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Enantioselective Synthesis of (−)-Terpestacin and Structural Revision of Siccanol Using Catalytic Stereoselective Fragment Couplings and Macrocyclizations

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Abstract: (−)-Terpestacin (**1**, naturally occurring enantiomer) and (+)-11-*epi*-terpestacin (**2**) were prepared using catalyst-controlled, stereoselective, intermolecular reductive coupling reactions of alkyne **9** and aldehyde **10**, affording allylic alcohols **42** or 11-*epi*-**42** in a 3:1 ratio (or 1:3 depending on the enantiomer of ligand **41a** used). These stereoselective fragment couplings were instrumental in confirming that "siccanol" is *not* 11-*epi*-terpestacin but, in fact, is (−)-terpestacin itself. Several intramolecular alkyne−aldehyde reductive coupling approaches to **1** and **2** were also investigated and are discussed herein.

Introduction

Over the past 10 years, several scientific communities have been drawn to the sesterterpene terpestacin (**1**), (Figure 1) and structurally related compounds (**2**, **3**) because of their unique structural architectures and biological activities. Originally isolated from the fungal strain *Arthrinium* sp. and studied collaboratively by Oka and Bristol-Myers Squibb, terpestacin was found to inhibit the formation of syncytia, giant-multi-nucleated cells that arise from expression of gp120 on cell surfaces in the course of HIV infection.[1] Recently, a study of the effects of terpestacin on bovine aortic endothelial cells (BAECs) and chorioallantoic membrane (CAM) from growing chick embryos has determined that this natural product also inhibits angiogenesis.[2]

A structurally related compound, proliferin, was discovered shortly after terpestacin and was renamed "fusaproliferin" (**3**) since a prolactin-related protein had already been named "proliferin".[3] In a subsequent report, the absolute configuration of fusaproliferin was initially assigned as the enantiomer of 23-*epi*-**3** (terpestacin numbering) based on statistical differences in R and Rw X-ray data between two enantiomorphs.[4]

Both terpestacin and fusaproliferin have been prepared by total synthesis (Scheme 1),[5] and Tatsuta was the first to prepare the racemate of the former in 1998. Later that same year, his group completed an enantiospecific, 38-step synthesis beginning

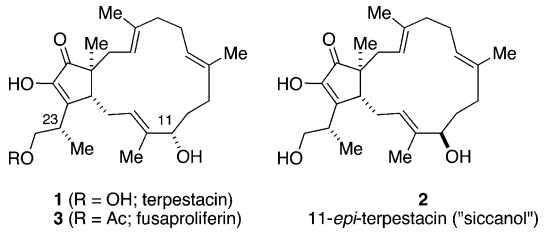
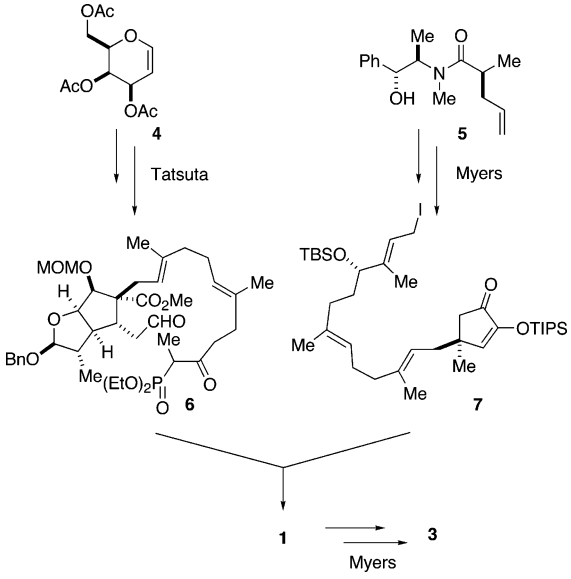


Figure 1. Terpestacin (**1**) and related molecules.

Scheme 1. Previous Enantioselective Syntheses of Terpestacin (**1**) and Fusaproliferin (**3**)

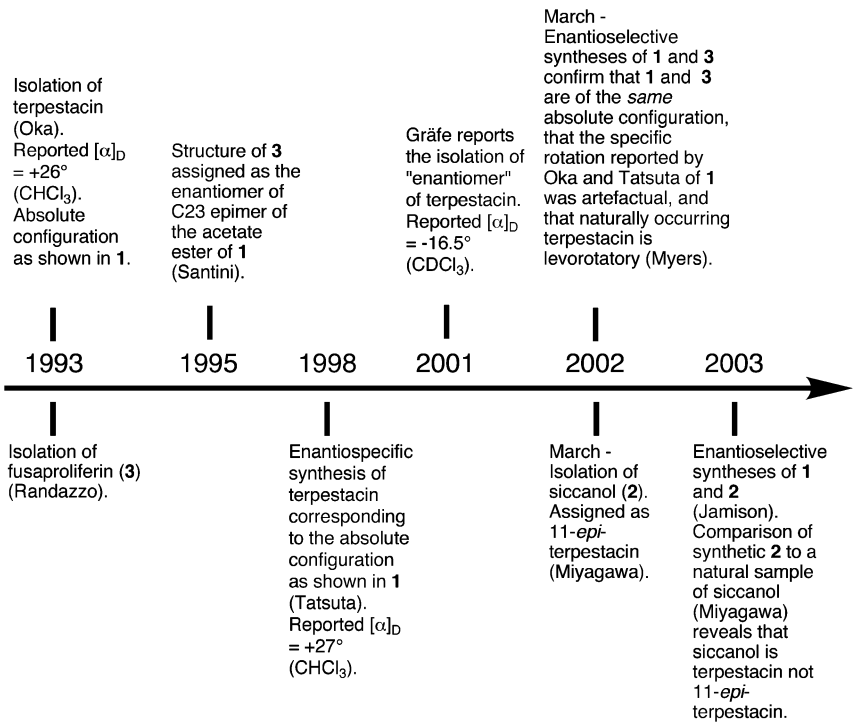


with tri-*O*-acetyl-D-galactal **4** that took advantage of a highly selective Horner−Wadsworth−Emmons reaction of **6** to solve a central structural challenge presented by these compounds, the 15-membered carbocycle. The specific rotation measured for synthetic terpestacin ($[\alpha]_D = +27$, *c* 0.22, $CHCl_3$) was consistent with that obtained by Oka ($[\alpha]_D = +26$, *c* 0.5,

(1) Oka, M.; Iimura, S.; Tenmyo, O.; Sawada, Y.; Sugawara, M.; Ohkusa, N.; Yamamoto, H.; Kawano, K.; Hu, S.-L.; Fukagawa, Y.; Oki, T. *J. Antibiotics* **1993**, *46*, 367−373.
(2) Jung, H. J.; Lee, H. B.; Kim, C. J.; Rho, J.-R.; Shin, J.; Kwon, H. J. *J. Antibiotics* **2003**, *56*, 492−496.
(3) Lee, S. J.; Nathans, D. *J. Biol. Chem.* **1988**, *263* (7), 3521−3527.
(4) (a) Randazzo, G.; Fogliano, V.; Ritieni, A.; Mannina, L.; Rossi, E.; Scarallo, A.; Segre, A. L. *Tetrahedron* **1993**, *49*, 10883−10896. (b) Manetti, C.; Fogliano, V.; Ritieni, A.; Santini, A.; Randazzo, G.; Logrieco, A.; Mannina, L.; Segre, A. L. *Struct. Chem.* **1995**, *6*, 183−189. (c) Santini, A.; Ritieni, A.; Fogliano, V.; Randazzo, G.; Mannina, L.; Logrieco, A.; Benedetti, E. *J. Nat. Prod.* **1996**, *59*, 109−112.
(5) Approaches toward the synthesis of terpestacin: (a) Takeda, K.; Nakajima, A.; Yoshii, E. *Synlett* **1995**, 249−250. (b) Mermet-Mouttet, M.-P.; Gabriel, K.; Heissler, D. *Tetrahedron Lett.* **1999**, *40*, 843−846.

10.1021/ja0470968 CCC: $27.50

Scheme 2. Structural Assignment Timeline of **1**, **2**, and **3**



$CHCl_3$), and so it appeared that the absolute configuration of terpestacin had been confirmed by means of chemical synthesis.[6]

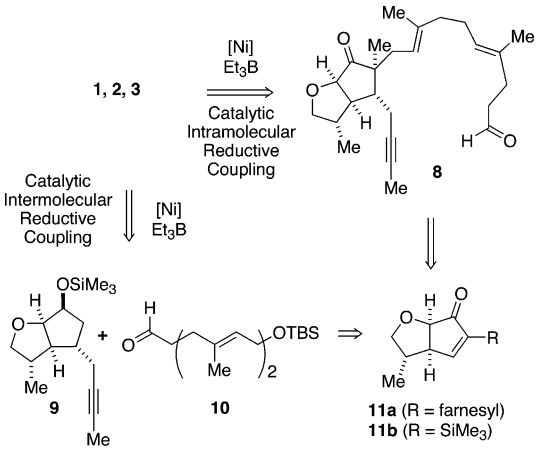
However, this conclusion was brought into question as a result of an unusual chain of events (Scheme 2). In 2001, Gräfe and co-workers isolated a molecule from *Ulocladium* sp. that was believed to be the enantiomer of terpestacin,[7] since it was spectroscopically identical to Oka's material, differing only in the sign of its specific rotation. Interestingly, both "(+)-terpestacin" (Oka) and "(−)-terpestacin" (Gräfe) inhibited syncytium formation. In March 2002, Myers reported enantioselective syntheses (Scheme 1) of terpestacin (**1**) and fusaproliferin (**3**) that began with an amide derived from pseudoephedrine (**5**) and should have lead to (+)-terpestacin, as reported by Oka and corroborated by Tatsuta. However, having unexpectedly obtained (−)-terpestacin at the end of the synthesis, Myers initiated a thorough series of investigations that ultimately revealed that exposure of (−)-terpestacin to chloroform stored over potassium carbonate gave rise to a chloroetherification product possessing a dextrorotatory sense of specific rotation, the same as that obtained previously for both natural (Oka) and synthetic (Tatsuta) "(+)-terpestacin".[8] Therefore, it is likely that the same enantiomer of terpestacin had been isolated by Oka and Gräfe but that Oka's material underwent a chloroetherification in the $CHCl_3$ (stored over K_2CO_3) used to obtain the specific rotation. In other words, only (−)-terpestacin has been isolated to date from natural sources. By acetylation of (−)-**1**, Myers obtained (−)-**3**, confirming that naturally occurring terpestacin (**1**) and fusaproliferin (**3**) formed a homochiral structural series. In other words, natural fusaproliferin was simply an acetate ester of natural terpestacin, not the enantiomeric C23 epimer, as was originally reported by Santini.

Nearly coincident with the Myers' report of the syntheses of terpestacin and fusaproliferin, Miyagawa reported the isolation of another natural product, siccanol (**2**) from *Bipolaris sorokiniana*, a fungal strain commonly found in decayed ryegrass leaves. Their structural determination led them to conclude that siccanol was diastereomeric to terpestacin at the allylic carbinol in the 15-membered ring (C11), i.e., 11-*epi*-terpestacin.[9] Differing only by the configuration about the C11 allylic carbinol, **1** and **2** provided an attractive context to pursue our ongoing interest in the stereoselective formation of allylic alcohols.[10] Herein, we provide a detailed account of our syntheses of (−)-terpestacin and (+)-11-*epi*-terpestacin that utilizes our recently developed intermolecular, stereoselective methods of nickel-catalyzed reductive coupling of alkynes and aldehydes. One outcome of these studies is the discovery that "siccanol" is *not* 11-*epi*-terpestacin but, in fact, is (−)-terpestacin itself.

Retrosynthetic Analysis. A central component of our approach to **1** and **2** was a disconnection at the C11−C12 allylic alcohol, such that we could examine the suitability of catalytic reductive coupling reactions of alkynes and aldehydes, related to methodology developed in our laboratory and by Montgomery.[11] Two contrasting approaches using this method were devised (Scheme 3). The first utilized an *intramolecular* reductive coupling of an alkyne and aldehyde to install the C11 carbinol stereocenter, construct the 15-membered carbocyclic ring, and establish the (*E*)-geometry at one of the three alkenes of this macrocycle. An alternate approach planned on controlling the C11 configuration via an *intermolecular* alkyne−aldehyde reductive coupling of **9** and **10**, with subsequent formation of

(6) Tatsuta, K.; Masuda, N. *J. Antibiotics* **1998**, *51*, 602−606.
(7) Schlegel, B.; Schmidtke, M.; Dörfelt, H.; Kleinwächter, P.; Gräfe, U. *J. Basic Microbiol.* **2001**, *41*, 179−183.
(8) Myers, A. G.; Siu, M.; Ren, F. *J. Am. Chem. Soc.* **2002**, *124*, 4230−4232.
(9) Nihashi, Y.; Lim, C.-H.; Tanaka, C.; Miyagawa, H.; Ueno, T. *Biosci. Biotechnol. Biochem.* **2002**, *66*, 685−688.
(10) (a) Huang, W.-S.; Chan, J.; Jamison, T. F. *Org. Lett.* **2000**, *2*, 4221−4223. (b) Chan, J.; Jamison, T. F. *J. Am. Chem. Soc.* **2003**, *125*, 11514−11515. (c) Colby, E. A.; Jamison, T. F. *J. Org. Chem.* **2003**, *68*, 156−166. (d) Miller, K. M.; Huang, W.-S.; Jamison, T. F. *J. Am. Chem. Soc.* **2003**, *125*, 3442−3443.
(11) Montgomery, J. *Acc. Chem. Res.* **2000**, *33*, 467−473.

Scheme 3. Nickel-Catalyzed Alkyne−Aldehyde Coupling Strategies



the macrocycle using an intramolecular allylation of a ketone enolate.

In both approaches, the synthesis of the reductive coupling precursors required the protection of two otherwise interfering functional groups, a latent 1,2-diketone located at (C16−C17) and the primary hydroxyl group at C24. We envisioned accomplishing both tasks by, in effect, lowering the oxidation state of C17 and attaching to it the C24 oxygen, thus forming a tetrahydrofuran that we planned to unravel at a late stage in the synthesis through an enolate hydroxylation reaction.

The tetrahydrofuran also addressed challenges common to both strategies, namely, establishing the remaining three stereogenic centers (Figure 2). A conjugate addition to oxabicyclo-

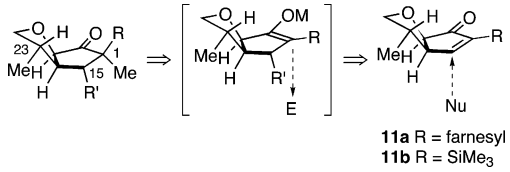


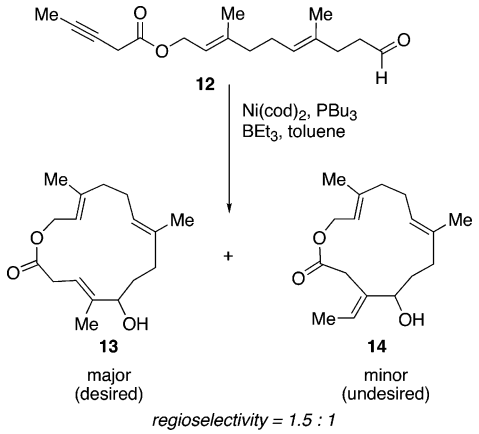
Figure 2. Proposed basis of stereoselectivity in conjugate addition−alkylation sequences of **11a** and **11b**.

[3.3.0]octenone **11a** or **11b** would relay the configuration of C23 to both the quaternary carbon center (C1) and its neighbor (C15) that together also comprise the junction of the five- and fifteen-membered rings. The first event was expected to occur on the convex face, but prediction of the major diastereomer in the subsequent alkylation was less clear (desired approach shown; E = MeI), since a substituent on this face, adjacent to the site of alkylation, might strongly influence the stereochemical course of the reaction.

Also unclear in both approaches a priori was the degree of influence of the existing stereocenters in determining the selectivity in the formation of the carbinol center at C11 using the nickel-catalyzed alkyne−aldehyde reductive coupling discussed above. In both cases, the nearest stereocenter would reside at C15, two bonds away from the site of asymmetric induction. An additional uncertainty particular to the intramolecular reductive coupling approach was the effect of the conformation of the nascent 15-membered ring not only on diastereoselectivity but also on regioselectivity (15-membered ring vs 14-membered ring).

Accordingly, a model substrate (**12**) was synthesized[12] and subjected to Et_3B and catalytic amounts of $Ni(cod)_2$ and PBu_3 in order to investigate the feasibility of this macrocylization strategy (Scheme 4). Although the model lacked several features,

Scheme 4

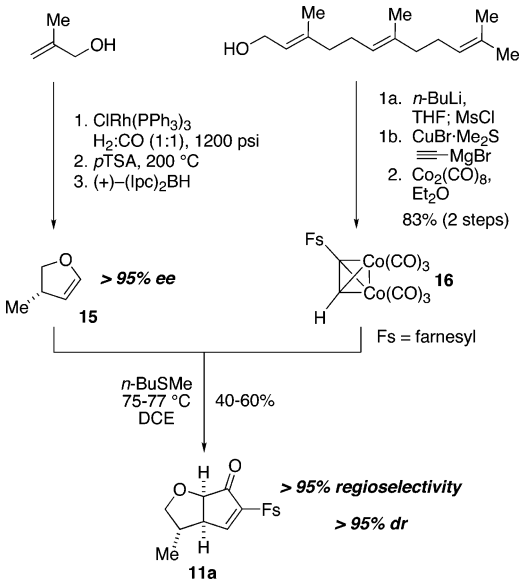


namely, the *cis*-fused 5,5-ring system and its corresponding functional groups, a 1.5:1 ratio was nevertheless obtained, favoring the formation of the desired regioisomer (**13**), demonstrating that forming a 15-membered macrocycle with three (*E*)-trisubstituted double bonds was possible using this approach.

Results and Discussion

Intramolecular Alkyne−Aldehyde Reductive Coupling Approach. Beginning with commercially available β-methallyl alcohol, mole-scale rhodium-catalyzed hydroformylation, followed by dehydration under acidic conditions, afforded multihundred-gram quantities of racemic dihydrofuran **15** in 72% yield[13] that was resolved to >95% ee at 55% conversion using (+)-$(Ipc)_2BH$ (Scheme 5).[14] Initial attempts to promote the

Scheme 5



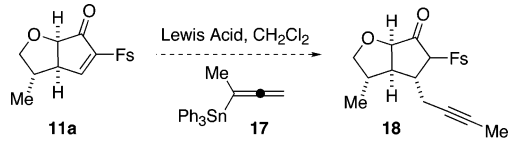
intermolecular Pauson−Khand reaction between **15** and cobalt cluster **16** involved the use of NMO,[15] cyclohexylamine,[16] and

(12) Model substrate **12** was synthesized through the DCC coupling of **40a** and pent-3-ynoic acid.
(13) Botteghi, C.; Consiglio, G.; Ceccarelli, G.; Stefani, A. *J. Org. Chem.* **1972**, *37*, 1835−1837.
(14) Brown, H. C.; Prasad, J. V. N. Vara *J. Am. Chem. Soc.* **1986**, *108*, 2049−2054.

a phosphine sulfide[17] or simply heating a solution of these two compounds. The greatest success was achieved using a sulfide-promoted intermolecular Pauson−Khand reaction,[18] furnishing the desired oxabicyclo[3.3.0]octenone (**11a**) in 40−60% yield. Notably, no other diastereomers, or any of the three other possible regioisomers, could be detected (^{1}H NMR).[19]

In 1990, Haruta and co-workers demonstrated that allenyltriphenylstannanes in $TiCl_4$-mediated conjugate additions to a variety of cyclic enones, afforded 1,5-ynones.[20] Unfortunately, our attempts to install the 2-butynyl moiety at C15 (terpestacin numbering) using this method with the corresponding allenyl stannane **17** were unsuccessful. In our studies we observed that enone **11a** underwent either decomposition or no reaction, despite evaluation of several Lewis acids of varying nature and strength ($TiCl_4$, BF_3·OEt_2, $SnCl_4$, Et_2AlCl, $MgBr_2$, Me_3SiCl, $ZnCl_2$, Ti(O*i*Pr)$_4$, Ti(O*i*Pr)$_3$Cl, and Yb(OTf)$_3$) (Scheme 6).

Scheme 6



Consequently, an alternate route was devised (Scheme 7). A highly diastereoselective conjugate addition of a lithium cuprate (**19**) to **11a** provided **20** in 72% yield and >95:5 diastereoselectivity. Notably, attempts at the use of a trimethylsilyl group in place of triisopropylsilyl on the alkyne gave rise to lower yields, possibly due to unimolecular or bimolecular decomposition of the nucleophile.[21] Following reduction, deprotection, isomerization of the terminal alkyne with KOtBu in DMSO,[22] and a TPAP/NMO oxidation, **18** was delivered in a four-step sequence in 57% yield overall. The reduction/oxidation tandem (steps 1 and 4) was necessary, since ketones such as **18** were not compatible with KOtBu in DMSO solutions.

Our studies of the methylation of an enolate derived from ketone **18** included a survey of a variety of bases and conditions. Nearly all conditions resulted in either decomposition of the starting material or the formation of an *O*-methyl vinyl ether as the primary product. Exclusively successful was the use of sodium hydride in benzene, effecting a reaction that proceeded with good conversion and site selectivity on a small scale (<10 mg). However, upon increasing the scale of the reaction (100 mg), slow decomposition of **10** was observed with no conversion to the desired product. We reasoned that adventitious water might be present in the small scale reaction, implying that finely dispersed sodium hydroxide was the operative base. Indeed, the addition of 100 mol % water to a mixture of sodium hydride, the ketone, and methyl iodide in toluene afforded **21** in 90% yield with a diastereoselectivity of 93:7 in favor of the desired isomer. The assignment of the newly formed quaternary center was based on an NOE experiment and the observation that the ^{1}H NMR resonance corresponding to the quaternary methyl group in the major product resided upfield relative to that in the undesired diastereomer (δ 0.92 ppm vs δ 1.06 ppm), likely due to magnetic anisotropy imparted by the triple bond. Selective cleavage of the terminal isopropylidene unit was effected in a two-step sequence that involved a catalytic dihydroxylation using Sharpless' (DHQD)$_2$PHAL ligand[23] and sodium periodate cleavage of the resulting diol, affording **8** in 25% yield for the two steps.

Intramolecular, nickel-catalyzed reductive cyclization of **8** afforded, unfortunately, the undesired 14-membered ring regioisomer (**22**) in 45% yield with no detectable trace of the desired 15-membered ring (Scheme 7). Formation of the undesired regioisomer was surprising, given our results with the model system **12**. The structural differences between **8** and **12**, as highlighted by the ovals in Figure 3, were thought to be

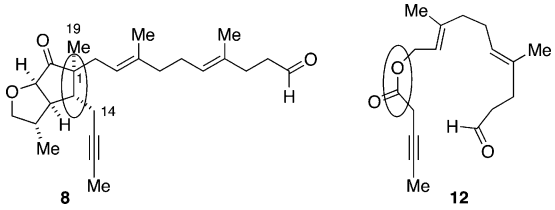


Figure 3. Comparison of **8** to a cyclization model compound (**12**); (*E*)-ester conformer shown for clarity.

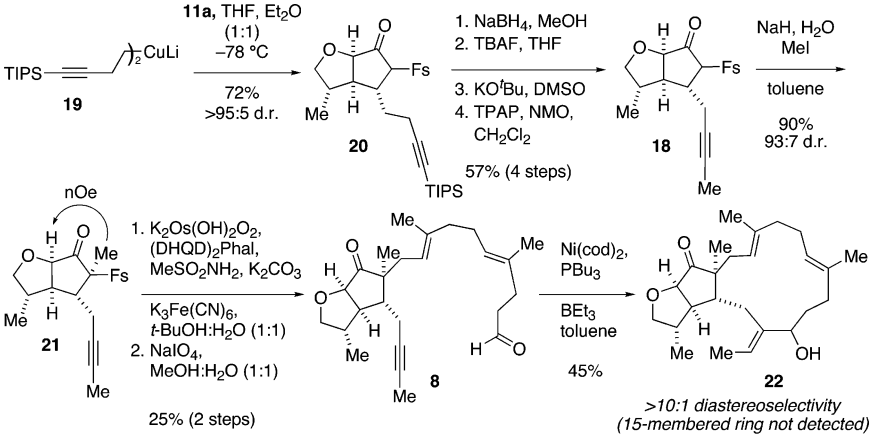
responsible for the divergent behavior in the macrocyclizations. Specifically, the critical structural features that may have affected the regioselectivities in the cyclization were the 5,15-ring junction and the stereogenic centers in **8**, which were not present in **12**. Since changing the C15 stereocenter would require major modifications of the existing route, we first focused on altering the nature of C1 through removal of the C19 quaternary methyl group in order to remove steric interactions with the 2-butynyl group. By this approach, more conformations of the alkyne might be accessible, possibly affecting regioselectivity in the macrocyclization.

Intramolecular Alkyne−Aldehyde Approach: Cyclization in the Absence of C19. To test these hypotheses, alkynal **23** was synthesized in an analogous fashion to the synthesis of **8**. Treatment with Ni(cod)$_2$, PBu_3, and BEt_3 in toluene afforded the undesired regioisomer (**25**) as well as **24**, a product derived from the intramolecular reductive coupling of the alkyne and, surprisingly, the ketone (Scheme 8). Acetone can be used as a solvent in intermolecular nickel-catalyzed reductive couplings, and alkyne−acetone coupling products have never been detected, suggesting that the proximity of the alkyne to the ketone may explain the formation of **24**.

The results obtained from these experiments suggested that the ketone might participate in the catalytic reaction, possibly through interaction with nickel. Accordingly, the next course of action was to alter this functional group. Reduction of the

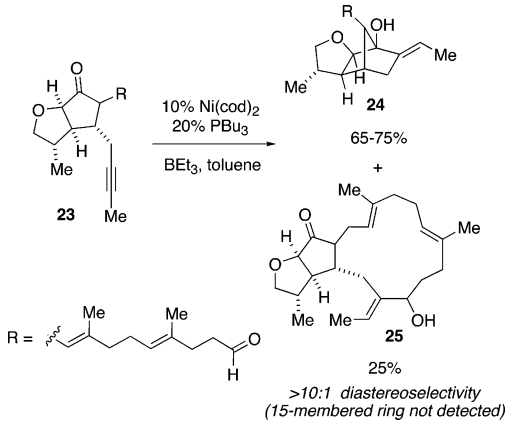
(15) Shambayati, S.; Crowe, W. E.; Schreiber, S. L. *Tetrahedron Lett.* **1990**, *31*, 5289−5292.
(16) Sugihara, T.; Yamada, M.; Ban, H.; Yamaguchi, M.; Kaneko, C. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2801−2804.
(17) Hayashi, M.; Hashimoto, Y.; Yamamoto, Y.; Usuki, J.; Saigo, K. *Angew. Chem., Int. Ed.* **2000**, *39*, 631.
(18) Sugihara, T.; Yamada, M.; Yamguchi, M.; Nishizawa, M. *Synlett* **1999**, *6*, 771−773.
(19) Kerr, W. J.; McLaughlin, M.; Pauson, P. L.; Robertson, S. M. *J. Organomet. Chem.* **2001**, *630*, 104−117.
(20) Haruta, J.; Nishi, K.; Matsuda, S.; Akai, S.; Tamura, Y.; Kita, Y. *J. Org. Chem.* **1990**, *55*, 4853−4859.
(21) A ^{1}H NMR spectrum of the unpurified reaction mixture displayed a large number of signals between 5.0 and 6.0 ppm when the trimethyl silyl protecting group was used in place of triisopropylsilyl.
(22) (a) Takano, S.; Sekiguchi, Y.; Sato, N.; Ogasawara, K. *Synthesis* **1987**, 139−141. (b) Recent application in total synthesis: Thompson, C. F.; Jamison, T. F.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2000**, *122*, 10482−10483.
(23) (a) Crispino, G. A.; Sharpless, K. B. *Tetrahedron Lett.* **1992**, *33*, 4273−4274. (b) Crispino, G. A.; Ho, P. T.; Sharpless, K. B. *Science* **1993**, *259*, 64−66. (c) Corey, E. J.; Noe, M. C.; Lin, S. *Tetrahedron Lett.* **1995**, *36*, 8741−8744. (d) Corey, E. J.; Zhang, J. *Org. Lett.* **2001**, *3*, 3211−3214.

Scheme 7



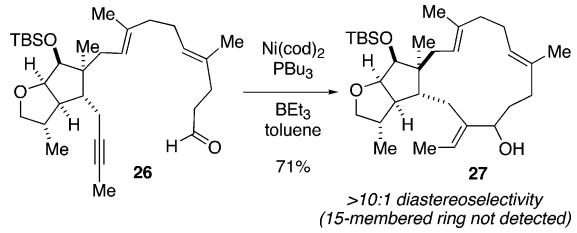
ketone with $NaBH_4$ and protection as its *tert*-butyldimethylsilyl ether accomplished this task, but unfortunately, cyclization of

Scheme 8



26 also afforded exclusively the 14-membered ring (**27**) in 71% yield (Scheme 9).

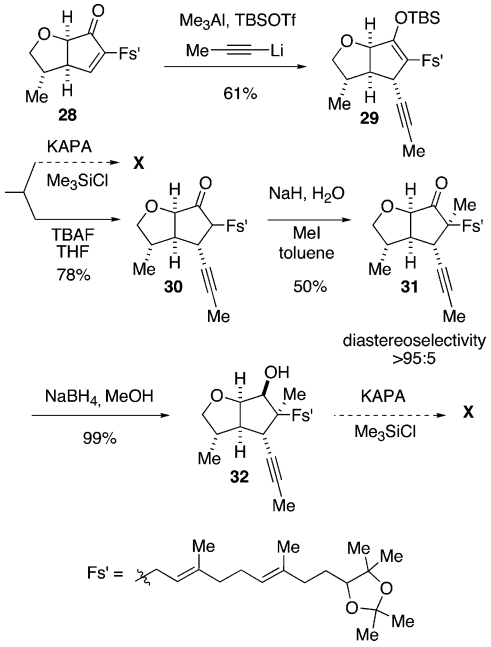
Scheme 9



Intramolecular Alkyne−Aldehyde Reductive Coupling Approach: Cyclization of an Alkynylsilane. Since changing nearby functional groups had no effect upon the cyclization regioselectivity, we next investigated the effects of altering the nature of the alkyne itself. In general, catalytic additions to internal acetylenes of the type $RCH_2-C\beta C$-Me, i.e., with substitutents nearly identical in electronic nature and steric demand, are typically nonregioselective.[24] In contrast, acetylenes of the type $R-C\beta C-SiMe_3$ couple with complete regioselectivity, favoring C−C bond formation adjacent to the $SiMe_3$ group.[10] Therefore, we targeted alkynylsilane **35** in hopes of observing the same regioselectivity in the catalytic macrocyclization similar to that seen in intermolecular cases.

An approach to making use of a KAPA-mediated isomerization[25] (KAPA = potassium 3-aminopropylamide) was undertaken (Scheme 10). Beginning with **28**, a 1,4-addition of

Scheme 10



1-lithio-1-propyne-$AlMe_3$ "ate" complex[26] afforded **29**. Following deprotection with TBAF, alkylation of **30** afforded **31** with greater than 95:5 diastereoselectivity, presumably due to the low steric demand of the propynyl group residing on the convex face of the bicyclic system.[27] Reduction by $NaBH_4$ furnished the desired product **29**. Unfortunately, attempts to utilize KAPA-mediated isomerizations of either **29** or **32**, followed by treatment with trimethylsilyl chloride, did not afford the desired alkynylsilanes. Fortunately, a remarkably functional group-tolerant alkyne cross metathesis[28] of **33**, using a catalyst

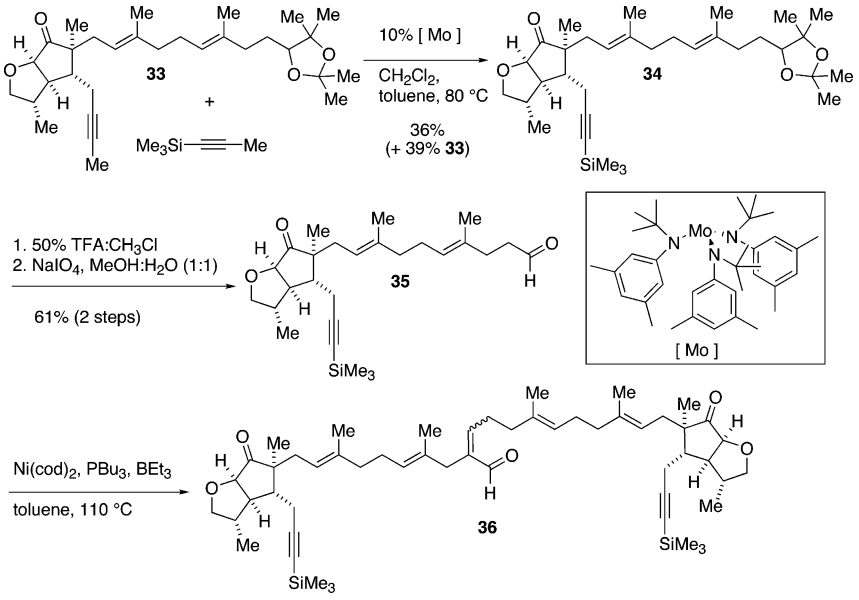
(24) Notable exceptions: (a) Et vs Me (2:1): Larock, R. C.; Yum, E. K. *J. Am. Chem. Soc.* **1991**, *113*, 6689−6690. (b) *i*-Bu vs Me (7.3:1): Molander, G. A.; Retsch, W. H. *Organometallics* **1995**, *14*, 4570−4575. (c) *n*-undecyl vs Me (2.4:1): Trost, B. M.; Ball, Z. T. *J. Am. Chem. Soc.* **2001**, *123*, 12726−12728.

(25) (a) Brown, C. A.; Yamashita, A. *J. Am. Chem. Soc.* **1975**, *97*, 891−892. (b) Midland, M. M.; Halterman, R. L. *Tetrahedron Lett.* **1981**, *22*, 4171−4172.

(26) Kim, S.; Park, J. K. *Synlett* **1995**, 163−164.

(27) We have observed that the diastereoselectivity of quaternary methylation reaction increases as the size of the β-substitutent decreases.

Scheme 11



developed by Cummins,[29] afforded the desired product (**34**) in 36% yield with 39% as recovered **33**. While removal of the acetonide and periodate cleavage of the resulting diol to **35** were straightforward, attempts at nickel-catalyzed reductive cyclization, even under forcing conditions (refluxing toluene), afforded only an aldol self-condensation product (**36**) and recovered starting material (Scheme 11).

This observation can be attributed to both the steric and electronic nature of the alkyne. We have observed in our investigations of alkyne scope in intermolecular couplings that alkynylsilanes generally exhibited reduced reactivity relative to internal acetylenes. In general, as the steric demand of the alkyne increases, as in the case of R**CH$_2$**−≡−Me versus ***t*-Bu**−≡−Me, reactivity decreases, and the electronic nature of the trimethylsilyl group likely reduces reactivity as well. For instance, (3-methyl-but-1-ynyl)benzene (Ph−β−***i*-Pr**) has been found to couple readily, whereas sterically similar phenylethynyltrimethylsilane (Ph−β−**SiMe$_3$**) exhibits markedly lower reactivity with various aldehydes.

From the previous cyclization experiments, it appears that the unusual regioselectivities observed may be rationalized through mechanistic considerations.[30] A recent report by Montgomery[31] suggests that the Ni(cod)$_2$/PBu$_3$ catalyst system can proceed through either an oxametallacyclopentene or through an alkenyl nickel intermediate (Figure 4). Taking into account these two contrasting mechanisms, four different transition states leading to the two macrocycles would be possible, as illustrated by intermediates **A**−**D**. Intermediates **A**/**B** lead to the 14-membered ring, while the **C**/**D** pair lead to the desired 15-membered ring. Intermediates **A**/**C** proceed through an oxametallacycle pathway, whereas regioisomeric intermediates **B**/**D** may form as a result of hydrometalation across the alkyne to form two possible alkenyl nickel intermediates.

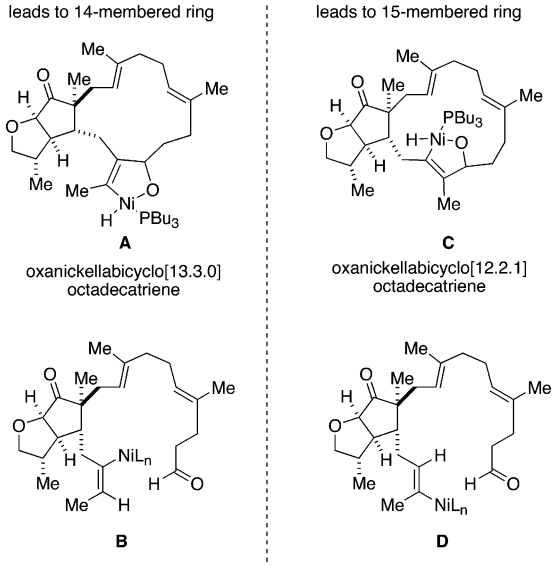


Figure 4. Putative intermediates in the formation of 14-membered and 15-membered rings.

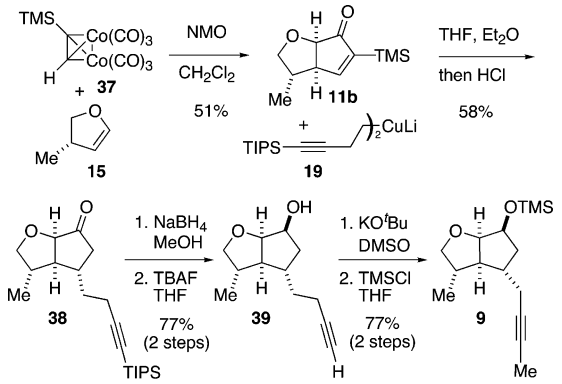
Our experiments would suggest that putative intermediates **C**/**D** leading to the 15-membered ring were highly disfavored relative to **A**/**B**. This bias toward **A**/**B** was originally postulated to have been caused by either the steric congestion of the C19 quaternary methyl group and/or the trans relationship of the C1/C15 stereocenters at the 5,15-ring junction. However, with no detectable formation of the 15-membered ring upon cyclization in the absence of C19, it appears more likely that the high barrier to **C**/**D** formation may be linked to the latter, which was not a factor included in model substrate **12**. If the cyclization proceeds via an oxametallacyclepentene (**A** vs **C**), the bicyclo[12.2.1] system in intermediate **C**, possessing a bridgehead olefin, may not form as readily as the bicyclo[13.3.0] found in **A**. Likewise, under the hydrometalation pathway (**B** vs **D**), incorporation of

(28) (a) Fürstner, A.; Mathes, C.; Lehmann, C. W. *J. Am. Chem. Soc.* **1999**, *121*, 9453−9454. (b) Fürstner, A.; Mathes, C. *Org. Lett.* **2001**, *3*, 221−223.
(29) (a) Laplaza, C. E.; Cummins, C. C. *Science* **1995**, *268*, 861−863. (b) Laplaza, C. E.; Odom, A. L.; Davis, W. M.; Cummins, C. C. *J. Am. Chem. Soc.* **1995**, *117*, 4999−5000. (c) Laplaza, C. E.; Johnson, A. R.; Cummins, C. C. *J. Am. Chem. Soc.* **1996**, *118*, 709−710. (d) Laplaza, C. E.; Johnson, M. J. A.; Peters, J. C.; Odom, A. L.; Kim, E.; Cummins, C. C.; George, G. N.; Pickering, I. J. *J. Am. Chem. Soc.* **1996**, *118*, 8623−8638.
(30) Oblinger, E.; Montgomery, J. *J. Am. Chem. Soc.* **1997**, *119*, 9065−9066.
(31) Mahandru, G. M.; Liu, G.; Montgomery, J. *J. Am. Chem. Soc.* **2004**, *126*, 3698−3699.

an extra (*E*)-double bond in **D** may be disfavored over **B** (exocyclic olefin) upon macrocycle formation. Finally, the added strain created by the trans relationship of the C1/C15 stereocenters may also bias the reaction to exclusive 14-membered ring formation. Unfortunately, this hypothesis could not be tested directly, since attempts to synthesize substrates with a cis relationship of the C1/C15 stereocenters led to epimerization to the thermodynamic trans product under all conditions attempted.

Intermolecular Alkyne−Aldehyde Reductive Coupling Approach. Since the intramolecular alkyne−aldehyde coupling approach consistently afforded 14-membered ring products, we aimed to overcome this regioselectivity problem through the assembly of the allylic alcohol by way of an *intermolecular* reductive coupling, using methods related to those we had developed in our laboratory. The synthesis of the alkyne fragment began with an NMO-promoted, intermolecular Pauson−Khand reaction between dihydrofuran **15** and the hexacarbonyldicobalt complex of trimethylsilylacetylene (**37**) to afford oxabicyclo[3.3.0]octenone **11b** in 51% yield (Scheme 12). As

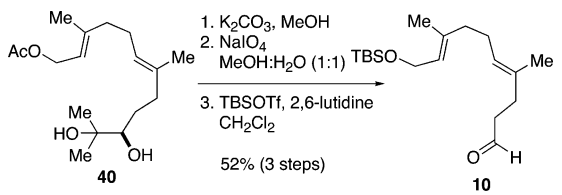
Scheme 12



observed in the Pauson−Khand reaction involving the farnesyl derived alkyne hexacobaltdicarbonyl complex (**16**, Scheme 5), no other diastereomers nor any of three other possible regioisomers could be detected (^{1}H NMR). Conjugate addition of a lithium dialkyl cuprate (**19**) afforded **38** which occurred with complete diastereoselectivity, as observed before. To place the triple bond in the proper position required for the catalytic reductive coupling, terminal acetylene **39** was isomerized with KO*t*-Bu in DMSO. Including protection of the secondary alcohol as a trimethylsilyl ether, **9** was provided in 77% yield over two steps.

Synthesis of the aldehyde coupling partner (**10**) commenced with diol **40**, obtained from site selective catalytic dihydroxylation of farnesyl acetate.[21] The acetate ester was cleaved quantitatively under basic conditions, and a sodium periodate cleavage of the unpurified triol afforded an aldehyde that was protected as a TBS ether (**10**) in 52% overall yield (Scheme 13).

Scheme 13

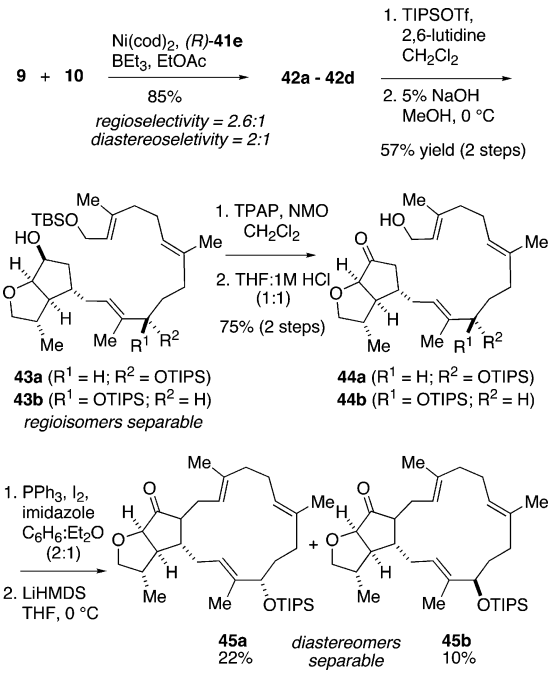


In the intramolecular reductive coupling approach described above, we had hoped for diastereocontrol of the C11 carbinol through a conformational bias during ring formation and/or ligand control. The absence of such a conformational bias in the intermolecular fragment coupling, however, predicted that diastereocontrol would be low, since the closest stereocenter would be two carbons removed from the site of reaction. In addition, little regiocontrol would also be expected as the catalytic process would have to differentiate between a methyl group vs an isobutyl-like group on the alkyne. Not surprisingly, the use of PBu_3 offered neither diastereoselectivity (1:1) nor regioselectivity (1.5:1).

We were pleased, however, to discover that our recently developed *P*-chiral ferrocenyl phosphine ligands[10] afforded a good level of control at the C11 stereocenter (Table 1). After evaluating a variety of these ligands, we found that a catalyst incorporating (*R*)-**41e** favored the diastereomer (2:1) and regioisomer (2.6:1) corresponding to (−)-terpestacin in a combined yield of 85% (Table 1, **42a**−**d**). Therefore, the desired allylic alcohol **42a** was obtained in an overall yield of 41% (85% × $^2/_3$ × 2.6/3.6). The diastereomer corresponding to 11-*epi*-terpestacin (**42b**) (terpestacin numbering) was obtained with *equal* regioselectivity and *equal and opposite* diastereoselectivity simply by using (*S*)-**41e**, the enantiomer of the ligand used in the terpestacin-series coupling. Notably, the use of (*R*)-**41a** provided the best diastereoselectivity (3:1) of all ligands examined. However, (*R*)-**41a** also gave reduced regiocontrol (2:1) and chemical yield (70%), corresponding to an overall 35% (70% × $^3/_4$ × $^2/_3$) yield of desired **42a**.

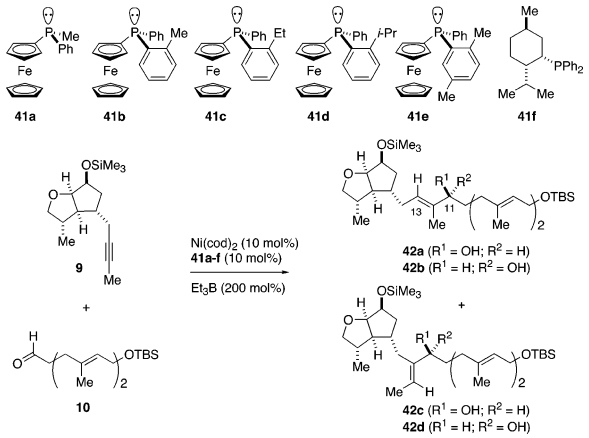
The choice of protective group on the newly formed allylic alcohol would prove crucial into the completion of the synthesis (Scheme 14). The main factors considered were balancing

Scheme 14



functional group compatibility with ease of removal following the late stage alkylation (installation of C19). While a pivaloyl ester of the secondary allylic alcohol initially appeared to be an attractive choice because of its ease of introduction and

Table 1. Evaluation of Phosphine Ligands in Catalytic, Stereoselective, and Regioselective Fragment Coupling (Alkyne **9** + Aldehyde **10**)



entry	ligand	solvent	temperature (°C)	yield[a] (%)	regioselectivity[b]	diastereoselectivity[c] (C11)
1	Bu_3P	toluene	23	70	1.5:1	1:1
2	**41f**	EtOAc	23	68	1:1.5	2:1
3	**41f**	EtOAc/DMI (1:1)	23	77[d]	n/a	
4	**41a**	EtOAc	23	81	2:1	2.5:1
5	**41a**	EtOAc	0	70	2:1	3:1
6	**41a**	EtOAc/DMI (1:1)	0	18	2:1	2:1
7	**41a**	THF	0	46	1.8:1	3:1
8	**41a**	toluene	0	35	2:1	3:1
9	**41a**	acetone	0	65	2:1	3:1
10	**41b**	EtOAc	0	65	2:1	2:1
11	**41c**	EtOAc	0	75	2:1	2:1
12	**41d**	EtOAc	0	83	2.5:1	2:1
13	**41e**	EtOAc	0	85	2.6:1	2:1
14	**41e**	EtOAc	−12	52	2.9:1	3:1
15	**41d**	EtOAc	−12	57	3:1	3:1

[a] Combined yield of all allylic alcohol products (**42a**−**d**). [b] Regioselectivity (**42a** + **42b**/**42c** + **42d**) determined by ^{1}H NMR. [c] Diastereoselectivity (**42a** + **42c**/**42b** + **42d**) estimated by ^{1}H NMR. [d] "Alkylative coupling" (Et at C13 instead of H).

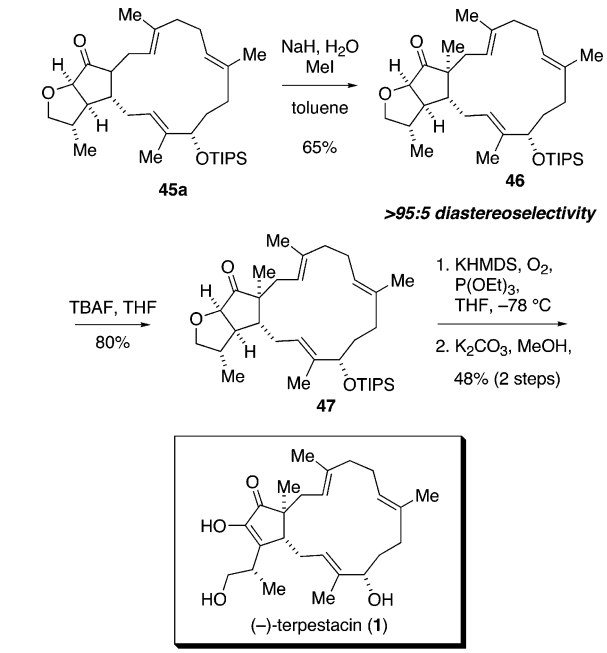
removal, we found that this protective group was not compatible under the conditions required for the installation of the quaternary methyl group.[32]

Therefore, the triisopropylsilyl ethers of **42a**−**d** were prepared, and the trimethylsilyl group was removed using 5% sodium hydroxide in methanol, giving **43a**−**d** in 80% yield over the two steps. At this stage, the regioisomers formed in the fragment coupling reaction were separated, and the desired regioisomers (**43a** and **44b**) were oxidized under Ley's conditions to afford the desired ketones in 89% yield. After removal of the primary TBS groups (1 M HCl/THF 1:1) in 84% yield, **44a** and **44b** were converted to the allylic iodides and treated with LiHMDS to afford a separable mixture of macrocycles **45a** and **45b** via a ketone enolate alkylation in a combined, an overall two-step yield of 32% (22% overall of **45a**).

As we had observed in the intramolecular reductive coupling approach, installation of the critical quaternary methyl group (C19) at C1 was best accomplished using methyl iodide, (presumably) sodium hydroxide generated from sodium hydride (300%), and H_2O (200 mol % relative to **45a**) giving the desired (**46**) in > 95:5 dr (NOE), with no trace of methylation at the 5,5-ring junction (Scheme 15).

Completion of the synthesis of (−)-terpestacin thus required three further transformations. The TIPS protective group was smoothly cleaved with TBAF to afford the desired secondary alcohol (**47**). Treatment of **47** with 300 mol % of potassium hexamethyldisilazane and $P(OEt)_3$ under an atmosphere of O_2 effected the enolate hydroxylation,[33] and opening of the hemiketal was best effected with potassium carbonate in methanol, furnishing (−)-terpestacin (**1**). Synthesis of 11-*epi*-

Scheme 15

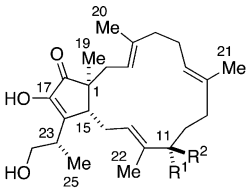


(32) Attempted alkylation of the pivaloyl-ester resulted in the isolation of multiple unidentifiable products.

terpestacin (**2**) was prepared utilizing the analogous method. Overall, preparation of **1** and **2** each required 17 steps from **15** (longest linear sequence).[34]

Comparison of 1 and 2 to Natural Samples of Terpestacin and Siccanol. The spectroscopic data we obtained for our synthetic (−)-terpestacin were identical in all respects to those previously reported for natural and synthetic material, and comparison of (−)-terpestacin differed from our synthetic 11-*epi*-terpestacin, particularly in the chemical shifts of the protons 3, 13, 15, and 19, as illustrated in Table 2. Remarkably, the

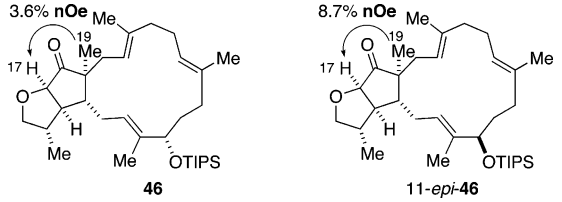
Table 2. Selected ^{1}H NMR Data for Terpestacin (**1**), 11-*epi*-Terpestacin (**2**), and Siccanol



1 (R^1 = OH; R^2 = H; terpestacin)
2 (R^1 = H; R^2 = OH; 11-*epi*-terpestacin)

carbon	terpestacin (Oka, Myers, Jamison)	11-*epi*-terpestacin (Jamison)	siccanol (Miyagawa)
2	1.68−1.80, 2.40	2.05−2.27	1.75, 2.36
3	**5.25**	***5.34***	**5.25**
5	1.90−2.04, 2.22−2.30	1.98, 2.05−2.27	2.01, 2.24
6	2.09−2.12, 2.22−2.30	2.05−2.27	2.11, 2.26
7	5.14	5.13	5.13
9	1.68−1.80, 2.09−2.12	1.70−1.88, 2.05−2.27	1.78, 2.18
10	1.68−1.80	1.70−1.88	1.70, 1.75
11	4.06	4.06	4.07
13	**5.41**	***5.50***	**5.38**
14	1.90−2.04, 2.45	1.70−1.88, 2.50	1.92, 2.44
15	**2.72**	***2.57***	**2.72**
19	**1.01**	***1.13***	**0.99**
23	2.68	2.7	2.66
24	3.83, 3.90	3.83, 3.89	3.80, 3.85
25	1.29	1.30	1.29

chemical shift of the proton at C11 was identical for 11-*epi*-terpestacin and (−)-terpestacin, while the biggest difference was observed for C19 (δ 0.99 vs δ 1.13), initially suggesting to us that the C19 diastereomer might have been obtained in the alkylation of ketone **45b**. To eliminate this possibility, separate NMR experiments conducted with **46** and 11-*epi*-**46** (Figure 5)



46 11-*epi*-**46**

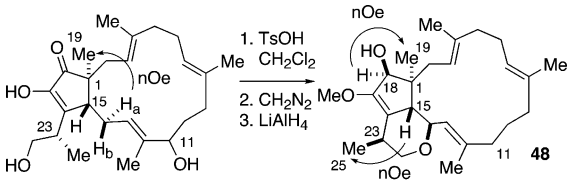
Figure 5. Both **46** and 11-*epi*-**46** exhibit NOE between H17 and H19.

showed an NOE between H17 and H19 in both cases, consistent with the conclusion that both compounds have the same relative configurations about C19.

Having established that 11-*epi*-**47** leads to 11-*epi*-terpestacin, a comparison of siccanol provided to us from Prof. Miyagawa did not agree with our data for synthetic 11-*epi*-terpestacin and, to our surprise, was *indistinguishable* from (−)-*terpestacin*, confirming a structural reassignment: "siccanol" is (−)-terpestacin, not 11-*epi*-terpestacin (Table 2).

The sequence of events that led Miyagawa to his original assignment of "siccanol" as 11-*epi*-terpestacin can be explained by his original structural elucidation studies and an unusual chain of events, beginning with Oka's discovery of terpestacin nearly 10 years before that. As Oka had done with natural terpestacin, Miyagawa's structural determination of "siccanol" began with differentiating the protons on C14 (H_a and H_b) based on their coupling constants with H15 (Scheme 16). An NOE between

Scheme 16. Structural Elucidation of Terpestacin (Oka) and Siccanol (Miyagawa)



48

Experiment	Conclusion
- Examination of coupling constants of H_a and H_b to H15.	- Differentiation of H_a and H_b
- nOe between Ha and H19	- trans relationship of H15 and H19
- nOe between H15 and H25 observed in **48**	- *relative* configurations of C1, C15, and C23
- nOe between H18 and H19	- *relative* configurations of C18 and C19
- chiral exciton analysis of benzoyl ester of **48**	- *absolute* configurations of C1, C15, and C23

H_a and H19 indicated a trans relationship between H15 and H19. Following acid-catalyzed elimination, methylation of the enol with diazomethane and reduction to afford **48**, an NOE between H15 and H25 established the *relative* relationships of stereocenters C1, C15, and C23. The *absolute* configuration of C18 was determined through the chiral exciton method after formation of the benzoyl ester of **48**, and from the presence of a nOe between H18 and H19, the *absolute* configurations of the remaining stereocenters were deduced, except for C11. A Mosher ester analysis led to the assignment that the C11 stereocenter was (*R*), consistent with 11-*epi*-terpestacin, whereas Oka assigned the C11 stereocenter as (*S*), also based on a Mosher analysis. Oka then proceeded further to obtain an X-ray crystal structure of terpestacin to confirm all relative stereocenters, but Miyagawa did not characterize "siccanol" crystallographically.

Given that "siccanol" was identical in every respect to natural terpestacin, including the *absolute* configurations of C1, C15, and C23, but possessed a specific rotation of opposite sign, it was certainly reasonable for Miyagawa to conclude that they had isolated the diastereomer of terpestacin at C11. Since Myers' total syntheses of terpestacin and fusaproliferin were published at about the same time as Miyagawa's report of "siccanol", it is likely that neither group would be aware of each other's findings through the chemical literature. Conse-

(33) (a) Gardner, J. N.; Carlon, F. E.; Gnoj, O. *J. Org. Chem.* **1968**, *33*, 3294−3297. (b) Harwig, W.; Born, L. *J. Org. Chem.* **1987**, *52*, 4352−4358. (c) Belletire, J. L.; Fry, D. F. *J. Org. Chem.* **1988**, *53*, 4724−4279.

(34) *epi*-terpestacin (**1b**) was prepared by the same sequence from 11-*epi*-**36**. The same NOE shown for **37** was observed in 11-*epi*-**37**.

quently, Miyagawa would not have known that the specific rotation of terpestacin originally reported by Oka was an artifact.

Thus the only remaining difference between Oka's determination of terpestacin and Miyagawa's of "siccanol" is the result of a Mosher ester analysis for the assignment of the stereochemistry of C11. No experimental details are provided in Miyagawa's paper, but the following excerpt suggests a plausible explanation for this discrepancy: "...a set of (*R*)-MTPA and (*S*)-MTPA esters (at C11) was prepared ...(from)... the *respective* MTPA *chlorides*." (Italics added for emphasis.) The Cahn−Ingold−Prelog convention for assigning absolute configuration indicates that the (*R*)-MTPA chloride leads to the (*S*)-MTPA ester. Therefore, if by "respective" Miyagawa meant that the (*R*)-acid chloride was used to (incorrectly) prepare the (*R*)-MTPA ester, then the assignment of the stereochemistry of C11 would be the opposite of the actual configuration. Professor Miyagawa, in addition to graciously providing us with a copy of the original notebook pages describing his Mosher ester determination, has corroborated this hypothesis.[35]

In short, the combination of the originally reported (artifactual) specific rotation of natural terpestacin and a Mosher ester analysis led to the original assignment of "siccanol" as 11-*epi*-terpestacin. However, our syntheses of both diastereomers by way of catalyst-controlled, stereoselective fragment couplings of late-stage alkyne and aldehyde intermediates indicate that 11-*epi*-terpestacin (**2**) has yet to be isolated from natural sources. That is, the natural product "siccanol" is not diastereomeric to naturally occurring terpestacin ((−)-**1**) but, in fact, is (−)-terpestacin itself.

(35) Miyagawa, H. Personal communication.

Acknowledgment. We are grateful to Professor Hisashi Miyagawa, Kyoto University, both for a generous supply of natural siccanol, as well as a copy of the primary data obtained in his Mosher ester determination of the configuration of C11 in this natural product. We thank Ryan K. Zeidan (Pfizer SURF) and Jianlong Tan for experimental assistance, as well as Fran Stephens and Professor Christopher C. Cummins for a generous donation of the tris(amido)molybdenum (III) complex used in the alkyne cross metathesis study. This work was supported by the National Institute of General Medical Sciences (GM-063755) and by Bristol Myers-Squibb and Boehringer-Ingelheim (research assistantships to J.C.). We also thank the NSF (CAREER CHE-0134704), Amgen, GlaxoSmithKline, Johnson & Johnson, Merck Research Laboratories, the Sloan Foundation, 3M, and MIT for generous financial support. The NSF (CHE-9809061 and DBI-9729592) and NIH (1S10RR13886-01) provide partial support for the MIT Department of Chemistry Instrumentation Facility.

Supporting Information Available: Experimental procedures and data for **1**, **2**, **8**−**16**, **18**, **20**−**35**, **38**−**40**, and **42**−**47**. This material is available free of charge via the Internet at http://pubs.acs.org.

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