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Preliminary communication

Application of the Pauson–Khand reaction to the synthesis of pentalenic acid *

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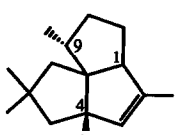
Abstract

A substituted pentynylcyclopentene precursor for the synthesis of pentalenic acid by intramolecular Pauson–Khand cycloaddition reaction has been prepared in high yield. Reaction with $Co_2(CO)_8$ produces triquinane econes in an overall yield of 33%. Three of the four possible stereoisomeric products are formed, with two of them, making up ca. 80% of the product mixture, possessing the necessary *exo*-methyl stereochemistry at C-9 for further elaboration into pentalenic acid. A formal synthesis of the latter was completed by reduction of one of the enone isomers into a ketone which had previously been carried on to the natural product.

Several years ago we demonstrated the use of the Pauson–Khand cycloaddition reaction in the preparation of the angularly fused triquinane ring system [1]. Our initial efforts at directing this methodology towards triquinane natural products led to a synthesis of (±)-pentalenene (**1**) [2]. In order to assess the applicability of this approach to more highly oxidized members of this class of natural products we recently turned our attention to pentalenic acid (**2**) [3,4]. This communication describes our results in this area.



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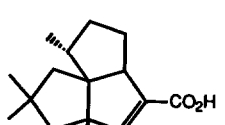

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In a Pauson–Khand-based synthesis of **2** the critical issues are the effects of the oxygen functionality at C-5 on the yield of the cycloaddition reaction and on the stereochemical outcome at C-9. In the synthesis of **1** stereocontrol at C-9 in the crucial cycloaddition step was high (**4** : **5** = ca. 8 : 1) and in the desired direction due to steric interference between the methylene at C-5 and the C-9 methyl in the

* Dedicated with the utmost respect and admiration to Professor Peter L. Pauson on the occasion of his retirement.

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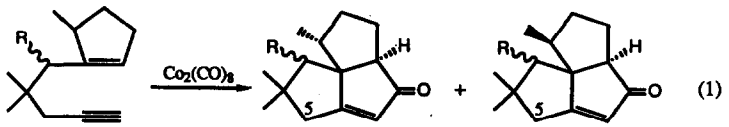
transition state leading to the undesired isomer (eq. 1). In contrast, the presence of a protected alcohol at C-7 totally reversed this preference due to new steric interactions introduced in the intermediates leading to diastereomers **7** relative to diastereomers **8**.

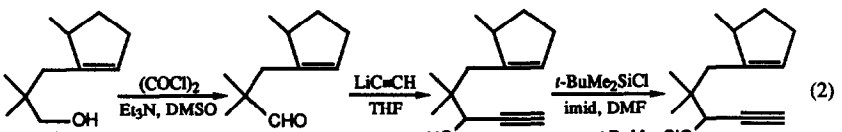


3, R = H
6, R = OCH_2OCH_3

4, major
7, minor

5, minor
8, major

The necessary cyclization precursor for the synthesis of pentalenic acid was prepared as shown in eq. 2. Oxidation of **9** [2] and treatment of the resulting aldehyde with lithium acetylide gave **10** as a ca. 55 : 45 mixture of diastereomers in 77% overall yield [5*]. Although only one of these has the correct alcohol configuration relative to that of the methyl group, it is known that the stereochemistry at C-5 may be corrected after formation of the tricyclic by oxidation followed by selective reduction [4b,d,e].



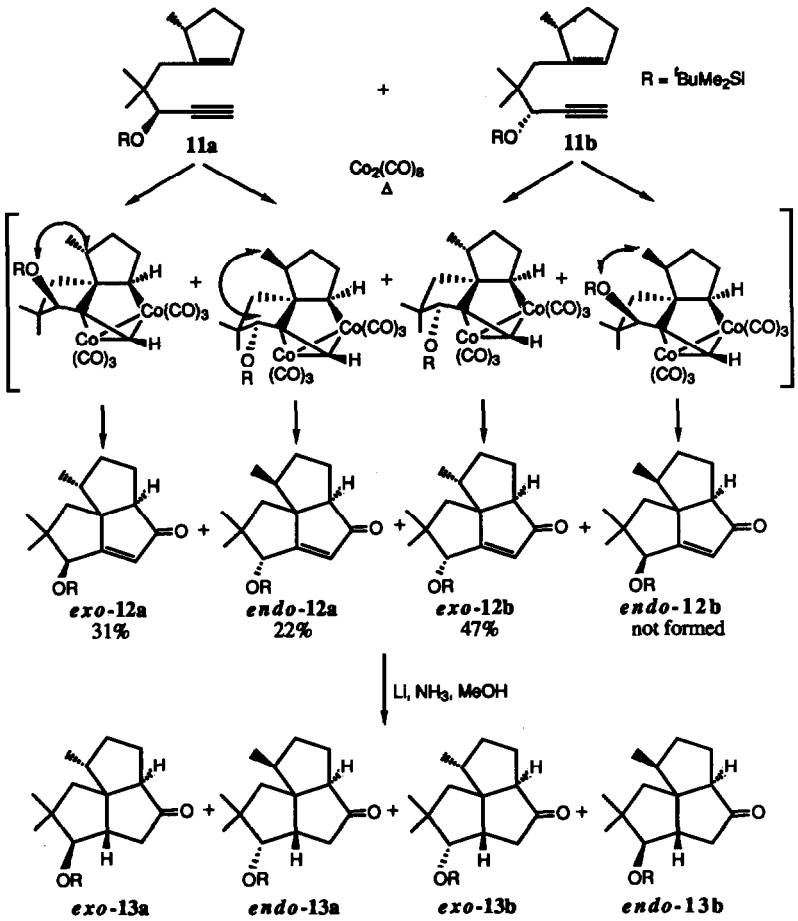
9 **10** **11**

Unprotected propargyl alcohols have generally not performed well as Pauson–Khand cycloaddition substrates [6], and alcohol **10** showed no indication of cyclization to an enone upon treatment with $Co_2(CO)_8$ and heating. The corresponding tert-butyldimethylsilyl ethers typically are much better substrates [7], and treatment of siloxy enyne **11** [8*] with dicobalt octacarbonyl under the same conditions used for cycloaddition of **3** (heptane, sealed tube, 115°C, 19 h) gave a 33% yield of a mixture of enones. The ^1H NMR spectrum of the product of this reaction showed three different vinyl signals, indicating that three of the four possible diastereomeric products had formed.

Using the analysis developed for the cycloaddition of **3**, one would expect the stereochemistry of cycloaddition of **11** to be directed in the following manner. Enyne diastereomer **11b** should give a more favorable ratio of enone products with respect to methyl stereochemistry at C-9 than the 88 : 12 ratio observed for **3**. When the alkene inserts into the cobalt complex so that the methyl group is on the *endo* face of the macrocycle, it will experience a severe steric interaction with the siloxy group at C-5, and thus this pathway should be extremely disfavored (Scheme 1). In contrast, the cycloaddition of **11a** should be less selective because a steric interaction will develop no matter which way the alkene inserts (i.e., either C-9 methyl ↔ C-5 H or C-9 H ↔ C-5 siloxy).

Table 1 presents partial ^1H NMR data for the three separated (by MPLC) isomers of **12** [9*]. Stereochemistry at C-5 was assigned on two bases: protons on the *endo* face of a bicyclo[3.3.0]octane fragment are shielded relative to protons on

* Reference number with asterisk indicates a note in the list of references.



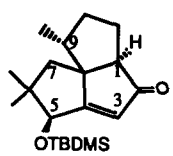
Scheme 1.

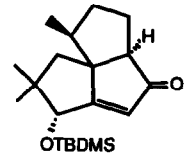
the *exo* face [10] and the coupling constant $J(H_3–H_5)$ is approximately 2 Hz when H-5 is *exo* and 0 Hz when it is *endo* [11]. The configuration of the methyl group was assigned by comparing the chemical shifts for the vinylic protons with those in enone **3** and its stereoisomer: **3**, with the *exo*-methyl, displays a vinyl signal 0.15 ppm upfield of its *endo*-methyl isomer. The assignments indicate that, as expected, enyne diastereomer **11b** cyclizes virtually exclusively to a single enone, *exo*-**12b**, while **11a** shows much lower selectivity (ca. 3 : 2). Overall, enones possessing the same *exo*-methyl configuration at C-9 as pentalenic acid make up nearly 80% of the product mixture.

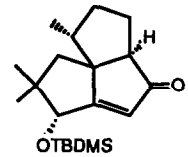
Reduction of the enone mixture with lithium in liquid ammonia and methanol gave tricyclic ketones **13** [12*,13*] which were easily separated by MPLC, permitting two-dimensional NMR experiments that supported the structural assignments of the three isomers. The identity of *exo*-**13a** with an intermediate in Hudlicky's pentalenic acid synthesis [4c] confirmed these assignments. The preparation of *exo*-**13a** thus represents a formal synthesis of the natural product. Note that *exo*-**13b**, the major isomer in this mixture, is also in principle a viable pentalic acid

Table 1

NMR data for enones **12**







Proton assignment	*exo*-**12a**	*endo*-**12a**	*exo*-**12b**
H-3	5.83, s	6.03, d, $J=1.7$ Hz	5.85, d, $J=1.7$ Hz
H-5	4.04, s	4.50, d, $J=1.7$ Hz	4.49, d, $J=1.7$ Hz
H-1	2.41, m	2.44, m	2.43, m
H-7	2.07, d, $J=13.8$ Hz	1.88, d, $J=13.8$ Hz	2.02, d, $J=13.8$ Hz
H-7	1.22, d, $J=13.8$ Hz	1.63, d, $J=13.8$ Hz	1.44, d, $J=13.8$ Hz
Me-6	1.11, s	1.14, s	1.17, s
Me-9	0.97, d, $J=7.2$ Hz	0.93, d, $J=6.9$ Hz	0.97, d, $J=7.2$ Hz
Me-6	0.87, s	0.69, s	0.80, s
^{t}Bu-Si	0.86, s	0.91, s	0.90 s
Me-Si	0.07, s	0.07, s	0.07, s
Me-Si	0.01, s	0.06, s	0.05, s

precursor via alcohol inversion (*vide supra*). Hudlicky also prepared ketone *endo*-**13b**, and the NMR spectrum of this isomer does not match the spectra of any product of our cycloaddition–reduction sequence. These results therefore confirm that the interaction of the *endo* substituent at C-9 and the *exo* substituent at C-5 control the stereochemistry of the Pauson–Khand reaction.

Although the stereoselectivity of this cycloaddition was acceptable for our purposes, the yield was only about 2/3 that of the corresponding reaction in the pentalenene synthesis. As a result, following the procedure of Smit and Caple [14] the $Co_2(CO)_6$ complex of **11** was adsorbed onto silica and the resulting red powder heated at 80–90 °C until the red color disappeared. Analysis showed that the reaction did not go to completion: enones **12** were obtained in only 16% yield while varying amounts of unreacted complexed and uncomplexed **11** were isolated together with an unidentified aromatic side product. This modification was not further pursued.

Nonetheless, the feasibility of application of the Pauson–Khand reaction to the synthesis of more highly functionalized triquinanes has been established, and dramatic confirmation of our previously suggested guidelines for stereocontrol has been provided as well. We are currently exploring the natural culmination of these studies, syntheses of the highly biologically active pentalenolactones using routes based on selective Pauson–Khand reaction. The results of these studies will be reported in due course.

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5 For **10**: partial ^{1}H NMR (300 MHz, $CDCl_3$) δ4.06 and 4.09 (two d, $J = 2.1$ Hz, total 1H), 5.40 and 5.43 (two s, total 1H).

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8 For **11**: ^{1}H NMR (300 MHz, $CDCl_3$) δ0.06 and 0.07 (two s, total 3H), 0.12 and 0.13 (two s, total 3H), 0.88 (s, 9H), 0.91 (s, 3H), 0.92 (s, 3H), 0.96 (d, $J = 6.6$ Hz, 3H), 1.2–2.3 (series of m, 6H), 2.35 (app t, $J = 2.0$ Hz, 1H), 4.01 (br s, 1H), 5.35 and 5.38 (two s, total 1H); high resolution MS, calculated for $C_{19}H_{34}OSi$–$(CH_3)_3C$: 249.1675; found: 249.1672.

9 For **12**: IR (neat film) 1709 cm^{-1}; high resolution MS, calculated for $C_{20}H_{34}O_2Si$–$(CH_3)_3C$: 277.1623; found: 277.1620.

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12 Typical yield of **13** is ca. 60%. Enone **3** is a side product of this reduction (ca. 20% yield). For **13** (mixture of isomers): IR (neat film) 1736 cm^{-1}, analysis: found: C 71.41, H 10.84; $C_{20}H_{36}O_2Si$ calc.: C 71.37, H 10.78%.

13 (a) For *exo*-**13a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ0.03 (s, 3H), 0.04 (s, 3H), 0.87 (s, 9H), 0.92 (s, 3H), 0.97 (d, $J = 6.6$ Hz, 3H), 0.99 (s, 3H), 1.24 (d, $J = 14.1$ Hz, 1H), 1.52 (m, 1H), 1.85 (d, $J = 14.1$ Hz, 1H), 1.95 (m, 1H), 2.28 (m, 1H), 2.33 (m, 1H), 2.48 (dd, $J = 8.7$, 20.7 Hz, 1H), 3.37 (d, $J = 9.5$ Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 86.9, 62.7, 48.3, 43.6, 42.8, 41.6, 34.0, 28.7, 26.2, 25.9, 22.4, 14.5, −3.8, −4.2.

(b) For *endo*-**13a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ0.01 (s, 3H), 0.03 (s, 3H), 0.82 (s, 3H), 0.87 (s, 9H), 0.94 (d, $J = 6.3$ Hz, 3H), 0.96 (s, 3H), 1.52 (d, $J = 13.2$ Hz, 1H), 1.66 (d, $J = 13.2$ Hz, 1H), 1.73 (m, 1H), 2.05 (dd, $J = 11.4$, 20.7 Hz, 1H), 2.47 (m, 1H), 2.55 (m, 1H), 2.72 (m, 1H), 3.62 (d, $J = 7.5$ Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 192.2, 82.5, 63.6, 52.0 46.7, 43.0, 41.2, 34.5, 30.8, 29.3, 26.5, 23.0, 13.9, −3.8, −4.2.

(c) For *exo*-**13b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ0.02 (s, 3H), 0.03 (s, 3H), 0.85 (s, 9H), 0.94 (s, 3H), 0.94 (d, J = ca. 6 Hz, 3H), 0.96 (s, 3H), 1.42 (d, $J = 13.5$ Hz, 1H), 1.50 (m, 1H), 1.68 (d, $J = 13.5$ Hz, 1H), 1.97 (m, 1H), 2.23 (dd, $J = 10.6$, 20.2 Hz, 1H), 2.50 (m, 1H), 2.55 (m, 1H), 3.64 (d, $J = 5.4$ Hz, 1H); ^{13}C NMR ($CDCl_3$) δ82.5, 63.0, 47.0, 44.2, 43.7, 38.4, 34.2, 28.5, 26.0, 24.4, 14.5, −4.1.

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