using ion-exchange chromatography,[2] we have not been successful in separating them by this technique. We are investigating separations of the mixtures with **7** (alcohol) and **8** or at the stage of peptides prepared from the mixture **5**.

It is likely that the yield of **8** can be optimized, but even without a higher yield this synthesis is applicable to the preparation of AHMHA in quantity. In addition, the optical rotation of the mixture **5** indicates no more than 2% racemization, an important consideration in the preparation of enzyme inhibitors.

Experimental Section

Amino acid analyses were performed on a Beckman 120-C amino acid analyzer using standard short and long columns and pH 4.25, 0.2 M sodium citrate buffer.[5] The mixture **5** eluted as a single symmetrical peak on the short (33 min) or long (308 min) columns as did natural AHMHA in hydrolysates from pepstatin. The ninhydrin constant is 36% of that of L-leucine.

4-Amino-3-hydroxy-6-methylheptanoic Acid (5). Under anhydrous conditions, 48.7 g (0.25 mol) of *tert*-butyl α-bromoacetate[4] and 19.6 g (0.3 mol) of activated zinc[6] were refluxed in 100 mL of dry tetrahydrofuran for 1.5 h. The solution was cooled, decanted into a dropping funnel, and added dropwise during 45 min, with stirring, to a solution of 41.7 g (0.17 mol) of *N*-phthalyl-L-leucinal[7] maintained at 0–5 °C. After an additional 30 min of stirring, the solvent was removed by distillation and the residue was refluxed in 200 mL of dry benzene for 5 h. The solvent was removed in vacuo, 200 mL of 2 N hydrochloric acid was added, and the solution was extracted with three 150-mL portions of ethyl acetate. The combined organic extracts were extracted with two 100-mL portions of 5% sodium bicarbonate. The basic extracts were acidified to pH 1 with hydrochloric acid and the product was extracted with two 100-mL portions of ether. The extracts were dried over sodium sulfate and evaporated to give 20.7 g (40% yield) of crude **8**. Deblocking was effected by refluxing the product (0.068 mol) with 2.3 g (0.068 mol) of 95% hydrazine hydrate for 1.5 h in 100 mL of ethanol. The solvent was removed in vacuo, the residue was stirred with 200 mL of 2 N hydrochloric acid, the phthalylhydrazide was filtered off, and the filtrate was evaporated to dryness. The residue was taken up into 200 mL of water and amino acid analysis of the solution indicated a quantitative yield in the deblocking step. The solution was applied to a 2.5 × 79 cm column of Dowex 50-X8 ion-exchange resin equilibrated with 0.1 M pyridine adjusted to pH 5 with acetic acid. Elution with this buffer yielded 11.5 g (38%) of the mixture **5**. The NMR spectrum agrees with that reported[2,8] for the 3*R*,4*S* and 3*S*,4*S* diastereomers and revealed a 45:55 mixture of the two: $[\alpha]^{21}_{365}$ −47.9° (C1, H_2O) [reported[3] for 3*R*,4*S* and 3*S*,4*S* $[\alpha]^{21}_{365}$ −49° (C1, H_2O)].

Anal. Calcd for $C_8H_{17}NO_3$: C, 54.83; H, 9.77; N, 7.99. Found: C, 54.77; H, 9.68; N, 7.89.

Acknowledgment. The authors thank the National Science Foundation (Grants GB-34245 and PCM76-15688) and the Robert A. Welch Foundation for their generous support of this work.

Registry No.—(3*R*,4*S*)-**5**, 49642-13-9; (3*S*,4*S*)-**5**, 49642-07-1; **6**, 64490-39-7; (3*R*,4*S*)-**8**, 64490-38-6; (3*S*,4*S*)-**8**, 64490-37-5; *tert*-butyl α-bromoacetate, 5292-43-3.

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Metal–Ammonia Reduction of *cis*-8,10-Dimethyl-1(9)-octal-2-one[1]

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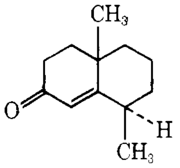
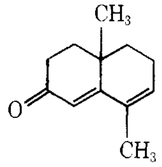
Recently, we reported the synthesis of *cis*-8,10-dimethyl-1(9)-octal-2-one (**1**) by transfer hydrogenation of the bicyclic dienone **2**.[2] The continued interest in the influence of substituents upon the metal–ammonia reductions of 1(9)-octal-2-ones[3] has prompted us to investigate the stereochemistry of the reduction of **1** with lithium and other metals in liquid ammonia.

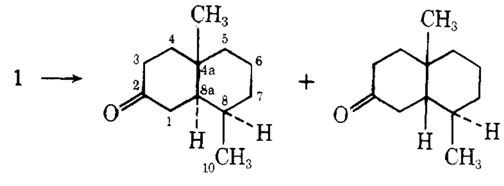


1



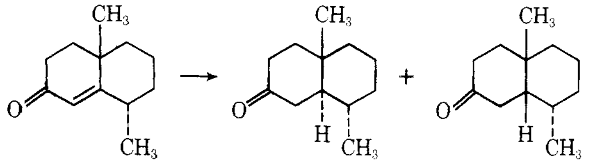
2

Reduction of **1** with lithium in liquid ammonia containing 1 equiv of *tert*-butyl alcohol under the usual conditions gave a 6.4:1 mixture of the known *trans*-decalone **3**[4] and an isomer which has been assigned the *cis*-decalone structure **4** in 85–91% yield. It was also found that catalytic hydrogenation of **1** using 10% palladium on carbon in 95% ethanol gave a 65:35 mixture of **3** and **4** in essentially quantitative yield.[5]



	3	**4**
Li/NH$_3$, ether, 1 equiv *t*-BuOH	87%	13%
H$_2$, Pd(C), 95% EtOH	65%	35%

In order to ascertain that isomerization of **1** into the thermodynamically more stable *trans*-octalone **5**[6] was not occurring prior to chemical (or catalytic) reduction, the latter enone was converted to the corresponding decalone derivatives. As expected lithium–ammonia reduction of **5** gave exclusively the *trans*-decalone **6**[4b] and a 5:95 mixture of **6** and the cis isomer **7**[7] was produced by catalytic hydrogenation of **5** in acidic 95% ethanol using 5% palladium on carbon as the catalyst. The isomeric decalones **3**, **4**, **6**, and **7** were readily separated from each other by GLC using a Carbowax column. Thus no significant isomerization of **1** into **5** occurred under either set of reduction conditions.[5]



5

	6	**7**
Li/NH$_3$, ether, 1 equiv *t*-BuOH	100%	—
H$_2$, Pd(c), 95% EtOH, HCl	5%	95%

The structural assignment of **4** is based upon the fact that

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Table I. Natural Abundance ^{13}C Chemical Shifts of *trans*- and *cis*-2-Decalones[a]

Registry no.	Decalone	Chemical shifts of C atoms[b]											
		1	2	3	4	4a	5	6	7	8	8a	9	10
941-23-1	3	(43.8)	211.6	(40.6)	(43.7)	33.4	(38.2)	17.2	(32.8)	32.8	46.4	18.6	14.1
64281-62-5	4	(39.6)	211.6	(37.6)	(39.6)	33.0	(35.9)	21.4	(31.4)	31.4	51.6	27.7	20.1
64281-60-3	6	(41.2)	212.0	(40.9)	(40.9)	33.2	(37.8)	21.4	(35.6)	32.3	50.6	19.6	15.9
52305-17-6	7	(41.1)	212.4	(36.9)	(37.5)	33.2	(28.7)	21.6	(27.7)	29.9	47.6	26.2	19.3

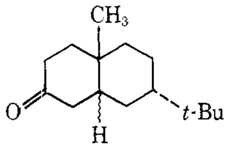
[a] For the numbering system of the decalones, see structure 3. [b] Chemical shifts are in ppm relative to internal Me_4Si.

Table II. Reduction of Enone 1 with Metals in Liquid Ammonia Containing 1 Equiv of *tert*-Butyl Alcohol at −33 °C

Metal	% 3[a]	% 4[a]	3/4 ratio	% yield[b]
Li	86.5 ± 2.3	13.6 ± 2.3	6.4	85–91
Na	80.4 ± 0.4	19.6 ± 0.4	4.1	88–98
K	78.6 ± 0.8	21.4 ± 0.8	3.7	78–90
Ca	93.2 ± 0.6	6.8 ± 0.6	13.7	96–97
Ba	88.1 ± 2.3	11.9 ± 2.3	7.4	93–95

[a] Percentages are an average of two or more runs. [b] Range of isolated yields of decalone mixtures after GLC analysis.

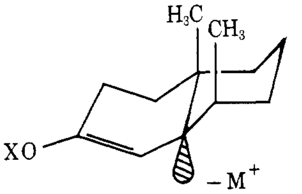
it is formed along with 3 in both the chemical and catalytic reduction of 1 and upon a comparison of its ^{13}C NMR spectrum with those of the other three isomeric decalones. The natural abundance ^{13}C chemical shifts of decalones 3, 4, 6, and 7 are recorded in Table I. These chemical shift assignments are consistent with off-resonance decoupling measurements. However, the assignments in parentheses are tentative. A significant feature of these ^{13}C spectra is that the angular carbon atoms (C-9) in the two cis-fused isomers 4 and 7 occur at 6–10 ppm lower field than the corresponding absorptions in the trans isomers 3 and 6. The latter compounds have a greater number of γ interactions[8] which contribute to the shielding of the angular carbon atoms. The angular carbon atoms in the cis- and trans-fused decalones 8a and 8b have been reported to have chemical shifts of 27.0 and 17.2 ppm.[3b] This provides another example of a pair of 2-decalones in which the angular carbon of the cis isomer absorbs at lower field.



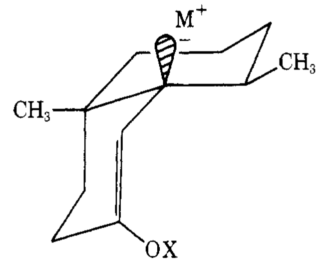
8a, cis-ring fusion
b, trans-ring fusion

Systematic studies on the influence of the nature of the metal on the course of metal–ammonia reductions of α,β-unsaturated ketones are rare and have not been reported for 1(9)-octalones.[3c] Therefore, since enone 1 gave a mixture of isomers using lithium in liquid ammonia, we have determined the ratio of the reduction products obtained using other alkali and alkaline-earth metals under the same conditions. These results and the lithium–ammonia reduction results are recorded in Table II.

Decalones 3 and 4 may be considered to arise via protonation of β-carbanionic intermediates 9 or 10, respectively, in which the oxygen atom is either protonated[9] or associated with a metal cation.[3c] Intermediate 9 is favored over 10 on stereoelectronic grounds and as predicted by the Stork–Darling axial protonation rule[10] the *trans*-decalone 3 is the favored reduction product with all metals investigated. On the basis of estimates of nonbonded interactions alone, species 10 which leads to the cis product should be 2–3 kcal/mol more stable than 9. Therefore, the ratios of 3/4 observed under various conditions support the previous suggestion that the orbital overlap (stereoelectronic) factor provides a stabilization energy of 3–5 kcal/mol.[3c]



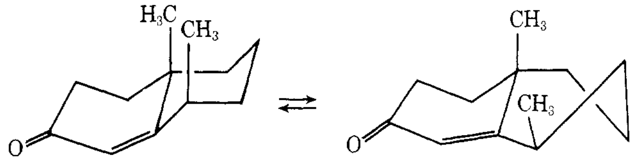
9



10

X = H or M

The amount of cis product 4 obtained from 1 was small with lithium and the other metals studied, but it was significantly greater than has been observed for other ring B substituted octalones except those having exceptionally bulky groups at the 6β or 7α positions.[3b,c] It seems to be generally true that when the B ring of the 1(9)-octal-2-one system is forced into an unusual conformation by substituent effects, cis reduction products are observed.[3b] In the case of 1 conformation **1B**, in which the B ring is in a twist-boat and the 1,3-diaxial methyl-methyl interaction is relieved, may be in equilibrium with conformation **1A**, in which the B ring is in a normal chair. On addition of two electrons, conformation **1B** may be converted into the cis β-carbanionic species 10 with a minimum amount of motion of atoms and solvent-shell reorganization.



1A 1B

The magnitude of the change in the stereochemistry of the reduction with the change in metal cation is small but outside the range of experimental error. The results show that within the alkali metal and alkaline-earth metal series the smaller cations, i.e., Li^+ and Ca^{2+}, respectively, yield less of the cis-fused product 4 than the larger cations. At first sight this is surprising, since the β-carbanion–metal complex seems to be in a slightly more crowded environment in configuration 10 than 9. Also, since the charge is more localized at the β position in 10 a closer approach of the metal to the carbanionic center might be expected to be necessary in this case. However, the literature contains a number of suggestions that the smaller metal cations are more extensively solvated by ammonia than larger cations.[3c] If the metal–ammonia complex is actually larger for the smaller than for the larger metal cations, this could account for the greater amounts of trans product obtained in the reductions using lithium and calcium. Also, if the species undergoing β protonation is a dianion rather than a hydroxyallyl anion, it might be expected that **9** would be stabilized relative to **10** when metal cations such as Li^+ and Ca^{2+} are involved. These cations should form more covalent bonds with the oxygen atom than the more electropositive metal cations, thus allowing more favorable overlap of the β-carbanion with the π-electron system of the metal enolate.

Experimental Section[11]

General Procedure for the Metal–Ammonia Reduction of Octalone 1.[3c] Anhydrous liquid ammonia (300 mL, distilled from sodium) was distilled under nitrogen into a flame-dried three-necked flask fitted with a mechanical stirrer, an addition funnel, and a Claisen adaptor holding a dry-ice condenser and a gas inlet tube. Freshly cut metal, 0.022 g-atom of alkali metal or 0.011 g-atom of the alkaline-earth metal, was then added and the mixture was stirred until the metal had completely dissolved (15–45 min). A mixture of 1.78 g (0.010 mol) of octalone **1** and 0.74 g (0.010 mol) of *tert*-butyl alcohol in 70 mL of anhydrous ether (distilled from $LiAlH_4$) was added dropwise with stirring over 30 min at −33 °C. Stirring was continued for 3 h and then 3.14 g of solid ammonium chloride was added as rapidly as possible. The ammonia was allowed to evaporate and the residue was dissolved in 200 mL of a 1:1 ether–water mixture. The layers were separated and the aqueous layer was saturated with sodium chloride and extracted with three 50-mL portions of ether. The ethereal extracts were combined and dried over magnesium sulfate. After removal of the solvent in vacuo the residue was analyzed by GLC and distilled to give a mixture of decalones **3** and **4** in the yields given in Table I.

Pure samples of ketones **3** and **4** were collected by preparative GLC. Ketone **3** showed identical IR, ^1H NMR, and mass spectral properties and GLC behavior to an authentic sample.[4] Its ^{13}C chemical shifts are recorded in Table I. Compound **4** showed: mp 51.0–52.0 °C; IR (CCl_4) 1711, 1460, 1442, 1379, 1330, 1305, 1157, 1142, 1110 cm^{-1}; NMR (CCl_4) δ 0.89 (d, 3 H, J = 3.8 Hz), 1.25 (s, 3 H); MS (70 eV) *m/e* 180 (28), 109 (100).

Anal. Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.19. Found: C, 79.85; H, 11.18.

The ^{13}C chemical shifts of **4** are recorded in Table I. It formed a semicarbazone, mp 182.0–183.0 °C.

Anal. Calcd for $C_{13}H_{20}N_3O$: C, 65.79; H, 9.77. Found: C, 65.70; H, 9.81.

Preparation of Ketone 6. Ketone **6** was prepared in ~90% yield by lithium–ammonia reduction of the enone **5** according to the general procedure described for the enone **1**. Ketone **6** [bp 110–112 °C (0.1 mm); lit.[4b] 80 °C (0.01 mm)] showed identical IR, ^1H NMR, and mass spectral properties with those reported for the optically active material.[4b] It formed a semicarbazone: mp 203–204 °C (lit.[7] mp 202.5–203.0 °C). The ^{13}C chemical shifts are shown in Table I.

Catalytic Hydrogenation of Enone 1. To a solution of 0.32 g of octalone **1** in 6 mL of 95% ethanol was added 0.056 g of 10% palladium on carbon. The mixture was hydrogenated in a Parr apparatus for 2 h at 35 psi of hydrogen pressure. Removal of the catalyst by filtration and removal of the solvent in vacuo gave a mixture of decalones **3** and **4** [bp 110–115 °C (bath temperature) (0.1 mm)] in essentially quantitative yield. Analysis of the mixture by GLC showed that it contained ~65% **3** and ~35% **4**. A trace (<3%) of decalone **6** was also present.[5]

Catalytic Hydrogenation of Enone 5 in Acidic Medium. To a solution prepared from 0.80 g of octalone **5**, 1.5 mL of 3.2 N hydrochloric acid, and 15 mL of 95% ethanol was added 0.15 g of 5% palladium on carbon. The mixture was hydrogenated in a Parr apparatus for 2 h at 35 psi of hydrogen pressure. On removal of the catalyst by filtration and removal of the solvent in vacuo, GLC analysis of the residue showed that it was composed of a 5:95 mixture of decalones **6** and **7**. Distillation of the mixture under reduced pressure gave 0.403 g (49%) of pure **7**: bp 108–112 °C (0.10 mm); IR (film) 1713, 1462, 1447, 1430, 1379, 1355, 1340, 1284, 1266, 1243, 1217, 1185, 1155, 1133, 1109, 1072, 1022, 1005, 934, 826, 755 cm^{-1}; NMR (CCl_4) δ 0.81 (d, 3 H, J = 6.6 Hz), 1.06 (s, 3 H); MS (70 eV) *m/e* 180 (37), 109 (100), 108 (88), 95 (65), 81 (53), 67 (54), 55 (84), 41 (79); semicarbazone mp 202.0–203.0 °C (lit.[7] 202.2–202.5 °C).

Registry No.—1, 64281-61-4; 4 semicarbazone, 64215-98-1.

References and Notes

(1) This investigation was supported by Grant No. CA12193, awarded by the National Cancer Institute, DHEW. The research was also assisted by Institutional Research Grants from the National Science Foundation for the purchase of a mass spectrometer and a Fourier transform NMR spectrometer.

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(4) (a) The major reduction product **3** showed identical NMR, IR, and mass spectral properties and chromatographic behavior to an authentic sample of racemic **3** which had identical spectral and chromatographic properties to the optically active material obtained by oxidative degradation of dihydroeudesmanol (ref 4b). We are grateful to Dr. B. Maurer for providing us with a generous supply of authentic racemic **3**. (b) B. Maurer, M. Fracheboud, A. Grieder, and G. Ohloff, *Helv. Chim. Acta*, **55**, 2371 (1972).

(5) A trace (<3%) of the decalone **6** was obtained in the catalytic reduction of **1**. This product may have arisen because **1** was slightly contaminated with the trans isomer **5** or a slight amount of isomerization of **1** into **5** may have occurred under the reaction conditions.

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(11) Melting points and boiling points are uncorrected. Infrared spectra were taken on a Perkin-Elmer Model 457 infrared spectrophotometer. The ^1H NMR spectra were obtained on a Varian T-60 NMR spectrometer and the ^{13}C NMR spectra were determined at 25 MHz with a Jeol Fourier transform spectrometer, Model PFT-100. The chemical shifts are expressed in δ values (ppm) to Me_4Si as an internal standard. The mass spectra were obtained with a Hitachi (Perkin-Elmer) Model RMU-7. Gas–liquid chromatography was carried out using a Perkin-Elmer 881 or an Aerograph A-90-P3 gas chromatograph. A 6 ft × 0.125 in. aluminum column packed with 20% Carbowax K-20M on acid washed Chromosorb W was employed for analytical work and a 10 ft × 0.25 in. stainless steel column containing the same packing material was used for preparative work. Microanalyses were obtained by Atlantic Microlab, Inc., Atlanta, Ga.

A Convenient Method for the Stereoselective Reduction of Alkynes to Alkenes by the New Reagents MgH_2–CuI and MgH_2–CuO-*t*-Bu

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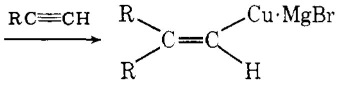
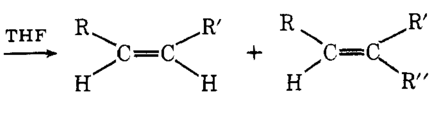
The most common method of reducing alkynes to cis olefins is by catalytic hydrogenation, whereas the most common method of reducing alkynes to trans olefins is by liquid ammonia reduction.[1] In catalytic hydrogenation, usually some trans olefin is also produced with the cis olefin and quite often the two isomers are difficult to separate completely. A more recent method of reducing alkynes to cis olefins is based on the work of Normant.[2,3] Normant has shown that organocopper reagents (RMgBr + CuBr) add to unactivated terminal alkynes (eq 1) to produce the alkyl addition product. More recently, Crandall reported that when the reagent 2RMgX–CuI is added to disubstituted alkynes, reduction is the predominant reaction (eq 2).[4] These reactions are potentially important because of their stereospecificity and versatility in organic synthesis.[5-10] However, the main re-

$$RMgBr + CuBr \longrightarrow RCu\cdot MgBr_2$$



(1)

$$RC\equiv CR' + 2R''MgX\text{-}CuI$$



(2)

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