Total Synthesis of (+)-Milbemycin β_3

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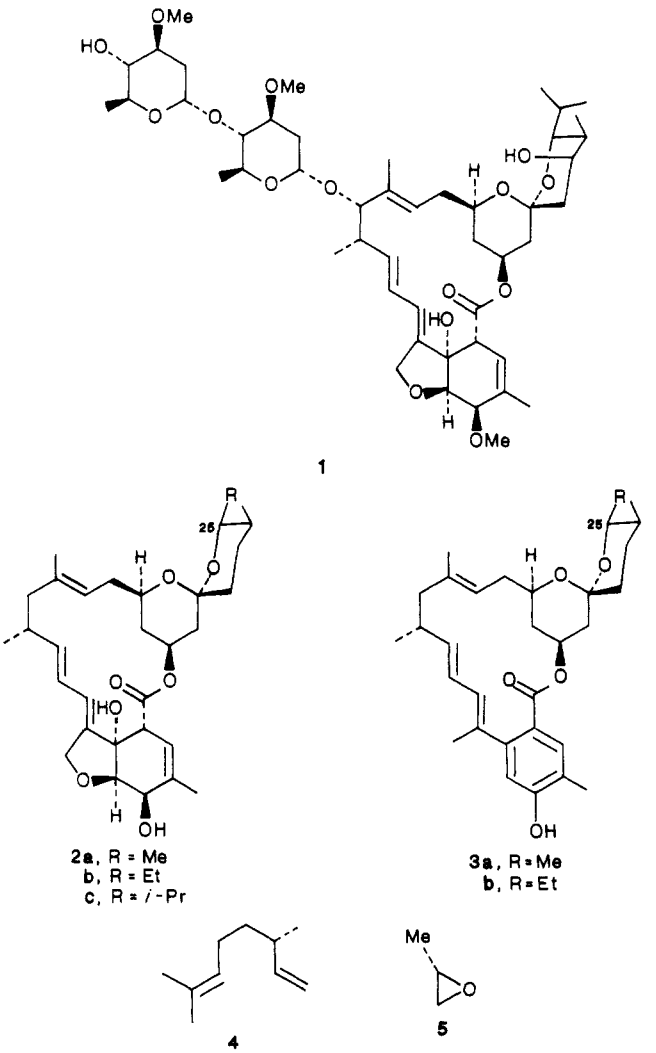
This report describes the total synthesis of (+)-milbemycin β_3 (**3a**), which is the simplest member of the avermectin milbemycin class of macrolide parasiticidal agents. The key features of the synthesis are the preparation of **3a** in optically pure form from only two chiral pool starting materials, (*S*)-(+)-citronellene and (*S*)-(−)-propylene oxide. Of particular note are (i) the construction of the spiro ketal moiety using the condensation reaction of 5(*S*),6(*R*)-dimethyltetrahydro-2-pyranone with 2,4-dilithioxy-1,1,1-trimethoxy-2,4-pentadiene to produce **10**; (ii) the construction of the macrolide carbon framework using Julia–Lythgoe and benzylic anion chemistry; and (iii) the efficient Mitsunobu closure of the lactone ring. The synthesis is concise and with the exception of the construction of Δ^{14} is highly stereochemically controlled.

The avermectins are a group of *Streptomyces avermilitis* metabolites noted for their biological activity against two major classes of parasites: the nematodes and arthropods.[1] Since the corresponding mammalian toxicity is very low, the avermectins are important anthelmintic and ectoparasiticidal agents. The milbemycins are a group of structurally related natural products that exhibit a comparable spectrum of activity.[2] Examples of both classes include avermectin A_{2b} (**1**),[3] milbemycin α_1 (**2a**),[4] and milbemycin β_3 (**3a**).[5] The key common features present in all the milbemycins and avermectins are the 16-membered macrocyclic ring and the spiro ketal moiety. Milbemycin β_3 (**3a**), which is the simplest member of the series since it lacks a highly functionalized mono- or bicyclic "southern hemisphere", has been totally synthesized several times. Smith[6] has reported a concise synthesis of racemic **3a** using a nitrile oxide strategy to construct the spiro ketal unit. Subsequent Ireland–Claisen and Horner–Emmons chemistry was crucial in elaboration of the final macrocycle. Williams[7] reported the first total synthesis of (+)-milbemycin using 2,3-*O*-isopropylidene-D-(+)-glyceraldehyde, (*S*)-(−)-citronellol, and (*S*)-(−)-citronellal as chiral starting materials. In 1985 Baker[8] and

Chart I



Kocienski[9] reported convergent syntheses of (+)-milbemycin β_3 (**3a**) from three chiral pool starting materials. In

(1) Albers-Schönberg, G.; Arison, B. H.; Chabala, J. C.; Douglas, A. W.; Eskola, P.; Fisher, M. H.; Hirshfield, J. M.; Hoogsteen, K.; Lusi, A.; Mrozik, H.; Smith, J. L.; Springer, J. P.; Tolman, R. L. Interscience Conference on Antimicrobial Agents and Chemotherapy, Atlanta, GA, Oct 1–4, 1978; Abstract No. 464. Egerton, J. R.; Ostlind, D. A.; Blair, L. S.; Eary, C. H.; Suhayda, D.; Cifelli, S.; Riek, R. F.; Campbell, W. F. *Antimicrob. Agents Chemother.* **1979**, *15*, 372. Ostlind, D. A.; Cifelli, S.; Lang, R. *Vet. Rec.* **1979**, *105*, 168. Fisher, M. H. In *Recent Advances in the Chemistry of Insect Control*; Janes, N. F., Ed.; The Royal Society of Chemistry: London, 1985; Special Publication No. 53, p 53 and references therein.

(2) Okazaki, T.; Ono, M.; Muramatsu, S.; Ide, J.; Mishima, H.; Terao, M. *J. Antibiot.* **1983**, *36*, 502. Ono, M.; Mishima, H.; Takiguchi, Y.; Terao, M. *Ibid.* **1983**, *36*, 509. Ono, M.; Mishima, H.; Takiguchi, Y.; Terao, M.; Kobayashi, H.; Iwasaki, S.; Okuda, S. *Ibid.* **1983**, *36*, 991.

(3) 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. *J. Am. Chem. Soc.* **1981**, *103*, 4221.

(4) 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.

(5) Mishima, H.; Kurabayashi, M.; Tamura, C. *Tetrahedron Lett.* **1975**, 711.

(6) Smith, A. B., III; Schow, S. R.; Bloom, J. D.; Thompson, A. S.; Winzenberg, K. N. *J. Am. Chem. Soc.* **1982**, *104*, 4015. Schow, S. R.; Bloom, J. D.; Thompson, A. S.; Winzenberg, K. N.; Smith, A. B. III *Ibid.* **1986**, *108*, 2662.

(7) Williams, D. R.; Barner, B. A.; Nishitani, K.; Phillips, J. G. *J. Am. Chem. Soc.* **1982**, *104*, 4708.

(8) Baker, R.; O'Mahony, M. J.; Swain, C. J. *J. Chem. Soc., Chem. Commun.* **1985**, 1326.

(9) 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.

0022-3263/86/1951-4840$01.50/0

Scheme I

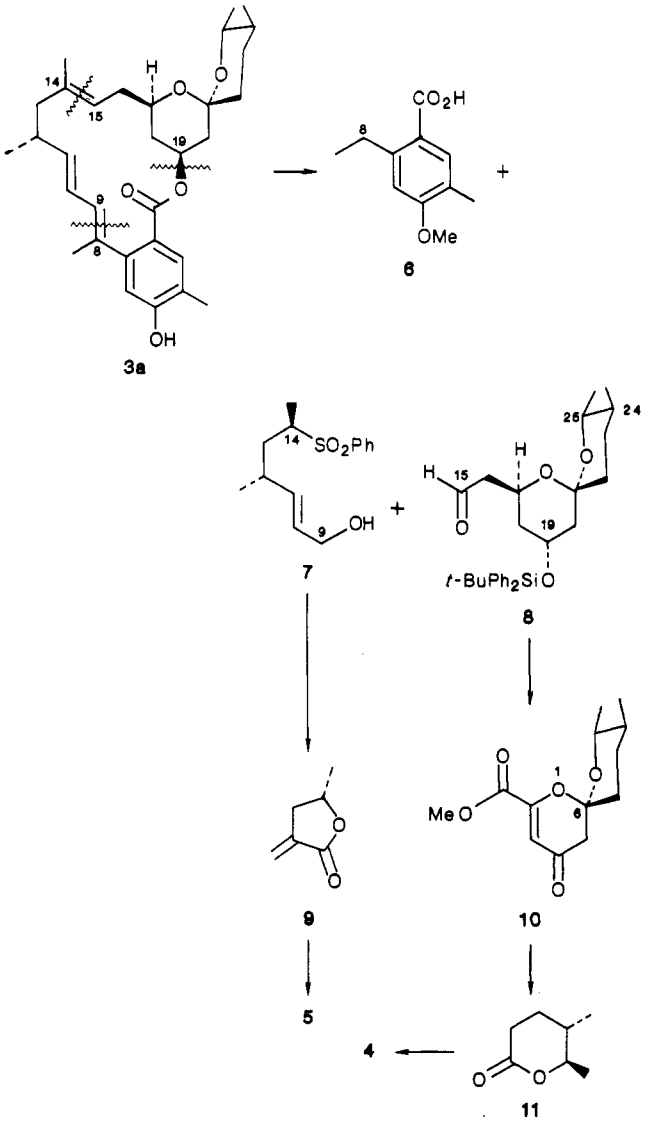
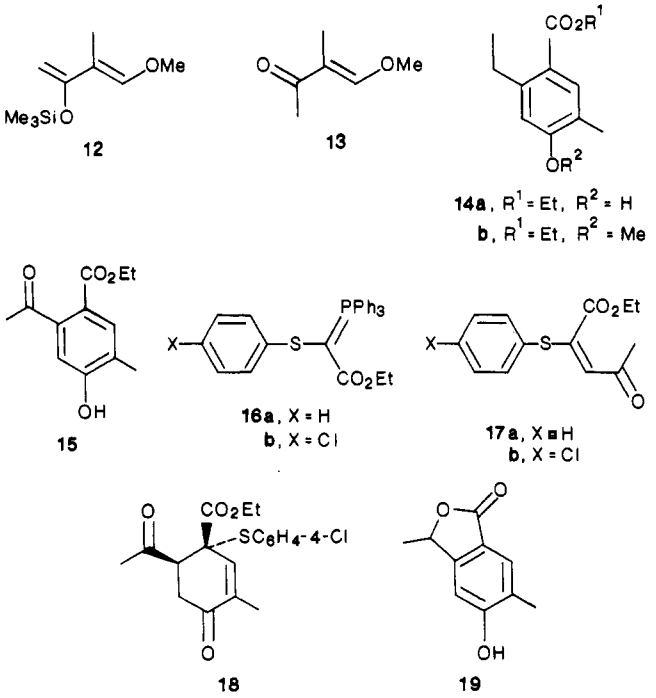


Chart II



addition, a considerable number of papers describing novel syntheses of spiro ketals[10] and approaches to the total synthesis of more complex milbemycins or avermectins[11] have been published. Recently Hanessian communicated the first total synthesis of an avermectin using both synthetic units and a degradation fragment obtained from the natural product.[12]

In this paper we provide details of our total synthesis of (+)-milbemycin β_3 (**3a**)[13] from two commercially available optically active starting materials: (*S*)-(+)-citronellene (**4**)[14] and (*S*)-(−)-propylene oxide (**5**).[15] The synthesis is concise, is convergent, and with the exception of the introduction of Δ^{14}, is highly stereochemically controlled (Chart I).

Synthetic Strategy. We sought to synthesize milbemycin β_3 (**3a**) using three key disconnections. Thus fragmentation across Δ^8,Δ^{14} and the lactone alkyl (C-19) oxygen bond would provide **6**, **7**, and **8** (Scheme I). In the final elaboration of the carbon framework Δ^{14} would be established by C-14 metalation of sulfone **7** and Julia–Lythgoe coupling[16] with the aldehyde **8**. After oxidation of the C-9 allylic alcohol to the aldehyde oxidation level, benzylic metalation of **6** and Williams coupling,[7] to introduce Δ^8, would complete the carbon framework. Finally, the lactone ring would be constructed by the formation of an alkyl oxygen bond with inversion of configuration at C-19. We anticipated that sulfone **7** should be available from (*S*)-(−)-propylene oxide (**5**) using as a key step the steric approach controlled hydrogenation of the α-methylene lactone **9**. In addition we sought to synthesize aldehyde **8** from (*S*)-(+)-citronellene (**4**) via the lactone **11** and the spiro dihydropyrone **10**.

Results and Discussion

Preparation of 2-Ethyl-4-methoxy-5-methylbenzoic Acid (6). The benzoic acid derivative **6** was readily pre-

(10) Kocienski, P. J.; Street, S. D. A. *Ibid.* **1984**, 571. Godoy, J.; Ley, S. V.; Lygo, B. *Ibid.* **1984**, 1381. Crimmins, M. T.; Bankaitis, D. M. *Tetrahedron Lett.* **1983**, *24*, 4551. Danishefsky, S. J.; Pearson, W. H. *J. Org. Chem.* **1983**, *48*, 3865. Baker, R.; Swain, C. J.; Head, J. In *Recent Advances in the Chemistry of Insect Control*; Janes, N. F., Ed.; The Royal Society of Chemistry: London, 1985; Special Publication No. 53, p 245. Culshaw, D.; Grice, P.; Ley, S. V.; Strange, G. A. *Tetrahedron Lett.* **1985**, *26*, 5837. Baker, R.; O'Mahony, M. J.; Swain, C. J. *Ibid.* **1986**, *27*, 3059.

(11) Kay, I. T.; Turnbull, M. D. In *Recent Advances in the Chemistry of Insect Control* Janes, N. F., Ed.; The Royal Society of Chemistry: London, 1985; Special Publication No. 53, 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. Baker, R.; Swain, C. J.; Head, J. C. *Ibid.* **1986**, 874. Jung, M. E.; Street, L. J. *J. Am. Chem. Soc.* **1984**, *106*, 8327. Kozikowski, A. P.; Maloney-Huss, K. E. *Tetrahedron Lett.* **1985**, *26*, 2759. Crimmins, M. T.; Lever, J. G. *Ibid.* **1986**, *27*, 291.

(12) Hanessian, S.; Ugolini, A.; Dubé, D.; Hodges, P. J.; André, C. *J. Am. Chem. Soc.* **1986**, *108*, 2776.

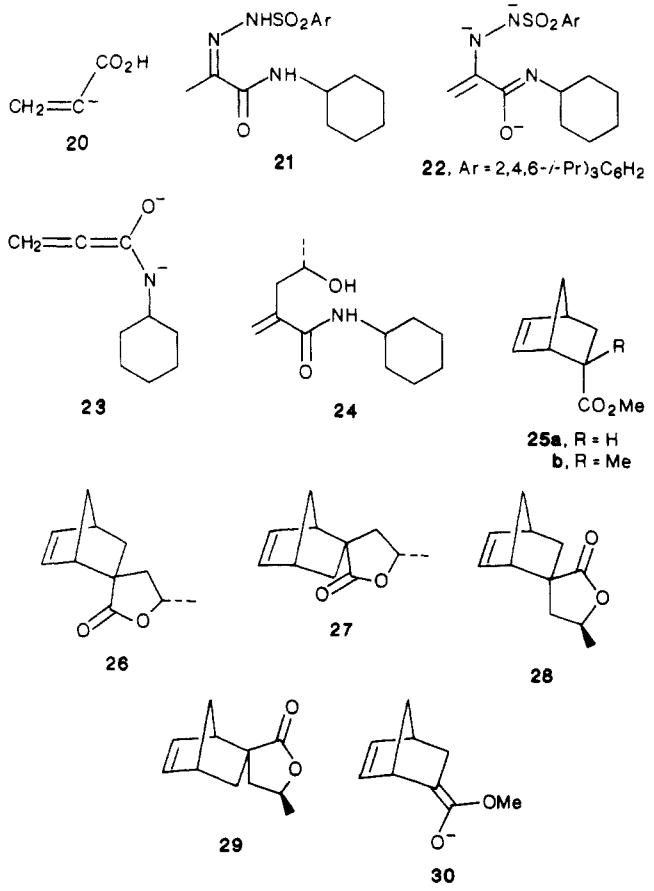
(13) Preliminary communication: Attwood, S. V.; Barrett, A. G. M.; Carr, R. A. E.; Richardson, G. *J. Chem. Soc., Chem. Commun.* **1986**, 479. Attwood, S. V.; Barrett, A. G. M.; Carr, R. A.; Finch, M. A. W.; Richardson, G. In *Recent Advances in the Chemistry of Insect Control*; Janes, N. F., Ed.; The Royal Society of Chemistry: London, 1985; Special Publication No. 53, p 257.

(14) Commercially available from Fluka; $[\alpha]^{20}_D$ +10 ± 1°. The optically pure (−)antipode has a rotation of −9.82° (*c* 6.18, $CHCl_3$). See: Arigoni, D.; Jeger, O. *Helv. Chim. Acta* **1954**, *37*, 881.

(15) Commercially available from Fluka; $[\alpha]^{20}_D$ −14 ± 1°. Alternatively readily available from (*S*)-(−)-ethyl lactate. See: Seebach, D.; Hungerbühler, E. In *Modern Synthetic Methods*, Scheffold, R., Ed.; Verlag Sauerländer: Aarau, 1980; p 142.

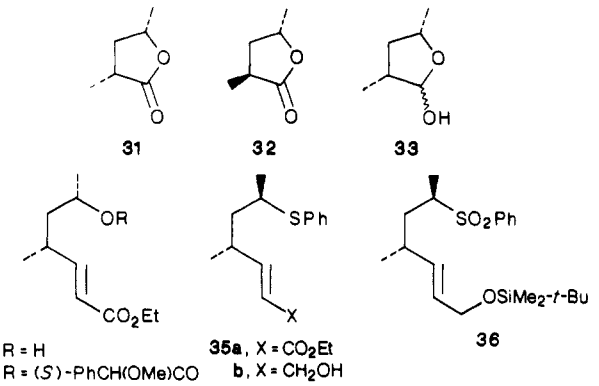
(16) Julia, M.; Paris, M.-J. *Tetrahedron Lett.* **1973**, 4833. Kocienski, P. J.; Lythgoe, B.; Waterhouse, I. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1045 and references therein.

Chart III



pared from a nonaromatic precursor by Danishefsky Diels–Alder chemistry.[17] Thus, the pure diene **12**, which was readily prepared from enone **13**, smoothly condensed with ethyl 2-pentynoate on reflux in xylene (Chart II). Workup with hydrochloric acid gave **14a** (52–74%). Methylation of **14a** using iodomethane and potassium carbonate in acetone gave **14b** (98%), which was subsequently converted into **6** (98%) via lithium hydroxide saponification. The Diels–Alder chemistry was equally efficient in the construction of the corresponding ketone **15**. Smith,[6] Baker,[8] and Kocienski[9] have utilized the southern aromatic moiety at the ketone oxidation level in their total syntheses. Thus phosphoranes **16a** and **16b** were reacted with 1,2-propanedione to respectively produce the dienophiles **17a** (87%) and **17b** (72%). Diene **12** and dienophile **17b** gave **18** (64%) on reflux in benzene and acidic workup. The adduct **18**, which was obtained as a single isomer, was aromatized to produce **15** (75%) by reaction with ethanolic sodium ethoxide. Alternatively **15** was prepared by a one-pot process. Thus, **12** and **17a** on reflux in benzene gave **15** (80%) on alkaline workup. The constitution of both **6** and **15** requires further comment. The structure of **6** is clearly consistent with the expected regioselectivity of the Diels–Alder reaction.[17,18] Additionally, the sample was in all respects identical with material prepared by Professor Amos B. Smith III.[19] The regioselectivity of the Diels–Alder reaction between **17** and **12** is more difficult to predict. However, the reaction was found to be regiospecific. The product **15** was identified by reduction to produce **19** on reaction with sodium borohydride. Consistent with the constitution, the phthalide derivative **19** exhibited a bathochromic shift in the ultraviolet spectrum in the presence of base.

Chart IV



Clearly the Diels–Alder reaction provides a concise and flexible method to prepare the aromatic moiety **6** required for our β_3 synthesis.

Preparation of 5(*S*)-Methyl-3-methylene-4,5-dihydro-2(3*H*)-furanone (9). The key optically pure furanone **9** should be available from (*S*)-(−)-propylene oxide (**5**) via condensation with an acrylic acid vinyl anion equivalent **20**[20] (Chart III). Several years ago we extended the Shapiro reaction to convert α-keto amides into such anion equivalents.[21] Thus, the (triisopropylphenyl)-sulfonyl hydrazone **21**, which is readily available either from pyruvic acid or acetyl chloride, was converted into the trianion **22** by metalation with *n*-butyllithium in THF at −78 °C. Upon warming up to 0 °C, **22** was smoothly converted into **23** by the expulsion of nitrogen and the arenesulfinate anion. Dianion **23** reacted cleanly, albeit slowly, with (*S*)-(−)-propylene oxide (**5**) to produce the α-methylene amide **24** (97%). On reflux in THF containing trifluoroacetic acid, **24** was cyclized to produce the α-methylene lactone **9**[22] (75%). The synthetic efficiency in the condensation of **23** with **5** and other diverse electrophiles[21] deserves particular emphasis.

In parallel we examined another strategy for preparing **9** using a different acrylate anion equivalent **20**. Thus, following exactly the Ponticello precedent for racemic propylene oxide,[23] ester **25a** was reacted with lithium diisopropylamide and with **5** to produce, on acidification, the four spiro lactones **26**, **27**, **28**, and **29** (total 66%). The mixture of isomers was partially resolved into a minor component (10%) and a major component (90%). The minor component was tentatively identified as the mixture of *exo*-lactones **28** and **29** whereas the major component was most probably the endo isomers **26** and **27** (90%). The assignment of stereochemistry was based upon comparisons of NMR spectra of **26**–**27** and **28**–**29** with reference

(17) Danishefsky, S. *Acc. Chem. Res.* **1981**, *14*, 400. Danishefsky, S.; Yan, C.-F.; Singh, R. K.; Gammill, R. B.; McCurry, P. M., Jr.; Fritsch, N.; Clardy, J. *J. Am. Chem. Soc.* **1979**, *101*, 7001. Sugasawa, S.; Yamada, S. I.; Harahashi, M. *J. Pharm. Soc. Jpn.* **1951**, *71*, 1345.

(18) Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; Wiley: New York, 1976; p 86.

(19) Smith, A. B. III; Kilenyi, S. N. *Tetrahedron Lett.* **1985**, *26*, 4419.

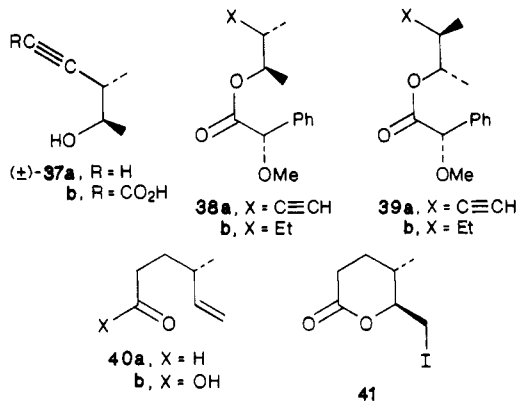
(20) For example, see: Adlington, R. M.; Barrett, A. G. M. *J. Chem. Soc., Chem. Commun.* **1981**, 65. Marino, J. P.; Floyd, D. M. *Tetrahedron Lett.* **1979**, 675. Marino, J. P.; Floyd, D. M., *Ibid.* **1975**, 3879. Gordon-Gray, C. G.; Whiteley, C. G. *J. Chem. Soc., Perkin Trans 1* **1977**, 2040. Boykin, D. W.; Parham, W. E. *J. Org. Chem.* **1979**, *44*, 424. Semmelhack, M. F.; Stauffer, R. D.; Yamashita, A. *Ibid.* **1977**, *42*, 3180. Schmidt, R. R.; Speer, H.; Schmid, B. *Tetrahedron Lett.* **1979**, 4277. Schmidt, R. R.; Talbierski, J.; Russegger, P. *Ibid.* **1979**, 4273. Boykin, D. W.; Parham, W. E. *J. Org. Chem.* **1977**, *42*, 260. Klein, J.; Levene, R. *J. Am. Chem. Soc.* **1972**, *94*, 2520. Corey, E. J.; Katzenellenbogen, J. A. *Ibid.* **1969**, *91*, 1851. Siddall, J. B.; Biskup, M.; Fried, J. H. *Ibid.* **1969**, *91*, 1853.

(21) Adlington, R. M.; Barrett, A. G. M. *Tetrahedron* **1981**, *37*, 3935.

(22) For the preparation of both antipodes, see: Barbier, P.; Benezra, C. *J. Med. Chem.* **1982**, *25*, 943.

(23) Ponticello, I. S. *J. Polym. Sci., Polym. Chem. Ed.* **1979**, *17*, 3509.

Chart V



spectra.[24] Additionally, the methylation of the enolate **30** was reported to predominantly produce **25b**,[25] and a comparable diastereoselectivity of reaction would be expected with epoxides. In any case the distinction between isomers **26–29** is irrelevant. Flash vacuum pyrolysis[26] of the isomer mixture at 660 °C gave the same α-methylene lactone **9**.

Preparation of Sulfone 7. Hydrogenation of the α-methylene lactone **9** over palladium on carbon gave the *cis*-dimethyl lactone **31** (61% based upon lactones **26–29**) (Chart IV). The diastereoselectivity of hydrogenation was excellent (>30:1), and only traces of the isomeric lactone **32** were detected by a NMR spectroscopy. The respective NMR spectra for **31** and authentic[27] racemic **32** were easily distinguishable. The high diastereoselectivity in the hydrogenation of **9** to produce **31** is well precedented in related systems.[28]

Diisobutylaluminum hydride reduction of **31** and subsequent Wittig homologation of the intermediate lactol **33** with ethyl (triphenylphosphorylidene)acetate gave the α,β-unsaturated ester **34a** (89%). Geometric selectivity in this process was good (>93:7) as was expected with the stabilized ylide. Subsequent reaction of the alcohol **34a** with *N*-(phenylsulfenyl)phthalimide and tributylphosphine[29] gave, with inversion of configuration, sulfide **35a** (57% overall from **31**). Diisobutylaluminum hydride reduction of **35a** to produce **35b** (88%) and subsequent Trost persulfate oxidation[30] gave the sulfone **7** (88%). Finally, *tert*-butyldimethylsilylation[31] of **7** gave the silyl ether **36** (95%).

It is crucial that in the conversion of (*S*)-(−)-propylene oxide (**5**) into **36** that racemization must not have occurred. It is conceivable that racemization may have taken place via double-bond migration during the hydrogenation reaction. Thus, to demonstrate that **36** was optically pure, a derivative of **34a** was prepared. Esterification of **34a** with optically pure (*S*)-*O*-methylmandelic acid[32] in the presence of DCC gave **34b** (81%). No additional diastereoisomeric esters were detected. In addition the high-field NMR spectrum of **34b** unequivocally established it to be diastereoisomerically pure.

Preparation of Lactone 11. Since we planned to utilize a spiro dihydropyrone such as **10** in our overall strategy, we required a convenient synthesis of the precursor lactone **11**. Initially we examined a resolution-based procedure. Thus, following the Meinwald precedent[33] *cis*-2,3-dimethyloxirane was condensed with lithium acetylide–1,2-ethylenediamine to produce the corresponding acetylene (±)-**37a** (51%) (Chart V). In the racemic series **37a** was converted into (±)-**11**[6,34] via sequential reaction with *n*-butyllithium, carbon dioxide, hydrogen over palladium on carbon, and toluene-4-sulfonic acid. Although the overall yield was modest (27%), it most probably could be improved by optimization. However, in our hands the resolution of **37a** proved tedious in the extreme, and thus optimization was not carried out. Alcohol **37a** could be partially resolved by formation of the (*S*)-*O*-methylmandelate esters **38a** and **39a** and HPLC. While on an analytic scale resolution was straightforward, preparative HPLC was at best synthetic lunacy. Baker has employed a partial resolution of **37a** in his studies on **3a**.[8] The two diastereoisomers **38a** and **39a** were clearly identified by hydrogenation over palladium on carbon to respectively produce **38b** (93%) and **39b** (93%). Isomer **38b** was identical with authentic material prepared from L-isoleucine via (2*R*,3*S*)-3-methyl-2-pentanol.[35]

Williams, in his total synthesis of milbemycin β_3 (**3a**), used the chiral lactone **11** that was prepared from (*S*)-(−)-citronellol.[7] In a variation of this very elegant synthesis we have prepared lactone **11** from (*S*)-(+)-citronellene[14] (**4**). Selective ozonolysis of **4** in dichloromethane gave aldehyde **40a**.[36] Without purification this was directly oxidized with either Jones' reagent or pyridinium dichromate[37] to produce **40b** (86%). Subsequent iodolactonization under Bartlett conditions of thermodynamic[38] control gave **41** (85%). Finally, tributylstannane reduction of **41** followed by a carbon tetrachloride and potassium fluoride workup[39] gave **11** (90%). Clearly this variation of the Williams procedure is synthetically very efficient: lactone **11** was obtained in 66% overall yield on a multigram scale.

Preparation of the Spiro Dihydropyrone 10: A Convenient Precursor for Spiro Ketal Synthesis. Several years ago we described a simple procedure for the preparation of spiro dihydropyrones from δ-lactones.[40] For example, condensation of the dianion **42a** with δ-valerolactone gave, on acidification, the spiro dihydropyrone **43** (91%). More recently, we have extended this chemistry to the construction of more heavily substituted spiro dihydropyrones.[41] In principle this chemistry should provide a convenient route to prepare **10** via the condensation of

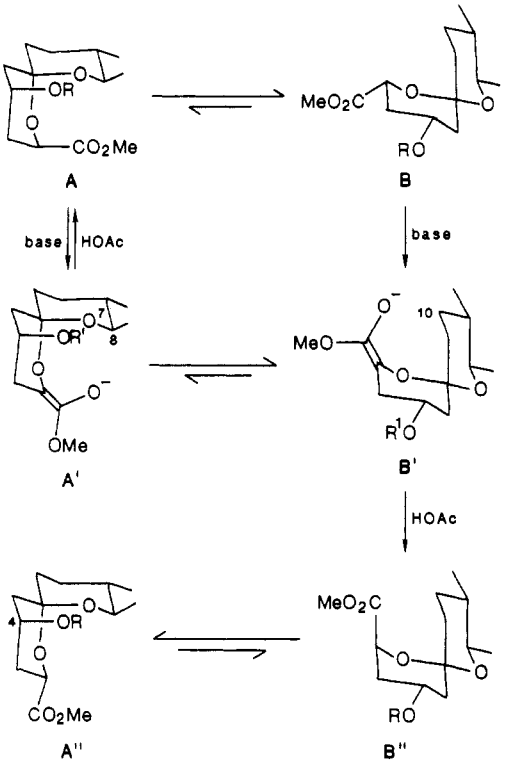
(24) Davis, J. C., Jr.; van Auken, T. V. *J. Am. Chem. Soc.* **1965**, *87*, 3900.
(25) Krapcho, A. P.; Dundulis, E. A. *J. Org. Chem.* **1980**, *45*, 3236.
(26) Anderson, D. J.; Horwell, D. C.; Stanton, E.; Gilchrist, T. G.; Rees, C. W. *J. Chem. Soc., Perkin Trans. 1* **1972**, 1317. We thank Professor Rees for advice on flash vacuum pyrrolysis and for the loan of apparatus.
(27) Prepared as a cis–trans mixture via the methylation (MeI) of the enolate derived form 5(*RS*)-methyl-4,5-dihydro-2(3*H*)-furanone. For an alternative preparation of racemic cis and trans lactones see: Tamaru, Y.; Mizutani, M.; Furukawa, Y.; Kawamura, S.; Yoshida, Z.; Yanagi, K.; Minobe, M. *J. Am. Chem. Soc.* **1984**, *106*, 1079.
(28) Hussain, S. A. M. T.; Ollis, W. D.; Smith, C.; Stoddart, J. F. *J. Chem. Soc., Perkin Trans 1* **1975**, 1480. Barrett, A. G. M.; Sheth, H. G. *J. Org. Chem.* **1983**, *48*, 5017.
(29) Walker, K. A. M. *Tetrahedron Lett.* **1977**, 4475.
(30) Trost, B. M.; Curran, D. P. *Tetrahedron Lett.* **1981**, 1287.
(31) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.
(32) Bonner, W. A. *J. Am. Chem. Soc.* **1951**, *73*, 3126.
(33) Adams, M. A.; Duggan, A. J.; Smolanoff, J.; Meinwald, J. *J. Am. Chem. Soc.* **1979**, *101*, 5364.
(34) Cooke, E.; Paradellis, T. C.; Edward, J. T. *Can. J. Chem.* **1982**, *60*, 29. See also ref 7.
(35) Winitz, M.; Bloch-Frankenthal, L.; Izumiya, N.; Birnbaum, S. M.; Baker, C. G.; Greenstein, J. P. *J. Am. Chem. Soc.* **1956**, *78*, 2423. Kirmse, W.; Prolingheuer, E.-C. *Chem. Ber.* **1980**, *113*, 104.
(36) For an example of another selective oxidation of (*S*)-(+)-citronellene, see: Mori, K.; Masuda, S.; Sugaro, T. *Tetrahedron* **1981**, *37*, 1329.
(37) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399.
(38) Bartlett, P. A.; Myerson, J. *J. Org. Chem.* **1979**, *44*, 1625.
(39) Leibner, J. E.; Jacobus, J. *J. Org. Chem.* **1979**, *44*, 449. Motherwell, W. B., personal communication.
(40) Attwood, S. V.; Barrett, A. G. M.; Florent, J.-C. *J. Chem. Soc., Chem. Commun.* **1981**, 556.
(41) Barrett, A. G. M.; Carr, R. A. E.; Finch, M. A. W.; Florent, J.-C.; Richardson, G.; Walshe, N. D. A. *J. Org. Chem.* in press.

11 with dianion **42b**. Methyl trimethoxyacetate **44a** was prepared from dimethyl oxalate via reaction with phosphorus pentachloride and methanol–pyridine.[42] Subsequent condensation with the acetone enolate under standard conditions[43] gave the β-diketone **44b** (88%). Following the Harris–Weiler protocol[44] **44b** was doubly metalated using lithium diisopropylamide and the resultant **42b** condensed with **11**. To our delight workup by acidification resulted in both spirocyclization and ortho ester hydrolysis to produce **10** (84%) as a single diastereoisomer at the spirane center. This is to be expected since the cyclization is most reasonably reversible and thereby subject to thermodynamic control. Assignment of the stereochemistry was based upon the anticipation of a strong anomeric effect[45] with the O-1–C-6 bond being axial, by analogy with other spiro dihydropyrones prepared in our laboratories[41] and by subsequent transformations (vide infra).

In order to transform **10** into an appropriate spiro ketal, it is necessary to doubly reduce the enone moiety. Although in structurally related spiro dihydropyrones including **43** this proved both troublesome and frustrating,[41] **10** proved to be an excellent substrate for further elaboration (Chart VI). Careful hydrogenation of **10** over rhodium on alumina initially gave ketone **45a** (62%) as a single isomer. On prolonged hydrogenation (2 h) **10** was converted into the two isomeric alcohols **45b** (58%) and **45c** (6%). In several small-scale experiments the yield of **45b** was considerably higher (90%). It is important to emphasize that attention to careful experimental control was absolutely essential for the hydrogenation reaction. We accidentally discovered that traces of acid completely suppressed the formation of **45b**. Thus, hydrogenation of **10** in the presence of acetic acid gave a single product **46** (85%). Presumably this was produced via selective ketone reduction, isomerization of the allylic alcohol, further hydrogenation of **47**, and final dehydration.

The stereochemistry of **45a**, **45b**, and **45c** requires substantiation. First, on the basis of CPK molecular models hydrogen should be delivered from the less hindered face of **10**, thereby providing **45a** and **45b** as the major isomers. This expectation was confirmed chemically and by an X-ray crystallographic study. Thus, the major alcohol **45b** was converted into **45c** via reaction of the toluene-4-sulfonate **45d** (86%) with potassium acetate in DMF solution to produce **45e** (73%) and Zemplen methanolysis (84%). Second, sodium borohydride reduction of **45a** gave the alcohols **45b** and **45c** (82%, 4:1). This diastereoselectivity again reflects steric approach control. Finally, *tert*-butyldiphenylsilylation[46] of **45b** at *0 °C* gave **45f** (96%), which was obtained as a crystalline solid. An X-ray crystallographic study of **45f**[47] confirmed the structural assignment. Additionally, at least in the solid state, the molecule adopts the conformation with only a single anomeric effect (the C-6–O-7 bond is equatorial) but with all the ring substituents equatorial (ORTEP diagram).

Scheme II[a]



[a] Enolate geometries are arbitrarily depicted.

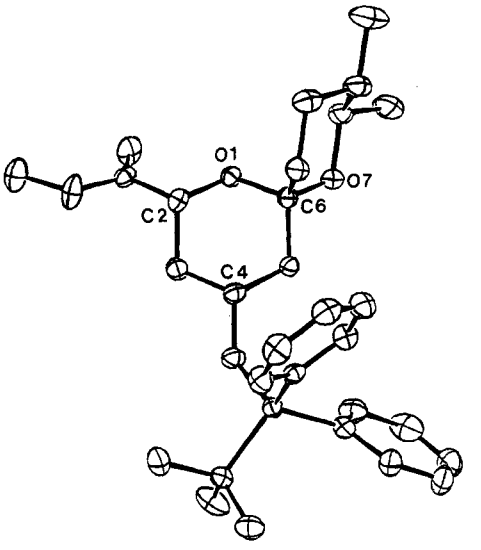
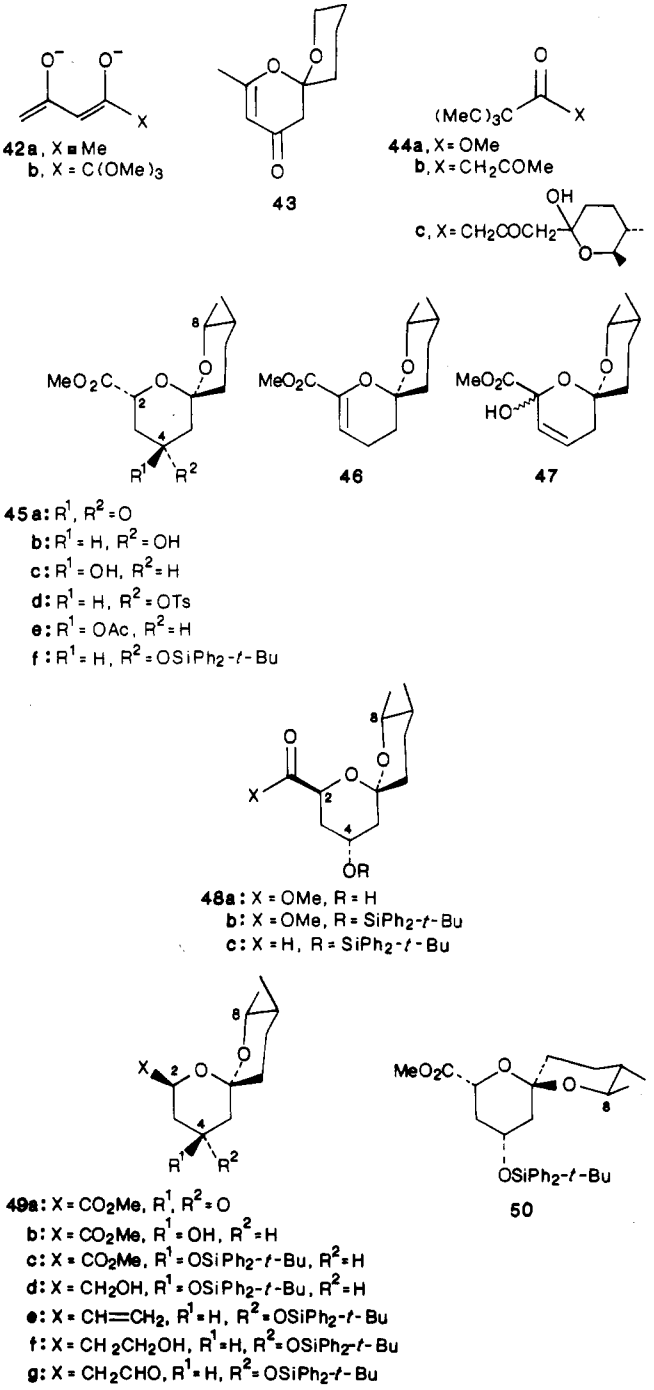


Figure 1. X-ray crystallographic perspective drawing of spiro ketal **45f**.

In order to transform **45f** to milbemycin β_3 (**3a**), it was first necessary to invert the stereochemistry at C-2. In principle this should be possible under basic conditions via the corresponding enolate. Although we initially planned to carry out the isomerization under thermodynamic control, we discovered that isomerization under kinetic control is superior. Ester **45b** was slowly metalated with lithium diisopropylamide and quenched with acetic acid to produce **48a** (30%) and recovered **45b** (63%). The amount of isomerization did not increase with prolonged metalation, and thus the **48a** to **45b** ratio probably reflected a kinetic ratio for reprotonation rather than incomplete metalation. In contrast, the silyl ether **45f** was smoothly and rapidly converted into **48b** (91%!) on metalation with lithium diisopropylamide at −78 °C and subsequent acidification. The isomerization reactions of

(42) Kantlehner, W.; Kapassakalidis, J. J.; Maier, T. *Annalen* **1980**, 1448.
(43) For a related transformation see: Levine, R.; Conroy, J. A.; Adams, J. T.; Hauser, C. R. *J. Am. Chem. Soc.* **1945**, *67*, 1510.
(44) Harris, T. M.; Harris, C. M. *Tetrahedron* **1977**, *33*, 2159. Huckin, S. N.; Weiler, L. *Can. J. Chem.* **1974**, *52*, 1343.
(45) Kirby, A. J. *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*; Springer-Verlag: New York, 1983. Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon: Toronto, 1983; Chapter 2.
(46) Hanessian, S.; Lavallee, P. *Can. J. Chem.* **1975**, *53*, 2975; **1977**, *55*, 562.
(47) Brock, C. P. *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.* **1986**, *C42*, 381.

Chart VI



45b into **48a** and of **45f** into **48b** are clearly very different. Ester **45f** in solution can exist as two interconverting conformational minima, **A** and **B** (R = Ph_2-*t*-BuSi) (Scheme II). As in the X-ray crystallographic study, the preferred conformation in solution is presumably **B**. On lithiation the predominant conformation in solution is still probably **B′**, with the very bulky silyloxy group equatorial. Thus, on protonation of **B′** the acid will predominantly approach from the less hindered face to produce the epimer **B″**. Clearly, in **B′** the C-10 methylene shields the top face of the enolate. Alternatively, protonation of the minor conformation **A′**, also subject to steric approach control (by the C-8 hydrogen), should regenerate **A**. On this basis the kinetically controlled isomerization of **45f** to produce **48b** reflects the domination of conformation **B′** (R^1 = Ph_2-*t*-BuSi) in solution. In contrast the alcohol **45b** on metalation gave the dianion **A′–B′** (R^1 = Li). It is most reasonable to expect that **A′** (R^1 = Li) is the major conformation for two reasons: first, the oxygen substituent is smaller; second, in **A′**, the lithium cation (R^1) is ideally placed for chelation by the spiro ketal oxygen O-7. Thus, reprotonation of the dianion **A′–B′** (R^1 = Li) predominantly regenerated the starting material **45b**. Williams has utilized an analogous chelation reaction in controlling stereochemistry in his excellent phyllanthoside synthesis.[48]

The structures of **48a** and **48b** were established as follows. Tetrabutylammonium fluoride[49] mediated desilylation of **48b** gave **48a** (91%). Then oxidation of **48a** using pyridinium chlorochromate[50] gave the ketone **49a** (87%). Sodium borohydride reduction of **49a** gave the epimeric alcohol **49b** (77%) and regenerated **48a** (12%). The diastereoselectivity in this reduction is consistent with the Williams precedent[51] and presumably reflects chelation control. Finally, sequential reaction of **49b** with *tert*-butyldiphenylsilyl chloride,[46] to produce **49c**, and lithium aluminum hydride gave **49d**. The sample of **49d** ($[\alpha]_D$ +26°) prepared in this way exhibited spectroscopic characteristics that were identical with data published by Baker[52] ($[\alpha]_D$ +23°).

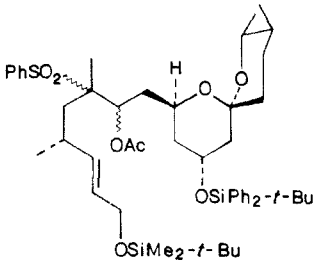
One further epimerization reaction was carried out on **45f**, albeit initially not by design! Spiro ketal **45f** was found to be very readily isomerized in the presence of acid to produce a new spiro ketal that was tentatively assigned as the C-6 epimer **50**. Williams has observed an equivalent epimerization reaction.[51]

For comparison purposes, key NMR characteristics of the spiro ketals are tabulated. First, it is interesting to note that the chemical shift of the C-8 proton is especially informative: it consistently shifts upfield as the stereochemistries at C-2 and C-4 are changed from *R* to *S*. Second, without exception the tetrahydropyran ring containing the two methyl is conformationally locked with both methyls equatorial. Finally, by examination of the *J* values for the C-2 protons, it is possible to confirm the conformational bias of the spiro ketal oxygen. Clearly, in **48a** and **48b**, the C-2 proton is axial; thus, these molecules must predominantly adopt conformation **A″** (Scheme II). In addition **49b** also possesses an axial C-2 proton, and in solution, it must also adopt conformation **A″** (epimeric at C-4). It should be emphasized that in conformation **A″** a double anomeric effect is operating. Additionally, in the ketones **45a** and **49a** the C-2 proton is pseudoaxial, which is consistent with the molecules existing predominantly as conformations **B** and **A″**, respectively (ketone analogues of these structures). It should also be noted that the C-2 proton in **45b** is clearly not predominantly axial and the *J* values (7.9, 5.1 Hz) reflect the fact that the NMR spectrum is an average for both conformations **A** and **B**. Unfortunately, the NMR spectrum for **45f** was insufficiently resolved-for *J* measurements. There is one final and remarkable observation: the chemical shift for the C-8 proton in **50** was observed at δ 2.05 (dq, J = 10, 6.6 Hz)! Examination of CPK molecular models showed that this proton was located in the shielding zone of one of the phenyl groups.

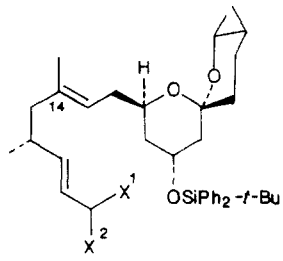
Elaboration of Spiro Ketal 48b into Milbemycin β_3 (3a). We planned to convert **48b** into **3a** via an initial homologation to produce **8**. Thus diisobutylaluminum hydride reduction of **48b** gave the aldehyde **48c** (89%).

(48) Williams, D. R.; Sit, S.-Y. *J. Am. Chem. Soc.* **1984**, *106*, 2949.
(49) Greene, T. W. *Protective Groups in Organic Synthesis*; Wiley: New York, 1981.
(50) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647.
(51) Williams, D. R.; Barner, B. A. *Tetrahedron Lett.* **1983**, *24*, 427.
(52) Baker, R.; Boyes, R. H. O.; Broom, D. M. P.; Devlin, J. A.; Swain, C. J. *J. Chem. Soc., Chem. Commun.* **1983**, 829.

Chart VII



51



Δ^{14} $E:Z$ = 5:3

52a: X^1 = H, X^2 = $OSiMe_2$-*t*-Bu

b: X^1 = H, X^2 = OH

c: X^1, X^2 = O

Table I. NMR Spectroscopic Characteristics for Spiro Ketals [δ, $CDCl_3$ (J, Hz)]

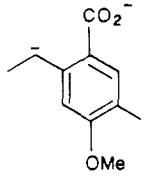
compd	2-H	4-H	8-H
45a	4.63 (dd, J = 10.0, 4.7)		3.79 (m)
45b	4.29 (dd, J = 7.9, 5.1)	4.04 (m)	3.87 (dq, J = 10.0, 6.6)
45c	4.41 (m)	4.41 (m)	3.55 (dq, J = 9.9, 6.6)
45f	3.79 (m)	3.79 (m)	3.79 (m)
48a	4.54 (dd, J = 12.5, 2.5)	4.18 (m)	3.40 (dq, J = 9.9, 6.6)
48b	4.85 (dd, J = 11.9, 2)	4.13 (m)	3.44 (dq, J = 9.9, 6.6)
49a	4.46 (dd, J = 10, 2.5)		3.31 (dq, J = 10.0, 6.5)
49b	4.20 (dd, J = 9.9, 2.0)	4.21 (m)	3.27 (dq, J = 9.9, 6.6)
50	4.57 (dd), J = 12.5, 2.6)	3.9 (dddd, J = 11, 11, 5, 5)	2.05 (dq, J = 10, 6.6)

This was converted into alcohol **49f** (95%) via alkene **49e** (90%) by Wittig methylenylation followed by hydroboration. The clean regioselectivity in the hydroboration reaction deserves particular emphasis. Subsequent oxidation of **49f** using pyridinium chlorochromate gave the aldehyde **49g** (89%).

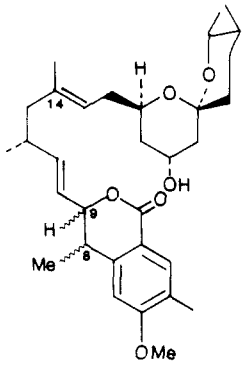
Initially we sought to convert sulfone **7** into the derived C-14, O-9 dianion, but the metalation proved to be extremely slow due in large part to the insolubility of the alkoxide. However, the silyl sulfone **36** was metalated with *n*-butyllithium and the resultant anion condensed with **49g** to produce **51** (86%) on workup with acetic anhydride (Chart VII). Although **51** was a complex mixture of diastereoisomers, reaction with sodium amalgam in THF–methanol gave the required alkene **52a**. The overall yield (86% from **36**) was good; however, the geometric selectivity in the Julia–Lythgoe[16] coupling was disappointing ($E:Z$ = 5:3). Although the geometric selectivity increased on reductive elimination at lower temperatures, the overall yield was considerably reduced.

The E–Z mixture of isomers was not separated at this stage. Selective deprotection of **52a** using aqueous acetic acid[53] gave **52b** (83%), which was smoothly oxidized with pyridinium chlorochromate[50] to produce the aldehyde **52c** (84%). The benzoic acid **6** was converted into the dianion **53** by reaction with sodium hydride followed by *tert*-butyllithium (Chart VIII). This intensely red-purple species smoothly condensed with **52c** to give **54** (73%) on workup with trifluoroacetic acid and tetrabutylammonium fluoride. The benzopyrone **54** was obtained as a mixture of isomers (C-8, C-9, C-14), which were not separated but used directly in the next step. In a variation of Williams chemistry,[7] **54** was reacted with potassium hydride and 18-crown-6 in THF solution at 0 °C to rapidly produce the seco acids **55** and **56**. In the original Williams publication an analogous elimination reaction without 18-crown-6 was considerably slower (5–7 h at reflux). Clearly the addition of the crown ether dramatically enhanced the rate of benzylic metalation[54] that preceded elimination. It must be emphasized that the major advantage of the Williams protocol is that the elimination is geometrically specific for the construction of Δ^8. At this point the two Δ^{14} geometric isomers were separated and the major isomer **55** (48% from **54**) cyclized.

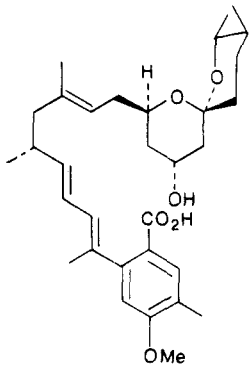
Chart VIII



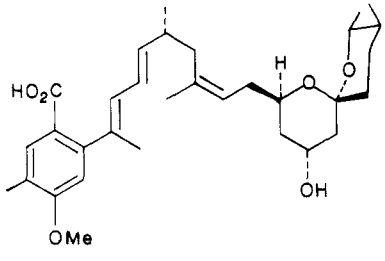
53



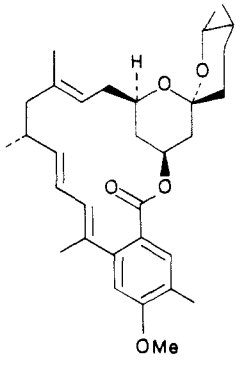
54 (Δ^{14} E:Z = 5:3)



55



56



57

Much to our satisfaction the Mitsunobu reaction[55] proved to be highly efficient in preparing the macrocyclic ring. Thus, **55** reacted rapidly and smoothly with diethyl azodicarboxylate and triphenylphosphine in benzene solution to produce 5-*O*-methylmilbemycin β_3 (**57**) (77%). Following exactly the Smith method,[6] it was deprotected with sodium ethanethiolate in DMF solution to produce milbemycin β_3 (**3a**). The ^1H NMR, ^{13}C NMR, IR, UV, and mass spectra of the product were in all respects identical with data provided by Professor Amos B. Smith III for their racemic synthetic material. In addition, our data were in complete agreement with Professor David R. Williams' spectroscopic data for (+)-milbemycin β_3 (**3a**). The melting point of our material (181–183 °C) was in good

(53) Nicolaou, K. C.; Papahatjis, D. P.; Claremon, D. A.; Magolda, R. L. *J. Org. Chem.* **1985**, *50*, 1440.

(54) Buncel, E.; Menon, B. *J. Am. Chem. Soc.* **1977**, *99*, 4457.

(55) Mitsunobu, O. *Synthesis* **1981**, 1.

agreement with the published values for synthetic[7-9] and natural[5] materials. However, we disagree with several of the values for the $[\alpha_D]$ of synthetic **3a**. The Sankyo chemists[5] did not record the $[\alpha]_D$ value for natural β_3 (**3a**), and the material is no longer available. In 1982 Professor Williams recorded an $[\alpha]_D$ of +26.5° (*c* 0.20, MeOH).[7] Similar values were subsequently observed by Baker[8] (+26.1°) and Kocienski[9] [+32.8° (*c* 0.30, MeOH)]. The optical rotation for our synthetic β_3 (**3a**) was +102° (*c* 0.17, MeOH),[13] which is significantly larger than the values hitherto published. We are however certain that our value is substantially more reliable. Although the optical rotation of natural β_3 (**3a**) is unknown, a new natural product milbemycin "X" has just been isolated. It is a homologue of β_3 (**3a**) with the structure **3b**. Most interestingly **3b** exhibits a rotation of +111° (*c* 0.5, Me_2CO).[56] It is well established that variation in substitution at C-25 has little effect on $[\alpha]_D$ values. For example, the milbemycins α_1 (**2a**), α_3 (**2b**), and D (**2c**), respectively, show $[\alpha_D]$ of +106, +106, and +107°.[4] It is most reasonable therefore to expect the $[\alpha_D]$ values for milbemycin β_3 (**3a**) and X (**3b**) to be substantially in agreement. On this basis we are confident that a value of +102° is reasonable, albeit perhaps a little low! Recently Baker has revised the $[\alpha]_D$ value for his synthetic material to +105°.[57] Additionally, Kocienski has just observed[58] that the $[\alpha]_D$ value for **3a** varies substantially with purity and nature of solvent. Very recently Professor Williams informed us that the optical rotation values that they now observe for their synthetic milbemycin β_3 (**3a**) are +103° (*c* 0.280, MeOH), +125.5° (*c* 0.270, $CHCl_3$), and +115.6° (*c* 0.250, Me_2CO).[59] Additionally, they have observed that milbemycin β_3 (**3a**) tenaciously retains water and extensive drying is necessary to obtain reliable $[\alpha]_D$ values. These observations probably account for the diversity of previously reported values.

In conclusion, we have completed a total synthesis of milbemycin β_3 (**3a**), using as key steps the construction of the spiro dihydropyrone **10** and its elaboration to produce spiro ketal **49g**; the preparation of sulfone **36** from (*S*)-(−)-propylene oxide (**5**); the elaboration to produce the seco acid **55** via Julia–Lythgoe and Williams chemistry; and the closure using an efficient Mitsunobu reaction. The product milbemycin β_3 (**3a**) was thus prepared from only two chiral pool starting materials by a concise procedure.

Experimental Section

Melting points were determined with a Kofler or a Reichert Thermovar hot stage 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 grating infrared spectrophotometer or a Sargent-Welch 3-100 infrared spectrophotometer. ^1H NMR were recorded on a Varian EM390, Joel FT90, Bruker WM250, Joel FT270, or Varian XL400. 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 microanalysis were purified by recrystallization, distillation, or, for oils, rechromatography with extensive drying of the sample under vacuum (<0.01 mm). The mass spectral data were recorded on an AEI MS12, V-G Micromass 7070B, a V-G 7070F, and a Hewlett-Packard 5985B GC/MS or by the University of Nebraska Spectrometry Service Laboratory.

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

Solvents were purified as follows: PhH and PhMe were distilled from sodium benzophenone ketyl onto 4-Å molecular sieves; CH_2Cl_2 and CCl_4 were redistilled from P_4O_{10}; EtOAc, hexane (petroleum fraction bp 40–60 °C) or pentane (30–50 °C), Et_2O, THF, and 1,2-dimethoxyethane (DME) were distilled from sodium benzophenone ketyl; DMF was distilled from CaH_2 onto 4-Å molecular sieves; EtOH and MeOH were absolute and were dried by distilling from Mg; $(i\text{-}Pr)_2NH$ was distilled from CaH_2 onto 4-Å molecular sieves. Reagents were purified according to standard procedures. Organic solutions were routinely dried over anhydrous sodium sulfate. Solvents were evaporated at reduced pressure on 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, 6.6 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.

(*E*)-1-Methoxy-2-methyl-3-[(trimethylsilyl)oxy]-1,3-butadiene (12). Anhydrous $ZnCl_2$ (0.75 g) was stirred with Et_3N (58.5 mL) at room temperature for 1 h. The reaction mixture was treated with Me_3SiCl (39g) and a solution of **13** (19.87 g) in dry PhH (45 mL), and the system was stirred vigorously at room temperature for 72 h. The solution was poured into Et_2O (500 mL) and filtered to remove Et_3NHCl, and the filtrate was concentrated in vacuo to afford a brown oil. Further trituration with Et_2O resulted in the isolation of a further quantity of a white solid. This process was repeated until no further white solid could be isolated. Distillation at reduced pressure, from base-washed glassware, afforded **12** [25.0 g (77%)] as a pure colorless liquid; bp 66 °C (10 mmHg) [lit.[17] bp 45–59 °C (5 mmHg)].

Ethyl 2-Ethyl-4-hydroxy-5-methylbenzoate (14a). In apparatus that was washed with $(Me_3Si)_2NH$ and dried at 200 °C for 12 h were heated ethyl 2-pentynoate[60] (8.87 g), 1-methoxy-2-methyl-3-[(trimethylsilyl)oxy]-1,3-butadiene (**12**; 25 g) and dry doubly distilled xylene (40 mL) to reflux under argon for 4 days. After cooling, 1 M hydrochloric acid and THF (1:1, 100 mL) were added and the mixture was stirred for 0.5 h. After concentration the residue was extracted with EtOAc (3 × 100 mL). The combined organic extracts were washed with H_2O (50 mL) and saturated aqueous $NaHCO_3$ (3 × 50 mL) and dried. Evaporation and chromatography on silica (170 g) gave (eluant Et_2O–hexane, 1:8) **14a** [7.5 g (52%)] as a white crystalline solid: mp 75–77 °C (from Et_2O–hexane); IR (CH_2Cl_2) 3600, 2900, 1720, 1630, 1590, 1510, 1460, 1380, 1220, 1140, 1080, 1060, 1030, 920, 870 cm^{-1}; ^1H NMR δ 7.71 (s, 1 H), 6.65 (s, 1 H), 6.35 (s, 1 H, aryl O*H*), 4.3 (q, 2 H, *J* = 7 Hz), 2.9 (q, 2 H, *J* = 7 Hz), 2.2 (s, 3 H), 1.4 (t, 3H, *J* = 7 Hz), 1.15 (t, 3 H, *J* = 7 Hz); mass spectrum, *m/e* 208 ($M^{\bullet+}$), 179, 163 (100%), 79, 77, 40, 39. Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.19; H, 7.75. Found: C, 69.19; H, 7.88. On a smaller scale (2 mmol) the yield of **14a** was superior (70%).

Ethyl 2-Ethyl-4-methoxy-5-methylbenzoate (14b). Ethyl 2-ethyl-4-hydroxy-5-methylbenzoate (**14a**; 0.996 g) was dissolved in Me_2CO (8 mL) and the resultant solution treated sequentially with K_2CO_3 (1.40 g) and MeI (10.2 g). The resulting suspension was rapidly stirred and heated to reflux. After 12 h the solution was cooled and the reaction mixture evaporated to dryness. Et_2O (25 mL) was added and the suspension chromatographed on silica, eluting with Et_2O. Evaporation of the solvent gave **14b** [1.04 g (98%)] as a colorless oil: R_f 0.85 (silica; Et_2O–hexane, 1:1); IR (film) 3000, 1715, 1625, 1510, 1470, 1370, 1340, 1260, 1150, 1040 cm^{-1}; ^1H NMR (270 MHz) δ 7.70 (s, 1 H), 6.60 (s, 1 H), 4.30 (q, 2 H, *J* = 7 Hz), 3.85 (s, 3 H), 3.00 (q, 2 H, *J* = 7 Hz), 2.20 (s, 3 H), 1.35 (t, 3 H, *J* = 7 Hz), 1.28 (t, 3 H, *J* = 7 Hz); mass spectrum, *m/e* 222 ($M^{\bullet+}$), 193, 177 (100%), 149, 133, 117, 105, 91, 77, 65,

(56) Mishima, H. Sankyo Co. Ltd., unpublished observations. We are indeed grateful to Drs. H. Mishima and Y. Takiguchi for this personal communication.
(57) Baker, R. *J. Chem. Soc., Chem. Commun.* **1986**, 276.
(58) Kocienski, P. J., unpublished observations.
(59) Williams, D. R., personal communication.
(60) Bradsma, L. *Preparative Acetylene Chemistry*; Elsevier: New York, 1971.

51, 43. Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.22; H, 8.17. Found: C, 70.12; H, 8.38.

2-Ethyl-4-methoxy-5-methylbenzoic Acid (6). To a solution of **14b** (0.242 g) in MeOH (1 mL) was added 1 M LiOH (0.250 mL). The resulting solution was refluxed for 8 h. The reaction mixture was acidified to pH 5 with trifluoroacetic acid, silica (1 g) added, and the solvent evaporated. The resulting powder was loaded onto a silica column and eluted with Et_2O–hexane (1:1) to give **6** [0.207 g (98%)] as a white crystalline solid: mp 152–154 °C (from Et_2O–hexane); R_f 0.40 (silica; Et_2O–hexane, 1:1); IR (CH_2Cl_2) 3500, 3100, 2900, 1740, 1680, 1620, 1510, 1400, 1250, 1170, 1140, 1090, 1020 cm^{-1}; ^1H NMR (270 MHz) δ 12–13 (1 H, br, CO_2H), 7.75 (s, 1 H), 6.55 (s, 1 H), 3.75 (s, 3 H), 2.95 (q, 2 H, J = 7.5 Hz), 2.15 (s, 3 H), 1.20 (t, 3 H, J = 7.5 Hz); mass spectrum, m/e 194 ($M^{\bullet+}$), 177, 149, 133, 108, 91, 77, 65, 51, 39. Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.00; H, 7.27. Found: C, 67.90; H, 7.31.

Ethyl 2-(Phenylsulfenyl)-4-oxo-2-pentenoate (17a). The phosphorane **16a**[61] (48.0 g) in PhH (1 L) was reacted with 40% aqueous MeCOCHO (11.52 g) at reflux for 48 h. After cooling, the mixture was concentrated in vacuo to yield a yellow semicrystalline oil that was filtered and washed, at the pump, with Et_2O–hexane (1:1). Concentration of the filtrate in vacuo followed by chromatography on silica (eluant Et_2O–pentane, 1:9) gave **17a** [17.9 g (87%)] as a yellow oil that crystallized on standing: mp 50–53 °C (from Et_2O–pentane); IR (film) 2990, 1720, 1665, 1545, 1475, 1365, 1360, 1240, 1190, 1095, 1050, 1015, 825, 755 cm^{-1}; ^1H NMR (250 MHz) δ 7.54–7.26 (m, 5 H), 6.73 (s, 1 H), 3.76 (q, 2 H, J = 7 Hz), 2.35 (s, 3 H), 0.88 (t, 3 H, J = 7 Hz); mass spectrum, m/e 250 ($M^{\bullet+}$), 207, 204, 179, 177, 161, 135, 134, 91, 85, 83, 43 (100%). Anal. Calcd for $C_{13}H_{14}O_3S$: C, 62.36; H, 5.64. Found: C, 62.35; H, 5.64.

Ethyl 2-[(4-Chlorophenyl)sulfenyl]-4-oxo-2-pentenoate (17b). The phosphorane **16b**[61] (8.0 g) in dry PhH (200 mL) was reacted with 40% aqueous MeCOCHO (1.84 g) at the reflux for 20 h. After cooling, the mixture was concentrated in vacuo to yield a yellow semicrystalline oil that was filtered and washed at the pump with Et_2O–pentane (1:1). Concentration of the filtrate in vacuo followed by chromatography on silica (eluant CH_2Cl_2–pentane) gave **17b** [3.33 g (72%)] as a yellow oil: IR (film) 1730, 1675, 1575, 1555, 1480, 1395, 1370, 1245, 1195, 1100, 1055, 1015, 830, 755 cm^{-1}; ^1H NMR (250 MHz) δ 7.39 and 7.30 (AB q, 4 H, J = 8.5 Hz), 6.76 (s, 1 H), 3.84 (q, 2 H, J = 7 Hz), 2.34 (s, 3 H), 0.95 (t, 3 H, J = 7 Hz); mass spectrum, m/e 284 ($M^{\bullet+}$), 279, 255, 241, 213, 197, 108, 43 (100%). Anal. Calcd for $C_{13}H_{13}ClO_3S$: C, 54.81; H, 4.60; S, 11.26; $M^{+\bullet}$ 284.0274. Found: C, 55.06; H, 4.63; S, 10.96; $M^{+\bullet}$ 284.0274.

5-Acetyl-4-[(4-chlorophenyl)sulfenyl]-4-(ethoxycarbonyl)-2-methylcyclohex-2-enone (18). A solution of (*E*)-1-methoxy-2-methyl-3-[(trimethylsilyl)oxy]-1,3-butadiene (**12**; 0.78 g) and **17b** (0.80 g) in dry PhH (2 mL) was heated at the reflux for 6 h. The cooled reaction mixture was treated with ethanolic hydrogen chloride and concentrated in vacuo to afford a dark oil. Trituration with Et_2O gave **18** [0.64 g (64%)] as a white crystalline solid: mp 116.5–119.5 °C (sublimed sample); IR (Nujol) 1745, 1720, 1675, 1480, 1410, 1360, 1280, 1240, 1190, 1095, 1015, 820, 750 cm^{-1}; UV (EtOH) λ_{max} 234 nm (sh) (log ϵ 4.15); ^1H NMR (250 MHz) δ 7.42 and 7.29 (AB q, 4 H, J = 8.5 Hz), 6.12 (q, 1 H, J = 1.5 Hz), 4.26 (q, 2 H, J = 7 Hz), 3.82 and 3.77 (dd, 1 H, J = 4 Hz), 3.10 and 3.05 (dd, 1 H, J = 17 Hz), 2.75 and 2.68 (dd, 1 H, J = 4 Hz), 2.30 (s, 3 H), 1.69 (d, 3 H, J = 1.5 Hz), 1.32 (t, 3 H, J = 7 Hz); ^{13}C NMR δ 205.1 (s), 195.6 (s), 170.9 (s), 142.0 (d), 139.5 (d), 136.6 (s), 135.7 (s), 128.7 (d), 128.3 (s), 62.7 (t), 56.1 (s), 52.3 (d), 36.8 (t), 29.8 (q), 15.3 (q), 13.9 (q); mass spectrum, m/e 366 ($M^{\bullet+}$), 251, 223, 181, 153, 144, 137, 109 (100%) 91, 77, and 43. Anal. Calcd for $C_{18}H_{19}ClO_4S$: C, 58.91; H, 5.22. Found: C, 59.09; H, 5.23.

Ethyl 2-Acetyl-4-hydroxy-5-methylbenzoate (15). Method 1. A solution of **18** (0.18 g) in dry PhH (5 mL) and EtOH (5 mL) was reacted at room temperature with Na (13 mg) in EtOH (5 mL). The resultant yellow solution was concentrated in vacuo, and the residue was chromatographed on silica (5 g, eluant CH_2Cl_2) to give **15** [83 mg (75%)] as a white crystalline solid: mp 128.5–129.5 °C; IR (Nujol) 3170, 1695, 1615, 1585, 1365, 1325, 1285, 1235, 1165, 1015 cm^{-1}; UV (EtOH) λ_{max} 264 nm (log ϵ 3.87); UV (EtOH + 1 drop of 2 N NaOH) λ_{max} 236, 310 nm; ^1H NMR (250 MHz) δ 7.69 (s, 1 H), 7.50 (br s, 1 H, exch D_2O), 6.67 (s, 1 H), 4.32 (q, 2 H, J = 7 Hz), 2.49 (s, 3 H), 2.23 (s, 3 H), 1.36 (t, 3 H, J = 7 Hz); ^{13}C NMR δ 205.3 (s), 166.4 (s), 157.9 (s), 143.4 (s), 133.1 (d), 126.1 (s), 119.7 (s), 112.7 (d), 61.4 (t), 30.7 (q) 15.5 (q), 14.1 (q); mass spectrum, m/e 222 ($M^{\bullet+}$), 207, 179 (100%), 177, 135, 109, 77, and 43. Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.83; H, 6.35. Found: C, 64.78; H, 6.35. In a separate experiment, the butadiene derivative **12** and the dienophile **17b** were converted directly to the title compound **15** (72%) without isolation of the intermediate enone **18**.

Method 2. A solution of **12** (1.35 g) and **17a** (1.25 g) in dry PhH (5 mL) was heated at the reflux for 18 h. After cooling, the reaction mixture was treated at room temperature with Na (0.17 g) in EtOH (50 mL). The resultant dark solution was evaporated in vacuo and the residue chromatographed on silica (25 g, eluant CH_2Cl_2) to give **15** [0.88 g (80%)] as a white crystalline solid, mp 129–129.5 °C.

5-Hydroxy-3,6-dimethylisobenzofuran-1(3*H*)-one (19). The benzoate **15** (50 mg) in EtOH (5 mL) was reacted with $NaBH_4$ (55 mg) at 0 °C for 1 h. The reaction mixture was stirred at room temperature overnight and quenched by addition of dilute hydrochloric acid. Extraction of the reaction mixture with Et_2O (×3), followed by concentration of the dried extracts in vacuo gave **19** [38 mg (95%)] as a white crystalline solid: mp 182.5–184 °C; IR (Nujol) 3175, 1725, 1620, 1600, 1330, 1280, 1135, 1045 cm^{-1}; UV (EtOH) λ_{max} 254 nm (log ϵ 4.09), 281 (3.79), 288 (3.79); UV (EtOH + 1 drop of 2 N NaOH) λ_{max} 228 nm (sh), 307; ^1H NMR (250 MHz) δ 7.65 (s, 1 H), 7.51 (br, 1 H, exch D_2O), 6.80 (s, 1 H), 5.46 (q, 1 H, J = 7 Hz), 2.33 (s, 3 H), 1.58 (d, 3 H, J = 7 Hz); mass spectrum, m/e 178 ($M^{\bullet+}$), 163, 135 (100%). Anal. Calcd for $C_{10}H_{10}O_3$: C, 67.39; H, 5.66. Found: C, 67.39; H, 5.67.

Spiro Lactones 26–29. *n*-BuLi (1.50 M, 26.5 mL) was added to $(i\text{-Pr})_2NH$ (5.56 mL) in dry THF (18 mL) at −78 °C under argon. After the mixture was warmed to 0 °C for 0.75 h and recooled to −78 °C, **25a** (5.5 g) in dry THF (9 mL) was added. After 1.75 h, 2(*S*)-methyloxirane (**5**; 4.2 g) in dry THF (4 mL) was added and the solution allowed to warm to room temperature over 2 h. After a further 8 h of stirring, concentrated hydrochloric acid (15 mL) in H_2O (60 mL) was cautiously added. The mixture was refluxed for 2 h and after cooling extracted with Et_2O (3 × 120 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (50 mL) and H_2O (10 mL), dried ($MgSO_4$), and evaporated. Chromatography on silica (120 g) gave a mixture of **26–29**, 4.2 g (66%). The mixture of isomers was partially resolved during the chromatographic separation. The less polar minor (~10%) component, which was an oil, contained two isomers tentatively assigned as **28** and **29**: $[\alpha]_D$ −54.9° (*c* 0.75, $CHCl_3$); IR (film) 3000, 1770 cm^{-1}; ^1H NMR (250 MHz) δ 6.34 and 6.28 (2 dd, 1 H, J = 5.5, 3 Hz; J = 5.5, 3 Hz), 6.15 (m, 1 H), 4.56 and 4.45 (2 m, 1 H), 2.97 and 2.90 (2 br s, 2 H), 2.36 (dd, ~0.5 H, J = 13, 5 Hz), 2.2–2.05 (m, ~2 H), 1.90 (dd, ~0.5 Hz, J = 13, 6 Hz), 1.79 (dd, ~0.5 H, J = 13, 10 Hz), 1.62 (dd, ~0.5 H, J = 14, 10 Hz), 1.38 (2-methyl d overlapping m, 4 H, J = 7, J = 7 Hz), 1.24 (dd, ~0.5 H, J = 12, 3 Hz), 1.03 (dd, ~0.5 H, J = 12, 4 Hz); mass spectrum, m/e 178 ($M^{\bullet+}$), 113, 95, 91, 79, 77, 66 (100%), 43, 40. Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.11; H, 7.92. Found: C, 74.29; H, 8.19. The more polar major (~90%) component, which was an oil, contained two isomers tentatively assigned as **26** and **27**: $[\alpha]_D$ −31.3° (*c* 1.43, $CHCl_3$); IR (film) 3000, 1785, 1460, 1400, 1380, 1200, 1110 cm^{-1}; ^1H NMR (250 MHz) δ 6.28 (m, ~1.5 H), 5.95 (m, ~0.5 H), 4.7–4.5 (m, 1 H), 2.95 and 2.83 (2 br s, 2 H), 2.42 (dd, ~0.5 H, J = 13, 6 Hz), 2.35 (dd, ~0.5 H, J = 12, 5 Hz), 2.12–1.92 (2 dd, 1 H, J = 13, 10 Hz, J = 13, 8 Hz), 1.86–1.73 (2 dd, 1 H, J = 11, 3.5 Hz, J = 11, 3.5 Hz), 1.7–1.4 (m, 3 H), 1.44 and 1.42 (2 methyl d, 3 H, J = 7, J = 7 Hz); mass spectrum, m/e 178 ($M^{\bullet+}$), 113, 95, 91, 79, 77, 66 (100%), 53, 51, 43, 39. Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.11; H, 7.92. Found: C, 74.01; H, 8.00.

(4*S*)-*N*-Cyclohexyl-4-hydroxy-2-methylenepentanamide (24). *n*-BuLi (1.50 M, 34 mL) was added to **21** (7.4 g) in dry 1,2-dimethoxyethane (80 mL) at −78 °C under argon. The organic solution was warmed to 25 °C over 2.5 h and recooled to −78 °C and 2(*S*)-methyloxirane[15] (**5**; 1 g) in dry 1,2-dimethoxyethane (1 mL) added. After 15 min the solution was allowed to warm to room temperature. After 9 h, evaporation gave a residue that was

(61) Saikachi, H.; Nakamura, S. *Yakugaku Zasshi* **1968**, *88*, 715; *Chem. Abstr.* **1968**, *69*, 106824*m*.

extracted with Et_2O (200 mL) and the extract washed with 1 M HCl (50 mL) and saturated aqueous $NaHCO_3$ (2 × 50 mL). The dried ($MgSO_4$) organic phase was evaporated and the residue chromatographed on silica (50 g) to give (eluant Et_2O–hexane, 1:1) **24**: 3.40 g (97%); mp 59–61 °C; IR 3300, 3070, 1640, 1600 cm^{-1}; ^1H NMR (90 MHz) δ 6.2 (m, 1 H, NH), 5.6 (s, 1 H), 5.3 (s, 1 H), 4.0–3.6 (m, 2 H), 3.45 (m, 1 H, OH), 2.4 (dd, 2 H, J = 8, 5 Hz), 2.0–1.3 (m, 10 H), 1.2 (d, 3 H, J = 5 Hz); mass spectrum, m/e 211 ($M^{\bullet+}$), 168, 167 (100%), 166, 152, 112, 98, 95. Anal. Calcd for $C_{12}H_{21}NO_2$: C, 68.19; H, 10.02. Found: C, 68.45; H, 10.10.

5(*S*)-Methyl-3-methylenedihydro-2(3*H*)-furanone (9). CF_3CO_2H (1.7 mL) was added to **24** (4.5 g) in dry THF (135 mL), and the solution was refluxed for 14 h. After cooling, the mixture was diluted with Et_2O (200 mL), washed with H_2O (35 mL) and $NaHCO_3$ (1.7 g) in H_2O (80 mL), and dried ($MgSO_4$). Evaporation and chromatography on silica gave (eluant Et_2O–hexane, 1:5) **9**[22] [1.8 g (75%)] as a colorless oil: IR (film) 1760 cm^{-1}; ^1H NMR (90 MHz) δ 6.24 (t, 1 H, J = 3 Hz), 5.64 (t, 1 H, J = 3 Hz), 4.7 (m, 1 H), 3.14 (ddt, 1 H, J = 18, 5, 2 Hz), 2.52 (ddt, 1 H, J = 18, 4.5, 2 Hz), 1.44 (d, 3 H, J = 6.6 Hz).

3(*R*),5(*S*)-Dimethyldihydro-2(3*H*)-furanone (31). The mixture of **26**, **27**, **28**, and **29** (4.2 g) was distilled through a quartz chip packed quartz tube (21 in. × 1 in.) heated to 660 °C (0.15 mmHg). The crude α-methylene lactone **9** was condensed at 40 °C and used without subsequent purification. The lactone **9** in EtOH (75 mL) was added to prehydrogenated 10% Pd–C (0.5 g) in EtOH (25 mL) and the mixture hydrogenated at atmospheric pressure. The catalyst was filtered off with Celite. Evaporation and Kugelrohr distillation of the residue gave **31** [1.60 g (61%)] as a colorless oil: bp 82 °C (oven temperature at 11 mmHg); $[\alpha]_D$ −4.9° (c 0.2, $CHCl_3$); IR (film) 1765, 1460, 1390, 1350, 1180, 1050, 955 cm^{-1}; ^1H NMR (250 MHz) δ 4.49 (m, 1 H), 2.70 (m, 1 H), 2.53 (m, 1 H), 1.50 (m, 1 H), 1.43 (d, 3 H, J = 7 Hz), 1.27 (d, 3 H, J = 7 Hz); mass spectrum, m/e 113, 107, 100, 95, 93, 91, 79, 77, 67, 65, 55, 53, 43, 41, 39. Anal. Calcd for $C_6H_{10}O_2$: C, 63.11; H, 8.84. Found: C, 63.18; H, 8.77.

3(*R*),5(*S*)-Dimethyltetrahydro-2-furanol (33). $(i\text{-Bu})_2AlH$ in PhMe (1.54 M, 10.0 mL) was added dropwise to **31** (1.6 g) in PhMe (2 mL) at −78 °C. After 2 h, HOAc (2.65 mL) was added dropwise. The resulting solution was allowed to warm to 0 °C over 45 min, the ice-cooled mixture was recooled to −78 °C, H_2O (0.84 mL) was added, and the solution was warmed to room temperature. Solid $NaHCO_3$ (6.0 g) and Et_2O (100 mL) were added, and the resulting slurry was stirred for 20 min. The slurry was filtered through Celite and the solid material washed exhaustively with Et_2O (3 × 100 mL) until the product (**33**) was absent by TLC. The combined organic washings were evaporated to give an oil [1.55 g (95%)] that was not routinely purified but used directly for the next reaction. Flash chromatography (silica, Et_2O–hexane, 7:13) gave pure **33** [1.14 g (71%)] as a mobile colorless oil: bp 97 °C (16 mmHg); $[\alpha]_D$ +2.6° (c 0.87, $CHCl_3$); R_f 0.65 (silica, Et_2O–hexane, 1:1); IR (film) 3400, 2950, 1100, 1000 cm^{-1}; ^1H NMR (250 MHz) δ 5.2 (d, 0.33 H, J = 6 Hz), 5.1 (d, 0.67 H, J = 3.5 Hz), 4.35 (m, 0.67 H), 4.15 (m, 0.33 H), 2.35–2.0 (m, 2 H), 1.6 (m, 2 H), 1.38 (d, 0.33 × 3 H, J = 7 Hz), 1.29 (d, 0.67 × 3 H, J = 7 Hz), 1.10 (d, 0.33 × 3 H, J = 7 Hz), 1.09 (d, 0.67 × 3 H, J = 7 Hz); mass spectrum, m/e 101, 98, 91, 83, 72, 70, 57, 55, 53, 45, 43, 41, 39. Anal. Calcd for $C_6H_{12}O_2$: C, 62.02; H, 10.42. Found: C, 62.21; H, 10.48.

Ethyl (4*R*,6*S*)-6-Hydroxy-4-methyl-2(*E*)-heptenoate (34a). To a solution of **33** (1.55 g) in PhH (30 mL) was added $Ph_3P{=}CHCO_2Et$ (7.05 g) and the resulting solution warmed to 60 °C for 4 h. The reaction mixture was cooled to room temperature and PhH evaporated. The residue was triturated with Et_2O–hexane (1:1, 100 mL), and the solid (excess Wittig reagent plus Ph_3PO) was filtered off through Celite. The filtrate was evaporated to a pale yellow oil (2.4 g) that by TLC (silica, Et_2O–hexane, 3:7) contained only the desired alkene (**34a**) and a small amount of Ph_3PO. The crude product was not routinely purified but used directly in the next reaction. Flash chromatography (silica, Et_2O–hexane, 3:7) gave **34a** as a colorless oil [2.2 (89%)] that by ^1H NMR contained traces (7%) of the unwanted *cis*-alkene: bp 110 °C (5 × 10^{-3} mmHg); $[\alpha]^{25}_D$ −19.2° (c 1.1, $CHCl_3$); R_f 0.50 (silica, Et_2O–hexane, 3:7); IR (film) 3500, 3000, 1730, 1660, 1380, 1300, 1190, 1140 cm^{-1}; ^1H NMR (250 MHz) δ 6.90 (dd, 1 H, J = 16, 8 Hz), 5.80 (dd, 1 H, J = 16, 1 Hz), 4.19 (q, 2 H, J = 7 Hz), 3.85 (m, 1 H), 2.50 (m, 1 H), 1.64 (m, 1 H), 1.30–1.45 (m, 2 H), 1.30 (t, 3 H, J = 7.5 Hz), 1.21 (d, 3 H, J = 7.5 Hz), 1.09 (d, 3 H, J = 7.5 Hz); mass spectrum, m/e 186 ($M^{\bullet+}$), 169, 141, 123, 111, 99, 95 (100%), 81, 70, 35. Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.47; H, 9.75. Found: C, 64.58; H, 9.83.

Ethyl (4*R*,6*R*)-4-Methyl-6-(phenylthio)-2(*E*)-heptenoate (35a). To a stirred solution of *N*-(phenylsulfenyl)phthalimide (4.06 g) in PhH (30 mL) was added dropwise $(n\text{-Bu})_3P$ (3.98 mL) and the resulting brown solution stirred for 10 min. A solution of the crude α,β-unsaturated ester **34a** (1.76 g) in PhH (20 mL) was added and the solution stirred for 3 h. The solvent was evaporated and the crude product purified by flash chromatography (silica, Et_2O–hexane, 1:19) to give **35a** [1.64 g (57% overall from lactone **31**)] as a pale yellow oil: bp 120 °C (5 × 10^{-3} mmHg); $[\alpha]^{25}_D$ −31° (c 0.70, $CHCl_3$); R_f 0.80 (silica, Et_2O–hexane, 1:19); IR (film) 1720, 1650, 1590, 1480, 1270, 1180, 750 cm^{-1}; ^1H NMR (250 MHz) δ 7.32–7.20 (m, 5 H), 6.73 (dd, 1 H, J = 7, 16 Hz), 5.75 (dd, 1 H, J = 2, 16 Hz), 4.11 (q, 2 H, J = 7 Hz), 3.04 (m, 1 H), 2.63 (m, 1 H), 1.50 (m, 2 H), 1.20 (t, 3 H, J = 7 Hz), 1.19 (d, 3 H, J = 7 Hz), 0.99 (d, 3 H, J = 7 Hz); mass spectrum, m/e 278 ($M^{\bullet+}$), 233, 191, 169, 137 (100%). Anal. Calcd for $C_{16}H_{22}O_2S$: C, 69.01; H, 7.97. Found, C, 68.88, H, 8.07. When **35a** was prepared from purified **34a** on a 1-mmol scale, the yield of isolated pure **35a** was 91%.

Ethyl (4*R*,6*S*)-6-[2(*S*)-Methoxy-2-phenylacetoxy]-4-methyl-2(*E*)-heptenoate (34b). 4-(Dimethylamino)pyridine (catalytic quantity) followed by dicyclohexylcarbodiimide (51 mg) and 2(*S*)-methoxy-2-phenylacetic acid (35 mg) were added to **34a** (36 mg) in CH_2Cl_2 (0.5 mL) at room temperature. After 3 h the solvent was evaporated and the residue partitioned between Et_2O (10 mL) and H_2O (5 mL). The Et_2O layer was washed with dilute hydrochloric acid (2 M, 5 mL) and H_2O (5 mL), dried, and evaporated. Chromatography on silica (0.3 g) gave (eluant hexane–Et_2O, 3:1) *only a single* ester component **34b** [55 mg (81%)] as a colorless oil: IR (film) 1740, 1715, 1650, 1450, 1270, 1180, 1110 cm^{-1}; ^1H NMR (250 MHz) δ 7.4 (m, 5 H), 6.7 (dd, 1 H, J = 15, 6 Hz), 5.5 (dd, 1 H, J = 15, 0.5 Hz), 5.0 (m, 1 H), 4.7 (s, 1 H), 4.15 (q, 2 H, J = 7 Hz), 3.4 (s, 3 H), 1.8–1.7 (m, 1 H), 1.7–1.6 (m, 2 H), 1.3 (q, 3 H, J = 7 Hz), 1.25 (d, 3 H, J = 7 Hz), 0.8 (d, 3 H, J = 7 Hz); mass spectrum, m/e 334 ($M^{\bullet+}$), 289, 279, 257, 243, 213, 149, 121; high-resolution mass spectrum for $C_{19}H_{26}O_5$ ($M^{\bullet+}$), calcd 334.178, found 334.178.

(4*R*,6*R*)-4-Methyl-6-(phenylthio)-2(*E*)-hepten-1-ol (35b). To **35a** (1.64 g) in dry PhMe (25 mL) at −6 °C was added dropwise, with stirring $(i\text{-Bu})_2AlH$ (1.5 M, 8.48 mL). After the addition was complete, the reaction mixture was stirred for 10 min and added to a slurry of ice (20 mL) and 2 M HCl (6.5 mL). The product was extracted with Et_2O (4 × 100 mL). The combined ether layers were washed with pH 7 phosphate buffer (5 mL), dried, and evaporated to give a pale yellow oil. The crude alcohol was flash chromatographed (silica, Et_2O–hexane, 1:1) to give **35b** [1.21 g (87%)] as a colorless oil: bp 150 °C (5 × 10^{-3} mmHg); $[\alpha]^{25}_D$ −16.2° (c 0.8, $CHCl_3$); R_f 0.40 (silica, Et_2O–hexane, 1:1); IR (film) 3360, 2980, 2940, 2880, 1595, 1490, 1450, 1390, 970 cm^{-1}; ^1H NMR (250 MHz) δ 7.4–7.2 (m, 5 H), 5.65 (dt, 1 H, J = 15, 6 Hz), 5.50 (dd, 1 H, J = 15, 7 Hz), 4.10 (br t, 2 H, J = 6 Hz), 3.18 (m, 1 H), 2.54 (m, 1 H), 1.50 (m, 2 H), 1.27 (d, 4 H, J = 7 Hz, Me + OH), 1.00 (d, 3 H, J = 7 Hz); mass spectrum, m/e 236 ($M^{\bullet+}$), 218, 177, 137, 110, 95, 82, 67, 55, 41. Anal. Calcd for $C_{14}H_{20}OS$: C, 71.12; H, 8.53. Found: C, 70.97; H, 8.64.

(4*R*,6*R*)-4-Methyl-6-(phenylsulfonyl)-2(*E*)-hepten-1-ol (7). Oxone (13.1 g) in H_2O (50 mL) was added dropwise to **35b** (1.21 g) in MeOH (20 mL) at room temperature. After 2 h the mixture was extracted with EtOAc (4 × 100 mL). The combined organic extracts were dried and evaporated. The crude product was not routinely purified but used directly for the subsequent step. In one experiment the product (1.26 g, 88%) was obtained microanalytically pure as a white crystalline solid after flash chromatography (silica, Et_2O–hexane, 1:1): mp 78–80 °C (from CH_2Cl_2–hexane); $[\alpha]_D$ +2.6° (c 1.6, $CHCl_3$); R_f 0.35 (silica, Et_2O–hexane, 1:1); IR (KBr disk) 3500, 2940, 1680, 1600, 1460, 1390, 1300, 1150, 1100, 1010, 980 cm^{-1}; ^1H NMR (250 MHz) δ 7.85, 7.60 (m, 5 H), 5.65 (dt, 1 H, J = 15, 3 Hz), 5.51 (dd, 1 H, J = 15, 7 Hz), 4.10 (br t, 2 H, J = 7 Hz, CH_2OH), 3.10 (m, 1 H), 2.30 (m, 1 H), 1.91 (ddd, 1 H, J = 10, 16, 4 Hz), 1.40 (ddd, 1 H, J = 10, 16, 8 Hz), 1.31 (t, 1 H, J = 6 Hz, CH_2OH), 1.25 (d, 3 H, J = 7

Hz), 0.95 (d, 3 H, J = 7 Hz); mass spectrum, m/e 250 ($M^{\bullet+} - H_2O$), 218, 212 (100%), 143, 127, 109, 108, 105, 93, 84, 67, 55. Anal. Calcd for $C_{14}H_{20}O_3S$: C, 62.63; H, 7.52. Found: C, 62.80; H, 7.50.

(4*R*,6*R*)-2-[(*tert*-Butyldimethylsilyl)oxy]-4-methyl-6-(phenylsulfonyl)-2(*E*)-heptene (36). *t*-$BuMe_2SiCl$ (0.120 g) and imidazole (0.120 g) were added sequentially to **7** (190 mg) in DMF (0.5 mL) at room temperature. After 2 h the reaction was diluted with H_2O (3 mL) and the product extracted with Et_2O (3 × 20 mL). The combined Et_2O layers were dried and evaporated, and the crude product was chromatographed (silica, Et_2O–hexane, 1:4) to give **36** [0.257 g (95%)] as a colorless oil. A small amount of *t*-$BuMe_2SiOH$ contaminated the product; this was successfully removed by drying the product under high vacuum (1×10^{-7} mmHg) for 8 h to obtain pure **36**: $[\alpha]^{25}_D$ +4.2° (*c* 0.6, $CHCl_3$); R_f 0.80 (silica, Et_2O–hexane, 2:3); IR (film) 1460, 1450, 1310, 1260, 1160, 1090, 835 cm^{-1}; ^1H NMR (270 MHz) δ 7.8, 7.7–7.5, (m, 5 H), 5.49 (m, 2 H), 4.08 (d, 2 H, J = 3.3 Hz), 3.07 (m, 1 H), 2.23 (m, 1 H), 1.87 (ddd, 1 H, J = 16, 10, 4 Hz), 1.35 (ddd, 1 H, J = 16, 10, 8 Hz), 1.23 (d, 3 H, J = 7.2 Hz), 0.93 (d, 3 H, J = 6.6 Hz), 0.90 (s, 9 H), 0.06 (s, 6 H); mass spectrum, m/e 382 ($M^{\bullet+}$), 367, 325, 267, 251, 237 (100%), 125, 109.

(2*SR*,3*RS*)-3-Methyl-4-pentyn-2-ol (37a). (2*SR*,3*RS*)-3-Methyl-4-pentyn-2-ol was prepared according to the modified procedure of Meinwald and his co-workers.[33] *cis*-2,3-Dimethyloxirane (11.6 g) in dry Me_2SO (100 mL) was treated with LiC≡CH·$NH_2CH_2CH_2NH_2$ (29.65 g) with external ice cooling. The reaction mixture was allowed to warm to room temperature and stirred under an atmosphere of N_2 for 290 h. The mixture was poured into saturated aqueous NH_4Cl (400 mL), and the solution was continuously extracted with light petroleum ether for 2 days. Evaporation followed by distillation at atmospheric pressure gave **37a** [9.30 g (51%)] as a colorless liquid: bp 121–123 °C: IR (film) 3410, 3300, 2980, 2930, 2900, 2880, 2110, 1450, 1380, 1300, 1265, 1160, 1100, 1075, 1040, 990, 920, 870, 635, 625 cm^{-1}; ^1H NMR (250 MHz) δ 3.75–3.62 (br m, 1 H), 2.55–2.41 (m, 1 H), 2.25 (br s, 1 H, exch D_2O), 2.16 (d, 1 H, J = 2.4 Hz), 1.25 (d, 3 H, J = 6.2 Hz), 1.21 (d, 3 H, J = 7.0 Hz); mass spectrum, m/e 98 ($M^{\bullet+}$), 97, 83, 69, 54 (100%), 53, 45, 43, 39. Anal. Calcd for $C_6H_{10}O$: C, 73.41; H, 10.28; ($M^{\bullet+}$), 98.0731. Found: C, 72.92; H, 10.45; ($M^{\bullet+}$), 98.0731.

(4*RS*,5*SR*)-5-Hydroxy-4-methyl-2-hexynoic Acid (37b). The acetylenic acid **37b** was prepared by a modification of Meinwald's procedure.[33] To **37a** (320 mg) in THF (10 mL) at −40 °C was added *n*-BuLi (1.6 M, 4.5 mL) and the solution stirred for 1.5 h. A stream of dry CO_2 was bubbled through the solution for 1 h. The reaction mixture was poured onto crushed ice (5 g) and acidified with hydrochloric acid (1 M) to pH 5. Extraction with Et_2O (3 × 15 mL) followed by drying (Na_2SO_4) gave, after evaporation of the solvent, **37b** (440 mg): IR (film) 3400 (br), 2940, 2220, 1710, 1600, 1370, 1030 cm^{-1}; ^1H NMR (90 MHz) δ 11.5 (br s, 1 H), 3.70 (m, 1 H), 2.50 (m, 1 H), 2.2 (m, 1 H), 1.25 (d, 3 H, J = 6 Hz), 1.21 (d, 3 H, J = 7 Hz); mass spectrum inter alia, m/e 143 ($M^+ + 1$), 125 (100%), 107, 81. The crude material was used directly without any further purification.

(5*SR*,6*RS*)-5,6-Dimethyltetrahydro-2(3*H*)-pyranone [(±)-11]. The crude acetylenic acid **37b** (400 mg) was dissolved in EtOH (50 mL) and added to a rapidly stirred suspension of 10% Pd–C (50 mg) in EtOH (10 mL) under a hydrogen atmosphere. After 10 h the reaction was judged complete by TLC. Evaporation of the solvent yielded the fully reduced hydroxy acid. This was dissolved in PhH (20 mL) and reacted with TsOH·H_2O (catalytic amount) to effect the rapid lactonization to (±)-**11** [0.108 g (27%)]. The lactone (±)-**11**[6,34] was purified by chromatography (silica, Et_2O–hexane, 3:1): R_f 0.45 (silica, Et_2O); mp ca. 20 °C; bp 79–81 °C (1 mmHg); IR (film) 2995, 1730, 1465, 1240, 1100, 1045, 730 cm^{-1}; ^1H NMR (270 MHz) δ 4.06 (dq, 1 H, J = 12, 6.1 Hz), 2.58 (m, 2 H) 1.89 (m, 1 H), 1.36 (d, 3 H, J = 6.1 Hz), 1.01 (d, 3 H, J = 6.0 Hz); mass spectrum, m/e 128 ($M^{\bullet+}$), 84, 56, (100%) 41.

(2*S*,3*R*)-3-Methyl-4-pentyn-2-yl 2(*S*)-Methoxy-2-phenylacetate (39a) and (2*R*,3*S*)-3-Methyl-4-pentyn-2-yl 2(*S*)-Methoxy-2-phenylacetate (38a). The acetylenic alcohols **37a** (1.52 g) and 2(*S*)-methoxy-2-phenylacetic acid (3.32 g) in dry CH_2Cl_2 (120 mL) containing 4-(dimethylamino)pyridine (0.25 g) were stirred together at 0 °C. The solution was treated with dicyclohexylcarbodiimide (4.16 g) and the reaction mixture allowed to warm to room temperature and stirred overnight. The mixture was filtered and concentrated in vacuo to yield a yellow oil. The oil was treated with a small volume of CH_2Cl_2 and filtered to remove a further quantity of white solid. Evaporation in vacuo followed by chromatography (silica, 40 g; CH_2Cl_2–pentane, 1:1) gave **38a** and **39a** [3.43 g (90%)] as a yellow oil; R_f 0.55 (silica, CH_2Cl_2). A sample was further purified by bulb-to-bulb distillation to afford a colorless oil: bp 150 °C (0.5 mmHg); IR (film) 3280, 3040, 3020, 2980, 2920, 2820, 2100, 1745, 1470, 1440, 1370, 1250, 1190, 1175, 1145, 1100, 1065, 1020, 990, 910, 850, 720, 690, 620 cm^{-1}. The two diastereoisomers **38a** and **39a** were readily distinguished: ^1H NMR (250 MHz) δ 7.53–7.29 (m, 10 H), 5.08–4.87 (m, 2 H), 4.78 (s, 1 H), 4.77 (s, 1 H) 3.42 (s, 6 H), 2.77–2.60 (m, 1 H), 2.60–2.47 (m, 1 H), 2.05 (d, 1 H, J = 2.5 Hz), 1.95 (d, 1 H, J = 2.5 Hz), 1.31 (d, 3 H, J = 6.3 Hz), 1.14 (d, 3 H, J = 7.3 Hz), 1.14 (d, 3 H, J = 6.0 Hz), 0.85 (d, 3 H, J = 7.1 Hz); mass spectrum, m/e 246 ($M^{\bullet+}$), 231, 121, 105, 91, 77, 57, 43. Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.13; H, 7.37; ($M^{\bullet+}$), 246.1256. Found: C, 72.87; H, 7.44; ($M^{\bullet+}$), 246.1250.

Resolution of the Diastereoisomers 38a and 39a. A sample of the mixture from the preceding experiment (1.70 g) was separated by HPLC on a Waters Prep 500 instrument. Two Waters Prepak 500 cartridges were used in sequence, and the sample was recycled (6×) with EtOAc–hexane (1:9). Separation was effected by peak shaving at each cycle. Concentration of the appropriate fractions gave (i) the less polar (2*R*,3*S*)-3-methyl-4-pentyn-yl 2(*S*)-methoxy-2-phenylacetate (**38a**) (387 mg, 80% de) as a pale yellow oil [IR (film) 3260, 3240, 3210, 2960, 2910, 2800, 2100, 1735, 1590, 1480, 1440, 1365, 1245, 1190, 1160, 1140, 1090, 1010, 980, 900, 840, 715, 680, and 625 cm^{-1}; ^1H NMR (250 MHz) δ 7.53–7.29 (m, 5 H), 5.08–4.87 [m, 1 H, C*H*(Me)O], 4.78 (s, 1 H, C*H*OMe), 3.42 (s, 3 H), 2.77–2.60 (m, 1 H, C*H*C≡CH), 2.05 (d, 1 H, J = 2.5 Hz, C≡C*H*), 1.14 (d, 3 H, J = 7.3 Hz), 1.14 (d, 3 H, J = 6.0 Hz). Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.13; H, 7.37. Found: C, 73.08; H, 7.39.] and (ii) the more polar (2*S*,3*R*)-3-methyl-4-pentyn-2-yl 2(*S*)-methoxy-2-phenylacetate (**39a**) (515 mg, 70% de) as a pale yellow oil [IR (film) 3280, 3040, 3020, 2980, 2920, 2820, 2100, 1745, 1470, 1440, 1370, 1250, 1190, 1175, 1145, 1100, 1065, 1020, 990, 910, 850, 720, 690, 620 cm^{-1}; ^1H NMR (250 MHz) δ 7.53–7.29 (m, 5 H), 5.08–4.87 [m, 1 H, C*H*(Me)O], 4.77 (s, 1 H, C*H*OMe), 3.42 (s, 3 H), 2.60–2.47 (m, 1 H, C*H*C≡CH), 1.95 (d, 1 H, J = 2.5 Hz, C≡C*H*), 1.31 (d, 3 H, J = 6.3 Hz), 0.85 (d, 3 H, J = 7.1 Hz). Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.13; H, 7.37. Found: C, 72.87; H, 7.44.] The purest fractions of each diastereoisomer were retained for use in the correlation experiment.

Hydrogenation of the Resolved Diastereoisomers 38a and 39a. (i) The less polar isomer **38a** (90% de, 93 mg) in THF (5 mL) was hydrogenated over 10% Pd–C (30 mg) for 7 h. The mixture was filtered through Celite and the filtrate evaporated to give **38b** [88 mg (93%)] as a colorless oil: IR (film) 3040, 3010, 2950, 2910, 2860, 2800, 1725, 1480, 1440, 1360, 1260, 1240, 1190, 1170, 1090, 990, 905, 835, 720, 690 cm^{-1}; ^1H NMR (250 MHz) δ 7.5–7.25 (m, 5 H), 4.94–4.80 (5-line m, 1 H, OC*H*Me), 4.74 (s, 1 H, C*H*OMe), 3.41 (s, 3 H), 1.68–1.50 (m, 1 H), 1.50–1.27 (m, 1 H), 1.20–1.02 (m, 1 H), 1.00 (d, 3 H, J = 6.4 Hz), 0.85 (t, 3 H, J = 7.6 Hz), 0.84 (d, 3 H, J = 7.1 Hz); mass spectrum, m/e 250 ($M^{\bullet+}$), 121 (100%), 105, 91, 85, 77, 57, 51, 43; molecular ion for $C_{15}H_{22}O_3$ ($M^{\bullet+}$), calcd 250.1569, found 250.1576. The major component (90%) in this material was identical with the ester derived from L-isoleucine. (ii) Hydrogenation of the more polar isomer **39a** (90% de, 87 mg) gave **39b** [82 mg (93%)] as a colorless oil: IR (film) 3040, 3010, 2950, 2910, 2860, 2800, 1725, 1480, 1440, 1360, 1260, 1240, 1190, 1170, 1090, 990, 905, 835, 720, 690 cm^{-1}; ^1H NMR (250 MHz) δ 7.5–7.25 (m, 5 H) 5.0–4.74 (m, 1 H, OC*H*Me), 4.72 (s, 1 H, C*H*OMe), 3.40 (s, 3 H, O*Me*), 1.55–1.36 (m, 1 H), 1.15 (d, 3 H, J = 6.4 Hz), 1.30–1.11 (m, 1 H), 1.0–0.8 (m, 1 H), 0.72 (d, 3 H, J = 7.4 Hz), 0.67 (d, 3 H, J = 6.9 Hz); mass spectrum, m/e 250 ($M^{\bullet+}$), 121, 105, 87, 85, 83 (100%), 77, 48, 47, 43. Molecular ion for $C_{15}H_{22}O_3$ ($M^{\bullet+}$), calcd 250.1569, found 250.1576.

(2*R*,3*S*)-3-Methyl-2-pentyl 2(*S*)-Methoxy-2-phenylacetate (38b). (2*R*,3*S*)-3-Methyl-2-pentanol[35] (0.46 g) and 2(*S*)-methoxy-2-phenylacetic acid (0.75 g) in dry CH_2Cl_2 (20 mL) containing 4-(dimethylamino)pyridine (0.147 g) were cooled to 0 °C. The solution was treated with dicyclohexylcarbodiimide (1.05 g) and was allowed to warm to room temperature and stirred overnight. The reaction mixture was filtered and concentrated to yield a pale yellow oil. Chromatography (silica, CH_2Cl_2–pentane, 1:1) gave

38b [0.92 g (82%)] as a pale yellow oil. A sample was further purified by bulb-to-bulb distillation to afford a colorless oil: bp 180 °C (10 mmHg); $[\alpha]^{22}_D$ +46.0° (*c* 1.34, $CHCl_3$); IR (film) 3040, 3010, 2950, 2910, 2860, 2800, 1725, 1480, 1440, 1360, 1260, 1240, 1190, 1170, 1090, 990, 905, 835, 720, 690 cm^{-1}; ^1H NMR (250 MHz) δ 7.5–7.25 (m, 5 H), 4.94–4.80 (m, 1 H, 5 lines, OC*H*Me), 4.74 (s, 1 H, C*H*OMe), 3.41 (s, 3 H, OMe), 1.68–1.50 (m, 1 H), 1.5–1.27 (m, 1 H), 1.20–1.02 (m, 1 H), 1.00 (d, 3 H, J = 6.4 Hz), 0.85 (t, 3 H, J = 7.6 Hz), 0.84 (d, 3 H, J = 7.1 Hz); mass spectrum, *m/e* 250 ($M^{\bullet+}$), 136, 121, 105, 91, 85, 77, 43. Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.95; H, 8.86. Found: C, 71.94; H, 9.11.

4(*S*)-Methyl-5-hexenoic Acid (40b). (*S*)-Citronellene (**4**;[14] 24 g) in CH_2Cl_2 (1.5 L) was ozonized at −78 °C for 1.5 h. The progress of the reaction was carefully monitored by TLC. Upon completion, the reaction mixture was treated with Me_2S (18 mL) and allowed to warm to room temperature. The solution was subsequently washed with H_2O (2 × 30 mL) and brine (30 mL) followed by the partial evaporation of the solvent to leave a solution of 4(*S*)-methyl-5-hexenal (**40a**). The aldehyde was not isolated but directly oxidized.

Oxidation Procedure 1. Freshly prepared Jones' reagent[62] [CrO_3 (25 g), concentrated H_2SO_4 (9 mL), H_2O (150 mL)] was added to the crude **40a** (~17 g) in Me_2CO (100 mL) at 0 °C at such a rate as to maintain the temperature of the solution below 10 °C. Upon completion of the oxidation the excess reagent was quenched by the addition of *i*-PrOH (30 mL), and stirring was continued at room temperature for 15 min. The Me_2CO was removed by rotary evaporation followed by the addition of H_2O (100 mL) and extraction of the product into Et_2O (3 × 400 mL). Evaporation of the solvent followed by flash chromatography (silica, Et_2O–hexane, 3:17–1:4) gave **40b** [19 g (86% based on **4**)] as a colorless oil: R_f 0.55 (silica, Et_2O–hexane, 1:4).

Oxidation Procedure 2. Pyridinium dichromate (4.4 g) was added portionwise over 1 h to crude **40a** (1 g) in DMF (20 mL) at room temperature. H_2O (50 mL) was added and the product extracted into Et_2O (3 × 50 mL). The Et_2O layers were combined, dried, and evaporated. The crude acid was purified by chromatography (silica, Et_2O–hexane, 1:4) to give **40b** as a colorless oil: 0.80 g (85%); $[\alpha]^{25}_D$ +9.4° (*c* 3.9, $CHCl_3$) [lit.[36] value $[\alpha]^{25}_D$ +14.3° (neat)]; R_f 0.35 (silica, Et_2O–hexane, 1:4); IR (film) 3500–2500, 2980, 1715, 1460, 1410, 1375 cm^{-1}; ^1H NMR (270 MHz) δ 10.80 (br s, 1 H), 5.61 (ddd, 1 H, J = 7.9, 10.6, 7.3 Hz), 4.98 (m, 2 H), 2.33 (m, 2 H), 2.18 (m, 1 H), 1.64 (m, 2 H), 1.01 (d, 3 H, J = 6.6 Hz); mass spectrum, *m/e* 128 ($M^{\bullet+}$), 110, 69, 55 (100%), 39.

(5*S*,6*S*)-6-(Iodomethyl)-5-methyltetrahydro-2(3*H*)-pyranone (41). A solution of **40b** (10 g) in dry MeCN (200 mL) was slowly added to a cooled (−25 °C) solution of I_2 (59 g) in MeCN (50 mL) over 3 h. The reaction mixture was stirred for a further 10 h at −25 °C followed by 4 h at 0 °C. The reaction mixture was diluted with Et_2O (300 mL) and neutralized with saturated aqueous $NaHCO_3$ (50 mL) and the excess I_2 quenched with saturated aqueous $Na_2S_2O_3 \cdot 7H_2O$ (150 mL) to give, upon evaporation of the solvent, a yellow oil. Chromatography (silica, Et_2O–hexane, 3:1) gave **41** [16.8 g (85%)] as a white solid: mp 74–75 °C (from Et_2O–hexane); R_f 0.50 (silica, Et_2O); IR ($CHCl_3$) 2980, 1735, 1460, 1415, 1340, 1290, 1250, 1230, 1215, 1175, 1040, 1000 cm^{-1}; ^1H NMR (270 MHz) δ 3.6 (m, 1 H), 3.49 (dd, 1 H, J = 2, 10.5 Hz), 3.33 (dd, 1 H, J = 4, 10.5 Hz), 2.56 (ddd, 1 H, J = 4.6, 6.0, 14.1 Hz), 2.50 (ddd, 1 H, J = 5.9, 9.9, 14.1 Hz), 1.89 (m, 2 H), 1.62 (m, 1 H), 0.95 (d, 3 H, J = 5.9 Hz); mass spectrum, *m/e* 254 ($M^{\bullet+}$), 127, 113, 99. Anal. Calcd for $C_7H_{11}IO_2$: C, 33.07; H, 4.37. Found, C, 33.14; H, 4.32.

5(*S*),6(*R*)-Dimethyltetrahydro-2(3*H*)-pyranone (11). Bu_3SnH (12.1 mL) was added to **41** (10.6 g) in dry PhH (100 mL) at room temperature. The solution was refluxed for 2 h and cooled to 0 °C and the excess tin hydride quenched with CCl_4 (10 mL). Saturated aqueous KF (50 mL) was added and the resulting suspension stirred for 30 min. The use of these two workup modifications allowed the removal of most of the trialkyltin compounds by simple filtration, greatly simplifying the purification of the product.[39] The alkyltin fluorides were filtered off through Celite. Evaporation of the solvent and chromatography (silica, Et_2O–hexane, 3:1) gave **11** [4.8 g (90%)] as a low-melting solid: mp ca. 20 °C; bp 80 °C (1 mmHg) [lit.[7] bp 80–82 °C (1 mmHg)]; R_f 0.55 (silica, Et_2O); $[\alpha]_D$ +15.0° (*c* 4.5, $CHCl_3$) [lit.[7] value +13.1° (*c* 4.9, $CHCl_3$)]; IR (film) 2980, 1727, 1460, 1380, 1350, 1305, 1250, 1230, 1200, 1160, 1115, 1100, 1050, 750 cm^{-1}; ^1H NMR (250 MHz) δ 4.06 (dq, 1 H, J = 12, 6.1 Hz), 2.58 (m, 2 H), 2.0–1.4 (m, 3 H), 1.36 (d, 3 H, J = 6.1 Hz), 1.01 (d, 3 H, J = 5.9 Hz); mass spectrum, *m/e* 128 ($M^{\bullet+}$), 84, 56 (100%), 41.

Methyl Trimethoxyacetate (44a). The title compound was prepared by a modification of a literature procedure.[42] To dimethyl oxalate (50 g) was added freshly ground PCl_5 (97 g) and the mixture heated to 135 °C for 60 h. The $POCl_3$ generated was distilled off [60 °C (20 mmHg)] and the residue diluted with Et_2O (200 mL). The solution was cooled to 0 °C, and MeOH (150 mL) was added dropwise. Pyridine (120 mL) was added dropwise and the resulting solution stirred for 10 h at room temperature. The pyridinium hydrochloride was filtered off through Celite and the excess pyridine removed by washing with a saturated aqueous $CuSO_4 \cdot 5H_2O$ solution (300 mL). The aqueous layer was back-extracted with Et_2O (3 × 200 mL), and the combined Et_2O solutions were dried. Evaporation of the solvent followed by careful fractional distillation gave **44a** [52 g (75%)] as a colorless oil: bp 60–61 °C (6 mmHg) [lit.[42] value 70 °C (8 mmHg)]; IR 2960, 1745, 1440, 1300, 1208, 1100 (br) cm^{-1}; ^1H NMR (90 MHz) δ 3.96 (s, 3 H), 3.41 (s, 9 H); mass spectrum, *m/e* 133 ($M^{\bullet+}$ − OMe), 105, 59.

1,1,1-Trimethoxy-2,4-pentanedione (44b). To NaH (4.6 g) in Et_2O (200 mL) at room temperature was added over 3 h **44a** (15 g) and Me_2CO (7.0 mL) in Et_2O (300 mL) followed by MeOH (0.5 mL). The resulting suspension was stirred overnight at room temperature. The reaction was quenched at −78 °C by the dropwise addition of AcOH (11.0 mL) in Et_2O (50 mL) over 45 min. Aqueous buffer (pH 7) (100 mL) was added and the reaction mixture allowed to warm to room temperature. The product was separated from the aqueous layer by extraction with Et_2O (3 × 50 mL), and the combined Et_2O layers were dried. Evaporation of the solvent followed by chromatography (silica, Et_2O–hexane, 1:4) gave **44b** [14.9 g (86%)] as a mobile pale yellow oil. The orthoester moiety underwent fairly facile hydrolysis. At room temperature in the presence of moist air, its half-life was several days. Pure material: bp 50–56 °C (0.5 mmHg); R_f 0.75 (silica, Et_2O–hexane, 1:3); IR (film) 2950, 1740, 1710, 1600 (strong), 1440, 1280 cm^{-1}; ^1H NMR (90 MHz) δ 5.98 (s, 1 H), 3.31 (s, 9 H), 2.19 (s, 3 H); NMR spectrum showed **44b** to exist in approximately 70% the enolic form; mass spectrum, *m/e* (CI) 159 (M^+ − OMe), 127, 105 (100%), 85, 75, 59, 43, 31. Anal. Calcd for $C_8H_{14}O_5$: C, 50.50; H, 7.42. Found: C, 50.68; H, 7.36.

(6*S*,8*R*,9*S*)-Methyl 8,9-Dimethyl-4-oxo-1,7-dioxaspiro[5.5]undec-2-ene-2-carboxylate (10). To a solution of LDA (58 mmol) in THF (200 mL) at −78 °C was added **44b** (5.0 g) in THF (15 mL) dropwise. After addition was complete, the reaction mixture was stirred at −78 °C for 15 min before warming to 0 °C for 1 h. Upon warming to 0 °C, the colorless solution became orange. The solution was recooled to −78 °C and lactone **11** (1.6 g) in THF (15 mL) was added dropwise. The solution was stirred at −78 °C for 15 min, after the addition, before warming to 0 °C for 1 h. The solution was recooled to −78 °C and AcOH (6.9 mL) in THF (30 mL) added. The reaction mixture was warmed to room temperature and H_2O (30 mL) added. The organic product was extracted with Et_2O (4 × 100 mL), the Et_2O layer dried, and the solvent evaporated to give a dark orange oil. TLC indicated one new compound [R_f 0.85 (silica, Et_2O–hexane, 3:7)] and was tentatively assigned as adduct **44c**. The adduct was rapidly filtered through silica (Et_2O–hexane, 1:1) to remove the excess β-dione **44b**. $TsOH \cdot H_2O$ (300 mg) in CH_2Cl_2 (10 mL) was added to the adduct, and the solution was stirred for 30 min. Silica (5 g) was added to the reaction mixture, the solvent was removed, and **10** [2.8 g (88%)] was obtained after flash chromatography (silica, Et_2O–hexane, 1:3). However, the product contained a trace contaminant, which necessitated rechromatography, and this lowered the yield to 2.2 g (69%). The contaminant was not isolated and did not appear to be a discrete single compound by TLC (silica, Et_2O–hexane, 2:3); its presence was indicated by its intense yellow coloration. The spiro dihydropyrone **10** was isolated as a pale yellow oil: $[\alpha]^{25}_D$ +189° (*c* 3.0, $CHCl_3$); R_f 0.50 (silica, Et_2O–hexane, 3:7); IR (film) 2870, 1730, 1674, 1605, 1370, 1090,

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985, 955 cm^{-1}; UV (EtOH) λ_{max} 252 nm (ϵ 11 800); ^{1}H NMR (270 MHz) δ 6.26 (s, 1 H, 3-*H*), 3.91 (s, 3 H, CO_2Me), 3.50 (dq, 1 H, J = 6.5, 10.1 Hz, 8-*H*), 2.78 (d, 1 H, J = 17.0 Hz, 5-*H*), 2.57 (d, 1 H, J = 17.0 Hz, 5-*H*), 2.18 (m, 1 H), 1.74 (m, 3 H), 1.35 (m, 1 H), 1.08 (d, 3 H, J = 6.5 Hz, 8-*Me*), 0.89 (d, 3 H, J = 6.6 Hz, 9-*Me*); mass spectrum, m/e 254 ($M^{\bullet+}$), 195, 166, 127, 111, 83, 69 (100%), 55, 41, 27, 15. Anal. Calcd for $C_{13}H_{18}O_5$: C, 61.38; H, 7.14. Found: C, 61.74; H, 7.37.

(2*R*,4*R*,6*S*,8*R*,9*S*)- and (2*R*,4*S*,6*S*,8*R*,9*S*)-Methyl 4-Hydroxy-8,9-dimethyl-1,7-dioxaspiro[5.5]undecane-2-carboxylate (45b and 45c). To 5% Rh/Al (1 g) in EtOH (AcOH free) (70 mL) under a H_2 atmosphere was added a solution of spiro dihydropyrone **10** (0.40 g) in EtOH (10 mL). The reaction was vigorously stirred for 2 h before filtering off the catalyst through a Celite pad. The solvent was removed and oily residue chromatographed (silica, Et_2O–hexane, 7:3) to give a diastereoisomeric mixture of the alcohols **45b** and **45c** [0.31 g (77%)] in an 8:1 ratio. The two alcohols were resolved by flash chromatography and separately characterized. The major alcohol **45b** [0.230 mg (58%)] was obtained as a colorless oil: $[\alpha]_D$ +17.6° (c 4.6, $CHCl_3$); R_f 0.35 (silica, Et_2O–hexane, 4:1); IR (film) 3430, 2970, 1730, 1445, 1375, 1230–1050 (broad) cm^{-1}; ^{1}H NMR (270 MHz) δ 4.29 (dd, 1 H, J = 5.1, 7.9 Hz, 2-*H*), 4.04 (m, 1 H, 4-*H*), 3.87 (dq, 1 H, J = 6.6, 10.0 Hz, 8-*H*), 3.77 (s, 3 H, O*Me*), 2.18 (m, 2 H), 1.70–1.90 (m, 4 H), 1.68 (m, 2 H), 1.50 (m, 2 H), 1.13 (d, 3 H, J = 6.6 Hz, 8-*Me*), 0.86 (d, 3 H, J = 6.4 Hz, 9-*Me*); mass spectrum, m/e 259 (M^+ + 1) 243, 241 (100%), 223, 199, 155, 143, 127, 113, 99. Anal. Calcd for $C_{13}H_{22}O_5$: C, 60.42; H, 8.59. Found: C, 60.05; H, 8.95.

The minor alcohol **45c** [26 mg (6%)] was obtained as a colorless oil: $[\alpha]^{25}_D$ +41.1° (c 3.36, $CHCl_3$); R_f 0.30 (silica, Et_2O–hexane, 4:1); IR (film) 3440, 2970, 1740, 1450, 1380, 1210, 1075 cm^{-1}; ^{1}H NMR (270 MHz) δ 4.41 (m, 2 H, 2-*H*, 4-*H*), 3.74 (s, 3 H, OMe), 3.55 (dq, 1 H, J = 6.6, 9.9 Hz, 8-H), 2.4 (s, 1 H, O*H*), 2.02 (m, 1 H), 1.89 (m, 1 H), 1.10–1.75 (m, 7 H), 1.02 (d, 3 H, J = 6.6 Hz, 8-Me), 0.88 (d, 3 H, J = 6.2 Hz, 9-*Me*); mass spectrum, m/e 258 ($M^{\bullet+}$), 243, 241 (100%), 227, 199, 155, 127, 113, 111, 99. Anal. Calcd for $C_{13}H_{22}O_5$: C, 60.42, H, 8.59. Found: C, 60.39, H, 8.31.

(6*S*,8*R*,9*S*)-Methyl 8,9-Dimethyl-1,7-dioxaspiro[5.5]undec-2-ene-2-carboxylate (46). To a suspension of 5% Rh/Al (1 g) in EtOH (60 mL), containing AcOH (1 drop) under a H_2 atmosphere, was added spiro dihydropyrone **10** (0.1 g) in EtOH (1 mL). After 2 h, the suspension was filtered through Celite and the EtOH removed by rotary evaporation. The resulting pale yellow oil was flash chromatographed to give **46** [71 mg (85%)] as a colorless oil: R_f 0.6 (silica, Et_2O–hexane, 1:1); ^{1}H NMR (270 MHz) δ 6.07 (dd, 1 H, J = 3, 5 Hz, 3-*H*), 3.72 (s, 3 H, O*Me*), 3.39 (dq, 1 H, J = 6, 10 Hz, 8-*H*), 2.30 (m, 1 H, 4-*H*), 2.00 (m, 1 H, 4-*H*), 1.15–1.8 (m, 7 H), 1.02 (d, 3 H, J = 6 Hz), 0.80 (d, 3 H, J = 6 Hz); mass spectrum, m/e 240 ($M^{\bullet+}$), 169, 149, 139, 126, 111, 83, 69, 55, 41. Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 65.16; H, 8.58.

(2*R*,4*R*,6*S*,8*R*,9*S*)-Methyl 8,9-Dimethyl-4-[[(4-methylphenyl)sulfonyl]oxy]-1,7-dioxaspiro[5.5]undecane-2-carboxylate (45d). TsCl (0.24 g) and 4-(dimethylamino)pyridine (5 mg) were added to **45b** (0.165 g) in pyridine (1 mL) at room temperature. After 5 h all the starting material was consumed. The solution was diluted with Et_2O (15 mL) and the pyridine washed out with saturated aqueous $CuSO_4 \cdot 5H_2O$ (3 mL). The H_2O layer was washed with Et_2O (3 × 10 mL), and the combined organic solutions were dried and evaporated to produce a pale yellow oil, which was chromatographed (silica, Et_2O–hexane, 3:7) to give **45d** [0.227 g (86%)] as a pale yellow oil: R_f 0.45 (silica, Et_2O–hexane, 1:1); IR (film) 2940, 1740, 1600, 1440, 1360, 1180, 1090, 1020, 960, 850, 690, 670 cm^{-1}; ^{1}H NMR (270 MHz) δ 7.8, 7.35 (AB q, 4 H, J = 8 Hz), 4.75 (m, 1 H, 4-*H*), 3.99 (dd, 1 H, J = 2.5, 11.9 Hz, 2-*H*), 3.79 (m, 4 H, O*Me*, 8-*H*), 2.49 (s, 3 H, Ar-C*H*$_3$), 2.32 (m, 1 H), 1.68–2.05 (m, 4 H), 1.21–1.49 (m, 4 H), 1.13 (d, 3 H, J = 6.8 Hz, 8-*Me*), 0.89 (d, 3 H, J = 6.4 Hz, 9-*Me*); mass spectrum, m/e 413 (M^+ + 1), 257, 241, 213, 199, 179, 149, 113. The material was used directly without further purification.

(2*R*,4*S*,6*S*,8*R*,9*S*)-Methyl 4-Acetoxy-8,9-dimethyl-1,7-dioxaspiro[5.5]undecane-2-carboxylate (45e). To a solution of tosylate **45d** (0.100 g) in dry DMF (0.5 mL) was added KOAc (0.475 g) and the suspension warmed to 55–60 °C for 48 h. The reaction mixture was cooled, H_2O (5 mL) added, and the product extracted into Et_2O (4 × 10 mL). The Et_2O was dried and the solvent removed to leave an oil, which was chromatographed to give **45e** [53 mg (73%)] as a colorless oil: $[\alpha]^{25}_D$ +14.5° (c 2.5, $CHCl_3$); R_f 0.55 (silica, Et_2O–hexane, 1:1); IR (film) 2980, 2890, 1735, 1435, 1374, 1240, 1210, 1070, 1041, 980 cm^{-1}; ^{1}H NMR (270 MHz) δ 5.39 (m, 1 H, 4-*H*), 4.43 (dd, 1 H, J = 5.0, 5.0 Hz, 2-*H*), 3.78 (s, 3 H, O*Me*), 3.59 (dq, 1 H, J = 5.9, 9.9 Hz, 8-*H*), 2.40 (m, 1 H), 2.04 (s, 3 H, OAc), 1.71–2.06 (m, 4 H), 1.15–1.61 (m, 4 H), 1.06 (d, 3 H, J = 5.9 Hz, 8-*Me*), 0.87 (d, 3 H, J = 5.8 Hz, 9-*Me*); mass spectrum, m/e 301 (M^+ + 1), 241 (100%), 215, 195, 181, 167, 157. Anal. Calcd for $C_{15}H_{24}O_6$: C, 59.96; H, 8.06. Found: C, 60.35; H, 8.04.

(2*R*,4*S*,6*S*,8*R*,9*S*)-Methyl 4-Hydroxy-8,9-dimethyl-1,7-dioxaspiro[5.5]undecane-2-carboxylate (45c). To a solution of acetate **45e** (25 mg) in dry MeOH (1 mL) was added 1 M NaOMe in MeOH (0.20 mL). After stirring overnight, the reaction was quenched with AcOH to pH 7, silica (0.5 g) was added, and the solvent was evaporated. The solid was added to a column of silica and eluted with Et_2O–hexane (4:1). The isolated product **45c** [18 mg (84%)] was identical with the minor alcohol **45c**, isolated from the hydrogenation of the spiro dihydropyrone **10**, as judged by TLC, chromatography, and high-field NMR spectroscopy.

(2*R*,6*S*,8*R*,9*S*)-Methyl 8,9-Dimethyl-4-oxo-1,7-dioxaspiro[5.5]undecane-2-carboxylate (45a). To a suspension of 5% Rh/Al (0.2 g) in EtOH (AcOH free) (50 mL) under a H_2 atmosphere was added a solution of spiro dihydropyrone **10** (0.50 g) in EtOH (10 mL). The solution was stirred and the disappearance of the UV-active **10** carefully monitored by TLC chromatography (silica, Et_2O–hexane, 3:7). The UV activity faded over approximately 40 min. The hydrogen was rapidly removed under reduced pressure, the catalyst filtered off, and the solvent evaporated. Chromatography (silica, Et_2O–hexane, 1:3) gave the pure ketone **45a** [0.31 g (62%)] as a colorless oil: $[\alpha]^{25}_D$ +64.2° (c 3.4, $CHCl_3$); R_f 0.60 (silica, Et_2O–hexane, 3:7); IR (film) 2940, 1730, 1440, 1220, 1190, 1045 cm^{-1}; ^{1}H NMR (270 MHz) δ 4.63 (dd, 1 H, J = 4.7, 10.0 Hz, 2-*H*), 3.79 (m, 4 H, O*Me*, 8-*H*), 2.99 (dd, 1 H, J = 9.9, 16.5 Hz, 3-*H*), 2.61 (dd, 1 H, J = 16.5, 5.3 Hz, 3-*H*), 2.55 (AB q, 2 H, J = 16 Hz, 5-H_2), 1.89 (m, 1 H), 1.2–1.7 (m, 4 H), 1.08 (d, 3 H, J = 5.9 Hz, 8-*Me*), 0.87 (d, 3 H, J = 6.6 Hz, 9-*Me*); mass spectrum, m/e 256 ($M^{\bullet+}$), 238, 224, 197 (100%), 111, 83, 69, 53, 41. Anal. Calcd for $C_{13}H_{20}O_5$: C, 60.90; H, 7.87. Found: C, 61.15; H, 7.93.

(2*R*,4*R*,6*S*,8*R*,9*S*)- and (2*R*,4*S*,6*S*,8*R*,9*S*)-Methyl 4-Hydroxy-8,9-dimethyl-1,7-dioxaspiro[5.5]undecane-2-carboxylate (45b and 45c). To an ice-cooled solution of ketone **45a** (100 mg) in dry DME (5 mL) was added $NaBH_4$ (50 mg). After stirring for 5 min, the reaction was judged complete by TLC (silica, Et_2O). The reaction was quenched with AcOH and acidified to pH 6, Et_2O (20 mL) was added, and the solution was washed with H_2O (1 mL). The Et_2O layer was dried, silica (1 g) was added, the solvent was evaporated, and chromatography (silica, Et_2O–hexane, 3:1) gave the two epimeric alcohols **45c** and **45b**, 41 mg (82%, 4:1).

(2*S*,4*R*,6*S*,8*R*,9*S*)-Methyl 4-Hydroxy-8,9-dimethyl-1,7-dioxaspiro[5.5]undecane-2-carboxylate (48a). To a solution of LDA (1.17 mmol) in THF (3 mL), at −78 °C, was added a solution of alcohol **45b** (0.127 g) in THF (0.5 mL) over 10 min. The solution was stirred at −78 °C for 4 h, during which time a slight yellow coloration appeared. The reaction was quenched with a solution of AcOH (0.12 mL) in THF (2 mL). After the mixture was warmed to room temperature, H_2O (1 mL) was added and the reaction diluted with Et_2O (10 mL) and separated. The H_2O layer was washed with Et_2O (3 × 10 mL). The combined Et_2O solutions were dried, evaporated, and chromatographed (silica, Et_2O–hexane, 1:1) to give starting alcohol **45b** [80 mg (63%)] and the epimerized alcohol **48a** [38 mg (30%)] as a colorless oil: $[\alpha]^{25}_D$ + 32.1° (c 2.6, $CHCl_3$); R_f 0.60 (silica, Et_2O–hexane, 1:1); IR (film) 3440, 2990, 1735, 1420, 1100 cm^{-1}; ^{1}H NMR (270 MHz) δ 4.54 (dd, 1 H, J = 12.5, 2.5 Hz, 2-*H*), 4.18 (m, 1 H, 4-*H*), 3.78 (s, 3 H, CO_2Me), 3.4 (dq, 1 H, J = 6.6, 9.9 Hz, 2-*H*), 2.15 (m, 1 H), 1.3–1.9 (m, 9 H), 1.18 (d, 3 H, J = 6.6 Hz, 8-*Me*), 0.85 (d, 3 H, J = 6.1 Hz, 9-*Me*); mass spectrum, m/e 258 ($M^{\bullet+}$), 240, 199, 181, 157, 95, 55, 43 (100%). Anal. Calcd for $C_{13}H_{22}O_5$: C, 60.42; H, 8.59. Found: C, 60.70; H, 8.67.

(2*R*,4*R*,6*S*,8*R*,9*S*)-Methyl 4-[(*tert*-Butyldiphenylsilyl)oxy]-8,9-dimethyl-1,7-dioxaspiro[5.5]undecane-2-carboxylate

(45f). To a solution of alcohol **45b** (0.703 g) in DMF (1 mL) were sequentially added at 0 °C *t*-$BuPh_2SiCl$ (0.75 mL) and imidazole (0.464 g). The reaction mixture was allowed to warm to room temperature for 1 h. H_2O (10 mL) was added and the product extracted into Et_2O (3 × 50 mL). The Et_2O solution was dried and evaporated and the resultant oil chromatographed (silica, Et_2O–hexane, 1:19). The silyl ether **45f** [1.3 g (96%)] was obtained as a waxy white solid, upon removal of the solvent. Recrystallization from Et_2O–hexane gave X-ray quality crystals: mp 112 °C; $[\alpha]^{25}_D$ +14.2° (*c* 2.7, $CHCl_3$); R_f 0.60 (Et_2O–hexane, 1:9); IR ($CHCl_3$) 3020, 2980, 1745, 1420, 1260, 730 cm^{-1}; ^1H NMR (270 MHz) δ 7.72 (m, 4 H, aryl-*H*), 7.37 (m, 6 H, aryl-*H*), 3.79 (m, 3 H, 2-*H*, 4-*H*, 8-*H*), 3.73 (s, 3 H, CO_2Me), 2.11 (m, 1 H), 1.20–1.85 (m, 8 H), 1.14 (d, 3 H, *J* = 6.4 Hz, 8-*Me*), 1.10 (s, 9 H, *t*-Bu), 0.79 (d, 3 H, *J* = 6.4 Hz, 9-*Me*); mass spectrum, *m/e* 497 (M^+ + 1), 481, 439, 419, 353, 241 (100%), 223. Anal. Calcd for $C_{29}H_{40}O_5Si$: C, 70.10; H, 8.12. Found: C, 70.44; H, 8.35.

(2*S*,4*R*,6*S*,8*R*,9*S*)-Methyl 4-[(*tert*-Butyldiphenylsilyl)oxy]-8,9-dimethyl-1,7-dioxaspiro[5.5]undecane-2-carboxylate (48b). To a solution of LDA (2.76 mmol) in THF (5 mL) at −78 °C was added dropwise a solution of **45f** (1.10 g) in THF (3 mL). The resulting solution was stirred for 1 h. The reaction was quenched by the slow dropwise addition of AcOH (0.32 mL) in THF (5 mL) at −78 °C. After the addition of the acid was complete, the reaction mixture was warmed to room temperature and H_2O (10 mL) added. The product was extracted into Et_2O (3 × 40 mL). The extract was dried and evaporated and the crude product chromatographed (silica, Et_2O–hexane, 1:19) to give the epimerized ester **48b** [1.0 g (91%)] as a colorless oil: $[\alpha]^{25}_D$ +10.4° (*c* 2.6, $CHCl_3$); R_f 0.55 (Et_2O–hexane, 1:9); IR (film) 2930, 1738, 1430, 1100, 820, 710 cm^{-1}; ^1H NMR (270 MHz) δ 7.75 (m, 4 H, aryl-*H*), 7.39 (m, 6 H, aryl-*H*), 4.85 (dd, 1 H, *J* = 2.0, 11.9 Hz, 2-*H*), 4.13 (m, 1 H, 4-*H*), 3.76 (s, 3 H, CO_2Me), 3.44 (dq, 1 H, *J* = 6.6, 9.9 Hz, 8-*H*), 1.3–2.0 (m, 9 H), 1.23 (d, 3 H, *J* = 6.6 Hz, 8-*Me*), 1.09 (s, 9 H, *t*-Bu), 0.85 (d, 3 H, *J* = 6.2 Hz, 9-*Me*); mass spectrum, *m/e* 497 (M^+ + 1), 481, 439, 419, 371, 353, 241 (100%), 223. Anal. Calcd for $C_{29}H_{40}O_5Si$: C, 70.10; H, 8.12. Found: C, 70.36; H, 8.28.

(2*S*,4*R*,6*S*,8*R*,9*S*)-Methyl 4-Hydroxy-8,9-dimethyl-1,7-dioxaspiro[5.5]undecane-2-carboxylate (48a). 1 M tetrabutylammonium fluoride in THF (2.0 mL) was added to **48b** (200 mg) in THF (0.5 mL). The resulting pale orange solution was warmed to 40–45 °C. After 6 h the reaction mixture was cooled to room temperature, diluted with Et_2O (20 mL), and washed with H_2O (2 × 2 mL). The H_2O layer was extracted with Et_2O (3 × 10 mL), and the combined Et_2O solutions were dried and evaporated. The crude brown oil was chromatographed (silica, Et_2O–hexane, 1:1) to give the alcohol **48a** [95 mg (91%)] as a colorless oil. By high-field NMR spectroscopy and TLC this sample was identical with that obtained from LDA isomerization of alcohol **45b**.

(2*S*,6*S*,8*R*,9*S*)-Methyl 8,9-Dimethyl-4-oxo-1,7-dioxaspiro[5.5]undecane-2-carboxylate (49a). Freshly ground pyridinium chlorochromate was added to **48a** (50 mg) in CH_2Cl_2 (2 mL). The resulting suspension was gently refluxed with vigorous stirring. After 4 h the reaction was judged complete by TLC chromatography, (silica, Et_2O–hexane, 1:1). The reaction mixture was cooled to room temperature and diluted with hexane (5 mL) and the suspension added to a silica column. After the column was eluted (Et_2O–hexane, 2:3), the ketone **49a** [43 mg (87%)] was isolated as a colorless oil: $[\alpha]^{25}_D$ +64.2° (*c* 0.6, $CHCl_3$); R_f 0.70 (Et_2O–hexane, 1:1); IR (film) 2940, 1735, 1440, 1220, 1195, 1040, 960 cm^{-1}; ^1H NMR (270 MHz) δ 4.46 (dd, 1 H, *J* = 2.5, 10 Hz, 2-*H*), 3.82 (s, 3 H, CO_2Me), 3.31 (dq, 1 H, *J* = 6.5, 10 Hz, 8-*H*), 2.60 (m, 2 H, 3-*H*), 2.47 (s, 2 H, 5-H_2), 1.98 (m, 1 H), 1.2–1.7 (m, 4 H), 1.11 (d, 3 H, *J* = 6.6 Hz, 8-*Me*), 0.86 (d, 3 H, *J* = 6.6 Hz, 9-*Me*); mass spectrum, *m/e* 256 ($M^{\cdot+}$), 225 (–OMe), 197, 181, 170, 111. Anal. Calcd for $C_{13}H_{20}O_5$: C, 60.90; H, 7.87. Found: C, 61.02; H, 7.98.

(2*S*,4*S*,6*S*,8*R*,9*S*)-Methyl 4-Hydroxy-8,9-dimethyl-1,7-dioxaspiro[5.5]undecane-2-carboxylate (49b). To a solution of ketone **49a** (67 mg) in DME (2.5 mL) at −20 °C was added $NaBH_4$ (99 mg). After 1 h the reaction was quenched with AcOH to pH 6–7 and diluted with Et_2O (20 mL), and H_2O (10 mL) was added. The H_2O layer was extracted with Et_2O (4 × 40 mL), and the combined ether solutions were evaporated. The crude product was chromatographed (silica, Et_2O) to give alcohol **49b** [52 mg (77%)] and the epimeric alcohol **48a** [8 mg (12%)]. The major alcohol **49b** showed the following properties: $[\alpha]^{25}_D$ +46.4° (*c* 0.7, $CHCl_3$); R_f 0.35 (silica, Et_2O); IR (film) 3440, 2995, 1735, 1440, 1110 cm^{-1}; ^1H NMR (270 MHz) δ 4.21 (m, 1 H, 4-*H*), 4.20 (dd, 1 H, *J* = 2.0, 9.9 Hz, 2-*H*), 3.78 (s, 3 H, CO_2Me), 3.27 (dq, 1 H, *J* = 6.6, 9.9 Hz, 8-*H*), 2.28 (ddd, 1 H, *J* = 13.2, 4, 3 Hz, 3-*H*), 2.03 (br dd, 1 H, *J* = 1, 6.5, 13 Hz, 3-*H*), 1.82 (m, 2 H, 5-H_2), 1.20–1.65 (m, 6 H), 1.11 (d, 3 H, *J* = 5.9 Hz, 8-*Me*), 0.83 (d, 3 H, *J* = 6.6 Hz, 9-*Me*); mass spectrum, *m/e* 258 ($M^{\cdot+}$), 240, 199, 181, 157, 55, 43 (100%).

(2*S*,4*S*,6*S*,8*R*,9*S*)-4-[(*tert*-Butyldiphenylsilyl)oxy]-8,9-dimethyl-1,7-dioxaspiro[5.5]undecane-2-methanol (49d). To a solution of alcohol **49b** (18 mg) in DMF (0.3 mL) at room temperature was added sequentially *t*-$BuPh_2SiCl$ (20 mg) and imidazole (12 mg). After stirring for 1 h, the solution was diluted with Et_2O (10 mL) and washed with H_2O (1 mL). The H_2O layer was extracted with Et_2O (3 × 5 mL), and the Et_2O solutions were combined, dried, and evaporated to give **49c** as a colorless oil. The crude ester **49c** (32 mg) in Et_2O (1 mL) at 0 °C was added to $LiAlH_4$ (20 mg). The suspension was stirred for 1 h. The reaction was quenched with a saturated aqueous Na_2SO_4 solution (0.3 mL) and the product extracted into Et_2O (5 × 3 mL). Silica (0.5 g) was added to the combined Et_2O extracts, the solvent evaporated, and the residue chromatographed (silica, Et_2O). The alcohol **49d** [20 mg (61%)] was obtained as a colorless oil. The spectral data exhibited by the sample were essentially identical with that published by Baker: $[\alpha]_D$ +26° (*c* 2.0, $CHCl_3$) [lit.[52] value $[\alpha]_D$ +23° (*c* 1.0, $CHCl_3$)]; IR (film) 3430, 2920, 1425, 1382, 1190, 1110, 700 cm^{-1}; ^1H NMR (270 MHz) δ 7.25–7.75 (m, 10 H, aryl-H), 4.20 (m, 1 H, 4-*H*), 3.35–3.48 (m, 3 H, 2-*H*, 2-CH_2OH), 3.13 (dq, 1 H, *J* = 5.9, 9.5 Hz, 8-*H*), 2.6 (br s, 1 H, O*H*), 1.89 (br dd, 1 H, *J* = 11.2, 4.6 Hz, 5-*H*), 1.58 (m, 1 H), 1.49 (m, 1 H), 1.00–1.48 (m, 6 H), 1.02 (s, 9 H, *t*-Bu), 0.94 (d, 3 H, *J* = 5.9 Hz, 8-*Me*), 0.74 (d, 3 H, *J* = 5.9 Hz, 9-*Me*); mass spectrum, *m/e* 333, 257, 239, 213 (100%), 199, 179, 161, 153, 113. Anal. Calcd for $C_{28}H_{40}O_4Si$: C, 71.73; H, 8.61. Found: C, 71.76; H, 8.68.

(2*R*,4*R*,6*R*,8*R*,9*S*)-Methyl 4-[(*tert*-Butyldiphenylsilyl)oxy]-8,9-dimethyl-1,7-dioxaspiro[5.5]undecane-2-carboxylate (50). $TsOH·H_2O$ (5 mg) was added to **45f** (100 mg) in THF (1 mL) and the resulting solution stirred at room temperature. The isomerization of the spiro ketal center was followed by TLC (silica, Et_2O–hexane, 1:9). The reaction appeared to reach equilibrium after 4 h to give an approximate 8:1 ratio of **50** to **45f**. Silica (0.5 g) was added to the reaction mixture, the solvent evaporated, and the resulting slurry chromatographed (silica, Et_2O–hexane, 1:9). The product spiro ketal **50** [74 mg (74%)] was obtained as a colorless oil: R_f 0.35 (silica, Et_2O–hexane, 1:9); IR (film) 3505, 2895, 1370, 1170, 1080, 1028, 997, 845 cm^{-1}; ^1H NMR (270 MHz) δ 7.20–7.80 (m, 10 H, aryl-*H*), 4.57 (dd, 1 H, *J* = 2.6, 12.5 Hz, 2-*H*), 3.90 (dddd, 1 H, *J* = 5, 5, 11, 11 Hz, 4-*H*), 3.73 (s, 3 H), 2.33 (m, 1 H), 2.2–2.0 (m, 1 H), 2.05 (dq, 1 H, *J* = 6.6, 10 Hz, 8-*H*), 1.75 (ddd, 1 H, *J* = 11, 12.5, 11 Hz, 3-*H*), 1.1–1.7 (m, 6 H), 1.07 (s, 9 H, *t*-Bu), 0.82 (d, 3 H, *J* = 6.6 Hz, 8-*Me*), 0.63 (d, 3 H, *J* = 6.9 Hz, 9-*Me*); mass spectrum, *m/e* 498 ($M^{\cdot+}$), 481, 439, 419, 241 (100%), 223, 195, 113. Anal. Calcd for $C_{29}H_{40}O_5Si$: C, 70.10; H, 8.12. Found: C, 69.82; H, 8.20.

(2*S*,4*R*,6*S*,8*R*,9*S*)-4-[(*tert*-Butyldiphenylsilyl)oxy]-8,9-dimethyl-1,7-dioxaspiro[5.5]undecane-2-carboxaldehyde (48c). A PhMe solution of $(i\text{-Bu})_2AlH$ (1.53 M, 3.30 mL) was added dropwise with stirring to **48b** (2.33 g) in PhMe (10 mL) at −78 °C. The resulting solution was stirred for 2.5 h at −78 °C. The reaction was not followed by TLC since the starting material and product cochromatographed (silica, Et_2O–hexane, 1:9). After 2.5 h at −78 °C AcOH (0.284 mL) in toluene (1 mL) was added. The resulting solution was very carefully warmed to 0 °C. The mixture exothermed strongly at approximately −15 °C. After 5 min at 0 °C the solution was recooled to −78 °C and treated with H_2O (0.30 mL) and the resulting suspension allowed to warm to room temperature. $NaHCO_3$ (1 g) was added and the suspension stirred for 30 min, before filtering off the aluminum salts through a pad of Celite. The Celite was washed with Et_2O (50 mL). The organic solution was evaporated and the residue chromatographed (silica, Et_2O–hexane, 2:3) to give the aldehyde **48c** [1.94 g (89%)] as a colorless oil: $[\alpha]^{25}_D$ +20.8° (*c* 0.60, $CHCl_3$); R_f 0.55 (silica, Et_2O–hexane, 1:9); IR (film) 2870, 1730, 1440, 1370, 1060, cm^{-1}; ^1H NMR (90 MHz) δ 9.8 (s, 1 H, C*H*O), 7.2–7.83 (m, 10 H, aryl-*H*),

4.69 (dd, 1 H, J = 2.5, 12 Hz, 2-*H*), 4.17 (m, 1 H, 4-*H*), 3.48 (dq, 1 H, J = 6.6, 10 Hz, 8-*H*), 1.95 (m, 1 H), 1.82 (m, 1 H), 1.25–1.70 (m, 7 H), 1.23 (d, 3 H, J = 6.6 Hz, 8-*Me*), 1.11 (s, 9 H, *t-Bu*), 0.89 (d, 3 H, J = 6.6 Hz, 9-*Me*); mass spectrum, m/e 466 ($M^{\bullet+}$, weak), 389, 239, 227, 211, 199, 179, 153, 127; fragment ion for $C_{24}H_{29}O_4Si$ (M^+ – *t*-Bu), calcd 409.1834, found 409.1834.

(2*S*,4*R*,6*S*,8*R*,9*S*)-4-[(*tert*-Butyldiphenylsilyl)oxy]-8,9-dimethyl-2-ethenyl-1,7-dioxaspiro[5.5]undecane (49e). To a suspension of $Ph_3P^+MeBr^-$ (2.56 g) in THF (20 mL) at 0 °C was added *n*-BuLi (1.5 M, 3.03 mL). After stirring for 2 h at 0 °C, a yellow solution formed. The Wittig solution was added dropwise over 20 min, via a double-ended needle, to a solution of the aldehyde **48c** (1.10 g) in THF (20 mL) at –78 °C. After the addition was complete, the resulting suspension was warmed to 0 °C for 20 min. The suspension was recooled to –78 °C and quenched with saturated aqueous NH_4Cl (20 mL). The product was extracted into Et_2O (2 × 70 mL); the solvent was dried and evaporated to give the crude alkene **49e** as a yellow gum. Chromatography (silica, Et_2O–hexane, 1:9) gave the alkene **49e**: 0.99 g (90%); $[\alpha]_D$ +25.8° (*c* 3.2, $CHCl_3$); R_f 0.80 (silica, Et_2O–hexane, 1:9); IR (film) 2910, 1460, 1425, 1375, 1105, 1080, 1015, 900, 820, 740, 700 cm^{-1}; ^1H NMR (270 MHz) δ 7.30–7.85 (m, 10 H, aryl-*H*), 5.85 (ddd, 1 H, J = 10.6, 17.2, 5.3 Hz, C*H*=CH_2), 5.26 (dd, 1 H, J = 17.5, 1 Hz, (*E*)-CH=CH_2) 5.08 (br d, 1 H, J = 10.6, 1 Hz, (*Z*)-CH=CH_2), 4.70 (m, 1 H, 2-*H*), 4.10 (m, 1 H, 4-*H*), 3.42 (dq, 1 H, J = 6.6, 10 Hz, 8-*H*), 1.85 (m, 1 H), 1.1–1.75 (m, 8 H), 1.22 (d, 3 H, J = 6.6 Hz, 8-*Me*), 1.09 (s, 9 H, *t-Bu*), 0.84 (d, 3 H, J = 6.6 Hz, 9-*Me*); mass spectrum, m/e 465 (M^+ + 1), 449, 407, 387, 239, 199, 179 (100%), 137, 119. Anal. Calcd for $C_{29}H_{40}O_3Si$: C, 74.93; H, 8.68. Found: C, 74.84; H, 8.77.

(2*R*,4*R*,6*R*,8*R*,9*S*)-4-[(*tert*-Butyldiphenylsilyl)oxy]-2-(2-hydroxyethyl)-8,9-dimethyl-1,7-dioxaspiro[5.5]undecane (49f). An Et_2O solution of borane–methyl sulfide complex (2 M, 3.06 mL) was added to alkene **49e** (2.80 g) in Et_2O (40 mL) at 0 °C. After the addition was complete, the reaction mixture was warmed to room temperature and stirred for 2.5 h. EtOH (3 mL) was added, followed by aqueous NaOH (3 M, 9.0 mL). The solution was cooled to 0 °C and treated with 30% H_2O_2 (80 mL). The resulting solution was stirred for 1 h before being diluted with Et_2O (200 mL) and H_2O (25 mL). The layers were separated, and the H_2O layer was washed with Et_2O (4 × 50 mL). The combined Et_2O layers were dried and evaporated, and the resulting oil was chromatographed (silica, Et_2O–hexane, 1:1) to give the alcohol **49f** [2.75 g (95%)] as a colorless oil: $[\alpha]^{25}_D$ +35.2° (*c* 2.4, $CHCl_3$); R_f 0.25 (silica, Et_2O–hexane, 1:4); IR (film) 3450, 2920, 1460, 1425, 1378, 1220, 1180, 1100, 1070, 1000, 900, 820, 740, 700 cm^{-1}; ^1H NMR (270 MHz) δ 7.25–7.85 (m, 10 H, aryl-*H*), 4.41 (m, 1 H, 2-*H*), 4.09 (m, 1 H, 4-*H*), 3.82 (m, 2 H, CH_2OH), 3.42 (dq, 1 H, J = 6.6, 9.9 Hz, 8-*H*), 2.94 (br s, 1 H), 1.66 (ddd, 1 H, J = 12.5, 2.5, 2.5 Hz), 1.51 (m, 2 H), 1.4–1.1 (m, 8 H), 1.24 (d, 3 H, J = 6.6 Hz, 8-*Me*), 1.07 (s, 9 H, *t-Bu*), 0.86 (d, 3 H, J = 5.9 Hz, 9-*Me*); ^{13}C NMR (90 MHz) δ 136, 129.5, 127.5, 97.7 (6-*C*), 71.8 (8-*C*), 65.5 (2-*C*, 4-*C*), 62.1 (CH_2CH_2OH), 41.0, 38.5, 37.5, 36.6, 36.5 (9-*C*), 28.0, 27.0 (*t-Bu*), 19.9 (8-*Me*), 19.1 (*t-Bu*), 17.9 (9-*Me*); mass spectrum, m/e 483 (M^+ + 1), 467, 425, 405, 255, 227 (100%), 209; accurate mass for $C_{25}H_{33}O_4Si$ (M^+ – *t*-Bu), calcd 425.2150, found 425.2145.

2-[(2*S*,4*R*,6*R*,8*R*,9*S*)-4-[(*tert*-Butyldiphenylsilyl)oxy]-8,9-dimethyl-1,7-dioxaspiro[5.5]undecyl]ethanal (49g). Freshly ground pyridinium chlorochromate (1.57 g) was added to alcohol **49f** (0.703 g) in CH_2Cl_2 (20 mL) at 0 °C. The resulting suspension was vigorously stirred and the progress of the reaction monitored by TLC (silica, Et_2O–hexane, 3:7). The reaction was too slow at 0 °C but proceeded to completion within 2 h upon warming to room temperature. The reaction mixture was diluted with Et_2O–hexane (3:7, 20 mL) and the suspension directly chromatographed (silica, Et_2O–hexane, 3:7) to give the aldehyde **49g** [0.62 g (89%)] as a colorless oil: $[\alpha]^{25}_D$ +10.6° (*c* 1.6, $CHCl_3$); R_f 0.80 (Et_2O–hexane, 3:7); IR (film) 2950, 2870, 2720, 1730, 1460, 1430, 1380, 1190, 1100 cm^{-1}; ^1H NMR (270 MHz) δ 9.86 (t, 1 H, J = 2 Hz, C*H*O), 7.30–7.78 (m, 10 H, aryl-*H*), 4.73 (m, 1 H, 2-*H*), 4.10 (m, 1 H, 4-*H*), 3.38 (dq, 1 H, J = 5.9, 9.2 Hz, 8-*H*), 2.52 (ddd, 1 H, J = 2.6, 8.6, 11.9 Hz, CH_2CHO), 2.41 (ddd, 1 H, J = 2.6, 4.6, 11.2 Hz, CH_2CHO), 1.88 (dt, 1 H, J = 2.2, 14 Hz), 1.1–1.65 (m, 8 H), 1.20 (d, 3 H, J = 6.6 Hz, 8-*Me*), 1.09 (s, 9 H, *t*-Bu), 0.79 (d, 3 H, J = 6.6 Hz, 9-*Me*); mass spectrum (FAB) m/e 481 (M^+ + H), 423 ($M^{\bullet+}$ – *t*-Bu); accurate mass for $C_{29}H_{41}O_4Si$ (M^+ + H), calcd 481.2775, found 481.2775.

(2*S*,4*R*,6*R*,8*R*,9*S*)-2-[(2*RS*,3*RS*,5*R*)-2-Acetoxy-8-[(*tert*-butyldimethylsilyl)oxy]-3,5-dimethyl-3-(phenylsulfonyl)-6-(*E*)-octenyl]-4-[(*tert*-butyldiphenylsilyl)oxy]-8,9-dimethyl-1,7-dioxaspiro[5.5]undecane (51). To sulfone **36** (0.22 g) in THF (4 mL) at –78 °C was added *n*-BuLi (1.5 M, 0.461 mL). After 10 min at –78 °C the pale yellow reaction mixture was warmed to 0 °C and stirred for 1 h. The reaction mixture was recooled to –78 °C and a solution of aldehyde **49g** (0.320 g) in THF (2 mL) added. After 30 min at –78 °C the reaction mixture was slowly warmed to 0 °C over 30 min. After 5 min at 0 °C the solution was recooled to –78 °C and sequentially quenched with Ac_2O (0.286 mL), pyridine (0.735 mL), and 4-(dimethylamino)-pyridine (catalytic quantity). The reaction mixture was allowed to warm to room temperature and stirred for a further 18 h. Et_2O (20 mL) was added and the pyridine washed out with saturated aqueous $CuSO_4 \cdot 5H_2O$ (5 mL). The H_2O layer was extracted with Et_2O (3 × 20 mL). The combined Et_2O solutions were dried and evaporated to give a pale yellow oil. Chromatography (silica, Et_2O–hexane, 1:4) gave sulfone acetate **51** [450 mg (86%)] as a mixture of diastereoisomers: R_f 0.75 (silica, Et_2O–hexane, 1:4); IR (film) 2960, 2930, 2860, 1725, 1450, 1430, 1378, 1290, 1260, 1210, 1175, 830, 740, 700 cm^{-1}; ^1H NMR (270 MHz) δ 7.1–7.90 (m, 15 H, aryl-*H*), 5.3–5.55 (m, 2 H, vinyl-C*H*), 4.05–4.30 (m, 5 H, CH_2OSiMe$_2$-*t*-Bu, 2-*H*, 4-*H*, C*H*OAc), 3.35–3.65 (m, 1 H, 8-*H*), 2.30 (s, 3 H), 1.05 (s, 9 H, *t*-Bu), 0.86 (s, 9 H, *t-Bu*), 0.05 (s, 6 H, Si*Me*$_2$); mass spectrum (FAB), m/e 904 ($M^{\bullet+}$), 848, 773, 731, 707 (100%), 649, 517, 199, 135, 105; High-resolution FAB m/e for $C_{51}H_{76}NaO_8SSi_2$ (M^+ + Na), calcd 927.4942, found 927.4820.

(2*R*,4*R*,6*R*,8*R*,9*S*)-2-[(5*R*)-8-[(*tert*-Butyldimethylsilyl)oxy]-3,5-dimethyl-2(*EZ*),6(*E*)-octadien-1-yl]-4-[(*tert*-butyldiphenylsilyl)oxy]-8,9-dimethyl-1,7-dioxaspiro[5.5]undecane (52a). To a solution of sulfone **51** (0.450 g) in THF (4.5 mL) and MeOH (1.5 mL) at –20 °C was added finely powdered 6% Na/Hg (1 g). The resulting suspension was rapidly stirred, and after 1 h the reaction mixture was diluted with Et_2O (20 mL) and the excess amalgam filtered off. The solution was neutralized with aqueous pH 7 buffer (5 mL) and the product extracted into Et_2O (3 × 10 mL). The combined ether layers were dried and evaporated. The crude product was purified by chromatography (silica, Et_2O–hexane, 1:19); the product **52a** [0.30 g (86% based on sulfone **36**)] was obtained as a viscous colorless oil. ^1H NMR spectroscopy showed the product to contain approximately 37% of the unwanted *Z* isomer. However, chromatographic separation of the double-bond isomers proved not possible at this stage, and the isomeric mixture was carried through subsequent steps for separation at a later stage. The oil exhibited the following properties: R_f 0.85 (silica, Et_2O–hexane, 1:9); IR (film) 2950, 2930, 2860, 1450, 1370, 1300, 1230, 1100 broad cm^{-1}; ^1H NMR (270 MHz) δ 7.25–7.80 (m, 10 H, aryl-*H*), 5.5 (m, 2 H, 6′-*H*, 7′-*H*), 5.28 (t, 0.35 H, J = 7 Hz, (*Z*)-2′-*H*), 5.19 (t, 0.63 H, J = 7 Hz, (*E*)-2′-*H*), 4.05 (m, 4 H, 2-*H*, 4-*H*, 8′-H$_2$), 3.45 (dq, 1 H, J = 6.6, 10 Hz, 8-*H*), 2.4 (m, 1 H), 2.05 (m, 2 H), 1.8 (m, 2 H), 1.70 (s, 0.37 × 3 H, 3′-*Me*), 1.58 (s, 0.63 × 3 H, (*E*)-3′-Me), 1.05 (s, 9 H, *t*-Bu), 0.90 (s, 9 H, *t-Bu*); mass spectrum, m/e 691 (M^+ – Me), 647 (M^+ – *t*-Bu), 573, 495, 449, 299, 199, 113, 75; high resolution mass spectrum for fragment (M^+ – OSi-*t*-BuPh$_2$ – OSi-*t*-BuMe$_2$), calcd 318.2525, found 318.2541. The crude material was used directly without further purification.

(2*R*,4*R*,6*R*,8*R*,9*S*)-4-[(*tert*-Butyldiphenylsilyl)oxy]-8,9-dimethyl-2-[(5*R*)-8-hydroxy-3,5-dimethyl-2(*EZ*),6(*E*)-octadien-1-yl]-1,7-dioxaspiro[5.5]undecane (52b). The silyl ethers **52a** (0.300 g) and THF–CH_3CO_2H–H_2O (2:3:2, 3 mL) were stirred for 8 h at 35 °C. The solution was diluted with Et_2O (10 mL), cooled to 0 °C, and neutralized with $NaHCO_3$ (2.1 g). The reaction mixture was washed with H_2O (5 mL) and the H_2O layer back-extracted with Et_2O (4 × 10 mL). The Et_2O layers were combined, dried, and evaporated to give the alcohols **52b** as a pale yellow oil. Chromatography (silica, Et_2O–hexane, 1:1) gave **52b** [208 mg (83%)] as a colorless oil: R_f 0.35 (silica, Et_2O–hexane, 1:1); IR (film) 3450, 2960, 2930, 2860, 1475, 1430, 1380, 1100 (br) cm^{-1}; ^1H NMR (270 MHz) δ 7.22–7.72 (m, 10 H, aryl-H), 5.53 (m, 2 H, 6′-*H*, 7′-*H*), 5.25, 5.13 (2 t, 1 H, J = 7 Hz, 2′-H), 4.05 (m, 4 H, 2-*H*, 4-H, 8′-H_2), 3.38 (dq, 1 H, J = 6.6, 9.7 Hz, 8-*H*), 2.25 (m, 1 H), 2.03 (m, 2 H), 1.62 (s, 0.37 × 3 H, (*Z*)-3′-*Me*), 1.50 (s, 0.63 × 3

H, (*E*)-3′-Me), 1.07 (s, 9 H, *t*-Bu), 0.80 (m, 6 H, 5′-Me, 9-Me); mass spectrum, *m/e* 590 ($M^{\cdot+}$), 573, 533, 391, 373, 335 (100%). Anal. Calcd for $C_{37}H_{54}O_4Si$: C, 75.19; H, 9.22. Found: C, 75.20; H, 9.29.

(2*R*,4*R*,6*R*,8*R*,9*S*)-4-[(*tert*-Butyldiphenylsilyl)oxy]-2-[(5*R*)-8-oxo-3,5-dimethyl-2(*EZ*),6(*E*)-octadien-1-yl]-8,9-dimethyl-1,7-dioxaspiro[5.5]undecane (52c). Freshly ground pyridinium chlorochromate (0.70 g) was added to **52b** (0.25 g) in CH_2Cl_2 (10 mL) at 0 °C. The resulting suspension was rapidly stirred for 2 h at 0 °C, diluted with Et_2O–hexane (3:7), and directly chromatographed (silica, Et_2O–hexane, 3:7). The α,β-unsaturated aldehyde **52c** [0.21 g (84%)] was obtained as a colorless oil: R_f 0.80 (silica, Et_2O–hexane, 1:1); IR (film) 2960, 2920, 2860, 2730, 1685, 1630, 1450, 1430, 1100 (br) cm^{-1}; ^1H NMR (270 MHz) δ 9.47 (2 d, 1 H, *J* = 7 Hz, 8′-*H*), 7.50 (m, 10 H, aryl-*H*), 6.78 (2 dd, 1 H, *J* = 8, 15 Hz, 6′-*H*), 6.08 (dd, 1 H, *J* = 7, 15 Hz, 7′-*H*), 5.38 (dd, 0.63 H, *J* = 7, 7 Hz, (*E*)-2′-*H*), 5.27 (dd, 0.37 H, *J* = 7, 7 Hz, (*Z*)-2′-*H*), 4.12 (m, 2 H, 2-*H*, 4-*H*), 3.43 (dq, 1 H, *J* = 7, 10 Hz, 8-*H*), 2.65 (m, 1 H, 5′-*H*), 2.15 (m, 4 H), 1.80 (m, 1 H), 1.71 (s, 0.37 × 3 H, (*Z*)-3′-*Me*), 1.61 (s, 0.63 × 3 H, (*E*)-3′-*Me*), 1.0–1.7 (m, 9 H), 1.20 (d, 3 H, *J* = 7 Hz, 8-*Me*), 1.12 (s + m, 11 H), 0.82 (d, 3 H, *J* = 7 Hz, 9-*Me*); mass spectrum, *m/e* 588 ($M^{\cdot+}$), 531, 389, 371, 333. The material was used directly without further purification.

(3*RS*,4*RS*)-3,4-Dihydro-3-[(3*R*)-7-[(2*R*,4*R*,6*R*,8*R*,9*S*)-4-hydroxy-8,9-dimethyl-1,7-dioxaspiro[5.5]undecan-2-yl]-3,5-dimethyl-1(*E*),5(*EZ*)-heptadien-1-yl]-6-methoxy-4,7-dimethyl-2(1*H*)-benzopyran-1-one (54). To NaH (78 mg) in THF (30 mL) was added the benzoic acid derivative **6** (420 mg). After stirring for 20 min at 25 °C the solution was cooled to −78 °C and *t*-BuLi (1.6 M, 1.36 mL) was added. The solution was warmed to −45 °C and stirred for 1 h. The dark burgundy solution was cooled to −78 °C and the aldehyde **52c** (260 mg) in THF (5 mL) added. After 30 min the reaction was quenched with CF_3CO_2H (0.84 mL) and warmed to room temperature. The resulting colorless solution was stirred for 3 h before adding H_2O (10 mL) and extracting the product into Et_2O (3 × 10 mL). The combined Et_2O layers were neutralized with aqueous $NaHCO_3$ before evaporation. The residue was reacted with Bu_4NF (1 M THF, 2 mL) in THF (1 mL). The resulting solution was gently warmed to 45 °C for 8 h before adding pH 7 buffer (5 mL) and extracting with Et_2O (3 × 8 mL). The combined Et_2O extracts were dried and evaporated, and the resulting oil was chromatographed (silica, Et_2O–hexane, 1:1). The benzopyranone derivative **54** [170 mg (73%)] was obtained as a pale yellow oil: R_f 0.2 (silica, Et_2O–hexane, 1:1); IR (film) 3500, 2940, 1700, 1597, 1495, 1455, 1250, 1100 (br) cm^{-1}; ^1H NMR δ 7.89 (s, 1 H), 6.65 (2 s, 1 H), 5.79 (m, 1 H), 5.50 (m, 1 H), 5.25 (m, 1 H), 4.98 (m, 0.5 H), 4.61 (m, 0.5 H), 4.26 (m, 1 H), 4.07 (m, 1 H), 3.89 (s, 3 H), 3.45 (m, 1 H), 2.95 (m, 1 H), 2.31 (s, 3 H), 1.14 (d, 3 H, *J* = 6 Hz), 0.82 (d, 3 H, *J* = 6 Hz); mass spectrum (CI), *m/e* 526 ($M^{\cdot+}$), 509 (100%), 491, 251, 203, 143, 129; high-resolution mass spectrum (FAB) for $C_{32}H_{47}O_6$ (M^+ + H), calcd 527.3372, found 527.3372.

2-[(5*R*)-9-[(2*R*,4*R*,6*R*,8*R*,9*S*)-4-Hydroxy-8,9-dimethyl-1,7-dioxaspiro[5.5]undec-2-yl]-1,5,7-trimethyl-1(*E*),3(*E*),7-(*E*)-nonatrien-1-yl]-4-methoxy-5-methylbenzoic Acid (55) and the *Z* Isomer 56. KH (35%, 0.47 g) was washed with hexane (3 × 1 mL) and Et_2O (3 × 1 mL). The white powder was treated with anhydrous [dried at 100 °C (1 mmHg), 1 h] 18-crown-6 (0.070 g) in THF (2 mL) and cooled to 0 °C. The dihydropyrone isomer mixture **54** (0.060 g) in THF (2 mL) was added dropwise with stirring. After 10 min the reaction mixture cooled to −78 °C and was quenched with CF_3CO_2H (0.620 mL). The resulting solution was warmed to room temperature and H_2O (2 mL) added; the pH was checked and adjusted to pH 6–7 with dilute CF_3CO_2H in THF. The product was extracted with Et_2O (3 × 10 mL) and dried and the solvent evaporated to leave a pale yellow oil. Chromatography (silica, Et_2O–hexane, 3:7) gave the trienes **55** and **56**, 49 mg (82%). The two isomers were separated by preparative TLC (silica, Et_2O–hexane, 1:4, four developments) to give the major isomer **55**: 29 mg (48%); R_f 0.58 (silica, Et_2O–hexane, 3:7); IR (film) 3500, 3200 (br), 2960, 1715, 1685, 1608, 1565, 1504, 1450, 1260, 1170, 1045, 975 cm^{-1}; UV (EtOH) λ_{max} 242 nm, (ϵ 24 000), 270 (sh) (ϵ 13 000); ^1H NMR (400 MHz) (assignments according to milbemycin numbering) δ 7.30 (s, 1 H, 3-*H*), 6.62 (s, 1 H, 6-*H*), 6.14 (dd, 1 H, *J* = 10.5, 15.2 Hz, 10-*H*), 5.71 (d, 1 H, *J* = 10.5 Hz, 9-*H*), 5.49 (dd, 1 H, *J* = 7.3, 15.2 Hz, 11-*H*), 5.26 (dd, 1 H, *J* = 9.2, 5.9 Hz, 15-*H*), 4.90 (d, 1 H, *J* = 9.2 Hz, OH), 3.82 (s + m, 5 H, CH_3, 17-*H*, 19-*H*), 3.28 (dq, 1 H, *J* = 6.6, 9.9 Hz, 25-*H*), 2.49 (m, 1 H, 12-*H*), 2.3–0.7 (m, 13 H) 2.19 (s, 3 H, 4-*Me*), 2.11 (s, 3 H, 8-*Me*), 1.60 (s, 3 H, 14-*Me*), 1.13 (d, 3 H, *J* = 6.3 Hz, 25-*Me*), 1.03 (d, 3 H, *J* = 6.6 Hz, 12-*Me*), 0.83 (d, 3 H, *J* = 6.0 Hz, 24-*Me*); mass spectrum, *m/e* 526 ($M^{\cdot+}$), 508 ($-H_2O$), 464, 259, 241 (100%), 181, 83, 69, 55; accurate mass for $C_{32}H_{46}O_6$ ($M^{\cdot+} - H_2O$), calcd 508.3189, found 508.3215. The isomer **56** [14 mg (23%)] was isolated as the crude minor component: R_f 0.55 (silica, Et_2O–hexane, 3:7); IR (film) 3500, 3100 (br), 2930, 1710, 1680, 1603, 1562, 1450, 1380, 1250, 1150 cm^{-1}; ^1H NMR (400 MHz) δ 7.64 (s, 1 H, 3-*H*), 6.63 (s, 1 H, 6-*H*), 6.29 (dd, 1 H, *J* = 11.1, 15.2 Hz, 10-*H*), 5.90 (d, 1 H, *J* = 10.6 Hz, 9-*H*), 5.54 (dd, 1 H, *J* = 7.9, 15.2 Hz, 11-*H*), 5.16 (t, 1 H, *J* = 6.6 Hz, 15-*H*), 4.2 (m, 1 H, 19-*H*), 3.8 (s + m, 4 H, O*Me*, 17-*H*), 3.41 (dq, 1 H, *J* = 6.6, 9.9 Hz, 25-*H*), 2.49 (m, 1 H, 12-*H*), 2.20 (s, 3 H, 4-*Me*), 2.10 (s, 3 H, 8-Me), 1.63 (s, 3 H, 14-Me), 1.16 (d, 3 H, *J* = 6.0 Hz, 25-*Me*), 1.02 (d, 3 H, *J* = 6.8 Hz, 12-*Me*), 0.84 (d, 3 H, *J* = 6.6 Hz, 24-*Me*).

5-*O*-Methylmilbemycin β_3 (57). Hydroxy acid **55** (19.0 mg) was dissolved in freshly distilled PhH (20 mL), and Ph_3P (30 mg) was added. The colorless solution was cooled to 8 °C and purged with dried N_2. Diethyl azodicarboxylate (0.18 μL) was added dropwise with stirring. The orange coloration of the diethyl azodicarboxylate immediately discharged, and TLC (silica, Et_2O–hexane, 3:17) showed the complete consumption of **55** and the appearance of a single less polar material. Silica (500 mg) was added to the reaction mixture and the solvent evaporated at room temperature under reduced pressure. The resulting powder was added to a column of silica and eluted with Et_2O–hexane (1:9). (+)-*O*-Methylmilbemycin β_3 [**57**; 14.2 mg (77%)] was obtained as a colorless waxy solid: R_f 0.80 (silica, Et_2O–hexane, 3:17); IR (film) 2910, 1707, 1682, 1608, 1520, 1350, 1110 cm^{-1}; UV (EtOH) λ_{max} 246 nm (ϵ 24 000); ^1H NMR (400 MHz) δ 7.35 (s, 1 H, 3-*H*), 6.62 (s, 1 H, 6-*H*), 6.14 (d, 1 H, *J* = 10.5, 15.5 Hz, 10-*H*), 5.72 (d, 1 H, *J* = 10.5 Hz, 9-*H*), 5.51 (m, 1 H, 19-*H*), 5.28 (dd, 1 H, *J* = 9.2, 14.5 Hz, 11-*H*), 4.90 (dd, 1 H, *J* = 2.0, 10.5 Hz, 15-*H*), 3.80 (s, 3 H, O*Me*), 3.69 (m, 1 H, 17-*H*), 3.28 (dq, 1 H, *J* = 9.6, 6.2 Hz, 25-*H*), 2.49 (m, 1 H, 12-*H*), 2.30 (m, 1 H), 2.18 (s, 3 H, 4-*Me*), 2.20 (m, 1 H), 2.11 (s, 3 H, 8-*Me*), 2.0–1.0 (m, ~10 H), 1.64 s, 3 H, 14-*Me*), 1.14 (d, 3 H, *J* = 6 Hz, 25-Me), 1.03 (d, 3 H, *J* = 6.6 Hz, 12-Me), 0.83 (d, 3 H, *J* = 6.6 Hz, 24-Me), 0.79 (m, 1 H); mass spectrum, *m/e* 508 ($M^{\cdot+}$), 490, 472, 259, 241, 215, 181, 153 (100%), 129, 95, 69, 55; accurate mass for $C_{32}H_{44}O_5$ ($M^{\cdot+}$), calcd 508.3189, found 508.3190.

(+)-Milbemycin β_3 (3a). Smith's procedure[6] was used to O-demethylate the ether **57**. NaH (60% oil dispersion, 60 mg) was washed with Et_2O (4 × 1 mL) and dried under N_2. Freshly distilled dry DMF (1 mL) was added followed by the addition of 1:1 EtSH–DMF to consume all of the sodium hydride. Methyl ether **57** (6.1 mg) in DMF (1 mL) was added to the pale yellow solution and the mixture heated to 145 °C for 45 min. The reaction mixture was cooled to −78 °C and quenched with CF_3CO_2H (approximately 0.22 mL) to pH 7. The solution was diluted with Et_2O (5 mL) and warmed to room temperature. Water (10 mL) was added and the product extracted into Et_2O (4 × 5 mL). The combined Et_2O extracts were dried and evaporated to give crude **3a** as a pale yellow oil. Chromatography (silica, EtOAc–hexane, 1:4) gave pure (+)-milbemydin β_3 [**3a**; 4.3 mg (73%)]. Recrystallization from CH_2Cl_2–hexane gave **3a** (4.1 mg) as white needles: mp 181–183 °C (lit.[7] mp 185–187 °C); $[\alpha]^{25}_D$ +102° (*c* 0.17, MeOH) [lit.[59] value +103° (*c* 0.280, MeOH)]; IR 33.91, 3420, 2980, 2930, 2875, 1678, 1612, 1578, 1450, 1380, 1311, 1280, 1164, 1094, 1054, 998 cm^{-1}; UV (EtOH) λ_{max} 246 nm (ϵ 23 200); ^1H NMR (400 MHz) δ 7.33 (s, 1 H, 3-*H*), 6.61 (s, 1 H, 6-*H*), 6.13 (dd, 1 H, *J* = 11.0, 15.0 Hz, 10-*H*), 5.72 (d, 1 H, *J* = 11 Hz, 9-*H*), 5.51 (m, 1 H, 19-*H*), 5.26 (dd, 1 H, *J* = 15.0, 9.6 Hz, 11-*H*), 4.96 (br s, 1 H, O*H*), 4.90 (br d, 1 H, *J* = 9.5 Hz, 15-*H*), 3.68 (m, 1 H, 17-*H*), 3.29 (dq, 1 H, *J* = 9.7, 6.0 Hz, 25-*H*), 2.48 (m, 1 H, 12-*H*), 2.30 (m, 1*H*), 2.22 (s, 3 H, 4-*Me*), 2.20 (m, 1*H*), 2.06 (s, 3 H, 8-*Me*), 2.03–1.8 (m, 4 H), 1.63 (s, 3 H, 14-*Me*), 1.6–1.4 (m, ~4 H), 1.25 (m, 2 H), 1.14 (d, 3 H, *J* = 6.0 Hz, 25-*Me*), 1.03 (d, 3 H, *J* = 6.6 Hz, 12-*Me*), 0.83 (d, 3 H, *J* = 6.6 Hz, 24-*Me*), 0.77 (m, 1 H); ^{13}C NMR (101 MHz) δ 169.38, 155.28, 144.07, 140.34, 135.83, 133.93, 131.84, 128.83, 125.40, 124.31, 122.20, 121.44, 114.11, 97.73, 71.18, 68.04, 67.63, 48.73, 41.22, 36.60, 36.28, 35.81, 33.91, 27.80, 21.63, 19.43, 18.01, 17.91, 16.13, 15.25; mass spectrum (70 eV), *m/e* 494

($M^{\cdot+}$, <10%), 476 (<5%), 408 (<5%), 245 (30%), 227 (35%), 181 (55%), 153 (100%); accurate mass for $C_{31}H_{42}O_5$ ($M^{\cdot+}$), calcd 494.3033, found 494.3049.

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Registry No. **3a**, 56198-39-1; **4**, 10281-55-7; **5**, 16088-62-3; **6**, 102740-25-0; **7**, 104705-92-2; **9**, 82190-18-9; **10**, 104705-88-6; (±)-**11**, 82045-40-7; **11**, 82467-25-2; **12**, 72476-03-0; **13**, 56279-34-6; **14a**, 102740-19-2; **14b**, 102740-24-9; **15**, 79091-60-4; **16a**, 20521-96-4; **16b**, 20521-97-5; **17a**, 104996-17-0; **17b**, 104996-17-0; (±)-**18**, 104996-18-1; (±)-**19**, 104996-19-2; **21**, 78257-87-1; **24**, 104996-21-6; **26**, 105087-12-5; **27**, 105087-13-6; **28**, 105087-14-7; **29**, 104996-20-5; **31**, 105087-15-8; **33**, 104996-22-7; **34a**, 104996-23-8; **34b**, 104996-25-0; **35a**, 104996-24-9; **35b**, 104996-26-1; **36**, 104996-27-2; (±)-**37a**, 104996-28-3; (±)-**37b**, 105087-16-9; (±)-**37b** (diol), 104996-29-4; **38a**, 104996-30-7; **38b**, 104996-31-8; **39a**, 105087-17-0; **39b**, 105087-18-1; **40a**, 93904-58-6; **40b**, 69274-86-8; **41**, 105087-19-2; **44a**, 18370-95-1; **44b**, 104996-32-9; **44c**, 104996-33-0; **45a**, 104996-37-4; **45b**, 104705-89-7; **45c**, 105087-20-5; **45d**, 104996-35-2; **45e**, 104996-36-3; **45f**, 105087-22-7; **46**, 104996-34-1; **48**, 105087-21-6; **48b**, 102140-79-4; **48c**, 105087-27-2; **49a**, 105087-24-9; **49b**, 105087-25-0; **49c**, 105087-23-8; **49d**, 82415-18-7; **49e**, 104996-38-5; **49f**, 104996-39-6; **49g**, 104705-91-1; **50**, 105087-26-1; **51**, 104996-40-9; (*E*)-**52a**, 104705-94-4; (*Z*)-**52a**, 105087-28-3; (*E*)-**52b**, 105087-29-4; (*Z*)-**52b**, 105087-30-7; (*E*)-**52c**, 104759-57-1; (*Z*)-**52c**, 104759-58-2; **54**, 104705-97-7; **55**, 104759-59-3; **56**, 104705-98-8; **57**, 101977-94-0; $MeCH_2C{\equiv}CCO_2Et$, 55314-57-3; MeCOCHO, 78-98-8; $Ph_3P{=}CHCO_2Et$, 1099-45-2; $PhCH(OMe)CO_2H$, 26164-26-1; $H_2N(CH_2)_2NH_2{\cdot}LiC{\equiv}CH$, 6867-30-7; (2*R*,3*S*)-MeCH(OH)CH(Me)Et, 73176-98-4; MeO_2CCO_2Me, 553-90-2; $Ph_3P^+MeBr^-$, 1779-49-3.

Chemistry of Naturally Occurring Polyamines. 10.[1] Nonmetabolizable Derivatives of Spermine and Spermidine

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Polyamine oxidases (PAO's) play an important role in the oxidative metabolism of spermidine, spermine, and their derivatives. Since the actual oxidation step involves deprotonation at the α-carbon(s) of the amine, *gem*-dimethyl substitution at those sites should retard catabolism. Moreover, synthetic methylated analogues of known biologically active polyamine conjugates may be expected to display enhanced activity and/or longer duration of action. This paper describes the synthesis of stable hydrochloride salts of five *gem*-dimethylspermidines **8**–**12** and two spermine analogues **13** and **14** that were designed to act as PAO inhibitors and to serve as useful probes of complex polyamine biosynthesis.

Naturally occurring polyamines are primary modulators of both normal and pathological cell growth, a fact that has recently stimulated much research into their biosynthesis and metabolism.[2,3] Polyamine oxidases (PAO's) play an important role in the latter process and are widely distributed in plants, bacteria, and fungi as well as in mammalian cells.[4,5] Enzymic oxidation of spermidine (**1**) and spermine (**2**) (and their acetylated derivatives) produces complex, highly labile mixtures of imines, aldehydes, imino aldehydes, and resultant lower amines, depending on the source and type of PAO used.[4,6] Besides helping to regulate intracellular levels of spermidine and spermine, the oxidation of polyamines generates products (including H_2O_2) that are toxic to a variety of cell types and may be involved in the immune response to certain microbial and parasitic pathogens.[7,8]

Most PAO's are flavin-containing enzymes, some of which are Cu^{2+}-dependent.[5,9,10] Although mechanistic details are incompletely understood, it would appear that the amine and flavin combine to form an imine **3** that isomerizes to **4** and hydrolyzes, furnishing aldehyde **5**, amine **6**, and reduced cofactor **7** (see Scheme I).[9] Since the actual oxidation step in this scheme involves proton removal at the carbon α to nitrogen in **3**, we reasoned that *gem*-dimethyl groups at that position would block deprotonation and retard catabolism. Such achiral *gem*-dimethyl polyamines might act as PAO inhibitors and/or serve as useful probes of complex polyamine biosynthesis. Moreover, the corresponding analogues of pharmacologically active polyamine conjugates (e.g., with amino acids, sugars, steroids, phospholipids, and peptides[11]) might ex-

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