the desired acyclic precursor 8[13] (80%) as a yellow oil after Florisil chromatography (20% EtOAc/CH_2Cl_2).[14] Dieckmann cyclization of **8** (2 equiv of potassium *tert*-butoxide/THF/−78 °C) followed by acid treatment (2 N HCl/THF/4 h) yielded the fully substituted and oxygen-differentiated benzofuran **9** (75%) as a yellow solid (mp 159.7–160.5 °C). Methylation (CH_3I/K_2CO_3/18-crown-6/PhH/Δ) of **9** yielded the highly versatile benzofuran intermediate **3** (90%).[15] Baeyer–Villiger oxidation (2.1 equiv, *m*-CPBA/2-propanol/16 h/room temperature) of **3** followed by a basic workup (10% aqueous Na_2CO_3/ether/30 min/room temperature) yielded the known hydroxy ester **10** (63%).[16] Conversion of **10** to khellinone was then achieved through the addition of methylmagnesium bromide (6 equiv) to **10** in the presence of triethylamine (17 equiv) in benzene (8–10 °C/6.5 h)[17]. The yield in this final step was 54%. The overall yield of khellinone from **7** was 12%.

This synthesis represents several important advances with respect to furochromone synthesis and particularly analogue synthesis. This new approach (furan → benzofuran → furochromone) to furochromone construction dealt very effectively with the assemblage of the fully substituted B ring and with the oxygen differentiation problems encountered in earlier syntheses of khellin. Furthermore, because of the extremely short route and method of benzofuran construction (furan → benzofuran), this synthesis represents a practical and flexible route that can accommodate changes in either early or late stages of the synthesis.

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Registry No. **1**, 82-02-0; **2**, 484-51-5; **3**, 87145-68-4; **5**, 87145-69-5; **6**, 108-30-5; **7**, 488-93-7; **8**, 87145-70-8; **9**, 87145-71-9; **10**, 87145-72-0; DMF–DMA, 4637-24-5.

Supplementary Material Available: Experimental procedures and spectral and analytical data for compounds **2**, **3**, **5**, **8**, **9**, and **10** (5 pages). Ordering information is given on any current masthead page.

(12) The amide acetal reactions carried out at room temperature for 3 days or less returned substantial amounts (20–30%) of the starting keto diester. Those reactions carried out at higher temperatures were more complex and rarely yielded starting material. We have also found that treatment of a mixture of **5** and *N,N*-dimethylformamide dimethyl acetal in refluxing THF with potassium *tert*-butoxide (25 mol %) likewise yields **8**. However, on scaleup (50–100-g scale), the acid-catalyzed reaction is superior. On a 10–20-mmol scale the base-catalyzed reaction works well (70–76%).

(13) Silica gel TLC, R_f 0.4 (5% CH_3OH/EtOAc); UV_{max} (EtOH) 260 nm (ε 9600), 309 (ε 13 650); IR ν_{max} ($CHCl_3$) 3000, 2950, 1725, 1640, 1560, 1430, 1405, 1390, 1320, 1160 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.45 (d, 1 H, J = 2 Hz), 6.95 (s, 1 H, vinyl proton), 6.73 (d, 1 H, J = 2 Hz), 3.82 (s, 3 H, OCH_3), 3.68 (s, 5 H, OCH_3, CH_2), 3.07 (s, 6 H, $N(CH_3)_2$); ^{13}C NMR ($CDCl_3$) δ 183.61, 173.21, 163.17, 156.87, 155.38, 142.26, 117.08, 111.01, 104.84, 52.00, 51.78, 43.53, 29.94 ppm. Anal. Calcd ($C_{14}H_{17}NO_6$) C, H, N.

(14) Compound **8** slowly hydrolyzes on silica gel. On basic or neutral Woelm alumina, it is virtually destroyed.

(15) Silica gel TLC, R_f 0.44 (5%; EtOAc/$CHCl_3$); mp 89.9–90.8 °C; UV_{max} (EtOH) 209 nm (ε 15 550), 232 (ε 21 500), 282 (ε 12 350), 334 (ε 6250); IR ν_{max} ($CHCl_3$) 1730, 1680, 1600, 1470, 1440, 1390, 1340, 1305, 1290, 1060, 980, 930 cm^{-1}; ^1H NMR ($CDCl_3$) δ 10.4 (s, 1 H, aldehyde), 7.83 (d, 1 H, J = 2 Hz), 6.97 (d, 1 H, J = 2 Hz), 4.38 (s, 3 H, OCH_3), 3.98 (s, 6 H, OCH_3). Anal. Calcd ($C_{13}H_{12}O_6$) C, H.

(16) Musante, C. *Gazz. Chim. Ital.* **1958**, *88*, 910.

(17) Kikkawa, I.; Yorifuji. *Synthesis* **1981**, 877.

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A New Strategy for the Synthesis of Spiroketals

Summary: The syntheses of various 1-(ω-hydroxyalkyl)-dihydropyran derivatives and their spirocyclizations are described.

Sir: The cyclocondensation of activated conjugated dienes with aldehydes, under the influence of Lewis acids, has broad possibilities for the synthesis of various oxygen heterocycles[1] and acyclic arrays which can be derived by disconnection of such rings.[2] Recently, in probing the range of feasibility of this reaction, it was found that cycloaddition can be realized with dienes bearing a carbon substituent at the 1-position and a silyloxy function at carbon 3 of the diene.[3] Thus, 1,3-dioxygen substitution[1] is not a sine qua non for the success of this reaction. It was of some interest to investigate the possibility that hetero-Diels–Alder processes might provide a new route to spiroketals.[4] The antiparasitic capabilities of the milbemycins[5] and the avermectins,[6] as well as the antibiotic properties of the polyether ionophores,[7] underscore the importance of gaining ready and versatile access to the spiroketal moieties of such systems. A new approach to this problem is described herein.

(Triethylsilyl)oxy dienes **3a**,[8a] and **3b**[8a] used in this study, were obtained (ca. 90%) from the reaction of the enones **2** with triethylsilyl triflate in the presence of triethylamine in ether.[9] The enones are easily prepared from the ω-(silyloxy) aldehydes **1**[10] by a Wadsworth–Emmons process (eq 1).[11]

Cyclocondensation of diene **3a** with benzaldehyde or propionaldehyde could be carried out at room temperature by using several Lewis acids. With benzaldehyde, either zinc chloride (ca. 1 equiv) in tetrahydrofuran or catalytic

(1) Danishefsky, S.; Kerwin, J. F., Jr.; Kobayashi, S. *J. Am. Chem. Soc.* **1982**, *104*, 358.

(2) Danishefsky, S.; Larson, E. R.; Askin, D. *J. Am. Chem. Soc.* **1982**, *104*, 6457.

(3) Harvey, D. F.; Uang, B.-J.; Quallich, G., unpublished results from these laboratories.

(4) (a) Evans, D. A.; Sacks, C. E.; Kleschick, W. A.; Taber, T. R. *J. Am. Chem. Soc.* **1979**, *101*, 6789. Martinez, G. R.; Grieco, P. A.; Williams, E.; Kanai, K.; Srinivasan, C. V. *Ibid.* **1982**, *104*, 1436. Baker, R.; Herbert, R. H.; Parton, A. H. *J. Chem. Soc., Chem. Commun.* **1982**, 601. Williams, D. R.; Barner, B. A. *Tetrahedron Lett.* **1983**, *24*, 427. Ireland, R. E.; Daub, J. P. *J. Org. Chem.* **1983**, *48*, 1303 and references therein. (b) Evans, D. A.; Sacks, C. E.; Whitney, R. A.; Mandel, N. G. *Tetrahedron Lett.* **1978**, 727. Deslongchamps, P.; Rowan, D. D.; Pothier, N.; Sauvé, T.; Saunders J. K. *Can. J. Chem.* **1981**, *59*, 1105.

(5) For recent syntheses of milbemycin β_3, see: Smith, A. B., III; Schow, S. R.; Bloom, J. D.; Thomson, A. S.; Winzenberg, K. N. *J. Am. Chem. Soc.* **1982**, *104*, 4015. Williams, D. R.; Barner, B. A.; Nishitani, K.; Phillips, J. G. *Ibid.* **1982**, *104*, 4708.

(6) Albers-Schönberg, G.; Arison, B. H.; Chabala, J. C.; Douglas, A. W.; Eskola, P.; Fisher, M. H.; Lusi, A.; Mrozik, H.; Smith, J. L.; Tolman, R. L. *J. Am. Chem. Soc.* **1981**, *103*, 4216. Springer, J. P.; Arison, B. H.; Hirshfield, J. M.; Hoogsteen, K. *Ibid.* **1981**, *103*, 4221.

(7) (a) For a review, see: Wierenga, W. "The Total Synthesis of Natural Products", ApSimon, J., Ed.; Wiley-Interscience: New York, 1981; Vol. 4, pp 263–351. (b) For syntheses of monensin: Fukuyama, T.; Akasaka, K.; Karenewsky, D. J.; Wang, C.-L. J.; Schmid, G.; Kishi, Y. *J. Am. Chem. Soc.* **1979**, *101*, 262. Collum, D. B.; McDonald, J. H., III; Still, W. C. *Ibid.* **1980**, *102*, 2121.

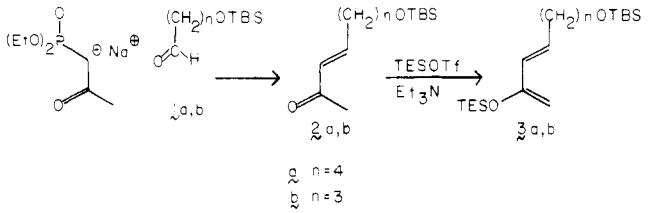
(8) (a) This compound exhibited satisfactory NMR, IR, and mass spectral data. (b) This compound gave a satisfactory carbon–hydrogen combustion analysis. For full experimental details and spectral data for all compounds described in this paper, see supplementary material.

(9) Emde, H.; Domsch, D.; Feger, H.; Frick, U.; Götz, A.; Hergott, H. H.; Hofmann, K.; Kober, W.; Krägeloh, K.; Oesterle, T.; Steppan, W.; West, W.; Simchen, G. *Synthesis* **1982**, 1.

(10) Aldehydes **1a** and **1b** were prepared from 1,5-pentanediol and 1,4-pentanediol, respectively, by silylation (1.1 equiv of *t*-$BuMe_2SiCl$, 1.2 equiv of NEt_3, catalytic DMAP in CH_2Cl_2) followed by oxidation (1.5 equiv of PCC in CH_2Cl_2). Full details may be found in the supplementary material.

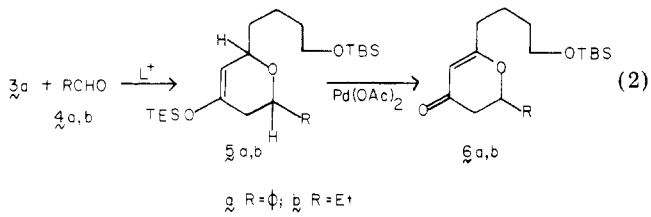
(11) Wadsworth, W. S.; Emmons, W. D. *J. Am. Chem. Soc.* **1961**, *83*, 1733. Crandall, J. K.; Mayer, C. F. *J. Org. Chem.* **1970**, *35*, 3049.

0022-3263/83/1948-3865$01.50/0



(1)

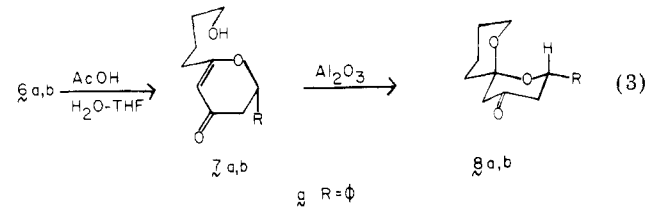
quantities of $Yb(fod)_3$[12] in chloroform suffice to promote cycloaddition. The crude adduct **5a** thus generated was oxidized with palladium acetate in acetonitrile[13] to afford dihydro-γ-pyrone **6a**.[8] The overall yield from the zinc chloride method was 72%, while that via the $Yb(fod)_3$ method 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.

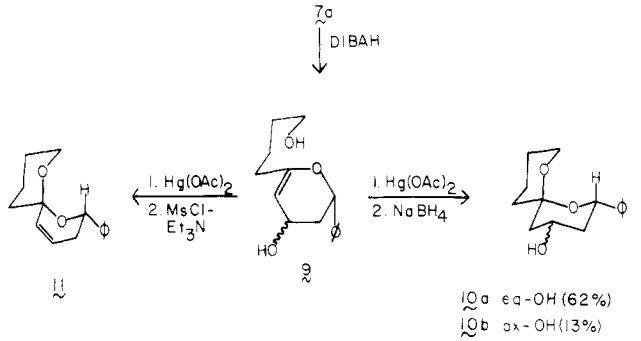
Desilylation of **6a** and **6b** was accomplished by using aqueous acetic acid in tetrahydrofuran. Surprisingly, compounds **7a**[8a] and **7b**,[8a] obtained in 93% and 74% yields, respectively, showed no tendency for spontaneous cyclization. Attempts at cyclization using strong acids were unrewarding. 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]

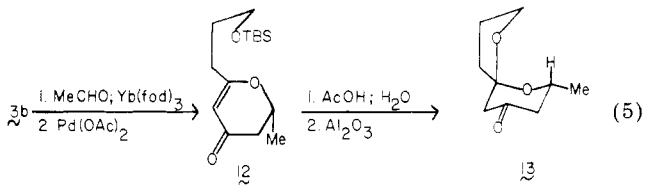
With an eventual aim toward the avermectins, other formats for spirocyclization were examined. Reduction of **7a** with DIBAH gave an 86% yield of diols **9** (eq 4).[15] Intramolecular oxymercuration[16] followed by reduction of the mercurial with sodium borohydride gave, after silica



(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.