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# Enantioselective Synthesis of (−)-Pentalenene

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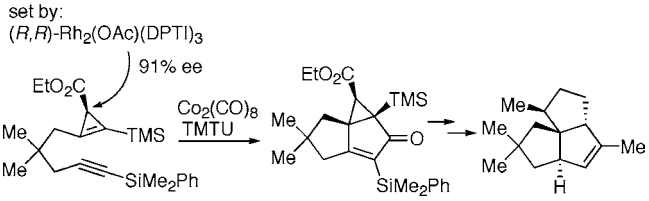
## ABSTRACT




**A short, enantioselective synthesis of (−)-pentalenene is described. Catalytic enantioselective cyclopropenation with (*R,R*)-Rh$_2$(OAc)(DPTI)$_3$ was used to set the absolute stereochemistry, and an intramolecular Pauson−Khand reaction of the resulting cyclopropenyne was used to establish the quaternary center.**

For the past three decades, triquinane natural products have been considered to be classic[1] targets for total synthesis because of their biological activity and because of their compact, structurally complex architectures.[2] As the biosynthetic precursor to the pentalenolactone family of antibiotics,[3] pentalenene has attracted intense and consistent interest from the synthetic community during the past 25 years, culminating in numerous total and formal syntheses.[4−25] However, all but one[10] of these syntheses produced racemic pentalenene, and an enantioselective synthesis has not been reported previously.[25] In general for the angular triquinane

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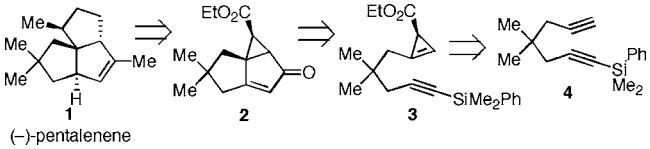
natural products, there are a large number of total syntheses but relatively few enantioselective syntheses.[26] Especially rare are syntheses of angular triquinine natural products that utilize enantioselective catalysis to establish the absolute stereochemistry.[26a,b] Integral to the challenge of an enantioselective synthesis of the angular triquinanes is the asymmetric installation of the central, quaternary carbon.[27]

The Pauson−Khand reaction is a multicomponent reaction that has found particular utility for the stereocontrolled construction of triquinane natural products.[28] In seminal work, Schore utilized an intramolecular, diastereoselective Pauson−Khand reaction as the key step for the synthesis of pentalenene.[13] In the only nonracemic synthesis of pentalenene, Hua utilized a Pauson−Khand reaction to prepare 7,7-dimethylbicyclo[3.3.0]-2-octen-3-one, which was obtained in enantiomerically enriched form via kinetic resolution.[10] More recently, Krafft utilized a tandem Pauson−Khand/aldol sequence to construct an angular triquinine skeleton,[29] and Pericas utilized chiral auxiliaries to control the asymmetry of the Pauson−Khand reaction in the synthesis of (+)-15-nor-methylpentalenene.[30] The angular triquinane framework has also been constructed by Malacria and co-workers with a Conia-ene/intramolecular Pauson−Khand sequence,[31] and by Serratosa and co-workers, who utilized an intermolecular Pauson−Khand reaction.[32]

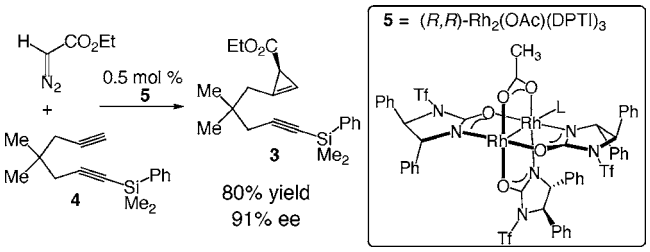
Recently, our group described intermolecular Pauson−Khand reactions of chiral cyclopropenes[33a]—substrates that are readily available in enantiomerically enriched form.[34] Because cyclopropenes are exceptionally reactive in intermolecular Pauson−Khand reactions,[33] we envisioned that an intramolecular variant[33e] of the reaction could be used to set the quaternary center of pentalenene. In a retrosynthetic analysis (Scheme 1), it was reasoned that **1** could be derived

**Scheme 1.** Retrosynthetic Analysis of (−)-Pentalenene




from tricycle **2**. The quaternary center of **2** could be established from an intramolecular Pauson−Khand reaction

**Scheme 2.** Enantioselective Cyclopropenation with Corey's $Rh_2(OAc)(R,R\text{-DPTI})_3$ Catalyst




of cyclopropenyne **3**, which itself could arise from an enantioselective cyclopropenation of diyne **4**. The successful execution of this strategy is reported herein for the synthesis of (−)-**1**, the unnatural enantiomer of the natural product pentalenene.[35]

(25) Burnell has reported a highly enantioselective synthesis of (4*R*,5*S*)-4-hydroxy-4,7,9,9-tetramethylspiro[4,5]dec-7-en-1-one using Baker's yeast reduction as the key step: Zhu, Y.-Y.; Burnell, D. J. *Tetrahedron: Asymmetry* **1996**, *7*, 3295. Burnell had previously reported the use of a similar derivative [7-ethyl-4-hydroxy-4,9,9-trimethylspiro[4,5]dec-7-en-1-one] in the synthesis of racemic pentalenene.[16]

(26) Nonracemic total syntheses have been described for the angular triquinines (−)-pentalenolactone,[26c,d,j,] (−)-isocomene,[26g] (+)-silphenene,[26a] (−)-retigeranic acid,[26e,k,l,m] (−)-silphiperfol-6-ene,[26b,h,i,q,n,o] (−)-methyl cantabradienate,[26i] and (−)-subergorgic acid.[26f] For total or formal syntheses that use nonenzymatic enantioselective catalysis to establish the absolute stereochemistry, see: (a) Hu, Q.-Y.; Zhou, G.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, *126*, 13708. (b) Demuth, M.; Hinsken, W. *Helv. Chim. Acta* **1988**, *71*, 569. For syntheses in which absolute stereochemistry is established via enzymatic desymmetrization or resolution: (c) Herrmann, E.; Gais, H.-J.; Rosenstock, B.; Raabe, G.; Lindner, H. J. *Eur. J. Org. Chem.* **1998**, 275. (d) Mori, K.; Tsuji, M. *Tetrahedron.* **1988**, *44*, 2835. (e) Wender, P. A.; Singh, S. K. *Tetrahedron Lett.* **1990**, *31*, 2517. (f) Paquette, L. A.; Meister, P. G.; Friedrich, D.; Sauer, D. R. *J. Am. Chem. Soc.* **1993**, *115*, 49. For syntheses in which chiral auxilaries are used to establish absolute stereochemistry: (g) Rawal, V. H.; Eschbach, A.; Dufour, C.; Iwasa, S. *Pure Appl. Chem.* **1996**, *68*, 675. (h) Meyers, A. I.; Lefker, B. A. *Tetrahedron* **1987**, *43*, 5663. (i) Vo, N. H.; Snider, B. B. *J. Org. Chem.* **1994**, *59*, 5419. For syntheses that originate from enantiomerically enriched natural products: (j) Testero, S. A.; Spanevello, R. A. *Org. Lett.* **2006**, *8*, 3793. (k) Llera, J. M.; Fraser-Reid, B. *J. Org. Chem.* **1989**, *54*, 5544. (l) Hudlicky, T.; Fleming, A.; Radesca, L. *J. Am. Chem. Soc.* **1989**, *111*, 6691. (m) Wright, J.; Drtina, G. J.; Roberts, R. A.; Paquette, L. A. *J. Am. Chem. Soc.* **1988**, *110*, 5806. (n) Paquette, L. A.; Roberts, R. A.; Drtina, G. J. *J. Am. Chem. Soc.* **1984**, *106*, 6690. (o) Sha, C.-K.; Santosh, K. C.; Lih, S.-H. *J. Org. Chem.* **1998**, *63*, 2699.

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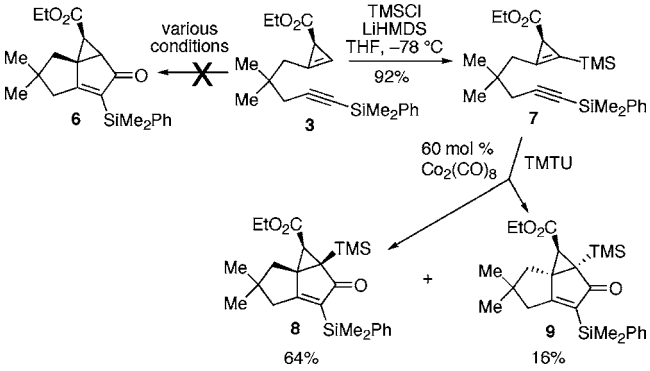
(35) (*S*,*S*)-$Rh_2(OAc)(DPTI)_3$ would give rise to natural (+)-pentalenene. We synthesized the unnatural enantiomer because we had (*R*,*R*)-$Rh_2(OAc)(DPTI)_3$ in hand from another project.

The enantioselective synthesis of (−)-pentalenene was initiated by catalytic, enantioselective cyclopropenation of diyne **4**, which can be readily synthesized on large scale from isophorone.[36] Cyclopropenation is selective for the terminal alkyne, and leaves the silyl protected alkyne available for subsequent cyclocarbonylation. The cyclopropenation reaction of **4** with Corey's[34a−c,35] (*R*,*R*)-$Rh_2$(OAc)(DPTI)$_3$ (**5**) proceeded with excellent enantioselectivity under optimized reaction conditions.

With enantiomerically enriched **3** in hand, the intramolecular Pauson−Khand reaction to obtain **6** was attempted with various promotors (Scheme 3). Unfortunately, these

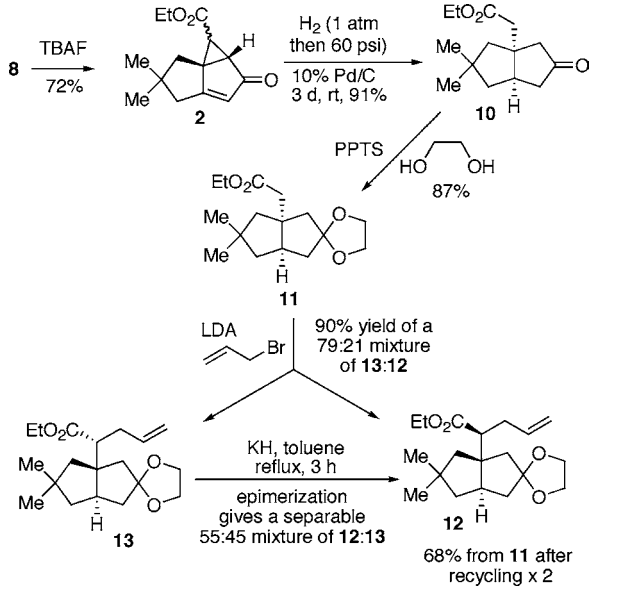
**Scheme 3.** TMTU-Promoted Intramolecular Pauson−Khand Reaction




experiments led to decomposition and only to trace amounts (<10%) of **6**. In our experience with intermolecular Pauson−Khand reactions of cyclopropenes, we noted that 1,2-disubstituted cyclopropenes were the most productive substrates.[33a] Accordingly, **3** was deprotonated with LiHMDS in the presence of TMSCl to provide **7**, which was treated with $Co_2(CO)_8$ under the action of several promotors of the Pauson−Khand reaction. Only starting materials were recovered from attempts to use N-oxides[37a,b] to promote the production of **8**. *n*-Butyl methylsulfide[37c] was a more effective promotor: reaction of **7** with $Co_2(CO)_8$ (1 equiv) followed by treatment with BuSMe (26 equiv) led to **8** as a single diastereomer in 45% yield. Optimal reactivity was achieved with tetramethylthiourea (TMTU)[37d]—a promotor described recently by Yang and co-workers. This promotor was found to be very effective even with substoichiometric amounts of $Co_2(CO)_8$ (0.6 equiv). The product **8** was obtained in 64% yield, along with 16% of the separable diastereomer **9**.

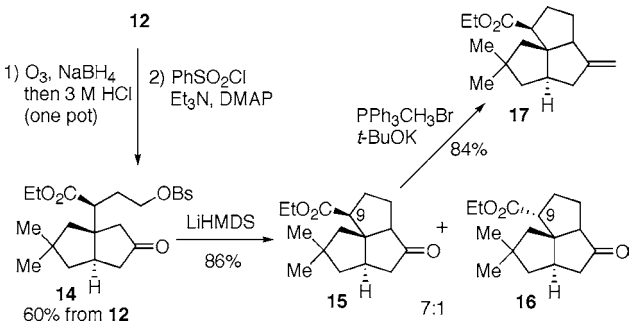
Treatment of **8** with tetrabutylammonium fluoride removed the silyl groups to provide **2** as a mixture of epimers (Scheme 4). Hydrogenation (1 atm $H_2$, then 60 psi $H_2$, 10% Pd/C)

**Scheme 4.** Cyclopropane Fragmentation/Alkylation Sequence




cleanly reduced both the alkene and the cyclopropane to provide **10** in 91% yield. Alternately, selective hydrogenation (1 atm $H_2$) of the alkene moiety followed by $SmI_2$ reduction of the cyclopropane gave **10** in 95% yield over 2 steps. Ketalization and treatment with LDA/allyl bromide gave in 90% yield a 79:21 mixture of diastereomers **13** and **12**, respectively. It is compound **12** that has the desired stereochemistry at C-9 for elaboration to pentalenene: the stereochemistry of **12** was assigned by conversion into **17**—an intermediate in Hudlicky's syntheses[12b] of pentalenene (Scheme 5). Although **12** was the minor kinetic product of

**Scheme 5.** Loss of C-9 Stereochemistry in an Initial Construction of the Triquinane Ring System




the alkylation, it was the major thermodynamic product. Thus, compound **13** can be equilibrated by KH[38]/toluene to give a 55:45 mixture of **12**:**13** with high mass recovery. Because diastereomers **12** and **13** are easily separable on silica, it is practical to obtain **12** in 68% yield from **11** after two recycling efforts.

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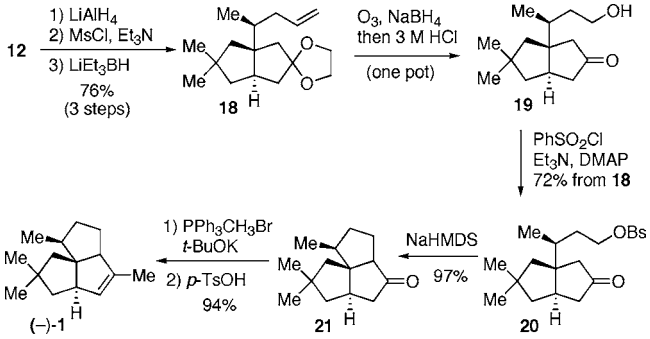
**Scheme 6.** Synthesis of (−)-Pentalenene




It was projected that (−)-pentalenene could be accessed via the ketone **15** (Scheme 5). Reductive ozonolysis of **12** followed by acidic workup and treatment with benzenesulfonyl chloride gave **14**, which cyclized upon treatment with LiHMDS. Unfortunately, the cyclization proceeded with epimerization to give a 7:1 mixture of **15**:**16** that could not easily be separated by column chromatography. A variety of conditions were investigated in order to avoid epimerization at C-9, but these attempts were unsuccessful. After repeated silica gel chromatography, a pure sample of **15** was obtained that could be treated under Wittig conditions to give the exocyclic alkene **17**.

Hudlicky had previously shown that **17** could be converted to pentalenene.[12b] However, the loss of stereochemistry at C-9 was undesirable, especially given the difficulty in separating **15** and **16**. Accordingly, an alternate route to pentalenene from **12** was sought.

The stereospecific synthesis of (−)-pentalenene from **12** was completed as shown in Scheme 6. Three-step conversion ($LiAlH_4$; MsCl, $Et_3N$; $LiEt_3BH$) of the ester of **12** to a methyl group took place in 76% yield to provide **18**. Reductive ozonolysis and ketal deprotection was carried out in one pot to give **19**. Reaction of **19** with benzenesulfonyl chloride gave **20** in 72% yield (from **18**). Compound **20** is similar to a previously described intermediate to pentalenene.[18] Cyclization to ketone **21** was effected by treatment of **20** with NaHMDS. Wittig olefination and acid-catalyzed isomerization of **21** gave (−)-pentalenene (**1**) in 94% yield.

In summary, the first enantioselective synthesis of pentalenene has been described. (−)-Pentalenene was obtained in 9% overall yield from the known diyne **4**,[36] and in 6% overall yield from commercially available isophorone oxide. The longest linear sequence from isophorone oxide was 18 steps. Keys to the success of the synthesis were the use of catalytic enantioselective cyclopropenation and a subsequent Pauson−Khand reaction to set the quaternary center.

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**Supporting Information Available:** Full experimental details and $^1H$ and $^{13}C$ NMR spectra are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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