Tandem Pauson–Khand reaction and Diels–Alder reaction for access to polycycles in a one-pot reaction†

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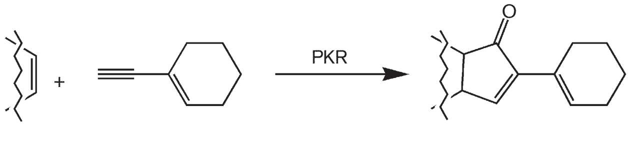
Starting from easily available cyclic alkenes, enynes, and dienophiles, a tandem intermolecular Pauson–Khand reaction and Diels–Alder reaction yields polycyclic compounds in high yields.

A tandem reaction utilizing a single catalyst to mediate more than one transformation in a selective manner has been recognized as one of the best methods for the synthesis of complex skeletal organic compounds.[1] Thus, there have been many examples,[2] indicating that transition metal-catalyzed tandem reactions enhance the reactivity and economical efficiency of the synthesis of complex organic molecules. We recently reported[3] on the synthesis of polycyclic compounds in high yields *via* sequential reactions of cobalt catalyzed-carbonylative cyclization and [2 + 2 + 2] or [4 + 2] cycloaddition. By way of extension of the previous studies, we studied the tandem reaction of a [2 + 2 + 1] cycloaddition of cyclic olefin, conjugated enyne, and carbon monoxide and a [4 + 2] cycloaddition of the resulting diene with an electron-deficient olefin.

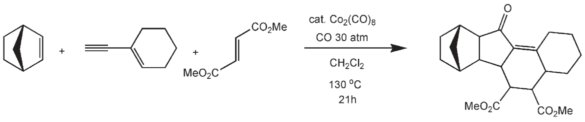
An important strategy for the synthesis of natural products consists of applying transition metal-catalyzed or -mediated reactions to simple starting materials to obtain polycyclic scaffolds that can be further functionalized. Two possible reactions that assist in realizing this aim are the Pauson–Khand reaction and the Diels–Alder reaction. By means of the intermolecular Pauson–Khand reaction of a suitable enyne with an alkene, a cyclopentenone bearing two double bonds is readily obtained. If the two double-bonds in the cyclopentenone are suitably situated, a Diels–Alder reaction between the diene and a dienophile would give a polycyclic structure bearing an α,β-unsaturated ketone.

While we were studying the Pauson–Khand reaction, a conjugated enyne, widely used as an alkyne substrate in the Pauson–Khand reaction, attracted our attention. As shown in Scheme 1, after the Pauson–Khand reaction, a diene will be produced and this will react with a dienophile to give a 6-membered ring compound. In order to perform a tandem reaction between four different reaction components, each has to participate in a specific transformation and they must not interfere with each other. Electron-deficient alkenes are known as poor substrates in the Pauson–Khand reaction.[4] However, in order to act as a dienophile in the Diels–Alder reaction, an alkene can react much more favorably if it has electron-deficient characteristics. In other words, in our strategy consisting of the Pauson–Khand reaction and Diels–Alder reaction, we envisioned that each component would react selectively in a specific reaction. Thus, our strategy was tested by adding together all the reagents (alkyne, alkene, and CO) for the Pauson–Khand reaction and a dienophile from the outset.



Scheme 1

We first reacted norbornene (2 equiv.), 1-ethynylcyclohexene (1 equiv.), and dimethyl fumarate (3 equiv.) in the presence of $Co_2(CO)_8$ (5 mol%) at 130 °C under 30 atm of CO for 21 h [eqn. (1)]. In order to enhance completion of the reaction, excess dimethyl fumarate was used. After work-up, a mixture of two isomers, **1a** and **1b**, (1.4:1) was obtained in 97% yield and nearly 1 equiv. of dimethyl fumarate was recovered. In order to confirm the structures of the isomers, single crystals of the two isomers suitable for an X-ray study were grown and their crystal structures determined (Fig. 1).‡ This initial investigation showed that a Pauson–Khand reaction occurred first and was then followed by the Diels–Alder reaction.



(1)

At this stage, we needed to know whether the one-pot reaction is more effective than the step-by-step Pauson–Khand and Diels–Alder reactions. Thus, we first isolated a Pauson–Khand reaction product of the reaction of norbornene with 1-ethynylcyclohexene and reacted it with dimethyl fumarate [eqn. (2)]. The second reaction step was conducted under two different reaction conditions: when the reaction was carried out in CH_2Cl_2 at 130 °C in a sealed tube, a mixture of two isomers was obtained in 28% yield with a ratio of 1.8:1. When the same reaction was carried out in CH_2Cl_2 under 30 atm of CO at 130 °C, a mixture of two isomers with a ratio of 1.2:1 was obtained in 21% yield. Thus, our initially employed reaction conditions produced a positive effect on the Diels–Alder reaction. Encouraged by this result, we screened a variety of cylic olefins and dienophiles with 1-ethynylcyclohexene (Table 1);‡ the amount of dienophile used was cut down to 2 equiv.§ When norbornadiene was used as the alkene (entry 2), a mixture of **2a** and **2b** was obtained in 84% yield with a ratio of 1.3:1. The isomer bearing an *endo*-situated ester group in

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† Electronic supplementary information (ESI) available: characterization of synthesized compounds. See http://www.rsc.org/suppdata/cc/b4/b413918f/

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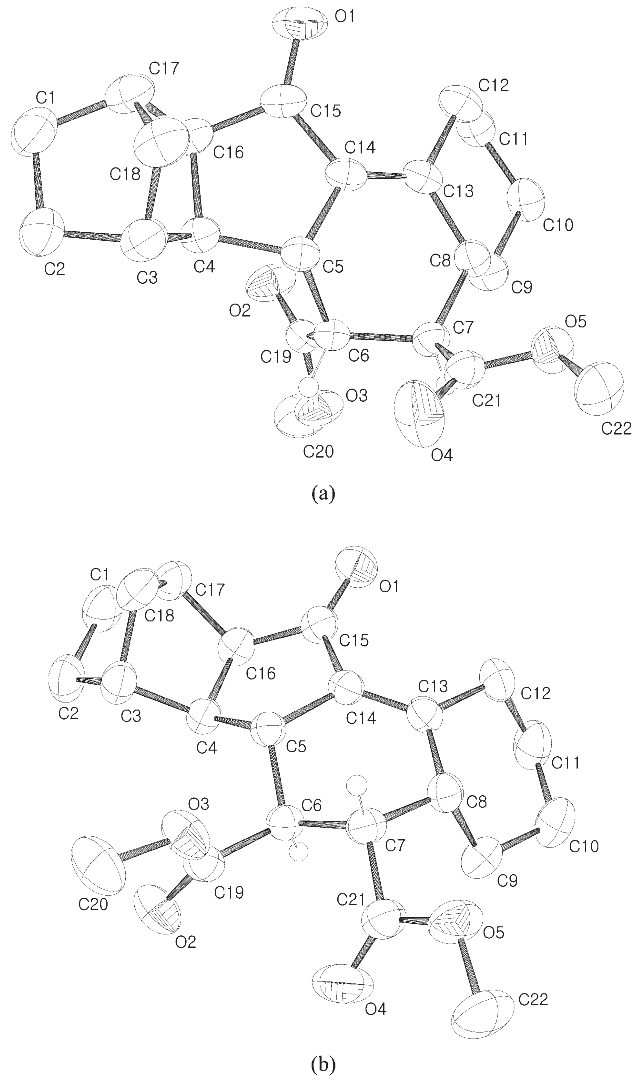
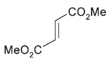
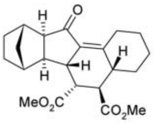
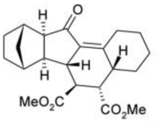
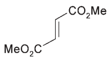
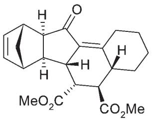
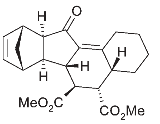
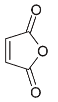
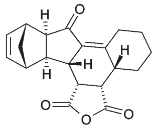
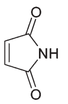
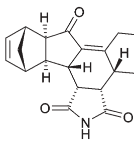
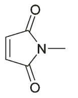
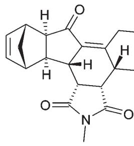
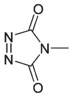
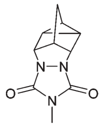
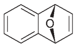
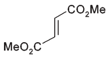
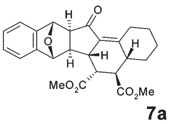
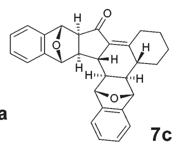


(a)

(b)

Fig. 1 Drawing of compound (a) **1a** and (b) **1b**. Atoms are represented by anisotropic displacement ellipsoids at the 30% probability level and hydrogens bonded to C6 and C7 are represented to show stereochemistry clearly.

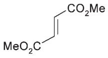
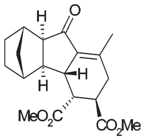
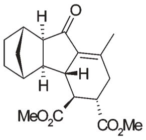
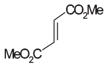
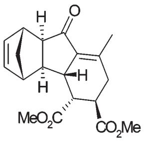
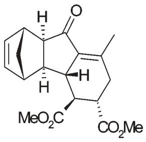
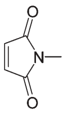
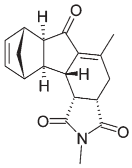
Table 1 Tandem [2 + 2 + 1]/[4 + 2] cycloaddition with 1-ethynylcyclohexene

Entry	Alkene	Dienophile	Product	Yield (%)[a]
1			 **1a**  **1b**	90 (1.1:1)
2			 **2a**  **2b**	84 (1.3:1)
3			 **3**	47
4			 **4**	53
5			 **5**	75
6			 **6**	34[b]
7			 **7a**  **7c**	67 (1.2:1)

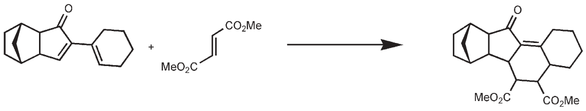
[a] Ratio of **a**:**b** or **a**:**c** in parentheses. [b] Yield based on a dienophile.

the γ-position relative to the carbonyl functionality exhibits a lower polarity than the other isomer. Therefore, both isomers are easily separated by column chromatography. When a *cis*-alkene such as maleic anhydride, maleimide and *N*-methylmaleimide (entries 3–5) was used as the dienophile, an *endo*-product was obtained as the sole product in reasonable to high yields. In the cases of maleic anhydride and maleimide, an insoluble product was in suspension after reaction. Thus, the product was easily obtained. However, it seemed that the solubility of the product affected the yield of the reaction. In the case of *N*-methylmaleimide, a higher yield was obtained than that when maleimide was used. When 4-methyl-1,2,4-triazoline-3,5-dione was used as a dienophile (entry 6), the expected polycyclic product was not obtained. Instead, a [2 + 2 + 2] cycloaddition product between norbornadiene and 4-methyl-1,2,4-triazoline-3,5-dione (**6**) was obtained as the major product. The formation was confirmed by comparison of its NMR spectrum with that from the literature.[6] When oxabenzonorbornadiene (entry 7), was used as an alkene, the isomer bearing an *endo*-situated ester group in the γ-position relative to the carbonyl group (**7a**) was obtained as the major product and a trace amount of the other isomer was obtained. Moreover, in addition to the expected products, a new product (**7c**) was obtained in 30% yield from a reaction in which oxabenzonorbornadiene acted both as a dienophile and an alkene. It seemed that the reaction was induced by an interaction of the C–O bond at the bridge position with the C=C double bond, yielding an electron-deficient C=C double bond.

Table 2 Tandem [2 + 2 + 1]/[4 + 2] cycloaddition with 2-methyl-1-buten-3-yne

Entry	Alkene	Dienophile	Product	Yield (%)[a]
1			 **8a**  **8b**	95 (1.3:1)
2			 **9a**  **9b**	77 (1:1)
3			 **10**	92

[a] Ratio of **a**:**b** in parentheses.


(2)

Next we investigated the reaction of 2-methyl-1-buten-3-yne with various alkenes. The results are summarized in Table 2. When dimethyl fumarate was used as the dienophile, the two isomers (**a** and **b**) were not separated by chromatography because they had the same R_f value. Inspection of the ^{1}H NMR spectra showed that the isomer ratio was 1.3:1 and 1:1 for norbornene (entry 1) and norbornadiene (entry 2), respectively. When norbornadiene was reacted with 2-methyl-1-buten-3-yne and *N*-methylmaleimide, the expected compound **10** was obtained in 92% yield.

We also investigated the reaction with a mono-activated dienophile such as methyl acrylate. However, due to the low reactivity of methyl acrylate and the difficulty in the separation of the reaction products, we failed to obtain valuable results to report herein.

In conclusion, we have demonstrated that complex organic molecules can be easily obtained by cobalt carbonyl-catalyzed tandem Pauson–Khand and Diels–Alder reactions in a one-pot reaction. The formation of several new C–C bonds and alternation of several C–C and one C–O bond orders in a one-pot reaction, which, at a glance, seems quite difficult and complex, has been easily achieved by judicious design of a strategy consisting of the Pauson–Khand and Diels–Alder reactions.

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Notes and references

‡ Crystal data: **1a**: $C_{22}H_{28}O_5$, M = 372.44, monoclinic, space group $P2(1)/a$, a = 17.0589(6), b = 7.3377(3), c = 17.2860(7) û, β = 118.849(2), V = 1895.21(13) û^3, Z = 4, D_c = 1.305 mg m^{-3}, μ(Mo–Kα) = 0.091 mm^{-1}, F(000) = 800. No. of data collected: 7660, no. of unique data: 4349, R = 0.0584, R_w = 0.1776. **1b**: $C_{22}H_{28}O_5$, M = 372.44, monoclinic, space group $P2(1)/n$, a = 10.8847(4), b = 9.8634(5), c = 18.9142(5) û, β = 103.398(2), V = 1975.37(13) û^3, Z = 4, D_c = 1.252 mg m^{-3}, μ(Mo–Kα) = 0.088 mm^{-1}, F(000) = 800. No. of data collected: 7780, no. of unique data: 4503, R = 0.0530, R_w = 0.1475. A single crystal placed on an Enraf-Nonius CCD single crystal X-ray diffractometer. The structures were solved by direct methods (SHELXS-97)[5] and refined against all F^2 data (SHELXS-97). All non-hydrogen atoms were refined with anisotropic thermal parameters. The hydrogen atoms were treated as idealized contributions. Data collected at 293(2) K with Mo–Kö˜ radiation (ö£(Kö˜) = 0.7107 û), $R(F)$ = öÈ| $|F_o| - |F_c|$ |/öÈ$|F_o|$ with $F_o > 2.0\sigma(I)$, R_w = [öÈ[$w(F_o{}^2 - F_c{}^2)^2$]/öÈ[$w(F_o)^2$]^2]$^{1/2}$ with F_o > 2.0ü (I). CCDC reference numbers 247698 and 247699. The stereochemistries of **4**, **7a**, and **7c** were determined by using X-ray diffraction data [CCDC reference numbers 257084 (**4**), 257083 (**7a**) and 257082 (**7c**)] and of **3** and **5** were determined by comparing with similar known compounds. See http://www.rsc.org/suppdata/cc/b4/b413918f/ for crystallographic data in .cif or other electronic format.

§ To a 100 mL high-pressure reactor were added 1-ethynylcyclohexene (0.50 mL, 4.25 mmol), norbornene (0.80 g, 8.50 mmol), dimethyl fumarate (1.23 g, 8.50 mmol), $Co_2(CO)_8$ [73 mg, 0.21 μmol (5 mol%)], and 30 mL of CH_2Cl_2. After the solution was flushed with CO gas for several seconds, the reactor was pressurized with 30 atm of CO. The reactor was heated at 130 °C for 21 h. After the reactor was cooled to rt and excess gas was vented, the solution was transferred into a flask and then evaporated to dryness. The residue was chromatographed on a silica gel column eluting with hexane and ethyl acetate (8:1 v/v).

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