ^{13}CNMR spectra and the Rychnovsky–Evans generalization.[11] The carbon resonances for the acetonide methyl groups of the *syn*-1,3-diol diastereomers **4a, b**, and **10** (Table 2) were quite distant one from the other, i.e. at 20 and 30 ppm, in agreement with a chair conformation with one methyl occupying the axial and the other the equatorial position. By contrast, the *anti*-diastereomers **6a, b**, and **12** (Table 2) which being in a twist boat conformation have both acetonide methyl groups in a similar geometrical arrangement, showed very close carbon resonance values in the range of 24–25 ppm. The opposite sense of asymmetric induction in the hydroxy directed reduction of acyclic β-hydroxy ketones with DIBALH and TETABH has been formulated to arise from an external[12] or intramolecular[10] hydride delivery in metal chelate structures. Accordingly, the model chelate structure **C** via oxygen–aluminum bond and structure **D** via oxygen–boron bond (Figure) appear to apply quite well to the hydroxy ketones **3a, b**, and **9**. This implies that the thiazole ring flanking the carbonyl group does not interfere with the above chelating processes.



C D

Figure.

Table 1. Reduction of β-Hydroxy Ketones to 1,3-Diols with DIBALH and TETABH

Ketone	Metal Hydride	*Syn/Anti*	1,3-Diol	Yield (%)
3a	DIBALH	> 95 : 5	**4a**	98
3a	TETABH	< 5 : 95	**6a**	96
3b	DIBALH	94 : 6	**4b**	91
3b	TETABH	< 5 : 95	**6b**	90
9	DIBALH	> 95 : 5	**10**	96
9	TETABH	< 5 : 95	**12**	98
14	DIBALH	93 : 7	**15**	92

The aldehydes **5a, b**, **7a, b**, **11**, and **13** (Table 3) were released in good yields from the isopropylidenedioxy-1-(2-thiazolyl)alkanes **4a, b**, **6a, b**, **10**, and **12** by the usual one-pot thiazole-to-formyl deblocking protocol or its recently improved version.[13] Quite interestingly, the 4-formyl *anti*-1,3-diol acetonides **7a, b** and **13** upon treatment with potassium carbonate in methanol epimerized almost quantitatively to the more stable *syn*-isomers **5a, b**, and **11**. This provides a route to *syn*-α,γ-dihydroxybutanal fragments via *anti*-stereoisomers which complements the above stereodivergent reductive approach.

In order to substantiate the utilization of the above three-carbon homologation strategy in an iterative form, the sequence was repeated with the aldehyde **5a** (Scheme 4). The aldol condensation of this aldehyde with the lithium enolate derived from 2-ATT (**1**), afforded a mixture of diastereomers in 90 : 10 ratio from which the major *anti*-isomer **14** was isolated in 60% yield. The stereochemistry of this compound was assumed to be *anti* in obtemperance to the Felkin–Anh model[9] and analogy with other aldols from 2-ATT (**1**). The reduction of **14**

Table 2. 2-[Bis- and Tris(isopropylidenedioxy)alkyl]thiazoles

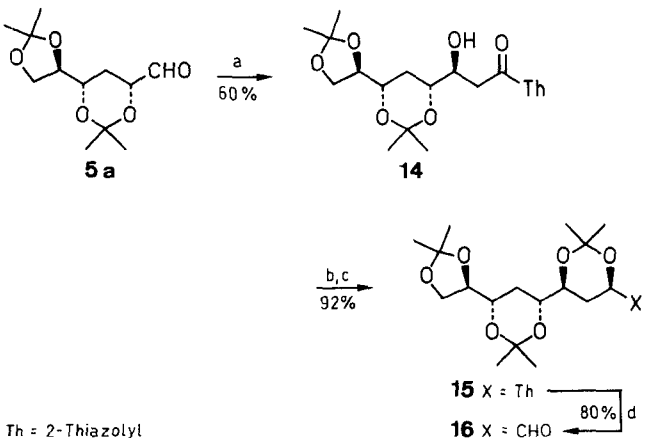
Entry[a,b]	Yield[c] (%)	$[\alpha]_D^{20}$ (*c*, $CHCl_3$)	^1H NMR ($CDCl_3$) (300 MHz) δ, *J* (Hz)	^{13}C NMR ($CDCl_3$) (75.5 MHz) δ
4a	98	+55.2° (0.21)	1.12 (s, 3H), 1.23 (s, 3H), 1.39 (s, 3H), 1.48 (s, 3H), 1.69 (ddd, 1H, *J* = 13.0, 11.6, 11.1), 2.46 (ddd, 1H, *J* = 13.0, 2.7, 2.3), 3.73 (ddd, 1H, *J* = 11.1, 6.9, 2.3), 3.80 (m, 2H), 3.94 (dd, 1H, *J* = 8.0, 6.3), 5.16 (dd, 1H, *J* = 11.6, 2.7), 6.62 (d, 1H, *J* = 3.2), 7.59 (d, 1H, *J* = 3.2)[d]	19.62, 24.86, 26.51, 29.57, 34.72, 66.93, 69.84, 70.33, 78.10, 99.77, 109.65, 119.06, 142.63, 172.65
6a	96	−19.2° (0.12)	1.21 (s, 3H), 1.25 (s, 3H), 1.28 (s, 3H), 1.39 (s, 3H), 2.36 (ddd, 1H, *J* = 13.4, 8.5, 6.4), 2.47 (ddd, 1H, *J* = 13.4, 8.4, 5.6), 3.79 (dd, 1H, *J* = 8.3, 5.1), 3.86 (dd, 1H, *J* = 8.3, 6.3), 3.94 (m, 2H), 5.22 (dd, 1H, *J* = 8.4, 6.4), 6.61 (d, 1H, *J* = 3.2), 7.54 (d, 1H, *J* = 3.2)[d]	24.57, 24.98, 25.57, 26.43, 33.90, 66.93, 67.43, 67.81, 77.82, 101.31, 109.81, 119.40, 142.67, 172.13
4b	91	−6.61° (0.92)	1.29 (s, 3H), 1.31 (s, 6H), 1.49 (s, 3H), 1.63 (ddd, 1H, *J* = 13.1, 11.7, 11.5), 2.25 (ddd, 1H, *J* = 13.1, 2.8, 2.5), 3.53 (dd, 1H, *J* = 10.5, 6.6), 3.64 (dd, 1H, *J* = 7.7, 6.9), 3.68 (dd, 1H, *J* = 10.5, 2.8), 4.00 (ddd, 1H, *J* = 11.5, 6.9, 2.5), 4.11 (ddd, 1H, *J* = 7.7, 6.6, 2.8), 4.55 (d, 1H, *J* = 12.4), 4.62 (d, 1H, *J* = 12.4), 5.25 (dd, 1H, *J* = 11.7, 2.8), 7.30 (m, 6H), 7.70 (d, 1H, *J* = 3.2)	19.51, 26.79, 26.86, 29.41, 34.84, 69.78, 70.79, 71.22, 73.39, 79.43, 79.59, 99.73, 110.15, 119.06, 127.86, 127.96, 128.61, 138.56, 142.63, 172.57
6b	90	−13.3° (0.45)	1.35 (s, 3H), 1.39 (s, 3H), 1.42 (s, 3H), 1.43 (s, 3H), 2.27 (ddd, 1H, *J* = 13.3, 9.0, 6.2), 2.40 (ddd, 1H, *J* = 13.3, 8.8, 6.2), 3.56 (dd, 1H, *J* = 10.4, 6.2), 3.65 (dd, 1H, *J* = 10.4, 3.5), 3.90 (dd, 1H, *J* = 7.9, 6.2), 4.03 (m, 2H), 4.55 (d, 1H, *J* = 12.3), 4.62 (d, 1H, *J* = 12.3), 7.30 (m, 6H), 7.71 (d, 1H, *J* = 3.2)	24.37, 25.35, 26.82, 26.92, 33.85, 67.40, 67.94, 71.07, 73.43, 78.89, 79.66, 101.34, 110.21, 119.38, 127.92, 127.99, 128.65, 138.52, 142.76, 172.55
10	96	+8.8° (0.40)	1.30 (s, 3H), 1.33 (s, 3H), 1.34 (s, 3H), 1.38 (s, 3H), 1.47 (s, 3H), 1.51 (s, 3H), 1.72 (pseudo dt, 1H, *J* = 12.8, 11.6), 2.12 (pseudo dt, 1H, *J* = 13.2, 2.7), 3.83 (dd, 1H, *J* = 6.1, 5.2), 3.93 (m, 2H), 4.04 (m, 1H), 4.10 (m, 2H), 5.26 (dd, 1H, *J* = 12.0, 2.9), 7.28 (d, 1H, *J* = 3.2), 7.70 (d, 1H, *J* = 3.2)	19.38, 24.95, 26.25, 27.14, 27.22, 29.44, 33.40, 66.48, 69.74, 69.87, 76.98, 78.66, 81.45, 99.82, 109.69, 110.41, 119.04, 142.48, 172.77
12	98	+13.5° (1.40)	1.32 (s, 3H), 1.37 (s, 6H), 1.39 (s, 3H), 1.40 (s, 3H), 1.47 (s, 3H), 2.18 (ddd, 1H, *J* = 13.4, 8.8, 6.1), 2.53 (ddd, 1H, *J* = 13.4, 9.3, 6.5), 3.77 (pseudo t, 1H, *J* = 6.4), 3.96 (m, 2H), 4.08 (m, 2H), 4.19 (m, 1H), 5.20 (dd, 1H, *J* = 8.8, 6.5), 7.29 (d, 1H, *J* = 3.2), 7.71 (d, 1H, *J* = 3.2)	24.28, 25.01, 25.45, 26.40, 26.70, 27.05, 27.25, 32.27, 66.96, 67.12, 67.61, 78.47, 81.56, 101.52, 109.87, 110.49, 119.42, 142.73, 172.69
15	92	−2.68° (0.56)	1.09 (s, 3H), 1.15 (s, 3H), 1.26 (s, 3H), 1.31 (ddd, 1H, *J* = 12.9, 11.9, 11.1), 1.36 (s, 3H), 1.40 (s, 3H), 1.48 (s, 3H), 1.66 (ddd, 1H, *J* = 13.1, 11.7, 11.3), 2.19 (ddd, 1H, *J* = 12.9, 2.4, 2.2), 2.50 (ddd, 1H, *J* = 13.1, 2.8, 2.5), 3.59 (ddd, 1H, *J* = 11.1, 7.0, 2.4), 3.68 (ddd, 1H, *J* = 7.0, 6.0, 2.9), 3.70 (ddd, 1H, *J* = 11.3, 6.4, 2.5), 3.91 (ddd, 1H, *J* = 11.9, 6.4, 2.2), 3.93 (dd, 1H, *J* = 10.2, 2.9), 4.01 (dd, 1H, *J* = 10.2, 6.0), 5.20 (dd, 1H, *J* = 11.7, 2.8), 6.61 (d, 1H, *J* = 3.2), 7.60 (d, 1H, *J* = 3.2)[d]	19.01, 24.78, 26.43, 29.47, 29.53, 31.15, 34.74, 67.44, 70.26, 70.92, 71.64, 71.97, 78.73, 98.51, 99.61, 109.29, 118.55, 142.77, 172.90

[a] All compounds are oils except **4a** (mp 107–108 °C).
[b] Satisfactory microanalyses obtained: C ±0.38, H ±0.22, N ±0.42.
[c] Yield of isolated products.
[d] Solvent C_6D_6.

Table 3. Bis- and Tris(isopropylidenedioxy)alkanals

Entry[a,b]	Yield[c] (%)	$[\alpha]_D^{20}$ (*c*, $CHCl_3$)	IR (cm^{-1}) ν (C=O)[d]	^1H NMR ($CDCl_3$/TMS) (300 MHz) δ, *J* (Hz)	^{13}C NMR ($CDCl_3$/TMS) (75.5 MHz) δ
5a	72	−6.5° (0.46)[e]	1720	1.06 (s, 3H), 1.20 (s, 3H), 1.27 (ddd, 1H, *J* = 13.1, 12.1, 11.3), 1.39 (s, 3H), 1.41 (s, 3H), 1.84 (ddd, 1H, *J* = 13.1, 3.1, 2.6), 3.53 (ddd, 1H, *J* = 11.3, 7.3, 2.6), 3.71 (ddd, 1H, *J* = 12.1, 3.1, 0.8), 3.74 (ddd, 1H, *J* = 7.3, 6.4, 5.1), 3.81 (dd, 1H, *J* = 8.4, 5.1), 3.88 (dd, 1H, *J* = 8.4, 6.4), 9.40 (d, 1H, *J* = 0.8)[f]	19.23, 24.78, 26.48, 27.92, 29.31, 66.94, 70.05, 73.67, 78.05, 99.25, 109.75, 201.33
7a	74	−10.6° (1.79)[e]	1725	1.33 (s, 3H), 1.38 (s, 3H), 1.40 (s, 6H), 1.90 (ddd, 1H, *J* = 13.3, 10.2, 6.9), 2.16 (ddd, 1H, *J* = 13.3, 6.3, 4.6), 3.65 (m, 2H), 4.02 (m, 2H), 4.28 (dd, 1H, *J* = 6.9, 6.3), 9.80 (br s, 1H)	23.73, 24.52, 24.90, 26.41, 26.77, 66.86, 67.42, 73.44, 77.88, 100.39, 109.87, 202.55
5b	84	−6.9° (0.51)	1730	1.33 (s, 3H), 1.37 (s, 3H), 1.39 (s, 3H), 1.40 (s, 3H), 1.43 (ddd, 1H, *J* = 13.0, 12.2, 11.4), 1.93 (ddd, 1H, *J* = 13.0, 3.0, 2.6), 3.51 (dd, 1H, *J* = 10.4, 6.5), 3.61 (dd, 1H, *J* = 7.1, 6.9), 3.66 (dd, 1H, *J* = 10.4, 3.0), 3.88 (ddd, 1H, *J* = 11.4, 6.9, 2.6), 4.06 (ddd, 1H, *J* = 7.7, 6.5, 3.0), 4.27 (ddd, 1H, *J* = 12.2, 3.0, 0.7), 4.55 (d, 1H, *J* = 12.2), 4.61 (dd, 1H, *J* = 12.2), 7.30 (m, 5H), 9.54 (d, 1H, *J* = 0.7)	19.12, 26.78, 28.02, 29.03, 29.14, 70.50, 71.14, 73.40, 73.54, 79.47, 79.50, 99.16, 110.22, 127.97, 128.24, 128.62, 138.52, 201.18
7b	82	−9.0 (0.92)	1725	1.26 (s, 3H), 1.32 (s, 3H), 1.39 (s, 3H), 1.42 (s, 3H), 1.95 (ddd, 1H, *J* = 13.2, 7.2, 9.7), 2.10 (ddd, 1H, *J* = 13.2, 6.5, 4.8), 3.53 (dd, 1H, *J* = 10.3, 6.3), 3.62 (dd, 1H, *J* = 10.3, 3.5), 3.72 (dd, 1H, *J* = 7.2, 6.4), 3.79 (ddd, 1H, *J* = 9.7, 6.4, 4.8), 4.00 (ddd, 1H, *J* = 7.2, 6.3, 3.5), 4.25 (dd, 1H, *J* = 7.2, 6.5), 4.54 (d, 1H, *J* = 12.2), 4.62 (d, 1H, *J* = 12.2), 7.30 (m, 5H), 9.76 (br s, 1H)	26.46, 26.78, 26.92, 27.01, 29.42, 67.73, 71.02, 73.24, 73.42, 79.03, 79.65, 100.44, 110.28, 127.98, 128.14, 128.65, 138.49, 202.33
11	80	+4.6° (0.87)	1725	1.32 (s, 3H), 1.37 (s, 3H), 1.40 (s, 3H), 1.43 (s, 3H), 1.46 (s, 6H), 1.55 (ddd, 1H, *J* = 13.2, 12.3, 11.6), 1.84 (ddd, 1H, *J* = 13.2, 3.1, 2.7), 3.84 (dd, 1H, *J* = 6.4, 5.3), 3.94 (m, 2H), 4.01 (ddd, 1H, *J* = 11.6, 6.4, 2.7), 4.11 (m, 2H), 4.29 (ddd, 1H, *J* = 12.3, 3.1, 0.8), 9.59 (d, 1H, *J* = 0.8)	19.12, 25.05, 26.37, 26.69, 27.23, 27.32, 29.34, 66.58, 69.57, 73.71, 76.76, 78.82, 81.52, 99.39, 109.84, 110.62, 201.59
13	82	+17.5° (0.65)	1720	1.32 (s, 3H), 1.37 (s, 6H), 1.38 (s, 3H), 1.39 (s, 3H), 1.42 (s, 3H), 2.00 (ddd, 1H, *J* = 13.1, 6.7, 2·5), 2.13 (ddd, 1H, *J* = 13.1, 7.2, 2.7), 3.97 (m, 3H), 4.10 (m, 3H), 4.30 (dd, 1H, *J* = 7.2, 6.7), 9.80 (br s, 1H)	23.67, 25.12, 25.60, 26.53, 26.70, 27.19, 27.43, 66.70, 67.03, 67.93, 73.44, 78.47, 81.53, 100.63, 109.77, 110.44, 204.43
16	80	+8.2° (0.85)	1720	1.03 (s, 3H), 1.11 (s, 3H), 1.21 (ddd, 1H, *J* = 12.9, 12.2, 11.0), 1.25 (s, 3H), 1.29 (ddd, 1H, *J* = 13.0, 11.4, 9.9), 1.37 (s, 3H), 1.38 (s, 3H), 1.39 (s, 3H), 1.87 (pseudo dt, 1H, *J* = 13.0, 2.6), 2.16 (dt, 1H, *J* = 12.9, 2.6), 3.47 (ddd, 1H, *J* = 11.0, 7.2, 2.6), 3.54 (ddd, 1H, *J* = 11.2, 7.3, 2.6), 3.68 (ddd, 1H, *J* = 11.4, 7.2, 2.6), 3.74 (ddd, 1H, *J* = 12.2, 3.2, 0.7), 3.92 (m, 2H), 4.05 (dd, 1H, *J* = 10.2, 8.6), 9.56 (d, 1H, *J* = 0.7)[f]	19.14, 19.53, 24.88, 26.47, 27.96, 29.38, 29.53, 30.74, 67.11, 70.41, 71.57, 71.66, 73.87, 78.49, 98.76, 99.33, 109.61, 201.63

[a] All compounds are oils.
[b] Satisfactory microanalyses obtained: C ± 0.40, H ± 0.24.
[c] Isolated yields.
[d] Solvent $CHCl_3$.
[e] Solvent MeOH.
[f] Solvent C_6D_6.



a) 2-ATT (**1**)/LiOBu-*t*/THF, −50°C, 2 h. b) DIBALH/THF, −78°C, 1 h. c) acetone/DMP/CSA, r.t., 2 h. d) 1. MeI/MeCN, reflux, 16 h; 2. $NaBH_4$/MeOH, r.t., 30 min; 3. $HgCl_2$/MeCN/H_2O, r.t., 15 min.

Scheme 4

with DIBALH and acetonization afforded the *syn*-1,3-dioxane derivative **15** whose stereochemistry was firmly established by ^{13}C NMR spectroscopy as above. Finally, the thiazole-to-formyl unmasking gave the polyalkoxynonanal **16** bearing a sequence of 1,2- and 1,3-diol groups.

In conclusion, 2-ATT (**1**) appears to be a valuable lactaldehyde equivalent in iterative methodology involving aldol condensation and stereocontrolled ketone reduction for the construction of polyhydroxylated carbon chains having a sequence of 1,2- and 1,3-diol units. The thiazole ring serves as a convenient masked formyl group since it tolerates various synthetic manipulations and is cleaved under mild and neutral conditions. The present strategy involves simple and reliable procedures which can be readily repeated and combined in appropriate ways to obtain polyol chains with various types of stereochemical arrays.

Melting points were taken using a Büchi 510 apparatus and are uncorrected. The ^1H and ^{13}C NMR spectra were recorded on a 300 MHz Gemini 300 Varian spectrometer unless otherwise stated using TMS as internal standard. IR spectra were recorded on a Perkin-Elmer Model 297 grating spectrophotometer. Elemental analyses were performed on a Model 1106 microanalyzer (Carlo Erba). Optical rotations were measured at ca. 20 °C using a Perkin-Elmer Model 214 polarimeter. TLC was carried out on glass-slides precoated with silica gel (Merck Kieselgel 60 F254) and preparative chromatography on columns of silica gel (Merck 70–230 mesh). All experiments were carried out with freshly distilled and dried solvents. 2-Acetylthiazole **(1)**, although commercially available, was conveniently prepared from 2-bromothiazole and EtOAc as described.[3] 2,3-*O*-Isopropylidene-D-glyceraldehyde[14] **(2a)**, 4-*O*-benzyl-2,3-*O*-isopropylidene-L-threose[8] **(2b)**, and 2,3:4,5-di-*O*-isopropylidene-D-arabinose[15] **(8)**, were prepared according to literature procedures. Satisfactory microanalyses also obtained for **3b** and **14**: C ± 0.15, H ± 0.35, N ± 0.13.

(3*S*,4*S*,5*S*)-6-*O*-Benzyl-4,5-*O*-isopropylidene-3,4,5,6-tetrahydroxy-1-(2-thiazolyl)-1-hexanone (3b):
To a well-stirred solution of *t*-BuOH (0.607 g, 8.2 mmol) in anhydr. THF (20 mL), BuLi (8.3 mmol, 5.2 mL of 1.6 M in hexanes) was added at r.t., and stirring was maintained for 30 min. The mixture was cooled to − 50 °C and a solution of the aldehyde **2b** (1.79 g, 7.16 mmol) and 2-acetylthiazole **(1)** (1.05 g, 8.3 mmol) in anhydr. THF (10 mL) was added dropwise. After 2 h the reaction was quenched with sat. aq NH_4Cl (20 mL), the mixture was stirred for additional 5 min at − 50 °C and then allowed to warm to r.t. H_2O was added (10 mL) and the organic layer separated. The aqueous layer was extracted with Et_2O (4 × 25 mL); the organic layers were combined, dried (Na_2SO_4), and the solvent was removed in vacuo to give the crude aldol **3b** in 96% diastereomeric purity by ^1H NMR analysis. The crude product was chromatographed (silica gel, hexane/Et_2O, 60:40) to give 1.67 g of pure **3b** (yield: 62%), oil; $[\alpha]_D^{20}$ − 14.6° (*c* = 0.7, $CHCl_3$).

IR ($CHCl_3$): ν = 1700 cm^{-1}.

^1H NMR ($D_2O/CDCl_3$): δ = 1.37 (s, 3 H), 1.39 (s, 3 H), 3.36 (dd, 1 H, *J* = 16.9, 8.7 Hz), 3.45 (dd, 1 H, *J* = 16.9, 3.6 Hz), 3.62 (m, 2 H), 3.79 (t, 1 H, *J* = 7.7 Hz), 4.20 (m, 2 H), 4.54 (s, 2 H), 7.29 (m, 5 H), 7.66 (d, 1 H, *J* = 3.2 Hz), 7.98 (d, 1 H, *J* = 3.2 Hz).

^{13}C NMR ($CDCl_3$): δ = 26.58, 26.64, 42.75, 69.27, 70.88, 73.63, 80.97, 82.08, 109.70, 126.68, 126.94, 128.07, 128.72, 137.94, 145.13, 167.62, 193.44.

Reduction with Diisobutylaluminum Hydride, DIBALH; General Procedure:
To a well-stirred solution of β-hydroxy ketone (2 mmol) in freshly distilled THF (40 mL) under N_2, DIBALH (4 mmol, 2.67 mL, 1.5 M in toluene) was added slowly at − 78 °C. After 1 h at − 78 °C, the solution was treated with MeOH (2 mL) and allowed to warm to r.t. The mixture was diluted with EtOAc (30 mL) and washed with aq 1 N NaOH (30 mL). The aqueous layer was extracted with EtOAc (3 × 25 mL) and the combined organic phases were washed with brine (2 × 30 mL), dried (Na_2SO_4) and concentrated in vacuo. The residue was filtered through a short column of silica gel with 2% MeOH in Et_2O as eluant to give the diol as a mixture of diastereomers whose ratio was determined by ^1H NMR analysis.

Reduction with Tetramethylammonium Triacetoxyborohydride, TETABH; General Procedure:
To a solution of TETABH (4.2 g, 16.0 mmol) in anhydr. MeCN (9 mL), anhydr. AcOH (9 mL) was added and the mixture stirred at r.t. for 30 min. The mixture was cooled to − 40 °C and a solution of β-hydroxy ketone (2 mmol) in anhydr. MeCN (3 mL) was added. The mixture was stirred at − 40 °C for 24 h, then quenched with 20 mL of 0.5 N aq sodium potassium tartrate and allowed to warm slowly to r.t. The mixture was diluted with EtOAc (50 mL) and washed with sat. aq $NaHCO_3$ (3 × 40 mL). The organic layer was dried (Na_2SO_4) and concentrated in vacuo. The residue was filtered through a short column of silica gel with 2% MeOH in Et_2O as eluant to give the diol as a mixture of diastereomers whose ratio was determined by ^1H NMR spectroscopy.

Acetonization of 1,3-Diols; General Procedure:
A solution of 1,3-diol (2 mmol), camphorsulfonic acid (CSA, 0.23 g, 1.0 mmol) in acetone (15 mL), and 2,2-dimethoxypropane (DMP, 15 mL) was stirred for 2 h. Sat. aq $NaHCO_3$ (25 mL) was addded and the mixture was extracted with Et_2O (3 × 30 mL). The combined organic layers were dried (Na_2SO_4) and distilled in vacuo. The residue was purified by column chromatography on silica gel (hexane/Et_2O, 70:30) to give the 1,3-diol acetonide (Table 2).

Formyl Deblocking; General Procedure:
A solution of the 2-thiazole derivative (1.5 mmol) in freshly distilled MeCN (25 mL) was treated with MeI (2.13 g, 15 mmol). The solution was refluxed until the starting material disappeared (8–10 h, TLC monitoring). The solution was concentrated in vacuo, then Et_2O was added to precipitate the *N*-methylthiazolium salt which was collected by filtration. The crude salt was dissolved in MeOH (30 mL) and the solution was treated with $NaBH_4$ (0.1 g, 2.63 mg) at − 10 °C. After 30 min, acetone (2 mL) was added and the solvent was evaporated. Brine (25 mL) was added and the mixture was extracted with CH_2Cl_2. The extract was dried (Na_2SO_4) and the solvent was concentrated in vacuo. The crude thiazolidine was dissolved in MeCN (5 mL) and the solution was treated with $HgCl_2$ (0.44 g, 1.6 mmol) in MeCN/H_2O (4:1, 20 mL). This solution was stirred at r.t. for 15 min., filtered and the solvent evaporated in vacuo. The residue was treated with sat. aq KI (25 mL), and extracted with $CHCl_3$ (3 × 30 mL). The combined extracts were dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography (hexane/Et_2O, 50:50) to give the aldehyde (Table 3).

Treatment of 4-formyl *anti*-1,3-diol acetonides with MeOH containing 5% K_2CO_3 at r.t. afforded the corresponding *syn*-diastereomer in quantitative yield.

(3*S*,4*R*,6*S*,7*R*)-4,6:7,8-Di-*O*-isopropylidene-3,4,6,7,8-pentahydroxy-1-(2-thiazolyl)-1-octanone (14):
To a well-stirred solution of *t*-BuOH (0.17 g, 10 mmol) in anhydr. THF (15 mL), BuLi (2.24 mmol, 1.4 mL of 1.6 M in hexanes) was added at r.t. and stirring was continued for 30 min. The mixture was cooled to − 50 °C and a solution of the aldehyde **5a** (0.48 g, 2 mmol) and 2-acetylthiazole (**1**; 0.27 g, 2.13 mmol) in anhydr. THF (10 mL) was added dropwise. After 2 h the solution was quenched with sat. aq NH_4Cl (20 mL) and the mixture was stirred for additional 5 min at − 50 °C and then allowed to warm to r.t. H_2O was added (10 mL) and the organic layer separated. The aqueous layer was extracted with Et_2O (4 × 25 mL); the organic layers were combined, dried (Na_2SO_4), and the solvent was removed in vacuo to give the crude aldol **14** in 90% diastereomeric purity by ^1H NMR analysis. The crude product was chromatographed (silica gel, hexane/Et_2O, 60:40) to give 0.45 g of pure **14**; yield: 60%; oil; $[\alpha]_D^{20}$ − 12.8° (*c* = 0.32, $CHCl_3$).

IR ($CHCl_3$): ν = 1690 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.31 (s, 3 H), 1.34 (s, 3 H), 1.40 (m, 1 H), 1.47 (s, 3 H), 1.48 (s, 3 H), 1.96 (pseudo dt, 1 H, *J* = 12.8, 2.6 Hz), 2.50 (m, 2 H), 3.21 (br s, 1 H, ex. D_2O), 3.76 (ddd, 1 H, *J* = 11.5, 7.1, 2.4 Hz), 3.90 (m, 3 H), 4.08 (dd, 1 H, *J* = 7.3, 4.8 Hz), 4.18 (ddd, 1 H, *J* = 7.5, 4.7, 4.2 Hz), 7.73 (d, 1 H, *J* = 3.2 Hz), 8.05 (d, 1 H, *J* = 3.2 Hz).

^{13}C NMR ($CDCl_3$): δ = 19.54, 24.88, 26.46, 29.26, 29.42, 41.33, 67.06, 70.42 (2 C), 71.26, 78.38, 98.90, 109.58, 126.69, 145.09, 167.75, 193.67.

We gratefully acknowledge the Progetto Finalizzato Chimica Fine II p (CNR, Rome) for financial support, and the Ministerio de Educacion y Ciencia for a postdoctoral fellowship to P.M.

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