Tetrahedron 64 (2008) 5482–5490

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

An approach toward the total synthesis of subergorgic acid

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ARTICLE INFO

Article history:
Received 15 February 2008
Received in revised form 31 March 2008
Accepted 1 April 2008
Available online 8 April 2008

Dedicated to Professor William von E. Doering on the occasion of his 90th birthday

Keywords:
Subergorgic acid
Ireland–Claisen rearrangement
Facial selectivity
Diastereoselectivity

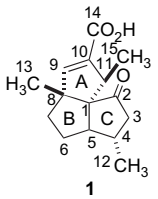
ABSTRACT

Ireland–Claisen rearrangement of a substituted alkenyl cyclopentanecarboxylate provided a monocyclic isomer containing the proper stereochemistry for four of the five stereogenic centers in subergorgic acid. Efforts to construct the additional rings in the molecule were thwarted as a result of steric and other factors. The results provide insights regarding the Ireland–Claisen rearrangement in five-membered ring systems. The formation of spiro-compounds from sterically and stereoelectronically demanding systems as reported herein has the potential to serve as a general strategy for the synthesis of such sub-units in both natural and unnatural products.

1. Introduction[1]

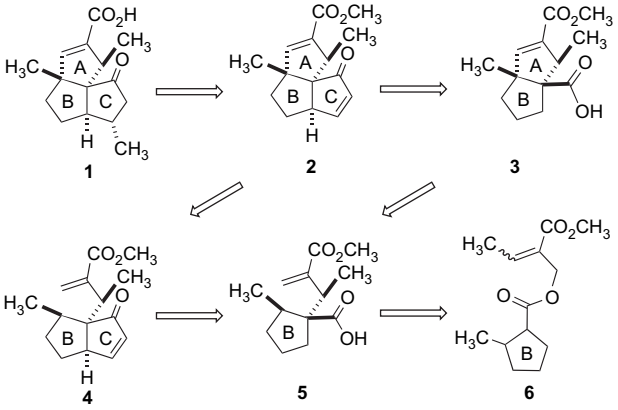
Over the past 35 years, organic chemists have been interested in developing synthetic methodologies for the rapid and efficient acquisition of triquinane natural products.[2] More than 80 such compounds from sources including plants, marine organisms, and microbes have been reported.[3] Many have been popular targets for total synthesis. The high level of interest in their synthesis is also attributable to the continuing disclosure of many new and unusual assemblies of the rings and the significant biological activities of this class of compounds.

Subergorgic acid (**1**) is a member of the angular triquinanes. Initially isolated from the gorgonian coral *Subergorgia suberosa*,[4,5] it is believed to be the first terpene having the triquinane framework to be obtained from marine sources.[4] Its structure was assigned using spectral, chemical, and X-ray crystallographic methods.[5]



1

A major challenge in synthesizing subergorgic acid lies in defining the relative stereochemistry of its three methyl groups, which sets it apart relative to the other known angular triquinane sesquiterpenes.[6] To date, five studies directed toward the total synthesis of subergorgic acid[6] and four successful total syntheses have been reported, with two of the latter being of the racemic[7] and two of the enantioselective category.[8] In our approach, we envisioned that a single Ireland–Claisen rearrangement[9] could be profitably applied to establish the critical cis relationship of the two methyl substituents at C8 and C11, as portrayed in the retrosynthetic analysis for a stereoselective approach to **1** shown in Scheme 1.



Scheme 1.

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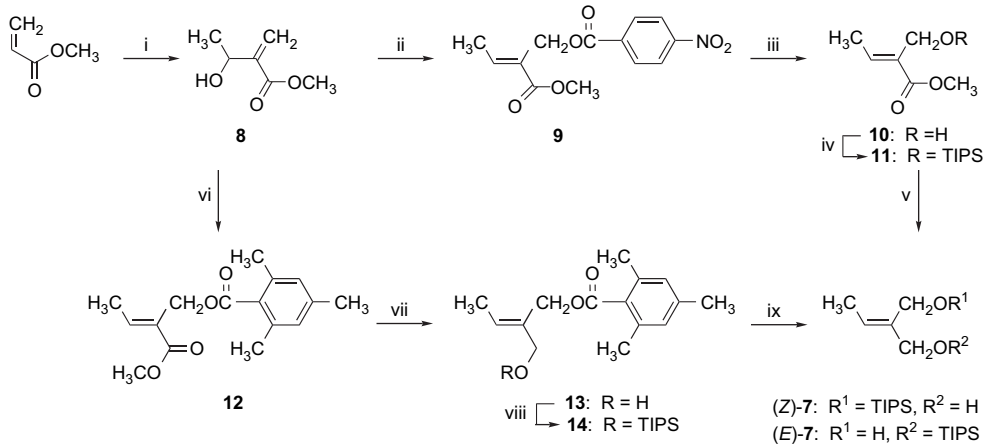
doi:10.1016/j.tet.2008.04.005



Scheme 2. Reagents: (i) CH_3CHO, DABCO, 90%; (ii) PPh_3, DEAD, *p*-nitrobenzoic acid, THF, −42 °C, 86%; (iii) K_2CO_3, MeOH, THF, 82%; (iv) TIPSOTf, 2,6-lutidine, CH_2Cl_2, 80%; (v) DIBAL-H, CH_2Cl_2, −23 °C; H_2O, 92%; (vi) PPh_3, DEAD, mesitoic acid, THF, −42 °C, 75%; (vii) DIBAL-H, CH_2Cl_2, −23 °C; H_2O, 92%; (viii) TIPSOTf, 2,6-lutidine, CH_2Cl_2, 91%; (ix) MeLi, Et_2O, −78 °C, 96%.

Subergorgic acid can potentially be derived from the precursor **2** through a stereocontrolled Michael addition of a methyl group followed by hydrolysis of the methyl ester. Ring C in **2** could be constructed from **3** via Dreiding's method,[10] i.e., transforming the carboxylic acid function into an α-alkynone, followed by flash vacuum pyrolysis (FVP) to form an alkylidenecarbene, which would undergo 1,5-C–H insertion leading specifically to the cyclopentenone ring. Ring A in **3** could be constructed from **5** through ozonolysis of the alkene to form a ketone, followed by a C–H insertion of the alkylidenecarbene intermediate, which could be generated from the ketone via a previously reported strategy.[11] The acid **5** should be available from the Ireland–Claisen rearrangement reaction of **6**. This key step was expected to provide the proper relative stereochemistry at C1, C8, and C11, based on the Ireland–Claisen rearrangement of crotyl or prenyl 2-methylcyclopentanecarboxylates as reported by Gilbert et al.[12] Alternatively, the sequence for the construction of rings A and C could be reversed, i.e., ring C in **4** could be formed before the formation of ring A in **2**.

Our approach, if successful, would give **1** by means of a novel and efficient strategy that potentially features high facial selectivity and diastereoselectivity and is more straightforward than previous approaches. Moreover, we envisioned that this diastereoselective total synthesis could readily be turned to an asymmetric total synthesis. This could be accomplished by starting with the desired enantiomer of **6** prepared from esterification involving the appropriate allylic alcohol and enantiomer of the carboxylic acid.

2. Results and discussion

An earlier model study showed that presence of the methoxycarbonyl group in ester (*E*)-**6** fostered fragmentation rather than rearrangement under the conditions of the Ireland–Claisen reaction.[13] To circumvent this, we planned to prepare an analog of (*E*)-**6** in which a protected alcohol would serve as a surrogate for the methoxycarbonyl group. It was also of interest to investigate whether the facial or diastereoselectivity would be affected by the substituents on the double bond. There were prior instances where both yield and diastereoselectivity of Ireland–Claisen rearrangements were strongly dependent on the protecting groups for the hydroxymethyl moiety.[14] Therefore, steric factors associated with the alkene might play an important role on the diastereoselectivity of the rearrangement.

Experimentally, the reduction of the methoxycarbonyl group in (*E*)-**6** was conducted before the esterification of allylic alcohols (*Z*)- and (*E*)-**7**, which were synthesized using conditions analogous to those established for similar compounds.[15] Methyl acrylate was first transformed to hydroxyester **8** (Scheme 2),[16] which afforded **9** via the modified Mitsunobu reaction[17] and transesterification gave **10**. Protecting the hydroxyl group using triisopropylsilyl trifluoromethanesulfonate (TIPSOTf)[18] furnished **11**, which was reduced to diol (*Z*)-**7**.[19] The overall yield was 47%.

For various reasons (vide infra), synthesis of (*E*)-**7** was also required and was accomplished using conditions similar to those of Charrette and Cote.[15] Analogous to the formation of **9**, an S_N2' reaction between **8** and mesitoic acid was used to form **12**, which was transformed to **14** by chemoselective reduction of **12** to **13**[19] and silylation;[18] cleavage of the mesitoate function afforded (*E*)-**7**.[20] The overall yield was 54%.

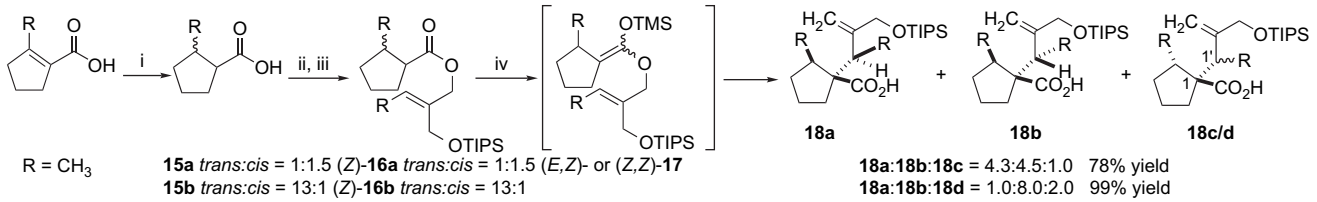
2-Methylcyclopentanecarboxylic acid (**15**),[§] the carboxylic acid component of ester (*Z*)-**16a**, was prepared as a mixture from 2-methyl-1-cyclopentene-1-carboxylic acid[21] by the Freifelder method (Scheme 3).[22] The acids were transformed to their acid chlorides,[24] which were esterified with (*Z*)-**7** to produce a 1:1.5 mixture of (*Z*)-**16a**.[25] Separating the isomers was unnecessary because the stereochemistry at C1 of the ring is destroyed upon forming the ester enolate.

Subjecting esters (*Z*)-**16a** to the modified[26] Ireland–Claisen rearrangement provided diastereomers **18a**, **18b**,[¶] and **18c** in a ratio of 4.3:4.5:1 in 78% yield (Scheme 3). This result was encouraging because the reaction provided a high facial selectivity of 8.8:1, the ratio of **18ab**:**18c**, in favor of the desired cis relationship between the methyl group of the ring and the carboxylic acid function. The facial selectivity in this rearrangement confirmed the previous supposition that the methyl substituent on the ring is sufficiently sterically demanding to bias the transfer of the allylic fragment of ketene silylacetal **17** to the *re*-face.[12]

Assigning the relative configuration in **18a** initially involved 500 MHz NMR spectroscopic techniques, viz., ^1H–^1H COSY, ^{13}C–^1H

[§] Carboxylic acid **15** obtained by hydrogenation was a mixture of trans- and cis-isomer in a 1:1.5 ratio. When the reaction was repeated, a 1:1 mixture of isomers was observed. A previous preparation by our group afforded a 2:1 mixture of the trans- and cis-isomer. To account for these variations, we found that the ratio of the isomeric carboxylic acids was dependent on the conditions of hydrogenation, a phenomenon that has been observed in the hydrogenation of other systems.[23]

[¶] Crystallographic data for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 675696–675699. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].



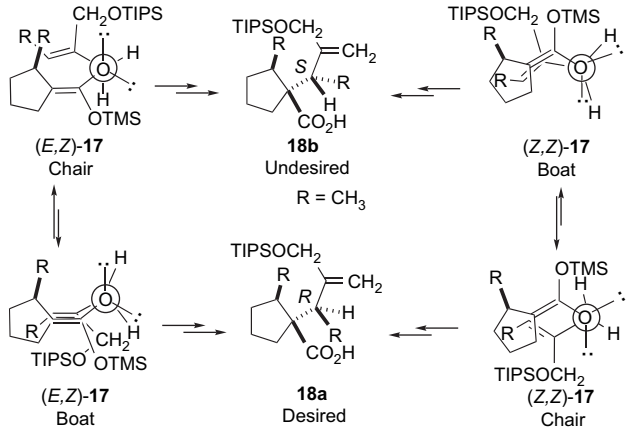
Scheme 3. Reagents: (i) H_2/5% Pd(C)/NaOH/H_2O/EtOH/rt, 96 h, 94%; (ii) $(COCl)_2$, C_6H_6, DMF, rt, 3 h, 94%; (iii) (*Z*)-**7**, Py, rt, 16 h, 95% (two steps); (iv) LDA, TMSCl, TEA, THF, −78 °C; −78 °C to rt, 24 h; satd NH_4Cl, 3 h, 99%.

COSY, NOESY, and DEPT, and these techniques were applied to **18b** as well. X-ray crystallography of three advanced intermediates derived from **18a** confirmed its relative stereochemistry and that of crystalline **18b** was proven directly by this technique. The stereochemistry of **18c** in terms of the relative configuration of the newly formed C1–C1′ bond was not determined.

The drawback of the rearrangement of (*Z*)-**16a** is that there is little diastereoselectivity at the newly formed chiral center C1′, the ratio of **18a** and **18b** being almost 1:1. Isomer **18a** is desired because it embodies the proper stereochemistry for C1, C8, and C11 of **1**. Moreover, because the stereochemistry of C1 ultimately defines that of C5, accomplishing a diastereoselective synthesis of **18a** results in stereochemical control for four out of the total of five asymmetric centers present in **1**.

As postulated by Gilbert et al.,[12] the diastereoselectivity associated with generating the new chiral center C1′ can be ascribed to two factors: the geometry of the intermediate ketene silylacetal **17**, (*E*,*Z*) versus (*Z*,*Z*), and the actual transition state of the [3,3]-sigmatropic rearrangement, chair-like versus boat-like. Analogous to an earlier analysis,[12] Scheme 4 portrays the formation of the desired **18a** and undesired **18b** from the two possible ketene silylacetals. We assume that the ratio of (*E*,*Z*)- versus (*Z*,*Z*)-**17** mirrors the 1:1.5 ratio of esters (*Z*)-**16a**. [3,3]-Sigmatropic rearrangement of (*E*,*Z*)-**17** via a chair-like transition state (TS) gives **18b**, whereas it provides the desired **18a** via a boat-like TS. The nature of the TSs is reversed for the formation of these two products through rearrangement of (*Z*,*Z*)-**17**.

Given that a chair-like TS is preferred in a [3,3]-sigmatropic rearrangement in the absence of unusual steric constraints, we felt that the geometry of the ketene silylacetal **17** played a critical role in the diastereochemical outcome of the rearrangement of (*Z*)-**16a**. In this context, it would be informative if either (*E*,*Z*)- or (*Z*,*Z*)-**17** could be produced preferentially from deprotonation of a pure trans- or cis-isomer of (*Z*)-**16**. Thus, formation of (*Z*,*Z*)-**17** followed by rearrangement would form the desired **18a** via the favored chair-like TS (Scheme 4), whereas generating (*E*,*Z*)-**17** and rearrangement through a chair-like TS would afford the undesired **18b**. This diastereoselectivity is reversed with (*E*)-**16**.



Scheme 4.

Consequently, we proposed to effect the Ireland–Claisen rearrangement using pure *trans*- or *cis*-(*Z*)-**16**. The mixture of acids **15** or esters (*Z*)-**16** was inseparable, but the approach of Nenitzescu and Ionescu[29a,b] gave **15** as a 13:1 mixture of trans-/cis-isomer.[‖]

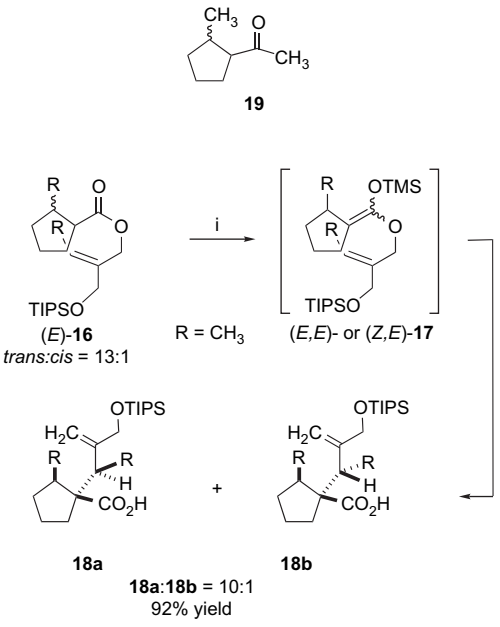
Esterifying this mixture with (*Z*)-**7** afforded a 13:1 mixture of isomers (*Z*)-**16b**, rearrangement of which produced 99% yield of three diastereomers, **18a**, **18b**, and **18d**, in a ratio of 1:8:2 (Scheme 3). The relative stereochemistry of **18d** was not determined but was different from **18c**, as shown by ^1H NMR spectroscopy.

This result was encouraging because the reasonably high *re*-facial selectivity (9:2) was analogous to that observed with (*Z*)-**16a**, where the substrate was a 1:1.5 mixture of two isomers. Additionally, the rearrangement of (*Z*)-**16b** featured acceptable diastereoselectivity, given the 1:8 ratio of **18a**/**18b**.

The results of the rearrangements of (*Z*)-**16ab** with different ratios of isomers suggested that the diastereoselectivity of the overall process was mainly defined by the stereochemistry of the starting esters, which in turn determines the geometry of the ketene silylacetals formed from them. This supports our previous hypothesis that the geometry of the intermediate ketene silylacetals plays a critical role in the diastereochemical outcome of the rearrangement of esters.[12] There was no diastereoselectivity with (*Z*)-**16a** because (*E*,*Z*)- and (*Z*,*Z*)-**17** were formed in nearly equal quantities; their rearrangements are destined to form **18a** and **18b**, respectively, in almost equal amounts (Scheme 4). With (*Z*)-**16b** (trans/cis=13:1), the diastereoselectivity of 1:8 arises because (*E*,*Z*)-**17** is the acetal predominantly formed from the trans-isomer (vide infra); its rearrangement gives **18b** as the major product.

To circumvent the formation of **18b**, we envisioned that inverting the diastereoselectivity by starting with (*E*)-**16** would afford (*E*,*E*)-**17**, which would preferentially rearrange to the desired **18a**. In a manner analogous to the synthesis of (*Z*)-**16**, a 13:1 trans/cis mixture of (*E*)-**16** was prepared by esterification of (*E*)-**7** with **15b**. Subjecting this ester to Ireland–Claisen rearrangement[26] gave a mixture comprising only **18a** and **18b** in a 10:1 ratio with complete *re*-facial selectivity and high diastereoselectivity (Scheme 5).

[‖] Attempts to prepare the pure trans- or cis-isomer of (*Z*)-**16** directly via esterification of (*Z*)-**7** with a pure isomer of acid **15** were challenging. Although most previous preparations of **15** by several different routes gave the trans-isomer as the major product or a mixture of both isomers in similar amounts,[22,27] there were reports claiming formation of either mainly or pure *cis*-**15**.[28] There were also reports claiming formation of pure *trans*-**15**.[29] For practical reasons, we adopted the method of Nenitzescu and Ionescu, which afforded the 13:1 mixture of the desired isomer by way of a haloform reaction on the corresponding mixture of isomeric 1-(2-methylcyclopentyl)ethanones (**19**). Although this route does not provide only *trans*-**15** as claimed,[29a,b] the approach is highly stereoselective and more so than the method reported by Jorgenson et al., who reported that pure *trans*-**15** could be obtained via selective basic hydrolysis of a trans/cis mixture of ethyl 2-methylcyclopentanecarboxylate;[29c] this was not the case in our hands.



Scheme 5. Reagents: (i) LDA, TMSCl, TEA, THF, −78 °C; −78 °C to rt, 24 h; satd NH_4Cl, 3 h, 92%.

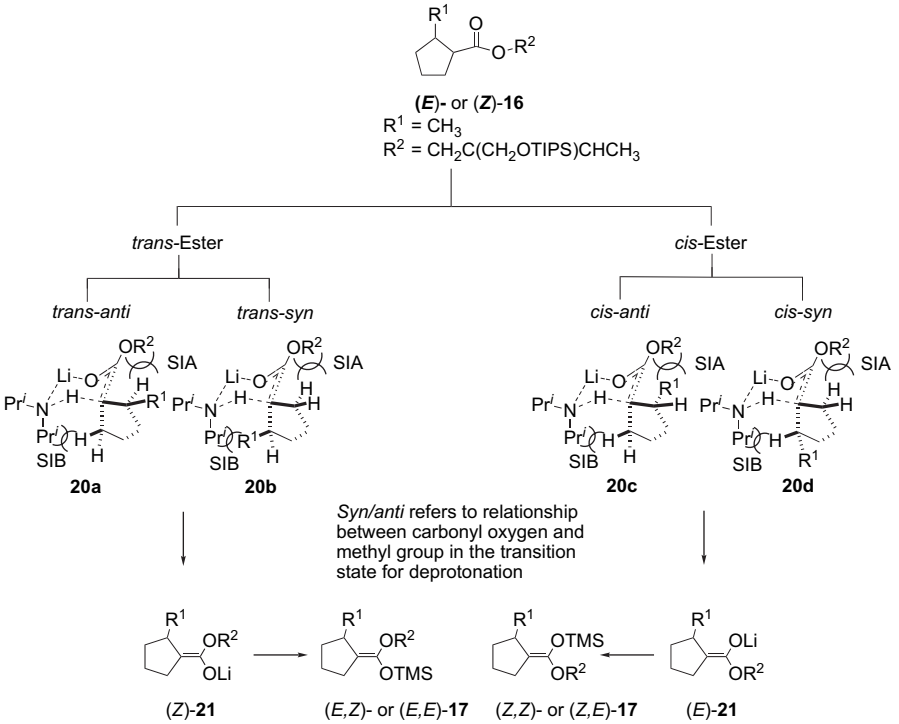
The diastereoselectivity of forming the ketenesilyl acetals clearly is a key factor in defining the stereochemical outcome of the Ireland–Claisen rearrangement of (*E*)- and (*Z*)-**16**. Based on Ireland's model for deprotonation in acyclic systems,[30] four types of chair-like TSs merit consideration for the kinetic enolization step that leads to the enolates serving as precursors to the acetals (Scheme 6). There are two competing steric interactions, one being an alkyl–alkoxy interaction (SIA), i.e., interaction between the ring methyl group and the alkoxy fragment of the ester ($A_{1,3}$-interaction), and the other being an interaction between the ring methyl group and the isopropyl fragment of LDA (SIB). The relative importance of these determines the preference for different transition states in the deprotonation.

For the trans-ester, SIB in the *trans-syn* TS (**20b**) is assumed to be stronger than SIA in the *trans-anti* analog **20a**, based on Ireland's chair-like TS model.[30] The kinetic enolization of the trans-ester occurs mainly through **20a** to form (*Z*)-**21**, which leads to (*E*,*Z*)- or (*E*,*E*)-ketene silylacetal **17**. From this point, the identity of the final products is determined by the rearrangement itself. Whether it gives the desired **18a** or undesired **18b** via a chair- or boat-like TS is solely a matter of the geometry of the allylic fragment of the starting ester. In another words, the stereochemical outcome after this stage would be governed by routes as shown in Scheme 4 for acetals (*E*,*Z*)- and (*Z*,*Z*)-**17**. A comparable analysis can be applied to (*E*,*E*)- and (*Z*,*E*)-**17**.

For the cis-isomer, SIA in *cis-anti* TS (**20c**) is speculated to be more important than SIB in *cis-syn* TS (**20d**). Consequently, deprotonation of the cis-ester would be expected to proceed largely via **20d**, generating an (*E*)-enolate that yields (*Z*)-ketene silylacetal. The identity of the final products is again defined by the rearrangement itself.

In summary, the relative importance of SIA versus SIB nicely rationalizes the diastereoselectivity of the Ireland–Claisen rearrangement of (*Z*)- and (*E*)-**16**. With (*Z*)-**16a** as a 1:1.5 mixture of trans- and cis-isomer, enolization proceeds almost equally through **20a** and **20d** to form the (*E*)-acetal for the trans-ester and the (*Z*)-acetal for the cis-ester, respectively. The two intermediates rearrange through chair-like/boat-like TSs to afford products **18a** and **18b** in a 1:1 ratio (Scheme 4).

As for (*E*)-**16** (trans/cis=13:1), enolization of the trans-ester occurs mainly through **20a** to form (*E*,*E*)-**17**, and predominantly via **20d** for the cis-ester to generate (*Z*,*E*)-**17**. The ratio of (*E*,*E*)-**17**/(*Z*,*E*)-**17** should be approximately 13:1, so **18a** is obtained as the major diastereomer from (*E*,*E*)-**17**, whereas **18b** is furnished as the minor isomer from (*Z*,*E*)-**17** (Scheme 4). The decline from 13:1 to 10:1 in the diastereoselectivity for the rearrangement of (*E*)-**16** might be due to the result of a combination of three factors: (1) inhomogeneity of the starting trans-ester; (2) preferred but not

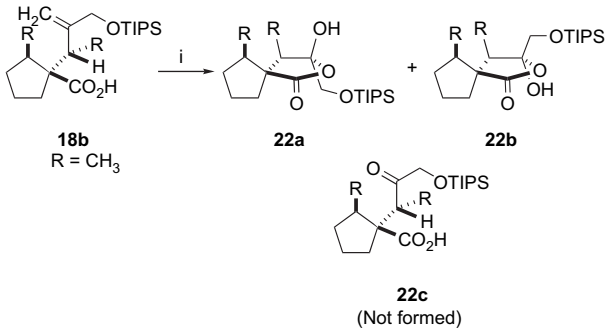


Scheme 6.

exclusive formation of the (*E*,*E*)-**17**; (3) preferred but not exclusive chair-like TS for (*E*,*E*)-**17**.

The second factor seems to be the most important, however. As discussed previously, the creation of diastereomeric rearrangement products was a result of poor selectivity in acetal formation rather than competition between chair- and boat-like TSs for the rearrangement.[12] Nevertheless, the diastereoselectivity of the rearrangement of (*E*)-**16** was substantially improved compared to that of the simpler systems,[12] though the role of the triisopropylsiloxymethyl group in the deprotonation of (*E*)-**16** is not clearly understood.

With the key intermediate **18a** in hand, efforts to construct rings A and C of **1** were pursued. An immediate problem was encountered in a model reaction where subjecting **18b** to ozonolysis[31] resulted in spirolactols **22a**¶ and **22b** rather than ketone **22c**, in a 5.3:1 ratio (Scheme 7). The relative configuration in **22a** was determined by X-ray crystallographic analysis.



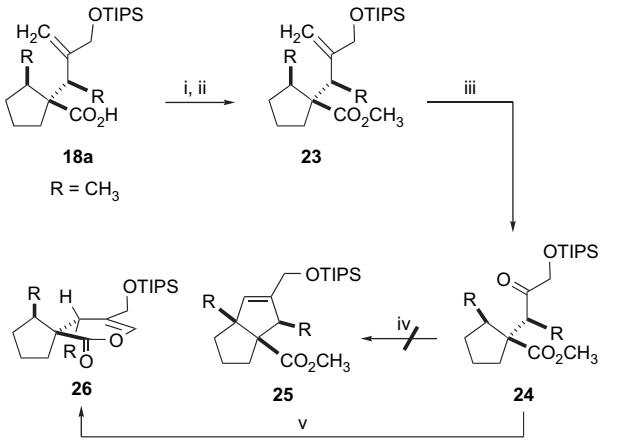
Scheme 7. Reagents: (i) O_3, CH_2Cl_2, −78 °C; Ph_3P, −78 °C to rt, 91%.

Esterifying the carboxylic acid group circumvented this problem, as ozonolysis of the methyl ester of **18a** afforded ketoester **24** in excellent yield. Attempts to convert **24** to **25** via the Wittig Horner type reaction[32] following known procedures[11] were unsuccessful, providing either recovered ketoester or a mixture of unidentifiable products; ^{1}H NMR of the mixture gave no evidence for **25**.

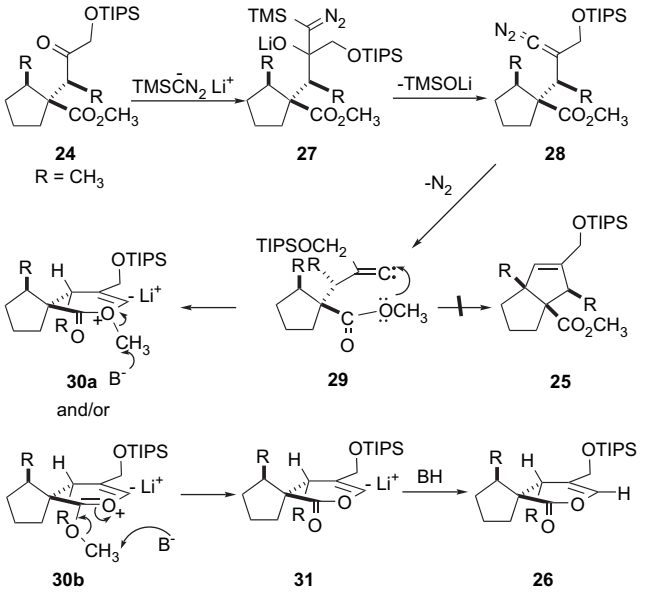
Use of (trimethylsilyl)diazomethane ($TMSCHN_2$),[33a] a more nucleophilic reagent[33b] in place of DAMP, caused complete disappearance of **24**. However, the isolated product was **26** (Scheme 8), as evidenced by ^{1}H NMR analysis of the purified product, which showed a pair of methyl doublets but no downfield singlet for an ester methyl group. Further spectroscopic analyses, viz., ^{1}H–^{1}H COSY, ^{13}C–^{1}H COSY, NOESY, and DEPT, confirmed this assignment.

A possible mechanism for forming **26** is provided in Scheme 9. Nucleophilic attack by the (trimethylsilyl)diazomethane anion on the carbonyl group of **24** gives **27**, which eliminates TMSOLi to produce **28**. Loss of dinitrogen provides carbene **29**, which is converted to ylide **30a** and/or **30b** rather than undergoing C–H insertion to yield the desired **25**. Removing the ester methyl group leaves anion **31**, which furnishes **26**. The diversion of **29** to **30ab** in principle should be reversible, but the ensuing nucleophilic attack on **30ab** would drive the process irreversibly to **31**.

This outcome, although disappointing with regard to our present goal, results in the formation of unsaturated spirolactone **26** under extremely mild conditions and represents a novel synthetic method for preparing such lactones.[34] This approach has the potential to serve as a general methodology in organic synthesis if optimization, which we did not pursue, affords yields higher than the moderate one obtained.



Scheme 8. Reagents: (i) $(COCl)_2$, C_6H_6, DMF; (ii) MeOH, Py, 85%; (iii) O_3, CH_2Cl_2, −78 °C; Ph_3P, −78 °C to rt, 12 h, 96%; (iv) $(EtO)_2P(O)CHN_2$ (DAMP), *t*-BuOK, THF, −78 °C; **24** in THF, −78 °C to rt, 12 h; (v) $TMSCHN_2$, *n*-BuLi, THF, −78 °C, 30 min; **24** in THF, −78 °C to rt, 12 h, 50%.

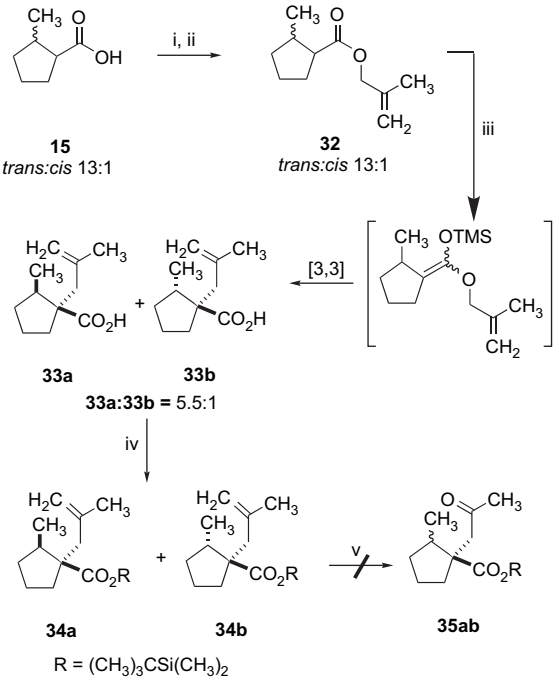


Scheme 9.

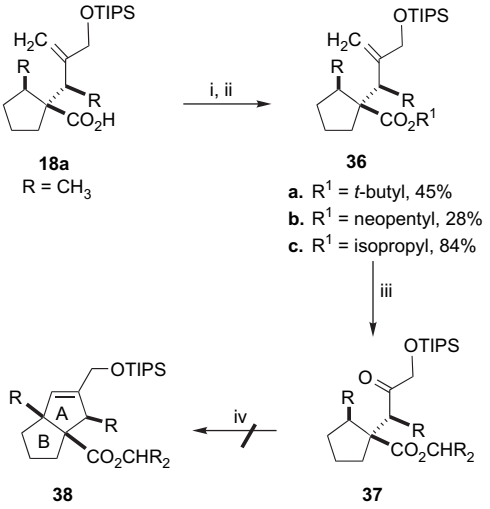
In the context of the proposed mechanism, lactol formation might be the consequence of the minimal steric hindrance associated with nucleophilic attack on the methyl group in ylides **30a** and **b**. Alternatively, if attack on **29** involves the oxygen atom of the methoxy group, the minimal steric bulk of this group optimizes the potential for attacking the carbenic center. Thus, an ester having a sterically bulkier alkoxy moiety might be less prone to such intramolecular nucleophilic attack, thereby favoring the desired C–H insertion.

To test this, a model study was undertaken. As seen in Scheme 10, **32** was synthesized and rearranged to afford *cis*- and *trans*-**33ab**. The cis relationship of the methyl and carboxylic acid groups in **33a** was assumed based on previous results. *tert*-Butyldimethylsilyl esters **34ab** were then produced,[35a] but their ozonolysis resulted in the formation of an unidentifiable mixture containing none of the desired **35ab**, despite reports that *such* esters survive ozonolysis conditions.[35b]

The *tert*-butyl, neopentyl, and isopropyl esters **36** were synthesized and subjected to ozonolysis (Scheme 11). The first two



Scheme 10. Reagents: (i) $(COCl)_2$, C_6H_6, DMF; (ii) 2-methyl-2-propen-1-ol, Py, 71% (two steps); (iii) LDA, TMSCl, TEA, THF, −78 °C; −78 °C to rt; satd NH_4Cl, 96%; (iv) C_6H_6, TBDMSCl, DBU, 75%; (v) O_3, CH_2Cl_2, −78 °C; Ph_3P, −78 °C to rt.



Scheme 11. Reagents: (i) $(COCl)_2$, C_6H_6, DMF; (ii) R^1OH, Py, rt, 16–20 h, or 120 °C, 20 h, 45%, 28%, 84%, respectively (two steps); (iii) O_3, CH_2Cl_2, −78 °C; Ph_3P, −78 °C to rt, 93%; (iv) $TMSCHN_2$, *n*-BuLi, THF, −78 °C; **38** in THF, with or without HMPA, −78 °C to rt.

afforded unidentifiable mixtures, but **36c** gave ketone **37**. Treating **37** with $TMSCHN_2$ anion, either with or without added HMPA, led to an intractable mixture in which no vinylic proton peaks attributable to **38** were detected via ^1H NMR analysis. This analysis also excluded the formation of spirolactone **26**.

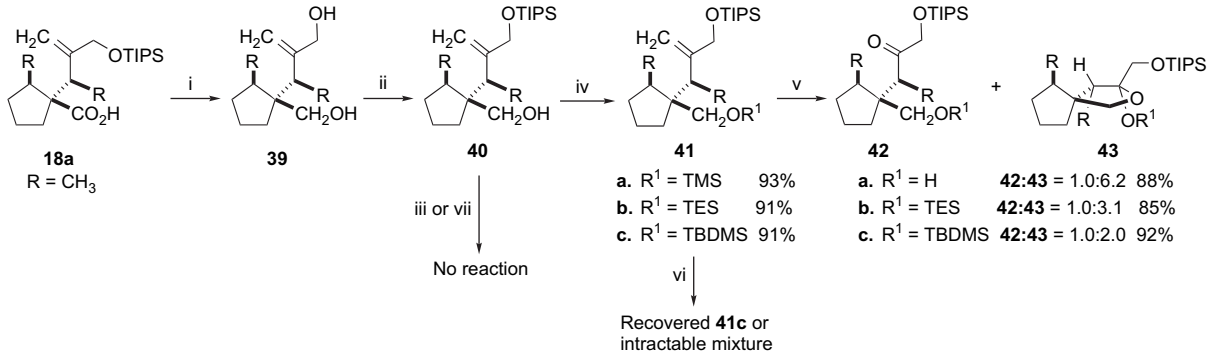
These results prompted exploration of a route to ring A of **1** in which the offending neopentyl-like carbonyl functional group was absent. Acid **18a** was reduced to form diol **39**, which was monoprotected to give **40** (Scheme 12). To preclude possible cyclization problems upon ozonolysis as with **18b**, **40** was converted to silyl ether **41a**, ozonolysis of which produced a mixture (1:6.2) in which the desired **42a** was the minor component. The major isomer was **43a**,[¶] the structure and relative configuration of which were unambiguously determined by X-ray crystallographic analysis.

The formation of **42a** and **43a** is explicable by the accepted mechanism of ozonolysis.[36] As portrayed in Scheme 13, zwitterion **45**, derived from **44**, reacts with formaldehyde in route a to form a secondary ozonide **46**, which is ultimately reduced to afford **42a**. Carbonyl oxide **45** is apparently also attacked by the oxygen atom of the trimethylsilyl group to give **47**, as shown in route b. The silyl group then migrates to produce **48**, silylation–desilylation of which provides **43a**, possibly via **49**.

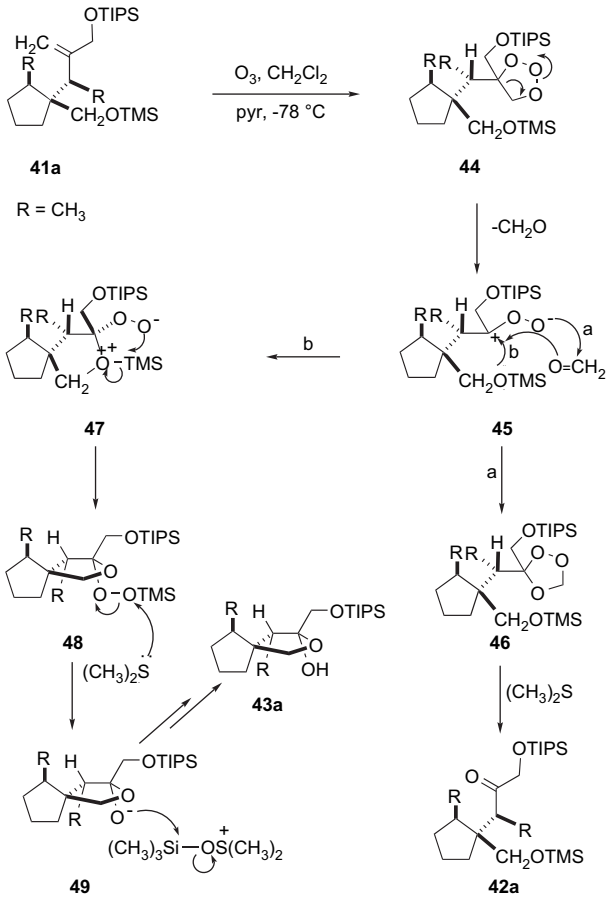
Increasing the steric hindrance at the oxygen atom of the silyl ether group represented a strategy for circumventing this problem, so triethylsilyl and *tert*-butyldimethylsilyl ethers **41b** and **c** were synthesized. However, ozonolysis of **41b** resulted in the formation of a 1:3.1 mixture of **42b** and **43b**, in which **42b** remained the minor component. This was also true for the *tert*-butyldimethylsilyl ether **41c**, although the ratio of **42c**/**43c** increased to 1:2. Our hypothesis that increasing the steric bulk of substituents on the silicon atom would suppress spirolactolization appears to be validated, but this undesired process remains dominant nonetheless.

Attempts to oxidize the double bond in **41c** using osmium tetroxide and sodium periodate in ether/H_2O provided only recovered starting material (Scheme 12), whereas these reagents gave a mixture of unidentifiable products in 1,4-dioxane/H_2O. Using non-migratory protecting groups, viz., benzyl and *p*-methoxybenzyl, for the alcohol function in **41** proved fruitless; starting material was quantitatively recovered each time.

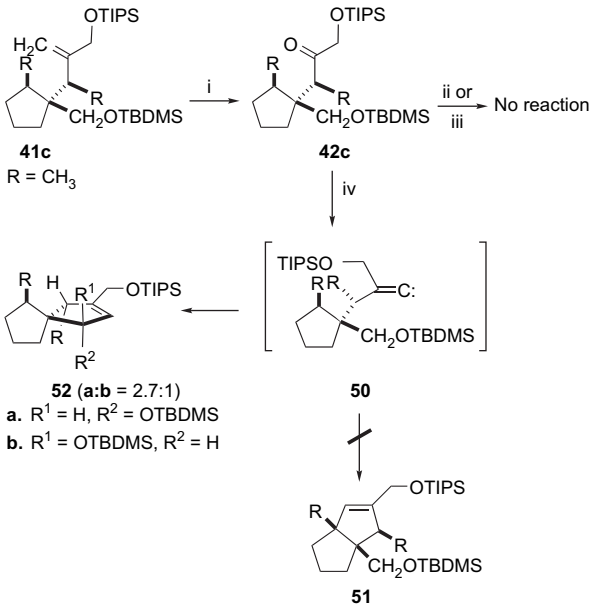
Modifying the ozonolysis conditions themselves proved successful for our purposes. Knowing that **45** could either react with an aldehyde or a ketone or be trapped by nucleophilic solvents,[37]



Scheme 12. Reagents: (i) $LiAlH_4$, Et_2O, 45 °C, 96%; (ii) TIPSCl, imidazole, DMF, 85%; (iii) TMSCl, TEA, THF, with or without HMDS and Py; (iv) R^1OTf, 2,6-lutidine, CH_2Cl_2, 93%, 91%, 91%, respectively; (v) O_3, CH_2Cl_2, Py, −78 °C; Me_2S, −78 °C to 0 °C, 88%, 85%, 92%, respectively; (vi) OsO_4, $NaIO_4$, H_2O, Et_2O or 1,4-dioxane; (vii) KH or NaH, $PhCH_2Br$ or *p*-$MeOC_6H_4CH_2Cl$, with or without Bu_4NI or HMPA, THF.



Scheme 13.



Scheme 14. Reagents: (i) O_3, CH_3CHO, Py, −78 °C; Me_2S, K_2CO_3, H_2O, −78 °C to 0 °C, 99%; (ii) $TMSCHN_2$, *n*-BuLi, THF or DME, −78 °C; **42c** in THF or DME, −78 °C to rt; (iii) $(EtO)_2P(O)CHN_2$, *t*-BuOK, THF, −78 °C; **42c** in THF, −78 °C to rt; (iv) $TMSCHN_2$, *n*-BuLi, THF, −78 °C; **42c** in THF, HMPA, −78 °C to rt, 52%.

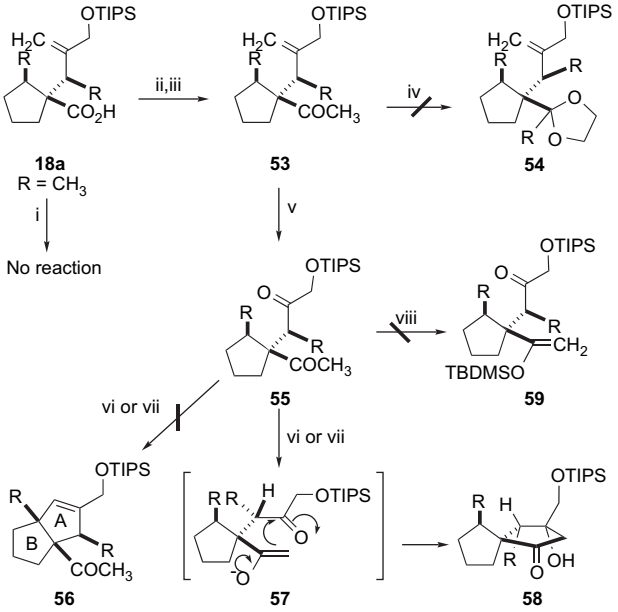
added formaldehyde could capture **45** and yield **46**, followed by the normal reduction to afford the desired ketone. As shown in Scheme 14, ozonolysis of **41c** in acetaldehyde instead of dichloromethane afforded **42c** as the sole product and in excellent yield.

With **42c** in hand, construction of ring A of subergorgic acid was attempted. Subjecting **42c** to reaction with $TMSCHN_2$ anion or DAMP anion in THF gave only recovered starting material (Scheme 14). When treated with a solution of $TMSCHN_2$ anion in HMPA/THF, **42c** was consumed but failed to produce **51**. Rather, NMR data suggested formation of a mixture of **52a** and **b** in a 2.7:1 ratio, and further spectroscopic analysis, viz., ^1H–^1H COSY, ^{13}C–^1H COSY, NOESY, and DEPT, confirmed the assignments.

The isolation of **52** is consistent with the formation of carbene **50**, which selectively inserts into the siloxy C–H bond rather than the methine C–H bond. This problem seemed solvable by making the siloxy C–H bond unavailable for carbene insertion. This strategy could be realized by transforming acid **18a** into ketone **53**, followed by protection of the ketone moiety as the ethylene acetal **54** (Scheme 15). In practice, attempts to produce **53** by directly treating **18a** with methyllithium in ether or THF all resulted in recovery of starting material. The inability for CH_3Li to add to **18a** and for ethylene glycol to convert **53** to **54** reflects the steric hindrance at the carbonyl function of **18a**. Fortunately, a two-step sequence was successful for the conversion of **18a** to **53**, ozonolysis of which afforded diketone **55** in good yield.

Expecting that nucleophilic attack would occur regioselectively on the less-hindered carbonyl, **55** was treated with $TMSCHN_2$ anion to produce **56**. Starting diketone was recovered when THF was used as solvent, but was consumed when the reaction was run in a 1:50 mixture of HMPA and THF (step vi or vii in Scheme 15). Unfortunately, no vinylic protons were seen in the ^1H NMR spectrum of the crude reaction mixture. The reaction did yield spiroketone **58**,¶ whose structure was confirmed by X-ray crystallographic analysis.

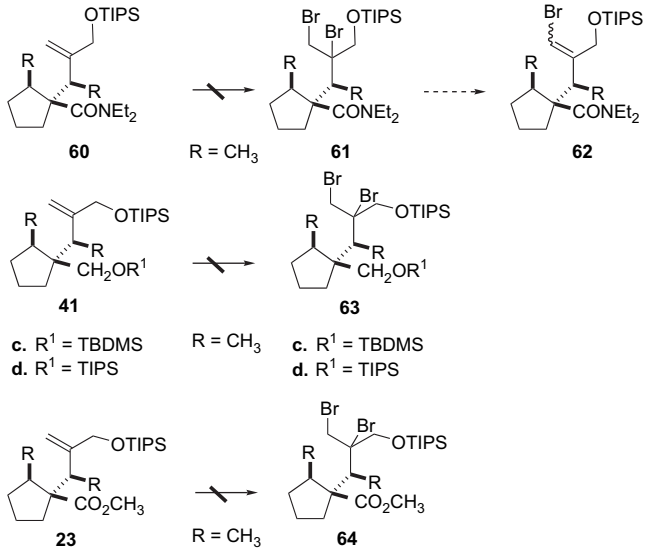
As expected, the relative configuration of **58** is consistent with that of **18a** and spiro-compounds **26**, **43a**, and **52**. Rationalizing the formation of **58** could involve $TMSCHN_2$ anion first deprotonating **55** to form **57**, followed by intramolecular aldol condensation. An attempted solution for this problem that involved trapping **57** as its



Scheme 15. Reagents: (i) MeLi, ether or THF, with or without HMPA, rt or reflux; NH_4Cl; (ii) $(COCl)_2$, C_6H_6, DMF; (iii) MeLi, THF, −78 °C to rt, 72% (two steps); (iv) $(CH_2OH)_2$, *p*-TSA, C_6H_6, 4 Å molecular sieves, 85 °C; (v) O_3, CH_2Cl_2, −78 °C; Ph_3P, −78 °C to rt, 86%; (vi) $TMSCHN_2$, *n*-BuLi, THF, −78 °C, **55** in THF, HMPA, −78 °C to rt, 60%; (vii) $(EtO)_2P(O)CHN_2$, *t*-BuOK, THF, −78 °C; **55** in THF, HMPA, −78 °C to rt, 60%; (viii) various conditions.

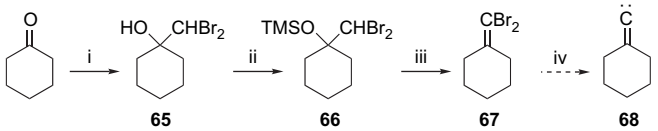
silyl enol ether failed. Experiments using various conditions resulted in recovery of **55** or formation of **58** and/or unidentifiable products.

The general strategy of using α-elimination of vinyl halide to generate alkylidenecarbenes failed in this case.[38] Dibromide **61**, the precursor to the necessary **62**, was not formed using a variety of conditions nor were dibromides **63** and **64**.

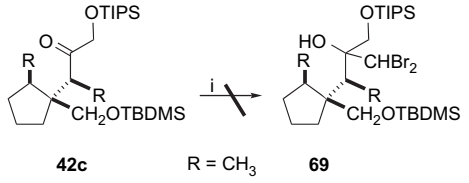


Applying α-elimination of a 1,1-dihaloalkene to produce an alkylidenecarbene[39] was also attempted. As a model for our goal, alcohol **65** was converted to **66** in good yield,[39] and this provided **67** upon treatment with LDA (Scheme 16). Carbene **68** should be accessible based on known procedures,[39b] although this was not tested. However, applying the addition reaction to **42c** (Scheme 17) gave only quantitative recovery of the starting ketone under various conditions.

In summary, steric and stereoelectronic factors thwarted formation of ring A in subergorgic acid. The nucleophilic oxygen atoms such as those in **24** presented a problem by trapping the carbene intermediate (Scheme 8). Inability to protect the neopentyl-like carbonyl group of **53** (Scheme 15) precluded ozonolysis of the alkene moiety to form a ketone that could possibly have been converted to the desired bicyclic compound according to the known procedures.[31,33] Finally, the activation of the secondary C–H bond



Scheme 16. Reagents: (i) $[(CH_2)_5CH]_2NH$, *n*-BuLi, THF; CH_2Br_2, cyclohexanone, −78 °C; 10% HCl; (ii) HMDS, TMSCl, Py, 50 °C, 52% (two steps); (iii) LDA, THF, −78 °C to rt; (iv) *n*-BuLi or MeLi, hexanes, low temperatures.



Scheme 17. Reagents: (i) $[(CH_2)_5CH]_2NH$, *n*-BuLi, THF; CH_2Br_2, −78 °C, 2 h; satd NH_4Cl and acidified to pH 3 with 10% aq HCl.

by the oxygen atom of the OTBDMS group in **42c** (Scheme 14) resulted in carbene insertion at that position rather than at the tertiary C–H bond of the cyclopentane ring to form ring A of **51**, a promising precursor to subergorgic acid.

The recalcitrance toward nucleophilic attack of a carbonyl group adjacent to a quaternary center and the undesired intramolecular nucleophilic trapping of an alkylidenecarbene prevented completion of the proposed expeditious route to subergorgic acid (**1**). Nonetheless, the Ireland–Claisen rearrangement of substituted alkenyl 2-methylcyclopentanecarboxylates has been demonstrated to be highly stereoselective in establishing four of the five stereocenters present in it. This is thus a powerful methodology for the synthesis of triquinanes and other five-membered ring-containing natural products if the challenges associated with steric hindrance and chemoselectivity encountered here can be solved.

3. Experimental

3.1. General procedure for the preparation of lithium diisopropylamide (LDA)

Following a standard procedure developed by Rathke et al.,[40] a solution of LDA (2.2 mmol) in THF was prepared as follows. To a 25-mL round-bottomed flask (rbf) was added THF (3 mL) at 0 °C under N_2 atmosphere. Diisopropylamine (0.3 mL, 2.2 mmol) was added, followed by the dropwise addition of *n*-BuLi (1.5 mL, 1.6 M in hexane) via syringe. The resulting mixture was stirred at 0 °C for 10 min, then cooled to −78 °C, at which time the solution was ready for use.

3.2. General procedures for the Ireland–Claisen rearrangement

All rearrangements were carried out under strictly anhydrous conditions according to the known procedures.[26] A solution of LDA[40] (2.2 mmol) in THF (3 mL) was prepared in a 25-mL rbf and cooled to −78 °C under a N_2 atmosphere. A 15-mL centrifuge tube was charged with TMSCl/TEA/THF (2.0:0.5:3.7, volume ratio), centrifuged for 10 min, then cooled to −78 °C, and kept under N_2. Three milliliters of the supernatant of the centrifugate was transferred via cannula to the LDA solution. The resulting mixture was stirred at −78 °C for 5 min. To this mixture was added, dropwise via cannula, a solution of the allyl ester in THF (1 mL), which had been prepared in a 5-mL rbf and precooled to −78 °C under a positive pressure of N_2. This mixture was stirred at −78 °C for 30 min before the cooling bath was removed. The mixture was then allowed to warm to rt and stirred at this temp for 18–48 h before the aqueous (aq) workup to effect hydrolysis. The resulting biphasic mixture (top org. phase with brown color, bottom aq phase with cream color) was transferred to a separatory funnel, the org. phase was separated, and the aq phase was extracted with Et_2O (3×10 mL). The combined org. phases were washed with brine (3×10 mL), dried, and concentrated. The resulting brown oil residue was subjected to flash chromatography to furnish the pure rearrangement products, e.g., (1*S**,2*R**,1′*R**)-1-(1-methyl-2-triisopropylsiloxymethyl-2-propenyl)-2-methylcyclopentanecarboxylic acid (**18a**). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.14 (d, *J*=1.8 Hz, 1H, vinylic), 4.90 (d, *J*=1.2 Hz, 1H, vinylic), 4.05–4.25 (m, 2H, CH_2O), 2.50 (q, *J*=7.2 Hz, 1H, allylic), 2.40–1.20 (m, 31H, ring Hs, homoallylic CH_3, and TIPS), 0.93 (d, *J*=6.9 Hz, 3H, ring CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 181.7, 152.9, 107.9, 66.0, 60.1, 42.1, 38.1, 32.8, 29.6, 23.1, 18.0, 15.9, 15.3, 12.0; ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.96 (s, 1H, COOH), 5.04 (d, *J*=2.0 Hz, 1H, vinylic), 4.83 (d, *J*=1.7 Hz, 1H, vinylic), 4.07–4.17 (m, 2H, CH_2O), 2.47 (q, *J*=7.2 Hz, 1H, allylic), 0.98–2.09 (m, 28H, ring Hs and TIPS), 0.98 (d, *J*=7.2 Hz, 3H, homoallylic CH_3), 0.88 (d, *J*=6.9 Hz, 3H, ring CH_3); ^{13}C NMR (125 MHz, DMSO-d_6): δ 176.3, 153.2, 106.9,

65.4, 59.0, 40.8, 37.6, 32.4, 29.1, 22.4, 17.8, 15.7, 15.2, 11.4; HRMS for $C_{21}H_{41}O_3Si$ $(M+H)^+$ calcd 369.2825, found 369.2826.

Acknowledgements

We thank the Robert A. Welch Foundation (Grant F-815) for partial financial support of this work; Professor Stephen F. Martin for providing access to an ozonator; Dr. Ben A. Shoulders for his invaluable dedication to and assistance in operating NMR spectrometers and helpful discussions with the results; Dr. Vincent Lynch for obtaining X-ray crystallographic data.

Supplementary data

General experimental methods, full experimental and characterization details, and copies of ^1H, ^{13}C, and 2D NMR spectra of the reported compounds. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.04.005.

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