Pergamon

Tetrahedron Letters, Vol. 37, No. 51, pp. 9259-9262, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)02138-7

A Versatile, Enantioselective, Stereocontrolled Synthesis of (1*S*,2*R*)-Imidazoleglycerol

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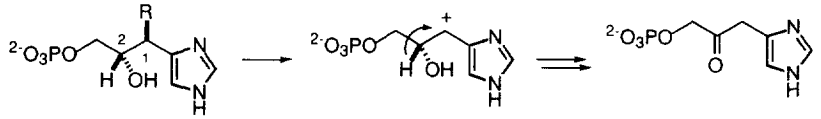
Abstract: An efficient (21% overall yield), enantio- and diastereoselective, 11-step synthesis of (1*S*,2*R*)-imidazoleglycerol has been developed. The key steps are the stereoselective hydroxylation of an acyloxazolidinone enolate, the alkylation of a thioester with $(MOMOCH_2)_2CuLi$ and the stereodivergent reduction of the resulting ketone. The scope of the reaction of the enolate derived from **10** with heteroatom electrophiles has been studied.

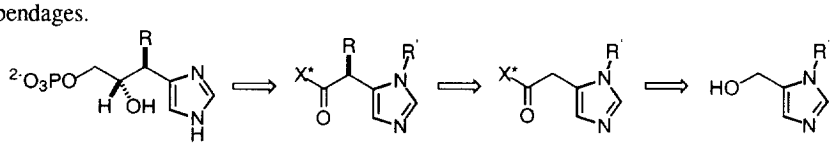
A highly unusual reaction occurs in the biosynthesis of histidine: the dehydration of (1*S*,2*R*)-imidazoleglycerol phosphate (IGP) (**1a**) to imidazoleacetol phosphate (**3**), catalyzed by IGP dehydratase.[1a] This reaction is uncommon since it appears to take place through an E1-type mechanism (followed by enol-ketone tautomerism), something that has not been observed for any other enzyme-catalyzed dehydration.[1b] To probe this unique mechanism we decided to synthesize several analogues of IGP that could function as substrates or inhibitors of the dehydratase. Our interest in this area was deepened further by the fact that inhibitors of this enzyme have great potential as herbicides.[2]



1a R = OH
1b R = F
1c R = NH_2

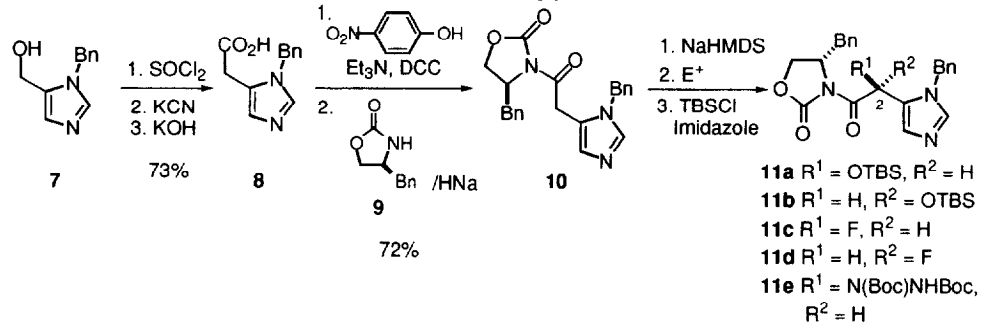
2 **3**

We focused our attention initially on the preparation of analogues of IGP with different substituents at the reacting centre (i. e. **1b**,**c**). To achieve this goal we needed a versatile approach towards this class of compounds, since the published syntheses of IGP and analogues do not lend themselves easily to the preparation of our target compounds.[2,3] The requirement of flexibility, as well as stereocontrol, during the introduction of the substituents at C1 could be met by reaction of enolates of imidazoleacetic acid derivatives (**5**, X* = chiral auxiliary) with the appropriate electrophiles.[4] Chain elongation of the resulting products (**4**), to procure ketones with 3-carbon side chains, and stereoselective carbonyl reduction should provide the desired glycerol appendages.



1a-c **4** **5** **6**

We report herein our preliminary studies on the enantioselective functionalization of enolates of **5** and the stereocontrolled synthesis of (1*S*,2*R*) and (1*S*,2*S*)-imidazoleglycerol.

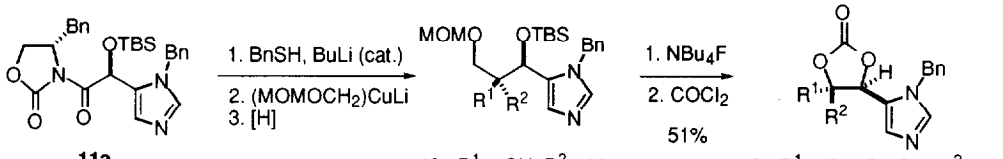


The starting alcohol **7** was prepared from dihydroxyacetone, KSCN and benzylamine, by a modification of a recently reported method.[5] Alcohol **7** was converted into a chloride which was displaced by cyanide, and the resulting nitrile was hydrolyzed to acid **8** in 73% overall yield.[6] Coupling of **8** to carbamate **9** using the standard acid chloride[7a] or acid anhydride[7b] methodology failed, but acylation of the Na^+ salt of **9** (from **9**, NaH, THF, -30 °C) with the *p*-nitrophenyl ester of **8** (from **8**, *p*-nitrophenol, Et_3N, DCC, DMF/THF, 0 °C) in DMF/THF at -30 °C did afford the desired acyloxazolidinone **10** in 72% yield.[6]

Careful optimization of the experimental conditions was required to achieve a high degree of stereoselectivity in the reaction of enolates of acyloxazolidinone **10** with electrophiles, due to the acidic nature of the 2 position in the products **11**. The best results were obtained with the Na^+ enolate of **10** (from **10**, NaHMDS, 110 mol%, THF, -78 °C). When this enolate was treated with MoOPH (200 mol%, THF, -78 °C), and the crude mixture of alcohols formed was silylated with TBSCl (CH_2Cl_2, imidazole, 0°C), an 8/1 ratio of silyl ethers **11a** and **11b**, easily separable by chromatography, was isolated (80% combined yield). The configuration of the newly created stereogenic centre of **11a,b** was assigned according to the model proposed by Evans for this kind of reactions.[4a]

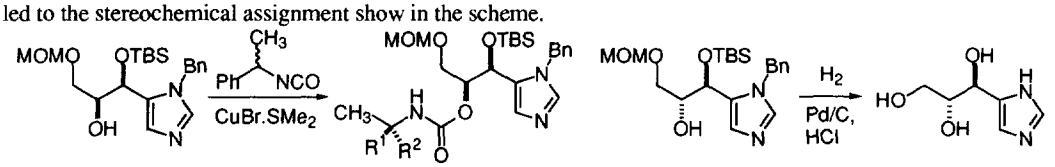
The fluorine analogues **11c,d** were obtained by reaction of the Na^+ enolate of **10** with *N*-fluorobenzenesulfonimide (120 mol%, -78°C).[8] The stereoselectivity of this reaction was strongly dependent on the reaction time: when the reaction was run for 20 min at -78°C a 5.5/1 mixture of **11c**[6] and **11d**[6] was obtained, while the ratio of diastereoisomers was raised to >30/1 (90%) when the reaction time was 5 min.

The hydrazido oxazolidinone **11e**[6] was obtained as the only product of the reaction of the enolate of **10** with di*tert*-butylazodicarboxylate (120 mol%, -78°C, 10 min, 77%).[4c]



To study the feasibility of the elongation of the side chain of **11a-e** to the glycerol stage we decided to use the silyloxy oxazolidinone **11a** as a model system. Thus **11a** was reacted with BnSH/BnSLi[9] (from BnSH, 200 mol%, and BuLi, 150 mol%, THF, 0 °C); the resulting thioester (95%) was treated with $(MOMOCH_2)_2CuLi$[10] to afford an unstable ketone which was immediately reduced with $NaBH_4$ to give a mixture of alcohols **12a**[6] and **12b**[6] in a 2/1 ratio (66% combined yield). Transformation of **12a,b** into carbonates **13a,b** allowed us to

establish the configuration of the newly created stereogenic centres. Desilylation of **12a** and **12b** with TBAF followed by cyclization of the resulting diols with phosgene gave **13a**[6] (51%) and **13b**[6] (52%), respectively. The absence of NOE between H1 and H2 in **13a**, and the presence of a strong NOE between H1 and H2 in **13b** led to the stereochemical assignment show in the scheme.



To check if the sequence from oxazolidinone **11a** to alcohols **12a,b** had taken place with retention of enantiomeric purity, **12a** was coupled to both (*R*)- and (*S*)- 1-phenylethylisocyanate (THF, $CuBr.SMe_2$) to give carbamates **14a** and **14b.** Unfortunately, ^{1}H-NMR analysis of the crude carbamates showed that the starting **12a** was essentially racemic.

In view of the configurational instability of the intermediates in the transformation of **11a** to **12** we decided to carry out the whole sequence without isolating the intermediate products. Thus **11a** was reacted with BnSH (120 mol%) and a catalytic amount of BuLi (20 mol%, THF, -50 °C) for 45 min; then the reaction mixture was added to a solution of $(MOMOCH_2)_2CuLi$ (400 mol%, THF, -78°C, 90 min). Addition of HOAc (to quench the acylation reaction) followed by the reducing agent to the above solution completed the sequence. In this way a mixture of **12a,b** (2/1 ratio) was obtained when $NaBH_4$ was used as reductant (84% overall combined yield). **12a** obtained through this route showed an enantiomer ratio of >98/2 (^{1}H-NMR analysis of carbamates **14a,b**). Thus by avoiding the isolation of the intermediate products not only the racemization was avoided but the overall yield of the sequence was improved considerably.

The only drawback that remained in this synthesis was the low stereocontrol in the reduction step. To improve this situation we tested several reducing agents and found that DIBAL gave the best results. Thus substitution of DIBAL for $NaBH_4$ in the above procedure afforded a 20/1 mixture of alcohols **12** (78%), favoring the undesired isomer **12a**. Surprisingly, when the HOAc quench prior to the DIBAL addition was eliminated, a reversal of selectivity was observed, and a 10/1 mixture of alcohols (80%), favoring the isomer with the IGP configuration (**12b**), was obtained.

Removal of all the protecting groups of **12b** was achieved by hydrogenolysis in acidic methanol (3 atm, Pd/C), to give imidazoleglycerol **15** in 77% yield. In this way an efficient (21% overall yield), enantio- and diastereoselective, 11-step synthesis of (1*S*,2*R*)-imidazoleglycerol from imidazolealcohol **7** was completed. We are currently exploring the application of the present methodology for the preparation of IGP (**1a**) and its fluoro- and amino- analogues (**1b,c**).

Acknowledgments: We thank the CICYT (SPAIN, grant SAF93-0767) and the *Xunta de Galicia* (grant XUGA 20908B94) for financial support. M.M.P. and M.I.C. thank the *Xunta de Galicia* for fellowships. J.C.C. thanks the *Instituto de Cooperación Iberoamericana* for a fellowship. We thank Prof. R. Suau (Univ. de Málaga, SPAIN) for the elemental analyses.

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6. (a) All new compounds showed the expected spectral properties and gave satisfactory elemental analyses. (b) Selected physical and spectral properties: **10**: mp 165-166 °C (EtOAc/hexanes). $[\alpha]^{20}D$ = +40.4° (c = 0.5, $CHCl_3$). ^1H RMN ($CDCl_3$) δ 2.64 (dd, J = 9.5, 13.4 Hz, 1 H); 3.14 (dd, J = 3.3, 13.4, 1 H); 4.02-4.12 (m, 4 H); 4.49 (ddd, J = 3.3, 6.6, 13.0 Hz, 1 H); 5.11 (s, 2 H); 7.00-7.28 (m, 11 H,); 7.47 (s, 1 H). ^{13}C RMN ($CDCl_3$) δ 30.8; 37.6; 48.8; 55.1; 66.2; 123.8; 126.8; 127.4; 128.1; 128.9; 129.3; 130.0; 134.8; 135.9; 138.6; 153.2; 168.8. **11a**: mp 101-103 °C (EtOAc/hexanes). $[\alpha]^{20}D$ = +127.1° (c = 0.28, $CHCl_3$). ^1H RMN ($CDCl_3$) δ -0.06 (s, 3 H); 0.04 (s, 3 H); 0.82 (s, 9 H); 2.64 (dd, J = 9.7, 13.2 Hz, 1 H); 3.24 (dd, J = 2.9, 13.2, 1 H); 3.92-4.02 (m, 3 H); 5.28 (d, J= 15.8 Hz, 1 H); 5.36 (d, J= 15.8 Hz, 1 H); 6.65 (s, 1 H); 7.00-7.28 (m, 11 H); 7.34 (s, 1 H). ^{13}C RMN ($CDCl_3$) δ -5.2; -5.0; 18.1; 25.6; 37.5; 49.1; 55.6; 65.4; 66.4; 127.1; 127.4; 127.8; 128.7; 129.0; 129.4; 130.1; 135.0; 136.8; 139.7; 152.7; 170.5. **11b**: mp 176-177 °C (EtOAc/hexanes). $[\alpha]^{20}D$ = -3.5° (c = 0.80, $CHCl_3$). ^1H RMN ($CDCl_3$) δ -0,03 (s, 3 H); -0.02 (s, 3 H); 0.85 (s, 9 H); 2.54 (dd, J = 9.2, 13.5 Hz, 1 H); 3.03 (dd, J = 3.6, 13.5, 1 H); 4.12 (dd, J = 3.5, 9.1 Hz, 1 H); 4.24 (t, J = 8.6 Hz, 1 H); 4.72-4.75 (m, 1 H); 5.31 (d, J = 15.4 Hz, 1 H); 5.47 (d, J = 15.4 Hz, 1 H); 6.75 (s, 1 H); 6.97-7.33 (m, 11 H); 7.36 (s, 1 H). ^{13}C RMN ($CDCl_3$) δ -5.1; -5.0; 18.1; 25.6; 37.1; 49.2; 54.8; 65.3; 66.5; 127.3; 127.5; 127.9; 128.0; 128.7; 129.2; 134.5; 136.2; 139.4; 152.8; 170.7. **11c**: mp 53-55 °C (EtOAc/hexanes). $[\alpha]^{20}D$ = +156.6° (c = 0.76, $CHCl_3$). ^1H RMN ($CDCl_3$) δ 2.66 (dd, J = 10.0, 13.3 Hz, 1 H); 3.41 (dd, 3.5, 13.3 Hz, 1 H); 4.2 (dd, J = 3.5, 9.3 Hz, 1 H); 4.29 (t, J = 9 Hz, 1 H); 4.74-4.84 (m, 1 H); 5.27 (d, J = 15.4 Hz, 1H): 5.35 (d, J = 15.4 Hz, 1 H); 6.87 (d, J = 50.9 Hz, 1H); 7.15-7.42 (m, 11 H); 7.55 (s, 1 H). ^{13}C RMN ($CDCl_3$) δ 37.2; 49.3; 55.0; 67.3; 79.2; (d, J = 182.4 Hz); 127.6; 127.7; 128.5; 128.9; 129.0; 129.1; 129.3; 131.5; 134.4; 134.8; 140.1; 152.7; 166.0 (d, J = 27.7 Hz). **12b**: $[\alpha]^{20}D$ = -18.9° (c = 1.07, $CHCl_3$). ^1H RMN ($CDCl_3$) δ -0.27 (s, 3 H); -0.12 (s, 3 H); 0.83 (s, 9 H); 3.36 (s, 3 H); 3.62 (dd, J = 4.5, 10.4 Hz, 1 H); 3.75 (m, 1 H); 3,77 (dd, J = 2.6, 10.4 Hz, 1H); 4.65 (m, 3 H); 5.18 (d, J = 15.6 Hz, 1 H); 5.33 (d, J = 15.6 Hz, 1 H); 7.13-7.35 (m, 7 H). ^{13}C RMN ($CDC1_3$) δ -5.8; -5.0; 17.9; 25.6; 49.9; 55.4; 68.0; 69.8; 74.0; 97.2; 127.2; 127.4; 128.2; 129.0; 136.1.
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(*Received in UK* 5 *September* 1996; *revised* 29 *October* 1996; *accepted* 31 *October* 1996)