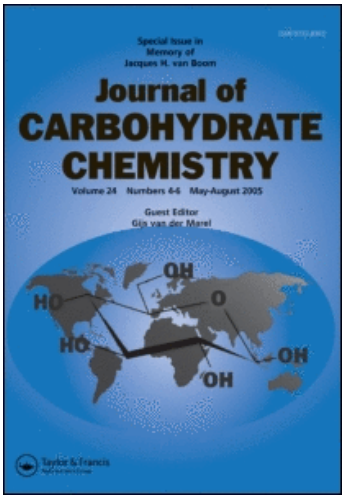

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The Intermolecular Pauson-Khand Reaction of Sugar-Derived Azaenynes: A Case of Total Diastereoselectivity

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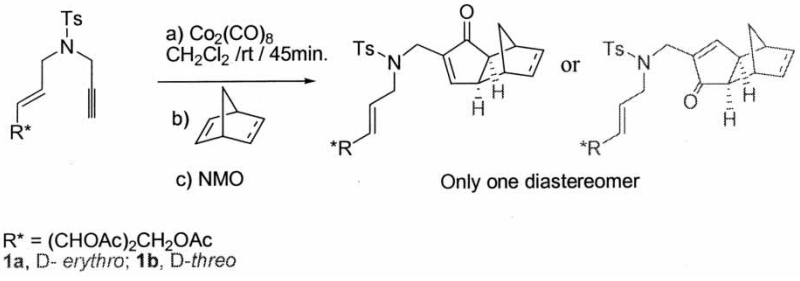
Sugar azaenynes **1a** and **1b**, easily available from D-glucal and D-galactal, respectively, react with norbornene and norbornadiene under Pauson-Khand conditions to give the intermolecular adducts as major or exclusive product. In all cases only one diastereomer was obtained in convenient yield. This reaction constitutes an unprecedented case of totally diastereoselective intermolecular Pauson-Khand reaction using a sugar moiety as chiral auxiliary.



Keywords Intermolecular Pauson-Khand reaction, Cyclopentenones, Carbohydrates

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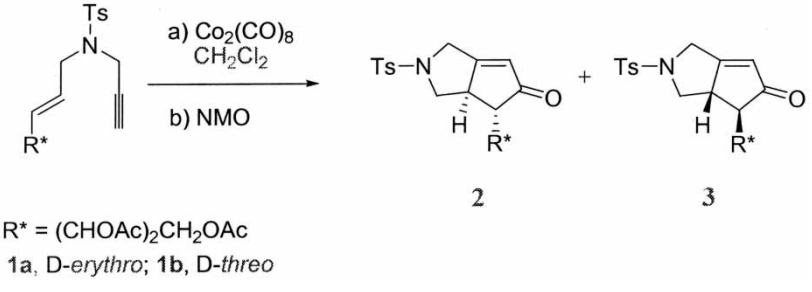
The Pauson-Khand (P-K) reaction, a cobalt carbonylative co-cyclization of an alkene and an alkyne, is the most popular organometallic-mediated reaction for the synthesis of cyclopentenones.[1] In the last few years, many efforts were devoted to the development of the enantioselective version of this reaction and, for the intermolecular process.[2] several methodologies in which a chiral inductor is covalently bonded to one of both partners have been developed.[3] Regarding the use of carbohydrates as a source of chirality, these compounds have been considered as chiral substrates in the intramolecular P-K reactions.[4] Recently we have reported the intramolecular P-K reaction of sugar azaenines **1a** and **1b**, derived from D-glucal and D-galactal, respectively, obtaining the expected cycloadducts **2** and **3** with poor[5] to moderate[6] diastereoselectivity (Sch. 1).

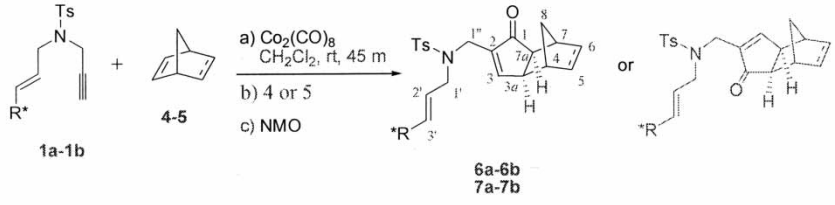
To the best of our knowledge, sugar derivatives have never been used as chiral auxiliaries in the intermolecular Pauson-Khand reactions. In this context we thought that compounds **1a** and **1b** may be interesting alkyne partners for the intermolecular Pauson-Khand reactions, assuming that the intermolecular reaction should be conveniently faster than the intramolecular process. Taking into account that the concurrence between intermolecular and intramolecular Pauson-Khand reactions have never been considered in substrates capable to undergo the intramolecular process, we have selected the reactive bicyclic alkenes norbornene **4** and norbornadiene **5** as olefinic counterparts. Norbornene and norbornadiene are very often used in the intermolecular Pauson-Khand reaction because of their high reactivity. In particular, these compounds are excellent reagents for testing the asymmetric version of the reaction. See literature quoted in reference 2, p. 3028. For the use of oxa- and azanorbornene derivatives in Pauson-Khand reaction, see ref.[7]

Compounds **1a** and **1b** reacted with norbornene and norbornadiene to give the intermolecular *exo* cycloadducts **6** and **7**, respectively (Table 1), as major (entry 1) or only (entries 2–4) reaction products. On the other hand, ^{1}H and ^{13}C NMR spectra of the reaction mixtures showed that each individual



Scheme 1.

Table 1: The intermolecular Pauson-Khand reaction of sugar azaenines **1a** and **1b** with norbornene (**4**) and norbornadiene (**5**).



Entry	Starting materials	Cycloadduct	Isolated yield
1	**1a** and **4**	**6a**	67%[a]
2	**1a** and **5**	**7a**	62%[b]
3	**1b** and **4**	**6b**	80%[b]
4	**1b** and **5**	**7b**	72%[b]

[a]Twenty percent of a mixture of intramolecular cycloadducts **2** and **3** was isolated.
[b]Only traces of intramolecular cycloadducts **2** and **3** were observed in the crude reaction mixture.

cyclopentenone was diastereomerically pure with only one set of peaks present in each case. Flash chromatography of the crude reaction mixture through a small column (silica gel, 3 cm high; hexane-ethyl acetate $3:1 \rightarrow$ ethyl acetate) followed by HPLC analysis and purification (Zorbax Rx-SIL column, isocratic normal phase separation, hexane-ethyl acetate 50 : 50) allowed us to isolate compounds **6** and **7** in moderate to good isolated yields and diastereomeric purity $>95\%$. General procedure for compounds **6a**, **6b**, **7a**, and **7b**. A 0.16 M solution of azaenine precursor (**1a** or **1b**) in freshly distilled CH_2Cl_2 was treated with $Co_2(CO)_8$ (1.1 equiv.) under a CO atmosphere. After 45 min of stirring, the corresponding alkene (**4** or **5**) was added, and the mixture was stirred 10 min more. Then, NMO (6 equiv.) was added portionwise over a 15-min period, and the reaction mixture was cooled to $0^\circ C$ before each addition and allowed to reach rt before a new one. The mixture was stirred for 45 min at rt; diluted with CH_2Cl_2; washed successively wtih 2 N HCl, a saturated solution of $NaHCO_3$, and water; dried ($MgSO_4$); and concentrated in vacuo. The residue was first eluted through a short column (3 cm long) of SiO_2 (hexane/ethyl acetate $3:1 \rightarrow$ ethyl acetate) to remove metal impurities, and the elution was concentrated; flash chromatography (hexane/ethyl acetate $3:1 \rightarrow 1:1$) or HPLC analysis (semipreparative system, Zorbax Rx-SIL column, isocratic normal phase separation, hexane/ethyl acetate 50 : 50) of the residue gave the cyclopentenone (**6** or **7**).

Compound 6a: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, 2H, $J_{3''',2'''} = 8.2$ Hz, H-3‴, H-5‴), 7.30 (d, 2H, $J_{5''',6'''} = 8.2$ Hz, H-2‴, H-6‴), 7.35 (s, H-3), 5.52–5.56 (m, 2H, H-2′, H-3′), 5.38 (m, H-4′), 5.12 (m, H-5), 4.20–4.00 (m, 2H, H-6′a, H-6′b), 3.95–3.60 (m, 4H, 2H-1′, 2H-1″), 2.59 (br s, H-3a), 2.43 (s, 3H, C*H*$_3$-Ar), 2.34 (m, H-7), 2.14 (m, 2H, H-7a, H-4), 2.06 (s, 3H, OAc), 2.05 (s, 3H, OAc), 2.04 (s, 3H, OAc), 1.70–1.50 (m, 2H, H-5), 1.35–1.20 (m, 2H, H-6), 0.97–0.80 (m, 2H, H-8); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.5 (C-1), 170.4, 169.9, 169.3 (3O-*C*O-CH$_3$), 162.6 (C-3), 144.4 (C-2), 143.5 (C-1‴), 136.5 (C-4‴), 130.0 (C-2′), 129.6 (C-3‴ and C-5‴), 128.0 (C-3′), 127.1 (C-2‴, C-6‴), 71.2 (C-4′, C-5′), 61.5 (C-6′), 54.0 (C-7a), 49.8, 49.7 (C-1′), 48.3 (C-3a), 41.9 (C-1″), 38.8 (C-7) 37.7 (C-4), 31.1 (C-8), 28.9 (C-5), 28.2 (C-6), 21.4 (C-7‴), 20.7, 20.5 (3O-CO-*C*H$_3$). HRMS calcd for $C_{30}H_{37}NO_9S + H$: 588.2267. Found: 588.2267.

Compound 6b: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, 2H, $J_{3''',2'''} = 8.2$ Hz, H-3‴, H-5‴), 7.35 (m, H-3), 7.30 (d, 2H, $J_{5''',6'''} = 8.2$ Hz, H-2‴, H-6‴, 5.59–5.53 (m, 2H, H-2′, H-3′), 5.39 (m, H-4′), 5.13 (m, H-5′), 4.27 (dd, $J_{5',6a'} = 4.0$ Hz, $J_{6b',6a'} = 12.0$ Hz, H-6′a), 3.98–3.93 (m, H-6′b), 3.90–3.73 (m, 4H, 2H-1′, 2H-1″), 2.59 (br s, H-3a), 2.43 8 (s, 3H, CH$_3$-Ar), 2.35 (br s, H-7), 2.17–2.14 (m, 2H, H-7*a*, H-4), 2.07 (s, 3H, OAc), 2.05 (s, 3H, OAc), 2.04 (s, 3H, OAc), 1.67–1.57 (m, 2H, H-5), 1.31–1.25 (m, 2H, H-6), 0.93–0.90 (m, 2H, H-8); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.7 (C-1), 170.4, 170.0, 169.5 (3O-*C*O-CH$_3$), 162.8 (C-3), 144.5 (C-2), 143.5 (C-1‴), 136.6 (C-4‴), 130.0 (C-3‴, C-5‴), 128.2 (C-3′), 127.1 (C-2‴, C-6‴), 71.1, 71.0 (C-4′, C-5′), 61.9 (C-6′), 54.1 (C-7a), 49.7 (C-1′), 48.4 (C-3a), 41.8 (C-1′), 38.9 (C-7), 37.8 (C-4), 31.2 (C-8), 29.0, 28.3 (C-5, C-6), 21.4 (C-7‴), 20.8, 20.7, 20.6 (3O-CO-*C*H$_3$); HRMS calcd for $C_{30}H_{37}NO_9S + H$: 588.2267. Found 588.2269.

Compound 7a: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, 2H, $J_{3''',2'''} = 8.2$ Hz, H-3‴, H-5‴), 7.43 (br s, H-3), 7.31 (d, 2H, $J_{5''',6'''} = 8.2$ Hz, H-2‴, H-6‴), 6.29 (dd, $J_{4,5} = 3.0$ Hz, $J_{5,6} = 5.5$ Hz, H-5), 6.19 (dd, $J_{6,7} = 2.9$ Hz, $J_{6,5} = 5.5$ Hz, H-6) 5.64–5.52 (m, 2H, H-2′, H-3′), 5.38 (m, H-4′), 5.12 (m, H-5′), 4.18–4.06 (m, 2H, H-6′a, H-6′b), 3.93–3.73 (m, 4H, 2 H-1′, 2 H-1″), 2.90 (br s, H-7), 2.73 (br s, H-3a), 2.68 (br s, H-4), 2.43 (s, 3H, CH$_3$-Ar), 2.26 (d, $J_{7a,7} = 5.0$ Hz, H-7a), 2.06 (s, 3H, OAc), 2.04 (s, 3H, OAc), 2.03 (s, 3H, OAc), 1.37 (d, $J_{8a,8b} = 9.1$ Hz, H-8b), 1.12 (d, $J_{8a,8b} = 9.1$ Hz, H-8a); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.4 (C-1), 170.0, 169.4 (3O-*C*O-CH$_3$), 162.7 (C-3), 145.7 (C-2), 143.6 (C-1‴), 138.5 (C-5), 137.0 (C-6), 136.6 (C-4‴), 130.2 (C-2′), 129.8, (C-3‴, C-5‴), 128.2 (C-3′), 127.2 (C-2‴, C-6‴), 71.4, (C-4′, C-5′), 61.6 (C-6′), 52.9 (C-7a), 50.1 (C-1′), 48.0 (C-3a), 43.6 (C-7), 42.8 (C-4), 42.0 (C-1″), 41.3 (C-8), 21.5 (C-7‴), 20.8, 20.7 (3O-CO-*C*H$_3$); HRMS calcd for $C_{30}H_{35}NO_9S + H$: 586.2110. Found: 586.2111.

Compound 7b: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, 2H, $J_{2''',3'''} = J_{5''',6'''} = 8.4$ Hz, H-3‴, H-5‴), 7.42 (br s, H-3), 7.31 (d, 2H, $J_{5''',6'''} = 8.4$ Hz,

H-2‴, H-6‴), 6.24 (dd, $J_{4,5} = 3.2$ Hz, $J_{5,6} = 5.2$ Hz, H-5), 6.19 (dd, $J_{6,7} = 2.8$ Hz, $J_{6,5} = 5.2$ Hz, H-6), 5.57 (m, 2H, H-2′, H-3′), 5.39 (m, H-4′), 5.13 (m, H-5′), 4.27 (dd, $J_{5',6'} = 4.4$ Hz, $J_{6'a,6'b} = 12.0$ Hz, H-6′a), 3.99-3.73 (m, H-6′b), 3.88–3.72 (m, 4H, 2H-1′, 2H-1″), 2.87 (br s, H-7), 2.73 (br s, H-3a), 2.68 (br s, H-4), 2.43 (s, 3H, CH_3-Ar), 2.26 (m, H-7a), 2.07 (s, 3H, OAc), 2.05 (s, 3H, OAc), 2.04 (s, 3H, OAc), 1.37 (d, $J_{8a,8b} = 9.6$ Hz, H-8a), 1.12 (d, $J_{8a,8b} = 9.6$ Hz, H-8a); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.0 (C-1), 171.0, 170.6, 170.1 (3O-*C*O-CH_3), 163.4 (C-3), 146.2 (C-2), 142.2 (C-1‴), 139.1 (C-5), 137.6 (C-6), 137.2 (C-4‴), 130.6 (C-2′), 130.4, 130.5 (C-3‴, C-5‴), 128.9 (C-3′), 127.8 (C-2‴, C-6‴), 71.7, 71.6 (C-4′, C-5′), 62.6 (C-6′), 53.5 (C-7a), 50.6 (C-1′), 48.6 (C-3*a*), 44.2 (C-7), 43.4 (C-4), 42.6 (C-1″), 41.9 (C-8), 22.1 (C-7‴), 21.4, 21.3 (3O-CO-*C*H_3); HRMS calcd for $C_{30}H_{35}NO_9S + H$: 586.2110. Found: 586.2113.

The assignment of the relative configuration at the new formed stereocenters in diastereomerically pure compounds **6** and **7** is being carried out and will be reported in due course. On the other hand, the *exo* stereochemistry of the cycloaddition was deduced from the lack of coupling between the *endo* hydrogens and the bridgehead protons in the norbornane framework.[8]

In summary, in this paper we have showed that the concurrence between inter- and intramolecular Pauson-Khand reactions in substrates such as **1a** and **1b** capable to give both types of reactions was clearly shifted toward the intermolecular process using reactive bicyclic alkenes such as **4** or **5**. Interestingly, only one diastereomer was obtained in these reactions, showing an unprecedent diastereoselective control, which must be exerted by the sugar side chain. Synthetic applications of this process are now under research in our laboratory.

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