Absolute Configurations of α-Substituted Glycidates. (−)-(*R*)-Ethyl 2-Methyl-1-oxaspiro[2.5]octane-2-carboxylate and (−)-(*R*)-Ethyl 2,3-Dimethyl-2,3-epoxybutanoate

Toshio Sugita,* Nobuyuki Nishio, and Katsuhiko Ichikawa

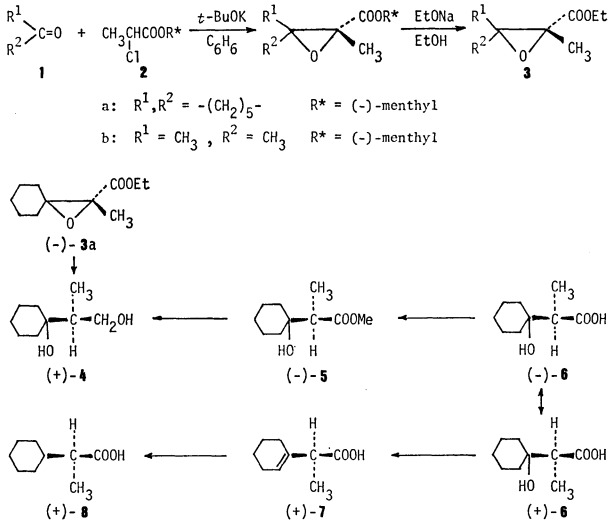
Department of Hydrocarbon Chemistry, Faculty of Engineering, Kyoto University, Sakyo-ku, Kyoto 606

(Received October 24, 1981)

Synopsis. The absolute configurations of the title compounds were determined by chemical correlation and by asymmetric syntheses.

In the course of stereochemical studies of the Darzens reaction, it has been necessary to distinguish the stereoisomerism of the α-carbon of glycidates from the geometrical isomerism. No model compound with a known absolute configuration at the α-carbon of glycidate has, however, been reported, to our knowledge. Thus, we determined the absolute configurations of some α-substituted glycidates, which were symmetrically β,β-disubstituted: (−)-ethyl 2-methyl-1-oxaspiro-[2.5]octane-2-carboxylate (**3a**) and (−)-ethyl 2,3-dimethyl-2,3-epoxybutanoate (**3b**).

The potassium *t*-butoxide-catalyzed Darzens reactions of (−)-menthyl 2-chloropropanoate (**2**) and cyclohexanone (**1a**) or acetone (**1b**), followed by sodium ethoxide-catalyzed transesterification, afforded **3a** or **3b** respectively, each of which was exceeded in the (−)-isomer.



The (−)-**3a** was reduced by lithium aluminium hydride to give a mixture of 1,2- and 1,3-glycols. By periodic acid oxidation, the 1,2-glycol was cleaved to cyclohexyl methyl ketone, while 2-(1-hydroxycyclohexyl)-1-propanol (**4**) was left unaffected, indicating dextrorotation. (−)-2-(1-Hydroxycyclohexyl)propanoic acid (**6**), prepared by the Reformatsky reaction of cyclohexanone and ethyl 2-bromopropanoate, followed by hydrolysis and resolution with (−)-1-phenylethylamine, was converted with diazomethane to its (−)-methyl ester (**5**). The lithium aluminium hydride reduction of (−)-**5** afforded (+)-**4**. On the other hand, (+)-**6** was dehydrated by heating with 10% sulfuric acid to give (+)-2-(1-cyclohexenyl)propanoic acid (**7**). The catalytic hydrogenation of (+)-**7** gave (+)-2-cyclohexylpropanoic acid (**8**), the absolute configuration of which had been established as *S*.[1] It has been known that the lithium aluminium hydride reductions of oxirane rings accompany inversion of configuration at the reduced carbon.[2] In the other steps of the reaction sequence, the chiral carbon is not subjected to chemical changes; thus, the absolute configuration of (−)-**3a** is established to be *R*.

The asymmetric Darzens syntheses of **3a** and **3b** were carried out under the same conditions, and both products were exceeded in the (−)-isomers. Thus, (−)-**3b** is expected to have the same *R* configuration as (−)-**3a**.

Experimental

The ^{1}H-NMR spectra (in $CDCl_3$ using TMS as an internal standard) were taken on a JEOL PMX-60 spectrometer. The optical rotations were obtained on a Zeiss polarimeter or a JASCO DIP-180 polarimeter in chloroform solutions, unless otherwise mentioned.

A Typical Asymmetric Synthesis of the Glycidates (3). To a well-stirred solution of **1a** (20 g, 0.20 mol) and (−)-**2** (bp 111—113 °C/4 mmHg (1 mmHg≈133.322 Pa); $[\alpha]_D^{31}$ −71.03° (*c* 5.56); 50 g, 0.20 mol) in 200 ml of benzene, powdered potassium *t*-butoxide, freshly prepared from potassium (7.8 g, 0.20 mol) and *t*-butyl alcohol, was added, portion to portion, over 30 min at 10—15 °C under a nitrogen atmosphere. The mixture was stirred for an additional 2 h and then allowed to stand overnight at room temperature. Water was added to the reaction mixture, and extracted with ether. The extract was washed with aqueous NaCl and dried ($MgSO_4$). By removal of the solvents, crude (−)-menthyl 2-methyl-1-oxaspiro[2.5]octane-2-carboxylate (63.3 g) was obtained. The crude menthyl ester was refluxed with a solution of sodium ethoxide, prepared by dissolving sodium (2.0 g, 87 mmol) in 150 ml of ethanol, for 10 h. The mixture was neutralized with acetic acid, concentrated, and extracted with ether. The extract was washed with aqueous $NaHCO_3$ and with aqueous NaCl, dried ($MgSO_4$), and distilled by means of a Vigreaux-column to give (−)-menthol (bp 91.5—101 °C/9 mmHg, 26.5 g (85%)) and **3a** (bp 101.5—117.5 °C/9 mmHg, 16.8 g (42%)), which was found by vpc analysis to contain a small amount of (−)-menthol. After repeated distillations (3 times), pure ethyl 2-methyl-1-oxaspiro[2.5]octane-2-carboxylate (**3a**) (bp 122—123 °C/12 mmHg (lit,[3] bp 154—156 °C/40 mmHg), $[\alpha]_D^{33}$ −4.10° (*c* 10.71)) was obtained.

From 12 g (0.21 mol) of **1b** and 37 g (0.15 mol) of **2**, (−)-menthyl 2,3-dimethyl-2,3-epoxybutanoate (bp 100—137 °C/15 mmHg, 34.8 g (64.2%)) was obtained. The menthyl ester was transesterified to **3b** (bp 95.5—100 °C/66 mmHg, 9.4 g (40% from **2**)), which was found by vpc to contain a small amount of ethyl 2-chloropropanoate and a trace of (−)-menthol. Pure ethyl 2,3-dimethyl-2,3-epoxybutanoate (**3b**) (bp 100 °C/66 mmHg (lit,[4] bp 80—82 °C/20 mmHg);

$[\alpha]_D^{17}$ −1.32° (*c* 12.21); Found: C, 61.16; H, 9.44%) was obtained after repeated distillations.

*(+)-2-(1-Hydroxycyclohexyl)-1-propanol (**4**) from (−)-**3a**.* A solution of (−)-**3a** ($[\alpha]_D^{12}$ −3.13° (*c* 8.69), 9.9 g, 50 mmol) in 60 ml of ether was added to a stirred suspension of $LiAlH_4$ (2.3 g, 60 mmol) in 100 ml of ether. The mixture was stirred for 2.5 h, and then worked-up as usual. By the distillation of the reaction product, a mixture of **4** and 2-cyclohexyl-1,2-propanediol (bp 117—120.5 °C/3 mmHg, 5.7 g (72.2%)) was obtained. To the glycol mixture was added 130 ml of a 0.2 M (1 M=1 mol dm^{-3}) aqueous HIO_4 solution; this mixture was kept at an ambient temperature for 4 h with occasional shaking. After the duration, the mixture was extracted with ether, the extract was washed with a small amount of cold aqueous $Na_2S_2O_3$ and with aqueous NaCl, dried ($MgSO_4$), and distilled to give cyclohexyl methyl ketone (bp 53—58 °C/9 mmHg, 1.5 g (36.1%)) and (+)-**4** (bp 103.5—104 °C/2 mmHg (lit,[5] bp 106—110 °C/1 mmHg); $[\alpha]_D^{13}$ +2.24° (*c* 4.29); 1.1 g (21.2%); ^{1}H-NMR: δ=0.9 (d, J=8, 3H), 1.5 (broad s, 11H), 2.5—3.3 (2H), 3.7 (d, J=5, 2H)).

*(−)-Methyl 2-(1-Hydroxycyclohexyl)propanoate (**5**).* An ether solution of diazomethane was added until the mixture turned pale yellow to (−)-**6** ($[\alpha]_D^{28}$ −2.58°; 1.5 g, 8.7 mmol), prepared by the Reformatsky reaction of **1a** and ethyl 2-bromopropanoate,[6] followed by hydrolysis with ethanolic KOH and resolution with (−)-1-phenylethylamine. The mixture was distilled to give (−)-**5** (bp 121—122 °C/17 mmHg (lit,[7] bp 132 °C/18 mmHg); $[\alpha]_D^{29}$ −3.41° (*c* 10.14); 1.3 g (80%); ^{1}H-NMR: δ=1.18 (d, 3H), 1.48 (broad s, 10H), 2.50 (q, 1H), 2.75 (s, 1H), 3.70 (s, 3H); Found: C, 64.76; H, 9.92%).

*(+)-2-(1-Hydroxycyclohexyl)-1-propanol (**4**) from (−)-**5**.* (−)-**5** ($[\alpha]_D^{20}$ −30.3° (*c* 0.957); 1.5 g, 8.1 mmol) in 20 ml of ether was added to a stirred suspension of $LiAlH_4$ (0.5 g, 13 mmol) in 20 ml of ether, then the mixture was refluxed for 2.5 h. After the usual work-up, **4** was obtained: bp 119—120.5 °C/4 mmHg, $[\alpha]_D^{21}$ +10.69° (*c* 4.66), 0.7 g (56%). (Found: C, 67.84; H, 11.50%). The IR and ^{1}H-NMR spectra of **4** obtained from (−)-**3a** and (−)-**5** were completely superimposable.

*(+)-2-(1-Cyclohexenyl)propanoic Acid (**7**).* (+)-**6** ($[\alpha]_D^{20}$ +5.89°; 1.3 g, 7.6 mmol) was suspended to 10 ml of 10% sulfuric acid and stirred at 95—100 °C for 5.25 h. The mixture was extracted with ether, the ethereal extract was washed with aqueous NaCl, dried ($MgSO_4$), and distilled to give crude **7** (bp 140—144 °C/11 mmHg, 0.8 g (80%)). The NMR data indicated that the product contained a small amount of **6**. The product was chromatographed on a silica-gel (Wakogel C-200) column, using hexane–benzene (1:1) as the eluent, to give **7** (bp 150—153 °C/21 mmHg (lit,[8] bp 154—156 °C/26 mmHg); $[\alpha]_D^{26}$ +20.84° (*c* 3.03); ^{1}H-NMR: δ=1.27 (d, 3H), 1.65 (broad s, 4H), 2.06 (broad s, 4H), 3.18 (q, 1H), 5.89 (broad s, 1H), 10.4 (s, 1H); Found: C, 70.38; H, 9.40%).

*(+)-2-Cyclohexylpropanoic Acid (**8**).* (+)-**7** ($[\alpha]_D^{28}$ +39.27°; 1.05 g, 6.8 mmol) in 40 ml of methanol was hydrogenated over a 5% Pd–$BaSO_4$ catalyst (2.3 g) at atmospheric pressure and at room temperature. The reduction product was freed from the catalyst and the solvent, and distilled to give (+)-**8** (bp 122—123 °C/6 mmHg; $[\alpha]_D^{22}$ +10.10° (*c* 1.248, ethanol) (lit,[9,1]) bp 121—123 °C/5 mmHg; $[\alpha]_D^{25}$ +18.9°)). ^{1}H-NMR δ=1.18 (d) and 0.7—2.6 (broad). (Found: C, 69.39; H, 10.64%).

References

1) D. J. Cram and F. D. Greene, *J. Am. Chem. Soc.*, **75**, 6005 (1953).
2) L. W. Trevoy and W. G. Brown, *J. Am. Chem. Soc.*, **71**, 1675 (1949); R. E. Parker and N. S. Isaacs, *Chem. Rev.*, **59**, 737 (1959).
3) G. Darzens, *C. R. Acad. Sci.*, **144**, 1123 (1907).
4) G. Darzens, *C. R. Acad. Sci.*, **141**, 766 (1905).
5) H. M. Walborsky and C. Colombini, *J. Org. Chem.*, **27**, 2387 (1962).
6) R. L. Shrinar, *Org. React.*, **1**, 1 (1942).
7) K. Auwers and P. Ellinger, *Justus Liebigs Ann. Chem.*, **387**, 228 (1912).
8) P. Rajzman, *Bull. Soc. Chim. Fr.*, **1948**, 754.
9) A. Maccioni, *Boll. Sci. Fac. Chim. Ind. Bologna*, **23**, 41 (1965); *Chem. Abstr.*, **63**, 8239 (1965).