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Studies on the Rh and Ir mediated tandem Pauson–Khand reaction. A new entry into the dicyclopenta[*a*,*d*]cyclooctene ring system

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Abstract—A Rh-mediated tandem Pauson–Khand reaction has been developed to provide the desired diastereomer **8a** in a 7:1 ratio over the undesired isomer(s), and this has been converted into the [5.8.5] system **11** to provide a potential new route to the ophiobolins.

The unusual fused [5.8.5] ring system, the dicyclopenta-[*a*,*d*]cyclooctene, commonly exists in the natural fusicoplagin A,[1] ophiobolins[2] and cotylenol[3] (representative examples from these families are shown in Fig. 1). Many strategies to gain entry into these systems have appeared and have been well documented in two recent reviews.[4,5] Only a few members from these families have been synthesized over the past two decades.[6–10] The construction of the core [5.8.5] ring system remains the focus of most recent efforts.[11–13]

During recent studies on the synthesis of a 14π annulene, a fused [5.5.5.5] ring system in **1** (Scheme 1) has been obtained efficiently on gram-scale. Obviously, selective cleavage of the middle single bond in the tetracycle **1** would generate a [5.8.5] ring system with similar features to those illustrated in the natural products in Figure 1. This method would fit into the 'ring expansion strategy' employed in the synthesis of a number of eight membered ring systems.[4,5,14] Herein, we wish to report our recent results in this area.

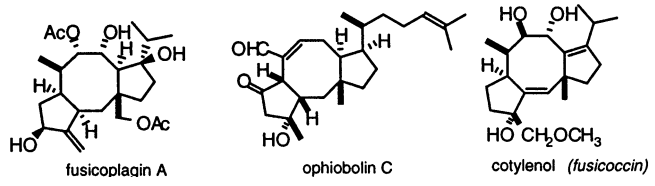
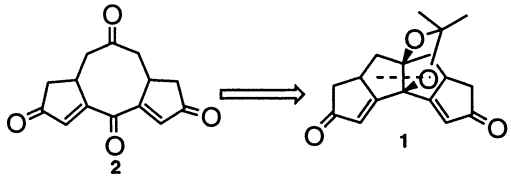


Figure 1.



Scheme 1.

Oxidative cleavage of glycols by periodate ion is well documented;[15] therefore, initial efforts focused on the synthesis of a diketone-diol such as **9** (Scheme 3). An efficient approach to the [5.5.5.5] tetracyclic ring system **1** via a tandem Pauson–Khand reaction had been developed.[16,17] The dialkene–dialkyne **5** could be synthesized on large scale[17] via a two step approach, as illustrated in Scheme 2. Diethyl oxalate **3** in THF was added to a mixture of allyl bromide and zinc in THF to afford the alpha hydroxy ester **4** in 84% yield on a scale of 140 grams. The ester **4** was purified by vacuum distillation. Ester **4** was then stirred with freshly prepared excess lithium trimethylsilylacetylide to provide the desired diol **5** in 76% yield on a scale ranging from 50 to 100 g. The diol **5** was then purified by crystallization from heptane at low temperature. The vicinal diol in **5** required protection to promote the cycloaddition reaction.[17] Not only did the *ortho* ester formation constrain the geometry of the dialkyne–diene in a geometry to facilitate the cycloaddition, but it was felt substrates that contain free hydroxyl groups are poor candidates for the tandem Pauson–Khand reaction. Since the protecting group required removal from the tetracycle **8** under mild conditions to generate **9**, care had to be

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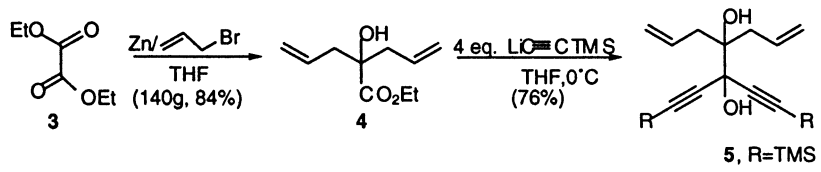
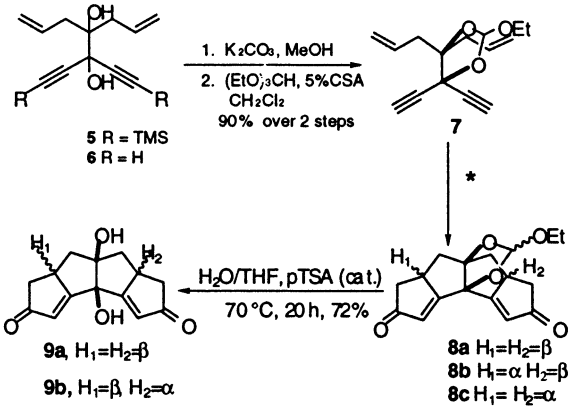


Scheme 2.

exercised in its choice. Among the protecting groups that were employed, the acetonide, benzylidene acetal and *para*-methoxybenzylidene acetal were less than successful in a practical sense. Even though the cycloaddition reaction produced the corresponding tetracycles in 60–65% yields, all attempts to remove these groups under mild conditions met with failure or decomposition. Finally, the choice of the cyclic *ortho* ester group provided a solution to this problem. This moiety was also employed in the synthesis of the 14π annulene, the 3,7-ditriisopropyl dicylopenta[*a*,*e*]pentalene.[18]

As illustrated in Scheme 3, the diene-diyne diol **5** was stirred in methanol with excess K_2CO_3 to remove the TMS protecting groups. The crude product **6** was then treated with triethyl orthoformate in the presence of a catalytic amount of camphor sulfonic acid in dichloromethane[19] to provide the constrained diene-diyne **7** in an overall yield of 90% for the two steps. The sequence of steps could be reversed to provide the desired **7**, but in lower overall yield (75%).

The dicobalt octacarbonyl-catalyzed tandem Pauson–Khand reaction[20,21] was employed initially under the conditions of Livinghouse et al., as shown in Scheme 3 (condition a). The diene-diyne **7** was stirred with 20–25 mol% of $Co_2(CO)_8$ and irradiated with a Q-Beam MAX MILLION 100W Xenon spotlight for 48 h at 60°C under an atmosphere of CO. The tetracyclic ring system **8a–c** was obtained in approximately 55% yield in a ratio of 2:3:1 (**8a**:**8b**:**8c**). The separation of these diastereomers was difficult, consequently the mixture was employed directly in the next step. When this mixture of **8a–c** was heated to reflux in aq. THF in the presence of a catalytic amount of pTSA, the *ortho* ester protecting group was smoothly removed, and the tetracyclic diol **9** was produced in 75% yield. The separation of diol **9a** from **9b** was not possible using flash column chromatography, although the diols were eventually separated through long and tedious repeated crystallization from methyl alcohol/ethyl acetate. Consequently, efforts turned to the search for conditions which would provide better diastereoselectivity of the desired **9a**. Promptly, one found the cobalt-catalyzed process would proceed at 60°C (condition b, in Scheme 3) in the absence of the light source. This thermally promoted cobalt catalyzed Pauson–Khand reaction had been reported also by Livinghouse et al.[22] In the present case, the yield obtained under the thermal conditions was actually slightly higher than that from the photochemical process. However, the diastereoselectivity was not appreciably improved. Molybdenum hexacarbonyl mediated conditions[23] were then evaluated (condition c, Scheme 3), since this metal carbonyl



*conditions for the tandem Pauson-Khand cyclization

a. $Co_2(CO)_8$ (25 mol%), DME, CO (1 atm), hv (Q-Beam), 60 °C, 48 h, 55%, **8a**:**8b**:**8c** = 2:3:1, d.r (**8b**) = 1:1.2

b. $Co_2(CO)_8$ (25 mol%), DME, CO (1 atm), Δ, 60 °C, 36h, 65% **8a**:**8b**:**8c** = 1.5:1:trace, d.r (**8b**) = 2: 1

c. $Mo(CO)_6$ (240 mol%), DMSO (10 eq), toluene, Ar, 90-100 °C, 4-8 h, 72%, **8a**:**8b**:**8c** = 1:2.5:trace, d.r (**8b**) = 1.5:1

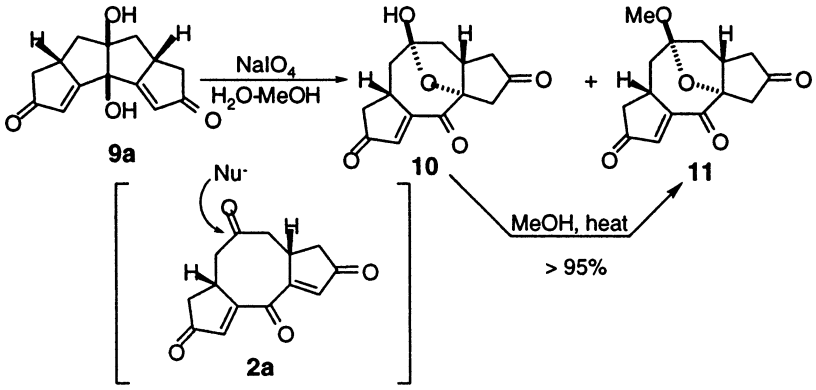
d. $[Rh(CO)_2Cl]_2$ (10 mol%), toluene, CO (1atm), 100 °C, 28 h, 36%, **8a**:**8b**:**8c** = 1: 1.2:trace, d.r (**8b**) = 5:3

e. $[Ir(COD)Cl]_2$ (20 mol%), Ph_3P (40 mol%), CO (1atm), toluene, reflux, 24 h, 76%, **8a**:**8b** = 4: 1, d.r (**8b**) = 5:1

f. $[RhCl(CO)dppp)_2$ (20 mol%), CO (1atm), CH_3CN, reflux, 24h, 68%, **8a**:**8b** = 7: 1, d.r (**8b**) = 10:1

All ratios were determined by NMR spectroscopy of the crude reaction mixture. **8b** was composed of two inseparable diastereomers. The d.r ratios were determined by analysis of the NMR spectra and the absolute stereochemistry was not assigned.

Scheme 3.



Scheme 4.

system has been employed earlier to provide a higher yield of these [5.5.5.5] systems.[24] The excess $Mo(CO)_6$ was heated with the diyne-diene **7** in the presence of DMSO and the process was completed in a few hours. The yield was higher than in the cobalt-mediated cases (72%), and purification was much easier. However, the diastereoselectivity was still disappointing (1:2.5 in favor of **8b**). The catalyst $[Rh(CO)_2Cl]_2$ employed initially by Narasaka and Brummond[25,26] was then applied to this reaction (condition d, in Scheme 3). The diyne–diene **7** was stirred with a catalytic amount of the $[Rh(CO)_2Cl]_2$ catalyst under 1 atmosphere of CO in toluene (100°C) to provide the tetracyclic diketone **8** in a yield of 30–40%. Furthermore, almost no diastereoselectivity was observed (**8a**:**8b**:**8c** = 1:1.2:trace) under these conditions. The Ir-catalyzed conditions reported by Shibata et al.[27] were then attempted (condition e in Scheme 3). The catalyst was generated by treating $[Ir(COD)Cl]_2$ with 4 equiv. of triphenyl phosphine (Ir:P = 1:2] in toluene under one atmosphere of CO. The diyne–diene **7** was then added, and the mixture was heated to reflux for 24 h. The tetracyclic diketone **8** was isolated in 76% yield. More importantly, the ratio of **8a**:**8b** was now as great as 4:1, none of the diastereomer **8c** was observed. Finally, the $[RhCl(CO)dppp]_2$-catalyzed cyclization conditions reported by Evans et al.[28] were attempted, as shown in Scheme 3 (condition f). The diyne–diene **7** was mixed with this Rh catalyst under one atmosphere of CO in acetonitrile and this mixture was heated to reflux for one day. This provided **8** in a yield of 68%, somewhat lower than the yield in the case of Ir, but the diastereoselectivity was now greater than 7:1 (**8a**:**8b**). The process to generate the desired diastereomer **8a**[30] was now synthetically useful. The yield of each of the six new C–C bonds formed in this one-pot process was greater than 90%.

With the tetracyclic ketone **8a** in hand, it was heated in an aqueous solution of THF (THF:H_2O = 20:1) in the presence of a catalytic amount of pTSA to provide the tetracyclic diol–diketone **9** in 72% yield. The desired diastereomer **9a**[31] was easily separated from **9b** by crystallization from a solution of methanol/ethyl acetate. Cleavage of the C–C bond between the vicinal diol functions in **9a** was then attempted (Scheme 4). The tetracyclic diol **9a** was dissolved in methanol, followed by addition of $NaIO_4$ in a phosphate buffer (pH 7).[15] The solution was stirred at room temperature for a few hours to provide two [5.8.5] systems **10** and **11**. The structure of acetal **11** was established by analysis of extensive NMR spectroscopic data.[32] An NOE effect was observed between the two bridgehead protons (Fig. 2) in the ROESY spectrum. It would be impossible to observe this effect if the bridged oxygen atom was on the same side as the two angular bridgehead protons, and located between them. The desired [5.8.5] tetraketone **2a** was, presumably, formed in solution, after which either water or methanol attacked the non-conjugated carbonyl group to generate an oxygen anion, which then attacked the α,β-unsaturated ketone in a Michael fashion at C(2)–C(3). Evidence for the proposed process was obtained by conversion of the hemiketal **10** into ketal **11** in hot methanol. When **10** was heated in methanol, a retro-Michael addition would regenerate the tetraketone **2a**, followed by addition of a molecule of methanol and reattack on the enone system to generate ketal **11**.

In summary, a highly selective entry into the *cis* fused [5.5.5.5] tetracyclic **8a** was developed by employing either a Rh- or Ir-catalyzed tandem Pauson–Khand reaction. The *ortho* ester protecting group, in terms of ease of introduction and removal, proved to be the practical choice in which to constrain and protect the vicinal tertiary diols of **6**. The ring expansion strategy via an oxidative glycol cleavage process provided a successful entry into the functionalized [5.8.5] ring system. Tuning the reaction to provide the other diastereomer as well as asymmetric entry into the [5.5.5.5]/[5.8.5] ring system are under investigation. This is deemed feasible based on the recent asymmetric Pauson–Khand 'type' processes reported using Ir[27] and Rh[29] BINAP catalysts. Routes to functionalized diene-

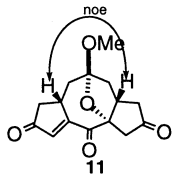


Figure 2.

diynes analogous to **5** (for example **12**[33]) are also under investigation.

Acknowledgements

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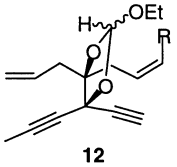
30. **8a** (*cis*): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.23 (1H, d, $J=2.3$ Hz), 6.20 (1H, d, $J=2.3$ Hz), 6.08 (1H, s), 4.08 (1H, m), 3.62 (2H, q, $J=7.1$ Hz), 3.53 (1H, m), 3.35 (1H, m), 2.69–2.57 (5H, m), 2.12 (1H, $J=3$ Hz), 2.05 (1H, d, $J=3$ Hz), 1.20 (3H, $J=7.1$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.74, 208.46, 179.81, 178.82, 128.64, 127.74, 119.57, 106.27, 86.60, 61.46, 45.42, 45.34, 42.97, 42.61, 42.41, 42.17, 41.61, 14.80.
31. **9a** (*cis* diol-diketone): ^{1}H NMR (300 MHz, D_2O) δ 6.23 (2H, d,), 3.69–3.59 (2H, m), 2.66 (2H, dd, $J_1=18.7$ Hz, $J_2=6.02$ Hz), 2.34 (2H, dd, $J_1=13.7$ Hz, $J_2=8.9$ Hz), 2.18 (2H, dd, $J_1=18.7$ Hz, $J_2=2.48$ Hz), 1.44 (2H, dd, $J_1=13.7$ Hz, $J_2=12.0$ Hz); ^{13}C NMR (75 MHz, D_2O) δ 215.38, 186.49, 126.54, 92.83, 77.67, 45.17, 43.59, 42.46; CIMS (*m*/*z*, relative intensity) 247 (M+1, 100), 229 (25), 165 (10); EIMS (15 eV, *m*/*z*, relative intensity) 246 (20), 203 (25), 95 (25), 91 (40), 77 (55), 53 (100); IR (thin film) 3344 (m), 1709 (s), 1681 (s), 1632 (m), 1150 (m), 1131 (m), 1058 (w), 879 (w).
9b (*trans* diol-diketone: ^{1}H NMR (300 MHz, D_2O) δ 6.11 (1H, d, $J=2.4$), 5.91 (1H, d, $J=2.1$ Hz), 3.60 (1H, m), 3.27 (1H, m), 3.06 (1H, d, $J=18.9$ Hz), 2.86 (1H, d, $J=18.7$ Hz), 2.26 (2H, m), 2.51 (2H, m), 2.30 (1H, dd, $J_1=18.4$ Hz, $J_2=2.8$ Hz), 1.64 (1H, t, $J=13.2$ Hz); ^{13}C NMR (75 MHz, D_2O) 213.5, 214.6, 187.3, 188.2, 129.0, 123.0, 79.1, 73.8, 51.6, 44.3, 41.1, 40.1, 38.5, 33.0; EIMS (15 eV, *m*/*z*, relative intensity) 246 (82), 228 (20), 201 (55), 186 (50), 159 (90), 131 (100), 117 (98); IR (thin film) 3334 (m), 3278 (m), 1700 (s), 1683 (s), 1628 (s), 1383 (w), 1255 (w), 1111 (m), 1055 (w), 905 (w).
32. The [5.8.5] **11**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.77 (1H, d, $J=1.42$ Hz), 3.37 (1H, dd, $J_1=2.1$ Hz, $J_2=1.14$ Hz), 3.33 (3H, s), 3.27 (1H, m), 3.07 (1H, m), 3.00–2.86 (2H, m), 2.62–2.55 (2H, m), 2.38–2.30 (2H, m), 2.27 (1H, dd, $J_1=19.2$ Hz, $J_2=1.78$ Hz), 2.15–2.05 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) 212.83, 205.28, 199.99, 172.95, 138.75, 112.31, 92.67, 49.49, 45.96 (two carbons overlapped, HMBC confirmed), 45.44, 43.09, 41.65, 39.19, 36.08; CIMS (*m*/*z*, relative intensity) 277 (M+1, 100), 245 (10).
33.



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