Note

Preparation of Chiral *trans*-2,4-Dimethyl-1-cyclohexanones, the Key Intermediates in Cycloheximide Synthesis, Using Microbial Resolution

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Cycloheximide (**1**), a powerful antimicrobial agent produced by *Streptomyces griseus*, have been synthesized by an aldol condensation of *trans*-2,4-dimethyl-1-cyclohexanone (**2**) with 4-(2-oxoethyl)-2,6-piperidinedione (**3**) by the authors.¹⁾ However, (+)-**2** that was used for the synthesis of **1** was obtained by the degradation of natural **1**, and a practical preparation for chiral *trans*-2,4-dimethyl-1-cyclohexanone (**2**) was desired. Already, we have demonstrated that microbial hydrolysis of (±)-*t*-2,4-dimethyl-*r*-1-cyclohexyl acetate, followed by the oxidation, gave (−)-(2*R*,4*R*)-*cis*-2,4-dimethyl-1-cyclohexanone (**6**).²⁾ Here, we describe a synthetic method for chiral *trans*-2,4-dimethyl-1-cyclohexanone (**2**) by using the microbiological system.

The condensation of 4-methyl-1-cyclohexanone (**4**) with pyrrolidine gave the enamine **5**, which was reacted with

methyl iodide to form a stereoisomeric mixture of (±)-2,4-dimethyl-1-cyclohexanones. The ketones consisted of 86% of (±)-*trans* form (**2**) and 14% of *cis* form (**6**) by gas chromatographic (GLC) analysis with a column of 20% Hyprose SP-80. Reduction of the (±)-ketones **2** and **6** with several reducing reagents afforded a stereoisomeric mixture of (±)-2,4-dimethyl-1-cyclohexanols, which were analyzed by GLC with a column of 5% PEG-20M to give the results shown in the table. The reduction of (±)-**2** with K-selectride (potassium tri-*sec*-butylborohydride) show the highest stereoselectivity to predominantly yield (±)-*c*-2,4-dimethyl-*r*-1-cyclohexanol (**7b**). The (±)-**7b** fraction was acetylated with acetic anhydride-pyridine to give the (±)-*c*-2,4-dimethyl-*r*-1-cyclohexyl acetate (**9**) fraction. Asymmetrical hydrolysis²⁾ of the acetate (±)-**9** with a culture broth of *Bacillus subtilis* var. *niger* (IFO 3108) afforded (+)-**7b**, [α]_D + 30.7° (MeOH), and the (−)-acetate

TABLE I. REDUCTION PRODUCTS OF (±)-*trans*-2,4-DIMETHYL-1-CYCLOHEXANONE (**2**) CONTAINING *ca.* 14% OF (±)-*cis*-2,4-DIMETHYL-1-CYCLOHEXANONE (**6**) WITH SEVERAL REDUCING REAGENTS

Reagent	Solvent	Reaction temperature (°C)	% Ratio of the products			
			(±)- <i>trans</i> -Alcohols		(±)- <i>cis</i> -Alcohols	
			(±)- 7a	(±)- 7b	(±)- 8a	(±)- 8b
LiAlH ₄	Ether	0	34	47	1	18
NaBH ₄	MeOH	−5	18	53	10	19
NaBH ₄ –CeCl ₃ ³⁾	MeOH	−5	10	78	11	1
K-Selectride ⁴⁾	THF	−30	1	80	19	—
LiAlH (OCH ₃) ₃ ⁵⁾	THF	0	12	73	13	2
Redal	THF	−3	29	51	4	16
((MeOCH ₂ CH ₂ O) ₂ AlH ₂)Na						
Cyclohex ₂ BH ⁶⁾	THF	0~10	11	49	24	16

fraction. Reductive cleavage of the acetate (–)-**9** with lithium aluminum hydride gave (–)-**7b**. The optical purity of (–)-**7b** and (+)-**7b** was determined by ¹H-NMR spectra of their (–)-(S)-MTPA esters to show a 100% enantiomeric excess (*e.e.*). Oxidation of (+)-**7b** with pyridinium chlorochromate (PCC) gave (+)-(2*S*,4*R*)-*trans*-2,4-dimethyl-1-cyclohexanone (**2**), $[\alpha]_D^{20} +63.1^\circ$ (EtOH), ref. 1, $+58.3^\circ$ (EtOH). This result means that the (+)-*c*,2,*t*-4-alcohol (**7b**), that was obtained by the microbial hydrolysis has the (1*R*,2*S*,4*R*)-configuration. Similarly, (–)-**7b** was oxidized with PCC to give a (–)-(2*R*,4*S*)-ketone (**2**).

EXPERIMENTAL

1) (+)-2,4-Dimethyl-1-cyclohexanone. A Solution of 4-methylcyclohexanone (**4**, 46.0 g), 53.0 g of pyrrolidine, and 300 mg of *p*-toluenesulfonic acid in 200 ml of benzene was refluxed for 20 hr with separation of the produced water to give a pyrrolidine enamine (**5**, 61.0 g, 89% yield), bp 126–128°C (30 mmHg). A mixture of the enamine (**5**, 61.0 g) and 105 g of methyl iodide in 450 ml of dry benzene was stirred for 20 hr at room temperature. After adding 100 ml of water, the reaction mixture was stirred for 2 hr before 100 ml of 20% acetic acid was added. Extraction with ether gave a fraction boiling at 85–90°C (45 mmHg, 45.0 g) which consisted of 36% of **6** and 55% of (±)-**2** by GLC analysis with a 2 m × 3 mm column of 20% Hyprose SP-80 (column temp., 130°C; He flow rate, 24 ml/min). The fraction was chromatographed on silica gel, elution with hexane–ether (9:1) giving (±)-2,4-dimethyl-1-cyclohexanone, bp 70–75°C (20 mmHg), which consisted of 86% of (±)-*trans*-ketone (**2**) and *ca.* 14% of (±)-*cis*-ketone (**6**). IR $\nu_{\max}^{\text{film}}$ cm^{–1}: 1720, 1130, 1000. *Anal.* Found: C, 76.21; H, 11.22. *Calcd.* for C₈H₁₄O: C, 76.14; H, 11.18%.

2) Reduction of (±)-2,4-dimethyl-1-cyclohexanone with *K*-selectride. To a stirred solution of (±)-2,4-dimethyl-1-cyclohexanone (1.92 g) in 20 ml of dry THF at –30°C was added 28 ml of a 1 M solution of *K*-selectride in THF, stirring being continued for 2 hr. After adding 30 ml of 10% NaOH and 25 ml of 30% H₂O₂, the reaction mixture was stirred for 3 hr at 20°C and then poured into water. Extraction with ether gave 1.70 g (86% yield) of (±)-2,4-dimethyl-1-cyclohexanol, bp 91–100°C (65 mmHg), which consisted of 1% of **7a** (*t_R*: 7.8 min), 19% of **8a** (*t_R*: 5.7 min) and **7b** (*t_R*: 8.5 min) by GLC analysis with a 2 m × 3 mm column of 5% PEG-20M on Chromosorb W (column temp., 90°C; N₂ flow rate, 20 ml/min). Each stereoisomer of (±)-2,4-dimethyl-1-cyclohexanol was identified by co-GLC with authentic specimens.²⁾ The (±)-alcohol was chromatographed on silica gel, elution with hexane–ethyl acetate (9:1) giving pure (±)-*c*-2,*t*-4-dimethyl-*r*-1-cyclohexanol (**7b**) as an oil. *MS m/z* (rel. int.): 128 (M⁺, 4.5), 95 (100). IR $\nu_{\max}^{\text{film}}$ cm^{–1}: 3350, 1100, 1050, 1010. ¹³C-NMR (CDCl₃, 25 MHz) δ : 12.5, 21.4, 25.6, 28.9, 32.3, 33.8, 39.3, 72.4.

3) (±)-2,4-Dimethyl-1-cyclohexanol acetate. (±)-2,4-dimethyl-1-cyclohexanol (1.70 g) was stirred with 2.7 g of acetic anhydride in 4.2 ml of pyridine for 20 hr at 20°C to give 1.80 g (80% yield) of (±)-2,4-dimethyl-1-cyclohexyl acetate, bp 93–96°C (30 mmHg) IR $\nu_{\max}^{\text{film}}$ cm^{–1}: 1740, 1250, 1040.

4) Microbial hydrolysis of (±)-2,4-dimethyl-1-cyclohexyl acetate. Treatment of 3.33 g of the (±)-acetate with 500 ml of a culture broth of *Bacillus subtilis* var. *niger* IFO 3108²⁾ for 2 days at 27°C, followed by steam distillation, gave an oily mixture, which was chromatographed on alumina to give 1.60 g of an acetate and 900 mg of an alcohol. Chromatography of the alcohol on silica gel gave 650 mg of (+)-**7b**, $[\alpha]_D^{20} +30.7^\circ$ (*c* = 1.39, MeOH), *ca.* 100% *e.e.* from ¹H-NMR of its (–)-MTPA ester. The 3,5-dinitrobenzoate had an mp of 85–86°C. The recovered acetate was re-treated with 500 ml of the cultured broth for 1 day and then chromatographed on alumina to give 900 mg of the (–)-acetate as an oil, $[\alpha]_D^{20} -11.4^\circ$ (*c* = 1.96, MeOH), which consisted of 76% of (–)-(**9**) and 24% of the **8a**-acetate. The (–)-acetate (800 mg) was reduced with 180 mg of LiAlH₄ in 50 ml of ether for 1.5 hr at 20°C, followed by silica gel chromatography, and gave (–)-**7b**, $[\alpha]_D^{20} -30.6^\circ$ (*c* = 0.45, MeOH), *ca.* 100% *e.e.* The 3,5-dinitrobenzoate of (–)-**7b** had an mp of 85–86°C. *Anal.* Found: C, 55.84; H, 5.54; N, 8.63. *Calcd.* for C₁₅H₁₈O₆N₂: C, 55.89; H, 5.63; N, 8.69%.

5) (–) and (+)-*trans*-2,4-Dimethyl-1-cyclohexanones (**2**). To a stirred suspension of 560 mg of pyridinium chlorochromate (PCC) and 43 mg of sodium acetate in 5 ml of dry CH₂Cl₂ was added (+)-**7b** (160 mg) in 3 ml of CH₂Cl₂, the mixture being stirred for 1.5 hr at 20°C. Chromatography of the reaction mixture on Florisil gave 140 mg (88% yield) of (+)-**2**, *ca.* 100% purity by GLC analysis with 5% PEG-20M. $[\alpha]_D^{22} +63.1^\circ$ (*c* = 0.63, EtOH), ORD (*c* = 0.063, EtOH)_{nm}: $[\phi]_{303} +1,745$ (peak), $[\phi]_{283}$ 0, $[\phi]_{262} -1,514$ (trough). *MS m/z* (rel. int.): 127 (M⁺ + 1, 6.6), 126 (M⁺, 52), 82 (100). Similarly, the oxidation of (–)-**7b** with PCC gave (–)-**2**, $[\alpha]_D^{21} -63.4^\circ$ (*c* = 0.49, EtOH).

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