JOC Article

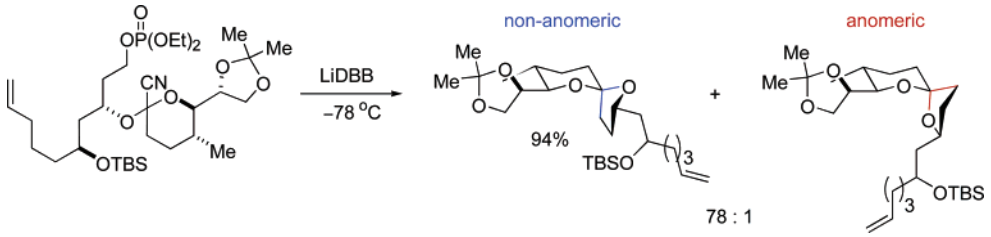
A Reductive Cyclization Approach to Attenol A

Thomas E. La Cruz and Scott D. Rychnovsky*

Department of Chemistry, 1102 Natural Sciences II, University of California—Irvine, Irvine, California 92697-2025

srychnov@uci.edu

Received December 22, 2006



A reductive cyclization strategy was applied to the synthesis of attenol A. This nontraditional approach to the spiroacetal structure illustrated several advantages of the reductive cyclization methodology. The attenol A core was formed in a carbon−carbon bond coupling that gave rise to a previously inaccessible spiroacetal epimer, a new method to synthesize thioketene acetals from a phenyl sulfone was realized, and the configurational stability of a nonanomeric spiroacetal was evaluated. A minor byproduct in the reductive cyclization reaction was identified that for the first time allowed direct evaluation of the stereoselectivity in a reductive cyclization of a dialkyloxy alkyllithium reagent.

Introduction

Attenol A (**1**) (Figure 1) was isolated from the extract of the Chinese bivalve *Pinna attenuata* by Uemura and co-workers.[1] The molecular architecture of attenol A features three contiguous stereogenic centers, two homoallylic alcohols, both terminal and *Z*-disubstituted olefins, and an anomeric stabilized [5.4]-spiroacetal core. Attenol B (**2**) was isolated from the same extract as attenol A (**1**), and its structure was determined by Uemura to be an isomeric form of attenol A (**1**).[1] Both attenol A and attenol B show moderate cytotoxic activity against P388 cells.[1] Its biological activity and scarcity have made attenol A an interesting synthetic target, and it has been prepared by three independent research groups: D. Uemura's,[2a,b] J. Eustache's,[3] and D. Enders'.[4] We describe a new synthesis of attenol A using a reductive cyclization strategy.

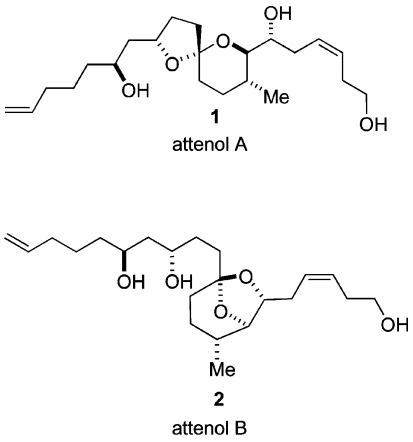


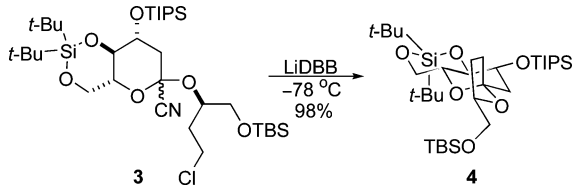
FIGURE 1. Structures of attenol A and B.

The reductive cyclization strategy was developed in our group to facilitate the stereoselective assembly of nonanomeric spiroacetals.[5] An example of this cyclization reaction is illustrated in Scheme 1. In contrast to traditional spiroacetal syntheses, this strategy is convergent and gives rise to a nonanomeric stabilized [5.4]-spiroacetal as a single stereoisomer. The resulting nonanomeric spiroacetal equilibrates under acidic

(1) Takada, N.; Suenaga, K.; Yamada, K.; Zheng, S.-Z.; Chen, H.-S.; Uemura, D. *Chem. Lett.* **1999**, 1025−1026.
(2) (a) Suenaga, K.; Araki, K.; Sengoku, T.; Uemura, D. *Org. Lett.* **2001**, *3*, 527−529. (b) Araki, K.; Suenaga, K.; Sengoku, T.; Uemura, D. *Tetrahedron* **2002**, *58*, 1983−1995.
(3) Aoun, D.; Boiteau, J. G.; Eustache, J.; Van de Weghe, P. *Org. Lett.* **2002**, *4*, 4105−4108.
(4) Enders, D.; Lenzen, A. *Synlett* **2003**, 2185−2187.
(5) Takaoka, L. R.; Buckmelter, A. J.; La Cruz, T. E.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2005**, *127*, 528−529.

10.1021/jo0626459 CCC: $37.00
Published on Web 03/09/2007

SCHEME 1. Stereoselective Preparation of Nonanomeric Spiroacetal



conditions to the more stable anomeric epimer.[5] Thus both spiroacetal epimers can be accessed from a common intermediate. The synthesis of attenol A illustrates the versatility of a reductive cyclization strategy to efficiently prepare both anomeric and nonanomeric spiroacetals.[6]

Many biologically active natural products contain anomeric spiroacetals, and these spiroacetals are presumably more stable than their nonanomeric epimer. On treatment with mild acid, one would expect that the nonanomeric spiroacetal epimer would cleanly isomerize to the natural epimer with a significant change in overall geometry. With such a rearrangement in mind, we considered that nonanomeric spiroacetals might act as pro-drugs for their natural epimers. Solid tumors are known to have unusually low extracellular pH,[7] and we considered that spiroacetal epimerization could be triggered by this low pH media and liberate the biologically active anomeric spiroacetal in the presence of the tumor. There are many difficulties with such a scheme, but one prerequisite that could be evaluated was the expected rate of isomerization of a nonanomeric spiroacetal to an anomeric spiroacetal in a low pH aqueous medium. We identified attenol A and its nonanomeric spiroacetal as a convenient test case to evaluate the lability of the spiroacetal linkages, and discuss the results below.

Results

The retrosynthetic analysis of attenol A is illustrated in Figure 2. The epoxide motif in **5**, where the planned addition of a vinyl cuprate reagent will install the *Z*-alkene side chain, lends flexibility to the synthetic route. Acid induced epimerization of the nonanomeric spiro intermediate **6** will give the appropriate configuration of the spiroacetal segment of attenol A (**1**). Spiroacetal **6** will be synthesized by reductive lithiation of cyanoacetal **7**, which itself is derived from spiro orthoester **8**. Spiro orthoester **8** will arise from the acid-catalyzed coupling of diol **9** and thiophenyl ketene acetal **10**, both of which can be derived from readily available chiral materials.

The preparation of diol **9** is summarized in Scheme 2. Optically pure epoxide **12**, prepared by Jacobsen resolution,[8] was treated with 2 equiv of the organolithium derived from the known dithiane **11** to give alcohol **13** in 97% yield.[9] Hydrolysis of the dithiane with $CuCl_2/CuO$,[10] $Hg(ClO_4)_2$,[11] or $(CF_3CO_2)_2$-IPh[12] gave unsatisfactory yields (16−63%) of β-hydroxy ketone **14**. Efficient deprotection of **13** finally was achieved with MeI in aqueous acetonitrile, which gave the desired ketone **14** in 94% yield (Scheme 2).[13] Ketone **14** was reduced to alcohol **15** (structure not shown) by using Schneider's variation of the Tishchenko reduction catalyzed by Zr(O*t*-Bu)$_4$.[14] Schneider's conditions led to the reduction of β-hydroxy ketone **14** with ca. 10:1 selectivity. The reduction of ketone **14** was best carried out at −78 °C to obtain the desired anti ester **15** with improved stereoselectivity (98:2 anti:syn)[15] and in acceptable yield (83%). Alcohol **15** was converted to *tert*-butyldimethylsilyl (TBS) ether **16** in 99% yield. The acyl and benzyl protecting groups of silyl ether **16** were simultaneously removed by treatment with Li/NH_3 to give diol **9** in 50% to 65% yields. Analysis of the crude reaction mixture revealed a side reaction in which the oxygen atom of the ester had been reductively removed. Similar ester deoxygenations under dissolving metal conditions have been reported previously.[16] We hypothesized that a mild reduction or prior acyl hydrolysis would avoid this side reaction. Reduction with sodium and ethanol at −78 °C led to slow cleavage of the benzyl ether; upon warming to 0 °C only trace amounts of the desired diol **9** were detected due to competing migration of the TBS group. Prior acyl cleavage was achieved in situ by adding MeLi to a solution of TBS ether **16** in THF/NH_3 to generate $LiNH_2$. Subsequent addition of Li° led to removal of the benzyl ether and gave diol **9** in excellent yield. With the successful synthesis of diol **9** our efforts turned toward the synthesis of its coupling partner.

Our initial strategy called for the introduction of the complete *Z*-alkene side chain prior to thioketene acetal formation. This route is illustrated in Scheme 3. Known homoallylic alcohol **17**[17] was reacted with allyl bromide to give allyl ether **18**. Allyl ether **18** was then subjected to a three-step reaction sequence. First, a RCM reaction using Grubbs' first generation catalyst gave the dihydropyran **19** (95% yield).[18] Hydrolysis of the acetonide protection group followed by cyclization of the resulting diol **20** gave epoxide **21** in good yield.[39] Vinyl cuprate **21**, prepared from vinyl iodide **25** (Scheme 3),[19] reacted with epoxide **26** to give the desired homoallylic alcohol **22**

(6) Recent reviews on spiroacetal synthesis: (a) Mead, K. T.; Brewer, B. N. *Curr. Org. Chem.* **2003**, *7*, 227−256. (b) Aho, J. E.; Pihko, P. M.; Rissa, T. K. *Chem. Rev.* **2005**, *105*, 4406−4440. See also: (c) Jacobs, M. F.; Kitching, W. *Curr. Org. Chem.* **1998**, *2*, 395−436. (d) Perron, F.; Albizati, K. F. *Chem. Rev.* **1989**, *89*, 1617−1661. (e) Boivin, T. L. B. *Tetrahedron* **1987**, *43*, 3309−3362.

(7) (a) Montcourrier, P.; Silver, I.; Farnoud, R.; Bird, I.; Rochefort, H. *Clin. Exp. Metastasis* **1997**, *15*, 382−392. (b) Stubbs, M.; McSheehy, P. M. J.; Griffiths, J. R.; Bashford, C. L. *Mol. Med. Today* **2000**, *6*, 15−19. (c) Han, S. K.; Na, K.; Bae, Y. H. *Colloids Surf., A* **2003**, *214*, 49−59. (d) Reddy, L. H. *J. Pharm. Pharmacol.* **2005**, *57*, 1231−1242.

(8) Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 1307−1315.

(9) For an account of natural product synthesis based on a dithiane strategy see: Smith, A. B., III; Adams, C. M. *Acc. Chem. Res.* **2004**, *37*, 365−377 and references cited therein.

(10) (a) Chikashita, H.; Kittaka, E.; Kimura, Y.; Itoh, K. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 833−837. (b) Also see Uemura, ref 2b.

(11) Furuta, H.; Hase, M.; Noyori, R.; Mori, Y. *Org. Lett.* **2005**, *7*, 4061−4064.

(12) Stork, G.; Zhao, K. *Tetrahedron Lett.* **1989**, *30*, 287−290.

(13) Petri, A. F.; Kühnert, S. M.; Scheufler, F.; Maier, M. E. *Synthesis* **2003**, 940−955.

(14) (a) Schneider, C.; Klapa, K.; Hansch, M. *Synlett* **2005**, 91−94. (b) Schneider, C.; Hansch, M.; Weide, T. *Chem. Eur. J.* **2005**, *11*, 3010−3021.

(15) The anti relationship of the two stereocenters of product **14** was confirmed by ^{13}C analysis of acetonide **14a**, where the appropriate ^{13}C resonance signals of both the acetal and methyl carbon atoms were observed: refer to the supporting information section. (a) Rychnovsky, S. D.; Skalitzky, D. J. *Tetrahedron Lett.* **1990**, *31*, 945−948. (b) Rychnovsky, S. D.; Rogers, B.; Yang, G. *J. Org. Chem.* **1993**, *58*, 3511−3515.

(16) Barrett, A. G. M.; Godfrey, C. R. A.; Hollinshead, D. M.; Prokopiou, P. A.; Barton, D. H. R.; Boar, R. B.; Joukhadar, L.; McGhie, J. F.; Misra, S. C. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1501−509.

(17) (a) Ronald, R. L.; Roush, W. R. *J. Am. Chem. Soc.* **1986**, *108*, 294−296. (b) Coe, J. W.; Roush, W. R. *J. Org. Chem.* **1989**, *54*, 915−930. (c) Roush, W. R.; Ando, K.; Powers, D. B.; Palkowitz, A. D.; Halterman, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 6339−6348.

(18) Schmidt, B. *J. Org. Chem.* **2004**, *69*, 7672−7687.

(19) (a) Takami, K.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2002**, *4*, 2993−2995. (b) Takami, K.; Mikami, S.; Yorimitsu, H.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* **2003**, *68*, 6627−6631.

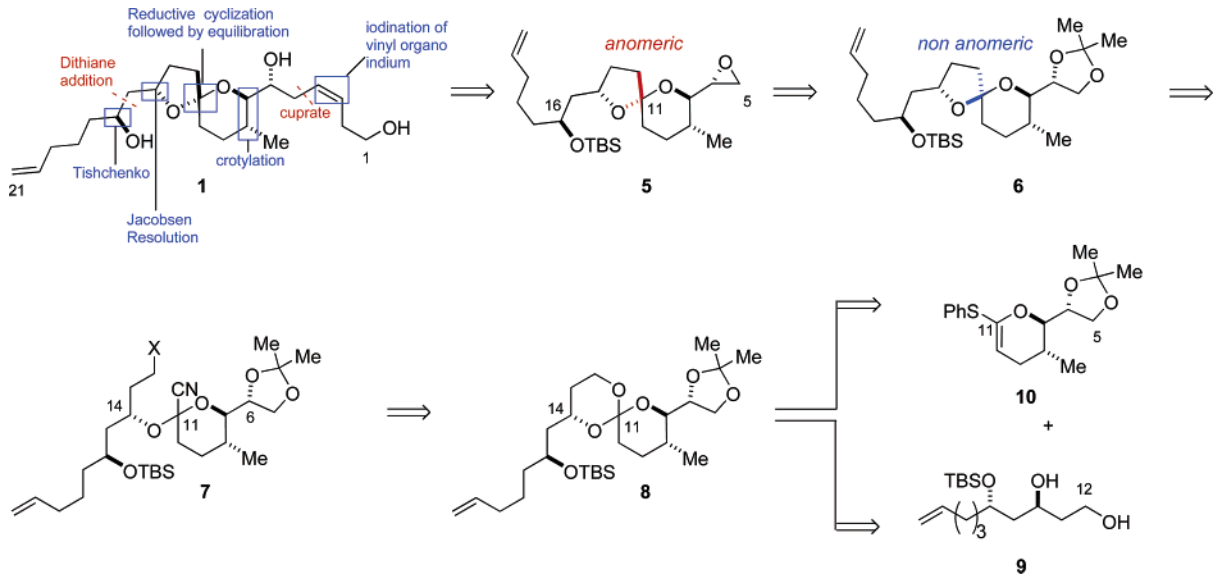
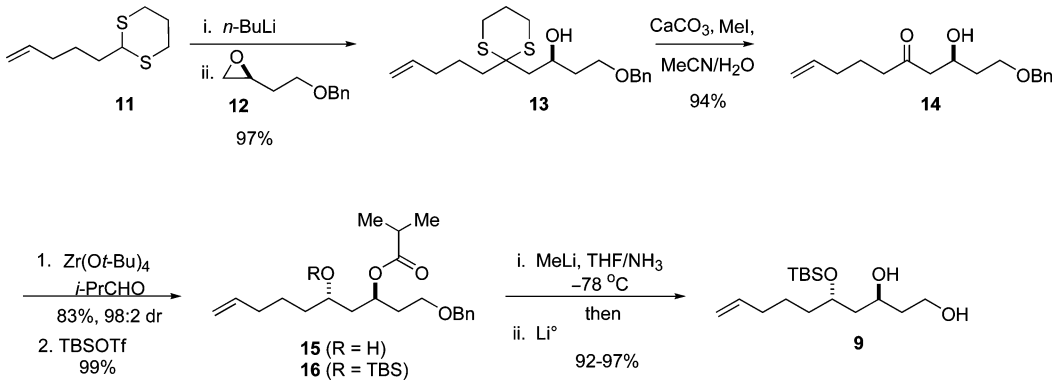


FIGURE 2. Disconnection plan.

SCHEME 2. Synthesis of Diol



in 85% yield.[20] The alcohol **22** was converted to triisopropylsilyl (TIPS) ether **23** in quantitative yield under standard reaction conditions. Silyl ether **23** represents half of the attenol A carbon skeleton. Although the route was satisfactory, the sequence placed the ring unsaturation at C3 rather than C2. Isomerization to the C2 enol ether was possible with similar compounds, but the exocyclic alkene complicated the process.[21,22] Selective alkene isomerization was not observed with Wilkinson's catalyst.[22] However, both Brimble and Nicolaou have reported base-induced alkene isomerizations of dihydropyran systems to form cyclic enol ethers.[23] When dihydropyran **23** was treated with LDA or *t*-BuOK under various conditions, only decomposition was observed. Failure of the base-induced alkene isomerization reactions forced us to examine a different approach to the enol ether **29**.

A new route to the desired enol ether **29** was investigated, and the outcome is illustrated in Scheme 4. The alkene isomerization of epoxide **21**, mediated by Wilkinson's catalyst,[22] gave volatile epoxide **27** in 70% yield. Addition of cuprate **26** to oxirane **27** followed by protection of the resulting homoallylic alcohol **28** completed the synthesis of enol ether **29**. All attempts to lithiate enol ether **29** under Boeckman or Myer's conditions led to the decomposition of starting enol ether **29**.[24] Loss of the homoallylic silyl ethers, presumably through $E1_{cb}$ elimination, was evident in the ^{1}H NMR spectrum of the crude reaction mixtures. The unsuccessful kinetic lithiation reaction forced us to develop an alternative method to generate thioketene acetal **30** from enol ether **29**.

Crich explored generating thioketene acetals directly from arylsulfones, but his endeavor was unsuccessful.[25] He showed that lithiation of sulfone **31** and subsequent treatment with diphenyl disulfide gave only dithioorthoester **34**, and not the expected thioketene acetal **33** (Scheme 5, part A). We repeated the experiment in our laboratories (Scheme 5, part B) and found that the reaction gave primarily two products. The major

(20) (a) Lipshutz, B. H. *Synthesis* **1987**, 325−341. (b) Solladié, G.; Hamdouchi, C.; Ziani-Chérif, C. *Tetrahedron*: *Asymmetry* **1991**, *2*, 457−469.

(21) (a) Leeuwenburgh, M. A.; Overkleeft, H. S.; van der Marel, G. A.; van Boom, J. H. *Synlett* **1997**, 1263−1264. (b) Clark, J. S.; Kettle, J. G. *Tetrahedron Lett.* **1997**, *38*, 127−130.

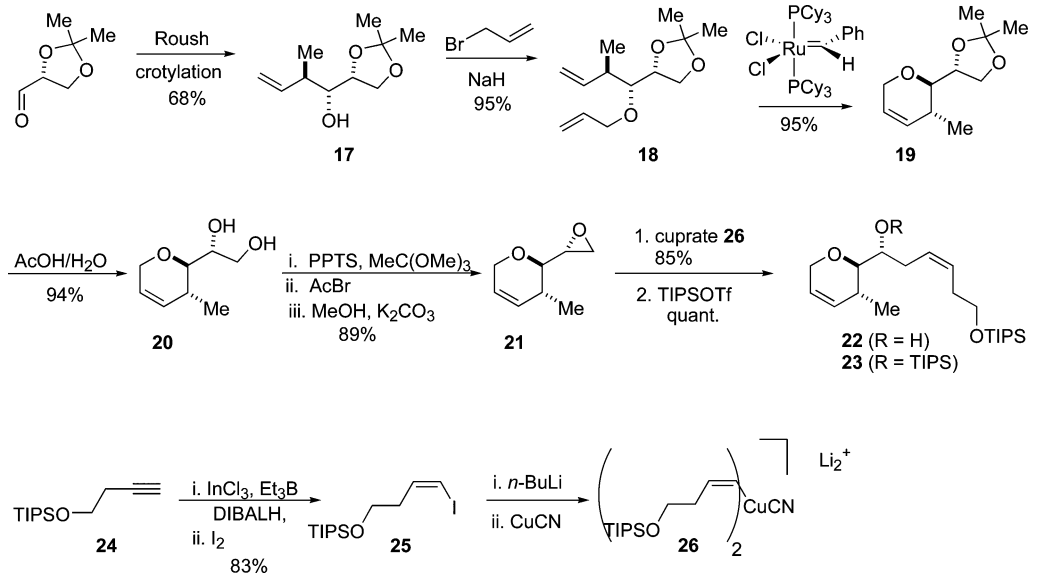
(22) Corey, E. J.; Suggs, J. W. *J. Org. Chem.* **1973**, *38*, 3224.

(23) (a) Nicolaou, K. C.; Veale, C. A.; Hwang, C.-K.; Hutchinson, J.; Prasad, C. V. C.; Ogilvie, W. W. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 299−303. (b) Furkert, D. P.; Brimble, M. A. *Org. Lett.* **2002**, *4*, 3655−3658.

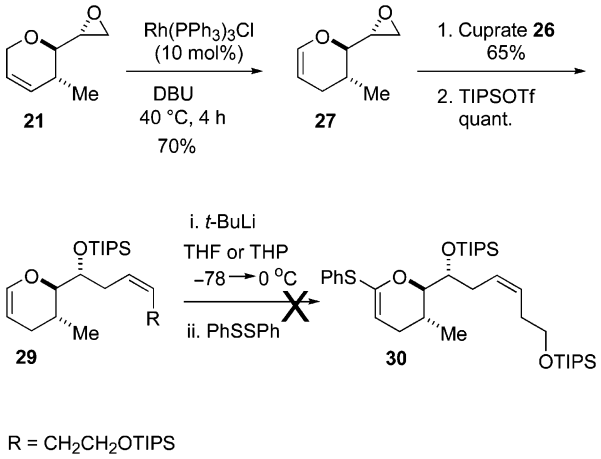
(24) For a review on the metalation of vinyl ethers see: Friesen, R. W. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1969−2001.

(25) Crich, D.; Ritchie, T. J. *Tetrahedron* **1988**, *44*, 2319−2328.

SCHEME 3. Synthesis of DHP and Organocuprate



SCHEME 4. Attempted Lithiation



constituent was dithioorthoester **34**. Surprisingly, the minor component was thioketene acetal **33**. Optimization of this reaction led to efficient formation of the desired thioketene acetal. The optimized procedure was applied to the synthesis of attenol A. Enol ether **29** reacted with benzenesulfinic acid to give sulfone **35** in 74−81% yield (Scheme 5, part C). Sulfone **35** was treated with *n*-BuLi at −100 °C to generate the unstable lithiated sulfone. The lithiated sulfone was quenched with $PhSSO_2Ph$,[26] and Et_3N was introduced into the reaction vessel to scavenge the benzenesulfinic acid generated in the elimination reaction. These conditions gave the desired thioketene acetal **30** in 65% yield with none of the corresponding dithioacetal detected. With thioketene acetal **30** in hand, the time came to test the spiro orthoester formation.

Thioketene acetal **30** was reacted with diol **9** under standard reaction conditions (0.1 M in DCM, 1−3 mol % camphorsulfonic acid (CSA), rt, 0.5 h),[27] and the desired spiro orthoester **36** was isolated in a disappointing 35% yield (Scheme 6). Several decomposition products were observed by TLC and by spectroscopic analysis of the crude reaction mixture. All attempts to improve the outcome by using a milder proton source, higher dilution, or rigorously anhydrous solvent were fruitless. The proximity of the bulk secondary TIPS ether apparently disfavors cyclization to the orthoester. With the outcome of these experiments in mind we revaluated the synthetic plan for attenol A.

A new route was designed that would delay introduction of the side chain until the end of the synthesis. As shown in Scheme 7, enol ether **37** was readily accessed from cyclic allyl ether **19** through an alkene isomerization reaction catalyzed by $(PPh_3)_3$-RhCl in 90% yield.[22] The acetonide protecting group of enol ether **37** was not compatible with *t*-BuLi treatment, so an alternative thioketene acetal synthesis was required. Applying the phenylsulfone protocol, sulfone **38** was prepared from enol ether **37** and subjected to the same sequence as sulfone **35** (Scheme 5) to produce thiophenylketene acetal **10** in 72% yield. This promising result could be applied to the synthesis of attenol A, but an even more efficient route was identified.

Kocienski recently reported a very effective route to thioketene acetals,[28] and application of Kocienski's strategy might streamline our synthesis of thioketene acetal **10**. The new synthetic sequence is shown in Scheme 8. Homoallylic alcohol **17** was converted to vinyl ester **39** in 87% yield.[29] Lactone **41** was accessed by a sequential RCM/hydrogen reaction with both steps mediated by Grubbs' second generation catalyst.[30] Kocienski's Ni^0 catalyzed protocol was applied to lactone **41**, and gave the desired thioketene acetal **10** in 75% yield. Clearly, this three-pot sequence to thioketene acetal **10** was superior to the previously explored routes. With thioketene acetal **10** in hand, the time came to test the orthoester formation.

Thioketene acetal **10** was coupled to diol **9** with use of catalytic CSA.[27] The desired spiro orthoester **8** was isolated in 86% yield as a single diastereomer (Scheme 9).[31] The [5.5]-spiro orthoester **8** was opened with $BF_3{\cdot}OEt_2$ and TMSCN with

(26) The sulfinating reagent $PhSSO_2Ph$ was crucial to the success of the reaction: Billard, T.; Langlois, B. R.; Large, S.; Anker, D.; Roidot, N.; Roure, P. *J. Org. Chem.* **1996**, *61*, 7545−7550.

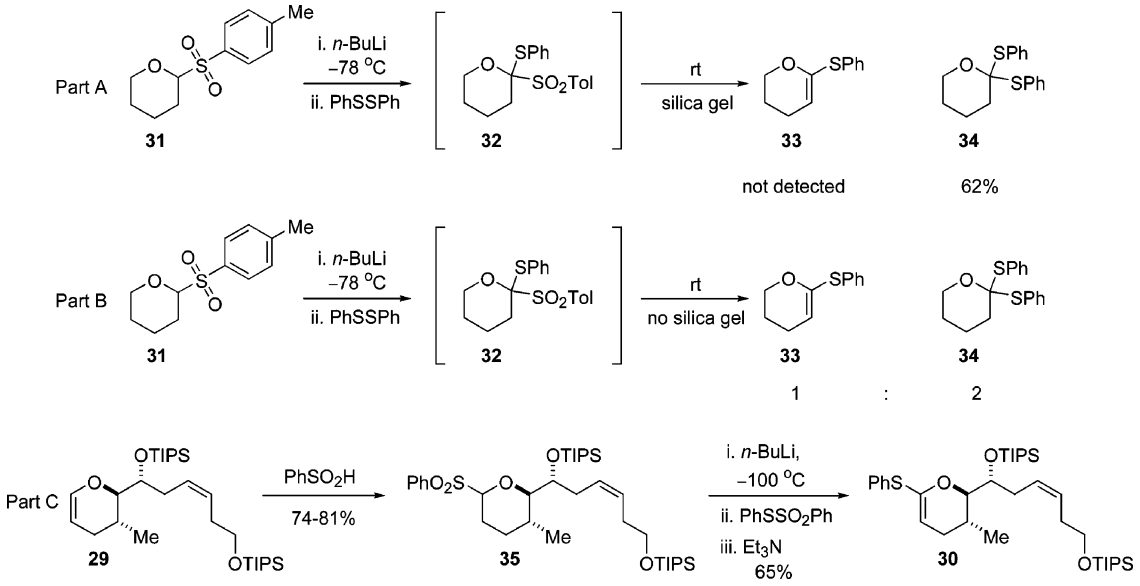
(27) La Cruz, T. E.; Rychnovsky, S. D. *Synlett* **2004**, 2013−2015.

(28) Milne, J. E.; Kocienski, P. J. *Synthesis* **2003**, 584−592.

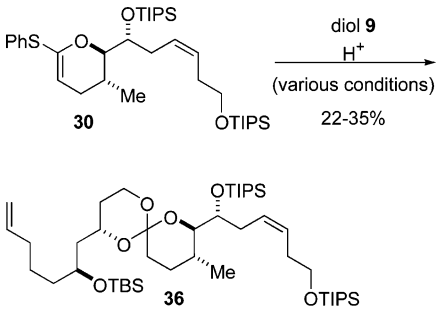
(29) Statsuk, A. V.; Liu, D.; Kozmin, S. A. *J. Am. Chem. Soc.* **2004**, *126*, 9546−9547.

(30) (a) Louie, J.; Bielawski, C. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 11312−11313. (b) Cossy, J.; Bauer, D.; Bellosta, V. *Tetrahedron* **2002**, *58*, 5909−5922.

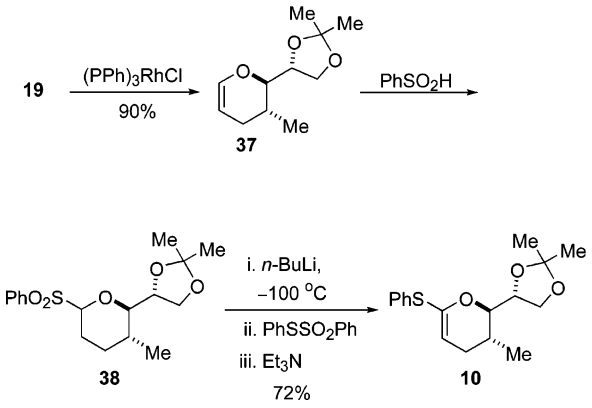
SCHEME 5. Sulfone Mediated Thioketene Acetal Synthesis



SCHEME 6. Disappointing Orthoester Synthesis



SCHEME 7. Truncated Thioketene Acetal



excellent regio- and chemoselectivity to give alcohol **44** (Scheme 9) in 71% yield as a single diastereomer.[5] The reaction proceeded to completion faster than the analogous reaction of a [5.4]-spiro orthoester. In our previous synthetic endeavors the electrophile, a primary alkyl chloride, was installed prior to cyanoacetal synthesis.[5] Unfortunately, the attenol A architecture does not lend itself to this approach, and the electrophile had to be installed after the cyanoacetal. Previous studies have shown that the cyanoacetal motif is incompatible with Ph_3P/CCl_4.[32] An alternative alcohol to alkyl chloride conversion, mesylate formation followed by treatment with LiCl in DMF, has been used successfully.[5] However, LiCl/DMF is known to cleave TBS ethers.[33] Phosphate esters can also serve as leaving groups in reductive cyclization reactions,[34] and primary alcohol can be converted to phosphate ester under mild reaction conditions. Thus, alcohol **44** was treated with $(EtO)_2P(O)Cl$ and *N*-methylimidazole to give the cyclization precursor, phosphate ester **45**, in 97% yield as a single stereoisomer (Scheme 9).[35]

The reductive cyclization of phosphate **45** produced the nonanomeric spiroacetal **6** as the major product in a remarkable 94% yield (Scheme 10). Both cyanoacetal **48**, a product of the competitive reduction of the phosphate motif by lithium di-*tert*-butylbiphenylide (LiDBB),[36] and anomeric spiroacetal **47** were identified as minor products. Analysis of the crude reaction mixture by GC returned a 78:1 ratio of nonanomeric spiroacetal **6** and anomeric spiroacetal **47**. NOESY correlation confirmed the nonanomeric configuration of spiroacetal **6** (Scheme 10). The key reductive cyclization was a very efficient process, and spiroacetal **6** was amendable to preparative scale synthesis.

Nonanomeric spiroacetal **6** was subjected to equilibrating conditions (PPTS/MeOH). The reaction was complicated by cleavage of the TBS ether and equilibration of spiroacetals **49** and **50**, the attenol B core.[37] Attempts to suppress the equilibration were unsuccessful, and therefore the mixture was used in the next reaction. The traditional technique of selective sulfonation and subsequent cyclization gave poor yields of epoxide **5**. Poor regioselectivity in the sulfonation of triol **49** by both

(31) The configuration of orthoester **8** was determined by 2D NMR analysis. The minor orthoester arising from the reaction of thioketene acetal **10** and syn stereoisomer of diol **9** was removed at this stage by column chromatography.

(32) Buckmelter, A. J. Ph.D. Thesis, University of California, Irvine, 2000.

(33) Farras, J.; Serra, C.; Vilarrasa, J. *Tetrahedron Lett.* **1998**, *39*, 327−330.

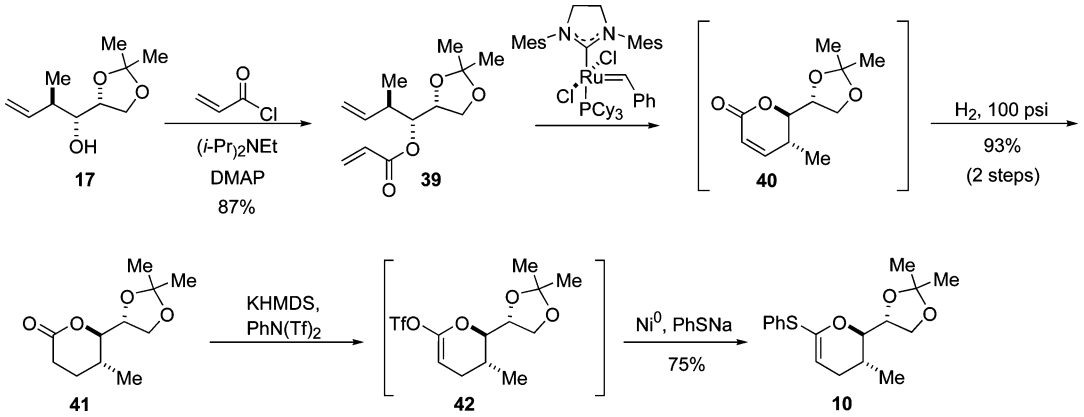
(34) (a) Zeller, E.; Sajus, H.; Grierson, D. S. *Synlett* **1991**, 44−46. (b) Zeller, E.; Grierson, D. S. *Synlett* **1991**, 878−880. (c) Wolckenhauer, S. A.; Rychnovsky, S. D. *Tetrahedron* **2005**, *61*, 3371−3381.

(35) Calaza, M. I.; Hupe, E.; Knochel, P. *Org. Lett.* **2003**, *5*, 1059−1061.

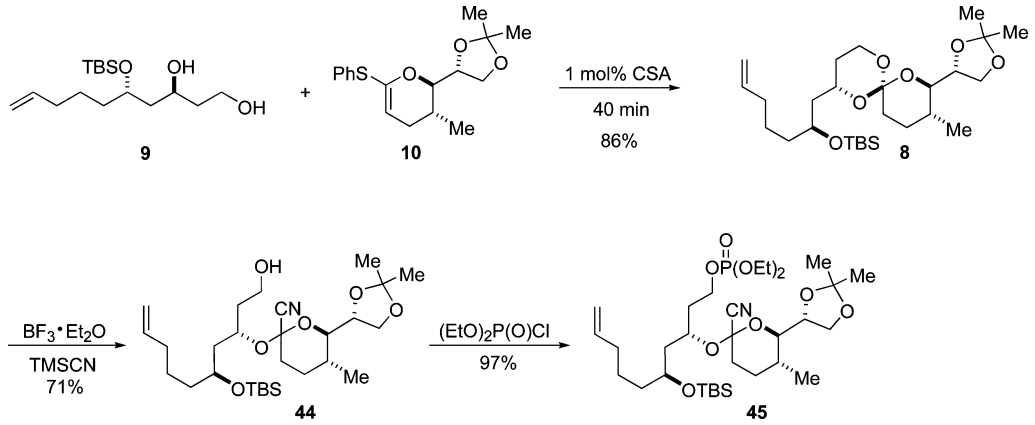
(36) Guijarro, D.; Mancheño, B.; Yus, M. *Tetrahedron* **1994**, *50*, 8551−8558.

(37) (a) Pihko, P. M.; Aho, J. E. *Org. Lett.* **2004**, *6*, 3849−3852. (b) Bender, T.; Schuhmann, T.; Magull, J.; Grond, S.; von Zezschwitz, P. *J. Org. Chem.* **2006**, *71*, 7125−7132.

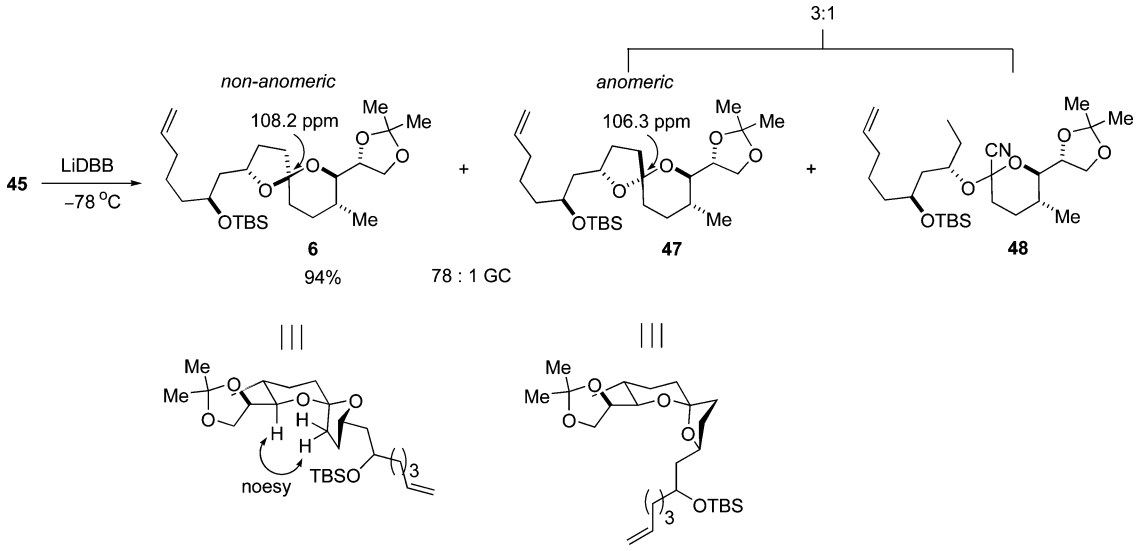
SCHEME 8. Revised Strategy to Thioketene Acetal



SCHEME 9. Spiro Orthoester and Cyclization Precursor Synthesis



SCHEME 10. Reductive Cyclization



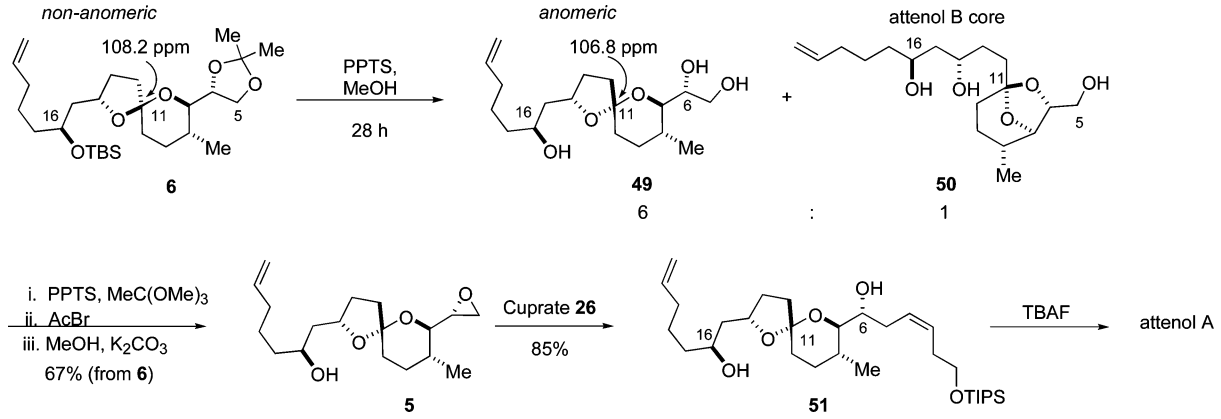
MsCl and 2,4,6-triisopropylsulfonylchloride was responsible for the inefficient epoxidation reaction.[38] An alternative epoxidation technique was required, and the Sharpless−Moffatt cyclization was investigated.[39] The desired epoxide **5** was generated in a satisfactory 67% yield over two steps (Scheme 11). The C16 alcohol did not interfere with the cyclization. Epoxide **5** reacted with an excess of vinyl cuprate **26** to yield alcohol **51** in 85% yield. Finally, removal of the TIPS silyl ether completed the total synthesis of attenol A.

Equilibration. Solid tumors have low extracellular pH (ca. 6.8), and exploiting this property to selectively target tumor cells has been proposed.[7] Acidic media could trigger the isomerization of nonanomeric spiroacetals to their anomeric isomers, in which case the nonanomeric spiroacetal would act as a pro-drug for its epimer. We selected nonanomeric spiroacetal **53** (Table 1)

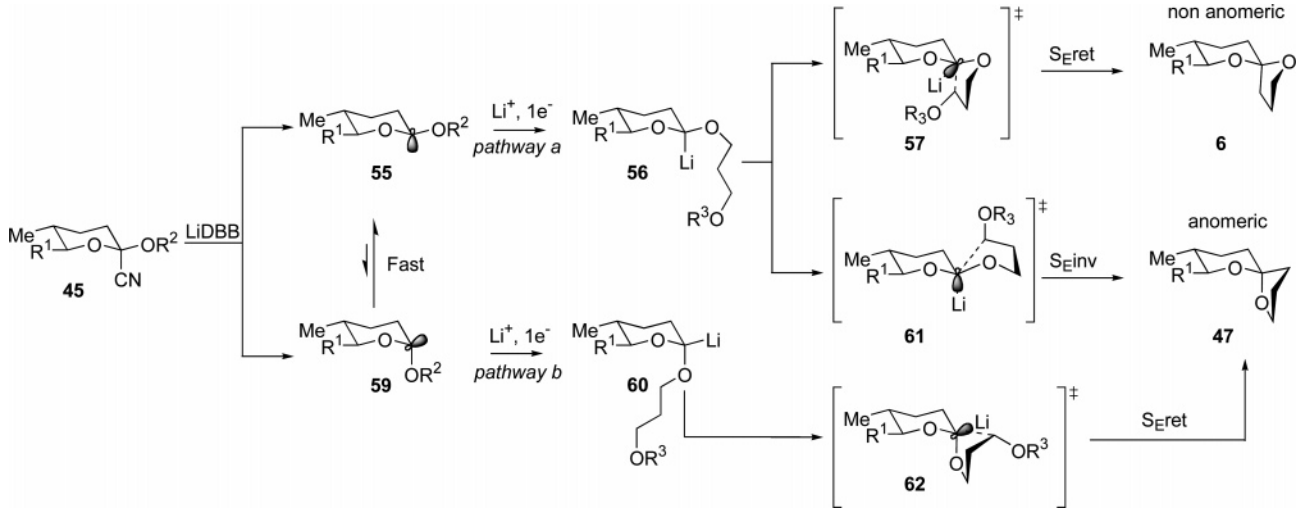
(38) (a) Hicks, D. R.; Fraser-Reid, B. *Synthesis* **1974**, 203. (b) Cink, R. D.; Forsyth, C. J. *J. Org. Chem.* **1995**, *60*, 8122−8123.

(39) Kolb, H. C.; Sharpless, K. B. *Tetrahedron* **1992**, *48*, 10515−10530.

SCHEME 11. Completion of the Synthetic Sequence

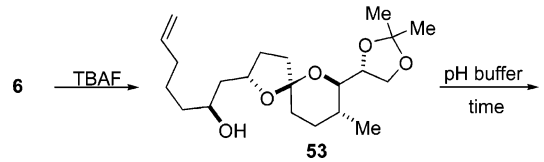


SCHEME 12. Mechanism of Cyclization



as a test case. The effect of pH on the rate of isomerization of spiroacetal **53** with its more stable epimer in aqueous buffer solutions was evalauted.[37] Spiroacetal **53** was prepared by removal of the TBS group from spiroacetal **6** to improve the solubility properties. The epimerization of the spiroacetal is summarized in Table 1. Spiroacetal **53** was dissolved in a NaOAc/HOAc buffer system, using THF as a cosolvent. After 3 days at pH 5.8, epimerization of spiroacetal **53** was not evident by TLC or GC analysis of the reaction mixture. Epimerization was not observed in a pH 5.0 environment over a 48 h time span. Partial epimerization of spiroacetal **53** took place in a pH 4.0 buffer, leading to a 10:1 ratio of nonanomeric to anomeric isomers. The half-life for the epimerization event could not be accurately deduced from these data due to concurrent acetonide cleavage, but it would be at least several days.[40] Under normal physiological conditions the nonanomeric spiroacetal **53** would be stable indefinitely. Thus the use of this class of nonanomeric spiroacetals as pro-drugs for solid tumors is impractical because the epimerization would be too slow at an extracellular pH of ca. 6.8.[7]

TABLE 1. Acetal Equilibration Studies



pH	*T* (°C)	time (h)	ratio (nonanomeric:anomeric)
5.8	23	72	no epimerization
5	23	48	no epimerization
4	23	22	10:1

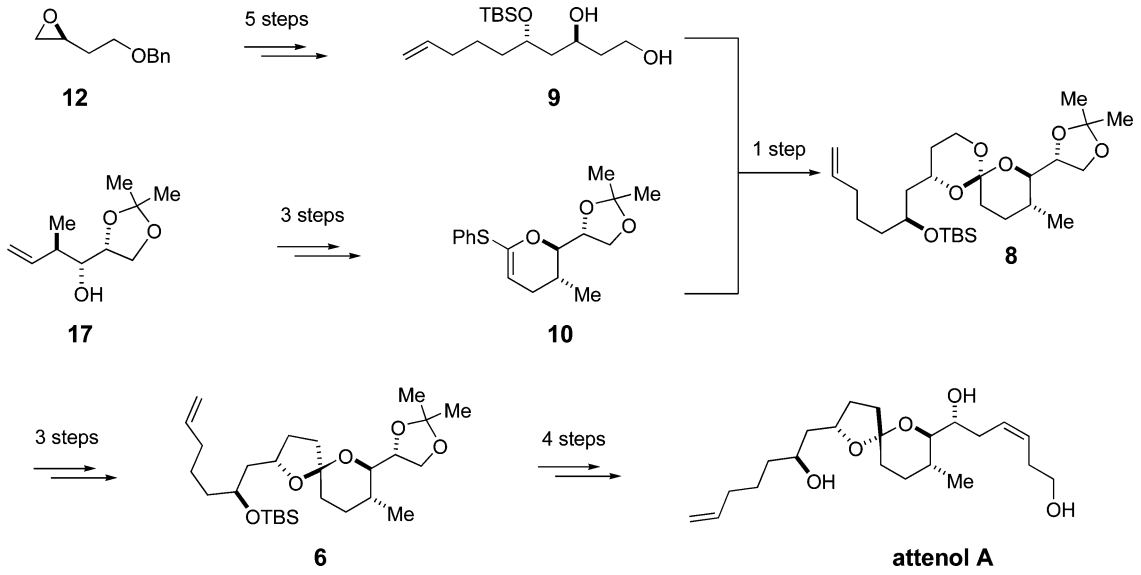
Discussion

The key reductive cyclization reaction proved to be a very efficient process, but we were interested in the origin of the minor anomeric spiroacetal **47**. The experiments summarized in Table 1 demonstrate that the nonanomeric spiroacetal **53**, and presumably **6**, is not susceptible to epimerization in a neutral aqueous solution. Detailed analysis of the radical lithiation reaction revealed that more than one pathway could be responsible for the genesis of anomeric spiroacetal **47**. These competing pathways are depicted in Scheme 12. Initial SET and subsequent C−CN bond fission reveals equilibrating radical species **55** and **59**.[41] Preference for the radical to occupy the axial position has been calculated to be ∼1.86 kcal/mol in a

(40) Acetonide cleavage is accompanied by formation of the attenol B core, structure **50**.

(41) (a) Rychnovsky, S. D.; Powers, J. P.; Lepage, T. J. *J. Am. Chem. Soc.* **1992**, *114*, 8375−8384.(b) Rychnovsky, S. D.; Hata, T.; Kim, A. I.; Buckmelter, A. J. *Org. Lett.* **2001**, *3*, 807−810.

SCHEME 13. Summary of the Synthesis



closely related model system (R^1, R^2 = Me).[42] If we take this enthalpy as an estimate for the ΔG between the two radical epimers, it would predict a 122:1 ratio favoring the axial radical at −78 °C. This value is in good agreement with the 78:1 ratio observed between the spiroacetals **6** and **47**.

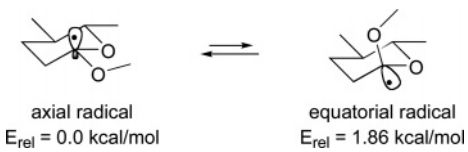
The observed selectivity for nonanomeric spiroacetal **6** is a bit lower than that predicted by the DFT modeling, but it falls within the uncertainty of the calculations. The difference may indicate a modest erosion of selectivity from the thermodynamic ratio between radicals **55** and **59**. If simplified Winstein−Holness kinetics apply,[43] the ratio of alkyllithium reagents **56**:**60** would reflect that of the corresponding radicals **55** and **59**. Any change in selectivity would result from differential efficiency in the reactions of **56** and **60**, or from cyclization with partial inversion of configuration.[44] Examples have been reported where stereogenic, sp^3-hybridized, α-hetero alkyllithium species undergo invertive electrophilic substitution reactions,[45] but the process has not been documented with α,α-dialkyloxy alkyllithium reagents. A second possibility is that the alkyllithium product ratio in the second SET does not precisely reflect the ratio of **55**:**59**. This outcome would be expected in a more general Curtin−Hammett situation where the rates of ET differ for the two radicals.[43] The minor isomer **47** then would arise from a larger proportion of alkyllithium **60** formed in the reduction. We know from previous studies that the calculated ratio of anomeric radicals is a good predictor of the product ratios,[41a] so the change in ratio that might be attributed to differential reduction rates is modest. The minor anomeric spiroacetal **47** may reflect the true equilibrium ratio between radicals **55** and **59**, or there may be a minor loss of selectivity attributable to either of the pathways discussed above. The formation of spiroacetal **47** is the first characterized anomeric spiroacetal formed directly in a reductive cyclization reaction.

Conclusion

The synthesis of attenol A is summarized in Scheme 13. The target molecule **1** was synthesized in 13 steps (longest linear sequence), starting from enantiomerically pure epoxide **12**, in 21.4% overall yield.[46] The key intermediates, thioketene acetal **10**, spiro orthoester **8**, and spiroacetal **6**, were efficiently accessed on preparative scales. The attenol A core was formed by a carbon−carbon bond reductive cyclization event that gave rise to a previously inaccessible spiroacetal epimer.

This nontraditional approach to an anomeric spiroacetal target illustrates several features of the reductive cyclization methodology. The synthesis is more efficient than previous approaches to attenol A, and demonstrates the potential of using reductive cyclization reactions to afford anomeric spiroacetals. A thioketene acetal and [5.5]-spiro orthoester, two uncommon chemical entities, were efficiently synthesized en route to the synthesis of attenol A. A new method to synthesize thioketene acetals from a phenyl sulfone was developed. The key reductive cyclization reaction once again proved to be an efficient process. The configurational stability of the nonanomeric spiroacetal moiety was also evaluated, and it was found to be unsuitable as a pH trigger in a pro-drug. For the first time an anomeric

(42) The relative energy difference between equatorial and axial radical isomers of 2-methoxyl-5,6-dimethyltetrahydropyran-2-yl were calculated (6-31G(d)/UB3LYP//6-31G(d)/UB3LYP) and found to favor the axial radical by 1.86 kcal/mol (with zero point correction; without ZPE correction the difference was 2.03 kcal/mol). Geometries and energies of the structures are included in the Supporting Information



.

(43) Seeman, J. I. *Chem. Rev.* **1983**, *83*, 83.

(44) Reviews on chiral organolithiums: (a) Basu, A.; Thayumanavan, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 716−738. (b) Hoppe, D.; Marr, F.; Brueggemann, M. *Top. Organomet. Chem.* **2003**, *5*, 61−137.

(45) Inversion of configuration at the lithium bearing carbon of α-oxy alkyllithiums has been observed in [1,2]- and [2,3]-Wittig rearrangements: (a) Verner, E. J.; Cohen, T. *J. Am. Chem. Soc.* **1992**, *114*, 375−377. (b) Hoffmann, R.; Brückner, R. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 647−649. (c) Hoffmann, R.; Rückert, T.; Brückner, R. *Tetrahedron Lett.* **1993**, *34*, 297−300. (d) For a computational study of this phenomenon see: Capó, M.; Saá, J. M. *J. Am. Chem. Soc.* **2004**, *126*, 16738−16739.

(46) The longest linear sequence proceeds from commercial 3-butene-1-ol, a precursor of epoxide **12**, in 16 steps and 7.3% overall yield, which includes a 44% yield on the resolution step.

spiroacetal was isolated from the reductive cyclization reaction, providing insight into the inherent selectivity of the cyclization.

Experimental Section

Thioketene Acetal 10. The following procedure was adopted from the protocol developed by Kocienski.[27] Flask 1: A solution of KHMDS (0.5 M in toluene, 24.8 mL, 12.4 mmol) and THF (37 mL) was cooled to −78 °C. A mixture consisting of $PhN(Tf)_2$ (3.80 g, 10.6 mmol), lactone **41** (1.90 g, 8.87 mmol), and THF (44 mL) was prepared and added dropwise over a 1 h 15 min period. After the addition was completed, the mixture was stirred at −78 °C for 15 min.

Flask 2: To a suspension of NaH (60% dispersion in mineral, 0.710 g, 17.7 mmol) in THF (8.8 mL), at room temperature, was added PhSH (1.09 mL, 10.6 mmol) dropwise. After the evolution of gas had ceased, the mixture was stirred at room temperature for 15 min and then cooled to −78 °C.

Flask 3: To a mixture of $Ni(PPh_3)_2Br_2$ (0.659 g, 0.887 mmol), PPh_3 (0.465 g, 1.77 mmol), and zinc powder (0.348 g, 5.32 mmol) was added THF (21 mL). The green suspension was stirred at room temperature for 20 min, after which the color of the reaction mixture became deep red.

The contents of flask 1 were transferred to flask 2 (via cannula), and the contents of flask 3 were transferred to flask 2 by syringe. The deep red mixture was removed from the cooling bath, warmed to room temperature, and stirred for 3.5 h. The reaction mixture was diluted with 5% $NaOH_{(aq)}$ (50 mL) and extracted with Et_2O (3 × 100 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product mixture was subsequently purified by silica gel chromatography (deactivated silica gel, 5−10% Et_2O/hexanes) to afford 2.05 g (75% yield) of the title compound as a colorless oil: R_f 0.43 (15% Et_2O/hexanes); $[\alpha]_D$ −40 (*c* 0.36, CH_2Cl_2); ^1H NMR (500 MHz, C_6D_6) δ 7.47 (dd, 2H, J = 1.5, 8.7 Hz), 7.05 (t, 2H, J = 7.5 Hz), 6.96 (m, 1H), 5.23 (dd, 1H, J = 2.7, 4.9 Hz), 3.95 (dt, 1H, J = 2.4, 7.3 Hz), 3.79 (t, 1H, J = 7.7 Hz), 3.61 (app t, 1H, J = 7.1 Hz), 2.93 (dd, 1H, J = 2.4, 9.1 Hz), 2.01 (m, 1H), 1.79 (dt, 1H, J = 5.3, 17.5 Hz), 1.46 (ddd, 1H, J = 2.7, 10.3, 17.5 Hz), 1.39 (s, 3H), 1.33 (s, 3H), 0.72 (d, 3H, J = 6.8 Hz) ppm; ^{13}C NMR (125 MHz, C_6D_6) δ 147.6, 135.4, 130.8, 129.4, 127.2, 109.8, 107.7, 81.1, 75.0, 65.3, 31.5, 28.7, 26.7 (2C), 17.2 ppm; IR (neat) 2914, 1634, 1584, 1480, 1379, 1070 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{23}O_3S$ $[M + H]^+$ 307.1368, found 307.1367.

Orthoester 8. To a solution of thiophenyl ketene acetal **10** (1.07 g, 3.49 mmol), in CH_2Cl_2 (17 mL), was added a solution of diol **9** (1.16 g, 3.83 mmol), in CH_2Cl_2 (19 mL), and 4 Å molecular sieves (700 mg). The mixture was stirred at room temperature for 2 h, and filtered through a 45 μm Whatman syringe filter into another flask that had been equipped with a magnetic stir bar. The solution was treated with CSA (8 mg, 3.49 μmol) then stirred at room temperature for 40 min. The reaction was quenched with Et_3N (0.10 mL, 0.717 mmol), and the solution was concentrated under reduced pressure. The resulting oil was purified by silica gel chromatography (15% Et_2O/hexanes) to afford 1.49 g (86% yield) of the desired orthoester **8** as a colorless oil: R_f 0.61 (20% Et_2O/hexanes); $[\alpha]_D$ +2.7 (*c* 0.75, CH_2Cl_2); ^1H NMR (500 MHz, C_6D_6) δ 5.79 (ddt, 1H, J = 6.7, 10.2, 16.9 Hz), 5.04 (dd, 1H, J = 1.8, 17.1 Hz), 4.99 (dd, 1H, J = 1.1, 10.2 Hz), 4.51 (ddt, 1H, J = 3.5, 7.3, 11.4 Hz), 4.15 (dt, 1H, J = 3.5, 7.1 Hz), 4.04−3.96 (m, 2H), 3.84 (t, 1H, J = 6.9 Hz), 3.75 (ddd, 1H, J = 2.6, 11.0, 13.2 Hz), 3.49 (dd, 1H, J = 4.3, 10.9 Hz), 3.18 (dd, 1H, J = 3.5, 10.1 Hz), 2.04−1.98 (m, 3H), 1.79−1.71 (m, 3H), 1.63−1.52 (m, 8H), 1.51−1.45 (m, 2H), 1.41−1.35 (m, 4H), 1.17−1.11 (m, 1H), 1.05 (s, 9H), 0.73 (d, 3H, J = 6.6 Hz), 0.25 (s, 3H), 0.16 (s, 3H) ppm; ^{13}C NMR (125 MHz, C_6D_6) δ139.4, 115.1, 110.7, 109.3, 77.2, 76.7, 69.8, 66.8, 65.8, 58.8, 45.1, 38.3, 35.3, 34.7, 32.1, 31.8, 30.2, 27.1, 26.7, 26.3, 24.8, 18.7, 17.4, −3.6, −3.7 ppm; IR (neat) 2930, 1462, 1379, 1256, 1063, 985 cm^{-1}; HRMS (ESI) calcd for $C_{27}H_{51}O_6Si$ $[M + H]^+$ 499.3455, found 499.3471.

Spiroacetal 6. A solution of phosphate **45** (0.730 g, 1.10 mmol), 1,10-phenanthroline (0.1 mg), and THF (11 mL) was cooled to −78 °C. To the vigorously stirring solution was added LiDBB (2 mL, over a 0.5 h period) in a dropwise fashion, directly to the center of the reaction mixture, whereby the green color of LiDBB was allowed to dissipate before the addition of the following drop. Another 3 mL of LiDBB were added over a 40 min period in an identical manner. The solution was stirred for 5 min at −78 °C, and then another 2.5 mL of LiDBB were added over a 35 min period in the same manner as described above. Then 0.8 mL of LiDBB was added over a 10 min period (8.3 mL total volume). After addition of the final drop of LiDBB its dark color persisted for 15 s, and then dissipated to give a red solution. The solution was allowed to stir at −78 °C for 2 h, and excess LiDBB was quenched by the addition of MeOH (1 mL). The mixture was warmed to room temperature, diluted with 40 mL of water, and extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with brine (1 × 40 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was determined to be a 78:1 ratio of spiroacetal **6** and spiroacetal **47** by GC analysis (R_t-**6** = 21.75 min, R_t-**47** = 19.55 min).[47] The resulting residue was purified by silica gel chromatography, eluting first with 100% hexanes (to remove DBB) then 15% Et_2O/hexanes. The desired spiroacetal **6** (0.502 g, 94% yield) was isolated as a colorless oil: R_f 0.44 (15% Et_2O/hexanes); $[\alpha]_D$ +20 (*c* 0.23, CH_2Cl_2); ^1H NMR (500 MHz, C_6D_6) δ 5.79 (ddt, 1H, J = 6.7, 10.2, 16.9 Hz), 5.04 (dq, 1H, J = 1.6, 17.1 Hz), 4.99 (ddt, 1H, J = 1.2, 2.2, 10.2 Hz), 4.50 (m, 1H), 4.22 (dq, 1H, J = 2.8, 6.9 Hz), 4.06−3.99 (m, 2H), 3.82 (t, 1H, J = 6.8 Hz), 2.74 (dd, 1H, J = 2.8, 9.3 Hz), 2.00 (app q, 2H, J = 7.4 Hz), 1.93−1.85 (m, 2H), 1.83−1.75 (m, 2H), 1.67−1.62 (m, 2H), 1.60 (s, 3H), 1.56−1.51 (m, 2H), 1.50−1.45 (m, 4H), 1.44 (s, 3H), 1.39−1.29 (m, 2H), 1.04 (s, 9H), 0.96 (m, 1H), 0.79 (d, 3H, J = 6.6 Hz), 0.28 (s, 3H), 0.15 (s, 3H) ppm; ^{13}C NMR (125 MHz, C_6D_6) δ 139.4, 115.1, 109.6, 108.2, 78.1, 76.4, 75.9, 70.4, 65.7, 44.7, 38.5, 35.1, 34.7, 32.9, 31.6 (2C), 31.5, 27.1, 26.7, 26.6, 24.9, 18.7, 17.6, −3.6, −3.8 ppm; IR (neat) 2933, 1624, 1460, 1251, 1064 cm^{-1}; HRMS (ESI) calcd for $C_{27}H_{50}O_5SiNa$ $[M + Na]^+$ 505.3325, found 505.3335.

Epoxide 5. Spiroacetal **6** (0.150 g, 0.311 mmol), PPTS (0.312 g, 1.24 mmol), and MeOH (3.1 mL) were combined and stirred at room temperature for 28 h. Then 4 mL of saturated $NaHCO_{3(aq)}$ was added, and the mixture was vigorously stirred for 5 min and then extracted with Et_2O (2 × 60 mL). The organic layers were combined, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give 0.112 g of an oil that was dried by azeotropic removal of moisture with benzene.

The oil (0.112 g, 0.34 mmol) was dissolved in CH_2Cl_2 (1.7 mL), then treated with trimethyl orthoacetate (0.10 mL, 0.82 mmol) and PPTS (9 mg, 0.034 mmol). The mixture was stirred at room temperature for 45 min, concentrated under reduced pressure, and placed under a vacuum (0.2 mmHg) for 2 min. The resulting residue was dissolved in CH_2Cl_2 (1.7 mL) then treated with Et_3N (0.01 mL, 0.072 mmol), and the reaction vessel was then placed in a room temperature water bath. The mixture was treated with acetyl bromide (0.061 mL, 0.82 mmol), stirred for 40 min, and then concentrated under reduced pressure. The resulting residue was dissolved in MeOH (3.2 mL), and the solution was then treated with $K_2CO_{3(s)}$ (0.471 g, 3.41 mmol). The mixture was stirred vigorously at room temperature for 15 h, diluted with 4 mL of brine, and extracted with Et_2O (2 × 20 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting oil was purified by silica gel chromatography (40% EtOAc/hexanes) to afford 0.0645 g (67% yield) of the title compound as a colorless oil: R_f 0.38 (40% EtOAc/hexanes); $[\alpha]_D$ −32 (*c* 1.3, $CHCl_3$); ^1H NMR (500 MHz, C_6D_6) δ

(47) GC conditions are reported in the Supporting Information.

5.80 (ddt, 1H, J = 6.7, 10.2, 17.0 Hz), 5.05 (dq, 1H, J = 1.7, 17.1 Hz), 4.99 (ddt, 1H, J = 1.1, 2.3, 10.2 Hz), 4.32 (m, 1H), 3.86 (m, 1H), 3.25 (dd, 1H, J = 6.9, 10.0 Hz), 2.78 (ddd, 1H, J = 2.6, 4.0, 6.8 Hz), 2.45 (dd, 1H, J = 2.6, 5.5 Hz), 2.39 (dd, 1H, J = 4.0, 5.3 Hz), 2.05−1.97 (m, 3H), 1.96−1.90 (m, 1H), 1.89−1.82 (m, 2H), 1.74−1.68 (m, 1H), 1.65−1.55 (m, 4H), 1.51−1.41 (m, 7H), 0.67 (d, 3H, J = 6.3 Hz) ppm; ^{13}C NMR (125 MHz, C_6D_6) δ 139.6, 115.0, 106.1, 78.4, 78.2, 69.8, 53.4, 45.5, 45.0, 39.1, 38.0, 34.6, 34.4, 33.2, 31.0, 29.9, 25.8, 17.9 ppm; IR (neat) 3439, 2927, 1640, 1459, 1373, 1015 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{30}O_4Na$ [M + Na]$^+$ 333.2042, found 333.2048.

Spiroacetal 51. A solution of vinyl iodide **25** (0.58 g, 1.6 mmol), in Et_2O (3.3 mL), was cooled to −78 °C, then treated with *n*-BuLi (2.5 M in hexanes, 0.65 mL, 1.6 mmol). The colorless solution was stirred at −78 °C for 1 h, then solid CuCN (0.076 g, 0.85 mmol) was added in one portion. The reaction flask was placed in a −30 °C bath, stirred for 1 h, and recooled to −78 °C. A solution of epoxide **5** (0.063 g, 0.20 mmol), in Et_2O (1 mL), was then added dropwise. The mixture was again placed in a −30 °C bath and stirred for 1.5 h, then 5 mL of concentrated $NH_4OH_{(aq)}$ was added in one portion. The mixture was warmed to room temperature, diluted with saturated $NH_4Cl_{(aq)}$ (1 mL), and stirred until the green copper salts were digested (∼20 min). The blue solution was extracted with Et_2O (3 × 70 mL), and the organic layers were combined and washed with saturated $NaHCO_{3(aq)}$ (1 × 20 mL) and then brine (1 × 20 mL). The organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give an oil that was purified by silica gel chromatography (30% EtOAc/hexanes) to afford 0.093 g (85% yield) of the title compound as a colorless oil: R_f 0.33 (30% EtOAc/hexanes); $[\alpha]_D$ −4.8 (*c* 0.60, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.80 (ddt, 1H, J = 6.7, 10.2, 16.9 Hz), 5.59−5.52 (m, 2H), 5.00 (dq, 1H, J = 1.6, 17.1 Hz), 4.94 (ddt, 1H, J = 1.2, 2.3, 10.1 Hz), 4.32 (m, 1H), 3.84 (m, 1H), 3.71−3.65 (m, 3H), 3.31 (dd, 1H, J = 1.0, 10.3 Hz), 2.50−2.43 (m, 1H), 2.38−2.30 (m, 2H), 2.21 (br s, 1H), 2.14−2.05 (m, 3H), 2.04−1.96 (m, 2H), 1.86−1.61 (m, 9H), 1.57−1.41 (m, 5H), 1.08−1.04 (m, 21H), 0.86 (d, 3H, J = 6.5 Hz) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ138.6, 128.3, 127.7, 114.5, 106.3, 77.7, 77.6, 70.1, 69.9, 63.0, 43.8, 38.5, 36.7, 33.9, 33.7, 32.7, 31.4, 30.9, 30.2, 29.0, 25.1, 18.0, 17.2, 12.0 ppm; IR (neat) 3430, 2942, 1641, 1461, 1380 cm^{-1}; HRMS (ESI) calcd for $C_{31}H_{58}O_5SiNa$ [M + Na]$^+$ 561.3951, found 561.3946.

Acknowledgment. The National Institutes of Health (GM-65388) provided support for this project. Novartis Pharmaceuticals is gratefully acknowledged for fellowship support to T.E.L.

Supporting Information Available: Experimental details for preparation of the cyclization substrates and the characterization and correlation of the products, and proton and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0626459