



A silicon-tethered allenic Pauson–Khand reaction

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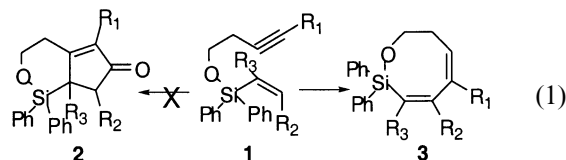
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Abstract—This manuscript describes a silicon-tethered Pauson–Khand reaction and subsequent cleavage of the resulting vinyl silane to afford functionalized alkylidene cyclopentenones. Altering the reaction conditions affords a selective reaction with either π -bond of the allene. © 2002 Published by Elsevier Science Ltd.

The Pauson–Khand reaction is a formal [2+2+1] cycloaddition involving an alkene, an alkyne and carbon monoxide to afford a cyclopentenone.¹ Despite many advances made in the Pauson–Khand reaction in the past three decades, the intermolecular Pauson–Khand reaction is still largely restricted to the use of strained olefins and is not considered regioselective with respect to the alkene.² Therefore, using this method to access monocyclic, cyclopentenone natural products is limiting.³ In one notable exception, Krafft has insightfully directed an intermolecular Pauson–Khand reaction by using a coordinating heteroatom tethered to the alkene.⁴ Unstrained olefins have been used successfully in the intramolecular version of the Pauson–Khand reaction and react with high regioselectivity. One strategy to access monocyclic compounds involves the removal or ring opening of a tether once the intramolecular cycloaddition has been effected. To date, the tethers have heteroatoms such as sulfur, nitrogen or oxygen. Smit was the first to show that the cobalt complex of an allylpropargyl ether undergoes cyclization to afford a hydrogenolyzed product under ‘dry’ alumina conditions.⁵

We are interested in developing a silicon-tethered Pauson–Khand reaction based upon the premise that the tether could be easily cleaved and the resulting cycloadducts used to synthesize cyclopentenone prostaglandins.⁶ Silicon tethers are certainly not a new idea⁷ and application of this omnipresent strategy has even been attempted with the Pauson–Khand reaction.

For example, researchers have found that treatment of the silyl ether **1** to dicobaltoctacarbonyl and *N*-morpholine *N*-oxide gave none of the expected cycloadduct **2** but afforded cyclooctadiene analog **3** in low to moderate yields based upon the substitution pattern (Eq. (1)).⁸

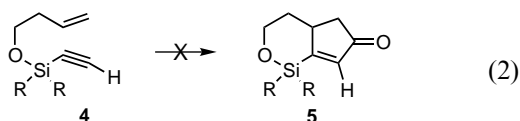


Whitby has shown that 1,6- and 1,7-enynes incorporating a silicon–nitrogen and silicon–oxygen tethers, respectively, can be cyclized using the Negishi cyclization protocol.⁹ The enynes possessing silicon–nitrogen tethers cyclized to afford cyclopentenones, but subsequent reactions resulted in decomposition. The enynes possessing silicon–oxygen tethers formed zirconacycles but CO insertion could not be effected.

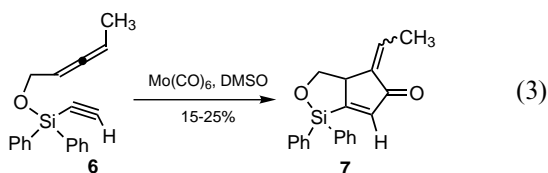
As part of our studies on transition metal mediated allenic Pauson–Khand reactions¹⁰ we too have explored the feasibility of the silicon-tethered Pauson–Khand reaction (Eq. (2)). Initially, a dimethylsilyl ether ($R = \text{CH}_3$) was examined due to the ease in which the tether could be hydrolytically cleaved after cyclization. The preparation of these differentially substituted silyl ether Pauson–Khand reaction precursors is straightforward.¹¹ Addition of dichlorodimethylsilane to bis(dimethylamino)dimethyl silane in THF at room temperature affords the (dimethylamino)chlorodimethyl silane.¹² This compound is not isolated but sequentially treated with ethynyl magnesium bromide then 3-butenol to afford the desired Pauson–Khand reaction precursor.

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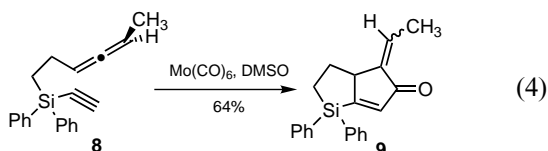
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All attempts to effect a silicon tethered Pauson–Khand reaction with the cobalt complex of this silyl ether **4** gave either decomplexation or decomposition. Replacement of the two methyl groups on the silane with phenyl or *tert*-butyl groups gave similar results. Treatment of these substrates with Mo(CO)₆ gave either no reaction or decomposition products.¹³ Replacement of the alkene moiety with an allene did give the Pauson–Khand cycloadduct (**6**→**7**) but in consistently low yields (Eq. (3)).



A solution to the instability problem was found by replacing the more labile silyl ether tether with a silyl carbon tether (attempts to effect the Pauson–Khand cyclization of a silicon-tethered alkynyl *alkene* substrate were still unsuccessful). Replacing the alkene with an allene group did provide the desired cycloadduct, presumably due to the increased reactivity of the allene. Treatment of compound **8**¹⁴ with molybdenum hexacarbonyl and DMSO in refluxing toluene affords only **9** in 64% yield as a 1:2 mixture of *E:Z* isomers (Eq. (4)).¹⁵



We have shown that the *E:Z* ratio can be increased marginally (1:4) by using mesitylene molybdenum tricarbonyl.¹⁶ Both of these reaction conditions give *E:Z* selectivity opposite of that observed in the all carbon tether, where the *E*-isomer predominates.¹⁰ Moreover, if the hydrogen on the terminus of the alkyne is replaced with a butyl **10**, trimethylsilyl **12** or phenyl **14** group, no Pauson–Khand cycloadduct is observed and only starting material was recovered when treated with Mo(CO)₆ (Table 1). Substituting a longer alkyl chain on allene **16** gives only a 36% yield of **17** in 1:2.5, *E:Z* ratio. Alkynyl allene **18** was prepared and readily underwent the allenic Pauson–Khand cycloaddition to afford the α -methylene cyclopentenone **19** in 48% yield using Mo(CO)₆. Conditions to effect the Pauson–Khand reaction in higher yields are currently being investigated. These investigation led to the discovery that treatment of **8** with 5 mol% [Rh(CO)₂Cl]₂ led to exclusive formation of the 4-alkylidene cyclopentenone **20** in 64% yield.¹⁷ Changing the substituent on the terminus of the alkyne (R = *n*-Bu, **10**, R = TMS, **12**, and

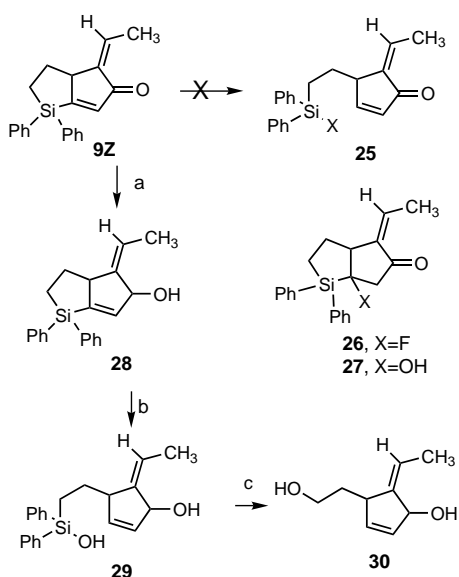
R = Ph, **14**) also provides good yields of the corresponding cycloadducts **21**, **22**, and **23**. A longer alkyl chain on allene **16** affords a 55% yield of **24**. [Rh(CO)₂Cl]₂, unlike Mo(CO)₆ appears to be tolerant of substitution on the terminus of the alkyne.

We are very interested in applying this new method to the synthesis of the cyclopentenone prostaglandin, 15-deoxy- $\Delta^{12,14}$ PGJ₂. Conditions to cleave the resulting vinyl silane were investigated (Scheme 1). All attempts to cleave the vinyl silane of enone **9-Z** to give cyclopentenone **25** led to nucleophilic addition to the endocyclic olefin of the enone to give either **26** or **27** or decomposition. Thus, direct desilylation of enone **9-Z** was judged as untenable. Moderation of the electrophilicity of **9-Z** could be accomplished by reduction of the carbonyl. Alcohol **28** was synthesized from **9-Z** as a single diastereomer using the Luche protocol. Treatment of **28** with tetra-*n*-butyl ammonium fluoride afforded the desired ring opened product **29** in 70% yield.¹⁸ To demonstrate versatility and show this method provides a suitable handle for the ultimate conversion to the desired prostaglandin skeleton, silanol **29** was subjected to a Tamao–Kumada oxidation protocol to afford the acid labile diol **30** in 78% yield.¹⁹ Chromatography of compound **30** was effected using silica gel treated with triethylamine prior to packing. Triethylamine was also used in the elution mixture. If this precaution was not taken diol **30** was converted quantitatively to a bicyclic ether via a S_N2' addition of the primary alcohol onto the protonated allylic alcohol.

Table 1. Silicon-tethered Pauson–Khand reaction

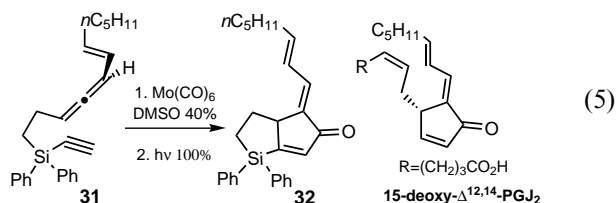
Substrate	Product	Conditions	Yield
		A	64%
8 , R=H, R ¹ =CH ₃	9 , R=H, R ¹ =CH ₃	A	64%
10 , R=Bu, R ¹ =CH ₃	11 , R=Bu, R ¹ =CH ₃	A	0%
12 , R=TMS, R ¹ =CH ₃	13 , R=TMS, R ¹ =CH ₃	A	0%
14 , R=Ph, R ¹ =CH ₃	15 , R=Ph, R ¹ =CH ₃	A	0%
16 , R=H, R ¹ =C ₅ H ₁₁	17 , R=H, R ¹ =C ₅ H ₁₁	A	36%
		A	48%
18	19	A	48%
		B	64%
8 , R=H, R ¹ =CH ₃	20 , R=H, R ¹ =CH ₃	B	64%
10 , R=Bu, R ¹ =CH ₃	21 , R=Bu, R ¹ =CH ₃	B	75%
12 , R=TMS, R ¹ =CH ₃	22 , R=TMS, R ¹ =CH ₃	B	74%
14 , R=Ph, R ¹ =CH ₃	23 , R=Ph, R ¹ =CH ₃	B	51%
16 , R=H, R ¹ =C ₅ H ₁₁	24 , R=H, R ¹ =C ₅ H ₁₁	B	55%

Conditions A: 1. 2 equiv. Mo(CO)₆, DMSO, toluene, 90 °C;
 Conditions B: 5 mol% [Rh(CO)₂Cl]₂, CO (1 atm), toluene, 90 °C



Scheme 1. Cleavage of the silicon tether. (a) NaBH₄, CeCl₃, CH₃OH, 0°C, 62%; (b) *n*Bu₄NF, THF, HMPA, 1 h, 0°C, 70%; (c) KF, NaHCO₃, H₂O₂, THF, CH₃OH, 80%.

To test the applicability of this cyclization strategy for the synthesis of 15-deoxy- $\Delta^{12,14}$ -PGJ₂, compound **31** was prepared and subjected to the molybdenum-mediated conditions (Eq. (5)). Compound **32** was obtained in 40% yield with an *E:Z* ratio of 1:3. Treatment of this mixture of isomers to light, gives 100% conversion to a 1:1, *E:Z* isomeric mixture.



In summary, we have successfully demonstrated a silicon-tethered allenic Pauson–Khand reaction and selective cleavage of the carbon–silicon bond of the vinyl silane.²⁰ Subsequent conversion of the ring-opened silanol to a hydroxyl moiety makes this a very useful method for the preparation of cross-conjugated α -alkylidene cyclopentenones, such as 15-deoxy- $\Delta^{12,14}$ -PGJ₂. The Mo(CO)₆ silicon-tethered allenic Pauson–Khand reaction does not appear to be tolerant of functionality other than a hydrogen on the terminus of the alkyne. [Rh(CO)₂Cl]₂ gives selective reaction with the distal π -bond of the allene to afford 4-alkylidene cyclopentenones. Further delineation of the scope and limitations of this reversal in regiochemistry will be published shortly.

Acknowledgements

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20. Representative experimental procedure for the preparation of **8**, **10**, **12**, **14**, **16**, **18** and **31**. **Ethynyl-hexa-3,4-dienyl-diphenyl-silane (8)**: To a stirred solution of the 6-iodo-2,3-hexadiene (11.05 g, 53.1 mmol) in 200 mL of dry Et_2O at -78°C was added *tert*-butyllithium (50.0 mL, 1.7 M in pentane, 85.0 mmol) dropwise over 10 min via an addition funnel and the reaction mixture stirred at -78°C for an additional 15 min. To the reaction mixture was then added diphenyldichlorosilane (10.6 mL, 50.4 mmol) and the mixture allowed to gradually warm to rt and stirred an additional 3 h during which time the reaction mixture became cloudy with precipitated lithium chloride. The reaction mixture was then recooled to -78°C and the addition funnel charged with ethynylmagnesium bromide (220 mL, 0.5 M in THF, 110 mmol) via cannula. The Grignard reagent was added dropwise over 20 min and the reaction mixture allowed to warm slowly to rt. After 2.5 h TLC showed complete consumption of starting material and the reaction mixture was quenched with 50 mL of satd NH_4Cl . The resulting reaction mixture was filtered through a plug of Celite[®] and the aqueous layer extracted with pentane (4×30 mL). The organic layers were combined and dried over Na_2SO_4 and filtered. The organic layers were concentrated under reduced pressure and the product purified by silica gel chromatography eluting with hexanes to afford 13.01 g (89%) of the allenyne **8** as a pale green oil: ^1H NMR (270 MHz, CDCl_3) δ 7.71–7.66 (m, 4H), 7.45–7.37 (m, 6H), 5.21–5.04 (m, 2H), 2.71 (s, 1H), 2.24–2.13 (m, 2H), 1.66 (dd, 3H, $J=6.9, 3.2$ Hz), 1.35–1.26 (m, 2H); ^{13}C NMR (67.9 MHz, CDCl_3) δ 204.3, 134.9, 133.6, 130.1, 128.3, 97.4, 92.9, 86.9, 85.6, 23.2, 14.8, 13.5; IR (neat) 3200, 3068, 2919, 2853, 2361, 2035, 1961, 1428, 1370, 1113, 907, 737 cm^{-1} ; MS (GC/MS) m/e 288 (M^+), 260, 210, 181, 105. Representative experimental procedure for the $\text{Mo}(\text{CO})_6$ reactions. **Ethylidene-1,1-diphenyl-2,3,3a,4-tetrahydro-1H-1-sila-pentalen-5-one (9)**: Allenyne **8** (2.0 g, 6.93 mmol) was azeotroped under vacuum with toluene (5×2 mL). To a flame dried three neck flask containing a stir bar and capped with a condenser was added the allenyne **8**, 30 mL of dry toluene and 4.5 mL of dry DMSO and then degassed with a stream of argon for 20 min. Next molybdenum hexacarbonyl (2.69 g, 10.2 mmol) was added in one portion. The reaction mixture was immersed into a preheated sand bath (110°C) and stirred for 5 h under an argon atmosphere, at which time visual inspection showed decomposition of the molybdenum catalyst and TLC showed no further reaction. The reaction mixture was cooled to rt and filtered through a plug of silica gel and the filter cake washed with EtOAc (100 mL). The organic layer was then washed with 50 mL of water, followed by brine (2×25 mL), and dried over Na_2SO_4 . The compound was purified by silica gel chromatography eluting with 5:95→10:90 EtOAc:hexanes to afford 64% yield of a 2:1 mixture of *Z* and *E* diastereomers: **9Z** ^1H NMR (270 MHz, CDCl_3) δ 7.64–7.61 (m, 2H), 7.58–7.54 (m, 2H), 7.48–7.37 (m, 6H), 6.72 (d, 1H, $J=2.7$ Hz), 6.21 (q, 1H, $J=7.4$ Hz), 3.58–3.48 (m, 1H), 2.62–2.49 (m, 1H), 2.29 (d, 3H, $J=7.4$ Hz), 1.68–1.25 (m, 3H); ^{13}C NMR (67.9 MHz, CDCl_3) δ 199.6, 178.3, 142.8, 139.4, 135.1, 135.0, 134.5, 132.9, 132.8, 130.4, 130.3, 128.4, 128.3, 55.5, 29.7, 13.8, 13.2; IR (neat) 3048, 3010, 2924, 2855, 1690, 1643, 1428, 1114, 1026, 974 cm^{-1} ; MS (GC/MS) m/e 316 (M^+), 301, 238, 212, 181, 105. **9E** ^1H NMR (270 MHz, CDCl_3): δ 7.64–7.61 (m, 2H), 7.56–7.53 (m, 2H), 7.48–7.35 (m, 6H), 6.73 (d, 1H, $J=2.5$ Hz), 6.68 (dq, 1H, $J=7.4, 1.9$ Hz), 3.69–3.58 (m, 1H), 2.82–2.72 (m, 1H), 1.96 (dd, 3H, $J=7.4, 0.6$ Hz), 1.68–1.28, (m, 3H); ^{13}C NMR (67.9 MHz, CDCl_3) δ : 197.8, 179.9, 141.5, 140.4, 135.2, 135.1, 132.8, 132.7, 131.3, 130.5, 128.5, 128.4, 53.2, 29.1, 15.6, 13.0; IR (neat) 3056, 2933, 2851, 1692, 1646, 1428, 1112, 738 cm^{-1} ; MS (GC/MS) m/e 316 (M^+), 288, 260, 238, 207, 181, 105, 79, 53. Representative experimental procedure for the $[\text{Rh}(\text{CO})_2\text{Cl}]_2$ catalyzed Pauson–Khand reaction. **3-Butyl-1-methyl-4,4-diphenyl-1,4,5,6-tetrahydro-4-sila-inden-2-one (21)**: Allenyne **10** (50 mg, 0.14 mmol) was azeotroped with benzene (3×1 mL) and then sealed with a septa and parafilm then evacuated and purged with nitrogen three times. A flame dried 2-neck flask containing a stir bar and capped with a condenser was charged with $[\text{Rh}(\text{CO})_2\text{Cl}]_2$ (4.2 mg, 0.01 mmol) and flushed with a stream of nitrogen for 10 min. Allenyne **10** was diluted with 8.0 mL of dry toluene and added via cannula to $[\text{Rh}(\text{CO})_2\text{Cl}]_2$. The entire system was then evacuated (mechanical pump) and purged with $\text{CO}(\text{g})$ three times, and left under a balloon of $\text{CO}(\text{g})$ after the final purge. The reaction mixture was then immersed in a 90°C sand bath and the reaction was followed via TLC. After 1.5 h TLC showed complete consumption of starting material and the reaction was cooled to rt and concentrated under reduced pressure. The products were purified by silica gel chromatography eluting with 10:90 EtOAc:hexanes to afford 41.1 mg (76%) of **21** as a brown crystalline solid. ^1H NMR (300 MHz, CDCl_3): δ 7.59–7.52 (m, 4H), 7.50–7.37 (m, 6H), 6.46 (td, 1H, $J=4.7, 0.6$ Hz), 2.79 (qd, 1H, $J=7.5, 1.0$ Hz), 2.50 (q, 2H, $J=6.2$ Hz), 2.04–2.00 (m, 2H), 1.43 (t, 2H, $J=6.6$ Hz), 1.26 (d, 3H, $J=7.5$ Hz), 1.05–0.83 (m, 4H), 0.58 (t, 3H, $J=7.1$ Hz); ^{13}C NMR (75 MHz, CDCl_3): δ 209.8, 158.0, 153.3, 146.9, 135.6, 132.9, 130.4, 128.5, 125.6, 44.2, 31.2, 26.5, 23.4, 23.1, 15.3, 13.8, 10.4; IR (neat) 3068, 3048, 2927, 2870, 1694, 1428, 1198, 1111, 973, 711 cm^{-1} ; MS (GC/MS) m/e 372 (M^+), 357, 315, 294, 252, 199, 183, 161, 105, 78; HRMS calcd for $\text{C}_{25}\text{H}_{28}\text{OSi}$: 372.190944; found: 372.190808. X-Ray crystallographic data have been obtained for compounds **21**, **22**, **23**.