A Rapid Synthesis of Hydroxymethylacylfulvene (HMAF) Using the Allenic Pauson−Khand Reaction. A Synthetic Approach to Either Enantiomer of This Illudane Structure

Kay M. Brummond,* Jianliang Lu, and Jeffrey Petersen‡

Contribution from the Department of Chemistry, West Virginia University, Morgantown, West Virginia 26506-6045

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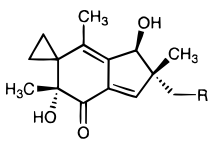
Abstract: An allenic Pauson−Khand reaction has been employed in the preparation of (±)-hydroxymethylacylfulvene (HMAF), an anticancer agent that is currently in Phase II clinical trials for a variety of solid tumor types. The synthesis is effected in 11 steps from commercially available starting materials. In addition, an asymmetric route to the title compound has been established by intersecting the racemic synthesis with an enantiomerically pure intermediate. The preparation of the enantiomerically pure intermediate involved the Sharpless asymmetric dihydroxylation (AD) of a trisubstituted olefin of an enyne system. This approach provides access to both enantiomers of HMAF simply by changing the ligands in the Sharpless AD reaction. Optimized conditions for the stereospecific synthesis of *E* or *Z* trisubstituted enynes from an aliphatic ketone using either Peterson olefination or Horner−Wadsworth−Emmons protocols are reported. Finally, a better understanding of the stereoelectronic requirements of the allenic P−K reaction is recognized.

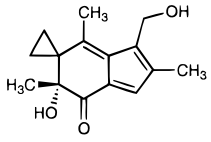
Introduction

The naturally occurring sesquiterpenes illudin M (**1**) and S (**2**) have been shown to possess potent antitumor activity, but when tested in vivo were found to have a poor therapeutic index.[1] Subsequently, illudin analogues have been prepared that show greatly improved efficacy when compared to the parent compounds.[2] One analogue in particular, hydroxymethylacylfulvene (HMAF) (**3**), has generated a tremendous amount of excitement since it has been proven effective against breast, lung, and colon tumors in animal models while exhibiting dramatically reduced toxicity.[3] HMAF (**3**) is currently in Phase II clinical trials which are being supported by the National Cancer Institute and MGI Pharma, Inc. Two of the Phase II studies, involving prostate and ovarian cancers, have been expanded within the last year based upon signs of positive clinical results. The mechanism by which HMAF selectively kills cancer cells is currently being studied. It is believed that HMAF binds covalently to protein, DNA and RNA, and that damage induced by alkylation of these multiple targets may contribute to the proapoptotic and antiproleferative action of this drug.[4]

The first total synthesis of HMAF was reported by McMorris,[2b] utilizing the Padwa carbonyl ylide 1,3-dipolar cycloaddition methodology[5] to arrive at the basic illudane skeleton. One impetus for an alternative synthesis of HMAF is that it provides a novel substructure for the preparation of new analogues. We have recently communicated a racemic synthesis of HMAF[6] utilizing an allenic Pauson−Khand reaction that has been developed in our group.[7] In this paper we describe our racemic approach in full detail and also disclose a route to enantiomerically pure HMAF. An asymmetric approach to hydroxymethylacylfulvene (**3**) is desirable since, while both enantiomers demonstrate antitumor properties, HMAF derived from the natural illudin S is twice as potent as its unnaturally derived enantiomer.



illudin M R = H (1)
illudin S R = OH (2)



hydroxymethylacylfulvene (HMAF) (3)

Synthetic Plan

The illudane skeleton possesses a novel structure unrelated to any other natural occurring compounds and synthetic methods to arrive at this substructure are limited.[8] An allenic variant of the Pauson−Khand (P−K) type cycloaddition has been devel-

* To whom correspondence should be addressed. Phone: (304) 293-3435 ext 4445. Fax: (304) 293-4904. E-mail: kbrummon@wvu.edu.

‡ X-ray crystallography.

(1) (a) McMorris, T. C.; Kelner, M. J.; Wang, W.; Diaz, M. A.; Estes, L. A.; Taetle, R. *Experientia* **1996**, *52*, 75. (b) McMorris, T. C.; Kelner, M. J.; Wang, W.; Yu, J.; Estes, L. A.; Taetle, R. *J. Nat. Prod.* **1996**, *59*, 896. (c) For previous syntheses of illudin M, see: Kinder, F. R., Jr.; Blair, K. W. *J. Org. Chem.* **1994**, *59*, 6965. (d) Matsumoto, T.; Shirahama, H.; Ichihara, A.; Shin, H.; Kagawa, S.; Sakan, F.; Matsumoto, S.; Nishida, S. *J. Am. Chem. Soc.* **1968**, *90*, 3280.

(2) (a) McMorris, T. C.; Yu, J.; Hu, Y.; Estes, L. A.; Kelner, M. J. *J. Org. Chem.* **1997**, *62*, 3015. (b) McMorris, T. C.; Hu, Y.; Yu, J.; Kelner, M. J. *Chem. Commun.* **1997**, 315. (c) McMorris, T. C.; Kelner, M. J.; Wang, W.; Estes, L. A.; Montoya, M. A.; Taetle, R. *J. Org. Chem.* **1992**, *57*, 6876.

(3) (a) MacDonald, J. R.; Muscoplat, C. C.; Dexter, D. L.; Mangold, G. L.; Chen, S.-F.; Kelner, M. J.; McMorris, T. C.; Von Hoff, D. D. *Cancer Res.* **1997**, *57*, 279. (b) Kelner, M. J.; McMorris, T. C.; Estes, L. A.; Wang, W.; Samson, K. M.; Taetle, R. *Investigational New Drugs* **1996**, *14*, 161.

(4) Woynarowski, J. M.; Napier, C.; Koester, S. K.; Chen, S.-F.; Troyer, D.; Chapman, W.; MacDonald, J. R. *Biochem. Pharmacol.* **1997**, *54*, 1181.

(5) Padwa, A.; Curtis, E. A.; Sandanayaka, V. P. *J. Org. Chem.* **1996**, *61*, 73.

(6) Brummond, K. M.; Lu, J. *J. Am. Chem. Soc.* **1999**, *121*, 5087.

(7) (a) Brummond, K. M.; Wan, H.; Kent, J. L. *J. Org. Chem.* **1998**, *63*, 6535. (b) Brummond, K. M.; Wan, H. *Tetrahedron Lett.* **1998**, *39*, 931. (c) Kent, J. L.; Wan, H.; Brummond, K. M. *Tetrahedron Lett.* **1995**, *36*, 2407.

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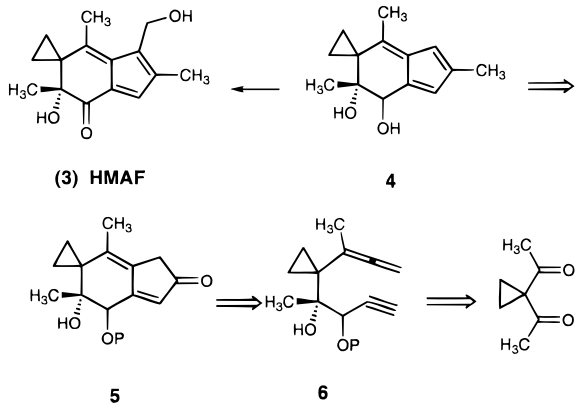
Scheme 1

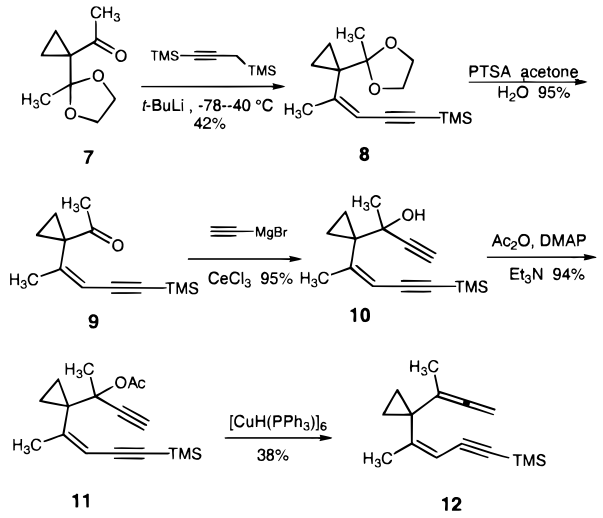


oped in our group which provides access to molecules possessing 4-alkylidene or α-methylene cyclopentenones depending upon the reactant structure and reaction conditions.[7] On the basis of our preliminary investigations, the substrate selectivity observed in the P−K type cycloadditions of 3,3-disubstituted allenes is ideally suited for the synthesis of the illudin class of compounds. The general retrosynthesis of our approach to HMAF (**3**) is presented in Scheme 1. The target structure was functionalized fulvene **4**, which has been previously converted to HMAF in two steps ((1) Dess−Martin periodinane, (2) H_2SO_4, CH_2O).[2b] We reasoned that fulvene **4** represented a thermodynamic well and could be obtained from the 4-alkylidene cyclopentenone **5** via the addition of a methyl anion to the ketone moiety and subsequent dehydration of the newly formed tertiary alcohol. The most challenging structural feature of retron **5** is the 4-alkylidene cyclopentenone substructure which we anticipated would result from an allenic P−K-type cycloaddition of the densely functionalized alkynyl allene **6**. Preliminary investigations strongly suggested that the cycloaddition would occur with the least substituted double bond of the allene. Retrosynthetic simplification of alkynyl allene **6** is relatively straightforward furnishing 1,1-diacetylcyclopropane as a potential precursor. 1,1-Diacetylcyclopropane represents a readily available starting material that can be prepared in good yields from 2,4-pentanedione.[9] In addition, 1,1-diacteylcyclopropane possesses C_2-symmetry, providing a variety of options for the construction of the alkynyl allene **6**.

Results and Discussion

Preparation of Cyclization Precursor 12. Initially, our synthetic strategy focused on the stereospecific preparation of the *Z*-enyne **8** (Scheme 2). Addition of the lithium anion of 1,3-bis(trimethylsilyl)propyne to the monoketal of 1,1-diacetylcyclopropane **7** using the Yamamoto protocol[10] afforded the Peterson olefination product **8** as the *Z* stereoisomer in a 42% yield. The stereoselectivity of this reaction was temperature dependent since a mixture of *E:Z* enynes was obtained if the reaction was allowed to warm above −40 °C. Subsequent treatment of the ketal of **8** with *p*-toluenesulfonic acid afforded ketone **9** in 95% yield. We initially turned our attention to the

Scheme 2



installation of the dihydroxyl moiety of compound **6** (Scheme 1). We reasoned that this substitution pattern could be achieved by the chemoselective, asymmetric dihydroxylation (AD) of the *Z*-enyne **9**. Literature precedent shows that mono- and disubstituted olefins of enynes can be selectively dihydroxylated in good yields and high ee's.[11] Unfortunately, initial attempts to effect a Sharpless AD of the olefin of the corresponding enyne moiety met with complications and recovery of the starting material. On the basis of these results, it was decided to delay the AD until after the key allenic P−K cyclization. Thus, the methyl ketone moiety was converted to the desired allene in the three-step process described below. Addition of ethynylmagnesium bromide in the presence of 1 equiv of cerium trichloride resulted in the propargylic alcohol **10** in 95% yield.[12] In the absence of $CeCl_3$ the yields for this ethynylation reaction were low (∼40%). Conversion of the sterically hindered propargylic alcohol to the propargylic acetate **11** was sluggish using standard acetylation conditions. For instance, treatment of the hydroxyl moiety to acetic anhydride, pyridine, and DMAP in CH_2Cl_2 gave only a 16% yield of the desired acetate **11** after 3 days. Likewise, deprotonation of **10** with sodium hydride and addition of acetyl chloride also gave very low yields of acetate **11**. The Vedejs dual-activation strategy for benzoylation of hindered alcohols using magnesium bromide and benzoic anhydride resulted in immediate decomposition of the starting material.[13] The rapid decomposition of **10** was attributed to the neighboring cyclopropyl moiety, that is most likely undergoing a Julia-type ring opening under the Lewis acidic reaction conditions.[14] Fortunately, a facile and high-yielding acylation was observed by the treatment of **10** with excess acetic anhydride and catalytic DMAP in neat triethylamine.[15] Within 1 h, the starting material was consumed and a simple filtration and removal of solvent furnished acetate **11** in 94% yield. To prevent decomposition of this acid-labile acetate, it was converted directly to the allene **12** without further purification. The conversion of the propargylic acetate **11** to allene **12** also

(8) (a) Ahmar, M.; Locatelli, C.; Colombier, D.; Cazes, B. *Tetrahedron Lett*. **1997**, *38*, 5281. (b) Shibata, T.; Koga, Y.; Narasaka, K. *Bull. Chem. Soc. Jpn*. **1995**, *68*, 911. (c) Johnson, W. S.; Cox, J. M.; Graham, D. W.; Whitlock, H. W., Jr. *J. Am. Chem. Soc*. **1967**, *89*, 4524.

(9) (a) Podder, R. K.; Sarkar, R. K.; Ray, S. *Indian J. Chem*. **1998**, *27B*, 530. (b) Ogoshi, H.; Kikuchi, Y.; Yamaguchi, T.; Toi, H.; Aoyama, Y. *Organometallics* **1987**, *6*, 2175. 1,1-Diacetylcyclopropane was prepared from 2,4-pentanedione, 1,2-dibromoethane, and potassium carbonate in DMF.

(10) Yamakado, Y.; Ishiguro, M.; Ikeda, N.; Yamamoto, H. *J. Am. Chem. Soc*. **1981**, *103*, 5568.

(11) (a) Jeong, K.-S.; Sjö, P.; Sharpless, K. B. *Tetrahedron Lett*. **1992**, *33*, 3833. (b) Tani, K.; Sato, Y.; Okamoto, S.; Sato, F. *Tetrahedron Lett*. **1993**, *34*, 4975. (c) Caddick, S.; Shanmugathasan, S.; Brasseur, D.; Delisser, V. M. *Tetrahedron Lett*. **1997**, *38*, 5735. (d) Wang, Z.-M.; Shen, M. *Tetrahedron: Asymmetry* **1997**, *8*, 3393.

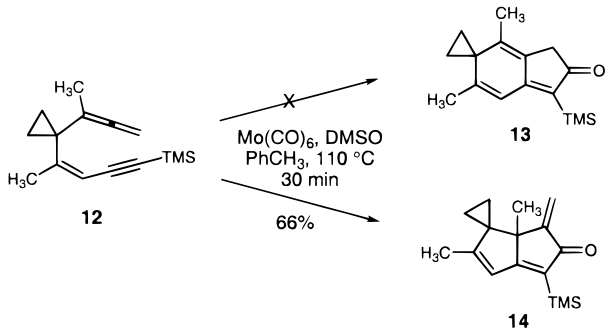
(12) Imamota, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc*. **1989**, *111*, 4392. For large scale drying of $CeCl_3 \cdot 7H_2O$, see: Takeda, N.; Imamota, T. *Org. Synth*. **1998**, *76*, 228.

(13) Vedejs, E.; Daugulis, O. *J. Org. Chem*. **1996**, *61*, 5702.

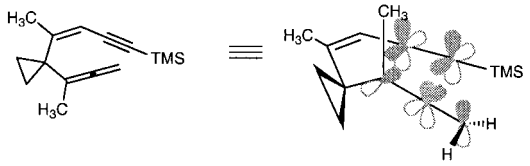
(14) Descoins, C.; Samain, D. *Tetrahedron Lett*. **1976**, *10*, 745.

(15) Hofle, G.; Steglich, W. *Synthesis* **1972**, 619.

Scheme 3



Scheme 4



proved problematic. Treatment of the acetate **11** with $Pd(PPh_3)_4$ and SmI_2 led to cyclopropane ring opening and concomitant elimination of the acetate.[16] Other methods of transforming propargylic acetates to allenes were tried with little or no success.[17] We were gratified to find that Strykers' reagent $[(PPh_3)CuH]_6$ delivers a hydride to afford the desired allene **12** without serious complications.[18] The low yield (38%) was in part attributed to volatility; however, with the P−K precursor in hand we set out to effect the key cyclization reaction.

Construction of Tricarbocyclic Skeleton. Treatment of alkynyl allene **12** to the standard allenic P−K conditions used in our laboratory[7] afforded a cyclization product in less than 30 min (Scheme 3). To our surprise, the cyclization afforded none of the desired 4-alkylidene cyclopentenone **13** but gave only the α-methylene cyclopentenone **14** in 66% yield. This was in direct contrast to all preliminary investigations[7] which suggested that cyclization would occur with the least substituted double bond of the allene to afford **13**. A more detailed examination of models shows the overlap of the π-bond orbitals of the internal double bond of the allene with the alkyne is more favorable than that of the external double bond of the allene (Scheme 4). While the desired cycloadduct **13** was not obtained from this experiment, this result was not entirely unexpected and provides us with a better understanding of the stereoelectronic requirements of the allenic P−K reaction. On the basis of these results we reasoned that a more conformationally flexible P−K precursor would be required to afford the desired skeleton.

Preparation of Precursor 18b. In an approach to a more conformationally flexible cyclization substrate, 1,1-diacetylcyclopropane **15**[9] was treated with the lithium anion of the *tert*-butyldimethylsilyl ether of 3-trimethylsilyl-3-propyn-1-ol (Scheme 5) to afford ketone **16** as a 1.3:1 (anti/syn) mixture of diastereomers in 57% yield.[19] The relative stereochemistry of the two newly generated centers was unambiguously assigned by X-ray crystallographic analysis of the syn-diastereomer (Figure

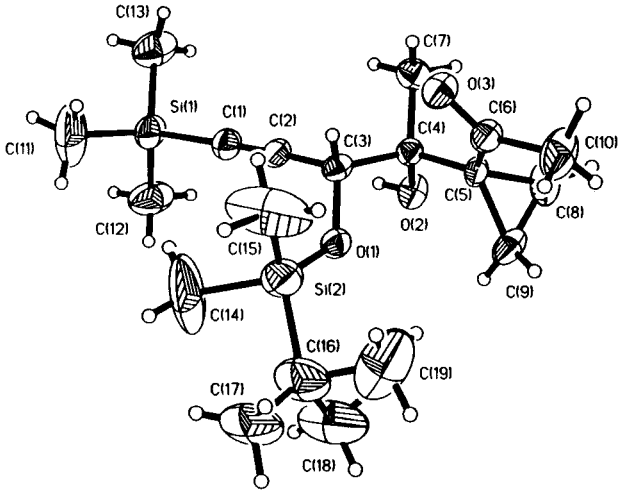
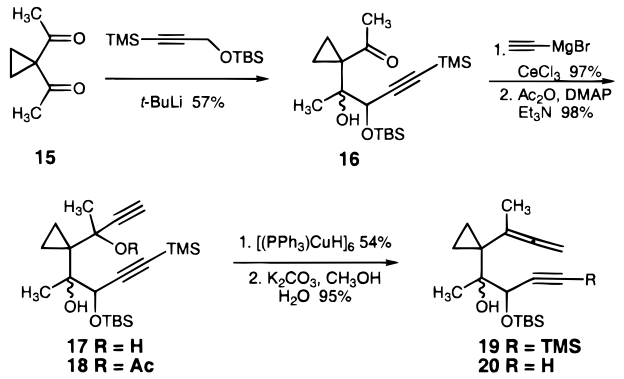


Figure 1.

Scheme 5



1). These diastereomers were advanced through the synthetic sequence in two ways. First, they were separated by column chromatography and converted to acylfulvene **21** independently, and second, they were taken on as a mixture to the final product, HMAF (**3**). Conversion of the methyl ketone **16** to the alkynyl allene **20** was achieved in a fashion analogous to the preparation of the alkynyl allene **12** (vide supra). Addition of ethynylmagnesium bromide to ketone **16** in the presence of cerium trichloride gave the desired propargylic alcohol **17** in 97% yield. Independent conversion of the diastereomers of ketone **16** to the propargylic alcohol **17** showed the major isomer (*anti*-**16**) affording a 9.2:1 mixture of inseparable diastereomers and the minor isomer (*syn*-**16**) affording only one diastereomer. Next, selective formation of the propargylic acetate of the less hindered tertiary alcohol gave diyne **18** in 98% yield. Treatment of propargylic acetate **18** with $[CuH(PPh_3)]_6$ afforded the allene **19** in 54% yield.[20] Finally, the trimethylsilyl moiety was removed from the alkyne terminus using a standard protocol to afford the desired cyclization precursor **20** in 95% yield.

The Allenic P−K Reaction and the Synthesis of Racemic Hydroxymethylacylfulvene. We were very pleased to discover

(16) (a) Tabuchi, T.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1986**, *27*, 5237. (b) Mikami, K.; Yoshida, A.; Matsumoto, S.; Feng, F.; Matsumoto, Y. *Tetrahedron Lett.* **1995**, *36*, 907. (c) Yoshida, A.; Mikami, K. *Synlett* **1997**, 1375.

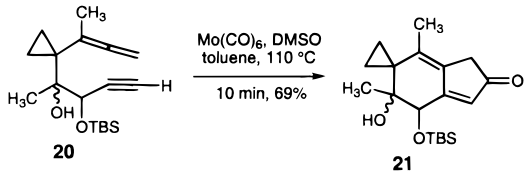
(17) (a) Borden, W. T.; Corey, E. J. *Tetrahedron Lett.* **1969** 313. (b) Leclair, M.; Jean, P.; Lopez, R.; Ricard, L.; Lallemand, H. P. *Tetrahedron* **1995**, *51*, 6983.

(18) Daeuble, J. F.; McGettigan, C.; Stryker, J. M. *Tetrahedron Lett.* **1990**, *31*, 2397.

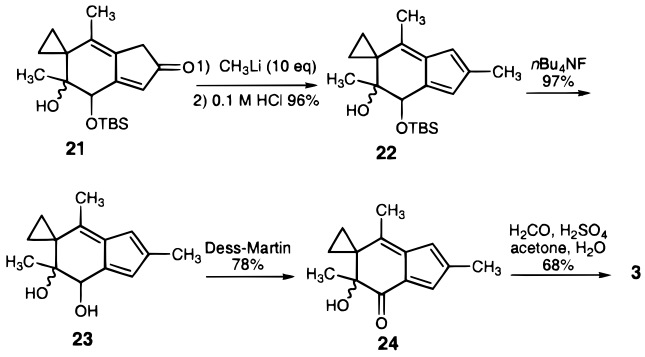
(19) We did not observe any product derived from the addition of the allenyl anion. For a review of the preparation and application of propargyl and allenyl organometallics, see: Yamamoto, H. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: New York, 1991; Vol. *2*, p 81.

(20) Attempts to convert the methyl ketone **16** directly to the allene **19** using (1-bromovinyl)trimethylsilane under Peterson olefination conditions were not successful. (a) Hudrlik, P. F.; Kassim, A. M.; Agwaramgbo, E. L. O.; Doonquah, K. A.; Roberts, R. R.; Hudrlik, A. M. *Organometallics* **1993**, *12*, 2367. (b) Paquette, L. A.; Wells, G. J.; Horn, K. A.; Yan, T.-H. *Tetrahedron* **1983**, *39*, 913.

Scheme 6



Scheme 7



that alkynyl allene **20** undergoes a rapid cycloaddition (10 min) under the standard allenic P−K conditions [$Mo(CO)_6$, DMSO, toluene, 110 °C] to produce the 4-alkylidene cyclopentenone **21** as the only observed cycloadduct in 69% yield (Scheme 6). With the successful construction of the key intermediate 4-alkylidene cyclopentenone **21**, we turned our attention to the completion of the racemic synthesis of the target compound **3**. Treatment of the ketone moiety of alkylidene cyclopentenone **21** with excess methyllithium in the presence of cerium trichloride gave the desired tertiary alcohol which underwent spontaneous dehydration upon acidic workup to afford fulvene **22** in 96% yield (Scheme 7). Removal of the TBS protecting group of the silyl ether was effected using tetra-*n*-butylammonium fluoride that provided diol **23** in 97% yield. The secondary alcohol of compound **23** was oxidized to the ketone with the Dess−Martin periodinane reagent to give the acylfulvene **24** in 78% yield. The ^{1}H NMR spectrum of synthetic **24** was identical with the spectrum of an authentic sample provided by MGI Pharma, Inc. The synthesis of HMAF (**3**) was completed using the previously reported procedure, whereby the hydroxymethyl moiety is introduced by treatment of acylfulvene **24** with formaldehyde and sulfuric acid in acetone/water.[2b]

An Enantioselective Synthesis of Hydroxymethylacylfulvene (3). Having developed a method for the rapid synthesis of (±)-hydroxymethylacylfulvene, we became interested in applying this method in an asymmetric approach to the title compound. This is of particular importance since HMAF derived from the natural illudin S (**2**) is two times more potent than the unnatural enantiomer. From a practical perspective, the ideal situation would be to develop an enantioselective route to one of the chiral intermediates in the racemic synthesis. We thus set about exploring this potential strategy.

Our first approach to enantiopure material involved a chiral ketal protecting group. During our investigations we had observed an unusual diastereoselectivity in the addition of the lithio derivative of the *tert*-butyldimethylsilyl ether of 3-trimethylsilyl-3-propyn-1-ol to ketone **7** (Scheme 8). We felt that this diastereoselectivity might be utilized to synthesize enantiomerically enriched material in the presence of a chiral ketal protecting group (Figure 2).[21]

Chiral Ketal Approach. To explore the directing potential of a chiral protecting group, chiral ketal **7a** was prepared by

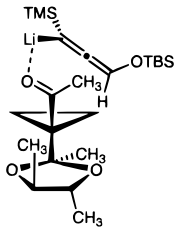


Figure 2.

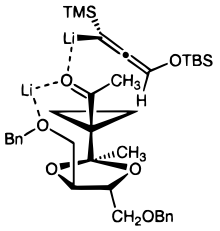
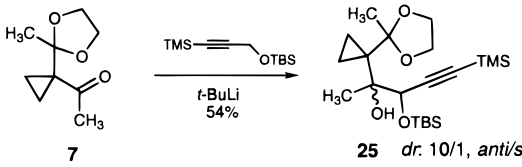


Figure 3.

Scheme 8



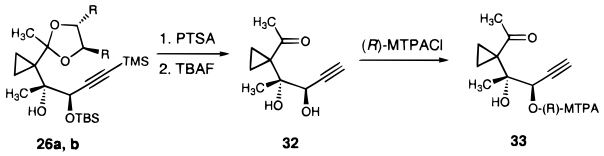
the treatment of 1,1-diacetylcyclopropane with (*2R*,*3R*)-(−)-butanediol and catalytic PTSA in refluxing benzene. Addition of the lithio anion of *tert*-butyldimethylsilyl ether of 3-trimethylsilyl-3-propyn-1-ol to ketone **7a** afforded **26a** in a 33% yield as a 10:1 anti/syn mixture of diastereomers. Separation of the diastereomers followed by deketalization and removal of the *tert*-butyldimethylsilyl protecting group afforded the dihydroxy ketone. The major anti-diastereomer was converted to the mono Mosher ester[22] by acylation of the more reactive propargylic hydroxyl group.[23] ^{1}H NMR analysis of the Mosher ester indicated the asymmetric addition had occurred in a disappointing 13% ee.

We felt that higher enantiomeric excesses might be accessible by incorporating a chiral ketal with groups capable of chelation. In particular, chelation between the ketone and benzyloxy-substituted ketal might limit the conformational mobility of the ketone and enhance the selectivity of the addition (Figure 3). Chiral ketal **7b** was prepared in 37% yield from (*2R*,*3R*)-(+)-1,4-dibenzyloxy-2,3-butanediol in a manner analogous to the preparation of **7a**. Addition of the propargyl anion in the presence of lithium bromide resulted in 37% yield of **26b** as a 10:1 anti/syn mixture of diastereomers. Conversion of **26b** to the mono Mosher ester as previously described[23] and analysis by ^{1}H NMR showed only a 15% ee. Since the levels of asymmetric induction as well as the chemical yields were undesirably low, this approach was abandoned. Other strategies

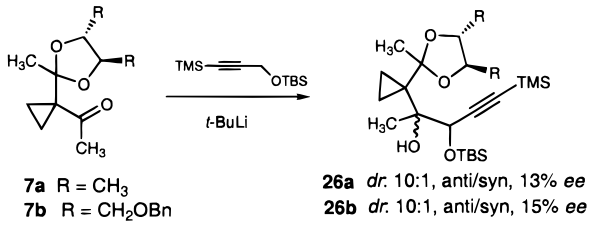
(21) Chiral ketals have been successfully employed as chiral auxiliaries in Diels−Alder reactions. Nemoto, H.; Nagai, M.; Kohzuki, K.; Fukumoto, K. *J. Chem. Soc., Perkin Trans 1* **1988**, 2835.

(22) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

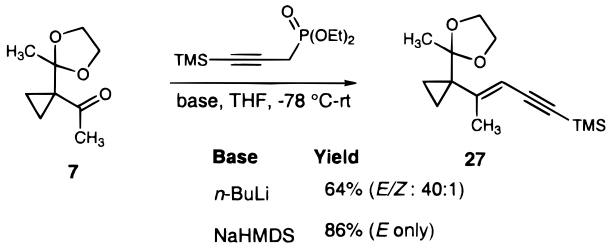
(23) For analysis of the enantiomeric excesses the Mosher esters were synthesized by the following transformations.



Scheme 9



Scheme 10



involving the asymmetric addition of the propargyl anion to 1,1-diacetylcyclopropane were examined (BOX ligands)[24] but none led to satisfactory chiral induction.

Asymmetric Dihydroxylation Approach. With the disappointing results from the various attempts at the asymmetric addition reaction, we decided to reinvestigate the Sharpless asymmetric dihydroxylation protocol as an alternative approach to the enantiomerically pure material.[11] Upon review of the literature, we noticed only a few examples of asymmetric dihydroxylation of enynes with no reported examples of trisubstituted enynes undergoing a Sharpless AD reaction. The unreactivity associated with the AD reaction of the trisubstituted enynes is presumably due to both sterics and the electron deficient nature of the enyne system. Further examination of the literature reveals that *E*-olefins are more reactive toward the asymmetric dihydroxylation conditions than *Z*-olefins. On the basis of this precedent we felt that our initial difficulty with the AD reaction might have been due to the *Z*-stereochemistry of **9** (Scheme 2) and that we might establish the absolute stereochemistry of our system utilizing a Sharpless AD reaction on a trisubstituted *E*-enyne system.

There are many methods which have been developed for the stereoselective preparation of enynes but each suffers from its own set of limitations. Among them, the Peterson olefination[10,25] and the Wittig[26] reaction have been used to generate terminal enynes. However, while both of these methods work well with aldehydes, lower *E/Z* selectivities and yields are reported when aliphatic ketones are employed.

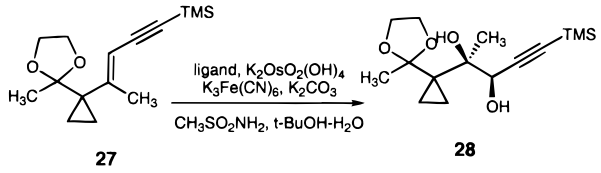
The stereoselective conversion of monoprotected diketone **7** was effected as follows. Peterson olefination of **7** with 1,3-bis-(trimethylsilyl)propyne afforded the *Z*-enyne **9** exclusively upon careful control of the temperature (Scheme 2). In contrast, the Horner−Wadsworth−Emmons protocol involving treatment of ketone **7** with the ylide of diethyl 3-trimethylsilylpropynyl phosphonate[27] affords the *E*-enyne **27** selectively (Scheme 10). Interestingly, when *n*-BuLi was used as the base, enyne **27** was obtained in a 64% yield with an *E/Z* ratio of 40:1. However, sodium hexamethyldisilyl azide afforded the enyne **27** in an 86% yield as the *E*-isomer exclusively.

Table 1. Asymmetric Dihydroxylation of Enyne **28**[a]

entry	ligand	% yield[b]	% ee[c]
1	$(DHQD)_2PHAL$	15	83
2[d]	$(DHQD)_2PHAL$	12	86
3	$(DHQD)_2AQN$	8	51
4	DHQD-MQE	9	82
5	$(DHQD)_2PYR$	39	>95
6[e]	$(DHQD)_2PYR$	37	>95

[a] The standard conditions for the AD reaction use $K_2OsO_2(OH)_4$ (2 mol %), ligand (10 mol %), $K_3Fe(CN)_6$ (3 equiv), K_2CO_3 (3 equiv), $CH_3SO_2NH_2$ (1 equiv), 0.1 M solution in *t*-BuOH, and H_2O for 48 h. [b] Isolated yield. [c] Determined by ^1H NMR analysis of the Mosher ester. [d] The reaction was carried out at 0 °C for 6 days. [e] Three equivalents of $CH_3SO_2NH_2$ were employed.

Scheme 11



With the stereoselective synthesis of *E*-enyne **27** secured, we turned our attention to the Sharpless asymmetric dihydroxylation. Sharpless reports that the optimum conditions for the dihydroxylation of mono- and disubstituted enynes utilize 1,4-bis(9-*O*-dihydroquinidine)phthalazine ($DHQD_2$-PHAL).[11a] Subjection of enyne **27** to the commercial AD-mix-β [$K_2OsO_2(OH)_4$, $K_3Fe(CN)_3$, $(DHQD)_2PHAL$] showed negligible amounts of product formation even after 2 days. Increasing the amount of potassium osmate to 2 mol % and the ligand $(DHQD)_2PHAL$ to 10 mol % did allow us to isolate **28** in a 15% yield (83% ee) (entry 1, Table 1).[28] Lowering the temperature showed no increase in yield or enantioselectivity (entry 2, Table 1). The enantiomeric excesses were determined by the conversion of the diol to the Mosher ester. With these promising results in hand, we set forth to optimize the efficiency and enantioselectivity of the AD reaction.

Other commercially available dihydroquinidine (DHQD)-derived ligands were surveyed for their ability to carry out the AD reaction and these results are summarized in Table 1. Under the standard conditions (2 mol % $K_2OsO_2(OH)_4$, 10 mol % ligand), inferior results were obtained from the recently developed anthraquinone ligand $(DHQD)_2AQN$ (entry 3, Table 1) and 4-methyl-2-quinolyl ligand DHQD-MQE (entry 4, Table 1). In each of these cases the diol **28** was isolated in very low yields and moderate enantiomeric excesses. Significant improvements were observed when using 2,5-diphenyl-4,6-pyrimidinediyl derived ligands. For example, when $(DHQD)_2PYR$ was used as a ligand, diol **28** was obtained in 39% yield as a single enantiomer by Mosher ester analysis (entry 5, Table 1). Increasing the amount of $CH_3SO_2NH_2$ had no effect on the AD reaction (entry 6, Table 1). In addition, increasing the amount of $K_2OsO_2(OH)_4$ to 5 mol % had a detrimental effect on the yield giving rise to only a 5% yield of the diol **28**. Protection of the acetylenic moiety of the enyne **27** with $Co_2(CO)_8$ prior to effecting the AD reaction resulted in extensive decomposition of the starting material.

Since it is known that the AD reactions are sensitive to steric effects, the ketal protecting group was removed and enyne **29** was subjected to the optimized AD conditions (Scheme 12). Diol **30** was obtained in a 49% yield (>95% ee) accompanied by diol **31** in 11% yield (>95% ee) where the TMS moiety

(24) Evans, D. A.; Woerpel, K. A.; Hinman, M. M.; Faul, M. M. *J. Am. Chem. Soc.* **1991**, *113*, 726.
(25) (a) Corey, E. J.; Rucker, C. *Tetrahedron Lett.* **1982**, *23*, 719. (b) Overman, L. E.; Thompson, A. S. *J. Am. Chem. Soc.* **1988**, *110*, 2248.
(26) Lipshutz, B. H.; Lindsley, C. *J. Am. Chem. Soc.* **1997**, *119*, 4555;
(27) Gibson, A. W.; Humphrey, G. R.; Kennedy, D. J.; Wright, S. H. B. *Synthesis* **1991**, 414.
(28) Walsh, P. J.; Sharpless, K. B. *Synlett* **1993**, 605.

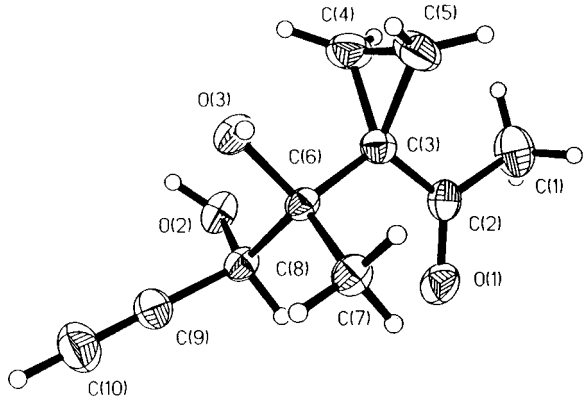
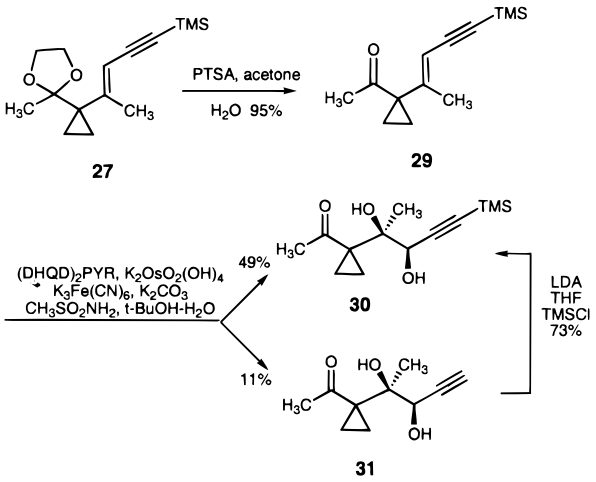


Figure 4.

Scheme 12



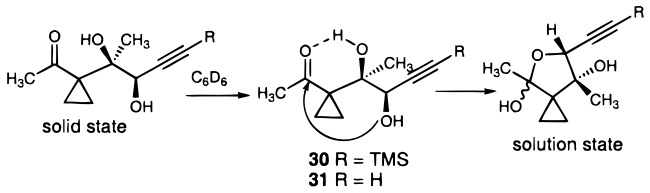
was removed under the reaction conditions. Conversion of diol **31** to **30** can be effected in good yield by deprotonation with lithium diisopropylamide and addition of trimethylsilyl chloride.

The structural assignments of compounds **30** and **31** and their absolute configuration warrants further comment. The absolute stereochemistry of the two centers has been assigned (*R,R*) based upon Sharpless' mnemonic device.[29] The structure and relative stereochemistry of diols **30** and **31** were established unambiguously by X-ray crystallographic analysis of diol **31** (Figure 4). The ^{1}H and ^{13}C NMR spectra of diols **30** and **31** were complicated due to diastereomeric intramolecular hemiketal formation that occurred spontaneously upon dissolution (Scheme 13).

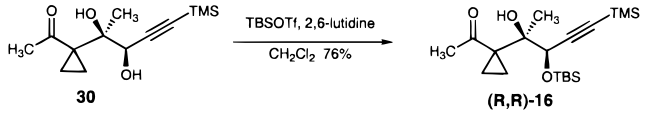
Enantiomerically pure diol **30** was transformed into the *O*-TBS protected propargyl alcohol **(*R,R*)-16** using TBSOTf and 2,6-lutidine in CH_2Cl_2 in 74% yield (Scheme 14). At this point, the enantioselective route intersects with the previously completed racemic synthesis of HMAF (**3**). This constitutes a formal enantioselective synthesis of HMAF (**3**) since conversion of (*R,R*)-**16** to the final product results in enantiopure **3**. It should also be noted that $(DHQ)_2PYR$ is known to afford the opposite diol stereochemistry with similar reactivity as $(DHQD)_2PYR$ in the Sharpless AD. Thus, this synthetic approach provides access to both enantiomers of HMAF (**3**).

(29) (a) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483. (b) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem*. **1992**, *57*, 2768.

Scheme 13



Scheme 14



Conclusions

We have rapidly assembled the potent antitumor agent hydroxymethylacylfulvene (**3**) in 11 steps from commercially available starting materials. This synthesis features a novel application of the allenic P−K-type cycloaddition to provide rapid entry into the illudane skeleton. In addition, we have reported optimized conditions for the stereospecific synthesis of *E* or *Z* trisubstituted enynes from an aliphatic ketone using either Peterson olefination or Horner−Wadsworth−Emmons protocols. Finally, we have established an asymmetric route to the title compound by intersecting the racemic synthesis with an enantiomerically pure intermediate (*R,R*)-**16**. The preparation of (*R,R*)-**16** involves an asymmetric dihydroxylation of a trisubstituted olefin of an enyne using $(DHQD)_2PYR$. This is the first reported example of a trisubstituted olefin of an *E*-enyne undergoing a Sharpless AD reaction. This approach also provides access to the enantiomeric (*S,S*)-**16** and consequently both enantiomeric forms of HMAF (**3**) simply by changing the ligands in the Sharpless AD reaction.

We are currently investigating the synthesis of HMAF derivatives. A benefit of this approach to the target structure is that it provides ready access to derivative structures not available from the degradative synthesis from illudin S (**2**) or the McMorris approach. These derivatives will be tested for antitumor activities and the results reported in subsequent publications.

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Supporting Information Available: Details for the preparations and characterizations of all new compounds, including copies of ^{1}H NMR, ^{13}C NMR, and IR spectra (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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