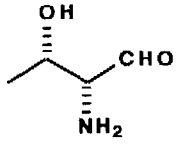
Tetrahedron Letters,Vol.30,No.40,pp 5511-5514,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

ENANTIOSPECIFIC AND DIASTEREOSELECTIVE PREPARATION OF SYNTHETIC EQUIVALENTS OF 2,4-DEOXY-2-AMINO-L-THREOSE AND -L-ERYTHROSE FROM (S) ETHYL β-HYDROXYBUTYRATE. STEREOCHEMICAL COURSE OF THEIR CONDENSATIONS WITH C-NUCLEOPHILES[1]

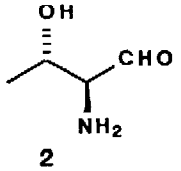
by Giuseppe Guanti,* Luca Banfi, and Enrica Narisano
Istituto di Chimica Organica e C.N.R., Centro di studio sui Diariloidi, corso Europa 26, 16132 GENOVA, Italy

Summary: The aldehydes **14** and **15**, which are synthetic equivalents of 2,4-deoxy-2-amino-L-erythrose **2** and -L-threose **1**, were straightforwardly prepared from (S) ethyl β-hydroxybutyrate. The asymmetric induction in the addition of some C-nucleophiles to these aldehydes was studied.

2,4-Deoxy-2-amino-L-threose **1** and -L-erythrose **2** are chiral building blocks of high potential utility for the synthesis of biologically active substances, like for example the pharmacologically important 2,4,6-trideoxy-4-amino-L-hexoses.[2] Some synthetic equivalents of **1** and **2** have been recently prepared, starting respectively from D-threonine[3] or from L-*allo*-threonine.[3c] Unfortunately, in the case of **2**, the high cost of L-*allo*-threonine makes this approach not convenient. We have recently reported[4] a new efficient preparation of L-*allo*-threonine starting from easily available ethyl (S) β-hydroxybutyrate **3**, in which the protected α-hydrazinoester **4** (see Scheme), obtained in good yield from **3** through a diastereoselective "electrophilic amination" with di-*t*-butylazodicarboxylate, was the key intermediate. The protected hydrazino group is to be considered synthetically equivalent to an amine, as hydrogenolytic cleavage of N-N bond in simple hydrazines is well documented.[4] Since in **4** the masked amino function as well as the carboxylic moiety are already in a protected form, we reasoned that it could be a convenient starting material for the preparation of synthetic equivalents of 2,4-deoxy-2-amino-L-erythrose **2**. In this communication we wish to report the successful accomplishment of this goal. Moreover we have found that also compounds with the *threo* relative configuration (as in **1**) are available from the same intermediate thanks to an equilibration reaction.



1



2

Treatment of **4**[5] with 2,2-dimethoxypropane under acid catalysis, according to Garner and Park[3a] allowed simultaneous protection of the OH and NH groups to give the N,O-*iso*-propylidene derivative **6** in good yield (75%). Base catalyzed equilibration of **6** gave the more stable *trans* epimer **7** (*trans* : *cis* ratio = 98 : 2), which was also less conveniently synthesized starting from the minor *syn* isomer **5**.[5] Both **6** and **7** were smoothly reduced in excellent yields (91% and 90% respectively) to the primary alcohols **10** and **11** by means of calcium borohydride, prepared *in situ* from $CaCl_2$ and $NaBH_4$.[6] The reduction of *cis* ester **6** was quite sensitive to small changes in reaction conditions. Thus, when $CaCl_2$ was used in slight excess compared to $NaBH_4$ (3.5 mmol $CaCl_2$ and 6 mmol $NaBH_4$ for each mmol of **6**) no epimerization took place. On the contrary, when $Ca(BH_4)_2$ was prepared from 3 mmol $CaCl_2$ and 6.5 mmol $NaBH_4$, or when a catalytic amount of EtONa was added to the hydride solution just before ester addition, nearly complete conversion to the *trans* alcohol **11** occurred (*trans*: *cis* ratio = 92:8).[7] Evidently *cis*-*trans* equilibration of **6** to **7** under the latter conditions is faster than reduction. This interesting behaviour allows the easy preparation of both isomers **10** and **11** from the same starting material, by simply changing reaction conditions. Finally, Swern oxidation of **10** and **11** furnished the

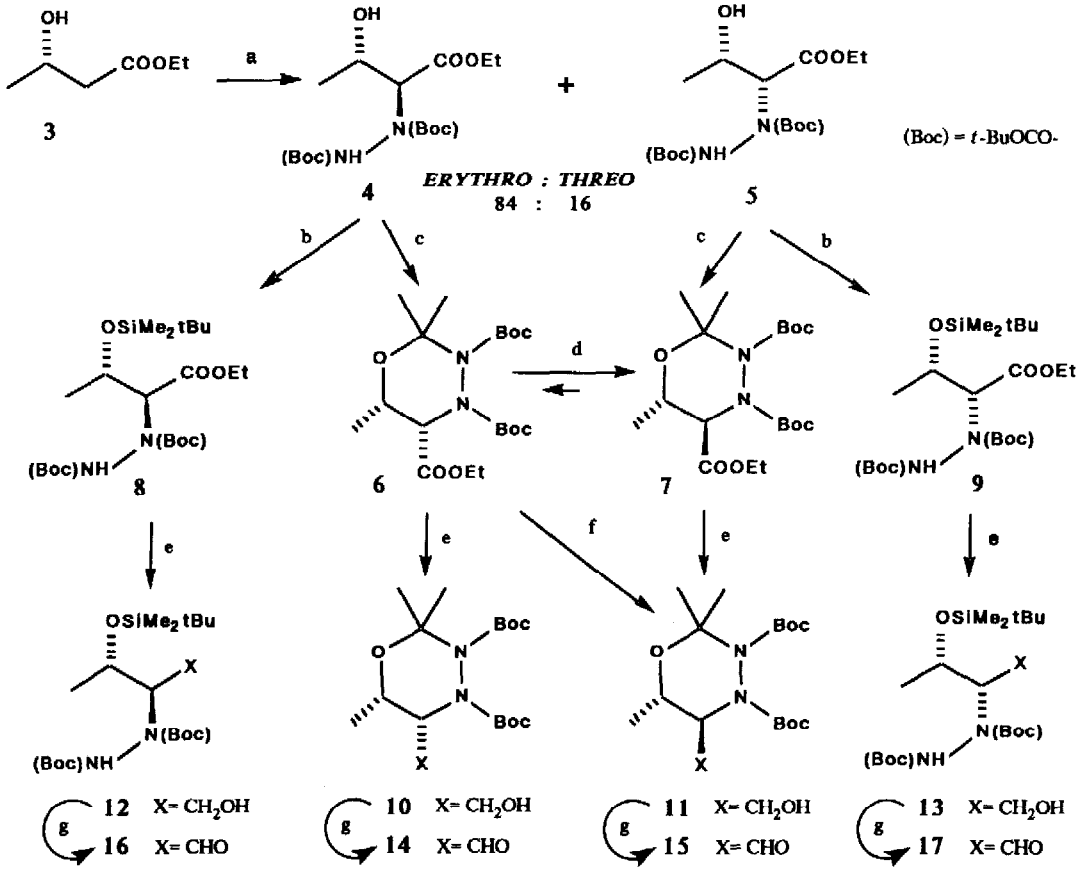
desired 2,4-deoxy-2-amino-L-erythrose and -L-threose equivalents **14** and **15**.[8]

We also converted, by a similar route, the protected hydrazinoesters **4** and **5** into the acyclic aldehydes **16** and **17**. In this case the *threo* isomer **17** cannot be obtained from the major protected hydrazinoester **4**, but requires the minor isomer **5** as starting material.[9] Therefore it is less easily synthesized than **14-16**.

Being obtained from (S) ethyl β-hydroxybutyrate quite straightforwardly, we believe that *erythro* aldehydes **14**, **16** and *threo* aldehyde **15**, which are synthetic equivalents of **2** and **1** respectively, can be viewed as useful chiral building blocks for the synthesis of biologically active substances containing an amino group, as well as their hydrazino analogues. The latter is a class of compounds still largely unexplored.

In order to gain an insight into the stereoselectivity of the nucleophilic additions to aldehydes **14-17**, we studied their reactions with some C-nucleophiles. The results are listed in the Table. The acyclic aldehydes **16** and **17** gave disappointing results, as regards to stereoselection, in the aldol-type condensation with the lithium enolate of *t*-butyl acetate (entries 1,2). This result is not unexpected, since previously reported condensations of simple acetate enolates with protected α-aminoaldehydes were usually stereorandom.[3c] On the contrary the cyclic aldehydes **14** and **15** were found to afford far better diastereomeric ratios in the condensation with the

SCHEME

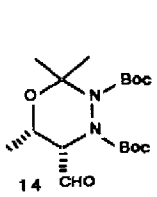
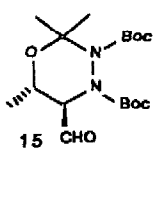


a) see note 5. b) Me_2t-BuSiCl, imidazole, DMF, r.t, 24h, 95% for **8**, 86% for **9**. c) $(MeO)_2C(CH_3)_2$, pTSA, benzene, reflux, 75% for **6**, 61% for **7**. d) NaH, EtOH, THF, r.t., 1 day, 78%. e) $Ca(BH_4)_2$ (from 3.5 eq. $CaCl_2$ and 6.0 eq. $NaBH_4$), EtOH, THF, -20°C → r.t., 20 h, 91% for **10**, 90% for **11**, 92% for **12**, 77% for **13**. f) $Ca(BH_4)_2$ (from 3 eq. $CaCl_2$ and 6.5 eq. $NaBH_4$), EtONa (0.5 eq.), EtOH, THF, -20°C→ r.t., 20 h, 86%. g) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78°C→ -30°C.

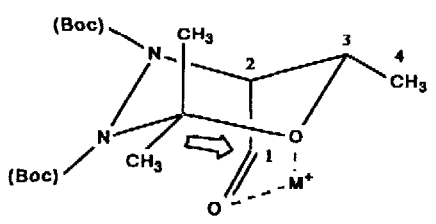
same enolate (entries 3,11),[10] and therefore their condensation reactions were studied more thoroughly. The results listed in the Table indicate that: a) both **14** and **15** gave preferentially *anti* [11] products when treated with reagents (ester enolate, allyl-metal compounds) which are known to react *via* a six-membered, metallo-Claisen,[12] transition state; b) with EtMgBr and $Me_3SiC{\equiv}C$-Li, a marked difference was noted between the *cis* and *trans* isomers. While the *trans* aldehyde **15** once again produced *anti* diastereoisomers as major product, the *cis* aldehyde **14** showed a surprising preference for *syn* products (entries 6,7,9,10). In the case of EtMgBr the addition of HMPA provoked a reversal of stereoselectivity (entry 8).

Although further study is probably necessary to better understand the mechanism of these reactions we think that the anomalous formation of *syn* diastereoisomers starting from **14** is due to the intervention of the cyclic chelated transition state **18** involving the β-oxygen.[13] In such transition state the nucleophile should attack the indicated carbonyl face, as the opposite face is obstructed by the C-4 methyl group. In the case of *trans* isomer, the corresponding cyclic chelated transition state **19** is less likely, because it would block the N,O-acetal ring in the disfavoured conformation in which the C-4 methyl group is axially oriented, and experiences a 1,3-diaxial interaction with one of the two *iso*-propylidene methyls. Anyway in **19** the front side, leading to the *anti* isomer, is no longer hindered by the C-4 methyl group. The presence of HMPA seems to inhibit such cyclic transition state in the case of EtMgBr (entry 8) but, surprisingly, not in the case of $Me_3SiC{\equiv}C$-Li (entry 10). The β-chelation is probably not operating also in the case of nucleophiles that react through a metallo-Claisen transition state.[12] The preferential formation of *anti* adducts when chelation is not involved can be explained either with the Felkin-Ahn or Cornforth models.[14,15]

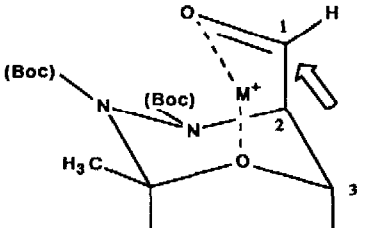
TABLE

Entry	Aldehyde	Reagent[a]	Solvent	*ANTI*:*SYN* ratio[b]	Yield[c]	Configuration of major product
1	**16**	$CH_2{=}C(Ot\text{-Bu})OLi$	THF	43 : 57[d]	78%	L-ARABINO
2	**17**	$CH_2{=}C(Ot\text{-Bu})OLi$	THF	68 : 32[d]	68%	L-LYXO
3	 **14**	$CH_2{=}C(Ot\text{-Bu})OLi$	THF	87 : 13[d]	84%	L-RIBO
4		allyl-MgBr	THF	65 : 35[e]	55%	L-RIBO
5		allyl-MgBr	THF/HMPA	84 : 16[e]	63%	L-RIBO
6		Et-MgBr	THF	25 : 75[e]	61%	L-ARABINO
7		Et-MgBr	Et_2O	24 : 76[e]	57%	L-ARABINO
8		Et-MgBr	THF/HMPA	75 : 25[e]	72%	L-RIBO
9		Me_3Si-C≡C-Li	THF	36 : 64[f]	70%	L-ARABINO
10		Me_3Si-C≡C-Li	THF/HMPA	31 : 69[f]	78%	L-ARABINO
11	 **15**	$CH_2{=}C(Ot\text{-Bu})OLi$	THF	91 : 9[d]	72%	L-LYXO
12		allyl-MgCl	THF	66 : 34[e]	74%	L-LYXO
13		allyl-MgCl	THF/HMPA	75 : 25[e]	77%	L-LYXO
14		allyl-MgBr	THF	68 : 32[e]	72%	L-LYXO
15		allyl-MgBr	THF/HMPA	63 : 37[e]	75%	L-LYXO
16		Et-MgBr	THF	86 : 14[e]	53%	L-LYXO
17		Et-MgBr	THF/HMPA	86 : 14[e]	64%	L-LYXO
18		Me_3Si-C≡C-Li	THF	93 : 7[f]	62%	L-LYXO

a) The reagent was added to the aldehyde solution at -78°C. In entries 1,2,3,11, the reaction was quenched after 10 min. at the same temp.. In the other cases the temperature was allowed to reach 0°C before quenching. b) for the use of *syn* and *anti* notations, see ref. 11. c) Isolated overall yields of *syn* + *anti* products from alcohols **10-13** (2 steps). d) Determined by HPLC (μPorasil™ column, refractometer, *n*-hexane / AcOEt for entries 1,3, and 4 and *n*-hexane/CH_2Cl_2/Et_2O for entry 2). e) Determined by capillary G.C., RSL-150 or Superox 4 (for entries 7 and 8) columns. f) Determined by capillary G.C. (RSL-150) on the desilylated derivatives, obtained by treatment with *n*-Bu_4NF in THF.



18



19

From the synthetic point of view, we must note that, by choosing appropriately the reagent and the reaction conditions, it is possible to obtain in moderate to excellent stereoselectivity useful intermediates for the synthesis of three of the four possible 2,4,6-trideoxy-4-amino-L-hexoses,[2] taking into account that *t*-butyl acetate, allylmagnesium halide and trimethylsilylacetylene are all synthetic equivalents of acetaldehyde. So *iso*-ristosamine could be derived from the *ribo* products of entries 1 and 8, *iso*-daunosamine from the *lyxo* products of entries 2, 6, and 18, and finally *iso*-acosamine from the *arabino* product of entry 17. Work toward the completion of these syntheses is in progress and will be reported in due course.

We wish to thank Miss Luciana Rossi for technical assistance and the C.N.R. and the Ministero della Pubblica Istruzione for financial assistance.

REFERENCES AND NOTES

1) Presented in part at the *7th IUPAC Conference on Organic Synthesis*, Nancy (France), July 4-7, **1988**, abstract 6-A21.
2) Fronza G., Fuganti C., Grasselli P., and Pedrocchi-Fantoni G., *Carbohydr. Res.*, **1985**, *136*, 115; Fronza G., Fuganti C., Pedrocchi-Fantoni G., and Servi S., *J. Org. Chem.*, **1987**, *52*, 1141; *Brit. Appl.*, 8 508 079 (March 28, 1985).
3) a) Garner P., Park J.M., *J. Org. Chem.*, **1987**, *52*, 2361; b) Kozikowski A.P., Nieduzak T.R., Konoike T., and Springer J.P., *J. Am. Chem. Soc.*, **1987**, *109*, 5167; c) Jurczak J., Golebiowski A., *Chem. Rev.*, **1989**, *89*, 149.
4) Guanti G., Banfi L., and Narisano E., *Tetrahedron*, **1988**, *44*, 5553.
5) 4 was prepared essentially as described in ref. 4. However, for large scale preparations (10-20 g) we found more convenient to use 2.5 mmol of LDA and 1.3 mmol of di-*tert*-butylazodicarboxylate for each mmol of 3. In this way we routinely obtained pure 4 and 5 in 62-66% and 6-9% yields respectively. Separation of 5 from di-*tert*-butylhydrazinodicarboxylate was accomplished by chromatography on silica gel eluted with CH_2Cl_2 / Et_2O 93:7 → 87:13. The ^1H n.m.r. spectra of all compounds here described were unresolved at 29°C, due to restricted rotation of the Boc groups. Nicely resolved spectra were obtained in most cases performing the ^1H n.m.r. measurement in d-6 DMSO at 90-100°C.
6) Luly J.R., Dellaria J.F., Plattner J.J., Soderquist J.L., Yi N., *J. Org. Chem.*, **1987**, *52*, 1487.
7) We presume that the presence of excess $NaBH_4$ in EtOH/THF causes the formation of some EtONa.
8) These aldehydes are liable to epimerize on standing. So we prefer to synthesize them from the corresponding primary alcohols just before the following reaction.
9) Equilibration of 4 to 5, or of 8 to 9 is not praticable due to low stereoselectivity and extensive decomposition under basic conditions.
10) Good stereoselectivities are often found in nucleophilic additions to N-(Boc)-N,O-*iso*-propylidene L-serinal: a) Garner P., Park J.M., and Malecki E., *J. Org. Chem.*, **1988**, *53*, 4395; b) Garner P., Park J.M., *J. Org. Chem.*, **1988**, *53*, 2979; c) Garner P., Ramakanth S., *J. Org. Chem.*, **1986**, *51*, 2609; d) Garner P., *Tetrahedron Lett.*, **1984**, 5855.
11) Masamune S., Ali A. Sk., Snitman D.L., and Garvey D.S., *Angew.Chem.Int. Ed. Engl.*, **1980**, *19*, 557.
12) Mead K., MacDonald T.L., *J. Org. Chem.*, **1985**, *50*, 422.
13) An alternative explanation is based on a cyclic model deriving from coordination of the metal by the nearest nitrogen (5-membered ring) or by the urethane oxygen (7-membered ring)(see ref. 10a,c,d). However in this hypothesis we were unable to explain the different behaviour of *cis* and *trans* aldehydes 14 and 15.
14) In this case we favour the Cornforth model, since in the Felkin transition state destabilizing non-bonding interactions between the incoming nucleophile and the C-4 methyl group are present both for 14 and 15.
15) Roush W.R., Adam M.A., Walts A.E., and Harris D.J., *J. Am. Chem. Soc.*, **1986**, *108*, 3422.

(Received in UK 9 August 1989)