JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

COMMUNICATION

pubs.acs.org/JACS

A Concise, Stereocontrolled Total Synthesis of Rippertenol

Scott A. Snyder,* Daniel A. Wespe, and J. Marian von Hof

Department of Chemistry, Columbia University, Havemeyer Hall, 3000 Broadway, New York, New York 10027, United States

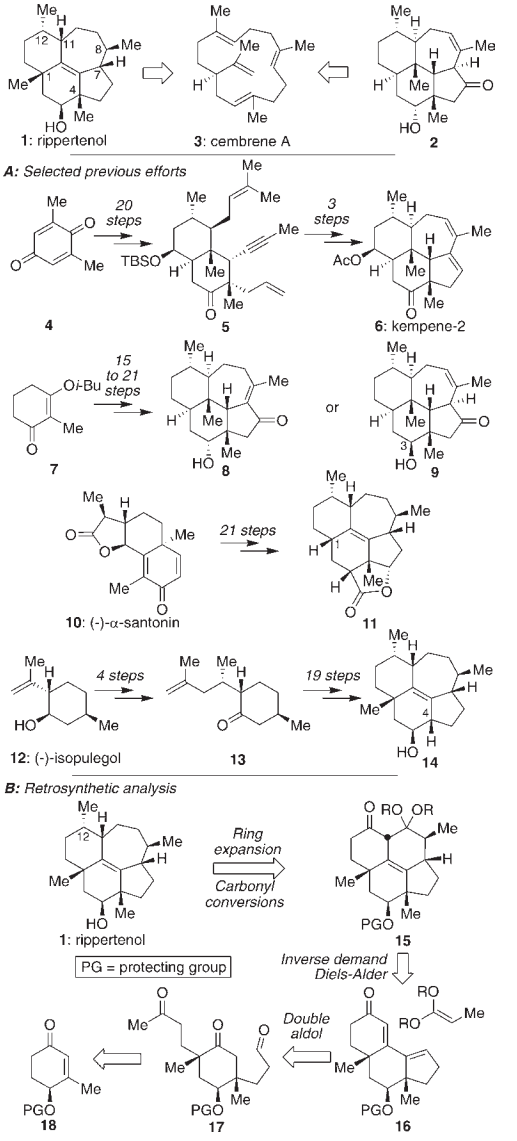
Supporting Information

ABSTRACT: The first total synthesis of the unique terpene rippertenol, a molecule with dense stereochemical complexity arrayed on a compact framework largely devoid of functional groups, is described. Key elements include orchestrated and unique applications of aldol condensations, Diels–Alder chemistry, and a ring expansion to advance a chiral starting material containing a single chiral center into the final target in a concise and diastereocontrolled manner.

Throughout the world, termites of the *Nasutitermes* genus utilize an array of structurally unique terpenes to defend themselves against potential predators.[1] Among the most complex of these materials are tightly packed, polycyclic, and stereochemically dense molecules which formally derive from cembrene A (**3**, Scheme 1). Nearly all (such as **2**) possess the conserved structural patterning of **3** as shown in Scheme 1, with variation between individual members resting largely on oxidation patterns.[2] There is one, however, that is structurally more distinct. That molecule is rippertenol (**1**, 3α-hydroxy-15-rippertene), which has a unique rearranged cembrene skeleton that likely results from 1,2-methyl migration at some point during its biosynthesis from **3**.[3] Despite several attempts,[4] this molecule has not succumbed to laboratory synthesis in the more than 30 years since its original isolation, presumably due to the general challenge associated with forging materials that are stereochemically rich but devoid of functionality to guide the formation of such complexity. Here, we show how rippertenol's seven stereogenic centers (two of which are quaternary) and compact polycyclic framework can be prepared in a diastereocontrolled and concise manner through a sequence whose step economy resulted from using each functional group multiple times to form and/or and become carbon-based components of the target.

Historically, the complexity of these termite-derived natural products has proven quite challenging. To date, only select members of the kempenes (such as **6**) have been successfully synthesized by the groups of Dauben[5] and Metz,[6] with the more recent of these efforts shown within Scheme 1. While many approaches[7] have proven capable of forging these carbocyclic cores, they are unable to coerce a single stereocenter, double bond, or methyl group to reside in the requisite location and thus fall short of a completed total synthesis. For example, the Paquette group smoothly prepared both **8** and **9** but found that they could neither isomerize the double bond within **8** out of conjugation nor invert the chirality of the alcohol en route to **9** to ultimately afford **2**.[8] These general challenges have proven even more difficult to solve with rippertenol (**1**) itself, where the absence of functionality affords few, if any, opportunities for structural corrections. Indeed, two separate endeavors from the

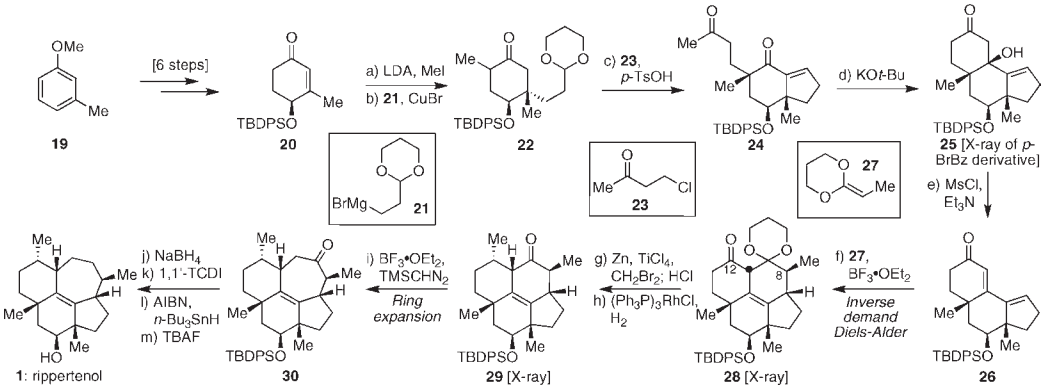
Scheme 1. Structure of Rippertenol (1) and a Related Terpene (2) Derived from Cembrene A (3), Synthetic Approaches to Such Frameworks, and Our Retrosynthetic Analysis of 1



Received: March 29, 2011
Published: May 17, 2011

   dx.doi.org/10.1021/ja202859f | J. Am. Chem. Soc. 2011, 133, 8850–8853

Scheme 2. Total Synthesis of Rippertenol[a]



[a] Reagents and conditions: (a) LDA (1.1 equiv), MeI (2 equiv), THF, −78 to 25 °C, 12 h, 88%, 94% brsm (based on recovered starting material); (b) **21** (2.5 equiv), CuBr•Me_2S (0.63 equiv), −78 to −50 °C, THF, 5.5 h, 86%; (c) **23** (1.5 equiv), *p*-TsOH (0.1 equiv), benzene, 80 °C, 48 h; (d) KO*t*-Bu (0.2 equiv), *t*-BuOH, THF, 25 °C, 45 min, 43% over two steps; (e) Et_3N (15 equiv), MsCl (6.0 equiv), CH_2Cl_2, 0 °C, 30 min, 72%; (f) BF_3•OEt_2 (0.9 equiv), **27** (2 equiv), CH_2Cl_2, −78 °C, 10 min, 68%, 2.6:1 dr; (g) Zn (12.1 equiv), CH_2Br_2 (4.0 equiv), $TiCl_4$ (3.0 equiv), THF, 25 °C, 16 h; HCl, 46%; (h) $(Ph_3P)_3RhCl$ (0.15 equiv), H_2 (1.5 atm), benzene, 25 °C, 12 h, 98%, >19:1 dr; (i) BF_3•OEt_2 (1.0 equiv), $TMSCHN_2$ (1.0 equiv), CH_2Cl_2, −78 to −50 °C, ∼3.5 h, 21% (71% brsm); (j) $NaBH_4$ (5.0 equiv), MeOH/THF (2/1), 0 to 25 °C, 1 h, 93%; (k) 1,1′-thiocarbonyldiimidazole (10 equiv), 4-DMAP (0.4 equiv), THF, 70 °C, 16.5 h, 66%; (l) *n*-Bu_3SnH (10 equiv), AIBN (0.25 equiv), toluene, 100 °C, 15 min, 69%; (m) TBAF (10 equiv), THF, 45 °C, 20 h, 93%.

Metz group came close starting from either (−)-α-santonin (**10**) or (−)-isopulegol (**12**). However, in each case, one methyl group could not be incorporated onto the final scaffold.[4]

Drawing from the lessons of these studies, we sought to develop a route to **1** that would stereoselectively install both the C-1 and C-4 methyl groups early in the sequence to use their pseudoaxial steric bulk to direct further transformations. Also, to render our route as concise as possible, we sought a design wherein any functional group utilized would have to exist for at least two specific purposes in the synthesis, be it C−C bond forming events, eventual conversion into a methyl group, chiral control, or combinations thereof. A retrosynthetic analysis that fits these goals is shown in Scheme 1.

As indicated, we decided to leave the formation of the 7-membered ring of **1** as the final annulation event. While potentially an illogical retrosynthetic choice in that this ring includes nearly half of the stereochemical complexity of the target (and thus might be the most challenging of all the rings to form in a stereocontrolled fashion), it was the mode of its anticipated synthesis that rendered the idea appealing. As shown, following the retrosynthetic conversion of the C-12 methyl group into a carbonyl and conversion of the 7-membered ring into a 6-membered alternative (**15**), we anticipated that a facially selective, inverse electron demand Diels−Alder reaction[9,10] with a suitably electron-rich dienophile could effect its diastereocontrolled formation as governed by the chirality within diene **16**. Thus, the ketone functional group within **16** would help unite the two fragments and then become a methyl group (via methylenation and a facially selective hydrogenation), while the ketal within the dienophile would function in the same initial goal and then become a handle through which to effect a ring expansion and complete **1**. To test this idea, we anticipated that **16** could arise through a set of orchestrated aldol condensations from precursor **17**, with a stereocontrolled synthesis of this key material being potentially achievable through controlled alkylations of starting material **18**. If true, then its lone chiral center would be the stereochemical lynchpin to the entire operation.

Using chemistry previously disclosed by Piers and Oballa,[11] we began our efforts to reduce this plan to practice by converting 3-methylanisole (**19**) into the known TBDPS-protected **20** over the course of six standard synthetic operations and on multigram scale (see Supporting Information (SI) for full details).[12] Following α-methylation, we were then able to add Grignard reagent **21** through a copper(I)-promoted conjugate alkylation to forge **22** as a mixture of diastereoisomers with complete control about the newly formed quaternary center. The observed stereocontrol is consistent with literature precedent,[11] though that example lacked the additional α-methyl group of the starting material; intriguingly, this level of stereocontrol required the specific 1,3-dioxane-based protecting group of **21**, as its corresponding 1,3-dioxolane led to both reduced stereoselectivity and yield.[13]

From here, we hoped to add the remaining atoms of the second alkyl side chain and complete a tandem set of aldol cyclizations to forge **26** in a single pot; as matters transpired, the strain and uniqueness of the system ultimately required a stepwise approach to achieve these goals. We began by treating **22** with chloride **23** in the presence of *p*-TsOH in refluxing benzene; this protocol was pioneered by Paquette to accomplish a variant of a standard Robinson annulation.[14] Here, it effected a fully diastereocontrolled alkylation, deprotection, and aldol condensation sequence leading to **24** wherein the second and final condensation had not been achieved; a series of studies (not shown) indicates that the alkylation reaction precedes the condensation in this sequence. The methyl ketone within **24**, however, proved highly resistant to reacting with the newly formed α,β-unsaturated ketone under several conditions (including Stork enamine chemistry).[15] However, we found that if we treated ketone **24** with KO*t*-Bu in a mixture of *t*-BuOH/THF at 25 °C for 45 min, we were able to generate tertiary alcohol **25**, with subsequent elimination using MsCl/Et_3N affording diene **26**. The overall yield for these three steps was 31% (∼80% yield for each of the five separate chemical events).

The stage was now set to test the ability of an inverse-demand Diels−Alder reaction to stereospecifically forge three chiral

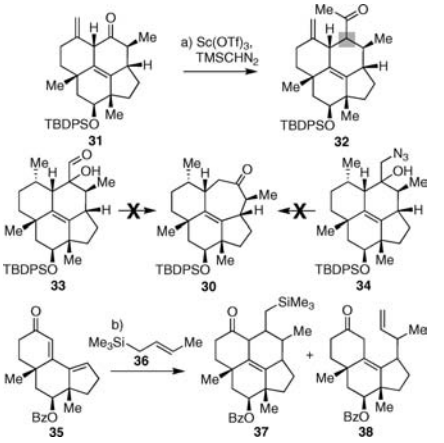
dx.doi.org/10.1021/ja202859f |*J. Am. Chem. Soc.* 2011, 133, 8850–8853

centers and generate the final ring of the target. Pleasingly, use of electron-rich dienophile **27**[16] along with slightly substoichiometric amounts of BF_3•OEt_2 in CH_2Cl_2 at −78 °C achieved that goal in just 10 min, providing **28** in 68% yield with 2.6:1 diastereoselectivity favoring the drawn product. It is important to note that only through Lewis acid activation did this reaction occur,[17] constituting a rare example of such a Lewis acid promoted process in an inverse-demand setting.[18] Moreover, the specific use of 2-ethyliden-1,3-dioxane (**27**) as the dienophile was predicated on a desire to have the protecting group survive the Diels−Alder sequence to differentiate what are effectively two carbonyls within **28**; acyclic variants tested showed a proclivity to hydrolyze following successful cycloaddition or in subsequent chemistry. As confirmation that the reaction proceeded as desired, the major diastereomer of **28** could be crystallized selectively from the mixture, providing the means to establish its stereochemistry as drawn in Scheme 2 through X-ray analysis. The minor isomer could be separated through column chromatography and, based on NMR analysis (see SI), had a structure that was diastereomeric only about the C-8 methyl group (rippertane numbering), indicating a complete facial preference for the addition.[19] In practice, such a purification proved unnecessary as only the major diastereomer of **28** was competent in the subsequent reactions needed to reach **1**, with the minor isomer degrading simply upon standing in certain solvents overnight or at some point in the ensuing sequence.

Pressing forward, the goal now was to convert the C-12 carbonyl (rippertane numbering) into a methyl group through a methylenation/hydrogenation sequence and utilize the protected ketone as a means to effect a ring expansion. Very careful orchestration was needed in executing these events as the steric bulk around these two positions proved impactful on any transformation attempted. We began by methylenating the ketone within **28**. Though this starting material proved stable to both air and silica gel, it was sensitive to a range of reaction conditions. The simple ylide derived from methyltriphenylphosphonium bromide, for instance, effected deprotonation adjacent to the ketone and expelled one arm of the dioxane protecting group to forge a new α,β-unsaturated (vinylogous ester) system (structure not shown). Pleasingly, however, we found that the mild Takai/Oshima−Lombardo procedure,[20] followed by an acidic aqueous workup (HCl) to cleave the 1,3-dioxane protecting group, could provide the desired intermediate in 46% yield in a single pot without isomerizing the newly formed olefin into conjugation.[21] Subsequent hydrogenation using Wilkinson's catalyst provided the C-12 center of **29** with at least 19:1 diastereoselectivity based on ^{1}H NMR analysis and in 98% yield; its favorable stereochemical outcome was confirmed by X-ray analysis.[22]

With this groundwork laid, the final critical operation, ring expansion to forge **30**, proved to be the most difficult and capricious of the sequence. Indeed, following much study we found that it could be achieved under Lewis acid promotion, but in reasonable yield only under specific conditions (1 equiv each of BF_3•OEt_2 and $TMSCHN_2$ in CH_2Cl_2 from −78 to −50 °C). Changing any of these variables led either to no reaction or to 8-membered ring formation in addition to **30**.[23] This outcome is suggestive of the enhanced accessibility of the ketone within **30** relative to starting material as well as the absence of any silyl enol ether ring-expanded intermediate that could have prevented a double addition.[24] Though the isolated yield for this process was low (21%), it was 71% if recovered starting material was taken into account. We note that the regioselective nature of this

Scheme 3. Additional Approaches To Form Rippertenol's 7-Membered Ring[a]



[a] Reagents and conditions: (a) $Sc(OTf)_3$ (1.0 equiv), $TMSCHN_2$ (20 equiv), CH_2Cl_2, 0 to 25 °C, 1 h, 33%; (b) $TiCl_4$ (1.3 equiv), **36** (1.5 equiv), CH_2Cl_2, −78 to 0 °C, 2 h, 25% of **37**, 18% of **38**.

expansion was not expected, though the location of the migrating bond relative to the central alkene may be the controlling factor. Equally intriguing, beyond the specificity of the reagents for the success of this process, it was also substrate specific. For example, as shown in Scheme 3, if the ring expansion was attempted with **31** under the same conditions as above, only starting material was recovered, with use of a different Lewis acid and excess $TMSCHN_2$ leading instead to methyl ketone **32** (forged as a single diastereomer with stereochemistry unestablished at the highlighted center; the structure was tentatively assigned through NMR and X-ray diffraction). Also unsuccessful were other variants of Tiffaneau−Demjanov chemistry,[25] with neither **33** nor **34** affording ring-expanded variants in detectable yields.

Nevertheless, with a synthesis of **30** achieved (Scheme 2), **1** was then completed through four final, conventional operations to afford material that was spectroscopically identical (^{1}H NMR, ^{13}C NMR, IR, HRMS) to that obtained from natural sources. As such, the total step count was 19,[26] of which only 13 steps were required following the synthesis of known starting material **20**. Given the published potential to form **20** in enantiopure form, the synthesis is formally enantioselective. To put the developed approach in context, it is worth noting that if the synthetic goal is the direct incorporation of a 7-membered ring onto a framework such as **26** or **35** (Scheme 3), present capabilities in the realm of [4 + 3]-cycloadditions do not provide the needed power.[27] Indeed, numerous studies to effect such a process in our laboratory, including those with silane **36**,[28] afforded only products of stepwise addition pathways (such as **37** and Sakurai product **38**) through nonstereocontrolled bond constructions which led, at best, to 6-membered rings (as regiocontrolled by the β-silicon effect). As such, the uniqueness and stereocontrol of the developed solution has much potential to address other problems in 7-membered ring synthesis beyond rippertenol.

In conclusion, the first total synthesis of rippertenol (**1**) has been achieved through a route that rapidly and controllably forged the stereochemical complexity of a functionally deficient terpene through operations deploying all functional groups for multiple purposes. Key discoveries include (1) a unique aldol-based condensation sequence to forge diene **26**; (2) a Lewis acid

promoted inverse-demand Diels–Alder reaction to set nearly half of the target's stereocenters in a single operation; (3) several highly orchestrated and substrate-specific events to finalize the target, foremost of which was a particularly challenging ring expansion; and (4) the observation on several occasions that remote chiral centers on the rippertane framework possessed the directing ability to lead to high diastereocontrol for new centers.

■ ASSOCIATED CONTENT

Supporting Information. Detailed experimental procedures, copies of all spectral data, and full characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author
sas2197@columbia.edu

■ ACKNOWLEDGMENT

We thank the NSF (CHE-0619638) for an X-ray diffractometer and Prof. Gerard Parkin, Mr. Wesley Sattler, and Mr. Aaron Sattler for performing all of the crystallographic analyses. Financial support was provided by Columbia University, Bristol-Myers Squibb, Eli Lilly, the Swiss Benevolent Society of New York (predoctoral fellowship to D.A.W.), and the Deutscher Akademischer Austausch Dienst (postdoctoral fellowship to J.M.v.H.). S.A.S. is a fellow of the Alfred P. Sloan Foundation.

■ REFERENCES

(1) (a) Prestwich, G. D. *Tetrahedron* **1982**, *38*, 1911. (b) Baker, R.; Walmsley, S. *Tetrahedron* **1982**, *38*, 1899.

(2) For the isolation of **2**, see: Prestwich, G. D.; Lauher, J. W.; Collins, M. S. *Tetrahedron Lett.* **1979**, *20*, 3828.

(3) (a) Prestwich, G. D.; Spanton, S. G.; Lauher, J.; Vrkoč, J. *J. Am. Chem. Soc.* **1980**, *102*, 6825 and references therein. Since this report, rippertenol has been isolated on at least two additional occasions: (b) Laurent, P.; Daloze, D.; Pasteels, J. M.; Braekman, J. C. *J. Nat. Prod.* **2005**, *68*, 532. (c) Chuah, C.-H. *Biochem. Syst. Ecol.* **2007**, *35*, 600.

(4) (a) Metz, P.; Bertels, S.; Fröhlich, R. *J. Am. Chem. Soc.* **1993**, *115*, 12595. (b) Hennig, R.; Metz, P. *Angew. Chem., Int. Ed.* **2009**, *48*, 1157. For a partial approach, see:(c) Kreuzer, T.; Metz, P. *Eur. J. Org. Chem.* **2008**, 572.

(5) Dauben, W. G.; Farkas, I.; Bridon, D. P.; Chuang, C.-P.; Henegar, K. E. *J. Am. Chem. Soc.* **1991**, *113*, 5883.

(6) Schubert, M.; Metz, P. *Angew. Chem., Int. Ed.* **2011**, *50*, 2954.

(7) For selected studies to prepare such molecules, see: (a) Caussanel, F.; Wang, K.; Ramachandran, S. A.; Deslongchamps, P. *J. Org. Chem.* **2006**, *71*, 7370. (b) Zhao, L.; Burnell, D. J. *Org. Lett.* **2006**, *8*, 155. (c) Kato, T.; Tanaka, M.; Hoshikawa, M.; Yagi, M. *Tetrahedron Lett.* **1998**, *39*, 7553.

(8) Paquette, L. A.; Sauer, D. R.; Cleary, D. G.; Kinsella, M. A.; Blackwell, C. M.; Anderson, L. G. *J. Am. Chem. Soc.* **1992**, *114*, 7375.

(9) Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 1668.

(10) For reviews, see: (a) Markó, I. E.; Evans, G. R.; Seres, P.; Chellé, I.; Janousek, Z. *Pure Appl. Chem.* **1996**, *68*, 113. (b) Boger, D. L.; Patel, M. *Prog. Heterocycl. Chem.* **1989**, *1*, 30.

(11) Piers, E.; Oballa, R. M. *J. Org. Chem.* **1996**, *61*, 8439.

(12) We prepared this piece racemically. It has been formed with high enantiocontrol through a kinetic resolution mediated by pig liver esterase with its acylated variant (see ref 11). In our own hands, we were able to obtain 84% ee through such a resolution process in initial experiments on a small scale; optimization is expected to enrich that outcome to the levels originally reported and on a preparative scale.

(13) We attribute this unique result to the effect of the differential metal coordination and/or aggregation state. We note that early approaches to **24** and **26** attempted to use the approach developed in the following manuscript, but the formation of the correct side chains proved unachievable through oxidation chemistry: Enquist, J. A.; Stoltz, B. M. *Nature* **2008**, *453*, 1228.

(14) Paquette, L. A.; Belmont, D. T.; Asu, Y. L. *J. Org. Chem.* **1985**, *50*, 4667.

(15) Formation of systems such as **26** are quite rare. For conditions that have worked in select cases, but which did not work for our substrates, see: Dana, G.; Weisbuch, F. *Tetrahedron* **1974**, *30*, 2879.

(16) Crivello, J. V.; Malik, R.; Lai, Y.-L. *J. Polym. Sci., Part A: Polym. Chem.* **1996**, *34*, 3091.

(17) Of other Lewis acids attempted, $TiCl_4$ afforded a small amount of product (~16% yield), while neither $SnCl_4$ nor $Sc(OTf)_3$ led to any reaction. Under thermal conditions, starting material decomposed.

(18) For recent examples, see: (a) El Sous, M.; Ganame, D.; Tregloan, P.; Rizzacasa, M. A. *Synthesis* **2010**, 3954. (b) Kessler, S. N.; Wegner, H. A. *Org. Lett.* **2010**, *12*, 4062. (c) Abraham, C. J.; Paull, D. H.; Scerba, M. T.; Grebinski, J. W.; Lectka, T. *J. Am. Chem. Soc.* **2006**, *128*, 13370. Formal variants of the process exist as well: Davies, H. M. L.; Dai, X. *J. Org. Chem.* **2005**, *70*, 6680.

(19) Formally, we cannot rule out the possibility that this reaction is a tandem Mukaiyama–Michael–aldol reaction instead of an inverse-demand Diels–Alder reaction. Worth noting is that the minor diastereomer still reflects an *endo* addition based on the other oxygen atom of the 1,3-dioxane system with respect to the diene.

(20) (a) Takai, K.; Hotta, Y.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1978**, *19*, 2417. (b) Lombardo, L. *Tetrahedron Lett.* **1982**, *23*, 4293.

(21) The olefination step is the cause of the observed yield; performing the two steps of methylation and deprotection separately had the same overall yield with the acid-based deprotection being quantitative.

(22) Use of simple H_2 with Pd/C (10%) afforded a 1.1/1 mixture in favor of the undesired C-12 methyl epimer.

(23) We found that the most critical variant for success was solvent, with neither benzene nor toluene providing much product. Other Lewis acids such as $Sc(OTf)_3$ and $AlMe_3$ provided some product in CH_2Cl_2, but in reduced yields. In all cases the reaction appeared to stall once it had been warmed to −50 °C; more $TMSCHN_2$ led to 8-membered ring synthesis. For protocals that were tried here without success, see: (a) Dabrowski, J. A.; Moebius, D. C.; Wommack, A. J.; Kornahrens, A. F.; Kingsbury, J. S. *Org. Lett.* **2010**, *12*, 3598. (b) Moebius, D. C.; Kingsbury, J. S. *J. Am. Chem. Soc.* **2009**, *131*, 878. (c) Maruoka, K.; Concepcion, A. B.; Yamamoto, H. *Synlett* **1994**, 521. (d) Maruoka, K.; Concepcion, A. B.; Yamamoto, H. *J. Org. Chem.* **1994**, *59*, 4725.

(24) In model systems, we did observe the smooth formation of silyl enol ether intermediates but never saw such materials in reactions with compound **29**, suggesting that the strain of the system may preclude a sufficient lifetime to prevent 8-membered ring formation.

(25) For references for these specific rearrangement variants, see: (a) Paquette, L. A.; Hoffebeth, J. E. *Org. React.* **2004**, *62*, 477. (b) Miyashita, M.; Yoshikoshi, A. *J. Am. Chem. Soc.* **1974**, *96*, 1917. We do not know the exact stereochemistry about the rearrangement position in either **33** or **34**, which could be the basis for reaction failure.

(26) Formally, compound **20** can be prepared in 4 steps (total step count of 17) using a more expensive, commercially available starting material (3-methyl-3-cyclohexenone) which we also prepared from **19**: Polla, M.; Frejd, T. *Tetrahedron* **1991**, *47*, 5883.

(27) For representative studies leading to highly complex systems through [4 + 3] chemistry, see: (a) Groaning, M. D.; Brengel, G. P.; Meyers, A. I. *J. Org. Chem.* **1998**, *63*, 5517. (b) Trost, B. M.; McDougall, P. J.; Hartmann, O.; Wathen, P. T. *J. Am. Chem. Soc.* **2008**, *130*, 14960. (c) Harmata, M. *Acc. Chem. Res.* **2001**, *34*, 595.

(28) Kamachi, T.; Kuno, A.; Matsuno, C.; Okamoto, S. *Tetrahedron Lett.* **2004**, *45*, 4677. We used other silanes as well, but obtained similar results. We believe these explorations are the first with extended dienone systems.