J|A|C|S
ARTICLES
Published on Web 10/07/2006

A Total Synthesis of Xestodecalactone A and Proof of Its Absolute Stereochemistry: Interesting Observations on Dienophilic Control with 1,3-Disubstituted Nonequivalent Allenes

Toshiharu Yoshino,[†] Fay Ng,[†] and Samuel J. Danishefsky*[,†,‡]

Contribution from the Department of Chemistry, Columbia University, Havemeyer Hall, 3000 Broadway, New York, New York 10027, and the Laboratory for Bioorganic Chemistry, Sloan-Kettering Institute for Cancer Research, 1275 York Avenue, New York, New York 10021

Received June 16, 2006; E-mail: s-danishefsky@ski.mskcc.org

Abstract: A concise total synthesis of xestodecalactone A, utilizing a Diels−Alder strategy is described. The focal Diels−Alder reaction relied on an "ynoate" dienophile to rapidly assemble the required resorcylinic acid scaffold. During this study, Diels−Alder cycloaddition reactions involving 1,3-disubstituted nonequivalent allene dienophiles were studied, and some surprising results were encountered.

Introduction

A variety of natural products can be viewed in the context of the fusion of a macrolactone moiety with a resorcinylic aromatic ring.[1] In most cases,[2] the fusion encompasses the carbons α and β to the lactonic carbonyl group and carbons 5 and 6 of the resorcinol. The resultant system, (cf. **1**, Figure 1) corresponds to a lactone based on an orsellinic acid format, functionalized at its benzylic site (see asterisk) with a side chain bearing a pendant ω-hydroxyl group. Classic examples of such systems are the 12-membered orsellinic acid type lactone lasiodiplodin[3] and the 14-membered orsellinic acid macrolides zearalenone[4] and radicicol.[5] Like radicicol, relatively new members to this group such as 14-membered aigialomycin D,[6] and hypothemycin[7] also possess potentially useful antitumor activity.

As early as 1978, our group described the synthesis of lasiodiplodin (**2**), employing a significant departure from the then prevailing strategies for synthesizing benzofused macrolactones.[8] As an alternative to starting with a prebuilt benzo structure around which would be built the cycloaliphatic macrolactone, we envisioned the possibility of using our then new Diels−Alder methodology to build the aromatic ring. For instance, in our lasiodiplodin synthesis,[9] cycloaddition of a synergisitic 1,1,3-trioxygenated diene **7** with β-alkylated propiolic ester dienophile **8** led to **9** and, shortly thereafter, to the target. Thus, in keeping with the broad classification *b* of Figure 1 (see dotted line), lasiodiplodin was built from an "ynoate" disconnection. While occurring with tight regiospecific control, such uncatalyzed Diels−Alder reactions of monoactivated acetylenic dienophiles (bearing substitution at the nonactivated acetylenic carbons) require rather high temperatures. This being the case, they tend to occur not surprisingly in mediocre yields.

A more pleasing route to related substructures was realized via Diels−Alder reaction between diene **7** and the highly reactive allene dienophile **10** (Scheme 1). Following regiospecific cycloaddition, elimination of one of the alkoxy groups from the erstwhile C1 of **7**, and aromatization (presumably of **11**) a hydroaromatic system (cf. **12**) was in hand.[10] Given the symmetrical character of allene **10**, chemoselectivity issues

[†] Columbia University.
[‡] Sloan-Kettering Institute for Cancer Research.

(1) Omura, S., Ed. *Macrolide Antibiotics: Chemistry, Biology, and Practice*, 2nd ed.; Academic Press: San Diego, CA, 2002.
(2) Betina, V. *Mycotoxins. Chemical, Biology and Environmental Aspects*; Elsevier: Amsterdam, 1989.
(3) For structure and isolation: (a) Aldridge, D. C.; Galt, S.; Giles, D.; Turner, W. B. *J. Chem. Soc. (C)* **1971**, 1623. (b) Lee, K.-H.; Hayashi, N.; Okano, M.; Hall, I. H.; Wu, R.-Y.; McPhail, A. T. *Phytochemistry* **1982**, *21*, 1119.
(4) For structure and isolation: (a) Stob, M.; Baldwin, R. S.; Tuite, J.; Andrews, F. N.; Gillette, K. G. *Nature* **1962**, *196*, 1318. (b) Urry, W. H.; Wehrmeister, H. L.; Hodge, E. B.; Hidy, P. H. *Tetrahedron Lett*. **1966**, 3109.
(5) For structure and isolation: (a) Delmotte, P.; Delmotte-Plaquee, J. *Nature* **1953**, *171*, 344. (b) Ayer, W. A.; Lee, S. P.; Tsunda, A.; Hiratsuka, Y. *Can. J. Microbiol*. **1980**, *26*, 766.
(6) For structure and isolation: Isaka, M.; Suyarnsestakorn, C.; Tanticharoen, M.; Kongaseree, P.; Thebtaranonth, Y. *J. Org. Chem*. **2002**, *67*, 1561.
(7) For structure and isolation: (a) Nair, M. S. R.; Carey, S. T. *Tetrahedron Lett*. **1980**, *21*, 2001. (b) Nair, M. S. R.; Carey, S. T.; James, J. C. *Tetrahedron* **1981**, *37*, 2445. (c) Agatsuma, T.; Takahashi, A.; Kabuto, C.; Nozoe, S. *Chem. Pharm. Bull*. **1993**, *41*, 373.
(8) For selected references of other syntheses of lasiodiplodin: (a) Gerlach, H.; Thalmann, A. *Helv. Chim. Acta* **1977**, *60*, 2866. (b) Takahashi, T.; Kasuga, K.; Tsuji, J. *Tetrahedron Lett*. **1978**, 4917. (c) Fink, M.; Gaier, H.; Gerlach, H. *Helv. Chim. Acta* **1982**, *65*, 2563. (d) Braun, M.; Mahler, U.; Houben, S. *Liebigs Ann*. **1990**, 513. (e) Jones, G. B.; Huber, R. S. *Synlett* **1993**, 367. (f) Brachen, F.; Schulte, B. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2619. (g) Furstner, A.; Thiel, O. R.; Kindler, N.; Bartkowska, B. *J. Org. Chem*. **2000**, *65*, 7990. For selected references of syntheses of zearalenone: (h) Vlattas, I.; Harrison, I. T.; Tokes, L. Fried, J. H.; Cross, A. D. *J. Org. Chem*. **1968**, *33*, 4176. (i) Girotra, N. N.; Wendler, N. L. *J. Org. Chem*. **1969**, *34*, 3192. (j) Corey, E. J.; Nicolaou, K. C. *J. Am. Chem. Soc*. **1974**, *96*, 5614. (k) Massamune, S.; Kamata, S.; Schilling, W. *J. Am. Chem. Soc*. **1975**, *97*, 3515. (l) Takahashi, T.; Kasuga, K.; Takahashi, M.; Tsuji, J. *J. Am. Chem. Soc*. **1979**, *101*, 5072. (m) Rao, A. V. R.; Deshmukh, M. N.; Sharma, G. V. M. *Tetrahedron* **1987**, *43*, 779. (n) Hitchcock, S. A.; Pattenden, G. *Tetrahedron Lett*. **1990**, *31*, 3641. For selected references on other syntheses of radicicol: (o) Tichkowsky, I.; Lett, R. *Tetrahedron Lett*. **2002**, *43*, 4003. For synthesis of hypothemycin: (p) Selles, P.; Lett, R. *Tetrahedron Lett*. **2002**, *43*, 4627.
(9) Danishefsky, S. J.; Etheridge, S. J. *J. Org. Chem*. **1979**, *44*, 4716.
(10) Danishefsky, S.; Yan, C.-F.; Singh, R. K.; Gammill, R. B.; McCurry, P. M.; Fritsch, N.; Clardy, J. *J. Am. Chem. Soc*. **1979**, *101*, 7001.

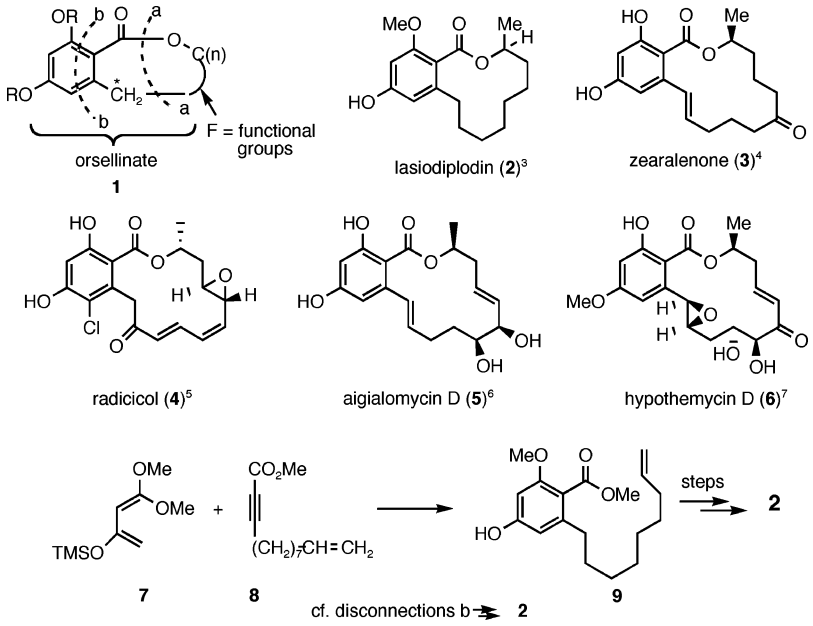


Figure 1. Structure of lasiodiplodin and its synthesis.

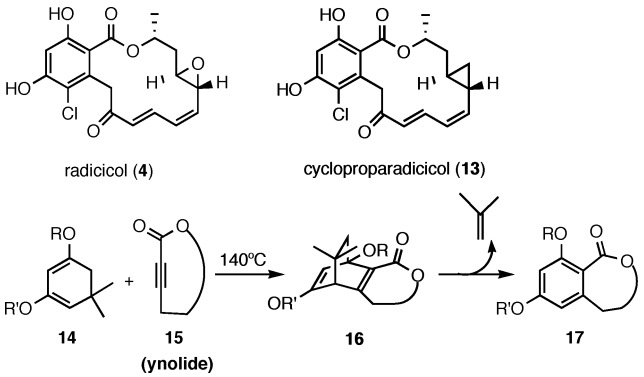
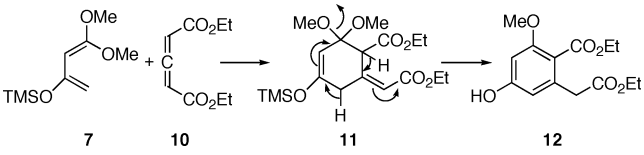


Figure 2. Radicicol and its synthetic strategy.

Scheme 1. Diels−Alder Cycloaddition of Symmetrical Allene Dienophile



which could arise from nonidentically substituted double bonds in allenes had not been addressed in these earlier studies.

Initially, we had hoped to exploit cycloaddition chemistry of the type described above to accomplish the synthesis of a fascinating analogue of radicicol **4**, bearing a cyclopropane in place of an epoxide (**13**) and congeners thereof (Figure 2).[11] Such targets were of interest to us, in light of the high affinity binding of the parent radicicol with the chaperone protein Hsp90.[12] Unfortunately, early projected applications of these findings to reach radicicol or some key analogues such as **13** failed to meet our requirements, owing to breakdowns after the successful Diels−Alder reactions.[13] Eventually, the synthesis of **13** in the radicicol-like series was solved by recourse to the broad logic of disconnection b implied in Figure 1.[14] Central to implementing this more elegant strategy was the retro Diels−Alder reaction of an "ynolide" type dienophile **15** with a dimedone-derived 1,3-dioxygenated diene **14** leading to resorcinylic scaffold **17**.[15]

The research described herein was addressed to reaching a related, but different class of fused resorcinylic macrolides of the general type **18** (Figure 3). In these target systems, a keto rather than an ester group is presented at the benzylic position. The ester bond corresponds to a macrolide of a formal phenylacetic acid. These macrolides have received much interest in agrochemical and pharmaceutical settings.[1] Sporostatin represents a 10-membered phenylacetic macrolactone macrolide that exhibits anti-cancer activity.[16] A representative of a 12-membered phenylacetic macrolactone is curvularin as well as its metabolites.[17] The curvalarin macrolides apparently stem from varied oxidation levels at the C11 and C12 position

(11) Yamamoto, K.; Gabaccio, R. M.; Stachel, S. J.; Solit, D. B.; Chiosis, G.; Rosen, N.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 1280.

(12) (a) For an overview of Hsp90 and its emerging role in cancer treatment: Chiosis, G.; Vilenchik, M.; Kim, J.; Solit, D. *Drug Discovery Today* **2004**, *9*, 881. (b) For radicicol−Hsp90 binding: Roe, S. M.; Prodromou, C.; O'Brien, R.; Ladbury, J. E.; Piper, P. W.; Pearl, C. H. *J. Med. Chem.* **1999**, *42*, 260. (c) For geldanamycin−Hsp90 binding: Stebbins, C. E.; Russo, A. A.; Schneider, C.; Rosen, N.; Haitl, F. U.; Pavletich, N. P. *Cell* **1997**, *89*, 239. (d) For AAG−Hsp90 binding (AAG, a derivative of geldanamycin, is the first Hsp90 inhibitor to enter clinical trials): Schulte, T. W.; Neckers, L. M. *Cancer Chemother. Pharmacol.* **1998**, *42*, 273. For selected references on Hsp90 inhibitors: (e) Llauger, L.; He, H.; Kim, J.; Aguirre, J.; Rosen, N.; Peters, U.; Davies, P.; Chiosis, G. *J. Med. Chem.* **2005**, *48*, 2892. (f) Chiosis, G.; Lucas, B.; Shtil, A.; Huezo, H.; Rosen, N. *Bioorg. Med. Chem.* **2002**, *10*, 3555. (g) Kuduk, S. C.; Harris, C. R.; Zheng, F. F.; Sepp-Lorenzino, L.; Ouerfelli, O.; Rosen, N.; Danishefsky, S. J. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1303.

(13) Garbaccio, R. M.; Stachel, S. J.; Baeschlin, D. K.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2001**, *123*, 10903.

(14) Yang, Z.-Q.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2003**, *125*, 9602.

(15) For reviews on retro Diels−Alder reactions: (a) Rickborn, B. *Org. React.* **1998**, *52*, 1. (b) Ichihara, A. *Synthesis* **1987**, 207. (c) Lasne, M.-C.; Ripoll, J.-L. *Synthesis* **1985**, 121. For examples of related retro-Diels−Alder reactions: (d) Reference 14. (e) Geng, X.; Danishefsky, S. J. *Org. Lett.* **2004**, *6*, 413. (f) Yang, Z.-Q.; Geng, X.; Solit, D.; Pratilas, C. A.; Rosen, N.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2004**, *126*, 7881.

(16) (a) Kinoshita, K.; Sasaki, T.; Awata, M.; Takada, M.; Yaginuma, S. *J. Antibiot.* **1997**, *50*, 961. (b) Murakami, Y.; Ishii, A.; Mizuno, S.; Yaginuma, S.; Uehara, Y. *Anticancer Res.* **1999**, *19*, 4145.

(17) (a) Musgrave, O. C. *J. Chem. Soc.* **1956**, 4301. (b) Musgrave, O. C. *J. Chem. Soc.* **1957**, 1104. (c) Birch, A. J.; Musgrave, O. C.; Richards, R. W.; Smith, H. *J. Chem. Soc.* **1959**, 3146. (d) Lai, S.; Shizuri, Y.; Yamamura, S.; Kawai, K.; Terada, Y.; Furukawa, H. *Tetrahedron Lett.* **1989**, *30*, 2241. (e) Ghisalberti, E. L.; Rowland, C. Y. *J. Nat. Prod.* **1993**, *56*, 2175. (f) Kusano, M.; Nakagami, K.; Fujioka, S.; Kawano, T.; Shimada, A.; Kimura, Y. *Biosci. Biotechnol. Biochem.* **2003**, *6*, 1413.

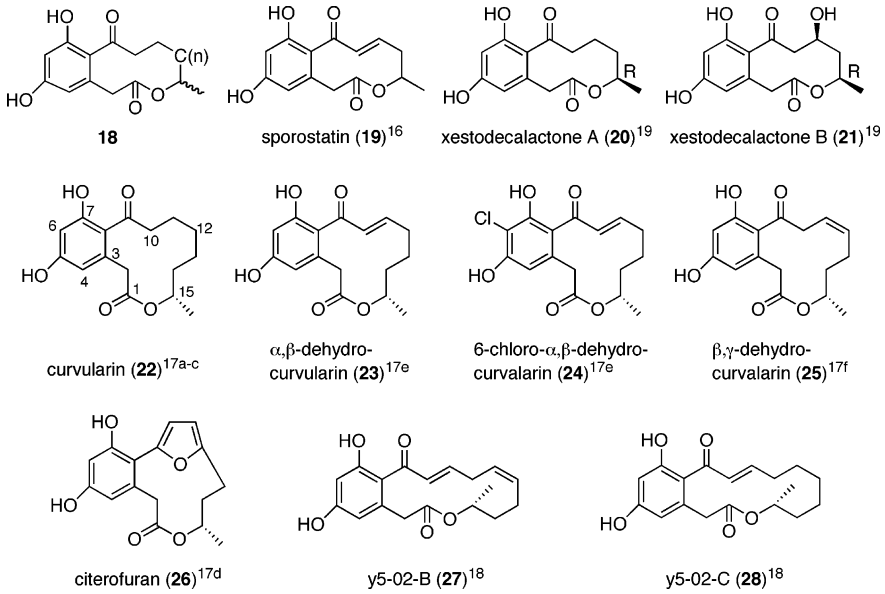
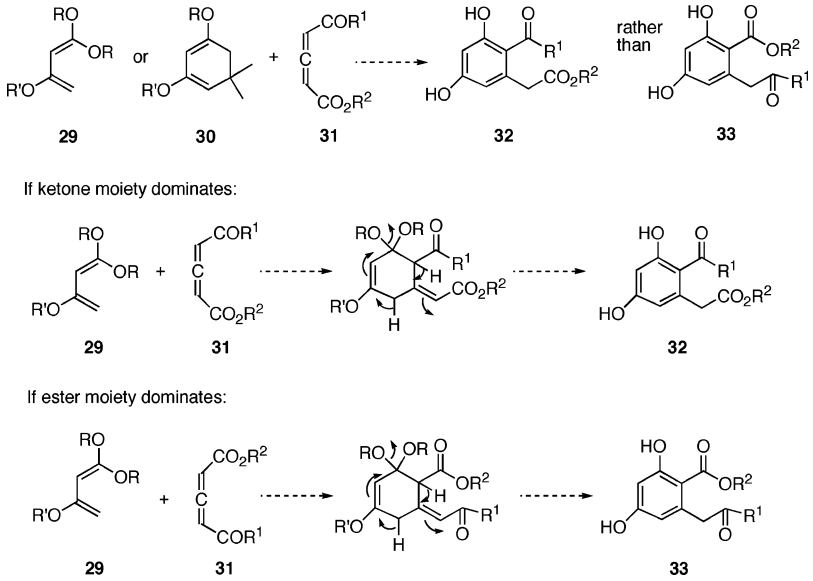


Figure 3. Structure of phenylacetic macrolactone macrolides.

Scheme 2. Proposed Synthesis of Phenylacetic Lactones



(curvularin numbering), and they have attracted interest in the agrochemical arena. The larger, naturally derived 14-membered macrolactones, y5-02-B and y5-02-C, are lead compounds in the inhibition of neuropeptide Y receptor for anti-obesity programs.[18]

The xestodecalactones A and B share the same carbon backbone as sporostatin. Xestodecalactone B was shown to exhibit antibacterial properties.[19] This paper concerns itself with the total synthesis of xestodecalactone A. These macrolides were isolated by Bringmann and associates as a metabolite of *Penicillium* cf. *montanense* from the marine sponge *Xestospongia exigua*.[19] An earlier synthesis of xestodecalactone A was reported by Bringmann et al.[20] Having successfully reached radicicol and aigialomycin D, it was of interest for our laboratory to try to develop a broadly applicable capability to synthesize phenylacetic lactones such as **18**. In particular we hoped to revisit the Diels−Alder reaction, this time directed to the alternate phenylacetic acid lactone goal as exemplified by xestodecalactone A.

Results and Discussion

In contemplating a cycloaddition route to a potential seco precursor of **18**, we first wondered about the possibility of a Diels−Alder reaction between an unsymmetrical allene system **31** and a diene of the acyclic type **29**.[21] Alternatively, we would consider a cyclic diene such as **30** (Scheme 2), hoping to gain access to the phenylacetic acid scaffold **32** as shown. At the outset, we envisioned that the unsymmetrical allene would be flanked by keto- and ester-type activating groups as implied in **31**.

(18) Hanasaki, K.; Kamigaito, T.; JP 2000287697 A2 20001017 (Japanese).
(19) Edrada, R. A., Heubes, M.; Brauers, G., Wray, V.; Berg, A.; Grafe, U.; Wohlfarth, M.; Muhlbacher, J.; Schaumann, K.; Sudarsono; Bringmann, G.; Proksch, P. *J. Nat. Prod.* **2002**, *65*, 1598.
(20) Bringmann, G.; Lang, G.; Michel, M.; Heubes, M. *Tetrahedron Lett*. **2004**, *45*, 2829.
(21) For Diels−Alder reactions with allenes: Murakami, M.; Matsuda, T. *Cycloadditions of Alenes In Modern Allene Chemistry*; Krause, W., Hashmi, A. S. K., Eds.; Wiley-VCH: Weinheim, 2004; Chapter 12, p 727.

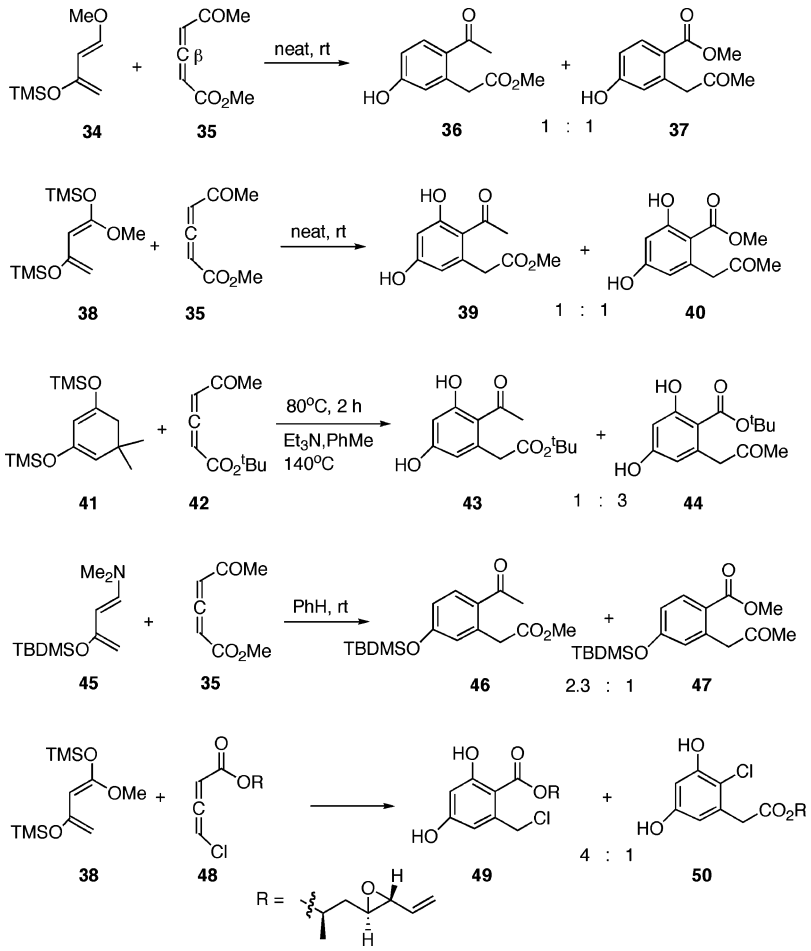


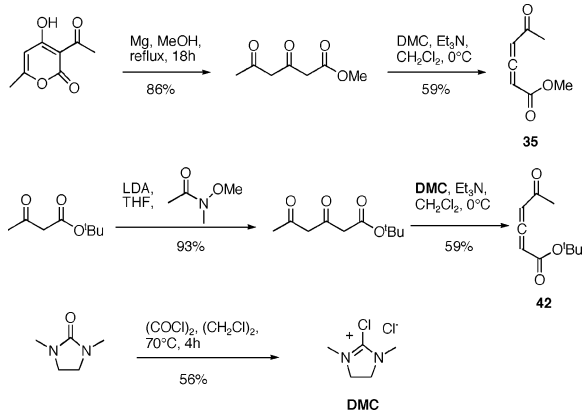
Figure 4. Regiochemical studies with unsymmetrical allenes.

As a first approximation, we expected there to be considerable regioselection in the cycloaddition of acyclic diene **29** or cyclic diene **30** with allene **31**. At this stage we were viewing a mixed allene such as **31** in the context of its presenting two *distinct* dienophiles, i.e., an α,*β*-unsaturated ketone and α,*β*-unsaturated ester. In the case at hand it was projected that such a reaction would provide predominantly cycloadduct **32**. This prediction was based on the perception that **32** would arise from the ketone moiety being the dominant activator in the cycloaddition of allene **31**. Of course, this cycloaddition could produce an alternative product, **33**. The potentially competitive product **33** would have arisen from dienophilic "control" by the ester rather than by the ketone moiety in **31**. Since it was assumed that the vinyl ketone group within **31** would be dominant, it was expected **32** would be the major product. This expectation seemed to follow from the elegant work of Rawal and associates. It had been demonstrated that the Rawal diene (**45**) reacts approximately 10 times faster with methyl vinyl ketone than with methyl acrylate.[22] Given our supposition that the outcome of the mixed allene Diels−Alder could be predicted by reference to the relative reactivities of the individual acrylyl-type dienophiles, control by the vinyl ketone was confidently expected.

To our surprise, the cycloaddition of diene **34** (1.5 equiv) and mixed allene **35**[23] (neat, ambient temperature) furnished a 1-to-1 mixture of adducts **36** and **37** (Figure 4) in unoptimized 38% yield. The mixture was not separated into its components, but we could readily discern and assign the key features of the spectra of each product in the mixture.[24] It was possible to increase its ratio (1:1.6 **36**/**37**), employing solvents such as PhH, PhMe, and $CHCl_3$. The combined yields of these products were increased to approximately 60%. Similarly, cycloaddition of acyclic diene **38** (2.0 equiv) and allene **35** (neat, ambient temperature) provided a 1-to-1 mixture of adducts **39** and **40**.

(22) Kozmin, S. A.; Green, M. T.; Rawal, V. H. *J. Org. Chem.* **1999**, *64*, 8045.

(23) For preparation of allene **35**: In a two-step process, dehydroacetic acid was unraveled to methyl 3,5-dioxohexanoate (preparation see: Solladie, G.; Colobert, F.; Denni, D. *Tetrahedron: Asymmetry* **1998**, *9*, 3081) followed by treatment with freshly prepared DMC (generated from 1,3-dimethyl-2-imidazolidinone) providing allene **35** (DMC protocol: Node, M.; Fujiwara, T.; Ichihashi, S.; Nishide, K. *Tetrahedron Lett.* **1998**, *39*, 6331). For preparation of allene **42**: Similarly, commercially available *tert*-butylacetoacetate was extended to *tert*-butyl 3,5-dioxohexanoate, and treatment with DMC furnished allene **42**.



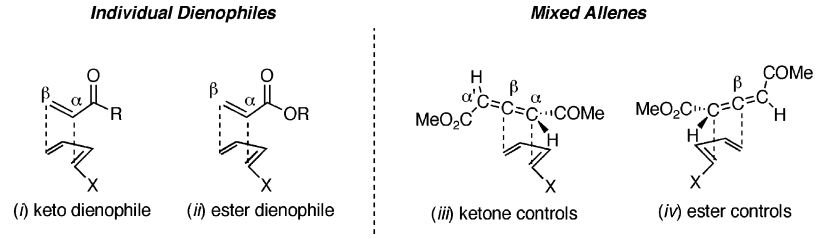
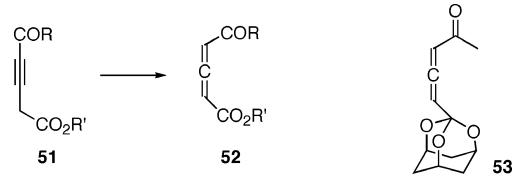


Figure 5. Diels−Alder reaction with mixed allenes.

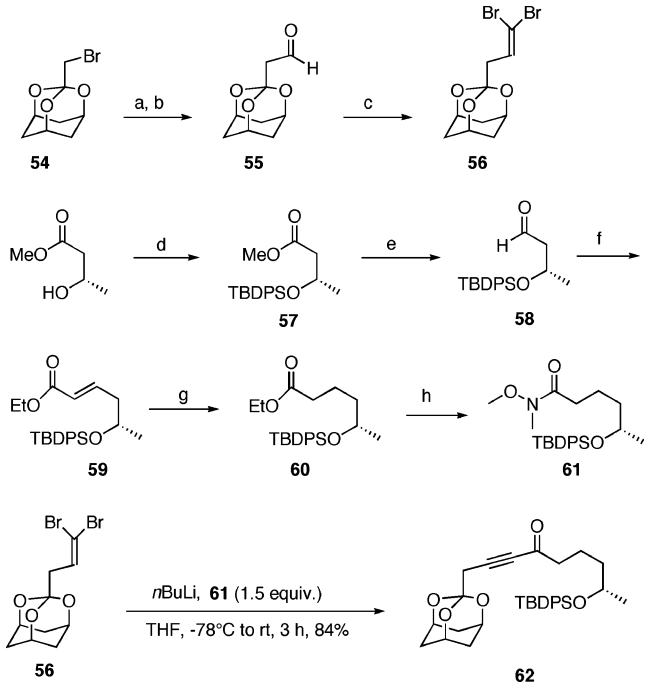
The unusual regiochemical outcome was even more pronounced in the reaction of cyclic diene **41** (1.8 equiv) and dienophile **42**[23] (80 °C, 2 h; Et_3N, PhMe, 140 °C). A ca. 1:3 mixture of adducts **43** and **44** was obtained. Curiously, the cycloaddition reaction of diene **45** (1.5 equiv) and allene **35** did give a 2.3-to-1 mixture of adducts **46** and **47** in 60% yield. In this instance, the product ratio reflected apparent control by the ketonic dienophile function. Apparently the high reactivity of the Rawal diene **45** tilts the sense of the mixed allene Diels−Alder reaction to more nearly reflect the behavior of its acrylyl ketone- and acrylyl ester-activated subcomponents.[22] It will be recalled that in our earlier radicicol synthesis,[13] the cycloaddition of diene **38** with unsymmetrical allene **48** had provided a 4 to 1 mixture of adducts **49** and **50**, favoring the aromatic benzoate **49**. Though the predominance of **49** was consistent with the anticipated dienophilic dominance by the α,*β*-unsaturated ester relative to that of the vinyl chloride segment of the mixed allene,[13] the rather modest observed ratio of **49**:**50** with allene **48** did not reflect the far greater dienophilicity of an acrylate ester relative to that of a vinyl chloride.

With the benefit of retrospection, it is now recognized that the reactivity patterns in the case of separate ester and ketonic dienophiles need not be not translatable to the more subtle case of the mixed allene. *Thus, in the mixed allene case, the β-carbon of the dienophile is common to the two activating* groups. The key reactivity difference between the individual ketone- and ester-based dienophiles must be at their α- rather than their *β*-olefinic carbons (cf. α and α′). In the separate dienophile model (Figure 5, *i* vs *ii*), the different activating functions impact primarily on the reactivity of the *β*-carbon of the two olefins. By contrast, in the mixed allene cycloaddition, the central (sp) carbon is, at once *β*- to *both* activating groups. Here, the pivotal question is really the "cyclizing affinities" of the presumably more closely balanced α-carbons of the ester and ketonic moieties (see *iii* and *iv*). The effect of the activating group on the cyclizing character of the α-carbon in the mixed allene may well hinge on the venerable but still unresolved issue of levels of synchroneity in the Diels−Alder reaction.[25] The mixed allene dienophile case may well constitute a unique opportunity to study the more subtle chemoselectivies and directivities of α-carbons in Diels−Alder dienophiles.

Scheme 3. Evaluation of Dienophiles **51** and **53**



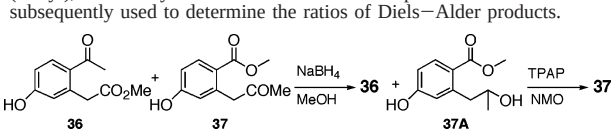
Scheme 4. Synthesis of Compound **62**[a]



[a] Reagents and conditions: a) *n*BuLi, HCHO, THF; b) Dess−Martin periodinane, CH_2Cl_2, 81% over 2 steps; c) CBr_4, PPh_3, CH_2Cl_2, 86%; d) TBDPSCl, imidazole, DMF, rt, overnight, 99%; e) DIBAL-H, CH_2Cl_2, −78 °C, 15 min, 94%; f) $(EtO)_2POCH_2CO_2Et$, LiCl, DBU, MeCN, rt, overnight, 90%; g) H_2, 10% Pd/C, EtOAc, rt, 2.5 h, quant.; h) MeNH(OMe)-HCl, *i*PrMgCl, THF, −20 °C, 30 min 96%.

Returning to the xestodecalactone problem, we took note of the possibility of building a dienophile of the type **51** to gain access to the *seco*-phenylacetic macrolactone scaffold was equally unproductive (Scheme 3). Unfortunately such structures are converted virtually instantaneously to their allenic tautomers (**51** → **52**).[26] In a similar vein, we explored the possibility of utilizing an unsymmetrical allene wherein the ester functionality was masked as an ortho ester group (cf. **53**).[27] However cyclo-

(24) The inseparable mixture of **36**/**37** was selectively reduced (sodium borohydride) to give alcohol **37A** and unreacted isomer **36**. On the basis of its proton NMR spectroscopic pattern (the benzylic methylene protons were each a dd, and the geminal proton of alcohol was a complex multiplet), alcohol **37A** was determined to arise from reduction of **37**. The alcohol was oxidized (TPAP/NMO) back to ketone **37**. It was then readily discernible which proton NMR peak of the Diels−Alder adducts mixture belong to which product, particularly the benzylic methylene, methyl ketone (acetyl), and methyl ester. These three distinct peaks in the NMR were subsequently used to determine the ratios of Diels−Alder products.

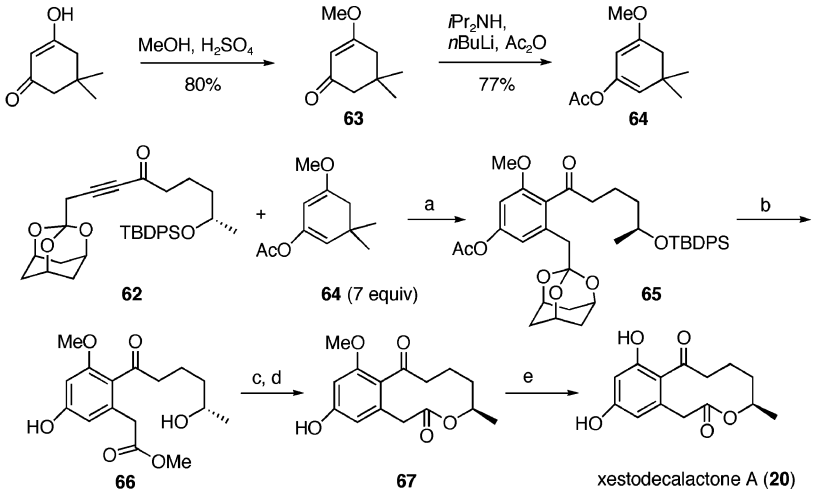


(25) For seminal discussions on the mechanism of the Diels−Alder reaction, concerted or stepwise: (a) Woodward, R. B.; Katz, R. B. *Tetrahedron* **1959**, *5*, 70. (b) Berson, J. A.; Mueller, W. A. *J. Am. Chem. Soc*. **1961**, 83, 4947.

(26) Unpublished results by T. Yoshino. For seminal work on this type of transformation: Jones, E. R. H.; Mansfield, G. H.; Whiting, M. C. *J. Chem. Soc*. **1954**, 3208.

(27) Unpublished results by T. Yoshino.

Scheme 5. Completion of Synthesis of Xestodecalactone A[a]



[a] Reagents and conditions: a) neat, 180 °C, 79%; b) H_2SO_4, MeOH, 59%; c) LiOH, H_2O, THF; d) PPh_3, DEAD, PhMe, THF, rt, 2 day, 54% over 2 steps; e) BCl_3, CH_2Cl_2, −78 °C to room temperature, 4 h, 58%.

additon of allene **53** and acyclic diene **38** or cyclic diene **41** produced complex mixtures. We suspect that some of the complexity may well have arisen from reactions which occurred after the cycloaddition event. Unlike the case of doubly activated allene **31**, the tautomerization en route to aromatizations after cycloaddition of **53** are less facile, and other chemistry intervenes.

A Total Synthesis of Xestodecalactone A. Following the difficulties described above, we retreated to a substantially revised, less ambitious, but in the end, successful strategy to reach the specific target, xestodecalactone A.[20] Our program sought to address several matters of importance. The overriding issue was to develop a more concise Diels−Alder-based strategy for reaching phenylacetic acid lactones. Moreover, at the time the synthesis was undertaken, there was no clear basis for assigning the absolute configuration of the xestodecalactones. At the time, we sought to answer this question as well, though in the interim, this problem was indeed solved by Bringmann and associates through their total synthesis of xestodecalactone A.[20] Herein, we relate our total synthesis of xestodecalactone A, which was accomplished by a variation of the type-*b* ynoate dienophile logic (cf. lasiodiplodin, Scheme 1). We also confirmed the Bringmann assignment of absolute stereochemistry of xestodecalactone A.

Our synthesis commenced with the known bromo ortho ester **54**[28] (Scheme 4). Chain extension as shown afforded aldehyde **55** which was converted to dibromo building block **56**. In a parallel series of experiments, the known (3*S*)-hydroxybutyrate was protected as shown (cf. **57**) en route to aldehyde **58**. Roush−Masamune modified Horner−Wadsworth−Emmons[29] chain extension to **59** was followed by catalytic reduction of the double bond of **59** to afford **60**. The latter lent itself to conversion to the Weinreb-type amide **61**.[30] At this stage, a key coupling step was accomplished. Treatment of **56** under Corey−Fuchs conditions[31] generated a lithioacetylide intermediate which did indeed couple with the Weinreb-type amide **61** to afford the acetylenic ketone **62**. Unlike the case of acetylene **51** which reverts to mixed allene **52**, ynoate **62** is a stable compound.

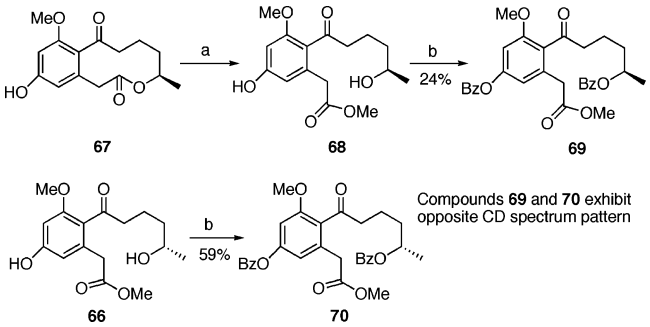
A variety of cyclohexadienes were screened as to their effectiveness as dienes in Diels−Alder reactions with **62**. In the end, we settled on compound **64** to optimize the requirement of stability to the harsh conditions which would be required for the upcoming Diels−Alder reaction, and eventual convertability to the required resorcinol. Compound **64** was prepared in a straightforward fashion from dimedone as shown.

In the event, Diels−Alder reaction of alkyne **62** with optimal diene **64**[32] proceeded smoothly at 180 °C to furnish resorcinylic adduct **65** in 79% yield in a single step (Scheme 5). To complete the synthesis of xestodecalactone A, acidolysis of **65** achieves unmasking of the ester functionality concomitant with desilylation to afford seco-compound **66**. A routine saponification to the corresponding carboxylic acid was followed by Mitsunobu reaction to secure macrolactone **67**. Subsequent demethylation indeed provided xestodecalactone A (**20)** which was identical to an authentic sample of the natural product kindly provided by Professor Bringmann.

At the time of the synthesis, the absolute configuration of xestodecalactone A had been reported as being S[19] (this was later revised[20]). On the basis of the original assignment we would have expected to reach *ent*-xestodecalactone A from our precursor since the Mitsunobu reaction would have been anticipated to proceed with its usual pattern of inversion of stereochemistry (the stereocenter was fashioned from 3*S*-hydroxybutyrate). Rather, we were both surprised and gratified to find that our synthetic xestodecalactone A exhibits substantially the same optical rotation as that reported by Bringmann and colleagues,[19] thereby confirming retrospectively their revised (R) assignment. For additional comparative analysis (Scheme 6), methanolysis of macrolactone **67** to its acyclic ester **68** followed by benzoylation provided benzoate **69**. In the same vein, Mitsunobu precursor **66** was similarly converted to benzoate **70**. Compounds **69** and **70** gave opposite CD patterns. Indeed, the Mitsunobu macrolactonization had proceeded as expected with complete inversion of stereochemistry.

(28) For halogen−metal exchange: (a) Chandrasekhar, S.; Roy, C. D. *Tetrahedron* **1994**, *50*, 8099. For preparation of compound **54**: (b) Stetter, H.; Steinacker, K. H. *Chem. Ber.* **1953**, *86*, 790.
(29) Masamune, S.; Roush, W. R. *Tetrahedron Lett.* **1984**, *25*, 2183.
(30) Williams, J. M.; Jobson, R. B.; Yasuda, N.; Marchesini, G.; Dolling, U.-H.; Grabowski, J. J. *Tetrahedron Lett.* **1995**, *36*, 5461.
(31) Corey, E. J.; Fuchs, P. C. *Tetrahedron Lett.* **1972**, 3769.
(32) The synthesis of diene **64** is described in Supporting Information. Cycloaddition of dienophile **62** and siloxyl diene was unsuccessful.

Scheme 6. CD Spectroscopic Pattern of Compounds **69** and **70**[a]



[a] Reagents and conditions: a) MeOH, K_2CO_3, reflux, 1 h, 64%; b) BzCl, pyridine, 4-(dimethylamino)pyridine, rt, overnight.

Conclusion

In summary, we have learned through this research that the Diels−Alder cycloaddition reaction involving an unsymmetrical allene dienophile results with modest chemoselection in difficultly predictable ways. Though from a synthetic perspective this was a disappointing finding, in retrospect it has considerable potential teaching value in Diels−Alder reactions, in that it allows for the examination of the subtle effects at the α-carbon of active dienophiles (see Figure 5) otherwise dwarfed by the major effects at the β-carbons. We expect that the chemoselection in the relative dienophilicity offers significant challenges and opportunities for estimating the concertedness of cycloadditions of the Diels−Alder genre.

Subsequently an efficient synthesis of xestodecalactone A, utilizing an "ynoate" dienophile, served to rapidly construct the resorcylinic scaffold. This strategy is amenable to assembling a broad range of biologically acive phenylacetic lactone macrolides with pleasingly high convergence.

Acknowledgment. This work was supported in part by a grant from the NIH (HL25848). T.Y. thanks Prof. Bringmann for an authentic sample of xestodecalactone A and for providing its spectroscopic data. Dr. Hideki Ishii is acknowledged for CD measurements. Mr. Mingji Dai is acknowledged for helpful discussions.

Supporting Information Available: Experimental procedures and characterization data for compounds **55**−**67**, **xestodecalactone A**, and **68**−**70**. This material is available free of charge via the Internet at http://pubs.acs.org.

JA064270E