Factors Affecting Diastereoselectivity in the Protiodemercuration of α-Mercurio Carbonyl Compounds

Frederick H. Gouzoules and Ralph Allen Whitney*

Department of Chemistry, Queen's University, Kingston, Ontario, Canada K7L 3N6

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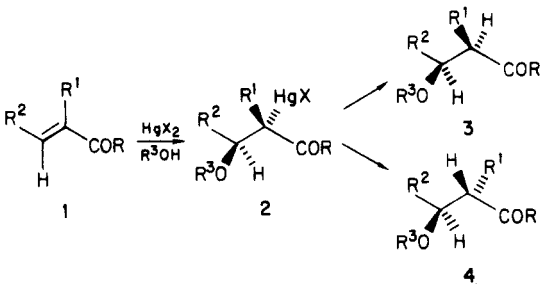
Organomercurials obtained by the oxymercuration of α-alkyl-α,β-unsaturated esters underwent demercuration in a manner distinct from organomercurials obtained by oxymercuration of isolated alkenes. The ratio of diastereomeric α-alkyl-β-alkoxy esters obtained may be controlled in order to afford predominantly either the erythro or the threo product. Demercuration with thiol reagents (in alcohol containing sodium bicarbonate) afforded predominantly the erythro isomer; the relative amount of the threo product was increased by the use of nonpolar solvents and triethylamine. Demercuration with sodium borohydride in ethanol gave predominantly the threo isomer, with the diastereomer ratio being highly sensitive to the amount of hydride used, the nature of the hydride source, and the ligand on mercury. A general trend for distinguishing erythro and threo isomers of α-alkyl-β-alkoxy carboxylate esters on the basis of proton NMR chemical shifts of the α-alkyl group has been noted.

The prevalence in acetate- and propionate-derived natural products of the 1,3-relationship of oxygen-based functional groups has resulted in recent years in considerable attention directed toward methods for the stereoselective synthesis of structural components of these natural products. A plethora of synthetic methods has been developed with particular attention having been focused on the stereoselective aldol condensation.[1] As yet methodologies based upon organomercurials[2] have received only limited attention. The stereo- and regiochemical outcome of the oxymercuration of α,β-unsaturated esters has been known for some time[3,4] and, with appropriate substituents on the double bond, an organomercurial (2) (Scheme I) is obtained which, upon substitution of hydrogen for mercury (protiodemercuration), generates two asymmetric centers in the resulting 3-alkoxy-2-alkyl ester. Control of the relative configuration, erythro 3 or threo 4, at these centers by a demercuration process has been examined previously with somewhat limited success. Maskens and Polgar[5] examined the demercuration of a pair of diastereomeric oxymercurials obtained from tiglic and angelic acids and observed the selective formation of the erythro isomer, irrespective of the stereochemistry of the oxymercurial, using alkaline hydrogen sulfide. Conversely, use of alkaline sodium borohydride produced, in each case, an equimolar mixture of diastereomers. Bartlett and Adams[6] examined the demercuration of oxymercurials derived from tiglic acid and from the intramolecular oxymercuration of appropriate unsaturated acids. Similar reagent systems (Na_2S pH 9 buffer, Na_2S–MeCN, Na_2S–aqueous NaOH, and H_2S–pyridine) gave widely differing diastereomer ratios from a given organomercurial. For each of the demercuration systems examined, a higher relative amount of the threo isomer was obtained with cyclic mercurials.

Of note in these previous results was the general inability to select for both 3 and 4 from a given oxymercurial diastereomer. In view of the significantly greater accessibility of (E)-substituted unsaturated esters from aldehydes by conventional Wittig–Horner–Emmons[7] methodology, and consequently the greater availability of the erythro oxymercurial 2, such selective transformations would clearly be of value.

Scheme I



We recently reported[8] in a preliminary communication that such diastereoselection in demercuration is possible. In particular, we observed that the use of 1,3-propanedithiol (PDT) as the demetalating reagent in ethanol effected demercuration with high selection for the erythro product 3 while demercuration using 0.25 equiv. of sodium borohydride in ethanol afforded predominantly the threo product 4. The use of sodium borohydride (usually in alkaline media) as an efficient demercuration reagent has been common for almost 20 years;[9] considerable evidence in support of a radical-type mechanism has been accumulated.[10,11] Our observation that the stereochemical outcome of the sodium borohydride demercuration of 2 was dependent upon the stoichiometry of the borohydride prompted us to further investigate the metal hydride demercuration of these organomercurials. This paper deals with some of the factors affecting the aforementioned diastereoselective demercurations by either thiol or hydride reagents.

Results and Discussion

The oxymercuration of α,β-unsaturated esters proceeds more slowly than does the oxymercuration of isolated al-

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(7) Some efforts at Z-trisubstituted olefin synthesis have had moderate success although usually with limited scope. (a) Larson, G. L.; Fernandez de Kaifer, C.; Seda, R.; Torres, L. E.; Ramirez, J. R. *J. Org. Chem.* **1984**, *49*, 3385. (b)Zweifel, G.; Steele, R. B. *J. Am. Chem. Soc.* **1967**, *89*, 5085. (c) Mini-zhi, D.; Yong-ti, Y.; Wei-hua, X. *Tetrahedron Lett.* **1984**, *25*, 1797. (d) Still, W. C.; Gennari, C. *Tetrahedron* Lett. **1983**, *24*, 4405.

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kenes. Substitution at the α or γ positions further reduces the reactivity of the double bond toward mercury electrophiles.[12] Thus while cyclohexene underwent methoxymercuration with mercuric acetate in 15 min and ethyl 2-butenoate reacted completely after 1 h, methyl (*E*)-2-methylbut-2-enoate required several hours and a catalyst to undergo methoxymercuration. Furthermore, both the methoxymercuration of methyl (*E*)-2,4-dimethylpent-2-enoate and the benzyloxymercuration of methyl (*E*)-2-methylbut-2-enoate were possible only with the use of mercuric trifluoroacetate; mercuric oxide was added to neutralize the equivalent of trifluoroacetic acid produced in these cases since it is known that some oxymercurials are unstable in its presence.[13] Attempts to effect direct acetoxymercuration of the α-alkyl-α,β-unsaturated carbonyl compounds were unsuccessful, as were all attempts to acetylate an initially formed hydroxymercurial by a variety of conventional methods. Also, attempted oxymercuration of methyl (*E*)-2-methyl-3-phenylpropenoate was unsuccessful even when mercuric trifluoroacetate was employed.

The oxymercurials obtained from oxymercuration of isolated alkenes with mercuric acetate were white crystalline compounds which eventually decomposed with concomitant deposition of metallic mercury. Oxymercurials obtained from the corresponding reaction on α,β-unsaturated carboxylic acids are reported to be insoluble inner salts which precipitate from the reaction mixture.[6] However, the organomercurials that we have obtained from the oxymercuration of other α,β-unsaturated carbonyl compounds (esters, ketone, amide) were always obtained as colorless syrups which were reasonably stable over time when precautions were taken to store them under nitrogen in the dark at ca. −10 °C. The α-acetoxy mercuri derivatives displayed extremely low mobility on silica gel as compared to the halo mercuri derivatives obtained by ligand exchange with aqueous sodium chloride or potassium bromide, making the former difficult to obtain analytically pure. Table I gives ^{1}H NMR data for the organomercurials used in this study; all were diastereomerically pure as evidence by NMR.

The demercuration products were in each case obtained as liquids. The ^{1}H NMR and, if necessary, the ^{13}C NMR spectra were run on solutions of the crude demercuration mixture in order to avoid any possible selective losses of one diastereomer during purification. In most cases, the diastereomers were distinguishable by single-development TLC, but the routine separation of the mixtures was not performed.

Organomercurials obtained by hydroxymercuration afforded, upon demercuration, diastereomeric 2-alkyl-3-hydroxy esters. Stereochemical assignments in these cases were greatly facilitated by the vast accumulation of data in the literature. The coupling constant H_2-H_3 threo is known to be larger (6-9 Hz) than H_2-H_3 erythro (2-4 Hz) resulting from the intramolecular hydrogen-bonded conformation.[14] Also, the chemical shifts for the H-2 and H-3 signals occur at lower field in the erythro isomer than in the threo isomer by 0.1–0.3 ppm.[5,15] The C2-methyl group occurs at higher field in the erythro isomer in one reported case.[5] Finally, it has been pointed out that the ^{13}C NMR carbon resonances for the C-2, C-3, and C2-methyl carbons occur upfield in the erythro isomer relative to the corresponding resonances in the threo isomers.[16]

Stereochemical assignment for the 2-alkyl-3-alkoxy esters, while less extensively detailed, has been reported. Unlike the 3-hydroxy-2-methylbutanoates, the C2-methyl signal occurs at lower field, and the H-2 signal occurs at higher field in the ^{1}H NMR spectrum of the erythro 3-alkoxy derivatives.[5,17-20]

Our results for similar cyclic as well as acyclic systems are consistent with the body of existing data on diastereomeric pairs. In each case, the isomer assigned the erythro configuration displays a C2-methyl doublet in the ^{1}H NMR spectrum centered downfield from that in the spectrum of the isomer assigned the threo configuration, with the trend being slightly less pronounced (0.06–0.11 ppm) in the acyclic cases than in the cyclic ones (0.09–0.10 ppm). No consistent trend in the chemical shifts of the common carbons in the ^{13}C NMR spectrum of β-alkoxy esters analogous to that observed by Heathcock[16] for β-hydroxy esters could be detected for the diastereomers examined. Table I summarizes the proton NMR data for erythro and threo demercuration products in addition to the organomercurials from which they were obtained.

1,3-Propanedithiol (PDT) has recently been used as a demetalating reagent.[21] We chose to examine the use of PDT for demercuration because it is known to form an insoluble oligomeric thiolate complex of mercury[22] and because we felt it might be capable of behaving in a manner similar to other sulfur-based reagents in promoting demercuration by an ionic mechanism.[6] Preliminary studies indicated the presence of a base was necessary; in the absence of an added base, deoxymercuration with PDT occurred to regenerate the unsaturated ester 1. Table II summarizes the results obtained in examining the effect of various sulfur-containing reagents on the stereochemical outcome of the demercuration process for a specific organomercurial. Qualitatively, the same result was obtained irrespective of the particular reagent used in that demercuration proceeded predominantly with retention of configuration; the use of PDT, however, resulted in the best yields. In our preliminary communication[8] we have shown that this erythro selectivity is general for a series of organomercurials using PDT under the specified conditions.

In view of the proposed[6] ionic pathway for these demercurations it seemed reasonable that the overall stereochemical outcome of the reaction might be influenced strongly by the nature of the solvent and base and the reaction temperature as well as the structure of the organomercurial. Table III summarizes the results obtained in a series of demercurations performed with PDT to determine the effect of these factors on the diastereomer ratios obtained. It has been observed that the erythro selectivity of the PDT demercuration of organomercurial **2A** was diminished upon varying the alcohol solvent from methanol through to *tert*-butyl alcohol (entries 1–4). This sequence corresponds to decreasing proton donor ability

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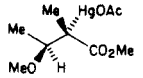
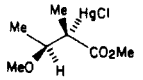
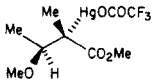
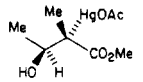
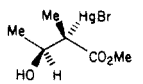
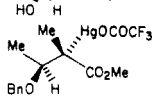
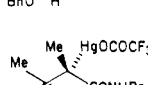
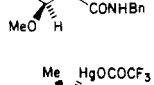
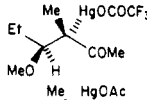
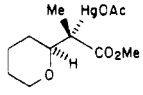
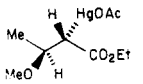
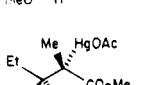
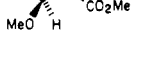
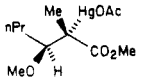
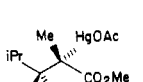
Table I. ^{1}H NMR Data for Organomercurials and Demercuration Products

organomercurials			products			
compd	structure	^{1}H NMR data	erythro	^{1}H NMR	threo	^{1}H NMR
2A		3.76 (1 H, q), 3.73, (3 H, s), 3.36 (3 H, s), 2.03 (3 H, s), 1.68 (3 H s), 1.31 (3 H, d)	**3A**	3.70 (3 H, s), 3.60 (1 H, m), 3.34 (3 H, s), 2.53 (1 H, m), 1.17 (3 H, d, C2-Me), 1.16 (3 H, s)	**4A**	3.70 (3 H, s), 3.50 (1 H, m), 3.31 (3 H, s), 2.60 (1 H, m), 1.13 (3 H, d), 1.10 (3 H, d, C2-Me)
2B		3.73 (3 H, s), 3.70 (1 H, q), 3.37 (3 H, s), 1.71 (3 H, s), 1.25 (3 H, d)	**3A**		**4A**	
2C		3.75 (3 H, s), 3.57 (1 H, q), 3.40 (3 H, s), 1.75 (3 H, s), 1.28 (3 H, d)	**3A**		**4A**	
2D		4.12 (1 H, q), 3.77 (3 H, s) 3.30 (1 H, b), 2.04 (3 H, s), 1.66 (3 H, s), 1.23 (3 H, d)	**3D**[a]	4.06 (1 H, m), 3.70 (3 H, s), 2.51 (1 H, m), 2.46 (1 H, b), 1.19 (3 H, d), 1.18 (3 H, d)	**4D**[a]	3.82 (1 H m), 3.71 (3 H, s), 2.56 (1 H, m), 1.79 (1 H, b), 1.22 (3 H, d), 1.18 (3 H, d)
2E		4.17 (1 H, m), 3.79 (3 H, s), 3.60 (1 H, b), 1.68 (3 H, s), 1.29 (3 H, d)	**3D**[a]		**4D**[a]	
2F		7.20–7.30 (5 H), 4.59 (2 H, s), 3.84 (1 H, q), 3.69 (3 H, s), 1.69 (3 H, s), 1.33 (3 H, d)	**3F**	7.20–7.30 (5 H), 4.68 (2 H, s), 3.80 (1 H, m), 3.63 (3 H, s), 2.58 (1 H, m), 1.21 (3 H, d, C2-Me), 1.19 (3 H, d)	**4F**	7.20–7.30 (5 H), 4.68 (2 H, s), 3.91 (1 H, m), 3.59 (3 H, d), 2.68 (1 H, m), 1.18 (3 H, d), 1.10 (3 H, d, C2-Me)
2G		7.19–7.40 (5 H), 4.38 (1 H, m), 3.70 (1 H, q), 3.43 (3 H, s), 1.66 (3 H, s), 1.20 (3 H, d)	**3G**	7.20–7.30 (5 H), 6.71 (1 H, b), 4.46 (2 H, m), 3.49 (1 H, q), 3.34 (3 H, s), 2.54 (1 H, m), 1.17 (3 H, d), 1.13 (3 H, d)	**4G**	7.20–7.30 (5 H), 6.71 (1 H, b), 4.45 (2 H, m), 3.44 (1 H, q), 3.31 (3 H, s), 2.31 (1 H, m), 1.18 (3 H, d), 1.16 (3 H, d)
2H		3.76 (1 H, t), 3.47 (3 H, s), 2.31 (3 H, s), 1.64 (3 H, s), 1.13 (2 H, m), 1.05 (3 H, t)	**3H**	not obtained, see text	**4H**	not obtained, see text
2J		4.00 (1 H, dd), 3.72 (3 H, s), 3.38–3.80 (2 H, m), 2.04 (3 H, s), 1.66 (3 H, s), 1.09–1.20 (6 H)	**3J**	3.98 (1 H, m), 3.69 (3 H, s), 3.34–3.54 (2 H, m), 2.50 (1 H, qu), 1.20–1.63 (6 H), 1.20 (3 H, d, C2-Me)	**4J**	3.96 (1 H, m), 3.70 (3 H, s), 3.33–3.56 (2 H), 2.53 (1 H, dq), 1.22–1.64 (6 H), 1.11 (3H, d, C2-Me)
2K		4.15 (1 H, dd), 3.95 (1 H, m), 3.80 (1 H, m), 3.73 (3 H, s), 2.28 (1 H, m), 2.04 (3 H, s), 1.98 (2 H), 1.75 (3 H, s), 1.70 (1 H)	**3K**	4.00 (1 H, q), 3.83 (1 H, m), 3.76 (1 H, m), 3.69 (3 H, s), 2.66 (1 H, q), 1.99 (1 H, m), 1.89 (2 H), 1.64 (1 H, m), 1.25 (3 H, d, C2-Me)	**4K**	4.02 (1 H, q), 3.88 (1 H, q), 3.77 (1 H, q), 3.73 (3 H, s), 2.54 (1 H, qu), 2.02 (1 H, m), 1.90 (2 H, m), 1.57 (1 H, m), 1.15 (3 H, d, C2-Me)
2L		4.12 (2 H, q), 3.95 (1 H, qu), 3.53 (1 H, d), 3.30 (3 H, s), 2.05 (3 H, s), 1.30 (3 H, d), 1.19 (3 H, t)	**3L**[b]	4.16 (1 H, q), 3.78 (1 H, m), 3.36 (3 H, s), 2.56 (1 H, bd), 1.29 (3 H, t), 1.23 (3 H, d)	**4L**[b]	4.16 (2 H, q), 3.78 (1 H, m), 3.36 (3 H, s), 2.35 (1 H, bd), 1.29 (3 H, t), 1.24 (3 H, d)
2M		3.73 (3 H, s), 3.62 (1 H, dd), 3.44 (3 H, s), 2.03 (3 H, s), 1.54–1.78 (2 H), 1.65 (3 H, s), 1.10 (3 H, t)	**3M**	3.69 (3 H, s), 3.38 (1 H, m), 3.35 (3 H, s), 2.58 (1 H, dq), 1.50 (2 H, m), 1.13 (3 H, d, C2-Me), 0.89 (3 H, t)	**4M**	3.69 (3 H, s), 3.33 (3 H, s), 2.30–3.36 (1 H, m), 2.70 (1 H, m), 1.35 (2 H), 1.06 (3 H, d, C2-Me), 0.91 (3 H, t)
2N		3.73 (3 H, s), 3.69 (1 H, m), 3.44 (3 H, s), 2.04 (3 H, s), 1.69 (3 H, s), 1.29–1.68 (4 H), 0.93 (3 H, t)	**3N**	3.68 (3 H, s), 3.47 (1 H, m), 3.34 (3 H, s), 2.58 (1 H, dq), 1.35–1.45 (4 H), 1.13 (3 H, d, C2-Me), 0.89 (3 H, m)	**4N**	3.69 (3 H, s), 3.45 (1 H, m), 3.33 (3 H, s), 2.73 (1 H, m), 1.39 (4 H), 1.06 (3 H, d, C2-Me), 0.89 (3 H, m)
2P		3.78 (3 H, s), 3.55 (3 H, s), 3.36 (3 H, d), 2.65 (1 H, m), 1.79 (3 H, s), 1.14 (3 H, d), 1.11 (3 H, d)	**3P**	3.70 (3 H, s), 3.41 (3 H, s), 3.23 (1 H, dd), 2.64 (1 H, m), 1.35–1.45 (4 H), 1.18 (3 H, d, C2-Me), 0.89 (3 H, m)	**4P**	3.70 (3 H, s), 3.40 (3 H, s), 3.20 (1 H, dd), 2.67 (1 H, q), 1.84 (1 H, m), 1.10 (3 H, d, C2-Me), 0.98 (3 H, d), 0.89 (3 H, d)
2Q		3.72 (3 H, s), 3.59 (1 H, q), 3.37 (3 H, s), 2.10 (2 H, m), 2.04 (3 H, s), 1.20 (3 H, d), 1.02 (3 H, t)	**3Q**	3.68 (3 H, s), 3.38 (1 H, m), 3.34 (3 H, s), 2.43 (1 H, m), 1.65 (2 H, m, C2-CH_2), 1.18 (3 H, d), 0.89 (3 H, t)	**4Q**	3.69 (3 H, s), 3.48 (1 H, m), 3.29 (3 H, s), 2.39 (1 H, m), 1.52 (2 H, m, C2-CH_2), 1.18 (3 H, d), 0.89 (3 H, t)
5		3.37 (3 H, s), 3.28 (1 H, td), 2.56 (1 H, td), 2.21 (2 H, m), 2.03 (3 H, s), 1.62–1.88 (3 H), 1.13–1.35 (3 H)	**6**[c]	3.41 (3 H, s), 3.00–3.51 (1 H), 0.98–2.25 (9 H)	**7**[c]	3.35 (3 H, s), 3.00–3.48 (1 H), 0.98–2.25 (9 H)

[a] See ref 16 and 37. [b] Spectra for deuteriated products, ref 36. [c] Spectra for deuteriated products.

and resulted in a decrease in selectivity. The use of a polar aprotic solvent (entry 5) also resulted in decreased selectivity. Other factors are also significant in contributing to the high erythro selectivity; substituting triethylamine for sodium bicarbonate resulted in a significant drop in the erythro/threo product ratio (entry 6). When demercurations were carried out under aprotic conditions (entries 7–11) with triethylamine, the demercurations resulted in

Table II. Effect of Sulfur Reagent[a]

entry	mercurial	reagent	solv	yield[b] (%)	ratio[c] (erythro/threo)
1	2A	$HS(CH_2)_2SH$	EtOH	43	90:10
2	2A	$HS(CH_2)_3SH$	EtOH	99	95:5
3	2A	$HS(CH_2)_4SH$	EtOH	54	90:10
4	2A	$HO(CH_2)_2SH$	EtOH	48	90:10
5	2A	HO_2CCH_2SH	EtOH	50	90:10
6[d]	2A	$NaS(CH_2)_3SH$	Et_2O	60	80:20
7[e]	2A	CH_3CH_2SH	EtOH	60	90:10
8	2A	Na_2CS_3	MeOH-H_2O	72	90:10

[a] Demercurations carried out by general procedure (Experimental Section) at 0 °C unless otherwise noted. [b] Isolated yield. [c] Ratio of diastereomers determined by integration of ^1H NMR of crude reaction mixture. [d] 1 equiv of NaH used as base. [e] 2 molar equiv of thiol used.

increased relative amounts of the threo isomer which was maximum in refluxing hexanes.

The structural variations in the organomercurial which were successfully accommodated in the PDT demercuration are indicated in Table III, entries (12–30). The β-hydroxymercurial **2D** obtained by solvomercuration in water underwent demercuration under the usual conditions (entry 12) with little selectivity. When the same reaction was carried out in water, some erythro selectivity was observed (entry 13). Apparently the presence of an internal proton source within the organomercurial has a detrimental influence.

Entries 16–18, 29, and 30 indicated that the cyclic mercurials **2J** and **2K** undergo demercuration to give the desired high erythro/threo ratio of products, a pleasantly consistent result in view of the results obtained by Bartlett.[6] Furthermore, the corresponding aprotic demercuration with triethylamine in dichloromethane resulted in a remarkable reversal of selectivity to a moderately high threo selectivity, a more dramatic result than was obtained in acyclic cases (entries 23–28).

The demercuration of **2G** (entry 20) gave an 85:15 ratio of erythro/threo products indicating that the demercuration process is similarly selective in the case of the mercurial obtained by oxymercuration of an α,β-unsaturated amide. However, in the case of **2H** (entry 21), the standard conditions resulted only in deoxymercuration occurring to afford the α,β-unsaturated ketone. It was also not surprising to observe the absence of any reaction in the case of **5** (entry 22) in view of the expected reaction mechanism and the absence of a carbanion stabilizing functional group.

The results of the metal hydride demercurations are given in Table IV. The sodium borohydride demercurations were found to be most threo selective when conducted in ethanol (entries 1–5). It can be seen that the diastereomeric ratio of products obtained is highly dependent on the amount of hydride to which the mercurial is exposed. The addition of a large excess of borohydride (entry 6) or the reversal of reagent addition (entry 7) both resulted in a reversal of the trend. In both cases, the erythro/threo ratio was moderately high. The rate of hydride addition was also found to be important (entries 8–9). The most dramatic effect was noted when 2 equiv. of sodium borohydride were used (entry 11) and the ratio of erythro/threo products was 88:12. Whereas oxymercurials obtained from isolated alkenes are reported to be insensitive to the nature of the hydride source,[24] the results in Table IV indicate that α-mercurio carbonyls do show some variation in stereochemical outcome with hydride source (entries 12–29). Although with most hydrides the threo product predominated, sodium cyanoborohydride and DiBAL-H gave equimolar mixtures of diastereomers, and lithium aluminum hydride and Lalancette's reagent gave higher erythro product mixtures. Organomercurials obtained from isolated alkenes reportedly undergo demercuration in such a way that the nature of the mercury ligand does not effect the reaction.[9,25] Entries 30 and 31 as compared to 1 and 26 indicated that the borohydride demercuration of these mercurials is extremely dependent on the nature of the mercury ligand. Surprisingly, the α-mercuri carboxamide **2G** (entry 34) afforded a 50:50 mixture with sodium borohydride in ethanol, and α-mercurio ketone **2H** underwent deoxymercuration. As expected **5** gave a 50:50 mixture of isomers (deuteriodemercuration).

The two most useful systems (PDT, EtOH, $NaHCO_3$ and $NaBH_4$, 1.1 equiv. H, EtOH) were examined more closely by the use of deuterium isotope studies. The results are given in Table V.

The demercuration of **2A** with 1.1 equiv. of sodium borodeuteride in ethanol (entry 1) resulted in substantial deuterium incorporation into the threo product as evidence by the appearance of a singlet centered at δ 1.10 rather than the usual doublet centered at δ 1.10 for the C2-methyl group of **4A**. The presence of a singlet at δ 1.18 as well as a doublet centered at δ 1.17 served to indicate that some deuterium incorporation into the erythro product **3A** had occurred. When the corresponding demercuration was performed with an excess of sodium borodeuteride in ethanol (entry 2), the threo isomer was again predominantly deuteriated; however, the increased amount of erythro isomer formed did not show a significant amount of deuterium incorporation. To check for the possibility of a competing ionic reaction being responsible for producing the erythro nondeuteriated isomer, the demercuration was performed (entry 3) with 1.1 equiv. of sodium borohydride in monodeuteriated ethanol (EtOD). The proton decoupled ^{13}C NMR showed no triplets, and the usual erythro/threo product ratio was obtained. This, in conjunction with the fact that H-abstraction by a radical from H-$CH(CH_3)OH$ over H-OCH_2CH_3 is favored by ca. 11 kcal/mol[26] suggests that a competing radical mechanism is operative; that is, the threo product is formed by borohydride (deuteride) reduction while the erythro product is formed by hydrogen abstraction from the alcohol solvent. The demercuration of **2L** (entry 4) with 1.1 equiv. of sodium borodeuteride in ethanol surprisingly afforded a mixture containing equimolar amounts of erythro and threo deuteriated products indicating that C2-alkyl substitution is required for the threo selectivity observed with a stoichiometric amount of hydride. The proton decoupled ^{13}C NMR spectrum displayed a singlet δ 41.7 and a triplet δ 41.3 in the ratio 20:80. The intergration of the C2-H region of the ^1H NMR spectrum indicated equal ratios for the two multiplets at δ 2.57 and δ 2.36 indicating that the ratio of erythro to threo deuteriated products must be equal.

The demercuration of **2A** with PDT in EtOD afforded predominantly the erythro deuteriated isomer as indicated (entry 5). The analogous demercuration of **2L** afforded a much lower amount of deuteriated product (entry 6), although the deuterium was incorporated specifically into

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(26) *Handbook of Chemistry and Physics*, 66th ed; Weast, R. C., Ed.; CRC Press: Boca Raton, FL.

Table III.[a] Effect of Solvent, Base, Temperature, and Mercurial Structure on Propanedithiol Demercuration

entry	mercurial	solv	base	temp (°C)	yield[b] (%)	ratio (erythro/threo)[c]
1	**2A**	MeOH	$NaHCO_3$	0	72	95:5
2	**2A**	EtOH	$NaHCO_3$	0	99	95:5
3	**2A**	*i*-PrOH	$NaHCO_3$	0	81	87:13
4	**2A**	*t*-BuOH	$NaHCO_3$	23	74	75:25
5	**2A**	DMF	$NaHCO_3$	0	75	85:15
6	**2A**	EtOH	Et_3N	0	60	60:40
7	**2A**	CH_2Cl_2	Et_3N	−70	98	58:42
8	**2A**	CH_2Cl_2	Et_3N	0	85	43:57
9	**2A**	CH_2Cl_2	Et_3N	23	76	44:56
10	**2A**	THF	Et_3N	68	76	40:60
11	**2A**	hexanes	Et_3N	68	79	37:63
12	**2D**	EtOH	$NaHCO_3$	0	75	57:43
13	**2D**	H_2O	$NaHCO_3$	3	55	80:20
14	**2D**	H_2O–EtOH	$NaHCO_3$	−23	66	72:28
15	**2D**	CH_3CN	$NaHCO_3$	0	89	60:40
16	**2J**	EtOH	$NaHCO_3$	0, 23	92	95:5
17	**2J**	CH_2Cl_2	$NaHCO_3$	0	92	50:50
18	**2J**	CH_2Cl_2	Et_3N	0	84	12:88
19	**2F**	EtOH	$NaHCO_3$	0	68	88:12
20	**2G**	EtOH	$NaHCO_3$	0	50	85:15
21	**2H**	EtOH	$NaHCO_3$	0	0	
22	**5**	EtOH	$NaHCO_3$	0	0	
23	**2M**	EtOH	$NaHCO_3$	0	72	95:5
24	**2M**	CH_2Cl_2	Et_3N	0	96	37:63
25	**2N**	EtOH	$NaHCO_3$	0	93	91:9
26	**2N**	CH_2Cl_2	Et_3N	0	78	44:56
27	**2Q**	EtOH	$NaHCO_3$	0	73	95:5
28	**2Q**	CH_2Cl_2	Et_3N	0	92	40:60
29	**2K**	EtOH	$NaHCO_3$	0	85	90:10
30	**2K**	CH_2Cl_2	Et_3N	0	95	15:85

[a] See Experimental Section for general protic and aprotic demercuration conditions. [b] Isolated yield. [c] Isomer ratio determined from ^1H NMR integration.

the erythro isomer. These results are consistent with demercuration occurring by an ionic mechanism with retention of configuration.

Summary and Conclusions

It has been determined that, for thiol demercuration of organomercurials derived from oxymercuration of α-alkyl-α,β-unsaturated esters, the erythro selectivity is enhanced in polar, protic solvents at lower temperatures and with sodium bicarbonate as base. The threo product is formed in significantly increased amounts upon going to nonpolar, aprotic solvents, higher temperature, and an amine base. This effect is most dramatic with cyclic mercurials. The borohydride demercuration has been observed to be a complex process in which competing mechanisms are apparently functioning; however, a useful threo selectivity is possible with this reagent. The stereoselective protiodemercuration of α-mercurio ketones and amides does not appear to be as successful as that of the carboxylate esters. In view of the recent work[3, 27-29] on stereoselectivity in acyclic oxymercuration processes, these procedures may be useful in extending the scope of asymmetric induction in acyclic molecules bearing contiguous chiral centers.

Experimental Section

General Methods. Unless otherwise noted, boiling points refer to Kugelrohr distillation, and temperatures quoted are oven temperatures. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Perkin-Elmer 598 infrared spectrometer as neat smears (liquids) or as solutions in carbon tetrachloride (solids). Organic solutions were dried with sodium sulfate; the dried solutions were filtered, and the solvent was removed by using a rotary evaporator with bath temperatures <40 °C, followed by static evaporation under high vacuum. Mass spectra (MS) were recorded on a V.G. 7070F at McMaster University, Hamilton, Ontario. ^1H NMR spectra were obtained in $CDCl_3$ solutions with tetramethylsilane (Me_4Si) as internal standard on a Bruker AM-400 spectrometer. Chemical shifts and coupling constants are reported in parts per million (δ) and hertz, respectively. ^{13}C NMR spectra were obtained at the corresponding frequency (100.6 MHz) on the same machine with proton decoupling. Dry column chromatography was performed with silica gel 60 (70–230 mesh) unless otherwise noted. Thinlayer chromatography (TLC) was performed on 0.25-mm silica gel 60 F-254 plates. Chromatography solvents were distilled prior to use. Anhydrous reactions were carried out under nitrogen by using standard techniques in oven-dried glassware. Tetrahydrofuran, hexanes, and Et_3N were distilled from CaH_2, CH_2Cl_2 was distilled from P_2O_5, and benzene was distilled from sodium metal. The demercurating reagents were obtained from commercial suppliers and were used without further purification. $NaBH_4$ (Aldrich, 98%) and $NaBD_4$ (Alfa) were weighed and dissolved immediately prior to use. All other reactants were reagent grade unless otherwise described. All structures depict racemates.

General Procedure for Preparation of α-Alkyl-α,β-unsaturated Esters. The esters were prepared from commercially available aldehydes by following the Wittig procedure as reported by House[30] or by the phosphonate procedure.[31] The products

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Table IV. Metal Hydride Demercurations[a]

entry	mercurial	hydride	solv	temp (°C)	yield[b] (%)	ratio (erythro/threo)[c]
1	**2A**	$NaBH_4$	EtOH	0	85	20:80
2	**2A**	$NaBH_4$	H_2O	2	81	42:58
3	**2A**	$NaBH_4$	MeOH	0	88	30:70
4	**2A**	$NaBH_4$	pyridine	23	80	40:60
5	**2A**	$NaBH_4$	CH_2Cl_2–H_2O	0	82	32:68
6[d]	**2A**	$NaBH_4$	EtOH	0	91	65:35
7[e]	**2A**	$NaBH_4$	EtOH	0	40	70:30
8[f]	**2A**	$NaBH_4$	EtOH	23	83	25:75
9[g]	**2A**	$NaBH_4$	EtOH	23	<20	25:75
10	**2A**	$NaBH_4$	EtOH	−72	84	25:75
11[h]	**2A**	$NaBH_4$	EtOH	−72	85	88:12
12	**2A**	$Na(MeO)_3BH$	THF	0	70	30:70
13	**2A**	$Na(AcO)_3BH$	THF	0	82	20:80
14	**2A**	$Na(AcO)_3BH$	EtOH	0	80	27:73
15	**2A**	$LiBH_4$	Et_2O	0	80	26:74
16	**2A**	$NaBH_3CN$	MeOH	0	74	50:50
17	**2A**	BH_3	THF	0	68	20:80
18	**2A**	9-BBN	THF	0	40	30:70
19[i]	**2A**	$Br_2BH{\cdot}Me_2S$	CH_2Cl_2	0	0	
20	**2A**	DiBAL-H	CH_2Cl_2	0	75	50:50
21	**2A**	$LiAlH_4$	Et_2O	0	58	69:31
22	**2A**	$Li(sec\text{-}Bu)_3BH$	THF	0	60	42:58
23	**2A**	Ph_3SiH	EtOH	0	70	30:70
24	**2A**	$n\text{-}Bu_3SnH$	THF	0	0	
25	**2A**	$(n\text{-}Bu)_4NBH_4$	H_2O	0	80	45:55
26	**2A**	$(n\text{-}Bu)_4NBH_4$	CH_2Cl_2	0	85	25:75
27	**2A**	$(n\text{-}Bu)_4NBH_4$	benzene	0	85	20:80
28	**2A**	$(n\text{-}Bu)_4NBH_4$	hexanes	0	74	20:80
29	**2A**	$NaBH_2S_3$	THF	0	50	70:30
30[i]	**2B**	$NaBH_4$	EtOH	0	0	
31	**2B**	$(n\text{-}Bu)_4NBH_4$	CH_2Cl_2	0	55	72:28
32	**2C**	$NaBH_4$	EtOH	0	70	25:75
33	**2F**	$NaBH_4$	EtOH	0	45	27:73
34	**2G**	$NaBH_4$	EtOH	0	70	50:50
35[i]	**2H**	$NaBH_4$	EtOH	0	0	
36	**5**	$NaBD_4$	EtOH	0	40	50:50
37	**2J**	$NaBH_4$	EtOH	0	90	14:86
38	**2K**	$NaBH_4$	EtOH	0	86	23:77

[a] See Experimental Section for general procedure. [b] Isolated yield. [c] Ratio determined from integration of ^1H NMR spectrum. [d] >4 equiv of hydride used. [e] The mercurial was added to hydride dropwise, H_2 evolved. [f] 0.95 equiv of hydride were added rapidly (2–3 s). [g] 0.95 equiv of hydride were added over 0.5 h. [h] 2.0 equiv of hydride were used. [i] Deoxymercuration occurred predominantly.

Table V. Deuterium Incorporation

entry	mercurial	reagt	solv	yield[a] (%)	ratio[b] (EH/TH/ ED/TD)
1	**2A**	$NaBD_4$	EtOH	74	10:0:10:80
2	**2A**	$NaBD_4$	EtOH	76	35:5:5:55
3	**2A**	$NaBH_4$	EtOD	81	20:80:0:0
4	**2L**	$NaBD_4$	EtOH	77	20:40:40[c]
5	**2A**	PDT	EtOD	95	30:5:65:0
6	**2L**	PDT	EtOD	85	50:50:0[c]

[a] Isolated yield. [b] Ratio of protonated erythro/protonated threo/deuteriated erythro/deuteriated threo isomers. [c] No EH/TH stereoisomers possible.

were routinely isolated by Kugelrohr distillation or by flushing through a silica gel column to remove the relatively immobile residual triphenylphosphine oxide (in the case of Wittig procedures). The following unsaturated esters were prepared: methyl (*E*)-2-methyl-2-butenoate, methyl (*E*)-2-methyl-2-pentenoate, methyl (*E*)-2-methyl-2-hexenoate, methyl (*E*)-2-ethyl-2-butenoate, methyl (*E*)-7-methyl-2-hydroxy-2-heptenoate, methyl (*E*)-6-hydroxy-2-methyl-2-hexenoate, and methyl (*E*)-2,4-dimethyl-2-pentenoate.

General Procedure for Oxymercuration with Mercuric Acetate. The unsaturated compound in CH_3OH (or H_2O for hydroxymercuration) containing mercuric acetate (1.1 equiv) was stirred at room temperature until no more starting material was detectable by TLC. The use of catalytic amount of $BF_3{\cdot}MeOH$ improved the efficiency of the reaction. The reaction mixture was concentrated, and the residue was partitioned between CH_2Cl_2 and H_2O. The dried organic phase was concentrated under reduced pressure, and then the resulting syrup was dried under high vacuum.

General Procedure for Oxymercuration with Mercuric Trifluoroacetate. The oxymercuration procedure was carried out essentially in the same manner as described for the use of mercuric acetate except that aliquots of mercuric oxide were periodically added to the stirred reaction mixture until the orange color persisted. The benzyloxymercuration was carried out in CH_2Cl_2.[3] The products were isolated in the usual manner.

General Procedure for Protic Thiol Demercuration. The organo mercurial (2–3 mM) in the alcohol (10 mL) was added dropwise to a well-stirred mixture of the sulfur reagent (1.1 equiv SH) and the base (2 equiv) in the alcohol (25 mL). After 0.5 h at the reaction temperature and 1 h at room temperature, mercuric acetate was added to the mixture to complex any residual thiol. The reaction mixture was filtered, and the filtrate was concentrated to a small volume under reduced pressure and partitioned between CH_2Cl_2 and H_2O. The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure.

General Procedure for Aprotic Thiol Demercuration. A solution of the oxymercurial (2–5 mM) and dry Et_3N (1.5 equiv) in dried solvent was added dropwise to a solution of PDT (1.1 equiv) in the solvent under nitrogen at the temperature indicated. The reaction mixture was stirred 0.5 h at the reaction temperature and 2 h at room temperature. The residual thiol was again removed by the addition of excess mercuric acetate. The mixture was filtered and processed in the manner described above.

General Procedure for Hydride Demercuration. Under nitrogen, a slight excess (1.1 equiv H) of the hydride reagent in solution was added dropwise (1 drop/2 s) to a well-stirred solution of the oxymercurial (2–3 mM) in the reaction solvent at the indicated temperature. After 0.5 h at that temperature and 0.5 h at room temperature, the reaction mixture was decanted, and the residue was washed with additional solvent. The combined

organic solution was reduced to a small volume (2–3 mL) under reduced pressure before being partitioned between CH_2Cl_2 and H_2O. The organic layer was separated, dried, filtered, and concentrated under reduced pressure. When necessary, the product was isolated from any remaining coproducts by chromatography on a silica gel column.

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Registry No. 1 (R = MeO, R^1 = Me, R^2 = Me), 6622-76-0; 1 (R = MeO, R^1 = Me, R^2 = Et), 1567-14-2; 1 (R = MeO, R^1 = Me, R^2 = *n*-Pr), 16493-96-2; 1 (R = MeO, R^1 = Me, R^2 = *i*-Pr), 20515-18-8; 1 (R = MeO, R^1 = Et, R^2 = Me), 101226-85-1; 1 (R = MeO, R^1 = Me, R^2 = $(CH_2)_4OH$), 101226-86-2; 1 (R = MeO, R^1 = Me, R^2 = $(CH_2)_3OH$), 101226-87-3; 1 (R = $NHCH_2Ph$, R^1 = Me, R^2 = Me), 83375-42-2; **2A**, 101019-17-4; **2B**, 101226-73-7; **2C**, 101019-21-0; **2D**, 101019-23-2; **2E**, 101226-74-8; **2F**, 101226-75-9; **2G**, 101226-76-0; **2H**, 101226-77-1; **2J**, 101019-24-3; **2K**, 101019-25-4; **2L**, 101226-78-2; **2M**, 101019-18-5; **2N**, 101019-19-6; **2P**, 101019-22-1; **2Q**, 101019-20-9; **3A**, 39788-68-6; **3D**, 39788-58-4; **3F**, 101226-79-3; **3G**, 101226-80-6; **3J**, 88222-48-4; **3K**, 88222-58-6; **3L**, 101226-81-7; **3M**, 101019-26-5; **3N**, 101019-28-7; **3P**, 101019-32-3; **3Q**, 101019-30-1; **4A**, 39788-67-5; **4D**, 39788-59-5; **4F**, 101226-82-8; **4G**, 101226-83-9; **4J**, 88222-47-3; **4K**, 88222-57-5; **4L**, 101226-84-0; **4M**, 101019-27-6; **4N**, 101019-29-8; **4P**, 101019-33-4; **4Q**, 101019-31-2; **5**, 38512-74-2; **6**, 75768-12-6; **7**, 75768-11-5; 9-BBN, 280-64-8; $Hg(OAc)_2$, 1600-27-7; $HgCl_2$, 7487-94-7; $Hg(O_2CCF_3)_2$, 13257-51-7; $HgBr_2$, 7789-47-1; $NaBH_4$, 16940-66-2; $Na(MeO)_3BH$, 16940-17-3; $Na(AcO)_3BH$, 56553-60-7; $LiBH_4$, 16949-15-8; $NaBH_3CN$, 25895-60-7; BH_3, 13283-31-3; $Br_2BH{\cdot}Me_2S$, 55671-55-1; DIBAL-H, 1191-15-7; $LiAlH_4$, 16853-85-3; Li(*sec*-Bu)$_3$BH, 38721-52-7; Ph_3SiH, 789-25-3; *n*-Bu_3SnH, 688-73-3; $(n\text{-}Bu)_4NBH_4$, 33725-74-5; $NaBH_2S_3$, 27735-90-6; $HS(CH_2)_2SH$, 540-63-6; $HS(CH_2)_3SH$, 109-80-8; $HS(CH_2)_4SH$, 1191-08-8; $HO(CH_2)_2SH$, 60-24-2; HO_2CCH_2SH, 68-11-1; CH_3CH_2SH, 75-08-1; $NaS(CH_2)_3SH$, 101248-11-7; Na_2CS_3, 534-18-9.

Supplementary Material Available: Physical and spectroscopic data (IR, Ms, ^1H, and ^{13}C NMR) for the α,β-unsaturated carbonyl compounds, the organomercurials **2A–Q** and the demercuration products **3A–Q** and **4A–Q** (10 pages). Ordering information is given on any current masthead page.

Alkylmetal Asymmetric Reduction. 17.[1] Stereochemical Course of Ketone Reduction by β-Branched Alkyl Derivatives of Beryllium and Aluminum

Massimo Falorni, Luciano Lardicci, Carlo Rosini, and Giampaolo Giacomelli*

Dipartimento di Chimica e Chimica Industriale dell'Universita', Centro di studio del CNR per le Macromolecole Stereordinate ed Otticamente Attive, I-56100 Pisa, Italy

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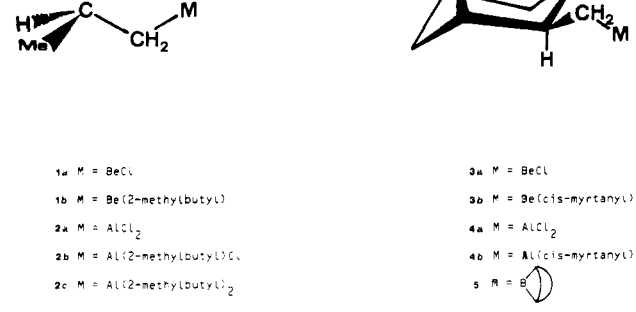
(*R*)-(2-Methylbutyl)beryllium chloride and tri-*cis*-myrtanylaluminum have been prepared; both these new organometallic derivatives are able to provide enantioselective reduction of prochiral ketones. Further investigations on the use of *cis*-myrtanylberyllium chloride, di-*cis*-myrtanylberyllium, and bis[(*R*)-2-methylbutyl]beryllium as reducing agents of ketones are also reported. The extent of enantioselectivity, along with the stereochemistry of the process, was found to depend mainly on the nature of metal atom and on the structure of the ketone employed. The stereochemical results obtained are discussed on the basis of previous reports too.

One of the most widely investigated aspects in the field of asymmetric induction has been the synthesis of optically active carbinols from enantioselective reduction of prochiral ketones.[2]

Recently we have studied the asymmetric reduction of alkyl phenyl and α-alkynyl ketones using [(*S*)-2-methylbuty]aluminum derivatives **2a–c**[3] and *cis*-myrtanylaluminum dichloride (**4a**).[4] This procedure affords optically active carbinols in short reaction times, good chemical and sometimes high optical yields. We have also noted that 2-methylbutyl derivatives reduce phenyl and α-alkynyl ketones with the same stereochemical course:[3] phenyl and α-alkynyl carbinols being recovered with *S* and *R* absolute configuration, respectively. On the other hand, using *cis*-myrtanylaluminum dichloride (**4a**) we observed a reversal of the stereochemistry of the process on passing from phenyl to α-alkynyl ketones: in fact, all carbinols recovered had *R* absolute configuration. At present, we have extended our studies to beryllium derivatives,[5] to look for the origin of this discrepancy in the stereochemical behavior of this kind of enantioselective reducing agent. Therefore we have prepared *cis*-myrtanylberyllium chloride (**3a**) and di-*cis*-myrtanylberyllium (**3b**), and we have checked their ability to reduce enantioselectively prochiral ketones:[5] we preliminarly found that both **3a** and **3b** had the same stereochemical trend shown by **4a**.



1a M = $BeCl$
1b M = Be(2-methylbutyl)
2a M = $AlCl_2$
2b M = Al(2-methylbutyl)Cl
2c M = Al(2-methylbutyl)$_2$
3a M = $BeCl$
3b M = Be(cis-myrtanyl)
4a M = $AlCl_2$
4b M = Al(cis-myrtanyl)$_2$
5 M = B

In the present work we report the data concerning the reduction of ketones by cis-myrtanyl organometallic derivatives **3a,b**[5] and **4b** and [(*R*)-2-methylbutyl]beryllium derivatives (**1a**,[6]**b**).

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