The Total Synthesis of Destomic Acid

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1-Benzoyloxy-2-t-butyldimethylsilyloxy-4-ethoxybuta-1,3-diene (**3**) reacts with *N*-benzyloxycarbonyl-*O*-t-butyldiphenylsilyl-L-serinal (**4**) to give, with high selectivity, compound (**5a**) which was subsequently transformed into derivatives of destomic acid (**7**) and (**8**).

6-Amino-6-deoxy-L-glycero-D-galacto-heptonic acid (**1**), commonly named destomic acid, is one of the three components of a new type of aminocyclitol antibiotic: destomycin A,[1,2] B,[2,3] and hygromycin B.[4] The syntheses of destomic acid and its 4-epimer, starting from D-galactose and D-glucose, respectively, have recently been published.[5]

During our studies on applications of chiral *N*-protected α-amino aldehydes in organic synthesis[6] we found that they are very convenient and versatile heterodienophiles. High-pressure[7–9] or Lewis acid-mediated[10–12] (4 + 2)cycloaddition of 1,3-dienes to *N*-protected α-amino aldehydes offers easy access to the respective optically pure adducts which were readily transformed into several natural products.[6]

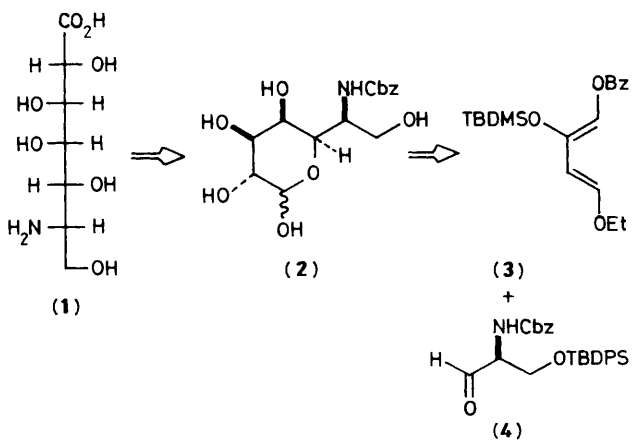
Now we report on a new application of this methodology to the total synthesis of destomic acid (**1**). Restrosynthetic analysis shown in Scheme 1 suggested that 1-benzoyloxy-2-t-butyldimethylsilyloxy-4-ethoxybuta-1,3-diene (**3**)[13] and *N*-benzyloxycarbonyl-*O*-t-butyldiphenylsilyl-L-serinal (**4**)† could serve as starting materials.

The cyclocondensation reaction of diene (**3**) with aldehyde (**4**) in the presence of $ZnBr_2$, followed by treatment with trifluoroacetic acid, led to a mixture of four possible diastereoisomeric adducts (**5**); as can be expected[10,12,14] (4*S*,5*R*)-diastereoisomer (**5a**) was formed as a major product‡ (Scheme 2).

† Compound (**4**) was prepared in the following reaction sequence starting from L-serine: i, $SOCl_2$, MeOH; ii, CbzCl, $NaHCO_3$, AcOEt; iii, TBDPSCl, imidazole, DMF; iv, DIBAL, Et_2O, −78 °C.

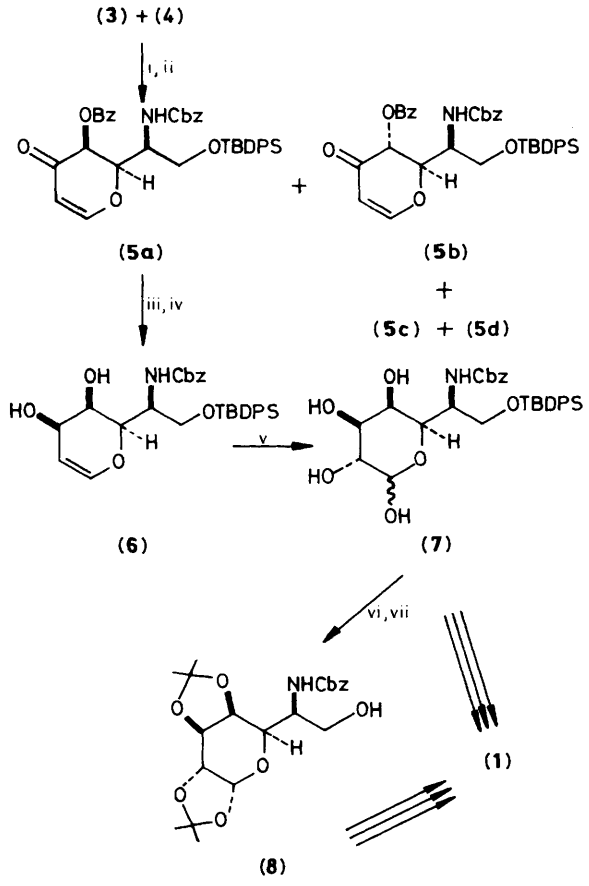
‡ The diastereoisomeric proportion was (**5a**) : (**5b**) : (**5c**) : (**5d**) = 87 : 8 : 4 : 1. The direction of asymmetric induction on the C-5 carbon atom can be rationalized on the ground of α-chelation-controlled cycloaddition.

The Luche-type reduction[15] of the chromatographically pure adduct (**5a**),§ followed by basic debenzoylation, afforded diol (**6**) which was subjected to the *cis*-hydroxylation reaction[16] to yield tetraol (**7**). Compound (**7**) can be easily transformed into destomic acid (**1**), but for direct comparison we converted it into the previously described[5] compound (**8**) and its 7-*O*-acetyl derivative. The latter compound has, after chromatographic purification, $[\alpha]_D^{25}$ −43.3° (*c* 0.9, chloroform); lit.[5] $[\alpha]_D^{RT}$ −47.8° (*c* 2.0, chloroform). The ^1H n.m.r. and i.r. spectra of compound (**8**) and of its 7-*O*-acetyl



Scheme 1

§ Satisfactory analyses and spectral data were obtained for all new compounds.



Scheme 2. *Reagents and conditions*: i, $ZnBr_2$, THF, rt; ii, TFA, CH_2Cl_2, rt; iii, $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, −78 °C; iv, K_2CO_3, MeOH, rt; v, OsO_4, NMO, Bu^tOH, H_2O, rt; vi, DMP, *p*-TsOH, Me_2CO, rt; vii, Bu_4NF, THF, rt.

derivative obtained by us were identical with those measured by Hashimoto *et al.*[5] Compound (**8**) can be transformed into destomic acid (**1**) according to the known procedure.[5]

The presented total synthesis of destomic acid proves to be a practical alternative to the known approach of Hashimoto *et al.*[5] Moreover, it exemplifies the usefulness of *N*-protected α-amino aldehydes in the synthesis of natural products.

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