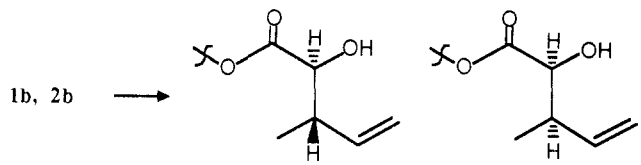

	threo	erythro
	threo/erythro	
glyoxylate	*cis*-butene	*trans*-butene	1-(trimethylsilyl)-*cis*-2-butene
1b	8:1	15:1	1:15
2b	6:1	1.6:1	1:2.5

conversion) while isomerization in the presence of **1b** is more rapid than the ene reaction. These observations are consistent with contrasting reaction pathways. We postulate that both proceed through an intermediate carbocation but that in the case of 8-phenylmenthol glyoxylate, reversal to starting materials from this species is faster than progression on to product while these relative rates are reversed with 2-phenylcyclohexanol glyoxylate. Alternatively, it is possible that the reaction with **2b** is a concerted process.

Because the auxiliary remains connected to the substrate after the ene reaction, the stereochemical analyses described above could be conducted with racemic **2a**. For application in asymmetric induction processes, a practical resolution of this alcohol is required. While **1a** has been resolved[7] via its half-phthalate ester salt with either brucine or strychnine to provide both enantiomers and prepared in 72% enantiomeric excess by hydroboration of 1-phenylcyclohexene with monoisopinocampheylborane,[8] neither of these approaches would appear to be a viable method for the production of large quantities of optically active **2a**. We have found that enzymatic hydrolysis (hog liver esterease, pH 7.8 phosphate buffer[9]) of the acetates derived from racemic **2a** is complete at 50% conversion, providing optically pure (−) alcohol ($[\alpha]_D$ −56.3°, lit.[8] $[\alpha]_D$ −55.5°), while the (+) enantiomer remained as the ester ($[\alpha]_D$ +6.2°) from which it can be freed by simple hydrolysis ($[\alpha]_D$ +54.5°). Reesterification of the (−) alcohol provided acetate with $[\alpha]_D$ −6.2°. Thus, each enantiomers can be obtained in an optically pure state, within experimental error.[10]

We anticipate that *trans*-2-phenylcyclohexanol will serve as an effective substitute for 8-phenylmenthol in many of the asymmetric induction processes where the latter has been used successfully. In this regard, we have found that similar levels of asymmetric induction are obtained in the reactions of the ene reactions of the *N*-sulfinylcarbamates of **2a** and **1a** and that the reactions of the former proceed in higher chemical yield.[12] PhCy-OH can be readily prepared by the copper-catalyzed opening of cyclohexene oxide[13] and we expect rapid and widespread acceptance of this new chiral auxiliary.

(7) Verbit, L.; Price, H. C. *J. Am. Chem. Soc.* **1972**, *94*, 5143.
(8) Brown, H. C.; Jadhav, P. K.; Mandal, A. K. *J. Org. Chem.* **1982**, *47*, 5074.
(9) Arita, M.; Adachi, K.; Yukishige, I.; Sawai, H.; Ohno, M. *J. Am. Chem. Soc.* **1983**, *105*, 4049.
(10) A level of enantiomeric purity greater than 99% for optically pure alcohol was determined by our published method[11] involving the formation of diastereomeric mandelic acid esters.
(11) Whitesell, J. K.; Reynolds, D. *J. Org. Chem.* **1983**, *48*, 3548–3551.
(12) See also: Whitesell, J. K.; James, D.; Carpenter, J. F. *J. Chem. Soc., Chem. Commun.*, in press.
(13) Huynh, C.; Derguini-Boumechal, F.; Linstrumelle, G. *Tetrahedron Lett.* **1979**, *17*, 1503.

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A New Method for the Preparation of γ,δ-Unsaturated Ketones via Claisen Rearrangement

Summary: Thermal rearrangement of monosodium salts of 3-(allyloxy)crotonates derived from primary and secondary allylic alcohols and of disodium salts of 3-(allyloxy)-2-alkenoic acids affords γ,δ-unsaturated ketones.

Sir: We previously reported[1] a convenient alternative to the traditional "allyl vinyl ether Claisen rearrangement" sequence[2] for the synthesis of γ,δ-unsaturated aldehydes. The method is experimentally simple to perform and avoids mercury catalysis which is generally required for the preparation of allyl vinyl ethers. In this paper, we disclose an extension of the method that allows the synthesis of γ,δ-unsaturated ketones.

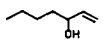
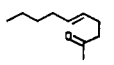
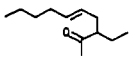
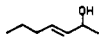
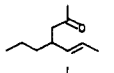
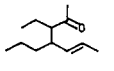
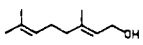
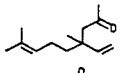
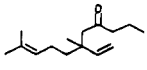
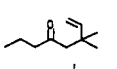
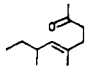
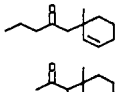
Autenrieth[3] was the first to show that a variety of nucleophiles displace chloride from both isomers of 3-chlorocrotonic acid. We found that the corresponding reaction with allylic alkoxides provides a general method for the preparation of 3-(allyloxy)crotonic acids (Table I). Good yields of the derived adducts **2** were obtained when an allylic alcohol[4] was heated with 2.20 equiv of sodium hydride and 1.15 equiv of 3-chlorocrotonic acid (**1**)[5] in THF at 65 °C for 4 h. When the sodium salts of these carboxylic acids were heated to 200–215 °C under reduced pressure (15 mm) in a Kugelrohr apparatus (method A), the desired γ,δ-unsaturated ketones **3** distilled from the reaction mixture (Scheme I).[6]

Some Claisen rearrangements were found to be accelerated by carbanion formation,[7] and the dianions of allylic acetoacetates undergo Carroll rearrangement at room

(1) Büchi, G.; Vogel, D. E. *J. Org. Chem.* **1983**, *48*, 5406.
(2) Ziegler, F. E. *Acc. Chem. Res.* **1977**, *10*, 227. Bennett, G. B. *Synthesis* **1977**, 589. Rhoads, S. J.; Raulins, N. R. *Org. React. (N.Y.)* **1974**, *22*, 1.
(3) Autenrieth, W. *Ber.* **1887**, *20*, 1531. Autenrieth, W. *Ber.* **1896**, *29*, 1639. Autenrieth, W. *Liebigs, Ann. Chem.* **1889**, *254*, 222. Autenrieth, W. *Liebigs Ann. Chem.* **1890**, *259*, 332.
(4) Although 3-chlorocrotonic acid reacts more rapidly with alcohols then the betaine described in ref 1, the reaction is again limited to primary and secondary alcohols.
(5) A mixture of *cis*- and *trans*-3-chlorocrotonic acid prepared by a modification of the procedure of Jones et al. (Jones, D. E.; Morris, R. O.; Vernon, C. A.; White, R. F. M. *J. Chem. Soc.* **1960**, 2349) was used. A mixture of PCl_5 in benzene was treated with 0.5 molar equiv of ethyl acetoacetate at 25 °C for 14 h followed by 7.5 molar equiv of water for 24 h. The benzene layer was separated and the crude product was sublimed (45–50 °C, 4 mm); 43% yield.
(6) Under these conditions, Claisen rearrangement of the carboxylates of **2** apparently occurs followed by decarboxylation to the corresponding enolates. These enolates are protonated, although the proton source is not certain, and ketones distill from the reaction mixture in a high state of purity.
(7) Denmark, S. E.; Harmata, M. A. *J. Am. Chem. Soc.* **1982**, *104*, 4972.

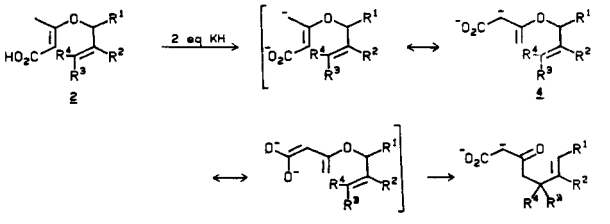
0022-3263/85/1950-4664$01.50/0

Table I

entry	starting material	chloroacid used 1 or 5	yield of 2 or 6%	Method[a]	product[b]	yield %
a		1	81	A		46
				B		58
		5	ref. c	B		38
b		1	76	A		50
				B		68
		5	ref. c	B		38[d]
c		1	90	A		68
		5	86	A		48
d		1	84	A		78
		5	59	A		40
e		1	70	A		78
				B		51
f		5	96	A		48
		5	ref. c	B		54[d]

[a] Method A. A solution of 2 or 6 in ether was treated with 1 equiv of sodium hydride followed by removal of solvent. Upon heating to 200–215 °C (at 15 mm in a Kugelrohr apparatus, the product distilled from the reaction mixture. Method B. A solution of 2 or 6 in toluene was treated with 2 equiv of potassium hydride and heated to 120 °C for 2–6 h. Following acidification and aqueous workup, the isolated material was heated at 15 mm until decarboxylation occurred and the products distilled. [b] Products were identified by IR, ^1H and ^{13}C NMR, high resolution MS, and spectral comparison with the corresponding aldehydes.[1] [c] Method B can be practiced in one pot. A solution of the alcohol in toluene was treated with 2.2 equiv of potassium hydride followed by 1.15 equiv of 3-chloro-2-hexenoic acid. After being heated to 65 °C for 4 h, an additional equivalent of potassium hydride was added, and the mixture was heated at 120 °C for an additional 2–6 h. Workup in the usual manner gave the products. Yields refer to overall yields from allylic alcohols to γ,δ-unsaturated ketones. [d] The product was a mixture of two diastereomers.

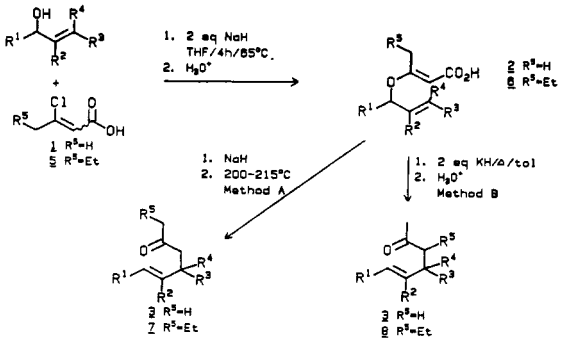
temperature.[8] In an effort to utilize this principle the (allyloxy)crotonic acids **2** were treated with *2* equiv of



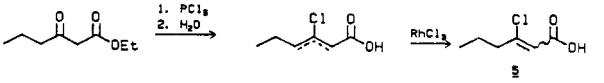
potassium hydride in toluene at 120 °C, followed by acidification and decarboxylation (method B). (Allyloxy)crotonates derived from primary allylic alcohols were

(8) Wilson, S. R.; Price, M. F. *J. Org. Chem.* 1984, *49*, 722.

Scheme I



Scheme II



stable under these conditions,[9] but those originating from secondary alcohols rearranged within a few hours and after hydrolysis and decarboxylation yielded ketones **3** identical with those prepared by method A (Scheme I). The rearrangement appears to occur within the dianion **4** leading to a dianion of a β-keto carboxylic acid. In agreement with this assumption exposure of the crotonic acids **2** to **1** equiv of potassium hydride in refluxing toluene caused no rearrangement.

In order to extend the usefulness of this method, 3-chloro-2-hexenoic acid (**5**) was prepared by treatment of ethyl butyrylacetate with phosphorus pentachloride followed by hydrolysis to a mixture of α,β- and β,γ-unsaturated acids which could be isomerized to a mixture of *cis*- and *trans*-3-chloro-2-hexenoic acids with rhodium chloride (Scheme II).[10] Claisen rearrangement of adducts **6** as their sodium carboxylates (method A) was predicted to yield propyl ketones while the corresponding dianion rearrangements (method B) should give α′-ethyl methyl ketones **8** (Scheme I). Experimental results presented in Table I confirmed the predictions.

Acknowledgment. This work was supported by the National Institutes of Health (Grant GM 09863), a National Research Service Award (No. 2T 32CA09112) from the National Cancer Institute, and Hoffmann-LaRoche, Inc., Nutley, NJ.

(9) Claisen rearrangements of ester enolates derived from primary allylic alcohols were found to rearrange much more slowly than those of the corresponding secondary alcohols (Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* 1976, *98*, 2868). Analogous observations were made by Denmark in ref 7.

(10) The isomeric mixture of 3-chloro-2- and -3-hexenoic acids was obtained in 49% yield by a method analogous to that described for 3-chlorocrotonic acid.[5] The material was rearranged to a mixture of *cis*- and *trans*-3-chloro-2-hexenoic acid in 40% yield by heating in *tert*-butyl alcohol–H_2O (10:1) with $RuCl_3 \cdot 3H_2O$ (10% by weight) at 70 °C for 12 h. The product was purified by distillation (85–95 °C, 1 mm).

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