Reaction of Silver Acetate and Iodine with 1g. Starting materials were 0.735 g of silver acetate and 0.396 g of **1g**; purification of the crude reaction product by preparative layer chromatography ($CHCl_3$) afforded 0.360 g (72%) of pure 2-iodocyclooctanone, **6c**: molecular distillation 45 °C (2 mm) [lit.[5] 45 °C (1.75 mm)]; n^{25}_D 1.5490 (lit.[5] n^{23}_D 1.5494); IR (neat) 1700 cm^{-1}.

Reaction of Silver Benzoate and Iodine with 1g. Starting materials were 1.010 g of silver benzoate and 0.396 g of **1g**; purification of the crude reaction product by preparative layer chromatography ($CHCl_3$) afforded 0.356 g (71%) of pure **6c**: molecular distillation 45 °C (2 mm) [lit.[5] 45 °C (1.75 mm)]; IR (neat) 1700 cm^{-1}.

Reaction of Silver Acetate and Iodine with 1h. Starting with 0.735 g of silver acetate and 0.508 g of **1h** afforded a 1:4 mixture (NMR) of **3q** and **6d**. Preparative layer chromatography ($CHCl_3$) of the mixture afforded pure 2-acetoxycyclododecanone, **3q**, and 2-iodocyclododecanone, **6d**.

2-Acetoxycyclododecanone, 3q: 0.072 g (15%); mp 83-84 °C IR (KBr) 1745, 1715 cm^{-1}; NMR (CCl_4) δ 1.00-2.70 (m, 20 H), 2.08 (s, 3 H), 5.00 (dd, 1 H, J = 5.5, 4 Hz); mass spectrum, m/e 240 (M^+, 7), 198 (21), 197 (100), metastables 163.4, 161.7. Anal. Calcd for $C_{14}H_{24}O_3$: C, 69.96; H, 10.07. Found: C, 69.75; H, 9.79.

2-Iodocyclododecanone, 6d: 0.300 g (49%); mp 52-52.5 °C (lit.[5] mp 52-52.5 °C); IR (KBr) 1695 cm^{-1}.

Reaction of Silver Benzoate and Iodine with 1h. Starting with 1.010 g of silver benzoate and 0.508 g of **1h** afforded a 2:3 mixture (NMR) of **3r** and **6d**. Preparative layer chromatography ($CHCl_3$) of the mixture afforded pure 2-(benzoyloxy)cyclododecanone, **3r**, and 2-iodododecanone, **6d**.

2-(Benzoyloxy)cyclododecanone, 3r: 0.201 g (33%); mp 96-97 °C; IR (KBr) 1725, 1715 cm^{-1}; NMR ($CDCl_3$) δ 1.03-2.93 (m, 20 H), 5.46 (dd, 1 H), J = 8, 6 Hz), 7.40-8.40 (m, 5 H); mass spectrum, m/e 302 (M^+, 27), 198 (15), 197 (100), 122 (11). Anal. Calcd for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 75.44; H, 8.56.

2-Iodocyclododecanone, 6d: 0.244 g (40%); mp 51.5-52.5 °C (lit.[5] mp 52-52.5 °C); IR (KBr) 1695 cm^{-1}.

Acknowledgment. We thank the Research Council of the University of Idaho and acknowledge the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

Registry No. 1a, 19980-43-9; **1b**, 6651-36-1; **1c**, 19980-33-7; **1d**, 61175-92-6; **1e**, 19980-35-9; **1f**, 22081-48-7; **1g**, 50338-42-6; (*E*)-**1h**, 55314-44-8; (*Z*)-**1h**, 55314-46-0; **3a**, 52789-75-0; **3b**, 59058-16-1; **3c**, 17472-04-7; **3d**, 7472-23-3; **3e**, 66197-69-1; **3f**, 77256-21-4; **3g**, 61543-83-7; **3h**, 66049-47-6; **3i**, 77256-22-5; *cis*-**3j**, 59058-21-8; *trans*-**3j**, 59058-25-2; **3k**, 77256-23-6; **3l**, 59058-22-9; **3m**, 19347-07-0; **3n**, 53429-51-9; **3o**, 23438-71-3; **3p**, 77256-24-7; **3q**, 26307-31-3; **3r**, 77269-99-9; **6a**, 77256-25-8; **6b**, 77256-26-9; **6c**, 63641-49-6; **6d**, 69381-33-5; silver acetate, 563-63-3; silver benzoate, 532-31-0; silver phenoxyacetate, 13126-87-9; silver 3-chlorobenzoate, 72247-97-3; silver 4-nitrobenzoate, 35363-49-6; silver 3,5-dinitrobenzoate, 57542-56-0; I_2, 7553-56-2; silver trifluoroacetate, 2966-50-9.

Direct and Regioselective Transformation of α-Chloro Carbonyl Compounds into Alkenes and Deuterioalkenes

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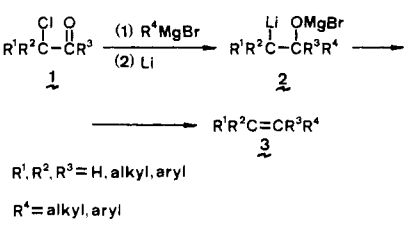
The successive treatment ethyl chloroacetate or chloroacetyl chloride with Grignard reagents and lithium powder leads to symmetrical terminal olefins in a regioselective manner. The best results are obtained with acid chlorides. The influence of the temperature and the reaction time on the overall yield of the process are studied; in general, yields are increased by working at low temperature (-60 °C). Internally substituted olefins are obtained from α-chloro acid chlorides through a similar process. The treatment of α-chloro aldehydes, ketones, and carboxylic acid derivatives (esters or acid chlorides) with lithium aluminium hydride or lithium aluminium hydride/aluminium chloride and lithium powder at low temperature (-60 °C) leads in a regioselective manner to olefins with the same carbon skeleton as the starting carbonyl compound. Reactions with lithium aluminium deuteride lead to incorporation of deuterium at predetermined positions in the alkene.

The key step of most of the methods for the synthesis of olefins is a β-elimination reaction which implies, as the main disadvantage, a loss of the regioselectivity.[1] However, in previous papers[2-4] we described the addition of Grignard reagents to α-chloro aldehydes or ketones **1** followed by metalation with lithium powder to give β-substituted organometallic compounds **2** which undergo a spontaneous β elimination to afford olefins **3** (see Scheme I).

Scheme I



Intermediate organometallics **2**[5] were recently prepared from organomercurials by transmetalation[6] under conditions in which they are stable species. Their application in the synthesis of bifunctional organic compounds[7] has been studied.

We report now the "one flask" regioselective transformation of carbonyl compounds (i.e., aldehydes, ketones, and carboxylic acid derivatives) into alkenes and deuter-

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(2) Barluenga, J.; Yus, M.; Bernad, P. *J. Chem. Soc., Chem. Commun.* **1978**, 847.
(3) Barluenga, J.; Yus, M.; Concellón, J. M.; Bernad, P. *J. Chem. Res., Synop.* **1980**, 41; *J. Chem. Res., Miniprint* **1980**, 677.
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(5) Crandall, J. K.; Lin, L.-H. C. *J. Am. Chem. Soc.* **1967**, *89*, 4526.
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(7) Barluenga, J.; Fañanás, F. J.; Yus, M. *J. Org. Chem.* **1979**, *44*, 4798.

0022-3263/81/1946-2721$01.25/0

Table I. Obtention of Olefins $R^1R^2C{=}CR^3_2$ (5) from α-Chloro Carboxylic Acid Derivatives (4)

entry	product	R^1	R^2	R^3	bp, °C (torr)[a]	X	yield, %[b] −60 °C/time, h[c]	yield, %[b] 0 °C[d]
1	5a	H	H	Et	64-66 (760)[e]	Cl	93/1.5	85
2						OEt	86/1.5	
3	5b	H	H	*n*-Pr	116-119 (760)[f]	Cl	87 (76)/1.5	59
4						OEt	45 (44)/1.5	
5	5c	H	H	allyl	70-72 (200)[g]	Cl	100 (92)/1.5	100
6						OEt	100 (88)/1.5	
7	5d	H	H	*n*-Bu	101-104 (100)[h]	Cl	87 (79)/1.5	70
8						OEt	78 (70)/1.5	
9	5e	H	H	*i*-Bu	94-98 (100)	Cl	54 (42)/1.5	11
10						OEt	27 (23)/1.5	
11[i]	5f	H	H	Ph	148-150 (15)[j]	Cl	53 (51)/1.5	22
12[i]						OEt	47 (39)/1.5	
13	5g	H	H	$PhCH_2$	76-80 (0.1)[k]	Cl	73 (71)/1.5	53
14						OEt	26 (22)/1.5	
15	5h	H	Me	Et	95-97 (760)[l]	Cl	94/3.5	44
16	5i	H	Me	allyl	75-77 (100)	Cl	100 (84)/2	85
17	5j	H	Me	*n*-Bu	76-78 (17)[m]	Cl	70 (66)/2	35
18	5k	H	Me	$PhCH_2$	90-92 (0.1)	Cl	50 (47)/2	17
19	5l	H	Et	Et	115-117 (760)[n]	Cl	90 (78)/3.5	56
20	5m	H	Et	allyl	93-95 (100)	Cl	95 (77)/2	95
21	5n	H	Et	*n*-Bu	131-133 (100)	Cl	91 (82)/5	45
22							61 (56)/2.5	
23	5o	H	Et	$PhCH_2$	96-98 (0.1)	Cl	70 (59)/5	22
24							27/2	
25[i]	5p	H	Ph	allyl	110-114 (10)	Cl	54 (52)/2.5	30
26[i]	5q	H	Ph	*n*-Bu	64-66 (0.1)	Cl	35 (30)/2.5	20
27	5r	$-(CH_2)_5-$		allyl	99-101 (10)	Cl	90 (82)/2.5	

[a] Distillation interval. [b] Yields were determined by GLC analysis with an internal standard; yields of isolated products are in parentheses. [c] Relative to the reaction time with the Grignard reagent. [d] Reaction time 1 h with the Grignard reagent. [e] Lit.[13] bp 64.6 °C (760 torr). [f] Lit.[14] bp 117.7 °C (760 torr). [g] Lit.[10] bp 109 °C (760 torr). [h] Lit.[15] bp 68-70 °C (30 torr). [i] The stoichiometric amount of lithium was used. [j] Lit.[16] bp 148 °C (17 torr). [k] Lit.[17] bp 97-101 °C (0.3 torr). [l] Lit.[18] bp 96.01 °C (760 torr). [m] Lit.[19] bp 80-81 °C (20 torr). [n] Lit.[20] bp 116 °C (760 torr).

ioalkenes, with the deuterium being incorporated at predetermined positions.

Results and Discussion

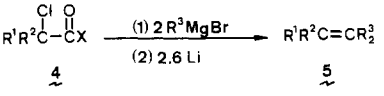
Synthesis of Olefins from α-Chloro Carboxylic Acid Derivatives, Grignard Reagents, and Lithium. Terminal olefins **5a–g** are obtained when chloroacetyl chloride (**4**; $R^1 = R^2 = H$, X = Cl) or ethyl chloroacetate (**4**; $R^1 = R^2 = H$, X = OEt) reacts with a Grignard reagent and then with a slight excess of lithium powder (1:2.6 molar ratio) in THF solution at −60 °C and the reaction mixture is allowed to warm up to room temperature (see Scheme II and Table I).

Although the olefins can be directly isolated once the process goes to completion, the best yields are obtained when the reaction mixture is hydrolyzed with aqueous hydrochloric acid prior to distillation of the product.

The double-addition reaction does not take place when secondary organomagnesium compounds are used, and, in these cases, the corresponding ketone, the alkane R^3H, and its dimer R^3_2 are obtained instead. These results can be rationalized by the hydrolysis of the Grignard compounds or by metal–halogen interconversion followed by a coupling process.

The anomalous behavior of the secondary Grignard reagents and the low yields of olefins obtained in reactions with isobutylmagnesium bromide (Table I, entries 9 and 10) are in good agreement with previous reports[8] suggesting that the addition of secondary and tertiary Grignard reagents to carbonyl compounds is subject to a strong steric hindrance.

Scheme II



$R^1 = H$

$R^2 = H, Me, Et, Ph$

$R^1–R^2 = -(CH_2)_5-$

$R^3 = Et, n\text{-}Pr, allyl, n\text{-}Bu, i\text{-}Bu, Ph, PhCH_2$

X = Cl, OEt

A stoichiometric amount of lithium was used when R^3 = Ph (Table I, entries 11 and 12) in order to avoid the reduction of the resulting conjugated double bond by the excess of metal.[9]

The best yields of olefin were obtained by starting from acetyl chloride (**4**; $R^1 = R^2 = H$, X = Cl; see Table I). This is probably due to the enhanced reactivity toward nucleophiles exhibited by the acid chlorides relative to the corresponding esters.

The influence of the reaction conditions on the course of the process was studied by treating chloroacetyl chloride with a Grignard reagent (1:2 molar ratio) in THF solution at 0 °C (bath temperature) for 1 h and then with lithium powder in slight excess (1:2.6 molar ratio) for an additional 2 h. After the hydrolysis, the expected olefins **5a–g** were obtained (see Scheme II and Table I).

From the above experiences it is noteworthy that: (a) yields at 0 °C are, in general, lower than those at −60 °C

(8) Ioffe, S. T.; Nesmeyanov, A. M. "Methods of Elemento-Organic Chemistry"; North-Holland Publishing Co.: Amsterdam, 1967; Vol. 2, p 253.

(9) House, H. O. In "Modern Synthetic Reactions", W. A. Benjamin: Menlo Park, CA, 1972; Chapter 3.

Table II. Obtention of Olefins 6 and 8 and their *vic*-Dibromo Derivatives 7 and 9 from α-Chloro Carbonyl Compounds 1 and 4

entry	starting compd	product	R^1	R^2	R^3	bp, °C (torr)[a]	X	yield,[b] %
1	1a	7a[c]	H	Et	H	74-77 (40)[d]		61
2	1b	7b	H	*n*-Pr	H	84-86 (30)[e]		52
3	1c	7c	H	*i*-Pr	H	61-63 (12)[f]		54
4	1d	7d	Me	Me	H	70-73 (60)[g]		60
5	1e	7e[h]	H	H	Me	137-140 (760)[i]		66 (53[j])
6	1f	7f[k]	H	Me	Me	51-54 (20)[l]		68 (52[j])
7	1g	7g[k]	H	$-(CH_2)_3-$		104-106 (45)[m]		57
8	1h	6h	H	$-(CH_2)_4-$		82-83 (760)[n]		90 (75[j])
9	4a	9a	H	H		131-133 (760)[o]	Cl	23[j]
10	4a′						OEt	48
11	4b	9b[h]	H	Me		136-140 (760)[i]	Cl	26[j]
12	4b′						OEt	73 (55[p])
13	4c	9c[c]	H	Et		74-77 (40)[d]	Cl	52[j]
14	4c′						OEt	65
15	4d	8d	$-(CH_2)_5-$			102-104 (760)[q]	Cl	95[j]

[a] Distillation interval. [b] Based on isolated product 6-9. [c] 7a and 9c are the same compound. [d] Lit.[23] bp 78-78.5 °C (45 torr). [e] Lit.[24] bp 85 °C (30 torr). [f] Lit.[25] bp 61-62 °C (12 torr). [g] Lit.[26] bp 140-150 °C (763 torr). [h] 7e and 9b are the same compound. [i] Lit.[27] bp 132 °C (760 torr). [j] With $LiAlH_4$ as reducing agent. [k] Mixture of erythro and threo isomers. [l] Lit.[28] bp 103-104 °C (160 torr). [m] Lit.[29] bp 94 °C (32.5 torr) (trans isomer). [n] Lit.[30] bp 83 °C (760 torr). [o] Lit.[31] bp 131.1 °C (760 torr). [p] At 0 °C (bath temperature). [q] Lit.[33] bp 102.8 °C (756 torr).

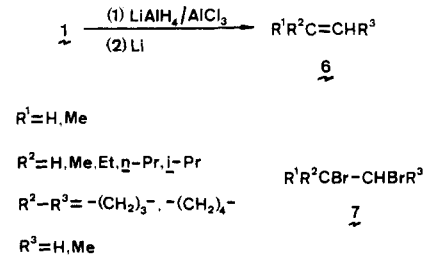
especially when R^3 = *i*-Bu or Ph in the Grignard reagent (Table I, entries 9 and 11); (b) reactions at low temperature are cleaner, giving the olefin as the sole product. At 0 °C the olefin is contaminated with side products but its purification is achieved directly by fractional distillation. Both workup procedures are complementary since the simpler the method, the more complicated the purification of the product.

The method was extended to the preparation of tri- or tetrasubstituted internal olefins **5h-r** by treating different α-chloro carboxylic acid chlorides (4; R^1 and/or $R^2 \neq H$, X = Cl) with Grignard reagents and lithium (see Scheme II and Table I) at 0 or −60 °C in a manner similar to that described above. Yields and purity of the resulting internal olefins vary with the modification of the reaction conditions and follow the same trends as those observed for terminal olefins (**5a-g**).

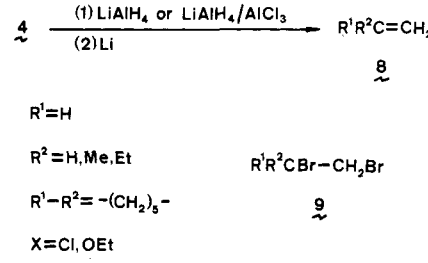
The procedure described herein is, in our opinion, a method of choice for the preparation of both symmetrical terminal[10] and substituted internal[11] olefins and represents a reasonable alternative to the Wittig reaction.[12]

Synthesis of Alkenes and Deuterioalkenes from α-Chloro Carbonyl Compounds, $LiAlH_4$ or $LiAlD_4$, and Lithium. α-Chloro aldehydes or ketones (1) were treated with $LiAlH_4/AlCl_3$[21] at −60 °C in ether/THF solution and then with a slight excess of lithium powder. The reaction mixture was allowed to warm up to room temperature to afford after hydrolysis with aqueous hydrochloric acid the corresponding olefins 6 (see Scheme III and Table II).

Scheme III



Scheme IV



Reductions can also be carried out with lithium aluminium hydride alone, but the yields decrease as compared with those obtained with the $LiAlH_4/AlCl_3$ mixture (see Table II). Results are less satisfactory with reducing agents such as $LiBH_4$ or $NaBH_4$.[21]

The low molecular weight olefins were isolated and identified as the *vic*-dibromo derivatives 7 which were obtained by addition of bromine to the olefin at the end of the reactions. The application of this synthetic procedure is especially interesting in the obtention of olefins derived from aldehydes since these products are difficult to obtain by the conventional routes.

The treatment of α-chloro esters or carboxylic acid chlorides (4) with $LiAlH_4$ or the $LiAlH_4/AlCl_3$ mixture and lithium powder under reaction conditions similar to those described above led to the olefins 8 (see Scheme IV and Table II) which, in the case of the lower members, were

(10) For the obtention of terminal olefins by β elimination in multistep a process see: Miginiac, L.; Lanoiselle, M. *Bull. Soc. Chim. Fr.* **1971**, *7*, 2716.
(11) For an excellent review on the obtention of internal substituted olefins see: Marfat, A.; McGuirk, P.; Helquist, P. *J. Org. Chem.* **1979**, *44*, 3888.
(12) For a review on the obtention of olefins and the Wittig reaction see, for instance: Sekiguchi, A.; Ando, W. *J. Org. Chem.* **1979**, *44*, 413.
(13) *Beilstein, 4th ed.* **1938**, 1^3, 814.
(14) *Beilstein, 4th ed.* **1938**, 1^4, 885.
(15) Commercon, A.; Normant, J. F.; Villieras, *J. J. Organomet. Chem.* **1977**, *128*, 1.
(16) Schoepfe, R. *J. Am. Chem. Soc.* **1932**, *54*, 3687.
(17) Bumgardner, C. L.; Iwerks, H. *J. Am. Chem. Soc.* **1966**, *88*, 5518.
(18) Sherrill, M. L.; Mollet, P. *J. Chem. Phys.* **1936**, *33*, 703.
(19) Cronyn, M. W.; Zavarin, E. *J. Org. Chem.* **1954**, *19*, 139.
(20) *Beilstein, 4th ed.* **1938**, 1^3, 845.

(21) This mixture is appropriate for the selective reduction of the carbonyl group in α-chloro carbonyl compounds: (a) Nystrom, R. F. *J. Am. Chem. Soc.* **1955**, *77*, 2544; (b) Nystrom, R. F.; Berger, C. R. A. *Ibid.* **1958**, *80*, 2896; (c) Nystrom, R. F. *Ibid.* **1959**, *81*, 610.

Table III. Obtention of Deuterioalkenes 12 and 13 and Their *vic*-Dibromo Derivatives 14

entry	starting compd	product	dibromo deriv	bp, °C (torr)[a]	yield,[b] %
1	1a	EtCH=CHD (12a)	14a[c]	75-77 (40)	59
2	1d	Me_2C=CHD (12b)	14b	60-63 (45)	58
3	1e	CH_2=CDMe (12c)	14c	77-79 (100)	60
4	1f	MeCH=CDMe (12d)	14d[c]	72-74 (50)	67
5	4b′	MeCH=CD_2 (13a)	14e	76-78 (100)[d]	70
6	4c′	EtCH=CD_2 (13b)	14f	58-60 (20)	59
7	4d	$(CH_2)_5$C=CD_2 (13c)		103-105 (760)	92[e]

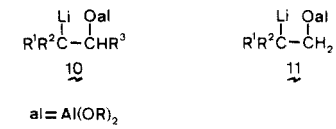
[a] Distillation interval. [b] Based on isolated product 14. [c] Mixture of erythro and threo isomers. [d] Lit.[34] bp 35-36 °C (14 torr). [e] Based on isolated olefin 13c.

also isolated and characterized as the corresponding *vic*-dibromo derivatives **9**.

The best results are obtained when α-chloro esters **4** (X = OEt) are used as the starting carbonyl compounds. It is noteworthy that in the synthesis of olefins with Grignard reagents and lithium the opposite trend is observed, and the yields of alkene are increased by starting from α-chloroacyl chlorides (see Table I).

Acid chlorides **4a** ($R^1 = R^2 = H$) and **4b** ($R^1 = H$, R^2 = Me) react with the intermediate 2-chloroalkoxide resulting from the addition of the hydride to the carbonyl group to give esters (ethyl acetate and ethyl chloroacetate from **4a** and propyl propionate from **4b**). This side reaction could account for the low yield of alkene obtained when **4a** or **4b** is used as the starting carbonyl compound (see Table II, entries 9 and 11).

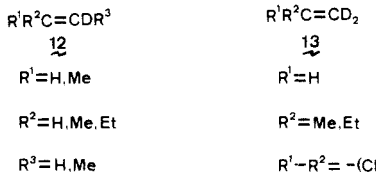
Olefins **6** and **8** are probably generated in a sequence of reactions which starts with the nucleophilic attack of the hydride on the carbonyl group followed by a halogen–lithium interconversion to give a β-substituted organolithium compound[5,6] **10** (from α-chloro aldehydes or ketones **1**) or **11** (from α-chloro acid derivatives **4**).



10 **11**

al = Al(OR)$_2$

The method was extended to the synthesis of deuterated olefins by using the $LiAlD_4/AlCl_3$ mixture as the reducing agent in the first step of the process. Deuterated alkenes **12** and **13** were obtained from α-chloro aldehydes and



12 **13**

R^1=H,Me R^1=H

R^2=H,Me,Et R^2=Me,Et

R^3=H,Me R^1–R^2= –$(CH_2)_5$–

ketones **1** or α-chloro acid derivatives **4**, respectively, when reactions were carried out under the same conditions as described above for the preparation of alkenes **6** and **8** (see Table III).

vic-Dibromo derivatives **14** were also prepared in this case in order to isolate and characterize the volatile olefins. The course of the reactions was unaffected by the substitution of deuterium for hydrogen in the starting hydride, and similar yields were also obtained (see Table III).

It can be concluded that the procedure described herein for the synthesis of deuterioalkenes carrying the deuterium at predetermined positions should be a method of choice for these compounds.[22]

Experimental Section

General Methods. Infrared spectra (IR) were run on a Pye-Unicam SP-1000 spectrometer. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Varian EM-390 spectrometer; assignments were confirmed by double-resonance experiments. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Varian FT-80 spectrometer. The chemical shifts are in δ relative to Me_4Si, and coupling constants (J values) are in hertz. Gas–liquid chromatographic analyses (GLC) were performed on a Varian Aerograph-2800 instrument equipped with a OV-101 Chromosorb column. Elemental analyses were carried out with a Perkin-Elmer 240 elemental analizer.

α-Chloro ketones (Merck, Aldrich), chloroacetyl chloride (Merck), ethyl chloroacetate (Fluka), lithium powder (<20 μm, Koch Ligh), aluminium chloride (Merck), lithium aluminium hydride (Merck), and lithium aluminium deuteride (Aldrich) were commercially available. α-Chloro aldehydes and other α-chloro acid chlorides were prepared from the corresponding aldehydes and acids (Merck, Aldrich) by the literature methods.[35,36] α-Chloro esters were prepared by esterification of the corresponding α-chloro acid chlorides with ethanol.[37] Grignard reagents were prepared in ether by treating the corresponding alkyl or aryl halide with magnesium (turnings, Merck) and were used as ca. 1 N solutions.[38] Ether was dried prior to use successively with anhydrous calcium chloride, sodium sulfate, sodium, and finally a K–Na (K_3Na) liquid alloy[39] under reflux, and then it was distilled and stored under argon. Tetrahydrofuran (THF) was dried successively with anhydrous calcium chloride and sodium sulfate; it was then refluxed with potassium, distilled, and stored under argon. Reactions were carried out in an argon atmosphere.

The products previously described (see notes in Tables I–III)

(22) For other methods of synthesis of deuterio olefins see: "Methoden der Organischen Chemie (Houben-Weyl)"; Georg Thieme Verlag: Stuttgart, 1972, Vol. 5/1b, pp 9–945.
(23) Woodburn, H. M.; Whitehouse, A. B.; Pantler, B. G. *J. Org. Chem.* **1959**, *24*, 210.
(24) Wilkinson, R. *J. Chem. Soc.* **1931**, 3058.
(25) *Beilstein, 4th ed.* **1938**, 1, 137.
(26) De la Mare, P. B. D.; Vernon, C. A. *J. Chem. Soc.* **1956**, 41.
(27) *Beilstein, 4th ed.* **1938**, 1[4], 215.
(28) Goering, H. L.; Larsen, D. W. *J. Am. Chem. Soc.* **1959**, *81*, 5937.
(29) Kumler, W. D.; Huitric, A. C.; Hall, H. K. *J. Am. Chem. Soc.* **1956**, *78*, 4345.
(30) *Beilstein, 4th ed.* **1942**, 5, 63.
(31) Mumfort, S. A.; Phillips, J. W. C. *J. Chem. Soc.* **1950**, 78.
(32) Very low yields of olefins are generally obtained at 0 °C. Decomposition products were obtained.
(33) Turner, R. B.; Garner, R. H. *J. Am. Chem. Soc.* **1958**, *80*, 1424.
(34) Farina, M.; Peraldo, M. *Gazz. Chim. Ital.* **1960**, *90*, 973.
(35) Stevens, C. L.; Parkas, E.; Gillis, B. *J. Am. Chem. Soc.* **1954**, *76*, 2695.
(36) Harpp, D. N.; Bao, L. Q.; Black, C. J.; Gleason, J. G.; Smith, R. A. *J. Org. Chem.* **1975**, *40*, 3420.
(37) Sonntag, N. O. V. *Chem. Rev.* **1953**, *52*, 312.
(38) For a general scope of the preparation of organomagnesium compounds see: "Methoden der Organischen Chemie (Houben-Weyl)"; Georg Thieme Verlag: Stuttgart, 1973; Vol. 13/2a, p 47.
(39) Gilman, H.; Young, R. W. *J. Org. Chem.* **1936**, *1*, 315.

were identified by comparison of ^1H NMR and IR spectra with those of authentic samples.

Synthesis of Olefins 5 from α-Chloro Acid Derivatives 4. (A) Low-Temperature (−60 °C) General Procedure. To a previously evacuated 250-mL, two-necked flask containing an ether solution of the Grignard reagent (60 mmol) and THF (20 mL) was added a THF (20 mL) solution of the appropriate α-chloro acid derivative **4** (30 mmol) under argon at −60 °C over a period of 15 min. After the mixture was stirred for 1.5–5 h (see Table I), lithium powder (0.54 g, 78 mmol)[40] was added, and the mixture was stirred at −60 °C for 8 additional h and then allowed to warm up to room temperature overnight. The resulting solution was hydrolyzed successively with water and aqueous hydrochloric acid, and it was extracted with ether. The organic layer was dried over anhydrous sodium sulfate and carefully distilled to afford the corresponding olefin **5**.

(B) 0 °C General Procedure. To a previously evacuated 100-mL, two-necked flask containing an ether solution of the Grignard reagent (20 mmol) and THF (10 mL) was added a THF (10 mL) solution of the appropriate α-chloro acid chloride **4** (10 mmol) under argon at 0 °C over a period of 15 min. After the mixture was stirred for 1 h, lithium powder (0.18 g, 25 mmol)[40] was added, and the mixture was stirred at 0 °C for 2 additional h. Then it was hydrolyzed successively with water and aqueous hydrochloric acid, and it was extracted with ether. The organic layer was dried over anhydrous sodium sulfate, and the solvents were removed by distillation. The residue was purified by trap to trap distillation to afford the corresponding olefins **5**. Products were identified by GLC analysis by comparison with an original sample.

5e: IR (film) 3050 (=CH), 1640 (C=C) cm^{-1}; ^1H NMR (CCl_4) δ 0.95 (d, J = 6 Hz, 12 H, 4 CH_3), 1.4–2.1 (m, 6 H, 2 CH_2CH), 4.7 (s, 2 H, CH_2=C). Anal. Calcd for $C_{10}H_{20}$: C, 85.73; H, 14.37. Found: C, 85.40; H, 14.42.

5i: IR (film) 3060 (=CH), 1640 (C=C) cm^{-1}; ^1H NMR (CCl_4) δ 1.6 (d, J = 6 Hz, 3 H, CH_3), 2.6–2.9 (m, 4 H, 2 CH_2C=C), 4.8–5.1 (m, 4 H, 2 CH_2=C), 5.3 (q, J = 6 Hz, 1 H, $CHCH_3$), 5.4–6.0 (m, 2 H, 2 CH=CH_2). Anal. Calcd for C_9H_{14}: C, 88.45; H, 11.55. Found: C, 88.27; H, 11.60.

5k: IR (film) 3070 (=CH), 1660 (C=C) cm^{-1}; ^1H NMR (CCl_4, capillary Me_4Si) δ 2.1 (d, J = 6 Hz, 3 H, CH_3), 3.5, 3.6 (2 s, 4 H, 2 CH_2), 5.8 (q, J = 6 Hz, 1 H, CH=C), 7.3–7.7 (m, 10 H, 2 Ph). Anal. Calcd for $C_{17}H_{18}$: C, 91.84; H, 8.16. Found: C, 91.70; H, 8.21.

5m: IR (film) 3050 (=CH), 1630 (C=C) cm^{-1}; ^1H NMR (CCl_4) δ 0.95 (t, J = 7 Hz, 3 H, CH_3), 2.05 (q, J = 7 Hz, 2 H, CH_2CH_3), 2.7 (t, J = 6 Hz, 4 H, 2 CH_2C=C), 4.8–5.1 (m, 4 H, 2 CH_2=C), 5.2 (t, J = 7 Hz, 1 H, CH=C), 5.5–6.0 (m, 2 H, 2 CH=CH_2). Anal. Calcd for $C_{10}H_{16}$: C, 88.16; H, 11.84. Found: C, 88.02; H, 11.90.

5n: IR (film) 3060 (=CH), 1660 (C=C) cm^{-1}; ^1H NMR (CCl_4) δ 0.9 (t, J = 6 Hz, 9 H, 3 CH_3), 1.0–1.7 (m, 8 H, 2 $CH_2CH_2CH_3$), 1.8–2.3 (m, 6 H, 3 CH_2C=C), 5.0 (t, J = 7 Hz, 1 H, CH). Anal. Calcd for $C_{12}H_{24}$: C, 85.63; H, 14.37. Found: C, 85.44; H, 14.43.

5o: IR (film) 3080 (=CH), 1670 (C=C) cm^{-1}; ^1H NMR (CCl_4) δ 1.0 (t, J = 7 Hz, 3 H, CH_3), 1.9–2.3 (m, 2 H, CH_2CH_3), 3.1, 3.2 (2 s, 4 H, 2 CH_2Ph), 5.35 (t, J = 7 Hz, 1 H, CH), 6.8–7.4 (m, 10 H, 2 Ph). Anal. Calcd for $C_{18}H_{20}$: C, 91.47; H, 8.53. Found: C, 91.30; H, 8.55.

5p: IR (film) 3090 (=CH), 1650 (C=C) cm^{-1}; ^1H NMR[41] (CCl_4, capillary Me_4Si) δ 3.1, 3.2 (2 d, J = 7 Hz, 4 H, 2 CH_2C), 5.2–5.5 (m, 4 H, 2 CH_2=C), 5.8–6.3 (m, 2 H, 2 CH=C), 6.6 (s, 1 H, CHPh), 7.2–7.3 (m, 5 H, Ph). Anal. Calcd for $C_{14}H_{16}$: C, 91.25; H, 8.75. Found: C, 91.05; H, 8.82.

5q: IR (film) 3080 (=CH), 1650 (C=C) cm^{-1}; ^1H NMR (CCl_4) δ 0.9 (t, J = 7 Hz, 6 H, 2 CH_3), 1.1–1.6 (m, 8 H, 2 $CH_2CH_2CH_3$), 2.0–2.3 (m, 4 H, 2 CH_2C=C), 6.2 (s, 1 H, CH), 7.0–7.3 (m, 5 H, Ph). Anal. Calcd for $C_{16}H_{24}$: C, 88.82; H, 11.18. Found: C, 88.64; H, 11.22.

5r: IR (film) 3080 (=CH), 1640 (C=C) cm^{-1}; ^1H NMR (CCl_4) δ 1.5–2.2 (m, 10 H, 5 CH_2 ring), 2.8 (d, J = 6 Hz, 4 H, 2 CH_2CH=C), 4.9–5.1 (m, 4 H, 2 CH_2=C), 4.5–6.0 (m, 2 H, 2 CH). Anal. Calcd for $C_{13}H_{20}$: C, 88.57; H, 11.43. Found: C, 88.40; H, 11.50.

Synthesis of Olefins 6 and 8 and Deuterio Olefins 12 and 13 by Reduction of α-Chloro Carbonyl Compounds 1 and 4; Isolation as *vic*-Dibromo Derivatives 7, 9, and 14. General Procedure. To a previously evacuated 250-mL, two-necked flask containing $LiAlH_4$ or $LiAlD_4$ (12.5 mmol)[42] in ether (10 mL) was added a solution of $AlCl_3$ (1.66 g, 12.5 mmol)[42] in ether (10 mL) under argon, and the mixture was stirred for 5 min. The corresponding α-chloro carbonyl compound **1** or **4** (40 mmol) dissolved in THF (20 mL)[42] was added at −60 °C over a period of 15 min, and, after the mixture was stirred for 2 h, lithium powder (0.72 g, 104 mmol) was added. A bubbler containing a solution of bromine (4.79 g, 60 mmol) in CCl_4 (40 mL) was connected to the reaction flask. After being stirred for 8 h at −60 °C, the mixture was allowed to warm up to room temperature overnight, and it was hydrolyzed with water and aqueous hydrochloric acid. The resulting solution was heated at 50 °C in a water bath, with a stream of argon being passed through the liquid. The CCl_4 solution contained in the bubbler was washed successively with an aqueous solution of potassium carbonate and water and extracted with ether. The organic layer was dried over anhydrous sodium sulfate, and the solvents were removed in vacuo at 15 torr. The residue was distilled to afford the *vic*-dibromo compound **7**, **9**, or **14**.

In the case of the obtention of compounds **6h**, **8d**, and **13c**, the olefin was directly extracted with ether from the reaction mixture after the hydrolysis with aqueous hydrochloric acid and water without the use of the bubbler containing bromine in CCl_4. The ether layer was dried over anhydrous sodium sulfate and the solvents were carefully removed. The residue was distilled by using a Vigreux column to afford compounds **6h**, **8d**, and **13c**.

13c: IR (CCl_4) 2900, 1820, 1615, 1445, 1260, 720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.3–1.6 (m, 6 H, 3 CH_2 ring), 1.9–2.2 (m, 4 H, 2 CH_2C=C); ^{13}C NMR ($CDCl_3$) δ 149.3, 105.9 (quintet, $^1J_{CD}$ = 23.6 Hz), 35.3, 28.3, 26.3. Anal. Calcd for $C_7H_{10}D_2$: C, 85.63; H/D, 14.37. Found: C, 85.50; H/D, 14.42.

14a: IR (CCl_4) 2940, 2900, 1460, 1380, 1150, 1080, 910, 640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.1 (t, J = 6 Hz, 3 H, CH_3), 1.6–2.5 (m, 2 H, CH_2), 3.5–4.4 (m, 2 H, 2 CH); ^{13}C NMR ($CDCl_3$) δ 54.3, 35.3 (t, $^1J_{CD}$ = 23.6 Hz), 29.2, 10.9. Anal. Calcd for $C_4H_7Br_2D$: C, 22.15; H/D, 4.18. Found: C, 21.98; H/D, 4.23.

14b: IR (CCl_4) 2960, 2920, 1450, 1370, 1300, 1100, 990, 890, 660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.95 (s, 6 H, 2 CH_3), 3.95 (s, 1 H, CH); ^{13}C NMR ($CDCl_3$) δ 61.6, 45.1 (t, $^1J_{CD}$ = 25.6 Hz), 31.4. Anal. Calcd for $C_4H_7Br_2D$: C, 22.15; H/D, 4.18. Found: C, 22.00; H/D, 4.20.

14c: IR (CCl_4) 2960, 2940, 1440, 1380, 1230, 1180, 1080, 1040, 900, 650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.9 (s, 3 H, CH_3), 3.6, 3.95 (2 d, J = 7 Hz, 2 H, CH_2); ^{13}C NMR ($CDCl_3$) δ 45.3 (t, $^1J_{CD}$ = 24.2 Hz), 37.4, 24.0. Anal. Calcd for $C_3H_5Br_2D$: C, 17.76; H/D, 3.48. Found: C, 17.58; H/D, 3.53.

14d: IR (CCl_4) 2950, 2900, 1450, 1380, 1200, 880, 640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.7–2.0 (m, 6 H, 2 CH_3), 4.2–4.5 (2 q, J = 5 Hz, 1 H, CH); ^{13}C NMR ($CDCl_3$) δ 53.8, 52.1, 53.6 and 51.9 (2 t, $^1J_{CD}$ = 23.7 Hz), 25.1, 20.3. Anal. Calcd for $C_4H_7Br_2D$: C, 22.15; H/D, 4.18. Found: C, 22.00; H/D, 4.22.

14f: IR (CCl_4) 2950, 2910, 1460, 1380, 1290, 1190, 940, 900, 660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.0 (t, J = 6 Hz, 3 H, CH_3), 1.6–2.4 (m, 2 H, CH_2), 4.0–4.3 (m, 1 H, CH); ^{13}C NMR ($CDCl_3$) δ 54.1, 35.0 (quintet, $^1J_{CD}$ = 23.7 Hz), 29.1, 10.8. Anal. Calcd for $C_4H_6Br_2D_2$: C, 22.05; H/D, 4.62. Found: C, 21.89; H/D, 4.68.

Registry No. **1a**, 28832-55-5; **1b**, 41718-47-2; **1c**, 53394-32-4; **1d**, 917-93-1; **1e**, 78-95-5; **1f**, 4091-39-8; **1g**, 694-28-0; **1h**, 822-87-7; **4a**, 79-04-9; **4a'**, 105-39-5; **4b**, 7623-09-8; **4b'**, 535-13-7; **4c**, 7623-11-2; **4c'**, 7425-45-8; **4d**, 52831-99-9; **4** (R^1 = H; R^2 = Ph; X = Cl), 2912-62-1; **5a**, 760-21-4; **5b**, 15918-08-8; **5c**, 32852-39-4; **5d**, 6795-79-5; **5e**, 75144-23-9; **5f**, 530-48-3; **5g**, 14213-80-0; **5h**, 816-79-5; **5i**, 24415-18-7;

(40) In the preparation of compounds **5f,p,q** the stoichiometric amount of lithium powder (1:2 molar ratio) was used; see notes in Table I and ref 9.

(41) Klein, J.; Levene, R. *Tetrahedron Lett.* **1974**, 2938.

(42) In the case of the preparation of **8** and **13**, 25 mmol of $LiAlH_4$ or $LiAlD_4$ in 20 mL of ether and 25 mmol of $AlCl_3$ in 20 mL of ether were used. Starting compounds **4** were dissolved in 40 mL of THF.

5j, 37549-88-5; **5k**, 40558-71-2; **5l**, 16789-51-8; **5m**, 77357-32-5; **5n**, 77341-87-8; **5o**, 77341-88-9; **5p**, 54624-35-0; **5q**, 77341-89-0; **5r**, 77341-90-3; **6h**, 110-83-8; **7a**, 533-98-2; **7b**, 3234-49-9; **7c**, 10288-13-8; **7d**, 594-34-3; **7e**, 78-75-1; *erythro*-**7f**, 5780-13-2; *threo*-**7f**, 40205-58-1; *cis*-**7g**, 33547-17-0; *trans*-**7g**, 10230-26-9; **8d**, 1192-37-6; **9a**, 106-93-4; **12a**, 77341-91-4; **12b**, 65087-61-8; **12c**, 1184-59-4; **12d**, 23042-68-4; **13a**, 1517-49-3; **13b**, 26119-76-6; **13c**, 1560-57-2; *erythro*-**14a**, 77341-92-5; *threo*-**14a**, 77341-93-6; **14b**, 77341-94-7; **14c**, 60623-79-2; *erythro*-**14d**, 77341-95-8; *threo*-**14d**, 77341-96-9; **14e**, 77341-97-0; **14f**, 77341-98-1; ethyl bromide, 74-96-4; propyl bromide, 106-94-5; allyl bromide, 106-95-6; butyl bromide, 109-65-9; isobutyl bromide, 507-19-7; phenyl bromide, 108-86-1; benzyl bromide, 100-39-0.

C_2-Ketone Rule in Horse Liver Alcohol Dehydrogenase (HLADH) Mediated Oxidoreduction[1]

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The enantiomer selectivity of HLADH with respect to various C_2 ketones and the corresponding C_2 alcohols was examined and revealed that the enzyme exhibits a marked enantiomer selectivity opposite to the microbial "(*P*)-C_2-ketone rule" found in *Curvularia lunata* and *Rhodotorula rubra*.

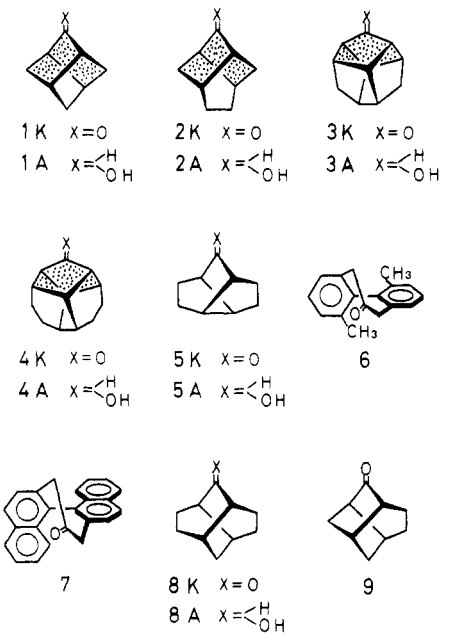
Contrary to a vast accumulation of information on the stereochemistry of microbial reduction of numerous ketones with a variety of structural features, it seems rather surprising to realize that so small an effort has been expended for exploring the microbiol stereodifferentiating reduction in cage-shaped compounds.

Our continuing interests in the synthetic studies of high-symmetry, chiral (gyrochiral), cage-shaped compounds had provided us with a considerable collection of cage-shaped polycyclic ketones, and this prompted us to investigate the expected microbial stereodifferentiating reactions toward these substrates.

To summarize the stereochemistry in microbial reduction of a large number of racemic cage-shaped C_1 ketones[2] with *Curvularia lunata* and *Rhodotorula rubra*, we have proposed[3] a "quadrant rule" whose successful applications[4] have been reported from our laboratory.

Our other efforts in studying the enantiomer selectivity of these microbes in a considerable number of C_2 ketones[2] (Chart I),[5] including D_{2d}-bisnoradamantanone (**1K**), 9-*twist*-brendanone (**2K**), D_3-trishomocubanone (**3K**), 4-C_2-methanoditwistanone (**4K**), 2-brexanone (**5K**), and the biaryl bridged ketones **6** and **7**, have been rewarded by our finding a microbial "(*P*)-C_2-ketone rule"[6] which states that both microbes selectively reduce the (*P*)-C_2-ketone enantiomers, furnishing the corresponding (*P*)-C_2 alcohol.[7]

Chart I



An interesting stereochemical characteristic common to these favored cage-shaped (*P*)-C_2 ketones **1K-4K** is the 7-bicyclo[2.2.1]heptanone framework (shown with dotting in Chart I) with a $(-90°, +20°, +55°)_2$[8] twist-boat cyclohexane moiety.

(1) A preliminary account of this work has been published: Nakazaki, M.; Chikamatsu, H.; Naemura, K.; Sasaki, Y.; Fujii, T. *J. Chem. Soc., Chem. Commun.* **1980**, 626-7.

(2) In this paper, ketones are conveniently classified according to their symmetry: C_s ketones belong to the C_s point group and have the plane of symmetry coincident with the carbonyl plane; C_2 ketones belong to the C_2 point group and have the C_2 axis coincident with the carbonyl axis; C_1 ketones belong to the C_1 point group and have no symmetry element passing through the carbonyl axis.

(3) (a) Nakazaki, M.; Chikamatsu, H.; Naemura, K.; Hirose, Y.; Shimizu, T.; Asao, M. *J. Chem. Soc., Chem. Commun.* **1978**, 668-70. (b) Nakazaki, M.; Chikamatsu, H.; Naemura, K.; Asao, M. *J. Org. Chem.* **1980**, *45*, 4432-40.

(4) (a) Nakazaki, M.; Chikamatsu, H.; Hirose, Y.; Shimizu, T. *J. Org. Chem.* **1979**, *44*, 1043-8. (b) Nakazaki, M.; Hirose, Y.; Shimizu, T.; Suzuki, T.; Ishii, A.; Makimura, M. *Ibid.* **1980**, *45*, 1428-35. (c) Nakazaki, M.; Chikamatsu, H.; Fujii, T.; Nakatsuji, T. *Ibid.* **1981**, *46*, 585-9.

(5) All structural formulas with (+) or (-) specification in this paper are presented in their absolute configurations.

(6) (a) Nakazaki, M.; Chikamatsu, H.; Naemura, K.; Nishino, M; Murakami, H.; Asao, M. *J. Chem. Soc., Chem. Commun.* **1978**, 667-8. (b) Nakazaki, M.; Chikamatsu, H.; Naemura, K.; Nishino, M.; Murakami, H.; Asao, M. *J. Org. Chem.* **1979**, *44*, 4588-93.

(7) Although the alcohols corresponding to the C_2-ketone precursors do not belong to C_2 point group, these are conveniently called C_2 alcohols in this paper.

(8) Klyne, W.; Prelog, V. *Experientia* **1960**, *16*, 521-3.

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