Communications

New Nonenzymatic Chiral Induction. A Highly Regioselective Differentiation between Two Identical Groups in *meso*-2,4-Dimethylglutaric Acid

Summary: A highly regioselective differentiation between two identical groups in *meso*-2,4-dimethylglutaric acid by utilizing 4(*R*)-MCTT is described.

Sir: Very recently we published a novel and useful nonenzymatic procedure for a highly selective transformation of enantiotopic groups attached to a prochiral center in a symmetrical molecule, 3-methylglutaric acid.[1] We also proposed a new concept that the introduction of two of the same chiral ligands, e.g., two 4(*R*)-MCTT[2] groups, into the prochiral ligands of a symmetrical molecule having a prochiral center changes its original symmetrical nature (environment) into an unsymmetrical nature (environment).[1] This novel concept should be widely applicable not only to other similar compounds having a prochiral center but also to the meso compounds.

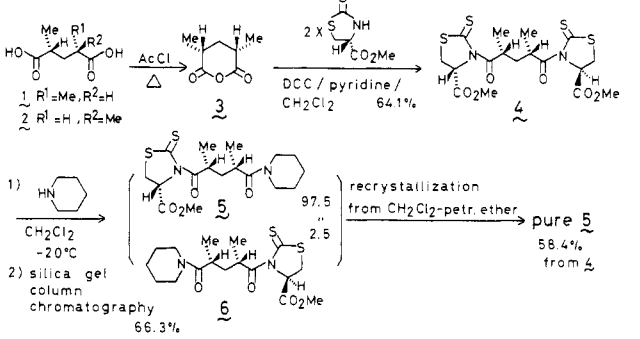
Now we report an extremely regioselective high-differentiation between two identical groups in *meso*-2,4-dimethylglutaric acid (**1**). The overall sequence is illustrated in Scheme I.

meso-2,4-Dimethylglutaric anhydride (**3**, 5.560 g), prepared from a mixture of *meso*- and *dl*-2,4-dimethylglutaric acid (**1** and **2**) by a known method,[3] was treated with 2 molar equiv of 4(*R*)-MCTT (13.860 g) in the presence of DCC (16.129 g) in pyridine (100 mL) and CH_2Cl_2 (20 mL) to give diamide **4**: yellow oil; 12 g (64.1% yield); $[\alpha]^{20}_D$ −169.23° (*c* 1.05, $CHCl_3$). Diamide **4** (1.817 g) on aminolysis with piperidine (0.324 g) in CH_2Cl_2 (100 mL) at −20 °C afforded a solid mixture (0.973 g, 66.3% yield), which was found to consist of **5** and **6** in a 97.5:2.5 ratio.[4] Recrystallization of the mixture from CH_2Cl_2–petroleum ether only once gave pure compound **5**: yellow plates; 0.858 g (58.4% yield); mp 111–112 °C; $[\alpha]^{20}_D$ −113.78° (*c* 1.10, $CHCl_3$). Its structure and absolute stereochemistry were established by X-ray analysis.[5]

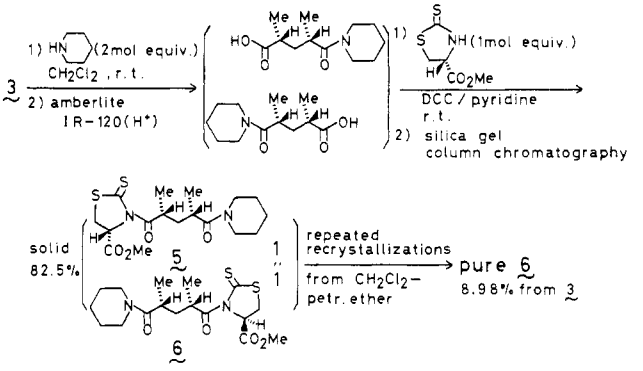
In order to get the minor product **6** in sufficient quantity, we employed the synthetic procedure shown in Scheme II. The material **3** was treated successively with 2 molar equiv of piperidine in CH_2Cl_2 at room temperature and Amberlite IR-120 (H^+) to give a racemic monoamide. This was converted into a solid mixture of diastereomers **5** and **6** in a ratio 1:1[4] by the usual treatment with 4-(*R*)-MCTT (1 molar equiv). Repeated recrystallization of the resulting mixture afforded pure crystals of **6**: yellow needles (from CH_2Cl_2–petroleum ether); mp 135–135.5 °C; $[\alpha]^{25}_D$ −46.35° (*c* 1.62, $CHCl_3$). Its structure and stereochemistry were determined by X-ray analysis.[5] The stereochemistry of **6** was also confirmed by its conversion into the enantiomer **9** of compound **8a** derived from **5** (see Scheme III and Table I).

Finally, compound **5** was subjected to "the monitored reaction"[1] with some nucleophiles to give optically pure acyclic products **8a–d** in high yields (Scheme III and Table I).

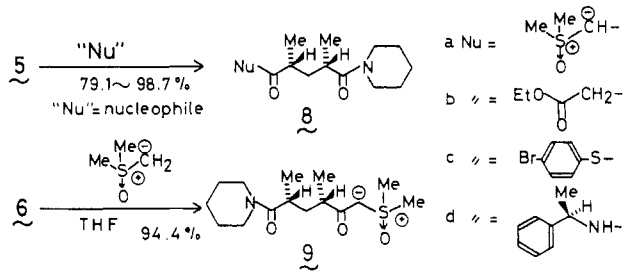
Scheme I



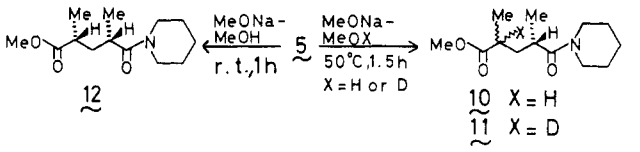
Scheme II



Scheme III



Scheme IV



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(2) 4(*R*)-MCTT: 4(*R*)-(methoxycarbonyl)-1,3-thiazolidine-2-thione. Nagao, Y.; Yagi, M.; Ikeda, T.; Fujita, E. *Tetrahedron Lett.* **1982**, *23*, 201.
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(4) The ratio of two diastereomers, **5** and **6**, was checked by high-pressure liquid chromatography: analytical conditions, JASCO Tri Rotar (UV-100) equipped with a JASCO DP-L220 LC data processor; column, JASCO PACK SS-05-250; solvent system, benzene–AcOEt (4:1); pressure, 150 kg/cm^2. Retention times: **5**, 14.39 min; **6**, 11.38 min.
(5) Crystallographic structures of compounds **5** and **6** and their data are available as supplementary material.
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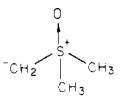
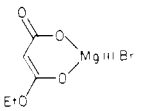
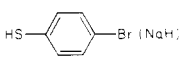
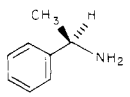
0022-3263/83/1948-0132$01.50/0

Table I. Treatment of 5 or 6 with Some Nucleophiles

nucleophiles	product[a]	mp, °C	$[\alpha]^{25}_D$, deg ($CHCl_3$)	% yield[b]
	8a[c]	110-111	-19.08 (c 1.09)	94.0
	9[c]	110-111	+19.11 (c 1.10)	94.4
	8b[d]	oil	+5.90 (c 2.03)	79.1
	8c[c]	oil	-9.95 (c 1.19)	98.7
	8d[c]	oil	+57.66 (c 1.07)	93.3

[a] Satisfactory spectral and analytical data were obtained for all products. [b] Isolated yield. [c] For the experimental procedure see ref 1. [d] To an in situ reagent[6] obtained from isopropylmagnesium bromide (5.1 mmol) and ethyl hydrogen malonate (2.5 mmol) in THF (5 mL) was added compound 5 (1 mmol) in THF (5 mL) at 0 °C, and then the mixture was stirred at room temperature overnight.[7]

It was confirmed by the ^1H NMR (100 MHz) analysis of products **8a-d** that no epimerization occurred at all during the transformation from **4** into **8**. On the ^1H NMR chart of the epimerized product, **10** or **11**, prepared under basic conditions at 50 °C (Scheme IV), signals (δ 1.08, 1.10, J = 7 Hz each) assignable to the methyl protons at C-4 were observed as two doublets. On the other hand, the ^1H NMR spectra of **8** and **12** formed under mild basic conditions showed a sharp doublet signal due to the methyl protons at C-4.

Thus, these products **8a-d** and **9** should be useful as "bifunctional chiral synthons"[8] for total synthesis of the optically active Prelog-Djerassi lactonic acid,[3b,9] methynolide,[10] 6-deoxyerythronolide B,[11] picromycin,[12] narbomycin,[13] and monensin.[14]

So far, the highly selective transformation of enantiotopic groups of the *meso*-2,4-dimethylglutaric acid derivative was performed exclusively by a special enzyme or a few microorganisms.[8] Our novel findings provide the first example of a highly selective chemical procedure of this type which is also practical.

Registry No. *meso*-**1**, 3891-70-1; (±)-**2**, 3891-69-8; *meso*-**3**, 4295-92-5; (-)-**4**, 83966-50-1; (-)-**5**, 83966-51-2; (-)-**6**, 84024-99-7; **8a**, 83966-55-6; **8b**, 83966-56-7; **8c**, 83983-94-2; **8d**, 83966-57-8; **9**, 83966-52-3; **10**, 83966-58-9; **11**, 83966-59-0; **12**, 83966-60-3; 4-(*R*)-MCTT, 80963-80-0; piperidine, 110-89-4; dimethylsulfoxonium methylide, 5367-24-8; bromomagnesium ethyl hydrogen malonate, 83966-54-5; 4-bromobenzenethiol, 106-53-6; (*R*)-α-methylbenzylamine, 3886-69-9; isopropylmagnesium bromide, 920-39-8; ethyl hydrogen malonate, 1071-46-1; (±)-(*R**,*S**)-2,4-dimethyl-5-oxa-5-piperidinylpentanoic acid, 83966-53-4.

Supplementary Material Available: Crystallographic details, tables of atomic positional and thermal parameters, and perspective views for **5** and **6** (10 pages). Ordering information is given on any current masthead page.

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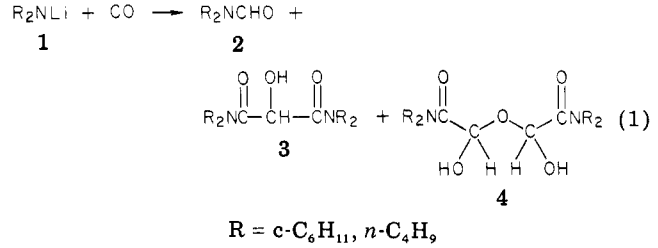
Received July 1, 1982

Insertion of Carbon Monoxide into Lithium-Nitrogen Bonds. One-Pot Synthesis of Dialkylformamides and Dialkylglyoxylamides[1]

Summary: Lithium dialkylamides react with CO to afford dialkylformamides **2**, tetralkylhydroxymalonamides **3**, and dialkylglyoxylamides **4**. Reaction conditions are described to produce **2** or **4** in good yields.

Sir: Continuing our investigations[2-4] on the carbon monoxide insertion into organolithium reagents and seeking for new modes of CO activation, we now report the usefulness of the reaction of lithium dialkylamides (**1**)[5] with CO to produce dialkylformamides **2** or dialkylglyoxylamides (hemihydrate) **4** in good yields (eq 1). The other reaction product which is obtained in varying yields is the tetralkylhydroxymalonamide **3**.



R = c-C_6H_{11}, *n*-C_4H_9

Previous studies of insertion of CO into N-Li bonds are scarce[6-8] and report contradictory results.[8] A common

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