under these conditions when **1** is dissolved in CD_3OD in the absence of base. The base-catalyzed proton exchanges presumably occur by deprotonation of the 2- or 5-position followed by rapid deuterium transfer from the CD_3OD solvent to give the deuterated product.

In order to probe the possibility that basic sites on Al_2O_3, used as a support in catalytic HDS studies, would facilitate exchange of surface protons with **1**, we prepared Al_2O_3 with surface OD groups by stirring γ-alumina[18] with D_2O for 1 day. After filtration and drying in vacuo for 16 h at room temperature, the powder (300 mg) was added to a solution of **1** (20 mg) in 0.5 mL of CD_2Cl_2; most of the complex adsorbed to the alumina. After 2 h, the CD_2Cl_2 was decanted and **1** was extracted from the Al_2O_3 with Me_2SO-d_6.[19] A ^1H NMR spectrum of the Me_2SO-d_6 solution indicated that approximately 10% of the 2,5-positions in **1** had been deuterated. Thus, surface OD groups on Al_2O_3 are capable of exchanging deuterium with adsorbed $[(\eta\text{-}C_4H_4S)Ru(\eta\text{-}C_5H_5)]BF_4$; this exchange is probably catalyzed by basic oxygen groups on the Al_2O_3 surface.

Others have explained[12,13] the preferential exchange of the 2,5-protons on HDS catalysts by assuming that thiophene adsorbs to the surface via the S atom only; this form of attachment places the 2,5-protons near the catalyst surface. There are, however, no model studies that support such an exchange mechanism. The results reported herein suggest that a more likely mechanism involves π-bound thiophene. By forming a π-complex with the transition metal of the catalyst, the thiophene would be susceptible to deprotonation by basic sites on the Al_2O_3 or MoS_2 which would facilitate exchange with OD or SD groups present on the catalyst surface.

(18) Alumina, Grade E, Test No. 52452, Ketjen Catalysts, Armak Catalysts Div., Pasadena, TX.

(19) **1** does not undergo deuteration in CD_2Cl_2 or Me_2SO-d_6 and no deuteration of **1** was observed when undeuterated Al_2O_3 was used.

Total Synthesis of (-)-Upial

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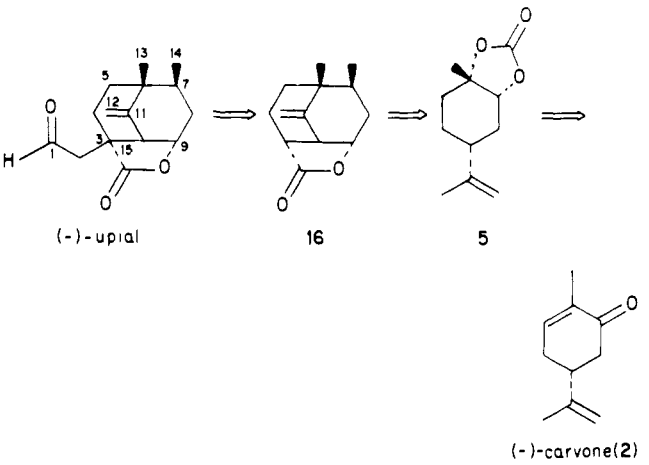
In 1979, Scheuer and co-workers isolated (+)-upial (**1**) from the Kaneohe Bay, Oahu, sponge *Dysidea fragilis*. Upial was found to be a nonisoprenoid sesquiterpene aldehyde lactone that contained the rare bicyclo[3.3.1]nonane skeleton. Its structure was assigned on the basis of elemental composition and spectral properties of the natural product and a number of degradation products. A large portion of evidence comes from the high-field NMR spectrum of upial and a lanthanide-induced-shift study of the $NaBH_4$ reduction product, upiol.[1] The structural assignment has yet to receive confirmation by X-ray crystallography or total synthesis. In this report we wish to delineate the *enantioselective* synthesis of (-)-upial. The synthesis, which is efficient and stereocontrolled, serves to confirm for the *first time* the structural assignment, as well as establish the absolute configuration for upial.

In our strategic analysis, we envisioned upial as ultimately being derivable from one of the carvones. We chose the less expensive (-)-carvone (**2**), since at the time we initiated our assault on this architechturally unique sesquiterpene the absolute configuration was unknown.[2]

Our synthesis (Scheme I) begins with the reductive alkylation of (-)-carvone (**2**) with ethyl bromoacetate utilizing the lithium–bronze conditions[3] to give an inseparable mixture of keto esters



3a and **3b** (83:17, respectively).[4,5] The mixture of esters was hydrolyzed to the keto acids **4a** and **4b**. Ketone reduction[6] and lactonization afforded lactone **5** [53% overall from **2**, $[\alpha]_D$ -9.0° (c 47.6, $CHCl_3$)].[5,7]

With lactone **5** in hand, we turned our attention to the introduction of the C14 methyl group (upial numbering system). We planned to take advantage of the concave–convex nature of lactone **5** and utilize the known propensity for reagents to add to the convex face of such systems.[7a] To this end, the lithium enolate of **5** was generated (LDA/THF) and alkylated with CH_3I to furnish the monomethylated lactone **6** as a single isomer [$[\alpha]_D$ 22.4° (*c* 50.0, $CHCl_3$)].[5,8]

Having controlled the relative configuration between the C13 and C14 methyls, we set about to elaborate lactone **6** into the bicyclic hydroxy ketone **10**. This was most effectively accomplished by first reducing lactone **6** to diol **7**.[5,9] A double-Swern oxidation[10] (2.2 equiv) transformed diol **7** into the sensitive keto aldehyde **8**, which was immediately subjected to the homologation reaction. Selective homologation of the aldehyde was accomplished by treating keto aldehyde **8** with (methoxymethylene)triphenylphosphorane[11,12] (1.05 equiv) to afford enol ether **9**[5] as mixture of double-bond isomers. Hydrolysis of the enol ethers was accompanied by concomitant intramolecular aldol cyclization[13] to furnish the hydroxy ketone **10** [mp 109–110 °C, $[\alpha]_D$ +67 (*c* 36.1, $CHCl_3$)].[5,14]

After assembling the bicyclo[3.3.1]nonane ring system,[15] some minor cosmetic surgery was required to transform the appropriately placed functionality on the bicyclic skeleton for ultimate conversion to tricyclic lactone **16**. The hydroxy ketone **10** was reacted with 2.5 equiv of CH_3MgBr to provide diol **11** [mp 139–140 °C, $[\alpha]_D$ +3.83° (*c* 30.0, $CHCl_3$)].[5] It was anticipated that the stereochemistry of the newly introduced methyl group

(1) Schulte, G.; Scheuer, P. J.; McConnel, O. J. *J. Org. Chem.* **1980**, *45*, 552.

(2) Personal Communication from Prof. P. J. Scheuer.

(3) Mueller, R. H.; Gillick, J. G. *J. Org. Chem.* **1978**, *43*, 4647.

(4) Similar ratios of alkylated products derived from carvone have been observed. (a) Reference 3. (b) Gassman, P. G.; Gilbert, D. P.; Cole, S. M. *J. Org. Chem* **1977**, *42*, 3233.

(5) All new compounds gave spectral data and C, H combustion analyses in accord with the structures given.

(6) Huffman, J. W.; Charles, J. T. *J. Am. Chem. Soc.* **1968**, *90*, 6486.

(7) The diastereomeric trans hydroxy acid was also isolated (11% overall from **2**). For similar findings, see: (a) Welch, S. C.; Gruber, J. M.; Chou, C.-Y.; Willcott, M. R.; Inners, R. J. *J. Org. Chem.* **1981**, *46*, 4816. (b) Marshall, J. A.; Cohen, J.; Hochstetler, A. R. *J. Am. Chem. Soc.* **1966**, *88*, 3408.

(8) We thank Prof. S. C. Welch for the generous exchange of experimental details and comparison spectra.

(9) Micovic, V. M.; Mihailovic, M. L. *J. Org. Chem.* **1958**, *18*, 1190.

(10) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

(11) Levine, S. G. *J. Am. Chem. Soc.* **1958**, *80*, 6150.

(12) The phosphorane was generated using LDA as the base.

(13) Corey, E. J.; Pearce, H. L. *J. Am. Chem. Soc.* **1979**, *101*, 5841.

(14) The $\nu_{C=O}$ for **10** was 1705 cm^{-1}. The 15-cm^{-1} reduction from the normal 1720-cm^{-1} absorption (see ref 1) is attributable to intramolecular hydrogen bonding. Also, the ^1H NMR of the acetate derived from **10** revealed the carbinyl proton as a broad singlet with a width at half-height of ~9 Hz. This is commensurate with the configurational assignment given to **10**.

(15) For other bicyclo[3.3.1]nonane syntheses, see: Schultz, A. G.; Dittami, J. P. *J. Org. Chem.* **1983**, *48*, 2318 and references therein.

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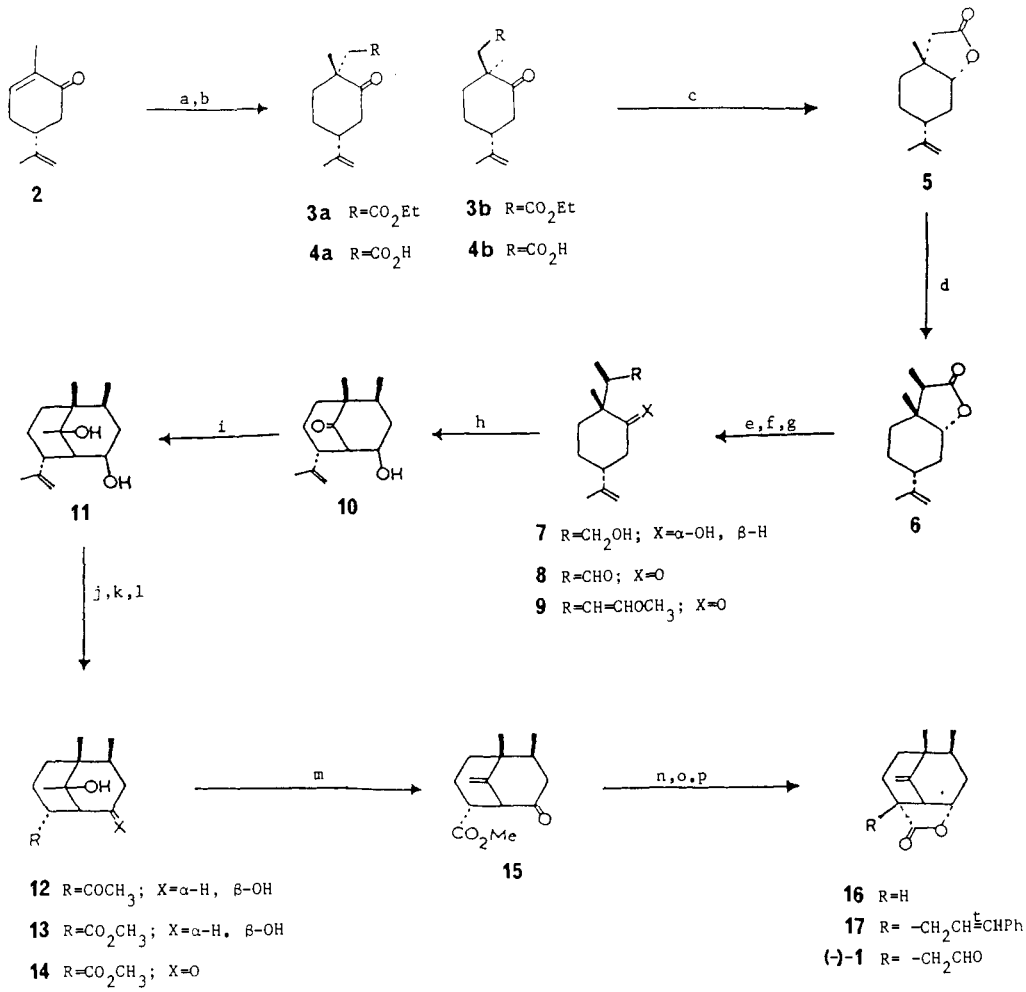
Scheme I[a]



[a] (a) Li·4NH$_3$, *t*-BuOH, BrCH$_2$CO$_2$Et (80%); (b) 3 M KOH, EtOH; (c) (i) Li, NH$_3$, EtOH, (ii) PTSA, benzene, 25 °C; (d) LDA, CH$_3$I (83%); (e) LiAlH$_4$, Et$_2$O (99%); (f) ClCOCOCl, Me$_2$SO, Et$_3$N (99%); (g) Ph$_3$P=CHOCH$_3$, THF (71%); (h) 10% HCl, THF/DME (5:1), 25 °C (70%); (i) 2.5 equiv of CH$_3$MgBr, Et$_2$O, 0 °C (95%); (j) OsO$_4$, NaIO$_4$ (75%); (k) KOCl, CH$_3$OH, 0 °C (87%); (l) ClCOCOCl, Me$_2$SO, Et$_3$N (95%); (m) SOCl$_2$, pyridine, 0 °C (82%); (n) NaCNBH$_3$, THF, AcOH, HCl (75%); (o) LDA, THF, HMPA, *t*-PhCH=CHCH$_2$Br (64%); (p) OsO$_4$/NaIO$_4$ (70%).

would result from the addition of the Grignard reagent to the least hindered face of the C11 carbonyl (upial numbering system), that being the one opposite the axial C14 methyl and C9 hydroxyl groups.[16] Our attention was now focused on the conversion of the isopropenyl side chain to a carboxyl group of one form or another. We had envisioned a simple, two-step sequence involving a haloform reaction of the methyl ketone derived from an ozonolytic-type cleavage of the isopropenyl group to be the most direct method for such a transformation.[17] The olefin was cleaved with OsO$_4$/NaIO$_4$[18] to furnish methyl ketone **12** [mp 123–124 °C, $[\alpha]_D$ −51 (*c* 22.6, CHCl$_3$)].[5] After a number of attempts, using a variety of conditions to effect the desired haloform reaction, it was found that treatment of **12** with aqueous KOCl[19] in CH$_3$OH[20] at 0 °C resulted in direct formation of methyl ester **13** [mp 128 °C, $[\alpha]_D$ −1.91° (*c* 18.3, CHCl$_3$)].[5] The synthesis of **16** was completed by first performing a Swern oxidation[10] (2.2 equiv) to afford ketone **14** [mp 134 °C, $[\alpha]_D$ +45° (*c* 14.4, CHCl$_3$)].[5] This was followed by dehydration[21] of the tertiary alcohol to give alkene **15** [mp 76–78 °C, $[\alpha]_D$ −34 (*c* 2.50, CHCl$_3$)].[5] Reduction (NaCNBH$_3$, THF, ACOH, HCl)[22] of the ketone led to the direct formation of tricyclic lactone **16** [mp 48 °C, $[\alpha]_D$ +22 (*c* 0.90, CHCl$_3$)].[5]

All that remained for realization of the final goal was the introduction of the acetaldehyde appendage. Our plan was to introduce the side chain via alkylation of the lactone enolate, using cinnamyl bromide as our acetaldehyde synthon. Thus, deprotonation of **16** (2.2 equiv of LDA/THF/HMPA) and reaction with cinnamyl bromide (2.2 equiv) provided the alkylated lactone **17** [$[\alpha]_D$ 43.9 (*c* 1.95, CHCl$_3$)].[5] Treatment of **17** with OsO$_4$/NaIO$_4$ resulted in selective cleavage of the styryl double bond and formation of (−)-upial (**1**) [$[\alpha]_D$ −37 (*c* 1.50, CHCl$_3$)].[23] The IR, high-field NMR (400 mHz), and high-resolution mass spectra of synthetic upial were identical with those kindly provided to us by Professor Scheuer.

In summary, the first enantioselective total synthesis of (−)-upial has been realized. Based on the known absolute configuration

(16) An internal methylenedioxy derivative of **11** was synthesized by an independent route and hydrolyzed back to diol **11**, thus confirming our stereochemical prediction. The details of this will be reported in our full account of this work.

(17) A somewhat longer sequence for a similar transformation has been reported, see: McGuirk, P. R.; Collum, D. B. *J. Org. Chem.* **1984**, *49*, 843.

(18) Pappo, R.; Allen, D. S.; Lemieux, R. U.; Johnson, W. S. *J. Org. Chem.* **1956**, *21*, 478.

(19) Harding, K. E.; Clement, K. S.; Gilbert, J. C.; Weichman, B. *J. Org. Chem.* **1984**, *49*, 2049.

(20) Arnold, R. T.; Buckles, R.; Stoltenberg, J. *J. Am. Chem. Soc.* **1944**, *66*, 208.

(21) Allen, W. S.; Bernstein, S. K. *J. Am. Chem. Soc.* **1955**, *77*, 1028.

(22) Borch, R. F.; Durst, H. D. *J. Am. Chem. Soc.* **1969**, *91*, 3996.

(23) The reported rotation for (+)-upial is $[\alpha]_D$ +92.6° (*c* 0.27, CHCl$_3$); see ref 1. We have reduced synthetic upial to upiol (NaBH$_4$, EtOH) and reacted it with (−)-α-metoxy-α-[(trifluoromethyl)phenyl]acetyl chloride to afford the (−)-MTPA ester. The MTPA ester appeared to be isomerically pure by ^{13}C, ^{19}F, and ^{1}H NMR.

(24) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

of (−)-carvone, the absolute configuration of the natural product should be opposite of that shown (vide supra). The highly stereocontrolled synthesis proceeded in 17 steps from (−)-carvone in 3.5% overall yield (average yield/step 82%) without the use of protecting groups. Studies are currently under way to improve the sequence as well as to investigate the isopropenyl to ester conversion and will be reported in due course.

Acknowledgment. We thank Professors Leo Paquette and David Hart of The Ohio State University for their assistance in obtaining some of the optical rotations. We also thank Dr. Dick Weisenburger of The Ohio State University Chemical Instrument Center for the high-resolution mass spectrum of (−)-upial. In addition, we thank Everett Santee for aid in obtaining the high-field NMR spectral data and the NSF (Grant DMR-82-194454) for funds for the 400-MHz spectrometer. Lastly, we acknowledge Professors P. J. Scheuer and S. C. Welch for the exchange of experimental and spectral data.

Anionic Oxy-Claisen Rearrangement of Enolates of α-Allyloxy Ketones. A Remarkable Rate-Accelerating Effect Exhibited by the Nature of the Counterion

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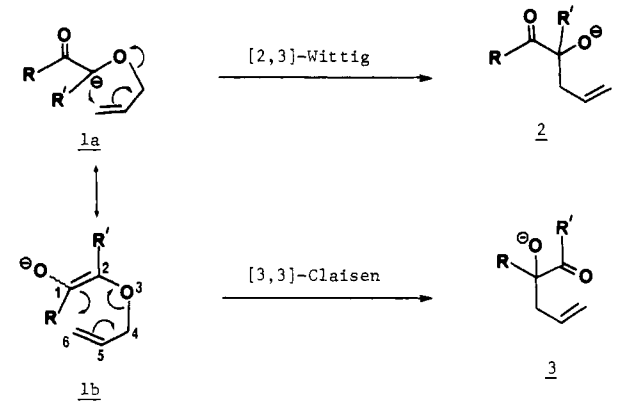
Sigmatropic rearrangements have proven to be powerful, invaluable tools in the stereo- and regiochemically controlled synthesis of a wide range of natural products.[1] In recent years, considerable attention has been focused on substituent effects of these reactions as variants that lead to milder conditions and improved stereoselective outcome.[2] Concurrent to these synthetic investigations, there have been a number of theoretical studies which attempt to correlate the nature of the substituent effect with the mechanism of the sigmatropic reaction.[3] We wish to report herein a potentially highly versatile, novel type of Claisen rearrangement, termed an *anionic oxy-Claisen rearrangement*, utilizing enolates of α-allyloxy ketones, that proceeds at strikingly low temperatures. Furthermore, the reaction was found to be dramatically influenced by the counterion and the solvent employed.

The enolates of α-allyloxy ketones present an intriguing case where two competing modes of sigmatropic rearrangement processes are conceivable (Scheme I). Thus, of the two resonance forms of these enolates, **1a** may be envisioned as an α-(allyloxy) α-carbanion which is capable of undergoing a [2,3]-Wittig rearrangement to give rise to α-alkoxy ketone **2**.[4] Whereas **1b** may

Scheme I



Scheme II

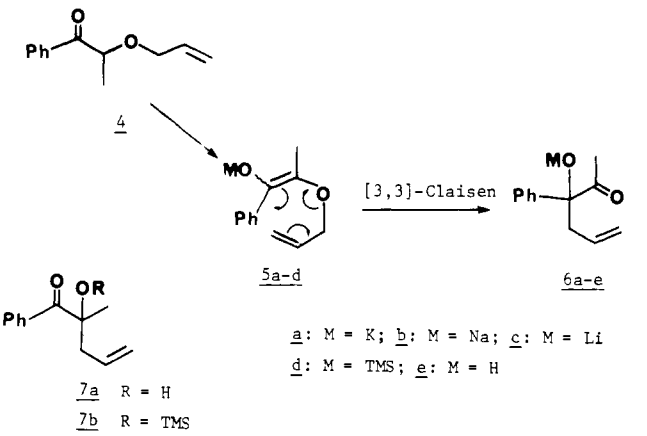


Table I. Results of [3,3]-Claisen Rearrangements of Enolates **5a–c** and Silyl Enol Ether **5d**[a]

entry	solvent	compd	temp, °C	half-life ($t_{1/2}$), h[b]
1	toluene	**5a**, M = K	−23	3.3
2	toluene	**5b**, M = Na	0	2.6
3	toluene	**5c**, M = Li	96.5	1.1
4	toluene	**5d**, M = Me_3Si	71	0.5
5	THF	**5a**, M = K	−42	6.2
6	THF	**5a**, M = K	−23	<0.1
7	THF	**5b**, M = Na	−23	2.4
8	THF	**5c**, M = Li	67	1.3

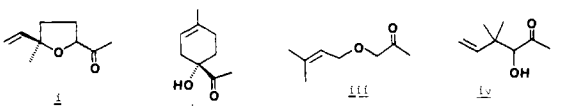
[a] All the reactions were carried out at 0.025 M concentration of substrates by treatment with 15 equiv of metal hydride and 10 equiv of methanol. [b] Times listed for **5a–c** refer to half-lives derived from the first-order rate constants obtained in the range of 10–90% conversion of **4**. All the reactions of **5a–c** except for entry 6 were preceded by an induction period (0.5–1.5 h) which is believed to account for the generation of the enolates from **4**.

(1) (a) Desimoni, G.; Tacconi, G.; Barco, A.; Pollini, G. P. *ACS Monogr.* **1983**, *180*. For reviews on [3,3]-sigmatropic rearrangements, see: (b) Rhoads, S. J.; Raulins, N. R. *Org. Reac. (N. Y.)* **1975**, *22*, 1. (c) Bennett, G. B. *Synthesis* **1977**, 589. (d) Ziegler, F. E. *Acc. Chem. Res.* **1977**, *10*, 227. (e) Lutz, R. P. *Chem. Rev.* **1984**, *84*, 205. For a review on [2,3]-sigmatropic rearrangements, see: (f) Hoffman, R. W. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 563. For mechanistic studies of sigmatropic rearrangements, see: (g) Gajewski, J. "Hydrocarbon Thermal Isomerizations"; Academic Press: New York, 1981.

(2) Electron-donor substituents at carbons 1, 2, and 6 have an accelerating effect on the Claisen rearrangement. 1-Donor: (a) Barluenga, J.; Aznar, F.; Liz, R.; Bayod, M. *J. Chem. Soc., Chem. Commun.* **1984**, 1427. 2-Donor: (b) Felix, D.; Gschwend-Steen, K.; Wick, A. E.; Eschenmoser, A. *Helv. Chim. Acta* **1969**, *52*, 1030. (c) Johnson, W. S.; Werthemann, L.; Bartlett, W. R.; Brocksom, T. J.; Li, T.; Faulkner, D. J.; Petersen, M. R. *J. Am. Chem. Soc.* **1970**, *92*, 471. (d) Ireland, R. E.; Mueller, R. H. *J. Am. Chem. Soc.* **1972**, *94*, 5897. (e) Denmark, S. E.; Harmata, M. A. *J. Am. Chem. Soc.* **1982**, *104*, 4972. (f) Ponaras, A. A. *J. Org. Chem.* **1983**, *48*, 3866. 6-Donor: (g) Curran, D. P.; Suh, Y.-G. *J. Am. Chem. Soc.* **1984**, *106*, 5002. (h) Childers, W. E., Jr.; Pinnick, H. W. *J. Org. Chem.* **1984**, *49*, 5276. 1,2-Bisdonor: (i) Ager, D. J.; Cookson, R. C. *Tetrahedron Lett.* **1982**, *23*, 3419. (j) Sato, T.; Tajima, K.; Fujisawa, T. *Tetrahedron Lett.* **1983**, *24*, 729. Both electron-acceptor and electron-donor substituents at carbon 3 accelerate the Cope rearrangement: (k) Breslow, R.; Hoffman, J. M., Jr. *J. Am. Chem. Soc.* **1972**, *94*, 211. (l) Evans, D. A.; Golob, A. M. *J. Am. Chem. Soc.* **1975**, *97*, 4765.

(3) (a) Carpenter, B. K. *Tetrahedron* **1978**, *34*, 1877. (b) Burrows, C. J.; Carpenter, B. K. *J. Am. Chem. Soc.* **1981**, *103*, 6983, 6984. (c) Delbecq, F.; Anh, N. T. *Nouv. J. Chim.* **1983**, 505. (d) Gajewski, J. J. *Acc. Chem. Res.* **1980**, *13*, 142. (e) Gajewski, J. J.; Gilbert, K. E. *J. Org. Chem.* **1984**, *49*, 11. (f) Gajewski, J. J.; Emrani, J. *J. Am. Chem. Soc.* **1984**, *106*, 5733.

(4) Two examples of [2,3] Wittig rearrangement of the enolates of acetonyl allyl ethers to 3-hydroxy 5-en-2-ones have been reported by Thomas and Dubini (Thomas, A. F.; Dubini, R. *Helv. Chim. Acta* **1974**, *57*, 2084). Thus treatment of ketone i with Grignard reagents or potassium tert-butoxide



resulted in the formation of compound ii. Although in this particular example the corresponding [3,3]-Claisen rearrangement is not feasible due to the rigidity of the system, the authors extended the method to the acyclic ketone iii. The reaction of iii with potassium *tert*-butoxide gave iv (product of [2,3] rearrangement) as the only isolable product.

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