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An intramolecular Pauson–Khand approach to the synthesis of chiral cyclopentadienes

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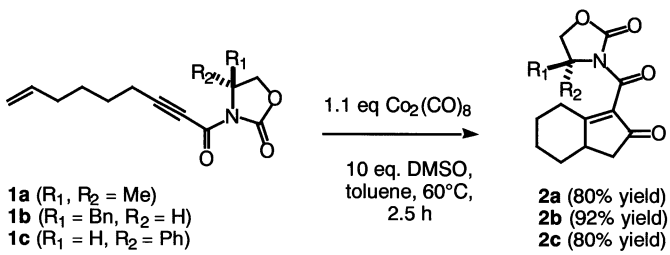
Abstract—A procedure for the synthesis of chirally-substituted cyclopentadienes has been developed by employing the intramolecular Pauson–Khand reaction of chiral amides derived from 8-nonen-2-ynoic acid. Hydride-mediated reduction of the resulting cyclopentenone adducts followed by acid-catalysed dehydration leads to the formation of the corresponding cyclopentadienes in good overall yield.

Although chirally-substituted cyclopentadienes are very popular ligands both in organometallic chemistry and in asymmetric catalysis,[1] the preparation of these compounds in enantiomerically pure form is not straightforward and is usually achieved either by resolution of racemic mixtures or by multi-step syntheses from natural products.[2] On the other hand, 2-cyclopentenones are convenient starting materials for substituted cyclopentadienes, and in the past few years the Pauson–Khand reaction (a most efficient tool for the construction of a cyclopentenone unit by the cobalt-mediated assembly of an alkyne, an alkene, and carbon monoxide)[3] has been used in several instances for the synthesis of substituted cyclopentadienes.[4,5] Up to now, however, all of the Pauson–Khand adducts used for this purpose have been obtained in racemic form from achiral precursors. We disclose herein a short and convenient approach to chirally-substituted, enantiopure cyclopentadienes, that is based on the intramolecular Pauson–Khand reaction of chiral amides derived from enynoic acids.

In the course of our studies on the Pauson–Khand reactivity of electron-deficient alkynes,[6,7] we discovered that under appropriate reaction conditions the cobalt-mediated cyclisation of *N*-(8-nonen-2-ynoyl)oxazolidinones **1** takes place with high yields (Scheme 1).[7] However, the resulting Pauson–Khand adducts **2** did not prove to be suitable for further elaboration into cyclopentadiene derivatives, since all of our attempts at effecting nucleophilic addition reactions at the cyclopentenone carbonyl led either to the recovery of starting materials (DIBAL, MeMgBr, PhLi, *n*BuLi) or to complete degradation ($NaBH_4/CeCl_3$,[8] lithium aminoborohydrides[9]).

We decided therefore to reduce the functional group complexity in our adducts, and we thought that the use



Scheme 1.

Keywords: cyclopentadienes; cyclopentenones; Pauson–Khand reactions.

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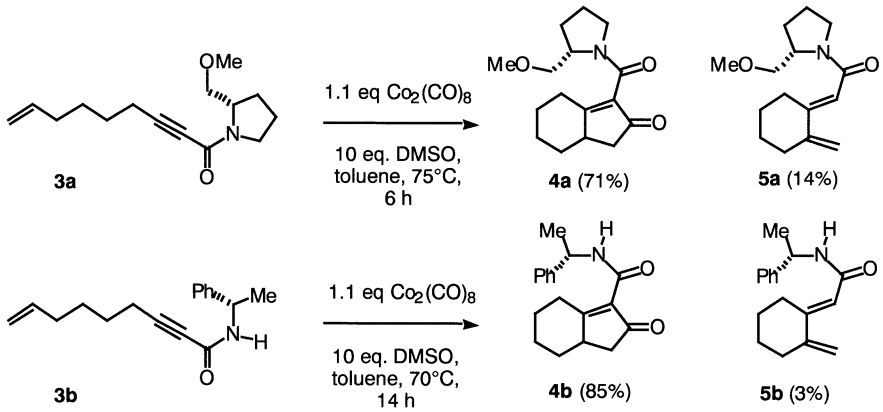
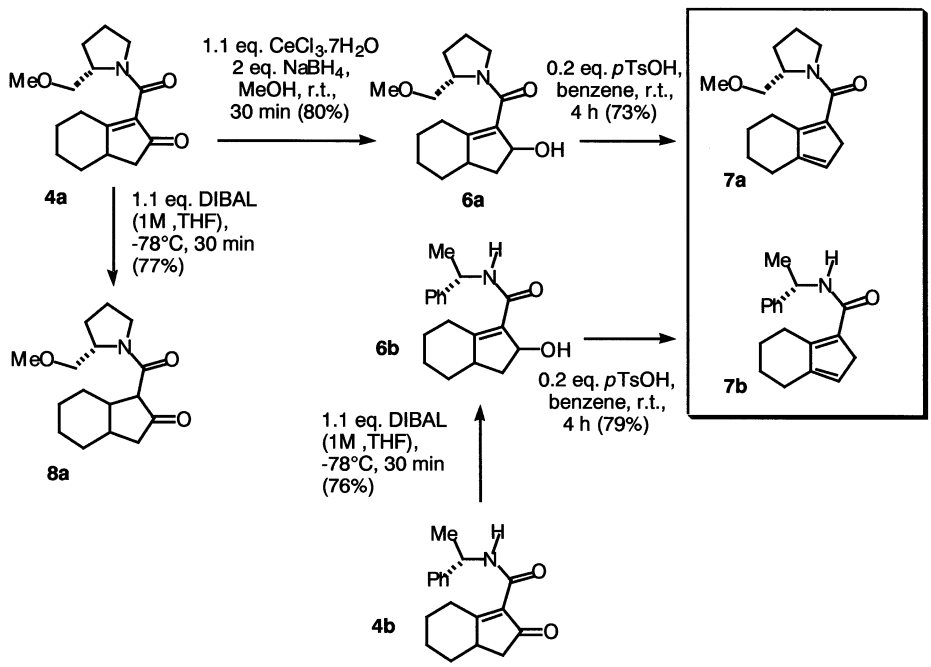
of chiral amides instead of *N*-acyloxazolidinones would be a reasonable choice. To that effect, we prepared the 8-nonen-2-ynamides **3a** and **3b**, derived from (*S*)-2-(methoxymethyl)pyrrolidine[10] and from (*S*)-2-phenylethylamine, respectively, by treatment of 8-nonen-2-ynoic acid[7] with *N*-hydroxysuccinimide (1.2 equiv.), *N*,*N*′-dicyclohexylcarbodiimide (1.2 equiv.) and the corresponding amine (1.0 equiv.) in dioxane at room temperature.[11] In this way, after chromatographic purification **3a** and **3b** were isolated in 86 and 79% yield, respectively. Optimal conditions for the Pauson–Khand cyclisation of **3a** and **3b** (Scheme 2) consisted of heating their dicobalt hexacarbonyl complexes (prepared in situ by treatment of the enynes with a slight excess of dicobalt octacarbonyl) in toluene in the presence of DMSO (10 equiv.).[12] The expected cycloadducts **4a** and **4b** (both as a 1:1 diastereomer mixture, as determined by HPLC) were obtained in satisfactory yields, together with small amounts of the exocyclic dienes **5a** and **5b**,[13,14] that were easily separated from the corresponding cyclopentenones by column chromatography.

We were next pleased to find that, unlike their oxazolidinone counterparts **2a**,**b**, hydride-mediated carbonyl reduction of the enones **4a** and **4b** took place uneventfully, giving rise to the allylic alcohols **6a** and **6b** in 80 and 76% yield, respectively (Scheme 3). It is worth noting that while the best results for the reduction of **4a** were achieved by means of Luche's reagent,[8] these reaction conditions, when applied to **4b**, afforded **6b** in only 42% yield, together with some overreduction products; on the other hand, treatment of **4a** with diisobutylaluminum hydride (that proved to be a totally selective



Scheme 2.



Scheme 3.

reagent for the reduction of **4b**) led to exclusive formation of the saturated ketone **8a**. Finally, when both **6a** and **6b** were submitted to acid-catalysed dehydration, the rather unstable, chirally-substituted cyclopentadienes **7a** and **7b** were obtained in good yields (73 and 79%, respectively).

In summary, we have disclosed a short, high-yielding route to chirally-substituted cyclopentadienes, that takes place in only four steps from readily available chiral amines.[15,16] Ongoing work in our laboratories is directed towards the preparation of enantiopure metal complexes derived from these ligands.[17]

Acknowledgements

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15. All previously unknown compounds were completely characterised and gave satisfactory spectral and/or analytical data. Selected data: (**3a**) ^{1}H NMR (300 MHz, $CDCl_3$, TMS): $\delta = 5.9$–5.7 (m, 1H), 5.1–4.9 (m, 2H), 4.25 (m, 1H), 3.75–3.4 (m, 4H), 3.36/3.34* (s, 3H), 2.35 (m, 2H), 2.2–1.8 (m, 6H), 1.7–1.5 (m, 4H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$, TMS): $\delta = 153.2/153.1$* (Cq), 138.2 (CH), 114.8/114.7* (CH_2), 91.3/91.1* (Cq), 75.2/75.1* (Cq), 73.7/72.0* (CH_2), 59.6 (CH_3), 58.2/58.1* (CH), 48.8 (CH_2), 45.5 (CH_2), 33.00/32.98* (CH_2), 27.91/27.87* (CH_2), 27.15/27.12* (CH_2), 23.6/22.4 (CH_2), 18.6 (CH_2) ppm; IR (NaCl): $\nu = 2242$, 1744, 1626 cm^{-1}; MS (CI, NH_3) m/e: 250 (M+1, 100%), 267 (M+18, 6%). HRMS calcd for $C_{15}H_{24}NO_2$: 250.1807. Found: 250.1811. (**3b**) ^{1}H NMR (300 MHz, $CDCl_3$, TMS): $\delta = 7.4$–7.2 (m, 5H), 6.2–6.1 (br, 1H), 5.9–5.7 (m, 1H), 5.2 (m, 1H), 5.1–4.9 (m, 2H), 2.27 (t, $J = 7.2$ Hz, 2H), 2.1 (m, 4H), 1.6–1.4 (m, 5H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$, TMS): $\delta = 152.6$ (Cq), 138.2 (CH), 128.7 (CH), 127.5 (CH), 126.2 (CH), 125.7 (Cq), 114.8 (CH_2), 87.2 (Cq), 75.9 (Cq), 49.1 (CH), 33.0 (CH_2), 27.9 (CH_2), 27.1 (CH_2), 21.4 (CH_2), 18.4 (CH_2) ppm; IR (NaCl): $\nu = 3260$, 2242, 1628, 1537 cm^{-1}; MS (CI, NH_3) m/e: 256 (M+1, 60%), 273 (M+18, 100%). HRMS calcd for $C_{17}H_{22}NO$: 256.1701. Found: 256.1696. (**4a**) ^{1}H NMR (300 MHz, $CDCl_3$, TMS): $\delta = 4.3$–4.2 (m, 1H), 3.9–3.1 (m, 7H), 3.0–2.8 (m, 1H), 2.7–2.5 (m, 2H), 2.3–2.1 (m, 2H), 2.0–1.7 (m, 7H), 1.6–1.3 (m, 2H), 1.3–1.1 (m, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$, TMS): $\delta =$ 203.6/203.3* (Cq), 181.9/181.8* (Cq), 164.0/163.9* (Cq),

136.1/136.0* (Cq), 74.2/72.1* (CH_2), 59.0 (CH_3), 57.6/57.5*/56.3*/56.2* (CH), 47.8/47.7* (CH_2), 45.8/45.7* (CH_2), 42.0/41.9* (CH_2), 40.8/40.7* (CH), 35.0/34.8*/34.3* (CH_2), 29.5/29.4* (CH_2), 28.3/28.2* (CH_2), 27.6/27.5* (CH_2), 26.6/26.4* (CH_2), 25.0/24.0* (CH_2) ppm; IR (NaCl): $\nu = 1701$, 1626 cm^{-1}; MS (CI, CH_4) m/e: 278 (M+1, 100%); HRMS calcd for $C_{16}H_{24}NO_3$: 278.1756. Found: 278.1758. (**4b**) ^1H NMR (300 MHz, $CDCl_3$, TMS): $\delta = 8.90$–8.80 (m, 1H), 7.40–7.20 (m, 5H), 5.30–5.10 (m, 1H), 4.34 (d, $J = 12.6$ Hz, 1H), 2.75–2.55 (m, 2H), 2.30–2.00 (m, 4H), 1.90–1.10 (m, 7H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$, TMS): $\delta = 207.7$ (Cq), 194.4/194.3* (Cq), 161.7 (Cq), 143.7 (Cq), 128.6 (CH), 127.6 (Cq), 127.0 (CH), 126.1/126.0* (CH), 48.1/48.0* (CH), 42.0 (CH_2), 41.1 (CH), 35.4/35.3* (CH_2), 30.1/30.0* (CH_2), 26.9/25.1* (CH_2), 22.7 (CH_2), 22.6 (CH_3) ppm; IR (NaCl): $\nu = 3303$, 1690, 1618 cm^{-1}; MS (CI, CH_4) m/e: 284 (M+1, 100%), 301 (M+18, 96%); HRMS calcd for $C_{18}H_{22}NO_2$: 284.1651. Found: 284.1652. (**7a**) ^1H NMR (300 MHz, $CDCl_3$, TMS): $\delta = 5.6$ (s, 1H), 4.3 (m, 1H), 3.8–3.2 (m, 3H), 3.3 (s, 3H), 2.6–1.4 (m, 14H). ppm; ^{13}C NMR (75 MHz, $CDCl_3$, TMS): $\delta = 167.8$ (Cq), 154.5 (Cq), 150.5 (Cq), 123.2 (Cq), 118.4 (CH), 72.3 (CH_2), 59.3 (CH_3), 56.1 (CH), 48.1 (CH_2), 43.1 (CH_2), 31.8 (CH_2), 27.8 (CH_2), 26.9 (CH_2), 24.6 (CH_2), 24.4 (CH_2), 22.1 (CH_2) ppm; IR (NaCl): $\nu = 2929$, 1616, 1420, 1339, 1252, 1198, 1115, 972, 748 cm^{-1}; MS (CI, CH_4) m/e: 262 (M+1, 100%); HRMS calcd for $C_{16}H_{24}NO_2$: 262.1807. Found: 262.1794. (**7b**) ^1H NMR (300 MHz, $CDCl_3$, TMS): $\delta = 7.8$ (m, 1H), 7.4–7.2 (m, 5H), 5.6 (s, 1H), 5.2 (m, 1H), 3.4–3.0 (m, 2H), 2.9 (m, 2H), 2.3 (m, 2H), 1.8–1.6 (m, 4H), 1.5 (d, $J = 6.9$ Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$, 25°C, TMS): $\delta = 169.7$ (Cq), 155.7 (Cq), 149.3 (Cq), 134.1 (Cq), 132.4 (CH), 131.1 (CH), 130.8 (Cq), 130.3 (CH), 118.4 (CH), 52.5 (CH), 44.2 (CH_2), 39.4 (CH_2), 33.5 (CH_2), 30.5 (CH_2), 30.0 (CH_2), 25.7 (CH_3) ppm; IR (NaCl): $\nu = 2929$, 1628, 1534, 1420, 1364, 1252, 1177, 1095, 978, 818 cm^{-1}; MS (CI, CH_4) m/e: 268 (M+1, 100%). (Signals marked with an asterisk correspond to a rotamer or to a diastereomer.)

16. It is worth noting that an alternative route to **7a**,**b** based on the Pauson–Khand cyclisation of 8-nonen-2-ynoic acid or of its esters and on the introduction of the chiral amine at a later stage would be thwarted by the low yields obtained in the Pauson–Khand reaction (see Ref. 7).
17. In a preliminary series of experiments, we have found that the reaction of **7a** with $Mn_2(CO)_{10}$ in refluxing toluene gives rise to the corresponding cyclopentadienyl–manganese tricarbonyl complex (30% yield); on the other hand, treatment of the potassium salt of **7a** with $CpZrCl_3$ in THF afforded the expected dichlorozirconocene complex (30% yield).