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Stereoselective synthesis of spiroannulated cyclopentenones by the Pauson–Khand reaction on carbohydrate derived enynes

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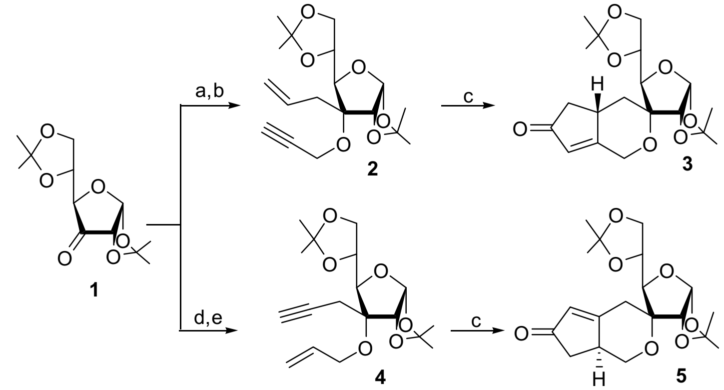
Abstract—The stereoselective synthesis of spiroannulated cyclopentenones by the Pauson–Khand reactions on hexose and pentose derived enynes was achieved under carbon monoxide free conditions using a stoichiometric quantity of $Co_2(CO)_8$. The cobalt complex of the alkyne was cleaved using dimethoxyethane–acetonitrile at 85 °C to furnish spiroannulated cyclopentenones in 75–94% yields.

Spirocyclic skeletons are present in many biologically active natural products.[1] Furthermore, molecules containing spirocycles have found many applications as the spiro system results in rigidity in the conformation of peptides,[2a] carbohydrates,[2b,c] etc. As a result, the synthesis of spiro moieties has attracted a lot of attention in recent times.[3] One of the preferred methods to prepare the spiro unit exploits a ring closing metathesis reaction using Grubbs' catalyst.[4] Several groups have investigated spirocyclisation by metathesis and have synthesised spiro compounds comprising peptides, carbohydrates and barbituric acids as their core scaffolds.[5] In our programme directed towards the synthesis of oxygen-rich, chirally homogeneous and polycyclic frameworks, we became interested in exploring the utility of an intramolecular Pauson–Khand reaction (PKR) to accomplish spiroannulation on carbohydrate scaffolds.

The Pauson–Khand reaction is a 2+2+1 cyclisation involving a suitably substituted alkyne and an alkene in the presence of $Co_2(CO)_8$ under a high pressure carbon monoxide atmosphere.[6] Two major milestones in



Scheme 1. Synthesis of spirocyclic compounds by intramolecular Pauson–Khand reactions reagents. Reagents and conditions: (a) allylzinc bromide, THF, 0 °C to rt, 2 h, 90%; (b) NaH, propargyl bromide, $Bu_4N^+I^-$, DMF, 0 °C to rt, 2 h, 95%; (c) $Co_2(CO)_8$, CH_2Cl_2, 3 h; then CH_3CN–DME (4:1), 85 °C, 3 h; (d) propargylzinc bromide, THF, 0 °C to rt, 2 h, 65%; (e) NaH, allyl bromide, $Bu_4N^+I^-$, DMF, 0 °C to rt, 4 h, 82%.

Keywords: Pauson–Khand reaction; Cyclopentenone; Diversity oriented synthesis; Carbohydrates.

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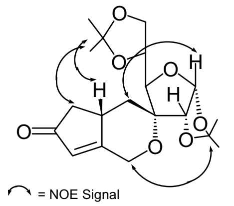
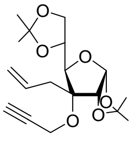
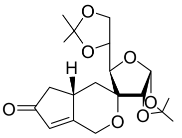
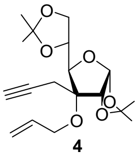
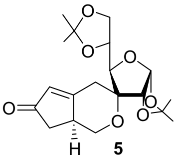
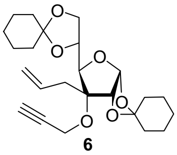
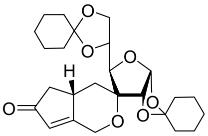
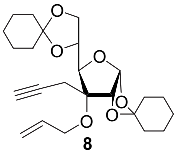
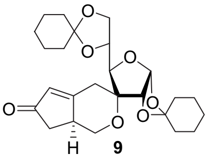
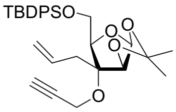
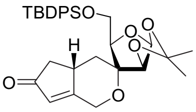
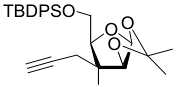
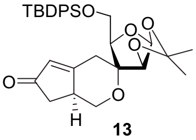
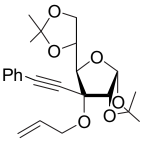
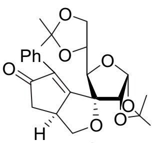


Figure 1. NOE Interactions in compound **3**.

the Pauson–Khand reaction are the carbon monoxide free protocol using stoichiometric $Co_2(CO)_8$ and cleavage of the resulting $Co_2(CO)_6$–alkyne complex using NMO[6d] and acetonitrile–dimethoxyethane.[6e] The intramolecular version of the PKR has been exploited in several ways to synthesise cyclopentenones by coupling of an alkene and an alkyne. The Pauson–Khand reaction was tested on various substrates but the use of this reaction in carbohydrate chemistry was initiated only a few years ago.[7] To the best of our knowledge, the PKR has not been utilised for the synthesis of spiro compounds using carbohydrates as starting materials. Thus, in this communication, we disclose an efficient procedure for the synthesis of spiroannulated cyclopentenone carbohydrate frameworks. It is worth mentioning that the spiroannulated cyclopentenone framework realised from our endeavour is present as a part of the structure of zidolactone A,[8] a constituent of curcumin that is used traditionally in India to treat inflammation and also as a flavour in spices. In our approach, the required enyne precursors for the PKR were synthesised by standard methods (Scheme 1).

To begin our investigation, commercially available di-acetone glucofuranose was oxidised to obtain 3-ulose **1**.[9] Subsequently, compound **1** was treated with allylzinc bromide in tetrahydrofuran at 0 °C and then at room temperature for 2 h to yield the 3-*C*-allyl derivative,

Table 1. Spiroannulated compounds prepared using the Pauson–Khand reaction on carbohydrate derived enynes

Entry number	Substrate	Product	% Yield	Time (h)
1	 **2**	 **3**	94	3
2	 **4**	 **5**	75	4
3	 **6**	 **7**	86	5
4	 **8**	 **9**	85	2
5	 **10**	 **11**	79	4
6	 **12**	 **13**	82	4
7	 **14**	 **15**	90	1

which was *O*-alkylated using NaH, propargyl bromide and *N*-tetrabutylammonium iodide in DMF to provide the required enyne **2**.[10] In the ^{1}H NMR spectrum of compound **2** the anomeric proton was observed at 5.57 ppm as a doublet, and the allylic methine occurred at δ 6.02 ppm as a multiplet and the acetylenic C*H* appeared at δ 2.42 ppm as a triplet. The other proton resonances of **2** were in accordance with the assigned structure. In the ^{13}C NMR spectrum, the resonances corresponding to the anomeric carbon at δ 102.9 ppm and the olefinic carbons at δ 132.2 and 118.9 ppm were observed with all the other signals in complete agreement with the assigned structure.

Compound **2** was then treated with $Co_2(CO)_8$ for 3 h under a nitrogen atmosphere in order to yield the $Co_2(CO)_6$–alkyne complex, which was passed through a pad of silica gel, dissolved in acetonitrile–dimethoxyethane (4:1) and then heated to 85 °C for 3 h to afford the spiroannulated cyclopentenone **3** in excellent yield.[11] In the ^{1}H NMR spectrum of compound **3**, resonances corresponding to the allylic and propargylic protons disappeared and a new singlet attributed to the olefinic proton was apparent at δ 6.02 ppm.[12,13] In addition, the anomeric proton was observed at δ 5.78 ppm as a doublet, whilst two methylene groups of the spirocyclic moiety were observed at δ 2.69 and 2.13 ppm as double doublets integrating for one proton each and a multiplet for two protons at δ 1.85 ppm. The presence of an α,β-unsaturated enone group in compound **3** was evident from the ^{13}C NMR spectrum wherein the diagnostic resonances of the carbonyl group and olefinic carbons were noticed at δ 206.9 ppm and δ 174.9 and 127.7 ppm, respectively. The anomeric carbon was present at δ 103.8 ppm whilst all the other resonances were in complete agreement with the assigned structure. The DEPT spectrum unambiguously confirmed the presence of four $-CH_2$-groups at δ 67.3, 63.9, 41.8 and 34.3 ppm. In addition, the structure was established by means of mass spectral and elemental analysis data. It was gratifying to observe that the spiroannulation resulted in the formation of a single diastereomer (Fig. 1). The formation of a single diastereomer can be rationalised based on steric factors as the $Co_2(CO)_6$–alkyne is disposed in a highly hindered fashion and thus the participation of the alkene during carbonyl insertion was unidirectional.

One of the advantages of the current spiroannulation procedure is the precision in which the newly created stereogenic centre can be installed. For instance, an interesting sequence of reactions on 3-ulose **1** comprising a Barbier reaction and an alkylation gives an enyne at *C-3* of the diacetone glucofuranose (Scheme 1). Accordingly, glucofuranosyl 3-ulose (**1**) was treated with propargylzinc bromide to afford the 3-*C*-propargyl moiety whose *tertiary* hydroxyl group was subsequently alkylated using NaH, allyl bromide and *N*-tetrabutylammonium iodide in DMF to give the required enyne **4** in good yield. Furthermore, cobalt complexation of enyne **4** and subsequent carbonyl insertion were successfully carried out under aforementioned reaction conditions to afford the spiroannulated compound **5**.[12,13]

We then checked the efficiency of the methodology on a panel of substrates utilising various pentose and hexose derived enynes. All the substrates (**4**, **6**, **8**, **10**, **12** and **14**) for the Pauson–Khand reaction were synthesised from the corresponding ketones via a Barbier reaction and *O*-alkylation strategy.[10] It is worth mentioning that in all cases single diastereomeric spiroannulated products (**3**, **5**, **7**, **9**, **11**, **13** and **15**) were obtained (Table 1).[13]

In conclusion, we have synthesised spiroannulated polycyclic compounds using an intramolecular Pauson–Khand reaction on hexose and pentose derived enynes. Furthermore, the current endeavour can be extended to the diversity oriented synthesis of natural product-like polycyclic compounds by exploiting α,β-unsaturated enone and acetonide moieties. We anticipate that this unexplored class of compounds will have interesting biological properties.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.06.013.

References and notes

1. Perron, F.; Albizati, K. F. *Chem. Rev.* **1989**, *89*, 1617–1661.
2. (a) Khasanov, A. B.; Ramirez-Weinhouse, M. M.; Webb, T. R.; Thiruvazhi, M. *J. Org. Chem.* **2004**, *69*, 5766–5769; (b) Sharma, G. V. M.; Reddy, V. G.; Krishna, P. R. *Tetrahedron Lett.* **1999**, *40*, 1783–1786; (c) van Hooft, P. A. V.; Leeuwenburgh, M. A.; Overkleeft, H. S.; van der Marel, G. A.; van Boeckel, C. A. A.; van Boom, J. H. *Tetrahedron Lett.* **1998**, *39*, 6061–6064.
3. (a) Benito, J. M.; Rubio, E.; Gomez-Garcia, M.; Mellet, C. O.; Fernandez, J. M. G. *Tetrahedron* **2004**, *60*, 5899–5906; (b) Mead, K. T.; Brewer, B. N. *Curr. Org. Chem.* **2003**, *7*, 227–256; (c) Hubbs, J. L.; Heathcock, C. H. *J. Am. Chem. Soc.* **2003**, *125*, 12836–12843.
4. (a) Dieters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199; (b) McReynolds, M. D.; Dougherty, J. M.; Hanson, P. R. *Chem. Rev.* **2004**, *104*, 2239; (c) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413.
5. (a) Gurjar, M. K.; Ravindranadh, S. V.; Karmakar, S. *Chem. Commun.* **2001**, 241–242; (b) Kotha, S.; Deb, A. C.; Kumar, R. V. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1039–1043; (c) Holt, D. J.; Barker, W. D.; Jenkins, P. R.; Davies, D. L.; Garratt, S.; Fawcett, J.; Russell, D. R.; Ghosh, S. *Angew. Chem., Int. Ed.* **1998**, *37*, 3298–3300.
6. (a) Brummond, K. M.; Kent, J. L. *Tetrahedron* **2000**, *56*, 3263; (b) Fletcher, A. J.; Christie, D. R. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1657; (c) Chung, Y. K. *Coord. Chem. Rev.* **1999**, *188*, 297; (d) Shambayati, S.; Crowe, W. E.;

Schreiber, S. L. *Tetrahedron Lett.* **1990**, *31*, 5289–5292; (e) Quintal, M. M.; Closser, K. D.; Shea, K. M. *Org. Lett.* **2004**, *6*, 4949–4952.

7. (a) Marco-Contelles, J.; Ruiz-Caro, J. *J. Org. Chem.* **1999**, *64*, 8302; (b) Pal, A.; Bhattacharjya, A. *J. Org. Chem.* **2001**, *66*, 9071–9074; (c) Kubota, H.; Lim, J.; Depew, K. M.; Schreiber, S. L. *Chem. Biol.* **2002**, *9*, 265–276.
8. (a) Blay, G.; Bargues, V.; Cardona, L.; Garcia, B.; Pedro, J. R. *J. Org. Chem.* **2000**, *65*, 6703–6707; (b) Takano, I.; Yasuda, I.; Takeya, K.; Itokawa, H. *Phytochem.* **1995**, *40*, 1197–1200.
9. Herscovici, J.; Antonakis, K. *J. Chem. Soc., Chem. Commun.* **1978**, 601–602.
10. Yanagisawa, A.; Habaue, S.; Yamamoto, H. *Tetrahedron* **1992**, *48*, 1969–1980.

11. General experimental procedure:
    To a solution of enyne (1 equiv) in anhydrous CH_2Cl_2 under a N_2 atmosphere was added dicobalt octacarbonyl (Strem Chemicals) (1.5 equiv) at room temperature and the resulting reddish brown solution was stirred for the specified time (see Table 1). At the end of the reaction (TLC monitored), the reaction mixture was concentrated in vacuo and the residue was passed through a bed of silica gel to obtain the alkyne–$Co_2(CO)_6$ complex which was then dissolved in acetonitrile (40 ml per 100 mg of complex) and dimethoxyethane (10 ml per 100 mg of complex) and kept at 85 °C for 1–5 h. The reaction mixture was cooled to room temperature and then filtered through a pad of silica gel–Celite, the filtrate was concentrated in vacuo and the resulting residue was purified by silica gel column chromatography.
12. Characterization data for **2**, **3**, **4**, **5** and **7**: Compound **2**: $[\alpha]_D$ (c 1.75, $CHCl_3$): +58.77; IR (cm^{-1}): 3276; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.33, 1.37, 1.45, 1.59 (4s, 12H), 2.29 (dd, 1H, $J = 7.8$, 15.16 Hz), 2.42 (t, 1H, $J = 2.40$ Hz), 2.73 (dd, 1H, $J = 6.19$, 15.16 Hz), 3.94 (m, 1H), 4.12 (m, 3H), 4.47 (m, 3H), 5.15 (d, 1H, $J = 7.96$ Hz), 5.22 (s, 1H), 5.57 (d, 1H, $J = 3.54$ Hz), 6.02 (m, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 25.3, 26.4, 26.4, 26.9, 35.1, 53.7, 68.2, 72.5, 73.7, 80.7, 81.1, 83.0, 83.8, 102.9, 109.7, 112.8, 118.9, 132.2; CHNS Anal. (Calcd for $C_{18}H_{26}O_6$: C, 63.89; H, 7.74). Found: C, 63.63; H, 8.07.
    Compound **3**: $[\alpha]_D$ (c 1.00, $CHCl_3$): +11.72; IR (cm^{-1}): 1709, 1634; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.33, 1.38, 1.42, 1.62 (4s, 12H), 1.85 (m, 2H), 2.13 (dd, 1H, $J = 2.93$, 18.58 Hz), 2.69 (dd, 1H, $J = 6.60$, 18.58 Hz), 3.15 (m, 1H), 3.94 (m, 1H), 4.05 (m, 3H), 4.63 (ABq, 2H, $J = 14.65$ Hz), 4.73 (d, 1H, $J = 3.66$ Hz), 5.78 (d, 1H, $J = 3.66$ Hz), 6.02 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 25.3, 26.5, 26.6, 26.8, 34.3, 35.2, 41.8, 63.9, 67.2, 73.2, 79.7, 81.2, 81.4, 103.8, 109.6, 113.1, 127.7, 174.9, 206.9; CHNS Anal. (Calcd for $C_{19}H_{26}O_7$: C, 62.28; H, 7.15). Found: C, 61.86; H, 7.35; MALDI-TOF (Calcd for $C_{19}H_{26}O_7$: 366.17). Found: 389.23 (M+23 for Na).
    Compound **4**: $[\alpha]_D$ (c 1.75, $CHCl_3$): +43.03; IR (cm^{-1}): 3308; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.35, 1.36, 1.43, 1.58 (4s, 12H), 2.11 (t, 1H, $J = 2.65$ Hz), 2.56 (dd, 1H, $J = 2.65$, 17.18 Hz), 2.77 (dd, 1H, $J = 2.66$, 17.31 Hz), 4.20 (m, 6H), 4.68 (d, 1H, $J = 3.79$ Hz), 5.13 (qd, 1H, $J = 1.52$, 3.16 Hz), 5.32 (qd, 1H, $J = 1.77$, 3.42 Hz), 5.76 (d, 1H, $J = 3.79$ Hz), 5.92 (m, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 21.6, 25.3, 26.6, 26.7, 26.9, 66.6, 67.6, 71.9, 73.3, 79.1, 81.6, 82.5, 83.5, 104.1, 109.5, 112.7, 115.6, 135.1; CHNS Anal. (Calcd for $C_{18}H_{26}O_6$: C, 63.89; H, 7.74). Found: C, 63.42; H, 7.87.
    Compound **5**: $[\alpha]_D$ (c 1.05, $CHCl_3$): −50.57; IR (cm^{-1}): 1708, 1627; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.32, 1.37, 1.46, 1.58 (4s, 12H), 1.96 (dd, 1H, $J = 2.15$, 18.95 Hz), 2.53 (dd, 2H, $J = 4.55$, 18.57 Hz), 2.93 (d, 1H, $J = 13.39$ Hz), 3.13 (m, 1H), 3.41 (t, 1H, $J = 11.24$ Hz), 3.92–4.28 (m, 5H), 4.31 (d, 1H, $J = 3.79$ Hz), 5.74 (d, 1H, $J = 3.79$ Hz), 6.06 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 25.3, 26.6, 26.6, 26.8, 33.2, 37.2, 40.7, 67.4, 69.9, 73.5, 79.4, 80.7, 83.1, 103.7, 109.8, 113.1, 129.6, 177.0, 207.3; CHNS Anal. (Calcd for $C_{19}H_{26}O_7$: C, 62.28; H, 7.15). Found: C, 61.93; H, 7.55; MALDI-TOF (Calcd for $C_{19}H_{26}O_7$: 366.17). Found: 389.25 (M+23 for Na).
    Compound **7**: $[\alpha]_D$ (c 1.05, $CHCl_3$): +9.77; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.29 (m, 22H), 2.12 (dd, 1H, $J = 2.56$, 18.21 Hz), 2.69 (dd, 1H, $J = 5.37$, 18.37 Hz), 3.13 (m, 1H), 3.90 (m, 1H), 4.03 (m, 3H), 4.63 (ABq, 2H, $J = 14.20$ Hz), 4.70 (d, 1H, $J = 3.92$ Hz), 5.79 (d, 1H, $J = 3.92$ Hz), 6.01 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 23.64, 23.79, 23.86, 23.90, 24.83, 25.01, 34.46, 34.79, 35.23, 36.11, 36.20, 36.21, 41.81, 63.80, 67.12, 72.93, 79.41, 81.38, 81.39, 103.58, 110.08, 113.74, 127.45, 175.35, 207.03; IR (cm^{-1}): 1707, 1634; CHNS Anal. (Calcd for $C_{25}H_{34}O_7$: C, 67.24; H, 7.67). Found: C, 67.51; H, 7.15.
13. See Supplementary data.