Synthesis and Epimerization Studies of 1-Alkyl-2-carbomethoxy-(benzyloxy)-4-methylazetidines

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A number of 1-alkyl-2-carbomethoxy(benzyloxy)-4-methylazetidines have been prepared by reaction of primary amines with α,γ-dibromo esters. Only one isomer was isolated from the reaction mixture. α-Aminolactones can also be obtained as the minor product of the reaction sequence.

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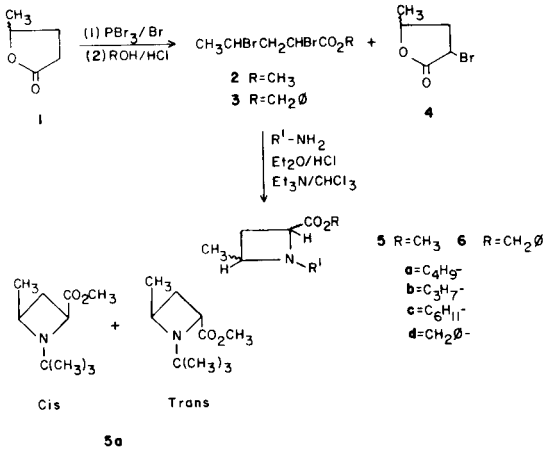
In previous publications (2,3,4) it was reported that several primary amines reacted with α,γ-dibromocarbonyl compounds to afford various functionalized carboazetidines. We now wish to report the further application of this scheme to the synthesis of selected 1-alkyl-2-carbo-4-methylazetidines which were desired for a continued study of the chemistry of comparable substituted aziridines and azetidines (5).

γ-Valerolactone (**1**) was converted to α,γ-dibromovaleryl bromide which was esterified, with the appropriate alcohol, to the α,γ-dibromovaleroster. Cyclization was carried out by refluxing in acetonitrile for a twelve to twenty-four hour time period. α-Bromovalerolactone (**4**) was concurrently produced during the course of preparation of **2** and **3** and could not be separated from the reaction mixture by normal distillation or chromatographic means. Presumption of structure of the dibromo esters followed from the complete structural proof of the azetidinyl esters **5,6a-d** (See Chart I).

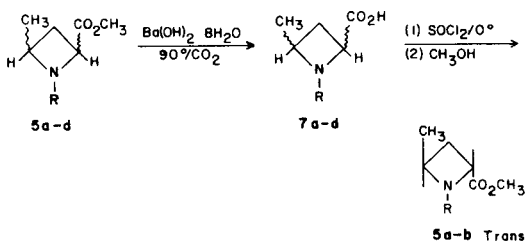
CHART I



The epimeric pair of azetidinyl esters (**5a**) was obtained by condensation of methyl α,γ-dibromovalerate (2) with *t*-butylamine the isomers being separated by preparative vpc (6). The originally assigned configurations of (**5a**) were later reversed (7). The nmr spectrum of one isomer showed the C-4 methine proton as a multiplet centered at 252 Hz, while the C-4 methine proton of the other isomer appeared at 190-213 Hz as a multiplet. It is known that protons lying in conical regions, extended above and below the plane of the carbonyl group will be shielded by this function while those lying elsewhere, and particularly those in the plane of the original atom, will be deshielded. Thus, the C-4 methine proton which came in the deshieleded zone appeared at relatively lower field. The isomer that showed the C-4 methine absorption at lower field has assumed the *trans* structure and the compound with the C-4 methine at 170-213 Hz was assigned the *cis* configuration. Discrimination of *cis-trans* isomers and configurational assignments on the basis of downfield shifts due to close proximity of ring substituents leading to deshielding has also been recently observed for the *trans* 2,4-disubstituted 1,3-dioxolanes as well as other heterocyclic ring systems (8,9,10,11).

Hydrolysis and partial epimerization, catalyzed by barium hydroxide, to the 1-alkyl-2-carboxy-4-methylazetidines revealed the presence of two isomers in an approximate ratio of 9:1. Re-esterification in acidic methanol

CHART II



yielded solely the *trans*-1-alkyl-2-carbomethoxy-4-methyl azetidines. This was indicative of the inherent thermodynamic stability of the *trans* geometry. Examination of the 220 MHz proton nmr spectrum of 1-cyclohexyl-2-carbomethoxy-4-methylazetidine (thermodynamic product) (**5c**) allowed straightforward elucidation of the C-2, C-3, C-4 vicinal couplings, which were interpreted according to the published procedure of Whipple and Evanega for the

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four-membered ring system (12,13). The results were in agreement with our assignment of the *trans* geometry to the thermodynamic product (14).

The nmr spectrum for compounds **6a-d** indicated the products to be only one isomer. Refluxing of compound **6a** with sodium methoxide in methanol for forty-eight hours did not effect epimerization to another isomer. Related substituted azetidines, prepared under similar conditions, have also previously been shown to consist of only one isomer (15,16). Thus, rapid epimerization to the thermodynamically more stable isomer occurred as these systems tended toward equilibrium.

Of general interest were the changes in chemical shift for C-2 and C-4 ring protons. It was found that the chemical shifts of the ring protons were sensitive functions of the steric requirements of the *N*-alkyl substituent especially when the *N*-alkyl group was bulky (Table I).

Table I

Chemical Shifts of C-2 Protons for *trans*-2-Carboazetidines

R_1	$R_2 = OCH_3$ (δ)	$R_2 = OCH_2C_6H_5$ (δ)
isopropyl	3.6	3.45
t-butyl	4.2	3.75
cyclo	3.55	3.50
benzyl	4.0	3.70
methyl (20)	3.38	---

Any shielding or deshielding exerted upon these protons by the *N*-alkyl group is a combination of anisotropy of the C-C and C-H single bonds (a shielding effect) and intramolecular Van der Waals-dispersion effects (a deshielding effect) (17,18).

Therefore, it was thought that a net shielding or deshielding of a proton may result depending on the magnitude of each of these parameters. In the related 2-aryl-3-aroylazetidines the C-2 and C-4 protons were found to occur at increasingly higher field strength as the *N*-alkyl substituent size decreased (19). These workers found that the chemical shift difference, $\Delta\gamma$, for these protons in the *N*-*t*-butyl and *N*-methyl derivatives was 20-35 Hz, with the values being less for non-methyl *N*-substituents. The C-2 chemical shifts of the 1-alkyl-2-carboazetidines seem to be affected by the same procedures to the same extent. Thus it was concluded that deshielding due to dispersion effects resulting from Van Der Waal interactions was significant in these compounds especially when the alkyl group was tertiary. An interesting exception to this trend was observed in the case of 1-benzyl-2-carbobenzyloxy-4-methyl azetidine (**6d**). Whereas a benzyl group roughly approximates the steric demand of a methyl group, the C-2 chemical shift is observed at δ 3.7 which was further downfield than for the other compounds examined. This decrease in shielding can be interpreted as paramagnetic shielding (deshielding) by the phenyl group. Dispersion effects in related azetidines are being examined further.

EXPERIMENTAL

Boiling points were determined at pressures recorded on a standard Virtis gauge and are uncorrected. Elemental analysis was performed by Micro-Tech Laboratories, Skokie, Illinois. Infra-red spectra were recorded on a Beckman Acu-Lab 4 spectrophotometer. The nmr were recorded on a Varian A-60 spectrometer and this was used as internal standard. Mass spectra were determined on a AEI MS 5076 spectrometer.

Methyl α,γ-Dibromovalerate.

This compound was prepared by the method of Rodebaugh and Cromwell, b.p. 53-55° (0.2 mm); lit. b.p. 50-52 (0.1 mm); ir (neat): 1740 cm^{-1}; lit. ir (neat): 1740 cm^{-1}.

Benzyl α,γ-Dibromovalerate.

A mixture of 100 g. (1.0 mole) of γ-valerolactone and a catalytic amount of red phosphorus was stirred for one hour and then heated to 115°. Bromine (65.0 ml.) was then added to the suspension dropwise beneath the surface of the liquid at a rate such that the temperature was maintained at 115-120°. After the addition of bromine was complete the reaction mixture was stirred for 1.5 hours at 115°. The mixture was then allowed to cool to room temperature and subsequently cooled to 0° in an ice bath. Benzyl alcohol (111.2 g.) was cooled to 0° and added to the original reaction mixture. The cooled solution was saturated with dry hydrogen chloride gas and stired at room temperature for thirty-six hours. The mixture was then dissolved in an equal volume of ethyl ether and washed with two five hundred ml. portions of five percent sodium bicarbonate solution. The ethereal layer was dried over anhydrous magnesium sulfate. Evaporation of the ether left a black mixture which when vacuum distilled yielded 223 g. of **3** and **4** as a light yellow mixture, b.p. 142-145° (0.1 mm); ir (carbon tetrachloride): 1780 cm^{-1} (C=O lactone), 1740 cm^{-1} (C=O ester); nmr (deuteriochloroform): δ 1.3 (d, 3H, J = 3.0 Hz, lactone methyl) 1.4 (d, 3H, J = 3.0 Hz, lactone methyl), 1.6 (d, 3H, J = 3.0 Hz, valerate methyl), 1.7 (d, 3H, J = 3.0 Hz valerate methyl), 1.9-2.65 (m, 4H, lactone methylene and ester methylene), 3.8-4.7 (m, 5H, lactone and ester methine), 5.15, 5.05 (2s, 2H each, carbobenzyloxy), 8.05 (s, 5H, aromatic). (**WARNING:** The above described mixture is a severe lachrymator and should only be handled in a well ventilated hood).

The following compounds (**5**) were prepared as reported previously (20).

Cis Isomer (**5a**).

This compound had ir (carbon tetrachloride): 1751/70 (ester, ν, C=O % abs) and 1725 cm^{-1} (ester ν_2 C=O % abs); nmr (deuteriochloroform): δ 3.78 (t, 1H, J = 8.2 Hz, C_2 proton), 3.72 (s, 3H, methoxy), 3.16-3.5 (m, 1H, C_4 methine proton), 1.6-2.55 (m, 2H, C_3 protons), 1.25 (d, 3H, J = 5.9 Hz, C_4 methyl) and 0.98 (s, 9H, *t*-butyl).

General Procedure for Synthesis of 1-Alkyl-2-carbobenzyloxy(methoxy)-4-methylazetidines.

A solution of benzyl(methyl)-α,δ-dibromovalerate (**2** or **3**) and three molar equivalents of the appropriate amine, in acetonitrile, was refluxed for 12-18 hours. The cooled reaction mixture was diluted with ether, filtered, and the solvent evaporated under reduced pressure. The residue was dissolved in ether, filtered, and exposed to a stream of dry hydrogen chloride gas for ten minutes, the ether was decanted and the residue was washed with ether and dissolved in chloroform. Five molar equivalents of triethyl amine was added, stirred for ten minutes, and chloroform was evaporated under reduced pressure. The residue was extracted with ether and the salt filtered. Evaporation of the ether yielded the crude products. The crude azetidines were purified by column chromatography and/or distillation.

Synthesis of 1-Isopropyl-2-carbobenzyloxy-4-methylazetidine (**6b**).

A 25.0 g. sample of **3** was reacted with the appropriate quantity of dried isopropylamine. This compound was purified by vacuum distilla-

tion and yielded a pale yellow liquid, b.p. 88-90° (0.1 mm). Redistillation, for an analytical sample, yielded a colorless liquid, b.p. 119-120° (0.1 mm) 42.8% yield, 7.53 g.; ir (carbon tetrachloride): 1755, 1730 cm^{-1} (ester); nmr (deuteriochloroform): δ 0.9 (d, 3H, J = 6.0 Hz), 1.45-2.7 (m, 3H, C_3 methylene and isopropyl methine), 2.7-4.18 (m, 1H, C_4 methine), 3.45 (t, 1H, J = 8.5 Hz, C_2 methine), 5.1 (s, 2H, benzyloxy), 8.13 (m, 5H, aromatic), 1.15 (d, 3H, J = 3.0 Hz, isopropyl methyl); high resolution ms: m/e Calcd.: 247.1570; Found: 274.1570. Tlc in several solvent systems showed one spot.

Anal. Calcd. for $C_{15}H_{21}NO_2$: C, 72.83; H, 8.53; N, 5.58. Found: C, 72.46; H, 8.47; N, 5.51.

Synthesis of 1-*t*-Butyl-2-carbobenzyloxy-4-methylazetidine (**6a**).

The appropriate quantity of *t*-butyl amine was reacted with 25.0 g. of **3**. After completion of reaction and routine work-up as described above a yellow liquid was isolated, b.p. 105-112° (0.25 mm). The material was chromatographed on silica gel and eluted with hexane-ether (1:1). This yielded a pale yellow liquid, 41.7% yield, 7.75 g.; ir (carbon tetrachloride): 1745, 1725 cm^{-1} (ester); nmr (deuteriochloroform): δ 0.9 (9H, *t*-butyl), 1.25 (d, 3H, C_4 methyl J = 5.5 Hz), 1.55-2.58 (m, 2H, C_3 methylene), 3.2-4.32 (m, 1H, C_4 methine), 3.75 (t, 1H, J = 8.3 Hz, C_2 methine), 5.1 (s, 2H, benzyloxy), 7.2 (s, 5H, aromatic); high resolution ms: m/e Calcd: 261.17287; Found: 261.17287. Tlc in several solvents revealed one spot.

Anal. Calcd. for $C_{16}H_{23}NO_2$: C, 73.27; H, 8.87; N, 5.31. Found: C, 72.91; H, 8.73; N, 4.94.

Synthesis of 1-Cyclohexyl-2-carbobenzyloxy-4-methylazetidine (**6c**).

A 25.0 g. sample of **3** was reacted with the appropriate quantity of dry cyclohexylamine. This compound was purified by vacuum distillation and yielded a pale yellow liquid, b.p. 119-121° (0.05 mm), 43.2% yield; 8.83 g.; ir (carbon tetrachloride): 1755, 1735 cm^{-1} (ester); nmr (deuteriochloroform): δ 0.9-1.9 (broad m, 14H, C_4 methyl and cyclohexyl protons), 1.9-2.6 (m, 2H, C_3 methylene), 2.9-4.2 (m, 1H, C_4 methine), 3.5 (t, 1H, J = 3.0 Hz, C_2 methine), 5.15 (s, 2H, benzyloxy), 7.35 (s, 5H, aromatic); high resolution ms: m/e Calcd: 287.1890; Found: 287.1890. Tlc showed one spot in several solvent systems.

Anal. Calcd. for $C_{15}H_{21}NO_2$: C, 75.23; H, 8.77; N, 4.87. Found: C, 74.96; H, 8.78; N, 4.69.

Synthesis of 1-Benzyl-2-carbobenzyloxy-4-methylazetidine (**6d**).

A 25.0 g. sample of **3** was reacted with the appropriate quantity of dry benzylamine. Purification of this compound was initiated by vacuum distillation which yielded a pale yellow liquid, b.p. 145-150° (0.3 mm). Chromatography on silica gel (200 cm × 20 cm column) and elution with chloroform-hexane (1:5) yielded a first fraction which was collected and redistilled under reduced pressure to yield a pale yellow liquid, b.p. 136-137° (0.05 mm), 45.7% yield, 9.6 g.; ir (carbon tetrachloride): 1747 cm^{-1} (ester); nmr (deuteriochloroform): δ 0.93 (d, 3H, J = 6.0 Hz, C_4 methyl), 1.0-2.1 (m, 2H, C_3 methylene), 2.85-3.5 (m, 1H, C_4 methine), 3.7 (t, 1H, J = 6.0 Hz, C_2 methine), 5.0 (s, 2H, benzyloxy), 4.5 (s, 2H, benzyl), 7.18 (s, 10H, aromatic); high resolution ms: m/e Calcd.: 295.1570; Found: 295.1570. Tlc indicated purity.

Anal. Calcd. for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.16; N, 4.54. Found: C, 77.43; H, 7.18; N, 4.44.

Synthesis of (*Z,E*)-1-Benzyl-2-carbomethoxy-4-methylazetidine (**5d**).

Following the generalized procedure outlined above, 55.0 g. of **2** gave 24.3 g. of a light yellow oil (**5d**), 57% yield, b.p. 105-107° (5.0 mm); ir (carbon tetrachloride): 1745 cm^{-1} (ester); nmr (deuteriochloroform): δ 1.1 (d, 3H, J = 6.5 Hz, C_4 methyl *trans*-isomer), 0.9 (d, 3H, partially masked by *trans*-isomer doublet, J = 6.0 Hz), 3.5 (s, 3H, CO_2CH_3 *trans*-isomer), 3.7 (3H, CO_2CH_3 *cis*-isomer), 3.45-2.9 (m, 5H, C_3 ring protons CH_2CHCO, *cis*-, *trans*-, and $CHCO$ *trans*-isomer), 3.9 (s, 2H, benzyl), 4.0 (q, $CHCO$, *trans*-C_2 methine), 7.35 (s, 5H, aromatic protons); high resolution ms: m/e Calcd: $C_{13}H_{17}O_2N$: 219.1259; Found: 219.1256 (± 0.0002).

Anal. Calcd. for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.82; N, 6.39. Found: C, 71.41; H, 7.78; N, 6.27.

Synthesis of (*Z,E*)-1-Isopropyl-2-carbomethoxy-4-methylazetidines (**5b**).

Following the generalized procedure a colorless liquid (**5b**) was obtained, b.p. 88-90° (0.6 mm); ir (carbon tetrachloride): 1740 cm^{-1} (ester); nmr (deuteriochloroform): δ 3.6 (q, 1H, J_{cis} = 5.1 Hz, J_{trans} = 3.0 Hz, C_2 methine *trans*), 4.0 (m, 1H, partially masked by C_2 multiplet, C_4 methine *cis*), 3.7 (s, 6H, carbomethoxy *cis* and *trans*), 3.3 (t, 1H, J = 7.8 Hz, C_2 methine), 1.3-3.1 (broad 23 line m, 6H, C_3 methylene and isopropylmethyl *cis, trans*), 1.2, 1.3 (2d, 6H, *cis*-, *trans*-C_4 methyl), 1.0 (d, 3H, J = 6.0 Hz, isopropyl methyl), 0.9 (d, 3H, J = 6.0 Hz, isopropyl methyl); high resolution ms: m/e Calcd: 171.1254; Found: 171.1261.

Anal. Calcd. for $C_9H_{17}NO_2$: C, 63.13; H, 10.01; N, 8.18. Found: C, 62.70; H, 9.94; N, 7.19.

Synthesis of (*Z,E*)-1-Cyclohexyl-2-carbomethoxy-4-methylazetidines (**5c**).

Following the generalized procedure described above a colorless oil (**5c**) was obtained by vacuum distillation in 40% yield, b.p. 88-90° (0.6 mm); ir (carbon tetrachloride): 1735 cm^{-1} (ester); nmr (deuteriochloroform): δ 3.55 (q, 1H, J_{cis} = 5.0 Hz, J_{trans} = 3.0 Hz, C_2 methine *trans*-isomer), 3.35 (m, 1H, C_4 methine *trans*-isomer) 3.4 (s, 6H, carbomethoxy *cis, trans*), 3.2 (m, 1H, C_4 methine *cis*-isomer), 2.0-2.5 (m, 4H, C_3 methylene *cis, trans*), 1.0-1.9 (m, 28H, cyclohexyl protons *cis, trans* and C_4 methyl protons); high resolution ms: m/e Calcd: 211.1572; Found: 211.1573.

Anal. Calcd. for $C_{12}H_{21}NO_2$: C, 68.20; H, 10.02; N, 6.63. Found: C, 68.30; H, 10.03; N, 6.83.

Generalized Procedure for the Hydrolysis and Epimerization of 1-Alkyl-2-carbomethoxy-4-methylazetidines.

The procedure is carried out essentially by the method described by Rodebaugh and Cromwell (18). A 0.01 mole sample of carbomethoxy azetidine was added to a solution of 0.006 mole. Barium hydroxide octahydrate in 30 ml. of water held at 90° for fifteen minutes, 40 additional ml. of water was added and the hot mixture was neutralized by bubbling in carbon dioxide until precipitation of barium carbonate was complete. The barium carbonate was removed by filtration, the water was evaporated from the filtrate under reduced pressure, and the residue was then dissolved in chloroform. Concentration of the solution yields high melting white solids (**7a-d**) which need no further purification. A 0.01 mole sample of the acids (**7a-d**) are suspended in dry ether (20 ml.) and cooled to 0° in an ice bath. Thionyl chloride (0.02 mole) was then added dropwise over thirty minutes, never permitting the reaction temperature to rise above 10°. The reaction mixture was then allowed to stir at room temperature for twelve hours. Evaporation of ether and excess thionyl chloride followed by dropwise addition of methanol at 0° gave approximately 90% of the crude *N*-alkyl-2-carbomethoxy-4-methyl azetidines as their hydrochlorides. The hydrochlorides were dissolved in the minimum amount of chloroform and triethylamine (0.03 mole) was added slowly. The reaction mixture was stirred at room temperature for one hour and then evaporated to dryness under reduced pressure at 25°. The residual solids were washed with anhydrous ether and the triethylamine hydrochloride was filtered. Evaporation of the ther gave an average yield of 65% of *N*-alkyl-2-carbomethoxy-4-methylazetidines **5a-d**. Inspection of the nmr spectrum for esters **5a-d** revealed the presence of only *trans* isomers as described above.

Synthesis of (*Z,E*)-1-Benzyl-2-carboxy-4-methylazetidine (**7d**).

This compound was prepared by the procedure outlined above from 5.0 g. of (**5d**); 4.1 g. (83%) of white solid (**7d**) was obtained, m.p. 169-170°; ir (potassium bromide): 1630 cm^{-1} (ionic carboxylate); nmr (deuterium oxide): 1.2 δ (3H, d, J-6.0 Hz, CH_3 *cis*-isomer), 1.55 (3H, d, J-7.0 Hz, CH_3 *trans*), 2.65-2.3 (1H, m, CH_3CHN *cis, trans*), 4.2 (2H, s, benzyl), 4.2-4.8 (4H, m, partially masked by deuterium oxide exchange, $CHCO$, CH_2CHCO), 4.7 (1H, s, CO_2H proton deuterium oxide exchange), 7.3 (5H, s, aromatic protons). Nmr integration of CH_3 doublets showed a *trans:cis* ratio of 9:1, respectively; exact mass measurement: Calcd. for

$C_{12}H_{15}NO_2$: 205.11027; Found: 205.11001 (± 0.0001).

Anal. Calcd. for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.83. Found: C, 70.05; H, 7.37; N, 6.72.

Synthesis of (*Z,E*)-1-*t*-Butyl-2-carboxy-4-methylazetidine (**7a**).

This compound was prepared by the procedure described above. From 5.0 g. of **5a** was obtained 4.4 g. (88%) of a white solid (**7a**), m.p. 172-174° dec.; ir, nmr and ms support the structure.

Anal. Calcd. for $C_9H_{17}NO_2$: C, 63.18; H, 9.94; N, 8.18. Found: C, 63.11; H, 9.91; N, 8.21.

Synthesis of (*Z,E*)-1-Isopropyl-2-carboxy-4-methylazetidine (**7b**).

This compound was prepared by the procedure described above. From 5.0 g. of **5b** was obtained 3.7 g. (74%) of a white, hygroscopic solid (**7b**), m.p. 143-145°; ir, nmr and ms support the structure.

Anal. Calcd. for $C_8H_{15}NO_2$: C, 61.17; H, 9.55; N, 8.91. Found: C, 61.13; H, 9.49; N, 8.81.

Synthesis of (*Z,E*)-1-Cyclohexyl-2-carboxy-4-methylazetidine (**7c**).

This compound was prepared by the procedure described above. From 5.0 g. of **5c** was obtained 4.25 g. (85%) of a white solid (**7c**), m.p. 166-169° dec.; ir, nmr and ms support the structure.

Anal. Calcd. for $C_{11}H_{19}NO_2$: C, 67.03; H, 9.64; N, 7.10. Found: C, 66.93; H, 9.47; N, 7.03.

Attempted Epimerization of 1-Alkyl-2-carbobenzyloxy-4-methylazetidines (**6a**).

A 0.5 g. sample of (**6a**) was refluxed in 10.0 ml. of benzyl alcohol with 0.1 g. of sodium hydroxide for up to one week intervals. At the end of the allotted time the benzyl alcohol was evaporated, ether was added, and the suspension was filtered. Ether removal yielded a yellow oil, the nmr spectrum of which indicated no epimerization to the other isomer.

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