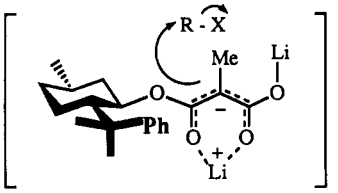


(A)

Figure 1. Transition state of alkylation of phenylmenthyl hydrogen methylmalonate 1.

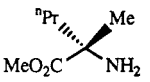
HPLC analysis following conversion to methyl ester using CH_2N_2. Absolute configurations at the 2-position of the major components were determined by comparisons with known compounds. Following Arndt–Eistert reaction of the product (entry 1) (51% yield) and HPLC separation, the major product **4** was converted into the (−)-(*R*)-di-*p*-nitrobenzoate **5**: mp 154 °C; $[\alpha]^{24}_D$ −1.93° ($CHCl_3$) [lit.[9] mp 154 °C; $[\alpha]^{20}_D$ −1.8° ($CHCl_3$) in 78% overall yield. The assignment was confirmed by transformation into the α-methyl α-amino acid **7**. Curtius type rearrangement[10] (77% yield), followed by hydrogenolysis (82% yield) and HPLC purification, gave the amino ester **6**, which was hydrolyzed using KOH and 18-crown-6 in hot toluene. The resulting amino acid was converted into the (+)-(*S*)-amide **7**, $[\alpha]^{20}_D$ +5.3° (benzene) [lit.[11] $[\alpha]^{20}_D$ +5.0° (benzene)], in 71% overall yield from **6** (Scheme II).

The major component of entry 2 was identical with the major one of the hydrogenated products of entry 3, and its stereochemistry was determined by similar conversion to the (+)-(*S*)-amino ester **8**, $[\alpha]^{28}_D$ +13.4° (EtOH) [lit.[12] (*R*)-form: $[\alpha]_D$ −13.0° (EtOH)]. The major isomer of entry 5 was similarly transformed to the (+)-(*S*)-acetamide **9**,

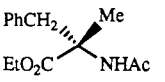
Table II. Methylation of Half Esters 10

entry	R	reaction temp, °C	reaction time, h	yield, %	ratio of 2 and 3
1	Et	−78	3	80	5:1
2	^{n}Pr	−78	3	63	5:1
3	$PhCH_2$	−78	5	61	15:1

$[\alpha]^{27}_D$ +49.2° ($CHCl_3$) [lit.[13] (*R*)-form: $[\alpha]_D$ −47.8° ($CHCl_3$)]. It is clear that the major products possess *R*



(8)



(9)

configurations at the 2-position. The actual *E*/*Z* distribution and conformations of the dianions are not known. The diastereofacial selectivity noted above could be attributed to easier access to the alkyl halides from the less hindered side of the transition-state geometry (A) depicted in Figure 1. In expectation of the preferential formation of the other isomers **3**, half esters **10**[4,14] were methylated (Scheme I), but the same isomers **2** were produced as the major products and in similar selectivities (Table II). Formation of the same diastereomers is not a serious drawback because chemoselective transformation of the major half ester would provide both enantiomers of various chiral building blocks. Further work will be required in order to clarify the mechanism of these suprising results.

In summary, a new methodology for the enantioselective construction of a quaternary asymmetric carbon and an efficient approach to α-alkyl α-amino acids were developed.

Acknowledgment. This work was supported in part by a Grant-in-Aid for Scientific Research on Priority Areas, 01607002, from the Ministry of Education, Science and Culture of Japan.

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(10) Yamada, S.; Ninomiya, K.; Shioiri, T. *Tetrahedron Lett.* **1973**, 2343. Shioiri, T.; Ninomiya, K.; Yamada, S. *J. Am. Chem. Soc.* **1972**, *94*, 6204.
(11) Achiwa, K.; Yamada, S. *Chem. Pharm. Bull.* **1966**, *14*, 537.
(12) Bajgrowicz, J. A.; Cossec, B.; Pigiere, Ch.; Jacquier, R.; Vallefont, Ph. *Tetrahedron Lett.* **1984**, *25*, 1789. Schöllkoph, U. *Tetrahedron* **1983**, *39*, 2085.
(13) Georg, G. I.; Guan, X.; Kant, J. *Tetrahedron Lett.* **1988**, *29*, 403.
(14) The half ester **10** (R = CH_2Ph) was prepared in 72% yield by reaction of (1*R*,3*R*,4*S*)-8-phenyl-*p*-methan-3-yl hydrogen malonate and benzyl bromide in the presence of 2 equiv of LDA at −78 °C.

Complete Control of the Rearrangement Modes of Enolates of α-Allyloxy Ketones: Reversal from the [3,3]-Claisen to the [2,3]-Wittig Pathway by the Use of the Metalated *N*,*N*-Dimethylhydrazones

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Received August 31, 1989

Summary: It has been shown that the predilection for the [3,3]-Claisen rearrangement pathway of enolates of α-allyloxy ketones is cleanly overridden by the [2,3]-Wittig rearrangement route with the use of carbanions of their corresponding *N*,*N*-dimethylhydrazones. Since the formation of these hydrazones as well as hydrolysis of the rearranged α-hydroxyhydrazones can be readily achieved, this approach allows a [2,3]-Wittig rearrangement pathway to take place in high yields starting from the α-allyloxy ketones.

Sir: Enolates of α-allyloxy ketones **1** (X = O) have recently been shown to undergo facile [3,3]-anionic oxy-Claisen rearrangement giving rise to α-hydroxy ketones **2** through a novel 1,2-carbonyl transposition.[1] In connection with another synthetic project in these laboratories, we required

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(1) (a) Koreeda, M.; Luengo, J. I. *J. Am. Chem. Soc.* **1985**, *107*, 5572. See also: (b) Kirchner, J. J.; Pratt, D. V.; Hopkins, P. B. *Tetrahedron Lett.* **1988**, *29*, 4229.

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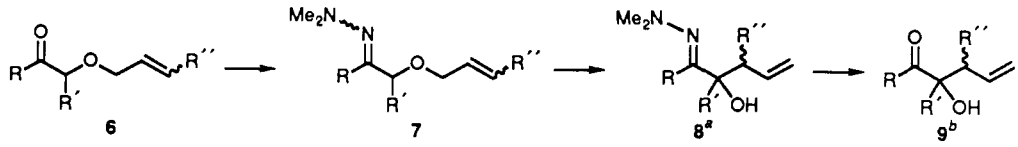
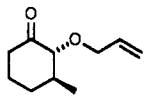
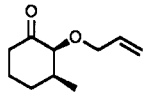
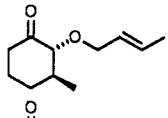
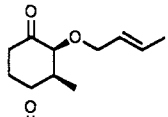
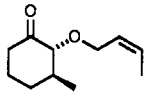
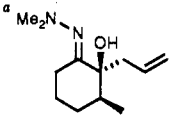
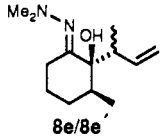
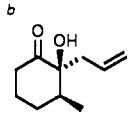
Table I. Summary of the *N,N*-Dimethylhydrazone Formation, the [2,3]-Wittig Rearrangement, and the Hydrolysis of α-Hydroxy-*N,N*-dimethylhydrazones

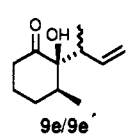


		compd	hydrazone geometry (*E*/*Z*)	yield, %	compd	yield, %	compd	yield, %
6a	R = Ph, R′ = R″ = H	**7a**	1:3	67	**8a**	95	**9a**	98
6b	R = Ph, R′ = Me, R″ = H	**7b**	2.9:1	84	**8b**	73	**9b**	88
6c		**7c**	>50:1	99	**8c**	91	**9c**	89
6d		**7d**	4:1	99	**8c**	92		
6e		**7e**	>50:1	100	**8e**/**8e′** (1.4/1)	88		
6f		**7f**	6:1	99	**8e**/**8e′** (1.1/1)	45	**9e**/**9e′**	78
6g		**7g**	>50:1	100	**8e**/**8e′** (1.25/1)	81		

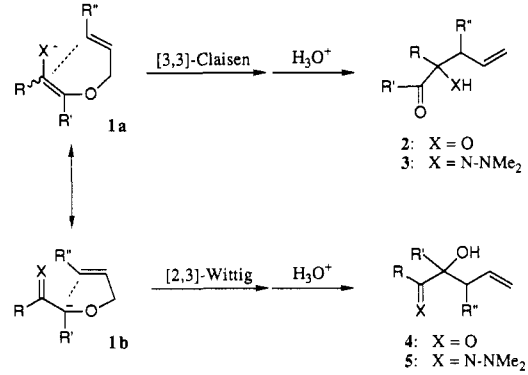
[a] 
8c


8e/8e′

[b] 
9c


9e/9e′

Scheme I



access to the regioisomeric α-hydroxy ketones **4**, which would be formed from **1** through the alternative [2,3]-Wittig mode of rearrangement (Scheme I).[2] It was envisaged that the predilection for the [3,3]-Claisen pathway of **1** may be effectively overridden by the [2,3]-Wittig route upon replacement of the carbonyl oxygen with the less electronegative nitrogen atom. Thus, in the case of the rearrangement of an anion of *N,N*-dimethylhydrazone **1** (X = N-NMe_2), the product **5** should be expected to be preferentially produced over **3** since the latter places a negative charge on the hydrazone nitrogen, while the former accommodates it on the more favorable oxygen atom.[3] Interestingly, in spite of recent intense investigations of the [2,3]-Wittig rearrangement,[2] there were no previous reports on the use of the hydrazones in the reaction. In this paper, we report that α-allyloxy-α-metalated *N,N*-dimethylhydrazones **1** (X = N-NMe_2) (azaenolates) undergo smooth [2,3]-Wittig rearrangement providing α-hydroxy hydrazones in excellent yields.[4]

The requisite hydrazones **7** were readily prepared from their corresponding ketones **6**[5-7] through reaction with *N,N*-dimethylhydrazine in benzene in the presence of a catalytic amount of *p*-TsOH (Table I). The conversion from **7** to **8** was effectively achieved with a potassium base. Thus, treatment of the hydrazones **7** with an excess of KH (15 equiv)/*t*-BuOH (2 equiv) in anhydrous THF at room temperature for 12–24 h resulted in the formation of, upon aqueous workup, the α-hydroxyhydrazones **8** as single *E* stereoisomers at the C=N bond. Under these conditions, **7a**, obtained as a 1:3 *E*/*Z* mixture, rearranged to **8a** in 95%

(2) For reviews on [2,3]-sigmatropic rearrangements, see: (a) Hoffman, R. W. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 563. (b) Nakai, T.; Mikami, K. *Chem. Rev.* **1986**, *86*, 885. See also: (c) Hill, R. K. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, p 503. (d) Ziegler, F. E. *Chem. Rev.* **1988**, *88*, 1423.

(3) Reviews on the chemistry of metalated Schiff's bases: (a) Fraser, R. R. In *Comprehensive Carbanion Chemistry*; Elsevier: New York, 1980; Vol. B, p 65. (b) Whitesell, J. K.; Whitesell, M. A. *Synthesis* **1983**, 517.

(4) Recently, Nakai reported that the lithium enolate of **6b** when generated in HMPA/THF at −70 °C undergoes, upon warming to 0 °C, [2,3]-Wittig rearrangement, albeit in low yield. See: Takahashi, O.; Saka, T.; Mikami, K.; Nakai, T. *Chem. Lett.* **1986**, 1599.

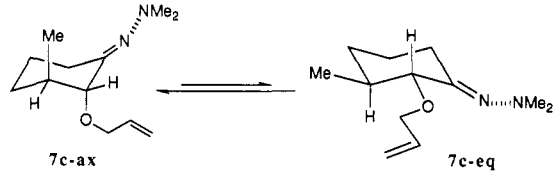
(5) **6a**: Kochinski, J. L. C.; Salomon, R. G. *Tetrahedron Lett.* **1977**, 3225.

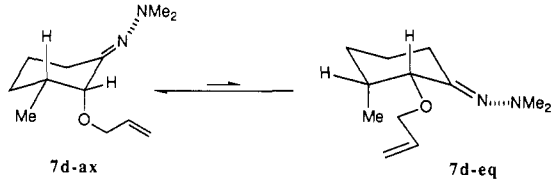
(6) **6b**: ref 1a.

(7) α-Allyloxy ketones **6c–g** were prepared by Me_2CuLi conjugate addition to their corresponding 2-allyloxy-2-cyclohexen-1-ones.

yield. In contrast, **7b** (2.9:1 *E*/*Z* mixture) provided **8b** in lower yield (73%); apparently under the above conditions only the less sterically hindered *E*-hydrazone **7b** was deprotonated and the *Z* isomer recovered unchanged.

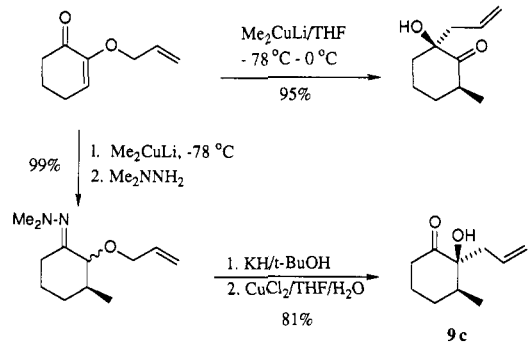
The cyclic hydrazones **7c–g** presented an interesting case as the presence of an acidic methylene next to the C=N group in these compounds could potentially be a source of complication upon deprotonation. The transformation of the *trans*-hydrazone **7c** proceeded smoothly after 10 h at room temperature under conditions identical with those above, furnishing **8c** (91%) with virtually complete stereoselectivity. Interestingly, the epimeric *cis*-hydrazones **7d** (4:1 *E*/*Z*) remained intact under these conditions and required refluxing in THF for 12 h, at which time the rearranged product **8c** was produced cleanly in 92% yield. The marked difference in reactivities of **7c** and **7d** may be accounted for in terms of the kinetic acidity of their respective C-2 methine protons. NMR analysis indicates that both **7c-ax** and **7d–ax** having the allyloxy group axially disposed are decisively the major conformers of these hydrazones primarily due to the *vinylogous anomeric effect*.[8] However, it is clearly these conformers **7c–eq** and **7d–eq** which possess C-2 axial methine protons that are required for deprotonation at C-2 with the base. Taking into consideration the magnitude of the 1,3-diaxial interaction involving the C-3 methyl group of both **7c** and **7d**, it may be reasonable to speculate that the fraction of the conformer having the axial C-2 H (i.e., **7c–eq** and **7d–eq**) should be greater for **7c** than for **7d**. Thus, the difference in energies between the ground-state and the reacting conformers must be manifested in a difference in kinetic acidities of the C-2 H in **7c** and **7d**.





The (*E*)- and (*Z*)-(crotyloxy)hydrazones **7e–g** were next investigated in order to obtain insight into the possible diastereoselection during the formation of the allylic methyl (R″ = Me in Table I). Both *trans*-hydrazones **7e** and **7g** underwent facile rearrangement upon base treatment at room temperature as above to give rise to [2,3]-Wittig products **8e** and **8e′** as a diastereomeric mixture in excellent yields. In contrast, as in the case of **7d**, refluxing in THF was required for the rearrangement of the *cis*-hydrazone **7f** to proceed, **8e** and **8e′** (1.1:1) being obtained in lower yield. In all three cases, the diastereofacial selection involving C-2 was complete providing the C-2 hydroxyl cis to the 3-methyl. However, the diastereoselectivity at the allylic carbon was found to be poor, pointing to the similar steric congestion near this center and C-2 for the two transition states originating from each of **7e-g**, thus leading to the low **8e**/**8e′** selectivity. Hydrolysis of the hydrazones was effectively carried out through the use of Corey's method with cupric chloride in buffered THF/water.[9] For the hydrazones **8a–c**, this reaction took place readily within a few hours at room temperature, providing the hydroxy ketones **9a–c** in very good yields. The more hindered hydrazones **9e** and **9f**, however, turned out to be somewhat resistant to hydrolysis, and harsher conditions (reflux for 2 days) had to be adopted.

Scheme II



The methodology delineated herein allows a [2,3]-Wittig rearrangement pathway to take place starting from the α-allyloxy ketones. Therefore, as the [3,3]-Claisen rearrangement has been readily effected for this system as reported,[1] it is now feasible to control the modes of the two rearrangement reactions of the α-allyloxy ketones as exemplified in Scheme II.[10]

Acknowledgment. We are grateful for financial support for this work provided by the National Institutes of Health (Grant DK 30025). We thank Professor Takeshi Nakai for helpful discussions.

Supplementary Material Available: Experimental procedure for the [2,3]-Wittig rearrangement reaction of the *N,N*-dimethylhydrazone derivatives of α-allyloxy ketones and spectroscopic and microanalytical data of the new compounds described in this report (10 pages). Ordering information is given on any current masthead page.

(8) Denmark, S. E.; Dappen, M. S. *J. Org. Chem.* **1984**, *49*, 798.

(9) Corey, E. J.; Knapp, S. *Tetrahedron Lett.* **1976**, 3667.

(10) It should be noted that direct cuprate addition to the *N,N*-dimethylhydrazone derivative of 2-(allyloxy)-2-cyclohexen-1-one was not possible under a variety of conditions including the BF_3·Et_2O-catalyzed cuprate reaction. Thus, the stepwise sequence involving the formation of hydrazone of the cuprate adducts had to be employed.