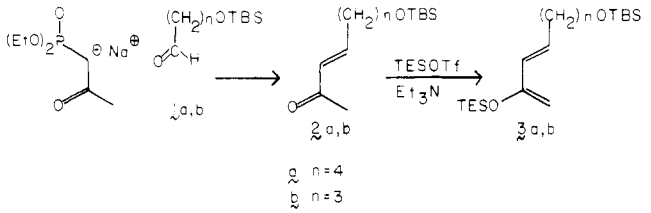
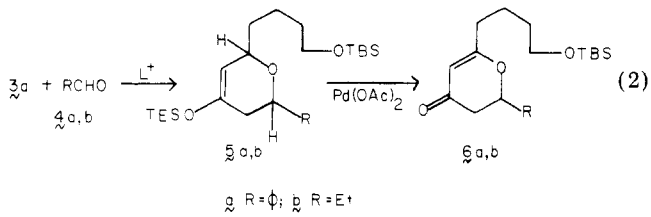


(1)

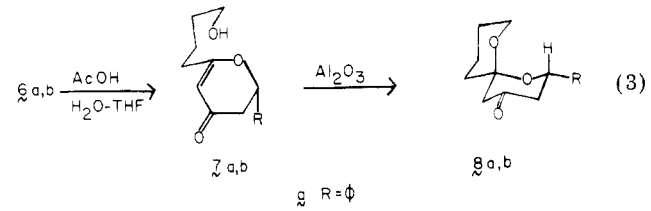
quantities of $Yb(fod)_3$[12] in chloroform suffice to promote cycloaddition. The crude adduct **5a** thus generated was oxidized with palladium acetate in acetonitrile[13] to afford dihydro-γ-pyrone **6a**.[8] The overall yield from the zinc chloride method was 72%, while that via the $Yb(fod)_3$ method was 75%. In these runs, intermediate **5a** was not fully characterized. In a separate run using $Yb(fod)_3$, compound **5a** was purified by silica gel chromatography, though only in 61% yield. Reaction of pure **5a** with palladium acetate as above gave an 84% yield of **6a** (eq 2). Similarly, reaction of diene **3a** with propionaldehyde



(2)

using zinc chloride catalysis afforded silyloxy dihydropyran **5b**, which on oxidation with palladium acetate afforded **6b**[8a] in 76% yield.

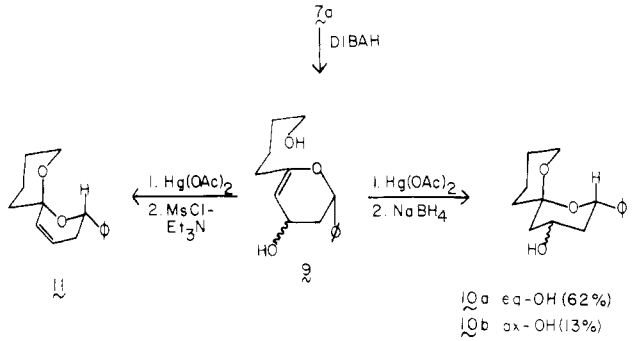
Desilylation of **6a** and **6b** was accomplished by using aqueous acetic acid in tetrahydrofuran. Surprisingly, compounds **7a**[8a] and **7b**,[8a] obtained in 93% and 74% yields, respectively, showed no tendency for spontaneous cyclization. Attempts at cyclization using strong acids were unrewarding. However, exposure of a chloroform solution of either **7a** or **7b** to neutral alumina[14] resulted in the formation of spiroketals **8a**[8] and **8b**[8a] in yields of 82% and 80%, respectively (eq 3). In these cyclizations, only a



(3)

single diastereomer is obtained. While the axial disposition of the methine protons in **8a** and **8b** could be established by NMR methods, the actual assignment of relative configurations relies on precedent.[4b]

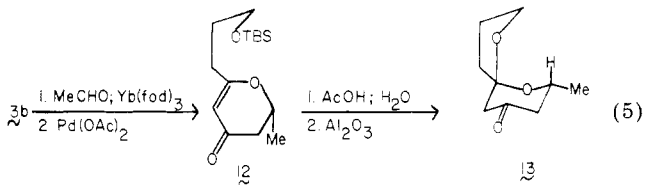
With an eventual aim toward the avermectins, other formats for spirocyclization were examined. Reduction of **7a** with DIBAH gave an 86% yield of diols **9** (eq 4).[15] Intramolecular oxymercuration[16] followed by reduction of the mercurial with sodium borohydride gave, after silica



(4)

gel chromatography, the epimers **10a**[8a] and **10b**[8a] in the indicated isolated yields.[17] When the intermediate mercurial is treated with mesyl chloride in the presence of triethylamine,[18] it suffers smooth conversion to **11**,[8a] most promising in planning a synthesis of avermectin B_{1a}.[6]

Similarly, diene **3b** reacts with acetaldehyde in chloroform under catalysis by $Yb(fod)_3$. The intermediate silyl enol ether was oxidized with palladium acetate to provide a 57% overall yield of **12**.[8a] Desilylation (80%) and alumina-induced Michael-type spirocyclization (56%) afforded **13**,[8a] again as a single isomer (eq 5).



(5)

Enlargement upon these findings and the application of this new chemistry to the synthesis of milbemycin/avermectin targets are matters of continuing interest in our laboratory.

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Supplementary Material Available: Experimental procedures for all reactions and spectral and analytical data (14 pages). Ordering information is given on any current masthead page.

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(12) $Yb(fod)_3$ = Tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)ytterbium. For the $Eu(fod)_3$-mediated hetero-Diels–Alder reaction, see: Bednarski, M.; Danishefsky, S. *J. Am. Chem. Soc.* **1983**, *105*, 3716. In the present work, $Yb(fod)_3$ catalysis allowed shorter reaction times and provided higher yields than $Eu(fod)_3$.

(13) Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011.

(14) Posner, G. H. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 487.

(15) (a) Ferrier-type rearrangement[15b] of **9** under a variety of conditions gave mixtures of **10a** and **11**. For example, treatment of **9** with 5 mol % of *p*-TsOH in benzene at room temperature gave **10a** (49%) and **11** (38%) with no detectable amount of **10b**. (b) Ferrier, R. J. *J. Chem. Soc.* **1964**, 5443.

(16) Negishi, E.-I. "Organometallics in Organic Synthesis"; Wiley-Interscience: New York, 1980; Vol. 1, pp 463-467.

(17) The ratio of **10a** to **10b** presumably reflects the ratio of equatorial to axial alcohols **9** formed in the reduction of **7a**.

(18) For a related oxymercuration–deoxymercuration sequence, where the oxymercuration was carried out in the intermolecular mode, see: Remy, G.; Cottier, L.; Descotes, G. *Can. J. Chem.* **1983**, *61*, 434.

A New Variant of the Claisen Rearrangement Capable of Creating the Bond between Two Quaternary Centers

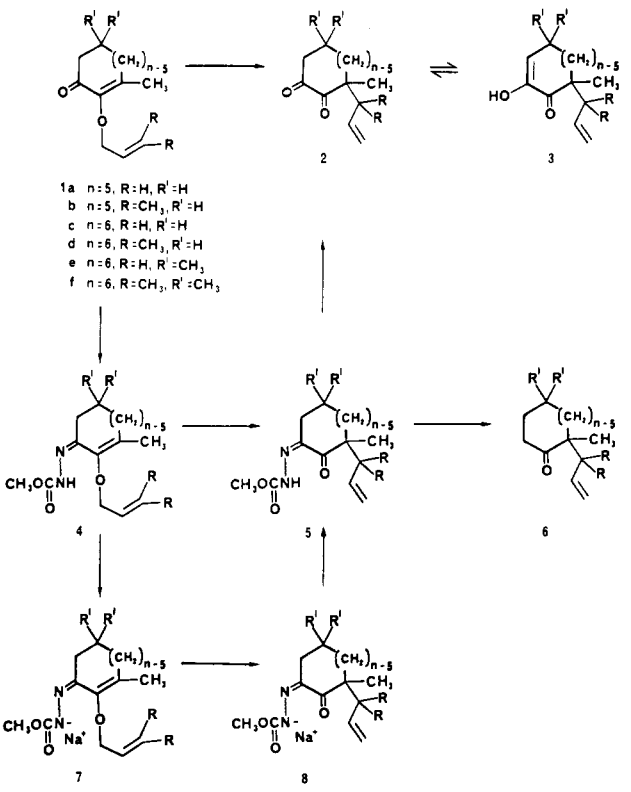
Summary: An anion-accelerated Claisen rearrangement capable of producing very crowded carbon–carbon bonds is described.

Sir: Thermal rearrangement of diosphenol allyl ethers[1] (e.g., **1** → **2** → **3**) is a useful method for effecting *regiocontrolled*[1a] cycloalkenyl allyl ether Claisen rearrangements. There are, however, two significant limitations to this procedure: (i) the rearrangement is rather slow, especially when compared to some other variants of the Claisen rearrangement[2] (at the temperatures necessary to effect rearrangement to very crowded centers (150–250 °C), side reactions such as aromatization or deallylation can occur) and (ii) the two carbonyl groups produced by the rearrangement cannot always be distinguished in the course of further synthetic elaboration. We describe here a simple modification of substrate that solves these problems.

It has been known for 100 years[3] that *mono* oximes, hydrazones, and other donor-imine[4] derivatives of α-dicarbonyl compounds are very stable, presumably due to electron donation from the donor atom into the adjacent carbonyl group. This fact suggested that Claisen rearrangement of donor-imine functionalized diosphenol allyl ethers would be facile. We have investigated this possibility and find that, indeed, diosphenol allyl ether oximes, hydrazones, and their alkyl and acyl derivatives rearrange considerably faster (and usually in better yield) than the parent carbonyl compound. More importantly from a synthetic point of view, very crowded C–C bonds can be created by means of this modification and the functionality produced by the rearrangement can be elaborated in several useful ways.[5,6]

In this initial disclosure we report on results in six simple carbocyclic systems **a**–**f** (Scheme I), where the stereochemical course of rearrangement is not an issue, using *carbomethoxyhydrazones* and their sodium salts;[7] in future publications we will report our studies with more complex systems and with other donor-imine groups and their anions.

Scheme I



Half-lives[8] and yields[9] for rearrangement of ca. 0.2 M solutions of **1**, **4**, and **7** under various conditions are listed in Table I.[10]

Inspection of the table shows three trends:

(1) A 6- to 31-fold rearrangement rate increase is produced by derivatization, and a further 15- to 145-fold increase is produced upon deprotonation. In the one case where **7** has been directly compared to **1**, **7c** rearranges over 200 times faster than does **1c** (in THF). Alternatively, one may compare temperatures necessary to effect rearrangement. For example, rearrangement of **7b** at 66 °C occurs at a comparable rate to (but in better yield than) rearrangement of **1b** at 178 °C.

(2) Allyloxy systems rearrange faster than prenyloxy systems in all cases, as would be expected from steric considerations, but the allyl/prenyl rate ratios for **4** and **7** are rather small.[11] It is noteworthy that the prenyloxy systems give complete allylic inversion in both branches, demonstrating that these are true [3,3] rearrangements.[12]

(3) Hydroxylic solvents promote the rearrangement of **4**, and, in general, heating **4** in methanol–water is the most convenient route to **5**. Rearrangement of very crowded systems is best effected by heating the anion **7** in an aprotic solvent.[13]

(1) (a) Ponaras, A. A. *Tetrahedron Lett.* **1980**, *21*, 4803. (b) Dauben, W. G.; Ponaras, A. A.; Chollet, A. *J. Org. Chem.* **1980**, *45*, 4413. (c) Ponaras, A. A. *Tetrahedron Lett.* **1983**, *24*, 3.

(2) The best known variant is the ester enolate Claisen rearrangement: (a) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868. For a discussion of some other rapid Claisen rearrangements, see: (b) Denmark, S. E.; Harmata, M. A. *J. Am. Chem. Soc.* **1982**, *104*, 4972.

(3) (a) Fischer, E.; Jourdan, F. *Ber.* **1883**, *16*, 2241. (b) Fischer, E.; Ach, F. *Justus Liebigs Ann. Chem.* **1889**, *253*, 57. (c) Hershberg, E. B. *J. Org. Chem.* **1948**, *13*, 542.

(4) We coin the term "donor-imine" group in order to unite oximes, hydrazones, and their derivatives, functional groups that are usually considered as separate classes of compounds. The common structural feature, a donor group attached to imino nitrogen, causes polarization in the sense opposite to that of the parent carbonyl group.

(5) α-Oximino ketones have been used extensively for ring cleavage through Beckmann fragmentation and for ring contraction via the Forster reaction followed by photolysis: (a) Conley, R. T.; Ghosh, S. In "Mechanisms of Molecular Migrations"; Thyagarajan, B. S., Ed.; Wiley-Interscience: New York, 1971; Vol. 4, p 233. (b) Kataoka, M.; Ohno, M. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 3474. (c) Redmore, D.; Gutsche, C. D. *Adv. Alicyclic Chem.* **1971**, *3*, 1. (d) Scribner, R. M. In "Organic Reactions in Steroid Chemistry"; Fried, J., Edwards, J. H., Eds.; Wiley-Interscience: New York, 1972; Vol. 2, p 408.

(6) A variety of functional group transformations are possible for α-keto hydrazones and their equivalents: (a) Szmant, H. H.; Harnsberger, H. F.; Butler, T. J.; Barie, W. P. *J. Am. Chem. Soc.* **1952**, *74*, 2724 and references therein. (b) Rosenblum, M.; Nayak, V.; DasGupta, S. K.; Longroy, A. *Ibid.* **1963**, *85*, 3874. (c) Regitz, M. In "The Chemistry of the Diazonium and Diazo Groups"; Patai, S., Ed.; Wiley-Interscience: Chichester, England, 1978; Vol. 2, p 751. (d) Daniil, D.; Merkle, U.; Meier, H. *Synthesis* **1978**, 535.

(7) Carbomethoxyhydrazones **4** were prepared by stirring a 1 M solution of the diosphenol allyl ether in anhydrous Me_2SO with 2 equiv of methyl carbazate and 1 equiv of fumaric acid for 24 h at 25–40 °C. The predominant isomer (syn) was isolated in pure form by filtration chromatography and crystallization from diisopropyl ether and used for the quantitative studies. For preparative purposes it is convenient to use the crude product (containing >90% yield of **4**), since both isomers rearrange. We defer discussion of syn/anti isomerism for the full paper. The anions **7** were generated with 1 equiv of sodium hydride.

(8) The term "half-life" is used in this communication to mean the time that it takes for one-half of the substrate to disappear, regardless of its fate. The values reported here were determined by VPC and/or NMR and are accurate to about 20%.

(9) Yields were measured when 90–95% of the starting material had been consumed.

(10) All new compounds were fully characterized by NMR, IR, and HRMS as well as by the chemical transformations indicated. Ketones **6a** and **6c** have been prepared bydirect alkylation: (a) Asselin, A. A.; Humber, L. G.; Dobson, T. A.; Komlossy, J.; Martel, R. R. *J. Med. Chem.* **1976**, *19*, 787. (b) House, H. O.; Manning, D. T.; Melillo, D. G.; Lee, F. L.; Haynes, O. R.; Wilkes, B. E. *J. Org. Chem.* **1976**, *41*, 855. We have also prepared **6a** through benzilic acid rearrangement of **3c** (see ref 1a).

(11) Examples of terminal substitution *increasing* the rate of anionic Claisen rearrangement have been noted (see ref 2) and are in accord with theoretical predictions: Burrows, C. J.; Carpenter, B. K. *J. Am. Chem. Soc.* **1981**, *103*, 6983, 6984.

(12) For a discussion of alternative pathways, see: Arnold, R. T.; Kulenović, S. T. *J. Org. Chem.* **1980**, *45*, 891.

0022-3263/83/1948-3867$01.50/0

Table I. Comparison of Half-Lives (h) for 1, 4, and 7 (Yields in Parentheses)

system	solvent	T, °C	1	4	7
a	THF	66		30	"4" (80[a,b])
a	HMPA	66		20	0.3 (70[a])
a	MeOH	66		4 (95[a])	
a	MeOH	111[c]	4 (83[a])		
a	toluene	111	16 (90[a])	0.7	
b	THF	66			2.2 (87[a])
b	HMPA	66		145	1.0 (83[a])
b	methanol-water, 1:1	79		0.4 (95[a])	
b	methoxyethanol	125		0.5 (90[a])	
b	methanol	132[c]		0.1 (80[a])	
b	chlorobenzene	132	25 (88[d])	0.8 (85[a])	
b	o-dichlorobenzene	178	1.5 (68[a])		
c	THF	66	340	22	1.5 (85[a])
c	methanol	66	90	15 (91[a])	
c	methanol-water, 1:1	79		0.8 (84[a])	
c	toluene	111	6	0.8	
d	THF	66			9 (86[a])
d	methanol-water, 1:1	79		2.5 (55[a])	
d	methanol	132[c]		0.8	
d	dioxane	101			0.5 (85[a])
d	chlorobenzene	132	"50" (45[d,e])	1 (45[a])	
e	THF	66		72	3 (88[a])
e	methanol	66		40 (87[a])	
e	methanol-water, 1:1	79		3 (95[a])	
e	chlorobenzene	132	4 (90[d])	0.3 (88[a])	
f	THF	66			15 (85[a])
f	HMPA	66			5.5 (80[a])
f	methanol-water, 1:1	79		4 (45[a])	
f	methoxyethanol-water, 1:1	102		0.5 (45[a])	
f	N-methylmorpholine	115			0.3 (85[a])
f	methanol	132[c]		0.8 (<10[a])	
f	chlorobenzene	132		1 (<5[a])	
f	o-dichlorobenzene	178	"15" (<2[d,f])		

[a] Isolated yield. [b] The anomalously long half-life is probably due to poor solubility of 7a in THF. [c] Sealed tube. [d] VPC yield. [e] See ref 19. [f] See text.

This reaction can be used to create very crowded bonds, including those between two quaternary carbons.[14,15] A striking illustration of this application is seen in the extremely crowded system **f** where Claisen rearrangement must create a severe 1,3-diaxial interaction in addition to two contiguous quaternary centers. Indeed, Claisen rearrangement of **1f** is not only unsuccessful but also contrathermodynamic (vide infra). Rearrangement of **7f**, on the other hand, proceeds in 85% yield. Hydrolysis[16] of the product gives a separable mixture[17] of **2f** and **3f**. When heated at 178 °C in an o-dichlorobenzene solution, **2f** is converted to a 3:1 mixture of **1f** and **3f**[18] within 5 min and completely (>95%) to **1f** in 90 min.[18] The process **2f** → **1f** represents one of the few known cases of aliphatic retro-Claisen rearrangement[20] and is the first example of the direction of a Claisen rearrangement being reversed by a change of functional groups.

A particularly useful product transformation[6] is Wolf–Kishner reduction under rather mild conditions.[6a] Thus, for example, treatment of **5** with 5 equiv of sodium hydroxide in boiling 2-methoxyethanol (120 °C) for 30 min furnishes **6** in 50%, 88%, 60%, 60%, 80%, and 90% yields from **5a–f**, respectively. It is noteworthy that α-allyl-α-alkylcycloalkanones cannot be obtained free of their α,-α′-isomers by cracking α-alkylcycloalkanone diallyl ketals[21] (the usual cycloalkenyl allyl ether Claisen rearrangement procedure[22]) and, furthermore, that ketones such as **6b**, **6d**, and **6f**, with the inverted prenyl substituent, are inaccessible by alkylation of ketones.[23]

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(13) Rearrangements of **7** are only slightly faster in HMPA than in THF, implying that **7** is significantly dissociated in the latter solvent. We have also noted that the potassium salts of **4** offer no significant rate advantages over the sodium salts. For another type of anionic [3,3] sigmatropic rearrangement where solvent and counterion effects are extremely important, see: Evans, D. A.; Golob, A. M. *J. Am. Chem. Soc.* **1975**, *97*, 4765.

(14) For a review on methodology for the construction of quaternary carbon centers, see: Martin, S. F. *Tetrahedron* **1980**, *36*, 419.

(15) There are very few reactions capable of creating the bond between two quaternary centers (see ref 14).

(16) Carbomethoxyhydrazones were hydrolyzed in the presence of formaldehyde (1 mL of 37% aqueous formaldehyde, 1 mL of 1 M aqueous perchloric acid, and 2 mL of acetic acid per mmol of carbomethoxyhydrazone, 24 h at room temperature). This is a modification of the method of Cava et al. (Cava, M. P.; Litle, R. L.; Napier, D. R. *J. Am. Chem. Soc.* **1958**, *80*, 2257), substituting perchloric acid for hydrochloric acid in order to supress deprenylation of the product diosphenol.

(17) Keto enol equilibria are established extremely slowly for α-diketones: Schwarzenbach, G.; Wittwer, C. *Helv. Chim. Acta* **1947**, *30*, 663.

(18) Diosphenol **3f** is half-converted to **1f** after 1 h in boiling o-dichlorobenzene, presumably via ketonization[17] to **2f**. The monoketone **6f** is stable under these conditions.

(19) Similarly, rearrangement of **1d** is complicated by the establishment of an equilibrium mixture of **1d** and **3d** and, at temperatures above about 140 °C, by deprenylation (forming 2-hydroxy-3-methyl-2-cyclohexenone). A chlorobenzene solution of **1d** heated for 100 h at 132 °C gives a 45% yield of **3d** (with 30% **1d** remaining).

(20) Bourelle-Wargnier, F.; Vincent, M.; Chuche, J. *J. Chem. Soc., Chem. Commun.* **1979**, 584 and references therein.

(21) Except for ketals derived from simple allylic alcohols, the synthesis of diallyl ketals is not practical.

(22) Lorette, N. B.; Howard, W. L. *J. Org. Chem.* **1961**, *26*, 3112.

(23) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 96.