Synthesis and Reactions of Derivatives of 1,7-Dioxaspiro[5.5]undec-2-en-4-one

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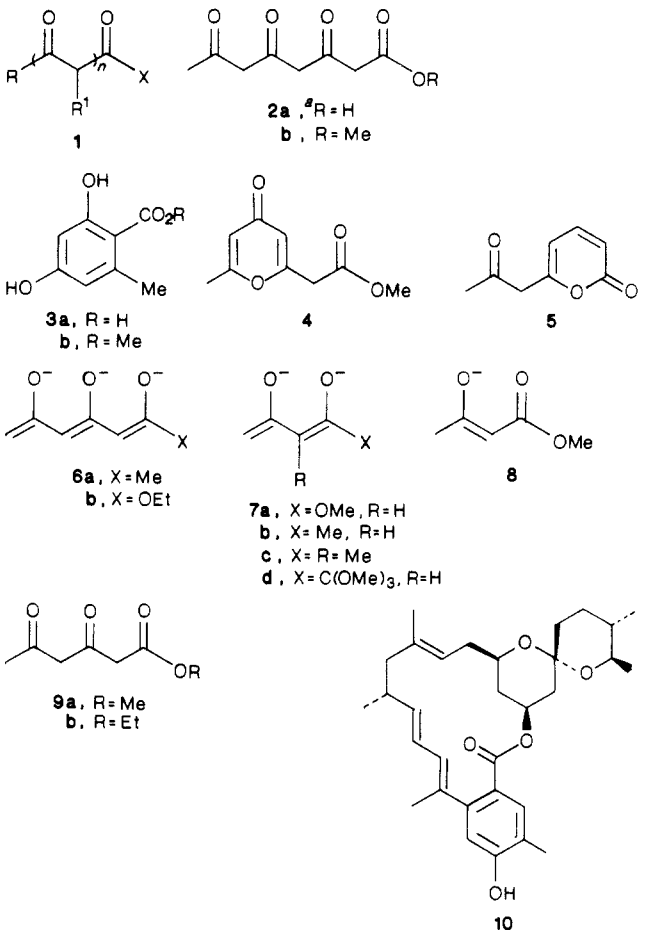
Received March 4, 1986

2,4-Pentanedione was reacted sequentially with lithium diisopropylamide and tetrahydro-2-pyranone (**11a**) to produce 2-methyl-1,7-dioxaspiro[5.5]undec-2-en-4-one (**13a**). The reaction was extended to the condensation reactions of 3-methyl-2,4-pentanedione, 1-phenyl-1,3-butanedione, and 1-(benzyloxy)-2,4-pentanedione with **11a** and of 1-(2,4,6-trimethoxyphenyl)-1,3-butanedione and ethyl 3,5-dioxohexanoate with 5,6-(5*RS*,6*SR*)-dimethyltetrahydro-2-pyranone (**11b**) to produce the corresponding spirodihydropyrones **13b**, **15**, **16**, and **18**. Reduction of these adducts with $LiAlH_4$, $LiAlH_4$–$AlCl_3$, H_2–Adams catalyst, or H_2–Pd/C was used to synthesize the spiroketals **21**, **23**, **26**, and **29**. Alternatively, the reaction of **13a** with lithium diisopropylamide and benzaldehyde stereospecifically gave the aldol adduct **24**. These studies are relevant to the syntheses of the avermectins and milbemycins.

The polyketides are a group of structurally diverse natural products biosynthetically derived from acetate, propanoate, etc., via the intermediacy of poly-β-keto compounds **1**. Harris,[1] Weiler,[2] and others have prepared several simple aromatic polyketides via a most elegant biomimetic strategy. For example, Harris has reported that 3,5,7-trioxooctanoic acid (**2a**) readily cyclized to produce orsellinic acid (**3a**) at pH 5. Alternatively, cyclization of **2a** gave **4** (50%) using methanolic sulfuric acid or **5** (66%) using acetic anhydride. The acyclic precursor **2a** was readily prepared from 2,4,6-heptanetrione via metalation with lithium diisopropylamide and subsequent carboxylation of the intermediate trianion **6a**. Alternatively, Weiler generated methyl 3,5,7-trioxooctanoate (**2b**) by the condensation of dianion **7a** with monoanion **8**. The triketo ester **2b** was readily cyclized by using methanolic sodium acetate to produce methyl orsellinate (**3b**) (50%) or with methanolic sulfuric acid to produce pyrone **4** (50%). The crucial step in all this chemistry is the generation of a poly-β-carbonyl polyanion, for example, **6a** or **7a**, its functionalization by an electrophile at the terminal carbon, and subsequent selective cyclization. The general utility of these species is underscored by one further example. Weiler observed that dianion **7a**, preferentially generated from methyl acetoacetate and sodium hydride followed by *n*-butyllithium, reacted with methyl acetate to produce methyl 3,5-dioxohexanoate (**9a**) (71%).

Several years ago we became interested in synthetic studies in the milbemycin[3] and avermectin[4] area. These natural products are intriguing both from a structural viewpoint and on account of their intense insecticidal and anthelmintic activities. Milbemycin β_3 (**10**) is the simplest member of the series and total syntheses of this molecule have been reported by Smith,[5] Williams,[6] Baker,[7] Kocienski,[8] and Barrett.[9] In addition, synthetic studies directed toward total synthesis of the avermectins or milbemycins have also been published.[10,11] As part of our

Chart I



[a] For simplicity poly-β-keto compounds are depicted as the nonenolized tautomers.

(1) Harris, T. M.; Harris, C. M. *Tetrahedron* **1977**, *33*, 2159.
(2) Huckin, S. N.; Weiler, L. *Can. J. Chem.* **1974**, *52*, 1343.
(3) Takiguchi, Y.; Mishima, H.; Okuda, M.; Terao, M.; Aoki, A.; Fukuda, R. *J. Antibiot.* **1980**, *33*, 1120. Mishima, H.; Ide, J.; Muramatsu, S.; Onu, M. *Ibid.* **1983**, *36*, 980 and references therein.
(4) Fisher, M. H. "The Avermectins" in *Recent Advances in the Chemistry of Insect Control*; Janes, N. F., Ed.; The Royal Society of Chemistry Special Publication No. 53, London, 1985; p 53 and references therein.
(5) Smith, A. B., III; Schow, S. R.; Bloom, J. D.; Thompson, A. S.; Winzenberg, K. N. *J. Am. Chem. Soc.* **1982**, *104*, 4015.
(6) Williams, D. R.; Barner, B. A.; Nishitani, K.; Phillips, J. G. *J. Am. Chem. Soc.* **1982**, *104*, 4708.
(7) Baker, R.; O'Mahoney, M. J.; Swain, C. J. *J. Chem. Soc., Chem. Commun.* **1985**, 1326.
(8) Street, S. D. A.; Yeates, C.; Kocienski, P.; Campbell, S. F. *J. Chem. Soc., Chem. Commun.* **1985**, 1386. Yeates, C.; Street, S. D. A.; Kocienski, P.; Campbell, S. F. *Ibid.* **1985**, 1388.
(9) Attwood, S. V.; Barrett, A. G. M.; Carr, R. A. E.; Richardson, G. *J. Chem. Soc., Chem. Commun.* **1986**, 479.

0022-3263/86/1951-4254$01.50/0

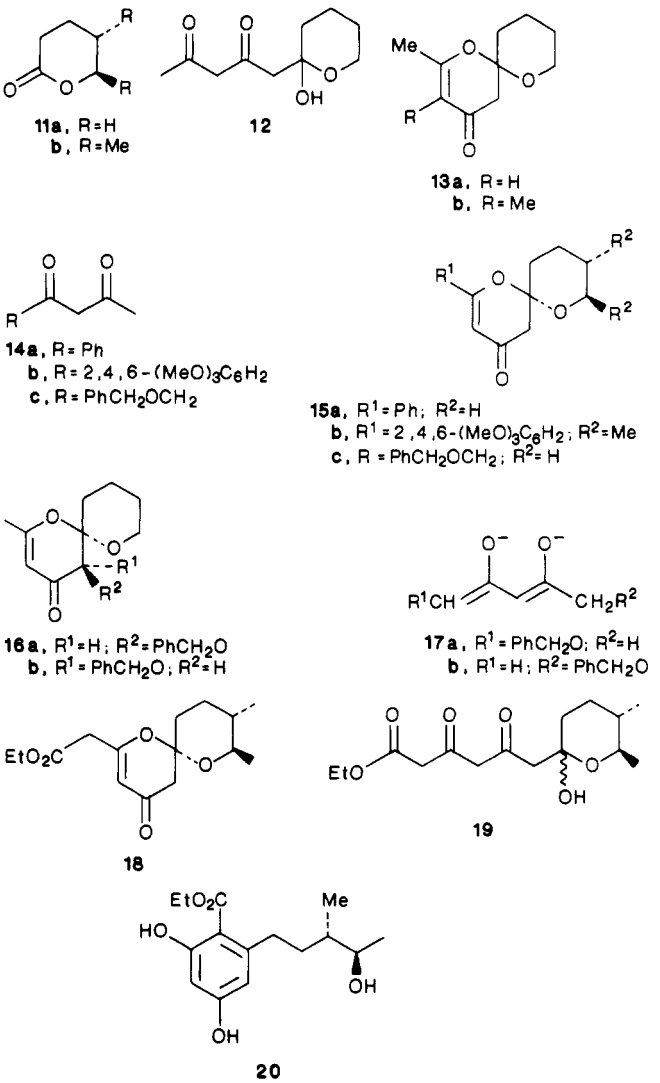
synthetic program, we examined the condensation reaction of β-diketone dianions with δ-lactones as a route to spiroketals. This chemistry, we anticipated, should be directly analogous to the Harris–Weiler acylation studies. Additionally, such an approach would mimic the partial polyketide biosynthetic origin[4] of the avermectins and milbemycins. Herein we report the preparation and reactions of 2-methyl-1,7-dioxaspiro[5.5]undec-2-en-4-one (**13a**) and related molecules.

Results and Discussion

Preparation of Spirodihydropyrones. 2,4-Pentanedione was metalated by using lithium diisopropylamide and the resultant dianion **7b**[12] condensed with tetrahydro-2-pyranone (**11a**). Acidification of the reaction mixture, which presumably contained **12**, gave the spirodihydropyrone **13a** (91%). The ^1H and ^{13}C NMR spectra of **13a** were especially informative as a means of structural elucidation. Thus, the presence of the dihydropyrone unit (^1H NMR δ 5.37 (s, 1 H, 3-*H*), 2.03 (s, 3 H, 2-*Me*); ^{13}C NMR δ 191.7 (4-*C*), 169.5 (2-*C*), 104.8 (3-*C*)) and the spirane framework (^1H NMR δ 2.53 (AB q, J = 15.4 Hz, 5-H_2); ^{13}C NMR δ 102.6 (6-*C*, spirane center)) were readily established. Additionally, the IR spectra (ν_{max} 1670, 1620 cm^{-1}) and UV spectra (λ_{max} (MeOH) 260 nm (ε 11 000)) confirmed the presence of the dihydropyrone moiety. These compare favorably with the reported spectroscopic data for 2,3-dihydro-2,2,6-trimethylpyran-4-one (ν_{max} 1675, 1618 cm^{-1} and λ_{max} (EtOH) 266nm (ε 11 800)).[13] In exactly the same way 3-methyl-2,4-pentanedione was converted into dianion **7c** which smoothly condensed with **11a** to produce the spirodihydropyrone **13b** (68%). Dianions **7** and related species have been alternatively generated with sodium hydride followed by butyllithium.[2] Thus, using this procedure ketones **14a** and **14b** were doubly metalated and respectively condensed with δ-lactones **11a** and **11b** to produce the spirodihydropyrones **15a** (50%) and **15b** (61%).

The spirodihydropyrone chemistry was also extended to more functionalized systems. Thus 1-(benzyloxy)-2,4-pentanedione (**14c**)[14] was metalated with sodium hydride

Chart II



followed by *sec*-butyllithium and the resultant dianion was condensed with δ-lactone **11a** to produce, on acidification, three isomeric spirodihydropyrones **15c** (30%), **16a** (25%), and **16b** (24%). The three isomers were readily distinguished by their respective NMR spectra: **15c** (δ 4.1 (AB q, 2 H, J = 14 Hz, 2-CH_2), 2.09 (AB q, 2 H, J = 14.5Hz, 5 H_2), **16a** (δ 3.35 (s, 1 H), 2.05 (s, 3 H)) and **16b** (δ 3.95 (s, 1 H), 2.02 (s, 3 H)). Presumably, the isomers **16** were produced via the more stable[15] dianion **17a** whereas **15c** was produced via **17b**. The ratio of **15c** to **16** was largely unchanged with variation in condensation reaction conditions: it was not possible to produce only **15c**. Ethyl 3,5-dioxohexanoate (**9b**) was reacted with lithium diisopropylamide in THF to produce the trianion **6b**. This condensed with the racemic lactone **11b**[16] to produce 18 (78%) on acidification. The spirodihydropyrone **18** was obtained as a single (racemic) diastereoisomer. Presumably, the spirocyclization was reversible and subject to thermodynamic control. Thus the formation of **18** as a single isomer resulted from an anomeric effect.[17] In the optimum preparation of **18**, it was necessary to rapidly

(10) Attwood, S. V.; Barrett, A. G. M.; Florent, J.-C. *J. Chem. Soc., Chem. Commun.* **1981**, 556. Baker, R.; Boyes, R. H. O.; Broom, D. M. P.; Devlin, J. A.; Swain, C. J. *Ibid.* **1983**, 829. Kocienski, P. J.; Street, S. D. A. *Ibid.* **1984**, 571. Godoy, J.; Ley, S. V.; Lygo, B. *Ibid.* **1984**, 1381. Williams, D. R.; Barner, B. A. *Tetrahedron Lett.* **1983**, *24*, 427. Crimmins, M. T.; Bankaitis, D. M. *Ibid.* **1983**, *24*, 4551. Baker, R.; Swain, C. J.; Head, J. "Synthetic Studies towards the Avermectins and Milbemycins" in *Recent Advances in the Chemistry of Insect Control*; Janes, N. F., Ed.; The Royal Society of Chemistry Special Publication No. 53, London, 1985; p 245. Culshaw, D.; Grice, P.; Ley, S. V.; Strange, G. A. *Tetrahedron Lett.* **1985**, *26*, 5837.

(11) Kay, I. T.; Turnbull, M. D. "Synthetic Approaches to the Avermectin Toxophore" in *Recent Advances in the Chemistry of Insect Control*; Janes, N. F., Ed.; The Royal Society of Chemistry Special Publication No. 53, London, 1985; p 229. Hanessian, S.; Ugolini, A.; Therien, M. *J. Org. Chem.* **1983**, *48*, 4427. Prashad, M.; Fraser-Reid, B.; *Ibid.* **1985**, *50*, 1566. Hughes, M. J.; Thomas, E. J.; Turnbull, M. D.; Jones, R. H.; Warner, R. E. *J. Chem. Soc., Chem. Commun.* **1985**, 755. Baker, R.; Swain, C. J.; Head, J. C. *Ibid.* **1985**, 309. Jung, M. E.; Street, L. J. *J. Am. Chem. Soc.* **1984**, *106*, 8327. Attwood, S. V.; Barrett, A. G. M.; Carr, R. A.; Finch, M. A. W.; Richardson, G. "The Application of Novel Carbanion Chemistry in Milbemycin-Avermectin Synthesis" in *Recent Advances in the Chemistry of Insect Control*; Janes, N. F., Ed.; The Royal Society of Chemistry Special Publication No. 53, London, 1985; p 257. Kozikowski, A. P.; Maloney Huss, K. E. *Tetrahedron Lett.* **1985**, *26*, 5759. Crimmins, M. T.; Lever, J. G. *Ibid.* **1986**, *27*, 291.

(12) Light, R. J.; Hauser, C. R. *J. Org. Chem.* **1960**, *25*, 538. Kirby, F. B.; Harris, T. M.; Hauser, C. R. *Ibid.* **1963**, *28*, 2266. Work, S. D.; Hauser, C. R. *Ibid.* **1963**, *28*, 725. Miles, M. L.; Harris, T. M.; Hauser, C. R. *Ibid.* **1965**, *30*, 1007. Wittek, P. J.; Hindley, K. B.; Harris, T. M. *Ibid.* **1973**, *38*, 896.

(13) Gelin, S.; Gelin, R. *Bull. Soc. Chim. Fr.* **1968**, 288.

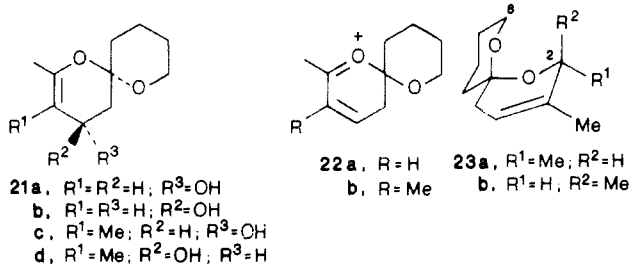
(14) Wenner, W.; Plati, J. T. *J. Org. Chem.* **1946**, *11*, 751.

(15) For a discussion on the increase of ketone acidities on substitution by a methoxy group, see: Bordwell, F. G.; Van der Puy, M.; Vanier, N. R. *J. Org. Chem.* **1976**, *41*, 1885.

(16) Cooke, E.; Paradellis, T. C.; Edward, J. T. *Can. J. Chem.* **1982**, *60*, 29.

(17) Deslongchamps, P.; Rowan, D. D.; Pothier, N.; Sauve, T.; Saunders, J. K. *Can. J. Chem.* **1981**, *59*, 1105.

Chart III



acidify the intermediate, presumably **19**. On storage or on reaction with sodium acetate **19** underwent the alternative cyclization to produce the resorcylate **20** (84%). The formation of **18** or **20** from **19** under these conditions is directly analogous to the cyclization of **2b** to produce **4** or **3**, respectively.[1]

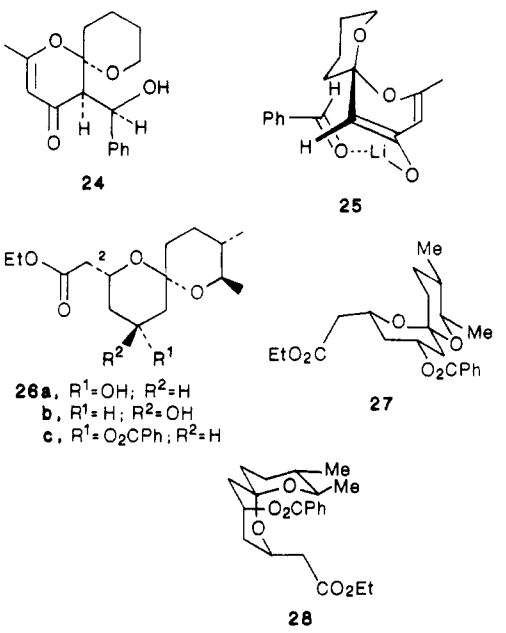
Reactions of Spirohydropyrones. Lithium aluminum hydride reduction of spirodihydropyrone **13a** gave two unstable alcohols **21a** (54%) and **21b** (27%). The two isomers were readily distinguished by NMR spectroscopy: **21a** (δ 4.85 (d, 1 H, J = 5Hz, 3-*H*), 3.81 (m, 1 H, 4-*H*)) and **21b** (δ 4.61 (broadened s, 1 H, 3-H), 4.33 (m, 1 H, 4-H)). The predominant formation of **21a** was consistent with steric approach controlled reduction. In exactly the same way lithium aluminum hydride reduction of **13b** gave the two unstable isomeric alcohols **21c** (72%) and **21d** (13%). All four alcohols **21** were unstable presumably due to facile formation of the cation **22**. Thus we sought to generate **22b** under aprotic conditions in the presence of a reducing agent. Thus sequential reaction of **13b** with lithium aluminum hydride followed by lithium aluminum hydride–aluminum chloride gave two alkenes **23a** (22%) and **23b** (7%). As an alternative procedure reduction of **13b** with lithium aluminum hydride followed by diborane and boron trifluoride etherate gave **23a** (15%) and **23b** (13%). The two isomers were readily distinguished by a difference nuclear Overhauser effect experiment. Thus, in the NMR spectrum of **23a** irradiation of 2-H (δ 4.15) resulted in an enhancement in the signal due to one of the C-8 protons (δ 3.78). In contrast irradiation of the 2-Me (δ 1.27) did not affect either of the C-8 protons. Alternatively, in the NMR spectrum of **23b** irradiation of the 2-Me (δ 1.38) resulted in an enhancement of the signal due to one of the C-8 protons (δ 4.04).

In principle it should be possible to functionalize spirodihydropyrones via enolate formation. Thus we explored the lithiation of **13a**. The spirodihydropyrone **13a** was reacted with lithium diisopropylamide followed by benzaldehyde to produce the crystalline aldol adduct **24**. Both TLC and NMR spectroscopy confirmed that the condensation reaction was highly diastereoselective in that only one product was detected. The structure of **24** was confirmed by an X-ray crystallographic study.[18] Presumably **24** was produced via the kinetic enolate and transition state **25**.

In order to transform spirodihydropyrones into spiroketals, it is necessary to reduce both Δ^2 and the ketone substituent. Since initial reduction of the carbonyl substitutent proved troublesome on account of instability of the intermediate alcohols **21**, we sought to establish conditions for the hydrogenation of the enone moiety. Hydrogenation of **18** over Adam's catalyst gave two diastereoisomeric alcohols **26a** (15%) and **26b** (8%). In spite of extensive investigation, the combined yield of these alcohols was consistently poor. Polar intractable material

(18) Raynham, T.; Taylor, S., unpublished observations.

Chart IV



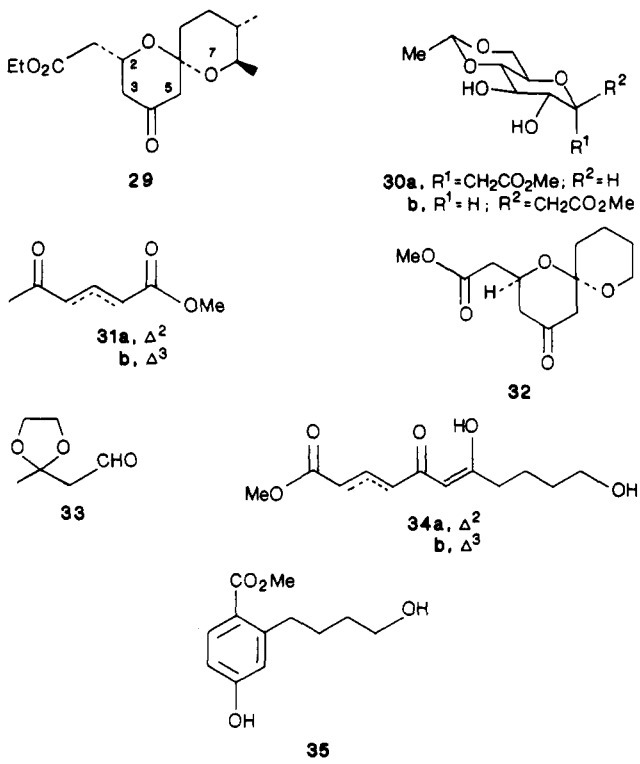
accounted for the mass balance. The stereochemistry of **26a** and **26b** was tentatively assigned on the basis of the respective NMR spectra (**26a** δ 3.95 (m, 2 H, 2-*H*, 4-*H*) and **26b** δ 4.45 (m, 1 H, 2-H), 4.30 (m, 1 H, 4-H)) and the anticipation of predominant steric approach control in the hydrogenation reaction. This assignment was unequivocally proven by interconversion and by an X-ray crystallographic study of a derivative. Thus reaction of **26b** with benzoic acid under the Mitsunobu reaction conditions[19] gave benzoate **26c** (52%). Alternatively, benzoylation of **26a** using benzoyl chloride and pyridine gave the same benzoate **26c** (84%). The structure of **26c** was confirmed by an X-ray crystallographic study.[20] This study additionally established that **26c** adopts the conformation **27** in the crystalline state. In this conformation all four substitutents are equatorial and only a single anomeric stabilization is possible. The alternative conformation **28** with double anomeric stabilization has two bulky ring substituents axial.

Hydrogenation of **18** over palladium on carbon gave the dihydro derivative **29** (56%). The structural assignment was confirmed by further reduction using sodium borohydride to produce **26a** (59%) and **26b** (15%). The predominant formation of **26a** was consistent with steric approach controlled reduction rather than control via precoordination of the reagent by the ring oxygen (O-7).

In principle compounds **26b** or **29** should be useful for milbemycin synthesis providing that the stereochemistry at C-2 is inverted. Fraser-Reid has reported an analogous epimerization reaction: the ester **30a** was readily isomerized to produce **30b** using methanolic sodium methoxide.[21] It is reasonable to assume that this conversion took place via an E_{1cb} elimination reaction followed by recyclization. However, in our hands all attempts to epimerize **26b** or **29** under basic conditions resulted in no epimerization or extensive degradation. For example, **29** underwent clean transesterification and deuteration at C-3, C-5, and α to the ester substituent on reaction with lithium methoxide-d_3 in methanol-d_4 but without epimerization.

(19) Mitsunobu, O. *Synthesis* **1981**, 1.
(20) Williams, D. J.; Imperial College, X-Ray Crystallographic Laboratory, unpublished observations.
(21) Fraser-Reid, B.; Dawe, R. D.; Tulshian, D. B. *Can. J. Chem.* **1979**, *57*, 1746.

Chart V



However, prolonged reaction resulted in degradation.

As an extension of the spirodihydropyrone chemistry, we sought to condense the dianion derived from **31** with δ-valerolactone (**11a**) as a potential route to the spiroketal **32**. The required enone-ester was obtained as a 1:1 mixture of regioisomers **31a** and **31b** by sequential reaction of **33**[22] with methyl (triphenylphosphorylidene)acetate and toluene-4-sulfonic acid in acetone. The mixture of **31a** and **31b** was smoothly dilithiated by using lithium diisopropylamide and condensed with lactone **11a** to produce the adducts **34a** and **34b** (51%). Unfortunately acidification of **34** resulted in fragmentation to regenerate lactone **11a** and the enone ester **31**. Cyclization of **34** under basic conditions resulted in formation of the anisic acid derivative **35** (86%).

Conclusion

The condensation reaction of several β-diketone dianions and the β,δ-diketo ester trianion **6b** with the δ-lactones **11a** and **11b** provides a convenient method for the preparation of the spirodihydropyrones **13**, **15**, **16**, and **18**. The adducts may be further elaborated by hydride reduction, hydrogenation, or hydroxyalkyation. Recently we have applied this chemistry in a total synthesis of (+)-milbemycin β_3 (**10**) using the condensation of (+)-lactone **11b** with dianion **7d** as a key step.[9] Clearly spirodihydropyrones are useful intermediates in synthesis.[23]

Experimental Section

Melting points were determined on a Kofler or Reichter Thermovar hotstage and are uncorrected. Ultraviolet spectra were recorded on a Unicam SP 800A ultraviolet spectrophotometer. Infrared spectra were recorded on a Perkin-Elmer 1579, 257, or 298 or a Sargent-Welch 3-100 infrared spectrophotometer. ^{1}H NMR were recorded on a Varian EM390, JOEL FT90, Bruker WM250, JOEL FT270, or Varian XL 400 spectrophotometer. NMR spectra were recorded in $CDCl_3$ with Me_4Si as the internal reference. Optical rotations were determined on a Perkin-Elmer 241 polarimeter. Microanalyses were carried out by the microanalysis laboratory at Imperial College or by Galbraith Laboratories, Knoxville, TN. Samples for microanalyses were purified by recrystallization, distillation, or, for oils, by rechromatography with extensive drying of the sample under vacuum (<0.01 mm). The mass spectra were recorded on an AEI MS12 V-G Micromass 7070B, a V-G 7070F, or a Hewlett Packard 5985B instrument or by the University of Nebraska Mass Spectrometry Service Laboratory.

Analytical and preparative thin layer chromatography was performed on Merck precoated GF_{254} silica gel or F_{254} (type E) alumina plates. Flash chromatography was carried out on either Merck Kieselgel H (type 60) silica gel or Merck Kieselgel (type 60, 230–400 mesh).

Solvents were purified as follows: PhH was distilled from sodium benzophenone ketyl onto 4-Å molecular sieves; CH_2Cl_2 was redistilled from P_4O_{10}, EtOAc and hexane (petroleum bp 40–60 °C), or pentane (petroleum bp 30–50 °C); Et_2O and THF were distilled from sodium benzophenone ketyl; EtOH and MeOH were absolute and dried by distilling from Mg; *i*-Pr_2NH was distilled from CaH_2 onto 4-Å molecular sieves. Organic solutions were routinely dried over anhydrous sodium sulfate. Solvents were evaporated at reduced pressure by using a rotary evaporator at or below 45 °C unless otherwise stated. All reactions were carried out under a nitrogen atmosphere under anhydrous conditions unless otherwise stated. Reaction temperatures were measured externally as bath temperatures.

Preparation of Lithium Diisopropylamide (LDA). To a solution of diisopropylamine (1.00 g, 9.9 mmol) in THF (20 mL) at −78 °C was added, dropwise with stirring, *n*-BuLi (1.5 M, 6.60 mL). The pale yellow solution was warmed to 0 °C and stirred for 45 min. The resulting solution of LDA was then recooled to −78 °C and used immediately.

2-Methyl-1,7-dioxaspiro[5.5]undec-2-en-4-one (13a). 2,4-Pentanedione (4 mL) was added to a solution of lithium diisopropylamide, from *i*-Pr_2NH (11.2 mL) and *n*-BuLi (1.47 M, 54 mL), in THF (200 mL) at 0 °C. After 1 h the solution was cooled to −78 °C and tetrahydro-2-pyranone (**11a**) (4 mL) was added. The solution was allowed to warm up to room temperature to provide a pale yellow suspension. After 0.5 h HOAc (9.6 mL) was added and the mixture evaporated. Aqueous Na_2SO_4 (50%, 100 mL) and Et_2O (150 mL) were added. The mixture was continuously extracted with Et_2O overnight. Evaporation gave an oil (7.5 g) which was dissolved in CH_2Cl_2 (200 mL) and $TsOH{\cdot}H_2O$ (1.0 g), and 4-Å molecular sieves (10 g) were added. After 3 h the decanted solution was washed with cold saturated aqueous $NaHCO_3$ (50 mL) and water. Evaporation of the dried CH_2Cl_2 solution and reevaporation from hexane after filtration gave **13a** (6.45 g, 91%) as a homogeneous oil (TLC, 2:1 hexane/Me_2CO). Recrystallization from hexane–Et_2O gave analytically pure material: mp 56–57 °C; IR ν_{max} ($CHCl_3$) 1720 w, 1670, 1620 cm^{-1}; UV (MeOH) λ_{max} 260 nm (ε 11 000); ^{1}H NMR (250 MHz) δ 5.37 (s, 1 H, 3-*H*), 3.72 (m, 2 H, 8-H_2), 2.53 (AB q, 2 H, J = 15.4 Hz, 5-H_2), 2.03 (s, 3 H), 2.0–1.35 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 191.71, 169.53, 104.82, 102.58, 62.63, 46.91, 33.74, 24.40, 20.87, 18.16; mass spectrum, *m/e* 182 ($M^{\cdot+}$), 167, 98 (base, retro-Diels–Alder). Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74. Found: C, 65.74; H, 7.73%.

2,3-Dimethyl-1,7-dioxaspiro[5.5]undec-2-en-4-one (13b). Following the procedure for **13a**, reaction of 3-methyl-2,4-pentanedione (11.07 g), lithium diisopropylamide (194 mmol), and tetrahydro-2-pyranone (**11a**) (9 mL) in THF (300 mL) [the yellow precipitate was stirred for 2 h at 0 °C prior to quenching with HOAc (24.6 mL) at −78 °C] gave **13b** (13 g, 68%) as an oil: IR ν_{max} (film) 1730 w, 1660, 1620 cm^{-1}; UV λ_{max} (MeOH) 272 nm (ε 6900); ^{1}H NMR (250 MHz) δ 3.69 (m, 2 H, 8-H_2), 2.56 (AB q, 2 H, J = 15.5 Hz, 5-H_2), 2.03 (s, 3 H, 2-*Me*), 1.72 (s, 3 H, 3-*Me*), 2.03–1.22 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 191.45, 164.43, 110.15, 101.06, 62.43, 46.93, 33.84, 24.49, 18.40, 18.17, 9.29; mass spectrum, *m/e* 196 ($M^{\cdot+}$), 181, 138, 98 (retro-Diels–Alder). Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.21. Found: C, 67.13; H, 8.41.

(22) Kelly, T. R.; Tsang, W.-G. *Tetrahedron Lett.* **1978**, 4457. Kelly, T. R.; Ananthasubramanian, L.; Borah, K.; Gillard, J. W.; Goerner, R. N., Jr.; King, P. F.; Lyding, J. M.; Tsang, W.-G.; Vaya, J. *Tetrahedron* **1984**, *40*, 4569.

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(6*SR*,8*RS*,9*SR*)-8,9-Dimethyl-2-(2,4,6-trimethoxyphenyl)-1,7-dioxaspiro[5.5]undec-2-en-4-one (15b). 1-(2,4,6-Trimethoxyphenyl)-1,3-butanedione[24] (**14b**) (100 mg) in THF (2.5 mL) was added to NaH (14 mg) in THF (2.5 mL) at 0 °C. After 30 min the mixture was cooled to −78 °C and *sec*-BuLi (1.4 M, 312 μL) added. After 30 min the solution was warmed up to 0 °C and, after 2 h, recooled to −78 °C and (±)-lactone **11b** (25 mg) was added. After 30 min the solution was warmed up to 0 °C for 1 h and recooled to −78 °C, and CF_3CO_2H (92 μL) was added. H_2O (8 mL) was added and the mixture extracted with CH_2Cl_2 (80 mL). The CH_2Cl_2 solution was dried ($MgSO_4$) and concentrated to ca. 5 mL, and $TsOH·H_2O$ (5 mg) was added. After 5 min the solution was directly chromatographed (silica gel, 7:3 Et_2O/hexane) to give the spirodihydropyrone **15b** (43 mg, 61%): mp 133–134 °C (from Et_2O); IR ν_{max} ($CHCl_3$) 1655, 1615, 1460, 1410, 1370, 1335, 1255, 1220, 1155, 1130, 980, 950 cm^{-1}; ^1H NMR (270 MHz) δ 6.13 (s, 2 H, aryl-H), 5.48 (s, 1 H, 3-H), 3.83 (s, 3 H, OMe), 3.9–3.7 (m, 1 H, 8-*H*), 3.76 (s, 6 H, OMe), 2.68 (AB q, 2 H, J = 15 Hz, 5H_2), 2.2–2.0 (m, 1 H), 1.7–1.2 (m, 4 H), 1.15 (d, 3 H, J = 6.1 Hz, 8-*Me*), 0.84 (d, 3 H, J = 6.1 Hz, 9-Me); mass spectrum, m/e 362 ($M^{\bullet+}$), 331, 237, 219, 195, 168. Anal. Calcd for $C_{20}H_{26}O_6$: C, 66.26; H, 7.24; ($M^{\bullet+}$), 362.1729. Found: C, 65.95; H, 6.97; ($M^{\bullet+}$), 362.1716.

2-Phenyl-1,7-dioxaspiro[5.5]undec-2-en-4-one (15a). Reaction of 1-phenyl-1,3-butanedione (**14a**) and δ-valerolactone (**11a**) using NaH and *sec*-BuLi gave the spirodihydropyrone **15a** (50%): mp 85–87 °C (from Et_2O); IR ν_{max} (CH_2Cl_2) 1650, 1600, 1570, 1360, 1270, 1225, 1140, 1070, 1040 cm^{-1}; ^1H NMR (270 MHz) δ 7.9–7.3 (m, 5 H), 6.1 (s, 1 H, 3-*H*), 3.8 (m, 2 H), 1.7 (AB q, 2 H, J = 15 Hz, 5-H_2), 2.4–1.5 (m, 6 H); mass spectrum, m/e 244 ($M^{\bullet+}$) 186, 147, 124, 105, 98, 77. Anal. Calcd for $C_{15}H_{16}O_3$: C, 73.73; H, 6.61. Found: C, 73.83; H, 6.67.

2-[(Benzyloxy)methyl]-1,7-dioxaspiro[5.5]undec-2-en-4-one (15c) and Isomers 16a and 16b. 1-Benzyloxy-2,4-pentanedione (**14c**)[14] (300 mg) in THF (1 mL) was added to NaH (45 mg) in THF (14 mL) at 0 °C. After 30 min at 0 °C the suspension was cooled to −78 °C and treated with *sec*-BuLi (1.4 M, 1.14 mL). After stirring for 1 h at −78 °C, a pale yellow solution was formed to which was added a solution of δ-valerolactone (**11a**) (73 mg) in THF (1 mL). After 1 h at −78 °C the reaction was quenched with AcOH (0.23 mL). H_2O (2 mL) was added, the reaction mixture was warmed up to room temperature, and the product was extracted into Et_2O (3 × 25 mL). The combined organic layers were dried and evaporated to give a yellow oil (200 mg), which by TLC was a nonresolvable streak R_f (0–0.5 (silica gel, 1:1 Et_2O/hexane). The crude oil was dissolved in CH_2Cl_2 (2 mL) and treated with $TsOH·H_2O$ (10 mg) and 3-Å molecular sieves (100 mg). After 45 min three new compounds had formed with the total consumption of the more polar material. The reaction mixture was added directly onto silica gel and elution with 1:3 Et_2O/hexane gave in order of increasing polarity **15c** (63 mg, 30%), **16b** (50 mg, 24%), and **16a** (52 mg, 25%), all as pale yellow oils. Spirodihydropyrone **15c**: R_f 0.55 (silica gel, 1:1 Et_2O/hexane); IR ν_{max} (film) 2940, 2860, 1665, 1620, 1320, 1100, 970, 870 cm^{-1}; UV λ_{max} (EtOH) 248 nm (ε 10 600); ^1H NMR (270 MHz) δ 7.35 (m, 5 H), 5.7 (s, 1 H), 4.6 (s, 2 H), 4.1 (AB q, 2 H, J = 14 Hz), 3.7 (m, 2 H), 2.09 (AB q, 2 H, J = 14.5 Hz), 2.2–1.3 (m, 6 H); mass spectrum, m/e 289 (M^+ + 1), 197, 182, 137, 107, 91 (base), 69. Anal. Calcd for $C_{17}H_{20}O_4$: C, 70.80; H, 7.00. Found: C, 70.63; H, 7.09. Spirodihydropyrone **16a**: R_f 0.40 (silica gel, 1:1 Et_2O/hexane); IR ν_{max} (film) 2970, 2880, 1665, 1612, 1380, 1100, 1020 cm^{-1}; UV λ_{max} (EtOH) 260 nm, (ε 11 200); ^1H NMR (90 MHz) δ 7.35 (m, 5 H), 5.31 (s, 1 H), 4.73 (d, 1 H, J = 15 Hz), 4.54 (d, 1 H, J = 15 Hz), 3.72 (m, 2 H), 3.35 (s, 1 H), 2.05 (s, 3 H), 1.2–2.2 (m, 6 H); mass spectrum, m/e 289 (M^+ + 1), 197, 182, 175, 145, 104 (base), 91, 78, 69. Anal. Calcd for $C_{17}H_{20}O_4$: C, 70.80; H, 7.00. Found: C, 71.03; H, 6.99. Spirodihydropyrone **16b**: R_f 0.45 (silica gel, 1:1 Et_2O/hexane); IR ν_{max} (film) 2940, 2870, 1680, 1620, 1380, 1260, 1105, 880 cm^{-1}; UV λ_{max} (EtOH) 262 nm (ε 11 400); ^1H NMR (90 MHz) δ 7.35 (m, 5 H), 5.3 (s, 1 H), 5.1 (d, 1 H, J = 12 Hz), 4.7 (d, 1 H, J = 12 Hz), 3.95 (s, 1 H), 3.75 (m, 2 H), 2.02 (s, 3 H), 1.4–2.20 (m, 6 H); mass spectrum, m/e 289 (M^+ + 1), 204, 197, 182, 175, 152, 113, 91. Anal. Calcd for $C_{17}H_{20}O_4$: C, 70.80; H, 7.00. Found: C, 70.80; H, 6.99%.

Ethyl 3,5-Dioxohexanoate (9b). To LDA (11 mmol) in THF (20 mL) at −78 °C was added a solution of 2,4-pentanedione (0.50 g). The reaction mixture was allowed to warm up to 0 °C and stirred for an additional 1 h. Upon recooling to −78 °C, a solution of EtOCOCl (0.27 g) in THF (5 mL) was added. After 1 h AcOH (1.26 mL) was added and the reaction mixture warmed up to room temperature. H_2O (5 mL) was added and the product extracted into Et_2O (4 × 30 mL). The organic layer was dried and evaporated to give a yellow oil which upon chromatography (silica gel, 3:7 Et_2O/hexane) gave **9b** (0.34 g, 80%) as a mobile colorless oil: IR ν_{max} ($CHCl_3$) 3500, 3010, 2950, 1730, 1620, 1600, 1260, 1050 cm^{-1}; UV λ_{max} (EtOH) 272 nm (ε 6900); ^1H NMR (60 MHz) δ 5.5 (s, 0.8 H), 4.15 (q, 2 H, J = 8 Hz), 3.35 (s, 2 H), 2.1 (s, 3 H), 1.3 (t, 3 H, J = 8 Hz); mass spectrum, m/e 172 ($M^{\bullet+}$), 157, 127, 115, 98, 85 (base), 43. Anal. Calcd for $C_8H_{12}O_4$: C, 55.78; H, 7.03. Found: C, 55.65; H, 6.90.

(6*SR*,8*RS*,9*SR*)-Ethyl 2-(8,9-Dimethyl-4-oxo-1,7-dioxaspiro[5.5]undec-2-en-2-yl)acetate (18). Ethyl 3,5-dioxohexanoate (**9b**) (1.34 g) in THF (3 mL) was added to LDA (27 mmol) in THF (50 mL) at −78 °C. After 5 min at −78 °C the solution was warmed up to 0 °C, stirred for 1 h, and recooled to −78 °C. Racemic lactone **11b**[15] (0.5 g) in THF (5 mL) was added. After 15 min at −78 °C the reaction mixture was warmed to 0 °C and stirred for 1 h. The reaction mixture was quenched at −78 °C with a THF solution of AcOH (0.49 mL, 8.6 mmol) and allowed to warm to room temperature. H_2O (20 mL) was added and the product was extracted into Et_2O (4 × 20 mL). The organic solution was dried and evaporated to approximately 3 mL, diluted with CH_2Cl_2 (5 mL), and reacted with $TsOH·H_2O$ (100 mg) and 3-Å molecular sieves (1 g). After being stirred for 1 h at room temperature, the reaction mixture was absorbed onto silica gel (5 g) and solvent evaporated. Chromatography (silica gel, Et_2O) gave **18** (0.86 g, 78%) as a pale yellow oil: R_f 0.60 (silica gel, Et_2O); IR ν_{max} (film) 2920, 2890, 1735, 1675, 1625, 1420, 1380, 1150, 985, 892 cm^{-1}; UV λ_{max} (EtOH) 264 nm (ε 10 300); ^1H NMR (250 MHz) δ 5.45 (s, 1 H, 3-*H*), 4.20 (m, 2 H, OCH_2Me), 3.50 (dq, 1 H, J = 6.0, 10.0 Hz, 8-*H*), 3.27 (s, 2 H, 2-H_2), 2.58 (AB q, 2 H, J = 16 Hz, 5-H_2), 2.05 (m, 1 H), 1.6 (m, 3 H), 1.29 (t, 3 H, J = 8 Hz, CH_2*Me*), 1.25 (m, 1 H), 1.12 (d, 3 H, J = 6.8 Hz, 8-Me), 0.87 (d, 3 H, J = 5.5 Hz, 9-Me); mass spectrum, m/e 282 ($M^{\bullet+}$), 209, 195, 152, 126, 111, 83, 55, 45. Anal. Calcd for $C_{15}H_{22}O_5$: C, 63.79; H, 7.87. Found: C, 63.86; H, 7.93.

Formation of Ethyl 2,4-Dihydroxy-6-((3*RS*,4*SR*)-4-hydroxy-3-methyl-1-pentyl)benzoate (20). The chromatographically (silica gel, 1:1 Et_2O/hexane) purified adduct **19** was converted into the resorcylate derivative **20** on storage at room temperature over several days. The reaction was catalyzed by the presence of a mild base, such as sodium acetate. To a solution of adduct **19** (100 mg) in THF (0.5 mL) was added solid NaOAc (20 mg), and the resulting suspension was stirred for 4 h. Chromatography of the reaction mixture gave **20** (84 mg, 84%) as a pale yellow oil: R_f 0.75 (silica gel, Et_2O); IR ν_{max} (film) 3580, 3000–3450, 2870, 1725 w, 1640, 1610, 1380, 1110, 1000 cm^{-1}; UV λ_{max} (EtOH) 300 nm (ε 3000), 266 (6800); ^1H NMR (270 MHz) δ 11.84 (br s, 2 H), 6.28 (d, 1 H, J = 2 Hz), 6.24 (d, 1 H, J = 2 Hz), 4.40 (q, 2 H, J = 7 Hz), 3.70 (dq, 1 H, J = 5.9, 7.5 Hz), 2.97 (ddd, 1 H, J = 3.9, 7.0, 13 Hz), 2.69 (ddd, 1 H, J = 3.9, 7.0, 13.0 Hz), 2.6 (br m, 1 H, OH), 1.58–1.73 (m, 2 H), 1.38 (t, 3 H, J = 7.3 Hz), 1.27 (m, 1 H), 1.15 (d, 3 H, J = 6.6 Hz), 0.93 (d, 3 H, J = 6.6Hz); mass spectrum, m/e 282 ($M^{\bullet+}$), 265, 264, 237, 218, 196, 183, 150, 121, 45. Anal. Calcd for $C_{15}H_{22}O_5$ ($M^{\bullet+}$): 282.1467. Found ($M^{\bullet+}$): 282.1461.

(4*SR*,6*SR*)- and (4*SR*,6*RS*)-2-Methyl-1,7-dioxaspiro[5.5]undec-2-en-4-ol (21a and 21b). $LiAlH_4$ (1.6 g) was added at 0 °C to **13a** (6.30 g) in THF (150 mL) at 0 °C. After 1 h saturated aqueous Na_2SO_4 was added to destroy the excess reagent. Evaporation, dilution with H_2O, and extraction with Et_2O gave crude **21a** and **21b** (5.69, 90%). Chromatography of an aliquot (400 mg) on alumina (12 g) gave (eluant 9:1 to 1:1 hexane/CH_2Cl_2 gradient) the less polar isomer **21a** (240 mg, 54%) as an oil [IR ν_{max} (film) 3520, 1675 cm^{-1}; ^1H NMR (90 MHz) δ 4.85 (d, 1 H, J = 5 Hz, 3-*H*), 3.81 (m, 1 H, 4-*H*), 3.58 (m, 2 H, 8-H_2), 2.49–1.09 (m, 9 H), 1.78 (s, 3 H); mass spectrum, m/e 184 ($M^{\bullet+}$), 166, 151, 123, 98 (base peak). Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.17; H, 8.76; ($M^{\bullet+}$), 184.1099. Found: C, 65.16; H, 8.93; ($M^{\bullet+}$),

(24) Mackenzie, J. B. D.; Robertson, A.; Whalley, W. B. *J. Chem. Soc.* **1950**, 2965.

184.1092;] and the more polar isomer **21b** (120 mg, 27%) as an oil [IR ν_{max} (film) 3340, 1680 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 4.61 (br s, 1 H, 3-*H*), 4.33 (m, 1 H, 4-*H*), 3.62 (m, 2 H, 8-H_2), 2.33–1.13 (m, 9 H), 1.75 (s, 3 H); mass spectrum, *m/e* 184 ($M^{\cdot+}$), 166, 151, 123, 98 (base peak). Anal. Calcd for $C_{10}H_{16}O_3$: 184.1099 ($M^{\cdot+}$). Found: 184.1096 ($M^{\cdot+}$). Both isomers, especially **21a**, were unstable to chromatography on silica gel, decomposing to more polar products.

(4*SR*,6*SR*)- and (4*SR*,6*RS*)-2,3-Dimethyl-1,7-dioxaspiro[5.5]undec-2-en-4-ol (21c and 21d). Reduction of **13b** (2 g) using $LiAlH_4$ (387 mg) in Et_2O (75 mL) for 1 h at 0 °C and workup as in the preceding experiment gave a mixture of **21c** and **21d** (1.75 g, 87%). Chromatography on alumina (30 g) gave (eluant hexane/CH_2Cl_2, 4:1 to 1:1 gradient) the unstable less polar **21c** (1.45 g, 72%) as an oil [IR ν_{max} (film) 3520, 1685 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 3.89 (m, 1 H), 3.73 (m, 2 H), 2.5–1.0 (m, 9 H), 1.84 (s, 3 H), 1.78 (s, 3 H); mass spectrum, *m/e* 198 ($M^{\cdot+}$), 180, 165, 137] and the more polar **21d** (0.25 g, 13%) as an oil [IR ν_{max} (film) 3380, 1685, 1660, 1610 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 4.29 (m, 1 H), 3.73 (m, 2 H), 2.5–1.0 (m, 9 H), 1.82 (s, 3 H), 1.70 (s, 3 H); mass spectrum, *m/e* 198 ($M^{\cdot+}$), 180, 165, 137.].

(2*SR*,6*RS*)- and (2*SR*,6*SR*)-2,3-Dimethyl-1,7-dioxaspiro[5.5]undec-3-ene (23a and 23b). Method 1. $LiAlH_4$ (50 mg) was added to **13b** (200 mg) in THF (4 mL) at 0 °C. After 0.5 h the solution was cooled to −78 °C and an aged (0 °C, 0.5 h) solution of $LiAlH_4$ (38 mg) and $AlCl_3$ (533 mg) in THF (5 mL) was added. After warming up to −10 °C during 1.5 h, saturated aqueous $NaHCO_3$ (10 mL) was added (0 °C), and the mixture extracted with Et_2O. The Et_2O extract was dried and evaporated. Chromatography of the residue on silica gel (6 g) gave (eluant hexane/CH_2Cl_2, 2:1) the less polar major isomer **23a** (40 mg, 22%) as an oil [IR ν_{max} (CH_2Cl_2) 1120, 1090, 1080, 1060, 1010 cm^{-1}; ^1H NMR (250 MHz) δ 5.35 (m, 1 H, 4-*H*), 4.15 (m, 1 H, 2-*H*), 3.78 (dd, 1 H, *J* = 11, 4 Hz, 8-*H*), 3.67 (m, 1 H), 2.2–1.9 (m, 3 H), 1.63 (s, 3 H, 3-*Me*), 1.7–1.4 (m, 5 H), 1.27 (d, 3 H, *J* = 6.6 Hz, 2-*Me*); mass spectrum, *m/e* 182 ($M^{\cdot+}$), 167, 110, 101, 82 (base peak), 67. Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.47; H, 9.96. Found: C, 72.21; H, 9.85.] and the crude more polar minor isomer **23b** (13mg, 7%) as an oil [^1H NMR ($CDCl_3$, 250 MHz) δ 5.37 (m, 1 H, 4-*H*), 4.13 (m, 1 H, 2-*H*), 4.04 (m, 1 H), 3.63 (m, 1 H), 2.15 (m, 2 H), 1.95–1.20 (m, 6 H), 1.63 (br s, 3 H, 3-*Me*), 1.38 (d, 3 H, *J* = 6.6 Hz, 2-*Me*); mass spectrum, *m/e* 182 ($M^{\cdot+}$), 167, 110, 101, 82 (base peak), 67.].

Method 2. $LiAlH_4$ (45 mg) was added to **13b** (200 mg) in Et_2O (10 mL) at 0 °C. After 0.5 h the solution was cooled to −78 °C and a solution of BH_3·THF (2 M, 1 mL) and BF_3·Et_2O (0.25 mL) in Et_2O (5 mL) was added. The solution was allowed to warm up to −10 °C over 1 h and quenched with saturated aqueous Na_2SO_4. Workup and chromatography gave **23a** (28 mg, 15%) and **23b** (24 mg, 13%).

(5*SR*,6*RS*)-5-((*RS*)-Hydroxyphenylmethyl)-2-methyl-1,7-dioxaspiro[5.5]undec-2-en-4-one (24). To a solution of hexane-free LDA (2.8 mmol) in THF (10 mL) at −78 °C was added HMPA (0.5 mL), and the resulting solution was stirred for 30 min. The solution was reacted with spiroketal **13a** (500 mg) in THF (2 mL) and the resulting solution was maintained at −78 °C for 1 h. PhCHO (300 mg) was added and stirring was continued at −78 °C for 1 h before quenching with AcOH (1.7 g). The THF was evaporated, H_2O (10 mL) added, and the product extracted into Et_2O (3 × 10 mL) to give, after chromatography (silica gel, Et_2O) **24** (480 mg, 61%) as a white crystalline solid: mp 128–130 °C (from Et_2O/hexane); IR ν_{max} (Nujol) 3400, 1680, 1620–1600 cm^{-1}; UV λ_{max} (EtOH) 262 nm (ϵ 11 200); ^1H NMR (250 MHz) δ 7.25 (m, 5 H), 5.05 (s, 1 H), 4.91 (t, 1 H, *J* = 6.5 Hz, d with D_2O, *J* = 6.8 Hz), 3.65 (m, 2 H), 3.10 (d, 1 H, *J* = 6.2 Hz, exchangeable D_2O), 2.84 (d, 1 H, *J* = 6.8 Hz), 2.33 (m, 1 H), 1.84 (s, 3 H), 1.42–1.93 (m, 5 H); mass spectrum, *m/e* 288 ($M^{\cdot+}$), 270, 182 (base), 124. Anal. Calcd for $C_{17}H_{20}O_4$: C, 70.79; H, 7.00; ($M^{\cdot+}$), 288.1362. Found: C, 71.13; H, 7.05; ($M^{\cdot+}$), 288.1353.

(2*RS*,4*RS*,6*SR*,8*RS*,9*SR*)-Ethyl (4-Hydroxy-8,9-dimethyl-1,7-dioxaspiro[5.5]undec-2-yl)acetate (26a) and Isomer 26b. To a prereduced suspension of PtO_2·H_2O (0.15 g) in distilled EtOAc (5 mL) was added a solution of dihydropyrone **18** (0.10 g) in EtOAc (5 mL). The reaction mixture was vigorously stirred under H_2 for 4 h. The catalyst was filtered off and the solvent evaporated. The resulting crude oil contained approximately six compounds by TLC (silica gel, Et_2O). Chromatography (silica gel, Et_2O/hexane, 3:1) gave the alcohols **26a** (15 mg, 15%) and **26b** (8 mg, 8%). The alcohol **26a** was obtained as a colorless oil: R_f 0.30 (silica gel, Et_2O); IR ν_{max} (film) 3440, 2960, 2930, 2880, 1730, 1460, 1380, 1190, 1100, 995 cm^{-1}; ^1H NMR (250 MHz) δ 4.15 (m, 2 H, OCH_2Me), 3.95 (m, 2 H, 2-H, 4-H), 3.68 (m, 1 H, 8-*H*), 2.65 (dd, 1 H, *J* = 8, 14 Hz, CH_2CO_2Et), 2.47 (dd, 1 H, *J* = 5, 14 Hz, CH_2CO_2Et), 2.08 (m, 1 H, O*H*), 2.03 (m, 4 H), 1.55–1.25 (m, 5 H), 1.29 (t, 3 H, *J* = 8Hz, *Me*CH_2O), 1.15 (d, 3 H, *J* = 6.8 Hz, 8-*Me*), 0.82 (d, 3 H, *J* = 6 Hz, 9-*Me*); mass spectrum, *m/e* 286 ($M^{\cdot+}$), 268, 241, 203, 185 (base), 157, 139, 115, 95. Anal. Calcd for $C_{15}H_{26}O_5$: C, 62.89; H, 9.16. Found: C, 62.84; H, 9.00. The alcohol **26b** was obtained as a colorless oil: R_f 0.35 (silica gel, Et_2O); IR ν_{max} (neat) 3450, 2965, 2880, 1730, 1462, 1385, 1184, 1100, 995 cm^{-1}; ^1H NMR (250 MHz) δ 4.45 (m, 1 H, 2-*H*), 4.30 (m, 1 H, 4-*H*), 4.15 (m, 2 H, OCH_2Me), 3.50 (dq, 1 H, *J* = 8, 12 Hz, 8-*H*), 2.75 (dd, 1 H, *J* = 8, 16 Hz, CH_2CO_2Et), 2.55 (dd, 1 H, *J* = 6, 16 Hz, CH_2CO_2Et), 2.18 (m, 1 H), 1.9–1.3 (m, 8 H), 1.27 (t, 3 H, *J* = 8 Hz, *Me*CH_2O), 1.20 (m, 1 H), 1.12 (d, 3 H, *J* = 6.8 Hz, 8-*Me*), 0.82 (d, 3 H, *J* = 7.0Hz, 9-*Me*); mass spectrum, *m/e* 286 ($M^{\cdot+}$), 268, 241, 203, 185 (base), 157, 139, 95.

(2*RS*,4*RS*,6*SR*,8*RS*,9*SR*)-Ethyl 2-[4-(Benzoyloxy)-8,9-dimethyl-1,7-dioxaspiro[5.5]undec-2-yl]acetate (26c). Method 1. A solution of Ph_3P (0.13 g) and the spiroketal alcohol **26b** (0.14 g) in Et_2O (5 mL) were added to $EtO_2CN{=}NCO_2Et$ (104 mg) and $PhCO_2H$ (60 mg) in Et_2O (5 mL) at room temperature. After 2 h silica gel (1 g) was added and the solvent evaporated. The resulting slurry was chromatographed (silica gel, Et_2O/hexane 1:1) to give **26c** as a pale yellow oil (0.10 g, 52%): R_f 0.85 (silica gel, Et_2O); IR ν_{max} (film) 2930, 1730, 1605, 1570 cm^{-1}; ^1H NMR (250 MHz) δ 8.02 (m, 2 H, aryl-*H*), 7.5 (m, 3 H, aryl-*H*), 5.28 (m, 1 H, 4-*H*), 4.18 (m, 2 H, OCH_2Me), 4.05 (m, 1 H, 2-*H*), 3.72 (dq, 1 H, *J* = 6.0, 12 Hz, 8-*H*), 2.68 (dd, 1 H, *J* = 8, 14 Hz, CH_2CO_2Et), 2.50 (dd, 1 H, *J* = 8, 14 Hz, CH_2CO_2Et), 2.20 (m, 2 H), 1.8–1.2 (m, 7 H), 1.28 (t, 3 H, *J* = 8 Hz, *Me*CH_2O), 1.17 (d, 3 H, *J* = 7 Hz, 8-*Me*), 0.83 (d, 3 H, *J* = 6 Hz, 9-*Me*); mass spectrum, *m/e* 390 ($M^{\cdot+}$), 372, 269, 250, 223, 185 (base), 105, 77, 55, 41. Anal. Calcd for $C_{22}H_{30}O_6$: C, 67.65; H, 7.75. Found: C, 67.89; H, 7.74.

Method 2. To a solution of the spiroketal alcohol **26a** (0.14 g) in pyridine (1 mL) was added PhCOCl (0.086 mL) at room temperature, and the reaction mixture was stirred overnight. Et_2O (10 mL) was added and the pyridine washed out with saturated aqueous $CuSO_4$·$5H_2O$ (2 × 3 mL). The Et_2O layer was dried, the solvent removed, and the residue chromatographed (silica gel, Et_2O/hexane, 1:1) to give **26c** (0.16 g, 84%) as a crystalline solid: mp 128–129 °C (from Et_2O–hexane). The product was identical with the Mitsunobu reaction product by 250-MHz NMR spectroscopy and TLC.

(2*RS*,6*SR*,8*RS*,9*SR*)-Ethyl 2-(8,9-Dimethyl-4-oxo-1,7-dioxaspiro[5.5]undec-2-yl)acetate (29). To a pre-hydrogenated suspension of 10% Pd/C (50mg) in EtOH (100 mL) under H_2 was added the dihydropyrone **18** (180 mg) in EtOH (10 mL). The reaction mixture was rapidly stirred and the disappearance of the UV-active starting material carefully monitored by TLC (Et_2O/hexane, 1:1). After 4 h, filtration through Celite and evaporation gave a pale yellow oil. Chromatography (silica gel, Et_2O/hexane, 2:3) gave the ketone **29** as a mobile colorless oil (100 mg, 56%): R_f 0.62, (silica gel, Et_2O/hexane, 1:1); IR ν_{max} (film) 2970, 2910, 1728, 1380, 1180, 1020 cm^{-1}; ^1H NMR (270 MHz) δ 4.35 (m, 1 H, 2-*H*), 4.20 (m, 2 H, OCH_2Me) 3.68 (dq, 1 H, *J* = 6.0, 9.8 Hz, 8-*H*), 2.73 (dd, 1 H, *J* = 7.9, 14.9 Hz, CH_2COCH_2), 2.35–2.68 (m, 5 H), 1.89 (m, 1 H), 1.2–1.5 (m, 4 H), 1.29 (t, 3 H, *J* = 8 Hz, CH_2*Me*), 1.13 (d, 3 H, *J* = 6.4 Hz, 8-*Me*), 0.85 (d, 3 H, *J* = 9.7 Hz, 9-*Me*); mass spectrum, *m/e* 284 ($M^{\cdot+}$), 266, 239, 201, 183, 111, 88 (base). Anal. Calcd for $C_{15}H_{24}O_5$: C, 63.34; H, 8.51. Found: C, 63.09; H, 8.65.

Sodium Borohydride Reduction of (2*RS*,6*SR*,8*RS*,9*SR*)-Ethyl 2-(8,9-Dimethyl-4-oxo-1,7-dioxaspiro[5.5]undec-2-yl)acetate (29). $NaBH_4$ (50 mg) was added to ketone **29** (150 mg) in DME (5 mL) at 0 °C. After 5 min of stirring, the reaction mixture was quenched with AcOH to pH 6, Et_2O (30 mL) was added, and the solution was washed with H_2O (1 mL). The Et_2O layer was dried, silica gel (1 g) was added, and the solvent was evaporated. Chromatography gave the two epimeric alcohols **26a** (89 mg, 59%) and **26b** (22 mg, 15%).

Methyl 5-Oxo-2(*E*)-hexenoate (31a) and Methyl 5-Oxo-3-(*E*)-hexenoate (31b). 2-Methyl-1,3-dioxolane-2-acetaldehyde

(33)[22] (1.0 g), $Ph_3P{=}CHCO_2Me$ (2.56 g), and THF (5 mL) were stirred for 1 h. Evaporation and chromatography (silica gel, Et_2O/hexane, 1:3) gave methyl 4-(2-methyl-1,3-dioxalan-2-yl)-2-butenoate (1.22 g, 85%) as a colorless oil. TLC and NMR spectroscopy indicated the presence of both *E* and *Z* isomers, in approximately a ratio of 3:1: R_f 0.55 (silica gel, Et_2O/hexane 1:4); IR ν_{max} (CH_2Cl_2) 2990, 1720, 1680, 1620 cm^{-1}; ^1H NMR (90 MHz) δ 6.85 (m, 1 H), 5.80 (d, 1 H, J = 15 Hz), 3.91 (s, 4 H), 3.65 (s, 3 H), 3.05 (m, 0.5 H), 2.53 (m, 1.5 H), 1.35 (s, 3 H); mass spectrum, m/e 171 ($M^+ - 15$), 99, 87 (base), 43, 32. The crude product was used directly without purification. The oil (610 mg) was dissolved in Me_2CO (8 mL) and reacted with $TsOH{\cdot}H_2O$ (63 mg). The solution was gently refluxed for 7 h. The solution was cooled to room temperature, diluted with Et_2O (50 mL), and treated with solid $NaHCO_3$ (1 g). The suspension was filtered, the solvent removed, and the crude product chromatographed (silica gel, Et_2O/hexane, 3:7) to give a 1:1 mixture of **31a** and **31b** (370 mg, 80%) as a pale yellow oil: R_f 0.5 (silica gel, Et_2O/hexane, 2:3); bp 60-63 °C at 0.5 mmHg; IR ν_{max} (CH_2Cl_2) 2984, 1730-1720, 1680, 1620 cm^{-1}; ^1H NMR (270 MHz) δ 6.9 (m, 1 H), 6.05 (m, 1 H), 3.78 (s, 3 H), 3.30 (dt, 2 H, J = 2.0, 8.0 Hz), 2.30 (s, 1.5 H), 2.20 (s, 1.5 H); mass spectrum, m/e 142 ($M^{\cdot+}$), 127, 111, 99 (base), 43.

Methyl 11-Hydroxy-5,7-dioxoundec-2-enoate (34a) and Methyl 11-Hydroxy-5,7-dioxoundec-3-enoate (34b). To LDA (4.44 mmol) in THF (12 mL) at -78 °C was added methyl 5-oxohexenoate **31** (300 mg) in THF (0.50 mL) over 5 min. The solution was stirred for a further 20 min before being warmed to -45 °C for 15 min. The dark orange solution was recooled to -78 °C and δ-valerolactone (**11a**) (100 mg) in THF (0.50 mL) added. After 30 min at -78 °C, the reaction mixture was warmed to -42 °C for 10 min and then to 0 °C for 10 min. The system was cooled to -78 °C and quenched with AcOH (0.30 mL) in THF (2 mL). The reaction mixture was slowly warmed up to room temperature, H_2O (3 mL) was added, and the products were extracted into Et_2O (4 × 20 mL). After drying, the solvent was removed and the resultant yellow oil chromatographed (silica gel, Et_2O) to give **34** (123 mg, 51%) as a colorless oil: R_f 0.40 (silica gel, Et_2O); IR ν_{max} ($CHCl_3$) 3400, 1720, 1660, 1595 cm^{-1}; ^1H NMR (270 MHz) δ 6.85 (2 dt, 1 H, J = 6, 14.8 Hz), 6.2, 5.95 (2 × d, 1 H, J = 14.8 Hz), 5.54 (s, 1 H), 3.72 (s, 3 H), 3.64 (t, 2 H, J = 6.1 Hz), 3.26 (2 d, 2 H, J = 6.1 Hz), 2.41 (t, 2 H, J = 7.0 Hz), 1.4-1.9 (m, 6 H); C^{13} NMR (25 MHz) δ 203, 177, 136, 131, 101, 91, 64, 54, 42, 39, 34, 23; mass spectrum, m/e 242 ($M^{\cdot+}$), 224, 169, 127, 101, 83, 69, 55. Anal. Calcd for $C_{12}H_{18}O_5$: C, 59.47; H, 7.49. Found: C, 59.39; H, 7.43.

Attempted Spiroketalization of Methyl 11-Hydroxy-5,7-dioxoundecenoate (34). Method 1: Base-Catalyzed Procedure. NaOMe in MeOH (1 M, 20 μL) was added to **34** (50 mg) in dry methanol (1 mL). Stirring for 5 h at room temperature resulted in no reaction. After reflux for 48 h, HOAc in THF (1 M, 10 drops) was added, the solution absorbed onto silica gel (100 mg), and the solvent evaporated. Chromatography (silica gel, Et_2O/hexane, 4:1) gave **35** (40 mg, 86%) as a white crystalline solid: mp 71-73 °C (from Et_2O-hexane); IR ν_{max} ($CHCl_3$) 3500, 3200, 1701, 1605, 1585, 1254, 1140 cm^{-1}; UV λ_{max} (EtOH) 255 nm (ϵ 10 000); ^1H NMR (90 MHz) δ 7.85 (d, 1 H, J = 9 Hz), 6.96 (m, 1 H, OH), 6.65 (m, 2 H), 3.80 (s, 3 H), 3.79 (m, 3 H), 3.00 (m, 2 H), 1.79-1.42 (m, 4 H); mass spectrum, m/e 224 ($M^{\cdot+}$), 206, 192, 147, 135, 107, 91, 77. Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.25; H, 7.20. Found: C, 64.50; H, 7.20.

Method 2: Acid-Catalyzed Procedure. CF_3CO_2H in THF (1 M, 20 μL) was added to **34** (50 mg) in THF (3 mL) and the mixture was stirred at room temperature. Over several hours the starting material was observed to fragment to produce methyl 5-oxohexenoate **31** and **11a** as judged by TLC (silica gel, Et_2O). The reaction was quenched after 10 h and the products isolated by chromatography were proven to be **31** and **11a** by NMR spectroscopy.

Acknowledgment. We thank Pfizer Central Research, the Science and Engineering Research Council, the Wolfson Foundation, The Royal Society, and Northwestern University for most generous support of our research program. We are additionally grateful to Drs. Michael R. G. Leaming and Bernard Banks for most helpful discussions, Dr. N. S. Mani for completing the characterization of several compounds, Tony Raynham and Sven Taylor at Northwestern University, and Dr. David J. Williams at Imperial College for determining the X-ray crystallographic structures for **24** and **26c**. Several mass spectral determinations were performed at the Midwest Center for Mass Spectrometry, an NSF Regional Instrumentation Facility (Grant CHE-8211164), and we are most grateful for access to this facility.

Supplementary Material Available: X-ray crystal structure analysis of **24** (6 pages); table of calculated and observed structure factors of **24** (17 pages). Ordering information is given on any current masthead page.

Heterocycles from the Marine Sponge *Xestospongia* sp.†

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Received February 7, 1986

The cytotoxic nonpolar extract of a Fiji sponge contains a simple chiral butenolide, 2-oxo-2,5-dihydrofuran-5-acetic acid methyl ester (**1**) which is accompanied by epimeric substituted 3,6-dihydro-1,2-dioxins, xestin A (**5**) and xestin B (**6**). A 5*R* absolute stereochemistry is proposed for **1** based on CD results. The relative stereochemistry of dioxin ring substituents is assigned by ^1H NMR J's, and from optical properties of reduction products. Among the three metabolites, xestin A is the most in vitro active compound against P388 cells.

Soft bodied marine sponges whose extracts are physiologically active are a prime target in our chemical study of taxa from south Pacific coral reefs.[1] During a 1984 expedition to the Island of Viti Levu, Fiji, we encountered thick sheets of a soft *Xestospongia* sp. whose crude extracts at 5 μg/mL were toxic (in vitro) to greater than 75% of P388 murine leukemia cells. The broad array of me-

† Dedicated to Prof. J. F. Bunnett (UCSC) on the occasion of his 65th birthday.

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0022-3263/86/1951-4260$01.50/0