Cyclopentenone Synthesis

A Cyclobutadiene Equivalent in the Catalytic Pauson–Khand Reaction**

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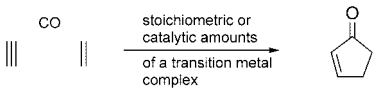
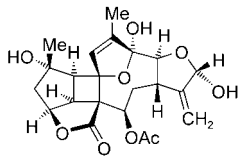
The Pauson–Khand reaction (PKR) is a transition-metal-mediated carbon–carbon bond-forming reaction that converts an alkyne, an alkene, and carbon monoxide into a cyclopentenone (Scheme 1).[1] The ubiquity of five-membered



Scheme 1. The Pauson–Khand reaction.

carbocycles in complex organic molecules such as the recently isolated antimalarial, anticancer diterpene bielschowskysin (**1**)[2] means that cyclopentenones are useful as building blocks



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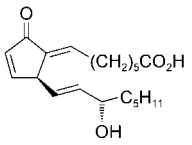

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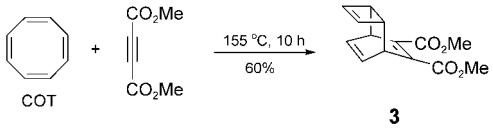
for the creation of larger organic molecules. Moreover, many cyclopentenones display their own interesting biological activity. For example, cyclopentenone prostaglandins such as Δ^7-PG-A_1 (**2**) have considerable therapeutic potential.[3]

To maximize the synthetic attractiveness of the PKR the development of efficient and versatile catalytic systems is required, some of which are asymmetric, and all of which work well for intermolecular reactions. Whilst good progress has been made in the last three to five years in the fields of catalysis and asymmetric catalysis using a variety of transition metals and ligands, almost all of the work reported has been based on *intra*molecular substrates, that is, enynes.[1]

Traditionally, the *inter*molecular PKR has been dominated by the strained alkenes norbornene and norbornadiene, although there are reports of the use of cyclopropenes[4a] and bicyclo[3.2.0]hept-6-enes.[4b–d] And, recently the donor-substituted alkenes *o*-(dimethylamino)phenyl vinyl sulfoxide[5a] and dimethyl(2-pyridyl)(vinyl)silane[5b] have been used successfully in cobalt-mediated and ruthenium-catalyzed PKRs, respectively. Very recently, 2,3-disubstituted 1,3-butadienes have been shown to act as alkene partners in a rhodium-catalyzed intermolecular PKR.[5c]

Our interest in catalytic[6] and asymmetric[7] aspects of the PKR led us to look for new alkene partners that would significantly increase the synthetic scope of the reaction. Cyclobutadiene is a very attractive "alkene" in this context insomuch as its participation in the reaction would create highly functionalized bicyclic products that could be manipulated further to produce a wide range of substituted cyclopentanes. The inherent instability of cyclobutadiene, however, meant that a convenient surrogate was required.

Dimethyl *anti*-tricyclo[4.2.2.$0^{2,5}$]deca-3,7,9-triene-7,8-dicarboxylate (**3**) was identified as a potential cyclobutadiene equivalent in the PKR. It was readily synthesized from cyclooctatetraene (COT) and dimethyl acetylenedicarboxylate in 10 h by a modified literature procedure (Scheme 2).[8]



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Scheme 2. Synthesis of cyclobutadiene equivalent **3**. 1.1 Equivalents of COT were used.

Initially, one equivalent of tricycle **3** was reacted with one equivalent of phenylacetylene (Table 1). Reaction occurred selectively at the most strained double bond and work-up led to the isolation of a single diastereomer of the novel Pauson–Khand product **4** in 60% yield (all products in Table 1 were fully characterized by standard analytical techniques). Use of 1.5 equivalents of **3** raised the yield to 77% (Table 1). The reaction was then performed with a range of monosubstituted alkynes, and these reactions led to the isolation of the Pauson–Khand products **5**–**8** in moderate to good yields (Table 1). (The disubstituted alkynes 3-hexyne and diphenylacetylene failed to give the expected products, although 1-phenylpropyne gave a single Pauson–Khand product in 33% yield when reacted with 1.5 equivalents of **3**.)

The Pauson–Khand products **4**–**8** were subsequently heated to induce a retro-Diels–Alder reaction. After 1 h of heating at 205 °C under a vacuum of 6 Torr, the 3-substituted bicyclo[3.2.0]hepta-3,6-diene-2-ones **9**–**13** were isolated in very good yields (Table 1).

The bicyclic compounds **9**–**13** can be regarded as the products of a formal PKR involving monosubstituted alkynes and cyclobutadiene. We have thus introduced a new route to bicyclo[3.2.0]hepta-3,6-diene-2-ones, a class of molecules which to date have been synthesized by irradiation of substituted tropolones;[9] interestingly, investigations of these bicyclic compounds appear to be limited to explorations of their photochemical and thermal behavior.[9] In view of this,

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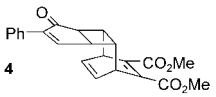
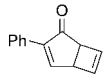
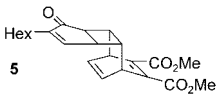
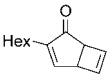
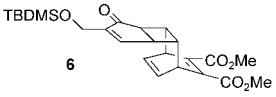
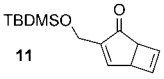
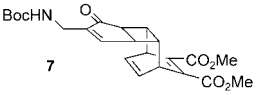
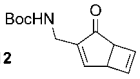
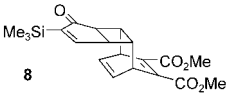
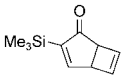
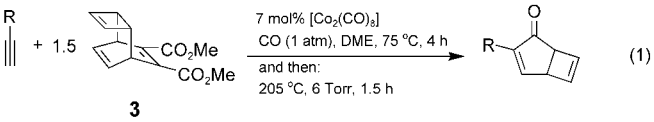
Table 1: Catalytic intermolecular PKR of diester **3** with various alkynes[a] and thermolysis of the Pauson–Khand products.[b]

Alkyne	Equiv of **3**[c]	PK product	Yield [%]	Retro-Diels–Alder product	Yield [%]
Ph	1.0		60		92
	1.5	**4**	77	**9**	
Hex	1.0		73		90
	1.5	**5**	85	**10**	
OTBDMS	1.0		45		90
	1.5	**6**	60	**11**	
NHBoc	1.0		67		90
	1.5	**7**	75	**12**	
$SiMe_3$	1.0		33		85
	5.0		46		
	10.0	**8**	86	**13**	

[a] 5 mol% $[Co_2(CO)_8]$, CO (1 atm), DME, 75 °C, 4 h (all reactions were performed with 0.5 mmol of alkyne). [b] 205 °C, 6 Torr, 1 h (reactions performed on a 0.3–0.4 mmol scale). [c] Unreacted **3** could be fully recovered.

and of the potential of bicyclo[3.2.0]hepta-3,6-diene-2-ones not only in organic synthesis, but also as an alternative to norbornene-based monomers in the ring-opening metathesis polymerisation,[10] it seemed worthwhile to streamline our synthetic approach by removing the isolation of the Pauson–Khand product from the protocol. Indeed, thermolysis of the crude product mixture from the PKR [Eq. (1)] followed by



(1)

chromatography gave the bicyclic ketones in good to excellent yields on a 0.5-mmol scale (Table 2, entries 1–3). Moreover, scale-up of the reaction with 1-octyne (use of 10 instead of 0.5 mmol) readily produced 1.71 g of bicyclo[3.2.0]hepta-3,6-diene-2-one **10** (entry 4).

Table 2: Direct conversion of alkynes into bicyclo[3.2.0]hepta-3,6-diene-2-ones [Eq. (1)].[a]

Entry	R	Scale [mmol]	Product	Yield [%][b]
1	Ph	0.5	**9**	75
2	Hex	0.5	**10**	98
3	$CH_2OTBDMS$	0.5	**11**	70
4	Hex	10.0	**10**	90

[a] See Experimental Section for a detailed description for entry 4. [b] Unreacted **3** could be fully recovered.

To conclude, we have used a cyclobutadiene equivalent in the Pauson–Khand reaction for the first time, to produce a little-studied class of compounds that has considerable potential in synthesis.

Experimental Section

3: A mixture of dimethyl acetylenedicarboxylate (5.29 mL, 43.0 mmol) and COT (5.32 mL, 47.3 mmol) in a 25-mL round-bottomed flask fitted with a reflux condenser was heated at 155 °C under an atmosphere of nitrogen for 10 h. Purification of the crude product by careful (the byproduct dimethyl phthalate has a very similar polarity) flash column chromatography (SiO_2; hexane/acetone, 100:0 to 99:1) afforded **3** as a colorless oil (6.35 g, 60%). R_f = 0.32 (SiO_2; hexane/acetone, 90:10); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.71–2.74 (m, 2H; cyclobutene bridgehead), 3.81–3.91 (m, 8H; 2 OCH_3 and cyclohexadiene bridgehead), 6.08–6.18 ppm (m, 4H; vinylic); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 43.2 and 44.2 (cyclobutene and cyclohexadiene bridgeheads), 52.1 (OCH_3), 129.7 (CH=CH, cyclobutene), 138.9 (CH=CH, cyclohexadiene), 143.1 (C=C), 166.7 (C=O); IR (neat): $\tilde{\nu}_{max}$ = 1560 (C=C), 1603 (C=C), 1640 (C=C), 1727 cm^{-1} (2 C=O); MS (CI): *m*/*z* (%): 264 (8) [*M*+NH_4^+], 247 (100) [*M*+H^+], 195 (24) [*M*−$(CH)_4$+H^+]; elemental analysis calcd (%) for $C_{14}H_{14}O_4$ (246.26): C 68.28, H 5.73; found: 68.36, H 5.81.

10: A 250-mL flask fitted with a reflux condenser and a magnetic stirring bar was charged with 1-octyne (1.47 mL, 10 mmol) and **3** (3.69 g, 15 mmol). The reaction vessel was evacuated (three times) and filled with CO. Anhydrous, CO-saturated DME (100 mL) and freshly sublimed octacarbonyldicobalt(0) (0.239 g, 0.7 mmol) were added to the reaction mixture. The flask was lowered into an oil bath preheated to 75 °C and left stirring at that temperature under a CO atmosphere (1.05 atm) for 4 h. The reaction was then stopped, the solvent evaporated under vacuum, and the flask fitted with a distillation apparatus. The pressure in the system was reduced to 6 Torr and the flask was lowered into a silicone oil bath preheated to 205 °C. The flask was kept in the bath for 1.5 h, at which point most of the reaction mixture had distilled over into the collecting flask. The distillate and the remaining reaction mixture were combined. Purification of the crude product by flash column chromatography (SiO_2; hexane/ethyl acetate, 100:0 to 90:10) afforded **10** as a colorless oil (1.71 g, 90%). R_f = 0.52 (SiO_2; hexane/ethyl acetate, 80:20); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.84–0.88 (m, 3H; CH_3), 1.27–1.32 (m, 6H; $CH_3(CH_2)_3$), 1.40–1.46 (m, 2H; $CH_3(CH_2)_3CH_2CH_2$), 2.05–2.15 (m, 2H; $CH_3(CH_2)_3CH_2CH_2$), 3.50 (dd, *J* = 1.3, 2.3 Hz, 1H; C=OC*H*CH), 3.80 (m, 1H; C=OCHC*H*), 6.35 (dd, *J* = 1.3, 2.3 Hz, 1H; C=OCHC*H*=CH), 6.55 (d, *J* = 2.3 Hz, 1H; C=OCHCH=C*H*), 7.24–7.25 ppm (m, 1H; CH_2C=C*H*); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.0 (CH_3), 22.5 (CH_3CH_2), 25.3, 27.5, 28.9, 31.5 ($CH_3CH_2CH_2CH_2CH_2CH_2$C), 47.9 (C=OCH*C*H), 53.8 (C=O*C*HCH), 136.7 (C=OCH*C*H=CH), 143.6 (C=OCHCH=*C*H), 146.8 CH_2C=CH), 154.9 (CH_2C=*C*H), 206.2 ppm (C=O); IR (neat): $\tilde{\nu}_{max}$ = 1564 (CH=CH), 1620 (CH=C), 1698 cm^{-1} (C=O); MS (CI): *m*/*z* (%): 208 (100) [*M*+NH_4^+], 191 (46) [*M*+H^+], 52 (18) [$(CH)_4^+$]; elemental

analysis calcd (%) for $C_{13}H_{18}O$ (190.28): C 82.06, H 9.53; found: C 82.15, H 9.54.

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