Stereocontrolled synthesis and cyclization of (+,–)-α,α′-dihydroxy-α,α′,β-trimethylglutaric acid derivatives

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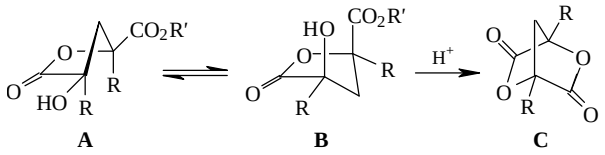
Hydrocyanation of 3-methylpentane-2,4-dione stereospecifically gave *trans*,*trans*-iminolactone **1**, whose configuration was established by X-ray diffraction of the corresponding lactone **2**; the rate of cyclization of the diastereoisomeric lactonic acids **3a**,**b** and their esters **4a**,**b** into dilactone **5** was controlled sterically by the methyl groups with *cis*,*cis*-isomers **3b**, **4b** predominating; alcoholysis of **5** regiospecifically afforded ester **4b**.

In preceding papers[1,2] we have reported the synthesis and stereochemical principles of cyclization in the series of α,α′-dihydroxy-α,α′-dialkylglutaric acids (DDG) derivatives. It was shown that an increase in the size of the alkyl substituents R by replacement of both Me groups with Bu^t groups leads to (i) a change of the stereoselectivity in the 1,3-diketone hydrocyanation from the formation of solely meso (R = Me)[1] to that of solely (+,–)-DDG derivatives (R = Bu^t)[2] and (ii) the facilitation of the dilactone **C** formation from (+,–)-DDG monolactones[1,2] owing to an increase in the population of the conformer **B**, which has functional groups suitably *cis*-pseudo-*a*,*a*-oriented for cyclization.



R = Me, Bu^t; R′ = H, Me

In the present report,[3] the influence of an additional β-methyl substituent upon the stereocontrolled formation and cyclization of DDG derivatives (R = Me) was investigated.

Hydrocyanation of 3-methylpentane-2,4-dione (MPD) was carried out under the described[4] reaction conditions (Scheme 1). The only compound obtained was the iminolactone **1**. It follows that the introduction of a methyl group at the α-position of pentane-2,4-dione results in a change of the hydrocyanation stereoselectivity, as in the case of dipivaloylmethane.[2]

In the strong predominant keto-form of MPD (*e.g.* 97.2% in aqueous medium)[5] the *anti*,*anti*-conformation (Scheme 1) is prefered[6] due to a minimization of both the dipole–dipole interactions of the carbonyl groups and the nonbonded 1,2-interactions of the methyl groups. Therefore, the stereospecificity of formation of the intermediate (+,–)-biscyanohydrin [(+,–)-BCH] may be mainly attributed to the steric control of the α-methyl group upon approach of the attacking nucleophile (CN^-) to the C=O group of MPD and then of intermediate monocyanohydrin (MCH, Scheme 1, only *R*,*R*-enantiomers are shown).

Spontaneous cyclization of (+,–)-BCH into the stereoisomer **1**, with a *trans*,*trans* mutual arrangement of the methyl groups, is the result of repulsive 1,2-interactions between the methyl groups and also by lesser steric hindrance from the β-methyl group upon cyclization of *anti*-oriented functional groups (Scheme 1).

The configuration of iminolactone **1**, namely, the *cis*-orientation of CN and OH groups as well as the preferable pseudo-*e*-positions of all the methyl groups, was established by an X-ray diffraction study† of the corresponding lactone **2** (Figure 1). The same configuration of lactone **2** in solution was determined by NMR spectroscopy‡ by comparison of the spin–spin coupling constants ($^3J_{C,H}$) with the dihedral angles in the crystal (Figure 1).

A mixture of the diastereomeric lactonic acids **3a** and **3b** (*ca.* 3 : 2, according to the ^{1}H NMR spectrum) was prepared by hydrolysis of **2** followed by separation by fractional crystallization from acetone–benzene. The preference of the isomer **3a** formation from intermediate (+,–)-α,α′-dihydroxy-α,α′,β-trimethylglutaric acid [(+,–)-DTG] may be caused by the steric effects of the methyl groups, as in the case of stereocontrolled cyclization of (+,–)-BCH (Scheme 1). The configuration of **3a** and **3b** assigned (+,–), was confirmed by identification of the alkaline hydrolysis products of **3a**,**b** and **5** with the (+,–)-DTG salt.‡

The relative rates of acid-catalysed lactonization of the diastereomeric monolactones **3a** and **3b** (in the presence of CF_3CO_2H) as well as their esters **4a** and **4b** (TsOH, Scheme 1) to the unsymmetrical dilactone **5** were estimated by ^{1}H NMR through the 'half-lives' of the reactants. It was found that the *cis*,*cis*-isomers **3b** and **4b** react 8 and 4 times faster than do the *trans*,*trans*-isomers **3a** and **4a**, respectively.

In contrast to the (+,–)-DDG derivatives, the relative acceleration of cyclization of **3b** and **4b** cannot be explained by an increase in the population of the conformer **B** (the Cohen model[9] of stereopopulation control), because this conformer strongly predominates over the conformer **A** in **3a** (90.4%) and **4a** (91.7%) in contrast to **3b** (27.8%) and **4b** (28.8%). The populations of conformers **A** and **B** were calculated using Allinger's MM2(91) program,[10] an improved version of the MM2(77) force field,[11] and confirmed by spectroscopy‡ of **3a** and **4a** ($^3J_{C\text{-}1,3\text{-}H}$ and $^3J_{C\text{-}5,3\text{-}H}$).

† *Crystal data* for **2**: $C_8H_{11}NO_3$, M =169.18, monoclinic, space group $P2_1/c$, a =11.140(2), b =13.334(3), c =12.266(2)Å, β =86.97(3)°, V =1819.5(3)Å^3, D_c =1.235gcm^{-3}, Z =4. Intensities of 3840 independent reflections with $I > 2\sigma(I)$ were collected on an automatic four-circle diffractometer KM-4 using MoKα radiation. The structure was solved by the direct method (SHELX-86 program[7]) and refined by full-matrix least-squares technique in anisotropic approximation for non-hydrogen atoms. H atoms were defined in the difference Fourier synthesis. The final value of *R*-factor is 0.044.

The characteristic feature of crystal packing of **2** is the presence of centrosymmetric dimer associates of *R*,*R*- and *S*,*S*-enantiomers (Figure 1), linked by intermolecular hydrogen bonds (IMHB): (i) O(2)··H(2a)=2.03Å, O(2)··O(3a)=2.858Å, C(1)=O(2)··H(2a) = 154.5°, O(2)··H(2a)–O(3a)=171.6°, E_1 =–2.4kcalmol^{-1}; (ii) O(2a)··H(2)=2.00Å, O(2a)··O(3) = 2.842 Å, C(1a)=O(2a)··H(2)=154.4°, O(2a)··H(2)–O(3)=172.6°, E_2 =–2.7kcalmol^{-1}. The IMHB energies (E_1 and E_2) (1 cal=4.184J) were calculated by a reported method.[8]

Atomic coordinates, thermal parameters, and bond lengths and angles have been deposited at the Cambridge Crystallographic Data Centre (CCDC). See Notice to Authors, *Mendeleev Commun.*, 1997, Issue 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 1135/14.

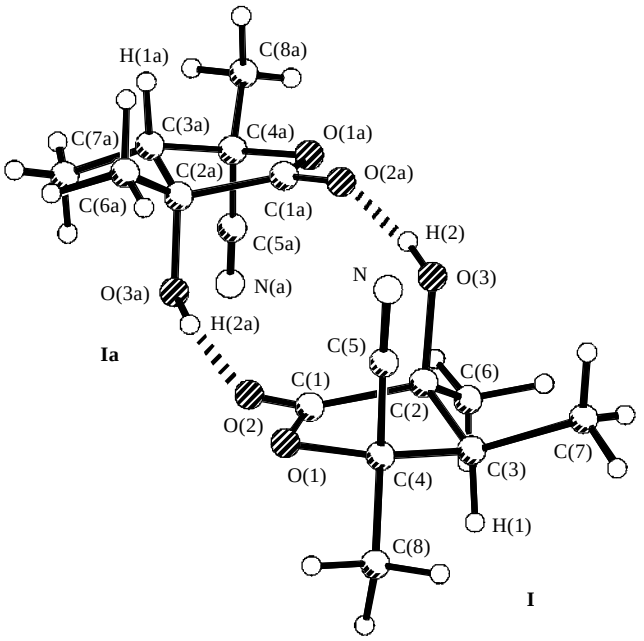


Figure 1 The structure of dimer associate of lactone **2** (dotted lines indicate possible H-bonds). Selected dihedral angles (°) in molecules **I** and **Ia** respectively: C(1)C(2)C(3)H(1) 79.9 and –75.5, C(6)C(2)C(3)H(1) –43.9 and 47.8, C(5)C(4)C(3)H(1) 165.8 and –162.6, C(8)C(4)C(3)H(1) 40.4 and –37.3.

‡ *Spectroscopic data* [IR ($CHCl_3$) ν_{max}/cm^{-1}, ^{1}H NMR (400.13MHz), ^{13}C NMR (100.62MHz) (data in square brackets were obtained under conditions of {4-Me}), δ/ppm, J/Hz] for **1**: yield 36.2%; mp 149–150 °C (from diethyl ether); IR: 1708 (C=N); ^{1}HNMR ($CDCl_3$) δ 1.31 (3H, d, ^3J 7.0, 3-Me), 1.48 (3H, s, 2-Me), 1.75 (3H, s, 4-Me), 1.98 (1H, q, 3-H).

For **2**: yield 83.5%; mp 81–82 °C (from benzene); IR: 1798 (C=O); ^{1}H NMR ($CDCl_3$) δ 1.35 (3H, d, ^3J 7.0, 3-Me), 1.46 (3H, s, 2-Me), 1.81 (3H, s, 4-Me), 2.06 (1H, q, 3-H); ^{13}C NMR ($CHCl_3$) δ 7.03 dq (3-Me, ^1J 128.6, ^2J 4.4), 20.99 dq (2-Me, ^1J 127.9, $^3J_{3\text{-H}}$ 2.5), 24.56 dq (4-Me, ^1J 131.5, $^3J_{3\text{-H}}$ 4.4), 49.93 dm (C-3, ^1J 130.8, J 3.6), 73.32 m (C-2, J 4.4), 78.03 m (C-4, J 5.1, [dq, ^2J 4.4, ^3J 5.8]), 117.02 dq (C-5, $^3J_{3\text{-H}}$ 8.7, $^3J_{4\text{-Me}}$ 4.4 [d, $^3J_{3\text{-H}}$ 8.7]), 175.50 q (C-1, $^3J_{2\text{-Me}}$ 4.4, $^3J_{3\text{-H}}$ <0.5).

For **3a**: yield 25%; mp 119–120 °C (from acetone–benzene); IR: 1786 [C(1)=O], 1718 [C(5)=O]; ^{1}H NMR ([$^2H_6$]acetone) δ 1.14 (3H, d, ^3J 7.3, 3-Me), 1.35 (3H, s, 2-Me), 1.61 (3H, s, 4-Me), 2.27 (1H, q, 3-H); ^{13}C NMR ([$^2H_6$]acetone) δ 7.20 dq (3-Me, ^1J 127.9, ^2J 4.4), 21.96 dq (Me, ^1J 127.9, $^3J_{3\text{-H}}$ 3.6), 22.52 dq (Me, ^1J 129.3, $^3J_{3\text{-H}}$ 5.1), 50.21 dm (C-3, ^1J 130.0, J 4.4), 73.35 m (C-2, J 4.4), 84.76 m (C-4, J 5.1), 172.95 dq (C-5, $^3J_{3\text{-H}}$ 7.3, $^3J_{4\text{-Me}}$ 4.0), 176.61 q (C-1, $^3J_{2\text{-Me}}$ 4.4, $^3J_{3\text{-H}}$ <0.5).

For **3b**: yield 21%; mp 148–149 °C (from acetone–benzene); IR: 1784 [C(1)=O], 1734 [C(5)=O]; ^{1}H NMR ([$^2H_6$]acetone) δ 1.11 (3H, d, ^3J 7.3, 3-Me), 1.34 (3H, s, 2-Me), 1.50 (3H, s, 4-Me), 2.76 (1H, q, 3-H); ^{13}C NMR ([$^2H_6$]acetone) δ 9.13 dq (3-Me, ^1J 127.2, ^2J 3.6), 19.00 dq (2-Me, ^1J 129.3, $^3J_{3\text{-H}}$ 2.9), 20.27 dq (4-Me, ^1J 127.9, $^3J_{3\text{-H}}$ 2.4), 46.62 dm (C-3, ^1J 133.0), 75.04 m (C-2, J 5.1, J 7.3), 82.94 m (C-4 [dq, ^2J 4.4, ^3J 4.4]), 173.10 dq (C-5, $^3J_{3\text{-H}}$ 4.4, $^3J_{4\text{-Me}}$ 4.4 [d, $^3J_{3\text{-H}}$ 4.4]), 176.67 dq (C-1, $^3J_{3\text{-H}}$ 4.4, $^3J_{2\text{-Me}}$ 4.0).

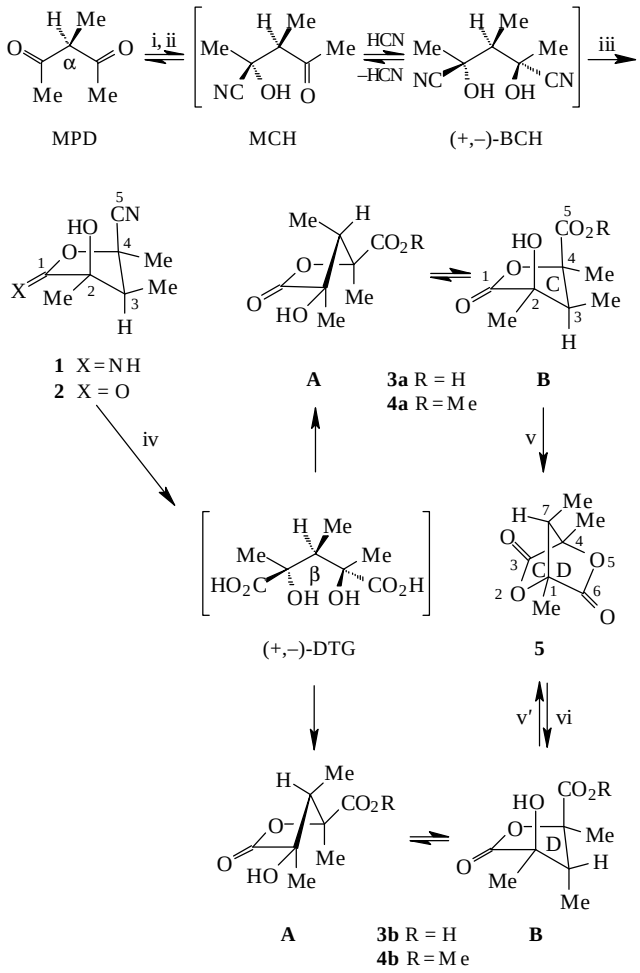
For **4a**: yield 86%; mp 71–72 °C (from light petroleum); IR: 1788 [C(1)=O], 1728 [C(5)=O]; ^{1}H NMR ($CDCl_3$) δ 1.07 (3H, d, ^3J 7.0, 3-Me), 1.42 (3H, s, 2-Me), 1.64 (3H, s, 4-Me), 2.10 (1H, q, 3-H), 3.83 (3H, s, OMe).

For **4b**: yield 84%; mp 88–89 °C (from light petroleum); IR: 1786 [C(1)=O], 1742 [C(5)=O]; ^{1}H NMR ($CDCl_3$) δ 1.11 (3H, d, ^3J 7.0, 3-Me), 1.40 (3H, s, 2-Me), 1.53 (3H, s, 4-Me), 2.79 (1H, q, 3-H), 3.79 (3H, s, OMe).

For **5**: yield 55%, mp 48–49 °C (from diethyl ether); IR: 1823 (C=O), 1808 (C=O); ^{1}HNMR ($CDCl_3$) δ 1.09 (3H, d, ^3J 6.7, 7-Me), 1.58 (3H, s, 4-Me), 1.63 (3H, s, 1-Me), 2.52 (1H, q, 7-H); ^{13}C NMR ($CDCl_3$) δ 6.07 dq (7-Me, ^1J 128.6, ^2J 2.9), 10.88 q and 10.98 q (1-Me and 4-Me, ^1J 129.3 and ^1J 129.3), 54.96 m (C-7, ^1J 135.2), 86.49 m and 88.70 m (C-1 and C-4), 170.77 q (C-3, $^3J_{4\text{-Me}}$ 4.4 [s, $^3J_{7\text{-H}}$ < 0.3]), 170.87 dq (C-6, $^3J_{7\text{-H}}$ 7.3, $^3J_{1\text{-Me}}$ 4.4).

(+,–)-DTG salt from **3a**,**b** and **5**; ^{1}H NMR (D_2O–KOH) δ 0.93 (3H, d, ^3J 7.0, β-Me), 1.23 and 1.32 (3H and 3H, 2s, α-Me and α′-Me), 2.45 (1H, q, β-H).

Compounds **1**–**5** gave satisfactory elemental analyses.



Scheme 1 *Reagents and conditions*: i, KCN–H_2O, –10°C; ii, aq. HCl (34%), –15 to –10 °C; iii, aq. HCl (10%), 6 h, 20 °C; iv, aq. HCl (25%), 3 h, reflux; then CH_2N_2–diethyl ether; v,v′, CF_3COOH or TsOH–toluene, reflux; vi, MeOH, 0.5 h, 50°C.

On the other hand, by comparison of the MM2 models of the **B** conformer of **3a** (or **4a**), **3b** (or **4b**) and **5**, the reaction rate enhancement observed for isomers **3b**, **4b** may be explained as follows. Firstly, the proximity of the reacting atoms [the nonbonded O(3)–C(5) distance] is smaller in **3b**, **4b** (2.88 Å) compared to **3a** (3.04 Å) and **4a** (3.06 Å) (the Menger[12] postulate of proximity factor). Secondly, the cyclization of **3b** (or **4b**), with the formation of the cycle **C** of **5**, probably proceeds *via* a less sterically hindered diastereomeric transition state (or tetrahedral intermediate) compared to that for **3a** (or **4a**) cyclization, leading to a more strain cycle **D** closure (Scheme 1). This is confirmed by a decreasing in both the non-bonded contacts between the carbon atoms of the vicinal methyl groups (3.21 and 3.22 Å) and the torsional strain of the C–Me bonds {φ[Me–C(1)–C(7)–Me] = 60.3°; φ[Me–C(4)–C(7)–Me] = –60.5°} in **5** compared to that for **3b** {2.92 and 2.94 Å; φ[Me–C(2)–C(3)–Me]) = 35.5°, φ[Me–C(3)–C(4)–Me]=–30.5°} and in contrast with that for **3a** (3.30 and 3.39 Å; –77.2°, 84.2°). Moreover, the van der Waals 1,2-interactions between the methyl groups results in the increase of **B** conformer puckering of the γ-lactone ring of **3b** and **4b** (ring-puckering amplitude[13] τ_m is 35.1°) unlike that of **3a** (33.5°) and **4a** (32.9°). This is one cause of the enforced proximity of the reacting centres in **3b**, **4b**.

Interestingly, alcoholysis of the dilactone **5** proceeds with only a ring **C** opening (Scheme 1) which is probably due to a steric control of the bridged 7-Me group.

Thus, the relative acceleration of cyclization of (+,–)-DTG monolactones is observed for the *e*,*a*,*e*-**B**-form (pseudo-*e*,*a*,*e*-orientation of the methyl groups), contrary to what might be

expected for the *e*,*e*,*e*-**B**-form on the basis of previous studies.[1,2]

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