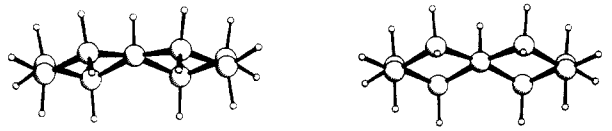
TRANS



MNDO MM2

Figure 1. Optimized structures for the *trans*-decalyl radical. The view is along the bridging bond from the radical site.

eterize their heat of formation calculations and were able to reproduce the experimental results by about 0.8 kcal/mol. The reported error from the MNDO study of Bischoff and Friedrich[9] was about 12 kcal/mol, suggesting that the MM2 heats are closer to the actual values.

Previous ESR results[1] led to the conclusions that the trans radical was of lower energy and the higher energy cis radical interconverted to *trans*-decalin through a common planar radical transition structure. An attempt was made to locate such a planar species by constraining the radical sites to planarity while allowing full relaxation of all other parameters. Depending upon the choice of starting geometry (cis or trans) two different "planarized" radicals resulted. Both of these planarized radicals were of higher energy than the fully relaxed radicals, and they are geometrically quite different (Table II). The present calculations do not preclude direct equilibration between the cis and trans radicals, but as only cis to trans isomerization is observed[1-3] this hypothesis seems unlikely. Furthermore, radical species derived from *trans*-decalin must quench with hydrogen atoms to give only *trans*-decalin. This suggests that the cis to trans isomerization results from the quenching of a cis-derived radical species by hydrogen atom abstraction to give *trans*-decalin, the lowest energy species on the manifold.

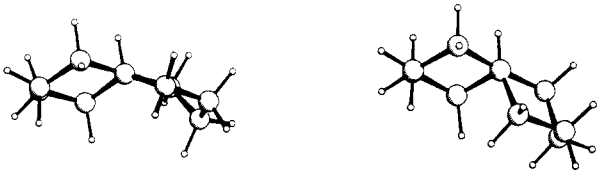
The most important difference between the MM2 and MNDO results is in the optimized geometries. The MNDO optimized cis and trans radicals are both highly planarized (α = 0.6° and 8.2°, respectively). The MM2 method predicts more pryamidal radical sites (α = 34.8° and 34.4°, respectively), somewhat intermediate between tetrahedral (55°) and planar (0°). In comparing the results of Bischoff and Friedrich[9] and Imam and Allinger[6] for smaller organic radicals, it seems that the MNDO method gives radical sites that are too planar. It is possible that the energy changes are very small in the direction of the ring puckering, and, therefore, the calculated MNDO heats of formation will not change appreciably.

Examination of Figure 1 reveals that the overall ring structures for the trans radical can be regarded as retaining essentially chair–chair conformations in both calculations, although the MNDO geometry is "flatter" than the MM2 geometry. This is in agreement with previous studies which have noted that MNDO leads to structures with reduced puckering for cyclic systems.[10] In contrast to the trans case, the two methods predict a major difference in the structure of the cis radical (Figure 2). The MNDO geometry is considerably distorted to a chair–pseudoboat form, while the MM2 calculation predicts retention of a chair–chair structure. Because of the previously noted tendency of the MNDO method to produce radical sites that are too planar and rings that are too flat, the MM2 geometries are probably more realistic.

Conclusions

This study indicates that two different conformations for the decalyl radical are possible, the more stable being

CIS



MNDO MM 2

Figure 2. Optimized structures for the *cis*-decalyl radical. The view is along the bridging bond from the radical site.

the one derived from *trans*-decalin. The fully optimized radical structures were located by both MM2 and MNDO methods starting with the parent *cis*- and *trans*-decalin parameters. Both radicals are predicted to be nonplanar at the radical site, and no evidence is found for a planar transition structure. Elucidation of the nature of the interconversion process would be an interesting topic for future study. In addition, the structure of the cis radical is still uncertain, and more demanding theoretical work is under way.

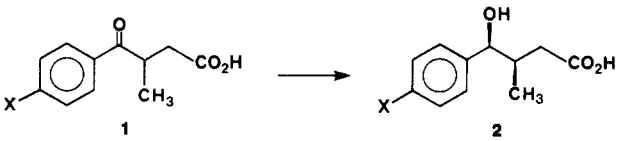
Stereoselective Reduction of γ-Oxo-γ-phenylbutanoic Acids

R. Frenette,*† M. Kakushima,† R. Zamboni,† R. N. Young,† and T. R. Verhoeven‡

Merck Frosst Canada, Inc., Pointe Claire-Dorval, Quebec, Canada H9R 4B8, and Merck & Co., Inc., Rahway, New Jersey 07065

Received June 10, 1986

In the course of research on selective receptor antagonists of leukotriene D_4, we were interested in devising an efficient and stereoselective synthesis of the (*RS,SR*)-γ-aryl-γ-hydroxy-β-methylbutanoic acid moiety **2** contained in the desired product,[1] that is, where the β-methyl and the γ-hydroxy groups are erythro.[2]



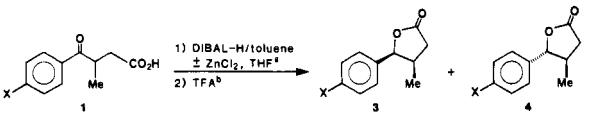
1 **2**

A logical method for the preparation of these γ-hydroxy-β-methyl acids was through a stereoselective reduction of the corresponding γ-oxobutanoic acids **1**. Although the erythro-selective reduction of α-substituted β-oxo acid derivatives is well documented,[3] there are few examples of erythro-selective γ-keto ester or acid reduction.[4] Initial attempts to obtain the desired (*RS,SR*)-γ-aryl-γ-hydroxy-β-methylbutanoic acids were discouraging. A ratio of 70:30 in favor of the desired isomers were obtained with sodium borohydride (as potentially a reagent which could deliver hydride from an internal complex) while $Na(CH_3OCH_2CH_2O)_2AlH_2$ (Vitride) showed a ratio of 50:50. Reduction of **1b** methyl ester using several reagents known to stereoselectively reduce α-substituted β-oxo acid derivatives was not more successful. For example, the hydrosilane-based reduction[3e,5] and zinc boro-

† Pointe Claire-Dorval, Quebec.
‡ Rahway, NJ.

0022-3263/87/1952-0304$01.50/0

Table I. Reduction of γ-Oxo-γ-phenylbutanoic Acids



entry	ketone	X	$ZnCl_2$ (1 equiv)	time (h)[c]	yield (isolated product),[d] (%)	product ratio[e] after lactonization 3:4 (ratio)
1	1a	CH_3SO_2	+	3	60[f]	3a:4a (99:1)
2	1a	CH_3SO_2	-	3	82	3a:4a (99:1)
3	1b	H	+	3	83	3b:4b (99:1)
4	1b	H	+	2[g]	89	3b:4b (95:5)
5	1b	H	-	3	87	3b:4b (95:5)
6	1b	H	-	2[g]	91	3b:4b (90:10)
7	1b	H	-	3[h]	85	3b:4b (55:45)
8	1c	CH_3S	+	3	90	3c:4c (99:1)
9	1c	CH_3S	-	3	90	3c:4c (96:4)
10	1d	CH_3O	+	3	92	3d:4d (99:1)[i]
11	1d	CH_3O	+	3	97	3d:4d (93:7)
12	1d	CH_3O	-	3	95	3d:4d (93:7)[i]
13	1d	CH_3O	-	3	95	3d:4d (93:7)

[a] Ratio of THF to toluene of 5:1 v/v. [b] Solution of 0.2% of trifluoroacetic acid in CH_2Cl_2. [c] Reactions were run at −78 °C. [d] Total isolated yields of mixture of 3 and 4 after silica gel chromatography. [e] Diastereomeric ratios were determined from intensities of relevant ^1H NMR signals. [f] 25% of starting material was recovered. [g] Reaction was run at −40 °C. [h] Reaction was run in pure toluene or CH_2Cl_2 instead of THF. [i] The lactonization was performed using DCC (2.4 equiv) in THF for 2 days.

hydride reduction[3b] showed respectively ratios of 66:34 and 60:40 while surprisingly only a 40:60 ratio in favor of the undesired isomers was obtained with hindered hydride such as Li(*i*-Bu_3)BH (L-Selectride, Aldrich).[4]

Considering that a trivalent aluminum based reducing agent might favor selective reduction through a cyclic bidentate complex, we investigated the use of diisobutylaluminium hydride (DIBAL-H) for this purpose. We would like to report that very high erythro selectivity (93–99%) is attained in the reduction of γ-aryl-β-methyl-γ-oxobutanoic acids by the use of DIBAL-H, particularly in the presence of zinc chloride ($ZnCl_2$). Our results are summarized in the Table I.

The reduction of 1 with DIBAL-H, in the presence or absence of $ZnCl_2$, proceeded in a highly stereoselective manner, giving product ratios of 93:7 to 99:1 in favor of the desired *RS,SR* products 2 (entries 1–5 and 8–13). To facilitate the isolation and isomer ratio characterization of the derived reduction products, they were converted to the corresponding γ-butyrolactones (lactonization catalyzed with trifluoroacetic acid).

The best diastereofacial selectivity was achieved when the γ-oxo acids were treated first with $ZnCl_2$ (1 equiv) in THF at room temperature followed by addition of DIBAL-H (2.4 equiv) in toluene at −78 °C. As can be seen in the table, under optimized conditions the nature of the substituent on the ring does not affect the selectivity of the reaction (entries 1, 3, 8, 10). When the benzene ring bears a para-electron-withdrawing group (entries 1, 2), the use of $ZnCl_2$ is not necessary to maintain optimum stereoselectivity. In this case $ZnCl_2$ has the effect of markedly slowing the rate of reduction (entry 1). The presence of $ZnCl_2$, in the case of unsubstituted aromatics (entries 3, 5), does increase the product ratio of 3:4 from 95:5 to 99:1. Similar results were obtained in the cases of electron-donating groups such as *p*-methylthio (entries, 8, 9) and *p*-methoxy (entries 10–13). In the latter cases, there was no apparent improvement in the stereoselectivity of the reduction when $ZnCl_2$ was used (entries 11, 13).

In the standard procedure, lactonization was catalyzed with a solution of 0.2% of trifluoroacetic acid (TFA) in dichloromethane. We were concerned about the potential for epimerization of the γ-center via a benzylic carbonium ion which would be stabilized by a *p*-methoxy group. In fact in this case when neutral conditions of lactonization were used (DCC (2.4 equiv) in THF for 2 days), high stereoselectivity in the reduction was revealed (entries 10 vs. 11), showing that the reduced center was indeed partially epimerized by the TFA used in the lactonization step. However, in other cases no improvement was observed. It was noted that the selectivity is significantly diminished (entries 4, 6) when the temperature of reaction is increased to −40 °C. As well, the nature of the solvent used was found to be very important. Under the optimized conditions, DIBAL-H in toluene is used and the reaction is run in THF such that the ratio of THF to toluene is 5:1. If the reaction is run in pure toluene or dichloromethane instead of THF while using DIBAL-H in toluene, the product ratio 3:4 decreases from 95:5 (entry 5) to 55:45 (entry 7) while the rate of the reaction is slightly increased. In pure THF, the rate of the reaction is markedly decreased and higher temperature (−40 °C, 5 h) is required to complete the reaction but with lower selectivity (85:15).

From the results presented above we discovered empirically conditions for a very high stereoselective reduction of these keto acids. Analysis of the results in the table in conjunction with some additional simple experiments suggests an important role for the metal ion in determining stereoselectivity. Under conditions as in entries 3 and 5 we have shown that the first equivalent of DIBAL-H

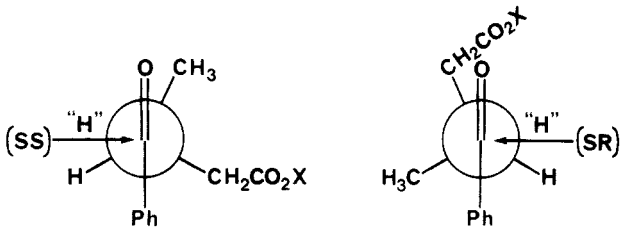
(1) Young, R. N.; Bélanger, P.; Champion, R.; DeHaven, R. N.; Denis, D.; Ford-Hutchinson, A. W.; Fortin, R.; Frenette, R.; Gauthier, J. Y.; Gillard, J.; Guindon, Y.; Jones, T. R.; Kakushima, M.; Masson, P.; Maycock, A.; McFarlane, C. S.; Piechuta, H.; Pong, S. S.; Rokach, J.; Williams, W. R.; Yoakim, C.; Zamboni, R. *J. Med. Chem.* **1986**, *29*, 1573.

(2) The threo–erythro nomenclature for the relative configuration of compounds possessing two adjacent asymmetric centers is somewhat confusing. We will use the relative stereochemical nomenclature proposed by Noyori (Nyori, R., Nishida, J.; Sakata, J. *J. Am. Chem. Soc.* **1983**, *105*, 1598, footnote 32).

(3) (a) Canceill, J.; Jacques, J. *Bull. Soc. Chem. Fr.* **1970**, 2180. (b) Nakata, T.; Oishi, T. *Tetrahedron Lett.* **1980**, *21*, 1641. (c) Glass, R. S.; Deardorff, D. R.; Henegar, K. *Ibid.* **1980**, *21*, 2467. (d) Brown, G. R.; Foubister, A. J. *J. Chem. Soc., Chem. Commun.* **1985**, 455. (e) Fujita, M.; Hiyama, T. *J. Am. Chem. Soc.* **1985**, *107*, 8294 and references cited therein.

(4) Pourahmady, N.; Eisenbraun, E. J. *J. Org. Chem.* **1983**, *48*, 3067.

(5) (a) Fujita, M.; Hiyama, T. *J. Am. Chem. Soc.* **1984**, *106*, 4629. (b) Hiyama, T.; Kobayashi, K.; Fujita, M. *Tetrahedron Lett.* **1984**, *25*, 4959.



I

Figure 1.

produces the aluminate salt of the carboxylate[6] and reduction only occurs on addition of the second equivalent. When 1 equiv of sodium hydride (NaH) was used to form the carboxylate followed by 1.2 equiv of DIBAL-H to effect reduction, selectivity was severely reduced (ratio 66:34). However, when this experiment was repeated but with addition of $ZnCl_2$ (1 equiv) prior to addition of DIBAL-H the stereoselectivity was restored (ratio 99:1).

One possible explanation of the observed selectivity could derive from an analysis in terms of steric approach control[7] using a Felkin-type model[8] where the approach of the hydride is directed by bulky alkyl groups. However, when such analysis is applied to our case, presuming that the carboxylate–aluminium or zinc complex is acting as a bulky group, one would predict favored attack of the hydride as in transition state I leading to a threo-selective or at best nonselective result (see Figure 1).

A more plausible explanation could involve the formation of a seven-membered ring complex with the aluminium or zinc atom bridging the ketone and carboxyl groups. Results from entries 3 and 5 strongly suggest that the aluminate salt of the acid formed with the first equivalent of DIBAL-H produces a cyclic seven-membered complex and the second equivalent of reagent reduces the ketone to give high erythro-selective reduction. Under optimized conditions $ZnCl_2$ probably exchanges with aluminium to form a zinc-based cyclic complex with geometry (undefined) more favorable to erythro selectivity. The formation of a seven-membered ring chelate structure as an intermediate has precedent in reports of a similar complex as the reactive species in the $TiCl_4$-catalyzed Diels-Alder reaction of allyl lactates with dienes,[9] where similar high facial selectivity was observed.

However, it would seem that definition of the reacting complex cannot be easily derived from simple conformational analysis as is shown by the importance of the solvent in these reductions. Highest selectivity is achieved in THF as opposed to CH_2Cl_2 whereas a cyclic complex would be expected to be stronger in CH_2Cl_2 than in THF. To date we have not been able to devise a conformational model taking into account structural and solvent factors which can adequately explain all of these results. There must be subtle effects involved because, for instance, when γ-cyclohexyl-β-methyl-γ-oxobutanoic acid was reacted under optimized conditions it gave a much reduced erythro-selective product ratio (70:30).

In conclusion the conditions described above offer highly efficient and stereoselective methodology for obtaining *erythro*-γ-hydroxy-β-methylbenzenebutanoic acids. The procedure has been shown to be useful in the preparation of important intermediates in the synthesis of receptor antagonists of leukotriene D_4.[1]

(6) Complete formation of a carboxylate anion was shown by isolation of the aluminate complex and regeneration of the starting keto acid on subsequent acid quenching of this complex.
(7) Cram, D. J.; Abd Elhafez, F. A. *J. Am. Chem. Soc.* **1952**, *74*, 5828.
(8) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199.
(9) Poll, T.; Metter, J. O.; Helmchen, G. *Angew, Chem., Int. Ed. Engl.* **1985**, *24*, 112.

Experimental Section

The melting points are not corrected. The NMR spectra were measured with a Bruker AM250 spectrometer. Propiophenone was purchased from a commercial source.

General Procedure for the Formation of Methyl γ-Aryl-β-methyl-γ-oxobutanoates (1, Methyl Ester). To a cooled solution of anisole (or thioanisole) (10 mmol) in dry 1,2-dichloroethane (15 mL) were added propionyl chloride (11 mmol) and then by portions solid aluminium chloride (12 mmol), and the solution was stirred at room temperature for 1 h. The reaction mixture was poured onto ice and water and extracted with CH_2Cl_2. The organic layer was separated, dried over Na_2SO_4, and evaporated under vacuum. The crude propiophenone derivatives were alkylated as following. A solution of 0.65 M of potassium hexamethyldisilazane (KHMDS) in toluene (11 mmol) was diluted in THF (15 mL) and cooled to −78 °C. To this mixture was added dropwise a solution of crude propiophenone derivative (10 mmol) in THF (5 mL), and the solution was stirred at −78 °C for 1 h. Then a solution of methyl bromoacetate (12 mmol) in THF (5 mL) was added dropwise and the solution was stirred at −78 °C for 1 h. The mixture was quenched in 1 N HCl and extracted with ether, and the organic layer was dried over Na_2SO_4 and evaporated at reduced pressure. The crude esters were chromatographed in a column of flash silica gel (230–400 mesh), eluting with 1:5 ethyl acetate–hexane to afford the corresponding γ-oxo esters (yields 75–85%).

Methyl β-methyl-γ-oxo-γ-phenylbutanoate: ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.27 (d, J = 6 Hz, 3 H, β-CH_3), 2.50 (dd, J = 16, 4 Hz, 1 H, α-H), 3.05 (dd, J = 16, 9 Hz, 1 H, α′-H), 3.6 (s, 3 H, CO_2CH_3), 3.8–4.0 (m, 1 H, β-H), 7.4–7.6 (m, 3 H, Ph), 8.0 (d, J = 6 Hz, 2 H, Ph). Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.70; H, 7.05.

Methyl β-methyl-γ-[4-(methylthio)phenyl]-γ-oxobutanoate: ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.25 (d, J = 6 Hz, 3 H, β-CH_3), 2.50 (dd, J = 16, 4 Hz, 1 H, α-H), 2.55 (s, 3 H, SCH_3), 2.98 (dd, J = 16, 9 Hz, 1 H, α′-H), 3.6 (s, 3 H, CO_2CH_3), 3.8–4.0 (m, 1 H, β-H), 7.23 (d, J = 6 Hz, 2 H, Ph), 7.90 (d, J = 6 Hz, 2 H, Ph). Anal. Calcd for $C_{13}H_{16}O_3S$: C, 61.88; H, 6.39; S, 12.71. Found: C, 61.58; H, 6.69; S, 12.77.

Methyl γ-(4-methoxyphenyl)-β-methyl-γ-oxobutanoate: ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.20 (d, J = 6 Hz, 3 H, β-CH_3), 2.45 (dd, J = 16 Hz, 1 H, α-H), 2.95 (dd, J = 16, 9 Hz, 1 H, α′-H), 3.55 (s, 3 H, CO_2CH_3), 3.78–3.95 (m, 1 H, β-H), 3.85 (s, 3 H, OCH_3), 6.95 (d, J = 6 Hz, 2 H, Ph), 8.0 (d, J = 6Hz, 2 H, Ph). Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.08; H, 6.83. Found: C, 66.14; H, 7.03.

Methyl β-methyl-γ-[4-(methylsulfonyl)phenyl]-γ-oxobutanoate: To a solution of 4-(methylthio)phenyl derivative (4 mmol) in CH_2Cl_2 (5 mL) was added a solution of *m*-CPBA (8.2 mmol) in CH_2Cl_2 (30 mL), and the solution was stirred overnight at room temperature. Calcium hydroxide (12 mmol) was added, and the solution was stirred for 15 min and filtered on bed of Celite. The filtrate was evaporated to dryness to afford the title product as an oil (100% yield): ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.30 (d, J = 6 Hz, 3 H, β-CH_3) 2.55 (dd, J = 16, 4 Hz, 1 H, α-H), 3.10 (dd, J = 16, 9 Hz, 1 H, α′-H), 3.18 (s, 3 H, SO_2CH_3), 3.6 (s, 3 H, CO_2CH_3), 3.82–4.0 (m, 1 H, β-H), 8.05 (d, J = 6 Hz, 2 H, Ph), 8.15 (d, J = 6 Hz, 2 H, Ph). Anal. Calcd for $C_{13}H_{16}O_5S$: C, 54.91; H, 5.67; S, 11.28. Found: C, 54.75; H, 5.72; S, 11.42.

General Preparation of the γ-Oxo Acids (1a–d). To a solution of γ-keto ester (10 mmol) in THF (30 mL) and MeOH (3 mL) was added 2 N NaOH (15 mmol), and the solution was stirred at room temperature for 2 h. Then the reaction mixture was diluted with H_2O, acidified with 1 N HCl, and extracted with ethyl acetate. The organic layer was dried over Na_2SO_4 and evaporated under vacuum to afford the γ-keto acid as a solid (yield 95–100%).

β-Methyl-γ-[4-(methylsulfonyl)phenyl]-γ-oxobutanoic acid (1a): mp 116–118 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.28 (d, J = 6 Hz, 3 H, β-CH_3), 2.55 (dd, J = 16, 4 Hz, 1 H, α-H), 3.10 (dd, J = 16, 9 Hz, 1 H, α′-H), 3.15 (s, 3 H, SO_2CH_3), 3.85–4.0 (m, 1 H, β-H), 8.10 (d, J = 6 Hz, 2 H, Ph), 8.18 (d, J = 6 Hz, 2 H,

Ph). Anal. Calcd for $C_{12}H_{14}O_5S$: C, 53.32; H, 5.22; S, 11.86. Found: C, 53.38; H, 5.29; S, 11.89.

β-Methyl-γ-oxo-γ-phenylbutanoic acid (1b): mp 56–57 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.25 (d, J = 6 Hz, 3 H, β-CH_3), 2.50 (dd, J = 16, 4 Hz, 1 H, α-H), 3.0 (dd, J = 16, 9 Hz, α′-H), 3.8–4.0 (m, 1 H, β-H), 7.48 (t, 2 H, Ph), 7.55 (t, 1 H, Ph), 7.96 (d, J = 6 Hz, 2 H, Ph). Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.73; H, 6.30. Found: C, 68.68; H, 6.36.

β-Methyl-γ-[4-(methylthio)phenyl]-γ-oxobutanoic acid (1c): mp 70–72 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.23 (d, J = 6 Hz, 3 H, β-CH_3), 2.48 (dd, J = 16, 4 Hz, 1 H, α-H), 2.52 (s, 3 H, SCH_3), 3.0 (dd, J = 16, 9 Hz, 1 H, α′-H), 3.78–3.95 (m, 1 H, β-H), 7.28 (d, J = 6 Hz, 2 H, Ph), 7.90 (d, J = 6 Hz, 2 H, Ph). Anal. Calcd for $C_{12}H_{14}O_3S$: C, 60.48; H, 5.92; S, 13.46. Found: C, 60.62; H, 5.91; S, 13.33.

γ-(4-Methoxyphenyl)-β-methyl-γ-oxobutanoic acid (1d): mp 65–67 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.22 (d, J = 6 Hz, 3 H, β-CH_3), 2.48 (dd, J = 16, 4 Hz, 1 H, α-H), 2.98 (dd, J = 16, 9 Hz, 1 H, α′-H), 3.78–3.95 (m, 1 H, β-H), 3.85 (s, 3 H, OCH_3), 6.95 (d, J = 6 Hz, 2 H, Ph), 7.98 (d, J = 6 Hz, 2 H, Ph). Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.93; H, 6.44.

General Preparation of the Lactones 3 and 4. γ-Aryl-β-methyl-γ-oxobutanoic acid (1 mmol) and zinc chloride (1 mmol as 1 M solution in THF) in anhydrous THF (5 mL) was cooled to −78 °C, and a solution of 1.5 M DIBAL-H in toluene (2.4 equiv) was added slowly and stirred at −78 °C for 3 h. The reaction was quenched in 1 N HCl (10 mL), and the reaction products were worked up by extraction with ethyl acetate (2 × 10 mL), dried over Na_2SO_4, and evaporated to give the crude γ-hydroxy acid which was treated as follows. The residue was dissolved in a solution of 0.2% of TFA in dichloromethane (2 mL) (i.e., 4 μL of TFA in 2 mL of CH_2Cl_2) and stirred at room temperature for 2 h. The mixture was evaporated to dryness and purified on column of flash silica gel (230–400 mesh), eluting with dichloromethane to afford the mixture of the desired cis (**3**) and trans (**4**) lactones where the product ratio was determined by ^{1}H NMR (250 MHz).[10] Because the mixtures of cis and trans lactones were not normally separable in pure form by flash chromatography (except in the case of **3b** and **4b**), cis lactones **3** were characterized as a mixture of **3** and **4** in a ratio of 99:1. Also the trans lactones **4** detected by NMR in small amount were identified by their characteristic peaks.[10]

***(RS,SR)*-γ-Hydroxy-β-methyl-γ-[4-(methylsulfonyl)-phenyl]butanoic acid lactone (3a)**: mp 145–146 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.70 (d, J = 6 Hz, 3 H, β-CH_3), 2.40 (dd, J = 16, 4 Hz, 1 H, α-H), 2.88–3.05 (m, 2 H, α′-H and β-H), 3.10 (s, 3 H, SO_2CH_3), 5.70 (d, J = 6 Hz, 1 H, γ-H), 7.50 (d, J = 6 Hz, 2 H, Ph), 8.0 (d, J = 6 Hz, 2 H, Ph). Anal. Calcd for $C_{12}H_{14}O_4S$: C, 56.67; H, 5.55; S, 12.61. Found: C, 56.54; H, 5.77; S, 12.68.

***(RS,SR)*-γ-Hydroxy-β-methyl-γ-phenylbutanoic acid lactone (3b)**:[11] ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.70 (d, J = 6 Hz, 3 H, β-CH_3), 2.35 (dd, J = 16, 4 Hz, 1 H, α-H), 2.78–2.95 (m, 2 H, α′-H and β-H), 5.60 (d, J = 6 Hz, 1 H, γ-H), 7.28 (d, J = 6 Hz, 2 H, Ph), 7.30–7.40 (m, 3 H, Ph). Anal. Calcd for $C_{11}H_{12}O_2$: C, 74.97; H, 6.87. Found: C, 74.96; H, 7.02.

***(RS,SR)*-γ-Hydroxy-β-methyl-γ-[4-(methylthio)phenyl]-butanoic acid lactone (3c)**: mp 52–53 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.70 (d, J = 6 Hz, 3 H, β-CH_3), 2.32 (dd, J = 16, 4 Hz, 1 H, α-H), 2.48 (s, 3 H, SCH_3) 2.75–2.95 (m, 2 H, α′-H and β-H), 5.55 (d, J = 6 Hz, 1 H, γ-H), 7.15 (d, J = 6 Hz, 2 H, Ph), 7.25 (d, J = 6 Hz, 2 H, Ph). Anal. Calcd for $C_{12}H_{14}O_2S$: C, 64.83; H, 6.35; S, 14.43. Found: C, 64.65; H, 6.25; S, 14.30.

***(RS,SR)*-γ-Hydroxy-γ-(4-methoxyphenyl)-β-methyl-butanoic acid lactone (3d)**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.70 (d, J = 6 Hz, 3 H, β-CH_3), 2.35 (dd, J = 16, 4 Hz, 1 H, α-H), 2.75–2.95 (m, 2 H, α′-H and β-H), 3.87 (s, 3 H, OCH_3), 5.58 (d, J = 6 Hz, 1 H, γ-H), 6.92 (d, J = 6 Hz, 2 H, Ph), 7.18 (d, J = 6 Hz, 2 H, Ph). Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.89; H, 7.12.

4a, 4b,[11] 4c, 4d: ^{1}H NMR (250 MHz, $CDCl_3$) characteristic peaks δ 1.18 (d, J = 6 Hz, 3 H, β-CH_3), 4.95 (d, J = 6 Hz, 1 H, γ-H).

(10) Characteristic signals for cis γ-lactones (*RS,SR* isomers) **3** and trans γ-lactones (*RS,SS* isomers) **4** were determined by simple nuclear Overhauser effect (NOE) studies on both pure lactones isolated, after careful silica gel chromatography of reduction products obtained from treatment of methyl γ-[4-[(*N,N*-dimethylcarbamyl)thio]phenyl]-β-methyl-γ-oxobutanoate with $NaBH_4$.[1] Cis lactone (**3**; X = $SCON(CH_3)_2$) (mp 116–117 °C): ^{1}H NMR (400 MHz, acetone-d_6) δ 0.78 (d, J = 6 Hz, 3 H, β-CH_3), 5.85 (d, J = 6 Hz, 1 H, γ-H). Trans lactone (**4**; X = $SCON(CH_3)_2$) (mp 75–77 °C): ^{1}H NMR (400 MHz, acetone-d_6) δ 1.30 (d, J = 6 Hz, 3 H, β-CH_3), 5.18 (d, J = 8 Hz, 1 H, γ-H).

(11) Nakamura, E.; Oshino, H.; Kuwajima, I. *J. Am. Chem. Soc.* **1986**, *108*, 3745.

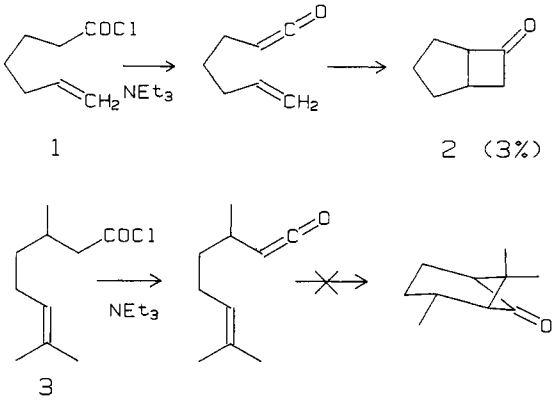
Preparation of Unsaturated α-Chloro Acids and Intramolecular [2 + 2] Cycloadditions of the Chloroketenes Derived from Them

Barry B. Snider*[1] and Yashwant S. Kulkarni

Department of Chemistry, Brandeis University, Waltham, Massachusetts 02255

Received May 27, 1986

We[2] and others[3] have recently begun to develop the intramolecular [2 + 2] cycloaddition of ketenes to alkenes into a general synthetic method. Although many isolated examples are known,[4] the development of this reaction has been hindered by the limited reactivity of simple alkylketenes. For instance, the ketene prepared by treatment of acid chloride **1** with triethylamine has been reported to provide only a 3% yield of the cycloadduct **2**.[3a] The ketene derived from **3** does not give any cycloadduct.[2a] We chose to examine the intramolecular [2 + 2] cycloadditions of chloroketenes with alkenes,[5] since methylchloroketene is much more reactive in intermolecular [2 + 2] cycloadditions than methylketene.[6]



The preparation of unsaturated chloroketenes required a facile method for the preparation of unsaturated α-chloro acids from the readily available unsaturated acids. This posed two problems. First, the ester enolate or acid di-

(1) Dreyfus Teacher–Scholar, 1982–1987.

(2) (a) Snider, B. B.; Hui, R. A. H. F.; Kulkarni, Y. S. *J. Am. Chem. Soc.* **1985**, *107*, 2194. (b) Kulkarni, Y. S.; Snider, B. B. *J. Org. Chem.* **1985**, *50*, 2809. (c) Snider, B. B.; Kulkarni, Y. S. *Tetrahedron Lett.* **1985**, *26*, 5675. (d) Kulkarni, Y. S.; Burbaum, B. W.; Snider, B. B. *Tetrahedron Lett.* **1985**, *26*, 5619. (e) Snider, B. B.; Hui, R. A. H. F. *J. Org. Chem.* **1985**, *50*, 5167.

(3) (a) Marko, I.; Ronsmans, B.; Hesbain-Frisque, A.-M.; Dumas, S.; Ghosez, L.; Ernst, B.; Greuter, H. *J. Am. Chem. Soc.* **1985**, *107*, 2192. (b) Corey, E. J.; Desai, M. C.; Engler, T. A. *J. Am. Chem. Soc.* **1985**, *107*, 4339. (c) Corey, E. J.; Desai, M. C. *Tetrahedron Lett.* **1985**, *26*, 3535. (d) Brady, W. T.; Giang, Y. F. *J. Org. Chem.* **1985**, *50*, 5177. (e) Wulff, W. D.; Kaesler, R. W. *Organometallics* **1985**, *4*, 1461.

(4) For references to earlier work, see ref 3 in 2e above.

(5) A portion of this work has been published in preliminary form.[2a]

(6) Brady, W. T.; Roe, R., Jr. *J. Am. Chem. Soc.* **1970**, *92*, 4618. Jaz, J.; Denis, E. *Bull. Soc. Chim. Belg.* **1966**, *75*, 845.

0022-3263/87/1952-0307$01.50/0