Pauson–Khand Reactions

Alkoxyallene-ynes: Selective Preparation of Bicyclo[5.3.0] Ring Systems Including a δ-Alkoxy Cyclopentadienone


Abstract: The development of an intramolecular rhodium(I)-catalyzed Pauson–Khand reaction of alkoxyallene-ynes with a proximal alkoxy group is reported. This reaction, in the presence of a [Rh(cycloocta-1,5-diene)Cl]/propane-1,3-diyli-bis(diphenylphosphane) system under a CO atmosphere, constitutes a powerful tool for selectively accessing carbonyl[5.3.0] frameworks featuring an enol ether moiety. Through this procedure, a straightforward access to guaiane skeletons with a tertiary hydroxy group at the C10 position was achieved.

Introduction

Sesquiterpenes represent the largest class of terpenes and, among the variety of ring systems that are featured in these natural products, the guaianes, characterized by fused five- and seven-membered rings (bicyclo[5.3.0]decane), are widespread. Although their core structures might differ in the oxidation level, many of them present a tertiary hydroxy group at the C10 position (guaiane numbering; Figure 1).[1]

Their total synthesis represents a real challenge including three key points: a medium ring, dense stereochemical complexity on a relatively flexible skeleton, and often highly elevated levels of oxidation. The intramolecular Pauson–Khand reaction (PKR), that is, an ene-yne or allene-yne carbonylative [2+2+1] reaction, constitutes an efficient and elegant method for synthesizing pethydroazulene skeletons.[2] Therefore, we hypothesized that the alkoxyallene-yne cyclocarbonylation reaction of substrates bearing an alkoxy group at the proximal position should permit the rapid elaboration of the carbon framework of guaianes possessing a tertiary alcohol group at the C10 position with the requisite unsaturation for further functionalization (guaiane numbering; Scheme 1).[3]

Figure 1. Natural products containing a guaiane skeleton with a tertiary hydroxy group at the C10 position.

Scheme 1. Strategy for the synthesis of guaianes possessing a tertiary alcohol at the C10 position.
In 1996, pioneering work performed by Pericas and co-workers already established that enol ether precursors can be used as olefinic partners with alkynes in the PKR.[4] One year later, Cazes and co-workers reported an intermolecular cobalt-mediated PKR involving a tert-butoxoylallene in the presence of a tertiary amine oxide as a promoter; however, the yields remained low (30%).[5] More recently, Pérez-Castells and co-workers studied the intramolecular PKR of aryloxoyallenes, promoted by a molybdenum complex. Nonetheless, the reaction suffered from a lack of selectivity, because both internal and external double bonds of the allene were prone to react.[6] Finally, in 2009, Brummond et al. described the conversion of allenol acetates into bicyclo[5.3.0] skeletons containing an α-acetoxy cyclopentadienone by means of Rh-catalyzed cyclocarbonylation, which selectively occurs through the external π bond of the allene. Notably, in this case, the allene is substituted by the alkoxy group at the distal position (Scheme 2).[7]

Results and Discussion

Investigation into the scope of this intramolecular cyclocarbonylation reaction was initiated with the preparation of a range of readily accessible alkoxyallene-ynes. To this end, three different allene-alkyne linkages were envisioned: one all-carbon and two heteroatom-containing tethers (respectively, the carbon, nitrogen, and oxygen series). The other variations involved the substitution pattern of the alkoxyallene (R') that features a benzyl (Bn), a para-methoxybenzyl (PMB), or a carbatm (CON(Pr)); Cb) group and the terminus of the alkyne (R”) exhibiting either hydrogen, methyl, ethyl, CH₂OBn, or trimethylsilyl groups.

Our strategy to access the required alkoxyallene-yne precursors involved the addition of lithiated alkoxyallenes onto aldehydes 1. The transformation of these compounds into the corresponding perhydroazulene systems 4 was then studied (Scheme 3).

![Scheme 3.](image)

**Scheme 3.** Investigation into intramolecular PKRs of alkoxyallene-ynes with the alkoxy group at the proximal position. TBS: tert-butyldimethylsilyl; Ts: toluene-4-sulfonyl.

**Synthesis of alkoxyallenic Pauson–Khand precursors**

The starting point for the study consisted of the preparation of the oxygen-substituted allenes 6a (OCb), 6b (OBr) and 6c (OPMB),[8] from propargyl carbatm 5a,[9] or propargyl ethers 5b and 5c by using a general procedure for base-promoted isomerization (Scheme 4).[10]

![Scheme 4.](image)

**Scheme 4.** Preparation of oxygen-substituted allenes. a) tBuOK (0.3 equiv), THF, RT, 1 h.

The synthesis of the aldehydes in the carbon series, 8a (R”= H), 8b (R”= Me), 8c (R”= Et), 8d (R”= TMS), and 8e (R”= CH₂OBn), was next performed from the corresponding alkenes 7a,[11] 7b,[12] 7c, 7d, and 7e by oxidative cleavage with good yields. Alkene 7d (R”= TMS) was prepared by silylation of terminal...
alkyne 7a; alkenes 7c (R²: Et) and 7e (R²: CH₂OBn) were obtained by following a two-step sequence: reduction of diesters 8a-14 and 9b and subsequent protection. Finally, alkylation of allylmalonate 10 with mesylate 1113 allowed the formation of diester 9b (R²: CH₂OBn; Scheme 5).

The synthesis of the required PKR precursors from aldehydes 8a-e was then readily performed in two steps: reaction of lithiated alkoxyallenes, generated by selective gem-deprotonation of the corresponding oxygen-substituted allenes 6a-c, with aldehydes 8a-e at low temperature and direct conversion of the resulting alcohols into the corresponding TBS ethers 12a-e, 13a, 13b, and 14a-d (Scheme 6).[16]

In the nitrogen series, alkoxyallene-yynes 16a-c, 17a-c, and 18a-d were similarly synthesized through coupling of lithiated alkoxyallenes derived from 6a-c with aldehydes 15a (R²: H),17 15b (R²: Et),[18] 15c (R²: TMS),[19] and 15d (R²: CH₂OBn) and subsequent protection as TBS ethers (Scheme 7). Aldehyde 15d was prepared in two steps from propargylic alcohol 19.[20,21]

Finally, in the oxygen series, the PKR precursors 23a-b and 24a-b were elaborated in a similar way from alkoxyallenes 6a and 6c and aldehyde 22. Aldehyde 22 was synthesized in a four-step sequence from known tertiary alcohol 20[22] via alkyne 21 (Scheme 8).

**Scheme 5.** Synthesis of aldehydes in the carbon series. a) O₂, CH₂Cl₂, –78 °C, then PPh₃, b) nBuLi, TMSCl, THF, quant. c) LiAlH₄, THF, 0 °C to RT, 1.5 h. d) 2,2-dimethoxypropane, PPTS, CH₂Cl₂, RT, 16 h. e) Naf, DMF, 0 °C, 15 min, then 11, 0 °C, 1 h, 91%. Ms: methanesulfonyl; PPTS: pyridinium p-toluene-sulfonate.

**Scheme 6.** Preparation of alkoxyallene-yynes in the carbon series. a) nBuLi, THF, –78 °C, 30 min, then 8a-e, THF, –78 °C, 30 min. b) TBSOTf, 2,6-lutidine, CH₂Cl₂, 0 °C, 3 h.

**Scheme 7.** Preparation of alkoxyallene-yynes in the nitrogen series. a) nBuLi, THF, –78 °C, 30 min, then 15a-d, THF, –78 °C, 30 min. b) TBSOTf, 2,6-lutidine, CH₂Cl₂, 0 °C, 3 h. c) DIAD, PPh₃, Nallyl-4-methyl-benzensulfonamide, 71%. d) O₂, CH₂Cl₂, –78 °C, then PPh₃, 95%. DIAD: disopropylazodicarboxylate.

**Alkoxyallene-yne Pauson–Khand reactions**

With a range of alkoxyallene-yynes in hand, the feasibility of the Pauson–Khand cyclocarbonylation was next investigated. Mukai and co-workers,[23] Brummond and co-workers,[24] and, more recently, our group[25] reported that the Rh¹-catalyzed intramolecular allene-yne PKR was a very efficient tool for the construction of bicyclo[5.3.0] ring frameworks.

Therefore, a first examination of the PKR conditions was performed with 12b (R²: Ocb; R²: Me) and 13a (R²: OBn; R²: Me) by using commercially available [Rh(II)(Cl)₂]₃ and [Rh(cod)(Cl)] (cod: cycloocta-1,5-diene) as catalysts.

When subjected to the conditions of Brummond and co-workers, that is, 10 mol% of [Rh(II)(Cl)₂]₃ in toluene at 90 °C under a carbon monoxide atmosphere, 12b and 13a afforded
the desired products 25b and 26a with full conversion within 1.5 h. Notably, 25b was isolated in good yield (70%); not 25b was isolated in good yield (70%), and 25b was isolated in good yield (70%).

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Optimization of the alkoxyallene-yne Pauson–Khand reaction with 12b (R1: Cb; R2: Me).

Table 1. Optimization of the alkoxyallene-yne Pauson–Khand reaction with 12b (R1: Cb; R2: Me).

<table>
<thead>
<tr>
<th>Catalyst/ligand</th>
<th>Solvent</th>
<th>T [°C]</th>
<th>t [h]</th>
<th>Conversion [%]</th>
<th>Yield of 25b [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 [Rh(CI)(CO)3]3</td>
<td>toluene</td>
<td>90</td>
<td>1.5</td>
<td>100</td>
<td>70</td>
</tr>
<tr>
<td>2 [Rh(CI)(CO)3]3</td>
<td>toluene</td>
<td>RT</td>
<td>8</td>
<td>100</td>
<td>70</td>
</tr>
<tr>
<td>3 [Rh(CI)(CO)3]3</td>
<td>THF</td>
<td>110</td>
<td>2</td>
<td>100</td>
<td>70</td>
</tr>
<tr>
<td>4 [Rh(CI)(CO)3]3</td>
<td>dppp</td>
<td>toluene</td>
<td>110</td>
<td>3</td>
<td>100</td>
</tr>
<tr>
<td>5 [Rh(CI)(CO)3]3</td>
<td>dppp</td>
<td>acetonitrile</td>
<td>110</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>6 [Rh(CI)(CO)3]3</td>
<td>dppp</td>
<td>THF</td>
<td>110</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>7 [Rh(CI)(CO)3]3</td>
<td>dppp</td>
<td>toluene</td>
<td>110</td>
<td>20</td>
<td>100</td>
</tr>
<tr>
<td>8 [Rh(CI)(CO)3]3</td>
<td>dppp</td>
<td>THF</td>
<td>110</td>
<td>20</td>
<td>0</td>
</tr>
</tbody>
</table>

[a] dppp: 1,3-bis(diphenylphosphino)propane.

Optimization of the alkoxyallene-yne Pauson–Khand reaction with 13a (R1: Cb; R2: Me).

Table 2. Optimization of the alkoxyallene-yne Pauson–Khand reaction with 13a (R1: Cb; R2: Me).

<table>
<thead>
<tr>
<th>Catalyst/ligand</th>
<th>Solvent</th>
<th>T [°C]</th>
<th>t [h]</th>
<th>Conversion [%]</th>
<th>Yield of 26a [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 [Rh(CI)(CO)3]3</td>
<td>toluene</td>
<td>90</td>
<td>1.5</td>
<td>100</td>
<td>38</td>
</tr>
<tr>
<td>2 [Rh(CI)(CO)3]3</td>
<td>toluene</td>
<td>RT</td>
<td>20</td>
<td>10</td>
<td>–</td>
</tr>
<tr>
<td>3 [Rh(CI)(CO)3]3</td>
<td>THF</td>
<td>110</td>
<td>2</td>
<td>100</td>
<td>20</td>
</tr>
<tr>
<td>4 [Rh(CI)(CO)3]3</td>
<td>dppp</td>
<td>toluene</td>
<td>110</td>
<td>6</td>
<td>100</td>
</tr>
<tr>
<td>5 [Rh(CI)(CO)3]3</td>
<td>dppp</td>
<td>acetonitrile</td>
<td>110</td>
<td>4</td>
<td>100</td>
</tr>
<tr>
<td>6 [Rh(CI)(CO)3]3</td>
<td>dppp</td>
<td>THF</td>
<td>110</td>
<td>4</td>
<td>100</td>
</tr>
<tr>
<td>7 [Rh(CI)(CO)3]3</td>
<td>dppp, AgOTf</td>
<td>toluene</td>
<td>110</td>
<td>1.5</td>
<td>100</td>
</tr>
<tr>
<td>8 [Rh(CI)(CO)3]3</td>
<td>dppp</td>
<td>toluene</td>
<td>110</td>
<td>28</td>
<td>100</td>
</tr>
<tr>
<td>9 [Rh(CI)(CO)3]3</td>
<td>dppp, AgOTf</td>
<td>toluene</td>
<td>110</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>10 [Rh(CI)(CO)3]3</td>
<td>Xantphos</td>
<td>THF</td>
<td>110</td>
<td>20</td>
<td>0</td>
</tr>
</tbody>
</table>

[a] PO: 1:2-(diphenylphosphinyloxy)ethane-1,2-diol.
mitted the preparation of dienones 27a–d (R²: H, Et, TMS, and CH₂OBn) in 44–59% yields from 14a–d (Scheme 11).

Our next task focused on the application of the optimal Rh²-catalyzed PKR conditions to the construction of aza- and oxabicyclo[5.3.0] ring systems.

In contrast to all-carbon alkoxylallene-yenes, the cyclocarbonylation reaction with nitrogen-tether compounds 16a–c, 17a–c, and 18a–d (R²: Cb, Bn, and PMB; R²: H, Et, TMS, and CH₂OBn) appeared more challenging (Scheme 12). Hence, under the previously developed conditions, the reaction led to the desired bicyclic systems 28a–c, 29a–c, 30a, and 30b in moderate yields ranging from 21 to 59% and to an intractable mixture for 30c and 30d (the target compound could never be separated from the byproducts). The best results were attained in the carbamate series, whereas lower yields were observed in the PMB series. Unidentifiable products were systematically obtained along with dienones, which provided evidence that either the starting material or the product is unstable under the reactions conditions.

Finally, similar results were observed in the oxygen-tethered series, for which the yields of the bicyclic [5,7] products 31a, 31b, 32a, and 32b varied from moderate to low (Scheme 13). In some instances, complete decomposition of the substrate occurred, particularly in the PMB series (R²: TMS).

Thus, we have clearly established the scope of the alkoxylallene-yene Pauson–Khand reaction from alkoxylallenes bearing alkoxy groups at the proximal position. Alkoxylallene-yenes presenting various substitution patterns at the allenol and the alkyne moiety, as well as three different tethers (carbon, nitrogen, and oxygen series), have been submitted to optimized PKR conditions ([Rh(cod)Cl₂], dppp). The ring-closing reaction has been found to occur exclusively between the distal double bond of the alkoxylallene moiety and the alkyne counterpart, which results in the formation of homo- or heterobicyclo[5.3.0]decadienone frameworks. Notably, the best results were obtained in the carbamate series, whatever the tether (C, N, or O), which provides evidence for the importance of the electronic effect of the carbamate on the stability of both the starting alkoxylallene and the resulting enol. Moreover, a strong
A substituent effect has been observed at the alkyne moiety, for which a TMS group systematically led to a substantial drop in yield. Finally, among the three elected tethers, the most promising results were observed in the carbon series. Although one cannot fully exclude the influence of heteroatoms, the most plausible explanation is the stronger Thorpe–Ingold effect in the carbon series than in the heteroatom series (Scheme 14).

![Scheme 14. Factors influencing the synthesis of bicyclo[5.3.0] ring systems through alkoxyallene-yn Pauson-Khand reactions.](image)

Finally, the success of the alkoxyallene-yn PKR in the carbamate series prompted us to examine the cleavage of this enol ether. Thereby, in a first trial, the reaction of Cb ether 31b with excess trimethylsilyl trifluoromethanesulfonate (TMSOTf) provided ketone (±)-33 as only one diastereomer, which thus demonstrates the synthetic utility of this cyclocarbonylation reaction for accessing tertiary-alcohol-containing guaiane systems (Scheme 15).

![Scheme 15. Cleavage of the carbamate enol ether moiety of 31b. a) TMSOTf (excess), toluene, -78 °C, then H2O, 20%, only one diastereomer observed in NMR spectra (not optimized).](image)

**Conclusion**

We have successfully performed intramolecular rhodium-catalyzed Pauson–Khand cyclocarbonylation reactions of alkoxyallene-ynes with the alkoxy group at the proximal position to access [5,7] ring systems bearing an enol ether. These reactions can be applied to the selective construction of all-carbon-containing bicyclo[5.3.0]decadienones, as well as aza- and oxabicyclo[5.3.0]decadienones. This study clearly establishes the versatility and tolerance of this reaction to a variety of useful functional groups present in the alkoxyallene-yn substrates. Moreover, cleavage of the carbamate enol ether was also accomplished, which demonstrates that this cyclocarbonylation reaction may become a method of choice as an access to the carbon framework of guaianes possessing a tertiary hydroxy group at the C10 position. The application of this Pauson–Khand reaction to the total synthesis of thapsigargin is now in progress.

**Experimental Section**

**Typical procedure for the PKR:** A microwave vial equipped with a Teflon-coated stirrer bar and a septum cap was charged with alkyne-yn and freshly distilled toluene (0.1 M). The solution was degassed by bubbling with argon for 5 min, then a CO atmosphere was installed. Dppp (0.50 equiv) and [Rh(CO)2Cl] (0.10 equiv; or [Rh(cod)Cl]2) were successively added in one portion, and the mixture was submitted to bubbling CO for 2 min. The reaction vial was placed in a preheated 110 °C oil bath and stirred under a CO atmosphere. The reaction was monitored by TLC. Upon completion, the mixture was cooled to room temperature and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel.

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**Keywords:** allenes · alkynes · cyclization · Pauson–Khand reactions · rhodium


[10]  In these reactions, complete conversion has never been achieved, despite heating of the mixture to 60 °C or addition of one equivalent of base.