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Regio- and stereocontrolled hydrocyanation of chiral 2-alkylglycidamides with Et_2AlCN: synthesis of enantiomerically pure mono- and disubstituted malic acid derivatives

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Abstract—The opening of the oxirane ring of glycidamides with Et_2AlCN takes place under mild conditions in a completely regio- and stereoselective manner to afford β-cyano carboxamide derivatives, which are immediate precursors of mono- and disubstituted malic acid derivatives. The complete control of the regioselectivity can be rationalized as a consequence of the association of the reagent with the carboxamide group prior to intramolecular cyanide transfer.

1. Introduction

In recent years, diethylaluminum cyanide (Et_2AlCN) has been widely used by our research group to achieve the hydrocyanation of α-sulfinylketones and other unsaturated sulfinyl substrates.[1] These processes have proved to be highly stereoselective due to the ability of the aluminium centre of the reagent to associate with the nucleophilic sulfinyl oxygen of the chiral auxiliary, which effectively directs the intramolecular cyanide transfer.[2] The resulting products could be transformed into biologically and pharmaceutically important polyfunctionalized structures. Among these compounds, special attention has to be paid to 2-alkyl and 2,3-dialkylglycidic acid derivatives,[3–6] which consequently can be considered as potential starting materials for the synthesis of chiral β-substituted α-alkyl (or α,β-dialkyl) α-hydroxycarboxylic acids by nucleophilic opening of the three-membered ring.[7–9]

In the course of our studies into the behavior of differently mono- and disubstituted glycidic carboxamides in the presence of nucleophilic reagents,[10] we considered the ring opening of these compounds in the presence of cyanide to yield α-hydroxy β-cyanocarboxamides, important chiral synthons. Oxirane opening with cyanide as the nucleophile is well documented in the literature. Reaction with hydrogen cyanide or potassium cyanide has given satisfactory results only on starting from simple aliphatic epoxides.[11–15] The use of diethylaluminum cyanide,[16,17] trimethylsilyl cyanide in the presence of aluminum derivatives[8,9] or the trimethylsilyl cyanide-potassium cyanide/18-crown-6 complex[7] have also been described, although a careful choice of the reaction conditions was necessary to avoid the undesired formation of isonitrile reaction products. Under these conditions the cyanide attack is essentially governed by steric factors, taking place on the less substituted carbon at the oxirane ring. The ring opening of epoxides has been performed in high yields and with good regioselectivities with potassium cyanide in the presence of lithium or magnesium perchlorate, although high temperatures were required for the reactions to reach completion.[18] The use of chelating metallic salts has controlled the nucleophilic attack on oxiranes bearing an oxygen function at C-α of one of the substituents. A good example is the nucleophilic opening of 2,3-epoxyalcohols in the presence of $Ti(O\text{-}i\text{-}Pr)_4$.[19]

Bearing in mind the electrophilic character of aluminum in Et_2AlCN, good selectivity was to be expected in its reaction with differently substituted glycidic amides by coordination of the metal with the carboxamide group, thus avoiding the use of the unpopular

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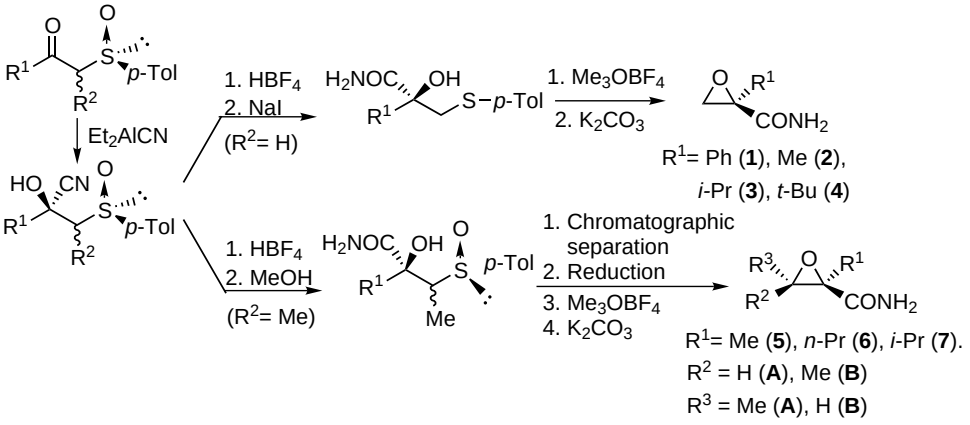
potassium cyanide. Herein, we report the results obtained in the reactions of the enantiomerically pure 2-alkyl and 2,3-dialkylglycidic carboxamides shown in Scheme 1 with Et_2AlCN to afford β-cyano α-hydroxycarboxamides. The application of this methodology to the synthesis of enantiomerically pure (*R*)-(−)-citramalic acid is also described.

2. Results and discussion

The synthesis of the starting enantiomerically pure (*R*)-2-alkyl (or aryl) oxirane 2-carboxamides **1**–**4** was achieved following a previously described four-step synthetic sequence[5] consisting of the reaction of chiral α-sulfinyl ketones and Et_2AlCN to afford diastereomerically pure cyanohydrins, which were hydrolyzed into the α-hydroxy, β-sulfenylcarboxamides and subsequently converted into glycidamides by treatment with $Me_3O^+BF_4^-$ and K_2CO_3 (Scheme 1). For the preparation of enantiomerically pure (*R*)-2,3-dialkyloxirane 2-carboxamides **5**–**7**,[5,20] the hydrolysis of the cyanohydrins was performed with HBF_4 and MeOH, thus yielding sulfinyl derivatives which were independently reduced to the sulfenyl analogues after chromatographic separation (Scheme 1).[21]

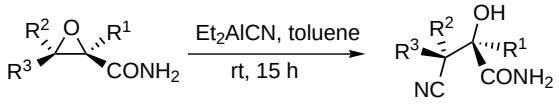
All attempts to perform the reaction of glycidic amides **1**–**7** with potassium cyanide as well as with trimethylsilyl cyanide—potassium cyanide/18-crown-6 failed, giving either complex product mixtures or unreacted starting materials. In contrast, the use of Et_2AlCN proved successful. Hence, treatment of **1**–**7** with Et_2AlCN in toluene for 12 h at room temperature yielded the corresponding 3-cyano-2-hydroxypropanamides **8**–**14** in excellent yields and enantiomeric purities. The reaction is thus a ready general method to obtain 2-alkyl and 2,3-dialkyl malic acid derivatives both regio- and stereoselectively, which expands the synthetic utility of the malic acid framework as an important source of the chirality for the construction of asymmetric molecules. All these results are collected in Table 1.

In all cases, ring opening was completely regioselective, occurring on the less substituted carbon of the oxirane ring. The reaction proceeded with complete inversion of configuration in those cases where the cyanide attacked a tertiary carbon, since only one isomer was detected. These results can be explained by assuming coordination of the reagent through aluminum with the nucleophilic oxygen of the carboxamide group prior to intramolecular cyanide transfer, which would occur through the relatively stable chair-like transition state



Scheme 1.

Table 1. Reaction of glycidic carboxamides with Et_2AlCN



Entry	R^1	R^2	R^3	Substrate	Product	Yield (%)
1	Ph	H	H	**1**	**8**	90
2	Me	H	H	**2**	**9**	87
3	*i*-Pr	H	H	**3**	**10**	89
4	*t*-Bu	H	H	**4**	**11**	92
5	Me	Me	H	**5A**	**12A**	90
6	*n*-Pr	Me	H	**6A**	**13A**	87
7	*n*-Pr	H	Me	**6B**	**13B**	92
8	*i*-Pr	H	Me	**7B**	**14B**	91

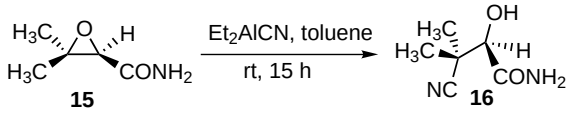
depicted in Scheme 2. A similar mechanistic proposal could account for the results observed in the oxirane ring opening of allylic epoxides with Et_2AlCN.[22]

Taking into account that all oxiranes collected in Table 1 exhibit a lower substitution at the carbon attacked by the cyanide, steric effects could also explain the observed regioselectivity. In support of the proposed coordination, the cyanide opening of the 3,3-dimethyloxirane-2-carboxamide **15**—prepared by conventional methods from 3,3-dimethylacrylic acid—was studied. The hydrocyanation with Et_2AlCN proceeded smoothly in toluene to afford the corresponding hydroxynitrile **16** in a completely regioselective manner (Scheme 3), resulting in ring opening at the C-β, which is now the electronically and sterically less favorable position of the oxirane. This transformation completely failed under other described hydrocyanation conditions.

The enantiomeric purity of the starting epoxides had been previously determined as >97% by using $Eu(tfc)_3$ as the chiral lanthanide shift reagent.[5] All the trials performed to establish the enantiomeric purity of compounds **8**–**14** by chiral HPLC or NMR, as well as their relative configuration by X-ray analysis, were unsuccessful. Nevertheless, as the cyanide opening of the oxirane ring must proceed in a completely stereoselective manner according to an S_N2 process on C-β without affecting the stereogenic center at C-α, we propose that the enantiomeric purity of the obtained cyanohydroxycarboxamides must also be >97% and their absolute configuration the one depicted in Scheme 2.

In order to confirm such a conclusion, and additionally to illustrate the utility of the procedure reported herein for the synthesis of malic acid derivatives, we transformed the enantiomerically pure cyanohydroxycarboxamide **9** into the commercially available (*R*)-citramalic acid [(*R*)-2-hydroxy-2-methylbutanedioic acid] **17**, the

Scheme 2.



Scheme 3.

α-methyl analog of (*R*)-malic acid, by reaction with $Ba(OH)_2$ in boiling water (Scheme 4).[23]

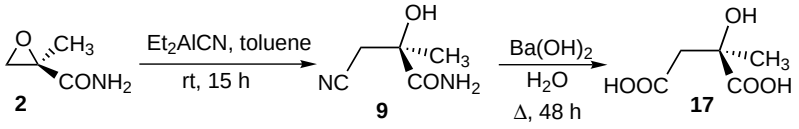
The specific rotation of the compound **17** (see Section 3) obtained from **9** exhibits the same sign and similar magnitude to that of commercially available (*R*)-citramalic acid (Aldrich Co),[24] which confirms the enantiomeric purity and the absolute configuration of the starting compound **9**. In this sense we must remark that the efficiency of the enzymatic or microbiological methods for the preparation of enantiomerically enriched citramalic acid[25] contrasts with the low efficiency of the chemical methods reported so far for the synthesis of chiral citramalates, since few of them give products of acceptable enantiomeric purity.[26] It enhances the interest of our method, which yields enantiomerically pure compounds in high yields and allows the synthesis of both enantiomers by choosing the configuration at sulfur in the starting sulfoxide.

3. Experimental

3.1. General methods

All reactions were carried out in flame-dried glassware under an argon atmosphere. Flash chromatography was performed with silica gel 60 (230–400 mesh ASTM) and silica gel F_{254} plates were used for preparative TLC. Melting points were determined in a Gallenkamp apparatus in open capillary tubes and are uncorrected. Optical rotations were measured at room temperature (20–23°C) using a Perkin–Elmer 241 MC polarimeter (concentration in g/100 mL). NMR spectra were determined in $CDCl_3$ solutions unless otherwise indicated at 200 (or 300) and 50.3 (or 75.5) MHz for ^1H and ^{13}C NMR, respectively. *J* values are given in hertz. All described compounds were over 97% pure by NMR analysis. Compounds **1**–**4** were synthesized and purified according to procedure described in Ref. 4, **1** and **4** having been already described. Compounds **5**–**7** were synthesized and purified according to procedure described in Ref. 6, although their actual physical and spectroscopical data are provided herein (see Ref. 20).

3.1.1. (*R*)-2-Methyloxirane-2-carboxamide, (*R*)-2. Compound (*R*)-**2** was purified by flash chromatography (ethyl acetate–hexane, 1:1) (yield 82%) and crystallized from dichloromethane–hexane, mp 98–99°C (white solid); $[\alpha]_D$ −13.6 (*c* 0.63, chloroform); δ_H 6.80 (bs, 1H), 5.90 (bs, 1H), 3.35 and 2.88 (AB system, 2H, *J* 5.3), 2.40 (s, 3H); δ_C 172.8, 59.6, 52.4, 25.4; IR 3540, 3429, 3015, 2985, 1687. MS: 101 (67) M^+, 57 (100), 86 (8), 85 (3), 59 (7), 42 (10). Anal. calcd for $C_4H_7NO_2$: C, 47.50; H, 10.88; N, 13.85. Found: C, 47.26; H, 11.33; N, 13.64%.



Scheme 4.

3.1.2. (*R*)-2-Isopropyloxirane-2-carboxamide, (*R*)-3. Compound (*R*)-**3** was purified by flash chromatography (ethyl acetate–hexane, 1:1) (yield 79%) and crystallized from ethyl acetate–hexane, mp 102–103°C (white solid); $[\alpha]_D$ −23.5 (*c* 0.5, chloroform); δ_H 6.38 (bs, 1H), 5.60 (bs, 1H), 2.90 and 2.74 (AB system, 2H, *J* 5.3), 2.40 (sept, 1H, *J* 7.1 Hz), 1.0.5 (d, 3H, *J* 7.1), 0.87 (d, 3H, *J* 7.1); δ_C 172.4, 54.2, 51.2, 30.3, 25.8; IR 3700, 3304, 3246, 2927, 1642. MS: 129 (54) M^+, 113 (4), 86 (10), 85 (100), 44 (9), 42 (6).

3.1.3. (2*R*,3*S*)-2,3-Dimethyloxirane-2-carboxamide, 5A. Compound **5A** was purified by flash chromatography (ethyl acetate–hexane, 1:1) (yield 75%) and crystallized from ether–hexane, mp 88–90°C (white solid); $[\alpha]_D$ +3.65 (*c* 0.3, acetone); δ_H 6.29 (bs, 1H), 5.21 (bs, 1H), 3.11 (q, 1H, *J* 5.4), 1.51 (s, 3H), 1.36 (d, 3H, *J* 5.4); δ_C 174.3, 59.7, 59.3, 13.5, 12.5; IR 3395, 3206, 2925, 1635.

3.1.4. (2*R*,3*S*)-3-Methyl-2-*n*-propyloxirane-2-carboxamide, 6A. Compound **5A** was purified by flash chromatography (ethyl acetate–hexane, 1:1) (yield 69%) and crystallized from ether–hexane, mp 136–138°C (white solid); $[\alpha]_D$ +59.9 (*c* 0.1, chloroform); δ_H 6.34 (bs, 1H), 5.70 (bs, 1H), 3.08 (q, 1H, *J* 5.5), 2.35–2.25 (ddd, 1H, *J* 6.9, 8.9, and 15.8), 1.57–1.45 (m, 2H), 1.35 (d, 3H, *J* 5.5), 1.33–1.23 (m, 1H), 0.95 (t, 3H, *J* 7.3); δ_C 174.1, 63.2, 59.3, 28.3, 18.2, 14.1, 13.5; IR 3416, 3269, 2961, 1693.

3.1.5. (2*R*,3*R*)-3-Methyl-2-*n*-propyloxirane-2-carboxamide, 6B. Compound **6B** was purified by flash chromatography (ethyl acetate–hexane, 1:1) (yield 67%) and crystallized from ether–hexane, mp 138–140°C (white solid); $[\alpha]_D$ +51.6 (*c* 0.55, chloroform); δ_H 6.28 (bs, 1H), 6.13 (bs, 1H), 3.09 (q, 1H, *J* 5.4), 2.35–2.22 (m, 1H), 1.54–1.15 (m, 3H), 1.33 (d, 3H, *J* 5.4), 0.91 (t, 3H, *J* 7.2); δ_C 172.2, 65.2, 59.7, 34.4, 17.9, 14.0, 13.5; IR 3382, 3198, 2955, 1638. Anal. calcd for $C_7H_{13}NO_2$: C, 58.72; H, 9.15; N, 9.78. Found: C, 58.48; H, 9.27; N, 9.45%.

3.1.6. (2*R*,3*R*)-2-Isopropyl-3-methyloxirane-2-carboxamide, 7B. Compound **7B** was purified by flash chromatography (ethyl acetate–hexane, 1:1) (yield 80%) and crystallized from ether–hexane, mp 80–82°C (white solid); $[\alpha]_D$ −14.05 (*c* 0.3, chloroform); δ_H 6.33 (bs, 1H), 5.30 (bs, 1H), 3.13 (q, 1H, *J* 5.4), 1.69 (sept, 1H, *J* 7.1), 1.41 (d, 3H, *J* 5.4), 1.32 (d, 3H, *J* 7.3), 1.13 (d, 3H, *J* 6.9); δ_C 173.4, 65.6, 59.8, 29.7, 18.8, 17.3, 13.0; IR 3409, 3193, 2963, 1684. MS: 144 (100) M^+, 127 (17), 126 (5), 101 (7).

3.2. Ring opening of oxirane carboxamides with Et_2AlCN. General procedure

To a solution of oxirane (0.23 mmol) in anhydrous toluene (0.95 mL) under argon, a solution of Et_2AlCN in toluene (1 M, 1.38 mL, 1.38 mmol) was added and the resulting mixture was stirred for 15 h at room temperature. Then the mixture was treated with a 4 mL aqueous saturated solution of sodium potassium tartrate–ethyl acetate (1:1) and stirring was continued for 15 min. The aqueous layer was extracted with ethyl acetate (3×4 mL) and the organic layer was dried (Na_2SO_4) and evaporated.

3.2.1. (*S*)-3-Cyano-2-hydroxy-2-phenylpropanamide, 8. Obtained from **1**. It crystallised from hexane (yield 90%), mp 100–101°C (white solid); $[\alpha]_D$ −23.2 (*c* 0.12, chloroform); δ_H 7.50–7.34 (m, 5H) 6.84 (bs, 1H), 5.97 (bs, 1H), 3.62 (bs, 1H), 3.26 and 3.13 (AB system, 2H, *J* 15.0); δ_C 174.9, 139.0, 129.8, 124.8, 117.5, 76.6, 29.1. IR: 3657, 3490, 3366, 2895, 2181, 1781, 1662, 1548. MS: 190 (1) M^+, 164 (7), 149 (48), 146 (25), 120 (16), 105 (100), 91 (25), 77 (54), 71 (13), 51 (15). Anal. calcd for $C_{10}H_{10}N_2O_2$: C, 63.31; H, 5.27; N, 14.82. Found: C, 63.62; H, 4.84; N, 14.94%.

3.2.2. (*R*)-3-Cyano-2-hydroxy-2-methylpropanamide, 9. Obtained from **2**. It crystallised from ethyl acetate–hexane (yield 87%), mp 89–90°C (white solid); $[\alpha]_D$ −11.8 (*c* 0.15, chloroform); δ_H 6.75 (bs, 1H, NH), 5.90 (bs, 1H, NH), 3.40 (bs, 1H, OH), 3.05 and 2.86 (AB system, 2H, *J* 16.0 Hz, CH_2), 2.03 (s, 3H, CH_3); δ_C 172.0 ($CONH_2$), 115.7 (CN), 89.3 (C), 27.4 (CH_2), 25.6 (CH_3). IR: 3359, 3102, 2890, 2648, 1648, 1650, 1581. MS: 128 (1) M^+, 113 (5), 102 (100), 88 (34), 84 (76), 67 (9), 40 (10). Anal. calcd for $C_5H_8N_2O_2$: C, 46.85; H, 6.24; N, 21.93. Found: C, 46.51; H, 6.56; N, 21.95%.

3.2.3. (*S*)-2-Cyanomethyl-2-hydroxy-3-methylbutanamide, 10. Obtained from **3**. It crystallised from ethyl acetate–hexane (yield 89%), mp 100–101°C (white solid); $[\alpha]_D$ −13.4 (*c* 0.09, chloroform); δ_H 6.73 (bs, 1H), 5.88 (bs, 1H), 3.40 (bs, 1H), 2.90 and 2.78 (AB system, 2H, *J* 16.0), 2.15 (sept, 1H, *J* 7.2), 1.03 (d, 3H, *J* 7.2), 1.01 (d, 3H, *J* 7.2); δ_C 173.3, 118.1, 108.1, 43.8, 28.7, 12.9. IR: 3352, 3102, 2876, 2254, 1710, 1612. MS: 156 (1) M^+, 113 (100), 115 (10), 113 (9), 112 (85), 95 (13), 43 (10). Anal. calcd for $C_7H_{12}N_2O_2$: C, 53.82; H, 7.68; N, 18.00. Found: C, 53.58; H, 7.79; N, 18.13%.

3.2.4. (*S*)-2-Cyanomethyl-3,3-dimethyl-2-hydroxybutanamide, 11. Obtained from **4**. It crystallised from ethyl acetate–hexane (yield 92%), mp 83–84°C (white solid); $[\alpha]_D$ −14.7 (*c* 0.2, chloroform); δ_H 7.01 (bs, 1H), 6.30 (bs, 1H), 4.50 (bs, 1H), 3.15 and 2.65 (AB system, 2H, *J* 17.5), 1.01 (s, 9H); δ_C 175.0, 118.1, 80.3, 37.5, 25.3. IR: 3497, 3385, 2893, 2813, 1575. MS: 170 (1) M^+, 126 (18), 114 (20), 85 (32), 70 (12), 57 (100). Anal. calcd for $C_8H_{14}N_2O_2$: C, 56.44; H, 8.30; N, 16.46. Found: C, 56.99; H, 8.45; N, 15.95%.

3.2.5. (2*R*,3*S*)-3-Cyano-2-hydroxy-2-methylbutanamide, 12A. Obtained from **6A** and purified by precipitation from the crude mixture with ethyl acetate–hexane (yield 90%), mp 190–192°C (white solid); $[\alpha]_D$ +54.2 (*c* 0.2, acetone); δ_H (acetone-d_6) 7.25 (bs, 1H), 6.75 (bs, 1H), 5.19 (s, 1H), 3.20 (q, 1H, *J* 7.4), 1.54 (s, 3H) 1.22 (d, 3H, *J* 7.4), 0.90; δ_C (acetone-d_6) 175.7, 121.3, 79.3, 75.4, 35.6, 25.6, 13.0; IR: 3375, 2923, 2258, 1635. MS: (electrospray) 143 M^+, 131, 102.

3.2.6. (*R*)-2-[(*S*)-1-Cyanoethyl]-2-hydroxy-2-pentanamide, 13A. Obtained from **6A** and purified by precipitation from the crude mixture with ethyl acetate–

hexane (yield 87%), mp 198–200°C (white solid); $[\alpha]_D$ +20.6 (*c* 0.4, acetone); δ_H (acetone-d_6) 7.23 (bs, 1H), 6.83 (bs, 1H), 3.18 (q, 1H, *J* 6.9), 1.87–1.52 (m, 4H), 1.22 (d, 3H, *J* 7.1), 0.90 (t, 3H, *J* 7.3); δ_C (acetone-d_6) 175.6, 122.4, 79.3, 42.2, 36.7, 18.3, 15.2, 14.0; IR: 3413, 3230, 3958, 2254, 1632. MS: 171 (100) M^+, 154 (10), 153 (72), 143 (10).

3.2.7. (*R*)-2-[(R)-1-Cyanoethyl]-2-hydroxy-2-pentanamide, 13B. Obtained from **6B** and was purified by precipitation from the crude mixture with ethyl acetate–hexane (yield 92%), mp 116–118°C (white solid); $[\alpha]_D$ −14.2 (*c* 0.5, acetone); δ_H (acetone-d_6) 7.15 (bs, 1H), 6.79 (bs, 1H), 3.10 (q, 1H, *J* 7.3), 1.87–1.42 (m, 4H), 1.31 (d, 3H, *J* 7.1), 0.88 (t, 3H, *J* 7.3); δ_C (acetone-d_6) 175.4, 121.5, 78.4, 39.2, 35.3, 17.5, 14.4, 12.4; IR: 3418, 3232, 2251, 1703.

3.2.8. (2*R*,3*R*)-3-Cyano-2-hydroxy-2-isopropylbutanamide, 14B. Obtained from **7B** and was purified by precipitation from the crude mixture with ethyl acetate–hexane (yield 91%), mp 118–120°C (white solid); $[\alpha]_D$ +9.57 (*c* 0.31, acetone) δ_H (acetone-d_6) 7.17 (bs, 1H), 6.75 (bs, 1H), 4.85 (s, 1H), 3.40 (q, 1H, *J* 7.1), 2.18 (sept, 1H, *J* 6.9), 1.25 (d, 3H, *J* 7.1), 1.06 (d, 3H, *J* 6.9), 1.04 (d, 3H, *J* 6.9); δ_C (acetone-d_6) 173.6, 121.7, 80.9, 36.4, 33.5, 17.4, 13.6; IR: 3459, 2950, 2248, 1689.

3.2.9. (*R*)-Citramalic acid [(*R*)-2-hydroxy-2-methylbutanedioic acid], 17. Obtained from **9** by heating under reflux with aqueous $Ba(OH)_2$ for 48 h (yield 81%), mp 106–108°C (white solid) [lit.[24] 108–110°C]; $[\alpha]_D$ −21.0 (*c* 1.0, H_2O) [lit.[24] −23.0 (*c* 3.0, H_2O)] δ_H (D_2O) 2.35 (AB system, 2H, *J* 16.6), 0.91 (s, 3H).

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20. To our surprise the spectroscopic (^1H and ^{13}C NMR) parameters and physical data of the 2,3-dialkylglycidic carboxamides **5**–**7** were not coincident with those previously reported in a preliminary paper (see Ref. 5). We wish to report herein the data that have been verified as the correct ones for **5**–**7** (see Section 3) as a corrigendum to those included in Ref. 5, which were inadvertently inaccurate.
21. Chromatographic separations of the diastereomeric mixtures of cyanohydrins, α-hydroxy, β-sulfenylcarboxamides and α,β-dialkylglycidamides derived from α-methyl β-ketosulfoxides were not possible in our hands.
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