# Total Synthesis of (±)-Asteriscanolide

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*Received June 18, 2001*

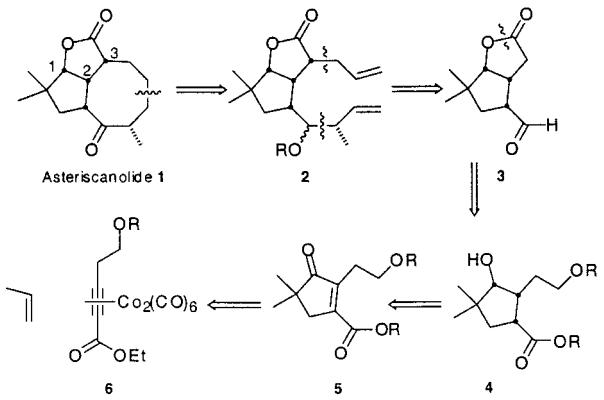
The total synthesis of asteriscanolide (**1**) has been achieved by taking advantage on an intermolecular Pauson−Khand cycloaddition and a ring-closing metathesis as key bond-forming transformations. The approach incorporates the cyclooctane stereogenic center prior to ring formation. Interestingly, the ring-closing metathesis generates a new eight-membered ring with an "in−out" intrabridgehead relationship.

## Introduction

The cyclooctane sesquiterpene lactone, asteriscanolide **1**, has recently been the focus of a number of research groups. Since its initial isolation from the hexane extract of *Asteriscus aquaticus* by Feliciano,[1] it has succumbed to total synthesis by the Wender group,[2] who incorporated a Ni(0)-catalyzed [4 + 4] cycloaddition as the pivotal step, very recently by the Snapper group[3] incorporating a ring-opening metathesis/Cope rearrangement strategy, and by the Paquette group.[4] However, the structural challenges associated with the construction of the [6.3.0] carbocyclic skeleton bearing a bridging butyrolactone and five *cis* stereocenters has prompted other creative approaches, which include both inter- and intramolecular [2 + 2] cycloadditions followed by a de Mayo type[5−7] fragmentation. Furthermore, the studies by Booker−Milburn have shown that the C-7 methyl cannot be introduced via alkylation of the corresponding des-methyl cyclooctane, and thus the stereocenter must be established prior to eight-membered ring formation.[7]

We have developed a novel synthetic strategy, which meets the criteria mentioned above and also features the Pauson−Khand cycloaddition[8] and ring-closing metathesis (RCM) as key steps (Scheme 1). Recently, there has been much effort devoted to the application of RCM for the formation of medium-sized rings,[9] but eight-membered rings are still generally regarded a most difficult ring size to achieve by this means.[10] Moreover, there is still relatively little known about the formation of bridging eight-membered rings via RCM. This was a major contributing factor to our judicious choice of C−C bond disconnection for the eight-membered ring of **1**. As a consequence of pursuing this challenging approach, we have developed a synthetic route, which proceeds via the stereoselective formation of an "inside−outside"[11] eight-membered ring. In this paper, we wish to present a detailed account of these synthetic studies, which culminated in the total synthesis of asteriscanolide, **1′**.[12]

**Scheme 1**




## Results and Discussion

In our retrosynthetic analysis we envisaged that the formation of the bridging eight-membered ring could be achieved through ring-closing metathesis of diene **2** (Scheme 1). This would enable stereoselective incorpora-

† University of Florida.

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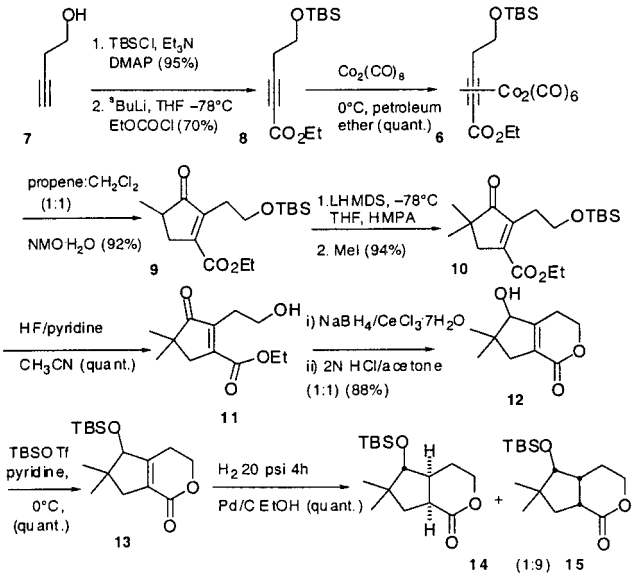
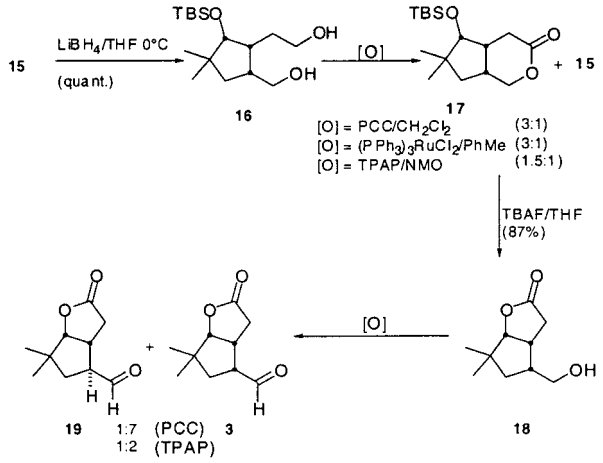
10.1021/jo010623a CCC: $20.00 
Published on Web 09/29/2001

**Scheme 2**




**Scheme 3**




tion of the C-7 methyl prior to cyclooctane ring formation. Further disconnection leads to the [3.3.0] oxabicyclooctane **3** as a key intermediate, which could be derived via **4** from the highly functionalized cyclopentenone **5**, the product of a cobalt-mediated Pauson−Khand [2 + 2 + 1] cycloaddition of the dicobalt hexcarbonyl complex **6** and propene. The strategy that we used for the construction of **5** takes advantage of our recent successes with the Pauson−Khand reaction of alkynoates. These results have shown that excellent regiocontrol in the cycloaddition can be achieved in the reaction of unsymmetrically substituted alkenes with alkynoates to give 1,4-dicarbonyl products. The regioselectivity observed in the cycloaddition across the alkyne has been rationalized on electronic grounds.[13] In addition, intermolecular reactions between internal alkynes and terminal alkenes give rise to 2,3,5-trisubstituted cyclopentenones in preference to the 2,3,4-trisubstituted isomer. A steric argument has been invoked to explain this regioselectivity.[14]

The preparation of our starting cobalt complex **6** commenced with the protection of 3-butyn-1-ol, **7**, as the corresponding *tert*-butyldimethylsilyl (TBS) ether, which was treated with $^{s}$BuLi in THF at −78 °C to generate the lithio alkyne and then added to ethyl chloroformate in THF at −78 °C to give the corresponding alkynoate **8** (Scheme 2). Treatment of **8** with dicobalt octacarbonyl in petroleum ether furnished the desired hexacarbonyldicobalt complexed alkyne **6** (Scheme 2). The cycloaddition of **6** with propene in methylene chloride proceeded via incremental addition of *N*-methyl-morpholine-*N*-oxide monohydrate to give the highly functionalized cyclopentenone **9**, which contained functional groups appropriately positioned for further manipulation of the side chains. Cycloaddition with isobutene or allylic thioalkyl derivatives[15] of isobutene did not yield the desired product. We therefore proceeded with the deprotonation of **9** using LiHMDS/HMPA followed by quenching the lithio-enolate with methyl iodide to give the gem-dimethylated ketone **10**.

Our goal at this stage was to set the three *cis* oriented stereocenters on the cyclopentane ring. All attempts to reduce the tetrasubstituted double bond of **10** by catalytic hydrogenation gave recovered starting material and dissolving metal reductions gave only the *trans* diastereoisomer. Desilylation of **10** with HF/pyridine yielded hydroxy ketone **11** (Scheme 2). Treatment of **11** with with $NaBH_4/CeCl_3 \cdot 7H_2O$ in ethanol gave the corresponding allylic alcohol, which yielded hydroxy lactone **12** after quenching with water and stirring for 12 h in the presence of 2 N HCl. Hydrogenation of enone **12** (Pd/C, 40 psi $H_2$) gave a 1.6:1 ratio of diastereoisomers favoring the all-*cis* diastereoisomer. The facial selectivity was improved by converting the allylic alcohol to the corresponding TBS ether **13**, which underwent hydrogenation (Pd/C, 20 psi $H_2$) to give the desired all-*cis* diastereoisomer **15** (90%) in addition to isomer **14** (10%).

Having established the requisite *cis* stereochemistry of all three substituents on the cyclopentane ring, we needed to convert lactone **15** to aldehyde **3**. This was achieved in two ways. The first was via a 1,3 carbonyl transposition where reduction of the lactone **15** with $LiBH_4$/THF gave the corresponding diol **16**, which was subjected to selective oxidation with a variety of oxidizing agents to give a mixture of the transposed lactone **17** and starting lactone **15** (Scheme 3). The optimum ratio for **17** and **15** was 3:1, which was achieved with either PCC/$CH_2Cl_2$[16] or $(PPh_3)_3RuCl_2$/PhMe.[17] Treatment of **17** with TBAF provided a one-pot conversion to the hydroxy lactone **18**. The hydroxyl group was oxidized with PCC/$CH_2Cl_2$ to give the desired aldehyde **3** and epimer **20** in a ratio of (7:1). Oxidation of **18** with tetra-*n*-propylammonium perruthenate gave aldehydes **3** and **19** in the ratio of (2:1).[18] The advantage of this route is that alkylation of **17** would, after translactonization, provide the correct stereogenic center at C-3 (asteriscane numbering). However, the poor selectivities for the oxidation of the diol and problems associated with epimerization of the chiral center adjacent to the aldehyde rendered this approach unfeasible.

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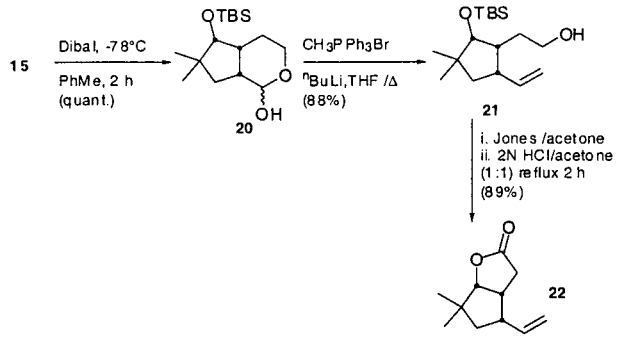
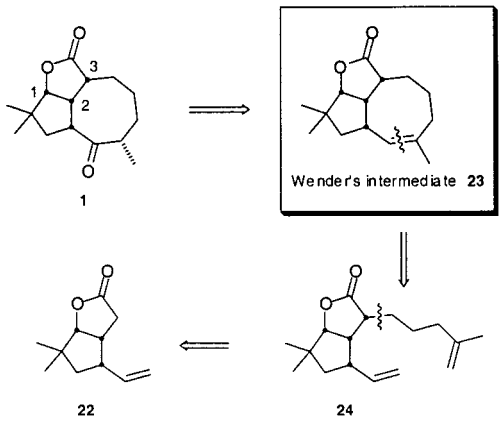
**Scheme 4**




**Scheme 5**

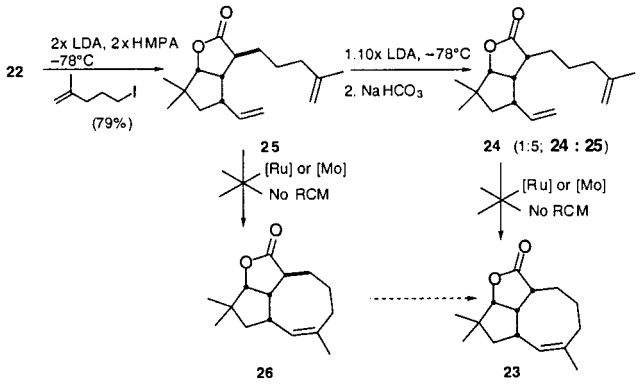



We therefore turned our attention to a Wittig approach, which proceeded by reduction of lactone **15** with DIBAL-H in toluene at −78 °C[19] to give a mixture of lactols **20,** which were subjected to reaction with 10 equiv of the ylide derived from $MePPh_3Br/^nBuLi$ in refluxing THF to give the corresponding alkene **21** (Scheme 4). The large excess of ylide was used to avoid epimerization of the stereocenter adjacent to the aldehyde prior to Wittig olefination. The carboxylic acid resulting from Jones oxidation of the primary alcohol was refluxed with 2 N HCl in acetone (1:1) for 2 h to give bicyclic lactone **22** (89%, two steps).

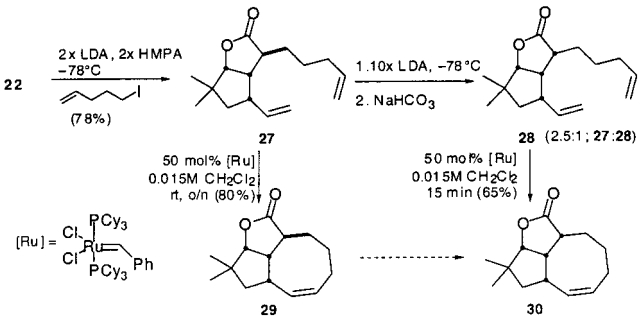
At this point we also considered the trisubstituted cyclooctene **23**, which was an advanced intermediate in Wender's synthesis, as a potential target. The successful synthesis of **23** would provide a formal synthesis of asteriscanolide. A metathesis disconnection leads to a diene, which could be easily derived from our bicyclic lactone via an alkylation with the appropriate side chain (Scheme 5). The only potential drawback of this approach was that alkylation of the lactone would provide the wrong relative stereochemistry of the side chain at C-3 (asteriscane numbering) and thus would require epimerization prior to or after RCM. Our initial understanding was that RCM would be more facile with the diene that had the correct relative stereochemistry at C-3, so epimerization prior to RCM was our first goal. Nevertheless, it was even more intriguing to investigate cyclization of the diene that had the undesirable stereochemistry at C-3, since there were no previous examples in the literature to provide a gauge for the outcome of such a reaction, i.e., the synthesis of inside−outside bridging compounds using RCM. Thus, we prepared both diastereoisomers and subjected them to RCM conditions.

Deprotonation of lactone **22** with LDA/HMPA at −78 °C and quenching with 4-methyl-4-iodide gave diene **25**

**Scheme 6**




**Scheme 7**




(Scheme 6). Epimerizaton of the side chain at C-3 was achieved by deprotonation with 10 equiv of LDA and kinetically quenching with saturated aqueous $NaHCO_3$ to give a 1:5 ratio of the all-*cis* diastereoisomer **24** to starting diene **25**. These dienes were separated and individually subjected to RCM conditions. Both dienes **24** and **25** failed to cyclize under a variety of conditions using either the Grubbs'[20] or Schrock catalysts[21] (up to 50 mol %) giving recovered starting material in each case. Failure of **25** or **24** to cyclize might be rationalized as resulting from an inability of the monosubstituted alkene, the presumed preferred starting point for the metathesis, to coordinate to the metal as a result of steric hindrance associated with its orientation on the concave face of the diene and/or the respective alkene chains being too far removed for RCM to occur. The additional steric requirements for the formation of a trisubstituted alkene within an eight-membered ring may also have been a contributing factor. To address the last issue, we prepared diene **27** and the corresponding all-*cis* diastereomer **28** in a similar manner (Scheme 7). Gratifyingly, we discovered that diene **28** underwent RCM using 50 mol % of Grubbs' catalyst in $CH_2Cl_2$ at room temperature to give the "outside−outside" tricycle **30**, and more significantly, diene **27** furnished the corresponding inside−outside tricycle **29** at room temperature. The relative stereochemistry of the hydrogen at C-3 for **28** and **30** was confirmed by NOE difference spectral data; the relative stereochemistry of the inside−outside tricycle **29** was deduced by analogy with other results (vide infra). While attempts to convert the inside−outside to the outside-

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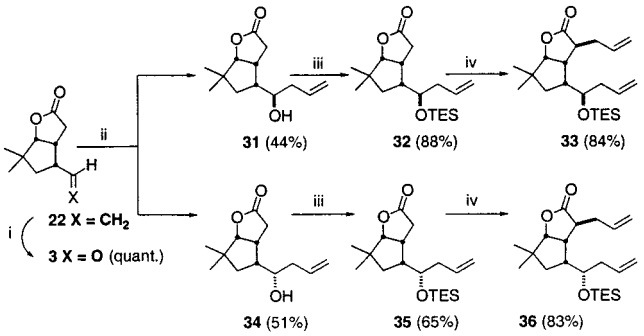
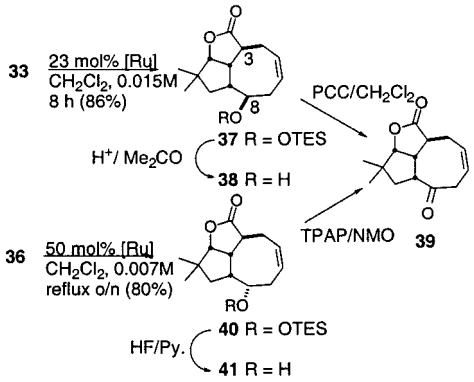
**Scheme 8**




i) $O_3/CH_2Cl_2$ -78 °C; $Me_2S$, ii) Allyl boronic acid pinacol cyclic ester; iii) TESOTf, py.; iv) LHMDS, HMPA/THF –78°C; allyl bromide.

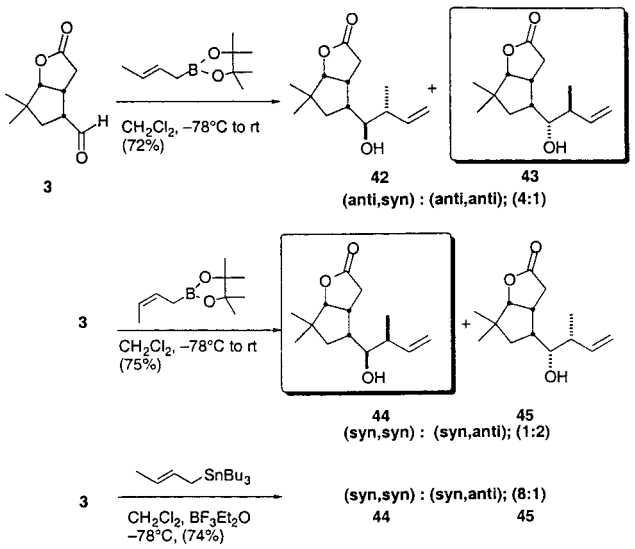
**Scheme 9**




outside tricycle proved unsuccessful, we had established the feasibility of the metathesis approach for the target molecule.

We decided to take advantage of the successful eight-membered ring synthesis by RCM and rationalized that this might be further facilitated if the alkene-bearing side chains of the diene to be cyclized were closer in length, with neither one encumbered by the concave face of the bicyclic lactone. Accordingly, we functionalized the lower side chain in **22** by ozonolysis with reductive workup using $Me_2S$, which gave the corresponding aldehyde **3** without epimerization (Scheme 8). Allylboration of aldehyde **3** with allylboronic acid pinacol cyclic ester[22] gave two homoallylic alcohols **31** and **34** in the ratio of ca. 1:1, which were separable by flash chromatography. The relative stereochemistry of the homoallylic alcohols was unknown at this stage and was assigned in hindsight from $^1$H NOE spectroscopic studies on their respective RCM products. Homoallylic alcohol **31** was converted to the corresponding TES ether **32** using TESOTf in pyridine at 0 °C. Deprotonation of lactone **32** with LiHMDS/HMPA at −78 °C followed by alkylation with allyl bromide gave diene **33**. Diene **36** was similarly prepared from homoallylic alcohol **34** (Scheme 9). Diene **33** underwent RCM upon refluxing with 23 mol % of Grubbs' catalyst in $CH_2Cl_2$ (0.015 M) for 8 h to give the corresponding inside−outside tricycle **37** (86%) (Scheme 9). The relative stereochemistry was determined from $^1$H NMR NOE difference experiments, which showed a NOE enhancement for $H_{3\alpha}$ when $H_{8\alpha}$ was irradiated. Cleavage of the TES group of **37** was effected by using 2 N HCl in acetone to give the corresponding hydroxy tricycle **38,**

**Scheme 10**




which was oxidized with $PCC/CH_2Cl_2$ to give the keto-lactone **39**. Similarly, diene **36** was subjected to reaction with 50 mol % of Grubbs' catalyst in refluxing $CH_2Cl_2$ overnight to give the corresponding inside−outside tricycle **40** (Scheme 9). The relatively larger amount of catalyst and longer reaction time required for diene **36** to cyclize can be attributed to the steric requirements for placing the bulky TES group under the newly formed bridging eight-membered ring. Again, the NOE studies on **40** corroborated with the expected inside−outside stereochemistry at the bridgehead. To further confirm this, alkene **40** was desilylated with HF/pyridine and the resulting alcohol **41** was oxidized with TPAP/NMO in $CH_2Cl_2$ to give the same keto-lactone **39**, the structure of which was unambiguously solved by X-ray analysis and is included in Supporting Information.

These results provided a sound basis for the synthesis of the fully functionalized bridging eight-membered ring via crotylation of aldehyde **3**. This would enable the stereoselective incorporation of the C-7 methyl, which was a problem in Booker−Milburn's approach toward the synthesis of **1**. Initial studies with E- and Z-crotylboration[23] gave homoallylic alcohols where the desired diastereomers **43** and **44** [(anti,anti) and (syn,syn)] bearing the correct relative stereochemistry of the methyl group (at C-7 of **1**) were the minor product in each case (Scheme 10). These results were consistent with previous crotylborations with chiral aldehydes and can be explained by invoking a chairlike transition state conformation based upon coordination between the boron and carbonyl oxygen. Steric requirements are minimized when the largest group on the chiral moiety is remote to the incoming nucleophile, and the desired diastereomers (anti, anti) and (syn, syn) must necessarily form via eclipsing interactions between the methyl group of the alkene and the medium group of the chiral moiety (Scheme 11). These interactions are larger than those present during formation of the (anti,syn) and (syn,anti) isomers where the methyl group of the alkene interacts with the smallest group on the chiral moiety.

However, we were able to improve the ratio for the (syn,syn):(syn, anti) isomers to 8:1 through E-crotylstan-

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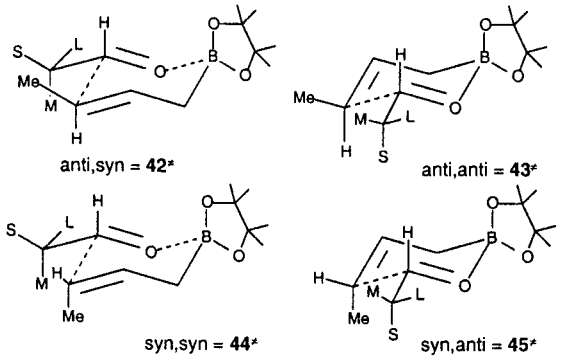
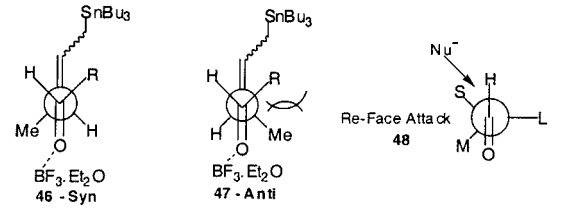
**Scheme 11**




**Scheme 12**

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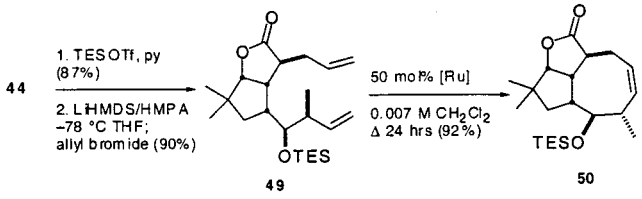


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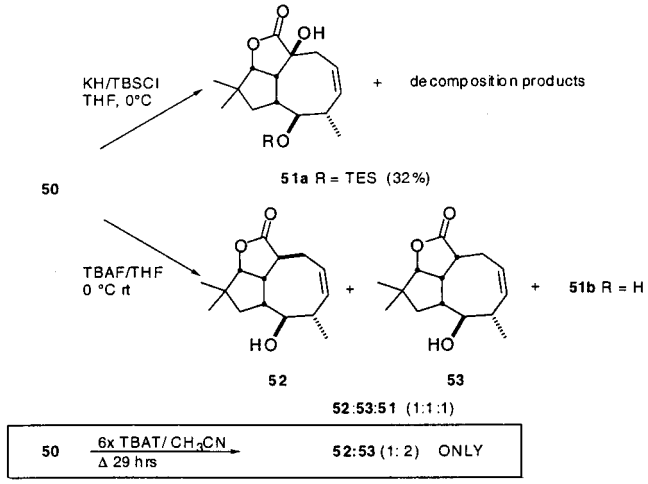
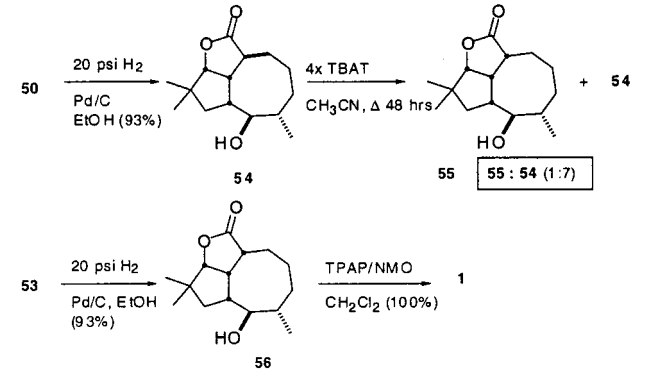



**Scheme 15**




nation in the presence of $BF_3.Et_2O$ at −78 °C (Scheme 10) which proceeds via an open transition state (Scheme 12).[24] The syn selectivity for crotylstannation of aldehydes is independent of alkene geometry and is rationalized by an anticlinal approach of the crotyl stannane to the aldehyde carbonyl. There are two diastereotopic faces available on the incoming nucleophile, but steric interactions between the R-group of the aldehyde and the Me group of the nucleophile as shown in **47** favors reaction via the diastereomeric transition state **46**, which leads to syn relative stereochemistry with respect to the newly formed C−C bond. Diastereofacial selectivity with respect to the carbonyl is governed by Felkin−Ahn control, which proceeds via **48** with syn selectivity.

Homoallylic alcohol **44** was converted to diene **49** in a manner similar to formation of alcohol **33** (Scheme 13). As demonstrated by earlier studies, we were unable to achieve efficient epimerization of the allylic side chain at C-3 prior to performing the key RCM step. Therefore, diene **49** was refluxed with Grubbs' catalyst (50 mol %) in $CH_2Cl_2$ for 24 h, which gave the inside−outside tricycle **50** in 92% yield. The relative stereochemistry of the bridgehead and the C-7 methyl group was deduced from $^1$H NMR NOE studies. At this stage, we were delighted with the formation of **50** by RCM, particularly with respect to the correct orientation of the methyl group at C-7. Our next goal was to epimerize the stereocenter at C-3, which proved more challenging than we had anticipated. Deprotonation of the "inside" hydrogen at C-3 of tricycle **50** was difficult to achieve under kinetically controlled conditions using hindered bases because of steric congestion on the concave face, and starting material was recovered unchanged. At higher temperatures (≥0 °C) any enolate that was formed was found to be unstable and decomposition occurred. In the case of the potassium enolate, oxidation to give the α-hydroxy lactone **51a** was a major byproduct. Attempts to generate and trap the enolate in an electrophilic manner using TBSOTf and $Et_3N$ (or lutidine) gave recovered starting material only. When TES ether **50** was treated with 2× TBAF in THF at 0 °C, we obtained clean desilylation to the corresponding alcohol **52**, which upon warming to room temperature for 4 h gave a 1:1:1 mixture of **52**, epimerized alcohol **53,** and α-hydroxy lactone **51b** (Scheme 14). However, the ratio of products could not be improved or reproduced. Since TBAF in THF is a strong base we wanted to minimize the formation of the α-hydroxy lactone and other decomposition products, so use of a milder source of fluoride and base was warranted. For this reason we turned our attention to tetra-*n*-butylammonium (triphenylsilyl)difluorosilicate (TBAT), which had been reported as a mild source of fluoride ion.[25] Treatment of **50** with 6× TBAT in refluxing $CH_3CN$ for 29 h gave alcohols **52** and **53** in the ratio of 1:2 with no detectable traces of the α-hydroxy lactone **51b**. We discovered that this was a thermodynamic ratio when **52** and **53** were individually resubjected to reaction with TBAT in refluxing $CH_3CN$ and the same ratio of **52** and

(24) Keck, G. E.; Savin, K. A.; Cressman, E. N. K.; Abbott, D. E. *J. Org. Chem.* **1994**, *59*, 7889. Keck, G. E.; Abbott, D. E. *Tetrahedron Lett.* **1984**, *25*, 1883.

(25) Pilcher, A. S.; Ammon, H. L.; DeShong, P. *J. Am. Chem. Soc.* **1995**, *117*, 5166.

**53** was obtained from each reaction. This result was in good agreement with Molecular Mechanics calculations obtained for **52** and **53**, which indicated that there was 0.5 kcal $mol^{-1}$ energy difference in favor of the outside−outside diastereomer **53**.[27] To further improve the ratio in favor of the outside−outside system, we wanted to increase rotational freedom within the tricyclic system. Accordingly, reduction of the double bond of **50** using 20 psi of $H_2$ and 10 mol % Pd/C in EtOH gave the desilylated saturated tricycle **54**. Treatment of **54** with 4 equiv of TBAT in refluxing $CH_3CN$ for 48 h gave only a 7:1 ratio of starting alcohol **54** to epimer **55**. This result proved not entirely in accord with Molecular Mechanics calculations, which indicated a 0.1 kcal $mol^{-1}$ difference in energy in favor of the inside−outside hydroxy tricycle **54**.[26] Howeve,r it was clear at this stage that we had achieved the optimum conditions for epimerization at C-3 with this substrate.

To complete the total synthesis, tricycle **53** was hydrogenated with Pd/C to give the saturated tricycle **56**, which was oxidized with TPAP/NMO[27] in $CH_2Cl_2$ to furnish the natural product **1** (identical to the natural product by $^1H$ NMR analysis; satisfactory spectral data, IR, MS, $^{13}C$, $^1H$ NMR NOE comparison and combustion analysis were also obtained) (Scheme 15).

(26) Structure minimizations were carried out using Molecular Mechanics available in the CAChe system (Oxford Molecular Group) version 4.0.

(27) Griffith, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. D. *J. Chem. Soc., Chem. Commun.* **1987**, 1625.

In summary, the synthesis of asteriscanolide was accomplished in 19 steps and 12% overall yield, where the pivotal steps are based on an intermolecular Pauson−Khand reaction and a ring-closing metathesis. The work leading up to this accomplishment has demonstrated that a number of simple and functionalized bridging eight-membered rings with an *in*−*out* intrabridgehead stereochemical relationship can be synthesized through RCM.

**Acknowledgment.** We thank the National Science Foundation and donors to the Krafft Research Fund for financial support. K.A.A. acknowledges the National Science Foundation and the University of Florida for funding of the purchase of the X-ray equipment. We also thank Professor Robert H. Grubbs for helpful suggestions on the metathesis step, Professor Paul A. Wender for providing $^1H$ NMR spectral data of synthetic and natural asteriscanolide, Professor James Panek for suggestions on the aldehyde crotylation, and Dr. Carmelinda Juliano for assistance with the preparation of enone **9**.

**Supporting Information Available:** Experimental details for all compounds and X-ray data tables for **39**. This material is available free of charge via the Internet at http://pubs.acs.org. Also, full crystallographic data for **39** has been deposited with the Cambridge Crystallographic Data Centre (CCDC 161294).

JO010623A